

Efficacy and Safety profile of combined regimen of dabrafenib and trametinib in Lung Cancer patients with BRAF mutation

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Abstract: Introduction: In China, adenocarcinomas and BRAF mutations are both features of non-small cell lung cancer. In particular, targeted medicines have improved outcomes for women who have BRAF V600E mutations and who do not smoke. Due to the wide variety of BRAF mutations and fusion partners, sophisticated mutation detection approaches are required. When compared to conventional chemotherapy, immunotherapy and BRAF inhibitors are preferable.

Aims and objectives: The objective of this study is to assess the effectiveness and safety of the combined treatment of dabrafenib and trametinib in individuals diagnosed with lung cancer and harbouring a BRAF mutation.

Method: This multi-centre retrospective research at our hospital examined the clinical features and outcomes of dabrafenib and trametinib-treated advanced NSCLC patients with the BRAF V600E mutation. PFS and OS were the main trial objectives, along with patient demographics and safety. This academic study covered consecutive adult NSCLC patients and was not industry-funded. Dabrafenib and trametinib's efficacy and safety in various NSCLC treatment scenarios are supported by the study's dedication to data integrity by not imputing missing data.

Result: Table 1 shows demographics for 60 advanced cancer patients, divided into "1st Line" (n = 9) and "2nd Line" (n = 51) categories. Significant age and smoking status variations exist between the groups. Figures 1 and 2 show therapy effectiveness over time using median progression-free survival percentages. Figure 3 shows cumulative progression-free survival probabilities at various intervals to analyse disease progression and survival trends.

Conclusion: This real-world trial confirms dabrafenib plus trametinib's efficacy and safety for BRAF V600E-mutant NSCLC patients, both treated and untreated. Limitations like retrospective design and selection bias need prospective investigations.

Keywords: BRAF mutations, lung cancer, chemotherapy, immunotherapy.

Introduction

Lung cancer accounted for the majority It was the most prevalent form of

cancer diagnosed throughout China at the time of cancer-related deaths. There are two types of lung cancer: non-small cell lung cancer, or NSCLC, and small cell lung cancer (SCLC). Of the two, adenocarcinomas are responsible for around 60% of NSCLC cases. In general, Driver roughly 80% of all lung adenocarcinomas among East Asians have mutations ^[1]. Earlier in the decades, targeted medicines have significantly changed how NSCLC is treated, and significantly enhanced the prognosis for individuals with NSCLC. The gene that codes for BRAF kinase is the gene known as BRAF, or Oncogene homolog B belongs to the human cytosolic serine/threonine kinases, V-Raf murine sarcoma virus that is important in cell signalling, development, and endurance. BRAF mutations account for 2% of lung adenocarcinomas and are infrequent abnormalities for lung cancer that is not small cell (NSCLC). ladies who never smoked, or aggressive histology types (micropapillary) are more likely to have these mutations ^[2]. Furthermore, the majority of druggable anomalies are present in this tumour, and BRAF V600E mutations seem to be mutually exclusive. It is important to note that certain KRAS and BRAF mutations can coexist. Routine platinum-based chemotherapy, on the other hand, has a worse prognosis and is less effective. Presently, the field Because of the development of BRAF-mutant Immunocheck-point inhibitors are used in the treatment of non-small cell lung cancer, or NSCLC (ICIs) as well as BRAF inhibitors (BRAFi) ^[3].

CANCER BRAF MUTATIONS

The MEK stands for extracellular signal-regulated kinase.-rapidly accelerating fibrosarcoma (RAF) -extracellular signal-activated protein -rat sarcoma (RAS)-ERK, or extracellular signal-regulated kinase. A mitogen-activated protein kinase system is impacted by BRAF. The activation of the epithelial growth factor receptor (EGFR) initiates the RAS-RAF-MEK-ERK pathway, which controls the survival and proliferation of cells ^[4]. In sound tissue, following the signal has progressed to the BRAF, the next stage in the cascade kinase typically is inhibited by negative feedback. Generally speaking, Eight per cent of human malignancies have BRAF mutations, with the highest incidence in thyroid carcinoma (10%–70%, dependent upon the histological classification), colon cancer (10%), lung cancer (1%–2%), hairy cell leukaemia (100%), and melanoma tumours (40%–50%) being the least common ^[5].

