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Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML

Courtney D. DiNardo[1,*], **Farhad Ravandi**[1], **Sam Agresta**[2], **Marina Konopleva**[1], **Koichi Takahashi**[1], **Tapan Kadia**[1], **Mark Routbort**[3], **Keyur P. Patel**[3], **Mark Brandt**[1], **Sherry Pierce**[1], **Guillermo Garcia-Manero**[1], **Jorge Cortes**[1], and **Hagop Kantarjian**[1]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas

[2]Agios Pharmaceuticals, Cambridge, Massachusetts

[3]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Abstract

The pathophysiology of *IDH* mutations in tumorigenesis is increasingly described, yet the prognostic significance of *IDH1* and *IDH2* mutations in AML remains controversial. The primary objective of this study was to define the natural history and prognosis of patients with AML and *IDH1* or *IDH2* mutations and provide historical survival expectations. A total of 826 patients treated from 2010 to 2014 at a single institution were evaluated, including 167 patients (20%) with AML and *IDH1* or *IDH2* mutations. Median age was 62 years (range 18–92). There were 59 *IDH1*-R132, 83 *IDH2*-R140, and 23 *IDH2*-R172 mutations. Clinicopathologic characteristics associated with *IDH*-mutations included older age, less frequent therapy-related status, and increased incidence of intermediate-risk cytogenetics, *FLT3-ITD* mutations, and *NPM1* mutations. Remission rates (CR/CRi) by AML treatment status were: induction, 68%; Salvage-1 (S1), 42%; and Salvage-2 and beyond (S2+), 27%. No difference in response was identified by *IDH* mutation status. Similarly, overall survival (OS) was not dependent on *IDH* status within any cohort. The median OS was 15.4 months in induction, 8.7 months in S1, and 4.8 months in S2+. This analysis defines the clinical outcome associated with *IDH*-mutations in both the front-line and salvage AML treatment settings, and confirms that response rate and OS for both *IDH*-mutated and *IDH* wild-type AML patients is comparable. This provides contemporary data to be used for comparison with results of novel investigational (e.g., selective *IDH* inhibitor) strategies.

[*]Correspondence to: Courtney DiNardo, MD, Department of Leukemia, UT MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 0428, TX.cdinardo@mdanderson.org.

Additional Supporting Information may be found in the online version of this article.

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Authors Contributions

SA is an employee of Agios Pharmaceuticals. HK has received research funding from Agios, and both CDD and HK have served on Agios advisory committees. The remaining authors declare no competing interests. CDD and HK designed the research, performed the research, analyzed the data, and wrote the paper. MB and SP analyzed the data and performed statistical analysis. MR and KPP performed the research and contributed vital analytical tools. FR, SA, MK, KT, TK, GGM, JC analyzed the data and wrote the paper.

Introduction

Since the discovery of mutations within the genes for the isocitrate dehydrogenase (*IDH*) enzymes *IDH1* and *IDH2* among patients with acute myeloid leukemia (AML), much insight has been gained regarding the incidence and unique pathophysiology of these mutations. The recurring trio of pathogenic *IDH* mutations in AML patients, *IDH1*-R132, *IDH2*-R172, and *IDH2*-R140, occur within the conserved active site and lead to loss of the expected Krebs Cycle reaction of isocitrate to alpha-ketoglutarate (αKG), while promoting a reverse reaction reducing αKG to the onco-metabolite 2-hydroxyglutarate (2HG) [1]. 2HG accumulation is purported to block normal cellular differentiation and promote tumorigenesis through competitive inhibition of αKG-dependent enzymatic activities, such as *TET2*-dependent DNA hydroxymethylation, histone demethylation, and HIF-1α activation [2–4]. Supporting evidence demonstrates AML with *IDH* mutations are specifically characterized by a distinct and globally hypermethylated DNA signature leading to impaired hematopoietic differentiation, which can be reversed with small molecule *IDH* inhibition [5–7].

*IDH*1/2 mutations are noted in ~20% in AML, including 6–16% for *IDH1* and 8–19% for *IDH2* mutations [8]. *IDH*1/2 mutations are identified more frequently in older patients, those with diploid or other intermediate-risk cytogenetics, and frequently co-occur with *FLT3-ITD* and *NPM1* mutations, while being nearly mutually exclusive with both *TET2* and *WT1* mutations [9–13].

