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Outcomes of Intermediate or High Risk Myelodysplastic Syndromes (MDS) Patients Post Azacitidine and/or Decitabine Treatment Failures with SGI-110, a Novel Second Generation Hypomethylating Agent (HMA)

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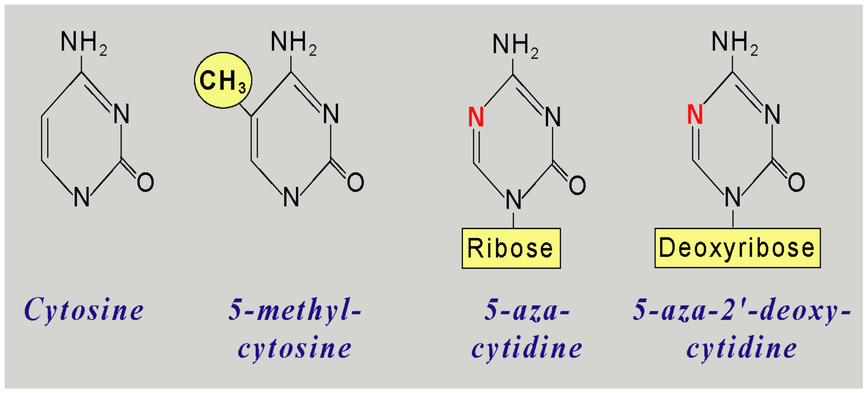
Background

- Myelodysplastic syndromes (MDS) comprise a spectrum of bone marrow stem cell malignancies, characterized by dysplastic and ineffective hematopoiesis – leading to variable grades of peripheral cytopenias – and an increased risk of progression to acute myeloid leukemia (AML).
- There are no proven effective treatments for intermediate or high risk MDS after failure of azacitidine or decitabine. SGI-110 is a novel potent hypomethylating agent (HMA) (Yoo et al. 2007) designed as a dinucleotide incorporating decitabine with deoxyguanosine. SGI-110, because of this design, result in a more sustained release of decitabine after subcutaneous administration with longer half life and longer exposure time than decitabine given as Dacogen IV (DAC) (Kantarjian et al. 2012). Since nucleosides such as azacitidine and decitabine are cell-cycle dependent drugs, the increased exposure time allows more cycling cells to be affected over time and potentially improve efficacy.
- We are conducting a phase 1/2 trial of SGI-110 in patients with relapsed or refractory MDS or AML. This presentation describes the clinical characteristics and outcome of the MDS patients treated in the phase 1 part of the trial.

Cytosine Analogues as Hypomethylating Agents (HMAs)



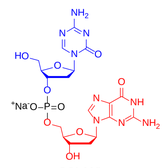
[1]Year approved by FDA for MDS treatment
[2]Year approved by EMA for AML treatment

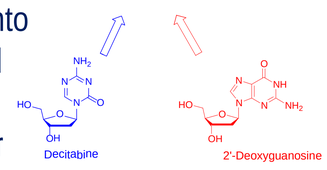
	Azacitidine	Decitabine
	(2004)[1]	(2006)[1] (2012) [2]

Santini V, et al. Ann Intern Med. 2001;134(7):573-86

SGI-110: Novel HMA with Improved Characteristics

- SGI-110 is a Decitabine-containing dinucleotide designed to have the following improvements over currently approved HMAs:
  - Protecting decitabine from deamination
  - Prolonging decitabine plasma half life as SGI-110 slowly releases decitabine.
  - Extending exposure time to decitabine after injection (incorporation into more cells as they go to S phase over time with potential of improved efficacy).
  - Improved small volume and stable formulation (estimated volume per daily SQ injection of 1-2 mL; and stability up to one month after reconstitution).


SGI-110



SGI-110-01 Phase 1/2 Clinical Trial

Part A Dose Escalation (78 pts)

Relapsed or Refractory Intermediate to High Risk MDS or Relapsed or Refractory AML; ECOG PS 0–2

Regimen 1
Daily SC Days 1–5 of a 28-day course

Regimen 2
Weekly SC x 3 of a 28-day course

Part B Dose Expansion (~ 200 pts)

Safety, Efficacy, PK – PD Assessments
C_{max}, AUC, Global Hypomethylation, Gene Re-Expression Studies

BED: 60 mg/m^2 dailyx5 **MTD**: 90 mg/m^2 dailyx5

4 Groups: Relapsed/refractory AML; Relapsed High Risk MDS (with prior HMA treatment); Treatment naïve elderly AML; Treatment naïve MDS.

