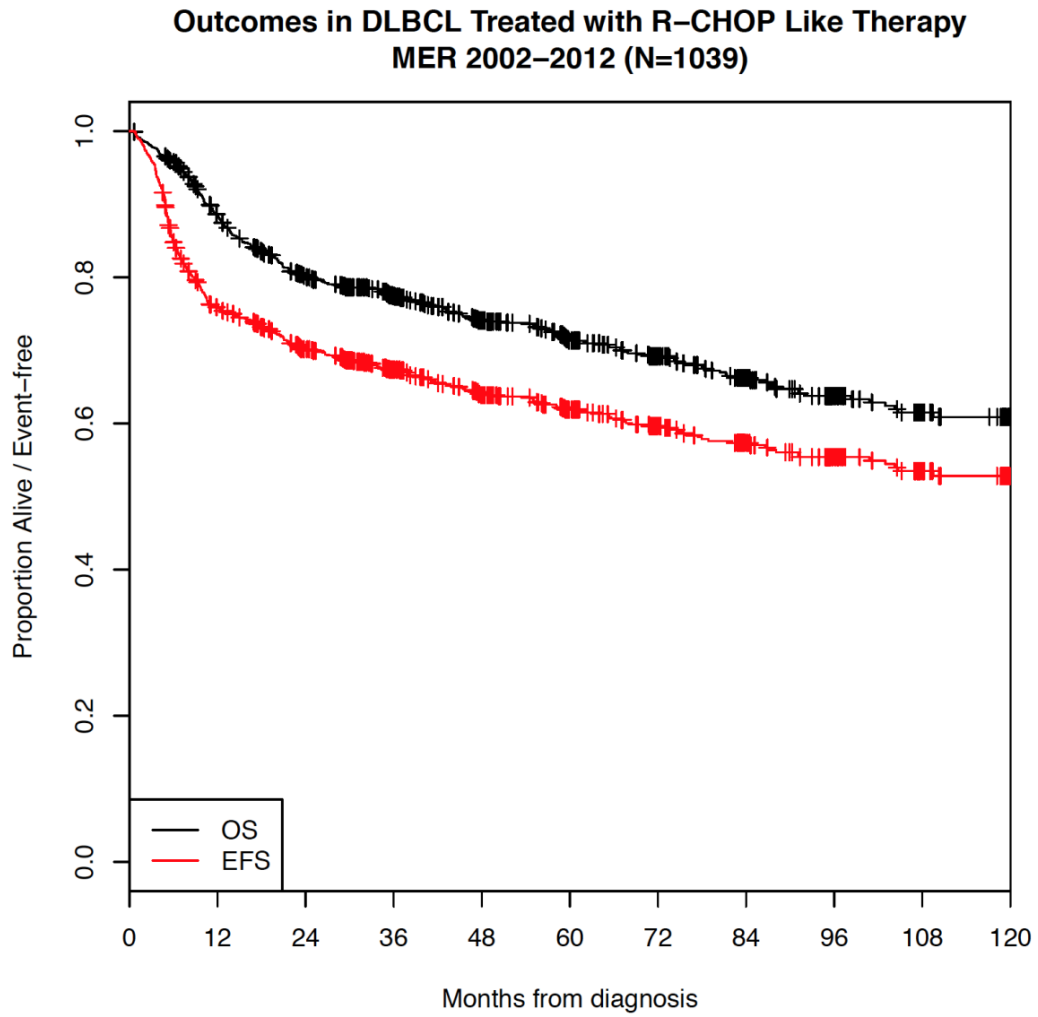
Rochester, Minnesota

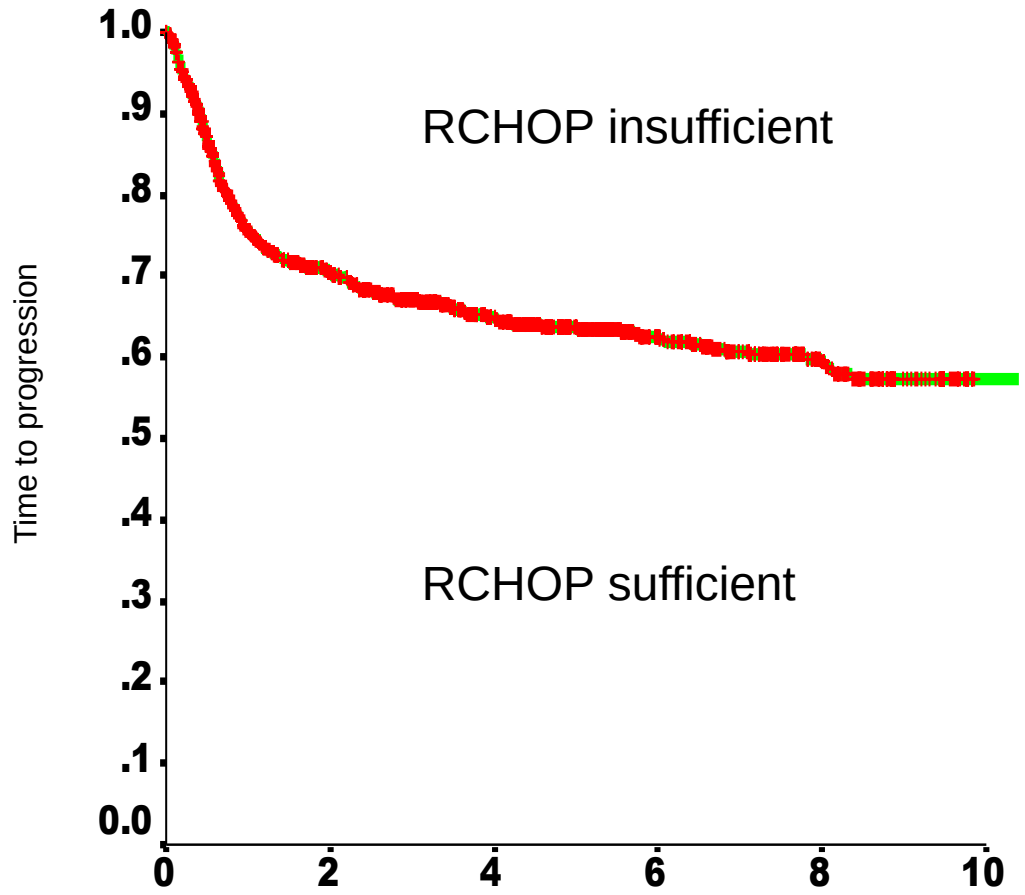
How I treat high risk DLBCL in first line?

Greg Nowakowski, MD
Director, Aggressive Lymphoma Program
Mayo Clinic

DLBCL Outcomes in Mayo Clinic Lymphoma SPORE Database



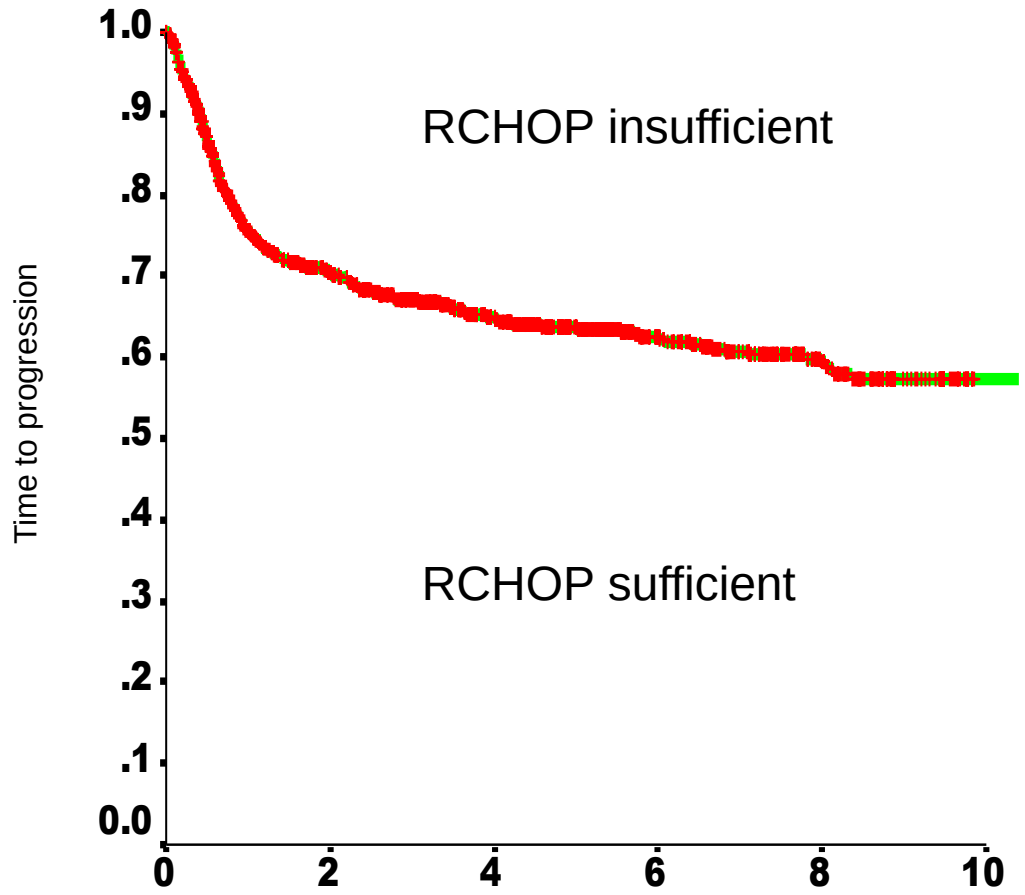
Heterogeneity of outcomes in DLBCL



Two broad strategies:

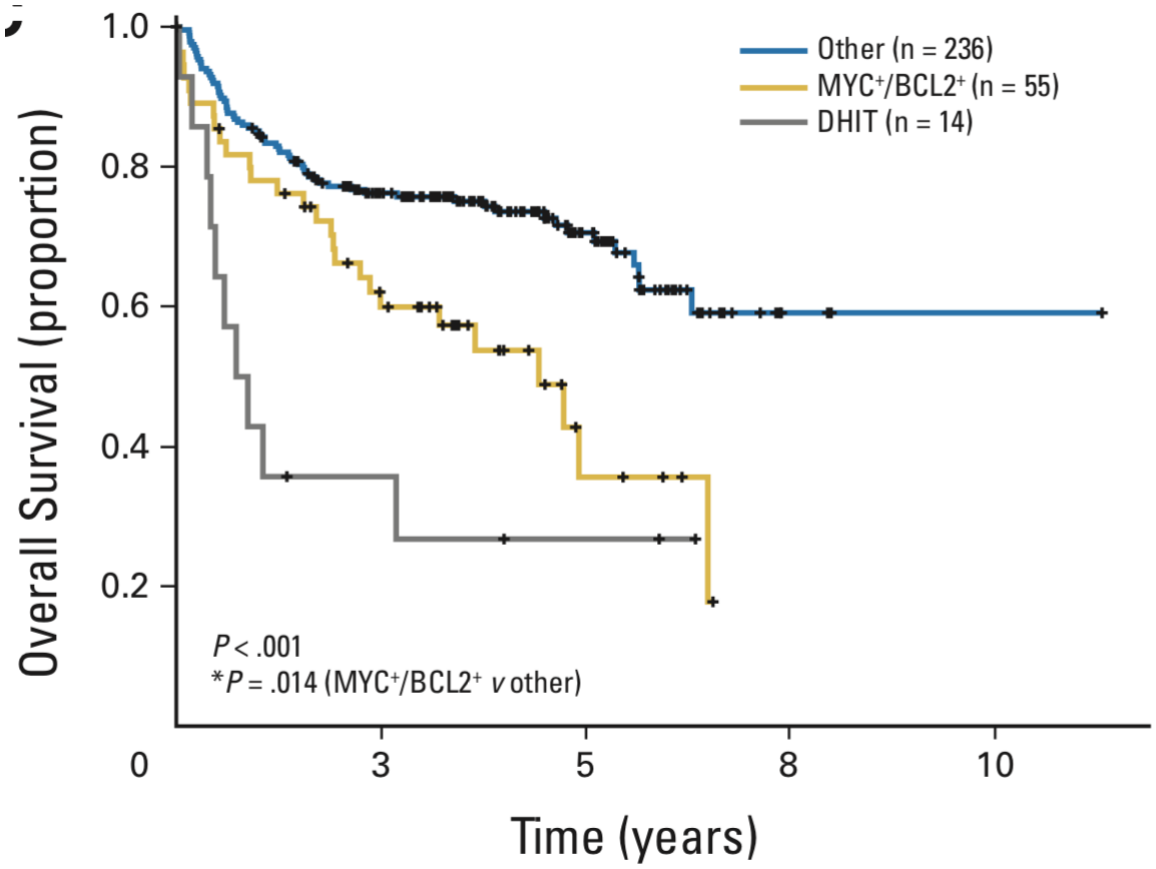
- Target both subgroups
  - possibly overtreating RCHOP "sufficient group"
- Target RCHOP "insufficient" group provided
  - it can be identified
  - It cab be targeted

Heterogeneity of outcomes in DLBCL



- Clinical factors
  - IPI (R-IPI)
- Interim PET scan
- GEP
  - ACB vs GCB
- Protein expression
  - MYC and BCL2
- Chromosomal alterations
  - MYC, BCL2, BCL6
- Deep sequencing mutation/combined expression analysis

Double hit lymphoma



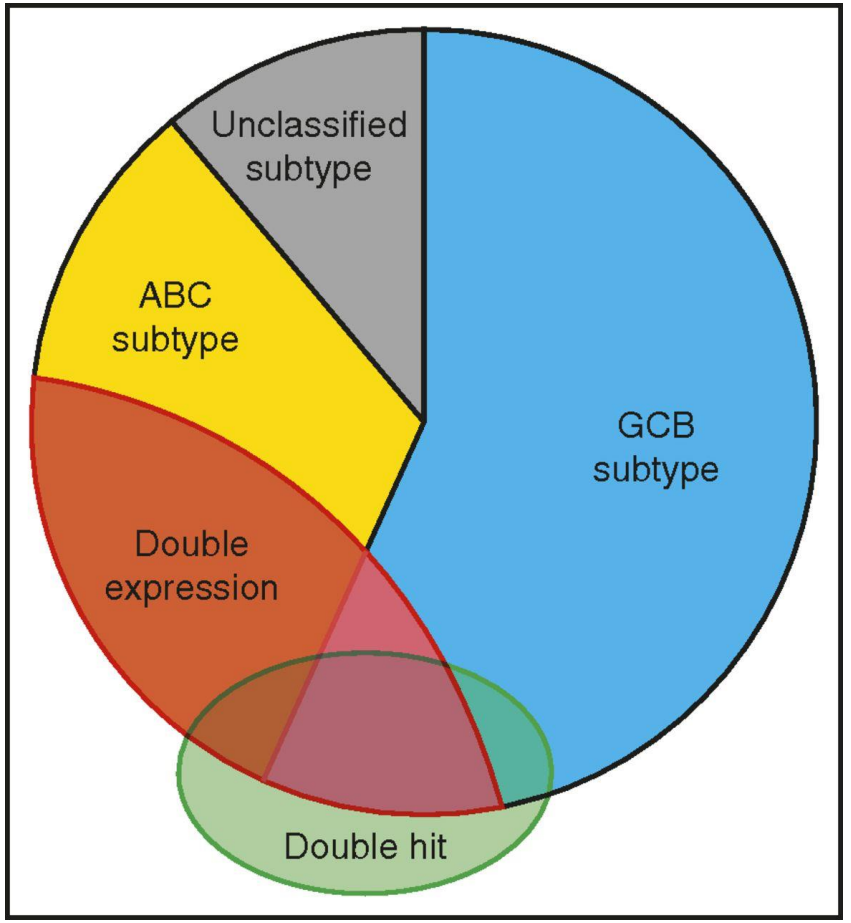
J Clin Onc 2012 Oct 1; 30(28): 3452–3459.

- "High grade B-cell lymphoma (HGBL) with MYC and BCL2 and/or BCL6 rearrangements" - entity in the 2016 revision of the World Health Organization Classification of Lymphoid Neoplasms
- Rearrangements as opposed to expression
- Outcomes have been reported to be poor

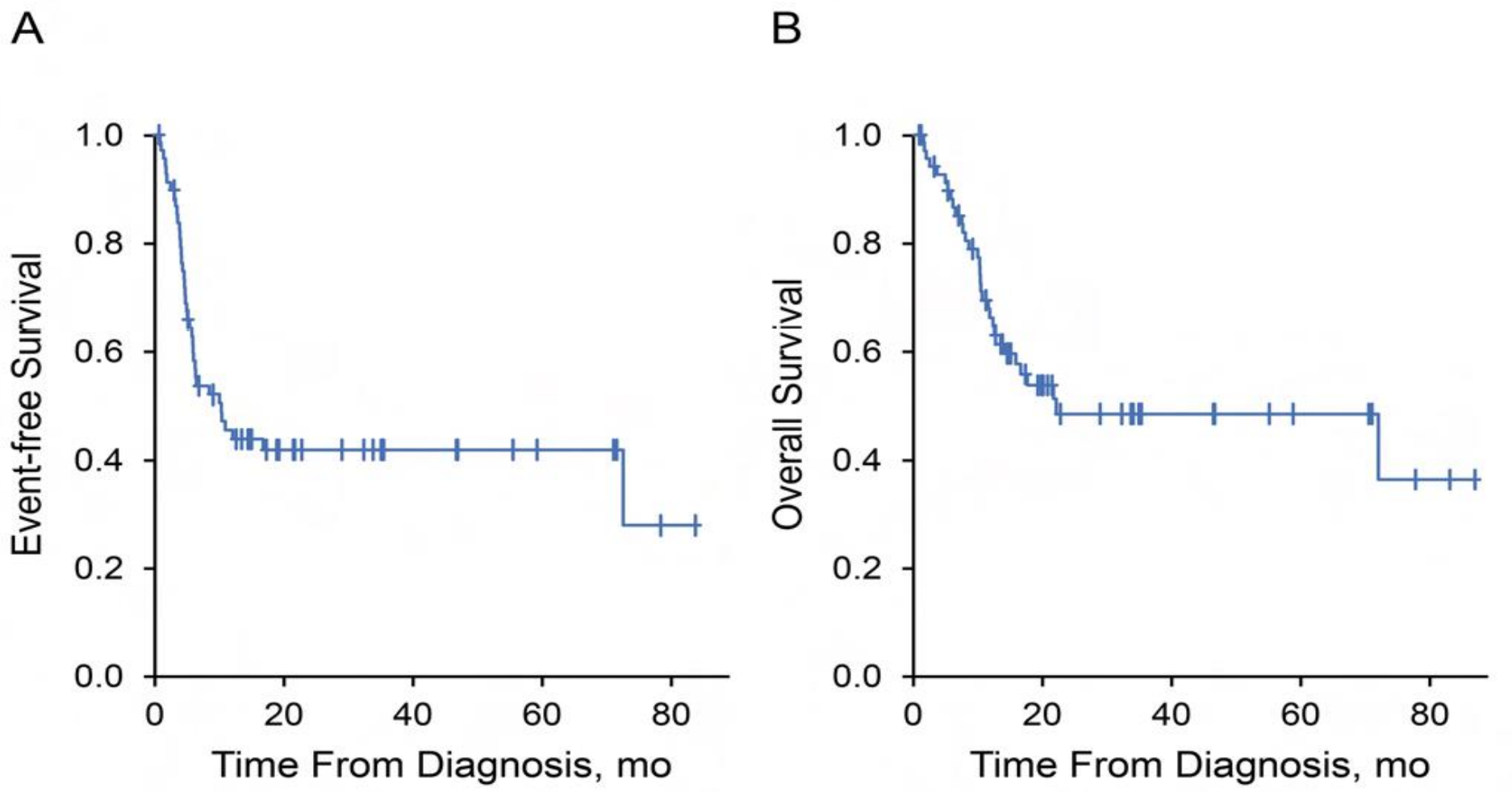
Swerdlow SH, Campo E, Pileri SA, et al. Blood. 2016;127:2375-2390.

