ACALABRUTINIB

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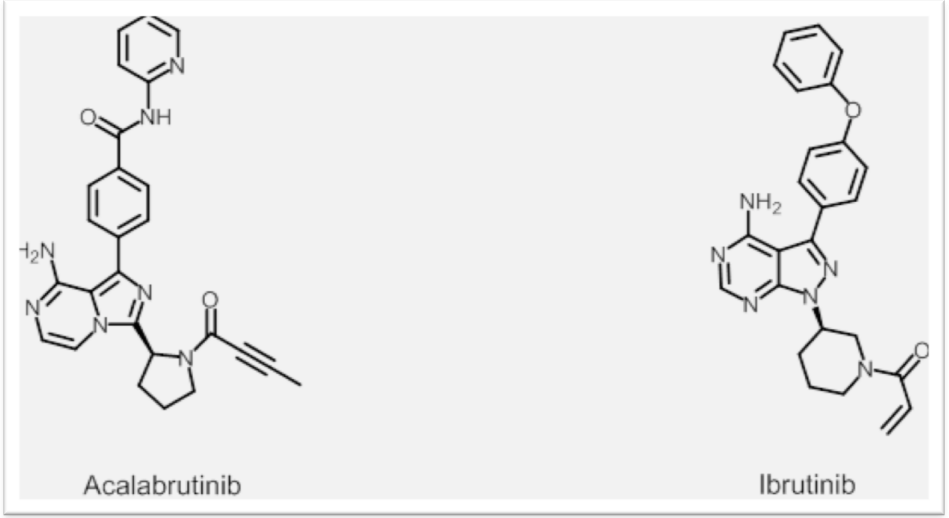
ACALABRUTINIB: A HIGHLY SELECTIVE, POTENT BRUTON TYROSINE KINASE (BTK) INHIBITOR

Acalabrutinib was developed to increase the degree of BTK inhibition

- Very low binding to interleukin-2 inducible T-cell kinase (ITK), TEC protein tyrosine kinase (TEC), and epidermal growth factor receptor (EGFR)

- Acalabrutinib selectively binds with a short half-life allowing twice-daily dosing and near total BTK inhibition
  - Potentially reducing drug resistance
- Acalabrutinib appears to improve substantially on the specificity of first generation BTK inhibitors

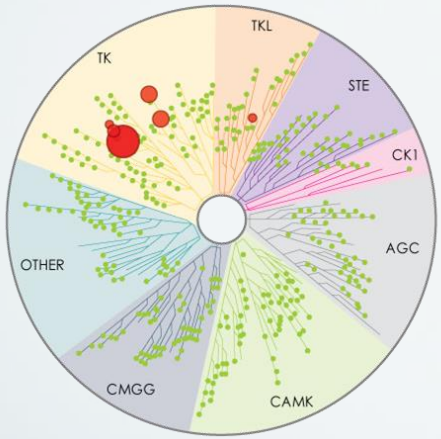


ACALABRUTINIB (ACP-196)

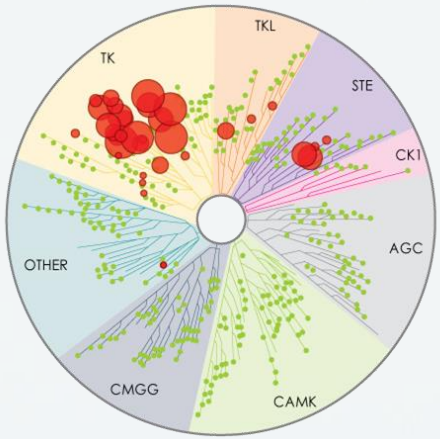
- Acalabrutinib is a highly selective, potent BTK inhibitor
- Minimal off-target effects on TEC, EGFR, or ITK signaling in vitro

Kinase Selectivity Profiling at 1 μmol/L[1]

Acalabrutinib



Ibrutinib



Larger red circles represent stronger inhibition

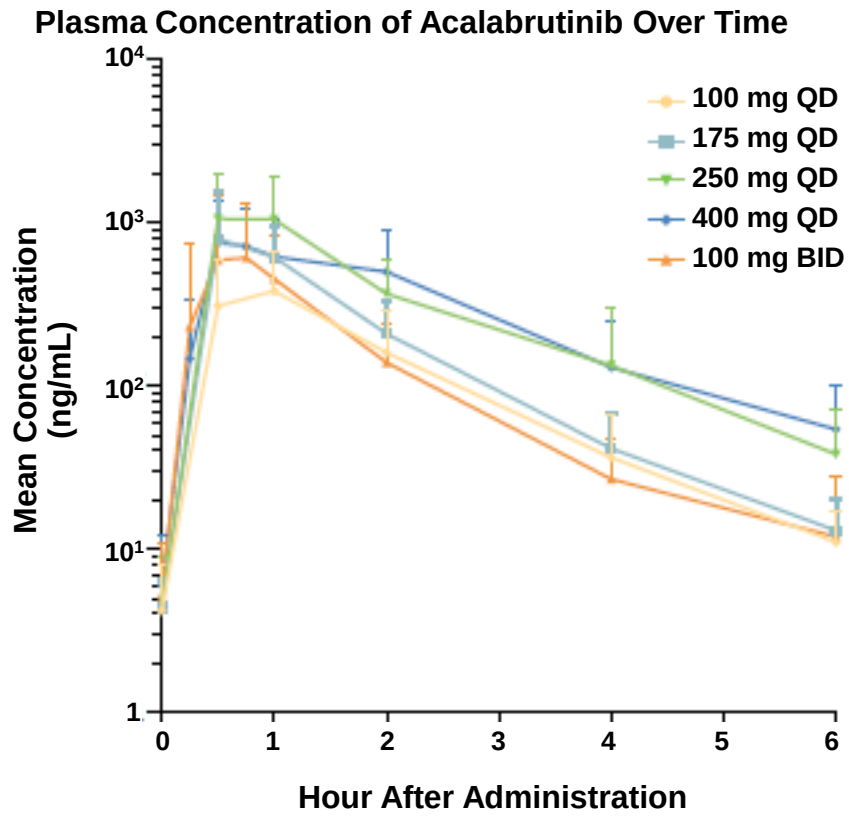
Kinase Inhibition IC_{50} (nmol/L)[1]

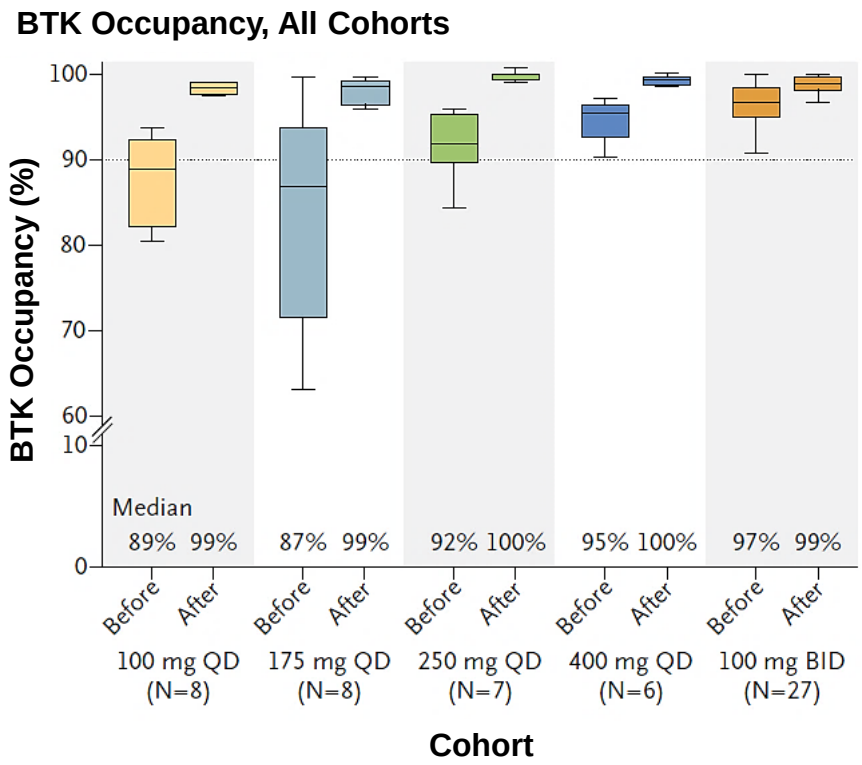
Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	93	7.0
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

[1]Covey AACR 2015. Abstract 2596.

