Online Data Supplement

Supplementary Methods

Cell line growth assay

Prostate cancer cell lines were obtained from the American Type Culture Collection. The Ty-82 cell line was obtained from the Japanese Collection of Research Bioresources Cell Bank.[1] PER-704 and PER-403 cell lines were a gift from Ursula Kees.[2] All cell lines were authenticated via short tandem repeat analysis. Cell lines were seeded into 384-well plates in the manufacturer's recommended medium at a density optimized for 7 days of growth. Time-zero (T_0) measurements were taken the following day using Cell Titer-Glo (Promega) following the manufacturer's instructions. Plates were read on a Synergy Neo microplate reader (BioTek). The remaining plates were treated with dimethylsulphoxide (DMSO) or a titration of molibresib or M5 / M13 metabolites for 6 days and developed as described previously. Results were plotted as a percent of the T_0 value (normalized to 100%) versus compound concentration, and a 4-parameter equation was used to generate concentration response curves. Growth IC_{50} (gIC_{50}) values correspond to the mid-point of the growth window (between DMSO and T_0 values). A minimum of 2 biological replicates were evaluated, and average values across biological replicates are reported.

Accelerated dose escalation and 3+3 dose escalation

One patient per dose level in the accelerated dose-escalation schema was treated to minimize suboptimal drug exposures, starting with 2 mg once daily. If 2 mg was not tolerated, lower doses may be explored by reducing the dose or by alternate dosing (e.g. every other day). If there were no patients with any ≥Grade 2 drug related toxicity (based on the Common Terminology Criteria for AEs v. 4.0 [3]) and no patients with any DLTs during the first 4 weeks of treatment, the dose was escalated ≥2-fold. Escalation continued until 1 patient experienced any Grade 2 or higher drug-related AE. Once this occurred, the accelerated dose escalation was terminated, and patients enrolled into a standard 3+3 design.

In the 3+3 dose escalation design, 2 additional patients were enrolled to the dose level at which accelerated dose titration ended. Each subsequent dose cohort enrolled at least 3 patients. Patients were entered in a staggered approach with at least 3 days between each patient, to minimize the risk of inadvertently exceeding the MTD in multiple patients. If no DLTs were observed in any of the 3 patients, then dosing proceeded to the next dose level (≤2-fold increase in dose). If 1 patient experienced a DLT, then an additional 3 patients were enrolled at the current dose level; if only 1 of these 6 evaluable patients experienced a DLT,

then dose escalation proceeded to the next dose level, but if 2 or more DLTs were observed then the MTD was exceeded and an intermediate dose lower than the current dose was evaluated, or a prior cohort was expanded. Dose escalation was continued until the MTD was determined or a dose of 200 mg per day was reached.

In the accelerated and 3+3 dose escalation cohorts, the dose was escalated based on all available data, including PK data and the safety profile of prior cohorts, as well as the predicted dose from the Neuenschwander Continuous Reassessment Method design [4], which made use of all the DLT information available at the time of each dose assignment. The DLT information of all subjects enrolled in the trial was used to update the dose-toxicity relationship and provide supportive information in addition to the 3+3 design in the next escalation/de-escalation decision.

Up to an additional 6 patients could also be enrolled at any dose level below the MTD to obtain additional safety, tolerability and PK information. Additional patients also were enrolled at the dose chosen as the RP2D for confirmation prior to enrollment of larger expansion cohorts.

Computed tomography imaging

For this study, an imaging-specific guidelines document was developed by GSK/BioClinica and distributed to all centers. All imaging obtained was anonymized, centrally collected and tracked, subjected to quality control inspection, and prepared for radiographic review. The imaging guidelines document also provided technical information to standardize acquisition factors wherever possible and ensure the consistent evaluation of imaging endpoints across centers.

Patient inclusion criteria

1. Males or females 16 years or older, at the time of signing the informed consent.
2. Capable of giving written informed consent, which included compliance with the requirements and restrictions listed in the consent form. If the patient was <18 years old, an Assent form and parental/guardian Consent form were required.
3. Diagnosis of one of the following (part 1 only):
    a. NUT carcinoma based on ectopic expression of NUT protein as determined by immunohistochemistry (IHC) and/or detection of NUT gene translocation as determined by fluorescence *in situ* hybridization (FISH). Patients could be treatment naïve or have had prior therapy.
    b. SCLC, CRC, NB, TNBC, ER positive BC, CRPC, NSCLC, and any other solid tumor that had been confirmed by clinical testing to be MYCN amplified

(defined as a MYCN gene copy number gain of ≥5). Patients had tumor progression after receiving ≥1 prior standard/approved chemotherapy, where there was no approved therapy, or where standard therapy was refused.

4. Patients with solid tumors, with the exception of CRPC, had measurable disease, per RECIST v1.1. NOTE: Patients with NC that did not meet the RECIST v1.1 criteria for measurable disease, but had evaluable disease, could be considered for enrollment after discussion with the Medical Monitor.
5. All prior treatment-related toxicities must have been CTCAE (Version 4.0) ≤Grade 1 (except alopecia and peripheral neuropathy) at the time of treatment allocation.[3]
6. ECOG Performance Status score of 0–2 for patients with NC; 0–1 for patients with other tumor types.
7. Adequate organ function, as defined in the following Table:

Definitions of adequate organ function	
System	Laboratory values
Hematologic	
Absolute neutrophil count	≥1.5 X 10^9/L
Hemoglobin	≥9.5 g/dL (patients that required transfusion or growth factor need to demonstrate stable hemoglobin for 7 days of 9.5 g/dL)
Platelets	≥100 X 10^9/L
PT/INR and PTT	≤ 1.5 X ULN
Hepatic	
Total bilirubin	≤1.5 X ULN (isolated bilirubin >1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or patient has a diagnosis of Gilbert's syndrome)
ALT and AST	≤2.5 X ULN
Renal	
Creatinine OR Calculated creatinine clearance [Cockcroft Gault formula] OR 24-hour urine creatinine clearance	≤1.5 X ULN ≥50 mL/min ≥50 mL/min
Cardiac	
Ejection fraction	≥LLN by ECHO (minimum of 50%)
Troponin	≤ULN
Potassium	≥LLN and ≤ULN
Magnesium	≥LLN
Thyroid	
TSH	≥LLN and ≤ULN
Reproductive/endocrine	
Testosterone	<50 ng/dL (only for patients with CRPC)

