The Best of American Society of Hematology

Top Research Studies Reviewed

John M. Burke, M.D.
Rocky Mountain Cancer Centers

Leukemia and Lymphoma Society Conference

April 11, 2015

Outline

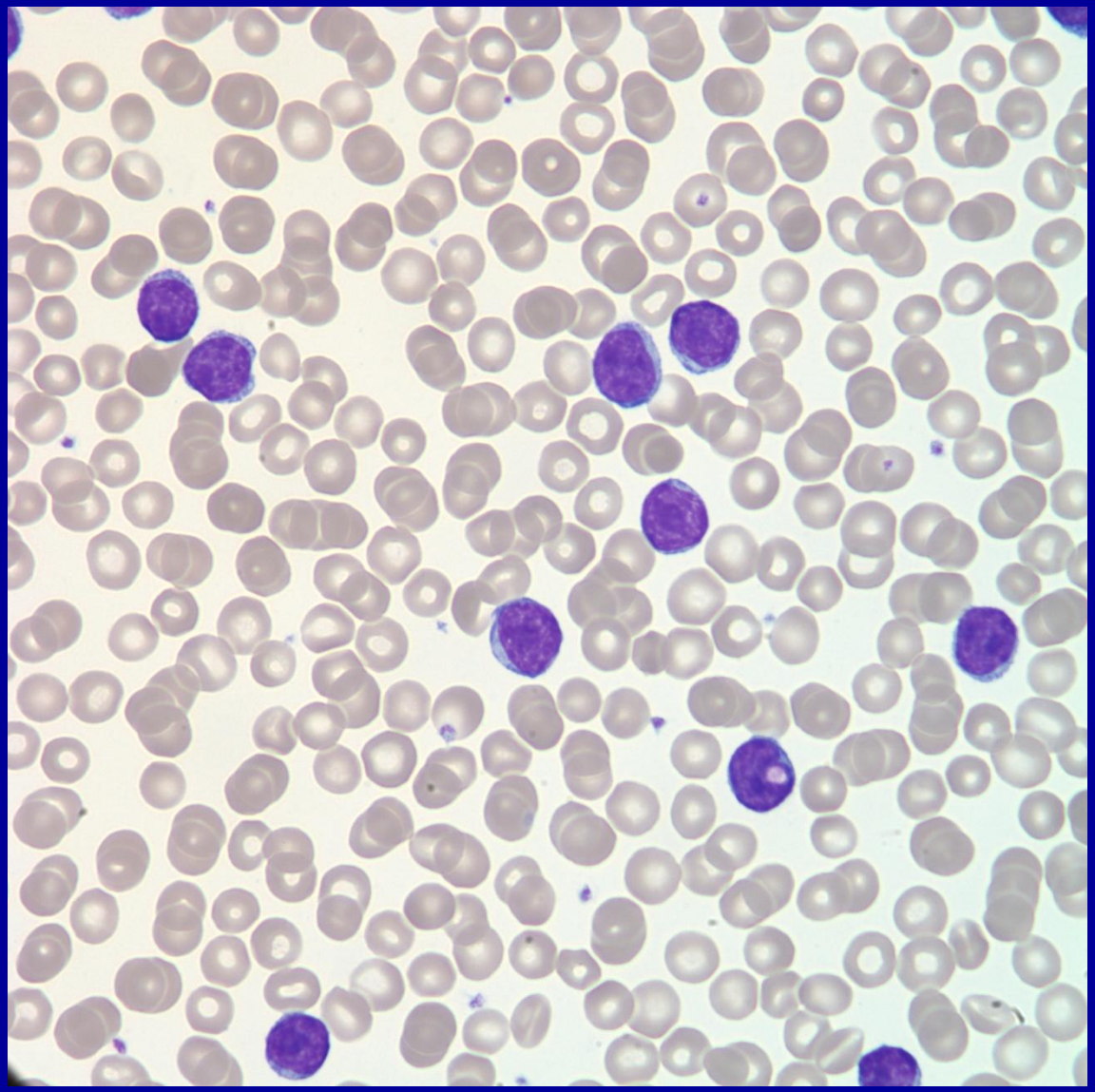
- Chronic lymphocytic leukemia
  - Background and impact of 17p- and *TP53* mutations
  - RESONATE-17: ibrutinib in R/R CLL with 17p-
    - O'Brien SM et al., ASH 2014; abstract 327.
  - Idelalisib-rituximab in genetic subgroups
    - Sharman JP et al., ASH 2014; abstract 330.

- Checkpoint blockade in cancer therapy
  - Phase 1 study of nivolumab in Hodgkin lymphoma
    - Ansell SM et al., N Engl J Med 2015; 372:211-319.

Epidemiology

- About 15,000 new cases per year in U.S.
- Median age at diagnosis is about 70 years
- Only 10% occur in patients under age 50 years
- M:F = 2:1

Peripheral Smear in CLL



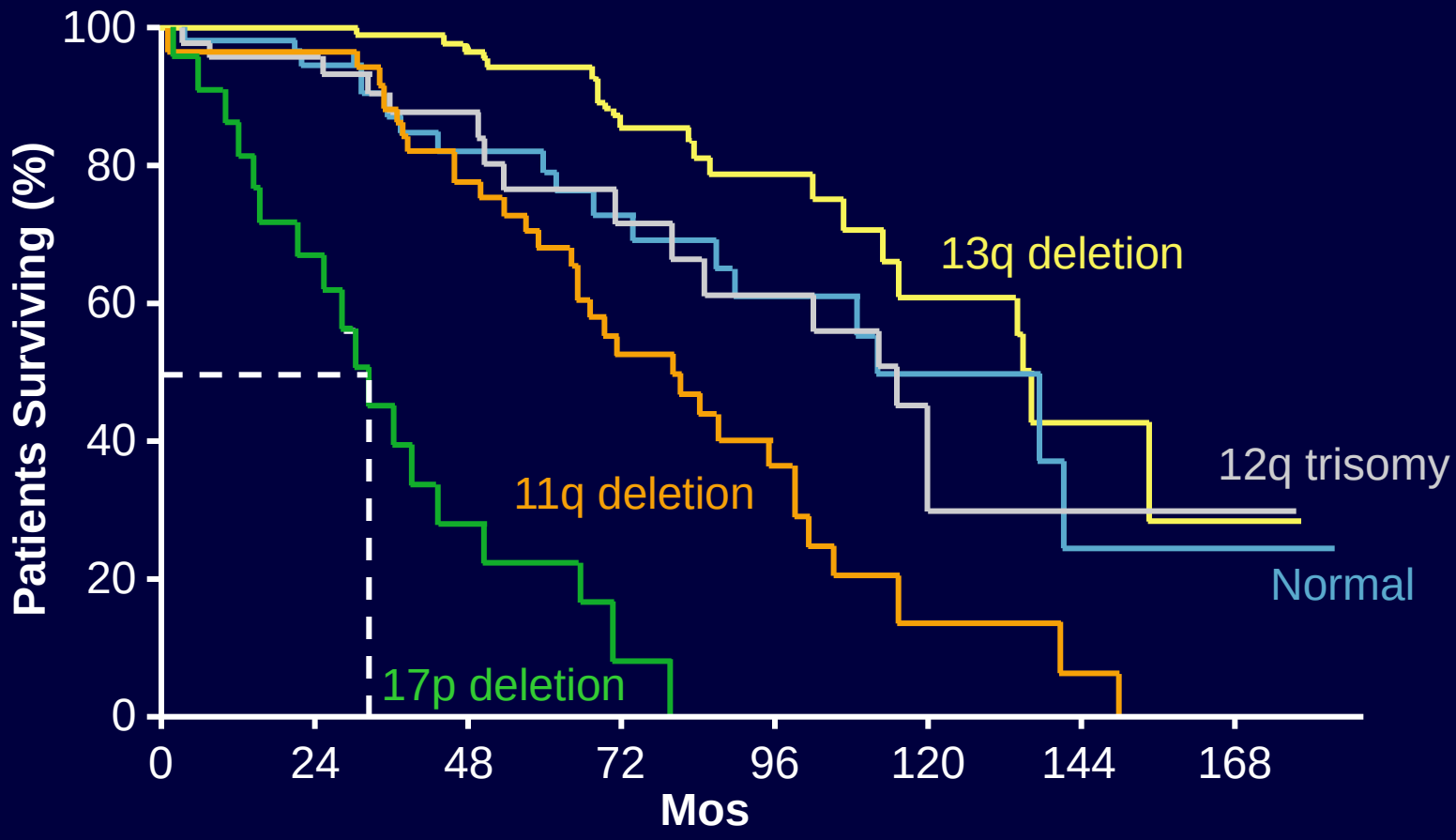
Burke JM. *Dx/Rx: Leukemia*. Jones & Bartlett, Sudbury, MA; 2012.

Prognostic Factors in CLL

- Rai (United States) and Binet (Europe) staging systems
- Serology: β_2-microglobulin, thymidine kinase
- IgV_H sequence mutation
- ZAP-70
- FISH cytogenetics: 17p-, 11q-, +12, 13q-
- CD38 on CLL cells

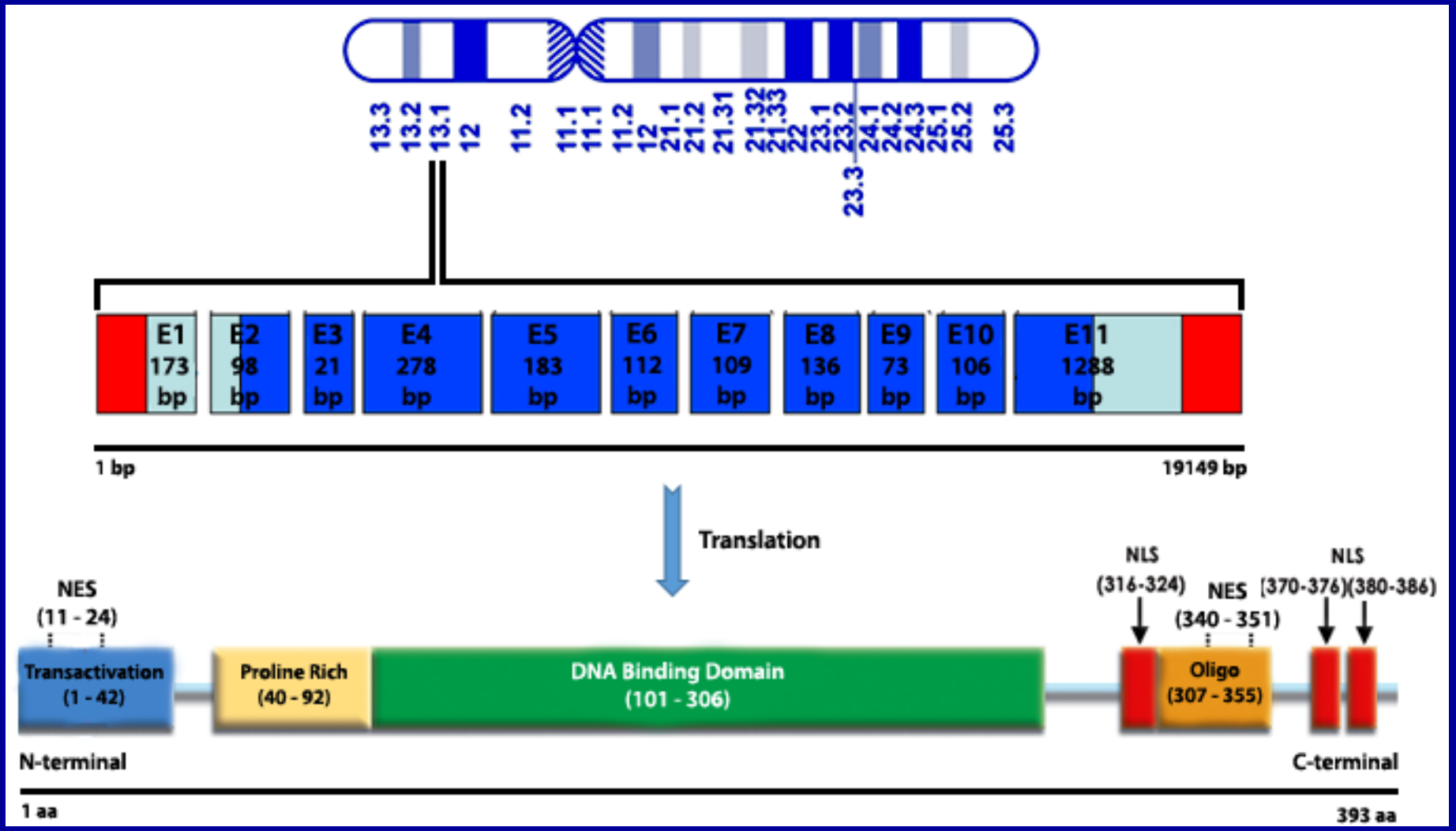
Seiler T, et al. Semin Oncol. 2006;33:186-194.

