BTKi in MCL

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Table of Various Treatment for R/R MCL

Treatment	Study or Literature Reference	N	ORR	CR	Median DOR (months)	Median PFS (months)	Median OS (months)
Ibrutinib	PCYC-1104-CA	111	68%	21%	17.5	13.9	Not reached
Bortezomib	Fischer 2006 Goy 2009	155[a]	33%	8%	9.2	6.5	23.5
Lenalidomide	Goy 2012	134	28%	8%	16.6	4.0	19.0
Temsirolimus[b]	Hess 2009	54	22%	2%	7.1	4.8	12.8

CR=complete response; DOR= duration of response; ORR=overall response rate; OS=overall survival; PFS= progression-free survival.

[a] Of the 155 patients enrolled, 141 were assessable for response.

[b] Results are presented for temsirolimus 175/75 mg dose group.

Campo & Rule Blood 2015 Jan 1;125(1):48-55

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Acalabrutinib	Wang 2017	124	81%	40%	Not reached	Not reached	Not reached

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IBRUTINIB

Overall Survival Outcomes in Patients With Mantle-Cell Lymphoma Treated With Ibrutinib: A Pooled Analysis of 370 Patients From 3 International Open-Label Studies

Simon Rule,[1] Martin Dreyling,[2] Georg Hess,[3] Rebecca Auer,[4] Brad Kahl,[5] Nora Cavazos,[6] Black Liu,[7] Fong Clow,[6] Jenna Goldberg,[8] Darrin Beaupre,[6] Jessica Vermeulen,[9] Mark Wildgust,[8] and Michael Wang[10]

[1]Derriford Hospital, Plymouth, UK; [2]Klinikum der Universität München, Munich, Germany; [3]University Medical School of the Johannes Gutenberg University, Mainz, Germany; [4]St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK; [5]Washington University School of Medicine, St. Louis, MO, USA; [6]Pharmacyclics, Sunnyvale, CA, USA; [7]Janssen China Research & Development, Shanghai, China; [8]Janssen Research & Development, Raritan, NJ, USA; [9]Janssen Research & Development, Leiden, The Netherlands;
[10]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Median 3.5-year follow-up of ibrutinib treatment in patients with relapsed/refractory MCL: A pooled analysis - Patient disposition

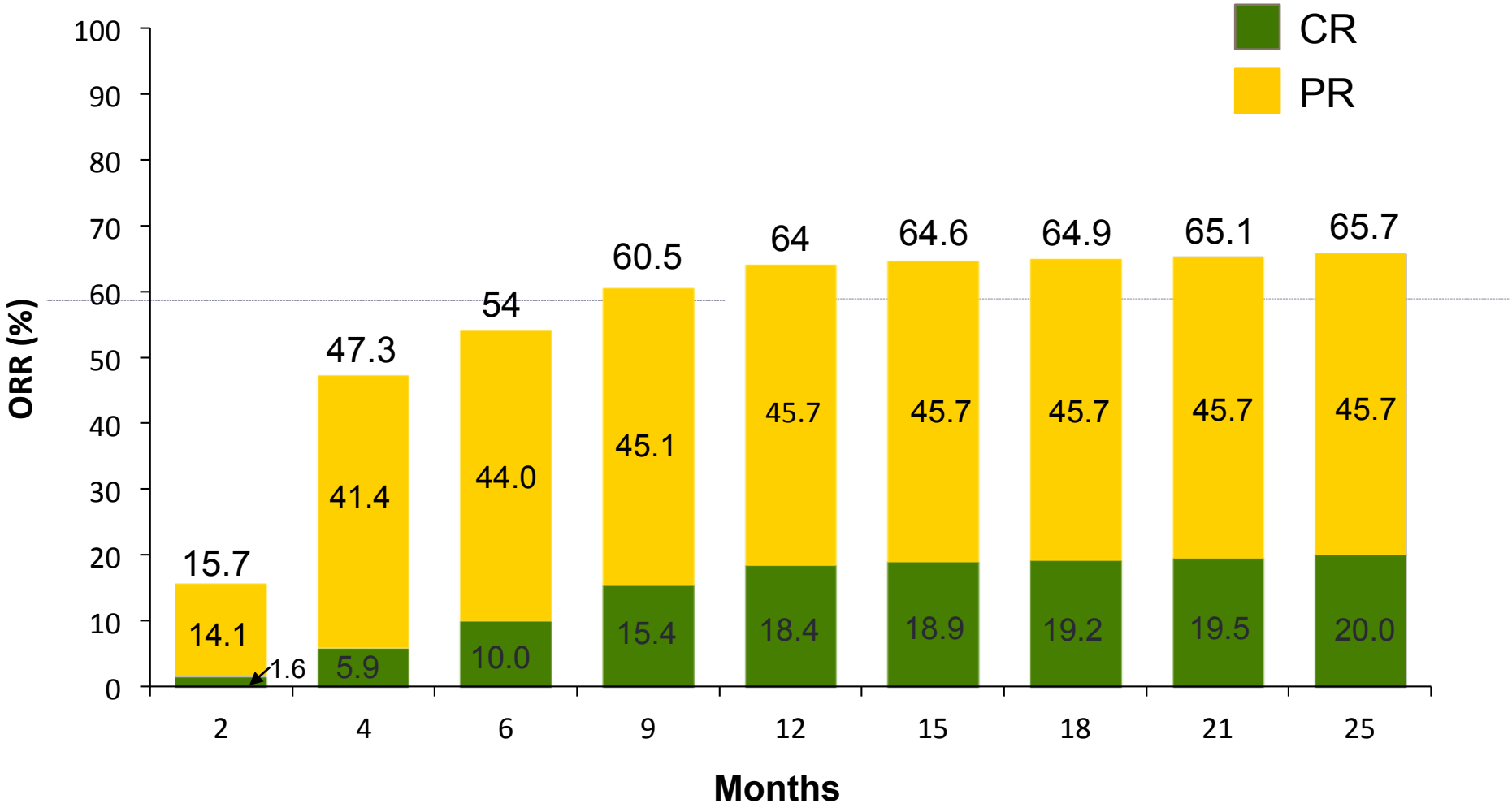
	Total (Pooled) (N = 370)
Study, n (%)	
PCYC-1104	111
SPARK	120
RAY	139
Patients rolled over to CAN3001, n (%)	87 (23.5)
Median duration of follow-up, months (range)	41.1 (0.2-72.1)
Treatment discontinuation, n (%)	316 (85.4)
AE	37 (10.0)
Disease progression	218 (58.9)
Death	19 (5.1)
Other*	42 (11.4)

- Discontinuation rates due to AEs at time of primary analysis (median follow-up):
  - PCYC-1104 (15.3 months): 7%
  - SPARK (14.9 months): 7%
  - RAY (20 months): 6%

*Includes: alternative access to ibrutinib (n = 1); physician decision (n = 14); withdrawal of consent (n = 24); other reasons (n = 3).

Rule et al., ASH 2017 (abstract 151, oral presentation)

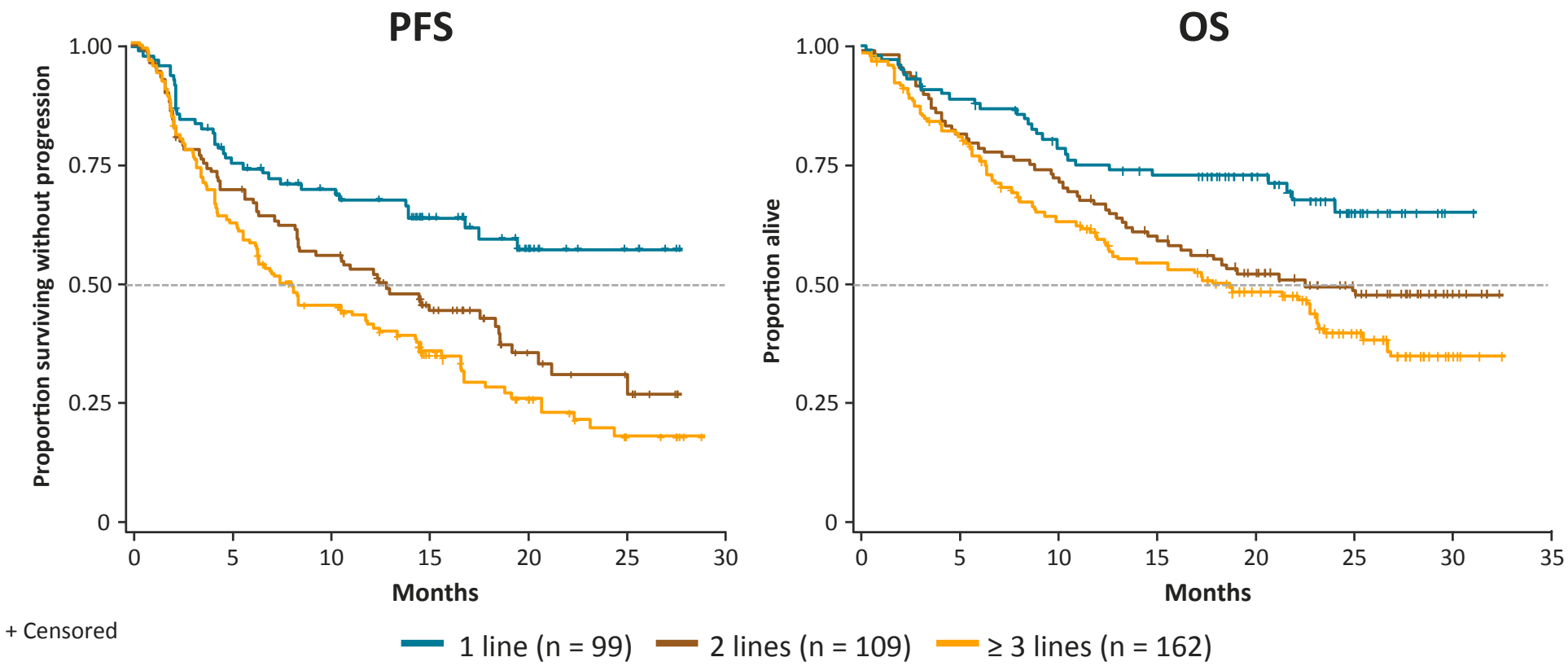
Pooled MCL Analysis: Improvement in Response Rates Over Time



PR, partial response.

