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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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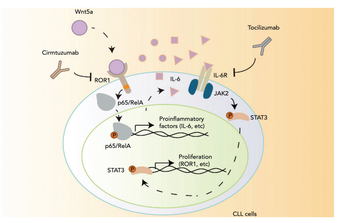
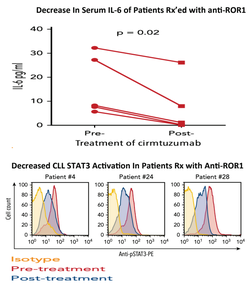
TP53/Del17p Pre-Clinical Hypothesis

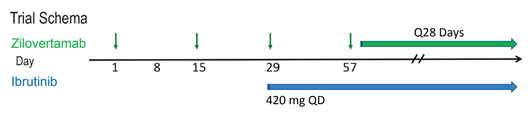
Wnt5a-induces Expression of Proinflammatory Cytokines Via ROR1-dependent NF-κB Activation, Which Induces Autocrine Activation of STAT3



Source: Chen, Blood 2019



Part 1 CLL – Zilovertamab + Ibrutinib

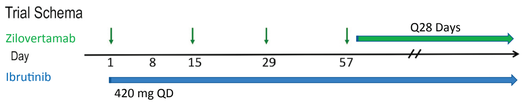


Gene Sets	Size	D0 vs D28 (n=15) ES	NES	NOM p-val	FDR q-val	Size	D0 vs D56 (n=14)* ES	NES	NOM p-val	FDR q-val
NFKB Targets (Castro-Mondragon Nucleic Acid Research 2022)	3159	0.04	2.15	0.000	0.006	3157	0.05	3.09	0.000	0.000
NRF1 Inducible Genes (Malhotra Nucleic Acids Researcy 2010)	536	0.11	2.83	0.000	0.000	531	0.06	1.42	0.105	0.148
STAT3 Target Genes (Dauer Oncogene 2005)	90	0.08	0.93	0.528	0.616	90	0.20	2.16	0.002	0.005

*For 1 pt, D56 sample was not received.

FISH data on 14 out of 15 cases: only 1 case with del17p.
IGHV data on 13 out of 15 cases: 10 UM IGHV, 3 MU IGHV.

Part 2 CLL – Zilovertamab + Ibrutinib



Inhibition of NRF2 and STAT3 pathways with zilovertamab treatment

Treatment with Zilovertamab + Ibrutinib D0 vs D28 del17p

Gene Sets	Size	ES	NES	NOM p-val	FDR q-val
NFKB Targets (Castro-Mondragon Nucleic Acid Research 2022)	2991	0.04	2.05	0.004	0.014
NRF1 Inducible Genes (Malhotra Nucleic Acids Researcy 2010)	513	0.08	2.24	0.000	0.006
STAT3 Target Genes (Dauer Oncogene 2005)	91	0.18	1.99	0.010	0.017

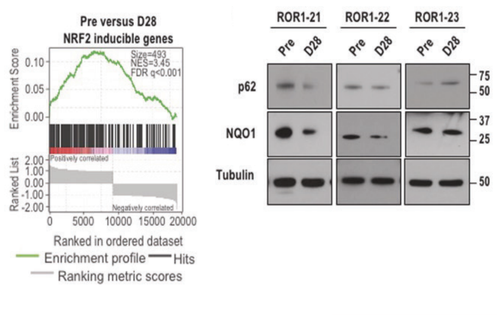
D0 vs D28 no del17p

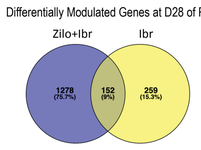
Gene Sets	Size	ES	NES	NOM p-val	FDR q-val
NFKB Targets (Castro-Mondragon Nucleic Acid Research 2022)	3104	0.03	2.04	0.006	0.011
NRF1 Inducible Genes (Malhotra Nucleic Acids Researcy 2010)	524	0.08	2.06	0.008	0.011
STAT3 Target Genes (Dauer Oncogene 2005)	89	0.24	2.71	0.000	0.001

Part 2: Zilovertamab and Ibrutinib treated CLL pts (n=14):
pts with CLL cells with del17p pre-Tx (n=5) and pts with CLL cells without del17p pre-Tx (n=9)

Treatment of Patients With Zilovertamab Inhibits Expression of NRF2-Target Genes In vivo

- Zilovertamab inhibits CLL cell expression of genes induced by activated ERK1/2, NF-κB, 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)