Objectives and Endpoints

- Primary:
  - Define Biologically Effective Dose (BED) [lowest dose that achieves a maximum hypomethylation or gene expression in at least 3 successive dose levels] and Maximum Tolerated Dose (MTD) [DLT incidence in Course 1].
- Secondary:
  - Incidence and severity grades of DLT, AEs, and labs; PK profile of SGI-110 and decitabine; Response rates, hematologic improvement and duration of response; Time to AML (only for MDS patients).

Baseline Characteristics of MDS Patients

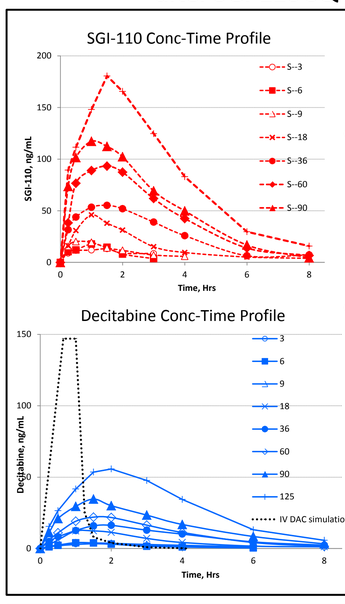
Baseline Characteristics	MDS (n=15)
Age, median years (range)	74 (46 – 82)
Gender, male (%)	10 (67%)
ECOG PS, 0–1 / 2	14 (93%) / 1 (7%)
WHO Classification	
Intermediate 1 / 2 / High Risk	3 / 6 / 5
CMML	1
BM blasts %, median (range)	8 (2 – 23)
Median number of prior regimens (range)	2 (2 – 6)
Prior decitabine / Prior azacitidine	8 (53%) / 13 (87%)
Prior decitabine and azacitidine	6 (40%)
Prior decitabine and/or azacitidine	15 (100%)

MDS Patient Enrollment By Dosing Regimen

- Daily x 5 (n=9): 1 (3 mg/m^2), 2 (18 mg/m^2), 1 (36 mg/m^2), 1 (60 mg/m^2), 1 (90 mg/m^2), 3 (125 mg/m^2).
- Weekly x 3 (n=6): 1 (6 mg/m^2), 3 (18 mg/m^2), 2 (90 mg/m^2).

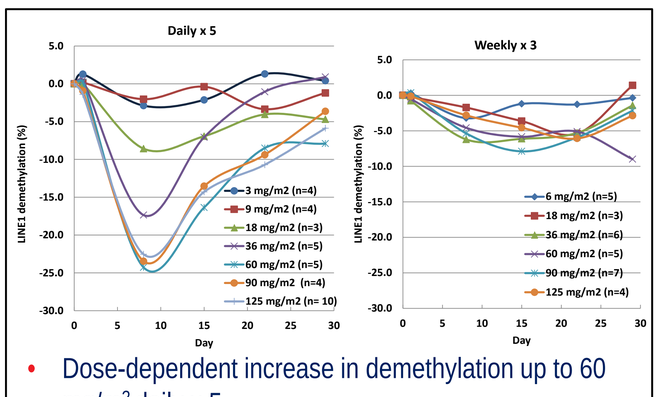
PK and PD in All Patients (MDS and AML)

SGI-110 and Decitabine Pharmacokinetic Profile after SGI-110 SQ Injection



- DAC IV $T_{1/2}$: 15 to 35 mins) versus decitabine from SGI-110: 1.5 to 2.5 hours.
- Overall exposure doubled with decitabine from SGI-110 versus DAC IV from 8 hours versus 3-4 hours.

Average LINE1 Demethylation by Cohort



- Dose-dependent increase in demethylation up to 60 mg/m^2 daily x 5.
- Similar demethylation of 60, 90 and 125 mg/m^2 daily x 5, therefore BED established at 60 mg/m^2 daily x 5.
- SGI-110 daily x 5 regimen achieved superior demethylation than the weekly x 3 regimen.

