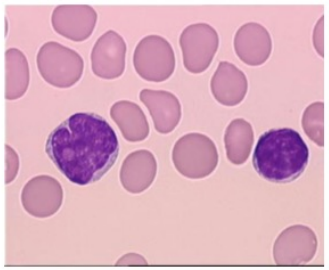
LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
MEDIZINISCHE KLINIK UND POLIKLINIK III
DIREKTOR: PROF. DR. M. VON BERGWELT

MANTLE CELL LYMPHOMA:

OTHER BTKI



German Lymphoma Alliance

European MCL Network

Mantle Cell Lymphoma
Disclosures

LMU KLINIKUM

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Research Support (institution)	**Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche**
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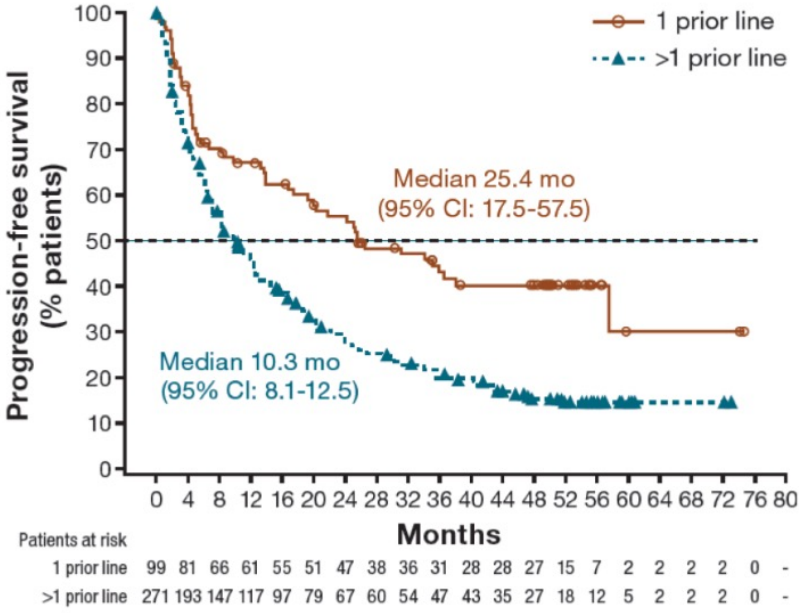
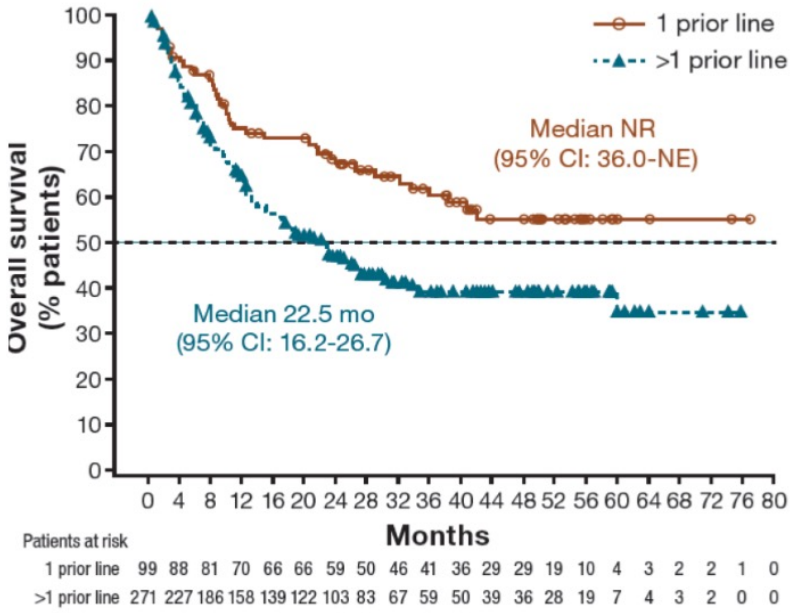
Scientific Advisory Board	**Astra Zeneca, Bayer, Beigene, BMS/Celgene, Genmab, Gilead/Kite, Incyte, Janssen, Lilly/Loxo, Morphosys, Novartis, Roche**

Ibrutinib in relapsed MCL
Progression-free survival

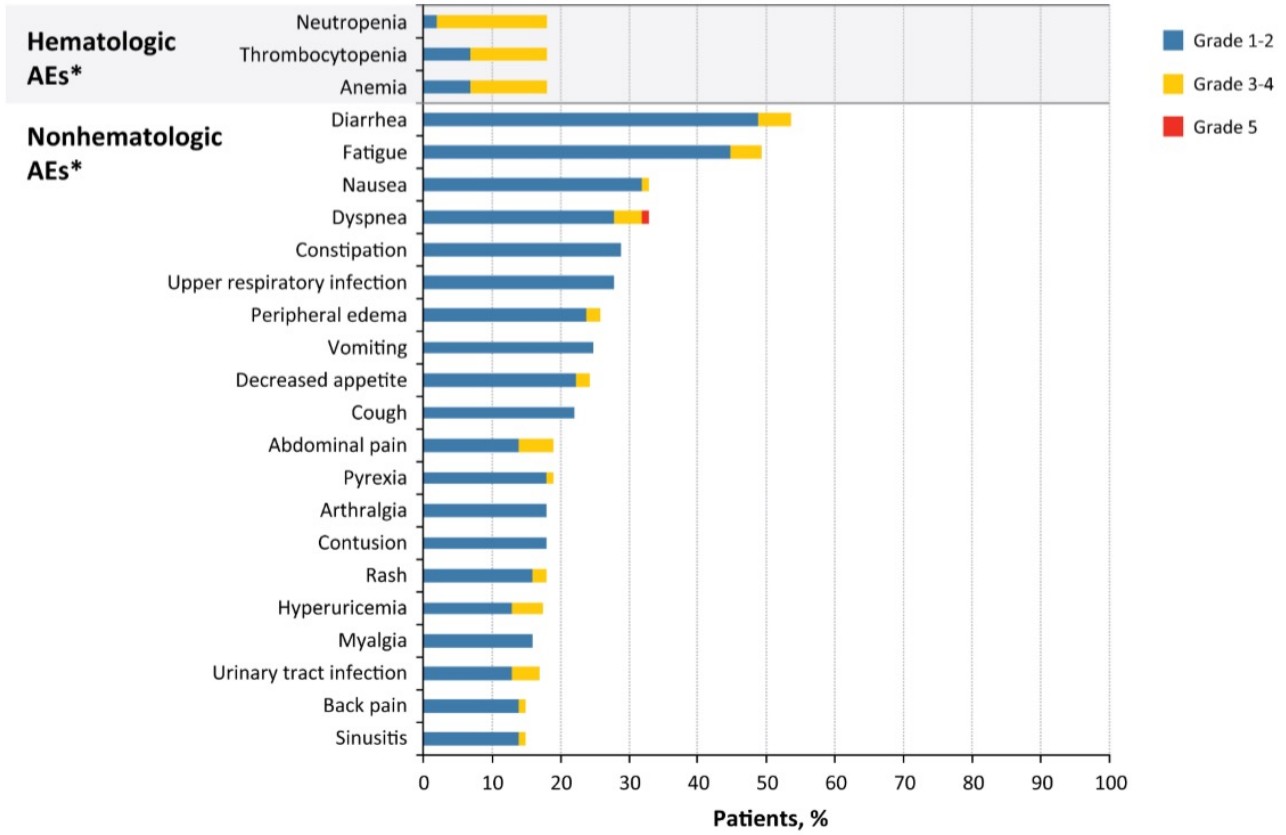




Rule, Haematologica 2019

BTK inhibitor Ibrutinib

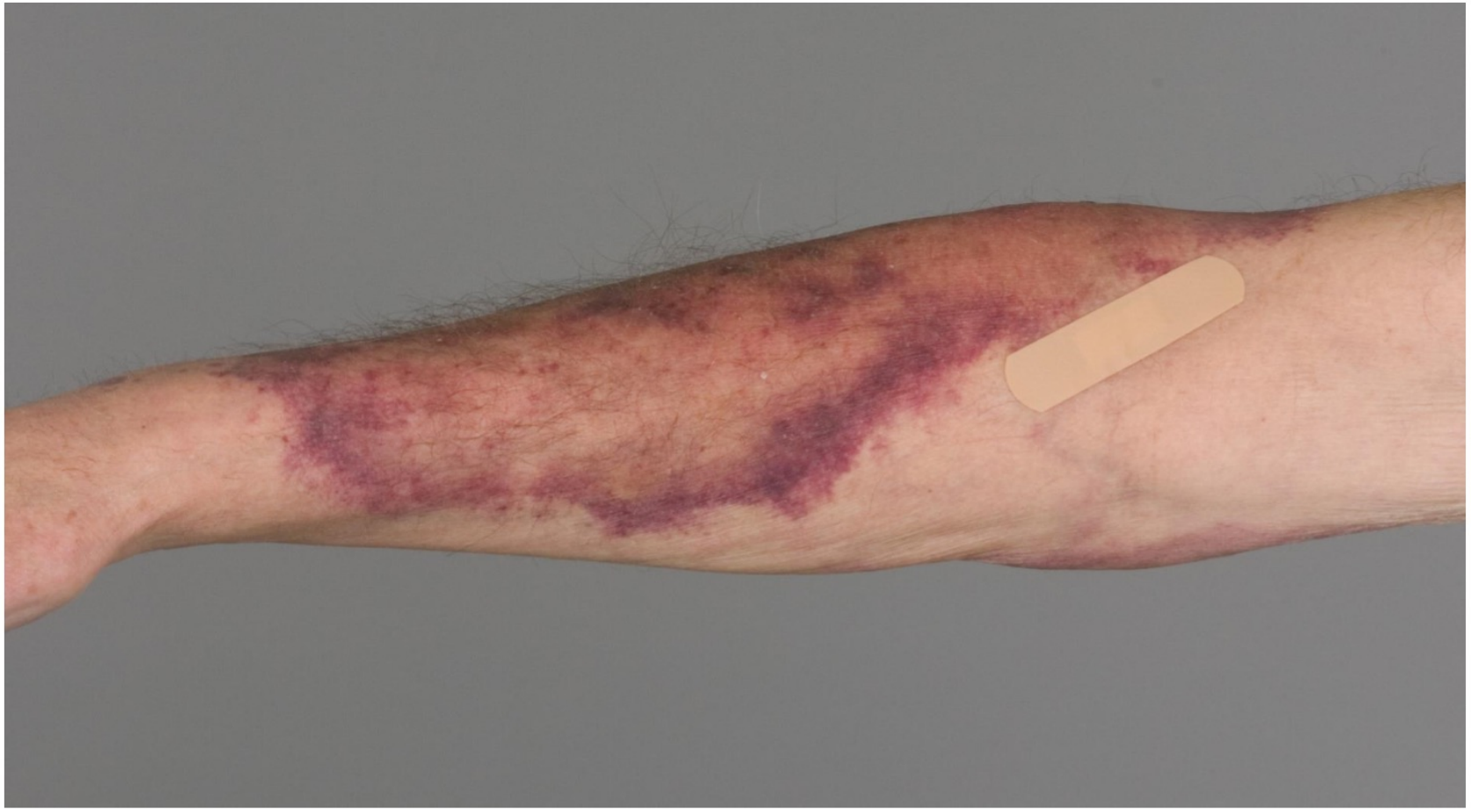
Adverse events (>15%)



