

Molecular Remission and Response Patterns in Patients with Mutant-IDH2 Acute Myeloid Leukemia Treated with Enasidenib
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ABSTRACT

Approximately 8-19% of patients with acute myeloid leukemia (AML) have isocitrate dehydrogenase-2 (IDH2) mutations, which occur at active site arginine residues, R140 and R172. IDH2 mutations produce an oncometabolite, 2-hydroxyglutarate (2-HG), that leads to DNA and histone hypermethylation and impaired hematopoietic differentiation. Enasidenib is an oral inhibitor of mutant-IDH2 proteins. This first-in-human phase I/II study evaluated enasidenib doses of 50-650 mg/day, administered in continuous 28-day cycles, in patients with mutant-IDH2 hematologic malignancies (ClinicalTrials.gov, NCT01915498). Overall, 214/345 patients (62%) with relapsed/refractory AML received enasidenib 100 mg/day. Median age was 68 years. Forty-two patients (19.6%) attained complete remission (CR), 19 patients (10.3%) proceeded to an allogeneic bone marrow transplant, and overall response rate was 38.8% (95%CI 32.2-45.7). Median overall survival was 8.8 months (95%CI 7.7-9.6). Response and survival were comparable among patients with IDH2-R140 or IDH2-R172 mutations. Response rates were similar among patients who, at study entry, were in relapse (37.7%), or were refractory to intensive (37.5%) or non-intensive (43.2%) therapies. Sixty-six RBC transfusion-dependent (43.1%) and 53 platelet transfusion-dependent (40.2%) patients achieved transfusion independence. The magnitude of 2-HG reduction on-study was associated with CR in IDH2-R172 patients. Clearance of mutant-IDH2 clones was also associated with achievement of CR. Among all 345 patients, the most common grade 3-4 treatment-related adverse events were hyperbilirubinemia (10%), thrombocytopenia (7%), and IDH differentiation syndrome (6%). Enasidenib was well-tolerated and induced molecular remissions and hematologic responses in patients with AML for whom prior treatments had failed. The study is registered to <https://clinicaltrials.gov> as NCT01915498.

INTRODUCTION

Few patients with relapsed or refractory acute myeloid leukemia (R/R AML) are cured.¹ In patients fit for intensive treatment, remission rates with reinduction chemotherapy are no higher than 40-50% and there are few long-term survivors.^{2,3} Estimated median overall survival (OS) among relapsed or refractory patients who are unfit for reinduction, many of whom are older adults, is only a few months.^{2,4}

Approximately 8-19% of patients with AML have an isocitrate dehydrogenase 2 (IDH2) mutation.⁵ Somatic IDH2 point mutations occur at the active site arginine residues, R140 and R172.⁶ Mutant-IDH2 proteins have neomorphic enzymatic activity, catalyzing NADPH-dependent reduction of alpha-ketoglutarate (α -KG) to an oncometabolite, the (R) enantiomer of 2-hydroxyglutarate (2-HG).^{7,8} High concentrations of 2-HG associated with mutant-IDH2 AML competitively inhibit α -KG-dependent dioxygenases, including DNA-demethylating TET-family proteins, leading to histone and DNA hypermethylation.⁹ These changes are associated with the blocked differentiation of immature hematopoietic cells that characterize AML.^{9,10}

Enasidenib (IDHIFA®; AG-221) is a small-molecule, oral inhibitor of mutant-IDH2 proteins approved by the US Food and Drug Administration at an initial dose of 100-mg once-daily for treatment of adult patients with mutant-IDH2 R/R AML.^{11,12} Enasidenib reduces 2-HG to normal levels and promotes maturation of leukemic progenitor and precursor cells.^{11,13} Interim safety and efficacy data for a subset of patients with R/R AML in the phase I/II dose-escalation and expansion study of enasidenib monotherapy (NCT01915498) have been

reported.¹⁴ Here, we describe for the first time, novel data on molecular clearance and molecular relationships between response or resistance to enasidenib. Additionally, we report the clinical outcomes for the entire cohort of patients with R/R AML treated on the trial, the relationship between prior AML treatment and response to enasidenib, the potential for delayed responses in patients who maintained stable disease (SD) during early treatment, the influence of pretreatment demographic and disease variables on response, and rates of transfusion independence during enasidenib therapy.

