Abst. No.

P249

OVERALL SURVIVAL (OS) AND SUBGROUP RESULTS FROM A RANDOMIZED PHASE 2 STUDY OF SGI-110 (GUADECITABINE) IN PREVIOUSLY TREATED MYELODYSPLASTIC SYNDROMES (MDS)

Guillermo Garcia-Manero*[1], Gail J. Roboz[2], Michael R. Savona[3], Patricia L. Kropf[4], Casey L. O'Connell[5], Katherine J. Walsh[6], Scott Lunin[7], Raoul Tibes[8], Todd L. Rosenblat[9], Elizabeth A. Griffiths[10], Joseph Mace[11], Nikolai A. Podoltsev[12], Jean-Pierre Issa[13], Valerie Ahanonu[14], Yong Hao[14], Mohammad Azab[14], Hagop M. Kantarjian[1]

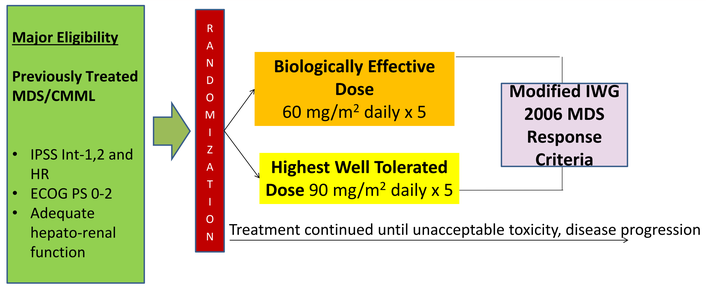
[1]UT MD Anderson Cancer Center, [2]Weill Cornell/NY Presbyterian Medical Center, [3]Vanderbilt University Medical Center, [4]Fox Chase Cancer Center, [5]University of Southern California, Keck School of Medicine, [6]The Ohio State University, [7]Florida Cancer Specialists, [8]Mayo Clinic Arizona, [9]New York-Presbyterian/Columbia University Medical Center, [10]Roswell Park Cancer Institute, [11]Florida Cancer Specialists, [12]Yale University School of Medicine, [13]Fels Institute, Temple University, [14]Astex Pharmaceuticals, Inc.

Background

Guadecitabine (SGI-110) is a next generation hypomethylating agent (HMA) designed as a dinucleotide of decitabine and deoxyguanosine that is resistant to deamination by cytidine deaminase (CDA). This results in a prolonged in vivo exposure to decitabine following small volume subcutaneous (SC) administration of guadecitabine. Safety and clinical activity in resistant MDS and AML have been shown in a Phase 1 trial (Issa et al, Lancet Oncology,

Methods

Figure 1: Phase 2 dose-response randomized study with the following design



- Primary Endpoint: Overall Response (CR, PR, mCR, HI)
- Secondary Endpoints: transfusion independence, overall survival, and safety

Results by dose were presented previously (Garcia-Manero ESH 2016). There were no major differences between the 2 dose groups in terms of patient characteristics, efficacy, or safety, so data from the 2 dose groups were combined for this analysis.

Results (Relapsed/Refractory MDS & CMML)

Table 1: Patient characteristics

Patient Characteristics		Total (n=53)*
Median Age (range)		72 (52-89)
Gender	M	60%
	F	40%
ECOG PS	0	21%
	1	58%
	2	21%
Prior decitabine (DAC) (%)		32%
Prior azacitidine (AZA) (%)		77%
Prior DAC **and** AZA		13%
Median prior regimens		1 (1-4)
IPSS Classification	Int-1	8%
	Int-2	25%
	HR	47%
	CMML	19%
Time from last prior Tx	< 3 m	59%
	3-6 m	23%
	≥ 6 m	18%
Duration of prior HMA	< 6 m	13 (25%)
	≥ 6 m	40 (75%)
Median Blasts %		8% (0-19%)
Baseline BM Blasts*	≤ 5%	19 (36%)
	> 5%	34 (64%)
Median Neutrophils/µL		810 (10-15,600)
Median Platelets/µL		37,000 (7,000-328,000)
Median Hb g/dL		9.3 (7.1-13.5)
RBCs or Platelet transf. dep.		35 (66%)

* 26 patients were randomized to 60 mg/m² Dailyx5 and 27 patients were randomized to 90 mg/m² Dailyx5

Table 2: Treatment and follow up

Treatment Cycles	Total N=53
Median # Tx Cycles	5 (1-29)
Dose Reduced Cycles	35%
Dose Delayed Cycles	45%
Median Follow Up (range) in months	25.2 (19.4-30.1)

Table 3: Response to treatment*

Response	Total N=53 N (%)
CR	2 (3.8%)
mCR **	15/34 (44%)
PR	0
HI	11 (20.8%)

* Based on modified IWG 2006 criteria
- CR; Complete Response
- mCR: marrow Complete Response
- PR: Partial Response
- HI: Hematological Improvement (Erythroid; Platelets; or Neutrophils)

** mCR Evaluated only in patients who had BM blasts > 5% at baseline (34 patients)

Table 4: Transfusion independence

	Nb* (%)
Guadecitabine 8-week **RBCs Transfusion Independent** n (%)	4/33 (12%)
Guadecitabine 8-week **Platelets Transfusion Independent** n (%)	5/16 (31%)

* Evaluated only for patients who were transfusion dependent at baseline (33 patients were RBCs transfusion-dependent; and 16 patients were platelets transfusion-dependent at baseline).

