BCR-RECEPTOR PATHWAY INHIBITORS IN LYMPHOMA

Simon Rule

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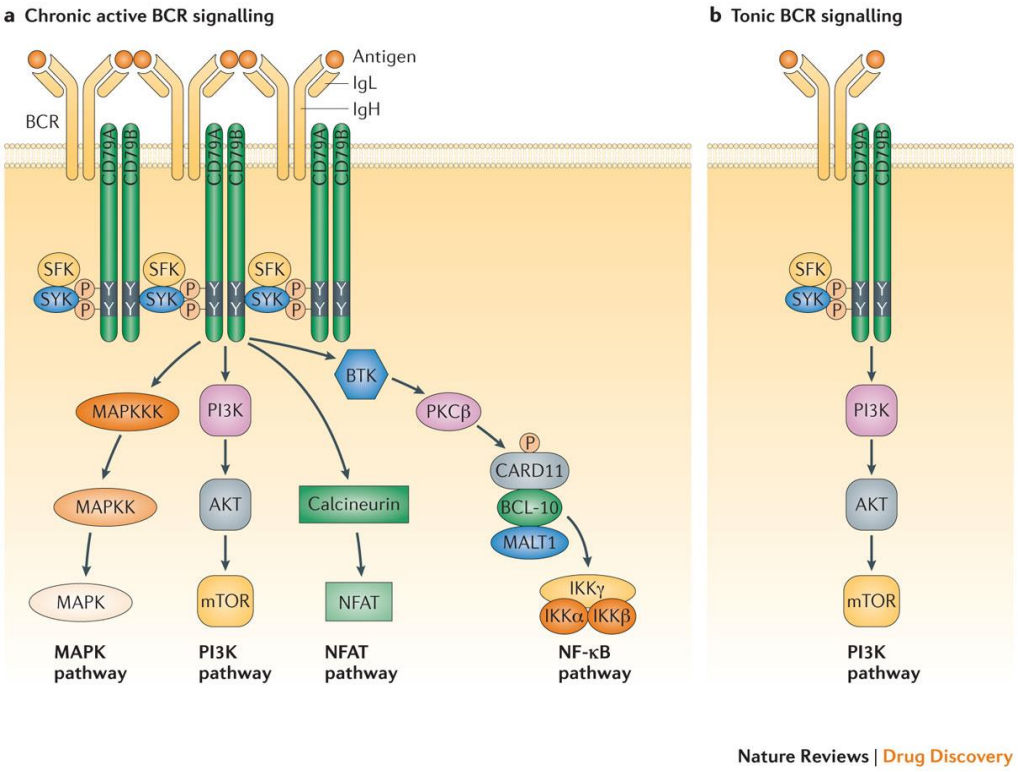
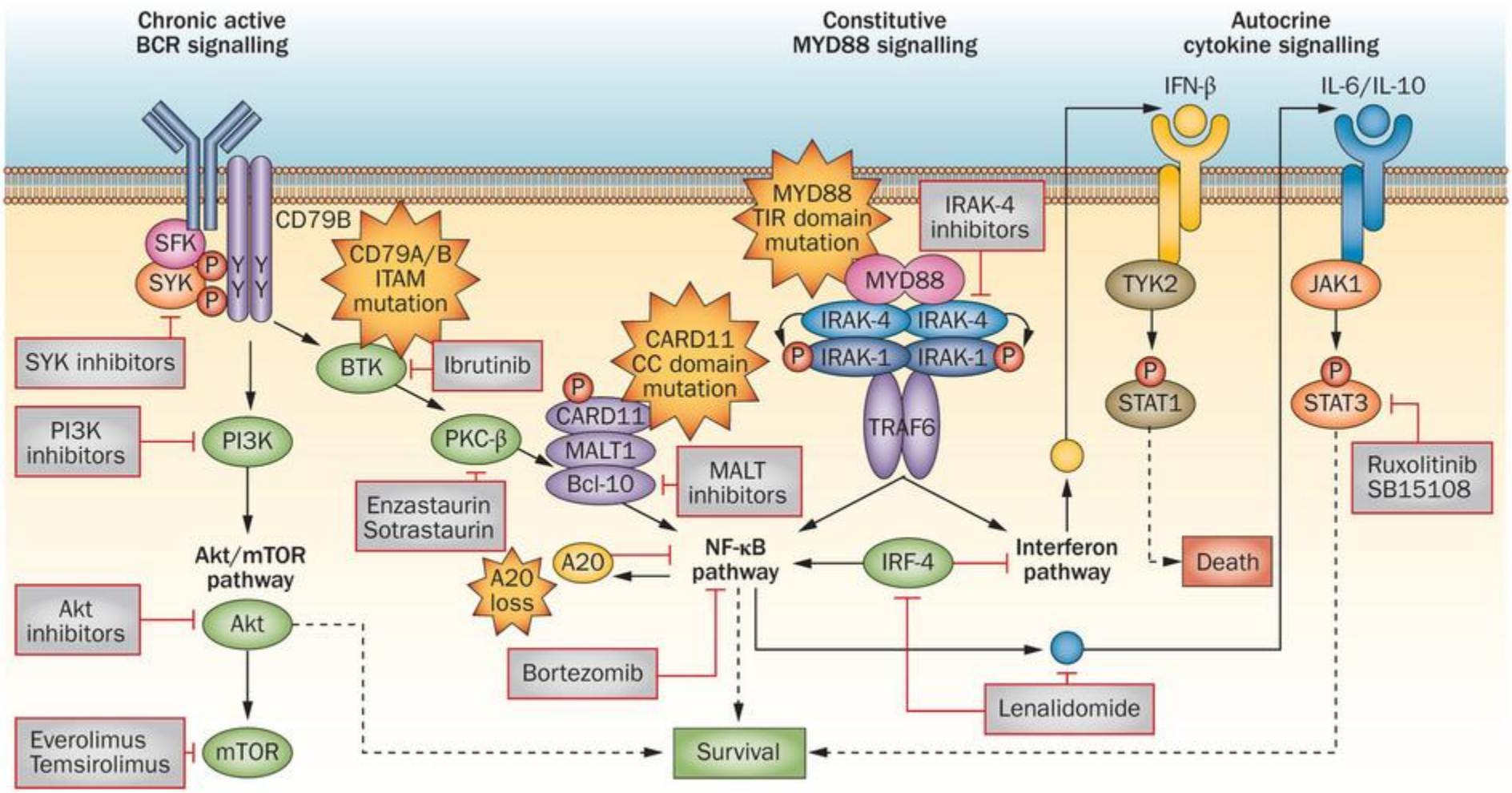
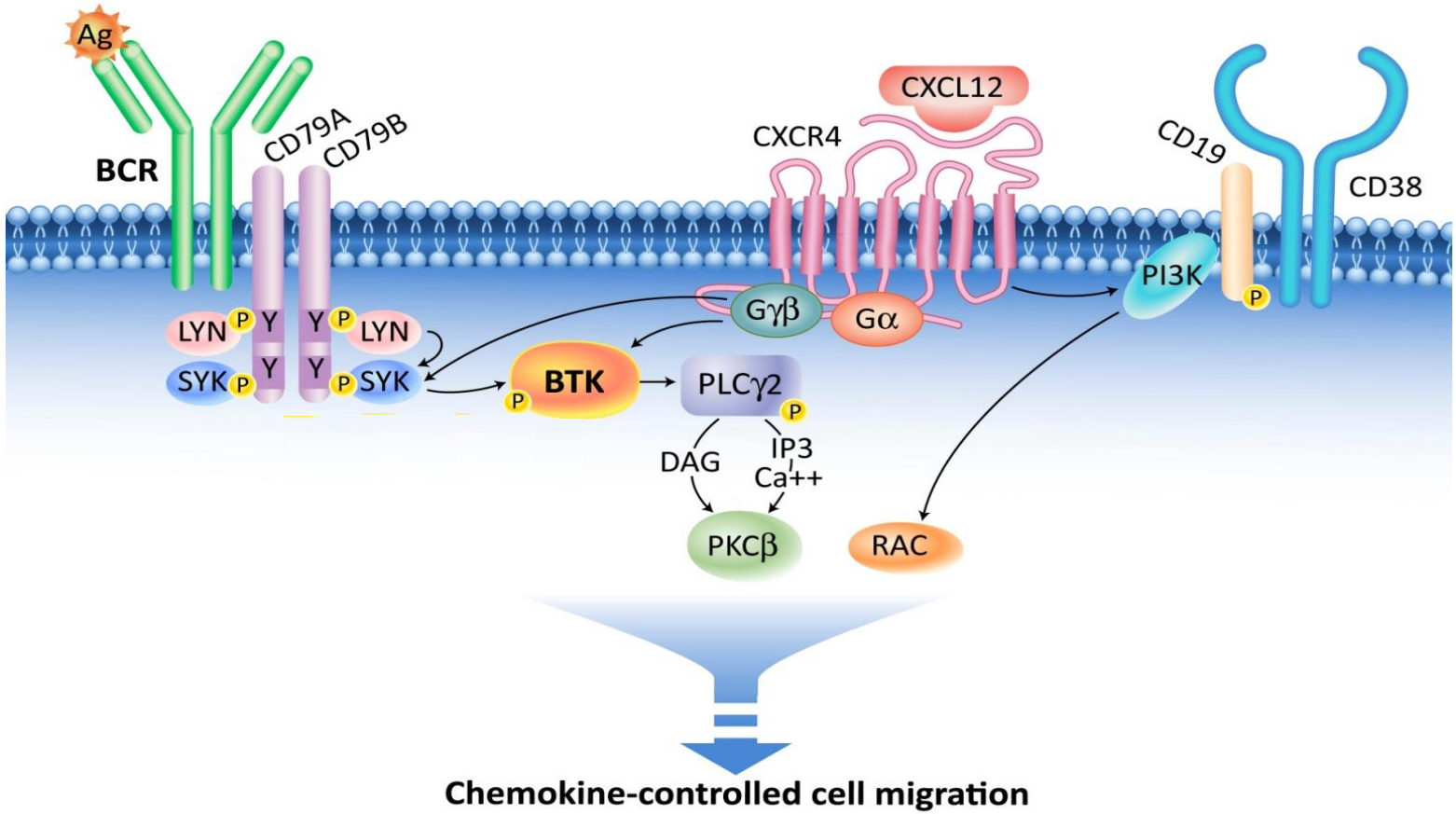
BCR signalling in lymphoid malignancy



Young & Staudt, Nature Reviews Drug Discovery 12, 229-243 (March 2013)

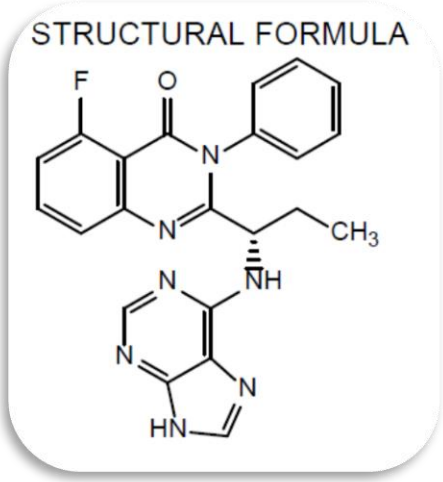

Chronic active BCR signalling
Constitutive MYD88 signalling
Autocrine cytokine signalling
IFN-β
IL-6/IL-10
CD79B
SFK
SYK
P
Y Y Y Y
CD79A/B ITAM mutation
MYD88 TIR domain mutation
IRAK-4 inhibitors
MYD88
IRAK-4
IRAK-1
TYK2
JAK1
STAT1
STAT3
SYK inhibitors
BTK
Ibrutinib
CARD11 CC domain mutation
CARD11
MALT1
Bcl-10
MALT inhibitors
TRAF6
PI3K inhibitors
PI3K
PKC-β
Enzastaurin Sotrastaurin
Ruxolitinib SB15108
Akt/mTOR pathway
A20
A20 loss
NF-κB pathway
IRF-4
Interferon pathway
Death
Akt inhibitors
Akt
Bortezomib
Lenalidomide
Everolimus Temsirolimus
mTOR
Survival

