Diffuse large B-cell lymphoma

Updates on therapy and monitoring

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U.S. Department of Health and Human Services



Disclosures for Mark Roschewski, MD

Research support	None
Employee	None
Consultant	None
Major stockholder	None
Speakers bureau	None
Scientific advisory board	None

To improve is to change; to be perfect is to change often

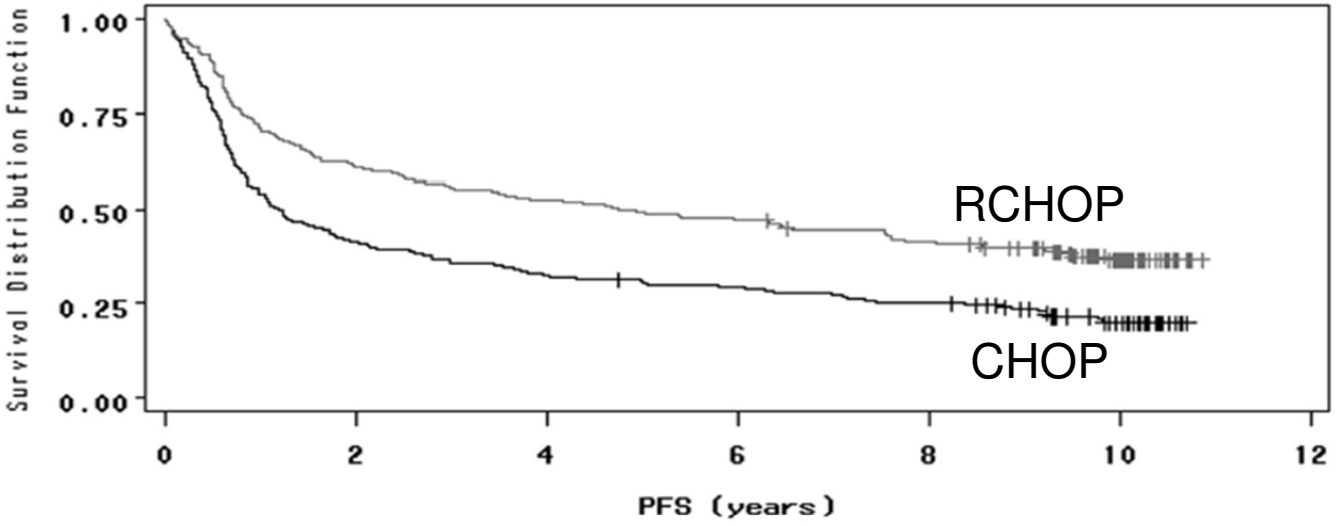
Winston Churchill

Diffuse Large B-cell Lymphoma

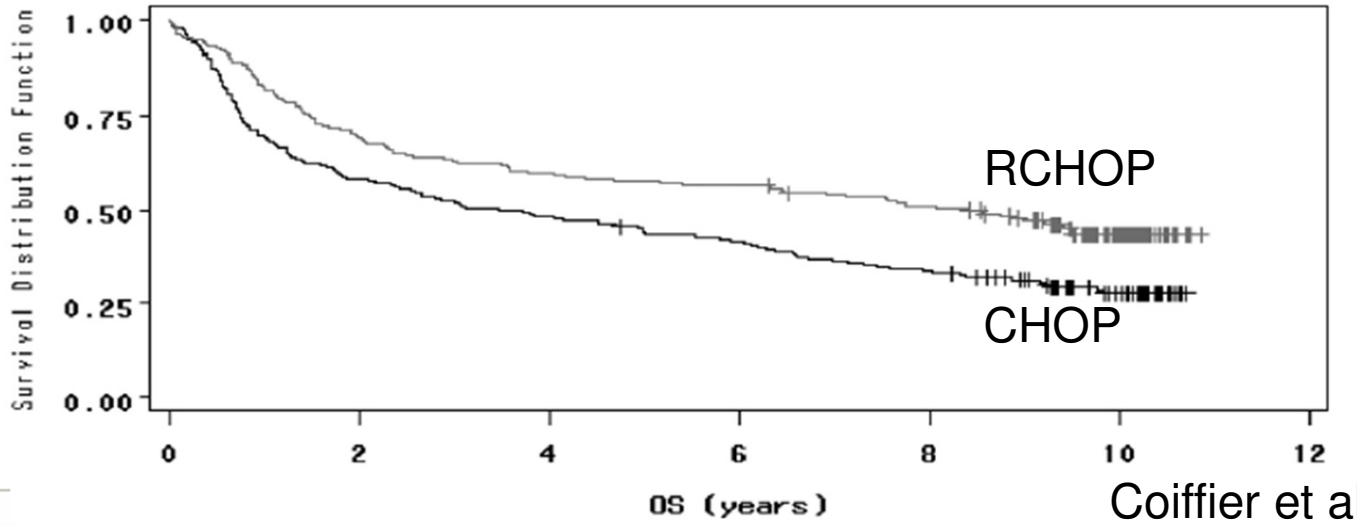
- ~70,000 new cases in US of NHL annually
- 1/3 are DLBCL = 23,000 cases/annum (most common)

- Average age at diagnosis 64 years
- Cure rate ~ 60%

R-CHOP vs CHOP over 60 y/o



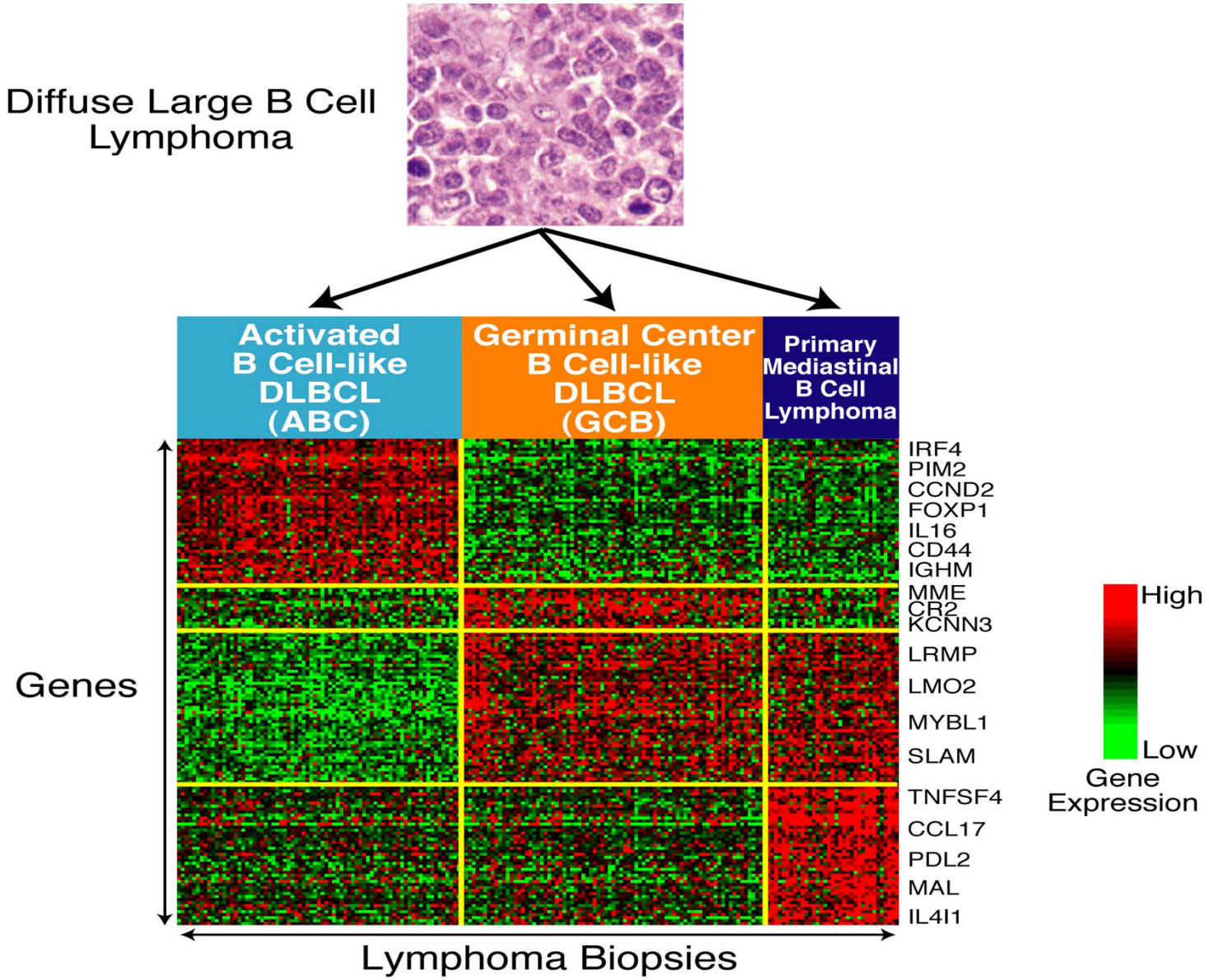
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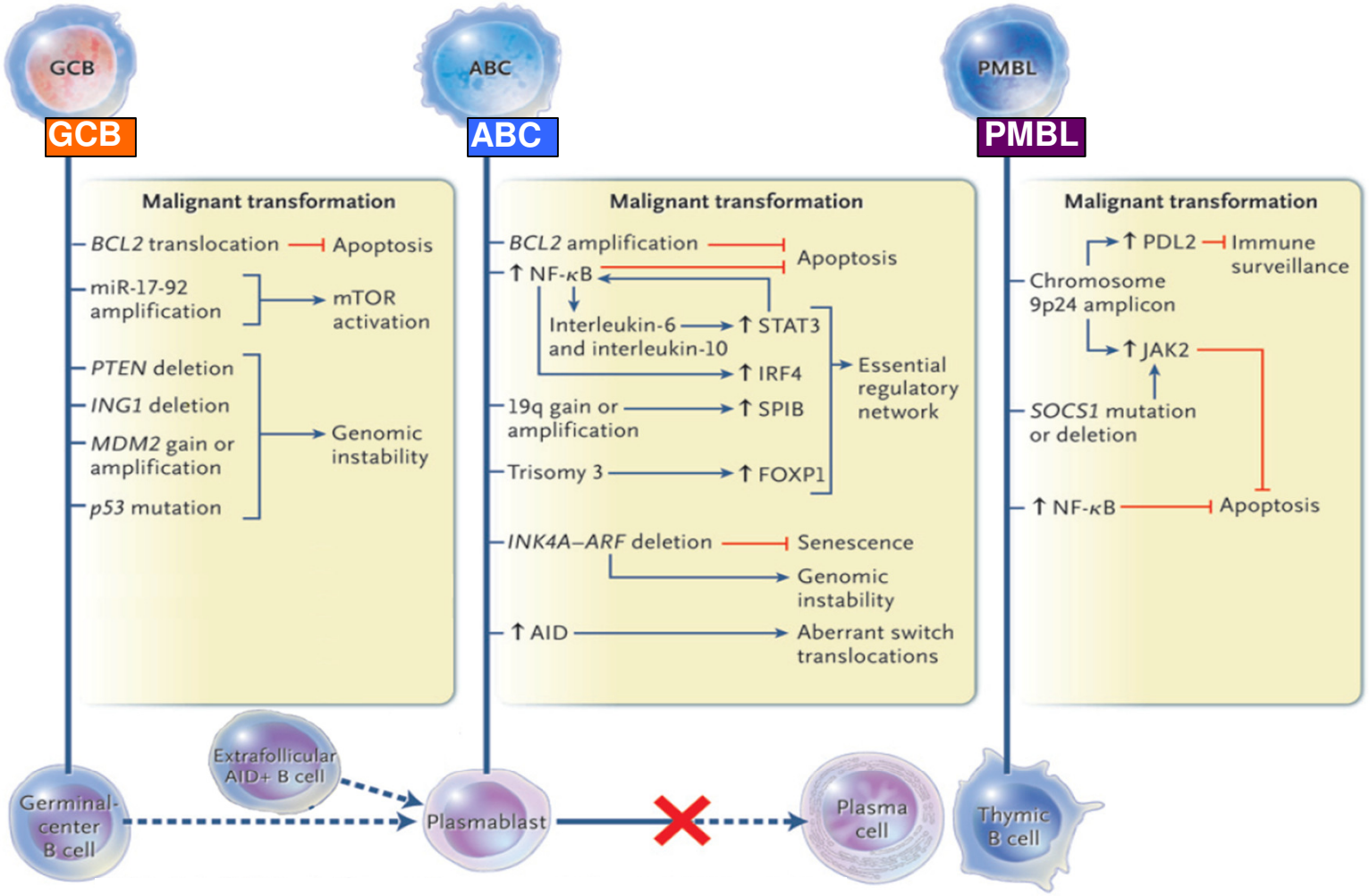
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Coiffier et al. Blood 2012

