Safety, Pharmacodynamic, and Anti-Tumor Activity of SL-172154 as Monotherapy and in Combination with Azacitidine (AZA) in Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML) and Higher-Risk Myelodysplastic Syndromes/Neoplasms (HR-MDS) Patients (pts)

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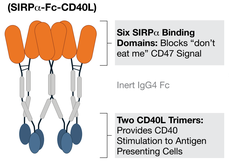
Background

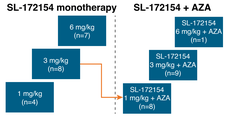
Figure 1



- SL-172154 (SIRPα-Fc-CD40L), a hexameric, bi-functional fusion protein, consists of SIRPα domains linked to CD40L domains through an inert Fc linker
- SIRPα-Fc-CD40L protein competitively inhibits CD47 to enhance tumor cell phagocytosis and activates CD40 to increase antigen processing and cross-presentation by antigen presenting cells (APCs) to CD8 T cells, thus bridging innate and adaptive immunity
- SL-172154 demonstrated improved anti-tumor activity in comparison to CD47 blocking antibodies in pre-clinical studies [de Silva 2020]
- SL-172154 was tolerable in patients (pts) with heavily pretreated platinum-resistant ovarian cancer [Lakhani 2023]
- Like CD47 inhibitors, the mechanism of action of SL-172154 in AML/HR-MDS requires combination with AZA to provide pro-phagocytic signals on leukemic stem cells and blasts to potentiate macrophage phagocytosis

Study Design and Objectives

Figure 2: Study Schema



Study Design

- Pts were assessed for DLT during the first cycle (28 days) of treatment
- Dose escalation followed mTPI-2 design
- Pts were enrolled into dose cohorts of 1 mg/kg to 6 mg/kg SL-172154 without or with AZA
- A dose of SL-172154 with AZA was selected for evaluation in the dose expansion cohorts

Objectives

- Evaluate the safety and tolerability of SL-172154 administered alone or with AZA and to select the recommended Phase 2 dose for SL-172154 with AZA
- Assess preliminary evidence of anti-tumor efficacy of SL-172154 administered alone or with AZA
- Assess pharmacodynamic biomarkers in peripheral blood and bone marrow aspirate prior to, on-treatment and following treatment with SL-172154 administered alone or with AZA

AZA: azacitidine; mTPI-2: Modified Toxicity Probability Interval; DLT: dose-limiting toxicity

Eligibility Criteria for Dose Escalation Cohorts

Key Inclusion Criteria

- Age 18 years or older
- ECOG performance status of 0, 1 or 2
- **Confirmed diagnosis of HR-MDS or AML by 2016 WHO criteria**
- Ineligible for rescue chemotherapy and allogeneic-HCT at the time of screening
- **Relapsed/refractory (R/R) disease following at least 1 prior line of therapy but no more than 4 prior lines of therapy**
- **Only for SL-172154+ Azacitidine cohort, previously untreated MDS pts with at least one TP53 gene mutation or deletion (TP53m) were eligible**

Key Exclusion Criteria

- Evidence of active CNS involvement with leukemia
- Prior treatment with an anti-CD47 or a CD40 agonist within 28 days prior to first dose of study treatment
- Prior treatment with anti-SIRPα targeting agent
- Pts requiring agents other than hydroxyurea to control blast counts within 14 days prior to first dose of study treatment
- Comorbidities such as clinically significant or uncontrolled cardiac, or chronic respiratory disease

Higher risk (HR)-MDS was defined by intermediate, high or very high-risk category by Revised International Prognostic Scoring System (IPSS-R). AML excludes pts with acute promyelocytic leukemia.

Patient and Disease Characteristics

Table 1: Demographics

	SL-172154 Monotherapy N=19	SL-172154 + AZA N=18
Median Age, years [range]	70 [55-81]	69 [44-78]
Male/Female	7 (37%) / 12 (63%)	16 (89%) / 2 (11%)
Race		
White	18 (95%)	16 (89%)
African American	0	1 (6%)
Other/not reported	1 (5%)	1 (6%)
Baseline ECOG n (%)		
0	2 (11%)	1 (6%)
1	15 (79%)	14 (78%)
2	2 (11%)	3 (17%)

All pts enrolled from US study sites except one enrolled from a Canadian site.

