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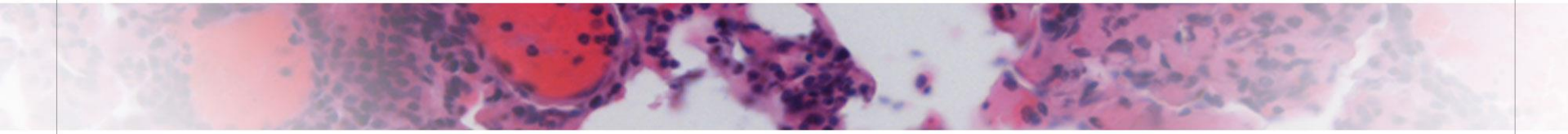

Oral Decitabine/Cedazuridine in Patients with Lower Risk Myelodysplastic Syndrome: a Longer-Term Follow-Up of from the ASCERTAIN Study

On behalf of the ASCERTAIN Investigators Team

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Disclosures

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- LB has consultancy with Novartis
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Introduction

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- **Myelodysplastic Syndromes (MDS)**
  - Heterogeneous group of clonal bone marrow stem cell disorders resulting in abnormal blood and bone marrow morphology, ineffective hematopoiesis, and increased risk of transformation to Acute Myeloid Leukemia (AML)
  - Degree of dysplasia, peripheral cytopenias, and cytogenetics reflect disease severity and AML risk

- **Hypomethylating agents (HMAs) established in higher risk MDS but less clear role in lower risk (int-1/LR) disease**
  - Randomized Phase 2 of low-dose decitabine vs. low-dose azacitidine showed activity in LR MDS[1]
  - Recent randomized study of an oral formulation of azacitidine (CC-486) showed no difference in survival (median OS 17.3 vs. 16.2 months), likely due to early infectious deaths in first 56 days (16 [15%] in CC-486 vs 6 [5.5%] placebo)[2]

- **Oral decitabine and cedazuridine (ASTX727)**
  - Orally available fixed-dose (FDC) combination of 35 mg decitabine and the cytidine deaminase (CDA) inhibitor cedazuridine (100 mg) that produces equivalent PK AUC exposure compared to IV decitabine[3]
  - ASCERTAIN, a phase 3 study leading to the approval of oral decitabine/cedazuridine, enrolled MDS subjects who were candidates for parenteral decitabine including 69 subjects with lower-risk MDS
  - The outcomes for this subgroup are presented here

[1]Jabbour, et al. Blood 2017: 130(13): 1514-1522; [2]Garcia-Manero, et al DOI: 10.1200/JCO.20.02619 *JCO* 39, no. 13 (May 01, 2021) 1426-1436; [3]Garcia-Manero, et al, [ASH Abstract 846] Blood. 2019;134 (suppl 1)

Methods/Study Design[3]

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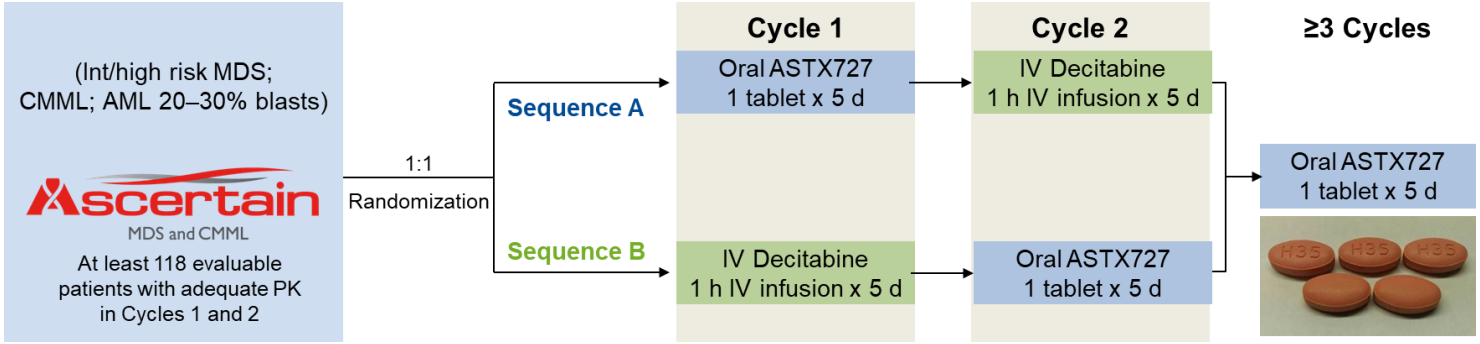

Major entry criteria:

- Candidates for IV decitabine
- ECOG PS 0-1
- Life expectancy of ≥3 months
- Adequate organ function
- One prior cycle of HMA is allowed

Candidates for decitabine include:

Adult patients with MDS, including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (**refractory anemia, refractory anemia with ringed sideroblasts**, refractory anemia with excess blasts, and chronic myelomonocytic leukemia[CMML] and **intermediate-1**, intermediate-2, and high-risk International Prognostic Scoring System groups.