Dissecting Cancer into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling

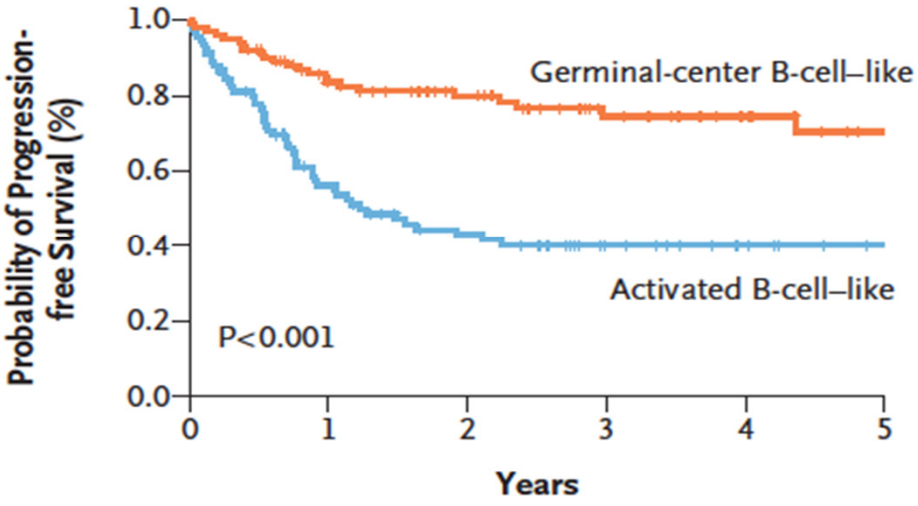


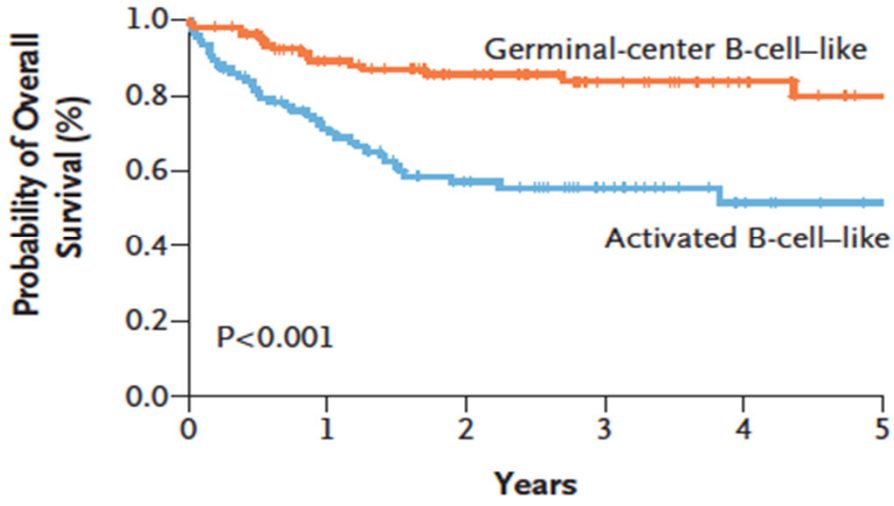
Molecular Pathogenesis of Diffuse Large B Cell Lymphoma



Lenz et al *N Eng J Med* 2010

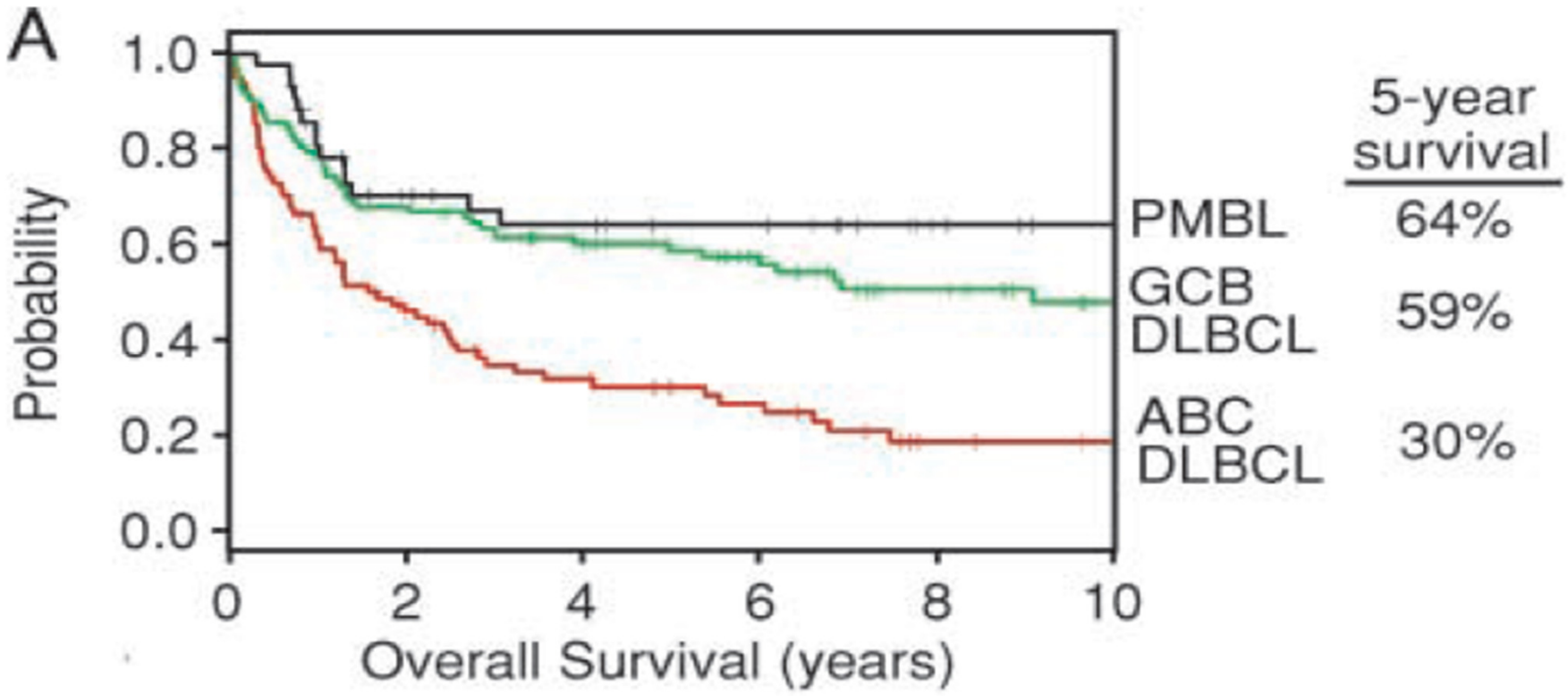
Gene-Expression Predictors of Survival among Patients with Diffuse Large-B-Cell Lymphoma Treated with R-CHOP





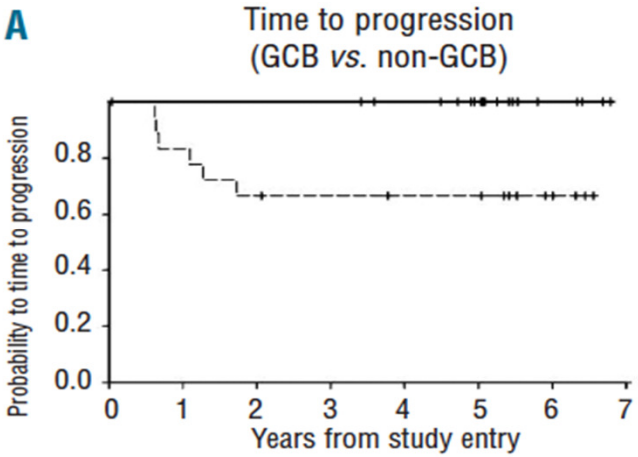
Lenz et al. NEJM 2008

Overall survival by subtype

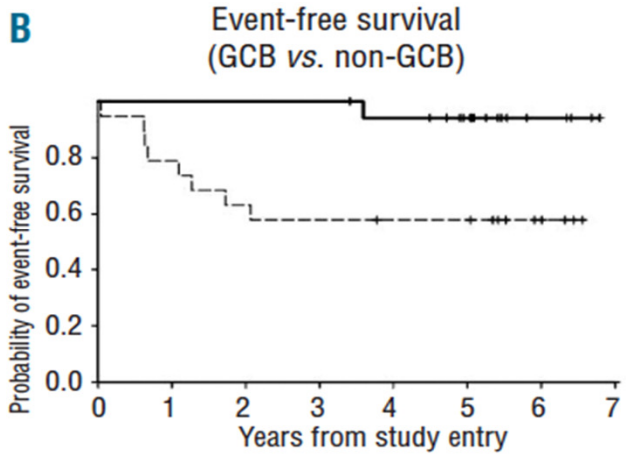


Rosenwald et al. The Journal of Experimental Medicine 2003

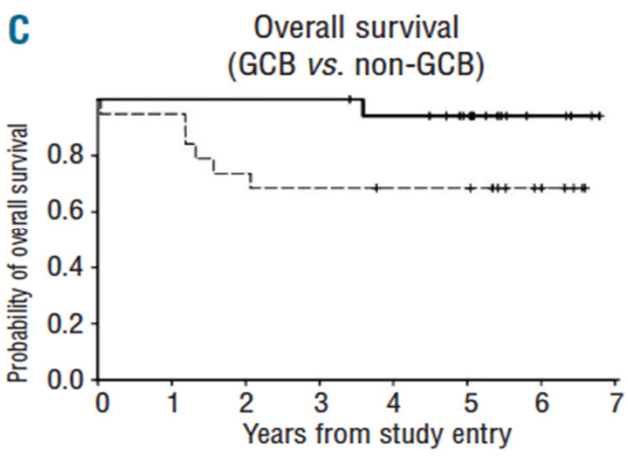
Survival outcomes of DA-EPOCH-R in GCB vs. non-GCB confirmed in CALGB study



p=0.008



p=0.008

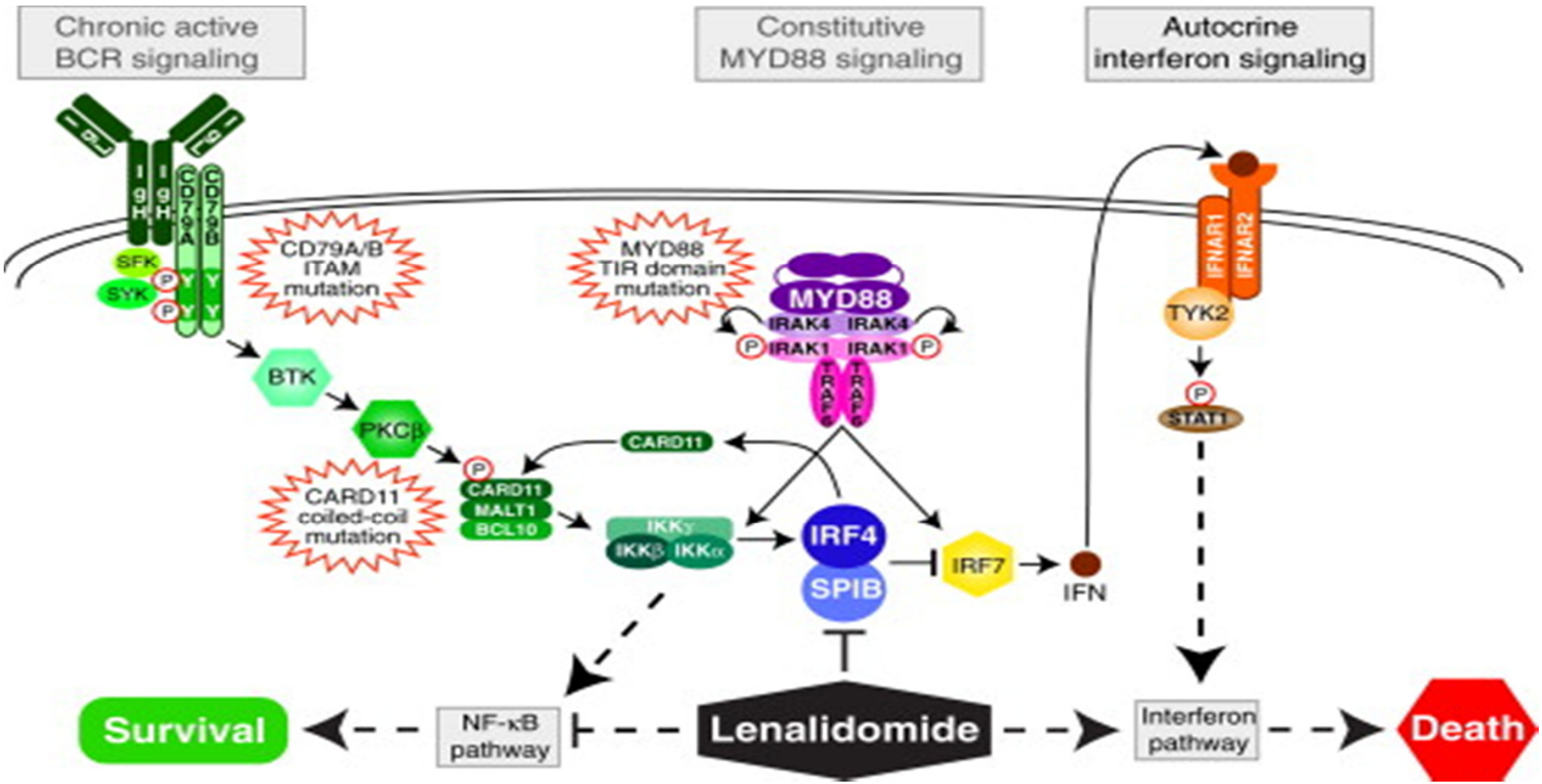


p=0.04

Wilson et al. Haematologica 2012

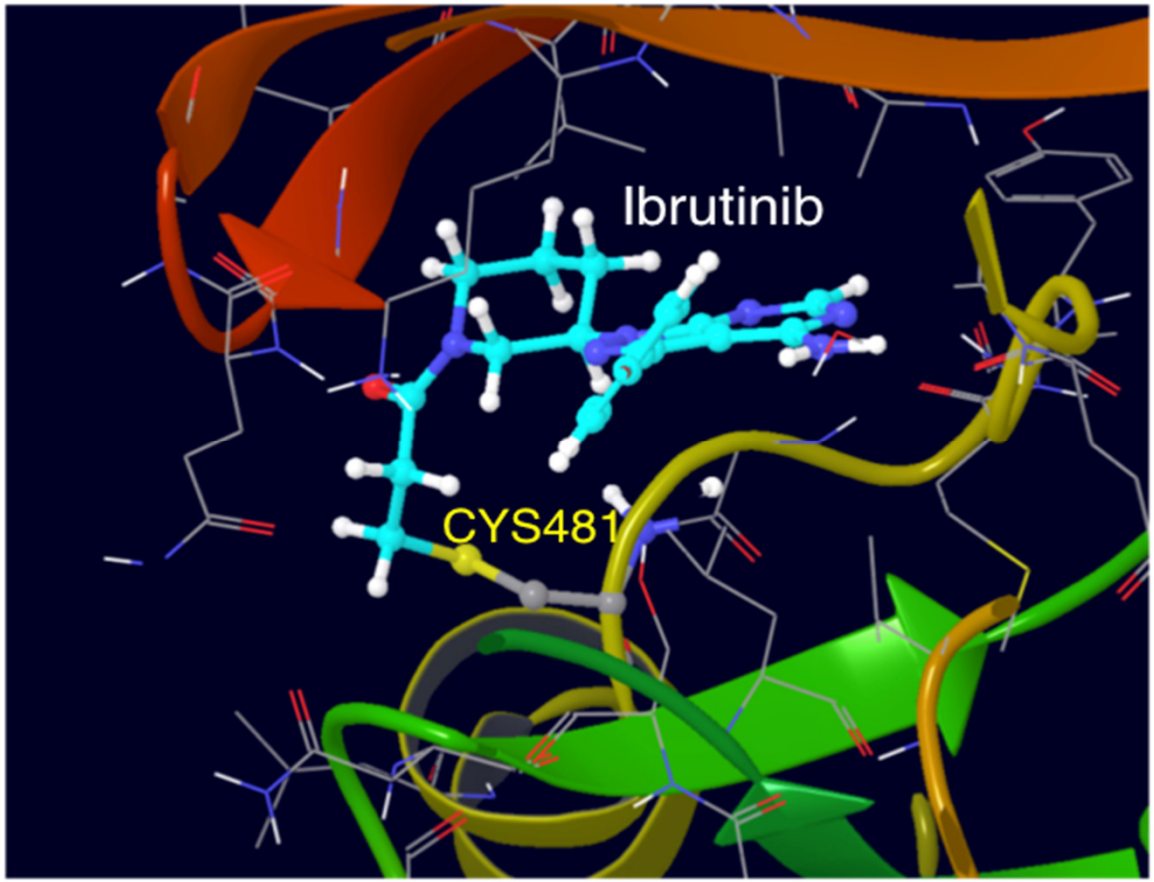
Gene-expression studies lessons

- DLBCL is molecularly heterogeneous with distinct subtypes
- ABC subtype has the worst prognosis
- NFKB pathway activated via multiple mechanisms
- Novel therapies should target oncogenic drivers in subsets