Despite the recent insights into the distinct pathophysiology of *IDH* mutants, the prognostic significance of *IDH* mutations remains controversial [14]. *IDH1/2* mutations in conjunction with *NPM1*-mutant and *FLT3-ITD* negative molecular status have been associated with particularly favorable outcome in otherwise intermediate-risk AML [11,15,16], while other large studies have identified worse OS with *IDH* mutations including the *NPM1*-mutated *IDH*-mutated subset of patients [9,17–20], and other studies report a lack of prognostic significance [21–25].

The purpose of this analysis is to better define the clinical characteristics, natural history, and prognosis of AML patients with *IDH*-mutations, and to define the outcomes of *IDH*-mutated patients. This can be used as a reference expectation against which novel approaches and treatment strategies may be evaluated.

Methods

Eligible patients comprised all adults with a diagnosis of AML treated at M.D. Anderson Cancer Center (Houston, TX) from January 2010 to December 2014. Newly diagnosed and previously treated patients were eligible. A total of 826 patients with known *IDH1* and *IDH2* status and who received treatment at MD Anderson were included; these included 167 patients with *IDH* mutations. Details of treatments received are provided in Supporting Information Table 1.

From January 2010 to September 2012, molecular analysis was performed using polymerase chain reaction (PCR) amplification followed by Sanger sequencing using previously

described methodology and PCR primers from Integrated DNA Technologies [26]. Beginning in September 2012, *IDH* molecular testing was performed within our institutional next-generation sequencing (NGS) hematologic malignancy platform within our CLIA-certified molecular diagnostics laboratory.

Patient characteristics are summarized using median (range) for continuous variables and frequency (percentage) for categorical variables. Categorical variables were compared for significance using the χ^2 or Fisher's exact test, and continuous variables were analyzed using the Wilcoxon Rank-Sum test. Statistical analyses were conducted in SAS 9.0 and significance was defined as a *P* value of <0.05. Overall survival (OS) was measured as the time from presentation to date of death or date of last follow-up (censored), and was calculated by Kaplan–Meier method using the log-rank test. Informed consent was obtained following institutional guidelines and in accordance with the Declaration of Helsinki.

Results

A total of 826 patients with known *IDH1* and *IDH2* status were evaluated, including 167 patients (20% of cohort) with *IDH1* or *IDH2* mutations. Patients with *IDH*-mutations included 59 (7%) with *IDH1*-R132, 83 (10%) with *IDH2*-R140 mutations, and 23 (3%) with *IDH2*-R172 mutations. Due to the low frequency of *IDH2-R172* mutations, patients with *IDH2-R140* and *IDH2-R172* mutations were analyzed together as *IDH2* mutants. In two patients, both an *IDH1*-R132 and *IDH2*-R140 mutation were identified concurrently. Within this cohort, 562 (68%) patients presented at the time of AML diagnosis for induction treatment, 120 (15%) patients at the time of salvage-1 (S1) and 144 (17%) patients at the time of salvage-2 or beyond (S2+). Detailed clinical and disease-specific characteristics by mutational status are shown in Table I. The median age for all patients was 62 years (range 18–92); 373 patients (45%) were ≥65 years of age.

Compared with *IDH* wild-type patients, *IDH1* and *IDH2* mutated patients were older (median age 67 years vs. 61 years, *P* <0.0005), had a higher platelet count (median 55 $\times 10^9$/L vs. 44 $\times 10^9$/L, *P* = 0.025) and increased bone marrow blast percentage at presentation (60% vs. 41%, *P* <0.0005) (Table I). While total white blood cell (WBC) count was similar for both *IDH*-mutated and wild-type patients, the peripheral blast percentage was significantly higher in *IDH*-mutants compared to *IDH* wild-type (30% vs. 14%, *P* <0.0005), while the absolute neutrophil count (ANC) of *IDH*-mutated patients was significantly lower (0.42×10^9/L vs. 1.1×10^9/L, *P* <0.0005). *IDH1*-mutated patients had a significantly lower ANC than the *IDH2*-mutated patients (*P* = 0.008), this was the only clinicopathologic characteristic evaluated that differed between *IDH1* and *IDH2*-mutated patients in our cohort (Table I). Additionally, *IDH*-mutated patients were more likely to have intermediate-risk cytogenetics (77% vs. 53%, *P* <0.0005), less likely to have therapy-related AML (8% vs. 17%, *P* = 0.003) and *IDH*-mutations were more frequently associated with the concurrent presence of *FLT3-ITD* mutations (27% vs. 19%, *P* = 0.035) and *NPM1* mutations (33% vs. 17%, *P* <0.0005).

