

Enasidenib plus azacitidine versus azacitidine alone in patients with newly diagnosed, mutant-IDH2 acute myeloid leukaemia (AG221-AML-005): a single-arm, phase 1b and randomised, phase 2 trial

Courtney D DiNardo, Andre C Schuh, Eytan M Stein, Pau Montesinos, Andrew H Wei, Stéphane de Botton, Amer M Zeidan, Amir T Fathi, Hagop M Kantarjian, John M Bennett, Mark G Frattini, Patricia Martin-Regueira, Frederik Lersch, Jing Gong, Maroof Hasan, Paresch Vyas*, Hartmut Döhner*

Summary

Background Enasidenib is an oral inhibitor of mutant isocitrate dehydrogenase-2 (IDH2) proteins. We evaluated the safety and activity of enasidenib plus azacitidine versus azacitidine alone in patients with newly diagnosed, mutant-IDH2 acute myeloid leukaemia ineligible for intensive chemotherapy. **Methods** This open-label, phase 1b/2 trial was done at 43 clinical sites in 12 countries (the USA, Germany, Canada, the UK, France, Spain, Australia, Italy, the Netherlands, Portugal, Switzerland, and South Korea). Eligible patients were aged 18 years or older and had newly diagnosed, mutant-IDH2 acute myeloid leukaemia, and an Eastern Cooperative Oncology Group performance status of 0–2. In the phase 1b dose-finding portion, patients received oral enasidenib 100 mg/day or 200 mg/day in continuous 28-day cycles, plus subcutaneous azacitidine 75 mg/m² per day for 7 days of each cycle. In phase 2, patients were randomly assigned (2:1) via an interactive web response system to enasidenib plus azacitidine or azacitidine-only, stratified by acute myeloid leukaemia subtype (de novo or secondary). The primary endpoint in the phase 2 portion was the overall response rate in the intention-to-treat population at a prespecified interim analysis (Aug 20, 2019) when all patients had at least 1 year of follow-up. Safety was assessed in all patients who received at least one dose of study drug. The trial is registered with ClinicalTrials.gov, NCT02677922, and is ongoing. **Findings** Between June 3, 2016, and Aug 2, 2018, 322 patients were screened and 107 patients with mutant-IDH2 acute myeloid leukaemia were enrolled. At data cutoff for the interim analysis, 24 patients (including two from the phase 1 portion) were still receiving their assigned treatment. Six patients were enrolled in the phase 1b dose-finding portion of the trial and received enasidenib 100 mg (n=3) or 200 mg (n=3) in combination with azacitidine. No dose-limiting toxicities occurred and the enasidenib 100 mg dose was selected for phase 2. In phase 2, 101 patients were randomly assigned to enasidenib plus azacitidine (n=68) or azacitidine only (n=33). Median age was 75 years (IQR 71–78). 50 (74%; 95% CI 61–84) patients in the enasidenib plus azacitidine combination group and 12 (36%; 20–55) patients in the azacitidine monotherapy group achieved an overall response (odds ratio 4.9 [95% CI 2.0–11.9]; p=0.0003). Common treatment-related grade 3 or 4 adverse events with enasidenib plus azacitidine were thrombocytopenia (25 [37%] of 68 vs six [19%] of 32 in the azacitidine-only group), neutropenia (25 [37%] vs eight [25%]), anaemia (13 [19%] vs seven [22%]), and febrile neutropenia (11 [16%] vs five [16%]). Serious treatment-related adverse events were reported in 29 (43%) patients in the combination group and 14 (44%) patients in the azacitidine-only group; serious treatment-related adverse events occurring in more than 5% of patients in either group were febrile neutropenia (nine [13%] in the combination group vs five [16%] in the azacitidine-only group), differentiation syndrome (seven [10%] vs none), and pneumonia (three [4%] vs two [6%]). No treatment-related

deaths were reported. Interpretation Combination enasidenib plus azacitidine was well tolerated and significantly improved overall response rates compared with azacitidine monotherapy, suggesting that this regimen can improve outcomes for patients with newly diagnosed, mutant-IDH2 acute myeloid leukaemia. Funding Bristol Myers Squibb. Copyright © 2021 Published by Elsevier Ltd. All rights reserved.

