Clinical Trial Protocol

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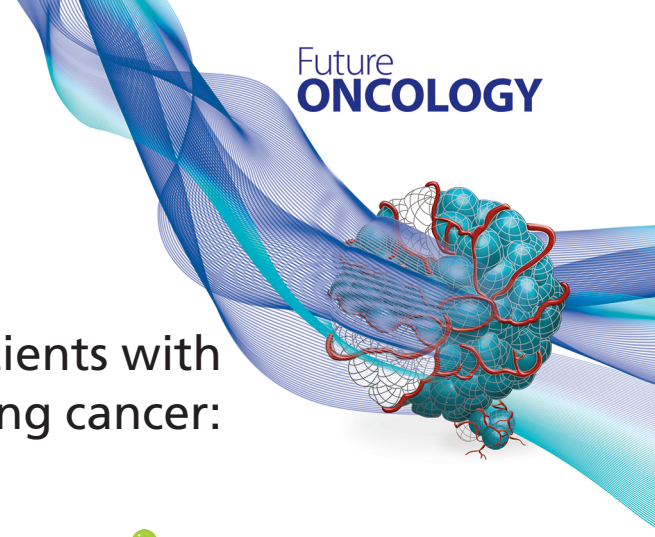

Encorafenib plus binimetinib in patients with *BRAF* ^{V600}-mutant non-small cell lung cancer: phase II PHAROS study design

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BRAF^{V600} oncogenic driver mutations occur in 1–2% of non-small-cell lung cancers (NSCLCs) and have been shown to be a clinically relevant target. Preclinical/clinical evidence support the efficacy and safety of BRAF and MEK inhibitor combinations in patients with NSCLC with these mutations. We describe the design of PHAROS, an ongoing, open-label, single-arm, phase II trial evaluating the BRAF inhibitor encorafenib plus the MEK inhibitor binimetinib in patients with metastatic *BRAF* ^{V600}-mutant NSCLC, as first- or second-line treatment. The primary end point is objective response rate, based on independent radiologic review (per RECIST v1.1); secondary objectives evaluated additional efficacy end points and safety. Results from PHAROS will describe the antitumor activity/safety of encorafenib plus binimetinib in patients with metastatic *BRAF* ^{V600}-mutant NSCLC.

Plain language summary: Some people with non-small-cell lung cancer (NSCLC) have changes in a gene called *BRAF* (known as 'gene mutations'). One common *BRAF* mutation is called 'V600'. Combinations of medicines that block proteins encoded by mutant *BRAF* and another gene called *MEK* can shrink tumors and slow their progression. We describe the design of PHAROS, a clinical trial investigating encorafenib (mutant BRAF inhibitor) combined with binimetinib (MEK inhibitor) in people with *BRAF* ^{V600}-mutant NSCLC that had spread to other parts of the body ('metastatic disease'). People are monitored for side effects and to see if their tumor shrunk. PHAROS includes people treated with encorafenib plus binimetinib as their first treatment for metastatic disease, and people whose cancer progressed after previous anticancer therapy.

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Molecularly targeted therapies are increasingly being developed for biomarker-selected patients with non-small-cell lung cancer (NSCLC) characterized by specific oncogenic driver mutations and gene rearrangements [1,2]. Significant advances in targeted therapy have been associated with improvements in population-level mortality in NSCLC in recent years [3].

