

Treatment of Newly Diagnosed Diffuse Large B-cell Lymphoma

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Disclosures

- ADC Therapeutics - Consultant

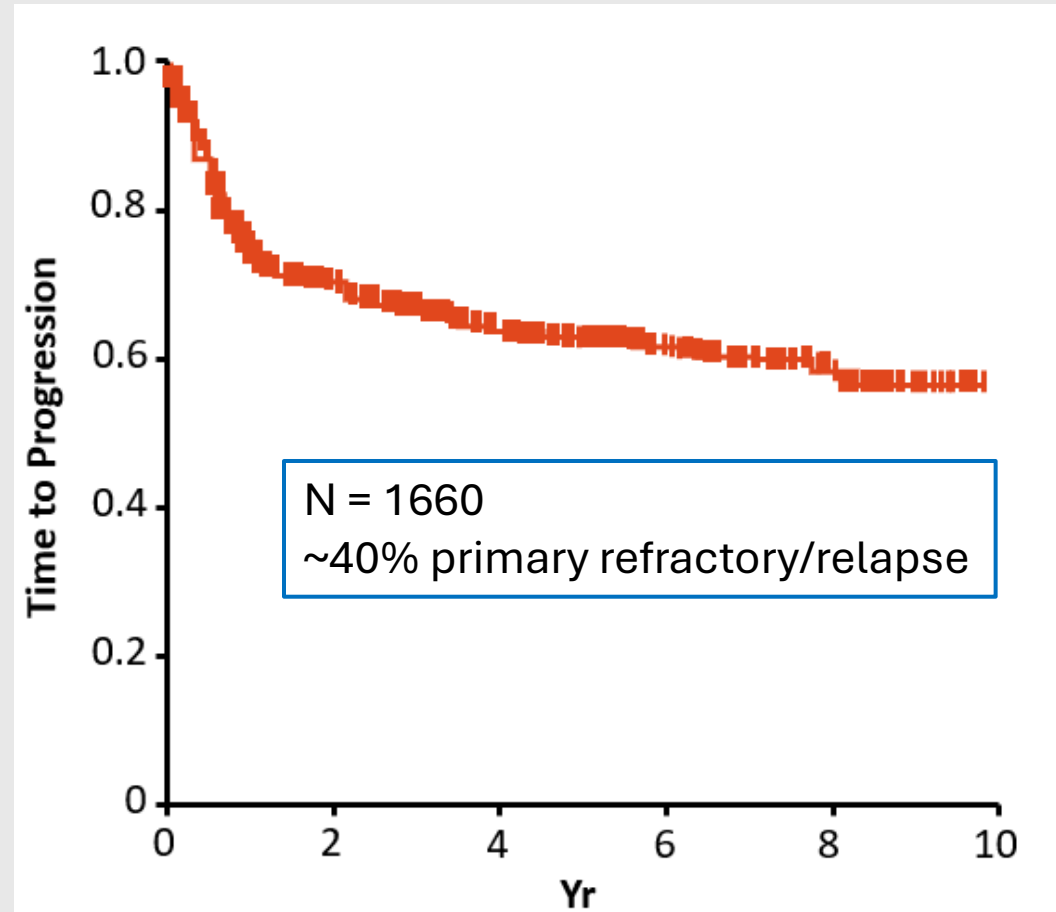
Demographic/Clinical Features at Diagnosis

- Median age: 65-74 yrs
- Gender: ~55% male
- Stage III or IV: 60-70%
- Constitutional symptoms: ~40%
- Elevated LDH: ~50-75%
- Extranodal involvement: 30-50%
- Bone marrow involvement: 10-30%
- CNS involvement: 5%

Background

- R-CHOP has long been the standard of care
 - GELA (Coiffier et al, NEJM 2002)
 - **Age 60-80**, Stage II-IV, n = 399
 - CHOP +/- rituximab x **8 cycles**
 - CR: 76% vs 63%, 2-yr OS: 70% vs 57%
 - MInT (Pfreundschuh et al, Lancet Oncol 2006)
 - **Age 18-60**, Stage II-IV/I bulky, n = 824
 - CHOP-like regimen +/- rituximab x **6 cycles**
 - 6 yr EFS: 74.3% vs 55.8% (p<0.0001)
- Many comparative regimens have failed to demonstrate improvement

Not all DLBCL pts receiving R-CHOP are the same...



