Genetic profiling and deep IDH1 mutation clearance to ≤0.04% in ivosidenib (AG-120)-treated patients with mutant IDH1 relapsed or refractory and untreated AML

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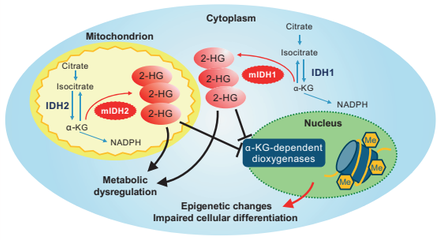
BACKGROUND

- Somatic mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene occur in 6–10% of patients with acute myeloid leukemia (AML).
- The mutant IDH1 (mIDH1) enzyme is capable of reducing α-ketoglutarate to the epigenetically active oncometabolite D-2-hydroxyglutarate (2-HG), resulting in accumulation of 2-HG[1] and impaired cellular differentiation.

Figure 1. Role of mIDH1 in oncogenesis



- Ivosidenib (AG-120) is a first-in-class, oral, potent, reversible, and targeted small-molecule inhibitor of the mIDH1 protein.[2]
- Ivosidenib has demonstrated efficacy in a phase 1 study (ClinicalTrials.gov NCT02074839). Among 125 mIDH1 relapsed/refractory (R/R) AML patients receiving ivosidenib 500 mg once daily (QD) across dose escalation and expansion who received their first dose ≥6 months prior to the analysis cutoff date of May 12, 2017, the complete response + complete response with partial hematologic recovery (CR+CRh) rate was 30.4% (95% CI 22.5%, 39.3%), including CR in 27 (21.6%), with an overall response rate of 41.6%.[3]
  - See oral presentation 725; Monday, December 11, 3:45 pm.
- The association between genetic mutations and response to therapy is an area of intense research in AML, as is the relationship between minimal residual disease (MRD) and long-term outcome.[4-6]
- In the **dose escalation** phase of the phase 1 study, molecular profiling using next-generation sequencing (NGS) technology (lower limit of detection of 1% for *mIDH1*) was performed on patient samples. Results demonstrated:
  - Clearance of *mIDH1* in 5 of 14 patients who achieved CR, compared with 2 of 52 patients who did not achieve CR (p=0.003).[7]
  - Co-occurring mutations in *DNMT3A*, *NPM1*, *SRSF2*, *NRAS*, *RUNX1*, and others were observed at baseline.[8]

Disclosures

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RMS: AbbVie, Agios, Amgen, Arog, Astellas, Celgene, Fuji Film, Jazz, Novartis, Ono, Pfizer, Sumitomo – consultancy. SC, VZ, HW, ECA, and BW: Agios – employment, equity ownership. BM and VP-L: no relevant financial relationship(s) to disclose. CDD: AbbVie, Agios, Celgene, Daiichi-Sankyo, Novartis – honoraria, research funding. EMS: Agios – consultancy, research funding; Celgene – consultancy, travel expenses, research funding; GSK – advisory board, research funding; Novartis – consultancy, research funding; Pfizer – consultancy, travel expenses; Seattle Genetics, Constellation Pharma – research funding. ATF: Agios – consultancy, honoraria, board of directors/advisory committee; Amgen, MedImmune – consultancy, board of directors/advisory committee; Celgene – consultancy, honoraria, board of directors/advisory committee, research funding; Juno – board of directors/advisory committee; Pfizer – honoraria; Seattle Genetics – consultancy, honoraria, board of directors/advisory committee, research funding; Takeda – research funding. MST: ADC Therapeutics, Agios, Arog, Bioline, Cellerant – research funding; Daiichi-Sankyo, Orsenix – advisory board. HMK: Amgen, ARIAD, Astex, BMS, Delta-Fly Pharma, Novartis, Pfizer – research funding; AbbVie, Actinium, Amgen, ARIAD, BMS, Immunogen, Orsinex, Pfizer – honoraria. SdB: Agios – honoraria, research funding; Celgene, Novartis, Pfizer, Servier – honoraria.

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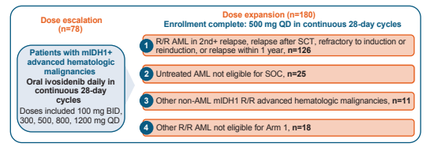
Figure 2. AG120-C-001 study design



Study objectives

Primary Safety and tolerability, maximum tolerated dose and/or RP2D, clinical activity in mIDH1 R/R AML enrolled in expansion Arm 1

Secondary Dose-limiting toxicities, pharmacokinetics, pharmacodynamics (including 2-HG), preliminary clinical activity in advanced hematologic malignancies

BID = twice daily; RP2D = recommended phase 2 dose; SCT = stem cell transplant; SOC = standard of care

EXPLORATORY OBJECTIVES

- For AML patients enrolled in the **expansion** phase of the phase 1 study, the objectives were to:
  - Study the impact of ivosidenib on longitudinal *mIDH1* variant allele frequency (VAF) in bone marrow mononuclear cells (BMMCs) and neutrophils.
  - Assess the depth of decrease in *mIDH1* VAF as a molecular marker of MRD, using a highly sensitive digital polymerase chain reaction (PCR) method.
  - Determine whether baseline co-occurring mutations are associated with clinical response.

