Clinical Cancer Research

First-in-Human Study of Mivebresib (ABBV-075), an Oral Pan-Inhibitor of Bromodomain and Extra Terminal Proteins, in Patients with Relapsed/Refractory Solid Tumors

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Abstract

Purpose: Bromodomain and extraterminal (BET) proteins play important roles in transcriptional regulation relevant to cancer pathogenesis, and therapeutic targeting/inhibition of BET causes apoptosis of cancer cells *in vitro*. In this first-in-human study of the pan-BET inhibitor mivebresib (ABBV-075), the safety profile, MTD, and recommended phase II dose (RP2D) were determined in patients with advanced solid tumors.

Patients and Methods: A 3 + 3 dose escalation for different mivebresib dosing schedules [daily, Monday/Wednesday/Friday (M-W-F), 4 days on/3 off (4/7)] was followed by dose expansion in patients with prostate cancer. Endpoints were safety, tolerability, pharmacokinetics, and preliminary antitumor activity.

Results: Seventy-two patients with solid tumors (14% uveal melanoma; 11% colorectal; 11% breast; 8% pancreatic; 7% head/neck; 49% others) were treated with mivebresib during dose escalation, and 12 additional patients with prostate cancer in expansion cohort. Most common treatment-emergent adverse events (TEAE) related to mivebresib were dysgeusia (49%), thrombocytopenia (48%), fatigue (26%), and nausea (25%). Most common grade 3/4 TEAEs related to mivebresib were thrombocytopenia (35%) and anemia (6%). Dose-limiting toxicities included thrombocytopenia (2 mg daily; 4.5 mg M-W-F), gastrointestinal bleed (2 mg daily), hypertension (2–3 mg 4/7), fatigue, decreased appetite, and aspartate aminotransferase elevation (4 mg M-W-F). Of 61 evaluable patients from dose escalation, 26 (43%) had stable disease and 35 (57%) had progressive disease. Median progression-free survival was 1.8 months (95% confidence interval, 1.8–1.9).

Conclusions: On the basis of safety and tolerability, mivebresib RP2D is 1.5 mg for the daily schedule, 2.5 mg for 4/7, and 3 mg for M-W-F. Mivebresib has a tolerable safety profile, and stable disease was observed in some patients with malignant solid tumors.

Introduction

Epigenetic regulators have received growing interest in the past several years of cancer research (1, 2). Bromodomains are epigenetic "reader" domains that bind to acetylated lysines such as those found on histone tails (3). The most well-studied bromodomain-containing proteins are members of the bromodomain and extraterminal domain (BET) family. Recognition of acetylated histone tails by BET proteins leads to the formation of transcriptional complexes that can drive the expression of a number of target genes involved in oncogenesis, such as c-Myc and IL7R (4–7).

Tumor types differ in their response to BET inhibition, as shown *in vitro*. For example, BET inhibition leads to apoptosis in most hematologic cancer cell lines, but drives G_1 cell-cycle arrest in most solid tumor cell lines (5, 8). BET inhibition can also downregulate cytokines and chemokines that are important in maintaining the tumor microenvironments of some malignancies (9). It is therefore hypothesized that targeting BET family proteins could lead to robust antitumor activity across a broad spectrum of cancer indications through mechanisms of action that include: (i) directly targeting transcriptional programs that drive oncogenesis [e.g., acute myeloid leukemia (6, 10), myelodysplastic syndrome (11), multiple myeloma (12, 13), and diffuse large B-cell lymphoma (14)]; (ii) blocking cell-cycle progression [e.g., breast cancer (15, 16)]; (iii) impairing the tumor microenvironment [e.g., non–small cell lung cancer (NSCLC;

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Translational Relevance

BET proteins are involved in a wide variety of malignancies, and their inhibition as a treatment concept provides the opportunity for transformational approaches in numerous indications. Although at least three phase I studies of BET inhibitors have been published since 2016, no drug of this class has yet been approved. This first-in-human dose escalation study reports the results of a dose escalation schema that evaluated the safety, pharmacokinetics/pharmacodynamics, and preliminary activity of the BET inhibitor mivebresib in patients with advanced solid tumors and an expansion cohort with relapsed/refractory prostate cancer. We established the mivebresib RP2D for three different dosing schedules. Four patients in the dose escalation cohort (7%) had stable disease lasting >6 months. In addition, we identified changes in whole blood gene expression of CD93 and DCXR, and changes in serum BDNF and ferritin as candidate pharmacodynamic biomarkers. Together, these data support further development of mivebresib for examination of BET inhibition in clinical studies of combination therapy strategies.

refs. 17, 18) and pancreatic cancer (19, 20)] and interrupting androgen receptor signaling (e.g., prostate cancer; refs. 21, 22). In support of this hypothesis, significant antitumor activities were reported for the BET inhibitors JQ-1, I-BET, MS-417, and OTX-015 in xenograft or genetically engineered mouse models of acute myeloid leukemia (6, 10), multiple myeloma (12, 13), non-Hodgkin lymphoma (23), acute lymphoblastic leukemia (7), malignant peripheral nerve sheath tumors (24), NUT-midline carcinoma (25), neuroblastoma (26), medulloblastoma (27), NSCLC (17), melanoma (28), and prostate cancers (21).

Mivebresib (ABBV-075) is an oral, small-molecule pan-BET inhibitor that induces cell death in culture and tumor regression in xenograft and animal models of acute myeloid leukemia, multiple myeloma, KRAS-mutant NSCLC, prostate cancer, and breast cancer (5, 8, 29). Mivebresib has also been shown to decrease androgen receptor–dependent transcriptional activation, induce senescence of castrate-resistant prostate cancer (CRPC) cells, and decrease growth of CRPC xenografts in animal studies (8). Accordingly, this molecule provides the prospect for activity in a broad range of human cancers. Preclinical toxicology studies showed effects on the gastrointestinal tract (rats/dogs), inflammation (lung in rats/dogs, oral mucosa and skin of dogs), and hemorrhage (rats/dogs) associated with reduced platelets and prolonged activated partial thromboplastin time (AbbVie, data on file). This first-in-human, phase I, two-part study assesses the safety and pharmacokinetics of mivebresib in patients with advanced tumors. We report safety, tolerability, activity, pharmacokinetic and pharmacodynamic results from the dose escalation in patients with relapsed/refractory solid tumors, as well as a dose expansion cohort of 12 patients with relapsed/refractory prostate cancers.

Patients and Methods

Study design

This is a phase I, multicenter, open-label, dose escalation study (NCT02391480) in adult patients with relapsed, refractory advanced solid tumors. Dose escalation followed a traditional 3 + 3 design (30). After the dose escalation was completed, 12 additional patients with prostate cancer were enrolled in an expansion cohort at the Monday, Wednesday, and Friday (M-W-F) recommended phase II dose (RP2D) to further evaluate safety and preliminary activity.