Biological tumor heterogeneity leads to differences in clinical outcomes

Prognostic Considerations

Clinical

- IPI and its modifications
- Disease bulk and burden/metabolic tumor volume
- Metabolic tumor heterogeneity
- Time from diagnosis to treatment
- Performance status
- Degree of symptomatology

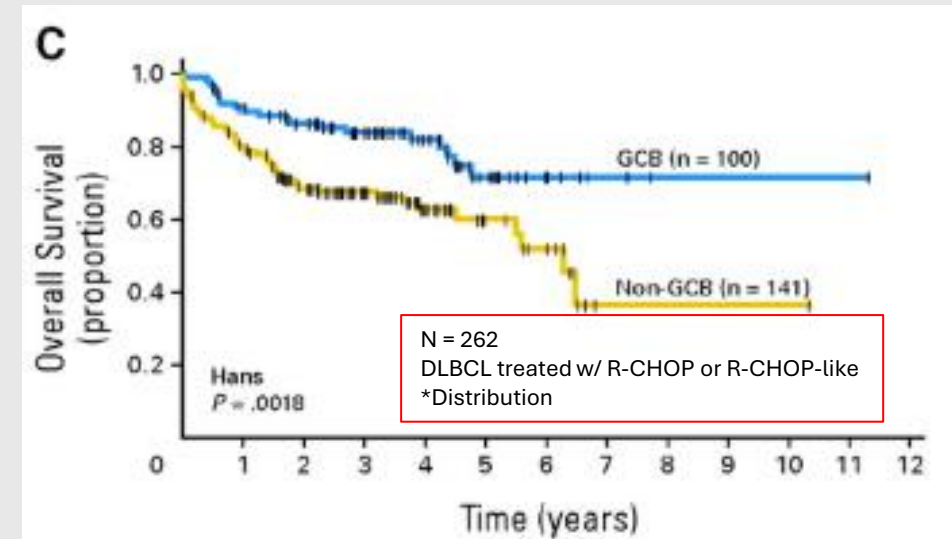
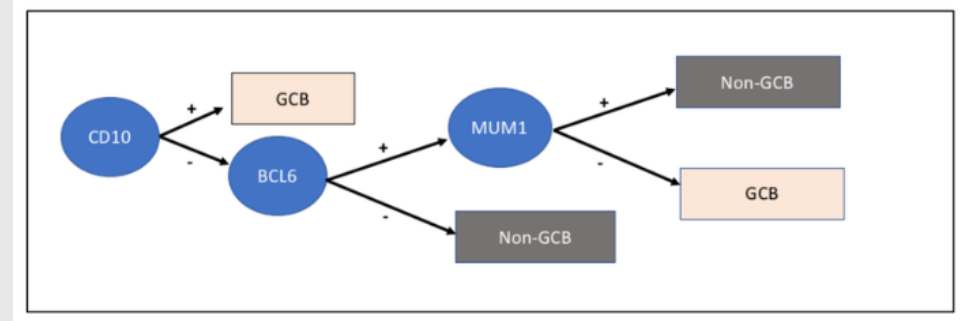
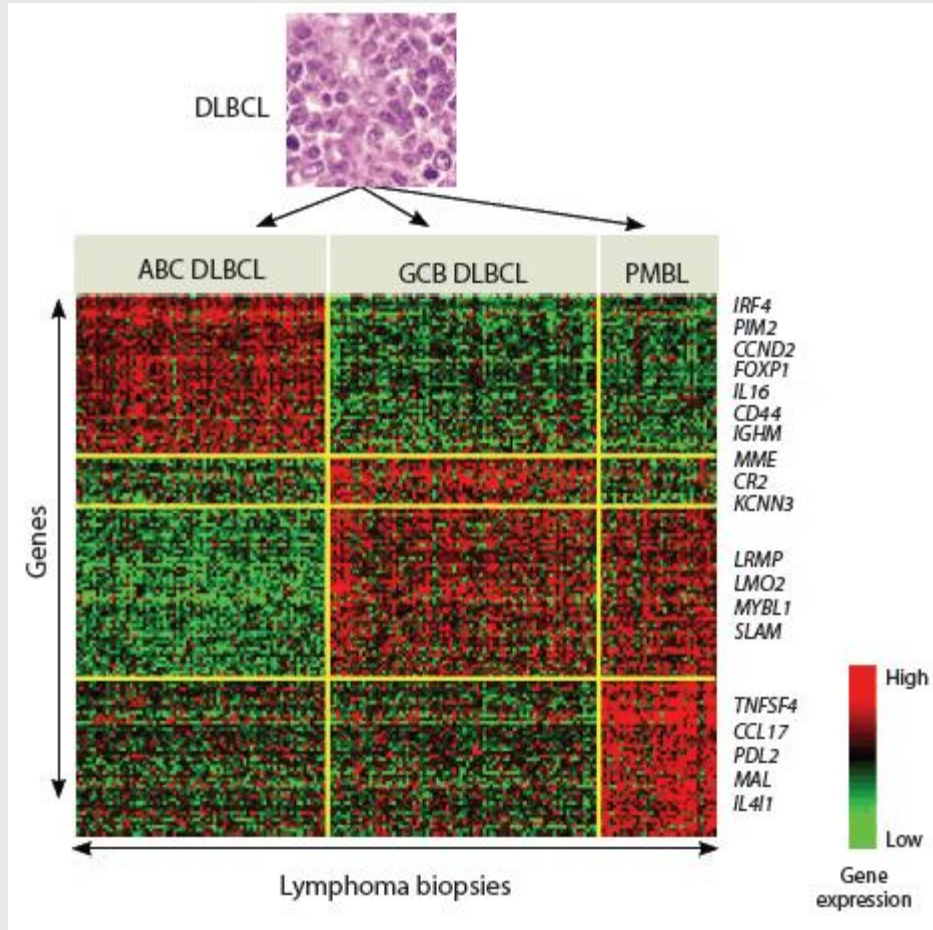
Response Based