MYC, BCL2, and BCL6

- *MYC* is a transcription factor:
  - Involved in cell cycle regulation, DNA damage repair, metabolism, protein synthesis, and response to stress
  - *MYC* rearranged in 7-12% of DLBCL; GCB or ABC subtype
  - In normal cells MYC activates the TP53 pathway
    - 1/3 of MYC-rearranged DLBCL's have concurrent TP53 inactivating mutations
- BCL2 has an anti-apoptotic function
  - *BCL2* rearranged in 14-21% of DLBCL; GCB subtype
- *BCL6* is a transcription repressor
  - Overexpression prevents apoptosis
  - *BCL6* rearranged in 23-32% of DLBCL; ABC or GCB subtype
  - Does not inhibit TP53



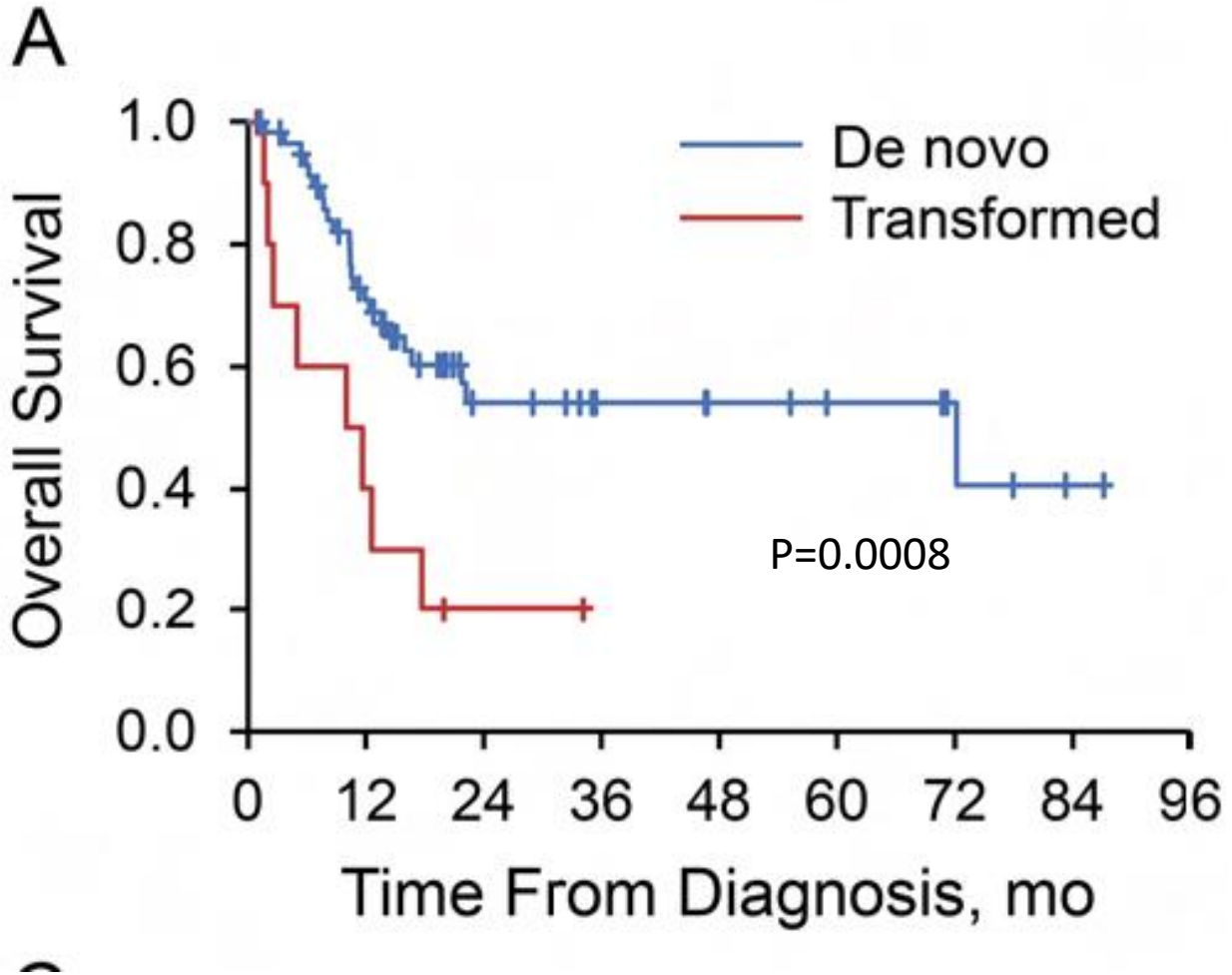
Mayo Clinic Lymphoma Database DHL/THL, Event-Free Survival and Overall Survival (n=100)



Haematologica. 2018; 103:doi:10.3324/haematol.2018.190157

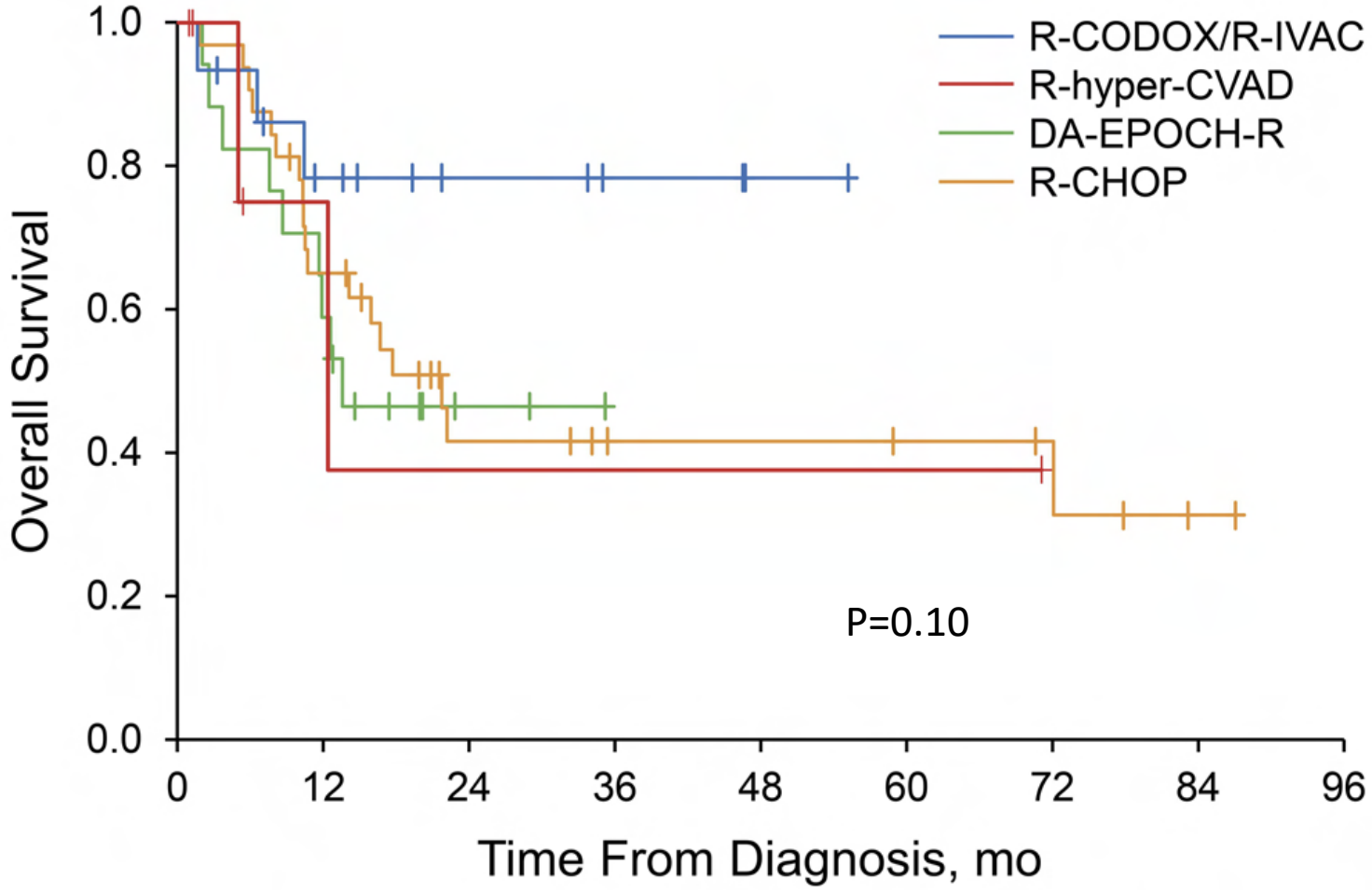
Not All DH/THL Are Created Equal

Event Free Survival (EFS) of Newly Diagnosed vs. Transformation Patients



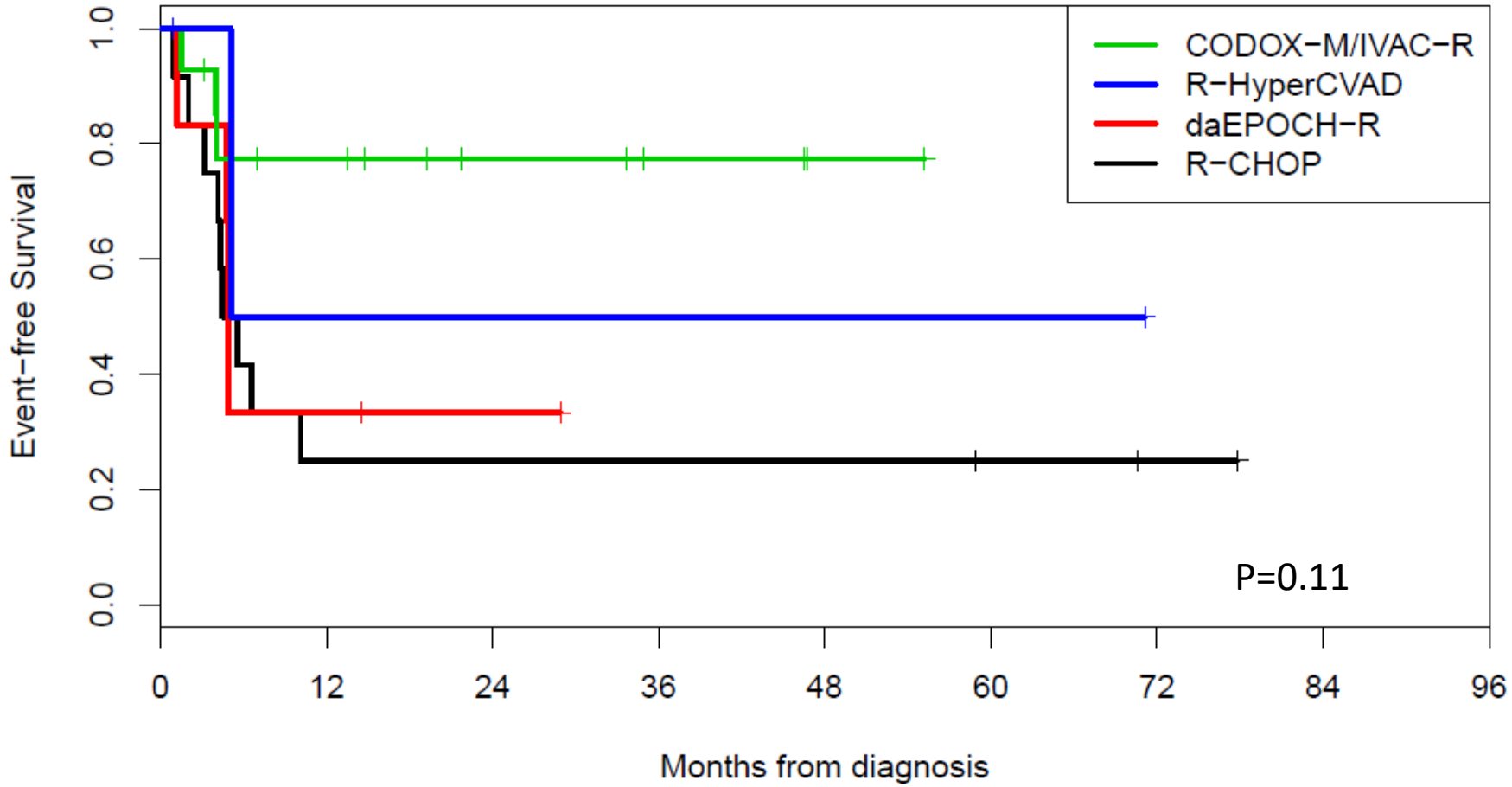
Haematologica. 2018; 103:doi:10.3324/haematol.2018.190157

EFS by Treatment



Haematologica. 2018; 103:doi:10.3324/haematol.2018.190157

EFS Age < 60 Years by Treatment



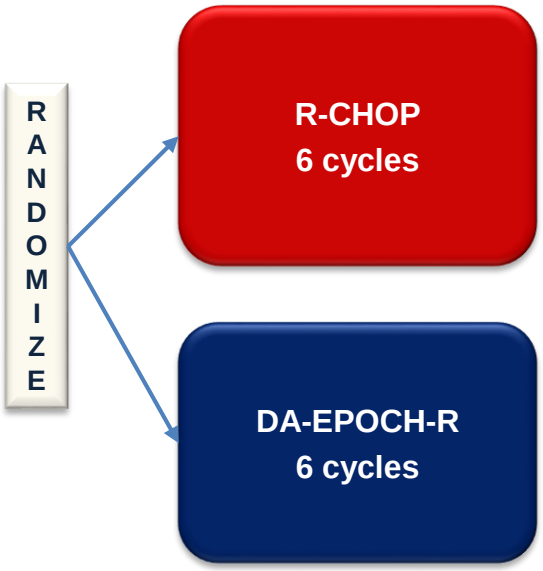
Haematologica. 2018; 103:doi:10.3324/haematol.2018.190157

Phase III study of R-CHOP vs DA-EPOCH-R in patients with untreated DLBCL (CALGB/Alliance 50303)

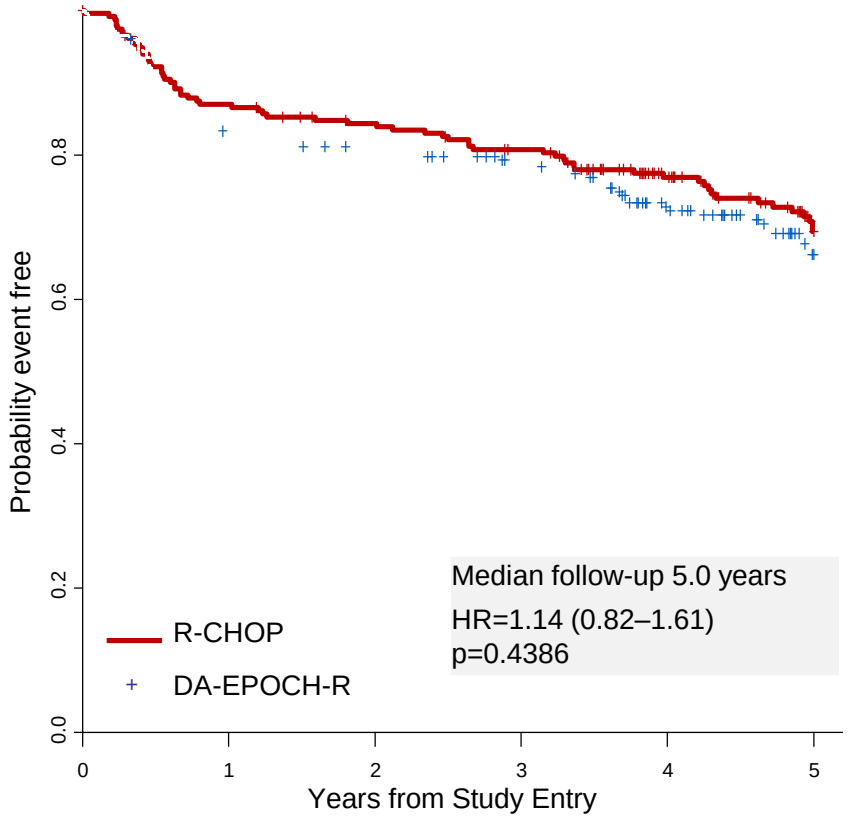
Key eligibility criteria (N=524)

- Age ≥18 years
- Stage II or higher newly diagnosed DLBCL (Stage I PMBCL)
- ECOG PS 0–2
- Fresh/frozen tumor biopsy (4 cores)

