High rate of *IDH1* mutation clearance and measurable residual disease (MRD) negativity in patients with *IDH1*-mutant newly diagnosed acute myeloid leukemia treated with ivosidenib (AG-120) and azacitidine

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BACKGROUND

- Somatic mutations in isocitrate dehydrogenase 1 (*IDH1*) occur in 6–10% of patients with acute myeloid leukemia (AML).[1-4]
- Mutant IDH1 (mIDH1) enzymes catalyze the reduction of alpha-ketoglutarate to the oncometabolite D-2-hydroxyglutarate (2-HG),[5] and the resulting 2-HG accumulation leads to epigenetic dysregulation and impaired cellular differentiation.[6-8]
- Ivosidenib (AG-120) is a first-in-class, oral, targeted inhibitor of the mIDH1 enzyme that is approved in the US for the treatment of AML with a susceptible *IDH1* mutation as detected by an FDA-approved test in adults with newly diagnosed AML who are ≥75 years of age or who have comorbidities that preclude the use of intensive induction chemotherapy and in adults with relapsed or refractory AML. It is currently under review for approval in Europe.

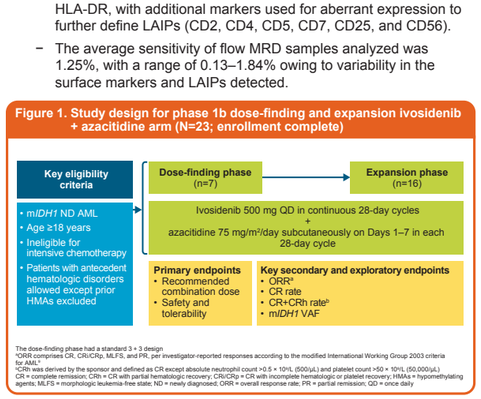
EXPLORATORY OBJECTIVES

- To study the impact of ivosidenib + azacitidine on longitudinal m*IDH1* variant allele frequency (VAF) in both bone marrow mononuclear cells (BMMCs) and peripheral blood mononuclear cells (PBMCs).
- To compare *IDH1* mutation clearance as a molecular marker of measurable residual disease (MRD) with clearance of co-mutations and MRD by flow cytometry (flow MRD).
- To utilize next-generation sequencing (NGS) to identify genetic alterations associated with clinical response, primary resistance, and relapse.

METHODS

- Samples for this analysis were obtained from patients with newly diagnosed m*IDH1* AML who were ineligible for intensive chemotherapy and treated in a phase 1b/2, open-label, multicenter trial with ivosidenib + azacitidine (ClinicalTrials.gov NCT02677922).
- m*IDH1* VAF in BMMCs and PBMCs was quantified by BEAMing digital PCR.
  - *IDH1* mutation clearance was defined as m*IDH1* VAF below the limit of detection of 0.02–0.04% (2–4 × 10^{-4}) for at least one on-study time point (Sysmex OncoBEAM™).
- Bulk baseline and longitudinal co-occurring mutations were identified using a 1400-gene NGS panel capable of detecting sequence mutations with VAF ≥2% (ACE Extended Cancer Panel, Personalis).
- Fresh bone marrow aspirates were assessed by flow cytometry (BD LSRFortessa X-20™) for MRD and leukemia-associated aberrant immunophenotypes (LAIPs).
  - Myeloid blast markers included CD34, CD117, CD13, CD33, and HLA-DR, with additional markers used for aberrant expression to further define LAIPs (CD2, CD4, CD5, CD7, CD25, and CD56).
  - The average sensitivity of flow MRD samples analyzed was 1.25%, with a range of 0.13–1.84% owing to variability in the surface markers and LAIPs detected.