Depending on the mutation location, there are three kinds of BRAF mutations. Strong stimulation of the BRAF kinase is caused by class I mutations, including the valine acid in the amino acid location 600 in exon 15 (V600E/K/D/R). Furthermore, this High sensitivity to MEK & BRAF inhibitors is frequently observed in mutations ^[6]. Mutants belonging to class II, such as The locations of The trigger segment containing K601, L597, G464, and G469, or as Ploop exhibit RAS-independent dimer behaviour. Raf-1 protooncogene CRAF stimulation increases MAPK pathway signalling activity, while Reduced BRAF kinase activ-

ity is seen in class III mutations including the DFG motif, catalytic loop, or P-loop. In conventional clinical settings, BRAF mutations are frequently classified as V600 mutations and non-V600 variants practise. Each change in classes II and III is not a V600 mutation. Actually, around half of the non-small cell lung cancer's BRAF mutations (NSCLC) are non-V600 variants. Additionally, the current BRAF inhibitors are vulnerable to class II as well as III BRAF mutations; hence, the development of novel-generation BRAF inhibitors is needed ^[7].

BRAF COMMISSIONS

In NSCLC, among other cancer types, at least 18 distinct 5' fusion partners were identified; AGK is the most frequently occurring fusion partner in NSCLC. Less than 1% of NSCLCs have BRAF fusions and all of those NSCLCs that did had adenocarcinomas or NSCLCs with characteristics of adenocarcinomas. With breakpoints in the bulk of BRAF, including BRAF kinase domain fusion sequences are inframe. Remarkably, 85% of all astrocytic pilocytomas have been observed to have preserved fusions. Class II BRAF mutant-like Deletions from the CR1 auto-inhibitory domain's N-terminal lead to activating BRAF fusions, constitutive activation on the BRAF pathway ^[8].

MUTATION DETECTION OF BRIEF

For BRAF mutations, single-gene tests are widely employed in melanoma and other cancers. RT-PCR is the most widely used test. Thus far, The United States United States Food and Drug Administration has authorised the THx-ID-BRAF kit and the Cobas 4800 BRAF V600 Mutant Test. as partner diagnostic tests (FDA). Furthermore, tests created in the lab may be used to determine whether a patient has a BRAF mutation; however, other techniques of confirmation testing are required. For BRAF mutations, immunohistochemistry (IHC) is the alternative type of single-gene test. But single-label antibody there is just one antibody, VE1, that can be utilised for immunohistochemistry (IHC) of mutant BRAF protein ^[9].

CURRENT MEDICATION AREA SCAPE

Chemo medicine

Chemotherapy has been well studied in people who have BRAF mutant V600 has advanced non-small cell lung cancer (NSCLC)E mutant. According to published research, individuals with BRAF V600E mutations in patients who have NSCLCs, or advanced non-small cell lung cancer, have a poor prognosis while receiving chemotherapy. Moreover, these patients seem to have been insensitive to platinum-based treatment ^[10].

Specific Therapy

An early-generation BRAF inhibitor sorafenib was created as a targeted therapy for BRAF mutant kinase. Multikinase oral inhibitors such as sorafenib target receptors for B/C, platelet-derived neurotrophic element receptor (PDGFR-b), & vascular endothelial growth factor -RAF. (VEGFR2/3), and c-Kit. The novel-generation BRAF inhibitors dabrafenib and vemurafenib block BRAF kinase by competing with ATP. The particular mutations of BRAF V600E are the focus of both medicines. The first “basket” research including vemurafenib involved many non-melanoma tumours with BRAF V600 mutations. The initial combination was dabrafenib plus trametinib, an instance of MEK inhibitor treatment studied that concentrated on blocking the BRAF pathway^[11].

Combining Immune Checkpoint Inhibitors

Counselling

Without oncogenic driver mutations, ICIs have revolutionised the way One gets treated for advanced lung cancer, non-small cell. However, ICI participation is relatively limited in NSCLC lacking oncogenic driver alterations. A case of stage IV NSCLC that has the BRAF V600E mutation has been described by Lu et al. Following treatment with atezolizumab and chemotherapy, the patient experienced a prolonged response^[12].

