CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, UNAHOTELS Galles

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Update della terapia dei PTLD

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Disclosures of Federica Cavallo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ROCHE	Y	N	N	N	Y	Y	Y
ABBVIE	N	N	N	N	N	N	Y
INCYTE	N	N	N	N	Y	Y	N
ASTRA ZENECA	N	N	N	N	N	Y	Y
SOBI	N	N	N	N	Y	Y	N
BRISTOL MYERS SQIBB	N	N	N	N	N	Y	N
PIERRE FABRE	N	N	N	N	Y	N	Y
NOVARTIS	N	N	N	N	Y	N	Y
GILEAD	N	N	N	N	Y	N	Y
TAKEDA	N	N	N	N	N	N	Y
LILLY	N	N	N	N	Y	N	N
BEIGENE	N	N	N	N	Y	N	Y

PTLD: Post transplant lymphoprolipherative disorders

PTLD is a well-known complication of solid organ (SOT) and stem cell transplant (SCT) procedures

Variable	SOT	HCT
Typical cell of origin[1]	Recipient origin	Donor origin
Frequency[1]	1–33%	0.8–4%
EBV-associated[2]	~50%	~100%
Onset time	Variable ~50% >1-year post-transplant[3]	Within the first year post-transplant[4]

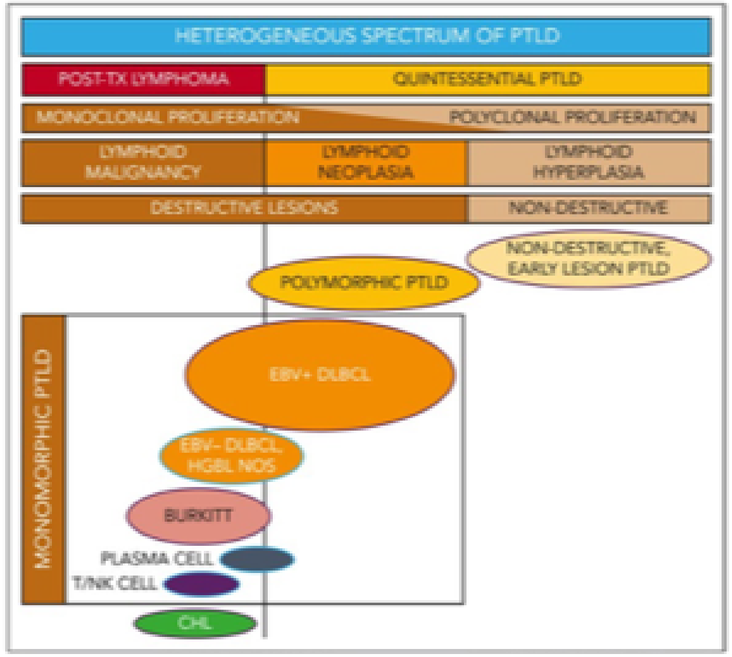
EBV, Epstein–Barr virus; HCT, haematopoietic cell transplantation; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.

1. Fujimoto A, et al. Cancers (Basel). 2020;12:328; 2. Dierickx D, et al. N Engl J Med. 2018;378:549–562; 3. Ghobrial IM, et al. Transplantation. 2005;79(2):244–247;
4. Tai R, et all. Br J Radiol. 2015;88(1052):20140861.

EBV and post-transplant lymphoproliferative disorder: a complex relationship

Hematology Am Soc Hematol Educ Program 2024

Nader Kim El-Mallawany[1,2] and Rayne H. Rouce[1-3]



Framework	Original category	Infiltrative pattern[a]	Histology	Typical therapy	EBV association	Think of as . . .
Post-transplant EBV	EBV viremia	None	Not applicable (no lesions present, therefore no biopsy)	RI and clinical observation	Always	Asymptomatic posttransplant EBV infection
Quintessential PTLD	Early lesion	Nondestructive	Plasmacytic hyperplasia	Most likely to respond to RIS or surgical resection	Virtually always EBV$^+$	EBV-driven reactive lymphoid hyperplasia
			Infectious mononucleosis-like			
			Florid follicular hyperplasia			
	Polymorphic	Destructive	Polymorphous infiltrate with various stages of B-cell maturation, often clonal	May respond to RIS, but often requires rituximab or CPR[b]	Typically EBV$^+$ (>95%)	Lymphoid neoplasia
	Monomorphic	Destructive	DLBCL	Low-dose CPR. Potentially, up to 50% respond to rituximab alone.	Quintessential cases are typically EBV$^+$	Lymphoid neoplasia
Post-transplant NHL	Monomorphic	Destructive	DLBCL	Multiagent chemotherapy for mature B-NHL	EBV$^-$ potential red flag Refractory EBV$^+$ cases	De novo lymphoma in an immunocompromised patient
Post-transplant NHL	Monomorphic	Destructive	Burkitt lymphoma	Require disease-specific multi-agent chemotherapy	Burkitt usually EBV$^+$	De novo lymphoma in an immunocompromised patient
			High-grade B-cell lymphoma			
			T/NK-cell lymphoma		Others often EBV$^-$	
			Plasma cell neoplasm			
Post-transplant HL	Hodgkin lymphoma	Destructive	Classic Hodgkin lymphoma	Requires disease-specific multiagent chemotherapy	Usually EBV$^+$ (>75%)	De novo lymphoma in an immunocompromised patient

