SUPPLEMENTAL APPENDIX

Ivosidenib or enasidenib combined with intensive chemotherapy in patients with newly diagnosed AML: a phase 1 study

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Contents

Additional treatment regimen details

After 1 cycle of induction therapy, patients could undergo a second cycle of induction according to institutional practice (ie, repeated treatment with 7+3, with 7+3 at attenuated doses, with 5+2, or with a cytarabine-only regimen). Patients who achieved at least a partial remission at the end of induction therapy (1 or 2 cycles) could then receive consolidation therapy with up to 4 cycles of intermediate- or high-dose cytarabine, or with 1 cycle of mitoxantrone/etoposide, while continuing to receive ivosidenib or enasidenib treatment. Alternatively, patients who completed induction therapy and had stable disease or better could continue receiving single-agent ivosidenib or enasidenib without receiving consolidation chemotherapy, at the investigator's discretion and with sponsor approval. Patients who remained in remission at the end of consolidation therapy could receive maintenance treatment with ivosidenib or enasidenib monotherapy daily until relapse, development of an unacceptable toxicity, or allogeneic

hematopoietic stem cell transplantation (HSCT). Patients appropriate for HSCT could proceed to HSCT at any point; resumption of mutant IDH (mIDH) inhibitor therapy was not allowed after HSCT.

Response assessment

Secondary objectives included assessment by the investigators of the clinical activity of ivosidenib and enasidenib in combination with acute myeloid leukemia (AML) induction and consolidation therapy, using the modified 2003 International Working Group response criteria for AML. Clinical activity measures included rates of complete remission (CR), CR with incomplete neutrophil recovery (CRi), CR with incomplete platelet recovery (CRp), partial remission, and morphologic leukemia-free state (MLFS). Response at the end of the induction phase was assessed, as well as the best overall response at any time during the induction, consolidation, and maintenance phases of the study. The end of the induction period was variable because it did not occur on a predetermined study day but rather was determined by the investigator on the basis of the day when the patient discontinued study treatment or moved to the next phase of the study (ie, consolidation or maintenance). The “treatment failures” category comprised patients who discontinued treatment without a response assessment on or after induction day 21 or who discontinued treatment with a best response of “not evaluable,” along with patients whose best overall response was stable disease or disease progression.

In order to assess overall survival, patients continued to be followed for survival after discontinuing study treatment. However, the duration of response could not be accurately estimated because patients who discontinued treatment were not followed for response after discontinuation.

Pharmacokinetics and pharmacodynamics

Pharmacokinetic (PK) and pharmacodynamic (PD) profiles of ivosidenib and enasidenib were evaluated during the induction, consolidation, and maintenance phases. Blood samples for PK/PD analyses of ivosidenib and enasidenib were collected on days 1 and 14 of the first cycle of induction therapy (or on days 8 and 21 in patients who started enasidenib on day 8 of the first induction cycle), and on day 1 of the first cycle of consolidation therapy. In addition, for patients who underwent maintenance therapy, predose PK/PD samples were collected on the first day of maintenance therapy and every 3 months thereafter. Plasma levels of ivosidenib, enasidenib, and the major metabolite of enasidenib (AGI-16903) were measured using validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) methods. In addition, 2-HG concentrations were measured in plasma using a qualified LC-MS/MS method. PK/PD relationships for ivosidenib and enasidenib with 2-HG in plasma were assessed using a validated version of Phoenix® WinNonlin® 7.0 (Certara, Princeton, NJ).

Sample collection for exploratory biomarker analysis

Baseline bone marrow aspirates and peripheral blood were collected in EDTA tubes for the confirmation of *IDH1/2* mutations and analysis of baseline co-occurring mutations. For exploratory studies, peripheral blood samples and bone marrow aspirates were collected in BD Vacutainer® CPT™ (Becton, Dickinson and Company, Franklin Lakes, NJ) sodium heparin tubes at baseline and at specified on-study time points. Bone marrow mononuclear cells (BMMCs) and peripheral blood mononuclear cells (PBMCs) were isolated from the buffy coat and viably frozen.

Co-occurring mutation analysis by targeted next-generation sequencing

DNA was extracted from baseline bone marrow aspirates and/or peripheral blood samples and retrospectively analyzed for the confirmation of *IDH* mutations, as well as for analysis of the presence of co-occurring mutations, by next-generation sequencing using the 95-gene Rapid Heme Panel, which has a detection sensitivity of 5%.[1] BMMC and/or PBMC samples at baseline and at specified on-study time points were analyzed for mutation evolution using the Personalis ACE Cancer Panel (Menlo Park, CA)[2] for ivosidenib-treated patients, and the Archer VariantPlex Core Myeloid Panel (Boulder, CO) for enasidenib-treated patients. In order to harmonize the data for the ivosidenib- and enasidenib-treated patients, the analyses were limited to the 33 genes represented on both platforms (see supplemental Table 9), and a 2% limit of detection for variant allele frequency (VAF) was applied to both datasets. The known or likely oncogenic effect of each detected variant was curated by Agios using a number of public resources: COSMIC (http://cancer.sanger.ac.uk/cosmic), varsome (https://varsome.com), gnomAD (http://gnomad.broadinstitute.org), CIViC (https://civic.genome.wustl.edu/home), oncoKB (http://oncokb.org), cBioPortal (http://www.cbioportal.org), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar), and PubMed (https://www.ncbi.nlm.nih.gov/pubmed). Heatmaps of co-occurring known or likely oncogenic mutations were produced in R version 3.6.0.