Treatment with Ibrutinib Alone D0 vs D28

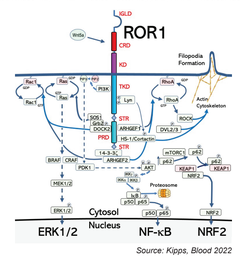
Gene Sets	Size	ES	NES	NOM p-val	FDR q-val
NFKB Targets (Castro-Mondragon Nucleic Acid Research 2022)	2888	0.03	1	0.019	0.119
NRF1 Inducible Genes (Malhotra Nucleic Acids Researcy 2010)	498	-0.05	-1.28	0.176	0.266
STAT3 Target Genes (Dauer Oncogene 2005)	89	-0.24	-2.61	0.000	0.000

Gene Sets	Size	ES	NES	NOM p-val	FDR q-val
CLL BCR Gene Signature (Herishanu Blood 2011 FIG1)	42	0.25	1	0.004	0.086
CLL BCR Gene Signature (Herishanu Blood 2011 FIG3)	54	0.28	2	0.000	0.008
CLL BCR Gene Signature (Herishanu Blood 2011 FIG4)	25	0.39	2	0.000	0.009

Phase 1/2 Study Background & Methods

- ROR1 is an onco-embryonic kinase-like receptor that is expressed at high levels by 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 ERK 1/2, NF-κB, 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.

*ERK 1/2 = extracellular signal-regulated kinase 1/2; NF-κB = nuclear factor kappa B; NRF2 = nuclear factor erythroid 2-related factor 2.



Source: Kipps, Blood 2022

Study Design and Patient Disposition

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

Phase 1	Phase 2	
Part 1 (MCL & CLL)	Part 2 (MCL, CLL & MZL)	Part 3 (CLL)
DOSE-FINDING COHORT • 2, 4, 8 & 16 mg/kg and 300 & 600 mg doses of zilovertamab[a] evaluated • Ibrutinib added after 1 month safety run-in (420 mg CLL, 560 mg MCL; qd po) • RP2D:[b] 600 mg IV Q2W x 3 then Q4W in combination with ibrutinib at approved doses	**DOSE-EXPANSION COHORT** • Primary Endpoints: safety, preliminary efficacy, pharmacology at RP2D • Confirm RP2D of zilovertamab (600 mg) + ibrutinib at approve dose (420 mg CLL, 560 mg MCL and MZL)	**RANDOMIZED EFFICACY** • Zilovertamab + ibrutinib vs ibrutinib • 2:1 randomization • Evaluate objective response, PFS, biomarkers

a – Formerly cirmtuzumab; b – RP2D: recommended phase 2 dose

	Parts 1 & 2[c]		Part 3	
	MCL zilo + ibrutinib	CLL zilo + ibrutinib	CLL zilo + ibrutinib	CLL ibrutinib
Study Population				
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[d] 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; c. At the time of the data cut (11Oct2022), there were no MZL patients available for efficacy, so MZL patients are not included in the analyses; d. most common reason for discontinue for CLL patients is completed 2 years of treatment, for MCL is disease progression.

Overall Results

Demographics and Disease Characteristics

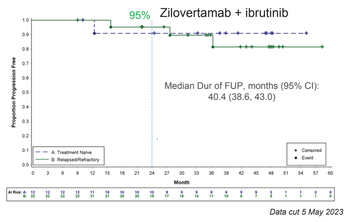
Population: High-risk disease and heavily pre-treated

Characteristics	Parts 1 & 2 zilo + ibrutinib MCL N=33	Parts 1 & 2 zilo + ibrutinib CLL N=34[a]	Part 3 zilo + ibrutinib CLL N= 18[a]	Part 3 ibrutinib CLL 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[b]	NA[b]	NA[b]
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.

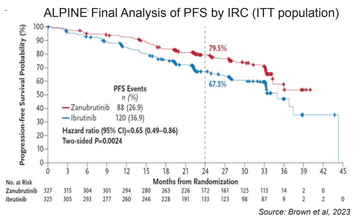
Data cut 11 Oct 2022

Overall CLL Efficacy: Progression-Free Survival



Data cut 5 May 2023

PFS for R/R CLL pts at 24 months was ~95%

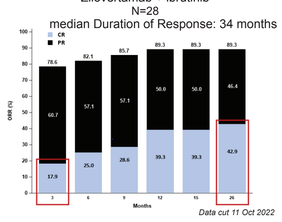


Source: Brown et al, 2023

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

Overall MCL Efficacy: Clinical Response Rates Over Time

Zilovertamab + ibrutinib combination demonstrates rapid achievement of response and response deepens over time



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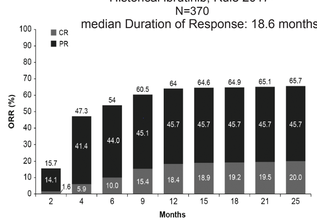
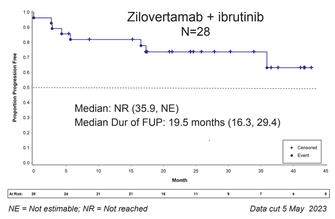


