PHASE 1/2 STUDY OF ZILOVERTAMAB (formerly CIRMTUZUMAB) AND IBRUTINIB IN MANTLE CELL LYMPHOMA (MCL) OR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

ONCTERNAL therapeutics

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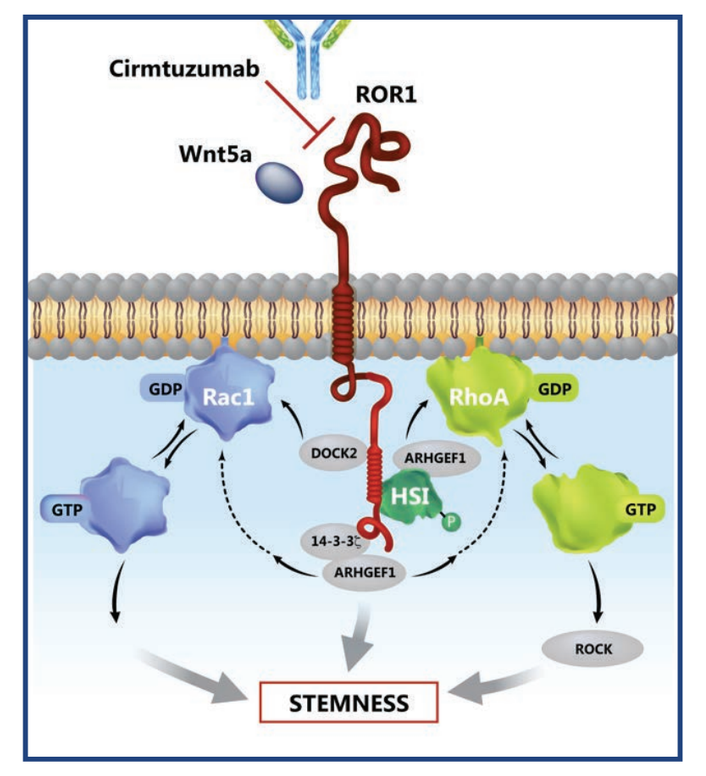
ASCO Annual Meeting 2022
June 3 – June 7
Hybrid Meeting
Abstract #7520

Background

Front-line use of multi-agent therapies are typically successful in suppressing chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL). However, these diseases are incurable, and patients require further therapy for disease control.

- ROR1 is an onco-embryonic tyrosine kinase-like receptor that is re-expressed at high levels on manysolid and hematologic cancers including MCL, CLL, and MZL but not on normal adult tissues. ROR1 binds Wnt5a, resulting in increased tumor growth, survival, metastasis, cancer cell stemness and epithelial mesenchymal transition.
- Zilovertamab (formerly cirmtuzumab) is a humanized monoclonal antibody designed to inhibit the tumor promoting activity of ROR1.



Phase 1/2 Study Design

Treatment naïve (TN) or Relapsed/Refractory (R/R) CLL/SLL; R/R MCL and MZL; prior BTKi allowed for MCL and MZL

Phase 1	Phase 2	
Part 1 (MCL & CLL)	Part 2 (MCL, CLL & MZL)	Part 3 (CLL)
DOSE-FINDING COHORT ▪ 2, 4, 8 & 16mg/kg and 300 & 600mg doses of zilovertamab[a] evaluated ▪ Ibrutinib added after 1 month (420mg CLL, 560mg MCL, qd po) ▪ No DLTs, MTD not reached ▪ RDR[b]: 600mg IV q2wks X 3 then q4wks in combination with ibrutinib at approved doses per indication	DOSE-EXPANSION COHORT ▪ Confirmed RDR[b] of zilovertamab[a] (600mg) + ibrutinib at approved dose (420mg CLL, 560mg MCL and MZL) ▪ Primary objective: To further characterize safety, pharmacology, and clinical response using RDR[b]	RANDOMIZED EFFICACY ▪ Zilovertamab[a] + ibrutinib vs. ibrutinib ▪ Randomization ratio = 2:1 ▪ Primary objective: Complete Response Rate
Enrolled CLL n = 18 MCL n = 12	*Enrolled* CLL n = 16 MCL n = 21 *MZL soon open for enrollment*	*Enrolled* n = 31

a – Formerly cirmtuzumab; b – recommended dosing regimen

Demography, Disease Characteristics and Disposition

Population: High-risk disease and heavily pre-treated. Most common reason for discontinuation is completion of 2-year treatment.

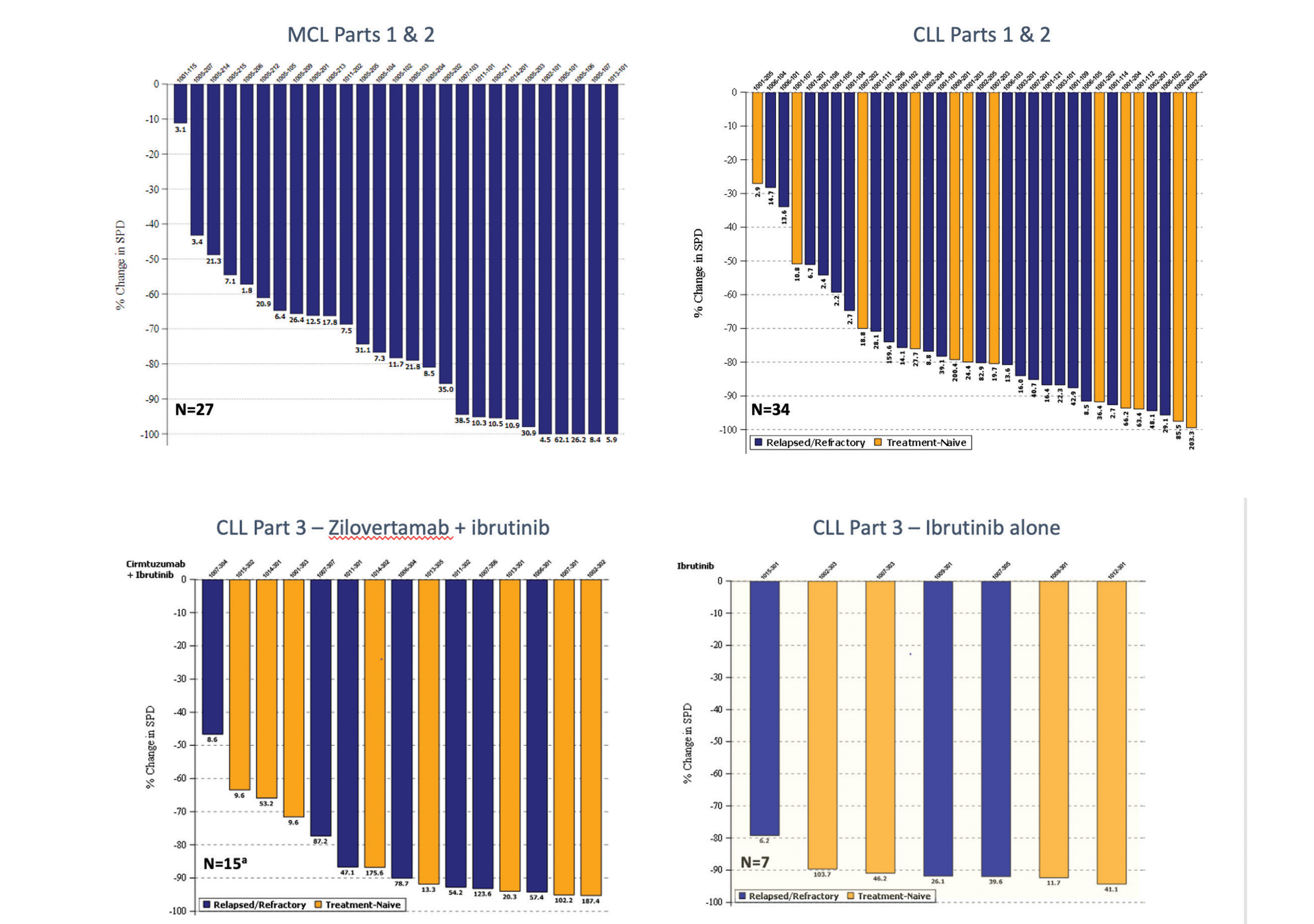
	Parts 1 & 2		Part 3	
	zilo + ibrutinib	zilo + ibrutinib	zilo + ibrutinib	ibrutinib
	MCL	CLL	CLL	
	N=33	N=34	N= 18	N= 10
Demography and Disease Characteristics				
Median Age, years (min, max)	65 (45, 85)	68 (37, 86)	67 (52, 84)	66 (53, 73)
Male, n (%)	27 (81.8)	26 (76.5)	10 (55.6)	3 (30)
ECOG 0-1, n (%)	30 (90.9)	34 (100.0)	16 (88.9)	10 (100)
Median time from diagnosis to study start, years (min, max)	1.96 (0.04, 9.15)	6 (0.03, 31.33)	7.50 (0.05, 21.85)	6.95 (0.05, 13.29)
Ki-67 ≥ 30%, n (%)	17 (51.5)	NA	NA	NA
sMIPI Intermediate/High, n (%)	15 (45.5)	NA	NA	NA
Bulky disease ≥ 5cm, n (%)	8 (24.2)	NA	NA	NA
RAI staging, ≥2, n (%)	NA	24 (70.6)	12 (66.7)	6 (60.0)
LDH >250 U/L, n (%)	NA	15 (44.1)	9 (50.0)	3 (50.0)
Received prior systemic regimens, n (%)	33 (100.0)	22 (64.7)	9 (50.0)	4 (40.0)
Median number of prior systemic regimens (min, max)	1 (1,4)	2.0 (1, 9)[b]	2.0 (1, 4)[b]	2.0 (1, 6)[b]
Prior BTK inhibitor, n (%)	5 (15.2)[a]	0	0	1[a] (10.0)
Prior Transplant/Cell Therapy, n (%)	8 (24.2)[c]	1 (2.9)[d]	0	0
p53 Mutation, n (%)	8 (50.0)[e]	6 (17.6)[f]	4 (23.5)[f]	1 (10.0)[f]
Study Population				
Patients Enrolled, n	33	34	21	10
Safety Population,[g] n	33	34	18	10
Efficacy Population[h], n (%)	27 (81.8)	34 (100)	16 (88.9)	7 (70.0)
Patient Disposition				
Ongoing, n (%)	17 (51.5)	0	3 (16.7)	1 (10.0)
Median Duration of zilovertamab exposure, months (min, max)	11.11 (0.0, 37.1)	12.03 (8.3, 36.1)	23.09 (0.0, 24.3)	0
Median Duration of Follow-up, months (95% CI)	15.1 (14.31, 22.13)	32.9 (31.01, 36.24)	24.1 (18.97, 24.23)	24.7 (18.04, 27.99)
Discontinued from Treatment, n (%)	16 (48.5)	34 (100)	15 (83.3)	9 (90.0)
Reason for Study Discontinuation				
Completed 2 years of treatment, n (%)	NA[i]	15 (44.1)	6 (33.3)	3 (30.0)
Disease Progression, n (%)	7 (21.2)[j]	1 (2.9)	1 (5.6)	1 (10.0)
Adverse Event, n (%)	2 (6.1)	4 (11.8)	5 (27.8)	3 (30.0)
Death, n (%)	1 (3.0)	1 (2.9)	0	0
Other, n (%)	6[k] (18.2)	13[l] (38.2)	3[m] (16.7)	2[n] (20.0)