***IDH1/2* mutation assessment by digital PCR**

The OncoBEAM™ BEAMing digital polymerase chain reaction (dPCR) assay (Sysmex Inostics Inc., Hamburg, Germany)[3] was selected as a highly sensitive method of monitoring m*IDH1/2* VAF in BMMCs or PBMCs longitudinally. This method has a lower limit of detection for *IDH1/2* mutant alleles of 0.02%-0.04%. Clearance of m*IDH1* or m*IDH2* was defined as a reduction in m*IDH1* or m*IDH2* VAF to a level below the limit of detection for ≥1 on-treatment time point on or after day 21 of induction therapy in patients who had detectable m*IDH1* or m*IDH2* at baseline.

For m*IDH1* VAF assessment, only mutations at position R132 (C/G/L/S/H) were analyzed. For *IDH2*, only mutations at position R140 (Q/L/W) and R172 (K/G) were analyzed.

MRD by multiparameter flow cytometry

Studies have shown that measurable residual disease (MRD) negativity at the time of remission is highly prognostic for clinical outcome. Recognizing this, the 2017 European LeukemiaNet guidelines recommend adding MRD status to the CR response category.[4] Centralized MRD testing by multiparameter flow cytometry was performed by the Department of Pathology at Memorial Sloan Kettering Cancer Center using BMMCs viably frozen at baseline and on-study fresh bone marrow aspirate samples from a subset of patients enrolled in the United States. An abnormal blast population was identified as MRD positive by assessment of antigen expression that was “different from normal,” as described previously.[5,6]

Statistical analysis

Analyses of time to hematologic recovery were conducted for the induction phase of the study. Recovery of the absolute neutrophil count (ANC) was defined as a count >500/μL and platelet count recovery was defined as a count >50 000/μL. The analyses of time to count recovery included only patients who had achieved a response of CR, CRi, CRp, or MLFS during induction cycle 1 on or after day 21. Patients who started treatment in induction cycle 2 or consolidation cycle 1 without meeting the count recovery criteria were censored at the time of the last available complete blood count prior to the first dose of induction cycle 2 or consolidation cycle 1, respectively. Patients with a response of MLFS were included in the analysis because they may have experienced ANC and/or platelet count recovery after this response assessment in the induction phase but prior to starting consolidation therapy. The count recovery analyses were conducted using Kaplan-Meier methods.

The percentage of patients with mutation clearance determined by VAF and MRD-negative status were summarized by the best response category.

Sensitivity analyses of overall survival estimates were also conducted by censoring patients undergoing HSCT at the date of either HSCT or the last dose of ivosidenib or enasidenib plus 28 days, if the date of HSCT was not available. These sensitivity analyses were conducted to evaluate the potential impact of HSCT on overall survival.

Event-free survival findings and limitations

Median event-free survival (EFS) was 8.4 months (95% CI, 3.71-not calculated) and 5.9 months (95% CI, 2.14-10.39) for ivosidenib-treated and enasidenib-treated patients, respectively. In the ivosidenib cohorts, the EFS rate at 12 months was 33% and in the enasidenib cohorts, the EFS rate at 12 months was 27%. For the EFS analysis, patients who did not achieve a CR, CRi, CRp, or PR by the end of the induction period were considered to have had an event on Day 1, and patients who did not have an event were censored at their last assessment date. A large number of patients were censored when they discontinued treatment to proceed to HSCT. Therefore, interpretation of the EFS results is difficult because of the low number of patients included in the analysis at the 12-month time point.

References

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Supplemental Table 1. Genes represented in both the Personalis ACE and ArcherDx Core Myeloid panels (n = 33)

ABL1	*GATA1*	*PTPN11*
ASXL1	*GATA2*	*RUNX1*
BCOR	*IDH1*	*SETBP1*
BRAF	*IDH2*	*SF3B1*
CBL	*JAK2*	*SRSF2*
CEBPA	*KIT*	*STAG2*
CSF3R	*KRAS*	*TET2*
DNMT3A	*MPL*	*TP53*
ETV6	*NPM1*	*U2AF1*
EZH2	*NRAS*	*WT1*
FLT3	*PHF6*	*ZRSR2*

Supplemental Table 2. Nonhematologic TEAEs of any grade reported in >10% of patients in any treatment group during the induction and consolidation periods, regardless of attribution

TEAE, n (%)	Induction period		Consolidation period	
	Ivosidenib 500 mg + chemotherapy, n = 60	Enasidenib 100 mg + chemotherapy, n = 93	Ivosidenib 500 mg + chemotherapy, n = 35	Enasidenib 100 mg + chemotherapy, n = 46
Diarrhea	43 (71.7)	55 (59.1)	7 (20.0)	17 (37.0)
Nausea	33 (55.0)	50 (53.8)	11 (31.4)	15 (32.6)
Rash*	33 (55.0)	51 (54.8)	12 (34.3)	13 (28.3)
Decreased appetite	32 (53.3)	31 (33.3)	4 (11.4)	11 (23.9)
Vomiting	21 (35.0)	31 (33.3)	9 (25.7)	10 (21.7)
Stomatitis	20 (33.3)	23 (24.7)	4 (11.4)	9 (19.6)
Fatigue	19 (31.7)	24 (25.8)	5 (14.3)	9 (19.6)
Hypokalemia	17 (28.3)	29 (31.2)	3 (8.6)	11 (23.9)
Pyrexia	16 (26.7)	31 (33.3)	8 (22.9)	13 (28.3)
Constipation	14 (23.3)	25 (26.9)	6 (17.1)	13 (28.3)
Hypophosphatemia	14 (23.3)	20 (21.5)	0	7 (15.2)
Edema peripheral	14 (23.3)	37 (39.8)	2 (5.7)	13(28.3)
Abdominal pain	13 (21.7)	19 (20.4)	4 (11.4)	8 (17.4)

