Successful Emulation of IV Decitabine Pharmacokinetics with an Oral Fixed-Dose Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine, in Subjects with Myelodysplastic Syndromes (MDS): Final Data of Phase 1 Study

On Behalf of the ASTX727 Investigative Team

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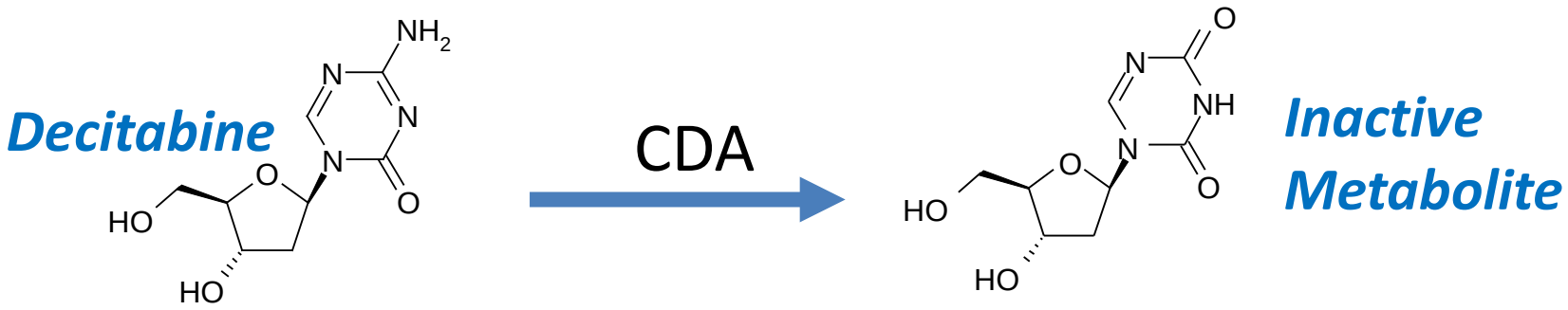
Background and Clinical Hypothesis

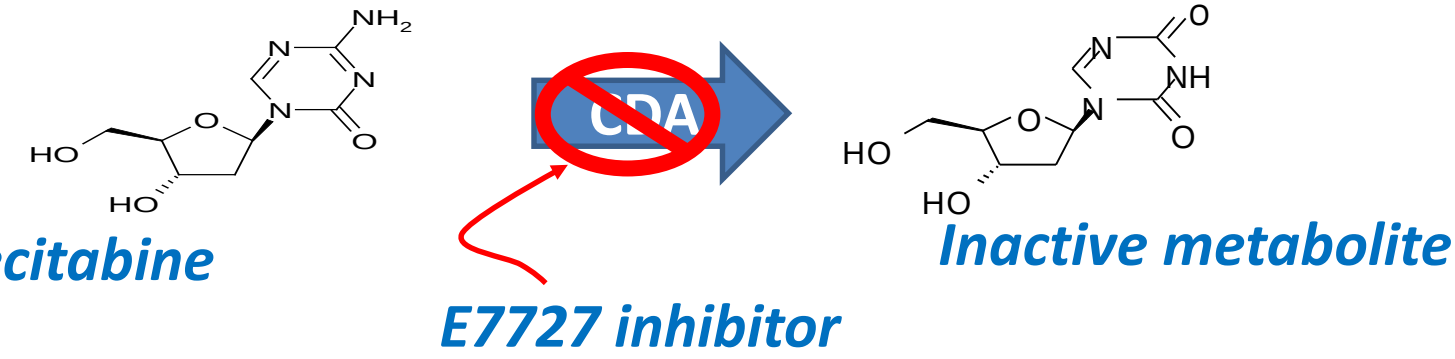
- Intravenous (IV) Decitabine(DAC) is an approved therapy for MDS
- Oral bioavailability of DAC is low due to degradation in the gut by cytidine deaminase (CDA)



- MDS treatment requires continued treatment for long periods.
- An oral decitabine would provide significant benefit
- Development of a potent safe CDA inhibitor should enable decitabine oral bioavailability

