### Title

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# A Phase 1 Study of the Pan-Bromodomain and Extraterminal Inhibitor Mivebresib (ABBV-075) Alone or in Combination With Venetoclax in Patients With Relapsed/Refractory Acute Myeloid Leukemia

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**BACKGROUND:** Acute myeloid leukemia (AML) is a heterogenous malignancy driven by genetic and epigenetic factors. Inhibition of bromodomain and extraterminal (BET) proteins, epigenetic readers that play pivotal roles in the regulation of genes relevant to cancer pathogenesis, constitutes a novel AML treatment approach. **METHODS:** In this first-in-human study of the pan-BET inhibitor mivebresib as monotherapy (MIV-mono) or in combination with venetoclax (MIV-Ven), the safety profile, efficacy, and pharmacodynamics of mivebresib were determined in patients with relapsed/refractory AML (ClinicalTrials.gov identifier NCT02391480). Mivebresib was administered at 3 monotherapy dose levels (1.5, 2.0, or 2.5 mg) or in combination with venetoclax (400 or 800 mg). **RESULTS:** Forty-four patients started treatment: of 19 who started MIV-mono, 5 went on to receive MIV-Ven combination therapy after disease progression and a washout period. Twenty-five patients started MIV-Ven, resulting in a total of 30 patients treated with the combination. The most common mivebresib-related treatment-emergent adverse events were dysgeusia (74%), decreased appetite (42%), and diarrhea (42%) in the MIV-mono group and decreased appetite (44%), vomiting (44%), and nausea (40%) in the MIV-Ven group. Serious adverse events occurred in 14 patients (74%) who received MIV-mono and in 22 patients (88%) who received MIV-Ven. In the MIV-mono group, responses were complete remission with incomplete blood count recovery in 1 patient and resistant disease in 15 patients. In the MIV-Ven group, responses were complete remission in 2 patients, partial remission in 2 patients, morphologic leukemia-free state in 2 patients, resistant disease in 12 patients, and aplasia in 1 patient. The pharmacodynamic effects of mivebresib were proportional to dose and drug exposure. **CONCLUSIONS:** Mivebresib was tolerated and showed antileukemic effects as monotherapy and in combination with venetoclax in patients with relapsed/refractory AML. ***Cancer* 2021;127:2943-2953**. 

**LAY SUMMARY:**

Mivebresib is a novel drug that influences the way cancer cells read genetic information. Mivebresib was tested together with venetoclax in patients with acute myeloid leukemia after standard medicines failed and the disease returned, or when standard medicine was unavailable. Adverse effects were described for different drug doses, and the dose that is tolerable was determined. In some patients, their leukemia improved for some time. More studies are necessary to determine whether mivebresib can be used to treat acute myeloid leukemia.

**KEYWORDS:** ABBV-075, acute myeloid leukemia, bromodomain and extraterminal domain protein, mivebresib, phase 1 clinical trial.

## INTRODUCTION

Despite mounting knowledge of the molecular pathogenesis of acute myeloid leukemia (AML), overall survival (OS) rates remain low, particularly for patients who have relapsed/refractory (R/R) disease. The 5-year OS rate is approximately 40% for newly diagnosed patients aged <60 years and <20% for those aged ≥60 years.[1,2] Genetic and epigenetic alterations that accumulate with age may partially explain the low rate of survival in elderly patients with AML.[1]

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Bromodomain and extraterminal (BET) family proteins are key epigenetic readers that bind to acetylated lysine found on histone tails,[3] forming transcriptional complexes that drive the expression of key oncogenes, such as *c-Myc* and *IL7R*.[4-6] BRD4 is critical for tumor maintenance in AML[7]; BET inhibitors (BETis) are known to target aberrant BRD4-dependent transcription in AML.[8] BETis also blunt the production of cytokines and chemokines that are pivotal in maintaining the tumor microenvironment.[9] In patient-derived AML cells, BETis cause apoptosis by the downregulation of BCL-$X_L$, the potential downregulation of BCL-2, and the upregulation of BIM/PUMA.[5] Therefore, targeting BET family proteins may inhibit AML tumor activity. The phase 1 study of BETi OTX015 demonstrated clinical activity and a manageable safety profile in patients with R/R AML (ClinicalTrials.gov identifier NCT01713582).[10]

Mivebresib (ABBV-075) is an oral, potent, small-molecule BETi that induces apoptosis in culture and tumor regression in animal models of AML, multiple myeloma, KRAS-mutant lung cancer, prostate cancer, and breast cancer.[5,11,12]

Venetoclax is a small molecule that selectively inhibits the antiapoptotic protein BCL-2, causing cell death. Because BCL-2 plays a key role in leukemic stem cell survival, BCL-2 inhibition is an attractive strategy for eliminating leukemia stem cells that become resistant to chemotherapy.[13] Venetoclax has demonstrated clinical activity in patients with high-risk R/R AML, both as monotherapy and in combination with other agents.[14,15] Preclinical studies demonstrated that mivebresib can trigger high levels of apoptosis in cells expressing low levels of BCL-2; indeed, mivebresib and venetoclax have demonstrated synergistic antileukemic activity in AML cell lines,[5,16] and Myc-activated and BCL-2–activated lymphoma cell lines exhibited higher cell death with BETi and venetoclax compared with either agent alone.[17]

Here, we report the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) results of this first-in-human, phase 1 study of mivebresib monotherapy (MIV-mono) and mivebresib in combination with venetoclax (MIV-Ven) in patients with R/R AML.

## MATERIALS AND METHODS

### *Study Design*

This study evaluated the safety, efficacy, PK, and PD (data cutoff, December 3, 2019) of MIV-mono or MIV-Ven in patients with R/R AML (ClinicalTrials.gov identifier NCT02391480). Dose escalation followed a traditional 3 + 3 design (see Supporting Table 1).