CRPC, castration-resistant prostate cancer; LLN, lower limit of normal; PT/INR, prothrombin time and international normalized ratio; PTT,prothrombin time; TSH, thyroid-stimulating hormone; ULN, upper limit of normal

8. Able to swallow and retain orally administered medication and did not have any clinically significant gastrointestinal abnormalities that may have altered absorption, such as malabsorption syndrome or major resection of the stomach or bowels.
9. A female patient was eligible to participate if she was of:
    a. Nonchildbearing potential, defined as premenopausal females with a documented tubal ligation or hysterectomy, or postmenopausal, defined as 12 months of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous follicle-stimulating hormone >40 MIU/mL and estradiol <40 pg/mL [<140 pmol/L] was confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status was in doubt were required to use a specified contraception method if they wished to continue their HRT during the study. Otherwise, HRT was discontinued to allow confirmation of postmenopausal status prior to study enrollment. For most forms of HRT, at least 2–4 weeks were required between the cessation of therapy and the blood draw; this interval depended on the type and dosage of HRT. Following confirmation of their postmenopausal status, female patients could resume use of HRT during the study without use of a contraceptive method.
    b. Childbearing potential and agreed to use a contraception method for an appropriate period of time (as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female patients agreed to use contraception until 7 months after the last dose of study medication.
    c. Negative serum pregnancy test ≤7 days prior to first study drug dose.
    d. Female patients who were lactating were required to discontinue nursing prior to the first dose of study treatment and to refrain from nursing throughout the treatment period and for 5 half-lives of molibresib or ≥28 days (whichever was longer) following the last dose of study treatment.
10. Male patients had to agree to use one of the methods of contraception specified. This method had to be used from the time of the first dose of study medication until 16 weeks after the last dose of study medication. In addition, male patients whose partners were, or became, pregnant while on study medication had to continue to use condoms for 7 days after stopping study medications.

Patient exclusion criteria

1. Primary malignancy of the central nervous system, or malignancies related to HIV or solid organ transplant. History of known HIV. History of known Hepatitis B surface antigen or positive Hepatitis C antibody (confirmed by RIBA).
2. Prior treatments usage as defined:
    a. Use of an investigational anticancer drug within 14 days or 5 half-lives, whichever was longer, prior to the first dose of the investigational products.
    b. A minimum of 14 days between termination of the investigational drug and administration of molibresib.
    c. Any therapy-related toxicities must also have resolved to Grade 1 or less. An investigational drug was defined as a drug without an approved oncologic indication.
    d. Chemotherapy, radiotherapy, antineoplastic antibody or targeted therapy or immunotherapy within 14 days, major surgery within 28 days (or 42 days for prior nitrosoureas or mitomycin C) prior to the first dose of the investigational product.
    e. Anti-androgen (eg, bicalutamide) therapies for prostate cancer were required to be stopped 4 weeks prior to enrollment. Second-line hormone therapies, such as enzalutamide, abiraterone, or orteronel, had to be stopped 2 weeks prior to enrollment. Patients with prostate cancer were required to remain on luteinizing hormone-releasing hormone agonists or antagonists. Patients with prostate cancer could also remain on low-dose prednisone or prednisolone (up to 10 mg/d) and still be eligible for the study.
3. Use of anticoagulants (eg, warfarin, heparin) at therapeutic levels within 7 days prior to the first dose of molibresib. Low-dose (prophylactic) low-molecular weight heparin was permitted. In addition, the International Normalized Ratio for coagulation had to be monitored in accordance with local institutional practices.
4. Current use of a prohibited medication or a requirement for any of these medications during treatment with the investigational drugs. This included exclusion of medications known or suspected to be associated QT prolongation.
5. Evidence of severe or uncontrolled systemic diseases (eg, unstable or uncompensated respiratory, hepatic, renal, cardiac disease, or clinically significant bleeding episodes). Any serious and/or unstable preexisting medical condition (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with a patient's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.

6. Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression.
    a. NOTE: Patients previously treated for these conditions and who had stable central nervous system disease (verified with consecutive imaging studies) for >1 month, were asymptomatic and off corticosteroids, or were on a stable dose of corticosteroids for ≥1 month prior to study day 1 were permitted. Stability of brain metastases had to be confirmed with imaging. Patients treated with gamma knife could be enrolled 2 weeks postprocedure provided there were no postprocedure complications/they were stable. In addition, patients treated or currently taking enzyme-inducing anticonvulsant were allowed on study.
7. Cardiac abnormalities as evidenced by any of the following:
    a. History or current untreated clinically significant uncontrolled arrhythmias.
    b. Clinically significant conduction abnormalities or arrhythmias, patients with Bundle Branch Block
    c. Presence of cardiac pacemaker
    d. History or evidence of current ≥Class II congestive heart failure, as defined by New York Heart Association (NYHA).
    e. History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months.
8. Any of the following EKG findings:
    a. Baseline QTcF interval ≥450 msec
    b. Any clinically significant ECG assessments had to be reviewed by the site cardiologist prior to study entry.
9. Molibresib is a benzodiazepine class molecule. Any serious known immediate or delayed hypersensitivity reaction(s) to molibresib or idiosyncrasy to drugs chemically related to the investigational drug.
10. Hemoptysis >1 teaspoon in 24 hours within the last 28 days.
11. History of major gastrointestinal bleeding within the last 6 months. Any evidence of active gastrointestinal bleeding excluded the patient.

References

1. Kuzume T, Kubonishi I, Takeuchi S*, et al.* Establishment and characterization of a thymic carcinoma cell line (Ty-82) carrying t(15;19)(q15;p13) chromosome abnormality. Int J Cancer 1992;50(2):259-64.
2. Beesley AH, Stirnweiss A, Ferrari E*, et al.* Comparative drug screening in NUT midline carcinoma. Br J Cancer 2014;110(5):1189-98.
3. National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0 2009, https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf.
4. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med 2008;27(13):2420-39.