Table 1. Number of patients in expansion phase with evaluable biomarker data from different sample types

Population @ 500 mg QD (expansion)	Longitudinal *mIDH1* VAF (BMMC)	Longitudinal *mIDH1* VAF (neutrophil)	Baseline co-occurring mutation (BM)
R/R AML (n=102)[a]	75	82	101
Untreated AML (n=25)[b]	24	22	25

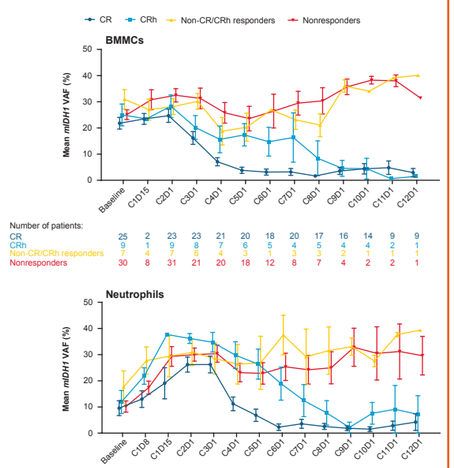
[a]R/R AML patients from expansion Arms 1 and 4 who received the first dose of ivosidenib ≥6 months prior to the analysis cutoff date of May 12, 2017
[b]Untreated AML patients from expansion Arm 2 who were enrolled and received at least one dose of study treatment
BM = bone marrow

METHODS

- *mIDH1* VAF was assessed in patient BMMCs and neutrophils by BEAMing Digital PCR Technology.[9]
  - Bone marrow aspirates and peripheral blood samples were collected into BD Vacutainer® CPT™ Cell Preparation Tubes and fractionated.
  - *IDH1* mutation clearance (*IDH1*-MC), or molecular MRD-negative status, was defined as a reduction in *mIDH1* VAF to below the limit of detection of 0.02–0.04% ($2–4\times10^{-4}$) for at least one on-study time point.
- Baseline co-occurring mutations were identified in whole bone marrow samples using a 95-gene NGS Rapid Heme Panel.
  - The Rapid Heme Panel detects single nucleotide variants and small insertions/deletions at allele frequencies of ≥5%.[10]

RESULTS

Figure 3. Ivosidenib treatment reduced *mIDH1* VAF in BMMCs and neutrophils from patients with best overall response of CR or CRh (R/R AML)



Mean ± SE is presented
Clinical response was assessed by the investigator according to the modified 2003 International Working Group criteria
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)
Non-CR/CRh responders include CRi/CRp and MLFS not meeting criteria for CRh, and PR; nonresponders include SD and PD
Numbers below the graph represent number of patients with *mIDH1* VAF data at each visit
CRh = CR with partial hematologic recovery; CRi = CR with incomplete hematologic recovery; CRp = CR with incomplete platelet recovery; MLFS = morphologic leukemia-free state; PD = progressive disease; PR = partial response; SD = stable disease

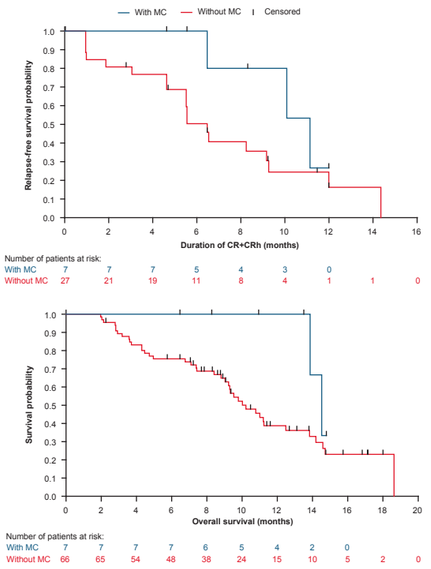
Table 2. Ivosidenib induces deep *IDH1*-MC in BMMCs from AML patients with best overall response of CR or CRh

Best response	R/R AML (n=73)		
	n	*IDH1*-MC n (%)	No *IDH1*-MC n (%)
CR+CRh	**34**	**7 (21)**	**27 (79)**
CR	25	7 (28)	18 (72)
CRh	9	0	9 (100)
Others	**39**	**0**	**39 (100)**
Non-CR+CRh responders	7	0	7 (100)
Nonresponders	32	0	32 (100)
p-value[a]		0.003	

