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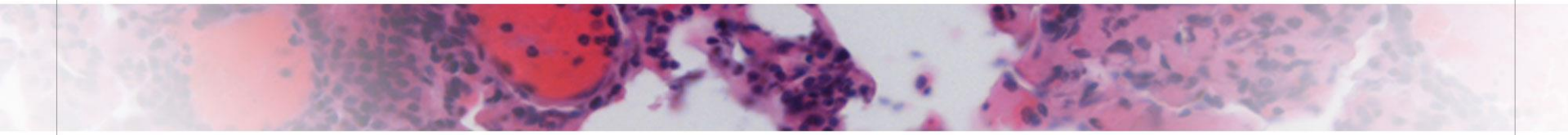

ASTX727-03: Phase 1 Study Evaluating Oral Decitabine/Cedazuridine (ASTX727) Low-Dose (LD) in Lower-Risk Myelodysplastic Syndromes (LR-MDS) Patients

On behalf of the ASTX727-03 Investigators Team

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Introduction (1): HMAs in Lower-Risk MDS

Hypomethylating agents (HMAs) are standard therapies in higher risk MDS but use in lower-risk disease (Int-1/LR) is less clear

- A prior study of low-dose decitabine (20 mg/m^2 vs. azacitidine 75 mg/m^2 x 3 q 28 d) suggested clinical benefit[1,2] leading to inclusion in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
- A recent randomized study of an oral formulation of azacitidine (CC-486) showed no difference in survival (median OS 17.3 vs. 16.2 months) compared to placebo
  - CC-486 exposure and schedule are different than parenteral azacitidine
  - Survival impacted by early infectious deaths in first 56 days (16 [15%] in CC-486 vs 6 [5.5%] placebo)[3]
- Optimizing dosing regimen for LR MDS is critical to balance clinical response with risk of myelosuppression

[1]Jabbour, et al. Blood 2017 Sep 28; 130(13):1514-1522 [NCT01720225]
[2]Sasaki, et al. NEJM Evid 2022 Aug 9; 1(10) [NCT01720225]
[3]Garcia-Manero, et al. JCO 2021 May 1; 39(13): 1426-1436 [NCT01566695]

Int - Intermediate; OS - overall survival

Introduction (2): Oral Decitabine/Cedazuridine

- Oral decitabine/cedazuridine (ASTX727)
  - fixed-dose (FDC) combination of 35 mg decitabine (DEC) and the cytidine deaminase (CDA) inhibitor cedazuridine (100 mg, C) produces equivalent PK AUC exposure compared to IV decitabine[1]

- ASCERTAIN: Phase 3 study led to the approval of oral DEC-C
  - LR MDS subjects who received the standard dose (SD) of ASTX727 for 5 days and demonstrated clinical benefit[2]

- Study ASTX727-03 (*NCT03502668*):
  - Phase 1 investigated multiple dosing regimens of oral DEC-C in LR MDS
  - With the Objective of obtaining clinical responses while avoiding myelotoxicity in patients who are expected to receive long-term treatment

