New
Drugs
in
Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

PRIMARY MEDIASTINAL B-CELL LYMPHOMA

Kieron Dunleavy

Director of Hematology
Lombardi Cancer Center
Professor of Medicine
Georgetown University
Washington DC

January 15, 2024

Georgetown | Lombardi
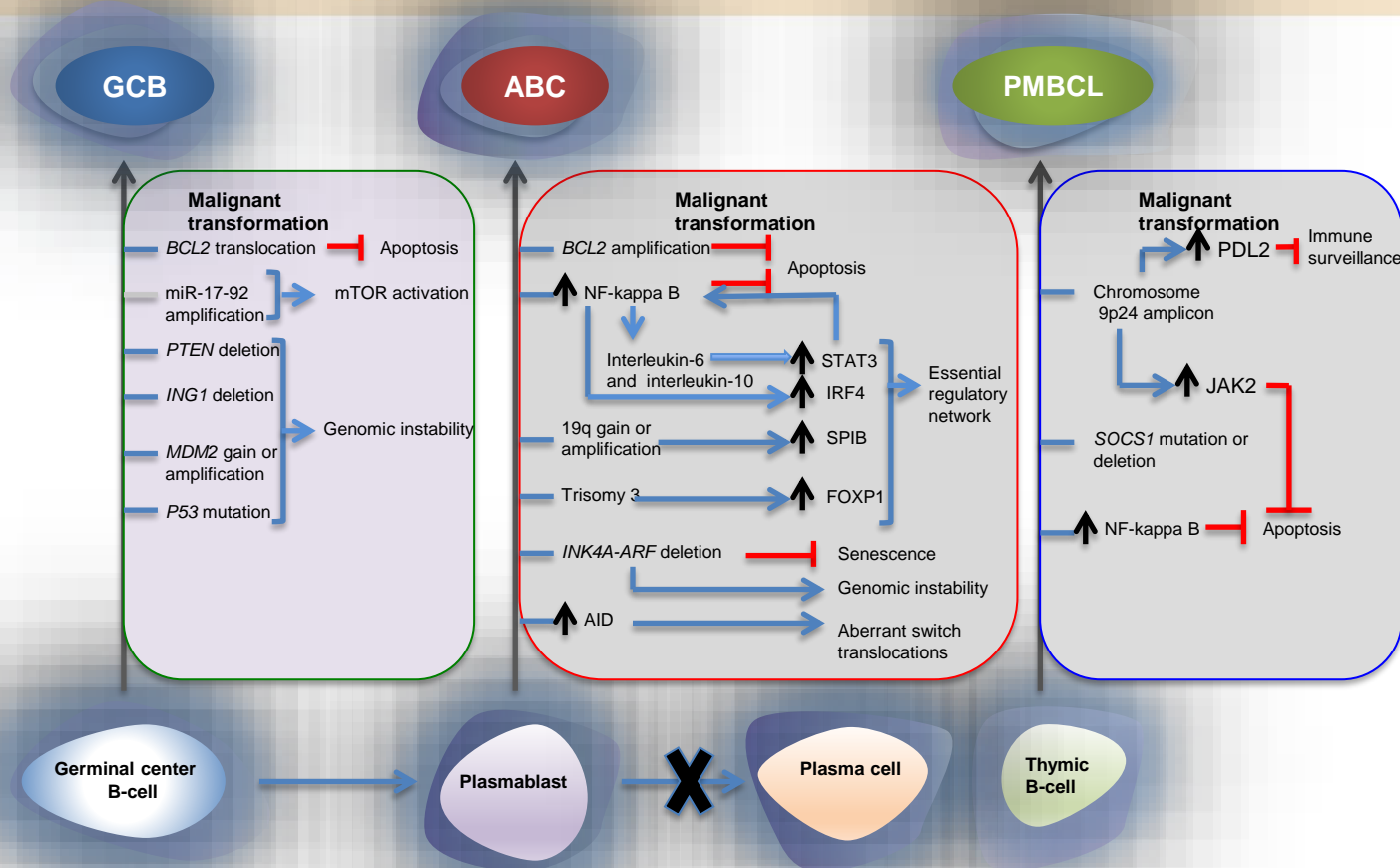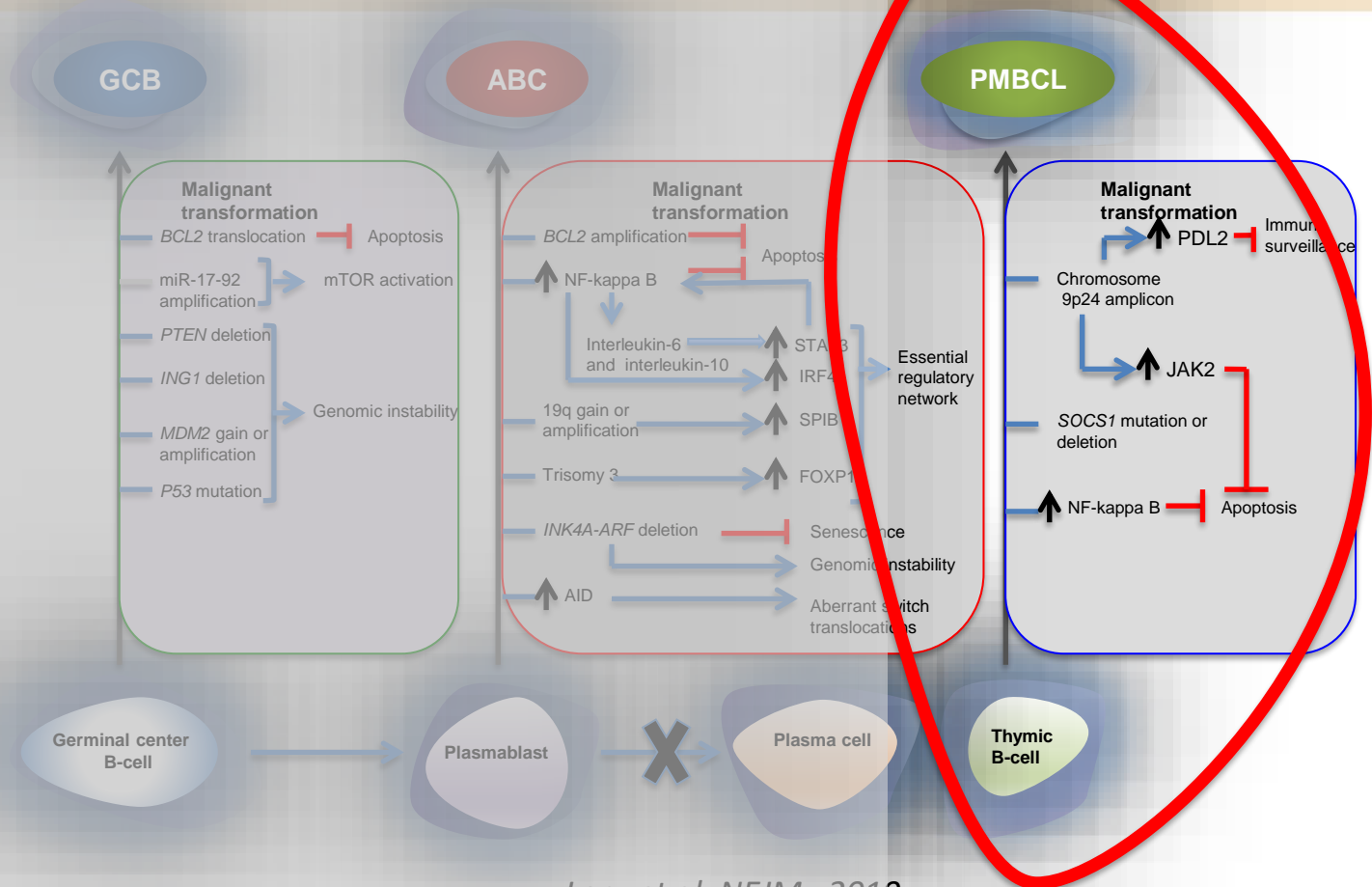COMPREHENSIVE CANCER CENTER

- Advisory Board: Astra Zeneca, Abbvie, Beigene, Bristol Myer Squibb, Amgen, Genentech, Genmab, Janssen, Kymera, Pharmacyclics, Incyte, ONO Pharmaceuticals, Celectar.
- Research Funding: Genentech, ONO Pharmaceuticals, Merck, Kymera.

PMBCL
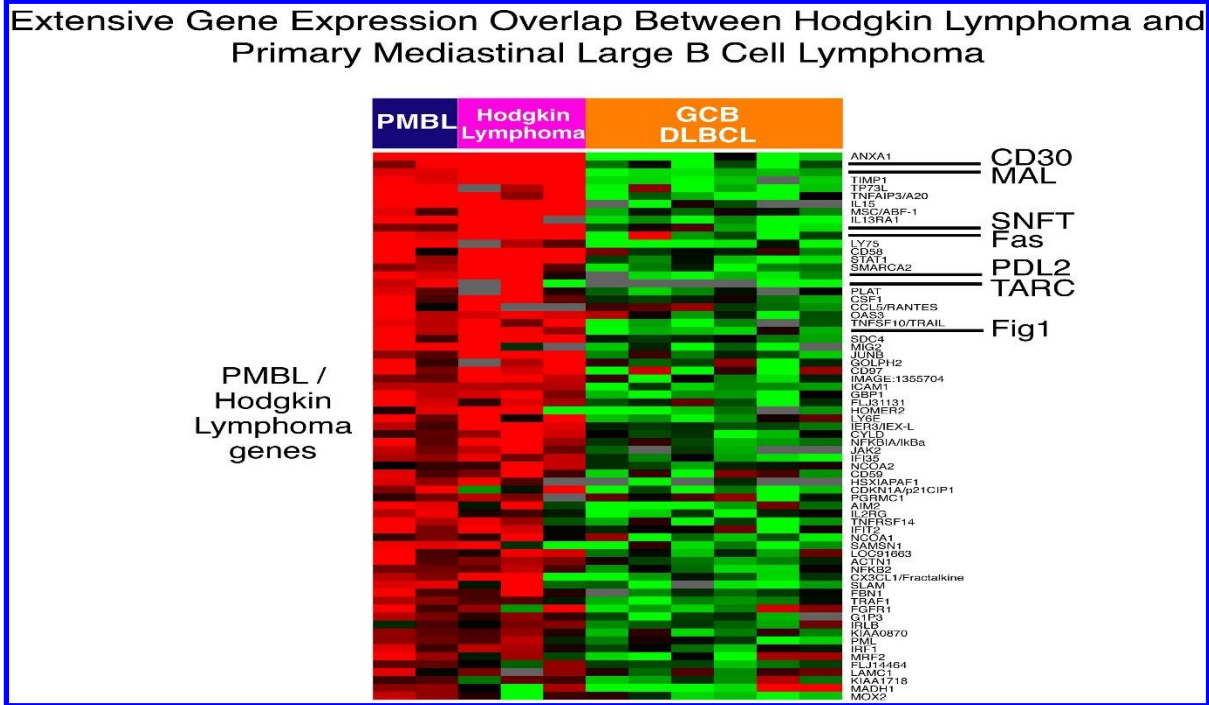## DISTINCT CLINICOPATHOLOGIC ENTITY

- THYMIC B-CELL ORIGIN

- PREDOMINANTLY YOUNG FEMALES (AYA 15-35Y)
  - LONG-TERM TOXICITIES IMPORTANT

- AGGRESSIVE PRESENTATION
  - LOCALIZED; BULKY MEDIASTINAL MASS
  - LESS COMMONLY EXTRA-NODAL SITES (LUNGS, KIDNEYS, LIVER)

