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Final phase I substudy results of ivosidenib in patients with mutant *IDH1* relapsed/refractory myelodysplastic syndrome

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Abstract:
Ivosidenib is a first-in-class mutant isocitrate dehydrogenase 1 (mIDH1) inhibitor and has shown efficacy and tolerability in patients with advanced mIDH1 hematologic malignancies, leading to approval in front-line and relapsed/refractory (R/R) mIDH1 AML populations. We report final data from a phase I single-arm substudy (NCT02074839) of patients with R/R mIDH1 MDS following failure of standard-of-care therapies. Oral ivosidenib was taken once daily on days 1-28 in 28-day cycles. Primary objectives were to determine safety, tolerability, and clinical activity. The primary efficacy endpoint was the complete remission + partial remission (CR+PR) rate. Nineteen patients were enrolled; 18 were included in the efficacy analysis. Treatment-related adverse events occurred in eight (42.1%) patients, including a grade 1 QT interval prolongation in one (5.3%) patient and grade 2 differentiation syndrome in two (10.5%) patients. Rates of CR+PR and objective response (CR +PR+marrow CR) were 38.9% (95% confidence interval [CI]: 17.3, 64.3) and 83.3% (95% CI: 58.6, 96.4), respectively. Kaplan-Meier estimates showed a 68.6% probability of patients in CR achieving a remission duration of >=5 years, and a median OS of 35.7 months. Of note, 71.4% and 75.0% baseline red blood cell (RBC) and platelet transfusion-dependent patients, respectively, became transfusion independent (TI; no transfusion >=56 days); 81.8% and 100% of baseline RBC and platelet TI patients, respectively, remained TI. One (5.3%) patient proceeded to a hematopoietic stem cell transplant by data cut-off. In conclusion, ivosidenib is clinically active, with durable remissions and a manageable safety profile observed in patients with mIDH1 R/R MDS.

Conflict of interest: COI declared - see note

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Final phase I substudy results of ivosidenib in patients with mutant *IDH1* relapsed/refractory myelodysplastic syndrome

Running title: Ivosidenib in patients with mutant *IDH1* R/R MDS

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Key Points

- Ivosidenib resulted in a CR rate of 38.9% and an ORR (CR+PR+mCR) of 83.3% in m*IDH1* R/R MDS; median DoR was not reached
- Median OS in this R/R MDS cohort was ~36 months; ~75% of RBC and platelet transfusion-dependent patients became transfusion-independent

Abstract

Ivosidenib is a first-in-class mutant isocitrate dehydrogenase 1 (m*IDH1*) inhibitor and has shown efficacy and tolerability in patients with advanced m*IDH1* hematologic malignancies, leading to approval in front-line and relapsed/refractory (R/R) m*IDH1* AML populations. We report final data from a phase I single-arm substudy (NCT02074839) of patients with R/R m*IDH1* MDS following failure of standard-of-care therapies. Oral ivosidenib was taken once daily on days 1–28 in 28-day cycles. Primary objectives were to determine safety, tolerability, and clinical activity. The primary efficacy endpoint was the complete remission + partial remission (CR+PR) rate. Nineteen patients were enrolled; 18 were included in the efficacy analysis. Treatment-related adverse events occurred in eight (42.1%) patients,

including a grade 1 QT interval prolongation in one (5.3%) patient and grade 2 differentiation syndrome in two (10.5%) patients. Rates of CR+PR and objective response (CR +PR+marrow CR) were 38.9% (95% confidence interval [CI]: 17.3, 64.3) and 83.3% (95% CI: 58.6, 96.4), respectively. Kaplan-Meier estimates showed a 68.6% probability of patients in CR achieving a remission duration of ≥5 years, and a median OS of 35.7 months. Of note, 71.4% and 75.0% baseline red blood cell (RBC) and platelet transfusion-dependent patients, respectively, became transfusion independent (TI; no transfusion ≥56 days); 81.8% and 100% of baseline RBC and platelet TI patients, respectively, remained TI. One (5.3%) patient proceeded to a hematopoietic stem cell transplant by data cut-off. In conclusion, ivosidenib is clinically active, with durable remissions and a manageable safety profile observed in patients with m*IDH1* R/R MDS.

Keywords: ivosidenib, mutant isocitrate dehydrogenase 1, 2-hydroxyglutarate, first-in-human, relapsed/refractory myelodysplastic syndromes

Introduction

Myelodysplastic syndromes (MDS) are a heterogenous group of clonal stem cell disorders characterized by ineffective hematopoiesis, resulting in peripheral blood cytopenias and an increased risk of transformation to acute myeloid leukemia (AML).[1,2] Standard-of-care therapy for MDS is determined by disease risk and patient prognosis, according to the Revised International Prognostic Scoring System (IPSS-R), and, more recently, the inclusion of somatic mutational profiles (Molecular IPSS [IPSS-M]).[3,4] Patients with low-risk MDS are managed with supportive care and agents that improve cytopenias, whereas patients with high-risk MDS are generally treated with hypomethylating agent (HMA)-based therapies.[2] Although an overall response rate of approximately 50% is observed with first-line HMA treatment, complete remissions (CRs) are uncommon, therapeutic benefits are transient and progression is near universal within a period of months to years.[5,6] Therapeutic options for HMA-resistant or refractory MDS are scarce, with no approved standard-of-care second-line treatments currently available, and with poor overall survival outcomes demonstrating an unmet need for these patients.[6-8]

Somatic mutations in the isocitrate dehydrogenase 1 (*IDH1)* gene have been reported in approximately 3% of patients with MDS.[9] *IDH1* mutations are often associated with high-risk MDS, neutropenia, and elevated bone marrow blast counts, and patients with mutant *IDH1* (m*IDH1*) MDS typically have a worse prognosis, including a higher risk of progression to AML, compared to patients with wild-type *IDH1* MDS.[10-12]

Isocitrate dehydrogenases are homodimeric enzymes involved in numerous cellular processes, including DNA modification and adaptation to hypoxia, and catalysis of the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG).[9] *IDH1* mutations most

often arise at a single amino acid residue, arginine 132, within the active site of IDH1.[13,14] The *IDH1* mutation reduces the ability to convert isocitrate to α-KG, and instead m*IDH1* gains a novel capacity to catalyze the nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reduction of α-KG to the *R* enantiomer of 2-hydroxyglutarate (2-HG), an oncometabolite.[9,15] 2-HG competitively inhibits various key epigenetic regulators, including histone lysine demethylases and members of the ten-eleven-translocation (TET) family of 5-methylcytosine hydroxylases.[9] Inhibition of these enzymes leads to a hypermethylation signature that alters gene expression, thereby preventing differentiation of hematopoietic stem cells into mature blood cells and contributing to oncogenesis.[9,16] Direct inhibition of m*IDH1* suppresses production of 2-HG, thereby enabling blast cell differentiation, potentially reducing the rate of oncogenic transformation.[17,18]

Ivosidenib (AG-120), a first-in-class m*IDH1* inhibitor, has been approved by the FDA as monotherapy or in combination with azacitidine in adult patients with newly diagnosed m*IDH1* AML who are >75 years old or who have comorbidities that preclude use of intensive induction. Ivosidenib monotherapy has also been approved in adult patients with m*IDH1* relapsed/refractory (R/R) AML and recently in patients with R/R MDS.[19-22]

In the first-in-human study of ivosidenib in patients with m*IDH1* advanced hematologic malignancies (ClinicalTrials.gov identifier: NCT02074839), 12 patients with R/R MDS received ivosidenib 500 mg once daily (QD).[23] Based on encouraging safety and efficacy findings, including an overall response rate (ORR) of 75%, the study was amended to enroll additional patients with R/R MDS.[24,25] We herein report the final analysis of data for patients with R/R m*IDH1* MDS.