Survival According to Chromosomal Abnormalities in CLL

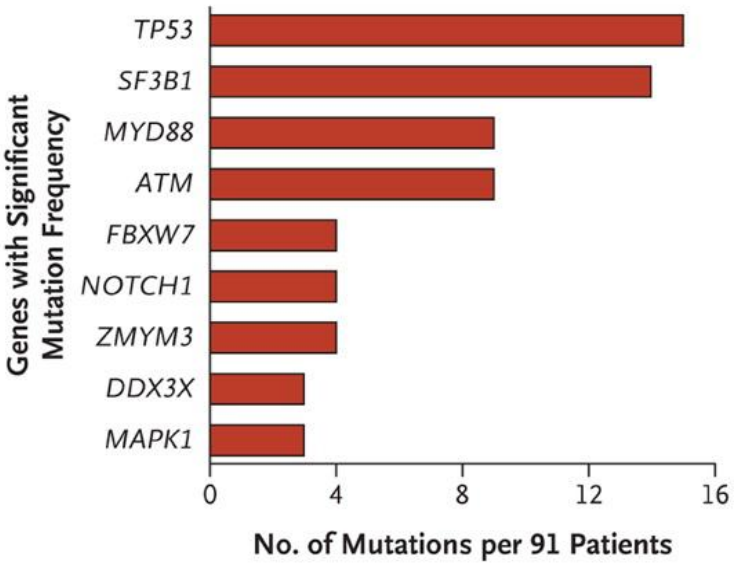


 Dohner H, et al. N Engl J Med. 2000;343:1910-1916.

The TP53 gene is located on the short arm of chromosome 17 (17p).



Genes with Significant Mutation Frequencies in 91 Patients with Chronic Lymphocytic Leukemia.

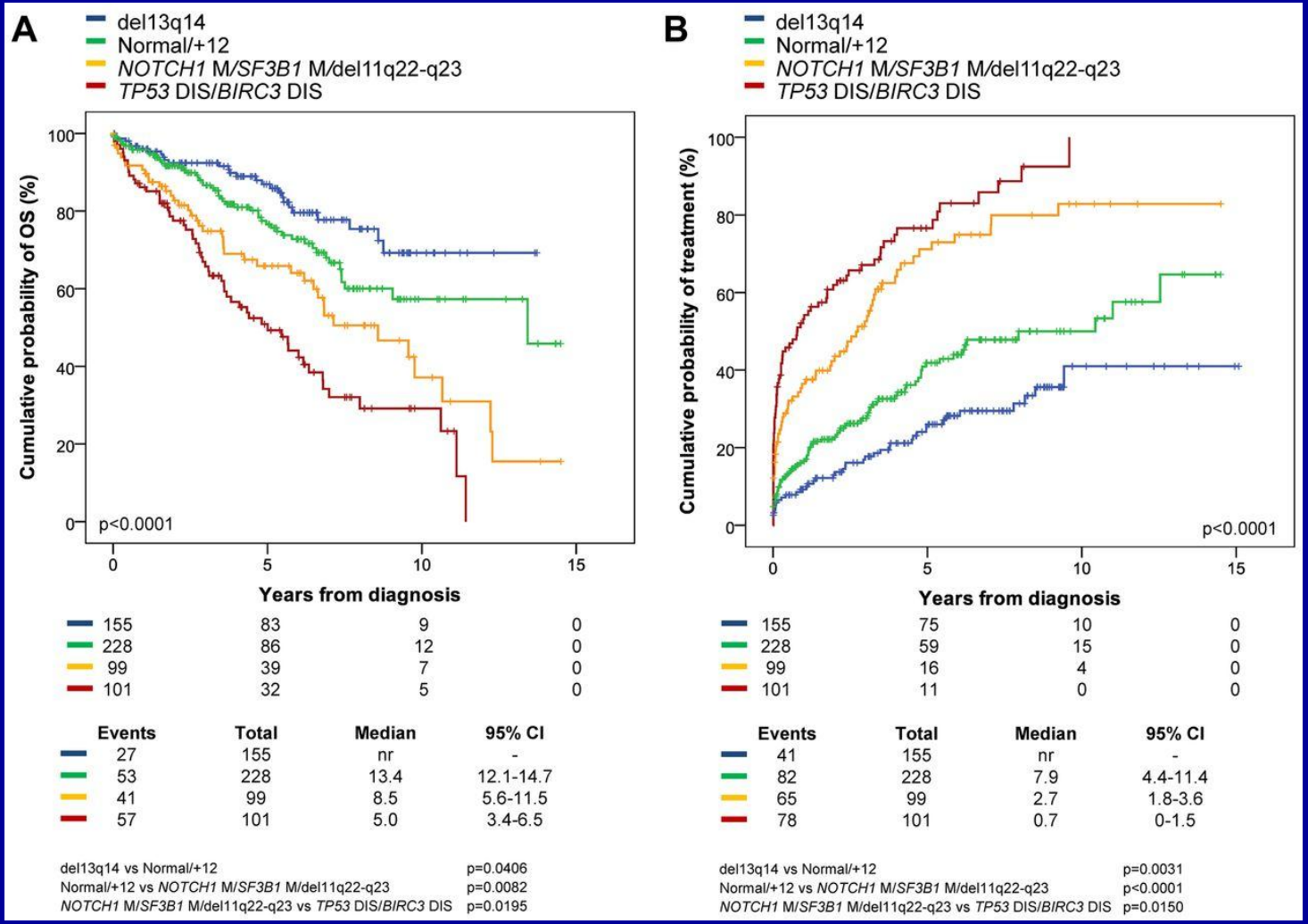


	No. of Mutations (%)	No. of Base Pairs	P Value	Q Value
TP53	15 (15)	119,041	$<1.0\times10^{-11}$	$<6.3\times10^{-8}$
SF3B1	14 (15)	359,856	$<1.0\times10^{-11}$	$<6.3\times10^{-8}$
MYD88	9 (10)	73,805	$<1.0\times10^{-11}$	$<6.3\times10^{-8}$
ATM	9 (9)	837,986	2.4×10^{-9}	1.1×10^{-5}
FBXW7	4 (4)	225,671	2.0×10^{-6}	7.4×10^{-3}
NOTCH1	4 (4)	306,968	3.3×10^{-6}	1.0×10^{-2}
ZMYM3	4 (4)	314,226	3.5×10^{-5}	7.4×10^{-2}
DDX3X	3 (3)	181,343	1.6×10^{-5}	4.3×10^{-2}
MAPK1	3 (3)	89,405	1.9×10^{-5}	4.4×10^{-2}

Wang L et al. N Engl J Med 2011;365:2497-2506.

The NEW ENGLAND JOURNAL of MEDICINE

In an integrated model using cytogenetic analysis and mutational analysis, *TP53* mutations (and *BIRC3* mutations) confer the worst prognosis.



Rossi D et al. Blood 2013;121:1403-1412

Cytogenetic Risk among Patients with Chronic Lymphocytic Leukemia.

Table 1. Cytogenetic Risk among Patients with Chronic Lymphocytic Leukemia.*

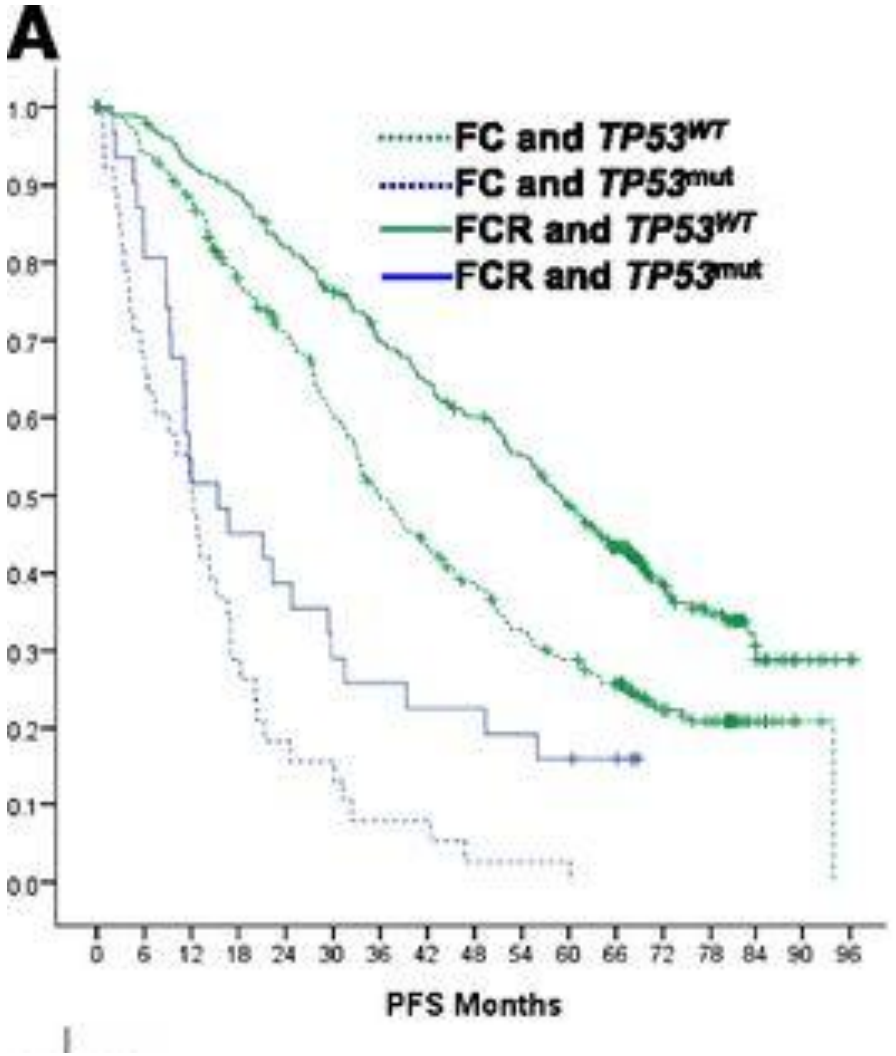
Level of Risk	Cytogenetic Abnormality	10-Yr Survival
		%
High	*TP53* abnormalities, *BIRC3* abnormalities, or both	29
Intermediate	*NOTCH1* mutations, *SF3B1* mutations, or both, with or without 11q22.3 deletion	37
Low	Trisomy 12 or normal cytogenetic profile	57
Very low	13q14 deletion only	69

* Data are from Rossi et al.[8]

Foà R, Guarini A. N Engl J Med 2013;369:85-87.

