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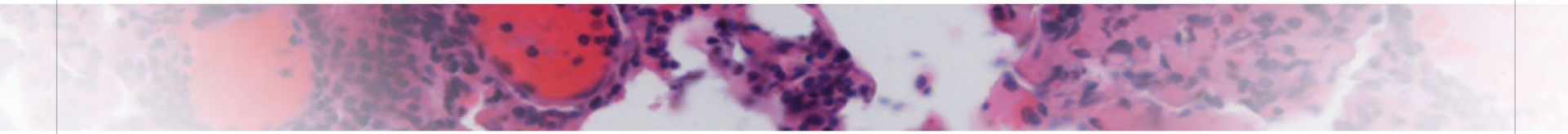

PHASE 1/2 STUDY OF ZILOVERTAMAB AND IBRUTINIB IN MANTLE CELL LYMPHOMA (MCL), CHRONIC LYMPHOCYTIC LEUKEMIA (CLL), OR MARGINAL ZONE LYMPHOMA (MZL)

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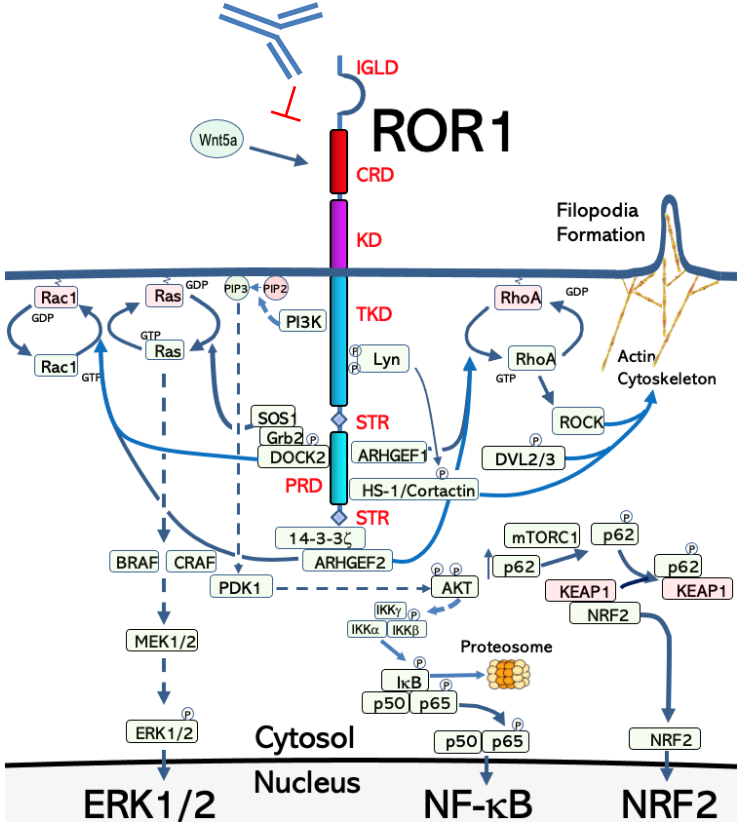
Data cut for all data presented is 11Oct2022

Background

- ROR1 is an onco-embryonic kinase-like receptor that is expressed at high levels in many solid and hematologic malignancies, including MCL, CLL, and MZL, but not on normal adult tissues.
- Wnt5a can activate ROR1-signaling, which enhances expression of genes induced by activation of ERK1/2, NF-kB, and NRF2 that can promote cancer-cell growth, migration, self-renewal, and resistance to therapy
- Zilovertamab (formerly cirmtuzumab) is a fully humanized anti-ROR1 mAb designed to inhibit ROR1-signaling
- Zilovertamab inhibits CLL-cell expression of genes induced by activated ERK1/2, NF-kB, STAT3, and NRF2 that may promote the survival and growth of CLL cells with mutated TP53 of patients treated with inhibitors of Bruton Tyrosine Kinase (BTK) (e.g. ibrutinib)



Source: Kipps, Blood 2022

Phase 1 – 2 Study Design and Patient Disposition

Treatment naïve (TN) or Relapsed/Refractory (R/R) CLL, R/R MCL, or R/R MZL

PART 1 (MCL & CLL)	PART 2 (MCL, MZL & CLL)	PART 3 (CLL)
DOSE-FINDING COHORT • 2, 4, 8, 16 mg/kg and 300, 600 mg doses zilovertamab evaluated • Ibrutinib (420 mg CLL, 560 mg MCL po daily) added after 1 month safety run-in • RP2D: Zilovertamab 600 mg IV Q2W x3 then Q4W in combination with ibrutinib approved doses	**DOSE-EXPANSION COHORT** • Primary Endpoints: safety, preliminary efficacy, pharmacology at RP2D • Confirm RP2D of Zilovertamab (600 mg) + ibrutinib (420 mg CLL, 560 mg MCL; po daily)	**RANDOMIZED EFFICACY** • Zilovertamab + ibrutinib vs ibrutinib • 2:1 randomization • Evaluate objective responses, PFS, biomarkers
Dose escalation completed	***CLL/MCL enrolled, MZL enrolling***	***Enrollment completed***

