Post Transplant Lymphoproliferative disorder – An update

Dr Paul Fields

Department of Haematology

Guys and St Thomas NHS Trust

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Definition of PTLD

Are lymphomas that occur after solid organ (up to 10%) or stem cell transplantation

Cause by a proliferation of lymphoid tissue

It is most common form of post transplant malignancy in children and in adults 2nd most common after skin Caner

In children and adults common cause of cancer related mortality after solid organ transplantation and reported overall mortality often exceeds 50%

In Europe and US 85% are B cell lineage and most > 80% are associated with EBV infection.

Around 10-15% of PTLD are of T cell lineage around 30% which are associated with EBV

Incidence PTLD : Adult and Paediatric

	Adult %	Paediatric %
Renal	1-2.3	1.2-10
Liver	1-2.8	4-15
Heart	1-6.3	6.4-19.5
Heart Lung	2.4-5.8	
Lung	4.2-10	
Small Bowel	20	

Risk higher in Children – higher incidence of EBV
Transplanted organ or bone marrow may contain EBV
Infected cells , EBV infection very common

Taylor et al Cr Review Oncology Haematology 2005

Comparison of SOT-PTLD and HSCT-PTLD

Transplant population	Incidence	Timing of PTLD development	EBV demonstrated in tumour	PTLD origin	Prognosis	Specific risk factors
SOT-PTLD	1–20% depending on the organ	Bimodal	Frequently EBV-positive	**Recipient**	Variable	EBV seromismatch, very young or very old recipients
HSCT-PTLD	<2%	Mainly early-onset	Mainly EBV-positive	**Donor**	Variable	EBV seromismatch, higher grades of graft-versus-host disease, pre-transplant splenectomy

Classified into 4 types

1. Early lesion – which normally regress if immune suppression reduced

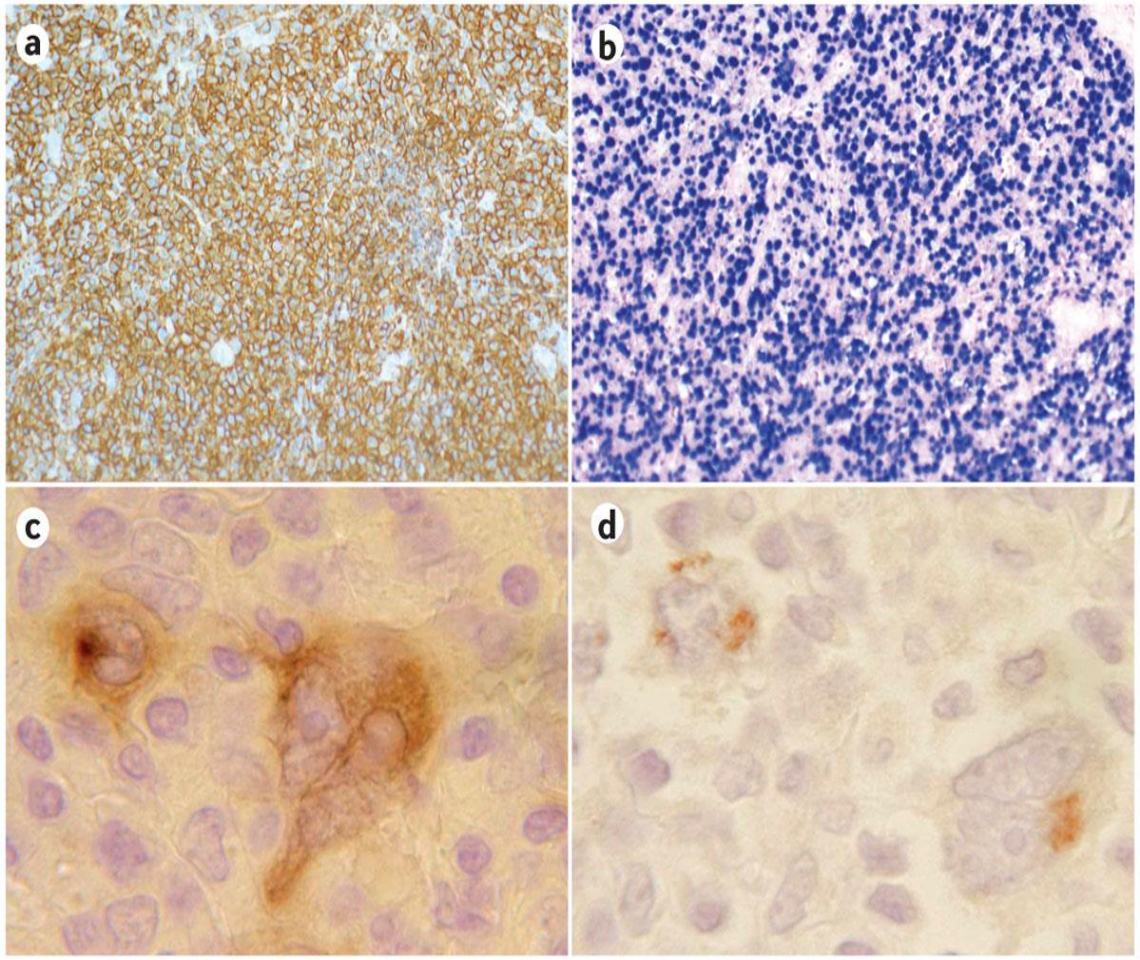
2. Polymorphic PTLD (P-PTLD) lesions which contain a mixture of different types of cells

3. Monomorphic (M-PTLD) : which contains 1 type of cell and is the most common type of PTLD

    It is usually a Non Hodgkin Lymphoma- Morphologically Diffuse Large B cell lymphoma is the most common type of M-PTLD, but occasionally other types such as Burkitt lymphoma and other rarer types can occur (such as T NHL)

4. Classical Hodgkin lymphoma type – which is very rare

Histopathological markers for PTLD



Nature Reviews | Disease Primers

a | CD20-positive stain in monomorphic post-transplant lymphoproliferative disease (PTLD).

b | Epstein–Barr virus (EBV)-encoded RNA (EBER)-positive stain in monomorphic PTLD.

c | Immunostaining for CD30 shows both cytoplasmic and Golgi staining characteristic of Reed–Sternberg cells in Hodgkin PTLD.

d | Immunostaining for CD15 shows its presence in the Reed–Sternberg cells in Hodgkin PTLD.

Dharnidharka, V. R. *et al.* (2016) Post-transplant lymphoproliferative disorders *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.88

Clinical features

Highly variable presentation : requires high index of clinical suspicion

50% fever, 30% lymphadenopathy (solitary or multiple)

Non specific symptoms such as tonsillitis (more in children) and weight loss / abdominal symptoms

15% emergency surgical presentation – intestinal perforation often small / large bowel

Small group fulminant presentation – disseminated disease / systemic symptoms

CNS involved into 30% of PTLD and in many of these cases the disease maybe confined to the CNS

Diagnosis

Histological examination of biopsy tissue

Excision is preferable to incision needle

FNA is not adequate

Histology

Presence of EBV by IHC and FISH

Cellular infiltrates with IHC CD Ag staining

Staging as for conventional NHL

Imaging

CT – C/A/P/N
PET/CT – (preferred method – excellent for extranodal disease)

Markers

IHC : Ki- 67, Ig Heavy chains, CD 10 , BCL 2 , BCL 6, Cyclin D1, CD21 , CD23, CD38 , IRF4/MUM-1, PAX 5

EBV : EBV – LMP-1 or EBER ISH (if EBV LMP 1 negative , EBER ISH is recommended)

Molecular : Ig and TCR gene re arrangements

Further tests in certain circumstances

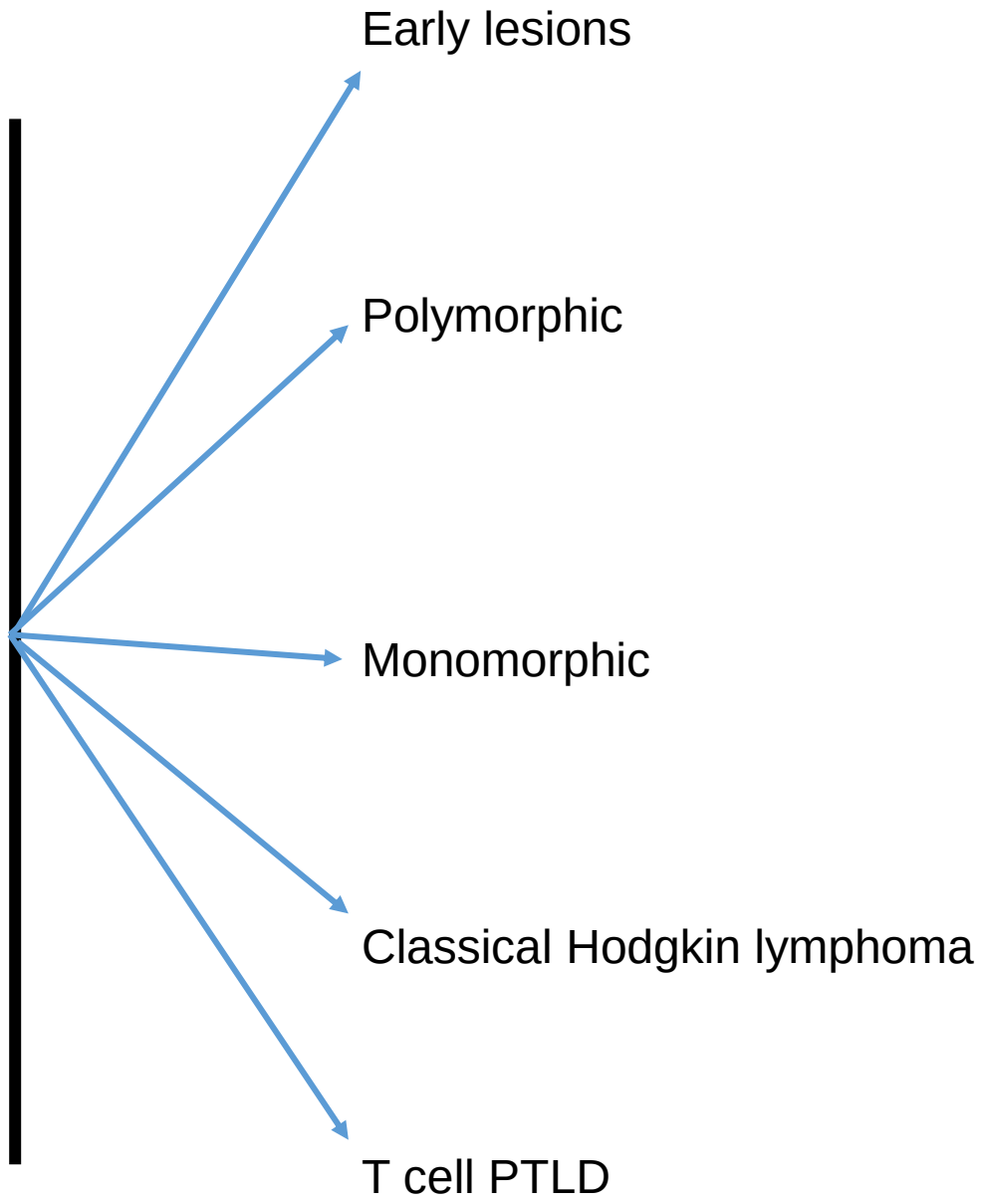
To reveal definitive histological subtype

