Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross-Over Phase 3 Study (ASCERTAIN) of an Oral Hypomethylating Agent ASTX727 (cedazuridine/decitabine) Compared to IV Decitabine

Guillermo Garcia-Manero[1], James McCloskey[2], Elizabeth Griffiths[3], Karen Yee[4], Amer Zeidan[5], Aref Al-Kali[6], Kim-Hien Dao[7], H Joachim Deeg[8], Prapti Patel[9], Mitchell Sabloff[10], Mary-Margaret Keating[11], Nancy Zhu[12*], Nashat Gabrail[13*], Salman Fazal[14], Joseph Maly[15], Olatoyosi Odenike[16], Aditi Shastri[17], Amy E DeZern[18], Casey O'Connell[19], Gail Roboz[20], Aram Oganesian[21*], Yong Hao[21*], Harold Keer[21], Mohammad Azab[21], Michael Savona[22]

On behalf of ASCERTAIN Investigators Team

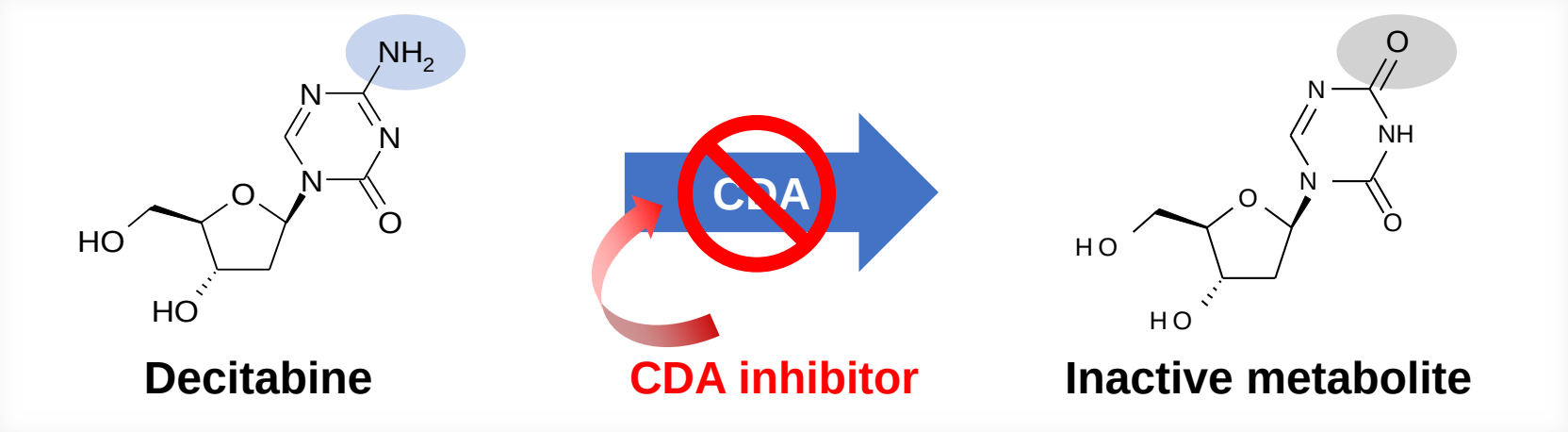
[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]John Theurer Cancer Center, Hackensack Medical Center, NJ; [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [4]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [5]Yale University and Yale Cancer Center, New Haven, CT; [6]Mayo Clinic, Rochester, MN; [7]Oregon Health & Science University, Portland, OR; [8]Fred Hutchinson Cancer Research Center, Seattle, WA; [9]University of Texas Southwestern Medical Center, Dallas, TX; [10]Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada; [11]Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; [12]University of Alberta, Edmonton, Alberta, Canada; [13]Gabrail Cancer Center, Canton, OH; [14]West Penn Hospital, Allegheny Health Network, Pittsburgh, PA; [15]Norton Cancer Institute, Louisville, KY; [16]University of Chicago, Chicago, IL; [17]Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY; [18]Johns Hopkins University Hospital, Baltimore, MD; [19]USC Keck School of Medicine, University of Southern California, Los Angeles, CA; [20]Weill Cornell Medicine, The New York Presbyterian Hospital, New York, NY; [21]Astex Pharmaceuticals, Inc., Pleasanton, CA; [22]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN

61st ASH Annual Meeting, Orlando, FL. Dec 7-10, 2019. Abstract #846

Clinicaltrials.gov NCT03306264

ASTX727 (cedazuridine/decitabine): Background

- Current HMA treatment poses significant patient burden due to 5–7 days per month of parenteral administration in a clinic setting
- Oral bioavailability of HMAs decitabine and azacitidine is limited due to rapid degradation by CDA in the gut and liver

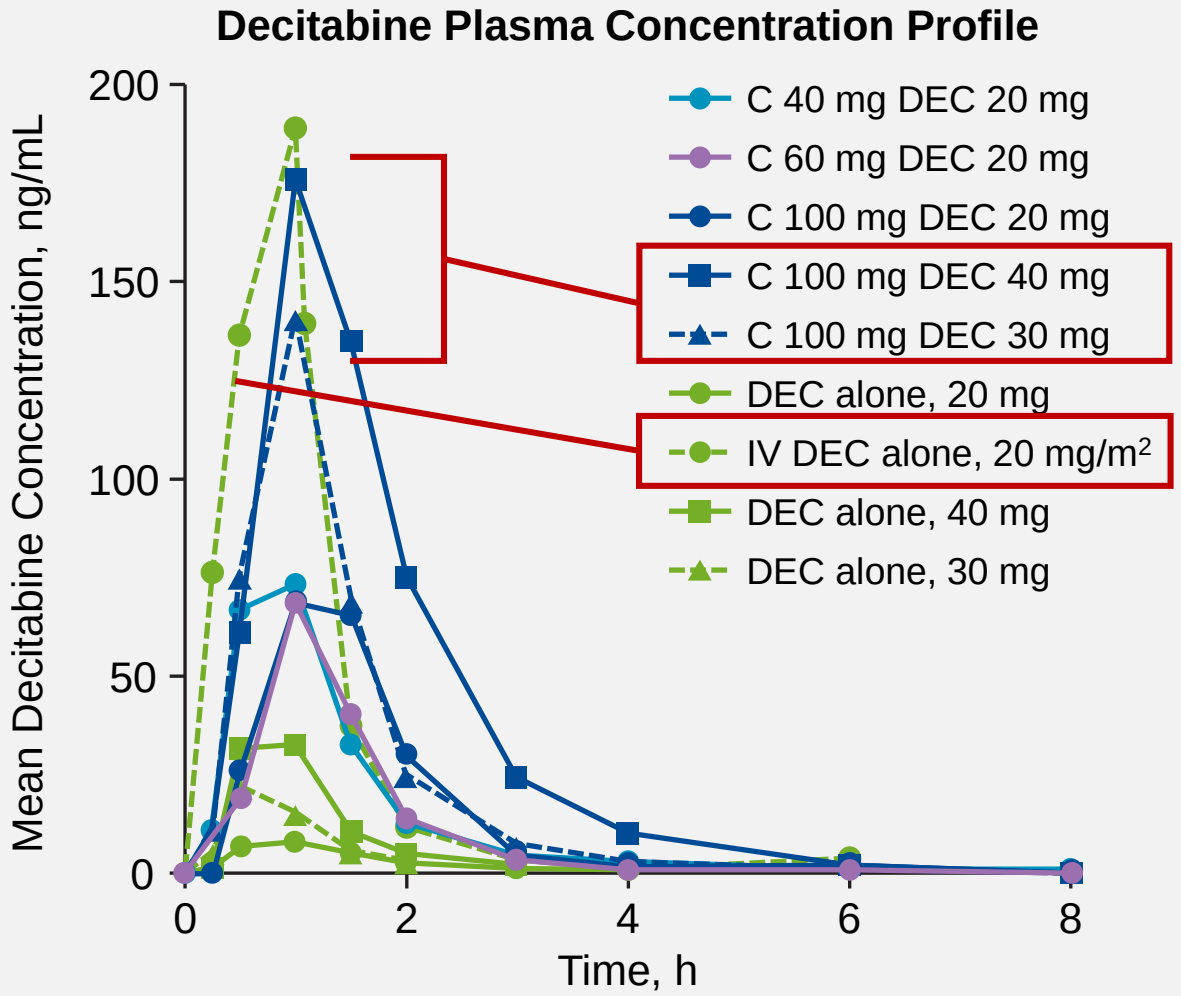


Decitabine **CDA inhibitor** **Inactive metabolite**

- Cedazuridine is a novel, potent, and safe CDA inhibitor
  - Large safety margin, with no adverse events at up to 200 mg/kg in monkeys (~2400 mg/m^2 human equivalent)

CDA, cytidine deaminase.