As expected, remission rates differed significantly based on AML treatment (salvage) status. Overall complete remission and complete remission with incomplete count recovery (CR/

CRi) rate was 68% for AML induction, 42% for S1, and 27% for S2+ patients. Within each stage of treatment, response rate was not impacted by *IDH* mutational status (Table II). Treatment strategies received were heterogeneous and were dependent on factors such as patient age, performance status, comorbidities, and therapies received prior to institutional referral in applicable patients, and are detailed in Supporting Information Table 1. In the (*n* = 219) patients less than 60 years of age receiving induction AML therapy, the CR/CRi rate was 83% (*n* = 183); in the (*n* = 343) patients ≥60 years of age, the CR/CRi rate was 53% (*n* = 182), and response by age group was not affected by the presence or absence of *IDH* mutations.

With regards to hypomethylating agent (HMA) therapy in AML patients with *IDH* mutations, we evaluated specifically the (*n* = 175) patients receiving induction AML therapy with a HMA-based regimen. This included 48 *IDH1/2*-mutated patients and 127 *IDH* wild-type patients, with a median age of 75 (range 37–92). In this HMA-based induction treatment cohort, there was no impact of *IDH*-mutations on the overall response rate (45% vs. 58%, *P* = 0.13) or overall survival (9.5 vs. 10.3 months, *P* = 0.8) in this elderly induction treatment cohort (Supporting Information Fig. 1).

Overall survival (OS) by *IDH* mutational status and treatment status is presented in Table II and Fig. 1. There were no statistically significant differences in OS based on the presence of *IDH1* or *IDH2* mutations for any treatment cohort, either in the induction setting, or in either salvage setting. As no significant survival differences were identified in *IDH2*-mutant patients based on the presence of an *IDH2-R140* versus *IDH2-R172* mutation, *IDH2*-mutant patients were analyzed together due to the low frequency of *IDH2-R172* mutations. In newly-diagnosed patients, median OS was 13.0 months for *IDH1*-mutated, 15.7 months for *IDH2*-mutated, and 15.3 months for *IDH* wild-type patients (*P* = 0.59). Median OS in the S1 setting was 5.9 months for *IDH1*-mutated, 11.1 months for *IDH2*-mutated, and 7.7 months for *IDH* wild-type patients (*P* = 0.44). For patients treated at the time of Salvage-2 and beyond, median OS was 4.0 months for *IDH1*-mutated, 5.9 months for *IDH2*-mutated, and 4.8 months for *IDH* wild-type (*P* = 0.16) (Fig. 2).

We then analyzed the 310 patients with intermediate-risk cytogenetics [27] presenting at diagnosis, in order to evaluate the impact of *FLT3-ITD*, *NPM1*, and *IDH1/2* molecular combinations on OS within this molecularly defined induction subgroup (Fig. 2). Patients with intermediate-risk cytogenetics and *NPM1* mutations alone (*n* = 42) had a median OS of 20.6 mo and a 2-yr OS of 43%, which was not unlike the outcome of intermediate-risk patients without *FLT3-ITD* and with concurrent *NPM1* and *IDH* mutations (*n* = 13, 2-yr OS of 51%, with median OS not yet reached, *P* = 0.59, Fig. 2a). This compares with a median OS of 13.0 months and 2-yr OS of 30% in the *IDH*-mutant only intermediate-risk cohort (*P* = 0.067). When further evaluating only those patients in the front-line intermediate-risk cohort with age restricted to less than 60 (*n* = 122), the 5 patients with concurrent *NPM1* and *IDH* mutations were noted to have 2-year OS of 100% [median follow-up time of 16 months], which was not significantly different from the outcome of *IDH*-only mutations (*n* = 10, 2-yr OS 60%, *P* = 0.10) and *NPM1*-only mutations (*n* = 16, 2-yr OS 58%, *P* = 0.10) (Supporting Information Fig. 1).