Study schema

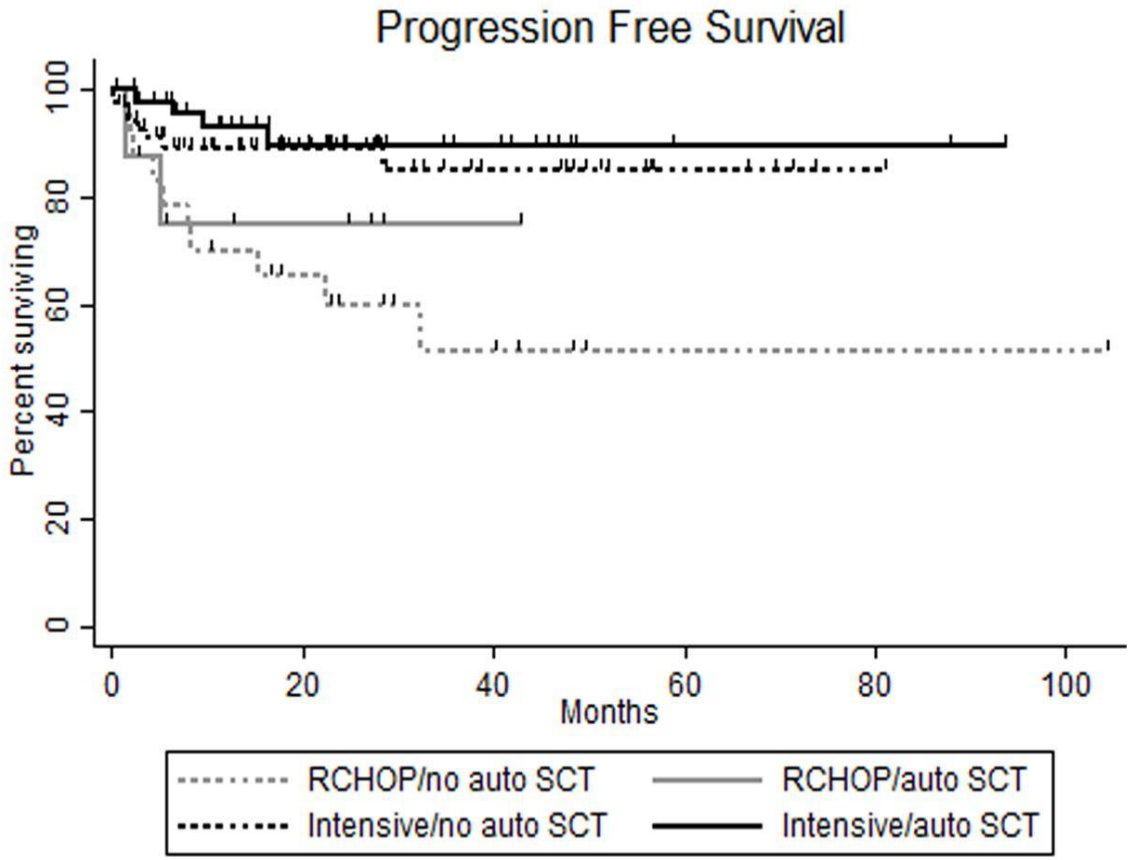


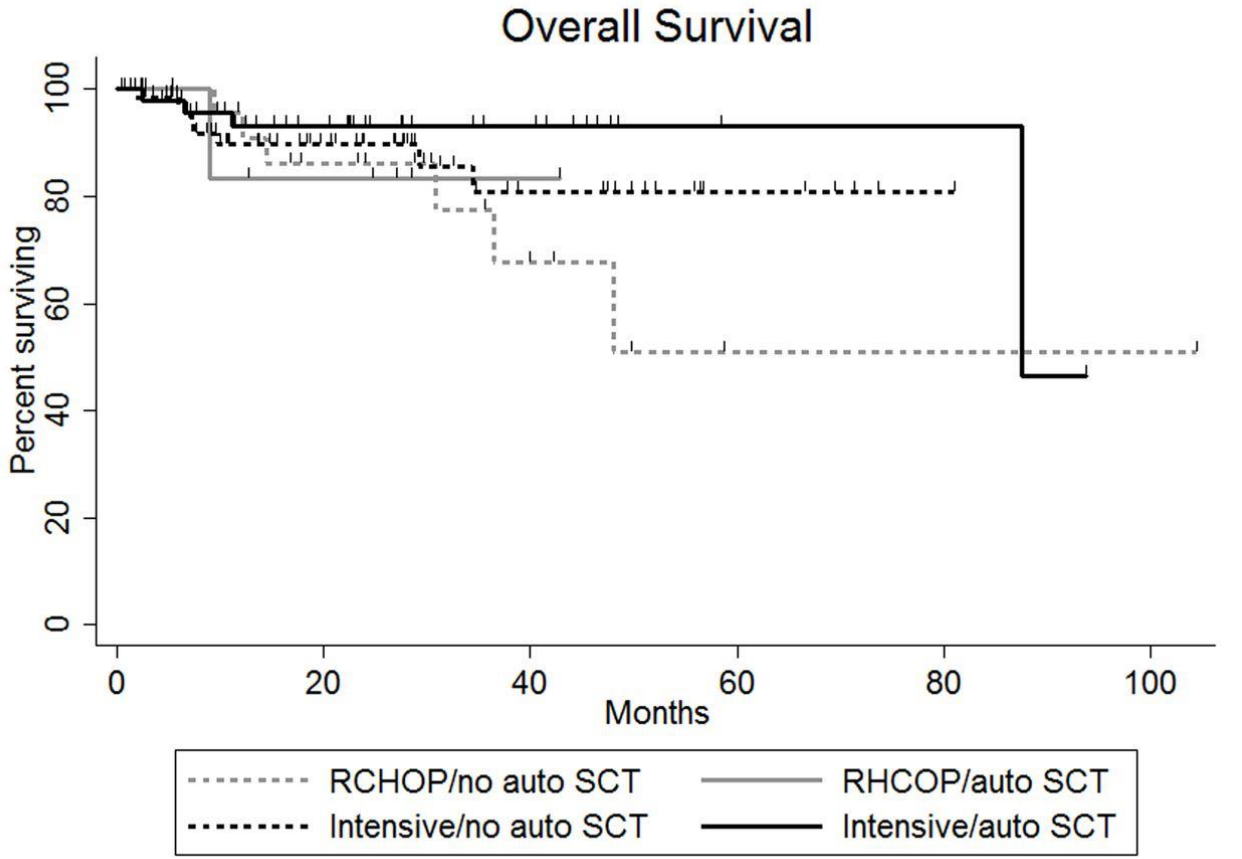
Event-free survival



Bartlett, Wilson et al. ASH 2016. Abstract 469.

Transplant in DH/THL



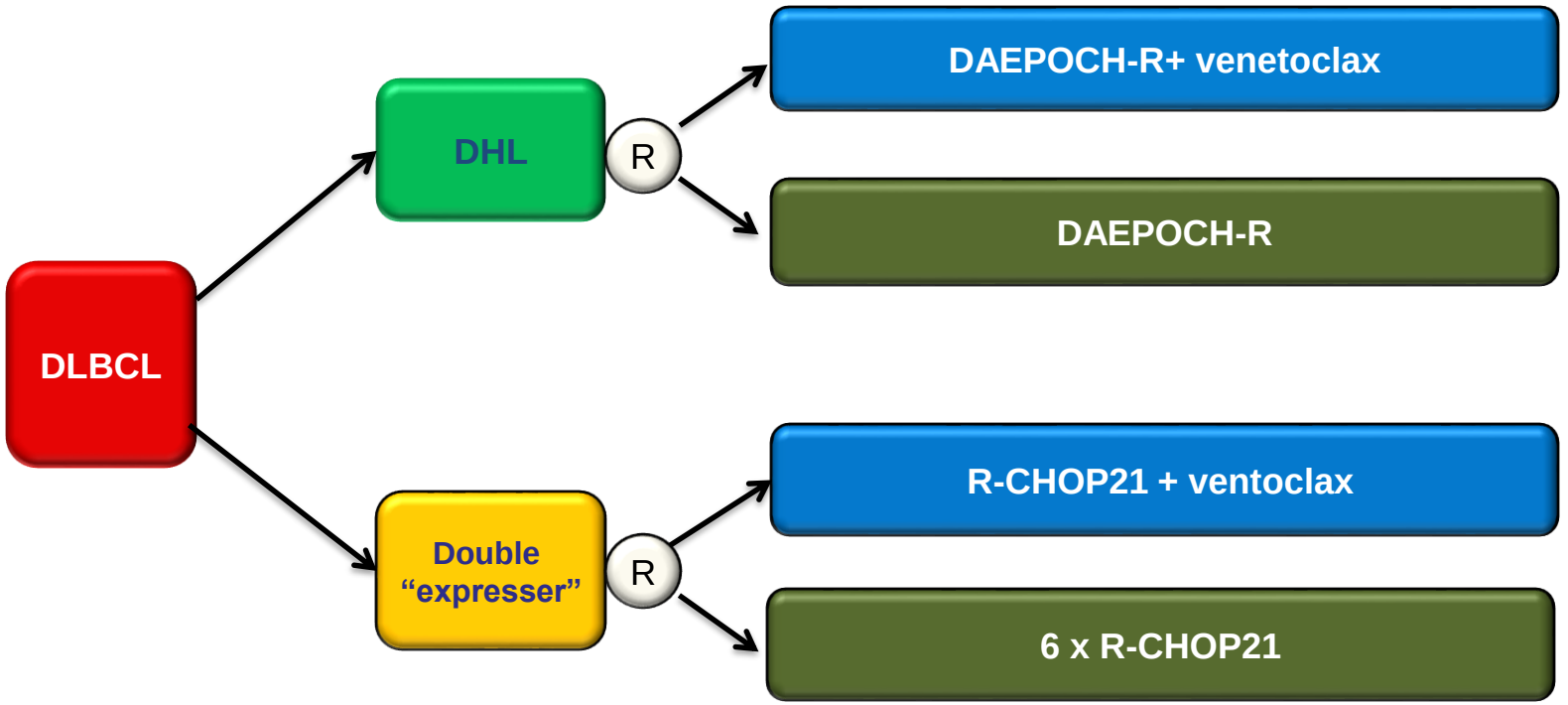


Landsburg DJ et al. ASH 2016

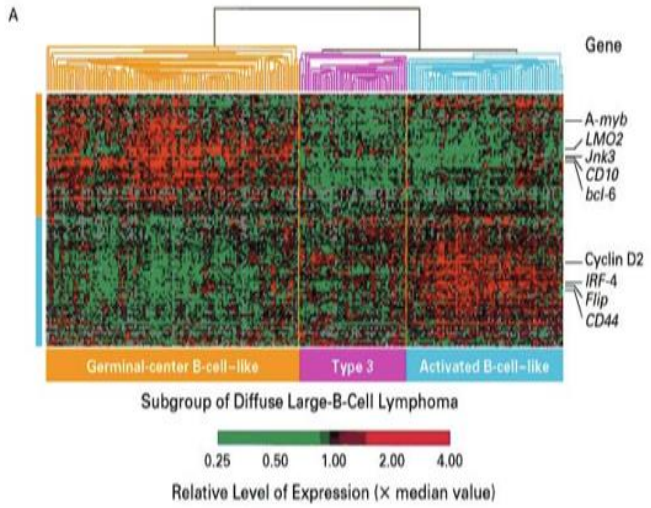
How do I treat DHL frontline?

- Patients ≤60 yo R-CODOX-M/IVAC
- > 60 RCHOP, RCHOP with ASCT consolidation or DAEPOCH-R

Current US Intergroup Study

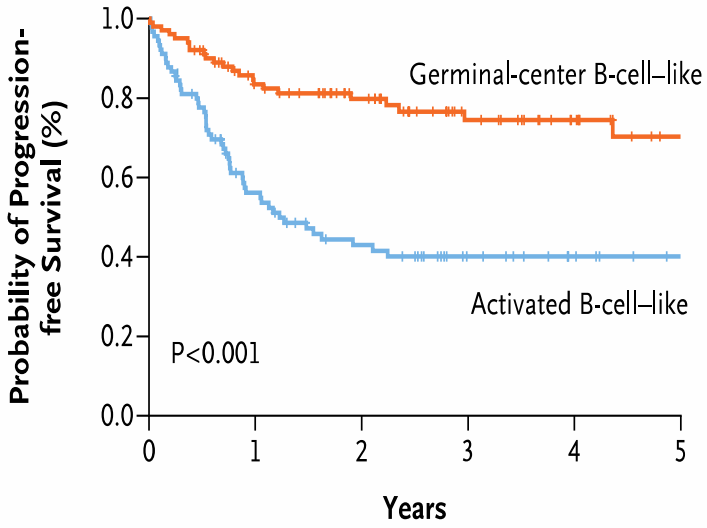


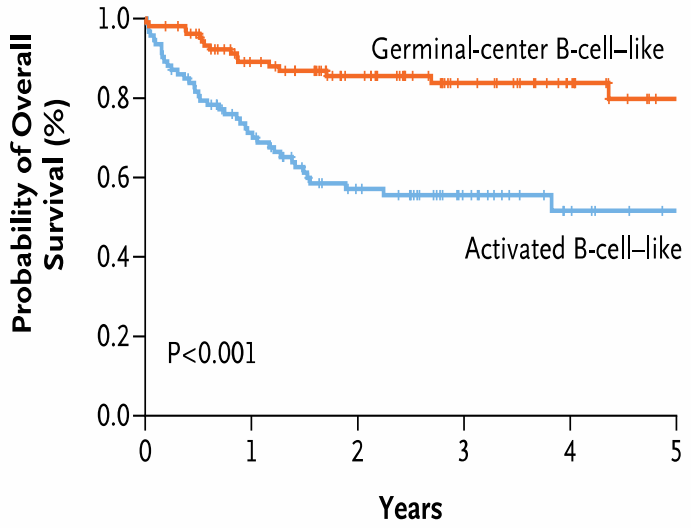
DLBCL Molecular Subtypes



Two major molecular subtypes:

- Activated B-cell like (ABC)
  - B-cell receptor driven
- Germinal center B-cell like (GCB)





l. N Engl J Med 2008;359:2313–2323.

Pathways with therapeutic potential in ABC DLBCL

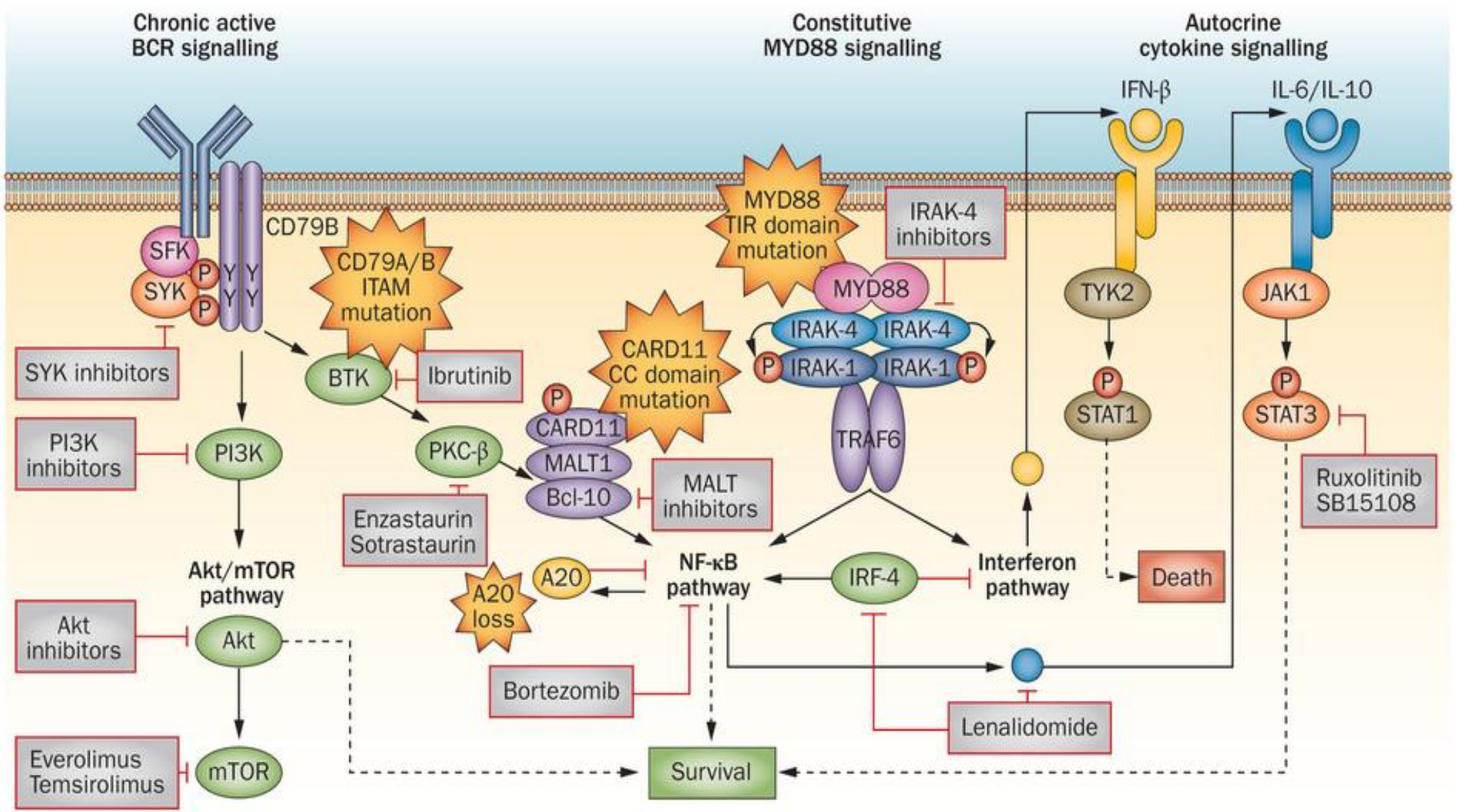


Figure from: Roschewski et al. Nat Rev Clin Oncol 2014;11:22–25.

XR-CHOP(s)

What X?

- Bortezomib: Bor-RCHOP (Phase 2/3)
- Ibrutinib: IR-CHOP (Phase 3)
- Everolimus: EveR-CHOP (Phase 1b)
- Lenalidomide: R2-CHOP (Phase 3)

PYRAMID: Non-GCB DLBCL

Study design

Prospective randomized, open-label, Phase II study

Treatment-naïve,
non-GCB DLBCL
by Hans IHC with measurable disease,
ECOG PS 0–2
(N=183)

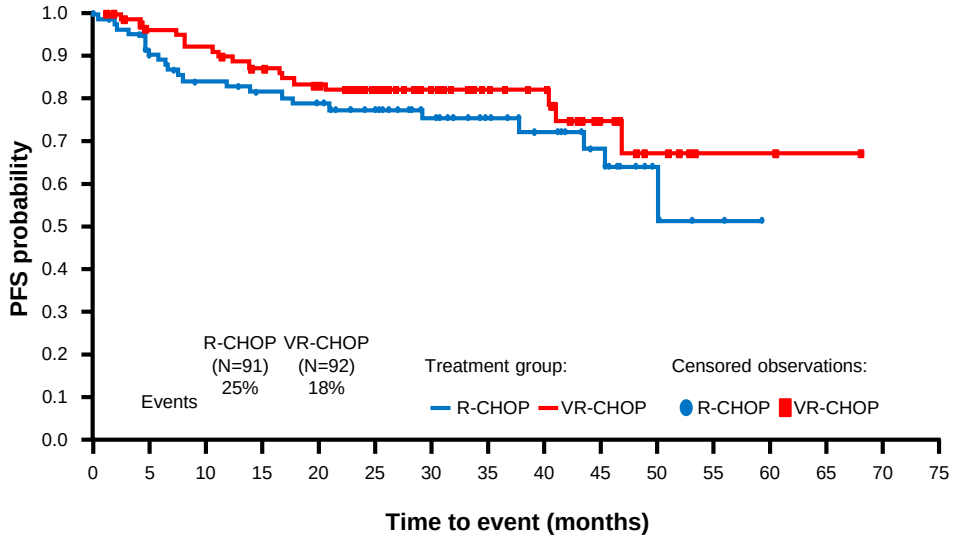
→ **Bortezomib 1.3 mg/m² i.v.**
Days 1, 4 +
R-CHOP* 21 days x 6 cycles
(n = 92)

→ **R-CHOP***
21 days x 6 cycles
(n = 91)

Limits:

- Patient selection in the PYRAMID trial may have played a role → R-CHOP alone produced better outcomes than expected
- IHC based on Hans algorithm