Yang Y et al. Cancer Cell 2012

Ibrutinib: A First-in-Class Inhibitor of BTK



- Forms covalent bond with cysteine-481 in BTK
- High BTK specificity
- IC_{50} = 0.5 nM
- Daily oral dosing produces 24-hr BTK inhibition
- Blocks NF-κB activation in DLBCL cell lines[1,2]

Phase II study of Ibrutinib in relapsed/refractory DLBCL

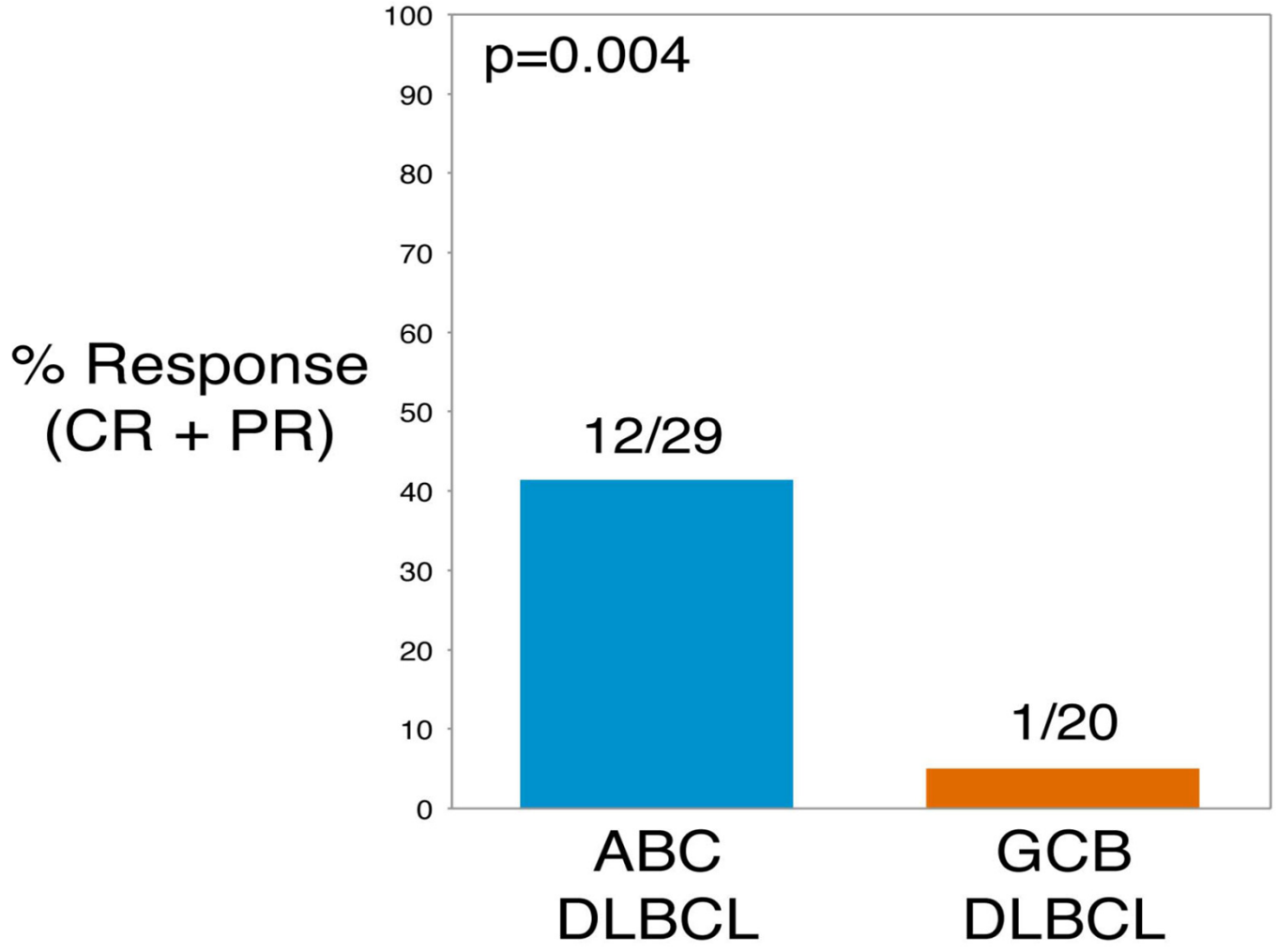
Eligibility (N = 70)

- Relapsed/refractory de novo DLBCL
- Progressive disease (PD) after ASCT or ineligible for ASCT
- Archival tissue for central review
- No primary mediastinal DLBCL, transformed DLBCL or CNS involvement

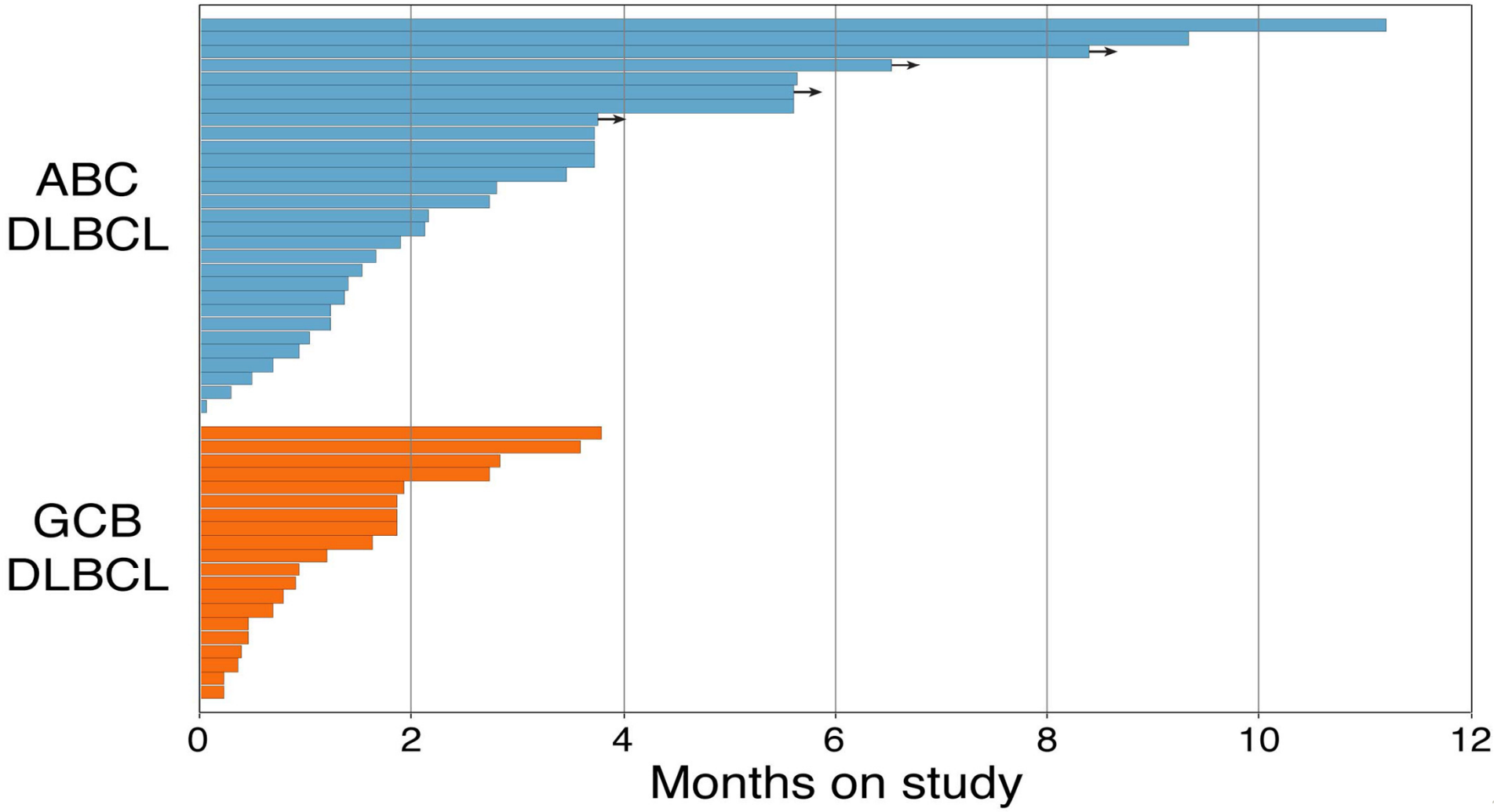
→ Ibrutinib:
560 mg/d, PO

Wilson WH et al. ASH 2012

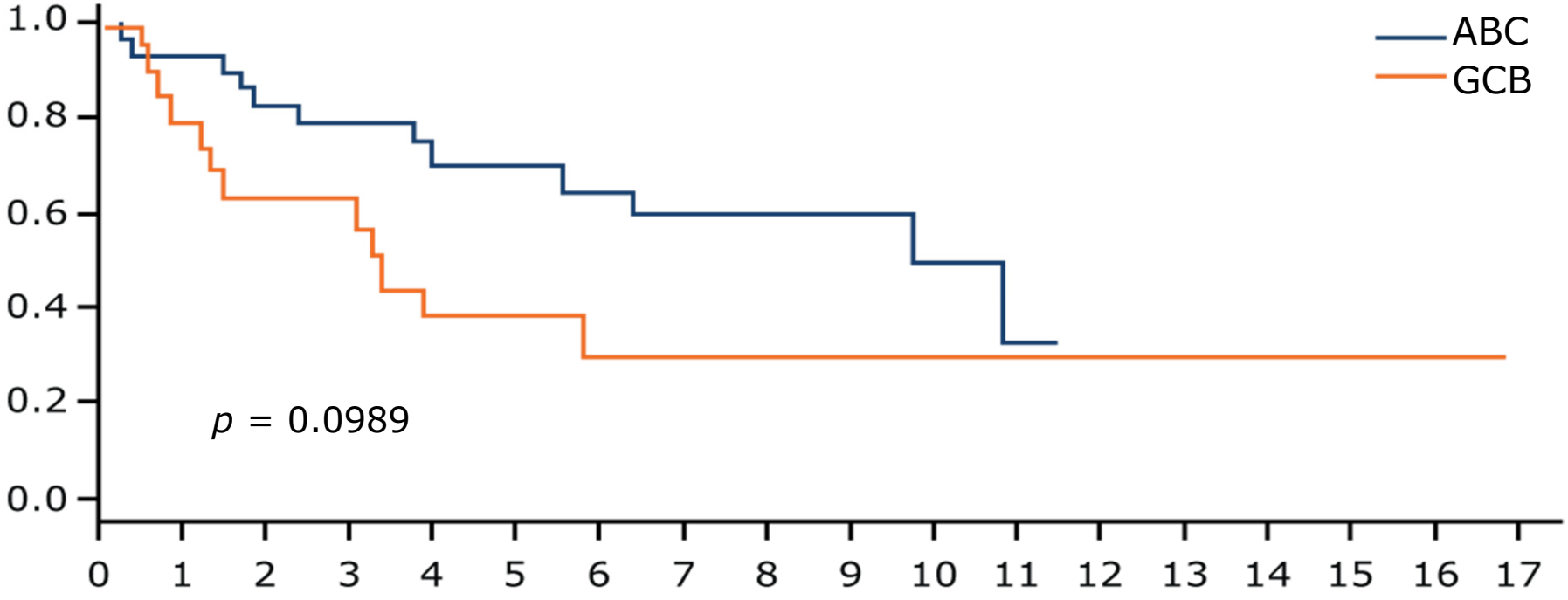
Higher Response Rate to Ibrutinib in ABC DLBCL Than GCB DLBCL



Ibrutinib Responses Can Extend Life in Patients With Relapsed/Refractory ABC DLBCL For > 6 Months



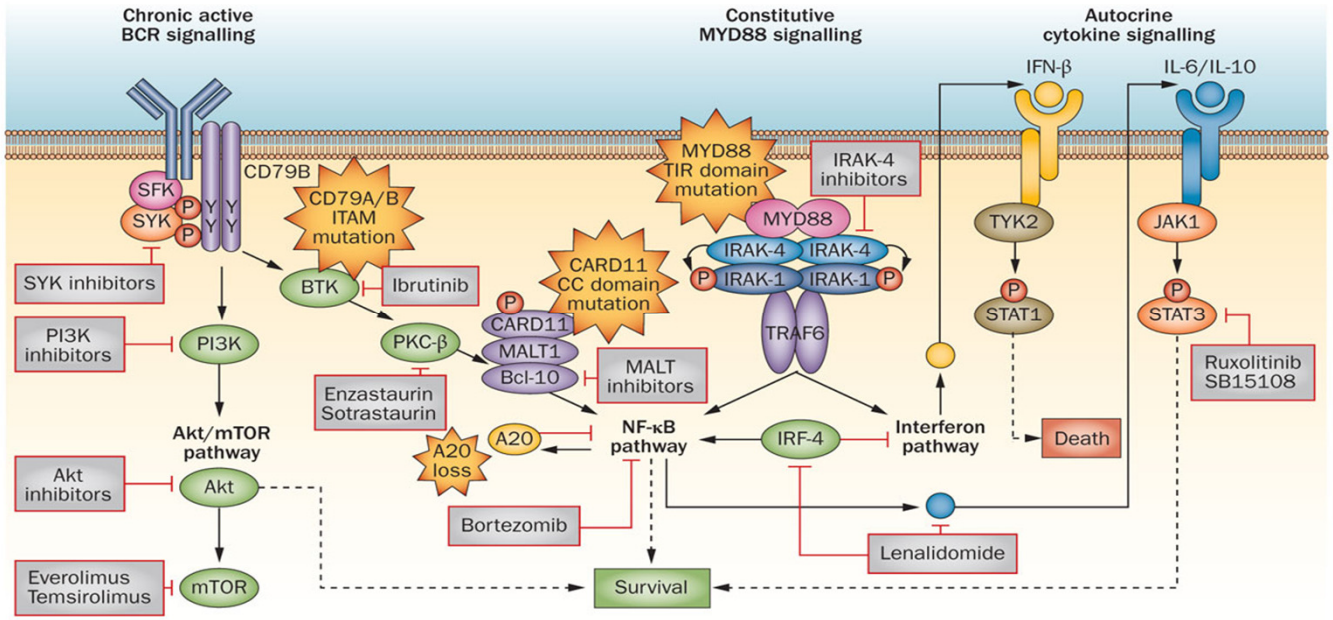
Overall Survival in ABC and GCB DLBCL



	ABC (n = 29)	GCB (n = 20)
Median OS	9.76 mo	3.35 mo

Wilson WH et al. *Proc ASH* 2012;Abstract 686.

