IBRUTINIB IN NHL

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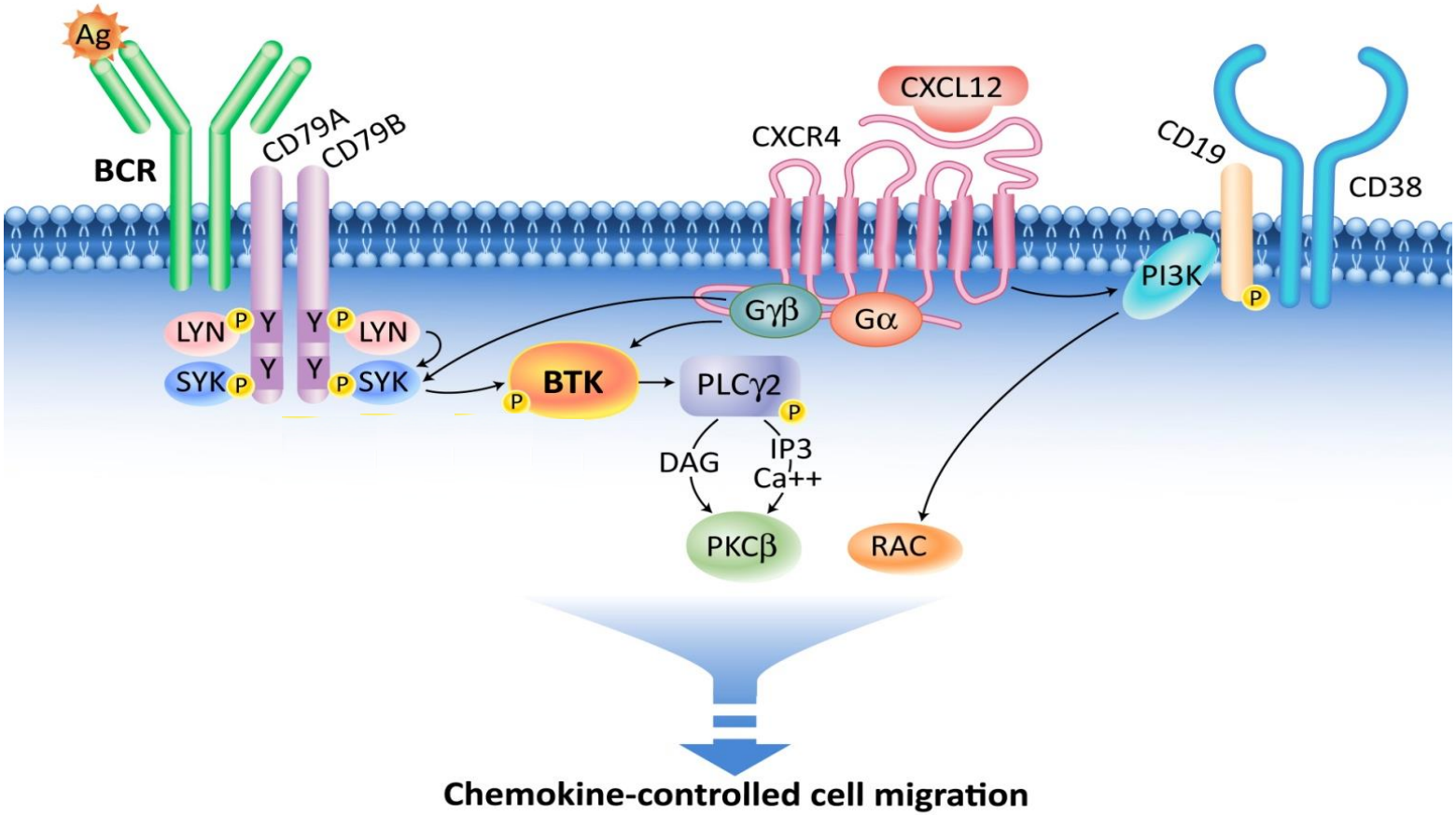
OUTLINE

- BTK Inhibition
- Ibrutinib
- MCL data
  - Single agent
  - Toxicity
- Combination data
- Resistance

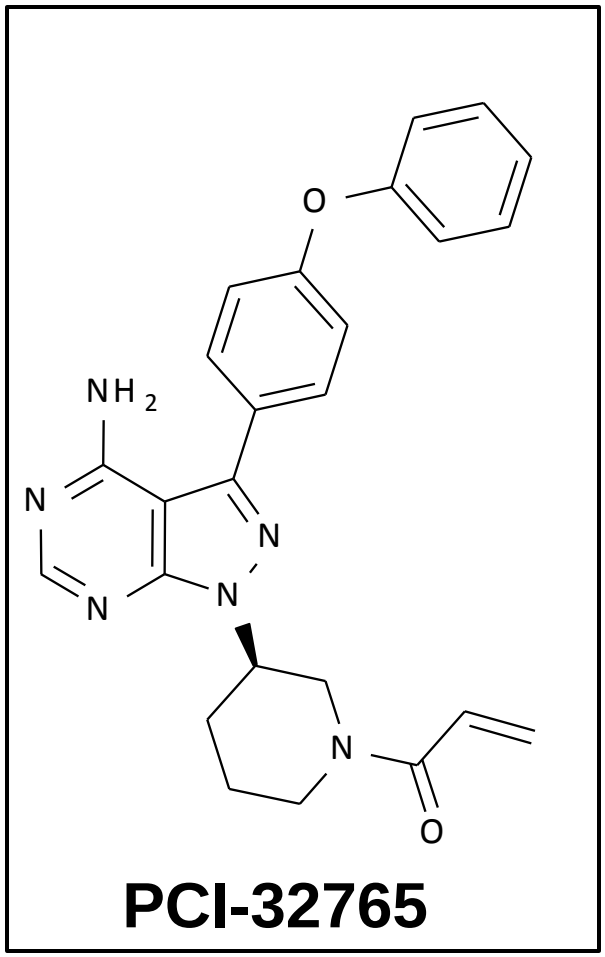
IBRUTINIB

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

PCI-32765: FIRST-IN CLASS INHIBITOR OF BTK

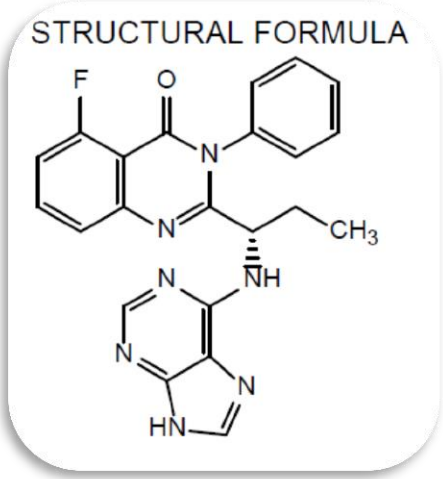


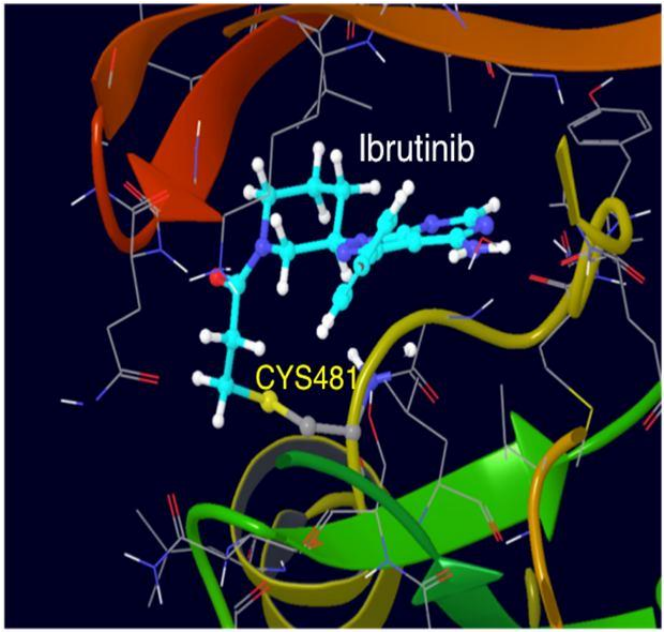
PCI-32765

- Forms a specific and irreversible bond with cysteine-481 in Btk
- Highly potent Btk inhibition at IC_{50} = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- Blocks mantle cell migration and adhesion
- Blocks pERK, pJNK, and NF-kB pathways in mantle cell lymphoma lines.

