Molecular mechanisms mediating relapse following ivosidenib monotherapy in patients with \textit{IDH1}-mutant relapsed or refractory acute myeloid leukemia

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Background

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

- Ivosidenib, a mutant IDH1 (m\textit{IDH1}) inhibitor, is approved in the US for m\textit{IDH1} R/R AML and newly diagnosed m\textit{IDH1} AML in patients $\geq$75 years old or with comorbidities precluding intensive induction chemotherapy.

- Durable remissions in m\textit{IDH1} R/R AML were achieved with ivosidenib in a phase 1 study (NCT02074839)\textsuperscript{1}
  - ORR 42\%, CR rate 22\%, and CR+CRh rate 30\%
  - Median duration of CR+CRh response: 8.2 months

2-HG, D-2-hydroxyglutarate; \(\alpha\)-KG, alpha-ketoglutarate; AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; IDH, isocitrate dehydrogenase; m, mutant; Me, methylation; ORR, overall response rate; R/R, relapsed or refractory

Objective

Charaterize the molecular predictors of response and mechanisms of relapse to ivosidenib monotherapy in mIDH1 R/R AML using comprehensive genomic profiling

- Hypothesis 1: Pre-therapy genetic profile predicts response
  - Mutations in single genes and pathways
  - Clonal vs subclonal status of mIDH1

- Hypothesis 2: Relapse is due to both IDH-dependent and IDH-independent mechanisms
  - Assess for IDH2 and/or novel IDH1 mutations at relapse\(^1,2\)
  - Compare mutational profile before therapy and at relapse

Molecular profiling by targeted next-generation sequencing (NGS)

Phase 1 study
m*IDH1* R/R AML, 500 mg QD ivosidenib
N = 174

Baseline
whole bone marrow
n = 167

Longitudinal analysis subset
Subjects with clinical relapse or disease progression
n = 105

Subjects with profiling data at baseline and at relapse or disease progression (BMMC or PBMC)

n = 74

Subjects who achieved *CR+CRh*

n = 26

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*a Genetic profiling was performed using the FoundationOne Heme (dose-escalation phase) or Brigham and Women’s Rapid Heme (dose-expansion phase) panels

*b Genetic profiling was performed with viably frozen BMMCs and/or PBMCs using the FoundationOne Heme (dose-escalation phase) or Personalis ACE Extended Cancer (dose-expansion phase) panels

Single nucleotide variants and short insertions/deletions are detected at allele frequencies of at least 2% (FoundationOne Heme, Personalis ACE) to 5% (Rapid Heme)

Clinical data cutoff: Nov 2, 2018
BMMC, bone marrow mononuclear cell; PBMC, peripheral blood mononuclear cell; QD, once daily
Data source: 167 patients with baseline NGS data from whole bone marrow

RTK, receptor tyrosine kinase

Most frequent co-mutations at baseline

- Included: gene mutations occurring at >5% frequency

- RTK pathway mutations (NRAS, PTPN11, KRAS, KIT, and FLT3) occurred in 25%

- IDH2 mutations were infrequent at baseline (2%)
Significant association of baseline RTK pathway mutations with a lack of CR or CRh response

- RTK pathway mutations, and mutations in the individual genes NRAS and PTPN11, are significantly associated with a lack of CR or CRh response

- 64% of patients with JAK2 mutations achieved CR or CRh

P-values: Fisher's exact test. NC denotes p-value not calculated owing to small number of patients with mutation
FLT3-TKD+ denotes FLT3-TKD or juxtamembrane domain point mutations
Data source: 167 patients with baseline NGS data from whole bone marrow; MUT = mutant; WT = wild type
**Relationship of baseline \textit{mIDH1} VAFs with co-mutation VAFs**

- \textit{mIDH1} VAFs are frequently higher than RTK pathway mutations (blue)
- \textit{mIDH1} VAFs are often lower than co-mutations that are characteristic of MDS/MPN and clonal hematopoiesis (orange)

Data source: 166 patients with baseline NGS data and \textit{mIDH1} detection from whole bone marrow
MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; VAF, variant allele frequency
Clinical response is not predicted by the position of m\(IDH1\) within the clonal hierarchy at baseline

<table>
<thead>
<tr>
<th>m(IDH1) status</th>
<th>n (%)</th>
<th>CR/CRh best response</th>
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<tbody>
<tr>
<td>Clonal</td>
<td>119 (72)</td>
<td>41/119 (34)</td>
</tr>
<tr>
<td>Subclonal</td>
<td>47 (28 )</td>
<td>16/47 (34)</td>
</tr>
<tr>
<td>Total</td>
<td>166</td>
<td></td>
</tr>
</tbody>
</table>

\(mIDH1\) was defined as subclonal if any co-mutation VAF was greater than \(mIDH1\) VAF +5%; otherwise, it was defined as clonal

Patients with clonal or subclonal \(mIDH1\) had the same frequency of CR/CRh response.

