Ivosidenib (AG-120) in IDH1-mutant newly diagnosed acute myeloid leukemia: Updated results from a phase 1 study

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BACKGROUND

- Somatic mutations in isocitrate dehydrogenase (IDH) 1 and 2 result in accumulation of the oncometabolite D-2-hydroxyglutarate (2-HG),[1,2] which leads to epigenetic changes and impaired cellular differentiation.[3-5]
- Mutant IDH (mIDH) has been identified in multiple solid and hematologic tumors. In acute myeloid leukemia (AML), mIDH1 is found in ~6–10% of patients,[2,6] and is associated with an adverse prognosis.[7-9]
- Ivosidenib (AG-120) is a first-in-class, oral, potent, reversible, targeted inhibitor of the mIDH1 enzyme,[10] and is under evaluation in multiple clinical trials as a single agent and in combinations.
- Ivosidenib has been approved by the US FDA for the treatment of adult patients (with a susceptible *IDH1* mutation as detected by an FDA-approved test) with relapsed or refractory (R/R) AML, or with newly diagnosed (ND) untreated AML who are ≥75 years of age or have comorbidities precluding chemotherapy.
  - The approval was on the basis of data from the ongoing phase 1 study of mIDH1 advanced hematologic malignancies (**Figure 1**).[11]

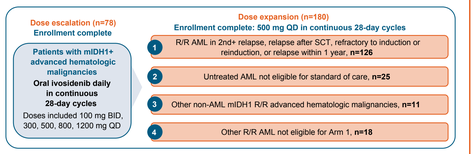
OBJECTIVE

- To report updated data on the safety and efficacy of ivosidenib in patients with ND AML not eligible for standard therapy, who are enrolled in the first-in-human, phase 1, dose escalation and expansion study of patients with mIDH1 advanced hematologic malignancies.

METHODS

- This study is an open-label, multicenter trial (ClinicalTrials.gov NCT02074839, **Figure 1**).
- Baseline co-occurring mutations were assessed using a targeted next-generation sequencing (NGS) panel that detects common variants in hematologic malignancies.
- m*IDH1* variant allele frequency (VAF) in bone marrow mononuclear cells was detected using BEAMing Digital PCR (Sysmex Inostics; lower limit of detection for m*IDH1*, 0.02–0.04%).

Figure 1. Study design



BID = twice daily; QD = once daily; SCT = stem cell transplant

- The primary efficacy endpoint was complete remission (CR) plus CR with partial hematologic recovery (CRh, **Table 1**).
- Additional endpoints were overall response rate (ORR), CR, duration of response, and time to response.
- ORR comprised CR, CR with incomplete hematologic or platelet recovery (CRi/CRp), partial remission (PR), and morphologic leukemia-free state (MLFS, **Table 1**).

Table 1. Response definitions[a]

Response	Bone marrow blasts, %	Absolute neutrophil count, /µL	Platelets, /µL
CR	<5	>1000	>100,000
CRh	<5	>500	>50,000
CRi	<5	<1000	>100,000
CRp	<5	>1000	<100,000
MLFS	<5	–	–
PR	5–25[b]	>1000	>100,000

IWG responses, including CR, reported by investigator; CRh derived by sponsor
[a]Modified IWG 2003 criteria[12]
[b]>50% reduction
IWG = International Working Group

- Enrollment completed on May 8, 2017. The data cutoff date for this analysis was November 2, 2018.
- The analysis set comprised all patients with ND AML whose ivosidenib starting dose was 500 mg QD, (n=34; n=9 from dose escalation and n=25 from dose expansion, Arm 2).
- Efficacy endpoints were assessed in patients with ND AML confirmed positive for m*IDH1* by the companion diagnostic test (n=33).
- Disposition, treatment duration, baseline characteristics, and baseline co-occurring mutations are shown in **Tables 2** and **3**, and **Figure 2**.