Figure 2: Overall survival

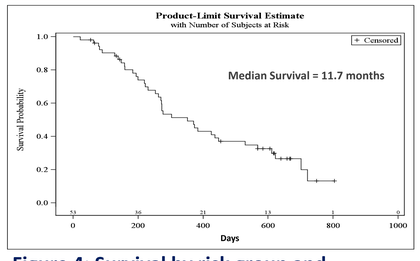


Figure 3: Survival by clinical response

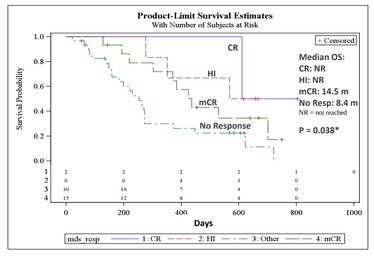


Figure 4: Survival by risk group and disease group

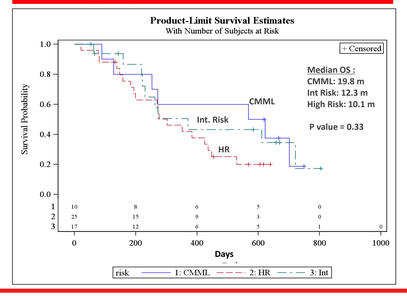


Figure 5: Survival by baseline BM blasts

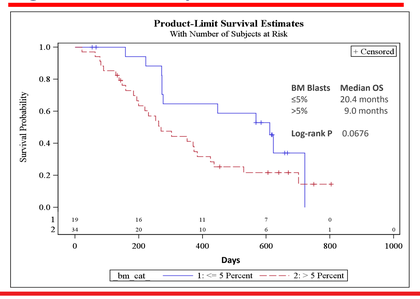


Figure 6: Survival by baseline RBC *or* platelets transfusion dependence

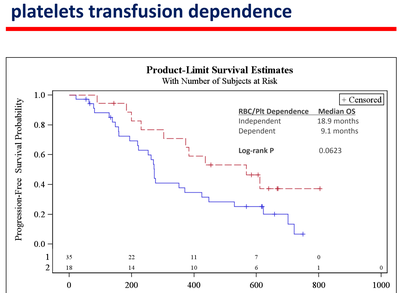


Figure 7: Survival by BM blasts and transfusion-dependence

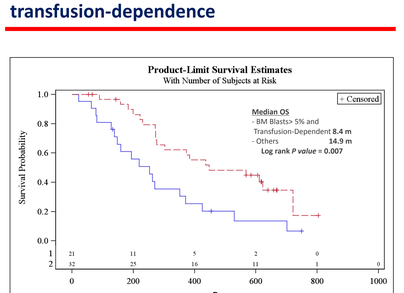


Table 5: Safety AEs grade ≥ 3 regardless of Tx relationship

	Total N=53
Thrombocytopenia	55%
Anemia	51%
Neutropenia	45%
Febrile neutropenia	38%
Pneumonia	32%
Fatigue	13%
Leukopenia	11%
Sepsis	11%

Table 6: All-cause early mortality

Dose	N	30-day	60-day *
Total	53	1 (1.9%)	1 (1.8%)

*includes patients who died at 30 days

Summary & Conclusions

- Guadecitabine (SGI-110) has promising clinical activity in MDS and CMML patients who were previously treated with other HMAs (azacitidine, decitabine, or both).
- Median Overall Survival (OS) of 11.7 months seems higher than historical data including median OS of 10.1 months in high risk MDS who failed other HMAs.
- Prognostic factors of OS in r/r MDS or CMML:
  - Clinical Response by IWG criteria (CR, mCR, or HI) was associated with better Survival.
  - Transfusion dependence, Baseline BM blasts >5%, or the combination of these factors was associated with worse survival.
- Guadecitabine safety was acceptable with low early mortality (< 2%).
- The Phase 2 study supports phase 3 development of guadecitabine 60 mg/m² Dailyx5 in relapsed/refractory MDS and CMML.
- A Phase 3 randomized study is being initiated (2:1 randomization of guadecitabine vs Treatment Choice of low dose cytarabine, intensive chemotherapy, or best supportive care).

© Astex Pharmaceuticals, Inc.

Poster presented at: 21st Congress of the European Hematology Association (EHA), June 9 – 12, 2016, Copenhagen, Denmark