Patients

Patients were 18 years of age or older with histologically confirmed locally advanced or metastatic solid tumor not amenable to curative therapy. For the prostate expansion cohort, patients had histologically confirmed prostate cancer that was refractory after standard of care therapy. Metastatic castration-resistant prostate cancer (CRPC) was defined as adenocarcinoma without neuroendocrine features, which had progressed during previous therapy with androgen synthesis inhibitor and/or androgen receptor antagonist. Disease progression during previous therapy was defined as either increase of prostate specific antigen (PSA progression: 2 consecutive rises in serum PSA, obtained at a minimum of 1-week intervals, and each value $\geq$ 2.0 ng/mL) or as radiographic progression (using RECIST 1.1 criteria for visceral or soft tissue lesions and PCWG3 criteria for bone lesions). All patients had an Eastern Cooperative Oncology Group performance status of 0 to 1, adequate bone marrow, renal and hepatic function, and QT interval corrected for heart rate (QTc) interval <480 milliseconds on the baseline electrocardiogram (ECG). All patients consented to provide an archived tissue sample of tumor lesion for biomarker analysis.

Patients were excluded if they had untreated brain or meningeal metastases, anticancer treatment within 21 days prior to first administration of mivebresib, unresolved grade $\geq$2 toxicities from most recent anticancer therapy (except alopecia), or a major surgical procedure within 28 days prior to first administration of mivebresib. Full exclusion criteria are provided in the Supplementary Material.

This study was conducted in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, applicable regulations and guidelines governing clinical study conduct, and ethical principles that have their origin in the Declaration of Helsinki. The human investigations were performed after approval by a local Human Investigations Committee and in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services. All patients provided written informed consent before participation in the trial.

Treatment

Mivebresib was administered in 28 day-cycles. We began the study with a daily schedule, but after encountering thrombocytopenia, additional schedules were explored. Thus, three different dosing schedules for mivebresib were evaluated: continuous daily dosing, four days on drug/3 days off (4/7) drug, and dosing on Monday, Wednesday, and Friday (M-W-F). The starting dose was 1 mg for each schedule, and doses doubled as long as neither a dose-limiting toxicity (DLT) was seen in 2/3 patients nor any grade $\geq$2 toxicity was observed. Once grade $\geq$2 toxicity was encountered, the escalation increment was reduced to ratios of 0.67, 0.5, and 0.33. A study schema with patient enrollment by treatment schedule is shown in Supplementary Fig. S1.

Safety and clinical activity assessments

Screening was performed within 28 days of cycle 1 day 1 (C1D1) and included a baseline tumor assessment (e.g., physical exam, CT, or MRI as indicated), laboratory tests, and pregnancy test (for childbearing females). Tumor assessments by RECIST version 1.1 were performed after every 2 cycles of therapy (every 8 weeks). Patients continued on study until they met protocol defined discontinuation criteria and were then followed for at least 30 days after the last dose of mivebresib.

Patients in the dose escalation cohorts had: (i) optional pretreatment tumor biopsy for the purpose of generating patient-derived xenograft mouse models for pharmacology studies to further define the biological activity of mivebresib; (ii) pharmacokinetic draws and serial blood pressure (BP) monitoring through 24 hours after dosing on C1D1, with a single ECG at each draw; (iii) pharmacokinetic draws and serial BP monitoring through 8 hours after dosing on C1D8, with a single ECG at each draw; and (iv) pharmacokinetics at 14, 17, and 20 hours after dosing and serial BP monitoring on C1D15, with a single ECG at each draw. Patients in the expansion cohort and select patients in the late dose escalation cohorts had: (i) optional pretreatment and on-treatment tumor biopsies; (ii) triplicate ECG at screening; and (iii) pharmacokinetics, serial BP, and triplicate ECG through 8 hours after dosing on C2D1.

Adverse event (AE) severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. A treatment-emergent adverse event (TEAE) was any AE reported by a patient with onset or worsening from the time the first dose of mivebresib until 30 days after discontinuation of mivebresib. A TEAE was considered serious if it led to death or life-threatening condition, inpatient hospitalization, prolonging existing hospitalization, persistent incapacitation, congenital anomaly, or required medical or surgical intervention to prevent serious outcome. Relation of TEAEs to study drug was assessed by the investigator.

Pharmacokinetics assessments

Blood samples (3 mL) for plasma mivebresib concentration analysis were collected by venipuncture K2EDTA-containing collection tubes at 0 (pre-dose) 1, 2, 3, 4, 6, 8, and 24 hours post-dose on day 1 and 8 of cycle 1 in the dose escalation cohorts, and on day 1 of cycle 2 in the prostate expansion cohort. Immediately after collection, all blood samples were mixed and placed in an ice bath. Samples were centrifuged and harvested plasma stored at −20°C or below until bioanalysis. Plasma concentrations of mivebresib were determined using a validated liquid chromatography-tandem mass spectrometry (LC/MS-MS) method with a lower limit of quantitation (LLOQ) of 1 ng/mL. The following pharmacokinetic parameters were estimated with noncompartmental methods on day 1 and 8: the maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), elimination half-life ($t_{1/2}$), and the area under the plasma concentration-time curve (AUC) over the 24-hour dosing interval (AUC_{24}), AUC from time 0 to infinity ($AUC_{0\text{-inf}}$), bioavailability normalized clearance (CL/F), and the steady-state AUC_{24} accumulation ratio (R_{ac}).

Pharmacodynamics assessments

BET target genes were identified after *ex vivo* treatment of healthy donor blood samples as well as xenograft blood samples with mivebresib for 6 hours followed by microarray profiling. Significantly modulated genes were further characterized using a targeted gene panel via the QuantiGene RNA Assay for Gene Expression Profiling (custom 16-plex). This assay is a hybridization-based assay that utilizes a branched DNA technology for signal amplification for the direct quantitation of gene expression transcripts (31). It was used in the study for gene expression measurement on RNA extracted from whole blood samples collected at multiple time points (pretreatment and after mivebresib administration). QuantiGene RNA Assay for Gene Expression Profiling (Branched DNA) was performed using a custom 16-plex gene panel (Affymetrix).

The BET inhibitor class of compounds is also known to modulate inflammatory cytokine signaling. A preliminary list of inflammatory targets modulated by mivebresib was determined by *ex vivo* treatment of healthy donor blood samples with mivebresib using a commercially available inflammatory cytokine assay. Results from these *ex vivo* studies then guided the development of an assay used to evaluate changes in soluble biomarkers from our clinical samples. Soluble cytokine modulation was evaluated in serum samples collected pre- and post-mivebresib treatment on Myriad Rules-Based Medicine's (RBM) InflammationMAP Panel (46 analytes; Myriad RBM). The Multi-Analyte Profile (MAP) panel includes inflammatory analytes and pathways including cytokine, chemokines, and acute-phase reactants. The targets included on the gene panel and the InflammationMAP panel are described in Supplementary Tables S1 and S2.