- HIGH CURE RATE
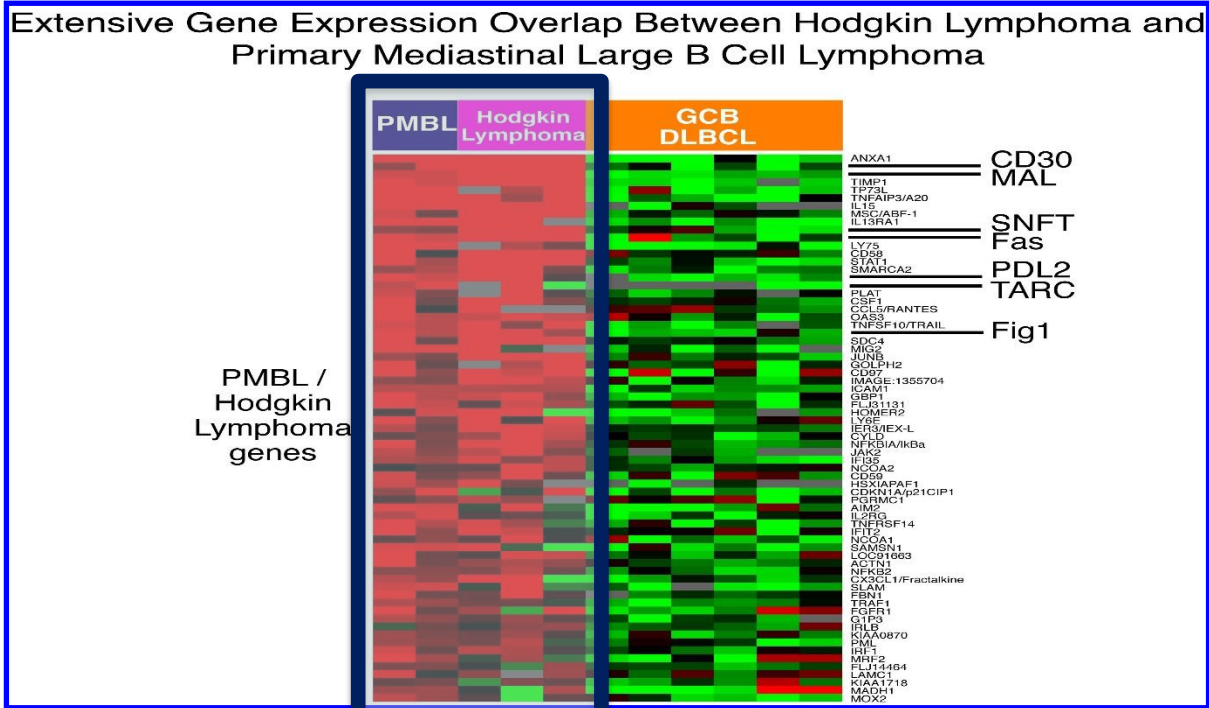 - HISTORICALLY POOR OUTCOMES FOR RELAPSED/REFRACTORY DISEASE

Lenz et al. NEJM. 2010

GCB

ABC

PMBCL

Malignant transformation

BCL2 translocation ⊣ Apoptosis

miR-17-92 amplification ⟩ mTOR activation

PTEN deletion

ING1 deletion

MDM2 gain or amplification ⟩ Genomic instability

P53 mutation

Malignant transformation

BCL2 amplification ⊣ Apoptosis

↑ NF-kappa B

Interleukin-6 and interleukin-10 → ↑ STAT3

↑ IRF4

19q gain or amplification → ↑ SPIB

Trisomy 3 → ↑ FOXP1

INK4A-ARF deletion ⊣ Senescence

Genomic instability

↑ AID → Aberrant switch translocations

Essential regulatory network

Malignant transformation

→ ↑ PDL2 ⊣ Immune surveillance

Chromosome 9p24 amplicon

↑ JAK2

SOCS1 mutation or deletion

↑ NF-kappa B ⊣ Apoptosis

Germinal center B-cell → Plasmablast ✗ Plasma cell

Thymic B-cell

Lenz et al. NEJM. 2010

Spectrum of Mediastinal Lymphomas

Extensive Gene Expression Overlap Between Hodgkin Lymphoma and Primary Mediastinal Large B Cell Lymphoma

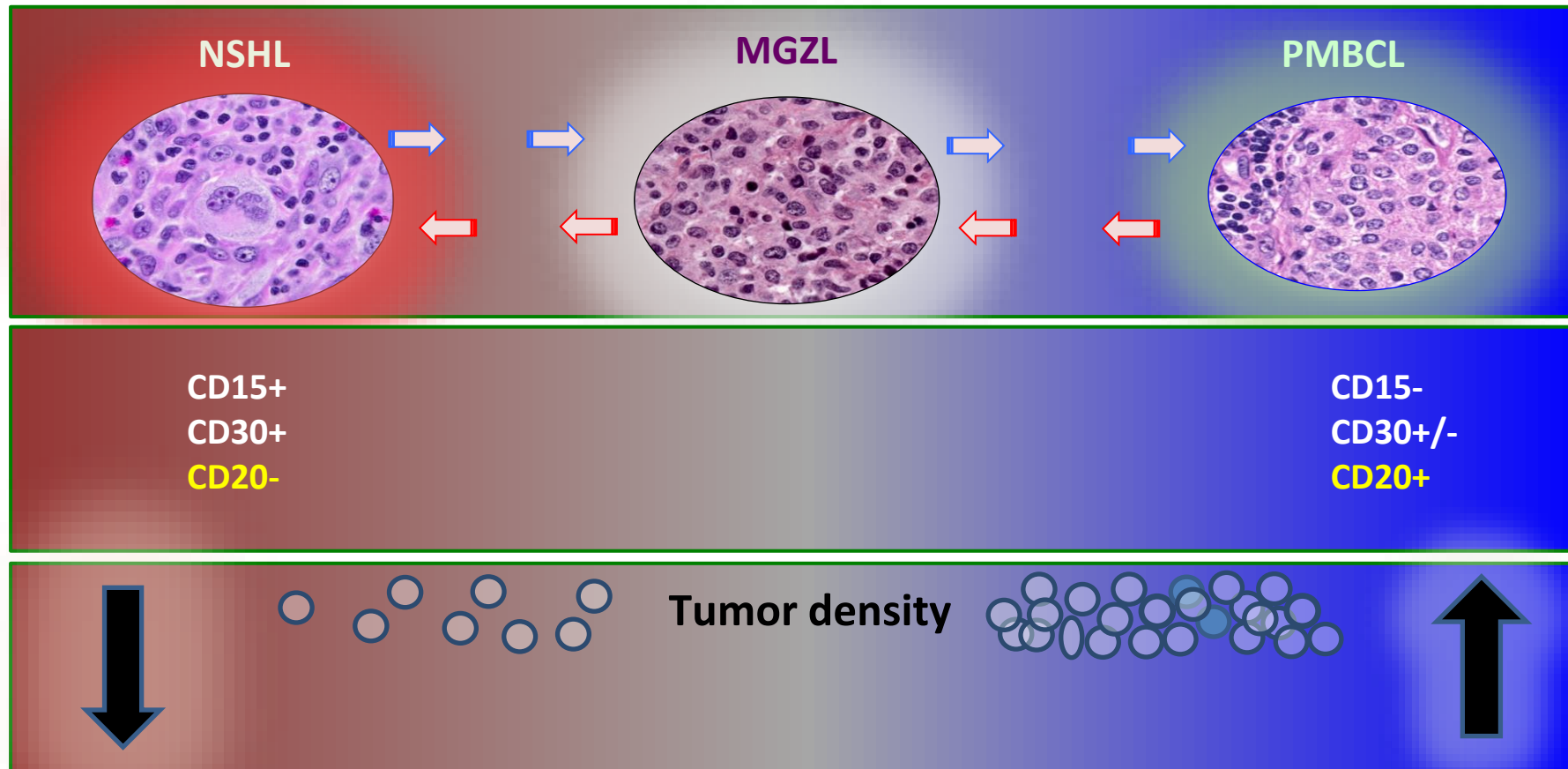*Rosenwald et al. J Exp Medicine 2003*

Spectrum of Mediastinal Lymphomas

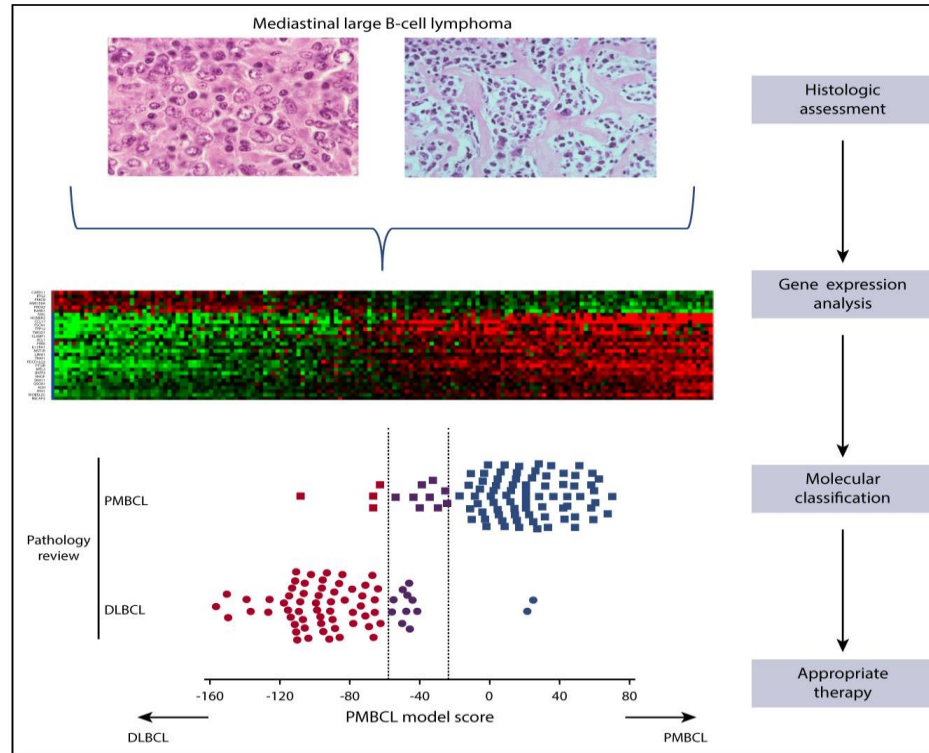*Rosenwald et al. J Exp Medicine 2003*

Spectrum of Mediastinal B-Cell Lymphomas

GENE-EXPRESSION BASED ASSAY FOR PMBCL

FFPE tissue samples

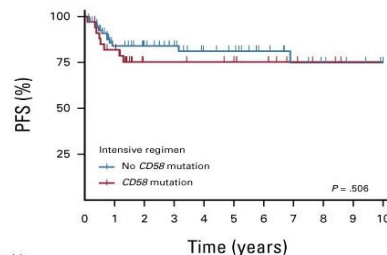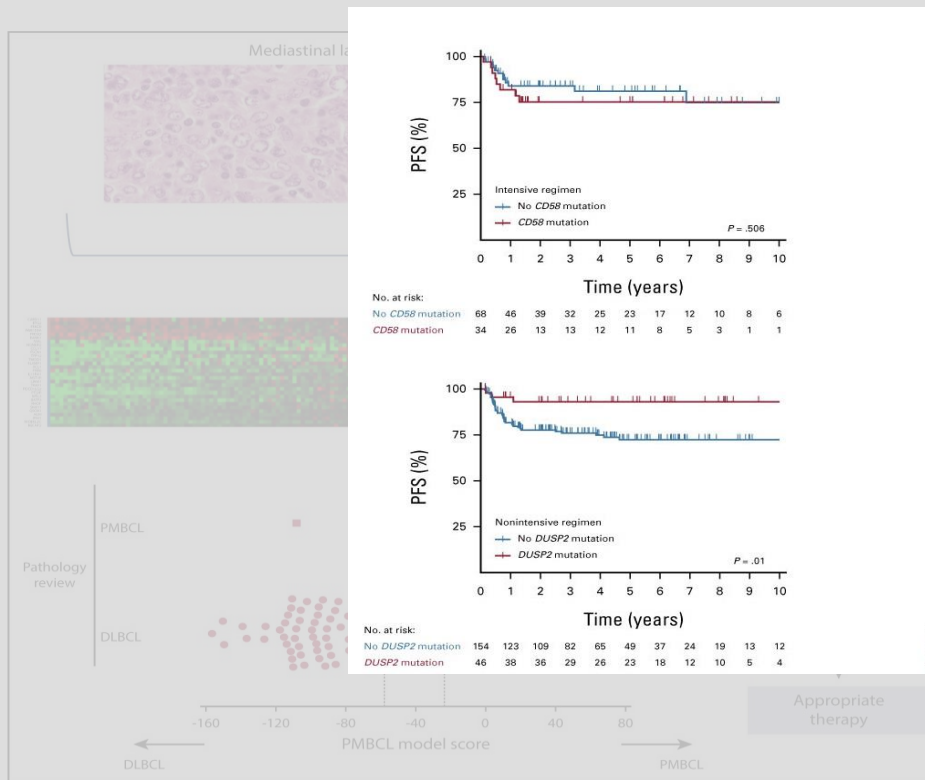58 genes analyzed
(Nanostring Lymph3Cx)