Wang, NEJM 2013

Ibrutinib in relapsed MCL

Bleeding events



Courtesy of S Rule

ACE-LY-004: Open-Label Phase 2 Study of Acalabrutinib in R/R MCL (NCT02213926)[1,2]

R/R MCL with 1-5 prior therapies
n=124

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 performance status ≤2
- Age ≥18 years

Exclusion Criteria

- Significant cardiovascular disease[a]
- Requiring or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug
- Previous treatment with BTK/BCL2 inhibitors

Acalabrutinib
100 mg BID PO in 28-day cycles until disease progression or unacceptable toxicity

Primary End Point

- **ORR by investigator assessment based on the Lugano Classification**

Secondary End Points

- **Investigator assessed DOR, PFS, OS**
- **Safety**
- **PK/PD**

Exploratory End Points

- **IRC-assessed ORR, DOR, and PFS per the 2007 International Harmonization Project criteria**
- **Patient-reported outcomes**
- **Time to response**

[a]Includes 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, or QTc >480 ms.

BID = twice daily; BTK = Bruton tyrosine kinase; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; IRC = Independent Review Committee; MCL = mantle cell lymphoma; ORR = overall response rate; OS = overall survival; PD = pharmacodynamics; PFS = progression-free survival; PK = pharmacokinetics; PO = orally; QTc = corrected QT interval; R/R = relapsed/refractory.

1. Wang M et al. *The Lancet*. 2018;391(10121):659-667. 2. Wang M et al. Article and supplementary appendix. Leukemia. 2019;33(11):2762-2766.

ACE-LY-004 (Final Results): Demographics and Baseline Characteristics

- A total of 124 patients were enrolled and patient characteristics were as previously reported

	All Patients (N=124)
Age, median (range), y	68 (42–90)
Male, n (%)	99 (80)
ECOG PS ≤1, n (%)	115 (93)
Bulky lymph nodes, n (%)	
≥5 cm	46 (37)
≥10 cm	10 (8)
Extra-nodal involvement, n (%)	89 (72)
Ann Arbor stage IV disease, n (%)	93 (75)
Simplified MIPI score, n (%)[a]	
Low risk (0–3)	48 (39)
Intermediate risk (4–5)	54 (44)
High-risk (6–11)	21 (17)
Number of prior systemic regimens, median (range)	2 (1–5)
Refractory disease, n (%)[b]	30 (24)
Blastoid/pleomorphic MCL, n (%)	26 (21)
Ki-67 proliferation index, n (%)[10]	
<50%	64 (52)
≥50%	32 (26)
Missing	28 (22)

Study Design

[a]Derived using the factors of age, ECOG PS score, lactate dehydrogenase level, and white cell count, with score range depending on the range of these factors. [b]Defined as a lack of at least partial response to last therapy before study entry.

ECOG PS = Eastern Cooperative Oncology Group performance status; MCL = mantle cell lymphoma; MIPI = Mantle cell lymphoma International Prognostic Index; y = years.

Wang M et al. Poster Presented at: ICML Virtual Meeting; June 18-22, 2021.

ACE-LY-004 (Final Results): Safety

- The adverse event profile remained consistent with the known acalabrutinib safety profile
- Dose reductions occurred in 13 (10.5%) patients with 3 (2.4%) due to AEs
- Treatment discontinuation due to TEAEs occurred in 15 (12.1%) patients

Selected AEs of clinical interest All Patients (N=124)		
n (%)	**Any Grade**	**Grade 3/4**
Atrial Fibrillation	3 (2.4%)	0
Hypertension	5 (4.0%)	2 (1.6%)
Hemorrhage	46 (37.1%)	5 (4.0%)
Infections	84 (67.7%)	21 (16.9%)

AE = adverse events; SAE = serious adverse event; TEAEs = treatment emergent adverse events.

Wang M et al. Poster Presented at: ICML Virtual Meeting; June 18-22, 2021.

ACE-LY-004 (Final Results): Most Common AEs in ≥10% of Patients

AE, n (%)[a]	N=124				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Headache	48 (39)	30 (24)	16 (13)	2 (2)	0
Diarrhea	47 (38)	25 (20)	17 (14)	5 (4)	0
Fatigue	37 (30)	26 (21)	8 (6)	2 (2)	0
Cough	29 (23)	24 (19)	5 (4)	0	0
Myalgia	27 (22)	19 (15)	6 (5)	2 (2)	0
Nausea	27 (22)	14 (11)	11 (9)	2 (2)	0
Asthenia	22 (18)	15 (12)	5 (4)	2 (2)	0
Constipation	20 (16)	15 (12)	5 (4)	0	0
URTI	20 (16)	4 (3)	14 (11)	2 (2)	0
Dyspnea	19 (15)	13 (10)	3 (2)	2 (2)	1 (0.8)
Pyrexia	19 (15)	13 (10)	6 (5)	0	0
Vomiting	19 (15)	10 (8)	6 (5)	3 (2)	0
Anemia	18 (15)	1 (0.8)	3 (2)	12 (10)	2 (2)
Dizziness	18 (15)	15 (12)	3 (2)	0	0
Rash	18 (15)	9 (7)	7 (6)	2 (2)	0
Contusion	16 (13)	14 (11)	2 (2)	0	0
Sinusitis	16 (13)	4 (3)	12 (10)	0	0
Abdominal pain	15 (12)	5 (4)	8 (6)	2 (2)	0
Pneumonia	15 (12)	1 (0.8)	5 (4)	9 (7)	0
Back pain	14 (11)	11 (9)	3 (2)	0	0
Neutropenia	14 (11)	0	0	7 (6)	7 (6)
Arthralgia	13 (10)	7 (6)	6 (5)	0	0

AE = adverse event; URTI = upper respiratory tract infection.

Wang M et al. Poster Presented at: ICML Virtual Meeting; June 18-22, 2021.

ACE-LY-004 (Final Results): Investigator-Assessed Response to Acalabrutinib

- ORR (CR + PR) was 81% and CR rate was 48%

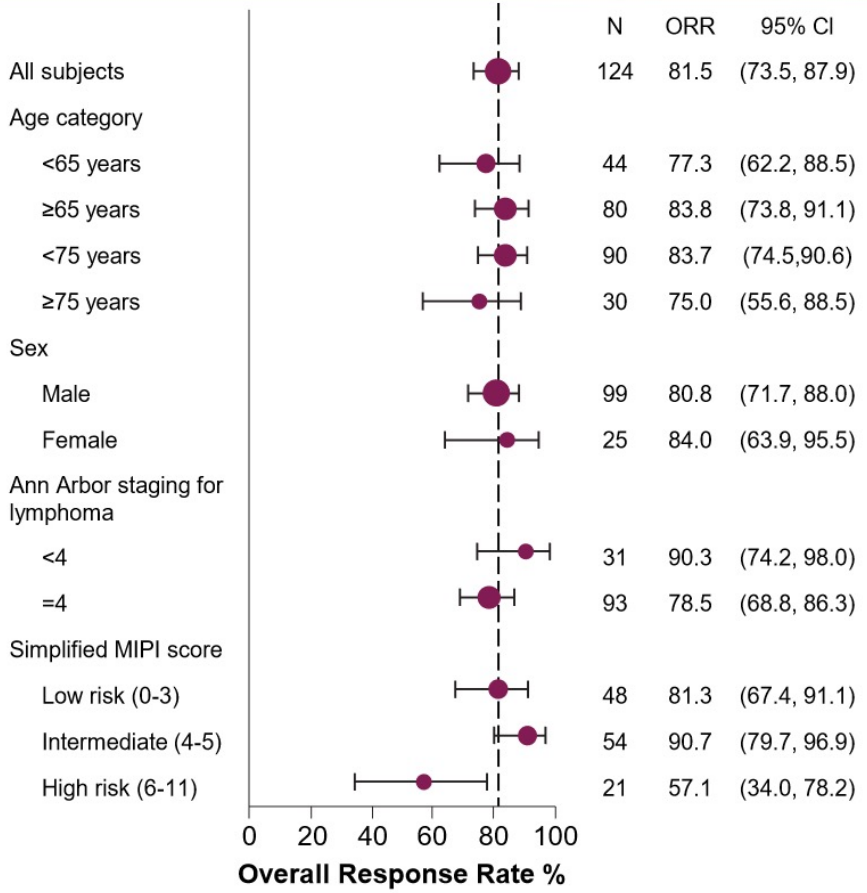
	All patients (N=124)					
	Interim 15.2 Months Follow-Up[1]		26.3-Month Follow-Up[2]		38.1-Month Follow-Up/Final Analysis[3,4]	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
ORR (CR + PR)	100 (81)	73, 87	100 (81)	73, 87	101 (81)	74, 88
Best Response						
CR	49 (40)	31, 49	53 (43)	34, 52	59 (48)	39, 57
PR	51 (41)	32, 50	47 (38)	29, 47	42 (34)	26, 43
SD	11 (9)	5, 15	11 (9)	5, 15	10 (8)	4, 14
PD	10 (8)	4, 14	10 (8)	4, 14	10 (8)	4, 14
Not evaluable[a]	3 (2)	1, 7	3 (2)	1, 7	3 (2)	1, 7