[a] Rule, British Journal of Haematology, 2017

Overall MCL Efficacy: Progression Free Survival

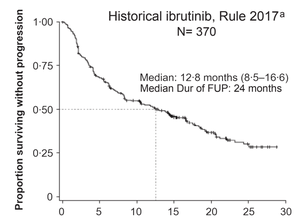
Zilovertamab + ibrutinib combination provides favorable PFS benefit compared to historical ibrutinib treatment alone



NE = Not estimable; NR = Not reached

Data cut 5 May 2023

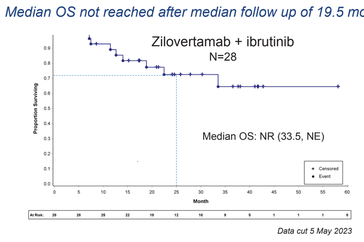
Durable PFS maintained in heavily pretreated subjects
(2 previous LOT or more, data on file)



[a] Rule, British Journal of Haematology, 2017.

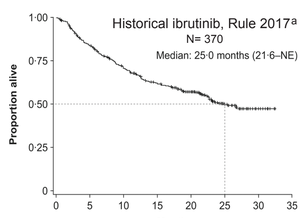
Overall MCL Efficacy: Overall Survival

Median OS not reached after median follow up of 19.5 months



Data cut 5 May 2023

Landmark OS at 25 months ~70%



[a] Rule, British Journal of Haematology, 2017.

Safety

Overall Safety: Treatment Emergent Adverse Events ≥20%

Zilovertamab + ibrutinib has been well tolerated with an overall safety profile that is similar to that of ibrutinib monotherapy

MCL/CLL Parts 1, 2 & 3: Zilovertamab + Ibrutinib N=85	Overall, n (%)	Grades 1-2, n (%)	Grades ≥3, n (%)
Fatigue	40 (47.1)	35 (41.2)	5 (5.9)
Diarrhoea	39 (45.9)	36 (42.4)	3 (3.5)
Contusion	35 (41.2)	35 (41.2)	0
Cough	26 (30.6)	26 (30.6)	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
Dizziness	21 (24.7)	21 (24.7)	0
Nausea	20 (23.5)	20 (23.5)	0
Haematuria	19 (22.4)	19 (22.4)	0
Rash	19 (22.4)	19 (22.4)	0
Thrombocytopenia	19 (22.4)	18 (21.2)	1 (1.2)
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
Peripheral Oedema	17 (20.0)	16 (18.8)	1 (1.2)
Onychoclasis	17 (20.0)	17 (20.0)	0

Note: Atrial fibrillation occurred in 9.4% of pts (n=8); febrile neutropenia occurred in 1.2% of pts (n=1).

Data cut 5 May 2023

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 CLL & MCL zilo + ibrutinib (N=85)	MCL Parts 1&2 zilo+ ibrutinib (N=33)	CLL Parts 1&2 zilo + ibrutinib (N=34)	CLL Part 3 zilo + ibrutinib (N=16)	CLL Part 3: ibrutinib alone (N=10)
Neutrophils decrease					
Any grade	31 (36.5%)	9 (27.3%)	16 (47.1%)	6 (33.3%)	3 (30.0%)
Grade 1 or 2	21 (24.7%)	6 (18.2%)	10 (29.4%)	5 (27.8%)	1 (10.0%)
Grade 3 or 4	10 (11.8%)	3 (9.1%)	6 (17.6%)	1 (5.6%)	2 (20.0%)
Platelets decrease					
Any grade	61 (71.8%)	23 (69.7%)	25 (73.5%)	13 (72.2%)	8 (80.0%)
Grade 1 or 2	57 (67.1%)	20 (60.6%)	24 (70.6%)	13 (72.2%)	7 (70.0%)
Grade 3 or 4	4 (4.7%)	3 (9.1%)	1 (2.9%)	0 (0.0%)	1 (10.0%)
Hemoglobin decrease					
Any grade	65 (76.5%)	24 (72.7%)	25 (73.5%)	16 (88.9%)	7 (70.0%)
Grade 1 or 2	62 (72.9%)	21 (63.6%)	25 (73.5%)	16 (88.9%)	6 (60.0%)
Grade 3 or 4	3 (3.5%)	3 (9.1%)	0 (0.0%)	0 (0.0%)	1 (10.0%)

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.

Data cut 11 Oct 2022

No grade 5 hematologic laboratory abnormalities were observed.

