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Dabrafenib-trametinib in BRAF V600-mutated non-small-cell lung cancer: a single center real world experience

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ABSTRACT

Aim: We retrospectively evaluated the effect of dabrafenib/trametinib combination in patients with BRAF-mutated non-small-cell lung cancer (NSCLC) treated in a single center from 2017 to 2022.

Patients: The response and safety data of 42 patients (27 treated in first-line and 15 as second/subsequent lines) were analyzed.

Results: The objective response was 73.8%, with no differences between patients undergoing first- or second-line. A longer, statistically significant median progression-free survival (PFS) was observed in patients receiving the combination in first-line vs those in the second/subsequent lines (19.9 months [95% CI: 19.7–20] vs 13.1 months [95% CI: 8.6–17.6], respectively; p = 0.012). The median overall survival (OS) was 29.9 months (95% CI: 14.1–45.7) for patients treated with the combination in first-line and 22.4 months (95% CI: 14.6–30.2) for those treated in subsequent lines. The combination was well tolerated

Conclusion: We confirm the efficacy of dabrafenib/trametinib in BRAF-V600-mutated NSCLC.

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KEYWORDS
BRAF mutation; drug combination; efficacy; NSCLC; real life

1. Background

Lung cancer represents one of the most common and malignant neoplasm worldwide. According to the last Global Cancer Statistics, lung cancer is the second cancer in terms of incidence but the first in terms of mortality worldwide [1].

Among all lung cancers, non-small-cell lung cancer (NSCLC) is the most abundant (~85%). The treatment options now available for patients with NSCLC include classical chemotherapy, targeted therapy and immunotherapy [2–5]. From a molecular point of view NSCLC is very heterogeneous with mutations occurring in different tumor suppressors, genes and oncogenes [6,7]. Among the different mutations, alterations in *TP53*, *KRAS*, *STK11* and *Keap1* genes are the most relevant in terms of abundance. Importantly, the discovery of actionable mutations in NSCLC led to the design, testing and approval of specific targeted therapies. The advent, for example, of specific drugs targeting mutated EGFR has changed the outcome of these patients [8]. The same is true for drugs specifically targeting other genomic alterations, like ALK/ROS1 rearrangement [9], up to the recently approved drugs for *KRAS* mutated tumors harboring the specific G12C mutation [10,11].

A small, but significant in terms of absolute number, proportion of patients (roughly 3–5%) with NSCLC have a mutation in *BRAF* gene [7,12,13]. The predominant mutation in the *BRAF* gene is the V600E, that is associated with a strong increase in the kinase activity of the *BRAF* gene product compared with that of the protein encoded by the wild-type gene [14].

Following the development of *BRAF* inhibitors in melanoma in which BRAF mutation is present is approximately 40% of metastatic cases [15], the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib, has been approved for the treatment of NSCLC patients in 2017 following the positive results of a multicenter phase II trial [16].

After approval, few data have been reported on the use of the BRAFi MEKi combination in real-life setting in patients with NSCLC. In this study, we report a single center retrospective analysis of real-life efficacy and safety of the dabrafenib/trametinib combination in patients with NSCLC presenting *BRAF*-V600 mutation.

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2. Materials & methods

This is a single center observational, retrospective study involving patients with advanced NSCLC with *BRAF* V600 (mostly V600E with one patient with V600K and one with V600D) mutation treated with the combination of dabrafenib and trametinib from 2017 to July 2022. Patients could be enrolled only after the expression of a written informed consent; the enrolment could be obtained at any point of the patients' history, even after the end of the treatment with dabrafenib and trametinib. The study was conducted according to the Good Clinical Practice Guidelines and the Declaration of Helsinki. The local Ethics committee (Comitato Etico di Area Vasta Nord Ovest Toscana) approved of the trial design. Dabrafenib plus trametinib therapy was administered in a compassionate-use setting from 2017 till December 2019, when the Italian pharmacy agency (Agenzia Italiana del Farmaco, AIFA) approved them for NSCLC treatment.

