Supplementary Online Content

Fathi AT, DiNardo CD, Kline I, et al; AG221-C-001 Study Investigators. Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: analysis of a phase 1/2 study. *JAMA Oncol*. Published January 18, 2018. doi:10.1001/jamaoncol.2017.4695

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. List of IECs/IRBs for AG221-C-001

Phase I

Site No.	Name/Address of IEC/IRB
101	IntegReview Ethical Review Board 3851 S. Capital of Texas Highway Suite 320 Austin, TX 78704 USA Previous address: 3001 S. Lamar Blvd. Suite 210 Austin, TX 78704 USA
102	IntegReview Ethical Review Board 3851 S. Capital of Texas Highway Suite 320 Austin, TX 78704 USA Previous address: 3001 S. Lamar Blvd. Suite 210 Austin, TX 78704 USA
103 / 900	Office for Human Research Studies Dana Farber Cancer Institute Boston, MA 02215 USA
104	Memorial Sloan Kettering Cancer Center Institutional Review Board 1275 York Avenue New York, NY 10065 USA
105	Western Institutional Review Board (WIRB) 1019 39th Ave SE Suite 120 Puyallup, WA 98374-2115 USA
106	UT Southwestern Institutional Review Board 5323 Harry Hines Blvd. Dallas, TX 75390-8843 USA
107	Stanford Institutional Review Board (IRB) 3000 El Camino Real Five Pala Alto Square, 4th Floor Palo Alto, CA 94306 USA Previous address: Stanford University Administrative Panel on Human Subjects in Medical Research 1501 S. California Avenue Palo Alto, CA 94303 USA

Site No.	Name/Address of IEC/IRB
108	University of Miami Institutional Review Board 1400 NW 10th Avenue Suite 1200A Miami, FL 33136 USA Previous Address: 1500 NW 12th Avenue Suite 1002 Miami, FL 33136 USA
109	Weill Cornell Medical College Institutional Review Board 407 East 61st Street RR110 New York, NY 10065 USA
110	Northwestern University Institutional Review Board 750 N. Lake Shore Drive – 7th Floor Chicago, IL 60611 USA
111	The University of Texas MD Anderson Cancer Center Institutional Review Board (FWA 363) 7007 Bertner Avenue, Unit 1637 Houston, TX 77030 USA
112	Cleveland Clinic IRB 9500 Euclid Avenue Cleveland, OH 44195 USA
117	Chesapeake IRB 6940 Columbia Gateway Drive Suite 110 Columbia, MD 21046 USA Previous: Liberty IRB 1450 S. Woodland Boulevard Suite 300A DeLand, FL 32720 USA
118	Western Institutional Review Board (WIRB) 1019 39th Ave SE Suite 120 Puyallup, WA 98374 USA
201	Comité de Protection des Personnes - Ile- de-France 3 Hôpital Tarnier-Cochin 89 rue d'Assas Paris FRANCE 75006
203	Comité de Protection des Personnes - Ile- de-France 3 Hôpital Tarnier-Cochin 89 rue d'Assas Paris FRANCE 75006

Phase II

Site No.	Name/Address of IEC/IRB
101	IntegReview Ethical Review Board 3851 S. Capital of Texas Highway Suite 320 Austin, TX 78704 USA Previous address: 3001 S. Lamar Blvd. Suite 210 Austin, TX 78704 USA
102	IntegReview Ethical Review Board 3851 S. Capital of Texas Highway Suite 320 Austin, TX 78704 USA Previous address: 3001 S. Lamar Blvd. Suite 210 Austin, TX 78704 USA
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106	UT Southwestern Institutional Review Board 5323 Harry Hines Blvd. Dallas, TX 75390-8843 USA
108	University of Miami Institutional Review Board 1400 NW 10th Avenue Suite 1200A Miami, FL 33136 USA Previous Address: 1500 NW 12th Avenue Suite 1002 Miami, FL 33136 USA