AUC – are under the curve; IV – intravenous

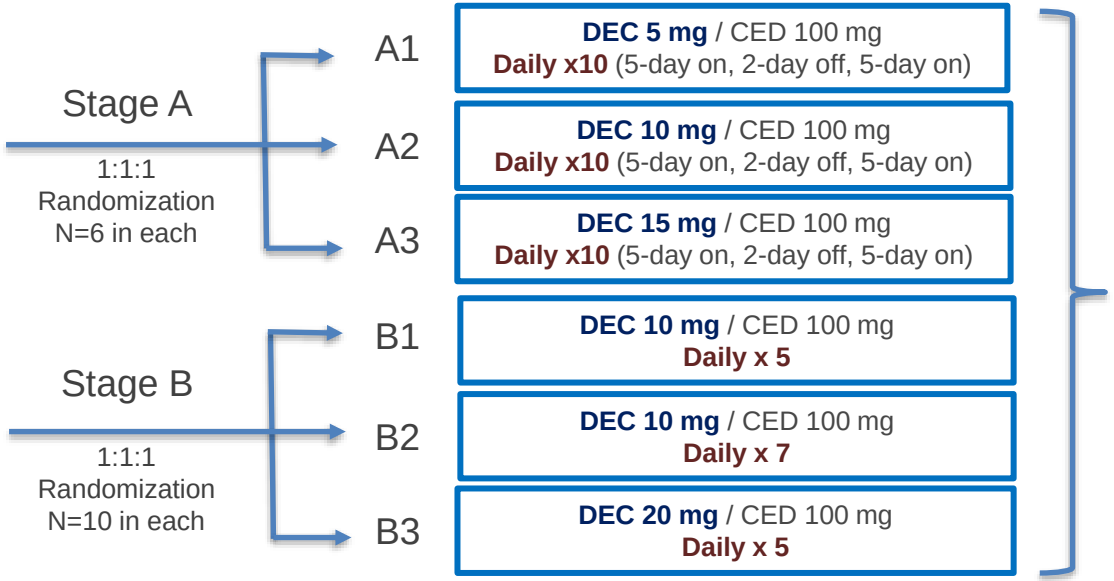
[1]Savona, et al, [ASH 2020 Abstract 1230]
[2]Garcia-Manero, et al, [ASH 2021 Abstract 66]

Phase 1 Study Design

Lower-Risk MDS (IPSS Low/Int-1 risk)

Cytopenia Requiring Treatment

- RBC transfusion dependence of >= 2 U or Hgb of < 8.5 g/dL, in 2 timepoints
  or
- ANC of 0.5 x 10^9/L in 2 timepoints,
  or
- Platelet count of < 50 x10^9/L in 2 timepoint



Major Entry Criteria:

- Cytopenia requiring treatment
- ECOG PS 0-2
- Adequate organ function
- Prior treatment with HMA is allowed
- Exclude CMML

Primary Endpoint

- Safety as determined by incidence of drug-related Grade ≥3 AEs or DLTs

Secondary Endpoint

- Hematologic Improvement (HI) based on modified 2016 IWG criteria
- Transfusion Independence
- Overall Survival (OS), Leukemia Free Survival (LFS)

IPSS – International Prognostic Scoring System; RBC – red blood cell; ANC – absolute neutrophil count; RP2D – recommended phase 2 dose; ECOG – Eastern Cooperative Oncology Group; PS – performance status; CMML – chronic myelomonocytic leukemia; AEs – adverse events; DLTs – dose-limiting toxicities; IWG – International Working Group

Patient Demographics/ Disease Characteristics

Characteristics		Total Treated N=47
Age in years (median, range)		76 (51-88)
Sex: Male/Female		30 (65%) / 17(35%)
Median weight, kg (range)/Median BSA, m2 (range)		80 (52-136) / 1.9 (1.5 – 2.5)
MDS, IPSS classification	Low-risk / Int-1	15 (32%) / 32 (68%)
Cytogenetics	Good	33 (70%)
	Intermediate	8 (17%)
	Poor	4 (9%)
Prior treatment for MDS		27 (57%)
ECOG PS	0/1/2	10(21%) / 34 (72%) / 3(6%)

Baseline Hematology Parameter	Median (Range)
Bone marrow blasts (%)	2.0 (0 8)
Hemoglobin (g/L)	81 (62-145)
Platelets (10^9/L)	123.8 (5-509)
ANC (10^9/L)	1.9 (0-7)
RBC transfusion dependent (TD)	21 (45%)
Platelets TD	3 (6%)

- Low and Int-1 IPSS risk category were 32% and 68%, respectively; 29 (60%) had an IPSS-R score of 3.5 or less
- Prior treatment for MDS was primarily ESA 16 (34%) and 13 (28%) each were treated with lenalidomide or parenteral HMAs

- RBC TD: 21 (45%), N= 34 (71%) with Hgb <90 g/L
- Platelet TD: 3 (6%), N= 17 (35%) with Platelet < 75 X 10^9/L

