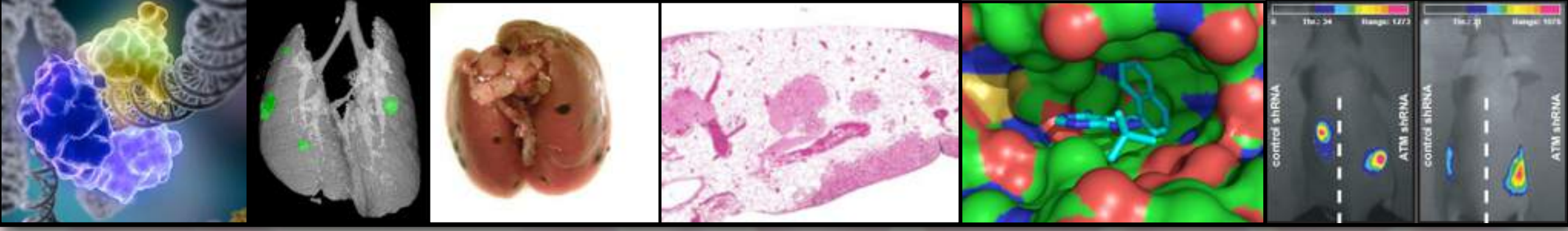


Chronic Lymphocytic Leukemia

–

Current and future therapeutic options

C. Reinhardt
Medical Clinic I, Hematology/Oncology
CECAD, Research Area C
Clinical and Molecular Oncology

CLL - a brief recapitulation

- What is CLL?

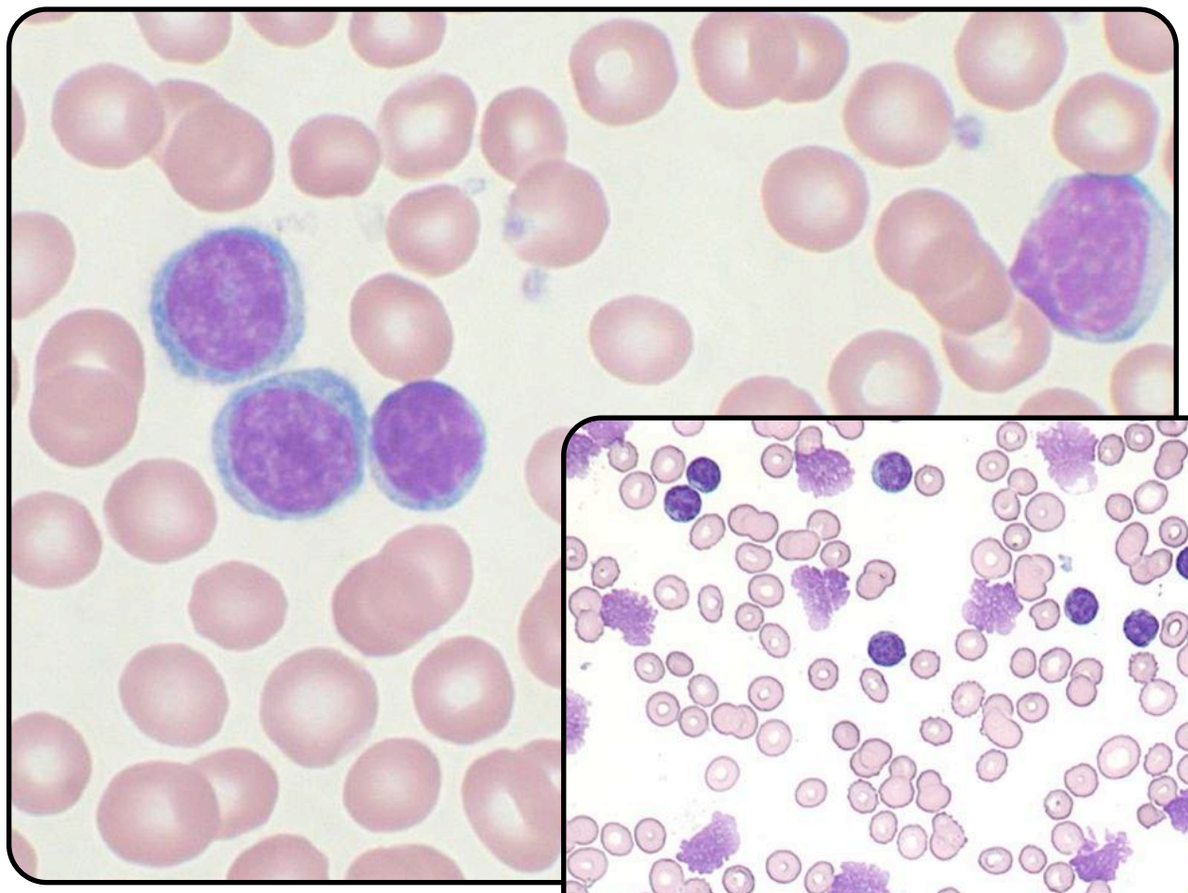
- Diagnostic tools

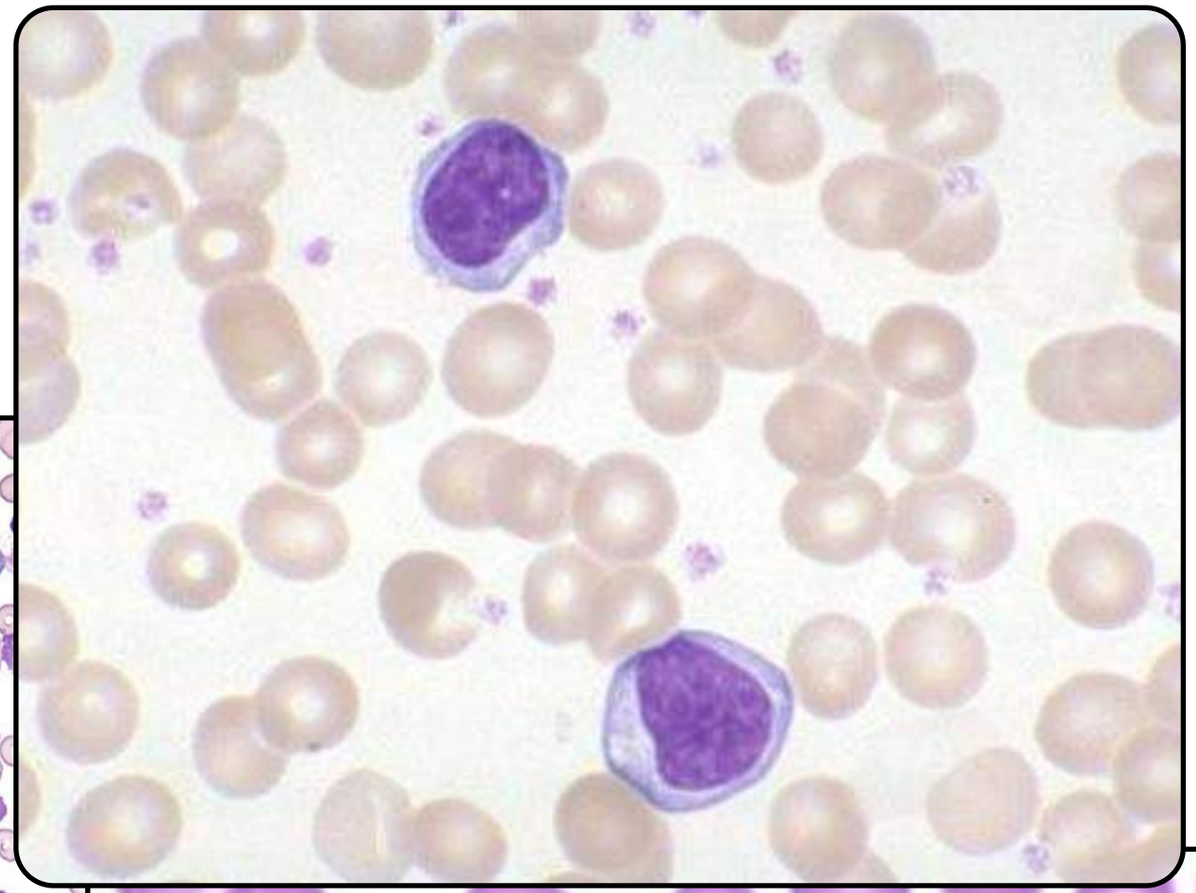
- Prognostic scores

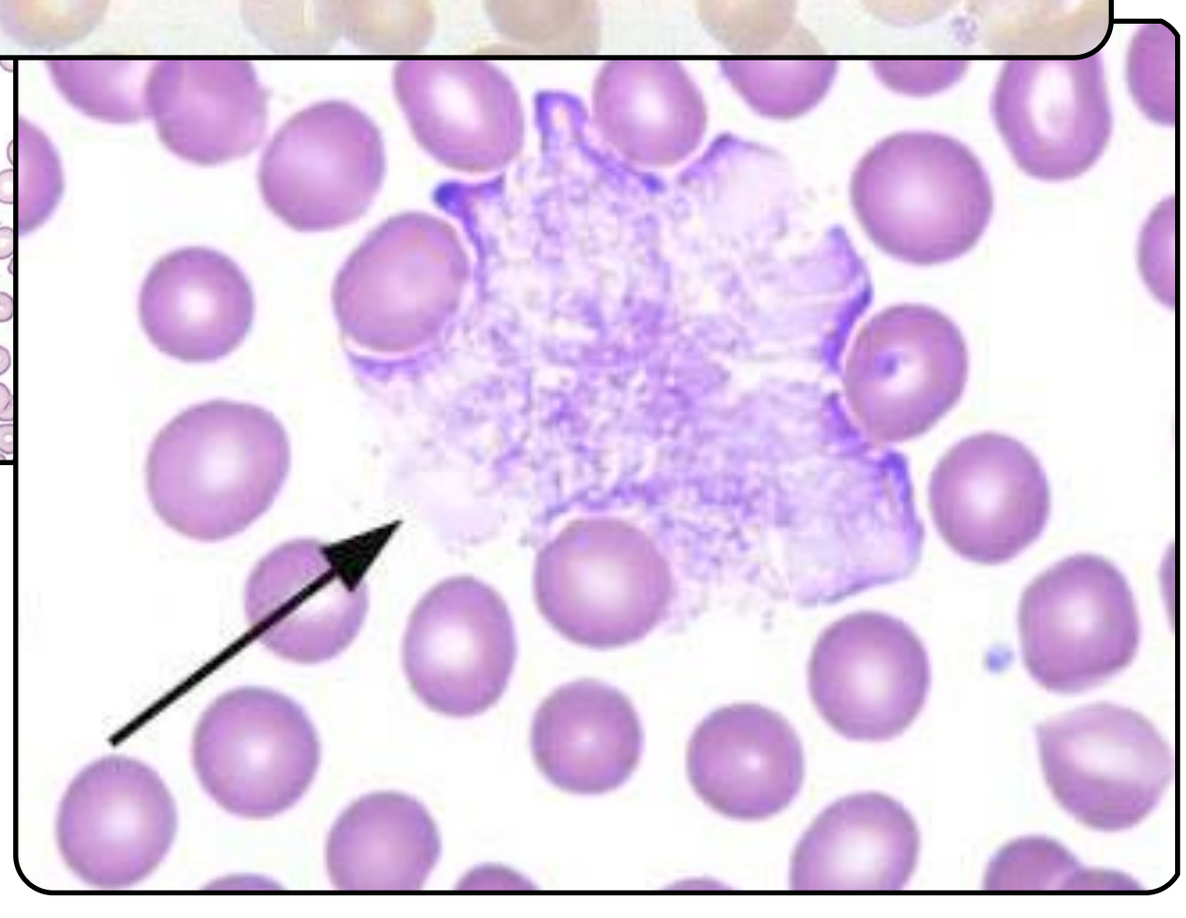
- Treatment of CLL

- Science becomes medicine (novel therapeutic approaches)

The blood smear reveals essential hints leading to the diagnosis

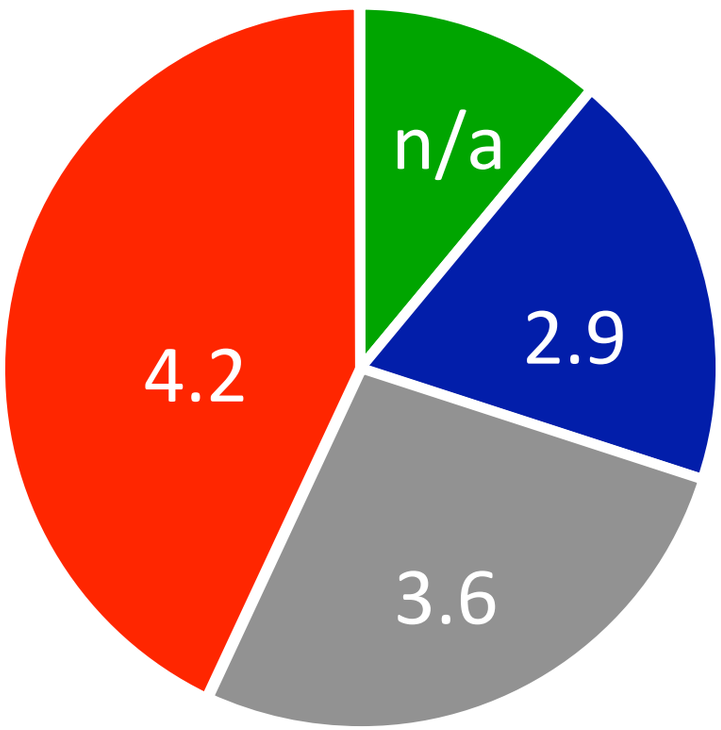






CLL is a disease of the elderly
→ a minority of patients qualifies for toxic therapy

- Most frequent leukemia in the Western hemisphere.
- Median age at diagnosis: 72 years[1]
- Elderly patients may have comorbidities



Age at CLL diagnosis (years)	Patients[1] (%)	Mean comorbidities[2] (all cancer types, n)
≤ 54	11	n/a
55–64	19	2.9
65–74	27	3.6
75+	43	4.2

1. Ries LAG, *et al.* SEER Cancer Statistics Review, 1975–2005.
2. Yancik R, *Cancer* 1997; 80:1273–1283.

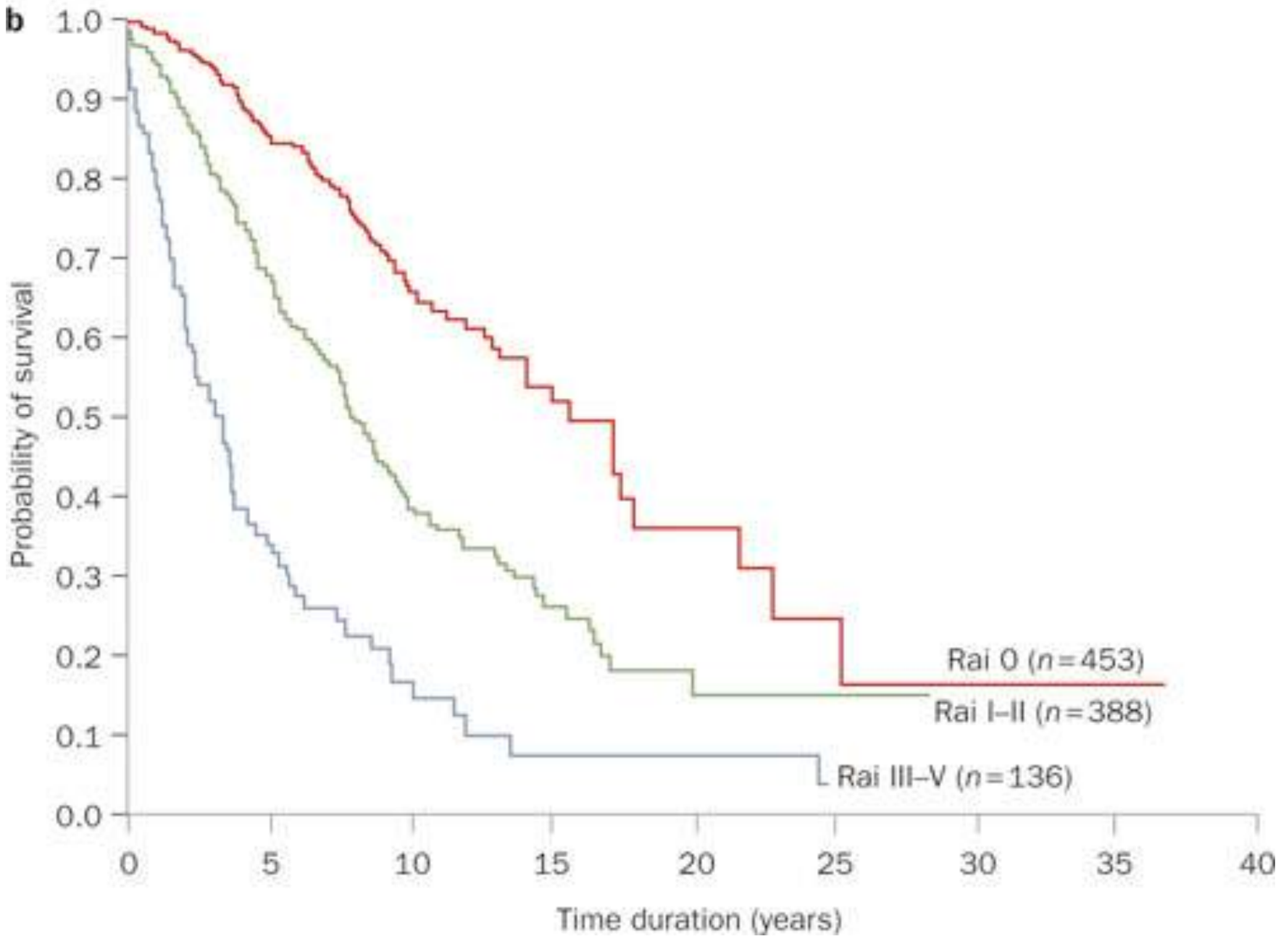
The Rai classification allows risk stratification

Table 1. Rai classification system*

Stage	Description	Median survival (months)	Risk status (Modified Rai)
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow	140	Low
I	Stage 0 with enlarged node(s)	100	Intermediate
II	Stage 0–1 with splenomegaly, hepatomegaly, or both	70	Intermediate
III	Stage 0–II with hemoglobin <11.0 g/dL or hematocrit <33%	20	High
IV	Stage 0–III with platelets <100,000/mcL	20	High