109	Weill Cornell Medical College Institutional Review Board 1300 York Avenue, Box 89 New York, NY 10065 Previous address: Weill Cornell Medical College Institutional Review Board 407 East 61st Street RR110 New York, NY 10065 USA
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112	Cleveland Clinic IRB 9500 Euclid Avenue Cleveland, OH 44195 USA
113	Western Institutional Review Board (WIRB) 1019 39th Ave SE Suite 120 Puyallup, WA 98374 USA
114	Washington University in St. Louis 660 S. Euclid Ave Box 8089 St. Louis, MO 63110 USA
116	OHSU Institutional Review Board 3181 SW Sam Jackson Park Road, L106-RI Portland, OR 97239 USA
117	Chesapeake IRB 6940 Columbia Gateway Drive Suite 110 Columbia, MD 21046 USA Previous: Liberty IRB 1450 S. Woodland Boulevard Suite 300A DeLand, FL 32720 USA
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eTable 1. MedDRA Terms Searched in the Safety Database for Assessment of Potential IDH-DS

Clinical manifestation	MedDRA terms
MedDRA screening criteria: Any reports	
Differentiation Syndrome	APL differentiation syndrome or retinoic acid syndrome (depending on MedDRA version)
Pneumonia	Lower respiratory tract and lung infections Parenchymal lung disorders
Dyspnea and Hypoxia	Acute central respiratory depression Respiratory failure
Pleural or Pericardial Effusion	Pericardial effusion Pleural effusion
Pulmonary Edema	Pulmonary edema
Pulmonary Infiltrates	Parenchymal lung disorder
DIC	Disseminated intravascular coagulation
MedDRA screening criteria: 2 or more of the events below, occurring within ±15 days of each other	
Fever	Pyrexia
Leukocytosis	Leukocytosis WBC count increased
Fluid Retention	Total Fluid Volume increased Edema NEC Hemodynamic edema Effusions and fluid overload Pulmonary edemas
Rash	Rashes, eruptions and exanthems NEC
Pain	Bone Pain Pain in extremity Pelvic pain Spinal pain Arthralgia
Lymphadenopathy	Lymphadenopathy
Renal insufficiency	SQ Acute renal failure