Figure 1. Study design for phase 1b dose-finding and expansion ivosidenib + azacitidine arm (N=23; enrollment complete)



The dose-finding phase had a standard 3 + 3 design
[a]ORR comprises CR, CRi/CRp, MLFS, and PR, per investigator-reported responses according to the modified International Working Group 2003 criteria for AML*
[b]CRh was derived by the sponsor and defined as CR except absolute neutrophil count >0.5 × 10^9/L (500/µL) and platelet count >50 × 10^9/L (50,000/µL)
CR = complete remission; CRh = CR with partial hematologic recovery; CRi/CRp = CR with incomplete hematologic or platelet recovery; HMAs = hypomethylating agents; MLFS = morphologic leukemia-free state; ND = newly diagnosed; ORR = overall response rate; PR = partial remission; QD = once daily

Table 1. Baseline demographic and disease characteristics

	All patients N=23
Age, median (range), years	76 (61–88)
≥75 years, n (%)	12 (52)
Male/female, n	11/12
m*IDH1* VAF in BMMCs, median (range), %[a,b]	42 (17–48)
ECOG PS, n (%)	
0	5 (22)
1	14 (61)
2	4 (17)
Disease history, n (%)	
De novo AML	15 (65)
Secondary AML	8 (35)
Cytogenetic risk status, n (%)	
Intermediate	15 (65)
Poor	5 (22)
Failure/missing	3 (13)

[a]17 of 23 patients had baseline BMMC samples available for retrospective analysis
[b]VAF quantified by NGS (ACE Cancer Panel, Personalis)
ECOG PS = Eastern Cooperative Oncology Group performance status

RESULTS

- As of February 19, 2019, 10 patients (43.5%) remained on study treatment and the median number of treatment cycles was 15 (range, 1–30).
- ORR was 78.3% (n=18), which included investigator-reported responses of CR (60.9%; n=14), CRi/CRp (8.7%; n=2), and MLFS (8.7%; n=2).
- The ivosidenib + azacitidine combination was well tolerated, with no deaths occurring within 30 days of treatment initiation and one death occurring within 60 days.

Table 2. Response rates

Response parameter	All patients N=23
CR, n (%) [95% CI]	14 (60.9) [38.5, 80.3]
Time to CR, median (range), months	3.7 (0.8–15.7)
Duration of CR, median [95% CI], months	NE [9.3, NE]
CR+CRh,[a] n (%) [95% CI]	16 (69.6) [47.1, 86.8]
Time to CR+CRh, median (range), months	2.8 (0.8–11.5)
Duration of CR+CRh, median [95% CI], months	NE [12.2, NE]
CRh, n (%)	2 (8.7)
ORR, n (%) [95% CI]	18 (78.3) [56.3, 92.5]
Time to response, median (range), months	1.8 (0.7–3.8)
Duration of response, median [95% CI], months	NE [10.3, NE]
Best response[b]	
CR, n (%) [95% CI]	14 (60.9) [38.5, 80.3]
CRi/CRp, n (%)	2 (8.7)
MLFS, n (%)	2 (8.7)
SD, n (%)	4 (17.4)
NA, n (%)	1 (4.3)
Overall survival, 12-month rate, % [95% CI][c]	82.0 [58.8, 92.8]
Duration of follow-up, median (range), months	16.1 (1.3–31.7)

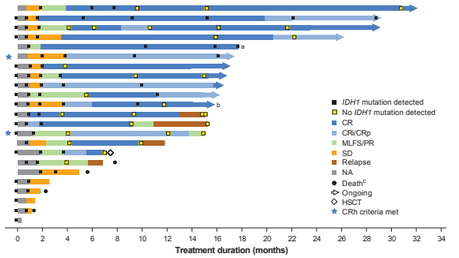
Data cutoff: February 19, 2019
[a]Sponsor derived
[b]Modified International Working Group criteria
[c]Determined using Kaplan-Meier method
NA = not assessed; NE = not estimable; SD = stable disease

Table 3. *IDH1* mutation clearance[a] by best overall response (BEAMing digital PCR)

	BMMCs N=21[b]	PBMCs N=23[c]
	n/N (%)	
CR/CRh	11/16 (69)	12/16 (75)
CR	10/14 (71)	11/14 (79)
CRh	1/2 (50)	1/2 (50)
Non-CR/CRh responders	1/2 (50)	1/2 (50)
Nonresponders	0/3 (0)	0/5 (0)