Honigberg LA et al: Proc Natl Acad Sci 2010
Chang, D et al. Proc ASH 2011

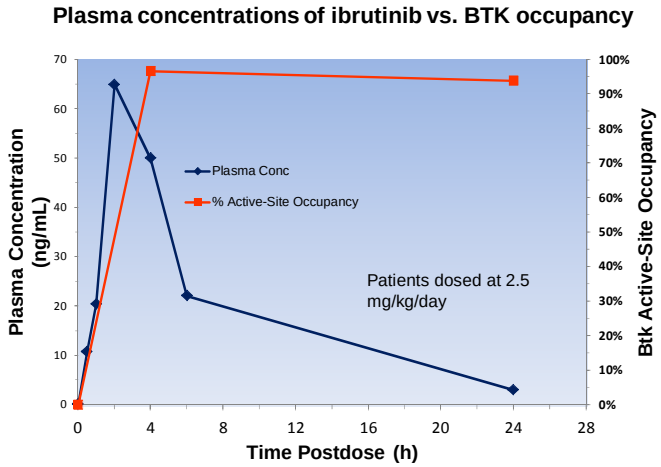
Ibrutinib: A potent BTK inhibitor





- 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

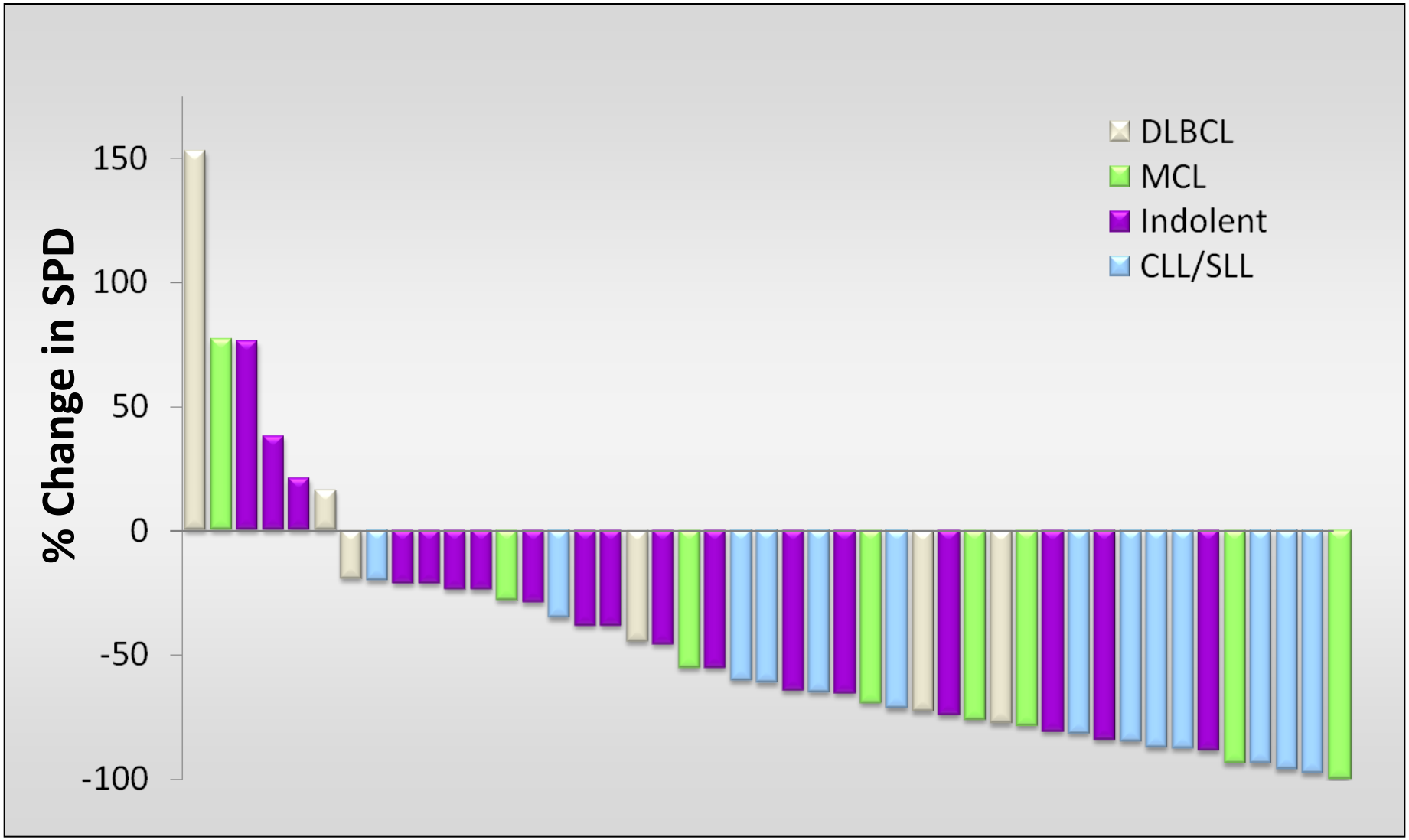
Durable Btk inhibition, despite rapid drug elimination



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

SINGLE AGENT

Btk inhibitor PCI-32765 Phase I



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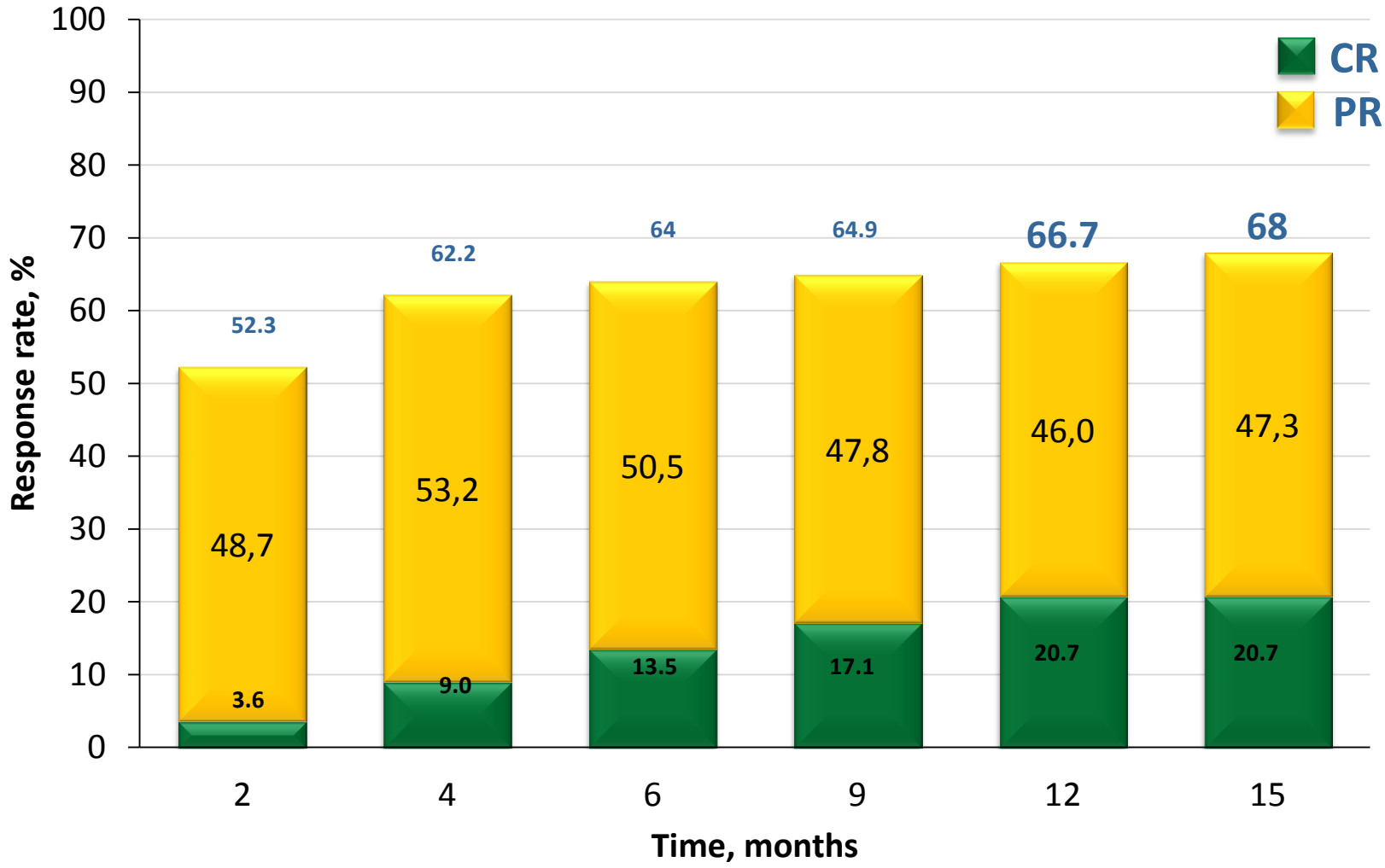
Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