Supplementary Tables

Supplementary Table 1. Summary of AEs Occurring in >10% of Patients (All Treated Patients)

	Once-daily molibresib dose					
	2–16 mg (N=11)	30 mg (N=4)	60 mg (N=9)	80 mg (N=32)	100 mg (N=9)	All doses (N=65)
Any event, No. (%)	11 (100)	3 (75)	9 (100)	31 (97)	9 (100)	63 (97)
Thrombocytopenia	1 (9)	1 (25)	3 (33)	23 (72)	7 (78)	35 (54)
Nausea	3 (27)	3 (75)	2 (22)	17 (53)	7 (78)	32 (49)
Decreased appetite	2 (18)	1 (25)	2 (22)	15 (47)	6 (67)	26 (40)
Vomiting	3 (27)	1 (25)	2 (22)	11 (34)	4 (44)	21 (32)
Fatigue	2 (18)	1 (25)	3 (33)	10 (31)	5 (56)	21 (32)
Anemia	0	1 (25)	1 (11)	13 (41)	5 (56)	20 (31)
Diarrhea	1 (9)	0	1 (11)	12 (38)	4 (44)	18 (28)
Dysgeusia	0	1 (25)	3 (33)	8 (25)	5 (56)	17 (26)
Blood bilirubin increased	0	0	1 (11)	9 (28)	5 (56)	15 (23)
Asthenia	0	0	0	12 (38)	0	12 (18)
Constipation	4 (36)	1 (25)	2 (22)	1 (3)	3 (33)	11 (17)
AST increased	1 (9)	1 (25)	1 (11)	5 (16)	2 (22)	10 (15)
Dyspnea	0	0	0	5 (16)	5 (56)	10 (15)
Cough	1 (9)	0	3 (33)	4 (13)	1 (11)	9 (14)
ALT increased	1 (9)	0	1 (11)	4 (13)	2 (22)	8 (12)
Dry mouth	3 (27)	2 (50)	0	3 (9)	0	8 (12)
Epistaxis	1 (9)	0	0	6 (19)	1 (11)	8 (12)
Hypokalemia	2 (18)	0	0	5 (16)	1 (11)	8 (12)
INR increased	1 (9)	0	0	5 (16)	2 (22)	8 (12)
Rash	0	0	2 (22)	4 (13)	2 (22)	8 (12)
Hyperglycemia	1 (9)	0	0	5 (16)	1 (11)	7 (11)
Hyponatremia	3 (27)	0	0	4 (13)	0	7 (11)
Pyrexia	2 (18)	0	0	5 (16)	0	7 (11)
Weight decreased	0	0	0	3 (9)	4 (44)	7 (11)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

Supplementary Table 2. Summary of SAEs Occurring in ≥2 Patients (All Treated Patients)

	Once-daily molibresib dose					
	2–16 mg (N=11)	30 mg (N=4)	60 mg (N=9)	80 mg (N=32)	100 mg (N=9)	All doses (N=65)
Any event, No. (%)	2 (18)	1 (25)	2 (22)	21 (66)	3 (33)	29 (45)
Thrombocytopenia	0	0	1 (11)	8 (25)	2 (22)	11 (17)
Nausea	0	0	0	4 (13)	0	4 (6)
Device-related infection	1 (9)	0	1 (11)	1 (3)	0	3 (5)
Vomiting	0	0	0	3 (9)	0	3 (5)
Anemia	0	0	0	2 (6)	0	2 (3)
Asthenia	0	0	0	2 (6)	0	2 (3)
Dehydration	0	1 (25)	0	1 (3)	0	2 (3)
Decreased appetite	0	0	0	2 (6)	0	2 (3)
Hematuria	0	0	0	2 (6)	0	2 (3)

Supplementary Table 3. Primary Pharmacokinetic Parameters Following Single- and Repeat-Dose Administration of Molibresib (Pharmacokinetic Population)

	Once-daily molibresib dose								Major metabolites
	2 mg (N=3)	4 mg (N=4)	8 mg (N=1)	16 mg (N=3)	30 mg (N=4)	60 mg (N=9)	80 mg (N=32)	100 mg (N=9)	80 mg molibresib dose (N=32)
Single dose	n=3	n=4	n=1	n=3	n=4	n=9	n=31	n=9	n=29
C_{max}, ng/mL	51.0 (41.5)	70.5 (29.2)	120.4 –	179.5 (39.9)	603.9 30.3)	889.5 (24.5)	1109.4 (63.7)	1080.5 (38.8)	369.8 (39.5)
t_{max}, median h (range)	0.58 (0.50–0.63)	1.23 (0.50–2.00)	1.10 –	2.02 (0.33–3.97)	2.01 (0.97–2.23)	1.00 (0.52–4.00)	1.00 (0.25–4.00)	1.00 (0.67–3.95)	2.08 (0.98–10.35)
$AUC_{0–24}$, ng*h/mL	169.2 (39.4)	354.3 (33.8)	431.5 –	867.9 (39.5)	3943.2 (49.5)	4255.0 (39.2)	5704.0 (62.6)	6958.3 (43.5)	4410.5 (41.5)
$AUC_{0–\infty}$, ng*h/mL	174.4 (44.3)	360.9 (35.1)	433.0 –	887.1 (39.1)	4375.2 (59.5)	4357.5 (42.1)	5902.0 (64.0)	7294.6 (45.2)	–
$t_{1/2}$, h	3.24 (98.4)	5.14 (36.3)	2.84 –	7.00 (43.5)	7.34 (29.0)	5.56 (28.2)	4.40 (35.3)	6.20 (14.8)	–

	Once-daily molibresib dose								Major metabolites
	2 mg (N=3)	4 mg (N=4)	8 mg (N=1)	16 mg (N=3)	30 mg (N=4)	60 mg (N=9)	80 mg (N=32)	100 mg (N=9)	80 mg molibresib dose (N=32)
Repeat dose	n=1	n=2	n=1	n=3	n=4	n=6	n=14	n=6	n=15
C_{max}, ng/mL	52.0 –	53.4 (16.3)	103.2 –	137.6 (25.1)	602.7 (17.2)	633.7 (52.6)	818.3 (43.3)	918.6 (41.4)	490.1 (35.3)
t_{max}, median h (range)	1.00 –	2.51 (1.02–4.00)	0.50 –	1.05 (0.77–4.00)	0.90 (0.32–4.00)	1.06 (0.50–2.03)	0.56 (0.30–4.02)	1.50 (0.50–2.00)	2.00 (0.95–4.08)
AUC_{0-24}, ng*h/mL	152.9 –	334.6 (60.5)	329.5 –	671.6 (21.4)	3146.2 (54.5)	2575.6 (47.3)	2822.2 (44.3)	3818.5 (35.8)	4723.0 (39.3)
$t_{1/2}$, h	4.45 –	4.23 (19.4)	4.92 –	4.44 (21.7)	5.52 (12.5)	3.87 (27.8)	4.11 (30.4)	3.82 (21.7)	NA

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; t_{max} time to achieve C_{max}; $t_{1/2}$, terminal phase half-life.
Data presented as geometric mean (CVb%) values unless otherwise indicated.