TEAE, n (%)	Induction period		Consolidation period	
	Ivosidenib 500 mg + chemotherapy, n = 60	**Enasidenib 100 mg + chemotherapy, n = 93**	**Ivosidenib 500 mg + chemotherapy, n = 35**	**Enasidenib 100 mg + chemotherapy, n = 46**
Aspartate aminotransferase increased	13 (21.7)	18 (19.4)	1 (2.9)	6 (13.0)
Electrocardiogram QT prolonged†	16 (26.7)	11 (11.8)	3 (8.6)	7 (15.2)
Alanine aminotransferase increased	11 (18.3)	22 (23.7)	2 (5.7)	6 (13.0)
Cough	11 (18.3)	22 (23.7)	3 (8.6)	9 (19.6)
Dysgeusia	11 (18.3)	14 (15.1)	0	3 (6.5)
Chills	10 (16.7)	8 (8.6)	3 (8.6)	3 (6.5)
Colitis	10 (16.7)	9 (9.7)	0	3 (6.5)
Headache	10 (16.7)	29 (31.2)	6 (17.1)	8 (17.4)
Hypoalbuminemia	10 (16.7)	21 (22.6)	1 (2.9)	3 (6.5)
Pruritus	10 (16.7)	9 (9.7)	3 (8.6)	5 (10.9)
Blood alkaline phosphatase increased	9 (15.0)	15 (16.1)	2 (5.7)	4 (8.7)
Dizziness	9 (15.0)	13 (14.0)	2 (5.7)	7 (15.2)
Epistaxis	9 (15.0)	17 (18.3)	4 (11.4)	8 (17.4)
Blood bilirubin increased‡	11 (18.3)	46 (49.5)	2 (5.7)	13 (28.3)
Hypocalcemia	9 (15.0)	24 (25.8)	2 (5.7)	6 (13.0)

TEAE, n (%)	Induction period		Consolidation period	
	Ivosidenib 500 mg + chemotherapy, n = 60	Enasidenib 100 mg + chemotherapy, n = 93	Ivosidenib 500 mg + chemotherapy, n = 35	Enasidenib 100 mg + chemotherapy, n = 46
Hypotension	9 (15.0)	14 (15.1)	4 (11.4)	14 (15.1)
Insomnia	9 (15.0)	10 (10.8)	0	4 (8.7)
Noncardiac chest pain	9 (15.0)	7 (7.5)	2 (5.7)	1 (2.2)
Back pain	8 (13.3)	14 (15.1)	3 (8.6)	8 (17.4)
Clostridia infections§	8 (13.3)	17 (18.3)	2 (5.7)	5 (10.9)
Hypertension	8 (13.3)	15 (16.1)	4 (11.4)	6 (13.0)
Hypomagnesemia	8 (13.3)	12 (12.9)	3 (8.6)	9 (19.6)
Nasal congestion	8 (13.3)	10 (10.8)	4 (11.4)	2 (4.3)
Hyperglycemia	7 (11.7)	11 (11.8)	0	6 (13.0)
Hyponatremia	7 (11.7)	15 (16.1)	1 (2.9)	3 (6.5)
Hypoxia	7 (11.7)	5 (5.4)	0	2 (4.3)
Oropharyngeal pain	7 (11.7)	8 (8.6)	0	2 (4.3)
Abdominal distension	6 (10.0)	7 (7.5)	0	5 (10.9)
Dyspnea	6 (10.0)	16 (17.2)	5 (14.3)	7 (15.2)
Petechiae	6 (10.0)	13 (14.0)	4 (11.4)	2 (4.3)

TEAE, n (%)	Induction period		Consolidation period	
	Ivosidenib 500 mg + chemotherapy, n = 60	**Enasidenib 100 mg + chemotherapy, n = 93**	**Ivosidenib 500 mg + chemotherapy, n = 35**	**Enasidenib 100 mg + chemotherapy, n = 46**
Pain in extremity	6 (10.0)	7 (7.5)	2 (5.7)	5 (10.9)
Pleural effusion	5 (8.3)	15 (16.1)	0	2 (4.3)
Fluid overload	4 (6.7)	11 (11.8)	1 (2.9)	5 (10.9)
Blood creatinine increased	3 (5.0)	5 (5.4)	1 (2.9)	6 (13.0)
Gastroesophageal reflux disease	3 (5.0)	12 (12.9)	1 (2.9)	3 (6.5)
Sepsis	3 (5.0)	4 (4.3)	4 (11.4)	7 (15.2)
Hemorrhoids	1 (1.7)	10 (10.8)	0	1 (2.2)
Pneumonia	1 (1.7)	8 (8.6)	3 (8.6)	5 (10.9)
Hyperuricemia	0	8 (8.6)	5 (14.3)	5 (10.9)
Toothache	0	2 (2.2)	4 (11.4)	1 (2.2)

TEAE, treatment-emergent adverse event.