Study Treatment Exposure

	Cohort A1 5mg 10-day (N=10)	Cohort A2 10mg 10-day (N=4)	Cohort B1 10mg 5-day (N=11)	Cohort B2 10mg 7-day (N=11)	Cohort B3 20mg 5-day (N=11)	Total (N=47)
Number of cycles						
Median	8.0	12.0	10.0	5.0	13.0	9.0
Min, Max	1, 34	3, 15	1, 28	1, 35	1, 31	1, 35
Delayed cycles, n (%)						
1-3	3 (30.0)	1 (25.0)	4 (36.4)	5 (45.5)	1 (9.1)	14 (29.8)
4-6	2 (20.0)	1 (25.0)	4 (36.4)	1 (9.1)	3 (27.3)	11 (23.4)
>6	2 (20.0)	2 (50.0)	1 (9.1)	3 (27.3)	3 (27.3)	11 (23.4)
At least one delayed cycle	7 (70.0)	4 (100.0)	9 (81.8)	9 (81.8)	7 (63.6)	36 (76.6)
Dose-reduced cycles, n (%)						
1-3	5 (50.0)	1 (25.0)	2 (18.2)	3 (27.3)	1 (9.1)	12 (25.5)
4-6	0	0	1 (9.1)	1 (9.1)	1 (9.1)	3 (6.4)
>6	2 (20.0)	3 (75.0)	3 (27.3)	3 (27.3)	2 (18.2)	13 (27.7)
At least one dose-reduced cycle	7 (70.0)	4 (100.0)	6 (54.5)	7 (63.6)	4 (36.4)	28 (59.6)

- Subjects received a median of 9.0 cycles; with 47% receiving ≥ 10 cycles
- 77% subjects had at least 1 dose delayed cycle and 60% had at least 1 dose reduced cycle
- Cycle delays and dose reductions were observed more frequently in longer treatment days per cycles and higher doses per day

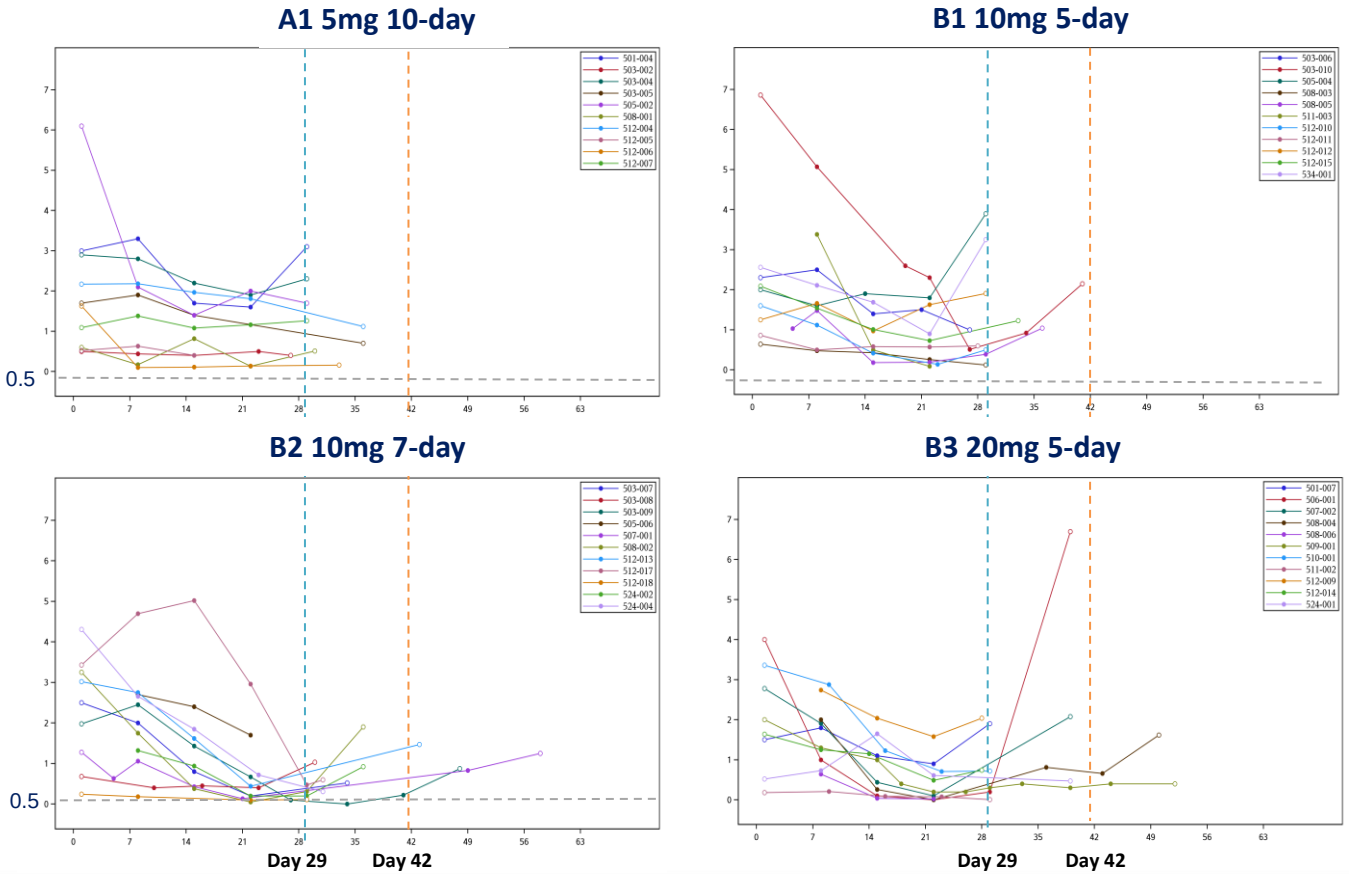
Dose Limiting Toxicity (DLT)