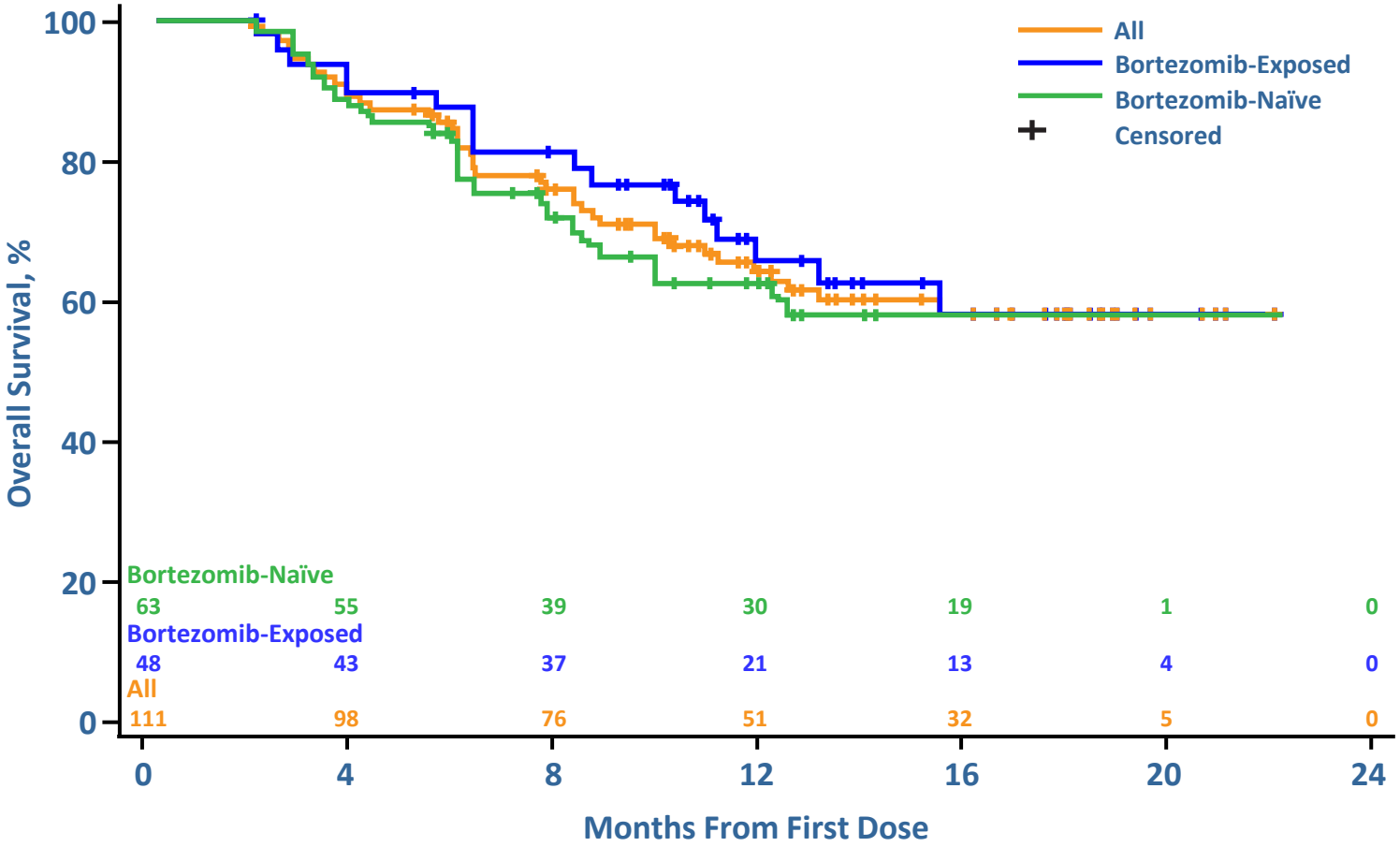
Michael L. Wang, M.D., Simon Rule, M.D., Peter Martin, M.D., Andre Goy, M.D., Rebecca Auer, M.D., Ph.D., Brad S. Kahl, M.D., Wojciech Jurczak, M.D., Ph.D., Ranjana H. Advani, M.D., Jorge E. Romaguera, M.D., Michael E. Williams, M.D., Jacqueline C. Barrientos, M.D., Ewa Chmielowska, M.D., John Radford, 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

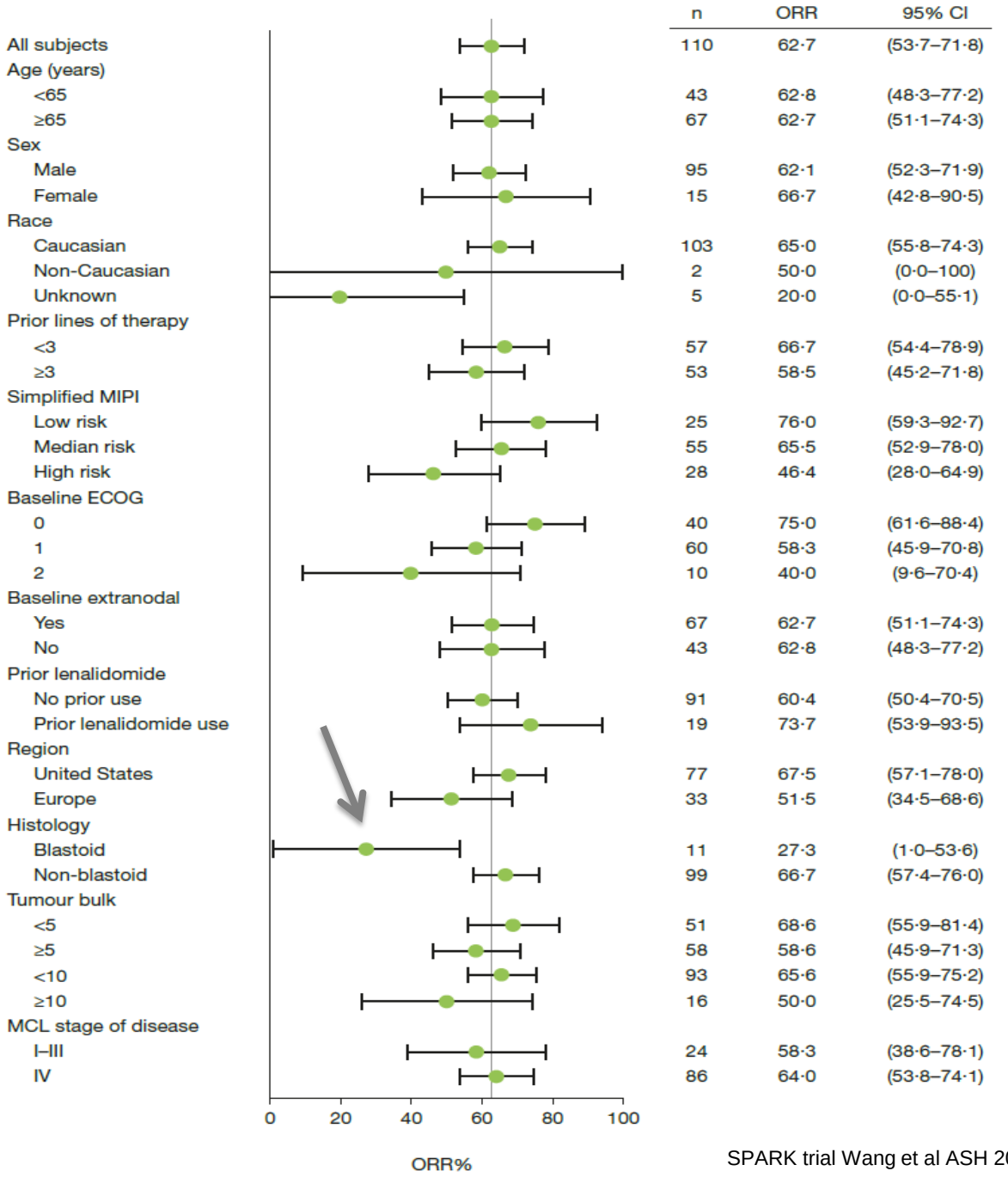


PCYC-1104-CA Phase 2 Study of Ibrutinib in R/R MCL

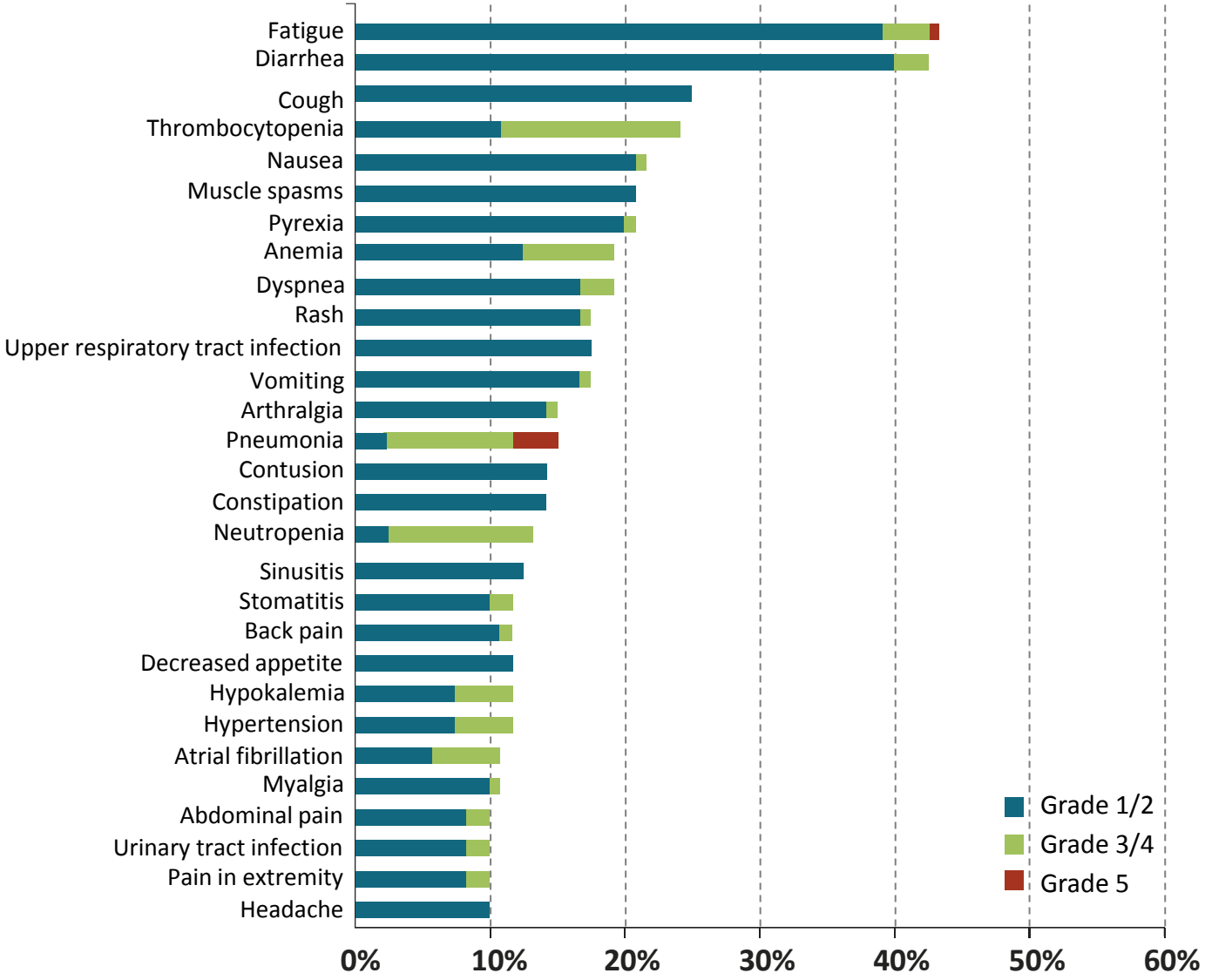
Kaplan-Meier overall survival (n=111)



