A Phase I/II Study of GSK525762 Combined with Fulvestrant in Patients with Hormone Receptor–positive/HER2-negative Advanced or Metastatic Breast Cancer

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ABSTRACT

Purpose: Endocrine-based therapy is the initial primary treatment option for hormone receptor–positive and human epidermal growth factor receptor 2-negative ($HR^+/HER2^-$) metastatic breast cancer (mBC). However, patients eventually experience disease progression due to resistance to endocrine therapy. Molibresib (GSK525762) is a small-molecule inhibitor of bromodomain and extraterminal (BET) family proteins (BRD2, BRD3, BRD4, and BRDT). Preclinical data suggested that the combination of molibresib with endocrine therapy might overcome endocrine resistance. This study aimed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy [objective response rate (ORR)] of molibresib combined with fulvestrant in women with $HR^+/HER2^-$ mBC.

Patients and Methods: In this phase I/II dose-escalation and dose-expansion study, patients received oral molibresib 60 or 80 mg once daily in combination with intramuscular fulvestrant. Patients enrolled had relapsed/refractory, advanced/metastatic $HR^+/HER2^-$ breast cancer with disease progression on prior treatment with an aromatase inhibitor, with or without a cyclin-dependent kinase 4/6 inhibitor.

Results: The study included 123 patients. The most common treatment-related adverse events (AE) were nausea (52%), dysgeusia (49%), and fatigue (45%). At a 60-mg dosage of molibresib, >90% of patients experienced treatment-related AE. Grade 3 or 4 treatment-related AE were observed in 47% and 48% of patients treated with molibresib 60 mg and molibresib 80 mg, respectively. The ORR was 13% [95% confidence interval (CI), 8–20], not meeting the 25% threshold for proceeding to phase II. Among 82 patients with detected circulating tumor DNA and clinical outcome at study enrollment, a strong association was observed between the detection of copy-number amplification and poor progression-free survival (HR, 2.89; 95% CI, 1.73–4.83; $P < 0.0001$).

Conclusions: Molibresib in combination with fulvestrant did not demonstrate clinically meaningful activity in this study.

Introduction

Breast cancer is the most common malignancy among women worldwide (1). One out of every eight females will be affected by invasive breast cancer during her lifetime (2). In the approximately 70% of people with metastatic breast cancer (mBC) whose tumors express hormone receptors (HR^+) in the absence of HER2 overexpression or amplification (i.e., $HR^+/HER2^-$ breast cancer), endocrine therapy is the cornerstone of initial treatment, reserving cytotoxic chemotherapy for when tumors no longer respond to endocrine agents (3, 4). While 50% of patients with estrogen receptor (ER)-positive mBC achieve a complete response (CR) or partial response (PR) with endocrine-based therapy, the remaining patients nearly all eventually experience disease progression due to intrinsic or acquired resistance (5). Current first-line treatment for $HR^+/HER2^-$ mBC includes targeted therapy with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in combination with an endocrine treatment (6). Subsequent lines of therapy are less clearly established (4). Fulvestrant, a selective ER degrader, is widely used in clinical practice; initial studies have demonstrated noninferiority of fulvestrant compared with tamoxifen, a selective ER modulator (7). However, response rates and progression-free survival (PFS) achieved with fulvestrant in the second-line setting are poor. Therefore, more effective therapies are needed and combining targeted agents with fulvestrant in this setting is a strategy of interest (8).

GSK525762 (molibresib) is a small-molecule inhibitor of bromodomain and extraterminal (BET) family proteins (BRD2, BRD3, BRD4, and BRDT). BET proteins are crucial for the transcription of many genes affecting cell proliferation, differentiation, and survival, and are currently being evaluated as a therapeutic target for certain hematologic malignancies and a range of solid tumors (9, 10). In the first-in-human phase I trial of molibresib monotherapy in NUT carcinoma and other solid tumors, 80 mg daily was identified as the recommended phase II dose (RP2D), with thrombocytopenia and gastrointestinal-related side effects being the principal adverse events

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Translational Relevance

Patients previously treated with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) tend to progress rapidly on second-line endocrine therapy. Ongoing efforts to improve endocrine-based strategies for CDK4/6i-resistant disease are required. This is the first study to investigate the clinical outcome of the combination of a bromodomain and extraterminal (BET) inhibitor, molibresib, in combination with a hormonal agent, the selective estrogen receptor degrader fulvestrant, in patients with advanced or metastatic hormone receptor–positive/HER2-negative breast cancer. The objective response rate (ORR) of molibresib at 60 mg combined with fulvestrant was 13%. The ORR in CDK4/6i-naïve and CDK4/6i-pretreated patients was 21% and 12%, respectively, which did not meet the criteria for ongoing development. Baseline circulating tumor DNA (ctDNA) level measured by somatic variants and copy-number amplification status correlated with poor progression-free survival in the study population. ctDNA kinetics assessed at baseline and on treatment may provide additional information to identify prognostic groups and provide early markers to anticipate treatment response or failure, enhancing patient stratification and ongoing drug development in this setting.

(AE) observed (11). Target engagement and proof-of-concept efficacy in NUT carcinoma were observed. Together, BET inhibition and fulvestrant demonstrate synergistic effects against tumor cell growth in treatment-resistant breast cancer cell lines *in vitro* and *in vivo* (12). The current study (NCT02964507) aimed to test the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of this combination in women with advanced HR$^+$/HER2$^-$ breast cancer. On the basis of the AE observed in the phase I study, dosing levels (DL) of 80 and 60 mg were selected for evaluation in combination with fulvestrant in this breast cancer population.