Data cut: 8Apr2022; Zilo – zilovertamab; NA- not applicable; sMIPI: Simplified Mantle Cell Lymphoma International Prognostic Index; LDH: lactate dehydrogenase; a – prior BTK inhibitor = ibrutinib; b – Median number of prior systemic regimens based on number of subjects who received prior treatments for CLL =22; c – Autologous stem cell transplant (n=8), Allogeneic stem cell transplant (n=1), CAR-T (n=1) patients could have received more than one; d – Autologous stem cell transplant (n=1); e – percentage of p53 mutation based on number of subject assessed for mutation, for MCL =16; f – percentage of p53 mutation based on number of subject assessed for mutation, for CLL Part 1&2 =34, CLL Part 3, zilovertamab + ibrutinib =17, CLL Part 3, ibrutinib alone =10, p53 mutation status manually calculated for CLL; g – Safety population is comprised of all enrolled subjects who received at least one dose of zilovertamab (or ibrutinib if Part 3 ibrutinib alone arm); h – Efficacy population is comprised of enrolled subjects who have received at least one dose of zilovertamab and have at least one post-baseline tumor assessment; i – NA- not applicable, zilovertamab treatment duration is not limited to 2 years for MCL patients; j – Includes 6 objective disease progression and 1 clinical progression; k – Other reasons for MCL include: initiation of alternative treatment (1), patient request to withdraw (3), thyroid cancer (1), investigator decision (1); l – Other reasons for CLL Parts 1&2 include: initiation of alternative treatment (3), investigator decision (4), patient request (6); m – Other reasons For CLL part 3 zilovertamab + ibrutinib arm include: investigator decision (1), noncompliance (1), patient request (1); n – Other reasons For CLL part 3 ibrutinib alone arm is investigator decision (1).

Results

Efficacy: Waterfall Plot of Best % Tumor Reduction from Baseline

Marked reduction in tumor size observed in both MCL & CLL patients



Data Cut: 8Apr2022; SPD = Sum of the Products of the Diameters, Number under bars represent baseline SPD; a – tumor measurements not available for 1 subject in zilovertamab + ibrutinib arm.

Safety

Treatment Emergent Adverse Events ≥20%

Zilovertamab + ibrutinib is generally well tolerated.

MCL Parts 1 & 2, N = 33	Overall, n (%)	Grades 1-2, n (%)	Grades ≥3, n (%)
Fatigue	16 (48.5)	12 (36.4)	4 (12.1)
Diarrhea	12 (36.4)	11 (33.3)	1 (3.0)
Nausea	11 (33.3)	11 (33.3)	0
Contusion	10 (30.3)	10 (30.3)	0
Cough	10 (30.3)	10 (30.3)	0
Dizziness	9 (27.3)	9 (27.3)	0
Stomatitis	9 (27.3)	6 (18.2)	3 (9.1)
Anemia	8 (24.2)	5 (15.2)	3 (9.1)
Myalgia	8 (24.2)	7 (21.2)	1 (3.0)
Arthralgia	7 (21.2)	6 (18.2)	1 (3.0)
Vomiting	7 (21.2)	6 (18.2)	1 (3.0)
Treatment Emergent Hematological Laboratory Abnormalities			
Neutrophils decrease	8 (24.2)	5 (15.2)	3 (9.1)
Platelets decrease	22 (66.7)	18 (54.5)	4 (12.1)
Hemoglobin decrease	23 (69.7)	20 (60.6)	3 (9.1)

CLL Parts 1 & 2, CLL N=34	Overall, n (%)	Grades 1-2, n (%)	Grades ≥3, n (%)
Contusion	16 (47.1)	16 (47.1)	0
Hypertension	16 (47.1)	9 (26.5)	7 (20.6)
Diarrhea	15 (44.1)	13 (38.2)	2 (5.9)
Upper respiratory tract infection	15 (44.1)	15 (44.1)	0
Fatigue	14 (41.2)	14 (41.2)	0
Muscle Spasms	11 (32.4)	11 (32.4)	0
Onycholclasis	11 (32.4)	11 (32.4)	0
Arthralgia	10 (29.4)	10 (29.4)	0
Cough	9 (26.5)	9 (26.5)	0
Gastroesophageal reflux disease	9 (26.5)	9 (26.5)	0
Hypophosphatemia	9 (26.5)	8 (23.5)	1 (2.9)
Rash	9 (26.5)	9 (26.5)	0
Haematuria	8 (23.5)	8 (23.5)	0
Dizziness	7 (20.6)	7 (20.6)	0
Dyspnea	7 (20.6)	6 (17.6)	1 (2.9)
Headache	7 (20.6)	7 (20.6)	0
Hypercreatinemia	7 (20.6)	6 (17.6)	1 (2.9)
Palpitations	7 (20.6)	7 (20.6)	0
Thrombocytopenia	7 (20.6)	6 (17.6)	1 (2.9)
Treatment Emergent Hematological Laboratory Abnormalities			
Neutrophils decrease	16 (47.1)	10 (29.4)	6 (17.6)
Platelets decrease	25 (73.5)	24 (70.6)	1 (2.9)
Hemoglobin decrease	25 (73.5)	25 (73.5)	0