Figure 3 The key signalling pathways implicated in ABC DLBCL with targeted novel agents in clinical development

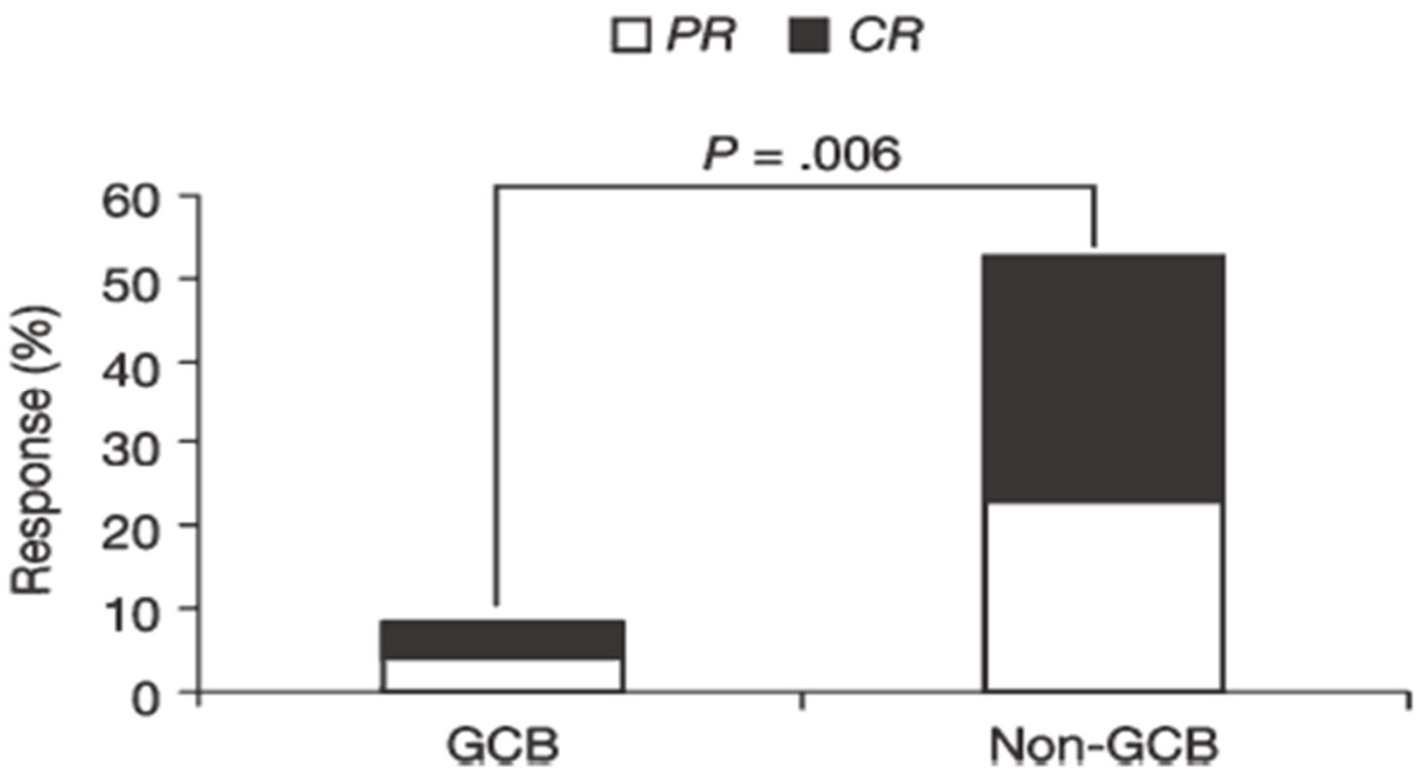


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Roschewski, M. *et al.* (2013) Diffuse large B-cell lymphoma—treatment approaches in the molecular era *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.197

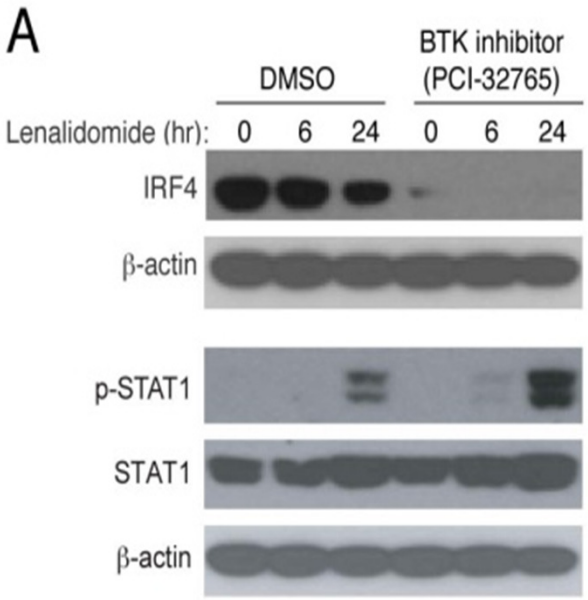
nature REVIEWS CLINICAL ONCOLOGY

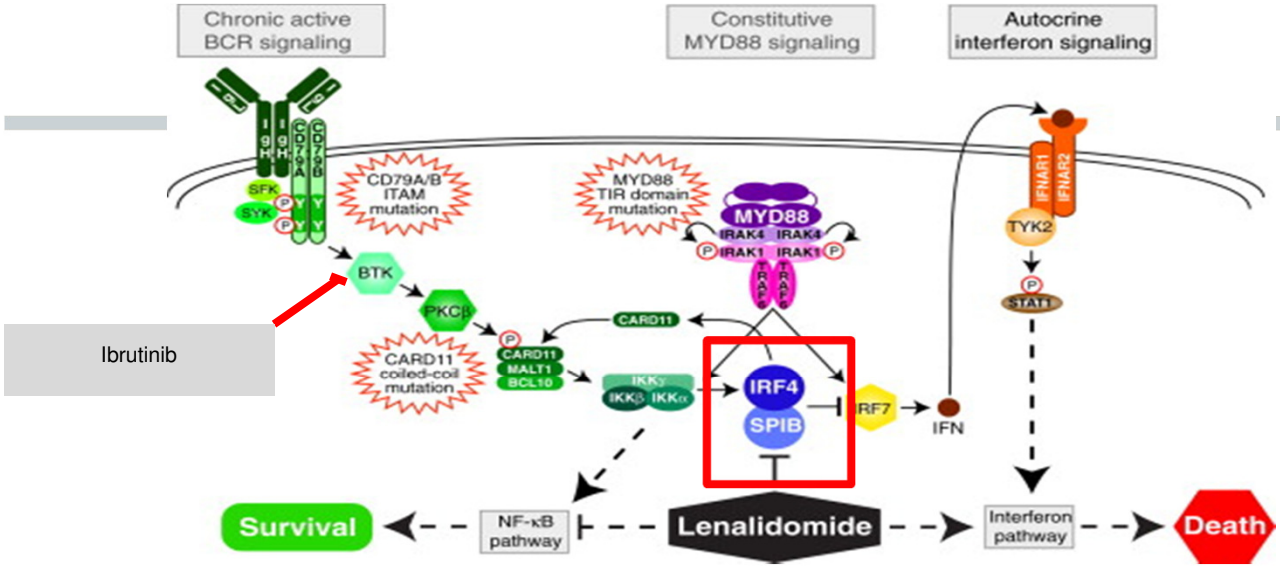
Non-GCB responds better to Lenalidomide

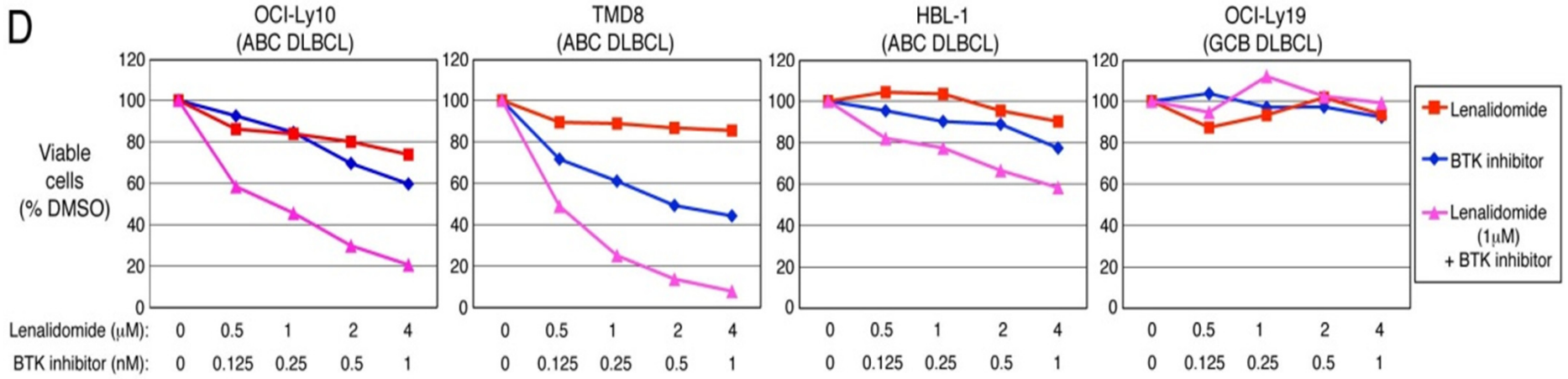


Hernandez-Ilizaliturri FJ et al, Cancer 2011.

Lenalidomide Synergizes with Ibrutinib in ABC Subtype







Yang et al. Cancer Cell 2012

Phase I/II of Ibrutinib and Lenalidomide with DA-EPOCH-R for Relapsed/Refractory DLBCL

- Phase I/II study of 37-44 patients
- Phase I: Lenalidomide will be escalated to determine the STD
- Phase II will assess efficacy of STD of lenalidomide and ibrutinib with DA-EPOCH-R in ABC subtype DLBCL.
- Phase I/II, treatment administered every 3-weeks

Treatment Schema

Relapsed/Refractory DLBCL

All subtypes

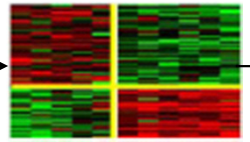
Phase I: Lenalidomide in escalated doses + Ibrutinib+ DA-EPOCH-R

Determine STD of Lenalidomide

ABC subtype only

Phase II: DA-EPOCH-RIR until disease progression or a maximum of 6 cycles

Pre-Rx Biopsy



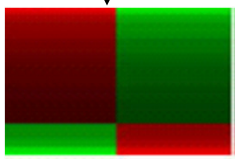
GCB DLBCL

ABC DLBCL

CD79B, CARD11, MYD88 mutations

On Rx Biopsy

ABC subtype only



NF-κB signature

Type I Interferon signature

A Pilot Phase I/II Study of Ibrutinib and Immuno-chemotherapy (Dose-Adjusted TEDDI-R) in PCNSL

K. Dunleavy, C. Grant, C. Lai, N. Lucas, M. Shovlin, B. Miller, S. Pittaluga, M. Roschewski, S. Steinberg, L. Staudt and WH Wilson

Dose Adjusted-TEDDI-R

Temozolomide 100 mg/m^2/day PO days 2 to 5

Etoposide 50 mg/m^2/day IV days 2 to 5

Doxil 50 mg/m^2 IV day 2

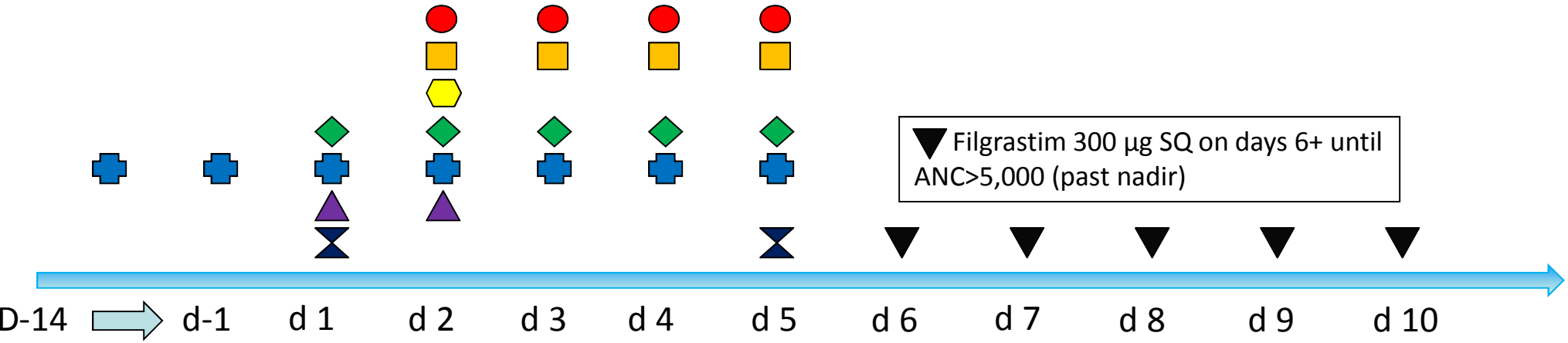
Dexamethasone 10 mg/m^2 BID PO days 1 to 5