E7727 – a Potent, Orally Active CDA inhibitor

- E7727, a novel potent CDA inhibitor (IC_{50} is 0.28±0.06 µM)
- Pharmaceutically stable unlike other known CDA inhibitors such as tetrahydrouridine (THU)
- Safe and well tolerated in animals with no observed adverse events up to 1000 mg/kg (mice) and 200 mg/kg (monkey)
- Administering decitabine orally with low dose E7727 (1 mg/Kg) increases decitabine exposure 14-fold in animals (monkey)



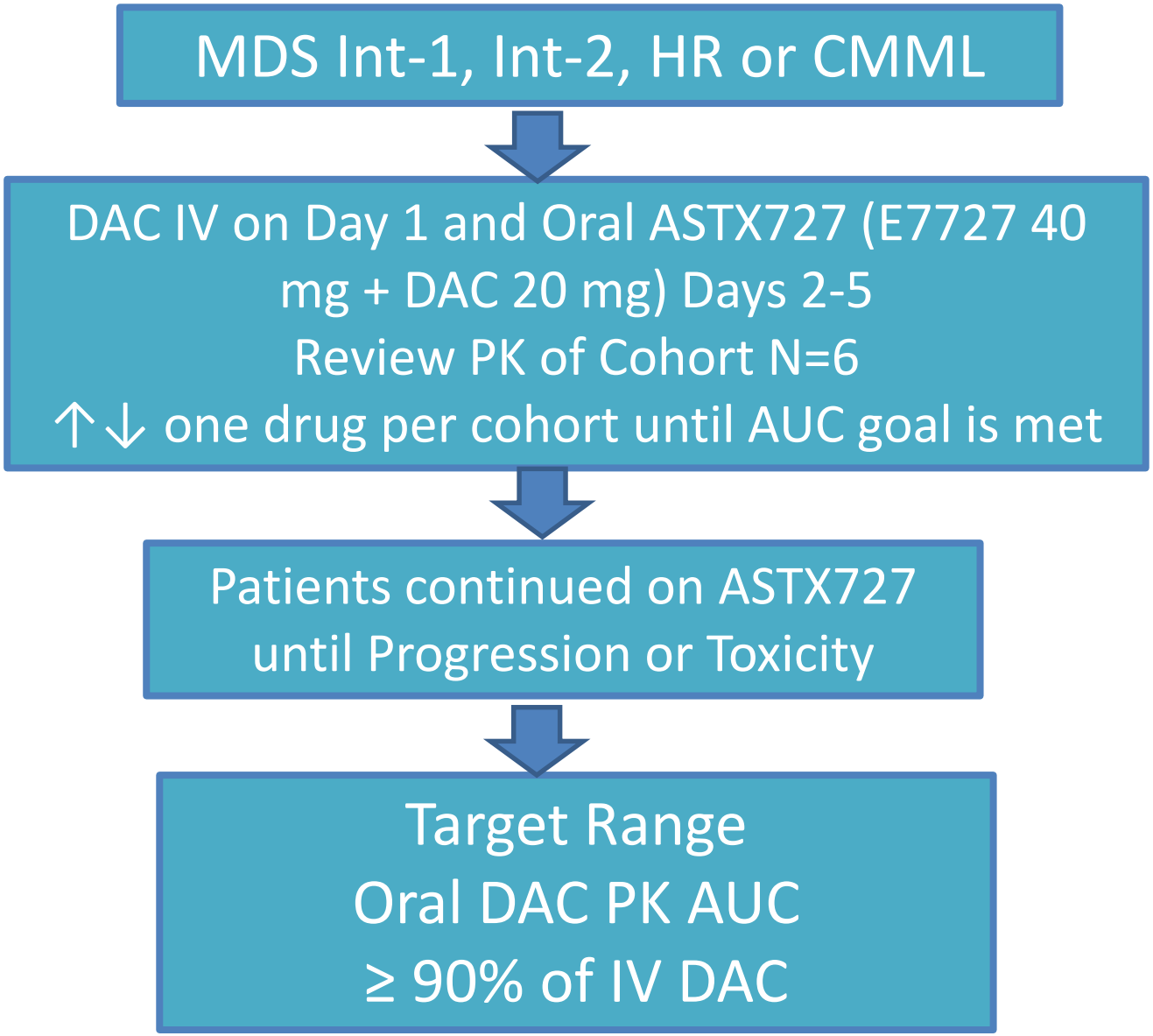