Introduction Acute myeloid leukaemia is an aggressive myeloid malignancy that occurs primarily in older adults.¹ In 2020, around 20 000 people in the USA were diagnosed with acute myeloid leukaemia and around 11 000 patients died from the disease.¹ Induction with myeloablative intensive chemotherapy has been the standard of care for the initial treatment of patients with acute myeloid leukaemia who are fit to receive it.² For patients with newly diagnosed acute myeloid leukaemia who are not candidates for intensive chemotherapy due to older age or poor performance status, lower-intensity strategies include low-dose cytarabine, hypomethylating agents, venetoclax, glasdegib, and targeted therapies for patients with FLT3 or isocitrate dehydrogenase-1 (IDH1) or IDH2 mutations.³ IDH2 gene mutations occur in 8–19% of patients with acute myeloid leukaemia.^{4–6} Functional IDH proteins catalyse the oxidative decarboxylation of isocitrate to α -ketoglutarate, a key effector of cellular function and epigenetic regulation.⁷ Mutations in the IDH2 active site arginine residues, Arg140 and Arg172, lead to accumulation of 2-hydroxyglutarate, an oncometabolite that competitively inhibits α -ketoglutarate-dependent enzymes. Among the oncogenic activities of 2-hydroxyglutarate are differentiation block via inhibition of TET family enzymes and histone demethylases, leading to aberrant hypermethylation of DNA and histones.^{8,9} Enasidenib is an oral, small-molecule IDH2 inhibitor shown to suppress 2-hydroxyglutarate concentrations and inhibit the gain-of-function activity of mutant IDH2 proteins, reversing the leukaemogenic block in differentiation.¹⁰ Enasidenib is approved in the USA and is conditionally approved in Canada for the treatment of adult patients with relapsed or refractory acute myeloid leukaemia with an IDH2 mutation, at a recommended starting dose of 100 mg/day. Regulatory approvals were based primarily on results of a phase 1/2 study that enrolled 345 patients with mutant-IDH2 haematological malignancies, including 39 older patients with treatment-naïve, newly diagnosed acute myeloid leukaemia who were not candidates for intensive chemotherapy.^{11–13} Enasidenib monotherapy was associated with a 31% (95% CI 17–48) response rate and median overall survival of 11.3 months (95% CI 5.7–15.1).¹¹ Azacitidine is a hypomethylating agent and DNA methyltransferase inhibitor shown to promote clinical responses and improve survival in patients with newly diagnosed acute myeloid leukaemia.¹⁴ The clinical activity of azacitidine is driven through hypomethylation of DNA, resulting in re-expression of tumour suppressor genes, and via cytotoxicity.¹⁵ For patients with newly diagnosed acute myeloid leukaemia, azacitidine monotherapy is associated with a modest morphological response rate (around 20–30%) and a median overall survival of around 10–12 months.^{14,16–18} Combining azacitidine and enasidenib in vitro enhances apoptosis versus azacitidine alone, and is associated with greater-than-additive increases in haemoglobin and reduced leukaemic stem cell and progenitor cell populations.¹⁹ This phase 1b/2 trial assessed the recommended combination enasidenib dose, safety, and antitumour activity of the mutant-IDH inhibitors, enasidenib (IDH2 inhibitor) or ivosidenib (IDH1 inhibitor), in combination with subcutaneous azacitidine in patients with newly diagnosed, mutant-IDH acute myeloid

leukaemia who were not candidates for intensive chemotherapy. Outcomes for patients with mutant-IDH1 acute myeloid leukaemia treated with ivosidenib plus azacitidine in this trial have been reported elsewhere.²⁰ Here, we report the recommended combination dose, safety, and activity of combination enasidenib plus azacitidine in patients with newly diagnosed, mutant-IDH2 acute myeloid leukaemia in the single-arm phase 1b dose-finding portion of this trial, and compare the safety and activity of enasidenib plus azacitidine versus azacitidine only in the randomised phase 2 portion.

Methods
Study design and participants AG221-AML-005 was a multicentre, open-label, phase 1b/2 study done at 43 clinical sites in 12 countries (the USA, Germany, Canada, the UK, France, Spain, Australia, Italy, the Netherlands, Portugal, Switzerland, and South Korea; appendix p 12). Eligible patients were aged 18 years or older, had newly diagnosed, mutant-IDH2 acute myeloid leukaemia (WHO criteria²¹) and Eastern Cooperative Oncology Group (ECOG) performance status scores of 0–2, and were not candidates to receive intensive chemotherapy. Diagnosis of acute myeloid leukaemia and IDH2 mutation status were based on local assessments. A full list of inclusion and exclusion criteria is available in the appendix. All patients provided written, informed consent before enrolment. The study protocol and amendments were approved by review boards and ethics committees at all participating sites.
Randomisation and masking In the phase 2 portion of the trial, patients were randomly assigned (2:1) in block sizes of three to receive enasidenib (at the recommended combination dose) plus azacitidine or azacitidine only. Random assignment was done via an interactive web response system and was stratified by acute myeloid leukaemia subtype (de novo vs secondary). This was an open-label trial.
Procedures The phase 1b dose-escalation part of the trial assessed two enasidenib doses—100 mg or 200 mg per day—each in combination with subcutaneous azacitidine 75 mg/m² per day, to establish the recommended combination dose of enasidenib for the randomised phase 2 study portion. Enasidenib doses were selected on the basis of the phase 1 trial of single-agent enasidenib, in which enasidenib was well tolerated at doses of up to 650 mg/day and had substantial clinical activity and 2-hydroxyglutarate reductions at 100 mg/day.¹³ Enasidenib was taken orally once daily in continuous 28-day treatment cycles, and subcutaneous azacitidine was administered on days 1–7 of each 28-day cycle. Enasidenib dose escalation followed a standard 3 + 3 study design. Dose-limiting toxicities were assessed during the first treatment cycle for patients receiving one or more enasidenib dose. The anticipated enasidenib dose for phase 2 was 100 mg/day. Safety was assessed by reporting adverse events, defined using National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) as any untoward occurrence that began or worsened between the first dose of study drugs to 28 days following the last dose. Adverse events of interest included differentiation syndrome (a novel event associated with the differentiating mechanism of enasidenib²²) and hyperbilirubinaemia (associated with off-target inhibition of the UGT1A1 enzyme responsible for bilirubin metabolism^{11,13}). Blood and bone marrow aspirates were collected at screening for local assessment of disease and IDH2 mutational status and then retrospectively evaluated by an independent pathologist (JMB) masked to treatment assignment. Aspirates were collected on day 1 of cycles 2, 3, and 5, every other cycle thereafter starting at cycle 7, at the end-of-treatment visit, and as clinically indicated. Peripheral blood samples were collected for assessment of haematology