** Adapted from the 2008 NCI guidelines; BC Cancer Agency 2008 guidelines.[3,4]*

The Rai classification allows risk stratification



The Binet classification allows risk stratification

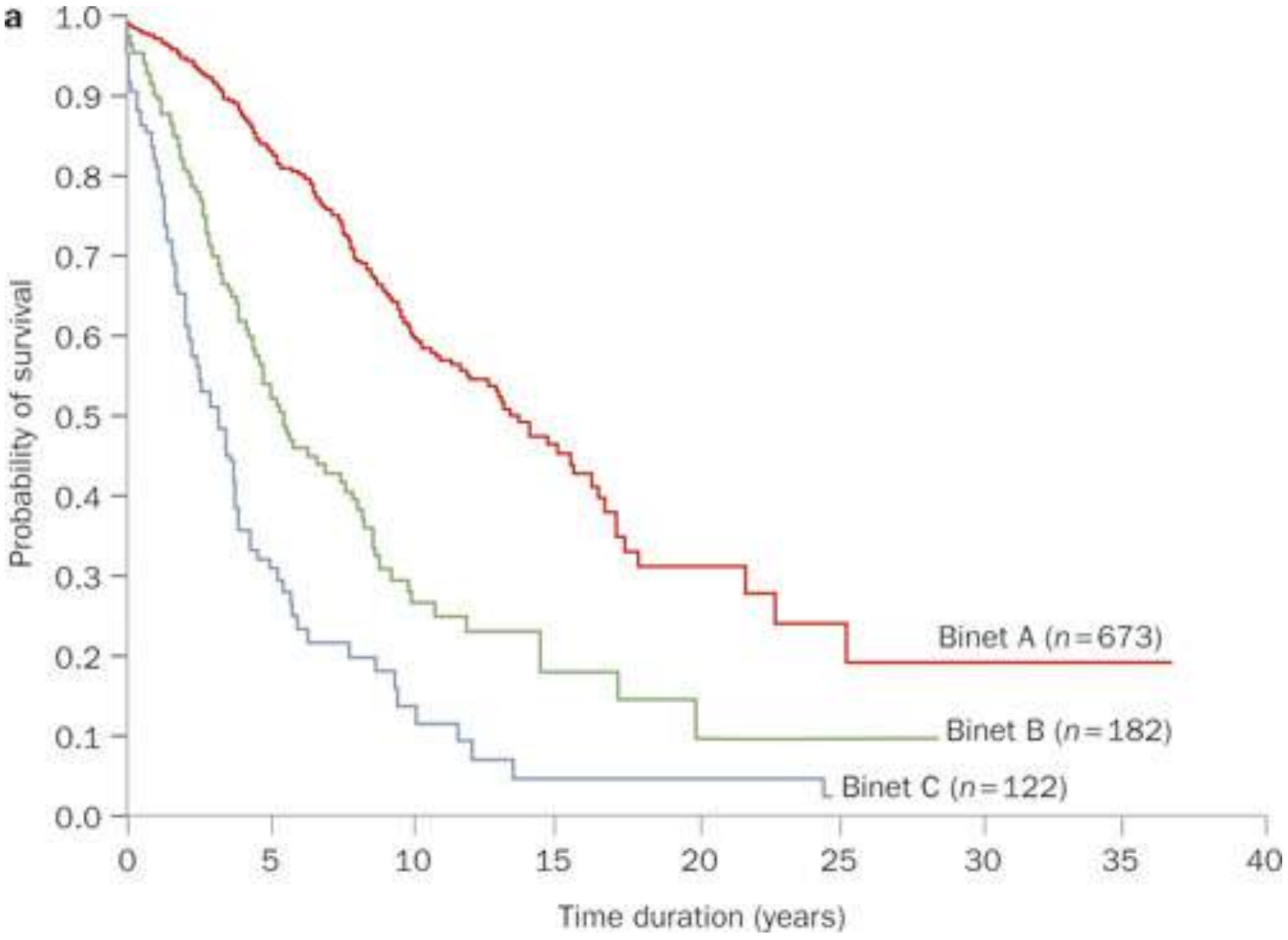
Table 2. Binet classification system*†

Stage	Description
A	Hemoglobin ≥10 g/dL and platelets ≥100,000/mm³ and <3 involved nodal areas
B	Hemoglobin ≥10 g/dL and platelets ≥100,000/mm³ and ≥3 involved nodal areas
C	Hemoglobin <10 g/dL and or platelets <100,000/mm³ and any number of involved nodal areas

**Adapted from the 2008 NCI guidelines.[3]*

†Areas of involvement considered for staging are as follows: (1) Head and neck, including the Waldeyer ring (this counts as one area, even if more than one group of nodes is enlarged). (2) Axillae (involvement of both axillae counts as one area). (3) Groins, including superficial femorals (involvement of both groins counts as one area). (4) Palpable spleen. (5) Palpable liver (clinically enlarged).

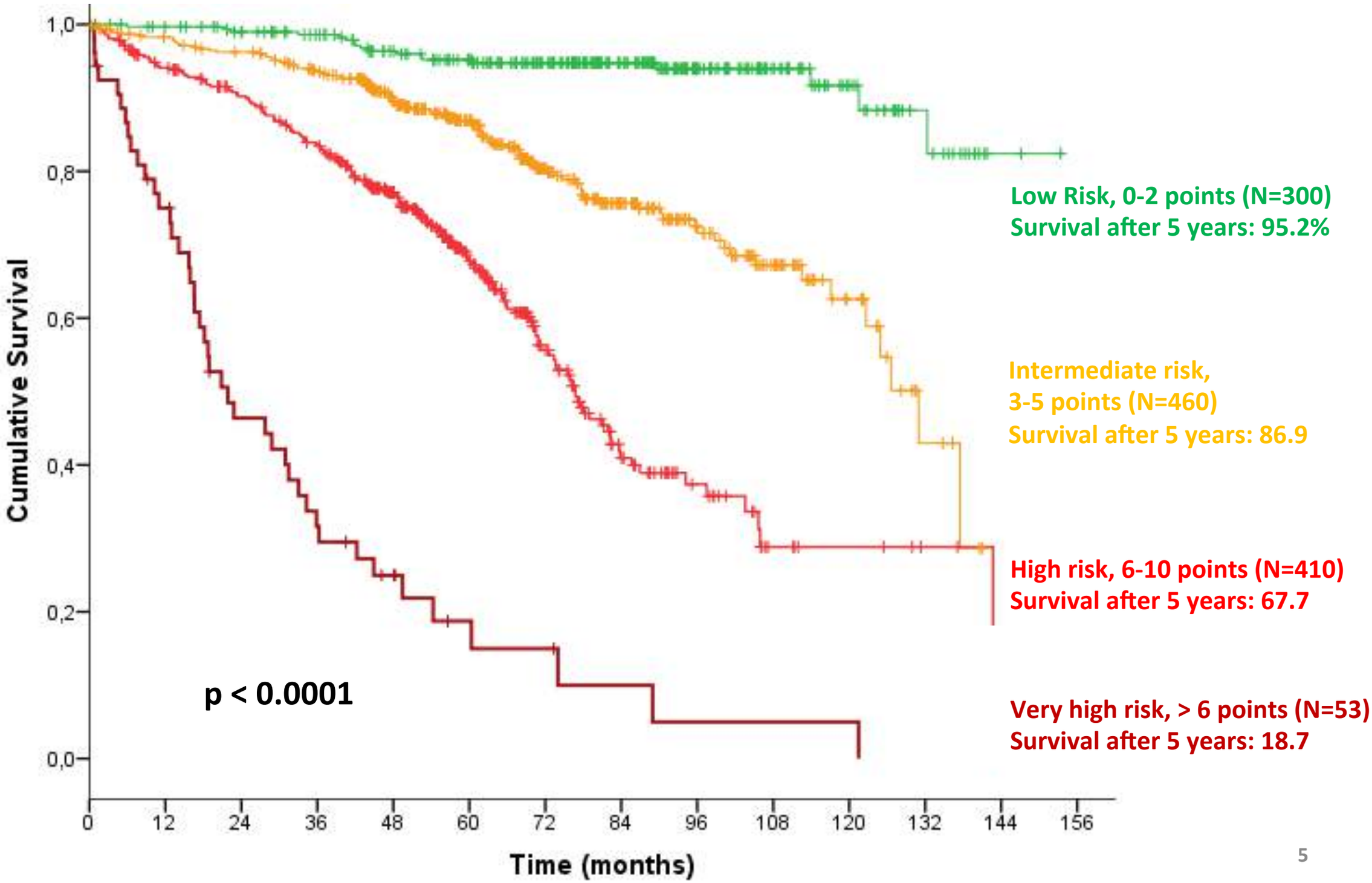
The Binet classification allows risk stratification



A novel, molecularly-guided risk score allows more detailed risk stratification

Variable	Adverse factor	Hazard ratio for death	Factor - grading
Chromosomal aberration	del(17p)	6.0	**6**
s-TK	> 10.0 U/L	2.8	**2**
s-β2m	> 3.5 mg/L	2.3	**2**
IgHV mutational status	unmutated	1.9	**1**
s-β2m	> 1.7 mg/L - ≤ 3.5 mg/L	1.7	**1**
ECOG	> 0	1.7	**1**
Chromosomal aberration	del(11q)	1.4	**1**
Gender	Male	1.3	**1**
Age	> 60 years	1.3	**1**

A novel, molecularly-guided risk score allows more detailed risk stratification



Summary I

- CLL is the most common leukemia in the Western World

- CLL is characterized by the accumulation of mature lymphocytes

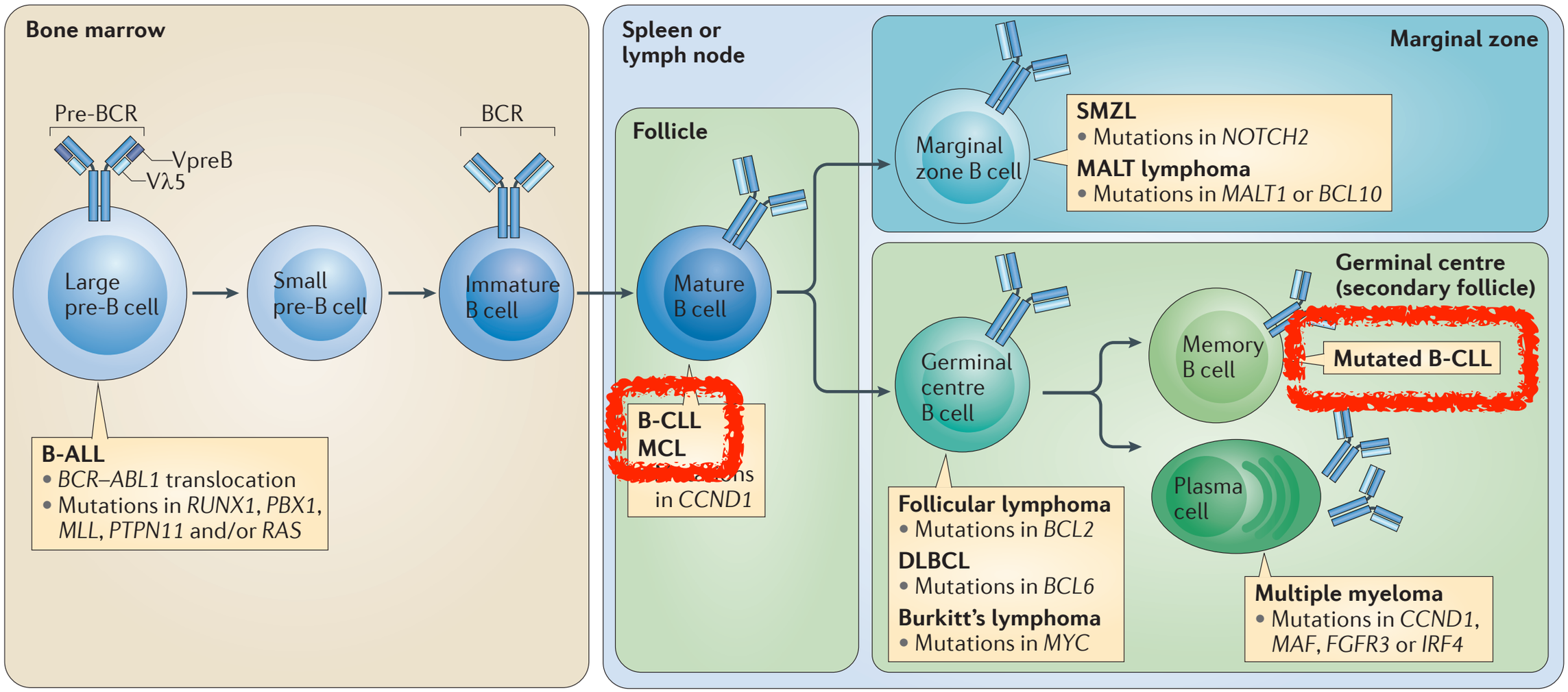
- Multiple risk scores exist and allow patient stratification

- CLL cells are addicted to micro-environmental stimuli

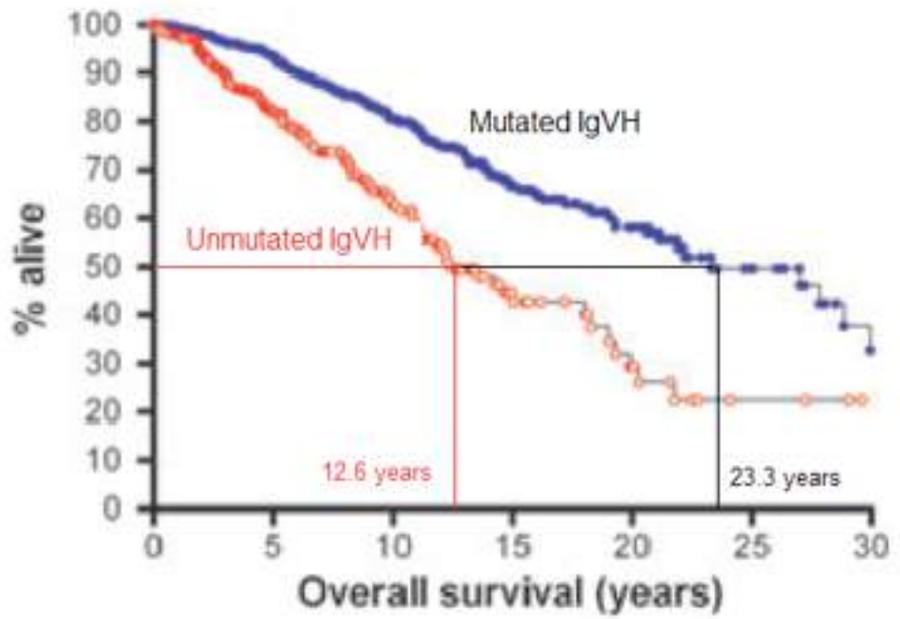
- Transformation can occur before or after somatic hypermutation

The genetics of high risk CLL

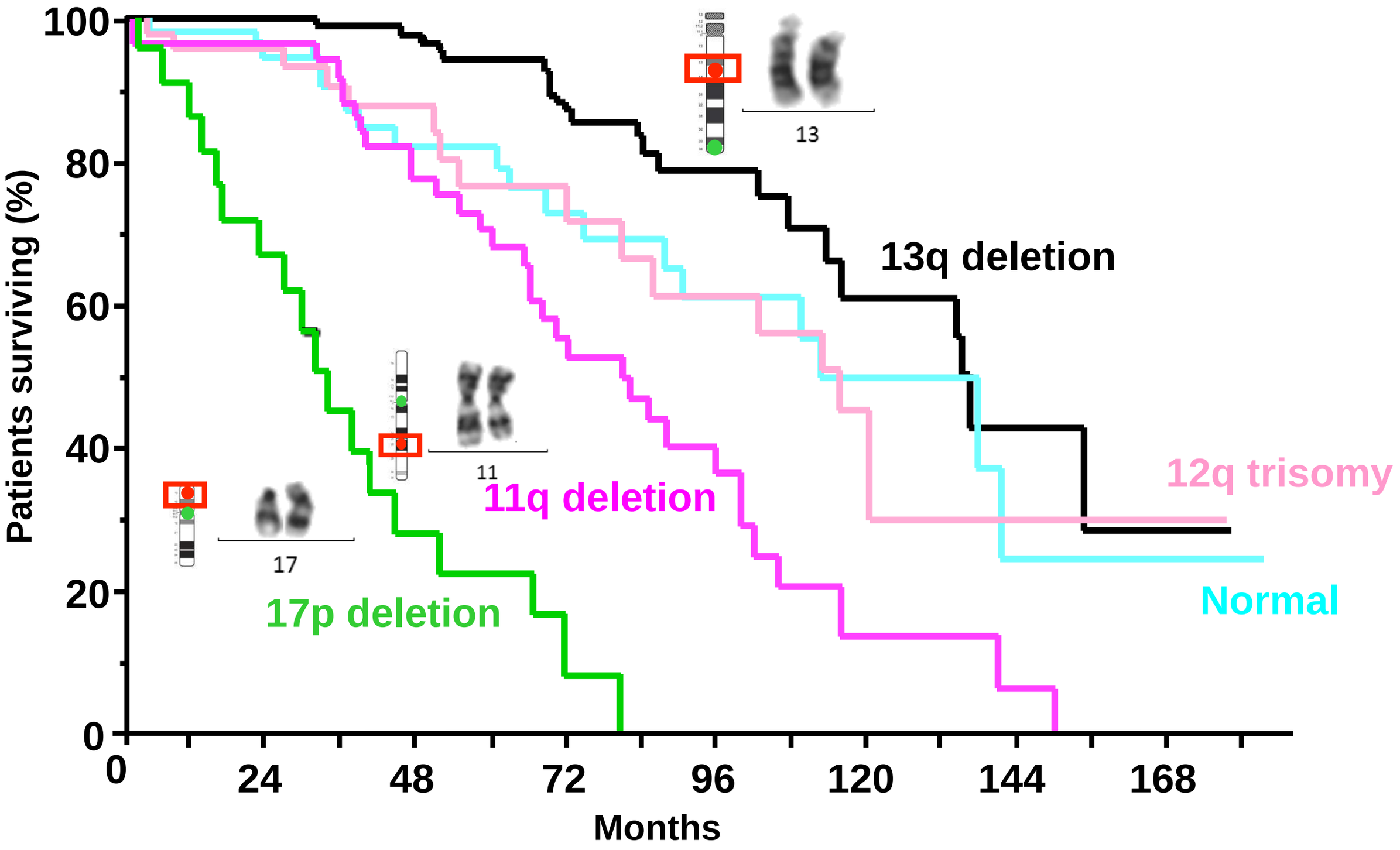
CLL clones can emerge before and after Ig hypermutation



