Is genetics-based treatment of DLBCL ready to be applied to patients ?

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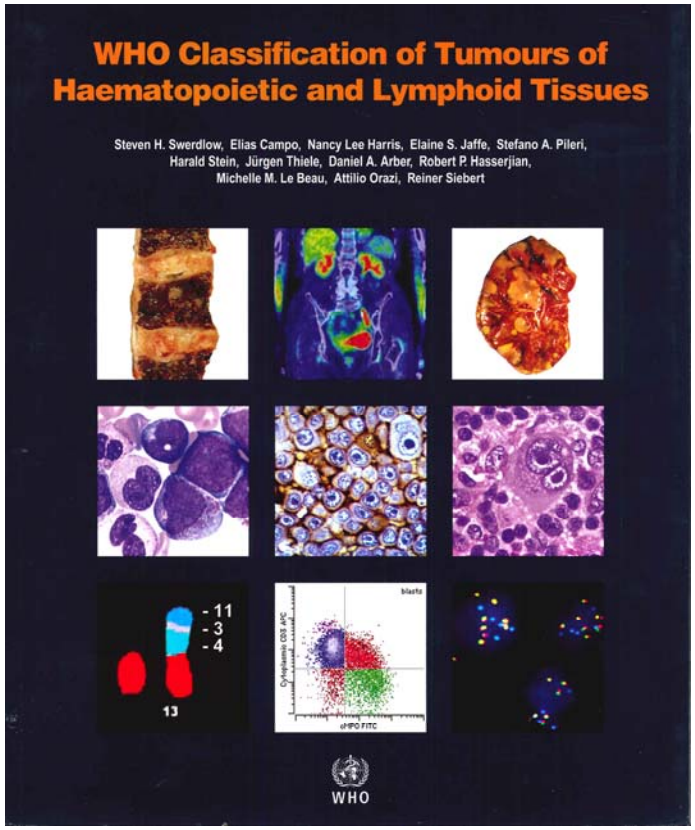
CH-LUCERNE, NOVEMBER 17, 2017

What oncologists need from pathologists



…a lymphoma classification & diagnosis

considering the advances…

- in molecular biology,
- clinical epidemiology,
- and incorporating smart observations by experienced hematopathologists

…and why?

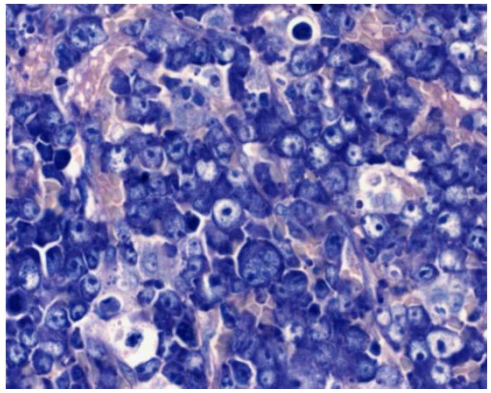
High grade B-cell lymphoma (HGBCL)…

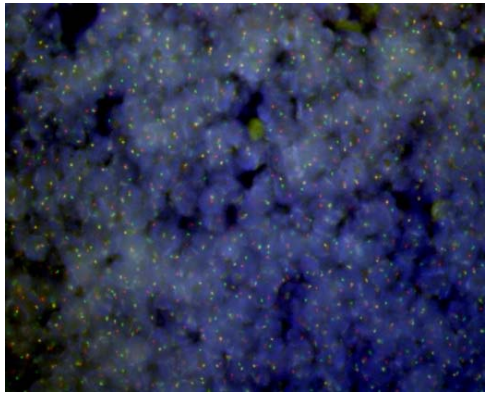
Courtesy:

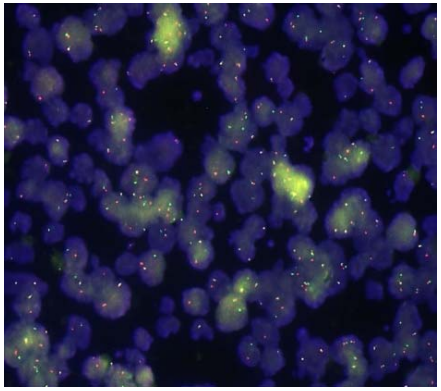
S. Dirnhofer

…a new category replacing BCL-u (iBL/DLBCL)

- **HGBCL with MYC and BCL2 and/or BCL6 translocations**
  - **all "double/triple hit" lymphomas other than FL or LBL**







EAHP 2016, LYWS case-236

- **HGBCL, NOS**
  - **Blastoid large B-cell lymphomas (formerly BCL-u)**

→ Aggressive lymphomas that need *another treatment than R-CHOP*

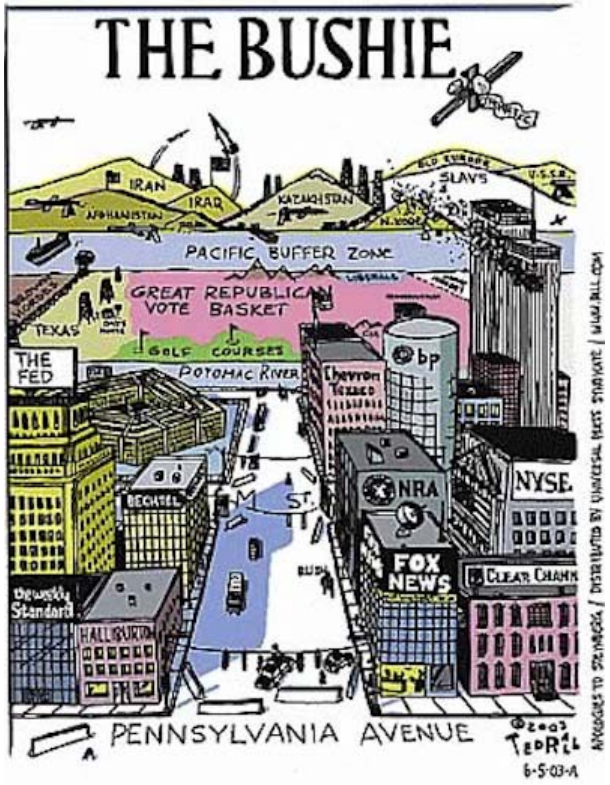
R-CHOP21 IS (STILL) THE STANDARD *GOY JCO 2017*

- 6 x R-CHOP or 3-4 x R-CHOP → IFRT

  reasonable option for stage IA or IIA non-bulky DLBCL

  Persky, JCO 2008; Stephens JCO 2016

- R-CHOP for advanced DLBCL

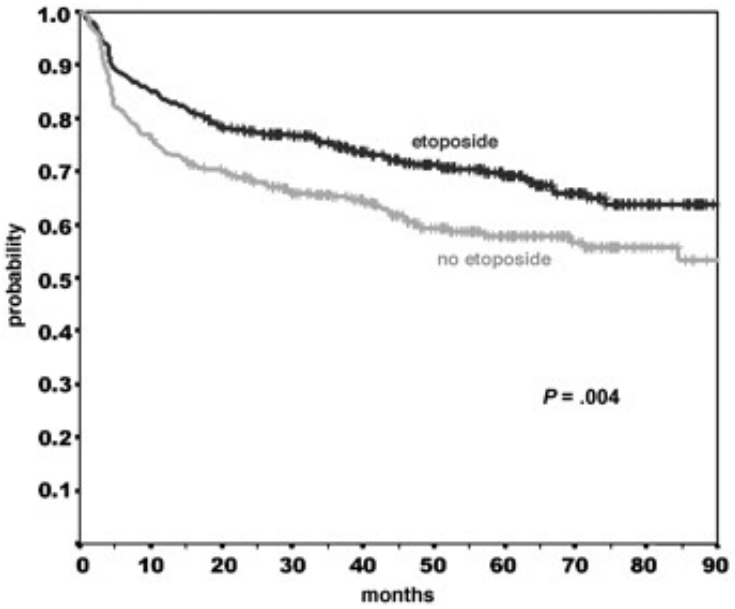


GOING BEYOND R-CHOP$_{21}$…

- Shorter treatment intervals ? *no advantage (french & british)*
- Maintenance rituximab ? *no advantage, men ?*
- Continuous infusions ?
- Radiotherapy to bulks ? *UNFOLDER awaited*
- 1st line autotransplants *(young, fit) ?*
- CNS prophylaxis ? *no randomized evidence*
- Add another *(more efficient)* antibody *no advantage (GOYA)*
- PET response-adapted treatments ? *no advantage (PETAL)*
- Addition of another drug (chemo) ?