ASTX727: A New Oral HMA – Phase 1 Study

- ***ASTX727*** is a new oral combination drug of both ***decitabine (DAC)*** and the new CDA inhibitor ***E7727***
- We designed a Phase 1 dose escalation study of ASTX727
- Primary Objective: To emulate DAC IV (20 mg/m^2) PK (AUC exposure) with a safe dose of oral ASTX727
- Secondary Objectives: Clinical Response, and PD (LINE-1 demethylation) of oral ASTX727

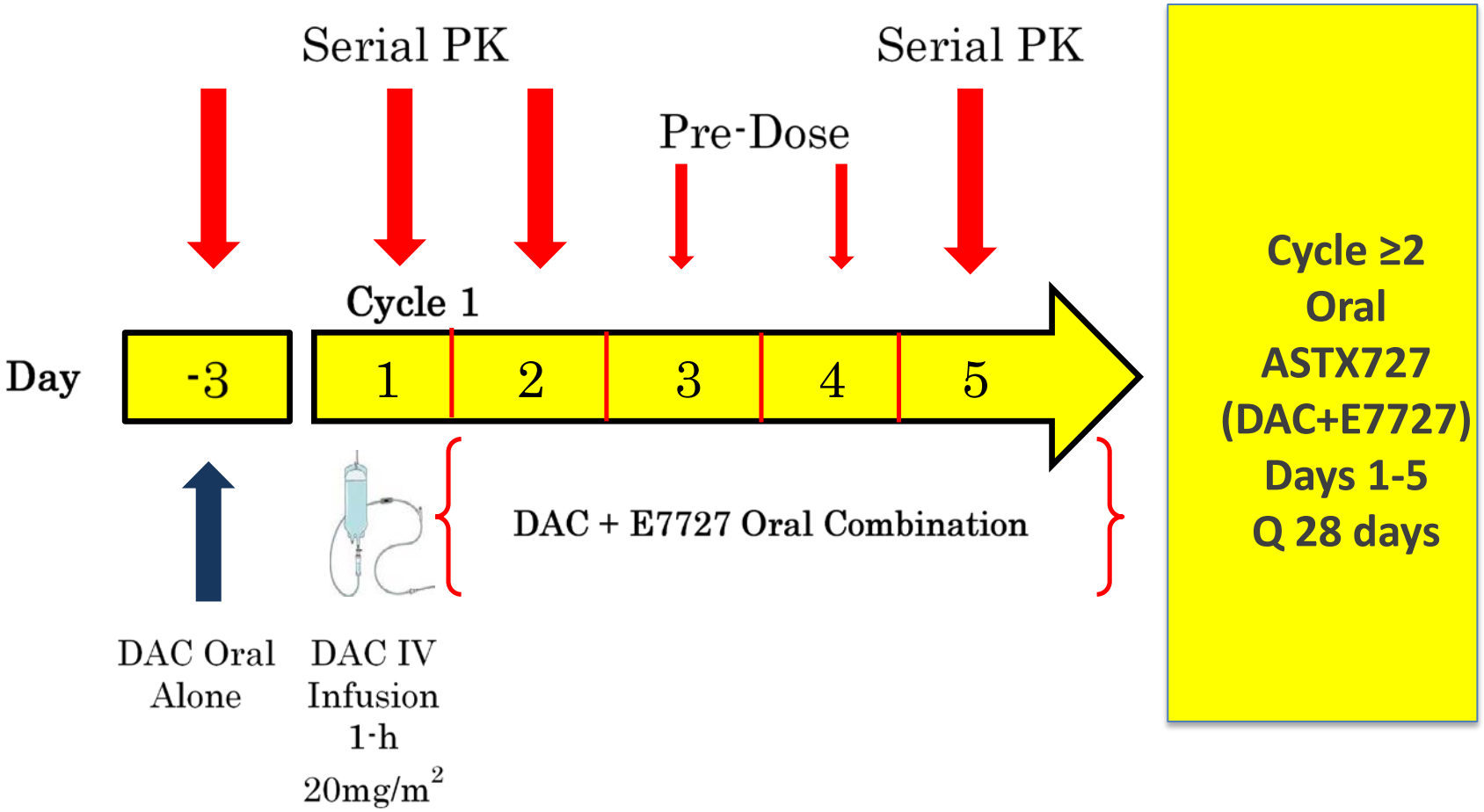
ASTX727 Phase 1 Study: Major Eligibility Criteria