- A total of 69 lower-risk (LR/Int-1) subjects were enrolled into ASCERTAIN

[3]Garcia-Manero, et al, [ASH Abstract 846] Blood. 2019;134 (suppl 1).

Patient Characteristics/Demographics

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Characteristics		Total Treated N=69[a]
Age in years (median, range)		70 (45-87)
Sex: Male/Female		45 (65%)/24 (35%)
Median weight, kg (range)/Median BSA, m^2 (range)		84 (50-127)/2.01 (1.4 - 2.6)
MDS, IPSS classification	Int-1 /Low-risk	64 (93%)/5 (7%)
Cytogenetics[b]	Intermediate-poor	28 (41%)
	Good	37 (54%)
Prior anticancer therapy		17 (24.6%)
Prior cycle of HMA		2 (2.8%)
Transfusion dependent	RBCs	27 (39%)
	Platelets	6 (9%)
ECOG PS	0/1	29 (42%)/40 (58%)

[a] 3 subjects received IV decitabine but did not receive ASTX727 and 1 subject received ASTX727 but not IV decitabine.
[b] Four (6%) were non-evaluable or missing.

Baseline Hematology Parameters

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Parameter	Median (Range)	Distribution
Bone marrow blasts	Median 4.0% (0,18)	>5%: 21 (31%)
Hemoglobin (g/L)	Median 89 (69.8,146.5)	<80: 15(22%)
		80-<100: 31 (45%)
		100-<110: 7 (10 %)
		≥ 110: 16 (23%)
Platelets, 10^9/L	Median 86 (5,703)	<25: 9 (13%)
		25-<50: 10 (15%)
		50-<75: 10 (15%
		75-<100: 7 (10%)
		≥ 100: 33 (48%)
ANC 10^9/L	Median 1.50 (0.11, 7.10)	< 0.5: 10 (15%)
		0.5- <1: 9 (13%)
		1-1.5: 16 (23%)
		> 1.5: 34 (49%)

- **RBC transfusion dependent: 27 (39%) N= 37 with Hgb < 90 g/L**
- **Platelet transfusion dependent: 6 (9%) N= 29 < 75 X 10^9**

Safety Results: Grade ≥ 3 Treatment-Emergent Adverse Events in >10% of Patients (Independent of Attribution)

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Preferred Term	Total in Cycles 1- 2 (N=66)	Total for Treatment Duration (N=66)
Neutropenia	30 (45.5%)	38 (57.6%)
Thrombocytopenia	26 (39.4%)	36 (54.5%)
Anemia	16 (24.2%)	27 (40.9%)
Leukopenia	13 (19.7%)	15 (22.7%)
Febrile Neutropenia	9 (13.6%)	19 (28.8%)
Pneumonia	3 (4.5%)	10 (15.2%)

- Safety profile consistent with that of decitabine
- Most grade 3 or higher events related to myelosuppression
- Febrile neutropenia and pneumonia increased with duration of treatment often reflecting progressive disease

There were no deaths in the first 56 days in patients receiving ASTX727.
A single subject died on study day 28 but had received IV decitabine cycle 1 and did not receive ASTX727
Total of subjects treated excludes 3 subjects who received IV decitabine cycle 1 but did not receive ASTX727

Results: ASCERTAIN Efficacy Response in Lower-Risk Pts[1]

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Response Category	Treated Patients (N=69[a]), n (%)	95% CI
Complete response (CR)	16 (23.2%)	(13.9, 34.9)
Partial response (PR)	0	
Marrow CR (mCR)	18 (26.1%)	(16.3, 38.1)
mCR with hematologic improvement	9 (13.0%)	(6.1, 23.3)
Hematologic improvement (HI)	5 (7.2%)	(2.4, 16.1)
HI-erythroid[3]	1 (1.4%)	(0.0, 7.8)
HI-neutrophils[3]	0	
HI-platelet[3]	4 (5.8%)	(1.6, 14.2)
Overall response (CR + PR + mCR + HI)	39 (56.5)	(44.0, 68.4)

[1]Responses adjudicated by independent review committee per IWG 2006
[a] Includes 3 subjects who did not receive ASTX727 (received IV decitabine cycle 1 and did not continue)

For subjects with ≥ 5% bone marrow blasts (n=26):

- CR 7 (26.9%)
- mCR 11 (42.3%)

For the entire group (n=69):

- Median CR duration was 15.3 months
- Median duration of best response was 13.4 months
- Median time to first and best response were 3.0 months and 4.3 months, respectively
- 18 (26.0%) subjects proceeded to HCT

