Phase 2a Study of SLS009, a Highly Selective CDK9 Inhibitor, In Combination with Azacitidine and Venetoclax for Relapsed/Refractory Acute Myeloid Leukemia After Prior Venetoclax Treatment

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Abstract

Context: Venetoclax in combination with hypomethylating agents is approved as a first line treatment in acute myeloid leukemia (AML) but is commonly used in patients at all stages of the disease due to high response rate and improvement in survival outcomes. However, patients who fail venetoclax based regimens, either primary refractory or relapsed, exhibit very short survival reported as <2.5 months. The mechanism of venetoclax resistance is believed to be largely reliant on cellular switch from BCL2 to MCL1 anti-apoptotic dependency. SLS009 is a highly selective Cyclin Dependent Kinase 9 (CDK9) inhibitor. CDK9 inhibition has been shown to decrease MCL1 transcription and potentially synergize with venetoclax BCL2 inhibition. **Objectives:** We sought to determine the efficacy of SLS009 addition to venetoclax combination with azacitidine in patients who were resistant to venetoclax based therapies in any line of previous therapy. Secondary endpoint was safety and toxicity of addition of SLS009 to aza/ven. **Design:** We conducted a multicenter Phase 2a single arm trial. **Patients:** Thirty patients (median age 71 yrs; range, 41-84 yrs) with relapsed and/or refractory AML who previously failed at least one venetoclax based therapy were treated. **Intervention:** Patients received a weekly or biweekly infusion of SLS009 at doses of 45 mg QW (n=10), 60 mg (n=9), or 30 mg BIW (n=11) in combination with standard aza/ven regimen. **Results:** Overall response rate (CR, CRi and MLFS) was 31%. Marrow blast reductions ≥ 50% were seen in 55% of evaluable patients. All responding patients had AML MRC. **Conclusions:** Addition of SLS009 to AZA/VEN was found to be safe and feasible without DLT's. SLS009 30 mg IV BIW (DL3) was chosen as the optimal dose. Clinical activity was seen particularly in patients with AML MRC.

Background

- Hypomethylating agent plus venetoclax (HMA/VEN) is a standard frontline treatment regimen for older/unfit patients (pts) with acute myeloid leukemia (AML)
  - ~1/3 of patients fail to respond and majority of patients who respond ultimately relapse
- In the absence of targetable mutations (i.e, *IDH1, IDH2* or *FLT3*), no known effective agents for relapsed/refractory (R/R) AML after HMA/VEN
- Outcomes are dismal in pts w/ R/R AML after HMA/VEN: **Median OS < 2.5 months**[1-5].
- Resistance to VEN includes up-regulation and dependence on MCL-1 activity[6,7]
- **Hypothesis**: Addition of SLS009 (CDK9 inhibitor) to AZA/VEN may abrogate resistance to venetoclax and result in clinical activity in R/R AML after VEN-based combinations.

Mechanism of Action

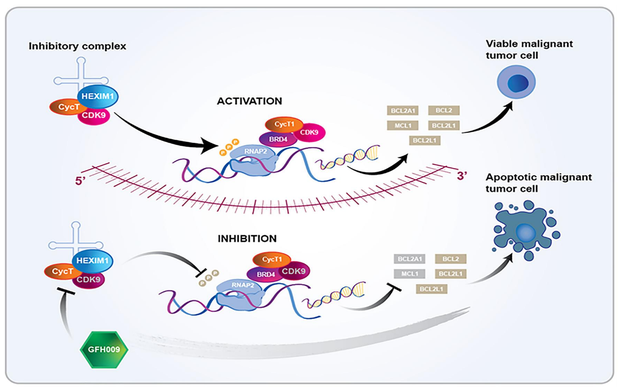


Figure 1. SLS009 Mechanism of Action. CDK9 is a transcriptional regulator of multiple oncogenes, including MCL-1 and c-MYC[8,9]. It is often upregulated in hematologic malignancies and plays a role in proliferation and survival of cancerous cells[8,9]. CDK9 inhibition can slow or stop cell cycle progression indirectly through perturbation of the P-TEFb complex required for continuous RNA Polymerase II transcription, leading to downregulation of short-lived downstream proteins including c-MYC and MCL-1[9-10].

Study Design

Target Population and Study Design

I/E criteria:

- Patients ≥ 18 yrs of age
- AML refractory to or relapsed after a venetoclax containing regimen
- Peripheral WBC counts < 50K/µL
- ECOG PS 0-2

Study design:

- Open Label
- Single Arm
- Combination therapy with: Azacitidine and Venetoclax
- Multi-center P 2a

Three SLS009 dose levels:

- 45 mg QW (~10 patients)
- 60 mg QW (~10 patients)
- 30 mg BIW (~10 patients)

Administration and Treatment Algorithm

Bi-Weekly Dosing

D1 D2 D8 D9 D15 D16 D22 D23 D28

Venetoclax PO Daily on D1-28

D1 D2 D8 D9 D15 D16 D22 D23 SLS009 IV

Azacitidine 75mg/m^2 IV D1-7

Weekly Dosing

D1 D2 D8 D9 D15 D16 D22 D23 D28

Venetoclax PO Daily on D1-28

D1 D8 D15 D22 SLS009 IV

Azacitidine 75mg/m^2 IV D1-7

Endpoints and Assessments

Primary Endpoints:

- Composite complete response rate (CRc)
- Duration of response (DOR)
- Safety and Tolerability of SLS009 in combination with aza/ven:
- Dose Limiting Toxicities (DLTs) Adverse events (AEs)
- The incidence and severity of all Aes

Secondary Endpoints:

- Event free survival (EFS)
- Overall Survival (OS)
- PK parameters for SLS009 and venetoclax in combination therapy: AUC0-t (Area under the plasma concentration-time curve (from zero to the time of the last measurable concentration))

Figure 2. Treatment Schema. Adult patients with relapsed and/or refractory AML who failed at least one venetoclax based therapy regimen were treated with AZA/VEN and SLS009. There were three different dose levels (DLs) of SLS009: DL1: 45 mg IV QW, DL2: 60 mg IV QW and DL3: 30 mg IV BIW (on day 1 and 2 of the week). AZA/VEN was administered as standard doses for 28-day cycles. Cycles were repeated until disease progression, unacceptable toxicity, death or withdrawal for any reason.