MTD and RP2D determination

DLT events were defined as clinically significant AE or abnormal laboratory values assessed as unrelated to disease progression, intercurrent illness, concomitant medications or identifiable cause different from the investigational product, and occurring during the first 4 weeks after administration of the first dose that meet any of the following criteria: grade $\geq$4 absolute neutrophil count (ANC) decrease lasting >1 week, or grade $\geq$3 ANC decrease with fever; grade $\geq$4 platelet count decrease; grade $\geq$2 neurotoxicity; grade $\geq$3 nausea or vomiting for >48 hours or diarrhea for >72 hours; grade $\geq$3 hypertension; unexpected grade 2 toxicity requiring dose reduction/delay lasting >1 week; or any grade $\geq$3 adverse event.

Statistical analyses

Safety analyses included all patients who received at least one dose of mivebresib. Clinical activity analyses included all dosed patients who had at least one measurable lesion at baseline and at least one post-baseline tumor measurement. Pharmacokinetic analyses included all subjects who had a complete concentration-time profile.

Pharmacodynamic markers after 6 hours of mivebresib treatment were compared to baseline samples drawn prior to mivebresib administration. Linear regression analysis was used to assess the correlation between mivebresib C_{max} and biomarker expression levels. Linear regression model was also performed on C_{max} and maximum decrease in platelets compared with baseline (C1D1). The response variable was maximum decrease in platelets compared to baseline and the explanatory variable was C_{max}.

Descriptive statistics were used for analyses of demographics, safety, pharmacokinetics, best response, progression-free survival, and duration of overall response. A linear mixed effects model analysis was performed on dose-normalized C_{max} and

the $AUC_{0\text{-inf}}$ to evaluate pharmacokinetic dose linearity. All statistical analyses were exploratory, and significance was determined using a two-sided P value ≤ 0.05 unless otherwise stated.

Results

Patients

Between April 29, 2015, and May 24, 2018, 72 patients with solid tumors were enrolled in the dose escalation cohort. The most common primary tumor types were uveal melanoma (14%), colorectal (11%), breast (11%), pancreatic (8%), and head and neck (7%). As CRPC is hypothesized to show increased sensitivity to mivebresib as supported by preclinical models, an additional 12 patients were enrolled in a prostate expansion cohort. Median age for all 84 patients was 62.5 years (range 23–83); 42% were male. Patient demographics are summarized in Table 1. The prostate expansion cohort patients were older than the dose-escalation cohort, with a higher percentage of patients having ≥4 prior therapies, including both hormonal therapies and chemotherapeutic agents. The most common sites of baseline metastases for the prostate cancer expansion subjects were bone (10/12), lymph node (9/12), and liver (4/12).

Median treatment duration across all schedules of mivebresib was 8 weeks (range 1–40) for all patients ($N = 84$), 8 weeks (range 1–40) in dose escalation cohort ($N = 72$), and 8 weeks (range 1–11) for prostate cohort ($N = 12$).

All solid tumor patients ($N = 84$) discontinued mivebresib. For the dose escalation (DE) cohort ($N = 72$), primary reasons for discontinuation were documented as: radiologic progressive disease (63%), clinical progressive disease (13%), withdrew consent (8%), AE related to progression (3%), AE not related to progression (3%), lost to follow-up (3%), and other (8%). For the prostate expansion cohort ($N = 12$), primary reasons for discontinuation of mivebresib were similar: radiologic progressive disease (58%), clinical progressive disease (25%), withdrew consent (8%), and other (8%).

Table 1. Patient demographics and baseline characteristics

Characteristic, *n* (%)	Dose escalation *n* = 72	Prostate expansion *n* = 12	All patients *n* = 84
Age, median (range), years	61.5 (23–83)	70.0 (57–81)	62.5 (23–83)
Gender			
Female	49 (68)	0	49 (58)
Male	23 (32)	12 (100)	35 (42)
Race, *n* (%)			
White	68 (94)	11 (92)	79 (94)
Black	2 (3)	1 (8)	3 (4)
Asian	2 (3)	0	2 (3)
ECOG performance status			
0	28 (39)	4 (33)	32 (38)
1	44 (61)	8 (67)	52 (62)
Primary tumor occurring in >4% of patients			
Uveal melanoma[a]	10 (14)	0	10 (12)
Colorectal carcinoma[b]	8 (11)	0	8 (10)
Breast	8 (11)	0	8 (10)
Pancreatic	6 (8)	0	6 (7)
Head and neck	5 (7)	0	5 (6)
Prostate	3 (4)	12 (100)	15 (18)
Median number of prior therapies			
0	4 (6)	0	4 (5)
1	6 (8)	1 (8)	7 (8)
2	7 (10)	0	7 (8)
3	17 (24)	2 (17)	19 (23)
≥4	38 (53)	9 (75)	47 (56)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]Includes ciliochoroidal and choroidal melanoma.
[b]Includes colon, rectal, and colorectal patients.

Safety

TEAEs were reported in 96% of all patients (97% of dose escalation cohort and 92% of prostate expansion cohort). TEAEs related to mivebresib were reported in 88% of all patients (89% of dose escalation cohort and 83% of prostate expansion cohort). The most frequently reported TEAEs in all patients related to mivebresib were dysgeusia (49%), thrombocytopenia (48%), fatigue (26%), nausea (25%), decreased appetite (24%), diarrhea (21%), and anemia (18%), as summarized in Table 2 and by dose cohort in Supplementary Table S3.

Table 2. Summary of adverse events

	Dose escalation (*n* = 72)		Prostate expansion (*n* = 12)		All patients (*n* = 84)	
n (%)	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
AE in >20% of all patients[a]	70 (97)	52 (72)	11 (92)	10 (83)	81 (96)	62 (74)
Thrombocytopenia	38 (53)	24 (33)	5 (42)	5 (42)	43 (51)	29 (35)
Dysgeusia	36 (50)	2 (3)	5 (42)	0	41 (49)	2 (2)
Fatigue	29 (40)	3 (4)	7 (58)	2 (17)	36 (43)	5 (6)
Nausea	25 (35)	1 (1)	5 (42)	1 (8)	30 (36)	2 (2)
Decreased appetite	20 (28)	3 (4)	5 (42)	0	25 (30)	3 (4)
Anemia	19 (26)	13 (18)	4 (33)	3 (25)	23 (27)	16 (19)
Diarrhea	18 (25)	4 (6)	3 (25)	0	21 (25)	4 (5)
Vomiting	17 (23)	1 (1)	3 (25)	0	20 (24)	1 (1)
Dyspnea	14 (19)	7 (10)	4 (33)	0	18 (21)	7 (8)
AE related to mivebresib in >5% of all patients	64 (89)	40 (56)	10 (83)	8 (67)	74 (88)	48 (57)
Dysgeusia	36 (50)	2 (3)	5 (42)	0	41 (49)	2 (2)
Thrombocytopenia	35 (49)	24 (33)	5 (42)	5 (42)	40 (48)	29 (35)
Fatigue	20 (28)	3 (4)	2 (17)	1 (8)	22 (26)	4 (5)
Nausea	17 (24)	1 (1)	4 (33)	1 (8)	21 (25)	2 (2)
Decreased appetite	16 (22)	2 (3)	4 (33)	0	20 (24)	2 (2)
Diarrhea	16 (22)	4 (6)	2 (17)	0	18 (21)	4 (5)
Anemia	12 (17)	4 (6)	3 (25)	1 (8)	15 (18)	5 (6)
Vomiting	10 (14)	1 (1)	1 (8)	0	11 (13)	1 (1)
Hypertension	7 (10)	4 (6)	0	0	7 (8)	4 (5)
Hyperbilirubinaemia	7 (10)	1 (1)	0	0	7 (8)	1 (1)
Weight decreased	4 (6)	0	1 (8)	0	5 (6)	0
Rash maculo-papular	5 (7)	0	0	0	5 (6)	0
Any serious AE[a] in >5% of all patients	25 (35)		7 (58)		32 (38)	
Malignant neoplasm progression	6 (8)		1 (8)		7 (8)	
Abdominal pain	6 (8)		1 (8)		7 (8)	
Dyspnea	6 (8)		0		6 (7)	
Any serious AE related to mivebresib	4 (6)		4 (33)		8 (10)	
Thrombocytopenia	1 (1)		1 (8)		2 (2)	
Anemia	0		1 (8)		1 (1)	
Pneumonia	0		1 (8)		1 (1)	
GI hemorrhage	1 (1)		0		1 (1)	
Hypertension	1 (1)		0		1 (1)	
Nausea	0		1 (8)		1 (1)	
Fatigue	0		1 (8)		1 (1)	