The mutational status of *BRAF* was determined by realtime-PCR or by DNA sequencing. RT-PCR was performed using the AmoyDx® *BRAF* V600 Mutations Detection Kit (AmoyDx, Xiamen, China). Each reaction mixture contained 2 μl of 10× BRAF OM (Oligo Mix), 3 μl of 8-methoxypsoralen solution to prevent carry-over contamination and 10 μl of 2× AmoyDx® BRAF V600 reaction solution containing DNA polymerase and buffer with deoxynucleoside triphosphates. The reaction mixture (15 μl) was dispensed into 0.2 ml PCR tubes. Genomic DNA (5 μl) in each sample was added to the reaction mixture tube.

Deep targeted sequencing and data analysis were carried out using Myriapod NGS Data Analysis Software (Diatech Pharmacogenetics, Jesi, AN, Italy) v.5.0.7 (DiaTech Pharmacogenetics). The targeted sequencing libraries were generated using the CE-IVD Myriapod® NGS Cancer panel DNA version 2022/05 (Diatech Pharmacogenetics).

In this retrospective cohort of patients, the efficacy and safety of the treatment dabrafenib/trametinib combination was analyzed. Patients were treated with the standard dosages of dabrafenib and trametinib, as approved by international and national authorities; dose reductions were allowed as in standard clinical practice. The patients were stratified in two groups one in which the treatment was given as first-line and the other receiving the combination as second and subsequent lines of therapy.

In the first-line group, all patients but two received platinum-based chemotherapy, with or without pembrolizumab. Two patients received only palliative care. In the second-line treatment group, all patients but two received only supportive care after progression, while the remaining two received weekly docetaxel and oral vinorelbine.

Demographic, clinical and pathological data (including age, sex, ethnicity, smoking habits, performance status, histology, stage and presence of metastasis) were retrieved for all the patients. In case of continuous variables, the values were expressed as median value and range; in case of categorical values, they were expressed as number of patients having such characteristics and percentage on the entire population. Efficacy was evaluated in term of objective response rate, progression-free survival (PFS) and overall survival (OS). Response was assessed as per standard clinical practice, that is usually after the first three cycles (that is, 3 months of therapy), then assessments were repeated with re-evaluation every 4–6 months. Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) were defined according to Recist Criteria.

The major aim of the study was to compare the PFS and OS in the two groups of patients. PFS and OS were analyzed using Kaplan–Meier curves.

Safety was assessed at each planned clinical visit, that is every month, and were registered according to NCI-CTCAE version 4.0. Statistical analysis was performed for PFS and OS using a Cox regression model.

3. Results

Forty-two patients were included in the analysis. Their demographic, clinical and pathological characteristics are reported in Table 1. Twenty-seven patients received the combination as first-line treatment, while 15 received the drugs as second, or subsequent lines of therapy. The population investigated is quite aged with a median age of 71 years. Half of the patients were current smokers and half were nonsmokers or former smokers. There was a slight predominance of male over female (with a percentage of male of ∼55%) and this prevalence was similar in the patients receiving the combination in first-line or in subsequent lines. The majority of the patients (∼80%) were in advanced stage (stage IV) and 7% of the subjects presented with an ECOG PS of 2 or more. Furthermore, a significant proportion of patients had brain metastasis (14% in the overall population). All but one had stereotactic radiotherapy. The one who did not receive radiotherapy underwent surgical excision of the brain met (pathology confirmed the mutation V600E on the metastasis). All these characteristics are in line with similar studies reported in the literature for advanced metastatic NSCLC [17–19].

The efficacy of the combination in terms of response is reported in Table 2. No differences were observed

Table 1. Characteristics of the patients entering the study.