IgVH-unmutated CLL clones are associated with poor prognosis

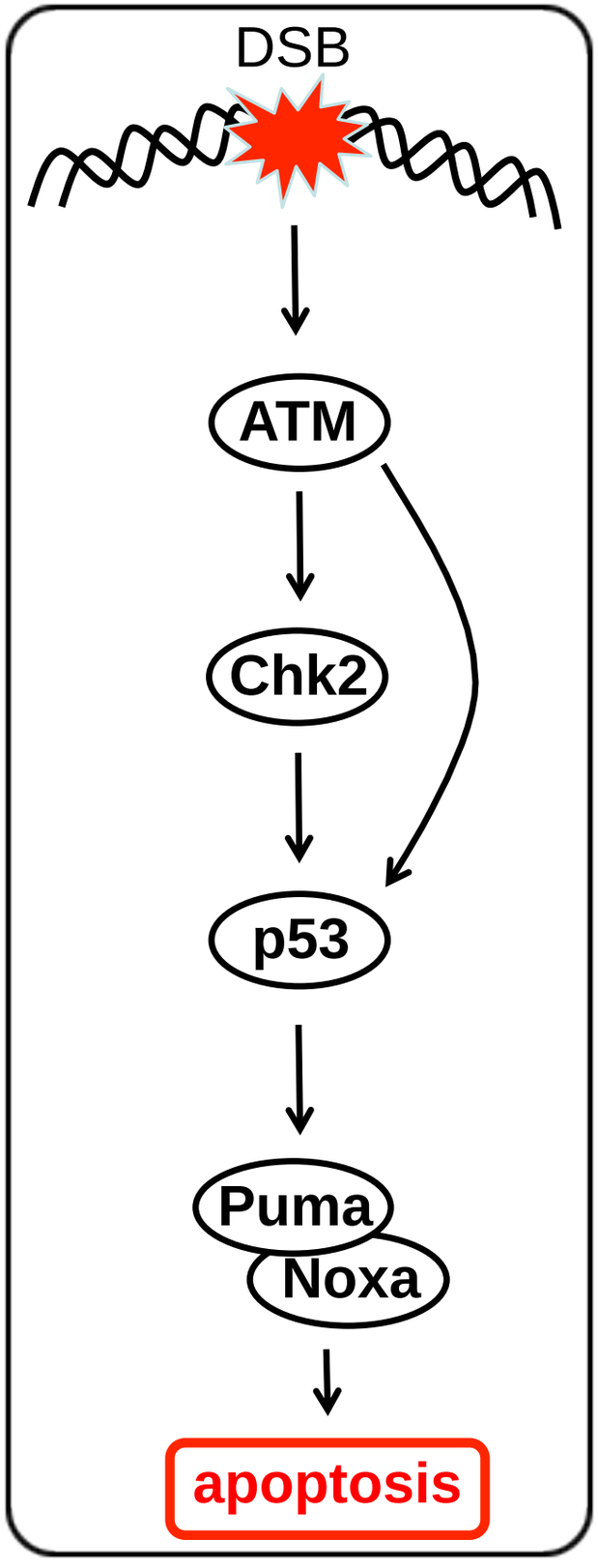


Two distinct cytogenetic aberrations are associated with poor survival



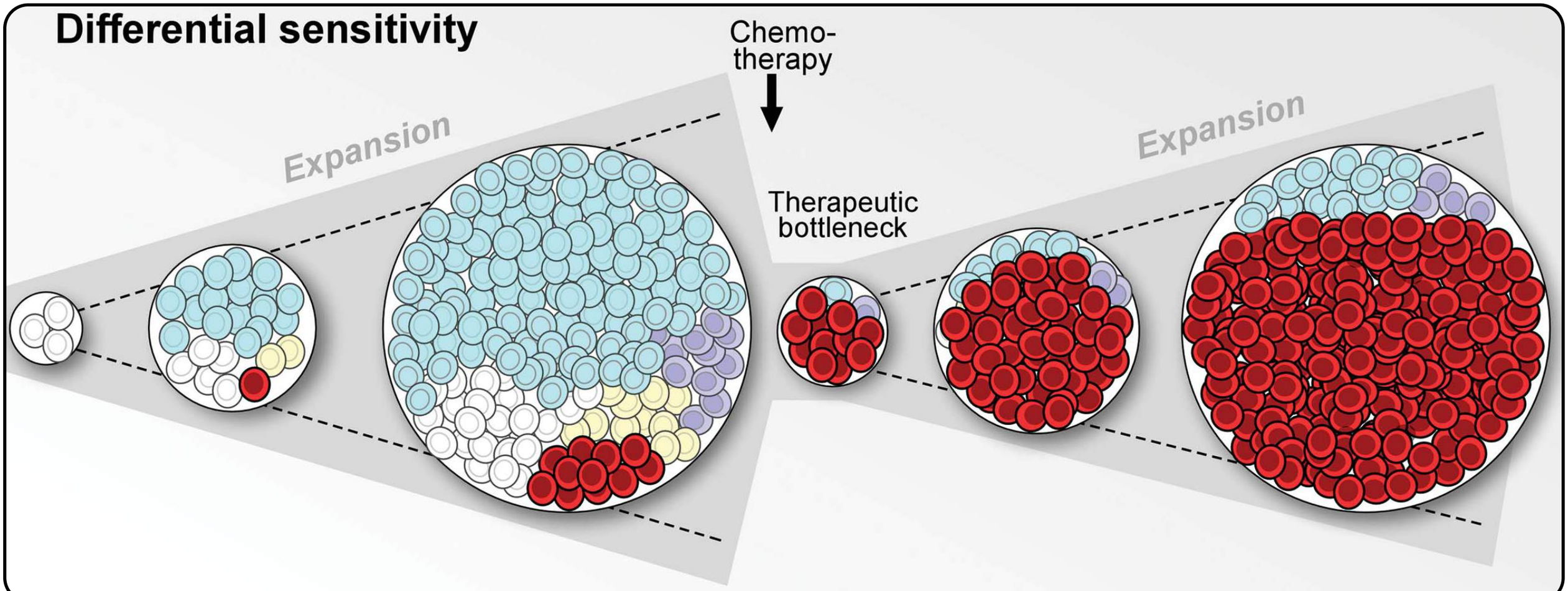
Döhner et al NEJM 2000 343:1910

Disabling mutations in apoptosis-mediating pathways represent high-risk aberrations in CLL

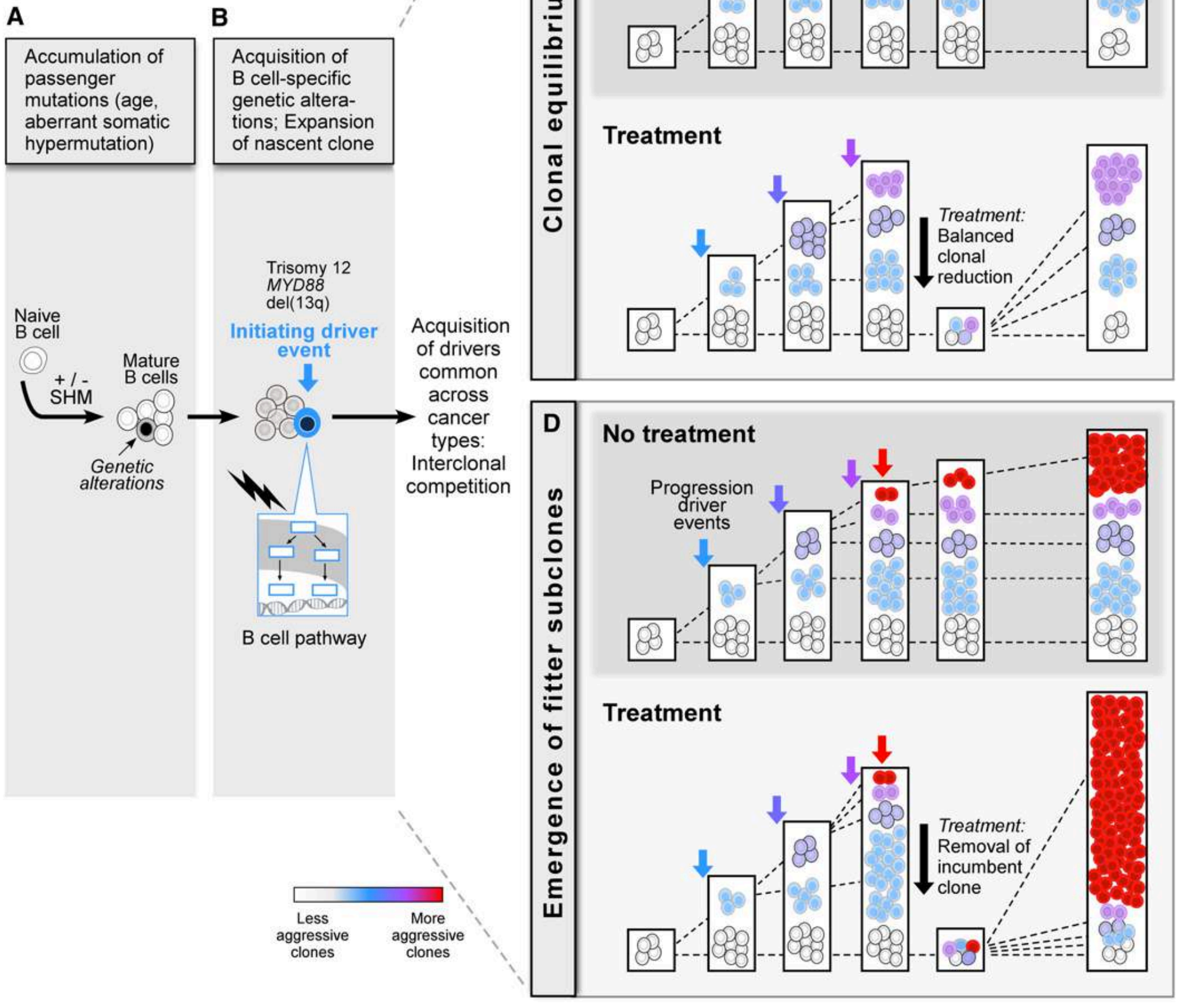


CLL is a dynamic disease and clonal evolution represents a clinical challenge

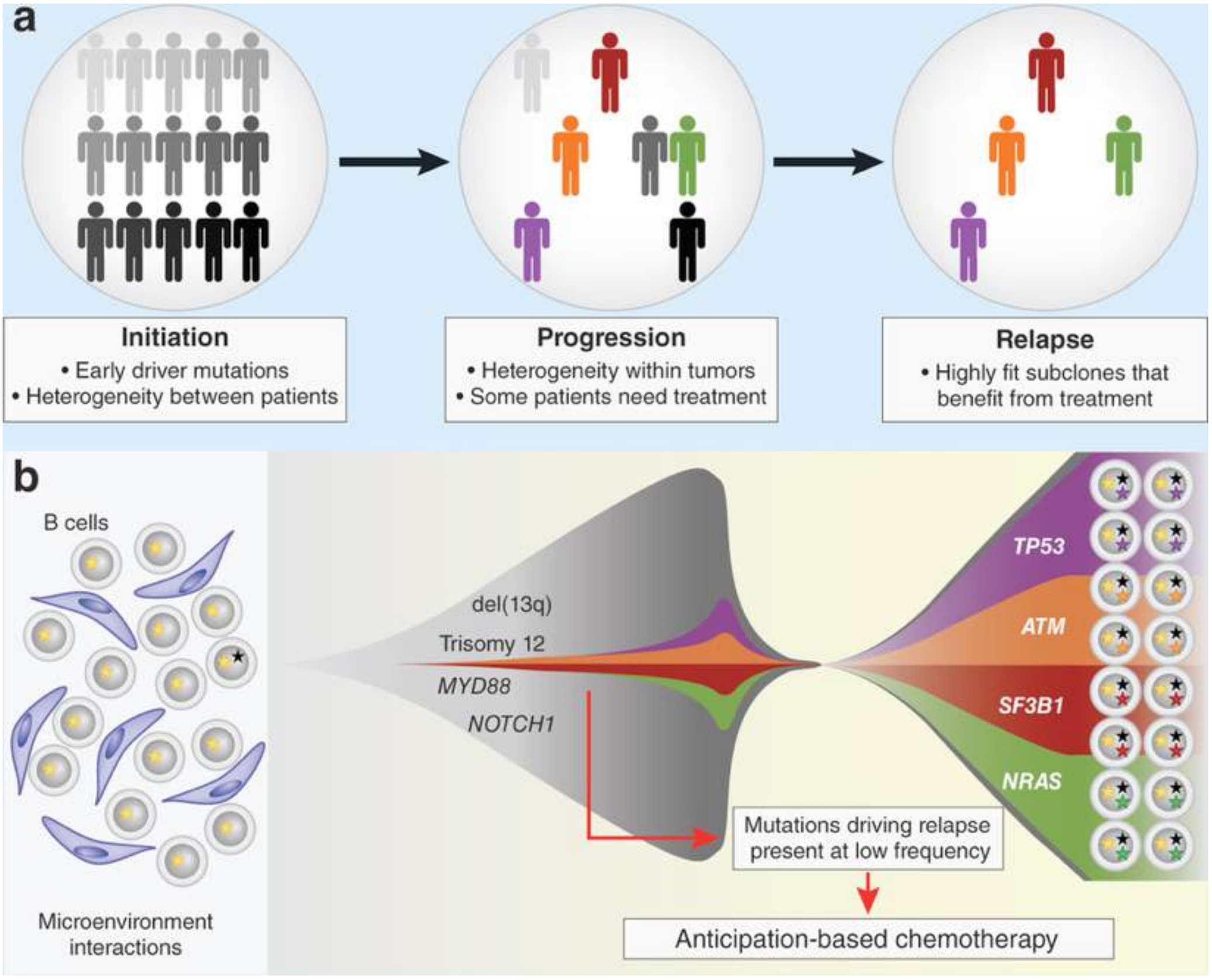
Therapeutic interventions shift the selective pressure



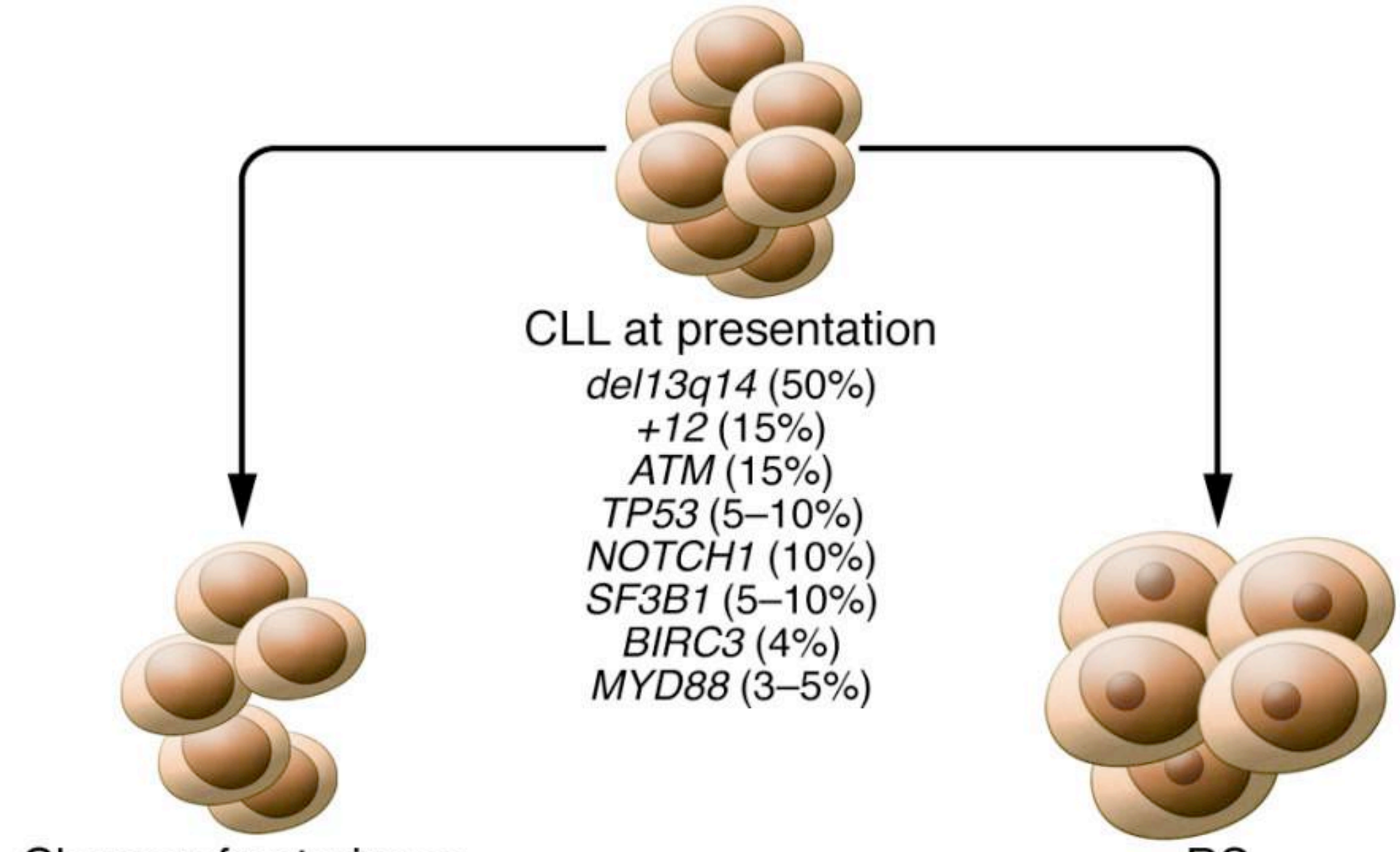
Therapeutic interventions shift the selective pressure



Multiple competing clones might exist in the same patient



CLL clones can acquire additional genetic aberrations

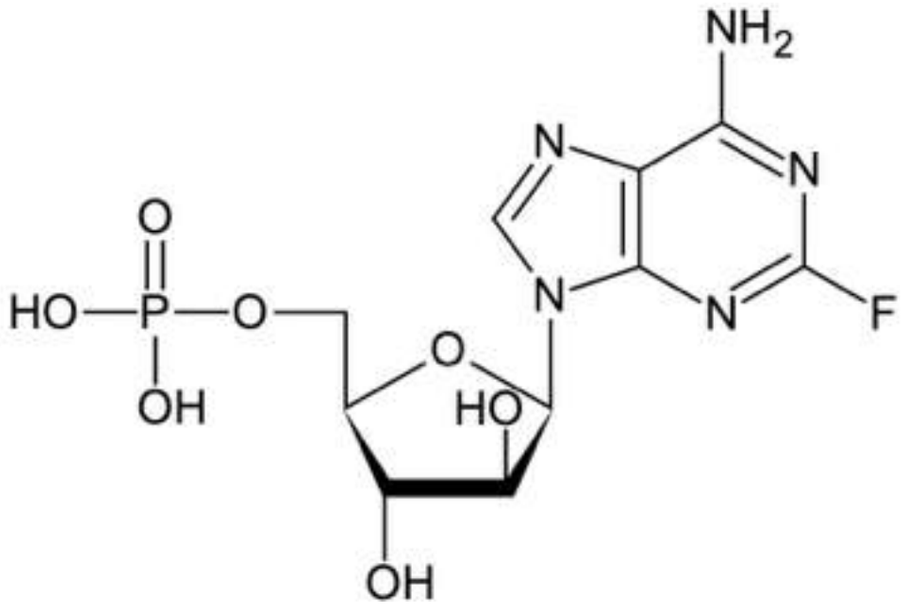


Summary II

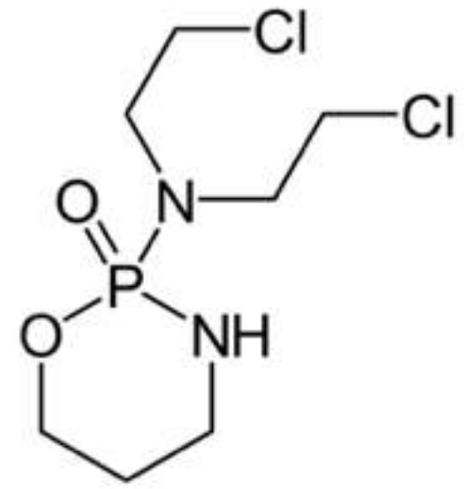
- CLL is the most common leukemia in the Western World

So, how do we actually treat CLL?

