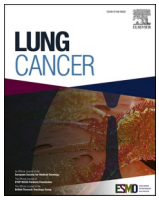
Lung Cancer 199 (2025) 108038

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan



Real-world efficacy of the dabrafenib-trametinib (D-T) combination in BRAF V600E-mutated metastatic non-small cell lung cancer (NSCLC): Results from the IFCT-2004 BLaDE cohort

Aurélie Swalduz [a,*], Michèle Beau-Faller [b], David Planchard [c], Julien Mazieres [d], Sophie Bayle-Bleuez [e], Didier Debieuvre [f], Vincent Fallet [g], Margaux Geier [h], Alexis Cortot [i], Sébastien Couraud [j], Catherine Daniel [k], Charlotte Domblides [l], Eric Pichon [m], Elizabeth Fabre [n], Sébastien Larivé [o], Ulrike Lerolle [p], Pascale Tomasini [q], Marie Wislez [r], Pascale Missy [s], Franck Morin [s], Virginie Westeel [t], Jean-Bernard Auliac [u]

[a] *Centre Léon Bérard, Department of Medical Oncology, Lyon, France*
[b] *Centre Hospitalier Universitaire Strasbourg, Laboratoire d'Onco-Biologie & Oncologie Thoracique Hôpital de Hautepierre & Nouvel Hôpital Civil, INSERM UMR 1260 – Nanomédecine Régénérative, Université de Strasbourg – CRBS, Strasbourg, France*
[c] *Gustave Roussy, Cancer Medicine Department, Villejuif, France*
[d] *CHU de Toulouse, Service de Pneumologie, France*
[e] *CHU Saint-Etienne, Hôpital Nord, Saint-Etienne, France*
[f] *Groupe Hospitalier de la Région Mulhouse Sud-Alsace, Hôpital Emile Muller, GHRMSA – Mulhouse, Mulhouse, France*
[g] *Tenon Hospital, Assistance Publique Hôpitaux de Paris, Department of Pneumology and Thoracic Oncology and GRC4, Theranoscan, Sorbonne Université, Paris, France*
[h] *University Hospital of Brest, Department of Medical Oncology France*
[i] *Department of Thoracic Oncology, CHU de Lille, CNRS, Inserm, Institut Pasteur de Lille, UMR9020-U1277-CANTHER, Lille, France*
[j] *Acute Respiratory Medicine and Thoracic Oncology Department, & CIRCAN Program Coordinator, Cancer Institute of Hospices Civils de Lyon, Lyon Sud Hospital, Pierre Bénite, France*
[k] *Institut Curie, Paris, France*
[l] *Department of Medical Oncology, University Hospital of Bordeaux, 33000 Bordeaux, France*
[m] *Centre Hospitalier Universitaire, Tours, France*
[n] *Department of Thoracic Oncology, Hôpital européen Georges Pompidou, APHP-Centre, Carpem Cancer Institute, Paris, France*
[o] *CH Les Chanaux, Service de Pneumologie, Mâcon, France*
[p] *Clinique Saint-Joseph, Service de Pneumologie, Trélazé, France*
[q] *APHM, Hôpital Nord, Service d'Oncologie Multidisciplinaire & Innovations Thérapeutiques, Marseille, France*
[r] *APHP, Hôpital Cochin, Service de Pneumologie, Unité d'Oncologie Thoracique, Paris, France*
[s] *Intergroupe Francophone de Cancérologie Thoracique, Paris, France*
[t] *Hôpital Jean Minjoz, Pneumology, Besançon, France*
[u] *CHI Créteil, Créteil, France*

ARTICLE INFO

Keywords:
Non-small-cell lung cancer
BRAF mutation
Targeted therapy
Dabrafenib-trametinib combination
Real-world evidence

ABSTRACT

Background: BRAF V600E mutations occur in 2–5 % of advanced non-small cell lung cancer (NSCLC) patients. The dabrafenib-trametinib (D-T) combination was associated with improved and durable OS in patients in phase II. This study (IFCT-2004 BLaDE study) reported the efficacy of D-T combination in a large retrospective French real-world multicenter cohort of patients with advanced BRAF V600E-mutated NSCLC.
Method: Patients with advanced BRAF V600E-mutated NSCLC diagnosed between 01.01.2016 and 31.12.2019 and treated with D-T in combination, regardless of the treatment line, were included. The primary endpoint was the 12-month OS rate (%) in patients receiving D-T as a second-line therapy or beyond.
Results: A total of 163 patients were included: 50.3 % were female, 30.2 % were never smokers, 95.1 % had adenocarcinoma, and 78.2 % had a PDL1 $\geq$ 1 %. The median age was 68.3 years. At D-T initiation, 80.8 % of patients had a PS of 0/1, 78.6 % had stage IV disease, and 20.9 % had brain metastasis. At the cutoff, the median follow-up was 27.4 months. The 12-month OS rate in patients receiving D + T as a second-line therapy or beyond

* Corresponding author.
E-mail address: Aurelie.SWALDUZ@lyon.unicancer.fr (A. Swalduz).

https://doi.org/10.1016/j.lungcan.2024.108038
Received 6 August 2024; Received in revised form 8 November 2024; Accepted 23 November 2024
Available online 26 November 2024

(n = 119) was 67.4 %, with a median progression-free survival (mPFS) of 10.4 months. Among the 44 patients who received D + T as a first-line therapy, the 12-month OS rate was 67.4 %, with an mPFS of 18.2 months. D-T discontinuation for toxicity was reported in 10.3 % of patients.
Conclusions: To our knowledge, this is the largest retrospective cohort of *BRAF*-mutated patients reported. The findings confirmed the significant efficacy of D-T in combination with BRAF V600E-mutated metastatic NSCLC in pretreated and untreated patients. These results under real-world conditions are consistent with those of other registered studies.

