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) result in 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 (Krivostov, 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 leukemica cell kill (I).

DOT1L Promotes MLL-r Leukemia via Aberrant H3K79 Methylation

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/m²/day
- Patients > 1 year of age = 70 mg/m²/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

Patient Characteristics (n=14)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Values</th>
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<tbody>
<tr>
<td>Median age, yrs. (range)</td>
<td>4.2 (0.33 - 15)</td>
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<tr>
<td>Sex (M/F)</td>
<td>8/6</td>
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Diagnosis

- AML: MLL-r: 4 (29)
- ALL: MLL-r: 8 (57)

Mixed Lineage Leukemia: 2 (14)

# of prior therapeutic regimens: >8 (1)

Prior allogeneic HCT: 6 (42)

Dose administered: 70 (mg/m²/day) 90 (75) 70 (mg/m²/day) 90 (75)

Clinical Safety

Adverse Events: in 24 patients (Regardless of Attribution)

- Hypokalemia
- Anemia
- Arthritis
- Neutropenia
- Hypersensitivity
- Diarrhea
- Platelet count decreased
- Lymphocyte count decreased
- Lymphoblast count decreased
- Rash
- Vomiting
- Dry skin
- Dysuria/diabetes GT prolonged
- Hyperglycemia
- Hypophosphatemia
- Alopecia
- Pain
- Palmar erythema

Non-Hematologic Grade ≥ 3 (Related)

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 21 %</th>
<th>Grade 314 %</th>
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<tbody>
<tr>
<td>Decreased appetite</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Elevated LFTs</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>90</td>
<td>90</td>
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<tr>
<td>Organizing pneumonia</td>
<td>90</td>
<td>90</td>
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Clinical Summary

Older age cohort
- One DLT in six patients: 70 mg/m²/day
- Two DLTs in seven patients: 90 mg/m²/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

References

Conflicts of Interest
NLM, NCI, MH, NIH, HHS, HHS and their successors have no conflicts to disclose; NW/EC, Seattle Genetics, research funding; MFE, Seattle Genetics, research funding; MLL, Mrice, consultancy; ET, NCI, SEIR, PF, NIH and PTH are Epzyme employees with equity ownership; SAI, Epzyme consultant.

Pediatric Plasma Exposure Comparable to Adults at Similar Doses

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

Tabulated Summary of CSS Exposure of Pinometostat in Pediatric Patients

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/m²/day cohort in patients > 1 year of age
- Dose determination
- RP2D in patients > 1 year of age is 70 mg/m²/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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