Chemotherapy still remains the backbone of CLL therapy

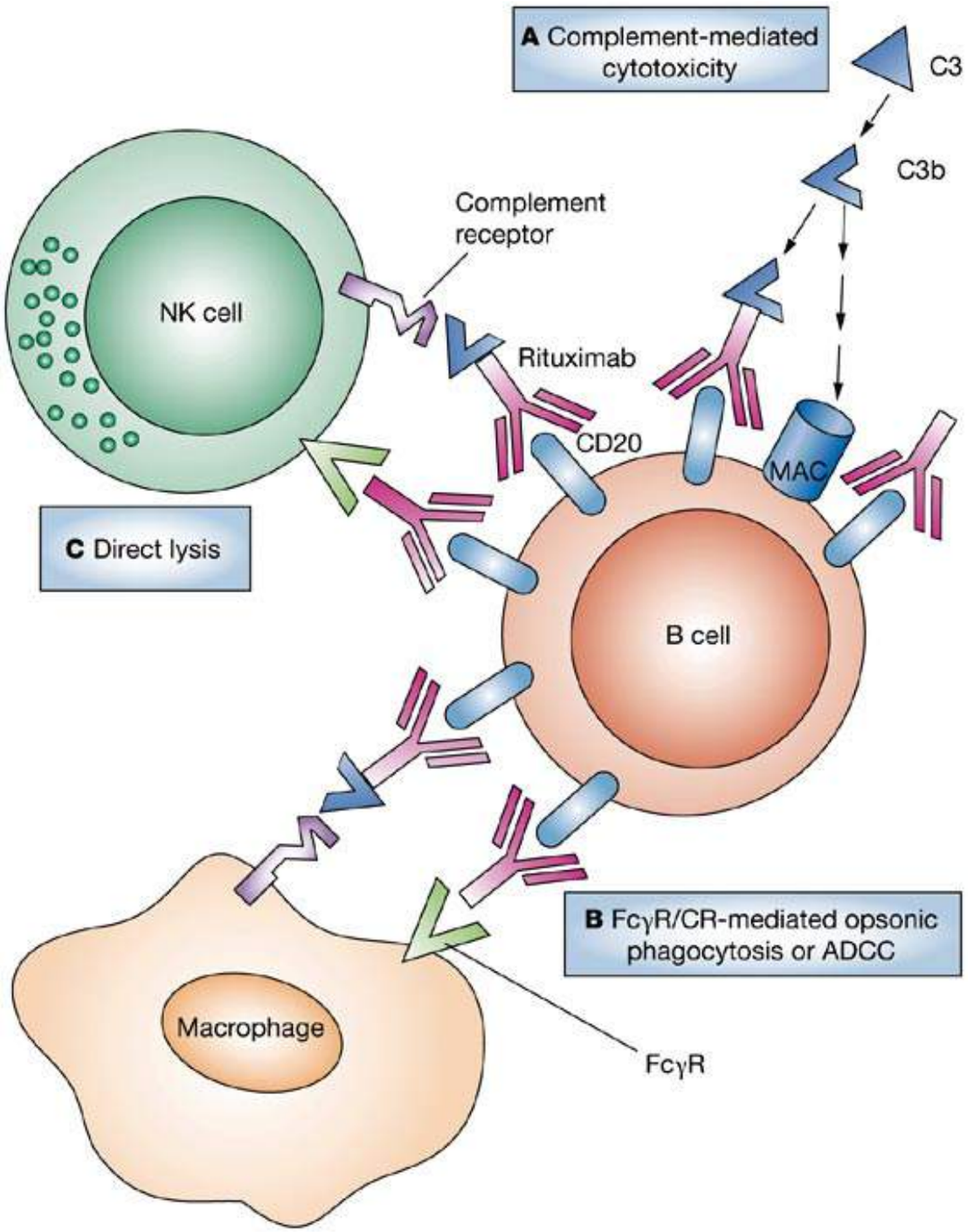


Purine analogue
fludarabine



Alkylating agent
cyclophosphamide

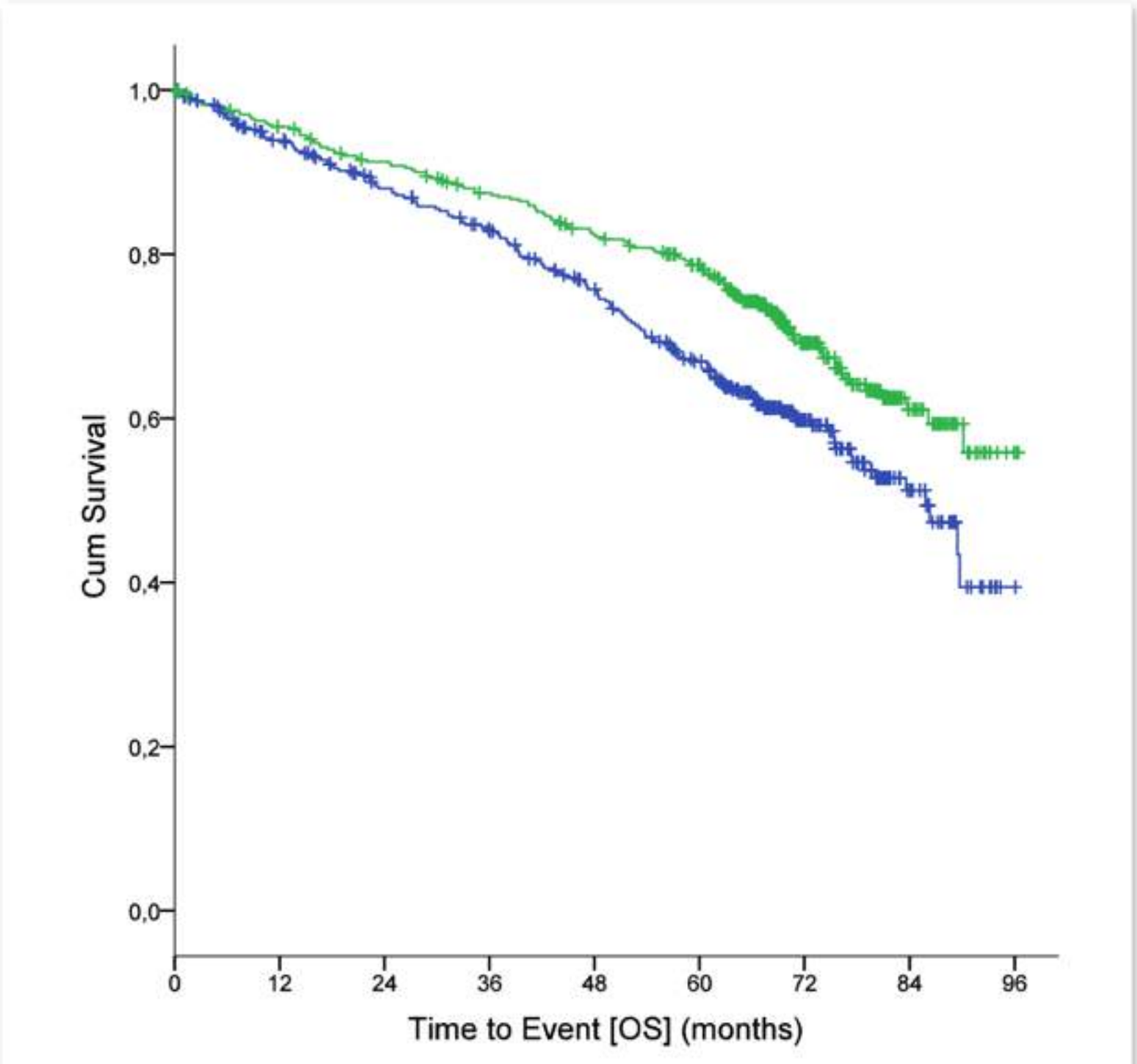
Antibodies constitute an important pillar of CLL therapy



Rituximab-opsonized B cells are subject to attack and killing by at least three pathways.

1) Complement-mediated membrane attack
2) Phagocytosis by macrophages
3) Antibody-dependent cell-mediated cytotoxicity

CLL8 trial: Overall survival, update 2012
FCR versus FC



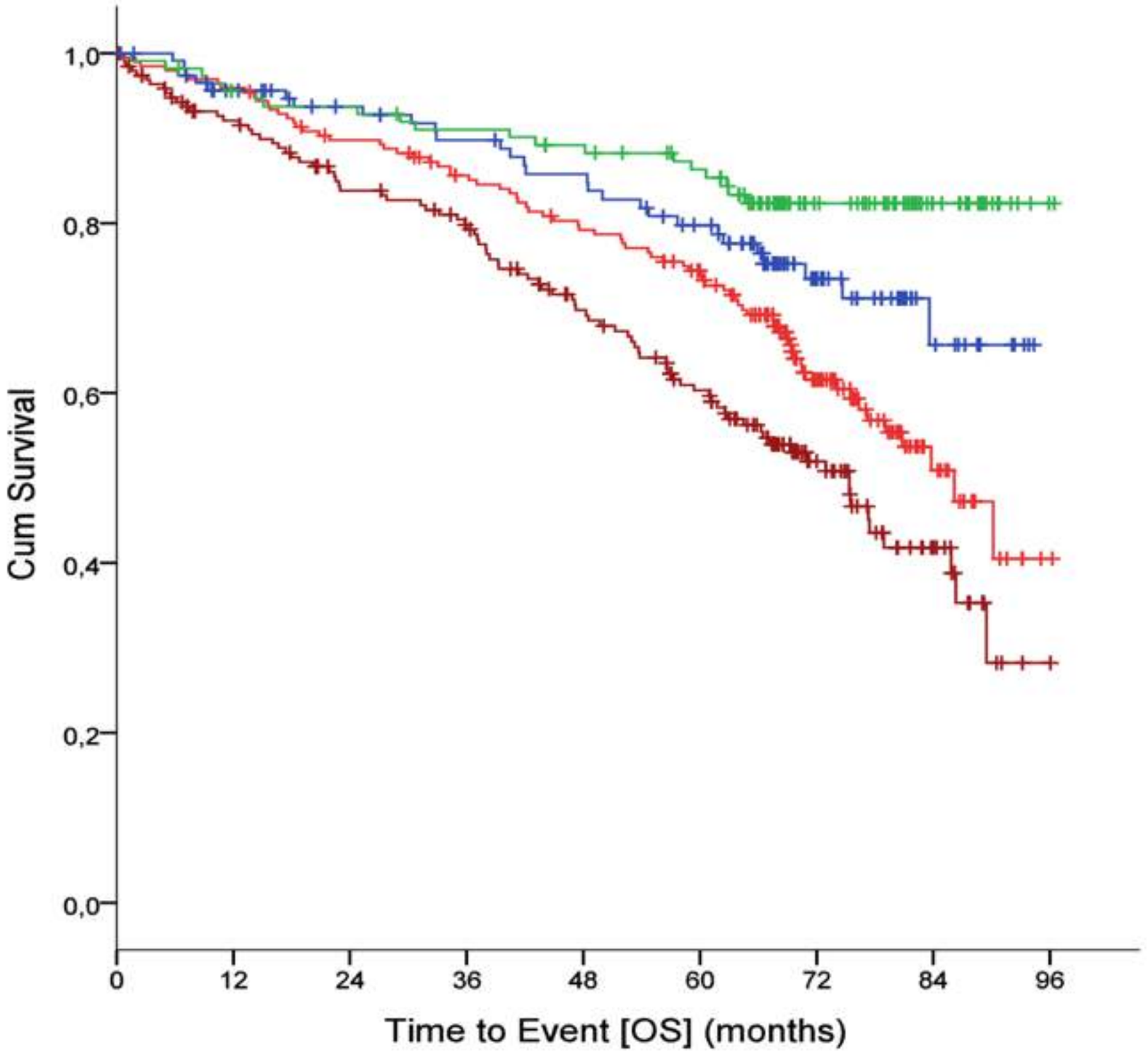
Median observation time 5.9 years

FCR 69.4% alive
Median not reached
FC 62.3% alive
Median 86 months

HR 0.68,
95% CI 0.535-0.858
p=0.001

Hallek et al. Lancet 2010; Fischer K et al. ASH 2012

Overall survival after FCR chemoimmunotherapy



Median observation time
5.9 years

Median OS
FCR *IGHV* mutated
Not reached
FC *IGHV* mutated
Not reached
FCR *IGHV* unmutated
86 months
FC *IGHV* unmutated
75 months

FC *vs.* FCR
HR 1.63,
95% CI 0.908 - 2.916

Fischer K et al.
iwCLL 2013

When should we initiate treatment?

Study Design

DEUTSCHE STUDIENGRUPPE

1 Registration

Binet A stage CLL
1st Dx ≤ 12 months, GFR 70 ml/min, untreated

2 Central diagnostics

Assessment of 4 defined risk factors:
- Unfavorable cytogenetics (del17p, del11q, tri12)
- Unmutated IGHV status
- Thymidine kinase > 10 U/L
- Lymphocyte doubling time ≤ 12 months

3 Risk stratification

Risk stratification

High risk
≥ 2 risk factors

Low risk
< 2 risk factors

4 Randomization (high risk)

6 cycles FCR *

watch & wait

watch & wait

*** FCR dosing: q28d**
Rituximab 375 mg/ m² iv, d0, #1,
Rituximab 500 mg/m² iv, d1, #2-6
Fludarabine 25 mg/m² iv, d1-3, #1-6
Cyclophosphamide 250 mg/m² iv, d1-3, #1-6

Study Population

DEUTSCHE STUDIENGRUPPE

n = 824 patients registered
(401pts, 423 pts)

24 patients w/ premature end of study:
PD, withdrawal, false diagnosis, 2nd malignancy

n = 800 patients available for risk stratification

High risk
n = 201 (25.1%)

Low risk
n= 599 (74.9%)

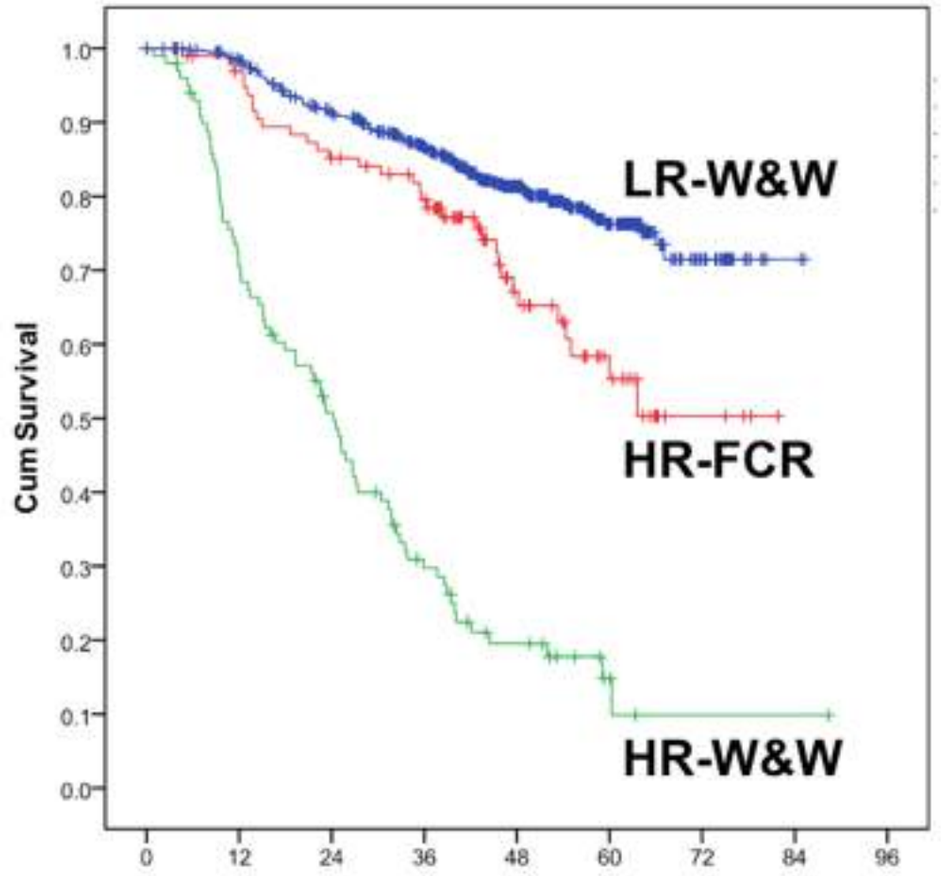
FCR
n = 100

w&w
n = 101

w&w
n= 599

- Primary endpoint: Event-free survival (EFS)
- Assumption: Improvement by FCR from 50 to 70% at month 36
- Median follow up at analysis: 49 months

Primary Endpoint: EFS



Log rank *P* < 0.001

	N events	Median EFS	5 year EFS
HR-FCR	33	n. r.	55.3%
HR-W&W	78	n. r.	14.8%
LR-W&W	111	24.2 months	80.1%
Cox regression: Variable	**P Value**	**Hazard Ratio**	**95% CI**
Cohort assignment	3.815E-43		
HR-FCR vs. LR-W&W	0.001	1.9	1.3 – 2.8
HR-W&W vs. LR-W&W	3.881E-44	8.2	6.1 – 11.0
HR-FCR vs. HR-W&W	5.846E-12	0.2	0.1 – 0.4

Can we optimize the components of our current regimens?