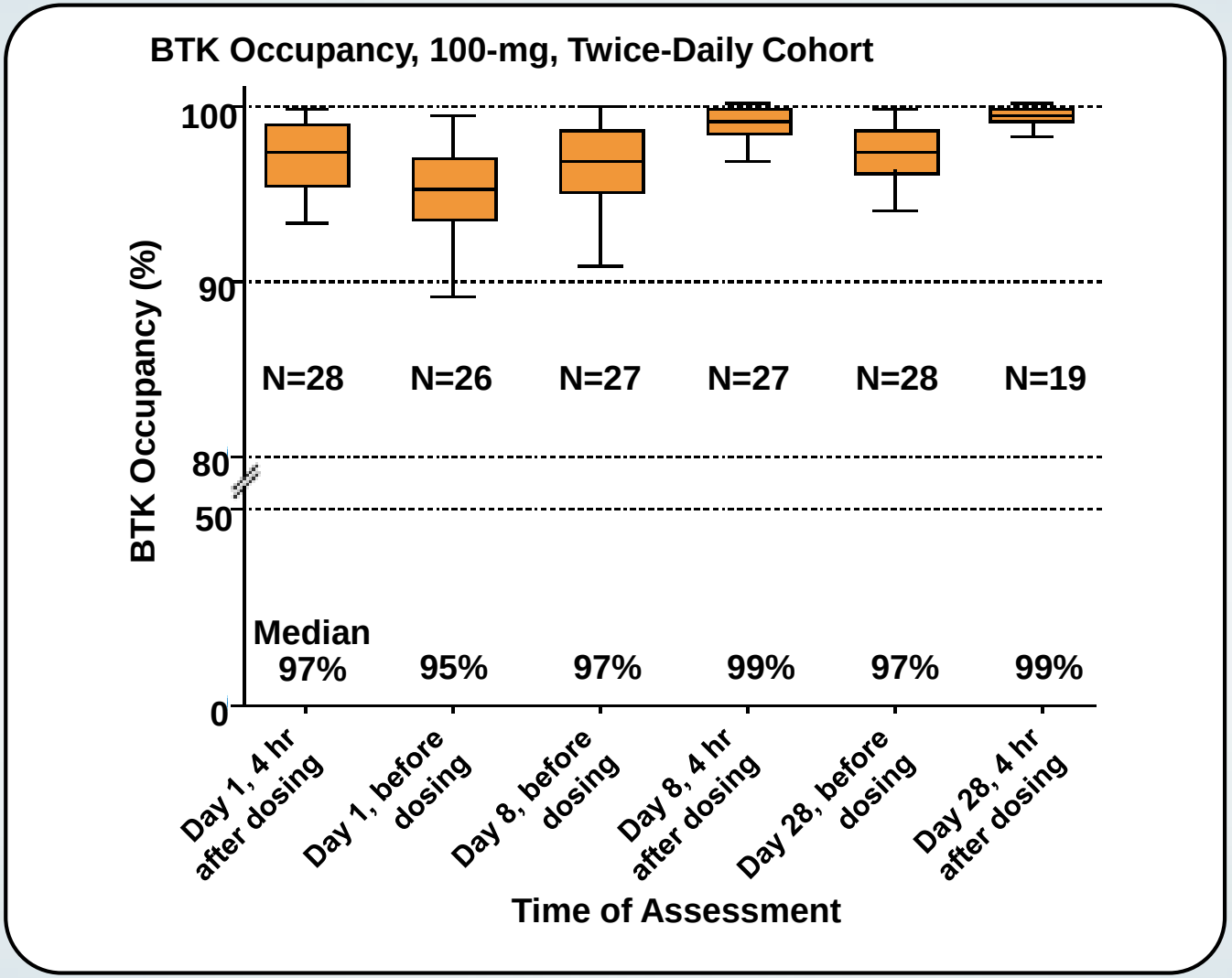
PHARMACOKINETICS/PHARMACODYNAMICS

1-hour half-life; rapid oral absorption; complete BTK occupancy





ACALABRUTINIB TWICE-DAILY DOSING (COMPLETE AND CONTINUOUS BTK COVERAGE)



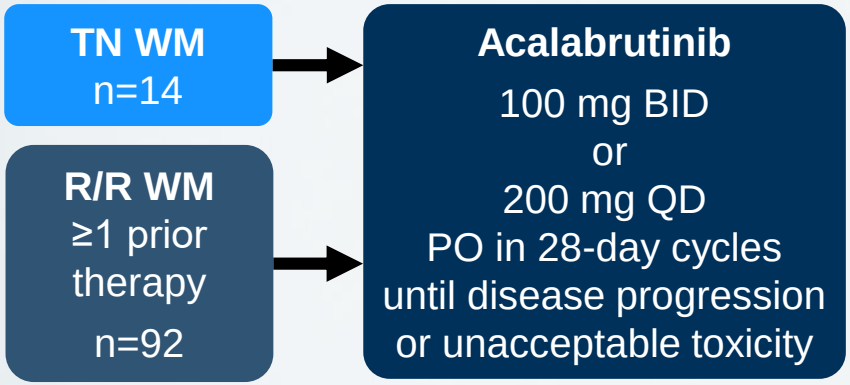
Acalabrutinib in Patients With Waldenström Macroglobulinemia

Roger Owen,[1] Helen McCarthy,[2] Simon Rule,[3] Shirley D'Sa,[4] Sheeba Thomas,[5] Francesco Forconi,[6] Thomas Anderson,[7] Marie José Kersten,[8] Pier Luigi Zinzani,[9] Sunil Iyengar,[10] Jaimal Kothari,[11] Monique Minnema,[12] Efstathios Kastritis,[13] Dih-Yih Chen,[14] Raquel Izumi,[14] Diana Mittag,[15] Priti Patel,[14] J. Greg Slatter,[14] Helen Wei,[14] and Richard R. Furman[16]

[1]St James's University Hospital, Leeds, UK; [2]Royal Bournemouth Hospital, Bournemouth, UK; [3]Plymouth University Medical School, Plymouth, UK; [4]University College London Hospitals NHS Trust, London, UK; [5]MD Anderson Cancer Center, Houston, TX, USA; [6]University of Southampton Hospital Trust, Southampton, UK; [7]Texas Oncology-Bedford, Bedford, TX, USA; [8]Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; on behalf of the Lunenburg Lymphoma Phase I/II Consortium – HOVON/LLPC; [9]Institute of Hematology University of Bologna, Bologna, IT; [10]Royal Marsden Hospital, London, UK; [11]Churchill Hospital, Oxford, UK; [12]University Medical Center Utrecht Cancer Center, Utrecht, The Netherlands; on behalf of the Lunenburg Lymphoma Phase I/II Consortium – HOVON/LLPC; [13]National and Kapodistrian University of Athens, Athens Greece; [14]Acerta Pharma, South San Francisco, CA, USA; [15]Acerta Pharma, Oss, The Netherlands; [16]Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA

ACE-WM-001: ACALABRUTINIB MONOTHERAPY IN WM

- Enrollment: September 8, 2014, through December 24, 2015, at 27 sites in 6 countries
- Data cutoff: February 13, 2018



All 200-mg QD patients (n=1 TN; n=5 R/R) were switched to 100 mg BID

Co-primary endpoints:

- ORR by investigator assessment based on the 6th IWWM Criteria[1]
- ORR by investigator assessment based on the modified 3rd IWWM Criteria[2]

Key secondary endpoints:

- DOR, PFS, OS
- Safety
- Pharmacokinetics

Exploratory endpoint:

- Pharmacodynamics

BID = twice daily; DOR = duration of response; IWWM = International Workshop on WM; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PO = orally; R/R = relapsed/refractory; TN = treatment naive; WM = Waldenström macroglobulinemia.

1. Owen RG, et al. *Br J Hematol*. 2013;160:171-176. 2. Kimby E, et al. *Clin Lymphoma Myeloma*. 2006;6(5):380-383.

KEY ELIGIBILITY CRITERIA

- Inclusion criteria:
  - TN cohort: patients with confirmed WM requiring treatment who are not eligible for chemoimmunotherapy
  - R/R cohort: relapsed after or refractory to ≥1 prior therapy for WM
  - Serum IgM > ULN or measurable nodal disease (≥1 lymph node ≥2 cm in longest diameter)
  - ECOG PS ≤2
- Exclusion criteria:
  - Prior BTK inhibitor therapy
  - Significant cardiovascular disease (uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any NYHA III-IV cardiac disease, or QTc >480 ms). Patients with prior or concurrent atrial fibrillation were not excluded
  - Required treatment with vitamin K antagonists or proton pump inhibitors

BTK = Bruton tyrosine kinase; ECOG PS = Eastern Cooperative Oncology Group performance status; Ig = immunoglobulin; NYYHA = New York Heart Association; QTc = corrected QT interval; R/R = relapsed/refractory; TN = treatment naive; ULN = upper limit of normal; WM = Waldenström macroglobulinemia.

BASELINE PATIENT CHARACTERISTICS

Characteristic	TN (n=14)	R/R (n=92)
Median age (range), years	73 (48-86)	69 (39-90)
Male sex, n (%)	10 (71)	63 (68)
ECOG PS ≤1, n (%)	12 (86)	88 (96)
Median time since initial WM diagnosis (range), years	0.4 (0.04-5.8)	6.1 (0.16-25.4)
Bone marrow involvement, n (%)	14 (100)	89 (97)[a]
Extramedullary disease, n (%)	9 (64)	59 (64)
Lymphadenopathy ≥1.5 cm	7 (78)	50 (85)
Splenomegaly ≥13 cm	4 (44)	26 (44)
Median serum IgM (range), mg/dL	4,615 (633-7530)	3,565 (291-9740)
>4,000 mg/dL, n (%)	9 (64)	37 (40)
Median absolute neutrophil count (range), cells $\times 10^9$/L	3.2 (0.4-7.6)	2.9 (0.6-9.2)
Median hemoglobin (range), g/dL	9.8 (6.2-14.1)	10.6 (6.0-15.4)
<11 g/dL, n (%)	11 (79)	53 (58)
<10 g/dL, n (%)	9 (64)	35 (38)
Median hematocrit (range), %	30 (19-41)	33 (19-46)
Median platelets (range), cells/mm^3	187,000 (36,00-364,000)	203,000 (20,000-526,000)
<100,000 cells/mm^3, n (%)	2 (14)	11 (12)

[a] The remaining n=3 patients were indeterminant.
ECOG PS = Eastern Cooperative Oncology Group performance status; Ig = immunoglobulin; R/R = relapsed/refractory; TN = treatment naive; WM = Waldenström macroglobulinemia.

