Abstract 7015

Differentiation Syndrome Associated with Enasidenib, a Selective Inhibitor of Mutant Isocitrate Dehydrogenase 2 (m*IDH2*)

[1,2]Amir T. Fathi, [3]Courtney D. DiNardo, [4]Irina Kline, [4]Laurie Kenvin, [4]Ira Gupta, [5]Eyal C. Attar, [6,7]Eytan M. Stein, and [8]Stephane de Botton, on behalf of the AG221-C-001 Study Investigators

[1]Massachusetts General Hospital Cancer Center, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Celgene Corporation, Summit, NJ; [5]Agios Pharmaceuticals, Inc., Cambridge, MA; [6]Memorial Sloan Kettering Cancer Center, New York, NY;[7]Weill Cornell Medical College, New York, NY; [8]Gustave Roussy, Villejuif, France

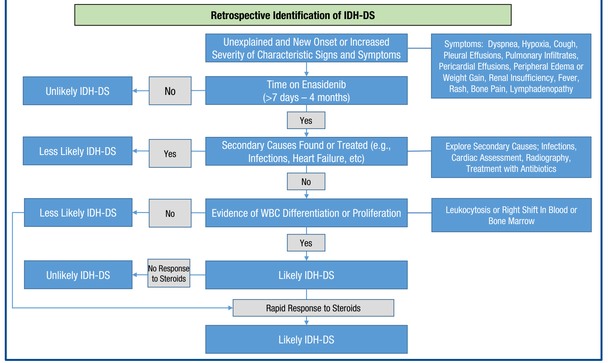
BACKGROUND

- Mutations in *isocitrate dehydrogenase 2* (m*IDH2*) genes occur in ~8-19% of patients with acute myeloid leukemia (AML)[1-4]
- Enasidenib (AG-221) is a first-in-class, oral, selective, small-molecule inhibitor of mIDH2 proteins shown to promote myeloid differentiation of leukemic blasts from patients with AML *ex vivo*[5]
- Treatment with enasidenib can result in IDH-inhibitor-associated differentiation syndrome (IDH-DS), with manifestations similar to DS seen during all-trans retinoic acid (ATRA) or arsenic trioxide (ATO) treatment of acute promyelocytic leukemia (APL)

METHODS

- An independent Differentiation Syndrome Review Committee (DSRC) was formed to review potential cases of IDH-DS occurring in a phase 1/2 study of enasidenib in patients with advanced hematologic malignancies (NCT01915498)
- Reported here are outcomes for 109 patients included in the phase 1 dose-escalation and expansion portions of the study who had relapsed or refractory (R/R) AML and who received enasidenib 100 mg daily–the dose currently under review for market authorization
- The study Sponsor reviewed patients' case report forms for signs and symptoms suggestive of IDH-DS, including fever, lung infiltrates, pleural or pericardial effusions, rapid weight gain, edema, and creatinine >2x baseline level, and provided them to the DSRC for review (**Figure 1**)
- Of the 109 R/R AML patients, the DSRC identified and retrospectively reviewed 27 cases suggestive of IDH-DS (8 investigator-reported IDH-DS cases and 19 suggestive cases based on reported signs and symptoms), to determine their consistency with IDH-DS

Figure 1. Process for retrospective identification of IDH-DS by DSRC members



RESULTS

- The DSRC found 13 of the 27 retrospectively reviewed cases to be possible or probable IDH-DS (11.9% of 109 patients in the R/R AML 100-mg daily subgroup)
- Baseline characteristics of R/R AML patients who received enasidenib 100-mg daily, with or without experiencing IDH-DS, are shown in **Table 1**
- Median time to IDH-DS onset was 30 days (range 7-116)
- Manifestations of IDH-DS in >2 patients were:
  - Dyspnea (n=10)
  - Pyrexia (n=9)
  - Lung infiltrates (n=8)
  - Pleural effusion (n=5)
  - Kidney injury (n=3)
- IDH-DS was effectively managed with systemic corticosteroids
- Investigator-reported leukocytosis accompanied 4 cases, with hydroxyurea used for cytoreduction
- Enasidenib treatment was interrupted for 9 patients (median interruption, 7 days)
  - Due to its long half life (>40 hours[6]), enasidenib interruption may not immediately reverse symptoms of IDH-DS
- Enasidenib dose reductions or permanent discontinuation of treatment were not required
- Six of 13 patients had a hematologic response (**Figure 2**); 6 patients maintained stable disease, in most cases with evidence of myeloid differentiation at the time of IDH-DS; and 1 patient experienced only disease progression on-study