Methods

Study design

We conducted a phase I, open-label, single-arm, first-in-human multinational substudy to assess ivosidenib in patients with m*IDH1* R/R MDS. This substudy was performed in compliance with the International Council for Harmonization Good Clinical Practice Guideline, in accordance with the Declaration of Helsinki and was approved by the relevant institutional review boards. All patients provided written informed consent before screening and enrollment.

Patient inclusion/exclusion criteria

Key inclusion criteria were an age of ≥18 years, documented mIDH1-R132 MDS, R/R MDS, defined as MDS that has relapsed (according to modified International Working Group [mIWG] 2006 criteria) following or is refractory to ≥1 of the following: high-intensity chemotherapy or intensive combination chemotherapy with investigational agents, novel combinations of standard treatments, hematopoietic stem cell transplant (HSCT) and/or HMA-based therapy. MDS refractory to HMA treatment per mIWG 2006 criteria was defined as the absence of CR, marrow CR (mCR), partial remission (PR), or hematologic improvement (HI) after a minimum of 4 cycles or if patients had disease progression prior to 4 cycles of HMA treatment.[26] Key exclusion criteria were prior treatment with an m*IDH1* inhibitor; hematopoietic stem cell transplant (HSCT) within 60 days of study start; documented AML (≥20% bone marrow or peripheral blood blasts); and treatment with systemic anticancer therapy, or radiotherapy, or an investigational agent within 14 days prior to first dose of study drug.

IPSS-R calculation

IPSS-R scores were calculated at diagnosis and at screening. Please see the Supplementary Materials for further details regarding IPSS-R calculations.[3]

Study schedule and treatment

Patients underwent a screening period of 28 days before day 1 and then received ivosidenib orally at the recommended phase II dose of 500 mg once daily from days 1–28 in 28-day cycles until disease progression, development of unacceptable toxicity, HSCT or another prespecified end-of-treatment criterion. There was a 28-day safety follow-up period post-treatment followed by a survival follow-up period.

Objectives and endpoints

The primary objectives were to determine the safety, tolerability and clinical activity of ivosidenib in patients with m*IDH1* R/R MDS. Adverse events of special interest were differentiation syndrome, leukocytosis and QTc prolongation. The primary efficacy endpoint was the CR+PR rate. Key secondary efficacy endpoints were duration of CR+PR, acquisition/maintenance of transfusion independence (TI), time to TI and duration of TI. TI was defined as no transfusion (red blood cells [RBCs] or platelets) for at least 56 days. Other efficacy endpoints included marrow CR (mCR), objective response rate (ORR; CR+PR+mCR), HI and overall survival (OS). Responses and HI were assessed according to mIWG 2006 criteria, the details of which are provided in the Supplementary Materials. Patients needed to meet certain pretreatment criteria to be evaluated for HI (Table 3).[26] For those patients alive at data cut-off, OS was reported as a censored observation.

Furthermore, translational, pharmacokinetic (PK) and pharmacodynamic (PD) analyses were performed. Translational analyses included baseline next-generation sequencing (NGS) and

longitudinal analysis of m*IDH1* VAF. NGS results were used to retrospectively derive the IPSS-M score.

Statistical analysis

Investigator-assessed response rates were evaluated as a binomial proportion and presented with associated exact binomial 95% confidence interval (CI). A CR+PR rate with an exact binomial 95% CI with a lower bound that excluded 10% was considered clinically meaningful. Approximately 23 eligible subjects (dose escalation/expansion population + substudy population) were planned based on testing a null CR+PR rate of 10% compared with a target CR+PR rate of 33% with 80% power and a 2-sided alpha of 0.05. Based on efficacy results from the data analysis reported here, it was agreed that enrollment of 18 subjects adequately supported the planned efficacy evaluation. Summaries were produced for subject disposition, demographic and baseline disease characteristics, efficacy, safety, PK, and PD, as appropriate.

Categorical data were summarized by frequency distributions (number and percentages of subjects). Continuous data were summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Time-to-event endpoints were estimated using the Kaplan-Meier method. Point estimates and 95% CIs were provided where appropriate, and estimates of the median and other quantiles, as well as individual time points (such as 3-, 6-, and 12-month rates), were generated.

Supplementary Materials

Please see the Methods section of the Supplementary Materials for additional inclusion/exclusion criteria, further details on the study schedule and the safety, efficacy, translational (including baseline IPSS-M calculations) and PK/PD analyses as well as

188 descriptions of the analysis sets evaluated in this substudy, a comprehensive list of
189 endpoints (Supplementary Table 1) and a schedule of study assessments (Supplementary
190 Table 2).

191 This substudy was performed in compliance with the International Council for
192 Harmonization Good Clinical Practice Guideline, in accordance with the Declaration of
193 Helsinki and was approved by the relevant institutional review boards. All patients provided
194 written informed consent before screening and enrollment.

Results

Patient demographics and baseline characteristics

As of 26 September 2022, 19 patients with R/R MDS had been enrolled and were included in the full analysis set. One patient had MDS that was refractory to an investigational agent and had not received prior intensive chemotherapy or HMAs. Therefore, the patient did not meet an inclusion criterion for the MDS substudy and was excluded from the efficacy analysis but was included in the safety analysis.

Most patients were male (78.9%), the median age was 73.0 years (range: 52–82 years) and a high proportion (78.9%) had received prior HMAs (Table 1 and Figure 1). Of the 18 patients with an available IPSS-R score at screening, 77.8% had an IPSS-R score >3 (intermediate risk or higher); 42.1% of patients had an IPSS-M score that was in the highest risk category ("very high"). IPSS-M scoring tended to upstage patients' risk category versus their IPSS-R score at screening (Figure 2A). This aligns with restratification data reported following development of the IPSS-M model, whereby 74% of patients were upstaged and 26% were downstaged from their original IPSS-R risk category.[4] Table 1 provides further demographic and disease characteristics data.

At the time of data cut-off, four (21.1%) patients remained on treatment and 15 (78.9%) had discontinued treatment. Reasons for discontinuation included disease progression (n=6 patients [31.6%]); non-treatment-related adverse events (TRAEs) (n=2 [10.5%]; sepsis and fatigue); progression of a concomitant medical condition, treating physician's decision and withdrawal of consent (n=1 [5.3%] for each category). One patient (5.3%) proceeded to an HSCT before data cut-off and another patient proceeded to an HSCT after data cut-off. One

patient withdrew to take ivosidenib commercially and another patient did not have recovery of platelet counts.

Seven of the 19 patients had died: two (10.5%) on study treatment and five (26.3%) after study treatment completion. Median treatment duration was 9.3 months (range: 3.3–78.8) and the median follow-up period for OS analysis was 27.1 months (range: 3.7–88.7).