### *Patients*

Patients aged ≥18 years with AML for whom no standard-of-care therapy exists or who were refractory after standard-of-care therapy were eligible. All patients had an Eastern Cooperative Oncology Group performance status from 0 to 2, adequate renal and hepatic function, and a QTc interval <480 milliseconds (corrected for heart rate) at baseline. Full inclusion and exclusion criteria are provided in the online Supporting Methods.

This study was conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines, all applicable regulations and guidelines, and the Declaration of Helsinki. The human investigations were performed after approval by a local Human Investigations Committee and were approved by the US Department of Health and Human Services. All patients provided written informed consent.

### *Treatment*

Mivebresib was administered daily in 28-day cycles. The dose levels were based on the solid tumor recommended phase 2 dose of 1.5 mg daily[18] and available tablet sizes. Patients in the MIV-mono group received 1.5, 2.0, or 2.5 mg of mivebresib. Patients in the MIV-Ven group received 0.5 mg of mivebresib with 400 mg of venetoclax (0.5 mg + 400 mg), 1.0 mg + 400 mg, 1.0 mg + 800 mg, or 2.5 mg + 800 mg. Venetoclax dosing started with a ramp-up phase of 4 days (100 mg on cycle 1 day 1 [C1D1], 200 mg on C1D2, 400 mg on C1D3) to mitigate the risk of tumor lysis syndrome. Mivebresib was added to venetoclax once the target dose was reached and was administered until patients developed progressive disease or unacceptable toxicity. Patients receiving MIV-mono who experienced progression could re-enroll in combination therapy after a 2-week washout period (*switched* patients). Antifungal medication was allowed, and venetoclax dose modifications were implemented for moderate or strong CYP3A inhibitors (see Supporting Table 2). All patients were hospitalized and monitored the day before starting combination therapy and for the first 48 hours after.

### *Safety and Clinical Activity Assessments*

Screening was performed within 28 days of C1D1 and included a baseline AML assessment and laboratory tests. Patients continued on study until they met protocol-defined discontinuation criteria and were followed for at least 30 days after the last dose. Bone marrow (BM) aspirate was collected for clinical assessment (performed

by a local laboratory) and for biomarker analyses, if possible (performed by a central/referral laboratory). Disease was assessed with BM aspirate and/or biopsy at screening, at C2D1, and as clinically indicated. Patients had triplicate electrocardiograms at screening and had PK analyses, serial blood pressure levels, and triplicate electrocardiograms through 8 hours after dosing on C2D1.

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. A treatment-emergent AE (TEAE) was defined as any AE with onset or worsening from the time of the first dose of mivebresib until 30 days after discontinuation. Definitions of dose-limiting toxicities (DLTs), serious TEAEs, and TEAE assessment are provided in the Supporting Methods.

Response was assessed using response criteria for AML from the revised guidelines by the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia.[19] A baseline BM sample and at least 1 postbaseline BM sample obtained during treatment were compared. Patients without at least 1 postbaseline BM sample were not considered evaluable for response.

### *Pharmacokinetics Assessments*

PK samples for plasma mivebresib concentration analysis were collected at specified time points predose and postdose (see Supporting Methods). PK analyses included all patients who had a complete concentration-time profile.

### *Pharmacodynamics Assessments*

RNA whole-transcriptome sequencing was performed on RNA extracted from whole blood samples collected pretreatment and after mivebresib administration (see Supporting Methods). PD markers after 6 hours of mivebresib treatment were compared with preadministration baseline samples. Linear regression analysis was used to assess the correlation between the mivebresib maximum observed plasma concentration ($C_{max}$) and biomarker expression levels. Cytogenetic analysis was performed at the site using standard institutional guidelines. Mutation profiling on BM aspirate was reported by the site and on peripheral blood (PB) by AbbVie using the TruSight Myeloid Sequencing Panel (Illumina) (see Supporting Methods).

### *Statistical Analyses*

Safety analyses were reported for all patients who received ≥1 dose of mivebresib. Clinical activity analyses included all dosed patients who had ≥1 baseline and ≥1 postbaseline measurement. Patient demographics, safety, PK, best response, and duration of overall response were analyzed using descriptive statistics. Analyses with separate summaries for switched patients included best response and progression-free survival (PFS). All statistical analyses were exploratory and were performed using SAS, version 9.2 (SAS Institute Inc, Cary, NC).

**TABLE 1.** Patient Demographics and Baseline Characteristics, N = 44

| Characteristic | No. of Patients (%) |
|---|---|
| Age: Median [range], y | 68 [29-84] |
| Sex | |
| Women | 24 (55) |
| Men | 20 (45) |
| ECOG PS | |
| 0 | 6 (14) |
| 1 | 35 (80) |
| 2 | 3 (7) |
| No. of prior therapies | |
| 1 | 6 (14) |
| 2 | 8 (18) |
| 3 | 8 (18) |
| >3 | 22 (50) |
| Cytogenetic risk category[a] | |
| Adverse | 30 (68) |
| Intermediate | 14 (32) |
| Favorable | 0 (0) |
| Molecular profile[b] | |
| *FLT3-ITD/TKD* | 13 (30) |
| *TET2* | 9 (20) |
| *NPM1* | 8 (18) |
| *ASXL1* | 7 (16) |
| *DNMT3A* | 7 (16) |

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]Cytogenetic risk groups were defined according to the 2017 European LeukemiaNet risk stratification by genetics.
[b]The top 5 mutated genes are listed.