- Interim PET/CT
- Post-treatment PET/CT
- MRD?

Molecular

- Cell of origin
- MYC/BCL2/BCL6 rearrangements
- Unique GE signatures
- MYC and BCL2 expression

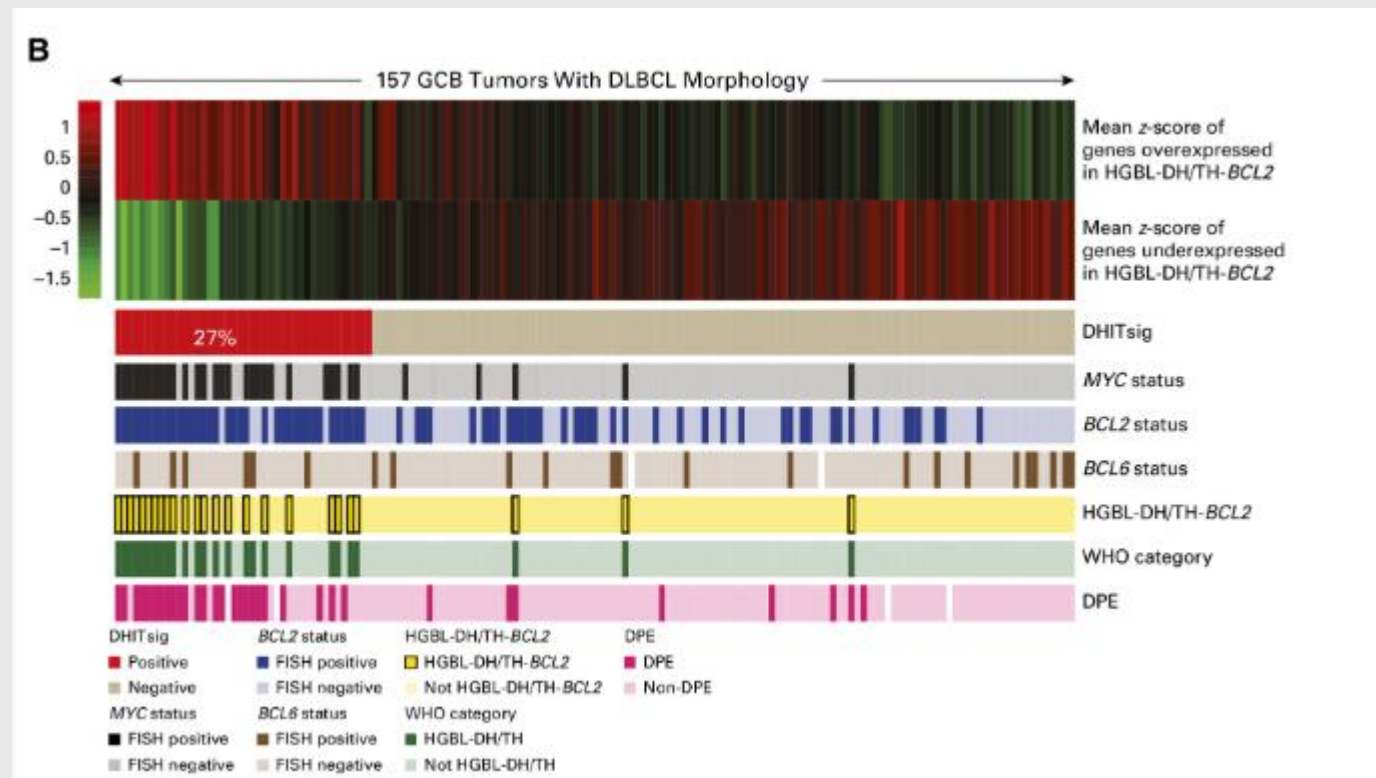
Cell of Origin in DLBCL



Alizadeh et al, Nature 2000
Dunleavy et al, Oncology 2014
Hans et al, Blood 2004
Meyer et al, JCO 2011

COO alone not enough...

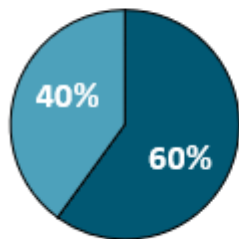
- Most DHL/THL are GCB COO!
- DH unique gene expression signature identifies distinct subgroup of GCB DLBCL



Geographical Variance in COO in DLBCL

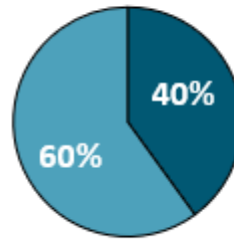
Region	ABC-Type, % (n/n)	Non-ABC-Type, % (n/n)
Asia/Pacific (China, Japan, South Korea, Taiwan)	60% (241/404)	40% (163/404)
Russia/Europe/Middle East (Belgium, Czech Republic, France, Ireland, Israel, Italy, Netherlands, Poland, Portugal, Russia, Spain, Switzerland, Turkey)	40% (441/1105)	60% (664/1105)
North America/Australia/New Zealand (United States, Canada, Australia, New Zealand)	37% (106/289)	63% (183/289)