RESULTS

Table 2. Disposition and treatment duration

	Patients with ND AML receiving 500 mg ivosidenib n=34
Ongoing treatment, n (%)	7 (20.6)
Discontinued treatment, n (%)	27 (79.4)
PD	13 (38.2)
AE	5 (14.7)
Hematopoietic SCT	3 (8.8)
Withdrawal of consent	4 (11.8)
Death	1 (2.9)
Investigator decision	1 (2.9)
In posttransplant follow-up, n (%)	2 (5.9)
Discontinued study, n (%)	24 (70.6)
Treatment duration, median (range), months	4.3 (0.3–40.9)

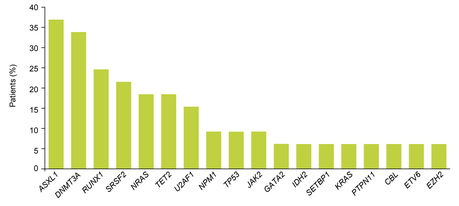
Data cutoff: November 2, 2018
AE = adverse event; PD = progressive disease

Table 3. Baseline characteristics

Characteristic	Patients with ND AML receiving 500 mg ivosidenib n=34[a]
Female/male, n	15/19
Age, median (range), years	76.5 (64–87)
Age category, n (%)	
60 to <75 years	15 (44.1)
≥75 years	19 (55.9)
ECOG PS at baseline, n (%)	
0	8 (23.5)
1	20 (58.8)
2	5 (14.7)
3	1 (2.9)
Nature of AML, n (%)	
De novo	8 (23.5)
Secondary	26 (76.5)
History of MDS	18 (52.9)
History of MPD	4 (11.8)
Treatment-related	3 (8.8)
Other	1 (2.9)
Prior HMA, n (%)	16 (47.1)
Cytogenetic risk status by investigator, n (%)	
Intermediate	24 (70.6)
Poor	9 (26.5)
Unknown	1 (2.9)

Data cutoff: November 2, 2018
[a]One patient enrolled in dose escalation tested positive for the IDH1-D54N mutation with local testing and did not test positive for the IDH1-R132 mutation with the companion diagnostic test
ECOG PS = Eastern Cooperative Oncology Group Performance Status; HMA = hypomethylating agent; MDS = myelodysplastic syndrome; MPD = myeloproliferative disease

Figure 2. Baseline co-mutation rates: Patients with ND AML receiving 500 mg ivosidenib (n=33)[a]



Data cutoff: November 2, 2018
Assessed using NGS panel for hematologic malignancies; mutations occurring in ≥2 patients shown
[a]One patient enrolled in dose escalation tested positive for the IDH1-D54N mutation with local testing and did not test positive for the IDH1-R132 mutation with the companion diagnostic test

- Common AEs of any causality are shown in **Table 4**. Most AEs were grades 1–2 and unrelated to treatment.
- AEs of interest were managed using standard-of-care treatments and ivosidenib dose modifications as required (**Figure 3**).

Table 4. AEs regardless of causality: Patients with ND AML receiving 500 mg ivosidenib (n=34)

Most common AEs (≥20% of patients)	Any grade, n (%)	Grade ≥3, n (%)
Diarrhea	18 (52.9)	2 (5.9)
Fatigue	16 (47.1)	4 (11.8)
Nausea	13 (38.2)	2 (5.9)
Decreased appetite	12 (35.3)	1 (2.9)
Leukocytosis	9 (26.5)	1 (2.9)
Anemia	9 (26.5)	4 (11.8)
Edema peripheral	9 (26.5)	0
Thrombocytopenia	9 (26.5)	5 (14.7)
Dyspnea	8 (23.5)	1 (2.9)
Hypomagnesemia	8 (23.5)	0
Dizziness	8 (23.5)	0
Arthralgia	7 (20.6)	1 (2.9)
Hypokalemia	7 (20.6)	1 (2.9)
Constipation	7 (20.6)	1 (2.9)
Abdominal pain	7 (20.6)	1 (2.9)
Insomnia	7 (20.6)	0
Epistaxis	7 (20.6)	0
Most common SAEs (≥5% of patients)		**SAE, n (%)**
IDH differentiation syndrome		5 (14.7)
Febrile neutropenia		3 (8.8)
Pneumonia		3 (8.8)
ECG QT prolonged		2 (5.9)
Fatigue		2 (5.9)