Safety

In the safety analysis set (N=19), 18 patients (94.7%) experienced ≥1 treatment-emergent adverse event (TEAE) and 12 (63.2%) experienced a grade ≥3 TEAE. Eight (42.1%) patients experienced ≥1 TRAE, almost all of which were mild-to-moderate in severity. Grade 3 TRAEs were reported in two (10.5%) patients (fatigue in one patient and hyponatremia in another). Three (15.8%) patients experienced a serious TRAE during the study period (grade 2 rash and skin infection in one [5.3%] patient and grade ≤2 differentiation syndrome in two [10.5%] patients). No patients discontinued treatment due to TRAEs.

One patient with grade 2 differentiation syndrome had their treatment held until the adverse event had resolved and the other patient experienced two events of differentiation syndrome (grade 2 then grade 1) for which treatment was reduced and held until this adverse event resolved. This patient experienced a third grade 1 differentiation syndrome event (day 122) which required supportive care and was ongoing at data cut-off. This patient came off the study on day 457, received ivosidenib + decitabine for eight months, and subsequently died six months after discontinuing this combination. Neither patient permanently discontinued ivosidenib due to differentiation syndrome.

Corrected QT interval (QTc) increases of a grade ≤2 severity occurred in two patients (10.5%); only one of these QTc increases was considered related to treatment and neither event required ivosidenib dose modification. Fewer than half of patients were taking concomitant QTc interval-prolonging medications, with ondansetron being the most common (36.8% of patients); please see the Supplementary Materials for further details on other concomitant QTc interval-prolonging medications.

Two patients had TEAEs which led to permanent discontinuation of ivosidenib; one patient discontinued due to sepsis and another patient discontinued due to grade 3 fatigue related to underlying MDS. Both AEs were considered to be due to disease progression and not related to treatment; both patients subsequently died. Table 2 provides further details on TEAEs and TRAEs.

Efficacy

Clinical activity

In the efficacy analysis set (N=18), the rate of CR+PR (primary endpoint) was 38.9% (n=7 patients, all of whom experienced a CR; 95% CI: 17.3, 64.3) (Figure 1). Median time to CR was 1.87 months (range: 1.0–5.6 months) (Table 3). Remissions were durable, with a Kaplan-Meier estimate showing a 68.6% probability of CR patients experiencing a remission duration of at least 5 years (Supplementary Figure S1). Median duration of CR has not yet been reached, according to Kaplan-Meier analyses, and maximum CR duration was 80.8 months (censored observation). No impact on median CR duration was shown when censoring for transplant. Fifteen patients (83.3%; 95% CI: 58.6, 96.4) experienced an objective response. Of the eight patients (44.4%) experiencing mCR, four (50.0%) experienced HI in ≥1 lineage (erythrocyte, platelet and/or neutrophil). Two (25.0%) patients

261 with mCR had an improvement in erythrocyte counts, two had an improvement in platelet
262 counts and four (50.0%) had an improvement in neutrophil counts, according to mIWG 2006
263 response criteria (Table 3).

264 Five of seven (71.4%) and three of four (75.0%) baseline red blood cell (RBC) and platelet
265 transfusion-dependent patients, respectively, became transfusion independent (TI; no
266 transfusion during ≥56 days) post-baseline; nine of 11 (81.8%) and all 14 (100%) baseline
267 RBC- and platelet-TI patients, respectively, remained TI post-baseline (Figure 3). Median
268 time to any transfusion independence was 2.43 months (range: 0.03–5.36); median duration
269 of any transfusion independence was not reached (range: 1.9–78.8 months [censored
270 observation]). Supplementary materials provide further information on response and
271 transfusion independence outcomes.

272 Kaplan-Meier analyses showed a median OS duration estimate of 35.7 months (range: 3.7–
273 88.7; 95% CI: 13.1, not reached) and the probabilities of patients being alive at one, three
274 and five years were 86.9%, 46.3% and 46.3%, respectively (Table 3 and Supplementary
275 Figure S2). Patients in “high” or “very high” IPSS-M risk categories tended to have shorter OS
276 than patients in “moderately high” or “low” IPSS-M risk categories (Figure 2A).

277 *Progression to AML*

278 Two (11.1%) patients progressed to AML, both of whom still had a detectable *IDH1*
279 mutation at their last bone marrow assessment. At baseline, one patient’s MDS had +8 on
280 cytogenetic evaluations, and *ASXL1, NRAS* and *PTPN11* co-mutations, with 4% bone marrow
281 blasts and a high IPSS-R score at diagnosis. This patient had a best response of progressive
282 disease. The other patient’s MDS had a poor-risk/monosomy 7 karyotype, 19% bone
283 marrow blasts and a very-high-risk IPSS-R score at diagnosis. This patient initially had an

overall duration of remission of 8.3 months, including a CR duration of 5.6 months, but then subsequently developed AML.

Correlative analyses

IDH1 R132 frequency

All 19 patients had at least one IDH1-R132 mutation detected in bone marrow and/or peripheral blood; two patients had more than one variant detected. Please see the Supplementary Materials for further details on these two patients. R132C was the most common *IDH1* variant (Figure 4).

Baseline mIDH1 VAF and clinical response

Median baseline m*IDH1* VAF was 19.7%; patients in CR (n=7) had a numerically lower median *mIDH1* VAF at baseline than those patients in mCR (n=8) (14% vs 25%). Median m*IDH1* VAF was 3% in the group of three non-responders, which included two patients with stable disease and a very low m*IDH1* VAF and one patient with progressive disease and a high m*IDH1* VAF (Figure 5A).

Longitudinal mIDH1 VAF and clinical response

No clear trends were observed with longitudinal VAF and clinical response. Although clearance of *IDH1* mutations was uncommon, responders with an available baseline sample tended to experience reduction in m*IDH1* VAF. However, m*IDH1* VAF clearance in peripheral blood was observed in one patient with stable disease suggesting that reduction of m*IDH1* VAF is not always indicative of clinical response (Figure 5B).

IDH1 mutation clearance in bone marrow in responders

Eighteen patients had longitudinal assessment of *IDH1* mutation burden in bone marrow

while on treatment. Fifteen (83.3%) of those patients were responders, with seven patients achieving a CR (46.7% of responders) and eight patients achieving an mCR (53.3% of responders). Of this group of responders, *IDH1* mutation clearance was observed in one of seven (14.3%) CRs and one of eight (12.5%) mCRs.

IDH1 mutation clearance in peripheral blood in responders

Seventeen patients had on-treatment peripheral blood assessments, 14 (82.4%) of whom were responders. In this group of responders, *IDH1* mutation clearance was observed for two of seven (28.6%) patients with CR and two of seven patients with mCR.

Co-mutated genes

The median number of co-mutated genes was 2 (range: 0–7). Patients with a CR had fewer co-mutated genes compared to patients with no response (median of 1 vs 3; Figure 2B). The most common co-mutated genes were *SRSF2* and *ASXL1,* both occurring in eight patients (42.1%) as well as *RUNX1* (n=3 patients [15.8%]) (Supplementary Figure S3). All eight patients with *SRSF2* co-mutations and six of eight patients with *ASXL1* co-mutations experienced CR or mCR. Two out of three patients with *RUNX1* co-mutations experienced mCRs. Both patients were alive at data cut-off, with one patient having experienced an OS duration of ~2 years.

TP53 was mutated at baseline in two patients, one of whom experienced CR (baseline VAF of 1%; remission duration: 65.3 months) and another of whom experienced mCR (baseline VAF of 5%; remission duration: 70.9 months) (Figure 2A); both remissions were ongoing at the time of data cut-off. Two patients had co-mutations in receptor tyrosine kinase pathway genes: one patient with an *NRAS* co-mutation who experienced mCR and another with both *NRAS* and *PTPN11* co-mutations who experienced progressive disease.

