



Original research

Braf-mutant metastatic non-small-cell lung cancer: Real world data from the Italian biomarker atlas database

Claudio Sini^{a,1}, Alessandro Russo^{b,c,1}, Diego Cortinovis^d, Lucia Anna Muscarella^e,
Marcello Tiseo^f, Emilio Bria^{g,h}, Salvatore Grisantiⁱ, Pierluigi Piovano^j, Antonello Vecchia^k,
Lorenzo Antonuzzo^l, Fabrizio Citarella^m, Sara Pilottoⁿ, Maria Lucia Reale^o,
Daniele Pignataro^p, Elisa Roca^q, Lorenzo Calvetti^r, Pamela Pizzutilo^s, Gabriele Minuti^t,
Giacomo Pelizzari^u, Greta Ali^v, Anna Bettini^w, Alberto Pavan^x, Diego Signorelli^y,
Serena Ricciardi^z, Giulia Meoni^{aa}, Concetta Sergi^{ab}, Carlo Genova^{ac,ad}, Vieri Scotti^{ae},
Tiziana Vavalà^{af}, Stefania Gori^{ag}, Giulia Pasello^{ah,ai},
Paolo Pedrazzoli^{aj,ak}, Rita Chiari^{al}, Alessandro D'Aveni^{am},
Roberta Buosi^{an}, Luca Toschi^{ao}, Hector Soto Parra^{ap}, Lucio Buffoni^{aq},
Brigida Stanzione^{ar}, Cinzia Ortega^{as}, Cristina Zannori^{at},
Diana Giannarelli^{au}, Umberto Malapelle^{av}, Silvia Novello^{aw,*},
Francesco Passiglia^{aw,2}, Editta Baldini^{ax,2}

^a Medical Oncology, CPDO, Ospedale Giovanni Paolo II, Olbia, Italy

^b Medical Oncology Department, Humanitas Istituto Clinico Catanese, Misterbianco, Catania, Italy

^c Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy

^d Fondazione IRCCS San Gerardo dei Tintori Monza, Monza/ University of Milano-Bicocca, Italy

^e Laboratory of Oncology, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo 71013, Italy

^f Department of Medicine and Surgery, University of Parma and Medical Oncology Unit, University Hospital of Parma, Parma, Italy

^g Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

^h Ospedale Isola Tiberina – Gemelli Isola, Rome, Italy

ⁱ Medical Oncology-ASST-Spedali Civili, Brescia, Italy

^j Medical Oncology-AO SS Antonio e Biagio, Alessandria, Italy

^k Medical Oncology, Ospedale di Trento, Italy

^l Medical Oncology, AOU Careggi-Firenze, Italy

^m Medical Oncology Department, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

ⁿ Section of Innovation Biomedicine - Oncology Area, Department of Engineering for Innovation Medicine (DIMI), University of Verona and University and Hospital Trust (AOUI) of Verona, Italy

^o Medical Oncology Unit, Vito Fazzi Hospital, Lecce, Italy

^p Medical Oncology, Ospedale Cardinal Massaia, Asti, Italy

^q Thoracic Oncology - Lung Unit, P. Pederzoli Hospital, Peschiera Del Garda, VR, Italy

^r Medical Oncology, East district - AULSS 8 BERICA, Vicenza, Italy

^s Medical Thoracic Oncology Unit IRCCS Istituto Tumori Giovanni Paolo II Bari, Italy

^t Clinical Trial Unit: Phase 1 and Precision Medicine, National Cancer Institute, IRCCS, Regina Elena, Rome, Italy

^u Department of Oncology, Azienda sanitaria universitaria Friuli Centrale, Udine, Italy

^v Pathological Anatomy, Surgical, Medical, Molecular and Critical Care Pathology Department, University Hospital of Pisa, Pisa, Italy

^w Medical Oncology, ASST Papa Giovanni XXIII, Bergamo, Italy

^x Department of Medical Oncology, AULSS 3 Serenissima, Venezia, Italy

^y Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan, Italy

^z Medical Oncology, San Camillo Forlanini Hospital, Roma, Italy

^{aa} SOS Medical Oncology, San Giovanni di Dio Hospital, Firenze, Italy

^{ab} Oncology Unit ARNAS Garibaldi Nesima, Catania, Italy

^{ac} Academic Medical Oncology Unit, IRCCS Ospedale Policlinico San Martino, Genoa 16132, Italy

^{ad} Department of Internal Medicine and Medical Specialties, University of Genoa, Italy

^{ae} Radiation Oncology Unit, Oncology Department, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

* Correspondence to: Department of Oncology, University of Turin, S. Luigi Hospital, Regione Gonzole, 10043 - Orbassano, Turin, Italy.

E-mail address: silvia.novello@unito.it (S. Novello).

^{af} AOU Città della Salute e della Scienza-Dipartimento di Oncologia, SC Oncologia 1U, Torino, Italy^{ag} IRCCS Sacro Cuore Don Calabria, Negrar di Valpolicella, Italy^{ah} Oncology 2, Istituto Oncologico Veneto IOV IRCCS, Padova, Italy^{ai} Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy^{aj} Medical Oncology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy^{ak} Department of Internal Medicine, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy^{al} Medical Oncology Unit, ASTI, Pesaro 61121, Italy^{am} Medical Oncology Unit, P.O. Saronno – ASST Valle Olona, Saronno, Italy^{an} Department of Medical Oncology, Ospedale Santo Spirito, Casale Monferrato, Alessandria, Italy^{ao} Medical Oncology and Haematology Unit, IRCCS Humanitas Research Hospital, Milan, Italy^{ap} Medical Oncology, Azienda Ospedaliero Universitaria Policlinico "G. Rodolico-S. Marco", Catania, Italy^{aq} Medical Oncology, Humanitas Gradenigo Hospital, Torino, Italy^{ar} Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano 33081, Italia^{as} Division of Oncology, Institute for Cancer Research and Treatment, Asl Cn2 -Alba-Brà, Italy^{at} Medical and Translational Oncology, Department of Oncology, Azienda Ospedaliera Santa Maria, Terni, Italy^{au} Fondazione Policlinico Universitario A. Gemelli, IRCCS - Facility of Epidemiology and Biostatistics, Rome, Italy^{av} Department of Public Health, University Federico II of Naples, Naples, Italy^{aw} Department of Oncology, University of Turin, San Luigi Hospital, Orbassano, Turin, Italy^{ax} Medical Oncology, Azienda Sanitaria Toscana, Lucca, Nord, Italy

ARTICLE INFO

Keywords:

BRAF mutations

Dabrafenib

Trametinib

Immunotherapy

BRAF V600E

NSCLC

Real-world evidence

ABSTRACT

Background: BRAF mutations identify a small subgroup of patients (pts) with non-small cell lung cancer (NSCLC). Dabrafenib/trametinib (D/T) combination is associated with high response rates and durable anti-tumor activity in BRAF-V600-mutants. Several open questions still remain unanswered in clinical practice, including the efficacy of treatments based on clinical and molecular characteristics, the activity in patients with brain metastases, the optimal sequence with immunotherapy-based therapies. Here we present outcomes among advanced BRAF-mutant NSCLC patients from the Italian ATLAS registry.