ASTX727 (Cedazuridine/Decitabine) Phase 1 Dose Finding Study in MDS and CMML



- Oral ASTX727 (cedazuridine 100 mg / decitabine 30 to 40 mg) achieved decitabine AUC 5-day exposures oral/IV ratio between 81% and 128%
- Oral ASTX727 (cedazuridine 100 mg / decitabine 35 mg) selected for Phase 2

Savona MR, et al. Lancet Hematology 2019;6:PE194-E203.

AUC, area under concentration-time curve; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome.

ASTX727 (Cedazuridine/Decitabine 100/35 mg) Phase 2 PK of Fixed-dose Combination (FDC) Tablet vs IV DEC

Primary Analysis: Plasma (ASTX727 FDC tablet vs IV DEC)

	N	IV DEC Geo. LSM	Oral ASTX727 FDC Geo. LSM	Ratio of Geo. LSM Oral/IV, % (80% CI)	Intrasubject (%CV)
Decitabine 5-day $AUC_{0\text{-}t}$ (h·ng/mL)	24	745	727	97.6% (80.48, 118.3)	53.8

IV DEC = IV decitabine 20 mg/m^2 IV 1-h infusion,
CI, confidence interval; CV, coefficient of variation; Geo. LSM, geometric least squares means.

- Oral/IV decitabine AUC ratio ~98%

Garcia-Manero G, et al. 15th International MDS symposium 2019, Copenhagen, Denmark.

ASTX727 Phase 2: Durable Clinical Responses in MDS/CMML Patients

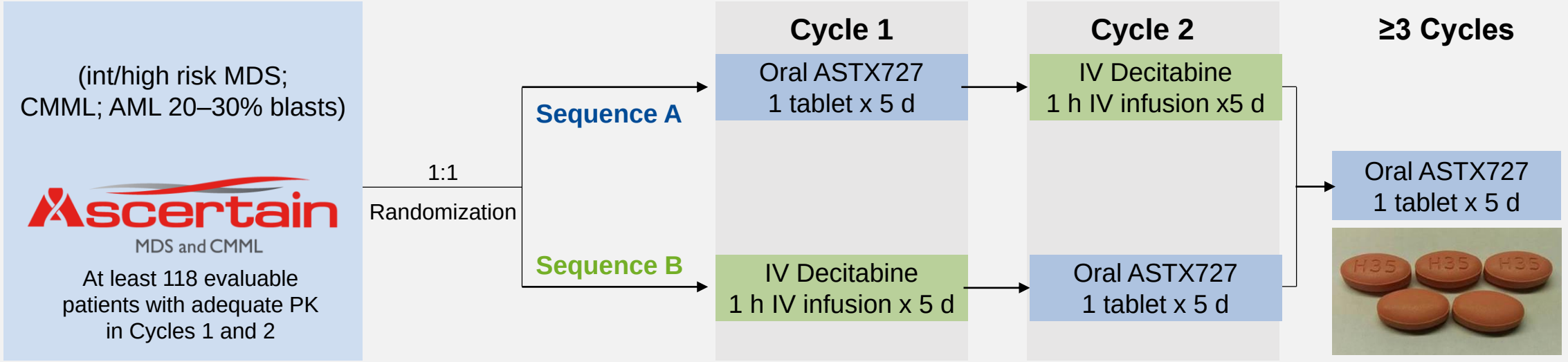
Best Response	N=80
Complete response (CR)	21.3%
Partial response (PR)	0
Marrow CR (mCR)	22.5%
mCR with hematologic improvement	7.5%
Hematologic improvement (HI)	16.3%
HI-erythroid	10%
HI-neutrophils	2.5%
HI-platelet	13.8%
Overall response (CR + PR + mCR + HI)	60%
RBCs transfusion independence (n=38)*	50%
Platelets transfusion independence (n=12)*	50%

Median FU: 24 months; median number of cycles: 7
CR median duration of response: 13.3 months
Median overall survival: 18.3 months

* No transfusion for at least 8 consecutive weeks in patients who were transfusion dependent at baseline.

Garcia-Manero 15th International MDS Symposium 2019.