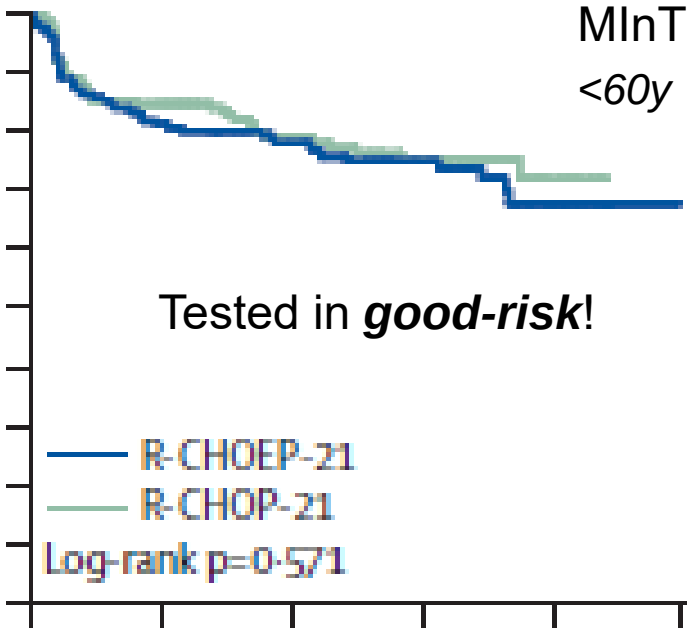
Adding Etoposide to (R-)CHOP ?

<60y; *IPI < 2, normal LDH)*



	EFS event‡§		
	RR	95% CI, upper limit; lower limit	P‖
CHOEP-21 vs CHOP-21	0.82	0.63;1.07	.145
CHOEP-14 vs CHOP-21	0.77	0.59;1.02	.064

Pfreundschuh Blood 2004



Pfreundschuh Lancet Oncol 2011

R-CHOP vs. R-CHO(E)P: equal PFS

Schmitz & Vitolo, ASH 2013

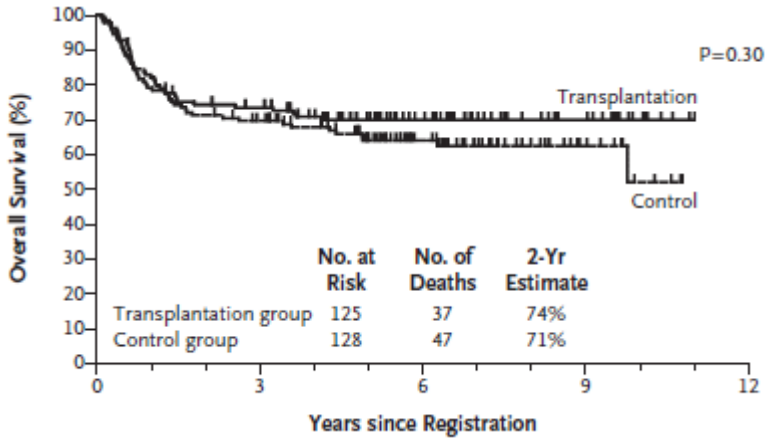
HIGH-DOSE CONSOLIDATION FOR CR / PR PATIENTS

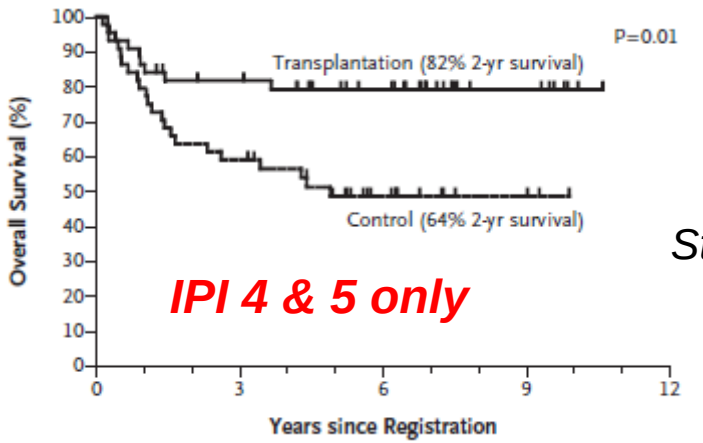
Phase III

Time To Remember To Forget Dose-Intensification in Lymphoma
Bruce D. Cheson,
JOURNAL OF CLINICAL ONCOLOGY EDITORIALS

