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ORIGINAL ARTICLE

Phase I study of ABM-1310 as monotherapy and in combination with cobimetinib for BRAF-mutated advanced solid tumors: safety, efficacy, and dose expansion

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Available online 27 January 2026

Background: ABM-1310 is an investigational, orally bioavailable BRAF V600 inhibitor with high blood—brain barrier (BBB) penetration.

Patients and methods: This first-in-human, phase I trial evaluated patients with BRAF V600-mutated advanced solid tumors, including brain metastases ($\leq$3 cm) and primary central nervous system (CNS) tumors. Patients received ABM-1310 monotherapy [25-250 mg twice a day (b.i.d.); Parts A/C] or in combination (ABM-1310 : 100-200 mg b.i.d.; cobimetinib 60 mg once a day, days 1-21 of each 28-day cycle; Part B). Primary endpoints included safety, tolerability, and maximum tolerated dose (MTD); secondary endpoints included pharmacokinetic (PK) profile and antitumor activity per RECIST v1.1 or Response Assessment in Neuro-Oncology criteria.

Results: Fifty-three patients were enrolled (36 monotherapy, 17 combination). Median age was 55 years; 68% were male, 72% had $\geq$3 prior treatment lines, 92.5% had BRAF V600E mutations, 75% of patients had received prior BRAF plus MEK inhibitor therapy, and 7.5% had BRAF inhibitor monotherapy. Common tumor types included melanoma (47%), glioblastoma (17%) and thyroid cancer (13%). The most frequent treatment-related adverse events were QT prolongation and rash. Dose-limiting toxicities (DLTs) occurred in 6/37 patients (16.2%), all at doses $\geq$150 mg. All DLTs involved asymptomatic electrocardiogram QT prolonged, with two cases presenting co-occurring toxicities: one with rash and one with renal failure—establishing the MTD at 200 mg b.i.d. Among 50 efficacy-evaluable patients, the objective response rate (ORR) was 12% and disease control rate (DCR) was 64%. Median progression-free survival was 4.96 months (2.07-8.31) and median overall survival was 24.48 months 11.6-not estimable. In patients with primary CNS tumors ($n = 13$), ORR was 23.1% and DCR 76.9%. PK analyses showed dose-proportional exposure and moderate accumulation.

Conclusions: ABM-1310 showed a favorable safety profile and encouraging intracranial activity. These findings support continued evaluation for CNS tumors and in cancer patients with prior BRAF inhibitor exposure.

Key words: ABM-1310, BRAF inhibitor, phase I dose escalation, dose expansion, solid tumors

INTRODUCTION

The B-Raf proto-oncogene, serine/threonine kinase (BRAF) protein transmits extracellular signals to the cell nucleus, and is part of a signaling pathway known as the rat sarcoma (RAS) mitogen-activated protein kinase (MAPK) pathway.[1,2] The MAPK pathway controls cell proliferation, division, differentiation, migration, and apoptosis.[3-5] Activating *BRAF* mutations lead to constitutive activation of BRAF and therefore the rapidly accelerated fibrosarcoma (RAF)-mitogen-activated protein kinase/extracellular signal-regulated pathway kinase (MEK)-extracellular regulated kinase (ERK) signaling cascade, promoting cell proliferation and survival while inhibiting apoptosis, and thus driving cancer growth.[6,7]

Activating alterations in the *BRAF* gene, including the V600E variant, are among the most prevalent oncogenic

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drivers across human cancers. Overall, ∼6%-8% of all tumors harbor *BRAF* mutations.[6,8] The distribution, however, varies widely by tumor type: the mutation is observed in ∼66% of melanomas, 41%-60% of thyroid cancers, ∼10% of colorectal cancers, 28%-33% of serous ovarian cancers, 9% of lung cancers, and 8.3% of gliomas.[6,8-12]

The United States Food and Drug Administration (FDA) has approved several BRAF inhibitors (BRAFi) for cancers harboring BRAF V600 alterations, including vemurafenib, dabrafenib, and encorafenib, used alone or in combination with MEK inhibitors (MEKi) cobimetinib, trametinib, and binimetinib, respectively, for the treatment of melanoma.[13-18] The dabrafenib/trametinib regimen is also approved for BRAF V600—mutant anaplastic thyroid cancer, non-small-cell lung cancer, and more recently for use in unresectable or metastatic solid tumors carrying the BRAF V600E alteration, excluding colorectal cancer.[8,19,20] These therapies have advanced clinical care, eliciting rapid and robust responses across multiple tumor types; however, acquired resistance remains a major limitation. This unmet need has driven development of next-generation BRAFi, including ABM-1310, which has demonstrated high potency and favorable blood—brain barrier (BBB) penetration in preclinical models, offering potential advantages in treating patients with central nervous system (CNS) involvement.

In preclinical studies, ABM-1310 achieved superior BBB penetration and stronger antitumor activity in intracranial melanoma and BRAF-mutant glioblastoma models than approved BRAFi.[21] ABM-1310 has much a higher brain concentration than marketed drugs based on rodent studies and one human sample.[21] ABM-1310 also demonstrated therapeutic effects in *in vitro* and *in vivo* models of melanoma, glioma, and colorectal cancer with BRAF V600E mutation. Furthermore, clinical activity in glioma with BRAF V600 mutation was observed in a separate phase I trial.[22] Pharmacokinetic assessment of ABM-1310 showed a favorable absorption, distribution, metabolism, and excretion profile in mice, rats, and dogs, and demonstrated brain penetration in mice with unbound brain-to-plasma concentration ratio ($K_{p,uu}$, brain) of 1.0.[23] Toxicology studies confirmed a good safety margin, with no observed adverse effect levels of 100 mg/kg/day in rats and 30 mg/kg/day in dogs.[23]

Based on the preclinical data of ABM-1310 in solid and primary brain tumors with BRAF V600 mutations, a first-in-human (FIH), phase I clinical study of ABM-1310 was conducted. Interim analyses for the study were reported at the 2024 American Society of Clinical Oncology annual meeting.[24,25] Here, we report the final results of this study. Clinical trial ID: NCT04190628.