Supplementary Table 4. Mean Change (SD) From Baseline or Predose in Circulating Cytokine Parameters at Week 1 Day 1 and Week 3 Day 4 (Pharmacokinetic Population)

		n	60 mg	n	80 mg	n	100 mg
Alpha-2-macroglobulin	W1D1 (vs. baseline)	8	−13.3 (6.7)	28	−19.2 (12.9)	9	0.8 (86.2)
	W3D4 (vs. baseline)	6	−18.5 (11.5)	15	−32.3 (23.1)	5	25.4 (85.0)
	W3D4 (vs. predose)	6	−13.5 (3.7)	15	−23.8 (17.6)	5	22.9 (48.0)
Alpha-1-antitrypsin	W1D1 (vs. baseline)	8	−15.5 (17.1)	28	−36.0 (26.0)	7	−19.5 (20.9)
	W3D4 (vs. baseline)	6	−20.9 (24.8)	15	−17.1 (21.0)	5	27.8 (82.4)
	W3D4 (vs. predose)	6	−35.4 (24.3)	15	−44.7 (20.2)	5	−13.2 (34.8)
Beta-2-microglobulin	W1D1 (vs. baseline)	8	−15.7 (7.0)	28	−17.6 (17.5)	7	−23.1 (20.7)
	W3D4 (vs. baseline)	6	−21.8 (8.6)	15	−7.9 (17.8)	3	−21.7 (11.5)
	W3D4 (vs. predose)	6	−21.1 (5.5)	15	−18.0 (13.3)	4	−7.4 (9.5)
Brain-derived neurotrophic factor	W1D1 (vs. baseline)	8	−70.5 (35.3)	28	−55.7 (38.5)	9	−65.3 (30.5)
	W3D4 (vs. baseline)	6	−81.0 (39.7)	15	−92.2 (9.3)	5	−90.6 (5.2)
	W3D4 (vs. predose)	6	−37.1 (48.4)	15	−46.9 (46.2)	5	−21.4 (31.9)

		n	60 mg	n	80 mg	n	100 mg
Complement C3	W1D1 (vs. baseline)	4	−23.4 (11.1)	28	−24.3 (21.6)	–	–
	W3D4 (vs. baseline)	3	−29.3 (10.5)	15	−40.4 (17.7)	–	–
	W3D4 (vs. predose)	3	−3.5 (8.0)	15	−30.7 (12.5)	–	–
C-reactive protein	W1D1 (vs. baseline)	8	−29.6 (19.1)	28	22.8 (308.9)	6	−21.9 (19.8)
	W3D4 (vs. baseline)	6	−72.3 (20.4)	15	−45.9 (89.5)	3	−61.8 (51.0)
	W3D4 (vs. predose)	6	−21.0 (9.3)	15	−40.4 (25.7)	4	−4.8 (22.4)
Eotaxin-1	W1D1 (vs. baseline)	8	−24.1 (27.6)	28	−40.8 (28.1)	9	−24.1 (24.3)
	W3D4 (vs. baseline)	6	−17.1 (27.6)	15	2.4 (57.1)	5	−19.4 (27.3)
	W3D4 (vs. predose)	6	−44.3 (30.9)	15	−9.2 (54.8)	5	−26.5 (36.4)
Ferritin	W1D1 (vs. baseline)	8	−19.0 (12.0)	28	−25.6 (19.0)	9	−2.6 (12.3)
	W3D4 (vs. baseline)	6	10.1 (36.1)	15	135.3 (206.9)	5	141.3 (107.2)
	W3D4 (vs. predose)	6	−11.7 (10.7)	15	5.7 (128.5)	5	−11.8 (18.2)
Factor VII	W1D1 (vs. baseline)	8	−27.5 (9.6)	28	−28.9 (21.8)	9	−26.4 (32.3)
	W3D4 (vs. baseline)	6	−62.0 (10.2)	15	−65.0 (11.3)	5	−65.1 (16.8)
	W3D4 (vs. predose)	6	−13.3 (7.4)	15	−21.3 (13.6)	5	−4.7 (13.2)

		n	60 mg	n	80 mg	n	100 mg
Fibrinogen	W1D1 (vs. baseline)	8	−29.2 (10.1)	28	−37.6 (22.8)	7	−4.2 (30.9)
	W3D4 (vs. baseline)	6	−35.3 (9.3)	15	−42.2 (22.5)	5	−25.7 (45.7)
	W3D4 (vs. predose)	6	−24.8 (19.5)	15	−35.3 (20.0)	5	−27.4 (20.3)
Haptoglobin	W1D1 (vs. baseline)	8	−32.7 (24.9)	28	−37.2 (28.3)	7	−19.0 (40.6)
	W3D4 (vs. baseline)	6	7.4 (50.0)	15	−32.6 (26.2)	5	65.5 (161.8)
	W3D4 (vs. predose)	6	−2.2 (15.2)	15	−41.5 (19.0)	5	−8.4 (26.0)
Intercellular adhesion molecule 1	W1D1 (vs. baseline)	8	−20.4 (11.8)	28	−24.8 (20.7)	9	−16.3 (15.8)
	W3D4 (vs. baseline)	6	−22.8 (11.7)	15	−14.9 (19.0)	5	−21.3 (23.4)
	W3D4 (vs. predose)	6	−12.6 (9.1)	15	−24.1 (17.2)	5	−17.6 (18.4)
Interleukin-12 subunit p40	W1D1 (vs. baseline)	8	−39.6 (9.3)	28	−21.9 (28.6)	9	−34.7 (24.1)
	W3D4 (vs. baseline)	6	−75.5 (10.0)	15	−28.1 (31.6)	5	−72.9 (25.3)
	W3D4 (vs. predose)	6	−27.5 (26.6)	15	−7.8 (20.6)	5	−10.3 (27.7)
Interleukin-6	W1D1 (vs. baseline)	8	−26.0 (25.5)	28	−17.1 (41.9)	9	−12.8 (27.2)
	W3D4 (vs. baseline)	6	−42.6 (34.4)	15	−10.7 (28.5)	5	−15.4 (34.5)
	W3D4 (vs. predose)	6	−19.3 (32.3)	15	−16.7 (29.3)	5	−13.9 (31.1)