GOELAMS 075 R-CHOP-14 x 8 vs. R-HDT: Equal ORR & 3y OS *(ASCO`11)*

DLCL04 FIL R-(Mega)CHOP14 ±HDC: 2y PFS 71 vs. 59 %, equal OS *(11-ICML)*





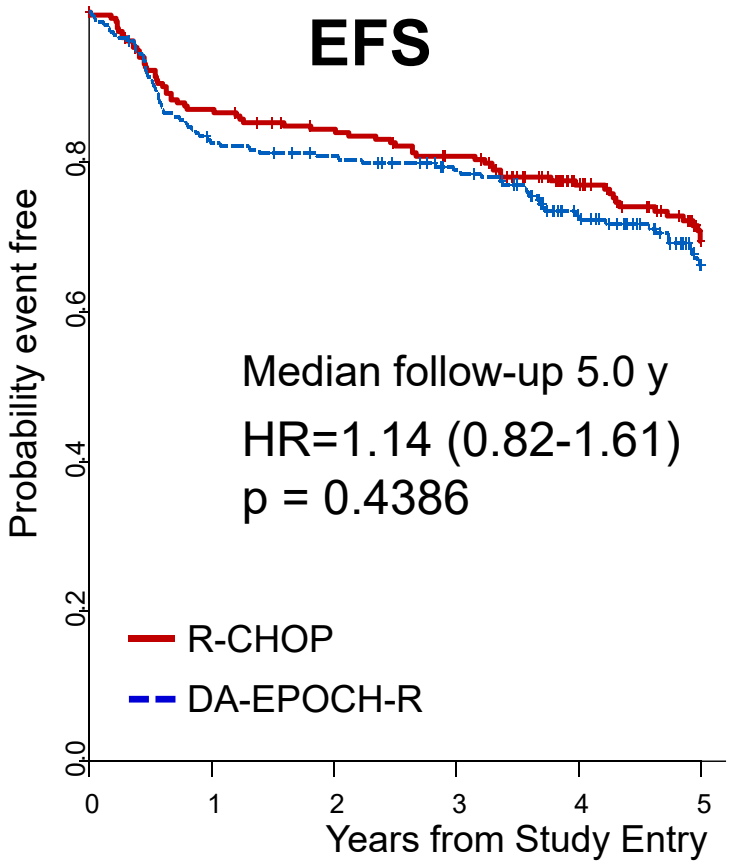
IPI 4 & 5 only

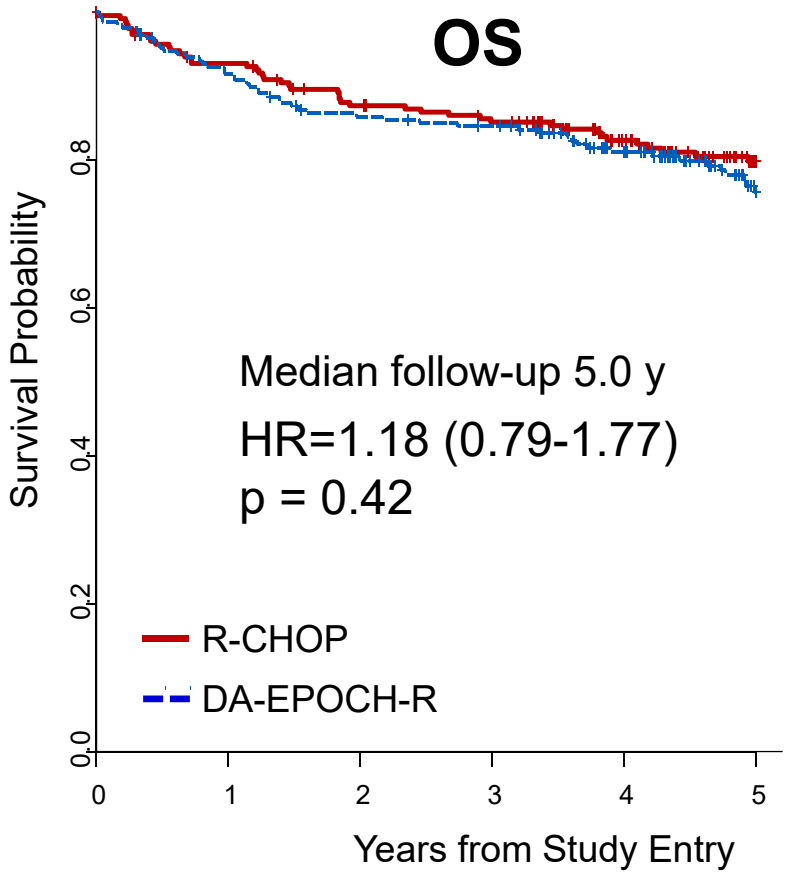
Stiff, NEJM 2013

Cave Combined endpoint: PFS & OS

Not powered for a difference R-CHOP → HDT vs. R-CHOP *(just consolidation)*

A disappointment for many: the CALGB/Alliance study 50303





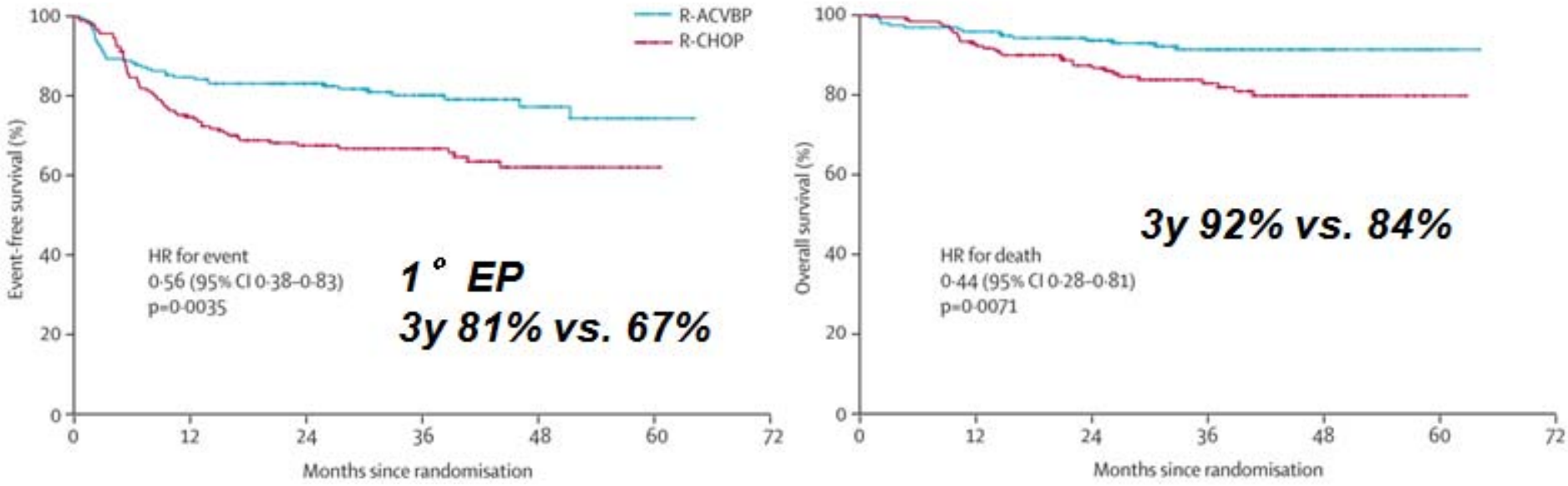
1st line treatment of 465 non-selected DLBCLs

Subtype information not yet communicated

Wilson, ASH 2016;abstract 469

THERE IS A BETTER CHEMOTHERAPY THAN R-CHOP !

LNH03-2B trial; Lancet 2011



380 good risk patients (aaIPI1), < 60 years

8 x R-CHOP$_{21}$ vs. 4 x R-ACVBP

Profit for ABC, *Molina JCO 2014*

Clinicians tend to mix it up: prognostic and predictive factors

Prognostic biomarker

→ *Information on outcome/natural history of disease, regardless of therapy*

Predictive biomarker

→ *Information about the response to a given therapy*

→ *Some factors are both prognostic and predictive*

→ *Many prognostic, few if any predictive (bio)marker for lymphomas*

Cianfrocca & Goldstein, *The Oncologist 2004*

What does the clinical oncologist need from the pathologist, and why?

…a lymphoma classification & diagnosis driven by

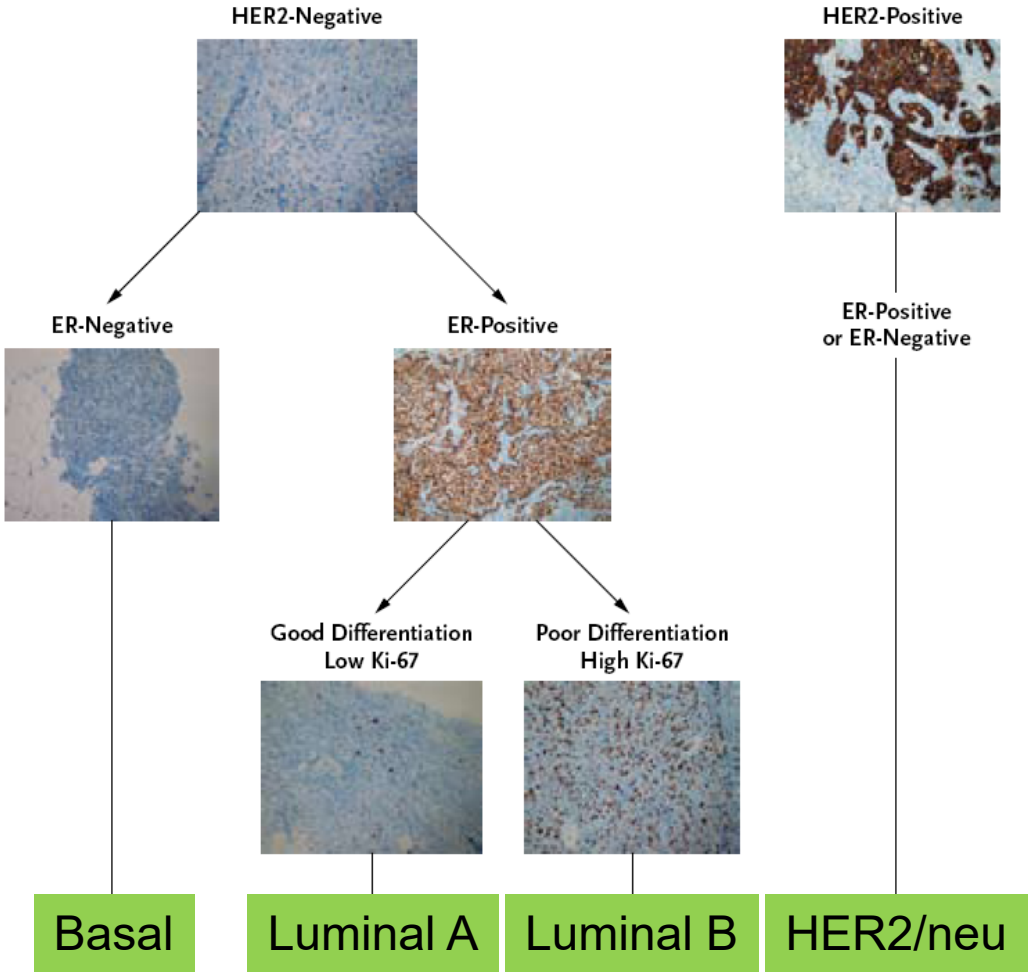
- predictive rather than prognostic biomarkers !

…and why?

The field should embrace the idea that:

- Targeted therapy with a target simply works better
- Targeting the whole population is not (cost) efficient

→ *Can we be satisfied with a RR of ~30 % with a targeted drug ?*

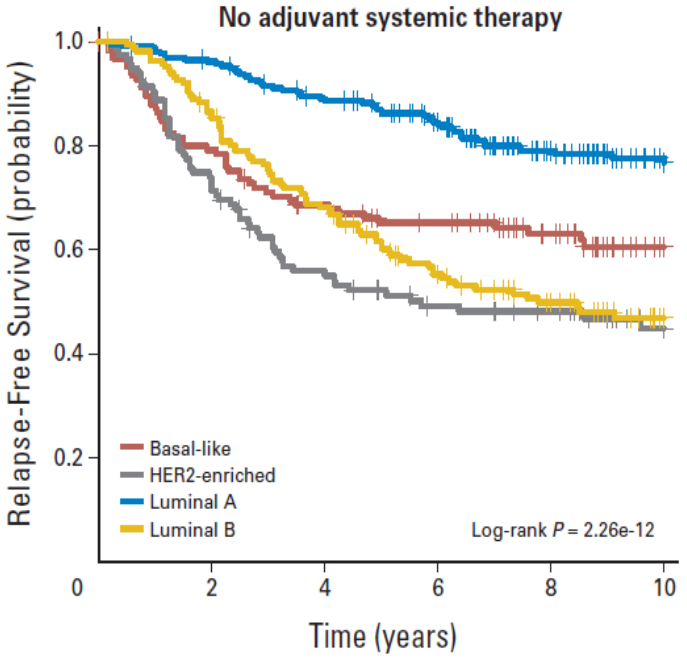


Basal	Luminal A	Luminal B	HER2/neu	
-	+	+	-/+	ER / PR
-	-	-	+	HER2/neu
high	low	high	high	Proliferation

N Engl J Med 2009;360:790-800.

