Published OnlineFirst May 11, 2020; DOI: 10.1158/1078-0432.CCR-20-0834

Differentiation Syndrome with Ivosidenib and Enasidenib Treatment in Patients with Relapsed or Refractory IDH-Mutated AML: A U.S. Food and Drug Administration Systematic Analysis

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ABSTRACT

Purpose: Differentiation syndrome (DS) is a serious adverse reaction of isocitrate dehydrogenase (IDH) inhibitors ivosidenib and enasidenib in patients with *(IDH)1*- and *IDH2*-mutated acute myeloid leukemia (AML), respectively.

Experimental Design: During FDA review of marketing applications for ivosidenib and enasidenib, data from pivotal trials were queried to identify cases of DS in patients with relapsed or refractory (R/R) AML. One hundred seventy-nine patients with R/R AML received ivosidenib and 214 received enasidenib. Adverse events, labs, and vital signs in the first 90 days of treatment were screened per diagnostic criteria, and narratives were reviewed to adjudicate DS cases.

Results: We identified 72 of 179 (40%) potential cases for ivosidenib and 86 of 214 (40%) for enasidenib; 34 of 179 (19%) and 41 of 214 (19%) were adjudicated as DS. Leukocytosis was present in 79% and 61% of cases, respectively. Median (range) time to onset was 20 (1–78) and 19 (1–86) days. Grade ≥ 3 adverse reactions occurred in 68% and 66%; 6% and 5% were fatal. Univariate analyses suggested baseline bone marrow blasts ≥ 48% and peripheral blood blasts ≥ 25% and 15% for ivosidenib and enasidenib, respectively, were associated with increased risk of DS. Complete remission (CR) + CR with partial hematologic recovery rates were lower in patients with versus without DS [ivosidenib 18% (95% confidence interval, 7%–35%) vs. 36% (28%–45%); enasidenib 18% (7%–33%) vs. 25% (18%–32%)].

Conclusions: DS is a common and potentially fatal adverse reaction of IDH inhibitors, and use of standardized diagnostic criteria may aid in earlier diagnosis and treatment.

See related commentary by Zeidner, p. 4174

Introduction

Mutations in isocitrate dehydrogenase (*IDH)1* and *IDH2* are found in 6% to 16% and 8% to 19% of patients with acute myeloid leukemia (AML), respectively (1). Mutated IDH produces the oncometabolite 2-hydroxyglutarate (2-HG), which alters normal DNA methylation and impairs differentiation (1). Ivosidenib (Agios Pharmaceuticals, Inc.) and enasidenib (Celgene) are small-molecule inhibitors of IDH1 and IDH2 approved by the FDA for treatment of adults with relapsed or refractory (R/R) *IDH1*- or *IDH2*-mutated AML, respectively. Ivosidenib was also approved by FDA for treatment of newly diagnosed *IDH1*-mutated AML in adults ≥ 75 years or with comorbidities that preclude use of intensive induction chemotherapy. Approvals were based on demonstration of durable complete remission (CR) + CR with partial hematologic recovery (CRh) and conversion from transfusion dependence to transfusion independence in the setting of a tolerable safety profile (2–4). Both drugs inhibit 2-HG formation and induce myeloid differentiation in patients with AML with *IDH1* or *IDH2* mutations (5, 6).

Differentiation syndrome (DS) is a clinical syndrome first described by Frankel and colleagues in 1992 in patients with acute promyelocytic leukemia (APL) treated with all-trans retinoic acid (ATRA). Symptoms included dyspnea, fever, weight gain, unexplained hypotension, acute renal failure, and chest radiograph demonstrating pulmonary infiltrates or pleuropericardial effusion (7). Montesinos and colleagues later classified patients with APL treated with ATRA in combination with idarubicin as having DS based on presence of 2 or more of the aforementioned signs and symptoms (8). Patients with two or three criteria were classified as having moderate and those with at least four were classified as having severe DS. DS was excluded in cases with an alternative explanation (e.g., septic shock, cardiac failure).

The incidence of DS in patients with R/R AML treated with ivosidenib and enasidenib on pivotal trials leading to FDA approval ranged from 11% to 14%, based on investigator report or review committee determination (5, 9, 10). During review of the New Drug Applications (NDA) for ivosidenib and enasidenib, FDA suspected that episodes of DS may have been underreported, as both trials were first-in-human experiences where the signs and symptoms were not initially recognized as DS. Furthermore, there was no codified adverse event (AE) term for DS outside of the context of APL or retinoic acid. Thus, FDA sought to perform a systematic analysis of DS cases based on AE terms, laboratory abnormalities, and vital sign results grouped per Montesinos criteria. We hypothesized that using an algorithmic

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Clin Cancer Res 2020;26:4280–8

doi: 10.1158/1078-0432.CCR-20-0834

Published OnlineFirst May 11, 2020; DOI: 10.1158/1078-0432.CCR-20-0834

Translational Relevance

Isocitrate dehydrogenase (*IDH*)*1*- and *IDH2*-mutated acute myeloid leukemia (AML) comprises a small subset of patients with AML characterized by production of the oncometabolite 2-hydroxyglutarate, which alters DNA methylation and impairs differentiation. The marketed IDH1 and IDH2 inhibitors ivosidenib and enasidenib, respectively, cause a differentiation syndrome (DS) that may be underrecognized. The FDA queried individual patient data from phase I/II trials of ivosidenib and enasidenib submitted in support of marketing applications, per prespecified clinical criteria, which demonstrated an increased incidence of DS comparative to initial reports. Relative risk (RR) of DS was higher for patients with baseline bone marrow blasts ≥ 48% and peripheral blood blasts ≥ 25% and 15% for ivosidenib and enasidenib, respectively. The occurrence of DS was not associated with responses to IDH inhibitor therapy. Exploratory genomic analyses indicated that mutations in *TET2* for ivosidenib and *SRSF2* for enasidenib may increase the RR of DS.

approach would uncover a higher incidence of DS than reported initially.