Patients Characteristics

Table 1. Patient Demographics and ELN Risk

Characteristic	N=30
Median Age (Range), Years	71 (41–84)
Age ≥ 70 years	20 (67%)
Female	13 (43%)
Number of prior lines of therapy: Median (Range)	2 (1–4)
ELN Risk Category Favorable-risk Intermediate-risk Adverse-risk	 0 (0%) 1 (3%) 29 (97%)
AML-MR	23 (77%)

Table 2. Mutations occurring in >10% of patiens and response outcomes

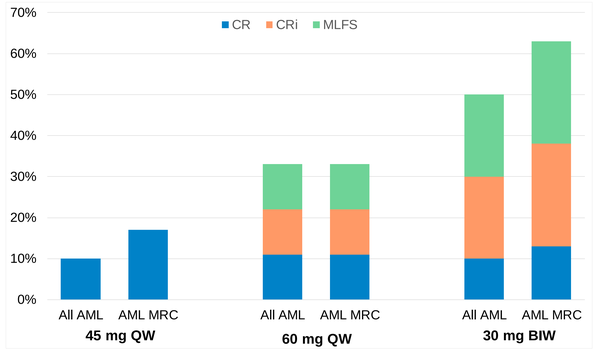
Mutation	Mutation frequency (%)	ORR (%)
RUNX1	11 (37%)	4 (36%)
ASXL1	9 (30%)	5 (56%)
TP53	9 (30%)	1 (11%)
TET2	6 (20%)	2 (33%)
NRAS	4 (13%)	1 (25%)
EZH2	4 (13%)	2 (50%)
SRSF2	4 (13%)	3 (75%)

Results

Table 3. Treatment Related Toxicities of Any Grade Occurring in ≥ 1 Patient

	45 mg QW (N=10)		60 mg QW (N=9)		30 mg BIW (N=11)		All patients (N=30)	
Toxicity	Any grade(%)	≥G3 (%)	Any grade(%)	≥G3 (%)	Any grade(%)	≥G3 (%)	Any grade(%)	≥G3 (%)
Nausea	3 (30%)	**0 (0%)**	2 (22%)	**0 (0%)**	2 (18%)	**0 (0%)**	7 (23%)	**0 (0%)**
Diarrhea	2 (20%)	**0 (0%)**	0 (0%)	**0 (0%)**	2 (18%)	**0 (0%)**	4 (13%)	**0 (0%)**
Pyrexia	1 (10%)	**0 (0%)**	1 (10%)	**0 (0%)**	0 (0%)	**0 (0%)**	2 (7%)	**0 (0%)**
Hyperphosph.	2 (20%)	**0 (0%)**	0 (0%)	**0 (0%)**	0 (0%)	**0 (0%)**	2 (7%)	**0 (0%)**
Leukopenias	3 (30%)	**3 (30%)**	1 (11%)	**1 (11%)**	0 (0%)	**0 (0%)**	4 (13%)	**4 (13%)**

Figure 3. Efficacy Assessments: ORR (CR+CRi+MLFS) per Dose Level



No DLTs observed at any dose level. Only high grade TRAEs were leukopenias. Among 29 evaluable pts, 16 (55%) had ≥50% reduction in bone marrow (BM) blasts (DL1: 60%; DL2: 33%; DL3: 80%). Nine (31%) pts achieved an overall response (CR+CRi+MLFS), including 5 (17%) who achieved CR/CRi. Response rates / dose level: DL1: 10%; DL2: 33%; DL3: 50%. Responses within 1st cycle of treatment in 8/9 of responders. All 9 responders had AML-MRC (9/23 of AML MRC pts responded). In pts with *ASXL1* mutations, 5/9 (56%) achieved an overall response. 2/9 (22%) with TP53 mutations achieved a response including one pt with concomitant TP53 and ASXL1 mutation. Two responders achieved MRD negativity. Among 9 responders, 1 proceeded to stem cell transplant (SCT), and 3 additional patients were under evaluation for SCT. Median follow-up was 3.6 months at data cutoff and median duration of responses was not reached as 7/9 responses were ongoing (Range: 1-6 months). Fifteen patients were still alive at the time of the data cutoff and the median OS for the trial had not been reached. At the first DL in which 8/10 pts died, mOS was 5.5 months.

Conclusions

- Addition of SLS009 to AZA/VEN safe and feasible without DLTs at any dose level in pts w/ R/R AML after prior Venetoclax
- RP2D of SLS009 30 mg IV BIW + Aza/Ven in R/R AML
- Responses were seen at all dose levels
- AML-MR enriched in responders; highest clinical activity seen in ***ASXL1*** mutation (**ORR = 56%**)
- AML MRC, including AML with *ASXL1* mutations may be a subset of patients with preferential sensitivity to SLS009 + AZA/VEN
- Further development will be focused on AML-MRC patients with and without *ASXL1* mutations.

References

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