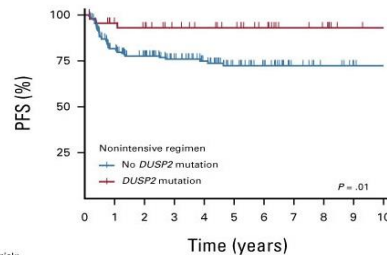*Mottok et al. Blood 2018; Lim. Blood 2018*

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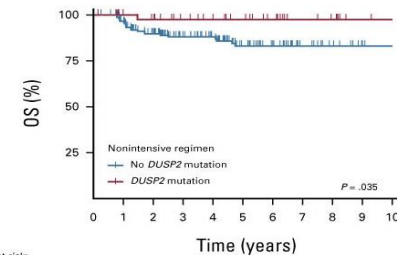

Mottok et al. Blood 2018; Lim **Noerenberg et al. JCO 2023**

Novel Targets in PMBCL

Dunleavy and Steidl. Semin in Hem. 2015

PMBCL-Current Approaches

- Optimal Therapy - Controversial

- Paucity of Prospective Data/Randomized studies

- Historically approached like DLBCL
  - R-CHOP 'de facto' standard
  - Mediastinal RT widely used

- Cure rate for refractory/progressive disease low
  - Critical to optimize up-front approaches

SELECT STUDIES IN PMBCL

Study	Treatment		Study type	Outcome
	Chemotherapy	RT +/-		
Savage et al. (2006)	CHOP/R-CHOP /MACOP-B/VACOP-B	Variable – included in primary therapy in 39%	Retrospective study N=153	PFS 69% at 5 years. Only MACOP-B/VACOP-B versus CHOP-like regimens were significantly different
Zinzani et al. (2009)	R-MACOP-B/VACOP-B	Yes	Retrospective study	DFS 88% at 5 years
Rieger et al. (2011)	CHOP/R-CHOP	Yes – RT intended in 87%	Retrospective analysis N=87	EFS was 78% for R-CHOP and 52% for CHOP at 3 years
Vassilakopoulos et al. (2012)	R-CHOP	Yes – in 76%	Retrospective study N=75	PFS was 81% at 5 years
Soumerai et al. (2014)	R-CHOP	Yes – 77% of responding patients	Retrospective study N=63	PFS was 68% at 5 years
Dunleavy et al. (2013)	DA-EPOCH-R	No	Prospective study N=51	EFS was 93% at 5 years
Martelli et al. (2014)	R-MACOP-B, R-VACOP-B, R-CHOP	Yes – 89%	Prospective study N=125	PFS is 86% at 5 years
Gleeson et al. (2016)	R-CHOP-14 versus R-CHOP-21	Yes – 57%	Retrospective analysis N=50	PFS was 80% at 5 years
Roth et al. (2017)	DA-EPOCH-R	15% of patients	Retrospective analysis N=153	EFS was 86% at 3 years
Hayden et al. (2020)	R-CHOP	44% of patients	Retrospective analysis N=159	TTP and OS: 80% and 89%
Camus et al. (2021)	R-ACVBP, R-CHOP-14, R-CHOP-21	5% (23% had ASCT)	Retrospective analysis	PFS > 80%; Inferior outcome for R-CHOP-21
Held et al. (2023)	R-CHOP-21 versus R-CHOP-14 (UNFOLDER trial)	Yes – 62%	Prospective analysis	R-CHOP-14 and R-CHOP-21 equivalent EFS improved following RT

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EARLY STUDIES: INTENSIVE VS STANDARD REGIMENS

Induction chemotherapy stategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients

PIER LUIGI ZINZANI, MAURIZIO MARTELLI, MARILENA BERTINI, ALESSANDRO M. GIANNI, LILIANA DEVIZZI, MASSIMO FEDERICO, GERASSIMOS PANGALIS, JORG MICHELS, EMANUELE ZUCCA, MARIA CANTONETTI, SERGIO CORTELAZZO, ANDREW WOTHERSPOON, ANDRÉS J.M. FERRERI, FRANCESCO ZAJA, FRANCESCO LAURIA, AMALIA DE RENZO, MARINA A. LIBERATI, BRUNANGELO FALINI, MONICA BALZAROTTI, ANTONELLO CALDERONI, ALFONSO ZACCARIA, PATRIZIA GENTILINI, PIER PAOLO FATTORI, ENZO PAVONE, MARIA K. ANGELOPOULOU, LAPO ALINARI, MAURA BRUGIATELLI, NICOLA DI RENZO, FRANCESCA BONIFAZI, STEFANO A. PILERI, FRANCO CAVALLI FOR THE INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP (IELSG)

Correspondence: Pier Luigi Zinzani, M.D., Istituto di Ematologia e Oncologia Medica "Seràgnoli" Policlinico S.Orsola, via Massarenti 9,
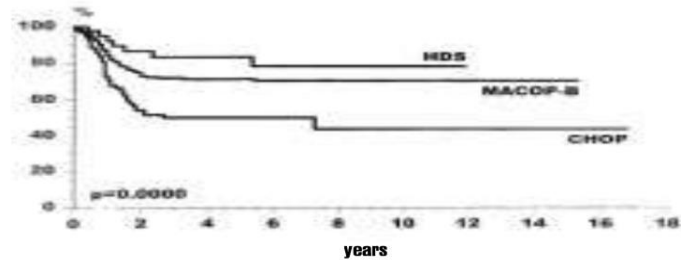

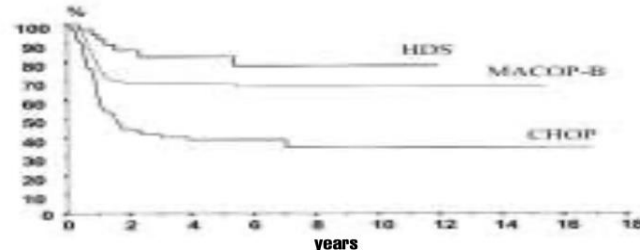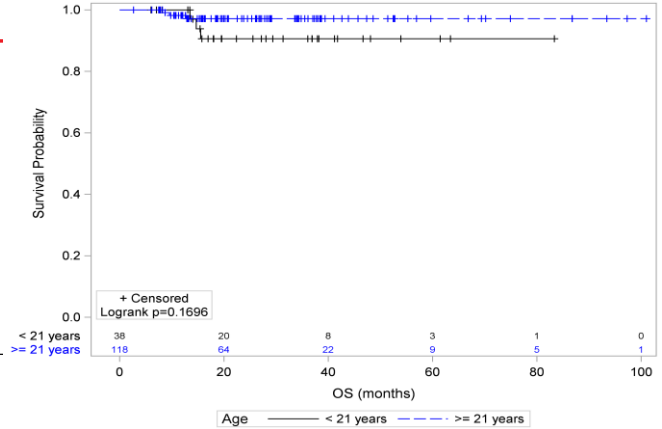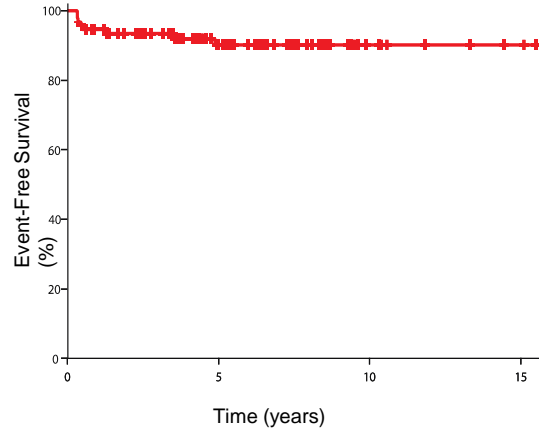Figure 3. OS curves of the three main chemotherapy subgroups.

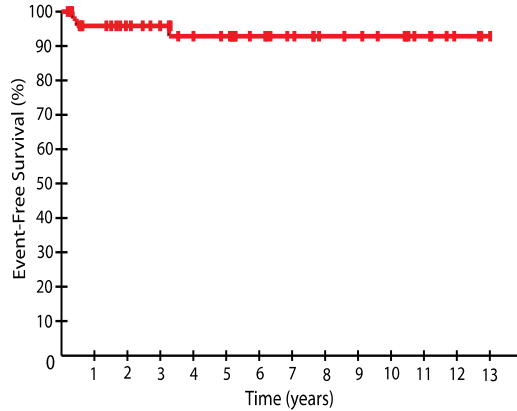
Figure 4. PFS curves of the three main chemotherapy subgroups.

Zinzani et al. Haematologica. 2002; 87:1258-1264

DA-EPOCH-R in PMBCL

Dunleavy et al. NEJM 2013   *Melani et al. Haematologica 2018*   *Roth-Guiliano et al. Br J Haem 2019*

LYSA Study – 313 patients with PMBCL
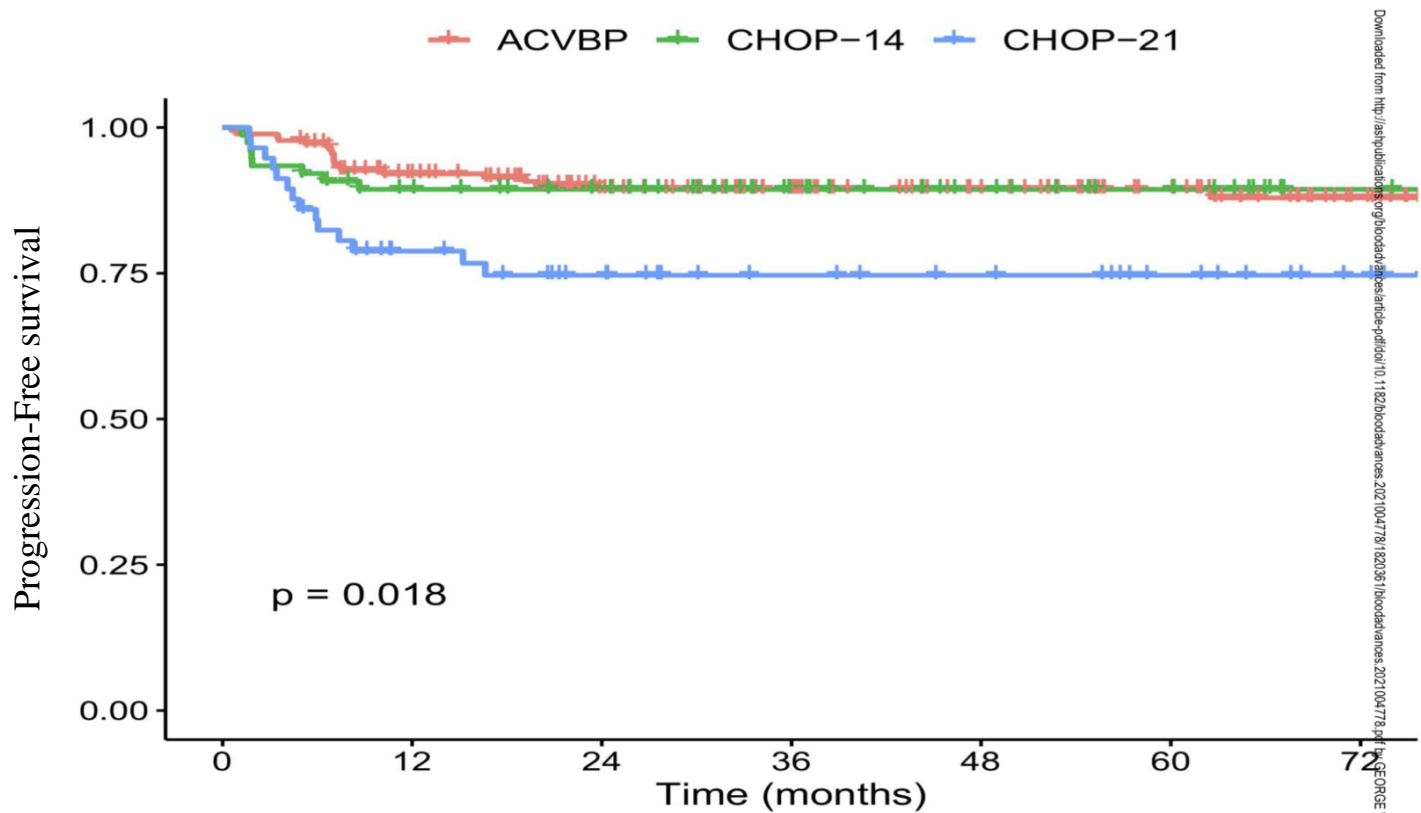
313 patients
ASCT in 25.6%(R-ACVBP) and 31.6% (R-CHOP-14)
Mediastinal RT: 5.4%

p = 0.018

ACVBP   CHOP-14   CHOP-21

Progression-Free survival

Time (months)