Patients and Methods

Study design

This study was a phase I/II, dose-escalation, dose-expansion (phase I), and randomized controlled (phase II) study with oral administration of molibresib in combination with fulvestrant in women with advanced or metastatic HR$^+$/HER2$^-$ breast cancer. The study was initiated on February 2, 2017. An overview of study enrollment, allocation, follow-up, and analysis is shown in **Fig. 1**. The study was approved by an Institutional Review Board and was conducted in accordance with all applicable regulatory requirements and the guiding principles of the Declaration of Helsinki. All patients provided signed informed consent.

Patients were enrolled into cohorts based on whether they had received a CDK4/6i in combination with an aromatase inhibitor (AI) in the metastatic setting, including those who relapsed during treatment or within 12 months of completion of adjuvant therapy with an AI, or who progressed to advanced/metastatic disease. In addition, patients who had disease that progressed after treatment with a CDK4/6i plus AI, whose treatment duration was of at least 12 months, were included (Supplementary Fig. S1). Patients with either measurable disease or bone-only disease were allowed. Prior ovarian suppression and/or tamoxifen were allowed if other criteria were met. The initial target enrollment was approximately 140 patients in phase I and approximately 154 patients in phase II.

The aim of phase I was to investigate the combination treatment of molibresib plus fulvestrant in two distinct populations, those with AI failure and those with CDK4/6i plus AI failure and to determine a recommended phase II dose (RP2D) based on safety, tolerability, pharmacokinetics, and efficacy profiles. To detect a clinically meaningful response rate, a target objective response rate (ORR) of 25% was selected. This represents a more than doubling of the historical rate and matches the ORR observed in the pivotal PALOMA3 trial of palbociclib/fulvestrant (13).

Phase II would explore the clinical activity of molibresib and fulvestrant when given in combination to participants with advanced or metastatic HR$^+$/HER2$^-$ breast cancer. The primary endpoint of phase II was PFS. The design for phase II was to be finalized based on the results from phase I; however, phase II of the study was not initiated on the basis of the results from phase I.

Phase I

The primary objective of phase I was to determine the RP2D of molibresib, when given in combination with fulvestrant, in women with advanced or metastatic HR$^+$/HER2$^-$ breast cancer. Secondary objectives included safety, tolerability, and maximum tolerated dose (MTD) of molibresib to evaluate clinical activity and to characterize the exposure of molibresib when given in combination with fulvestrant (see **Table 1** for details).

This phase comprised two parallel cohorts in which patients received molibresib 60 mg plus fulvestrant (DL1). DL1 cohort 1 comprised patients with previous AI failure (with no prior CDK4/6i) and DL1 cohort 2 comprised patients with previous CDK4/6i plus AI failure. DL2 included patients from both cohorts and patients were treated with molibresib 80 mg plus fulvestrant. Each DL included the standard fixed dose of fulvestrant 500 mg intramuscularly (i.m.) on days 1, 15, and 29 of cycle 1 and then monthly thereafter.

If unacceptable toxicity was observed at the 60-mg DL, then 40 mg once daily would be explored. If unacceptable toxicity was observed at the 80-mg DL, then 60 mg once daily would be further explored. Additional doses and schedules could be explored on the basis of emerging safety, pharmacokinetic, and pharmacodynamic data. Patients continued treatment until unacceptable toxicity, progression of disease, withdrawal of consent, or death. After the RP2D was established, any patients who were still receiving therapy with molibresib and fulvestrant could continue receiving the drug(s) until progression, death, withdrawal of consent, or unacceptable toxicity. Dose-escalation decisions were made based on data from a sentinel group (comprising patients enrolled in both cohorts) of at least three and up to 10 patients, who were formally evaluated for safety using a modified toxicity probability interval method (mTPI) in a given DL prior to expansion of the DL (14). If the dose-limiting toxicity (DLT) rate of the DL1 sentinel group did not exceed the maximum permitted toxicity rate as defined by the mTPI, then two events would occur in parallel: (i) At DL1, additional participants were enrolled into each cohort and (ii) evaluation of DL2 would begin. Each cohort (two at each DL) could enroll up to 35 patients, for a total of approximately 70 patients enrolled at each DL. The total number of patients enrolled into each cohort could vary, as interim analyses for safety and efficacy could terminate any cohort if the DLT rate exceeded the maximum permitted toxicity rate per the mTPI, or if the efficacy rate did not exceed the historical ORR. The mTPI design assumed that approximately 30 patients would complete the DLT evaluation period and that the true underlying toxicity rate for molibresib in combination with fulvestrant would fall between 25% and 35% and would be centered at 30%. The mTPI decision rules were based on the number of DLTs; an event was