PRIOR THERAPIES

Characteristic	R/R (n=92)
Median no. of prior therapies (range)	2 (1-7)
≥3 prior therapies, n (%)	41 (45)
Refractory disease, n (%)[a]	33 (36)
Prior therapies, n (%)	
Anti-CD20 therapy (single agent or part of a regimen)	80 (87)
Cyclophosphamide-based regimen	32 (35)
Chlorambucil-based regimen	29 (32)
Proteasome inhibitor-based regimen	28 (30)
Purine analogue +/- rituximab	21 (23)
Bendamustine +/- rituximab	18 (20)
CHOP/CVP/COP +/- rituximab	18 (20)
Purine analogue + cyclophosphamide +/- rituximab	15 (16)
Other[b]	22 (24)

[a] Best overall response rate was stable disease or progressive disease.
[b] Includes plasmapheresis (n=7), other chemotherapy regimens not listed (n=6), DHAP/ESHAP +/- rituximab (n=4), corticosteroids alone (n=3), IMiD alone (n=3), IMiD + cyclophosphamide-based regimen (n=2), and proteasome inhibitor + cyclophosphamide-based regimen (n=1).
R/R = relapsed/refractory.

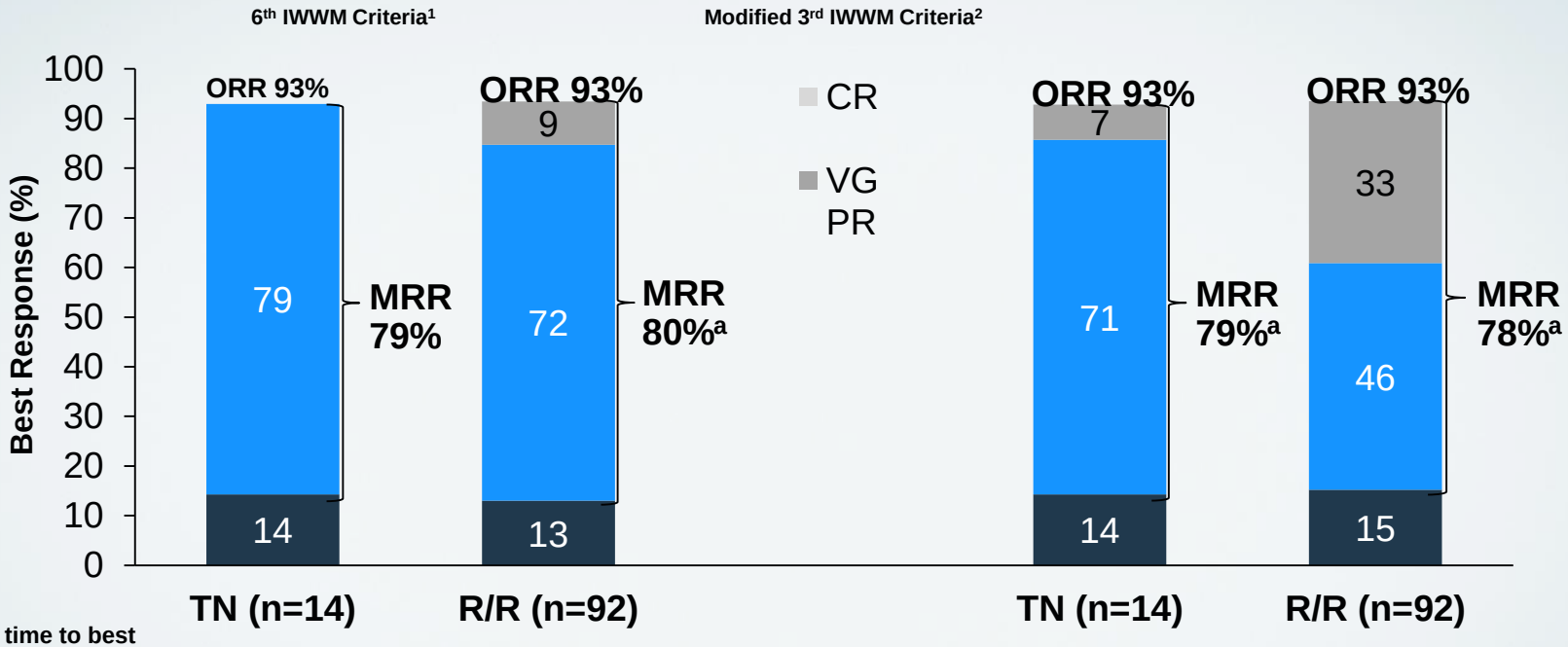
PATIENT DISPOSITION

- At a median follow-up of 27.4 months, 72% of all patients remain on study therapy

Characteristic	TN (n=14)	R/R (n=92)
Median follow-up (range), months	29.2 (10.2-32.9)	27.3 (4.6-40.7)
Remain on acalabrutinib, n (%)	7 (50)	69 (75)
Reason for discontinuation of acalabrutinib, n (%)		
Disease progression	0	9 (10)
Adverse event[a]	3 (21)	4 (4)
Investigator's discretion[b]	2 (14)	4 (4)
Death[c]	1 (7)	3 (3)
Withdrawal of consent	1 (7)	1 (1)
Initiation of alternative cancer therapy[d]	0	2 (2)

[a] Adverse events leading to discontinuation in TN patients: coronary artery disease, Crohn's disease, and increased transaminases (n=1/each); in R/R patients: cold-type hemolytic anemia, glioblastoma multiforme, malignant ascites, seizure (due to glioblastoma), and metastatic malignant melanoma (n=1/each).
[b] Removed from study by investigator decision due to inadequate response (n=3); overall clinical decline not related to a specific AE (n=2); not having a confirmatory IgM for PD (n=1).
[c] TN (n=1): ischemic heart disease (not treatment-related); R/R (n=1 each): chronic inflammatory demyelinating polyneuropathy (not treatment-related), intracranial hematoma (treatment-related), and unknown (317 days after last dose).
[d] Due to esophageal cancer (n=1) and unresponsiveness to acalabrutinib treatment leading to initiation of another therapy (n=1).
AE = adverse event; PD = progressive disease; IG = immunoglobulin; R/R = relapsed/refractory; TN = treatment naive.

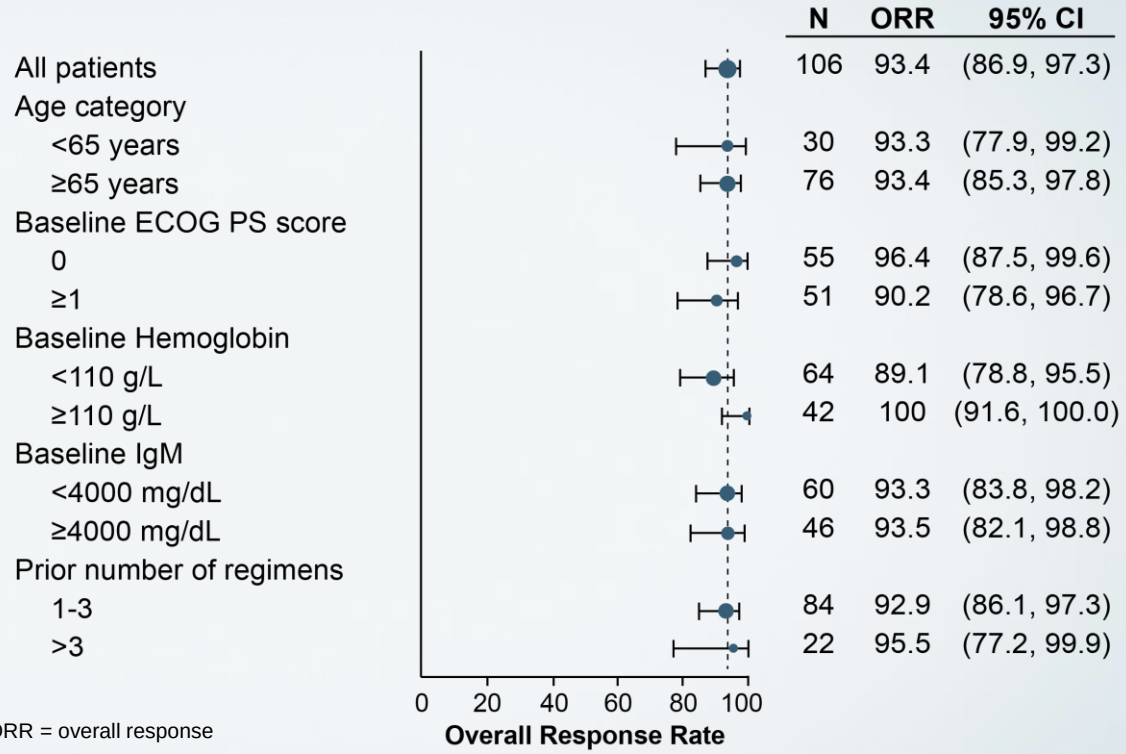
RESPONSE TO ACALABRUTINIB



[a] MRR may not equal PR + VGPR + CR as shown due to rounding.
CR = complete response; IWWM = International Workshop on Waldenström macroglobulinemia; MR = minor response; MRR = major response rate (≥ PR); ORR = overall response rate (≥ MR); PR = partial response; R/R = relapsed/refractory; TN = treatment-naive; VGPR = very good partial response.
1. Owen RG, et al. *Br J Hematol*. 2013;160:171-176. 2. Kimby E, et al. *Clin Lymphoma Myeloma*. 2006;6(5):380-383.