N = 370

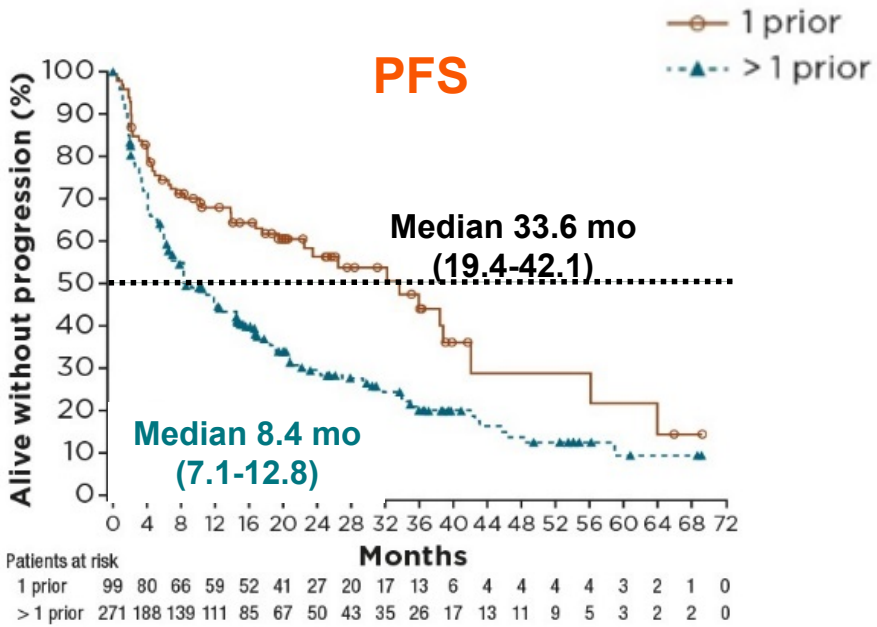
Pooled MCL Analysis: PFS and OS by Prior Lines of Therapy (1, 2, ≥ 3)



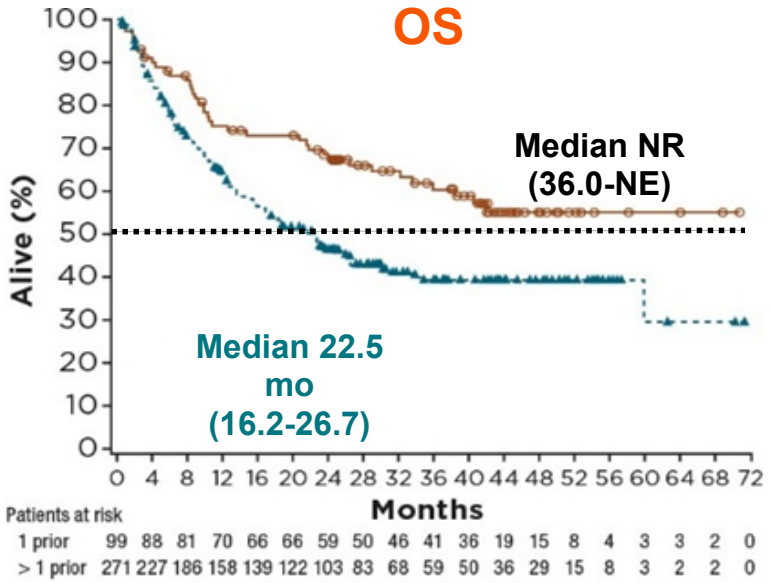
- Patients who had received only 1 prior line of therapy had the longest PFS and OS; 2-year PFS and OS were 57% and 68%, respectively

Rule et al ASH 2015 oral presentation

Ibrutinib in MCL: PFS and OS by prior line of therapy



Median PFS overall (95% CI): 13.0 (8.4-16.8) months



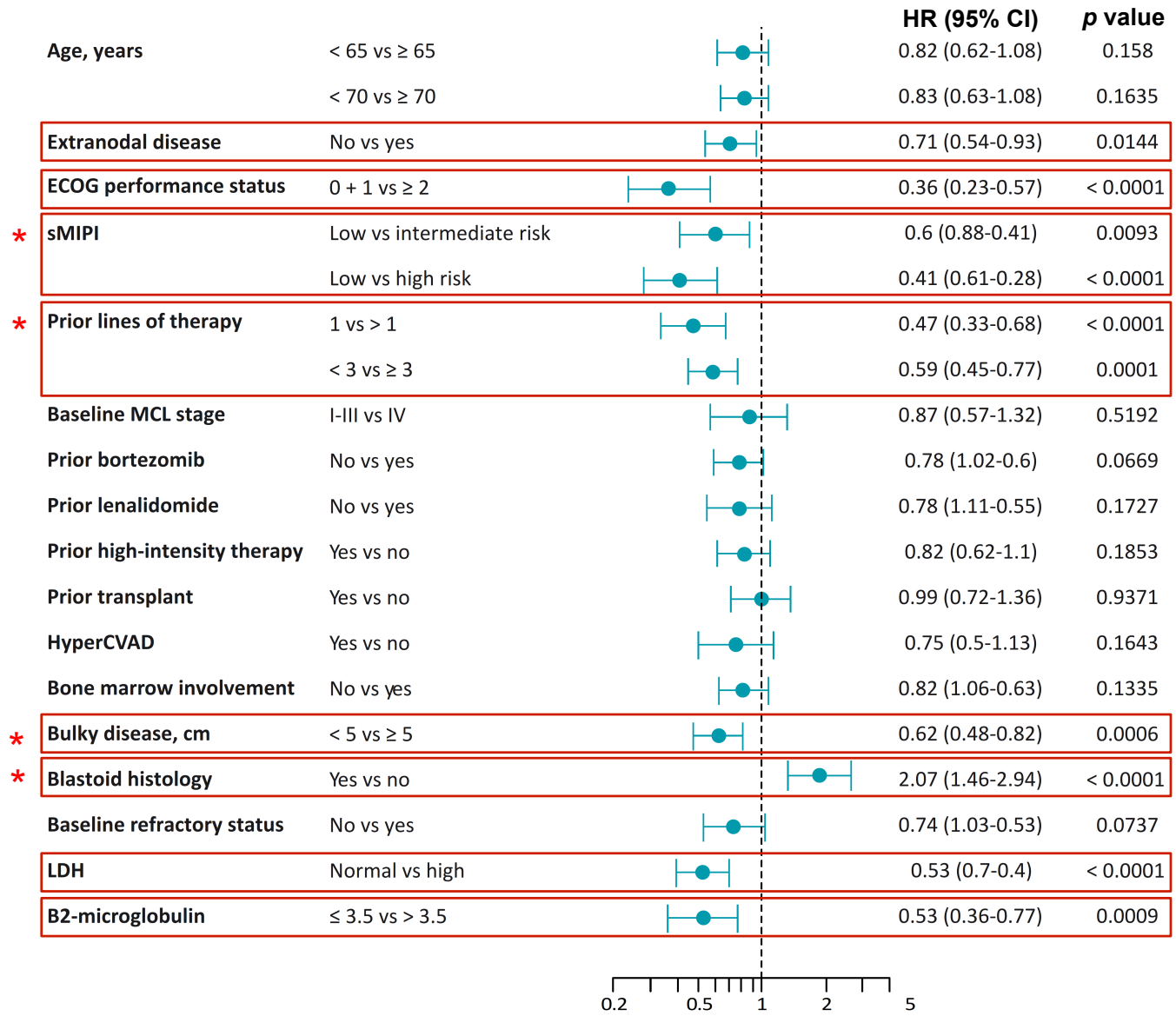
Median OS overall (95% CI): 26.7 (22.5-38.4) months