Treatment Emergent Adverse

Safety profile with zilovertamab + ibrutinib is consistent with ibrutinib alone

CLL Part 3: Zilovertamab + ibrutinib, N = 18	Overall, n (%)	Grades 1-2, n (%)	Grades ≥3, n (%)
Contusion	7 (38.9)	7 (38.9)	0
Back pain	6 (33.3)	4 (22.2)	2 (11.1)
Fatigue	6 (33.3)	5 (27.8)	1 (5.6)
Cough	5 (27.8)	5 (27.8)	0
Diarrhea	5 (27.8)	5 (27.8)	0
Pain in extremity	5 (27.8)	5 (27.8)	0
Thrombocytopenia	5 (27.8)	5 (27.8)	0
Decreased appetite	4 (22.2)	4 (22.2)	0
Dizziness	4 (22.2)	4 (22.2)	0
Dry skin	4 (22.2)	4 (22.2)	0
Dyspnea	4 (22.2)	4 (22.2)	0
Gastroesophageal reflux disease	4 (22.2)	4 (22.2)	0
Hypertension	4 (22.2)	4 (22.2)	1 (5.6)
Edema peripheral	4 (22.2)	4 (22.2)	0
Pneumonia	4 (22.2)	2 (11.1)	2 (11.1)
Sinusitis	4 (22.2)	3 (16.7)	1 (5.6)
Treatment Emergent Hematological Laboratory Abnormalities			
Neutrophils decrease	6 (33.3)	5 (27.8)	1 (5.6)
Platelets decrease	13 (72.2)	13 (72.2)	0
Hemoglobin decrease	16 (88.9)	16 (88.9)	0

CLL Part 3: Ibrutinib, N = 10	Overall, n (%)	Grades 1-2, n (%)	Grades ≥3, n (%)
Diarrhea	4 (40.0)	4 (40.0)	0
Headache	4 (40.0)	3 (30.0)	1 (10.0)
Constipation	3 (30.0)	3 (30.0)	0
Contusion	3 (30.0)	3 (30.0)	0
Dizziness	3 (30.0)	3 (30.0)	0
Hematuria	3 (30.0)	3 (30.0)	0
Nausea	3 (30.0)	3 (30.0)	0
Upper respiratory tract infection	3 (30.0)	3 (30.0)	0
Atrial Fibrillation	2 (20.0)	1 (10.0)	1 (10.0)
Back pain	2 (20.0)	2 (20.0)	0
Coronavirus Infection	2 (20.0)	1 (10.0)	1 (10.0)
Fall	2 (20.0)	2 (20.0)	0
Fatigue	2 (20.0)	2 (20.0)	0
Hypertension	2 (20.0)	1 (10.0)	1 (10.0)
Muscle spasms	2 (20.0)	2 (20.0)	0
Pneumonia	2 (20.0)	0	2 (20.0)
Pruritis	2 (20.0)	2 (20.0)	0
Treatment Emergent Hematological Laboratory Abnormalities			
Neutrophils decrease	3 (30.0)	1 (10.0)	2 (20.0)
Platelets decrease	8 (80.0)	7 (70.0)	1 (10.0)
Hemoglobin decrease	7 (70.0)	6 (60.0)	1 (10.0)

MCL Efficacy: Clinical Response Rates in Subgroups

High response rates and durable responses observed in high risk MCL subgroups

	Overall	Ki67 ≥ 30%	Prior BTKi[a]	Prior SCT +/- CAR-T[b]	Bulky disease (≥ 5cm)	Low sMIPI	Int sMIPI	High sMIPI	1 Prior Regimen	2 Prior Regimens	≥ 3 Prior Regimens	p53 mutation
	N=27	N=14	N=5	N=7	N=4	N=15	N=9	N=3	N=15	N=8	N=4	N=6
ORR, n (%)	23 (85.2)	12 (85.7)	4 (80.8)	7 (100.0)	4 (100.0)	13 (86.7)	8 (88.9)	2 (66.7)	13 (86.7)	6 (75.0)	4 (100.0)	5 (83.3)
CR, n (%)	11[c] (40.7)	5[c] (35.7)	2 (40.0)	5 (71.4)	3 (75.0)	5 (33.3)	5[c] (55.6)	1 (33.3)	4[c] (26.7)	5 (62.5)	2 (50.0)	1 (16.7)
PR, n (%)	12 (44.4)	7 (50.0)	2 (40.0)	2 (28.6)	1 (25.0)	8 (53.3)	3 (33.3)	1 (33.3)	9 (60.0)	1 (12.5)	2 (50.0)	4 (66.7)
SD, n (%)	2 (7.4)	0	1 (20.0)	0	0	1 (6.7)	0	1 (33.3)	0	2 (25.0)	0	0
PD, n (%)	2 (7.4)	2 (14.3)	0	0	0	1 (6.7)	1 (11.1)	0	2 (13.3)	0	0	1 (16.7)
Median Duration of Response, months (95% CI)	34.13 (13.67, NE)	NR (13.67, NE)	13.67 (11.93, NE)	34.13 (13.84, NE)	23.90 (11.93, NE)	NR (11.93, NE)	34.13 (NE)	NR (13.84, NE)	NR (11.93, NE)	NR (1.51, NE)	34.13 (13.84, NE)	13.84 (11.93, NE)

Data Cut: 8Apr2022; MCL Efficacy in Parts 1 & 2; NE = Not estimable; NR = Not reached; N=number of evaluable patients; sMIPI: Simplified Mantle Cell Lymphoma International Prognostic Index; a – prior BTK inhibitor = ibrutinib; b – Autologous stem cell transplant (n=8), Allogeneic stem cell transplant (n=1), CAR-T (n=1) patients could have received more than one; c – includes 1 unconfirmed CR

CLL Efficacy: Clinical Response Rates in Subgroups

Encouraging ORR in heavily pre-treated CLL patients.

	Parts 1 & 2 Zilovertamab + Ibrutinib					Part 3 Zilovertamab + Ibrutinib					Part 3 Ibrutinib alone				
	Overall	TN	1 Prior	2 Prior	≥3 Prior	Overall	TN	1 Prior	2 Prior	≥3 Prior	Overall	TN	1 Prior	2 Prior	≥3 Prior
	N=34	N=12	N=10	N=4	N=8	N=16	N=8	N=4	N=2	N=2	N=7	N=4	N=2	N=0	N=1
ORR, n (%)	31 (91.2)	11 (91.7)	10 (100.0)	3 (75.0)	7 (87.5)	15 (93.8)	8 (100.0)	4 (100)	1 (50.0)	2 (100.0)	7 (100.0)	4 (100.0)	2 (100.0)	0	1 (100.0)
CR, n (%)	3[a] (8.8)	1[a] (8.3)	2 (20.0)	0	0	0	0	0	0	0	0	0	0	0	0
PR, n (%)	28[b] (82.3)	10 (83.3)	8 (80.0)	3 (100.0)	7[b] (87.5)	15 (93.8)	8 (100.0)	4 (100.0)	1 (100.0)	2 (100.0)	7 (100.0)	4 (100.0)	2 (100.0)	0	1 (100.0)
SD, n (%)	3 (8.8)	1 (8.3)	0	1 (25.0)	1 (12.5)	1 (6.3)	0	0	1 (100.0)	0	0	0	0	0	0
PD, n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Median DoR, months (95% CI)	33.54 (33.54, NE)	NR (9.70, NE)	NR (7.4, 28.0)[c]	NR (5.5, 28.1)[c]	33.54 (19.57, NE)	NR (0, 22.2)[c]	NR (8.49, NE)	NR (16.6, 22.2)[c]	NR (20.9, 20.9)[c]	NR (0.0, 13.8)[c]	NR (8.30, NE)	NR (8.3, 21.3)[c]	NR (19.3, 19.5)[c]	NA	8.3 (NE)