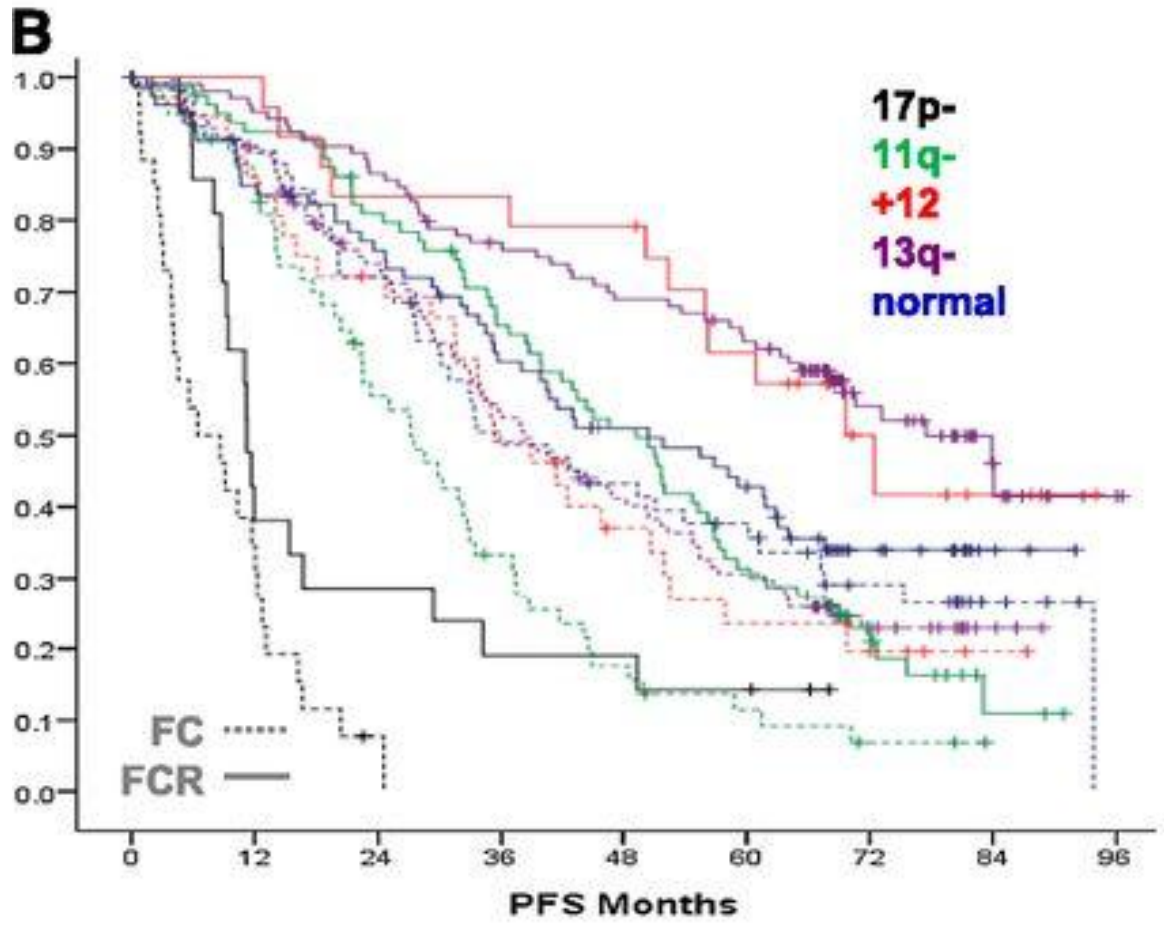
The NEW ENGLAND JOURNAL of MEDICINE

In the CLL8 trial, patients with TP53 mutations did poorly regardless of whether they received FCR or FC.



Stephan Stilgenbauer et al. Blood 2014;123:3247-3254

Almost all patients with 17p- in the CLL8 trial progressed in less than 2 years.



Stephan Stilgenbauer et al. Blood 2014;123:3247-3254

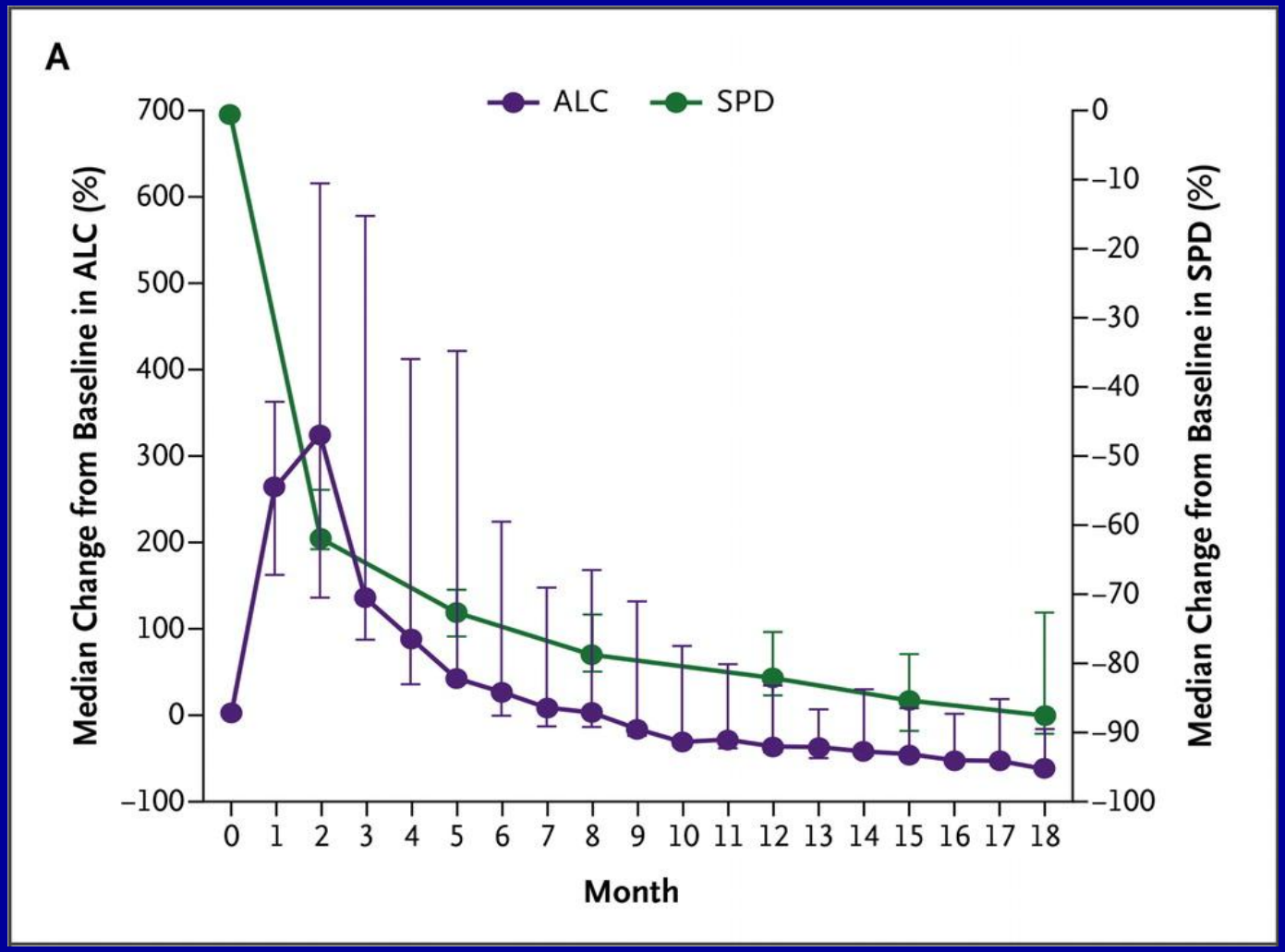
The NEW ENGLAND JOURNAL of MEDICINE

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.

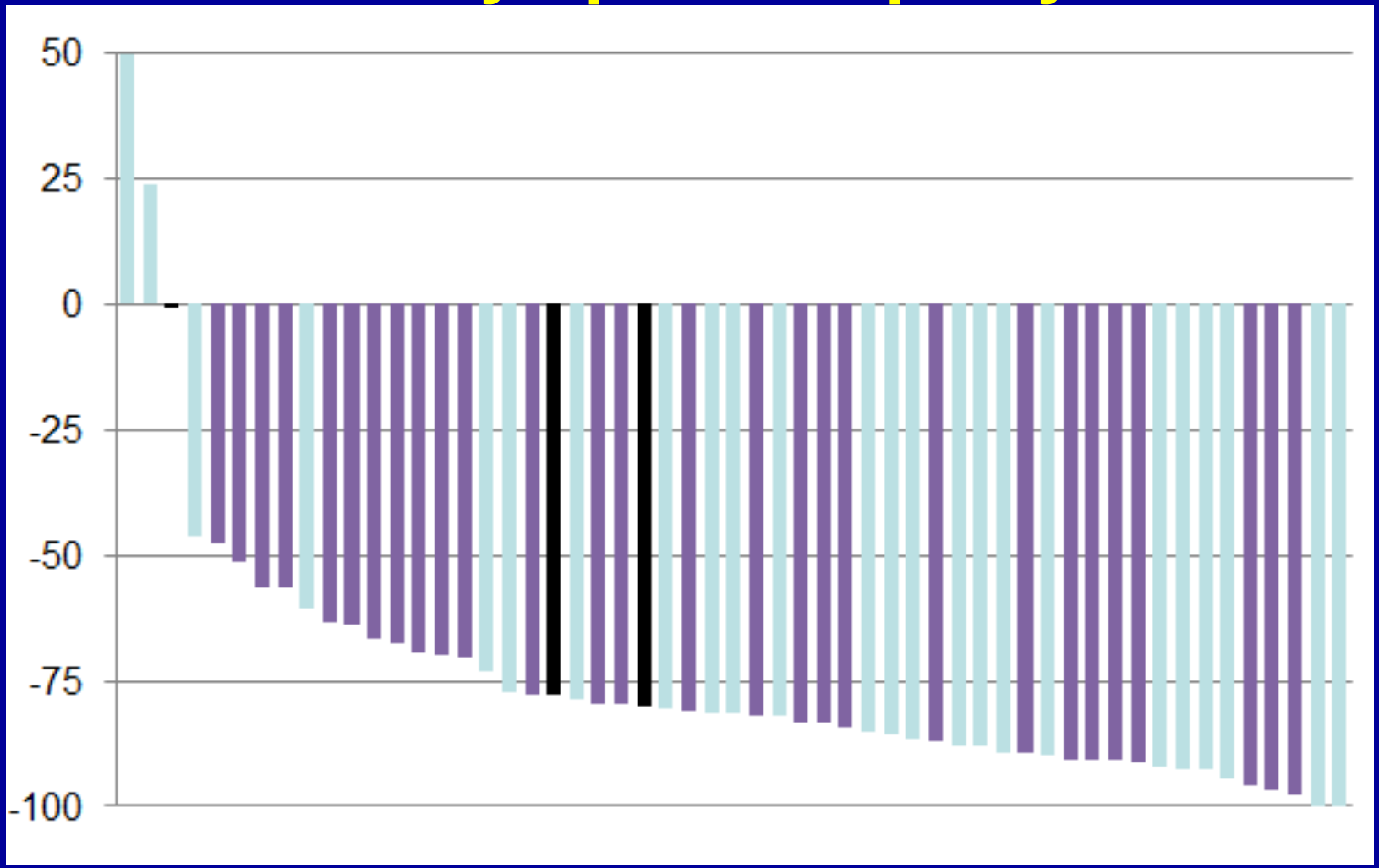
Ibrutinib causes immediate movement of CLL cells from nodes to peripheral blood, followed by reduction in peripheral blood lymphocytosis.