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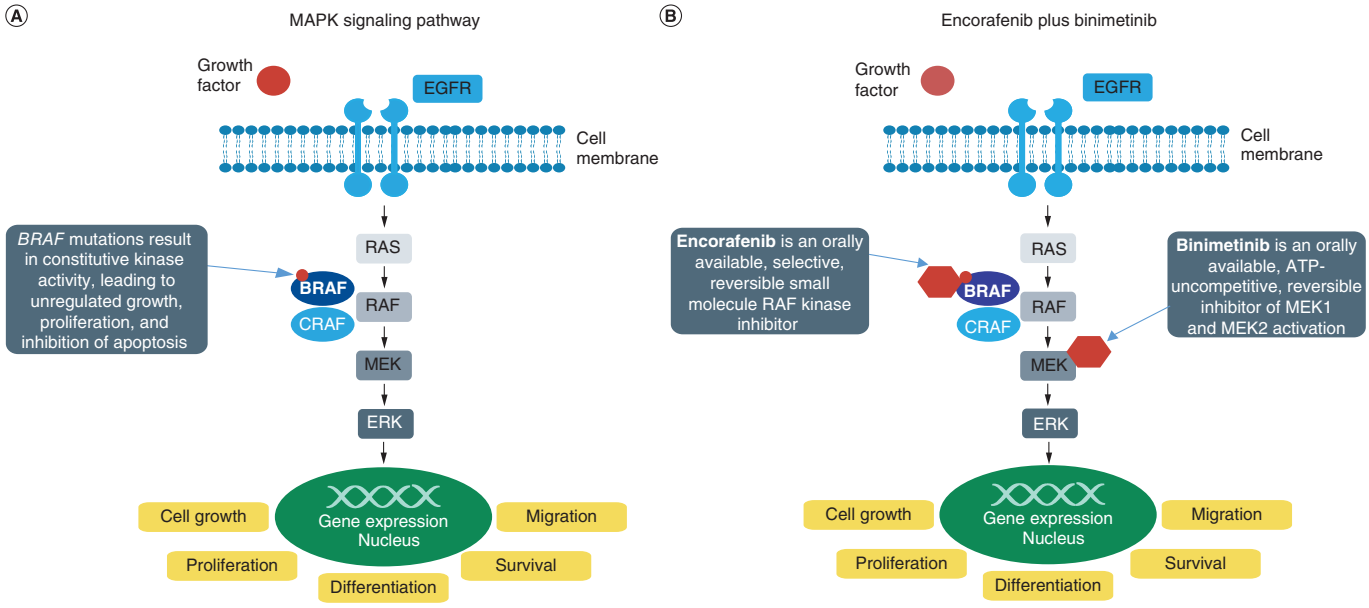

Figure 1. BRAF and MEK inhibitor combination mechanism of action. (A) Activating *BRAF* mutations drive aberrant cell growth and proliferation through constitutive MAPK pathway activation. **(B)** The combination of encorafenib plus binimetinib targets two kinases within the MAPK pathway to inhibit deregulated growth and proliferation caused by *BRAF* driver mutations.

Activating *BRAF* driver mutations occur in approximately 3–4% of patients with NSCLC [4–11], with most of these mutations (~85%) being observed in adenocarcinomas [9–11]. While they are a small subset of all patients with NSCLC, some of the recent and significant advances in NSCLC treatment have been seen with use of novel therapies targeted to specific mutations [1,2]. Moreover, since NSCLC is quite prevalent (i.e., >2 million new cases and >1.7 million deaths annually worldwide, based on 2018 estimates [12]), patients with *BRAF*-mutant NSCLC represent a relatively large number of patients.

The most common activating *BRAF* mutations occur on codon 600 ($BRAF^{V600}$), with most cases involving the $BRAF^{V600E}$ point mutation, which represents approximately 50% of all *BRAF* mutations in lung cancer [13]. There is variability across studies in the identified associations between *BRAF* mutations and clinical and pathological NSCLC features; however, *BRAF* mutations appear to occur more frequently in patients with adenocarcinoma, a history of smoking, and in women [7–10]. There is also evidence that $BRAF^{V600E}$-mutated tumors are associated with an aggressive phenotype, poor prognosis and lack of chemosensitivity to platinum-based chemotherapy [7–9].

Rationale & clinical proof-of-concept validation for BRAF plus MEK inhibitor combinations

BRAF is part of the MAPK pathway, which controls cell growth and proliferation (Figure 1). Activating *BRAF* mutations act as oncogenic drivers by causing constitutive activation of downstream MAPK pathway signaling, resulting in unchecked cell growth and proliferation [9]. In targeting *BRAF*-mutant cancers, BRAF inhibitors are typically used in combination with inhibitors of the downstream kinase MEK. Targeting two kinases within the same RAS/RAF/MEK/ERK pathway achieves a greater antitumor activity and prolongs progression-free survival (PFS) [9,10,14,15]. The addition of a MEK inhibitor also mitigates the paradoxical activation of the MAPK pathway and associated adverse events (AEs) that can occur as a result of BRAF inhibitor monotherapy [14,16,17]. Multiple BRAF and MEK inhibitor combinations have been validated clinically in the treatment of $BRAF^{V600E/K}$-mutant metastatic or unresectable melanoma where such combinations are an established standard of care [18–23].