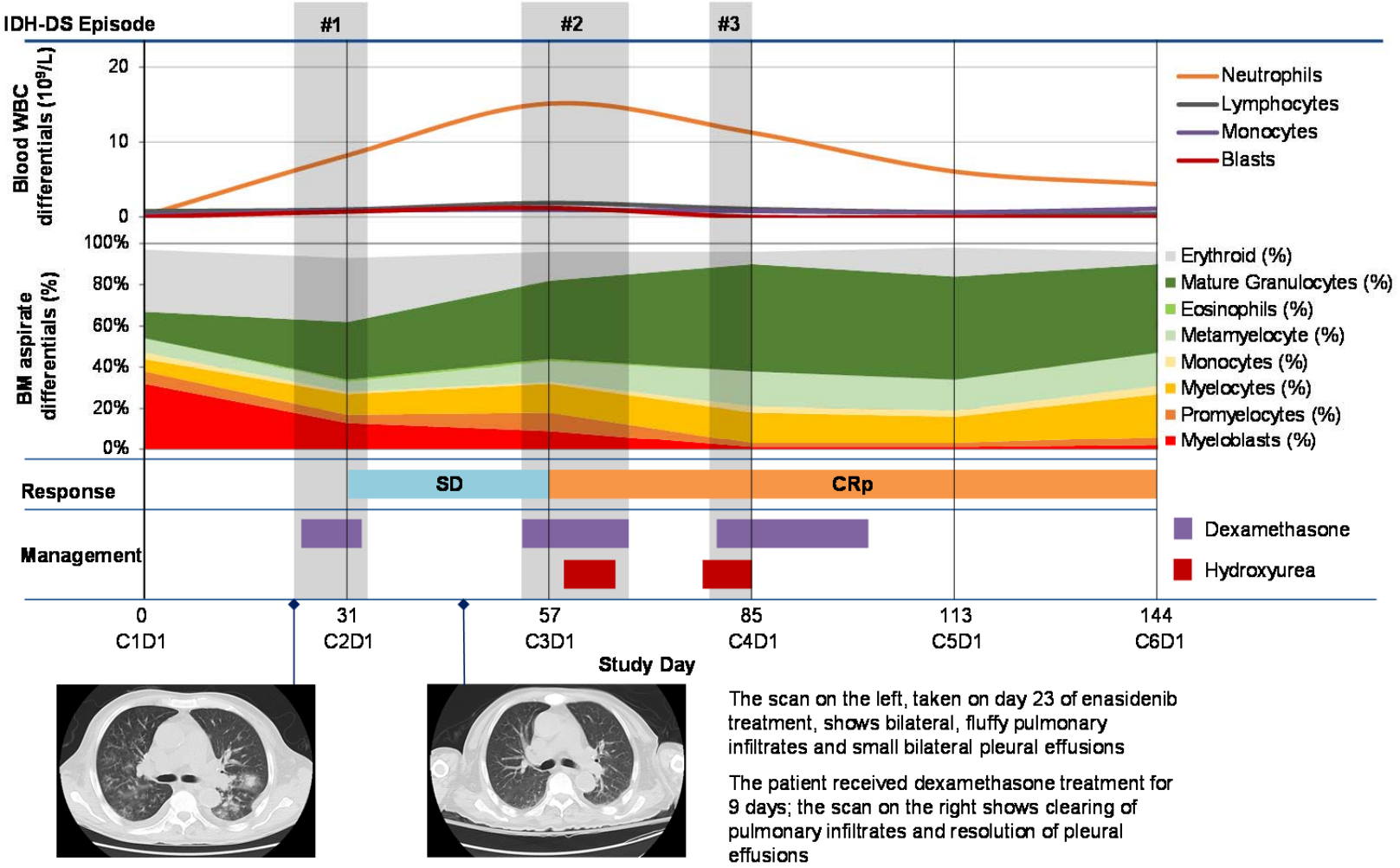
eTable 2. Baseline Characteristics

Characteristic	IDH-DS (n=33[a])	No IDH-DS (n=248[a])	*P* value
Age (years), median (range)	70.0 (38-80)	68.0 (19-100)	0.908
Age < 65, n (%)	12 (36)	93 (38)	0.417
Age ≥ 65 - < 75, n (%)	16 (48)	94 (38)	
Age ≥ 75, n (%)	5 (15)	61 (25)	
Sex, n (%)			
Male	20 (61)	133 (54)	0.465
Female	13 (39)	115 (46)	
ECOG PS, n (%)			
0	9 (27)	54 (22)	0.410
1	21 (64)	149 (60)	
2	3 (9)	44 (18)	
IDH2 mutation site, n (%)			
R140	25 (76)	183 (74)	1.000
R172	8 (24)	62 (25)	
Prior anti-cancer regimens, median (range)	1.0 (1-4)	2.0 (1-14)	0.048
1 prior anti-cancer regimen, n (%)	19 (58)	104 (42)	0.225
2 to 5 prior anti-cancer regimens, n (%)	14 (42)	141 (57)	
> 5 prior anti-cancer regimens, n (%)	0	3 (1)	
Prior MDS, n (%)			
Yes	8 (24)	51 (21)	0.650
No	25 (76)	197 (79)	
Hemoglobin (g/dL), median (range)	9.2 (7.0-11.2)	9.0 (6.9-15.6)	0.600
≤ 10 g/dL, n (%)	29 (88)	181 (73)	0.086
> 10 g/dL, n (%)	4 (12)	66 (27)	
Platelet count (x10^9/L), median (range)	41.0 (7-372)	39.0 (1-1288)	0.700
< 10 x10^9/L, n (%)	2 (6)	9 (4)	0.718
10 - < 40 x10^9/L, n (%)	14 (42)	115 (46)	
≥ 40 x10^9/L, n (%)	17 (51)	123 (50)	
WBC count (x10^9/L), median (range)	3.0 (0.5-32.0)	2.2 (0.2-93.8)	0.342
< 2 x10^9/L, n (%)	11 (33)	108 (44)	0.527
2 to < 5 x10^9/L, n (%)	8 (24)	60 (24)	
5 to < 10 x10^9/L, n (%)	5 (15)	24 (10)	
10 to < 50 x10^9/L, n (%)	9 (27)	48 (19)	
≥ 50 x10^9/L, n (%)	0	7 (3)	