Camus et al. Blood Advances 2021

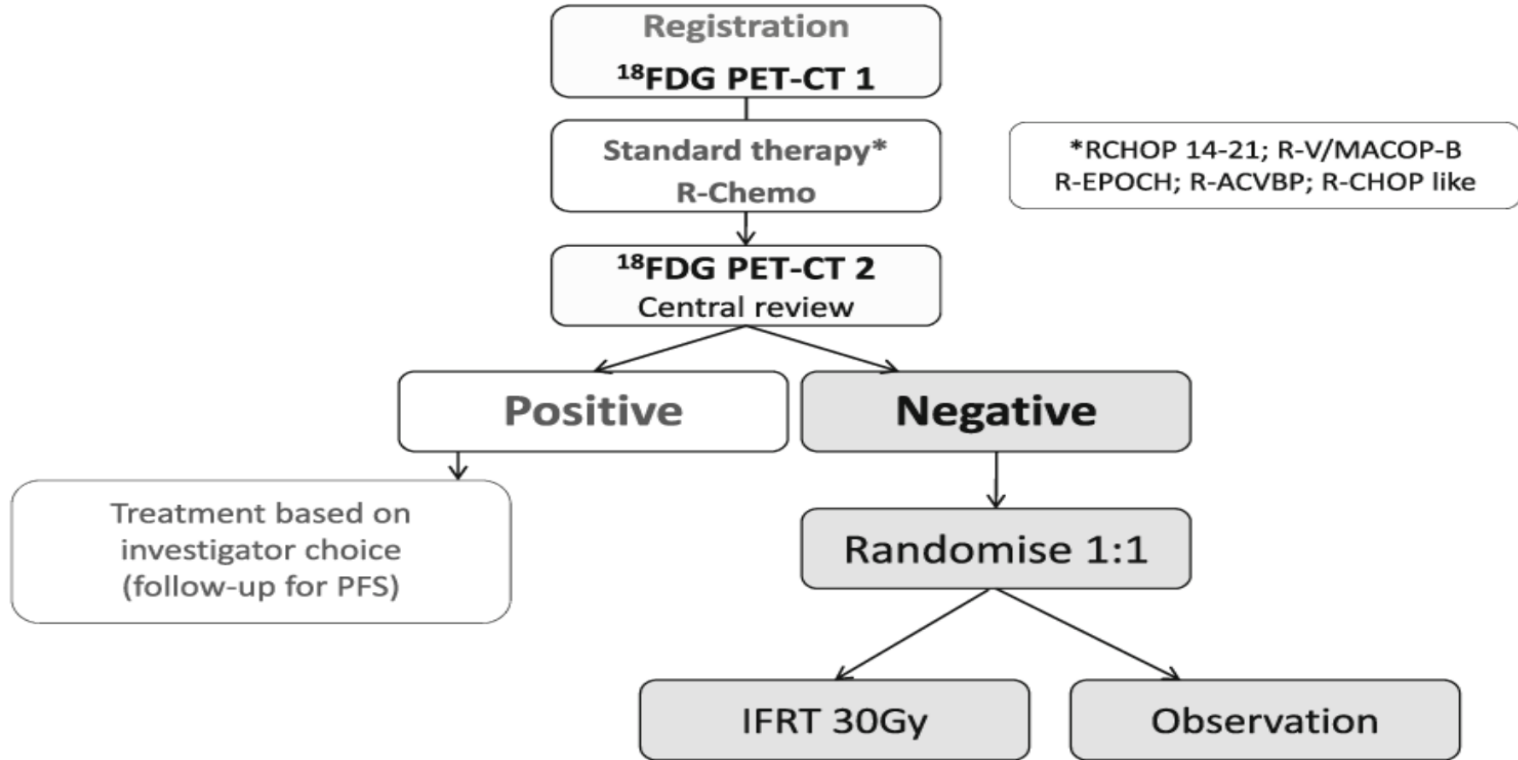# PET Adapted Approach Using CHOP-Based Therapy

159 patients
94% - R-CHOP
44% - RT

R-CHOP - 5yr
PFS: 78%
DS4: 72%
received RT

Hayden et al, Blood 2020

IELSG 37 study algorithm

Registration
18FDG PET-CT 1

Standard therapy*
R-Chemo

*RCHOP 14-21; R-V/MACOP-B
R-EPOCH; R-ACVBP; R-CHOP like

18FDG PET-CT 2
Central review

Positive

Negative

Treatment based on investigator choice (follow-up for PFS)

Randomise 1:1

IFRT 30Gy

Observation

Davies et al, Haematological Oncology (Proc Lugano meeting) 2023   Martelli et al. JCO 2014 (IELSG 26)

IELSG 37 study algorithm

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Central review

545 enrolled
530 assessed

Positive

Negative — 286 (50.6%)

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Zucca et al. ASCO 2023

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IELSG – 37 : Preliminary Analysis

IELSG37 preliminary analysis: Complete metabolic response and risk factor rates by induction regimens in PMBCL

Regimen	Median age years (IQR)	Age >40 years	CR rate (DS1-3)	DS5	ECOG PS>1	Bulk >10 cm	High LDH	Extranodal infiltration	R-IPI very good risk	Median MTV ml (IQR)
N analyzed	*545*	*545*	*526*	*526*	*533*	*536*	*499*	*534*	*495*	*486*
R-CHOP21	32 (27-45)	34%	53%	25%	7%	65%	75%	24%	21%	316 (186-482)
R-CHOP14	37 (30-47)	45%	56%	7%	8%	78%	67%	36%	30%	360 (224-593)
R-V/MACOP-B	34 (28-45)	38%	54%	10%	12%	70%	69%	36%	24%	320 (202-498)
DA-EPOCH-R	33.5 (26-39)	25%	65%	6%	10%	68%	70%	28%	22%	333 (204-521)
Other, intensive	33 (29-38)	22%	60%	7%	19%	64%	78%	33%	22%	280 (172-443)
P-value (Fisher exact)	*0.220*	***0.006***	*0.546*	***0.001***	*0.231*	*0.150*	*0.568*	*0.262*	*0.488*	*0.521*

Martelli et al, Haematological Oncology (Proc Lugano meeting) 2021

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Martelli et al, Haematological Oncology (Proc Lugano meeting) 2021

Improved Survival Outcomes for Intensive versus Standard Chemoimmunotherapy in Primary Mediastinal B-cell Lymphoma: A Meta-Analysis of 4068 Patients

Michael R. Cook [1], Lacey Williams[1], C. Scott Dorris[2], Yutong Luo[3], Kepher Makambi[3], Paul Kolm[3], Kieron Dunleavy[1]
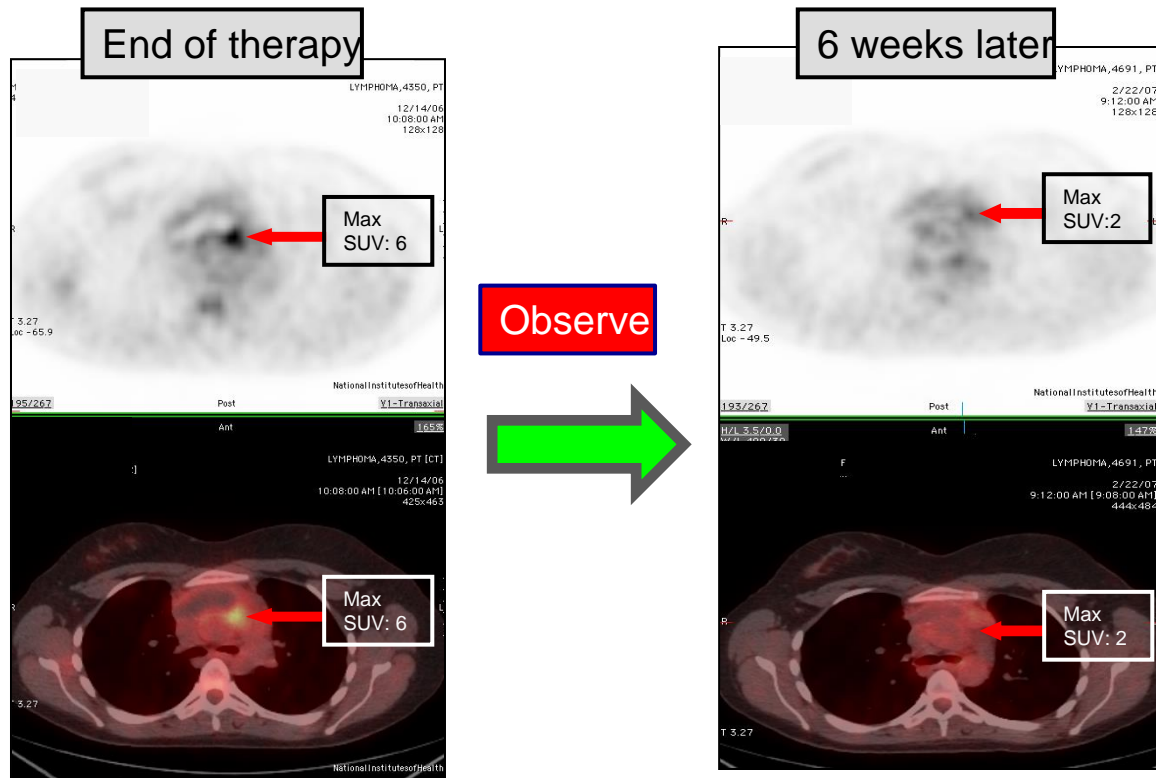
1. Lombardi Comprehensive Cancer Center, MedStar Georgetown University Hospital, Washington D.C
2. Dahlgren Memorial Library, Georgetown University; 3. Department of Biostatistics, Bioinformatics and Biomathematics, Georgetown University

Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER
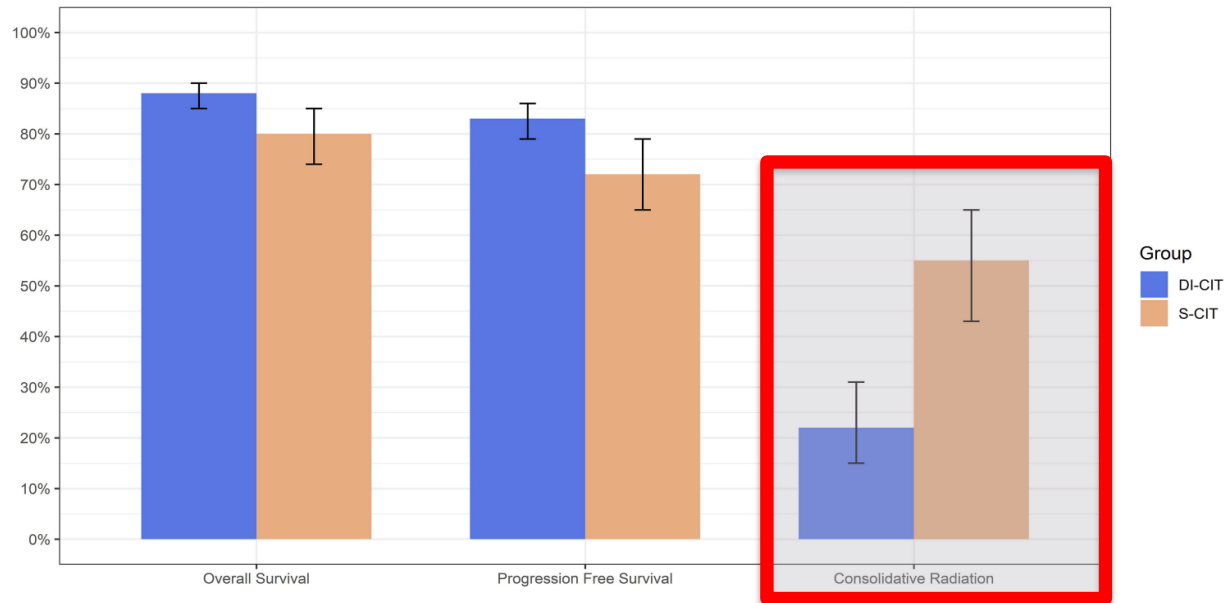
S-CIT: CHOP-21 or CHOP-21