## RESULTS

### *Demographics and Baseline Characteristics*

As of 3 December 2019, 44 patients with AML were enrolled in the dose-escalation cohort; 19 received MIV-mono, and 25 received MIV-Ven. In addition, 5 patients in the MIV-mono group experienced disease progression/relapse, discontinued mivebresib, held treatment for a 2-week washout period, and re-enrolled in the MIV-Ven arm (*switched* patients). Thus, in total, 30 patients received MIV-Ven. The median age for all patients was 68 years (range, 29-84 years); 22 patients had received ≥3 lines of previous therapy, and 13 had *FLT3* mutations. Patient demographics are summarized in Table 1. One patient has been reported previously.[20]

**TABLE 2.** Summary of Treatment-Emergent Adverse Events

| TEAEs | No. of Patients (%) | | |
|---|---|---|---|
| | Started Monotherapy, n = 19[a] | Started Combination Therapy, n = 25 | Switched to Combination Therapy, n = 5[b] |
| Any TEAEs | 19 (100) | 25 (100) | 5 (100) |
| AEs in >20% | | | |
| Fatigue | 13 (68) | 12 (48) | 3 (60) |
| Nausea | 9 (47) | 15 (60) | 2 (40) |
| Decreased appetite | 11 (58) | 11 (44) | 1 (20) |
| Diarrhea | 9 (47) | 12 (48) | 1 (20) |
| Dysgeusia | 15 (79) | 6 (24) | 1 (20) |
| Febrile neutropenia | 7 (37) | 13 (52) | 1 (20) |
| Vomiting | 6 (32) | 15 (60) | 0 (0) |
| Anemia | 13 (68) | 3 (12) | 2 (40) |
| Thrombocytopenia | 10 (53) | 5 (20) | 2 (40) |
| Dyspnea | 6 (32) | 7 (28) | 2 (40) |
| Cough | 6 (32) | 5 (20) | 1 (20) |
| Muscular weakness | 7 (37) | 4 (16) | 1 (20) |
| Epistaxis | 4 (21) | 7 (28) | 0 (0) |
| Hyperbilirubinemia | 6 (32) | 5 (20) | 0 (0) |
| Hypokalemia | 3 (16) | 8 (32) | 0 (0) |
| Hypomagnesemia | 2 (11) | 9 (36) | 0 (0) |
| AEs related to mivebresib in >10% | | | |
| Dysgeusia | 14 (74) | 6 (24) | 1 (20) |
| Decreased appetite | 8 (42) | 11 (44) | 1 (20) |
| Nausea | 7 (37) | 10 (40) | 2 (40) |
| Fatigue | 7 (37) | 9 (36) | 2 (40) |
| Diarrhea | 8 (42) | 8 (32) | 0 (0) |
| Vomiting | 5 (26) | 11 (44) | 0 (0) |
| Thrombocytopenia | 7 (37) | 4 (16) | 2 (40) |
| Anemia | 7 (37) | 1 (4) | 0 (0) |
| ALT increased | 1 (5) | 4 (16) | 1 (20) |
| AST increased | 0 (0) | 6 (24) | 0 (0) |
| Dry mouth | 2 (11) | 2 (8) | 0 (0) |
| Epistaxis | 3 (16) | 1 (4) | 0 (0) |
| Neutrophil count decreased | 2 (11) | 2 (8) | 0 (0) |
| Platelet count decreased | 2 (11) | 2 (8) | 0 (0) |
| Stomatitis | 1 (5) | 3 (12) | 0 (0) |
| Weight decreased | 2 (11) | 2 (8) | 0 (0) |
| WBC count decreased | 1 (5) | 2 (8) | 1 (20) |
| Febrile neutropenia | 0 (0) | 3 (12) | 0 (0) |
| Headache | 0 (0) | 3 (12) | 0 (0) |

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; WBC, white blood cell.

[a]The TEAEs that occurred in the 5 patients who switched arms (from the mivebresib monotherapy arm to the mivebresib plus venetoclax combination therapy arm) are reflected in this column if the TEAE occurred while the patient was in the monotherapy arm.

[b]The TEAEs that occurred in the 5 patients who switched arms (from monotherapy to combination therapy) are reflected in this column if the TEAE occurred while the patient was in the combination arm (after monotherapy and a washout period).

### *Safety*

No DLTs occurred. TEAEs were reported in all patients (n = 44). The most frequently reported TEAEs related to mivebresib were dysgeusia, decreased appetite, nausea, and fatigue (Table 2). Among the patients receiving MIV-mono, the observed frequencies were dysgeusia in 79%, fatigue in 68% (21% grade ≥3), decreased appetite in 58% (11% grade ≥3), nausea in 47% (5% grade ≥3), and diarrhea in 47% (no grade ≥3). Thirteen patients (68%) receiving MIV-mono, 15 patients (60%) receiving MIV-Ven, and 3 (60%) switched patients reported grade ≥3 mivebresib-related TEAEs. Grade ≥3 mivebresib-related TEAEs occurring in >2 patients/cohort were thrombocytopenia (32%) and anemia (26%) in the MIV-mono group and thrombocytopenia (16%), diarrhea (12%), and febrile neutropenia (12%) in the MIV-Ven group; no mivebresib-related grade ≥3 TEAEs occurred in >2 switched patients. Serious TEAEs regardless of relatedness to mivebresib occurred in 14 (74%) patients receiving MIV-mono, 22 (88%) patients receiving MIV-Ven, and 2 (40%) switched patients and included febrile neutropenia, AML progression, and pneumonia (all 16%) in the MIV-mono group; febrile neutropenia (28%), sepsis (20%), and AML (12%) in the MIV-Ven group; and AML progression, pneumonia, acidosis, myocardial infarction, and acute kidney injury