Median PFS was nearly 3 years in patients with 1 prior line of therapy

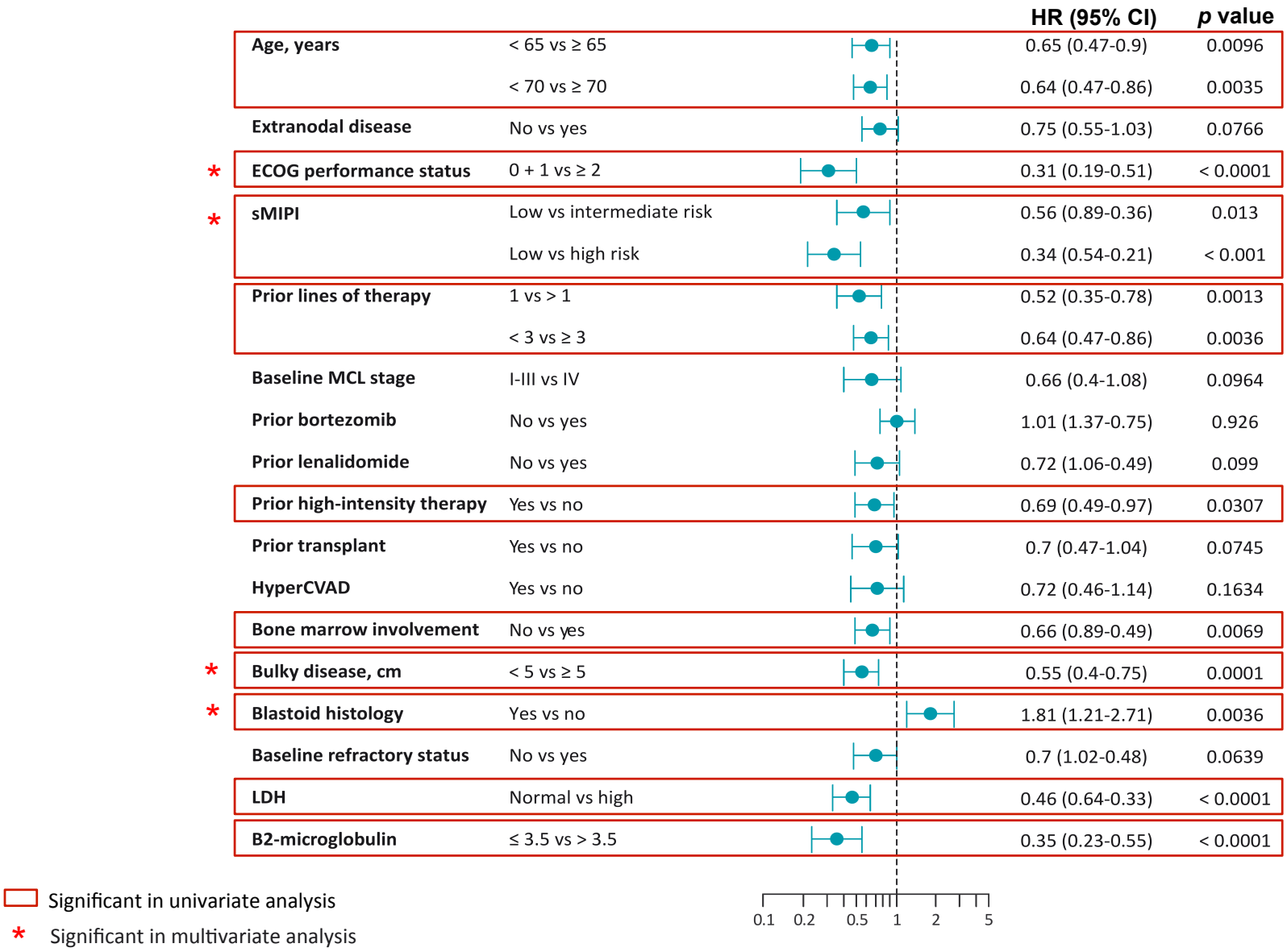
Patients censored from OS analysis upon study discontinuation. CI, confidence interval; NE, not estimable.

Rule et al., ASH 2017 (abstract 151, oral presentation)

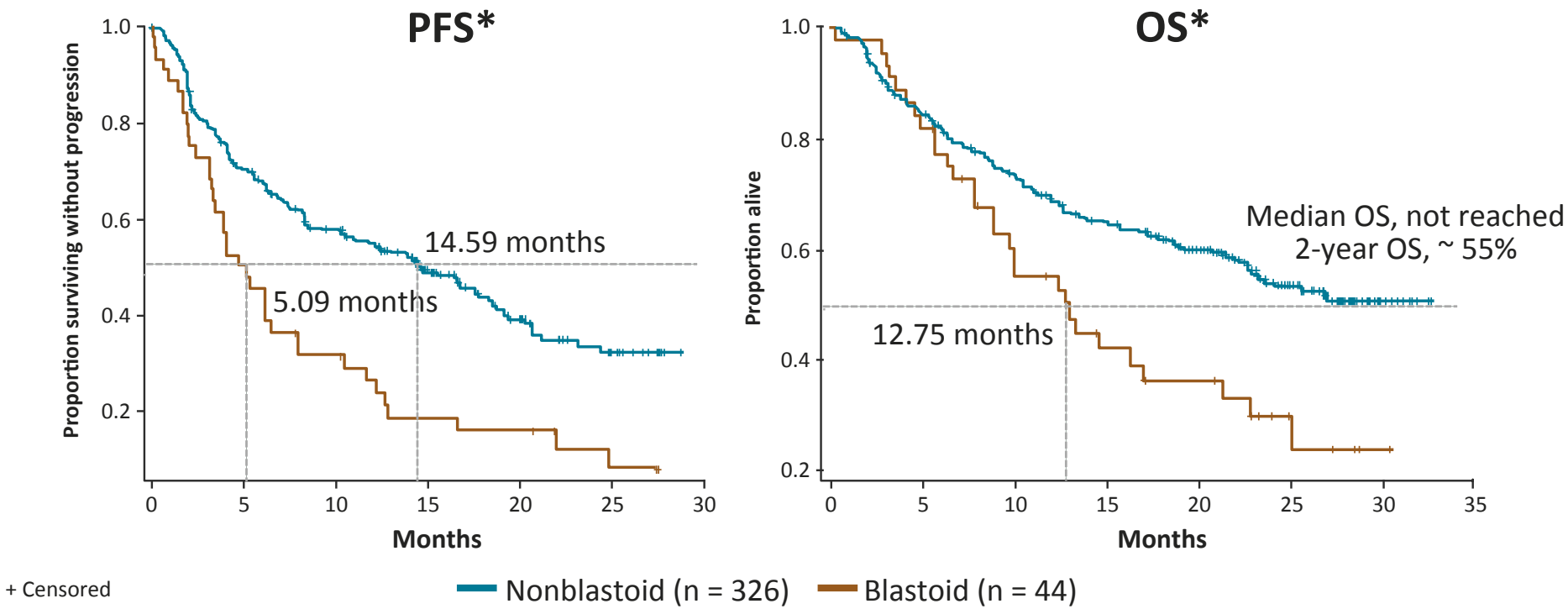
Pooled MCL Analysis: PFS by Baseline Patient Characteristics



Pooled MCL Analysis: OS by Baseline Patient Characteristics



Pooled MCL Analysis: PFS and OS by Blastoid Histology

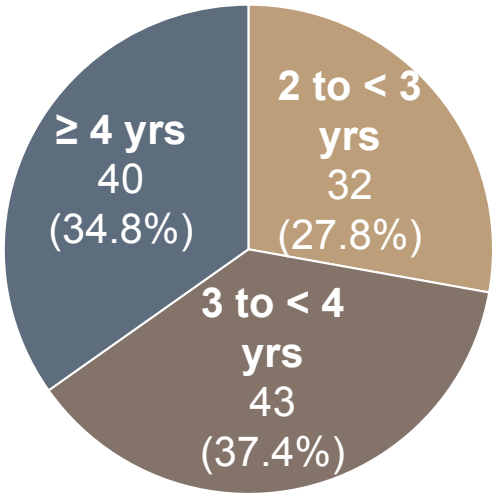


CI, confidence interval.
*Statistically significant.

Median 3.5-Year follow-up of ibrutinib treatment in patients with relapsed/refractory MCL: a pooled analysis

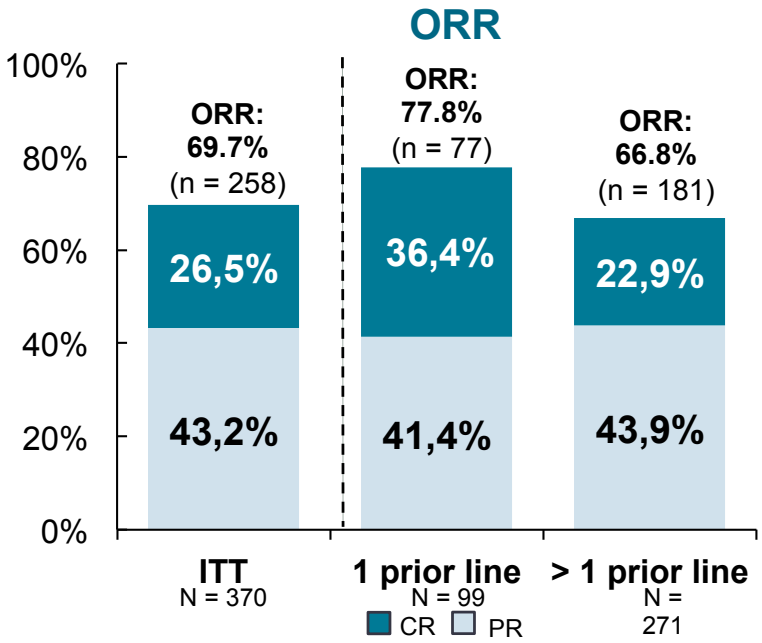
- In this pooled analysis of 370 patients:
  - Approximately one-third (n = 115, 31.1%) were treated with ibrutinib for ≥ 2 years
  - 54 remained on ibrutinib at time of analysis, with a median exposure of 46.3 months (range 28.8-72.1)
  - Maximum treatment exposure was 72 months

Ibrutinib Exposure in Patients With ≥ 2 Years of Exposure (N = 115)



Rule et al., ASH 2017 (abstract 151, oral presentation)

Ibrutinib in MCL: Overall response and PFS/OS by best response



Median, Months (95% CI)	Best Response	
	CR (n = 98)	PR (n = 160)
PFS	46.2 (42.1-NE)	14.3 (10.4-17.5)
OS	NE (59.9-NE)	26.2 (21.6-34.7)

Kaplan-Meier estimate of median.

CR rate was 36% in patients with 1 prior line of therapy

Median PFS was nearly 4 years in patients who achieved a CR

ITT, intent-to treat; ORR, overall response rate; PR, partial response.