Research Design

This retrospective observational multicenter study in our hospital examined the clinical characteristics and outcomes of dabrafenib plus trametinib-treated advanced non-small cell lung cancer (NSCLC) patients with the BRAF V600E mutation. Starting with dabrafenib with trametinib, the main goal was to analyse PFS and OS. Secondary goals were patient demographics, PFS and OS in first-line and subsequent-line subgroups, and dabrafenib with trametinib safety. Note that this research was scholarly, not industry-funded. The research included consecutive adult BRAF V600E-mutant NSCLC patients who received dabrafenib and trametinib independent of the treatment line. Patient demographics, clinical features at NSCLC diagnosis, treatment history, and clinical outcomes were gathered for the research. The analysis did not impute missing data, maintaining research integrity and reliability. This study illuminates the efficacy and safety of dabrafenib with trametinib in various clinical scenarios, advancing NSCLC treatment.

Inclusion and exclusion criteria

Inclusion

Senior citizens and patients over the age of 18.

Patients with NSCLC who have been tested and shown to have the BRAF V600E mutation.

People who have undergone dabrafenib (150 mg BD per os) and trametinib

(2 mg OD per os) as a first-line, second-line, or later therapy.

Regular molecular testing at regional molecular genetics centres confirmed the BRAF V600E mutation.

Exclusion

Patients with small cell lung cancer, as the focus of this trial is on NSCLC rather than SCLC.

Patients with BRAF V600E-mutant NSCLC who had not previously been treated with dabrafenib plus trametinib combination therapy.

Individuals who lack definitive confirmation of a BRAF V600E mutation.

Statistical analysis

Progression-free survival (PFS) was the time from dabrafenib plus trametinib therapy to radiological or clinical progression as per RECIST 1.1 criteria or death in this research. Overall Survival (OS) was assessed from treatment start until death. Each centre assessed PFS and OS without centralised imaging review. For the whole patient cohort, Kaplan-Meier survival estimates were generated and segregated by treatment lines to analyse survival probability over time and facilitate inter-group comparisons. The 95% confidence intervals were determined using the Greenwood technique to measure estimate uncertainty. An unstratified log-rank test assessed group survival differences. All statistical analyses were done with RStudio, assuring data reliability.

Result

Table 1 presents a summary of 60 patients with advanced cancer, separating them into “1st Line” (n = 9) and “2nd Line” (n = 51) groups based on their treatment stage. Useful information about the patient’s demographics is revealed by the data. The “1st Line” group averaged 74.3 years old with a narrower range of ages, while the “2nd Line” group averaged 68.8 years old with a wider age spectrum. There was a change in the percentage of current smokers within the “2nd Line” demographic. The majority of patients had an ECOG performance status of 0-1, with more “2nd Line” patients reporting weight loss > 5% at diagnosis and stage IV cancer. There was no difference between the two groups with regard to histology, PDL-1 status, or BRAF V600E mutations. These data give useful insights into the demographic and clinical features of patients at different phases of their treatment journey.

Table 1. Table 1. Characteristics of patients

Characteristics	All Patients n = 60	1st Line n = 9	≥2nd Line a n = 51
Age (years)			
Mean (SD)	70.1 (9.8)	74.3 (9.8)	68.8 (9.6)
Range	49–94	64–94	49–84
Women, n (%)	25 (55)	4(56)	25 (55)
Smoking status, n (%)			
Current smokers	8 (13.33%)	3 (33.33%)	8 (16.68%)

Former smokers	30 (50.00)	2 (22.22%)	25 (49.01%)
Never-smokers	22 (36.66%)	4 (44.44%)	18 (35.29%)
ECOG performance status at diagnosis, n (%)			
0–1	48 (80.00%)	5 (55.55%)	41 (80.39%)
≥2	9 (15.00%)	4 (44.44%)	8 (15.68%)
Missing	3 (5.00%)	0	2 (3.92%)
Weight loss > 5% at diagnosis, n (%)	35 (58.33%)	5 (55.55%)	48 (94.11%)
Missing	2 (3.33%)	0	2 (3.92%)
Cancer-related symptoms at diagnosis, n (%)	46 (76.66%)	9 (100)	47 (92.15%)
Missing	1 (1.66%)	0	1 (1.96%)
Stage IV at diagnosis, n (%)	40 (66.66%)	7 (77.77%)	33 (64.70%)
Histology, n (%)			
Adenocarcinoma	58 (96.66%)	9 (100)	49 (96.07%)
Large-cell carcinoma	1 (1.66%)	0	1 (1.96%)
Squamous cell carcinoma	1 (1.66%)	0	1 (1.96%)
PDL-1 status, n (%)			
PDL-1 > 1%	24 (40.00%)	5 (55.55%)	9 (17.64%)
Missing	36 (60.00%)	4	42 (82.35%)
BRAF V600E at dabrafenib plus trametinib initiation, n (%)	60 (100)	9 (100)	51 (100)
Concomitant mutation, n (%)	0	0	0
Stage IV at dabrafenib plus trametinib initiation, n (%)	58 (96.66%)	8 (88.88%)	30 (58.82%)
Number of metastatic sites, n (%)			
0	2 (3.33%)	1 (11.11%)	1 (1.96%)
1	19 (31.66%)	1 (11.11%)	9 (17.64%)
≥2	38 (63.33%)	6 (66.66%)	41 (80.39%)
Missing	1 (1.66%)	1 (11.11%)	0
Metastatic sites, n (%)			
Pleura	21 (12.60)	4 ()	15 (29.41%)
Bone	19 (11.40)	3 ()	15 (29.41%)
Lung	17 (10.20)	1 ()	16 (31.37%)
Brain	3 (1.80)	0	5 (9.80%)
Prior treatments (first line), n (%)			
Platinum-based doublet chemotherapy	-	-	46 (90.19%)
Vemurafenib	-	-	1 (1.96%)
Immunotherapy	-	-	2 (3.92%)
Missing	-	-	2 (3.92%)