	Total population	First-line	Subsequent lines
Number of patients	42	27	15
Age median (min-max)	71 (54–92)	69 (54–92)	74 (54–88)
Sex, n (%)			
Female	19 (45.2)	12 (44.4)	7 (46.7)
Male	23 (54.8)	15 (55.6)	8 (53.3)
Smoking history, n (%)			
Never smoked	14 (33.3)	10 (37.1)	4 (26.7)
Former smoker	7 (16.7)	5 (18.5)	2 (13.3)
Current smoker	21 (50)	12 (44.4)	9 (60.0)
Race, n (%)			
White	41(97.6)	26 (96.3)	15 (100)
Other	1 (2.4)	1 (3.7)	0 (0)
ECOG PS, n (%)			
0	13 (31.0)	9 (33.3)	4 (26.7)
1	26 (61.9)	16 (59.3)	10 (66.7)
≥2	3 (7.1)	2 (7.4)	1 (6.6)
Histology, n (%)			
Adenocarcinoma	41 (97.6)	27 (100)	14 (93.3)
Adeno-squamous	1 (2.4)	0 (0)	1 (6.7)
BRAF mutation, n (%)			
V600E	39 (92.8)	27 (100)	12 (80)
V600 non-E	3 (7.2)	0 (0)	3 (20)
PD-L1, n (%)			
<1%	31 (73.8)	20 (74.1)	12 (80)
1–49%	5 (11.9)	3 (11.1)	2 (13.3)
≥50%	6 (14.3)	4 (14.8)	1 (6.7)
Stage at diagnosis, n (%)			
IV	33 (78.6)	21 (77.8)	12 (80)
Other	9 (21.4)	6 (22.2)	3 (20)
Site of metastases, n (%)			
Lung	21 (50)	13 (48.1)	8 (53.3)
Pleura	20 (47.6)	12 (44.4)	8 (53.3)
Bone	19 (45.2)	12 (44.4)	7 (46.7)
Liver	9 (21.4)	4 (14.8)	5 (33.3)
Brain	6 (14.3)	2 (7.4)	4 (26.7)
Previous therapy (median)			2

ECOG PS: Performance status according to the Eastern Cooperative Oncology Group (ECOG); PD-L1: Programmed death 1 ligand.

Table 2. Objective response rate.

	Total population (n = 42)	First-line (n = 27)	Subsequent lines (n = 15)
CR (%)	1 (2.5)	1 (3.7)	0 (0)
PR (%)	30 (71.4)	19 (70.4)	11 (73.3)
SD (%)	8 (19)	5 (18.5)	3 (20)
PD (%)	3 (7.1)	2 (7.4)	1 (6.7)
ORR (CR + PR) (%)	31 (73.8)	20 (74.1)	11 (73.3)
DCR (CR + PR + SD) (%)	39 (92.9)	25 (92.6)	14 (93.3)

CR: Complete response; DCR: Disease control rate; ORR: Overall response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease.

in terms of response between patients receiving the combination as first-line or those at second or subsequent lines. The vast majority of the patients (more than 70%) had a PR. PD was observed in three out of 42 patients. Overall, the disease control rate (DCR, calculated as the sum of CR, PR and SD) was greater than 90% (92.6% in patients receiving the treatment in first-line and 93.3% in the other group). ORR, (overall response rate, CR + PR) was also very high: respectively 73.3 and 74.1% in the first-line group and in the second or subsequent lines group (it is to note that for the six patients with brain metastasis, the ORR was 50% either for patients receiving the treatment in first-line or in subsequent lines).

This translated in a PFS and OS of 18.9 and 29.9 months, respectively, in the total population (Figure 1). When the two groups were analyzed separately, a statistically significant difference ($p = 0.012$) was found, with patients treated in first-line showing a longer PFS, 19.9 months (95% CI: 19.7–20) compared with 13.1 months (95% CI: 8.6–17.6) observed in the groups receiving the treatment in subsequent lines (Figure 2A). The difference between the two groups was maintained for OS with 29.9 months (95% CI: 14.1–45.7) and 22.4 months (95% CI: 14.6–30) for first-line treated patients and second and further lines treated patients, respectively (Figure 2B). However, the trend observed did not reach a statistical significance.