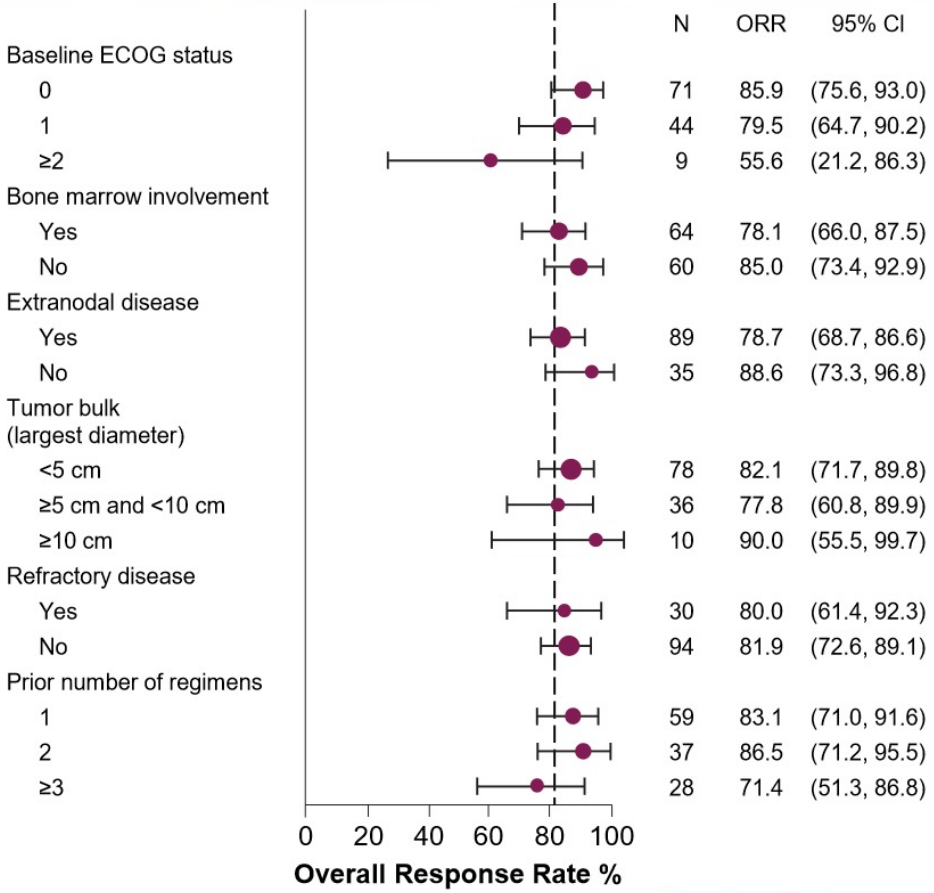
[a]Includes patients without any adequate post-baseline disease assessments.

CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

1. Wang M et al. *The Lancet*. 2018;391(10121):659-667. 2. Wang M, et al. *Leukemia*. 2019;33:2762-6. 3. Wang M, et al. Poster presented at: ASH; Dec 5-8, 2020; Virtual Meeting. Poster #2040. 4. Wang M et al. Poster Presented at: ICML Virtual Meeting; June 18-22, 2021.

ACE-LY-004 (Final Results): Subgroup Analysis of ORR





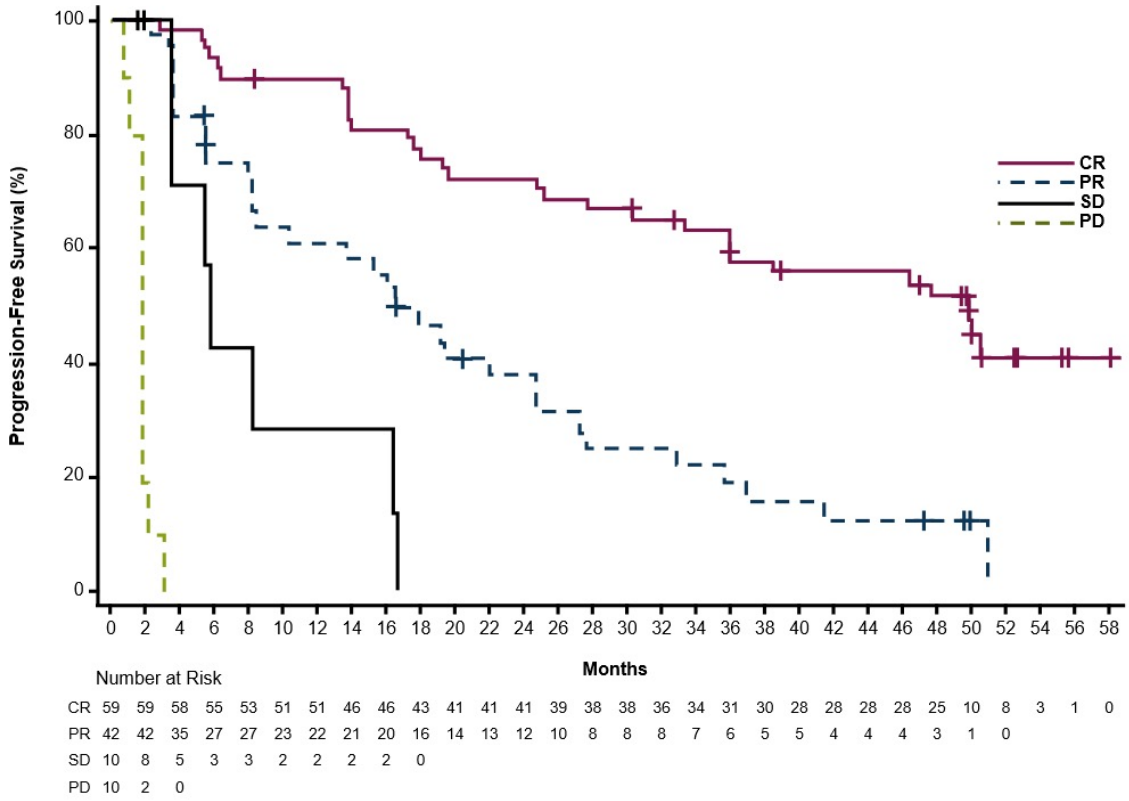
More ORR subgroup analysis (ASH 2020 Poster)

CI = confidence interval; CR = complete response; CRR = complete response rate; ECOG PS = Eastern Cooperative Oncology Group performance status; MIPI = Mantle cell lymphoma International Prognostic Index; ORR = overall response rate.

Wang M et al. Poster Presented at: ICML Virtual Meeting; June 18-22, 2021.

ACE-LY-004 (38-Month Data Update): PFS by Best Response

Progression-Free Survival



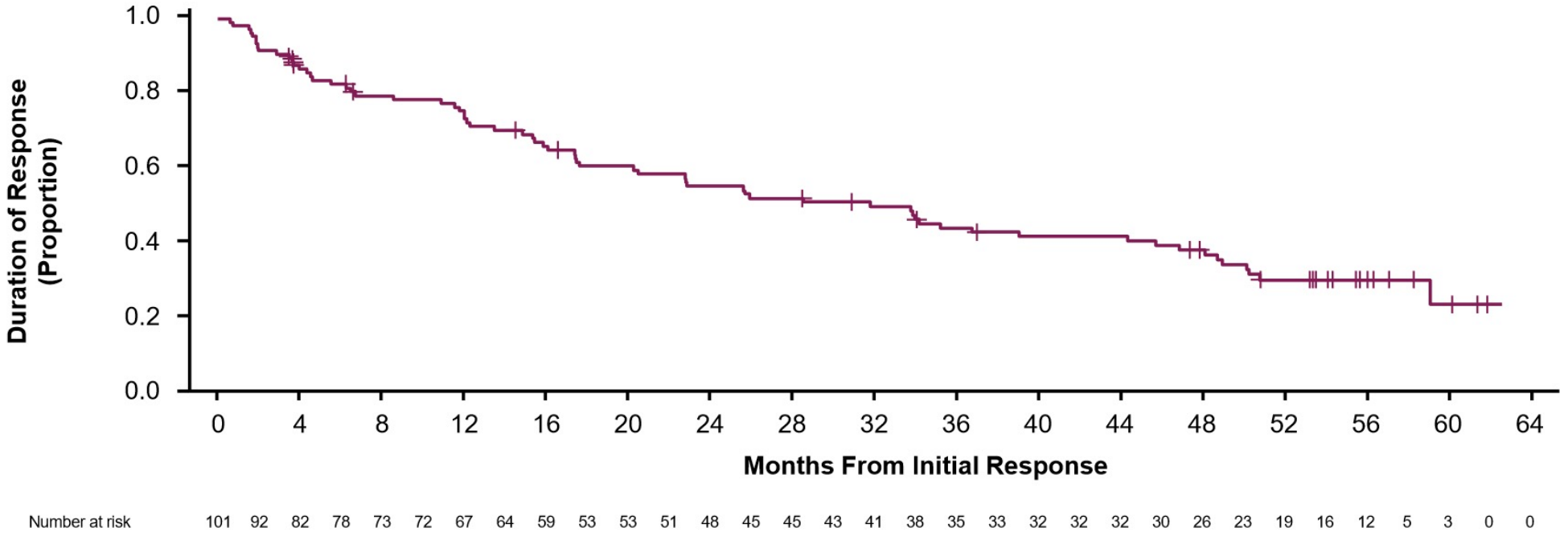
[a]Median PFS at 26-month follow-up: 20 months (95% CI: 16.5, 27.7); median OS at 26-month follow-up: not reached (95% CI: 32.2, not estimable).[1]

CR = complete response; mo = months; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

1. Wang M, et al. *Leukemia*. 2019;33(11):2762-6. **2**. Wang M, et al. Poster presented at: ASH; Dec 5-8, 2020; Virtual Meeting. Poster #2040.

ACE-LY-004 (Final Results): Duration of Response

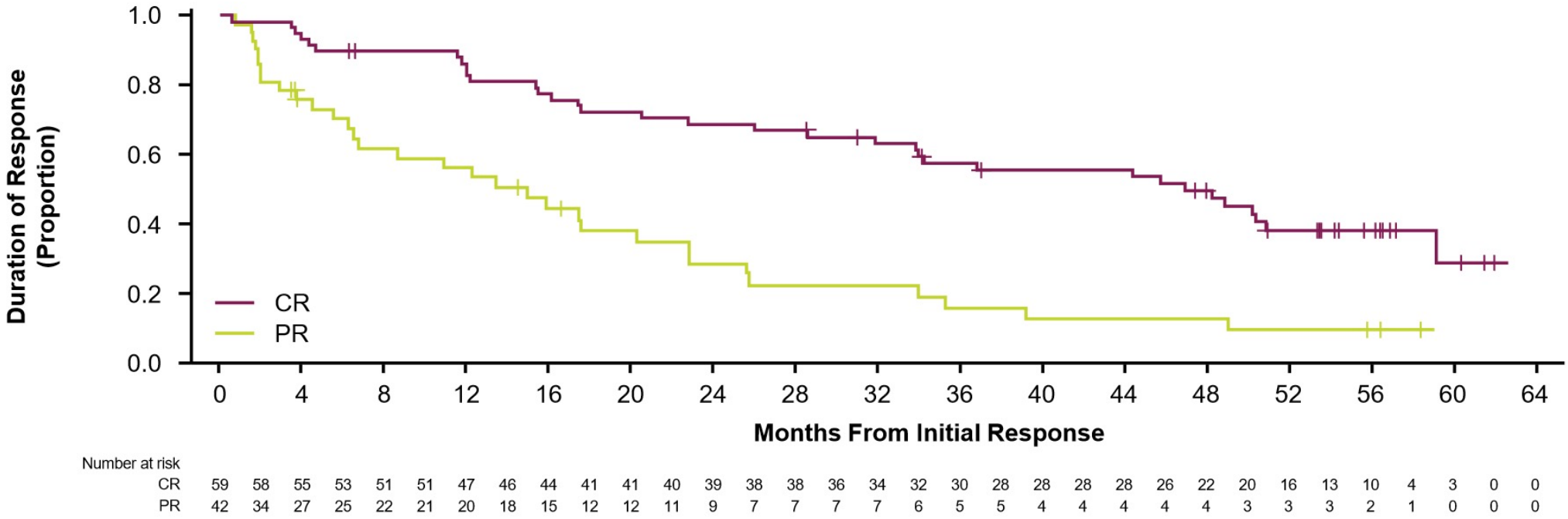
- Median DOR: 28.6 months (95% CI: 17.5, 39.1)
- Estimated 36-month DOR: 41.9% (95% CI: 31.7, 51.8)



CI = confidence interval; DOR = duration of response.