The median progression-free survival (PFS) percentages at various time intervals are displayed in **Figure 1** below. The numbers indicate the percentage of patients who have not experienced a worsening of their condition or death by the indicated milestones. Median progression-free survival (PFS) grows consistently

from 10 months to 20 months, showing that a growing proportion of patients can delay or avoid the onset of disease progression or death. Higher percentages indicate a more positive outcome for the patients being researched, hence this data is significant in analysing the efficacy and durability of a specific treatment or intervention over time.

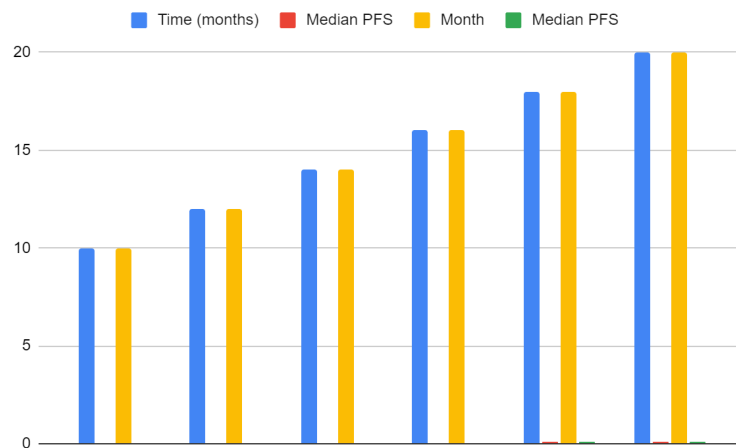


Figure 1 Median Progression-Free Survival (PFS) percentages at different time points in months

Figure 2 shows the median progression-free survival (PFS) rates across various time periods, along with their associated probabilities. Median progression-free survival (PFS) is zero in October 2023, meaning that no patient in the trial has had disease progression or death up to that date. In November 2023, the Median PFS is 2.3 months, with a likelihood of 10.82%. This means that around 10.82% of patients were free from illness progression or death at this time. The median PFS is expected to rise to 0.63 months (probability of 0.4%) in December 2023. This information is useful for gauging the success of treatments and tracking the health of patients over time.

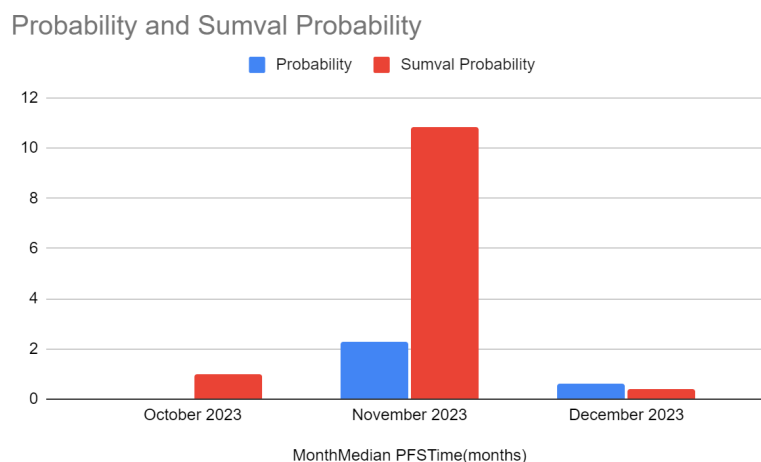


Figure 2. Median progression-free survival (PFS) rates across various time periods