Current PTLD treatment options

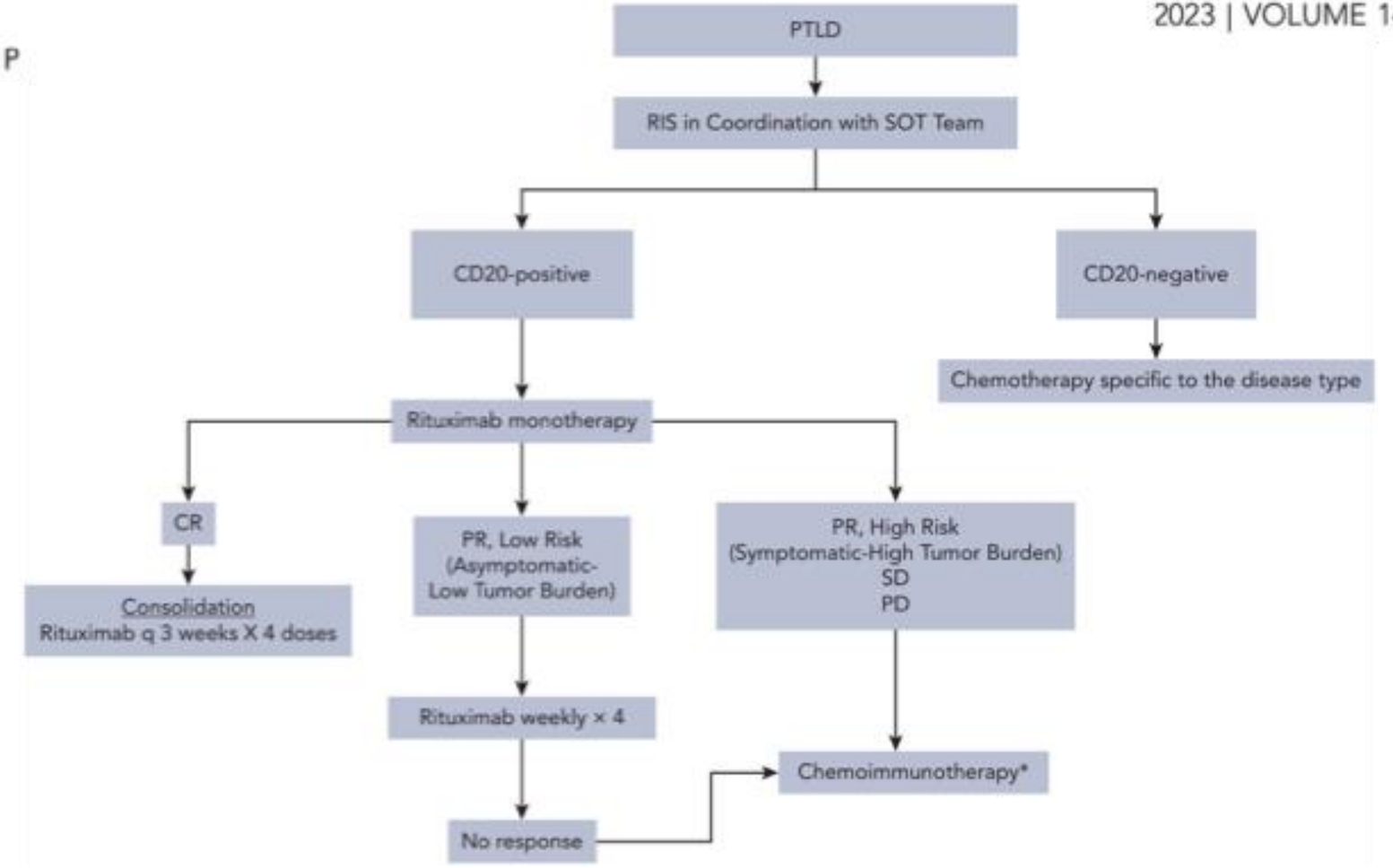
Restoring T cell function[1,2]	• Reduction of immune suppression • Adoptive immunotherapy
Reducing tumor[1,2]	• Local therapy • Rituximab and/or chemotherapy
Targeting EBV[1-3]	• Inducers of lytic cycle • Antiviral agents

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

How I treat posttransplant lymphoproliferative disorder

Jennifer E. Amengual and Barbara P

blood
2023 | VOLUME 142, NUMBER 17



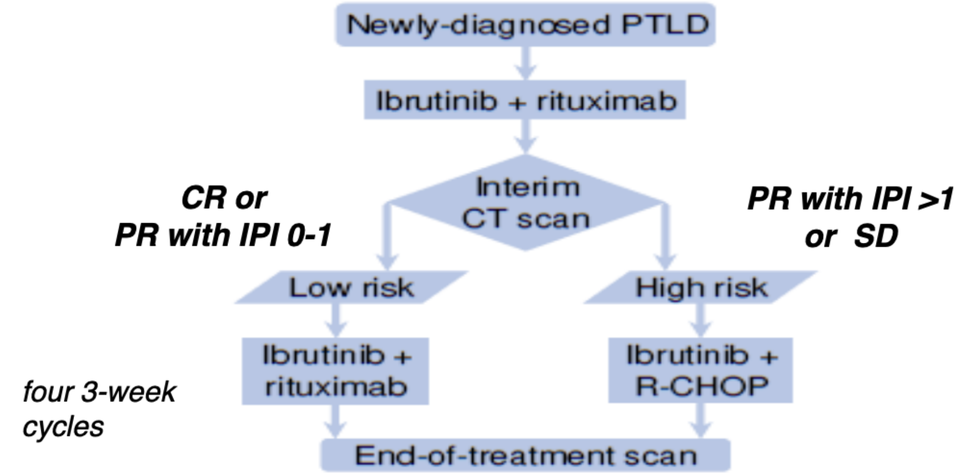
TIDAL

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



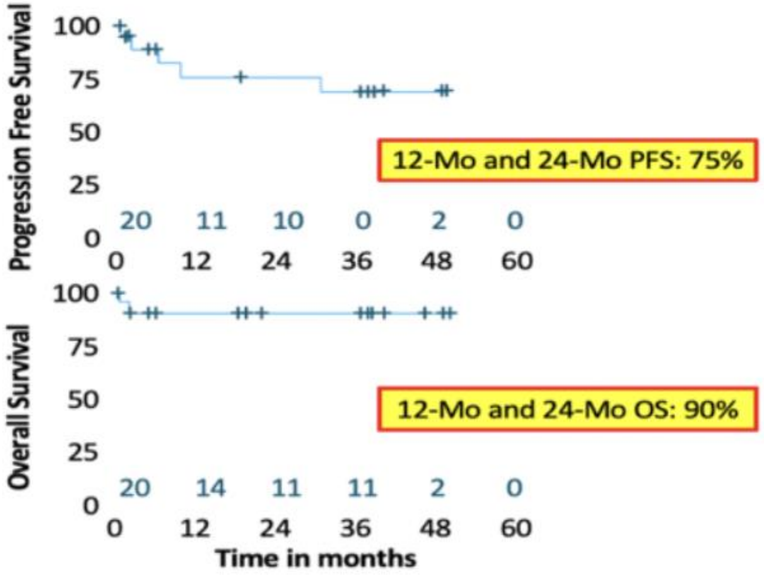
Chaganti, Blood 2024

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CR, complete response; IPI, international prognostic index; IS, immunosuppression; ORR, overall response rate; PD, progressive disease; PR, partial response; PTLD, post-transplant lymphoproliferative disorder; PFS, progression free survival; OS, overall survival.

Brentuximab-Rituximab phase I/II trial

- Investigate efficacy of Bv+R once weekly for 4 weeks, followed by maitenance
- Schedule:
  - pts in PD after induction: chemotherapy
  - pts in CR/PR/SD after induction → maintenance with Bv+R for 12 months