Results: Transfusion Independence

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	RBC Transfusion Dependent on Entry (N=27)	Platelet Transfusion Dependent on Entry (N=6)
Transfusion independent at 56-days	13 (48.1%) (28.7, 68.1)	4 (66.7%) (22.3, 95.7)
Transfusion independent at 84-days	11 (40.7%) (22.4, 61.2)	2 (33.3%) (4.3, 77.7)

Results: ASCERTAIN Leukemia-Free Survival in Lower Risk Patients

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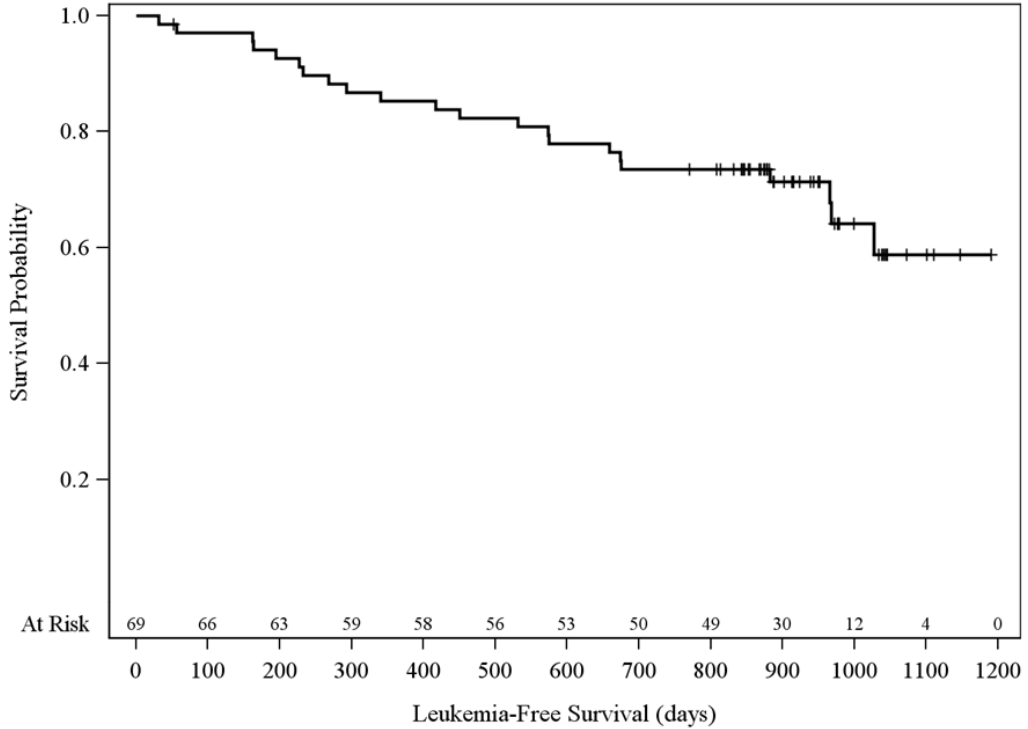

- **Median follow up is ~32 months.**
- **For events of leukemia or death, median time has not yet been reached.**
- **95% CI (31.7 months, NE).**

NE = not estimable

Results: ASCERTAIN Overall Survival in Lower Risk patients (N=69)

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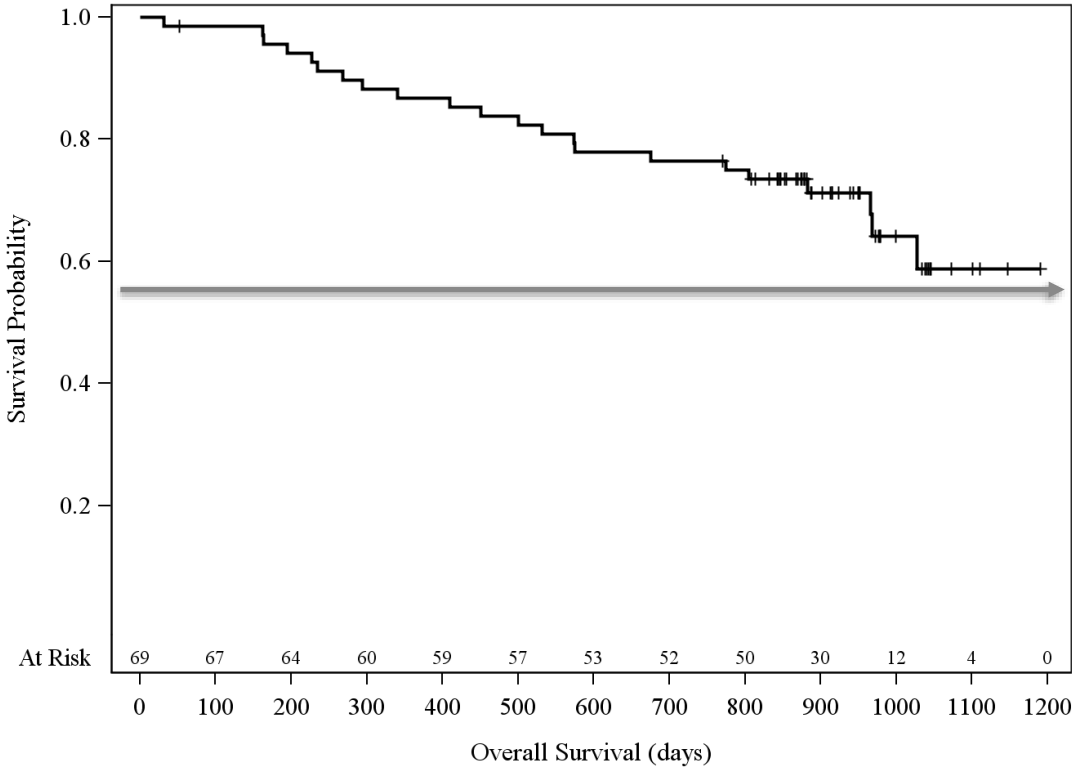