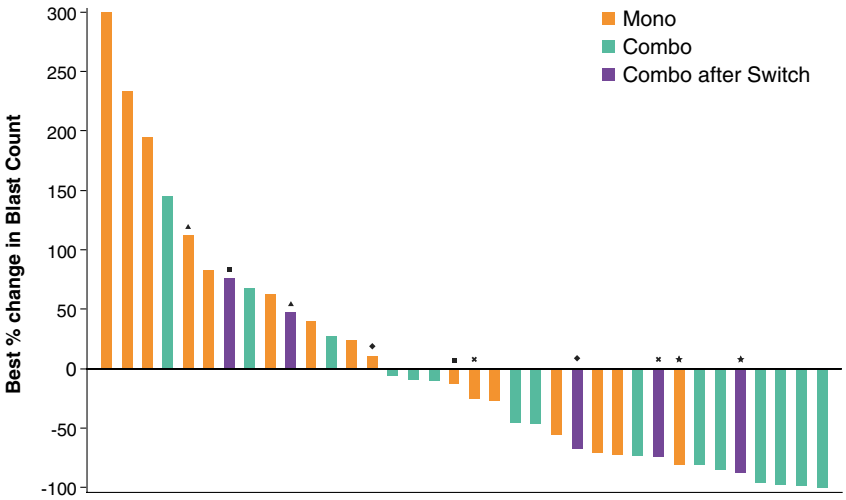


**Figure 1.** The best percentage change in the bone marrow blast count from baseline is illustrated. A linear regression model was fitted with the response variable *percent change in blast count*. Paired symbols (triangles, squares, diamonds, crosses, and stars) designate bars for each of the 5 patients who switched from the mivebresib monotherapy (Mono) arm to the mivebresib combined with venetoclax (Combo) arm (*switchers*; ie, their response on monotherapy and their subsequent response on combination therapy).

(all n = 1; 20%) in switched patients (see Supporting Table 3). Seventeen patients experienced an AE leading to discontinuation, and 17 (35%) died while on study (see Supporting Table 4).

### *Efficacy*

Thirty-six patients were able to be assessed for a change of leukemia burden from baseline (Fig. 1). Of these, 16 (44%) received MIV-mono, 15 (42%) received only MIV-Ven, and 5 (14%) were switched patients. A measurable reduction in BM blasts was observed in 7 patients (44%) receiving MIV-mono and in 12 patients (80%) receiving MIV-Ven. Three switched patients (60%) experienced a reduction in BM blasts (Fig. 1).

Among the 19 patients who received MIV-mono, responses were complete remission with incomplete blood count recovery (CRi) in 1 patient (5%) and resistant disease in 15 patients (79%) (Table 3). The median PFS in the MIV-mono group was 7.2, 13.9, and 10.6 weeks at the 1.5, 2.0, and 2.5 mg dose levels, respectively; and the median OS in the MIV-mono group was 15.7, 22.0, and 12.6 weeks at the 1.5, 2.0, and 2.5 mg dose levels, respectively (Fig. 2). Five patients who received MIV-mono experienced a relapse and were treated later with MIV-Ven.

Among the 30 patients who received MIV-Ven, responses were complete remission (CR) in 2 patients (7%), partial remission (PR) in 2 patients (7%), morphologic leukemia-free state in 2 patients (7%), resistant disease in 12 patients (40%), and aplasia in 1 patient (3%) (Table 3). Of these 30 patients, responses among the 5 switched patients who relapsed on MIV-mono were CR in 1 patient, PR in 1 patient, and resistant disease in 3 patients. The median PFS was 6.1, 11.8, and 7.7 weeks in 25 patients who started MIV-Ven at the 1.0 mg + 400 mg, 1.0 mg + 800 mg, and 2.5 mg + 800 mg dose levels, respectively and 22.5 weeks in 5 switched patients. The median OS in the MIV-Ven group was 37.4, 11.8, and 11.4 weeks at the 1.0 mg + 400 mg, 1.0 mg + 800 mg, and 2.5 mg + 800 mg dose levels, respectively (Fig. 2).

### *Pharmacokinetics*

PK data were analyzed for 45 patients at doses of 1.5, 2.0, and 2.5 mg for MIV-mono (Fig. 3A) and 1.0 and 2.5 mg of mivebresib (with 400 mg and 800 mg of venetoclax) for MIV-Ven (Fig. 3B). Steady state was achieved on C1D8, and the PK of mivebresib was approximately dose proportional over the studied dosing range based on the dose-normalized C1D8 $C_{max}$ and the area under the plasma concentration-time curve over the 24-hour dosing interval ($AUC_{24}$) (Supporting Table 5). The estimated median time to achieve $C_{max}$ ($T_{max}$) was 3 hours (range, 0-8 hours) across all dosage regimens. Mivebresib had a generally monophasic drug disposition, with an estimated harmonic mean terminal phase half-life of 16.4 hours. The mivebresib steady-state accumulation ratio was approximately 2-fold, as measured by the $AUC_{0\text{-}24}$ on C1D8 versus C1D1 with daily dosing. The PK of mivebresib appeared to be similar in the monotherapy and combination

**TABLE 3.** Best International Working Group Responses in Patients With Relapsed/Refractory Acute Myeloid Leukemia

| IWG Response | No. of Patients (%) | | |
|---|---|---|---|
| | Started Monotherapy, n = 19[a] | Started Combination Therapy, n = 25[b] | Switched to Combination Therapy, n = 5[c] |
| CR | 0 (0) | 1 (4) | 1 (20) |
| CRi | 1 (5) | 0 (0) | 0 (0) |
| MLFS | 0 (0) | 2 (8) | 0 (0) |
| PR | 0 (0) | 1 (4) | 1 (20) |
| Resistant disease | 15 (79) | 9 (36) | 3 (60) |
| Aplasia | 0 (0) | 1 (4) | 0 (0) |
| Unknown: Not assessable or insufficient data | 3 (16) | 11 (44) | 0 (0) |

Abbreviations: CR, complete remission; CRi, complete remission with incomplete blood count recovery; IWG, International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia; MLFS, morphological leukemia-free state; PR, partial remission.

[a]For patients who were enrolled to receive mivebresib monotherapy but received mivebresib plus venetoclax combination therapy after disease progression and a washout period, data are summarized in the *Started Monotherapy* column up to the point the patient began receiving combination therapy; data from that point onward are summarized in the *Switched to Combination Therapy* column.

[b]Data in this column do not include responses of the patients who switched, only of the patients who started on combination therapy.

