# A phase 1b study of glasdegib + azacitidine in patients with untreated acute myeloid leukemia and higher-risk myelodysplastic syndromes

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## Abstract

This phase 1b study evaluated glasdegib (100 mg once daily) + azacitidine in adults with newly diagnosed acute myeloid leukemia (AML), higher-risk myelodysplastic syndromes (MDS), or chronic myelomonocytic leukemia (CMML) who were ineligible for intensive chemotherapy. Of 72 patients enrolled, 12 were in a lead-in safety cohort (LIC) and 60 were in the AML and MDS (including CMML) expansion cohorts. In the LIC, the safety profile of glasdegib + azacitidine was determined to be consistent with those of glasdegib or azacitidine alone, with no evidence of drug–drug interaction. In the expansion cohort, the most frequently (≥ 10%) reported non-hematologic Grade ≥ 3 treatment-emergent adverse events were decreased appetite, electrocardiogram QT prolongation, and hypertension in the AML cohort and sepsis, diarrhea, hypoten- sion, pneumonia, and hyperglycemia in the MDS cohort. Overall response rates in the AML and MDS cohorts were 30.0% and 33.3%, respectively; 47.4% and 46.7% of patients who were transfusion dependent at baseline achieved independence. Median overall survival (95% confidence interval) was 9.2 (6.2–14.0) months and 15.8 (9.3–21.9) months, respectively, and response was associated with molecular mutation clearance. Glasdegib + azacitidine in patients with newly diagnosed AML or MDS demonstrated an acceptable safety profile and preliminary evidence of clinical benefits.

Trial registration: ClinicalTrials.gov NCT02367456.

## Introduction

Acute myeloid leukemia (AML) in older adults and higher- risk myelodysplastic syndromes (MDS) and chronic myelo- monocytic leukemia (CMML) are widely recognized to be diagnoses associated with eventual resistance to therapy and severe truncation of life [1, 2]. As the typical age at diagno- sis for these disorders is 65–75 years, and occurs in patients who frequently have comorbidities and desire outpatient therapy, less intensive treatment approaches are commonly adopted, most typically involving hypomethylating agents or low-dose cytarabine (LDAC) [3–6]. Over the past decade, attempts have been made to evoke initial deeper responses, delay relapse, and improve overall survival (OS) by com- bining hypomethylating agents or LDAC with other active drugs (e.g., glasdegib or venetoclax) [3, 6].

Glasdegib, an oral inhibitor of the Hedgehog (Hh) signal- ing pathway component Smoothened (SMO), is approved in Europe and the USA in combination with LDAC to treat patients with newly diagnosed AML not eligible to receive intensive chemotherapy due to comorbidities or age (≥ 75 years) [7, 8]. In a phase 2 randomized study that included patients with newly diagnosed AML or higher-risk MDS who were ineligible for intensive chemotherapy, the addition of glasdegib to LDAC demonstrated superior OS versus LDAC alone and was well tolerated [9]. Whether glasdegib would have the same safety and efficacy profile when combined with azacitidine, which is more commonly used in most areas of the world, and whether high-risk molecular subgroups could derive particular benefit from the combination, has not been determined.

This phase 1b study was designed to evaluate the safety and efficacy of glasdegib combined with azacitidine in patients with newly diagnosed AML, higher-risk MDS, and CMML who were not candidates for intensive induc- tion chemotherapy.

## Subjects and methods

### Study design and patients

BRIGHT 1012 MDS & AML (ClinicalTrials.gov NCT02367456) was a multicenter, open-label, phase 1b study of glasdegib + azacitidine in adult patients aged ≥ 18 years with newly diagnosed AML, higher-risk MDS, and CMML. The phase 1b trial consisted of a lead- in safety cohort and an expansion phase with AML and MDS cohorts.

The primary objective of the lead-in safety cohort was to assess the safety and tolerability of glasdegib in combination with azacitidine in patients with intermedi- ate-II or high-risk MDS per International Prognostic Scor- ing System (IPSS), AML with 20–30% blasts and multilin- eage dysplasia, and CMML. Diagnoses were determined according to the World Health Organization 2008 clas- sification [10]. Secondary endpoints included the rate of response and pharmacokinetics (PK).

The primary objective of the expansion phase was to determine the rate of complete remission (CR) in patients with previously untreated intermediate-, high-, or very high- risk MDS per revised IPSS (IPSS-R), AML, and CMML (World Health Organization 2016 classification) for whom the risk/benefit profile of intensive chemotherapy was unacceptable per investigator decision [11, 12]. Secondary endpoints included time to CR, duration of CR, disease- specific efficacy measures, OS, safety and tolerability, and PK. Exploratory analyses included pharmacodynamics, bio- marker assessments, patient-reported outcomes (PROs), and the rate and duration of transfusion independence.

In the lead-in safety cohort and expansion phase, patients with AML were eligible for treatment if they were not can- didates for first-line intensive induction chemotherapy. Prior therapy with an SMO inhibitor or hypomethylating agent was not permitted.

The study was conducted in accordance with the Decla- ration of Helsinki. All patients provided written informed consent before study procedures began, and the protocol was approved at each study site according to local regula- tions (see Online Resource, Supplementary Methods). This analysis was based on the primary completion date (January 29, 2020).

**Study treatment**

Glasdegib 100 mg once daily was administered orally in 28-day cycles on a continuous basis, and azacitidine was administered subcutaneously or intravenously (expansion phase only) at a dose of 75 $mg/m^2$/day on days 1–7 of a 28-day cycle. Treatment was continued for a minimum of 6 cycles, or until disease progression, unacceptable toxicity, death, or patient refusal. Treatment was continued beyond 6 cycles if a clinical benefit was demonstrated (see Supple- mentary Methods).

**Assessments**

Response to treatment was evaluated using the 2006 Inter- national Working Group modified response criteria for all patients in the safety lead-in cohort and in the MDS and CMML expansion cohorts. The 2017 European Leukemi- aNet (ELN) response criteria were applied to patients in the AML expansion cohort (see Supplementary Methods) [13, 14]. Patient blood samples were collected for PK analysis of glasdegib at protocol-defined time points. In the lead-in safety cohort, glasdegib treatment started on cycle 1, day 2 to permit drug–drug interaction evaluation.

Safety assessments included adverse events (AEs), classified and graded based on the National Cancer Institute Common Ter- minology Criteria for AEs v4.03, laboratory evaluations, vital signs, physical examinations, and 12-lead electrocardiograms.