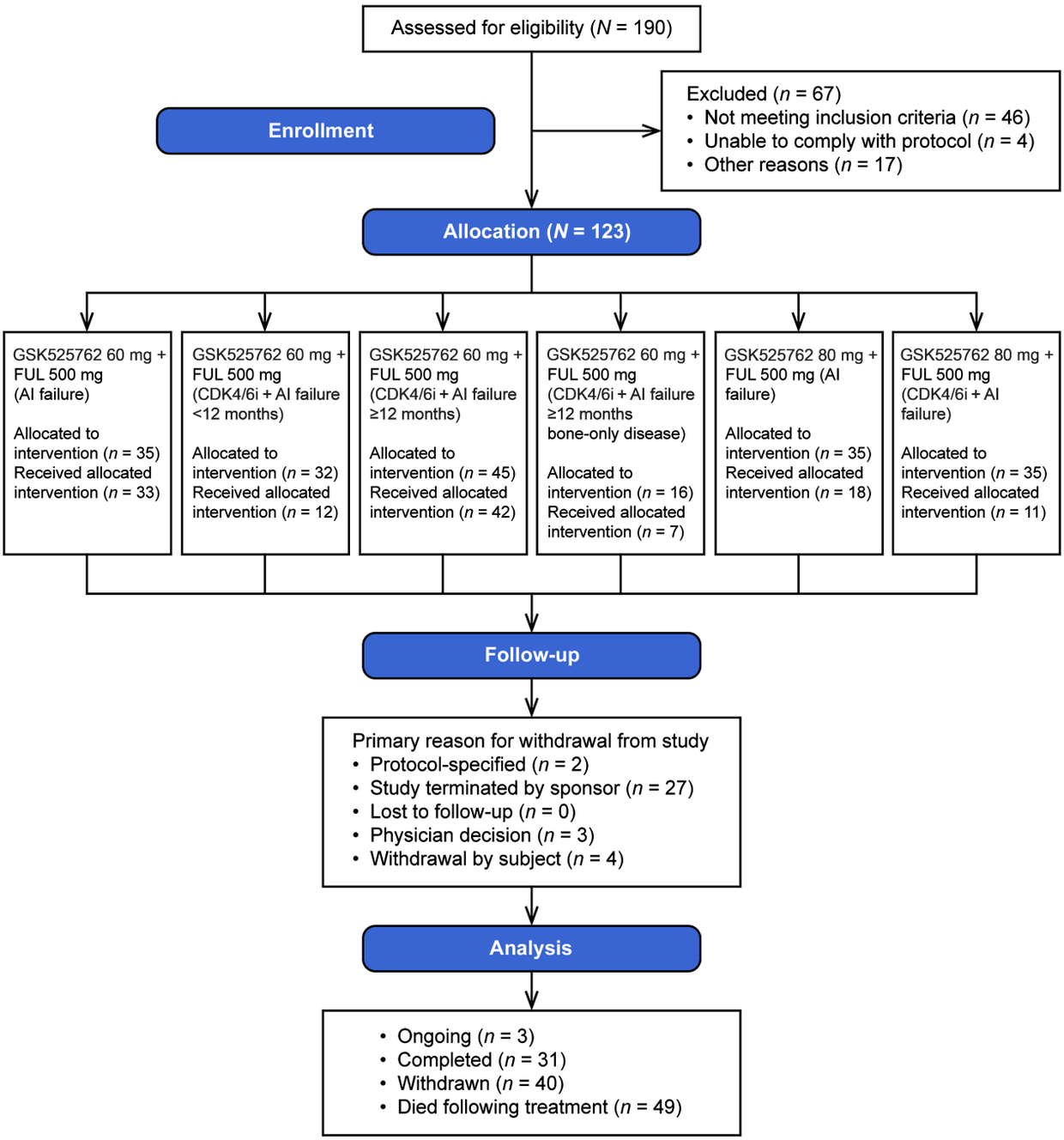


Figure 1.

CONSORT diagram for study 201973. Allocation to the GSK525762 60 mg + FUL 500 mg (CDK4/6i + AI failure ≥12 months bone-only disease), GSK525762 80 mg + FUL 500 mg (AI failure), and GSK525762 80 mg + FUL 500 mg (CDK4/6i + AI failure) groups was low because enrollment time was not adequate before the termination of the study. This is because the bone-only disease group was added later in the study, and the 80-mg cohort was stopped early; high rates of treatment discontinuation due to AE resulted in the 80-mg dose being judged to be nontolerable. AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; FUL, fulvestrant.

considered to be a DLT if it occurred within the first 28 days of treatment and met at least one of the criteria shown in Supplementary Table S1. Unacceptable toxicity was defined as the execution of the dose-exclusion rule in the mTPI. Patients in the sentinel groups were replaced if they were unable to receive at least 75% of the scheduled doses (of both agents, at the intended strength) during the 28-day DLT observation period for reasons other than toxicity. Once the sentinel groups had cleared, all further patients were not replaced if they discontinued prematurely.

Upon completion of phase I, all available data (including data from patients who prematurely discontinued therapy) were compiled and summarized. The decision not to proceed to phase II was based on the

Table 1. Phase I study 201973: primary and secondary objectives and endpoints.

Objectives	Endpoints
Primary	
To determine a RP2D of molibresib, when given in combination with fulvestrant, in women with advanced or metastatic HR$^+$/HER2$^-$ breast cancer	Safety profile (e.g., AE, SAE, DLT, dose reductions, or delays), ORR, defined as CR rate plus PR rate, PK data
Secondary	
• To determine the safety, tolerability, and MTD of molibresib, when given in combination with fulvestrant, in women with advanced or metastatic HR$^+$/HER2$^-$ breast cancer • To evaluate the clinical activity of molibresib and fulvestrant, when given in combination, in women with advanced or metastatic HR$^+$/HER2$^-$ breast cancer • To characterize the exposure to molibresib and fulvestrant, when given in combination	• AE, SAE, dose reductions or delays, withdrawals due to toxicities, and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc.) • DCR (defined as CR plus PR plus SD rate ≥6 mo), duration of response, and PFS • Concentrations of molibresib, molibresib-relevant metabolites, and fulvestrant following administration in combination

Abbreviations: AE, adverse event; CR, complete response; DCR, disease control rate; DLT, dose-limiting toxicity; ECG, electrocardiogram; HR$^+$/HER2$^-$, hormone receptor-positive/human epidermal growth factor receptor 2-negative; MTD, maximum tolerated dose; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; RP2D, recommended phase II dose; SAE; serious adverse event; SD, stable disease.

totality of data from phase I, including safety, efficacy (with target ORRs as detailed in the "Statistical analysis" section), pharmacokinetic, and pharmacodynamic data.