Methods: Patients with metastatic BRAF-mutated NSCLC were included. Clinical-pathological features, treatment effectiveness and safety outcomes were retrospectively collected from the Italian real-world ATLAS registry.

Results: A total of 244 BRAF-mutated NSCLC pts were enrolled, including 70 % V600E mutations. The median PFS of first line D/T was 19.8 months (95 % CI: 10.7–29.0), with a 2-year OS rate of 65.4 % and a PFS2 of 6.6 months (95 % CI: 0–14.3). The activity of D/T differs among sex (mPFS was 13.6 mos and 25.3 mos and 2-yr OS rate were 54.9 % and 72.3 % in males and females, respectively) and smoking status (mPFS was 18.4 mos, 25.6 mos and 24 mos in never, former and current smokers, respectively). Concomitant MET amplification was associated with a shorter median PFS (mPFS was 13.6 mos vs. 44.3 mos with and without MET amplification respectively) in pts treated with D/T as 1st line.

Conclusions: These data confirm the efficacy and safety of first line D/T in BRAF V600E-mutated pts in the real-world setting consistently with prior studies, suggesting a differential activity among key clinical-molecular subgroups.

1. Introduction

BRAF (V-Raf Murine Sarcoma Viral Oncogene Homolog B) mutations identify a small clinically defined subgroup of non-small cell lung cancer (NSCLC) that accounts for approximately 1–3 % of the cases [1]. Based on dimerization status and kinase activity level, BRAF mutations are divided into three classes: V600-mutant kinase-activating monomers (class I), kinase activating dimers (class II), and kinase-inactivating heterodimers (class III) [2]. Currently, the only targetable BRAF alterations are class I mutations, with the most frequent V600E point mutation (T7199A) resulting in the substitution of valine (V) with glutamic acid (E) at codon 600, leading to a constitutive activation of BRAF-kinase activity [3]. Since 2017 the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved dabrafenib/trametinib (D/T) combination in NSCLC patients harboring BRAF V600mutation, based on the efficacy data from a phase II trial in the absence of a comparative phase III study [4–6]. The efficacy of D/T was similar in both pre-treated and in treatment-naïve patients with an overall response rate (ORR) of 68.4 % and 64 % and a median progression-free-survival (PFS) of 9.8 months and 14.6 months, respectively. At 4 and 5 years, the survival rate was 34 % and 22 % in treatment naïve patients and 26 % and 19 % in pretreated patients, respectively [4–6]. Recently, the US FDA granted tumor-agnostic

approval for this combination in BRAF V600E mutant solid tumors regardless of tissue of origin (except colorectal cancer), based on the evidence from several adult and pediatric studies (ROAR basket trial, NCI-MATCH trial, and Study X2101), demonstrating efficacy across different tumor types [7].

In addition to D/T, another combination of a BRAF and MEK inhibitors, encorafenib/binimetinib (E/B), has been recently FDA/EMA approved for BRAF V600E mutant NSCLCs, based on a single arm, non-randomized, study (PHAROS) including both treatment-naïve and previously treated patients with BRAF V600-mutated metastatic NSCLC [8, 9]. E/B reported an ORR of 75 % and 46 %, a median PFS of 30.2 and 9.3 months, and a 3-year overall survival (OS) rate of 53 % and 29 % respectively in treatment-naïve and pretreated patients [8,9].

Despite these impressive data, several open questions still remain unanswered in clinical practice, including the efficacy of treatments based on clinical characteristics, the activity of such combinations in patients with brain metastases, the optimal sequence with immunotherapy-based therapies and the impact of concomitant genomic aberrations. Here we present treatment patterns and clinical outcomes among BRAF-mutant advanced NSCLC patients from the Italian, real-world, ATLAS registry.

2. Patients and methods

2.1. Study design

This is a multicenter, retrospective, observational study conducted

¹ co-first authors² co-senior authors

on advanced NSCLC patients harboring BRAF molecular alterations participating in the ATLAS, Italian real-world registry (<https://biomarkersatlas.com/>), a web-based platform created to collect and share NSCLC clinical and molecular data among Italian centers, as previously described [10]. All cases diagnosed between January 2019 and December 2023 were included in this analysis. BRAF status was determined by a local laboratory with DNA/RNA next-generation sequencing (NGS) or real-time polymerase chain reaction (RT-PCR), using tissue and/or blood-based samples.

Written informed consent was obtained from all the patients, in accordance with the general authorization to process personal data for scientific research purposes from “The Italian Data Protection Authority” (<http://www.garanteprivacy.it/web/guest/home/docweb/-/docwebdisplay/export/2485392>). All data were anonymously managed using numerical codes, and all samples were handled in compliance with the Helsinki Declaration (<https://www.wma.net/fr/news-post/en-matierede-transfert-des-taches-la-securite-des-patients-et-la-qualitedes-soins-devraient-etre-primordiales/>).

2.1.1. Study objectives

The data on patients’ and disease’s characteristics including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking history, PD-L1 expression and *de-novo* MET expression were reported. Treatment patterns and clinical outcomes with targeted and chemo-immunotherapy treatments were analyzed.

The primary objective was to assess the efficacy of targeted therapy with dabrafenib/trametinib in BRAF-V600E advanced NSCLC patients, included in the ATLAS registry, to provide a reliable picture of treatment efficacy in the real-world clinical setting.

The secondary objectives were the evaluation of the efficacy of chemo-immunotherapy sequence; intracranial activity of dabrafenib/trametinib in BRAF-V600E patients with brain metastases; assess the potential correlation between clinical and molecular characteristics and the effectiveness of targeted therapies in BRAF-V600E advanced NSCLC patients; and, finally, the safety profile of dabrafenib/trametinib in BRAF-V600E NSCLC patients.

2.1.2. Statistical analysis

The number and percentage of participants with BRAF-V600 patients receiving anticancer therapies as well as their clinical, pathological, and molecular characteristics, and administered therapies have been summarized either by descriptive statistics or categorical tables. Descriptive analysis has been carried out, including medians, quartiles, and absolute/relative frequencies [with their respective two-sided 95 % confidence intervals (CIs) limits, where relevant], according to the specific variables. The Mann-Whitney test was used for intergroup comparisons of two independent samples while chi square or Fisher’s tests were used for categorical values. Radiological evaluation of treatment efficacy by computed tomography scan was carried out, as per clinical practice, every 12 weeks of therapy, and thereafter until disease progression. ORR is defined as the proportion of participants who have a best overall response of either complete response (CR) and partial responses (PRs) as assessed by the investigator’s review according to RECIST 1.1. PFS is defined as the time from the date of treatment starting until either disease progression, as assessed by the investigator’s review according to RECIST v1.1 criteria, or death due to any cause, whichever occurs first. Progression-free survival 2 (PFS2) was defined as the time from 2nd line treatment start to second disease progression or death. OS is defined as the time from the date of treatment starting to death due to any cause. The non-parametric Kaplan-Meier method was used to estimate the survival curves. Medians and two-sided 95 % CIs have been calculated, with the use of the log-rank test for comparisons and a P value < 0.05 set as the threshold for statistical significance. In these analyses, patients were considered as censored observations in case the event of interest (e.g. death or disease progression) did not occur as long as the patient was under observation, while patients were

counted as failures in case the event of interest occurred. Univariate and multivariable analyses were carried out using the Cox proportional hazards and logistic regression models. Adverse events have been reported and graded in severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The number of months of treatment have been investigated by summarizing the number of months from the first dose of study drug to the last dose of study drug. The number of patients with at least one dose reduction or interruption have been summarized with frequencies and percentages reported. The statistical analysis was carried out by using SPSS Statistics software version 20 (IBM, Armonk, NY).