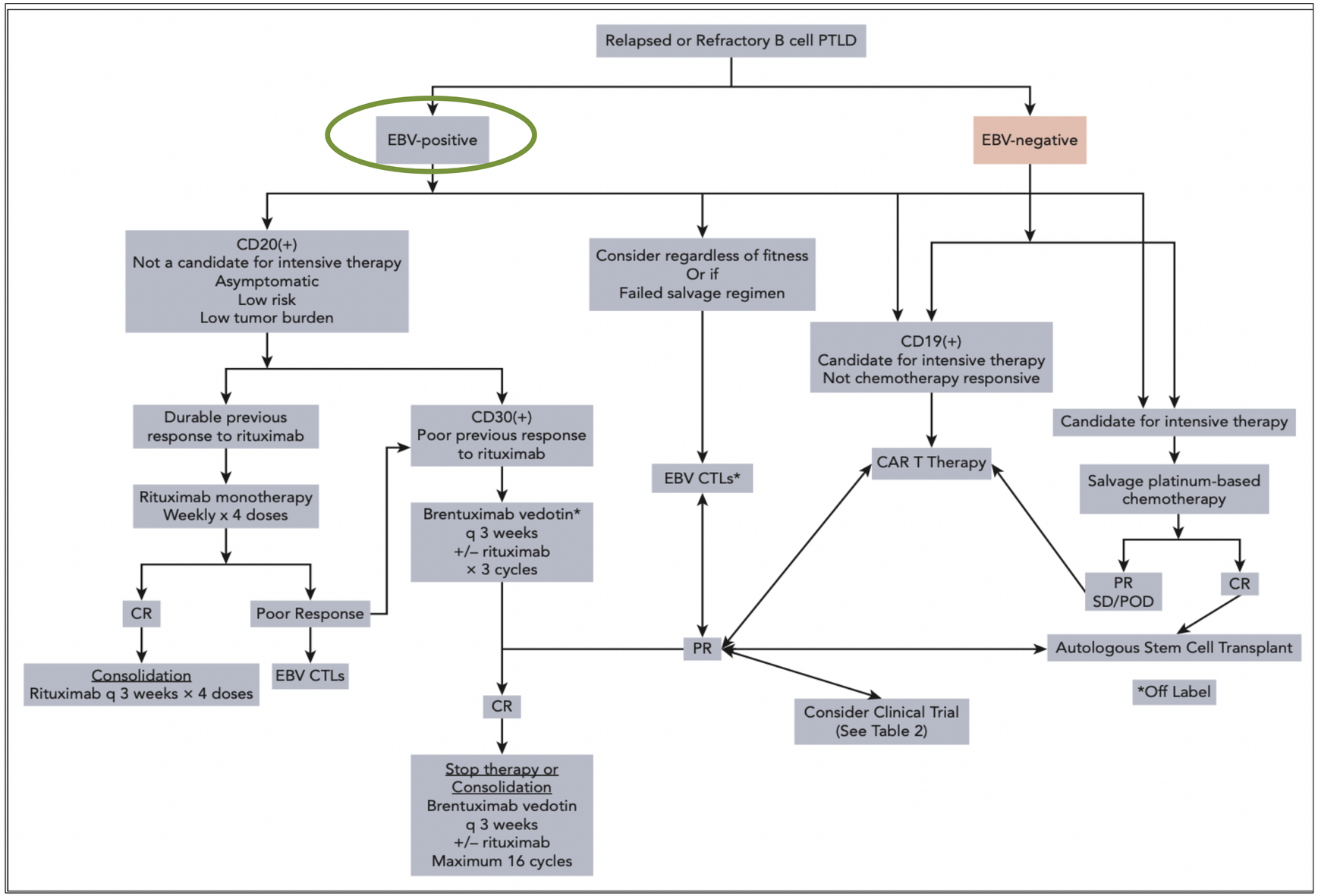
- 20 pts enrolled: (55% monomorphic, IPI >2, 35% ECOG 2)
- **ORR 75%, CR 60%**
- Median time to response: 28 days
- High rate of toxicities: 40% neutropenia, 30% hypertension, 25% infections, 13% pheripheral neuropathy



Bv, brentuximab vedotin; R, rituximab; CR, complete response; IPI, international prognostic index; IS, immunosuppression; ORR, overall response rate; PD, progressive disease; PR, partial response; PFS, progression free survival; OS, overall survival.

Pearse et al, Leuk Lymphoma 2021

Treatment at relapse

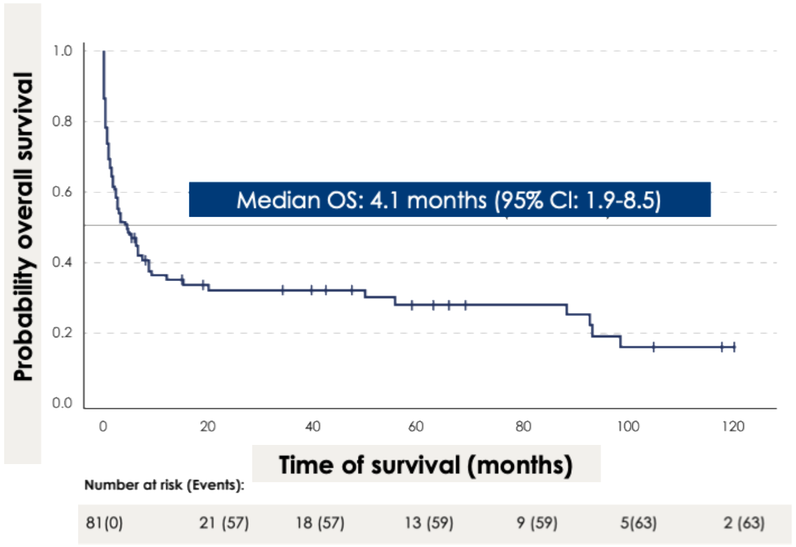


Amengual J and Pro B, Blood 2023

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

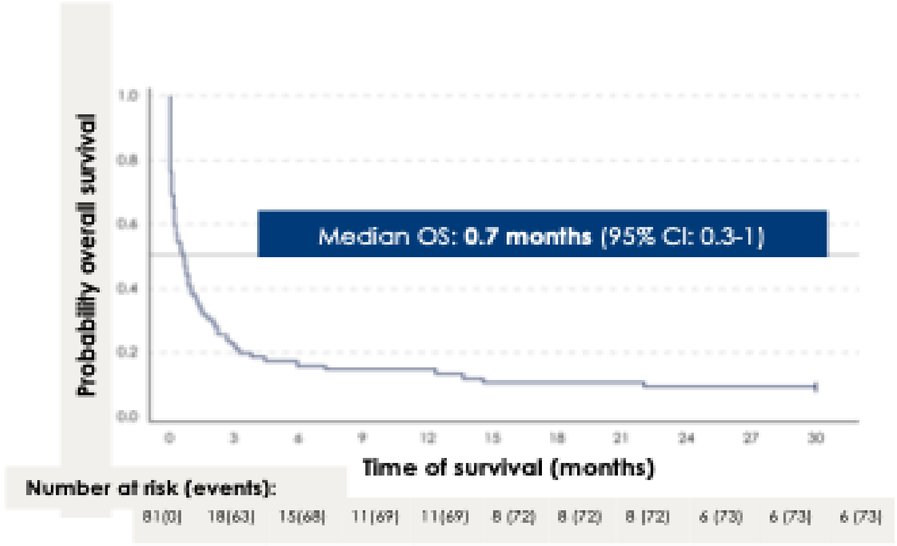
A large multinational, multicenter* retrospective chart review study of EBV+ PTLD patients following HCT or SOT who received rituximab or rituximab plus chemotherapy between January 2000–December 2018 and were refractory or relapsed at any point after such therapy[1,2]

Overall survival in Patients with R/R EBV+ PTLD Following SOT (N=86)[1]



Adapted from Dhamidharka V, et al. 2022.

Overall survival in Patients with R/R EBV+ PTLD Following HCT (N=81)[2]



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

EBV+, Epstein-Barr virus positive, GvHD, graft vs host disease; HCT, haematopoietic cell transplant; OS, overall survival; PTLD, post-transplant lymphoproliferative disorder; R/R, relapsed/refractory; SOT, solid organ transplantation.