*Rash includes preferred terms rash, rash maculo-papular, rash pruritic, rash erythematous, rash macular, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, exfoliative rash, skin ulcer, drug eruption, and urticaria.

†Electrocardiogram QT prolonged includes ventricular tachycardia, ventricular arrhythmia, cardiac arrest, cardiorespiratory arrest, electrocardiogram QT prolonged, multiple organ dysfunction syndrome, and syncope.

‡Blood bilirubin increased includes preferred terms of increased blood bilirubin and hyperbilirubinemia.

§Clostridia infections includes preferred terms Clostridium difficile colitis, Clostridium difficile infection, and clostridial infection.

Supplemental Table 3. Nonhematologic TEAEs of grade ≥3 reported in ≥10% of patients in any group during the induction and consolidation periods, regardless of attribution

TEAE, n (%)	Induction period		Consolidation period	
	Ivosidenib 500 mg + chemotherapy, n = 60	Enasidenib 100 mg + chemotherapy, n = 93	Ivosidenib 500 mg + chemotherapy, n = 35	Enasidenib 100 mg + chemotherapy, n = 46
Any grade ≥3 TEAE	58 (96.7)	87 (93.5)	34 (97.1)	41 (89.1)
Hypophosphatemia	10 (16.7)	12 (12.9)	0	4 (8.7)
Colitis	8 (13.3)	3 (3.2)	0	0
Clostridia infections*	6 (10.0)	7 (7.5)	1 (2.9)	4 (8.7)
Electrocardiogram QT prolonged†	6 (10.0)	7 (7.5)	1 (2.9)	3 (6.5)
Hypokalemia	7 (11.7)	9 (9.7)	1 (2.9)	4 (8.7)
Hypertension	6 (10.0)	6 (6.5)	0	4 (8.7)
Blood bilirubin increased‡	4 (6.7)	15 (16.1)	1 (2.9)	5 (10.9)
Sepsis	3 (5.0)	4 (4.3)	4 (11.4)	7 (15.2)
Rash§	3 (5.0)	13 (14.0)	1 (2.9)	1 (2.2)

TEAE, treatment-emergent adverse event.

*Clostridia infections includes preferred terms Clostridium difficile colitis, Clostridium difficile infection and clostridial infection.

†Electrocardiogram QT prolonged includes ventricular tachycardia, ventricular arrhythmia, cardiac arrest, cardiorespiratory arrest, electrocardiogram QT prolonged, multiple organ dysfunction syndrome, and syncope.

‡Blood bilirubin increased includes preferred terms of increased blood bilirubin and hyperbilirubinemia.

§Rash includes preferred terms rash, rash maculo-papular, rash pruritic, rash erythematous, rash macular, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, exfoliative rash, skin ulcer, drug eruption, and urticaria.

Supplemental Table 4. Hematological recovery* from induction therapy in the ivosidenib and enasidenib cohorts

	Ivosidenib + chemotherapy		Enasidenib + chemotherapy	
	n	Median (95% CI) days	n	Median (95% CI) days
Time to ANC recovery >500/μL				
Overall cohort	41	28 (28-30)	60	34 (30-36)
De novo AML	32	28 (27-30)	36	33 (29-36)
Secondary AML	9	29 (22-45)	24	35 (30-44)
Time to platelet recovery >50 000/μL				
Overall cohort	41	28 (27-32)	60	29 (28-31)
De novo AML	32	28 (26-31)	36	29 (28-29)
Secondary AML	9	34 (22-41)	24	34 (29-50)

AML, acute myeloid leukemia; ANC, absolute neutrophil count; CI, confidence interval.

*The time to count recovery analysis included only patients who had achieved a response of complete remission, complete remission with incomplete neutrophil or platelet recovery, or morphologic leukemia-free state.

CRi, CRp, or MLFS during induction cycle 1 on or after day 21. Patients who received additional chemotherapy, either as induction cycle 2 or consolidation cycle 1, without meeting the count recovery criteria were censored at the last available laboratory assessment prior to the first dose of induction cycle 2 or consolidation cycle 1, respectively.

Supplemental Table 5. Hematological recovery from induction therapy in patients who started enasidenib on day 1 vs day 8

	Enasidenib day 1 + chemotherapy		Enasidenib day 8 + chemotherapy	
	n	Median (95% CI) days	n	Median (95% CI) days
Time to ANC recovery >500/μL				
Overall cohort	46	34 (31-36)	14	31 (28-40)
De novo AML	23	34 (29-36)	13	29 (28-37)
Secondary AML	23	35 (30-40)	1	77 (NC to NC)
Time to platelet recovery >50 000/μL				
Overall cohort	46	30 (29-34)	14	28.5 (28-35)
De novo AML	23	29 (28-30)	13	28 (28-29)
Secondary AML	23	33 (29-50)	1	58 (NC to NC)

AML, acute myeloid leukemia; ANC, absolute neutrophil count; NC, not calculable.