In $BRAF^{V600E}$-mutant NSCLC, combined BRAF/MEK inhibition is associated with better response rates and PFS compared with BRAF inhibitor monotherapy. In an open-label, phase II clinical trial, the combination of the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib elicited an objective response rate (ORR; primary end point), as determined by the investigator, of 64% (23/36 patients; 95% CI: 46–79) for treatment-naive patients and 63% (36/57 patients; 95% CI: 49–76) for patients who received prior systemic chemotherapy with $BRAF^{V600E}$-mutant metastatic NSCLC [24,25]. In comparison, dabrafenib monotherapy was associated with

an ORR of 33% (95% CI: 23–45) for previously treated patients (four of six treatment-naive patients also responded) [26]. Among responders who received dabrafenib plus trametinib, the median duration of response (DOR) was 10.4 months (95% CI: 8.3–17.9) for treatment-naive patients and 9.0 months (95% CI: 6.9–18.3) for previously treated patients [24,25]. After a minimum of 5-year follow-up, the 4- and 5-year survival rates were 34 and 22%, respectively, in treatment-naive patients (median overall survival [OS]: 17.3 months) and 26 and 19%, respectively, in pretreated patients (median OS: 18.2 months) and patients who received dabrafenib plus trametinib [27]. Based on results from this trial, the combination of dabrafenib and trametinib is a current standard-of-care regimen for *BRAF* ^{V600E}-mutant metastatic NSCLC in the first-line setting or after progression on first-line platinum-based therapy with or without a PD-1/PD-L1 inhibitor [1,28]. The National Comprehensive Cancer Network NSCLC panel also currently recommends that all patients with metastatic nonsquamous NSCLC be tested for *BRAF* mutations and recommends initiation of targeted therapies for those patients whose tumors harbor *BRAF*^{V600E} [28].

Encorafenib in combination with binimetinib

Encorafenib and binimetinib have been developed as selective BRAF and MEK inhibitors, respectively [29,30]. Encorafenib has a relatively long dissociation half-life from mutant *BRAF*^{V600E} (>30 h) compared with other BRAF inhibitors (e.g., 2 h for dabrafenib and 0.5 h for vemurafenib), resulting in prolonged target inhibition and higher potency compared with BRAF inhibitors that dissociate more quickly [31,32]. The clinical efficacy of the combination of encorafenib plus binimetinib versus vemurafenib monotherapy in *BRAF* $^{V600E/K}$-mutant melanoma was established in the COLUMBUS trial based on improved PFS and OS [22,33]. The combination of encorafenib plus binimetinib is associated with a generally manageable side-effect profile relative to the drug class [16,17,22,33,34]. In particular, pyrexia has been identified as a common treatment-limiting toxicity of substantial concern associated with dabrafenib plus trametinib, and as such pyrexia management algorithms are in development to reduce related adverse outcomes [35,36]. While pyrexia has been observed in more than half of patients treated with dabrafenib plus trametinib, pyrexia was relatively less frequent (18% of patients overall) in patients treated with encorafenib plus binimetinib in the COLUMBUS trial [17,35]. Most cases of pyrexia in COLUMBUS were mild (66%; no patients experienced grade 4 pyrexia) and led to dosing interruption/adjustments in 4% of patients and discontinuation in less than 1% of patients [17]. Based on the COLUMBUS trial, the combination of encorafenib plus binimetinib was approved for the treatment of patients with *BRAF* $^{V600E/K}$-mutant unresectable or metastatic melanoma [37].

PHAROS trial

Given the manageable safety profile and antitumor activity in patients with melanoma, encorafenib plus binimetinib may represent an alternative BRAF/MEK inhibitor combination for the treatment of *BRAF* ^{V600}-mutant metastatic NSCLC.

Objectives

We report the design of the PHAROS trial (NCT03915951), which was initiated to explore the antitumor activity and safety of encorafenib plus binimetinib in patients with *BRAF* ^{V600}-mutant metastatic NSCLC, who are either treatment-naive or who have been previously treated with platinum-based chemotherapy and/or anti-PD-1/PD-L1 inhibitor therapy.

Study design

PHAROS is an ongoing, open-label, single-arm, phase II trial evaluating encorafenib plus binimetinib in patients with metastatic *BRAF* ^{V600}-mutant NSCLC. The overall study design is summarized in Figure 2. Eligible patients receive encorafenib 450 mg once daily (q.d) plus binimetinib 45 mg twice daily (b.i.d), administered orally. These dosages are consistent with the approved doses and administration schedule for this combination in patients with *BRAF* $^{V600E/K}$-mutant unresectable or metastatic melanoma [37,38]. Treatment is administered until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, death or end of study.