Clinical work up

PS
LDH, U&Es, Creatinine
FBC differential
Hep B testing
C/A/P CT
Full body PET/CT

Further

Echocardiogram / MUGA
Bone marrow exam
Brain MRI with / without Contrast
EBV serology : Primary versus reactivation
EBV PCR
CMV PCR



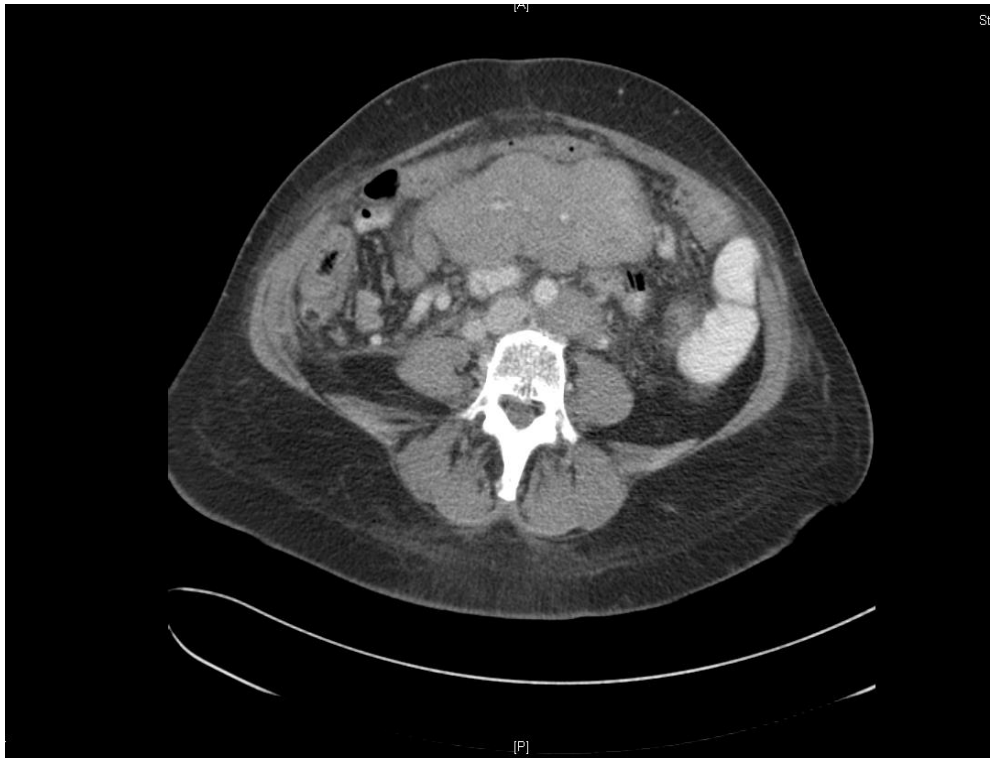
Typical case

2004

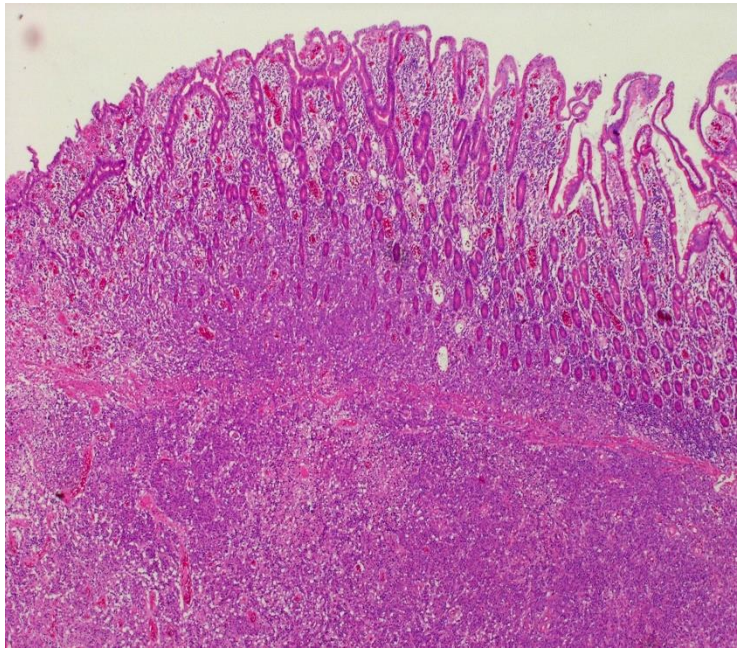
1 stone weight loss ,
change in BH
Central / upper abdominal pain 5/52