The cumulative probability of Progression-Free Survival (PFS) at different months is shown in **Figure 3**. The left side represents months, whereas the right side shows cumulative probability. The cumulative probability is 0.8 at 0 months, suggesting that 80% of patients will not have progressed or died. At 4 months, the cumulative likelihood drops to 0.6, indicating that 60% of patients would retain PFS. After 8 months, the cumulative probability drops to 0.4, indicating that 40% of patients would not improve or die. A cumulative likelihood of 0.2 indicates that 20% of patients will still have PFS after 10 months. Once the cumulative likelihood reaches 0, no patient is likely to retain PFS beyond 12 months. This data is crucial for measuring longitudinal survival and illness progression in the examined population.

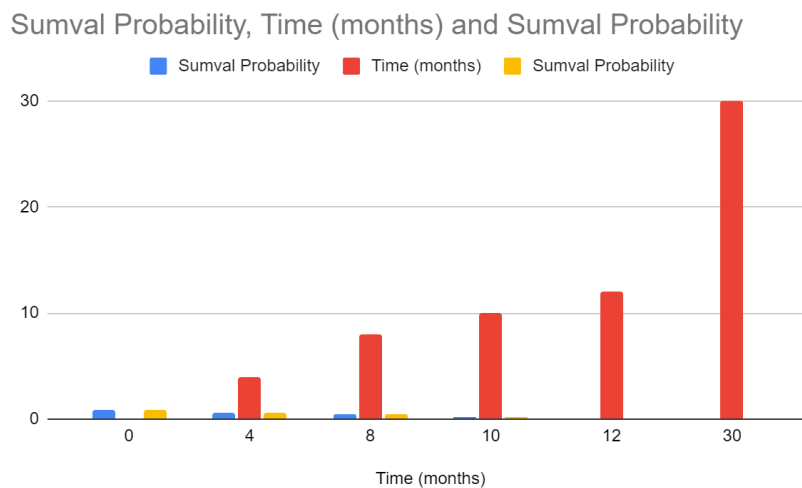


Figure 3. Cumulative probability of Progression-Free Survival (PFS) at different time intervals in months

Discussion

Europe has authorised trametinib with dabrafenib combined for the treatment of metastatic non-small-cell lung cancer with a BRAF V600E mutation (NSCLC). The study's goal was to evaluate this combination's safety and effectiveness in an actual environment. In this retrospective multicentric research, 40 patients who had progressed BRAF V600E-mutant non-small cell lung cancer (NSCLC) were treated with dabrafenib in addition to trametinib ^[13]. The cohort as a whole had an average median free of progression (PFS) of 17.5 months and an overall survival (OS) of 25.5 months. The median overall survival and progression-free survival among the nine patients receiving first-line treatment were still 16.8 months & 21.5 months, respectively; in the thirty-one patients on second-line therapy, second-line or more therapies, these figures were the same. Adverse effects resulted in dosage decrease in 12, treatment interruption in 8, (20%) and permanent cessation in 7 individuals ^[14].

When Chinese individuals do have lung cancer called non-small cell lung

cancer (NSCLC), the prevalence of the BRAF V600 mutation ranges from 1.7% to 1.8%; however, at this time, no BRAF-targeted treatment is authorised in China. A combination of trametinib and dabrafenib has been authorised in the United States in the management of lung cancer that is not a small cell with a BRAF mutation ^[15]. Japan, the US, the EU, and other countries. Whenever Chinese The study assessed the safety and effectiveness of trametinib with dabrafenib for patients with metastatic BRAF V600E-mutant non-small cell lung cancer (NSCLC). Based on preliminary findings, Chinese NSCLC BRAF V600E mutation carriers appeared to benefit effectively and safely effectively from a dabrafenib and trametinib combo. Safety and effectiveness were in line with earlier reports from the worldwide phase II research ^[16].