	Parts 1 & 2		Part 3	
	MCL: zilo + ibrutinib	CLL: zilo + ibrutinib	CLL: zilo + ibrutinib	CLL: ibrutinib
Patients Enrolled, n	33	34	21	10
Safety Population[a], n	33	34	18	10
Efficacy Population[b], n (%)	28 (84.8)	34 (100)	16 (88.9)	7 (70.0)
Patient Disposition				
Ongoing, n (%)	13 (39.4)	0	2 (11.1)	1 (10.0)
Discontinued from Treatment, n (%)	20 (60.6)	34 (100)	16 (88.9)	9 (90.0)

a – Safety population is comprised of all enrolled subjects who received at least one dose of zilovertamab (or ibrutinib if Part 3 ibrutinib alone arm); b –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

Demographics and Disease Characteristics

Population: High-risk disease and heavily pre-treated

Characteristics	Parts 1 & 2		Part 3	
	zilo + ibrutinib	zilo + ibrutinib	zilo + ibrutinib	ibrutinib
	MCL	CLL	CLL	
	N=33	N=34[a]	N= 18[a]	N= 10[a]
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)
Median Ki-67 ≥ 30%, n (%)	17 (51.5)	NA[b]	NA[b]	NA[b]
Lymphocytosis at Screening (ALC > 4 x 10/L)	3 (9.1)	22 (64.7)	12 (66.7)	6 (60.0)
sMIPI Intermediate/High, n (%)	15 (45.5)	NA	NA	NA
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 (1,5)	2.0 (1, 10)	2.0 (1, 4)	2.0 (1, 6)
Prior BTK inhibitor (ibrutinib), n (%)	5 (15.2)	0	0	1 (10.0)
Prior Transplant/Cell Therapy, n (%)	8 (24.2)	1 (2.9)	0	0
TP53 Mutation/del(17p), n (%)	8 (47.0)[c]	6 (17.6)[c]	4 (23.5)[c]	1 (10.0)[c]

a, CLL parts 1,2 (n= 12 TN, n= 22 R/R); CLL part 3: zilo+ibr (n= 9 TN, n= 9 R/R); CLL part 3: ibr (n= 6 TN, n= 4 R/R); b, not applicable
c, based on number assessed for TP53/del(17p): MCL = 17; CLL, parts 1,2 = 34; CLL (zilo+ibr) part 3 = 17; CLL (ibr) part 3 = 10

Overall Safety: Treatment Emergent Adverse Events ≥20%

Zilovertamab + ibrutinib has been well tolerated with an overall safety profile that is consistent with ibrutinib monotherapy

MCL/CLL Parts 1,2 & 3: Zilovertamab + Ibrutinib			
N=85	**Overall, n (%)**	**Grades 1-2, n (%)**	**Grades ≥3, n (%)**
Diarrhea	39 (45.9)	36 (42.4)	3 (3.5)
Fatigue	39 (45.9)	34 (40.0)	5 (5.9)
Contusion	33 (38.8)	33 (38.8)	0 (0)
Cough	26 (30.6)	26 (30.6)	0 (0)
Arthralgia	24 (28.2)	22 (25.9)	2 (2.4)
Hypertension	23 (27.1)	14 (16.5)	9 (10.6)
Upper Respiratory Tract Infection	22 (25.9)	22 (25.9)	0 (0)
Dizziness	21 (24.7)	21 (24.7)	0 (0)
Thrombocytopenia	21 (24.7)	19 (22.4)	2 (2.4)
Nausea	20 (23.5)	20 (23.5)	0 (0)
Haematuria	19 (22.4)	19 (22.4)	0 (0)
Rash	19 (22.4)	19 (22.4)	0 (0)
Anaemia	18 (21.2)	14 (16.5)	4 (4.7)
Dyspnoea	18 (21.2)	17 (20.0)	1 (1.2)
Gastrooesophageal Reflux Disease	17 (20.0)	17 (20.0)	0 (0)
Onychoclasis	17 (20.0)	17 (20.0)	0 (0)

Note: Atrial fibrillation occurred in 9.4% of pts; febrile neutropenia occurred in 1.2% of pts

Treatment Emergent Hematologic Laboratory Abnormalities

Most hematologic lab abnormalities observed with zilovertamab + ibrutinib were Grade 1 – 2 with few being Grade 3 or higher

All zilovertamab + ibrutinib (N=85)	All Grades	Grade 1 or 2	Grade 3 or 4
Neutrophils decrease	31 (36.5%)	21 (24.7%)	10 (11.8%)
Platelets decrease	61 (71.8%)	57 (67.1%)	4 (4.7%)
Hemoglobin decrease	65 (76.5%)	62 (72.9%)	3 (3.5%)

MCL Parts 1&2: zilovertamab + ibrutinib			
N = 33	All grades	Grade 1 or 2	Grade 3 or 4
Neutrophils decrease	9 (27.3%)	6 (18.2%)	3 (9.1%)
Platelets decrease	23 (69.7%)	20 (60.6%)	3 (9.1%)
Hemoglobin decrease	24 (72.7%)	21 (63.6%)	3 (9.1%)

CLL Parts 1&2: zilovertamab + ibrutinib			
N = 34	All grades	Grade 1 or 2	Grade 3 or 4
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 (0.0%)