RESPONSE TO ACALABRUTINIB: SUBGROUP ANALYSIS

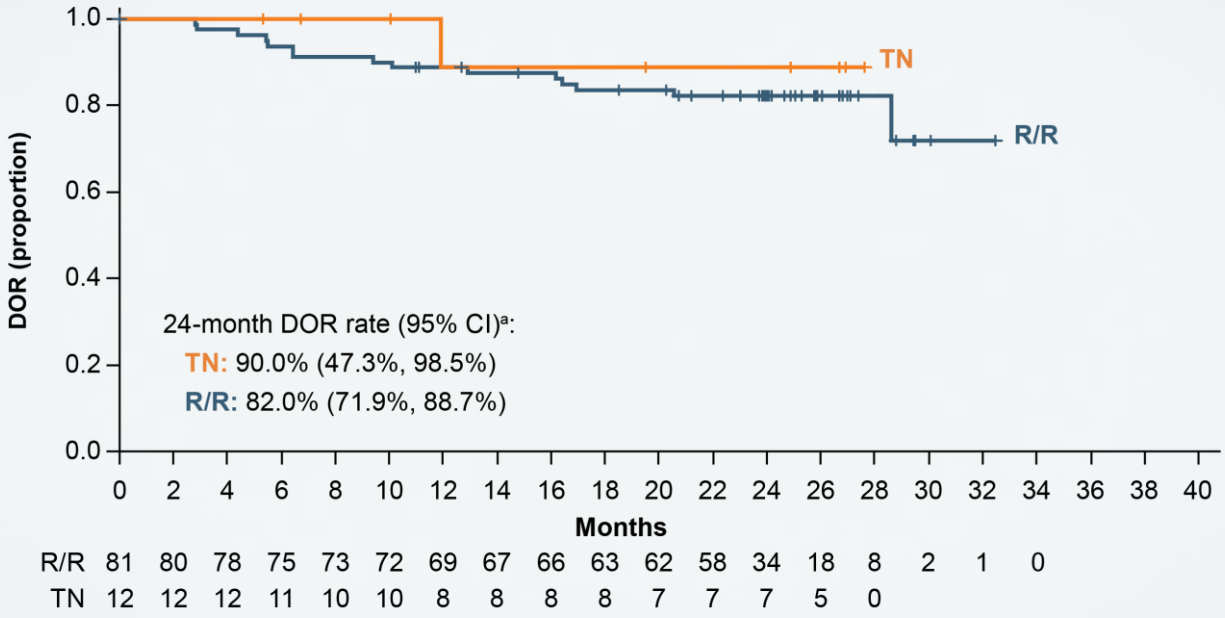
- ORR was consistent across prespecified subgroups, including patients with:
  - ≥3 Prior therapies (95.5%)
  - Age ≥65 years (93.4%)



ECOG = Eastern Cooperative Oncology Group; Ig = immunoglobulin; ORR = overall response rate.

DURATION OF RESPONSE

- Median DOR was not reached in either cohort

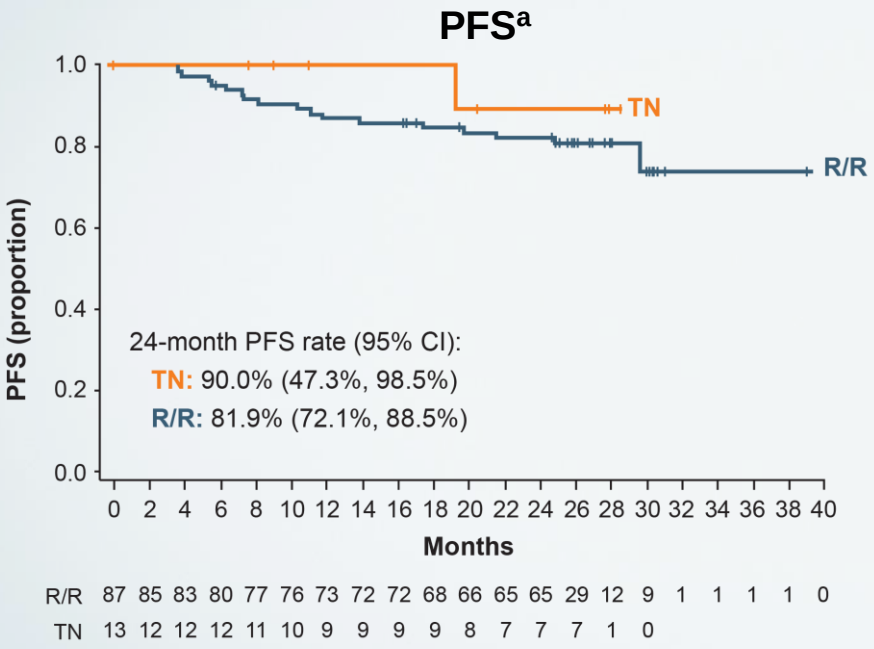


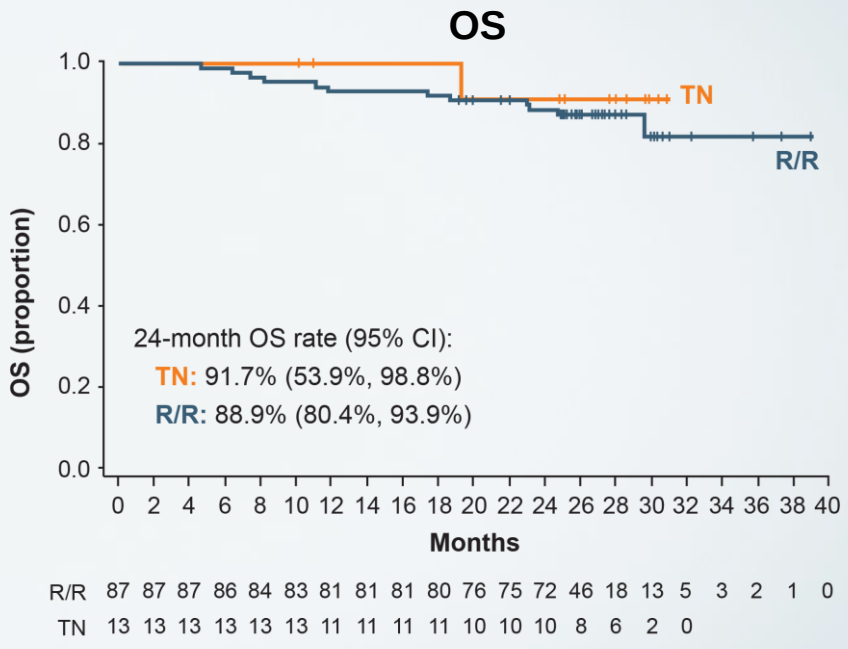
[a] Investigator-assessed DOR using the Modified 3rd IWWM Criteria is shown. Results were consistent with those using the 6th IWWM Criteria.
DOR = duration of response; IWWM = International Workshop on Waldenström macroglobulinemia; R/R = relapsed/refractory; TN = treatment-naive.

PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL

Owen R, et al. EHA 2018

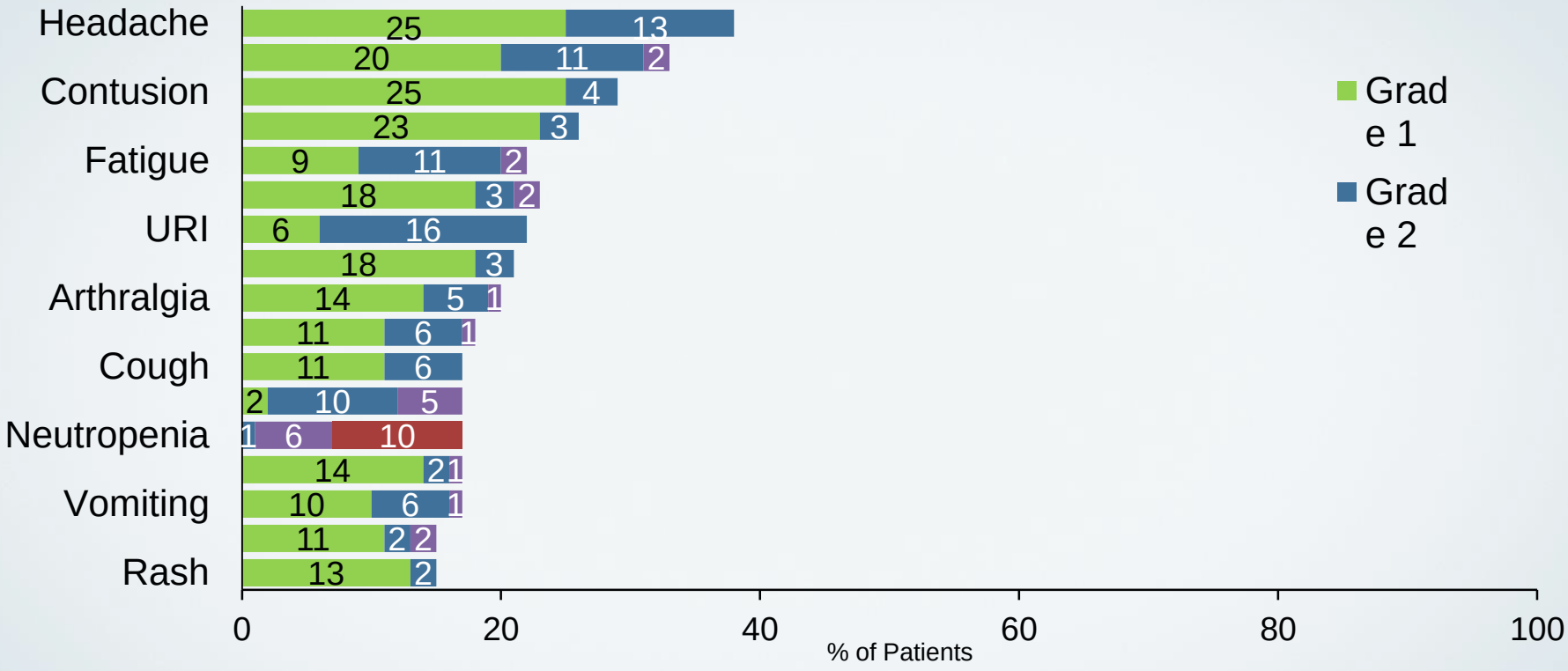
- Median PFS and OS were not reached





[a] Investigator-assessed PFS using the Modified 3rd IWWM Criteria is shown. Results were consistent with those using the 6th IWWM Criteria.
IWWM = International Workshop on Waldenström macroglobulinemia; OS = overall survival; PFS = progression-free survival; R/R = relapsed/refractory; TN = treatment-naive.

MOST COMMON ADVERSE EVENTS[A] (≥15% OF ALL PATIENTS [N=106])



[a] MedDRA preferred terms.
LRI = lower respiratory tract infection; URI = upper respiratory tract infection.

GRADE ≥3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

	All Patients (N=106)	
Preferred Term	**Any Grade**	**Grade 3/4**
Neutropenia	18 (17)	17 (16)
Lower respiratory tract infection	18 (17)	5 (5)
Anemia	10 (9)	5 (5)
Pneumonia	10 (9)	7 (7)
Alanine aminotransferase increased	6 (6)	5 (5)
Hyponatremia	5 (5)	5 (5)

- SAEs occurred in 6 of 14 (43%) TN patients and 50 of 92 (54%) R/R patients
  - No SAE occurred in >1 TN patient
  - SAEs occurring in ≥3 R/R patients included lower respiratory tract infection (n=7), pneumonia (n=7; 1 patient had aspergillus), pyrexia (n=4), cellulitis (n=3), fall (n=3), and sepsis (n=3)

AE = adverse event; SAE = serious adverse event; R/R = relapsed/refractory; TN = treatment-naive.

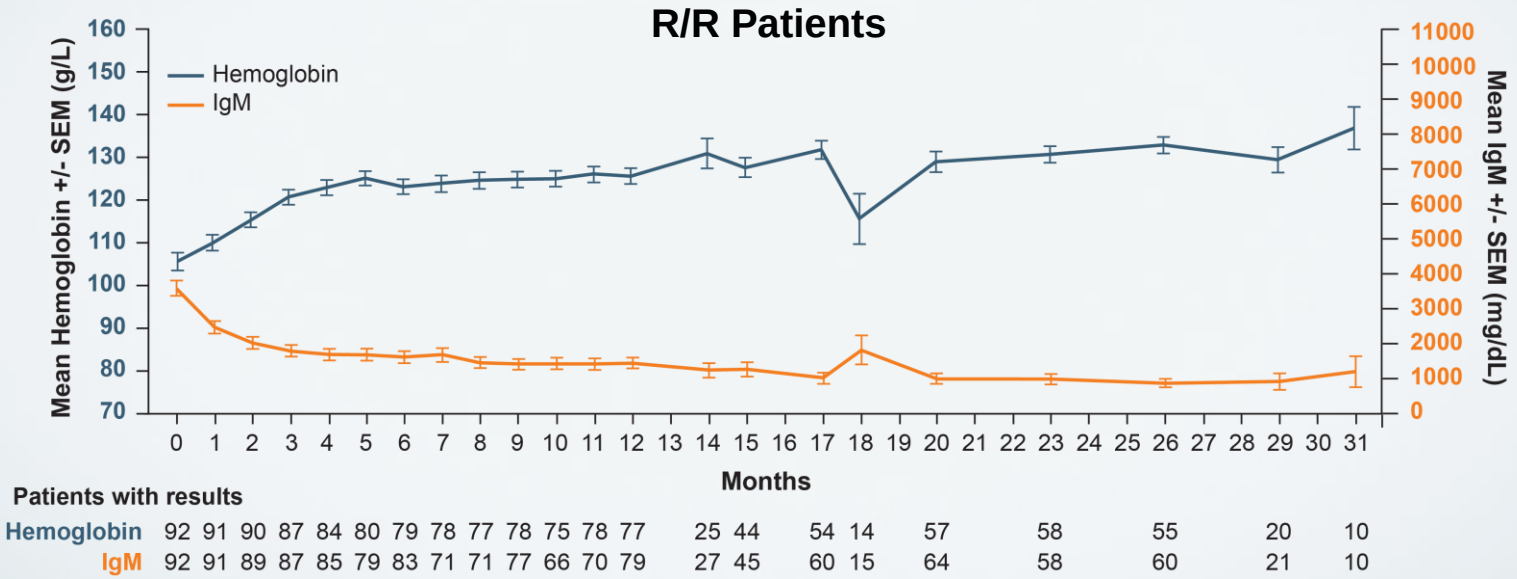
KEY EVENTS OF CLINICAL INTEREST

- Atrial fibrillation occurred in 4 R/R patients and 1 TN patient
  - One event was Grade 3 (all others were Grade 1 or 2)
  - Study treatment was not held or discontinued in any patient
- Grade 3 hypertension occurred in 3 R/R patients
- Bleeding events occurred in 56% of all patients (commonly contusion [29%] and epistaxis [11%])
  - Three R/R patients had Grade 3 events (each in 1 patient):
    - Epistaxis, dysfunctional uterine bleeding, and retinal hemorrhage
  - All 3 Grade 3 events were resolved, and no patient discontinued study treatment

AE = adverse event; R/R = relapsed/refractory; TN = treatment naive.

CHANGES IN SERUM IGM AND HEMOGLOBIN LEVELS

- Rapid reductions in IgM and improvement in serum hemoglobin occurred with acalabrutinib treatment in R/R patients
- Similar results were observed in TN patients



Ig = immunoglobulin; R/R relapsed/refractory; TN = treatment naive.

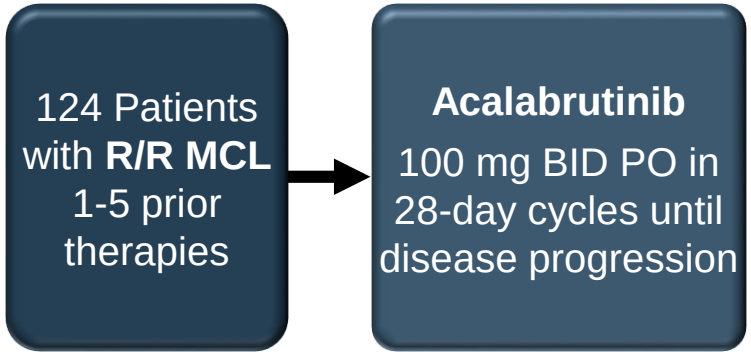
EFFICACY AND SAFETY OF ACALABRUTINIB MONOTHERAPY IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA IN THE PHASE 2 ACE-LY-004 STUDY

Michael Wang,[1] Simon Rule,[2] Pier Luigi Zinzani,[3] Andre Goy,[4] Olivier Casasnovas,[5] Stephen D. Smith,[6] Gandhi Damaj,[7] Jeanette Doorduijn,[8] Thierry Lamy,[9] Franck Morschhauser,[10] Carlos Panizo Santos,[11] Bijal Shah,[12] Andrew Davies,[13] Richard Eek,[14] Jehan Dupuis,[15] Eric Jacobsen,[16] Arnon P. Kater,[17] Steven Le Gouill,[18] Lucie Oberic,[19] Taduesz Robak,[20] Todd Covey,[21] Richa Dua,[21] Ahmed Hamdy,[21] Xin Huang,[21] Raquel Izumi,[21] Priti Patel,[21] J. Greg Slatter[21] and Wojciech Jurczak[22]

[1]University of Texas MD Anderson Cancer Center, Houston, TX; [2]Plymouth University Medical School, Plymouth, United Kingdom; [3]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [4]John Theurer Cancer Center at Hackensack-UMC, Hackensack, NJ; [5]CHU Dijon - Hôpital d'Enfants, Dijon, France; [6]Fred Hutchinson Cancer Research Center, Seattle, WA; [7]Institut d'Hématologie de Basse-Normandie, Caen, France; [8]Erasmus MC, Lunenburg Lymphoma Phase I/II Consortium, Rotterdam, Netherlands; [9]CHU de Rennes, Rennes, France; [10]CHRU Lille - Hôpital Claude Huriez, Lille Cedex, France; [11]Clínica Universidad de Navarra, Pamplona, Spain; [12]H. Lee Moffitt Cancer Center, Tampa, FL; [13]University Hospital Southampton NHS Foundation Trust Southampton General Hospital, Southhampton, United Kingdom; [14]Border Medical Oncology, Wodonga, VIC, Australia; [15]Unité Hémopathies Lymphoïdes, AP-HP Hôpital Henri Mondor, Créteil, France; [16]Dana Farber Cancer Institute/Harvard, Boston, MA; [17]Academic Medical Center, Lunenburg Lymphoma Phase I/II Consortium, Amsterdam, Netherlands; [18]CHU de Nantes - Hotel Dieu, Nantes, France; [19]Institut Universitaire du Cancer - Oncopole Toulouse (IUCT-O), Toulouse, France; [20]Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; [21]Acerta Pharma, Redwood City, CA; [22]Dept of Haematology, Jagiellonian University, Krakow, Poland

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.

