GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

MALATTIA LINFOPROLIFERATIVA POST-TRAPIANTO

FAD SINCRONA
4 dicembre 2024

con il patrocinio di: S·I·T·O· SOCIETÀ ITALIANA DEI TRAPIANTI D'ORGANO E DI TESSUTI

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STATO DELL'ARTE PTLD

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Conflict-of-interest disclosure: S.C. served on the scientific advisory board for Roche,Italfarmaco, Takeda, Atara, and Pierre Fabre

Post –transplant lymphoproliferative disorder: CLINICAL PRESENTATION

Factor	Clinical presentation
Heterogeneity[1]	• Heterogeneous (from incidental asymptomatic findings to fulminant presentation), including organ failure and spontaneous tumour lysis
Symptoms[2]	• **Most common:** lymphadenopathy and fever • **Rare (EBV end-organ disease):** encephalitis/myelitis, pneumonitis, hepatitis, and hemophagocytic lymphohistiocytosis
Target organs[2]	• lymph nodes • CNS 5-20%, GI tract 20-30%, lungs, liver, graft 10-15% (early onset>late onset PTLD)
Progression[3]	• After HCT, PTLD often progresses rapidly and is more frequently at an advanced stage than after SOT

CNS, central nervous system; EBV, Epstein–Barr virus; GI, gastrointestinal; HCT, haematopoietic cell transplantation; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.

1. Dierickx D, et al. N Engl J Med. 2018;378:549–562; 2. Styczynski J, and Giebel S. EBMT Handbook 2019; Chapter 45; 3. Fujimoto A, et al. Cancers (Basel). 2020;12:328.

PTLD : DIAGNOSIS

Non-invasive diagnostic methods[1,2]

- Quantitative determination of EBV-DNA-aemia*
- Imaging: CT or PET-CT** or MRI†

Invasive diagnostic methods[1,2]

- Biopsy: of the lymph node and/or other suspected sites
- Endoscopy: when GI symptoms present
- Histological examination
- Detection of viral antigens or in situ hybridisation for EBV-encoded RNA transcripts
- Immunohistochemistry
- Flow cytometry for B-cell, T-cell, and plasma cell lineage-specific antigens

- Currently the method of choice for early detection and monitoring progression and response to treatment of EBV+ PTLD starting no later than 4 weeks after HCT.1 ** For avid structures, localised in the lymph nodes, spleen, liver, GI tract, skin, lungs, bone,1 BM. † In CNS disease and non-avid histologies.1
ATG, anti-thymocyte globulin; BM, bone marrow; CNS, central nervous system; CT, computed tomography; EBV, Epstein–Barr virus; GI, gastrointestinal; GvHD, graft-versus-host disease; HCT, haematopoietic cell transplantation; MRI, magnetic resonance imaging; PET-CT; positron emission tomography–computed tomography; PTLD, post-transplant lymphoproliferative disorder; TCD, T-cell depletion.

- 1. Styczynski J and Giebel S EBMT Handbook 2019; Chapter 45; 2. Samant H, et al. Posttransplant Lymphoproliferative Disorders. StatPearls 2023.

PTLD :STAGING SYSTEM

There is NO official grading system for EBV+ PTLD[1]

The use of PET-CT is an important imaging tool for both PTLD diagnosis and staging[1]

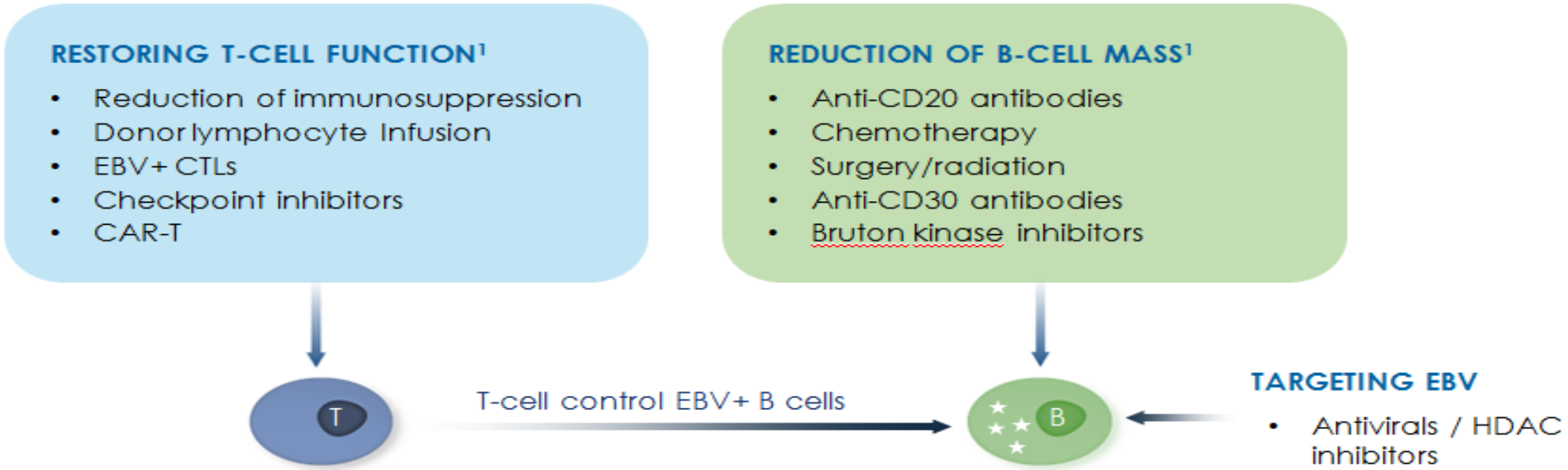
Possible staging of PTLD:[1]		
Clinical end-organ staging: nodal vs extra nodal disease	**Clinical severity staging:** limited (unifocal) vs advanced (multifocal) disease	**ECIL-6 staging*:** limited (stages I–II), advanced forms (stages III–IV)

Based on the Lugano lymphoma classification by PET-CT imaging.[1]

EBV, Epstein–Barr virus; ECIL, European Conference on Infections in Leukaemia; PET-CT, positron emission tomography–computed tomography; PTLD, post-transplant lymphoproliferative disorder.

1. Styczynski J, and Giebel S. EBMT Handbook

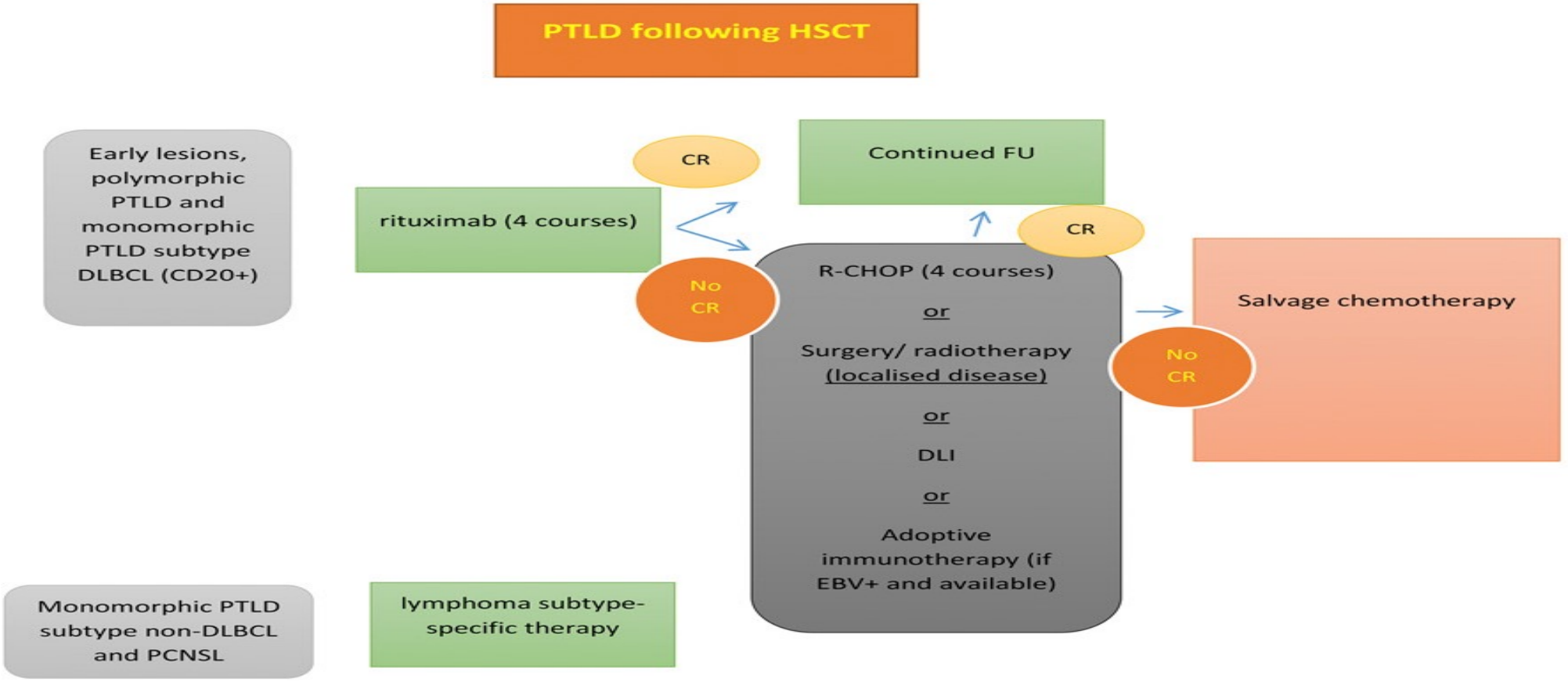
PTLD :THERAPEUTIC STRATEGIES



CAR-T, chimeric antigen receptor T-cell therapy; CD20/30, cluster of differentiation 20/30; CTL, cytotoxic T lymphocyte; EBV+, Epstein–Barr virus positive; HDAC, histone deacetylase; PTLD, post-transplant lymphoproliferative disorder.