		n	60 mg	n	80 mg	n	100 mg
Interleukin-8	W1D1 (vs. baseline)	8	−38.0 (19.5)	28	−39.8 (29.2)	9	−23.3 (31.3)
	W3D4 (vs. baseline)	6	−36.4 (50.3)	15	−20.6 (41.7)	5	−24.5 (53.6)
	W3D4 (vs. predose)	6	−44.6 (27.7)	15	−26.7 (27.9)	5	−42.7 (34.2)
Interleukin-18	W1D1 (vs. baseline)	8	−19.5 (10.8)	28	−29.8 (28.3)	9	−15.0 (13.8)
	W3D4 (vs. baseline)	6	−60.0 (9.5)	15	−43.5 (24.2)	5	−50.0 (10.6)
	W3D4 (vs. predose)	6	−21.1 (7.9)	15	−11.0 (68.0)	5	−10.6 (21.0)
Interleukin-23	W1D1 (vs. baseline)	8	−49.4 (17.2)	28	−17.1 (24.6)	9	−17.9 (43.5)
	W3D4 (vs. baseline)	6	−64.5 (12.6)	15	−23.3 (30.0)	5	−64.1 (16.6)
	W3D4 (vs. predose)	6	0 (0)	15	−7.8 (20.6)	5	−11.8 (26.4)
Interleukin-1 receptor antagonist	W1D1 (vs. baseline)	8	−38.9 (23.1)	28	−39.1 (27.6)	9	−37.7 (24.1)
	W3D4 (vs. baseline)	6	−61.7 (30.8)	15	−35.7 (32.9)	5	−56.3 (15.3)
	W3D4 (vs. predose)	6	−17.1 (29.2)	15	−30.5 (34.3)	5	12.7 (99.2)
Monocyte chemotactic protein 1	W1D1 (vs. baseline)	8	−45.2 (18.3)	28	−57.5 (25.7)	9	−49.4 (23.1)
	W3D4 (vs. baseline)	6	−18.6 (43.7)	15	8.6 (59.8)	5	48.1 (89.2)
	W3D4 (vs. predose)	6	−49.1 (22.6)	15	−24.3 (60.2)	5	−55.2 (19.8)

		n	60 mg	n	80 mg	n	100 mg
Macrophage inflammatory protein-1β	W1D1 (vs. baseline)	8	−18.0 (17.3)	28	−18.0 (28.1)	9	−8.6 (13.2)
	W3D4 (vs. baseline)	6	26.9 (72.3)	15	119.1 (142.2)	5	142.6 (70.8)
	W3D4 (vs. predose)	6	−33.1 (28.1)	15	−3.8 (41.2)	5	−20.9 (13.0)
Matrix Metalloproteinase-3	W1D1 (vs. baseline)	8	−36.0 (8.7)	28	−31.5 (21.3)	9	−22.5 (17.6)
	W3D4 (vs. baseline)	6	−34.3 (26.7)	15	−26.9 (34.4)	5	6.5 (35.0)
	W3D4 (vs. predose)	6	−26.2 (16.7)	15	−30.2 (17.2)	5	−24.5 (15.8)
Matrix metalloproteinase-9	W1D1 (vs. baseline)	8	−25.3 (26.1)	28	−33.5 (60.2)	9	−17.7 (40.1)
	W3D4 (vs. baseline)	6	−68.9 (19.4)	15	−54.1 (50.1)	5	−39.7 (39.3)
	W3D4 (vs. predose)	6	−56.6 (26.9)	15	−57.9 (22.7)	5	−21.4 (53.1)
Stem cell factor	W1D1 (vs. baseline)	8	−30.5 (13.8)	28	−31.6 (20.4)	9	−17.3 (32.5)
	W3D4 (vs. baseline)	6	−48.7 (20.4)	15	−44.3 (17.2)	5	−36.7 (30.5)
	W3D4 (vs. predose)	6	−32.7 (16.0)	15	−20.5 (46.8)	5	−10.0 (9.4)
T-cell-specific protein RANTES	W1D1 (vs. baseline)	8	−78.1 (23.0)	28	−45.8 (33.0)	9	−54.4 (29.5)
	W3D4 (vs. baseline)	6	−93.1 (5.1)	15	−85.5 (18.7)	5	−84.4 (14.0)
	W3D4 (vs. predose)	6	34.4 (233.5)	15	−69.1 (38.5)	5	−20.6 (69.0)