METHODS

The study protocol was approved by institutional review boards or ethics committees at all participating sites. All patients provided written informed consent before study participation. This study was funded by Celgene Corporation (Summit, NJ) and Agios Pharmaceuticals, Inc (Cambridge, MA). All authors had full access to study data, participated in data interpretation, contributed to the manuscript, and approved final content. The corresponding author made the final decision to submit the paper.

Study design and methods of the phase I dose-escalation and expansion portions of this study are described elsewhere.^{13,14} Enrollment in phase II was limited to patients aged ≥ 18 years with mutant-IDH2 R/R AML who had relapsed after allogeneic stem cell transplant; were in second or later relapse; were refractory to initial induction or re-induction treatment; or had relapsed within 1 year of initial treatment, excluding those with favorable cytogenetic risk (per National Comprehensive Cancer Network [NCCN] 2015 guidelines¹⁵). All patients in the phase I expansion and phase II study portions received enasidenib 100-mg once-daily in continuous 28-day cycles.

Bone marrow biopsies and/or aspirates and peripheral blood were collected at screening, on cycle 2 day 1, and every 28 days for the next 12 months, and then every 56 days thereafter while receiving enasidenib.

Efficacy Endpoints

Investigator-assessed clinical responses, per International Working Group (IWG) AML response criteria,¹⁶ are reported for all R/R AML patients, and for the subgroup of patients with R/R AML who received enasidenib 100mg daily (R/R AML100 cohort), who accounted for three-fourths of all study participants. Overall response rate (ORR) included complete remission (CR), and “non-CR responses” of CR with incomplete count recovery (CRi/CRp), partial remission (PR), and morphologic leukemia-free state (MLFS).¹⁶ Red blood cell (RBC) and platelet transfusion independence were defined as no transfusions for ≥ 56 consecutive days on-study, among patients who had received one or more transfusion within 4 weeks (phase I) or 8 weeks (phase II) before study entry.

OS was measured as the interval between first enasidenib dose and death from any cause.

Event-free survival (EFS) describes the interval between first enasidenib dose and AML relapse ($\geq 5\%$ bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death, whichever occurred first.

Among R/R AML100 patients, response and survival were evaluated based on baseline demographic and disease characteristics, number of prior AML treatments, and whether, at study start, patients were refractory to induction chemotherapy, refractory to non-intensive AML treatment (hypomethylating agents, low-dose cytarabine), or were in first or later relapse. Response and survival outcomes were also evaluated among R/R AML100 patients

who maintained SD for the first 90 days of enasidenib treatment (per European LeukemiaNet definition¹⁷).

Translational Endpoints

Exploratory translational analyses were performed on samples from R/R AML100 patients with at least 1 on-study efficacy assessment, and included assessment of plasma 2-HG levels and mutant-IDH2 variant allele frequency (VAF) in bone marrow mononuclear cells at baseline and during treatment, and co-mutations at baseline. Methods of sample preparation, 2-HG and mutant-IDH2 VAF assessment, and DNA sequencing were reported previously¹³ and are described in detail in the Supplementary Appendix. Endpoints are reported by IDH2 variant, R140 or R172. Relationships between clinical response and 2-HG concentrations and mutant-IDH2 VAF were determined using response data from an October 14, 2016 cutoff date (Supplementary Table S1).

Statistical Analyses

For adequate estimations of response rate, duration of response, and EFS, 291 patients were to be enrolled: 66 in the dose-escalation phase, 100 in the phase I expansion, and 125 in the phase II study portion. Hematologic response rates were calculated using point estimates of proportions with 2-sided exact binomial 95% confidence intervals (CI). OS and 1-year survival rates were estimated using Kaplan-Meier methods.

Relationships between response and individual co-mutations were evaluated using a 2-tailed Fisher's exact test.

RESULTS

Patients

Between September 20, 2013, and data cutoff on September 1, 2017, 345 patients were enrolled at 21 sites and received at least one enasidenib dose (Supplementary Figure S1). In all, 280 patients with R/R AML participated, 214 of whom (76.2%) comprised the R/R AML100 cohort. The median number of enasidenib treatment cycles was 5.0 (range 1-38). At data cutoff, 16 patients (4.6%) remained on-study.