Patients and Methods

Study design and participants

This analysis included Studies AG120-C-001 (NCT02074839; ref. 5) for ivosidenib and AG221-C-001 (NCT01915498; refs. 6, 11) for enasidenib submitted to FDA in support of marketing applications by Agios Pharmaceuticals, Inc. and Celgene, respectively, before January 1, 2019. These studies were multicenter, open-label, single-arm, dose-escalation, and expansion trials of ivosidenib or enasidenib in patients with hematologic malignancies with mutant-*IDH1* or *IDH2*, respectively. Eligibility criteria and treatment details have been described elsewhere (5, 6, 11). This analysis focused on patients with R/R AML treated with approved doses of ivosidenib (500 mg orally once daily) or enasidenib (100 mg orally once daily). All patients in the included trials were required to provide written informed consent, and the trials had institutional review board or ethics committee approval.

Protocol amendments for both studies in February 2015 provided management guidelines for suspected DS, including prompt administration of dexamethasone 10 mg i.v. every 12 hours until disappearance of signs and symptoms for at least 3 days (3, 12). Hydroxyurea 2 to 3 g orally twice or three times daily was recommended for subjects with an elevated white blood cell (WBC) count. Furosemide and/or leukapheresis were recommended if indicated clinically. The study drugs could be withheld at investigators' discretion and resumed once signs/symptoms of DS resolved.

Procedures

During review of NDA submissions for ivosidenib and enasidenib, we devised an algorithm (Supplementary Table S1) to screen patient-level data for potential DS using AE, laboratory, and vital sign data within the first 90 days of treatment with ivosidenib or enasidenib. Using data from patients who received at least one dose of therapy, the algorithm grouped search terms based on Montesinos criteria (8): (i) dyspnea, (ii) unexplained fever, (iii) weight gain, (iv) unexplained hypotension, (v) acute renal failure, and (vi) pulmonary infiltrates or pleuropericardial effusion. Furthermore, we added a category for multiple organ dysfunction syndrome, because this could satisfy multiple criteria. Patients with two or more criteria within 7 days of one another, or a single AE of IDH DS or retinoic acid syndrome, were considered potential DS. Two FDA oncologists reviewed narratives and laboratory data from algorithmically identified cases, considering signs of cellular differentiation in the blood and bone marrow and presence of an alternative explanation for signs and symptoms (i.e., confirmed infection, inconsistent clinical course, or progressive disease), and reached consensus agreement via mutual discussion regarding final adjudication of DS. DS was considered moderate when 2 or 3 criteria were met and severe with 4 or more criteria. Repeat DS episodes were defined as distinct episodes separated by >14 days. Concomitant leukocytosis was defined as an AE of leukocytosis, hyperleukocytosis, or WBC count increased, and/or laboratory result of leukocytes > 10 Gi/L within 7 days of clinical signs/symptoms.

Next-generation sequencing (NGS) data from bone marrow and/or peripheral blood were available at baseline for a subset of patients. Study AG120-C-001 (ivosidenib) data were generated with the FoundationOne Heme panel (Foundation Medicine, Inc.; ref. 13) during dose escalation ($n = 35$) and Brigham and Women's Hospital Rapid Heme Panel (14) during dose expansion ($n = 144$). Study AG221-C-001 (enasidenib) data from dose escalation and expansion were generated with the FoundationOne Heme panel ($n = 47$), which detects short variants, rearrangements, and copy-number alterations in 405 genes. The Rapid Heme Panel detects single-nucleotide variants and small insertions/deletions in 95 genes. There are 58 genes in common between the panels. All reported variant types annotated as known or likely oncogenic were included. The number of comutated genes was calculated as the number of genes mutated per patient, not including *IDH1* (for ivosidenib) or *IDH2* (for enasidenib); mutations in multiple samples and unique mutations in the same gene were not counted more than once. Oncoprints were generated using cBioPortal version 3.1.0 (https://www.cbioportal.org/; ref. 15).

Outcomes

Both trials included efficacy endpoints of CR, defined per Cheson and colleagues (16), and CRh, defined as CR but with absolute neutrophil count (ANC) > 0.5 to 1.0 Gi/L and platelets > 50 to 100 Gi/L. Efficacy analyses by occurrence of DS considered patients treated with ivosidenib ($n = 174$) or enasidenib ($n = 199$) with confirmed *IDH* mutations using FDA-approved companion diagnostic tests. Duration of response (DOR) was defined as time from first response of CR/CRh to relapse or death, whichever was earlier. Overall survival (OS) was defined from the date of treatment initiation until death from any cause.

Statistical methods

To identify potential risk factors for DS, exploratory analyses of relative risk (RR) of DS according to baseline patient and disease characteristics were quantified. Available demographic and clinical characteristics included age, sex, race, Eastern Cooperative Oncology Group performance status, number of prior treatment regimens, and prior hematopoietic stem cell transplantation (HSCT). Baseline laboratory and disease characteristics included lactate dehydrogenase (LDH), creatinine clearance, WBC count, peripheral blood blast percentage, bone marrow blast percentage, ANC, secondary versus *de novo* AML, poor versus intermediate cytogenetics, and *IDH* mutation subtype. Multivariable models were built based on characteristics found to have a large unadjusted estimated effect size in the univariate setting, defined as those with lower bound of 95% confidence interval

Published OnlineFirst May 11, 2020; DOI: 10.1158/1078-0432.CCR-20-0834

(CI) ≥ 0.9. Variables were assessed initially in their continuous form but are presented in tables categorized by median values to aid in interpretation. Separate exploratory univariate analyses were performed for the subset of patients with available genomic data.