METHOD

Study design

This phase I, FIH, multicenter, open label, dose escalation and expansion study evaluated the safety, tolerability, pharmacokinetic (PK) profile, and preliminary anticancer activity of ABM-1310 in adult patients with locally advanced or metastatic BRAF V600-mutant solid tumors, as monotherapy or in combination with cobimetinib (Cotellic®). The study consisted of three parts: Part A (ABM-1310 monotherapy dose escalation), Part B (ABM-1310 in combination with cobimetinib dose escalation), and Part C (expansion cohorts assessing safety and preliminary efficacy). Planned patient enrollment included up to 36 patients in Part A, 24 patients in Part B, and ∼10-15 patients in each of the four-part C cohorts. Enrollment was discontinued by the sponsor on 25 January 2024, during Part C enrollment, therefore, Parts C-3 and C-4 were not initiated. Part A and Part B evaluated the safety, tolerability, PK profile, and preliminary efficacy of ABM-1310 to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) as monotherapy and in combination therapy with cobimetinib. Dose finding was guided by the classic 3+3 design.[26] The starting dose of ABM-1310 was 25 mg twice daily (b.i.d.) as monotherapy and 100 mg b.i.d. in combination with cobimetinib. Part C evaluated the safety, tolerability, and preliminary antitumor activity of ABM-1310 as monotherapy at the RP2D in patients with primary CNS tumors (Part C-1) and locally advanced or metastatic solid tumors with BRAF V600 alterations (Part C-2). ABM-1310 was administered b.i.d. continuously in 28-day cycles for Part A and Part C, and with cobimetinib 60 mg once daily for the first 21 days of each 28-day treatment cycle for Part B. This study was completed on 2 June 2024.

The study complied with the Declaration of Helsinki, International Council for Harmonization Good Clinical Practice Guidelines, and all applicable local regulatory requirements and privacy laws. The protocol, amendments, and informed consent documentation were reviewed and approved by institutional review boards. All patients provided written informed consent before enrollment.

Objectives, endpoints, and assessments

For Part A, primary objectives were to determine the MTD/RP2D of ABM-1310 monotherapy. Primary endpoints were dose-limiting toxicities (DLTs), adverse events (AEs), tolerability and laboratory abnormalities. Secondary objectives were single- and multiple-dose PKs at different dose levels and antitumor activity. Secondary endpoints were PK parameters, and objective response rate (ORR) and duration of response (DoR) based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)[27] and for patients with primary CNS tumors, Response Assessment in Neuro-Oncology (RANO).[28] Follow-up was defined as date from first dose of study treatment to death or last known contact, whichever occurred first, with observations censored at the data cut-off.

For Part B, the primary objective was to determine the RP2D of ABM-1310 in combination with cobimetinib. For Part C, the primary objectives were to assess the safety and tolerability of ABM-1310 as a monotherapy at the MTD in Part A. In both parts, primary endpoints were DLTs (Part B only), AEs, tolerability and laboratory abnormalities.

Secondary objectives were to characterize single- and/or multiple-dose PKs at different dose levels and antitumor activity. Secondary endpoints were PK parameters, ORR, and DoR per RECIST v1.1 and RANO.

Tumor assessment by computed tomography or magnetic resonance imaging (MRI) took place at screening, every 2 cycles for the first 6 cycles, every 3 cycles from cycle 7-12, and every 4 cycles thereafter, or as clinically indicated. For patients with primary CNS tumors, such as gliomas, tumor response was re-evaluated at the end of every two cycles. Asymptomatic patients with solid tumors and active brain metastases (BrM; untreated or radiographically progressing) underwent brain MRI at baseline and on day 1 of every cycle starting from cycle 2. Patients with previously irradiated BrM that were stable or radiographically improved at baseline were excluded from this subgroup analysis.

Patient population

Eligible patients were aged $\geq$18 years with histologically or cytologically documented, locally advanced or metastatic solid tumor malignancy that had progressed on $\geq$1 line of prior standard systemic therapy, had no standard therapy options, or considered ineligible for remaining standard therapy. There was no limit to the number of prior treatment regimens. Part A enrolled patients with advanced/metastatic solid tumors with BRAF V600E or any other BRAF V600 mutation. Part B enrolled patients with advanced/metastatic solid tumors harboring activating *BRAF* mutation. Part C included: C-1, patients with primary CNS tumors with BRAF V600 mutation; C-2, patients with advanced/metastatic BRAF V600-mutant solid tumors excluding primary CNS tumors. Patients with active or stable, asymptomatic brain metastases, or symptomatic lesions controlled with $\leq$4 mg/day dexamethasone (or equivalent) and either stable dosing or tapering dosing for $\geq$2 weeks, were eligible for enrollment. Brain lesions $>$3 cm were excluded. Key inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 or Karnofsky performance status of $\geq$70, at least one measurable lesion per RECIST v1.1 criteria for solid tumors or the RANO criteria for primary CNS tumors, and adequate organ function.

Patients were ineligible if they had any synchronous malignancy, carcinomatous meningitis (leptomeningeal disease), stroke $\leq$6 months before starting the study drug, seizure within 14 days before first dose, impaired cardiac function or clinically significant cardiac diseases, or other concurrent severe and/or uncontrolled concomitant conditions that could cause unacceptable safety risks or compromise protocol compliance.

For patients who developed QT prolongation, investigators carried out close monitoring with repeat electrocardiograms (ECGs), consulted cardiology, and assessed/corrected electrolyte abnormalities as needed. Per protocol, temporary dose interruption, dose modification, or discontinuation of ABM-1310 was implemented at the investigator's discretion.

Pharmacokinetics and statistical analyses

Data were summarized by dose group and cohort. Descriptive statistics for continuous variables included number of non-missing observations (n), arithmetic mean, standard deviation, minimum, median, and maximum. For categorical variables, descriptive statistics including the counts and percentages of different categories are used. Unless otherwise specified, missing data (i.e. data not collected, not recorded, or otherwise unavailable) were not included in percentage calculations. All analyses used two-sided tests with a significance level of $\alpha = 0.05$, and two-sided 95% confidence intervals (CIs) were calculated. No formal statistical hypothesis testing was planned. The screened set included all consented patients and was used for patient disposition. The full analysis set (FAS) included all patients who received $\geq$1 dose of ABM-1310 and was used for both safety and PK analyses, and for baseline/demographic summaries. The dose-determining set included DLT-evaluable FAS patients and was used for the primary analyses of DLTs and MTD determination. Safety analyses were descriptive and based on treatment-emergent AEs. PK parameters were estimated for subjects in the PK population using Phoenix WinNonlin® version 8.3 or higher (Certara USA, Inc., Princeton, NJ). All secondary endpoints were analyzed descriptively.

RESULTS

Demographic and clinical characteristics

Between June 2020 and April 2024, 53 patients received treatment: 36 patients with ABM-1310 monotherapy (Part A, $n = 23$; Part C, $n = 13$) and 17 with ABM-1310 plus cobimetinib (Part B) (CONSORT, Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.106047). Enrollment and dose escalation are shown in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.106047. Baseline demographic and clinical characteristics are summarized in Figure 1. Melanoma was the most common primary malignancy (47%, $n = 25$), followed by glioblastoma multiforme (GBM) (17%, $n = 9$) and thyroid cancer (13%, $n = 7$) (Figure 1A). Most patients were male (68%) and white (85%), had an ECOG performance status of 1 (74%) (Figure 1B). The median age was 55 years (range 30-77 years) (Figure 1C). BRAF V600E mutation was identified in 92.5% ($n = 49$) of patients. The remaining 7.5% ($n = 4$) had other BRAF alterations, including V600K mutations ($n = 2$), *BRAF* gene rearrangement ($n = 1$), and other non-V600E mutations ($n = 1$) (Figure 1D).