Among all R/R AML patients, the genes most frequently co-mutated with IDH2 were SRSF2 (42.0%), DNMT3A (38.5%), ASXL1 (27.0%), and RUNX1 (20.1%). Three genes were preferentially co-mutated with IDH2-R140 (SRSF2, RUNX1, NPM1) and two with IDH2-R172 (BCOR, ARID2) (Supplementary Table S2).

In the R/R AML100 cohort, median age at study entry was 68 years (range 19-100), 162 patients (75.7%) had IDH2-R140Q mutations, 46 (21.5%) had AML secondary to a myelodysplastic syndrome (MDS), and 48 (22.4%) had received ≥ 3 prior AML therapies (Table 1).

Safety

Safety outcomes for all patients were consistent with those reported previously.¹⁴ The most frequent treatment-emergent adverse events (TEAEs; any grade) related to enasidenib treatment were indirect hyperbilirubinemia (40.3%), nausea (28%) and decreased appetite (17.7%) (Supplementary Table S3). The most frequent enasidenib-related grade 3-4 TEAEs were hyperbilirubinemia (10.4%), IDH differentiation syndrome (IDH-DS; 6.4%), and anemia (5.5%).

Response

Response rates were similar in the R/R AML100 patient cohort and in all patients with R/R AML (Table 2). In the R/R AML100 cohort, 42 patients (19.6%) attained CR, ORR was 38.8% (95%CI 32.2, 45.7), and 19 patients (8.9%) proceeded to allogeneic bone marrow transplant. Median time to first response was 1.9 months (range 0.5-9.4) and to best response was 3.7 months (0.6-14.7). Among responding patients, 46% (38/83) attained their best response by cycle 4 and 80% (66/83) did so by cycle 6. There was no significant difference in ORR between R/R AML100 patients with IDH2-R140 (35.8% [95%CI 28.4%, 43.7%]) or IDH2-R172 (47.1% [32.9%, 61.5%]) mutations (P=0.187).

In univariate analyses, age, prior stem cell transplant, and ECOG performance status at entry had no significant effect on likelihood of response to enasidenib; only cytogenetic risk at baseline was significantly predictive of response, with poor-risk cytogenetic classification associated with a lower ORR compared with intermediate-risk cytogenetics (18.2% vs. 46.3%; P<0.001) (Supplementary Figure S2). Similarly, in univariate analysis median OS was shorter for R/R AML100 patients with poor-risk cytogenetics compared with patients who had intermediate-risk cytogenetics (7.0 vs 9.3 months, respectively; P=0.006). For patients who had received 1, 2, or ≥3 prior AML therapies, ORRs were 46.5% (47/101), 36.9% (24/65), and 25.0% (12/48), respectively (Fisher's exact test P=0.040) (Supplementary Figure S3).

Response by Outcome of Prior AML Therapy

At study entry, 40 R/R AML100 patients (19%) were refractory to induction chemotherapy, 44 patients (21%) were refractory to lower-intensity regimens and had never received intensive AML treatment, and 130 patients (61%) were in relapse following prior AML treatment. Patients refractory to induction chemotherapy were younger (median age 60.5 years) than those in the other two categories; patients refractory to non-intensive regimens were older (median 74.0 years) and more likely to have had a prior diagnosis of myelodysplastic syndromes (MDS); and patients in relapse were most likely to have received multiple prior AML regimens (Supplementary Table S4). For patients who were refractory to intensive chemotherapy, ORR was 37.5%, including 4 patients (10.0%) who attained CR (Table 3); for patients who were refractory to non-intensive regimens, ORR was 43.2% with 12 patients (27.3%) attaining CR; and for patients in relapse, ORR was 37.7% with 26 patients (20.0%) attaining CR.

Association Between Mutant-IDH2 VAF and Response

Baseline mutant-IDH2 VAF was assessed for 103 efficacy-evaluable R/R AML100 patients and ranged from 0.96% to 44.1%, with similar mean values in patients with IDH2-R140 (n=79) or IDH2-R172 (n=24) mutations (26.3% and 27.0%, respectively). Mean mutant-IDH2 VAF at baseline was significantly lower in IDH2-R140 patients who attained CR on-study compared with non-responders (20.5% vs. 30.6%, respectively; P=0.002) (Supplementary Figure S4), though baseline IDH2-R140 VAF varied widely (from 1.6% to 40.1%) in patients who attained CR. Baseline mutant-IDH2 VAF among IDH2-R172 patients who attained CR was proportionately lower but not statistically different from that for non-responding patients (23.7% vs. 33.0%, respectively; P=0.114).