parameters on days 1, 8, 15, and 22 of cycles 1 and 2, days 1 and 15 of cycles 3 and 4, and on day 1 of cycle 5 and beyond. Correlative biomarker analyses in the phase 2 study portion included serial quantification of 2-hydroxyglutarate in peripheral blood by liquid chromatography tandem mass spectrometry (Covance; Princeton, NJ, USA), quantification of IDH2 variant allele frequency in bone marrow mononuclear cells by Sysmex OncoBEAM digital PCR (Sysmex Inostics; Baltimore, MD, USA), and assessment of co-occurring gene mutations by targeted next-generation sequencing of bone marrow mononuclear cells collected at screening using the 37-gene Archer VariantPlex Core Myeloid panel (ArcherDx; Boulder, CO, USA) at a 1% cutoff threshold. Patients could continue treatment until disease progression, unacceptable toxicity, withdrawal of consent, or eligibility to undergo haematopoietic stem-cell transplantation (HSCT). Enasidenib or azacitidine dosing could be interrupted or reduced to manage toxicities; investigators could discontinue enasidenib or azacitidine and keep the patient on-study if the patient continued to show clinical benefit with either monotherapy. A dose-review team comprised sponsor designees and treating physicians who monitored adverse events and were responsible for dosing decisions, including determination of the recommended combination dose. Patients were followed up for adverse events, blood product trans-fusions, and haematological response status for 28 days following the last study drug dose. Patients were followed up for survival and use of subsequent acute myeloid leukaemia therapies until death, loss to follow-up, withdrawal of consent, or study termination.

Outcomes The primary endpoints in the phase 1b dose-escalation phase were safety, tolerability, and the recommended combination dose of enasidenib, and the secondary endpoints were overall response rate and rate of complete remission plus complete remission with partial haematological recovery (defined as $<5\%$ bone marrow blasts and partial recovery of peripheral blood counts [platelet count $>50 \times 10^9$ per L and absolute neutrophil count $>5 \times 10^9$ cells per L], absence of leukaemic blasts in the peripheral blood, and no evidence of extramedullary disease). The primary endpoint in the phase 2 portion was overall response rate. Secondary phase 2 endpoints were complete remission rate; rate of complete remission plus complete remission with partial haematological recovery; rate of haematological improvement in the erythroid, neutrophil, or platelet lineages; time to and duration of response; time to and duration of complete remission plus complete remission with partial haematological recovery; event-free survival; overall survival; and 1-year overall survival rate. Other secondary endpoints were pharmacokinetic parameters and patient-reported health-related quality of life; analyses of these outcomes are ongoing and will be reported elsewhere. Exploratory endpoints included changes in 2-hydroxyglutarate concentrations and IDH2 variant allele frequency; associations between 2-hydroxyglutarate, IDH2 variant allele frequency, and baseline mutations and clinical response category (complete remission, incomplete response, or no response); and overall response rate by IDH2 mutation type (IDH2-Arg140 or IDH2-Arg172). Overall response rate was the proportion of patients with complete remission, complete remission with incomplete blood count or platelet recovery, partial remission, or morphological leukaemia-free state, as defined by International Working Group (IWG) 2003 acute myeloid leukaemia response criteria and assessed by the treating physician.²³ Rates of complete remission plus complete remission with partial haematological recovery were derived by the sponsor using laboratory data.