KEY ELIGIBILITY CRITERIA

- **Inclusion criteria:**
  - Relapsed after or refractory to 1-5 prior treatments
  - Confirmed MCL with translocation t(11;14)(q13;q32) and/or overexpressed cyclin D1
  - Measurable nodal disease (≥1 lymph node >2 cm in longest diameter)
  - ECOG PS ≤2
  - Age ≥18 years
- **Exclusion criteria:**
  - Significant cardiovascular disease:
    - Uncontrolled or symptomatic arrhythmias
    - Congestive heart failure or myocardial infarction within 6 months of screening
    - Any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification
    - QTc >480 ms
  - Concomitant use of warfarin or equivalent vitamin K antagonists
  - Previous treatment with BTK inhibitors

BTK = Bruton tyrosine kinase; ECOG PS = Eastern Cooperative Oncology Group performance status; MCL = mantle cell lymphoma; QTc = corrected QT interval.

Wang M, et al. ASH 2017

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 M, et al. ASH 2017

PRIOR THERAPIES

Characteristic	N=124
Median no. of prior therapies (range)	2 (1-5)
Refractory disease, n (%)[a]	30 (24)
Prior therapy, n (%)	
Rituximab as single agent or part of a regimen	118 (95)
CHOP-based regimen	64 (52)
Bendamustine ± rituximab	27 (22)
Hyper-CVAD	26 (21)
Bortezomib/carfilzomib	24 (19)
Stem cell transplant	22 (18)
Lenalidomide	9 (7)

[a] Refractory disease was defined as a lack of at least a partial response to the last therapy before study entry.
CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CVAD = cyclophosphamide, vincristine, doxorubicin and dexamethasone.

PATIENT DISPOSITION

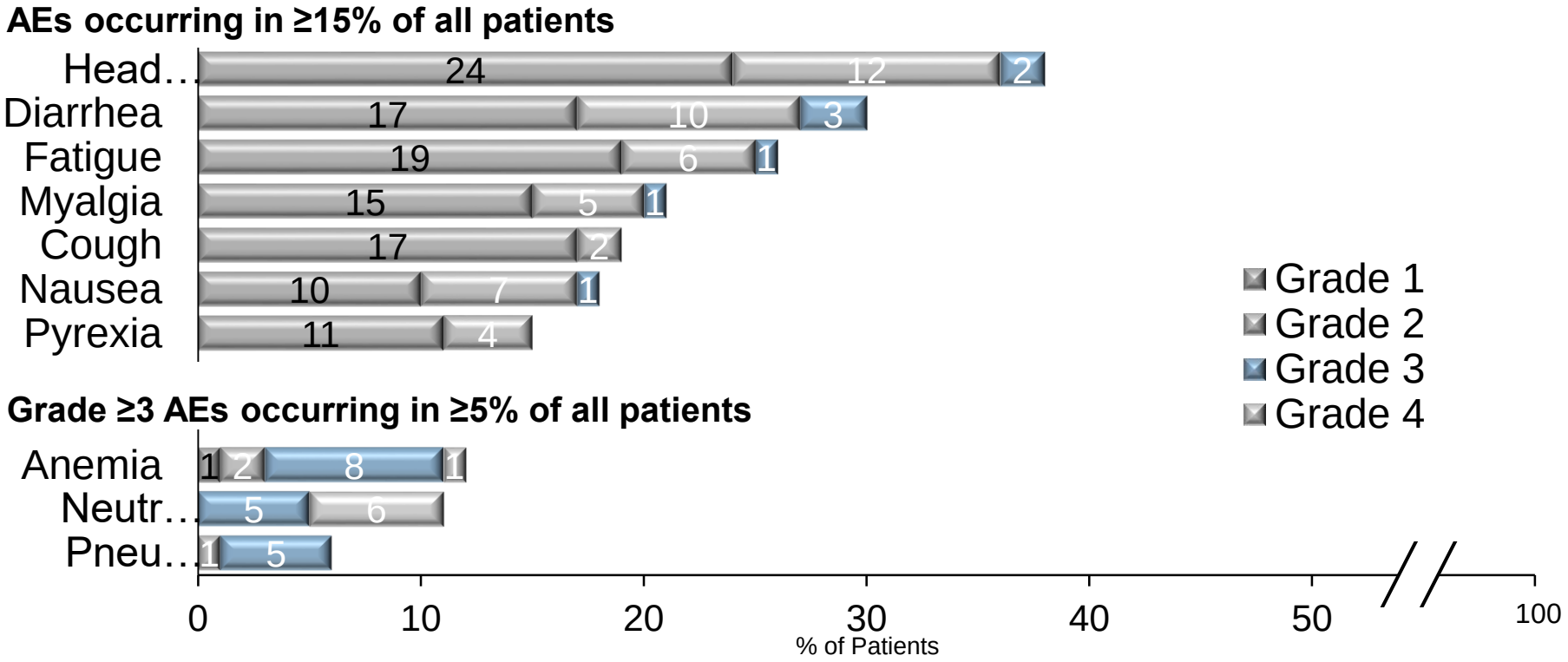
- At a median follow-up of 15.2 months, 56% of patients remain on treatment

	N=124
Median follow-up, months (range)	15.2 (0.3-23.7)
On acalabrutinib, n (%)	70 (56)
Discontinued acalabrutinib, n (%)	54 (44)
Disease progression	39 (31)
Adverse event[a]	7 (6)
Initiation of subsequent anticancer therapy[b]	5 (4)
Lost to follow-up	1 (1)
Withdrawal of consent	1 (1)
Other[c]	1 (1)
Median relative dose intensity, % (range)	98.5 (27.1-100.0)

[a] AEs leading to discontinuation occurred in only one patient each and were aortic stenosis, B-cell lymphoma (DLBCL), blood blister and petechiae (both in 1 patient with Grade 3 acute coronary syndrome which was treated with Plavix, resulting in blood blister/petechiae formation [considered related]), dyspnea and leukostasis syndrome (in the same patient), noncardiac chest pain, pulmonary fibrosis and thrombocytopenia.
[b] All 5 patients received a stem cell transplant.
[c] Patient decision to stop treatment.

Wang M, et al. ASH 2017

MOST COMMON ADVERSE EVENTS



AE = adverse event.

Wang M, et al. ASH 2017

SERIOUS ADVERSE EVENTS

- SAEs occurred in 48 patients (39%)
  - SAEs reported in ≥2 patients:
    - Pneumonia (n=5 [4%])
    - Anemia (n=4 [3%])
    - General physical health deterioration (n=3 [2%])
    - Sepsis (n=2 [2%])
    - Tumor lysis syndrome (n=2 [2%])
    - Vomiting (n=2 [2%])
- One Grade 3 GI hemorrhage occurred in a patient with a history of GI ulcer
- One Grade 5 AE (aortic stenosis) occurred in a patient with a history of aortic stenosis (not treatment related)

AE = adverse event; GI = gastrointestinal; SAE = serious adverse event.

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EVENTS OF CLINICAL INTEREST

- There were no cases of atrial fibrillation
- Grade 3/4 cardiac AEs (n=3):
  - Grade 3 acute coronary syndrome (n=1, treatment-related)
  - Grade 3 acute myocardial infarction (n=1, not treatment-related)
  - Grade 4 cardiorespiratory arrest (n=1, not treatment-related)
- Infections of any grade occurred in 53% of patients, with Grade 3/4 infections in 13% of patients
- Bleeding events, the most frequent being were contusion (13%) and petechiae (9%), occurred in 31% of patients and were all Grade 1/2 except for one Grade 3 GI hemorrhage (1%) in a patient with a history of GI ulcer

AE = adverse event; GI = gastrointestinal.