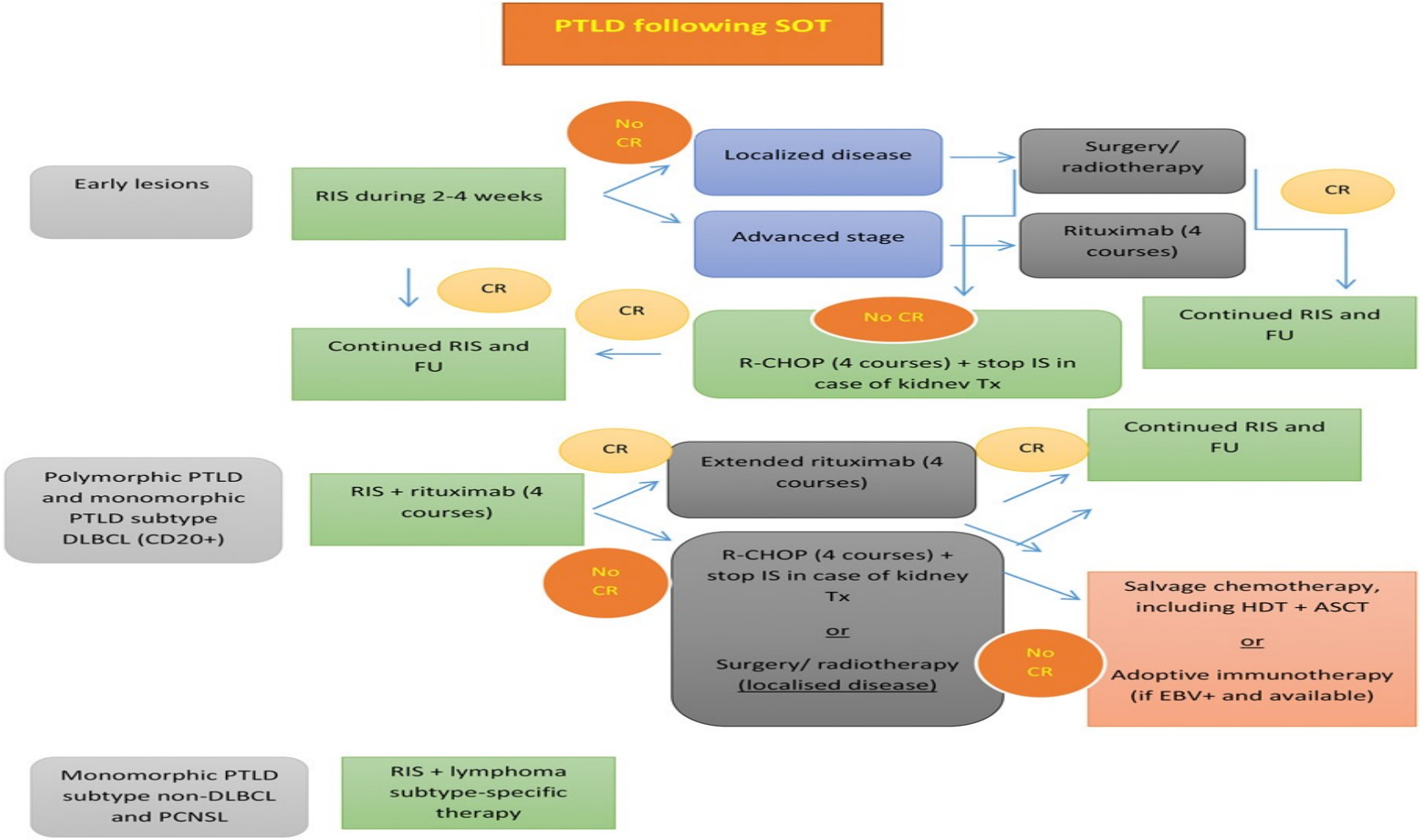
1. Styczynski J, et al. Anti cancer Research. 2022;42(11):5181–5186.

PTLD:TREATMENT ALGORITHM post HSCT



Abbreviations: PTLD, posttransplant lymphoproliferative disorder; SOT, solid organ transplantation; HSCT, hematopoietic stem cell transplantation;CR, complete remission; FU, follow up; R, rituximab; CHOP, cyclophosphamide-doxorubicine-vincristine-prednisone; DLBCL, diffuse large B cell lymphoma; Tx, transplantation; HDT, high dose therapy; ASCT, autologous stem cell transplantation; EBV, Epstein-Barr virus; PCNSL, primary central nervous stem lymphoma; DLI, donor lymphocyte infusion.

PTLD:TREATMENT ALGORITHM post SOT



PTLD:FRONTLINE TREATMENT ALGORITHM post SOT

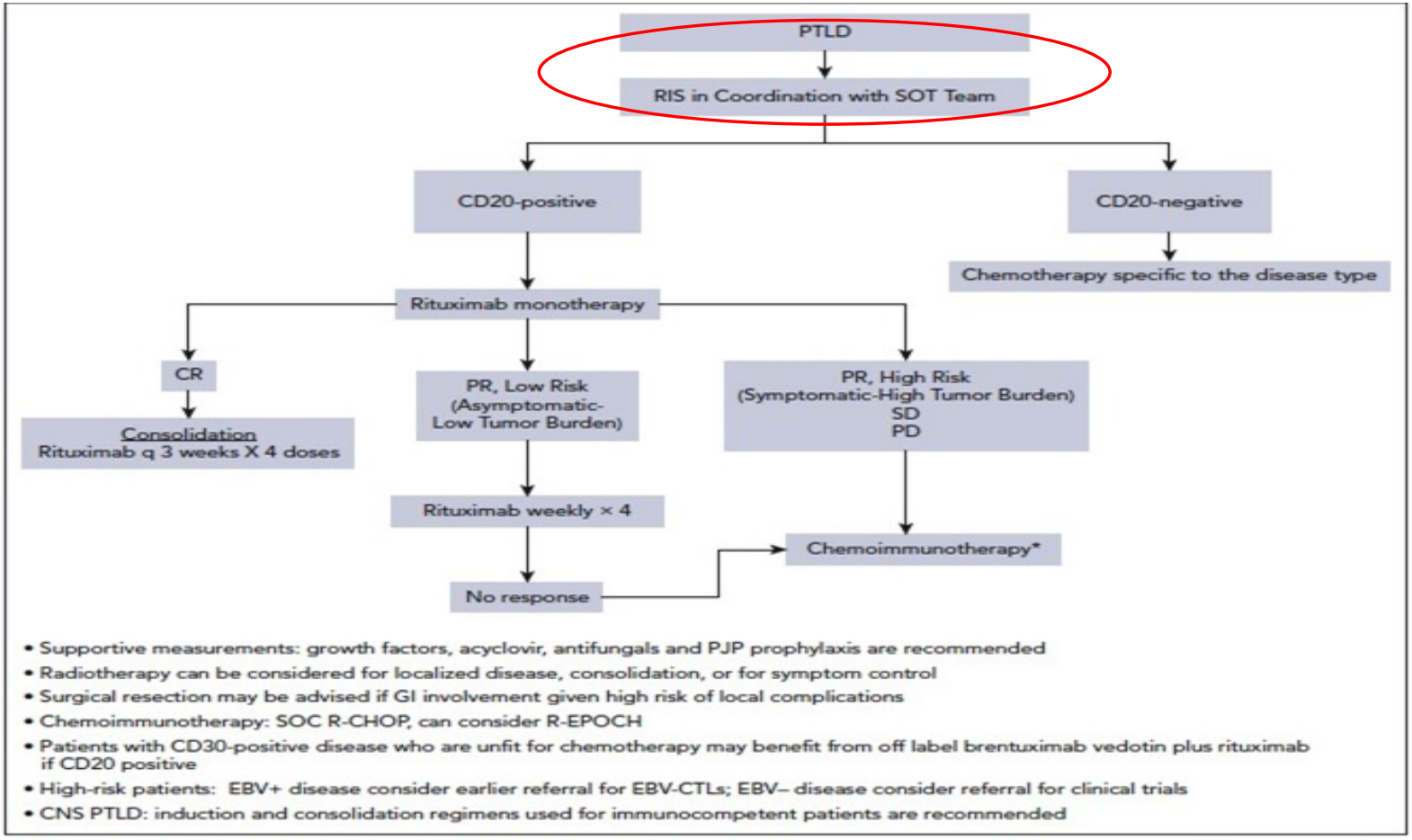


Figure 1. Algorithm for management of PTLD in a frontline setting. GI, gastrointestinal; PJP, *Pneumocystis jirovecii* pneumonia; q, every; SD, stable disease; SOC, standard of care.

Jennifer E. Amengual,Barbara Pro, How I treat posttransplant lymphoproliferative disorder, Blood, 2023, Figure 1.