Phase II

Phase II of the study was designed as a randomized, double-blind, placebo-controlled cohort to evaluate the RP2D dose selected at the end of phase I. This cohort would compare the efficacy of molibresib in combination with fulvestrant versus fulvestrant with molibresib-matched placebo in patients with disease that progressed on anti-estrogen and/or one or more AI, or failure of a combination treatment with CDK4/6i plus AI, or a combination of both groups/patient populations.

Pharmacokinetics

Blood samples for pharmacokinetic analysis of molibresib and its active metabolite composite in plasma were collected. Sparse sampling was utilized, and samples were collected on week 1 day 1 (predose, 30 minutes ± 5 minutes, 1 hour ± 10 minutes, and 3 hours ± 30 minutes), week 3 day 1 (predose, 30 minutes ± 5 minutes, 1 hour ± 10 minutes, and 3 hours ± 30 minutes), week 5 day 1 (predose, 0.5–1 hour postdose, and optional sample 4–8 hours postdose), and at week 9 and thereafter (predose and 0.5–1 hour postdose) until study termination. Predose samples were split to obtain a pharmacokinetic sample for fulvestrant analysis. Plasma concentrations of molibresib, its two active metabolites [measured together and termed the "active metabolite composite" (GSK3529246)] and total active moiety, were quantified using a validated high-performance liquid chromatography–mass spectrometry–mass spectrometry method (GSK data on file). The pharmacokinetic parameters estimated for molibresib, GSK3529246, and total active moiety included the maximum observed plasma concentration (C_{max}), the time to C_{max} (t_{max}), and trough concentration (C_{trough}).

Biomarker analysis

Plasma samples were collected at baseline and week 4 posttreatment and were sequenced using the Guardant 360 panel (74 genes). Baseline circulating tumor DNA (ctDNA) level was calculated as mean variant allelic frequency (VAF) values of baseline somatic variants; ctDNA high was defined as ≥ median and ctDNA low as < median. Genes with nonsynonymous mutations were assessed for outcome association. For ctDNA molecular response (MR) calculation, only somatic variants with VAF ≥0.3% at either baseline or week 4 were included, and a decrease of ≥50% from baseline mean VAF was used as in previous studies (15). A sample was defined as having copy-number amplification (CNA) if the copy number (CN) of a gene was >2, otherwise it was defined as CN neutral. Correlations of baseline ctDNA, gene mutations, and MR with outcome were estimated using the Kaplan–Meier method.

Statistical analysis

For the evaluation of safety in phase I, no formal statistical hypotheses were tested; all data were pooled, and descriptive analyses were summarized and listed by dosing cohort at the end of phase I. Dosing escalation decisions were based on the totality of clinical safety assessment data in addition to pharmacokinetic data. For the evaluation of efficacy, the primary goal was to demonstrate a clinically meaningful response rate, defined as an ORR (CR+PR) of ≥25% (vs. ≤10% per the null hypothesis) in the AI failure cohort and ≥20% (vs. ≤5% per the null hypothesis) in the CDK4/6i + AI failure cohort. Up to 35 patients with measurable disease per DL in cohort 1 and 32 patients with measurable disease per DL in cohort 2 could be enrolled to collect safety/tolerability, pharmacokinetic, pharmacodynamic, and efficacy data. Sixteen patients with bone-only disease could be enrolled into DL1 cohort 2. To determine the maximum sample size for each cohort, Bayesian predictive adaptive design was used for testing hypotheses and sample size determination, per the null and alternative hypotheses listed above. For cohort 1, with a maximum sample size of 35 patients, the design had a type I error (α) of 0.098 and 80% power. For cohort 2, with a maximum sample size of 32, the design had a type I error (α) of 0.0535 and 81% power. If the treatment effect was positive, the design would maintain at least 80% power and a type I error rate of ≤0.09 for individual cohorts. If both DL were positive, the chance of advancing to phase II would be as high as 94%.

Data availability

Information on GSK's data-sharing commitments and requesting access to anonymized individual participant data and associated documents from GSK-sponsored studies can be found at https://www.clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-GSK.aspx.

Results

In total, 190 patients were screened for phase I, 124 were enrolled, and 123 patients received at least one dose of oral molibresib 60 or 80 mg in combination with i.m. fulvestrant (500 mg; **Fig. 1**). Fifty-eight percent of the patients were exposed to molibresib for <3 months. Among the patients treated, 119 patients experienced at least one AE related to the study treatment. An overview of AE is given in **Table 2** and Supplementary Table S2. The most common treatment-related AE

Table 2. AE overview.

Cohort	DL1 molibresib 60 mg + FUL 500 mg (*n* = 94)	DL2 molibresib 80 mg + FUL 500 mg (*n* = 29)	Total (*N* = 123)
Any AE, *n* (%)	94 (100)	29 (100)	123 (100)
AE related to study treatment	90 (96)	29 (100)	119 (97)
AE leading to permanent discontinuation of study treatment	14 (15)	3 (10)	17 (14)
AE leading to dose reduction	22 (23)	13 (45)	35 (28)
AE leading to dose interruption/delay	64 (68)	22 (76)	86 (70)
Any SAE, *n* (%)	19 (20)	8 (28)	27 (22)
SAE related to study treatment	11 (12)	4 (14)	15 (12)
Fatal SAE	2 (2)	0	2 (2)
Fatal SAE related to study treatment	0	0	0

Abbreviations: AE, adverse event; DL, dosing level; FUL, fulvestrant; SAE; serious adverse event.