Response rates were reported with exact two-sided 95% CIs calculated using Clopper–Pearson methods. Kaplan–Meier methods (17) were used to estimate OS and DOR. Given the lack of prespecified hypothesis testing, *P* values are not provided, in conformance with published guidelines (18). Comutation analyses were generated, and figures created using JMP software version 13.1.0. All additional analyses were generated using SAS software version 9.4, R version 3.4.3, and RStudio 1.1.456.

Results

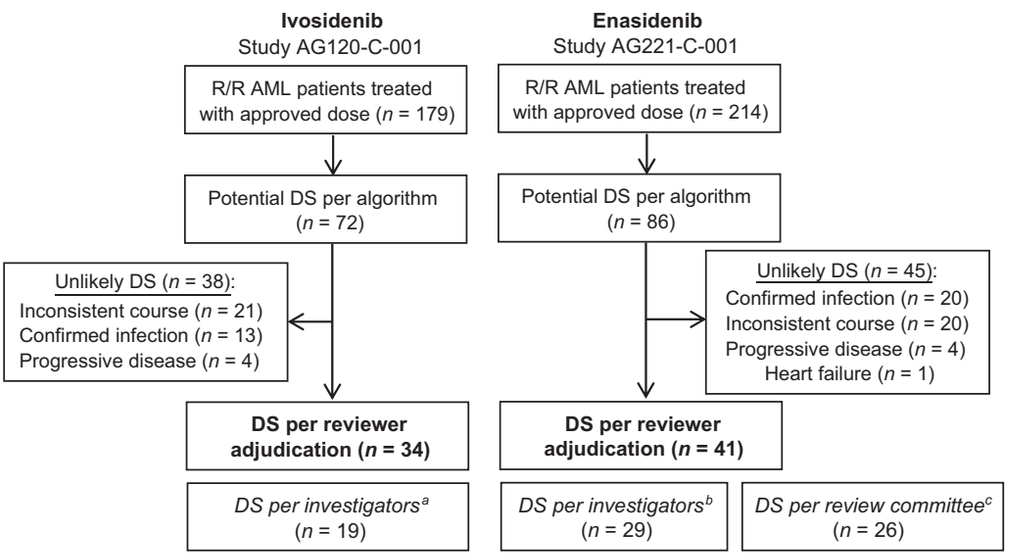
Incidence of DS

On Study AG120-C-001, 179 patients with R/R AML initiated treatment with ivosidenib 500 mg orally once daily between July 29, 2014, and May 8, 2017, with data cutoff November 10, 2017. On Study AG221-C-001, 214 patients were treated with enasidenib 100 mg orally once daily between December 9, 2013, and May 19, 2016, with data cutoff October 14, 2016. The algorithm identified potential DS in 40% of patients treated with ivosidenib (72/179) and enasidenib (86/214; **Fig. 1**). FDA reviewer adjudication revealed that roughly half the cases identified by the algorithm were DS for ivosidenib (34/179, 19%) and enasidenib (41/214, 19%). The most common reasons for excluding DS were inconsistent clinical course and confirmed infection. Reasons for a clinical course inconsistent with DS included presence of only mild, nonspecific symptoms (e.g., grade 1 cough, creatinine in normal range; $n = 12$ ivosidenib, $n = 12$ enasidenib), explained hypotension ($n = 3$ ivosidenib, $n = 2$ enasidenib), symptoms present at baseline ($n = 3$ ivosidenib), isolated leukocytosis without clinical symptoms in investigator-diagnosed cases ($n = 2$ ivosidenib), explained edema ($n = 2$ enasidenib), improvement with antibiotics without confirmed infection ($n = 2$ enasidenib), high suspicion of infection without signs of cellular differentiation ($n = 1$ enasidenib), and postoperative complications ($n = 1$ ivosidenib and enasidenib). **Table 1** shows demographics and disease characteristics by FDA-adjudicated DS. The relationship between FDA-adjudicated DS cases and cases diagnosed by investigators or review committee determination is described in more detail in Supplementary Fig. S1.

Prognostic factors for DS

Univariate analysis of potential risk factors suggested patients with baseline peripheral blood and bone marrow blast percentages ≥ median for both drugs (peripheral blasts ≥ 25% for ivosidenib and ≥ 15% for enasidenib; bone marrow blasts ≥ 48% for both drugs) and secondary versus *de novo* AML for ivosidenib had higher RR of DS (**Table 2**). The multivariable model for ivosidenib included baseline bone marrow and peripheral blood blast percentages, secondary versus *de novo* AML, WBC, and LDH. Multivariable model for enasidenib included baseline bone marrow and peripheral blood blast percentages. Neither multivariable model identified a baseline characteristic with lower bound of 95% CI ≥ 1, but peripheral blood and bone marrow blast percentages retained the largest effect sizes across both drugs.

Of 144 patients from the expansion phase of the ivosidenib trial with available genomic data, RR of DS was higher in patients with comutation of *TET2* [6/28 with DS, 7/116 without DS; RR 2.7 (95% CI, 1.4–5.5; Supplementary Fig. S2]. No genomic associations were observed with DS using data from the dose-escalation phase of the ivosidenib trial ($n = 35$; 6 with DS, Supplementary Fig. S2); *TET2* was mutated in only 1 of 35 patients. For enasidenib ($n = 47$), RR of DS was higher in patients with comutation in *SRSF2* [7/10 with DS, 13/37 without DS; RR 3.2 (95% CI, 0.9–10.7); Supplementary Fig. S2). Of note, *SRSF2* was the most frequently comutated gene [in 20/47 (43%) patients] in the



[a]DiNardo et al. (5)
[b]IDHIFA prescribing information (10)
[c]Fathi et al. (9)

Figure 1.
Flow diagram for ascertainment of DS cases.

Published OnlineFirst May 11, 2020; DOI: 10.1158/1078-0432.CCR-20-0834

Table 1. Baseline patient and disease characteristics by DS.