Table 2: Disease Characteristics

R/R AML, n (%)	SL-172154 Monotherapy N=14	SL-17215 + AZA N=13
De novo AML	8 (57)	7 (54)
Secondary AML	6 (43)	6 (46)
Prior MDS	4 (29)	3 (23)
Others	2 (14)	3 (23)
Adverse genetic abnormalities (2017 ELN classification)	13 (93)	10 (77)
TP53m	6 (43)	3 (23)
Prior AML therapy		
Number of lines, median [range]	2 [1-4]	2 [1-4]
Prior HMA	12 (86)	12 (92)
Prior VEN	13 (93)	12 (92)
Prior allogeneic HCT	2 (14)	2 (15)

R/R HR-MDS, n (%)	SL-172154 Monotherapy N=5
Complex karyotype with TP53m	2 (40)
Prior MDS therapy	
Number of lines, median [range]	2 [1-2]
Prior HMA	5 (100)
Prior VEN	2 (40)
Prior allogeneic HCT	1 (20)

Previously Untreated HR-MDS with TP53m, n (%)	SL-172154 + AZA N=5
Treatment related MDS	1 (20)
IPPS-R	
Very high	3 (60)
High	2 (40)

HR-MDS: higher-risk myelodysplastic syndrome; R/R: relapsed/refractory; HMA: hypomethylating agents; VEN: venetoclax; HCT: hematopoietic cell transplantation

Safety

Table 3: Summary of Adverse Events

Category, n (%)	SL-172154 Monotherapy N=19	SL-172154 + AZA N=18
Any AE	19 (100%)	18 (100%)
SL-172154 Related AE	16 (84%)	12 (67%)
SAE*	13 (68%)	11 (61%)
SL-172154 Related SAE	1 (5%)	2 (11%)**
AE leading to infusion interruption	7 (37%)	6 (33%)
AE leading to SL-172154 dose delay	4 (21%)	10 (56%)
AE leading to SL-172154 dose reduction	2 (11%)	3 (17%)
AE leading to SL-172154 discontinuation	3 (16%)	1 (6%)

*One fatal AE unrelated to SL-172154 in the monotherapy group
**One Dose Limiting Toxicity (DLT)

Table 4: SL-172154 Related AEs in >10% of Pts

A: SL-172154 Monotherapy (N=19)

Preferred Term, n (%)	Any grade	≥ Grade 3
Any related AEs	**16 (84%)**	**6 (32%)**
IRR	13 (68%)	2 (11%)
ALT increased	3 (16%)	1 (5%)
AST increased	3 (16%)	1 (5%)
Nausea	3 (16%)	0

B: SL-172154 + AZA (N=18)

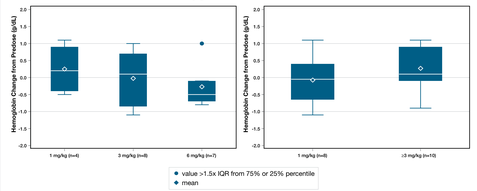
Preferred Term, n (%)	Any grade	≥ Grade 3
Any related AEs	**12 (67%)**	**3 (17%)**
IRR	9 (50%)	2 (11%)
Nausea	3 (17%)	0
ALT increased	2 (11%)	1 (6%)
AST increased	2 (11%)	0
Headache	2 (11%)	0

- Grade 3 IRRs: n=2 (11%) at 3 mg/kg (monotherapy and combination) and n=2 (25%) at 6 mg/kg (monotherapy and combination). One Grade 3 IRR was a DLT (6 mg/kg SL-172154 + AZA).
- Grade 3 ALT/AST elevations were transient: (n=1 at 3 mg/kg combination and n=1 at 6 mg/kg monotherapy)
- SL-172154 related SAEs (n=3): 2 IRRs (one pt in each cohort) and one maculopapular rash (combination cohort)

IRR: Infusion Related Reaction

Safety (cont.)