CLL Part 3: zilovertamab + ibrutinib			
N = 18	All grades	Grade 1 or 2	Grade 3 or 4
Neutrophils decrease	6 (33.3%)	5 (27.8%)	1 (5.6%)
Platelets decrease	13 (72.2%)	13 (72.2%)	0 (0.0%)
Hemoglobin decrease	16 (88.9%)	16 (88.9%)	0 (0.0%)

CLL Part 3: ibrutinib			
N = 10	All grades	Grade 1 or 2	Grade 3 or 4
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%)

NCI CTCAE v5.0 for hematologic toxicity used to grade laboratory values. Subjects counted only once at max grade observed after first dose of study treatment

Efficacy: Clinical Response

High response rates and durable responses observed in both MCL and CLL

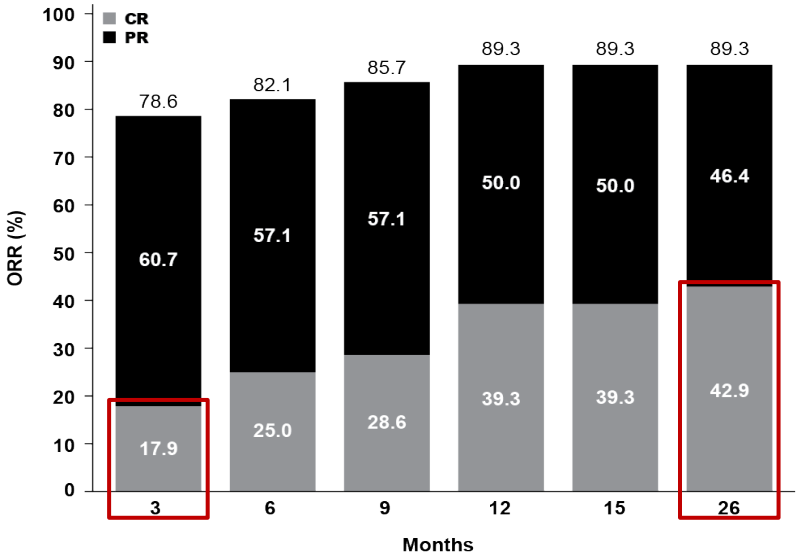
Endpoints	MCL (Parts 1 & 2) Zilo + Ibr (N=28)	CLL (Parts 1 & 2) Zilo + Ibr (N=34)	CLL (Part 3) Zilo+ Ibr (n=16)	CLL (Part 3) Ibr (n=7)
Overall Response Rate (ORR), n (%)	25 (89.3%)	31 (91.2%)	15 (93.8%)	7 (100.0%)
CR, n (%)	12 (42.9%)	3 (8.8%)	0	1 (14.3%)
PR, n (%)	13 (46.4%)	27 (79.4%)	15 (93.8%)	6 (85.7%)
SD, n (%)	1 (3.6%)	3 (8.8%)	1 (6.3%)	0
Median Duration of response, months (95% CI)	34.1 (13.84, NE)	33.5 (33.5, NE)	NR (22.23, NE)	NR (8.3, NE)
Median Duration of follow-up[a], months (95% CI)	19.5 (19.4, 28.5)	40.0 (38.6, 43.5)	29.2 (27.4, 30.3)	30.0 (19.1, 33.1)

a, Efficacy evaluable population

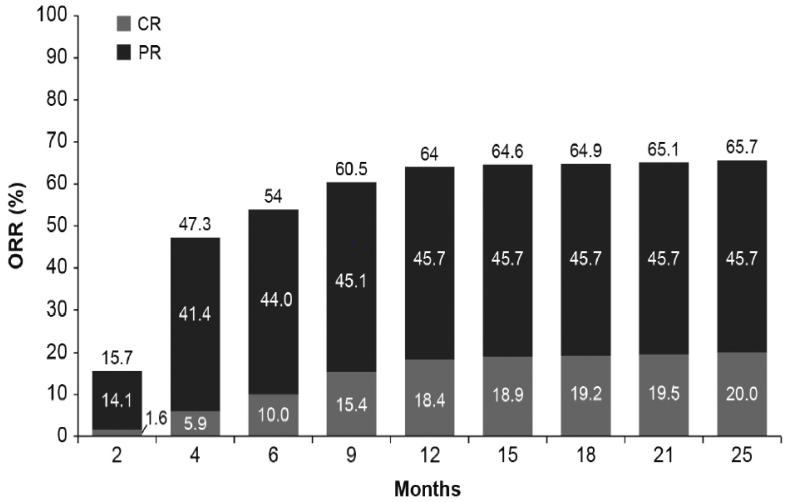
MCL Efficacy: Clinical Response Rates Over Time

