Complex polyclonal resistance mechanisms to ivosidenib monotherapy in \textit{IDH1}-mutant relapsed or refractory acute myeloid leukemia revealed by single-cell sequencing analyses

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Background

▪ Somatic mutations in IDH1 (IDH2) occur in 6–10% (9–13%) of patients with AML, resulting in production of the oncometabolite 2-HG

▪ Ivosidenib, a mutant IDH1 (mIDH1) inhibitor, is approved in the US for m IDH1 R/R AML, and newly diagnosed m IDH1 AML in patients ≥75 years old or with comorbidities precluding intensive induction chemotherapy

▪ Durable remissions in m IDH1 R/R AML were achieved with ivosidenib in a phase 1 study (NCT02074839)¹
  – ORR 42%, CR 22%, and CR+CRh 30%
  – Median duration of CR+CRh: 8.2 months

▪ Initial case report identified two patients with m IDH1 acquiring m IDH2 at relapse following ivosidenib monotherapy²

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Objectives

- Use single-cell mutation profiling to explore the evolution of mi\(IDH2\) clones under the selective pressure of ivosidenib monotherapy in a subset of patients

- Resolve clonal architecture

- Examine the genetic mechanism by which AML retains dependency on 2-HG
Analysis dataset and methods

Phase 1 study
mIDH1 R/R AML, 500 mg QD ivosidenib
N = 174

Baseline and any on-treatment time point
(targeted NGS profiling, sensitivity 2–5%)
N = 129

mIDH2 detected on treatment
(targeted NGS profiling, sensitivity 2–5%)
N = 15

Available single-cell DNAseq data (PBMC)
(sensitivity 0.1%)
N = 9

Tapestri® with a 19-gene AML panel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene</th>
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<tbody>
<tr>
<td>ASXL1</td>
<td>JAK2</td>
<td>RUNX1</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>KIT</td>
<td>SF3B1</td>
</tr>
<tr>
<td>EZH2</td>
<td>KRAS</td>
<td>SRSF2</td>
</tr>
<tr>
<td>FLT3</td>
<td>NPM1</td>
<td>TP53</td>
</tr>
<tr>
<td>GATA2</td>
<td>NRAS</td>
<td>U2AF1</td>
</tr>
<tr>
<td>IDH1</td>
<td>PTPN11</td>
<td>WT1</td>
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<tr>
<td>IDH2</td>
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Clinical data cutoff: Nov 2, 2018
DNAseq, DNA sequencing; NGS, next-generation sequencing; PBMC, peripheral blood mononuclear cell; QD, once daily
Case 1:
62 y, M, de novo AML, prior IC, then R/R to azacitidine and decitabine (HMA)

- Blast %: 58
- Plasma 2-HG (ng/mL): 911

<table>
<thead>
<tr>
<th>Cell % (n)</th>
<th>Single-cell clonal prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH1, NPM1, FLT3</td>
<td>40% (373)</td>
</tr>
<tr>
<td>IDH1, NPM1, NRAS</td>
<td>60% (568)</td>
</tr>
<tr>
<td>FLT3</td>
<td>91% (96)</td>
</tr>
<tr>
<td>IDH1, NPM1, FLT3, IDH2</td>
<td>94% (475)</td>
</tr>
</tbody>
</table>

- Clonal structure: Single cell
  - Both mIDH1/NPM1/NRAS and mIDH1/NPM1/FLT3-TKD clones are sensitive to ivosidenib
  - Resistance evolves through acquisition of mIDH2 within mIDH1 clone (2-HG–dependent mechanism)

C, cycle; IC, intensive chemotherapy; HMA, hypomethylating agent; M, male; NA, not available; y, years; LLOQ, lower limit of quantification; RL, relapse; SCR, screening; SD, stable disease; TKD, tyrosine kinase domain; VAF, variant allele frequency
**Case 2:**
85 y, F, sAML, prior therapy with azacitidine and lenalidomide, del 5q

**Kinetics of relapse**
- Early: subclonal expansion of *PTPN11* (2-HG–independent)
- Late: acquisition of mIDH2 within mIDH1 clone (2-HG–dependent)

**Clonal structure:**
- Single cell

**Graphical Representation:**
- **SF3B1**, **IDH1**, **PTPN11**, **IDH2**
- **Blast %**
- **Plasma 2-HG (ng/mL)**
- **Cell % (n)**
- **Single-cell clonal prevalence**
Case 3:
67 y, M, de novo AML, prior decitabine and vosaroxin, refractory AML with +8 karyotype

*RL: only 6% blasts

- Plasma 2-HG (ng/mL)

- Blast %

- Cell % (n)

- Single-cell clonal prevalence

- Clonal structure:
  - Single cell

- Polyclonal disease with mIDH1 clone being cleared with ivosidenib treatment
- Relapse due to:
  - Evolution of IDH-wild type clone
  - Expansion or evolution of multiple mIDH2 clones
2-HG restoration via mIDH2 in diverse clonal architecture

Baseline

Relapse

IDH1

IDH1

IDH1

IDH2

IDH1 IDH2

Evolved progeny

n = 6

Evolution

n = 1

Selection

n = 2
Conclusions

- Single-cell mutation profiling reveals multiple evolutionary mechanisms by which \( mIDH2 \) contributes to relapse

- 2-HG restoration via \( mIDH2 \) acquisition underscores the key role of 2-HG production in \( mIDH \) AML

- These results inform the design of combination or sequential treatment strategies with ivosidenib in \( mIDH1 \) AML, for example, enasidenib treatment at relapse

- Frequency of relapse mechanisms via comprehensive genomic analysis will be presented shortly in this session (Presentation 545, 8:00 AM)
Acknowledgments

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