Changes in mutant-IDH2 VAF during enasidenib treatment were assessed for 101 patients with at least one on-treatment measurement. Median baseline-normalized VAF in patients with IDH2-R140 mutations was reduced more than 50% beginning at cycle 5, and reached 90% reduction by cycle 9 (Figure 1A). Median maximum IDH2-R140 VAF reductions were

greatest in patients who achieved CR compared with non-responders (−98% vs. −16%, respectively; $P<0.0001$) (Figure 1B). Median baseline-normalized VAF in patients with IDH2-R172 mutations did not decrease more than 10% at any time-point, though patients who achieved CR demonstrated significant VAF reductions (−62%) compared with non-CR responders (+54%, $P=0.0164$) and non-responders (+7%, $P=0.0134$) (Figure 1B).

Twelve of 101 R/R AML100 patients (11.9%) achieved mutant-IDH2 molecular remission, defined as IDH2 VAF below the limit of detection (0.02%–0.04%) at one or more time-point; all 12 patients had IDH2-R140 mutations. Molecular remission was significantly associated with achievement of hematologic response (Chi-squared $P=0.0003$ vs. non-response). Ten of the 12 patients attained morphologic CR, 1 achieved CRp and 1 achieved PR (Supplementary Table S5). There was a significant survival advantage among the 12 patients who attained molecular remission vs those who did not ($n=89$) (median OS 22.9 months vs 8.8 months, respectively, $P=0.0153$). However, among the 35 patients who achieved morphologic CR, there was no significant survival difference between the 10 patients who also attained IDH2 molecular remission (median OS 22.9 months) vs. patients in morphologic CR with detectable mutant-IDH2 ($n=25$; median OS 20.7 months). Although no patient with an IDH2-R172 mutation achieved molecular remission, 2 of 23 patients reached IDH2-R172 VAF levels below 2%; both patients also achieved morphologic CRs (Supplementary Figure S5).

Co-mutations and Resistance to Enasidenib

Co-occurring mutation patterns among R/R AML100 patients are shown in Supplementary Figure S6. The most common mutations in this cohort were SRSF2 (39.4%), DNMT3A (35.4%), ASXL1 (26.0%), RUNX1 (21.3%), NRAS (13.4%), BCOR (13.4%) and NPM1 (13.4%). Co-mutation burden at baseline was significantly greater in patients with IDH2-R140 mutations than those with IDH2-R172 mutations (mean 3.3 vs 2.4 co-mutated genes, respectively; $P=0.0115$) (Supplementary Figure S7). Responding patients had significantly fewer baseline mutations than non-responding patients (Figure 2A). When patients were segregated into approximate tertiles by total number of baseline mutations (≤ 3 , $n=42$; >3 and <6 , $n=53$; ≥ 6 , $n=32$), a trend for lower ORR was observed in patients with ≥ 6 mutations vs. patients with ≤ 3 mutations (31.3% vs. 54.8%, respectively, $P=0.06$) (Figure 2B).

In univariate analysis of data from 127 R/R AML100 patients, the only baseline co-mutation identified as significantly associated with non-response was FLT3 (−ITD or −TKD; $n=12$) (Fisher's exact $P=0.014$ vs. any response). Though not observed in the R/R AML100 subgroup, NRAS co-mutations were significantly associated with non-response among the overall R/R AML patient cohort (3.0% of patients with an NRAS mutation attained CR vs. 19% of patients with no response, $P=0.025$). Univariate analysis within functional gene groups¹⁸ showed patients with mutations in genes related to the Splicing and the Receptors/Kinases/Signaling functional categories were less likely to have any response to enasidenib ($P=0.007$ and 0.005 , respectively) (Supplementary Figure S8).

Association Between 2-HG and Response

Baseline total 2-HG levels in plasma were available for 159 R/R AML100 patients (IDH2-R140, $n=119$; IDH2-R172, $n=40$). In patients with IDH2-R140 mutations, no significant differences in baseline 2-HG levels were noted among clinical response categories: median 2-HG concentrations at study entry were 629, 716, and 807 ng/mL for patients who later achieved CR, any non-CR response, or no response, respectively (Supplementary Figure S9).