Zilovertamab + ibrutinib combination demonstrates rapid achievement of response

Zilovertamab + ibrutinib



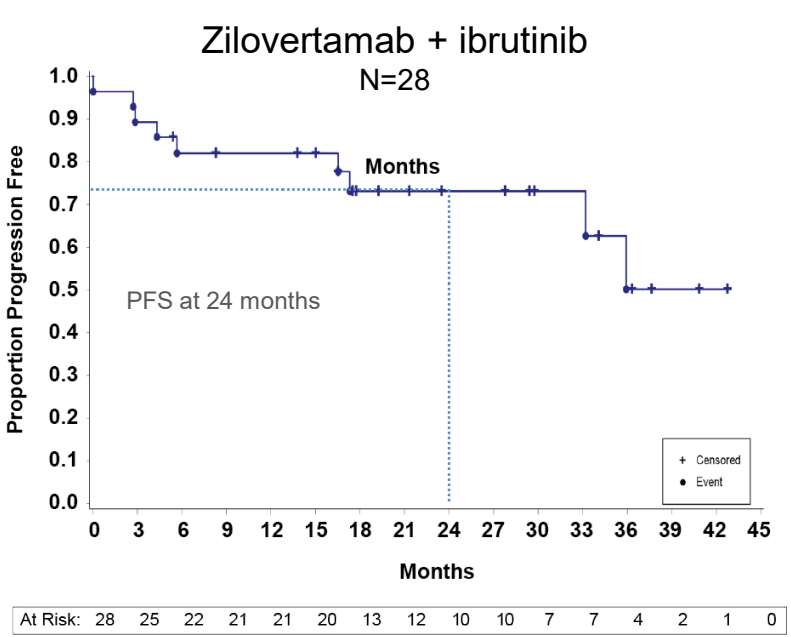
Historical ibrutinib, Rule 2017[a]

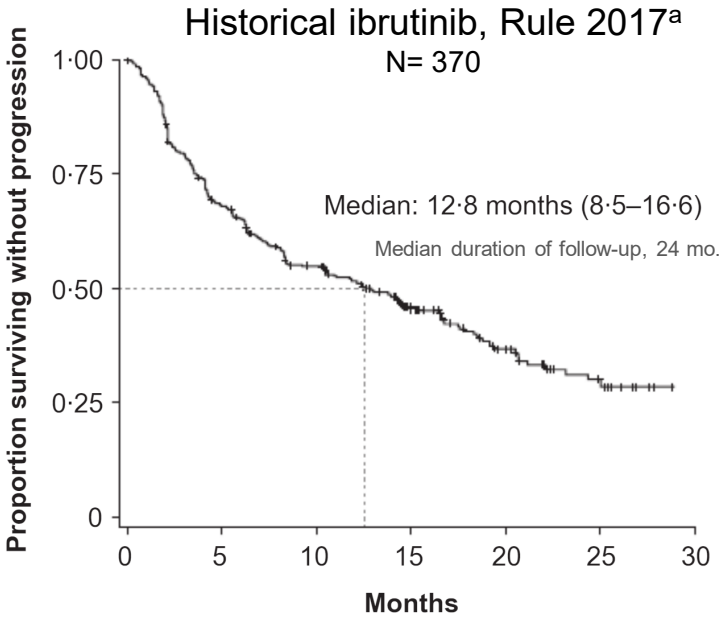


[a] Rule, British Journal of Haematology, 2017

MCL Efficacy: Progression Free Survival

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





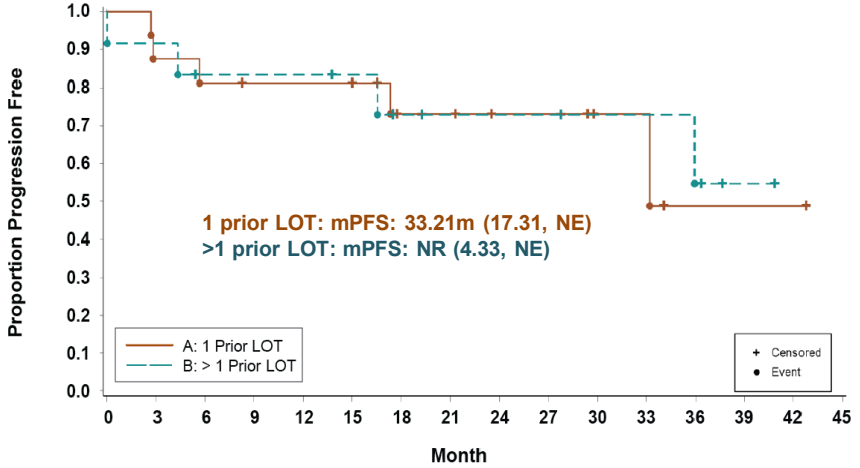
[a] Rule, British Journal of Haematology, 2017

MCL Efficacy: PFS by Prior Line of Therapy (LOT)

Durable PFS maintained in 2L and more heavily pretreated subjects

Zilovertamab + ibrutinib

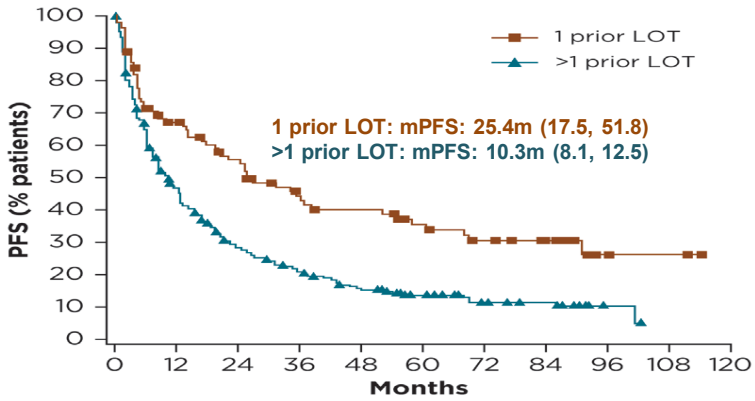
N=28



At Risk:																
	A:	16	14	13	12	12	12	7	7	5	3	3	1	1	1	0
	B:	12	11	9	9	9	8	6	5	5	4	4	3	1	0	0