	Ivosidenib			Enasidenib		
	Total (*n* = 179)	**DS (*n* = 34)**	**No DS (*n* = 145)**	**Total (*n* = 214)**	**DS (*n* = 41)**	**No DS (*n* = 173)**
Age						
Median (range)	67 (18–87)	68 (45–87)	67 (18–86)	68 (19–100)	67 (42–89)	68 (19–100)
<65 y, *n* (%)	67 (37)	13 (38)	54 (37)	85 (40)	18 (44)	67 (39)
≥65 y, *n* (%)	112 (63)	21 (62)	91 (63)	129 (60)	23 (56)	106 (61)
Sex, *n* (%)						
Female	89 (50)	19 (56)	70 (48)	105 (49)	19 (46)	86 (50)
Male	90 (50)	15 (44)	75 (52)	109 (51)	22 (54)	87 (50)
Race, *n* (%)						
White	112 (63)	20 (59)	92 (63)	164 (77)	29 (71)	135 (78)
Black	10 (6)	3 (9)	7 (5)	12 (6)	2 (5)	10 (6)
Asian	6 (3)	0 (0)	6 (4)	1 (<1)	1 (2)	0 (0)
Other	9 (5)	3 (9)	6 (4)	3 (1)	1 (2)	2 (1)
Not provided	42 (23)	8 (24)	34 (23)	34 (16)	8 (20)	26 (15)
ECOG PS, *n* (%)						
0–1	135 (75)	23 (68)	112 (77)	181 (85)	34 (83)	147 (85)
≥2	44 (25)	11 (32)	33 (23)	32 (15)	7 (17)	25 (14)
Missing	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (1)
Type of AML, *n* (%)						
De novo	120 (67)	17 (50)	103 (71)	163 (76)	30 (73)	133 (77)
Secondary	59 (33)	17 (50)	42 (29)	51 (24)	11 (27)	40 (23)
Cytogenetics,[a] *n* (%)						
Intermediate	105 (59)	18 (53)	87 (60)	108 (50)	18 (44)	90 (52)
Poor	50 (28)	11 (32)	39 (27)	55 (26)	13 (32)	42 (24)
Unknown/missing	24 (14)	5 (15)	19 (13)	51 (24)	10 (24)	41 (23)
IDH mutation, *n* (%)						
IDH1 R132C	102 (57)	19 (56)	83 (57)	—	—	—
IDH1 R132H	42 (23)	12 (35)	30 (21)	—	—	—
IDH1 R132G/L/S	29 (16)	3 (9)	26 (18)	—	—	—
NA/ND	6 (4)	0 (0)	6 (4)	3 (1)	0 (0)	3 (2)
IDH2 R140	—	—	—	161 (75)	33 (80)	128 (74)
IDH2 R172	—	—	—	50 (23)	8 (20)	42 (24)
Prior regimens, *n* (%)						
1 prior regimen	75 (42)	12 (35)	63 (43)	98 (46)	23 (56)	75 (43)
≥2 prior regimens	102 (57)	21 (62)	81 (56)	116 (54)	18 (44)	98 (57)
Missing	2 (1)	1 (3)	1 (1)	0 (0)	0 (0)	0 (0)
Prior HSCT, *n* (%)						
Yes	43 (24)	11 (32)	32 (22)	29 (14)	7 (17)	22 (13)
WBC count (Gi/L)						
Median (range)	1.9 (0.1–47.5)	3.6 (0.3–32.5)	1.6 (0.1–47.5)	2.3 (0.2–93.8)	2.8 (0.4–93.8)	2.3 (0.2–88.2)
<10, *n* (%)	145 (81)	27 (79)	118 (81)	164 (77)	28 (68)	136 (79)
≥10, *n* (%)	34 (19)	7 (21)	27 (19)	49 (23)	13 (32)	36 (21)
Missing, *n* (%)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (1)
ANC (Gi/L)						
Median (range)	0.19 (0–10.9)	0.20 (0–4.5)	0.15 (0–10.9)	0.39 (0–38)	0.40 (0–38)	0.39 (0–18)
ANC < 500, *n* (%)	124 (69)	23 (68)	101 (70)	119 (56)	23 (56)	96 (55)
ANC ≥ 500, *n* (%)	48 (27)	11 (32)	37 (26)	91 (43)	17 (41)	74 (43)
Missing, *n* (%)	7 (4)	0 (0)	7 (5)	4 (2)	1 (2)	3 (2)
Peripheral blast (%)						
Median (range)	24.5 (0–97)	34 (0–96.5)	19.5 (0–97)	14.5 (0–98)	43.5 (0–96)	13 (0–98)
<20%, *n* (%)	75 (42)	9 (26)	66 (46)	101 (47)	13 (32)	88 (51)
≥20%, *n* (%)	89 (50)	23 (68)	66 (46)	81 (38)	20 (49)	61 (35)
Missing, *n* (%)	15 (8)	2 (6)	13 (9)	32 (15)	8 (20)	24 (14)
BM blast (%)						
Median (range)	48 (0–98)	59 (0–97)	42 (4–98)	48 (0–98)	63 (1–98)	42 (0–96)
<50%, *n* (%)	90 (50)	12 (35)	78 (54)	104 (49)	13 (32)	91 (53)
≥50%, *n* (%)	89 (50)	22 (65)	67 (46)	100 (47)	28 (68)	72 (42)
Missing, *n* (%)	0 (0)	0 (0)	0 (0)	10 (5)	0 (0)	10 (6)

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Published OnlineFirst May 11, 2020; DOI: 10.1158/1078-0432.CCR-20-0834

Table 1. Baseline patient and disease characteristics by DS. (Cont'd)