ASTX727 Phase 3 Study (ASCERTAIN) in MDS/CMML Trial Design: Randomized Cross-Over



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

Primary endpoint

- Total 5-d decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

Secondary endpoints

- Efficacy: Response rate; Transfusion independence; duration of response; Leukemia-free and overall survival
- Safety of ASTX727
- Max LINE-1 demethylation

ASTX727 Phase 3 Baseline Characteristics Randomized Treated Population

		Sequence A[1] N=66	Sequence B[2] N=67	Total Treated N=133
Median age, y (range)		70 (44-85)	72 (49-88)	71 (44–88)
Sex	Male	64%	67%	65%
	Female	36%	33%	35%
Median weight, kg (range)		79 (45-158)	85 (51-127)	83 (45 -158)
Median BSA, m^2 (range)		1.93 (1.4-2.9)	2.0 (1.5-2.6)	1.99 (1.4 - 2.9)
CMML		8%	16%	12%
MDS, IPSS classification	High risk	21%	11%	16%
	Int-1 and 2	65%	63%	64%
	Low risk	6%	10%	8%
Transfusion dependent	RBCs	39%	39%	39%
	Platelets	9%	6%	7.5%
ECOG PS	0	38%	45%	41%
	1	62%	55%	59%

[1] Oral ASTX727 in Cycle 1 → IV decitabine in Cycle 2
[2] IV decitabine in Cycle 1 → Oral ASTX727 in Cycle 2

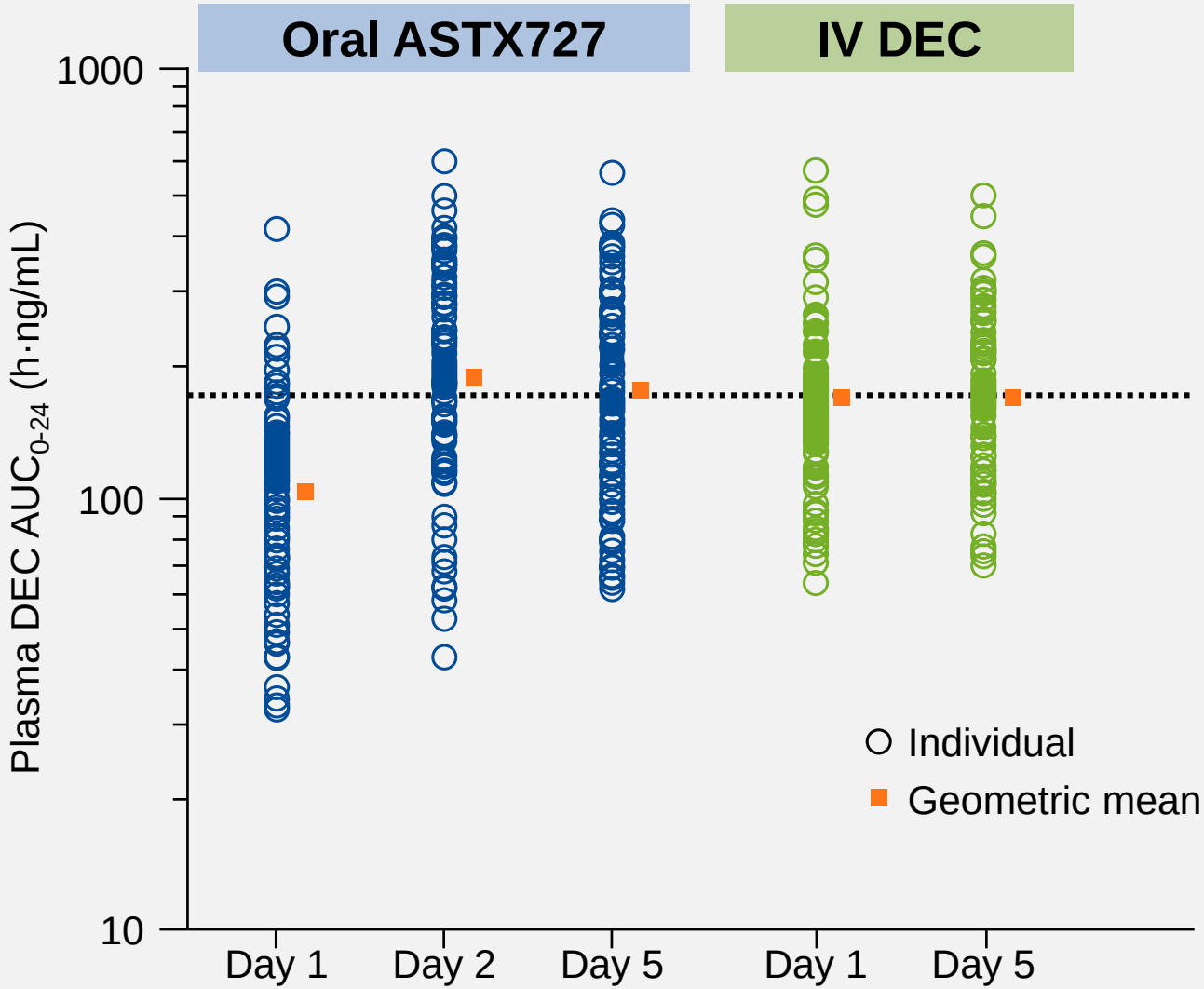
Primary Endpoint (5-day Decitabine AUC Equivalence)

Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
		N	Geo. LSM	N	Geo. LSM		
Primary Analysis	**Paired[1]**	**123**	**864.9**	**123**	**855.7**	**98.9 (92.7, 105.6)**	**31.7**

[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

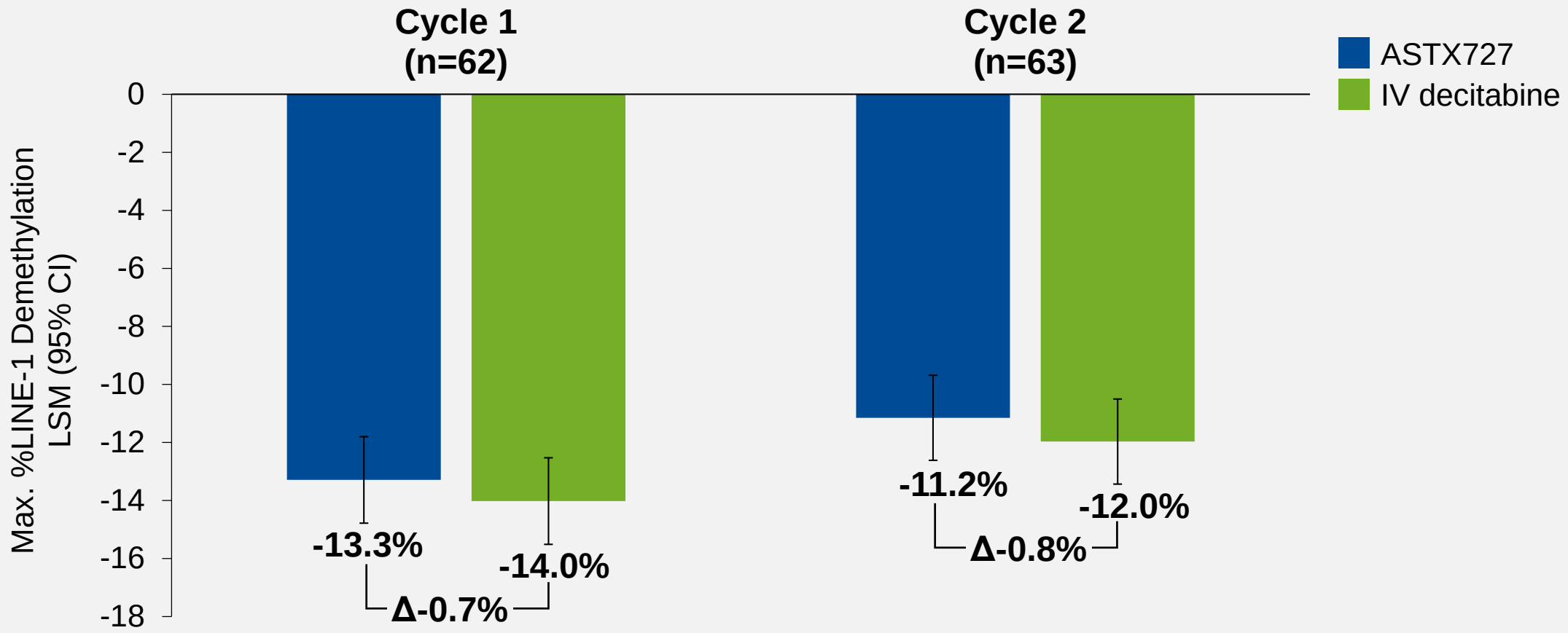
- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All Sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Decitabine Individual AUC_{0-24} Oral ASTX727 and IV Decitabine