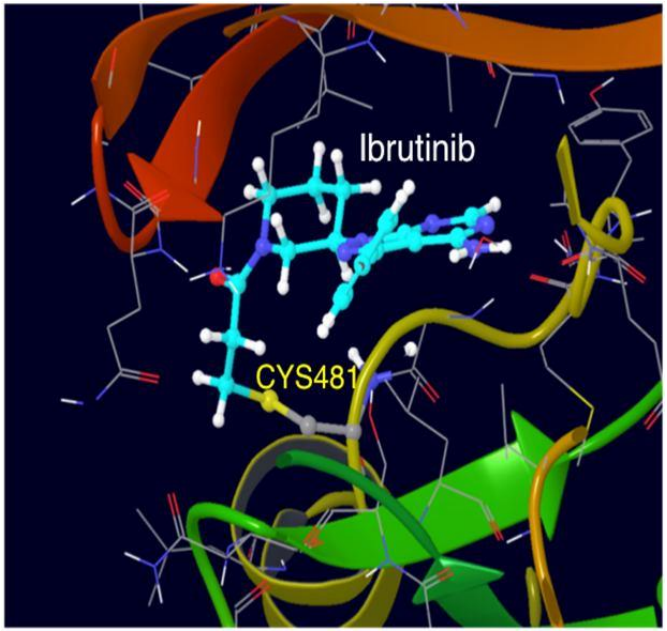
Bruton's Tyrosine Kinase (BTK):
A Critical Kinase for Lymphoma Cell Survival and Proliferation



- **Bruton's tyrosine kinase (BTK) is an essential element of the BCR signaling pathway (Niiro, NRI 2002)**
- **Inhibitors of BTK block BCR signaling and induce apoptosis**
- **BTK also acts downstream of certain chemokine receptors impacting integrin molecules that help in promoting egression from the lymph node environment**

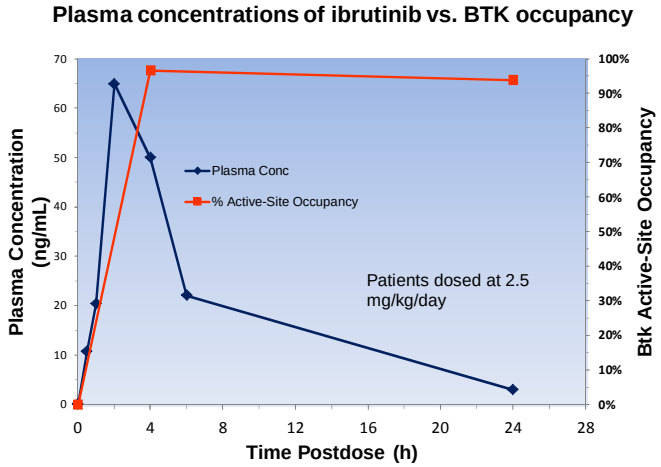
Ibrutinib: A potent BTK inhibitor





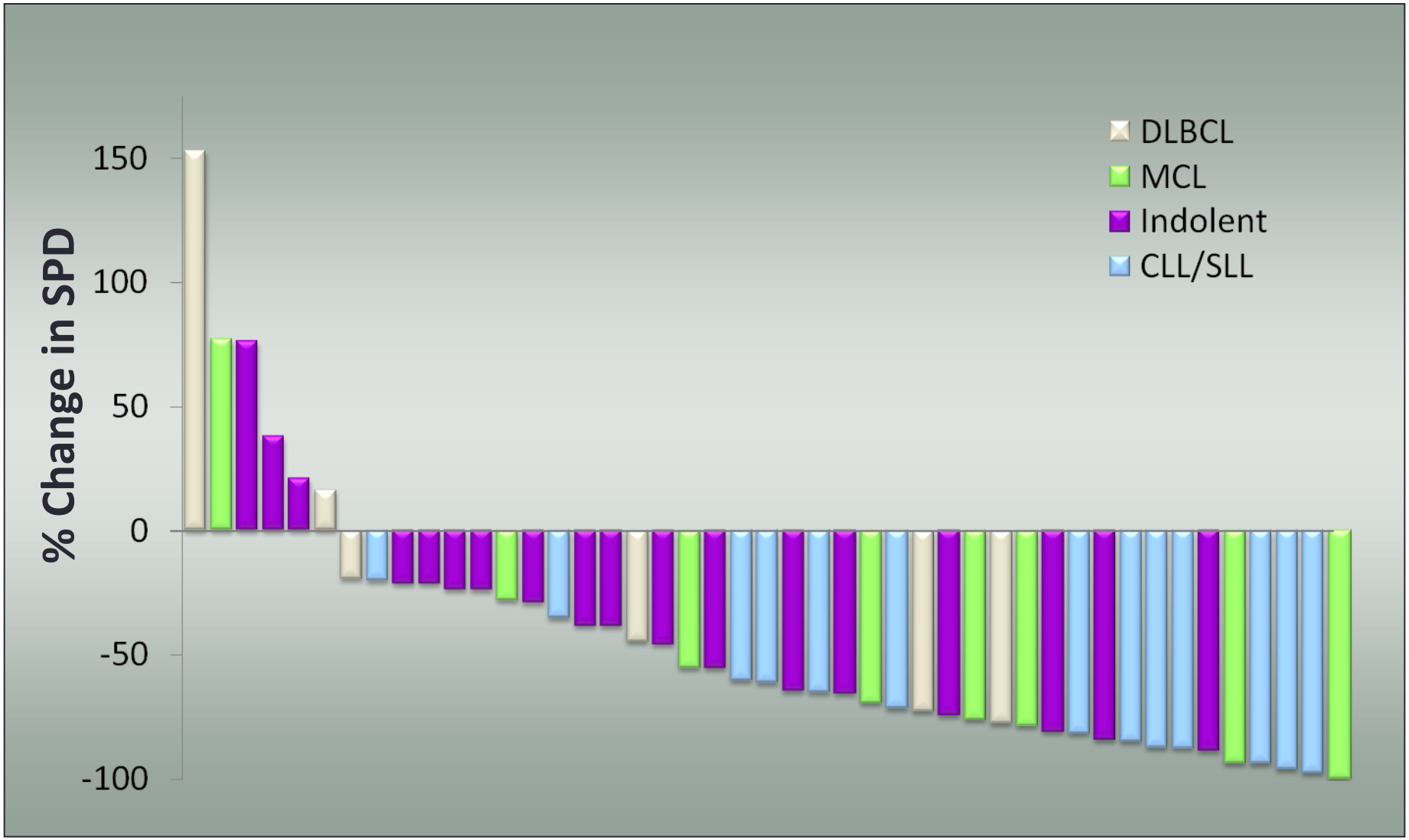
- Ibrutinib (PCI-32765) forms a bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC_{50} = 0.5 nM
- High degree of specificity for hematopoietic cells
- Orally administered once daily dosing until PD or no longer tolerated by patient

Durable Btk inhibition, despite rapid drug elimination



Advani et al. J Clin Oncol 28:15s, 2010 (suppl; abstr 8012)