Discussion

The primary aim of the current analysis was to define the prognostic significance of *IDH1* and *IDH2* mutations in patients with AML. While several studies have reported on the incidence and prognosis of *IDH* mutations in patients with AML, available data is conflicting and the significance of IDH mutations on AML outcome has been unclear. This question is of primary importance given the recent development of novel therapeutic agents targeting mutant *IDH1* or *IDH2* with promising preliminary clinical results, with objective responses seen in ~50% of AML patients treated in the relapsed/refractory setting with IDH1 or IDH2 inhibitors [28,29]. Importantly, our study provides a useful baseline expectation for patient outcomes, against which investigational strategies can be assessed.

We confirm that *IDH*-mutated patients have distinctive clinicopathologic characteristics including older age, increased incidence of *FLT3-ITD* and *NPM1* mutations, intermediate-risk cytogenetics, higher platelet count, and increased bone marrow blast percentage at diagnosis [14]. We additionally identify increased circulating blasts and decreased ANC in *IDH*-mutated patients, and less frequent occurrence of *IDH*-mutations in the setting of therapy-related AML.

We were unable to confirm a uniquely improved OS of patients with AML with *FLT3-ITD* negative, *NPM1*-mutated, and *IDH1/2*-mutated intermediate-risk disease. In the study by Patel et al., the 21 patients with this molecular phenotype had a 3-year OS of 89%, compared with 31% in the *FLT3-ITD* negative, *NPM1*-mutated, and *IDH* wild-type population [11]. This compares to 2-year OS of 51% and 43% in our cohort equivalents. This disparity is likely in part accounted for by difference in patient age between studies, with exclusively patients <60 years in the former study, and a median age of 62 years in our current study population. Notably, when we analyzed only those front-line induction AML patients with intermediate-risk cytogenetics and *FLT3-ITD* negative, *NPM1*-mutated, and *IDH* wild-type status who were also <60 years of age, the five corresponding patients were noted to have 100% OS with a median follow-up time of 16 months, which due to the small numbers of younger induction patients in our cohort was not of statistical significance.

Most importantly, we describe the natural history of patients with *IDH*-mutated AML, which to the best of our knowledge is one of the largest studies of clinical outcomes by *IDH* status and salvage treatment status to date. We confirm that response rate and OS for *IDH*-mutated is not dissimilar to *IDH* wild-type AML at all treatment junctures, and provide a useful reference for comparison for future studies in this patient population. Lastly, we enthusiastically note the improved outcomes in AML salvage therapy among all AML patients compared to historical controls, particularly including historical analyses from our institution [30,31]. Compared to an OS of less than 2 months for S2+ AML two decades ago, current S2+ median survival has more than tripled, due to continued gains in supportive care, participation in promising clinical trials, and available effective salvage therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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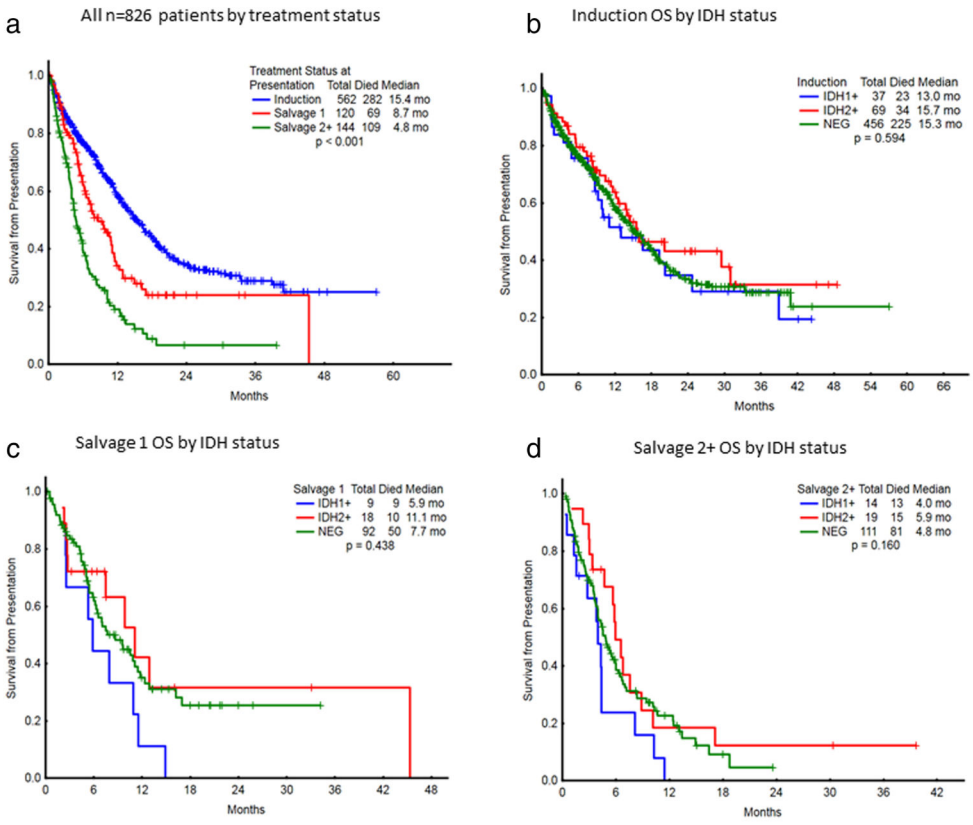

