BRAF^{V600E}-MUTATED ADVANCED NSCLC

Summary

Webinar
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On October 3, 2024, following the approval of encorafenib plus binimetinib for treatment of adult patients with advanced $BRAF^{V600E}$-mutated non-small cell lung cancer (NSCLC), Pierre Fabre arranged a national symposium in Stockholm, Sweden. Moderated by Luigi De Petris, the symposium gathered physicians and nurses managing this patient group, both on site and as a webinar at clinics across the country.

Moderator

Senior clinical oncologist Luigi De Petris,
Thoracic Oncology Unit, Karolinska University Hospital, Sweden

Professor Egbert Smit, Department of Pulmonary Diseases,
Leiden University Medical Center (LUMC), The Netherlands

Professor Egbert Smit

Encorafenib and binimetinib for BRAF^{V600E} NSCLC

Egbert Smit reviewed the background to dabrafenib/trametinib combination therapy for BRAF^{V600E}-mutated NSCLC and presented data from the latest update of the PHAROS trial.

BRAF mutations are grouped into three classes. Class I, to which V600E mutations belong, activate RAS-independent signalling as monomers, while Classes II and III rely on dimerisation of RAS to elicit signalling. While the activity of Class III mutations is dependent upon receptor tyrosine kinase activation, Class II mutation activity is not (Planchard D et al. NPJ Precis Oncol 2024; 8: 90). The prevalence of BRAF mutations in lung adenocarcinoma is approx. 3% (Chen R et al. J Hematol Oncol 2020; 13: 58).

Key advances

Important advances in the treatment of BRAF^{V600E} NSCLC have been made over the past decade. In 2015, the BRAF inhibitor vemurafenib was shown to elicit short-lived responses in B-RAFV600E-mutated NSCLC and in 2016, this was also shown for dabrafenib. Soon after, BRAF inhibitor treatment alone was shown to confer constitutive activation of the MAPK pathway, leading to enhanced growth, proliferation and survival of tumour cells. To overcome these issues of resistance, BRAF-MEK inhibitor combination therapy was applied, specifically with dabrafenib plus trametinib (Planchard D et al. NPJ Precis Oncol 2024; 8: 90).

The effects of dabrafenib/trametinib combination therapy were investigated in an open-label phase II trial including 34 patients with previously untreated metastatic BRAF^{V600E}-mutated NSCLC (Planchard D et al. Lancet Oncol 2017; 18: 1307–16). In this group, objective response rate (ORR) was 64% and disease control rate (DCR) 75%. Median progression-free survival (PFS) was 10.9 months and median overall survival (OS) 24.6 months.

In 2018, immune checkpoint inhibitors pembrolizumab, nivolumab and atezolizumab were approved for $BRAF^{V600E}$-mutated NSCLC. In 2023, encorafenib/binimetinib combination therapy was approved for this indication in the US and in 2024, also in the EU (Planchard D et al. NPJ Precis Oncol 2024; 8: 90).

First approved for melanoma

As early as 2018, encorafenib/binimetinib combination therapy was approved for BRAF-mutant metastatic melanoma. In the phase III COLUMBUS trial, 577 patients were randomised to encorafenib or binimetinib or the combination of both. Results showed improved OS with combination therapy: 33.6 months (95% CI 24.4–39.2) compared to 16.9 months (95% CI 14.0–24.5) with vemurafenib (HR 0.61 [95% CI 0.47–0.79]; two-sided p<0.0001). Moreover, combination therapy resulted in a different tolerability profile compared to both monotherapies (Dummer R et al. Lancet Oncol 2018; 19: 1315–27).

Thanks to experience gained from melanoma, solid knowledge among oncology clinics regarding how this treatment is managed already exists.