Wang M et al. Poster Presented at: ICML Virtual Meeting; June 18-22, 2021.

ACE-LY-004 (Final Results): Duration of Response by Best Response



Number at risk

CR	59	58	55	53	51	51	47	46	44	41	41	40	39	38	38	36	34	32	30	28	28	28	28	26	22	20	16	13	10	4	3	0	0
PR	42	34	27	25	22	21	20	18	15	12	12	11	9	7	7	7	7	6	5	5	4	4	4	4	4	3	3	3	2	1	0	0	0

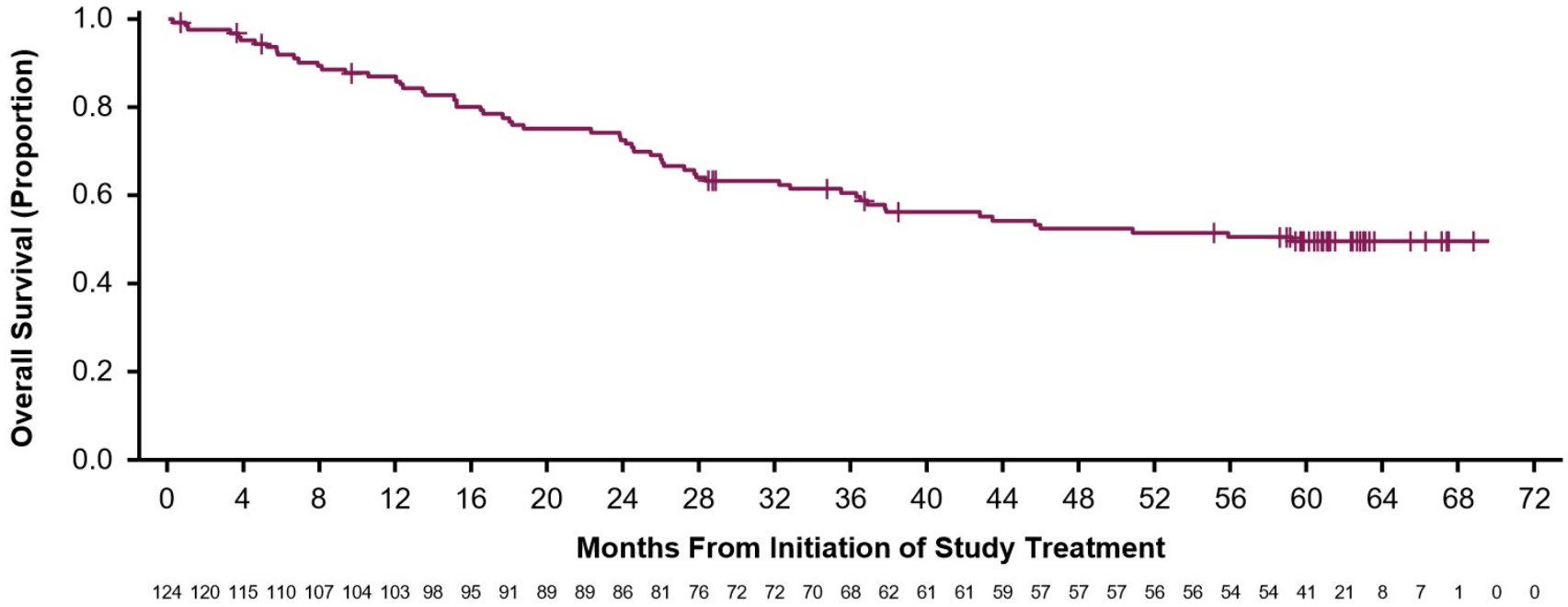
More DOR analysis (ASH 2020 Poster)

CR = complete response; PR = partial response.

Wang M et al. Poster Presented at: ICML Virtual Meeting; June 18-22, 2021.

ACE-LY-004 (Final Results): Overall Survival

- Median OS was reached at 59.2 months (95% CI: 36.5, not evaluable)

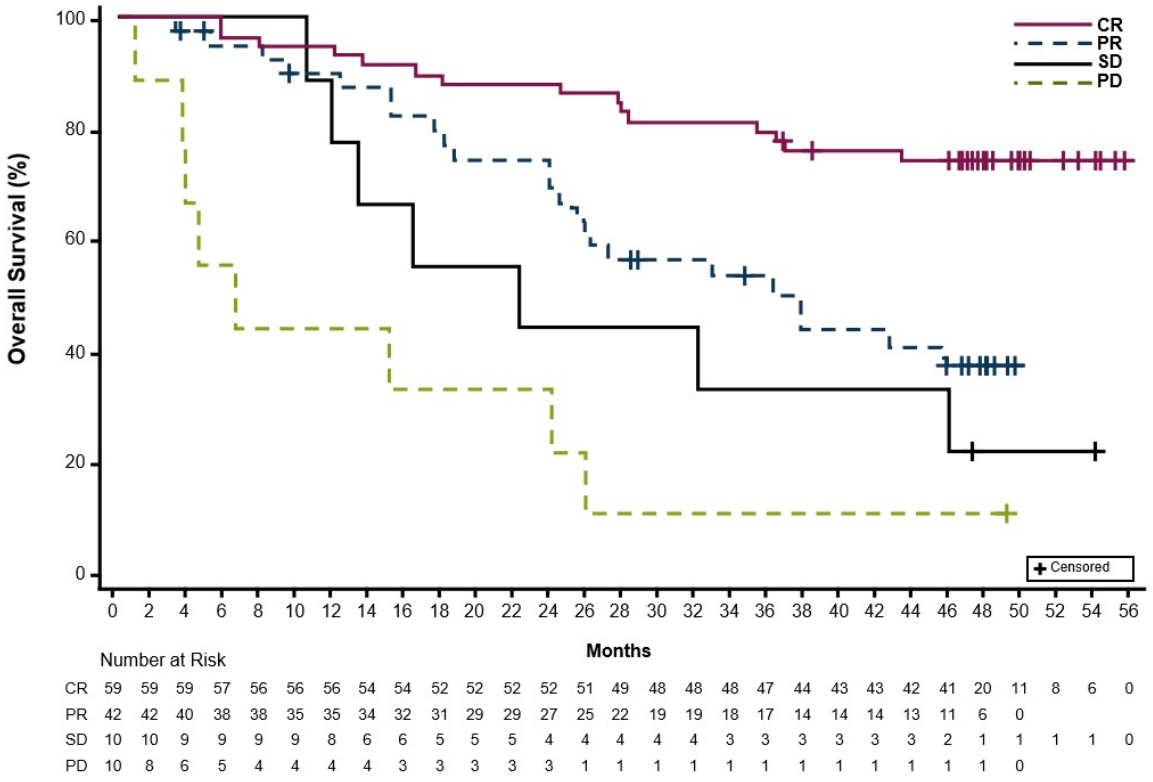


CI = confidence interval; NE = not estimable; OS = overall survival.

Wang M et al. Poster Presented at: ICML Virtual Meeting; June 18-22, 2021.

ACE-LY-004 (38-Month Data Update): Overall Survival by Best Response

Overall Survival



Number at Risk

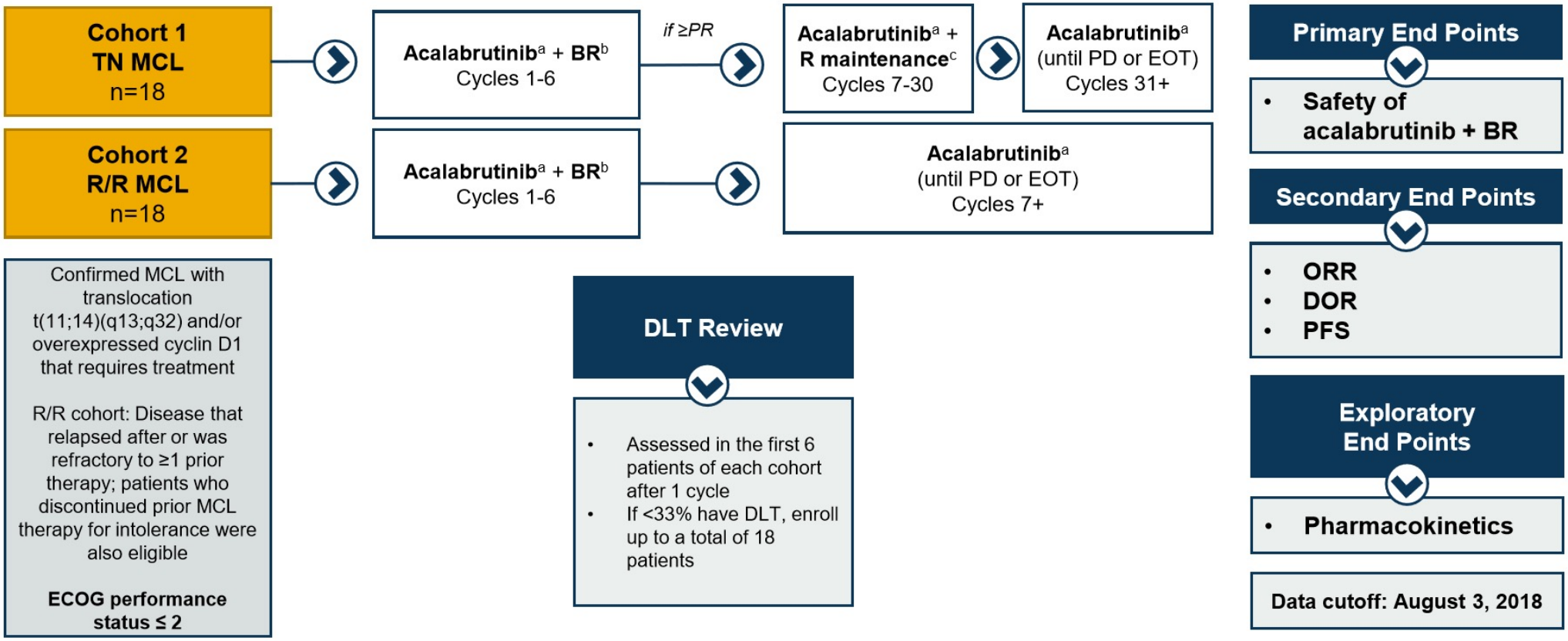
CR	59	59	59	57	56	56	56	54	54	52	52	52	52	51	49	48	48	48	47	44	43	43	42	41	20	11	8	6	0
PR	42	42	40	38	38	35	35	34	32	31	29	29	27	25	22	19	19	18	17	14	14	14	13	11	6	0			
SD	10	10	9	9	9	9	8	6	6	5	5	5	4	4	4	4	4	3	3	3	3	3	3	2	1	1	1	1	0
PD	10	8	6	5	4	4	4	4	3	3	3	3	3	1	1	1	1	1	1	1	1	1	1	1	1	0			

[a]Median PFS at 26-month follow-up: 20 months (95% CI: 16.5, 27.7); median OS at 26-month follow-up: not reached (95% CI: 32.2, not estimable).[1]

CR = complete response; mo = months; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

1. Wang M, et al. *Leukemia*. 2019;33(11):2762-6. **2**. Wang M, et al. Poster presented at: ASH; Dec 5-8, 2020; Virtual Meeting. Poster #2040.

