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Preliminary Report of the Phase 1 Study of the DOT1L Inhibitor Pinometostat (EPZ-5676) in Children with MLL-r Acute Leukemia: Safety, Exposure and Evidence of Target Inhibition

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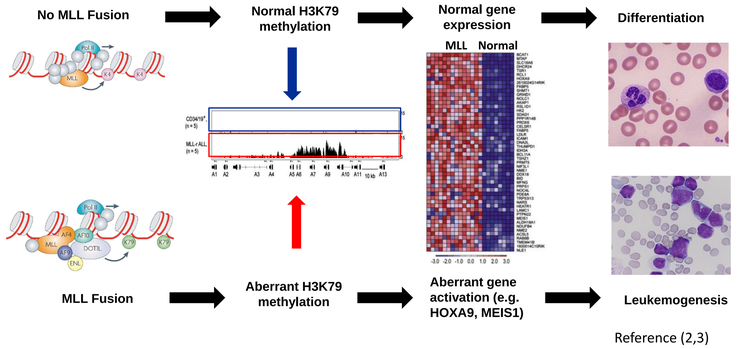
Background

MLL-rearranged (MLL-r) acute leukemia in children is characterized by young age at presentation and a poor overall prognosis despite multi-agent chemotherapy. Aberrant fusion proteins involving the MLL histone methyltransferase (HMT) recruit another HMT, DOT1L, to a multi-protein complex leading to aberrant methylation of histone H3 lysine 79 (H3K79) at MLL target genes. This results in enhanced expression of critical genes for hematopoietic differentiation, including HOXA9 and MEIS1, and has been established as a key mechanism for leukemogenesis in MLL-r leukemias (Krivstov, 2007). Pinometostat is a small molecule inhibitor of DOT1L with sub-nanomolar affinity and >37,000 fold selectivity against other HMTs. Treatment of MLL-rearranged cells and xenograft models with pinometostat led to reduced H3K79 methylation, decreased MLL target gene expression and selective leukemia cell kill (1).

DOT1L Promotes *MLL*-r Leukemia via Aberrant H3K79 Methylation



Reference (2,3)

Study Design and Objectives

Study Design:

Open label dose escalation and planned expansion at MTD for children with MLL-r relapsed/refractory leukemia (CNS 1 or 2)

Separate dose escalation (rolling six design):

- Starting dose: patients ≤ 1 year of age = 45 mg/m^2/day
  patients > 1 year of age = 70 mg/m^2/day

Objectives:

Primary: 1) Determine Maximum Tolerated Dose (MTD) and/or Recommended Phase 2 Dose (RP2D)
2) Evaluate safety profile and tolerability

Secondary: 1) Determine Pharmacokinetic profile of pinometostat
2) Investigate Pharmacodynamic effect in blood PBMC and bone marrow
3) Evaluate objective response

Results

Patient Characteristics (n=14)

Patient Characteristics		n (%)
Median age, yrs. (range)		4.2 (0.33 - 15)
Sex (M / F)		8/6
Diagnosis	AML: MLL-r	4 (29)
	ALL: MLL-r	8 (57)
	Mixed Lineage Leukemia	2 (14)
# of prior therapeutic regimens	1 - 2	4 (29)
	3 - 7	9 (65)
	>8	1 (7)
Prior allogeneic HCT		6 (42)
Dose administered (mg/m^2/day)	45	1 (7)
	70	6 (42)
	90	7 (50)

Clinical Safety

Adverse Events: in ≥4 patients (Regardless of Attribution)

Adverse event	All Grades n=14 (%)	Grade ≥3 n=14 (%)
Hypokalaemia	8 (57)	7 (50)
Anemia	7 (50)	5 (36)
Febrile neutropenia	7 (50)	7 (50)
Hypocalcaemia	7 (50)	3 (21)
Diarrhea	6 (43)	1 (7)
Lymphocyte count decreased	6 (43)	2 (14)
White blood cell count decreased	6 (43)	5 (36)
Platelet count decreased	5 (36)	4 (29)
Dry skin	4 (29)	0
Electrocardiogram QT prolonged	4 (29)	1 (7)
Hypertension	4 (29)	2 (14)
Hypophosphataemia	4 (29)	2 (14)
Nausea	4 (29)	1 (7)
Pain	4 (29)	0
Pleural effusion	4 (29)	2 (14)
Rash maculopapular	4 (29)	0
Respiratory failure	4 (29)	4 (29)

Non-Hematologic Grade ≥3 (Related)