Figure 1.

(a) Overall survival of all *n* = 826 patients by treatment status. (b) Induction OS by IDH status. (c) Salvage 1 OS by IDH status. (d) Salvage 2+OS by IDH status.

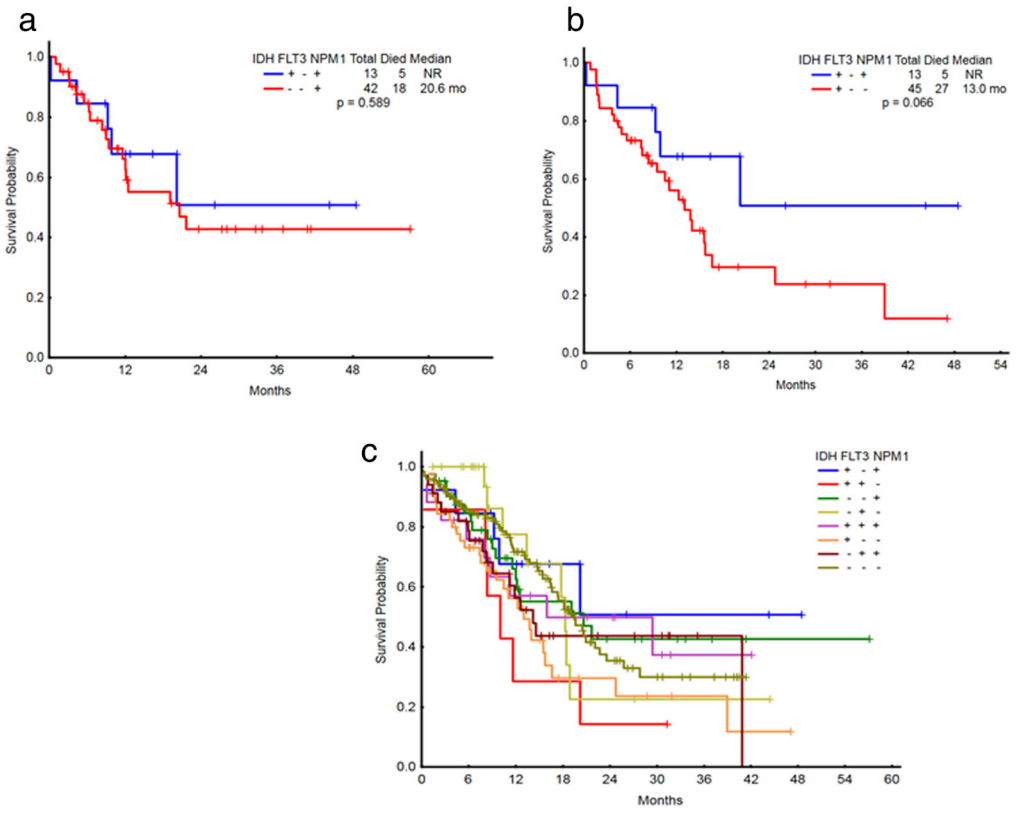

Figure 2.