ACE-LY-106: Phase 1b Open-Label Study of Acalabrutinib + BR in MCL (NCT02717624)



[a]Acalabrutinib 100 mg BID PO. [b]B 90 mg/m^2 IV on days 1 and 2 and R 375 mg/m^2 IV on day 1 in each 28-day cycle. [c]R 375 mg/m^2 IV on Day 1 of every other (28-day) cycle for up to 12 doses starting on cycle 8 for patients who achieve PR or CR.

BR = bendamustine and rituximab; CR = complete response; DLT = dose-limiting toxicity; DOR = duration of response; ECOG = Eastern cooperative oncology group; EOT = end of treatment; IV = intravenous; MCL = mantle cell lymphoma; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; R = rituximab; R/R = relapsed/refractory; TN = treatment-naïve.

Phillips T et al. Presented at: ASH; December 1-4, 2018; San Diego, CA.

ACE-LY-106: Grade 3 or 4 AEs in ≥2 Patients (≥5%) Overall

Patients With AE, n (%)	TN (n=18)		RR (n=20)		Total (N=38)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Preferred term						
Neutropenia	4 (22)	3 (17)	5 (25)	5 (25)	9 (24)	8 (21)
Decreased neutrophil count	0	1 (6)	2 (10)	1 (5)	2 (5)	2 (5)
Pneumonia	2 (11)	0	2 (10)	0	4 (11)	0
Thrombocytopenia	1 (6)	0	1 (5)	1 (5)	2 (5)	1 (3)
Abdominal pain	1 (6)	0	1 (5)	0	2 (5)	0
Acute kidney injury	1 (6)	0	1 (5)	0	2 (5)	0
Anemia	1 (6)	0	1 (5)	0	2 (5)	0
Decreased white blood cell count	0	0	2 (10)	0	2 (5)	0
Diarrhea	0	0	2 (10)	0	2 (5)	0
Hypertension	1 (6)	0	1 (5)	0	2 (5)	0
Hyperuricemia	0	1 (6)	1 (5)	0	1 (3)	1 (3)
Hypotension	1 (6)	0	1 (5)	0	2 (5)	0
Leukopenia	0	0	1 (5)	1 (5)	1 (3)	1 (3)

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

Phillips T et al. Presented at: ASH; December 1-4, 2018; San Diego, CA.

ACE-LY-106: Best Response[a] to Acalabrutinib + BR[1]

Best Response, n (%)	TN (n=18)	R/R (n=20)
ORR (CR + PR), n (%)	17 (94) 95% CI: 73, 100	17 (85) 95% CI: 62, 97
CR	13 (72)	13 (65)
PR	4 (22)	4 (20)
SD	0	1 (5)
PD	0	0
Not evaluable[b]	1 (6)	2 (10)
Time to initial response, median (min, max), months	1.9 (1.6, 2.8)	1.8 (1.6, 2.3)
Time to best response, median (min, max), months	1.9 (1.6, 10.1)	2.0 (1.6, 14.8)

[a]Assessed using Lugano criteria.[2] [b]Includes patients without adequate postbaseline response assessment.

BR = bendamustine and rituximab; CI = confidence interval; CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; R/R = relapsed/refractory; SD = stable disease; TN = treatment-naïve.

1. Phillips T et al. Presented at: ASH; December 1-4, 2018; San Diego, CA. 2. Cheson BD, et al. *J Clin Oncol.* 2014;32(27):3059-3068.

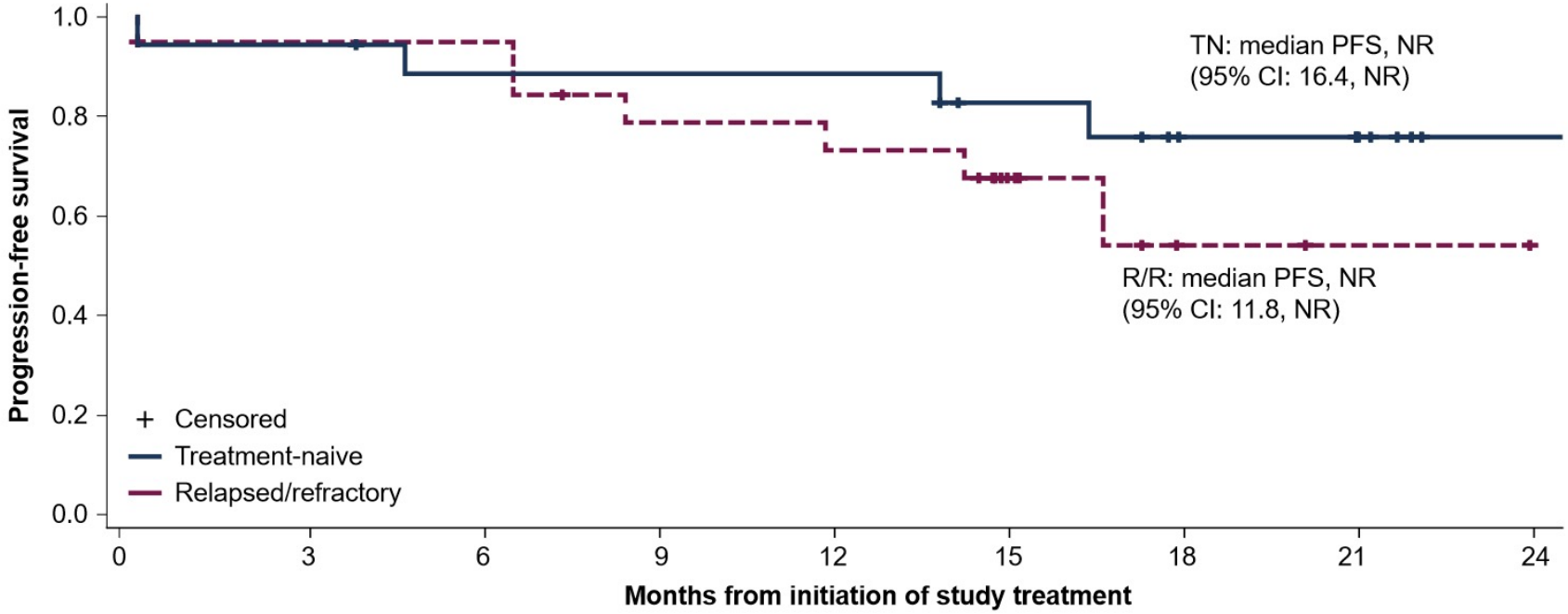
ACE-LY-106: Maximum Change From Baseline in SPD[a]

[a]Three patients were not evaluable. *Patient had bone marrow involvement at screening and achieved complete metabolic response by PET-CT after study treatment; however, patient refused posttreatment bone marrow biopsy to confirm CR.

CR = complete response; PET-CT = positron emission tomography-computed tomography; PR = partial response; R/R = relapsed/refractory; SD = stable disease; SPD = sum of product diameters; TN = treatment-naïve.

Phillips T et al. Presented at: ASH; December 1-4, 2018; San Diego, CA.

ACE-LY-106: PFS by Cohort



Number at risk

18	17	15	15	15	12	8	5	1
20	18	18	14	13	7	2	1	0

NR = not reached; PFS = progression-free survival; R/R = relapsed/refractory; TN = treatment-naïve.

Phillips T et al. Presented at: ASH; December 1-4, 2018; San Diego, CA.

ACE-LY-004 (38-Month Data Update): Summary

With the long-term 38.1-month median follow-up of R/R MCL patients, this study confirmed that acalabrutinib is highly active with a median time on treatment of 17.5 months

Median PFS: 22.0 months

Median DOR: 28.6 months

Median OS: 59.2 months

- Median OS in patients with 1 line of prior therapy has not been reached
- Median OS in patients with ≥2 lines of prior therapy: 55.9 (95% CI: 27.7, NE)

High response rates were observed with an **ORR of 81% and CR of 48%**

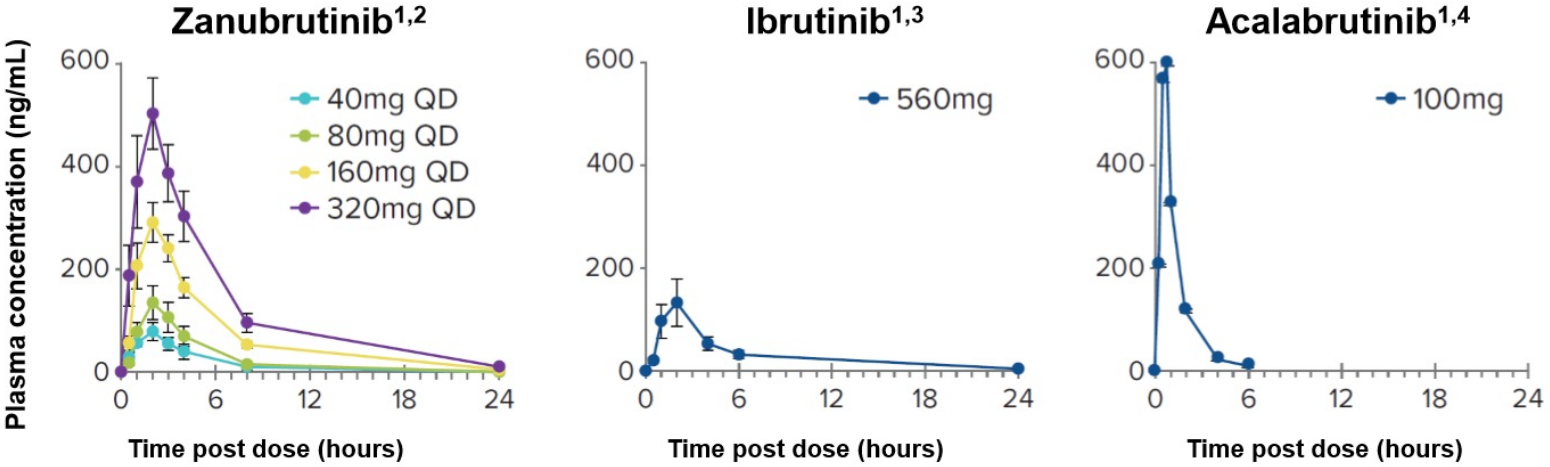
With the 38.1-month follow-up, no new safety signals were observed