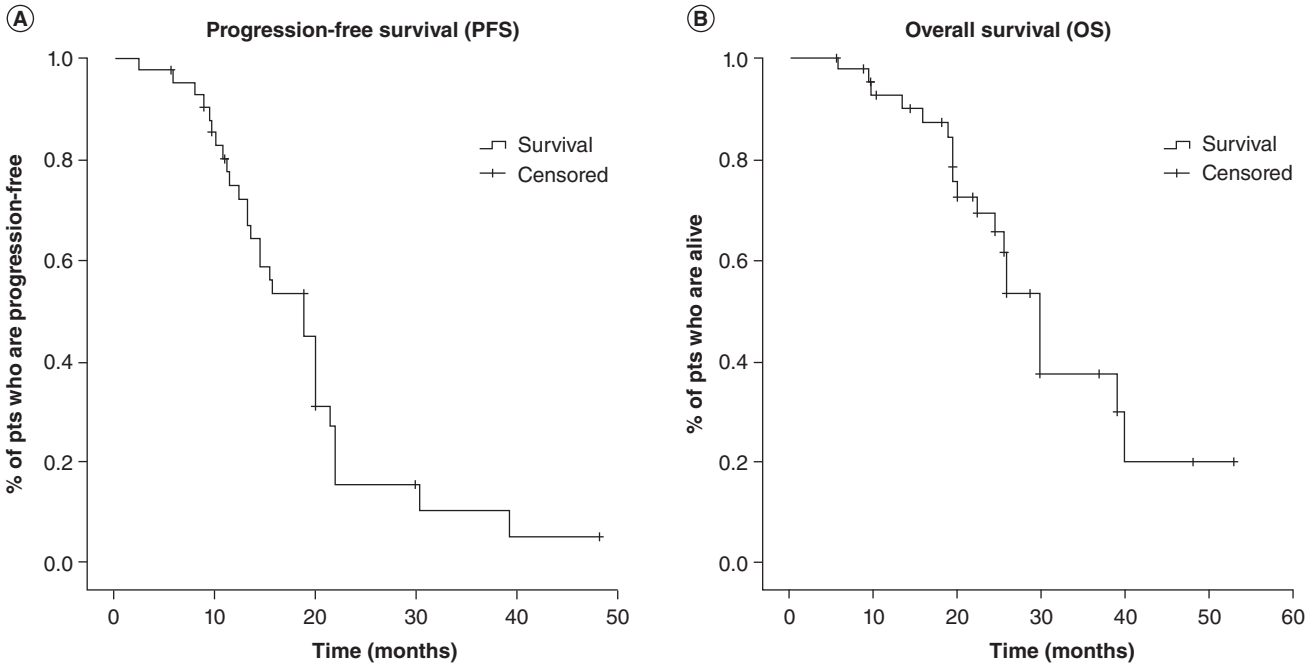

Figure 1. Kaplan–Meier curves in the overall population. **(A)** Reports PFS, **(B)** reports OS.
OS: Overall survival; PFS: Progression-free survival.