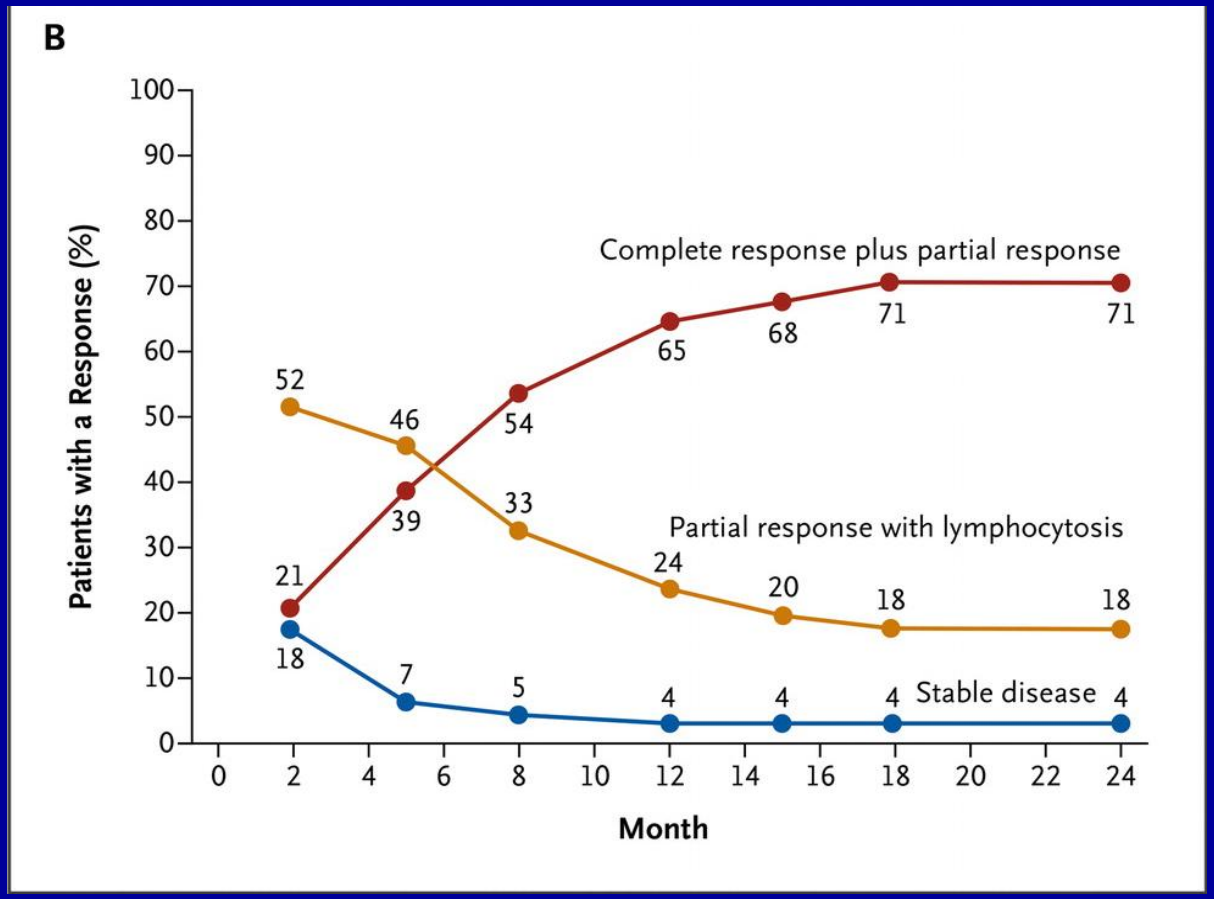
Byrd JC et al. N Engl J Med 2013;369:32-42.

The NEW ENGLAND JOURNAL of MEDICINE

Ibrutinib causes almost universal reduction in lymphadenopathy in CLL.



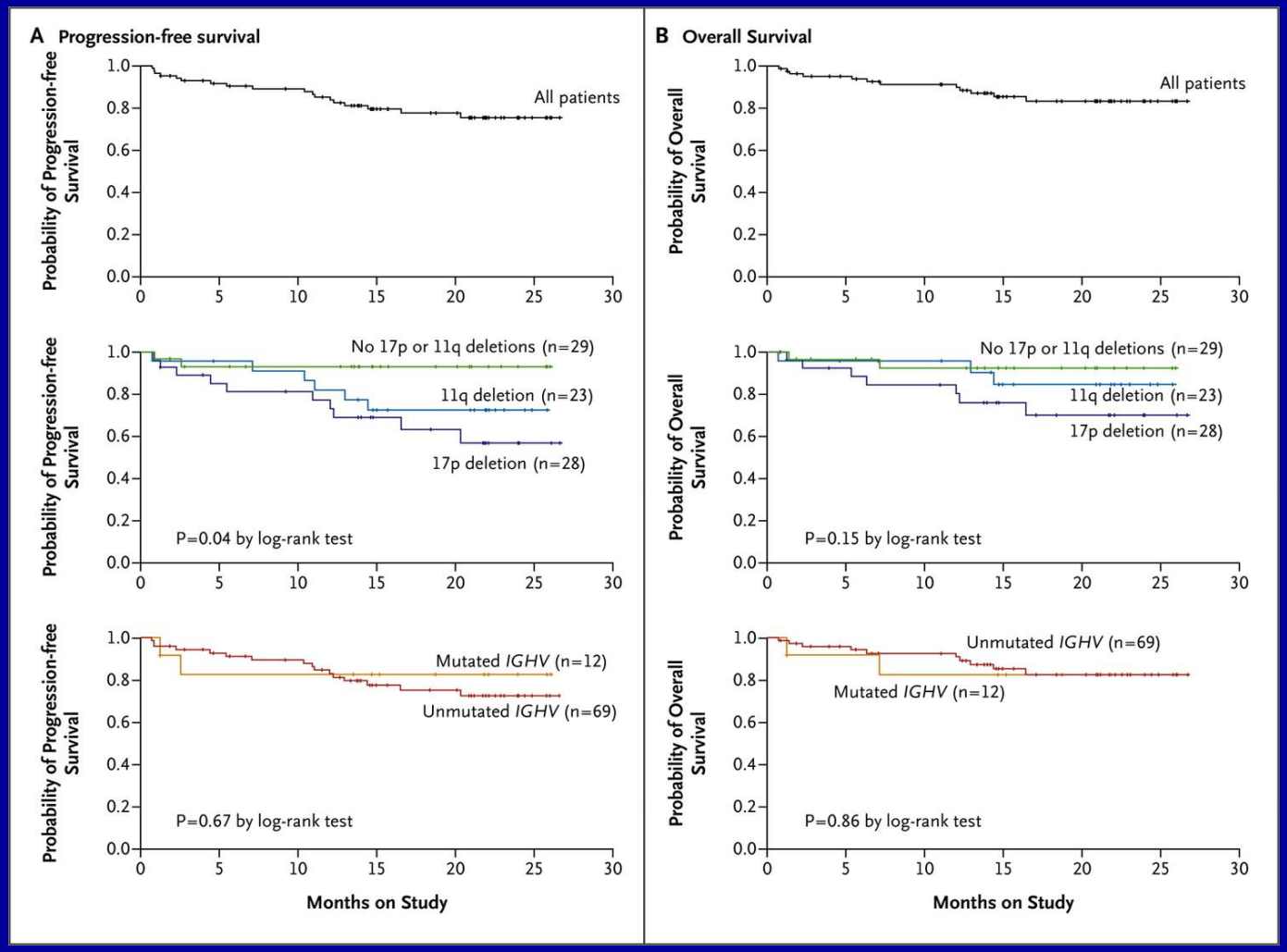
Single-agent ibrutinib results in a high rate of response over time in patients with CLL.



Byrd JC et al. N Engl J Med 2013;369:32-42.

The NEW ENGLAND JOURNAL of MEDICINE

Ibrutinib seems to overcome some of the adverse genetic prognostic factors in CLL.



Byrd JC et al. N Engl J Med 2013;369:32-42.

The NEW ENGLAND JOURNAL of MEDICINE

RESONATE-17: Phase II Ibrutinib in del(17p) Relapsed/Refractory CLL/SLL

- CLL/SLL
  - Relapsed/refractory disease after 1-4 prior therapies
  - del(17p)13.1 in peripheral blood*
  - ECOG PS 0-1
  - Measurable nodal disease

Until unacceptable toxicity or disease progression
Primary analysis 12 mos after last enrolled pt

Ibrutinib
420 mg/day PO
(N = 144)

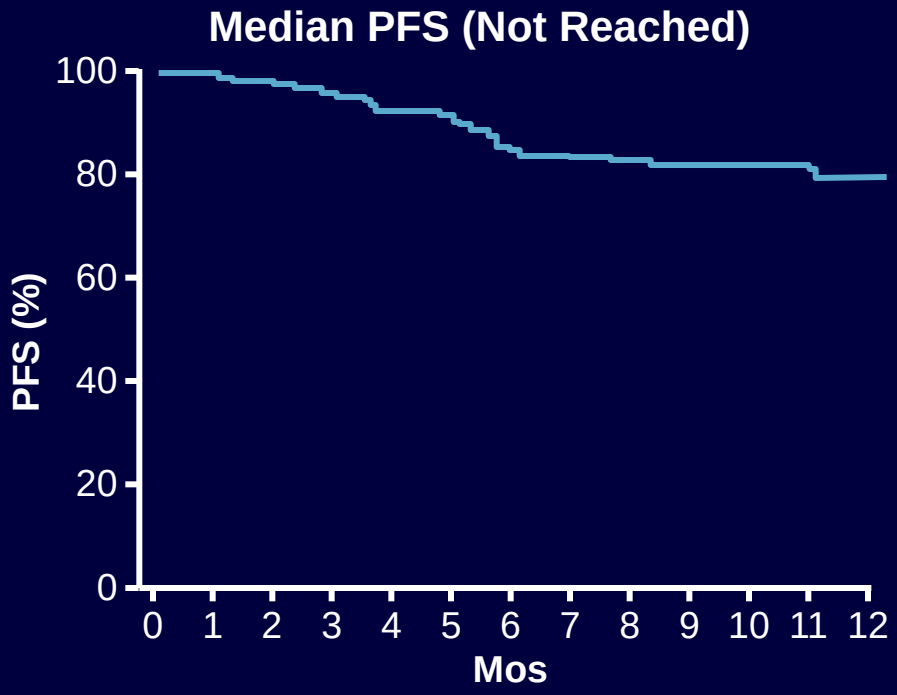
- Primary endpoint: ORR
- Secondary endpoints
  - DoR
  - Safety
  - Tolerability
- Exploratory endpoints
  - PFS
  - OS

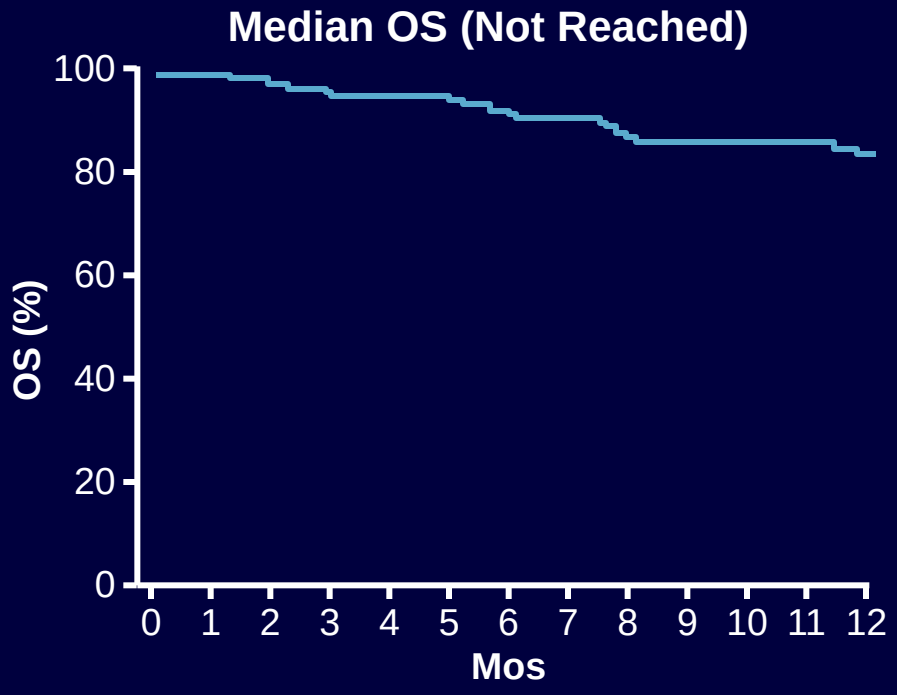
*Confirmed by FISH.

O'Brien SM, et al. ASH 2014. Abstract 327.