Pharmacokinetic/pharmacodynamic analyses

Ivosidenib (500 mg) reached steady-state exposure within 14 days of continuous daily dosing. Ivosidenib rapidly reduced both plasma and bone marrow levels of 2-HG, preceding changes in m*IDH1* VAF, and demonstrating on-target effects, with plasma 2-HG levels at steady state (day 1 of cycle 2) resembling those of volunteers (72.6±21.8 ng/mL; data not published). At steady state, more than 90% reduction of 2-HG in plasma and bone marrow was seen across the observed range of plasma ivosidenib $AUC_{0\text{-}24}$ values, demonstrating sustained duration of inhibition. Of the 14 evaluable patients on day 1 of cycle 2, 12 (85.7%) showed inhibition of 2-HG plasma levels of at least 94%. Supplementary Materials provides further PK/PD data, including Table S3.

Discussion

This is currently the largest prospective study performed specifically in patients with m*IDH1* R/R MDS, with final results demonstrating an acceptable safety profile and clinically meaningful activity of ivosidenib in a molecularly defined m*IDH1* R/R MDS patient population with a poor prognosis. No new safety signals or trends were observed, demonstrating the long-term tolerability of ivosidenib monotherapy, further confirmed by the median treatment duration of 9.3 months.[23,27,28] Most TEAEs were not treatment-related, and those which were related were typically of a lower grade and could be managed with standard-of-care interventions.

Two patients (10.5%) experienced differentiation syndrome events of a grade ≤2 severity, both of whom were managed with standard therapeutic approaches and remained on ivosidenib treatment. No patients experienced grade ≥3 differentiation syndrome. In comparison, albeit in larger patient cohorts, rates of grade ≥3 differentiation syndrome occurred in 9.0% and 5.0% of patients receiving ivosidenib monotherapy for newly diagnosed or R/R m*IDH1* AML, respectively, and 7.0% of patients with mutant isocitrate dehydrogenase 2 (m*IDH2*) R/R AML who were treated with m*IDH2* inhibitor enasidenib.[23,27,29] A lower incidence of treatment-related QTc interval prolongation was observed (grade 1 event in one patient [5.3%]; no grade 3 or higher QTc interval increases), likely because fewer prophylactic concomitant QTc-prolonging agents were administered in this study compared with AML cohorts receiving ivosidenib.[23] Only two grade 3 TRAEs (fatigue and hyponatremia) were reported; neither led to treatment discontinuation. Overall, these data support an improved safety profile compared with that observed in

patients with AML, which may be secondary to the lower disease burden at baseline, and which may also support earlier utilization of ivosidenib within the treatment paradigm.

Ivosidenib demonstrated a favorable CR+PR rate (38.9% of patients; 95% CI: 17.3, 64.3; primary endpoint), exceeding the pre-specified definition of clinically relevant activity in this high-risk population. All seven responders who achieved a CR by IWG 2006 response criteria had durable responses with Kaplan-Meier estimates showing a 68.6% probability achieving a CR duration of at least 5 years. The median duration of CR was not reached (95% CI 1.9, not reached) during a median follow-up period of 65.3 months for these patients, among whom two patients transitioned to HSCT (one before and one after data cut-off).

Half of patients in mCR experienced HI in at least one lineage (erythrocyte, platelet and/or neutrophil), helping to confirm that ongoing ivosidenib therapy provides clinical benefit, as demonstrated in prior studies of ivosidenib in other settings.[23,27] Importantly, approximately 75% of RBC or platelet transfusion-dependent patients at baseline achieved TI, and almost all patients with RBC or platelet TI at baseline maintained their TI status (81.8% and 100.0%, respectively). These outcomes are of particular relevance for patients who experience the detrimental clinical, economic and quality-of-life effects from frequent transfusion requirements, a defining feature of advanced MDS.[30-33]

OS outcomes in patients with HMA-refractory MDS are generally poor, with one study reporting a median OS duration of 5.6 months and 1- and 2-year survival estimates of 28.9% and 15.3%, respectively, in patients with high-risk R/R MDS.[7] In our substudy, median OS duration was 35.7 months and the probabilities of patients being alive for at least 1 year and 5 years were 86.9% and 46.3%, respectively, according to Kaplan-Meier analysis. Although it should be noted that our study sample size was small, and not solely comprised of patients

with high-risk disease, although they did form a substantial proportion of the patient population.

IDH1 mutations are often associated with a higher risk of leukemic transformation in patients with MDS or myeloproliferative neoplasms and ivosidenib may prolong the time to transformation to AML.[34,35] In this study, two (11.1%) patients progressed to AML during a median follow-up period of 27.1 months, which appears favourable compared to a retrospective review in which almost half of patients (48%) with R/R MDS following HMA therapy experienced transformation to AML during a median follow-up period of 19.5 months. However, the patients included in the retrospective review who developed AML tended to be younger (<65 years) with higher-risk MDS and often had *TP53* mutations, and thus differ somewhat from our overall study population.[36]

Overall, co-mutations were heterogenous and typical for MDS, suggesting generalizability of these results to a larger MDS population. No clear correlation between *IDH1* mutation clearance and clinical response or other efficacy outcomes was reported in our study, which differs from what was observed in a cohort with R/R AML who received ivosidenib.[23] However, this difference should be interpreted cautiously due to the small sample size. Although *IDH1* mutation clearance was uncommon in this study, most responding patients demonstrated reduction of m*IDH1* variant allele frequency while on-treatment.

PK and PD parameters in R/R MDS patients were comparable to those patients with R/R AML treated with ivosidenib 500 mg QD.[23] After multiple ivosidenib doses, steady-state exposure was achieved within 14 days with only minor accumulation and plasma 2-HG decreased to similar levels observed in healthy participants, with >90% reduction of 2-HG in

plasma and bone marrow in the majority of patients regardless of response, demonstrating on-target effects.[37,38]

Study limitations were the small sample size which may have led to our study being underpowered to detect infrequent events such as QT interval prolongation, as well as the single-arm study design; however, both limitations are expected due to the relative rarity of the *IDH1* mutation in patients with MDS.

In conclusion, ivosidenib induced durable remissions in patients with m*IDH1* R/R MDS, including a substantial proportion of CRs, accompanied by low rates of serious or severe TEAEs. Ivosidenib therefore represents a well-tolerated and efficacious oral therapy for patients with this aggressive life-threatening disease who currently have no approved disease-modifying therapeutic options and may potentially change the future treatment landscape for this poor-prognosis population. Data from this study will form the basis of an upcoming priority review by the FDA and the efficacy and safety of ivosidenib are being further studied in patients with R/R mIDH1 MDS in the ongoing phase II IDIOME study (NCT03503409).[39]

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Authorship contributions

Courtney D. DiNardo designed research, performed research, collected data, analysed and interpreted data, contributed to the writing of the manuscript and critically reviewed the manuscript.

Gail J. Roboz performed research, collected data, analysed and interpreted data, and critically reviewed the manuscript.

Justin M. Watts performed research, collected data, analysed and interpreted data, contributed to the writing of the manuscript and critically reviewed the manuscript.

Yazan F. Madanat performed research, collected data, analysed and interpreted data, contributed to the writing of the manuscript and critically reviewed the manuscript.

Gabrielle T. Prince performed research, collected data and critically reviewed the manuscript.