**Statistical analysis**

Twelve patients were included in the lead-in safety cohort, which provided ≥ 80% probability to observe ≥ 1 AE if the true incidence of the AE in the population was ≥ 15%. In the expansion phase, a total of 30 patients each were enrolled in the MDS and AML cohorts, which provided the maximum width of the exact 2-sided 95% confidence interval (CI) for CR of ≤ 0.374 in each cohort. The full safety and efficacy analysis set included all enrolled patients who received ≥ 1 dose of study medication. The PK analysis population included all treated patients who had ≥ 1 PK parameter

estimated. The biomarker analysis population included all treated patients evaluable for baseline and post-baseline mutational status. Descriptive statistics were used through- out the study unless otherwise stated. Time-to-event end- points were summarized using the Kaplan–Meier method. Median event times and 2-sided 95% CIs were included.

## Results

### Disposition, demography, and baseline characteristics

A total of 72 patients were treated with glasdegib + azac- itidine across the study phases: 12 patients in the lead-in afety cohort, and 30 patients in each of the AML and MDS (including 3 patients with CMML) cohorts of the expan- sion phase. In the lead-in safety, AML, and MDS cohorts, respectively, the median (range) age was 72 (59–89), 74 (56–87), and 72 (55–89) years; 58.3%, 60.0%, and 80.0% of patients were male. Patient demographic and baseline characteristics are summarized in the Online Resource, Table S1. As of the data cutoff, 100%, 93.3%, and 86.7% of patients in the lead-in safety, AML, and MDS cohorts, respectively, had discontinued glasdegib and/or azacitidine treatment (Table S2).

### Lead-in safety cohort

In the lead-in safety cohort, the median (range) treatment duration was 2.7 months (0.8–14.0); the median (range) exposure to both glasdegib and azacitidine was 3.5 cycles (1–15). Any-grade all-causality treatment-emergent AEs (TEAEs) occurred in 100% (maximum Grade 3/4, 66.7%) of patients in the lead-in safety cohort (Table 1). The most frequently (≥ 30%) reported TEAEs were predomi- nantly gastrointestinal, hematologic, and Hh-inhibitor class effects (e.g., muscle spasms, dysgeusia, alopecia, weight loss) (Table S3). Serious AEs were reported by 9 patients (75.0%); 7 patients (58.3%) had serious AEs con- sidered to be treatment related (per investigator's assess-ment), of which none were reported in > 1 patient except for febrile neutropenia (4 patients [33.3%]). Six patients (50.0%) permanently discontinued study treatments due to AEs, with 4 patients (33.3%) discontinuing both glas- degib and azacitidine. One patient permanently discontin- ued glasdegib treatment due to glasdegib-related muscle spasms. Eight patients (66.7%) temporarily discontin- ued or reduced the dose of glasdegib and/or azacytidine due to AEs. Nine patients (75.0%) died, the major cause being the disease under study (41.7%). No patients died within 30 days after the first dose of study treatment; 1 patient (8.3%) died within 60 days of the first dose of study treatment.

### Expansion phase

In the AML and MDS cohorts, respectively, the median (range) treatment duration was 5.0 months (0.3–20.2) and 4.7 months (0.4–16.4); the median (range) exposure of glasdegib and azacitidine was 5 cycles (1–19) and 5 cycles (1–16). Any-grade all-causality TEAEs occurred in 100% (maximum Grade 3/4, 66.7%) of patients in the AML cohort and 100% (maximum Grade 3/4, 80.0%) of patients in the MDS cohort (Table 1; Online Resource Tables S4 and S5). The most frequently (≥ 10%) reported non-hematologic Grade ≥ 3 TEAEs were decreased appe- tite (20.0%), electrocardiogram QT prolongation (10.0%), and hypertension (10.0%) in the AML cohort; and sepsis (20.0%), diarrhea (10.0%), hypotension (10.0%), pneu- monia (10.0%), and hyperglycemia (10.0%) in the MDS cohort. The most frequently (≥ 5%) reported non-hema- tologic serious AEs were pyrexia (13.3%), electrocardio- gram QT prolongation (6.7%), and urinary tract infection (6.7%) in the AML cohort, and sepsis (16.7%) and pyrexia (6.7%) in the MDS cohort.

Eleven patients (36.7%) in the AML cohort and 10 (33.3%) in the MDS cohort permanently discon-tinued study treatments due to AEs, with 9 patients (30.0%) in each cohort discontinuing both glasdegib and azacitidine. While no patients in the AML cohort discontinued glasdegib because of AEs associated with the inhibition of the Hh signaling pathway in normal tissues, two patients in the MDS cohort did perma- nently discontinue both glasdegib and azacitidine due to dysgeusia. Both AEs were considered associated with glasdegib/Hh-related signaling pathway AEs in normal tissues. In the AML and MDS cohorts, respec- tively, 19 (63.3%) and 21 (70.0%) patients temporarily discontinued or reduced the dose of glasdegib and/or azacitidine due to AEs.

Six (20.0%) and 3 (10.0%) patients in the AML and MDS cohorts, respectively, had electrocardiogram QT prolongation, 5 (16.7%) and 2 (6.7%) of which were con- sidered to be treatment related; 1 (3.3%) in each cohort was considered to be related to concomitant drug treat- ment. Glasdegib was temporarily discontinued or the glasdegib dose was reduced due to electrocardiogram QT prolongation in 5 (16.7%) and 2 (6.7%) patients in the AML and MDS cohorts, respectively. None of the elec- trocardiogram QT prolongations resulted in permanent treatment discontinuation.

## Efficacy

### Lead-in safety cohort

Of the 12 patients in the lead-in safety cohort, 3 patients with AML (25.0%) achieved CR, 2 patients with MDS (16.7%) achieved marrow CR, and hematologic improvement of ≥ 1 lineage was observed in 6 patients (50.0%).

### Expansion phase

The overall response rate was 30.0% in the AML cohort (defined as CR + CR with incomplete hematologic recov- ery + partial remission), and 33.3% in the MDS cohort (defined as CR + partial remission + hematologic improve- ment). An additional 3.3% of patients in the AML cohort achieved a morphologic leukemia-free state, and 15.7% of patients in the MDS cohort achieved a marrow CR. Six patients (20.0%) in the AML cohort and 4 (13.3%) in the MDS cohort achieved CR. Best overall response with other outcomes of interest for patients in the AML and MDS cohorts are summarized in Table 2. For patients in the AML and MDS cohorts, respectively, the median (range) time to response was 0.5 months (0.23–3.12) and 0.6 months (0.20–2.69); median (range) duration of response was 5.2 months (0.03–14.13) and 6.2 months (0.03–21.03).