Asia/Pacific



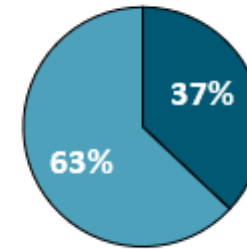
■ ABC ■ Non-ABC

Russia/Europe/Middle East



■ ABC ■ Non-ABC

**North America/Australia/
New Zealand**

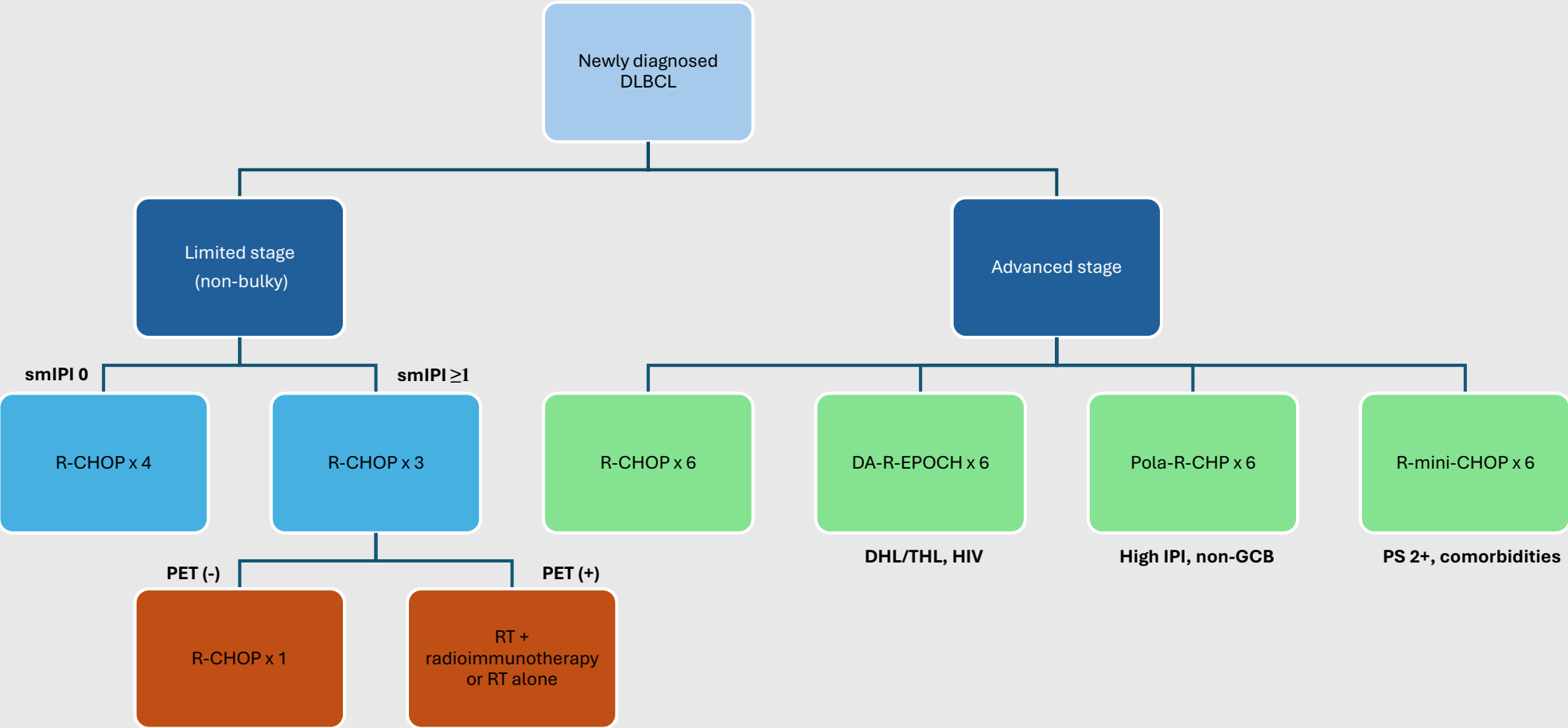


■ ABC ■ Non-ABC