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

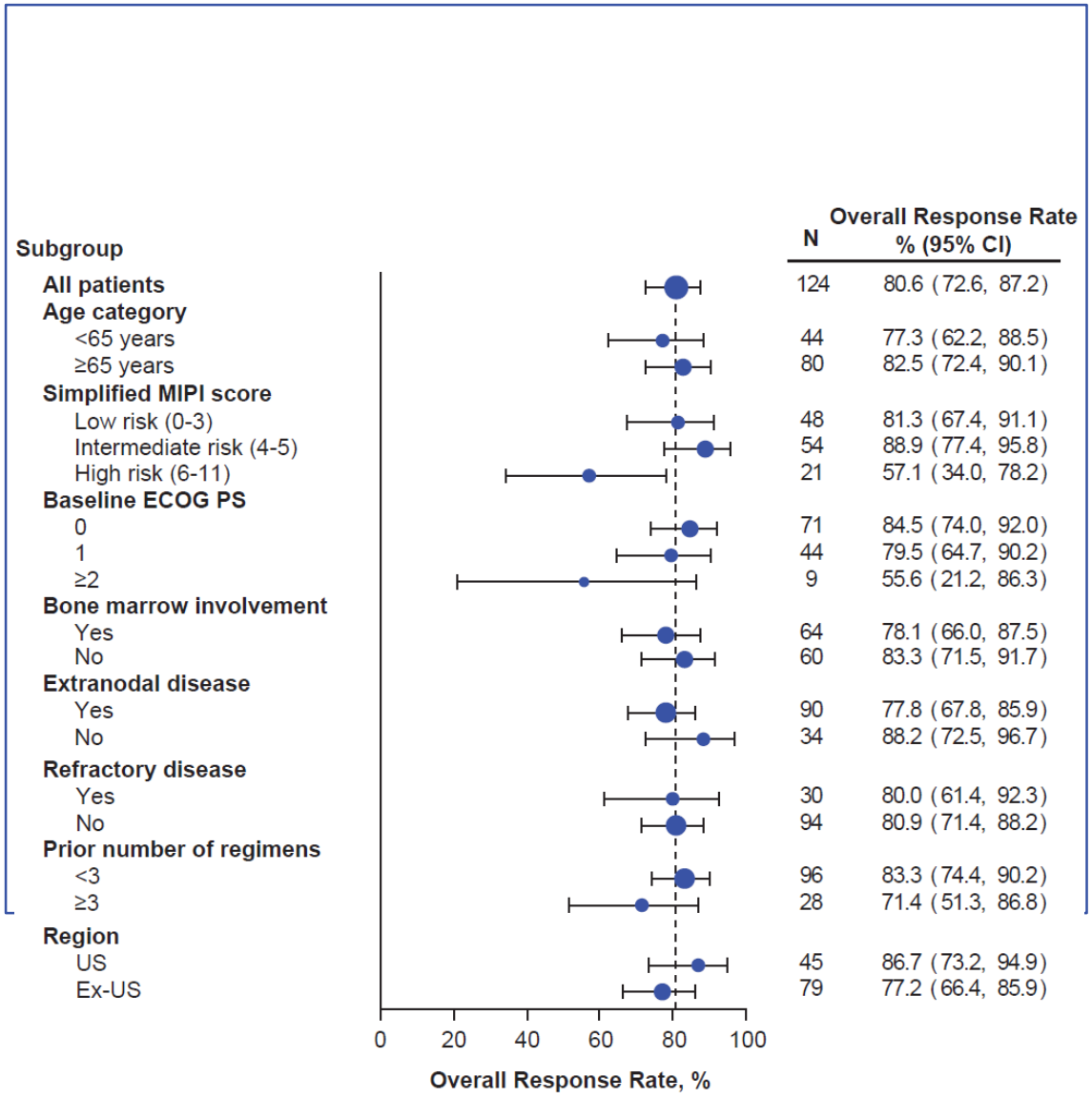
	N=124	
	Investigator assessed n (%)	**IRC assessed n (%)**
ORR (CR + PR)	100 (81)	99 (80)
Best response		
CR	49 (40)	49 (40)
PR	51 (41)	50 (40)
SD	11 (9)	9 (7)
PD	10 (8)	11 (9)
Not evaluable	3 (2)	5 (4)

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.

SUBGROUP ANALYSIS OF ORR

- ORR was consistent across all prespecified subgroups



95% confidence interval was based on exact binomial distribution. No differences were observed by sex, race, Ann Arbor stage, tumor bulk, or prior lenalidomide exposure (data not shown).
ECOG PS = Eastern Cooperative Oncology Group Performance Status; MIPI = Mantle Cell Lymphoma International Prognostic Index; ORR = overall response rate; US = United States.

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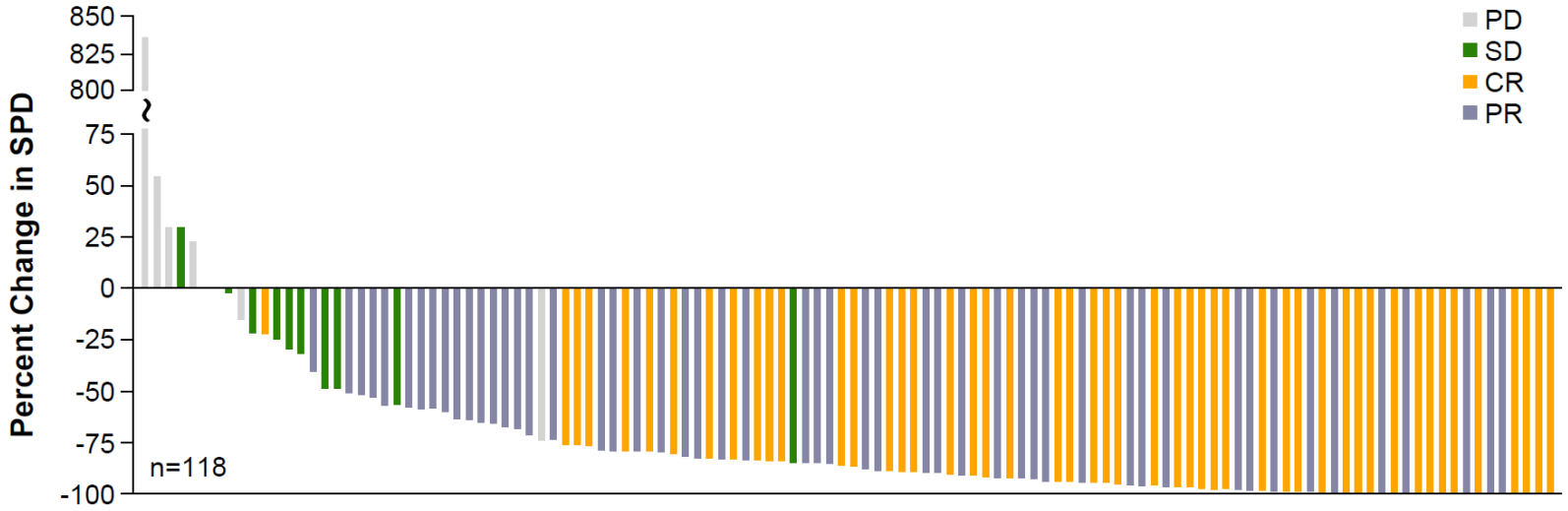
CHANGE IN TUMOR BURDEN AND BEST RESPONSE STATUS PER LUGANO CLASSIFICATION[1]

- Most patients (94%) experienced a reduction in lymphadenopathy[a]

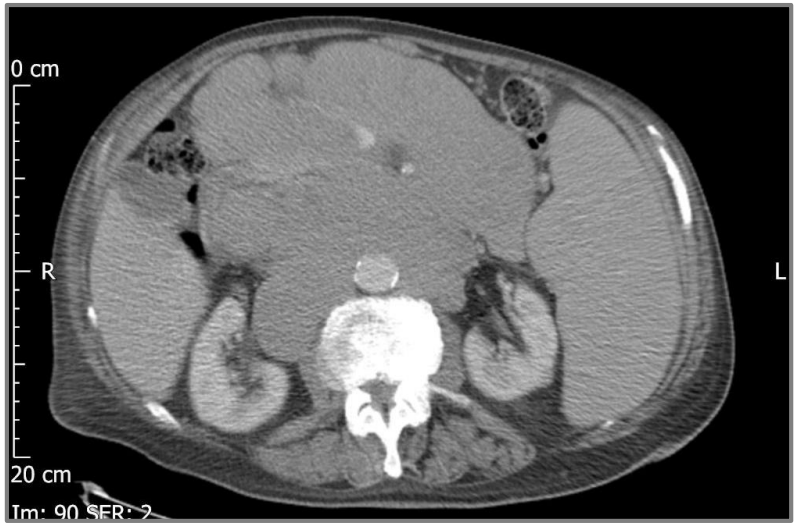


[a] Maximum change from baseline in SPD for all treated patients with baseline and ≥1 postbaseline lesion measurement. Six subjects were excluded due to early PD by evidence other than CT (n=4), started subsequent anticancer therapy (n=1) or death (n=1).
CR = complete response; CT = computed tomography; PD = progressive disease; PR = partial response; SD = stable disease; SPD = sum of product diameters.
1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-68.

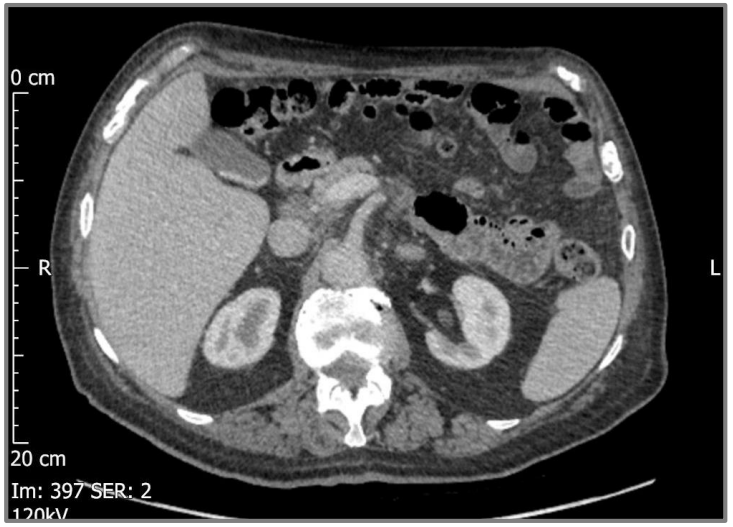
CT SCANS OF TUMOR RESPONSE TO ACALABRUTINIB

- Axial images of a 92-year-old male with chemorefractory MCL treated with acalabrutinib

Before Treatment



After 7 Months of Treatment



CT = computed tomography; MCL = mantle cell lymphoma.