PTLD:RIS

Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients – BCSH and BTS Guidelines , Parker ed al.:

- Limited disease : a reduction 25% in immunosuppression

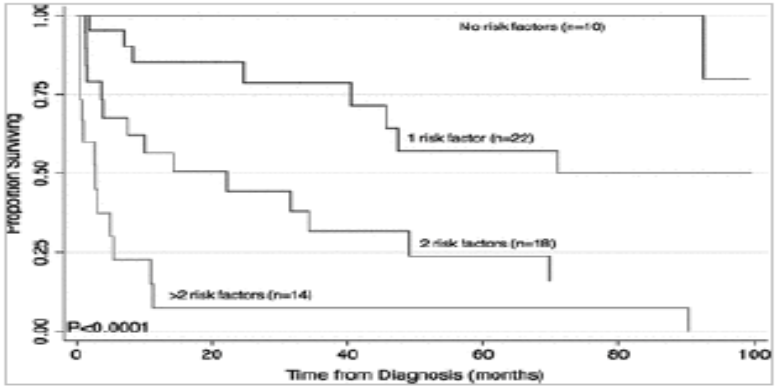
- Extensive disease and critically ill: stop all agents except prednisone 7,5 mg-10mg/die

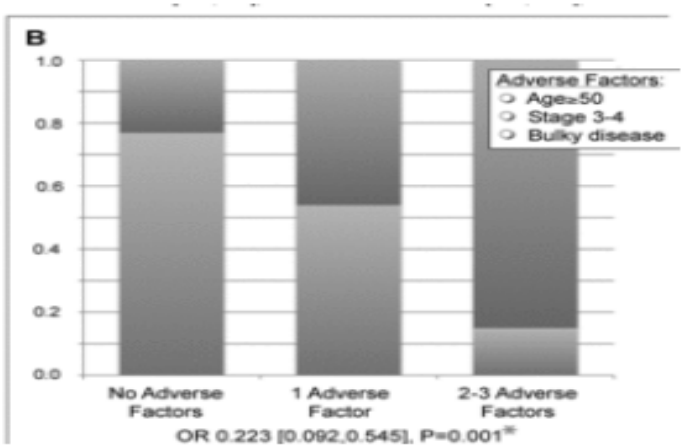
- Extensive disease and not critically ill: decrease ciclosporine/tacrolimus by 50%, discontinue azathioprine/mycophenolate and maintain prednisone 7,5 mg-10mg/die

- European guidelines: recommending steroid maintenance alone or reducing ciclosporine/tacrolimys by 50% and stopping all other agents: azathioprine/mycophenolate

PTLD:RIS

- Reduction of immunosuppression
  - Reshef, et al. (Am J Transplant, 2011)
    - 67 SOT PTLD patients (1988-2008), managed with RI alone
      - 37% polymorphic, 63% monomorphic
      - 70% EBV+
    - ORR 45% (CR 37%, PR 8%)
    - Acute rejection rate: 32%
    - mOS: 44mo





PTLD:RIS

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**

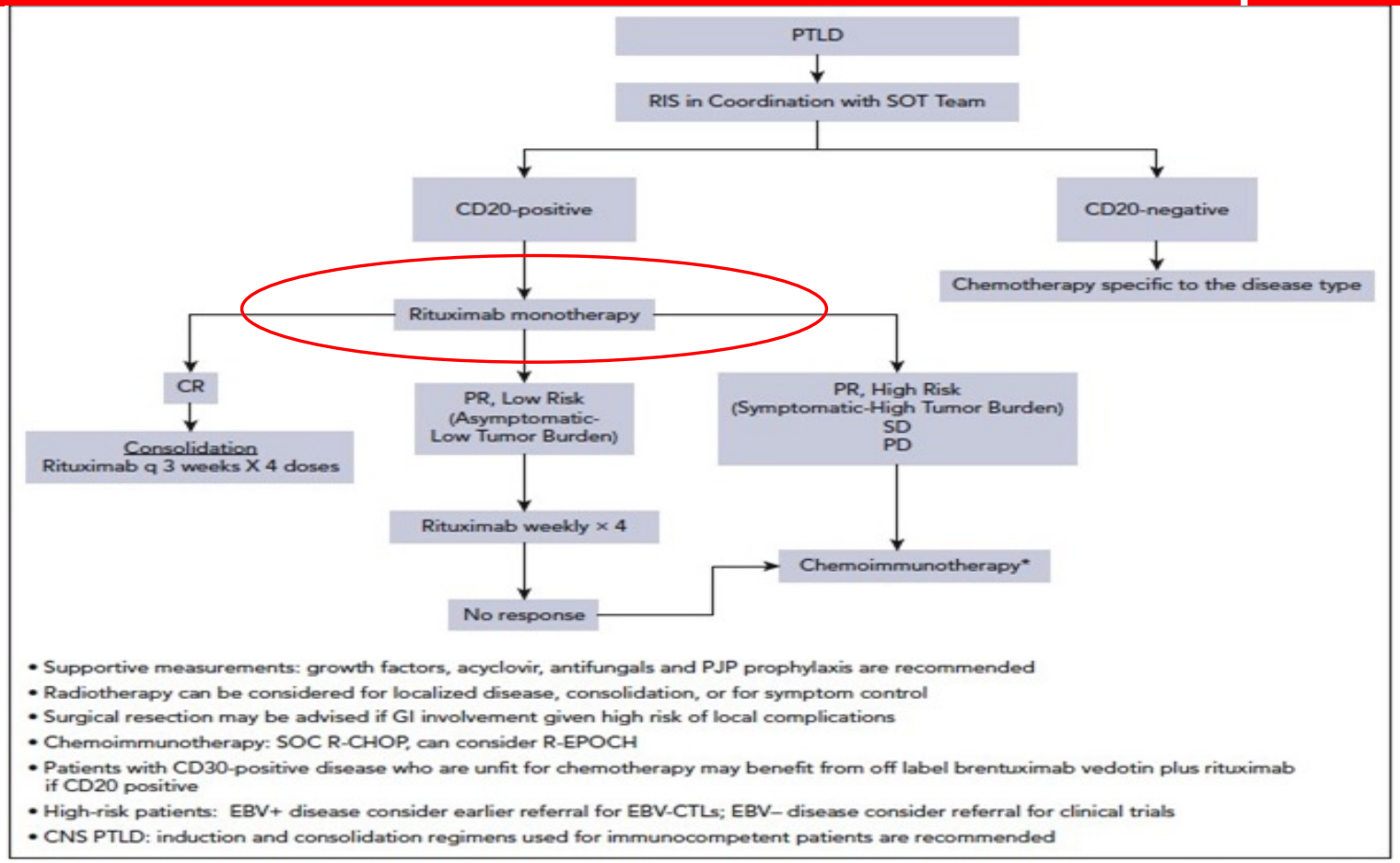
• Prospective study (*Swinnen, Transplantation 2001) in SOT only 6% ORR, all PR,* ***38% rejection rate during RIS***

Rivalutation after 2-4 weeks from RIS, monitoring any signs of rejection

1–4 weeks → response rates: 0 – ~50%[1,2]

	Treatment	Overall response rate (CR)
Pennsylvania[1*]	RIS only	45% (37%)
Baltimore[2†]	Sequential therapy (RIS – IFNα – chemo)	6% (0%)
Organ dependent risk in graft failure		
Kidney: dialysis rescue Heart: risk sudden death[4§]		
Rejection rates: 18–40%[5‖]		

PTLD:FRONTLINE TREATMENT ALGORITHM post SOT



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Jennifer E. Amengual,Barbara Pro, How I treat posttransplant lymphoproliferative disorder, Blood, 2023, Figure 1.

PTLD treatment

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)

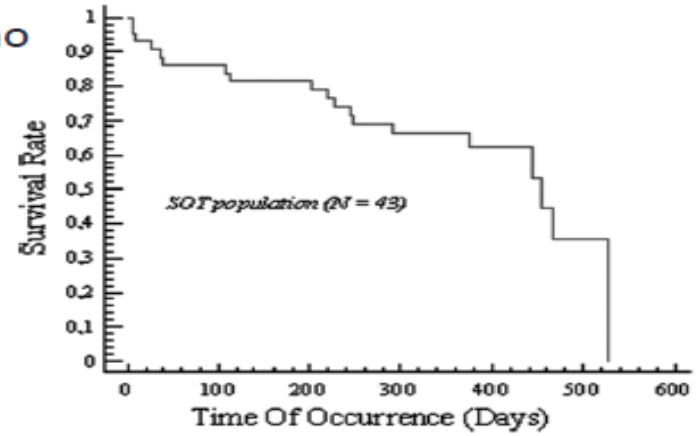
BETTER OUTCOME: Early PTLD, young age, single site lesion

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

PTLD: rituximab monotherapy

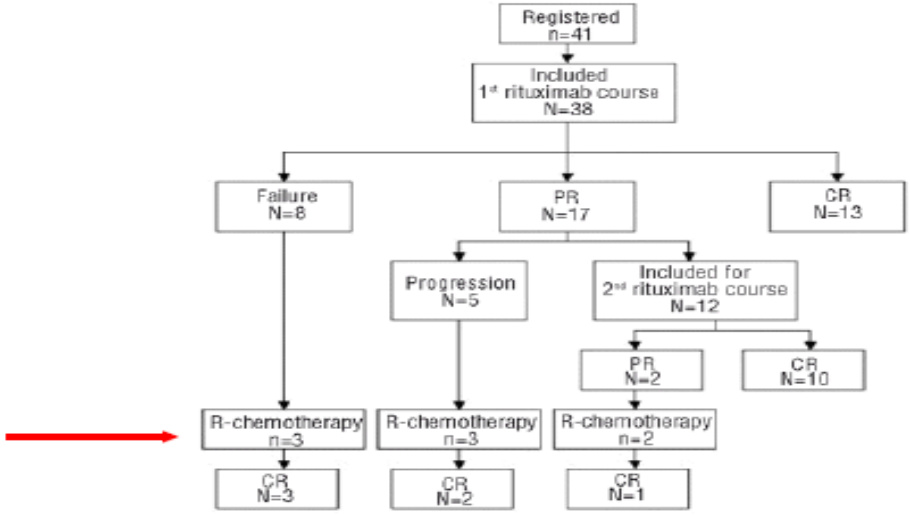
- Eradication of the malignant clone: role of rituxan
  - Choquet, et al (Blood 2006)
    - **First prospective treatment trial in PTLD**
    - 43 patients with SD/PD despite RI treated with rituxan monotherapy (375mg/m2 weekly x4weeks)
    - 10% polymorphic PTLD, 65% monomorphic

- ORR: 44% (27% CR); 1 year OS: 67%, mOS: 15mo
  - Only factor predictive of response: LDH wnl



PTLD: more rituximab therapy

- Eradication of the malignant clone: role of (more) rituxan
  - Gonzalez-Barca, et al. (Haematologica, 2007)
    - Multi-center, prospective phase II trial
    - 38 patients: all prior RI; 18% P-PTLD, 82% M-PTLD (90%DLBCL); 70% EBV+
    - Adaptive trial design with initial +/- additional rituxan course