1. Introduction

In non-small cell lung cancer (NSCLC), BRAF V600E (V Raf murine sarcoma viral oncogene homolog) mutations account for 2–5 % of cases [1,2]. The *BRAF* gene (long arm of chromosome 7) encodes a serine/threonine kinase protein that regulates the signaling pathway *RAS-RAF-MEK-ERK* and plays an important role in proliferation, cell survival, angiogenesis, cell invasion and migration [4–7]. *BRAF* mutations can be divided into three different classes, which differ in terms of *RAS* dependency and the activity of each catalytic domain. Class I proteins are constitutively active regardless of *RAS* signaling pathway (*RAS*-independent monomers) and have high BRAF kinase activity; class II proteins are RAS-independent dimers that also have BRAF kinase activity; and class III proteins are *RAS*-dependent dimers and require associated upstream signaling to activate downstream pathways [8–10]. The V600E mutation, a class I mutation, is the most common mutation in NSCLC and represents approximately 50 % of *BRAF* mutations [3,11]. BRAF V600E-mutated NSCLC is more strongly associated with adenocarcinoma histology, female sex and nonsmoking history, whereas *BRAF* non-V600-mutated patients are more likely to be smokers, former smokers or males [11–13]. However, the prognostic value of *BRAF* mutations, including V600E, remains debated. Different retrospective trials based on small cohorts have led to contradictory results, suggesting that patient outcomes may be related to the type of *BRAF* alteration [14–16]. Since the identification and positive development of *BRAF* inhibitors in melanoma, anti-BRAF agents have also been evaluated in other tumors, including advanced NSCLC. The first series of efficacy data was reported for vemurafenib [17–20]. Dabrafenib also demonstrated clinical activity; however, preclinical data suggested reactivation of the MAPK pathway as a mechanism of resistance [21], and the addition of the MEK inhibitor trametinib demonstrated superiority over the BRAF inhibitor alone in melanoma [22]. Despite the lack of comparative phase III trials, targeting *BRAF* V600 mutations with the anti-BRAF anti-MEK combination dabrafenib-trametinib (D-T) also demonstrated significant antitumor activity in terms of response rate and progression-free survival (PFS) in patients with NSCLC harboring the BRAF V600E mutation, even when they were pretreated or not [23–25], leading to approval from the European Medicines Agency and United States Food and Drug Administration. In January 2020, the French Transparency Committee validated its possible use for second-line BRAF V600E mutation after failure of a first therapeutic line (whatever its nature) only. Given that clinical outcome data on *BRAF*-mutated V600 NSCLC patients treated with D-T in combination therapy are limited, we conducted a retrospective multicenter observational study to better describe, in a real-world setting, the characteristics and evolution of NSCLC patients with a BRAF V600E mutation treated with D-T in combination.

2. Materials and methods

2.1. Study design and population

The IFCT-2004 BLaDE (*BRAF* V600-mutated Lung carcinoma treated with the combination of dabrafenib and trametinib: a retrospective evaluation) study is a retrospective, noninterventional, French multicenter study that aimed to collect real-world data on BRAF V600E-mutated NSCLC patients treated with dabrafenib and trametinib. Patients with advanced NSCLC harboring the BRAF V600E mutation, diagnosed on tumor tissue and/or on liquid biopsy between January 2016 and December 2019, identified through the use of a molecular platform, and treated with dabrafenib and trametinib in combination, regardless of the treatment line, were included.

2.2. Data collection

This study was conducted by the French Collaborative Thoracic Intergroup (IFCT). Demographic, clinical, pathological and survival data were extracted from medical records.

2.3. Study endpoints and assessment

The primary endpoint was the 12-month overall survival (OS) rate (%) in patients receiving D-T as second-line or subsequent treatment. OS was measured from the date of the D-T first dose to the date of death from any cause. Secondary endpoints included: (i) 12 month-OS rate (%) in patients receiving the D-T in first-line, (ii) 18- and 24-months OS rates in second-line and beyond and in first-line and (iii) median OS; (iv) median PFS (defined as the interval between the first dose of D-T and the earliest date of disease progression according to investigator assessment (the use of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was strongly recommended) or death from any cause; (v) 12-month PFS rate (%); (vi) objective response rate (ORR) (defined as the percentage of patients with partial or complete response according to investigator assessment (the use of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was strongly recommended); (vii) disease control rate (DCR) (percentage of patients with partial or complete response or stable disease according to RECIST 1.1 evaluated by investigators); (viii) duration of response (defined as the time from first documented evidence of complete or partial response until the time of first documented disease progression or death from any cause, whichever occurred first assessed by investigator); (ix) duration of treatment (DOT) was calculated from the date of D-T first dose to the date of treatment discontinuation or death from any cause during the study; (x) post-progression DOT (defined as the date of first progression with D-T treatment to the date of treatment discontinuation).

2.4. Statistical considerations

The database was locked on December 21, 2021. The cutoff date (i.e., the date beyond which events were no longer considered in the survival analysis) was set at June 30, 2021.

The quantitative variables are described by the number of values entered, the number of missing data points, the mean, the standard deviation, the median, and the 1st and 3rd quartiles. If relevant, 95 % confidence intervals were calculated. The qualitative variables were described by the number of values entered, the number of missing values, the frequency and the percentage per category. If relevant, 95 % confidence intervals were calculated. The risk of the first species α was fixed at 5 % in the [bilateral] situation for the whole analysis.

OS was estimated using the Kaplan–Meier method (non-diagnografted patients at the end of follow-up were censored as of the date of the latest publication). The median OS was calculated along with Kaplan–Meier estimates at 12 months with associated 95 % confidence

intervals. A single data collection campaign allowed us to calculate 12-month overall survival. The real-world PFS was estimated using the Kaplan–Meier method (patients who had not progressed by the end of the follow-up without subsequent treatment were censored as of the date of the latest news or censored to the subsequent treatment). The median PFS was described, as were the Kaplan–Meier estimates at 6 months, with associated 95 % confidence intervals.

The prognostic factors of patient survival were sought from the baseline characteristics of patients using a Cox regression model. The following parameters were tested in a univariate model: minimum, sex (male/female), age (<65 y/>*65 y), performance status* (PS), brain metastases (yes/no), liver metastases (yes/no), and smoking status. A multivariate model was tested with variables whose p value was less than or equal to 20 % according to the univariate model. All the statistical analyses were performed with SAS 9.4 software.

2.5. Ethics

This study was conducted in full conformity with the Guidelines for GPP published by the International Society of Pharmaco-epidemiology (ISPE). The study was conducted in accordance with the French law "Informatique et Libertés" concerning research in the health field not involving human persons and in strict compliance with the reference methodology MR-004 published by the CNIL, for which the IFCT has made a compliance commitment and was registered in the National Institute for Health Data (INDS) public directory (https://www.indsante.fr/fr/repertoire-public-des-etudes-realisees-sous-mr). In accordance with the MR-004 guidelines, each eligible patient was informed by mail or during a routine visit to the study via a dedicated information note drafted in accordance with article 14 of the European GDPR regulations. Patients were able to exercise their rights at any time with their doctors or the DPO of the IFCT (clinical trial information: NCT04775095).

3. Results

3.1. Patients

Among 585 patients with the *BRAF* V600 mutation identified in 58 centers, 170 met the inclusion criteria, and 163 patients were ultimately included in the analysis (Supplementary Fig. 1). Patient characteristics are reported in Table 1. Overall, 119 patients were pretreated and received a median of one treatment (range: 1–5), while 44 patients were treated with D-T first-line. D-T was administered as second-line or third-line therapy or beyond in 70 and 49 patients, respectively. The median age was 68.3 years (range: 32.5–93.4), the sex ratio was 1, and most patients were current or former smokers (69.8 %). Nearly all patients had adenocarcinoma histology, and molecular co-alterations were reported for 6 patients (3 with *KRAS* mutations, 2 with *EGFR* mutations, 1 with *ALK* rearrangement and 1 with *HER2* mutation). PD-L1 status was available for 81.6 % of patients and was highly positive (≥50 %) for 45.9 %. Brain metastases were present at D-T initiation in 20.9 % of patients. Among the pretreated patients, 94/119 received platinum-based chemotherapy, 21/119 received immune checkpoint inhibitors alone, and 4/119 received chemo-immunotherapy in combination.

Table 1
Patient characteristics.