(≥20%) were nausea (52%), dysgeusia (49%), fatigue (45%), decreased appetite (39%), diarrhea (38%), hyperglycemia (30%), platelet count decreased (25%), blood bilirubin increased (24%), alanine aminotransferase increased (21%), aspartate aminotransferase increased (20%), thrombocytopenia (20%), and anemia (20%); a summary of treatment-related AE occurring in ≥10% of patients is shown in **Table 3**.

The most common AE (≥5%) leading to dose delays or interruptions in 86 patients (70%) were platelet count decreased, fatigue, decreased appetite, nausea, blood bilirubin increased, thrombocytopenia, troponin T increased, asthenia, and vomiting. In addition, the most common AE (≥5%) leading to dose reductions in 35 patients (28%) were platelet count decreased and decreased appetite. Overall, a total of 67% of patients had dose interruptions or delays of molibresib at any dose. Thirty-six percent of patients had a dose reduction; the majority of these (78%) were due to experiencing an AE. A summary of AE classified as DLT is shown in Supplementary Table S3. A total of 97% of patients discontinued study treatment; the majority of discontinuations (72%) were due to progressive disease. The most common AE leading to permanent discontinuation in 17 patients (14%) were acute kidney injury (2%) and dysgeusia (2%). Finally, the most common treatment-related serious AE in 15 patients (12%) was acute kidney injury (mostly secondary to related gastrointestinal toxicity).

A total of 47% and 48% of patients experienced grade 3 to 4 AE related to study treatment in the DL1 and DL2 cohorts, respectively.

Table 3. Summary of most common (≥10%) treatment-related AE by maximum grade for any treatment.

Preferred term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3+4+5	Total (*N* = 123)
Nausea	41 (33%)	21 (17%)	2 (2%)	0	0	2 (2%)	64 (52%)
Dysgeusia	39 (32%)	21 (17%)	0	0	0	0	60 (49%)
Fatigue	17 (14%)	31 (25%)	7 (6%)	0	0	7 (6%)	55 (45%)
Decreased appetite	22 (18%)	23 (19%)	3 (2%)	0	0	3 (2%)	48 (39%)
Diarrhea	37 (30%)	8 (7%)	2 (2%)	0	0	2 (2%)	47 (38%)
Hyperglycemia	21 (17%)	11 (9%)	5 (4%)	0	0	5 (4%)	37 (30%)
Platelet count decreased	8 (7%)	8 (7%)	15 (12%)	0	0	15 (12%)	31 (25%)
Blood bilirubin increased	12 (10%)	15 (12%)	2 (2%)	0	0	2 (2%)	29 (24%)
ALT increased	23 (19%)	1 (<1%)	2 (2%)	0	0	2 (2%)	26 (21%)
AST increased	21 (17%)	4 (3%)	0	0	0	0	25 (20%)
Anemia	12 (10%)	9 (7%)	3 (2%)	0	0	3 (2%)	24 (20%)
Thrombocytopenia	10 (8%)	7 (6%)	8 (7%)	0	0	8 (7%)	25 (20%)
Dyspnea	12 (10%)	6 (5%)	1 (<1%)	0	0	1 (<1%)	19 (15%)
Vomiting	17 (14%)	4 (3%)	0	0	0	0	21 (17%)
Dry mouth	19 (15%)	1 (<1%)	0	0	0	0	20 (16%)
Rash	18 (15%)	2 (2%)	0	0	0	0	20 (16%)
Pruritus	12 (10%)	4 (3%)	0	0	0	0	16 (13%)
Asthenia	6 (5%)	5 (4%)	4 (3%)	0	0	4 (3%)	15 (12%)
Headache	10 (8%)	4 (3%)	1 (<1%)	0	0	1 (<1%)	15 (12%)
Cough	9 (7%)	5 (4%)	0	0	0	0	14 (11%)
Stomatitis	9 (7%)	4 (3%)	0	0	0	0	13 (11%)
Amylase increased	5 (4%)	4 (3%)	3 (2%)	0	0	3 (2%)	12 (10%)
Dry skin	12 (10%)	0	0	0	0	0	12 (10%)
Epistaxis	12 (10%)	0	0	0	0	0	12 (10%)
Hot flush	12 (10%)	0	0	0	0	0	12 (10%)
Weight decreased	9 (7%)	2 (2%)	1 (<1%)	0	0	1 (<1%)	12 (10%)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4. Summary of investigator-assessed best overall response (RECIST v1.1 criteria).