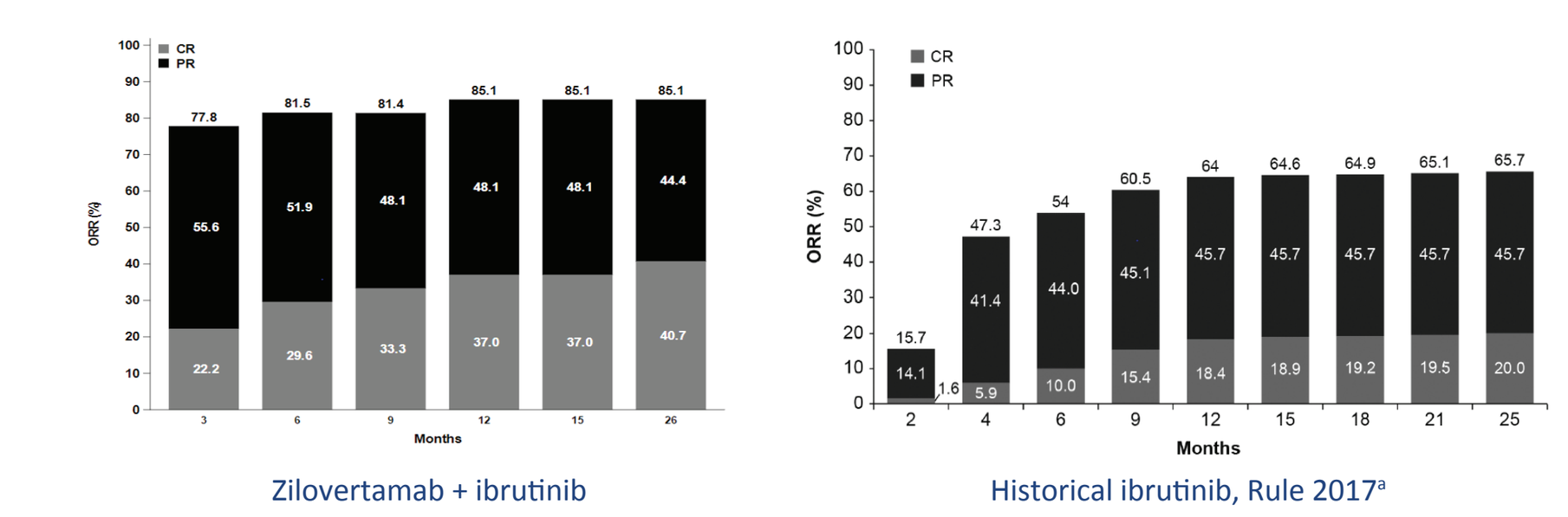
Data Cut: 8Apr2022; a – includes 1 unconfirmed CR; b - Includes 1 PR-L c – min/max used when confidence interval is not estimable; NA = Not applicable; NE = Not estimable; NR = Not reached; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; DoR = duration of response.

MCL Efficacy: Clinical Response Rates

Zilovertamab + ibrutinib combination demonstrates encouraging response rates when compared to historical ibrutinib treatment over time, by prior regimen and by p53 mutation status.

Clinical Response	Zilovertamab + ibrutinib	Historical ibrutinib Rule, 2017[a]
	N = 27	N = 370
ORR, n (%)	23 (85.2)	234 (63.2)
CR, n (%)	11[b] (40.7)	74 (20.0)
PR, n (%)	12 (44.4)	160 (45.6)
SD, n (%)	2 (7.4)	50 (13.5)
PD, n (%)	2 (7.4)	86 (23.2)

Clinical Response Rates Over Time

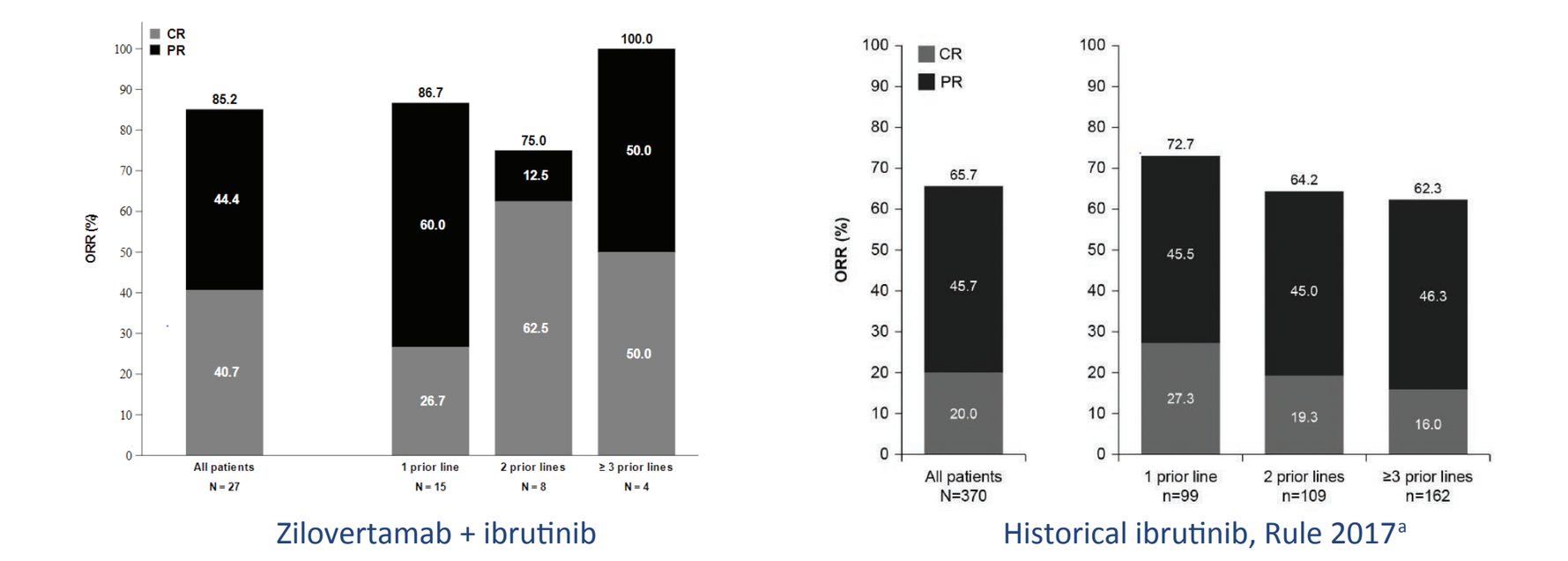


Zilovertamab + ibrutinib | Historical ibrutinib, Rule 2017[a]

Data Cut: 8Apr2022; MCL Efficacy in Parts 1 & 2; a – Patient-level data from three single-agent ibrutinib studies, N = 370 from Rule, Br J Haematol., 2017; b – includes 1 unconfirmed CR.