DLT frequency for each regimen

Stage	Ph1 Stage A			Ph1 Stage B		
Cohort	**A1**	**A2**	**A3**	**B1**	**B2**	**B3**
Regimen	5mg 10-day	10mg 10-day	15mg 10-day	10mg 5-day	10mg 7-day	20mg 5-day
DLT /Evaluable subject #	**3/10**	**4/4**	**-**	**3/11**	**7/10**	**7/11**

- All DLTs were related to grade 4 neutropenia (last longer than 10 days in Cycle 1)
- Cohort A3 was closed with no enrollment due to the high incidence of DLT observed in cohort A2
- The DLT incidences were proportional to the dose intensity (total DEC dose per cycle) and number of days of study drug administration

ANC Changes in Cycle 1



- Deeper neutrophil nadir points were observed in regimens with higher total DEC doses per cycle (B3)
- Slower neutrophil count recovery to baseline was observed in regimens with longer dosing periods (7-10 days; A1 and B2)
- Regimens with higher doses per cycle (B3) and longer dosing periods (B2) resulted in delay of Cycle 2

Safety Results: Treatment-Emergent Adverse Events in >20% of Patients (Independent of Attribution)

Preferred Term	Cohort A1 5mg 10-day (N=10)	Cohort A2 10mg 10-day (N=4)	Cohort B1 10mg 5-day (N=11)	Cohort B2 10mg 7-day (N=11)	Cohort B3 20mg 5-day (N=11)	Total (N=47)
Subjects with any AE	10 (100)	4 (100)	11 (100)	11 (100)	11 (100)	47 (100)
Total number of AEs	162	54	290	265	317	1093
Fatigue	6 (60.0)	2 (50.0)	4 (36.4)	5 (45.5)	4 (36.4)	21 (44.7)
Neutropenia	3 (30.0)	3 (75.0)	5 (45.5)	5 (45.5)	3 (27.3)	19 (40.4)
Neutrophil count decreased	1 (10.0)	2 (50.0)	2 (18.2)	5 (45.5)	8 (72.7)	18 (38.3)
Anaemia	1 (10.0)	2 (50.0)	5 (45.5)	3 (27.3)	5 (45.5)	16 (34.0)
Constipation	2 (20.0)	1 (25.0)	3 (27.3)	6 (54.5)	4 (36.4)	16 (34.0)
Diarrhoea	1 (10.0)	1 (25.0)	3 (27.3)	3 (27.3)	5 (45.5)	13 (27.7)
Decreased appetite	0	2 (50.0)	3 (27.3)	4 (36.4)	3 (27.3)	12 (25.5)
Cough	2 (20.0)	3 (75.0)	3 (27.3)	1 (9.1)	3 (27.3)	12 (25.5)
Pyrexia	3 (30.0)	1 (25.0)	4 (36.4)	2 (18.2)	1 (9.1)	11 (23.4)
Platelet count decreased	2 (20.0)	0	3 (27.3)	3 (27.3)	3 (27.3)	11 (23.4)
Oedema peripheral	2 (20.0)	1 (25.0)	4 (36.4)	1 (9.1)	3 (27.3)	11 (23.4)
Dyspnoea	0	2 (50.0)	4 (36.4)	2 (18.2)	2 (18.2)	10 (21.3)