[a]Regardless of relatedness to mivebresib, as assessed by the investigator.

Grade 3 or 4 TEAEs related to mivebresib were reported in 57% of all patients (56% of dose escalation cohort and 67% of prostate expansion cohort, and thrombocytopenia (35%) was the most common. Serious TEAEs regardless of relatedness to mivebresib were reported in 38% of all patients. Serious TEAEs related to mivebresib occurred in 10% of all patients (6% of dose escalation cohort and 33% of prostate expansion cohort), and thrombocytopenia (2%) was the most common (Table 2). There were no Grade 5 TEAEs reported that were related to mivebresib.

Based on the DLT of thrombocytopenia, we tested whether there was a significant ($P < 0.05$) negative correlation between platelet count decrease from baseline and C_{max} for each of the dose schedules (Supplementary Fig. S2). A linear regression model was performed on C_{max} and maximum decrease in platelets compared with baseline. P values were 0.237, 0.004, and 0.344 for daily, 4/7, and M-W-F dosing schedules, respectively (Supplementary Fig. S2). These results indicate that there is a linear relationship between C_{max} and platelets compared with baseline for the 4/7 dosing schedule, but not for daily and M-W-F dosing schedules. A statistically confirmed relationship between mivebresib plasma concentrations and blood pressure changes could not be established.

MTD and RP2D

In total, 23 patients entered the daily dosing schedule. The DLT for daily dosing was thrombocytopenia, which was reversible upon cessation of mivebresib dosing. In an attempt to allow platelet recovery, dose escalation using M-W-F and 4/7 dosing schedules were then initiated. Twenty-seven patients were enrolled on the M-W-F schedule and 22 patients entered the 4/7 schedule. Indeed, these alternate dosing schedules allowed higher daily doses to be tolerated, although the maximum tolerated total weekly doses were similar between schedules. Like daily dosing, the DLT for M-W-F was reversible thrombocytopenia. The DLT for the 4/7 schedule was reversible hypertension. Enrollment by cohort is presented in Table 3. In total, 12 DLTs were experienced by 10 patients (two patients experienced two DLTs each). The RP2D was determined to be the dose at which DLTs occurred in <17% of enrolled patients (no more than 1 in 6). The RP2Ds were determined to be 1.5 mg for the daily schedule, 2.5 mg for the 4/7 schedule, and 3 mg for the M-W-F schedule.

Clinical activity

There were 61 patients with solid tumors who were evaluable for tumor size change from baseline (Fig. 1A). Of those 26 (43%) had stable disease and 35 (57%) had progressive disease. For 10 additional patients, tumor size change was not evaluable, but the investigator concluded there was disease progression without quantification of tumor size change. Thus, there were 71 patients with a measurable disease response ($n = 61$ in the dose escalation and $n = 10$ in the prostate expansion).

As the study cohorts were small, it was difficult to evaluate whether the mivebresib schedule had influence on the clinical activity. It was observed that 8 of 19 patients on the daily schedule, 10 of 17 patients on the 4 of 7 schedule, and 8 of 25 patients on the M-W-F schedule had stable disease in the dose escalation cohort, which showed no detectable influence of the schedule on activity.

When analyzing the influence of dose, the large number of cohorts made statistical comparisons meaningless. Therefore, the cohorts were grouped as those with less than 8 mg dose/week, 8–10 and over 10 mg per week (Fig. 1A). Ten of 19 patients on <8 mg/week, 6 of 18 patients on 8–10 mg/week, and 10 of 24 patients on >10 mg/week had stable disease. A linear regression model is fitted with the response variable being tumor size percent change and the predictor variable being the weekly dose. The resulting p-value is 0.329. For the dose escalation cohort, 26 (43%) patients had a best response of stable disease, including four patients with stable disease ≥6 months, and 35 (57%) patients had progressive disease. For the prostate expansion cohort, 6 (60%) patients had stable disease and 4 (40%) patients had progressive disease. Among

Table 3. Patient enrollment by cohort and summary of DLTs and TTP

Cohort	Patients enrolled, *n*	Patients who completed DLT period	# Patients with DLTs, *n*	Number of DLTs	TTP median (months)	TTP range (months)
Daily						
1 mg	5	5	0	N/A	3.65	1.84–5.56
1.5 mg	10	8	0	N/A	0.97	0.03–7.33
2 mg	8	7	3	Thrombocytopenia, $n = 2$; Gastrointestinal hemorrhage, $n = 1$	1.79	0.95–2.89
4/7 days						
1 mg	5	4	0	N/A	3.65	0.03–3.78
2 mg	11	8	1	Hypertension, $n = 1$	1.74	0.03–9.17
2.5 mg	4	3	0	N/A	1.73	0.03–3.68
3 mg	2	2	2	Hypertension, $n = 3$	4.18	1.81–6.54
M-W-F						
1 mg	6	4	0	N/A	1.79	0.23–7.30
2 mg	4	4	0	N/A	1.86	1.68–3.75
3 mg	7	5	0	N/A	1.55	0.59–1.84
4 mg	5	5	2	Decreased appetite, $n = 1$ Fatigue, $n = 1$ AST elevation, $n = 1$	1.81	1.45–2.17
4.5 mg	5	4	2	Thrombocytopenia, $n = 2$	1.58	1.12–3.19

Abbreviations: AST, aspartate aminotransferase; M-W-F, Monday, Wednesday, Friday; N/A, not applicable.