[a]Reduction in m*IDH1* VAF to below the limit of detection of 0.02–0.04% for at least one on-study time point
[b]If ≤1% VAF cutoff was applied, *IDH1* mutation clearance in BMMCs was observed in 15/16 (94%) CR/CRh patients, including 13/14 (93%) with CR
[c]Two nonresponding patients had VAF data available from PBMCs only

Figure 2. Treatment duration, response, and mutation clearance (N=23)



[a]Patient continued on commercially available ivosidenib
[b]Patient had m*IDH1* clearance in PBMCs only (BMMCs not available); all other patients had m*IDH1* clearance in both BMMCs and PBMCs
[c]Only deaths occurring within 60 days of last dose were included
HSCT = hematopoietic stem cell transplantation

Figure 3. *IDH1* mutation clearance is deep and durable with VAF reductions associating with CR/CRh (BEAMing digital PCR)

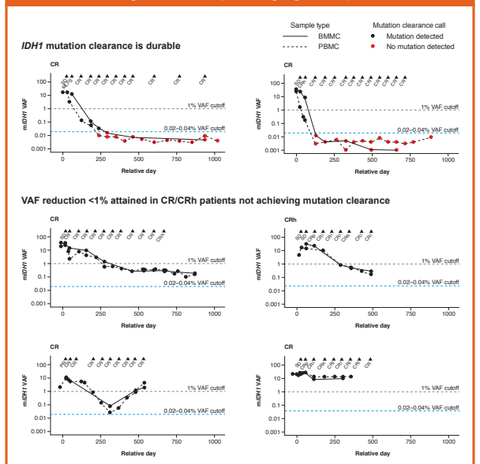


Table 4. Longitudinal analysis by NGS demonstrates VAF reduction of non-*IDH1* mutations[a] below the level of detection

Mutation clearance – NGS (BMMC, 2% VAF cutoff)			
	N	CR/CRh n/N (%)	Non-CR/CRh n/N (%)
IDH1	20	14/16 (88)	1/4 (25)
SRSF2	7	3/4 (75)	1/3 (33)
DNMT3A	6	3/5 (60)	0/1 (0)
RUNX1	6	4/4 (100)	0/2 (0)
ATM	3	0/1 (0)	0/2 (0)
NRAS	3	2/2 (100)	0/1 (0)
NPM1	3	2/2 (100)	0/1 (0)
ASXL1	2	1/1 (100)	0/1 (0)
BCOR	2	2/2 (100)	0/0 (0)
CEBPA	2	1/1 (100)	1/1 (100)
KRAS	2	0/0 (0)	0/2 (0)
SF3B1	2	1/2 (50)	0/0 (0)
TP53	2	1/1 (100)	0/1 (0)
U2AF1	2	2/2 (100)	0/0 (0)

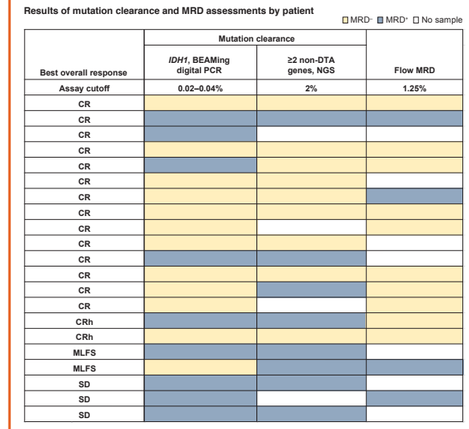
[a]Baseline mutations occurring in ≥2 patients are shown

Figure 4. Multiple orthogonal measures of MRD in bone marrow samples demonstrate high rate of molecular remissions