DI-CIT: Inc. freq, dose and no. of syst. agents

Group
DI-CIT
S-CIT

Overall Survival   Progression Free Survival   Consolidative Radiation

Cook et al. Haematologica 2023

Cook et al. Haematologica 2023

EOT-PET IMAGING IN PMBCL

EOT-PET IMAGING IN PMBCL

Lymphoma Status	Deauville Score				
(N = 83 total with EOT FDG-PET)	Negative (57/83, 69%)			Positive (26/83, 31%)	
	1 (30%)	2 (23%)	3 (16%)	4 (22%)	5 (10%)
No treatment failure- no. patients	25*	18	13	17*	4
Treatment failure- no. patients	0	1	0	1	4

Melani et al. Haematologica 2018

EVOLUTION OF PET FINDINGS IN PMBCL
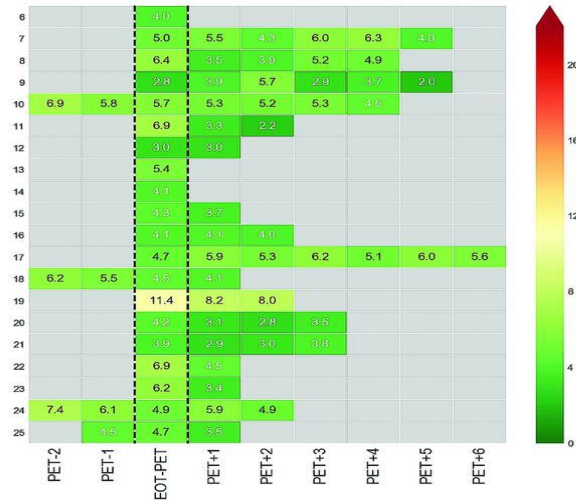
Melani et al. Haematologica 2018
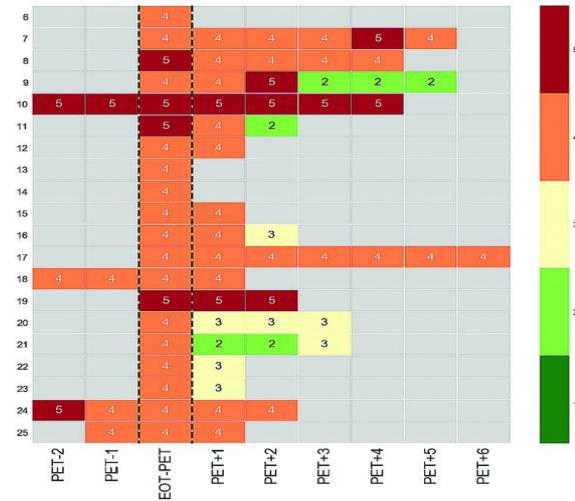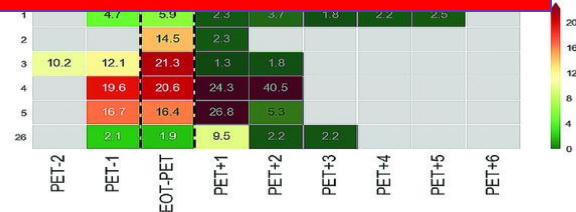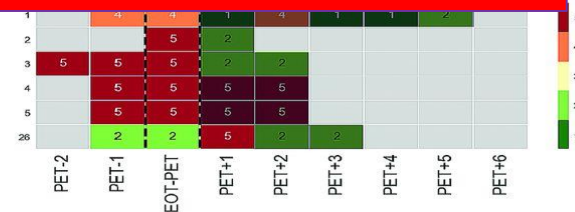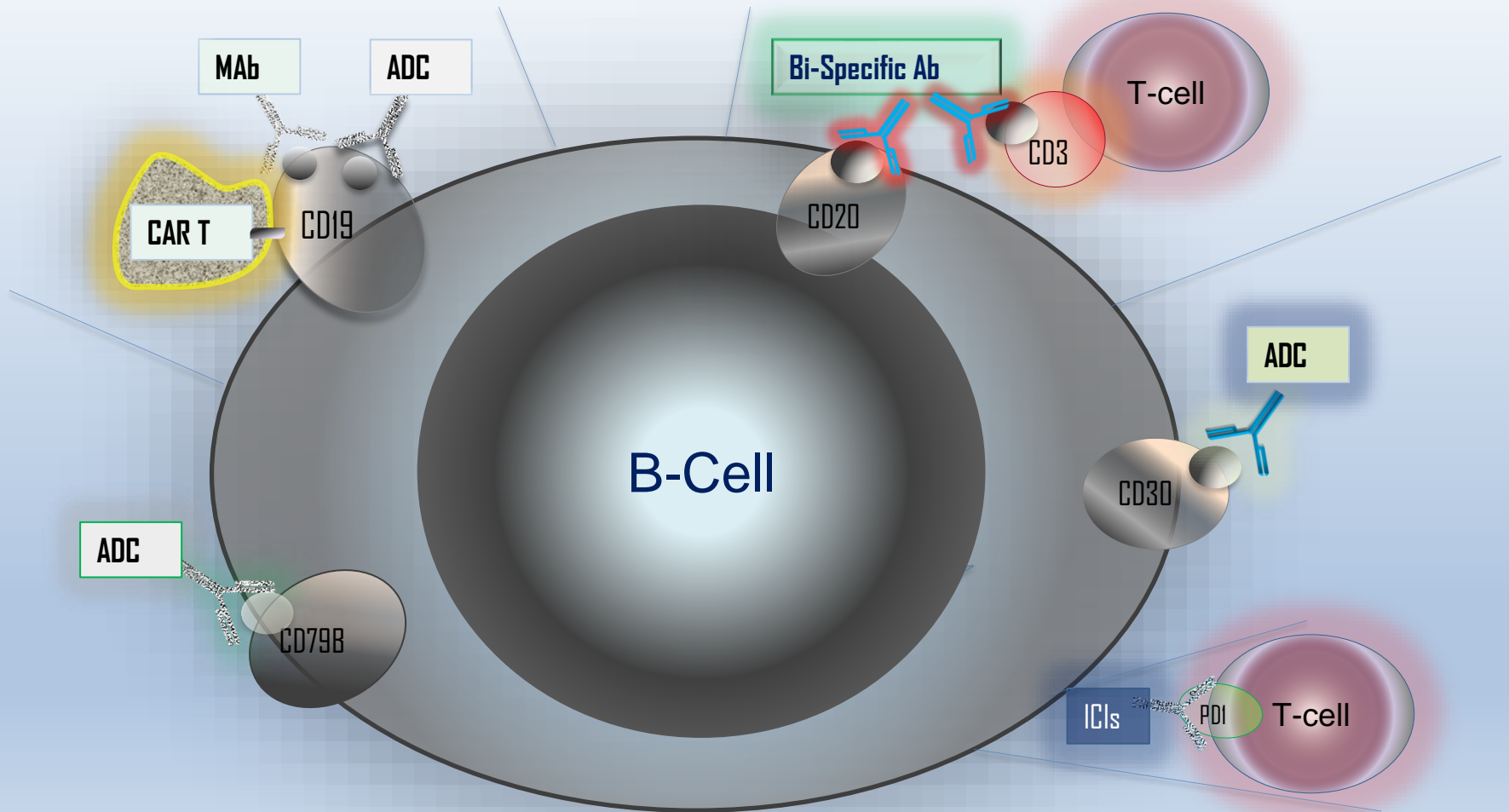
RATIONALE FOR CHECKPOINT INHIBITION IN PMBCL

- **Biologic features:**
  - 9p24.1 alterations – PD-L1/2 up-regulation
  - Microenviroment similar to Hodgkin lymphoma

- **Clinical Experience:**
  - Pembrolizumab: monoclonal anti-PD-1 Ab
  - Studied in adults with relapsed/refractory PMBCL in phase I/II trials
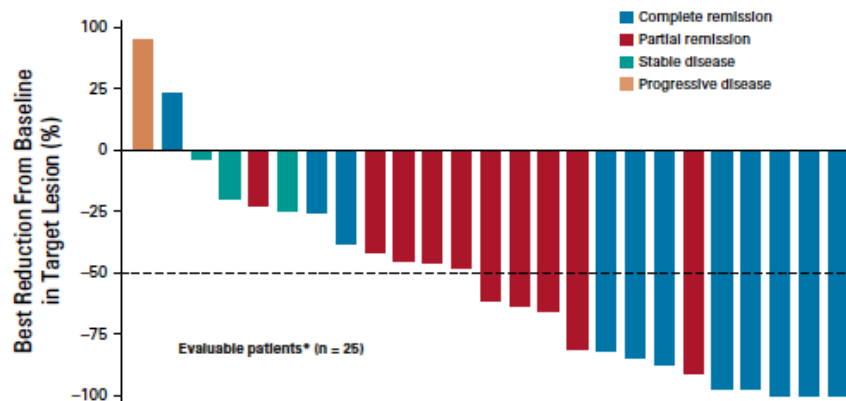 - Association between PD-L1 expression and outcome

Pembrolizumab

Phase Ib n=21

Phase II n=53

ORR 48%, CR 33% n=21

ORR 45%, CR 13%
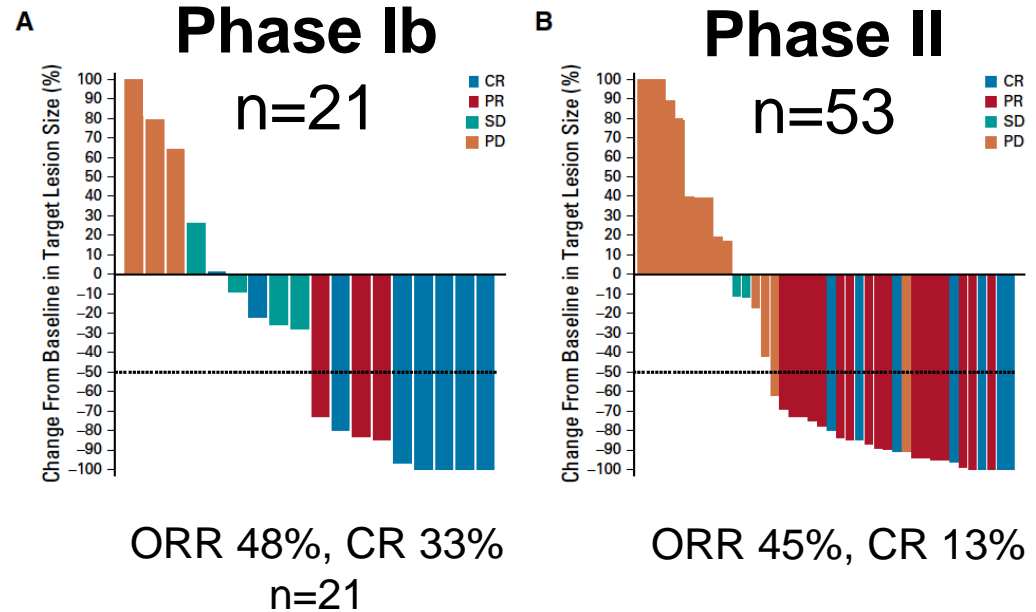
Zinzani et al, Blood, 2017
Armande et al, JCO 2019