Haematological improvement of the erythroid, neutrophil, or platelet lineages, and red blood cell and platelet transfusion independence, were assessed using the IWG 2006 response criteria for myelodysplastic syndromes.²⁴ Transfusion independence was assessed in patients who were transfusion-dependent at baseline (received ≥ 1 transfusion within the previous 8 weeks), and required 56 or more consecutive days on-study without a transfusion. Duration of response was the time from first response until relapse, disease progression (modified IWG criteria), or death; event-free survival was time from first dose (phase 1b) or random assignment (phase 2) until date of relapse, disease progression, or death; and overall survival was defined as time from first dose (phase 1b) or random assignment (phase 2) until death. Statistical analysis Safety was assessed in all patients who received at least one dose of study drug. Activity analyses were done in patients who received study drug in the dose-escalation portion and in all randomly assigned patients in phase 2. Planned enrolment in the dose-escalation phase was six patients; three in each enasidenib dose group. In phase 2, assuming an overall response rate of 50% with combination enasidenib plus azacitidine and 30% with azacitidine only, enrolling 66 patients to the combination regimen and 33 to azacitidine only would provide 75% power to detect a 20% difference in overall response rate between the groups at a two-sided type 1 error rate of 0.02. Sample size calculations did not consider multiple comparisons. These outcomes are from a prespecified formal interim analysis performed at a data cutoff of Aug 20, 2019, when all patients had at least 1 year of follow-up from time of enrolment. We also did post-hoc analyses with a data cutoff of Aug 19, 2020, to assess updated survival and response durations with at least 2 years of follow-up for all patients. Rates of red blood cell and platelet transfusion independence lasting 56 days or longer were also assessed post hoc. Baseline demographics and disease characteristics are summarised using descriptive statistics. Activity outcomes are summarised descriptively for the single-arm, phase 1b, dose-escalation phase. In phase 2, overall response rate and complete remission rate with enasidenib plus azacitidine were compared versus azacitidine alone using odds ratios (ORs) and p values from χ^2 tests. Sponsor-derived rates of complete remission plus complete remission with partial haematological recovery were compared between groups using Fisher's exact test. Time-to-event endpoints, including duration of response, event-free survival, and overall survival, were estimated using Kaplan-Meier methods. Survival was compared between groups with hazard ratios (HRs) and 95% CIs from Cox proportional hazards regression models and p values from log-rank tests, but the trial was not prospectively powered to detect significant differences in overall survival or event-free survival between treatment groups. Exposure-adjusted incidence rates of adverse events per 100 patient-years of exposure were prospectively assessed for each treatment group in phase 2. We also did a post-hoc analysis to determine median overall survival for the patients in each treatment group who had complete remission. All statistical tests were two-sided at a significance level of 0.05. Clinical endpoint analyses were done using SAS (version 9.4), and correlative biomarker analyses were assessed using GraphPad Prism. This trial is registered with ClinicalTrials.gov, NCT02677922. Role of the funding source The sponsors of the study were involved in study design, data collection, data interpretation, and data analysis. The lead author prepared the initial draft with assistance from a medical communications agency, funded by the sponsor. Results Between June 3, 2016, and Aug 2, 2018, 322 patients with newly diagnosed acute myeloid leukaemia were

assessed for eligibility and 130 were enrolled, including 107 patients with mutant-IDH2 acute myeloid leukaemia (23 patients had mutant-IDH1 acute myeloid leukaemia and are described elsewhere²⁰). At data cutoff for the interim analysis, 24 patients (including two from phase 1) were still receiving their assigned treatment. Six patients received the enasidenib plus azacitidine combination in the phase 1b dose-finding portion, and 101 patients in phase 2 were randomly assigned to enasidenib plus azacitidine (n=68) or azacitidine only (n=33; figure 1). Of the six patients who were enrolled in the phase 1b dose-escalation portion of the trial, three received the enasidenib 100 mg dose and three received the 200 mg dose. Median age was 68 years (IQR 65–76); all six patients had intermediate-risk cytogenetics, and median bone marrow blast count was 73% (IQR 30–75; table 1). Two patients in the enasidenib 100 mg dosing cohort had discontinued, one due to disease progression and one to undergo HSCT, and two patients in the enasidenib 200 mg cohort had discontinued, one due to disease progression and one to transition to commercially available enasidenib. In this phase, two patients (one in each enasidenib dosing cohort) discontinued azacitidine due to toxicity (upper respiratory tract infection; prolonged neutropenia) and continued to receive enasidenib monotherapy. One patient in the 100 mg enasidenib dosing group received enasidenib monotherapy for 269 days, had a final response assessment of complete remission with platelet recovery, and then proceeded to HSCT. One patient in the 200 mg enasidenib dosing cohort received enasidenib monotherapy for 82 days and then discontinued from the study due to disease progression. Two patients in phase 1b remained on-study, with treatment durations of 37 months and 35 months at the interim data cutoff. The enasidenib plus azacitidine combination was generally well tolerated at both the enasidenib 100 mg and 200 mg doses, and the overall safety profile was consistent with that of each agent as monotherapy.^{11,14} All six patients had an adverse event considered by the treating investigator to be potentially related to enasidenib, azacitidine, or both while on study; events reported in more than one patient were nausea in four patients, and hyperbilirubinaemia, diarrhoea, fatigue, neutropenia, thrombocytopenia, and vomiting in two patients each. Treatment-related grade 3 or 4 adverse events reported in more than one patient were neutropenia, thrombocytopenia, and hyperbilirubinaemia (n=2 each). No dose-limiting toxicity was reported in either dosing cohort. The median treatment duration in phase 1b was 11 cycles (IQR 5–30). Four (67%) of six patients in the dose-escalation phase had an overall response, including three (50%) with complete remissions (one in the 100 mg cohort and two in the 200 mg cohort) and one with a complete remission with incomplete blood count (in the 100 mg cohort). In phase 1b, two (67%) of three patients in each dosing cohort had a complete remission or complete remission with partial haematological recovery. The enasidenib 100 mg dose, which in previous pharmacokinetic and pharmacodynamic analyses was shown to produce robust steady-state plasma concentrations, induce substantial 2-hydroxyglutarate inhibition, and was clinically effective,¹³ was chosen as the phase 2 recommended combination dose. Baseline demographic and disease characteristics of patients assigned to each treatment group in phase 2 are shown in table 1. At the primary data cutoff for the interim analysis, median follow-up was 14·9 months (IQR 8·7–20·0) in the enasidenib plus azacitidine group and 13·7 months (9·2–24·6) in the azacitidine-only group. At data cutoff, 47 (69%) of 68 patients in the combination group and 31 (97%) of 32 patients in the azacitidine-only group had discontinued treatment