	L2+ (n = 119)	L1 (n = 44)	All (n = 163)
Age: median, years	68,2	71,6	68,3
Sex, n (%) Male	59 (49,6)	22 (50)	81 (49,4)
Smoking status, n (%)			
Never	37 (31,4)	12 (27,3)	49 (30,2)
Current/former	81 (68,1)	32 (72,7)	113 (69,8)
pack year	30	30	30
Stage, n (%)			
IVA	54 (45,4)	20 (45,5)	74 (45,4)
IVB	51 (42,9)	20 (45,5)	71 (43,6)
PS, n (%)			
0–1	80 (82,5)	25 (75,7)	105 (80,8)
2–3	17 (17,6)	8 (24,2)	25 (19,2)
Adenocarcinoma, n (%)	113 (95)	42 (95,5)	155 (95,1)
PD-L1 expression, n (%)			
≥50 %	46 (48,9)	15 (39,5)	61 (45,9)
1–49 %	29 (30,5)	14 (36,8)	43 (32,3)
>1 %	20 (21,1)	9 (23,7)	29 (21,8)
Brain metastasis, n (%)	27 (22,7)	7 (15,9)	34 (20,9)

3.2. Efficacy and safety data

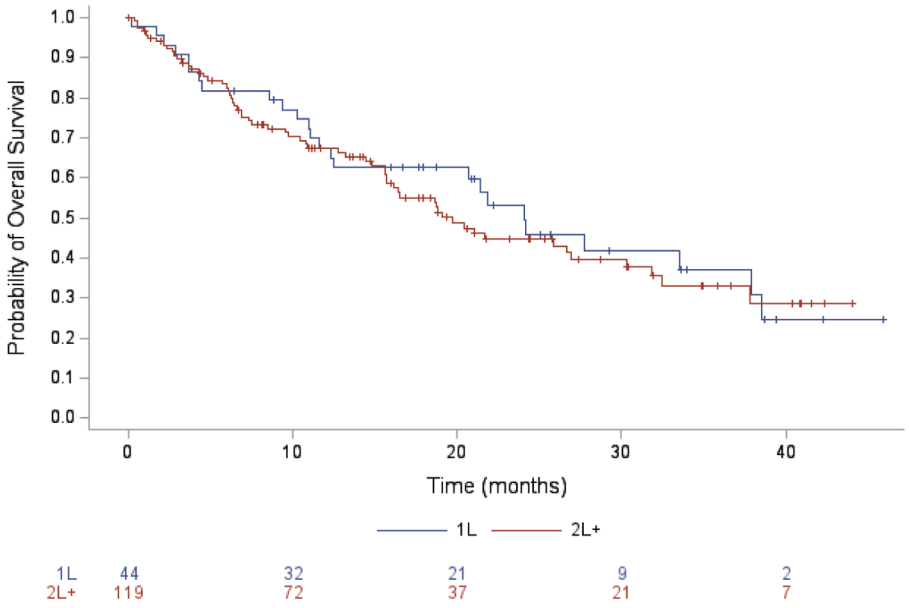
At the data cutoff (June 30, 2021), the median follow-up was 27.4 months (95 % CI 22.2–31.9), and 47 patients (28.8 %) remained on study treatment. Among the 119 patients who received D-T as second-line therapy or beyond, the 12-month OS rate was 67.4 % (95 % CI 57.8–75.3). The median PFS was 10.4 months (95 % CI 7.3–13.1), and the median OS was 19.7 months (95 % CI 15.7–26.9). Among the 44 patients who received D-T for the first-line therapy, a similar 12-month OS rate was 67.4 % (95 % CI 51.2–79.3), with a median PFS of 18.2 months (95 % CI 7.7–21.3) and a median OS of 24.1 months (95 % CI 12.3–37.9) (Fig. 1). The objective response rates were 73.8 % (95 % CI 65.5–82.2) and 82.9 % (95 % CI 71.4–94.4), and progressive disease was observed as the best response in 3.7 % and 0 % of patients, respectively (Table 2). The median durations of response were 10.6 months (95 % CI 7.7–12.0) and 16.3 months (95 % CI 7.8–21.9) in patients treated with D-T in the second-line and beyond and first-line, respectively. In terms of duration of treatment, exposure to dabrafenib and trametinib was similar to the median duration of first-line DOT (7.9 months for trametinib, 8.8 months for dabrafenib, and 11.4 months for both drugs). D-T was mainly discontinued due to progressive disease (60.3 %) or death (15.5 %). Among the 34 patients with brain metastases at D-T initiation, objective response rate was observed in 25 (80.6 %). Their median PFS was 7.5 months (95 % CI 3.6–15.7) and median OS was 24.1 months (95 % CI6.3-NR).

This study was not designed for an exhaustive collection of tolerance data. The main reason of treatment discontinuation was toxicity in 10.3 % (n = 12) in the general population (15.6 % in first-line therapy; 8.3 % in second-line therapy and beyond), followed by patient's decision (n = 6) and intercurrent event (n = 5). Main reported toxicities leading to treatment discontinuation were asthenia (n = 2), fever and chills (n = 2), polyarthralgia (n = 1), left ventricular failure (n = 1), rhabdomyolysis (n = 1), anicteric hepatic cytolysis and cholestasis (n = 1), erythroderma (n = 1), febrile neutropenia (n = 1), rash and vomiting (n = 1), and keratosis (n = 1).

3.3. Subsequent treatments

Overall, 51.2 % and 43.7 % of patients received subsequent second-line and second-line treatment, respectively, whereas 29.4 % and 27.3 % were still receiving D-T therapy. For previously treated patients, subsequent treatments were immune checkpoints inhibitors (ICI) −based in 37.2 % and chemotherapy only in 60.5 % of the patients. For patients receiving D-T first-line therapy, 42.9 % were ICI −based, and 42.9 % were chemotherapy-based (Fig. 2). Overall survival did not differ based on whether the patient received chemotherapy or immunotherapy post D-T (Fig. 2).

(A) Overall survival



(B) Progression free survival

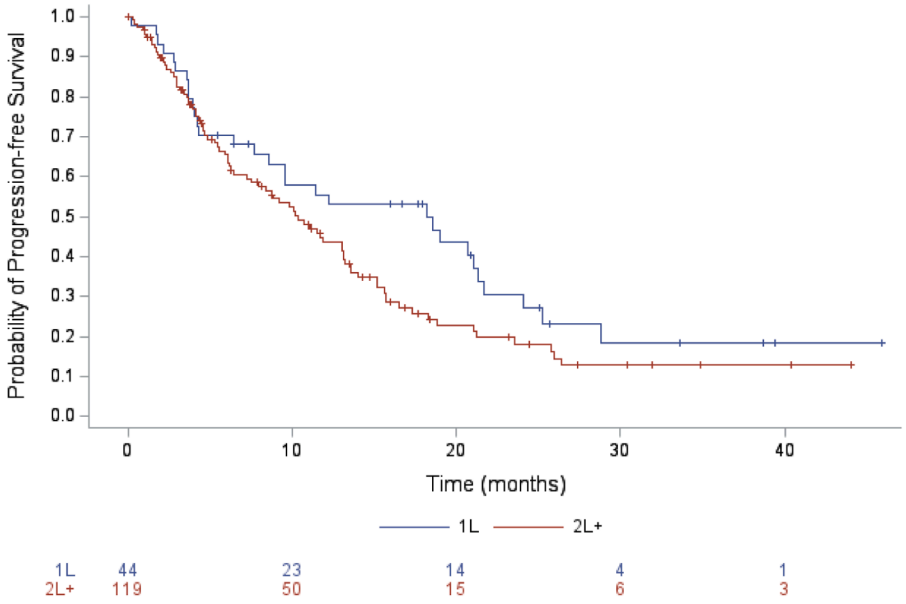


Fig. 1. Kaplan Meier curve for OS and PFS.