Ibrutinib in del(17p) Relapsed/Refractory CLL/SLL: Main Findings

- Best response (ORR + PR-L) by IRC (no 2nd confirmatory CT scan) was 74% (95% CI: 66% to 80%)
- Median DOR was not reached at median follow-up of 11.5 mos; 12-mo DOR was 88.3%





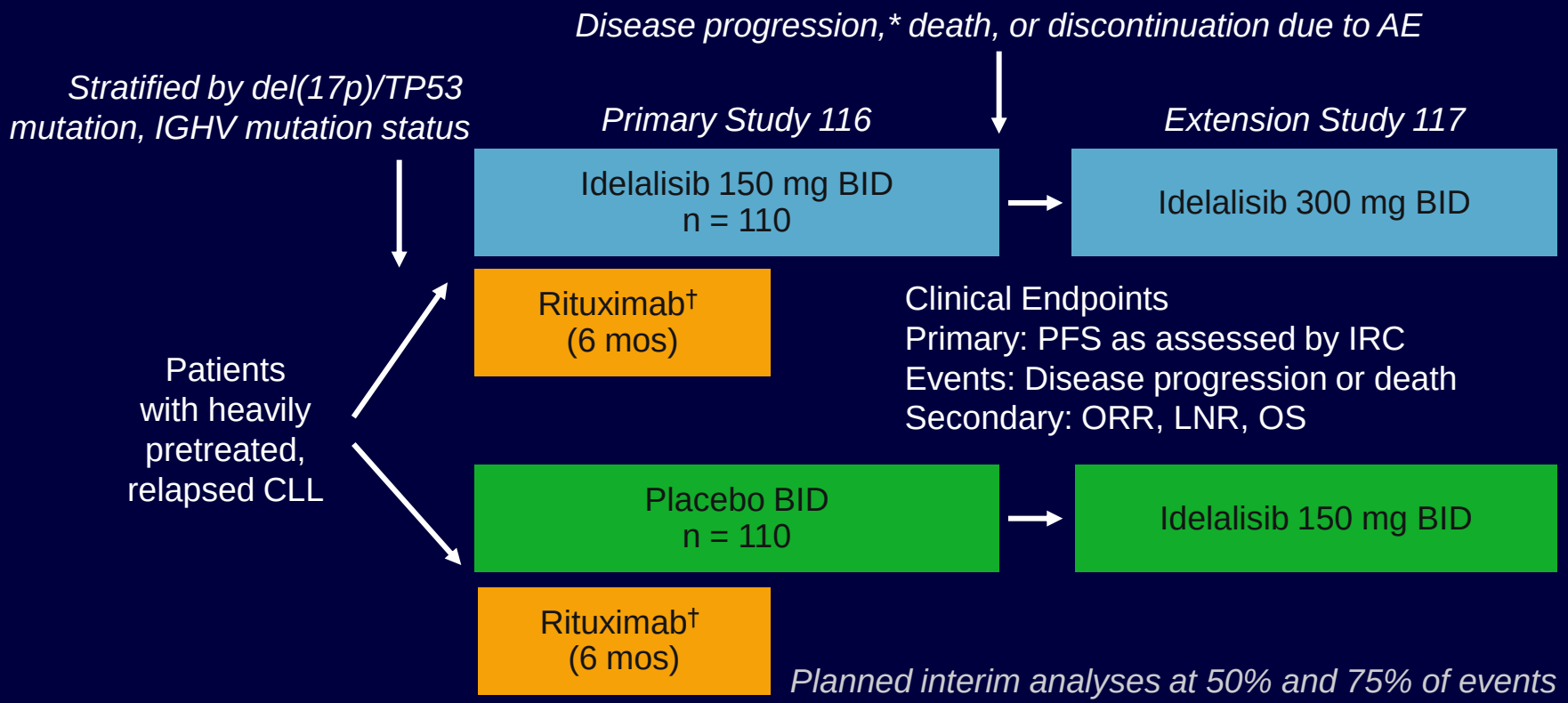
O'Brien SM, et al. ASH 2014. Abstract 327.

Ibrutinib in del(17p) Relapsed/Refractory CLL/SLL: Conclusions

- Ibrutinib showed efficacy with favorable risk–benefit profile in pts with del(17p) CLL/SLL
- 12-mo PFS: 79%, consistent with previous study of 26-mo PFS (75%)
- PFS outcomes in this relapsed/refractory setting favorable compared with previous results for frontline FCR regimen or alemtuzumab in del(17p) CLL (median PFS: 11 mos)
- Safety profile consistent with known profile for ibrutinib

O'Brien SM, et al. ASH 2014. Abstract 327. Byrd JC, et al. N Engl J Med. 2013;369:32-42.

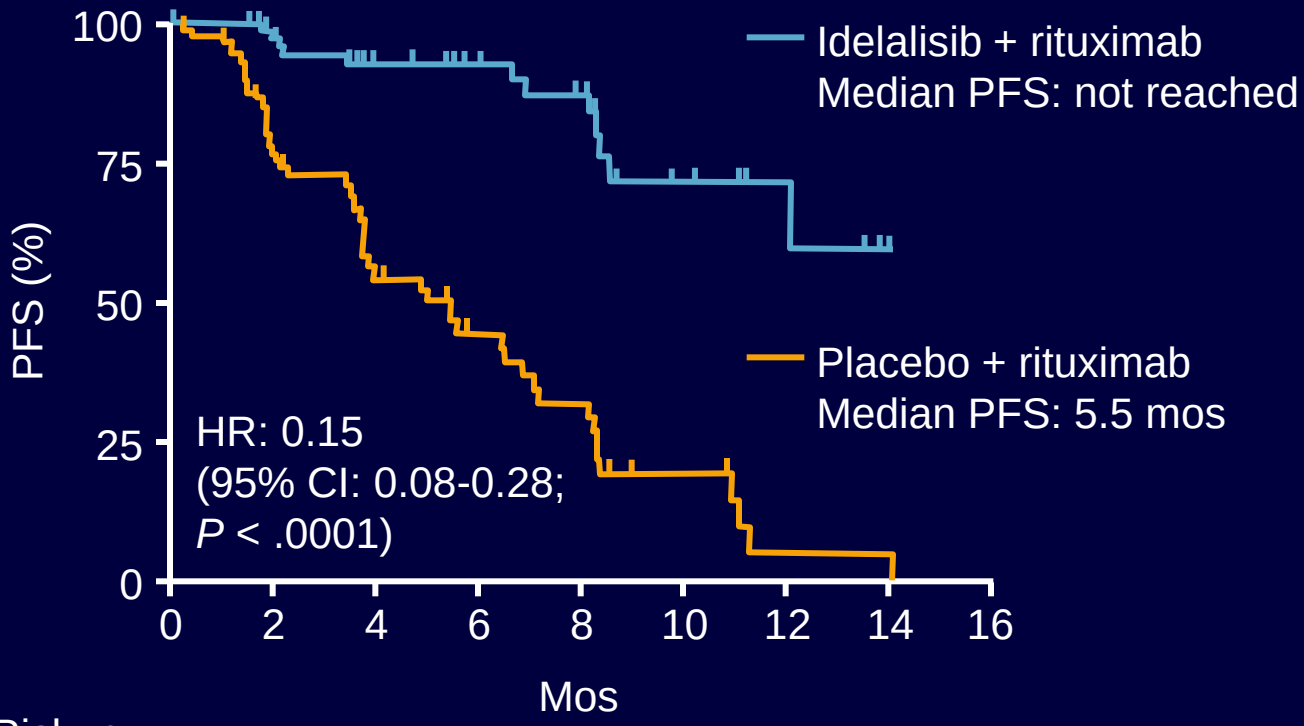
Phase III Idelalisib and Rituximab for Previously Treated Patients With CLL: Study Design



*Patients with disease progression continued on idelalisib Extension Study 117.
†Rituximab schedule: 375 mg/m^2, then 500 mg/m^2 every 2 wks x 4, then 500 mg/m^2 every 4 wks x 3.

Furman R, et al. ASH 2013. Abstract LBA-6.

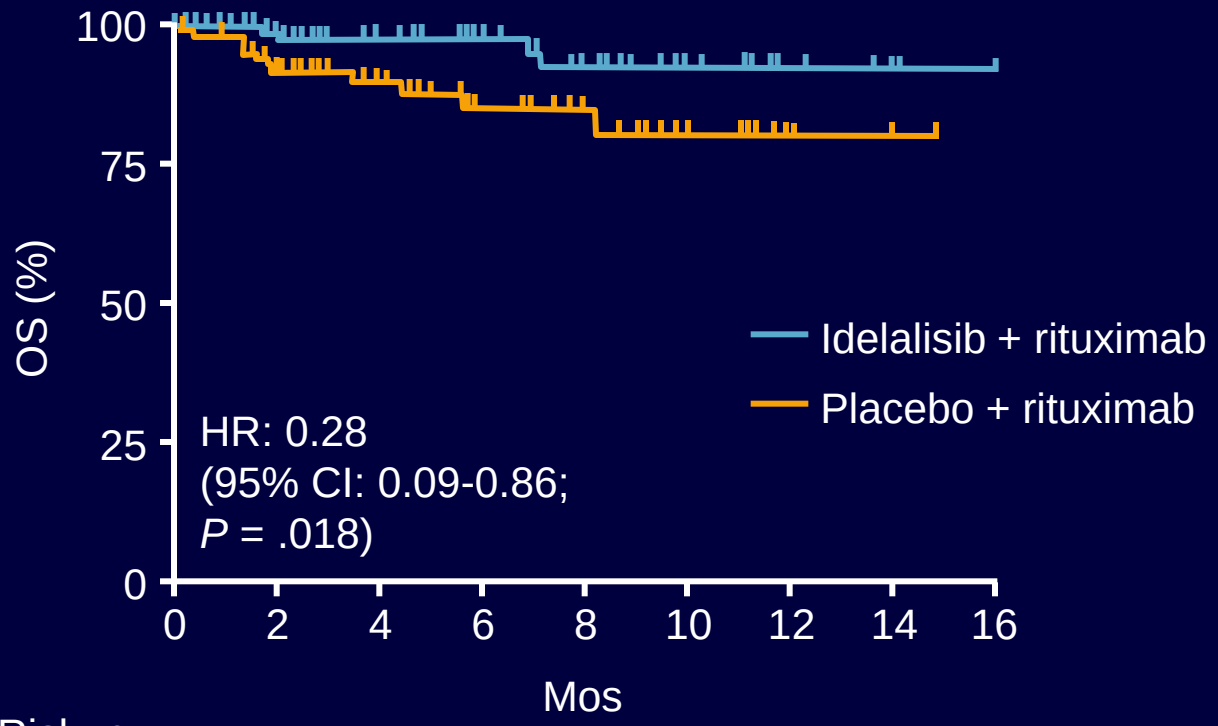
Idelalisib and Rituximab for Previously Treated Patients With CLL: PFS



Pts at Risk, n									
Idelalisib + rituximab:	110	69	44	34	30	14	6	2	0
Placebo + rituximab:	110	62	30	18	13	6	1	1	0

Furman R, et al. ASH 2013. Abstract LBA-6.