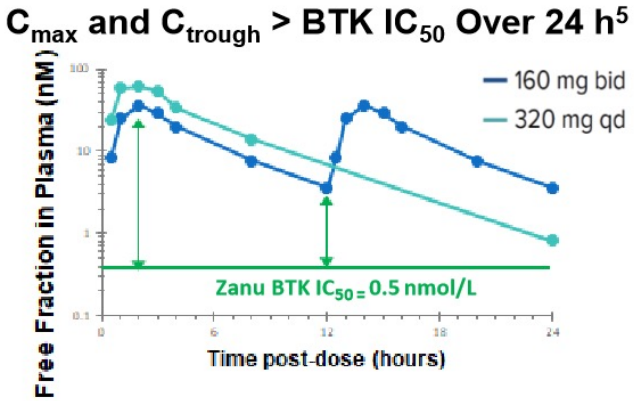
CI = confidence interval; CR = complete response; DOR = duration of response; MCL = mantle cell lymphoma; NE = Not evaluable; OS = overall survival; ORR =overall response rate; PFS = progression-free survival; R/R = relapsed/refractory.

BeiGene

Wang M et al. Poster Presented at: ICML Virtual Meeting; June 18-22, 2021.

Zanubrutinib
Pharmacokinetics





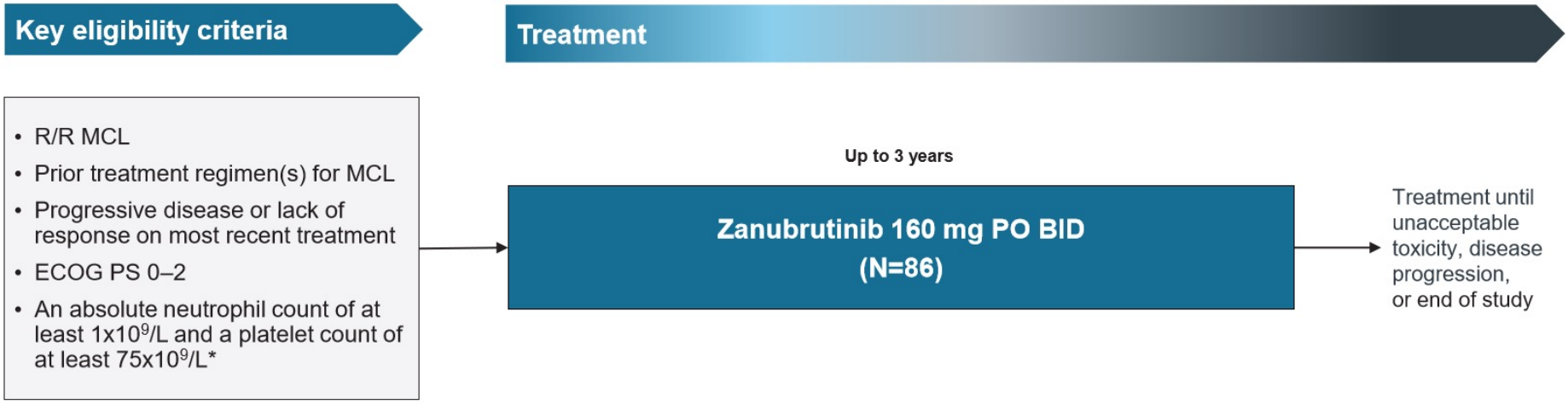
1. Seymour JF et al. ICML 2017. 2. Tam CS et al. *Blood*. 2015;126:832 [oral presentation]. 3. Adapted from Advani RH et al. *J Clin Oncol*. 2013;31(1):88-94. 4. Adapted from Byrd JC et al. *N Engl J Med*. 2016;374:323-33. 5. Figure presented at ASCO 2020 [Tam CS et al ASCO 2020, Abstract 8007].

Zanubrutinib Multicentre, Open-Label, Single-Arm Trial in China[1–3]

Phase 2

Study Identifier: BGB-3111-206, NCT03206970

Primary Endpoint: ORR assessed by IRC using PET-based imaging per the Lugano criteria[4]
Key Secondary Endpoints: PFS, DOR, OS, safety



Zanubrutinib is not authorized for the treatment of patients with Mantle Cell Lymphoma (MCL) in Europe

*50x109/L for patients with bone marrow involvement; independent of growth factor support or transfusion for at least 7 days. BID=twice daily, DOR=duration of response, ECOG PS=Eastern Cooperative Oncology Group performance status, IRC=independent review committee, MCL=mantle cell lymphoma, ORR=objective response rate, OS=overall survival, PET=positron emission tomography, PFS=progression-free survival, PO=per oral, R/R=relapsed/refractory. 1. Song Y et al. Clin Cancer Res. 2020;26(16):4216–4224. 2. Song Y et al. ICML 2019. 3. ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT03206970. Accessed January 29, 2021. 4. Cheson BD et al. J Clin Oncol. 2014;32(27):3059–3067.

Patient and Disease Characteristics

Characteristic	Total (N=86)
Age, years Median (range), years ≥65 years, n (%)	 60.5 (34.0–75.0) 22 (25.6%)
Race, n (%) Chinese	 86 (100.0%)
Sex, n (%) Male Female	 67 (77.9%) 19 (22.1%)
ECOG PS, n (%) 0/1 2	 82 (95.3%) 4 (4.7%)
Extranodal disease, n (%) Bone marrow involvement Gastrointestinal involvement	61 (70.9%) 39 (45.3%) 15 (17.4%)
Refractory disease	45 (52.3%)
TP53-mutated (N=54)	15 (27.8%)
Bulky disease, n (%) LDi >5 cm	 37 (43.0%)
Blastoid variant of MCL, n (%)	12 (14.0%)

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Data cutoff 15 February 2019. Note: Percentages may not add up to 100% because of rounding.
ECOG PS=Eastern Cooperative Oncology Group performance status, LDi=longest diameter, MCL=mantle cell lymphoma, TP53=tumor protein 53 gene.
Song Y et al. Clin Cancer Res. 2020;26(16):4216–4224. This study is registered at ClinicalTrials.gov (NCT03206970).

Patient and Disease Characteristics (2)

Characteristic	Total (N=86)
Patients with prior lines of therapy, n (%)	86 (100.0%)
Median (range) number of prior therapies	2 (1–4)
≥3 prior therapies, n (%)	29 (33.7%)
Prior regimens,* n (%)	
Patients with ≥1 rituximab-containing regimen	64 (74.4%)
R-CHOP, R-CHOP-like	46 (53.5%)
CHOP, CHOP-like	31 (36.0%)
High-dose cytarabine-containing regimen†	33 (38.4%)
(R) hyper-CVAD (A)/EPOCH	23 (26.7%)
Lenalidomide	12 (14.0%)
Bortezomib	7 (8.1%)
Stem cell transplant	3 (3.5%)
MIPI-b, n (%)‡	
Low-risk	12 (14.0%)
Intermediate-risk	39 (45.3%)
High-risk	33 (38.4%)
Missing	2 (2.3%)

Data cutoff 15 February 2019. Note: Percentages may not add up to 100% because of rounding.

**Categories are not mutually exclusive, as patients may be included under multiple regimens. †High-dose cytarabine-containing regimens included dexamethasone, cytarabine, and cisplatin (DHAP); etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP); methotrexate and cytarabine (hyper-CVAD B); cyclophosphamide, etoposide, cytarabine, methylprednisolone, vincristine, and nedaplatin (CDEADP). ‡MIPI-b score was derived with the use of four baseline clinical prognostic factors (age, ECOG PS, lactate dehydrogenase level, and white blood cell count) plus percentage Ki-67 expression in tumor cells, and its range depends on the range of these characteristics. The index classifies patients as having low-, intermediate-, or high-risk disease, as defined by scores of <5.7, ≥5.7 to <6.5, and ≥6.5, respectively.*
CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone, ECOG PS=Eastern Cooperative Oncology Group performance status, EPOCH=etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, hyper-CVAD=cyclophosphamide, vincristine, doxorubicin, and dexamethasone, MIPI-b=Biologic Mantle Cell Lymphoma International Prognostic Index, R=rituximab.

Song Y et al. *Clin Cancer Res*. 2020;26(16):4216–4224. This study is registered at ClinicalTrials.gov (NCT03206970).

Summary of Adverse Events*

Event, n (%)	All Grades	Grade ≥3
Patients with at least one adverse event	83 (96.5%)	34 (41.9%)
Hematologic events		
Neutropenia†	42 (48.8%)	17 (19.8%)
Leukopenia‡	30 (34.9%)	6 (7.0%)
Thrombocytopenia§	28 (32.6%)	4 (4.7%)
Anemia	13 (15.1%)	5 (5.8%)
Non-hematologic events		
Upper respiratory tract infection	30 (34.9%)	0 (0)
Rash	29 (33.7%)	0 (0)
Hypokalemia	14 (16.3%)	1 (1.2%)
Diarrhea	13 (15.1%)	0
Hypertension¶	13 (15.1%)	3 (3.5%)
Alanine aminotransferase increased	12 (14.0%)	1 (1.2%)
Lung infection**	11 (12.8%)	8 (9.3%)

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Data cutoff 15 February 2019.
*Data are for adverse events reported from first dose date to 30 days following study drug discontinuation or initiation of new anticancer therapy in the 86 patients included in the study. Any-grade events occurred in at least 10% of patients and Grade ≥3 events occurred in at least 3% of patients on or before the data cut-off date of February 15, 2019. "Bolded" terms correspond to individual categories of AEI.
†Includes preferred terms neutropenia, febrile neutropenia (n=1, Grade 3), and neutrophil count decreased. ‡Includes preferred terms leukopenia and white blood cell count decreased. §Includes preferred terms thrombocytopenia and platelet count decreased. ¶Includes preferred terms hypertension and blood pressure increased. **Includes preferred terms lung infection and pneumonia. AEI=adverse events of interest.
Song Y et al. Clin Cancer Res. 2020;26(16):4216–4224. This study is registered at ClinicalTrials.gov (NCT03206970).