Phase I PCI-32765



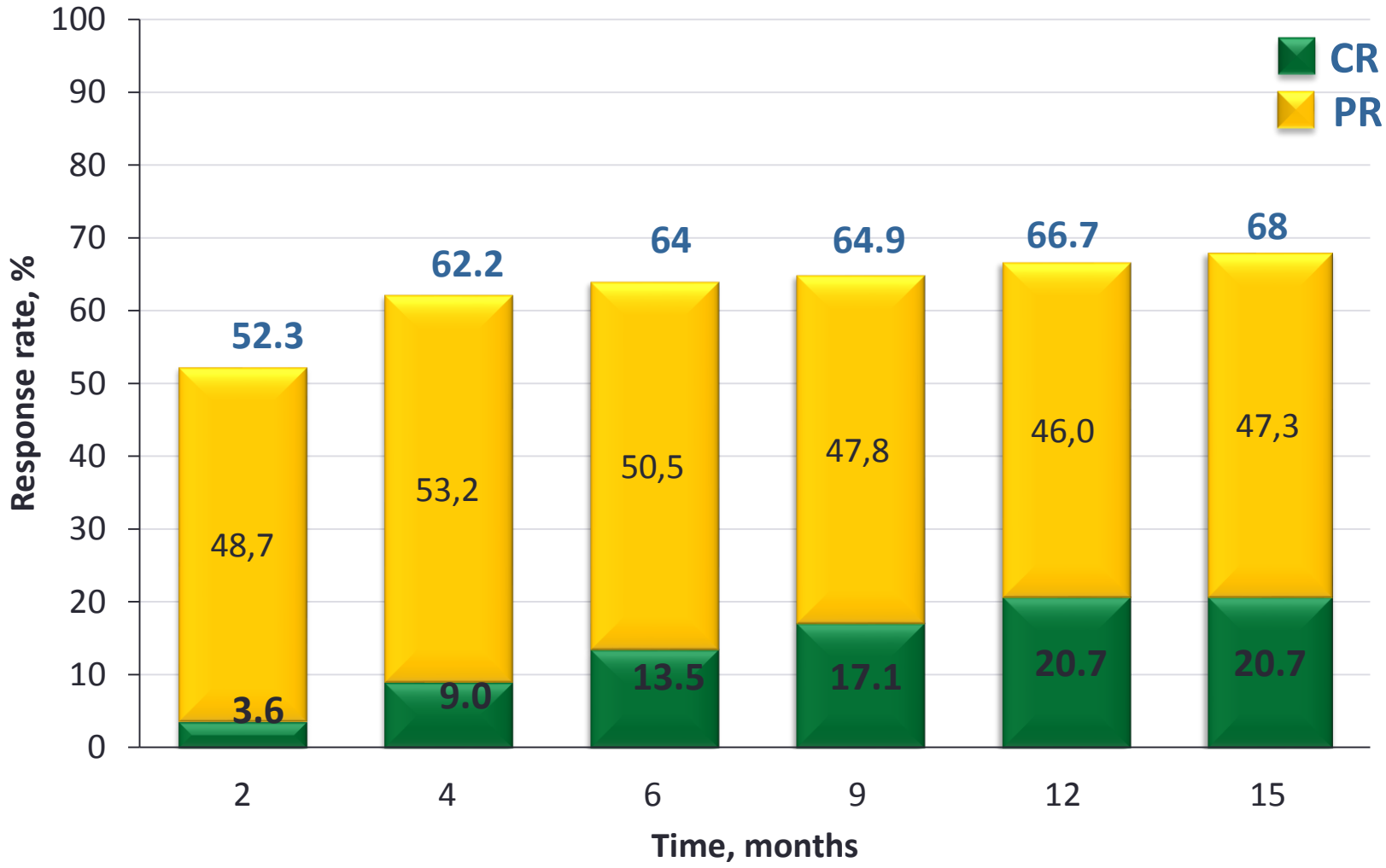
The NEW ENGLAND JOURNAL of MEDICINE

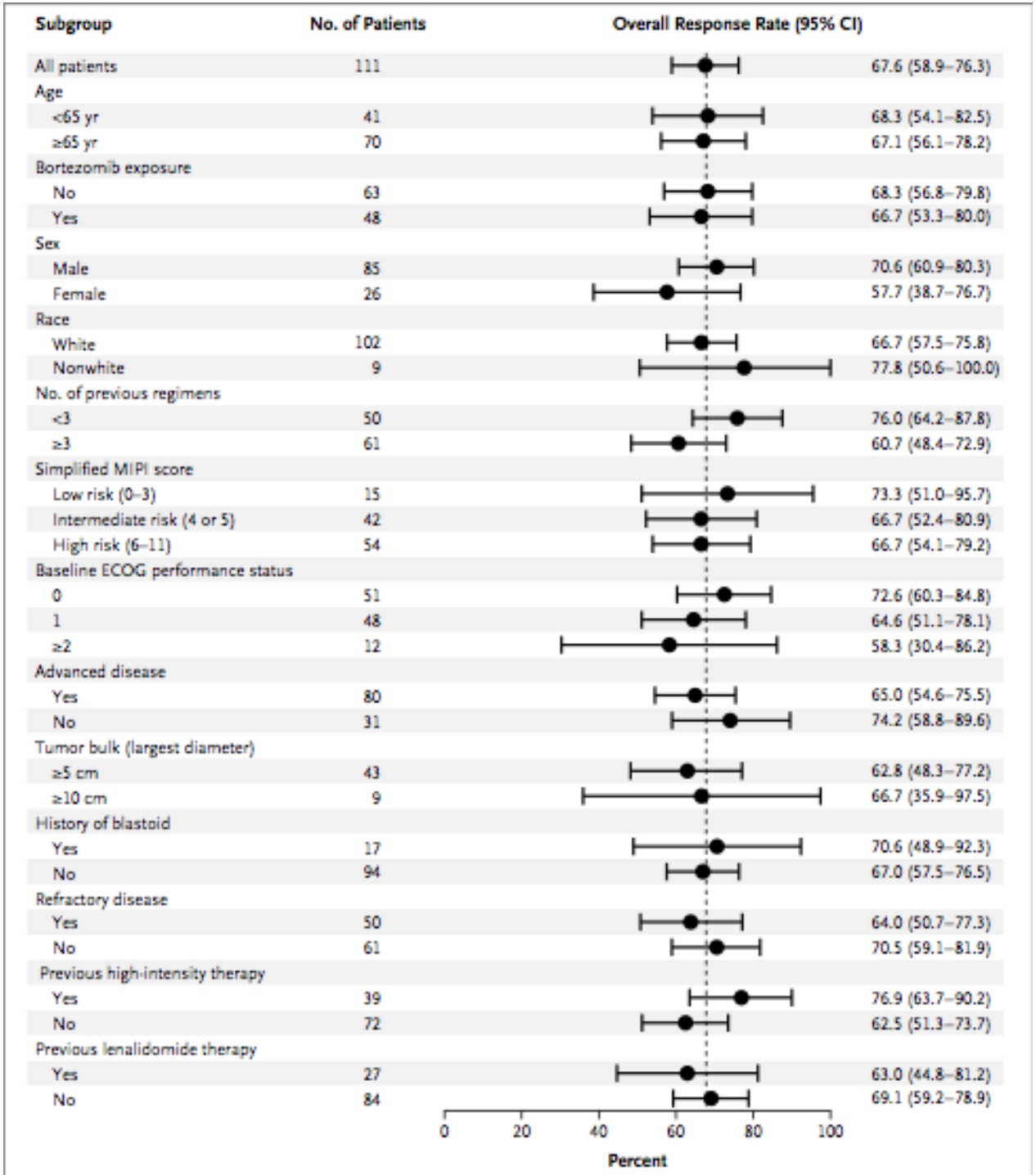
ESTABLISHED IN 1812 AUGUST 8, 2013 VOL. 369 NO. 6

Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

Michael L. Wang, M.D., Simon Rule, M.D., Peter Martin, M.D., Andre Goy, M.D., Rebecca Auer, M.D., Ph.D., Brad S. Kahl, M.D., Wojciech Jurczak, M.D., Ph.D., Ranjana H. Advani, M.D., Jorge E. Romaguera, M.D., Michael E. Williams, M.D., Jacqueline C. Barrientos, M.D., Ewa Chmielowska, M.D., John Radford, M.D., Stephan Stilgenbauer, M.D., Martin Dreyling, M.D., Wieslaw Wiktor Jedrzejczak, M.D., Peter Johnson, M.D., Stephen E. Spurgeon, M.D., Lei Li, Ph.D., Liang Zhang, M.D., Ph.D., Kate Newberry, Ph.D., Zhishuo Ou, M.D., Nancy Cheng, M.S., Bingliang Fang, Ph.D., Jesse McGreivy, M.D., Fong Clow, Sc.D., Joseph J. Buggy, Ph.D., Betty Y. Chang, Ph.D., Darrin M. Beaupre, M.D., Ph.D., Lori A. Kunkel, M.D., and Kristie A. Blum, M.D.

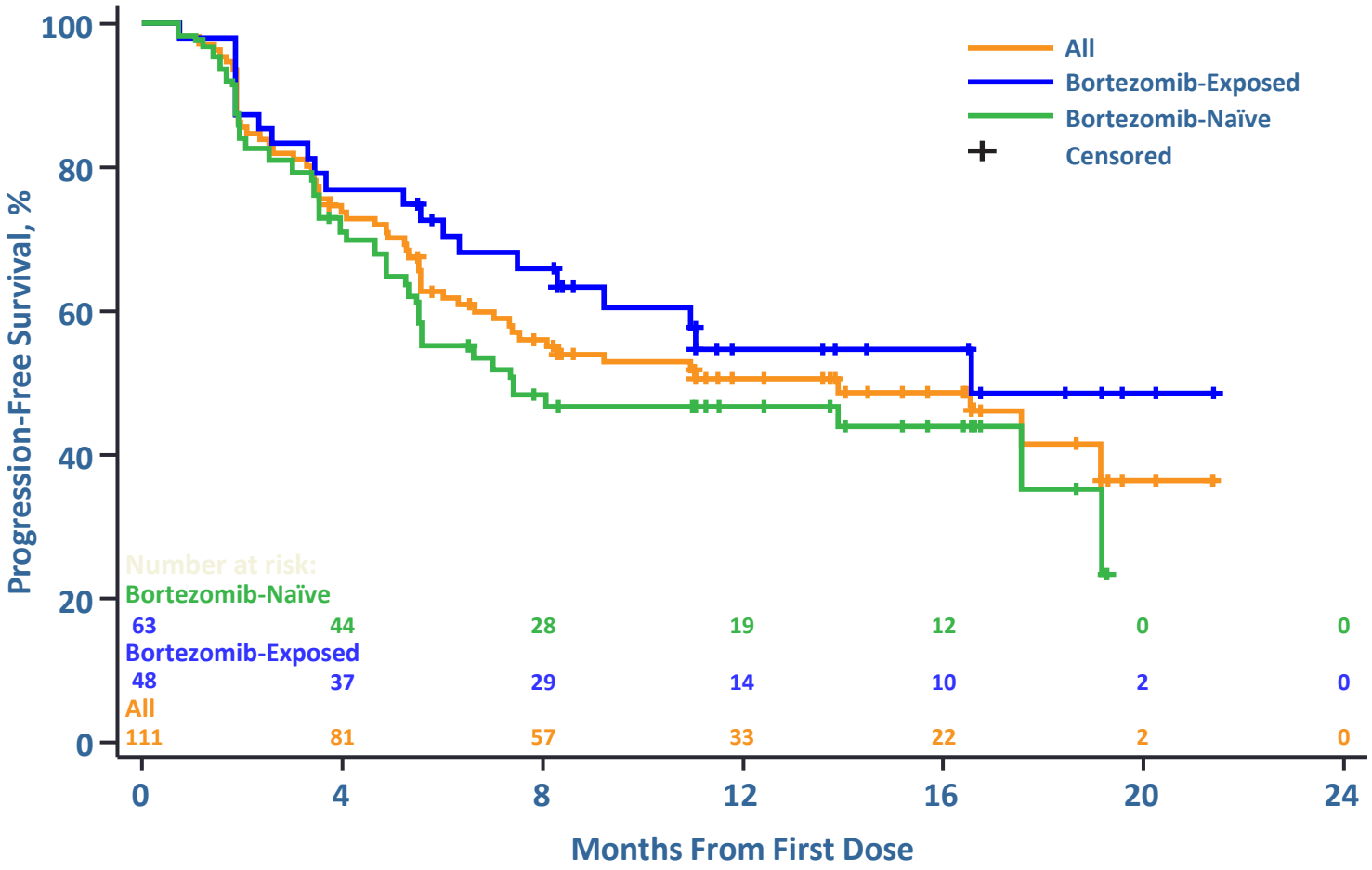
PCYC-1104-CA Phase 2 Study of Ibrutinib in R/R MCL




Subgroup
No. of Patients
Overall Response Rate (95% CI)
All patients 111 67.6 (58.9–76.3)
Age
<65 yr 41 68.3 (54.1–82.5)
≥65 yr 70 67.1 (56.1–78.2)
Bortezomib exposure
No 63 68.3 (56.8–79.8)
Yes 48 66.7 (53.3–80.0)
Sex
Male 85 70.6 (60.9–80.3)
Female 26 57.7 (38.7–76.7)
Race
White 102 66.7 (57.5–75.8)
Nonwhite 9 77.8 (50.6–100.0)
No. of previous regimens
<3 50 76.0 (64.2–87.8)
≥3 61 60.7 (48.4–72.9)
Simplified MIPI score
Low risk (0–3) 15 73.3 (51.0–95.7)
Intermediate risk (4 or 5) 42 66.7 (52.4–80.9)
High risk (6–11) 54 66.7 (54.1–79.2)
Baseline ECOG performance status
0 51 72.6 (60.3–84.8)
1 48 64.6 (51.1–78.1)
≥2 12 58.3 (30.4–86.2)
Advanced disease
Yes 80 65.0 (54.6–75.5)
No 31 74.2 (58.8–89.6)
Tumor bulk (largest diameter)
≥5 cm 43 62.8 (48.3–77.2)
≥10 cm 9 66.7 (35.9–97.5)
History of blastoid
Yes 17 70.6 (48.9–92.3)
No 94 67.0 (57.5–76.5)
Refractory disease
Yes 50 64.0 (50.7–77.3)
No 61 70.5 (59.1–81.9)
Previous high-intensity therapy
Yes 39 76.9 (63.7–90.2)
No 72 62.5 (51.3–73.7)
Previous lenalidomide therapy
Yes 27 63.0 (44.8–81.2)
No 84 69.1 (59.2–78.9)
0 20 40 60 80 100
Percent

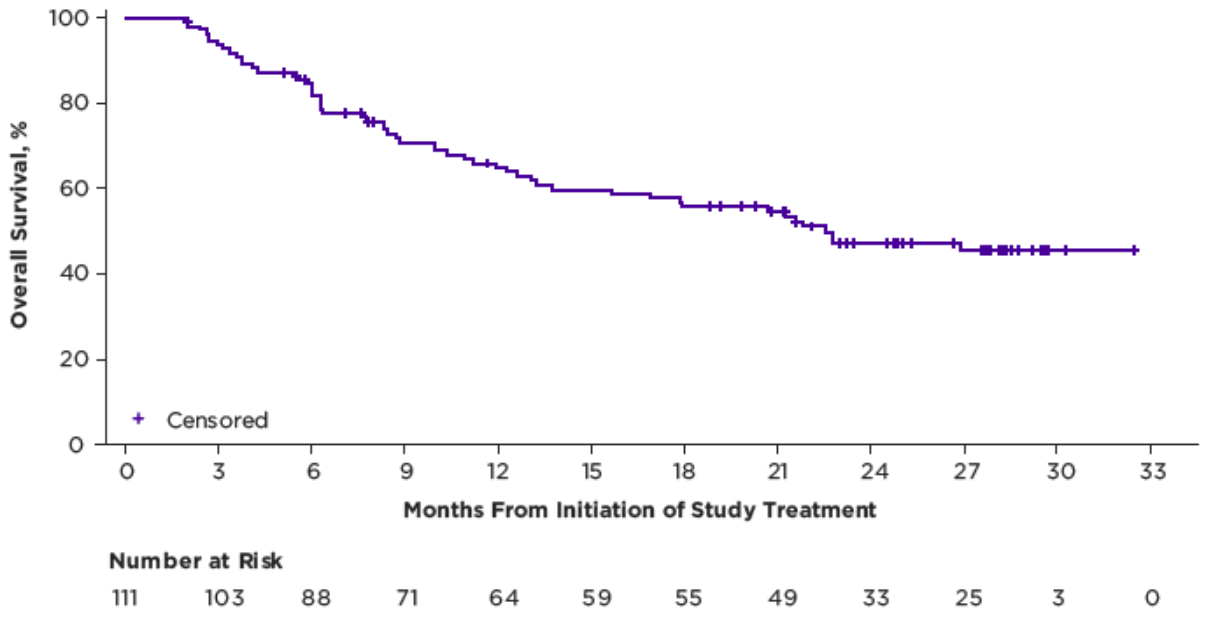
PCYC-1104-CA Phase 2 Study of Ibrutinib in R/R MCL

