Zilovertamab:
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STUDY ZILO-301: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF ZILOVERTAMAB PLUS IBRUTINIB VS IBRUTINIB IN PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA

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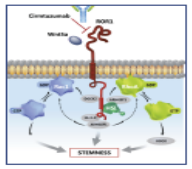
Background

Zilovertamab is a humanized monoclonal antibody designed to inhibit the tumor promoting activity of ROR1 that has demonstrated synergistic activity with anti-cancer agents including ibrutinib.

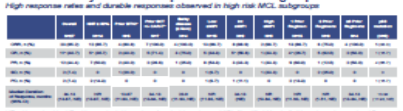
- ROR1 is an onco-embryonic tyrosine kinase-like receptor that is re-expressed at high levels on many solid and hematologic cancers including Mantle Cell Lymphoma, but not on normal adult tissues
- ROR1 binds Wnt5a, resulting in increased tumor growth, survival, metastasis and epithelial mesenchymal transition.
- In the ongoing Phase 1/2 study (CIRM-0001, NCT03088878) of zilovertamab in combination with ibrutinib in relapsed/refractory MCL patients, zilovertamab is well-tolerated and demonstrates promising efficacy in a high-risk and heavily pretreated patient population.



Phase 1/2 Data

Phase 1/2 Study: Clinical Response Rates in Subgroups

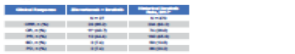
High response rates and durable responses observed in high risk MCL subgroups



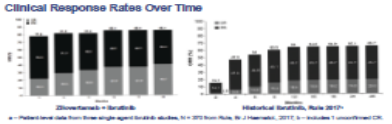
NR = Not estimable; NR+ = Not reached; N/number of evaluable patients; eMIPI, Simplified Mantle Cell Lymphoma International Prognostic Index; HSCT, Hematopoietic stem cell transplant; Allo-HSCT, Allogeneic stem cell transplant [n=7]; CAR-T [n=1], patients would have received more than one; a – Includes 1 unconfirmed CR.

Phase 1/2 Study: Clinical Response Rates

Zilovertamab + ibrutinib combination demonstrates favorable response rates when compared to historical ibrutinib monotherapy.

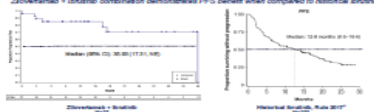


Clinical Response Rates Over Time



Phase 1/2 Study: Progression Free Survival

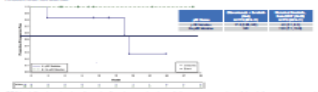
Zilovertamab + ibrutinib combination demonstrates PFS benefit when compared to historical ibrutinib



PFS is defined as the time from the first dose to the time of disease progression or death from any cause, whichever comes first; NE = Not evaluable; a – Patient-level data from three single-agent ibrutinib studies, N = 370 from Rule, W J Haematol., 2017

Phase 1/2 Study: Progression-free Survival by p53 mutation subgroup

Encouraging PFS benefit in patients with or without p53 mutation when compared with historical ibrutinib



PFS is defined as the time from the first dose to the time of disease progression or death from any cause, whichever comes first; NE = not evaluable; NR = not reached; a – Rule, Hematologica, 2019.

Phase 1/2 Study Safety: TEAEs ≥20%

Zilovertamab + ibrutinib has been well tolerated, with treatment emergent adverse events and hematologic abnormalities consistent with or slightly lower than ibrutinib alone.

MCL NHEI	Overall, n (%)	Grades 1-2, n (%)	Grades ≥3, n (%)
Fatigue	18 (48.6)	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 Hematologic and 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	22 (66.7)	20 (60.6)	3 (9.1)

a – No grade 4 or grade 5 TRAEs ≥20%.

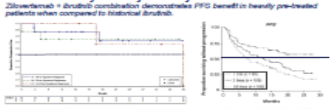
Phase 1/2 Study: Clinical Response by Prior Regimens

Zilovertamab + ibrutinib combination demonstrates encouraging response rates in heavily pre-treated patients when compared to historical ibrutinib.

a – Patient-level data from three single-agent ibrutinib studies, N = 370 from Rule, W J Haematol., 2017; b – Includes 1 unconfirmed CR

Phase 1/2 Study: PFS by Prior Systemic Treatment

Zilovertamab + ibrutinib combination demonstrates PFS benefit in heavily pre-treated patients when compared to historical ibrutinib.