	Ivosidenib			Enasidenib		
	Total ($n = 179$)	DS ($n = 34$)	No DS ($n = 145$)	Total ($n = 214$)	DS ($n = 41$)	No DS ($n = 173$)
CrCl (mL/min)						
Median (range)	86 (21–253)	80 (41–253)	86 (21–231)	83 (29–237)	79 (37–197)	85 (29–237)
<60 mL/min, *n* (%)	33 (18)	6 (18)	27 (19)	44 (21)	9 (22)	35 (20)
≥60 mL/min, *n* (%)	143 (80)	28 (82)	115 (79)	169 (79)	32 (78)	137 (79)
Missing, *n* (%)	3 (2)	0 (0)	3 (2)	1 (<1)	0 (0)	1 (1)
LDH (U/L)						
Median (range)	248 (63–3059)	288 (127–1957)	246 (63–3059)	258 (57–5938)	275 (84–1937)	252 (57–5938)
Low/normal, *n* (%)	99 (55)	14 (41)	85 (59)	131 (61)	22 (54)	109 (63)
Elevated, *n* (%)	80 (45)	20 (59)	60 (41)	78 (36)	17 (41)	61 (35)
Missing, *n* (%)	0 (0)	0 (0)	0 (0)	5 (2)	2 (5)	3 (2)

Abbreviations: BM, bone marrow; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; NA/ND, not analyzable/not detected.
[a]Cytogenetic risk was reported per investigator determination.

enasidenib cohort. For both drugs, there was no difference between number of comutated genes at baseline in patients who did or did not develop DS (Supplementary Table S2).

Characteristics of DS cases

The most common clinical criteria were dyspnea and pulmonary infiltrates or pleuropericardial effusion (**Table 3**). Hypotension was the least common criterion. Most cases of DS were moderate in severity, yet about two thirds included grade ≥ 3 adverse reactions (AR). Of eight severe cases with ivosidenib and five with enasidenib, only 2 patients treated with each drug had DS recorded as an AE; the rest recorded only component events (e.g., pleural effusion). FDA identified 2 patients with fatal DS on each trial, only one of which was recognized as potential DS.

Median time to onset of DS was 20 days (range, 1–78) for ivosidenib and 19 days (range, 1–86) for enasidenib (**Table 3** and **Fig. 2**). Most [88% (30/34) ivosidenib; 85% (35/41) enasidenib] cases occurred > 7 days following initiation of IDH inhibitor therapy (**Table 3**). Median time to onset of severe versus moderate cases was 17 versus 20 days for ivosidenib and 14 versus 19 days for enasidenib.

Concomitant leukocytosis was reported in 79% (27/34) of ivosidenib and 61% (25/41) of enasidenib DS cases (**Table 3**). Other AEs reported 7 days before or after the first sign/symptom of DS are shown in Supplementary Table S3. Review of blood count trends by occurrence of DS revealed that WBC count and ANC tended to increase earlier in patients with versus without DS and peaked around the time of maximal occurrence of DS (Supplementary

Table 2. Univariate and multivariable analyses of risk factors for DS.

		Ivosidenib		Enasidenib	
Variable	Category	Univariate RR (95% CI)	Multivariable RR (95% CI)	Univariate RR (95% CI)	Multivariable RR (95% CI)
Bone marrow blast (%)	≥median[a] vs. <median	1.98 (1.03–3.81)	1.23 (0.59–2.54)	2.42 (1.31–4.47)	1.91 (0.89–4.09)
Peripheral blast %	≥median[b] vs. <median	2.20 (1.11–4.35)	1.78 (0.77–4.10)	2.00 (1.03–3.88)	1.41 (0.68–2.95)
Type of AML	Secondary vs. *de novo*	2.03 (1.12–3.69)	1.75 (0.95–3.23)	1.17 (0.63–2.17)	
WBC count (Gi/L)	≥median[c] vs. <median	1.77 (0.94–3.36)	1.08 (0.48–2.42)	1.22 (0.70–2.12)	
LDH (U/L)	Elevated vs. low/normal	1.77 (0.95–3.27)	1.27 (0.63–2.55)	1.30 (0.74–2.29)	
IDH1 mutation	R132H vs. R132C	1.53 (0.82–2.87)			
	R132G/L/S vs. R132C	0.56 (0.18–1.75)			
IDH2 mutation	R172 vs. R140			0.78 (0.39–1.58)	
Prior HSCT	Yes vs. no	1.51 (0.80–2.84)		1.31 (0.64–2.68)	
ECOG PS	≥2 vs. 0–1	1.47 (0.78–2.76)		1.16 (0.57–2.40)	
Cytogenetics	Poor vs. intermediate	1.28 (0.66–2.51)		1.42 (0.75–2.68)	
Race	Non-White vs. White	1.17 (0.63–2.16)		1.36 (0.75–2.46)	
Prior regimens	≥2 vs. 1	1.29 (0.68–2.45)		0.66 (0.38–1.15)	
ANC (Gi/L)	≥500 vs. <500	1.24 (0.65–2.34)		0.97 (0.55–1.70)	
Sex	Male vs. female	0.78 (0.42–1.44)		1.12 (0.64–1.94)	
CrCl (mL/min)	<60 vs. ≥60	1.08 (0.49–2.39)		0.93 (0.48–1.79)	
Age	≥65 years vs. <65 years	0.97 (0.52–1.80)		0.84 (0.48–1.46)	

Abbreviations: CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]Median was 48% for both ivosidenib and enasidenib.
[b]Median was 25% for ivosidenib and 15% for enasidenib.
[c]Median WBC was 1.9 for ivosidenib and 2.3 for enasidenib.

Published OnlineFirst May 11, 2020; DOI: 10.1158/1078-0432.CCR-20-0834

Table 3. Characteristics of FDA-adjudicated DS cases.