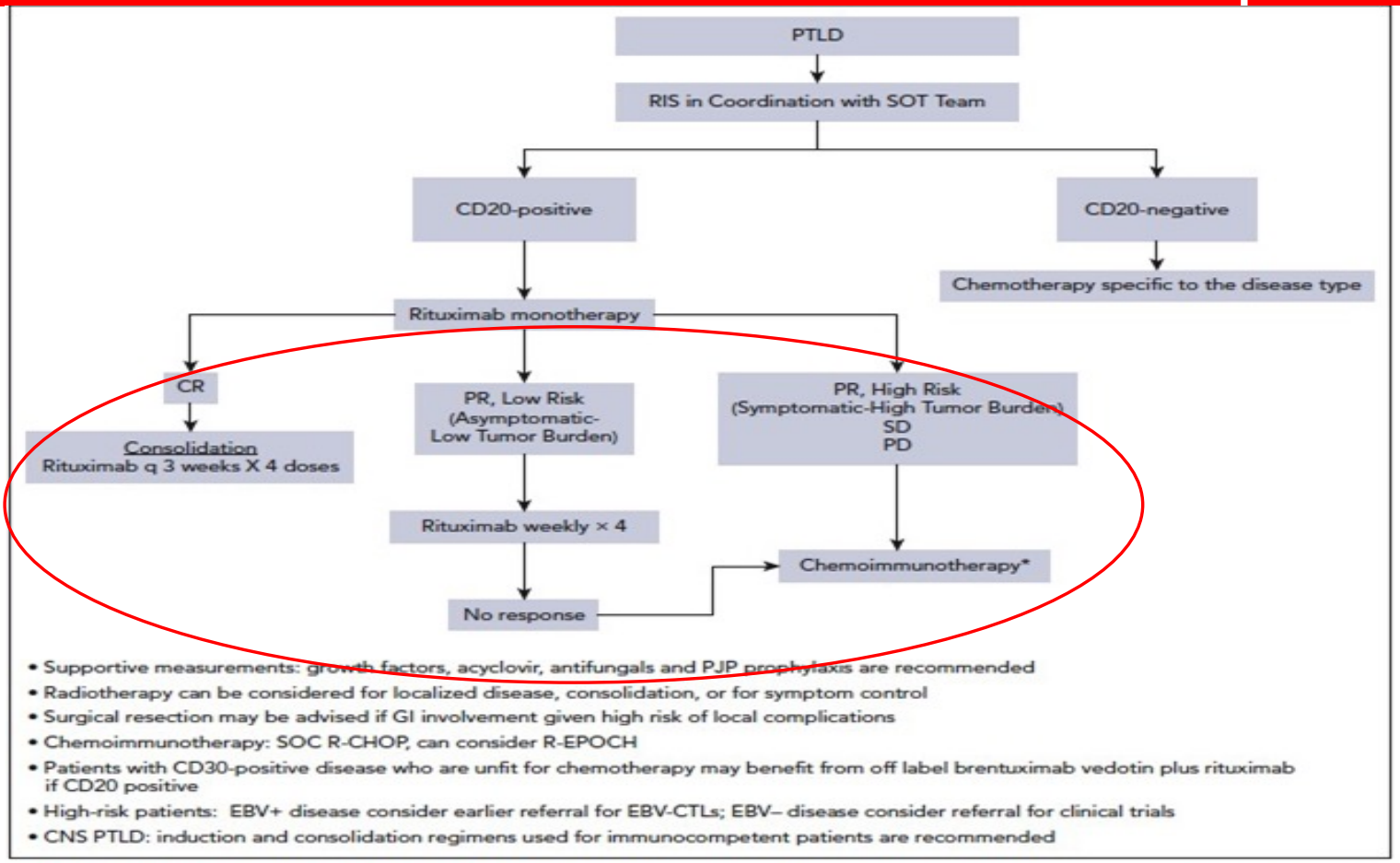
34% CR

83% CR

60.5% CR ITT

Authors	Study Population	Treatment schema		Outcomes
Gonzalez-Barca et al. 2021	80% monomorphic 71% DLBCL 50% EBV+	Weekly R ×4	If CR, no further treatment	*N* = 38 on clinical trial, CR in 61% 5-yr DSS 68.6%, 94.4% if CR achieved 10-yr DSS 64.7%, 88.1% if CR achieved
			If PR, 4 more weekly cycles R	*N* = 21 in "real-world" cohort, CR in 38% 5-yr DSS 75.2%, 87.5% if CR achieved 10-yr DSS 64.7%

PTLD:FRONTLINE TREATMENT ALGORITHM post SOT



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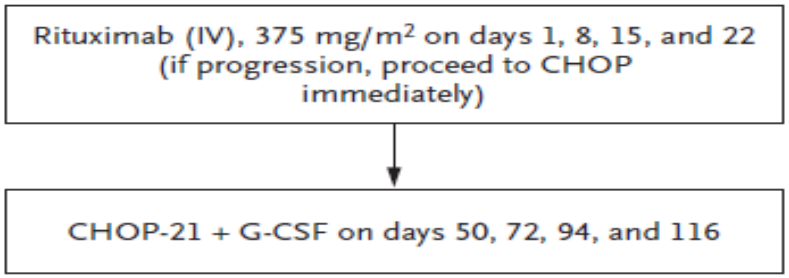
PTLD treatment

				10-yr DSS 64.7%		
Trappe et al. 2012 "PTLD-1"	96% monomorphic 81% DLBCL 44% EBV+	Weekly R ×4 followed by 4 cycles of CHOP q3 weeks		*N* = 74 ORR 90% CR 40% mOS 6.6 years		
Trappe et al. 2017 "PTLD-1"	85% monomorphic 74% DLBCL 47% EBV+	Weekly R ×4	If CR, 4 cycles of R q3 weeks	*N* = 34 received induction + consolidation R	ORR 88% CR 70% mOS 6.6 years	
			If not in CR, 4 cycles R-CHOP-21	*N* = 92 received induction R then R-CHOP-21		
Zimmerman et al. 2022 "PTLD-2"	97% monomorphic 75% DLBCL 38% EBV+	Weekly R ×4	If CR, or PR with low IPI, 4 cycles of R q3 weeks (low risk)	*N* = 21 low risk	ORR 95% CR 52% 2-yr OS 100%	ORR 94% CR 46% 2-yr OS 68%
			If PR/SD/PD, 4 cycles of R-CHOP-21 (high risk)	*N* = 22 high risk	ORR 100% CR 41% 2-yr OS 59%	
			If PD in thoracic SOT-PTLD, 4 alternating cycles of R-CHOP-21 and modified R-DHAOx (very high risk)	*N* = 5 very high risk	ORR 60% CR 40% 2-yr OS 30%	

CHOP cyclophosphamide/doxorubicin/vincristine/ prednisone, *CR* complete response, *DLBCL* diffuse large B-cell lymphoma, *DSS* disease-specific survival, *EBV* Epstein-Barr virus, *IPI* international prognostic index, *mOS* median overall survival, *ORR* overall response rate, *OS* overall survival, *PD* progressive disease, *PR* partial response, *R*, rituximab 375 mg/m^2, *R-CHOP*-21 rituximab plus CHOP given every 21 days, *R-DHAOx* rituximab plus oxaliplatin/cytarabine/dexamethasone given every 21 days, *SD* stable disease, *yr* year

PTLD: sequential therapy PTLD 1 trial Phase 2

PTLD-1 Trial, Sequential Treatment



No. of Patients	74
Overall Response Rate	90%
Complete Response Rate	40%
Treatment-Related Mortality	11%
Median Overall Survival	6.6 Yr

• Phase 2 prospective trial, accrued 70 pts (96% monomorphic, 81% DLBCL ,44% EBV+. ,)
• Schedule: 4 weekly doses of rituximab monotherapy 375mg/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

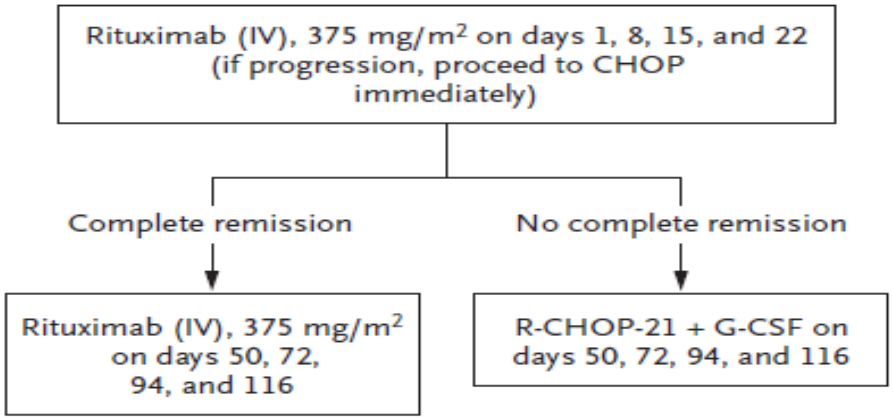
• **TRM 11%, > in pts non responder to Rituximab monotherapy**

• **Response to Rituximab in monotherapy important prognostic factor for OS**

• **Advanced Age and ECOG>2 most important baseline characteristics predicting outcomes**

PTLD -1 risk-stratified sequential treatment trial Phase 2

PTLD-1 Trial, Risk-Stratified Sequential Treatment



No. of Patients	152
Overall Response Rate	88%
Complete Response Rate	70%
Treatment-Related Mortality	8%
Median Overall Survival	6.6 Yr

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Response to Rituximab Induction Is a Predictive Marker in B-Cell Post-Transplant Lymphoproliferative Disorder and Allows Successful Stratification Into Rituximab or R-CHOP Consolidation in an International, Prospective, Multicenter Phase II Trial

Ralf U. Trappe, Dean Dierickx, Heinz Zimmermann, Franck Morschhauser, Peter Mollee, Jan M. Zaucha, Martin H. Dreyling, Ulrich Dührsen, Petra Reinke, Gregor Verhoef, Marion Subklewe, Andreas Hüttmann, Thomas Tousseyn, Gilles Salles, Volker Kliem, Ingeborg A. Hauser, Corrado Tarella, Eric Van Den Neste, Olivier Gluyssen, Ioannis Anagnostopoulos, Veronique Leblond, Hannes Reiser, and Sylvain Choquet

Trappe et al. 2017 "PTLD-1"	85% monomorphic 74% DLBCL 47% EBV+	Weekly R ×4	If CR, 4 cycles of R q3 weeks	*N* = 34 received induction + consolidation R	ORR 88% CR 70% mOS 6.6 years
			If not in CR, 4 cycles R-CHOP-21	*N* = 92 received induction R then R-CHOP-21	

PTLD -1 risk-stratified sequential treatment trial Phase 2

In the international, multicenter, prospective phase II PTLD-1 trial, EBV association was not found to be a significant factor neither for overall survival nor time to progression. Thus, there is currently no evidence that upfront treatment of EBV- and EBV+ PTLD should be different. Of course this does not apply to the use of EBV-specific adoptive immunotherapy, which is restricted to EBV+ cases.