Supplemental Table 6. Best overall responses at any time during the study by disease type

	Ivosidenib 500 mg + chemotherapy n (%)			Enasidenib 100 mg + chemotherapy n (%)		
	De novo without MDS-related cytogenetic abnormalities, n = 36	De novo with MDS-related cytogenetic abnormalities, n = 6	sAML, n = 18	De novo without MDS-related cytogenetic abnormalities, n = 46	De novo with MDS-related cytogenetic abnormalities, n = 10	sAML, n = 35
CR/CRi/CRp	32 (89)	5 (83)	9 (50)	40 (87)	5 (50)	22 (63)
CR	27 (75)	5 (83)	9 (50)	34 (74)	2 (20)	14 (40)
CRi/CRp	5 (14)	0	0	6 (13)	3 (30)	8 (23)
MLFS	3 (8)	0	1 (6)	3 (7)	2 (20)	5 (14)
PR	0	0	2 (11)	1 (2)	0	1 (3)
Treatment failure	1 (3)	1 (17)	6 (33)	2 (4)	3 (30)	7 (20)

CR, complete remission; CRi, CR with incomplete neutrophil recovery; CRp, CR with incomplete platelet recovery; MDS, myelodysplastic syndrome; MLFS, morphologic leukemia-free state; PR, partial response; sAML, secondary acute myeloid leukemia.

Treatment failure = stable disease + progressive disease + discontinuation before response assessment on or after induction day 21 + discontinuation with best response of not evaluable.

Supplemental Table 7. Best overall responses at any time during the study in patients with sAML by prior HMA therapy

	Ivosidenib 500 mg + chemotherapy, n (%)		Enasidenib 100 mg + chemotherapy, n (%)	
	sAML without prior HMA, n = 14	sAML with prior HMA, n = 4	sAML without prior HMA, n = 18	sAML with prior HMA, n = 17
CR/CRi/CRp	8 (57)	1 (25)	12 (67)	10 (59)
CR	8 (57)	1 (25)	8 (44)	6 (35)
CRi/CRp	0	0	4 (22)	4 (24)
MLFS	0	1 (25)	3 (17)	2 (12)
PR	1 (7)	1 (25)	0	1 (6)
Treatment failure	5 (36)	1 (25)	3 (17)	4 (24)

CR, complete remission; CRi, CR with incomplete neutrophil recovery; CRp, CR with incomplete platelet recovery; HMA, hypomethylating agent; MLFS, morphologic leukemia-free state; PR, partial response; sAML, secondary acute myeloid leukemia.

Treatment failure = stable disease + progressive disease + discontinuation before response assessment on or after induction day 21 + discontinuation with best response of not evaluable.

Supplemental Table 8. Best overall responses at any time during the study in the enasidenib cohort by IDH2 mutation

	Enasidenib 100 mg + chemotherapy, n (%)	
	R140, n = 64	**R172, n = 25**
CR/CRi/CRp	46 (72)	19 (76)
CR	31 (48)	18 (72)
CRi/CRp	15 (23)	1 (4)
MLFS	10 (16)	0
PR	1 (2)	1 (4)
Treatment failure	7 (11)	5 (20)

CR, complete remission; CRi, CR with incomplete neutrophil recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; PR, partial response.

Treatment failure = stable disease + progressive disease + discontinuation before response assessment on or after induction day 21 + discontinuation with best response of not evaluable.

Supplemental Table 9. Summary of pharmacokinetic/pharmacodynamic parameters after multiple oral administration of ivosidenib at induction cycle 1 day 14 or enasidenib at induction cycle 1 day 14 or cycle 1 day 21

	Ivosidenib **Mean (CV%), n = 50**	**Enasidenib** **Mean (CV%), n = 75**
C_{max}, ng/mL*	7650 (40.5)	8200 (40.4)
T_{max}, h†	3.92 (0.52, 22.75)	4.18 (0.00, 23.75)
AUC_{0-24}, h•ng/mL*	137 000 (44.6)	161 000 (40.4)
R_{acc} AUC_{0-24}‡	2.4	8.2
R_{acc} C_{max}‡	1.7	6.5
2-HG inhibition, %§	90.6 (22.5)	84.0 (28.8)¶ / 82.6 (31.9)#

2-HG, D-2-hydroxyglutarate; AUC_{0-24}, area under the plasma concentration-time curve from time zero to 24 hours post dose; C_{max}, maximum observed plasma concentration; CV%, percentage coefficient of variation; n, total number of observations; R_{acc}, accumulation ratio for AUC_{0-24} and C_{max}, calculated as induction cycle 1 day 14/induction cycle 1 day 1; T_{max}, time of maximum observed plasma concentration.

*Geometric mean (GeoCV%).

†Median (minimum, maximum).

‡Mean.

§Percentage inhibition for area under the effect time curve from time zero to 8 hours post dose.

¶At cycle 1 day 14 (patients receiving enasidenib beginning on day 1 of the first induction cycle).

#At cycle 1 day 21 (patients receiving enasidenib beginning on day 8 of the first induction cycle).

Supplemental Table 10. Mutations significantly associated with response in ivosidenib and enasidenib cohorts

Gene or pathway with mutation	Best response CR/CRi/CRp, n (%)		Non-CR/CRi/CRp, n (%)		Odds ratio	*P* (Fisher's exact test)
	Mutant	Wild type	Mutant	Wild type		
Ivosidenib cohorts						
	n = 44		**n = 12**			
None	-	-	-	-	-	-
Enasidenib cohorts						
	n = 63		**n = 24**			
ASXL1	9 (14.3)	54 (85.7)	11 (45.8)	13 (54.2)	0.2	.004
NRAS	2 (3.2)	61 (96.8)	6 (25.0)	18 (75.0)	0.1	.005
U2AF1	1(1.6)	62 (98.4)	5 (20.8)	19 (79.2)	0.06	.006
TP53	0	63 (100)	3 (12.5)	21 (87.5)	0	.019
DNMT3A	29 (46.0)	34 (54.0)	5 (20.8)	19 (79.2)	3.2	.048

Baseline bone marrow or peripheral blood samples were retrospectively analyzed for comutations by next-generation sequencing using the 95-gene Rapid Heme Panel, which has a detection sensitivity of 5%.