Kaplan-Meier progression-free survival (n=111)

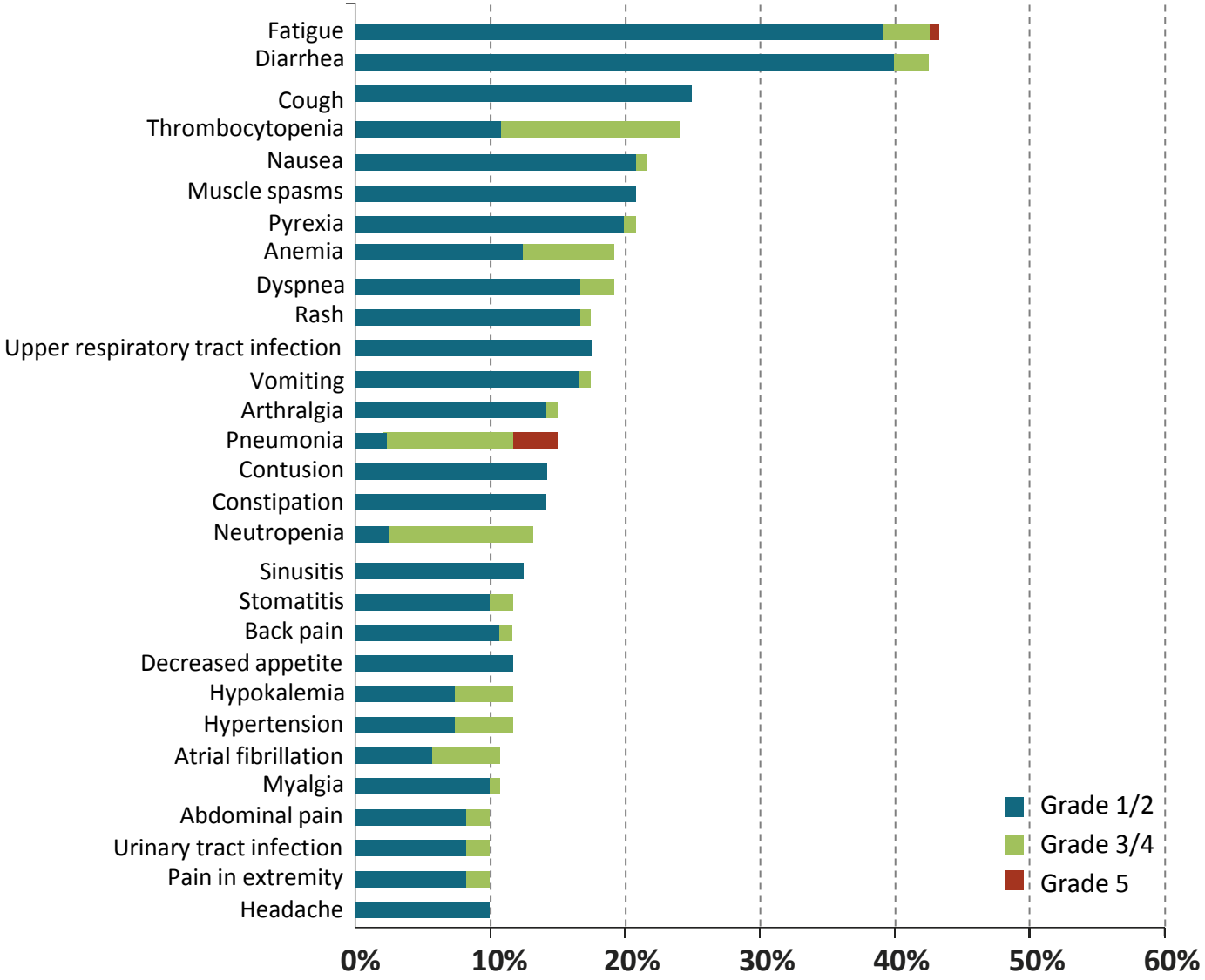


- Estimated Median PFS (CI 95%) 13.9 months (7.0, NE)

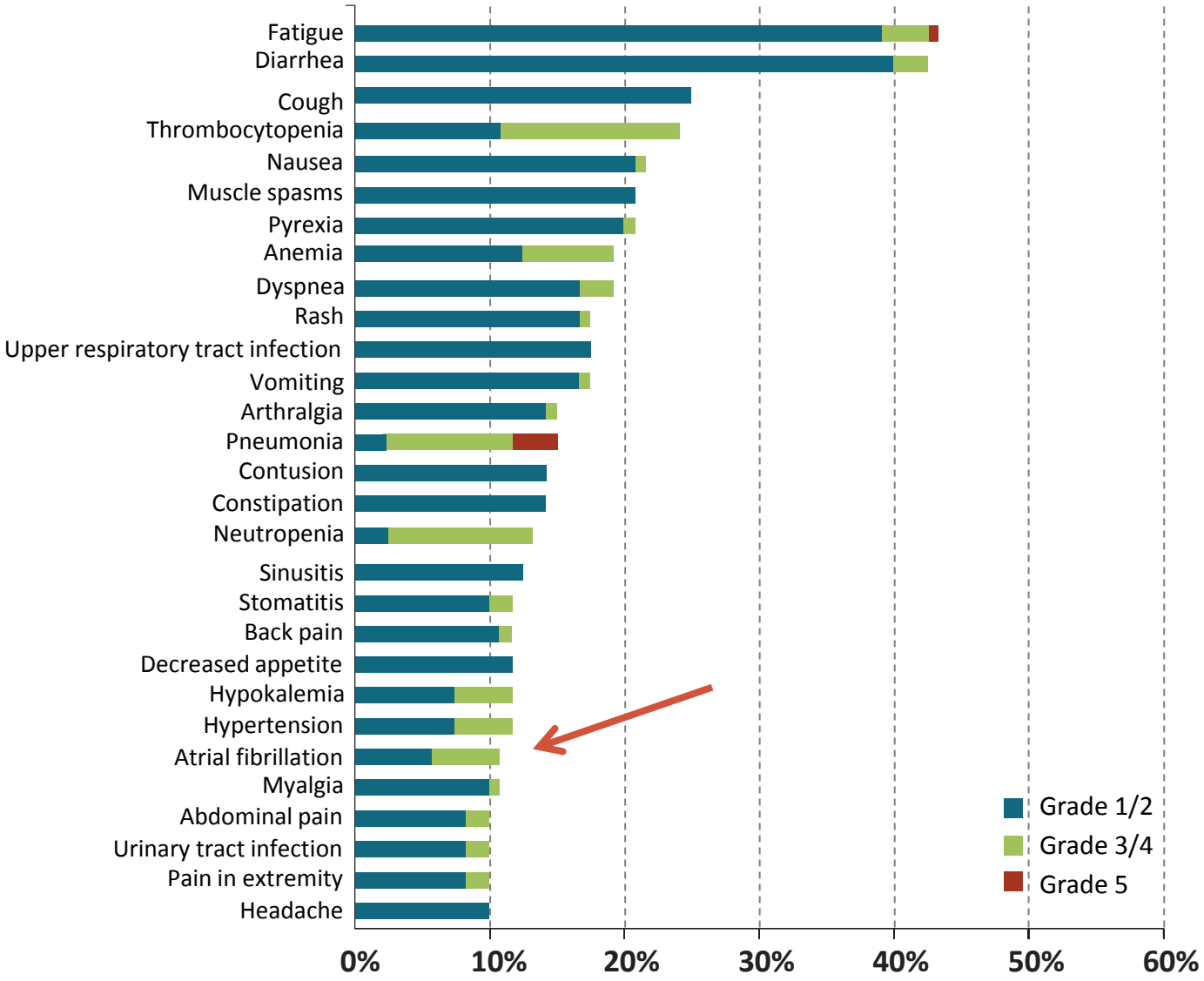
Long term follow up



Wang *et al* Blood 2015



SPARK trial Wang et al ASH 2015



SPARK trial Wang et al ASH 2015

THROMBOSIS AND HEMOSTASIS

Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions

Marie Levade,[1,2] Elodie David,[2] Cédric Garcia,[2] Pierre-Alexandre Laurent,[1] Sarah Cadot,[2] Anne-Sophie Michallet,[3] Jean-Claude Bordet,[4] Constantine Tam,[5] Pierre Sié,[1,2] Loïc Ysebaert,[6] and Bernard Payrastre[1,2]

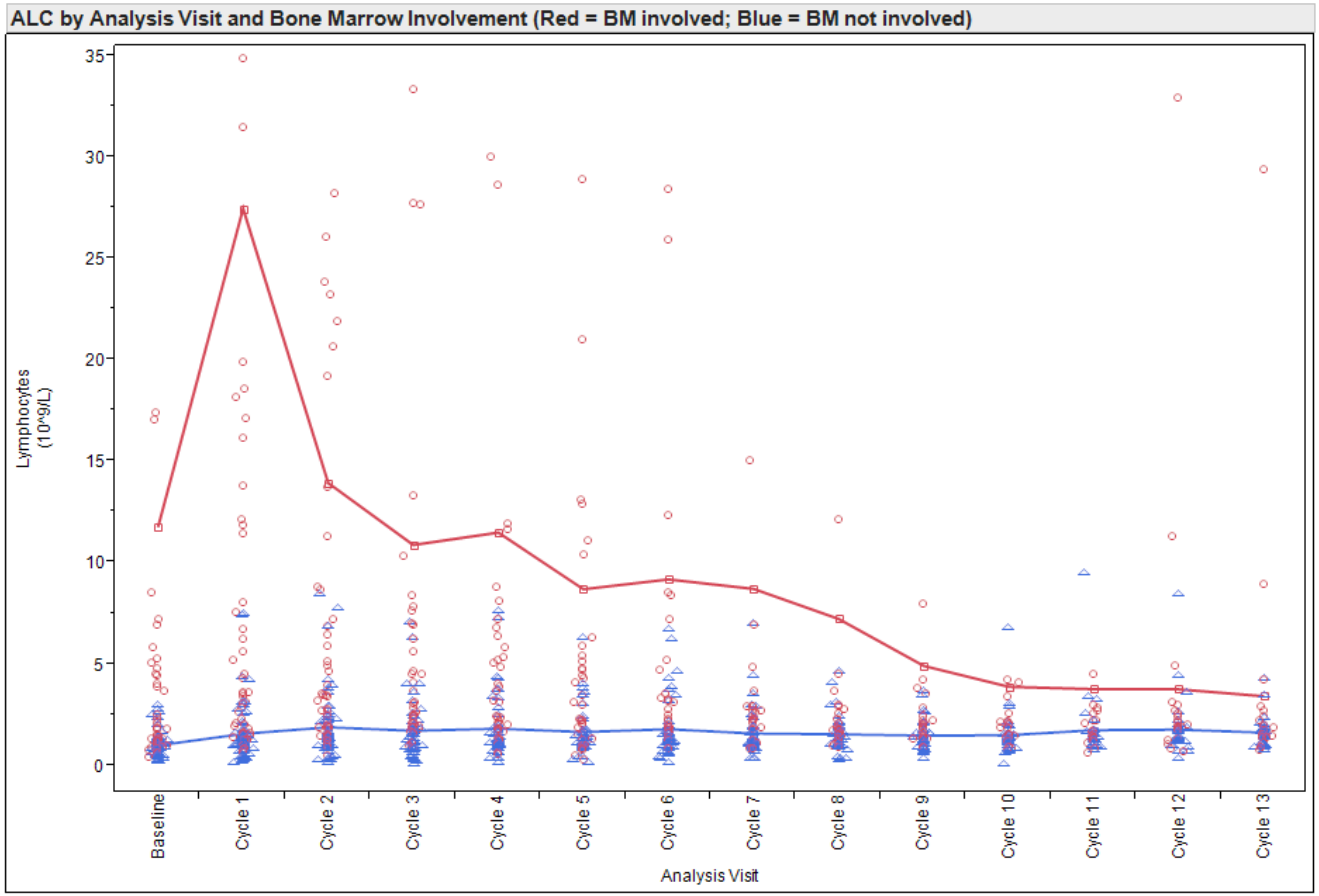
[1]INSERM, U1048 and Université Toulouse 3, Institut des Maladies Métaboliques et Cardiovasculaires, Toulouse, France; [2]Laboratoire d'Hématologie Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [3]Service d'Hématologie, Centre Hospitalier Lyon Sud, Pierre Bénite, France; [4]Laboratoire d'Hémostase, Centre Hospitalier Universitaire Hôpital Edouard Herriot, Lyon, France; [5]Department of Hematology, Peter MacCallum Cancer Center, East Melbourne, VIC, Australia; and [6]Service d'Hématologie Institut Universitaire du Cancer de Toulouse-Oncopôle, Toulouse, France

Key Points

- Ibrutinib affects collagen and VWF-mediated platelet activation.
- The bleeding diathesis correlates with defects in collagen-induced platelet aggregation and firm adhesion on VWF at arterial shear rate.