Summary of mutation clearance and MRD assessments

	Mutation clearance		
	m*IDH1*, BEAMing digital PCR (n=21)	≥2 non-DTA[a] genes, NGS (n=17)	Flow MRD (n=14)
Assay cutoff	0.02–0.04%	2%	1.25%[b]
CR+CRh	11/16 (69)	9/13 (69)	10/12 (83)
CR	10/14 (71)	8/11 (73)	8/10 (80)
CRh	1/2 (50)	1/2 (50)	2/2 (100)
Non-CR+CRh responders	1/2 (50)	0/2 (0)	0/1 (0)
Nonresponders	0/3 (0)	0/2 (0)	0/1 (0)

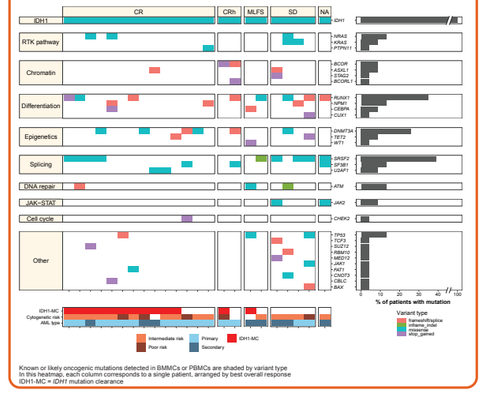
Results of mutation clearance and MRD assessments by patient



[a]Mutation clearance of all baseline co-mutations identified by NGS, excluding genes involved in clonal hematopoiesis (*DNMT3A*/*TET2*/*ASXL1* – 'DTA' genes)
[b]The average sensitivity is 1.25%, with a range from 0.13% to 1.84% owing to variability in the surface markers and LAIPs detected
DTA = *DNMT3A*/*TET2*/*ASXL1*

Figure 5. Co-occurring baseline mutations identified by NGS (2% VAF cutoff; N=23)

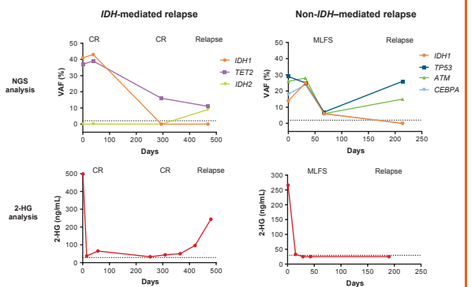
- No statistically significant relationship between baseline genetic variants and clinical response or primary resistance was observed.
- CR/CRh was achieved in four of five patients with poor-risk karyotypes.
- CR/CRh was achieved in three of five patients with receptor tyrosine kinase (RTK) pathway mutations (*KRAS, NRAS, PTPN11*).



Known or likely oncogenic mutations detected in BMMCs or PBMCs are shaded by variant type
In this heatmap, each column corresponds to a single patient, arranged by best overall response
IDH1-MC = *IDH1* mutation clearance

Figure 6. Examples of relapse

- To date, of 18 patients achieving a clinical response (CR, CRh, or MLFS), four have relapsed (22%).
  - Emergence of an *IDH2* mutation occurred in two of four patients, with concurrent increases in plasma 2-HG.
  - Outgrowth of non-*IDH* clones occurred in two of four patients, with both cases having *TP53* mutations at baseline.



Dotted line represents the lower limit of detection for each analysis

CONCLUSIONS

- Ivosidenib + azacitidine treatment leads to a high rate of durable molecular remissions in intensive chemotherapy–ineligible patients with newly diagnosed AML.
- With a limited dataset, a greater fraction of patients (3/5) with RTK pathway mutations (*KRAS, NRAS, PTPN11*) achieved CR/CRh with ivosidenib and azacitidine combination therapy compared with ivosidenib monotherapy (0/7).[10]
- A strong association between mutation clearance and other MRD analyses warrants further investigation of m*IDH1* VAF as a biomarker for monitoring response in patients with m*IDH1* AML treated with ivosidenib + azacitidine.
- On the basis of these phase 1b results, the ivosidenib + azacitidine combination is currently being investigated in the actively enrolling phase 3 AGILE study (ClinicalTrials.gov NCT03173248).

Disclosures
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