In the AML and MDS cohorts, respectively, median (range) follow-up for OS was 8.5 months (0.8–20.4) and 12.9 months (0.5–22.0), with 22 (77.3%) and 15 (50.0%) patients known to have died by the time of data cutoff. In both cohorts, the main cause of death was the disease under study or complications of the disease related to bleeding or infections. Of the patients in the AML and MDS cohorts, respectively, 3 (10.0%) and 1 (3.3%) died within 30 days of the first dose of study treatment, and 6 (20.0%) and 1 (3.3%) died within 60 days. In the AML cohort, median OS was 9.2 (95% CI 6.2–14.0) months (Fig. 1a). The median OS (95% CI) in patients with favorable/intermediate, adverse, and unknown ELN genetic risk was 14.0 (7.7–not evaluable [NE]), 5.3 (1.6–10.5), and 8.2 (NE–NE) months, respec- tively (Fig. 1b). In the MDS cohort, the median OS was 15.8 (95% CI 9.3–21.9) months (Fig. 1c). The median (95% CI) OS in patients with intermediate, high, and very high IPSS- R genetic risk was 21.9 (NE–NE), NE (4.7–NE), and 12.1 (0.5–17.5) months, respectively (Fig. 1d).

In both the AML and MDS cohorts, bone marrow recovery of absolute neutrophil count, hemoglobin, and platelet counts at 2 thresholds was seen following glasdegib + azacitidine treatment, regardless of baseline counts (Table 3). Recovery occurred as early as cycle 1 in a meaningful proportion of patients. In the MDS cohort, early platelet recovery corre- lated with response to treatment; 54.0% ($n$ = 7/13) of patients with platelets ≥ 100,000/μL at cycle 2, day 1 achieved com- plete or partial remission versus 0.0% ($n$ = 0/13) of patients with < 100,000/μL, $P$ = 0.002. Transfusion independence was achieved by 47.4% of patients ($n$ = 9/19) in the AML cohort and 46.7% of patients ($n$ = 7/15) in the MDS cohort who were transfusion-dependent at baseline (Table 3); the median (range) duration of independence was 5.1 (1.9–17.4) and 4.8 (2.0–14.4) months, respectively.

## Pharmacokinetics

A summary of PK parameters for glasdegib and azaciti- dine from the lead-in safety cohort, when dosed alone or in combination, are presented in the Online Resource, Tables S6 and S7. There was no evidence of change in area under the concentration–time curve (AUC) or maxi- mum plasma concentration ($C_{max}$) of either glasdegib or azacitidine when dosed in combination. Glasdegib plasma concentration data for patients in the AML and MDS cohorts are provided in the Online Resource, Supplemen- tary Results 1.

## Biomarkers

### Gene mutations that correlate with overall survival and response

Whole-exome sequencing was performed using bone mar- row aspirate samples from 26 patients in the AML cohort and 23 patients in the MDS cohort. The primary analysis focused on 115 genes with a known role in AML/MDS or the Hh signaling pathway, although an analysis of all genes was performed. Of the 115 genes of interest, those with a mutation frequency of > 10% are shown in Fig. 2: the most common (> 20%) were *TET2* (35%), *ASXL1* (29%), *SMO* (27%), *TP53* (27%), *GBP4* (25%), *DNMT3A* (21%), and *RUNX1* (21%). While 13 patients (27.0%) had a *SMO* mutation, none of these mutations were in regions previ- ously identified as playing a role in resistance to SMO inhibitors. Twelve of the 13 patients had a D25G nonsyn- onymous germ-line variant, including one patient who also had a somatic R173H mutation in the Frizzled domain. One patient had a somatic P698R *SMO* mutation alone. Neither of these somatic mutations were previously described to be involved in mediating resistance to SMO inhibitors. Among patients in the AML cohort, of all the genes iden- tified with a mutation at baseline, only 31 genes (with ≥ 4 mutations) showed a significant association with OS ($P < 0.05$) (Online Resource Table S8). Of the 115 genes previously implicated in AML/MDS or the Hh signaling pathway, improved OS was only found to correlate with mutations in *FLT3* (mutated vs wild-type, hazard ratio [HR] 0.20 [95% CI 0.04–0.93]; $P = 0.039$; Fig. 3a). We detected *FLT3* mutations in 6/26 patients (23.1%) in the AML cohort, which is similar to the previously reported rate of 20–30% in patients with AML [15]. Three were tyrosine kinase domain mutations, and 2 were *FLT3* internal tandem duplication (*FLT3*-ITD). Additionally, these patients were classified as adverse ($n = 3$) and intermediate ($n = 3$) ELN risk. Of these 6 patients, with a median age of 77.5 years, the median OS was not reached even after 20 months, and 2 patients (33.3%) achieved a CR. Five of the 6 patients were categorized as de novo AML (Table S9). Among patients in the MDS cohort, mutations in only 8 genes (with ≥ 4 mutations) were found to correlate with OS (Table S10). Of these genes, *TP53* was the only gene known to be directly associated with AML/MDS or the Hh signaling pathway and was associated with worse OS (mutated vs wild-type, HR 4.45 [95% CI 1.24–16.01]; $P = 0.022$) (Fig. 3b). *TP53* mutations occurred in 4/22 patients (18.2%) in the MDS cohort, which is similar to the previously reported rate of 13% in patients with MDS [16]. Mutations in the Hh signaling pathway did not cor- relate with OS in patients in the AML or MDS cohorts. We also observed mutations in other genes that correlate with OS (e.g., CYP2D6), although the functional relation- ship of these genes remains to be determined. The effect of baseline mutations on response (defined as CR) are reported in the Online Resource, Table S11; no correlation with any genes associated with the Hh pathway or the development of AML or MDS was determined.