Efficacy: Best Overall Response Assessed by IRC

Efficacy variable	N=86
Objective response, n (%)	
Complete response	59 (68.6%)
Partial response	13 (15.1%)
No response*	14 (16.3%)
Overall	72 (84.0%)
95% CI for overall response	(74.0–91.0)
Time to response (months)	
Median (range)	2.7 (2.5–16.6)
Response duration (months)	
Median† (range)	19.5 (0.9–19.5)
95% CI	(16.6–NE)
Event-free rates at 12 months (%)	78.3%
95% CI	(67.0–86.0)
PFS (months)	
Median† (range)	22.1 (0.0+ – 22.3+)
95% CI	(17.4–NE)
Event-free rates‡ at 12 months (%)	75.5%
95% CI	(65.0–83.0)

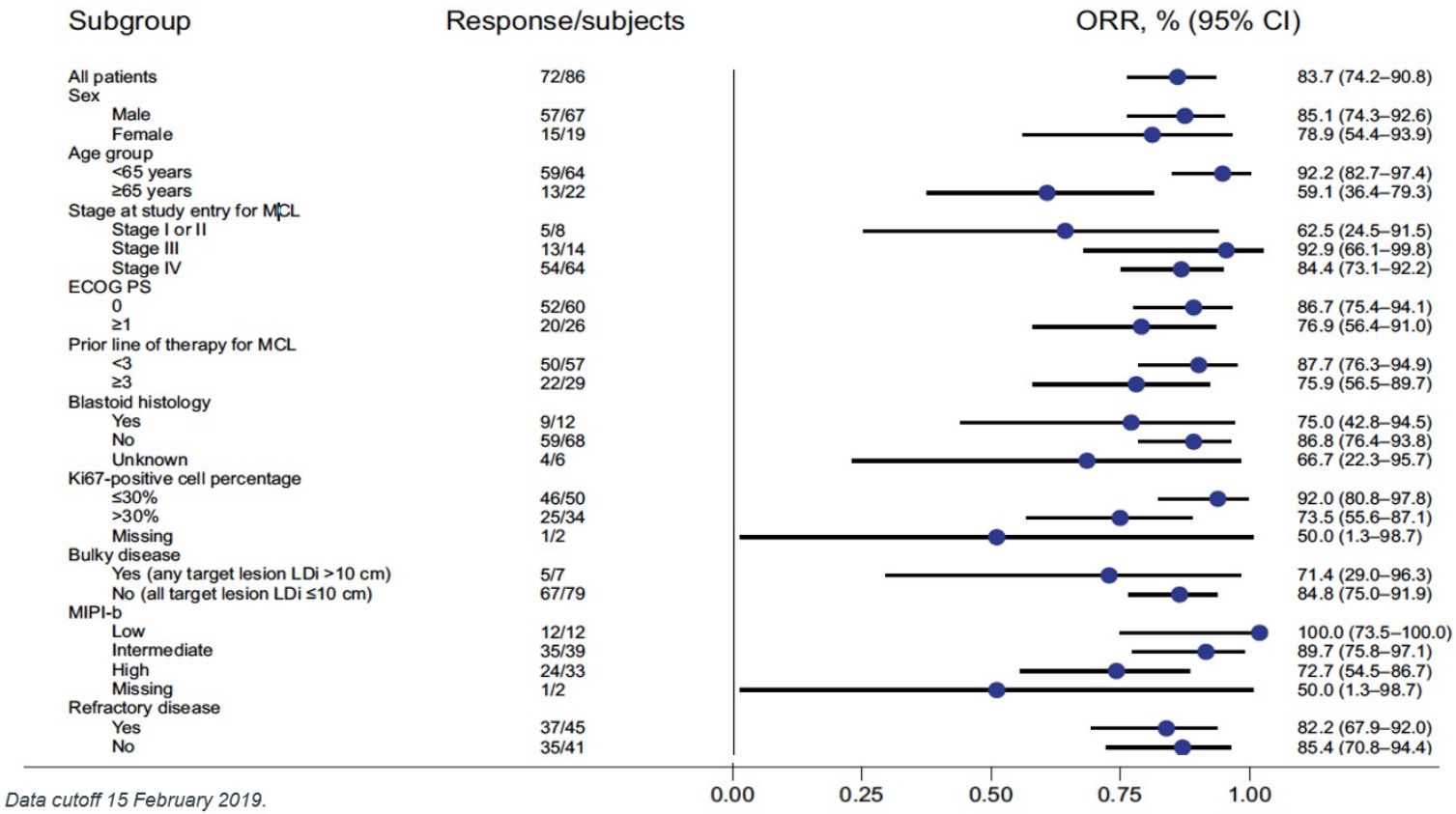
- Median follow-up: 18.4 months

Data cutoff 15 February 2019.

**No response was defined as a best response of stable disease (n=1) or progressive disease (n=6). Six patients with no on-treatment response assessments and one with no evidence of disease at baseline are also included in the no response category. †Medians were estimated by Kaplan–Meier methodology, with 95% CIs estimated using the Brookmeyer and Crowley method. + denotes censored observations. ‡Denotes the proportion of patients who neither progressed nor died. Event-free rates were estimated by Kaplan–Meier methodology, with 95% CIs estimated using Greenwood's formula.*
CI=confidence interval, IRC=independent review committee, NE=not estimable, PFS=progression-free survival.

Song Y et al. *Clin Cancer Res*. 2020;26(16):4216–4224. This study is registered at ClinicalTrials.gov (NCT03206970).

ORR Based on Investigator Assessment by Subgroup (1)

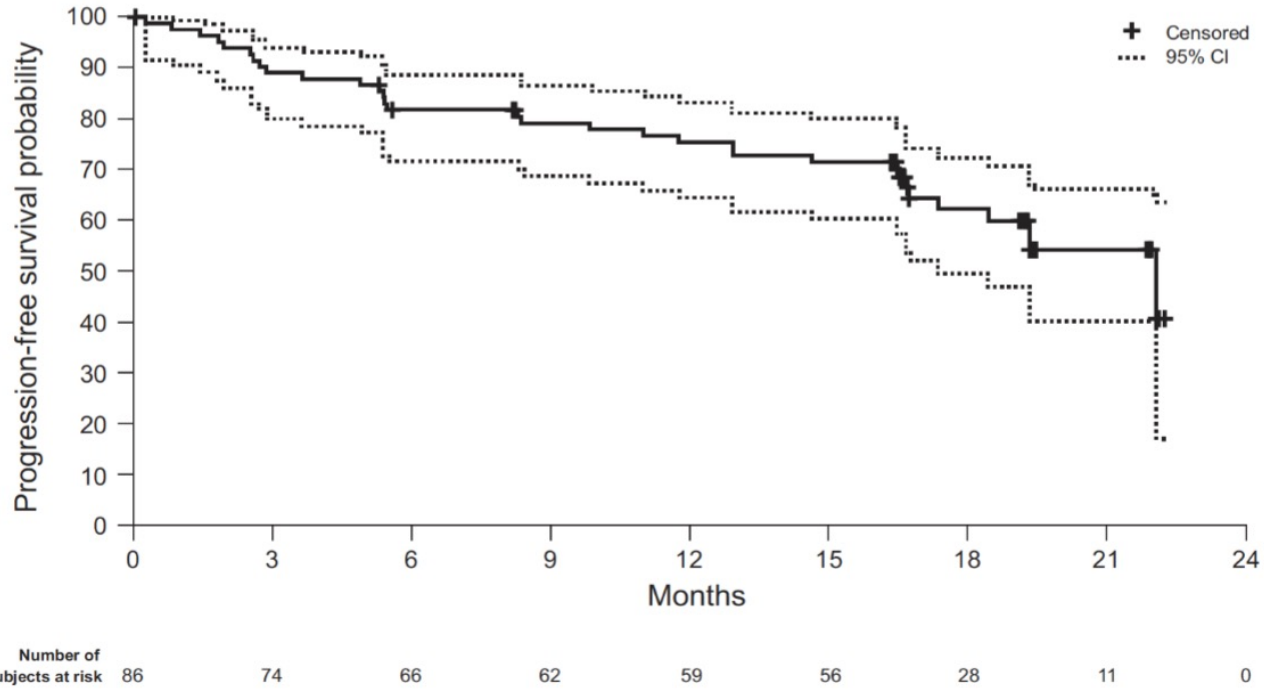


Data cutoff 15 February 2019.

CI=confidence interval, ECOG PS=Eastern Cooperative Oncology Group performance status, LDi=longest diameter, MCL=mantle cell lymphoma, MIPI-b=Biologic Mantle Cell Lymphoma International Prognostic Index, ORR=overall response rate.

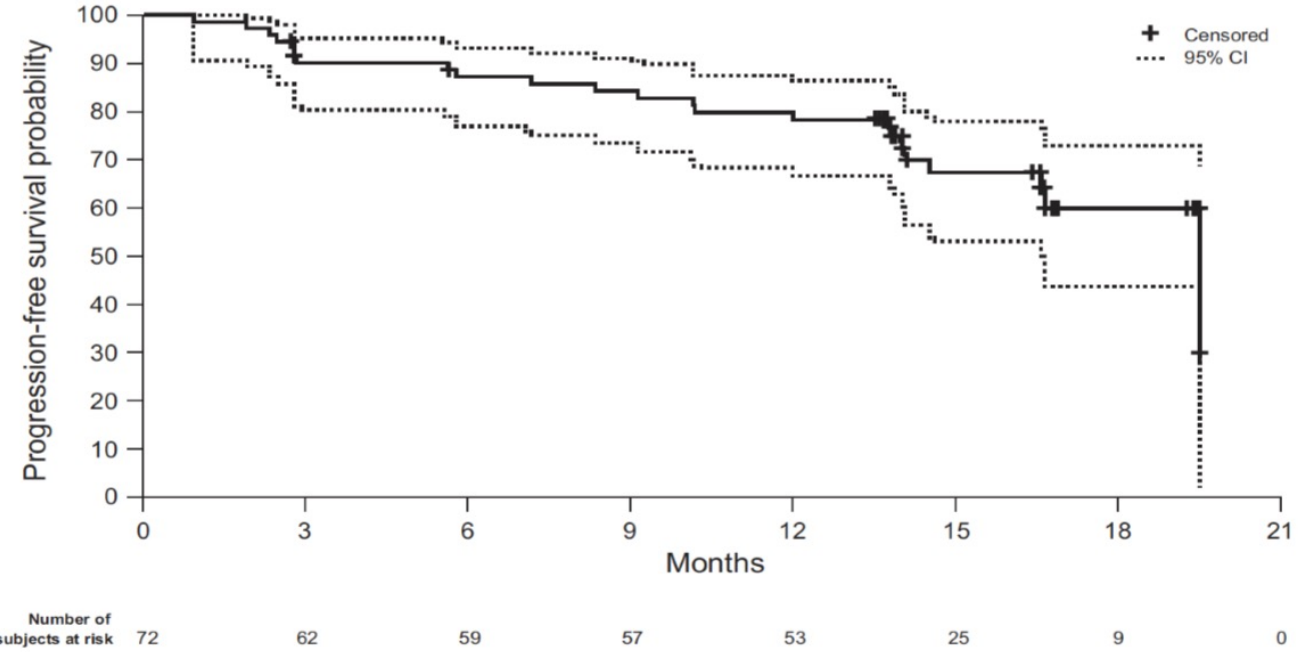
Song Y et al. *Clin Cancer Res*. 2020;26(16):4216–4224. This study is registered at ClinicalTrials.gov (NCT03206970).