4. Discussion

Data on the efficacy of D-T in combination with BRAF V600E-mutated advanced NSCLC, especially in the real world, are scarce. To our knowledge, this retrospective study includes one of the largest numbers of patients with the BRAF V600E mutation treated with D-T in combination with other agents, whether as first-line treatment or beyond. One originality of our study stems from the selection of patients through molecular biology platforms, ensuring that our cohort offers a broad and representative view of the management of BRAF V600E-mutated NSCLC patients in France. This approach allows us to capture a better representation of real-world practices across the entire territory, which we believe adds significant value and relevance to our real-world findings.

The population of our study was representative and comparable to what has already been described, with a predominance of adenocarcinomas, a sex ratio of 1, a discrete majority of smokers and former smokers, and a median age of 68 years (12,26–28). As previously described, the proportion of patients with a PDL-1 expression ≥50 % was greater than that in the general population [13,27]. Patient

Table 2
Patient outcomes.

	L2+ (n = 119)	L1 (n = 44)	All (n = 163)
mPFS, months	10.4	18.2	11.4
PFS rates, %			
6 months	65.4	70.4	66.9
12 months	43.7	55.5	47.2
mOS, months	19.7	24.1	21.4
OS rates, %			
12 months	67.4	67.4	67.4
18 months	55.2	62.6	57.5
24 months	44.7	53.0	47.3
ORR (%)	73.8	82.9	76.3

mPFS: median progression-free survival, mOS: median overall survival, ORR: overall response rate, L2+: second-line and beyond, L1: first-line.

characteristics were broadly comparable in terms of age, PS, stage at treatment initiation, and proportion of brain metastases, regardless of the line of D-T initiation. The study confirmed the real-world disease landscape, highlighting a high proportion of patients with PS 2 or higher (20 %) and brain metastases (20.9 %), which are independent factors of poor prognosis and often underrepresented in prospective clinical trials [23–25] where 93 % of patients had a PS < 2, only 1 had brain metastasis, and more recently in the PHAROS study where100 % of patients had a PS 0–1 and less than 10 % had brain metastasis [28,29]. At the genomic level, *BRAF* was associated with a very low rate of associated genomic driver alterations, given that molecular biology techniques used were not uniform, varying across different centers and that the panels used might also differ. However, interestingly, the spectrum of co-alterations associated with *BRAF* has been described as significantly different among the classes of mutations [3,30,31].

The benchmark data for this combination remains that published by Planchard *et al*, both in the first-line and beyond. Recently, two trials evaluating the combination of encorafenib and binimetinib, BRAF and MEK inhibitors, were reported: the PHAROS study, an international single-arm trial, detailed the results of this combination in treatment-naïve (n = 59) and previously treated (n = 39) BRAF V600E-mutated NSCLC patients; additionally, IFCT-1904 EncoBRAF, a second trial conducted in France with treatment-naïve patients, was also reported [33]. First of all, it is interesting to note that efficacy results in second-line or later are very similar over the different study with a median PFS around 10 months, median OS between 18 and 23 months and 12-months OS rate of 68 % (Table 3). However, in first-line, efficacy data tends to differ between the different trials, with median PFS of 10.8 and 10.9 months in Planchard *et al* study and ENCOBRAF respectively, whereas higher median PFS were reported in our real-world study (18.2 months) and in PHAROS trial with a median PFS of 30.2 months (Table 3).

Superiority of efficacy observed in BLaDE patients in first-line among those reported by Planchard *et al* were not expected particularly in real-world situations. This difference does not seem to be explained by patient characteristics, and as the D-T combination was not supposed to be administered first-line in France, it is important to emphasize that the D-T combination was probably proposed out of conviction of efficacy rather than ineligibility for chemotherapy, as approximately 75 % of patients received post-D-T treatment, which was similar in both groups. One hypothesis is that the retrospective analysis reported in the files by the investigators and not systematically evaluated according to RECIST1.1 may overestimate response rates and PFS duration.

The efficacy data obtained in the BLaDE study for the first-line are consistent with the idea of the oncogenic addictive role of the BRAF V600E mutation and a potential benefice in the initiation of a targeted treatment as earlier as possible, as previously observed in other oncogene-addicted NSCLC such as *EGFR*-mutated or *ALK*-rearranged NSCLC patients. Moreover, the improvement in PFS also translated into OS, suggesting that using the D-T combination in first-line *BRAF* V600-mutated NSCLC could be the best strategy. An indirect real-world comparison of the use of D-T versus first-line platinum-based chemotherapy revealed that the risk of death was lower and the median OS was longer with first-line D-T versus platinum-based chemotherapy [26]. Similar results were also reported in a real-world retrospective analysis of 129 *BRAF* V600 Chinese patients with a median PFS of 25 months and 12 months PFS rate of 67 % when D-T was given in first-line [33]. Anyway, it is important to note that Chinese population is not perfectly comparable to Caucasian with a higher proportion of *EGFR* mutated patients in this cohort. In second-line, while no comparative studies were conducted, results obtained with BRAF inhibitors seem superior to those expected with second-line chemotherapy. In the Biomarkers study, the median second-line PFS was 6 months in a cohort of 83 patients, with a quarter of these patients having been treated with BRAF inhibitors [31]. Overall survival was 13.4 months, which is also lower than the 19.7 months reported here for second-line treatment.

If the therapeutic sequence for patients with BRAF inhibitors is not yet clearly defined, another question remains unresolved: the role of immunotherapy in these patients. The combination of ICI and chemotherapy is approved for first-line treatment of patients with metastatic NSCLC, and while immunotherapy is well-established for BRAF-mutated melanoma, its efficacy in BRAF-mutant NSCLC is mainly supported by retrospective studies. Various multi-institutional studies have shown that patients treated with immune checkpoint inhibitors (ICIs) demonstrated similar outcomes to those in unselected NSCLC populations. Specific cohorts reported objective response rates (ORR) of 25–33 % and median progression-free survival (mPFS) of 3.0–4.7 months [34–36]. High tumor mutational burden (TMB) and PD-L1 expression reported to be higher in BRAF-mutant NSCLC may explain higher response rates to ICIs. Further research is needed to solidify the role of immunotherapy in this subset of patients. Specific randomized trials are needed to determine the best treatment strategy or sequence; however, they are unlikely to be conducted given the rarity of *BRAF* mutations.