I/S : FK506 3mg bd

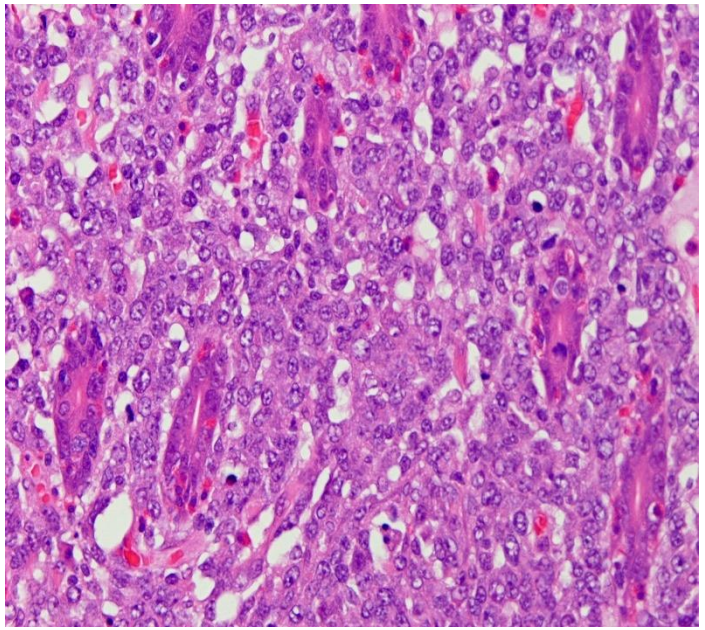
Azathioprine 150mg od



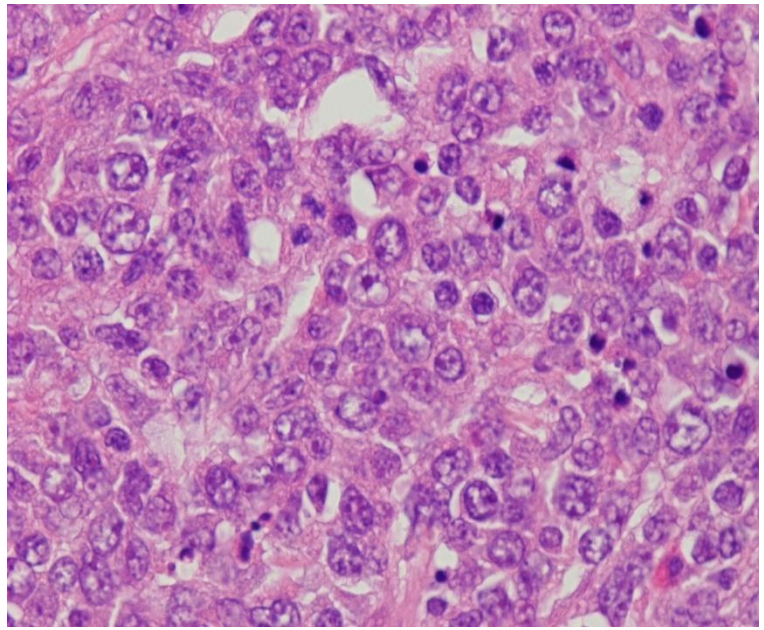
Jejunal biopsy



No evidence of Carcinoma

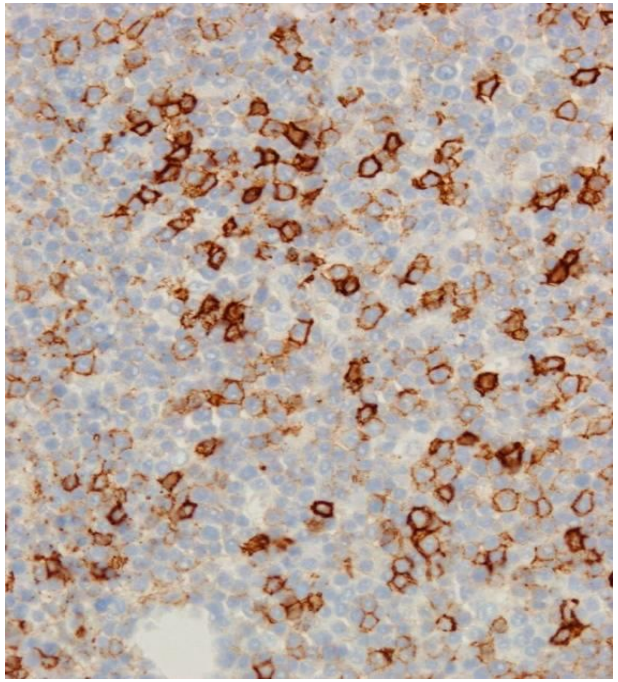


High power

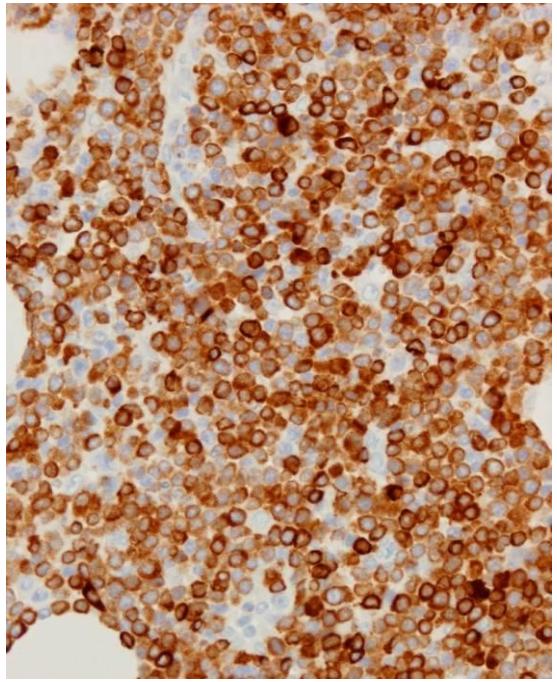


Immunohistochemistry

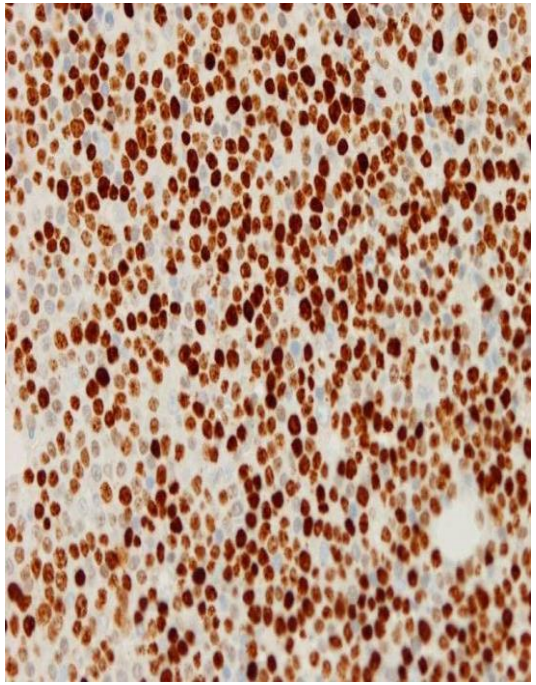
CD20



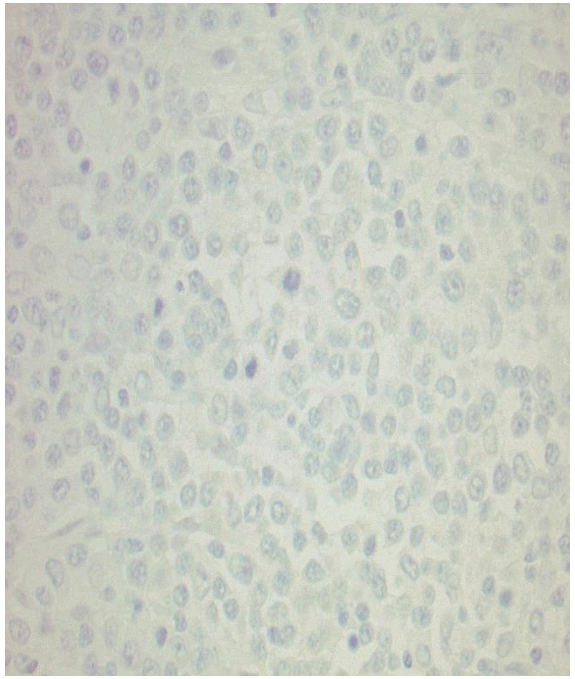
CD79a



Mib-1



EBER



Final diagnosis = DLBCL [EBV –ve]