[c]Responses of patients who switched arms (monotherapy to combination therapy after a washout period) are reflected in this column.

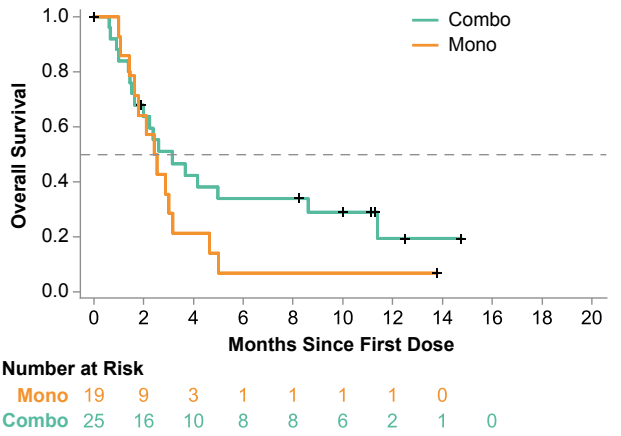


**Figure 2.** An analysis of overall survival is illustrated for patients with relapsed/refractory acute myeloid leukemia who received mivebresib monotherapy (Mono) and mivebresib combined with venetoclax (Combo). Kaplan-Meier survival curves were used to determine the overall survival of patients in the Mono cohort (n = 19) and the Combo cohort (n = 25).

therapy cohorts, suggesting no effect of venetoclax coadministration on mivebresib PK (see Supporting Table 5).

### *Pharmacodynamics*

HEXIM1 and MYC are established PD biomarkers of the BETi class of compounds. It was demonstrated previously that HEXIM1 is modulated in a dose-dependent manner by mivebresib. MYC is a tumor PD marker and thus is not evaluable in PB from patients with solid tumors.[18] In PB samples from patients who had R/R AML, an increase in *DCXR* and *HEXIM1* ($P < .001$) gene expression and a decrease in *CD93* ($P < .001$) and *MYC* ($P < .083$) expression were observed 6 hours after MIV-mono administration, confirming a PD effect. The correlation with PK data confirmed the dose dependency ($P < .05$) (Fig. 4). Changes were dose-dependent, and gene modulation did not reach a plateau at the highest dose administered (2.5 mg), suggesting that superior target engagement may be achieved at higher doses. In addition, the antiapoptotic gene *BCL2* was inhibited ($P < .01$) and the proapoptotic genes *PUMA* ($P < .064$) and *BIM* ($P < .0005$) were increased 6 hours after MIV-mono (data not shown).

### *Mutation Profile and Biologic Activity*

Molecular profiles of the patients are summarized in Supporting Figure 1. An evaluation of the relation of the mutational profile to efficacy was not statistically significant. However, certain trends were noted (Fig. 5): in the MIV-Ven cohort, 4 of 10 patients who had *FLT3-ITD/TKD* mutations and 4 of 6 who had *PTPN11* mutations had a reduction in BM blasts. None of the 3 patients who had *FLT3* and *NPM1* co-occurrence responded to MIV-mono; however, in the MIV-Ven cohort 4 of 10 patients with *FLT3* mutations had a co-occurrence of *FLT3-ITD/TKD* and *NPM1* (including 1 who had a reduction in BM blasts with MIV-Ven). In addition, 3 of 6 patients (50%) with an *FLT3* mutation who had wild-type *NPM1* had a reduction in BM blasts with combination treatment.

## DISCUSSION

Targeting epigenetic readers, such as the BET family of proteins, has emerged as a promising anticancer