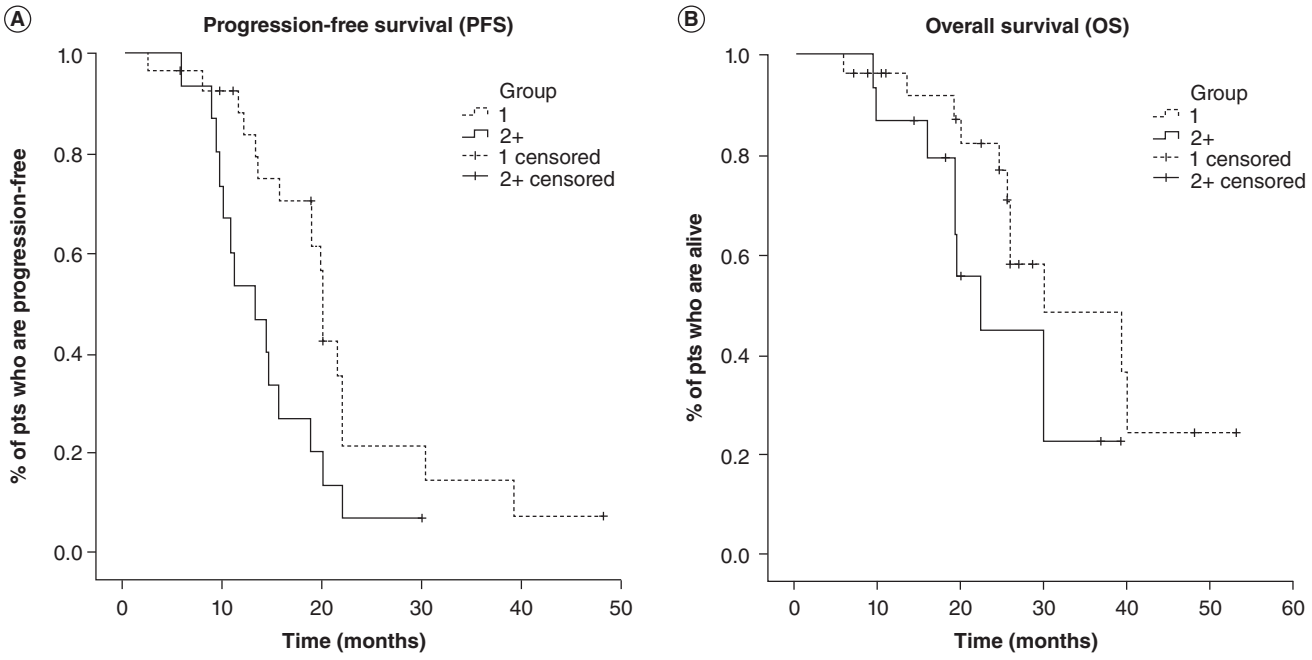

Figure 2. Kaplan–Meier curves **(A)** reporting PFS or **(B)** OS in patients receiving the combination in first-line or is second/subsequent lines.
OS: Overall survival; PFS: Progression-free survival; pts: Patients.

Regarding safety, the treatment was well tolerated (Table 3). Dose reduction was necessary for only two patients, both due to pyrexia. One of these two patients had to stop treatment because the pyrexia did not resolve with dose reduction. Treatment was rescued 24 h after the end of pyrexia.

4. Discussion

The present study aimed at investigating the efficacy and safety of the combination of dabrafenib and trametinib in real-life setting in patients with BRAF V600-mutated NSCLC. This mutation is quite rare in NSCLC accounting

Table 3. Adverse events.

Adverse event	Grade 1–2	Grade 3–4
Pyrexia	20 (47.6%)	2 (4.8%)
Nausea and vomiting	17 (40.5%)	0 (0)
Fatigue	14 (33.5%)	1 (2.4%)
Cutaneous reaction	9 (21.4%)	1 (2.4%)
Myalgia	5 (11.9%)	0 (0)
Anemia	3 (7.1%)	1 (2.4%)
Increased AST/ALT	4 (9.5%)	0 (0)
Interstitial lung disease	0 (0)	1 (2.4%)

AST/ALT: Alanine aminotransferase/aspartate aminotransferase.