(figure 1). 16 (24%) patients in the combination group and 19 (58%) patients in the azacitidine-only group received one or more acute myeloid leukaemia-directed therapy after discontinuation of the study regimen, including 11 (33%) of 33 patients in the azacitidine-only group who received commercially available enasidenib (appendix p 1). The primary endpoint of the phase 2 study portion was met: 50 (74% [95% CI 61–84]) patients in the enasidenib plus azacitidine combination and 12 (36% [20–55]) patients in the azacitidine monotherapy group had an overall response (OR 4.9 [95% CI 2.0–11.9]; $p=0.0003$; table 2). The complete remission rate was also significantly higher in the enasidenib plus azacitidine group compared with the azacitidine-only group (OR 8.7 [95% CI 2.7–27.3]; $p<0.0001$), as was the rate of complete remission plus complete remission with incomplete blood count or platelet recovery (43 [63%] of 68 vs ten [30%] of 33; OR 4.0 [1.6–9.6]; $p=0.0019$). In the combination group, overall response rates were similar for patients with an IDH2-Arg140 mutation (37 [73%] of 51) and patients with an IDH2-Arg172 mutation (12 [75%] of 16). The median time to response and the estimated median duration of response are shown in table 2. At the primary data cutoff, 12 (24%) of 50 responding patients in the combination group and seven (58%) of 12 responding patients in the azacitidine-only group had relapsed or progressed. 58% of patients in the combination group and 40% in the azacitidine-only group had sustained responses lasting at least 12 months. At the Aug 19, 2020, updated data cutoff (median follow-up 18.5 months [IQR 7.6–28.2] in the combination group and 14.3 months [6.7–25.7] in the azacitidine-only group), the estimated median duration of response had decreased to 13.9 months (95% CI 10.0–not reached) in the combination group and remained at 9.9 months (5.5–13.6) in the azacitidine-only group. The sponsor-derived proportion of patients with complete remission plus complete remission with partial haematological recovery was greater in the combination group than in the azacitidine-only group (OR 6.1 [95% CI 2.2–16.6]; $p=0.0002$). Median time to complete remission plus complete remission with partial haematological recovery was 4.6 months (IQR 2.3–6.7) in the combination group and 3.8 months (3.5–5.4) in the azacitidine-only group. Estimated median duration of complete remission plus complete remission with partial haematological recovery was not reached (95% CI 10.2–not reached) in the combination group and 14.6 months (3.7–not reached) in the azacitidine-only group. 48 (71%) of 68 patients in the combination group had haematological improvement in the erythroid, platelet, or neutrophil lineages, compared with 19 (58%) of 33 in the azacitidine-only group ($p=0.19$; appendix p 2). In post-hoc analyses, 27 (59%) of 46 patients in the combination group and seven (41%) of 17 patients in the azacitidine-only group who were red blood cell transfusion-dependent at baseline became red blood cell transfusion-independent for 56 days or longer on-study. Red blood cell transfusion independence was sustained for a median of 10.6 months (range 2.2–27.3) in the combination group and 7.6 months (range 4.3–24.5) in the azacitidine-only group. Additionally, eight (47%) of 17 platelet transfusion-dependent patients in the combination group and five (63%) of eight in the azacitidine-only group became platelet transfusion independent, with a median transfusion independence duration of 7.9 months (range 3.5–17.1) in the combination group and 4.7 months (1.9–9.5) in the azacitidine-only group. Estimated median event-free survival and overall survival are shown in figure 2. 1-year overall survival rates were 72% (95% CI 60–82) in the combination group versus 70% (50–83) in the azacitidine-only group. In post-hoc analysis, median overall