### Molecular clearance of mutations in paired samples in patients who achieve CR

Molecular clearance of mutations at CR was analyzed in 6 patients in the AML cohort and 3 patients in the MDS cohort. Of the 115 genes of interest, Table 4 shows mutations that were detected at baseline (variant allele frequency [VAF] ≥ 0.05) in each of these patients, and that were found to be significantly reduced or cleared (VAF < 0.05) at CR. Online Resource Fig. S1 shows mutations in all of the genes that displayed a ≥ threefold decrease or increase in VAF when patients achieved CR and when they subsequently relapsed (i.e., bone marrow blast > 5%). Three of the 4 patients with an *FLT3* muta- tion at baseline cleared their *FLT3* mutation at CR; the 1 instance where *FLT3* was not cleared was in a patient with AML who had a *V194M* mutation, and it is not clear if this

mutation is functionally relevant to driving *FLT3* activa- tion (data suggest it is a VUS [variant of unknown sig- nificance]). Additionally, this patient had a well-described *IDH1* (R132C) mutation that was effectively cleared by glasdegib + azacitidine. In the 3 cases where *FLT3* muta- tions were cleared, these were an *FLT3* (N676S) and an *FLT3*-ITD mutation in patients with AML, and an *FLT3* (D835E) mutation in a patient with MDS who achieved CR. Additional data regarding the clearance of mutations in patients who achieved CR are provided in the Online Resource, Supplementary Results 2.

### Gene expression signatures correlate with overall survival

Gene expression was assessed using bone marrow aspirate samples. Gene expression signatures indicated that genes associated with cell cycle are indicative of a poorer OS in patients with AML,

whereas those associated with immune/ interferon pathways correlate with improved OS (Online Resource Figs. S2 and S3). These gene expression signa- tures did not correlate with OS in patients with MDS (Figs. S4 and S5).

### Cytokine levels in the AML and MDS cohorts

Of evaluable patients with AML, correlation of OS and response with baseline serum cytokine levels identified that lower levels of interleukin (IL)-1 receptor antago- nist and IL-18 correlated with improved OS with glas- degib + azacitidine (Online Resource, Table S12), and that lower levels of brain-derived neurotrophic factor correlated with achieving CR (Table S13). A significant decrease in monocyte chemotactic protein 1 was observed when baseline cytokine levels were compared with those at end of treatment (ratio relative baseline 2.43; $P = 0.023$); no differences in cytokine levels were observed at cycle 2, day 1. Of evaluable patients with MDS, correlation of OS and baseline cytokine levels identified that higher levels of eotaxin-1, factor VII, IL-1β, IL-15, and macrophage inflam- matory protein 1β correlated with improved OS (Table S12). There were no correlations with baseline cytokine levels and response, nor were there any correlations with cytokine lev- els at cycle 2, day 1, or end of treatment and response.

### Patient-reported outcomes

Health-related quality of life (HRQoL) was measured by the MD Anderson Symptom Inventory for acute myeloid leukemia/myelodysplastic syndrome, Patient Global Impres- sion of Severity, and Patient Global Impression of Change; in both the AML and MDS cohorts, PROs remained stable over time (Online Resource Figs. S6–S8).

## Discussion

This phase 1b study demonstrated that the addition of glas- degib to azacitidine was generally well tolerated and man- ageable for patients with newly diagnosed AML, higher-risk MDS, or CMML who are not candidates for intensive induc- tion chemotherapy. Clinical efficacy, as reflected by overall response rate and transfusion independence, was achieved in patients with AML and patients with MDS receiving glasdegib + azacitidine. Furthermore, a clinical benefit was demonstrated across groups when stratified by genetic risk, and was associated with molecular mutation clearance and with a signal for improved outcomes in patients with AML who had an *FLT3* mutation. The safety data were consistent with the known safety profiles of glasdegib, azacitidine monotherapy, and other SMO inhibitors [9, 17–20]. In the current study, treatment discontinuation due to AEs associated with inhibition of the Hh signaling pathway in normal tissues (e.g., muscle spasms, myalgia, and dysgeusia) while infrequent, did occur in a total of three patients across study phases (4.2%). In the lead-in safety cohort, there was no evidence of potential for drug–drug interaction between glasdegib and azacitidine, as the exposure parameters (AUC and $C_{max}$) for both drugs were similar when dosed alone or in combination. While comparisons between trials should be considered with caution, in the context of the patient population and duration of follow-up, the response rate and median OS in the AML and MDS cohorts were at least comparable with those previously reported for azacitidine monotherapy. In a phase 3 trial investigating the effects of azacitidine mono- therapy in patients with AML, the rate of CR was 19.5% and the median OS was 10.4 months after a median follow-up of 24 months [20]. In a study of patients with higher-risk MDS and CMML, the overall response rate (CR + partial remis- sion + hematologic improvement) was 38.0% and the median OS was 15 months after a median follow-up of 23 months [21]. In addition, the median OS for glasdegib + azacitidine is equivalent to or possibly higher than what was reported previously for glasdegib + LDAC (AML, 8.3 months; MDS, 10.9 months) and therefore appears to be a reasonable alter- native combination [9]. Mutations in *FLT3*, which are commonly associated with a poor prognosis in patients with AML, were associated in these patients with significantly improved OS following treat- ment with glasdegib + azacitidine [22]. Together with results from the BRIGHT AML & MDS 1003 study in patients with AML eligible for intensive chemotherapy receiving glas- degib + cytarabine + daunorubicin on a 7 + 3 schedule, these studies suggest that combining glasdegib with 7 + 3 or with azacitidine enhances survival of patients with mutations in *FLT3* [23]. Due to small sample sizes and the exploratory nature of the biomarker analyses, additional verification of these findings in larger randomized trials would be of interest. Of the 3 patients in the AML and MDS cohorts who had an *FLT3* mutation at baseline and achieved CR, *FLT3* mutations were cleared (VAF < 0.05) in all the patients at CR. One of these

patients subsequently relapsed and had a bone mar- row aspirate sample that could be used for analysis and, at relapse, the VAF of the *FLT3* mutation increased, suggesting that clones containing this mutation were not fully cleared at CR. Our observations that some mutations are either fully or partially cleared at CR, but then some of these reappear at relapse, suggest that glasdegib plus azacitidine does not completely clear these mutations from the bone marrow, but rather these mutations persist and may drive relapse. A previous study in patients with AML demonstrated that the expression of *GLI2*, a major signaling component of the Hh signaling pathway, was increased in the bone marrow of patients with *FLT3*-ITD mutations versus those with wild-type *FLT3* [24]. Using a transgenic mouse model, the authors dem- onstrated that *FLT3*-ITD expression and constitutive Hh signal- ing resulted in enhanced STAT5 signaling and the proliferation of bone marrow myeloid progenitors. The combined inhibition of FLT3 and the Hh pathway reduced leukemic growth both in vitro and in vivo [24]. Together, these results suggest that *FLT3* and Hh signaling cooperate to promote the development of AML, possibly explaining why the inhibition of Hh signaling in the context of *FLT*3 mutation may improve OS. In both the AML and MDS cohorts, treatment with glas- degib + azacitidine did not negatively impact patient HRQoL as measured by several PROs. A recent study in patients with AML and patients with MDS who were ineligible for intensive chemotherapy demonstrated that a negative impact on HRQoL was the most cited reason for a patient refusing certain treatments [25].