for approximately 3–5% of all NSCLC cases. Starting from the approval of the combination of dabrafenib and trametinib in this specific setting, back in 2017, few data have been reported on the outcome of patients treated in real-life setting with this combination. We were able to retrieve 42 patients, treated in our center from 2017 to 2022, with all the clinicopathological data, the outcome and the safety profile available. Overall, the characteristics of the patients analyzed is similar to what reported in other studies. We have a slight prevalence of male (54.8%), in contrast to Marchetti *et al.* [20] who reported a prevalence of woman among patients with NSCLC harboring V600E mutation in *BRAF*, but similar to what reported in other collections, including the phase II registry trial [17,18,21,22]. ECOG-PS, histology and stage were also similar to the characteristics reported for this specific subset of patients. The median age of the population here analyzed was 71 years. For comparison, in the phase II trial [22], the median was 64. Our cohort was therefore relatively old and in addition included roughly 80% of cases as stage IV. Nonetheless the responses observed in this retrospective analysis was superior to what reported in the phase II trial, with an ORR of 73.8% compared with 63.2% in the phase II trial. The ORR remained higher when we consider in our cohort only those receiving the combination in second and subsequent lines (thus comparable to the phase II, mostly conducted in patients as second-line), in which we found an ORR of 73.3%. Interestingly, our data are superimposable to those obtained in the French real-word multicenter cohort, reporting an ORR of 73.8 and 82.9% for patients receiving dabrafenib/trametinib combination in second or subsequent lines and in first-line, respectively [23]. Our data in terms of response indicate no differences between patients receiving the combination in first-line compared with those receiving the treatment in second- and subsequent lines. However, we observed a statistically significant more prolonged PFS in patients treated in first-line compared with those treated in second/subsequent lines (19.9 versus 13.1 months). In the French cohort, PFS was 18.2 and 10.1 months for the same group of patients [23]. The same trend, although not reaches the statistical significance was observed for OS that was 29.4 and 22.4 months for patients treated in first-line and second/subsequent lines, respectively. Since every patient, with the exception of two, had the opportunity to undergo at least two lines of treatment, we believe that comparing overall survival (OS) for patients treated in first or subsequent lines still holds significance.

In terms of safety, dose reduction was necessary for only two patients, both due to pyrexia, an adverse event already reported for this treatment [22,24].

The study has some limitations. Its retrospective design and relatively small sample size could have hampered its statistical power. However, it is to note that even with these limitations we could detect a statistically significant difference in PFS between patients receiving the combination in first-line compared with those receiving the treatment in subsequent lines. Properly designed, prospective studies could potentially highlight differences also in the response rate. It is, however, to note that the results of this study have been obtained in a single center in a real-life setting and this counterbalances its retrospective nature and confirms feasibility and activity of the combination in this specific setting.

5. Conclusion

In conclusion, our data not only support the use of the combination of dabrafenib and trametinib in first-line in patients with advanced, metastatic NSCLC with V600 mutated *BRAF*, but clearly show the feasibility of this regimen in elder patients.

Summary points

- First-line treatment of dabrafenib and trametinib is effective in non-small-cell lung cancer patients with V600 BRAF mutation.
- A longer, statistically significant median progression-free survival was found in patients receiving the combination in first-line versus those in the second/subsequent lines.
- The efficacy is confirmed in real-world setting from a single center.
- More than 70% of the patients reached a partial response.
- The combination is safe with dose reduction necessary only in two patients for pyrexia.
- The treatment is feasible in elder patients.

Author contributions

A Sbrana: conceptualization, data curation, writing – original draft, visualization. S Cappelli: data curation, writing – review & editing. I Petrini: data curation, writing – review & editing. L Bernardini: data curation, visualization, writing – review & editing. V Massa: data curation, visualization, writing – review & editing. L Carrozzi: data curation, visualization, writing – review & editing. A Chella: conceptualization, methodology, writing – review & editing and supervision.

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

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Ethical conduct of Research

Patients could be enrolled only after the expression of a written informed consent; the enrolment could be obtained at any point of the patients' history, even after the end of the treatment with dabrafenib and trametinib. The study was conducted according to the Good Clinical Practice Guidelines and the Declaration of Helsinki. The local Ethics committee (Comitato Etico di Area Vasta Nord Ovest Toscana) approved of the trial design.

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