Ivosidenib (IVO) prior to hematopoietic cell transplant for patients with *IDH1*-mutant relapsed or refractory acute myeloid leukemia (R/R AML)

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Courtney D DiNardo[1], Eytan Stein[2], Arnaud Pigneux[3], Jessica K Altman[4], Robert Collins[5], Harry P Erba[6], Justin M Watts[7], Geoffrey L Uy[8], Bin Wu[9], Sung Choe[9], Stephanie M Kapsalis[9], Hua Liu[9], Thomas Winkler[9], Gail J Roboz[10], Stéphane de Botton[11]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; [4]Northwestern University, Chicago, IL, USA; [5]University of Texas Southwestern Medical Center, Dallas, TX, USA; [6]University of Alabama at Birmingham, Birmingham, AL, USA; [7]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [8]Washington University School of Medicine, St. Louis, MO, USA; [9]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [10]Weill Cornell Medicine and The New York Presbyterian Hospital, New York, NY, USA; [11]Institut Gustave Roussy, Villejuif, France

Email: medinfo@agios.com

BACKGROUND

- Allogeneic hematopoietic cell transplantation (HCT) provides a potentially curative option for patients with relapsed or refractory (R/R) acute myeloid leukemia (AML)[1]
- Pre-HCT remission status is a major determinant of long-term prognosis[2,3]
- Older and/or heavily pretreated patients frequently cannot tolerate intensive salvage chemotherapy to obtain adequate disease control prior to HCT[4]
- Mutations in the metabolic enzyme isocitrate dehydrogenase 1 (IDH1) are detected in approximately 6–10% of patients with AML[5-7] and result in the production of D-2-hydroxyglutarate (2-HG)
  - 2-HG production is suppressed through targeted inhibition of the mutant IDH1 (mIDH1) enzyme, which restores cell differentiation[8]
- Ivosidenib (IVO) 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
  - adults with R/R AML

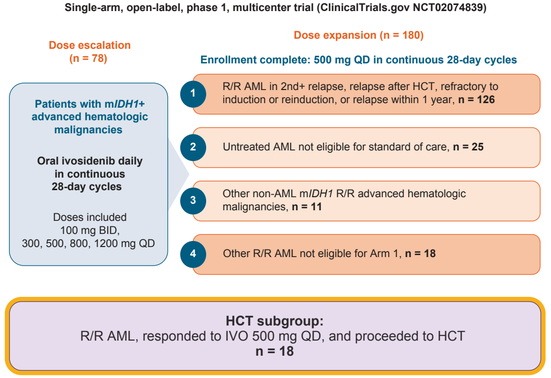
OBJECTIVE

- To assess HCT outcomes in 18 patients with m*IDH1* R/R AML who proceeded to HCT after responding to treatment with IVO in the AG120-C-001 phase 1 study

METHODS

- Here we report outcomes in patients with m*IDH1* R/R AML from the phase 1 study who received a starting dose of IVO 500 mg once daily (QD), responded to treatment, and then proceeded to HCT
- This was a multicenter, open-label, dose-escalation and expansion study enrolling patients ≥ 18 years of age with an advanced m*IDH1* hematologic malignancy (ClinicalTrials.gov NCT02074839)[9]
- IVO monotherapy was administered orally, daily, in continuous 28-day cycles (**Figure 1**)
  - During dose escalation, IVO was administered at doses of 200–1200 mg daily; 500 mg QD was selected for expansion
- Per protocol, patients with R/R AML achieving an adequate response to IVO and meeting other criteria required for transplant could proceed to HCT after discontinuation of IVO

Figure 1. Study design



From *N Engl J Med*, DiNardo CD et al, Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML, 378., Supplementary Appendix

BID = twice daily

- m*IDH1* variant allele frequency (VAF) from bone marrow mononuclear cells was assessed using BEAMing digital PCR (0.02–0.04% VAF detection limit)[9]
- Baseline co-mutation analysis was performed by next-generation sequencing on bone marrow samples[9]
- The data cutoff date for this analysis was 02Nov2018

RESULTS

- Baseline demographic and disease characteristics are reported in **Table 1**
- For patients who underwent HCT (n = 18), median (range) duration of IVO treatment prior to HCT was 3.9 (2.1–15.2) months

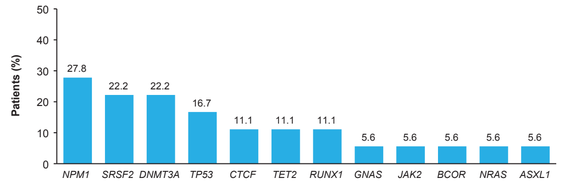
Table 1. Baseline demographic and disease characteristics