Overall, 75% ($n = 40$) of patients had received prior treatment with BRAFi plus MEKi, whereas 7.5% ($n = 4$) had received only BRAFi. No patients received MEKi alone. Common prior BRAFi plus MEKi treatments included

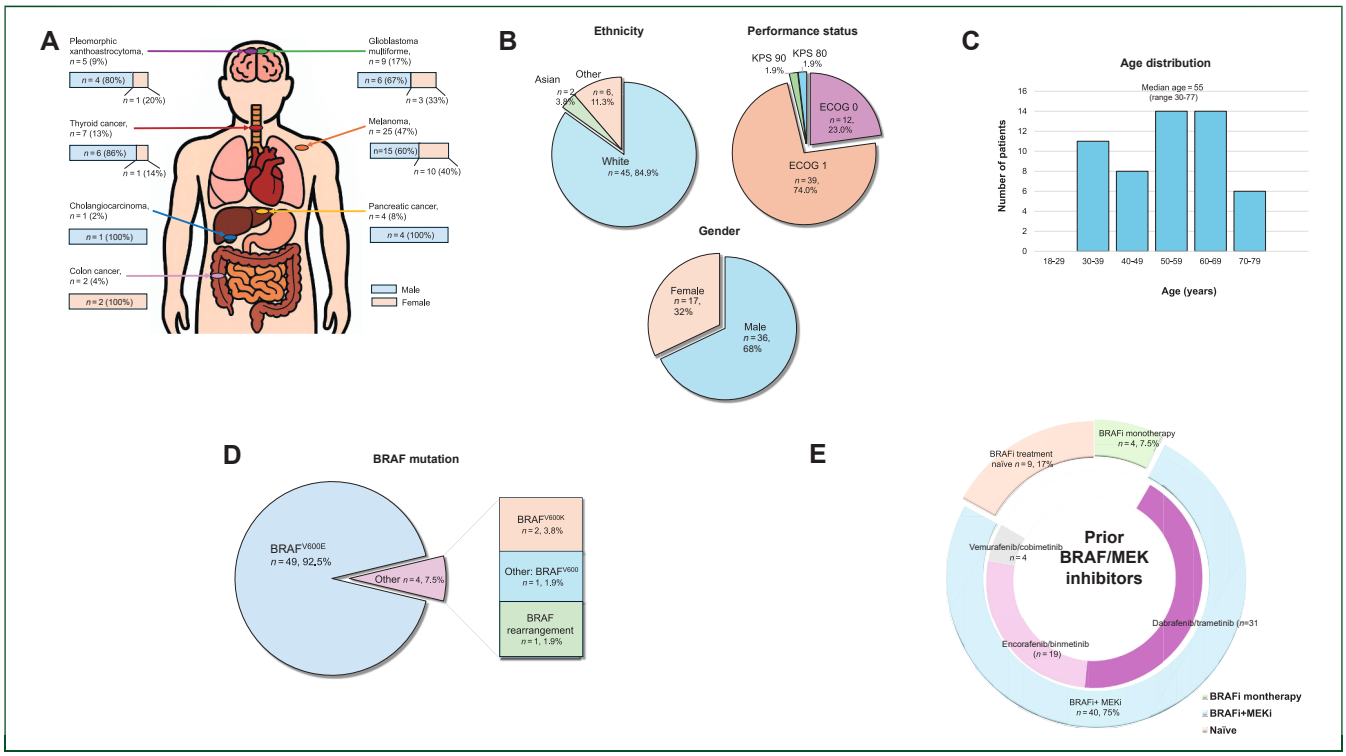

Figure 1. Baseline demographic and clinical characteristics of the study population. (A) Distribution of primary tumor types annotated on a human body schematic. Melanoma was the most common malignancy (47%), followed by glioblastoma multiforme (17%) and thyroid cancer (13%). Other tumors included cholangiocarcinoma, pancreatic, colon, and PXA. (B) Patient demographics and ECOG performance status shown as pie charts. Most patients were male (68%), white (85%), and had an ECOG performance status of 1 (74%). (C) Bar graph depicting age distribution; median age was 55 years (range 30-77). (D) *BRAF* mutation profile represented as a pie chart. Most patients carried BRAF V600E (92.5%); other alterations included V600K (3.8%), *BRAF* rearrangement (1.9%), and other non-V600E mutations (1.9%). (E) Prior BRAFi/MEKi use illustrated by a donut chart. The outer ring shows the proportion of treatment-naïve (17%), BRAFi alone (7.5%) versus previously treated (75%) patients. The inner ring displays the most common agents used: dabrafenib/trametinib ($n = 31$), encorafenib/binimetinib ($n = 19$) and vemurafenib/cobimetinib ($n = 4$).
BRAFi, B-Raf proto-oncogene, serine/threonine kinase inhibitor; MEKi, mitogen-activated protein kinase kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; PXA, pleomorphic xanthoastrocytoma.

dabrafenib/trametinib ($n = 31$), encorafenib/binimetinib ($n = 19$) and vemurafenib/cobimetinib ($n = 4$) (Figure 1E).

Adverse events

Table 1 summarizes treatment-related adverse events (TRAEs) with ABM-1310 monotherapy ($n = 36$) and combination therapy with cobimetinib ($n = 17$). For monotherapy, frequent TRAEs (≥10%) were electrocardiogram QT prolonged (EQTP, 41.7%), rash (27.8%), dry skin (13.9%), myalgia (11.1%), dry eye (11.1%), and headache (11.1%). In the combination therapy group, commonly reported TRAEs (≥10%) included EQTP (64.7%), rash (35.3%), increased lipase (23.5%), increased blood creatine phosphokinase (23.5%), pruritus (23.5%), increased blood creatinine (17.6%), and diarrhea (17.6%); amylase increased, dermatitis acneiform, anemia, neutropenia, nausea, vomiting, and fatigue each occurred in 11.8% of patients. The most frequent grade 3 TRAE was EQTP (11.1% with monotherapy; 5.9% with combination therapy). Additional grade 3 TRAEs included myalgia (5.6%), rash, nausea, and vomiting (2.8% each) in monotherapy whereas neutropenia, rash, and lipase elevation (each 5.9%) occurred in combination therapy. No grade 4 or 5 TRAEs were reported. DLTs occurred in 6/37 patients (16.2%) in the dose-determining cohorts (Parts A and B).