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

Tabelecleucel is an allogeneic T-cell immunotherapy licensed for the treatment of relapsed/refractory EBV+ PTLD[1]

Tabelecleucel is indicated:[1]

As monotherapy for the treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory EBV+ PTLD who have received at least one prior therapy

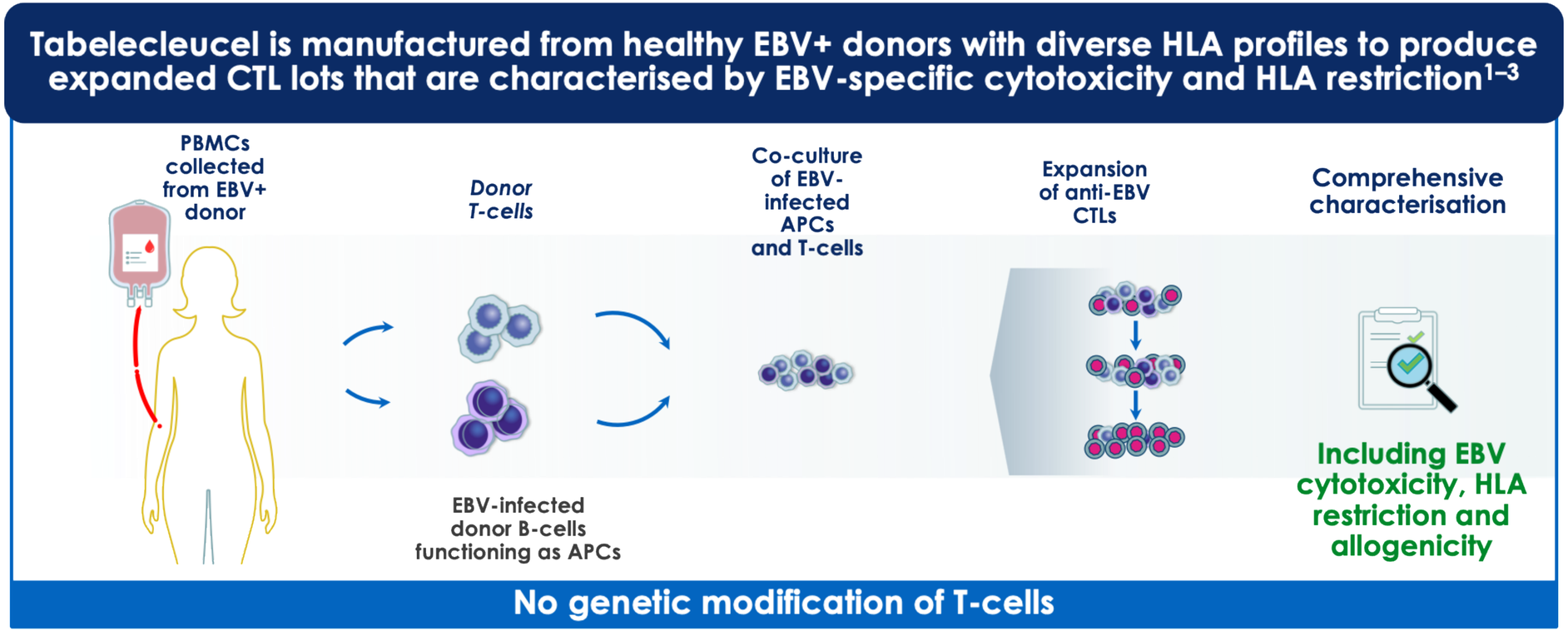
For SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

Tabelecleucel is licensed in Europe, including the UK and Switzerland in the outlined indication[1–3] and is currently marketed in Italy.

EBV+, Epstein Barr virus positive; UK, United Kingdom; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation

1. tabelecleucel EU SmPC; 2. tabelecleucel UK SmPC; 3. tabelecleucel CH SmPC

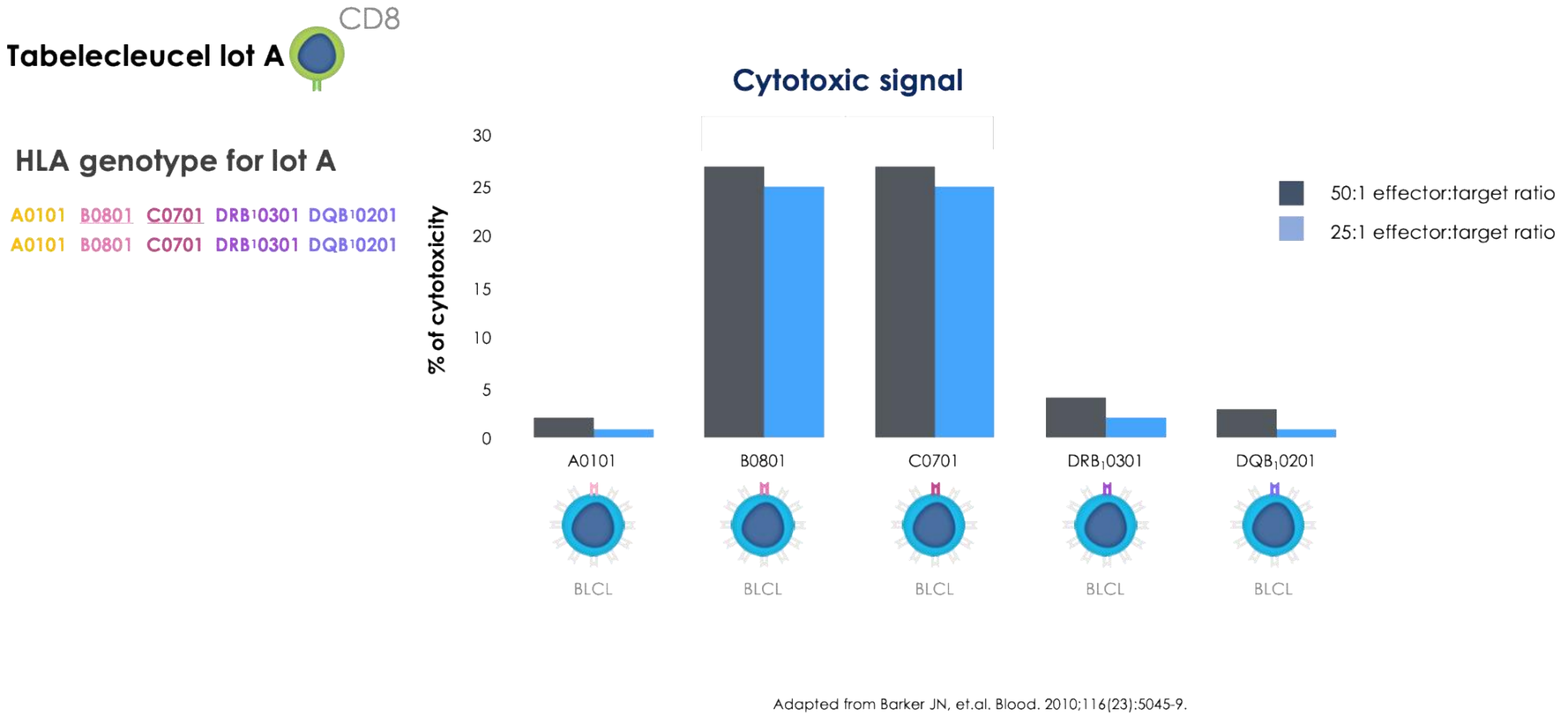
Manufacturing of tabelecleucel



EBV, Epstein-Barr virus; EBV+, Epstein Barr virus positive; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disease; TCR, T-cell receptor.

1. Prockop S, et al. Biol Blood Marrow Transplant. 2018:24(3_suppl):S41–S42; 2. Prockop S, et al. J Clin Oncol. 2016:34(15_suppl):Abstract 3012.

Characterising the tabelecleucel lots with a cytotoxic assay: determining cytotoxicity (HLA restriction)[1]



Adapted from Barker JN, et.al. Blood. 2010;116(23):5045-9.