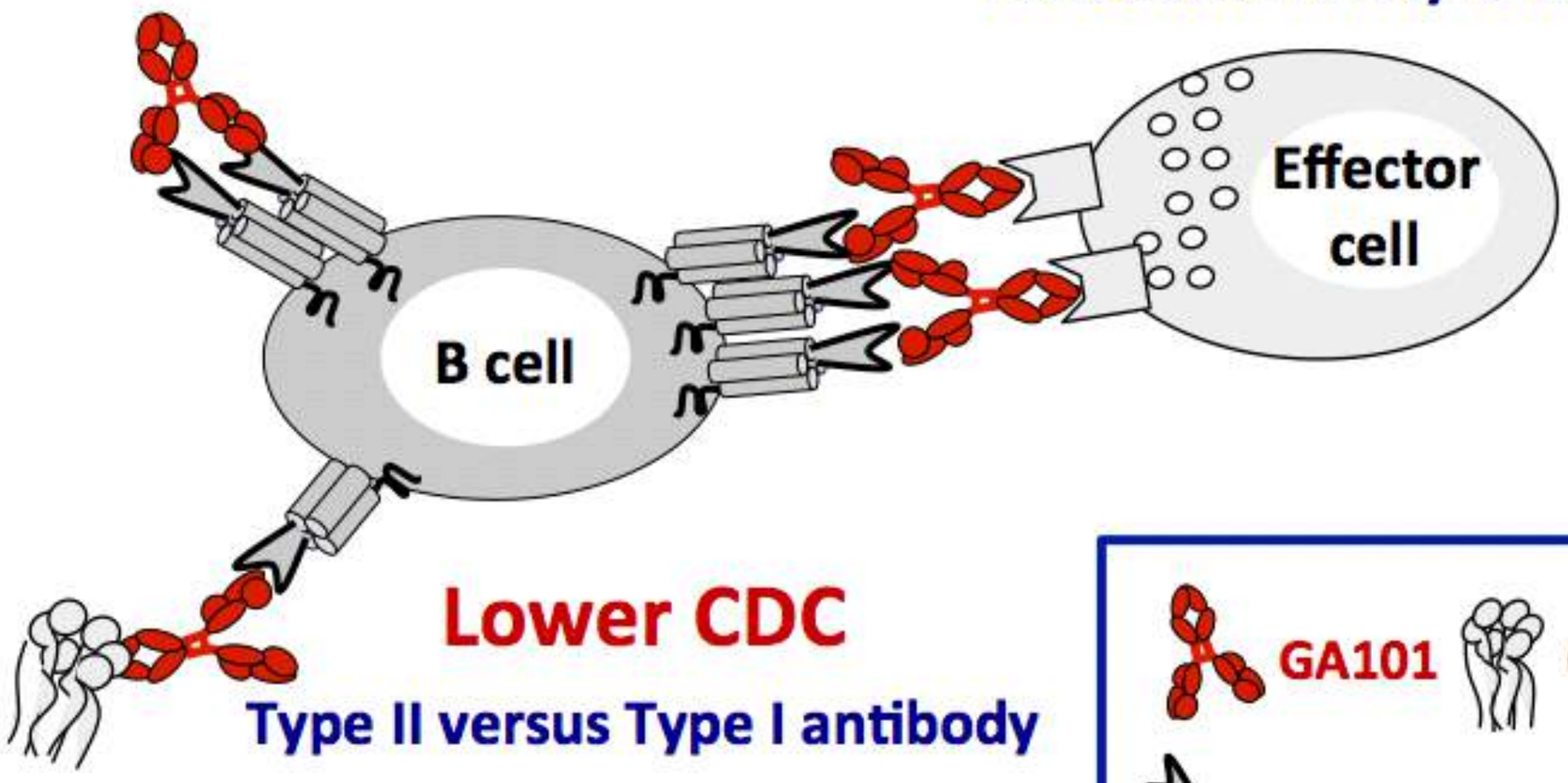
GA101: Mechanisms of action

Increased Direct Cell Death

Type II versus Type I antibody

Enhanced ADCC

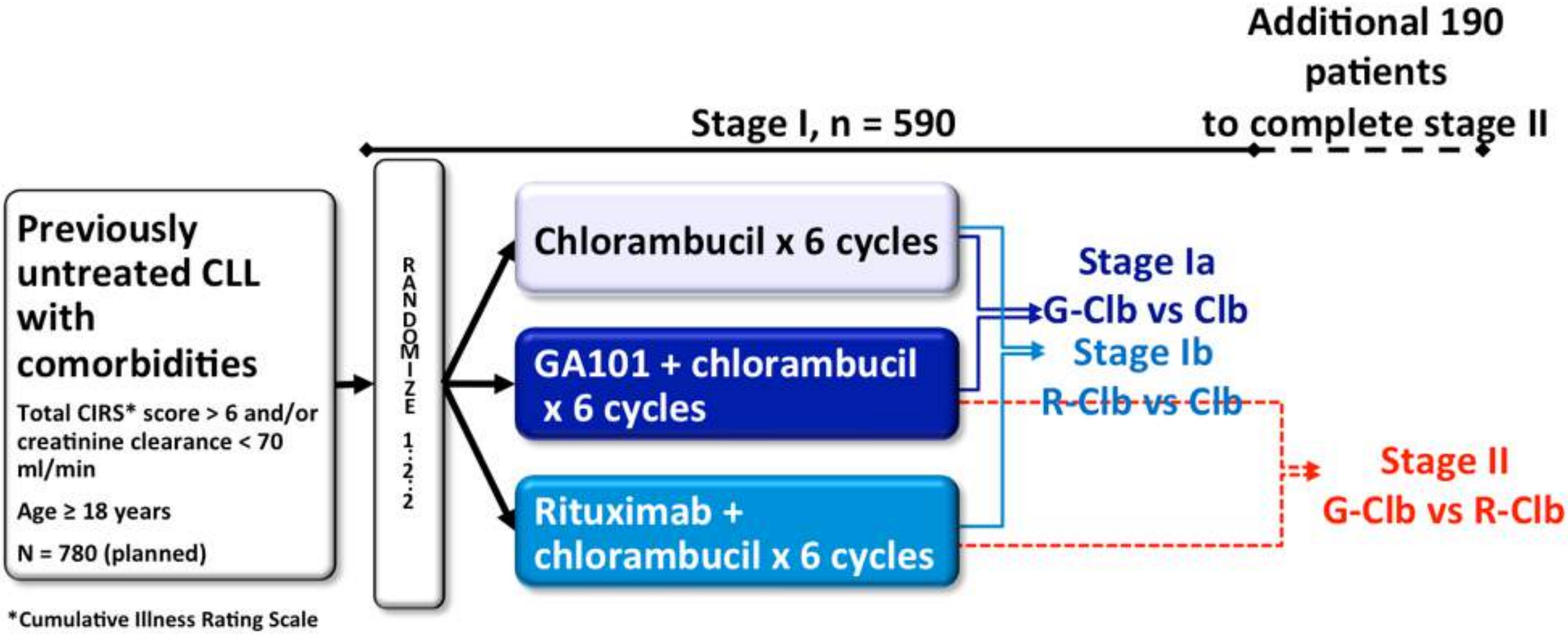
Glycoengineering for increased affinity to FcγRIIIa



ADCC, antibody-dependent cell-mediated cytotoxicity
CDC, complement-dependent cytotoxicity
Mössner E, *et al*. *Blood* 2010; 115:4393-4402

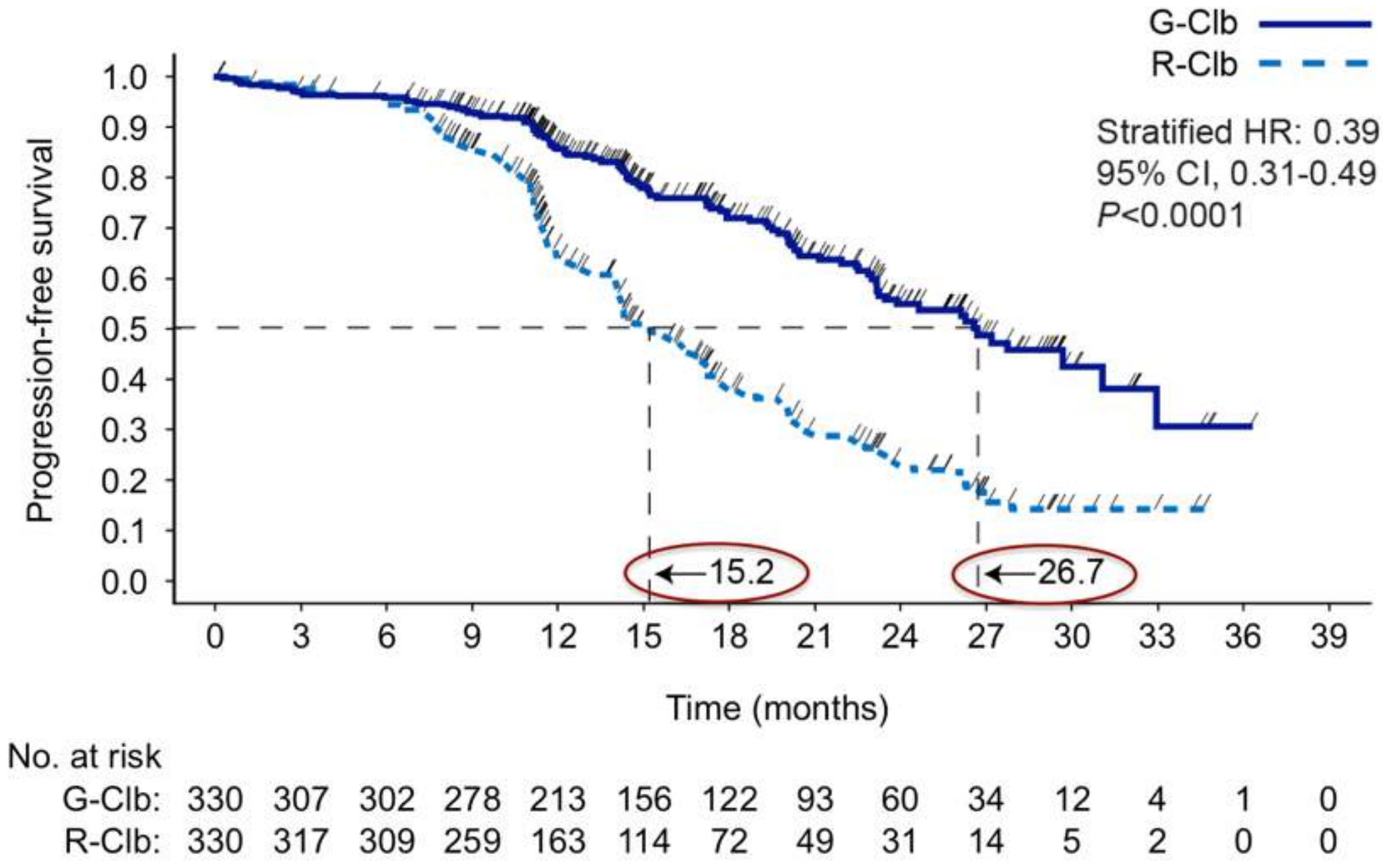
CLL11: Study design

(Goede et al. ASH plenary session, Sunday 8 December, abstract #6; New England Journal of Medicine, in press)



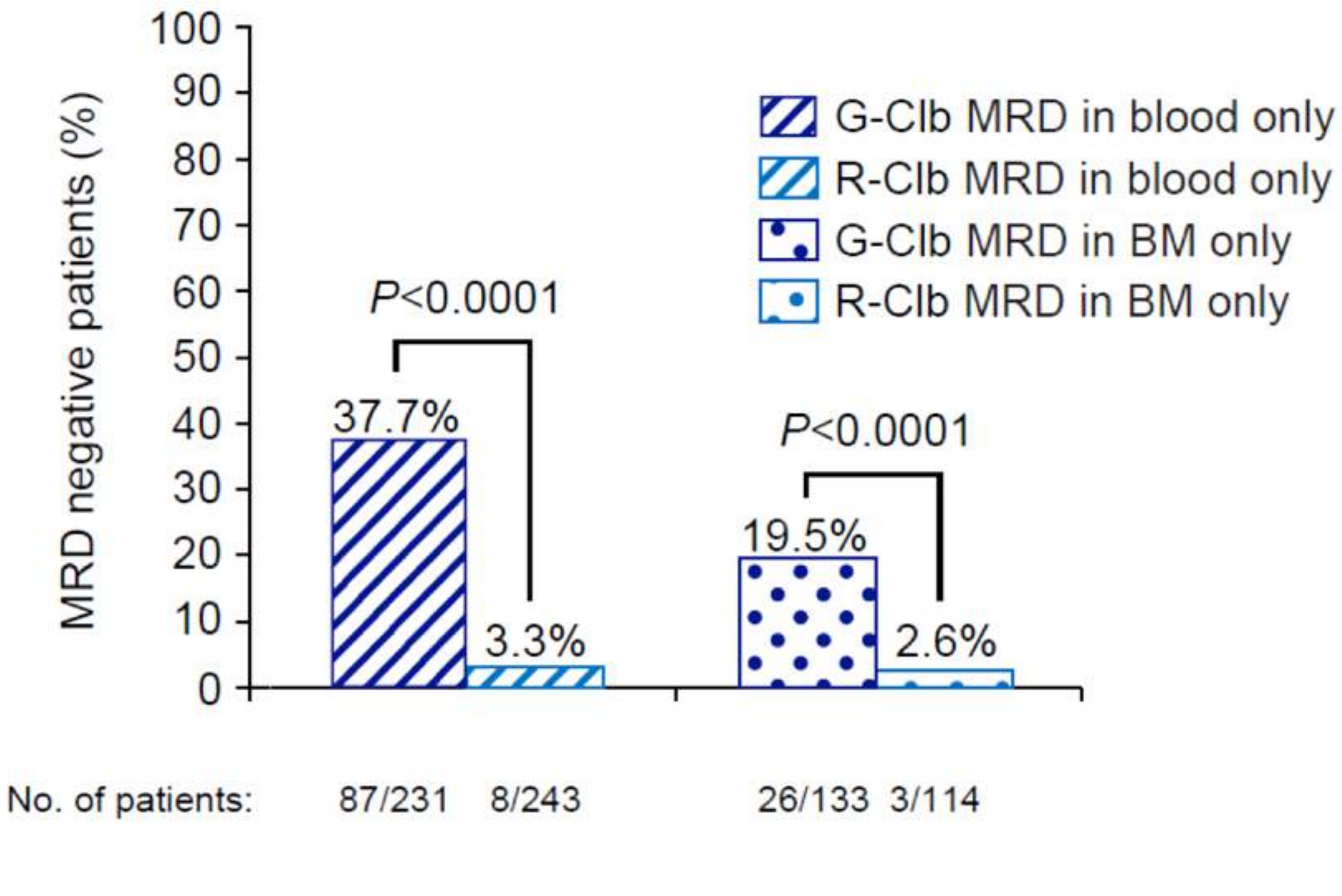
- GA101: 1,000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- Rituximab: 375 mg/m^2 day 1 cycle 1, 500 mg/m^2 day 1 cycles 2–6, every 28 days
- Clb: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
- Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb

Obinutuzumab displays enhanced response rates compared to rituximab, when combined with Clb



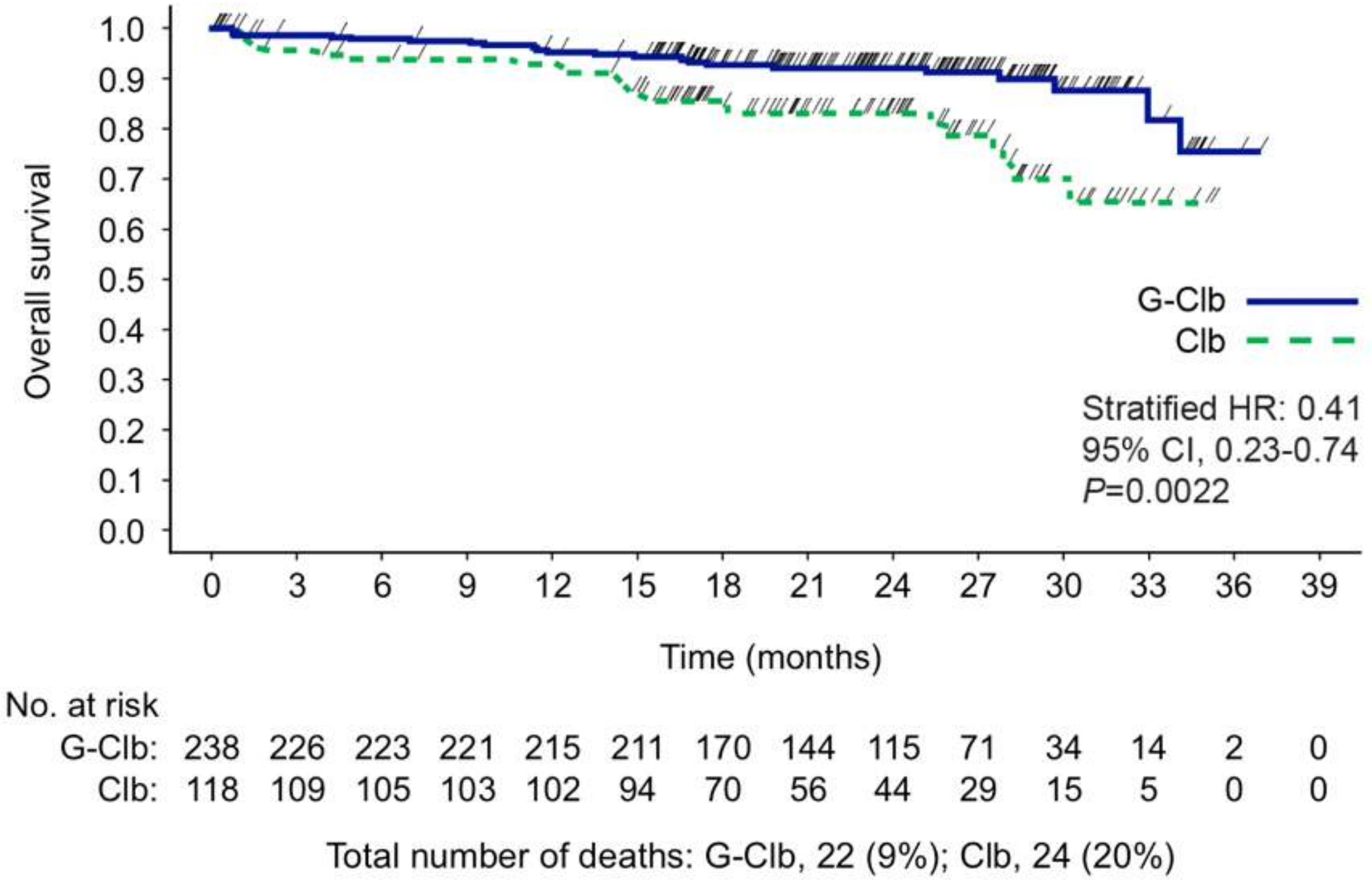
Median observation time: G-Clb, 18.8 months; R-Clb, 18.6 months
Type 1 error controlled through closed test procedure; *P* value of the global test was <0.0001
Independent Review Committee-assessed progression-free survival (PFS) was consistent with investigator-assessed PFS

Obinutuzumab displays enhanced response rates compared to rituximab, when combined with Clb



As measured by central laboratory assessment (ASO-RQ-PCR) at 3 months after end of treatment; bone marrow samples were usually only taken from patients thought to be in CR
MRD, minimal residual disease; BM, bone marrow