3. Results

3.1. Clinical characteristics

From 2019–2023 a total of 244 NSCLC patients harboring a BRAF mutation diagnosed in 18 Italian centers were enrolled, including 70 % V600E mutations, 27.5 % non-V600E mutations (G466A, G469A, G464A, D549G, K601E, and others) and 2.5 % non-otherwise specified BRAF mutations. Clinic-pathological and molecular characteristics of BRAF-V600 mutated patients are reported in Table 1. Among the 238 BRAF mutated patients, median age was 70 years (range 42–88 years). The majority of patients were male (58.4 %), former or never smokers (60 %) with an ECOG PS < 2 (80 %). The most frequent histological subtype was adenocarcinoma (90 %) and PD-L1 expression was less than 50 % in 81 % of cases. The percentage of patients with brain metastases was 11.8 %.

3.2. Dabrafenib/Trametinib (D/T) activity in BRAF V600E mutants

Among BRAF-V600E patients, D/T was used as 1st line therapy in 74.9 % (128/171) and as 2nd line therapy in 7 % (12/171) of patients respectively. ORR and DCR were 60.1 % (77/128) and 75.8 % (97/128). Median PFS of first line D/T was 19.8 months (95 % CI: 10.7–29.0), with a 2 and 3-year OS rate of 65.4 % and 61 %, respectively. Analyzing clinically relevant subgroups of patients, we evaluated D/T activity across different gender and smoking history statuses. In respect to sex, median PFS was shorter in males than females (13.6 months and 25.3 months, respectively, $p = 0.13$), with a 2-year OS rate of 54.8 % and 77.5 %, respectively, ($p = 0.11$). Furthermore, a differential effect of smoking status was observed on D/T activity, as median PFS was 18.4 months, 25.6 months, and 24 months in never, former and current smokers, respectively ($p = 0.67$). The 2-year OS rate was 61.4 %, 76.5 % and 59.2 % in never, former and current smoker, respectively ($p = 0.28$). No difference in outcomes was observed for patients with negative/low (PD-L1 TPS 0 % and 1–49 %) or strong expression (PD-L1 ≥ 50 %) both in terms of PFS ($p = 0.99$) and OS ($p = 0.80$) (Suppl. Table 1 and Suppl. Table 2).

Among BRAF-V600E patients, non-targeted 1st line treatment was used in 15.7 % of the cases with a median PFS of 13.6 months (95 % CI: 3.9–23.3) and 2-year OS of 91.4 % (Fig. 1 A-B). Immuno-monotherapy was used in 9.4 % (16/171) of the patients with a median PFS of 10 months (4.4–15.6), platinum-based therapy or chemo-immunotherapy were used in 3.5 % (6/171) and 1.8 % (3/171) of patients with a median PFS of 41.3 (0–89.7) months and 10.4 (N.E.) months respectively (Suppl. Table 3).

The differences in terms of PFS and OS between D/T and other therapies did not reach statistical significance: HR for PFS: 0.81 (95 % CI: 0.45–1.45), $p = 0.47$; HR for OS: 2.65 (95 % CI: 0.91–7.68) $p = 0.073$.

The multivariate Cox regression analysis confirmed that male sex is associated with shorter survival with HR 2.47(CI:1.13–5.40) (Table 2, Suppl. Tab. 3 and Suppl. Tab. 4).

We further explored the activity of the D/T combination among the subgroup of patients with brain metastases (11.8 % of the cases). 1st line

Table 1
Clinical-pathological and molecular characteristics of BRAF-mutant patients included in the study. Abbreviations: IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed death ligand 1; TPS, tumor proportion score. P-values are calculated with the Mann-Whitney test for age and chi-square for the remaining items, missing values were not considered.

	V600E (n = 171)	Other (n = 67)	Total (n = 238)	P values
Age in years (median, IQR)	70 (62–76)	71 (65–77)	70 (63–76)	0.27
GenderMaleFemale	92 (53.8)79 (46.2)	47 (70.1)20 (29.9)	139 (58.4)99 (41.6)	0.021
ECOG PS012Missing	75 (43.8)67 (39.2)16 (9.4)	20 (29.9)29 (43.3)9 (13.4)	95 (39.9)96 (40.3)25 (10.5)22 (9.3)	0.20
HistologyAdenocarcinomaSquamous cell carcinomaOtherMissing	158 (92.4)07 (4.1)6 (3.5)	58 (86.6)3 (4.5)3 (4.5)	216 (90.8)3 (1.3)10 (4.2)9 (3.8)	0.13
Smoking historyNever smokerCurrent smokerFormer smokerMissing	55 (32.2)43 (25.1)58 (33.9)15 (8.8)	10 (14.9)24 (35.8)22 (32.8)11 (16.4)	65 (27.3)67 (28.2)80 (33.6)26 (10.9)	0.028
PD-L1 TPS0 %1–49 %≥ 50 %Missing	28 (16.4)59 (34.5)69 (40.4)15 (8.8)	18 (26.9)25 (37.3)18 (26.9)6 (8.9)	46 (19.3)84 (35.3)87 (36.6)21 (8.8)	0.072
Co-alteration* KRAS EGFR ALK ROS1 HER2 MET	1 (0.6)3 (1.8)1 (0.6)2 (1.2)	6 (9.0)3 (4.5)001 (1.5)30 (44.7)	7 (2.9)6 (2.5)1 (0.4)2 (0.8)1 (0.4)105(44.1)	0.00050.23———0.59
Metastatic site Liver Bone Brain	20 (11.7)40 (23.4)20 (11.7)	9 (13.4)14 (20.9)14 (20.9)	29 (12.2)54 (22.7)34 (14.3)	0.710.680.07
Dabrafenib/Trametinib line First Second Third	128(74.8)12(7.0)2(1.2)	7(10.4)4(6.0)0	135(56.7)16(6.7)2(0.8)	0.008

*These alterations did not include driver alterations (i.e. KRAS G12C, ALK rearrangements, etc.), which were excluded from this study.