PFS

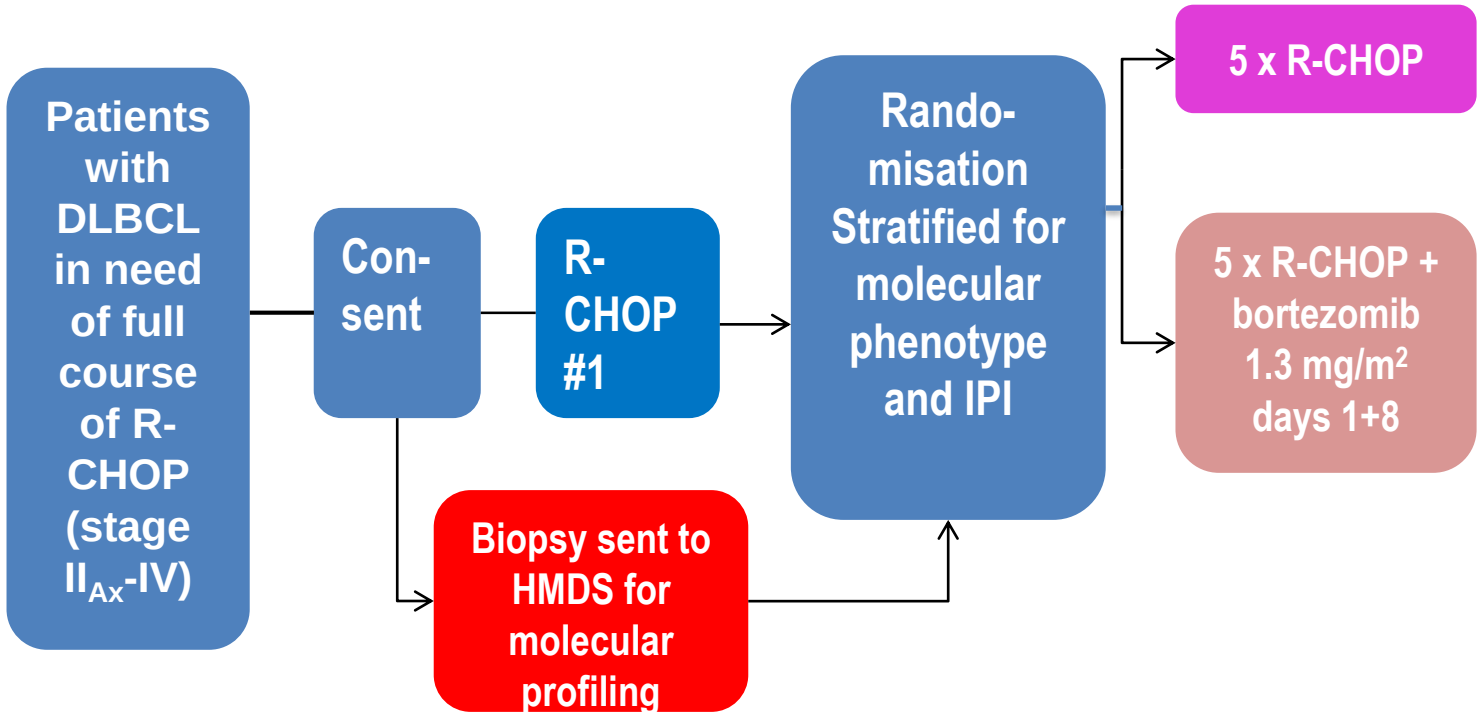


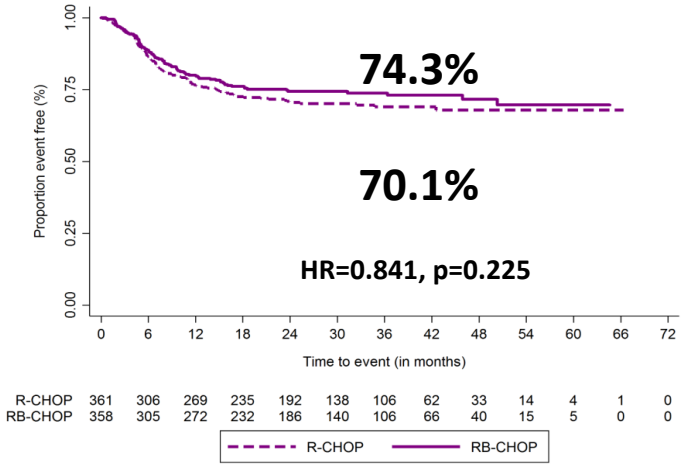
- **2-year PFS: 78% R-CHOP vs 82% VR-CHOP**
  - **HR (95% CI): 0.73 (0.43–1.24); p=0.611**

VR-CHOP, bortezomib, rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone.

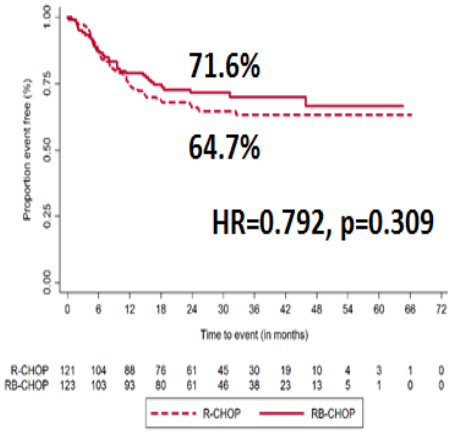
Leonard JP, et al. Blood 2015;126:811a.
(Updated data presented in oral presentation at ASH annual meeting)

REMoDL trial

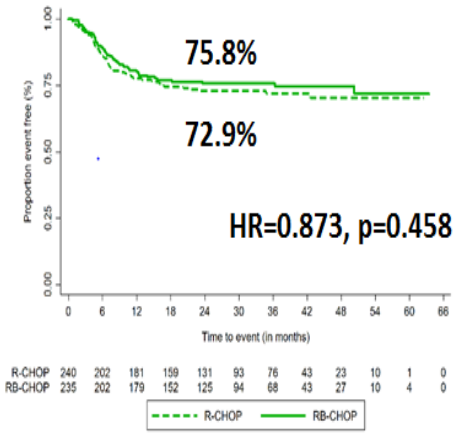




ABC: N=244



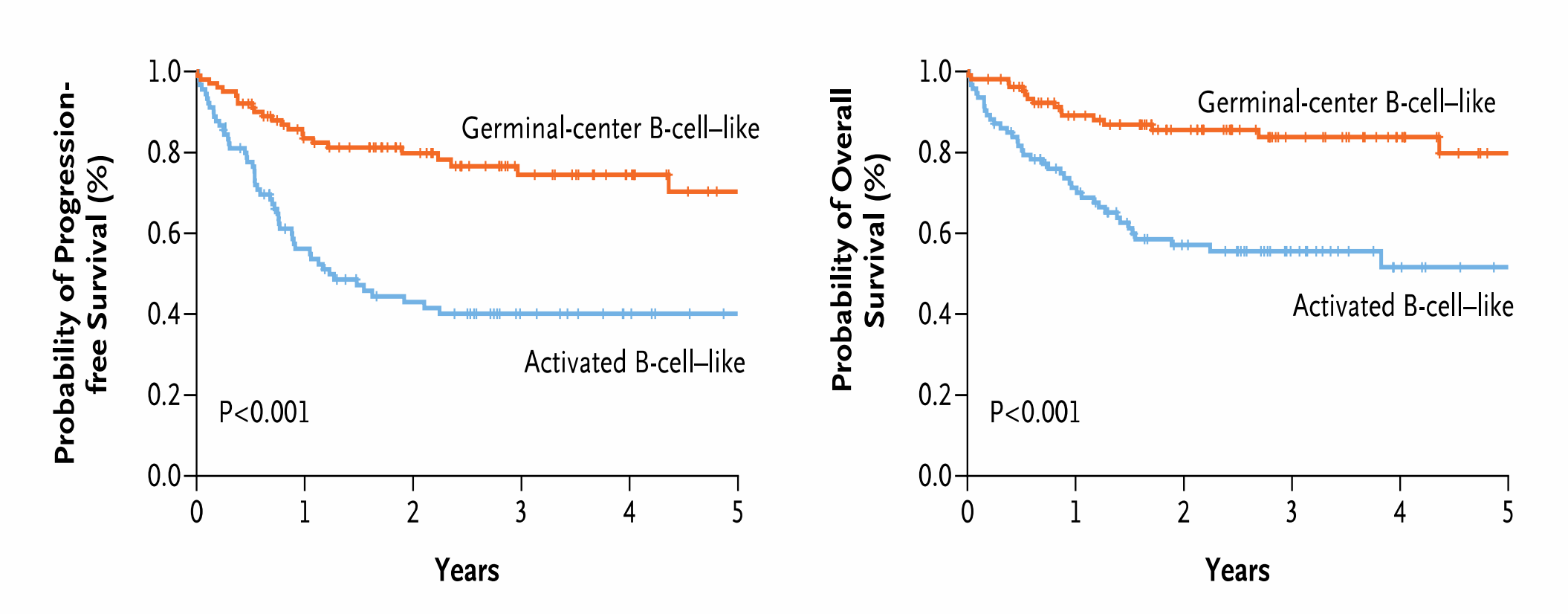
GCB: N=475



DASL, cDNA-mediated annealing, selection, extension and ligation;
HMDS, Haematological Malignancy Diagnostic Service.

Davies AJ, et al. ICML 2017. Abstract 121. Updated data presented at ICML.

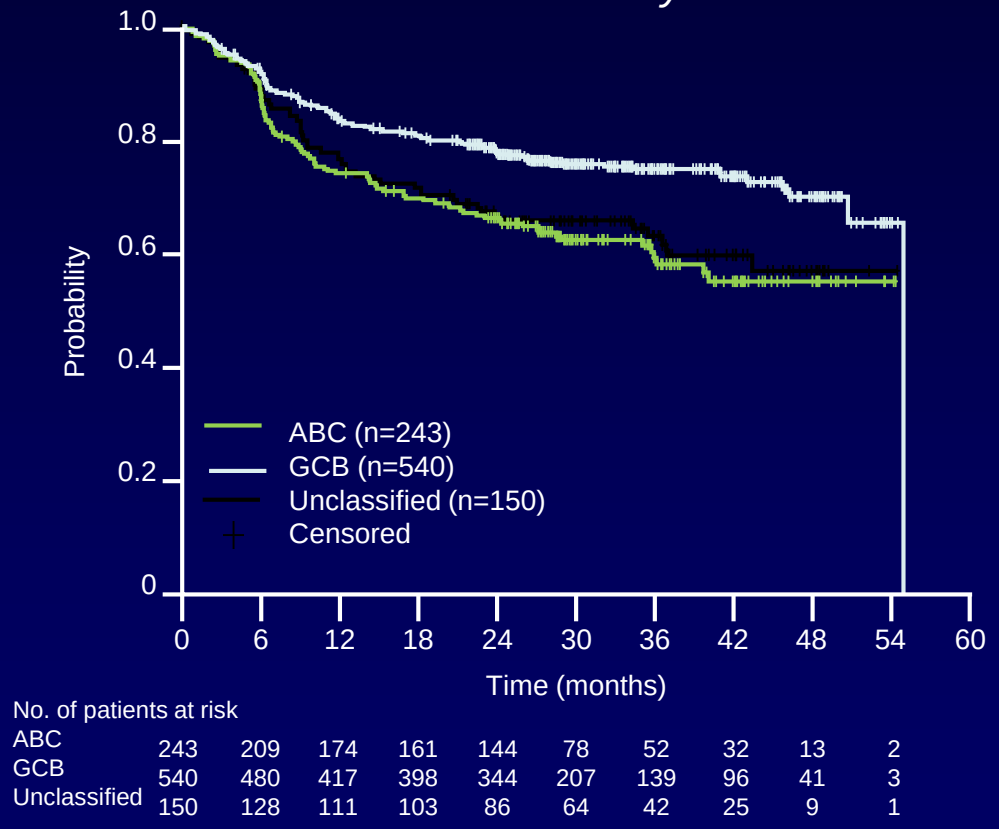
DLBCL Molecular Subtypes and Outcomes



Lenz et al. N Engl J Med 2008;359:2313–2323.

Investigator-assessed PFS by Cell of Origin*

Kaplan-Meier plot of investigator-assessed PFS by COO

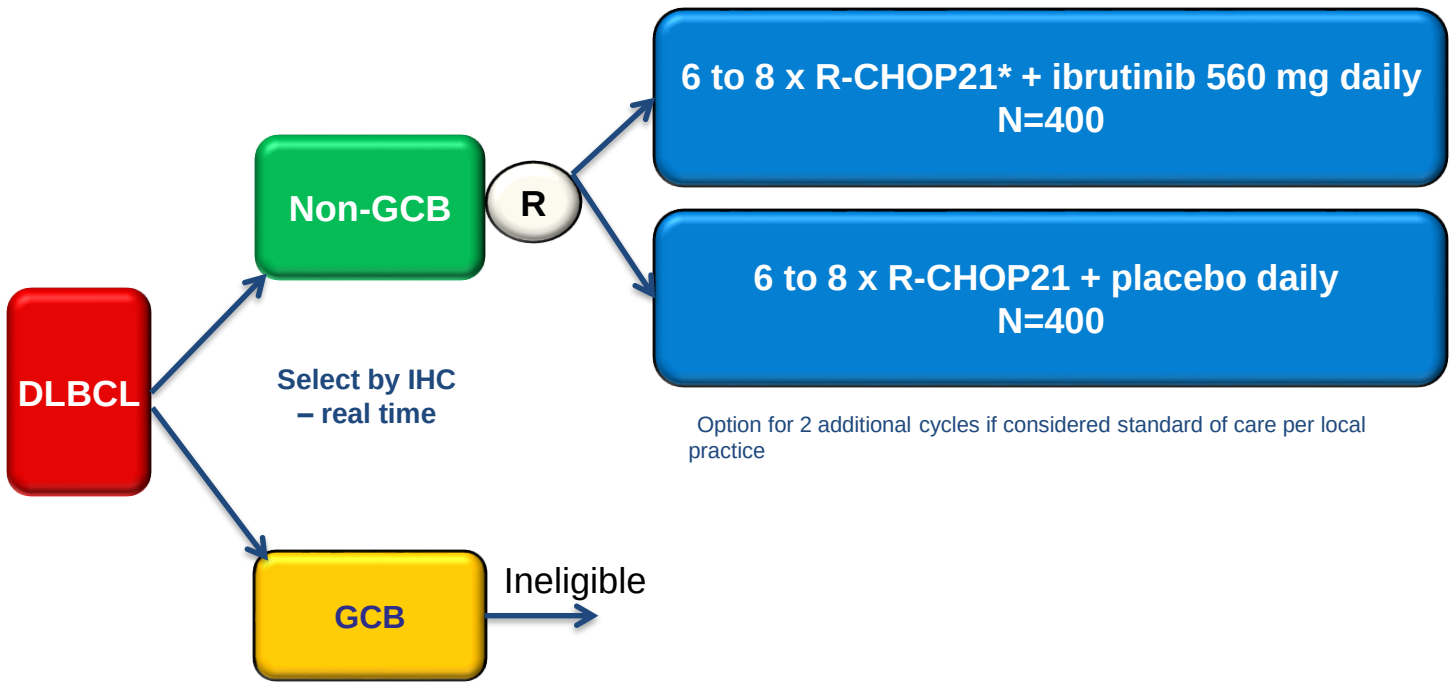


	ABC, n=243	*GCB, n=540*	*Unclassified, n=150*
Pts with event, n (%)	92 (37.9)	129 (23.9)	54 (36.0)
2-year PFS, %	66.4	78.0	65.9
3-year PFS, %	59.3	75.0	63.2
HR (95% CI)			
ABC vs GCB		1.70 (1.30, 2.23)	
Unclassified vs GCB		1.57 (1.14, 2.16)	

*Exploratory analysis; COO classification determined for 933 pts by gene expression profiling assay (Nanostring); missing COO classifications due to: restricted Chinese export license, n=252; CD20+ DLBCL not confirmed, n=102; missing/inadequate tissue, n=131; PFS HR=0.82 (0.64, 1.04) in pts with COO classification; PFS HR=1.18 (0.85, 1.64) in pts without COO classification

Vitolo et al. ASH 2016. Abstract 470.

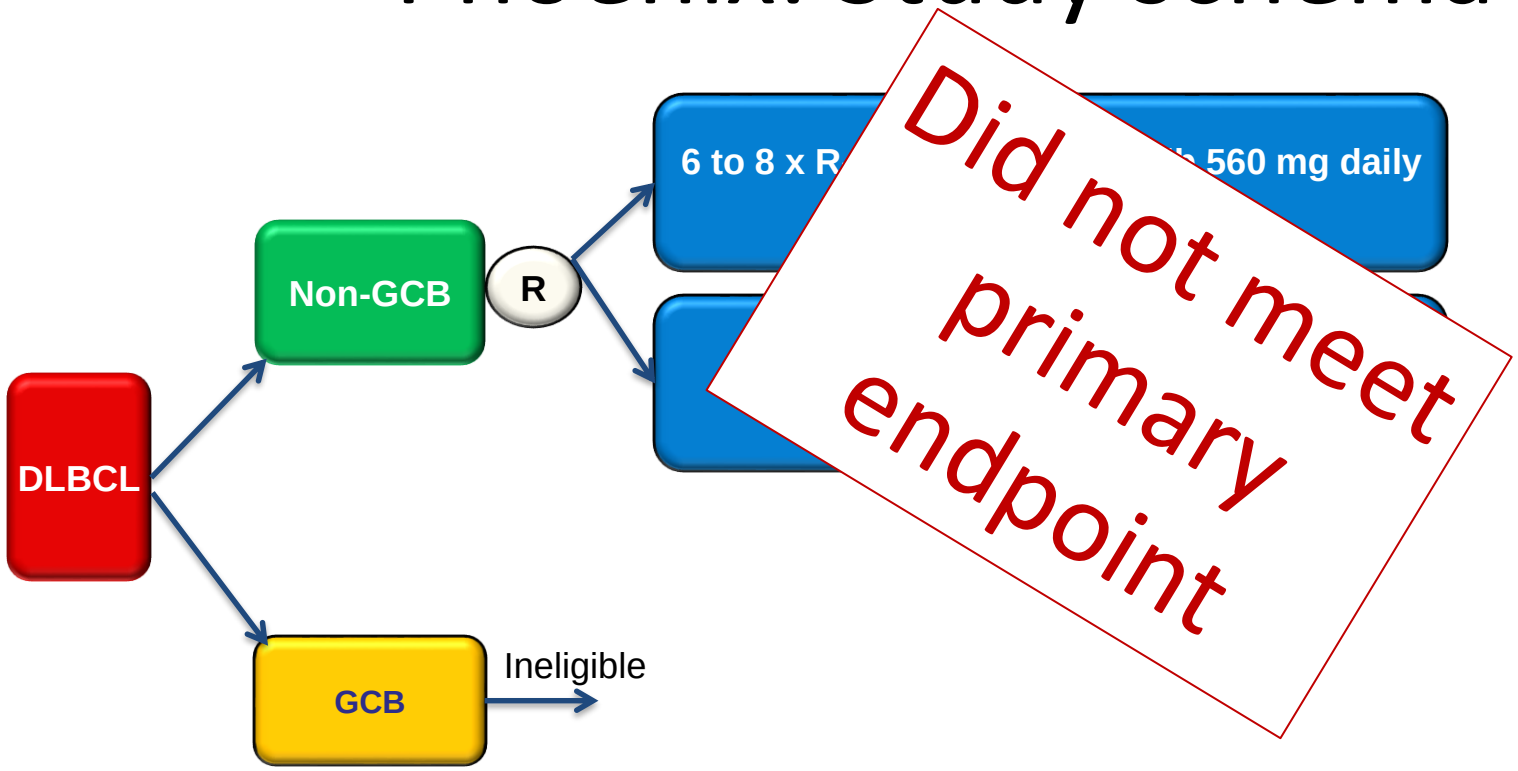
Phoenix: Study schema



- Newly diagnosed DLBCL of non-GCB type
- IPI ≥ 2; ECOG PS ≤ 2; Age >18
- Primary Endpoint = EFS
- N = 800

ClinicalTrials.gov Identifier: NCT02285062.