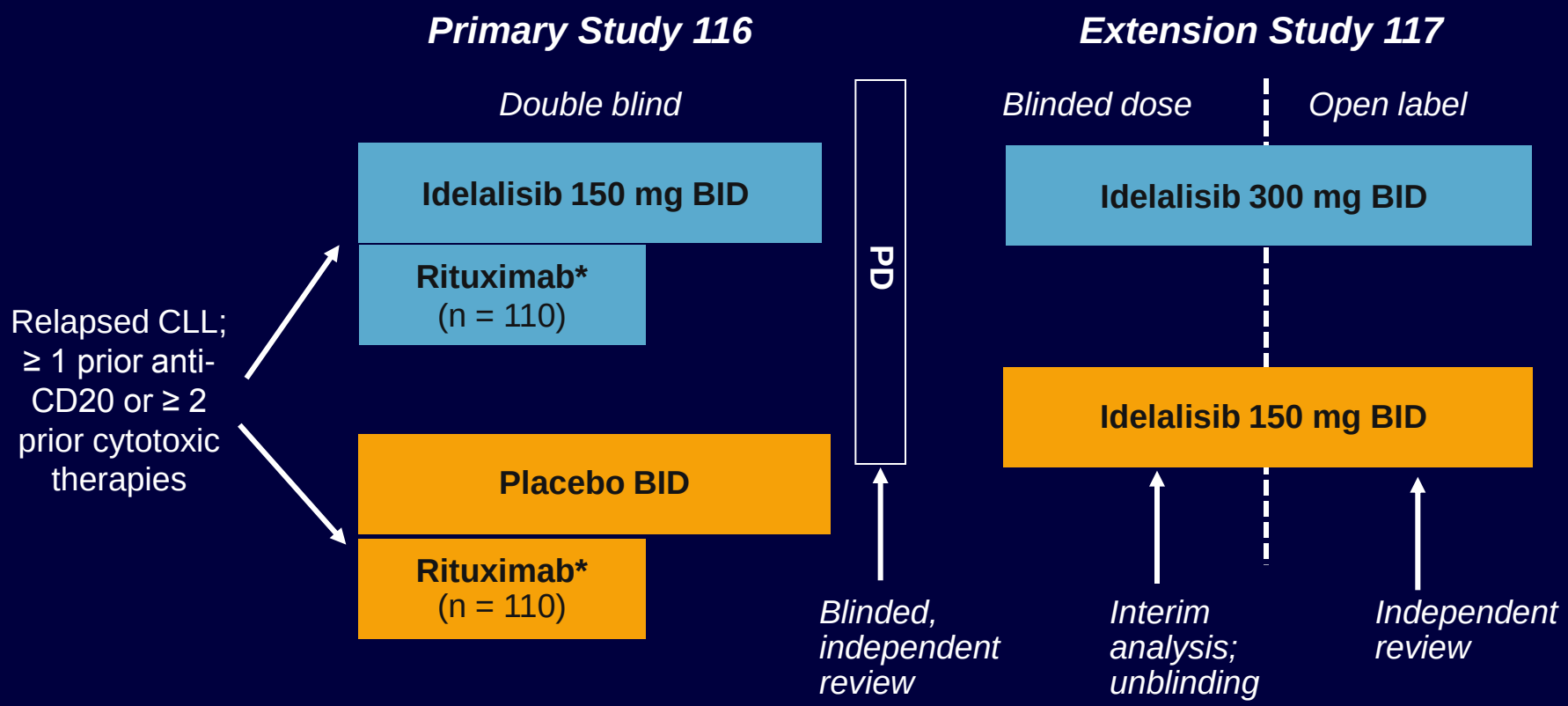
Idelalisib and Rituximab for Previously Treated Patients With CLL: OS



Pts at Risk, n									
Idelalisib + rituximab:	110	88	55	40	31	16	7	4	0
Placebo + rituximab:	110	76	43	25	18	8	2	1	0

Furman R, et al. ASH 2013. Abstract LBA-6.

Phase III 2nd Interim Analysis: Idelalisib + Rituximab in Relapsed CLL

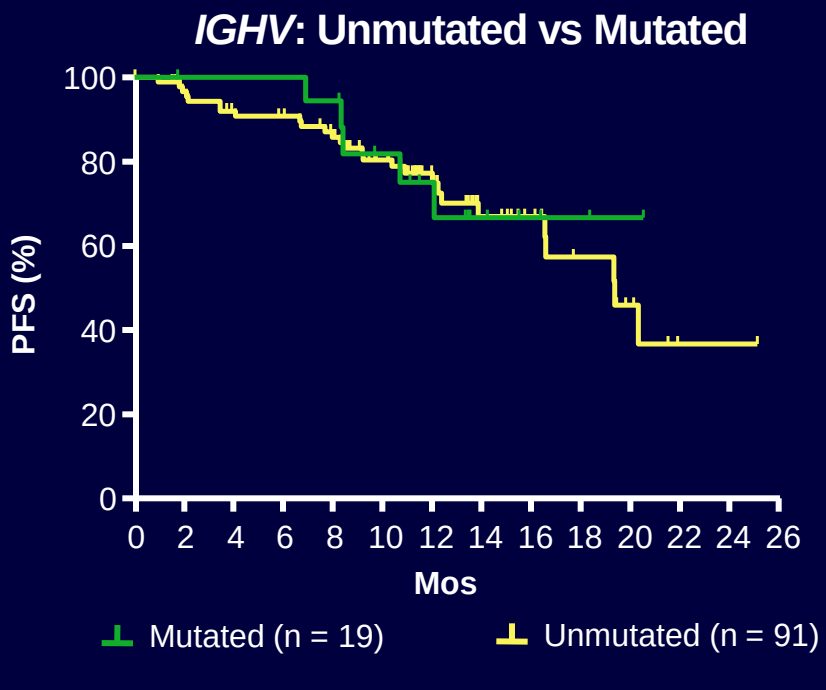


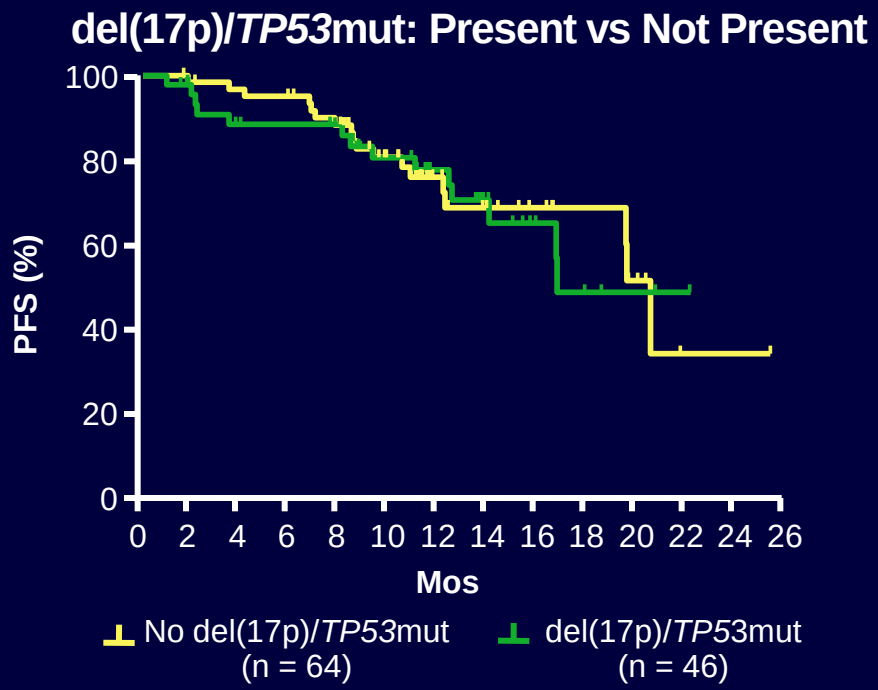
- Primary endpoint: PFS, OS by subgroup analysis

*Rituximab given in 8 doses; first dose 375 mg/m^2, then 500 mg/m^2 every 2 wks x 4, then every 4 wks x 3

Sharman JP, et al. ASH 2014. Abstract 330.

Idelalisib + Rituximab in Relapsed CLL: PFS Subgroup Analysis* (n = 110)





	Median PFS, Mos (95% CI)	*P* Value
Mut	NR (10.7-NR)	.75
Unmut	19.4 (16.6-NR)	

	Median PFS, Mos (95% CI)	*P* Value
No del	20.3 (19.4-NR)	.94
Del	16.6 (13.9-NR)	

*Including extension study.

Sharman JP, et al. ASH 2014. Abstract 330.

Idelalisib + Rituximab in Relapsed CLL: PFS Subgroup Analysis* (n = 110)

- PFS: Idelalisib + rituximab favored in all subgroups vs placebo + rituximab (median follow-up: idelalisib, 13 mos; placebo, 11 mos)

Median PFS, Mos	Idelalisib + Rituximab (n = 110)	Placebo + Rituximab (n = 110)
All pts	NR	5.5
Subgroup		
•Rai stage III/IV	NR	13
•del(17p)/*TP53* mutation	NR	4.0
•del(11q)	10.7	6.9
•Unmutated *IGHV*	NR	5.5
•Zap70+	NR	5.5
•CD38+	NR	6.9
•B_2-microglobulin > 4 mg/L	NR	5.0

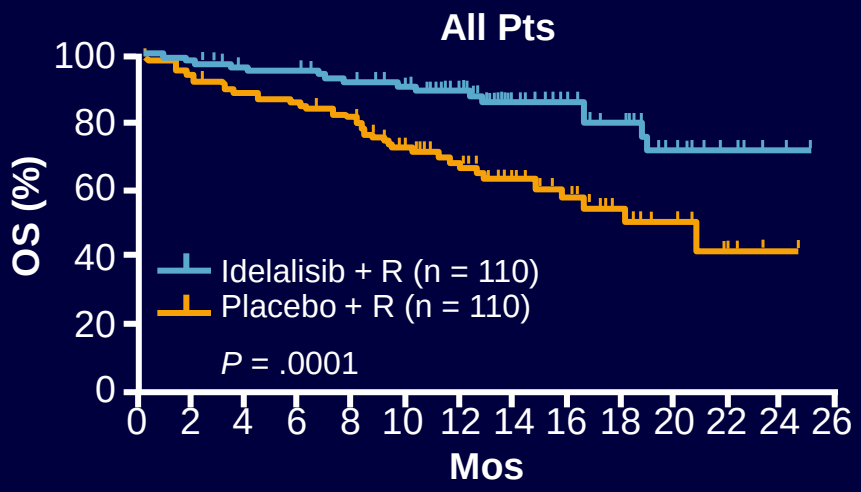
- PFS improvement with idelalisib + rituximab vs placebo + rituximab significant after crossover in extension study

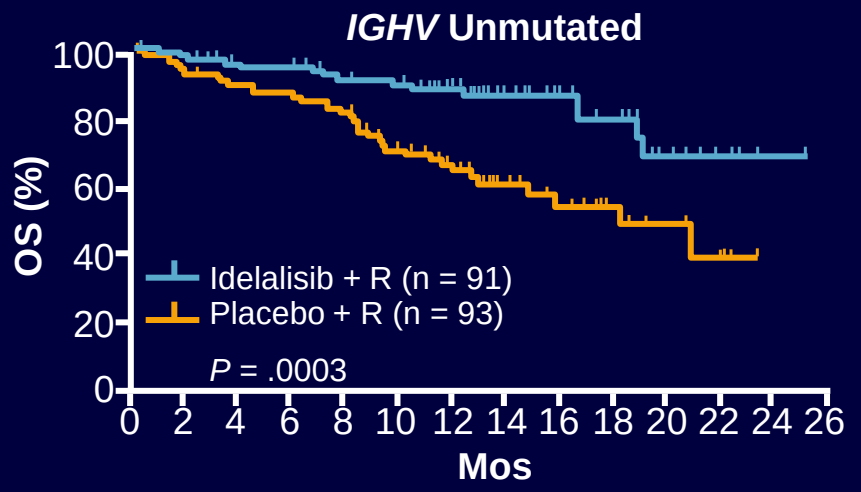
Therapy	Median PFS, Mos (95% CI)	HR (95% CI)	*P* Value
Idelalisib + rituximab (n = 110)	19.4 (16.6 to NR)	0.25 (0.16-0.39)	< .0001
Placebo + rituximab (n = 110)	7.3 (5.5-8.5)		

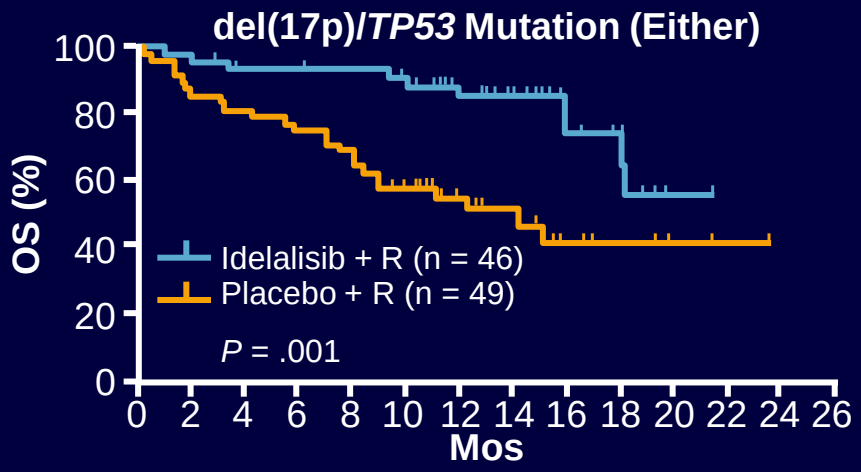
*Including extension study.