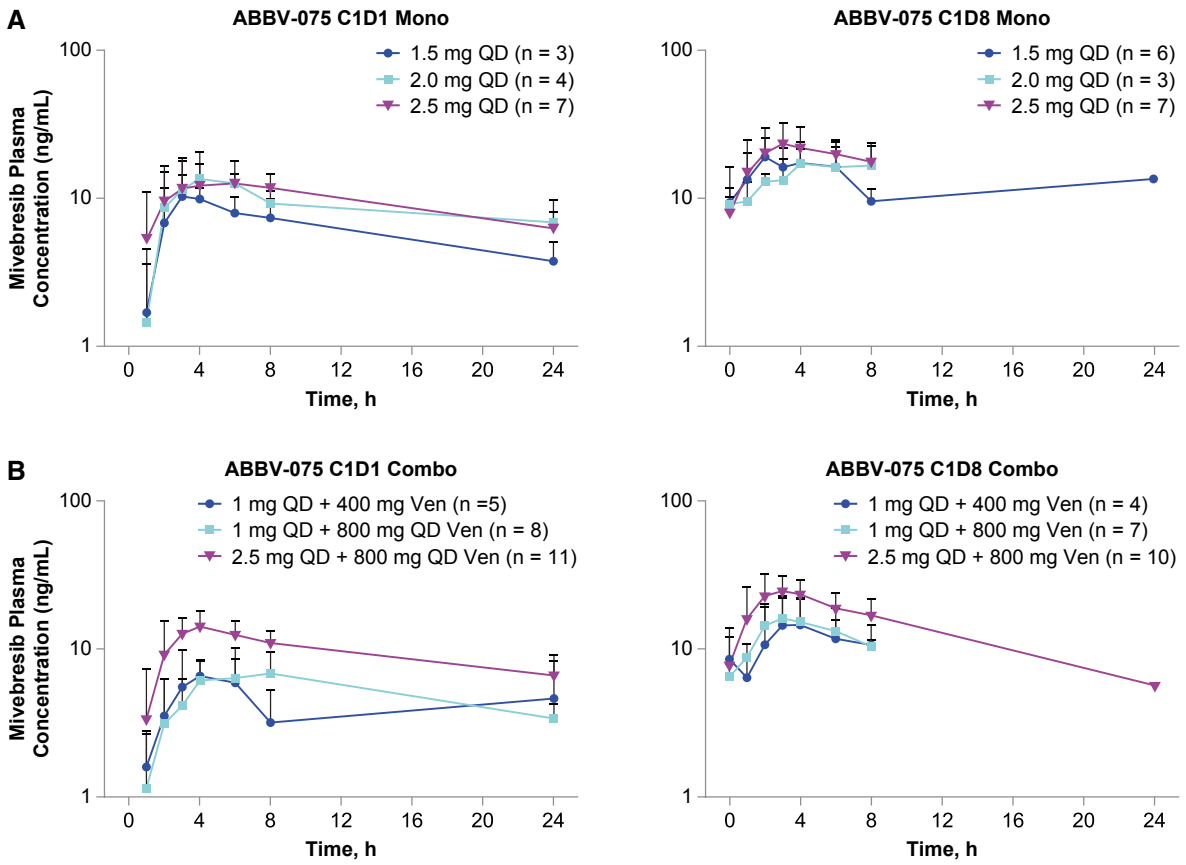


**Figure 3.** Pharmacokinetics profiles of mivebresib (ABBV-075) are charted in patients with relapsed/refractory acute myeloid leukemia who received (A) mivebresib monotherapy (Mono) and (B) mivebresib combined with venetoclax (Combo) on cycle 1 day 1 (C1D1) and cycle 1 day 8 (C1D8). Dosing schedules and concentration time profiles with standard error bars are shown. QD indicates daily.

therapy. Previous preclinical studies demonstrated that BETis have broad antiproliferative activities across cancer cell lines and are highly effective in tumor models.[5,18] Data from patients who had solid tumor in this study demonstrated a tolerable safety profile and stable disease in some patients who received treatment with mivebresib.[18]

This is the first-in-human study to describe the safety, tolerability, efficacy, PK, and PD of the BETi mivebresib as monotherapy or in combination with venetoclax in patients with R/R AML. The safety profile of mivebresib in this study is consistent with previous findings,[18] with the most common TEAEs being fatigue, nausea, decreased appetite, diarrhea, and dysgeusia. Fatigue and gastrointestinal AEs were also among the most common AEs in the phase 1 study of BETi OTX015.[10] Rates of gastrointestinal AEs in the current study, including diarrhea (47% MIV-mono, 43% MIV-Ven), nausea, (47% MIV-mono, 57% MIV-Ven), and vomiting (32% MIV-mono, 50% MIV-Ven), were higher compared with rates of diarrhea, nausea, and vomiting (34%, 22%, and 7%, respectively) reported with OTX015 monotherapy,[10] although patient numbers were small in both studies, and any comparison should be made with caution.

The efficacy of MIV-mono was modest; 1 patient achieved CRi. Patients in the MIV-mono group had BM blast changes from baseline in a shorter median time than patients in the MIV-Ven group. MIV-Ven resulted in higher efficacy, with CR in 2 patients, a PR in 2 patients, and morphologic leukemia-free state in 2 patients. Interestingly, this activity included 2 switched patients who experienced a relapse with MIV-mono. Three switched patients had BM blast reductions when treated with MIV-Ven. This demonstrates the notable additional effect of venetoclax. Most patients were heavily pretreated (≥3 prior lines), and 68% had poor-risk cytogenetics, which may explain the observed moderate clinical