The PHAROS study

PHAROS is an ongoing phase II single-arm, multicenter, open-label study in which patients with $BRAF^{V600E}$-mutant metastatic NSCLC are divided into two groups: treatment-naïve patients (n=59) and previously treated patients with no more than one prior line of treatment in the advanced setting (n=39). (A third cohort of treatment-naïve patients with other V600 mutations was planned but no such patients were recruited.) Patients with symptomatic brain metastases were excluded from the trial (Riely GJ et al. J Clin Oncol 2023; 41: 3700–11).
All patients received encorafenib 450 mg QD + binimetinib 45 mg BID. Primary endpoint was ORR while secondary endpoints included duration of response (DOR), DCR, PFS, OS and incidence of adverse events (AEs). Baseline patient characteristics are shown in Table 1. Importantly, a majority of patients were former smokers.

At the data cut-off of September 22, 2022, ORR was 75% (95% CI, 62–85) in treatment-naïve patients and 46% in previously treated patients (95% CI, 30–63). Median DOR was not estimable (NE) in the therapy-naïve group (95% CI, 23.1– NE) and 16.7 months (95% CI, 7.4–NE) in the previously treated group. DCR after 24 weeks was 64% in treatment-naïve and 41% in previously treated patients. Median PFS was not estimable at this time.

Updated 2024 analysis

The most recent analysis was presented at ESMO in September, with data cut-off on April 1, 2024 (Riely GJ et al. ESMO Congress 2024, LBA56). These results add 18 months of follow-up to the original primary analysis, with 41% of treatment-naïve and 10% of previously treated patients having received more than two years' treatment.

Results show an unchanged ORR for both treatment-naïve and previously treated patients (Fig. 1). Median PFS was still not mature. Median OS was not estimable in the treatment-naïve group and was 22.7 months (95% CI 14.1–32.2) in the previously treated group. Notably, very few patients had progressive disease as best overall response: only 6.8% in the former group and 15.4% in the latter.

Safety findings in the 2024 analysis were consistent with the primary analysis. Treatment discontinuation due to adverse events was seen in 12/59 patients (20.3%) in the treatment-naïve group and in 6/39 patients (15.4%) in the previously treated group. In the combined treatment group, primary reasons for discontinuation were adverse events (18.4%), disease progression (37.8%) and patient decision (4.1%). Only one withdrew patient consent.

Treatment-related adverse events (TRAEs) occurring in more than 10% of the overall population in the primary analysis and in the 2024 analysis are shown in Figure 2. Principal toxicities were nausea and diarrhoea, affecting about half of the patients, and fatigue, occurring in approx. one third. Fortunately, most events were of grade 1–2. No major differences were seen in the adverse event profiles between untreated and previously treated patients.

One way of evaluating the toxicity of a regimen is to assess the proportion of TRAEs that lead to dose modification or discontinuation. In the original analysis, 15 of the 98 patients permanently discontinued therapy. In the 2024 analysis, 16 discontinued.

Considerations for choice of therapy

Pyrexia or chills were seen in 8% of patients with encorafenib-binimetinib in the PHAROS study, and all treatment-related events of pyrexia were grade 1 or 2. Prior immunotherapy did not alter the side effect profile to any great extent. In particular, excess hepatic toxicity by prior immunotherapy was not observed. When considering alternative treatment options, one important question is whether immune checkpoint inhibitors (ICIs) are efficacious in patients with $BRAF^{V600E}$-mutated NSCLC. Data is currently scarce, but the effects of ICIs after progression on dabrafenib alone or in combination with trametinib have been

assessed in a French retrospective study (Guisier F et al. J Thorac Oncol 2020; 15: 628–36). In this group of patients, median PFS was 4.7 months (95% CI, 2.3–7.4) in ICI-treated patients, whereas the overall population had a median PFS of 5.3 months (95% CI, 2.1–NR).

Whether a patient's history of tobacco smoking plays a role in guiding treatment with respect to the use of ICIs is currently unclear as no randomised, controlled trials are available. However, a literature review on the association of tobacco use and tumour biology in relation to immunotherapy indicates that patients with a smoking history may have a greater benefit from ICIs than never smokers in both treatment-naïve and previously treated settings (Corke LK. Curr Oncol 2022; 29: 6260–76).