- Individual decitabine exposures from oral fixed-dose ASTX727 dosing largely overlapped with IV decitabine BSA-based dosing

Pharmacodynamics (*LINE-1* DNA Demethylation in Cycles 1 and 2)



- No significant difference in *% LINE-1* DNA demethylation between ASTX727 and IV decitabine (<1% difference in each cycle)

Efficacy: Preliminary Response in MDS/CMML Central Review by Independent Review Committee (IRC)

	Evaluable Patients[1] N=101 n (%)
Complete response (CR)	12 (11.9%)
Partial response (PR)	0
Marrow CR (mCR)	46 (45.5%)
mCR with hematologic improvement	14 (13.9%)
Hematologic improvement (HI)	7 (5.3%)
HI-erythroid	2 (2.0%)
HI-neutrophils	1 (1.0%)
HI-platelet	6 (5.9%)
Overall response (CR + PR + mCR + HI)	65 (64.4%)
Stable disease	28 (27.7%)
Progressive disease	8 (7.9%)

[1] Due to short median follow up (~ 5 months) at data cutoff, 32 patients could not be evaluated for response by the Central IRC. Response was assessed by IWG 2006 criteria

Longer term follow up response assessment and molecular/cytogenetic analyses are pending

Preliminary Transfusion Independence Results[1]

		≥8 weeks	≥12 weeks	≥16 weeks
RBC	Transfusion dependent at Baseline, n=52			
	Post-treatment transfusion independent, n (%)	17 (32.7%)	11 (21.2%)	8 (15.4%)
Platelets	Transfusion dependent at Baseline, n=10			
	Post-treatment transfusion independent, n (%)	3 (30.0%)	1 (10%)	1 (10%)

[1] Pending longer term follow-up

Safety: Most Common All Grades AEs in the First 2 Randomized Cycles (All Causality)

Patients, n (%)	**IV Decitabine** Cycle 1 or 2 **N=132***	**ASTX727** Cycle 1 or 2 **N=130***
Thrombocytopenia	50 (37.9%)	57 (43.8%)
Neutropenia	42 (31.8%)	46 (35.4%)
Anemia	42 (31.8%)	48 (36.9%)
Fatigue	22 (16.7%)	31 (23.8%)
Constipation	25 (18.9%)	21 (16.2%)
Nausea	21 (15.9%)	23 (17.7%)
Leukopenia	22 (16.7%)	25 (19.2%)
Diarrhea	14 (10.6%)	19 (14.6%)
Febrile neutropenia	10 (7.6%)	18 (13.8%)
Headache	18 (13.6%)	19 (14.6%)

*2 patients received only IV decitabine, and 1 patient received only ASTX727.

- None of the differences was statistically significant (All *P values* ≥ *0.10*)
- GI AEs Grade ≥ 3 incidence <1% for each of ASTX727 and IV decitabine in Cycles 1 or 2

Oral ASTX727 (Cedazuridine/Decitabine) Summary

- **PK:** Oral ASTX727 fixed-dose tablet (cedazuridine/decitabine 100/35 mg) achieved ~99% of decitabine 5-day AUC systemic exposures compared with IV decitabine 20 mg/m^2 (primary endpoint)
  - Robust results confirmed in all AUC sensitivity and secondary analyses
- **PD:** Oral ASTX727 achieved almost identical PD effect to IV decitabine (<1% difference in *LINE-1* % DNA demethylation)
- **Efficacy:** Durable clinical responses, 50% transfusion independence, and median survival of 18.3 months observed in Phase 2 with long term follow up consistent with IV decitabine
  - Supportive preliminary clinical responses, and transfusion independence results from Phase 3 pending longer term follow-up
- **Safety:** No significant differences in AEs including GI AEs between oral ASTX727 and IV decitabine in the randomized first 2 cycles
- **Conclusion:** Oral ASTX727 is the only oral HMA in development with systemic exposure equivalent to its IV form, providing a more patient friendly oral dosing alternative to IV decitabine

Acknowledgments

- All participating patients
- All ASCERTAIN study investigators and all site staff, nurses, study coordinators, caregivers, and our partner CROs