Praneeth Baratam performed research, collected data, analysed and interpreted data, contributed to the writing of the manuscript and critically reviewed the manuscript.

Stéphane de Botton performed research, collected data and critically reviewed the manuscript.

Anthony Stein performed research, collected data, and critically reviewed the manuscript.

James M. Foran designed research, collected data and critically reviewed the manuscript.

Martha L. Arellano performed research, collected data and critically reviewed the manuscript.

David A. Sallman performed research, collected data, contributed to the writing of the manuscript and critically reviewed the manuscript.

Mohammad Hossain designed research, performed research, analysed and interpreted data, contributed to the writing of the manuscript and critically reviewed the manuscript.

Dylan Marchione designed research, performed research, analysed and interpreted data, contributed to the writing of the manuscript and critically reviewed the manuscript.

Xiaofei Bai designed research, performed research, analysed and interpreted data, performed statistical analyses, contributed to the writing of the manuscript and critically reviewed the manuscript.

Prapti A. Patel designed research, performed research, analysed and interpreted data, contributed to the writing of the manuscript and critically reviewed the manuscript.

Stephanie M. Kapsalis designed research, performed research, analysed and interpreted data, contributed to the writing of the manuscript and critically reviewed the manuscript

Guillermo Garcia-Manero performed research, collected data and critically reviewed the manuscript.

Amir T. Fathi designed research, performed research, collected data, analysed and interpreted data, contributed to the writing of the manuscript and critically reviewed the manuscript.

Conflict of Interest Disclosures

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641 # Tables

642 Table 1. Baseline patient demographics and disease characteristics for the full analysis set
643 (N=19).

Characteristic	(N=19)
Sex, n (%)	
Female	4 (21.1)
Male	15 (78.9)
Age, years	
Median (min, max)	73.0 (52, 82)
Race	
White	15 (78.9)
Black or African American	1 (5.3)
Not reported	3 (15.8)
Ethnicity	
Hispanic or Latino	1 (5.3)
Not Hispanic or Latino	12 (63.2)
Not reported	6 (31.6)
ECOG PS	
0	5 (26.3)
1	11 (57.9)
2	3 (15.8)

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Prior therapy, n (%)	
Intensive chemotherapy	3 (15.8)
One line of HMA-based therapy	14 (73.7)
Two lines of HMA-based therapy	1 (5.3)
Investigational	3 (15.8)
Other[a]	1 (5.3)
IPSS-R score at initial diagnosis, n (%)[b]	
≤1.5 (very low)	0
>1.5–3 (low)	2 (10.5)
>3–4.5 (intermediate)	6 (31.6)
>4.5–6 (high)	2 (10.5)
>6 (very high)	2 (10.5)
Unknown	7 (36.8)
IPSS-R score at screening, n (%)	
≤1.5 (very low)	0
>1.5–3 (low)[c]	4 (21.1)
>3–4.5 (intermediate)[d]	8 (42.1)
>4.5–6 (high)[e]	3 (15.8)
>6 (very high)[f]	3 (15.8)
Unknown[g]	1 (5.3)
IPSS-M score at screening, n (%)[h]	
Low	3 (15.8)
Moderate low	1 (5.3)
Moderate high	4 (21.1)
High	3 (15.8)

Very high	8 (42.1)
WHO Classification at screening, n (%)	
MDS with excess blasts (MDS-EB1)[i]	4 (21.1)
MDS with excess blasts (MDS-EB2)[j]	1 (5.3)
MDS, with multilineage dysplasia (MDS-MLD)	4 (21.1)
MDS, unclassifiable	10 (52.6)
Cytogenetic result, n (%)	
Normal	9 (47.4)
Abnormal	9 (47.4)
Missing	1 (5.3)

[a]Patient received lenalidomide.

[b]Six patients did not have an IPSS-R score at diagnosis due to being treated locally before being referred to the clinical trial site.

[c]Karyotypes in the IPSS-R low risk group were: 46, XX[20]; 46, XY[20]; 46 XY[20] and normal male karyotype.
[d]Karyotypes in the IPSS-R intermediate-risk group were: 46, XX [20];
47,XY,+21[1]/46,XY,DEL(7)(Q22)[1]/46,XY[18]; 43,XY,+1,DER(1;15)(Q10;Q10),-5,-9,-12 (1)/46,XY,DUP(1)[19];
46, XX[20]; unknown;
46,X,DEL(X)(Q26),T(1;17)(Q12;Q25),T(12;16)(Q15;P11.2)[4]/46,XX,T(3;16)(P21;P13.1)[2]/46,XX[7]//46,XY[2];
and normal male karyotype; 46,XY[4]
[e]Karyotypes in the IPSS-R high-risk group were: 47,XY,+8[3]/46,XY[17] (twenty male metaphases (3 abnormal and 17 normal) were analysed. The previously reported clone remained in the bone marrow, indicating persistent disease); 47,XY,+8[6]/46,XY[14]; and 46, XY[20].
[f]Karyotypes in the IPSS-R very-high-risk group were: 45,XY,-7[17]/46,XY,DER(7;18)(P10;Q10),+11[3] (twenty abnormal male metaphases were analyzed. The previously reported abnormal clones remain fully predominant in the bone marrow indicating persistent disease); 46,XY,+1,DER(1;7)(Q10;P10)[3]; and 47,XX,+21[13]/46,XX[7] (abnormal result showing previously unreported abnormality).
[g]The karyotype in the patient whose IPSS-R score was unknown at screening was 46,XY[20].

[h]Derived retrospectively by internal Sponsor review.

[i]MDS-EB1: 5–9% of bone marrow cells, or 2–4% of blood cells, are blasts.

[j]MDS-EB2: 10–19% of bone marrow cells, or 5–19% of blood cells, are blasts.
EB, excess blasts; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HMA, hypomethylating agent; IDH, isocitrate dehydrogenase; max, maximum; IPSS-M, Molecular International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; min, minimum; MLD, multilineage dysplasia; n, number of patients; N, total number of patients; SD, standard deviation.

673 Table 2. Overview of TEAEs.

Adverse event outcomes, n (% patients)	**Safety analysis set (N=19)**
AE summary	
Any TEAE	18 (94.7)
Any treatment-related SAE	3 (15.8)
Any grade ≥3 treatment-related TEAE	2 (10.5)
Any TEAE leading to ivosidenib discontinuation[a]	2 (10.5)
Any TEAE leading to ivosidenib interruption	5 (26.3)
Any treatment-related TEAE leading to ivosidenib dose modification[b]	4 (21.1)
TEAEs by preferred term considered possibly or probably related to treatment[c]	
Any-grade	8 (42.1)
Fatigue	3 (15.8)
Diarrhea	2 (10.5)
Differentiation syndrome[d]	2 (10.5)
Rash	2 (10.5)
Dyspnea	2 (10.5)
ECG QT prolonged[e]	1 (5.3)
Dyspepsia	1 (5.3)
Decreased appetite	1 (5.3)
Skin infection	1 (5.3)
Anemia	1 (5.3)
Platelet count decrease	1 (5.3)

Blood alkaline phosphatase increased	1 (5.3)
Hyponatremia	1 (5.3)
Grade 3 or higher	
Fatigue	1 (5.3)
Hyponatremia	1 (5.3)

AE, adverse event; n, number of patients; QTc, corrected QT interval; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]These AEs were grade 5 sepsis and grade 3 fatigue; neither was considered related to ivosidenib [b]Modification refers to dose reduction, interruption or discontinuation

[c]Six patients experienced multiple treatment-related TEAEs

[d]One patient experienced 3 differentiation syndrome events (two grade 1 events and one grade 2 event) and the other patient experienced one grade 2 differentiation syndrome event

[e]Grade 1 severity.