Data source: 166 patients with baseline NGS data and \(mIDH1\) detection from whole bone marrow
Multiple mechanisms contribute to relapse or progression

Data source: 74 patients with NGS data at baseline and at relapse or disease progression (BMMC/PBMC, all evaluable response groups)

CRi/CRp, CR with incomplete hematologic or platelet recovery; MLFS, morphologic leukemia-free state; PD, progressive disease; RL, relapse; SD, stable disease

Heatmap showing variants detected at relapse or progression (n = 74)
Multiple mechanisms contribute to relapse or progression

Detected at baseline  Not detected at baseline  IDH1 second-site mutation  mIDH1 detected at baseline but not at RL/PD

IDH  RTK Pathway  Chromatin  Differentiation  Epigenetics  Splicing  Other

Heatmap showing variants detected at relapse or progression (n = 74)

Data source: 74 patients with NGS data at baseline and at relapse or disease progression (BMMC/PBMC, all evaluable response groups)

CR/CRIp, CR with incomplete hematologic or platelet recovery; MLFS, morphologic leukemia-free state; PD, progressive disease; RL, relapse; SD, stable disease
Multiple mechanisms contribute to relapse or progression

Heatmap showing variants detected at relapse or progression (n = 74)

IDH with other mechanisms

Data source: 74 patients with NGS data at baseline and at relapse or disease progression (BMMC/PBMC, all evaluable response groups)

CRi/CRp, CR with incomplete hematologic or platelet recovery; MLFS, morphologic leukemia-free state; PD, progressive disease; RL, relapse; SD, stable disease
## Summary of mutations observed at relapse

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Patients with mutations emerging at relapse or progression by pathway</th>
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<tbody>
<tr>
<td></td>
<td>All n = 74</td>
<td>Best response of CR or CRh n = 26</td>
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<tr>
<td><strong>IDH-related</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><em>IDH1</em> second-site</td>
<td>10 (14%)</td>
<td>5 (19%)</td>
<td></td>
</tr>
<tr>
<td><em>IDH2-R140Q</em></td>
<td>9 (12%)</td>
<td>6 (23%)</td>
<td></td>
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<tr>
<td><strong>Non-IDH-related</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTK pathway</td>
<td>20 (27%)</td>
<td>9 (35%)</td>
<td></td>
</tr>
<tr>
<td>Differentiation</td>
<td>13 (18%)</td>
<td>8 (31%)</td>
<td></td>
</tr>
<tr>
<td>Chromatin</td>
<td>9 (12%)</td>
<td>8 (31%)</td>
<td></td>
</tr>
<tr>
<td>Epigenetics</td>
<td>6 (8%)</td>
<td>2 (8%)</td>
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Data source: 74 patients with NGS data at baseline and at relapse or disease progression (BMMC/PBMC, all evaluable response groups)
Novel *IDH1* second-site mutations observed on therapy

- *IDH1* second-site mutations were detected during ivosidenib treatment in 10 patients.
- All of these second-site mutations were detected at relapse or disease progression, with concurrent increase in 2-HG.

- Biochemical testing of S280F and R119P confirmed loss of ivosidenib potency.

<table>
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<tr>
<th><em>IDH1</em> mutant</th>
<th>Ivosidenib IC$_{50}$, μM</th>
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<tbody>
<tr>
<td>IDH1_R132C</td>
<td>0.019</td>
</tr>
<tr>
<td>IDH1_R132L</td>
<td>0.013</td>
</tr>
<tr>
<td>IDH1_R132C_S280F</td>
<td>&gt;100</td>
</tr>
<tr>
<td>IDH1_R132C_R119P</td>
<td>0.15</td>
</tr>
<tr>
<td>IDH1_R132L_R119P</td>
<td>0.51</td>
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Other variants are not yet tested.

The number of circles indicates the number of patients with detection of the mutation. Two of the 10 patients had detection of two *IDH1* second-site mutations. *IDH1_S280F* was previously reported in one patient (Intlekofer AM et al. *Nature* 2018;559:125-29). IC$_{50}$, 50% inhibitory concentration.
RTK pathway mutations (including NRAS and PTPN11) were associated with a lower likelihood of clinical response to ivosidenib monotherapy in R/R AML.

Acquired resistance is mediated via diverse mechanisms:
- Mutations are acquired in multiple pathways, most frequently in RTK and 2-HG-restoring pathways (IDH2 and second-site IDH1 mutations).
- These mechanisms are not mutually exclusive within an individual patient.
- 2-HG restoration at relapse 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, including, for example, enasidenib treatment at relapse, RTK pathway targeted agents, or standard of care.

Ongoing ivosidenib combination trials:
- Ivosidenib + azacitidine: phase 1 (Poster 2706, NCT02677922), and phase 3 (AGILE, NCT03173248).
- Ivosidenib + intensive chemotherapy: phase 3 (HOVON 150 AML/AMLSG 29-18, NCT03839771).
Acknowledgments

- We would like to thank the patients who agreed to participate in this study
- This study was funded by Agios Pharmaceuticals, Inc.
Clinical study design

Dose escalation (n=78)
Enrollment complete

Patients with mIDH1+ advanced hematologic malignancies
Oral ivosidenib daily in continuous 28-day cycles
Doses included 100 mg BID, 300, 500, 800, 1200 mg QD

Dose expansion (n=180)
Enrollment complete: 500 mg QD in continuous 28-day cycles

1. R/R AML in 2nd+ relapse, relapse after SCT, refractory to induction or reinduction, or relapse within 1 year, n=126
2. Untreated AML not eligible for standard of care, n=25
3. Other non-AML mIDH1 R/R advanced hematologic malignancies, n=11
4. Other R/R AML not eligible for Arm 1, n=18

BID, twice daily; SCT, stem cell transplant