In terms of tolerance, the most common adverse events (AEs) observed with dabrafenib − trametinib association in studies conducted by Planchard *et al* were pyrexia (64 %), nausea (56 %), and diarrhea (36 %); grade 3–4 AEs occurred in 69 % of patients in first line treatment including pyrexia (46 %), nausea (40 %), and vomiting (35 %); grade 3–4 AEs occurred in 49 % of patients in second line treatement, including pyrexia (2 %) [23–25]. In our study, discontinuation of the D-T combination due to toxicity was reported in 8.3 % and 15.6 % of patients who were treated in second-line or later and first-line, respectively, which was comparable to the findings in other trials (9 %–20 %) [28,32,37].

This analysis has several unavoidable limitations, given its retrospective nature. Selection bias is partly limited here by the identification of patients via molecular biology platforms, enabling exhaustive listings of all BRAF V600E-mutated patients and not those reported by the clinician. One of the main limitations of this study is the interpretability of the PFS results in real-life studies. Indeed, the measure of disease progression here was defined by the investigators according to their usual clinical practice, which does not involve the systematic achievement of RECIST1.1 objective criteria. It is therefore likely that the D-T combination was continued beyond the RECIST1.1 progression threshold, with a consequent prolongation of PFS. However, overall survival (OS) remains a relevant and robust objective parameter with good statistical precision.

5. Conclusion

This large retrospective cohort of *BRAF*-mutated patients contributes to existing evidence supporting the effectiveness of dual BRAF/MEK inhibition in all advanced *BRAF* V600-mutated NSCLC patients, with an acceptable safety profile and a trend toward first-line D-T initiation. These real-world results are consistent with those of other registered

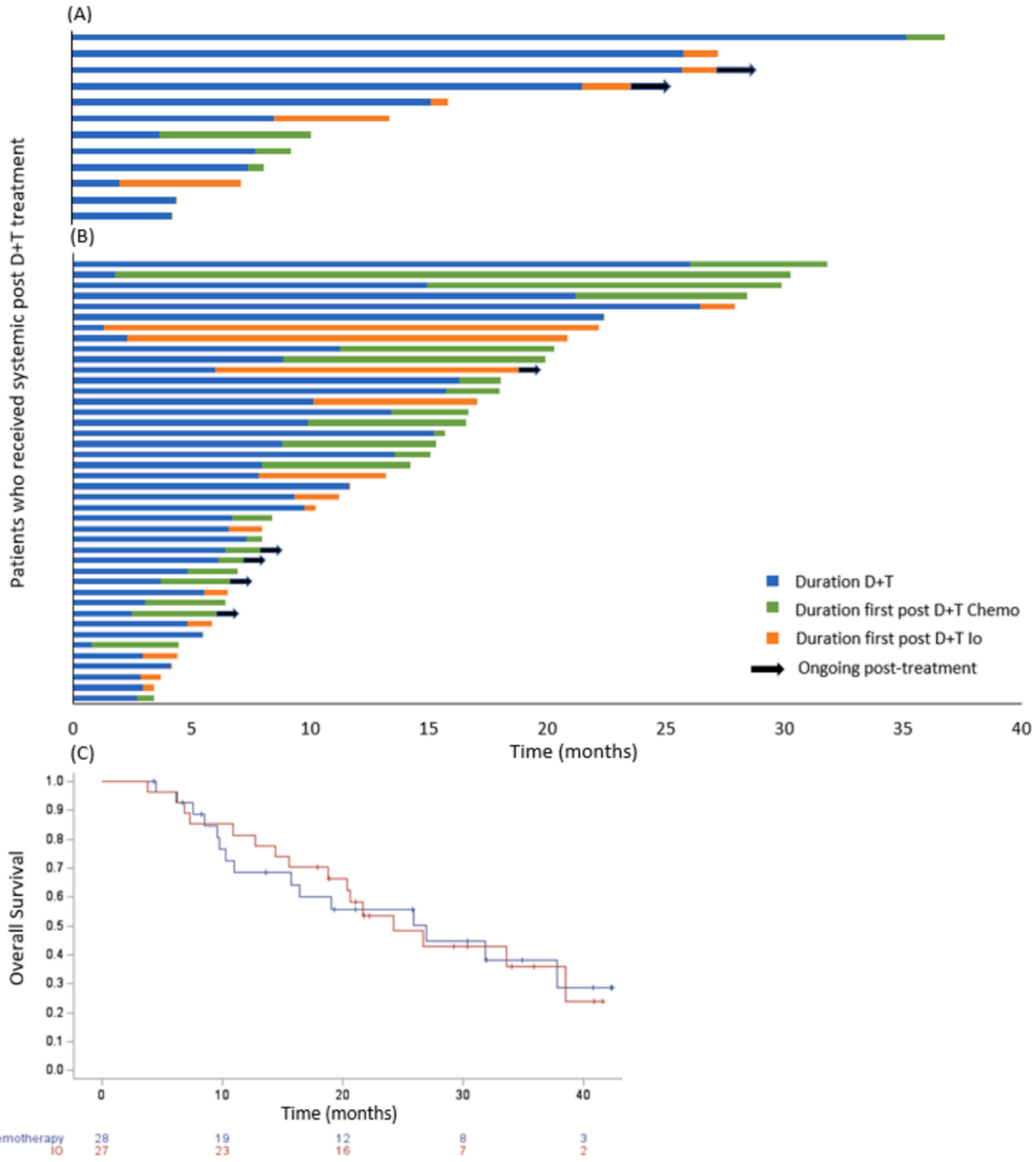


Fig. 2. Post-D-T duration of treatment for treatment-naive (A) or pretreated patients (B) and Kaplan-Meier curves of overall survival for treatments received post D-T (C).

studies suggesting that non-selected patients benefit as much as patients treated in clinical trials. Therefore, *BRAF* mutations must be included in the panel of molecular alterations screened as soon as patients present with advanced non-squamous NSCLC. As the role of immunotherapy is still a matter of debate, additional data will be needed to refine the therapeutic strategy and treatment sequences used in these patients.

ClinicalTrials.gov Identifier: NCT04775095.