Will not be covering...

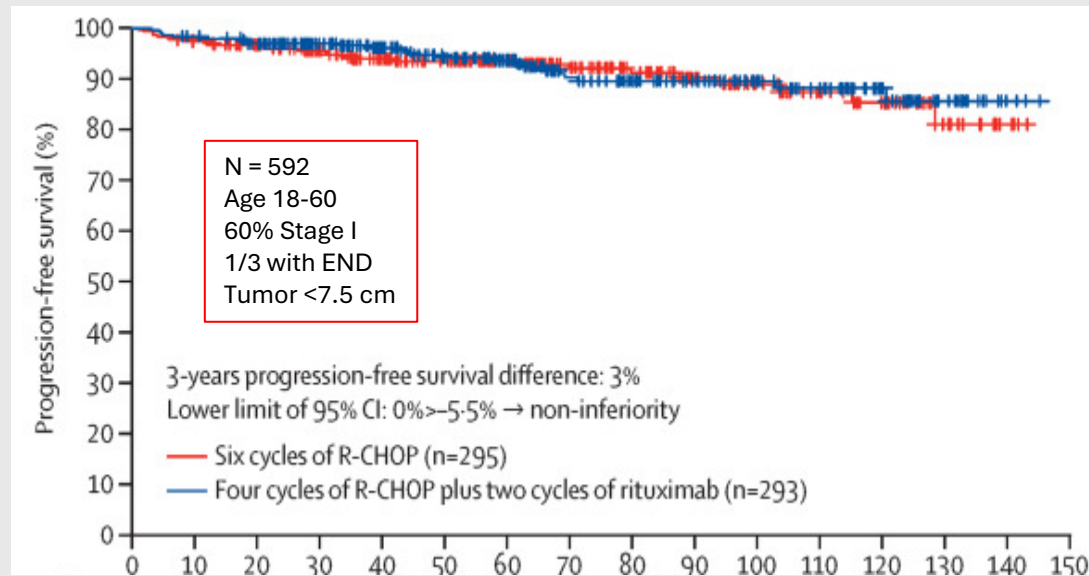
- CNS disease at presentation
- CNS prophylaxis
- Early-stage with bulky disease
- Primary mediastinal
- PTLD
- Low EF/contraindication to anthracycline

