Phase 1/2 Study of Zilovertamab and Ibrutinib: Durable Responses Suggest A Novel Mechanism for Synthetic Lethality in TP53 Aberrant Disease.

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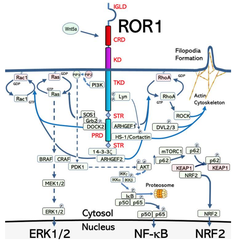
Background

Zilovertamab (Zilo) is a humanized monoclonal antibody that inhibits the tumor-promoting activity of the cancer stem cell receptor, ROR1, which is highly expressed in many hematologic malignancies but not on normal adult tissues.



Overall Phase 1/2 Study Design

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]: 600mg 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 (600mg) + ibrutinib at approved dose (420 mg CLL, 560 mg MCL and MZL)	**RANDOMIZED EFFICACY** • Zilovertamab + ibrutinib vs ibrutinib • 2:1 randomization • Evaluate objective responses, PFS, biomarkers

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

Demographics and Disease Characteristics

High-risk disease and heavily pre-treated population

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[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

Overall Results

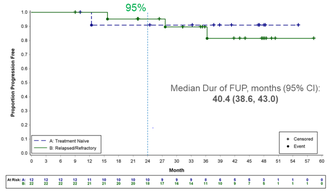
Safety: Treatment Emergent AEs ≥20%

Safety profile is consistent with 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

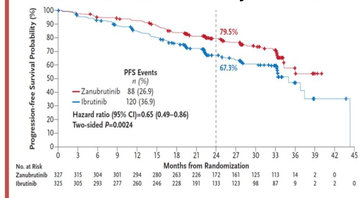
Overall CLL Efficacy: Progression-Free Survival

Zilovertamab + ibrutinib



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

ALPINE: Finals Analysis of PFS



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**

TP53/Del17p Results

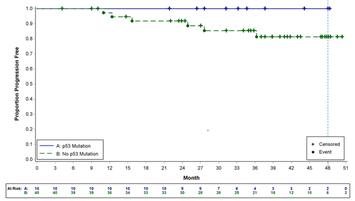
Clinical Response Rates

High response rates and durable responses in pts with del17p

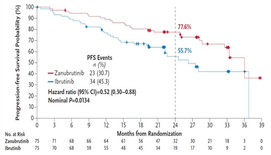
Endpoints	Parts 1 & 2 (N=34)	Part 3 - Zilo+ Ibr (N=16)	Part 3 - Ibr (N=7)	TP53 mutation/del17p (N=10)
Overall Response Rate (ORR), n (%)	31 (91.2)	15 (93.8)	7 (100.0)	10 (100.0)
Complete Response (CR), n (%)	3 (8.8)[a]	0	1 (14.3)	1 (10.0)
Partial Response (PR), n (%)	28 (82.4)[b]	15 (93.8)	6 (85.7)	9(90.0)[b]
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)

PFS by TP53 mutation/del17p: 100% PFS at 48mo

Zilovertamab + ibrutinib
Pooled Analysis of Parts 1, 2 & 3
(N=5 R/R, N=5 TN)



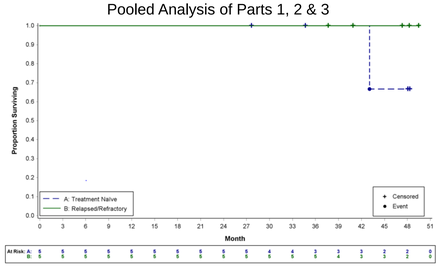
ALPINE Final Analysis of PFS by IRC (ITT population)



Overall Survival by TP53 mutation/Del17p

Median OS not reached after 42 months

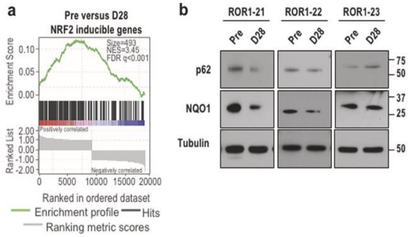
Zilovertamab + ibrutinib
Pooled Analysis of Parts 1, 2 & 3



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

Proposed Mechanism for sensitivity of TP53 aberrant disease: NRF2 Inhibition

- Nuclear factor erythroid 2-related factor (NRF2) regulates cellular responses to oxidative stress.
- Cancer cells with mutated TP53 are more dependent on NRF2 and have higher NRF2 target activation.
- Treatment of Patients With Zilovertamab Inhibits Expression of NRF2-Target Genes In vivo



Conclusions

- Zilo+Ibr is well-tolerated with a safety profile that is comparable to Ibr alone.
- The PFS and OS for the subgroup with TP53 mut/del(17p) are particularly encouraging in reference to other trials of BTK inhibitors, maintaining 100% PFS and OS at ~42 mos.
- Suppression of NRF2 via inhibition of ROR1 may represent a novel strategy for treatment of TP53 mutated CLL.

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- Oncternal Study Team. Contact: clinops@oncternal.com

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