CRediT authorship contribution statement

Aurélie Swalduz: Writing – original draft, Visualization, Validation, Investigation, Funding acquisition, Conceptualization. **Michèle Beau-Faller:** Writing – review & editing, Writing – original draft, Validation, Investigation. **David Planchard:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Julien Mazieres:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Sophie Bayle-Bleuez:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Didier Debieuvre:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Vincent Fallet:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Margaux Geier:** Writing – review & editing, Validation, Investigation. **Alexis Cortot:** Writing – review & editing, Writing –

Supplementary Figure 1. Flowchart

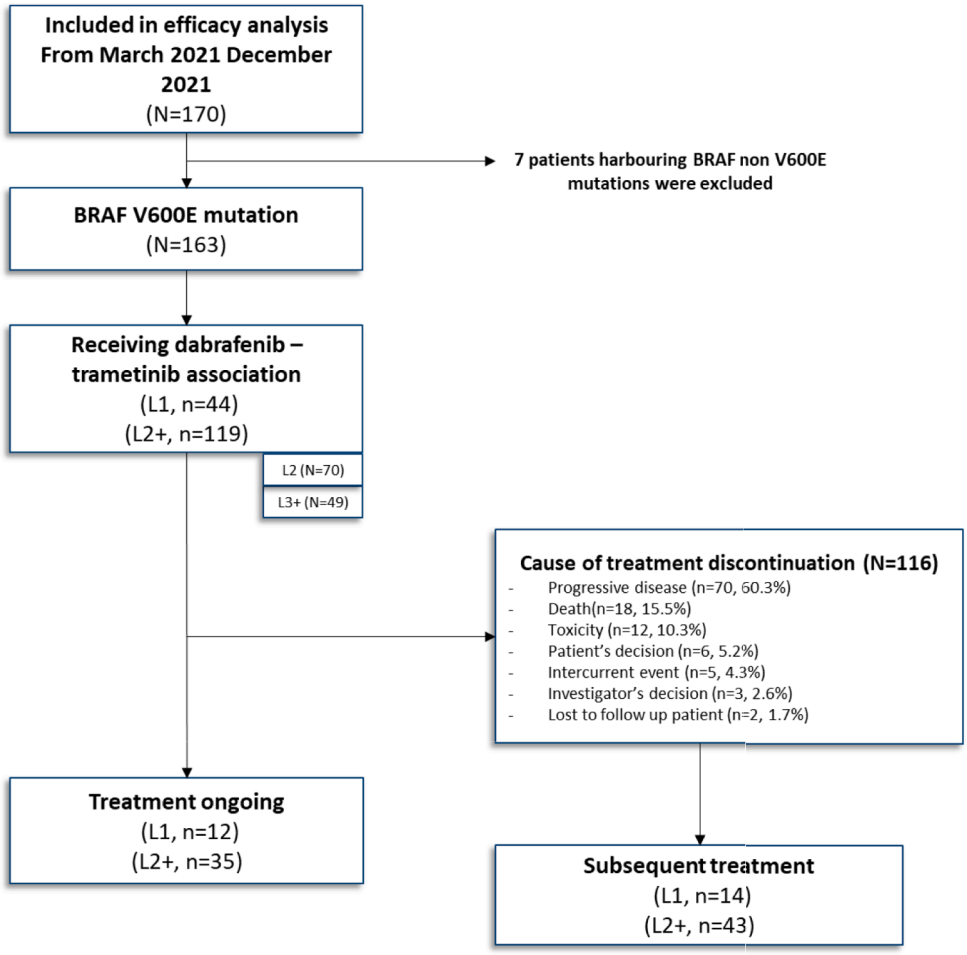


Fig. 2. (*continued*).

Table 3
Reported clinical activity of BRAF inhibitors and MEK inhibitors association in BRAF V600E-mutant NSCLC.

Study	Drug combination	# of pts (n)	Line of treatment	ORR (%)	mPFS (months)	mOS (months)	12 months OS rate (%)	Ref
Planchard	Dabra-Trame	36	1L	63.9	10.8	17.3	75	[23]
PHAROS	Enco-Bini	59	1L	75	30.2	NE	83	[28,29]
IFCT-1904 ENCO-BRAF	Enco-Bini	61	1L	65.5	10.9	NR	–	[32]
BLADE	Dabra-Trame	44	1L	82.9	18.2	24.1	67.4	
Planchard	Dabra-Trame	57	2L	68.4	10.2	18.2	68	[25]
PHAROS	Enco-Bini	39	2L	46	9.3	22.7	68	[28,29]
BLADE	Dabra-Trame	119	2L	73.8	10.4	19.7	67.4	

Dabra-trame: dabrafenib-trametinib; enco-bini: encorafenib-binimetinib; #: number; pts: patients; ref: reference.

original draft, Validation, Investigation. **Sébastien Couraud:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Catherine Daniel:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Charlotte Domblides:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Eric Pichon:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Elizabeth Fabre:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Sébastien Larivé:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Ulrike Lerolle:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Pascale Tomasini:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Marie Wislez:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Pascale Missy:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Franck Morin:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Virginie Westeel:** Writing – review & editing, Writing – original draft, Validation, Investigation, Funding acquisition. **Jean-Bernard Auliac:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Funding

This study was financed by Novartis but Novartis had no role in either data collection or manuscript writing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: A. Swalduz: honoraria: AstraZeneca, Janssen, Roche, Amgen, and BMS; consulting or advisory role: AstraZeneca, Janssen, Roche, Amgen, BMS, Pfizer, and Lilly

D Planchard: Consulting, advisory role or lectures: AstraZeneca, Abbvie, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Janssen, Pfizer, Roche, Pierre-fabre, Takeda, ArriVent, Mirati, Seagen; Clinical trials research as principal or coinvestigator (institutional financial interests): AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo, Abbvie, Janssen, Pierre-fabre, Takeda, ArriVent, Mirati, Seagen; Travel, Accommodations, Expenses: AstraZeneca, Roche, Novartis, Pfizer.

S Bayle-Beuez: Employment: Roche, Amgen; honoraria: Roche, Amgen; research funding: Roche; consulting or advisory role: Amgen.

V Fallet: Consulting or advisory role: Pfizer, Jansen, AstraZeneca, BMS, Takeda, Roche; speakers' bureau: AstraZeneca, BMS, Takeda

M Geier: consulting or advisory role; Pfizer, Sanofi, Chugai, BMS.

S Couraud: honoraria: Amgen, Astra Zeneca, BMS, MSD, Roche, Sanofi, Fabentech, Boehringher Ingelheim, Takeda; research funding: Amgen, Astra Zeneca, BMS, MSD, Roche, Sanofi, Chugai, Novartis, Pfizer, Sysmex, Cellgene, Takeda, Janssen; travel, accomodations, travels: Astra Zeneca, Roche, Takeda.

C Domblides: Consulting or advisory role: Astra-Zeneca, Amgen, BMS, Takeda; Travel, accomodations, expenses: Amgen, Astra-Zeneca, Bristol-Myers Squibb, MSD, Pfizer, Pierre Fabre, Roche.

E Pichon: honoraria: Takeda, Bristol Myers Squibb, Astra Zeneca.

M Wislez: Consulting fees from BMS, MSD, Novartis, AstraZeneca, Roche, Amgen.

V Westeel: Honoraria: Astra Zeneca, BMS, Amgen, Roche; consulting or advisory role: MSD, Takeda; speakers'bureua: BMS, Astra Zeneca, Roche, MSD, Pfizer, Amgen; Travel, accomodations, expenses: BMS, Astra Zeneca, Sanofi

JB Auliac: Honoraria for attending scientific meetings, speaking, organizing research or consulting, from Boehringer Ingelheim, Hoffman-Roche, Takeda, BMS, MSD, Astra Zeneca, Amgen, Janssen and Pfizer.

All the other authors declare that they have no conflicts of interest.

Acknowledgments

We thank the BLaDE contributors listed here who collaborated in this project and provided data for at least 1 patient (not included in the list of authors):

Nicolas ALBIN, Institut Daniel Hollard, Service de Pneumologie, Grenoble, France.