In Part A (monotherapy, $n = 22$), DLTs were reported at 200 mg (one patient with grade 1-2 asymptomatic EQTP) and 250 mg dose levels (three patients with grade 2 asymptomatic EQTP, including one with concurrent grade 2 renal failure). In Part B (combination therapy, $n = 15$), DLTs occurred in two patients: one developed grade 3 asymptomatic EQTP at 150 mg, and another experienced grade 1 asymptomatic EQTP with grade 2 rash at 200 mg (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.106047).

Three patients (5.7%) experienced treatment-related serious adverse events (SAEs): a 40-year-old male with GBM receiving ABM-1310 monotherapy (100 mg b.i.d.) developed grade 3 nausea and vomiting that was managed with supportive care and drug interruption; a 67-year-old male with metastatic pancreatic cancer receiving monotherapy (250 mg b.i.d.) developed grade 2 renal failure; and a 42-year-old male with GBM receiving combination therapy (150 mg b.i.d.) experienced grade 3 asymptomatic EQTP, which resolved with supportive care (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.106047). Grade 3 asymptomatic EQTP occurred more frequently in BRAFi-naïve patients than in those with prior exposure (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.106047). No treatment-related deaths or permanent treatment discontinuations occurred. Clinically significant

Table 1. Incidence of treatment-related adverse events (TRAEs) occurring in ≥10% of subjects by system organ class, preferred term

Preferred term	ABM-1310 monotherapy ($n = 36$)		ABM-1310 with cobimetinib ($n = 17$)	
	All grades *n* (%)	Grade 3[a] *n* (%)	All grades *n* (%)	Grade 3[a] *n* (%)
Electrocardiogram QT prolonged	15 (41.7%)[b]	4 (11.1%)	11 (64.7%)[b]	1 (5.9%)[b]
Lipase increased	3 (8.3%)	0	4 (23.5%)	1 (5.9%)
Blood creatine phosphokinase increased	0	0	4 (23.5%)	0
Blood creatinine increased	2 (5.6%)[b]	0	3 (17.6%)	0
Amylase increased	0	0	2 (11.8%)	0
Rash	10 (27.8%)	1 (2.8%)	6 (35.3%)[b]	1 (5.9%)
Pruritus	3 (8.3%)	0	4 (23.5%)	0
Dry skin	5 (13.9%)	0	0	0
Dermatitis acneiform	1 (2.8%)	0	2 (11.8%)	0
Alopecia	2 (5.6%)	0	1 (5.9%)	0
Myalgia	4 (11.1%)	2 (5.6%)	0	0
Dry eye	4 (11.1%)	0	0	0
Nausea	3 (8.3%)	1 (2.8%)	2 (11.8%)	0
Vomiting	3 (8.3%)	1 (2.8%)	2 (11.8%)	0
Diarrhea	2 (5.6%)	0	3 (17.6%)	0
Headache	4 (11.1%)	0	1 (5.9%)	0
Fatigue	3 (8.3%)	0	2 (11.8%)	0
Anemia	0	0	2 (11.8%)	
Neutropenia	1 (2.8%)	0	2 (11.8%)	1 (5.9%)

TRAE is defined as all adverse events that occur at the time of and following administration of the study drug and deemed as related (suspected) to the study drug.
[a]no Grade 4-5 TRAE occurred.
[b]Dose limiting toxicity (monotherapy: electrocardiogram QT prolonged $n = 3$, electrocardiogram QT prolonged and creatine increase $n = 1$. Combination therapy: electrocardiogram QT prolonged $n = 1$, QT prolonged and rash $n = 1$). Subjects with multiple occurrences of adverse events in the same preferred term are counted only once within that preferred term.

ECG abnormalities were observed only at doses >100 mg b.i.d. No significant ophthalmic toxicities were reported. Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2025.106047 details TRAE-associated study drug interruptions and dose reductions across ABM-1310 dose levels.

Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2025.106047 summarizes patients requiring dose modifications for EQTP. Events occurred early, with all initial dosing interruptions in cycle 1. The median time to EQTP resolution was 7 days (range 3-56 days). Among the eight patients with dosing interruptions, one achieved partial response (PR), four achieved stable disease (SD), and three had progressive disease, with PR/SD lasting 2-10 months despite treatment holds.

Efficacy

All 53 patients enrolled in the study had measurable disease at baseline by RECIST v1.1, RANO, or modified RECIST v1.1 (for BrM). Three patients were excluded from the efficacy analysis due to the lack of tumor assessments following treatment. Consequently, 50 patients were evaluable for response and included in the waterfall and swimmer plots (Figure 2A and B), comprising 34 patients from Parts A and C (monotherapy) and 16 patients from Part B (combination therapy).

In the monotherapy cohorts, four confirmed PRs were observed including three patients with primary CNS tumors—GBM, and grade 2 and grade 3 pleomorphic xanthoastrocytoma—and one patient with pancreatic cancer. Sixteen patients achieved SD as their best response, resulting in a DCR (defined as percentage of patients with CR + PR + SD) of 58.8%. Patient 01019 (GBM, right frontal lobe) had an unconfirmed PR. The swimmer plot (Figure 2B) illustrates response duration. Notably, four of the six patients who achieved PR were followed only until the time of early trial termination. All patients with PRs in the monotherapy cohorts received ABM-1310 at 200 mg b.i.d.

In Part B (ABM-1310 plus cobimetinib), two confirmed PRs were observed (one melanoma and one thyroid cancer). Among 16 efficacy-evaluable patients in this cohort, the ORR was 12.5%, and the DCR was 75% (Figure 2).

Overall, 14 patients had primary CNS tumors (13 were treated on monotherapy: Parts A and C) and 1 was treated on combination therapy (Part B: GBM patient not evaluable due to early death). Among 13 efficacy-evaluable patients with primary CNS tumors, ORR was 23.1%, rising to 42.9% at 200 mg b.i.d. The DCR across all primary CNS tumor patients was 76.9% (Table 2B). Within the solid tumor cohort, 43.6% (17/39) had active BrM at baseline, of which 16 patients were efficacy-evaluable; 1 was unevaluable due to incomplete tumor assessment before study withdrawal. Seven of these BrM patients received ABM-1310 monotherapy (Parts A and C) and nine received combination therapy (Part B). For solid tumor patients with BrM, the overall DCR was 42.9% in the monotherapy groups (Parts A and C) and 55.6% in the combination group (Part B) (Table 2A).

Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2025.106047 summarizes progression-free survival (PFS) and overall survival (OS). Median PFS was 4.96 months (2.07-8.31) and median OS was 24.48 months (11.60-NE). The median follow-up time for treated patients

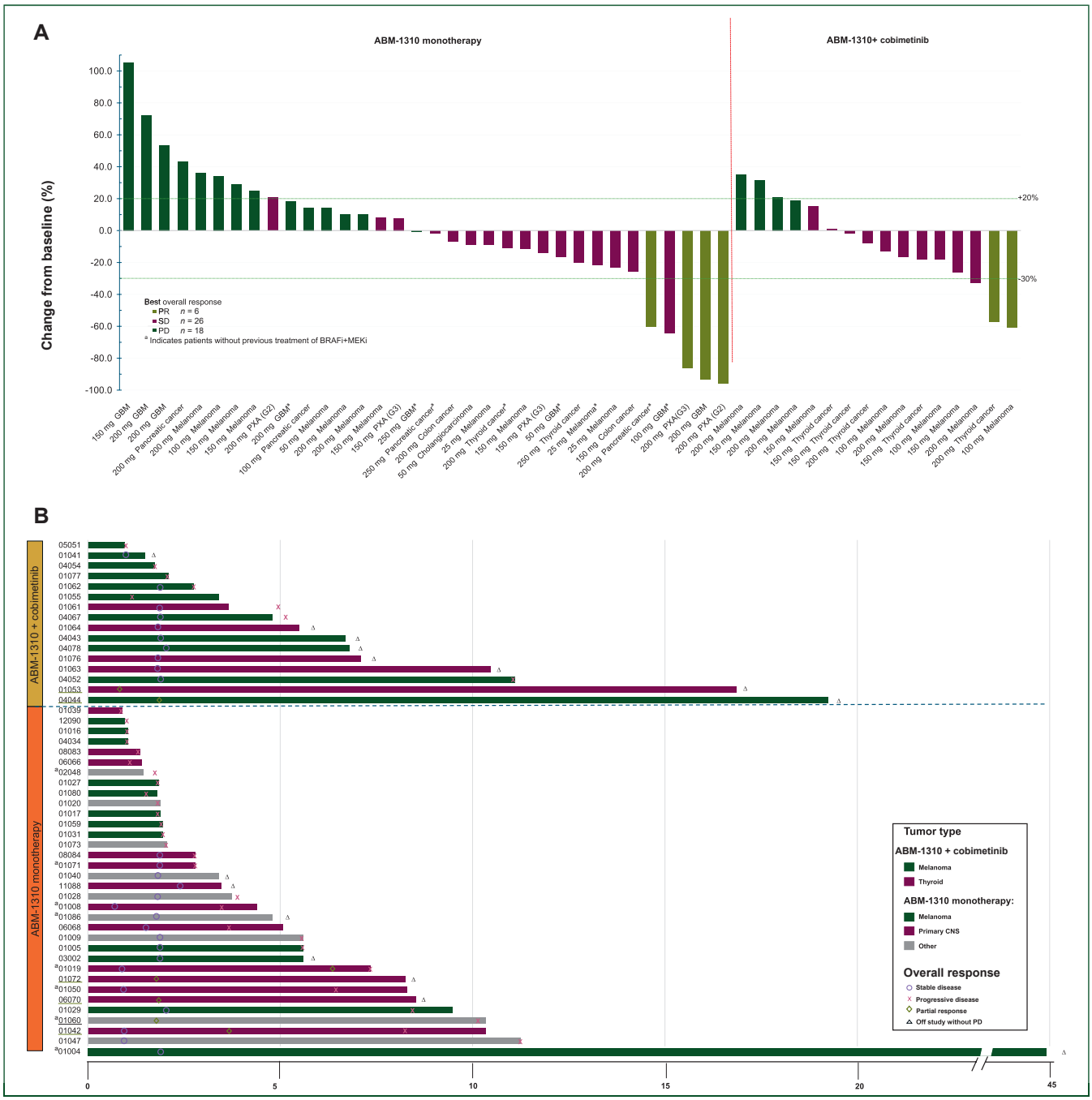

Figure 2. Antitumor activity of ABM-1310 monotherapy and combination therapy. (A) Waterfall plot showing the best percentage change in target lesion size from baseline among efficacy-evaluable patients treated with ABM-1310 monotherapy (left) or in combination with cobimetinib. GBM patient 01019 had unconfirmed PR. (B) Swimmer plot depicting treatment duration by patient, grouped by treatment regimen. Bars are color-coded by tumor type: melanoma (Green), thyroid cancer (combination, purple), primary CNS tumor (monotherapy, purple), and other tumors (monotherapy, gray). Symbols indicate best overall response: partial response (green diamond), stable disease (blue circle), progressive disease (pink cross), and off-study without progression (gray triangle). Patient 01019 had unconfirmed PR. BRAFi, B-Raf proto-oncogene, serine/threonine kinase inhibitor; CNS, central nervous system; GBM, glioblastoma multiforme; MEKi, mitogen-activated protein kinase kinase inhibitor; mg, milligram; PD, progressive disease; PR, partial response; PXA (G), pleomorphic xanthoastrocytoma (Grade); RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Indicates patients without previous treatment of BRAFi + MEKi. Responders are indicated by underlined patient IDs. Green underlining denotes patients with prior BRAF inhibitor (BRAFi) exposure, whereas black underlining denotes BRAFi-naïve patients.

was 5.1 months (range 0.9-44.9 months). PFS was longer in patients receiving combination therapy (10.97 months) compared with those on monotherapy (3.6 months). PFS in patients with BrM and primary CNS tumors is shown in Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2025.106047. Notably, in patients with BrM, median intracranial PFS exceeded extracranial PFS in both treatment groups. Intracranial PFS was 5.55 months (0.99-NE) with monotherapy and 5.16 months (0.99-NE) with combination therapy, whereas extracranial PFS was

Table 2. Summary of objective response in solid tumor with brain metastasis and primary CNS

(A) Solid tumor with brain metastasis	ABM-1310 monotherapy			ABM-1310 with cobimetinib		
	Intracranial response ($n = 7$) *n* (%)	Extracranial response ($n = 7$) *n* (%)	Overall response ($n = 7$) *n* (%)	Intracranial response ($n = 9$) *n* (%)	Extracranial response ($n = 9$) *n* (%)	Overall response ($n = 9$) *n* (%)
Complete response	0	0	0	0	0	0
95% CI	(0.0%-41.0%)	(0.0%-41.0%)	(0.0%-41.0%)	(0.0%-33.6%)	(0.0%-33.6%)	(0.0%-33.6%)
Partial response	1 (14.3%)	1 (14.3%)	0	0	0	0
95% CI	(0.4%-57.9%)	(0.4%-57.9%)	(0.0%-41.0%)	(0.0%-33.6%)	(0.0%-33.6%)	(0.0%-33.6%)
Stable disease	4 (57.1%)	2 (28.6%)	3 (42.9%)	4 (44.4%)	6 (66.7%)	5 (55.6%)
95% CI	(18.4%-90.1%)	(3.7%-71.0%)	(9.9%-81.6%)	(13.7%-78.8%)	(29.9%-92.5%)	(21.2%-86.3%)
Progressive disease	2 (28.6%)	4 (57.1%)	4 (57.1%)	3 (33.3%)	2 (22.2%)	3 (33.3%)
95% CI	(3.7%-71.0%)	(18.4%-90.1%)	(18.4%-90.1%)	(7.5%-70.1%)	(2.8%- 60.0%)	(7.5%-70.1%)
Not evaluable	0	0	0	1 (11.1%)	0	0
Not done	0	0	0	1 (11.1%)	1 (11.1%)	1 (11.1%)
Number of responders (CR + PR) (Objective response rate)	1 (14.3%)	1 (14.3%)	0	0	0	0
95% CI of objective response rate	(0.4%-57.9%)	(0.4%-57.9%)	(0.0%-41.0%)	(0.0%-33.6%)	(0.0%-33.6%)	(0.0%-33.6%)
Number of clinical benefit responders (CR + PR + SD) (Disease control rate)	5 (71.4%)	3 (42.9%)	3 (42.9%)	4 (44.4%)	6 (66.7%)	5 (55.6%)
95% CI of disease control rate	(29.0%-96.3%)	(9.9%-81.6%)	(9.9%-81.6%)	(13.7%-78.8%)	(29.9%-92.5%)	(21.2%-86.3%)