Example of a teacher:

→ *breast cancer !*



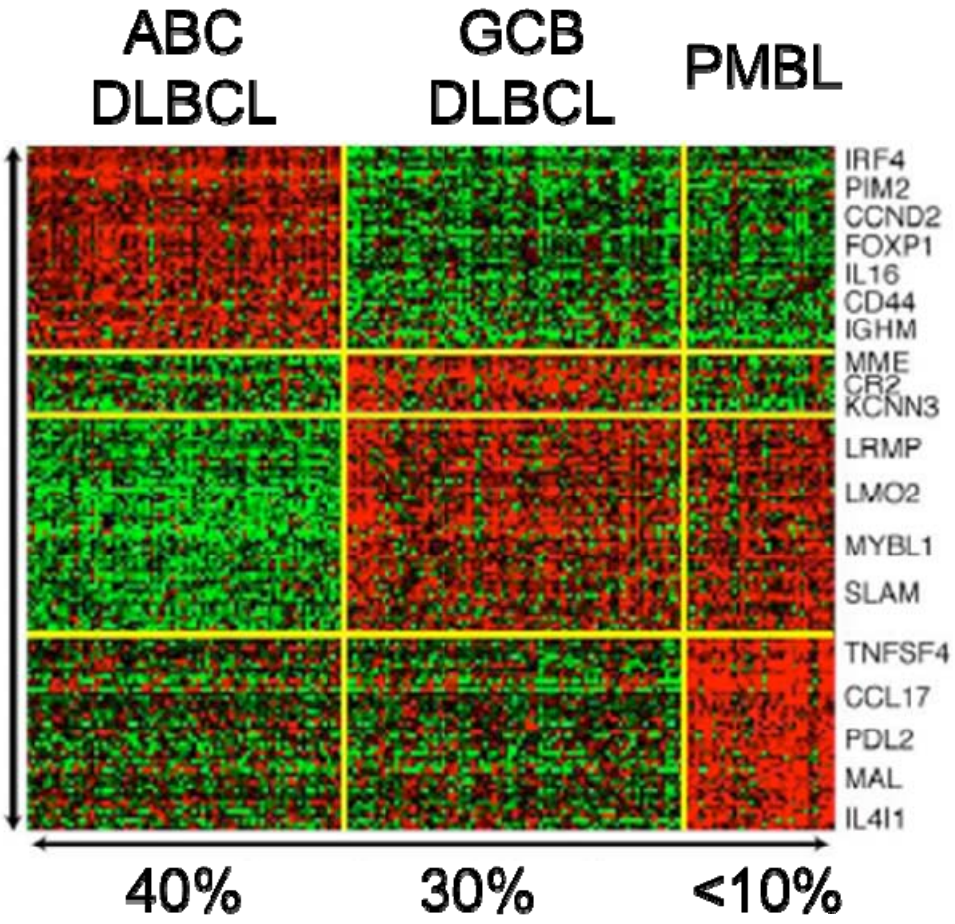
NEW WHO CLASSIFICATION: MOST IMPORTANT CHANGES

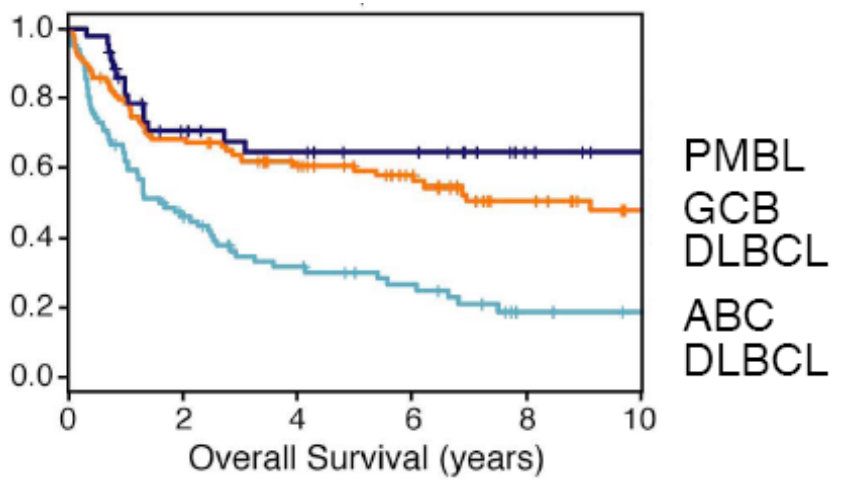
- ***NEW***
  - High grade B-cell lymphomas NOS ≠ BCLUS
  - High grade B-cell lymphomas with MYC/BCL2/BCL6

- ***Subtype required***
  - GCB vs. ABC

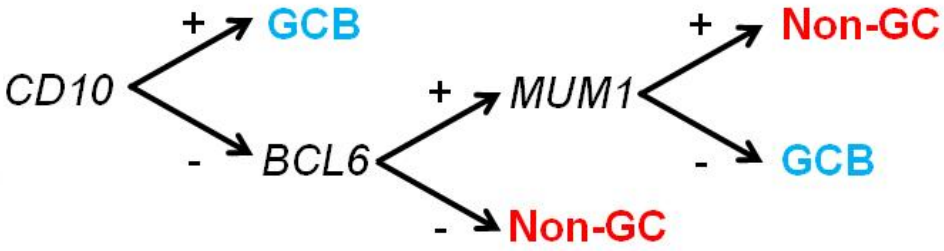
- ***Prognostic factors***
  - Myc, Bcl2
  - MYC/BCL2/BCL6

THE COO SUBTYPES OF DLBCL





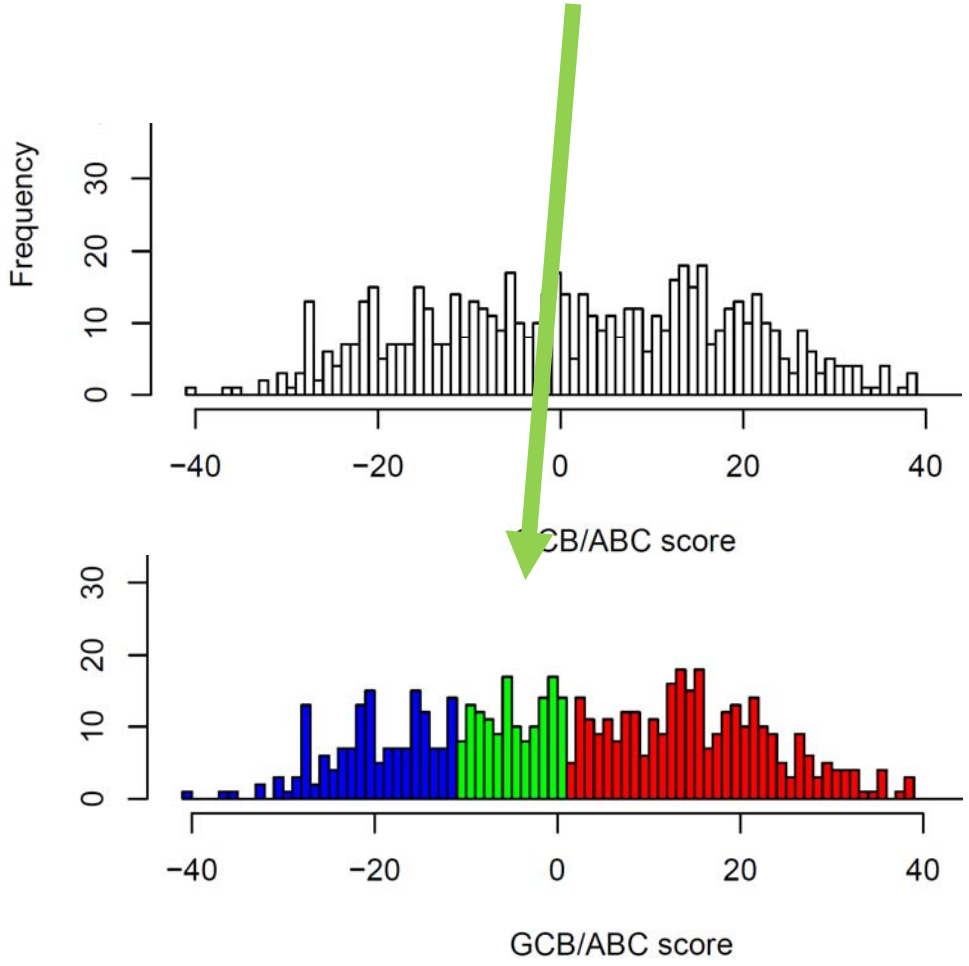
Hans, Blood 2004



Not standardized in CH!