Characteristic	IDH-DS (n=33[a])	No IDH-DS (n=248[a])	*P* value
Serum creatinine (mg/dL), median (range)	0.9 (0.4-1.4)	0.8 (0.3-1.9)	0.549
≤ 1.4 mg/dL, n (%)	32 (97)	238 (96)	1.000
> 1.4 mg/dL, n (%)	1 (3)	9 (4%)	
Creatinine clearance (mL/min), median (range)	79 (38-181)	81 (26-237)	0.890
< 40 mL/min, n (%)	1 (3)	8 (3)	1.000
≥ 40 mL/min, n (%)	32 (97)	239 (96)	
LDH (U/L), median (range)	275 (84-1153)	257 (57-5938)	0.906
≤ 1 x ULN, n (%)	16 (48)	158 (64)	0.090
> 1 x ULN, n (%)	17 (51)	89 (36)	
Albumin (g/dL), median (range)	3.6 (2.4-4.6)	3.7 (2.1-35.0)	0.706
≤ 3.5 g/dL, n (%)	14 (42)	95 (38)	
> 3.5 g/dL, n (%)	19 (58)	152 (61)	
Peripheral blasts (%)	n=22	n=210	
Median (range)	31 (0-88)	13 (0-98)	0.054
≤ 50%, n (%)	13 (39)	153 (62)	0.214
> 50%, n (%)	9 (27)	57 (23)	
≤ 70%, n (%)	18 (55)	162 (65)	0.791
> 70%, n (%)	4 (12)	48 (19)	
Bone marrow blasts (%), median (range)	53 (15 ,97)	46 (0-98)	0.204
< 20%, n (%)	2 (6%)	55 (22%)	0.043
20%-50%, n (%)	14 (42%)	69 (27%)	
> 50%, n (%)	16 (48%)	115 (46%)	
Cytogenetic risk status, n (%)	[n=24]	[n=187]	
Intermediate-Risk	16 (67)	126 (67)	1.000
Poor-Risk	8 (33)	61 (33)	

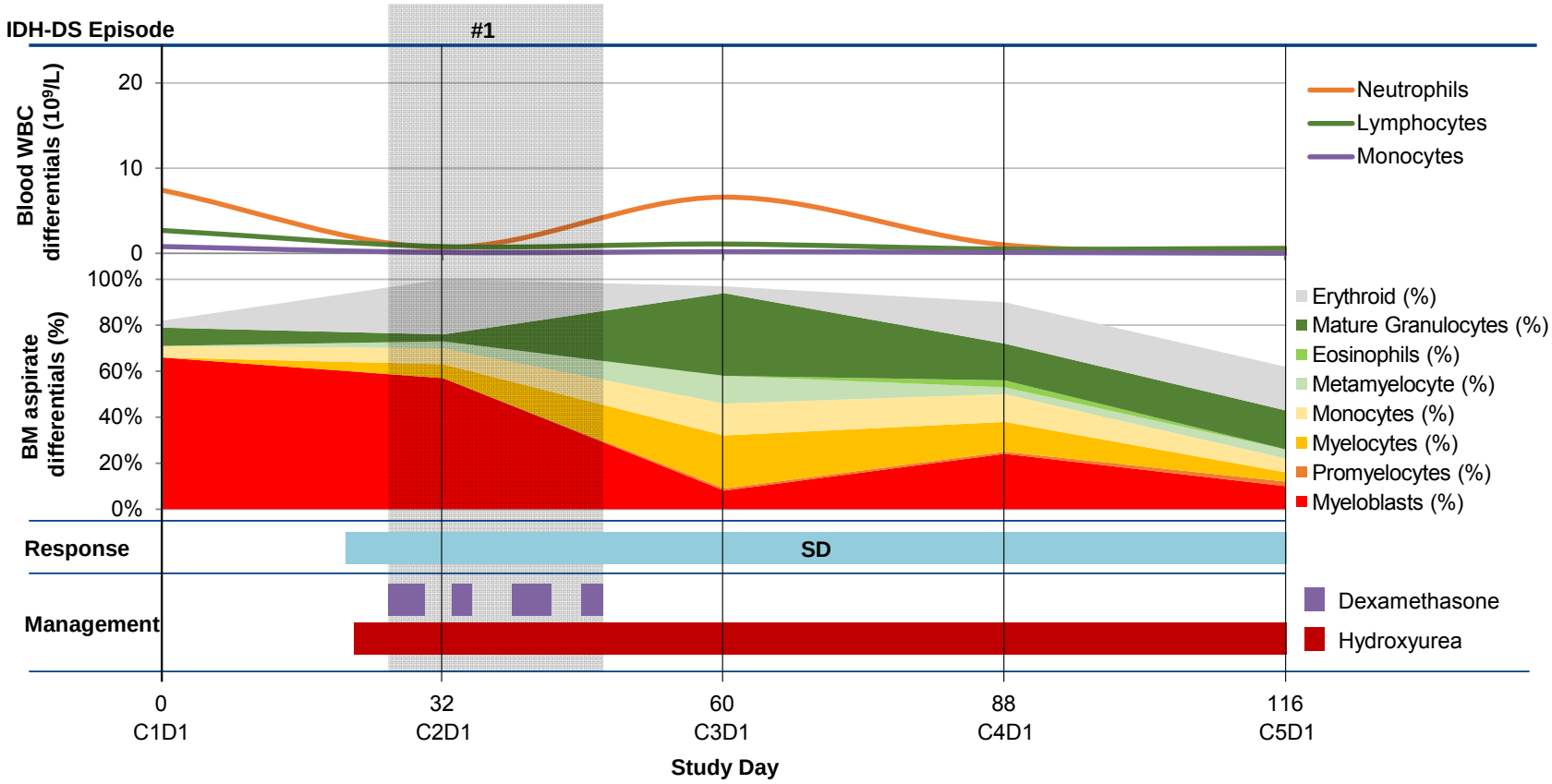
[a]Data were not available for all patients for some variables, hence proportions do not add to 100% in some cases.
Baseline characteristics of patients who did, and who did not, experience IDH-DS were compared by Wilcoxon Mann-Whitney test (continuous variables) or Fisher's Exact test (categorical variables).
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