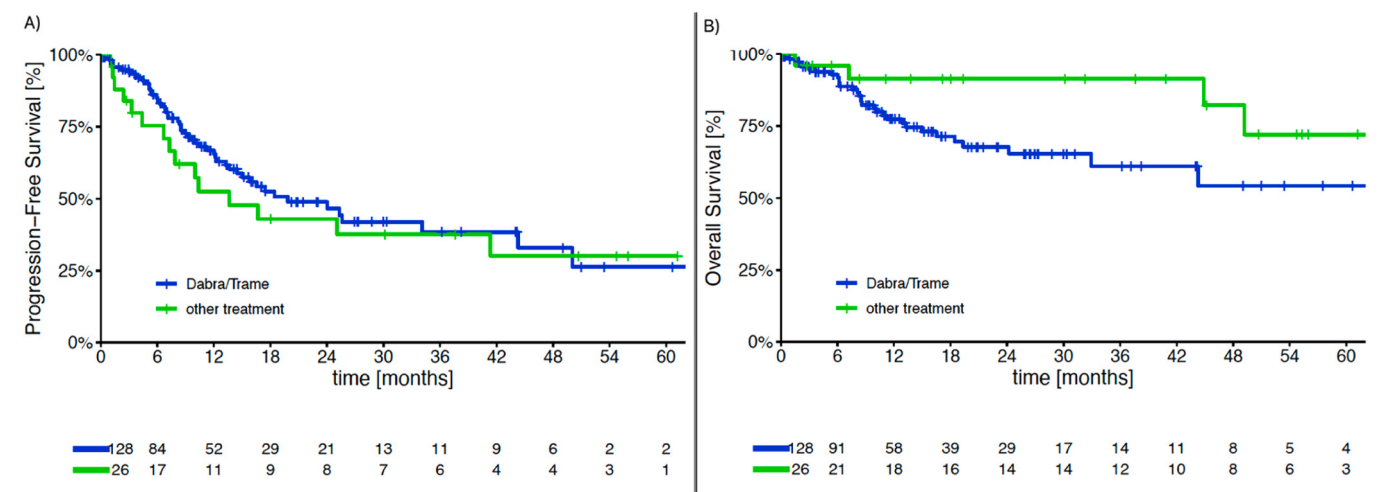


Fig. 1. Progression-free survival (A) and overall survival (B) in BRAF V600E mutants with 1st line dabrafenib/trametinib or other systemic therapies.

Table 2
Multivariable Cox regression analysis for progression-free survival (PFS) and overall survival (OS) and correlation with Sex, Smoking history and Therapy (full data for 139 patients).

	PFSHR (95 % CI)	OSHR (95 % CI)
GenderMaleFemale	1.97 (1.09–3.56) Ref.	2.47 (1.13–5.40) Ref.
Smoking historyNever smokerCurrent smokerFormer smoker	Ref.0.87 (0.46–1.64) 0.45 (0.22–0.90)	Ref.0.74 (0.32–1.71) 0.34 (0.13–0.86)
TherapyDabrafenib/trametinibOther	0.75 (0.41–1.39)Ref.	2.30 (0.78–6.78)Ref.

D/T was associated with 9.2 months median PFS (95 % CI: 0.8–17.6) and 2-year OS rate of 49.5 %. Intracranial overall response rate (IC-ORR) was 33.3 % (13.3 % complete response, 20 % partial response) and an equal ORR and DCR of 66.7 %.

Among 12 patients treated with D/T in 2nd line setting, median PFS was not reached, with a 1-year PFS rate of 71.3 % as compared with a median of 6.6 months and a PFS rate at 1-year of 40.9 % with other treatments. ORR for D/T treated was 58.3 % (7/12) and DCR 91.7 % (11/12). The 2-year OS rates were 100 % with D/T (n = 12) and 45.0 % with other treatments (n = 33), respectively.

Among patients harboring a BRAF V600E mutation who had

received D/T as first line, median PFS2 was 6.6 months (95 % CI: 0–14.3). More in detail the subsequent use of chemotherapy + /- immunotherapy or immunotherapy as single agent was associated with a median PFS of 6.1 months (95 % CI: 0.7–11.5) and 6.6 months (95 % CI: 2.1–11.2), respectively and a 2-year OS rate of 46.5 % and 44.4 %, respectively (Suppl. Fig. 1 A-B). No differences were seen between chemo-immunotherapy or immunotherapy alone as 2nd line: HR for PFS 0.96 (95 % CI: 0.32–2.81) p = 0.93.

Dabrafenib/Trametinib (D/T) activity in BRAF non-V600E mutants

Among BRAF-non V600E patients of class I, D/T was used as 1st line therapy in 10.4 % (7/67) and as 2nd line therapy in 5.9 % (4/67) of patients respectively. ORR was 14.3 % (1/7) and DCR was 71.4 % (5/7). Median PFS of first line D/T was 10.6 months (95 % CI: NE-NE), with a 2 and 3-year OS rate of 67.3 % and 57.7 %, respectively.

In this subgroup 1st line chemo-immunotherapy, immunotherapy as single agent or chemotherapy alone was used in 11 (16.4 %), 12 (17.9 %) and 11 (16.4 %) patients with a median PFS of 12, 37.5, and 9 months, respectively. Chemo-immunotherapy or immunotherapy were not associated with a statistically significant difference in terms of PFS, albeit a trend towards a benefit from immunotherapy alone was seen (HR 0.38, 95 % CI: 0.13–1.14), p = 0.085 (Suppl. Fig. 2).

A minor proportion of patients with strong PD-L1 expression (TPS ≥50 %) and concomitant BRAF V600E (n = 6) or non-V600E (n = 7) mutations receive first line immunotherapy (n = 13) with numerically

higher response rates in the latter subgroup of patients (4/5 patients with a PR, 1 SD, and 2 nonvaluable patients for response in non-V600E subgroup as compared with 3/6 PR, 2 SD, and 1 PD in the V600E subgroup).

3.3. Dabrafenib/Trametinib (D/T) activity and de novo MET amplification

An exploratory analysis was conducted to evaluate the impact of concomitant *MET* amplification, which was evaluated in 60 % (103/171) of V600E patients with 1st line treatment (D/T or non-targeted therapies). Concomitant *MET* amplification was associated with similar ORR rates (63.7 % vs. 54.3 % among *MET* amplified and not amplified patients) a numerically shorter PFS, but the difference did not reach statistical significance ($p = 0.054$), HR 1.87 (95 % CI: 0.99–3.54). Among patients treated with D/T as 1st line, *MET* amplification was associated with similar ORR rates (60.9 % vs. 61.4 % among *MET* amplified and not amplified patients), median PFS was 13.6 months (CI 95 %, 7.9–19.3) vs. 44.3 months (CI 95 %, 2.6–86.0) with ($n = 23$ patients) and without a concomitant *MET* amplification ($n = 57$ patients), respectively, with HR 1.73 (95 % CI: 0.84–3.56) ($p = 0.14$) (Fig. 2).

3.4. Safety of Dabrafenib/Trametinib (D/T) in BRAF V600E mutants

The incidence of treatment-related toxicities was summarized in Table 3.

Any-grade TRAEs with D/T inhibitors were reported in 39.4 % of cases (56 patients out of 142), with only 11 % of patients having grade 3 or higher toxicities. The most frequently reported toxicity was pyrexia in 20.4 % (29 patients) with grade 3 in only 2 pts, gastrointestinal toxicity in 5.6 % (8 pts) in and arthralgia in 4.9 % (7 patients). TRAEs led to a dose reduction in 19 (13.3 %) of the patients and to permanent discontinuation in 4 patients (2.8 %). Major causes of drug interruptions, reduction or discontinuation are summarized in Table 4.