G-Clb enhances OS in CLL patients with comorbidities compared with Clb

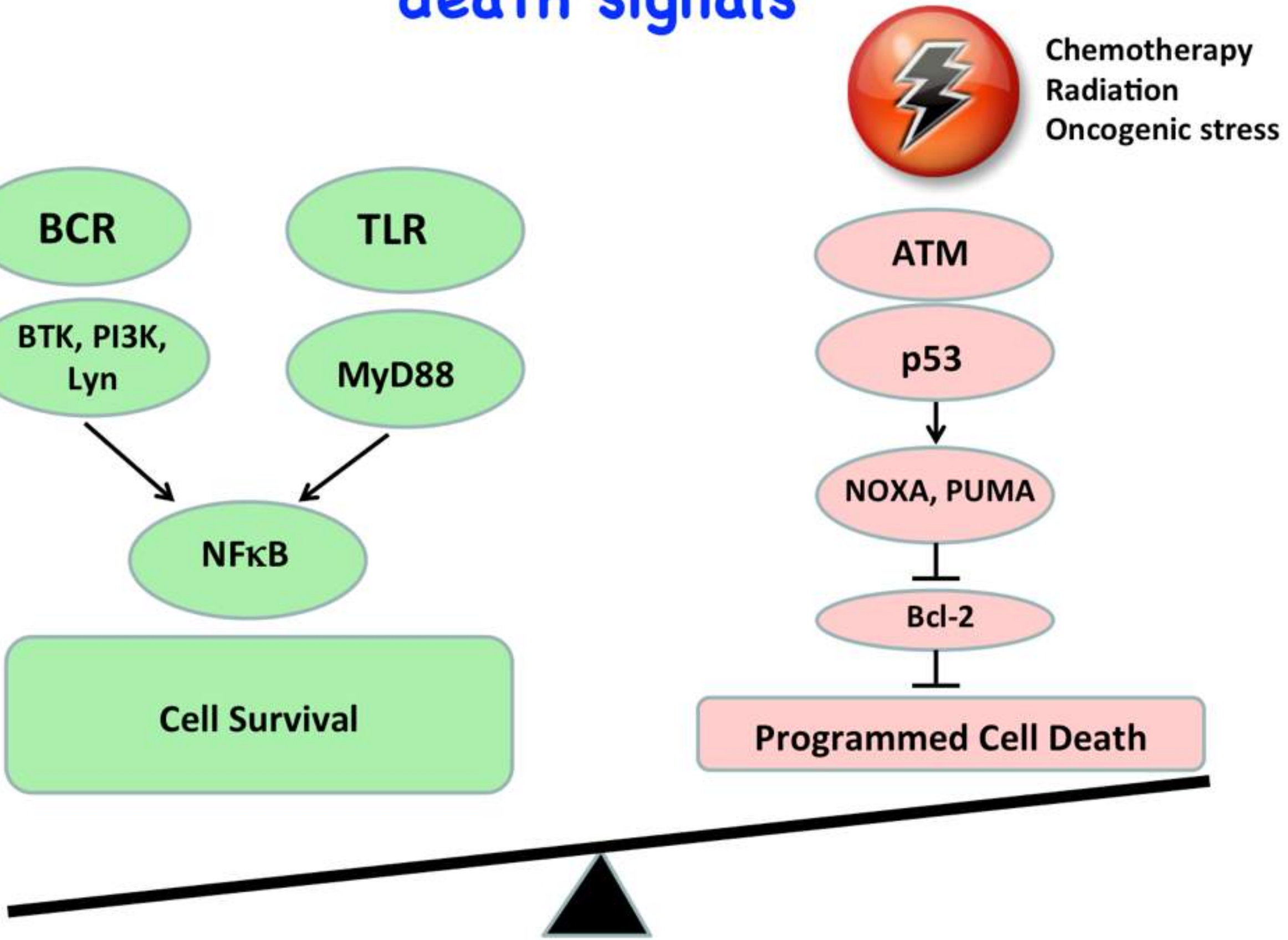


Total number of deaths: G-Clb, 22 (9%); Clb, 24 (20%)

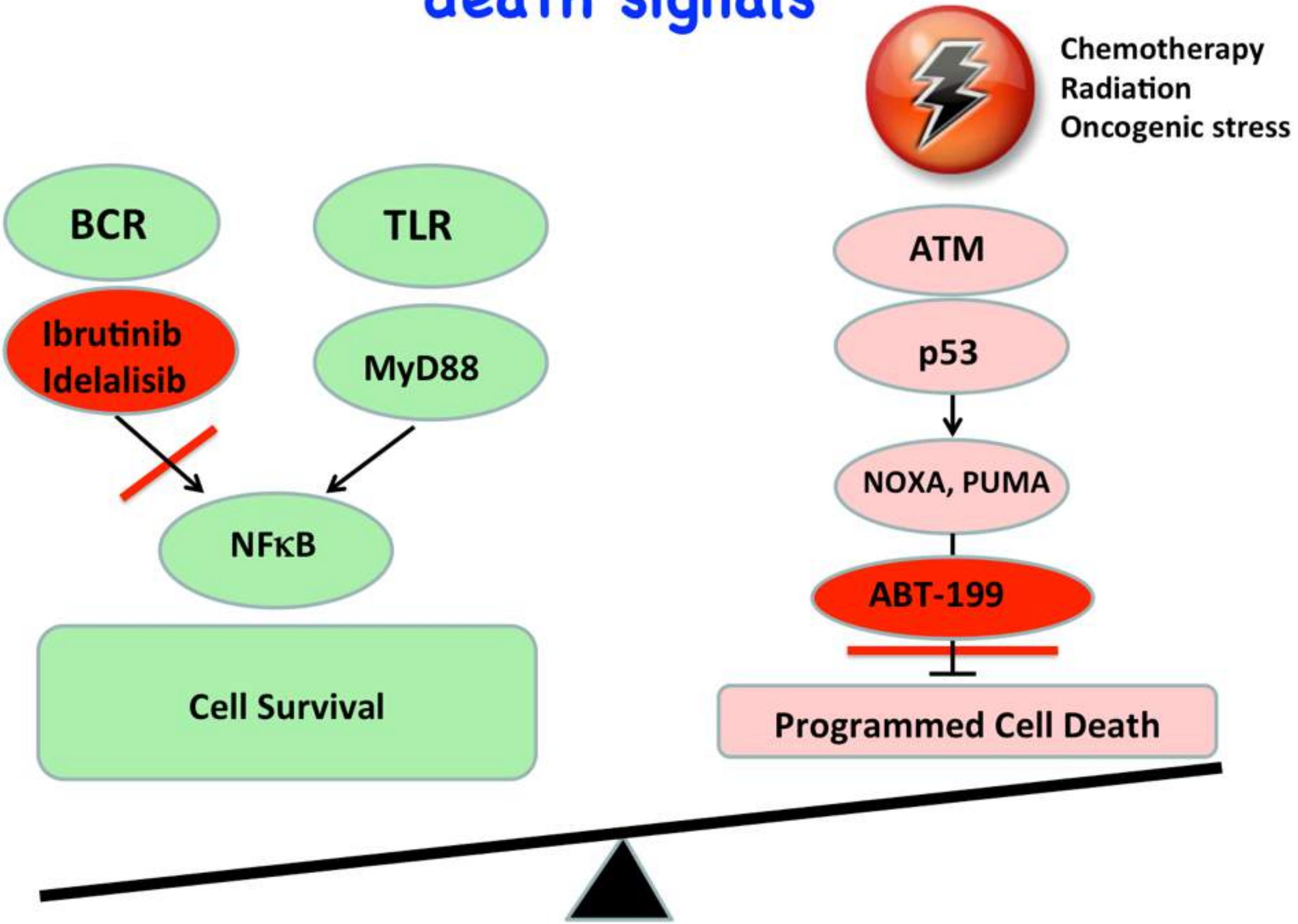
Median observation time: G-Clb, 23.2 months; Clb, 20.4 months
No multiplicity adjustment was done for secondary endpoints

Can we be smarter?

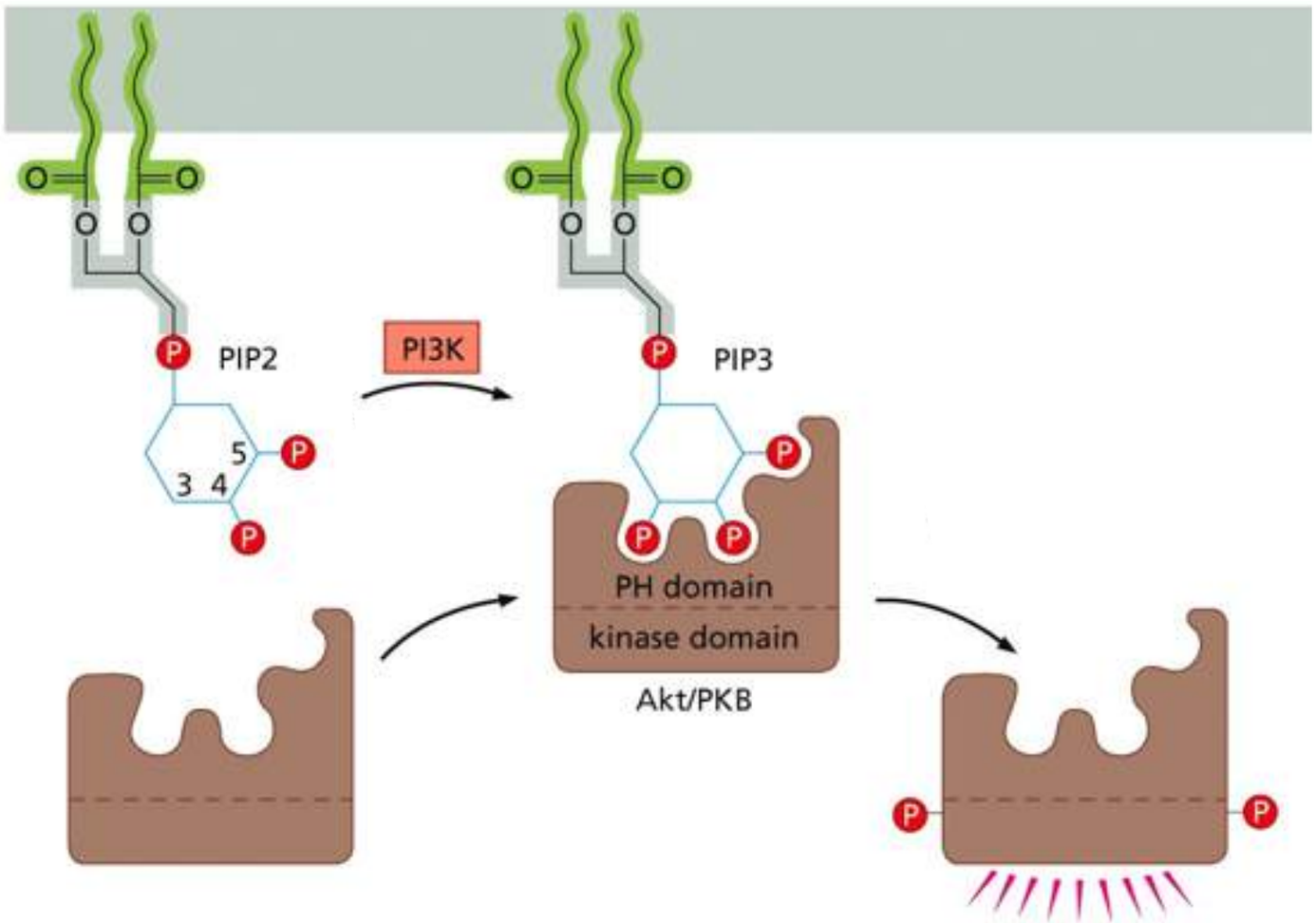
CLL results from an imbalance of life and death signals

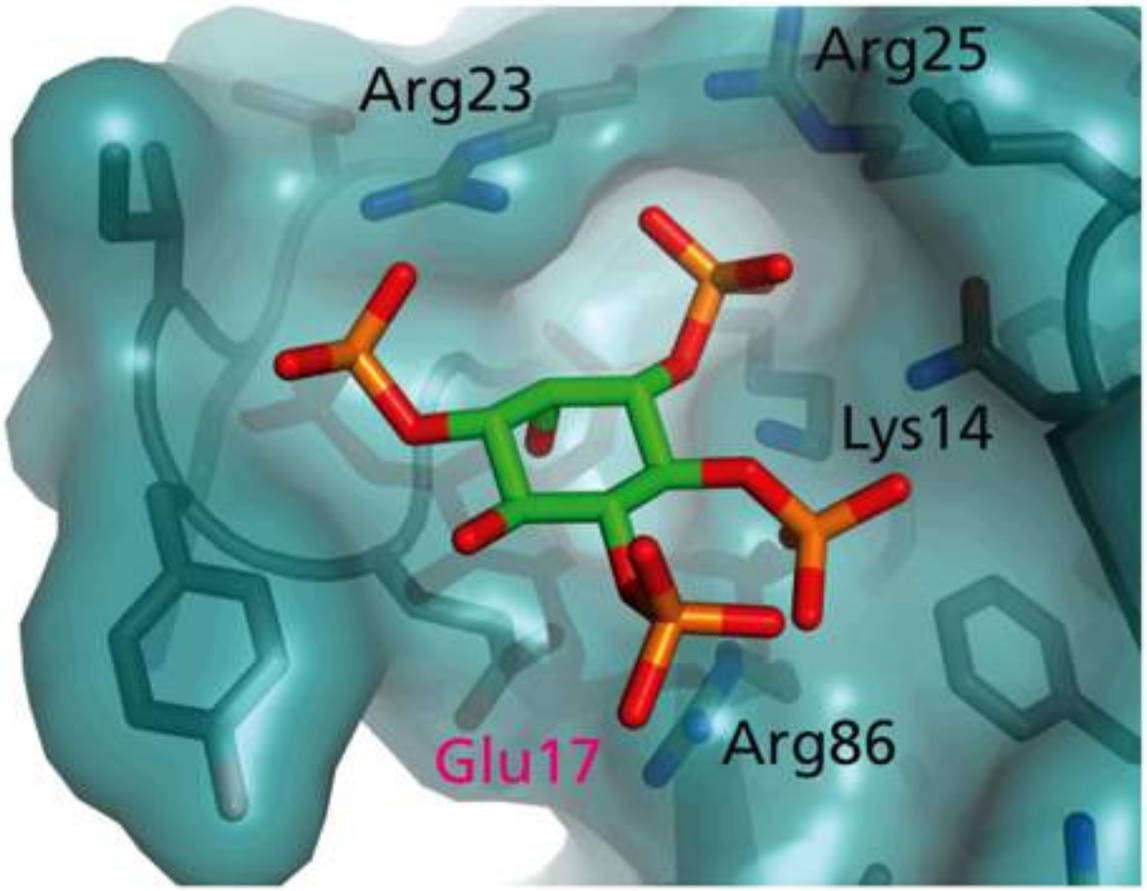


CLL results from an imbalance of life and death signals

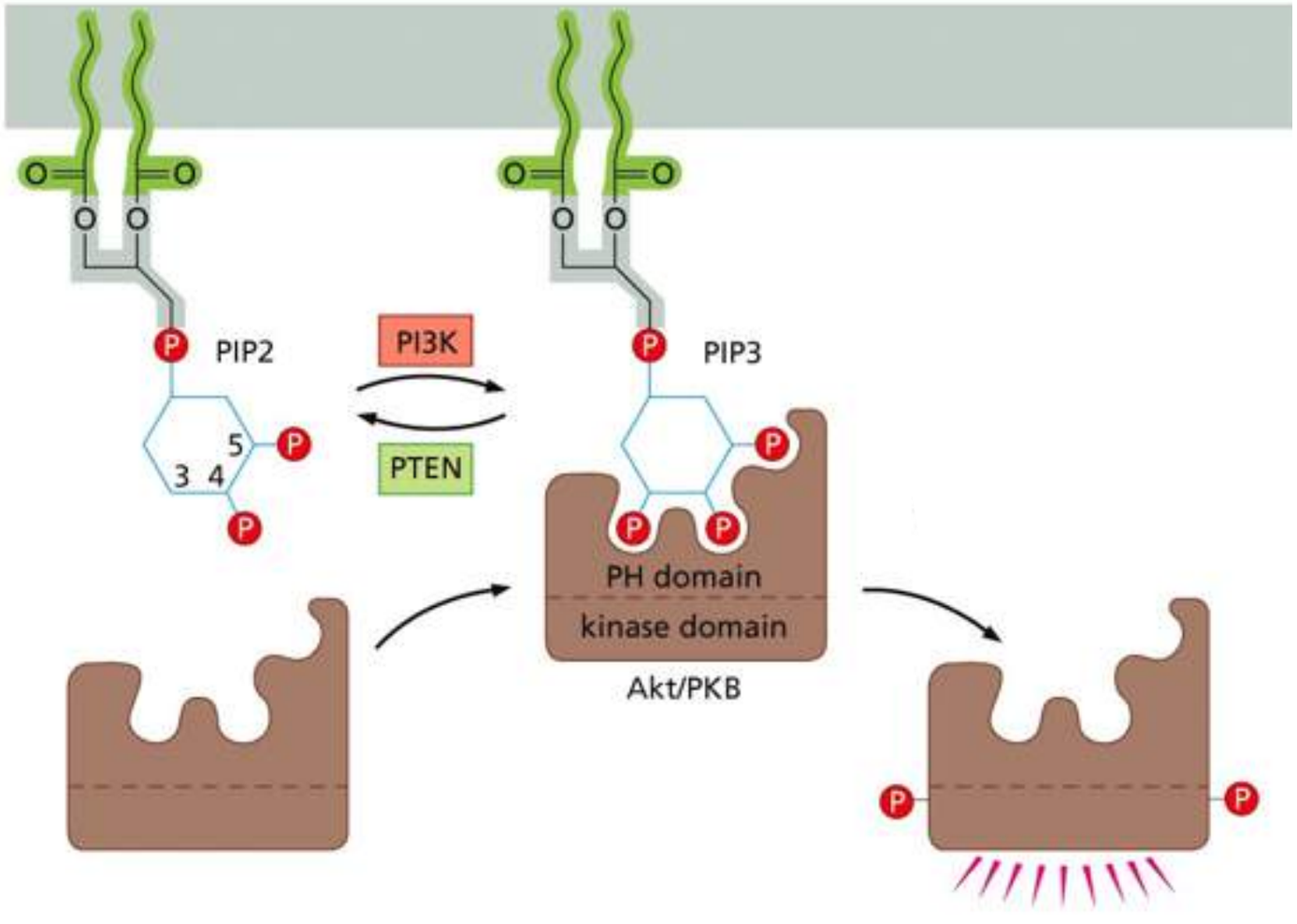


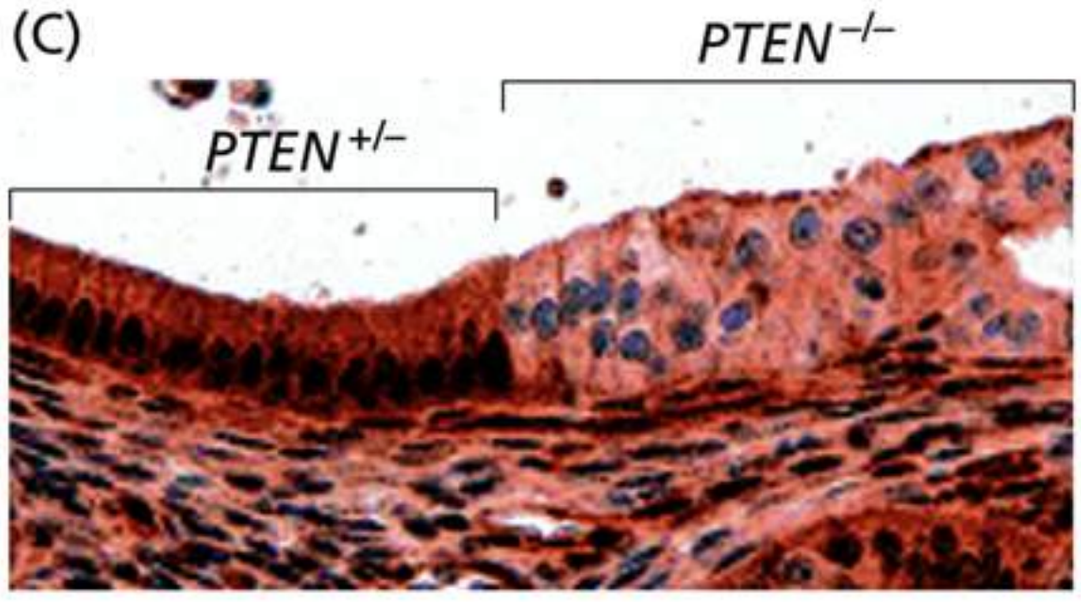
Through activating PI3K generates PIP3 to activate AKT signaling