- Estimated Median OS was not reached
- Estimated OS of 58% at 18 months



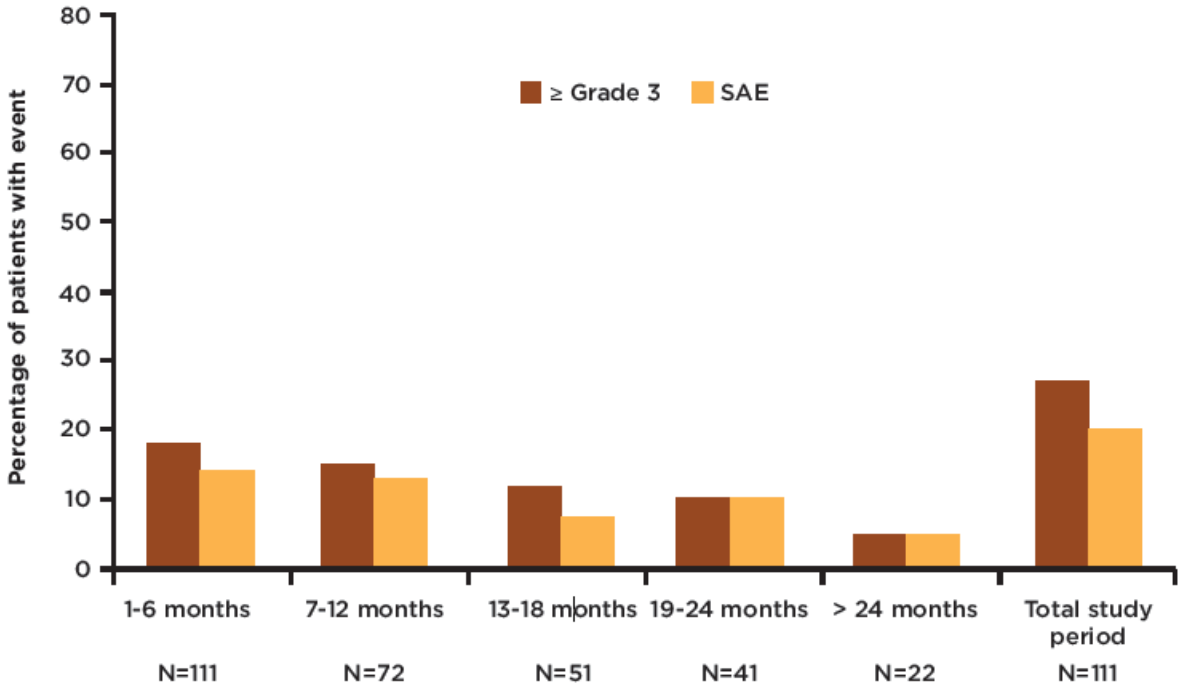
SPARK trial Wang et al ASH 2015



SPARK trial Wang et al ASH 2015

RESULTS: SAFETY ANALYSIS - INFECTIONS

Prevalence of infections by time period and grade



27%

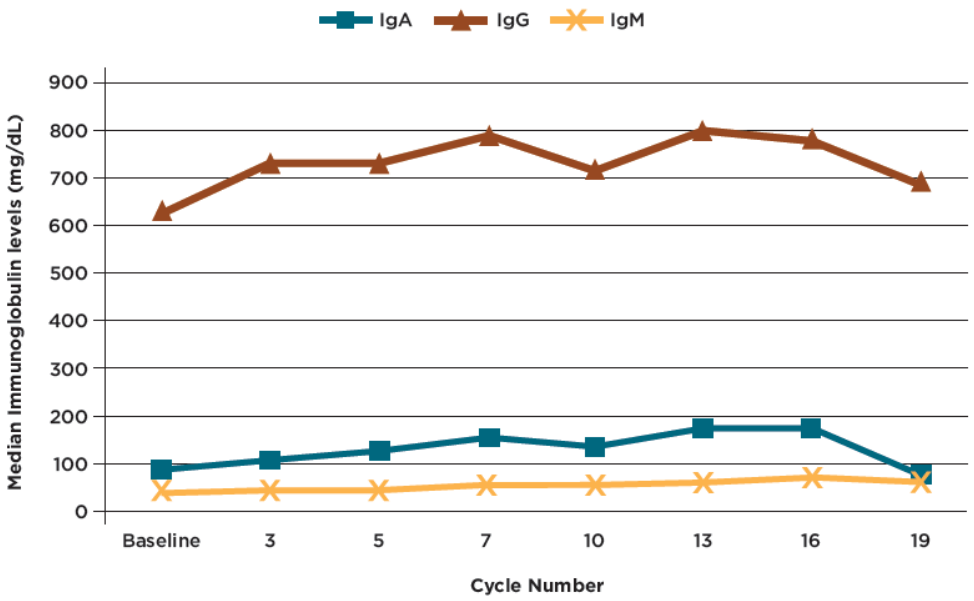
20%

Percentage of patients with a new episode of the corresponding event in the period or an episode started in prior 6-month period and lasted to the current period is shown. N = number of patients who entered the time period

Rule S, et al. EHA 2014; Poster/Abstract P461.

RESULTS: SAFETY ANALYSIS - IMMUNOGLOBULINS

Immunoglobulin levels over time

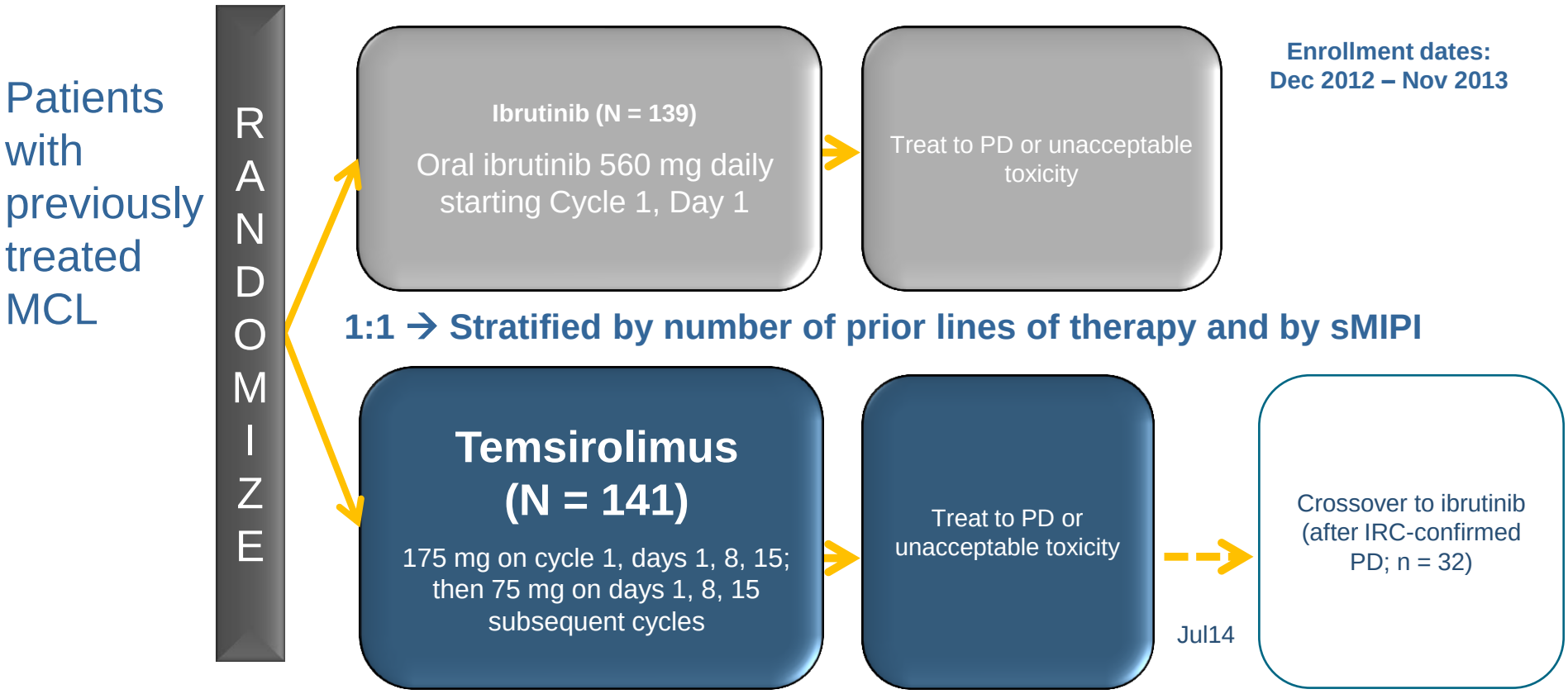


Data cutoff for immunoglobulin assessment: December 26, 2012.
4 patients excluded from this summary due to use of intravenous immunoglobulins
One additional patient excluded from IgG and IgM summaries due to baseline >1.5 ULN
Each cycle of ibrutinib is 28 days

- No substantial changes in serum Ig levels (IgA, IgG, IgM) were observed over time

Rule S, et al. EHA 2014; Poster/Abstract P461.