4. Discussion

To date, this is one of the largest real-world studies evaluating the role of dabrafenib/trametinib and other therapies in *BRAF* V600E mutant metastatic NSCLC. Herein, we confirmed in a real-world setting the activity of this combination in this small but clinically relevant subgroup of patients, reporting a median PFS of 19.8 months (95 % CI: 10.3–29.3), with a 2-year OS rate of 64.9 % in the first line setting and a

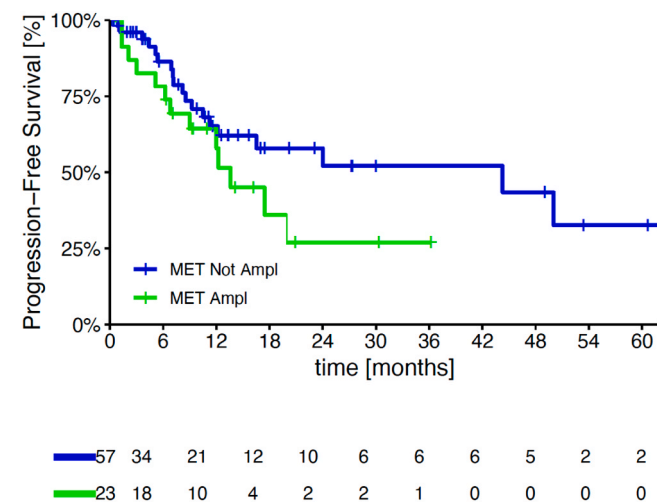


Fig. 2. Kaplan-Meier progression-free survival (PFS) curves in patients harboring *BRAF* V600E mutation with or without concomitant *MET* amplification and treated with first line dabrafenib/trametinib.

Table 3

Safety of Dabrafenib/Trametinib in *BRAF* V600E mutants.

Overview of AEs, n (%)					
	G1	G2	G3	G4	G5
Pyrexia	16 (11.4 %)	11 (7.9 %)	2 (1.4 %)		
Diarrhea	2 (1.4 %)	2 (1.4 %)			
Nausea/vomiting	3 (2.1 %)	1 (0.7 %)			
Interstitial pneumonia		1 (0.7 %)	1 (0.7 %)		
Staphylococcus hominis infection				1 (0.7 %)	
Sepsis					1 (0.7 %)
Encephalopathy			1 (0.7 %)		
Mucositis	1 (0.7 %)		1 (0.7 %)		
Rash	2 (1.4 %)	2 (1.4 %)	2 (1.4 %)		
Asthenia	8 (5.7 %)	1 (0.7 %)			
Arthralgia	6 (4.3 %)	1 (0.7 %)			
CPK increase		2 (1.4 %)	2 (1.4 %)		
Cardiotoxicity	1 (0.7 %)	1 (0.7 %)	3 (2.1 %)		
Liver toxicity	1 (0.7 %)		1 (0.7 %)		
Neutropenia		2 (1.4 %)		1 (0.7 %)	

Table 4

Dose adjustments and modifications with D/T.

Summary of dose adjustments and modifications, n (%)	
AEs leading to dose interruption	16 (11.2 %)
Major causes for dose interruptions:	
• Pyrexia, 7	
• Hepatotoxicity, 1	
• CPK increase, 1	
• Neutropenia, 1	
• Other causes, 4	
AEs leading to dose reduction	17 (12 %)
Major causes for dose reduction:	
• Pyrexia, 10	
• Hepatotoxicity, 2	
• CPK increase, 3	
• Neutropenia, 1	
• Skin rash, 1	
AEs leading to treatment discontinuation	4 (2.8 %)
Major causes for definitive discontinuation:	
• Cardiotoxicity, 3	
• Encephalopathy, 1	

median PFS not reached with a 1-year PFS rate of 69.3 % in the 2nd line setting. These results compared favorably with those of the single arm phase II registrative trial [4–6] and other real-world analyses [11–14] reported to date.

BRAF mutations are predominantly found in adenocarcinomas, but the association with treatment outcomes and specific clinic-pathological characteristics such as gender and smoking status and/or poor prognostic value is not clearly defined with conflicting results between studies [15–19]. In the present analysis an association between gender and *BRAF* mutation type was observed, with *BRAF* non-V600E mutations more frequently seen in male patients and *BRAF* V600E in female patients ($p = 0.028$, Tab. 1). These results are in line with previous findings reporting an association between non-V600E mutations and smoking history [20]. Previous studies reported a potential association

between gender and BRAF/MEK inhibitors activity. For instance, in patients with melanoma, response to BRAF and MEK inhibitors has been shown to vary according to sex, with women deriving more benefit from targeted therapies than men [21]. Initial studies with D/T in NSCLC patients did not identify any association between outcomes and gender or smoking history [6,11]. More recently, an association between female sex and improved outcomes with D/T was reported [34]. These data are line with our study, as female patients seem to derive higher benefit with this combination. Furthermore, the PHAROS trial reported lower ORR for treatment-naïve current smokers as compared with former or never smokers, but such differences were not observed in pretreated patients [8]. Reasons supporting this observation are unclear and might be partially explained by the smoking interference in binimetinib metabolism, inducing CYP1A2 isoform, with subsequent reduction in plasma concentration [22,23]. Furthermore, patients with history of smoking have often tumors harboring a higher rate of co-mutations that could reduce targeted therapy efficacy [24], including D/T activity [20,25].

MET amplification is a known mechanism of acquired resistance to several tyrosine kinase inhibitors in NSCLC, including D/T [26]. Pre-treatment *MET* amplification has been associated with poor prognosis in NSCLC and concomitant presence of *MET* amplification with other oncogene drivers is a poor predictive factor in patients treated with targeted therapies [27,28]. In our population, a concomitant presence of *MET* amplification was detected in 42 % (65/154) of patients harboring *BRAF* V600E mutations treated with D/T as 1st line therapy. For this subgroup of patients, the median PFS was 13.6 months (CI 95 %, 7.9–19.3) for those with *MET* amplification (*n* = 23 patients) and 44.3 months (CI 95 %, 2.6–86.0) for those without (*n* = 57 patients), although this difference did not reach the statistical significance, likely due to the small sample size (*p* = 0.054). This is the first report demonstrating the poor prognostic role of de novo *MET* amplification in *BRAF* V600E mutant NSCLCs treated with D/T. This data is limited by the small sample size and *MET* amplification was not centralized, which might introduce some discrepancies in the definition of positive cases. Given the relatively paucity of patients included, this analysis should be considered only exploratory and further studies will better define the optimal therapeutic strategy in these patients.

An indirect comparison using real-world cohorts from a deidentified real-world database showed that, for patients with *BRAF*-mutated advanced NSCLC, the risk of death was lower, and median OS was longer with first-line D/T versus platinum-based chemotherapy. However, inconclusive data were reported for single agent immunotherapy or chemo-immunotherapy, due to small sample size [29]. The role of immunotherapy-based therapies in *BRAF* mutant NSCLC has been evaluated in some retrospective studies, producing conflicting results. These studies were limited by small sample size and significant heterogeneity among the patients included (*BRAF* V600E vs. non-V600E, treatment-naïve vs. pretreated) and/or therapies considered (single agent immunotherapy with or without chemotherapy). Taken together, these studies suggest that single agent immunotherapy is somewhat effective in *BRAF* mutant NSCLCs (ORRs ranging from 9.1 % to 43 % with median PFS of 1.8–10.8 months) [13], with some potential differences between V600E and non-V600E mutations and according to smoking status [13,30]. As a significant proportion of *BRAF* V600E mutants (42–48 %) co-express high PD-L1 (TPS $\geq$ 50 %) [13,31], it remains unclear whether these patients would benefit more from single agent immunotherapy as first line therapy rather than targeted therapy. This is an important topic of discussion especially in European countries, including Italy, as only single agent immunotherapy is permitted in PD-L1 strong expressors. However, there is very limited data available in this setting, mostly from small retrospective analyses, which suggest that immune checkpoint blockade has some activity (ORR 36 %, median PFS 5.3 months) [13]. Similarly, in our study single agent immunotherapy is associated with some clinical activity, with higher ORRs in non-V600E mutations (4/5 patients with a PR, 1 SD, and 2 non valuable patients for response) as compared with V600E mutations (3/6 PR, 2 SD, and 1