Rule et al., ASH 2017 (abstract 151, oral presentation)

Ibrutinib in MCL: DOR by best response and line of therapy

Median DOR, Months (Range)	Overall (n = 258)	Prior Lines of Therapy	
		1 (n = 77)	> 1 (n = 181)
Overall (n = 258)	22.2 (16.5-28.8)	34.4 (23.1-NE)	16.0 (12.9-23.5)
CR (n = 98)	55.7 (55.7-NE)	55.7 (33.1-NE)	NE (40.7-NE)
PR (n = 160)	10.4 (7.7-14.9)	22.1 (10.6-34.4)	8.5 (6.2-12.1)

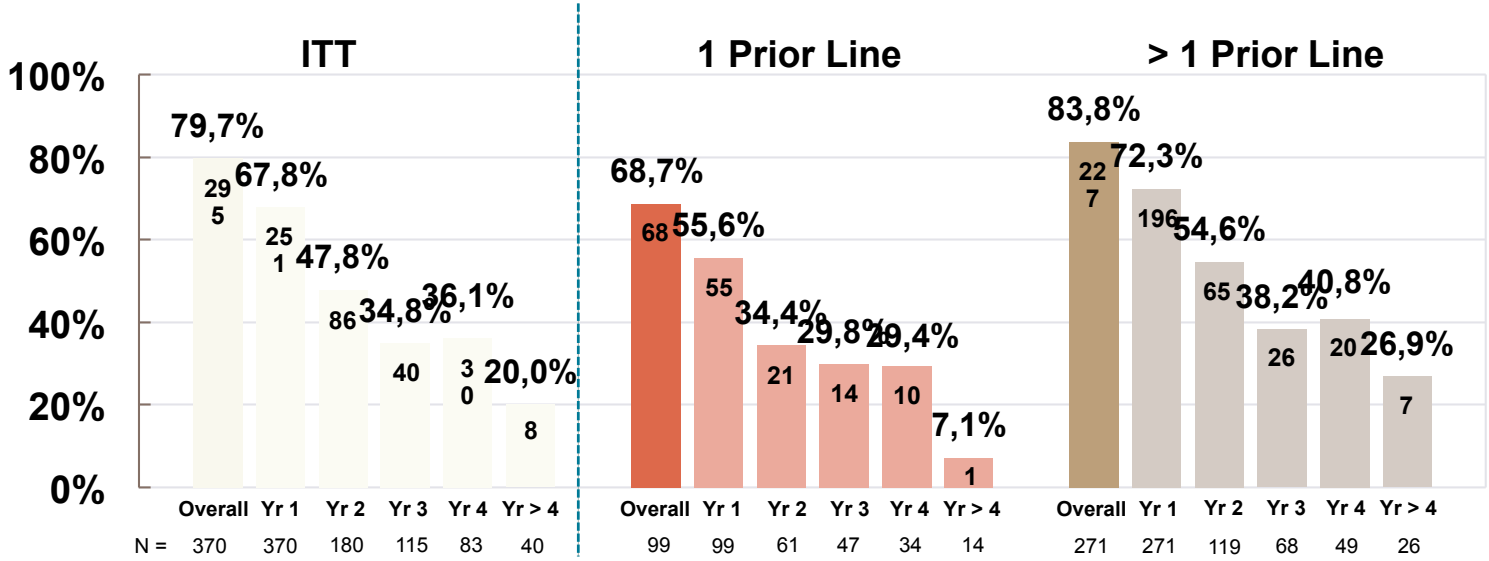
Median DOR was 4.5 years in patients achieving a CR

Patients with 1 prior line had 2× longer DOR than patients with > 1 prior line

DOR, duration of response.

Rule et al., ASH 2017 (abstract 151, oral presentation)

Ibrutinib in MCL: Grade ≥ 3 treatment-emergent AEs over time and by line of therapy



- **New onset grade ≥ 3 TEAEs generally decreased after the first year of treatment**
  - **Similar trend was seen for atrial fibrillation (AF) and bleeding**
- **New onset grade ≥ 3 TEAEs were generally lower in patients with 1 vs > 1 prior line**

Number of patients with event shown on bars.

Rule et al., ASH 2017 (abstract 151, oral presentation)

Ibrutinib in MCL: Cardiac risk factors and atrial fibrillation

- Studies enrolled patients with significant cardiac risk factors, including 53 patients with a history of (or ongoing controlled) AF/arrhythmia

Patient History: Factors that May Increase Cardiac Risk, n (%)	Total (N = 370)
Hypertension	176 (47.6)
Hyperlipidemia	60 (16.2)
Atrial fibrillation/abnormal heart rhythm	53 (14.3)
Diabetes	48 (13.0)
Coronary artery disease	31 (8.4)

The majority (70%; 37 of 53) of patients who entered the study with a history of AF or arrhythmia did not have a recurrence

Exclusion criterion: Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any class 3 (moderate) or 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.

Rule et al., ASH 2017 (abstract 151, oral presentation)

Ibrutinib in MCL: Management of ibrutinib in patients with bleeding or atrial fibrillation

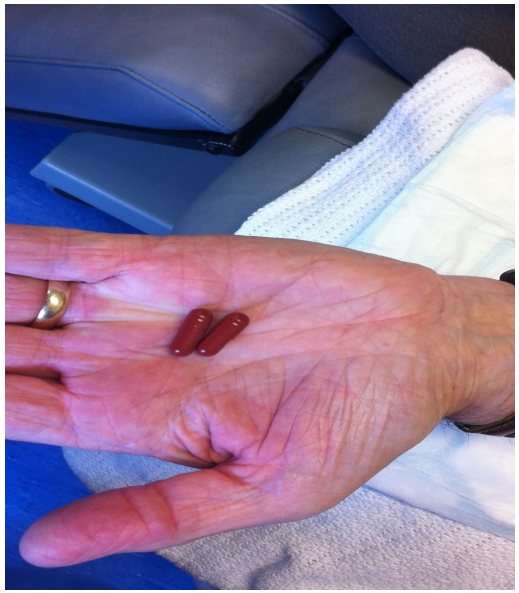
Safety Population	Ibrutinib (N = 370)
Grade ≥ 3 bleeding	21 (5.7%)
Dose reduction	1 (0.3%)
Discontinuation*	3 (0.8%)
Grade ≥ 3 atrial fibrillation	22 (5.9%)
Dose reduction	2 (0.5%)
Discontinuation*	0

*Treatment discontinuation

- **< 2% of 370 patients treated with ibrutinib discontinued or had a dose reduction due to grade ≥ 3 bleeding or AF**
- **No patients discontinued ibrutinib due to grade ≥ 3 AF**

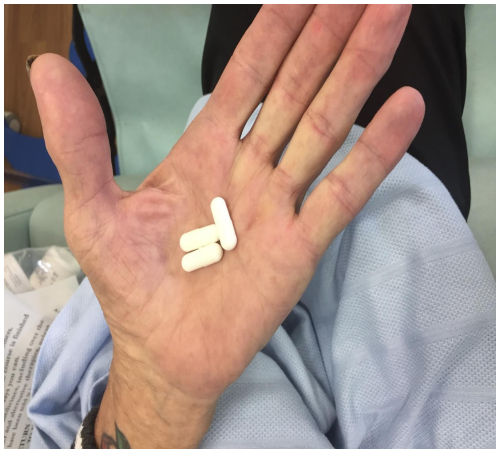
Rule et al., ASH 2017 (abstract 151, oral presentation)

Next generation BTKi's



ONO 4059

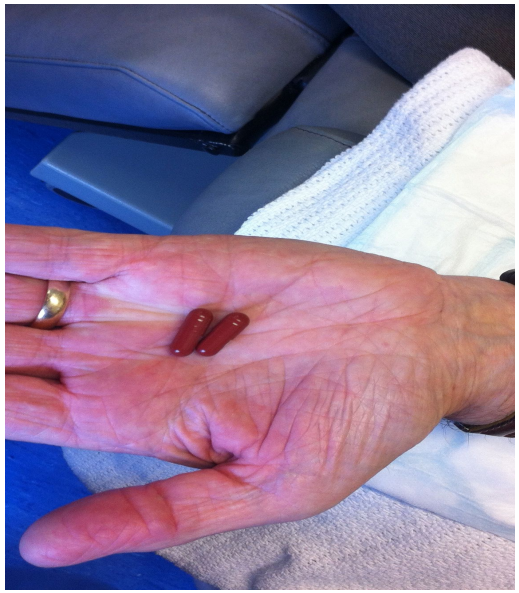
ACP 196



BGB 3111

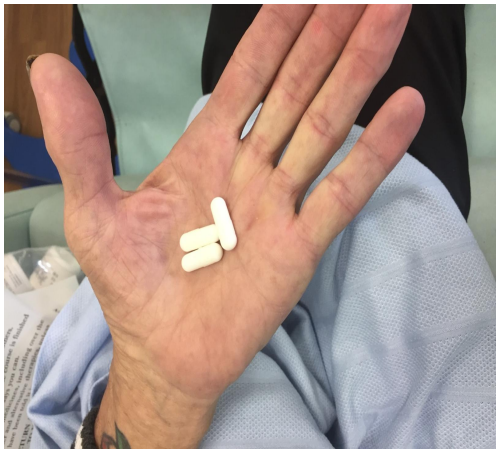
M 7583

Next generation BTKi's



Tirabrutinib

Acalabrutinib



Zanubrutinib

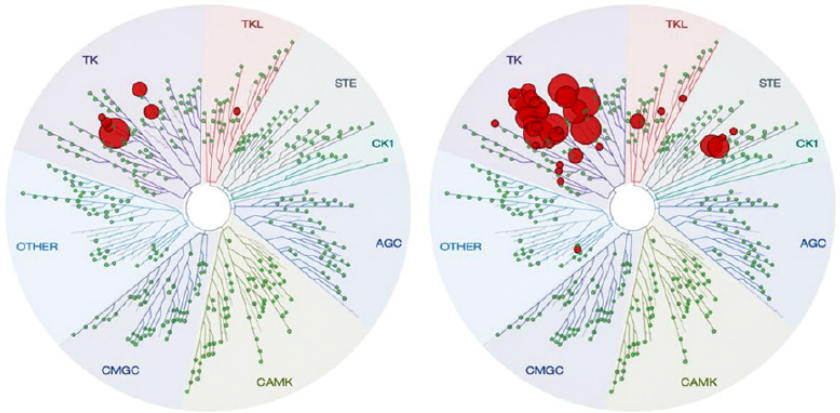
M 7583


Member
Michael Wang, MD
U.T. M.D. Anderson Cancer Center
Houston, TX
Member

Acalabrutinib (ACP-196)

- Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib *in vitro*

Kinase Selectivity Profiling at 1 μM



Larger red circles represent stronger inhibition

Kinase Inhibition Average IC_{50} (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10
ITK	>1000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1000	5.3
ERBB2	~1000	6.4
ERBB4	16	3.4
BLK	>1000	0.1
JAK3	>1000	32

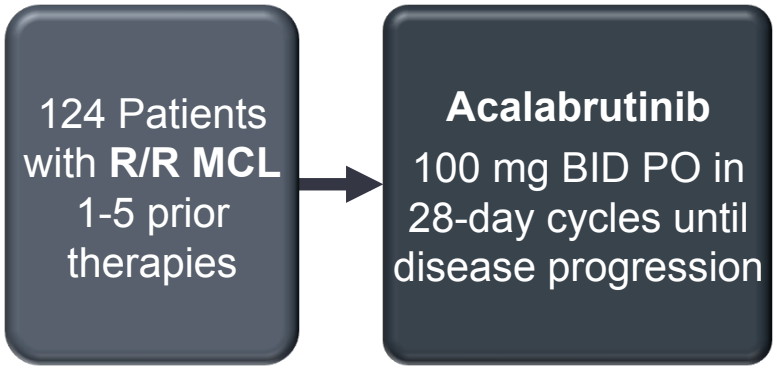
BLK = B lymphocyte kinase; BMX = bone marrow tyrosine kinase gene in chromosome X; BTK = Bruton tyrosine kinase; EGFR = epidermal growth factor receptor; ERBB2 = erb-b2 receptor tyrosine kinase; ERBB4 = erb-b4 receptor tyrosine kinase; IC50 = inhibitory concentration of 50%; ITK = interleukin-2-inducible T-cell kinase; JAK3 = Janus kinase 3; TEC = tyrosine kinase expressed in hepatocellular carcinoma; TXK = T and X cell expressed kinase.

Barf T, et al. *J Pharmacol Exp Ther*. 2017;363(2):240-252.

Byrd et al., ASH 2017 (abstract 498, oral presentation)

ACE-LY-004: Acalabrutinib monotherapy in R/R MCL

- Enrollment: March 12th, 2015, through January 5th, 2016, at 40 sites across 9 countries



Data cutoff: February 28, 2017

Primary endpoint:
- ORR by investigator assessment based on the Lugano Classification[1]

Secondary endpoints:
- ORR by Independent Review Committee (IRC) assessment
- DOR, PFS, OS
- Safety
- Pharmacokinetics and pharmacodynamics

Exploratory endpoints:
- Time to response
- IRC-assessed ORR per the 2007 International Harmonization Project criteria[2]

BID = twice daily; DOR = duration of response; MCL = mantle cell lymphoma; ORR = overall response rate; PFS = progression-free survival; PO = orally; R/R = relapsed/refractory.
1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-68. 2. Cheson BD, et al. *J Clin Oncol.* 2007;25:579-86.

Wang et al., ASH 2017 (abstract 155, oral presentation)

ACE-LY-004: Baseline patient characteristics

Characteristic	N=124
Median age, years (range)	68 (42-90)
Male sex, n (%)	99 (80)
ECOG PS ≤1, n (%)	115 (93)
Simplified MIPI score, n (%)[a]	
Low risk (0-3)	48 (39)
Intermediate risk (4-5)	54 (44)
High risk (6-11)	21 (17)
Ann Arbor Stage IV disease, n (%)	93 (75)
Tumor bulk, n (%)	
≥5 cm	46 (37)
≥10 cm	10 (8)
Extranodal disease, n (%)	90 (73)
Bone marrow	63 (51)
Gastrointestinal	13 (10)
Lung	12 (10)

[a] Missing data, n=1 patient.
ECOG PS = Eastern Cooperative Oncology Group performance status; MIPI = Mantle Cell Lymphoma International Prognostic Index.

Wang et al., ASH 2017 (abstract 155, oral presentation)

Response to acalabrutinib

- The primary endpoint was investigator-assessed ORR according to the 2014 Lugano Classification[1]
- High concordance was observed between investigator- and IRC-assessed ORR and CR (91% and 94%, respectively)
- IRC-assessed ORR by 2007 IHP criteria (exploratory endpoint) was 75% with a CR rate of 30%[2]

ORR using the 2014 Lugano Classification

	N=124	
	Investigator assessed n (%)	**IRC assessed n (%)**
ORR (CR + PR)	100 (81)	99 (80)
Best response		
CR	49 (40)	49 (40)
PR	51 (41)	50 (40)
SD	11 (9)	9 (7)
PD	10 (8)	11 (9)
Not evaluable	3 (2)	5 (4)

CR = complete response; IHP = International Harmonization Project; IRC = Independent Review Committee; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.

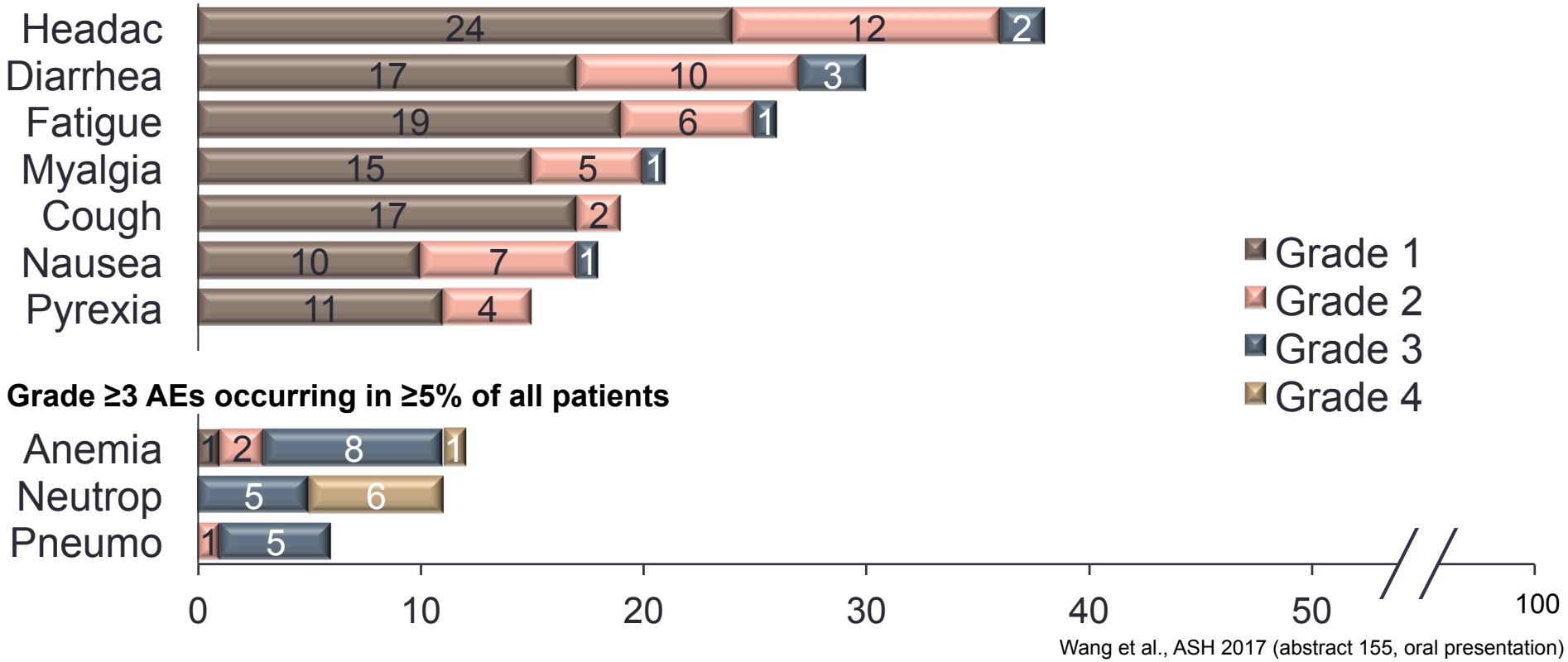
1. Cheson BD, et al. *J Clin Oncol* 2014;32:3059-68. 2. Cheson BD, et al. *J Clin Oncol* 2007;25:579-86.

Wang et al., ASH 2017 (abstract 155, oral presentation)

ACE-LY-004: Results

- At a median follow-up of 15.2 months, 56% of patients remain on treatment

AEs occurring in ≥15% of all patients

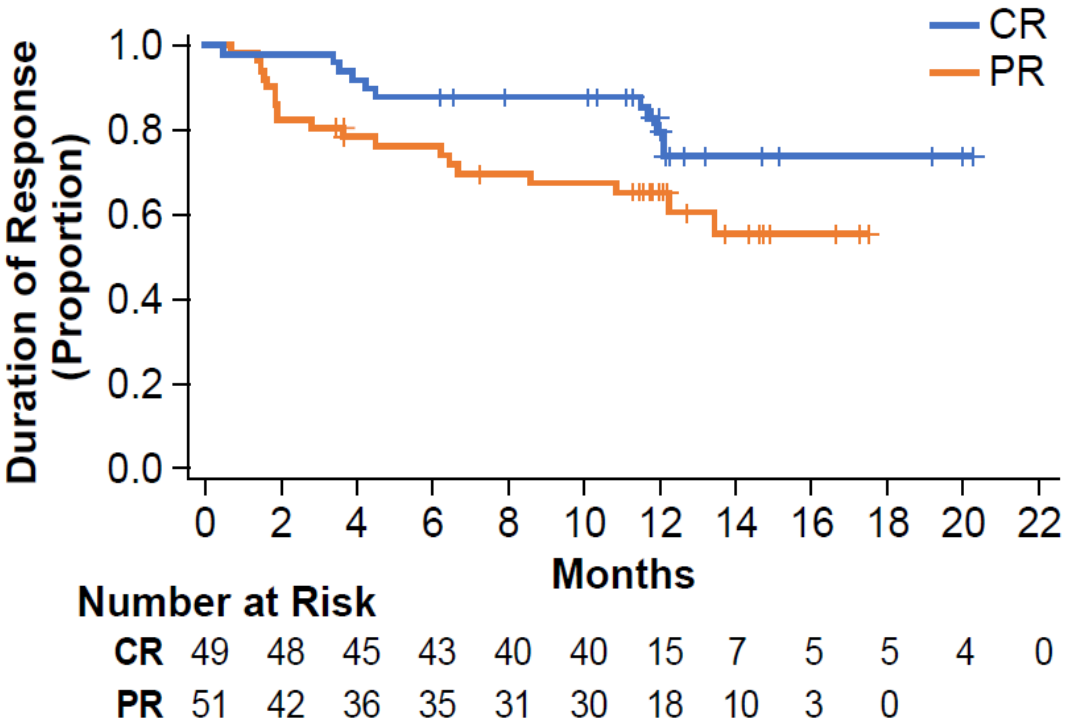


Grade ≥3 AEs occurring in ≥5% of all patients

Wang et al., ASH 2017 (abstract 155, oral presentation)