MCL3001 (RAY): PHASE 3 OPEN-LABEL STUDY



Primary end point:

- IRC-assessed PFS

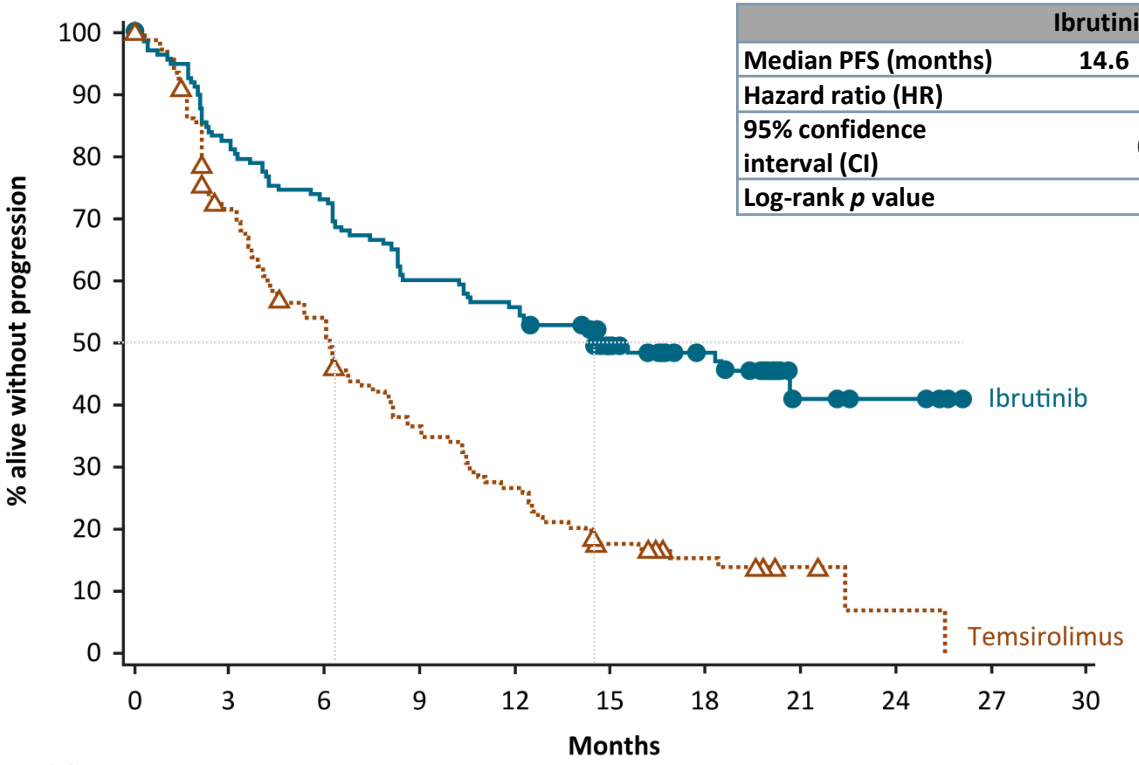
Secondary end points included:

- 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	



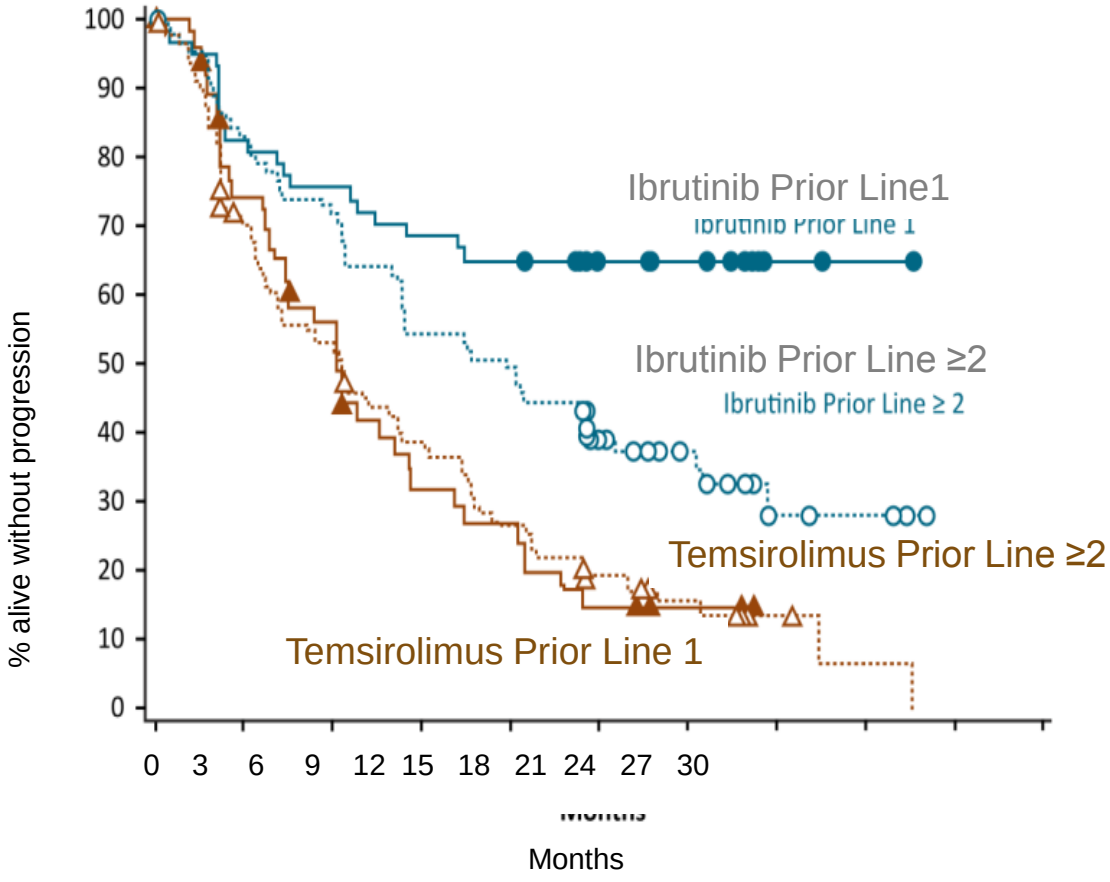
Patients at risk

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

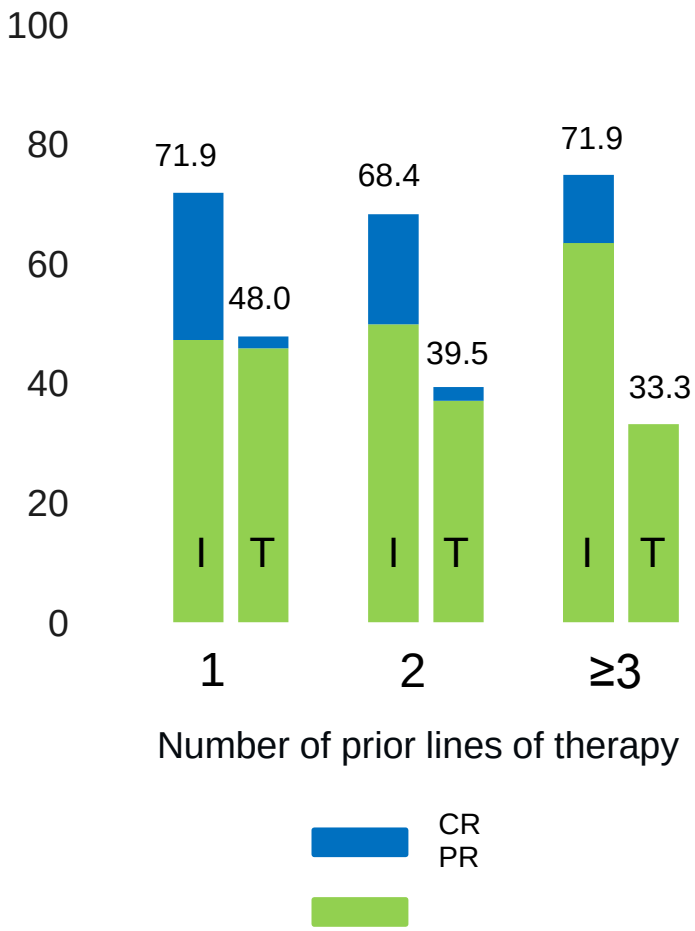
- At a 2-year landmark, the PFS rate was 41% for ibrutinib versus 7% for temsirolimus
- Investigator-assessed HR for ibrutinib versus temsirolimus was 0.43 (95% CI, 0.32-0.58)

RAY: Ibrutinib vs Temsirolimus in R/R MCL

PFS by number of lines of therapy
(IRC assessed)