Dose reductions and temporary dosing interruptions are permitted for toxicity management, and in cases of medical or surgical events or logistical reasons unrelated to the study. However, encorafenib and/or binimetinib will be permanently discontinued for patients missing more than 6 consecutive weeks of dosing with either or both study drug(s). Patients permanently discontinuing treatment with encorafenib must also discontinue treatment

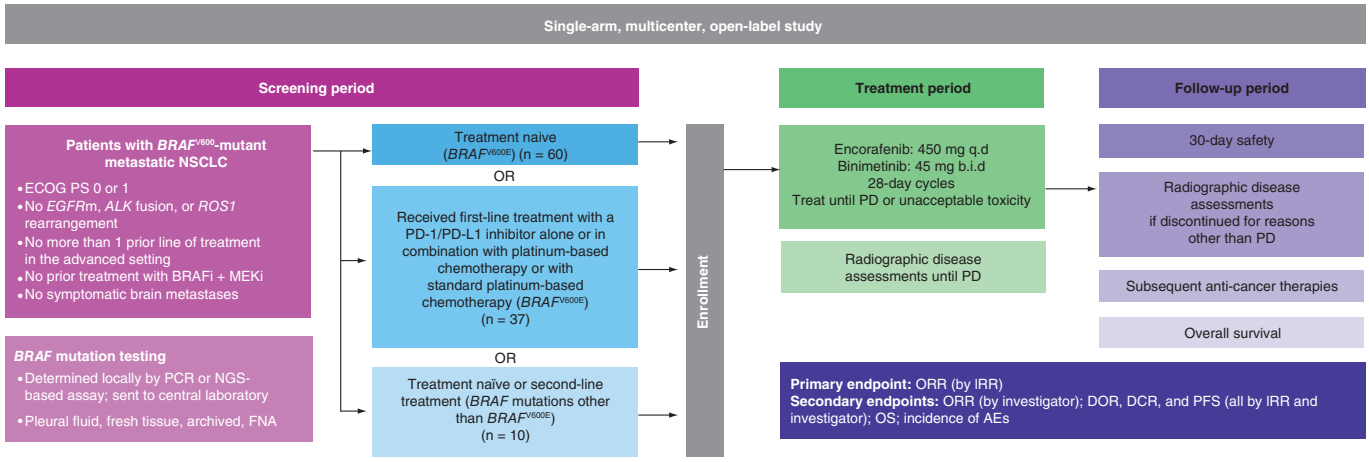

Figure 2. PHAROS trial design.
AE: Adverse event; b.i.d: Twice daily; BRAFi: BRAF inhibitor; DCR: Disease control rate; DOR: Duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; *EGFR*m: *EGFR* mutation; FNA: Fine needle aspiration; IRR: Independent radiology review; MEKi: MEK inhibitor; NGS: Next-generation sequencing; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; q.d: Once daily.

with binimetinib. Those permanently discontinuing treatment with binimetinib may continue treatment with encorafenib, but encorafenib dose modification may be needed due to the potential for increased toxicity of encorafenib administered without binimetinib. Following a dose reduction, the dose can be re-escalated to the next higher dose level at the discretion of the investigator once the AE that resulted in dose reduction improves and remains stable to the patient's baseline for ≥14 days in the absence of concomitant toxicities. Dose re-escalations are not allowed after a dose reduction due to prolonged QTcF ≥501 ms (encorafenib), left ventricular ejection fraction dysfunction (binimetinib) or ocular toxicity grade ≥2 (both drugs).

The study is being performed in accordance with the requirements of the applicable local regulatory authorities and International Council of Harmonisation good clinical practice guidelines. Institutional review board/independent ethics committee approval of the protocol and all amendments was required prior to implementation.

Key eligibility criteria

As summarized in Table 1, the study includes adults (≥18 years) with histologically confirmed stage IV or metastatic NSCLC and measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Two cohorts are being enrolled, a cohort including patients who have had no prior treatment for metastatic disease and another cohort who have received either first-line platinum-based chemotherapy or first-line anti-PD-1/PD-L1 inhibitor treatment (alone or in combination with another immunotherapy and/or platinum-based chemotherapy). Patients will be eligible based on identification of the $BRAF^{V600E}$ mutation in tumor tissue or blood, as determined by a PCR or next-generation sequencing-based local laboratory assay. Other less common class 1 $BRAF^{V600}$ mutations (e.g., K or D) are also permitted. While patients must have tumor tissue available for central laboratory confirmation of $BRAF^{V600}$ mutations, central laboratory testing is not used to determine study eligibility. Patients must have written documentation from a local pathology report of a $BRAF^{V600}$ mutation in tumor tissue or blood. Patients who have received prior treatment with a BRAF or MEK inhibitor are excluded. In addition, patients with other driver mutations (*EGFR* mutation, *ALK* rearrangement or *ROS1* rearrangement) or untreated symptomatic brain metastasis, leptomeningeal disease or other active central nervous system metastases are not eligible for the study. All the patients must provide written informed consent before enrollment.

Table 1. Key inclusion and exclusion criteria.