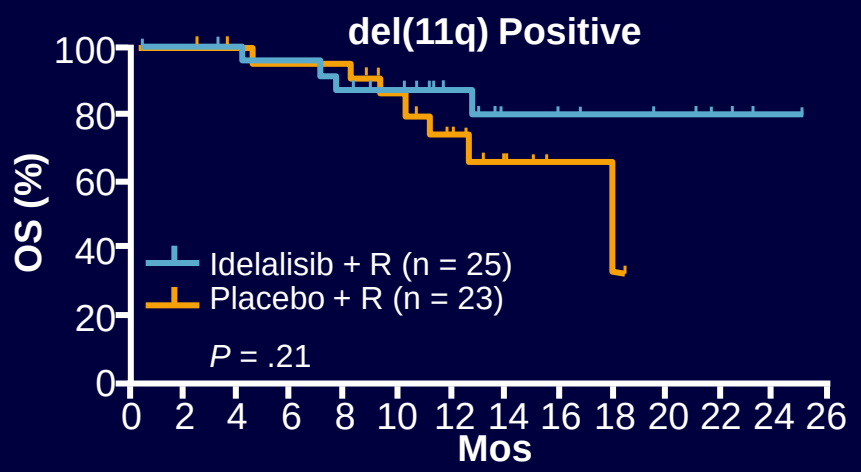
Sharman JP, et al. ASH 2014. Abstract 330.

Idelalisib + Rituximab in Relapsed CLL: OS









Sharman JP, et al. ASH 2014. Abstract 330.

Idelalisib + Rituximab in Relapsed CLL: Conclusions

- Overall, median PFS has not been reached in idelalisib + rituximab arm vs 5.5 mos for rituximab monotherapy
- Idelalisib + rituximab had comparable efficacy in pts with relapsed CLL regardless of high-risk genomic features, including del(11q), del(17p)/*TP53* mutation, and unmutated *IGHV*
- OS significantly improved for pts receiving idelalisib + rituximab vs rituximab monotherapy despite crossover in extension trial design
- Combination has manageable toxicity profile in pts with relapsed/refractory CLL

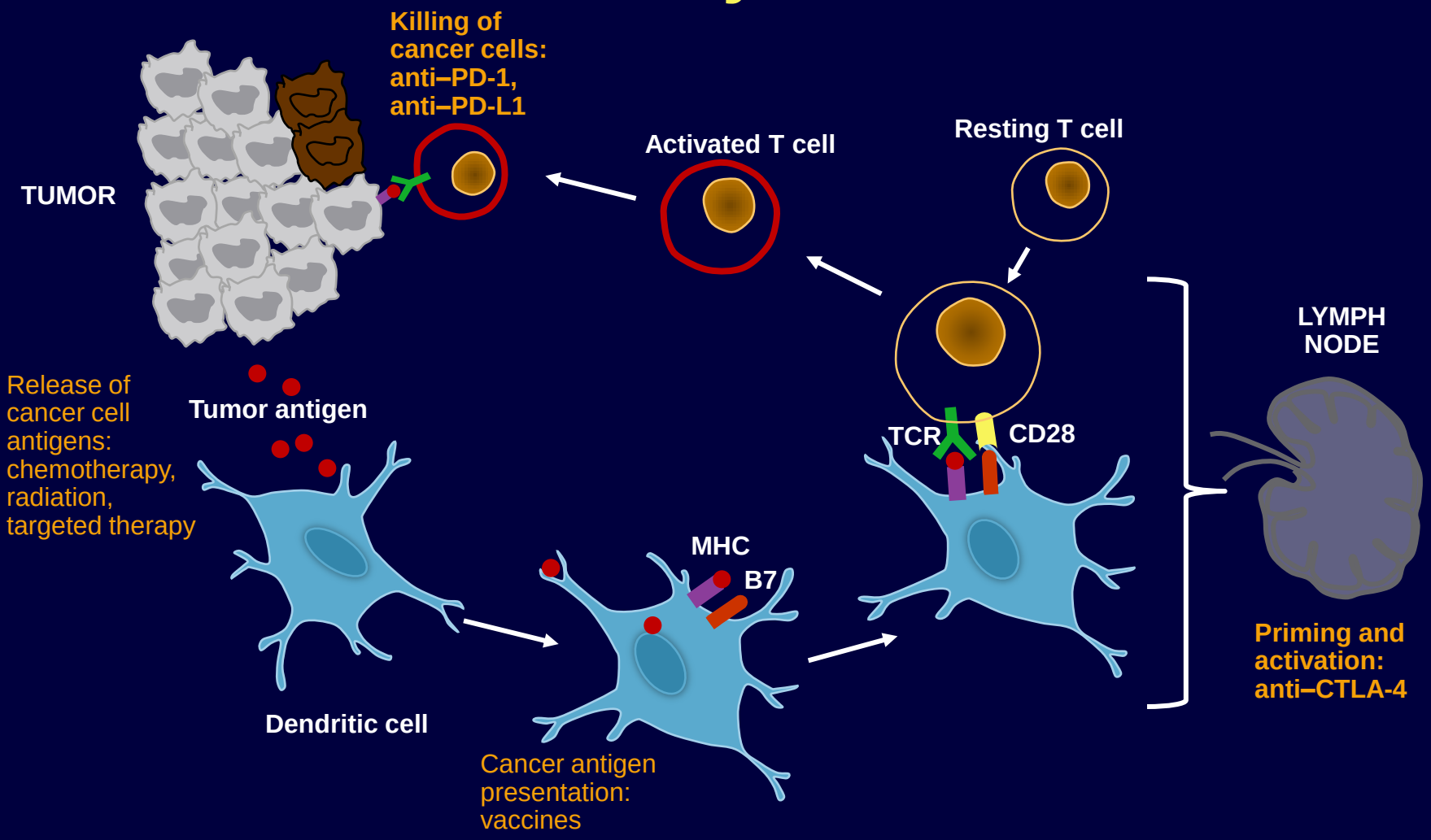
Sharman JP, et al. ASH 2014. Abstract 330.

Outline

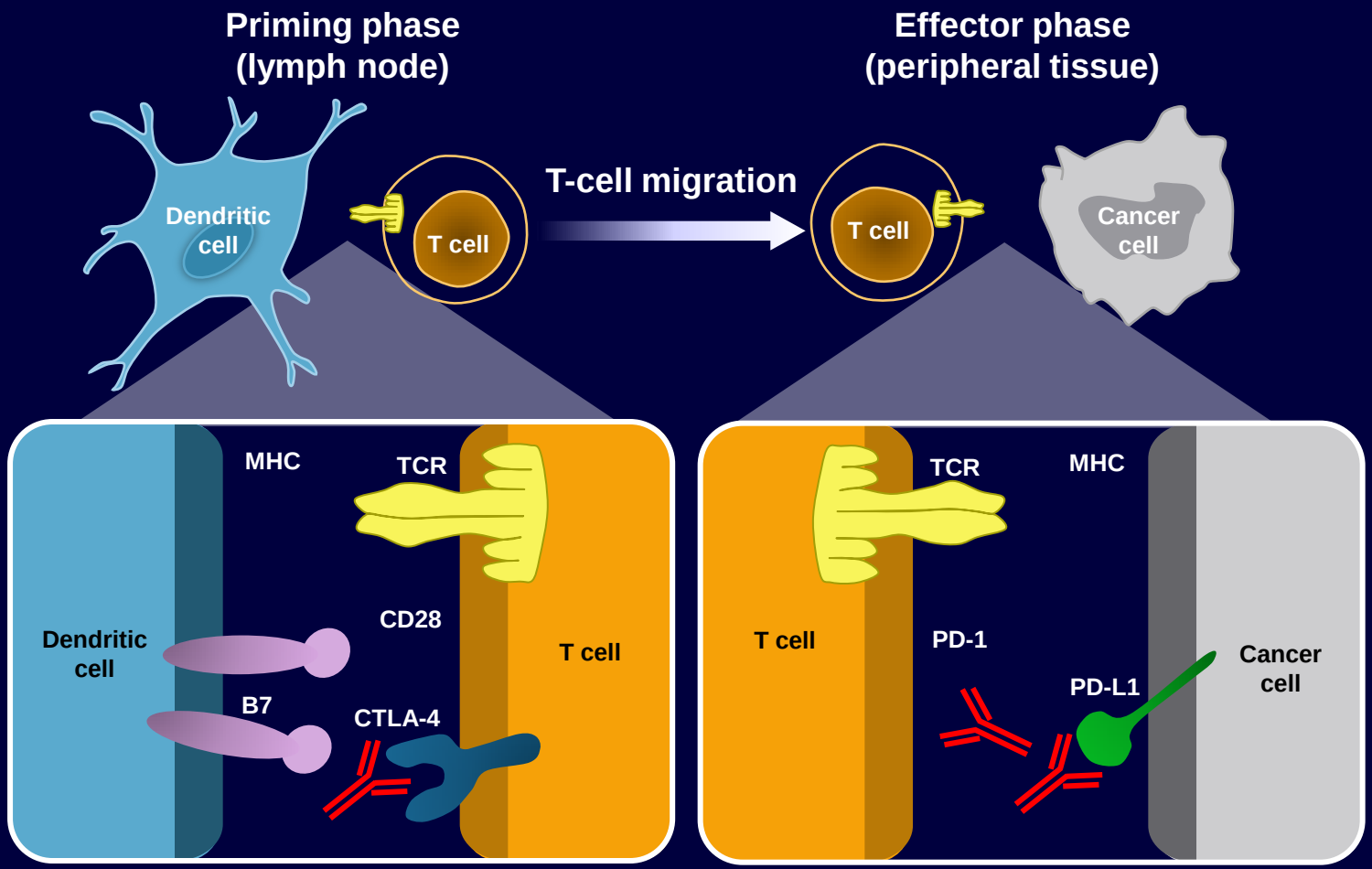
- Chronic lymphocytic leukemia
  - Background and impact of 17p- and *TP53* mutations
  - RESONATE-17: ibrutinib in R/R CLL with 17p-
  - Idelalisib-rituximab in genetic subgroups

- **Checkpoint blockade in cancer therapy**
  - **Phase 1 study of nivolumab in Hodgkin lymphoma**

A Roadmap of Immunotherapy Agents in the Cancer: Immune System Interaction



CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment



Ribas A. N Engl J Med. 2012;366:2517-2519.

Nivolumab

- Anti-PD1 antibody
- FDA approvals
  - Melanoma no longer responding to other drugs, 12/22/2014
  - Squamous cell lung cancer progressing after prior platinum-based therapy, 3/4/2015
- Administered IV every 2 weeks

Study Design

- Phase 1 study with dose escalation and expansion cohorts
- Included patients with relapsed/refractory hematologic cancers (only HL reported in this paper)
- Starting dose 1 mg/kg, then escalated to 3 mg/kg
- Administered week 1, then week 4, then every 2 weeks until progression, complete remission, or a maximum of 2 years
- No maximum tolerated dose (MTD) was reached

Ansell SM et al. N Engl J Med 2015;372:311-319.

Characteristics of the 23 Patients at Baseline in the Phase 1 Study.

Table 1. Characteristics of the 23 Patients at Baseline.

Characteristic	Value
Age — yr	
Median	35
Range	20–54
Male sex — no. (%)	12 (52)
Race — no. (%)*	
White	20 (87)
Black	2 (9)
Other	1 (4)
ECOG performance-status score — no. (%)†	
0	6 (26)
1	17 (74)
Histologic findings — no. (%)	
Nodular sclerosis	22 (96)
Mixed cellularity	1 (4)
No. of previous systemic therapies — no. (%)	
2 or 3	8 (35)
4 or 5	7 (30)
≥6	8 (35)
Previous treatment — no. (%)	
Brentuximab vedotin	18 (78)
Autologous stem-cell transplantation	18 (78)
Radiotherapy	19 (83)
Extranodal involvement — no. (%)‡	4 (17)

Ansell SM et al. N Engl J Med 2015;372:311-319.