Historic Ibrutinib: Dreyling 2022[a]

N=370



Patients at risk

1 prior LOT	99	61	47	31	28	22	17	11	2	2	0
>1 prior LOT	271	117	67	47	33	23	14	11	2	0	0

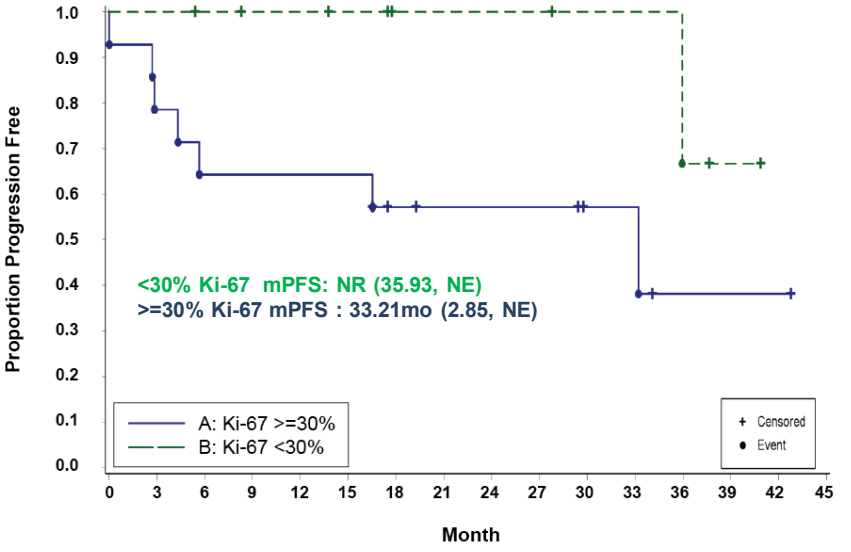
[a] Dreyling, HemaSphere, 2022

MCL Efficacy: PFS by Ki-67% and TP53 mutation/del(17p)

Demonstrates encouraging mPFS in subgroups with poor prognosis

Ki-67%: Zilovertamab + ibrutinib

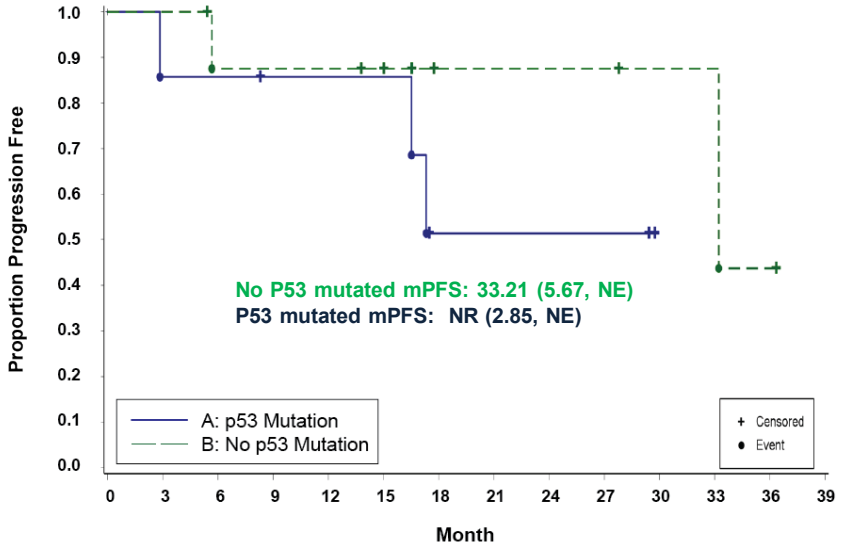
N=23



At Risk:																
	A:	14	11	9	9	9	9	6	5	5	5	3	3	1	1	1	0
	B:	9	9	8	7	7	6	4	4	4	4	3	3	2	1	0	0

TP53: Zilovertamab + ibrutinib

N=16



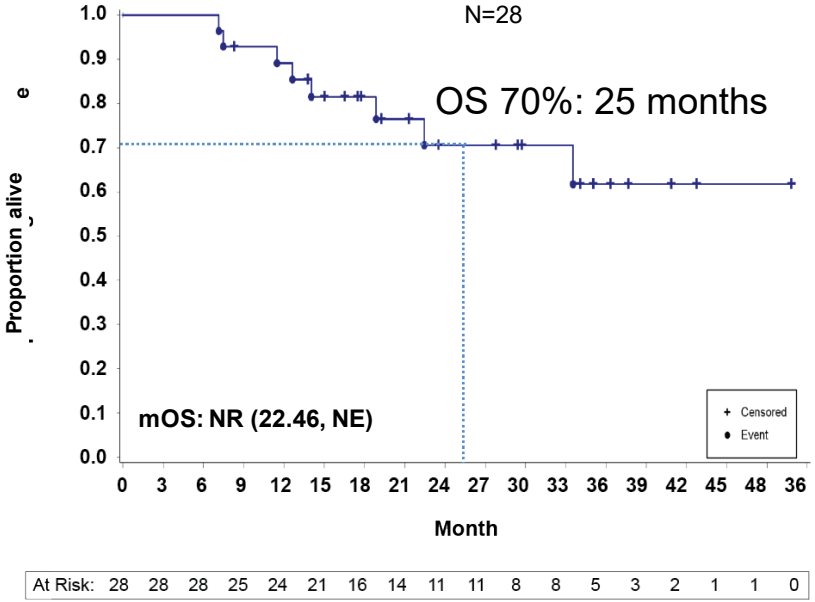
At Risk:																
	A:	7	6	6	5	5	5	2	2	2	2	0	0	0	0	
	B:	9	9	7	7	7	6	3	3	3	3	2	2	1	0	