CR, complete remission; CRi, CR with incomplete neutrophil recovery; CRp, CR with incomplete platelet recovery.

Supplemental Table 11. *IDH* mutation clearance and MRD status in patients by best response and by *IDH2* mutation type

	***IDH* mutation clearance**			**Flow cytometry**	
	n	**VAF 0.02-0.04%, n (%)**	**VAF <1%, n (%)**	**n**	**MRD negative, n (%)**
Ivosidenib + chemotherapy in patients with m*IDH1*					
Total	50	21 (42)	37 (74)	22	18 (82)
CR	36	14 (39)	26 (72)	17	13 (76)
CRi	1	0 (0)	0 (0)	-	-
CRp	4	2 (50)	3 (75)	3	3 (100)
MLFS	4	3 (75)	4 (100)	2	2 (100)
PR	2	1 (50)	1 (50)	-	-
SD	2	0 (0)	2 (100)	-	-
NE	1	1 (100)	1 (100)	-	-
Enasidenib + chemotherapy in patients with m*IDH2*-R140					
Total	60	14 (23)	31 (52)	14	10 (71)
CR	32	9 (28)	17 (53)	7	5 (71)
CRi	7	1 (14)	3 (43)	5	3 (60)
CRp	8	1 (13)	4 (50)	-	-
MLFS	10	3 (30)	6 (60)	2	2 (100)
PR	1	0 (0)	0 (0)	-	-
SD	1	0 (0)	0 (0)	-	-
PD	1	0 (0)	1 (100)	-	-
Enasidenib + chemotherapy in patients with m*IDH2*-R172					
Total	19	4 (21)	11 (58)	5	2 (40)
CR	16	4 (25)	11 (69)	4	2 (50)
CRp	1	0 (0)	0 (0)	-	-

PR	1	0 (0)	0 (0)	-	-
NE	1	0 (0)	0 (0)	1	0 (0)

CR, complete remission; CRi, CR with incomplete neutrophil recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; VAF, variant allele frequency.

Supplemental Table 12. Concordance between *IDH1/2* mutation clearance by dPCR and MRD status by flow cytometry in patients with a best overall response of CR/CRi/CRp who had data available for both tests

	MRD positive	MRD negative
Ivosidenib cohort, n = 19		
IDH1 mutation detected	4	9
IDH1 mutation cleared	0	6
Enasidenib cohort, n = 15		
IDH2 mutation detected	4	9
IDH2 mutation cleared	1	1

CR, complete remission; CRi, CR with incomplete neutrophil recovery; CRp, CR with incomplete platelet recovery; MRD, measurable residual disease.

Supplemental Table 13. Summary of mutation clearance by next-generation sequencing at the end of induction

Best response	Ivosidenib cohort,* n = 34		Enasidenib cohort,† n = 25		Enasidenib cohort,† n = 8	
	m*IDH1*	Non-DTA genes	m*IDH2*-R140	Non-DTA genes	m*IDH2*-R172	Non-DTA genes
CR/CRi/CRp	20/30 (67%)	18/31 (58%)	15/20 (75%)	9/21 (43%)	3/7 (43%)	3/7 (43%)
CR	16/25 (64%)	14/26 (54%)	14/17 (82%)	8/18 (44%)	3/7 (43%)	3/7 (43%)
CRi + CRp	4/5 (90%)	4/5 (80%)	1/3 (33%)	1/3 (33%)	0/0 (0%)	0/0 (0%)
Other‡	2/3 (67%)	2/3 (67%)	2/4 (50%)	1/4 (25%)	0/1 (0%)	0/1 (0%)

Analyses were limited to the 33 genes represented on both platforms (Personalis ACE Cancer panel and ArcherDx Core Myeloid panel).

CR, complete remission; CRi, CR with incomplete neutrophil recovery; CRp, CR with incomplete platelet recovery; DTA genes, *DNMT3A*, *TET2*, and/or *ASXL1*.