PFS is defined as the time from the first dose to the time of disease progression or death from any cause, whichever comes first; a – Patient-level data from three single-agent ibrutinib studies, N = 370 from Rule, W J Haematol., 2017

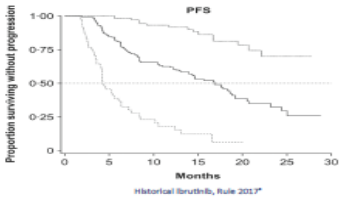
Phase 1/2 Study : Overall Survival

	MCL Pats 182	MCL Historical Ibrutinib Rule, 2017
	Zilovertamab + Ibrutinib Relapsed/Refractory (n=182)	Ibrutinib Relapsed/Refractory (n=370)
Median OS (95% CI)	NR (19.44, NR)	28.5
Median Duration of Follow-up (months), (95% CI)	18.1 (14.31, 22.18)	54.6*

Overall Survival (OS) is defined as the time from the first dose to the time of death from any cause, whichever comes first; NR = not estimable; NR+ = Not reached; a – Patient-level data from three single-agent ibrutinib studies, N = 370 from Rule, W J Haematol., 2017; b – adapted median follow-up of 3 pooled trials (average = 55.6 months) from Rule, W J Haematol., 2017

Rationale

Phase 3 Study ZILO-301: Rationale based on Historical Ibrutinib PFS data



a – Rule Haematologica 2017: Meta-analysis of three studies of patients with relapsed/refractory MCL receiving ibrutinib as second or higher line of therapy (n = 370)

Treatment for MCL patients with an inadequate response to ibrutinib is an unmet medical need.

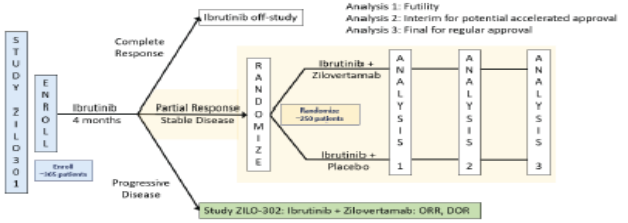
- In patients who achieve PR or SD, outcome can be optimized
- Patients who achieve CR don't require additional medical intervention

Study Design

Phase 3 Study ZILO-301:Study Design

ZILO-301: Randomized, Double-Blind, Placebo-controlled, 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.

ZILO-302: Open-label companion study of zilovertamab plus ibrutinib for rescue of patients refractory to ibrutinib during 4-month run-in.



Global registrational study expected to be initiated in 3Q 2022

Phase 3 Study Details

Phase 3 Study ZILO-301: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Men and women ≥ 18 years
- Histologically confirmed MCL
- Received at least 1 prior line of therapy
- Relapsed or refractory disease
- Measurable (≥2.0 cm in LD)
- ECOG of 0 or 1
- Stable laboratory parameters
- Highly effective contraceptive use

Key Exclusion Criteria

- >1-month prior BTKi therapy
- Transfusion dependent thrombocytopenia
- Known CNS or cardiac involvement
- History or presence of CNS disorder
- Bleeding disorder
- Chronic liver disease
- Pregnant or breastfeeding

Phase 3 Study ZilLO-301: Primary and Secondary Objectives

Primary Objective

- Progression-free survival (PFS) among subjects who had a PR or SD after open-label ibrutinib monotherapy phase and were randomized to receive zilovertamab + ibrutinib or ibrutinib + placebo

Secondary Objectives

- Objective Response Rate (ORR) and Duration of Response (DoR)
- Complete Response Rate (CR Rate)
- Overall Survival (OS)
- Proportion of subjects experiencing grade 3 or 4 neutrophil count decrease and overall safety profile

Phase 3 Study ZILO-301: Planned Analysis

- **Analysis 1**: Futility Analysis based on ORR
- **Analysis 2**: Analysis of ORR, DoR and Safety
  - 85% Power
  - Expected as early as 2+ years after the first patient is enrolled
  - Potential application for early marketing authorization
  - Regardless of results, study will proceed without modification
- **Analysis 3**: End of study analysis for primary endpoint of PFS and remaining secondary endpoints
  - >90% Power
  - Expected as early as 3+ years after first patient is enrolled

Conclusion

- Novel, enrichment phase 3 study ZILO-301 design to show potential benefit for patients with SD or PR on prior open-label ibrutinib (unmet medical need)
- This enrichment design allows for a smaller sample size
- Early opportunity for marketing authorization based on an accepted surrogate endpoint: ORR
- Confirmatory study for approval based on PFS is built into the study design
- Study ZILO-302 may also support additional labeling for the combination treatment of zilovertamab + ibrutinib

References

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Contact Information
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