Best response	Untreated AML (n=23)		
	n	*IDH1*-MC n (%)	No *IDH1*-MC n (%)
CR+CRh	**9**	**5 (56)**	**4 (44)**
CR	5	3 (60)	2 (40)
CRh	4	2 (50)	2 (50)
Others	**14**	**0**	**14 (100)**
Non-CR+CRh responders	5	0	5 (100)
Nonresponders	9	0	9 (100)
p-value[a]		0.004	

Data cutoff: May 12, 2017
[a]p-value is based on Fisher's exact test comparing *IDH1* mutation clearance in patients with best overall response of CR+CRh to patients with others (non-CR+CRh responders and nonresponders)

Figure 4. Patients with *IDH1*-MC had improved duration of CR+CRh and overall survival (R/R AML, BMMCs)



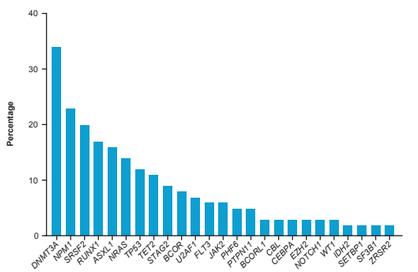
Duration of CR+CRh = date of first documented CR/CRh to date of first documented confirmed relapse or death
Overall survival = time from first dose to the date of death due to any cause
Statistical testing not provided owing to small sample size and low event rate

Table 3. Significant association of *IDH1*-MC between neutrophils and BMMCs in R/R AML patients with best response of CR or CRh

CR or CRh (n=31)		Neutrophils	
		IDH1-MC	NO *IDH1*-MC
BMMCs	*IDH1*-MC	7 (23)	0
	No *IDH1*-MC	6 (19)	18 (58)

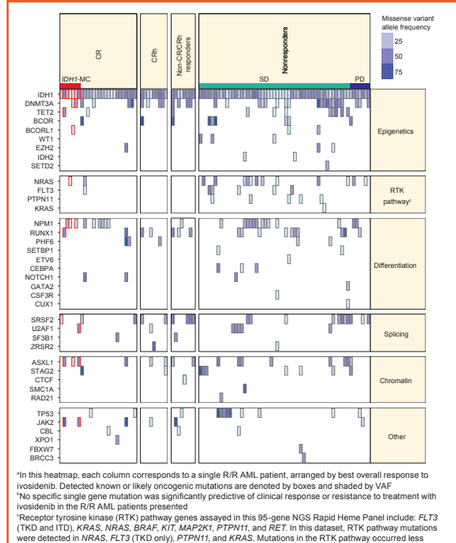
p<0.001, based on Fisher's exact test examining the association of *IDH1*-MC status between BMMCs and neutrophils

Figure 5. Most frequent (n≥2) co-occurring mutations at baseline in mIDH1 R/R AML patients (bone marrow)



Top five most frequently co-occurring mutations (*DNMT3A*, *NPM1*, *SRSF2*, *ASXL1*, *RUNX1*) in AG120-C-001 are consistent with published AML literature[8,11,12]

Figure 6. Co-occurring mutations at baseline (NGS, bone marrow, n=101)[a,b]



[a]In this heatmap, each column corresponds to a single R/R AML patient, arranged by best overall response to ivosidenib. Detected known or likely oncogenic mutations are denoted by boxes and shaded by VAF
[b]No specific single gene mutation was significantly predictive of clinical response or resistance to treatment with ivosidenib in the R/R AML patients presented
[c]Receptor tyrosine kinase (RTK) pathway genes assayed in this 95-gene NGS Rapid Heme Panel include: *FLT3* (TKD and ITD), *KRAS, NRAS, BRAF, KIT, MAP2K1, PTPN11*, and *RET*. In this dataset, RTK pathway mutations were detected in *NRAS, FLT3* (TKD only), *PTPN11*, and *KRAS*. Mutations in the RTK pathway occurred less frequently in patients who achieved CR or CRh as a best response relative to those who did not achieve CR or CRh (p=0.003 by Fisher's exact test)

CONCLUSIONS

- Ivosidenib reduced *mIDH1* allele burden in both BMMCs and neutrophils in R/R AML patients in the expansion phase who achieved CR or CRh.
- MRD-negative CR was observed in 7 of 25 (28%) R/R AML patients who achieved CR.
  - Patients with MRD-negative CR had improved duration of CR compared to patients with CR with persistent MRD in this limited dataset.
  - Patients with MRD-negative CR had improved overall survival compared to all other R/R AML patients with persistent MRD.
- MRD-negative status was also observed in 5 of 9 patients with untreated AML who achieved CR or CRh.
- No specific single gene mutation was significantly predictive of clinical response or resistance to treatment with ivosidenib in the R/R AML patients presented. However, RTK pathway mutations were associated with a lack of response.

Acknowledgments

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