MDS Response[1*]

Type of Response	# of Patients (n=15)
Hematological Improvement Erythrocytes (HI/E)	3 (20%)
Hematological Improvement Neutrophils (HI/N)	1 (6.5%)
Hematological Improvement Platelets (HI/P)	1 (6.5%)
Marrow Complete Response (mCR)	2 (13%)
Total MDS Responders	6[2] (40%) [95% CI = 16%, 68%]

[1]Available data as of 23 May 2013; *International Working Group 2006 MDS Criteria; [2]One subject had a HI bi-lineage response

Patient # (MDS Category)	SGI-110 Dose (mg/m^2)	Response*	Response Duration	Prior Therapies (Response)
		Daily (QD x 5)		
120 (HR)	18	mCR	119	azacitidine (PR), decitabine (CR), lenalidomide/decitabine (PR)
188 (Int-2)	125	mCR	28	azacitidine (not reported), lenalidomide (not reported), arsenic trioxide (not reported) , decitabine (SD), hydroxyurea (not reported)
		Weekly (QW x 3)		
108 (HR)	6	HI-E / HI-N	100	azacitidine (PR), decitabine (not reported)
110 (Int-2)	18	HI-E	77	azacitidine (PR), lenalidomide (not reported)
158 (HR)	90	HI-E	84	azacitidine/entinostat (PR), azacitidine (not reported)
160 (Int-1)	90	HI-P	126	azacitidine (PR), ezatiostat HCL (TLK-199) (PR)

- Median duration of response = 92 days (range, 28–126 days).

LINE1 Demethylation and Correlation with Response in MDS Patients

- There was no significant difference in median or mean LINE1 demethylation between overall responders and non responders in MDS patients.
- Two patients who achieved mCR showed excellent LINE1 demethylation of > 10% (-19% and -38%).

SGI-110 Related Adverse Events in > 1 Patient (n=15) [MDS]

Adverse Event	All Grades (# of Patients)	Grade 3 / 4 (# of Patients)
Injection Site Pain	7	0 / 0
Thrombocytopenia	5	0 / 4
Anemia	4	4 / 0
Neutropenia	4	0 / 3
Fatigue	3	0 / 0
AST Increase	2	0 / 0
Asthenia	2	0 / 0
Decreased Appetite	2	0 / 0
Diarrhea	2	0 / 0
Dizziness	2	0 / 0
Epistaxis	2	0 / 0
Febrile Neutropenia	2	1 / 1
Hyperhidrosis	2	0 / 0
Nausea	2	0 / 0
Pyrexia	2	0 / 0

Conclusions

- SGI-110 delivers extended exposure of decitabine enabling:
  - Longer exposure window of decitabine up to 8+ hours
  - $T_{1/2}$ of decitabine from SGI-110 is 4-fold longer than decitabine IV
  - Lower C_{max} than decitabine IV
- Pronounced demethylation with dailyx5; less demethylation with weeklyx3.
- Responses observed in heavily pre-treated MDS patients for an overall response rate of 40% [95% CI = 16%, 68%]. Median response duration 92 days (range, 28–126 days); all patients enrolled were previously exposed to a hypomethylating agent.
- BED 60 mg/m^2 dailyx5; MTD 90 mg/m^2 dailyx5 highest tolerable dose for MDS. Most common AEs: Injection site pain (mostly Grade 1) and myelosuppression.
- Phase 2 Dose Expansion ongoing: randomization to 60 or 90 mg/m^2 dailyx5 for treatment naïve and relapsed/refractory MDS. As of 10 June 2013, more than 40 patients were enrolled in treatment naïve MDS group.

References

1. Yoo, CB, Jeong, S, Egger, G, et al. Cancer Res, 2007; 67(13):6400-6408.
2. Kantarjian H, Roboz G, Rizzieri D, et al. American Society of Hematology, abs. 120 (21).
3. Santini V, Kantarjian, HM, Issa, JPet al. Ann Intern Med. 2001;134(7):573–586.