	Ivosidenib ($n = 34$)	Enasidenib ($n = 41$)
Severity, *n* (%)		
Moderate	24 (71)	33 (80)[a]
Severe	8 (24)	5 (12)[a]
Indeterminate	2 (6)	4 (10)
Grade ≥ 3 ARs, *n* (%)		
Yes	23 (68)	27 (66)
Fatal	2 (6)	2 (5)
Clinical criteria, *n* (%)		
Dyspnea	26 (76)	28 (68)
Pulmonary infiltrates, pleuropericardial effusion	26 (76)	25 (61)
Weight gain	18 (53)	17 (41)
Fever	15 (44)	21 (51)
Acute renal failure	8 (24)	7 (17)
Hypotension	6 (18)	3 (7)
Leukocytosis		
Yes	27 (79)	25 (61)
Time to onset		
Median (range), d	20 (1–78)	19 (1–86)
≤7 days, *n* (%)	4 (12)	6 (15)
>7 days, *n* (%)	30 (88)	35 (85)
Multiple episodes		
Yes	4 (12)	6 (15)

Abbreviation: d, days.
[a]One patient with multiple episodes of DS had both severe and moderate episodes.

Fig. S3). A similar relationship was not observed for platelet counts. Furthermore, an analysis of WBC counts at the time of onset of DS revealed increases from baseline in median total WBC count, ANC, and absolute monocyte count, along with decreases from baseline in median peripheral blast percentage (Supplementary Table S4).

Repeat episodes of DS with ivosidenib and enasidenib occurred in 12% (4/34) and 15% (6/41) of patients with DS with median 19 and 22.5 days between the first two episodes, respectively. Patients treated with ivosidenib experienced at most two episodes, whereas 3 patients treated with enasidenib experienced three episodes of DS, with time between episodes ranging from 16 to 45 days.

Impact of DS on outcome

We examined the impact of DS on early mortality, remission rate, OS, and DOR. Early deaths within 30 and 60 days were similar in patients with versus without DS [30-day mortality: ivosidenib 3% (1/34) vs. 8% (11/145), enasidenib 5% (2/41) vs. 4% (7/173); 60-day mortality: ivosidenib 15% (5/34) vs. 14% (21/145), enasidenib 15% (6/41) vs. 11% (19/173)]. CR + CRh rates were lower in patients with versus without DS [ivosidenib 18% (95% CI, 7%–35%) vs. 36% (28–45%); enasidenib 18% (7–33%) vs. 25% (18–32%); **Table 4**]. The median DOR and median OS were also lower in patients who experienced DS compared with those who did not (**Table 4**). Median OS with versus without DS was 4.7 (95% CI, 2.8–7.1) versus 10.0 (95% CI, 8.8–12.0) months for ivosidenib and 8.0 (95% CI, 3.2–11.4) versus 8.3 (95% CI, 7.5–9.9) months for enasidenib.

Patients with versus without DS had shorter median duration of IDH inhibitor exposure [3.2 months (range, 0.4–19.6) vs. 4.2 months (range, 0.07–39.5) ivosidenib and 3.7 months (range, 0.4–23.6) vs. 4.6 months (range, 0.3–21.0) enasidenib; Supplementary Table S5]. Similarly, patients with versus without DS were more likely to have median relative dose intensity ≤ 80% [20.6% (7/34) vs. 11.7% (17/145) ivosidenib and 12.2% (5/41) vs. 7.5% (13/173) enasidenib].

Treatment of DS

In the first 90 days of IDH inhibitor therapy, most patients with FDA-adjudicated DS received systemic corticosteroids [24/34 (71%) ivosidenib, 32/41 (78%) enasidenib], with more than half receiving dexamethasone [19/34 (56%) ivosidenib, 21/41 (51%) enasidenib;

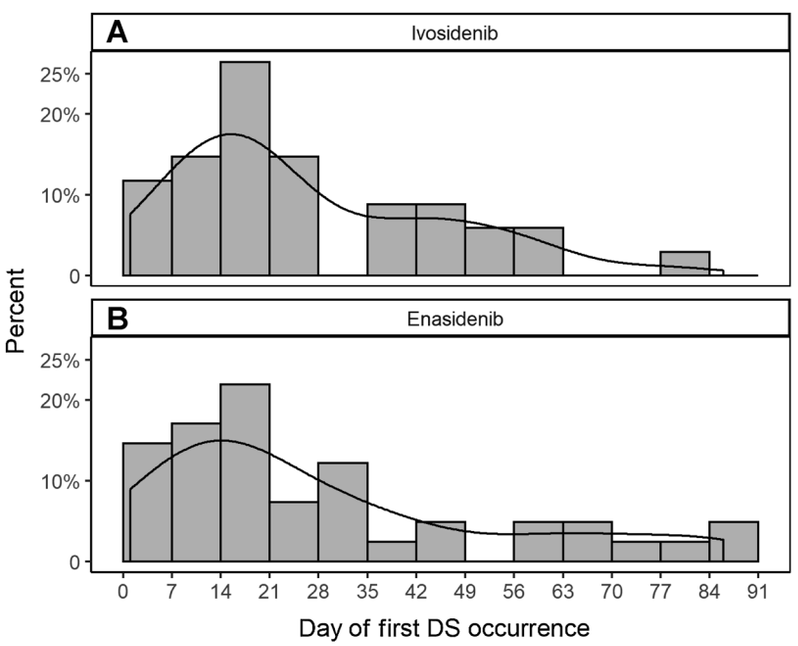

Figure 2.
Time to onset of DS. Number of days to first occurrence of DS for patients treated with ivosidenib (**A**) or enasidenib (**B**).

Published OnlineFirst May 11, 2020; DOI: 10.1158/1078-0432.CCR-20-0834

Table 4. Response and survival by occurrence of DS in efficacy populations[a].