BLCL, B lymphoblastoid cell line; EBV-CTL, Epstein-Barr virus-specific cytotoxic T lymphocyte; HLA; human leukocyte antigen;

1. Barker JN et.al., Blood 2010;116(23):5045–5949.

How to establish the suspected origin of EBV+ PTLD disease

The suspected **origin of the disease** is required to ensure an appropriate tabelecleucel lot is selected

The **BEST OPTION** is to obtain **high resolution HLA typing** of the disease biopsy

If biopsy high resolution HLA typing is **not** available, the **origin of the disease must be defined:**

If the patient and donor gender are matched:

Use clinical assumptions:

- Patient/donor EBV serostatus before transplant
- Timing of PTLD diagnosis from transplant
- Disease location (eg. organ involvement)

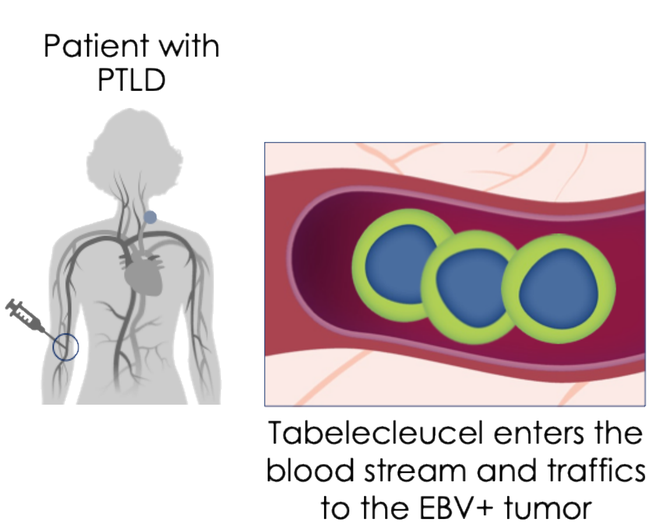
If the patient and donor gender are mis-matched:

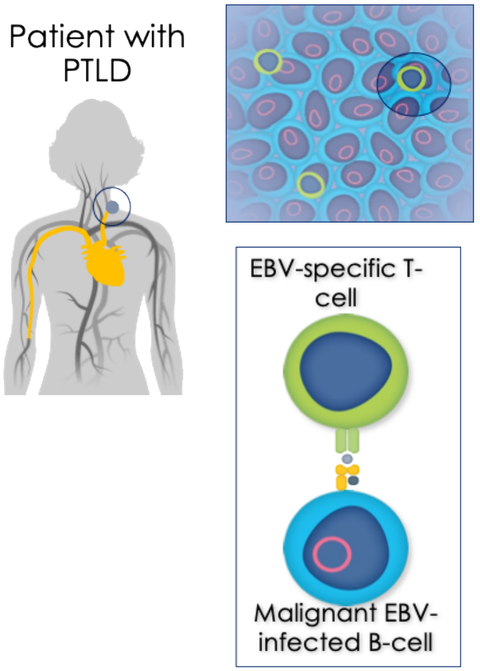
Recommend to perform a **chromosome FISH test**

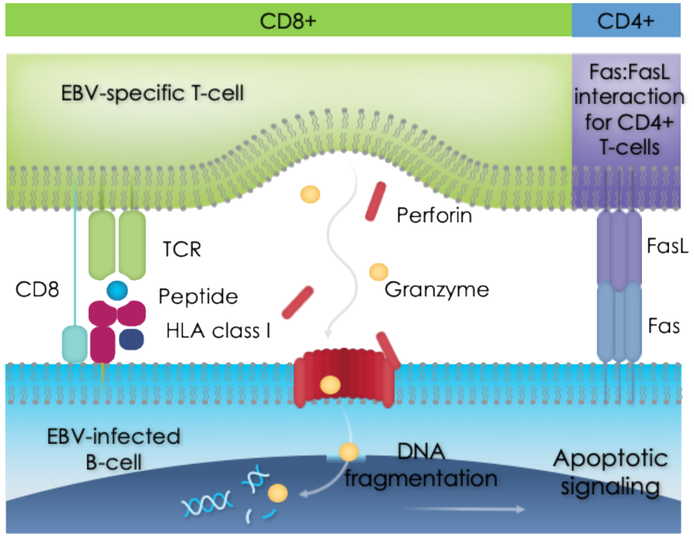
EBV+, Epstein-Barr virus positive; FISH, fluorescence *in situ* hybridisation; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disorder.

Tabelecleucel mechanism of action

1. Tabelecleucel infusion[1,2] → **2. Trafficking and homing to PTLD tumor, and recognition of EBV antigens[1,2]** → **3. Induce lysis of EBV+ cancer cells[1,2]**



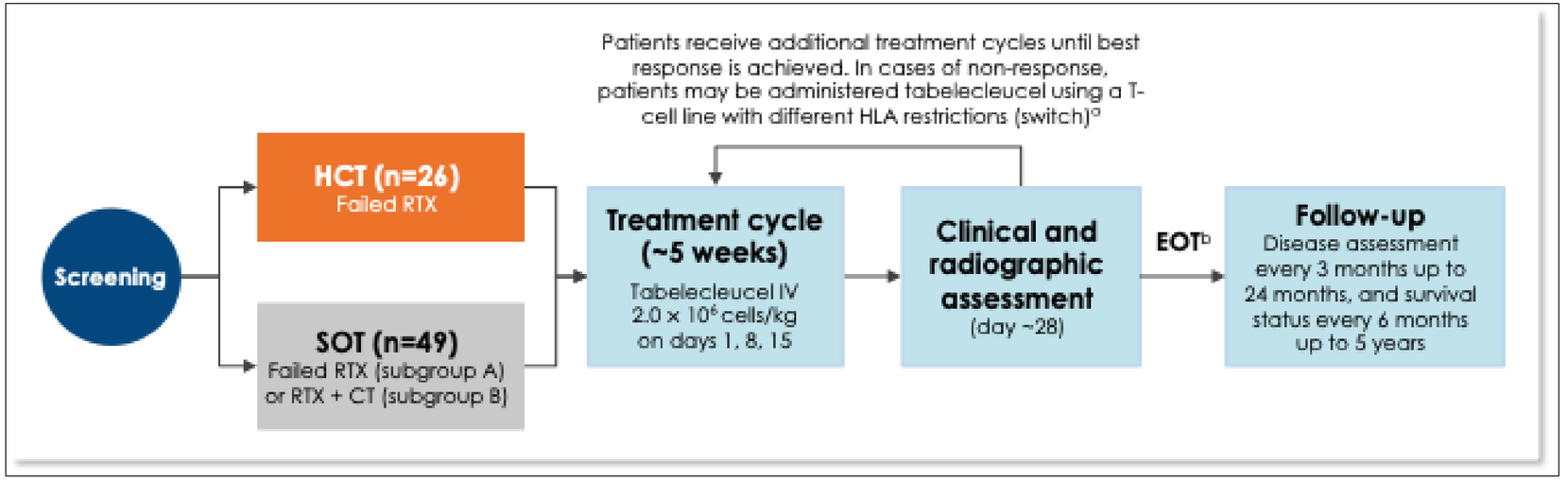




CD4/8, cluster of differentiation 4/8; DNA, deoxynucleic acid; EBV, Epstein-Barr virus; EBV+, Epstein Barr virus positive; FasL, fas ligand; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disease; TCR, T-cell receptor.