Ibrutinib (560-TBD mg) PO days -14 to 5

Rituximab 375 mg/m^2 IV on days 1 and 2

Filgrastim 300 µg SQ on days 6+ until ANC>5,000 (past nadir)

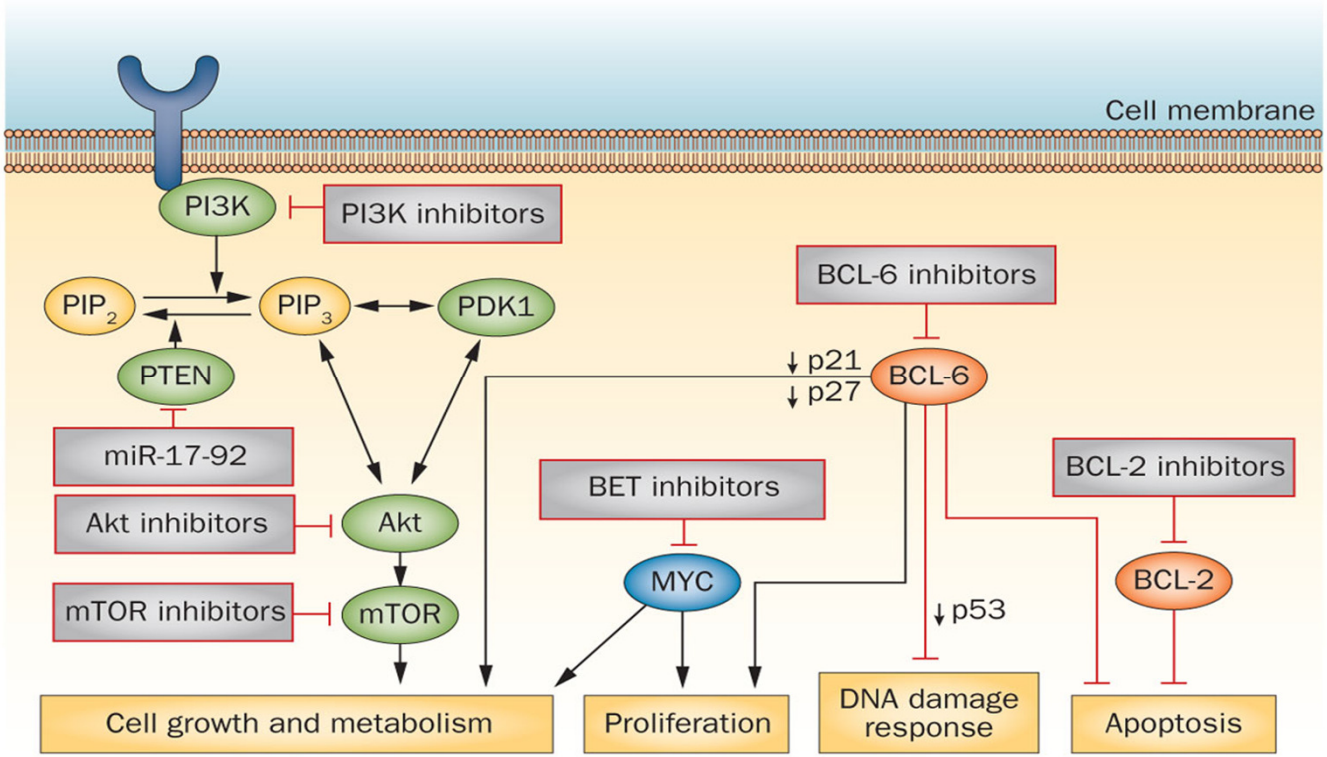
Cytarabine 70 mg IT or ICV on days 1 and 5 of cycles 2 to 6



Repeat cycle q21 days x 6

Dose-Adjustment: Etoposide and Temozolomide increase 20% if ANC nadir > 500

Figure 2 The key signalling pathways implicated in GCB DLBCL with targeted novel agents in clinical development



Roschewski, M. *et al.* (2013) Diffuse large B-cell lymphoma—treatment approaches in the molecular era *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.197

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Molecular Monitoring of Diffuse Large B-cell Lymphoma

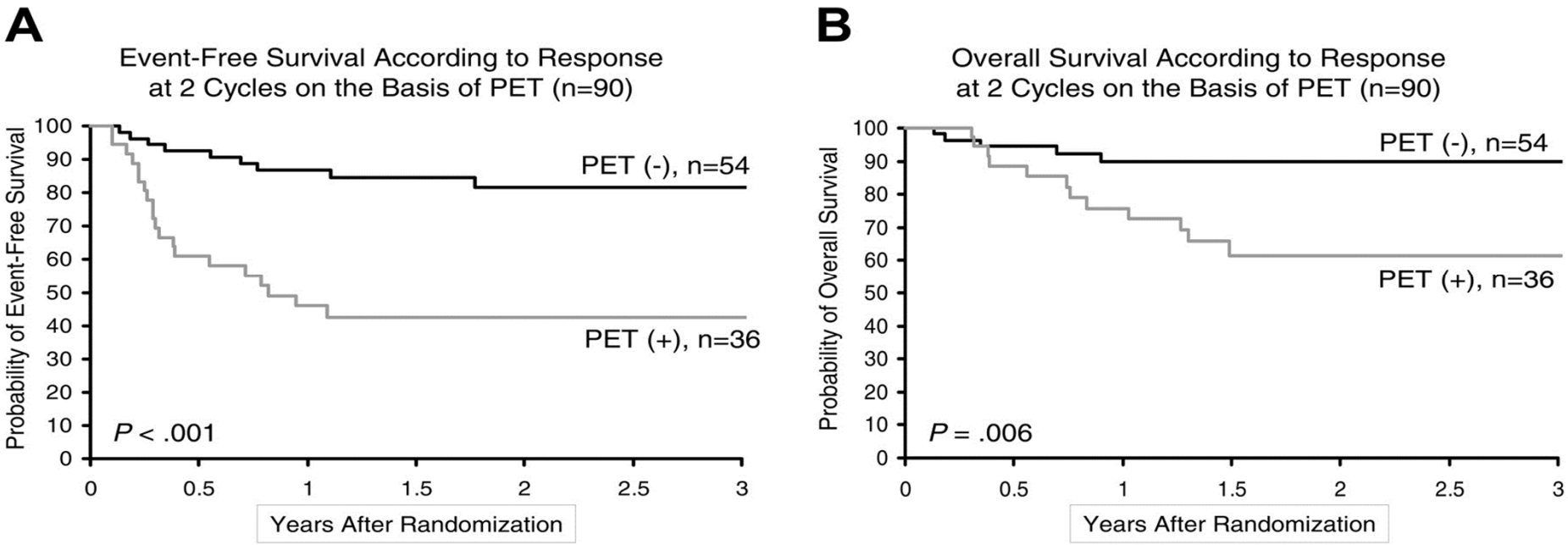
Molecular Monitoring of DLBCL

- Monitoring of a tumor-specific target in peripheral blood
  - More specific than imaging scans
  - Lowest possible disease burden (minimal residual disease)

- Interim monitoring – identify early treatment failure
  - Majority of DLBCL relapse within 2 years
  - Tumor dynamics can be assessed with multiple data points

- Surveillance monitoring – identify late recurrence
  - Less common, but more curable (?)
  - After 5 years, risk of indolent clone rises

Two-year estimates of survival according to “early PET” status.



Haioun C et al. Blood 2005;106:1376-1381

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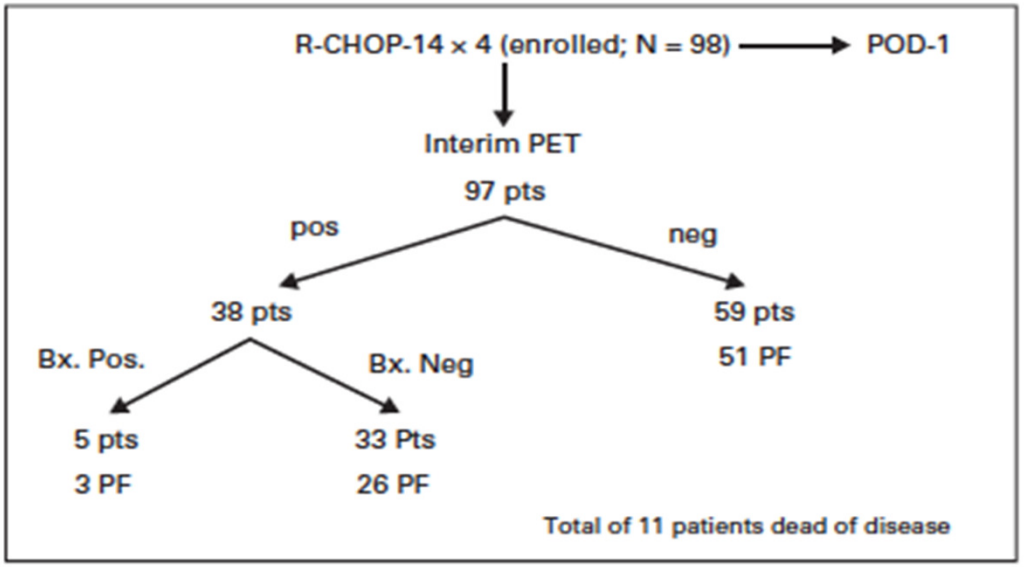
blood

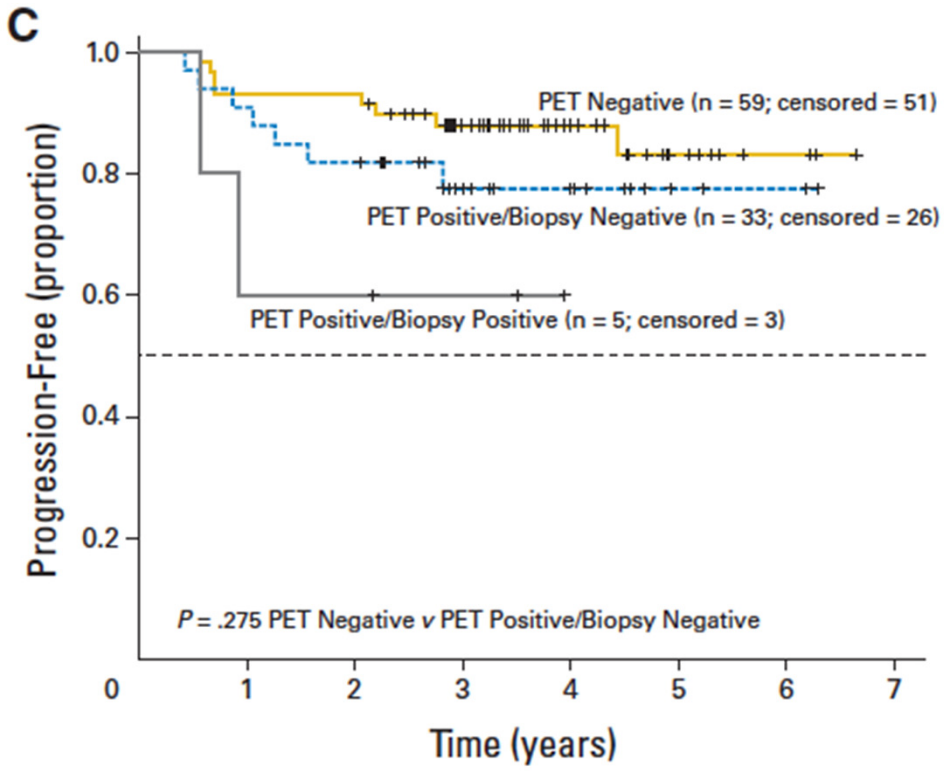
VOLUME 28 · NUMBER 11 · APRIL 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

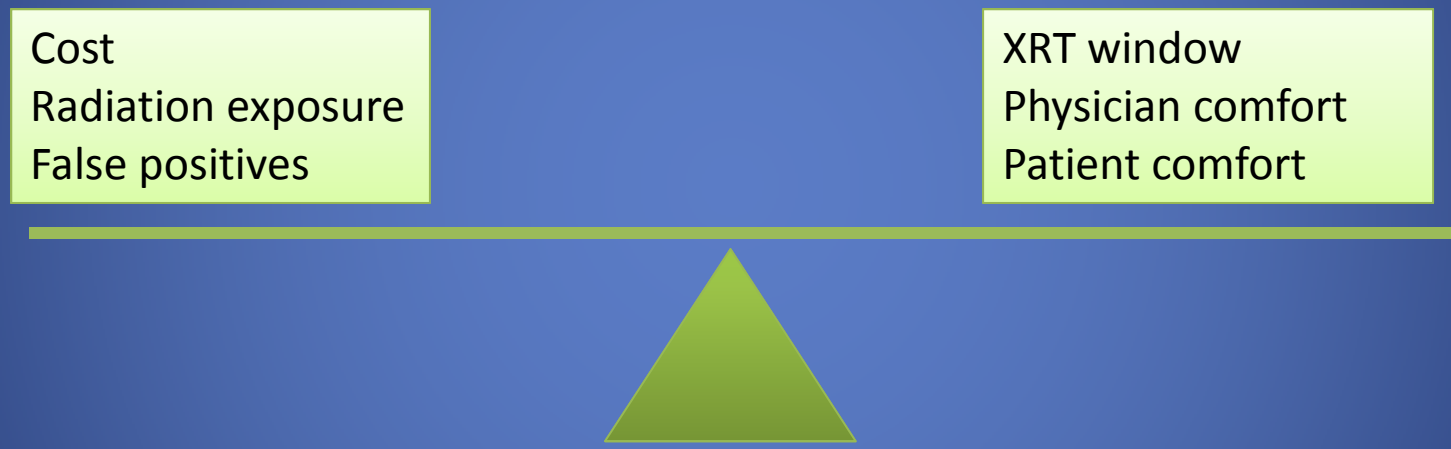
Risk-Adapted Dose-Dense Immunochemotherapy Determined by Interim FDG-PET in Advanced-Stage Diffuse Large B-Cell Lymphoma





Moskowitz et al. *J Clin Oncol* 2010

Surveillance?