Key inclusion criteria	
Demographics	• Aged ≥18 years
NSCLC disease characteristics	• Histologically confirmed NSCLC stage IV or metastatic disease (M1a, M1b, M1c – AJCC 8th edition) • Presence of measurable disease (per RECIST v1.1) • ECOG performance status 0 or 1 • Presence of *BRAF*^{V600} mutation† • Adequate tumor tissue for submission to central laboratory for confirmation of mutation status
Prior treatment	• Treatment-naive OR • Prior treatment with: ◦ First-line platinum-based chemotherapy OR ◦ First-line treatment with an anti-PD-1/PD-L1 inhibitor alone or in combination with platinum-based chemotherapy, or in combination with immunotherapy with or without platinum-based chemotherapy
Key exclusion criteria	
NSCLC disease characteristics	• Documented *EGFR* mutation, *ALK* fusion oncogene or *ROS1* rearrangement • Symptomatic brain metastasis, leptomeningeal disease or other active CNS metastases
Prior treatment	• Prior treatment with any BRAF inhibitor or MEK inhibitor
Other	• Evidence of active noninfectious pneumonitis or history of interstitial lung disease

† *BRAF* ^{V600E}; other less common Class 1 *BRAF*^{V600} mutations (e.g., K or D) permitted with prior discussion with the Sponsor.
AJCC: American Joint Committee on Cancer; ECOG: Eastern Cooperation Oncology Group; NSCLC: Non-small-cell lung cancer; RECIST: Response Evaluation Criteria in Solid Tumors.

Table 2. Study objectives and end points.

Primary objective	Primary end point
• To evaluate the antitumor activity of encorafenib plus binimetinib in treatment-naive and previously treated patients with *BRAF* ^{V600E}-mutant NSCLC as measured by ORR	• Confirmed ORR as determined by IRR per RECIST v1.1 in treatment-naive and previously treated patients
Secondary objectives	**Secondary end points**
• To evaluate the antitumor activity of encorafenib plus binimetinib in treatment-naive and previously treated patients with *BRAF* ^{V600E}-mutant NSCLC as measured by ORR, DOR, TTR†, DCR, PFS and OS	• Confirmed investigator-determined ORR per RECIST v1.1 • DOR (by IRR and investigator) • TTR (by IRR and investigator)† • DCR (by IRR and investigator) • PFS (by IRR and investigator) • OS
• To evaluate the safety and tolerability of encorafenib plus binimetinib in treatment-naive and previously treated patients with *BRAF* ^{V600E}-mutant NSCLC	• Incidence and severity of AEs graded according to NCI CTCAE v4.03 • Changes in clinical laboratory test parameters, vital signs, ECGs and echocardiogram/MUGA scans
Exploratory objectives	**Exploratory end points**
• To evaluate the PK of encorafenib and its metabolite LHY746 and binimetinib in patients with *BRAF* ^{V600}-mutant NSCLC	• Plasma concentration–time profiles and PK parameter estimates for encorafenib and its metabolite LHY746 and binimetinib
• To assess blood ctDNA mutation status	• Genomic analysis of ctDNA in blood samples

† End point will be analyzed but was not prespecified in the study protocol.
AE: Adverse event DCR: Disease control rate; DOR: Duration of response; ECG: Electrocardiogram; IRR: Independent radiology review; MUGA: Multigated acquisition; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PK: Pharmacokinetics; RECIST: Response Evaluation Criteria in Solid Tumors; TTR: Time-to-tumor response.

Enrollment

PHAROS plans to enroll approximately 107 patients, including at least 60 treatment-naive and 37 previously treated patients with locally confirmed *BRAF*^{V600E} mutations. Up to ten additional patients with other *BRAF*^{V600} mutations may also be included. Patients are being enrolled at study sites in five countries: Italy (five sites), The Netherlands (two sites), South Korea (three sites), Spain (four sites) and the USA (39 sites).

Efficacy end points & assessments

Study objectives are summarized in Table 2. Antitumor activity as measured by ORR based on independent radiology review (IRR) is the primary end point. ORR is defined as the proportion of patients achieving a confirmed best overall response (complete response [CR] or partial response [PR]). ORR will be analyzed in treatment-naive and previously treated patients.

Secondary efficacy end points include: confirmed ORR as determined by the investigator; DOR (time from first confirmed CR or PR to earliest instance of disease progression or death), disease control rate at week 24 (DCR;

proportion of patients with a confirmed CR or PR or stable disease), PFS (time from first dose of study drug to earliest instance of disease progression or death) and time-to-tumor response (TTR; evaluated for responders as the time from first dose of study treatment to first confirmed objective response [CR or PR]), by IRR and investigator assessment; and OS (time from first dose of study treatment to death).