Subsequent joint follow up management ::: Renal and Haematology

Treatment commenced with R-CHOP

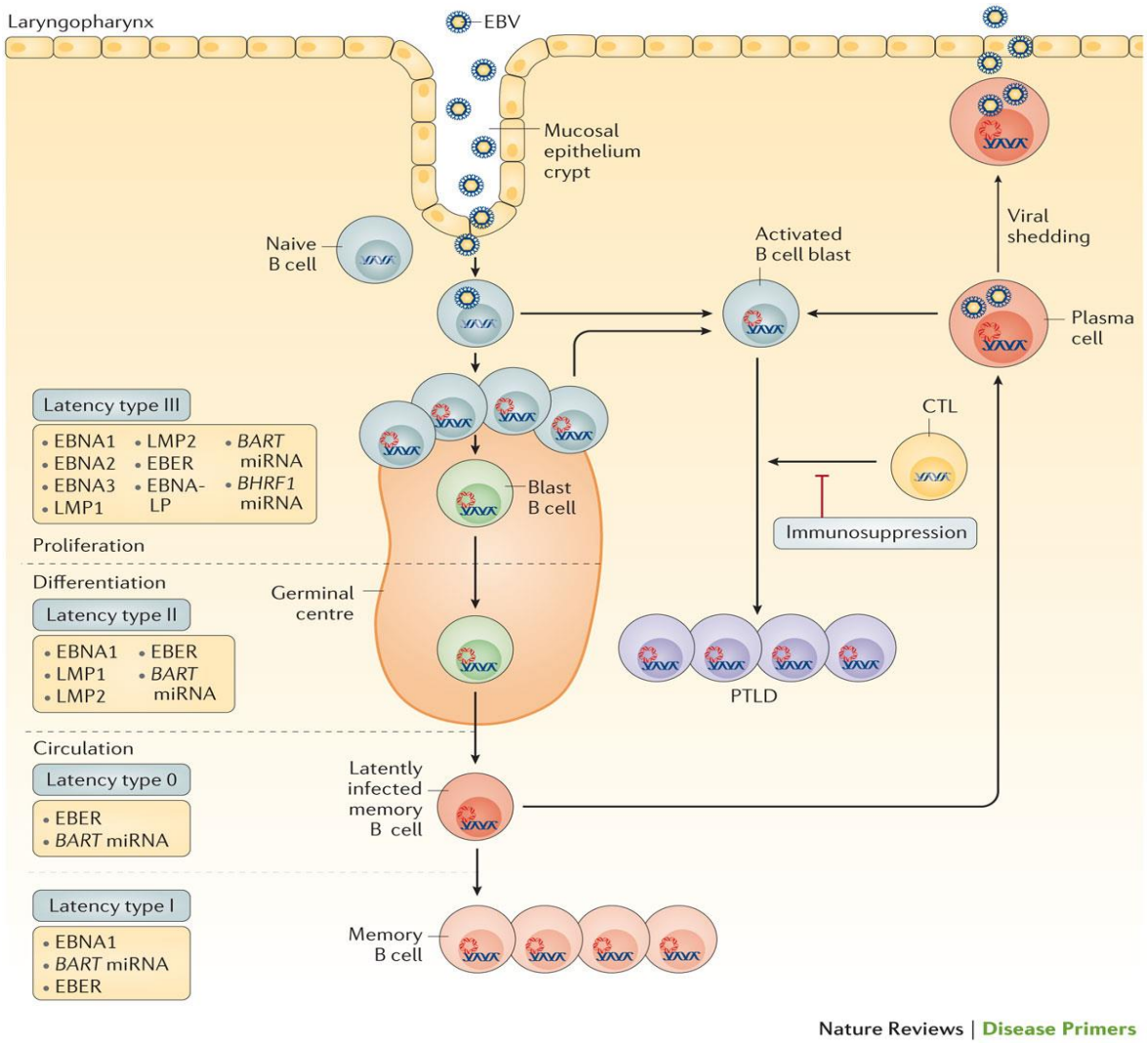
6 Further cycles well tolerated

Repeat interim CT –PET complete response

End of treatment scan CMR

Pathogenesis

Life cycle of EBV infection to PTLD development



EBV enters submucosal cells

↓

Viral gene expression induced

↓

B cell blasts kept in check by host CTLs

↓

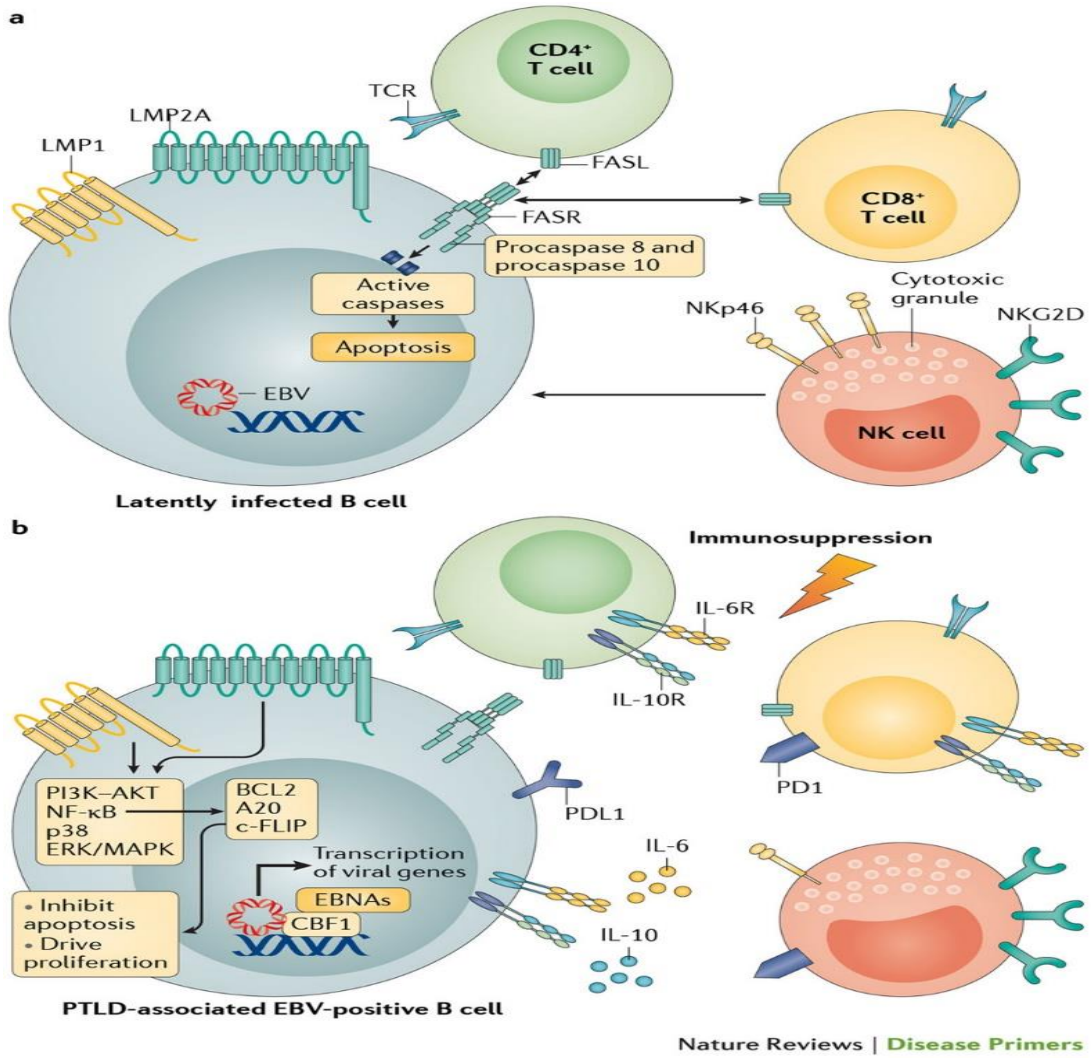
Immune suppression : ↓CTL

↓

PTLD development

Dharnidharka, V. R. *et al.* (2016) Post-transplant lymphoproliferative disorders *Nat. Rev. Dis. Primers* doi:10.1038/2015/

Immune response triggered by latently infected B cells with or without immunosuppression



Normal response

EBV Ag expression : LMP1, 2A, EBNA

Infected cell recognised by host CD4/ CD8

Apoptosis induced via FAS/FASL (Caspase 8 mediated)

Transplant scenario

I/S : Blunt immune response

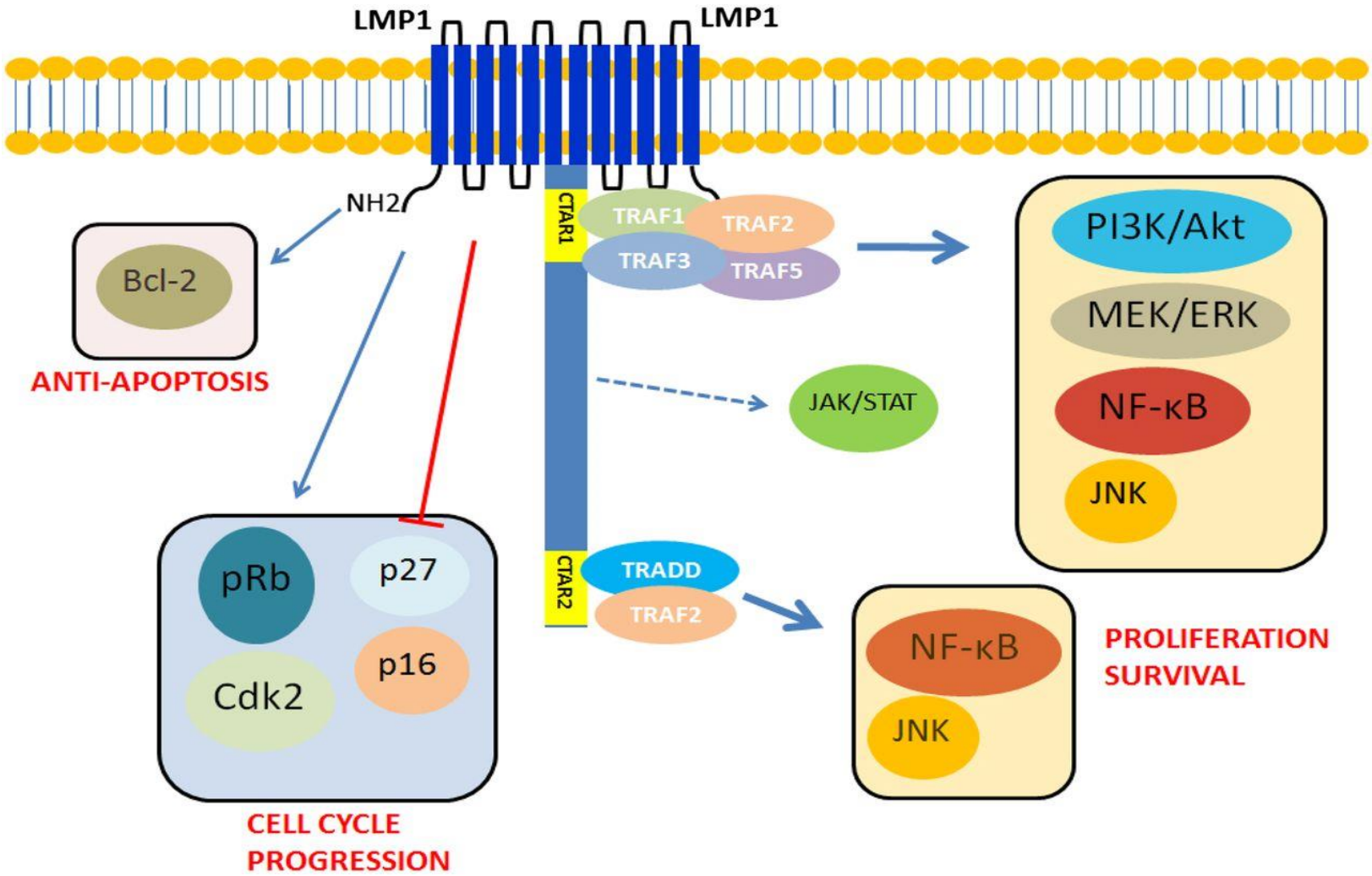
EBV cell + IL-6 autocrine growth factor . IL-10 supress Antiviral activity

Exhaustion via PDL-1 , PD-1

c FLIP – homologue of caspase 8 –disrupts activation

Dharnidharka, V. R. *et al.* (2016) Post-transplant lymphoproliferative disorders *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.88

Schematic diagram of EBV-mediated oncogenic signalling pathway activation in EBV-positive diffuse large B-cell lymphoma of the elderly.



Chi Young Ok et al. Blood 2013;122:328-340

Treatment

Options

Reduced immune suppression

Immunotherapy – Single Agent Rituximab

Chemotherapy agents

Radiotherapy

Surgery – often required for fulminant emergency presentation , excision and assessment for Further adjuvant therapies above

Future : Novel agents

European PTLD trials

Dr R Trappe, Dr S Choquet

(Germany/France)

Results

PTLD-1 :

70 Patients – trial examined use of single agent 4 x R followed by R-CHOP

ORR 60% after rituximab alone (20% CR)
90% after R-CHOP
Median PFS 4 years
Median OS 6.6 years