The oral Bruton's tyrosine kinase inhibitor, ibrutinib, has recently demonstrated high efficiency in patients with relapsed B-cell malignancies. Occurrence of bleeding events has been reported in a subgroup of ibrutinib-treated patients. We demonstrate that ibrutinib selectively inhibits platelet signaling and functions downstream of the collagen receptor glycoprotein VI and strongly affects firm platelet adhesion on von Willebrand factor (VWF) under arterial flow. A longitudinal study of 14 patients indicated a correlation between occurrence of bleeding events and decreased platelet aggregation in response to collagen in platelet-rich plasma and firm adhesion on VWF under arterial flow. The addition of 50% untreated platelets was sufficient to efficiently reverse the effects of ibrutinib, and platelet functions recovered after treatment interruption as physiological platelet renewal occurred. These data have important clinical implications and provide a basis for hemostasis management during ibrutinib treatment. (*Blood*. 2014;124(26):3991-3995)

Lymphocytosis and Ibrutinib in MCL



Furtado *et al.* in press BJHaem

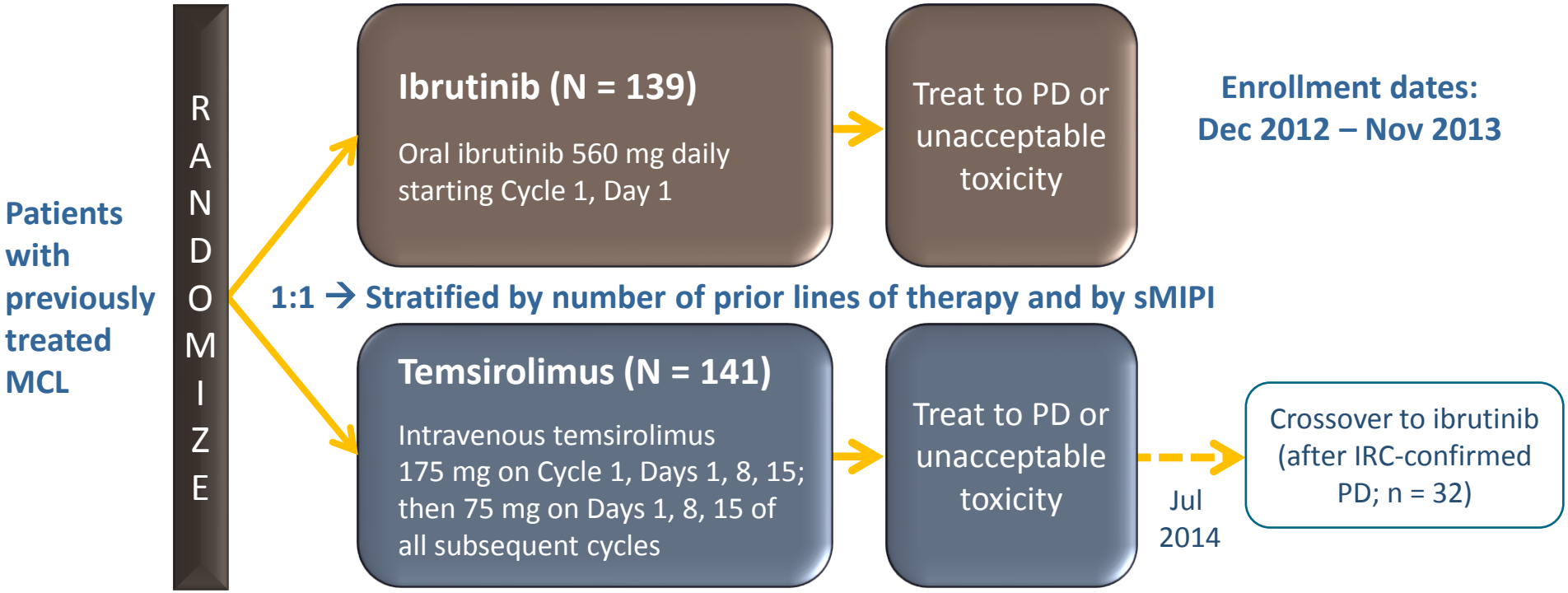
Ibrutinib Versus Temsirolimus: Results From a Phase 3, International, Randomized, Open-Label, Multicenter Study in Patients With Previously Treated Mantle-Cell Lymphoma

Simon Rule,[1*] Wojciech Jurczak,[2*] Mats Jerkeman,[3*] Rodrigo Santucci Silva,[4] Chiara Rusconi,[5*] Marek Trneny,[6*] Fritz Offner,[7*] Dolores Caballero,[8*] Cristina Joao,[9*] Mathias Witzens-Harig,[10*] Georg Hess,[11*] Isabelle Bence-Bruckler,[12] Seok-Goo Cho,[13] John Bothos,[14] Jenna D. Goldberg,[14] Christopher Enny,[14] Shana Traina,[14] Sriram Balasubramanian,[15] Nibedita Bandyopadhyay,[14] Steven Sun,[14] Aleksandra Rizo,[14] Jessica Vermeulen,[16] and Martin Dreyling[17*]

[1]Derriford Hospital, Plymouth, UK; [2]Jagiellonian University, Krakow, Poland; [3]Skånes University Hospital, Lund University, Lund, Sweden; [4]Instituto de Ensino e Pesquisa Sao Lucas, Sao Paulo, Brazil; [5]Niguarda Cancer Center, Niguarda Hospital, Milan, Italy; [6]Charles University General Hospital, Prague, Czech Republic; [7]University Hospital Ghent, Ghent, Belgium; [8]Hospital Universitario de Salamanca, Salamanca, Spain; [9]Champalimaud Centre for the Unknown, Lisbon, Portugal; [10]University Hospital Heidelberg, Heidelberg, Germany; [11]University Medical School of the Johannes Gutenberg University, Mainz, Germany; [12]The Ottawa Hospital, Ottawa, ON, Canada; [13]Seoul St. Mary's Hospital, Seoul, Korea; [14] Janssen Research & Development, Raritan, NJ, USA; [15]Janssen Research & Development, Spring House, PA, USA; [16]Janssen Research & Development, Leiden, The Netherlands; [17]Klinikum der Universität München, Munich, Germany

*Member of the European MCL Network.

MCL3001 (RAY): Phase 3 Open-Label Study



Primary end point:

- IRC-assessed PFS

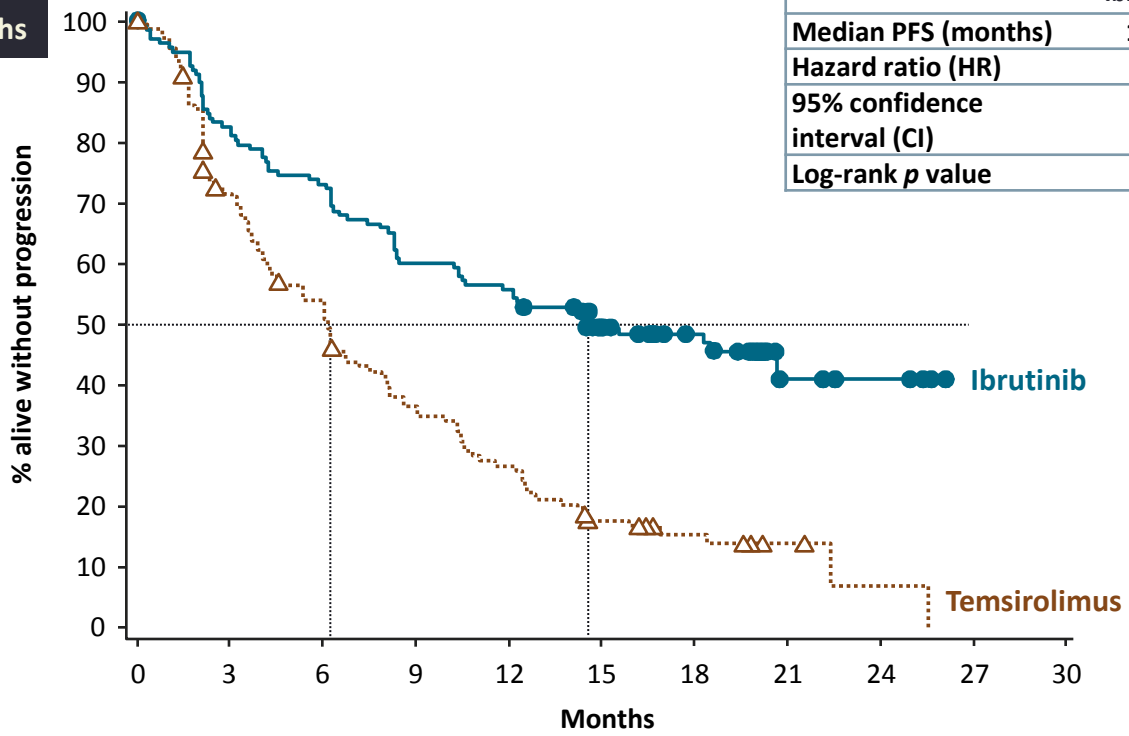
Secondary end points included:

- IRC-assessed ORR (CR + PR)
- Overall survival
- Duration of response
- Time to next treatment
- Safety
- Patient-reported outcomes (FACT-Lym)

Primary End Point: IRC-Assessed PFS

ITT population
Median follow-up: 20 months

	Ibrutinib	Temsirolimus
Median PFS (months)	14.6	6.2
Hazard ratio (HR)	0.43	
95% confidence interval (CI)	0.32-0.58	
Log-rank *p* value	< 0.0001	