Clinical Response Rates by Prior Regimen in MCL

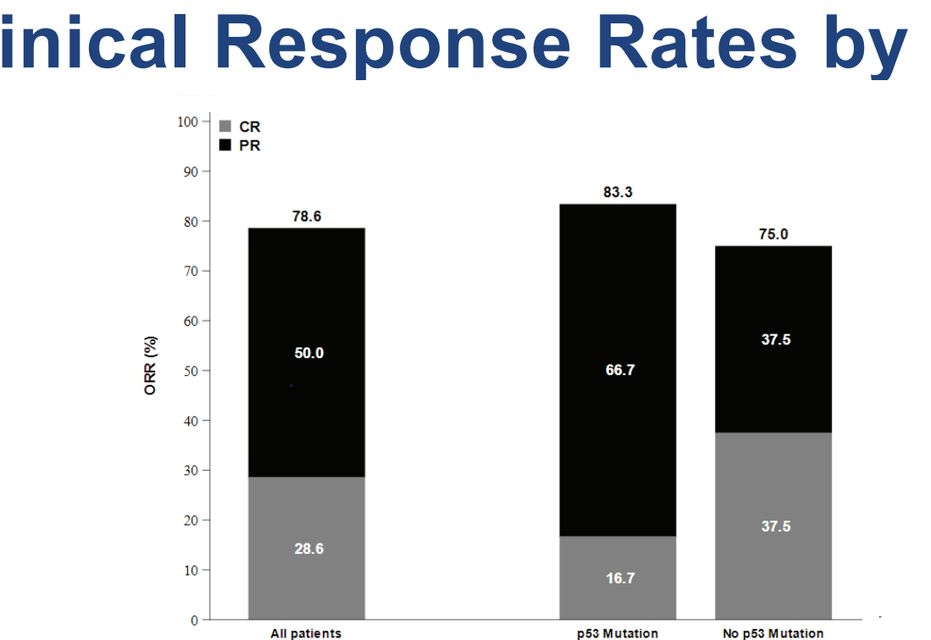
	Zilovertamab + ibrutinib				Historical ibrutinib Rule, 2017[a]			
	All patients	1 Prior	2 Prior	≥3 Prior	All patients	1 Prior	2 Prior	≥3 Prior
	N=27	N=15	N=8	N=4	N = 370	N=99	N=109	N=162
ORR, n (%)	23 (85.2)	13 (86.7)	6 (75.0)	4 (100.0)	243 (65.7)	72 (72.7)	70 (64.2)	101 (62.3)
CR, n (%)	11[b] (40.7)	4[b] (26.7)	5 (62.5)	2 (50.0)	74 (20.0)	27 (27.3)	21 (19.3)	26 (16.0)
PR, n (%)	12 (44.4)	9 (60.0)	1 (12.5)	2 (50.0)	169 (45.7)	45 (45.4)	49 (45.0)	75 (46.3)
SD, n (%)	2 (7.4)	0	2 (25.0)	0	50 (13.5)	12 (12.1)	14 (12.8)	24 (14.8)



Zilovertamab + ibrutinib | Historical ibrutinib, Rule 2017[a]

Data Cut: 8Apr2022; MCL Efficacy in Parts 1 & 2; a – Patient-level data from three single-agent ibrutinib studies, N = 370 from Rule, Br J Haematol., 2017; b – includes 1 unconfirmed CR

Clinical Response Rates by p53 Mutation in MCL

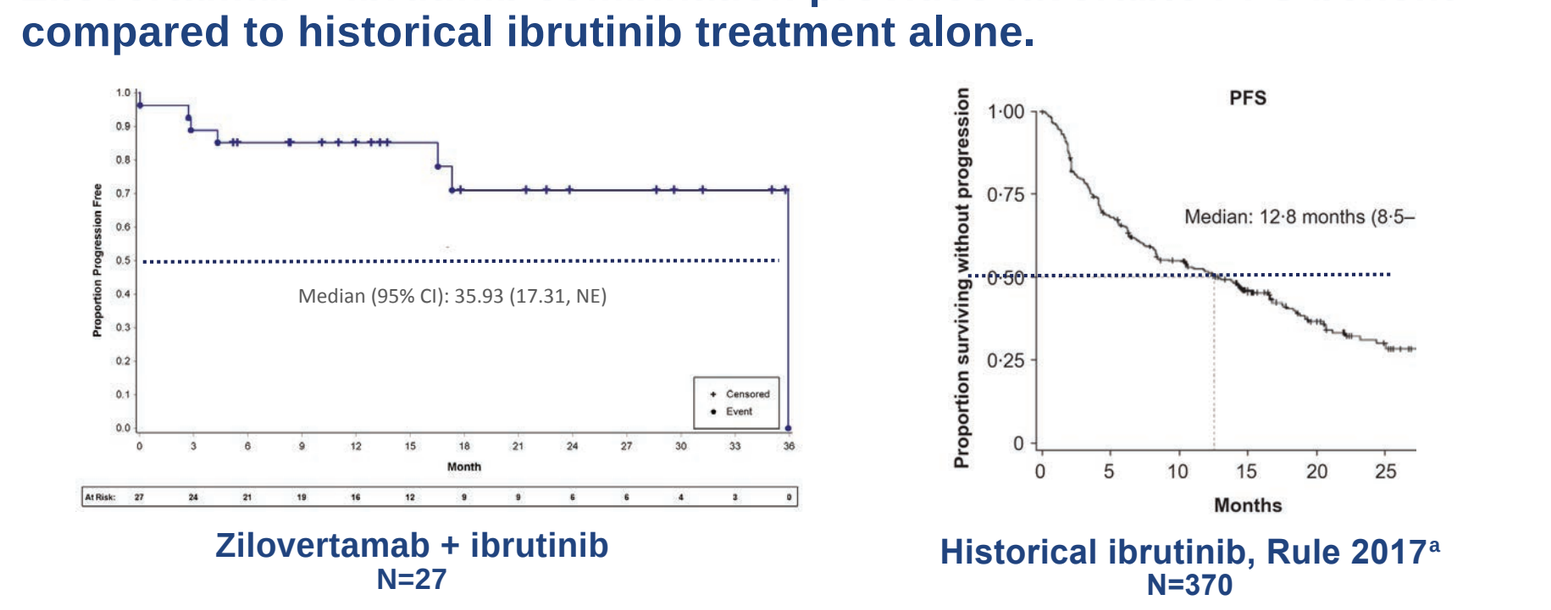


	Zilovertamab + ibrutiniba		Historical ibrutinib, Rule, 2019[a]	
	p53 mutation	No p53 mutation	p53 mutation	No p53 mutation
	N=6	N=8	N=20	N=124
ORR, n (%)	5 (83.3)	6 (75.0)	11 (55.0)	87 (70.2)
CR, n (%)	1 (16.7)	3[b] (37.5)	0	31 (25.0)
PR, n (%)	4 (66.7)	3 (37.5)	11 (55.0)	56 (45.2)

Data Cut: 8Apr2022; MCL Efficacy in Parts 1 & 2; Tumor Response reflects best response achieved by each subject; a - Rule, Hematologica, 2019; b – includes 1 unconfirmed CR.

MCL Efficacy: Progression Free Survival

Zilovertamab + ibrutinib combination provides favorable PFS benefit compared to historical ibrutinib treatment alone.