NCCN= CT scans no more than q 6 months for 2 years then as clinically indicated

Scan-only relapse detection is uncommon

Reference	Pts in surveillance	Relapse rate	Scan only relapse (% of relapses)	Scan-only relapse rate in surveillance
Weeks JCO 1991	139	35 (26%)	2 (6%)	1%
Nakamura Int J Clin Oncol 2001	121	39 (32%)	5 (13%)	4%
Guppy Leuk & Ly 2003	117	35 (30%)	2 (6%)	2%
Zinzani JCO 2009	183	56 (31%)	16 (29%)	9%
Petrausch Ann Onc 2010	75	23 (31%)	3 (13%)	4%
El-Galaly Leuk Lymph 2011	52	4 (8%)	4 (100%)	8%
Abel Leuk Lymph 2012	575	50 (9%)	13 (26%)	2%
Lin Ann Hematol 2012	341	118 (35%)	25 (22%)	7%
Avivi Am J Heme 2013	119	31 (26%)	9 (29%)	8%

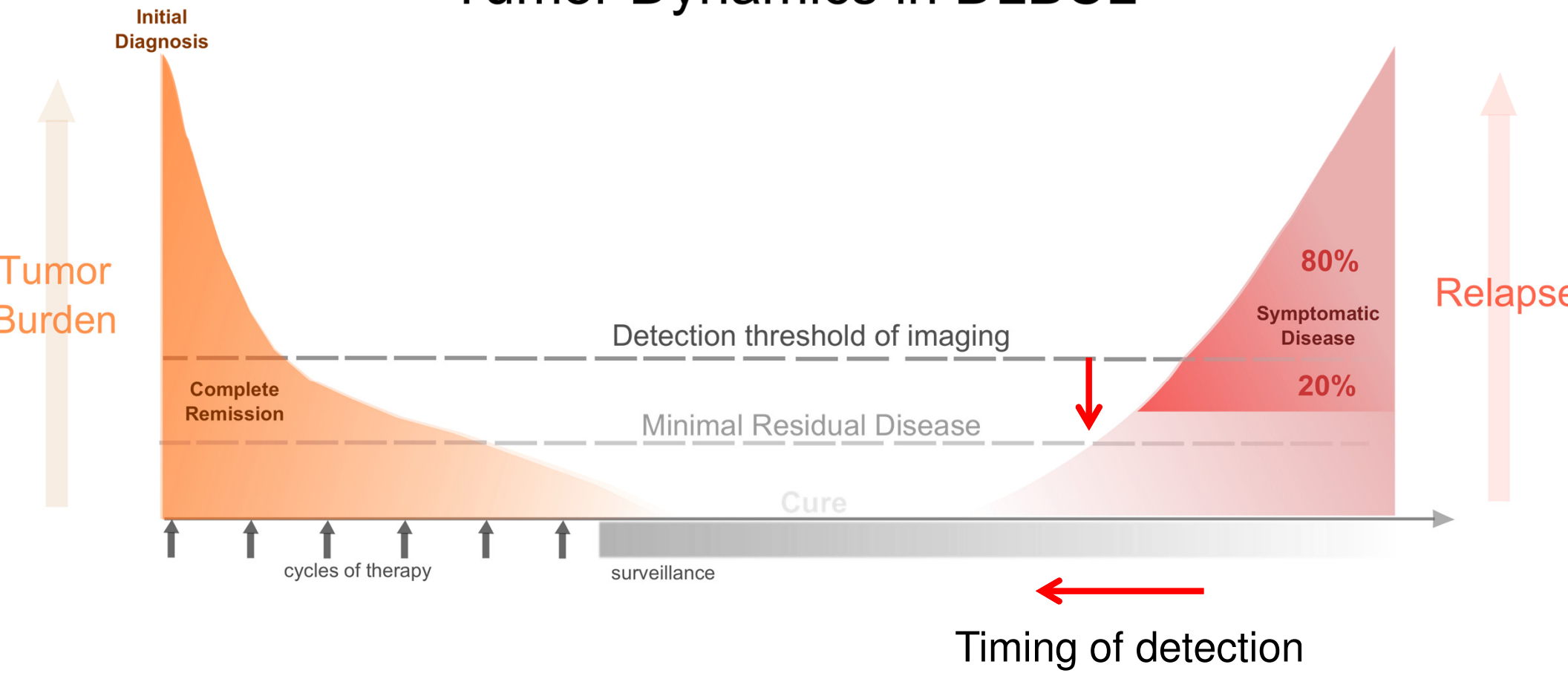
Presented By Christopher Flowers at 2014 ASCO Annual Meeting

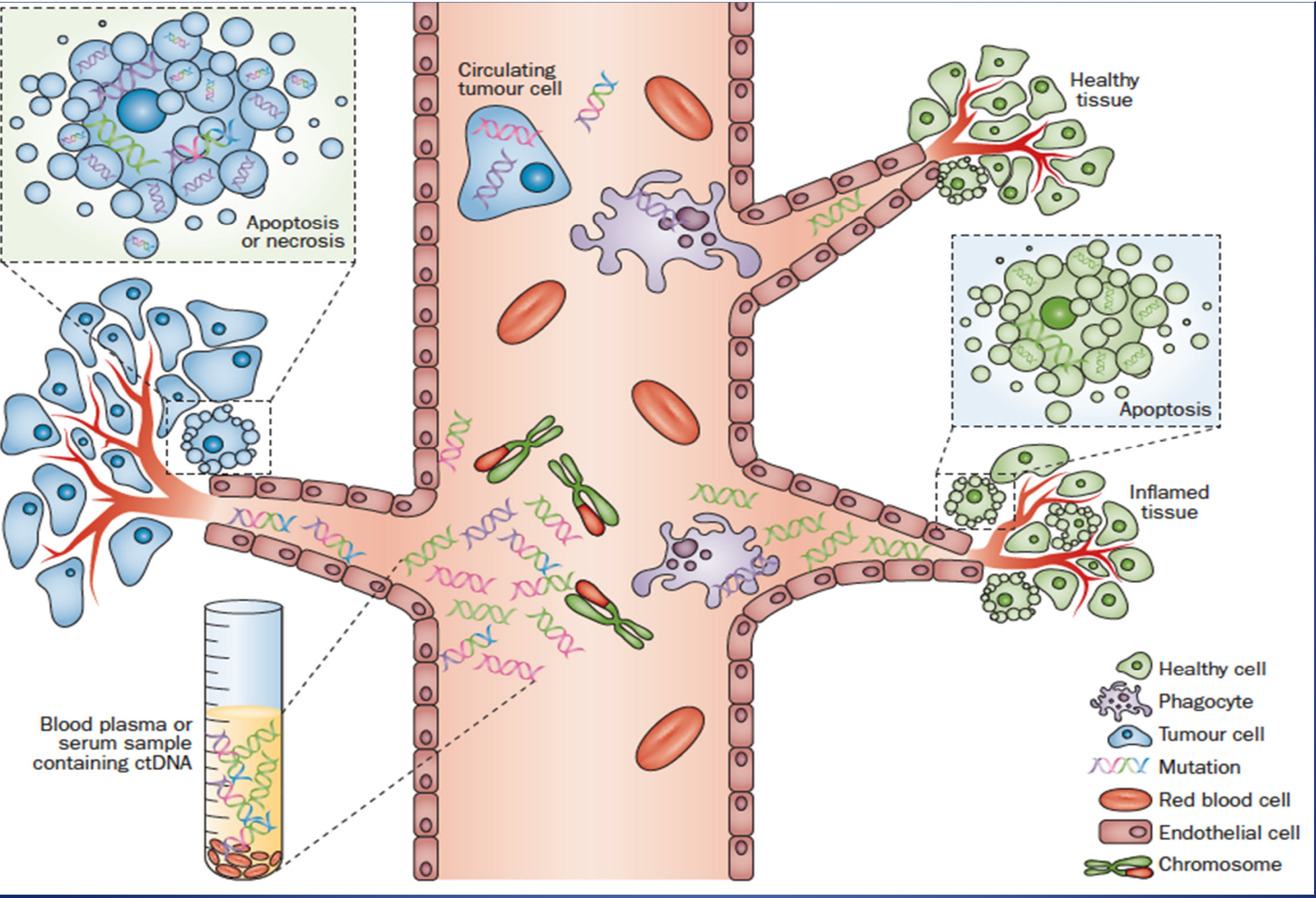
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5 Limit surveillance computed tomography (CT) scans in asymptomatic patients following curative-intent treatment for aggressive lymphoma.

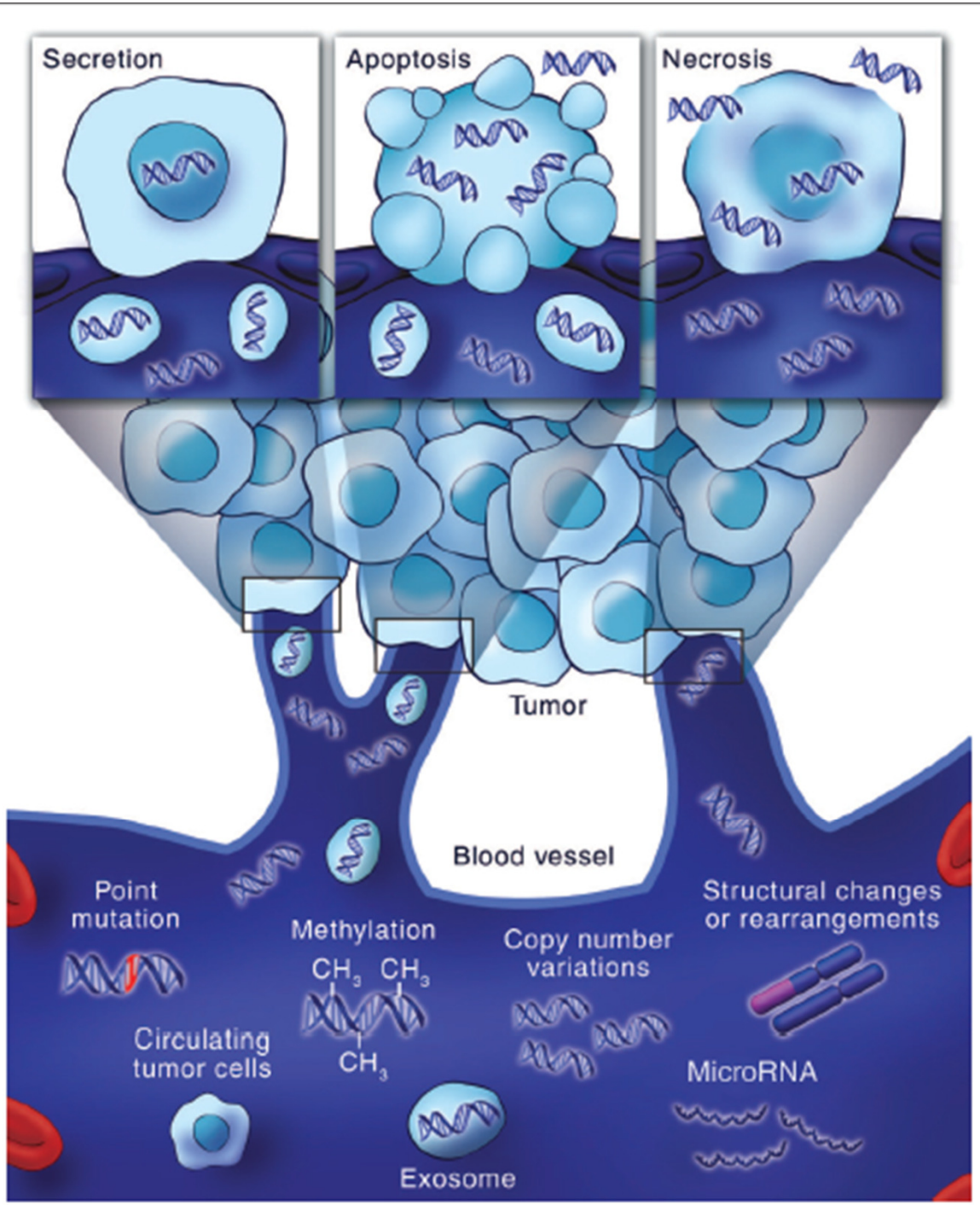
- CT surveillance in asymptomatic patients in remission from aggressive lymphoma may be harmful, is costly (approximately $1000 per scan), and has not been demonstrated to improve survival
- In particular, surveillance CT scans more than 2 years beyond the completion of curative treatment for lymphoma are rarely advisable