survival was not reached (95% CI 22.0 months to not reached) for the 37 patients in the combination group who had a morphological complete remission. In post-hoc analyses at a minimum of 2 years of follow-up for all patients (Aug 19, 2020, data cutoff), event-free survival remained similar to the original analysis; median overall survival was unchanged in the combination group, but decreased in the azacitidine-only group (appendix p 3). Median baseline 2-hydroxyglutarate concentration in all enrolled patients in the phase 2 part was 766.5 ng/mL (IQR 384.5–1731.0), and was similar between the groups (combination group 741.5 ng/mL [IQR 279.5–1900.0]; azacitidine-only group 780.0 ng/mL [520.8–1169.0]). On study, the median maximum 2-hydroxyglutarate reduction from baseline was significantly greater with the combination (–98% [IQR –100 to –88]) than with azacitidine-only (–54% [–82 to –25]; $p < 0.0001$; appendix p 4). Marked reductions from baseline 2-hydroxyglutarate concentrations were observed in the combination group in patients with a complete remission (median –100% [–100 to –91]), incomplete response (–98% [–100 to –93]), or no response (–93% [–100 to –82]; appendix p 5). At baseline, the median IDH2 variant allele frequency was 28.4% (IQR 20.9–36.3) in the combination group and 33.7% (25.0–38.0) in the azacitidine-only group ($p = 0.063$). During treatment, statistically significant reductions from baseline in IDH2 variant allele frequency were observed between cycle 3 and cycle 17 in the combination group and at cycle 11 in the azacitidine-only group. The median maximum IDH2 variant allele frequency reductions were 81.5% (IQR 27.7–99.0) in the combination group and 14.0% (2.0–46.0) in the azacitidine-only group ($p = 0.0005$; appendix p 6). Within the combination group, patients with complete or incomplete responses had significant reductions in IDH2 variant allele frequency compared with non-responders ($p = 0.0001$ and $p = 0.036$, respectively; appendix p 7). The most common gene mutations at study entry other than IDH2 were ASXL1 (54%), SRSF2 (49%), DNMT3A (46%), CEBPA (40%), and TET2 (40%; appendix p 8). No individual gene mutation was significantly associated with clinical response in either group (appendix p 9). The enasidenib plus azacitidine combination was generally well tolerated. Median treatment exposure at data cutoff was 12.1 months (IQR 3.7–16.7) with enasidenib and azacitidine and 6.2 months (3.2–10.6) with azacitidine only. In the combination group, 28 (41%) patients received more than 12 treatment cycles as did six (19%) patients in the azacitidine-only group. The most common adverse events in the combination group were gastrointestinal and haematological events, which were reported in a higher proportion of patients in the combination group than in the azacitidine-only group. 62 (91%) of 68 in the combination group and 26 (81%) of 32 in the azacitidine-only group had a treatment-related adverse event. The most common treatment-related events were nausea, neutropenia, Enasidenib plus azacitidine ($n = 68$) Azacitidine only ($n = 33$) p value

Event	Enasidenib plus azacitidine ($n = 68$)	Azacitidine only ($n = 33$)	p value
Overall response	50 (74%; 95% CI 61–84)	12 (36%; 95% CI 20–55)	0.0003
Complete remission	37 (54%; 95% CI 42–67)	4 (12%; 95% CI 3–28)	<0.0001
Complete remission or complete remission with partial haematological recovery	39 (57%)	6 (18%)	0.0002
Complete remission with incomplete blood count or platelet recovery	6 (9%)	6 (18%)	0.0002
Partial remission	4 (6%)	2 (6%)	0.0002
Morphological leukaemia-free state	3 (4%)	0	0.0002
Stable disease	13 (19%)	16 (48%)	0.0002
Disease progression	1 (1%)	1 (3%)	0.0002
Not evaluable or missing data	4 (6%)	4 (12%)	0.0002
Time to first response, months	1.9 (1.1–3.9)	3.6 (1.9–4.4)	0.0002
Time to complete remission, months	5.4 (3.8–7.6)	4.4 (3.8–5.6)	0.0002
Duration of response, months	24.1 (95% CI 10.0–NR)	9.9 (95% CI 5.5–13.6)	0.0002
Duration of complete remission, months	NR (95% CI 7.7–NR)	12.7 (95% CI 11.7–NR)	0.0002

Data are n (%; 95% CI), n (%), median (IQR), or median (95% CI).