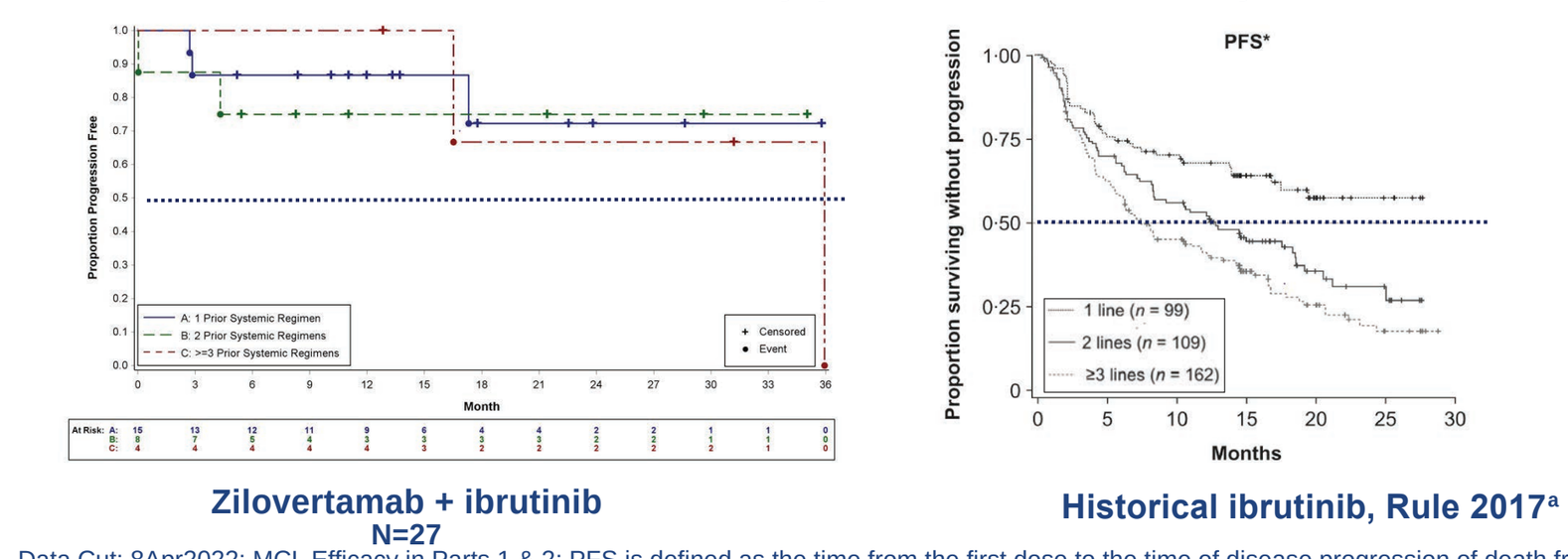


Zilovertamab + ibrutinib, N=27 | Historical ibrutinib, Rule 2017[a], N=370

Data Cut: 8Apr2022; MCL Efficacy in Parts 1 &2; PFS is defined as the time from the first dose to the time of disease progression of death from any cause, whichever comes first; NE = not evaluable; NR = not reached; a – Patient-level data from three single-agent ibrutinib studies, N = 370 from Rule, Br J Haematol., 2017.

MCL Efficacy: PFS by Prior Systemic Treatment

Favorable PFS is sustained in heavily pre-treated MCL subjects

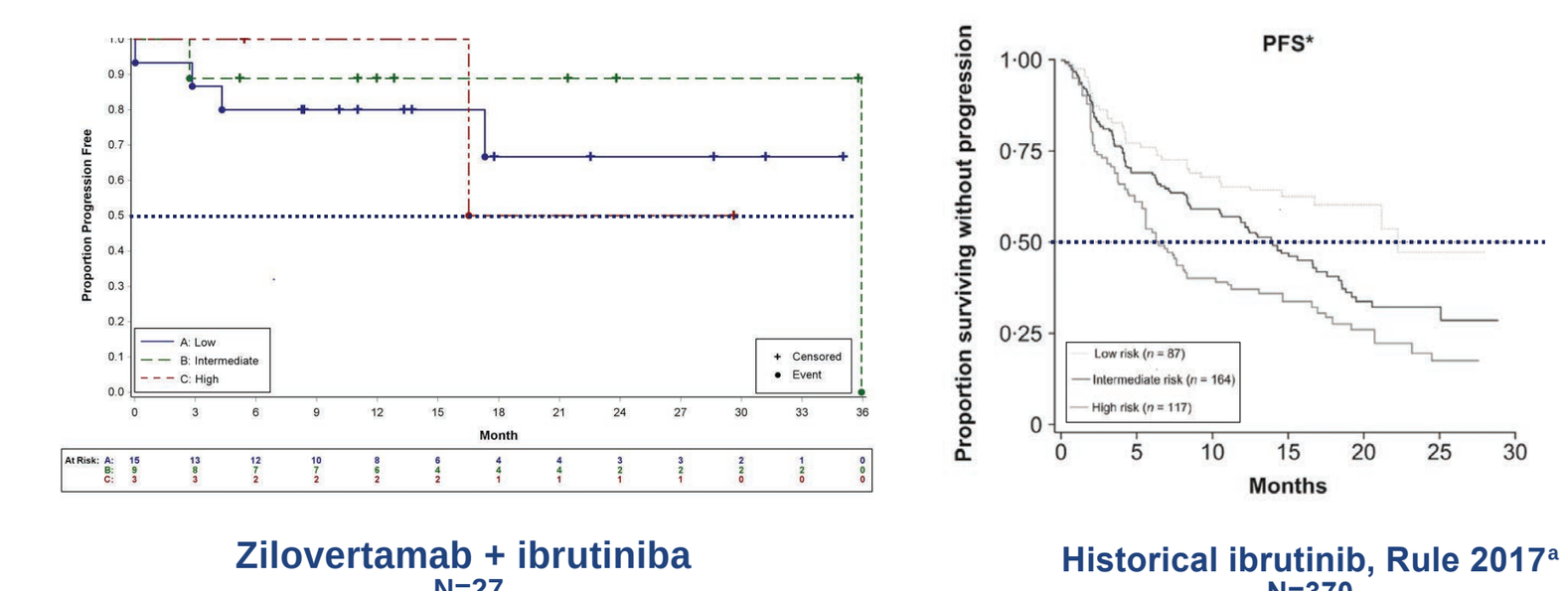


Zilovertamab + ibrutinib, N=27 | Historical ibrutinib, Rule 2017[a], N=370

Data Cut: 8Apr2022; MCL Efficacy in Parts 1 & 2; PFS is defined as the time from the first dose to the time of disease progression of death from any cause, whichever comes first; a – Patient-level data from three single-agent ibrutinib studies, N = 370 from Rule, Br J Haematol., 2017.

MCL Efficacy: PFS by MIPI Subgroups

Favorable PFS is sustained in higher risk MIPI subgroups

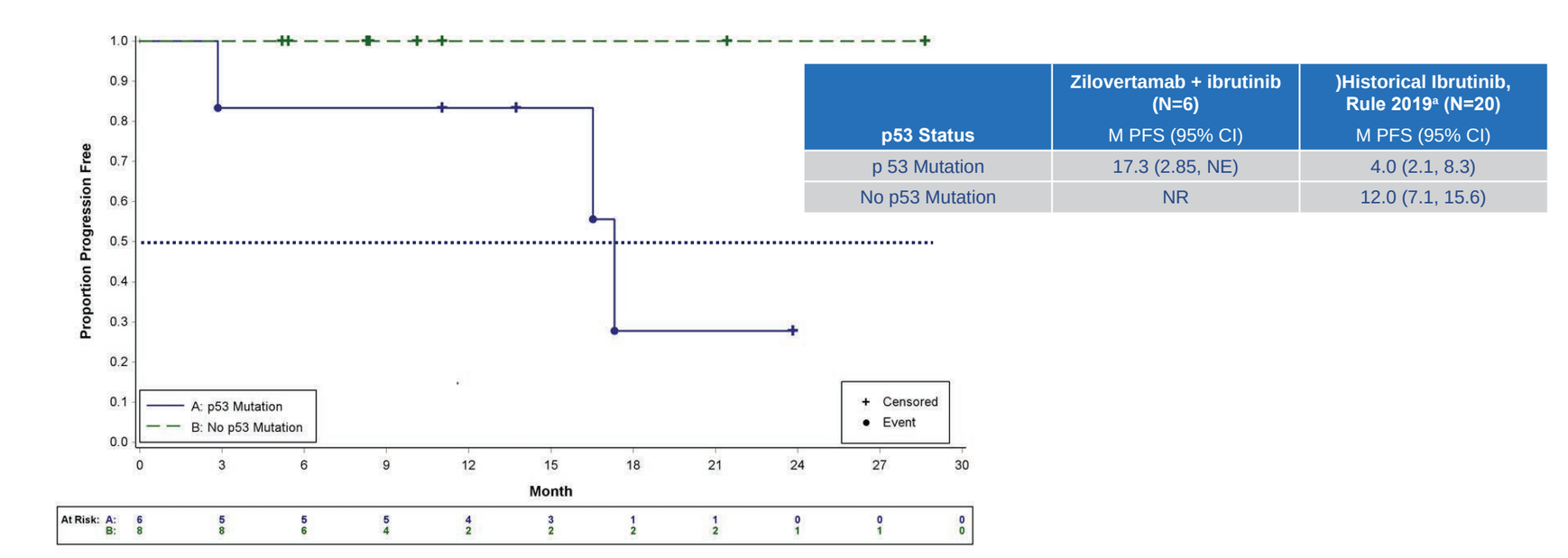


Zilovertamab + ibrutinib, N=27 | Historical ibrutinib, Rule 2017[a], N=370

Data Cut: 8Apr2022; MCL Efficacy in Parts 1 &2; PFS = Progression Free Survival is defined as the time from the first dose to the time of disease progression of death from any cause, whichever comes first; a – subgroups by sMIPI: Simplified Mantle Cell Lymphoma International Prognostic Index; Patient-level data from three single-agent ibrutinib studies, N = 370 from Rule, Br J Haematol., 2017.