(B) Primary CNS patients	ABM-1310 monotherapy							ABM-1310 with cobimetinib			
	25 mg ($n = 0$) *n* (%)	50 mg ($n = 1$) *n* (%)	100 mg ($n = 1$) *n* (%)	150 mg ($n = 3$) *n* (%)	200 mg ($n = 7$) *n* (%)	250 mg ($n = 1$) *n* (%)	Total ($n = 13$) *n* (%)	100 mg ($n = 0$) *n* (%)	150 mg ($n = 0$) *n* (%)	200 mg ($n = 0$) *n* (%)	Total ($n = 0$) *n* (%)
Complete response	0	0	0	0	0	0	0	0	0	0	0
95% CI		(0.0%- 97.5%)	(0.0%- 97.5%)	(0.0%- 70.8%)	(0.0%- 41.0%)	(0.0%- 97.5%)	(0.0%- 24.7%)				
Partial response	0	0	0	0	3 (42.9%)	0	3 (23.1%)	0	0	0	0
95% CI		(0.0%-97.5%)	(0.0%-97.5%)	(0.0%-70.8%)	(9.9%-81.6%)	(0.0%-97.5%)	(5.0%-53.8%)				
Stable disease	0	1 (100%)	1 (100%)	2 (66.7%)	2 (28.6%)	1 (100%)	7 (53.8%)	0	0	0	0
95% CI		(2.5%-100%)	(2.5%-100%)	(9.4%-99.2%)	(3.7%-71.0%)	(2.5%-100%)	(25.1%-80.8%)				
Progressive disease	0	0	0	1 (33.3%)	2 (28.6%)	0	3 (23.1%)	0	0	0	0
95% CI		(0.0%-97.5%)	(0.0%-97.5%)	(0.8%-90.6%)	(3.7%-71.0%)	(0.0%-97.5%)	(5.0%-53.8%)				
Number of responders (CR + PR) (Objective response rate)	0	0	0	0	3 (42.9%)	0	3 (23.1%)	0	0	0	0
95% CI of objective response rate		(0.0%-97.5%)	(0.0%-97.5%)	(0.0%-70.8%)	(9.9%-81.6%)	(0.0%-97.5%)	(5.0%-53.8%)				
Number of clinical benefit responders (CR + PR + SD) (Disease control rate)	0	1 (100%)	1 (100%)	2 (66.7%)	5 (71.4%)	1 (100%)	10 (76.9%)	0	0	0	0
95% CI of disease control rate		(2.5%-100%)	(2.5%-100%)	(9.4%-99.2%)	(29.0%-96.3%)	(2.5%-100%)	(46.2%-95.0%)				

The 95% confidence intervals are calculated using the Clopper Pearson method.
Subject 01-053 was removed from the table because the tumor response for this patient was evaluated using RECIST, which is not consistent with the criteria used for other patients.

https://doi.org/10.1016/j.esmoop.2025.106047

Table 3. ABM-1310 PK parameters—multiple dose

A) Part A: mean (STD) plasma ABM-1310 PK parameters

Parameters	Part A: dose groups			
	100 mg	150 mg	200 mg	250 mg
$AUC_{0\text{-last}}$ (h*ng/ml)	65 800 (12 100)	135 000 (31 100)	125 000 (63 200)	106 000 (83 600)
$AUC_{0\text{-tau}}$ (h*ng/ml)	67 200 (13 000)	139 000 (31 800)	162 000 (38 800)	206 000
C_{max} (ng/ml)	8 950 (1 640)	15 900 (6 080)	18 000 (8 700)	14 400 (11 600)
T_{max}[a] (h)	2.00 (1.03, 2.00)	2.04 (2.00, 2.08)	2.00 (0.98, 4.08)	7.58 (1.00, 8.32)
CL_{ss}/F (l/h)	1.53 (0.266)	1.53 (0.266)	1.28 (0.281)	1.21
R_{acCmax}	2.27 (0.968)	1.70 (0.311)	1.25 (0.428)	0.624 (0.295)
R_{acAUC}	1.74 (0.0566)	2.16	1.76 (0.314)	0.952

B) Part B: Mean (STD) plasma ABM-1310 PK parameters

Parameters	Part B: dose groups	
	100 mg	150 mg
$AUC_{0\text{-last}}$ (h*ng/ml)	34 100 (4 560)	95 300 (50 900)
$AUC_{0\text{-tau}}$ (h*ng/ml)	36 800	117 000 (33 300)
C_{max} (ng/ml)	8 250 (3 990)	13 200 (4 450)
T_{max}[a] (h)	1.03 (0.95, 1.98)	1.53 (1.02, 2.05)
CL_{ss}/F (l/h)	2.72	1.35 (0.304)
R_{acCmax}	1.51 (0.153)	1.49 (0.479)
R_{acAUC}	1.79	1.82 (0.544)

C) Part C: Mean (STD) plasma ABM-1310 PK parameters

Parameters	Part C: dose groups	
	150 mg	200 mg
$AUC_{0\text{-last}}$ (h*ng/ml)	91 200 (14 100)	109 000 (46 000)
$AUC_{0\text{-tau}}$ (h*ng/ml)	129 000 (15 600)	139 000 (43 300)
C_{max} (ng/ml)	16 800 (2 910)	18 200 (8 010)
T_{max}[a] (h)	1.12 (0.95, 2.15)	1.08 (1.00, 3.97)
CL_{ss}/F (l/h)	1.17 (0.141)	1.65 (0.822)
R_{acCmax}	2.38 (1.06)	1.63 (0.770)
R_{acAUC}		1.40 (0.418)

$AUC_{0\text{-last}}$, area under the plasma concentration-time curve up to the last measurable plasma concentration-time point; $AUC_{0\text{-tau}}$, area under the plasma concentration-time curve from time 0 to tau; C_{max}, maximum plasma concentration at T_{max}; CL_{ss}/F, apparent total body clearance; max, maximum; min, minimum; R_{ac}, accumulation ratio; STD, standard deviation; T_{max}, time to reach maximum plasma concentration.
[a]For T_{max} is median (min, max).