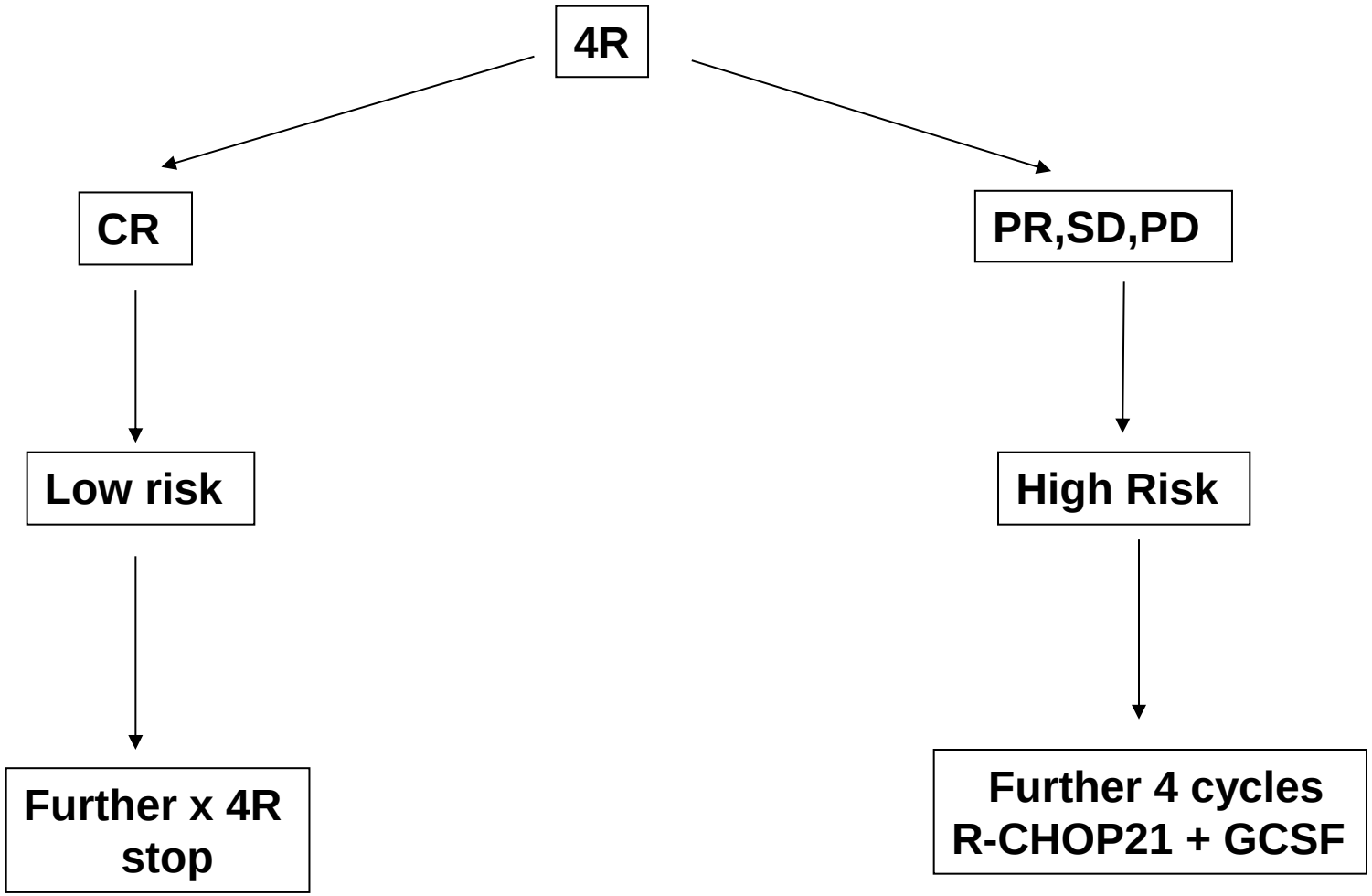
Treatment related mortality 10.6%

PTLD-2 :

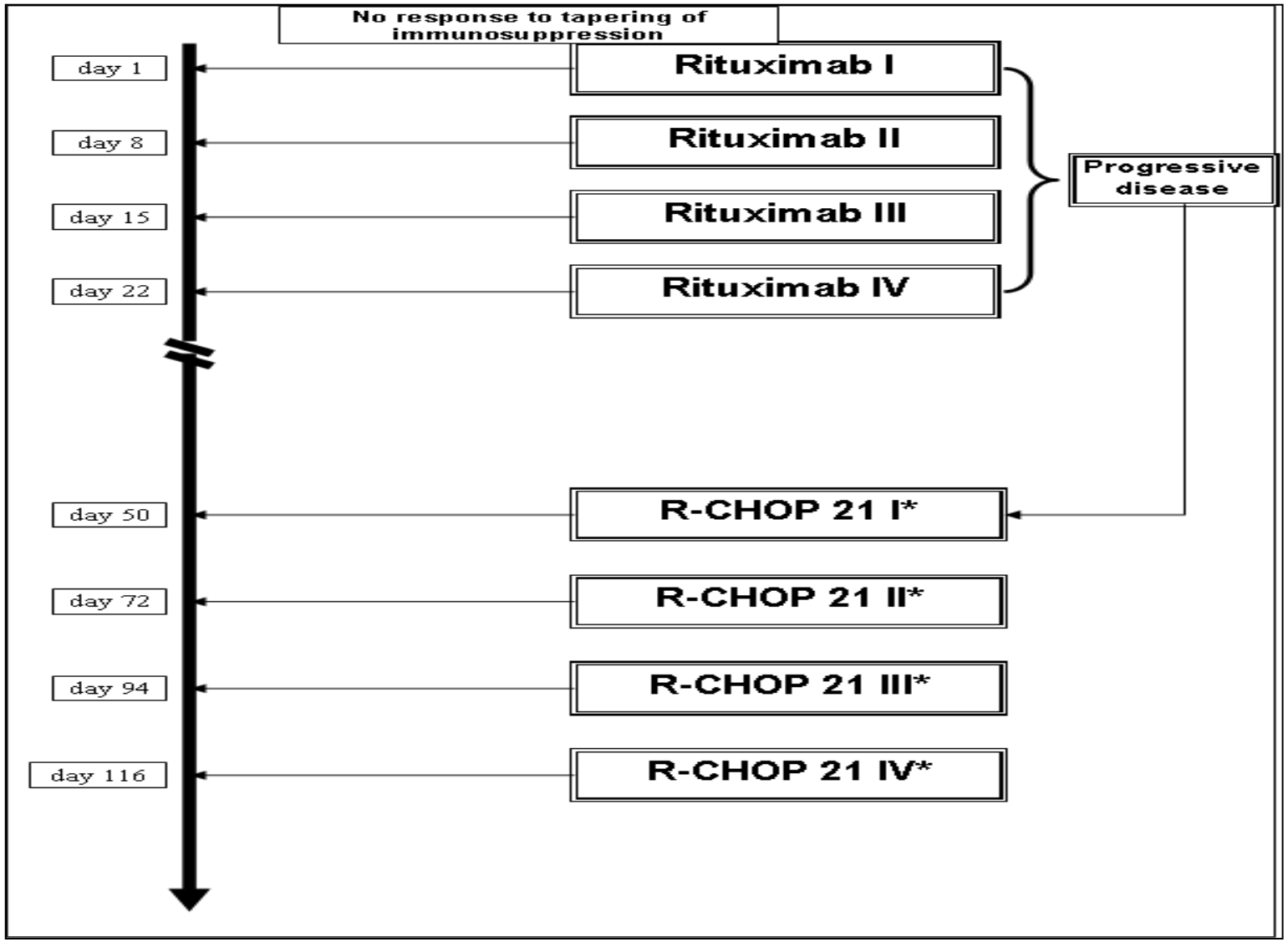
Patients who received rituximab monotherapy and achieved CR – amendment made so patients received 4 further injections rituximab injections every 3 weeks and stopped (so 8 injections in total alone)

If the response was incomplete patients received 4 cycles of R-CHOP,
The results published in abstract form (ASH 2016) show similar results CR to 4R + 4- R-CHOP but lower toxicity = termed “sequential treatment”