- Adult patients with MDS Int-1; Int-2; or High Risk IPSS score, or CMML
- All prior treatments (including HSCT) allowed except more than one cycle of DAC IV
- Adequate hepatic and renal function
  - Bilirubin ≤2 ULN; AST/ALT ≤ 2.5 ULN
  - Serum creatinine ≤ 1.5 ULN or Cr CL >50 ml/min
- Patients with AML (≥ 20% blasts in BM or PB) were excluded

ASTX727 Phase 1 Study Design
Dose Escalation Scheme

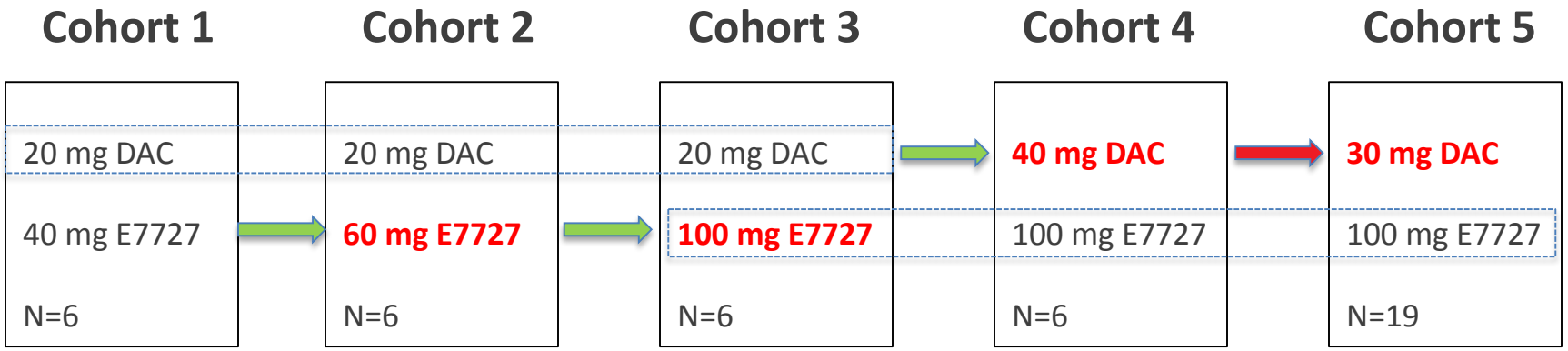


ASTX727 Phase 1 Study Design
Dosing and PK Schedule



ASTX727 Phase 1 Results
Disposition and Study Cohorts

- Goal: Oral ASTX727 combination with DAC AUC ≥90% of DAC IV AUC
- Maximum Tolerated Dose (MTD) not a goal



Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
No DLT AUC < 90% IV Escalate E7727	No DLT AUC < 90% IV Escalate E7727	No DLT AUC < 90% IV Escalate DAC	No DLT AUC >110% IV De-escalate DAC	No DLT AUC ~ 90% Expand