The NEW ENGLAND JOURNAL of MEDICINE

Drug-Related Adverse Events in the 23 Patients.

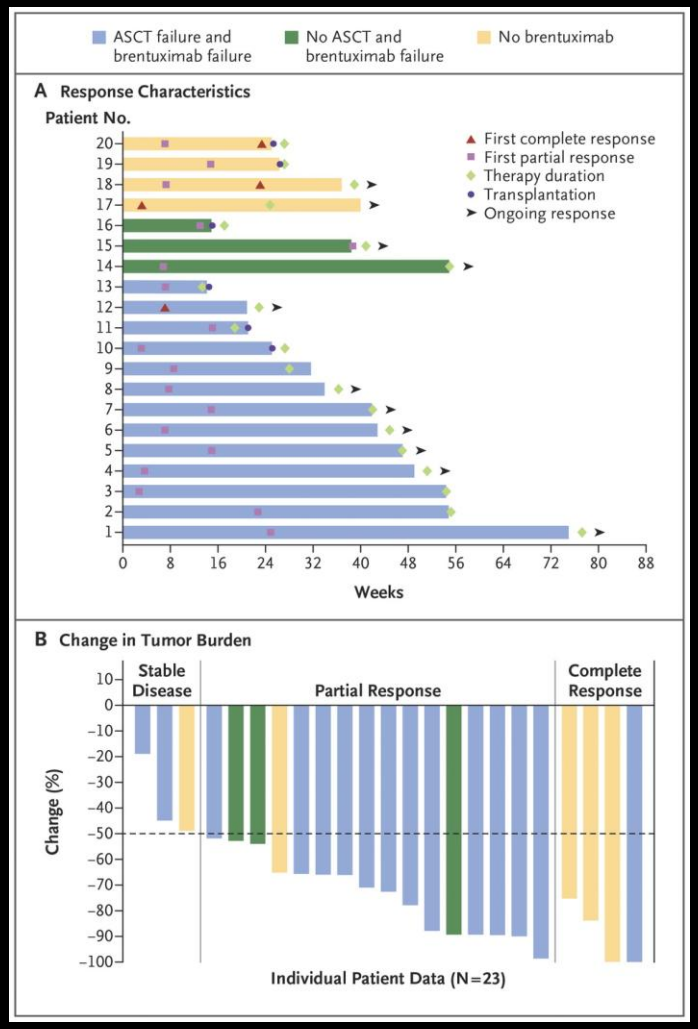
Table 2. Drug-Related Adverse Events in the 23 Patients.*

Event	Any Grade	Grade 3
	no. of patients (%)	
Any adverse event	18 (78)	5 (22)
Drug-related adverse events reported in ≥5% of patients		
Rash	5 (22)	0
Decreased platelet count	4 (17)	0
Fatigue	3 (13)	0
Pyrexia	3 (13)	0
Diarrhea	3 (13)	0
Nausea	3 (13)	0
Pruritus	3 (13)	0
Cough	2 (9)	0
Hypothyroidism	2 (9)	0
Decreased lymphocyte count	2 (9)	1 (4)
Hypophosphatemia	2 (9)	0
Hypercalcemia	2 (9)	0
Increased lipase level	2 (9)	1 (4)
Stomatitis	2 (9)	1 (4)
Drug-related serious adverse events		
Myelodysplastic syndrome	1 (4)	1 (4)
Lymph-node pain	1 (4)	0
Pancreatitis	1 (4)	1 (4)

Ansell SM et al. N Engl J Med 2015;372:311-319.

The NEW ENGLAND JOURNAL of MEDICINE

Nivolumab therapy results in a high response rate in patients with relapsed-refractory Hodgkin lymphoma.

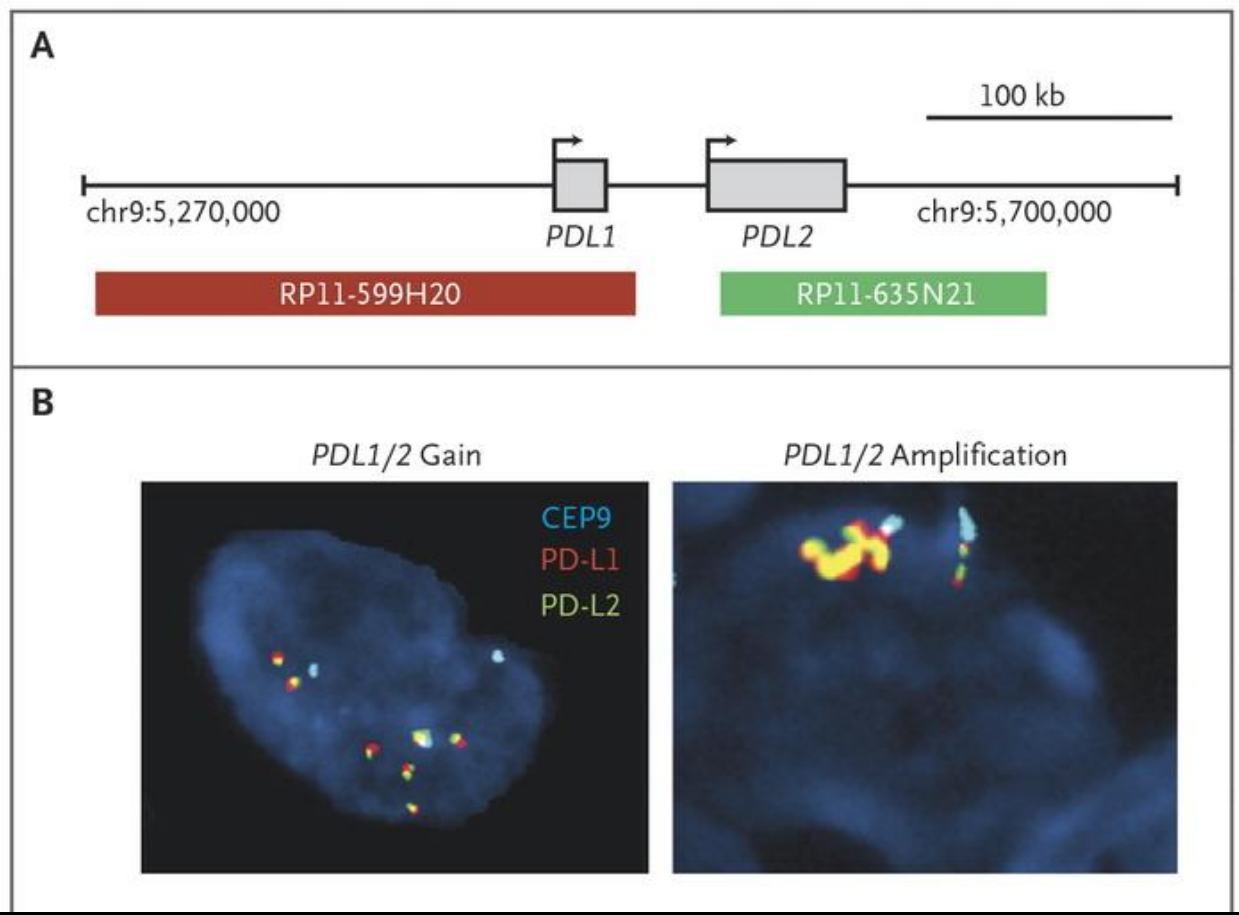


Ansell SM et al. N Engl J Med 2015;372:311-319.

The NEW ENGLAND JOURNAL of MEDICINE

Reed-Sternberg cells demonstrate gain of copy numbers and amplification of PDL1 and PDL2.

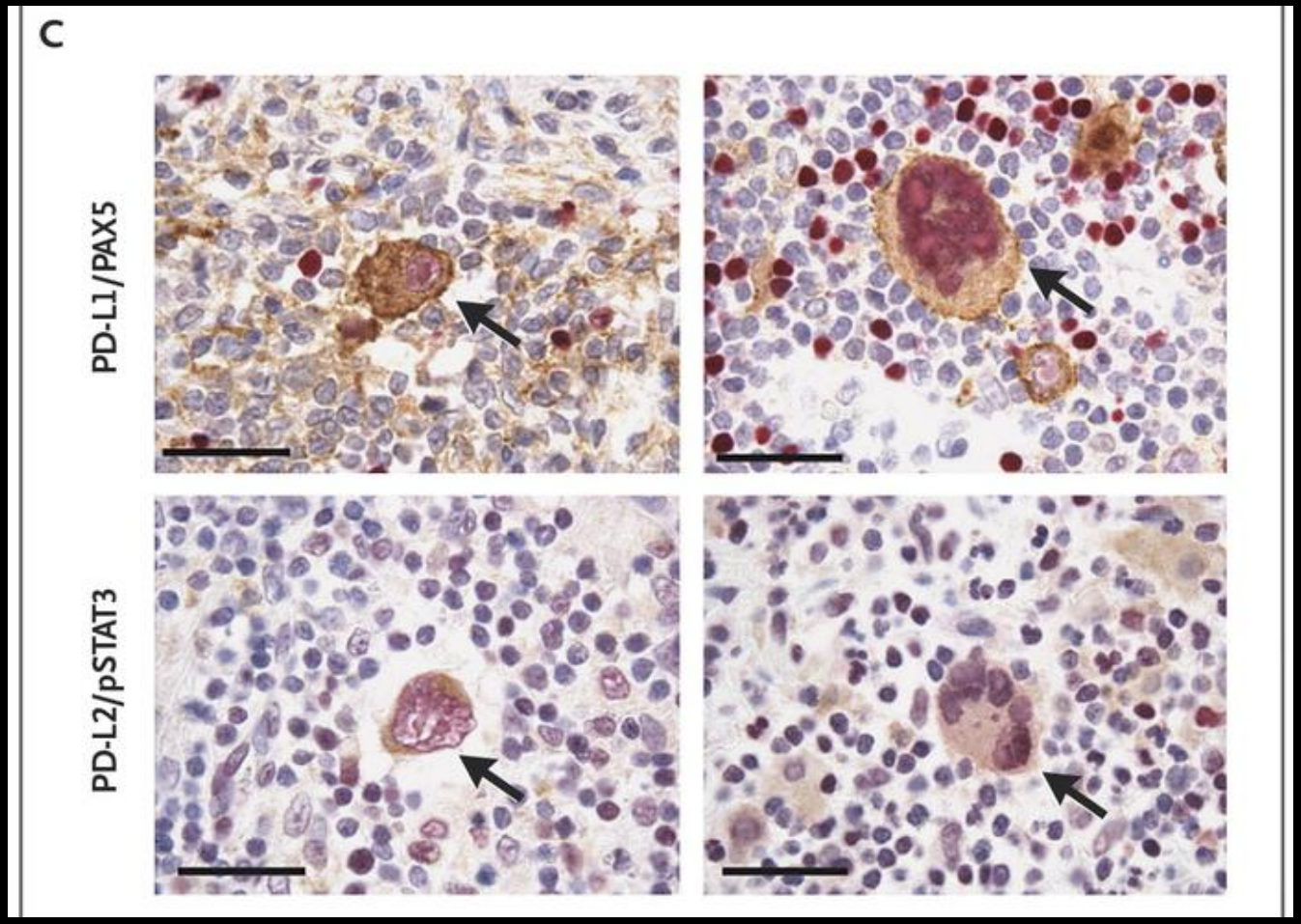
6 green-red (yellow) fusion signals > 3 centromeric signals (aqua) indicates copy number gain in *PDL1* and *PDL2*



More yellow signals than aqua indicates amplification of *PDL1* and *PDL2.*

Ansell SM et al. N Engl J Med 2015;372:311-319.

The malignant Reed-Sternberg cells (arrows) show high expression of PD-L1 (top row) and PD-L2 (bottom row).



Ansell SM et al. N Engl J Med 2015;372:311-319.

The NEW ENGLAND JOURNAL of MEDICINE

Conclusions

- In patients with CLL with 17p- or *TP53* mutations, both ibrutinib and idelalisib-rituximab appear more promising than conventional chemoimmunotherapy.

- Anti-PD-1 antibodies offer great promise in patients with relapsed Hodgkin lymphoma. Additional research needs to be done to determine how best to incorporate these agents into treatment algorithms.