In contrast, for patients with IDH2-R172 mutations, higher median baseline 2-HG levels were significantly associated with subsequent achievement of CR vs. non-response (1727 vs. 491 ng/mL; $P=0.0381$).

Longitudinal changes in plasma 2-HG concentrations during enasidenib treatment were assessed in 155 R/R AML100 patients. Baseline-normalized median 2-HG reductions approached or exceeded 10-fold for patients with IDH2-R140 mutations within the first treatment cycle and were sustained through subsequent cycles; however, this was not observed for patients with IDH2-R172 mutations (Figure 3A). During treatment, patients with IDH2-R140 mutations showed significantly greater maximum 2-HG reductions from baseline (median -92.9%) compared with IDH2-R172 patients (median -47.4%) ($P=0.0004$). In patients with IDH2-R140 mutations, 2-HG levels were suppressed from baseline irrespective of clinical response category (-94.2%, -94.6%, and -90.0% in patients achieving CR, non-CR responses, and no response, respectively). For IDH2-R172 patients, 2-HG reductions were significantly greater in patients achieving CR (-82.0%) than in non-CR responders (-44.3%; $P=0.0352$) and non-responding patients (-38.4%; $P=0.0324$) (Figure 3B).

Clinical Responses Following Early Stable Disease

Enasidenib acts as a differentiating agent and responses to treatment may be delayed.¹¹ Eighty-two R/R AML100 patients (38%) maintained SD during the first 90 days on-study. Of them, 25 patients (30%) achieved an IWG-defined response after day 90 ("Late Responders"), including 16 patients who attained CR; 29 patients (35%) continued to maintain SD at all subsequent visits ("SD Only"); and 28 patients (34%) experienced only progressive disease (PD) after day 90 (Supplementary Table S6). At baseline, Late Responders were less likely than patients who later developed PD to have received more than 2 prior anti-cancer treatments (8% vs. 32%, respectively; $P=0.0432$) or to have poor-risk cytogenetics (8% vs. 43%; $P=0.0019$) (Supplementary Table S7). Seven Late Responders (28%) proceeded to transplant. Of those who maintained SD at all response evaluations after day 90, 11 of 21 patients (52%) who were RBC transfusion dependent at baseline attained RBC transfusion independence on-study, and 8 of 22 patients (36%) who were platelet transfusion dependent at baseline achieved platelet transfusion independence.

Transfusion Independence

Among all R/R AML100 patients who were transfusion-dependent at baseline, 43.1% (66/153) achieved RBC transfusion independence and 40.2% (53/132) achieved platelet transfusion independence on-study.

Survival

At a median follow-up of 7.8 months, estimated median OS for all 280 R/R AML patients was 8.8 months (95%CI 7.8, 9.9) (Supplementary Figure S10). Median OS among R/R AML100 patients was also 8.8 months (95%CI 7.7, 9.6) (Figure 4A). Median EFS was 4.7 months (95%CI 3.7, 5.6) (Table 2). There was no statistical difference in median OS between patients with IDH2-R140 (8.2 months [95%CI 7.0, 9.3]) or IDH2-R172 (10.6 months [7.5, 12.7]) mutations. Estimated median OS was 22.9 months for the 42 R/R AML100 patients who achieved CR, 10.6 months for patients who achieved a non-CR response, and 5.6 months for non-responders. Among patients who proceeded to transplant during the study, median OS was 23.6 months (95%CI 10.6, not reached [NR]). Estimated median OS among patients who had received 1, 2, or ≥ 3 prior AML treatments before study entry was 11.8 months (95%CI 8.3, 15.4), 7.8 months (5.8, 9.1), and 7.0 months (4.9, 8.8), respectively (log

rank $P=0.001$) (Supplementary Figure S3). No significant relationships emerged between any individual co-mutation and OS in univariate analyses.

Overall Survival by Prior AML Treatment Outcome

There was no significant difference in median OS among patient subgroups defined by response to prior AML treatment. For patients who were refractory to intensive chemotherapy prior to study entry, median OS was 12.4 months (95%CI 8.2, 22.9), for patients who were refractory to non-intensive AML treatment, median OS was 8.0 months (5.6, 11.7), and for patients in first or later relapse, median OS was 8.1 months (7.0, 9.3) (log-rank $P=0.270$) (Figure 4B).