Phoenix: Study schema



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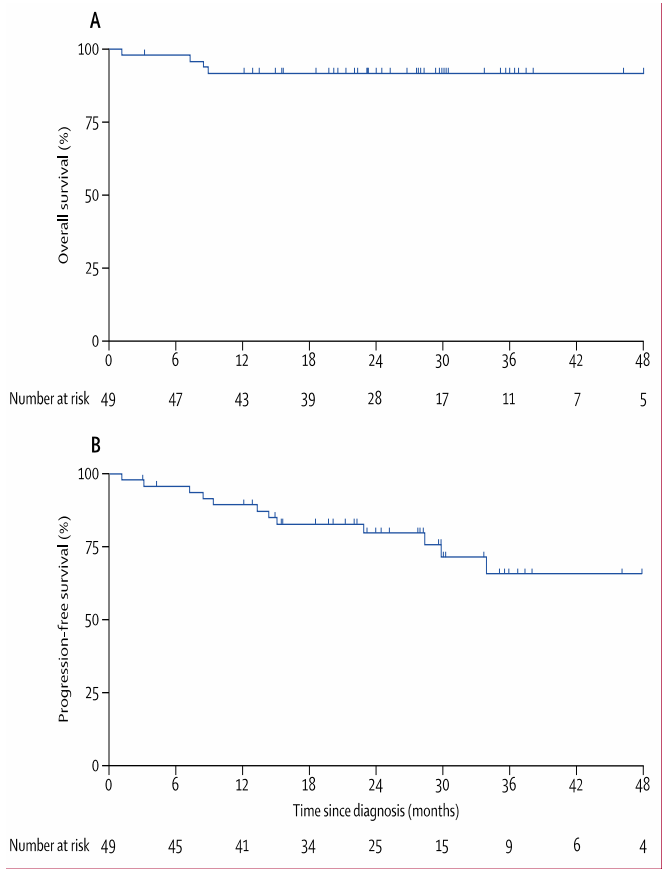
- N = 800

ClinicalTrials.gov Identifier: NCT02285062.
Press release available from: https://www.jnj.com/janssen-provides-update-on-imbruvica-ibrutinib-phase-3-phoenix-trial-in-newly-diagnosed-non-germinal-center-b-cell-non-gcb-subtype-of-diffuse-large-b-cell-lymphoma-dlbcl

Phase II studies of lenalidomide R-CHOP (R2-CHOP) in front-line DLBCL

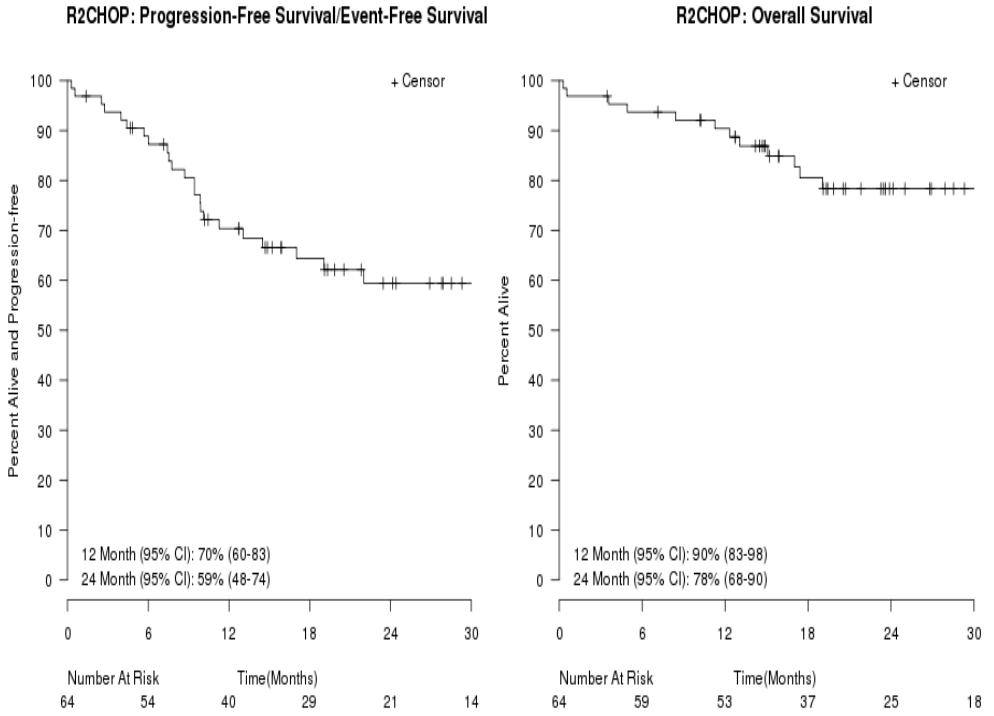
N=44
ORR 92%
CR 86%



Vitolo et al. Lancet Oncol 2014;15:730–737.

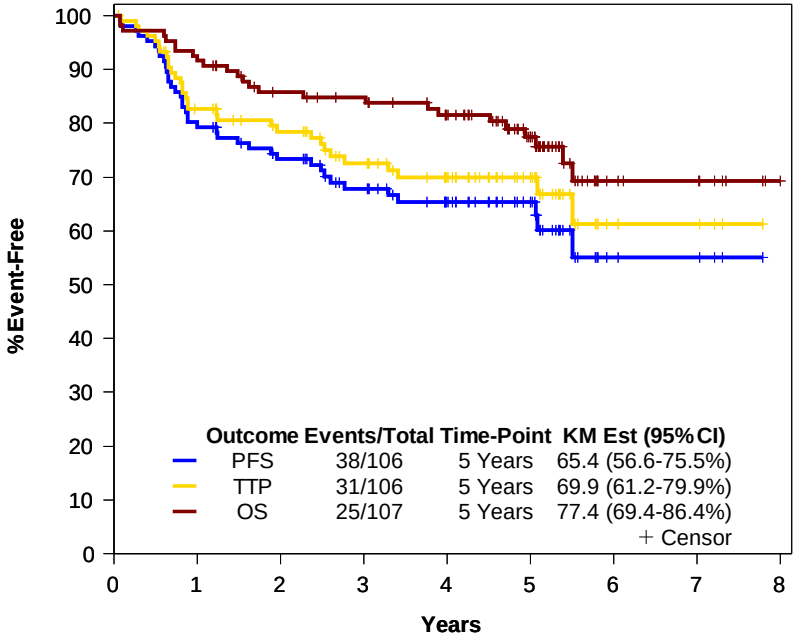
MAYO CLINIC

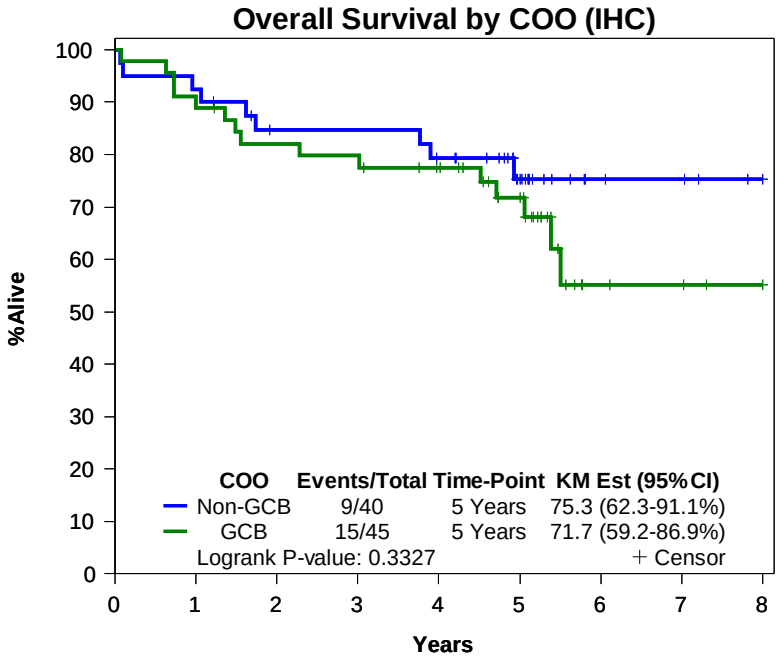
N=64
ORR 98%
CR 80%

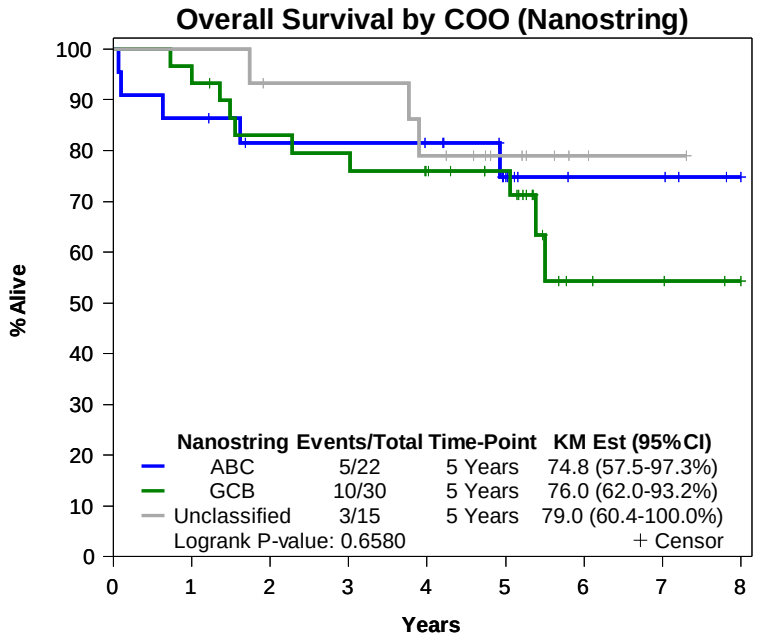


Nowakowski et al. J Clin Oncol 2015;33:251–257;

Long Term Results of R2CHOP: Combined Analysis of Two Phase 2 Studies (n=108)

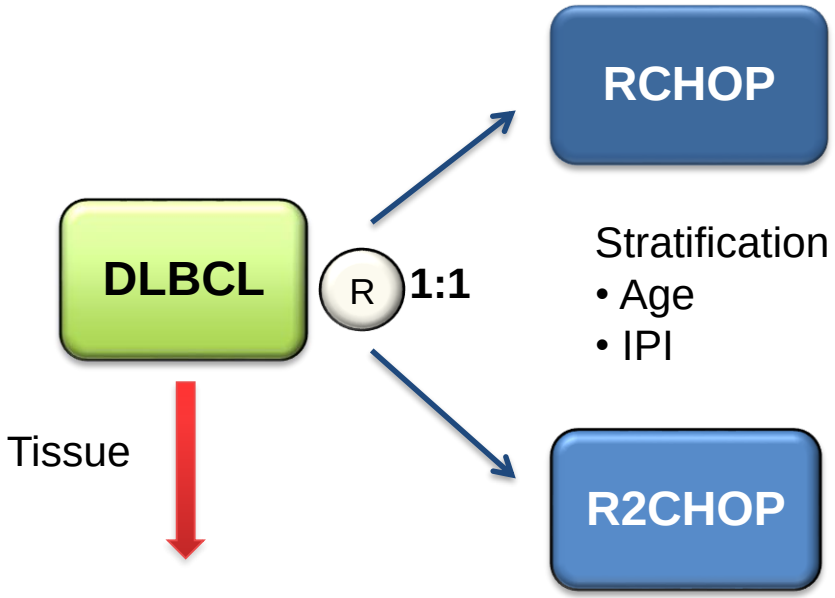






Castellino et al. ASCO, 2018, *In Press*

E1412: R2CHOP vs RCHOP



N=346

Accrual met January 2017

50 ABC patients per arm

GCB vs non-GCB tissue analysis:
- GEP - NanoStrings
- IHC - Hans and other algorithms

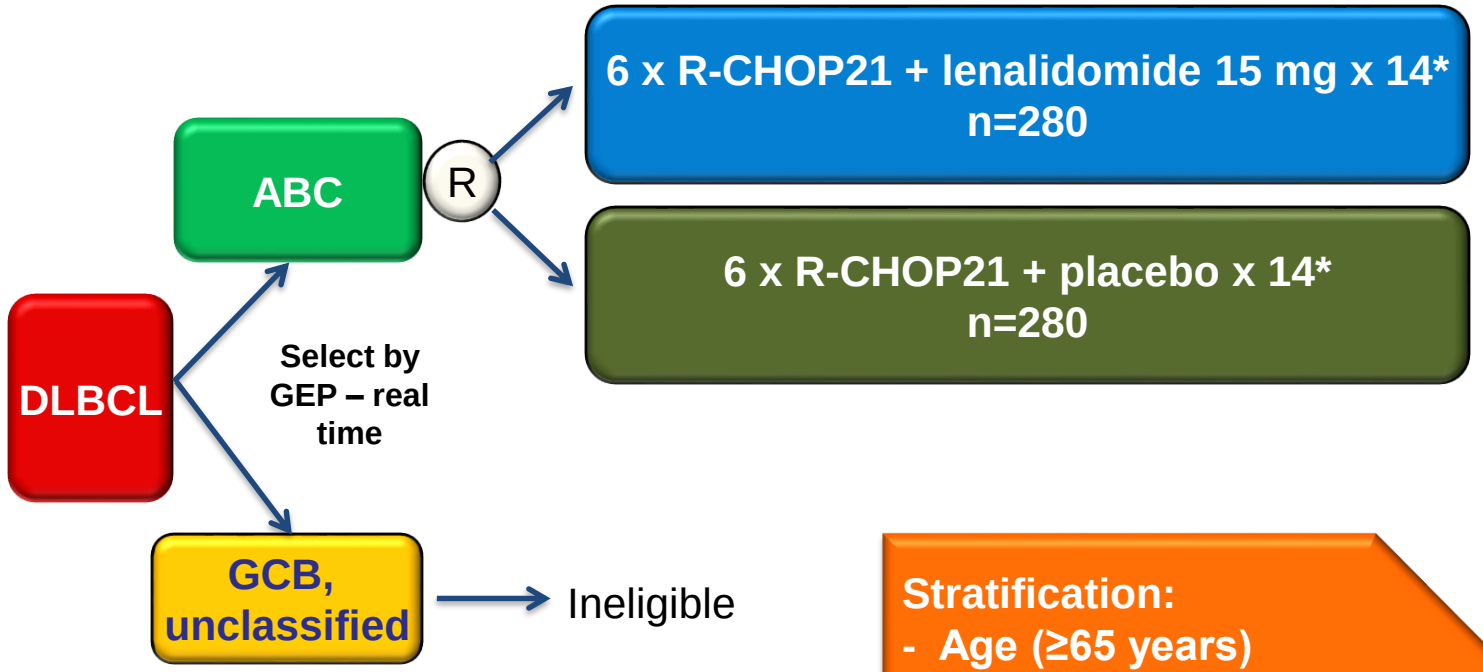
→ **Efficacy analysis based on DLBCL subtype**

ClinicalTrials.gov Identifier: NCT01856192.

DLC-002 (ROBUST) study schema

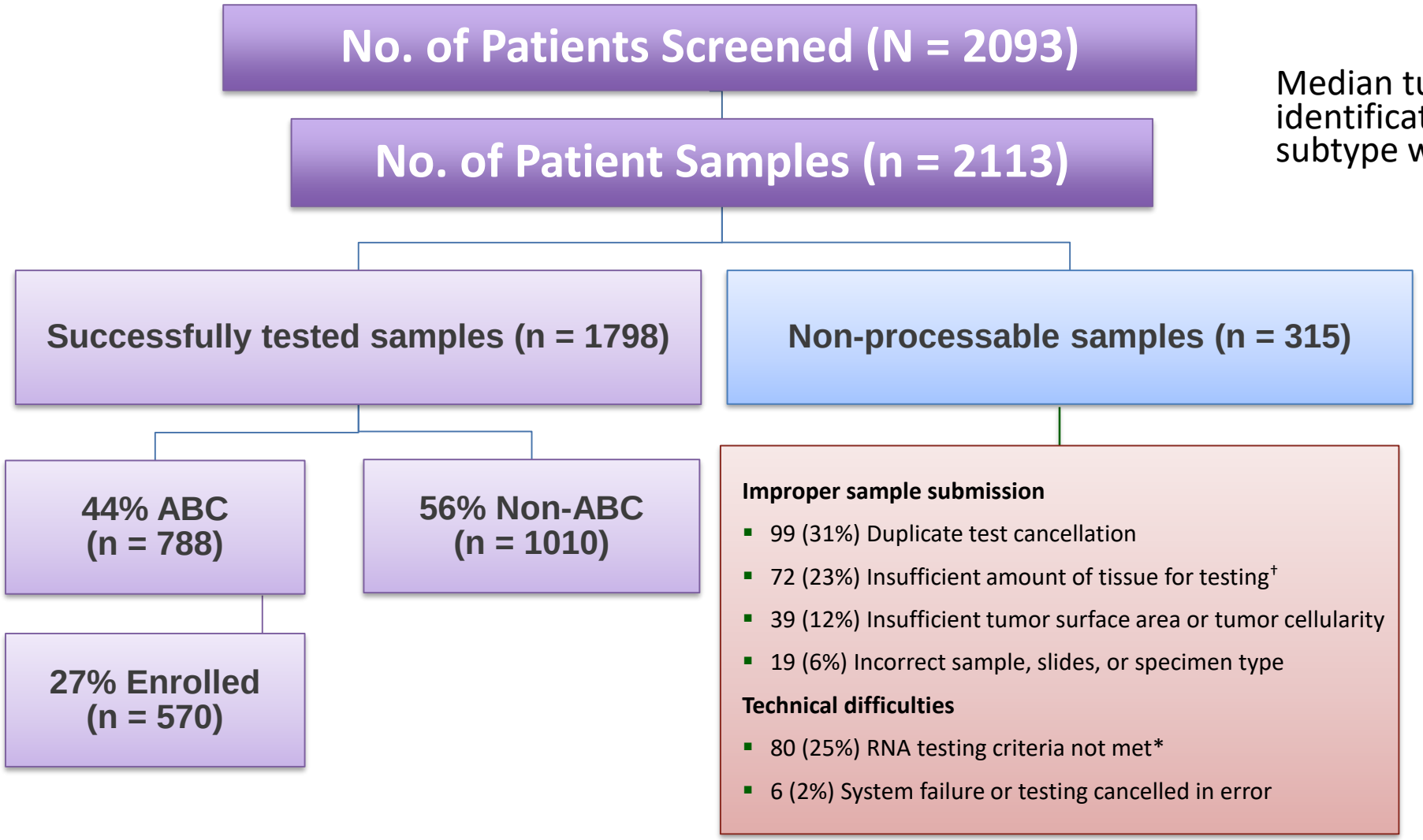
Phase III, randomised, double-blind, placebo controlled, multicenter study to compare the efficacy and safety of lenalidomide plus R-CHOP chemotherapy (R2-CHOP) versus placebo plus R-CHOP chemotherapy in subjects with previously untreated ABC type DLBCL

- Newly diagnosed DLBCL of ABC type
- IPI ≥2; ECOG PS ≤2; age 18–80 years
- Primary endpoint = PFS
- N=560



ClinicalTrials.gov Identifier: NCT02285062.