MCL Efficacy: Overall Survival

Median OS not reached after median follow up of 19.5 mo

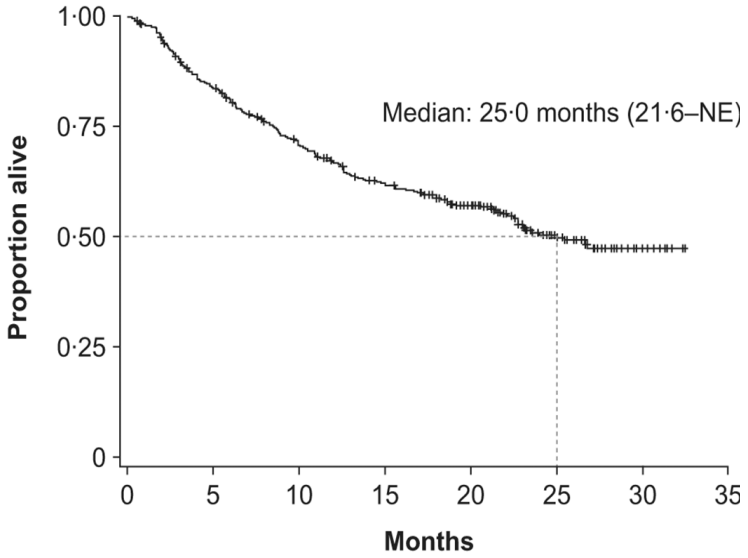
Zilovertamab + ibrutinib

N=28



Historical ibrutinib, Rule 2017[a]

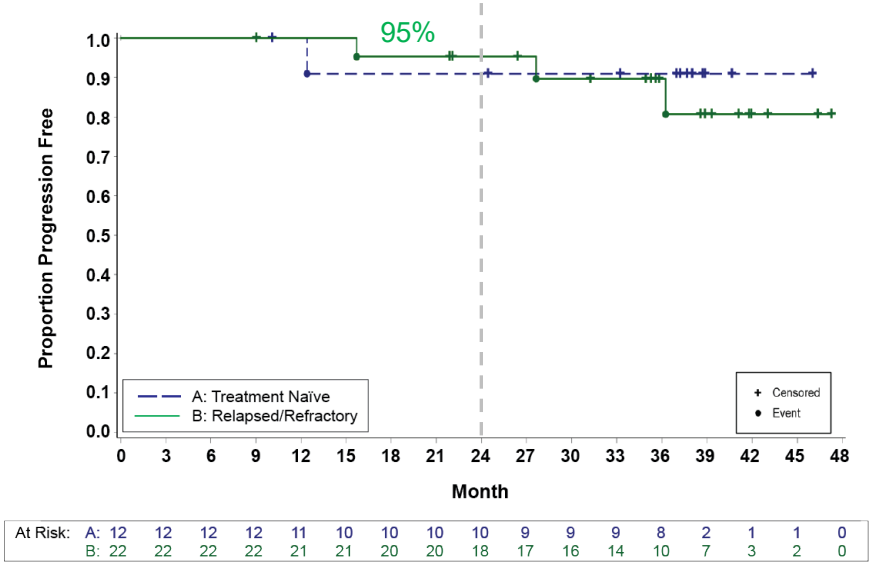
N= 370



[a]Rule, British Journal of Haematology, 2017

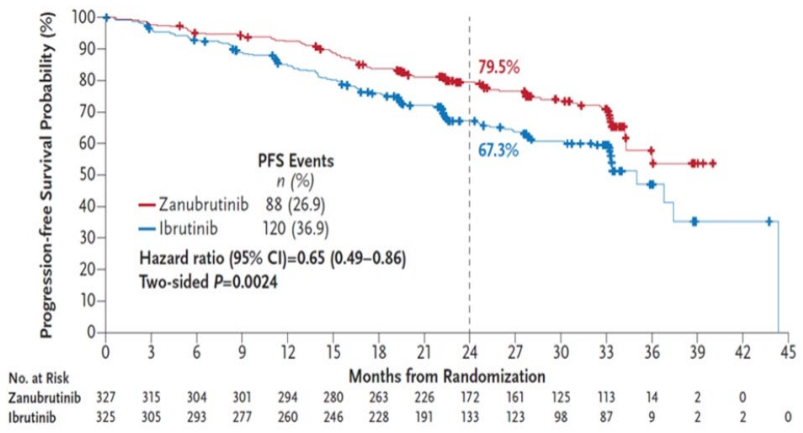
CLL Efficacy: Progression-Free Survival

Median PFS not reached after median follow up of 40 mo



PFS for R/R CLL pts at **24 months** was ~95%
for zilovertamab + ibrutinib

ALPINE: PFS by IRC (ITT population)