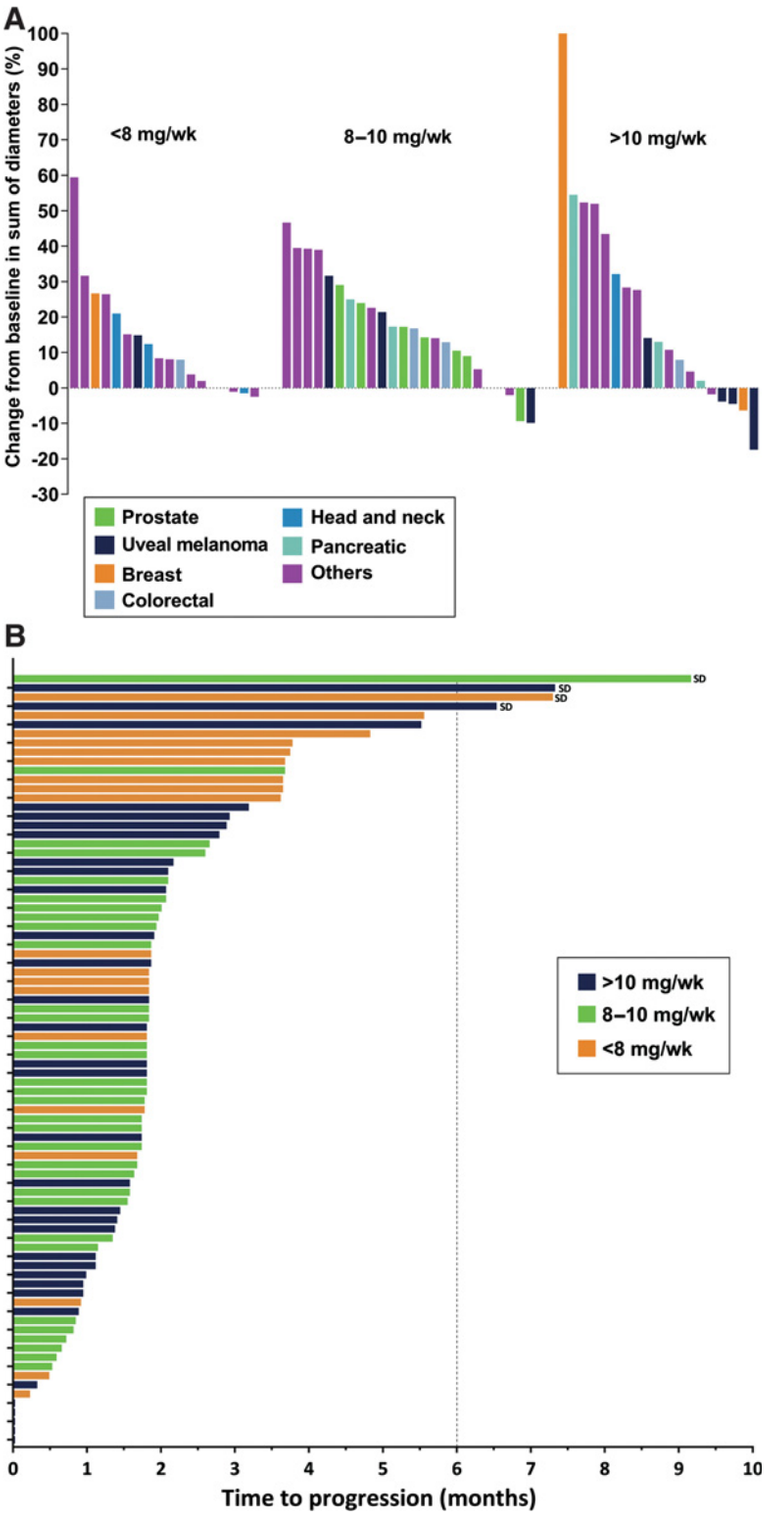

Figure 1.

A and **B,** Best percent change from baseline in sum of tumor diameters (**A**) and time to progression for all patients (**B**). A linear regression model was fitted with the response variable being tumor size percent change, and the predictor variable being the weekly dose (calculated based on dosing schedule). The resulting *P* value is 0.329. SD, stable disease: denotes four patients with a best response of stable disease for ≥6 months.

patients in the prostate cancer expansion cohort, new liver lesions were reported for 2 patients and a new lung lesion was reported for one patient. No new bone lesions were reported. PSA levels were measured at multiple time points for 11/12 prostate patients but did not show a consistent trend with clinical response (Supplementary Fig. S3).

Median time to progression was 1.8 months [95% confidence interval (CI), 1.8–2.0] for all 84 patients, and 1.9 months (95%