(a) OS of newly diagnosed AML patients with intermediate-risk cytogenetics by molecular status (IDH+/NPM1+compared to NPM1+alone). (b) OS of newly diagnosed AML patients with intermediate-risk cytogenetics by molecular status (IDH+/NPM1+compared to IDH +alone). (c) OS of newly diagnosed AML patients with intermediate-risk cytogenetics by molecular status.

TABLE I

Clinical Characteristics and Patient Outcome of Study Cohort

Characteristic	IDH wild-type [*n* = 659]	IDH-mutated [*n* = 167]	*P*-value	IDH1 mutated [*n* = 59]	IDH2-mutated [*n* = 106]	*P*-value
Median age (range)	61 (18–92)	67 (22–90)	<**0.0005**	67 (45–83)	66 (22–90)	0.31
Male sex (%)	376 (57)	94 (56)	0.857	32 (52)	62 (58)	0.45
WBC count (×10^9/L)	5.2 (0.2–363)	3.6 (0.2–227.1)	0.18	2.8 (0.4–164.7)	4.8 (0.2–227.1)	0.11
ANC (×10^9/L)	1.1 (0–103.7)	0.42 (0–24.2)	<**0.0005**	0.3 (0–11.0)	0.7 (0–24.2)	**0.008**
PLT count (×10^9/L)	44 (2–568)	55 (1–547)	**0.025**	59 (1–553)	55 (4–547)	0.98
BM Blasts (%)	41 (0–98)	60 (2–99)	<**0.0005**	67 (1–98)	57 (1–99)	0.28
PB Blasts (%)	14 (0–99)	30 (0–99)	<**0.0005**	30 (0–99)	29 (0–99)	0.76
LDH[a]	760 (7–17,486)	624 (142–42,000)	**0.003**	602 (323–6,639)	626 (142–42,000)	0.41
Therapy-related	112 (17)	13 (8)	**0.003**	5 (8)	8 (8)	0.80
Cytogenetics[b]			<**0.0005**			0.15
Favorable	58 (9)	1 (2)		1 (2)	0 (0)	
Intermediate	350 (53)	129 (77)		43 (70)	86 (81)	
Unfavorable	227 (34)	32 (19)		16 (26)	16 (15)	
Indeterminate	24 (4)	5 (3)		1 (2)	4 (4)	
FLT3-ITD mutations (%)	126 (19)	45 (27)	**0.035**	12 (21)	32 (30)	0.20
NPM1 mutations (%)	112 (17)	55 (33)	<**0.0005**	23 (38)	32 (30)	0.37

IDH indicates isocitrate dehydrogenase; WBC, white blood cell; ANC, absolute neutrophil count; PLT, platelet; BM, bone marrow; PB, peripheral blood; LDH; lactate dehydrogenase; FLT3-ITD, FLT3 internal tandem duplication; NPM1, nucleophosmin.

[a] Institutional normal reference range for LDH is 313 to 618 IU/L.

[b] ECOG/SWOG classification system.

TABLE II

Response to Treatment by Salvage Status and IDH Mutation Status

	n	CR/CRi	*P*-value	Median OS	*P*-value
Induction	562	382 (68%)	0.33	15.4 mo	0.59
IDH1+	37	24 (65)		13.0 mo	
IDH2+	69	42 (61)		15.7 mo	
IDH wild-type	456	316 (69)		15.3 mo	
Salvage-1	120	50 (42%)	0.76	8.7 mo	0.44
IDH1+	9	4 (40)		5.9 mo	
IDH2+	18	9 (50)		11.1 mo	
IDH wild-type	92	37 (41)		7.7 mo	
≥ Salvage-2	144	40 (27%)	0.76	4.8 mo	0.16
IDH1+	14	5 (36)		4.0 mo	
IDH2+	19	5 (26)		5.9 mo	
IDH wild-type	111	30 (27)		4.8 mo	

IDH indicates isocitrate dehydrogenase; CR, complete remission; CRi, complete remission with incomplete count recovery; OS, overall survival.