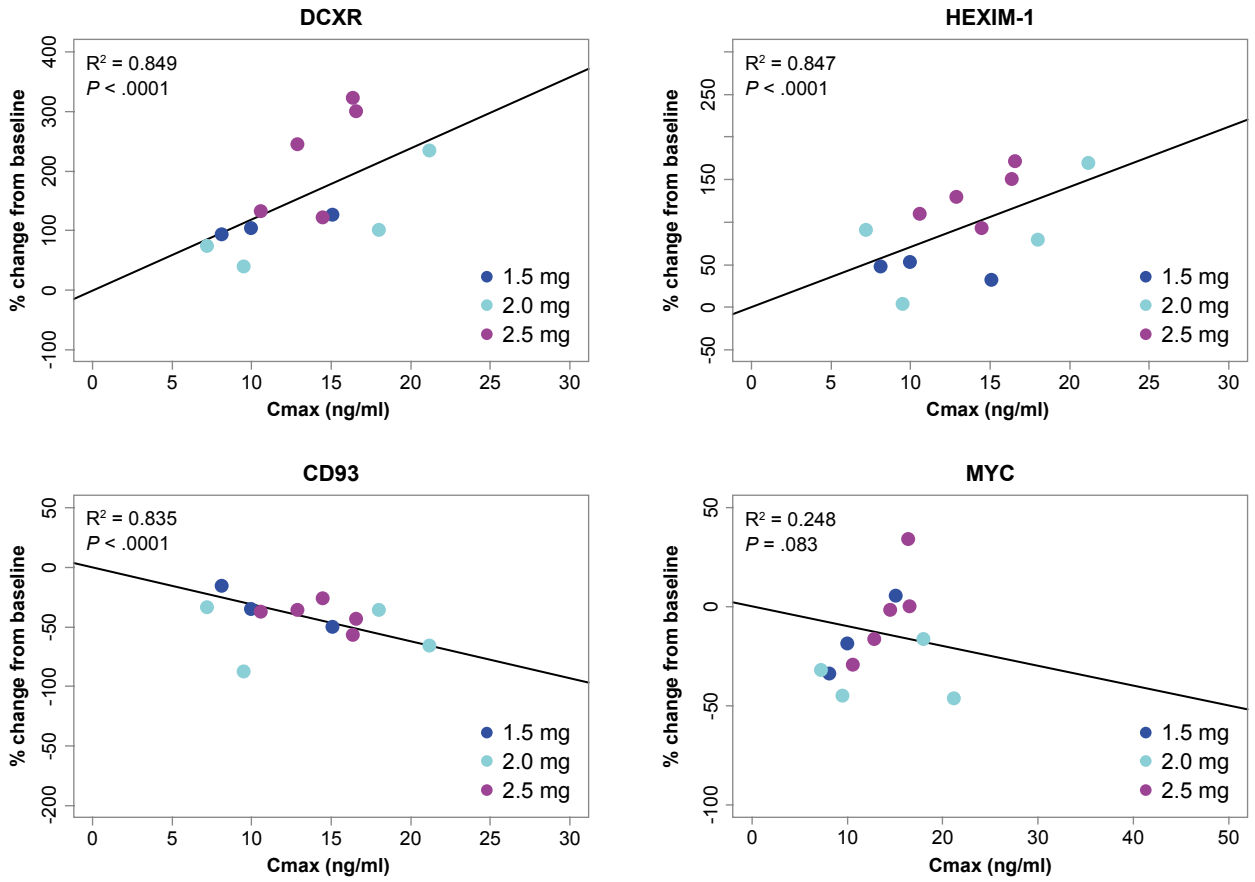


**Figure 4.** The correlation between drug exposure (maximum observed plasma concentration [$C_{max}$]) and gene modulation at 6 hours posttreatment with mivebresib monotherapy on cycle 1 day 1 in peripheral blood from patients with relapsed/refractory acute myeloid leukemia is illustrated. Linear regression was used to determine the correlation ($R^2$) between the cycle 1 day 1 $C_{max}$ and the biomarker percent change from baseline at 6 hours postdosing. The $R^2$ and $P$ values are shown. The number of patients at each dose was n = 3 at 1 mg, n = 4 at 1.5 mg, and n = 5 at 2 mg.

activity. Given this patient population, the overall activity of MIV-Ven is clinically significant.

Analyzing a diverse set of transcriptional pathways modulated by the BET family of proteins revealed a significant correlation between mivebresib exposure and PD effect. In our phase 1 study, the most pronounced indicators of target engagement were *DCXR*, *CD93*, and *HEXIM1* and were more robust than modulations in *MYC* and *BCL2*.[18] *DCXR* encodes for a protein that plays an important role in glucose metabolism. *CD93* is a myeloid marker involved in cell adhesion and clearance of apoptotic cells. In preclinical studies, *MYC* inhibition has been used as a marker of BETi activity.[21] *MYC* is an established tumor PD marker of pan-BETi, and the inhibition of *MYC* in patients who received MIV-mono confirms the on-target effect of mivebresib. *BCL2* is an antiapoptotic gene that is overexpressed in multiple tumor types, including AML. In addition, proapoptotic genes like *PUMA* and *BIM* were upregulated in our study (data not shown). Inhibition of *BCL2* and induction of *BIM/PUMA* by mivebresib and other pan-BETis, which was previously demonstrated, suggests that BETi modulation of proapoptosis and antiapoptosis family genes is a class effect.[5] Our data are consistent with these preclinical findings, yet the observed modulation did not correlate with biologic activity, suggesting that additional pathways may require modulation to achieve long-term, sustained responses.

Understanding potential biomarkers predictive of patient response will provide a unique insight for the design of future trials with drugs of this class. Preliminary analysis of the mutational context of mivebresib sensitivity/resistance revealed that, in patients with both *NPM1* and *FLT3-ITD* mutations, there was no detectable efficacy, although patient numbers were small. Whereas it is known that *FLT3-ITD* imparts a particularly poor