MCL Efficacy: Progression-free Survival by p53 Mutation

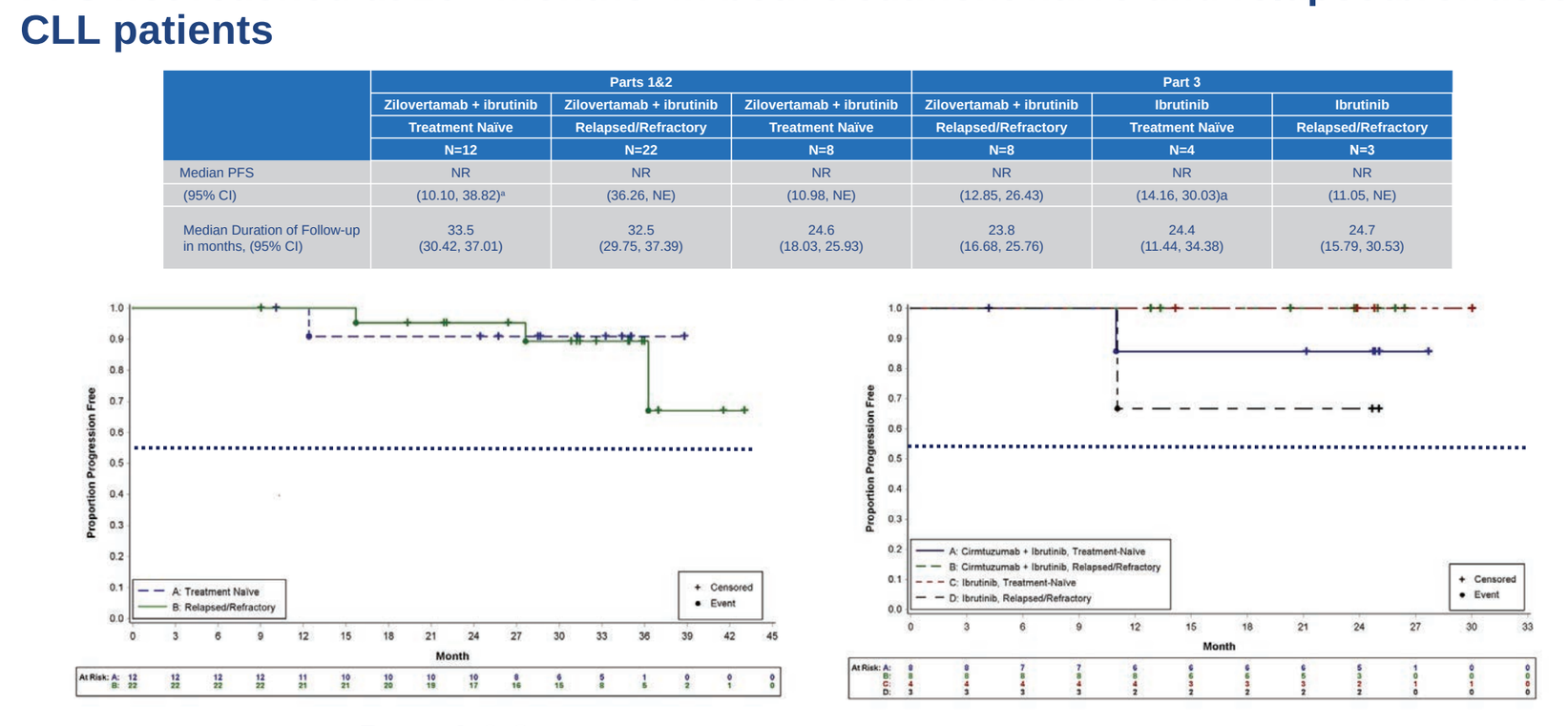
Even with p53 mutation, increase in median PFS observed when compared with historical ibrutinib



Data Cut: 8Apr2022; MCL Efficacy in Parts 1 &2; PFS is defined as the time from the first dose to the time of disease progression of death from any cause, whichever comes first; NE = not evaluable; NR = not reached; a - Rule, Hematologica, 2019.

CLL Efficacy: Progression-free Survival

PFS not reached at 33+ months in both treatment naïve and relapsed/refractory CLL patients

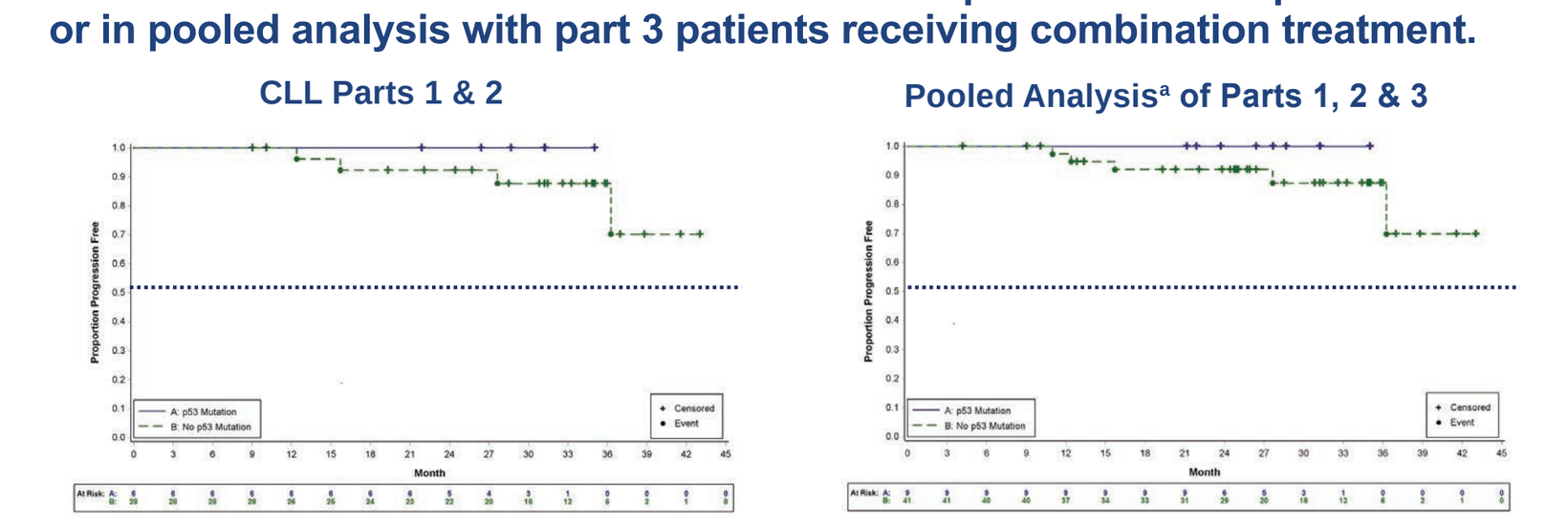


Parts 1 & 2 | Part 3

Data Cut: 8Apr2022; NA = Not applicable; NE = Not estimable; NR = Not reached; N = number of evaluable patients; a – min/max used when confidence interval is not estimable.