683 Table 3. Efficacy outcomes in the efficacy analysis set, according to IWG 2006 response
684 criteria

Efficacy outcomes	MDS substudy efficacy analysis set (N=18)	95% CI
Primary endpoint, n (%)		
CR+PR	7 (38.9)	(17.3, 64.2)
Secondary endpoints,		
Time to CR+PR, median months (min, max)	1.87 (1.0, 5.6)	(58.6, 96.4)
Duration of CR+PR[a], median months (min, max)	NR (1.9, NR)	
Probability of patients maintaining CR+PR[a], n (%)		
At 3 months	85.7	
At 24 months	68.6	
At 60 months	68.6	
Best overall response,		
ORR[b]	15 (83.3)	(58.6, 96.4)
CR	7 (38.9)	(17.3, 64.3)
PR	0	(0.0, 18.5)
mCR	8 (44.4)	(21.5, 96.2)
SD	2 (11.1)	(1.4, 34.7)
PD	1 (5.6)	(0.1, 27.3)
Time to OR[b], median months (min, max)	0.99 (0.9, 4.6)	
HI in non-CR/PR patients, n (%)		
Erythrocyte lineage	2 (18.2)[c]	
Platelet lineage	2 (25.0)[d]	
Neutrophil lineage	4 (57.1)[e]	
Any HI lineage	4 (36.4)[f]	
OS[a], median months, [95% CI] (min, max)	35.7 [13.1, NE] (3.7[g], 88.7[g])	
OS rate[a], (%)		
1 year	86.9	
3 years	46.3	
5 years	46.3	
7 years	46.3	

685 [a]Kaplan-Meier estimate of duration of CR+PR
686 [b]OR comprised CR, PR or mCR
687 [c]% based on number of patients with mCR and pretreatment hemoglobin <11 g/dL (N1=11)
688 [d]% based on number of patients with mCR and pretreatment platelet count <100 x 10^9/L (N2=8)

[e]% based on patients with mCR and pretreatment absolute neutrophil count <1.0 x 10^9/L (N3=7)

[f]% based on patients with mCR and who satisfy the pretreatment criteria for HI-erythrocyte, HI-platelet, or HI-neutrophil (N4=11)

[g]Censored observation

CI, confidence interval; CR, complete remission; HI, hematologic improvement; IWG, International Working Group; MDS, myelodysplastic syndrome; mCR, marrow complete remission; NR, not estimable; OR, objective response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial remission; SD, stable disease.

Figure legends

Figure 1. Swimmer plot of treatment duration and best overall response in the efficacy analysis set (N=18)[a]

[a]One patient was excluded from the efficacy analysis due to not meeting an inclusion criterion.
AML, acute myeloid leukemia; CR, complete remission; HI, hematologic improvement; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; INV, investigational agent; mCR, marrow complete remission; PD, progressive disease; PR, partial remission; PT, prior therapy; SD, stable disease.

Figure 2AB. Heatmap showing IPSS-R, IPSS-M and IPSS-R cytogenetic risk categories, best overall response, baseline co-mutations, baseline VAF, and OS in the efficacy analysis set (A; N=18) and distribution of number of co-mutated genes with best overall response (B; N=18)

Please note that the numbers within the boxes correspond to the VAF of the alteration.
[a]If a patient had multiple alterations in a gene, the largest VAF was shown.
[b]This patient did not have any of the co-mutations evaluated in the panel but did have a poor-risk karyotype, including monosomy 7.
AML, acute myeloid leukemia; CR, complete remission; IPSS-M, International Prognostic Staging System-Molecular; IPSS-R, International Prognostic Scoring System-Revised; mCR, marrow complete remission; OS, overall survival; PD, progressive disease; RTK, receptor tyrosine kinase; SD, stable disease; VAF, variant allele frequency.

Figure 3AB. Proportions of patients with post-baseline RBC (3A) or platelet transfusion (3b) independence (N=18)

[a]Post-baseline transfusion independence was defined as no transfusion for at least one 56-day period.

n, number of patients; RBC, red blood cell

Figure 4. *IDH1* mutation type, based on central testing (n [% patients]; N=19)

IDH1, isocitrate dehydrogenase 1.

Figure 5. Association of NGS-assessed baseline m*IDH1* VAF with response in the efficacy analysis set (A; N=18) and longitudinal m*IDH1* VAF as measured in BMMCs or PBMCs, stratified by BOR (B; N=18)

Figure 5A. Please note: PB data is only plotted for patients who did not have BM samples available. Of the 18 patients, 4 had NGS results available for BM only, 3 had NGS results available for PB only, and the remaining 11 had results available for both sample types.

Figure 5B. Please note: baseline m*IDH1* VAF is plotted in grey, and the minimum post-treatment m*IDH1* VAF is plotted in pink (indicating persistent m*IDH1*) or cyan (for m*IDH1* clearance, defined as having a measured VAF below the validated LOD of the assay, which was 0.02%). Data are stratified by BOR and sample type. Lines connect pre- and post-treatment data for patients with data available.

BM, bone marrow; BMMCs, bone marrow mononuclear cells; BOR, best overall response; CR, complete remission; LOD, limit of detection; mCR, marrow complete remission; m*IDH1*, mutant isocitrate dehydrogenase 1; NGS, next-generation sequencing; PB, peripheral blood; PBMCs, peripheral blood mononuclear cells; PD, progressive disease; SD, stable disease; Tx, treatment; VAF, variant allele frequency.