- Similar survival outcomes as EBV+ disease:

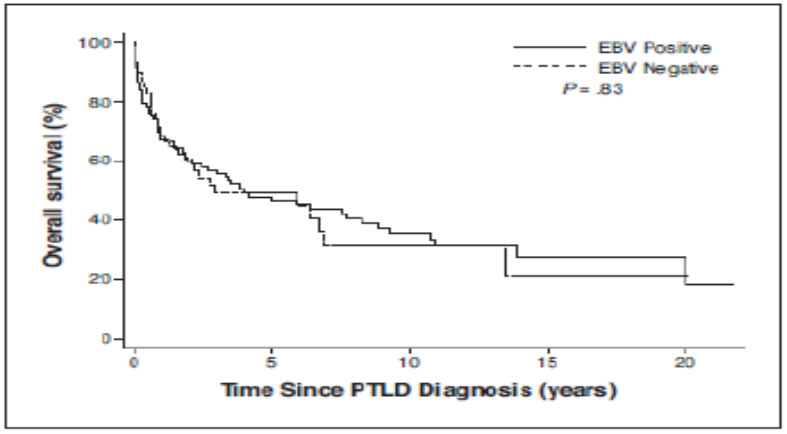


Table 2: Best response to initial therapy

Response	EBV-negative PTLD	EBV-positive PTLD	p
All patients			
Complete response, n (%)	23 (44)	56 (55)	0.30
Partial response, n (%)	10 (19)	13 (13)	
Stable disease, n (%)	8 (16)	8 (8)	
Progressive disease, n (%)	11 (21)	24 (24)	
Unknown, n	6	17	
RI only			
Complete response, n (%)	8 (35)	18 (43)	0.54
Partial response, n (%)	2 (9)	4 (9)	
Stable disease, n (%)	6 (26)	5 (12)	
Progressive disease, n (%)	7 (30)	15 (36)	
Unknown, n	1	4	
Rituximab with or without RI			
Complete response, n (%)	6 (43)	9 (47)	0.84
Partial response, n (%)	5 (36)	4 (21)	
Stable disease, n (%)	0 (0)	1 (5)	
Progressive disease, n (%)	3 (21)	5 (27)	
Unknown, n	0	0	
Chemo ± RI ± Rituximab			
Complete response, n (%)	7 (37)	14 (47)	0.88
Partial response, n (%)	8 (42)	9 (30)	
Stable disease, n (%)	1 (5)	2 (7)	
Progressive disease, n (%)	3 (16)	5 (16)	
Unknown, n	1	0	

EBV, Epstein–Barr virus; PTLD, posttransplantation lymphoproliferative disorder; RI, reduction of immunosuppression.

Trappe et al, Lancet Oncol. 2012;13(2):196-206

PTLD -1 risk-stratified sequential treatment trial Phase 2: RISK ADAPTED

American Journal of Transplantation 2015; 15: 1091–1100
Wiley Periodicals Inc.

doi: 10.1111/ajt.13086

Brief Communication

International Prognostic Index, Type of Transplant and Response to Rituximab Are Key Parameters to Tailor Treatment in Adults With CD20-Positive B Cell PTLD: Clues From the PTLD-1 Trial

R. U. Trappe[1,2,*], S. Choquet[3], D. Dierickx[4],

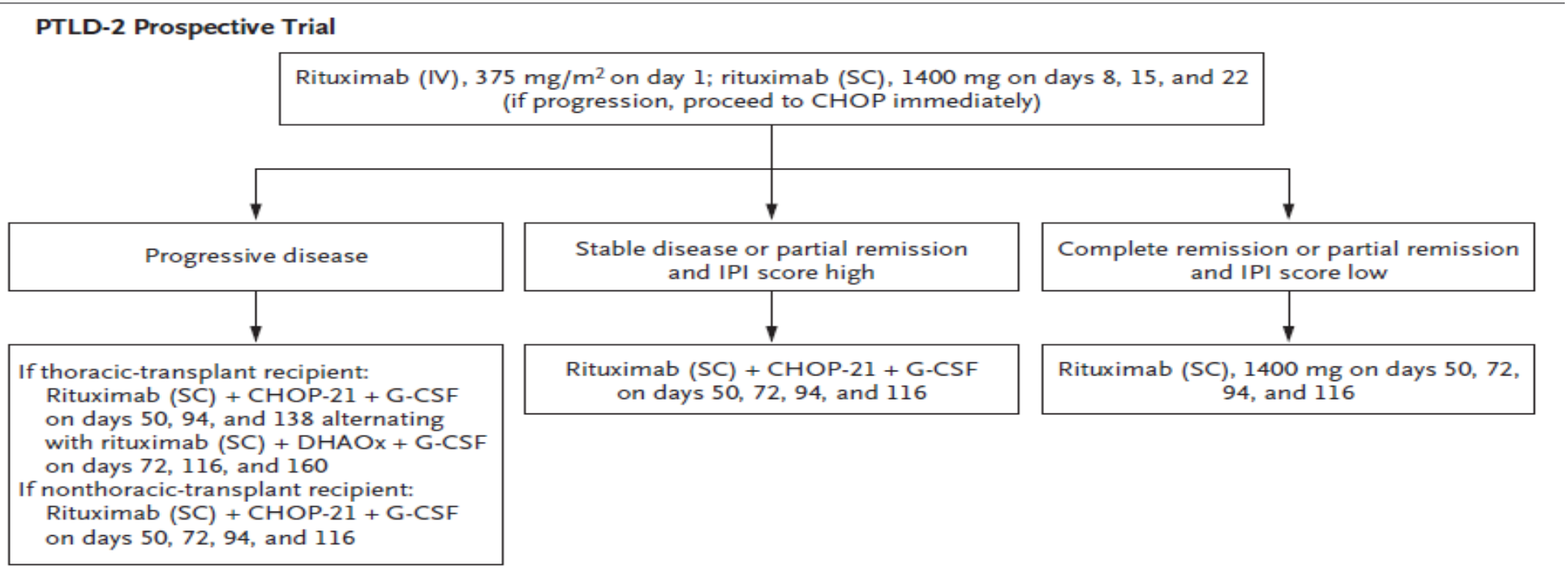
Table 3: Multivariable Cox-regression analyses for overall survival and time to progression in the PTLD-1 trial

Risk factor	p**	HR	95% CI
Cox regression model n = 62, Step 6, p = 0.001*			
Overall survival			
Thoracic organ transplantation	<0.001	7.827	2.626–23.333
Age > 60	0.001	4.423	1.823–10.734
Overall response to rituximab	0.017	0.322	0.127–0.816
Late PTLD	0.052	0.415	0.171–1.007
Advanced Stage	0.063	2.537	0.949–6.781
Cox regression model n = 60, Step 9, p = 0.020*			
Time to progression			
Overall response to rituximab	0.008	0.213	0.067–0.671
Thoracic organ transplantation	0.075	2.983	0.896–9.930

Factors included in these analyses were: age > 60, sex, late PTLD (x year after transplantation), EBV association, advanced stage, extranodal disease, elevated serum LDH, ECOG ≥ 2, thoracic organ transplantation and overall response to rituximab (CR/PR versus SD/PD)
HR, hazard ratio; CI, confidence interval * Overall significance of the Cox-regression models is assessed based on the likelihood ratio test. ** This p-value is based on the Wald test. The discriminatory power of the models assessed by Somer's D is −0.47 for the overall survival model (optimism corrected: −0.33) and −0.41 for the time to progression model (optimism corrected: −0.18). The mean calibration error of the overall survival model is 0.14 (90%-quantile: 0.18). The mean calibration error of the time to progression model is 0.2 (90%-quantile: 0.31). Bootstrap estimates of calibration accuracy for 2-year survival for the prognostic models using adaptive linear spline hazard regression are shown in supplemental Figure S2.

- IPI (età> 60 anni, ECOG>2, LDH>ULN, sedi extranodali, Stadio III-IV,).
  si definiscono Low risk (LR) i pazienti con IPI score 0-2 e High Risk (HR) con IPI score 3-5
- organo trapiantato
- valutazione della risposta al Rituximab

PTLD -2 modified risk-stratified sequential treatment trial Phase 2



Modified risk-stratified sequential treatment (subcutaneous rituximab with or without chemotherapy) in B-cell Post-transplant lymphoproliferative disorder (PTLD) after Solid organ transplantation (SOT): the prospective multicentre phase II PTLD-2 trial

Heiner Zimmermann[1,2], Christian Koeneke[3], Martin H. Dreyling[4], Christiane Pott[5], Ulrich Dührsen[6], Dennis Hahn[7], Norbert Meidenbauer[8], Ingeborg A. Hauser[9], Mathias J. Rummel[10], Dominik Wolf[11,12], Michael Heuser[13], Christian Schmidt[4], Peter Schlattmann[14], Matthias Ritgen[5], Reiner Siebert[15], Ilske Oschlies[16], Ioannis Anagnostopoulos[16] and Ralf U. Trappe[17,18]