Survival Outcomes for Patients with Early Stable Disease

Among the 82 patients who maintained SD for the first 90 days on-study, median OS for Late Responders was 15.1 months (95%CI 10.7, NR), for the SD Only subgroup was 9.0 months (7.7, 11.4), and for patients who later developed PD was 5.8 months (5.4, 8.3). Estimated 1-year survival rates were 58%, 24%, and 8%, respectively. Risk of death was significantly reduced in Late Responders by 59% compared with the SD Only subgroup and by 79% compared with patients who developed PD after day 90 (Supplementary Table S6). SD sustained at all response evaluations beyond day 90 was associated with a significant 51% reduced risk of death compared with early SD followed by PD after day 90.

DISCUSSION

Patients with relapsed or refractory AML have few available treatment options. This study demonstrates that enasidenib is an effective salvage therapy, inducing responses in ~40% of patients with mutant-IDH2 R/R AML, many of whom had received multiple prior AML treatments. Response and survival outcomes in this larger patient group support initial findings from phase I of the study and new analyses in this paper offer further insight into enasidenib use.¹⁴ Enasidenib served as a bridge to transplant for several patients with relapsed or refractory disease, and those patients who achieved CR during enasidenib treatment had a median OS of almost 2 years. Enasidenib is noncytotoxic¹¹; tolerability is especially important for older patients who may have additional comorbidities and who have received prior cytotoxic chemotherapy regimens, and an important consideration for use in combination regimens. Enasidenib has been shown to promote differentiation of leukemic hematopoietic progenitor cells, producing functional neutrophils that retained the IDH2 mutation.^{11,13} Thus, clearance of mutant-IDH2 VAF is not required to obtain a therapeutic response; however, patients who attained CR showed significantly greater VAF reductions than non-responders, and these are the first data to show that clearance of IDH2 mutations was associated with a 100% clinical response rate. Substantial, sustained 2-HG decreases during treatment were observed in IDH2-R140 patients. In patients with IDH2-R172 mutations, 2-HG levels were less suppressed overall; however, 2-HG reductions were significantly correlated with attainment of CR. As also demonstrated in the phase I study portion,¹⁴ there were no statistical differences in response rates or median OS between patient groups with IDH2-R140 or IDH2-R172 mutations; nominally better efficacy in patients with mutant-IDH2-R172 may reflect the significantly lower co-mutation burden in that group.

The presence of a FLT3 co-mutation at study entry was significantly associated with lack of response in the R/R AML100 cohort and NRAS co-mutations were correlated with non-achievement of CR among the entire R/R AML cohort. To target multiple pathogenic mechanisms, combining enasidenib with other targeted drugs such as a FLT3 inhibitor, or

with agents with broader antileukemic activity such as a hypomethylating agent, could improve response. In an IDH2R140Q/FLT3ITD murine AML model, combination therapy with enasidenib and the tyrosine kinase inhibitor, quizartinib, showed additive effects on reducing leukemic blasts in liver, spleen, and bone marrow, and significant reversal of hypermethylated genes, compared with either treatment alone.¹⁹ Both FLT3 and NRAS mutations are highly prevalent in AML, occurring in ~20% and 15% of AML patients, respectively.⁵ RAS pathway mutations have been linked to drug resistance in other malignancies, including pediatric B-cell precursor acute lymphoblastic leukemia²⁰ and colorectal cancer.^{21,22} Much effort over recent decades has been made to develop effective MEK1/2 inhibitors, though single-agent effects in AML have been relatively modest.^{23,24} Preliminary data from a phase I/II study of enasidenib with azacitidine in patients with newly diagnosed AML

(NCT02677922) suggest this combination may have additive effects on response compared with either monotherapy.²⁵