PD), but no firm conclusions can be made, given the limited number of patients with strong PD-L1 expression (TPS $\geq$ 50 %) treated with 1st line pembrolizumab (*n* = 13). The efficacy of chemo-immunotherapy has been evaluated in *BRAF*-mutant NSCLCs in some recent retrospective studies, reporting ORRs ranging from 40.7 % to 58.8 % and a median PFS of 9–17.5 months [32,33]. These data should be interpreted with caution given the high heterogeneity of patients included (V600E with or without non-V600E mutations), the retrospective nature of these studies and the small numbers of cases evaluated. A recent retrospective study reported no OS differences between *BRAF* mutant patients receiving D/T or (chemo)-IO (28.0 vs. 27.8 months, HR 1.1 [CI 0.7 – 1.73], *p* = 0.68), albeit a trend towards superior OS in patients receiving chemo-IO (median OS mono-IO 21.0 months, D/T 28.0 months, chemo-IO 31.8 months, overall *p* = 0.4). However, in this study no PFS or PFS2 data were reported, limiting the interpretation of these results [34]. More recently, the FRONT-BRAF retrospective multicenter study reported that immune checkpoint inhibitors with or without chemotherapy were associated with improved OS compared with *BRAF*/MEK inhibitors (40.9 months vs 25.2 months, HR 0.69, *p* = 0.039), in particular in patients with a history of smoking (HR 0.60, *p* = 0.013), with a PD-L1 TPS $\geq$ 1 % (HR 0.66, *p* = 0.039), elderly (HR in patients $\geq$ 70 years old 0.54, *p* = 0.029), with TP53 co-mutations (HR 0.46, *p* = 0.0048), and without brain metastases (HR 0.66, *p* = 0.045). In contrast, *BRAF*/MEK inhibitors led to a higher ORR, whereas PFS was similar between the two treatments [35]. These results are in line with our present analysis, showing a higher ORR as well as a trend towards longer PFS and shorter OS for D/T as compared with other therapies (Figure 1), although these differences did not reach statistical significance. Considering potential bias related to retrospective analysis and small sample size, these data should be cautiously interpreted, supporting a further investigation of the optimal sequential approach for *BRAF* V600 mutant NSCLCs between targeted therapy and IO/chemo-IO.

Brain metastases occur in a significant proportion of NSCLC at diagnosis (~10 %) and the incidence increases up to 20–40 % over the disease course [36]. The incidence of brain metastases in *BRAF* mutant NSCLCs is unclear, albeit some reports suggest a higher frequency among class II and III as compared with class I mutations [2]. Efficacy data of novel agents in this subgroup of patients are often limited, as most clinical trials exclude patients with brain metastases, including the registrative phase 2 trial of D/T, which enrolled only stable treated brain metastases or asymptomatic small brain metastases [4,5]. However, the results from the phase 2 COMBI-MB trial, showing activity of D/T in patients with *BRAF* V600-mutant melanoma with brain metastases might support further exploration of this combination in patients with *BRAF* V600-mutant NSCLC with brain metastases [37]. Similarly, in the PHAROS study untreated symptomatic brain metastasis, or leptomeningeal disease were excluded. Patients with untreated small brain metastases (<5 mm) and previously treated brain metastases were eligible if they were asymptomatic and had stable intracranial disease for $\geq$ 28 days before the first dose of study treatment. Therefore, only 8 % of the enrolled patients had baseline brain metastases [8]. In this study, E/B showed some intracranial activity in four of eight patients with baseline brain metastases (all four of the treatment-naïve patients and none of the previously treated patients had an objective response), but data on intracranial response rate was not reported.

In our study, 11.8 % of *BRAF* V600E mutant NSCLCs had baseline brain metastases, a reported incidence in line with previous studies [2]. D/T showed some intracranial activity (intracranial response rate of 33.3 %, including 13.3 % of complete responses) in this real-world population with 9.2 months median PFS (95 % CI: 0.8–17.6) and 2-year OS rate of 49.5 % in the upfront setting. These data should be interpreted with caution due to the small number of patients included but suggest a certain intracranial activity for D/T in *BRAF* V600E mutant NSCLCs with brain metastases. No patient had received E/B, as this combination was not reimbursed in Italy at the time of study conduction,

and data on previous loco-regional therapies received were not always available due to the retrospective nature of the study. Further studies in this setting are awaited to better elucidate the optimal sequence of targeted therapies and loco-regional treatments.

Another important data emerging from our study is the activity of D/T in patients harboring non-V600E mutations of class I, with a median PFS of 10.6 months (95 % CI: NE) and a 2 and 3-year OS rate of 67.3 % and 57.7 %, respectively. These data, albeit limited by the small sample size (n = 7), suggest that this relatively uncommon, but clinically relevant, subgroup of *BRAF* mutants might benefit from a targeted approach, expanding the use of this combination beyond the V600E population included in the pivotal trial.

Safety results are in line with those of the registrative trials [4–6] and previous retrospective studies [11,12,29]. Interestingly, the reported grade 3 pyrexia is less than 11 % reported in the pivotal trial, reflecting the implementation prophylactic medications and novel management algorithms for this AE [38].

The present study has some limitations, including the retrospective nature of this analysis. Furthermore, some patient cohorts are relatively small, despite the large sample size of the study due to the relative low frequency of *BRAF* mutations in NSCLC, limiting the interpretation of the results of some subgroup analyses, which might introduce statistical biases due to unbalanced distribution of favorable prognostic features and/or differential treatment adherence or supportive care measures. In addition, all the patients receiving targeted therapies were treated with D/T and no patients underwent E/B treatment, reflecting the approval of these agents in Italy at the time of study conduction.

Despite these limitations, the present study provides a comprehensive picture of *BRAF* mutant NSCLCs and the role of D/T in *BRAF* V600E mutations, including clinically relevant subgroups of patients, such as those with brain metastases or with co-expression of other genomic events, which are often underexplored in clinical trials. These data further support the clinical activity of D/T in clinical practice, expanding the findings of previous prospective and retrospective studies in this setting, drawing from a large real-world database.

5. Conclusions

In this large, multicenter study we confirm the efficacy of D/T in patients with *BRAF* V600E mutant NSCLC in a real-world setting. This combination was associated with a sustained activity in treatment-naïve patients, including those with brain metastases. Albeit a trend toward OS improvement, however, the clinical impact of immunotherapy with or without chemotherapy in *BRAF*-mutants as first or subsequent line across different PD-L1 levels and molecular subgroups remains to be defined in the context of randomized studies. Furthermore, future studies will address some pending questions, such as the optimal therapeutic strategy in *BRAF* V600E mutants with concomitant genomic aberrations, (e.g., *de novo* *MET* amplification), or in *BRAF* class II and III mutations, the mechanisms of acquired resistance to *BRAF*/MEK inhibitors in NSCLC and the potential strategies to overcome them.