PTLD -2 modified risk-stratified sequential treatment trial Phase 2

Zimmerman et al. 2022 "PTLD-2"	97% monomorphic 75% DLBCL 38% EBV+	Weekly R ×4	If CR, or PR with low IPI, 4 cycles of R q3 weeks (low risk)	$N = 21$ low risk	ORR 95% CR 52% 2-yr OS 100%	ORR 94% CR 46% 2-yr OS 68%
			If PR/SD/PD, 4 cycles of R-CHOP-21 (high risk)	$N = 22$ high risk	ORR 100% CR 41% 2-yr OS 59%	
			If PD in thoracic SOT-PTLD, 4 alternating cycles of R-CHOP-21 and modified R-DHAOx (very high risk)	$N = 5$ very high risk	ORR 60% CR 40% 2-yr OS 30%	

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

In an interim analyses adopting this strategy increased the proprtion of pts who avoid CHT to 33% vs 25% in PTLD 1trial

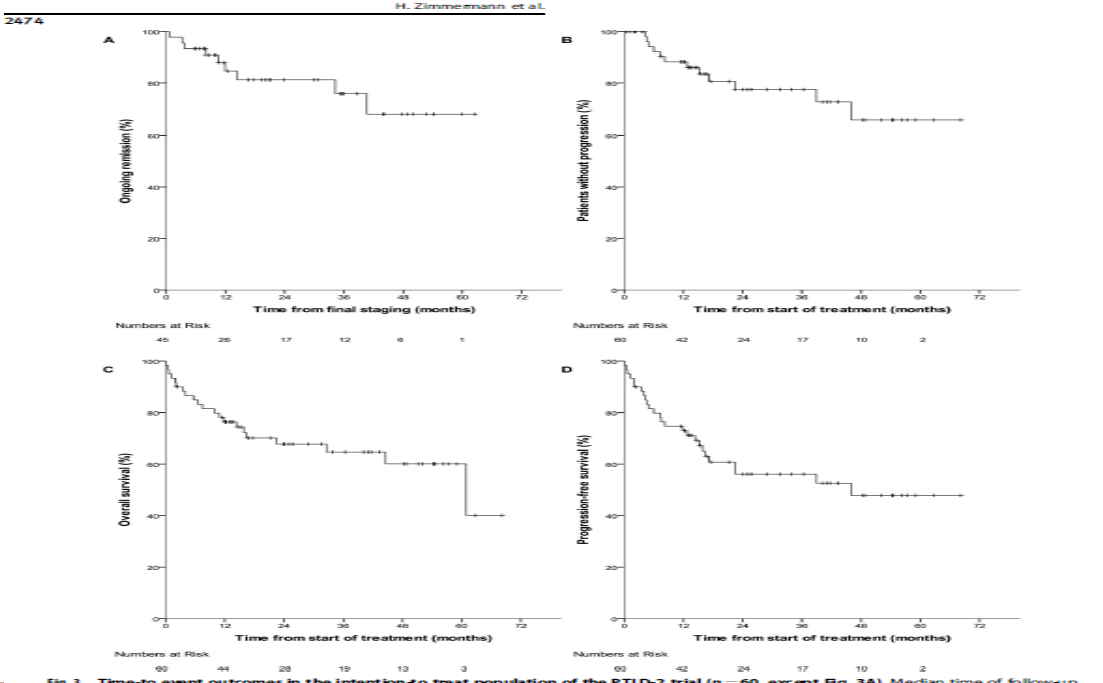


Fig. 3 Time-to event outcomes in the intention-to treat population of the PTLD-2 trial ($n = 60$, except Fig. 3A). Median time of follow-up was 2.8 years. Numbers at risk are indicated at the bottom of each graph. **A** Response duration (patients in CR or PR, $n = 45$). **B** Time to progression. **C** Overall survival. **D** Progression-free survival.

PTLD: new agents

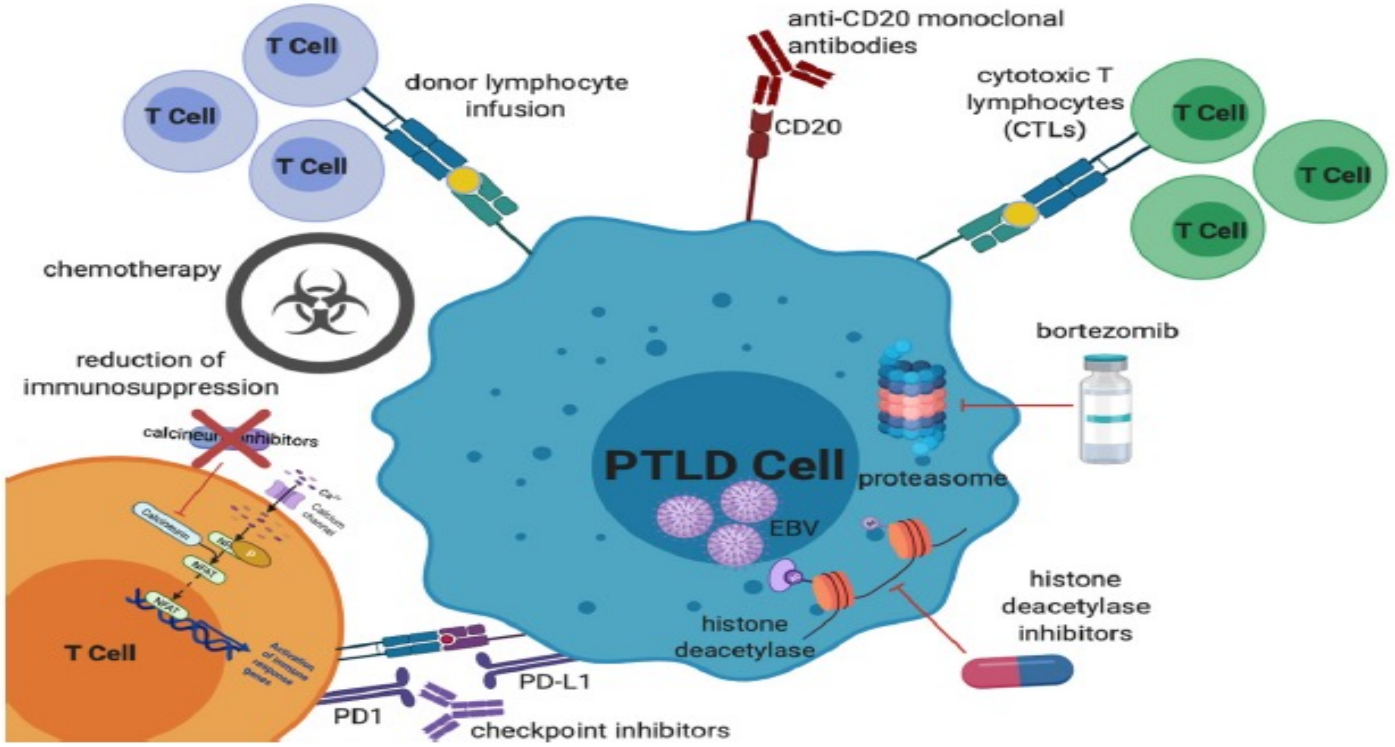


Figure 1. Mechanisms of treatment of EBV PTLD. Treatment options, which will all be discussed in further detail in this review, include reduction of immunosuppression, chemotherapy (including classical multi-agent lymphoma-based regimens as well as single agent anti-metabolite therapy), donor lymphocyte infusions, anti-CD20 monoclonal antibodies, cytotoxic T lymphocytes, proteasome inhibitors, histone deacetylase inhibitors, and checkpoint inhibitors. EBV: Epstein-Barr virus; PTLD: post-transplant lymphoproliferative disorder.

PTLD: new agents

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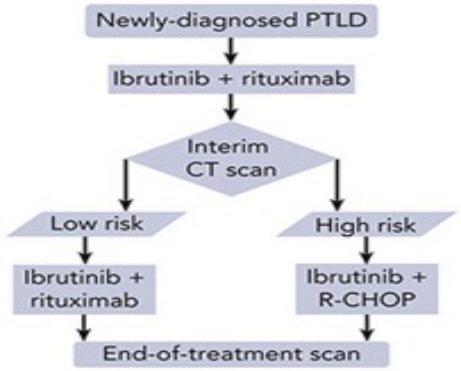
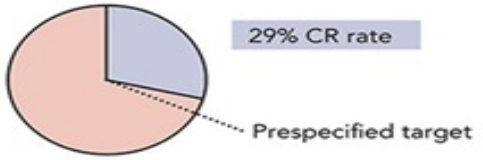
TIDAL trial Phase 2

Ibrutinib as Part of Risk-Stratified Treatment for Posttransplant Lymphoproliferative Disorder (PTLD): the Phase 2 TIDaL Trial

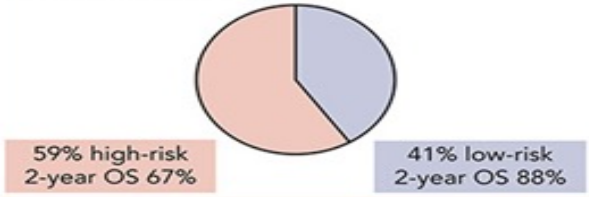
Context of research: Ibrutinib added to first-line, risk-stratified sequential treatment for PTLD (ISRCTN32667607)



Primary outcome: Complete response after initial ibrutinib + rituximab



Key secondary outcomes: Allocation to low-risk, overall survival



Conclusions: 1) Adding ibrutinib to initial rituximab did not result in a clinically significant interim response rate in untreated PTLD. 2) Increasing the proportion of low-risk patients, who have favorable survival outcomes, is a priority.