ACE-LY-004: Duration of response

- Median time to response was 1.9 months (range 1.5-4.4)
  - 92% of responders had initial response by end of cycle 2
- Median DOR has not been reached; the 12-month DOR rate was 72% (95% CI: 62%, 80%)

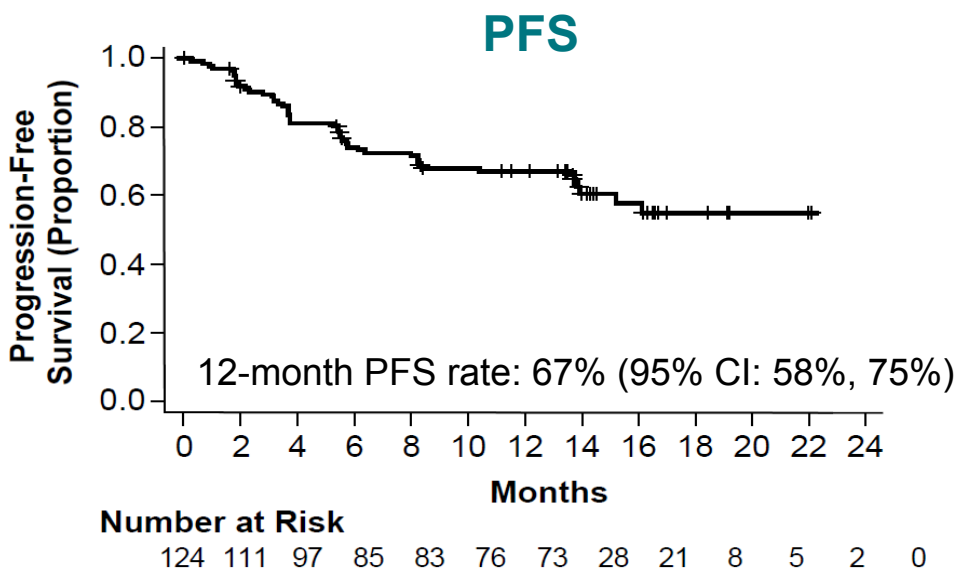


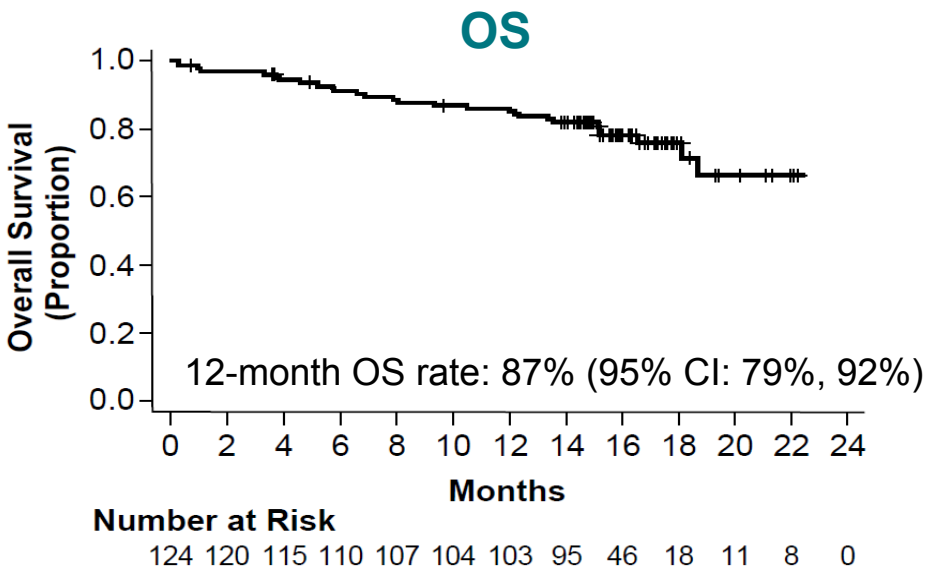
CR = complete response; DOR = duration of response; PR = partial response.

Wang et al., ASH 2017 (abstract 155, oral presentation)

ACE-LY-004: PFS and OS

- Median PFS and median OS have not been reached





Wang et al., ASH 2017 (abstract 155, oral presentation)

OS = overall survival; PFS = progression-free survival.

Safety and Activity of BTK Inhibitor BGB-3111 in patients with DLBCL, MCL, FL and MZL

Dose escalation

Dose	Enrolled (indolent, aggressive)
40 mg QD	4 (0,1)
80 mg QD	5 (0,1)
160 mg QD	6 (0,2)
320 mg QD	6 (0,1)
160 mg BID	4 (0,2)

Recommended Phase 2 dose (RP2D)

320 mg QD
or
160 mg BID

Dose expansion

Population	RP2D	Disease	Planned
R/R	BID, QD	MCL, MZL, FL, GCB DLBCL	40
R/R	BID	Non-GCB DLBCL	40
R/R	BID, QD	MCL	20
TN	BID, QD	MCL	20
R/R	BID	iNHL	40

Eligibility

- WHO-defined B-cell malignancy
- No available higher priority treatment
- ECOG 0-2
- ANC > 1000μ L, platelets > 100,000/μL
- Adequate renal and hepatic function
- No significant cardiac disease

Primary endpoints

- Safety including AEs and SAEs
- Recommended phase 2 dose

Select secondary endpoints

- Pharmacokinetics
- Efficacy

Tam et al., ASH 2017 (abstract 152, oral presentation)

BGB-3111 in patients with DLBCL/MCL (n=65): most frequent and selected AEs

Adverse event	All grades, n(%)	Grade 3-5, n(%)
Petechiae/purpura/contusion	16 (25)	0
Diarrhea	15 (23)	1 (2)
Constipation	14 (22)	0
Fatigue	12 (18)	0
Upper respiratory tract infection	12 (18)	1 (2)
Anemia	11 (17)	7 (11)
Cough	10 (15)	0
Pyrexia	10 (15)	2 (3)
Thrombocytopenia	10 (15)	6 (9)
Neutropenia	8 (12)	6 (9)
Pneumonia	6 (9)	4 (6)*

Event, n(%)	DLBCL/MCL (n=65)
Patients with ≥1 AE grade ≥3	39 (60)
Patients with ≥1 serious AE	26 (40)
Event leading to treatment discontinuation	8 (12)
Fatal AE	6 (9)
AE of special interest	
Petechiae/purpura/contusion	16 (25)
Diarrhea	15 (23)
Hypertension	5 (8)
Severe haemorrhage	2 (3)
Atrial fibrillation	2 (3)

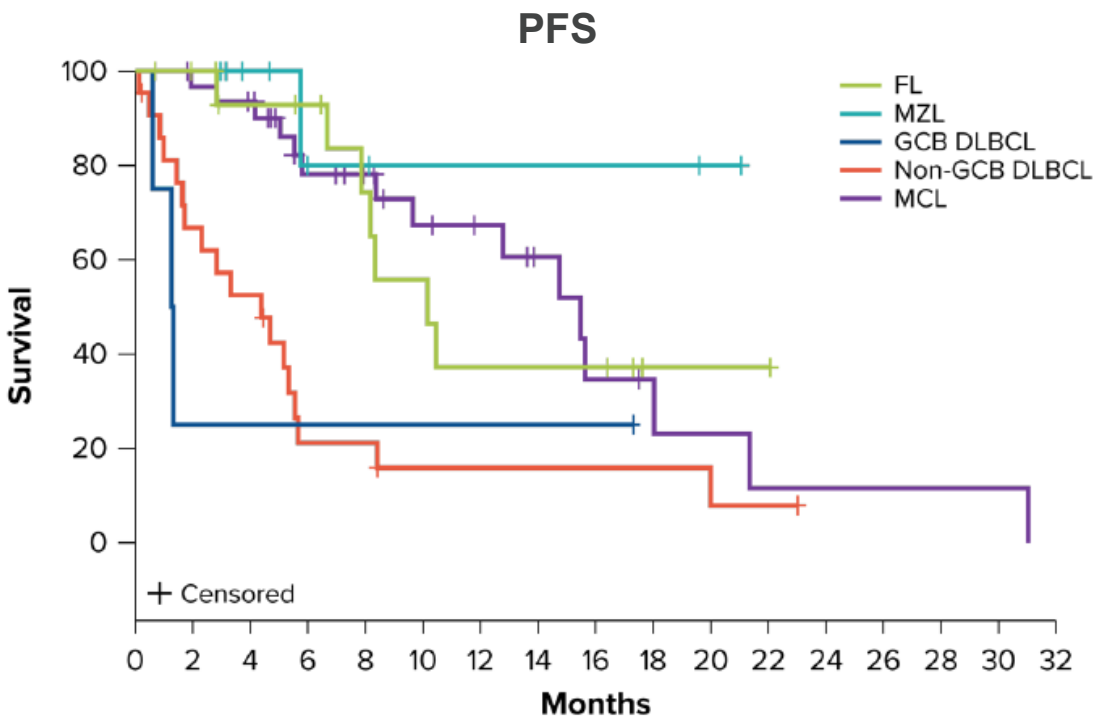
*1 Grade 5 event in the setting of progressive disease