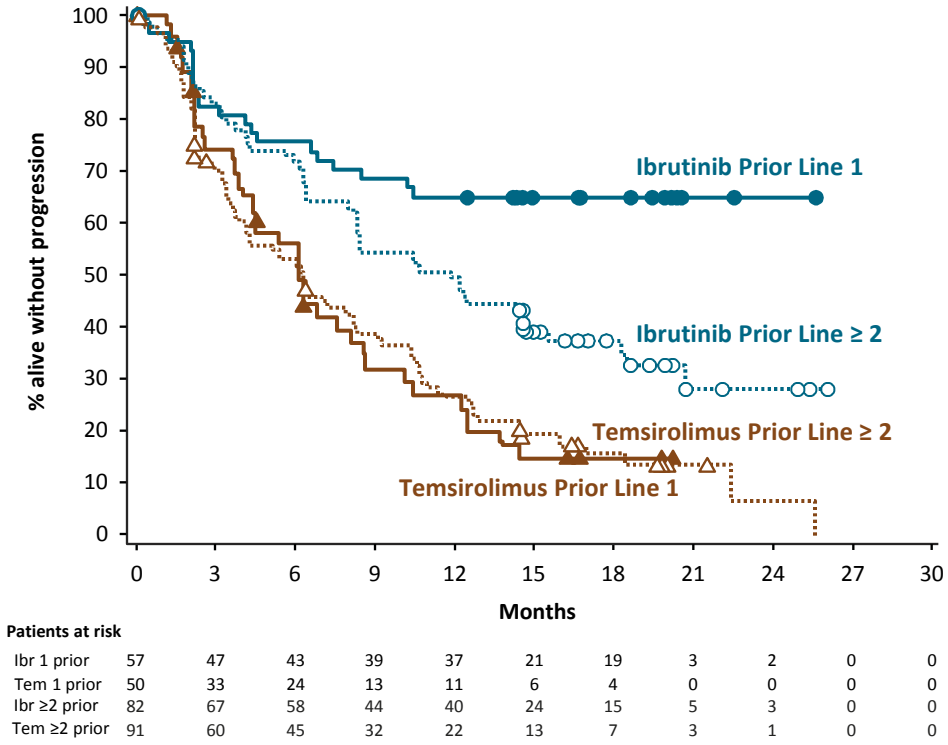


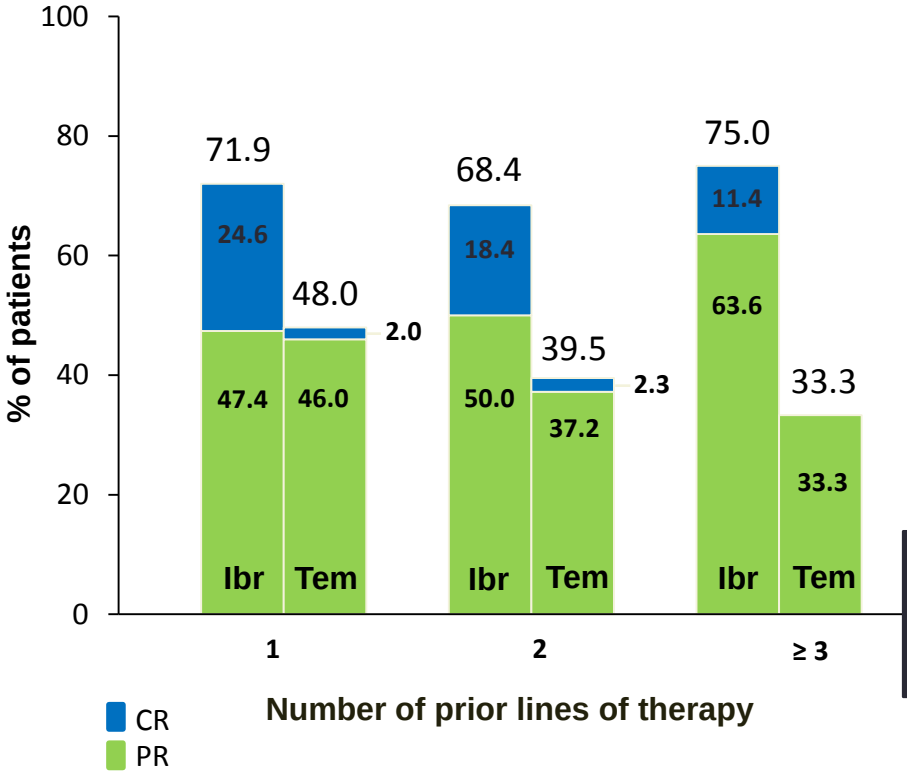
Patients at risk

Ibrutinib	139	114	101	83	77	45	34	8	5	0	0
Temsirolimus	141	93	69	45	33	19	11	3	1	0	0

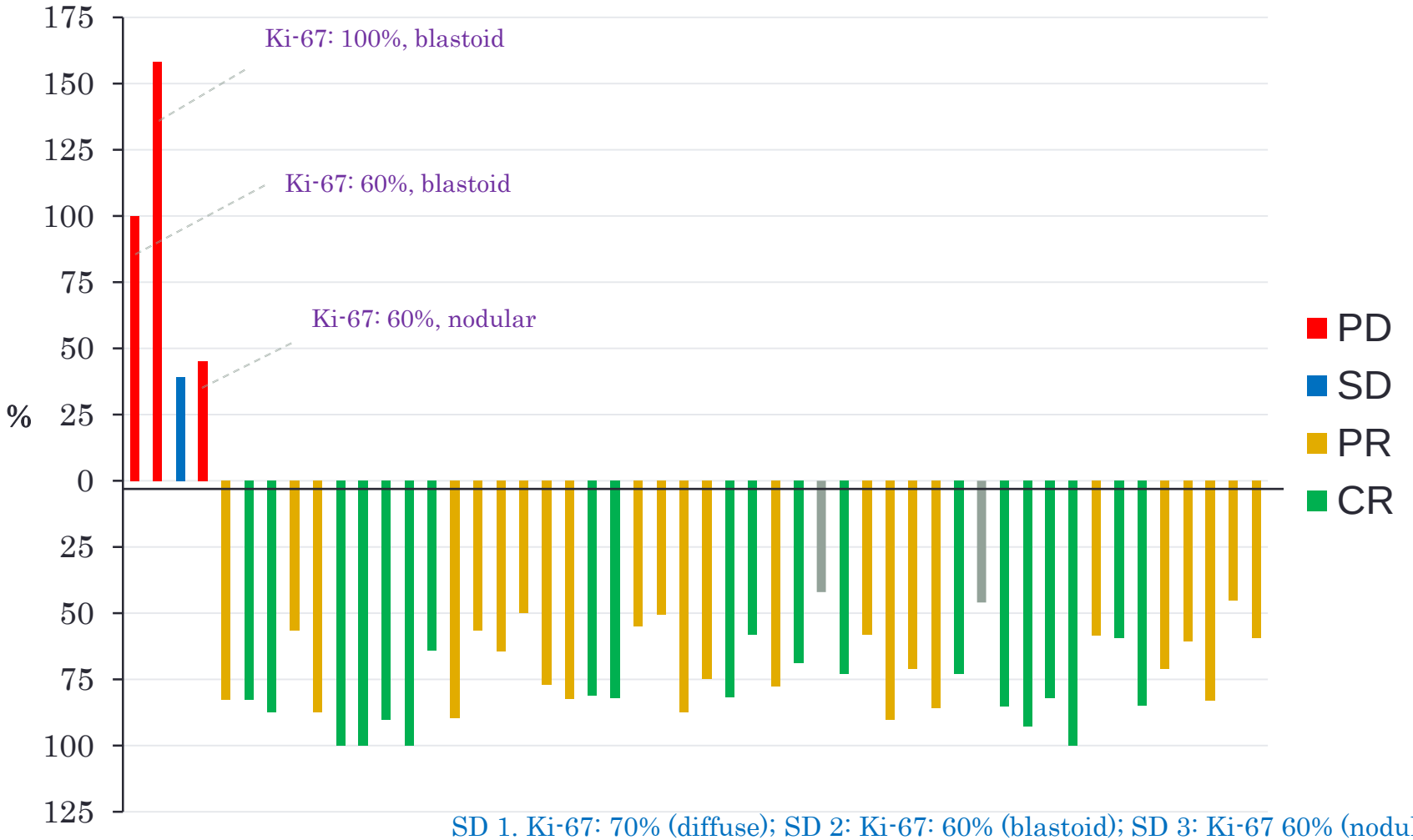
- At a 2-year landmark, the PFS rate was 41% for ibrutinib versus 7% for temsirolimus
- Investigator-assessed HR for ibrutinib versus temsirolimus was 0.43 (95% CI, 0.32-0.58)

PFS and ORR: Outcomes by Number of Lines of Prior Therapy





Ibrutinib + Rituximab



SD 1. Ki-67: 70% (diffuse); SD 2: Ki-67: 60% (blastoid); SD 3: Ki-67 60% (nodular)

Wang et al Lancet Oncology 2015

ENRICH – NCRI MULTICENTRE RANDOMISED OPEN LABEL PHASE II/III TRIAL OF RITUXIMAB & IBRUTINIB *VS* RITUXIMAB & CHEMOTHERAPY IN ELDERLY MANTLE CELL LYMPHOMA

ENRICH

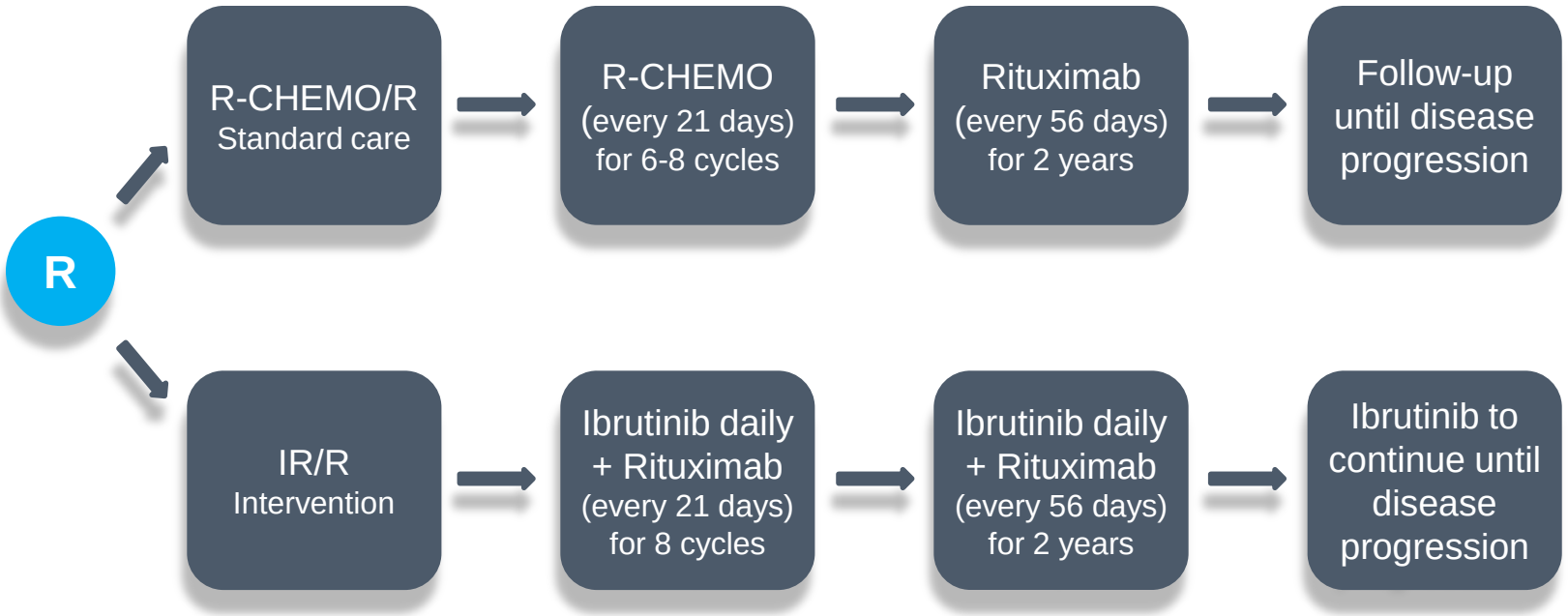
Plymouth Hospitals NHS
NHS Trust

UKCRN
UK Clinical Research Network

CANCER RESEARCH UK

PLYMOUTH UNIVERSITY PENINSULA CLINICAL TRIALS UNIT

ENRICH – NCRI multicentre Randomised open label phase III trial of Rituximab & Ibrutinib *vs* Rituximab & CHemotherapy in Elderly mantle cell lymphoma