1. Prockop S, et al. Biol Blood Marrow Transplant. 2018:24(3_suppl):S41–S42; 2. Prockop S, et al. J Clin Oncol. 2016:34(15_suppl):Abstract 3012.

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



Key eligibility criteria:

- Prior allogeneic HCT or SOT
- Biopsy-proven EBV+ PTLD
- Previous RTX or RTX-CT[c] failure
- ECOG PS ≤3

Primary endpoint: ORR[d]

Key secondary endpoints:

- TTR and time to best response
- OS in responders vs non-responders

[a]Patients may receive up to 4 (in HCT group) or 2 (in SOT group) different HLA restrictions. [b]Evaluated by independent review. [c]Including R-CHOP. [d]Defined as any of the following: maximal response achieved; unacceptable toxicity; initiation of non-protocol therapy; or failure of up to 4 (in HCT group) or 2 (in SOT group) different HLA restrictions; CT, chemotherapy; EBV+, Epstein–Barr virus-positive; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplant; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; RTX, rituximab; SOT, solid organ transplant; TTR, time to response.

Mahadeo KM, et al. *Lancet Oncol* 2024;25:376–87.

Baseline Demographics and Disease Characteristics (1/2)

Demographics	HCT (n = 26)	SOT (n = 49)	All (N = 75)
Age, median (range), years	49.3 (3.2–73.2)	42.8(2.7–81.5)	44.4 (2.7–81.5)
Male sex, n (%)	15 (57.7)	29 (59.2)	44 (58.7)
ECOG PS score, median (range)[a]	1 (0–3)	1 (0–3)	1 (0–3)
ECOG PS score ≥2, n (%)[b]	6 (24)	12 (27.9)	18 (26.5)
Disease characteristics			
Extranodal disease at screening, n (%)	16 (61.5)	40 (81.6)	56 (74.7)
PTLD-adapted prognostic index, n (%)[c]	n = 25	n = 43	N = 68
High risk	12 (48.0)	17 (39.5)	29 (42.6)
Intermediate risk	13 (52.0)	21 (48.8)	34 (50.0)
Low risk	0	4 (9.3)	4 (5.9)
Unknown	0	1 (2.3)	1 (1.5)
PTLD morphology, n (%)	n = 26	n = 49	N = 75
Diffuse large B-cell lymphoma	18 (69.2)	34 (69.4)	52 (69.3)
Plasmablastic lymphoma	1 (3.8)	2 (4.1)	3 (4.0)
Other[d]	7 (26.9)	12 (24.5)	19 (25.3)
Median (range) time, months			
From transplant to EBV⁺ PTLD diagnosis	3.9 (0.6–66.0)	10.8 (2.4-314.4)	–
From EBV⁺ PTLD diagnosis to first tabelecleucel administration	2.1 (0.6–28.1)	6.9 (1.3–190.5)	4.6 (0.6–190.5)

Data cutoff date: Oct 9, 2023.
[a]Data are shown in patients aged ≥16 years and having baseline ECOG measurement (n=35; n=13 for HCT and n=22 for SOT). [b]Data are shown in patients aged ≥16 years (n=68; n=25 for HCT and n=43 for SOT) . [c]PTLD-adapted prognostic index at study entry: low risk (no high risk factors among age, ECOG, and LDH vs intermediate risk (one high risk factor) vs high risk (two or three high risk factors); data is shown in patients aged ≥16 years.
[d]Morphologies not clearly diffuse large B-cell lymphoma or plasmablastic lymphoma were categorized as Other.
ECOG = Eastern Cooperative Oncology Group; HCT = hematopoietic cell transplant; SOT = solid organ transplant.

Chaganti S, et al. EBMT 2025

Baseline Demographics and Disease Characteristics (2/2)

Treatment and prior therapies	HCT (n=26)	SOT (n=49)	All (N=75)
Median number of lines of prior systemic treatment, n (range)	1 (1–4)	1 (1–5)	1 (1–5)
Prior rituximab monotherapy, n (%)	26 (100.0)	39 (79.6)	65 (86.7)
Prior chemotherapy, n (%)	4 (15.4)	31 (63.3)	35 (46.7)
Prior chemotherapy in combination with rituximab, n (%)	0	28 (57.1)	28 (37.3)
Prior immunotherapy, n (%)	1 (3.8)	2 (4.1)	3 (4.0)
Transplant type, n (%)			
Kidney	–	14 (28.6)	–
Heart	–	12 (24.5)	–
Lung	–	9 (18.4)	–
Liver	–	4 (8.2)	–
Multivisceral	–	10 (20.4)	–

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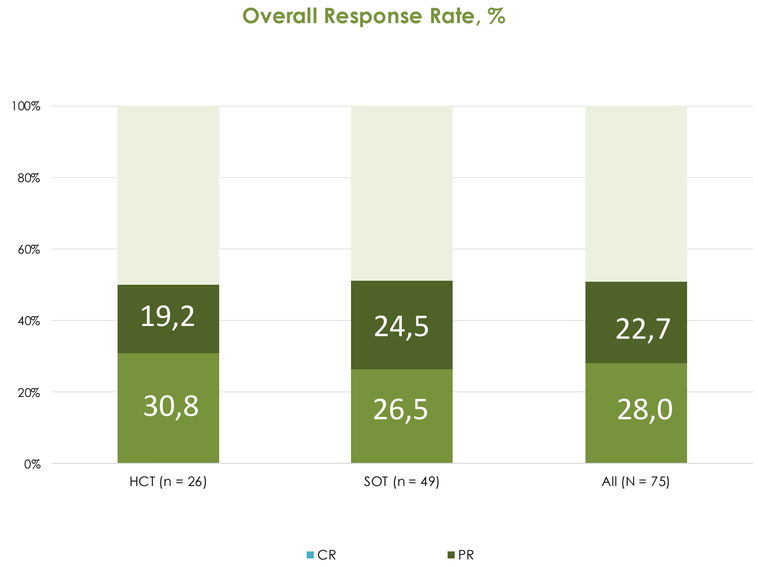
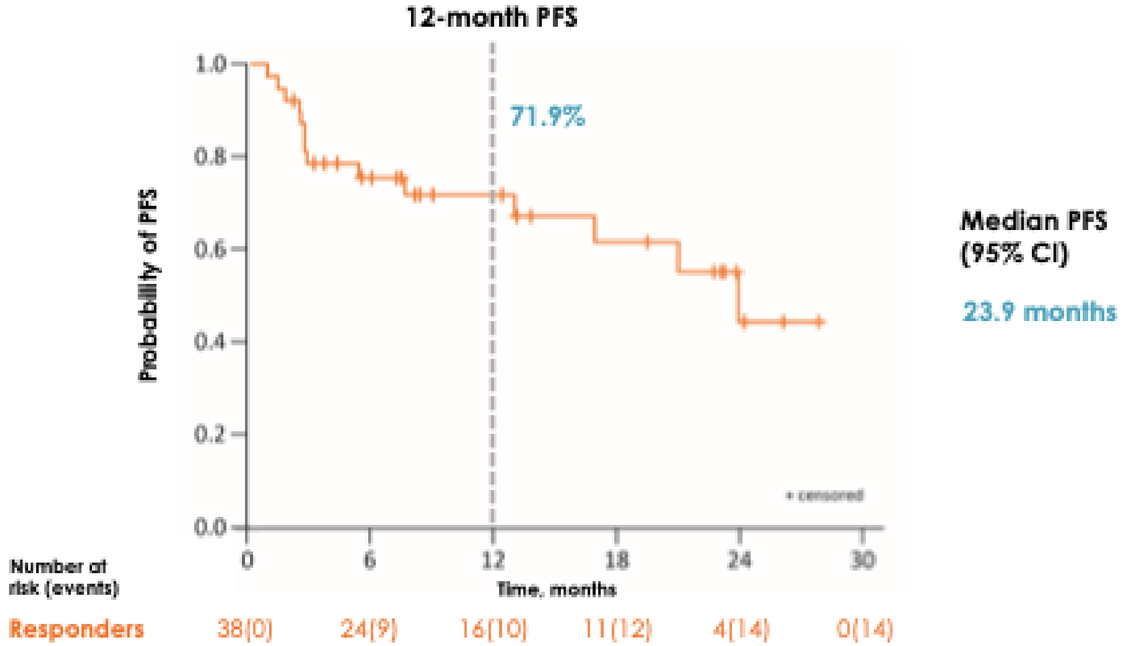
Response and survival in the ALLELE trial