Overall Response Rate



Waldenstroms Macroglobulinaemia

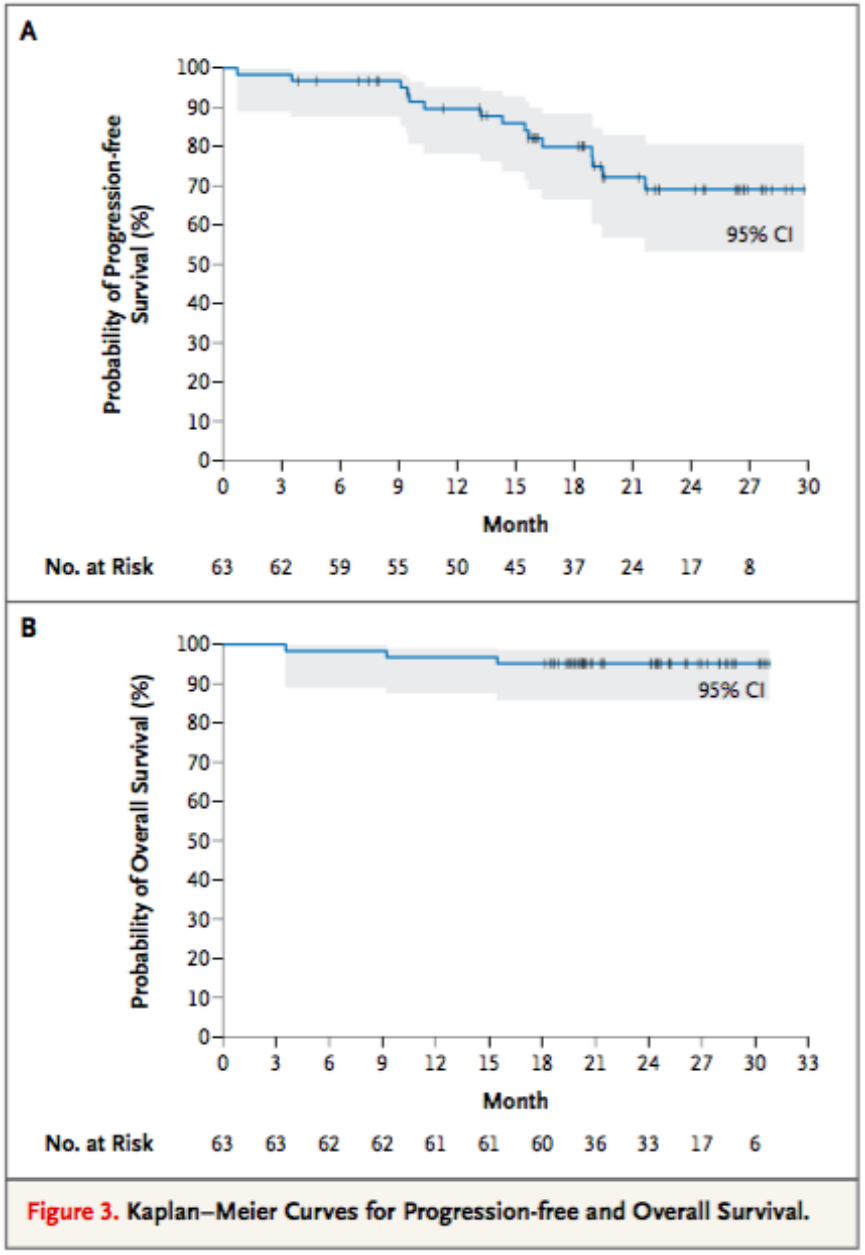


Figure 3. Kaplan–Meier Curves for Progression-free and Overall Survival.

COMBINATION DATA

IBRUTINIB AND RITUXIMAB ARE AN EFFICACIOUS AND SAFE COMBINATION IN RELAPSED MANTLE CELL LYMPHOMA: PRELIMINARY RESULTS FROM A PHASE II CLINICAL TRIAL

Michael Wang, MD , Fredrick Hagemeister, MD, Jason Westin, MD, Luis Fayad, MD, Felipe Samaniego, MD, MPH, Francesco Turturro, MD, Wendy Chen, Liang Zhang, MD, PhD, Maria Badillo, BS, Maria Rosa, Alicia Addison, Larry Kwak, MD, PhD and Jorge Romaguera, MD

Department of Lymphoma/Myeloma

Department of Stem Cell Transplantation and Cellular Therapy

Michael Wang, MD

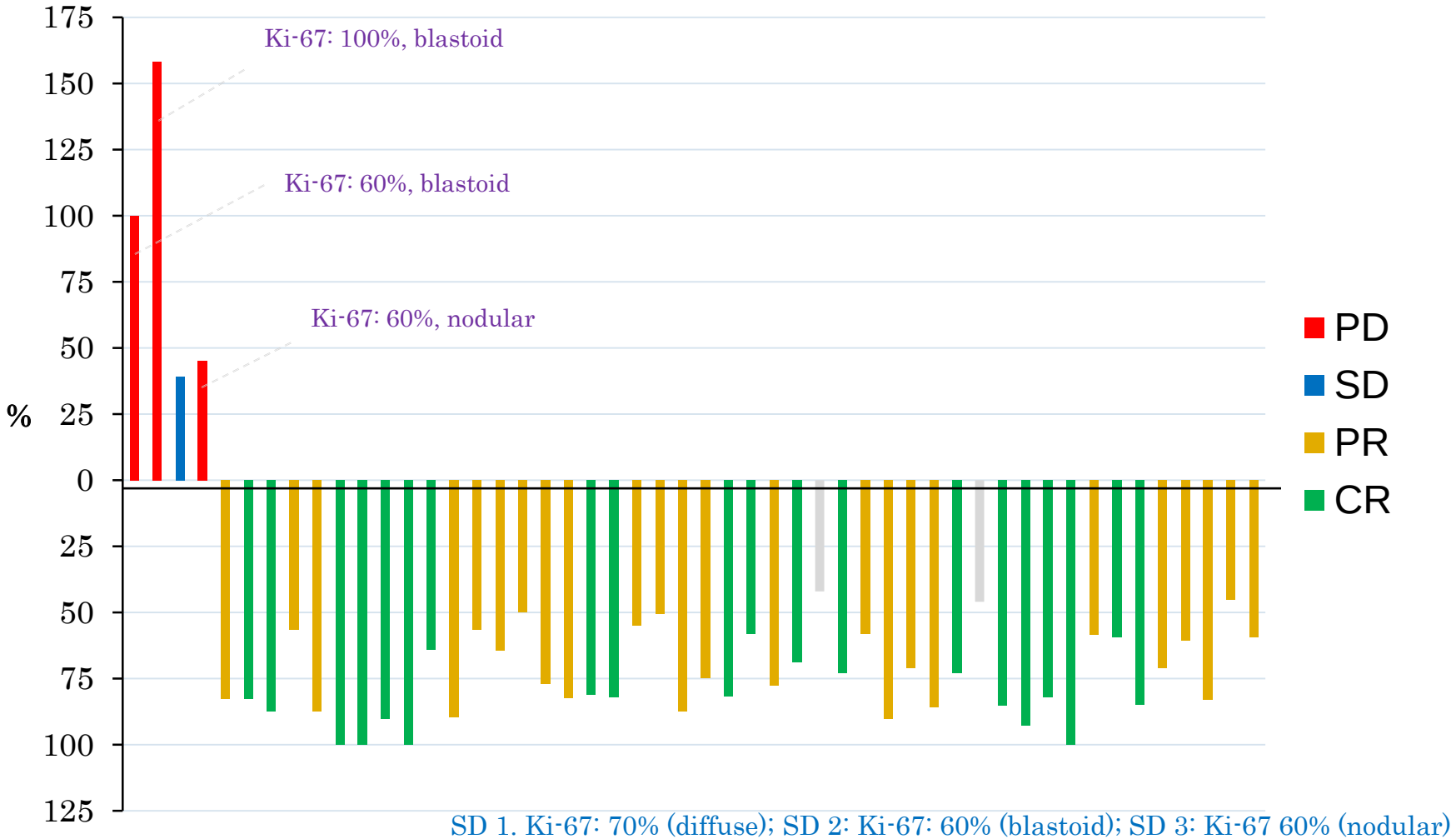
Professor

Director, Mantle Cell Lymphoma Program of Excellence

Co-Director, Clinical Investigation and Translational Research for Clinical Trials

ASH 2014

BEST RESPONSE



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

Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B-cell non-Hodgkin lymphoma: a non-randomised, phase 1b study

Anas Younes, Catherine Thieblemont, Franck Morschhauser, Ian Flinn, Jonathan W Friedberg, Sandy Amorim, Benedicte Hivert, Jason Westin, Jessica Vermeulen, Nibedita Bandyopadhyay, Ronald de Vries, Sriram Balasubramanian, Peter Hellemans, Johan W Smit, Nele Fourneau, Yasuhiro Oki

	280 mg (n=7)	420 mg (n=4)	560 mg (n=21)	Combined (n=32)	All (n=33)*
Overall response	6 (86%)	4 (100%)	20 (95%)	30 (94%)	30 (91%)
Complete response	5 (71%)	3 (75%)	15 (71%)	23 (72%)	23 (70%)
Partial response	1 (14%)	1 (25%)	5 (24%)	7 (22%)	7 (21%)
Stable disease	0	0	0	0	0
Progressive disease	0	0	0	0	0
Not evaluable	1 (14%)	0	1 (5%)	2 (6%)	3 (9%)

Data are n (%). *One patient received only rituximab.