Alexandre AMPERE, CH, Service de Pneumologie, Béthune, France.

Karim AMRANE, CH, Service de Pneumologie, Morlaix, France.

Clarisse AUDIGIER-VALETTE, CHI, Service de Pneumologie, Toulon, France.

Philippe BRUN, CH, Service de Pneumologie, Valence, France.

Olivier BYLICKI, Sainte Anne HIA, Service de Pneumologie, Toulon, France.

Nicolas CLOAREC, Service d'Oncologie, CH, Avignon, France.

Marc DEROLLEZ, Polyclinique du Val de Sambre, Service de Pneumologie, Maubeuge, France.

Pascale DUBRAY-LONGERAS, Centre Jean Perrin, Service de Pneumologie, Clermont-Ferrand, France.

Boris DUCHEMANN, APHP, Hôpital Avicenne, Service de Pneumologie, Bobigny, France.

Thomas EGENOD, CHU, Service de Pneumologie, Limoges, France.

Pierre FOURNEL, Département d'Oncologie Médicale, Institut de Cancérologie Lucien Neuwirth, Saint-Priest en Jarez, France.

Frédéric GIRARD, CH, Service de Pneumologie, Briançon, France.

Cyril GUIBERT, CH, Service de Pneumologie, La Roche-Sur-Yon, France.

Florian GUISIER, CHU, Service de Pneumologie, Rouen, France.

José, HUREAUX, CHU, Service de Pneumologie, Angers, France.

Laurent KEDZIORA, CH, Service de Pneumologie, Denain, France.

Aurélie LAGRANGE, CRLCC, Service de Pneumologie, Dijon, France.

Gwenaëlle LE GARFF, CHG, Service de Pneumologie, Saint-Brieuc, France.

Hervé LENA, CHU, Service de Pneumologie, Rennes, France.

Patrick MERLE, CHU, Service de Pneumologie, Clermont-Ferrand, France.

Anne-Cécile METIVIER-BARRE, Foch, Service de Pneumologie, Suresnes, France.

Olivier MOLINIER, CHG, Service de Pneumologie, Le Mans, France.

Lionel MOREAU, CH, Service de Pneumologie, Colmar, France.

Hugues MOREL, CHR, Service de Pneumologie, Orléans, France.

Thierry MURON, CHPL, Service de Pneumologie, Saint-Etienne, France.

Luc ODIER, CH, Service de Pneumologie, Villefranche sur Saône, France.

Claire POULET, CHU, Service de Pneumologie, Amiens, France.

Judith RAIMBOURG, CRLCC, Service de Pneumologie, Nantes, France.

Magali ROA, Saint Raphaël CHI, Service de Pneumologie, Fréjus, France.

Benoit ROCH, CHU, Service de Pneumologie, Montpellier, France.

Anne-Claire TOFFART, CHU, Service de Pneumologie, Grenoble, France.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2024.108038.

References

[1] F. Barlesi, J. Mazieres, J.P. Merlio, D. Debieuvre, J. Mosser, H. Lena, et al., Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT), Lancet 387 (10026) (2016) 1415–1426.

[2] A. Leonetti, F. Facchinetti, G. Rossi, R. Minari, A. Conti, L. Friboulet, M. Tiseo, D. Planchard, BRAF in non-small cell lung cancer (NSCLC): pickaxing another brick in the wall, Cancer Treat Rev. 66 (2018) 82–94, https://doi.org/10.1016/j.ctrv.2018.04.006. Epub 2018 Apr 24 PMID: 29729495.

[3] A. Di Federico, A. De Giglio, F. Gelsomino, D. De Biase, F. Giunchi, A. Palladini, et al., Genomic landscape, clinical features and outcomes of non-small cell lung cancer patients harboring BRAF alterations of distinct functional classes, Cancers 14 (14) (2022) 3472.

[4] M.J. Garnett, R. Marais, Guilty as charged: B-RAF is a human oncogene, Cancer Cell (2004).

[5] H. Davies, G.R. Bignell, C. Cox, P. Stephens, S. Edkins, S. Clegg, et al., Mutations of the BRAF gene in human cancer, Nature 417 (6892) (2002) 949–954.

[6] P.T.C. Wan, M.J. Garnett, S.M. Roe, S. Lee, D. Niculescu-Duvaz, V.M. Good, et al., Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF, Cell 116 (6) (2004) 855–867.

[7] C.S. Baik, N.J. Myall, H.A. Wakelee, Targeting *BRAF* -mutant non-small cell lung cancer: from molecular profiling to rationally designed therapy, Oncologist 22 (7) (2017) 786–796.

[8] R. Yaeger, R.B. Corcoran, Targeting alterations in the RAF–MEK pathway, Cancer Discov. 9 (3) (2019) 329–341.

[9] F. Tabbò, C. Pisano, J. Mazieres, L. Mezquita, E. Nadal, D. Planchard, et al., How far we have come targeting BRAF-mutant non-small cell lung cancer (NSCLC), Cancer Treat. Rev. 103 (2022) 102335.

[10] Q. Lin, H. Zhang, H. Ding, J. Qian, A. Lizaso, J. Lin, et al., The association between BRAF mutation class and clinical features in BRAF-mutant Chinese non-small cell lung cancer patients, J. Transl. Med. 17 (1) (2019) 298.

[11] A. Marchetti, L. Felicioni, S. Malatesta, M. Grazia Sciarrotta, L. Guetti, A. Chella, et al., Clinical features and outcome of patients with non–small-cell lung cancer harboring *BRAF* mutations, JCO 29 (26) (2011) 3574–3579.

[12] J.B. Auliac, S. Bayle, P. Do, G. Le Garff, M. Roa, L. Falchero, et al., Efficacy of dabrafenib plus trametinib combination in patients with BRAF V600E-mutant NSCLC in real-world setting: GFPC 01-2019, Cancers 12 (12) (2020) 3608.

[13] F. Perrone, G. Mazzaschi, R. Minari, M. Verzè, C. Azzoni, L. Bottarelli, et al., Multicenter observational study on metastatic non-small cell lung cancer harboring