- Safety profile consistent with that of standard (approved) DEC-C dosing
- No significant safety differences between the cohorts, with the exception of increase of AE frequency of decreased neutrophil counts observed in regiments with higher DEC doses per cycle (A2, B2, & B3)
- No clinically significant incidence of GI events at all the investigated doses were attributed to oral DEC-C

Efficacy Results: Hematologic Improvement (HI) and Transfusion Independence (TI)

	Phase 1 Stage A		Phase 1 Stage B			
	Cohort A1 5mg 10-day N=10	Cohort A2 10mg 10-day N=4	Cohort B1 10mg 5-day N=11	Cohort B2 10mg 7-day N=11	Cohort B3 20mg 5-Day N=11	Total
Total HI endpoint evaluable subjects	10	4	11	11	11	47
HI, n (%)	2 (20.0)	2 (50.0)	4 (36.4)	3 (27.3)	3 (27.3)	14 (29.8)
HI-E endpoint evaluable subjects, n	9	3	11	10	9	42
HI-E, n (%)	1 (11.1)	1 (33.3)	4 (36.4)	2 (20.0)	2 (22.2)	10 (23.8)
HI-P endpoint evaluable subjects, n	5	3	4	4	6	22
HI-P, n (%)	1 (20.0)	1 (33.3)	2 (50.0)	2 (50.0)	2 (33.3)	8 (36.4)
HI-N endpoint evaluable subjects, n	3	2	2	1	4	12
HI-N, n (%)	1 (33.3)	1 (50.0)	0	0	0	2 (16.7)
RBC TD at baseline, n	4	1	7	5	4	21
Post treatment RBC TI, n (%)	1 (25.0)	0	4 (57.1)	1 (20.0)	1 (25.0)	7 (33.3)
Platelet TD at baseline, n	0	1	1	0	1	3
Post-Treatment Platelet TI, n (%)	0	0	0	0	1 (100.0)	1 (33.3)

- All cohorts showed early emerging evidence of clinical activity (achieving HI and transfusion independence)

HI: Hematological Improvement based on IWG 2006 MDS response criteria
HI-E=erythroid response;
HI-N=neutrophil response;
HI-P=platelet response,
TD: Transfusion Dependence

Results: Pharmacokinetics (PK) Profile of Decitabine Exposure

Cohort	Daily Decitabine Dose (mg)	Cycle Cumulative Dose (mg)	% FDC Cycle Cumulative Dose	Total Cycle $_4AUC_{0\text{-}2h}$ (ng*hr/mL)	% FDC Total Cycle $AUC_{0\text{-}24h}$ (5 Days)
B1	10 x 5 days	50	29%	235	**27%**
B2	10 x 7 days	70	40%	269	**31%**
B3	20 x 5 days	100	57%	431	**50%**
Standard dose (SD)[1]	35 x 5 days	175	100%	856	**100%**