While overall response rates (~40%) and CR rates (~20%) in this larger group of patients with R/R AML corroborate those reported for the smaller cohort of patients in phase I of the study, we evaluated several aspects of enasidenib therapy not previously explored. Past research suggests that among prognostic factors for response to salvage therapy in R/R AML is the presence or absence of primary induction failure.^{26,27} These are the first data to show response rates with enasidenib among patient subgroups defined by whether they were in relapse or were resistant to prior AML treatment at study entry. Despite proportionally higher CR rates in patients who were refractory to non-intensive treatments (27.3%) compared with those who were refractory to induction chemotherapy (10%), survival outcomes were not statistically different between these two groups (median OS 8.0 and 12.4 months, respectively). Compared with patients who were refractory to intensive chemotherapy, or those who relapsed following prior AML therapy, patients who were refractory to non-intensive AML treatment options (who were likely ineligible for high-intensity chemotherapy) were substantially older and more likely to have developed AML secondary to MDS. Nevertheless, the 8-month median OS among these patients compares favorably with OS obtained with other salvage regimens in a similar patient population.⁴ These data also reinforce that the kinetics of response to enasidenib differ from those of intensive chemotherapy.¹⁴ In contrast to the CR-driven response paradigm characteristic of high-intensity chemotherapy, responses with enasidenib may require multiple treatment cycles, and initial responses may deepen with continued treatment. By restoring the activity of α -KG dependent enzymes that regulate DNA and histone methylation, the epigenetic effects of enasidenib may be akin to those of hypomethylating agents, which can require 4-6 treatment cycles to induce responses.²⁸ More than one-half of responding patients in this study achieved their best response in cycle 5 or later. Given the potential for delayed response, we evaluated clinical outcomes for patients who maintained SD during initial treatment cycles. Results of these analyses also demonstrate that responses with enasidenib, as reported for other differentiating agents, can manifest gradually.^{29,30} Almost one-third of patients who maintained SD during the first three months of enasidenib treatment had a later response, and of them, two-thirds attained complete morphologic remissions. The 2017 update to the ELN recommendations for AML states, "...it is unknown whether PD augurs a poorer prognosis than stable disease and warrants investigation."¹⁷ The answer is likely dependent on the nature of therapy and specific AML patient populations. In our study, patients who experienced sustained SD for the duration of

treatment (ie, beyond 90 days) but who did not achieve an IWG-defined response to enasidenib had a significantly reduced risk of death compared with patients who later developed PD on-study. Together, these data suggest enasidenib therapy should be continued for at least 6 months, or until disease progression or intolerable toxicity. These are the first data to demonstrate the relationship between enasidenib and transfusion independence: over 40% of R/R AML100 patients who were RBC or platelet transfusion-dependent at baseline attained transfusion independence during enasidenib therapy. Moreover, substantial proportions of patients who maintained SD on-study, in the absence of a formal IWG-defined response, attained RBC and/or platelet transfusion independence during treatment. Transfusion independence is associated with improved survival in AML.³¹

As reported for other differentiating agents,^{30,32,33} enasidenib can induce a differentiation syndrome. IDH-DS is reported for ~10% of enasidenib-treated patients.³⁴ Signs or symptoms of IDH-DS are recognizable and treatable with prompt corticosteroid administration. Enasidenib treatment need not be interrupted unless severe pulmonary symptoms and/or renal dysfunction last more than 48 hours after corticosteroid initiation. IDH-DS is frequently accompanied by leukocytosis, which can be effectively treated with hydroxyurea if WBC count rises above $30 \times 10^9/L$.^{12,34}

Enasidenib is an important treatment option for patients with mutant-IDH2 R/R AML. A randomized, phase III study in older patients with late-stage mutant-IDH2 R/R AML (NCT02577406) is ongoing to evaluate the efficacy of enasidenib compared with conventional care regimens. Enasidenib is also under investigation in phase I/II clinical trials for use in combination therapeutic regimens in patients with newly diagnosed AML (NCT02677922; NCT02632708).

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Disclosures:

EMS served on advisory boards for Astellas, Daiichi, Bayer, Novartis, Pfizer, Agios, and Celgene. CDD consulted for Agios and Celgene. ATF consulted for Takeda, Seattle Genetics, and Celgene; and served on advisory boards for Agios, Jazz, Boehringer Ingelheim, and Astellas. DAP received honoraria from Agios and Pfizer; and served on advisory boards for Pfizer, Celyad, Agios, Celgene, AbbVie, Argenx, and Curis. RMS consulted for AbbVie, Agios, Amgen, Arog, Astellas, Celator, Celgene, Cornerstone, Fujifilm, Janssen, Jazz, Juno, Karyopharm, Merck, Novartis, Ono, Orsenix, Pfizer, Roche, and Sumitomo; received research funding from Agios, Arog, and Novartis; served on advisory boards for Actinium;

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