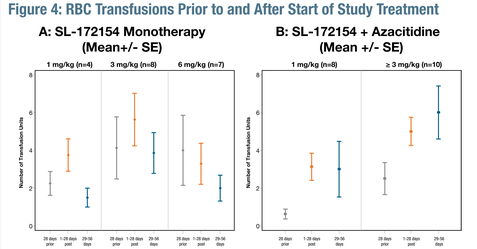
Figure 3: Hemoglobin Change After the First Dose of SL-172154



Transient decreases in hemoglobin were observed after SL-172154 infusion. The maximum decrease among all pts was 1.1 g/dl.

The upper, middle and lower line of the box are 75%, 50% and 25% percentiles.
Whiskers are maximum values within 1.5 x interquartile range (IQR) from 75% or 25% percentile.

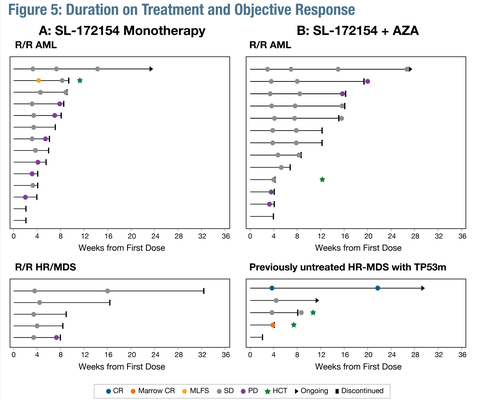
Figure 4: RBC Transfusions Prior to and After Start of Study Treatment



- No significant change in RBC transfusion requirement during treatment with SL-172154 monotherapy vs prior to treatment
- RBC transfusion requirement increased during treatment with SL-172154 + AZA which is likely due to cytopenia/ myelosuppression induced by AZA

Efficacy

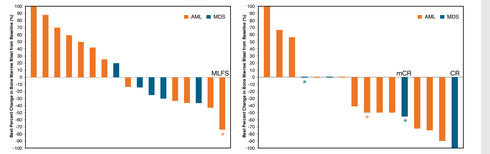
Figure 5: Duration on Treatment and Objective Response



- Median (range) duration on treatment was 8 (2-32) weeks. One pt with R/R AML achieved MLFS.
- Median (range) duration on treatment was 10 (2-29) weeks. Objective response in 2/4 evaluable pts with previously untreated HR-MDS; 2/4 pts proceeded to allo-HCT; 1 subject continues in a CR without allo-HCT.

Efficacy (cont.)

Figure 6: Bone Marrow Blast Changes

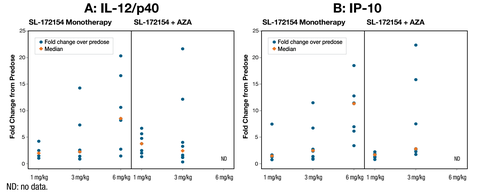


- A pt with R/R AML previously treated with 7+3, FLAG and VEN/AZA, achieved MLFS (last reduction from 19% to <5%) after 1 cycle of 6 mg/kg SL-172154 monotherapy. After 2 cycles of SL-172154, the pt proceeded to allo-HCT.
- Two OR (CR and mCR) were observed out of four evaluable pts with previously untreated HR-MDS with TP53m, two pts underwent allo-HCT
- No objective response was reported in pts with R/R AML. However, relative reduction in BM blasts from baseline was observed in 2/5 pts at 1 mg/kg cohort (-50%, -75%) and 5/7 pts at 3 mg/kg cohort (ranging from -35% to -90%).