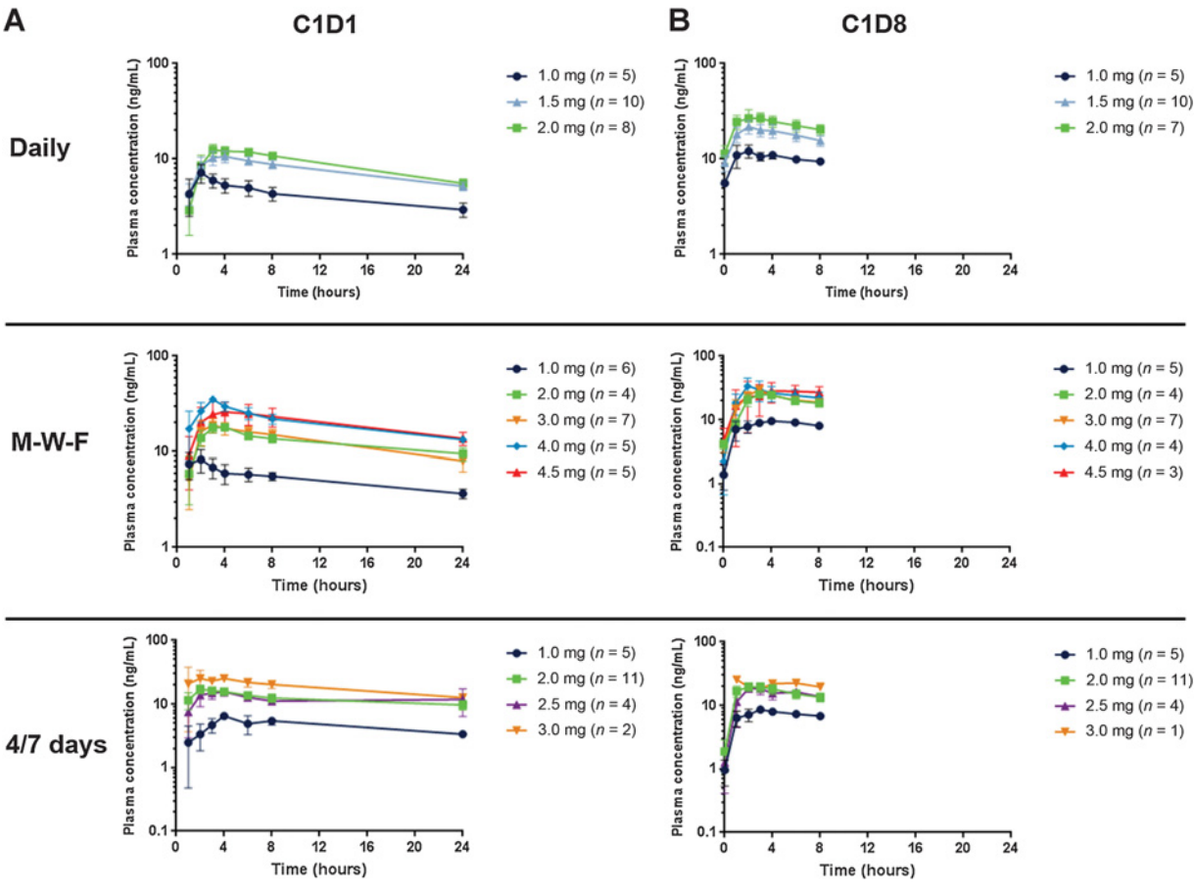

Figure 2.

Mean concentration–time profiles of mivebresib in cycle 1 day 1 (**A**) and cycle 1 day 8 (**B**) on a log-linear scale. Standard error bars are shown.

CI, 1.1–2.1) for the 12 patients in the prostate cohort (Fig. 1B; Supplementary Fig. S4). Time to progression by dose cohort is shown in Table 3.

Pharmacokinetics

Pharmacokinetic data are available from 72 patients at doses of 1, 1.5, 2, 2.5, 3, 4, and 4.5 mg (Fig. 2). Following a single oral 1 mg dose, the geometric mean (% coefficient of variation) of the C_{max} and the $AUC_{0\text{-}inf}$ were 6.98 (44%) ng/mL and 195 (40%) ng/h/mL, respectively (Supplementary Tables S4–S6).

The pharmacokinetics of mivebresib were not significantly different from linearity (i.e., were approximately dose proportional) over the studied dosing range based on dose-normalized cycle 1 day 1 C_{max} and the $AUC_{0\text{-}inf}$ ($P = 0.435$ and $P = 0.192$, respectively; Supplementary Fig. S5). The estimated median T_{max} was 3 hours (range: 1–8 hours) across all dosage regimens. Mivebresib had a generally monophasic drug disposition with an estimated harmonic mean terminal phase half-life of 16.1 to 19.9 hours across dosing schedules. On the basis of trough mivebresib plasma concentrations, steady-state pharmacokinetics was reached by cycle 1 day 8 with daily dose administration. The mivebresib steady-state accumulation ratio was approximately 2-fold, as measured by the $AUC_{0\text{-}24}$ on cycle 1 day 8 compared with cycle 1 day 1 with daily dosing. Pharmacokinetics appeared independent of the dosage regimen, as judged by mean concentrations by dose and dose-normalized exposure (AUC and C_{max}; Fig. 2, Supplementary Tables S4–S6).

Pharmacodynamic effects of mivebresib

In whole blood clinical samples, an increase of dicarbonyl and L-xylulose reductase (DCXR) gene expression and HEXIM1, and a decrease in CD93 expression were observed 6 hours after mivebresib administration (Fig. 3A). The changes were dose dependent; and the gene modulation did not reach a plateau at the highest dose administered (4.5 mg), suggesting that superior target engagement may be achieved at higher doses. The correlation with pharmacokinetics data confirmed the dose dependency, as shown by linear regression of C_{max} to gene expression modulation at 6 hours after dosing ($P < 0.05$). An association with DCXR ($P = 0.0004$) and CD93 ($P = 0.002$) was found, but not HEXIM1 ($P = 0.44$) (Fig. 3A; Supplementary Table S7).

Consistent downregulation of soluble brain-derived neurotrophic factor (BDNF) and upregulation of ferritin (FRTN) was observed in serum samples after mivebresib treatment (Fig. 3B). This modulation was time-dependent, and P-values were statistically significant ($P < 0.0001$) for both BDNF and FRTN when comparing each post baseline visit (C1D8, C2D1, and C3D1) to the baseline visit. When data were grouped on the basis of total