CRediT authorship contribution statement

Tiziana Vavalà: Validation, Supervision. **Salvatore Grisanti:** Validation, Supervision. **Stefania Gori:** Validation, Supervision. **Pierluigi Piovano:** Validation, Supervision. **Carlo Genova:** Validation, Supervision. **Marcello Tiseo:** Validation, Supervision. **Vieri Scotti:** Visualization, Validation. **Emilio Bria:** Validation, Supervision. **Rita Chiari:** Validation, Supervision. **Fabrizio Citarella:** Visualization, Validation. **D'aveni Alessandro:** Validation, Supervision. **Reale Maria lucia:** Validation, Supervision. **Giulia Pasello:** Visualization. **Veccia Antonella:** Validation, Supervision. **Paolo Pedrazzoli:** Validation, Supervision. **Lorenzo Antonuzzo:** Validation, Supervision. **Giulia Meoni:** Validation, Supervision. **Concetta Sergi:** Validation, Supervision. **Francesco Passiglia:** Writing – review & editing, Visualization,

Validation, Supervision, Data curation, Conceptualization. **Editta Baldini:** Visualization, Validation, Supervision, Conceptualization. **Lucia Anna Muscarella:** Validation, Supervision. **Serena Ricciardi:** Visualization, Validation. **Alessandro Russo:** Writing – review & editing, Writing – original draft, Validation, Data curation, Conceptualization. **Diego Cortinovis:** Writing – review & editing, Supervision. **Cinzia Ortega:** Visualization, Validation. **Gabriele Minuti:** Visualization, Validation. **Cristina Zannori:** Visualization, Validation. **Pellizzari Giacomo:** Validation, Supervision. **Lucio Buffoni:** Validation, Supervision. **Lorenzo Calvetti:** Visualization, Validation. **Brigida Stanzione:** Visualization, Validation. **Pamela Pizzutilo:** Visualization, Validation. **novello silvia:** Writing – review & editing, Validation, Supervision, Conceptualization. **Alberto Pavan:** Validation, Supervision. **Signorelli Diego:** Validation, Supervision. **Claudio Sini:** Writing – review & editing, Conceptualization. **Diana Giannarelli:** Visualization, Validation. **Greta Ali:** Visualization, Validation. **Umberto Malapelle:** Visualization, Validation, Supervision, Conceptualization. **Anna Bettini:** Validation, Supervision. **Luca Toschi:** Validation, Supervision. **Hector Soto Parra:** Validation, Supervision. **Elisa Roca:** Visualization, Validation. **Roberta Buosi:** Validation, Supervision. **Sara Pilotto:** Validation, Supervision. **Daniele Pignataro:** Visualization, Validation.

Funding

None.

Declaration of Competing Interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.116191.

References

- [1] Malapelle U, Rossi G, Pisapia P, Barberis M, Buttitta F, Castiglione F, et al. *BRAF* as a positive predictive biomarker: focus on lung cancer and melanoma patients. *Crit Rev Oncol Hematol* 2020;156:103118. <https://doi.org/10.1016/j.critrevonc.2020.103118>.
- [2] Dagogo-Jack I, Martinez P, Yeap BY, Ambrogio C, Ferris LA, Lydon C, et al. Impact of *BRAF* mutation class on disease characteristics and clinical outcomes in *BRAF*-mutant lung cancer. *Clin Cancer Res* 2019;25:158–65. <https://doi.org/10.1158/1078-0432.CCR-18-2062>.
- [3] Tabbò F, Pisano C, Mazieres J, Mezquita L, Nadal E, Planchard D, et al. How far we have come targeting *BRAF*-mutant non-small cell lung cancer (NSCLC). *Cancer Treat Rev* 2022;103:102335. <https://doi.org/10.1016/j.ctrv.2021.102335>.
- [4] Planchard D, Besse B, Groen HJM, Souquet P-J, Quoix E, Baik CS, et al. Dabrafenib plus trametinib in patients with previously treated *BRAF*(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol* 2016;17:984–93. [https://doi.org/10.1016/S1470-2045\(16\)30146-2](https://doi.org/10.1016/S1470-2045(16)30146-2).
- [5] Planchard D, Smit EF, Groen HJM, Mazieres J, Besse B, Helland Å, et al. Dabrafenib plus trametinib in patients with previously untreated *BRAF*(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol* 2017;18:1307–16. [https://doi.org/10.1016/S1470-2045\(17\)30679-4](https://doi.org/10.1016/S1470-2045(17)30679-4).
- [6] Planchard D, Besse B, Groen HJM, Hashemi SMS, Mazieres J, Kim TM, 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* 2022;17:103–15. <https://doi.org/10.1016/j.jtho.2021.08.011>.
- [7] Gouda MA, Subbiah V. Expanding the benefit: dabrafenib/trametinib as tissue-agnostic therapy for *BRAF* V600E-positive adult and pediatric solid tumors. *Am Soc Clin Oncol Educ Book* 2023;(43):e404770. <https://doi.org/10.1200/EDBK.404770>.
- [8] Riely GJ, Smit EF, Ahn M-J, Felip E, Ramalingam SS, Tsao A, et al. Phase II, open-label study of encorafenib plus binimetinib in patients with *BRAF*(V600)-mutant metastatic non-small-cell lung cancer. *J Clin Oncol* 2023;41:3700–11. <https://doi.org/10.1200/JCO.23.00774>.
- [9] Riely GJ, Ahn M-J, Clarke J, Dagogo-Jack I, Felip E, Gelsomino F, 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* 2024;35:S1246–7. <https://doi.org/10.1016/j.annonc.2024.08.2298>.
- [10] Malapelle U, Passiglia F, Pepe F, Pisapia P, Lucia Reale M, Cortinovis D, et al. The biomarkers ATLAS: an audit on 1100 non-small cell lung cancer from an Italian