Best overall response	Molibresib 60 mg + FUL 500 mg (AI failure) ($n = 33$)	Molibresib 60 mg + FUL 500 mg (CDK4/6i + AI failure <12 mo) ($n = 12$)	Molibresib 60 mg + FUL 500 mg (CDK4/6i + AI failure ≥12 mo) ($n = 42$)	Molibresib 60 mg + FUL 500 mg (CDK4/6i + AI failure ≥12 mo bone-only disease) ($n = 7$)	Molibresib 80 mg + FUL 500 mg (AI failure) ($n = 18$)	Molibresib 80 mg + FUL 500 mg (CDK4/6i + AI failure) ($n = 11$)	Total ($N = 123$)
CR confirmed	0	0	0	0	0	0	0
CR unconfirmed	0	0	0	0	0	0	0
PR confirmed	7 (21%)	0	5 (12%)	0	3 (17%)	1 (9%)	16 (13%)
PR unconfirmed	1 (3%)	0	3 (7%)	0	0	0	4 (3%)
SD	15 (45%)	2 (17%)	12 (29%)	4 (57%)	8 (44%)	3 (27%)	44 (36%)
PD	7 (21%)	8 (67%)	19 (45%)	1 (14%)	5 (28%)	7 (64%)	47 (38%)
NE	1 (3%)	2 (17%)	1 (2%)	1 (14%)	1 (6%)	0	6 (5%)
ORR							
CR + PR	7 (21%)	0	5 (12%)	0	3 (17%)	1 (9%)	16 (13%)
95% CI	(9.0–38.9)	(0.0–26.5)	(4.0–25.6)	(0.0–41.0)	(3.6–41.4)	(0.2–41.3)	(7.6–20.3)
DCR (CR + PR + SD)	12 (36%)	0	7 (17%)	1 (14%)	5 (28%)	1 (9%)	
95% CI	(20.4–54.9)	(0.0–26.5)	(7.0–31.4)	(0.4–57.9)	(9.7–53.5)	(0.2–41.3)	

Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; CR, complete response; DCR, disease control rate; FUL, fulvestrant; NE, not evaluable; ORR, objective response rate; PD, progressive disease, PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

There were no grade 5 AE observed in any treatment group in this study (Supplementary Table S4).

Following the administration of molibresib, in combination with fulvestrant, molibresib was rapidly absorbed, with a maximum concentration occurring mostly within 3 hours after dosing. Exposure (C_{max} and C_{trough}) for molibresib, active metabolites GSK3529246, and total active moiety was as anticipated on the basis of the previous monotherapy studies BET115521 and BET116183 (11, 16, 17), showing a lack of effect of fulvestrant on the pharmacokinetics of molibresib (data not shown). In addition, exposure was mostly similar among the different treatment groups taking molibresib dose into consideration. Fulvestrant predose concentrations were within the range anticipated (18), showing a lack of effect of molibresib on fulvestrant pharmacokinetics (data not shown).

The total ORR was 13% and no patients achieved a CR (**Table 4**). Among those who displayed a PR, disease progressed within 7 months of PR confirmation. Clinically meaningful response rates were not observed among evaluable patients in either the AI cohort or the CDK4/6i and AI cohort (either with ≥12 or <12 months prior treatment). The estimated overall median PFS was 3.6 months. Median PFS across all cohorts is shown in **Table 5**. Kaplan–Meier PFS curves for the two largest cohorts (AI failure and CDK4/6i + AI failure ≥12 months) are shown in Supplementary Fig. S2 and S3, respectively. Of note, one patient experienced a very long PFS of >33 months (Supplementary Fig. S2).

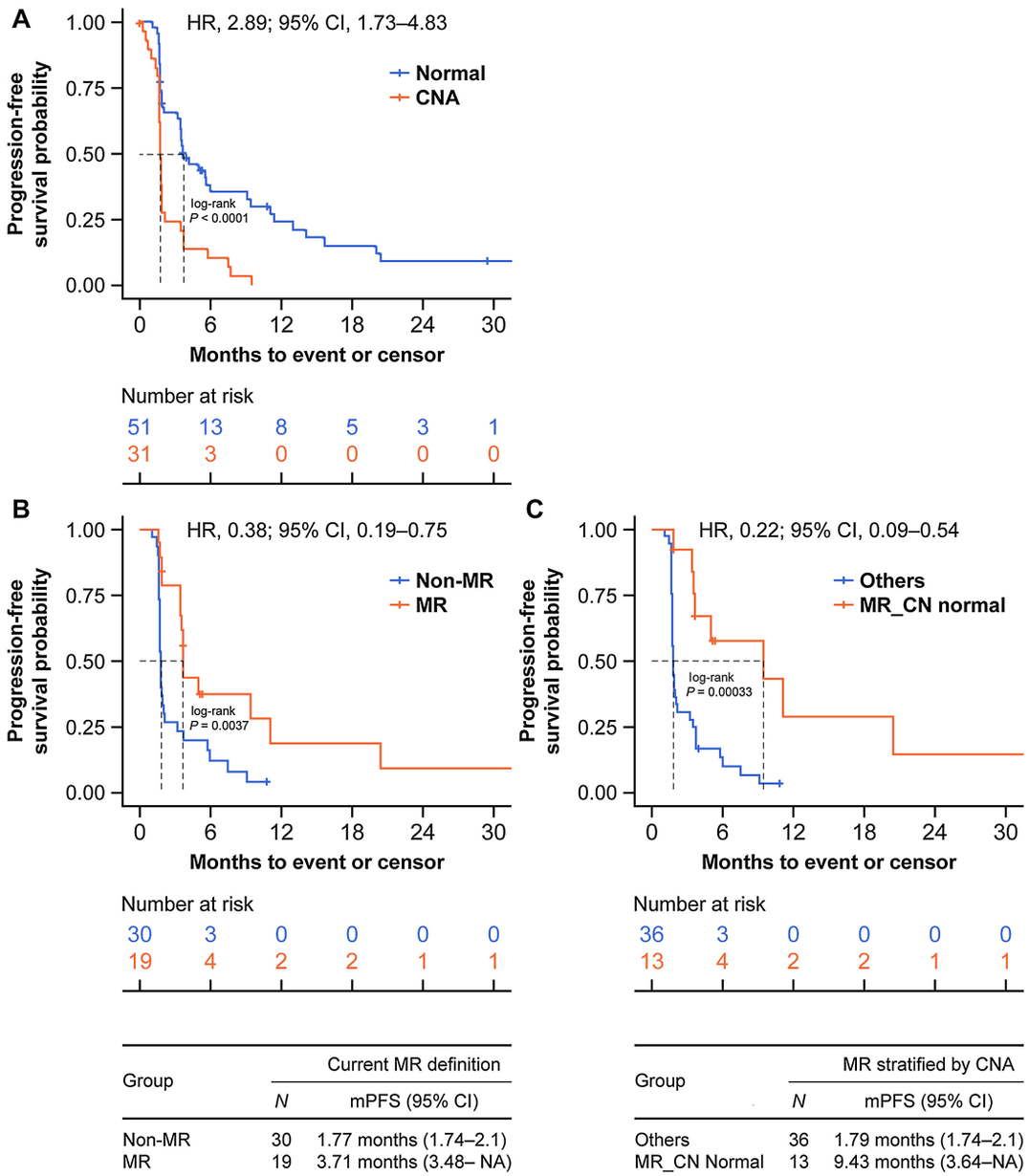
Baseline ctDNA data were successfully acquired in 82 patients with clinical outcome available; an oncoprint of genetic variants among patients with available baseline ctDNA is shown in Supplementary Fig. S4. Low (<median) ctDNA correlated with improved PFS [HR, 0.64; 95% confidence interval (CI), 0.4–1.04; log-rank $P = 0.066$]. A strong association of baseline CNA status and poor PFS was observed (HR, 2.89; 95% CI, 1.73–4.83; log-rank $P < 0.0001$; **Fig. 2A**). In 49 patients with paired longitudinal ctDNA data and clinical outcome,