Treatment Approach

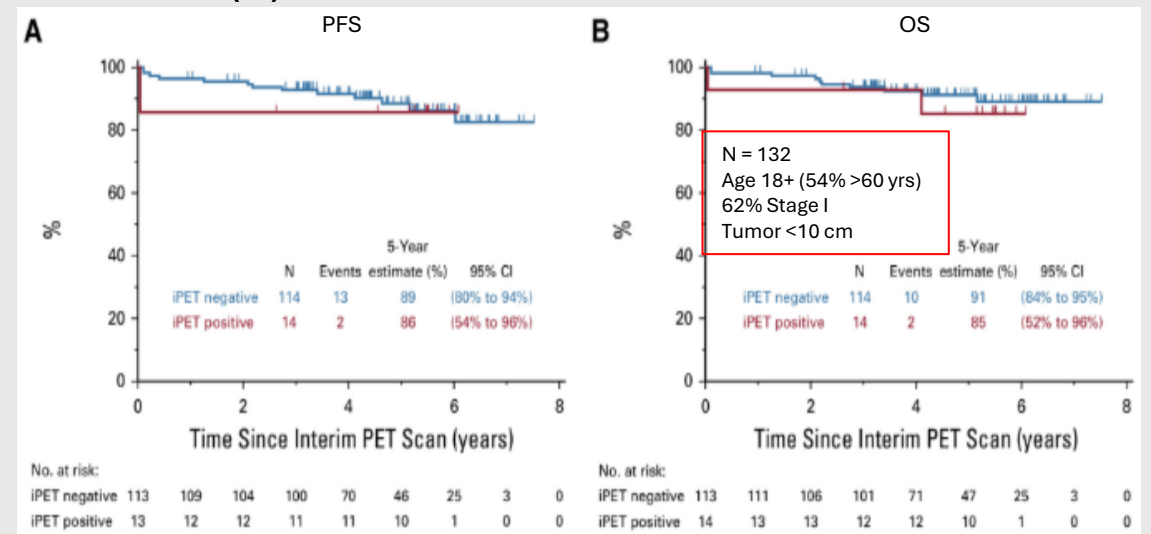


Early stage non-bulky disease

- FLYER P3 RCT
 - 4 cycles of R-CHOP (+ rituximab x 2) non-inferior to 6 cycles

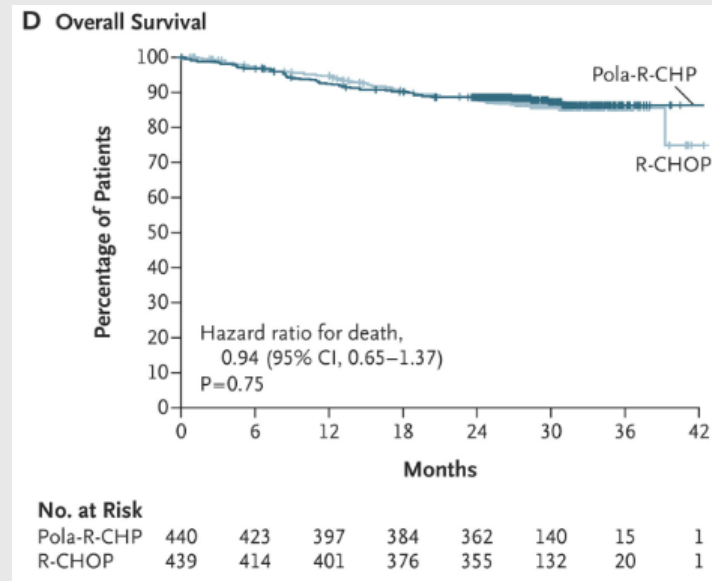
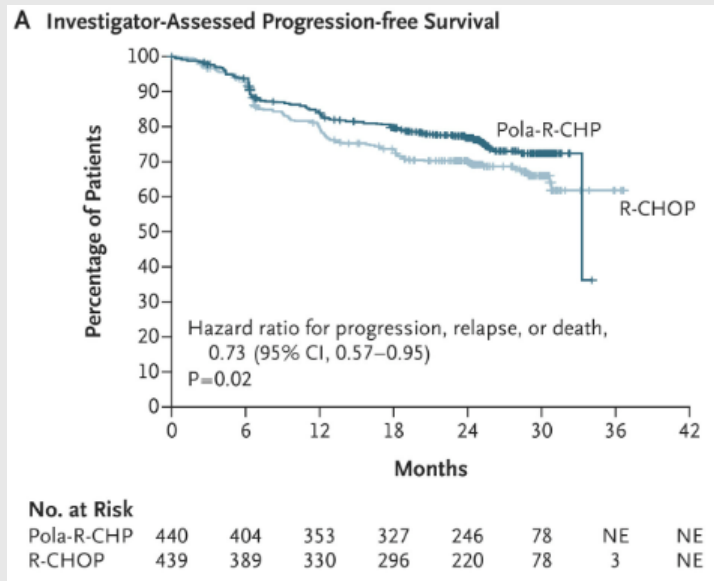


- SWOG S1001 P2 NR (imaging guided)
 - R-CHOP x 3 → PET/CT
 - (-) PET → R-CHOP x 1 cycle
 - (+) PET → RT + RIT



Advanced stage

- High-risk IPI (≥ 2)
 - POLARIX \rightarrow R-CHOP x 6 vs pola-R-CHP x 6
 - N=879, age 18-80 (69% >60 yrs), majority Stage III and IV (89%)
 - Pola-R-CHP w/ improved PFS but no difference in OS



HIV-associated DLBCL

- N=39 (aggressive HIV lymphomas), treated w/ EPOCH (no rituximab)
 - Poor outcomes w/ CHOP --> high proliferation rate and increased p53 expression thought to be overcome by EPOCH
 - Overall CRR: 74% (vs 33% historical)
 - DLBCL OS 66% at median follow-up 53 mos (vs 25% at 36 mos historical)
 - ART held (CD4 >100: OS 87% vs 16%)
- AMC 010: randomized 2:1 R-CHOP vs CHOP
 - No improvement in CR, TTP, PFS, OS w/ addition of rituximab
 - Increased TRM 2/2 infection in rituximab arm