		n	60 mg	n	80 mg	n	100 mg
Tissue inhibitor of metalloproteinases 1	W1D1 (vs. baseline)	8	−20.7 (12.0)	28	−22.3 (13.6)	9	−4.6 (14.6)
	W3D4 (vs. baseline)	6	−22.7 (17.4)	15	−14.3 (23.3)	5	2.0 (27.6)
	W3D4 (vs. predose)	6	−15.7 (6.2)	15	−26.3 (13.7)	5	−12.1 (14.9)
Tumor necrosis factor receptor 2	W1D1 (vs. baseline)	8	−21.3 (13.2)	28	−23.4 (11.6)	9	−10.0 (20.7)
	W3D4 (vs. baseline)	6	−14.3 (13.5)	15	7.2 (48.9)	5	14.6 (44.5)
	W3D4 (vs. predose)	6	−14.3 (11.5)	15	−28.2 (20.5)	5	−11.7 (18.3)
Vascular cell adhesion molecule-1	W1D1 (vs. baseline)	8	−18.9 (10.6)	28	−20.7 (12.6)	9	−9.4 (16.0)
	W3D4 (vs. baseline)	6	−12.2 (7.9)	15	−3.6 (22.0)	5	15.0 (18.6)
	W3D4 (vs. predose)	6	−12.0 (4.2)	15	−26.7 (18.6)	5	−3.1 (15.9)
Vitamin D-binding protein	W1D1 (vs. baseline)	8	−17.5 (11.3)	28	−24.0 (16.4)	7	−11.1 (16.5)
	W3D4 (vs. baseline)	6	−18.5 (12.8)	15	−23.7 (18.3)	5	−17.6 (29.8)
	W3D4 (vs. predose)	6	−15.5 (5.8)	15	−27.5 (16.1)	5	−3.8 (12.2)
Vascular endothelial growth factor	W1D1 (vs. baseline)	8	−30.1 (13.4)	28	−27.4 (33.9)	9	−16.3 (23.1)
	W3D4 (vs. baseline)	6	−57.6 (12.4)	15	−56.1 (26.5)	5	−49.0 (46.5)
	W3D4 (vs. predose)	6	−16.2 (17.4)	15	−39.4 (31.9)	5	−25.0 (30.3)

		n	60 mg	n	80 mg	n	100 mg
von Willebrand factor	W1D1 (vs. baseline)	8	−63.4 (8.9)	28	−49.2 (25.4)	7	−24.6 (28.0)
	W3D4 (vs. baseline)	6	−31.9 (33.6)	15	−9.7 (55.1)	3	−46.4 (24.2)
	W3D4 (vs. predose)	6	−51.6 (20.9)	15	−37.7 (32.7)	4	−58.5 (31.4)

Abbreviations: D, day; W, week.

Predose refers to values measured prior to dosing on week 3, day 4.

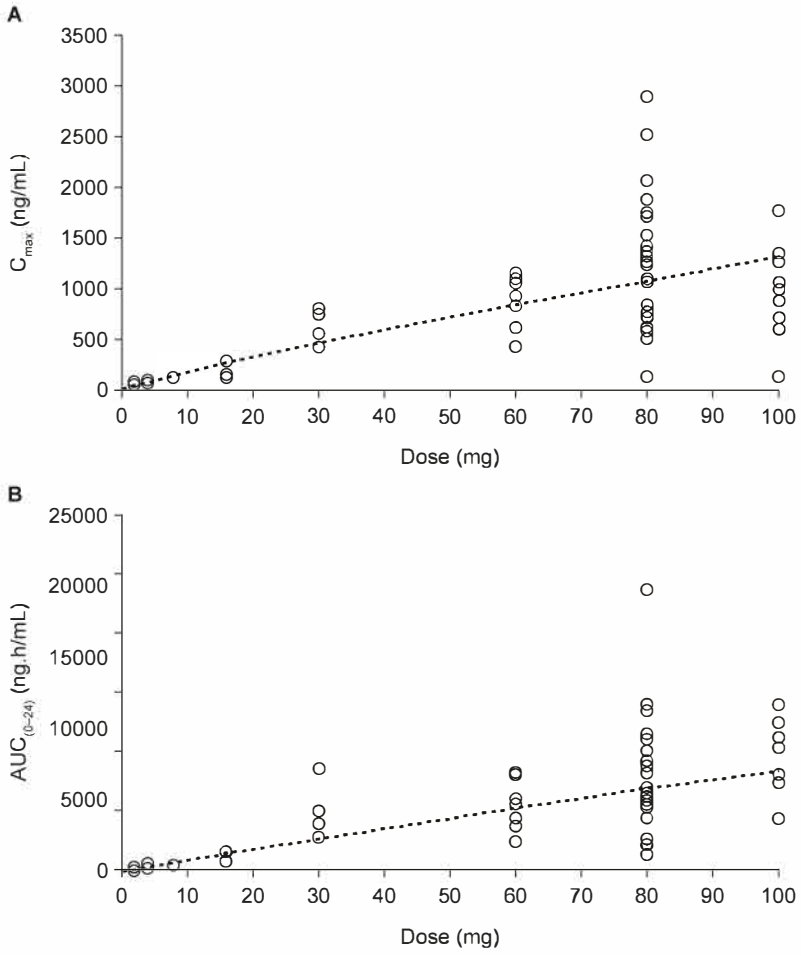
Cytokines with mostly or all values below the lower level of quantification at baseline and excluded from the table were: Granulocyte-macrophage colony-stimulating factor; Interferon gamma; Interleukins 1 alpha, 1 beta, 2, 3, 4, 5, 7, 10, 12 subunit p70, 15, and 17; Macrophage inflammatory protein-1 alpha; tumor necrosis factor alpha and beta.

Supplementary Table 5. Summary of Investigator-Assessed Best Response, With and Without Confirmation (NC Cohort)

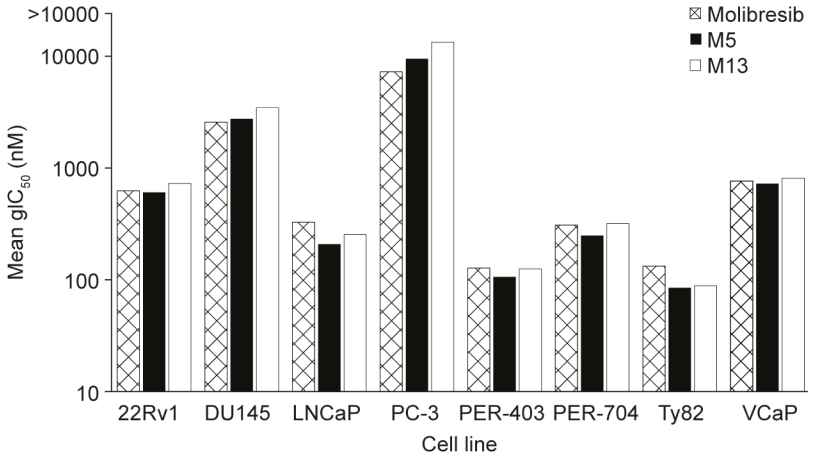
	Investigator-assessed best response											
	With confirmation, No. (%)						Without confirmation, No. (%)					
	2–16 mg (N=5)	30 mg (N=1)	60 mg (N=2)	80 mg (N=9)	100 mg (N=2)	Total (N=19)	2–16 mg (N=5)	30 mg (N=1)	60 mg (N=2)	80 mg (N=9)	100 mg (N=2)	Total (N=19)
CR	0	0	0	0	0	0	0	0	0	0	0	0
PR	0	0	0	1 (11)	1 (50)	2 (11)	0	0	1 (50)	2 (22)	1 (50)	4 (21)
SD	2 (40)	0	0	5 (56)	1 (50)	8 (42)	2 (40)	0	0	4 (44)	1 (50)	7 (37)
Non PR/ non-PD	0	0	0	1 (11)	0	1 (5)	0	0	0	1 (11)	0	1 (5)
PD	1 (20)	1 (100)	2 (100)	1 (11)	0	5 (26)	1 (20)	1 (100)	1 (50)	1 (11)	0	4 (21)
NE	2 (40)	0	0	1 (11)	0	3 (16)	2 (40)	0	0	1 (11)	0	3 (16)
Response rate 95% CI	0	0	0	1 (11) 0.3, 48.2	1 (50) 1.3, 98.7	2 (11) 1.3, 33.1	0	0	1 (50) 1.3, 98.7	2 (22) 2.8, 60.0	1 (50) 1.3, 98.7	4 (21) 6.1, 45.6