Trial Schema : response adapted approach



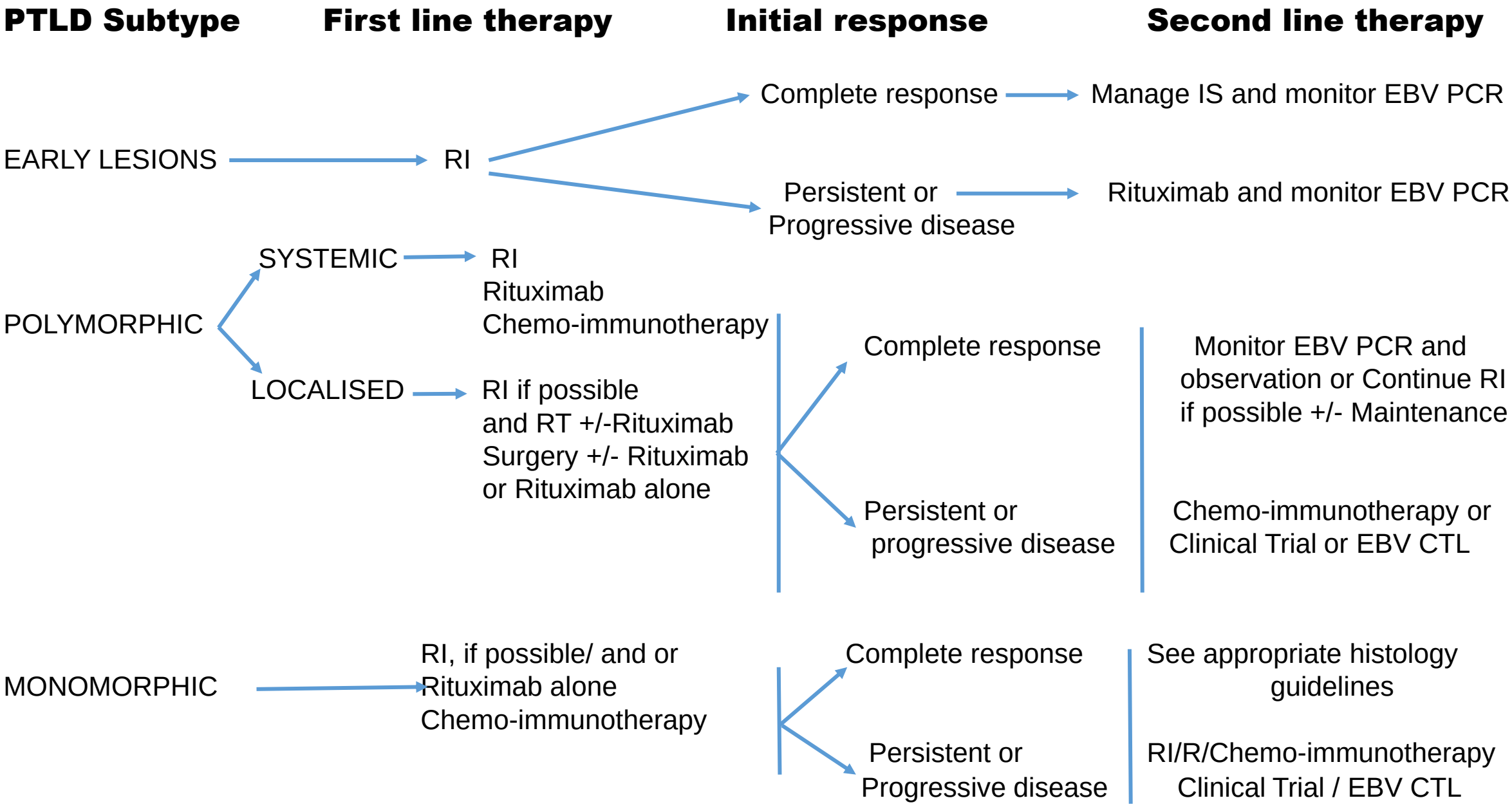
PTLD-1, PTLD-2



Patients with a complete remission at day 50 will not receive chemotherapy and will go on with rituximab (R) single agent (8 injections in total)

Establishing the concept of "response adapted approach"

Current PTLD Management approach



Treatment Regimens

Sequential chemo-immunotherapy

Rituximab 375 mg/m2 x 4 weeks

Restage with PET/CT

- If PET/CT scan negative , rituximab 375mg/m2 every 3/52 x 4 cycles

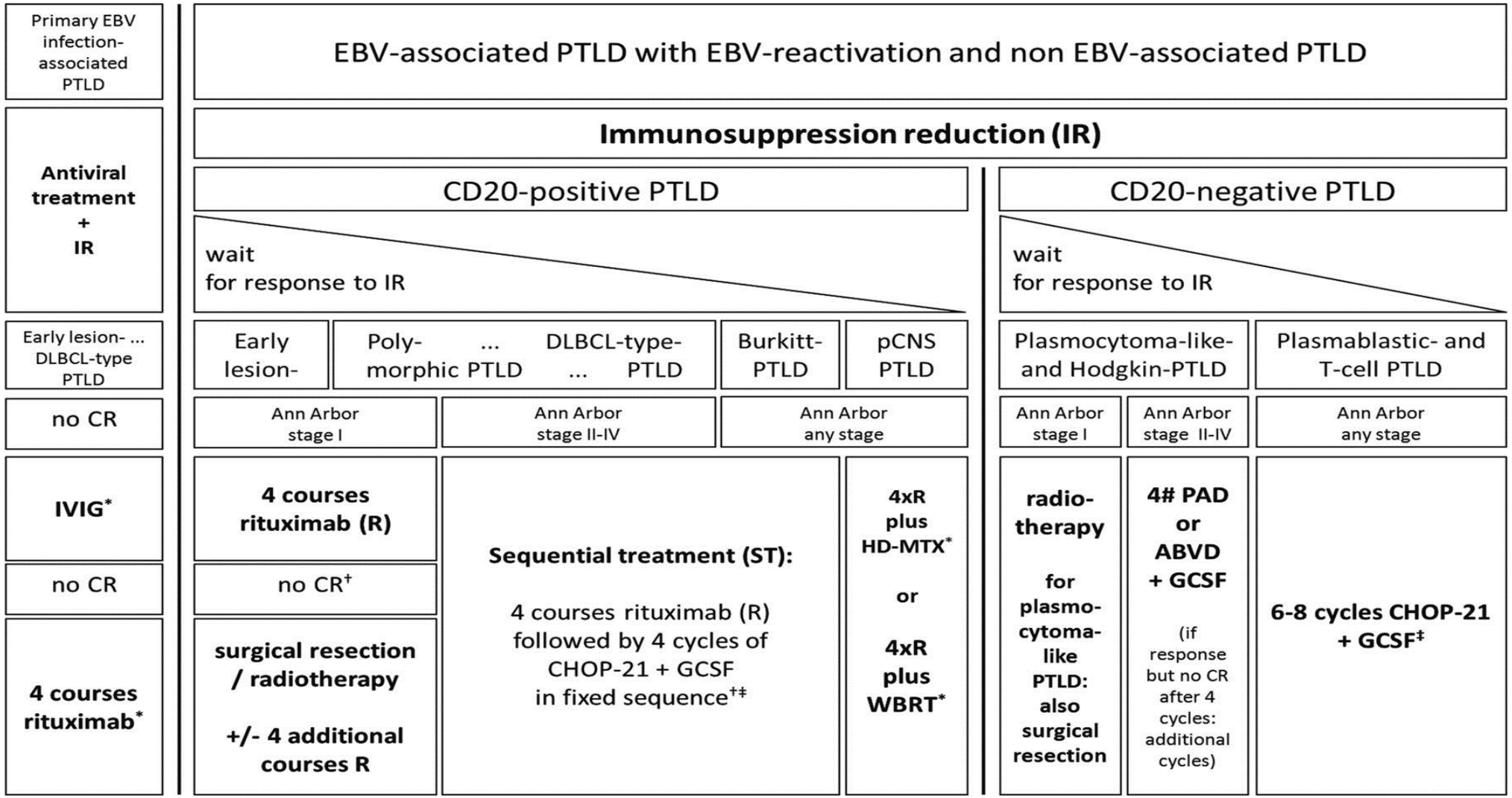
- If PET/CT scan positive, CHOP 21 every 3 weeks x 4cycles
  Prophylaxis for tumour lysis syndrome

Concurrent immuno-therapy

R-CHOP (rituximab , cyclophosphamide, doxorubicin, vincristine, prednisolone)

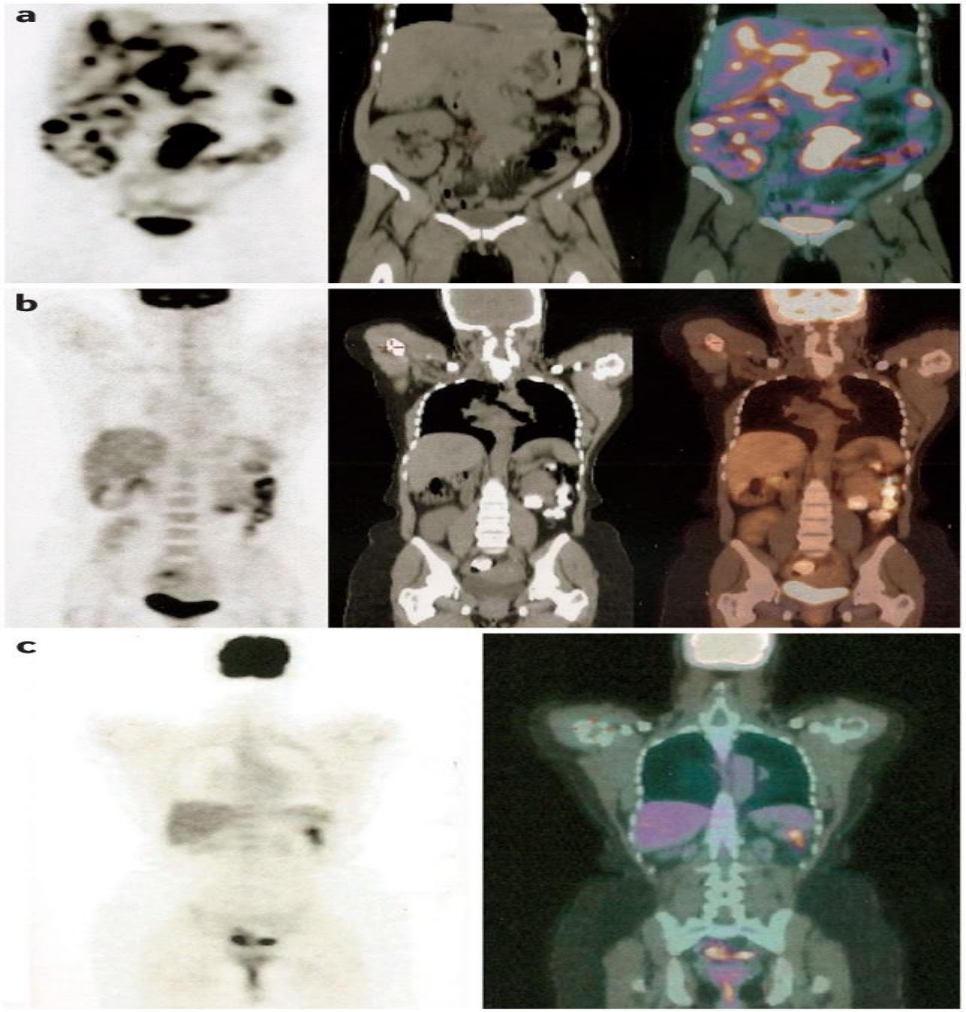
For frail patients :
R-CVP
R-CEPP
R-CEOP