Reber, Swiss Medical Weekly 2013

THE „UNCLASSIFIED“ DLBCL VANISHES OVER TIME



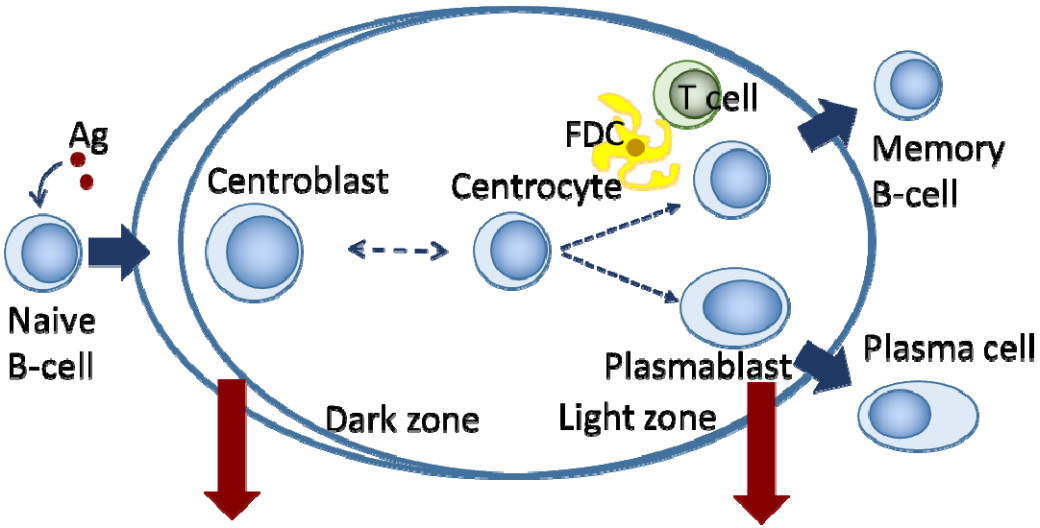
Altenbuchinger, unpublished

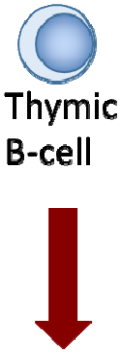
Rosenwald, *NEJM 2003*	21%
Lenz, *NEJM 2008*	14%
Scott, *JCO 2015*	11%

«Burkitt-like DLBCL» in REMoDL

14-ICML abstract #121

COO SUBTYPES ARE FAR MORE COMPLEX…





GCB-DLBCL	ABC-DLBCL	PMBL
BCL2 translocation	A20 loss	9p24 amplification
CMYC translocation	CARD11 mutations	CIITA translocation
EZH2 mutations	CD79A/B mutations	STAT6 mutations
BCL6 prom. mutations	MYD88 mutations	JAK2 mutations
MEF2B mutations	BLIMP1 loss	REL amplification
GNA mutations	BCL2 amplification	SOCS1 mutations

Mutations: MLL2/MLL3, CREBBP/EP300
Loss: B2M & CD58
BCL6 translocations

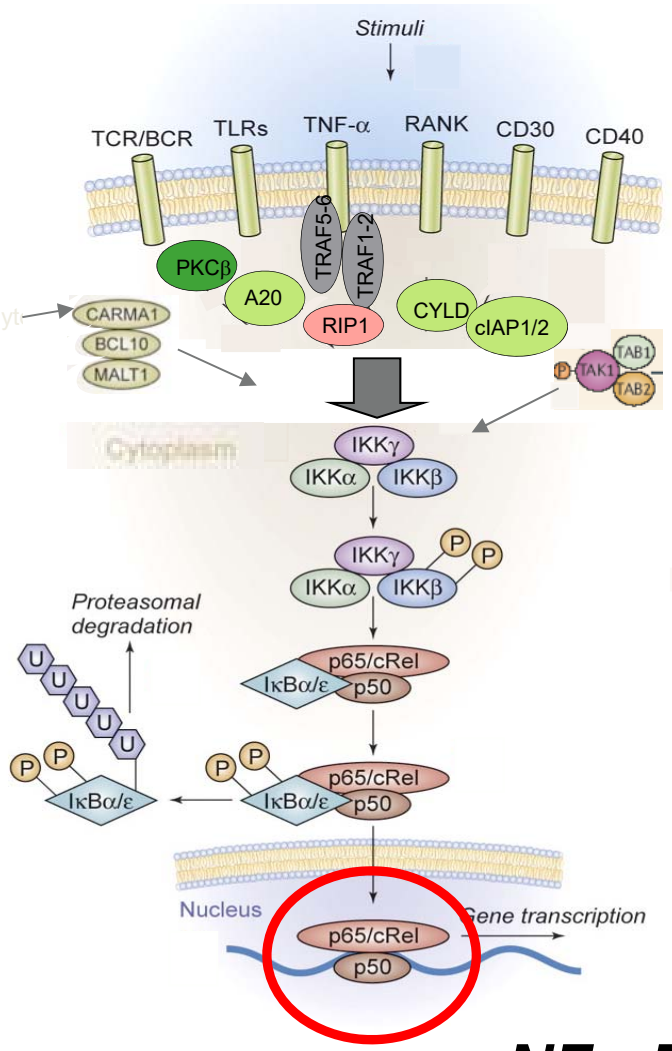
NF-κB activation

A20 loss

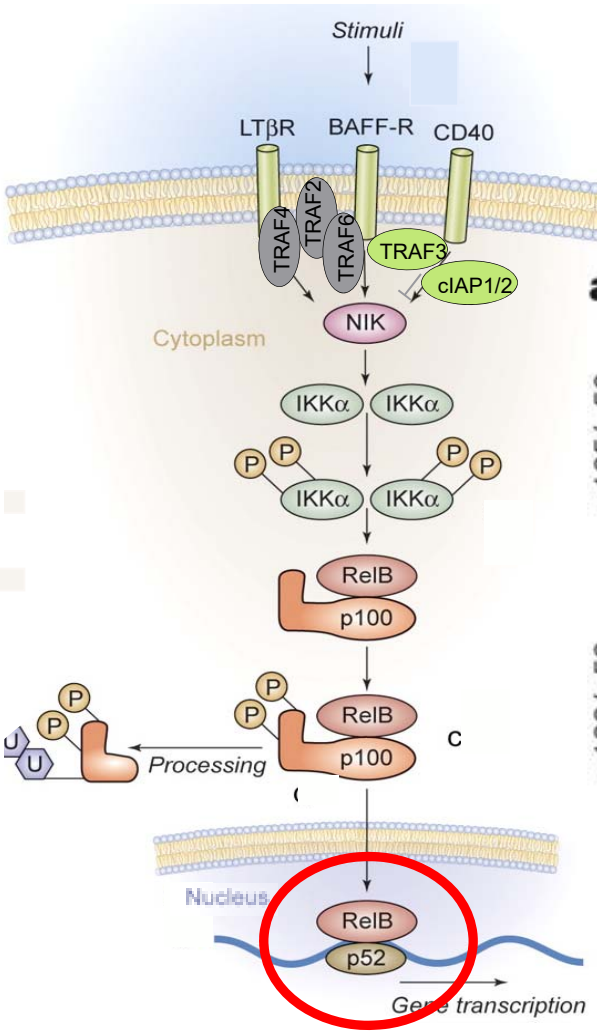
Pasqualucci, Nat Genet 2011; Morin, Nature 2011; Steidl, Blood 2011; Lohr, PNAS 2011, Ying Nat Immunol 2013, Twa, Blood 2014

NF-κB: SURROGATE FOR A THERAPEUTIC TARGET !?!

canonical

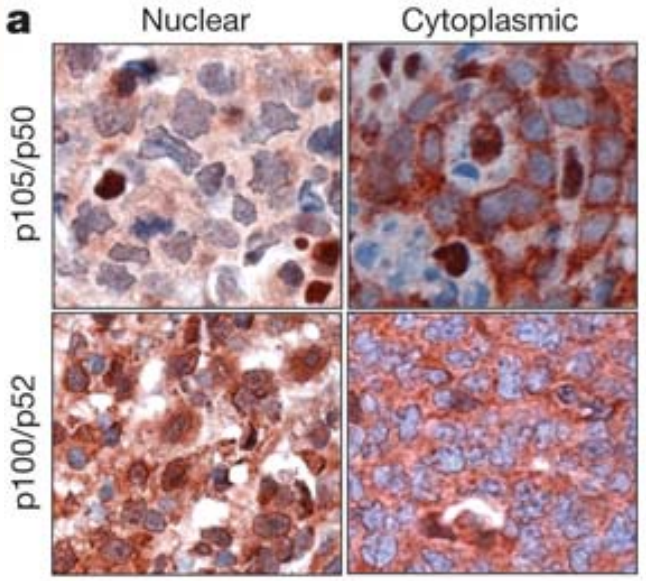


alternative



survival, proliferation & differentiation

Immunohistochemistry?



60 % ABC, 30 % GCB

Compagno, Nature 2009

NF-κB pathways

DLBCL COO SUBTYPES: NO LONGER PROGNOSTIC…

…AND NOT YET PREDICTIVE !!

PROGNOSTIC ?