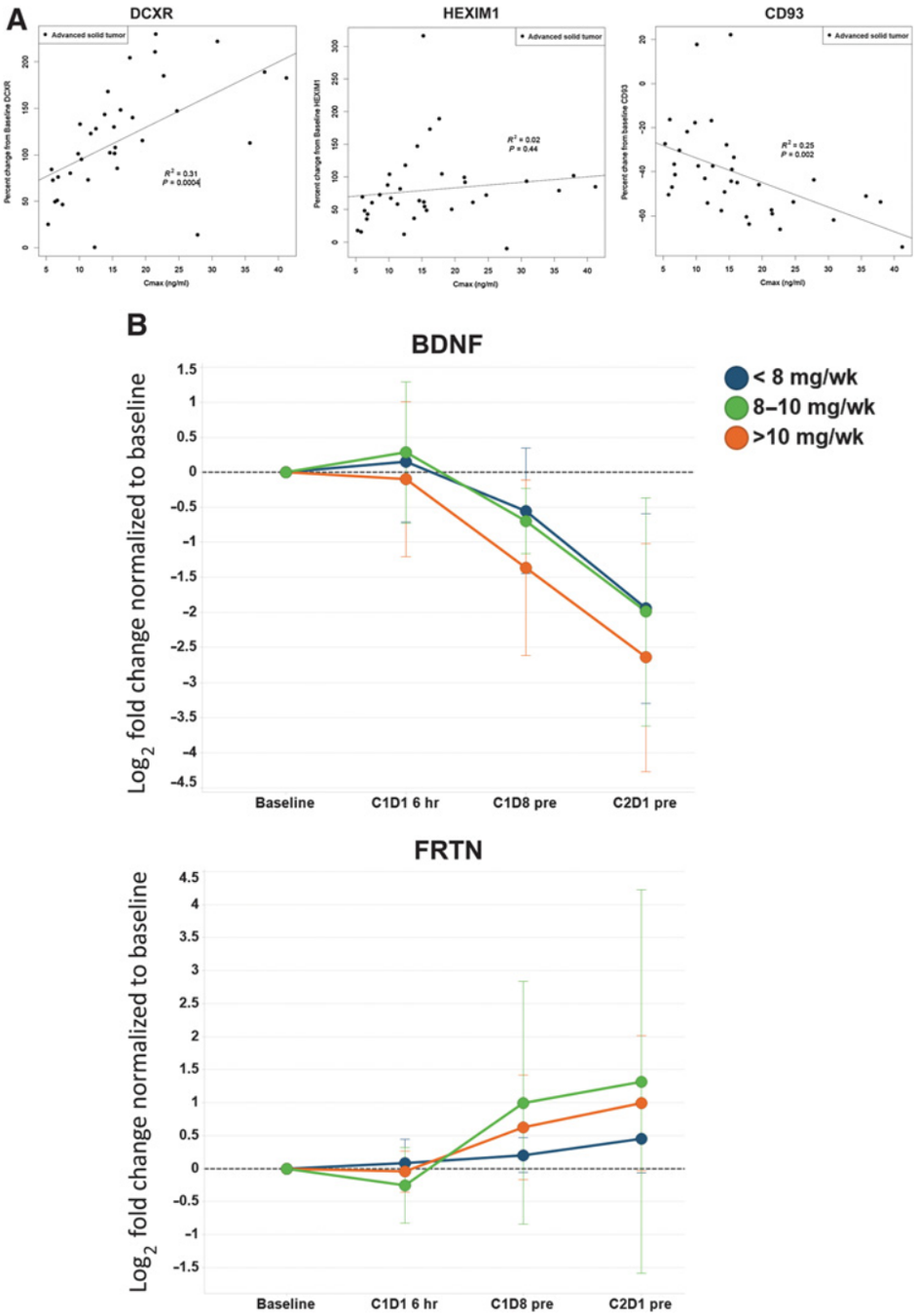

Figure 3.

A, Biomarker percent change from baseline versus mivebresib concentration at 6 hours after a single dose of mivebresib (on cycle 1 day 1) shows dose-dependent modulation in DCXR, HEXIM1, and CD93 expression. **B,** Time-dependent modulation of BDNF and ferritin in response to mivebresib. Linear regression was used to determine the correlation between cycle 1 day 1 C_{max} and biomarker percent change from baseline at 6 hours postdosing. The R^2 and P values are shown. C1D1, cycle 1 day 1; C1D8, cycle 1 day 8; C2D1, cycle 2 day; pre, prior to treatment with mivebresib. Part A: The number of patients at each dose was 1 mg: $n = 10$; 1.5 mg: $n = 9$; 2 mg: $n = 14$; 3 mg: $n = 8$; 4.5 mg: $n = 3$. Part B: The number of patients in each cohort was <8 mg/wk: $n = 20$; 8–10 mg/wk: $n = 18$; and >10 mg/wk: $n = 22$. A linear mixed model with repeated measurement was performed for the response variable BDNF or ferritin (FRTN) level change from baseline, and the predictor variable cycle time. P values were statistically significant ($P < 0.0001$) for BDNF and FRTN when comparing each post baseline visit (C1D8, C2D1, and C3D1) to baseline visit. A linear mixed model with repeated measurement was performed for the response variable FRTN (or BDNF) change from baseline and the predictor variable weekly dose. For FRTN, the least squares means were 0.4356, 0.2095, and 0.3225 for 8–10 mg/week, <8 mg/week, and >10 mg/week, respectively. For BDNF, the least squares means were -0.4496, -0.6594, and -0.9331 for 8–10 mg/week, <8 mg/week, and >10 mg/week, respectively. There was no statistically significant difference between 8–10 mg/week versus <8 mg/week and <8 mg/week versus >10 mg/week.

amount of mivebresib administered per week, a comparison across the various cohorts dosing schedules became possible. For this purpose, groups were defined as: <8 mg/week, 8 to 10 mg/week, or >10 mg/week mivebresib. We tested whether this showed dose dependence of the soluble biomarker modulation (Fig. 3B). A linear mixed model with repeated measurement was performed for the response variable FRTN (or BDNF) change from baseline and the predictor variable weekly dose. For FRTN, the least squares means were 0.4356, 0.2095 and 0.3225 for 8 to 10 mg/week, <8 mg/week, and >10 mg/week, respectively. There was no statistically significant difference among the three weekly dose groups. For BDNF, the least squares means were −0.4496, −0.6594, and −0.9331 for 8–10 mg/week, <8 mg/week, and >10 mg/week, respectively. There was no statistically significant difference between 8–10 mg/week *vs* <8 mg/week and <8 mg/week versus >10 mg/week.

Fresh tumor samples were collected from 36 patients to generate patient-derived xenograft mouse models to further define the biological activity of mivebresib. These studies are ongoing.

Discussion

This is the first study to describe the human pharmacokinetics, safety, and tolerability of the BET inhibitor mivebresib. Here, we report the results of a comprehensive dose escalation schema which evaluated mivebresib monotherapy in patients with advanced solid tumors. Among solid tumor patients, the recommended phase 2 doses varied with schedule between 9 and 10.5 mg/week. The most common treatment related adverse events were dysgeusia, thrombocytopenia, and fatigue, all of which were reversible. However, the observed activity in solid tumors was modest, with 26 of 61 patients achieving stable disease as assessed by the investigators. No complete or partial responses were reported. At the time of manuscript submission, an expansion study evaluating mivebresib monotherapy and combination with venetoclax in relapsed/refractory acute myeloid leukemia is ongoing.

The optimal schedule for BET inhibitors remains undetermined (32). Ideally, preclinical and clinical data would reveal the drug exposure and kinetics that maximize activity and minimize toxicity to determine the optimal clinical schedule. Unfortunately, for BET inhibitors this information is not yet available. With the theoretical concept of maximizing the area under the exposure curve, we began the mivebresib dose escalation with dosing daily. However, when a DLT of reversible thrombocytopenia was observed, other dosing schedules were evaluated. For all the schedules, dysgeusia was the most common adverse event attributed to mivebresib (49%), which correlates quite well with preclinically observed weight loss in rodents (data not shown). Also consistent with preclinical toxicology studies, thrombocytopenia and gastrointestinal effects were among the most common adverse events attributed to mivebresib clinically. The only suggestion of a schedule-dependent AE was hypertension, which was reported as a DLT in the 4/7 schedule. However, when available blood pressure measures were compared with PK exposure, a dose dependency could not be confirmed. One therefore can conclude that no clear schedule dependent adverse events pattern was observed clinically. The RP2D of mivebresib was 1.5 mg for the daily schedule, 2.5 mg for the 4/7 schedule, and 3 mg for the M-W-F schedule. When these daily doses are multiplied with the days of dosing per week, they represent weekly doses between 9 and 10.5 mg. Those values are as close as they could be given the available tablet sizes. Consistent with this, the mivebresib pharmacokinetics were also dose proportional and schedule independent across the dose range studied (1–4.5 mg). While PD markers were altered in a dose-dependent manner, neither the biomarker analyses nor the clinical activity showed schedule dependency. We therefore suggest that the schedule of mivebresib may be selected based on other criteria such as the schedule of other drugs given in combination, or the preference of the patient. After the dose escalation, the sponsor selected the M-W-F schedule for monotherapy in prostate cancer and daily doses for drug combinations with venetoclax in acute myeloid leukemia.