Data cutoff: November 2, 2018
ECG = electrocardiogram; SAE = serious adverse event

Figure 3. AEs of interest: Patients with ND AML receiving 500 mg ivosidenib (n=34)

Leukocytosis[a]
- Grade ≥3 leukocytosis reported in 1/34 patients (3%)
- Not fatal

ECG QT prolongation
- All grades reported in 6/34 patients (17.6%)
- Grade ≥3 reported in 3/34 patients (8.8%)
- Study drug was reduced in 2 patients and held in 4 patients
- No instances were fatal
- QT-prolonging medications such as antifungals and fluoroquinolone anti-infectives were allowed on study with monitoring

Differentiation syndrome (DS)[b]
- All grades reported in 6/34 patients (17.6%)
- Resolved in all 6 patients
- Grade ≥3 DS in 3 (8.8%) patients
- 2/6 patients had co-occurring leukocytosis
- Study drug held in 3 patients (8.8%)
- No instances of DS led to dose reduction, permanent treatment discontinuation, or death
- Best response in patients with DS: 3 CR, 2 CRh, 1 NA

Data cutoff: November 2, 2018
[a]Grade 3 = white blood cell count >100,000/mm; grade 4 = clinical manifestation of leukostasis, urgent intervention indicated
[b]Reported by investigator
NA = not assessed

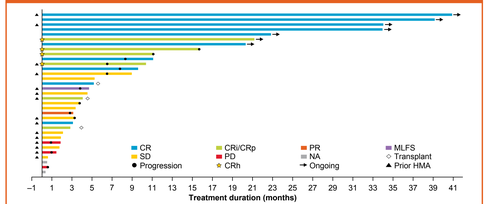
- CR+CRh and CR rates were 42.4% and 30.3%, respectively (**Table 5**).
- CR+CRh rate was 26.7% (4/15) in patients who had previously been treated with HMAs, and 55.6% (10/18) in those who had not.
- Ivosidenib induced durable responses (**Table 5** and **Figure 4**).
- Of 21 patients who were transfusion dependent at baseline, 43% became transfusion independent for ≥56 consecutive days while on treatment (**Figure 5**). In seven of 12 patients (58%) who were transfusion independent at baseline, independence was maintained for ≥56 days while on treatment.
- Ivosidenib induced *IDH1* mutation clearance in bone marrow mononuclear cells (**Table 6**).
- The most frequent co-occurring mutations and mutational burden by clinical response are shown in **Figure 6**.

Table 5. Responses in patients receiving 500 mg ivosidenib

	Patients with ND AML receiving 500 mg ivosidenib n=33
CR+CRh rate, n (%) [95% CI]	**14 (42.4) [25.5, 60.8]**
Time to CR/CRh, median (range), months	2.8 (1.9–12.9)
Duration of CR/CRh, median [95% CI], months	NE [4.6, NE]
CR rate, n (%) [95% CI]	10 (30.3) [15.6, 48.7]
Time to CR, median (range), months	2.8 (1.9–4.6)
Duration of CR, median [95% CI], months	NE [4.2, NE]
CRh rate, n (%) [95% CI]	4 (12.1) [3.4, 28.2]
Time to CRh, median (range), months	3.7 (1.9–12.9)
Duration of CRh, median [95% CI], months	6.5 [2.8, NE]
ORR[a] by mIWG, n (%) [95% CI]	**18 (54.5) [36.4, 71.9]**
Time to first response, median (range), months	1.9 (0.9–3.6)
Duration of response, median [95% CI], months	NE [4.6, NE]
Best response by mIWG, n (%)	
CR	10 (30.3)
CRi/CRp	6 (18.2)
PR	1 (3.0)
MLFS	1 (3.0)
SD	10 (30.3)
PD	3 (9.1)
NA	2 (6.1)

Data cutoff: November 2, 2018
[a]ORR includes CR, CRi/CRp, MLFS, and PR
mIWG = modified IWG; NE = not estimable; SD = stable disease; NA = not assessed