20 mg /m^2 IV DAC Day 1 Cycle 1 used as the intra-patient comparator N=43

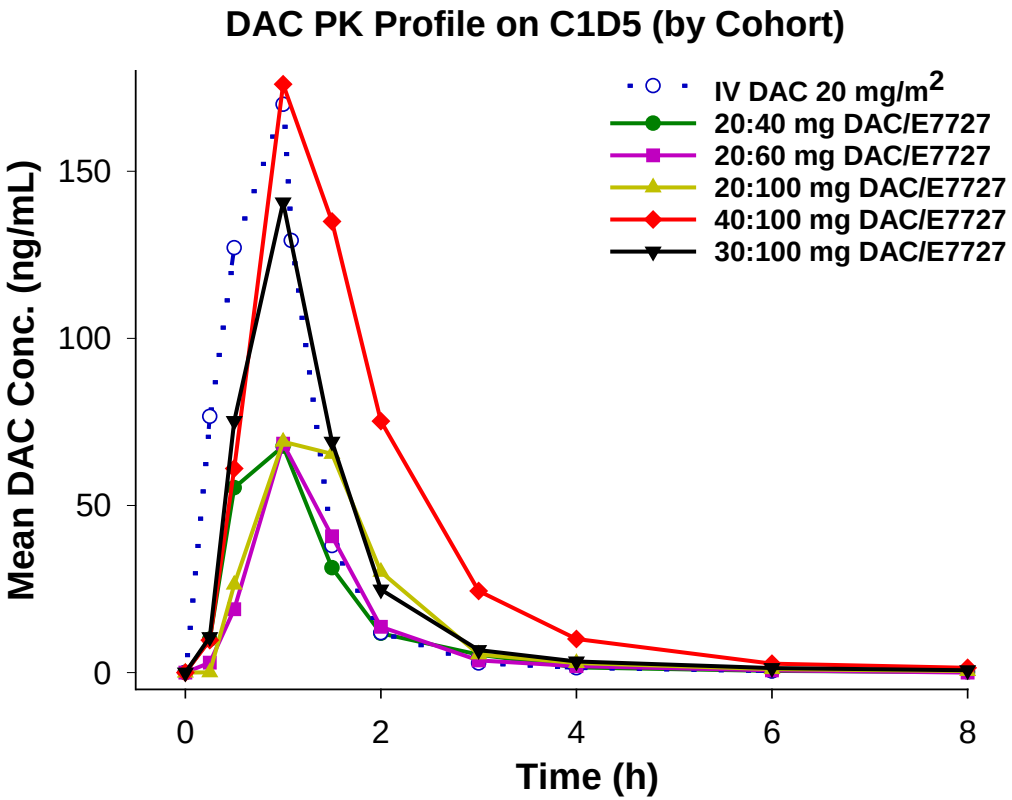
ASTX727 Phase 1 Results
Patient Characteristics

Cohort Number	1	2	3	4	5	Total
Number of patients	6	6	6	6	19*	43
Age Median (range)	68 (59-81)	71 (63-79)	72 (70-83)	76 (66-85)	73 (59-86)	**71 (59-86)**
Sex M n (%) F n (%)	3 (50) 3 (50)	5 (83) 1 (17)	3 (50) 3 (50)	4 (67) 2 (33)	15 (79) 4 (21)	**30 (70)** **13 (30)**
ECOG PS n (%) 0-1 2	6 (100) 0	5 (83) 1 (17)	5 (83) 1 (17)	5 (83) 1 (17)	16 (84) 3 (16)	**37 (86)** **6 (14)**
IPSS** n (%) MDS INT-1 MDS INT-2 MDS High Risk CMML	4 (67) 2 (33)	2 (33) 1 (17) 1 (17) 2 (33)	2 (33) 3 (50) 1 (17)	2 (33) 1 (17) 2 (33) 1 (17)	10 (53) 3 (27) 4 (7) 2 (7)	**20 (47)** **7 (16)** **10 (23)** **6 (14)**
Prior Treatment n (%) Prior HMA n (%)	1 (17) 0	2 (33) 1 (17)	1 (17) 0	6 (100) 4 (67)	13 (68) 10 (53)	**23 (53)** **15 (35)**

*Includes 13 from dose expansion

**International Prognostic Scoring System for MDS (Cheson et al, 2000)

ASTX727 Phase 1 Results
IV DAC PK (Day 1) vs Oral (Day 5) by Cohort



- ASTX727: Co-administration of E7727 with DAC enhances oral DAC bioavailability
- Dose-dependent increase in DAC exposure with escalation of either drug
- At fixed ASTX727 dose of 100 mg E7727 and DAC 40 mg the oral DAC exposure exceeded that of IV DAC.