ROBUST Subtype Analysis Results

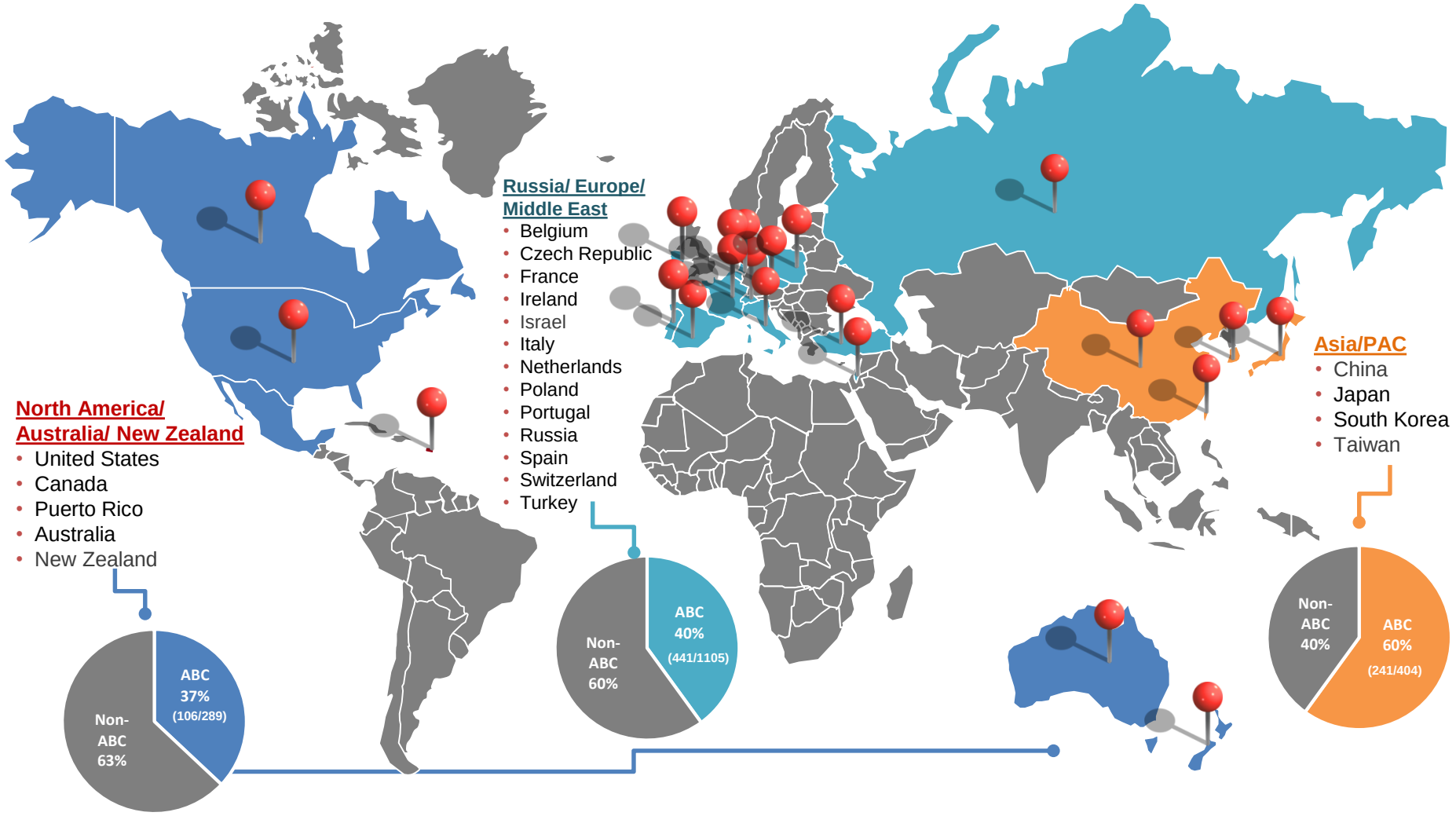


Median turnaround time for identification of DLBCL subtype was 2.4 days

Chiappella et al. EHA 2018

*RNA concentration and/or purity did not meet criteria or low RNA signal at hybridization step.
†Tissue/block from site was small core or tissue biopsy, block from site nearly exhausted, insufficient slide numbers, or no tissue or tumor on slides.

Geography and COO in ROBUST Trial



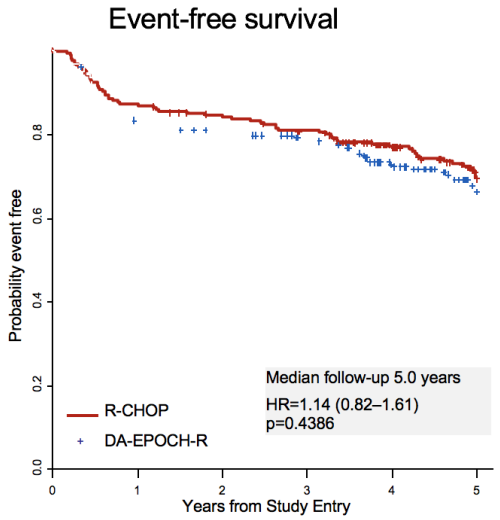
Nowakowski et al. ASCO 2018, Chiappella et al. EHA 2018

How do I treat ABC DLBCL?

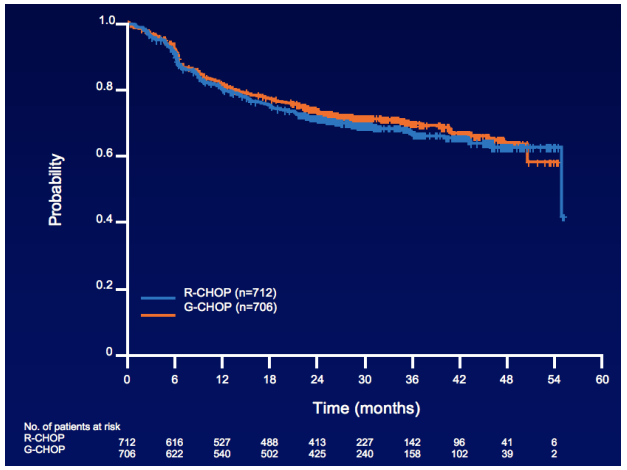
- R-CHOP remains standard of care

PFS/EFS in Recent Trials

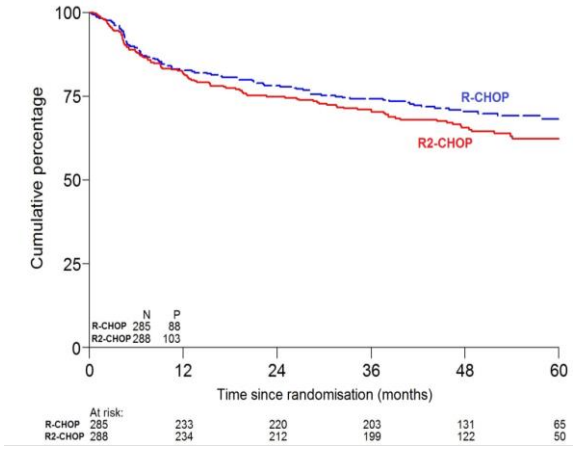
CALGB



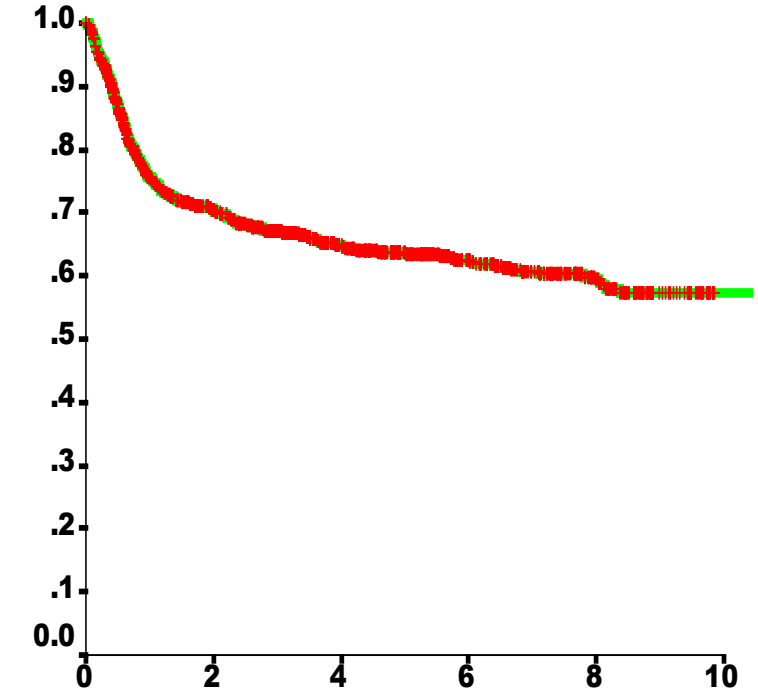
GOYA



HOVON



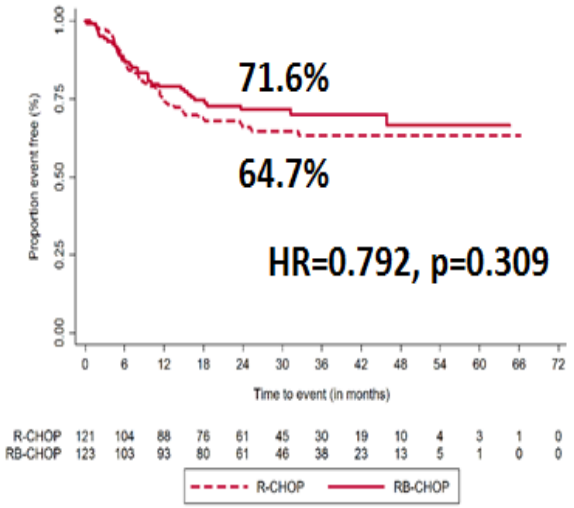
TTF BCCA Population >1200 pts



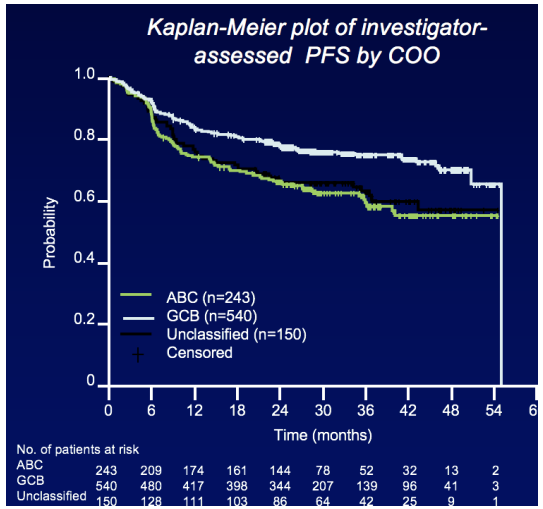
Bartlett, Wilson et al. ASH 2016. Abstract 469;
Vitolo U, et al. J Clin Oncol. 2017 Nov 1;35(31):3529-3537;
Lugtenburg PJ, et al. ASCO Annual Meeting 2016, abstract 7504 – updated data presented at ASCO;
Sehn LH, and Gascoyne RD, Blood. 2015 Jan 1;125(1):22-32.

PFS in non-GCB and ABC DLBCL in Recent Trials

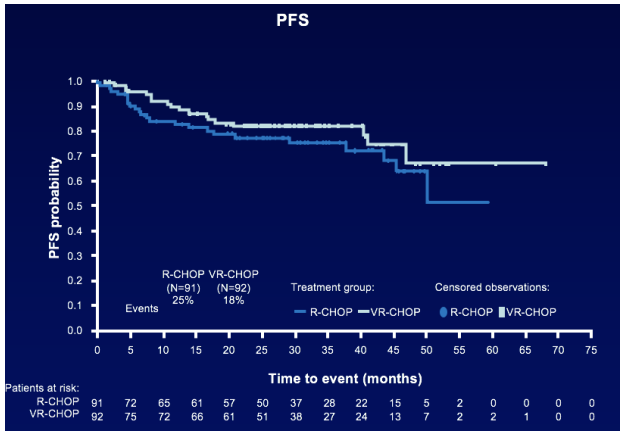
Remodel B

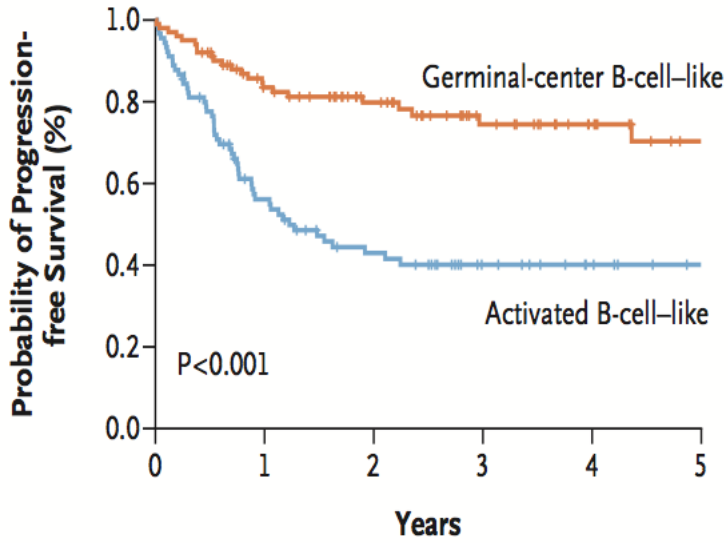


GOYA



PYRAMID





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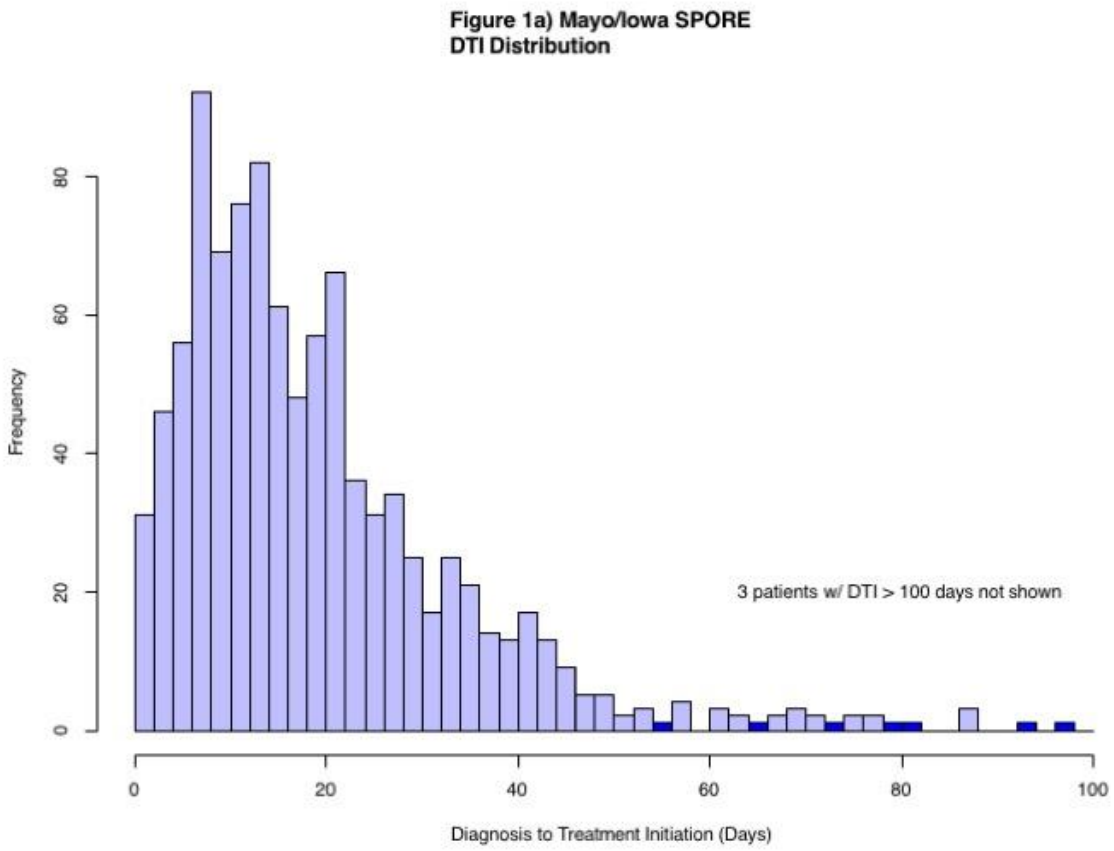
Vitolo U, et al. J Clin Oncol. 2017 Nov 1;35(31):3529-3537;
Leonard JP, et al. Blood 2015;126:811a. (Updated data presented in oral presentation at ASH);
Lenz et al. N Engl J Med 2008;359:2313–2323.

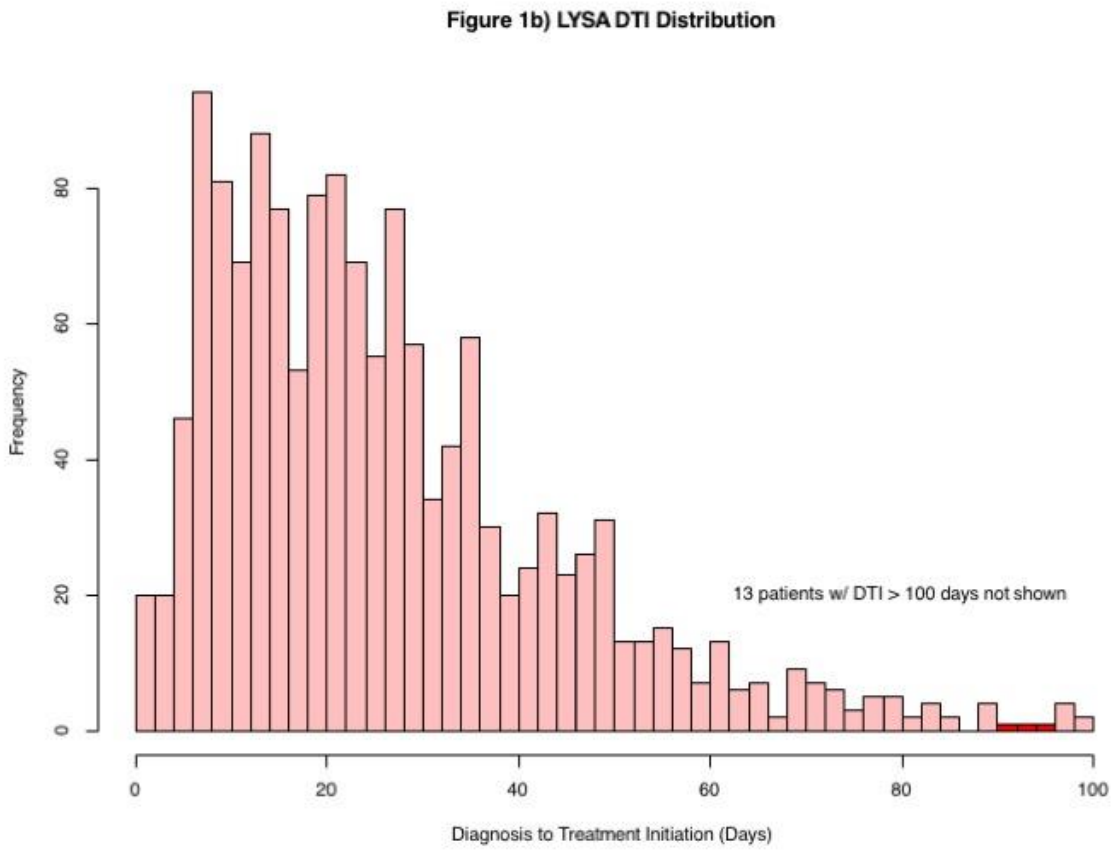
Signor Presto and Signor Lento

- 67 yo male
- Newly diagnosed non-GCB DLBCL stage 4
- LDH 800
- Extranodal bone and liver involvement
- ECOG PS2
- **IPI 4**
- Large abdominal mass with obstructive symptoms, biliary obstruction requiring stenting
- Initiated urgently on RCHOP in the hospital

- 67 yo male
- Newly diagnosed non-GCB DLBCL stage 4
- LDH 400
- Extranodal bone and lung involvement
- ECOG PS2
- **IPI 4**
- Screened; path centrally reviewed and GEP – ABC - successfully enrolled in ongoing clinical trial
- Initiated on XRCHOP trial