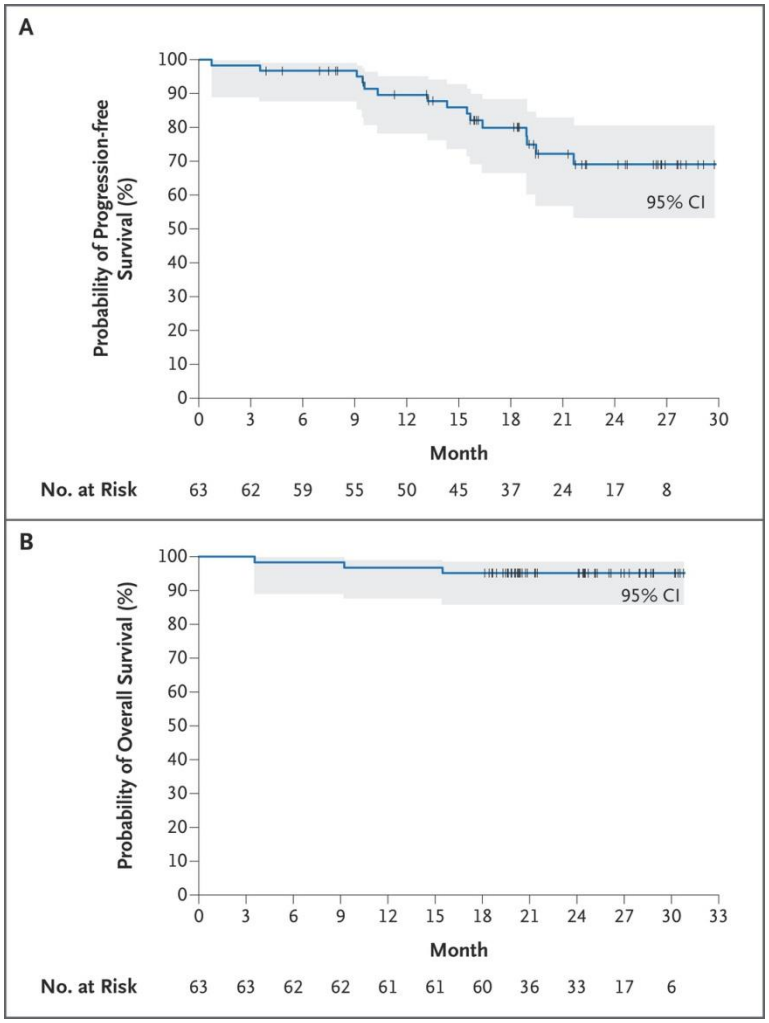
CI S Rule

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

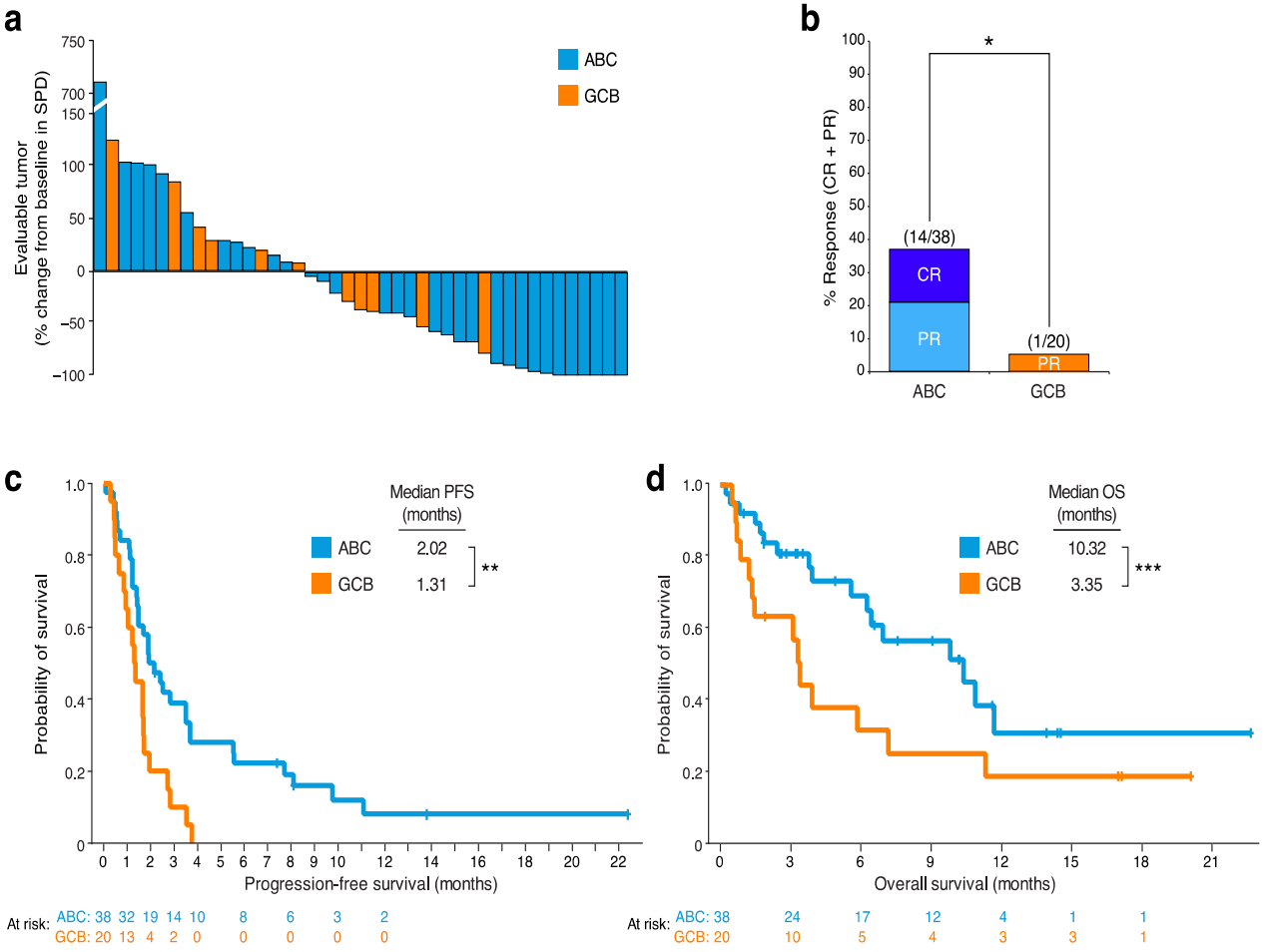
Steven P. Treon, M.D., Ph.D, Christina K. Tripsas, M.A., Kirsten Meid, M.P.H., Diane Warren, B.S., Gaurav Varma, M.S.P.H., Rebecca Green, B.S., Kimon V. Argyropoulos, M.D., Guang Yang, Ph.D., Yang Cao, M.D., Lian Xu, M.S., Christopher J. Patterson, M.S., Scott Rodig, M.D., Ph.D., James L. Zehnder, M.D., Jon C. Aster, M.D., Ph.D., Nancy Lee Harris, M.D., Sandra Kanan, M.S., Irene Ghobrial, M.D., Jorge J. Castillo, M.D., Jacob P. Laubach, M.D., Zachary R. Hunter, Ph.D., Zeena Salman, B.A., Jianling Li, M.S., Mei Cheng, Ph.D., Fong Clow, Sc.D., Thorsten Graef, M.D., M. Lia Palomba, M.D., and Ranjana H. Advani, M.D.



Treon SP et al. N Engl J Med 2015;372:1430-1440.