Conclusions

To conclude, results from the PHAROS study establish encorafenib/binimetinib combination therapy as a viable treatment option for patients with metastatic $BRAF^{V600E}$-mutated NSCLC in both the untreated and previously treated settings.

	Treatment-naïve (n=59)	Previously treated (n=39)
Median age	68 (47-83)	71 (53-86)
Sex, n (%)		
Female	33 (56)	19 (49)
Male	26 (44)	20 (51)
Race, (%)		
White	53 (90)	33 (85)
Asian	3 (5)	4 (10)
Black	1 (2)	2 (5)
American Indian	1 (2)	0
Unknown	1 (2)	0
ECOG performance status, n (%)		
0	19 (32)	7 (18)
1	40 (68)	32 (82)
Smoking status, n (%)		
Current	8 (14)	5 (13)
Former	33 (56)	23 (59)
Never	18 (31)	11 (28)
Prior systemic treatment for metastatic disease, n (%)		
Immunotherapy	Not applicable	24 (62)[a]
Monotherapy	Not applicable	12 (31)
Combination therapy	Not applicable	12 (31)
Chemotherapy	Not applicable	18 (46)

Table 1. Baseline patient characteristics in the PHAROS study (Riely GJ et al. J Clin Oncol 2023; 41: 3700–11).

	Primary analysis (data cutoff: Sep 22, 2022)		Current analysis (data cutoff: Apr 1, 2024)	
	Treatment-naïve	Previously treated	Treatment-naïve	Previously treated
Objective response rate (95% CI), %[a]	75 (62, 85)	46 (30, 63)	75 (62, 85)	46 (30, 63)
Complete response	9 (15)	4 (10)	9 (15)	4 (36)
Partial response	35 (59)	14 (36)	35 (59)	14 (36)
Stable disease	10 (17)	13 (33)	10 (17)	13 (33)
Progressive disease	2 (3)	3 (8)	2 (3)	3 (8)
Disease control rate at 24 weeks (95% CI), %	64 (51, 76)	41 (26, 58)	64 (51, 76)	44 (28, 60)
Median time to response (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)	1.9 (1.1-19.1)	1.7 (1.2-7.3)
Median duration of response (98% CI), months	NE (23.1, NE)	16.7 (7.4, NE)	**40.0 (23.1, NE)**	**16.7 (7.4, NE)**

Figure 1. Anti-tumour activity endpoints by independent radiology review in the primary and the updated analysis of the PHAROS study (Riely GJ et al. ESMO Congress 2024, LBA56).

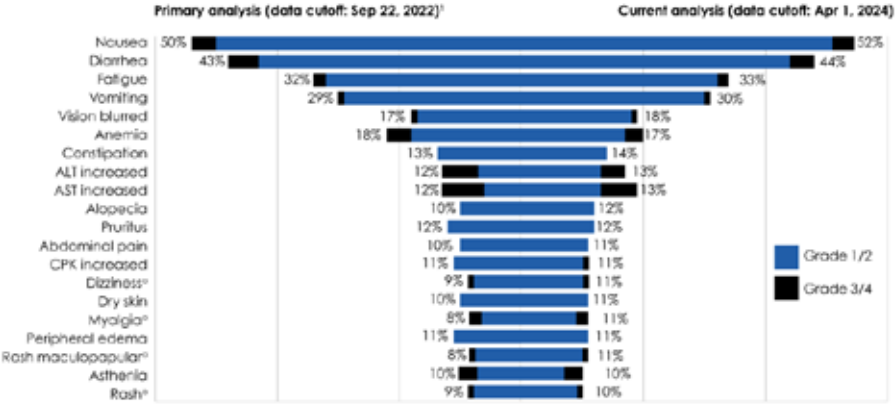

Figure 2. Treatment-related adverse events (≥10%) in the overall population (N=98) in the primary analysis (left) and the updated analysis (right) of the PHAROS study (Riely GJ et al. ESMO Congress 2024, LBA56).