RECIST v1.1 criteria [39] will be used for tumor assessment and response. The imaging assessments are to be conducted at screening, every 8 weeks (56 ± 7 days) for 12 months, and every 12 weeks (±7 days) thereafter until disease progression or the end of the study. Radiologic disease follow-up is to be continued in patients who permanently discontinue study treatment for a reason other than disease progression. Radiologic images from screening and follow-up are to be sent to a central imaging vendor for IRR. Per RECIST v1.1, responses (CR and PR) require confirmation by repeat radiographic assessments performed at least 4 weeks after the criteria for response are first met and no later than the next per-protocol scheduled scan, whichever is clinically indicated.

The OS follow-up is to be continued every 12 weeks (±7 days) after the last dose of study treatment until withdrawal of consent, loss to follow-up, death or end of study. Subsequent anticancer therapies are also to be recorded during the survival follow-up period.

Safety end points & assessments

Safety and tolerability are evaluated as secondary objectives (Table 2). AEs and serious AEs (SAEs) are to be monitored throughout the treatment period and during the 30-day post-treatment follow-up. In patients starting new anticancer therapy within 30 days after the end of study treatment, safety follow-up is to be continued up to the start of the new therapy.

AEs of special interest for PHAROS were established based on the COLUMBUS trial [17], including left ventricular dysfunction, hemorrhage, venous thromboembolism, ocular toxicities, pneumonitis/interstitial lung disease, hepatotoxicity, creatine phosphokinase elevations or rhabdomyolysis, and QTc prolongation.

Physical examinations and evaluation of vital signs, Eastern Cooperative Oncology Group performance status and clinical laboratory test parameters (hematology/chemistries) are to be obtained at screening, on day 1 of each treatment cycle, at the end of study treatment, and at the safety follow-up visit 30 days after the end of study treatment. Dermatologic exams, electrocardiography, echocardiogram/multigated acquisition (MUGA) scans and visual acuity assessments are also to be performed to investigate potential class-specific AEs.

Pharmacokinetic & biomarker assessments

Prespecified exploratory end points will evaluate pharmacokinetic (PK) parameters for encorafenib (and its metabolite LHY746) and binimetinib, as well as blood–ctDNA mutation status. For patients enrolling before protocol amendment 4 (dated 16 February 2021), serial blood samples for plasma PK analysis of encorafenib, LHY746 (encorafenib metabolite) and binimetinib were to be collected at 0.5 (±5 min), 1.5 (±5 min), 3 (±10 min) and 6 (±20 min) h postdose on day 1 and day 15 of the first treatment cycle, and within 30 min predose on Day 1 of the second cycle. For patients enrolling after protocol amendment 4, predose PK samples are to be collected within 30 min prior to dosing on Day 1 of treatment cycles 1–6. On PK visit days, morning doses of study drug are administered under observation by site personnel, after collecting the predose PK sample.

For ctDNA biomarker assessments, blood samples are to be collected at screening, on day 1 of treatment cycle 2 and each treatment cycle thereafter, and at the end of study treatment. Purified ctDNA will be analyzed for potential genomic markers of encorafenib and/or binimetinib activity. Blood samples may also be used for additional exploratory research (e.g., investigating genetic variants in ctDNA, such as $BRAF^{V600}$ mutations, and additional tumor mutations). Peripheral blood samples (serum) will also be used for analysis of potential proteomic or metabolomic factors and signals.

Statistical analysis methods

The primary efficacy and safety analyses will be conducted using the safety analysis set, which will include all patients who receive ≥1 dose of study treatment. A sensitivity analysis of the primary end point (ORR by IRR) will be conducted in the response evaluable set, comprising patients in the safety analysis set with an adequate baseline disease assessment who meet at least one of the following criteria: have ≥1 postbaseline disease assessment ≥6 weeks from first dose, or withdrew from the study or experienced progressive disease or death at any time during the study. Data will be summarized for treatment-naive patients, previously treated patients and overall.

For the primary efficacy end point, the study was designed to test the null hypothesis of ORR ≤39% for treatment-naive patients (n = 60) and ≤20% for previously treated patients (n = 37) with *BRAF* ^{V600E}-mutant NSCLC, which are considered not sufficiently clinically meaningful compared with available therapies. For treatment-naive patients, the null hypothesis was based on results observed in patients with NSCLC with a PD-L1 tumor proportion score of ≥50% who received pembrolizumab as a single agent (KEYNOTE-042), in which the ORR per IRR was 39% (95% CI: 34–45) [40]. For previously treated patients, the null hypothesis was based on the ORR of 18% (95% CI: 14–23) observed in previously treated patients with NSCLC with a PD-L1 tumor proportion score of ≥1% who received single-agent pembrolizumab [41].