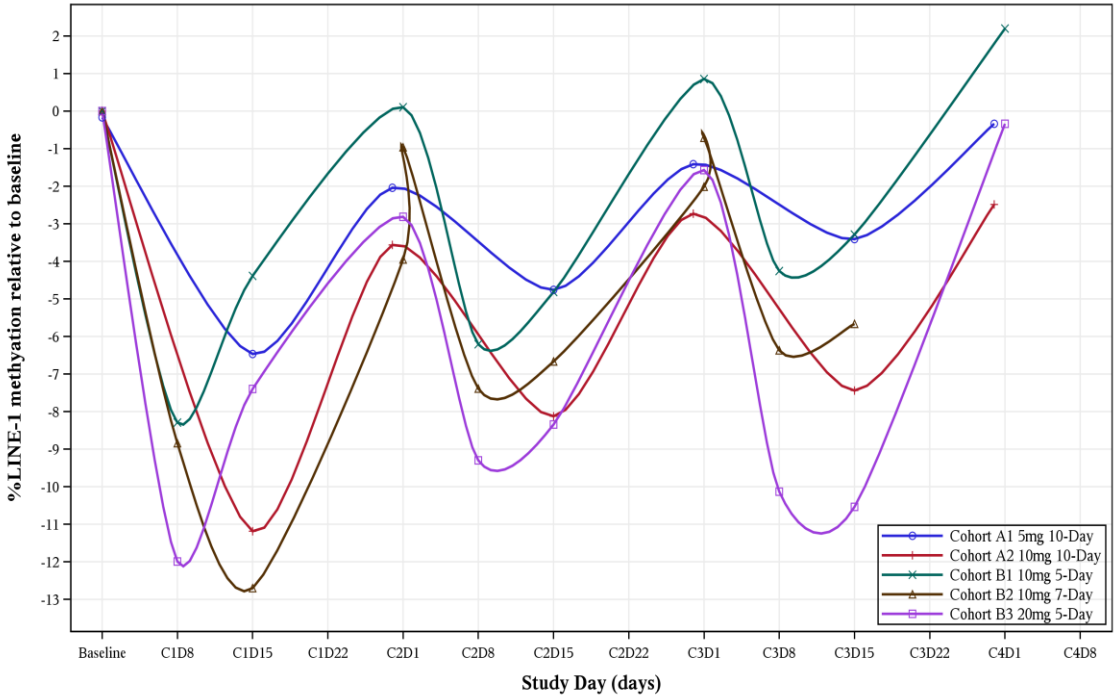
[1] ASTX727-02 phase 3 fixed-dose combination primary analysis (paired population): plasma decitabine results for AUC equivalence assessment; oral geometric least squares means

Total cycle $AUC_{0\text{-}24}$, is proportional to the total dose of decitabine per cycle

i. e. Cohort B1's cycle cumulative dose is 50 mg, which is 29% of the cycle cumulative dose of the SD of 35 mg over 5 days, and total cycle $AUC_{0\text{-}24h}$ is 27% of the total cycle $AUC_{0\text{-}24h}$ of the SD of 35 mg over 5 days

Results: Pharmacodynamic (PD) %LINE-1 Demethylation

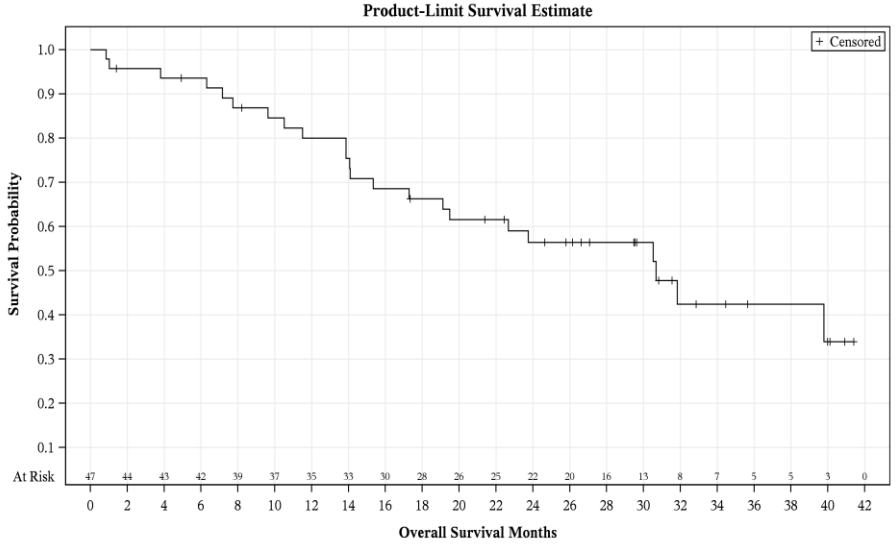
%LINE-1 Demethylation in Cycles 1-3 Per Cohort