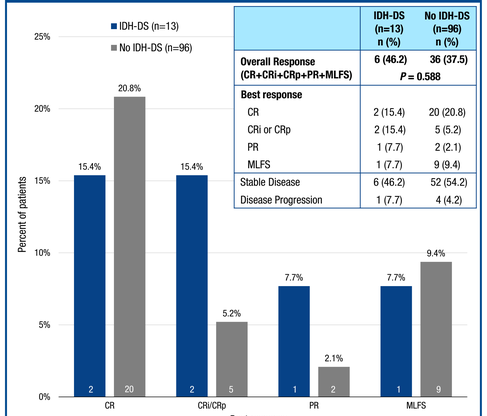
RESULTS

Table 1. Baseline characteristics of patients with or without IDH-DS

Characteristic	IDH-DS (n=13*)	No IDH-DS (n=96*)	*P* value
Age (years), median (range)	67 (42, 74)	66.5 (19, 100)	0.620
Sex, n (%)			
Male	4 (31)	42 (44)	0.551
Female	9 (69)	54 (56)	
ECOG PS, n (%)			
0	4 (31)	21 (22)	0.759
1	8 (62)	60 (63)	
2	1 (8)	15 (16)	
IDH2 mutation site, n (%)			
R140	9 (69)	74 (78)	0.493
R172	4 (31)	21 (22)	
Mutant *IDH2* variant allele frequency	19.5 (2.1, 36.6)	12.3 (1.6, 40.4)	0.917
Prior anti-cancer regimens, median (range)	1.0 (1.0, 3.0)	1.0 (1.0, 6.0)	0.386
Prior MDS, n (%)			
Yes	3 (23)	14 (15)	0.424
No	10 (77)	82 (85)	
WBC count (x10^9/L), median (range)	5.7 (0.8, 32.0)	2.7 (0.2, 88.2)	0.210
Peripheral blasts (%), median (range)	21.3 (4.0, 76.0)	14.0 (0.0, 96.0)	0.485
Bone marrow blasts (%), median (range)	49.0 (15.0, 85.0)	51.5 (0.0, 96.0)	0.943
Hemoglobin (g/dL), median (range)	9.7 (7.0, 10.3)	9.3 (6.9, 13.8)	0.822
Platelet count (x10^9/L)), median (range)	31.0 (10.0, 372.0)	39.0 (1.0, 292.0)	0.948
Serum creatinine (mg/dL), median (range)	0.7 (0.4, 1.0)	0.8 (0.3, 1.7)	0.413
LDH (U/L), median (range)	249 (153, 718)	286 (98, 4979)	0.516
NPM1 co-mutation, n (%)	1 (8)	7 (7)	1.000
FLT3-TKD co-mutation, n (%)	0	6 (6)	1.000
FLT3-ITD co-mutation, n (%)	0	1 (1)	1.000
Cytogenetic risk status, n (%)	n=10	n=70	
Intermediate-Risk	6 (60)	45 (64)	1.000
Poor-Risk	4 (40)	25 (36)	

*Data not available for all patients for some variables
ECOG PS, Eastern Cooperative Oncology Group performance status; IDH-DS, IDH-inhibitor-associated differentiation syndrome; LDH, lactate dehydrogenase; MDS, myelodysplastic syndromes; ULN, upper limit of normal; WBC, white blood cell

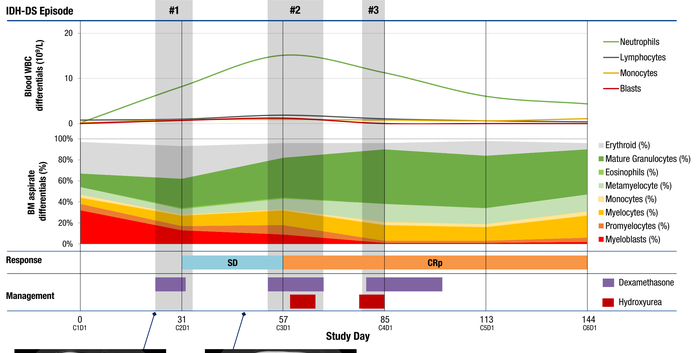
Figure 2. Response outcomes for patients with or without IDH-DS

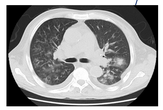


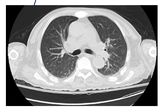
	IDH-DS (n=13) n (%)	No IDH-DS (n=96) n (%)
Overall Response (CR+CRi+CRp+PR+MLFS)	**6 (46.2)**	**36 (37.5)**
	***P* = 0.588**	
Best response		
CR	2 (15.4)	20 (20.8)
CRi or CRp	2 (15.4)	5 (5.2)
PR	1 (7.7)	2 (2.1)
MLFS	1 (7.7)	9 (9.4)
Stable Disease	6 (46.2)	52 (54.2)
Disease Progression	1 (7.7)	4 (4.2)

One patient was not evaluable for response; the patient developed IDH-DS on the 9th study day and discontinued treatment before a response assessment.
CR, complete remission; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; PR, partial remission

Figure 3. Clinical and laboratory profiles for a responding patient with enasidenib-induced IDH-DS







The scan on the left, taken on day 23 of enasidenib treatment, shows bilateral, fluffy pulmonary infiltrates and small bilateral pleural effusions

The patient received dexamethasone treatment for 9 days; the scan on the right shows clearing of pulmonary infiltrates and resolution of pleural effusions

Patient characteristics and medical history; enasidenib treatment

- 72-year-old male R/R AML patient in phase 2 study extension
- Prior history of MDS
- Refractory to 7+3 standard chemotherapy
- Received enasidenib 100 mg QD