Tam et al., ASH 2017 (abstract 152, oral presentation)

BGB-3111 in patients with MCL: response

Response (based on CT for majority of patients)	MCL* (n=32)
Median efficacy follow-up, months (range)	9.5 (0.8-31.9)
Best response, n(%)	
ORR	28 (88)
CR	8 (25)
PR	20 (63)
SD	1 (3)
PD	1 (3)
NE	2** (6)

*In MCL patients treated with minimum of 320 mg/d ORR is 93% and CR is 28%
** Off study for AE before response assessment



Tam et al., ASH 2017 (abstract 152, oral presentation)

BTKI TRIALS IN MCL (2017)

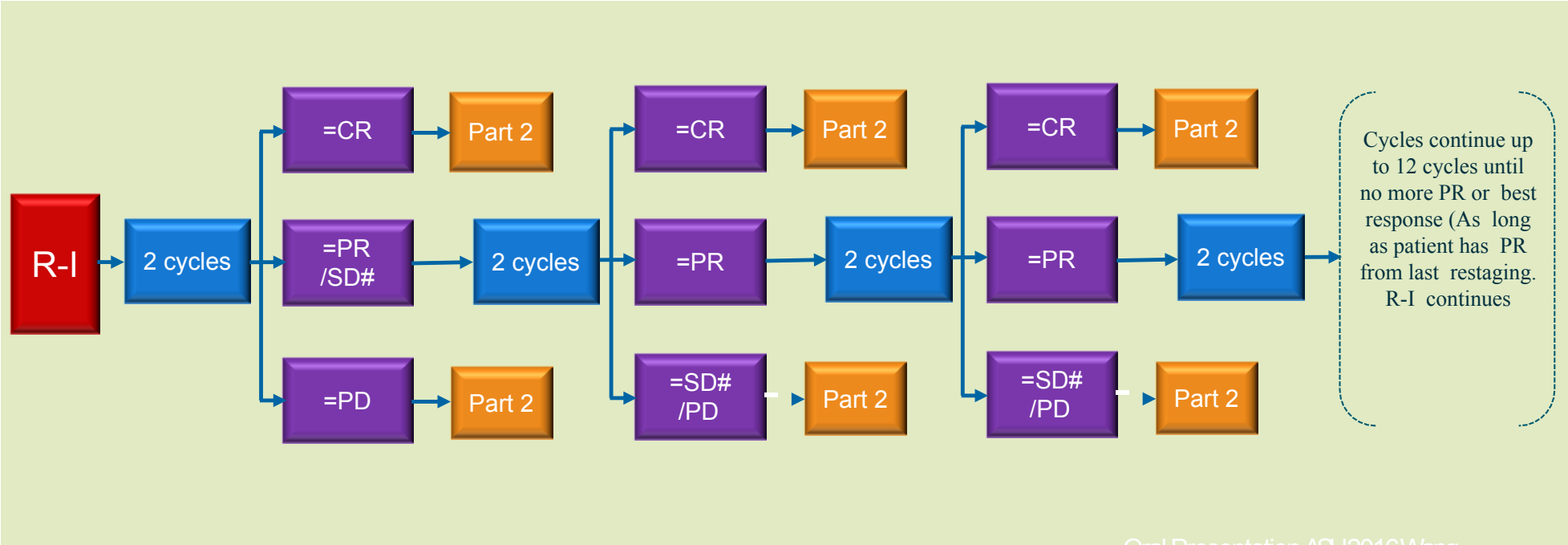
Trials with BTKi in MCL

Study ID	Intervention	Condition	Phase	Primary endpoint(s)	N	Completion[a]	Approvals
NCT02213926	Acalabrutinib	R/R MCL	2	ORR (at least 1 year)	124	Feb 2017	FDA (Aug 2017)
NCT02328014	Acalabrutinib + ACP-319	NHL, MM and B-ALL[b]	1/2	AEs (up to 1 year)	126[c]	Aug 2017	None
NCT02981745	CT-1530	R/R BCNHL, CLL, MCL, WM, MZL, DFCL and DLBCL	1/2	DLTs (28 days) MTD and/or RP2D	200[c]	Sep 2018	None
NCT03037645	SNS-062	R/R CLL, LL, MCL, SLL and WM	1/2	MTD and/or RP2D (up to 21 months) ORR (up to 24 months)	124[c]	Sep 2018	None
NCT03206970	BGB-3111	R/R MCL	2	ORR (up to 3 years)	80[c]	Nov 2018	None
NCT03162536	ARQ-531	R/R BCL, DLBCL, SLL, CLL, MCL, WM	1	AEs (up to 28 weeks) RP2D (up to 24 weeks)	120[c]	Dec 2018	None
NCT02825836	M7583	R/R BCM, MCL and DLBCL	1/2	DLTs (up to 28 days) BOR (up to 6 months)	60[c]	Oct 2019	None
NCT02717624	Acalabrutinib + BR	Untreated and R/R MCL	1b	TEAEs (timeframe unclear)	48[c]	Feb 2021	None
NCT02362035	Acalabrutinib + Pembrolizumab	NHL, MM, HL, CLL, RS, WM[b]	1b/2	TEAEs (2 years)	159	Apr 2021	None
NCT02972840	Acalabrutinib + BR vs placebo + BR	Untreated MCL	3	PFS (48 months)	546[c]	Oct 2022	None

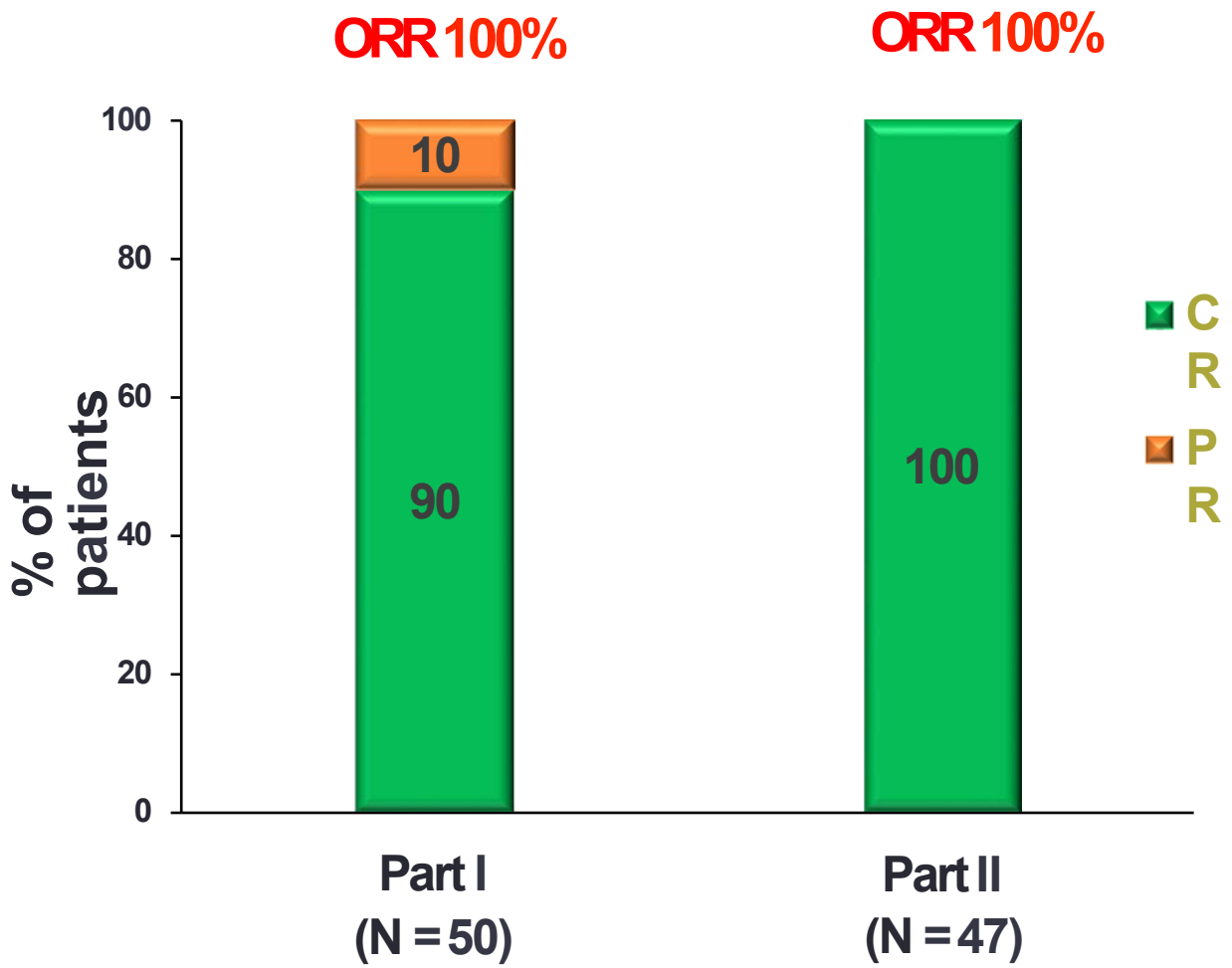
NCCN guideline placement	Treatment	Phase 1	Phase 1/2	Phase 2	Phase 3	Approved
Aggressive induction	Ibrutinib (maintenance)			NCT02242097		
	Ibrutinib + R-DHAP or R-DHAOx	NCT02055924[c]				
	Ibrutinib + R-CHOP	NCT01569750[b]				
Less aggressive induction	Ibrutinib + BR				NCT01776840	
	Acalabrutinib + BR	NCT02717624			NCT02972840	
	Ibrutinib + LR		NCT03232307			
	Acalabrutinib + ACP-319		NCT02328014[a,b]			
	Acalabrutinib + pembrolizumab		NCT02362035[a,b]			
	Ibrutinib + pembrolizumab		NCT03153202[a,c]			
Second-line	Ibrutinib	NCT00849654[b]		NCT01236391	NCT01804686	November 2013
	Acalabrutinib			NCT02213926		August 2017
	Ibrutinib + venetoclax	NCT02419560		NCT02471391	NCT03112174	
	Ibrutinib vs temsirolimus				NCT01646021	
	BGB-3111			NCT03206970		
	Ibrutinib + R			NCT01880567		
	Ibrutinib + LR	NCT02446236		NCT02460276		
	Ibrutinib + obinutuzumab			NCT02736617		
	Acalabrutinib + ACP-319		NCT02328014[a,b]			
	Acalabrutinib + pembrolizumab		NCT02362035[a,b]			
	CT-1530		NCT02981745[b]			
	SNS-062		NCT03037645[c]			
	M7583		NCT02825836[c]			
	ARQ-531		NCT03162536[c]			
	Ibrutinib + obinutuzumab + GDC-0199		NCT02558816			
	Ibrutinib + Ublituximab		NCT02013128[c]			
	Ibrutinib + bortezomib		NCT02356458			
	Ibrutinib + Ixazomib		NCT03323151			
	Ibrutinib + pembrolizumab	NCT02950220[c]	NCT03153202[a,c]			
	Ibrutinib + carfilzomib		NCT02269085			
	Ibrutinib + cirmtuzumab		NCT03088878[c]			
	Ibrutinib + lenalidomide	NCT01955499[c]				
	Ibrutinib + BR	NCT01479842[c]				
	Ibrutinib + BR + venetoclax	NCT03295240				
	Ibrutinib + palbociclib	NCT02159755				
	Ibrutinib + selinexor	NCT02303392[c]				
	Ibrutinib + umbralisib	NCT02268851[c]				
	Ibrutinib + buparlisib	NCT02756247[c]				
Third-line and beyond	Ibrutinib (after bortezomib)			NCT01599949		
	Ibrutinib (after DSCT)			NCT02869633[c]		