Baseline characteristic	IVO 500 mg QD, R/R AML	
	Patients who underwent HCT (n = 18)	Overall cohort (n = 179)[a]
Median (range) age, years	61.5 (36–68)	67.0 (18–87)
Female/male, n	8/10	89/90
Prior history of MDS, n (%)	1 (5.6)	29 (16.2)
AML classification, n (%)		
De novo	15 (83.3)	120 (67.0)
Secondary	3 (16.7)	59 (33.0)
ECOG PS, n (%)		
0	7 (38.9)	36 (20.1)
1	9 (50.0)	99 (55.3)
2	2 (11.1)	42 (23.5)
3[b]	0	2 (1.1)
Prior regimens, n (%)		
0	0	2 (1.1)[c]
1	10 (55.6)	75 (41.9)
2	5 (27.8)	52 (29.1)
≥ 3	3 (16.7)	50 (27.9)
Prior therapy type,[d] n (%)		
Intensive chemotherapy	18 (100.0)	127 (70.9)
Nonintensive therapy	5 (27.8)	115 (64.2)
Investigational	4 (22.2)	55 (30.7)
Prior HCT for AML, n (%)	2 (11.1)	43 (24.0)
Cytogenetic risk status, n (%)		
Intermediate	12 (66.7)	105 (58.7)
Poor	3 (16.7)	50 (27.9)
Unknown	0	5 (2.8)
Missing	3 (16.7)	19 (10.6)
Baseline cytogenetic results, n (%)		
Normal	10 (55.6)	60 (33.5)
Abnormal	5 (27.8)	100 (55.9)
Missing	3 (16.7)	19 (10.6)
Prior AML therapy outcomes,[e] n (%)		
Relapsed after transplant	2 (11.1)	43 (24.0)
In second or later relapse	2 (11.1)	26 (14.5)
Refractory to initial induction/reinduction therapy	13 (72.2)	106 (59.2)
Relapsed ≤ 1 year of initial therapy[f]	1 (5.6)	17 (9.5)
Other	2 (11.1)	20 (11.2)

[a]The overall cohort of 179 patients with R/R AML treated with IVO in the phase 1 study
[b]Patients met eligibility criteria at screening but had a decline in ECOG PS at time of treatment initiation
[c]Patients received prior AML therapies that were not cytotoxic regimens
[d]Patients may have received more than one type of therapy either simultaneously or sequentially
[e]Patients may appear in more than one category
[f]Excluding patients with favorable risk status according to National Comprehensive Cancer Network guidelines
ECOG PS = Eastern Cooperative Oncology Group Performance Status; MDS = myelodysplastic syndrome

- Baseline co-mutations in patients with m*IDH1* R/R AML who underwent HCT are shown in **Figure 2**

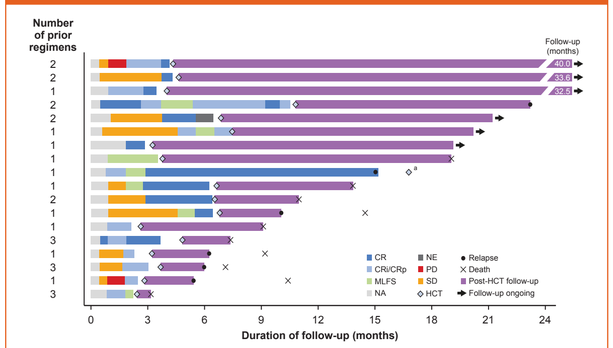
Figure 2. Baseline co-mutation rates: Patients with m*IDH1* R/R AML who underwent HCT (n = 18)[a]



[a]Assessed using a next-generation sequencing panel for hematologic malignancies; mutations occurring in at least one patient shown

- In the HCT subgroup, the best overall response (BOR) on IVO prior to HCT was complete remission (CR) in 66.7% (12 / 18) of patients, and last response prior to HCT was CR in 50% (9 / 18) of patients (**Figure 3**, **Table 2**)
  - The median (range) time from last IVO dose to HCT was 13.5 (1–50) days

Figure 3. Treatment duration, response, and post-HCT follow-up duration in patients who underwent HCT (n = 18)



[a]Patient underwent HCT as salvage therapy; no post-HCT follow-up data are available
NA = not assessed; PD = progressive disease; SD = stable disease

Table 2. BOR, duration on IVO, and last response prior to HCT for patients who underwent HCT (n = 18)