*Chaganti et al. DOI: 10.1182/**blood**.2024023847*

blood Visual Abstract

TIDAL trial Phase 2

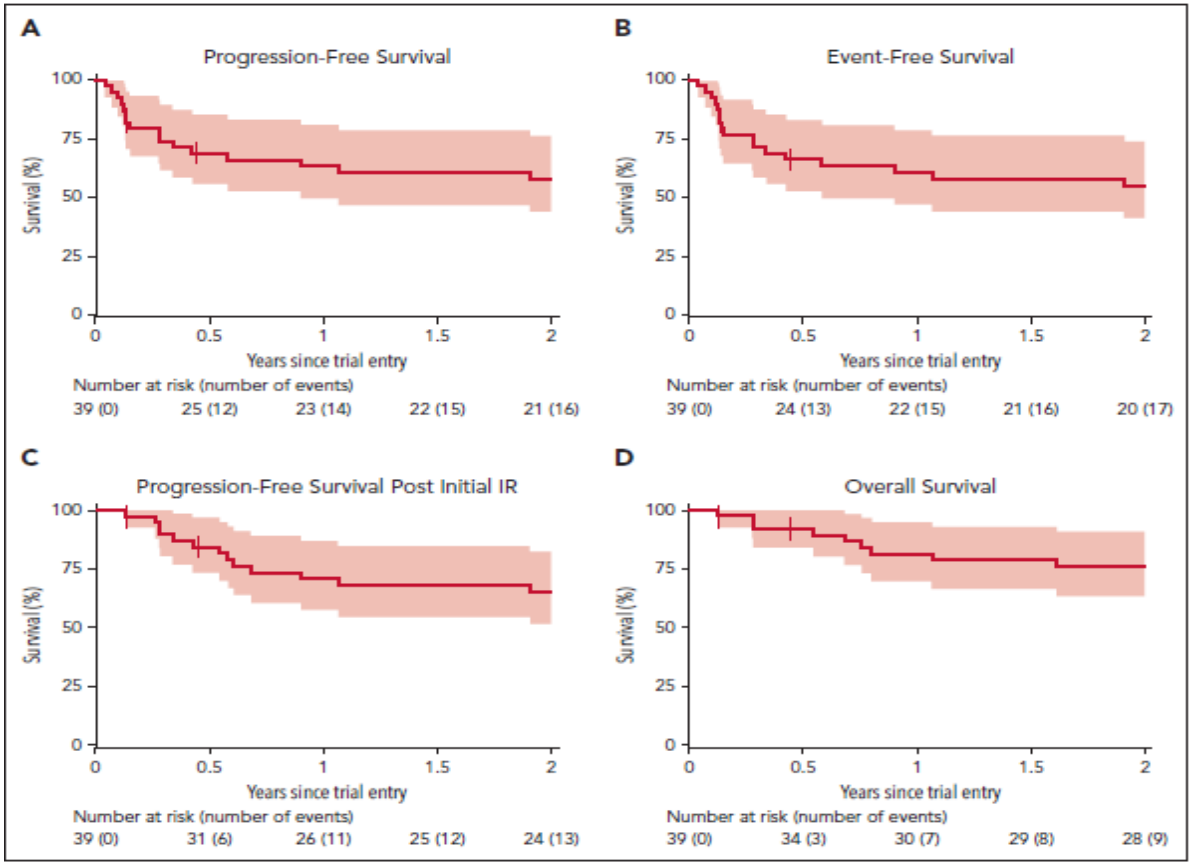


Figure 2. Survival outcomes. Survival Kaplan-Meier curves of PFS (A), event-free survival (B), PFS after initial IR therapy (C), and OS (D).

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

The role of IPI2 and TC vs PET/TC ad interim

PTLD: new agents

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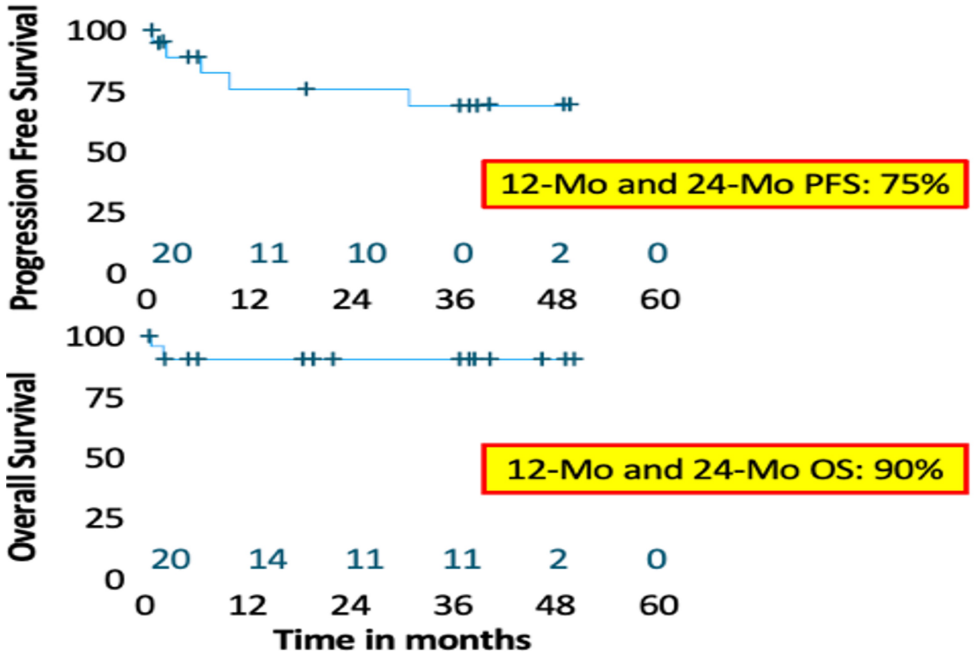
A Phase I/II Trial of Brentuximab Vedotin (BV) Plus Rituximab (R) As Frontline Therapy for Patients with Immunosuppression-Associated CD30+ and/or EBV+ Lymphomas

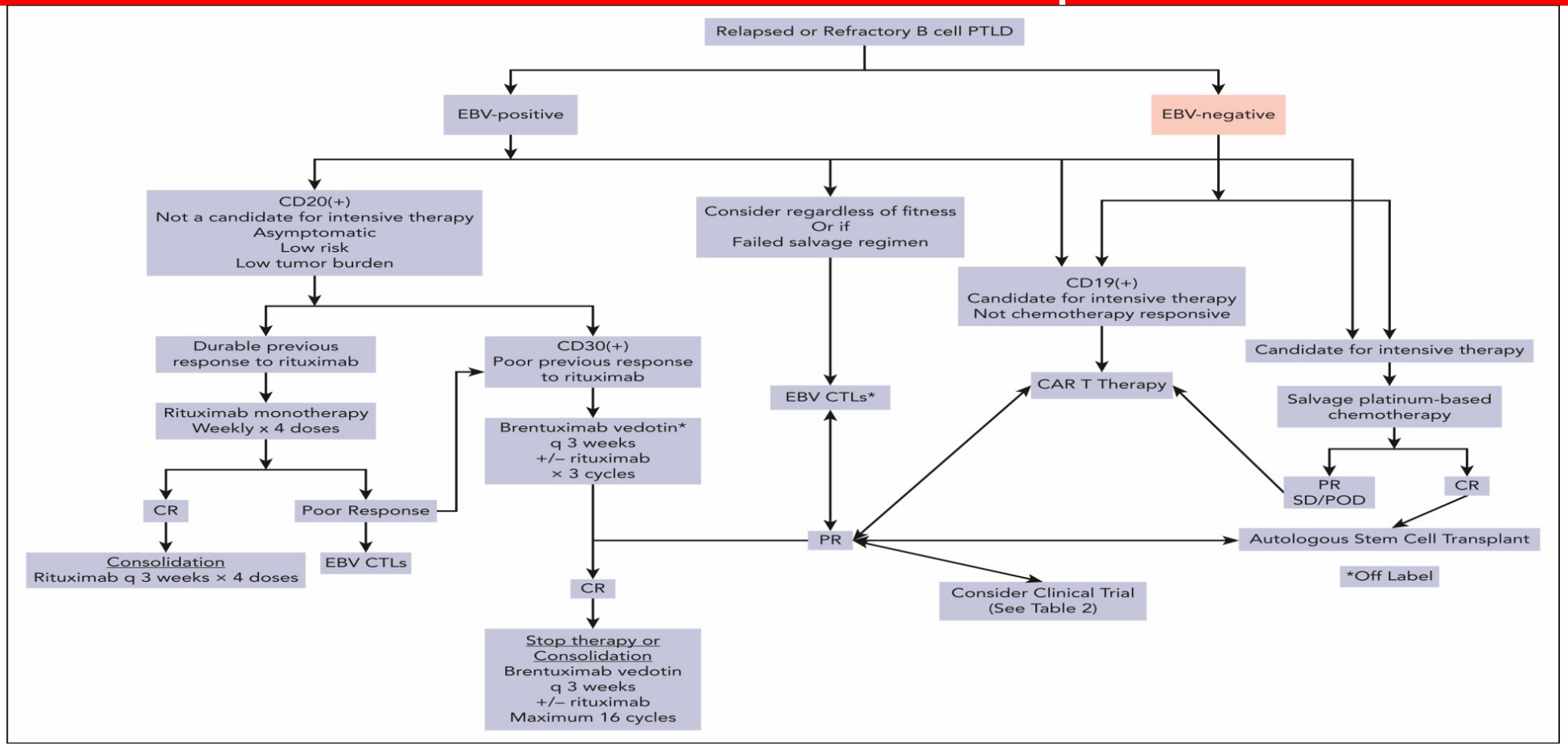
Investigate efficacy of Bv+R once weekly for 4 weeks, followed by manteinance

• Schedule:
– Pts in PD after induction therapy --> CT
– Pts in CR/PR/SD --> manteinance with Bv+R for 12 months

• 20 pts enrolled (55% monomorphic, 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



PTLD: SECOND LINE TREATMENT ALGORITHM post SOT &HSCT

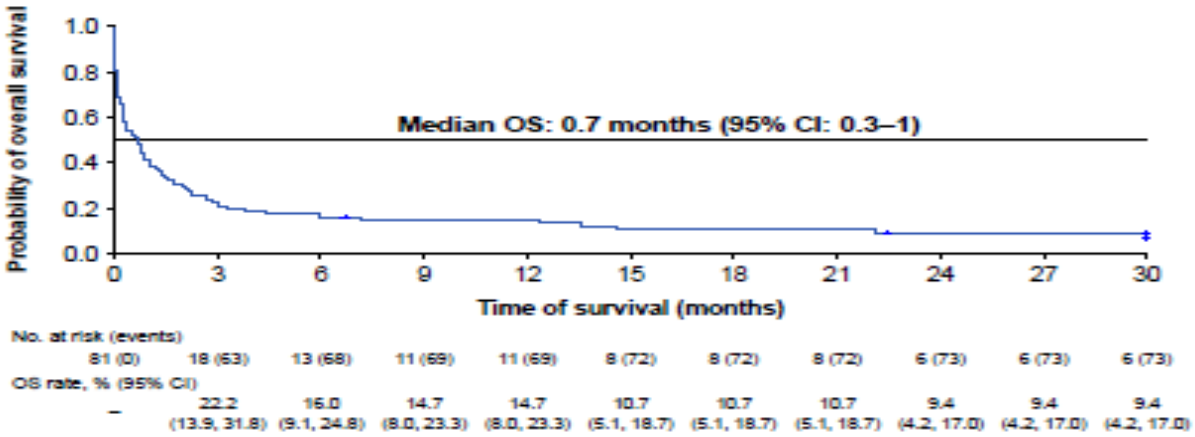


Jennifer E. Amengual,Barbara Pro, How I treat posttransplant lymphoproliferative disorder, Blood, 2023, Figure 1.