The sample size calculation is based on the primary efficacy end point. With 60 evaluable treatment-naive patients with *BRAF* ^{V600E}-mutant NSCLC, the power is more than 95% to test the null hypothesis of ORR ≤39% versus the alternative hypothesis assuming an alternative target rate of 65% with a one-sided $\alpha \leq 0.025$ based on a single-stage design using the exact test. The null hypothesis will be rejected if ≥32 confirmed objective responses are observed among the 60 patients. With 37 evaluable previously treated patients with *BRAF* ^{V600E}-mutant NSCLC, the study has at least 90% power to test the null hypothesis of ORR ≤20%, assuming an alternative target rate of 45% with a one-sided $\alpha \leq 0.025$ as described above. The null hypothesis will be rejected if ≥13 objective responses are observed among the 37 previously treated patients.

The ORR and DCR will be calculated with corresponding exact two-sided Clopper–Pearson 95% CIs. For analyses of PFS, DOR (among patients achieving a confirmed response) and OS, estimates of survival functions will be constructed using the Kaplan–Meier (KM) method [42]; medians and 95% CIs will be provided. For PFS and OS, KM curves will be generated. TTR will be calculated for patients with a confirmed objective tumor response and summarized using descriptive statistics.

For analysis of safety, treatment-emergent AEs and SAEs will be summarized (counts and percentages) by MedDRA preferred term and system organ class. AEs are classified by severity, based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03, and relationship to study drug will be assigned by the investigator. AEs and SAEs of special interest (all-causality and treatment-related) will be summarized by frequency and severity. All deaths occurring during the treatment period, within 30 days after the last dose of study treatment and more than 30 days after the last dose of study treatment will be summarized.

Discussion & future perspective

There is an unmet clinical need for additional effective, less toxic, therapeutics for patients with *BRAF*-mutant metastatic NSCLC.

The PHAROS trial was initiated on 4 June 2019 and is ongoing at the time of this report. Data from PHAROS will provide insight into the antitumor activity and safety of encorafenib plus binimetinib in patients with *BRAF* ^{V600}-mutant NSCLC. While PHAROS represents the first clinical trial of encorafenib plus binimetinib in NSCLC, evidence supporting the clinical activity of this combination against *BRAF*-driven tumors along with a manageable side-effect profile comes from patients with unresectable or metastatic *BRAF* ^{V600}-mutant melanoma, where the combination is one of the MEK/BRAF inhibitor standard-of-care regimens [18,22,33,34]. The dose modifications for toxicity management for PHAROS are consistent with the recommendations for this approved combination in patients with *BRAF* $^{V600E/K}$-mutant unresectable or metastatic melanoma [37,38].

PHAROS will also collect information about AEs of interest that are consistent with the known class-based safety profile of BRAF and MEK inhibitors [16,17]. Safety concerns associated with this class of drugs in combination include skin toxicities, gastrointestinal disorders, pyrexia, ocular events and musculoskeletal and cardiovascular events [16,17,19,22,24,25,33,34]. While some tolerability issues with this class of drugs in combination (e.g., most cutaneous and ophthalmologic side effects) are generally manageable and do not typically result in treatment discontinuation, others (e.g., cardiovascular events including left ventricular dysfunction), while less common, are associated with treatment discontinuation [16]. Some safety concerns have been identified as particularly relevant for individual BRAF and MEK inhibitors (e.g., photosensitivity is common with vemurafenib while pyrexia is an important side effect of dabrafenib; both are less common with encorafenib) [16]. Coadministration of encorafenib 450 mg q.d with binimetinib 45 mg b.i.d reduces the incidence of drug-related-specific toxicities for binimetinib (acneiform dermatitis, peripheral edema and rash) and encorafenib (arthralgia, myalgia, headache, rash, and palmoplantar keratoderma) [16,17,43]. Encorafenib plus binimetinib could represent a potential alternative BRAF/MEK inhibitor combination with a unique safety profile for the treatment of metastatic NSCLC with *BRAF* mutations, adding a new treatment option for this subset of patients.