Another important finding of this analysis is that patients receiving glasdegib + azacitidine demonstrated early marrow recovery as evidenced by absolute neutro- phil count, hemoglobin, and platelet recoveries beginning in cycle 1. More than half of evaluable patients who were transfusion dependent at baseline became transfusion independent. Few patients required cycle 2 dose delays due to AEs. In contrast, venetoclax + azacitidine is asso- ciated with prolonged cytopenias, with thrombocytopenia (45.0% of patients) and neutropenia (42.0% of patients) indicated as the primary toxicities reported with the treat- ment combination [26]. Dose interruptions, including dose delays between treatment cycles, were frequently required to allow for hematologic recovery in patients with a response following venetoclax + azacitidine.

In conclusion, this analysis of the BRIGHT AML & MDS 1012 study in patients with newly diagnosed AML, higher-risk MDS, or CMML showed glasdegib + azaciti- dine to be generally well tolerated, with a manageable safety profile consistent with toxicities associated with azacitidine monotherapy and other marketed inhibitors of the Hh signaling pathway. Clinical benefit was observed in both patients with AML and MDS who received glas- degib + azacitidine. Patients with AML and *FLT3* muta- tions had improved OS compared with those who were wild-type for *FLT3*. These data suggest that further stud- ies of glasdegib + azacitidine in patients with higher- risk MDS and AML harboring *FLT3* mutations may be warranted.

**Supplementary Information** The online version contains supplemen- tary material available at https://doi.org/10.1007/s00277-022-04853-4.

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**Author contribution** M. A. S., A. M. Z., and G. C. conceived and designed the study. M. A. S., M. S., M. J., J. K., J. M., D. B., E. G., T. K., A. V., P. V., E. S. W., and A. M. Z. recruited the patients and col- lected the data. All authors analyzed and interpreted the data, wrote the manuscript, and approved the final version of the manuscript.

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**Data availability** Upon request, and subject to review, Pfizer will pro- vide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

**Declarations**

**Ethics approval** The study was conducted in accordance with the Dec- laration of Helsinki. All patients provided written informed consent before study procedures began, and the protocol was approved at each study site according to local regulations.

**Conflict of interest** M. A. S.: consulting or advisory role (Celgene, Millennium, Syros Pharmaceuticals), research funding (Pfizer, Take- da). M. S., M. J., J. M., D. B., and T. K.: no disclosures. J. K.: consult- ing or advisory role (Amgen, Astellas Pharma, Bristol Myers Squibb, Daiichi Sankyo, Pfizer), honoraria (Amgen, Astellas Pharma, Bris- tol Myers Squibb, Daiichi Sankyo, Pfizer). E. G.: honoraria (Pfizer, Bristol Myers Squibb/Celgene). A. V.: stock (Stelexis Therapeutics), honoraria (Acceleron Pharma, Celgene, Stelexis Therapeutics), re- search funding (Bristol Myers Squibb, Janssen Oncology). P. V.: stock (OxStem), honoraria (AbbVie, Celgene, Daiichi Sankyo, Jazz Phar- maceuticals, Pfizer), research funding (Celgene, Forty Seven). E. S. W.: advisory boards (AbbVie, Astellas, Bristol Myers Squibb/Celgene, Genentech, GlaxoSmithKline, Jazz Pharmaceuticals, Kite Pharmaceu- ticals, Kura Oncology, Novartis, Pfizer, Stemline, Takeda), consulting (Mana Therapeutics), speaker (Stemline, Kura, Pfizer, Dava Oncol- ogy), data safety monitoring committees (AbbVie, Rafael Pharmaceu- ticals). K. C., T. O.'B., C. G. S., W. W. M., A. K., and G. C.: employ- ees of Pfizer, own stock in Pfizer. A. M. Z.: honoraria (Boehringer Ingelheim, Bristol Myers Squibb, Cardinal Health, Celgene, Daiichi Sankyo, Epizyme, Incyte, Ions Pharmaceuticals, Jazz Pharmaceuti- cals, Novartis, Otsuka, Pfizer, Seattle Genetics, Taiho Pharmaceutical, Takeda, Trovagene), consulting or advisory role (AbbVie, Acceleron Pharma, Agios, Astellas Pharma, BeyondSpring Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Cardinal Health, Cel- gene, Daiichi Sankyo, Epizyme, Incyte, Ions Pharmaceuticals, Jazz Pharmaceuticals, Novartis, Otsuka, Pfizer, Seattle Genetics, Taiho Pharmaceutical, Takeda, Trovagene), research funding (AbbVie, ADC Therapeutics, Aprea AB, Astex Pharmaceuticals, AstraZeneca/Med- Immune, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, In- cyte, Novartis, Pfizer, Takeda, Trovagene).

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**Table 1** TEAEs (all causalities) in the lead-in safety, AML, and MDS cohorts

| | Lead-in safety cohort ($n=12$) | AML cohort ($n=30$) | MDS cohort ($n=30$) |
|---|---|---|---|
| AEs | 12 (100) | 30 (100) | 30 (100) |
| Serious AEs | 9 (75.0) | 24 (80.0) | 18 (60.0) |
| Grade 3 or 4 AEs | 8 (66.7) | 20 (66.7) | 24 (80.0) |
| Grade 5 AEs | 2 (16.7) | 8 (26.7) | 4 (13.3) |
| Discontinued glasdegib due to AEs | 6 (50.0) | 10 (33.3) | 10 (33.3) |
| Discontinued azacitidine due to AEs | 4 (33.3) | 10 (33.3) | 9 (30.0) |
| Glasdegib dose reduced or temporarily discontinued due to AEs | 8 (66.7) | 19 (63.3) | 19 (63.3) |
| Azacitidine dose reduced or temporarily discontinued due to AEs | 4 (33.3) | 10 (33.3) | 16 (53.3) |

All data given as *n* (%)

*AE* adverse event, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndromes, *TEAE* treatment-emergent adverse event