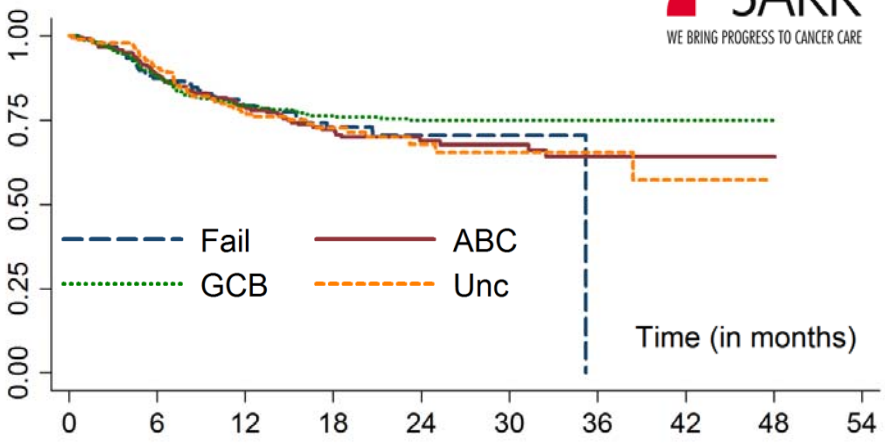
PFS *(2y)* ABC 40 % *(Lenz, NEJM 2008)*

non-GC 62 % *(Fu, JCO 2008)*

R-CHOP ±Bortezomib *(Leonard JCO 2017)*

- R-CHOP performed better (2y PFS 78%)
- *Selected population in randomized trials?*

REMoDL *(ASH'15 # 812)*



Not prognostic: RICOVER *(Ott, Blood 2010)*

Prognostic: GOYA *(Vitolo, JCO 2017)*

PREDICTIVE ?

+ Bortezomib, a purported NF-κB inhibitor, to R-CHOP:

→ outcome of the NF-κB dependent ABC / non-GC subtype not improved !

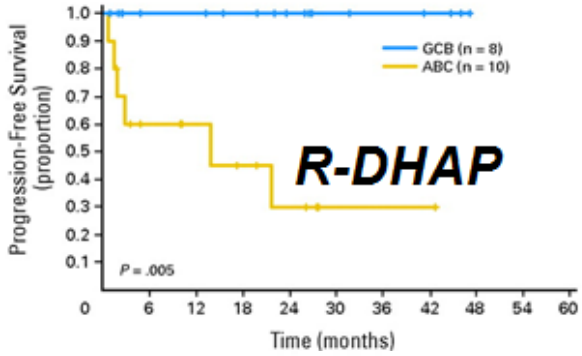
Offner Blood 2015, Leonard JCO 2017, Davies ASH'15 # 812

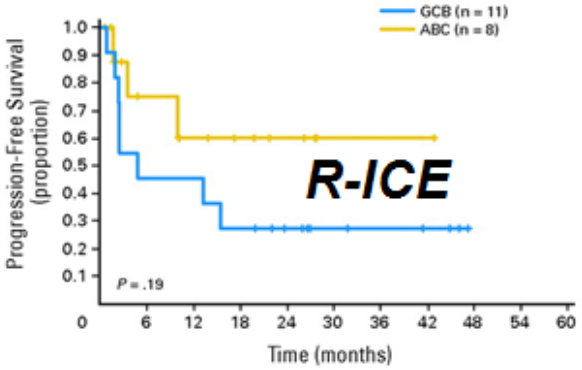
CLINICAL IMPACT OF DLBCL SUBTYPES

Lenz, NEJM 2008
Thieblemont, JCO 2011
Dunleavy, Blood 2009
Molina, JCO 2014

GCB-DLBCL

→ ***R-DHAP ?***

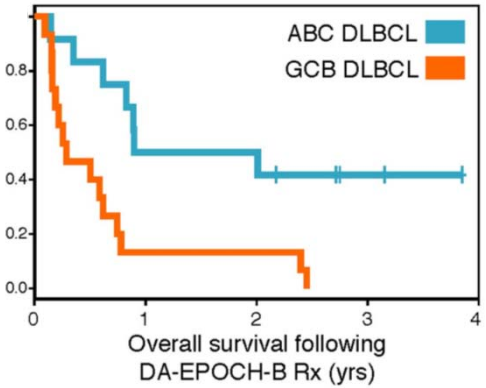


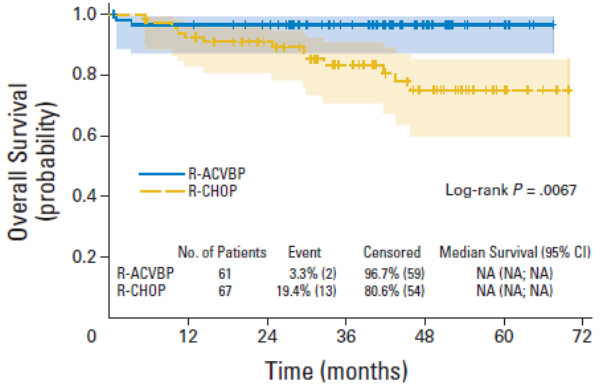


ABC-DLBCL

→ ***DA-EPOCH-RB ?***

→ ***R-ACVBP ?***

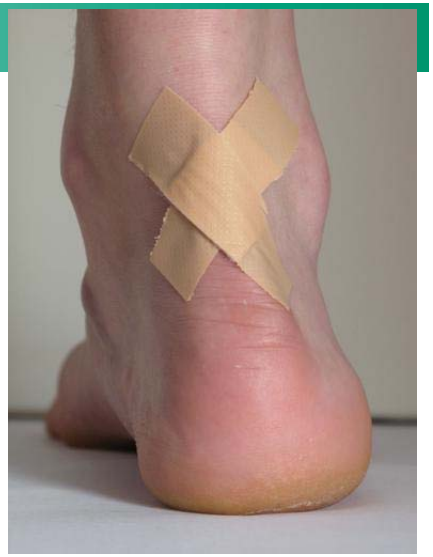




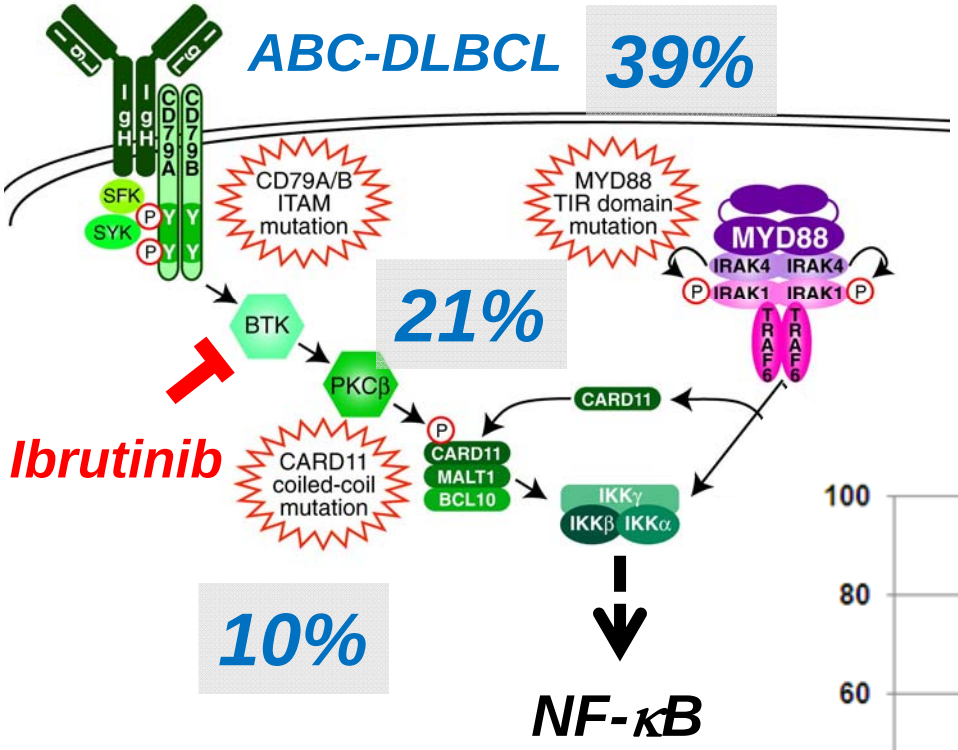
Pending ROBUST *(R-CHOP +/- LEN)*, PHOENIXr *(R-CHOP +/- Ibrut.)*