- **Median follow up is ~32 months.**
- **mOS has not yet been reached.**
- **95% CI (31.7 months, NE).**

NE = not estimable

Results: Overall Survival With and Without HCT

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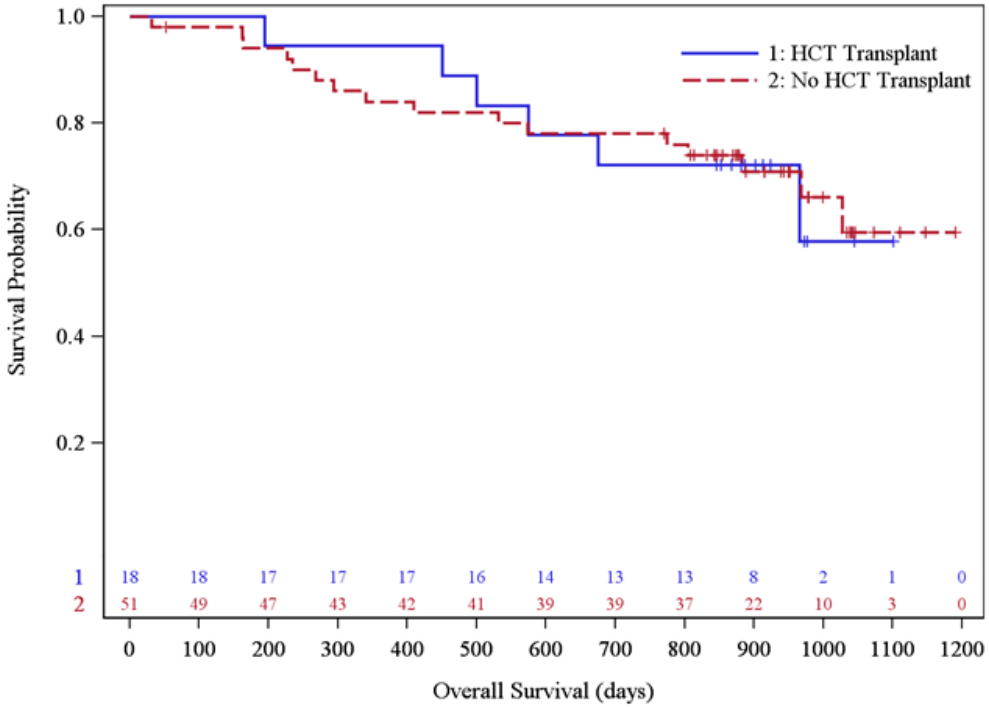

- 18 subjects proceeded to receive transplant for lower-risk MDS
- These ranged from 4.3-16 months after start of treatment
- There was no apparent survival difference in those transplanted and not transplanted

Conclusions

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- **In IPSS Int-1/LR MDS patients, oral decitabine/cedazuridine:**
  - Demonstrated a safety profile consistent with decitabine
    - No noteworthy new safety signals emerged
    - Treatment-emergent events were typically related to myelosuppression
  - Produced clinical efficacy similar to IV decitabine
    - With almost 32 months of follow up, median survival for this population has not been reached
    - CR rate of 26.9%, ORR of 51%, 26% of subjects were able to proceed to transplant
- **Oral decitabine and cedazuridine (35 mg/100 mg tablets) can be given safely to MDS patients with lower risk disease, though care must be taken to avoid infectious complications**
- **The activity of a lower dose of oral decitabine/cedazuridine is being studied in a low-risk population**

Acknowledgements

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We thank the investigators and the patients and their families for participating in the study.

- **This trial is registered at ClinicalTrials.gov under identifier *NCT03306264*.**