Questions from the audience

Moderated by Luigi De Petris

Even in the frail, elderly population, the strategy with BRAF/MEK inhibitors seems to be to hit hard and reduce the dose if side effects are seen. As lung oncologists, we are used to treating these patients by starting with a lower dose and then increasing it if side effects do not materialise, even if this may increase the risk for resistance development. What is your approach?

Egbert Smit: We see no reason to start with a reduced dose in anticipation of side effects. The mean age of patients included in the PHAROS study was close to 70 years and many had comorbid conditions. We are well equipped to deal with toxicities such as nausea, and patients should be instructed in how to avoid them. I tend to maintain the dose but still feel confident to apply dose interruptions in that setting.

If treatment is interrupted due to side effects, should it be restarted with one drug at a time or both at the same time, and should the dose be reduced?

Egbert Smit: Both drugs at the same time, but it makes sense to reduce the dose of the BRAF inhibitor.

If a patient has persistently increased liver enzymes on encorafenib/binimetinib in spite of dose reduction, could changing to another combination therapy be an option?

Egbert Smit: I don't have that experience but if the liver enzymes really are problematic, it would make sense to switch to another therapy, such as immunotherapy or chemotherapy. Side effect profiles differ and do not necessarily include induction of liver enzyme elevations.

BRAF^{V600E} is sometimes detected as a resistance marker in other drivers, such as EFGR or ALK. Our experience in actioning both drivers has been conflicting, or even disappointing. What's your approach when there is no evidence of possible interactions?

Egbert Smit: BRAF^{V600E} is a very rare mechanism of resistance. We have just analysed 200 patients with EGFR mutations and found less than 1%. As it's a different signalling pathway, it's important to maintain the EGFR inhibition, otherwise time to progression will be very short. This combination is very well tolerated but it has substantial financial toxicity.

Luigi De Petris: Still, it's only a few patients every year, and the duration of response is normally only a few months.

Egbert Smit: Agreed. Importantly, patients with only one resistance mechanism have a very favourable outcome on targeted treatments while patients with two or more mechanisms treated with only one targeted agent do not. They are better off with chemotherapy.

Can BRAK/MEK inhibition therapies be maintained during stereotactic radiosurgery for brain metastases or should a safety interruption be applied due to the risk of necrosis?

Egbert Smit: Some radiotherapists want us to stop for a five-day wash-out but we do not. In practice, we stop the day before radiation and resume the day after, and we have not experienced any enhanced toxicities of radiotherapy for brain metastases with neither dabrafenib/trametinib nor encorafenib/binimetinib.

What's your experience of the efficacy of the chemo/immuno combinations after progression on BRAF/TKI and following that, what is your experience of rechallenging with TKIs upon progression on chemo/immuno?

Egbert Smit: Retreatment strategies need to be better defined, but they really do work. After progression on a non-targeted regimen, it's always worthwhile to go back to the previous or first regimen to see whether you can induce a response. These responses are shorter but it's still a valuable strategy