Response	Ivosidenib		Enasidenib	
	DS ($n = 34$)	No DS ($n = 140$)	DS ($n = 40$)	No DS ($n = 159$)
CR, *n* (%) (95% CI)	6 (18) (7–35)	37 (26) (19–35)	6 (15) (6–30)	31 (19) (14–27)
Median DOCR, months (95% CI)	4.6 (1.9–15.9)	10.1 (6.5–18.3)	3.7 (0.9-NR)	9.7 (4.7–NR)
Median time to CR, months (range)	4.0 (3.7–4.6)	2.8 (0.9–8.3)	3.7 (1.9–7.4)	3.7 (0.6–11.2)
CR+CRh, *n* (%) (95% CI)	6 (18) (7–35)	51 (36) (28–45)	7 (18) (7–33)	39 (25) (18–32)
Median DOCR+CRh, months (95% CI)	5.6 (1.9–15.9)	8.3 (5.5–12.9)	3.7 (0.8–5.5)	9.6 (4.7-NR)
Median time to CR+CRh, months (range)	3.8 (2.8–4.6)	1.9 (0.9–5.6)	NA	NA
Median OS, months (95% CI)	4.7 (2.8–7.1)	10.0 (8.8–12.0)	8.0 (3.2–11.4)	8.3 (7.5–9.9)

Abbreviations: DOCR, duration of CR; DOCR+CRh, duration of CR+CRh; NA, not available; NR, not reached.
[a]Efficacy populations included all treated patients at the recommended dose of ivosidenib or enasidenib with confirmed *IDH1* or *IDH2* mutation per the respective companion diagnostic test.

Supplementary Table S6]. A total of 20 of 34 (59%) and 23 of 41 (56%) patients with FDA-adjudicated DS treated with ivosidenib and enasidenib, respectively, received systemic corticosteroids for a stated indication of DS or signs/symptoms of DS, the majority being the investigator-diagnosed cases ($n = 14$ ivosidenib, $n = 17$ enasidenib). The remainder of patients with FDA-adjudicated DS who received steroids in the first 90 days received them for a variety of other recorded indications (e.g., premedication for transfusions, pain, fatigue, and rash). Of patients who developed severe DS following ivosidenib and enasidenib, 5 of 8 (63%) and 4 of 5 (80%) received systemic corticosteroids in the first 90 days of therapy, respectively. Only one of 4 fatal cases was recognized as potential DS and treated with steroids.

Hydroxyurea and furosemide were more frequently used in patients with DS compared with those without DS (Supplementary Table S6). Use of leukapheresis, mechanical ventilation, and dialysis was rare (<5%) in patients with or without DS.

Discussion

To our knowledge, this is the first comprehensive algorithmic analysis to identify cases of DS with the marketed IDH inhibitors. These therapies provide durable responses and transfusion benefits to patients with R/R AML with mutated *IDH1* or *IDH2* (2, 3). Given their differentiating mechanism of action, DS has been the major associated risk of ivosidenib and enasidenib. Our algorithmic analysis of AEs, laboratory tests, and vital signs grouped by standardized criteria led to recognition of additional cases not initially identified and helped to inform FDA's review of ivosidenib and enasidenib, which include boxed warnings for DS.

Both ivosidenib and enasidenib caused DS in 19% of patients, and grade ≥ 3 ARs were present in over half of cases; rare fatalities were observed. Although common, leukocytosis was not always present, which may have contributed to underrecognition. Furthermore, protocol amendments specifying management guidelines for suspected DS were not instituted until roughly 7 and 14 months following initiation of these first-in-human clinical studies for ivosidenib and enasidenib, respectively (3, 12). Missed cases occurred before and after the institution of the protocol amendments, however, as well as in the postmarketing setting. FDA released a Drug Safety Communication in November 2018 announcing that signs and symptoms of DS were not being recognized and treated in patients receiving enasidenib in the postmarketing setting, with fatal cases being observed (19). Underrecognition of the syndrome is likely multifaceted, including limited experience with differentiating therapies in non-APL AML, differences in IDH-inhibitor induced DS in IDH-mutated AML compared with ATRA-induced DS in APL (see Supplementary Table S7), and treatment in a background of R/R AML with its coincident comorbidities and infectious complications that may obscure a diagnosis of DS. Use of our standardized diagnostic methods increased recognition of the syndrome and may help to further mitigate the risk of DS moving forward.

Approximately half of cases identified by the algorithm were deemed unlikely DS, often due to confirmed underlying infection. It is important to acknowledge that infections are extremely common in patients with R/R AML and often a clear source is not identified. Given the overlapping clinical symptoms of infection and DS, it is possible that some of the cases designated as DS represented infection. In addition, because mechanistically the occurrence of DS and infection need not be mutually exclusive, it is possible that some patients designated as unlikely DS due to confirmed infection had concomitant DS. There is evidence that ATRA-differentiated cells express high levels of CXCR4 and traffic to lung tissue, especially in the presence of stromal cell–derived factor-1 α (20), which is upregulated in acute lung injury/infection (21, 22). Therefore, it is possible that aberrant leukemic neutrophil trafficking to a nidus of pre-existing infection could lead to clinical manifestations of DS. This would need to be confirmed with correlative studies in future trials of differentiation therapies. However, it would be prudent for physicians to consider DS when diagnostic criteria are present, even in the presence of confirmed infection, given that delaying steroid therapy could be life-threatening or fatal. Treatment with empirical antibiotics would be equally important to consider in patients with suspected DS.

Although small sample sizes limit the ability to clearly define which factors increase risk of DS, our analysis identified potential risk factors for further investigation. In univariate analyses, baseline bone marrow blast percentages ≥ 48% and peripheral blood blasts ≥ 25% and 15% for ivosidenib and enasidenib, respectively, conveyed a higher risk of DS. Comutations in *TET2*, previously reported to be mutually exclusive with *IDH* mutations (23), were found to be a possible genomic predictor of DS in patients treated with ivosidenib in the dose-expansion cohort of the trial. *TET2* mediates the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, eventually resulting in DNA demethylation. This process is inhibited by the oncometabolite 2-HG produced by mutant *IDH1/2* (23). A recent study in a *TET2*-knockout mouse model found that *TET2* mutation skews uncommitted hematopoietic stem cells (HSC) toward myelomonocytic cell fates; knockout mice had increased expression of monocyte-related genes in HSCs and increased peripheral blood monocytes (24). Therefore,

Published OnlineFirst May 11, 2020; DOI: 10.1158/1078-0432.CCR-20-0834

cancer cells with *TET2* mutations may be more likely to differentiate into monocytes upon treatment with ivosidenib.