Clinical Outcomes of Patients With Epstein–Barr Virus-driven (EBV+) Post-Transplant Lymphoproliferative Disease (PTLD) following Hematopoietic Stem Cell Transplantation Who Fail Rituximab Plus Chemotherapy: A Multinational, Retrospective Chart Review Study

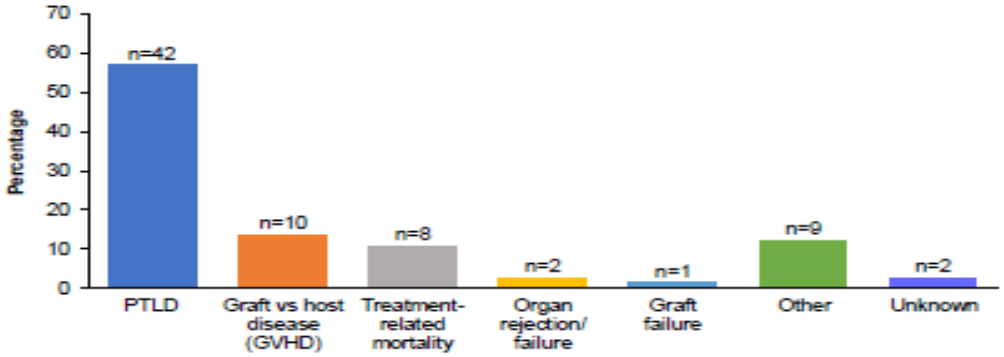
- Evaluating the data from a large multinational, multicenter retrospective chart review of EBV+ PTLD patients following HCT after failure of rituximab ± CT demonstrated poor OS with median OS of 0.7 months.
- A vast majority of the patients (91%) ultimately died; more than 2/3 of the deaths (68%) were related to PTLD and therapy.
- There remains a significant unmet need for post-HCT EBV+ PTLD patients who fail rituximab ± CT.

Figure 2. KM Plot for Overall Survival for EBV+ PTLD Patients Post-HCT Who Failed Rituximab ± CT (n=81)



Survival was measured from the earliest date when patients became refractory or relapsed to rituximab ± CT

Figure 1. PTLD is the Most Common Reason for Death Among EBV+ PTLD Patients Following HCT (n=74)

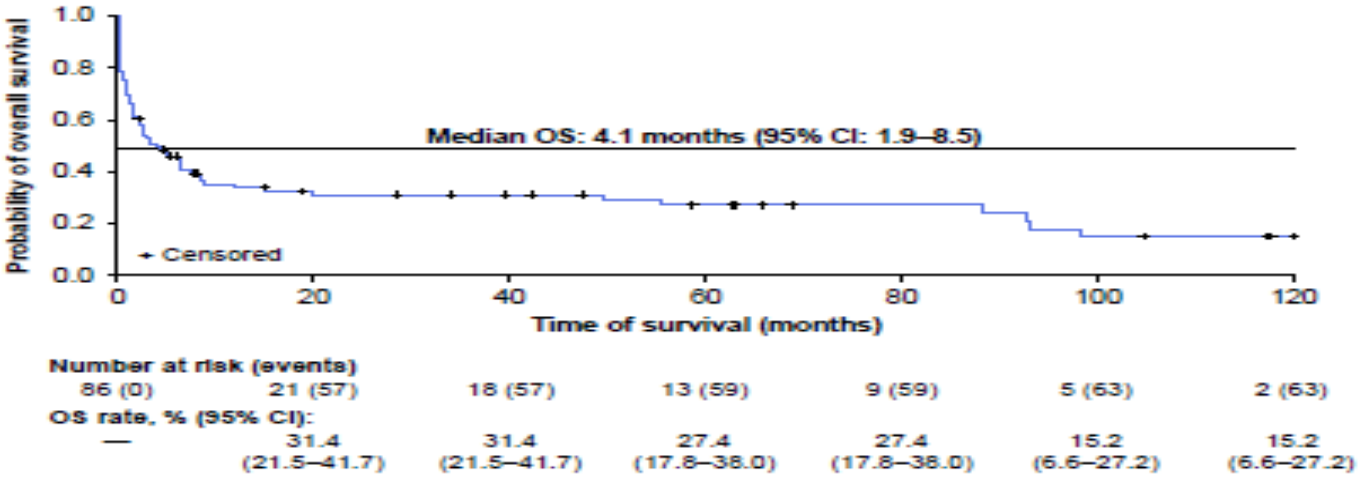


Jaime Sanz1, Jan Storek2, Gérard Socié3, DhanalakshmiThirumalai4, Norma Guzman-Beccera4, PengchengXun4, Deepali Kumar5, Natalia Sadetsky6, DaanDierickx7, John Reitan8, ArieBarlev6,Mohamad Mohty9

Clinical Outcomes of Solid Organ Transplant Patients With Epstein–Barr Virus-driven (EBV+) Post-Transplant Lymphoproliferative Disease (PTLD) Who Fail Rituximab Plus Chemotherapy: A Multinational, Retrospective Chart Review Study

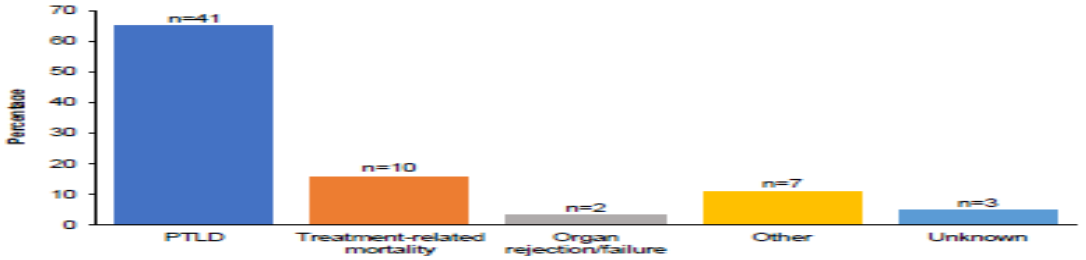
- Evaluating the data from large multinational, multicenter retrospective chart review of EBV+ PTLD patients following solid organ transplantation after failure of rituximab plus CT demonstrated poor OS with median OS of 4.1 months.
- Three-fourths of rituximab plus CT failure patients ultimately died; nearly 2/3 of the deaths (65.1%) were from PTLD and 16% were from treatment-related causes.
- There remains a significant unmet need for effective and well-tolerated therapies for EBV+ PTLD post-SOT patients who fail rituximab plus CT.

Figure 2. KM Plot for Overall Survival for Post-SOT EBV+ PTLD Patients Who Failed Rituximab Plus CT (n=86)



Survival was estimated from the earliest date when patients became refractory or relapsed following rituximab plus CT

Figure 1. PTLD is the Most Common Reason for Death Among EBV+ PTLD Patients Post-SOT (n=63)



Vikas Dharnidharka1, DhanalakshmiThirumalai2, Ulrich Jaeger3, WeizhiZhao2, DaanDierickx4, PengchengXun2, PerianaMinga5, Ahmed Sawas6, Natalia Sadetsky7, Paul Chauvet8, Erin Sundaram9, Arie Barlev7, Heiner Zimmermann10, Ralf Ulrich Trappe10

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PTLD: new agents

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

PTLD:antiviral therapy

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

Options for lytic induction:[3]

The use of antivirals and HDAC inhibitors in treatment of PTLD is currently limited to investigational settings[1]

BARF, bamh1-a reading frame; EBNA, Epstein-Barr nuclear antigen; EBV, Epstein-Barr virus; HDAC, histone deacetylase; HIV, human immunodeficiency virus; LMP, latent membrane protein; NHL, non-Hodgkin lymphoma;

1. Atallah-Yunes SA, et al. Br J Haematol. 2023;201:383–395; 2. Heslop HE. BloodNK, natural killer; PTLD, post-transplant lymphoproliferative disorder.. 2020;135:1822–1823; 3. Dugan JP, et al. Front Oncol. 2019;9:127.

NAVAL-1 trial Phase 2

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

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

Rationale:
• EBV in latent form is not susceptible to the cytotoxic activity of ganciclovir
• Nanatinostat induces EBV lytic activation and expression 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

PTLD:adoptive immunotherapy

Different sources and applications for adoptive immune therapy in EBV+ PTLD1

Transplantation cell type	AHCT: donor origin	SOT: recipient origin
Donor lymphocytes	Yes (GvHD risk)	No
Autologous EBV-CTLs	No (donor derived)	Yes (often EBV-naïve, ongoing IS)
Donor-derived EBV-CTLs	Yes	No (mostly receptor derived)
Third party EBV-CTLs	Yes	Yes

EBV antigens expressed in the different latency programmes can be targeted by different immunotherapies[1]

AHCT, autologous haematopoietic cell transplantation; CTL, cytotoxic T-lymphocyte; EBV, Epstein-Barr virus; GvHD, graft vs host disease; IS, Immunosuppression; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.

1. Dierickx D, et al. Curr Opin Oncol 2022;34:413–421.