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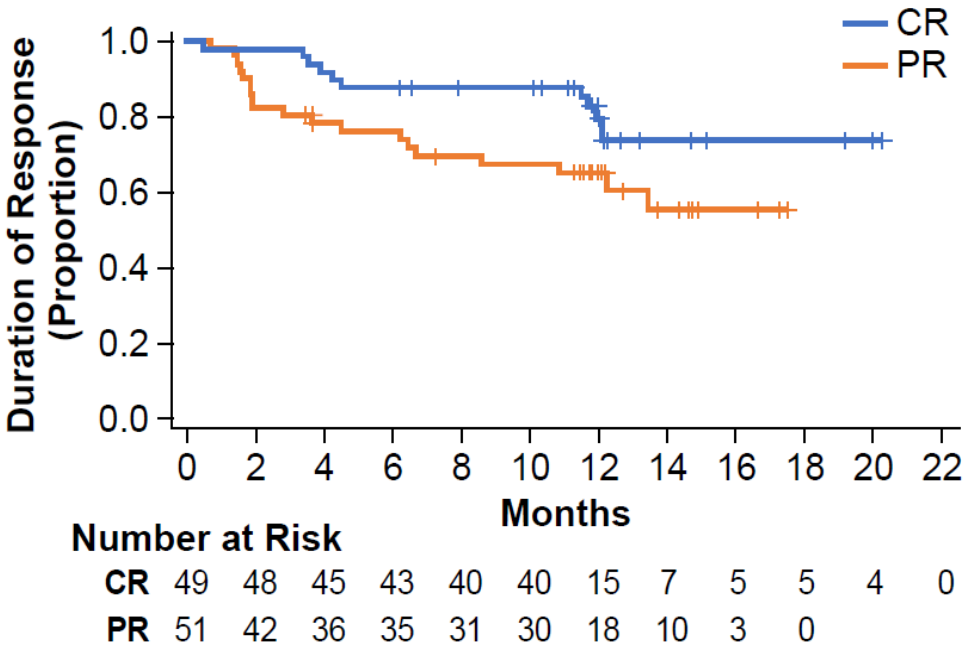
DURATION OF RESPONSE

- 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.

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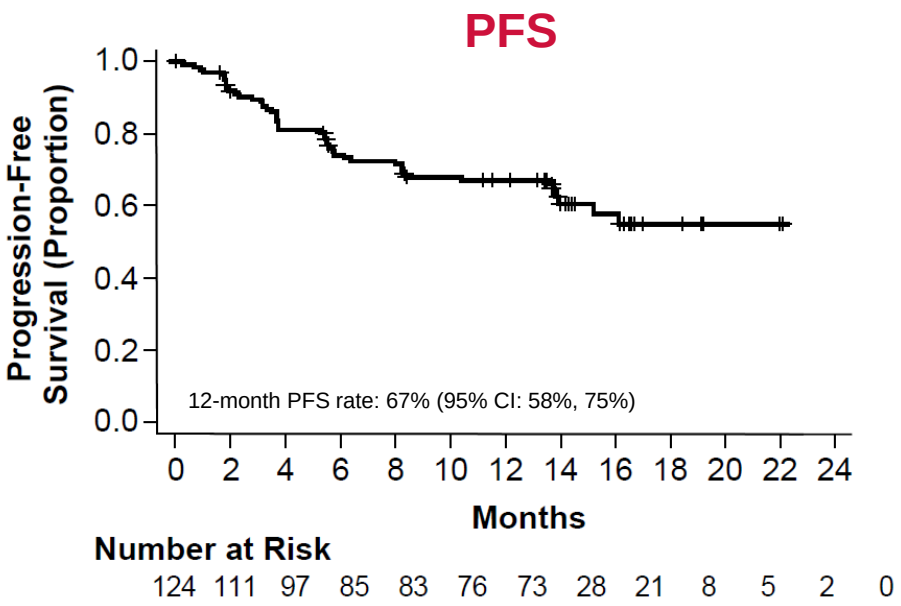
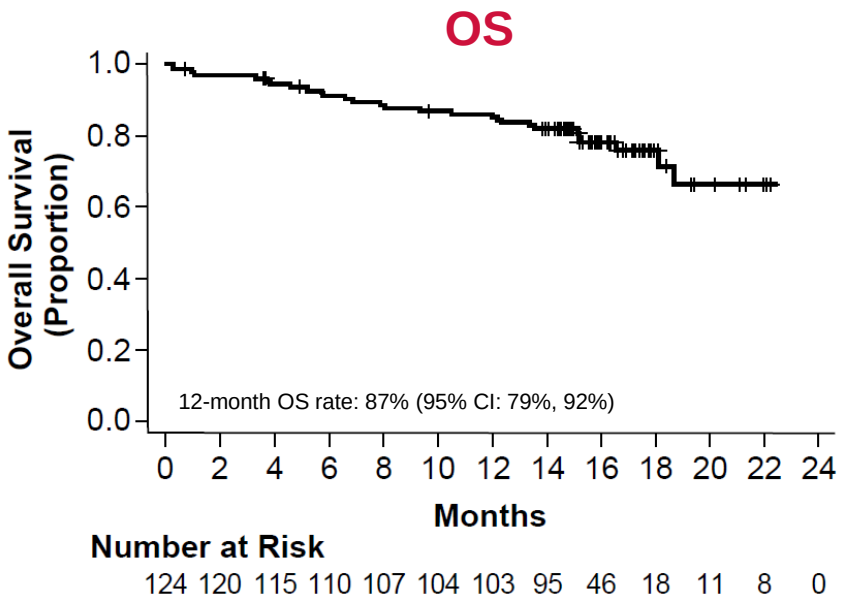
PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL

- Median PFS and median OS have not been reached





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

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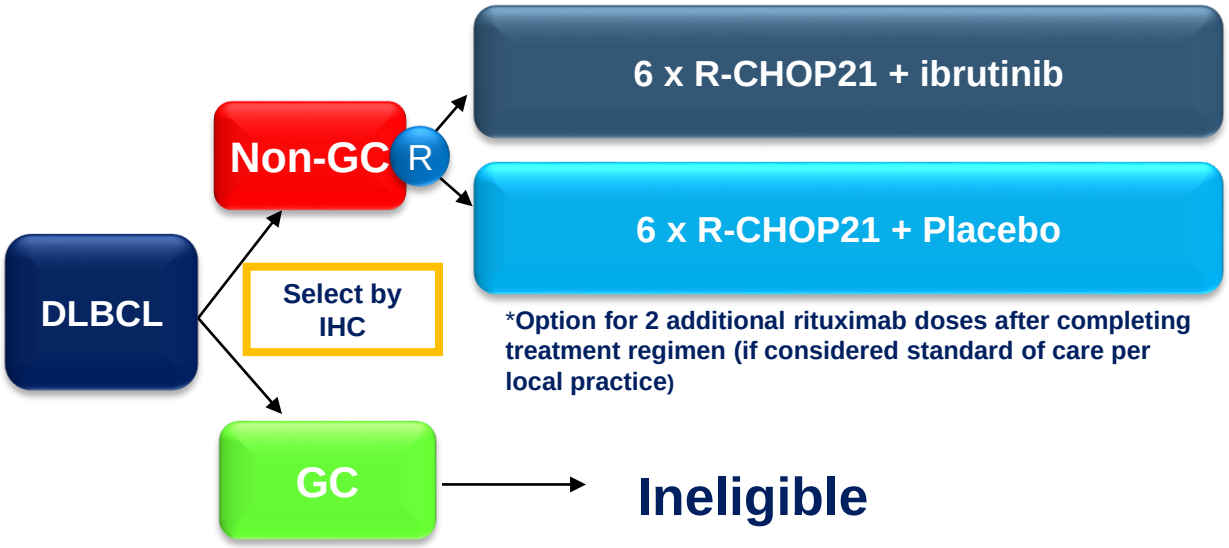
ACE-LY-308 ECHO: TRIAL

- **Global, two arm, randomized, double blind, placebo controlled trial**
  - Treatment naïve MCL patients age ≥ 65
- **N=546**
- **Randomized 1:1**
  - Test: Bendamustine + rituximab + acalabrutinib
  - Control: Bendamustine + rituximab + acalabrutinib
    - 6 cycles of B+ R with continuous acalabrutinib/placebo treatment
    - Rituximab maintenance after cycle 6 if CR or PR
- **Primary endpoint:**
  - PFS as determined by blinded independent review committee (IRC) using Lugano Classification for NHL (Cheson 2014) response criteria
- **Crossover:**
  - Option of crossover to acalabrutinib for patients who progress during study via unblinding

PHEONIX

CLINICAL STUDY DESIGN: DOUBLE BLIND RANDOMISED PHASE III



- Newly diagnosed DLBCL of non-GC
- ECOG PS ≤ 2; Age 18–80
- Primary Endpoint = EFS
- N = 800

CONCLUSION

ACP-196 is a second-generation, selective Btk inhibitor with favorable biochemical and pharmacokinetic properties.

ACP-196 has a promising safety profile

In MCL (but not WM) no episodes of atrial fibrillation or major bleeding observed at this time.

Head to head trial v ibrutinib on-going in CLL

Early onset treatment-related lymphocytosis was not as significant or persistent as reported with other BCR antagonists.

Is it more active …..