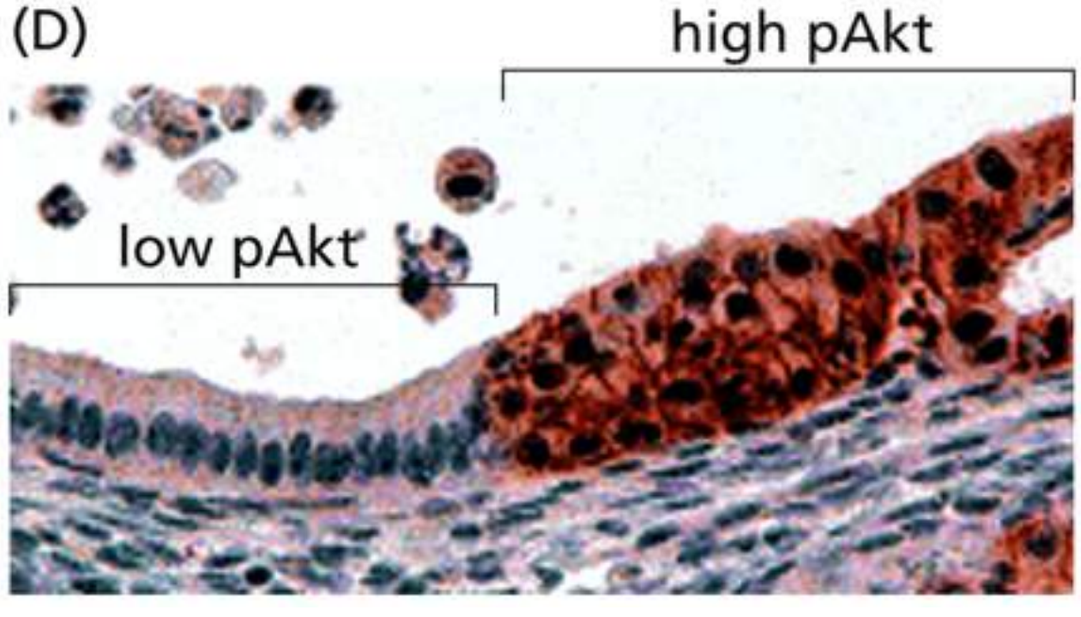




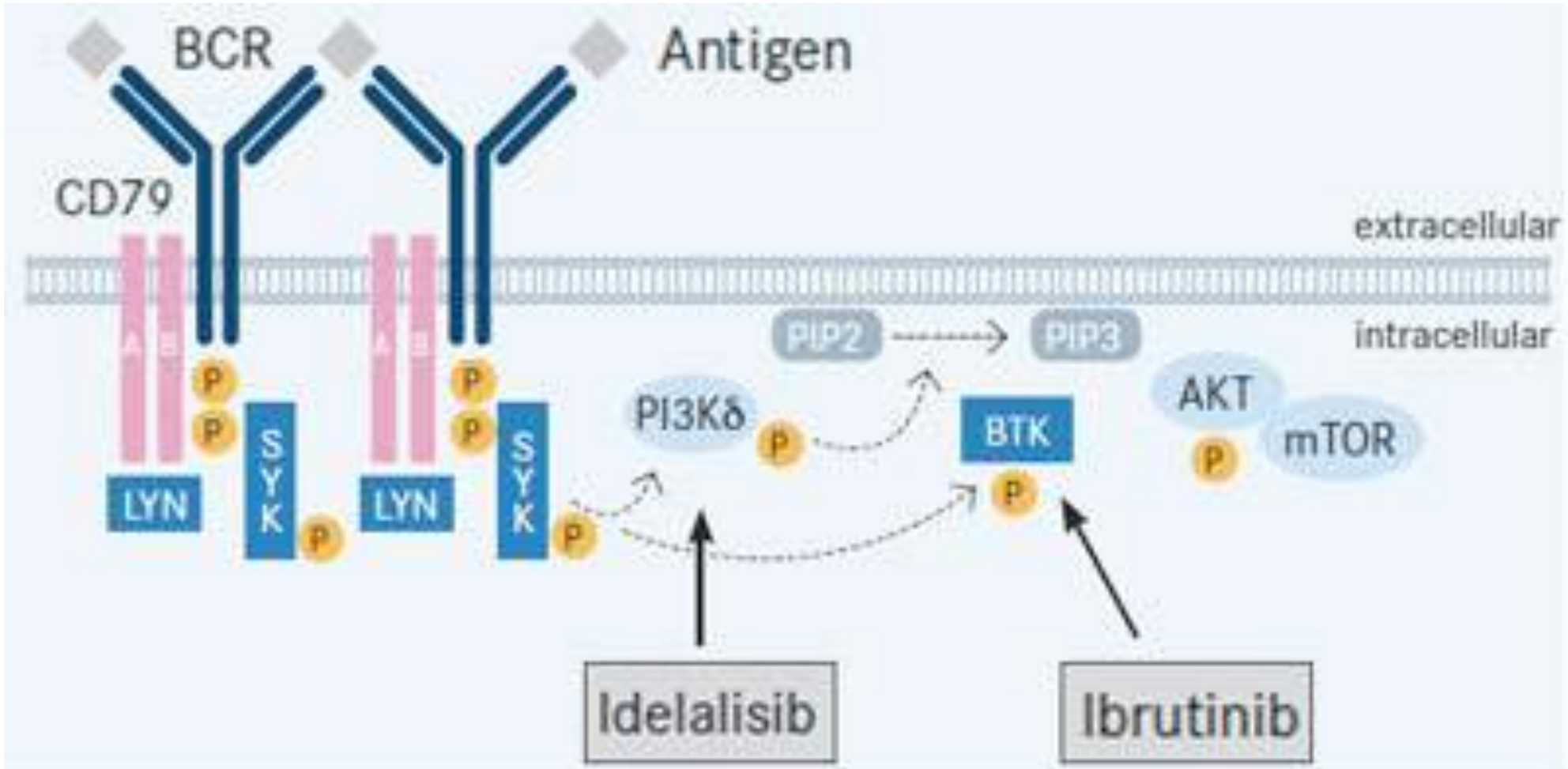
PTEN is a phosphatase the counteracts PI3K-mediated AKT activation







PI3K inhibitors have recently been developed



PI3K inhibition proves effective in CLL

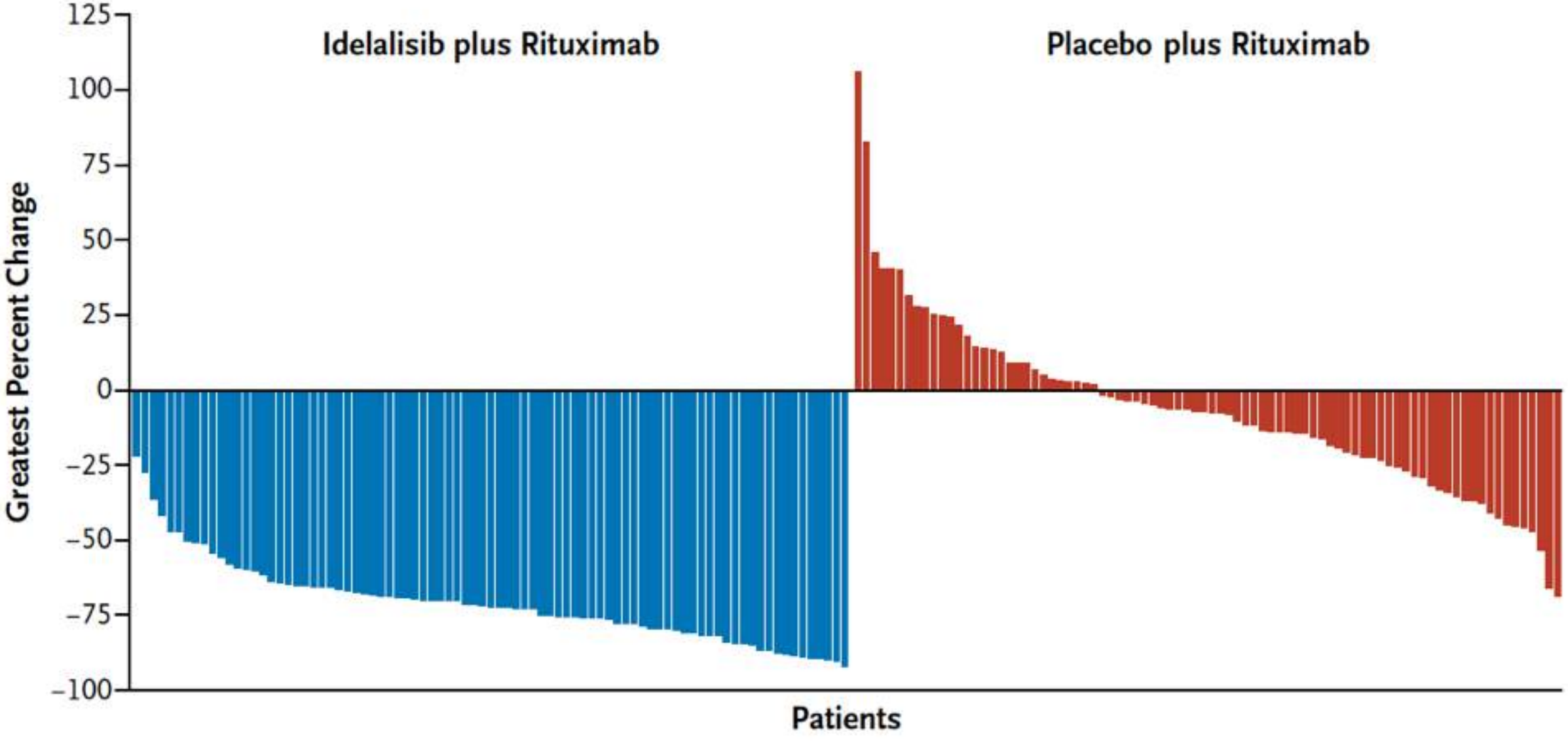
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 13, 2014 VOL. 370 NO. 11

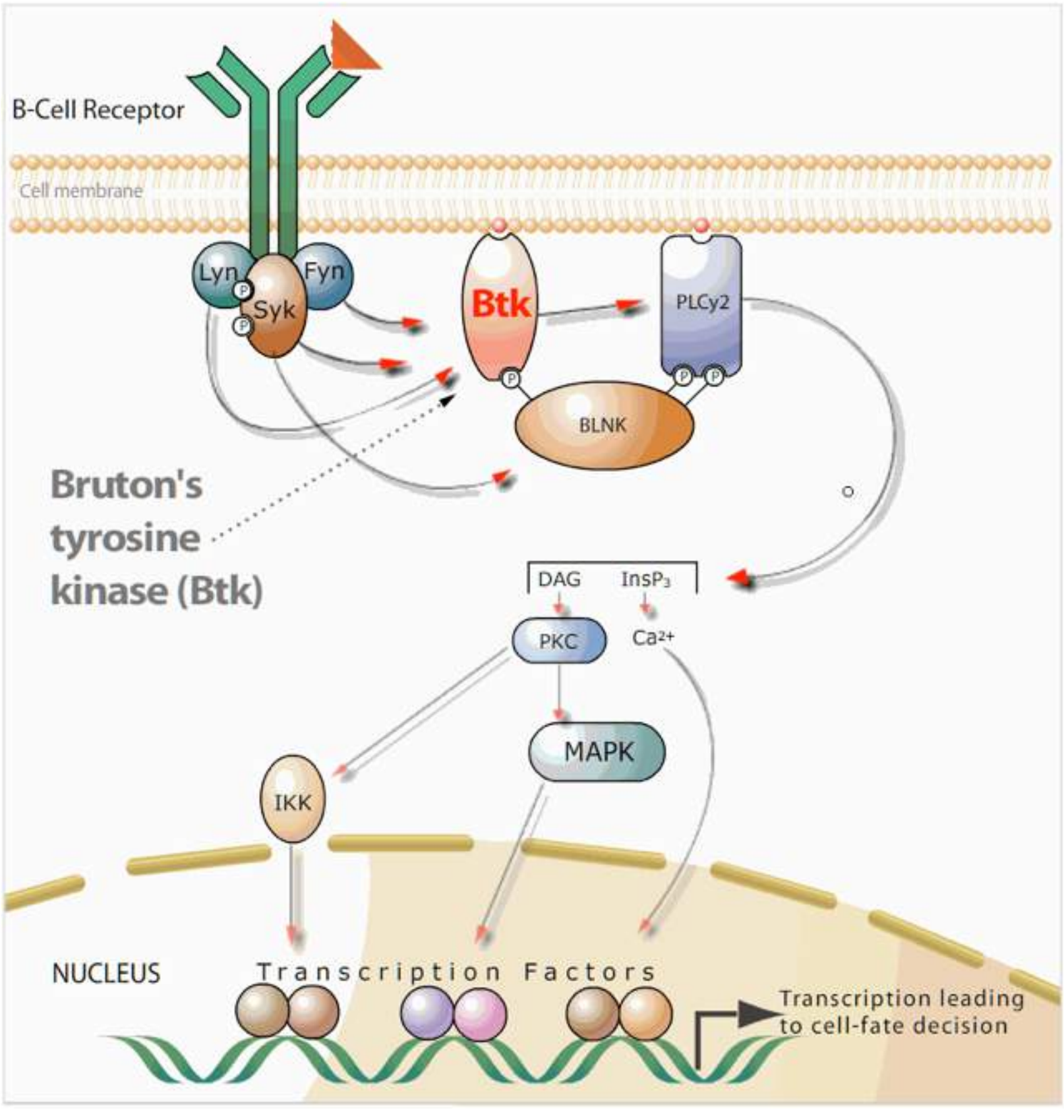
Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia

Richard R. Furman, M.D., Jeff P. Sharman, M.D., Steven E. Coutre, M.D., Bruce D. Cheson, M.D., John M. Pagel, M.D., Ph.D., Peter Hillmen, M.B., Ch.B., Ph.D., Jacqueline C. Barrientos, M.D., Andrew D. Zelenetz, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Ian Flinn, M.D., Ph.D., Paolo Ghia, M.D., Ph.D., Herbert Eradat, M.D., Thomas Ervin, M.D., Nicole Lamanna, M.D., Bertrand Coiffier, M.D., Ph.D., Andrew R. Pettitt, Ph.D., F.R.C.Path., Shuo Ma, M.D., Ph.D., Stephan Stilgenbauer, M.D., Paula Cramer, M.D., Maria Aiello, M.A., Dave M. Johnson, B.S., Langdon L. Miller, M.D., Daniel Li, Ph.D., Thomas M. Jahn, M.D., Ph.D., Roger D. Dansey, M.D., Michael Hallek, M.D., and Susan M. O'Brien, M.D.