Adverse Event	Dose (mg/m^2/day)	DLT	N (%)
Apnea	70	Yes	1 (7)
Decreased appetite	90	No	1 (7)
Elevated LFTs	90	Yes	2 (14)
Febrile neutropenia	70	No	1 (7)
Organizing pneumonia	90	No	1 (7)

Clinical Summary

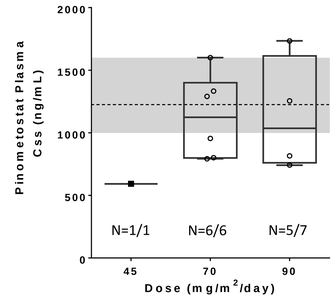
Older age cohort
- One DLT in six patients: 70 mg/m^2/day
- Two DLTs in seven patients: 90 mg/m^2/day

Younger age cohort
- No DLTs, continues dose escalation

Clinical efficacy
- No objective responses seen to date
- Decreased peripheral or marrow leukemic blasts: 7/14

Pediatric Plasma Exposure Comparable to Adults at Similar Doses

Plasma Pinometostat Css in Pediatric Patients 0-18 years of Age

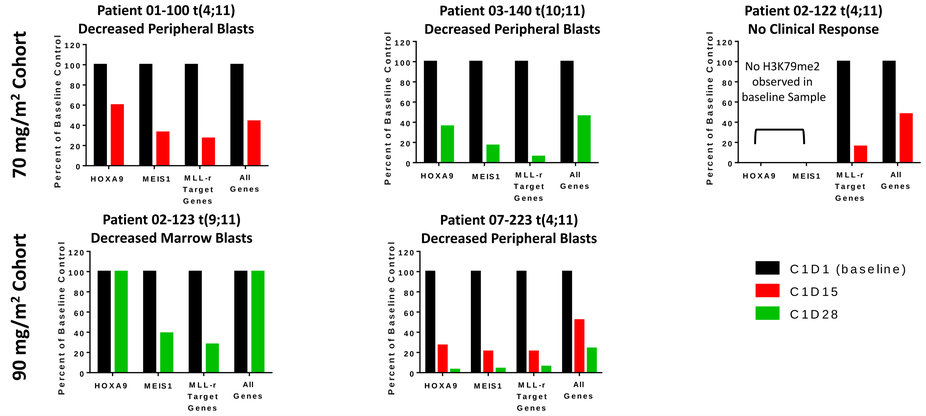


- Dotted line represents the median Css in adult patients at 90 mg/m^2/day
- Shaded area represents predicted Css range based on prior PBPK modeling at 90 mg/m^2/day

Tabulated Summary of CSF Exposure of Pinometostat in Pediatric Patients

Pt. ID	Dose mg/m^2/day	Age (y)	CSF Css (ng/mL)
01-100	70	11	<LLOQ (1mg/mL)
01-101	70	7	<LLOQ (1mg/mL)
02-121	70	4	<LLOQ (1mg/mL)
02-122	70	1	1.5
03-140	70	15	1.7
03-141	70	1	Not Determined
01-102	90	15	12
02-123	90	4	8
04-162	90	1	<LLOQ (1mg/mL)
07-223	90	13	<LLOQ (1mg/mL)
07-222	90	1	Not Determined
04-161	45	< 1	<LLOQ (1mg/mL)

Evidence of Pharmacodynamic Response Through H3K79me2 ChIP-seq



Conclusions

Pharmacokinetics
- Pediatric plasma exposure comparable to adults at similar doses
- Low concentration of drug observed in CSF suggesting negligible CNS exposure

Pharmacodynamics
- Clinical exposures at RP2D is sufficient to inhibit H3K79me2 at key MLL-r target genes as demonstrated through H3K79me2 ChIP-seq

Safety
- Elevated LFTs (2) observed as DLT at 90 mg/m^2/day cohort in patients > 1 year of age

Dose determination
- RP2D in patients > 1 year of age is 70 mg/m^2/day
  - Dose expansion cohort at RP2D currently enrolling
- Continued enrollment in dose escalation cohorts for patients ≤ 1 year of age

Acknowledgments

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References
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[3] Krivstov, A.V. (2008) Cancer Cell, 14(5), 355-368

Conflicts of Interest
NS, LBS, JAW, PB, AVK, RK and LG have no conflicts to disclose; MMO, Seattle Genetics, research funding; MP, Seattle Genetics, research funding; MLL, Incyte, consultancy; BT, SJB, SRD, PP, NJW and PTH are Epizyme employees with equity ownership; SAA, Epizyme consultant;