Data cutoff Aug 20, 2019. NR=not reached. *Overall response defined as proportion of patients with complete remission, complete remission with incomplete blood count or platelet recovery, partial remission, or morphological leukaemia-free state. Table 2: Haematological responses in the randomised phase 2 study portion thrombocytopenia, vomiting, and anaemia (table 3). Exposure-adjusted incidence rates of common adverse events are shown in the appendix (p 10). All patients in the combination group, and all but one patient in the azacitidine-only group, had a grade 3 or 4 adverse event. Cytopenias were the most common grade 3 or 4 events, including thrombocytopenia, anaemia, neutropenia, and febrile neutropenia, which were reported in more than 25% of patients in each group (appendix p 11). When adjusted for treatment exposure, incidence of thrombocytopenia, hypokalaemia, hyperbilirubinaemia, and differentiation syndrome remained higher in the combination group than in the azacitidine-only group (appendix p 11). In the combination group, the most common treatment-related grade 3 or 4 events were thrombocytopenia (25 [37%] of 68 vs six [19%] of 32 in the azacitidine-only group) and neutropenia (25 [37%] vs eight [25%]; table 3). When adjusted for duration of treatment exposure, incidence of treatment-related grade 3 or 4 neutropenia was 58 events per 100 patient-years in the combination group and 61 events per 100 patient-years in the azacitidine-only group. The incidence of treatment-related grade 3 or 4 thrombocytopenia was 57 events per 100 person-years in the combination group and 35 events per 100 patient-years in the azacitidine-only group. Serious treatment-related adverse events were reported in 29 (43%) patients in the combination group and 14 (44%) patients in the azacitidine-only group; serious treatment-related adverse events occurring in more than 5% of patients in either group were febrile neutropenia (in nine [13%] patients in the combination group and five [16%] in the azacitidine-only group), differentiation syndrome (in seven [10%] and none), and pneumonia (in three [4%] and two [6%]). Adverse events led to interruption of enasidenib, azacitidine, or both in 28 (41%) of 68 patients in the combination group, and azacitidine was interrupted in nine (28%) of 32 patients in the azacitidine-only group. Events requiring interruption in more than two patients in either group were neutropenia (in 12 [18%] patients in the combination group and four [13%] in the azacitidine-only group), thrombocytopenia (three [4%] and one [3%]), pyrexia (three [4%] and none), and differentiation syndrome (three [4%] and none). In the combination group, five (7%) patients required enasidenib dose reductions due to hyperbilirubinaemia (n=2), corrected QT interval prolongation (n=1), neutropenia (n=1), and syncope (n=1); and 14 (21%) patients had azacitidine dosage reduced due to neutropenia and thrombocytopenia (n=6 each), acute kidney injury (n=1), corrected QT interval prolongation (n=1), leukopenia (n=1), nausea (n=1), and pyrexia (n=1; some patients might have had more than one adverse event leading to dose reduction). Five (7%) patients discontinued combination therapy because of adverse events, including bronchioalveolar carcinoma, bone marrow failure, fatigue, febrile neutropenia, and sepsis (n=1 each); the fatigue and bone marrow failure events were suspected to be related to treatment. In the combination group, adverse events led to discontinuation of enasidenib only for three (4%) patients (pleural effusion, diarrhoea, and differentiation syndrome [n=1 each]) and to discontinuation of azacitidine for three (4%) patients (pneumonia, injection site rash, and fatigue [n=1 each]), and patients continued to receive the other agent as monotherapy on-study. 29 (43%) patients in the combination group had died at data cutoff (Aug 20,

2019): 15 (22%) during treatment, and 14 (21%) during survival follow-up (>28 days after last study drug dose). On-treatment deaths were related to underlying disease progression for four (6%) patients in the combination group. Three (4%) patients in the combination group had clinical responses of partial remission, morphological leukaemia-free state or complete remission at last assessment before death; causes of death for these patients were pneumonitis, bronchopneumonia, and pneumonia plus stroke, respectively. Adverse events leading to death in the combination group were respiratory failure and sepsis in two (3%) patients each, and lung infection, pneumonia, fungal pneumonia, urosepsis, pleural effusion, pneumonitis, febrile neutropenia, leukocytosis, and cardiac arrest in one (1%) patient each. In the azacitidine-only group, 14 (44%) patients died, two (6%) during treatment (both related to disease progression) and 12 (38%) while in survival follow-up. No grade 5 adverse event in either group was considered by investigators to be related to either study drug. At 60 days, five (7%) patients in the combination group and one (3%) patient in the azacitidine-only group had died. 14 differentiation syndrome events were reported in 12 (18%) patients in the combination group, with median time to onset of 28.5 days (IQR 17.0–34.5). Median baseline blast count for these patients was 65% (IQR 44–79), and eight (67%) of 12 patients had a haematological response (complete remission, n=7; partial remission, n=1). All 12 patients received corticosteroids for differentiation syndrome (median duration 7.5 days [range 2.0–32.0]), four (6%) patients underwent leukapheresis, and seven (10%) patients had enasidenib interrupted (n=6) or discontinued (n=1). All 14 events resolved by a median of 11.5 days (IQR 7.0–19.0). Six (9%) patients had leukocytosis concurrent with differentiation syndrome; these patients had higher baseline blast counts than those without leukocytosis (median 75% [IQR 67–80] vs 49% [40–55]) and more patients with leukocytosis had a complete remission than those without (five [83%] of six vs two [33%] of six). Hyperbilirubinaemia occurred in 25 (37%) patients receiving enasidenib plus azacitidine. Median time to onset was 15 days (range 3–274). Two (3%) patients had enasidenib dose reductions for bilirubinaemia and enasidenib was interrupted for six (9%) patients. Events resolved for 19 (76%) of 25 patients at a median of 19 days (range 1–40).