1.91 (0.99-NE) and 3.96 months (1.68-NE), respectively. The median overall PFS in patients with primary CNS tumors was 3.71 months (1.28-8.31).

Pharmacokinetics

Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.106047 summarizes dose levels and patient numbers included in the PK analysis. PK was assessed in all 53 treated patients with ≥1 safety assessment following baseline and provided evaluable PK samples. Following a single oral dose of ABM-1310 (25-250 mg) in Parts A, B, and C, median T_{max} ranged from 1.03 to 2.07 hours, with dose escalation or combination with cobimetinib having minimal impact on absorption rate. Elimination patterns were generally consistent across dose levels, and mean plasma concentrations increased with dose (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2025.106047).

In the multiple-dose setting (100-250 mg b.i.d.), median T_{max} remained between 1.03 and 2.04 hours, except at 250 mg in Part A where time of maximum observed plasma concentration (T_{max}) was delayed (7.58 h), likely due to high interpatient variability and the small number of patients ($n = 3$). Elimination trends were consistent, and mean plasma exposure increased with dose. Apparent clearance (CL_{ss}/F) was stable across most cohorts, suggesting no dose-dependent saturation of elimination (Table 3).

Drug accumulation was observed following b.i.d. dosing. Accumulation rates for C_{max} ($R_{ac}C_{max}$) and area under curve ($R_{ac}AUC$) ranged from 1.25 to 2.38 and 1.40 to 2.16, respectively, in most dose groups, indicating moderate accumulation. Notably, lower accumulation was seen at 250 mg in Part A ($R_{ac}C_{max} = 0.624$; $R_{ac}AUC = 0.952$). Steady-state concentrations were achieved by cycle 2 day 1.

DISCUSSION

This FIH phase I trial evaluated the safety, PK, and preliminary antitumor activity of ABM-1310 in patients with advanced solid tumors and primary CNS malignancies. The MTD was established at 200 mg b.i.d. for both monotherapy and combination with cobimetinib at 60 mg q.d. for the first 21 days of each 28-day treatment cycle. Treatment was generally well tolerated, with no grade 4 or 5 TRAEs. Grade 3 EQTP occurred more frequently in BRAFi-naïve patients, possibly reflecting selection bias as patients previously treated with BRAFi may represent a more cardiac-tolerant population or exclusion of individuals

predisposed to QT prolongation. Although the mechanism for ABM-1310-related EQTP remains unclear, preclinically, ABM-1310 inhibited human ether-à-go-go—related gene (hERG) current *in vitro* with a half maximal inhibitory concentration of 0.76 µmol/l, and resulted in a small, transient QTc increase in Beagle dogs at 20 mg/kg, indicating a modest, exposure-dependent effect on cardiac repolarization (unpublished).

ABM-1310 exhibited a safety profile generally consistent with approved BRAF-targeted therapies, though EQTP was more frequent; 41.7% with monotherapy and 64.7% with combination therapy versus <10% reported for agents such as dabrafenib plus trametinib, encorafenib, or vemurafenib. All EQTPs were asymptomatic on clinical evaluation and were successfully managed with temporary treatment interruption. Other TRAEs, such as rash and elevations in serum creatinine, were comparable with those observed with existing BRAFi, whereas gastrointestinal symptoms and fatigue were less frequently reported, with nausea, diarrhea, and vomiting reported at roughly half the rates observed with approved BRAFi/MEKi regimens (Supplementary Table S10, available at https://doi.org/10.1016/j.esmoop.2025.106047).[14,18,29,30] Overall, ABM-1310 was associated with a manageable safety profile, although enhanced cardiac monitoring is recommended due to the higher incidence of QT prolongation.

The PK profile of ABM-1310 demonstrated rapid absorption, with median T_{max} values ranging from 1.03 to 2.07 hours following single-dose administration and 1.03 to 2.04 hours following multiple doses, consistent across study parts and dose levels. Exposure parameters (C_{max} and AUC) generally increased with dose, and moderate accumulation was observed with b.i.d. dosing (mean $R_{ac}C_{max}$ 1.25-2.38, mean R_{ac}AUC 1.40-2.16). Notably, exposure at the 250 mg b.i.d. dose showed greater interpatient variability, with delayed T_{max} (7.58 h) and lower accumulation ratios, likely due to the limited sample size, individual differences and interrupted treatment exposure resulting from early dose modifications due to AEs. Steady-state concentrations were reached by cycle 2 day 1 across most cohorts. Compared with approved BRAFi, ABM-1310 demonstrated a faster absorption profile than vemurafenib (T_{max} ∼3-4 h) and similar or slightly faster absorption than dabrafenib and encorafenib (T_{max} ∼1.5-2 h).[16,31–33] Clearance (CL_{ss}/F) remained relatively stable across dose levels, indicating linear elimination within the 100-200 mg b.i.d. range. Collectively, these results support the selection of 100-200 mg b.i.d. as the recommended dose range for further clinical investigation. The predictable PK, manageable accumulation, and reliable attainment of steady state, combined with demonstrated intracranial activity, reinforce the potential of ABM-1310 for use in BRAF V600-mutant malignancies, particularly those involving the CNS.

Despite early sponsor-initiated study termination and limitations such as small cohorts and limited follow-up, ABM-1310 demonstrated encouraging clinical activity in a heavily pretreated and heterogeneous patient population. In primary CNS tumors, ABM-1310 monotherapy achieved an ORR of 23.1% and a DCR of 76.9%, highlighting its ability to cross the BBB and provide clinical benefit in CNS malignancies. In patients with BrM, intracranial disease control rate (DCR, 71.4%) was comparable with or exceeded extracranial responses (42.9%) and median intracranial PFS (5.55 and 5.16 months) surpassed extracranial PFS (1.91 and 3.96 months) in both monotherapy and combination therapy, respectively, supporting its CNS activity (Table 2 and Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2025.106047). Notably, five out of six PRs occurred in patients with prior BRAFi exposure, suggesting that ABM-1310 may retain activity in some BRAFi-refractory tumors, potentially in cases that remain MAPK-dependent and responsive to rechallenge. This observation is likely influenced by small sample size and tumor heterogeneity. In contrast, treatment-naïve patients exhibited a higher DCR to ABM-1310 (Supplementary Table S11, available at https://doi.org/10.1016/j.esmoop.2025.106047). Combination therapy with cobimetinib further improved outcomes, achieving a DCR of 75% and a median PFS of 10.97 months, compared with 58.8% and 3.6 months, respectively, with monotherapy.