TP53/Del17p Results

MCL Efficacy by TP53 mutation: Clinical Response Rates

High response rates and durable responses in MCL patients with TP53 mutation

Endpoints	Overall (N=28)	TP53 mutation (N=7)
Overall Response Rate (ORR), n (%)	25 (89.3)	6 (85.7)
Complete Response (CR), n (%)	12[a] (42.9)	1 (14.3)
Partial Response (PR), n (%)	13 (46.4)	5 (71.4)
Stable Disease (SD), n (%)	1 (3.6)	0
Progressive Disease (PD), n(%)	2 (7.1)	1 (14.3)
Median Duration of response, months (95% CI)	34.13 (13.84, NE)	13.84 (11.93, NE)

N=number of evaluable patients; NE= not estimable; a – includes 1 unconfirmed CR. Data cut 5 May 2023

CLL Efficacy by TP53 mutation/del17p: Clinical Response Rates

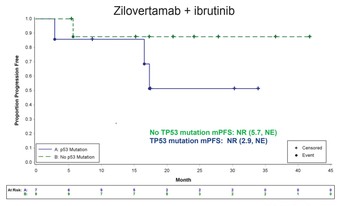
High response rates and durable responses CLL patients with TP53 mutation/del 17p

Endpoints	Parts 1 & 2 (N=34)	Part 3 - Zilo+ Ibr (N=16)	Part 3 - Ibr (N=7)	TP53 mutation/ del17p (N=10)
Overall Response Rate (ORR), n (%)	31 (91.2)	15 (93.8)	7 (100.0)	10 (100.0)
Complete Response (CR), n (%)	3 (8.8)[a]	0	1 (14.3)	1 (10.0)
Partial Response (PR), n (%)	28 (82.4)[b]	15 (93.8)	6 (85.7)	9 (90.0)[b]
Stable Disease (SD), n (%)	3 (8.8)	1 (6.3)	0	0
Median Duration of response, months (95% CI)	40.3 (33.5, NE)	NR (22.2, NE)	NR (8.3, NE)	40.3 (NE, NE)

N=number of evaluable patients; NE= not estimable; a – includes 1 unconfirmed CR, b – includes 1 PR-L. Data cut 5 May 2023

MCL Efficacy by TP53 mutation: Progression Free Survival

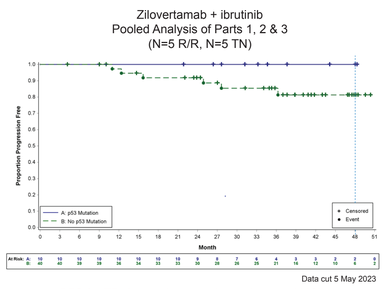
Demonstrates encouraging mPFS in subgroups with poor prognosis



Data cut 5 May 2023

CLL Efficacy: PFS by TP53 mutation/del17p

Very encouraging landmark PFS at ~42 mo

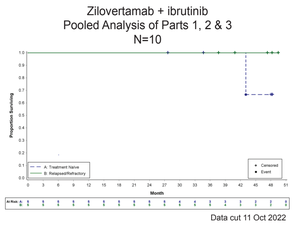


Data cut 5 May 2023

PFS for TP53 mutation at ~48 months was 100%

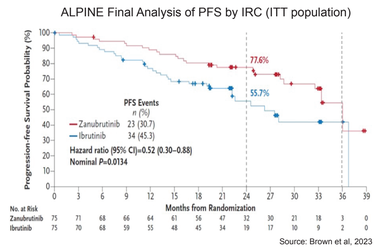
CLL Efficacy by TP53 mutation/del17p: Overall Survival

Median OS not reached after 42 months



Data cut 11 Oct 2022

Landmark OS 100% at ~42 months for both R/R and TN CLL and
Landmark OS 100% at ~51 months for R/R CLL with TP53/del17p



Source: Brown et al, 2023

PFS for TP53 mutation at **36 months** was ~55% for **Zanubrutinib**
PFS for TP53 mutation at **36 months** was ~42% for **Ibrutinib**

Conclusions

- Zilovertamab is a humanized mAb designed to inhibit the tumor promoting activity of ROR1
  - In CLL patients with TP53 mutation who have been treated with BTKi, zilovertamab inhibits CLL-cell expression of genes induced by activated ERK1/2, NF-κB, STAT3, and NRF2
- Very encouraging PFS in CLL patients was 100% at ~48 months for patients with TP53 mutations/del 17p
- 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 42.9% and median DOR 34.1 months for patients with R/R MCL on zilovertamab + ibrutinib
- PFS for zilovertamab + ibrutinib was ~95% at 24 months in patients with R/R CLL (median 2 prior LOT)

References

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