- knowledge-based database. *Lung Cancer* 2024;191:107787. <https://doi.org/10.1016/j.lungcan.2024.107787>.
- [11] Swaldutz A, Beau-Faller M, Planchard D, Mazieres J, Bayle-Bleuez S, Debieve D, et al. 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. *Lung Cancer* 2025;199:108038. <https://doi.org/10.1016/j.lungcan.2024.108038>.
 - [12] Auliac J-B, Bayle S, Do P, Le Garff G, Roa M, Falchero L, et al. Efficacy of dabrafenib plus trametinib combination in patients with BRAF V600E-mutant NSCLC in real-world setting: GFPC 01-2019. *Cancers (Basel)* 2020;12. <https://doi.org/10.3390/cancers12123608>.
 - [13] Dudnik E, Bar J, Peled N, Bshara E, Kuznetsov T, Cohen AY, et al. Efficacy and safety of BRAF inhibitors with or without MEK inhibitors in BRAF-mutant advanced non-small-cell lung cancer: findings from a real-life cohort. *Clin Lung Cancer* 2019;20:278–286.e1. <https://doi.org/10.1016/j.clcc.2019.03.007>.
 - [14] Horn L, Bauml J, Forde PM, Davis KL, Myall NJ, Sasane M, et al. Real-world treatment patterns and survival of patients with BRAF V600-mutated metastatic non-small cell lung cancer. *Lung Cancer* 2019;128:74–90. <https://doi.org/10.1016/j.lungcan.2018.12.003>.
 - [15] Cardarella S, Ogino A, Nishino M, Butaney M, Shen J, Lydon C, et al. Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. *Clin Cancer Res* 2013;19:4532–40. <https://doi.org/10.1158/1078-0432.CCR-13-0657>.
 - [16] Marchetti A, Felicioni L, Malatesta S, Grazia Sciarrotta M, Guetti L, Chella A, et al. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. *J Clin Oncol* 2011;29:3574–9. <https://doi.org/10.1200/JCO.2011.35.9638>.
 - [17] Barlesi F, Mazieres J, Merlio J-P, Debieve D, Mosser J, Lena H, 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* 2016;387:1415–26. [https://doi.org/10.1016/S0140-6736\(16\)00004-0](https://doi.org/10.1016/S0140-6736(16)00004-0).
 - [18] Paik PK, Arcila ME, Fara M, Sima CS, Miller VA, Kris MG, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. *J Clin Oncol* 2011;29:2046–51. <https://doi.org/10.1200/JCO.2010.33.1280>.
 - [19] Villarruz LC, Socinski MA, Abberbock S, Berry LD, Johnson BE, Kwiatkowski DJ, et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the lung cancer mutation consortium. *Cancer* 2015;121:448–56. <https://doi.org/10.1002/cncr.29042>.
 - [20] Myall NJ, Henry S, Wood D, Neal JW, Han SS, Padma SK, 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* 2019;20:e208–17. <https://doi.org/10.1016/j.clcc.2018.10.003>.
 - [21] Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med* 2019;381:626–36. <https://doi.org/10.1056/NEJMoal904059>.
 - [22] O'Malley M, King AN, Conte M, Ellingrod VL, Ramnath N. Effects of cigarette smoking on metabolism and effectiveness of systemic therapy for lung cancer. *J Thorac Oncol* 2014;9:917–26. <https://doi.org/10.1097/JTO.0000000000000191>.
 - [23] Murayama N, Yamada T, Yamazoe Y. Application of CYP1A2-template system to understand metabolic processes in the safety assessment. *Food Saf* 2022;10: 129–39. <https://doi.org/10.14252/foodsafetyfscj.D-22-00008>.
 - [24] Wang X, Ricciuti B, Nguyen T, Li X, Rabin MS, Awad MM, et al. Association between smoking history and tumor mutation burden in advanced non-small cell lung cancer. *Cancer Res* 2021;81:2566–73. <https://doi.org/10.1158/0008-5472.CAN-20-3991>.
 - [25] Qu J, Shen Q, Li Y, Kalyani FS, Liu L, Zhou J, et al. Clinical characteristics, co-mutations, and treatment outcomes in advanced non-small-cell lung cancer patients with the BRAF-V600E mutation. *Front Oncol* 2022;12:911303. <https://doi.org/10.3389/fonc.2022.911303>.
 - [26] Pluchino M, Testi I, Minari R, Dodi A, Airo G, Mazzaschi G, et al. MET alterations as resistance mechanisms of dabrafenib-trametinib in BRAF p.V600E mutated non-small cell lung cancer patient. *Anticancer Drugs* 2024;35:761–3. <https://doi.org/10.1097/CAD.0000000000001623>.
 - [27] Yin W, Cheng J, Tang Z, Toruner G, Hu S, Guo M, et al. MET amplification (MET/CEP7 Ratio ≥ 1.8) is an independent poor prognostic marker in patients with treatment-naïve non-small-cell lung cancer. *Clin Lung Cancer* 2021;22:e512–8. <https://doi.org/10.1016/j.clcc.2020.11.002>.
 - [28] Yu HA, Suzawa K, Jordan E, Zehir A, Ni A, Kim R, et al. Concurrent alterations in EGFR-mutant lung cancers associated with resistance to EGFR Kinase inhibitors and characterization of MTOR as a mediator of resistance. *Clin Cancer Res* 2018; 24:3108–18. <https://doi.org/10.1158/1078-0432.CCR-17-2961>.
 - [29] Johnson BE, Baik CS, Mazieres J, Groen HJM, Melosky B, Wolf J, 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* 2022;3:100324. <https://doi.org/10.1016/j.jtocrr.2022.100324>.
 - [30] Mazieres J, Drilon A, Lusque A, Mhanna L, Cortot AB, Mezquita L, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol* 2019;30: 1321–8. <https://doi.org/10.1093/annonc/mdz167>.
 - [31] Negrao MV, Skoulidis F, Montesion M, Schulze K, Bara I, Shen V, et al. Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. *J Immunother Cancer* 2021;9. <https://doi.org/10.1136/jitc-2021-002891>.
 - [32] Yamaguchi T, Shimizu J, Matsuzawa R, Watanabe N, Horio Y, Fujiwara Y. Efficacy of chemotherapy plus immune checkpoint inhibitors in patients with non-small cell lung cancer who have rare oncogenic driver mutations: a retrospective analysis. *BMC Cancer* 2024;24:842. <https://doi.org/10.1186/s12885-024-12554-6>.
 - [33] Qin H, Yan H, Chen Y, Xu Q, Huang Z, Jiang W, et al. Clinical outcomes for immune checkpoint inhibitors plus chemotherapy in non-small-cell lung cancer patients with uncommon driver gene alterations. *BMC Cancer* 2024;24:952. <https://doi.org/10.1186/s12885-024-12748-y>.
 - [34] Wiesweg M, Alaffas A, Rasokat A, Saalfeld FC, Rost M, Assmann C, et al. Treatment sequences in BRAF-V600-mutated non-small cell lung cancer: First-line targeted therapy versus first-line (chemo-) immunotherapy. *3 J Thorac Oncol* 2025;S1556-0864(25):00706. <https://doi.org/10.1016/j.jtho.2025.04.016>.
 - [35] Di Federico A, Wang K, Chen MF, Barsouk AA, Pagliaro A, Chen LN, et al. First-line immunotherapy with or without chemotherapy versus BRAF plus MEK inhibitors in BRAFV600E-mutated metastatic non-small-cell lung cancer (FRONT-BRAF): a multicentre, retrospective cohort study. *Lancet Oncol* 2025;26:1357–69. [https://doi.org/10.1016/S1470-2045\(25\)00409-7](https://doi.org/10.1016/S1470-2045(25)00409-7).
 - [36] Tsui DCC, Camidge DR, Rusthoven CG. Managing central nervous system spread of lung cancer: the state of the art. *J Clin Oncol* 2022;40:642–60. <https://doi.org/10.1200/JCO.21.01715>.
 - [37] Davies MA, Saiag P, Robert C, Grob J-J, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol* 2017;18:863–73. [https://doi.org/10.1016/S1470-2045\(17\)30429-1](https://doi.org/10.1016/S1470-2045(17)30429-1).
 - [38] Schadendorf D, Robert C, Dummer R, Flaherty KT, Tawbi HA, Menzies AM, et al. Pyrexia in patients treated with dabrafenib plus trametinib across clinical trials in BRAF-mutant cancers. *Eur J Cancer* 2021;153:234–41. <https://doi.org/10.1016/j.ejca.2021.05.005>.