Figure 1

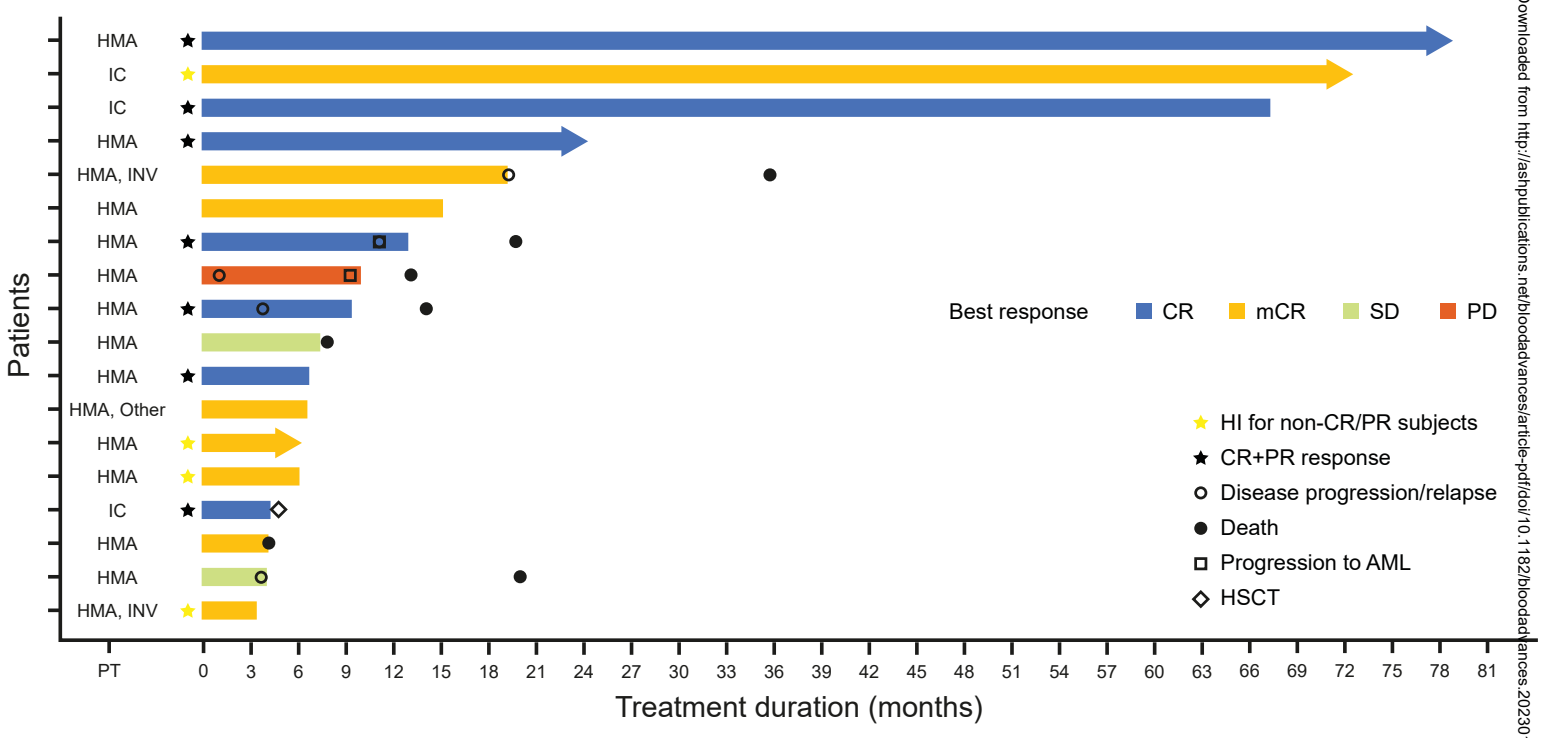
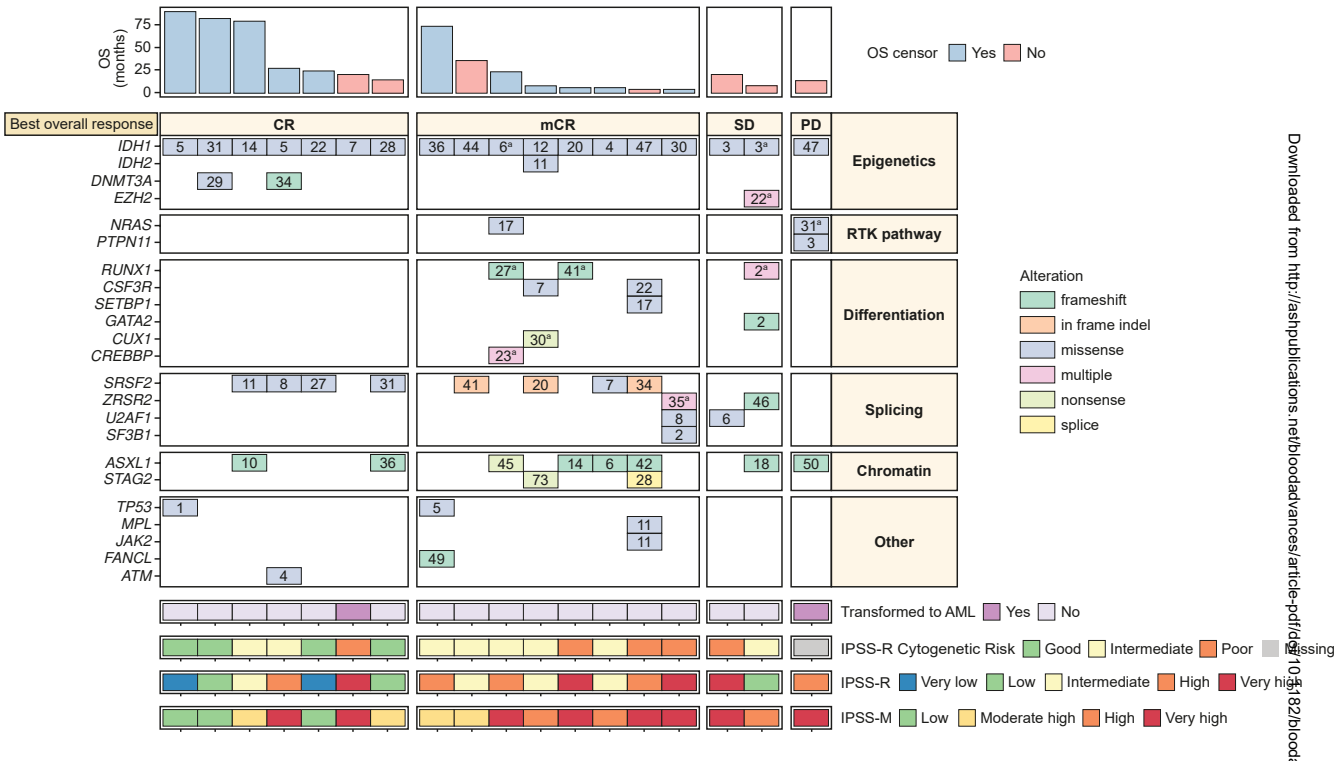


Figure 2

2A



2B

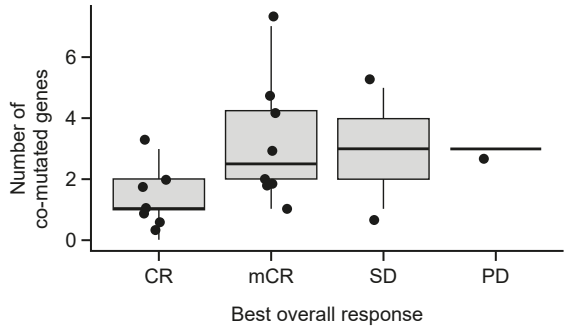
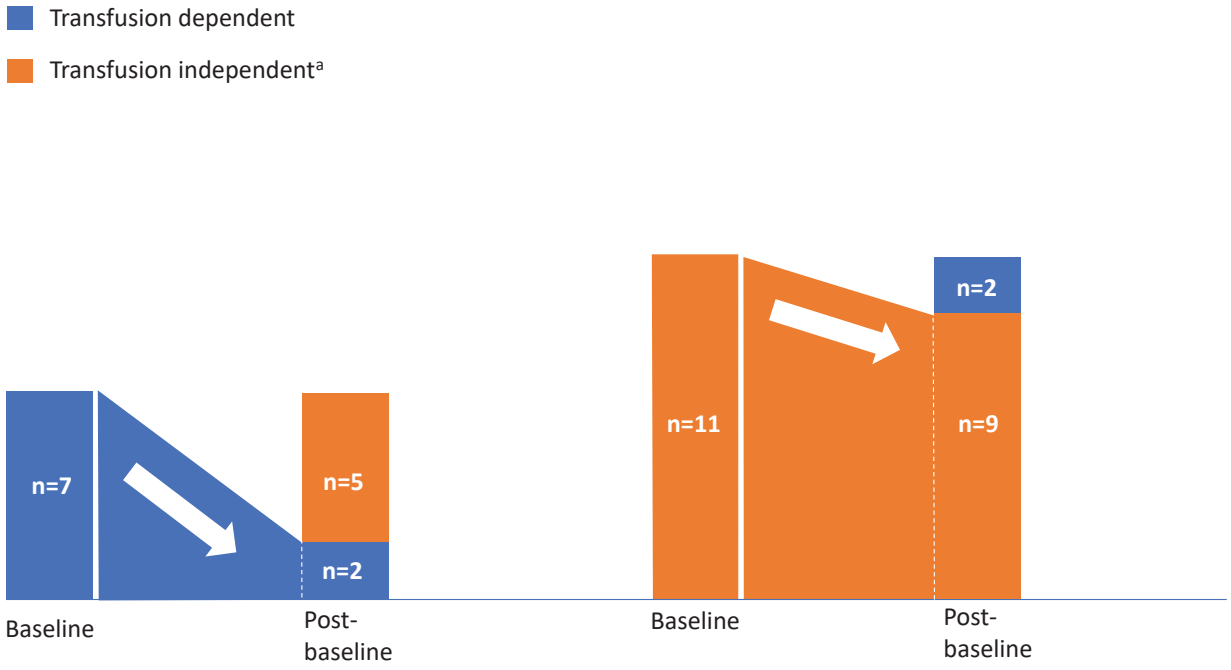