Table 5. Summary of PFS.

	Molibresib 60 mg + FUL 500 mg (AI failure) ($n = 33$)	Molibresib 60 mg + FUL 500 mg (CDK4/6i + AI failure <12 mo) ($n = 12$)	Molibresib 60 mg + FUL 500 mg (CDK4/6i + AI failure ≥12 mo) ($n = 42$)	Molibresib 60 mg + FUL 500 mg (CDK4/6i + AI failure ≥12 mo bone-only disease) ($n = 7$)	Molibresib 80 mg + FUL 500 mg (AI failure) ($n = 18$)	Molibresib 80 mg + FUL 500 mg (CDK4/6i + AI failure) ($n = 11$)	Total ($N = 123$)
Number of patients (N)	33	12	42	7	18	11	123
Event	26 (79%)	10 (83%)	32 (76%)	3 (43%)	14 (78%)	10 (91%)	95 (77%)
Censored	7 (21%)	2 (17%)	10 (24%)	4 (57%)	4 (22%)	1 (9%)	28 (23%)
Event summary							
PD per RECIST v1.1	26 (79%)	10 (83%)	31 (74%)	3 (43%)	13 (72%)	10 (91%)	93 (76%)
Death due to any cause	0	0	1 (2%)	0	1 (6%)	0	2 (2%)
PFS (mo)							
1st quartile 95% CI	3.5 (1.7–4.2)	1.6 (0.7–1.7)	1.7 (1.6–1.8)	3.7 (1.8–7.2)	1.8 (1.6–5.9)	1.7 (1.4–1.8)	1.7 (1.7–1.8)
Median 95% CI	5.6 (3.7–11.1)	1.7 (1.6–2.1)	2.1 (1.8–3.6)	7.2 (1.8–NR)	4.0 (1.8–9.4)	1.8 (1.7–3.6)	3.6 (1.9–4.0)
3rd quartile 95% CI	14.1 (5.8–20.5)	2.1 (1.7–6.1)	7.1 (3.5–9.2)	NR (3.7–NR)	9.4 (4.0–15.7)	3.6 (1.8–11.4)	7.7 (5.6–11.4)

Note: PFS is defined as the time interval from date of first dose to date of first documented PD, as assessed by the investigator per RECIST v1.1 criteria, or to the date of death due to any cause.

Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; FUL, fulvestrant; NR, no result; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.



Group	Current MR definition	
	N	mPFS (95% CI)
Non-MR	30	1.77 months (1.74–2.1)
MR	19	3.71 months (3.48– NA)

Group	MR stratified by CNA	
	N	mPFS (95% CI)
Others	36	1.79 months (1.74–2.1)
MR_CN Normal	13	9.43 months (3.64–NA)

Figure 2.
Kaplan–Meier plots of PFS in patients with copy-number normal versus baseline copy-number amplification (**A**), patients with a molecular response versus those with no molecular response (**B**), and patients with a molecular response and copy-number normal versus patients with no molecular response or molecular response and baseline copy-number amplification (**C**). "Others" includes patients with no MR or MR and baseline CNA. CI, confidence interval; CN, copy number; CNA, copy-number amplification; HR, hazard ratio; mPFS, median progression-free survival; MR, molecular response; NA, not available; PFS, progression-free survival.

ctDNA change was significantly associated with RECIST response (Kruskal–Wallis $P = 0.0017$) and MR had longer PFS versus molecular nonresponders (HR, 0.38; 95% CI, 0.19–0.75; log-rank $P = 0.0037$), which still holds after adjusting previous treatment (**Fig. 2B**). When MR was further stratified into two groups based on CN status at baseline (i.e., MR with CN normal and MR with CNA at baseline), MR with CN normal showed further improvement in PFS compared with patients with no MR or those with MR and baseline CNA (HR, 0.22; 95% CI, 0.09–0.54; log-rank $P = 0.0003$; **Fig. 2C**).