Median time to response in all patients was **1.1 months**

Estimated median duration of response (DOR) was **23 months**

Data cutoff date: Oct 9, 2023

[a]Response assessed per Lugano classification with LYRIC modification by IORA. [b]Estimated by the Kaplan–Meier method.

CI, confidence interval; CR, complete response; DOR, duration of response; HCT, hematopoietic cell transplant; IORA, independent oncologic response adjudication; NE, not estimable; PR = partial response; SOT, solid organ transplant; TTR, time to response.

Median PFS was estimated by the Kaplan–Meier method.

CI, confidence interval; NE, not estimable; PFS, progression-free survival.

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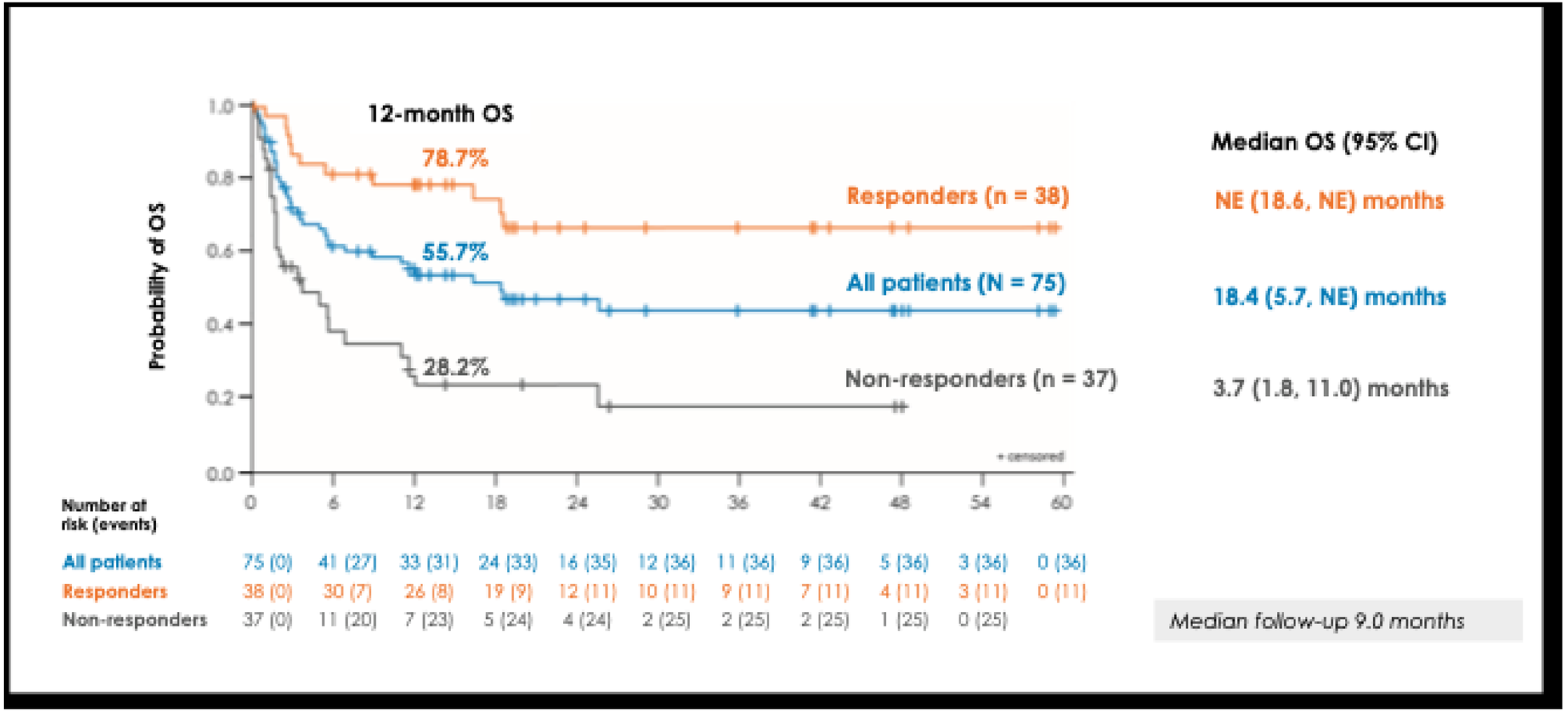
Responders to tabelecleucel had improved 1-y OS rate



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Safety Outcomes

	HCT (n = 26)	SOT (n = 49)	All (N = 75)
TESAEs, n (%)			
Any	17 (65.4)	30 (61.2)	47 (62.7)
Treatment-related[a]	2 (7.7)	4 (8.2)	6 (8.0)
Treatment-related fatal	0	0	0
Treatment Emergent Identified and Potential Risks including AESI by SOC, n (%)			
Tumor flare reaction	0	0	0
Infusion-related reaction	0	0	0
Cytokine release syndrome	0	0	0
Transmission of infectious disease	0	0	0
Graft-vs-host disease	3 (11.5)	0	3 (4.0)
Bone marrow/organ rejection	0	3 (6.1)	3 (4.0)
ICANS	0	0	0
Immunogenicity[b]	0	0	0

- Most treatment-emergent serious adverse events (TESAEs) were not treatment related
- None of the fatal TESAEs were related to tabelecleucel
- There were **no reports** of
  - tumor flare reaction
  - infusion-related reaction
  - cytokine release syndrome
  - bone marrow rejection
  - immune effector cell-associated neurotoxicity syndrome (ICANS),
  - Immunogenicity
  - transmission of infectious diseases (including cytomegalovirus)
- **No cases of tabelecleucel-related graft-vs-host disease or organ rejection were reported**

Data cutoff date: Oct 9, 2023

Fatal TEASAEs were disease progression (n = 7), multiple organ dysfunction syndrome (n = 2), respiratory failure (n = 1), COVID-19 (n=1), acute respiratory distress (n=1), pneumococcal sepsis (n=1), shock (n=1). [a]Treatment-related TESAEs were pyrexia, diarrhea, hypoxia, hypotension, rash, erythematous, and tachycardia [b] 47 subjects had pan anti-HLA antibody testing completed, 18 of which were evaluable (18 in target population) for anti-HLA antibody assessment

AESI, adverse event of special interest; HCT, hematopoietic cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome; SOT, solid organ transplant; TESAE, treatment-emergent serious adverse event.