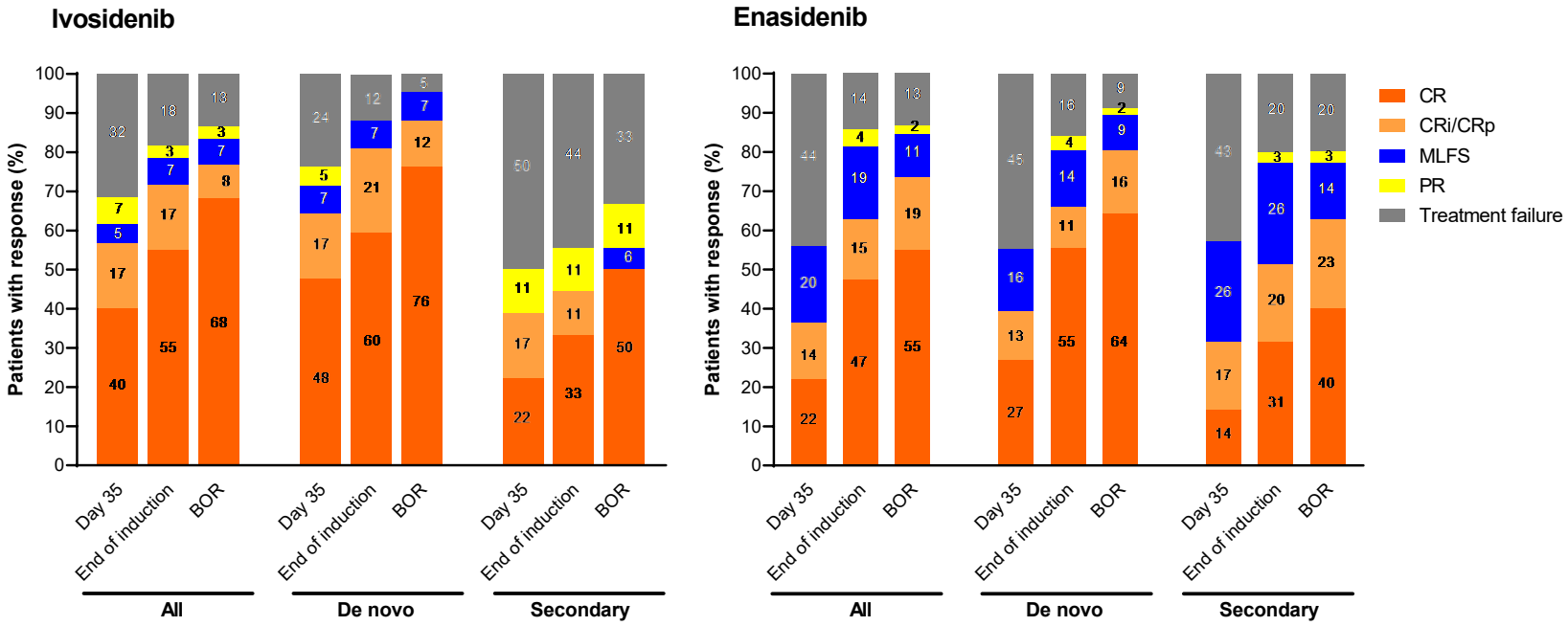
*Personalis ACE Cancer panel.

†ArcherDx Core Myeloid panel.

‡Responses other than CR, CRi, or CRp.

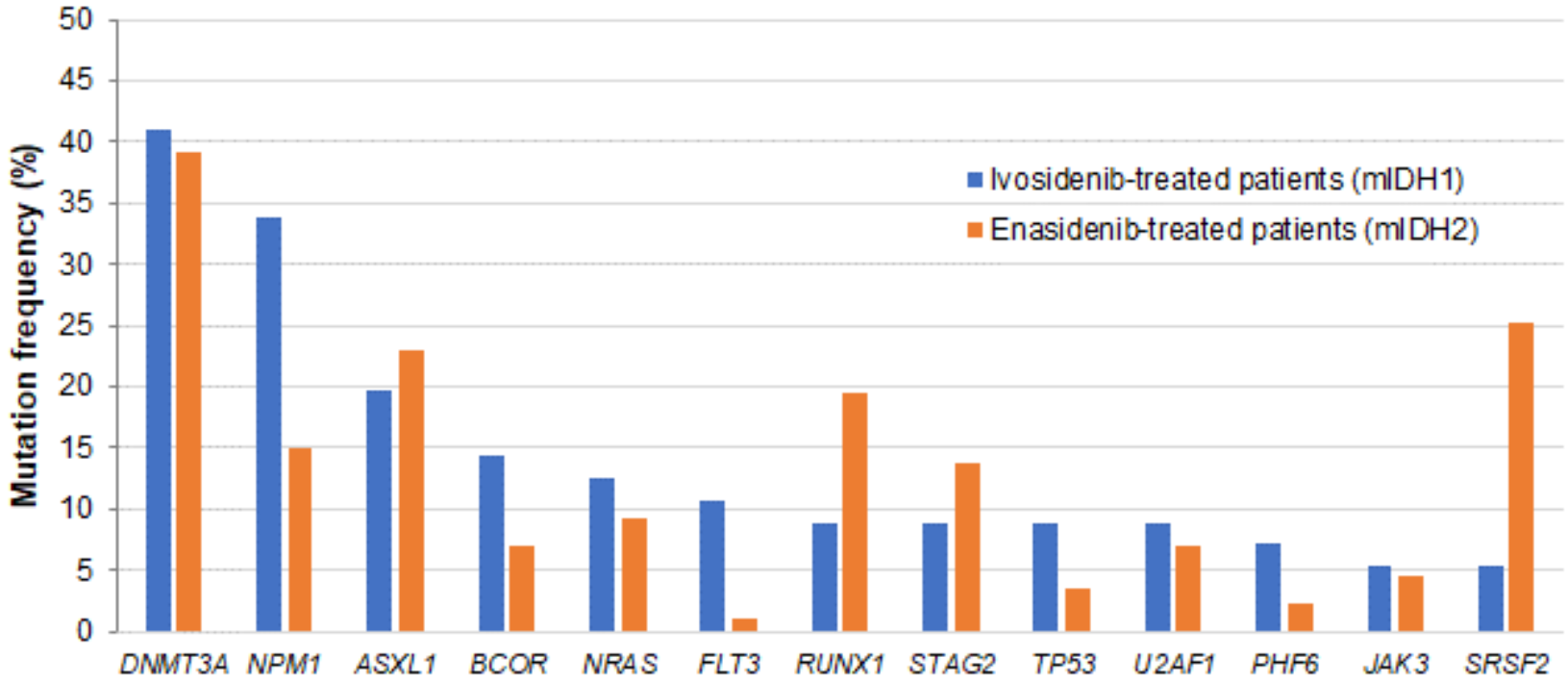
Supplemental Figure 1. Treatment responses over time.