Figure 3

3a) RBC transfusions



3b) Platelet transfusions

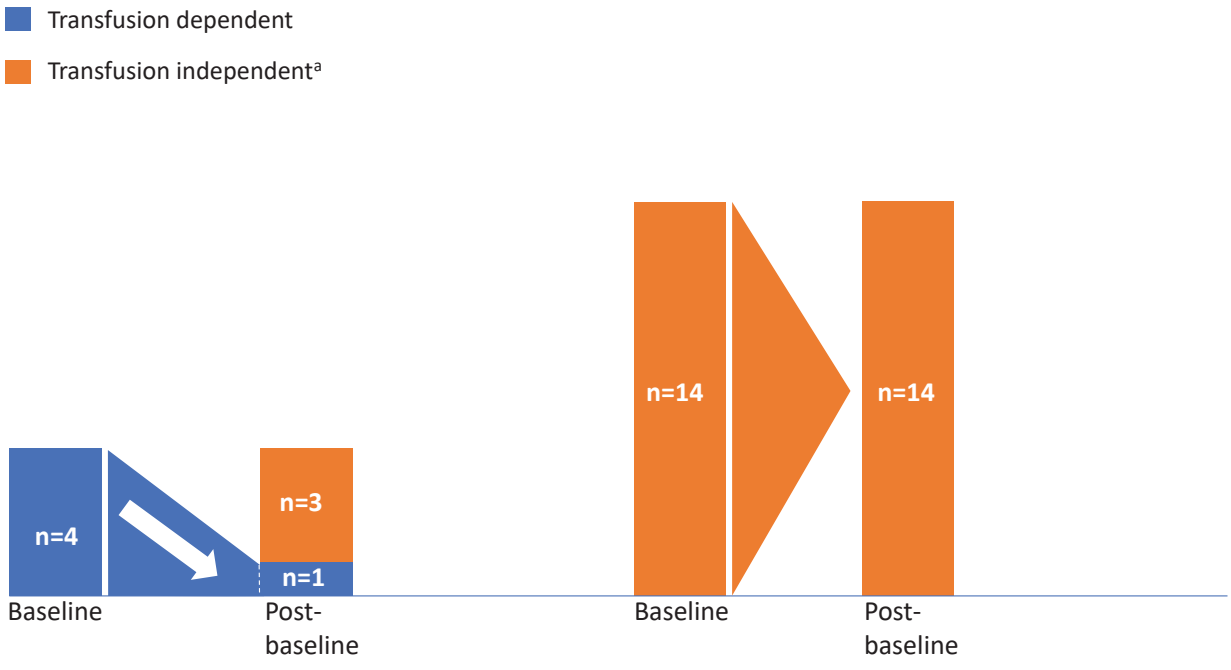


Figure 4

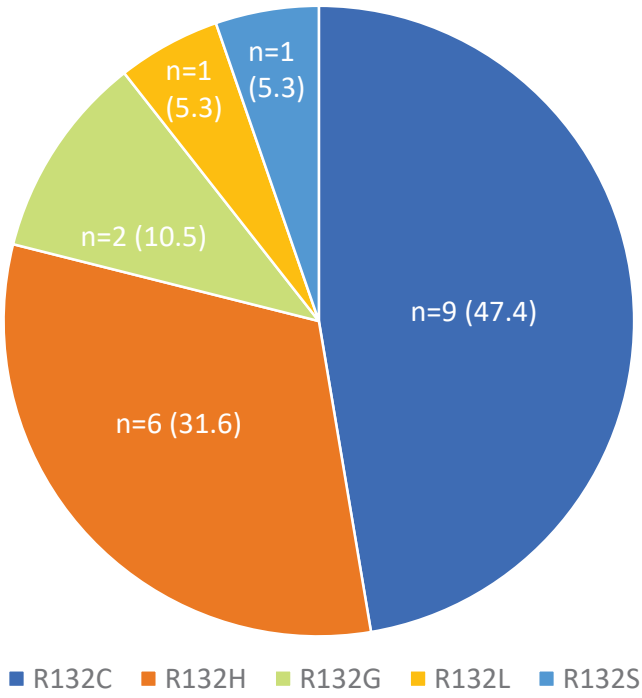
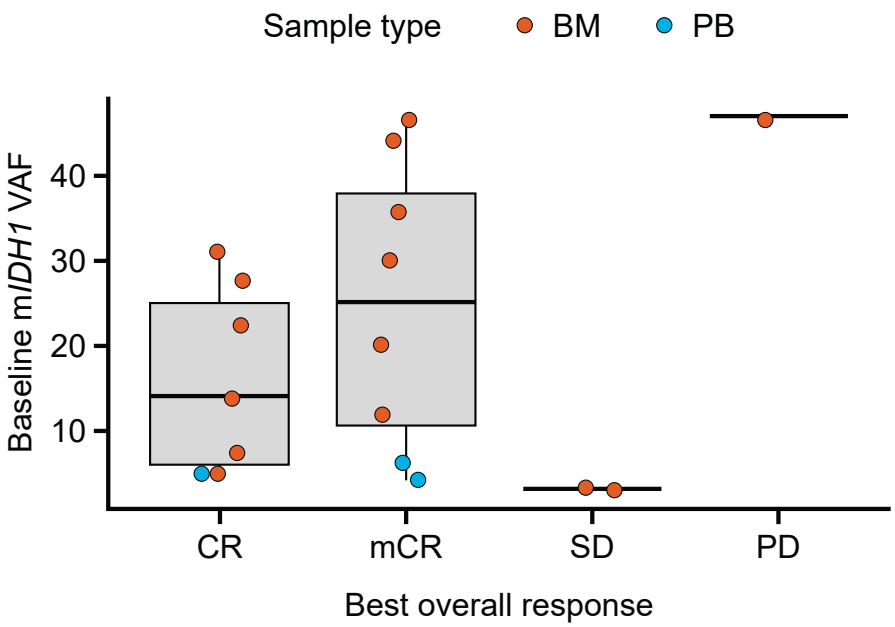


Figure 5

5A



5B