PTLD in adults after SOT: What to do? a treatment algorithm



Heiner Zimmermann, and Ralf U. Trappe
Heamatology 2013;2013:95-102

Rituximab monotherapy



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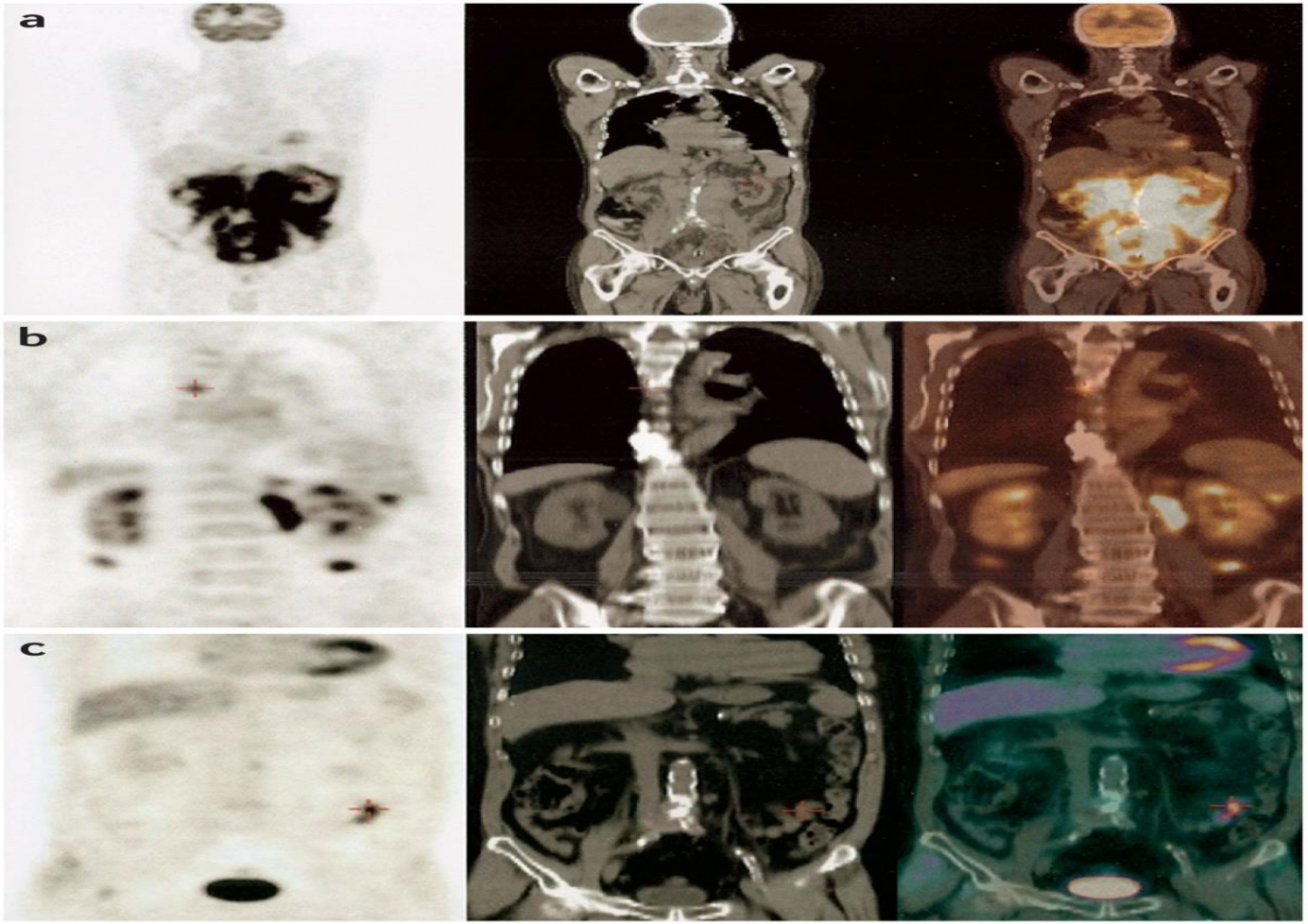
Serial FDG-PET/CT scans are shown from a patient presenting with a massive abdominal localization of a Burkitt non-Hodgkin post-transplant lymphoproliferative disease (PTLD) (part a)

After four weekly injections of rituximab, a complete response was obtained (part b)

The patient received 4 more rituximab injections at 21-day intervals. At the last evaluation, 5 years later, complete response was maintained (part c)

Dharnidharka, V. R. et al. (2016) Post-transplant lymphoproliferative disorders Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.88

Sequential therapy



Nature Reviews | Disease Primers

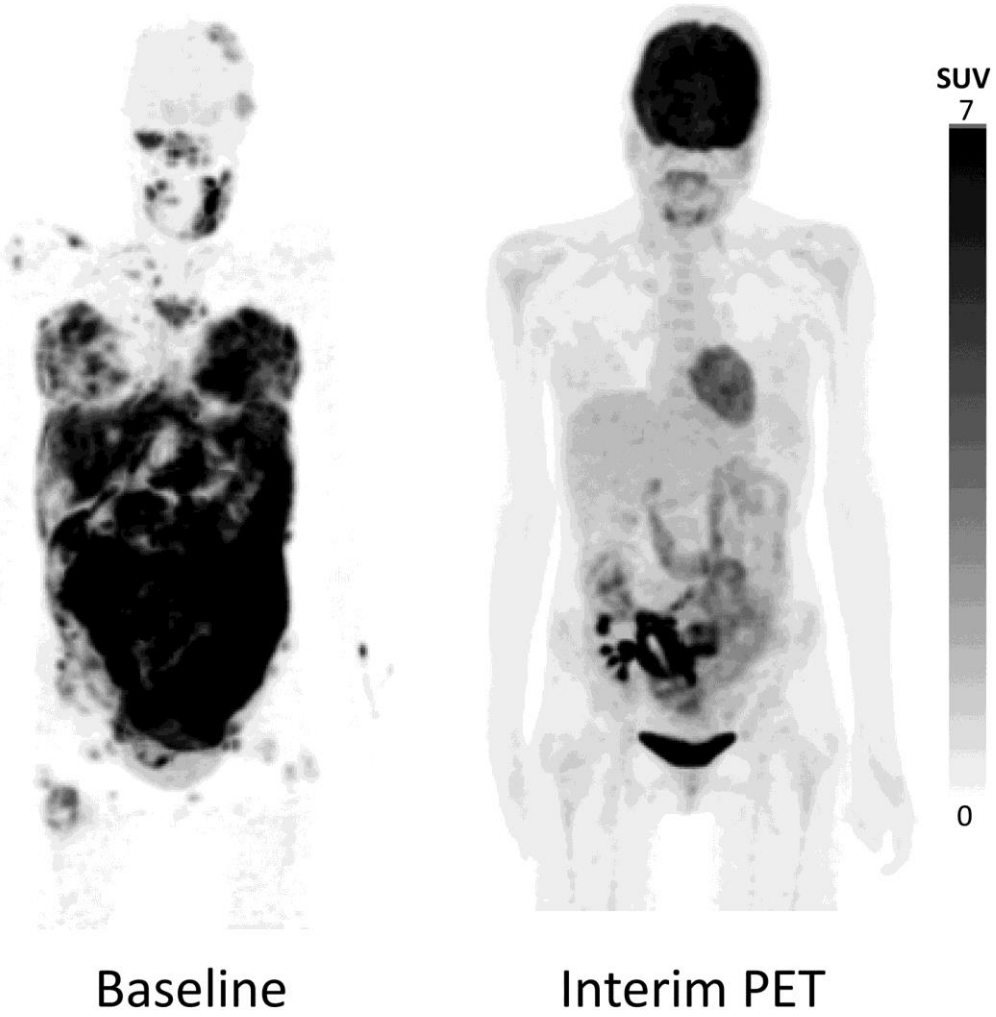
PTLD : DLBCL abdominal

Post 4 x R weekly : PR

4 Further R-CHOP : CMR

Dharnidharka, V. R. et al. (2016) Post-transplant lymphoproliferative disorders Nat. Rev. Dis. Primers : 2015: 88

Maximum-intensity projection 18F-FDG–PET/CT images.



Maximum-intensity projection ^{18}F-FDG–PET/CT images

Baseline image showed multiple supra- and infradiaphragmatic nodal lesions and extranodal lesions in breast, intestines, and bone marrow (left);

^{18}F-FDG–PET/CT after 4 cycles of therapy showed a complete metabolic response in all nodal and extranodal lesions, with the exception of limited residual hypermetabolic lesions in the intestinal tract adjacent to the kidney transplant in the right iliac fossa (right).

Daan Dierickx et al. Blood 2015;126:2274-2283

Future : Use of targeted agents

“TIDAL” study

Risk-stratified sequential Treatment with Ibrutinib and Rituximab (IR) and IR-CHOP for De-novo post-transplant Lymphoproliferative disorder (PTLD) :
CI : Dr T Manne : Newcastle

Trial Design : This is a prospective, phase 2, single arm trial evaluating the addition of ibrutinib to rituximab (IR) therapy in patients diagnosed with PTLD.

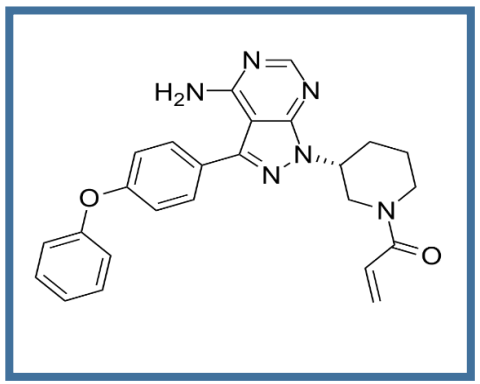
Patients will receive IR combination therapy for seven weeks, after which they will receive IR (if categorised as low risk) or IR-CHOP chemotherapy (if categorised as high risk).