Limitations of this study include the lack of a control arm. However, the small sample size in PHAROS is consistent with a molecularly targeted approach intended for tumors driven by relatively uncommon oncogenes [24,25,44]. The cohort of patients who received prior treatment in the metastatic setting is heterogenous in terms of the nature of the prior therapy (i.e., immunotherapy, immunotherapy plus chemotherapy, and chemotherapy alone), potentially complicating analysis in this cohort. Given the challenges of conducting an adequately powered randomized trial in a disease with the rarity of *BRAF*-mutant NSCLC, a nonrandomized, single-arm trial design was implemented. The primary end point in PHAROS (ORR by IRR) is intended to provide evidence of antitumor activity. Indeed, nonrandomized trials showing meaningful and durable ORR and DOR have been used to support regulatory approvals for other treatments targeting unique molecular drivers in NSCLC [24,44,45]. In this study, the primary end point is based on IRR to help overcome potential bias due to the lack of a control arm. While PHAROS allows for enrollment of a small number ($\leq$10) of patients with less common *BRAF*^{V600} mutations, the study is not designed to draw statistical conclusions about response rates in patients with *BRAF*^{V600} mutations other than V600E. Given this is a small phase II study, a pragmatic prospective study with a larger number of patients would be needed to confirm the results of this study.

PHAROS will enroll a biomarker-selected patient population, based on the known mechanism of action of encorafenib. Molecular testing for *BRAF* mutations is consistent with the current standard of care during the clinical evaluation of advanced or metastatic NSCLC [28]. The study includes a relatively broad population in terms of prior treatments for metastatic disease. Importantly, the study includes both a treatment-naive cohort and a cohort of patients who have progressed on one prior line of treatment. Furthermore, given the recent approvals of PD-1/PD-L1 inhibitors and their progressive use in the first-line treatment setting, the PHAROS trial includes patients who received prior first-line immunotherapy. It should also be noted that there is an ongoing phase II trial of encorafenib with binimetinib in patients with *BRAF* ^{V600E}-mutant metastatic NSCLC, which is being conducted in France (Clinical Trials identifier: NCT04526782; study ID number: IFCT-1904).

Conclusion

Herein, we describe the study design of PHAROS, an ongoing, open-label, single-arm, phase II trial evaluating the BRAF inhibitor encorafenib plus the MEK inhibitor binimetinib in patients with metastatic *BRAF* ^{V600}-mutant NSCLC. PHAROS includes both treatment-naive patients and patients who have progressed on a prior line of immunotherapy and/or chemotherapy. Results from the PHAROS trial will provide insight into the antitumor activity and safety of encorafenib plus binimetinib in patients with *BRAF* ^{V600}-mutant metastatic NSCLC.

Executive summary

Background

- BRAF and MEK inhibitor combinations can achieve greater antitumor activity than each as a single agent and are associated with a more favorable side effect profile compared with BRAF inhibitor monotherapy.
- BRAF and MEK inhibitor combinations have been validated clinically in *BRAF* $^{V600E/K}$-mutant metastatic melanoma, where they are an established standard of care.
- *BRAF* oncogenic driver mutations occur in a subset of 3–4% of patients with non-small-cell lung cancer (NSCLC), and the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib demonstrated efficacy and safety in *BRAF* ^{V600E}-mutant metastatic NSCLC.
- Encorafenib and binimetinib are selective and potent BRAF and MEK inhibitors, respectively, that have demonstrated efficacy and a distinct, favorable safety profile compared with other anti-BRAF/MEK-targeted therapies in patients with *BRAF* $^{V600E/K}$-mutant metastatic melanoma.

PHAROS trial

- The PHAROS trial was initiated to explore the antitumor activity and safety of encorafenib plus binimetinib in patients with *BRAF* ^{V600}-mutant metastatic NSCLC who are either treatment-naive or who have been previously treated with platinum-based chemotherapy and/or anti-PD-1/PD-L1 inhibitor therapy.
- Approximately 107 patients, including at least 60 treatment-naive and 37 previously treated patients with *BRAF* ^{V600E}-mutant metastatic NSCLC, will receive encorafenib 450 mg once daily plus binimetinib 45 mg twice daily in continuous 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, death or end of study.
- The primary end point is the objective response rate, based on independent radiology review.
- Information about adverse events will be collected, including adverse events of interest, based on the known safety profile of this class of drugs in combination.
- Results from PHAROS will provide insight into the antitumor activity and safety of encorafenib plus binimetinib in patients with *BRAF* ^{V600}-mutant metastatic NSCLC.

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: http://www.futuremedicine.com/doi/suppl/10.2217/fon-2021-1250

Author contributions

All the authors met the criteria for authorship set forth by the International Committee of Medical Journal Editors, and were involved in the conception, preparation and approval of the manuscript.

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Ethical conduct of research

The study is being conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Council for Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki.

Data-sharing statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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