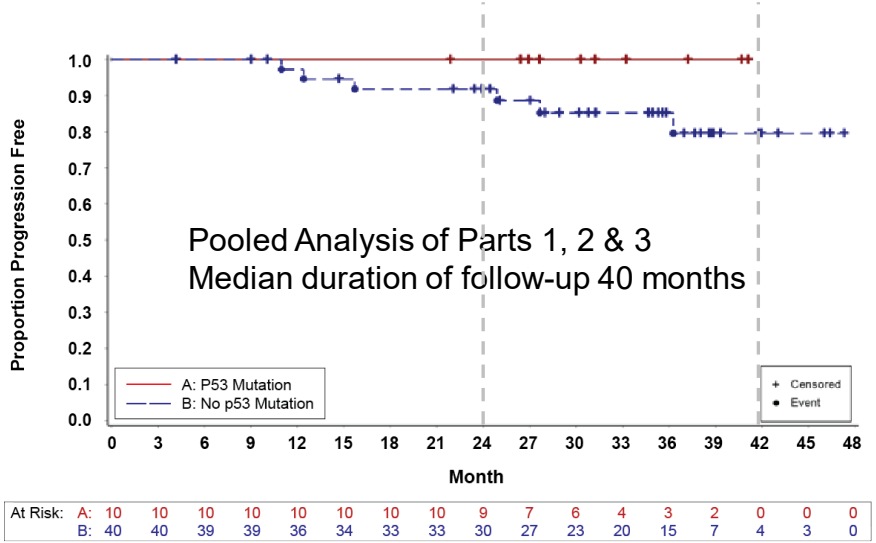


Brown et al 2022 ASH

PFS for R/R CLL pts at **24 months** was ~79.5% for **Zanubrutinib**
PFS for R/R CLL pts at **24 months** was ~ 67.3% for **Ibrutinib**

CLL Efficacy: PFS by TP53 mutation/del(17p)

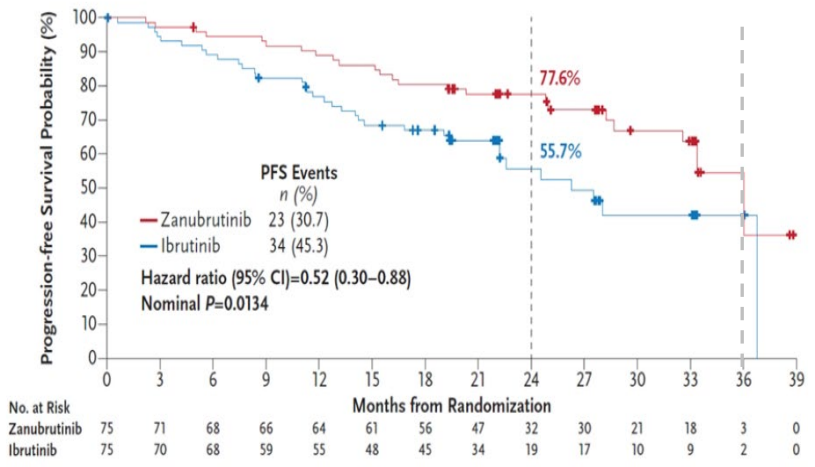
Very encouraging landmark PFS at ~42 mo



PFS for TP53 mut/del(17p) at **~42 months** was 100%

for zilovertamab + ibrutinib (N=5 R/R, N=5 TN)