Two melanoma cases demonstrated notable durability with ABM-1310: one BRAFi-naïve patient (01-004) maintained sustained SD for ∼45 months on monotherapy after intrapatient dose escalation, and another (04-044), BRAFi/MEKi pretreated patient achieved PR with a DoR of 17.8 months on ABM-1310 plus cobimetinib. These observations highlight the potential long-term clinical benefit of ABM-1310.

In comparison, established BRAFi/MEKi combinations in treatment-naïve metastatic melanoma report substantially higher ORRs—68% with dabrafenib plus trametinib (COMBI-d/v),[34] 70% with vemurafenib plus cobimetinib (coBRIM)[14] and 64% with encorafenib plus binimetinib (COLUMBUS)[29]—with median PFS ranging from 11.1 to 14.9 months and DCRs typically exceeding 85%. However, these trials excluded patients with prior BRAFi exposure and those with active CNS disease.[14,29,35] In this study, the pharmacodynamic-intracranial activity correlations were not assessed; however, interim findings from a separate phase I study in China (NCT05892653) supported the intracranial activity of ABM-1310, with 3 of 13 patients with recurrent BRAF V600-mutated primary CNS tumors achieving PRs, two lasting >8 months.[22] Exploratory PK analyses demonstrated high CNS penetration ($K_{p,uu}$ 86%-100%),[22] and preclinical studies showed an unbound brain-to-plasma ratio of 1.44 in mice (unpublished). Together with the clinical benefit observed with ABM-1310, particularly in prior BRAFi-treated and CNS-involved patients, these findings support its continued development.

Our study has several limitations. Patients had diverse primary tumor types and varying intracranial disease burden, complicating cross-cohort comparisons. Treatment regimens differed across study parts (monotherapy versus combination), and no randomized comparator arm was included. Most patients were heavily pretreated: 72% had ≥3 prior lines of therapy, 75% had received both prior

BRAFi and MEKi, and 7.5% received BRAFi alone, which may have influenced both efficacy and tolerability profiles. One patient with a *BRAF* gene rearrangement was enrolled in deviation from eligibility criteria; however, this single case is unlikely to have affected the phase I safety-focused objectives. Early study termination also limited follow-up, likely underestimating true durability of response. These limitations should be considered when interpreting the study results and considering future clinical development.

Conclusion

ABM-1310 was generally well tolerated and demonstrated predictable PK and preliminary antitumor activity across a range of tumor types, including BRAFi-refractory and CNS-involved malignancies. Our results support further evaluation of ABM-1310.

ACKNOWLEDGEMENTS

The authors extend their gratitude to the patients and their families for their invaluable participation and support throughout the study.

FUNDING

This work was supported by ABM Therapeutics, and was also supported in part by the National Cancer Institute Cancer Center Support Grant [grant number P30CA016672] and the Clinical Translational Science Award Grant [grant numbers UM1 TR0045906 and 1UL1 TR003167] to The University of Texas MD Anderson Cancer Center. The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect only those of the authors.

DISCLOSURE

SPP reports clinical trial research funding/grant support through the institution from ABM Therapeutics, Inc., Alkermes, Aminex Therapeutics, Axcynsis Therapeutics Pte. Ltd., BioMarin Pharmaceutical, Inc, Boehringer Ingelheim, Cullinan Oncology, Inc., Chugai Pharmaceutical Co., Ltd., Cyclacel Pharmaceuticals, Day One Biopharmaceuticals Inc., Daiichi Sankyo, ENB Therapeutics, Epigenetix Inc., Genmab US, Inc., Gilead Sciences, Inc., Hengrui Pharmaceuticals, Co., Ltd., Immunity Bio, Inc., Immunome, Inc., Immunomedics, Inc., Incyte Corp., Innovent Biologics Co., Ltd., iTEOS Belgium SA, Jazz Pharmaceuticals, Johnson & Johnson, Loxo Oncology, Inc., Merck Sharp and Dohme Corp., Mitsubishi Tanabe Pharma America (MTPA) Inc., Nectin Therapeutics, Ltd., Nested Therapeutics, Inc., NRG Oncology, Nurix, OncoNano Medicine, Inc., Pyxis Oncology, Pieris Pharmaceuticals, Inc., Pfizer, Phanes Therapeutics, Puma Biotechnology, Inc., Purinomia Biotech, Inc., Replimune, Roche/Blueprint, Solve Therapeutics, Strand Therapeutics, Inc., Tallac Therapeutics, Inc., Toragen Therapeutics, Inc., TransThera Bio, Xencor, Inc., NCI/NIH: P30CA016672 — Core Grant (CCSG Shared Resources), CPRIT Grant: Cancer Prevention Research Institute of Texas (CPRIT) Precision Oncology Decision Support Core (RP150535), and Clinical and Translational Science Award Grant (CTSA): 1UM1TR0045906. She has also worked as a consultant for MTPA Inc. FB reports honoraria and/or speaker engagement from Bristol Myers Squibb (BMS), Roche/Genentech, Lilly, Amgen, BeOne Medicines, Guardant Health, Incyte, Ipsen, Jazz Pharmaceuticals, Merck, Johnson and Johnson, Regeneron, Taiho, Takeda, Astella. SN reports funding support for the brain mets space—consultant fees from EnClear, Plus Therapeutics, Daiichi Sankyo; institutional research funding from Plus Therapeutics and Quadriga. FI reports clinical trial research funding/grant support through the institution from Merck, BMS, Tocagen, FORMA Therapeutics, Celldex, Northwest Biotherapeutics, Sapience Therapeutics, Novocure, Pfizer, ABM, AnHeart, AstraZeneca. He holds stock from Praesidia Biotherapeutics and works in a consulting or advisory role for Novocure, Regeneron, AbbVie, Merck, Tocagen, Alexion, Guidepoint Global, Gennao Bio, xCures, Innovation Spec, Medtronic, MassiveBio, Kiyatec, MimiVax, Praesidia Biotherapeutics, Clearview, Ono Pharmaceutical, AnHeart Therapeutics, SERVIER. He receives speakers' bureau funds from Prime Oncology and travel, accommodations support from Oncoceutics. ZY, CC, and YF were ABM employees. KKT reports institutional funding from ABM Therapeutics, AstraZeneca, BMS, Genentech, Georgiamune, Ideaya Biosciences, Innovent Biologics, Linnaeus, OnKure, Merck, Pfizer, Regeneron, Replimune; grant/research support from Eli Lilly; consulting/advisory role with BMS, Replimune. All remaining authors have declared no conflicts of interest.

DATA SHARING

The dataset created during and/or analyzed in this study, excluding patient's protected health information, is available from the corresponding author upon reasonable request.

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