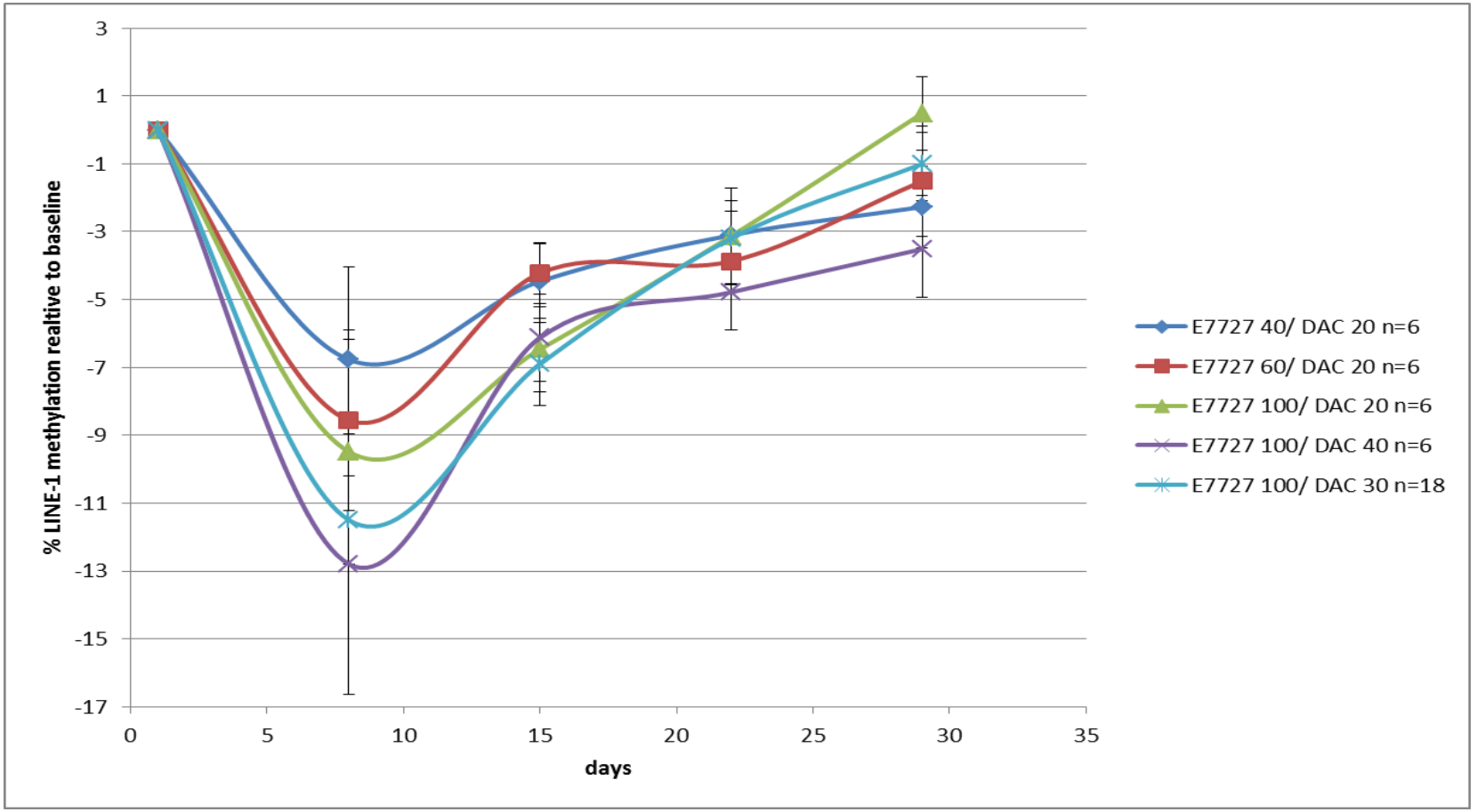
ASTX727 Phase 1 Results
5 Days total DAC AUC: Oral/IV