The pharmacokinetics of mivebresib were found to be quite independent of potential influences such as comedication. Based on a terminal phase half-life of 16.1 to 19.9 hours and a daily dosing accumulation ratio of 1.91-fold, administering mivebresib once-a-day will maintain continuous pharmacologic activity. Compared with other BET inhibitors evaluated in patients, mivebresib CL/F (4.94 L/hour) was comparable with birabresib (OTX-015; ref. 33) and RG6146 (3.55 to 6.21 L/hour; ref. 34), but somewhat lower than molibresib (GSK-525762; 9.17 L/hour; ref. 35). Both mivebresib and molibresib were rapidly absorbed, with T_{max} occurring within a few hours of dosing. Mivebresib, birabresib, and molibresib have all reported dose-proportional pharmacokinetics. The terminal phase half-life of mivebresib was 16.1 to 19.9 hours, about 1.5- to 3-fold longer than the $t_{1/2}$ of birabresib (5.8 hours) and RG6146 (10 hours). However, the accumulation ratio for mivebresib and RG6146 were similar, indicating the differences in effective half-life are likely minimal.

Biomarker analyses of BET inhibitor effects are challenged by the diverse set of transcriptional pathways, which are modulated by the BET family of proteins. In general, the measurable effects of mivebresib on pharmacodynamic markers are fast. In *ex vivo* studies, gene modulation was seen to be acute, with the strongest effect at 6 hours. The effect was rapidly reversible and returned to baseline within 24 hours. In our phase I study, the most robust indicators of target engagement appeared to be CD93 and DCXR. DCXR encodes for a protein that plays an important role in glucose metabolism (36, 37). CD93 is known as a myeloid marker involved in cell adhesion and clearance of apoptotic cells (38). The mechanism of mivebresib-induced modulation of these biomarkers remains to be elucidated. Among other BET inhibitors, HEXIM1 is an established PD marker for monitoring target engagement (39, 40). However, although HEXIM1 was consistently modulated in our data, the correlation of gene modulation with exposure was suboptimal. Our findings suggest that DCXR and CD93 may be superior PD markers for mivebresib than HEXIM1 in whole blood. When analyzing serum only, inflammatory markers may serve as biomarkers as they are also known to show robust modulation after BET inhibition (41). The current study confirmed that finding: mivebresib induced a consistent downregulation of BDNF and upregulation of ferritin in serum samples.

The safety of mivebresib is consistent with other BET inhibitors that have been described. A recent study of the BET inhibitor birabresib in solid tumor patients reported nausea (39%), diarrhea (37%) and thrombocytopenia (22%) among the most common AEs (32). Similarly, molibresib treatment resulted in thrombocytopenia (44%), nausea (40%), and vomiting (29%) (42). A first-in-human study of BMS-986158 in patients with solid tumors also reported reversible thrombocytopenia as the only dose-limiting toxicity (43).

Tumor activity is not the primary endpoint of a typical first-in-human study. The data presented here show evidence of modest clinical antitumor activity in the dose escalation study, with 26 of 61 patients (43%) experiencing stable disease, of which 4 patients had stable disease $\geq$6 months. There was no hint of a schedule dependency for the clinical activity. Although dose dependency cannot be established, data in Fig. 1A suggest that the patients receiving higher doses may have experienced greater decreases in tumor size. With respect to tumor type, only two cancer diagnoses were common enough to consider diagnosis-specific effects: prostate cancer and uveal melanoma. As mivebresib has shown preclinical activity in castrate-resistant prostate cancer models, we enrolled an additional 12 patients in a prostate cancer expansion cohort. Slightly higher stable disease rates were observed (60%) in the prostate cancer expansion cohort. However, this may reflect a dose response effect rather than the tumor specific sensitivity, since these patients were treated at the RP2D. The uveal melanoma patients were all enrolled during the dose escalation and thus

treated with different doses and schedules. Among those patients, there is the suggestion of a dose-dependent relationship.

As the monotherapy activity of mivebresib at the doses tested in this trial was modest, understanding potential biomarkers that are predictive of response will be very important for the design of future clinical trials. In addition, emerging data from *in vitro* studies indicate that BET inhibitors, such as mivebresib, may have improved activity when used in combination therapy (5, 44). To this end, studies of the BET inhibitors GS-5829 and ZEN-3694 in combination with enzalutamide are ongoing in CRPC (NCT02607228, NCT02711956). Several recent studies have also provided strong preclinical rationale for the combination of a BET inhibitor and PARP inhibitor in solid tumors (45–47). In addition, BET inhibitors may be more efficacious in hematological cancers than in solid tumors (5, 48, 49), and preclinical studies have demonstrated synergy between mivebresib and venetoclax in acute myeloid leukemia (5). A phase I expansion study is therefore currently ongoing to evaluate the activity of mivebresib as a monotherapy and in combination with venetoclax in acute myeloid leukemia (NCT02391480).

Disclosure of Potential Conflicts of Interest

S.A. Piha-Paul reports receiving other commercial research support from AbbVie, Inc., Aminex Therapeutics, Genmab A/S, GlaxoSmithKline, Helix BioPharma Corp, Incyte Corp., Jacobio Pharmaceuticals Co., Ltd., Medimmune, LLC, Medivation, Inc., Merck Sharp and Dohme Corp., NewLink Genetics Corporation/Blue Link Pharmaceuticals, Novartis Pharmaceuticals, BioMarin Pharmaceutical, Inc., Pieris Pharmaceuticals, Inc., Pfizer, Principia Biopharma, Inc., Puma Biotechnology, Inc., Seattle Genetics, Taiho Oncology, Tesaro, Inc., TransThera Bio, XuanZhu Biopharma, Boehringer Inglheim, Bristol-Myers Squib, Cerulean Pharma Inc., Chugai Pharmaceutical Co., Ltd., Curis, Inc., Five Prime Therapeutics, and Flex Bio, Inc. J.C. Sachdev reports receiving commercial research grants from Pfizer, Genentech, and Celgene and is a consulting/advisory board member for Novartis, Puma, SyndevRx, TapImmune, TTC Oncology, Ipsen, and Celgene. P.M. LoRusso is a consultant/advisory board member for AbbVie, Agenus, Cybrexa, SOTIO, I-MAB, Genmab, TRGR, IQVIA, Pfizer, and CytomX and has provided expert testimony for Agios, Five Prime, Tyme, and Halozyme. R.Z. Szmulewitz is a consultant/advisory board member for Abbvie, Astellas, Pfizer, Janssen, and Merck. S.P. Patel has received speakers bureau honoraria from Merck and is a consultant/advisory board member for Castle Biosciences, Incyte, and Cardinal Health. P.N. Lara is a consultant/advisory board member for AstraZeneca, Genentech, Janssen, Foundation Medicine, Merck, CellMax, and Nektar. X. Chen has ownership interest (including stock, patents, etc.) in AbbVie. K.J. Freise has ownership interest (including stock, patents, etc.) in AbbVie. A. Sood has ownership interest (including stock, patents, etc.) in AbbVie Inc. J.E. Hutti has ownership interest (including stock, patents, etc.) in AbbVie Inc. J. Wolff has ownership interest (including stock, patents, etc.) in AbbVie. B.H. O'Neil is the medical director at Lilly. No potential conflicts of interest were disclosed by the other authors.

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