Changes in the Measured Size of Lymph Nodes from Baseline



BTK inhibitors have recently been developed



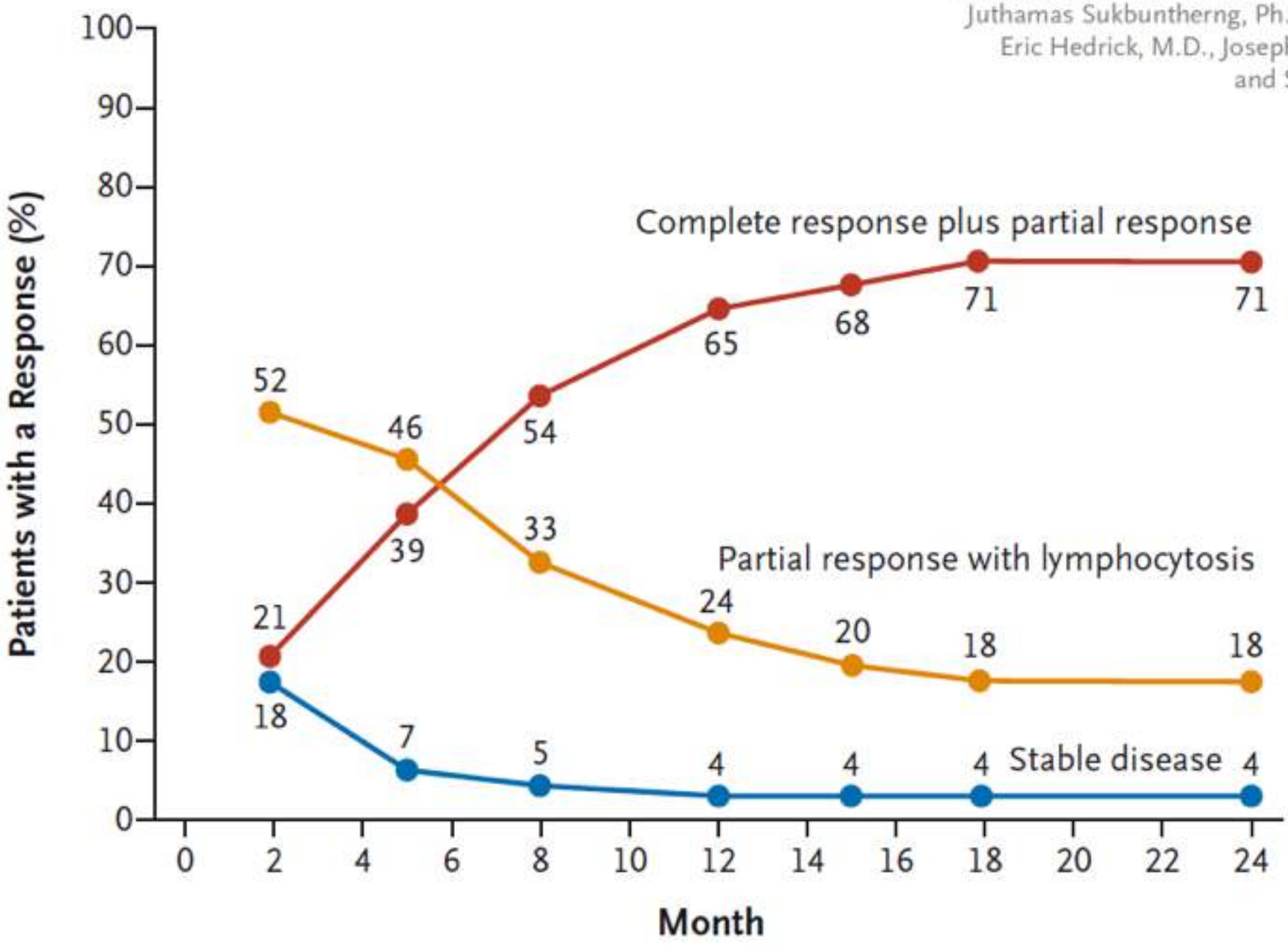
BTK inhibition proves effective in CLL

ORIGINAL ARTICLE

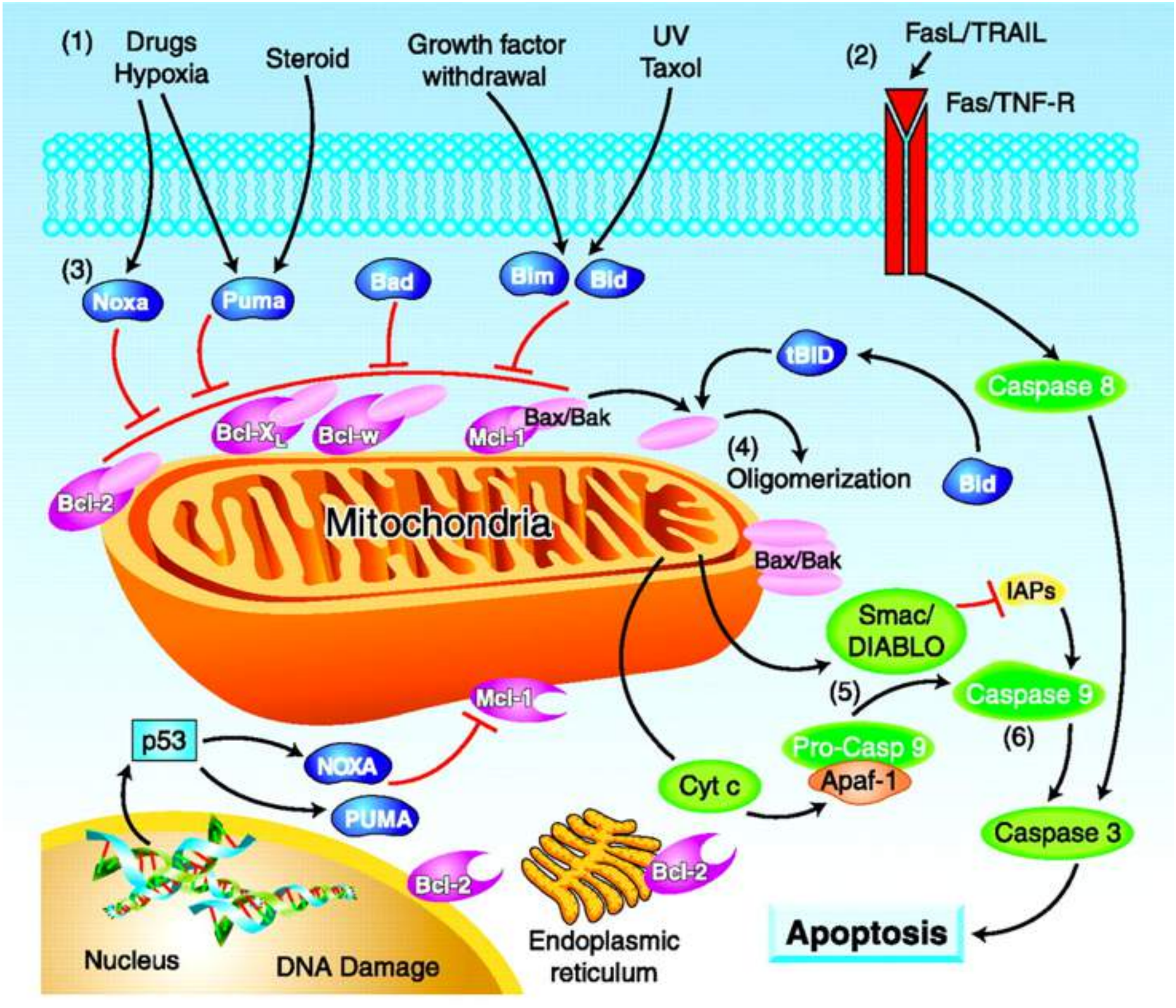
Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.

B

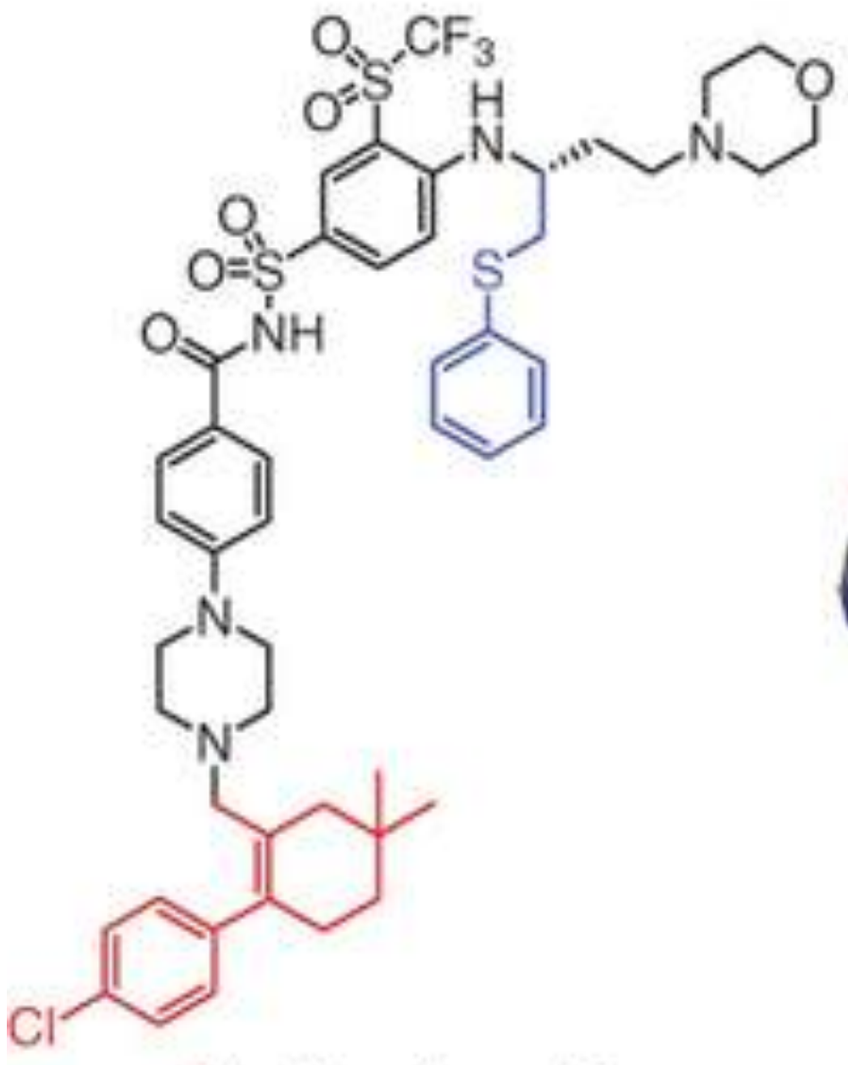


BCL2 stabilizes the mitochondrial membrane and antagonizes apoptosis

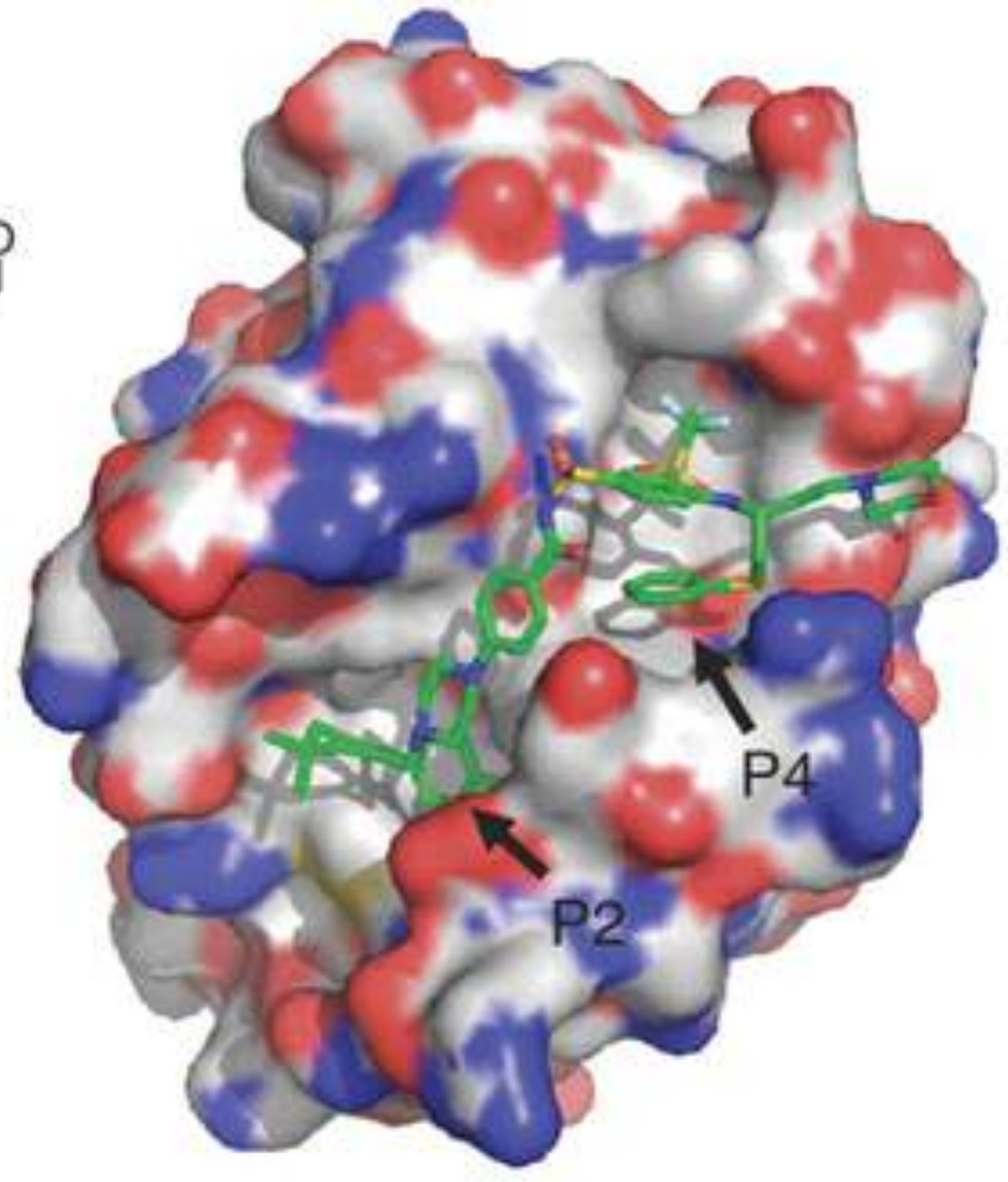


BCL2 inhibitors have recently been developed

a

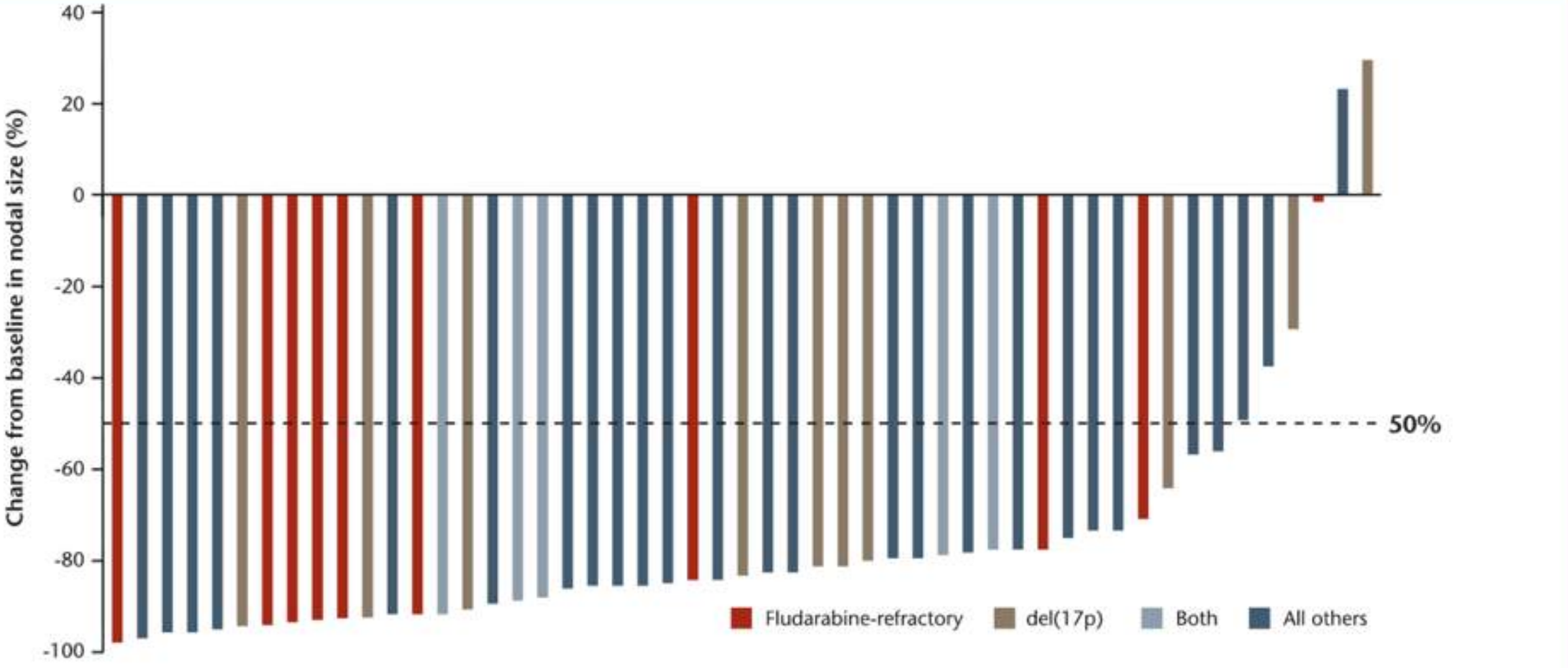


Navitoclax (**1**)



The BCL2 inhibitor ABT-199 displays remarkable activity against CLL

Figure 1. Best percent change from baseline in nodal size, as assessed by CT scan*



CT = computed tomography; del(17p) = deletion of chromosome 17p

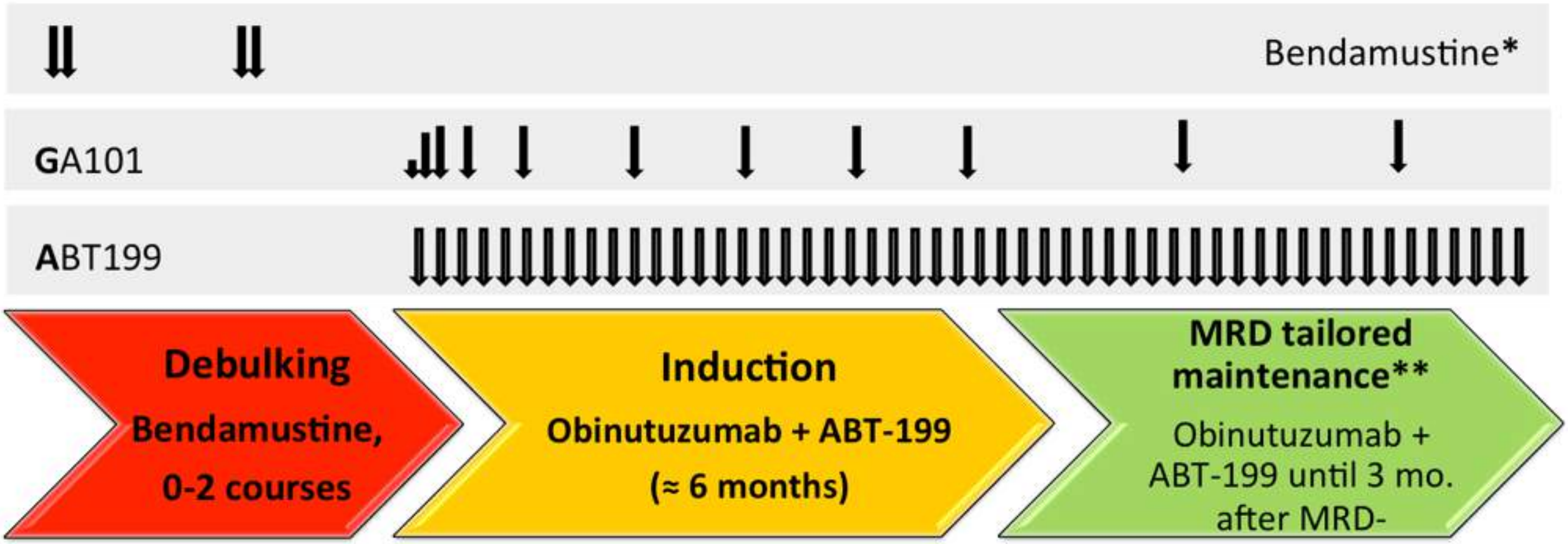
**CT assessment occurred at minimum after 6 weeks of treatment in 51 evaluable patients.*

Potential future strategies to achieve long-term control of CLL: **"sequential triple T": tailored, targeted, total** eradication of MRD

Debulking	Induction (combination therapy)	MRD tailored maintenance (single agents)
• Mild chemotherapy with agents like bendamustine or fludarabine	• Kinase inhibitor(s) • Antibody • Bcl2 antagonist	• Antibody • Lenalidomide • Kinase inhibitor • Bcl2 antagonist
1-2 months (1–2 courses)	6-12 months	1 year - ∞

Design of a phase II trial for CLL patients

(Bendamustine, ABT199, GA101 → BAG trial of the GCLLSG)

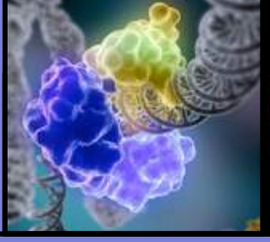
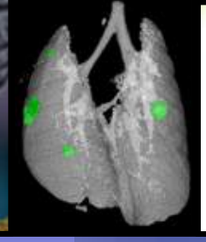
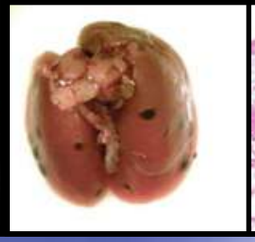
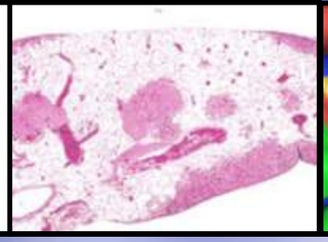
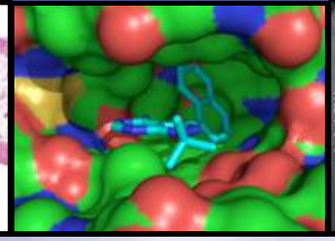
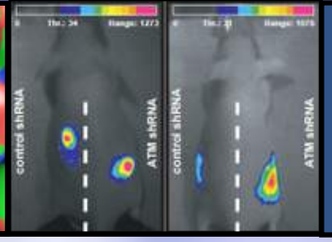


* number of cycles depending on tumor burden

** up to 30 months after completion of last cycle

Summary III

- FC-R chemoimmunotherapy is the standard for fit patients

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