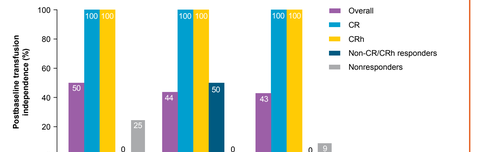
Figure 4. Duration of treatment and best overall response: Patients with ND AML receiving 500 mg ivosidenib (n=33)



Duration of response	CR+CRh	CR	Overall response
Median (95% CI), months	NE (4.6, NE)	NE (4.2, NE)	NE (4.6, NE)
Kaplan-Meier survival rate, 6 months	76.9%	77.8%	75.6%
Kaplan-Meier survival rate, 12 months	61.5%	77.8%	63.0%
Overall survival, median (95% CI), months		12.6 (4.5, 25.7)	
Duration of follow-up, median (range), months		23.5 (0.6–40.9)	

Data cutoff: November 2, 2018
HMA = hypomethylating agent

Figure 5. Transfusion independence across response categories in patients who were dependent at baseline (n=21): Patients with ND AML receiving 500 mg ivosidenib (n=33)



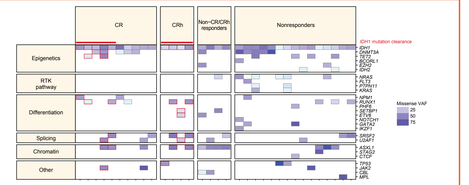
Postbaseline transfusion independence defined as no transfusion for at least one 56-day period. Data cutoff: November 2, 2018. Non-CR/CRh responders include patients who achieved CRi, CRp, or MLFS but not CRh

Table 6. *IDH1* mutation clearance: Patients with ND AML receiving 500 mg ivosidenib (n=30)

	n	*IDH1* mutation clearance[a] n (%)
CR+CRh	14	9 (64)
CR	10	5 (50)
CRh	4	4 (100)
Others	16	0
Non-CR+CRh responders	4	0
Nonresponders	12	0
p-value[b]		<0.001

[a]Defined as a reduction in m*IDH1* VAF to levels below the limit of detection of 0.02–0.04% (2–4 × 10^{-4}) by digital PCR for at least one on-study time point
[b]p-value based on Fisher's exact test comparing *IDH1* mutation clearance in patients with a best overall response of CR+CRh with patients with other responses (non-CR+CRh responders and nonresponders)

Figure 6. Co-occurring mutations at baseline (NGS, n=33)



In this heatmap, each column corresponds to a single patient, arranged by best overall response to ivosidenib. Detected known or likely oncogenic mutations are denoted by boxes and shaded by VAF category
RTK = receptor tyrosine kinase

CONCLUSIONS

- This cohort of patients with mIDH1 ND AML not eligible for standard therapy represent a molecularly defined elderly population with a poor prognosis.
- Ivosidenib induced durable responses, including in patients who had previously been treated with HMAs:
  - Overall CR+CRh rate of 42.4%, median duration not estimable, lower bound of 95% CI 4.6 months.
  - ORR of 54.5%, median duration not estimable.
- Ivosidenib was well tolerated.
  - AEs of interest were managed with standard-of-care treatments and brief ivosidenib dose interruptions as required.
  - There was a low rate of grade ≥3 AEs, including febrile neutropenia.
- Transfusion independence was observed across response categories.
- Ivosidenib induced *IDH1* mutation clearance in five of 10 patients with CR and in all four patients with CRh.
- These results support the ongoing studies of ivosidenib in patients with mIDH1 AML:
  - Phase 1 ivosidenib + azacitidine in patients with ND AML not eligible for intensive chemotherapy (see Poster 7011, DiNardo CD et al).
  - AGILE: global, phase 3, ivosidenib + azacitidine versus placebo + azacitidine in patients with ND AML not eligible for intensive chemotherapy.[13]
  - Phase 1 ivosidenib in combination with standard AML induction and consolidation therapy in patients with ND AML eligible for intensive chemotherapy.[14]
  - HOVON 150 AML/AMLSG 29-18: phase 3, multicenter, randomized, placebo-controlled ivosidenib in combination with induction, consolidation, and maintenance therapy in patients with ND AML or MDS with excess blasts-2 eligible for intensive chemotherapy (ClinicalTrials.gov NCT03839771).

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