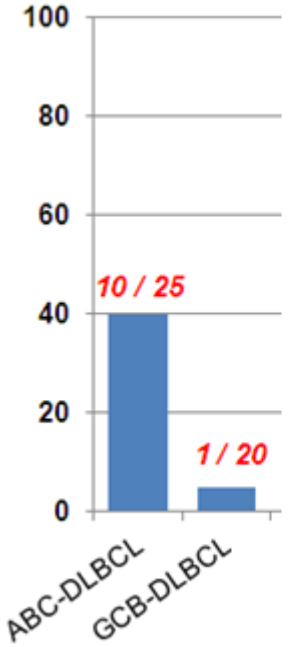
Trials for GCB-DLBCL…

TARGETS FOR ABC-DLBCLS



Crump JCO 2016; Flinn, EJC 2016; Witzig, Blood Cancer 2017; Thieblemont JCO 2017





MUTATIONS IN THE BCR DO NOT PREDICT THE RESPONSE TO IBRUTINIB

→ *Most responses in BCR WT ABC*

→ *oncogenic BCR signaling by non-genetic mechanisms !?!*

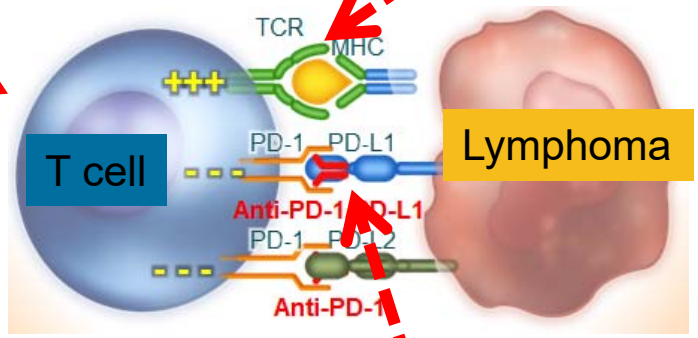
Wilson, ASH 2012 & Nat Med 2015

Cheung, ASH 2015 # 2642

ESSENTIALS FOR AN EFFECTIVE IMMUNOTHERAPY

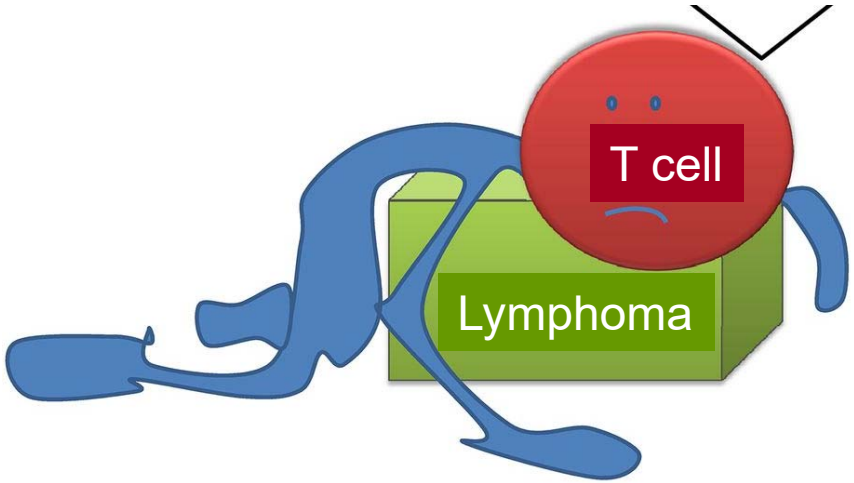
Antigen

Activated T cell



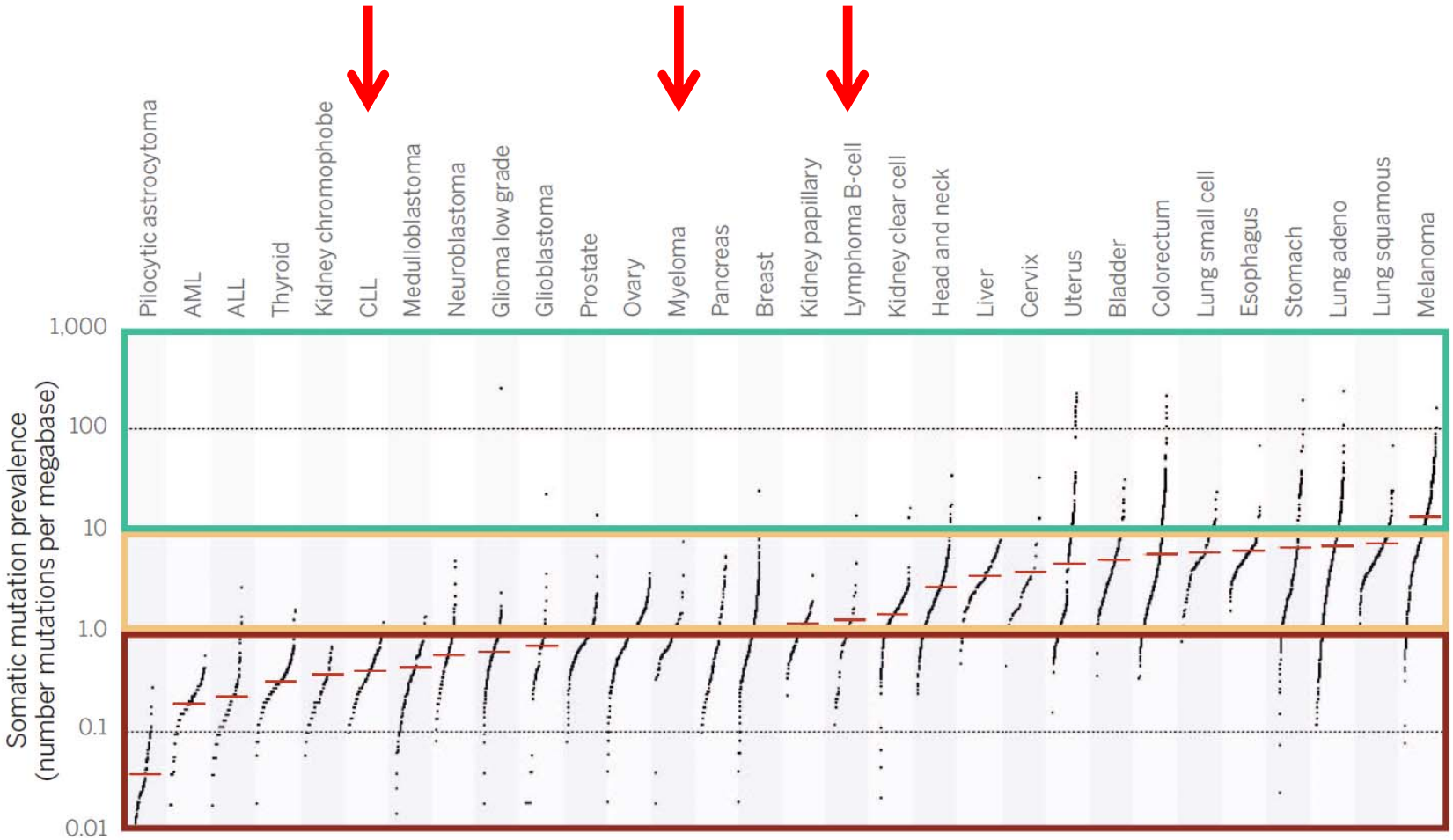
«Weak» immune system

in lymphomas



Expression of PD-L1

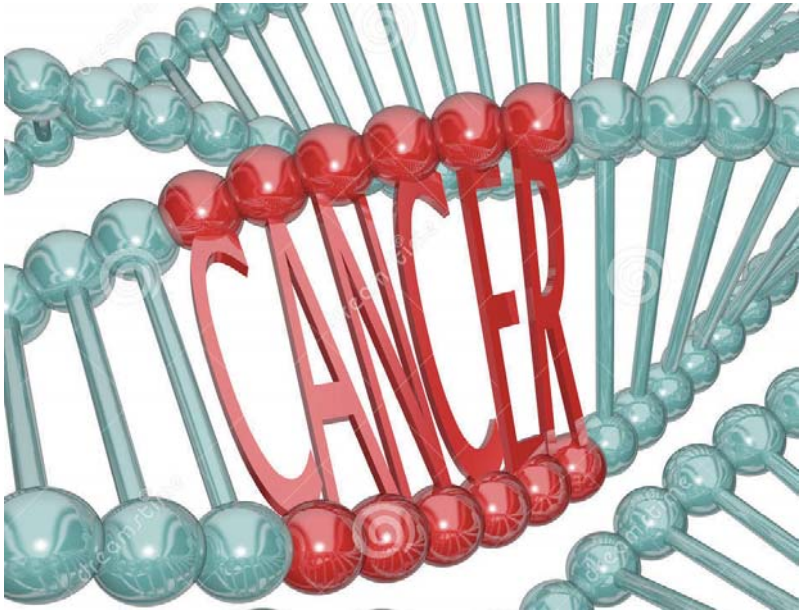
COMPARABLY FEW GENETIC LESIONS IN LYMPHOMAS



The genome of a DLBCL case contains ~100 mutations

c.f. > 30'000 in melanomas

Alexandrov LB, Nature 2013
Pasqualucci, Nat Genet 2011



Cancers harbor genetic lesions

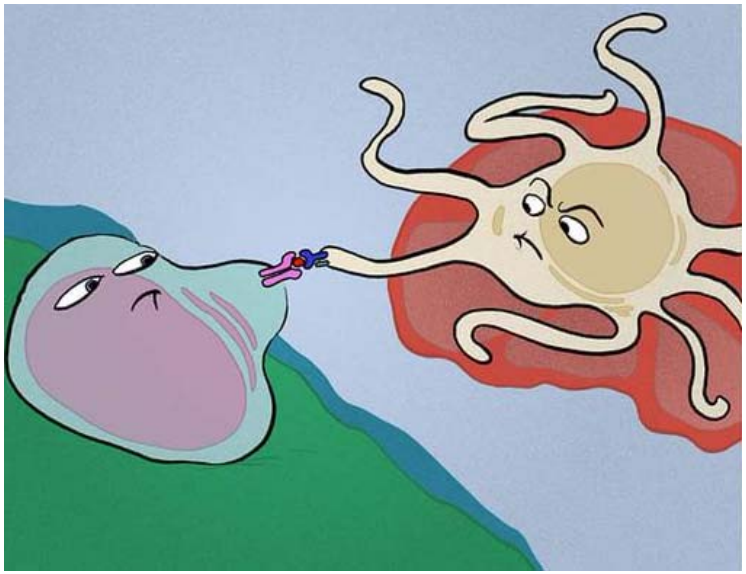
Acquired through failures during DNA repair