Comutations in *SRSF2* were found to be a possible genomic predictor of DS in patients treated with enasidenib. *SRSF2* is a splicing factor that has frequent gain-of-function mutations in myeloid malignancies (25). *SRSF2* mutations have been previously associated with *IDH2* mutations in AML (6, 25), as was observed here. *SRSF2* mutations cause alternative splicing of other splicing and RNA-processing genes, initiating a "splicing cascade" (26) that leads to global changes in splicing with broad and varied functional impacts. Human cell lines with *SRSF2* mutation have impaired HSC function, including loss of repopulating potential along with a relative increase in monocyte lineage cells in a colony-forming assay. This preference for monocyte differentiation is consistent with the high rate of *SRSF2* mutation in chronic myelomonocytic leukemia (26). Perhaps *SRSF2* may also mediate increased risk for DS by skewing cancer cell differentiation toward monocytes. It is important to note, however, that our results are limited based on small sample size, missing genomic data, and use of different NGS panels on the ivosidenib trial. Thus, further studies are needed to confirm our findings.

We observed that response rates, DOR, and OS were lower in patients with versus without DS. Although firm conclusions regarding impact on response cannot be inferred based on our *post hoc* subgroup analyses of single-arm trials, it is possible that lower responses were observed in patients with DS due to less frequent dose intensity > 80%. It is also possible that baseline imbalances between patients with versus without DS affected our findings (see **Table 1**). For example, the larger difference in response rates and OS for ivosidenib may have been due to more pronounced baseline imbalances between the DS and no DS groups on the ivosidenib trial (e.g., with regards to ECOG performance status ≥ 2, secondary AML, and prior HSCT), compared with the enasidenib trial. Fathi and colleagues reported comparable CR rates in patients with versus without DS treated with enasidenib (18.2% vs. 19.8%), but DOR and survival were not reported (9). Their analysis methods differed from our own, given that they included all patients with R/R AML regardless of dose and DS was determined by a review committee using an algorithm that considered investigator-reported DS and suggestive AEs (9). They also described requirements for concurrent evidence of cellular differentiation and proliferation in blood or marrow, as well as clinical response to corticosteroids (9). DiNardo and colleagues reported that CR rate was 26% in patients with investigator-diagnosed DS with R/R AML treated with the approved dose of ivosidenib; the CR rate for the overall patient population was slightly lower at 22% (5). The true effect of DS on outcomes cannot be discerned based on the available data. However, occurrence of DS by no means predicts for efficacy of *IDH* inhibitor therapy. This is in contrast to the experience with differentiating therapies in APL, which lead to remissions in most patients (27, 28). This is not surprising given that APL is a monogenic disease, as opposed to the heterogeneous nature of R/R AML. Occurrence of DS with the IDH inhibitors suggests differentiation of *IDH*-mutated clones, but this may not be sufficient to induce a CR in the presence of multiple different clones.

An important limitation of our analysis is that it was performed retrospectively. It would be ideal for similar diagnostic algorithms to be instituted prospectively in clinical trials of targeted differentiation therapies early in clinical development to better characterize the incidence and severity of DS. This may provide advantages of earlier recognition and treatment, as well as identification and documentation of more plausible alternative diagnoses in real-time. Another potential limitation of our analysis is that we utilized a 90-day window for our query. Therefore, it is possible that we missed additional cases. Although there were no investigator-diagnosed cases of DS beyond 90 days with ivosidenib, there were 5 reported between 90 days and 5 months with enasidenib. Given that a minority of patients treated with either drug achieve *IDH* mutation clearance (5, 6), it is not surprising that clones may surge and differentiate at a later time over the duration of therapy. It would be prudent to remain vigilant for DS throughout the course of therapy, particularly in patients with active disease and those who resume therapy following treatment interruption.

It is worth noting that results using our algorithm were derived based on the reported clinical data specifically from trials of ivosidenib and enasidenib. Algorithms for other drugs with differentiating properties may differ. For example, DS with FLT3 inhibitors often includes development of rash or acute febrile neutrophilic dermatosis (29–31). Therefore, it may be reasonable to add a criterion for rash, including the appropriate codified AE terms, for investigations of DS with FLT3 inhibitors.

In conclusion, DS is a common and potentially fatal clinical syndrome in patients treated with ivosidenib and enasidenib. Increased recognition of the signs and symptoms of DS through the framework of the Montesinos criteria may lead to earlier diagnosis and treatment, which may decrease severe complications and mortality.

Disclosure of Potential Conflicts of Interest

A.F. Ward is an employee/paid consultant for Foundation Medicine. No potential conflicts of interest were disclosed by the other authors.

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Acknowledgments

This work was funded in part by an appointment to the Research Participation Program at the Office of Oncologic Diseases, Center for Drug Evaluation and Research at the FDA administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the FDA.

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Received March 3, 2020; revised April 28, 2020; accepted May 6, 2020; published first May 11, 2020.

Published OnlineFirst May 11, 2020; DOI: 10.1158/1078-0432.CCR-20-0834

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Differentiation Syndrome with Ivosidenib and Enasidenib Treatment in Patients with Relapsed or Refractory IDH-Mutated AML: A U.S. Food and Drug Administration Systematic Analysis

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Clin Cancer Res 2020;26:4280-4288. Published OnlineFirst May 11, 2020.