BRAF mutations: focus on clinical characteristics and treatment outcome of V600E and non-V600E subgroups, Cancers 14 (8) (2022) 2019.
[14] D. Frisone, A. Friedlaender, U. Malapelle, G. Banna, A. Addeo, A BRAF new world, Crit. Rev. Oncol. Hematol. 152 (2020) 103008.
[15] A.M. Litvak, P.K. Paik, K.M. Woo, C.S. Sima, M.D. Hellmann, M.E. Arcila, et al., Clinical characteristics and course of 63 patients with BRAF mutant lung cancers, J. Thorac. Oncol. 9 (11) (2014) 1669–1674.
[16] I. Tan, T.E. Stinchcombe, N.E. Ready, J. Crawford, M.B. Datto, R.J. Nagy, et al., Therapeutic outcomes in non-small cell lung cancer with BRAF mutations: a single institution, retrospective cohort study, Transl. Lung Cancer Res. 8 (3) (2019) 258–267.
[17] S. Peters, O. Michielin, S. Zimmermann, Dramatic response induced by vemurafenib in a *BRAF V600E*-mutated lung adenocarcinoma, JCO. 31 (20) (2013) e341–e344.
[18] D.M. Hyman, I. Puzanov, V. Subbiah, J.E. Faris, I. Chau, J.Y. Blay, et al., Vemurafenib in multiple nonmelanoma cancers with *BRAF* V600 mutations, N. Engl. J. Med. 373 (8) (2015) 726–736.
[19] J. Mazieres, C. Cropet, L. Montané, F. Barlesi, P.J. Souquet, X. Quantin, et al., Vemurafenib in non-small-cell lung cancer patients with BRAFV600 and BRAFnonV600 mutations, Ann. Oncol. 31 (2) (2020) 289–294.
[20] O. Gautschi, J. Milia, B. Cabarrou, M.V. Bluthgen, B. Besse, E.F. Smit, et al., Targeted therapy for patients with BRAF-mutant lung cancer results from the European EURAF cohort, J. Thorac. Oncol. 10 (10) (2015) 1451–1457.
[21] X. Chan, A. Singh, N. Osman, T. Piva, Role played by signalling pathways in overcoming BRAF inhibitor resistance in melanoma, IJMS 18 (7) (2017) 1527.
[22] G.V. Long, K.T. Flaherty, D. Stroyakovskiy, H. Gogas, E. Levchenko, F. de Braud, et al., Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study, Ann. Oncol. 28 (7) (2017) 1631–1639.
[23] D. Planchard, E.F. Smit, H.J.M. Groen, J. Mazieres, B. Besse, Å. Helland, et al., Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial, Lancet Oncol. 18 (10) (2017) 1307–1316.
[24] D. Planchard, B. Besse, H.J.M. Groen, S.M.S. Hashemi, J. Mazieres, T.M. Kim, et al., Phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant metastatic NSCLC: updated 5-year survival rates and genomic analysis, J. Thorac. Oncol. 17 (1) (2022) 103–115.
[25] D. Planchard, B. Besse, H.J.M. Groen, S.M.S. Hashemi, J. Mazieres, T.M. Kim, et al. The updated overall survival and genomic analysis from a single-arm phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E Mutant Metastatic Non-Small Cell Lung Cancer.
[26] B.E. Johnson, C.S. Baik, J. Mazieres, H.J.M. Groen, B. Melosky, J. Wolf, et al., Clinical outcomes with dabrafenib plus trametinib in a clinical trial versus real-world standard of care in patients with BRAF-mutated advanced NSCLC, JTO Clin. Res. Rep. 3 (5) (2022) 100324.
[27] A.J.W. Gibson, A. Pabani, M.L. Dean, G. Martos, W.Y. Cheung, V. Navani, Real-world treatment patterns and effectiveness of targeted and immune checkpoint inhibitor-based systemic therapy in BRAF mutation-positive NSCLC, JTO Clin. Res. Rep. 4 (3) (2023) 100460.
[28] G.J. Riely, E.F. Smit, M.J. Ahn, E. Felip, S.S. Ramalingam, A. Tsao, et al., Phase II, open-label study of encorafenib plus binimetinib in patients with *BRAF* ^{V600} -mutant metastatic non–small-cell lung cancer, JCO 41 (21) (2023) 3700–3711.
[29] G.J. Riely, M-J. Ahn, J. Clarke, I. Dagogo-Jack, E. Felip, F. Gelsomino, et al., LBA56 Updated efficacy and safety from the phase II PHAROS study of encorafenib plus binimetinib in patients with BRAF V600E-mutant metastatic NSCLC (mNSCLC), Ann. Oncol. 35, S1246–S1247.
[30] N.J. Myall, S. Henry, D. Wood, J.W. Neal, S.S. Han, S.K. Padda, et al., Natural disease history, outcomes, and co-mutations in a series of patients with BRAF-mutated non–small-cell lung cancer, Clin. Lung Cancer 20 (2) (2019) e208–e217.
[31] S. Couraud, F. Barlesi, C. Fontaine-Deraluelle, D. Debieuvre, J.P. Merlio, L. Moreau, et al., Clinical outcomes of non–small-cell lung cancer patients with BRAF mutations: results from the French Cooperative Thoracic Intergroup biomarkers France study, Eur. J. Cancer 116 (2019) 86–97.
[32] D. Planchard, J. Mazieres, C. Mascaux, F. Guisier, P. Tomasini, M. Wislez, et al., 1259MO - Encorafenib plus binimetinib in patients (pts) with previously untreated BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC): an open-label, multicenter phase II trial (IFCT-1904 ENCO-BRAF), Ann. Oncol. 35 (suppl_2) (2024) S802–S877, https://doi.org/10.1016/annonc/annonc1602.
[33] B. Jia, J. Zhao, B. Jin, F. Zhang, S. Wang, L. Zhang, et al., Prevalence, clinical characteristics, and treatment outcomes of patients with BRAF-mutated advanced NSCLC in China: a real-world multi-center study, J. Thorac. Oncol. 18 (4S) (2023) S61.
[34] H. Li, Y. Zhang, Y. Xu, Z. Huang, G. Cheng, M. Xie, Z. Zhou, Y. Yu, W. Xi, Y. Fan, Tumor immune microenvironment and immunotherapy efficacy in BRAF mutation non-small-cell lung cancer, Cell Death Dis. 13 (12) (2022) 1064, https://doi.org/10.1038/s41419-022-05510-4. PMID: 36543792; PMCID: PMC9772302.
[35] M. Offin, T. Pak, S. Mondaca, J. Montecalvo, N. Rekhtman, D. Halpenny, et al., P1.0439 molecular characteristics, immunophenotype, and immune checkpoint inhibitor response in BRAF Non-V600 mutant lung cancers, J. Thoracic Oncol. (2019).
[36] F. Guisier, C. Dubos-Arvis, F. Viñas, H. Doubre, C. Ricordel, S. Ropert, H. Janicot, M. Bernardi, P. Fournel, R. Lamy, M. Pérol, J. Dauba, G. Gonzales, L. Falchero, C. Decroisette, P. Assouline, C. Chouaid, O. Bylicki, Efficacy and safety of anti-PD-1 immunotherapy in patients with advanced NSCLC with BRAF, HER2, or MET mutations or RET translocation: GFPC 01-2018, J. Thorac Oncol. 15 (4) (2020) 628–636, https://doi.org/10.1016/j.jtho.2019.12.129. Epub 2020 Jan 13. PMID: 31945494.
[37] J.B. Auliac, S. Bayle, P. Do, G. Le Garff, M. Roa, L. Falchero, E. Huchot, G. Quéré, G. Jeannin, A.C. Métivier, J. Hobeika, F. Guisier, C. Chouaid, Efficacy of dabrafenib plus trametinib combination in patients with *BRAF* V600E-mutant NSCLC in real-world setting: GFPC 01-2019, Cancers (Basel) 12 (12) (2020) 3608, https://doi.org/10.3390/cancers12123608. PMID: 33276639; PMCID: PMC7761573.