- Peak %LINE-1 demethylation in Cohort A2 (10mg 10-day), B2 (10mg 7-day), and B3 (20mg 5-day) ranged from 11-13%; similar to the demethylation rate of the SD of 35mg DEC for 5 days
- Peak %LINE-1 demethylation in Cohort A1 (5mg 10-day) and B1 (10mg 5-day) was 5-7%, about half the demethylation rate of the SD of 35mg DEC for 5 days

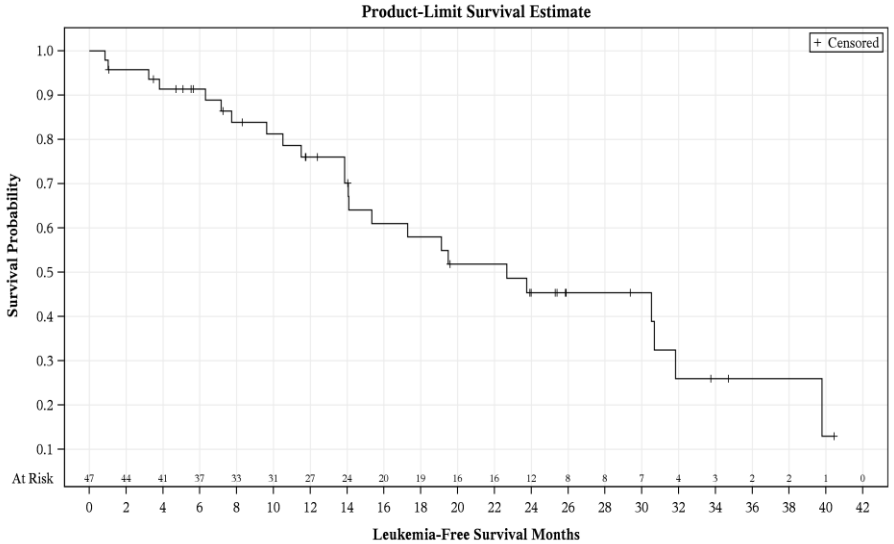
Results: Overall Survival and Leukemia Free Survival in Phase 1 (N=47)

Kaplan-Meier Curves of Overall Survival



- Median follow up is ~34 months
- mOS is 31 months 95% CI (19 months, NE)

Kaplan-Meier Curves of Leukemia-Free Survival



- mLFS is 23 months 95% CI (14, 32 months)

mOS – median overall survival; mLFS – median leukemia fee survival; NE – not evaluated

Conclusions

- Investigation of oral administration of various low-dose DEC-C regimens in IPSS Low/Int-1 risk MDS showed:
  - Safety profile consistent with standard dose of DEC-C
    - Treatment-emergent events were typically related to myelosuppression
    - Lower doses and shorter dosing regimens have fewer occurrences of neutropenia
    - No clinically significant GI adverse effects
  - All dosing cohorts demonstrated clinical activity
    - Endpoints evaluated: HI and transfusion independence, 31 months survival
    - Lower doses of decitabine administered orally appear to maintain clinical activity with lower levels of LINE-1 demethylation but less neutropenia
- Dose schedule 10 mg DEC/100 mg CED daily X 5 days (Cohort B1) was selected as the RP2D based on clinical efficacy and safety profile
- RP2D regimen is being currently compared to 35 mg DEC/100 mg CED for 3 days in a 28-day cycle in the ongoing Phase 2 study [*NCT03502668*]

Acknowledgements

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This trial is registered at ClinicalTrials.gov under identifier *NCT03502668*.