- AMC 034: RP2 rituximab (C vs S) + EPOCH
 - 73% CR in concurrent arm
 - High infectious death rate in concurrent arm
- Pooled analysis of AMC trials
 - AMC 010: R-CHOP, n=99
 - AMC 034: R-EPOCH, n=51
 - R-EPOCH w/ improvement in EFS (HR 0.4; $P < .001$) and OS (HR 0.38; $P < .001$) over R-CHOP

Little RF et al, Blood 2003
 Kaplan et al, Blood 2005
 Barta et al, Cancer 2012
 Sparano et al, Blood 2010

Baseline CD4 Count	No./Total No. (%)	
	AMC Trial 010: R-CHOP, n = 99	AMC Trial 034: R-EPOCH, n = 51
Total TRM: All patients	13/99 (13)	5/51 (9)
<50/ μ L	8/22 (36)	3/8 (38)
\geq 50/ μ L	5/77 (6)	2/43 (5)
P^a	.001	.02

High-grade BCL and MYC-rearranged

- Multiple studies noted poor outcomes w/ R-CHOP
- ~5% of aggressive B-cell lymphomas w/ MYC-R/BCL2-R
- NCI P2 study of MYC-R aggressive B-cell lymphoma (n = 53 total, DH n = 24) --> improved outcomes w/ DA-R-EPOCH compared to historical controls (48 mo EFS 71%, OS 77%, no diff b/t SH vs DH)
- Retrospective study noted no difference between R-CHOP and R-EPOCH in DHL/THL

Newly diagnosed DLBCL treatment algorithm