Discussion

The study evaluated the oral administration of molibresib plus fulvestrant in patients with advanced or metastatic $HR^+/HER2^-$ breast cancer. The aim of phase I was to explore the safety, tolerability, pharmacokinetics, and efficacy profiles observed after administration of molibresib plus fulvestrant. The ORR for this trial of molibresib plus fulvestrant was 13%; ORR was 21% in CDK4/6i-naïve patients and 12% in CDK4/6i-pretreated patients with AI

failure ≥12 months (for molibresib 60 mg), which did not reach the prespecified target ORR to move on to phase II. As one of the first studies conducted in the post-CDK4/6i setting, little information was available on which to estimate baseline response rates to fulvestrant. Prior HR$^+$/HER2$^-$ breast cancer clinical trials with fulvestrant in CDK4/6i-naïve patients have shown higher ORRs than those observed in the current study. For example, among patients with *PIK3CA* mutations enrolled in the SOLAR-1 trial of the PI3K inhibitor alpelisib plus fulvestrant, ORR was 26.6% with the combination (compared with 12.8% with fulvestrant alone), but this trial included few patients treated with CDK4/6i (19). In the BYLIEVE study of alpelisib and fulvestrant, in which prior treatment with CDK4/6i was required, ORR was 21% (20). FAKTION, which evaluated the AKT inhibitor capivasertib in combination with fulvestrant, showed an ORR of 29%, but again enrolled CDK4/6i-naïve patients (21, 22). Outcomes of second-line endocrine strategies in the post-CDK4/6i setting are beginning to be understood and generally exhibit lower response rates. In the randomized VERONICA trial of fulvestrant ± venetoclax (conducted September 2018–February 2020), ORR was 3.9% for the combination and 5.9% for fulvestrant alone (23). Furthermore, when the current study was conducted in 2017, first-line CDK4/6i had only been available for a limited time. Consequently, the post-CDK4/6i population tended to reflect early CDK4/6i failure: despite an amendment to limit the minimum duration of prior CDK4/6i, the median prior treatment duration was substantially shorter than the median PFS achieved with these agents in pivotal trials or observed in real-world data (24). Therefore, the clinical characteristics and underlying tumor biology of the patients enrolled here are likely to reflect more endocrine-refractory disease.

In the current study, the combination of molibresib plus fulvestrant did not demonstrate clinically meaningful activity in patients with advanced or mBC previously treated with AI or CDK4/6i plus AI. Neither the AI cohort nor the CDK4/6i and AI cohort (either ≥12 or <12 months prior treatment) demonstrated response rates that met the prespecified targets. Tolerability for this treatment combination was poor; 47% and 48% of patients in the DL1 and DL2 cohorts experienced grade 3 or 4 treatment-related AE, respectively. Overall, 67% of patients required dose interruptions or delays of molibresib at any dose, and 36% of patients had a dose reduction. On the basis of tolerability and lack of efficacy, as per protocol guidance, enrollment was closed after phase I and the study was terminated. New enrollment for this study was stopped as of April 7, 2020, with the intention of closing the study after the last patient had discontinued study treatment and follow-up study visits. The information presented here represents data through October 2, 2020 (primary analysis). At that time, three patients remained on treatment (two receiving the combination of molibresib and fulvestrant and one receiving only fulvestrant). As there are no other studies of BET inhibitors combined with fulvestrant in this disease setting, it is unclear whether the failure of this trial was due to insufficient target engagement of molibresib or whether similar results would be seen with other BET inhibitors. However, our findings suggest that any therapeutic window is small for BET inhibitors among unselected patients in this setting.

Coadministration of fulvestrant showed a lack of effect of fulvestrant on the pharmacokinetics of molibresib. Similar to previously observed in the monotherapy studies (11, 16, 17) following repeated administration, it seems based on the limited concentration data that the exposure (C_{max}) to molibresib was reduced with an increase in the active metabolite composite (GSK3529246) exposure, leading to a modest change in total active moiety exposure. Overall, all pharmacokinetic findings for molibresib and fulvestrant were as anticipated on the basis of previous evidence, with neither treatment affecting the pharmacokinetics of the other (9, 18).

The biomarker analysis conducted in this study provides insights into the ctDNA landscape of this study population and provides additional evidence of the association between ctDNA features and ctDNA kinetics, as measured in a prospective clinical trial. Baseline ctDNA level measured by somatic variants and CNA status are correlated with PFS in HR$^+$ mBC treated with the molibresib and fulvestrant combination. MR is also associated with the outcome of this endocrine + targeted therapy combination, providing additional evidence for the potential utility of such biomarkers as surrogates of response. Stratifying MR by baseline CNA status in this cohort identifies an additional feature with potential to further improve predictive value for long-term outcomes and enabling early decision-making. Additional pharmacodynamic analyses for molibresib monotherapy, based on transcriptomic data, have been published previously (25).

In summary, molibresib added to standard fulvestrant exhibited low levels of clinical activity in patients with pretreated advanced or metastatic HR$^+$/HER2$^-$ breast cancer and it was poorly tolerated. Patients previously treated with CDK4/6i tended to progress rapidly, as observed in other studies of second-line endocrine therapy. Ongoing efforts to improve endocrine strategies for CDK4/6i-resistant disease are required. ctDNA features measured at baseline and on treatment capturing ctDNA kinetics may provide additional information to identify prognostic groups and provide early markers to anticipate treatment response or failure and could enhance the development of future therapeutic strategies in this setting.

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Note

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