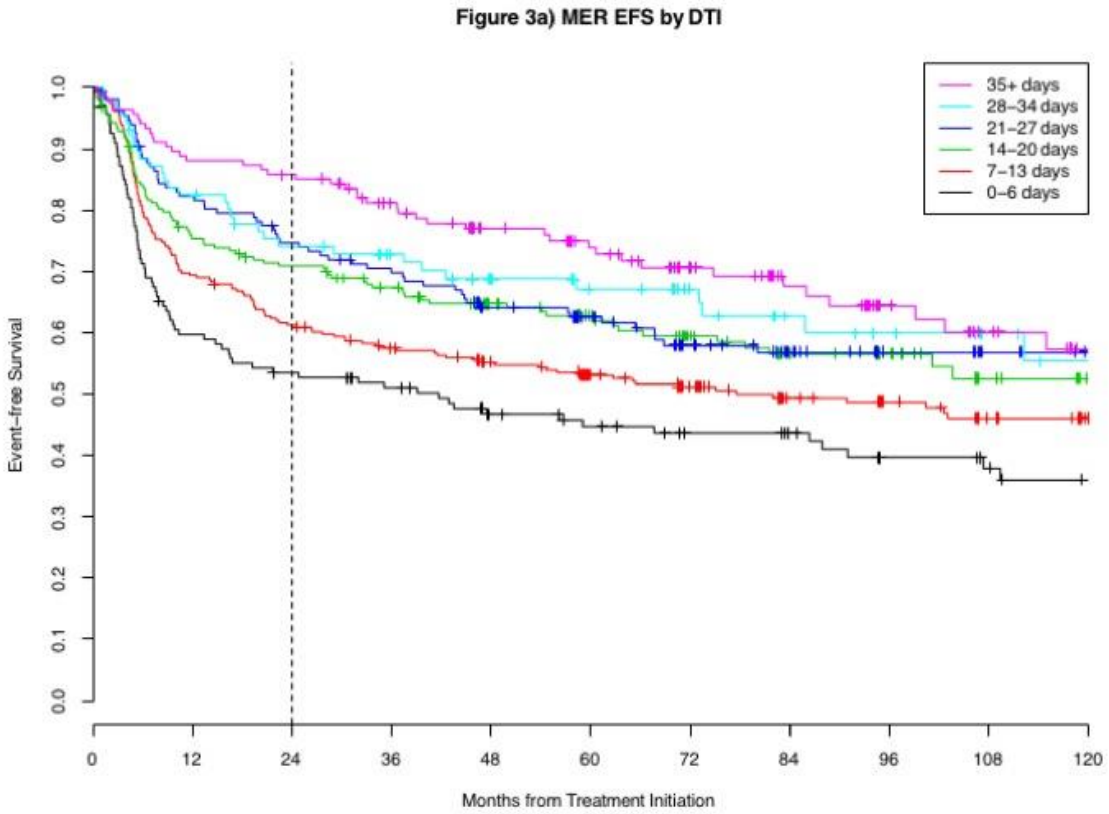
Time from Diagnosis to Treatment Mayo and LYSA

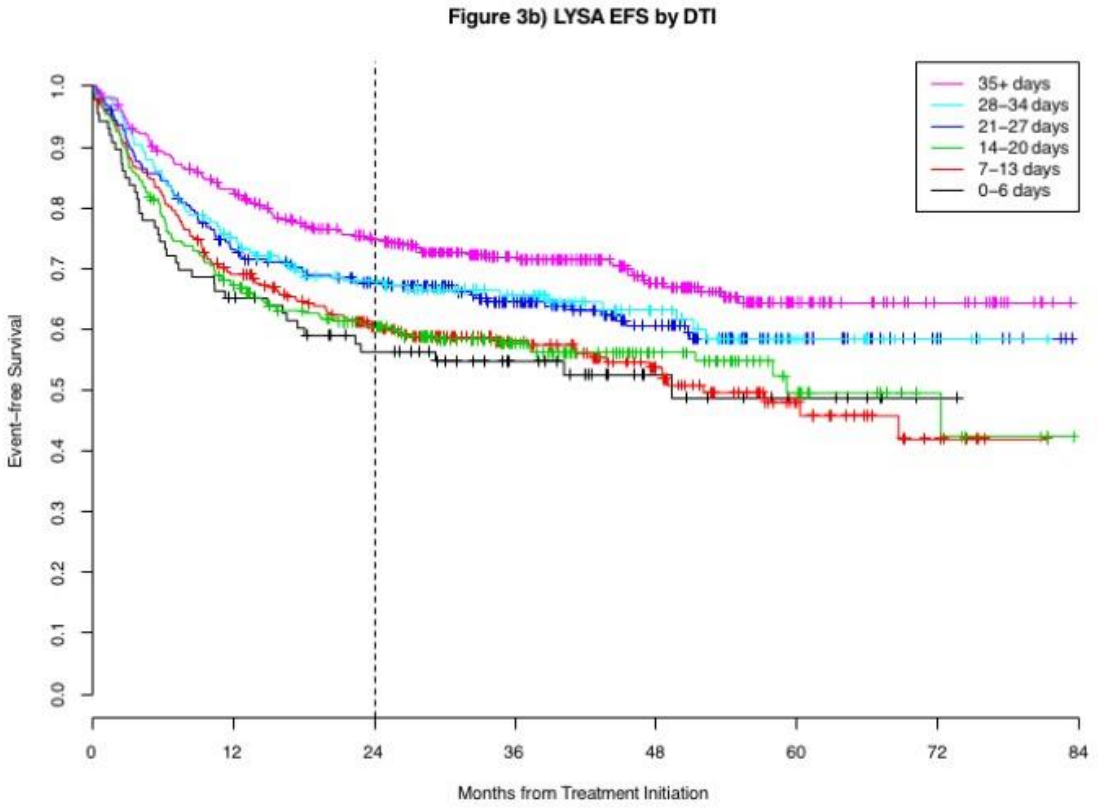




Maurer, Nowakowski JCO, 2018

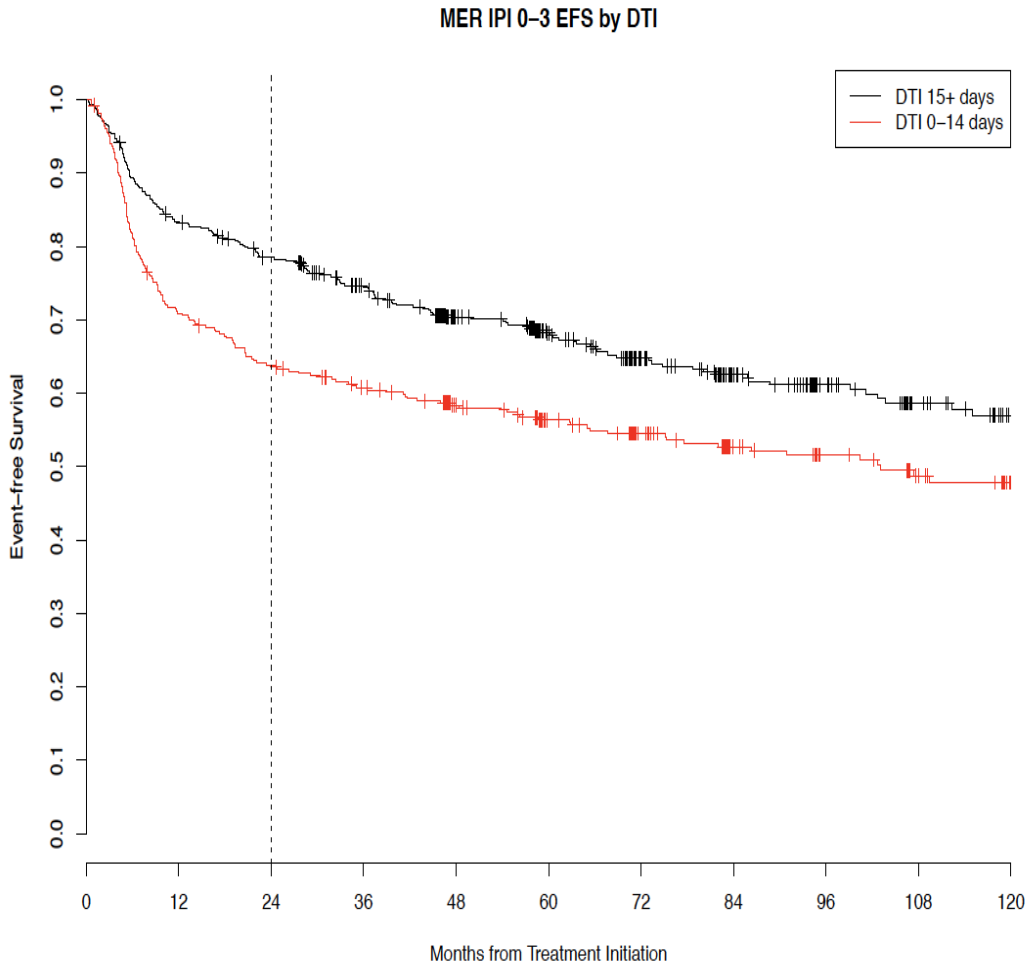
Time from Diagnosis to Treatment and Outcome

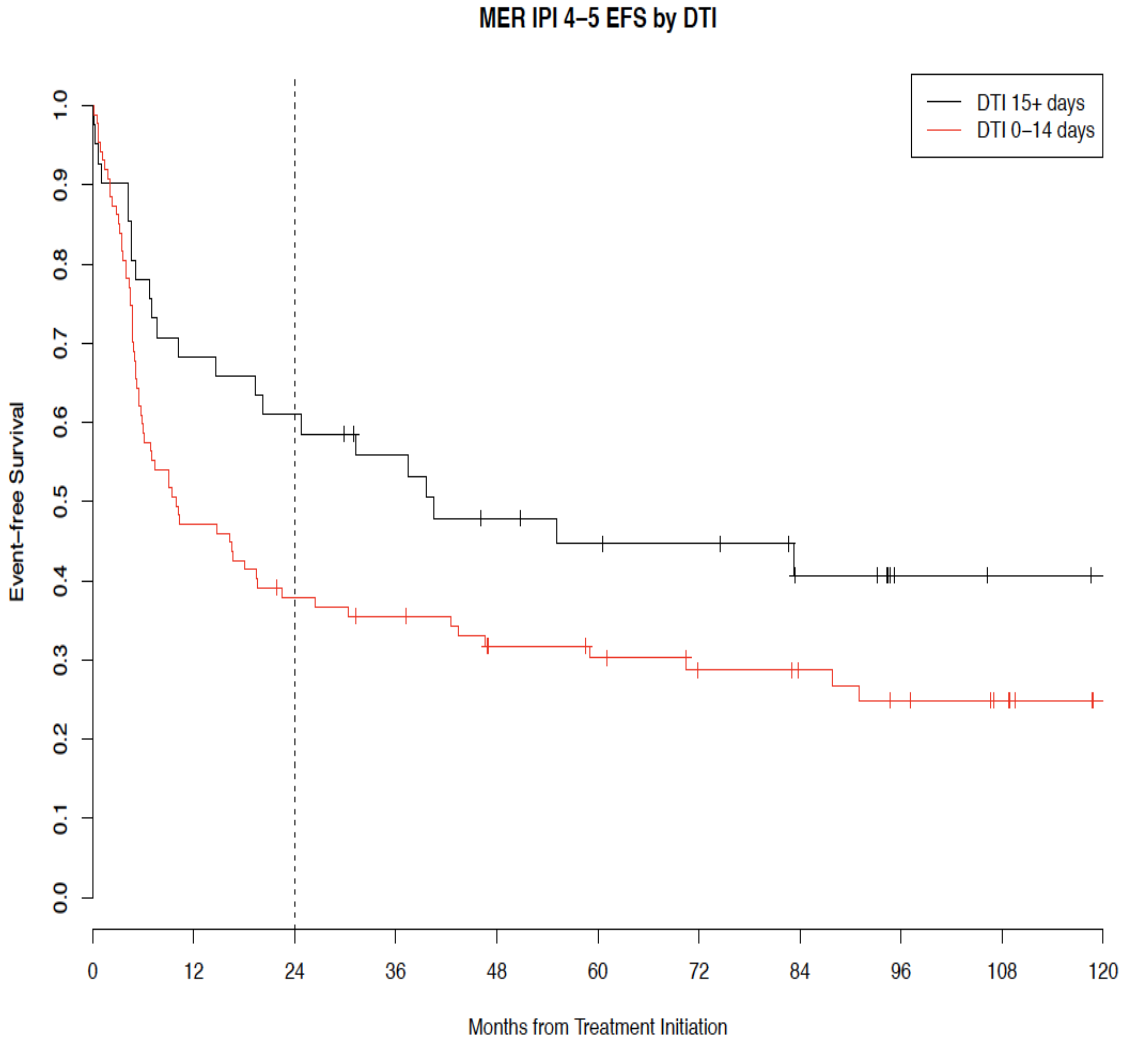




Maurer, Nowakowski JCO, 2018

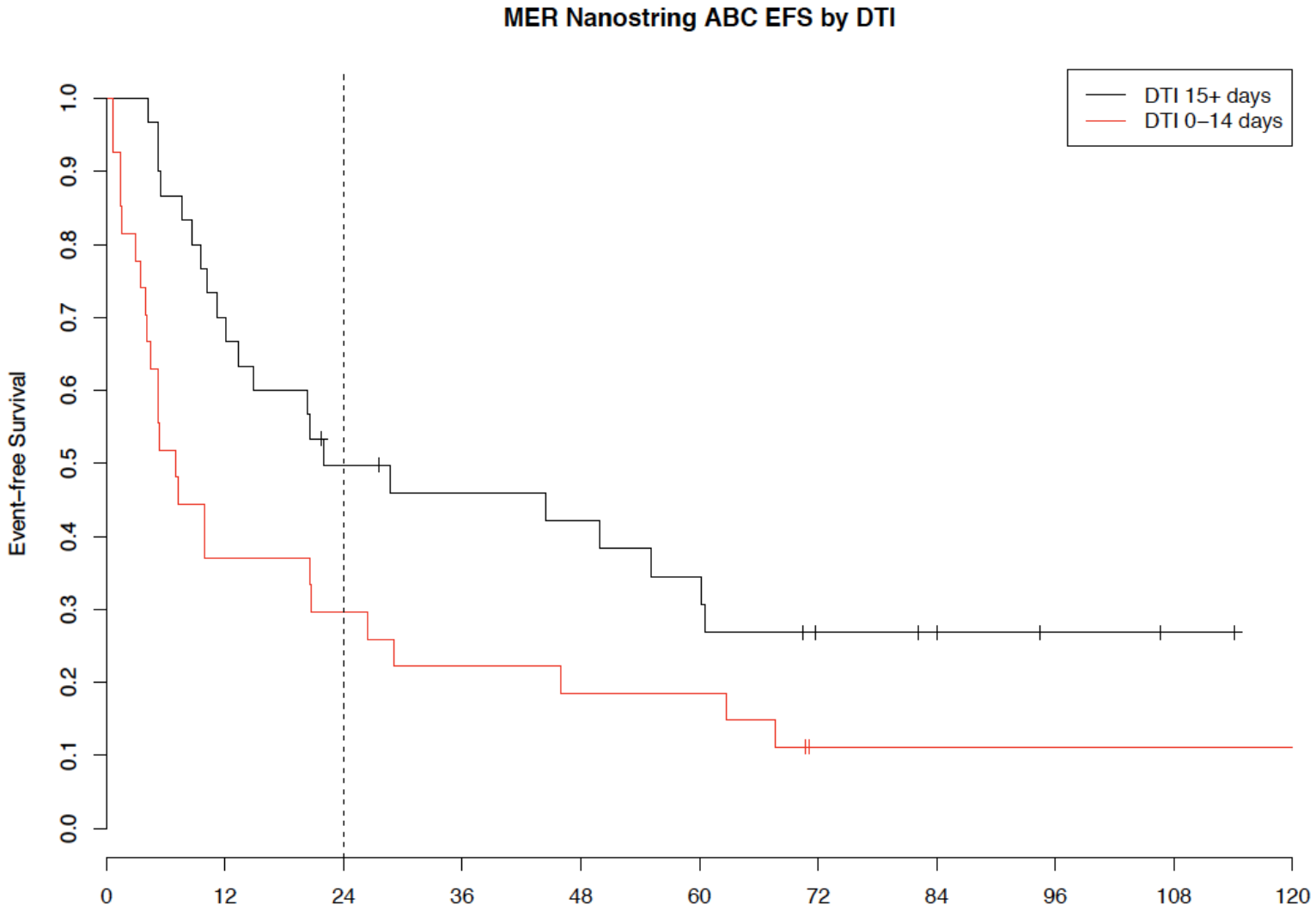
Time From Diagnosis to Initiation of Treatment, IPI and Outcomes in DLBCL





Unpublished data

Time From Diagnosis to Initiation of Treatment, ABC by GEP and Outcomes in DLBCL

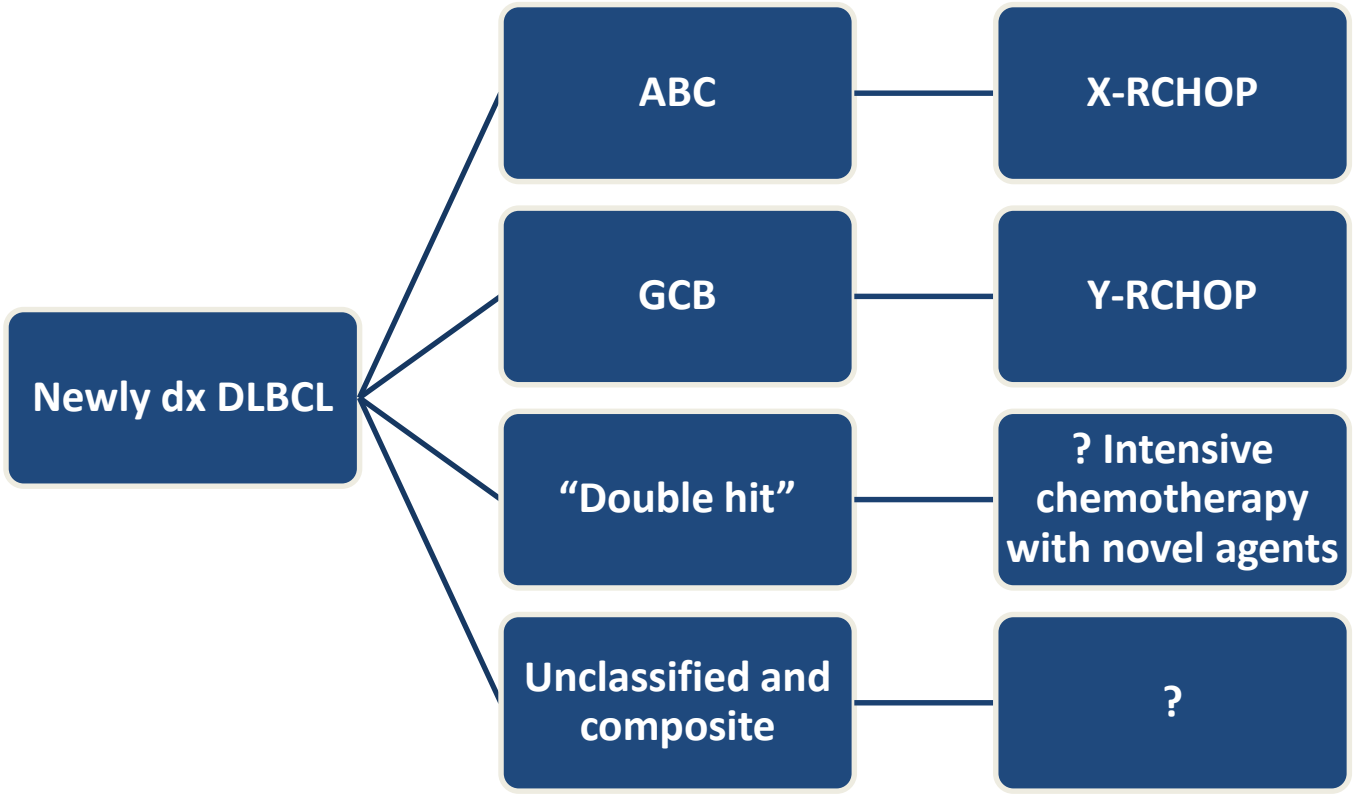


Unpublished data

New Prognostic Factor – Urgency of Therapy

- Patients with urgent need of therapy (signore preste) have poor outcomes
  - < 14 days
  - Regardless of IPI and COO
- These patients are frequently excluded from clinical trials
  - Need for inclusive clinical trials including allowing for pretreatment, cycle 1 of therapy, poor PS and labs