NIVOLUMAB IN PMBCL

Nivolumab Combined With Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma: Efficacy and Safety From the Phase II CheckMate 436 Study
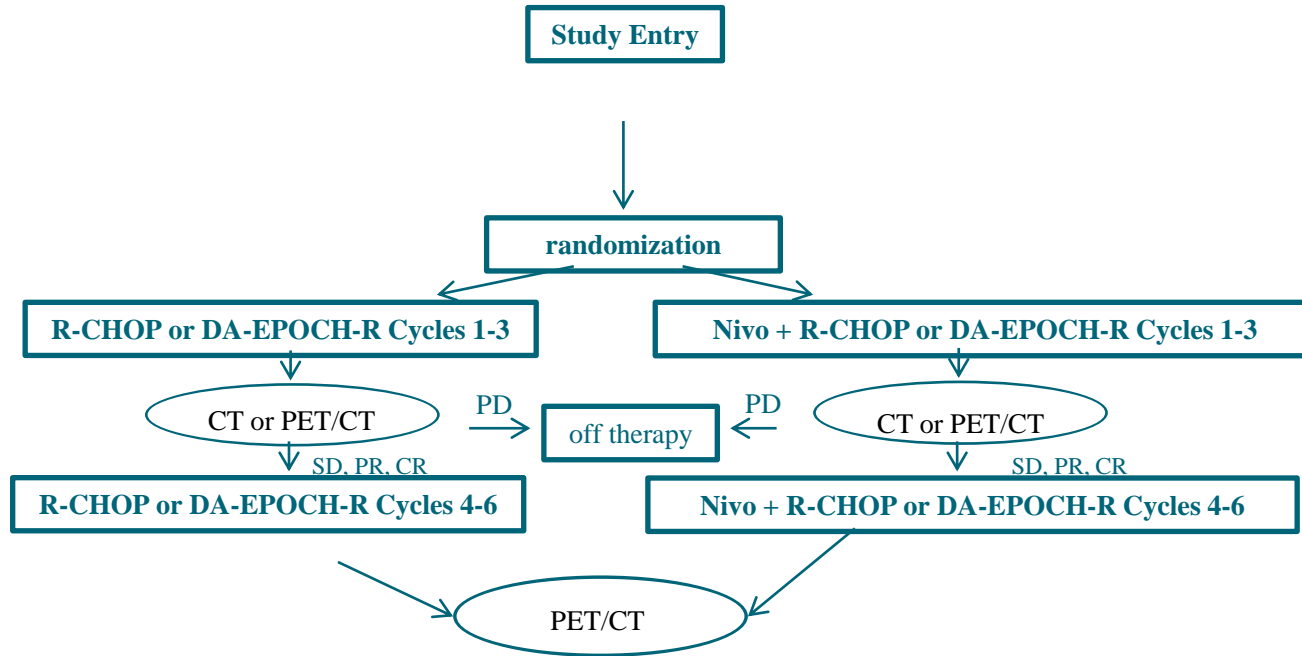
- Prior ASCT or 2 or more LOT
- 30 patients accrued

ORR: 22/30 (73%)
CR: 11/30 (37%)

Zinzani et al, JCO 2019
Zinzani et al. Blood 2017

ANHL 1931 - Schema

Study Entry

↓

randomization

R-CHOP or DA-EPOCH-R Cycles 1-3   Nivo + R-CHOP or DA-EPOCH-R Cycles 1-3

CT or PET/CT   PD → off therapy ← PD   CT or PET/CT

SD, PR, CR   SD, PR, CR

R-CHOP or DA-EPOCH-R Cycles 4-6   Nivo + R-CHOP or DA-EPOCH-R Cycles 4-6

PET/CT

100+/186

Lisa Roth PI

NCI – Use of CD19-CAR.28z T cells for Large cell Lymphoma

Patient	Lymphoma type	Number of prior therapies	Infused CAR+ T cells/kg	Response (duration in months)
1	PMBCL	4	5×10^6	CR (35+)
2	PMBCL	3	2.5×10^6	NE, death
3	DLBCL, NOS	5	2.5×10^6	CR (25+)
4	PMBCL	10	2.5×10^6	CR (21+)
5	PMBCL	3	2.5×10^6	SD (1)
6	CLL→ DLBCL	13	1×10^6	PR (1)
7	DLBCL, NOS	3	1×10^6	NE
8	DLBCL, NOS	2	1×10^6	CR (6)
9	DLBCL, NOS	3	1×10^6	CR (17+)

DEFINED LYMPHODEPLETING REGIMEN WITH IL-2:
CY 60 mg/kg for 2 doses and FLU 25 mg/m^2 for 5 doses

Kochenderfer et al, JCO 2015

NCI – Use of CD19-CAR.28z T cells for Large cell Lymphoma

Patient	Lymphoma type	Number of prior therapies	Infused CAR+ T cells/kg	Response (duration in months)
1	PMBCL	4	5×10^6	CR (35+)
2	PMBCL	3	2.5×10^6	NE, death
3	DLBCL, NOS	5	2.5×10^6	CR (25+)
4	PMBCL	10	2.5×10^6	CR (21+)
5	PMBCL	3	2.5×10^6	SD (1)
6	CLL→ DLBCL	13	1×10^6	PR (1)
7	DLBCL, NOS	3	1×10^6	NE
8	DLBCL, NOS	2	1×10^6	CR (6)
9	DLBCL, NOS	3	1×10^6	CR (17+)

DEFINED LYMPHODEPLETING REGIMEN WITH IL-2:
CY 60 mg/kg for 2 doses and FLU 25 mg/m^2 for 5 doses

Kochenderfer et al, JCO 2015

NCI – Use of CD19-CAR.28z T cells for Large cell Lymphoma

Patient	Lymphoma type	Number of prior therapies	Infused CAR+ T cells/kg	Response (duration in months)
1	PMBCL			
2				

- 33 patients
- Median 3 prior treatments
- Auto: 1/3; RT 2/3
- PFS @ 24 mos 64%
- No difference with prior ICI

RESEARCH LETTER — blood advances

TO THE EDITOR:

Real-world outcomes of axicabtagene ciloleucel in adult patients with primary mediastinal B-cell lymphoma

Jennifer L. Crombie,[1,*] Loretta J. Nastoupil,[2,*] Robert Redd,[1] Kevin Tang,[3] Geoffrey Shouse,[4] Alex F. Herrera,[4] Victor A. Chow,[5] Mazyar Shadman,[5] Omar Castaneda Puglianini,[6] Anna Saucier,[1] Caron A. Jacobson,[1] Philippe Armand,[1,†] and Gary Simmons[6,†]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]University of Texas MD Anderson Cancer Center, Houston, TX; [3]Baylor School of Medicine, Houston, TX; [4]City of Hope Cancer Center, Duarte, CA; [5]University of Washington/Fred Hutchinson Cancer Research Center/Seattle Cancer Alliance, Seattle, WA; and [6]Virginia Commonwealth University Medical Center, Richmond, VA