**Table 2** Investigator-reported best overall response for patients in the AML and MDS cohorts

| Best overall response, *n* (%) | | | | |
|---|---|---|---|---|
| AML cohort | All patients ($n=30$) | Favorable/intermediate[a] ($n=11$) | Adverse risk[a] ($n=18$) | Unknown[a] ($n=1$) |
| CR | 6 (20.0) | 3 (27.3) | 3 (16.7) | 0 |
| CRi | 1 (3.3) | 1 (9.1) | 0 | 0 |
| CR + CRi | 7 (23.3) | 4 (36.4) | 3 (16.7) | 0 |
| PR | 2 (6.7) | 1 (9.1) | 1 (5.6) | 0 |
| MLFS | 1 (3.3) | 0 | 1 (5.6) | 0 |
| SD | 6 (20.0) | 3 (27.3) | 2 (11.1) | 1 (100) |
| PD | 4 (13.3) | 1 (9.1) | 3 (16.7) | 0 |
| Treatment failure | 1 (3.3) | 1 (9.1) | 0 | 0 |
| Not evaluable | 9 (30.0) | 1 (9.1) | 8 (44.4) | 0 |
| MDS cohort | All patients ($n=30$) | Intermediate risk[b] ($n=3$) | High risk[b] ($n=15$) | Very high risk[b] ($n=9$) |
| CR | 4 (13.3) | 0 | 3 (20.0) | 0 |
| PR | 3 (10.0) | 0 | 1 (6.7) | 1 (11.1) |
| HI without CR or PR | 3 (10.0) | 0 | 2 (13.3) | 1 (11.1) |
| CR + PR + HI without CR or PR | 10 (33.3) | 0 | 6 (40.0) | 2 (22.2) |
| mCR | 5 (16.7) | 0 | 2 (13.3) | 2 (22.2) |
| SD | 8 (26.7) | 2 (66.7) | 4 (26.7) | 2 (22.2) |
| CR + PR + mCR + SD | 20 (66.7) | 2 (66.7) | 10 (66.7) | 5 (55.6) |
| Treatment failure | 3 (10.0) | 0 | 2 (13.3) | 1 (11.1) |
| Not evaluable | 7 (23.3) | 1 (33.3) | 3 (20.0) | 3 (33.3) |

*AML* acute myeloid leukemia, *CR* complete remission, *CRi* complete remission with incomplete hematologic response, *ELN* European LeukemiaNet, *HI* hematologic improvement, *IPSS-R* revised International Prognostic Scoring System, *mCR* marrow complete remission, *MDS* myelodysplastic syndromes, *MLFS* morphologic leukemia-free state, *PD* progressive disease, *PR* partial remission, *SD* stable disease

[a]ELN risk category[27]

[b]IPSS-R risk category for patients with MDS only[12]

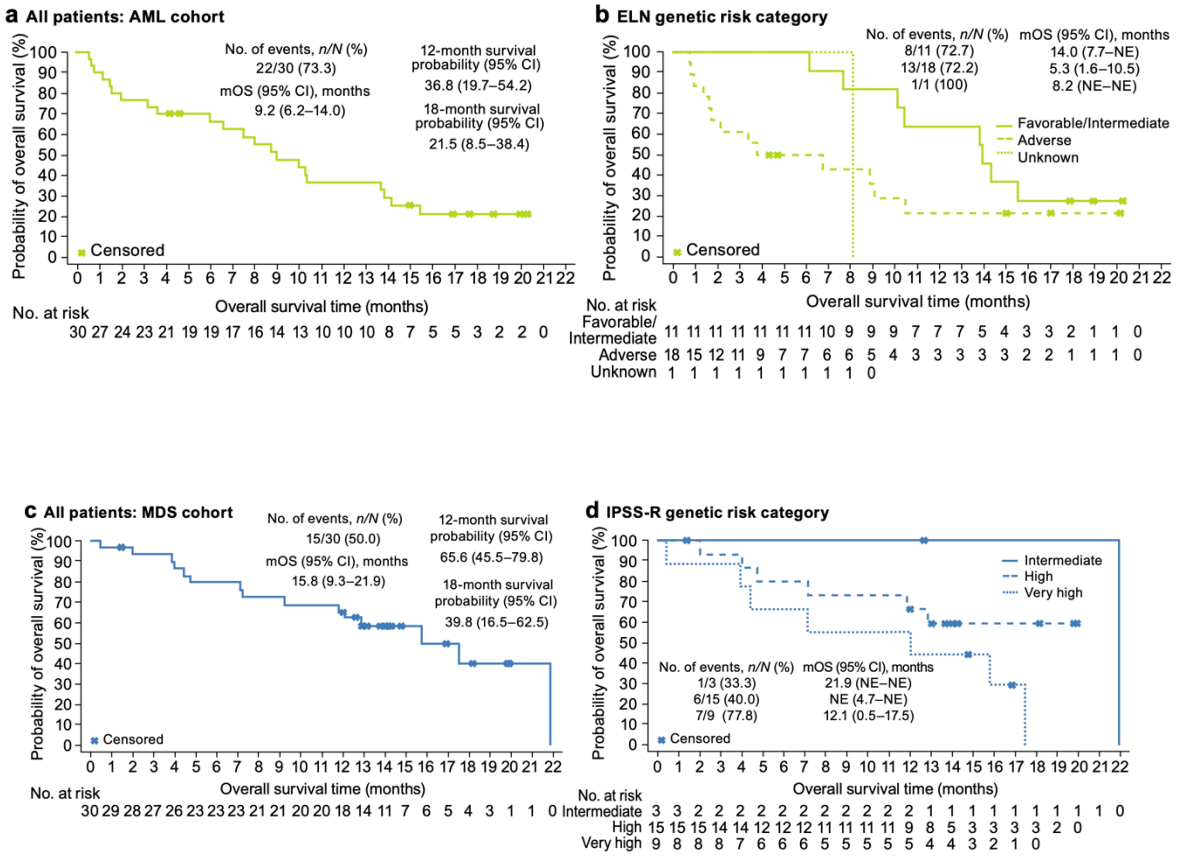


**Fig. 1** Kaplan–Meier estimated OS in the AML (**a** and **b**) and MDS (**c** and **d**) cohorts. *AML* acute myeloid leukemia, *ELN* European LeukemiaNet, *IPSS-R* revised International Prognostic Scoring System, *MDS* myelodysplastic syndromes, *mOS* median overall survival, *NE* not evaluable, *OS* overall survival