Progression-Free Survival by Investigator



Zanubrutinib is not authorized for the treatment of patients with Mantle Cell Lymphoma (MCL) in Europe
Data cutoff 15 February 2019. Note: Only four patients were at risk at the last time event. CI=confidence interval.
Song Y et al. Clin Cancer Res. 2020;26(16):4216–4224. This study is registered at ClinicalTrials.gov (NCT03206970).

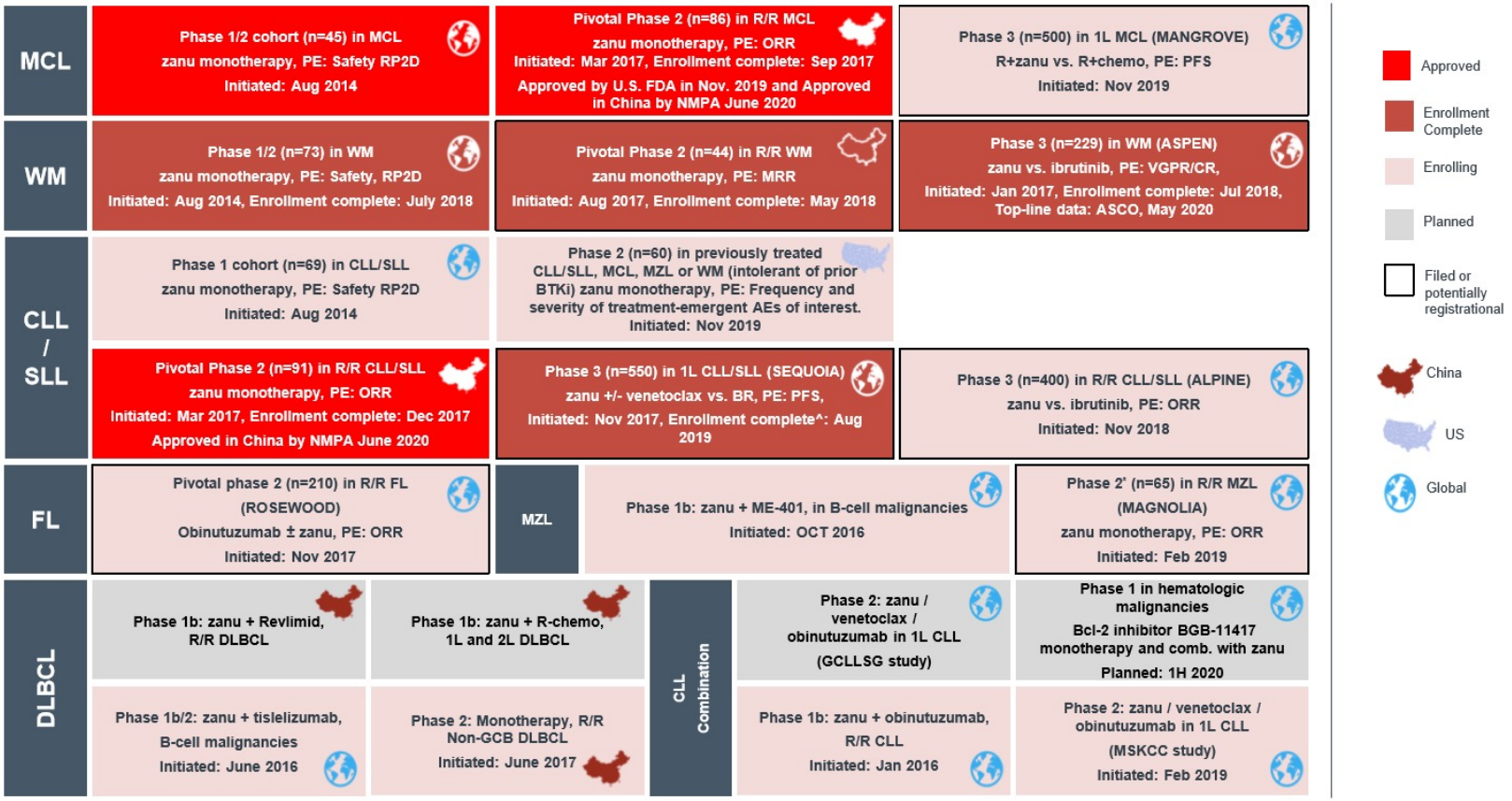
Duration of Response by Investigator



Data cutoff 15 February 2019.

Note: Only two patients were at risk at the last time event.
CI=confidence interval.
Song Y et al. *Clin Cancer Res*. 2020;26(16):4216–4224. This study is registered at ClinicalTrials.gov (NCT03206970).

Zanubrutinib Clinical Program by Hematological Malignancy



*global trial and potentially registration-enabling in certain countries.
1L=first line, ASCO=American Society of Clinical Oncology, BR=bendamustine + rituximab, BTKi=Bruton Tyrosine Kinase inhibitor, CLL/SLL=Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, CR=complete response; DLBCL=Diffuse Large B-Cell Lymphoma, FL=Follicular Lymphoma; GCB=germinal center B-cell-like, MCL=Mantle Cell Lymphoma, MRR=major response rate, MSKCC=Memorial Sloan Kettering Cancer Center, MZL=Marginal Zone Lymphoma, NHL=Non-Hodgkin's Lymphoma, NMPA=National Medical Products Administration, ORR=overall response rate, PCNSL=Primary Central Nervous System Lymphoma, PE=primary endpoint, PFS=progression-free survival, RP2D=recommended Phase 2 dose, R/R=relapsed/refractory, RT=Richter's Transformation, VGPR=very good partial response, WM=Waldenström's macroglobulinemia.

BGB-3111-306: MANGROVE

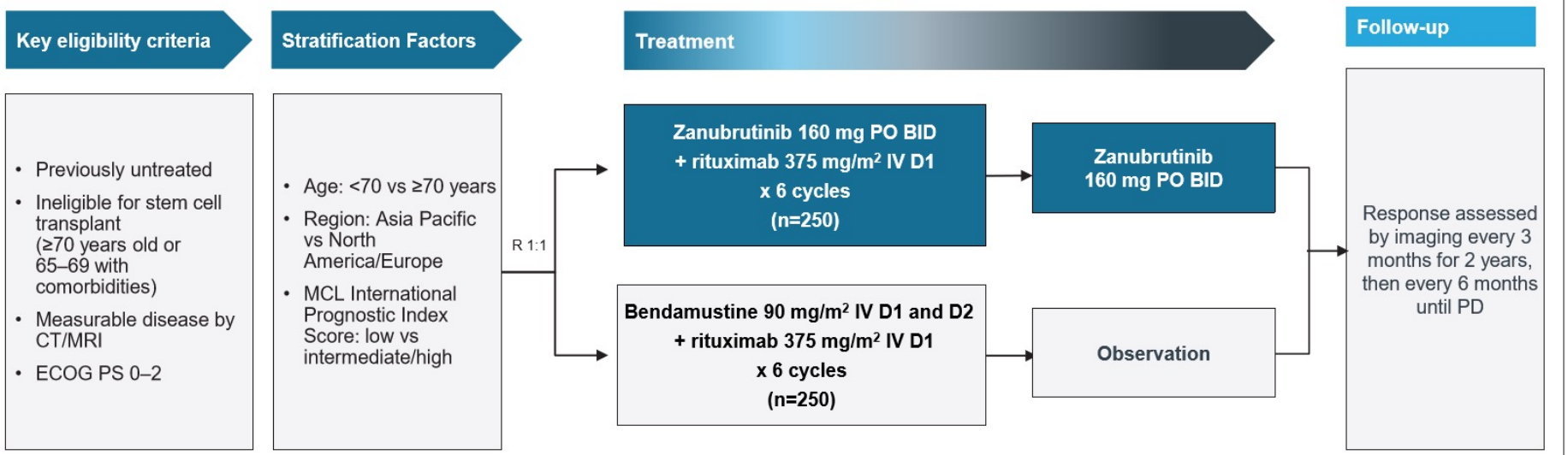
MANGROVE
Phase 3 Treatment-Naïve MCL

Non-inferiority Phase 3 Study of Zanubrutinib + Rituximab vs Bendamustine + Rituximab in 1L Treatment of MCL*

Phase 3

Study Identifier: BGB-3111-306, NCT04002297

Primary Endpoint: PFS by IRC using the 2014 Lugano Classification for NHL
Key Secondary Endpoints: PFS by IA, ORR, DOR, OS, CR (or complete metabolic response), TTR by IRC and IA, PROs, safety



Zanubrutinib is not authorized for the treatment of patients with Mantle Cell Lymphoma (MCL) in Europe
*Previously treated patients ineligible for SCT. 1L=1st line, BICR=blinded independent central review, BID=twice daily, CR=complete response, CT=computed tomography, D=day, DOR=duration of response, ECOG PS=Eastern Cooperative Oncology Group performance status, IA=investigator assessment, IRC=independent review committee, IV=intravenous, MCL=mantle cell lymphoma, MRI=magnetic resonance imaging, NHL=non-Hodgkin lymphoma, ORR=objective response rate, OS=overall survival, PFS=progression-free survival, PO=per oral, PR=partial response, PRO=patient-reported outcome, R=randomized, TTR=time to response.
Dreyling M, et al. ASCO 2020. Abstract TPS8071. This study is registered at ClinicalTrials.gov (NCT04002297).

Mantle cell Lymphome
Novel treatments 2022

LMU KLINIKUM

- high risk in clinical routine: Ki-67, p53 mut, blastoid

- first line: - younger: R/DHAP-autologous SCT- R-maintenance ?

  Elderly: IR-CHOP/Benda **(+ I)** + R-maintenance

  in studies: **non-chemo (combined) approaches**

- in early relapses: **BTKi (combinations?)**

  - in studies: non-covalent BTKi, CAR –T cells, bispecific antibodies (combinations?)

Acknowledgement