Pts with more than 100% increase are displayed at 100%.
* Pts who received allogeneic hematopoietic cell transplant (allo-HCT) after discontinuation of SL-172154.
OR: objective response; CR: complete remission; mCR: marrow CR; MLFS: Morphologic Leukemia-Free State; FLAG: fludarabine, cytarabine and G-CSF

Pharmacodynamics

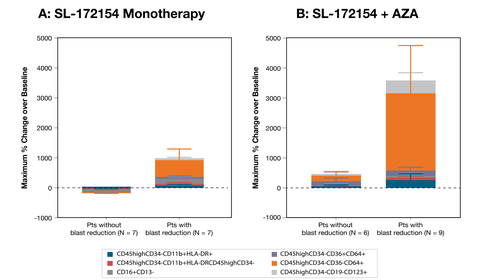
Figure 7: SL-172154 Induced Elevations in On-target Innate and Adaptive Serum Cytokines



ND: no data.

- The administration of SL-172154 induced dose-dependent production of IL-12p40 (Figure A), IP-10 (Figure B)
- IL-8, IL-10, MIP3α and MCP1 were also induced in a dose dependent manner

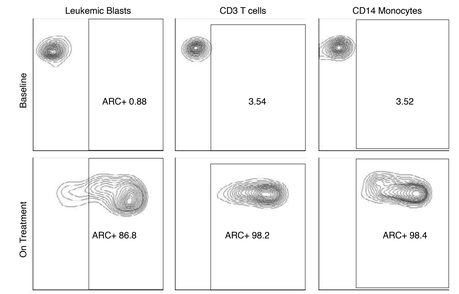
Figure 8: Bone Marrow Blast Reduction was Associated with Increased Frequencies of Mature Phagocytic Myeloid Cells in the Regenerative Bone Marrow



- Blast reduction in SL-172154 monotherapy or in SL-172154 and AZA combination was associated with increase in the frequency of mature phagocytic cells in the bone marrow
- The magnitude of percent increase in these phagocytic cells is higher in SL-172154 and AZA combination compared to SL-172154 monotherapy
- A small percentage increase in the frequency of mature phagocytic cells in the bone marrow of patients with no reduction in blast was observed in the SL-172154 and AZA combination

Pharmacodynamics (cont.)

Figure 9: SL-172154 Binding to Leukemic Blasts (CD45lowCD34+) and Mature Leukocytes (CD45highCD34-) was Observed in the on Treatment Bone Marrow Biopsies



- Intense staining of SL-172154 was observed on both bone marrow blasts and leukocytes 2 hours after infusion
- Both staining intensity and the frequency of SL-172154 positive cells wanes over a 3-to-4-day period. This may be explained by cellular proliferation and drug exposure.

Conclusions

- SL-172154 was tolerable up to 3 mg/kg as monotherapy and in combination with AZA. Safety of the combination is consistent with the safety profiles of the individual agents.
- SL-172154 demonstrated antileukemic activity as a single agent in relapsed/refractory AML
- 1 CR and 1 mCR were observed from four evaluable pts with previously untreated HR-MDS with TP53 mutation or deletion
- SL-172154 increased on-target innate and adaptive serum cytokine levels of IL-12p40, IP-10, IL-8, IL-10, MIP3α and MCP1 at 3.0 mg/kg
- The administration of SL172154 monotherapy was associated with increase of the frequencies of phagocytic cells (such as CD45highCD34-CD11b+HLA-DR+ and CD45highCD34-CD36+CD64+) in bone marrow of patients with reduction in leukemic blasts. The magnitude of increase was higher in SL-172154 plus AZA cohort compared to SL-172154 monotherapy cohort.
- SL-172154 was detected on leukemic blasts and non-leukemic leukocytes in bone marrow
- Based on the safety, tolerability, anti-leukemic activity, and pharmacodynamic activity, 3.0 mg/kg SL-172154 + AZA is being evaluated in treatment naïve pts with TP53m AML and HR-MDS

Acknowledgements

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Ethics Approval

This study is being conducted in full conformity with the Declaration of Helsinki and was approved by all IRBs/ethics committees from each clinical site participating in the study. Specific approval numbers can be provided upon request.

References

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Lakhani NJ, Stewart D, Richardson D, et al. Phase 1 dose escalation study of SL-172154 (SIRPα-Fc-CD40L) in platinum-resistant ovarian cancer. ASCO 2022 Abstract Number: 5544