Treatment failure includes stable disease + progressive disease + discontinuation before response assessment on or after induction day 21 + discontinuation with best response of not evaluable. CR, complete remission; CRi, CR with incomplete neutrophil recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; PR, partial remission.



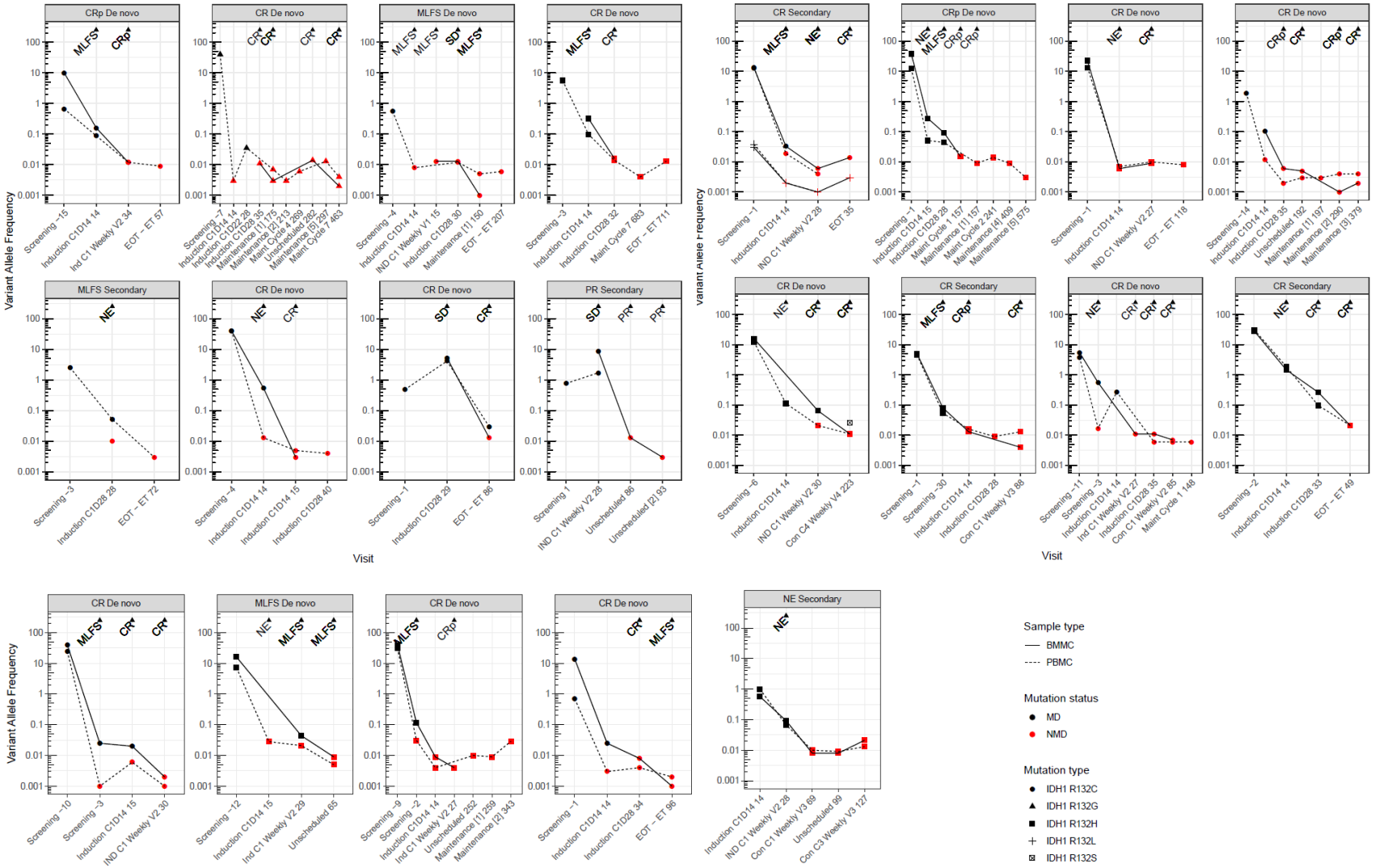
Supplemental Figure 2. Baseline co-occurring mutational landscape in the ivosidenib and enasidenib cohorts.

Baseline bone marrow or peripheral blood samples were retrospectively analyzed for comutations by next-generation sequencing using the 95-gene Rapid Heme Panel, which has a detection sensitivity of 5%.



Supplemental Figure 3. m*IDH1* variant allele frequency over time at the per-patient level in the ivosidenib cohorts

BMMC, bone marrow mononuclear cell; PBMC, peripheral blood mononuclear cell; MD, mutation detected; NMD, no mutation detected



Supplemental Figure 4. m*IDH2* variant allele frequency over time at the per-patient level in the enasidenib cohorts

BMMC, bone marrow mononuclear cell; PBMC, peripheral blood mononuclear cell; MD, mutation detected; NMD, no mutation detected