Table 3: **Best response to treatment, assessed by Revised Response Criteria for Malignant Lymphoma**[31]

Lancet Oncol 2014; 15: 1019–26

A phase 1/1b study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma

Kami Maddocks,[1] Beth Christian,[1] Samantha Jaglowski,[1] Joseph Flynn,[1] Jeffery A. Jones,[1] Pierluigi Porcu,[1] Lai Wei,[2] Cynthia Jenkins,[3] Gerard Lozanski,[4] John C. Byrd,[1] and Kristie A. Blum[1]

Table 3. Response by NHL subtype

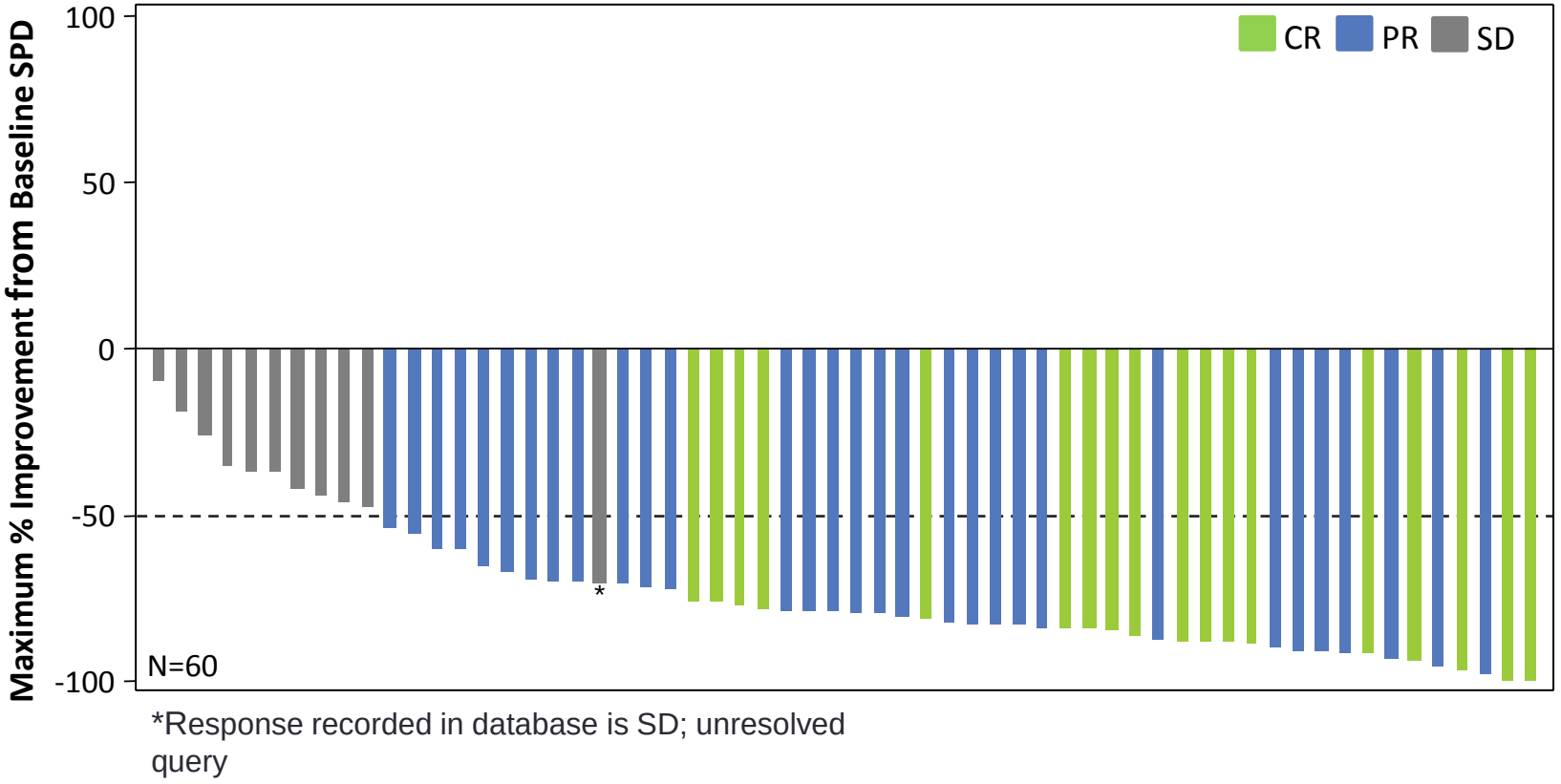
Histology	No. evaluable patients*	CR (%)	PR (%)	OR (%)
MCL	17	13 (76)	3 (18)	16 (94)
DLCL	16	5† (31)	1† (6)	6 (37)
FL	10*	5 (50)	4 (40)	9 (90)
MZL	1	0	1 (100)	1 (100)
Transformed lymphoma	2	1 (50)	0	1 (50)
All patients	46*	24 (52)	9 (20)	33 (72)

IBRUTINIB PLUS RITUXIMAB IN TREATMENT-NAÏVE PATIENTS WITH FOLLICULAR LYMPHOMA: RESULTS FROM A MULTICENTER, PHASE 2 STUDY

Nathan H. Fowler, MD[1], Loretta Nastoupil, MD[1], Sven De Vos, MD, PhD[2], Mark Knapp, MD[3], Ian W. Flinn, MD, PhD[4], Robert Chen, MD[5], Ranjana H. Advani, MD[6], Sumeet Bhatia, MD[7], Peter Martin, MD[8], Raul Mena, MD[9], Samuel Suzuki, MS, MBA[10], Darrin M. Beaupre, MD, PhD[10], Jutta K. Neuenburg, MD, PhD[10], M. Lia Palomba, MD[11]

[1]University of Texas MD Anderson Cancer Center, Houston, TX; [2]David Geffen School of Medicine at UCLA, Los Angeles, CA; [3]Mid Ohio Oncology/Hematology, Inc., Columbus, OH; [4]Sarah Cannon Research Institute, Nashville, TN; [5]City of Hope National Medical Center, Duarte, CA; [6]Stanford University School of Medicine, Stanford, CA; [7]Community Health Network, Indianapolis, IN; [8]Weill Cornell Medical College, New York, NY; [9]Providence Saint Joseph Medical Center/Disney Family Cancer Center, Burbank, CA; [10]Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA; [11]Memorial Sloan Kettering Cancer Center, New York, NY

MAXIMUM PERCENTAGE IMPROVEMENT FOR TARGET LESION SPD – ARM 1

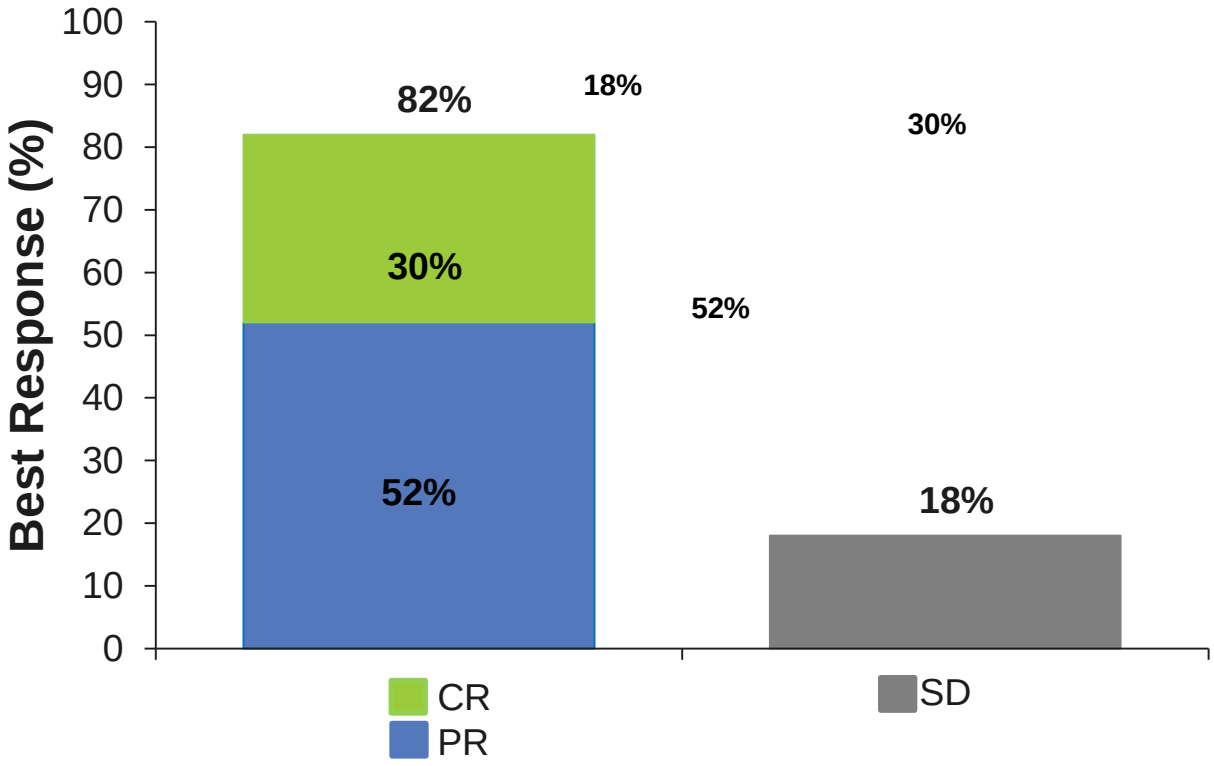


*Response recorded in database is SD; unresolved query

- Median target lesion SPD at baseline: 23.7 cm^2 (range, 2.9-135.5)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; SPD, sum of the products of the greatest perpendicul diameters

Best Response – Arm 1



- Median follow-up 13.8 months (range, 5.8-19.3)
- ORR 82% in all treated patients (49 of 60)
- Median time to best response: 2.7 months (range, 1.1-13.6)
- Median duration of ibrutinib treatment: 12.55 months (range, 0.8, 19.6)

PHASE I STUDY OF RITUXIMAB, LENALIDOMIDE, AND IBRUTINIB IN PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA (ALLIANCE 051103)

Chaitra S. Ujjani, Sin-Ho Jung, Brandelyn Pitcher, Peter Martin, Steven I. Park, Kristie A. Blum, Sonali M. Smith, Myron S. Czuczman, Matthew S. Davids, John P. Leonard and Bruce D. Cheson.