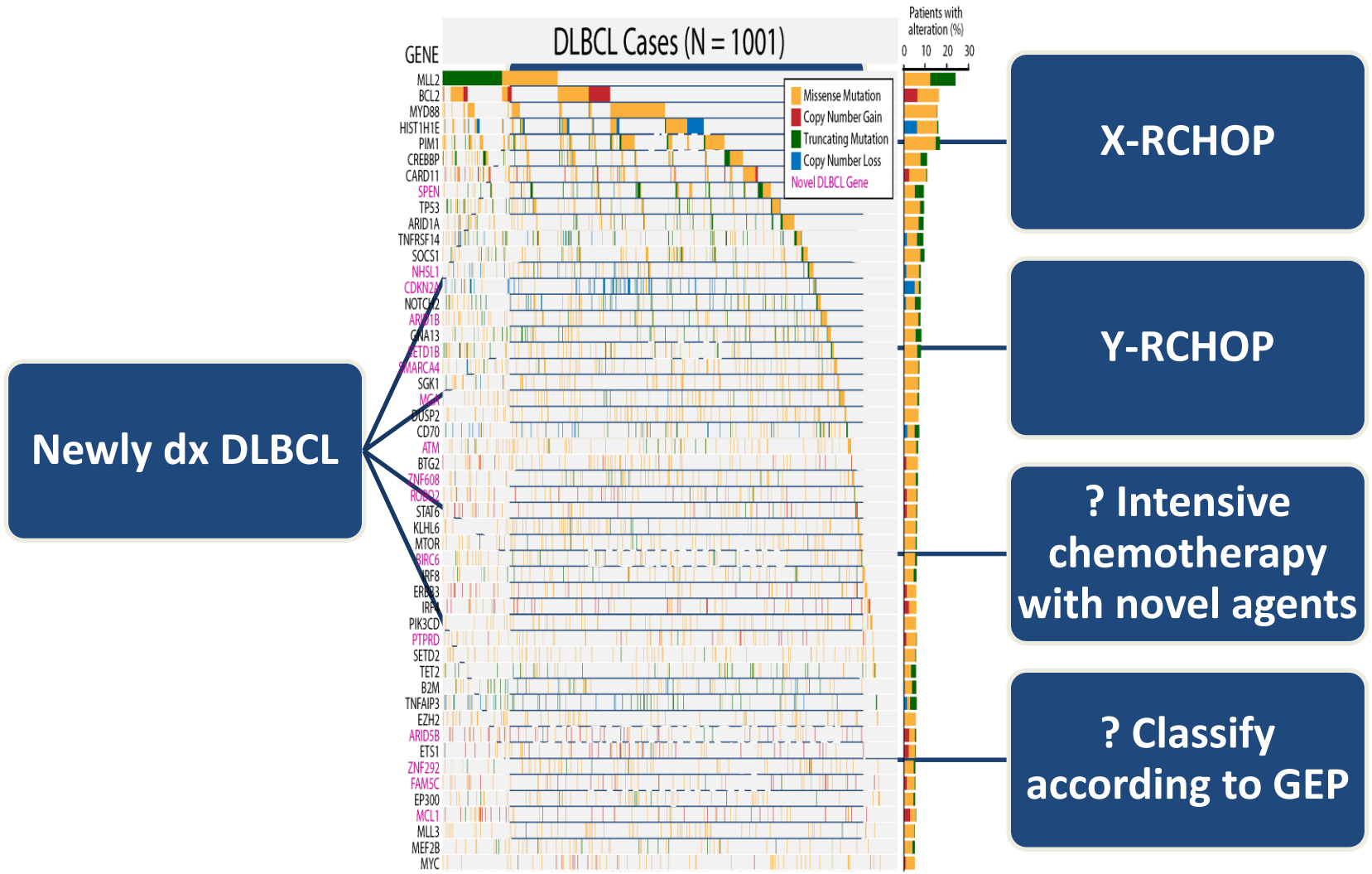
Near Future of DLBCL Therapy – XRCHOP
Precision Medicine Approach



- Several X candidates
- X likely DLBCL subtype specific (ABC)
  - X in non-GCB (ABC) DLBCL)
  - Y-RCHOP in GCB DLBCL

Near Future of DLBCL Therapy – XRCHOP

Precision Medicine Approach



- Several X candidates
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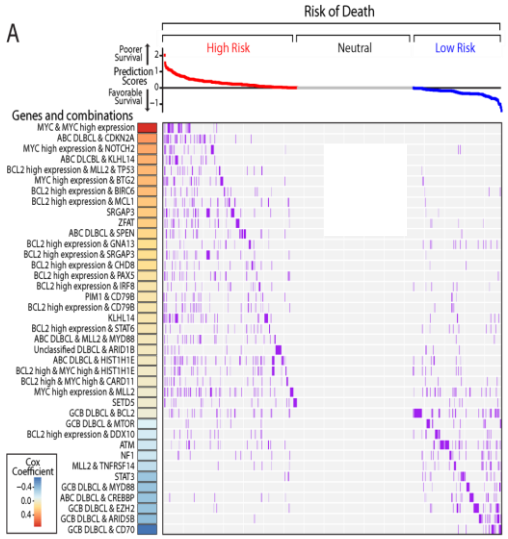
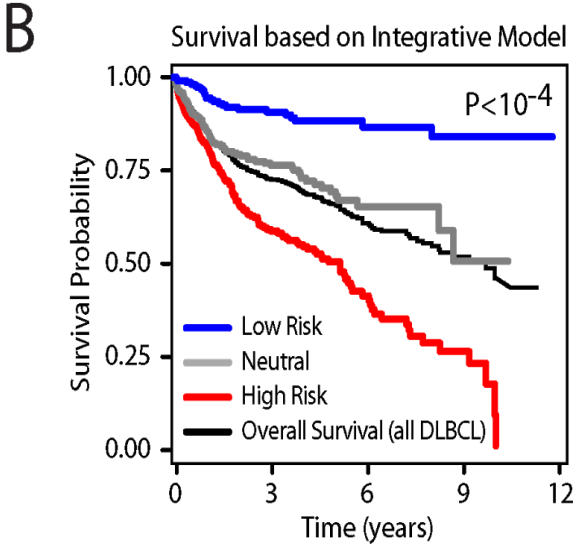
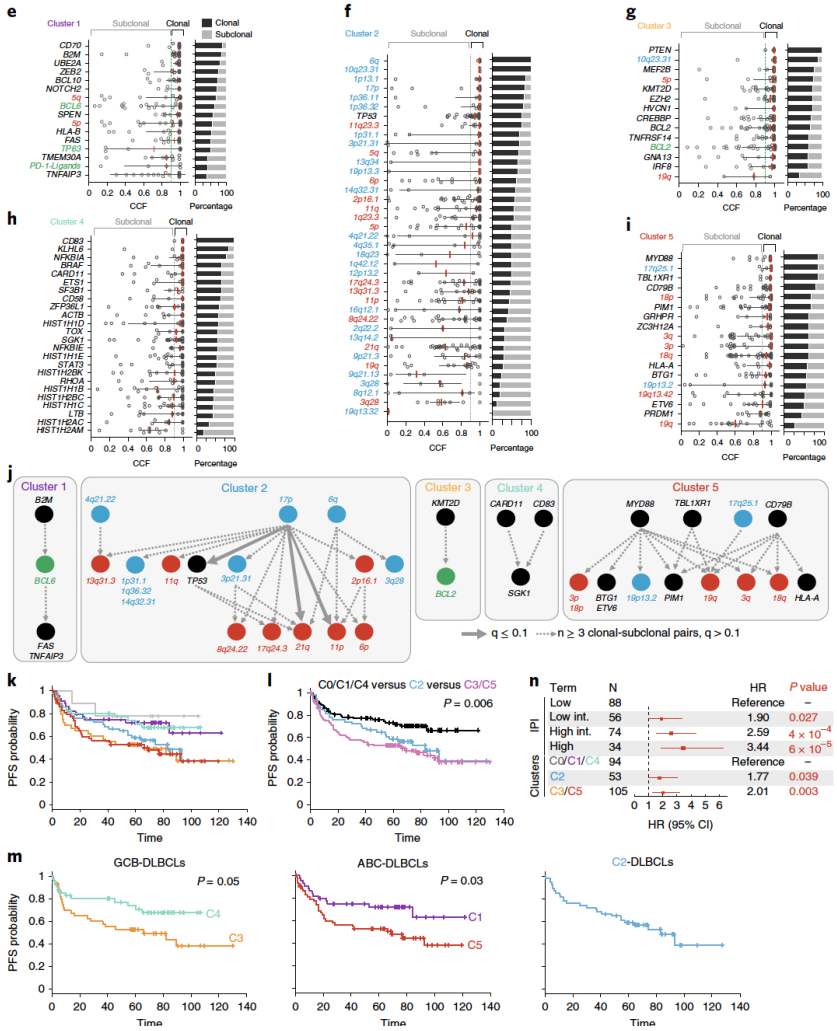
How Do I Treat High Genomic Risk DLBCL

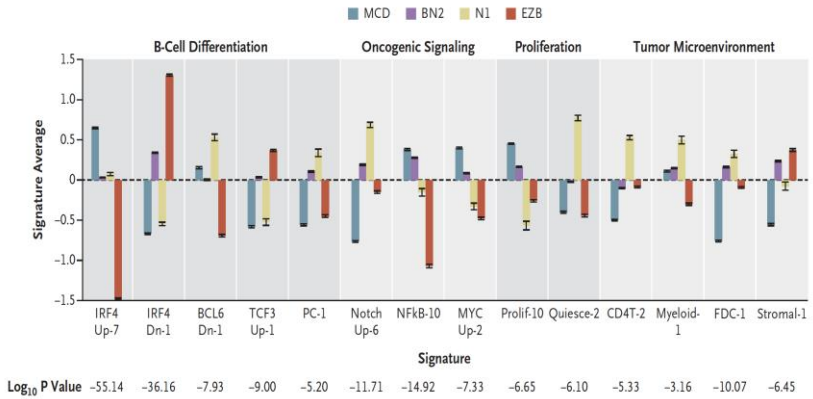


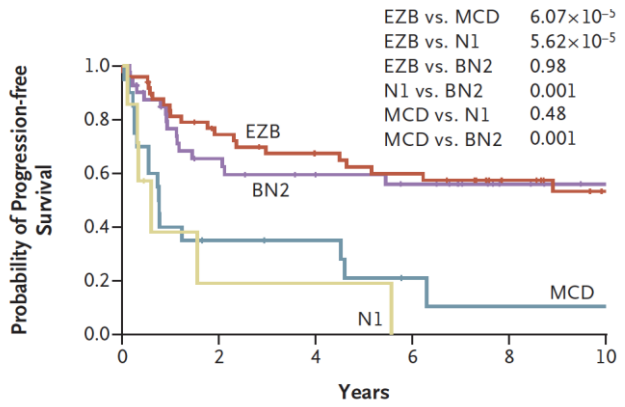


Nat Med 9:2016: 218–221



Nat Med 18:2018: 679–690

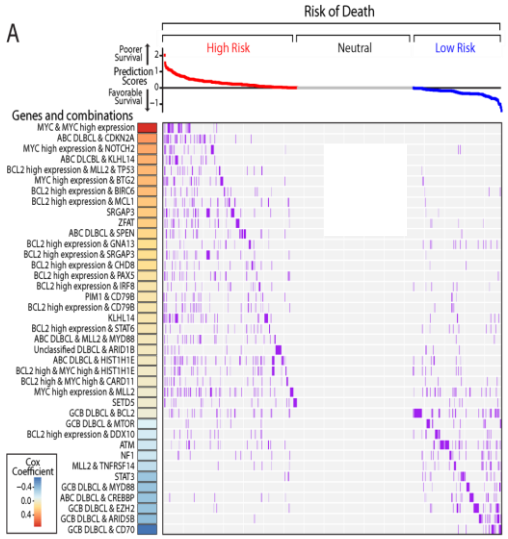


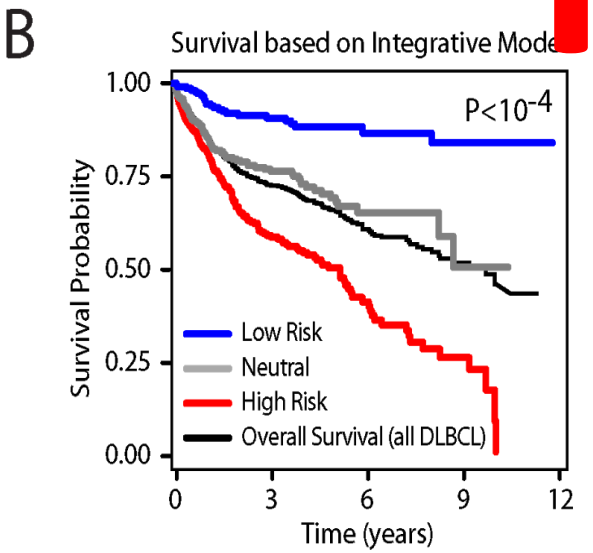


No. at Risk						
MCD	20	6	5	2	1	1
BN2	41	22	17	15	8	5
N1	7	1	1	0	0	0
EZB	49	32	27	24	17	11

N Engl J Med 2018;378:1396-407.

How Do I Treat High Genomic Risk DLBCL





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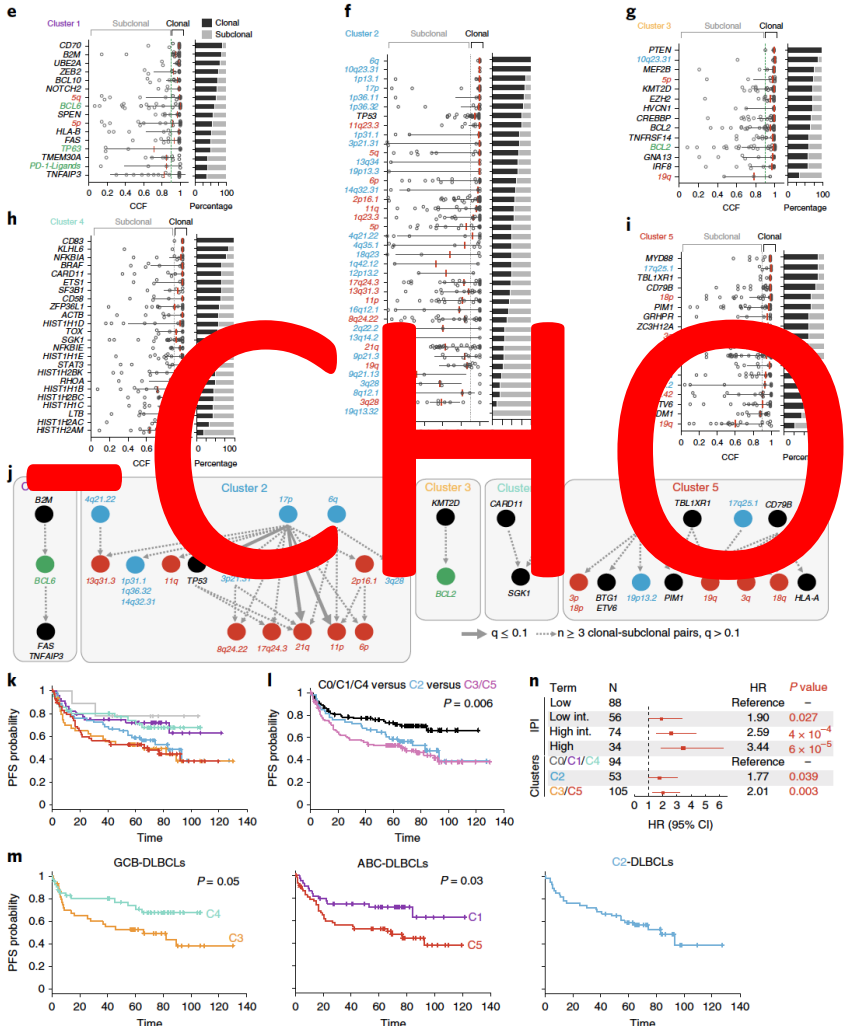

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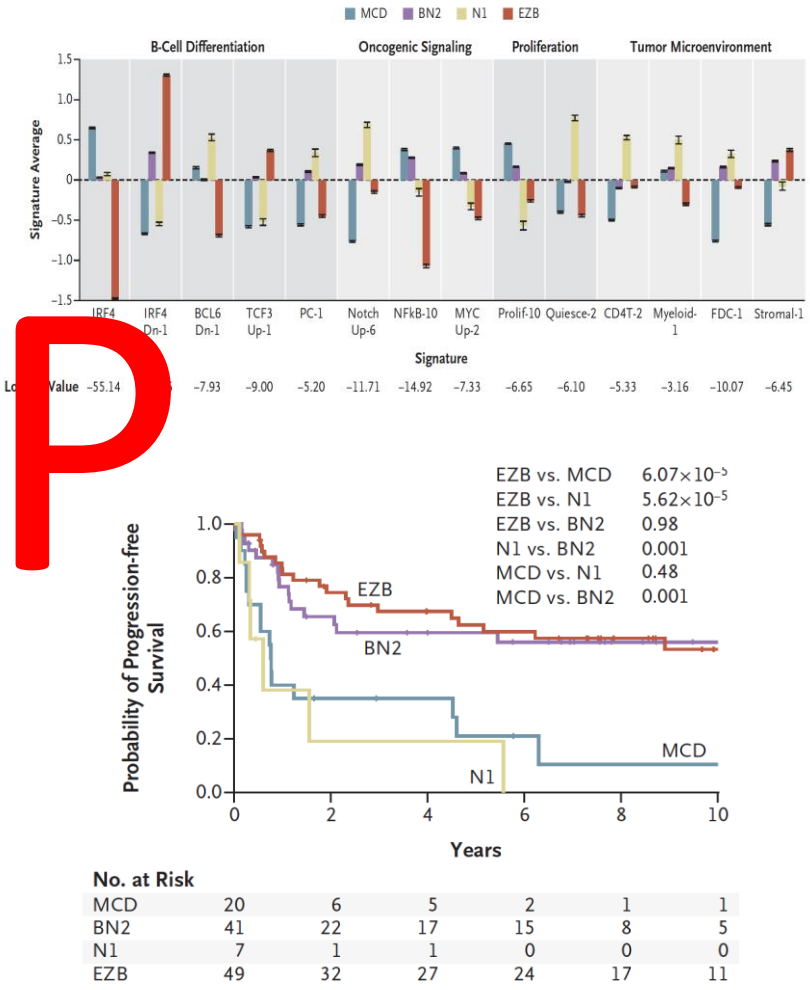

N Engl J Med 2018;378:1396-407.

R-CHOP

Thank you

nowakowski.grzegorz@mayo.edu