Abbreviations: CI, confidence interval; CR, complete response; NC, NUT carcinoma; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

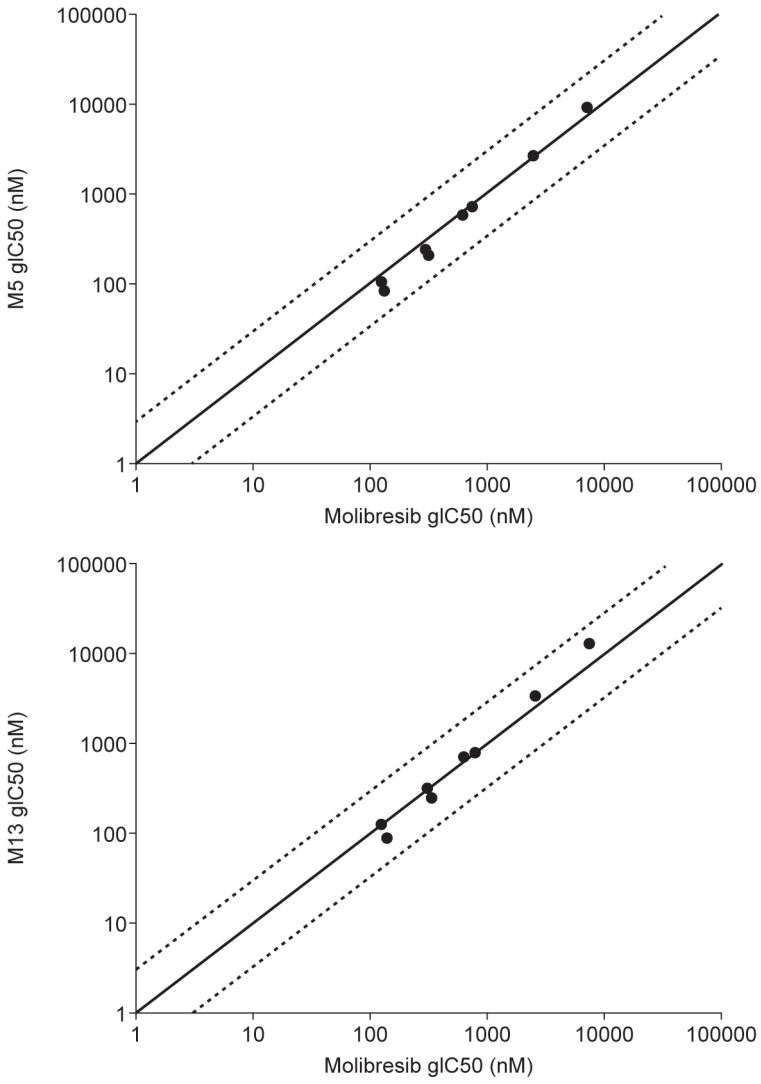
Supplementary Figures



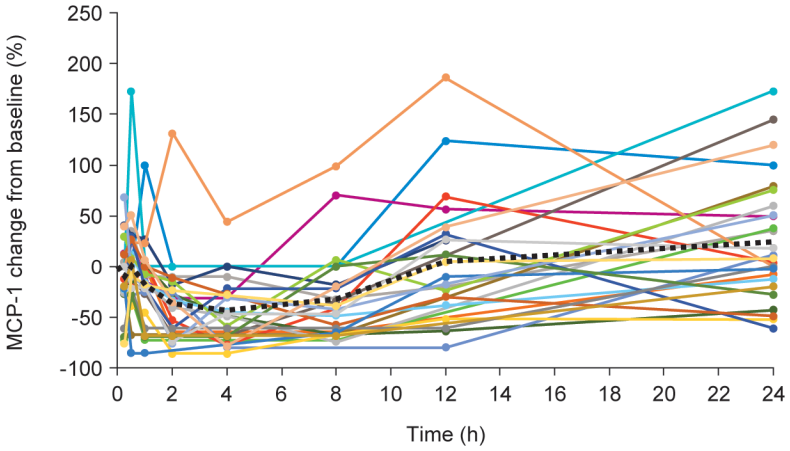
Supplementary Figure 1. Molibresib pharmacokinetics. (A) Maximum plasma concentration and **(B)** Exposure following single dose administration of molibresib (pharmacokinetic population). AUC(0–24), area under the concentration-time curve from 0 to 24 hours; Cmax, maximum plasma concentration.