CLL Efficacy: PFS by p53 mutation

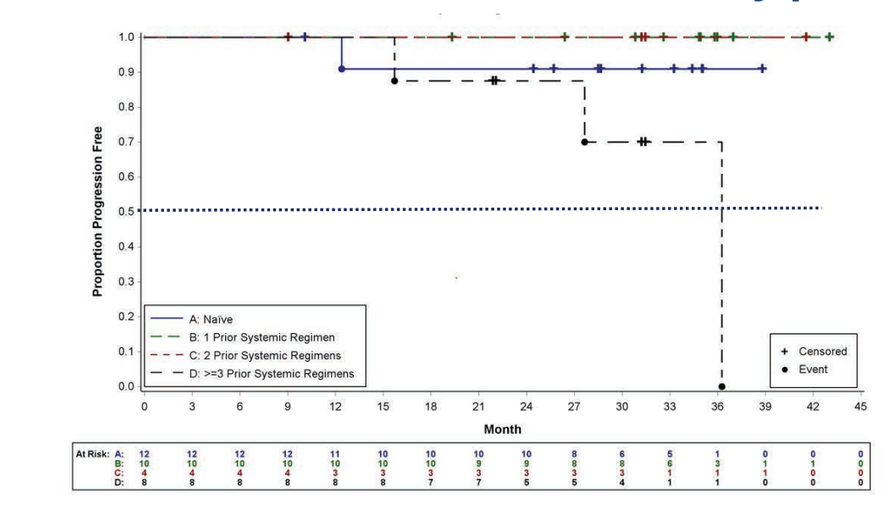
PFS not reached at 33+ months with or without p53 mutation in parts 1&2 CLL or in pooled analysis with part 3 patients receiving combination treatment.



Data Cut: 8Apr2022; PFS is defined as the time from the first dose to the time of disease progression of death from any cause, whichever comes first; a – Pooled analysis includes all part 1 and 2 CLL patients + Part 3 CLL patients randomized to treatment with zilovertamab + ibrutinib.

CLL Efficacy (Parts 1 & 2): PFS by Prior Systemic Treatment

Favorable PFS maintained in heavily pre-treated CLL subjects

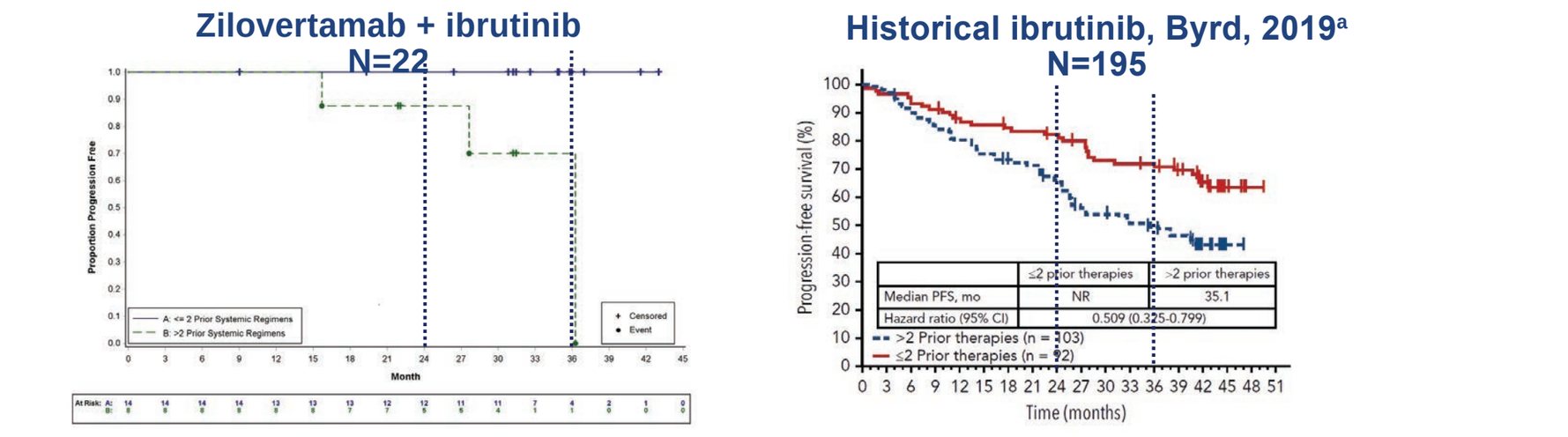


Prior Systemic Treatment	CLL Parts 1 & 2 MPFS (95% CI)
Treatment Naïve	NR (10.10, 38.82)[a]
1 Prior Regimen	NR (19.34, 43.05)[a]
2 Prior Regimens	NR (9.05, 41.57)[a]
≥3 Prior Regimens	36.26 (15.70, NE)

Data Cut: 8Apr2022; PFS is defined as the time from the first dose to the time of disease progression of death from any cause, whichever comes first; NR = not reached; NE = not estimable; a – min, max used when confidence interval is not estimable.

CLL Efficacy (R/R Parts 1 & 2): Landmark PFS by Prior Systemic Treatment

Zilovertamab + ibrutinib demonstrates encouraging Landmark PFS based on number of prior lines of therapy compared to historical ibrutinib treatment alone



Prior Systemic Therapy	Zilovertamab + ibrutinib: Landmark PFS 24 months	Zilovertamab + ibrutinib: Landmark PFS 36 months	Byrd, 2019[a]: Landmark PFS 24 months	Byrd, 2019[a]: Landmark PFS 36 months
1 or 2	~100%	~100%	~82%	~73%
> 2	~88%	~70%	~65%	~50%

Data Cut: 8Apr2022; CLL Efficacy measured in relapsed refractory (R/R) patients in Part 1 &2 (N=22); PFS is defined as the time from the first dose to the time of disease progression of death from any cause, whichever comes first; NR = not reached; a – PFS by prior therapies from sing-agent ibrutinib treatment in high-risk, relapsed patients with CLL (N=195), Byrd, Blood 2019.

MCL & CLL Efficacy: Overall Survival

Median OS not reached for MCL and CLL patients on combination treatment or on ibrutinib alone.

	MCL Parts 1&2	MCL Rule, 2017[a]	CLL Parts 1&2		CLL Part 3			
	Zilovertamab + ibrutinib	Ibrutinib	Zilovertamab + ibrutinib	Zilovertamab + ibrutinib	Zilovertamab + ibrutinib	Zilovertamab + ibrutinib	Ibrutinib	Ibrutinib
	Relapsed/Refractory	Relapsed/Refractory	Treatment Naïve	Relapsed/Refractory	Treatment Naïve	Relapsed/Refractory	Treatment Naïve	Relapsed/Refractory
	N=27	N=370	N=12	N=22	N=8	N=8	N=4	N=3
Median OS (95% CI)	NR (18.85, NE)	25.0	NR (25.74, 42.03)[c]	NR (36.26, NE)	NR (12.92, 27.70)[c]	NR (12.85, 26.43)[c]	NR (14.16, 30.03)[c]	NR (19.74, 25.05)
Median Duration of Follow-up in months, (95% CI)	15.1 (14.31, 22.13)	16.8[b]	33.5 (30.42, 37.01)	32.5 (29.75, 37.39)	24.6 (18.03, 25.93)	23.8 (16.68, 25.76)	24.4 (11.44, 34.38)	24.7 (15.79, 30.53)

Data Cut: 8Apr2022; OS is defined as the time from the first dose to the time of death from any cause, whichever comes first; NE = not estimable; NR = not reached; a - Patient-level data from three single-agent ibrutinib studies, N = 370 from Rule, Br J Haematol., 2017; b – adapted median follow-up of 3 pooled trials (average = 16.8) from Rule, Br J Haematol., 2017, c – min, max used when confidence interval is not estimable.

Conclusion

- Zilovertamab (formerly cirmtuzumab) is a humanized monoclonal antibody designed to inhibit the tumor promoting activity of ROR1
- Combination treatment with zilovertamab + ibrutinib is generally well tolerated, with a safety profile similar to that of ibrutinib alone
  - In patients with MCL, Grade 3 or 4 neutrophil decrease was seen in 9.1% of patients taking zilovertamab + ibrutinib, compared to 29% for ibrutinib alone from its registration study
- There was robust efficacy of zilovertamab + ibrutinib compared to the reported outcomes of ibrutinib alone in patients with MCL or CLL
  - MCL: Indirect comparison to ibrutinib (Rule 2017; 2019), CLL: Indirect comparison to ibrutinib (Byrd, 2019)
- We observed prolonged PFS for treated patients with MCL or CLL who had TP53 mutations and/or were in high-risk subgroups
- We observed high objective response rates and durable responses in heavily pre-treated patients with MCL who were treated with zilovertamab + ibrutinib
- Phase 2 study in R/R MZL will soon be open to enrollment

References

Acknowledgements
Ibrutinib provided by Pharmacyclics LLC, an AbbVie Company

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