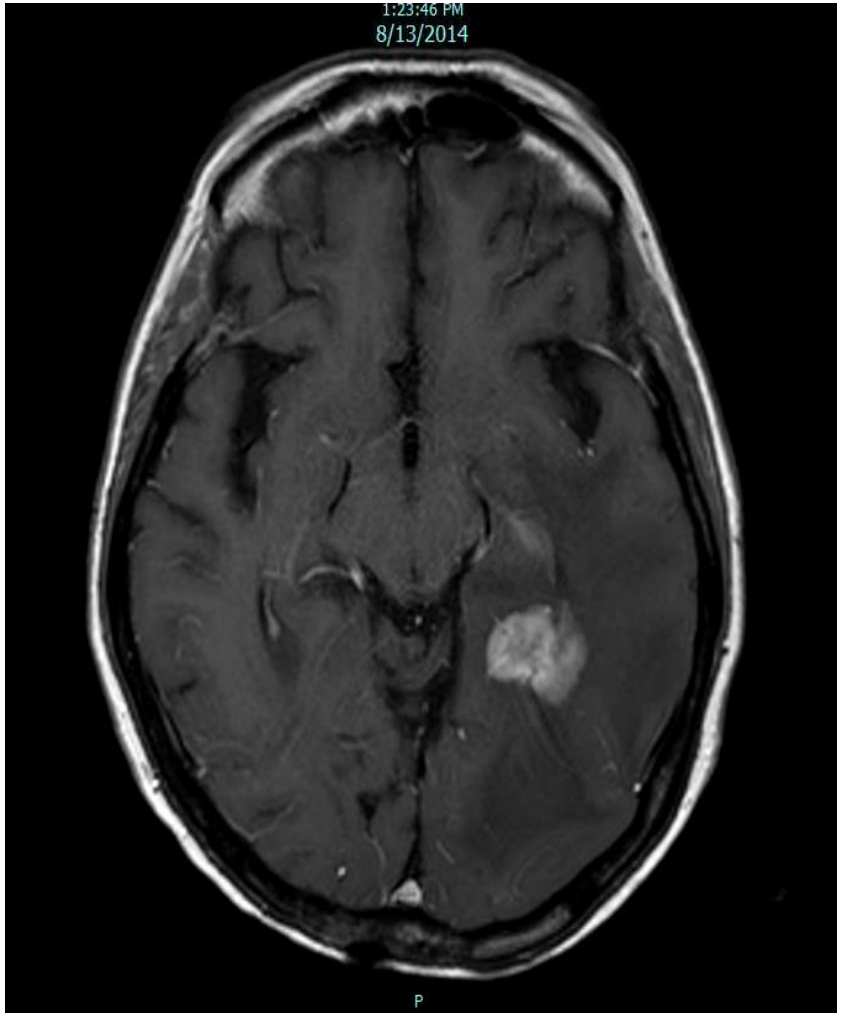
Ibrutinib in ABC DLBCL

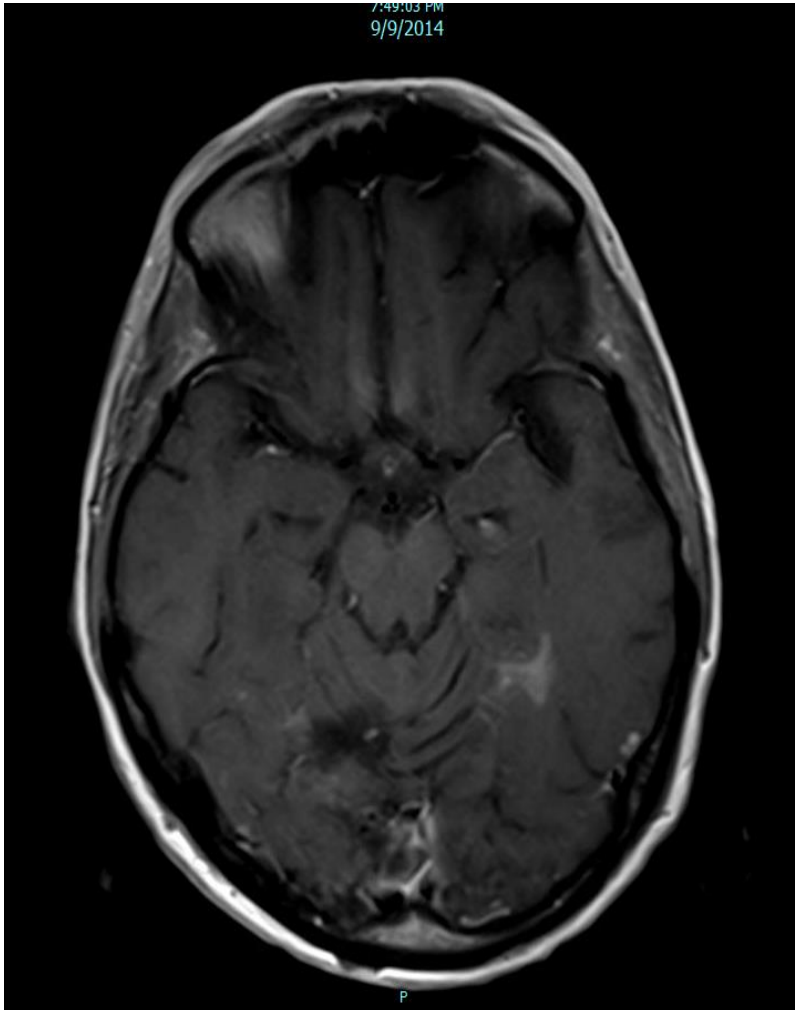
Figure 1



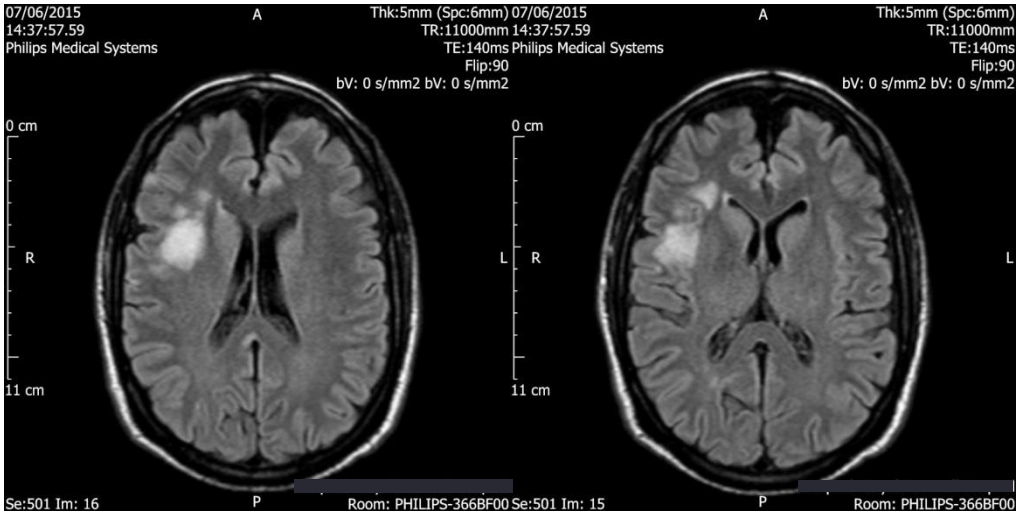
Wilson et al Nat Med 2015

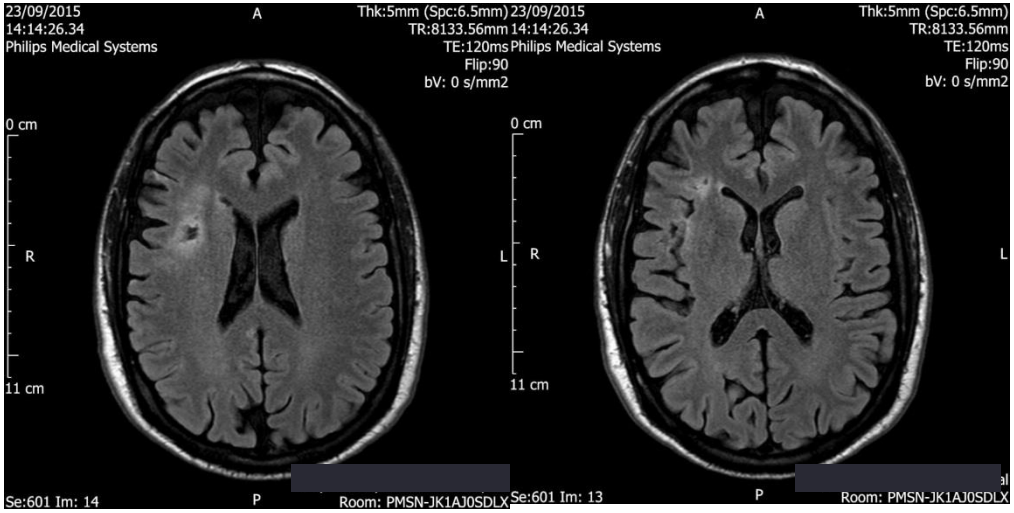
Patient 1: pre and post ibrutinib alone



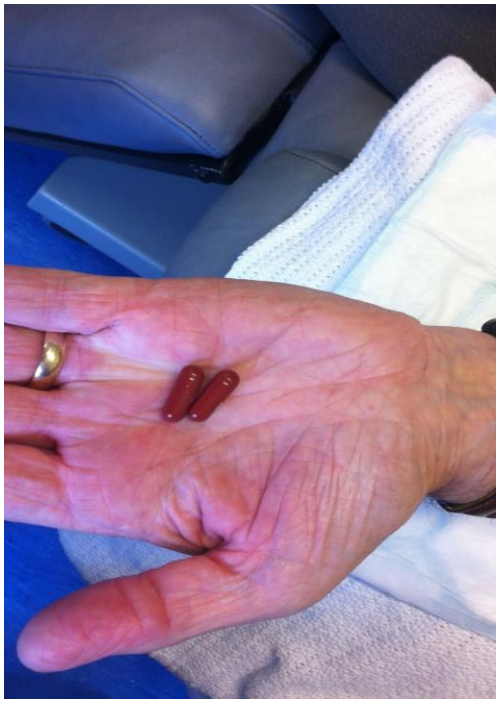


Ibrutinib for CNS mantle cell NHL





Next generation BTKi's



ONO 4059

ACP 196

Class I PI3K isoforms

Class I PI3K isoform	Cellular expression	Primary physiological role
Alpha (α)	Broad	Insulin signaling and angiogenesis
Beta (β)	Broad	Platelet function
Gamma (γ)	Leukocytes	Neutrophil and T-cell function
Delta (δ)	Leukocytes	B-cell signaling, development, and survival

Okkenhaug, Vanhaesebroeck. *Nat Rev Immunol* 2003; 3: 317-330

Clinical Activity in B-cell Lymphomas

Population	Treated / Evaluable	Best Response, n (%)						Time to Response Median Mo. (range)
		Overall Response Rate	CR	PR	MR*	SD	PD	
iNHL	26 / 19	13 (68)	3 (16)	10 (53)	1 (5)	3 (16)	2 (11)	1.8 (1.7 - 4.1)
MCL	9 / 6	4 (67)	1 (17)	3 (50)	n/a	1 (17)	1 (17)	1.8 (1.6 - 1.9)
HL	3 / 3	1 (33)	1 (33)	0	n/a	1 (33)	1 (33)	1.7
aNHL	13 / 10	0	0	0	n/a	4 (40)	6 (60)	n/a

- Responses observed (including CRs) in indolent, mantle and Hodgkin lymphomas
- Responses occurred early: 16/18 (89%) by first assessment (~2 months)

*MR = Minor response for Waldenström's

Follicular NHL

- PI3Kinase inhibition remains leading pathway target
- Idelalisib most mature data, but
  - Copanlisib
  - Duvelisib
  - TG Therapeutics
  - Curis Incorporated – novel tagged PI3K / HDACi

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma

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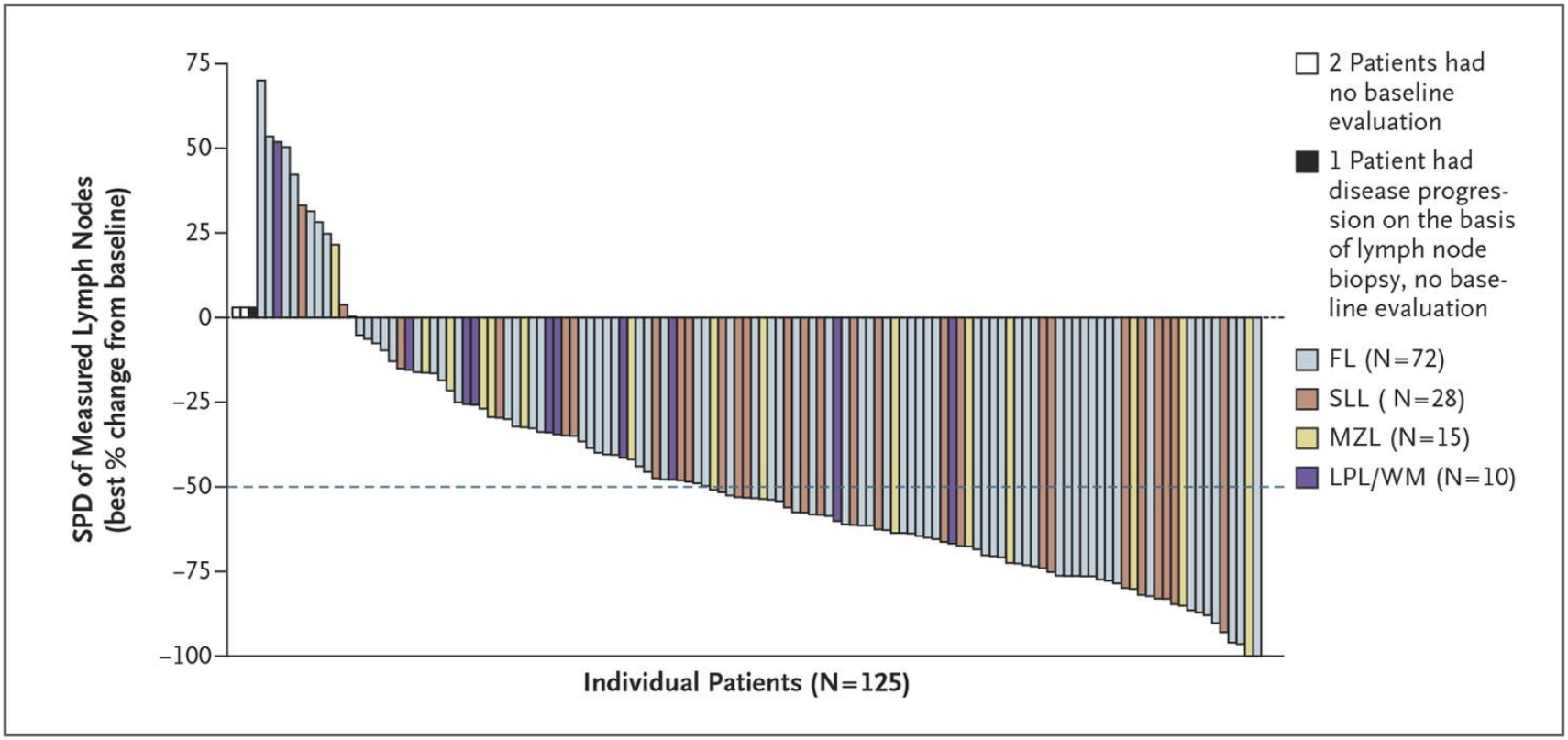

Gopal AK et al. N Engl J Med 2014;370:1008-1018.

Study 101-09: SAEs and AEs Leading to Discontinuation

Serious Adverse Event*, n (%)	
Pyrexia	10 (8.0%)
Pneumonia	8 (6.4%)
Diarrhea	7 (5.6%)
Dehydration	4 (3.2%)
Fever/Neutropenia	4 (3.2%)
Colitis	3 (2.4%)
Acute Renal Failure	3 (2.4%)

*SAE occurring in more than 2 subjects

AE leading to Discontinuation	
Transaminase elevations	4 (3%)
Infections	3 (2%)
Diarrhea	2 (1.6%)
Colitis	2 (1.6%)
Neutropenia	2 (1.6%)
Pneumonia	2 (1.6%)
Pneumonitis	2 (1.6%)
ARDS	1 (0.8%)
Failure to Thrive	1 (0.8%)
Mucositis	1 (0.8%)

and finally …

Combination therapy?

To the editor:

Lenalidomide, idelalisib, and rituximab are unacceptably toxic in patients with relapsed/ refractory indolent lymphoma

Understanding of the tumor microenvironment has led to the development of novel agents for lymphoma, although few studies have combined these as a therapeutic strategy. We report unacceptable

50 and 98) ALT elevations (Figure 1A). All patients had imaging: 2 showed diffuse hypoechogenicity and 1 borderline fatty hepatomegaly. The median time to resolution of ALT and aspartate aminotrans-

Lugano 2015

Combination trial of idelalisib and SYK inhibitor stopped early due to unexpected pneumonitis

12 out of 66 patients with 2 deaths