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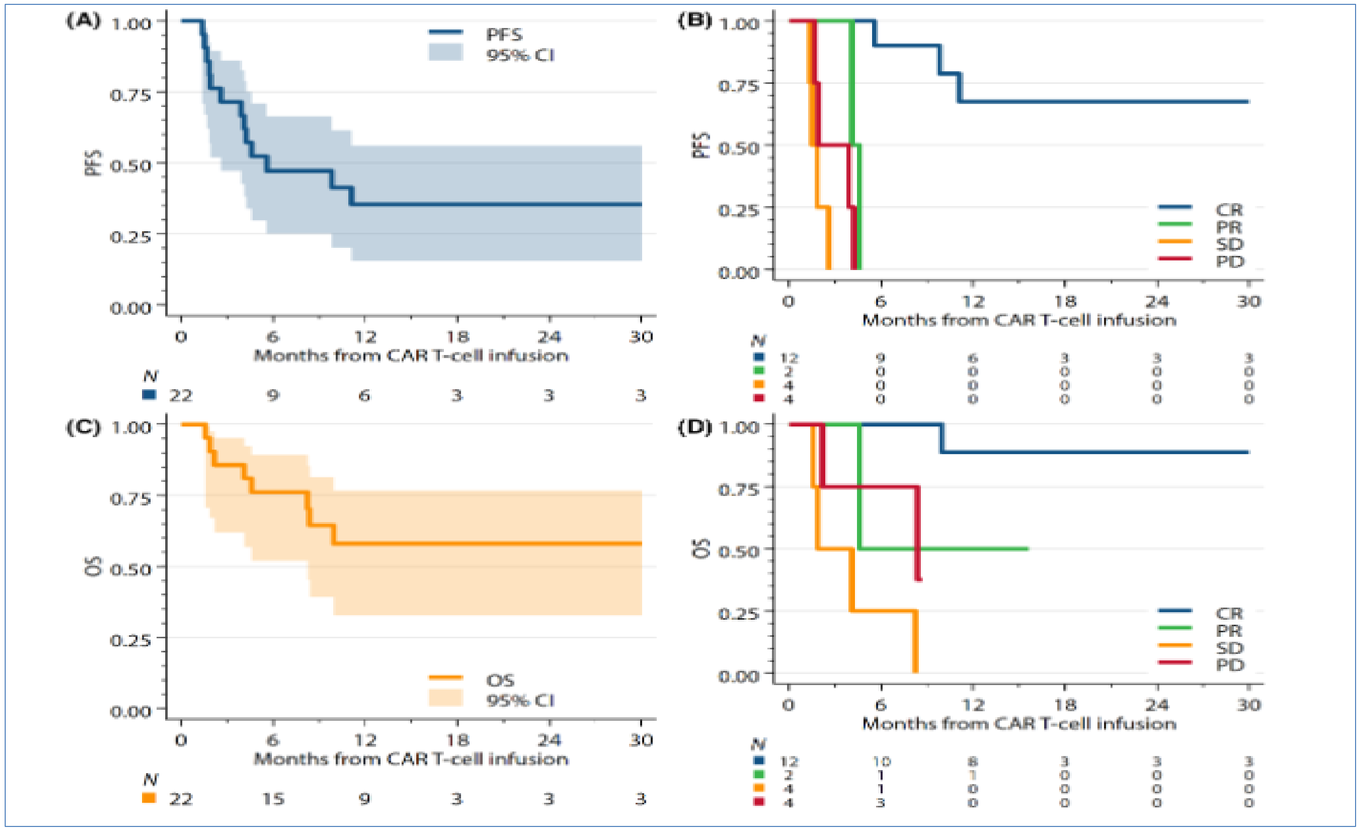
CAR-T limited literature

Age at PTLD diagnosis, *N* (%)		Bulky disease (≥10 cm at CAR-T), *N* (%)	
Age <60	14 (64)	Yes	5 (23)
Age ≥60	8 (36)	No	17 (77)
Gender, *N* (%)		Bone marrow involvement, *N* (%)	
Male	16 (73)	Yes	4 (18)
Female	5 (22)	No	10 (45)
Unavailable	1 (5)	Unavailable	8 (36)
ECOG at PTLD relapse, *N* (%)		Extranodal sites present, *N* (%)	
0	9 (41)	≤1	17 (77)
1	12 (55)	>1	5 (23)
2	1 (5)		
IPI score prior to CAR-T, *N* (%)		CNS disease involvement, *N* (%)	
1	1 (5)	Yes	1 (5)
2	5 (23)	No	21 (95)
3	11 (50)		
4	2 (9)		
5	1 (5)		
Unavailable	2 (9)		
PTLD stage, *N* (%)		Organ transplant, *N* (%)	
I to II	2 (9)	Kidney	14 (64)
III to IV	20 (91)	Liver	3 (14)
LDH, *N* (%)		Heart	2 (9)
Elevated	18 (82)	Kidney, Pancreas	1 (5)
Normal	4 (18)	Intestine	1 (5)
		Lung	1 (5)
EBV tumour status, *N* (%)			
Positive	1 (5)		
Negative	18 (82)		
Unavailable	3 (14)		



ORR 64%, CR 55%

2y PFS and OS: 35% and 58%

CRS G1 45%, G2 27%, G3-4 5%

ICANS 72%, G1 9%, G2-3 27%, G4 9%

TRM 9%

McKenna M, et al. Br J Haematol 2023;202:248-55

Take Home messages

- PTLD are rare and heterogenous diseases
- Multidisciplinary approach
- Dismal survival for R/R PTLD
- EBV+ PTLD: EBV-CTLs now available
- Early detection of potential candidates for tabelecleucel treatment
- Prospective international trials to further improve outcome
- Further development of CAR-T strategies, new drugs for R/R EBV- PTLD

Ringraziamenti

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Daniela Drandi
Elisa Genuardi
Aurora Civita

Study Coordinators
Alessio Lonardo
Velleda Ilaria Zorzetto
Sonia Rizzitelli

Medici Specializzandi
Chiara Consoli

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UNIVERSITÀ DI TORINO

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Città della Salute e della Scienza di Torino

DBMSS
Dipartimento di Biotecnologie Molecolari e Scienze per la Salute

Antiviral: NAVAL-1 trial

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 with allo/AutoSCT or CAR-T; no CNS involvement, adeguate hepatic and hematological fuction

- Aim: evaluate safety and efficacy of the all oral combination of nanatinostat (class I HDAC inhibitor) with valganciclovir in R/R EBV+ lymphoma pts (PTCL, PTLD, DLBCL)

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

•Nanatinostat induces EBV lytic activation and express of the EBV BGLF4 proteine kinase → activates ganciclovir via phosphorylation → ganciclovir-induced inhibition of viral and cellular DNA synthesis and apoptosis

• 13 PTLD patients

•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

HD-CT high dose chemotheraphy, SCT, stem cell transplant; R/R, relapse/refractory; CNS, central nervous system; HDAC, histone deacetylase ; DLBCL, diffuse large B cell lymphoma, PTCL, pheripheral T cell lymphoma; EBV, Epstein-Barr virus; HDAC, histone deacetylase; PTLD, post-transplant lymphoproliferative disorder.

Haverkos B, et al. Blood Adv 2023