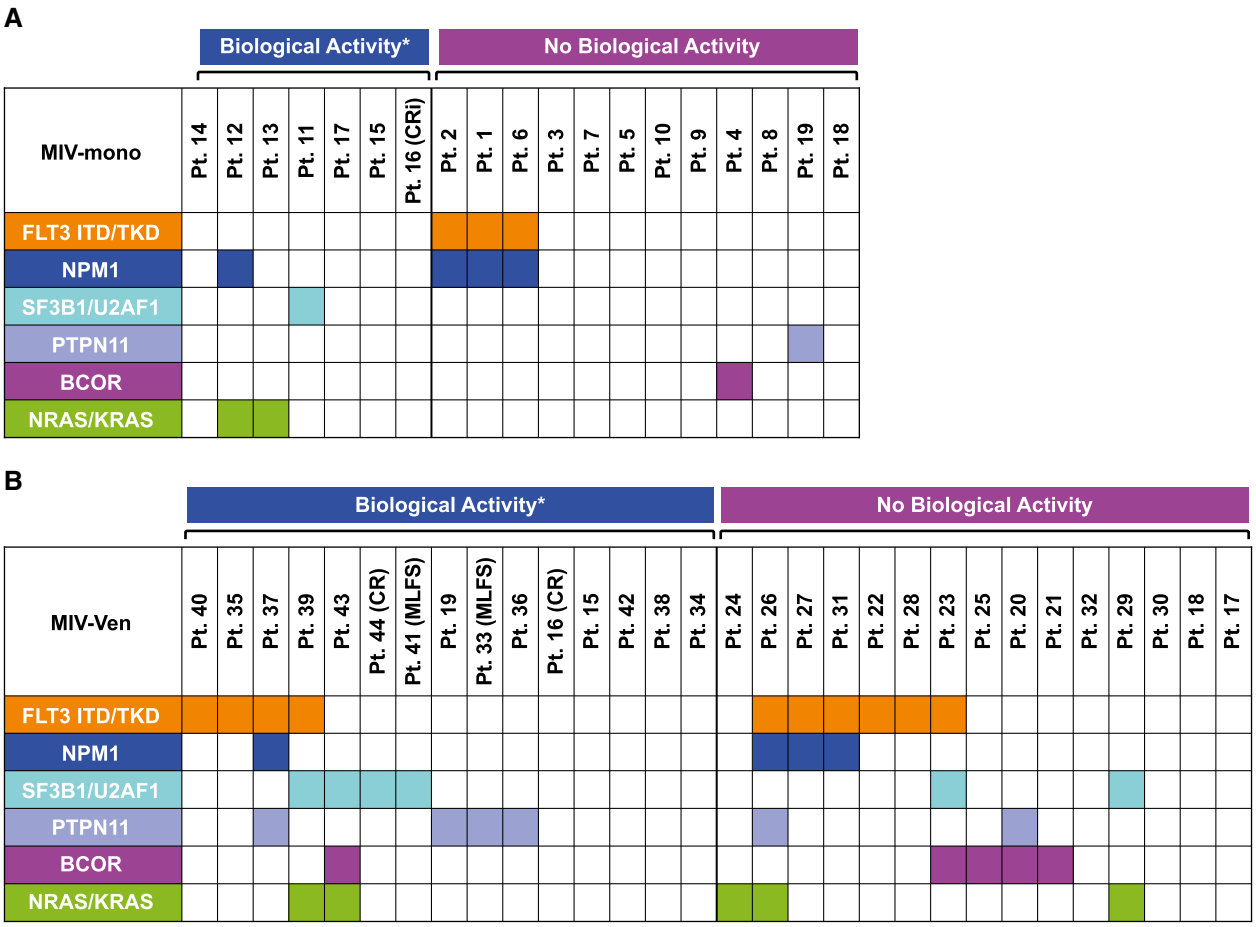


**Figure 5.** Molecular biomarkers of sensitivity and resistance to (A) mivebresib monotherapy (MIV-mono) and (B) mivebresib in combination with venetoclax (MIV-Ven) are illustrated. Baseline molecular markers that differentiate each patient (Pt.) with and without biologic activity in the MIV-mono and MIV-Ven cohorts are listed. The mutations reported were detected in blood and/or bone marrow samples using the TruSight Myeloid Sequencing Panel (Illumina) or institution-specific next-generation sequencing–based myeloid panels. *Note that biologic activity was defined as any reduction in the bone marrow blast count while on MIV-mono or MIV-Ven therapy. CR indicates complete response; CRi, complete remission with incomplete blood count recovery; MLFS, morphologic leukemia-free state.

prognosis,[22] in this study, a subset of patients who had *FLT3-ITD* mutations showed biologic activity (a measurable reduction in BM blasts) in response to MIV-Ven. In the phase 1 study of the BETi OTX015 in R/R AML, 3 of 5 patients who had clinical activity had ab *FLT3-ITD* mutation, suggesting that the BETi class of compounds may have the potential to target a subset of patients with AML who have a poor prognosis, although a larger study is needed to confirm this.[10] Biologic activity in this study was also observed in several high-risk mutation groups, such as patients with *SF3B1* or *U2AF1* (splicing factor). In addition, some patients with mutations in *NRAS* and/or *PTPN11* responded to treatment. Overall, these results may hint that patients who have several high-risk mutations may have a higher probability of responding to MIV-Ven. Because of limited patient numbers, it was challenging to identify a specific subset of molecular alterations that made patients with R/R AML sensitive or resistant to MIV-mono or MIV-Ven.

Although DLTs were not encountered, systemic AEs, such as dysgeusia and fatigue, were clinically problematic. The optimal clinical schedule that would maximize activity and minimize toxicity for BETi is not fully understood.[23] Recently, Piha-Paul and colleagues suggested that the optimal schedule of mivebresib may be selected based on the schedule of other drugs given in combination or the preference of the patient.[18] Here, we combined 0.5, 1.0, or 2.5 mg of mivebresib with 400 or 800 mg of venetoclax. The MIV-mono expansion phase started with a dose of 1.5 mg daily

because this was determined to be the recommended phase 2 dose in the solid tumor cohorts of this study.[18] Comparable mivebresib exposures between monotherapy and combination therapy suggest that mivebresib can be effectively given in combination with venetoclax. The biologic activity of combination therapy at a lower-than-maximum dose of mivebresib also supports the notion that combination strategies will allow for lower but continuous dosing of BETis, a strategy that may be essential for epigenetic modulators.

The current study demonstrated safety and efficacy of combining a BETi with venetoclax and suggests that BETi monotherapy is more efficacious in hematologic cancers than in solid tumors, as previously observed.[5,24,25] Therefore, use of a BETi as a single agent may have a modest effect compared with more promising combination therapies.[5,25,26] Another study is investigating combinations of BETis with azacitidine in this patient population (ClinicalTrials.gov identifier NCT02543879). Further exploration of BETi combinations for synergy and to overcome potential resistance mechanisms against targeted therapies in patients with hematologic malignancies are needed; perhaps a study in *PTPN11* and/or *RAS* mutations could be considered.

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## CONFLICT OF INTEREST DISCLOSURES

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**Gautam Borthakur:** Conceptualization, data curation, investigation, validation, writing–original draft, and writing–review and editing. **Olatoyosi Odenike:** Conceptualization, data curation, investigation, validation, writing–original draft, and writing–review and editing. **Ibrahim Aldoss:** Conceptualization, data curation, investigation, validation, writing–original draft, and writing–review and editing. **David A. Rizzieri:** Conceptualization, data curation, investigation, validation, writing–original draft, and writing–review and editing. **Thomas Prebet:** Conceptualization, data curation, investigation, validation, writing–original draft, and writing–review and editing **Chris Chen:** Data curation, formal analysis, investigation, software, validation, visualization, writing–original draft, and writing–review and editing. **Relja Popovic:** Methodology, validation, visualization, writing–original draft, and writing–review and editing. **Dimple A. Modi:** Conceptualization, data curation, formal analysis, methodology, project administration, resources, validation, visualization, writing–original draft, and writing–review and editing. **Rujuta H. Joshi:** Methodology, project administration, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Johannes E. Wolff:** Conceptualization, formal analysis, funding acquisition, methodology, project administration, resources, software, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Brian A. Jonas:** Conceptualization, data curation, methodology, validation, writing–original draft, and writing–review and editing.

## DATA AVAILABILITY

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided after review and approval of a research proposal and a Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered (for more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html).

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