Braftovi® (enkorafenib) hårda kapslar 50 mg eller 75 mg, Rx, F. Farmakoterapeutisk grupp: Antineoplastiska medel, proteinkinashämmare, ATC-kod: L01EC03. **Indikation:** I kombination med binimetinib för behandling av vuxna patienter med icke-resektabelt eller metastaserat melanom med en BRAFV600-mutation. I kombination med cetuximab för behandling av vuxna patienter med metastaserad kolorektal (CRC) cancer med en BRAF V600E-mutation, som tidigare har fått systemisk behandling. I kombination med binimetinib för behandling av vuxna patienter med avancerad icke-småcellig lungcancer (NSCLC) med en BRAF V600E-mutation. **Varningar och försiktighet:** Innan enkorafenib tas måste patientens BRAF V600E mutation bekräftas. Risk för blödningar, synrubbningar och/eller ögonbiverkningar såsom uveit, irit och iridocyklit, nya primära maligniteter, samt avvikande levervärden. Iaktta försiktighet vid behandling av patienter vars sjukdom progredierat på en tidigare BRAF-hämmare och hos patienter med: hjärnmetastaser, vänsterkammardysfunktion, riskfaktorer för QT-förlängning, lätt nedsatt leverfunktion, samt gravt nedsatt njurfunktion. Rekommenderas inte till patienter med måttligt eller gravt nedsatt leverfunktion. Förekomsten av TLS, vilket kan vara dödligt, har associerats med användandet av enkorafenib i kombination med binimetinib. Samtidig administrering med potenta CYP3A-hämmare eller grapefruktjuice ska undvikas. Måttliga CYP3A4-hämmare, inducerare samt substrat ska administreras med försiktighet. Substanser som är substrat till UGT1A1 eller transportproteiner ska administreras med försiktighet. **Fertilitet, graviditet och amning:** Enkorafenib rekommenderas inte under graviditet eller till fertila kvinnor som inte använder preventivmedel. Användare av hormonella preventivmedel rekommenderas att använda ytterligare en metod, t.ex. barriärmetod (som kondom). Det är okänt om enkorafenib eller dess metaboliter utsöndras i bröstmjölk. Manliga patienter ska informeras om potentiell risk för försämrad spermatogenes. **Kontakt:** Pierre Fabre Pharma Norden AB, www.pierrefabrepharma.se. Datum för översyn av produktresumén: 2024-11-14.
För mer information och pris, se www.fass.se.

Mektovi® (binimetinib) filmdragerade tabletter 15 mg och 45 mg, Rx, F. Farmakoterapeutisk grupp: Antineoplastiska medel, proteinkinashämmare, ATC-kod: L01EE03. **Indikation:** I kombination med enkorafenib för behandling av vuxna patienter med icke-resektabelt eller metastaserat melanom med en BRAFV600-mutation. I kombination med enkorafenib för behandling av vuxna patienter med avancerad icke-småcellig lungcancer (NSCLC) med en BRAF V600E-mutation. **Varningar och försiktighet:** Innan binimetinib tas i kombination med enkorafenib måste patientens BRAF V600E-mutation bekräftas. Risk för blödningar, synrubbningar och/eller ögonbiverkningar såsom RPED och RVO, förhöjt kreatinfosfokinas och rabdomyolys, hypertoni, venös tromboembolism, pneumoni/interstitiell lungsjukdom, nya primära maligniteter, samt avvikande levervärden. Iaktta försiktighet vid behandling av patienter vars sjukdom progredierat på en tidigare BRAF-hämmare, med hjärnmetastaser, samt vänsterkammardysfunktion. Rekommenderas inte till patienter med RVO i anamnesen, måttligt eller gravt nedsatt leverfunktion, eller med laktosintolerans. Förekomsten av TLS, vilket kan vara dödligt, har associerats med användandet av binimetinib i kombination med enkorafenib. Samtidig administrering med UGT1A1-inducerare ska användas med försiktighet. OAT3- samt CYP1A2-substrat ska användas med försiktighet. CYP1A2-inducerare och inducerare av P-gp transportproteiner kan minska binimetinibexponeringen. **Graviditet och amning:** Binimetinib rekommenderas inte under graviditet eller till fertila kvinnor som inte använder preventivmedel. Fertila kvinnor ska använda effektiv preventivmetod under behandlingen med binimetinib och i minst 1 månad efter den sista dosen. Det är okänt om binimetinib eller dess metaboliter utsöndras i bröstmjölk. **Kontakt:** Pierre Fabre Pharma Norden AB, www.pierrefabrepharma.se. Datum för översyn av produktresumén: 2024-11-14.
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