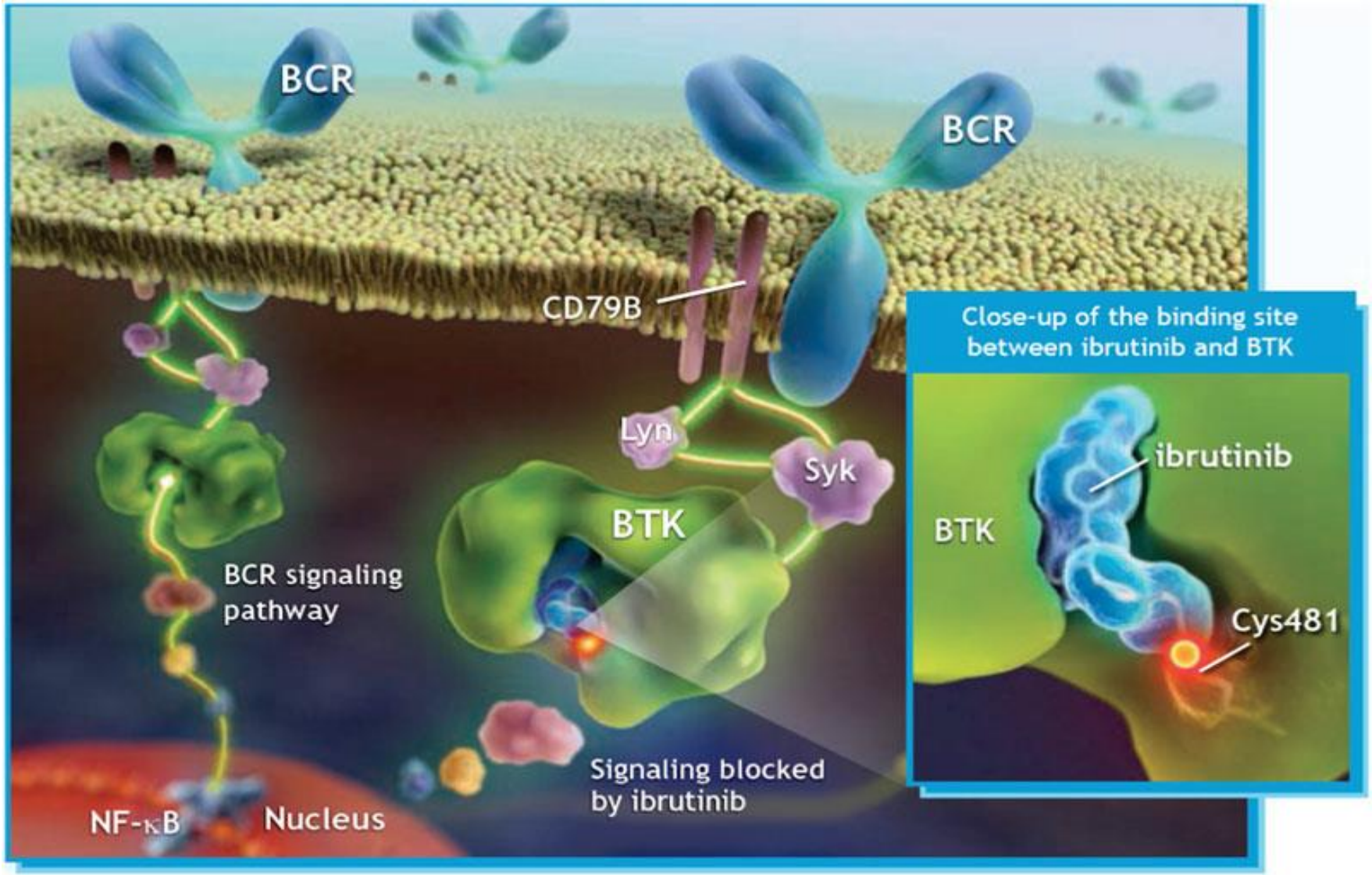
Objectives

Primary objective : The primary objective is to evaluate complete remission (CR) after seven weeks of therapy.

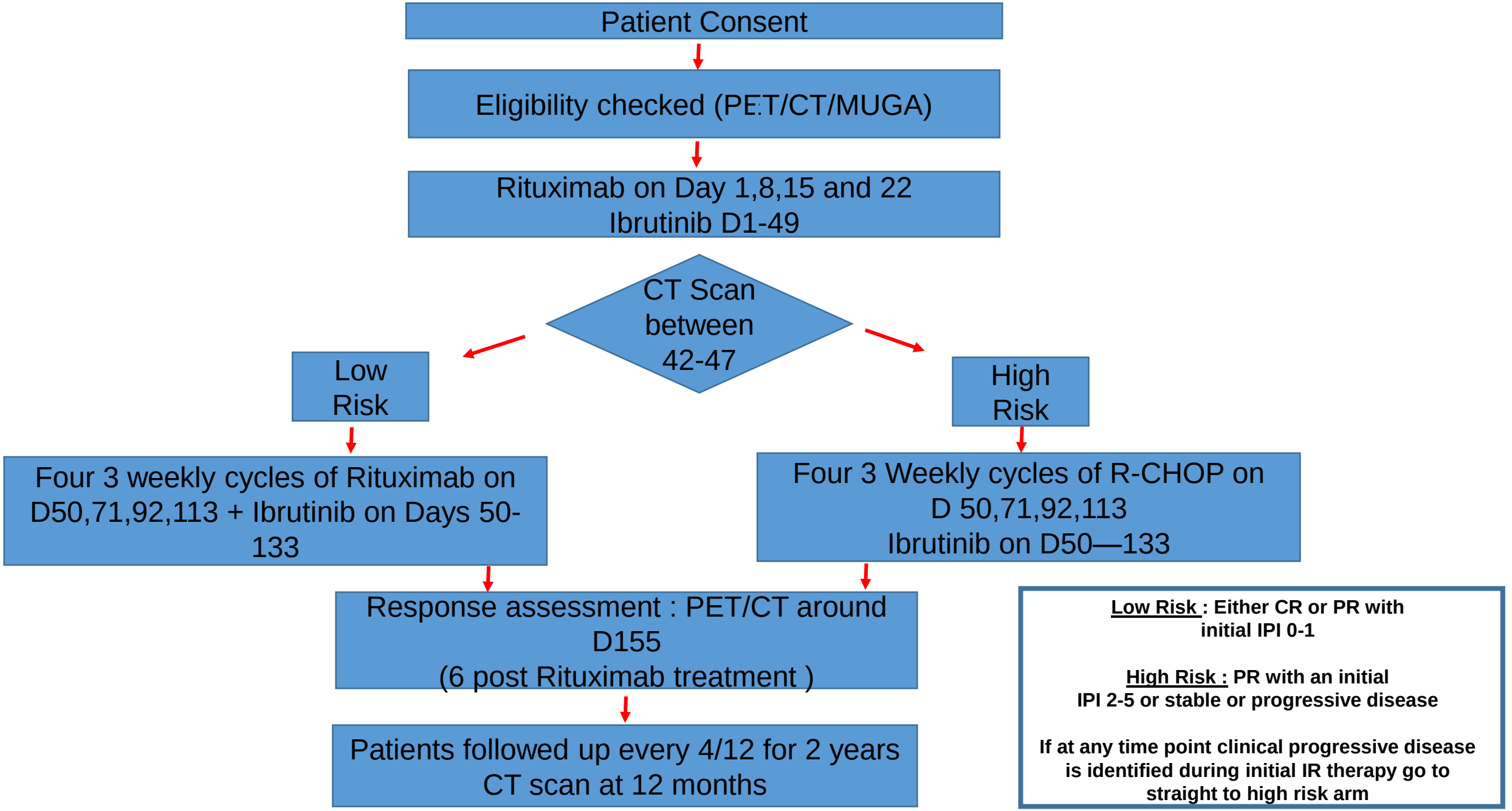
Secondary objectives : The secondary objectives are to evaluate response, event-free survival (EFS), overall survival (OS), progression-free survival (PFS), treatment-related mortality, frequency of grade III and IV leucocytopaenia and grade III and IV infections and patients entering into low and high risk arms after IR therapy.

Mechanism of action of Ibrutinib – BTK inhibitor





TIDAL trial Schema



Inclusion criteria

- Untreated CD20 positive PTLD with or without EBV association , biopsy positive
  upfront reduction of immune suppression with or without anti viral therapy is permissible
- PTLD with meningeal or CNS involvement can be included
- Clinically insufficient response to upfront RI
- Plts > 100 or > 50 if BM + ve , ANC > 1 , independent of GCF
- CrCl ≥ 30 ml/min , AST or ALT ≤ 3 ULN , Bilirubin ≤ 1.5 ULN
- PTT / APPT ≤ 1.2 ULN
- LVEF > 50%
- ECOG ≤ 2 , Age > 16

Conclusions / Future perspectives

Response adapted approach according to risk internationally adopted, has improved results

Integrating national registries prospectively – mandatory reporting of PTLD in all transplant trials, better capture of data

Identifying new risk factors – better assessment/ surrogates for immune suppression load and association with PTLD risk , with HLA association and Non EBV

Refining WHO 2008 classification to include impact of EBV (negative,positive,latency type,lytic activation) stromal microenvironment, molecular findings

Better preventive strategies (e.g. EBV PCR , cytokine gene polymorphisms)

Drive to create international cooperation and inclusion of patients in prospective international trials

Enhanced risk adapted strategies to pick our poor risk

Better biological understanding EBV –ve cases ; why in EBV + cases primary infection carries a higher risk of PTLD versus reactivation infection

References

1) Pathogenesis of PTLD : Morscio et al, World Journal of transplantation 2016
2) PTLDs Dharnidhraka V et al, Nature Reviews 2: 2-18 ,2016
3) PTLD after SOT, Taylor A, et al 2005 Oncology/Haematology 2005
4) How I treat PTLD Dierickx D, et al Blood 2015

Thank you !