IDH-DS signs & symptoms

Parameter	Yes/No
Unexplained fever	Yes
Dyspnea	Yes
Hypoxia	Yes
Pulmonary infiltrates	Yes
Pleural effusion	Yes
Pericardial effusion	Yes
Weight gain >5 kg	Yes
Rash	Yes
Lymphadenopathy	No
Bone pain	No
Acute kidney injury	No
DIC	No

TEAEs associated with IDH-DS episode

Episode #1: Days 23-34
Differentiation syndrome (preferred term: "Retinoic acid syndrome"; grade 3)
Peripheral edema (grade 1)
Febrile neutropenia (grade 3)
Leukocytosis (grade 2)
Respiratory failure (grade 4)

Episode #2: Days 53-68
Differentiation syndrome (grade 2)
Pyrexia (grade 2)
Dyspnea (grade 1)

Episode #3: Days 79-85
Differentiation syndrome (grade 2)
Pyrexia (grade 1)

IDH-DS management

Episode #1: days 23-34
Dexamethasone: days 24-33
No hydroxyurea
Drug interruption: days 25-26

Episode #2: days 53-68
Dexamethasone: days 53-68
Hydroxyurea: days 59-66
Drug interruptions: days 54-58

Episode #3: days 79-85
Dexamethasone: days 80-101
Hydroxyurea: days 78-85
No drug interruptions

Duration of treatment and response

- Date of first dose of enasidenib: 29 Feb 2016
- CRp achieved on 23 May 2016 (day 85); patient relapsed on 10 Oct 2016 (day 225)
- Date of last dose: 28 Jan 2017
- Duration of treatment: 335 days
- Reason for discontinuation: adverse event (grade 4 respiratory failure)
- Non-IDH-DS-related respiratory failure ultimately led to death

CRp, CR with incomplete platelet count recovery; DIC, disseminated intravascular coagulation; IDH-DS, IDH-inhibitor-associated differentiation syndrome; MDS, myelodysplastic syndromes; R/R AML, relapsed/refractory acute myeloid leukemia; SD, stable disease; TEAE, treatment-emergent adverse event

CONCLUSIONS

- The characteristic IDH-DS signs and symptoms are recognizable and treatable; the potential for this event should not deter use of enasidenib for patients with m*IDH2* hematologic malignancies who may benefit from enasidenib
- Systemic corticosteroids (e.g., dexamethasone 10 mg every 12 hours), close hemodynamic monitoring, and hydroxyurea (in the presence of leukocytosis) are effective management strategies, and should be administered promptly when IDH-DS is suspected, and continued until improvement (**Table 2**)
- Enasidenib interruption can be considered for severe pulmonary symptoms or renal dysfunction, if initial intervention is unsuccessful
- IDH-DS represents a novel clinical finding in patients with m*IDH2* AML treated with enasidenib, and is likely due to its purported mechanism of action; i.e., differentiation of leukemic cells

Table 2. Management of patients with suspected IDH-DS

Conditions with signs and symptoms of IDH-DS, and refractory to treatment for other potential or suspected cause(s), or that worsen within the first 48 hours after treatment initiation, should be managed as IDH-DS

The measures below are recommended to be taken at the earliest manifestations of suspected IDH-DS:

- Patients with severe or rapidly progressing IDH-DS should be hospitalized for continued observation
- In case of uncertainty with the diagnosis, e.g., presence of less specific symptoms of moderate severity, patients should be closely monitored, as the condition may rapidly worsen
- Corticosteroids should be promptly initiated (e.g., 10 mg of dexamethasone every 12 hours until resolution of IDH-DS), after which the corticosteroid dose can be progressively reduced over 1-2 weeks
- Enasidenib may be withheld at the physician's discretion. Due to the long half-life of enasidenib, treatment interruption may not immediately reverse symptoms of IDH-DS. If interrupted, enasidenib treatment may be reinitiated at the original or a reduced dose, once the signs and symptoms resolve and the patient's clinical condition improves
- In patients with elevated WBC counts, prompt initiation of hydroxyurea is suggested, or treated as per standard local practice (e.g., dose of 2 to 3g PO 2- or 3-times daily for WBC >30x10^9/L)
- In cases of severe leukocytosis, use of leukapheresis may be appropriate
- For substantial fluid accumulation, initiation of furosemide may be appropriate, as per local standard practice
- Pericardial effusion (a less common manifestation of IDH-DS) can be a life-threatening condition that requires urgent cardiac intervention
- Patients with increasing serum creatinine levels should be evaluated for tumor lysis syndrome
- Patients experiencing a rapid increase in peripheral blood cells should be monitored for disseminated intravascular coagulopathy and hemorrhage
- Imaging techniques such as standard or high-resolution computerized tomography (CT) scan and chest X-ray are useful in establishing a diagnosis of IDH-DS by identifying pulmonary infiltrates or effusions; however, chest X-ray is less sensitive in detecting early radiological signs of IDH-DS–associated changes

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CORRESPONDENCE

Amir T. Fathi – AFATHI@mgh.harvard.edu

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