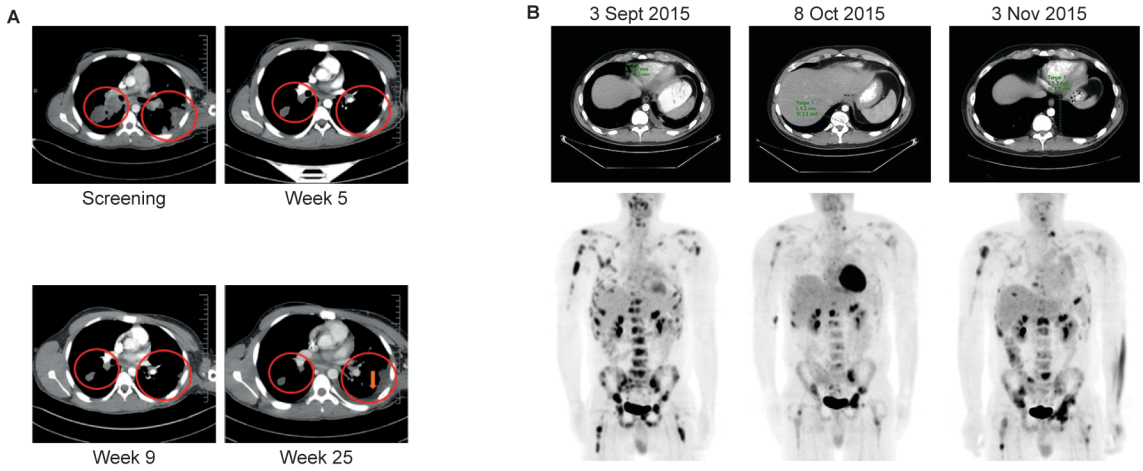
Supplementary Figure 2. Activity of molibresib metabolites. Mean gIC50 values for molibresib and its major human metabolites, M5 (N-desethyl, GSK3529246) and M13 (Ethyl-hydroxyl, GSK3536835), across various solid tumor cell lines. gIC50, growth half-maximal inhibitory concentration.



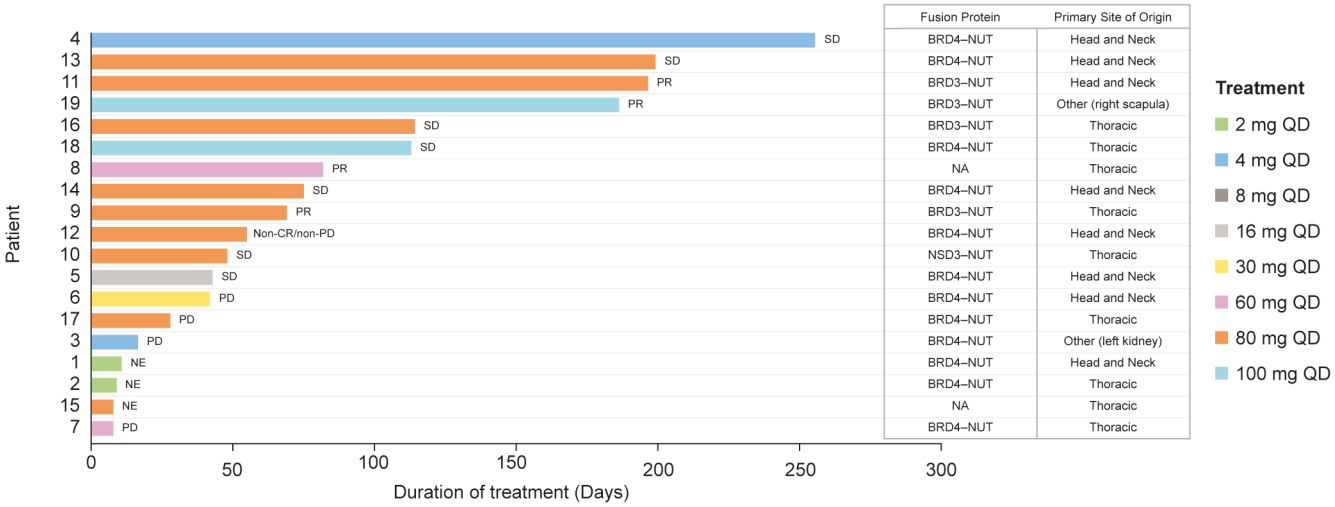
Supplementary Figure 3. Growth inhibitory activity of the M5 and M13 metabolites compared with molibresib in cancer cell lines. Correlation plots indicating the gIC_{50} values of the M5 (GSK3529246; *top*) and M13 (GSK3536835; *bottom*) metabolites compared to molibresib in a panel of cancer cell lines treated for 6 days. Solid line indicates 1:1 correlation. Dashed lines indicate 3:1 and 1:3 correlations. gIC_{50}, growth half maximal inhibitory concentration.



Supplementary Figure 4. Reduced MCP-1 expression as a pharmacodynamic biomarker of molibresib activity. Change from baseline (%) up to 24 hours post-dose of 80 mg molibresib. Individualized data are shown for the pharmacokinetic population. Data were unavailable for 2 patients. Extreme values >1.5-fold above or below the interquartile range were excluded. The dashed line shows the mean at each time point. MCP-1, monocyte chemoattractant protein 1.



Supplementary Figure 5. Examples of the anti-tumor activity of molibresib in patients with NC. **(A)** CT images showing tumor reduction in a patient with NC, who achieved a confirmed PR (patient 19). The primary site was in the right scapula, with measurable right lung, right hilar, and left pleural-based lesions at screening. PR was achieved by week 5 of molibresib treatment with a –57% reduction from baseline in target lesions, including absence of right middle lobe and subcranial lesions. Target lesions remained reduced at week 9 (–59%) and week 25 (–68%). However, at week 25, a new left upper lobe lesion and new left pleural disease (orange arrow) were identified. **(B)** CT and 18F-FDG scan images in a patient who achieved an unconfirmed PR (patient 9). After one month of study treatment there was substantial improvement in left pleural-based disease and significant interval decrease in the intensity of the diffuse uptake in multiple areas of bone marrow involvement throughout the axial and appendicular skeleton. During this time, the patient experienced substantial palliation with marked decrease in pain. After an additional month of molibresib, pleural-based disease remained improved, but there was worsening of disease in the right humerus, several ribs, thoracic and lumbar spine, and the left acetabulum. 18F-FDG, 18F-fluorodeoxyglucose; CT, computed tomography; NC, NUT carcinoma; PR, partial response.



Supplementary Figure 6. Antitumor activity of molibresib. Swimmer plot for the NC population (n=19). NC, NUT carcinoma; NUT, nuclear protein in testis; PD, progressive disease; PR, partial response; SD, stable disease; QD, once daily.