Discussion Combination therapy with enasidenib plus azacitidine was safe, generally well tolerated, and had antileukaemic activity in these older patients with mutant-IDH2 acute myeloid leukaemia who were ineligible for intensive chemotherapy. The overall response rate and complete remission rate in the combination group were more than two times greater than in the azacitidine-only group, and more than double the rates with enasidenib mono-therapy in patients with newly diagnosed acute myeloid leukaemia (12 [31%] of 39 had an overall response and seven [18%] of 39 had complete remission¹¹), suggesting a greater-than-additive effect when combining these drugs. Responses to the combination regimen were durable (around 14 months). Despite greater response rates, no significant difference in event-free survival or overall survival was observed between treatment groups. The study was not prospectively powered to detect significant differences between treatment groups in survival outcomes, and further study in a larger patient sample is required to provide more definitive overall survival and event-free survival results. Of substantial interest, the median event-free survival (11.9 months) and overall survival (22.3 months) in the azacitidine-only group were markedly higher than in previous reports of azacitidine in newly diagnosed acute myeloid leukaemia;^{14,25}

for example, in the phase 3 VIALE-A study of venetoclax plus azacitidine versus azacitidine plus placebo in patients with untreated acute myeloid leukaemia with an IDH mutation, median overall survival with azacitidine plus placebo was only 6·2 months (95% CI 2·3–12·7).²⁶ Survival outcomes with enasidenib plus azacitidine were also substantially improved compared with previous findings with enasidenib monotherapy in newly diagnosed acute myeloid leukaemia (median event-free survival 5·7 months [95% CI 2·8–16·0], median overall survival 11·3 months [5·7–15·1]).¹¹ Survival outcomes in this trial might have been confounded by the use of subsequent acute myeloid leukaemia-directed therapies in more than half of all patients randomly assigned to azacitidine-only, including a third of patients who received subsequent enasidenib during survival follow-up. Sensitivity analyses have been used in other acute myeloid leukaemia trials, censoring patients at the time they receive subsequent therapy, to understand the confounding influence of subsequent therapy on overall survival findings for a drug under study.¹⁴ In this trial, patient sample sizes (especially considering the 2:1 randomisation scheme) were too small to provide meaningful data from a subsequent therapy sensitivity analysis. The safety profile of the enasidenib plus azacitidine combination was similar to that of each drug used as monotherapy.^{11,13,14} No dose-limiting toxicity was observed in the dose-finding phase, and the enasidenib 100 mg dose was chosen for further assessment in the randomised phase 2 portion on the basis of the clinical activity shown at this dose in a previous trial.^{11–13} As expected, haematological and gastrointestinal events were the most common adverse events in each treatment group. These events were more frequent with the combination regimen than with azacitidine-only, but when adjusting for the two times longer median exposure to enasidenib plus azacitidine, the incidence of cytopenias and most other adverse events were similar between treatment groups. Adverse events were generally manageable with appropriate intervention, including treatment interruptions, and rarely required treatment discontinuation. The differentiation syndrome rate (18%) with enasidenib plus azacitidine was consistent with the rate with enasidenib as monotherapy in patients with relapsed or refractory acute myeloid leukaemia (12–19%).^{22,27} Patients with leukocytosis concurrent with differentiation syndrome had higher baseline blast counts and seemed to be more likely to have a complete remission than those who did not. Patients should be monitored closely for infections and differentiation syndrome, especially during early treatment cycles, with prompt corticosteroid intervention in patients showing signs or symptoms of differentiation syndrome. Combination enasidenib plus azacitidine was associated with early, robust on-target inhibition of both 2-hydroxyglutarate and IDH2 variant allele frequency. In the combination group, significant correlations were observed between maximum on-treatment reductions in IDH2 variant allele frequency (but not 2-hydroxyglutarate) and a clinical response. Although 2-hydroxyglutarate reductions have been observed in responding patients treated with other acute myeloid leukaemia therapies, probably owing to mutant-IDH2 leukaemic cell death,²⁸ significantly greater 2-hydroxyglutarate reductions with enasidenib plus azacitidine versus azacitidine-only—regardless of response—suggest that direct on-target activity of enasidenib for reducing 2-hydroxyglutarate is not predicated on response. Findings for patients with relapsed or refractory acute myeloid leukaemia in the pivotal trial of enasidenib monotherapy²⁹ showed robust 2-hydroxyglutarate suppression by enasidenib is

necessary, but not sufficient, for clinical response. In that trial, mutations in NRAS and other MAPK pathway effectors were inversely correlated with clinical response;²⁹ in this study, patients with RAS pathway mutations had responses with enasidenib plus azacitidine. Combination venetoclax plus azacitidine seems to have antileukaemic activity in patients with newly diagnosed, mutant-IDH acute myeloid leukaemia. In a subgroup of patients with IDH mutations receiving combination venetoclax plus azacitidine in the phase 3 VIALE-A trial (n=61), the rate of complete remission plus complete remission with partial haematological recovery was 75% in patients aged 75 years or older with newly diagnosed acute myeloid leukaemia who were ineligible for intensive chemotherapy.¹⁸ It is unknown whether combining or sequential treatment with enasidenib, venetoclax, and azacitidine might further improve patient outcomes.

Contributors The sponsors collected and analysed data in conjunction with all authors. CDD wrote the first draft of the manuscript. The data were reviewed and verified by CDD, MGF, PM-R, FL, JG, and MH. All authors revised the manuscript and reviewed and approved the final version. All authors had access to all study data. All authors had final responsibility for the decision to submit the manuscript for publication. Trial oversight was provided by an independent data monitoring committee.

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