Patient	BOR on IVO	Duration on IVO, days	Time from last IVO dose to HCT, days	Last response evaluation prior to HCT	Post-HCT OS, months
1	CRh	227	1	CRi	12.7[a]
2	CR	63	18	CR	6.5
3	CR	105	18	CR	28.5[a]
4	CR	113	35	CR	2.6
5	CR	190	13	CR	7.3
6	MLFS	107	9	NE	15.3
7	CR	130	12	CR	29.4[a]
8	CRi/CRp	72	15	CRp	7.6
9	CRi/CRp	68	31	MLFS	6.0
10	CRi/CRp	90	23	CRp	3.4
11	CRi/CRp	67	8	MLFS	0.8
12	CR	462	50	RL	17.2[a]
13	CR	320	10	CRp	31.1[a]
14	CR	125	8	CR	35.7[a]
15	CR	195	5	CR	4.5
16	CR	196	14	NE	14.2[a]
17	CR	195	13	CR	7.7
18	CR	86	14	CR	15.8[a]

[a]Indicates censored observation
CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; CRp = complete remission with incomplete platelet recovery; MLFS = morphologic leukemia-free state; NE = not evaluable; OS = overall survival; RL = relapse

- In the HCT subgroup:
  - Median (95% CI) OS was 16.8 months (9.2, NE), calculated from the start of IVO treatment, compared with 9.0 months (7.1, 10.2) in the overall R/R AML study cohort (**Table 3**)
  - 6-month OS was 94.4% and 12-month OS was 61.1% (**Table 3**)
  - Median (range) duration of follow-up was 33.2 months (3.2–41.9)
- For patients achieving a BOR of CR, median (95% CI) OS was:
  - NE (9.1, NE) in the HCT subgroup (n = 12)
  - 20.5 months (16.4, NE) in those who did not undergo HCT (n = 31)
- Survival post HCT (**Table 3**):
  - Median (95% CI) relapse-free survival (RFS) post HCT was 7.3 months (2.6, NE); 6- and 12-month RFS rates post HCT were 58.8% and 47.1%, respectively
  - 6- and 12-month post-HCT OS rates were 77.8% and 50.0%, respectively

Table 3. OS and RFS outcomes

Outcome	IVO 500 mg QD, R/R AML	
	Patients who underwent HCT (n = 18)	Overall cohort (n = 179)[a]
OS[b]		
Median (95% CI), months	16.8 (9.2, NE)	9.0 (7.1, 10.2)
Censored,[c] n (%)	8 (44.4)	32 (17.9)
Survival rates, %		
6 months	94.4	61.9
12 months	61.1	37.5
OS post HCT[d]		
Median (95% CI), months	11.5 (6.0, NE)	-
Censored, n (%)	8 (44.4)	-
Survival rates, %		
6 months	77.8	-
12 months	50.0	-
RFS post HCT[e]		
Median (95% CI), months	7.3 (2.6, NE)	-
Censored, n (%)	6 (35.3)	-
Survival rates, %		
6 months	58.8	-
12 months	47.1	-

[a]The overall cohort of 179 patients with R/R AML treated with IVO in the phase 1 study
[b]Calculated as the time from the first dose to the date of death due to any cause
[c]Five patients in remission, two relapsed and in survival follow-up, and one lost to follow-up
[d]Calculated as the time from transplant to the date of death due to any cause
[e]Calculated as the time from date of transplant to date of documented confirmed PD/relapse or death, whichever occurs first

- In the HCT subgroup, m*IDH1* clearance occurred in 1 of 12 (8.3%) patients with BOR of CR, and in 0 of 1 patient with BOR of CRh (**Table 4**)

Table 4. *IDH1* mutation clearance status at any assessment prior to HCT

IDH1 mutation clearance, n / N (%)	IVO 500 mg QD, R/R AML	
	Patients who underwent HCT (n = 18)	Overall cohort (n = 179)[a]
Detection limit 0.02–0.04%[b]		
All patients	1 / 18 (5.6)	14 / 145 (9.7)
CR	1 / 12 (8.3)	12 / 43 (27.9)
CRh	0 / 1 (0)	2 / 14 (14.3)

[a]The overall cohort of 179 patients with R/R AML treated with IVO in the phase 1 study
[b]When ≤ 1% VAF cutoff was applied, *IDH1* mutation clearance was observed in 6 of 18 (33.3%) patients in the HCT subgroup with CR/CRh, including 6 of 12 (50.0%) with CR

CONCLUSIONS

- **IVO monotherapy is a potential treatment option to induce remissions prior to HCT for patients with m*IDH1* R/R AML who were not previously considered candidates for intensive salvage therapy**
- **Post-transplant survival rates are encouraging and warrant further investigation of IVO monotherapy or combination salvage therapies prior to HCT**
- **The molecular clearance of m*IDH1* before HCT does not appear to be a prerequisite for successful HCT**
- **The potential of IVO is being assessed in other HCT settings**
  - **An ongoing phase 1 study (ClinicalTrials.gov NCT03564821) is assessing IVO in post-HCT maintenance in patients with m*IDH1* myeloid neoplasms**

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Disclosures
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