Tumor Dynamics in DLBCL



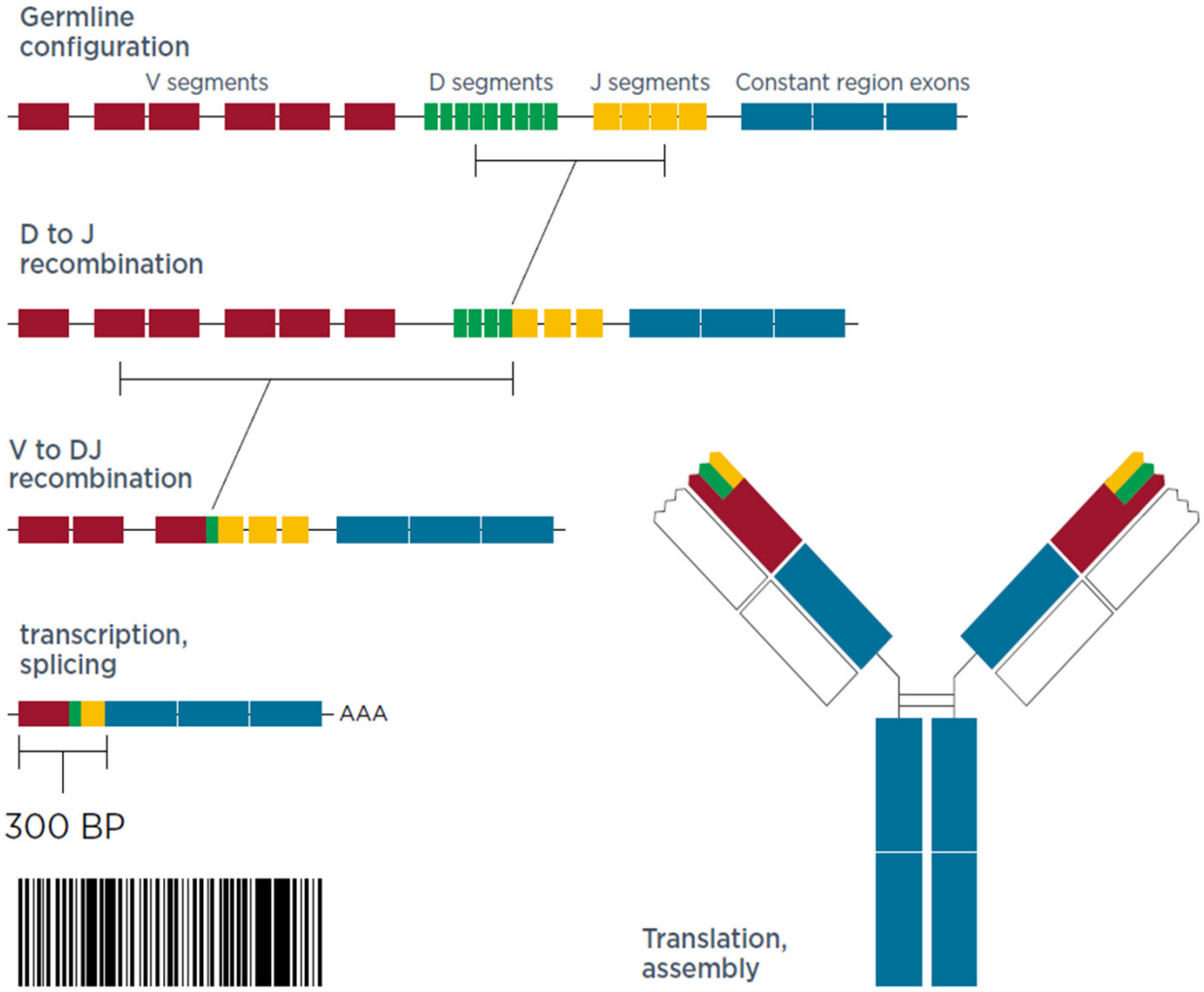


Crowley et al. *Nat Rev Clin Oncol* 2013



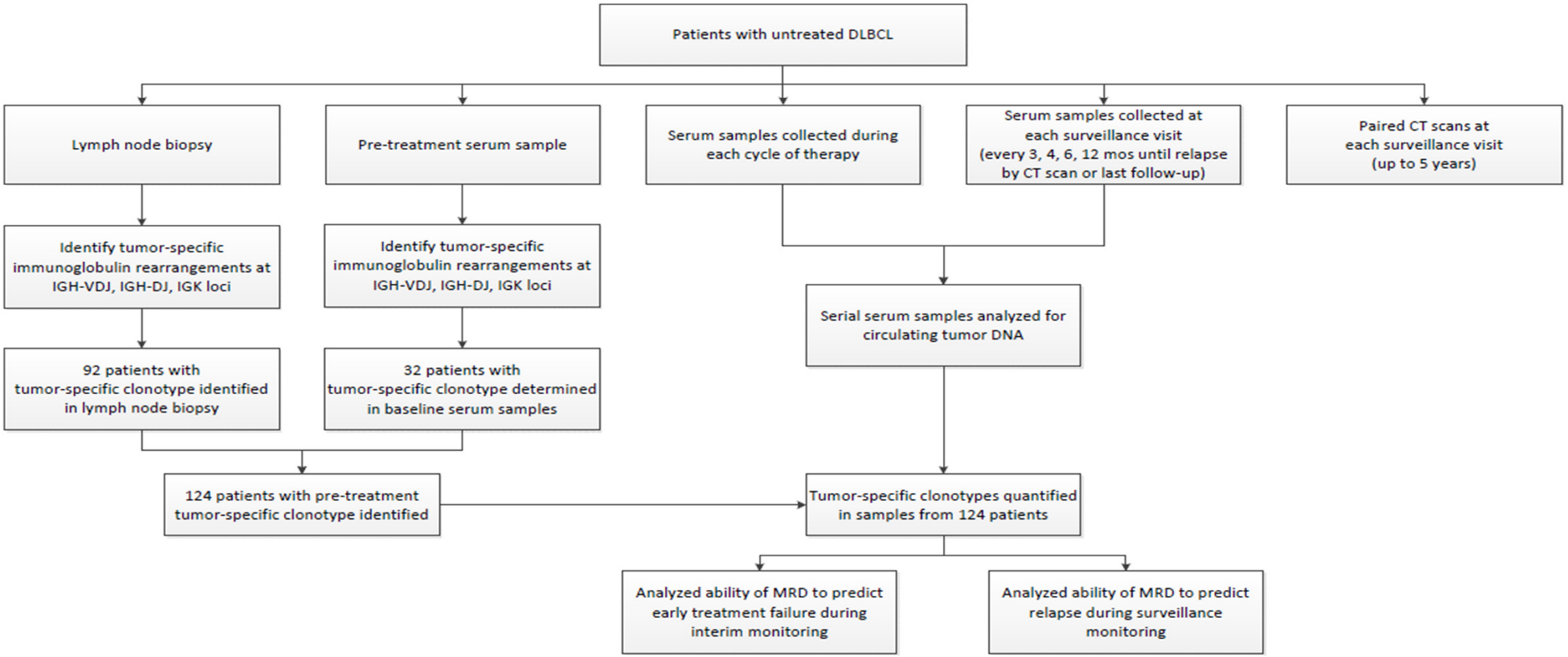
Diaz and Bardelli *J Clin Oncol* 2014

DNA Sequencing: Fingerprinting Cells



- Immunoglobulin cell receptor loci
  - Source of genetic immune diversity
- Deep sequencing enables
  - Identify all “clonotypes”
  - Determine frequency of each clonotype

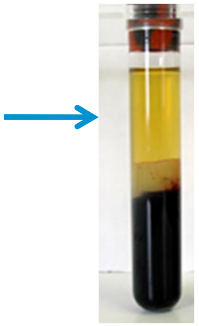
Study Schema



LymphoSIGHT™ Laboratory Workflow

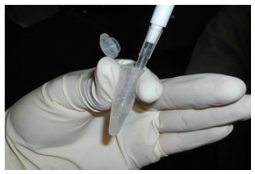
1) Collect 10cc peripheral blood

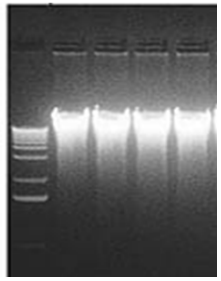




Serum

2) Extract DNA

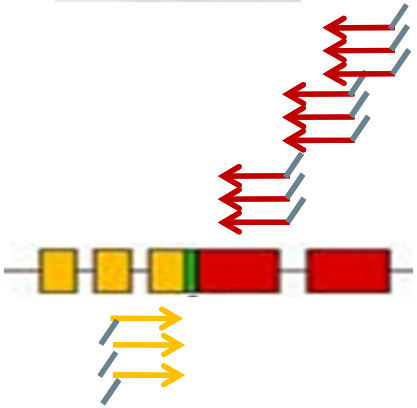




Genomic DNA

3) Amplify VDJ with multiplex PCR

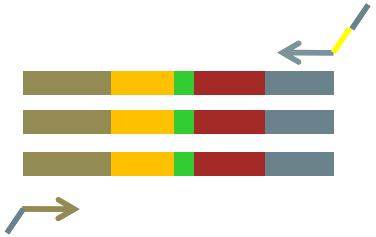




PCR amplicons

4) Prepare for sequencing with common PCR





Sequencing library

5) Sequence ~1M 100bp reads



```
CTGGCCCCAGTAGTCATACCAACTAGCG
TTGGCCCCAGAAATCAAGACCATCTAAA
ACGGCCCCAGAGATCGAAGTACCAGTGT
TTGGCCCCAGACGTCCATATTGTAGTAG
CTGGCCCCAGAAGTCAGACCGGCTAACA
```

Sequence data

Determine Specific Tumor Clonotype

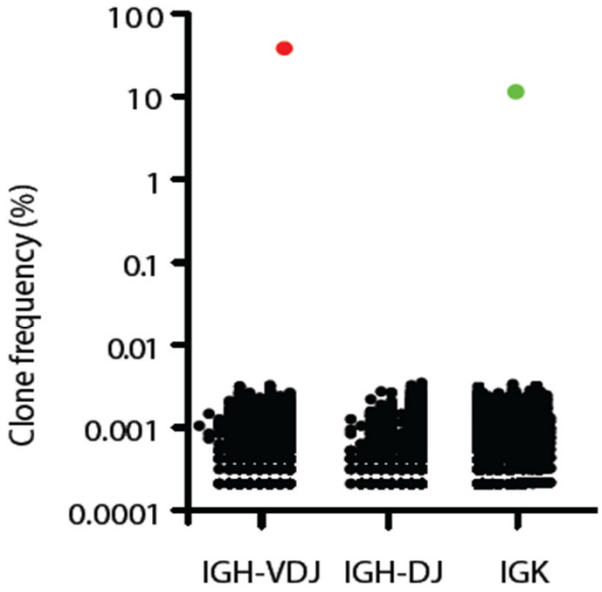
Sample collection	Clonality test for all receptors	Identify lymphoma clone based on frequency in immune cell repertoire