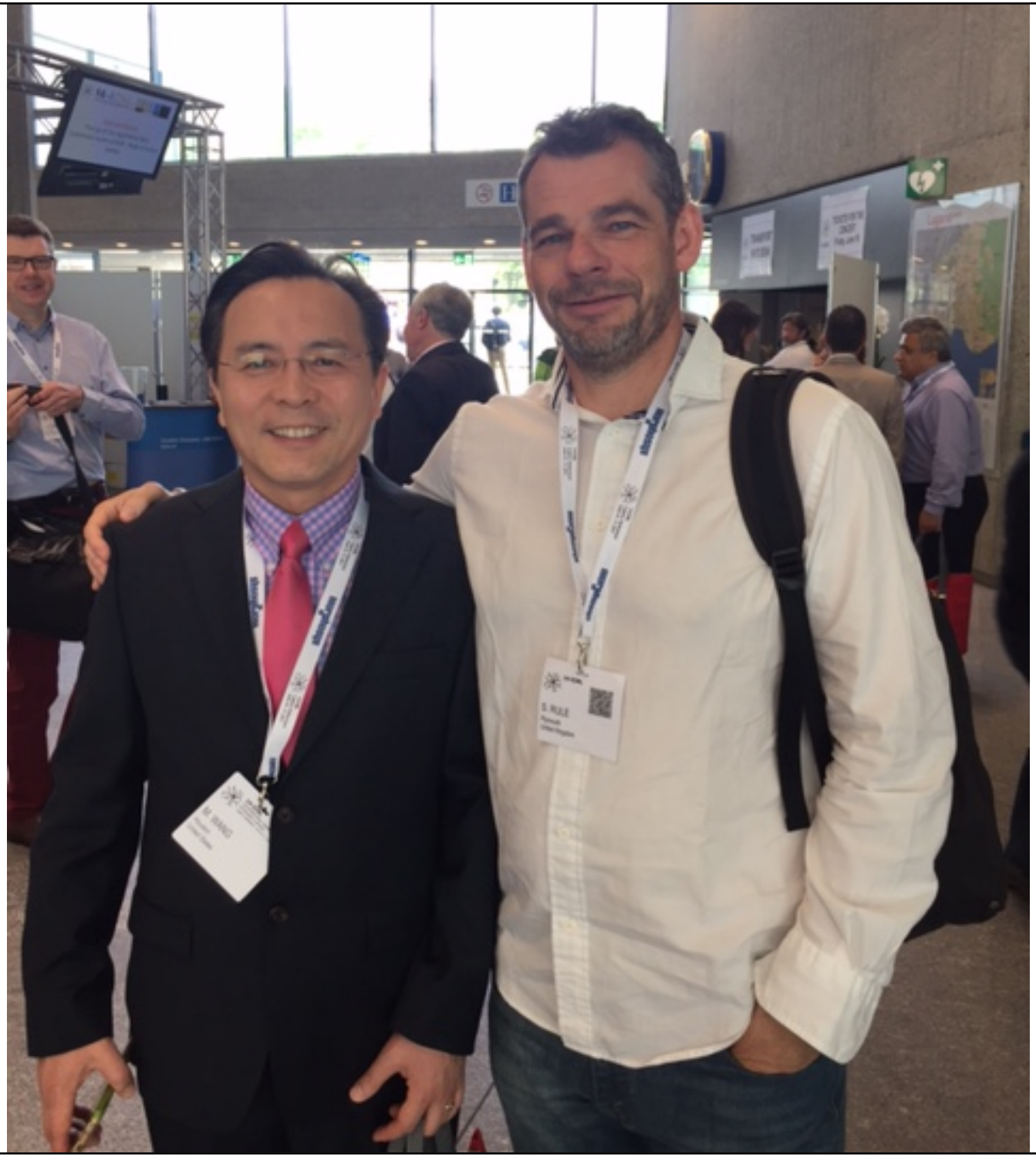
Study Therapy PART I: Chemo-free Ibrutinib + Rituximab

- Oral ibrutinib at 560 mg daily, each cycle is 28 days
- 4 weekly loading doses IV rituximab at 375 mg/m² in Cycle 1, then 1 dose/cycle in Cycles 3-12
- Restage every 2 cycles
- Any time CR in PART I, will enter PART II
- Up to 12 months to reach best response.



Window I/II Study: the Best Response Rate





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

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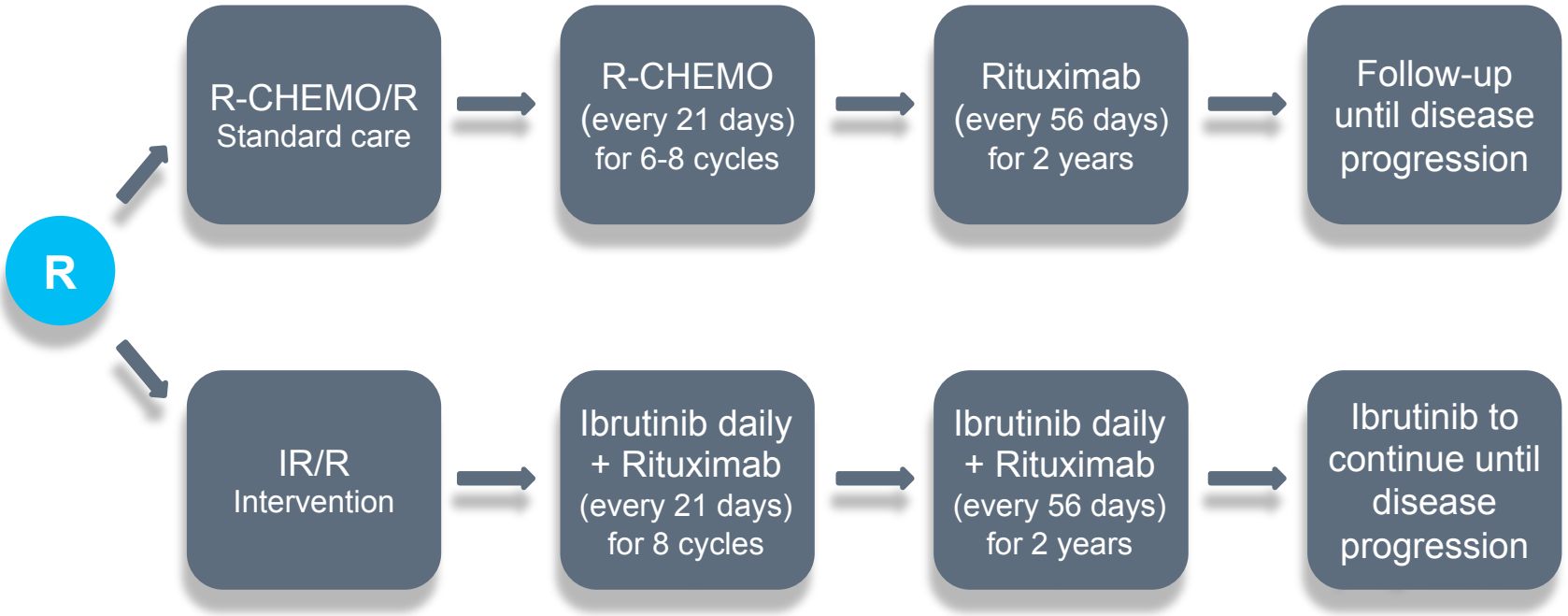
NHS Trust

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

Summary

- Ibrutinib
  - Early use translates into better outcomes
  - No evolving toxicity
  - Combination trials on-going
- ‘Second generation BTKi’
  - Efficacy is broadly the same
  - Appear to have fewer cardiac events
  - Acalabrutinib licensed in the USA for MCL