1. Neelapu et al. NEJM. 2018 2. Schuster et al. NEJM. 2019; 3. Abramson et al. Lancet. 2020

DEFINED LYM
CY 60 mg/kg fo

Kochenderfer et al, JCO 2015

Crombie et al. Blood Advances 2021

PMBCL: Emerging Therapeutic Questions

New diagnosis
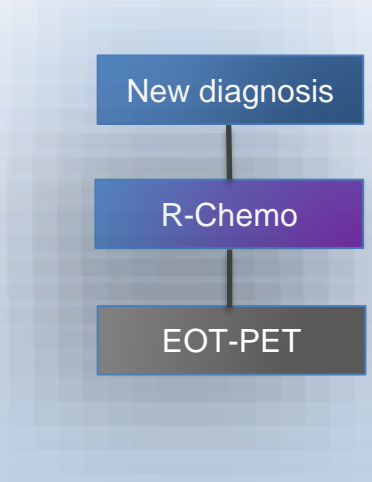
R-Chemo

EOT-PET

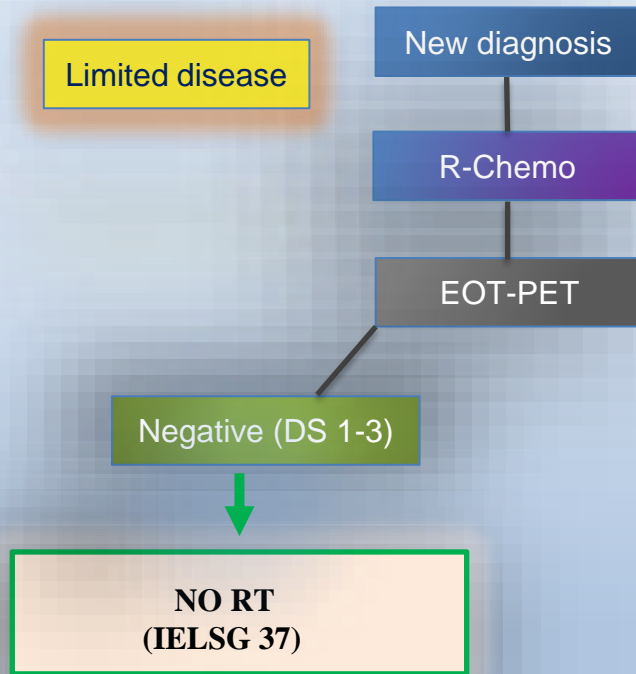# PMBCL: Emerging Therapeutic Questions
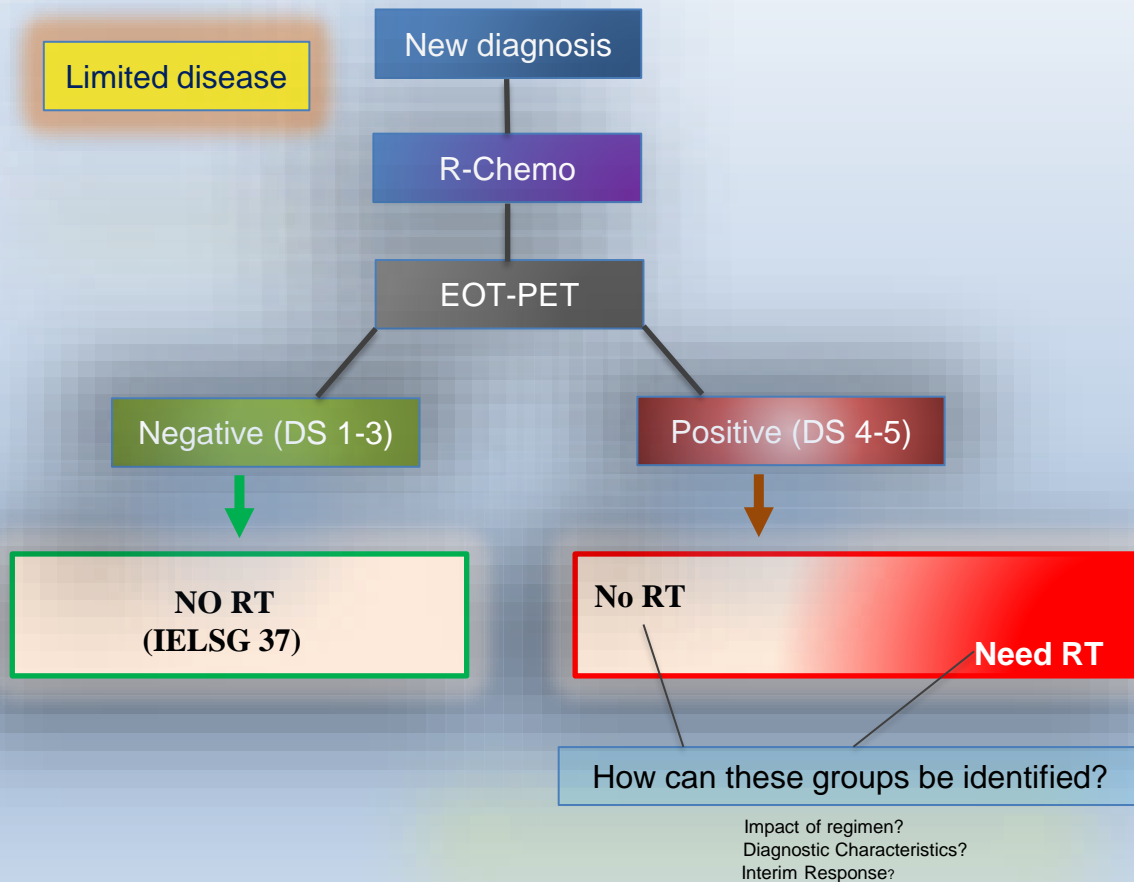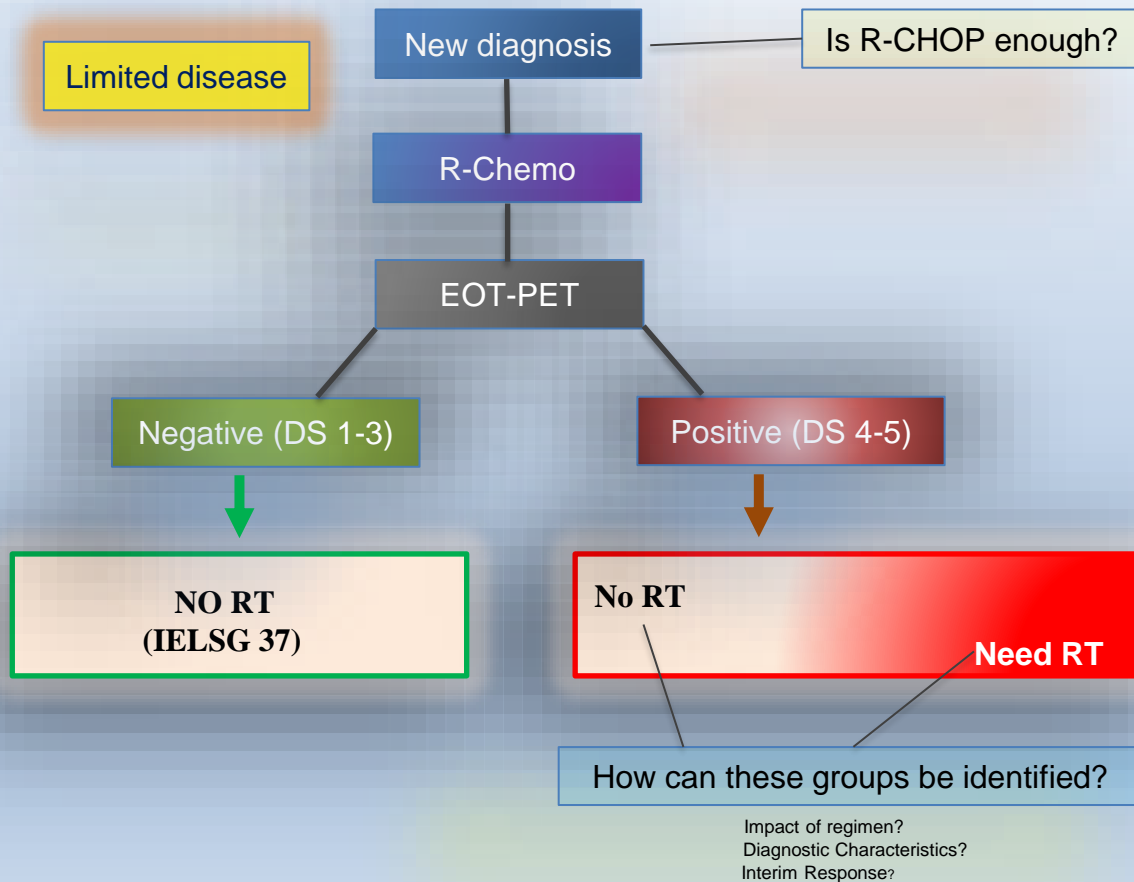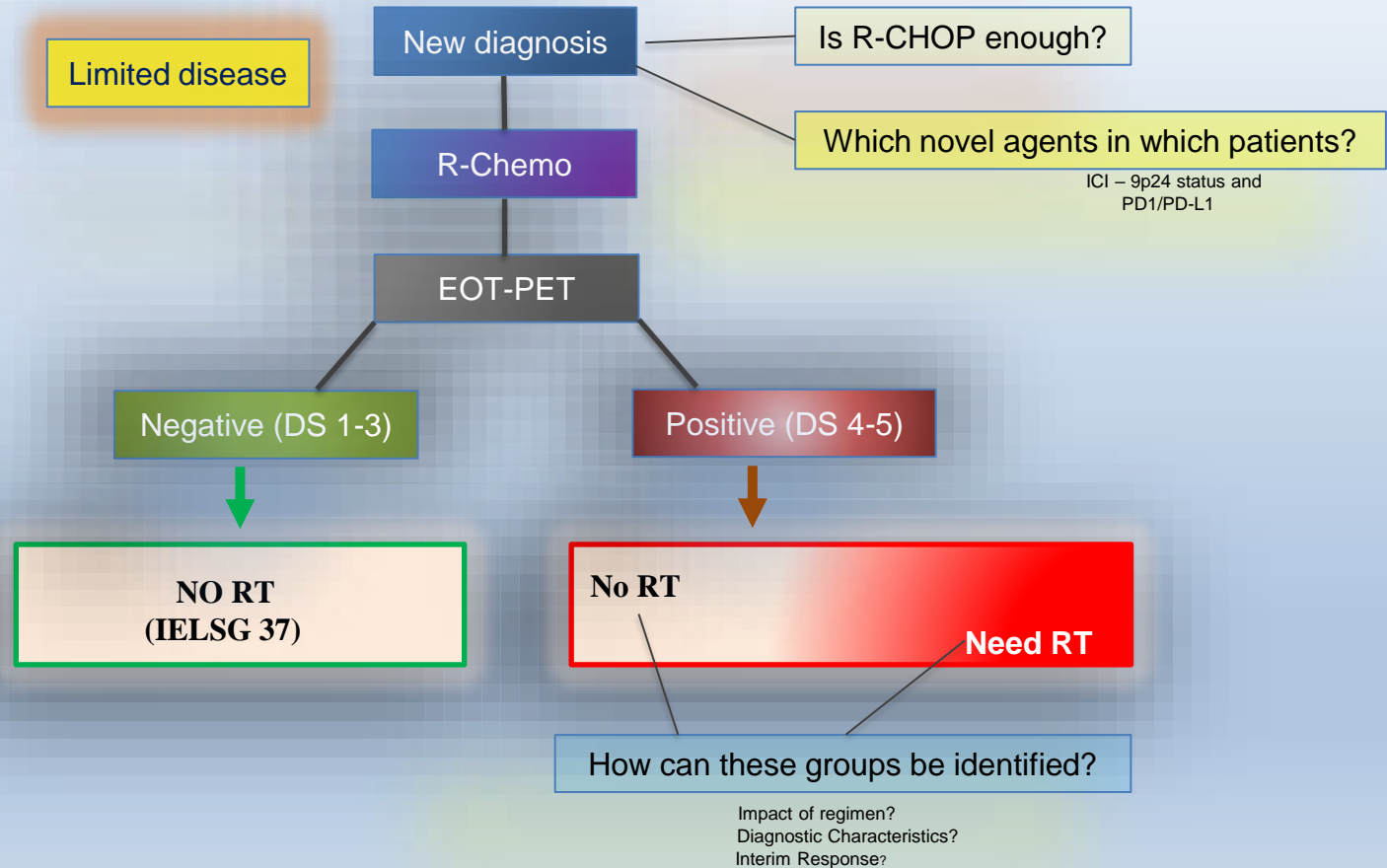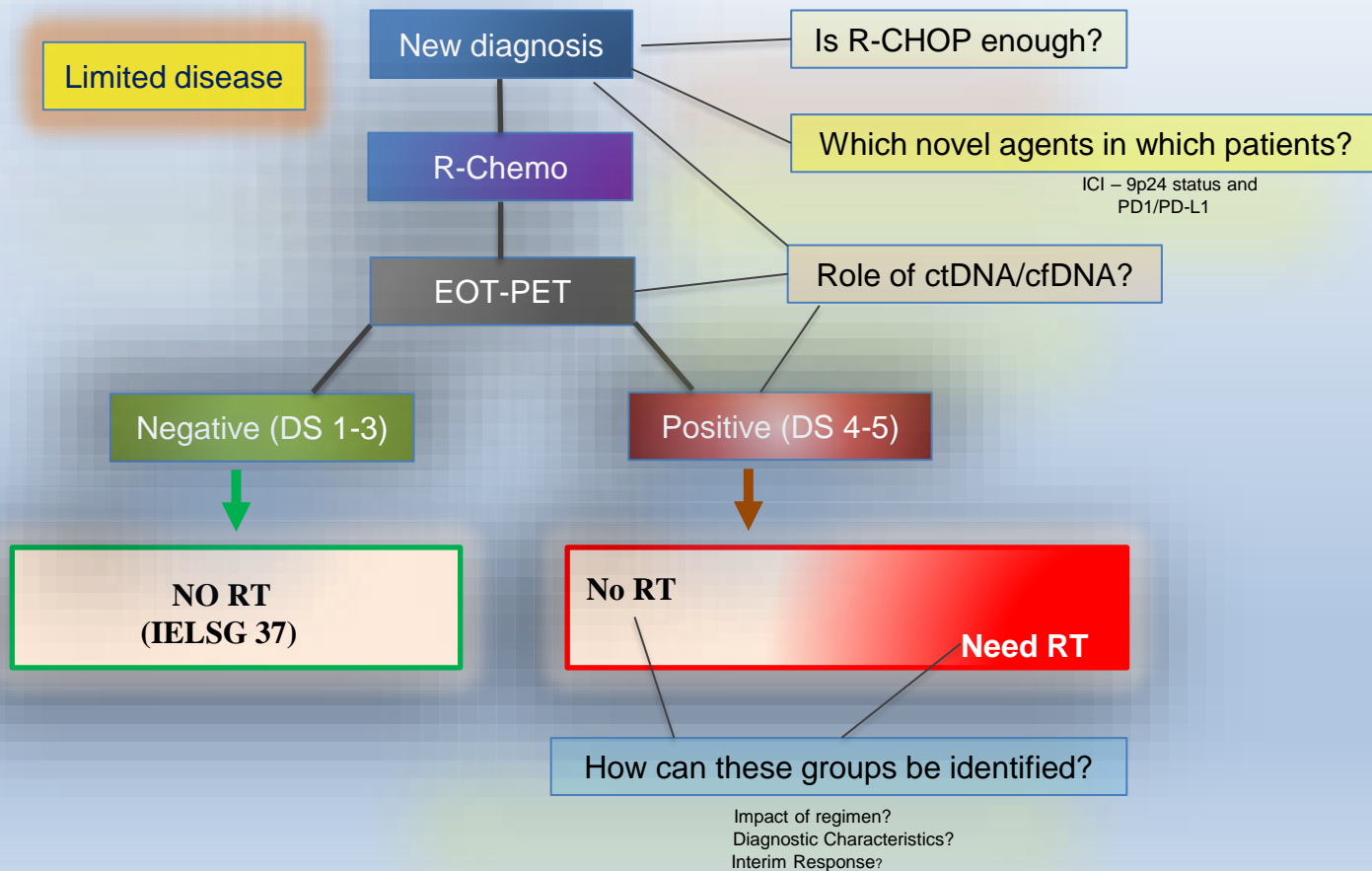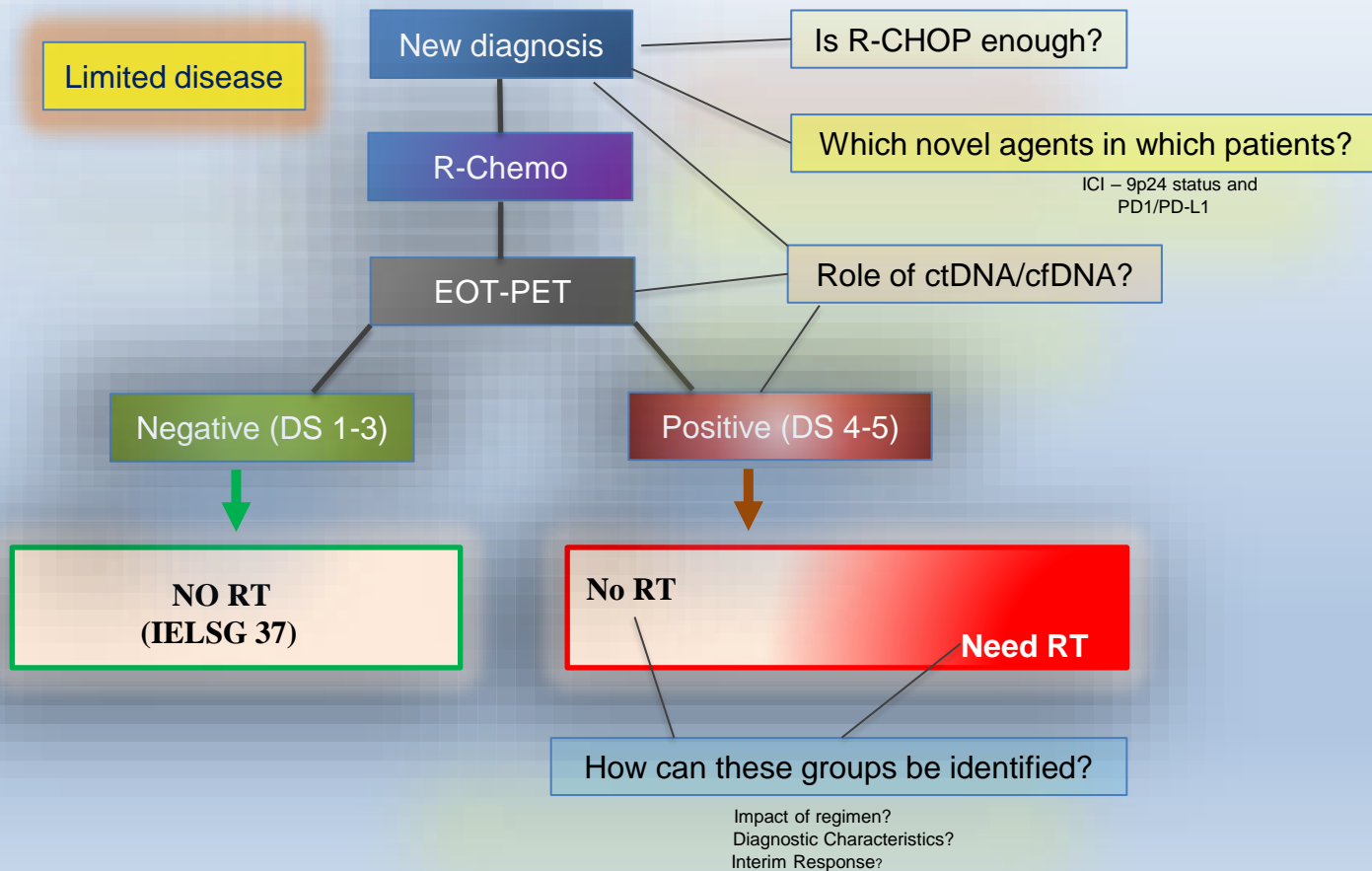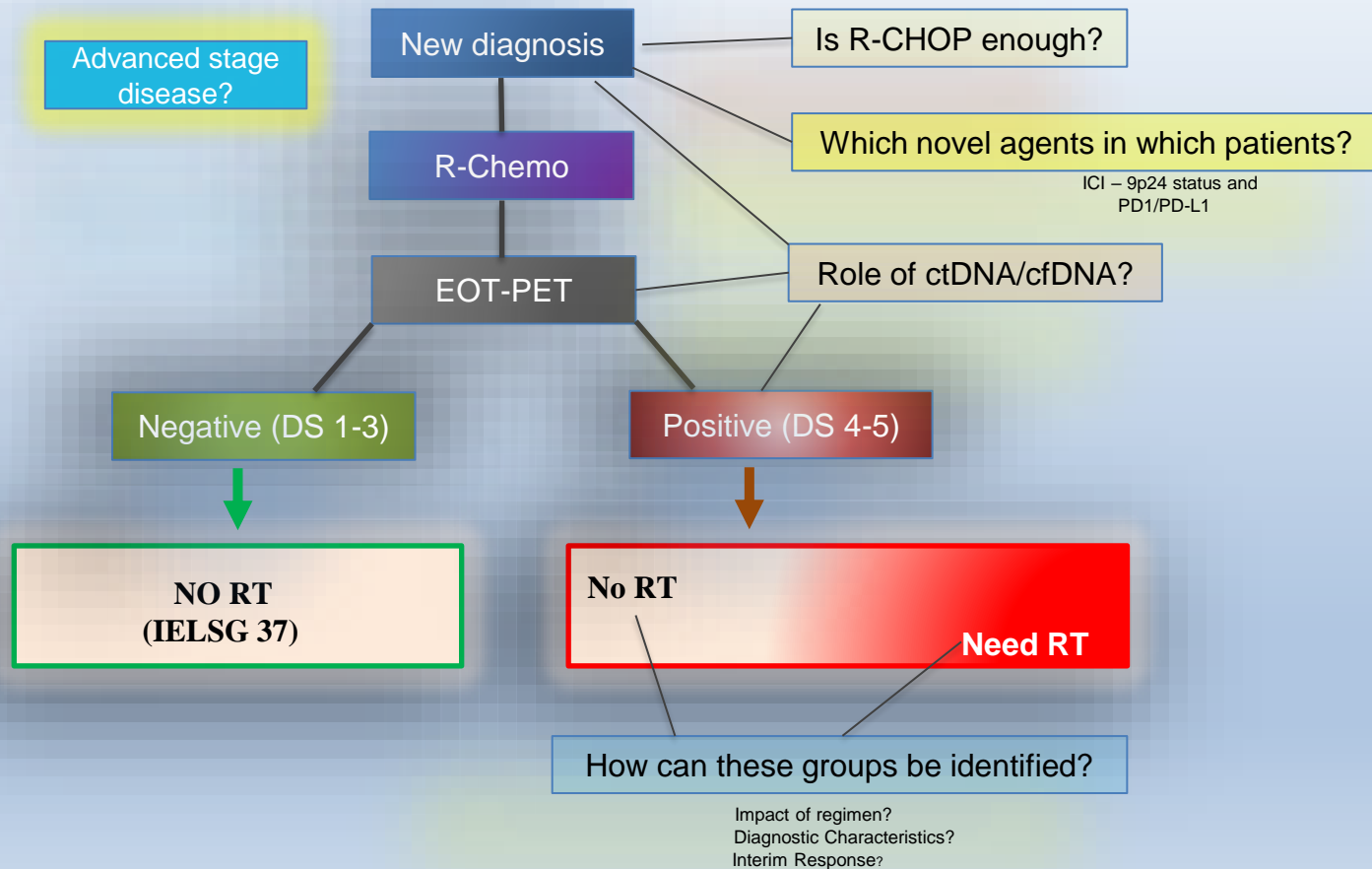
Limited disease