	ASTX727 Oral Dose (mg)			5-Days Total (AUC_{last})		% of AUC
Cohort	DAC[1]	E7727	N	Oral	IV	(Oral/IV)
1	20	40	5[2]	260	753	**35%**
2	20	60	6	346	899	**39%**
3	20	100	6	482	992	**49%**
4	40	100	6	1120	775	**144%**
5	30	100	19[3]	701	852	**85%**

[1] DAC oral dose not adjusted by Weight or BSA
[2] One significant outlier excluded from the PK analysis
[3] Includes 13 patient dose expansion

- Cohort 4 Oral DAC (at 40 mg) exposure achieved primary objective and exceeded that of IV DAC at 20 mg/m2 (Oral/IV 144%)
- Cohort 5 Oral DAC (at 30 mg) exposure was 85% of IV DAC at 20 mg/m2
- Oral DAC dose of 35 mg in ASTX727 (Ongoing Phase 2) should achieve AUC of ~ 85-140% of IV DAC

ASTX727 Phase 1 Results
PD (LINE-1 demethylation) by Cohort



- ASTX727 cohorts 4 and 5 achieved LINE-1 demethylation from baseline of > 10% (comparable to historical data of DAC IV)

ASTX727 Phase 1 Results
Clinical Activity

Clinical Response [1]	N = 43 [2] N (%)
Complete Response (CR)	4 (9%)
Marrow Complete Response (mCR)	2 (5%)
Hematologic Improvement (HI)	6 (14%)
Transfusion Independence Response	7/23 (31%)
Still On Treatment	10 (23%)

[1] Assessed by IWG criteria (Cheson et al, 2006)

[2] All treated patients included in the analyses

- Responses were observed in all cohorts and in patients previously treated with HMAs (56% of patients in Cohort 4-5 were previously treated with azacitidine)
- Five patients went on to Hematopoietic Stem Cell Transplant (HSCT)
- Median of 5 cycles was administered (Range 1-26)

ASTX 727 Phase 1 Results
Safety (AEs)

Most Common Grade ≥ 3 AEs regardless of relationship to ASTX727

Cohort / Adverse Event	1 n=6 N	2 n=6 N	3 n=6 N	4 n=6 N	5 n=19 N	Total n=43 N (%)
Thrombocytopenia	4	1	4	1	6	16 (37)
Anemia	3	1	3	2	4	13 (30)
Neutropenia	3	2	2	1	4	12 (28)
Febrile Neutropenia	1	1	2	3	2	9 (21)
Pneumonia	0	1	0	2	3	6 (14)
Leukopenia	1	2	1	0	2	6 (14)
Sepsis	0	0	0	1	3	4 (9)

- **No reported Grade ≥ 3 GI AEs**

ASTX727 Phase 1 Results
Safety (Related AEs)

Most Common Grade ≥ 3 AEs reported as related to ASTX727

Adverse Event	Total n=43 N (%)
Thrombocytopenia	8 (18)
Neutropenia	4 (9)
Anemia	3 (7)
Bacteremia	1 (2)
C. Difficile colitis	1(2)
Pneumonia	1 (2)

ASTX727 Phase 1 Conclusions

- ***ASTX727***, an oral combination of a novel CDA inhibitor ***E7727*** with low doses of ***decitabine*** can emulate the PK and PD of IV decitabine
- ***ASTX727*** Safety is consistent with IV decitabine with no GI toxicity
- Clinical responses and DNA demethylation observed at all doses
- ***ASTX727*** Phase 2 trial is ongoing with the recommended doses of ***100 mg E7727+35 mg decitabine:***
  - Randomized Cross over Design comparing 5 days of ***oral ASTX727*** to 5 days of IV decitabine