RESULTS

22 patients (16 at max dose)

ORR 91% (CR/CRu 63%)

12 month PFS 84%

Toxicity:

- Rash 73% (32% Gd III)
- Neutropenia 18% Gd III

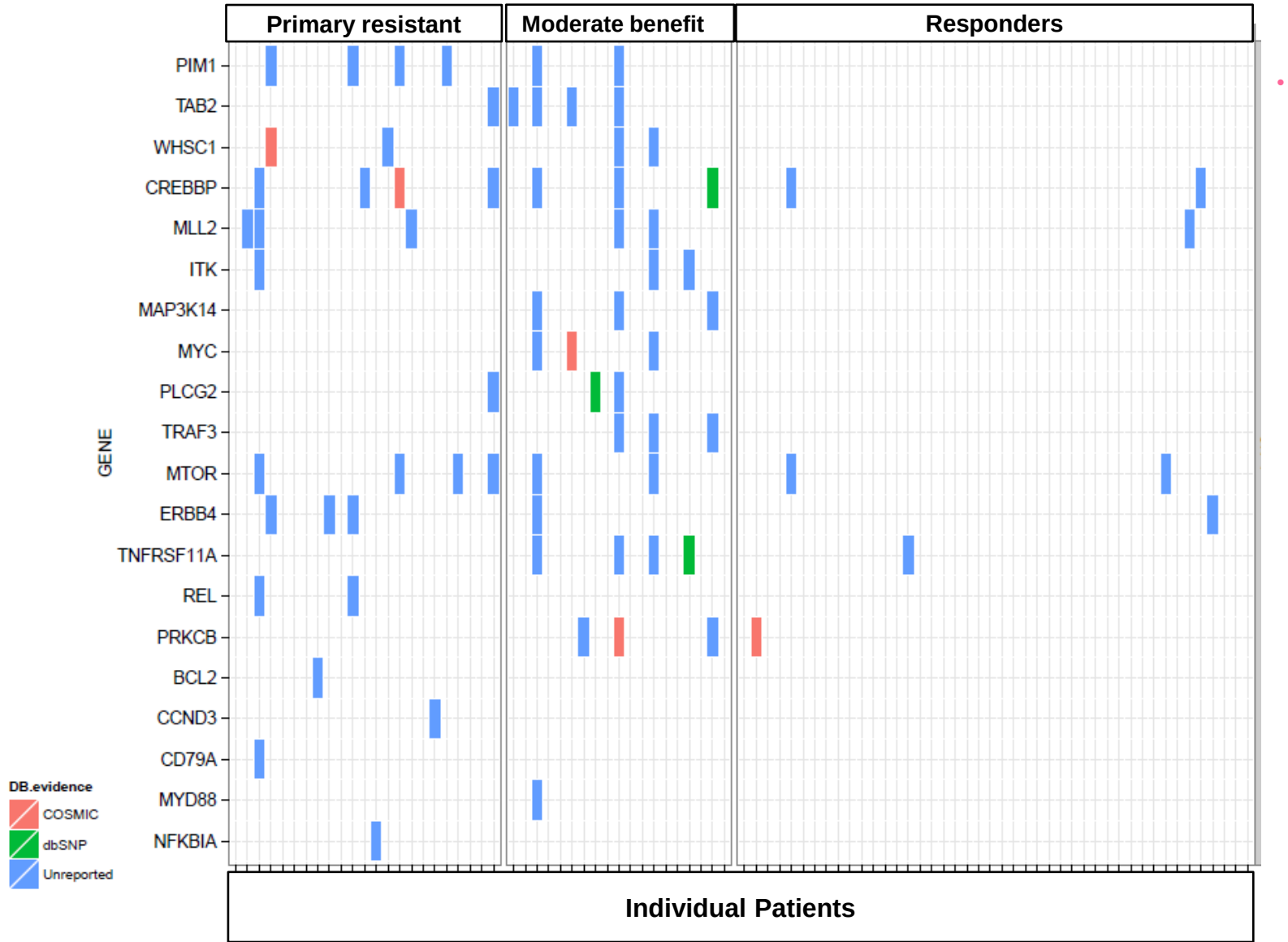
11 dose reductions, 8 due to rash

Mutational Analysis of Patients With Primary Resistance to Single-Agent Ibrutinib in Relapsed or Refractory Mantle Cell Lymphoma (MCL)

Sriram Balasubramanian[1], Michael Schaffer[1], William Deraedt[2], Cuc Davis[1], Emily Stepanchick[1], Regina Aquino[1], Zhilong Yuan[3], Britte Kranenburg[4], Irit Avivi[5], Martin Dreyling[6], Simon Rule[7], Michael Wang[8], Sen Hong Zhuang[3], Mark Wildgust[3], Aleksandra Rizo[3], and Georg Lenz[9]

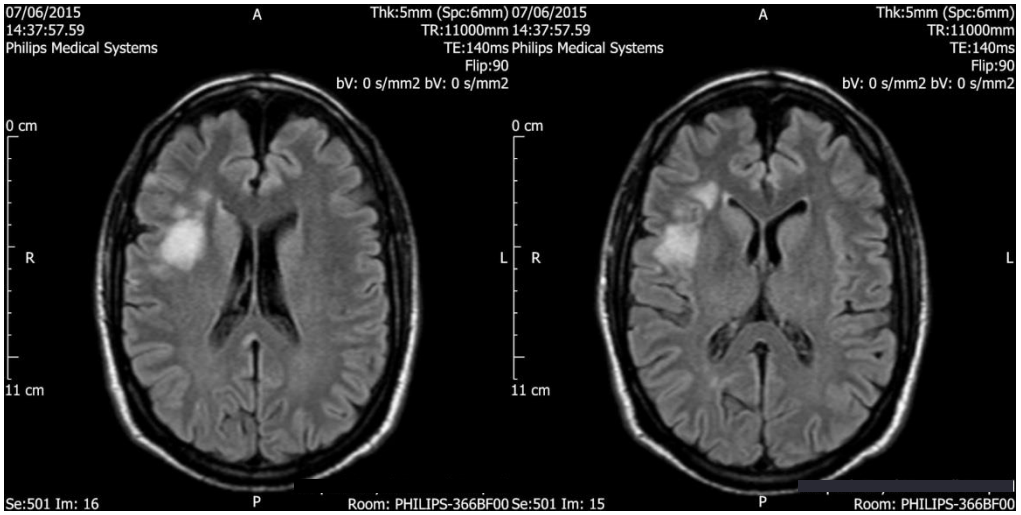
[1]Janssen Research & Development, LLC, Springhouse, PA; [2]Janssen Research & Development, LLC, Beerse, Belgium; [3]Janssen Research & Development, LLC, Raritan, NJ; [4]Janssen Biologics B.V., South Holland, Netherlands; [5]Tel Aviv Medical Center, Tel Aviv, Israel; [6]Klinikum der Universität München-Campus Grosshadern, Munich, Germany; [7]Derriford Hospital, Plymouth, United Kingdom; [8]The University of Texas MD Anderson Cancer Center, Houston, TX; [9]Charité – Universitätsmedizin, Berlin, Germany

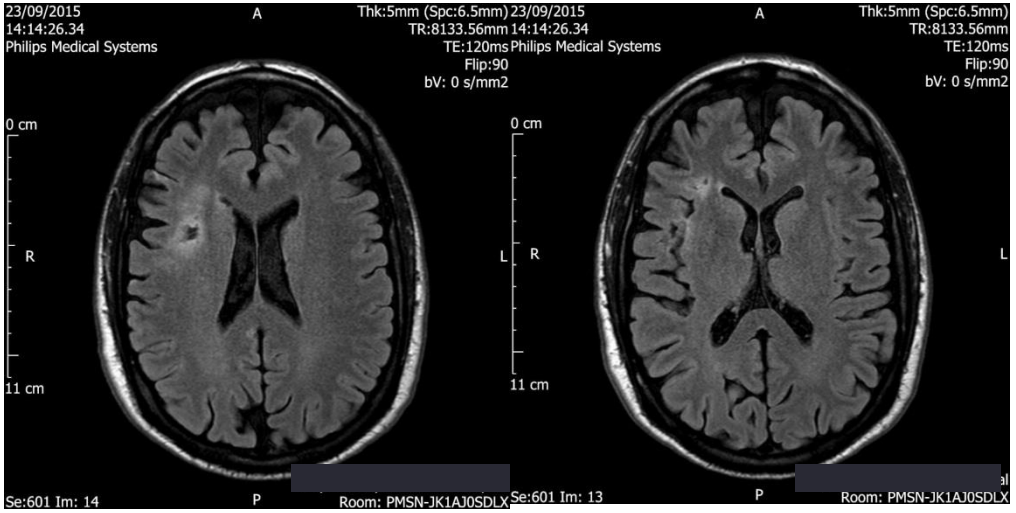
PATIENTS WITH DURABLE RESPONSE HAVE FEW OR NO MUTATIONS IN THESE GENES



AND FINALLY

IBRUTINIB FOR CNS MANTLE CELL NHL





CONCLUSION

- Highly active agent
  - Especially MCL / WM
- Potential to fundamentally change treatment approaches
- Challenge to chemotherapy