eFigure 1. Case 1: Clinical and Laboratory Profiles for a Responding Patient With Enasidenib-Induced IDH-DS



Case 1: A 72-year-old male with AML secondary to MDS, and refractory to intensive chemotherapy, received enasidenib 100-mg daily and experienced 3 separate episodes of IDH-DS. Episode 1 occurred on days 23-24 of treatment cycle 1; signs and symptoms included febrile neutropenia (CTCAE grade 3), respiratory failure (grade 4), and peripheral edema (grade 1). The patient received IV dexamethasone on days 24-33, and enasidenib dosing was interrupted on days 25 and 26. The patient had stable disease at the cycle 2, day 1 response assessment. The second IDH-DS episode occurred between days 53-68 of treatment, when the patient presented with dyspnea (grade 1), fever (grade 2), and leukocytosis (grade 2); he received dexamethasone, and hydroxyurea for elevated WBC count. Enasidenib dosing was interrupted between days 54-58. At the cycle 3 response assessment, the patient had attained CRp. The third IDH-DS occurred between study days 79-85, 11 days after the patient's enasidenib dose had been doubled to 200-mg/day, with unexplained fever (grade 3) as the primary symptom. Dexamethasone was administered between days 80-101, along with hydroxyurea for elevated WBC count on days 78-85, with no enasidenib dosing interruption. CRp was sustained through cycle 8 (day 225), after which the patient experienced disease relapse but remained on-study due to potential for continued clinical benefit. His total duration of enasidenib treatment was 335 days.

eFigure 2. Case 2: Clinical and Laboratory Profiles for a Patient With Enasidenib-Induced IDH-DS With Sustained Stable Disease



Case 2: A 74-year-old female with cytogenetically normal AML and co-occurring NPM1 mutation, who had relapsed after attaining first remission following induction chemotherapy, received enasidenib 50-mg BID in the dose-escalation phase of the study. Between days 26-30 of enasidenib treatment, the patient was reported to have experienced retinoic acid syndrome (grade 2); concurrent signs and symptoms included renal failure (grade 2), pyrexia (grade 2), bone pain (grade 2), exertional dyspnea (grade 1), and leukocytosis (grade 2). Enasidenib treatment was not interrupted. The patient was treated intermittently with oral and IV dexamethasone 10 mg BID on days 26 through 48. She had been receiving hydroxyurea for 4 days before IDH-DS onset (day 22) and continued to receive it after IDH-DS had resolved. Following resolution of IDH-DS, bone marrow blasts decreased to between 8-24%, but did not reach the threshold for an IWG-defined response. The patient maintained stable disease at all response assessments until day 175. On day 175, the patient showed evidence of disease progression, confirmed by a bone marrow biopsy with 59% myeloblasts. Treatment with enasidenib was discontinued.