ALPINE: PFS by IRC in pts with del(17p)/TP53 mutation



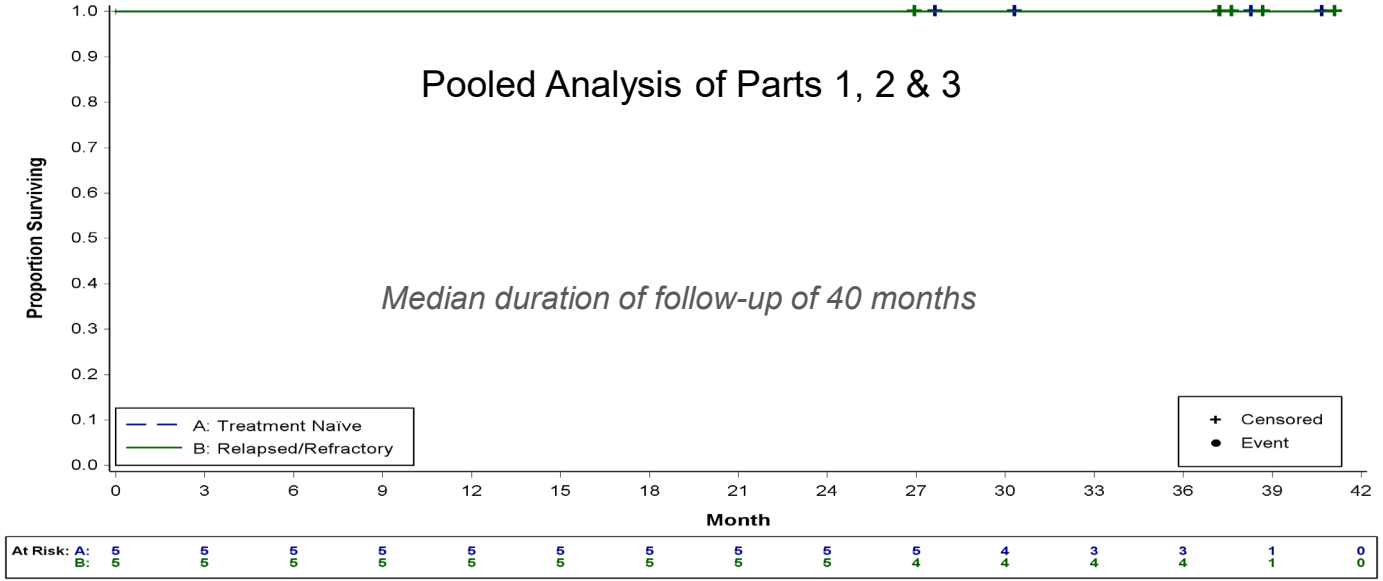
Brown et al 2022 ASH

PFS for TP53 mut/del(17p) at **36 months** was ~55% for **Zanubrutinib**

PFS for TP53 mut/del(17p) at **36 months** was ~42% for **Ibrutinib**

CLL Efficacy: OS by TP53 mutation/del(17p)

Median OS not reached after median follow up of 40 months



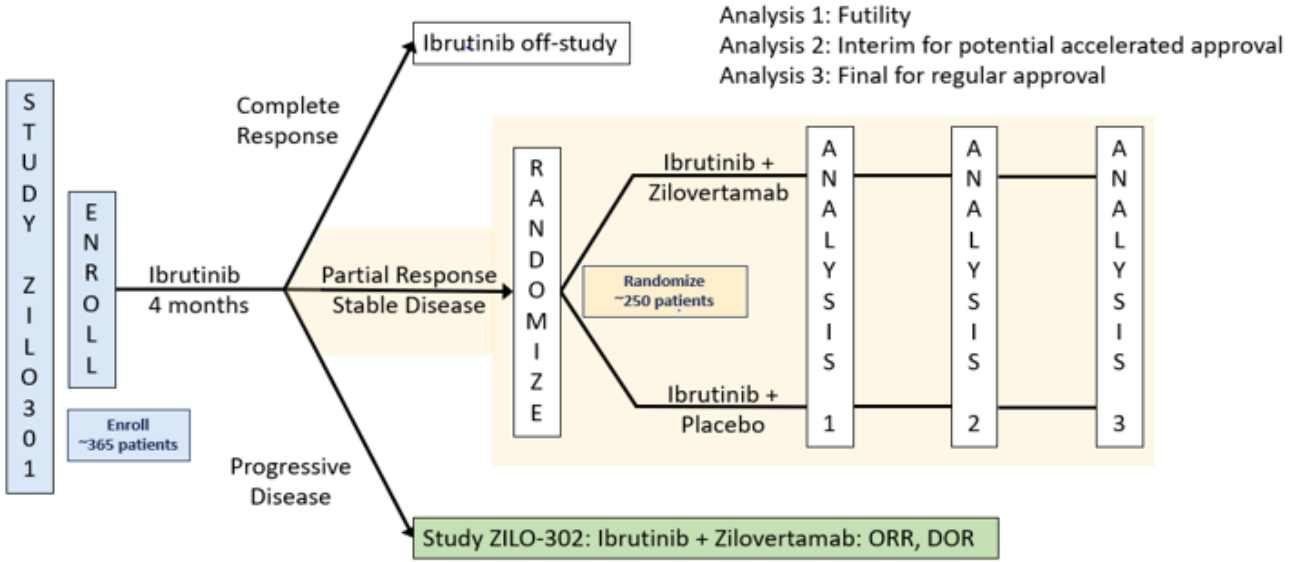
Landmark OS 100% at ~40 months for both R/R and TN CLL

Conclusions

- Zilovertamab is a humanized mAb designed to inhibit the tumor promoting activity of ROR1
- In patients with MCL and CLL, the combination of zilovertamab + ibrutinib was well tolerated, with a safety profile comparable to ibrutinib alone. Some side effects appeared less frequently than expected.
- The ORR was 89.3%, CRR 43% and median DOR 34.1 months for patients with R/R MCL on zilovertamab + ibrutinib
  - Robust efficacy across multiple high-risk subpopulations
- PFS for Zilovertamab + Ibrutinib was ~95% at 24 months in patients with R/R CLL (median 2 prior LOT) and the PFS was 100% at ~42 months for patients with TP53 mutations/del(17p) on zilovertamab + ibrutinib
- The current study remains open to enrollment for patients with R/R MZL
- Based on these encouraging data, a global DBPC Phase 3 trial of ibrutinib ± zilovertamab for patients with R/R MCL has been initiated

ZILO-301 Phase 3 Study Design

Randomized, double-blind, placebo-controlled, global, multi-center phase 3 study of zilovertamab (An ROR1 Antibody) plus ibrutinib versus ibrutinib plus placebo in patients with relapsed or refractory mantle cell lymphoma.



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- Oncternal Study Team

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