New diagnosis

R-Chemo

EOT-PET

PMBCL: Emerging Therapeutic Questions

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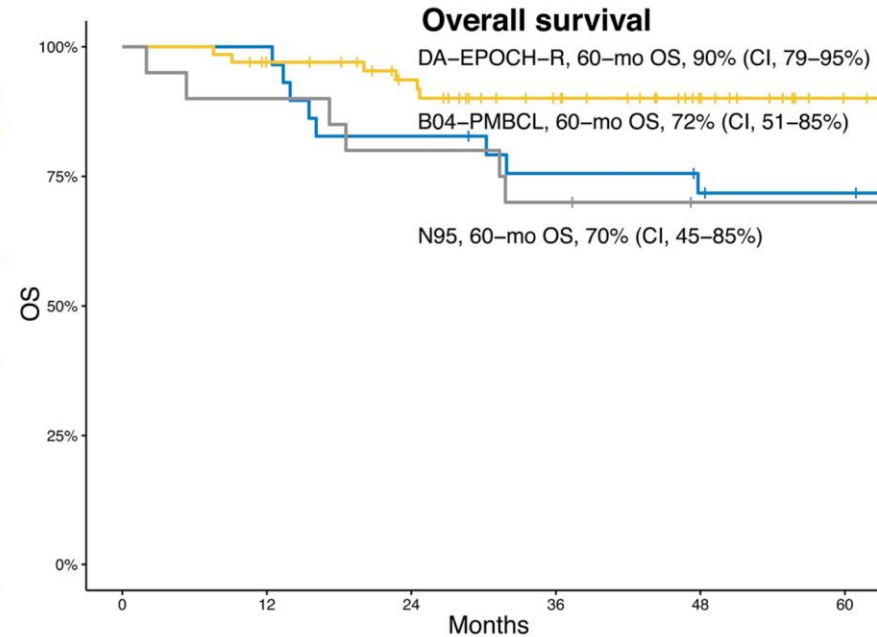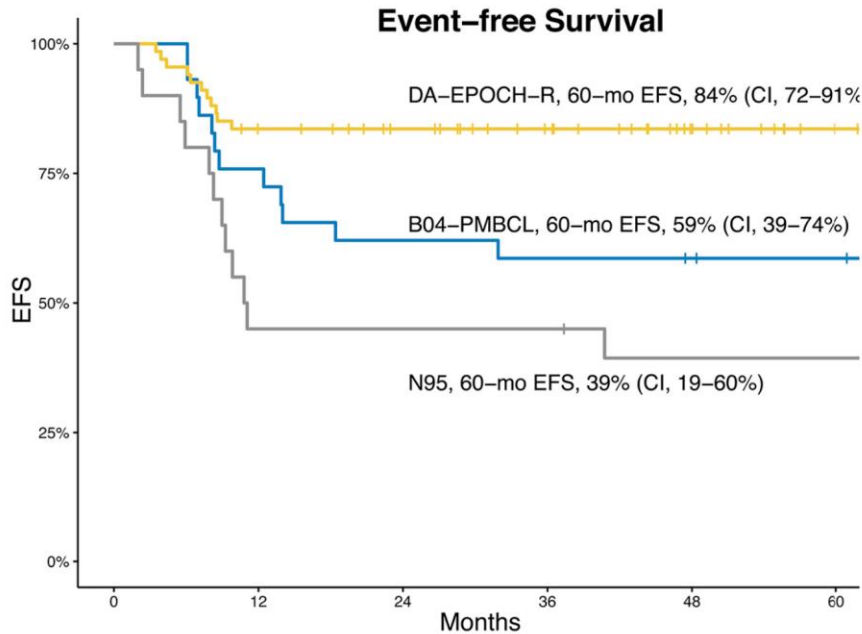
PMBCL: Emerging Therapeutic Questions

New diagnosis

Is R-CHOP enough?

Which novel agents in which patients?

ICI – 9p24 status and
PD1/PD-L1

Limited disease

R-Chemo

EOT-PET

Negative (DS 1-3)

Positive (DS 4-5)

NO RT
(IELSG 37)

No RT

Need RT

How can these groups be identified?

Impact of regimen?
Diagnostic Characteristics?
Interim Response?

PMBCL: Emerging Therapeutic Questions

PMBCL: Emerging Therapeutic Questions

PMBCL: Conclusions

- WHAT IS OPTIMAL REGIMEN FOR PMBCL?

    - ARE DOSE-INTENSIVE APPROACHES SUPERIOR?
    - OBVIATING NEED FOR RT

- WHICH EOT + PATIENTS NEED RT?

    - DOES THIS DEPEND ON UP-FRONT REGIMEN?
    - NEED FOR ALTERNATIVE EOT RESPONSE ASSESSMENT TOOLS

- NOVEL AGENTS

    - ROLE OF ANTI-CD19 CAR-T/BITES/OTHER NOVEL AGENTS
    - ROLE OF IMMUNE CHECKPOINT INHIBITORS
        - IN UPFRONT TREATMENT? (ONGOING US COOPERATIVE GROUP STUDY)
        - FOR SELECT BIOLOGICAL SUBTYPES (9P24/PD-L1 STATUS)

Questions

Knorr et al. Haematologica 2021

Disclosures of NAME SURNAME

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other