Some lesions may be biologically irrelevant **“passengers”**

Oncogenetic in essential biological processes **“drivers” & ther. targets**

GENETIC BASIS FOR IMMUNOTHERAPY

How lymphomas escape the immune system



Challa-Malladi, Cancer Cell 2011

Pasqualucci, Nat Genet 2011

Steidl, Nature 2011

Pasqualucci Cell Reports 2014

Georgiou, Blood 2016

Loss of antigen presentation through structural defects…

1. Mutations / losses of CD58 and B2M

> 60 % of DLBCLs, rare in other lymphomas

GENETIC BASIS FOR IMMUNOTHERAPY

Strong expression of PD-1 (~100 %)

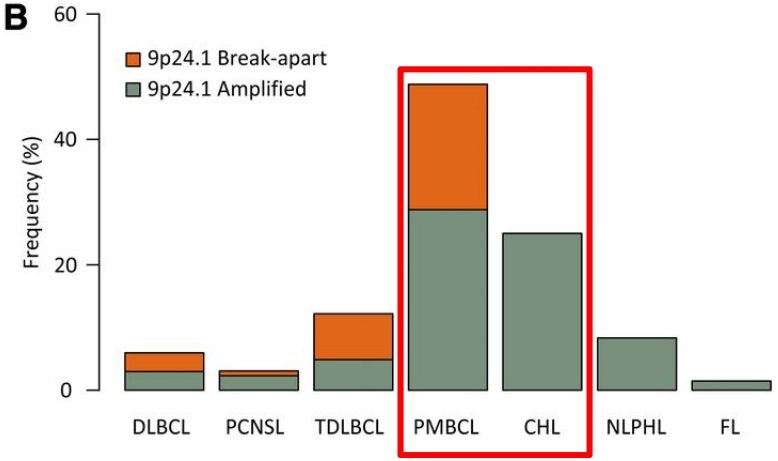
1. ***through specific translocation in primary mediastinal lymphomas***
2. ***Through genetic lesions***

   e.g. gains on chromosome 9p24

   in Hodgkin's and primary mediastinal lymphomas

   & testicular and CNS lymphomas *

   * *immune privileged lymphomas*



Steidl Nature 2011; Twa, Blood 2014; Roemer JCO 2016

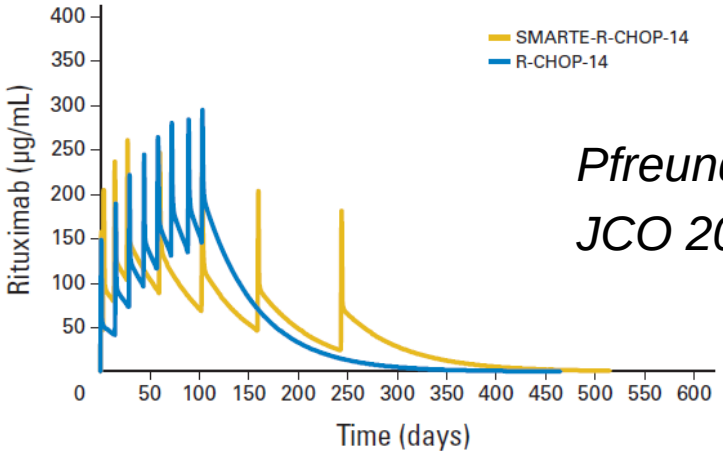
GENETICS +/- PREDICT THE PROFIT FROM PD-L1 INHIBITORS

Disease control through Nivolumab (Opdivo®) or * Pembrolizumab (Keytruda®)

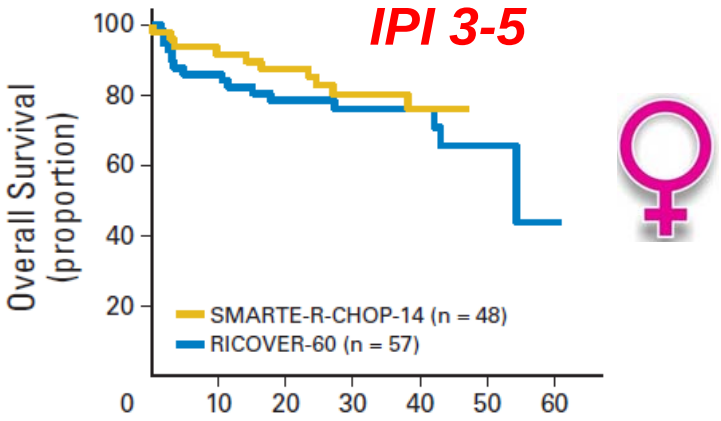
Disease	Number	Response (%)
Hodgkin's lymphoma	23	87
Primary mediastinal lymphoma *	19 *	41 *
Follicular lymphoma	11	40
T-cell lymphoma	5	40
Diffuse large B-cell lymphoma	11	36
Mycosis fungoides	13	15
Multiple myeloma	27	4
Various lymphomas	10	0

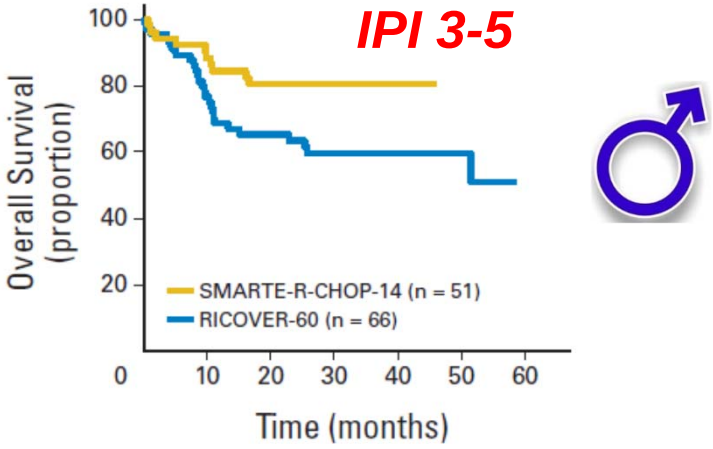
Ansell NEJM 2015; Lesokhin JCO 2016
Younes Lancet Oncol 2016; Chen JCO 2017; Zinzani Blood 2017

SEX IS FOR SURE A GENETIC FACTOR: to be considered…?!?



Pfreundschuh
JCO 2014





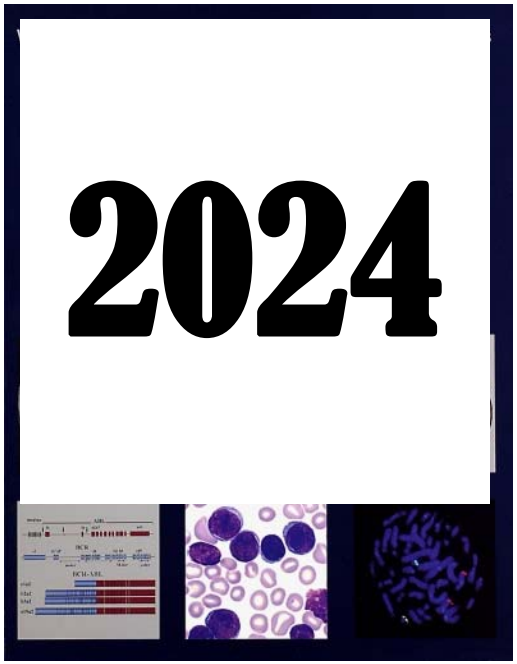
For elderly male:

Outcome ↑ by extended rituximab exposure ?

Increased Body Mass Index Is Associated With Improved Survival in United States Veterans With Diffuse Large B-Cell Lymphoma

Carson, JCO 2012

$$\text{DISAPPOINTMENT} = \frac{\text{EXPECTATION}}{\text{REALITY}}$$



As a clinician…
…I need predictive markers to guide my therapy
…I don't mind prognostic markers once I have a proven better therapy than R-CHOP

DLBCL treatment is ***NOT*** keeping up with progress in molec. pathology/biology

I accept that one needs to split before you can lump again (*N.L. Harris quoted*)

Oncologists should…
…not ignore their gut feelings, but should not believe that this is enough
…listen, talk, and continuously discuss with their ***pathologists before…***