**Table 3** Recovery of ANC, hemoglobin, and platelets, and rates of transfusions in the AML and MDS cohorts

| | AML cohort Recovery threshold | | MDS cohort Recovery threshold | |
|---|---|---|---|---|
| ANC | ≥1000/μL | ≥500/μL | ≥1000/μL | ≥500/μL |
| | *n* = 30 | *n* = 30 | *n* = 28 | *n* = 28 |
| Recovery in all patients[a] | 19 (63.3) | 21 (70.0) | 16 (57.1) | 22 (78.6) |
| Achieved recovery during cycle 1 | 17 (56.7) | 21 (70.0) | 16 (57.1) | 21 (75.0) |
| | *n* = 14 | *n* = 10 | *n* = 15 | *n* = 7 |
| Recovery in patients with baseline ANC < threshold[a] | 7 (50.0) | 5 (50.0) | 5 (33.3) | 5 (71.4) |
| Achieved recovery during cycle 1 | 3 (21.4) | 3 (30.0) | 3 (20.0) | 1 (14.3) |
| Hemoglobin | ≥10 g/dL | ≥9 g/dL | ≥10 g/dL | ≥9 g/dL |
| | *n* = 30 | *n* = 30 | *n* = 29 | *n* = 29 |
| Recovery in all patients[a] | 11 (36.7) | 15 (50.0) | 13 (44.8) | 17 (58.6) |
| Achieved recovery during cycle 1 | 7 (23.3) | 21 (70.0) | 9 (31.0) | 18 (62.1) |
| | *n* = 25 | *n* = 19 | *n* = 22 | *n* = 15 |
| Recovery in patients with baseline hemoglobin < threshold[a] | 6 (24.0) | 5 (26.3) | 6 (27.3) | 6 (40.0) |
| Achieved recovery during cycle 1 | 4 (16.0) | 11 (57.9) | 3 (13.6) | 6 (40.0) |
| Platelets | ≥100,000/μL | ≥50,000/μL | ≥100,000/μL | ≥50,000/μL |
| | *n* = 30 | *n* = 30 | *n* = 29 | *n* = 29 |
| Recovery in all patients[a] | 14 (46.7) | 19 (63.3) | 15 (51.7) | 24 (82.8) |
| Achieved recovery during cycle 1 | 11 (36.7) | 17 (56.7) | 17 (58.6) | 24 (82.8) |
| | *n* = 25 | *n* = 16 | *n* = 21 | *n* = 7 |
| Recovery in patients with baseline platelets < threshold[a] | 10 (40.0) | 7 (43.8) | 9 (42.9) | 4 (57.1) |
| Achieved recovery during cycle 1 | 7 (28.0) | 3 (18.8) | 9 (42.9) | 4 (57.1) |
| Transfusion independence rates[b] | *n* = 19 | | *n* = 15 | |
| Patients with transfusion dependence at baseline | 9 (47.4) | | 7 (46.7) | |
| Median duration of independence | 154 (58–528) | | 145 (61–438) | |

Data given as *n* (%) except median duration of independence, given as days (range)

*AML* acute myeloid leukemia, *ANC* absolute neutrophil count, *MDS* myelodysplastic syndromes

[a]Required measurement at ≥ 2 consecutive visits

[b]Required no packed red blood cell or platelet transfusions for ≥ 8 weeks

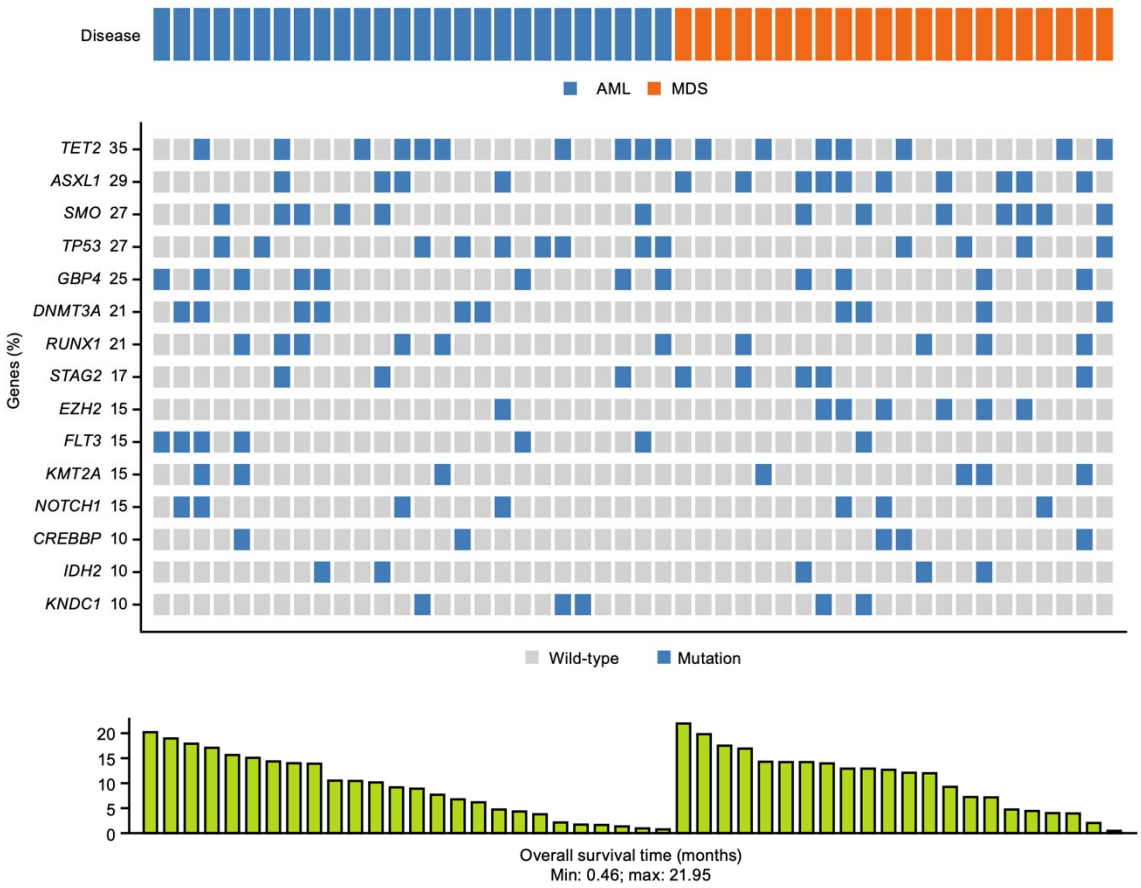


**Fig. 2** Baseline mutations occurring in > 10% of patients with AML and MDS. *AML* acute myeloid leukemia, *MDS* myelodysplastic syndromes