FFPE Biopsy

or

Baseline serum sample





Detect Tumor Clonotype in Serum as Minimal Residual Disease

Sample collection during and after therapy

Assess positive receptors for MRD

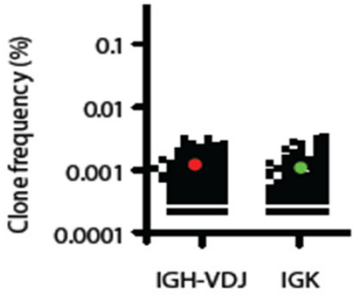
Monitor MRD in serial samples



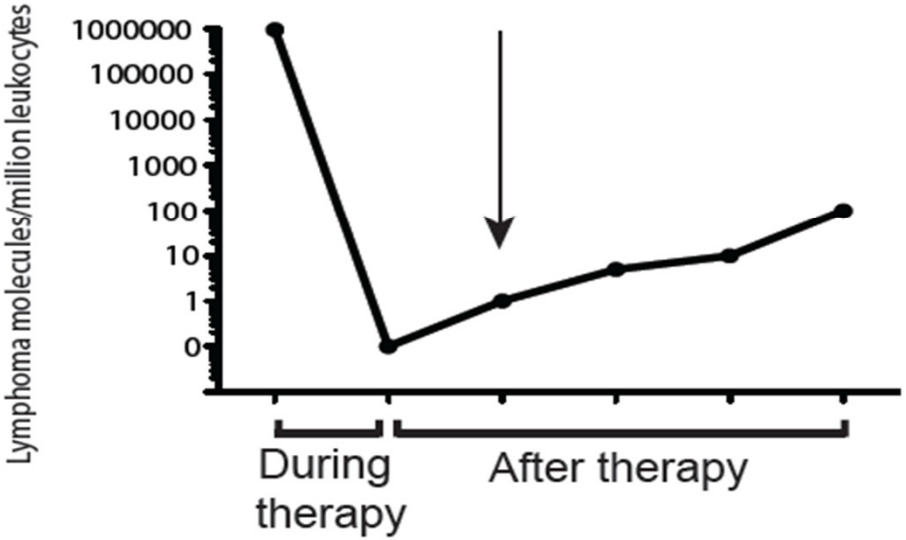
Serum samples

IGH-VDJ

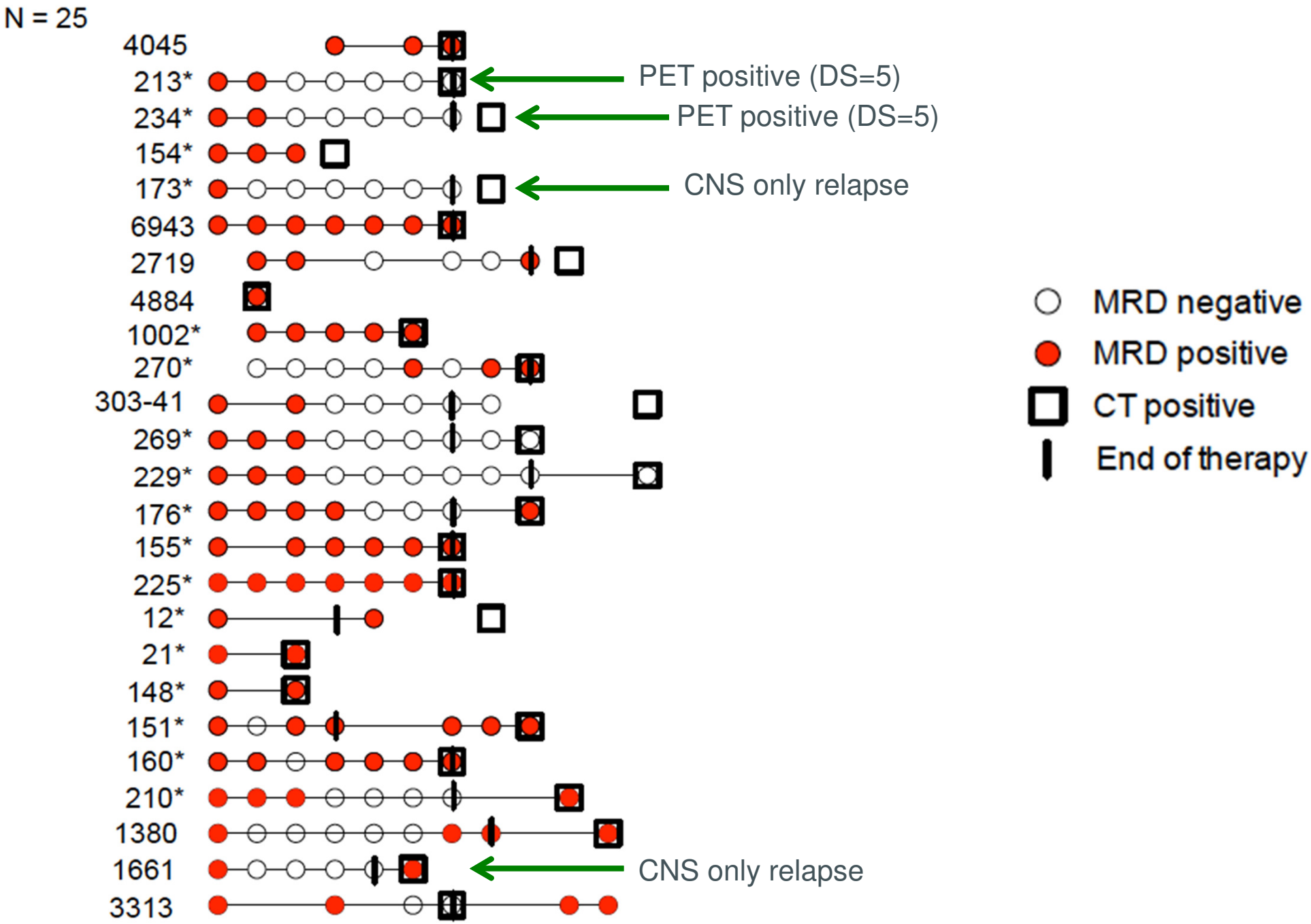
IGK



MRD detected before clinical progression

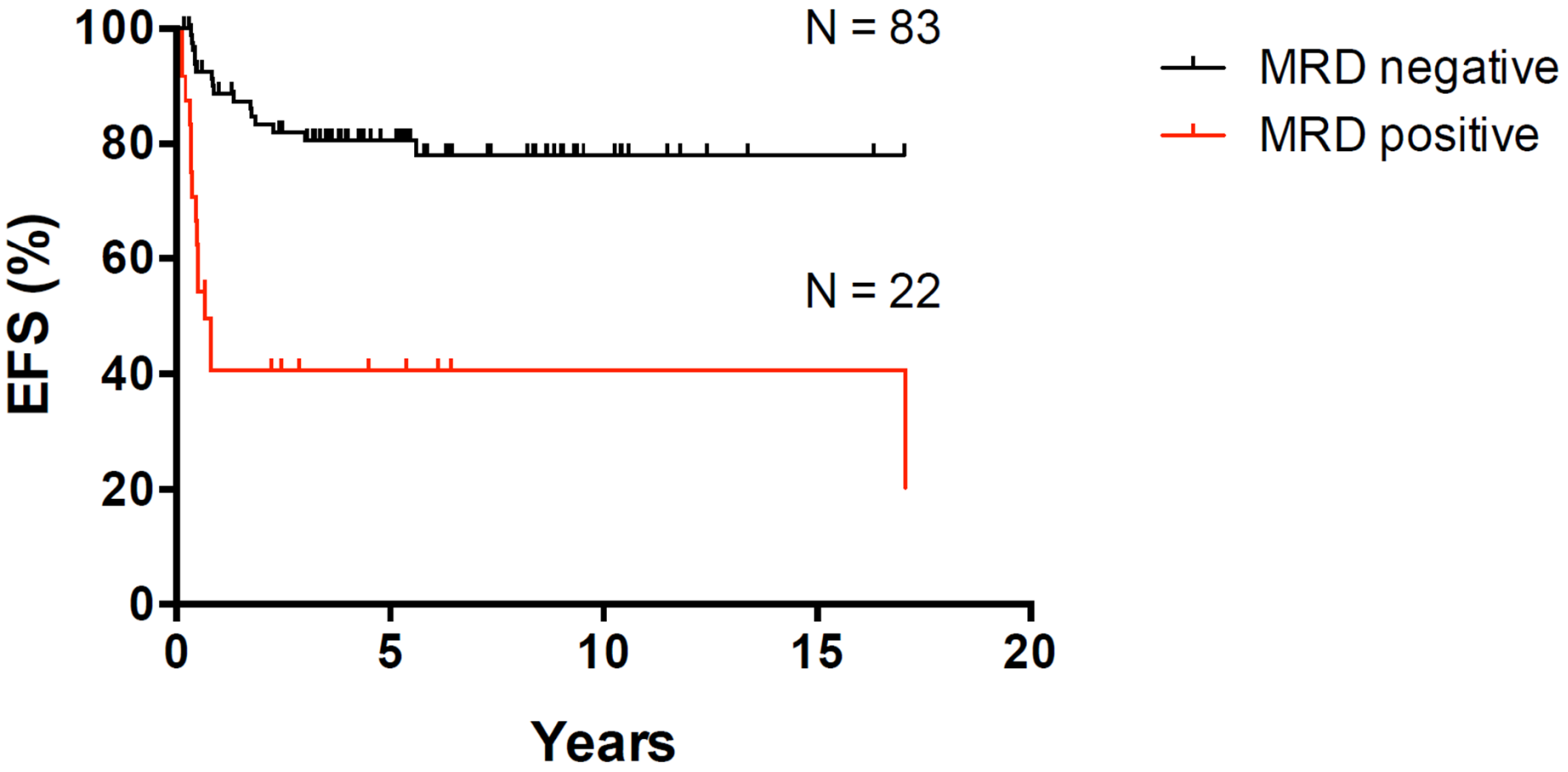


INTERIM MRD IN EARLY TREATMENT FAILURE



Interim monitoring (after C2)

5 yr. EFS 80.6% vs. 40.6% (p<0.0001)

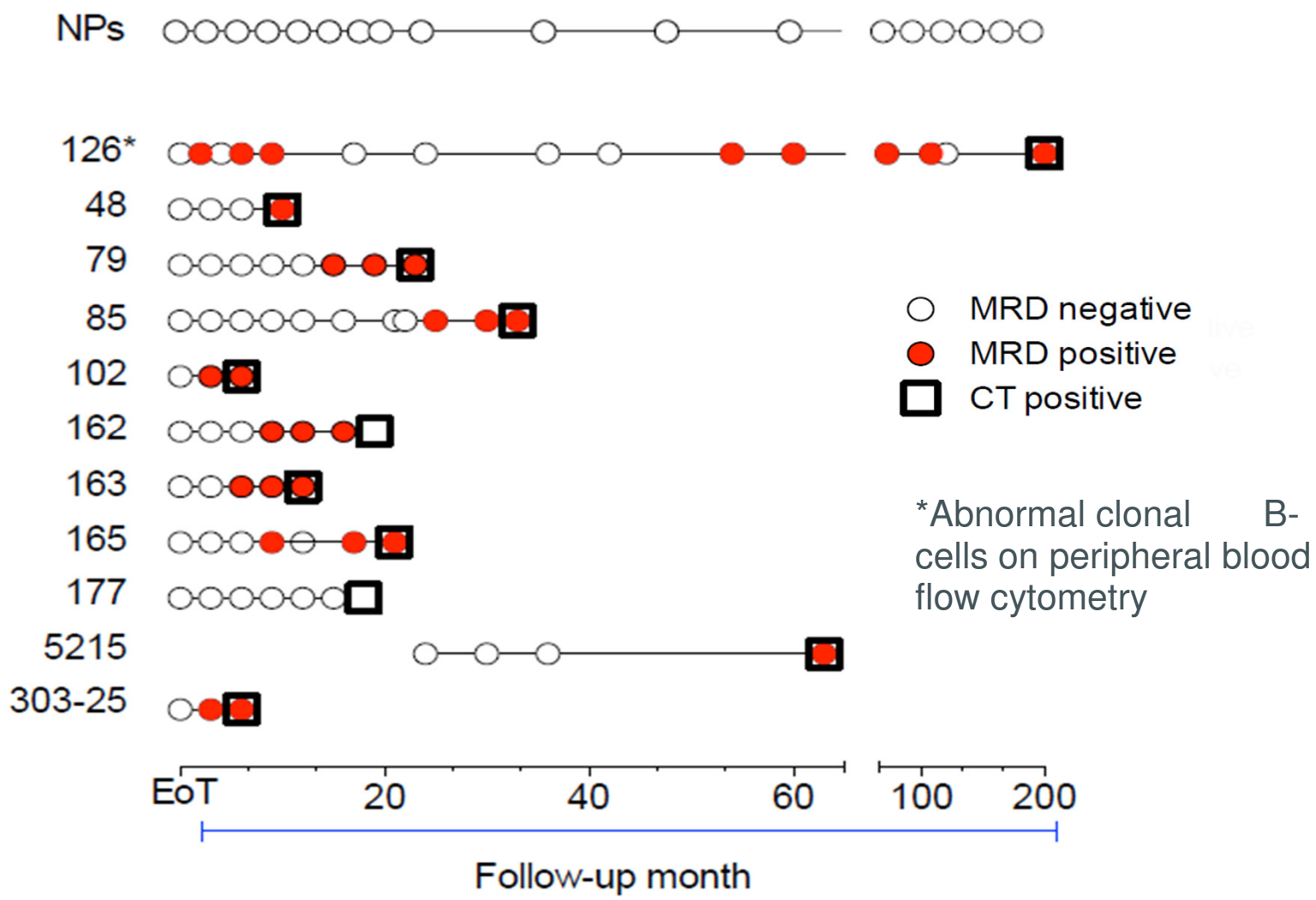


Surveillance Monitoring in Remission

N = 91

N = 11

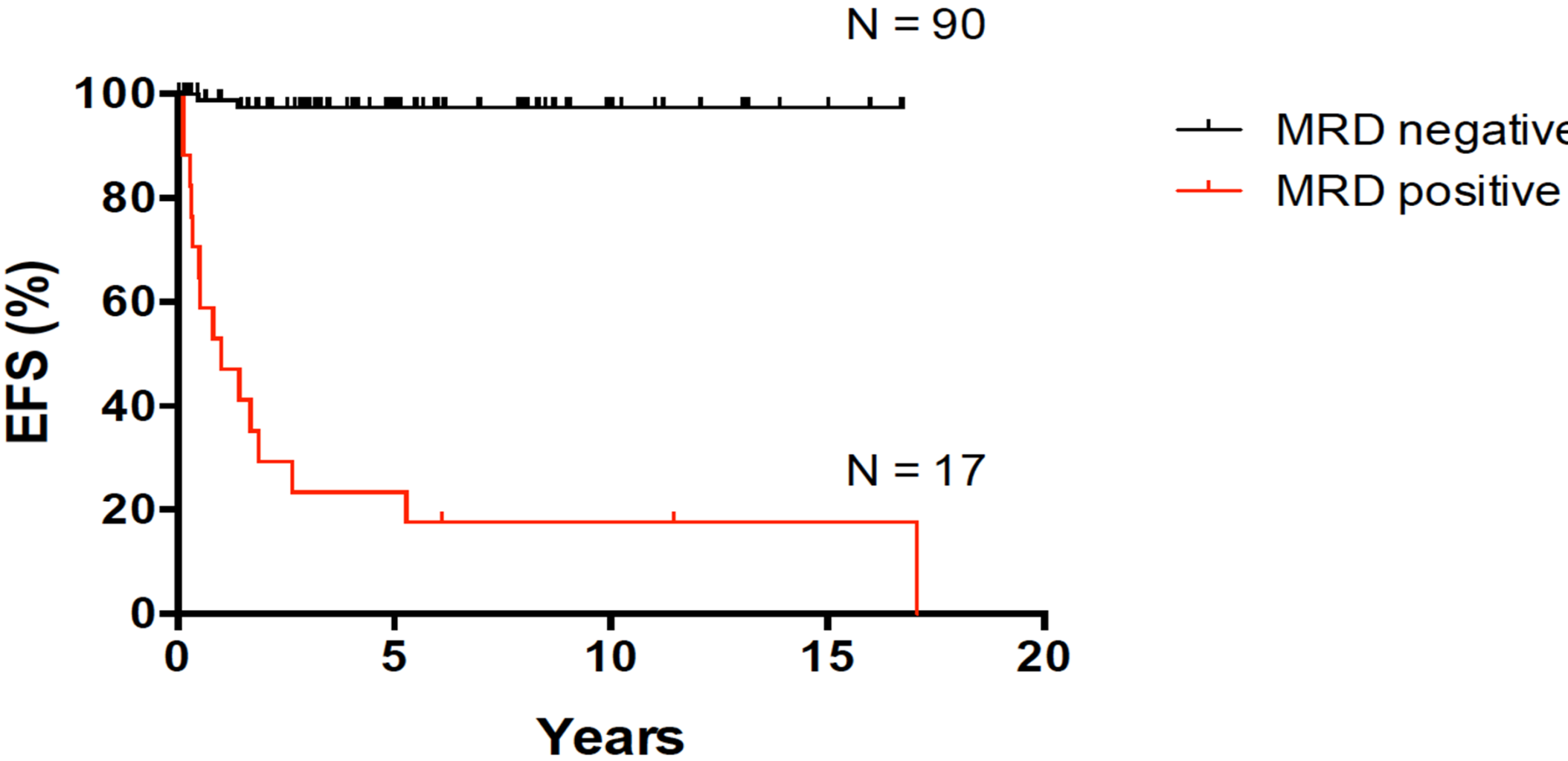
Lead time of 7.4 months



*Abnormal clonal B-cells on peripheral blood flow cytometry

MRD monitoring after complete remission

5 yr. EFS 97% vs. 23% (p<0.0001)



Conclusions and Provocative Questions

- Monitoring of cell-free tumor DNA in serum predicts both early treatment failure and late recurrence of DLBCL
- Molecular monitoring should be prospectively validated in DLBCL
- Can molecular monitoring replace routine surveillance imaging?
- Can dynamic MRD monitoring +/- PET be used in a response-adapted strategy?

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