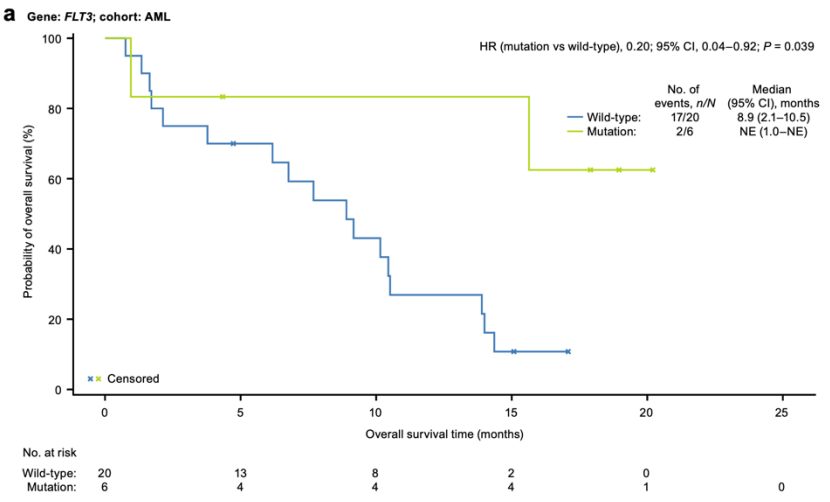


**Fig. 3** Biomarker correlation with OS in patients with (**a**) AML and (**b**) MDS. *AML* acute myeloid leukemia, *CI* confidence interval, *HR* hazard ratio, *MDS* myelodysplastic syndromes, *NE* not evaluable, *OS* overall survival

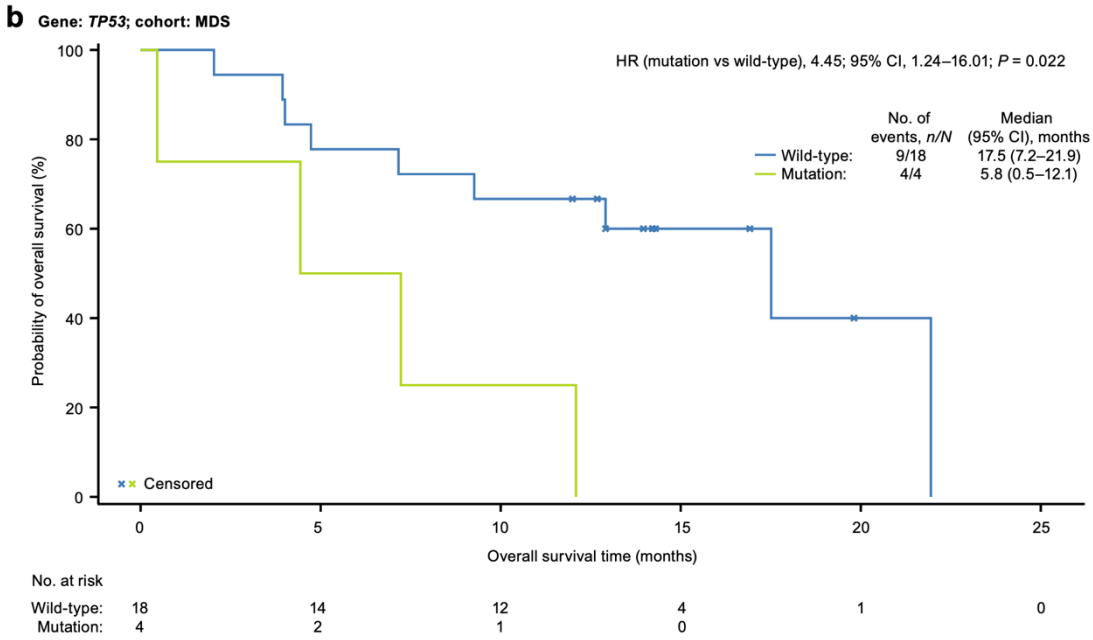


**Table 4** Mutations cleared (VAF < 0.05) at response in patients with AML and MDS

| | Best overall response | Pathway mutations at screening | Mutations cleared at best overall response (VAF at screening) | Additional information |
|---|---|---|---|---|
| Patients with AML | | | | |
| Patient 1 | CR MRD− | *GBP4*, *IDH1*, *FLT3* | *IDH1* (0.23), *GBP4* (0.81) | *IDH1* = R132C |
| Patient 3 | CR MRD− | *GDP4*, *KMT2A*, *NOTCH1*, *ETV6*, *TET2*, *DNMT3A*, *FLT3*, *NPM1* | *DNMT3A* (0.25), *FLT3* (0.22), *NPM1* (0.20), *TET2* (0.43) | |
| Patient 6 | CR | *CREBBP*, *FLT3*, *MECOM*, *RUNX1* | *FLT3* (0.20) | |
| Patient 7 | CR MRD+ | *AKT1*, *ASXL1*, *ANKRD26*, *CDH24*, *EZH2*, *GLI3*, *NCOA7*, *NOTCH1*, *TP53* | None | *EZH2* increased (0.13 to 0.29) |
| Patient 8 | CR MRD+ | *CARD11*, *CDRH2*, *TET2*, *WT1* | *WT1* (0.22) | |
| Patient 9 | CR MRD+ | *ETV6*, *GLI2*, *IMPG2*, *PRAM1*, *SMO* | *ETV6* (0.22) | |
| Patients with MDS | | | | |
| Patient 1 | mCR | *ASXL1*, *EZH2*, *SMO*, *TP53* | *EZH2* (0.78), *TP53* (0.77) | *EZH1* = Q612; *TP53* = R282W, decreased VAF for SMO (0.91 to 0.54) |
| Patient 2 | CR | *DNMT3A*, *FLT3*, *KNDC1*, *LTA4H*, *NPM1*, *NUMA1*, *PLEKHH1*, *SMO* | *DNMT3A* (0.26), *FLT3* (0.14), *NPM1* (0.27) | |
| Patient 3 | CR | *BCOR*, *NUMA1*, *TET2*, *U2AF1* | None | Decreased VAF for *BCOR* (0.59 to 0.19), *NUMA* (0.46 to 0.08), and *U2AF1* (0.29 to 0.1) |

*AML* acute myeloid leukemia, *CR* complete remission, *mCR* marrow complete remission, *MDS* myelodysplastic syndromes, *MRD+* minimal residual disease—positive, *MRD* minimal residual disease—negative, *SMO* Smoothened, *VAF* variant allele frequency