Patients having BRAF V600E mutation-positive metastatic non-small cell lung cancer (mNSCLC) showed strong anticancer efficacy when dabrafenib with trametinib was given to them. We present updated genomic data and a study of a phase 2 trial's survival (NCT01336634) that included at least a 5-year follow-up. Patients having BRAF V600E-mutant mNSCLC who were in Either cohort B (pretreated) or cohort C (treatment-naïve) were administered 2 mg of trametinib once a day or 150 mg if dabrafenib every day ^[17]. The overall rate of response as established according to Response Evaluation Standards for Solid Tumours was the main outcome measure. Safety, The three main the progression-free survival rate, total survival rate, and & response time secondary end objectives. Regardless of prior treatment history, dabrafenib + trametinib therapy was reported to offer a significant and long-lasting therapeutic benefit with a manageable safety profile for individuals with BRAF V600E mutation-positive mNSCLC ^[18].

Two to four per cent of individuals with BRAF oncogene mutations are linked to lung cancer with non-small cells (NSCLC). among the BRAF oncogene's activating mutations, the most prevalent one was found to have been attributed to the BRAF kinase's substitution of valine with glutamate on position 600 (V600E). Individuals with melanoma and non-small cell lung cancer who are positive for the BRAF V600E mutation respond well to BRAF-targeted treatments ^[19]. When melanoma and NSCLC are treated with combined response rates to BRAF inhibition as well as mitogen-activated proteins kinase (MEK) are higher than when BRAF inhibition is used alone. Following a recent phase II clinical research that showed both tolerance and effectiveness, Individuals Dabrafenib and trametinib are now available to patients with advanced non-small cell lung cancer, or NSCLC, as part of the BRAF-MEK combo therapy that has been authorised by the US Food and Drug Administration and the European Medicines Agency BRAF V600E mutant ^[20].

One to two per cent of lung adenocarcinomas have the BRAFV600E mutation, which serves as an oncogenic driver. Dabrafenib has demonstrated a significant antitumor effect when used alone or in individuals suffering from progression-stage non-small-cell lung cancer (NSCLC) along with trametinib which has been previously treated and has a BRAFV600E mutation. Our objective was to

evaluate the efficacy and safety of dabrafenib in addition to trametinib in patients having metastatic non-small cell lung cancer (NSCLC) patients without prior treatment BRAFV600E-mutant disease therapy ^[21].

Cohort C of the ongoing stage 2 study comprises adults (≥ 18 years old) with treated advanced BRAFV600E-mutant NSCLC who were previously registered in 19 sites across eight nations in Asia, Europe, and North America. The experiment is a non-randomised, open-label, multicohort, and multicentre trial. Oral trametinib two milligrams twice a day and oral it 150 mg was administered to the patients on two separate occasions until the illness progressed, they stopped responding to the treatment, they withdrew their permission, or they passed away ^[22]. The proportion lists individuals who met the requirements for Response Evaluation Criteria For Solid and received a confirmed full response or partial response Tumours were the main outcome, which was the total answer evaluated by the investigator. The group specified by the procedure, which included those who had not received treatment previously, was the focus of the main and safety studies. Although the research is still going on, no new patients are being recruited ^[23].

Patients with untreated BRAFV600E- One new Treatment for lung cancer with no small cells, or NSCLC, that is mutant may use dabrafenib combined with trametinib, which has a tolerable safety profile and clinically significant antitumour effect.

In the trial (NCT02083354), individuals with progressed BRAF V600-mutant melanoma of the skin from East Asia were evaluated for the safety and effectiveness of dabrafenib + trametinib. These findings validate that When trametinib and dabrafenib are combined, the effectiveness and security of East Asian patients who have metastatic or incurable BRAF V600-mutant carcinoma of the skin ^[24].

BRAF mutations are uncommon in NSCLC patients, and there are few available treatments. Drawing from the results of a phase II study (NCT01336634), dabrafenib with trametinib (dab-tram) was authorised for BRAFV600-mutated advanced lung cancer, non-small cell (SCLC). Drawing from previously released clinical trial data, this retrospective research contrasted the efficacy of dab-tram with the accepted course of therapy for patients via BRAF-mutated SCLC. In this indirect comparison, PBC vs. first-line dab-tram was linked to a longer median overall survival and a decreased risk of mortality among those with aNSCLC who have a BRAF mutation. Sample numbers were Several studies contrasting dab-tram containing second-line ICI and first-line PBC, with the findings being equivocal with overlapping confidence ranges. The study offers helpful information for this uncommon patient population despite several limitations ^[25].

Conclusion

This study confirms clinical trial results that dabrafenib with trametinib is

efficacious and safe for BRAF V600E-mutant metastatic non-small cell lung cancer (NSCLC). Note that this real-world study shows that the therapy improves both untreated and treated patients. The translational significance of clinical trial outcomes to real-world patient groups supports this therapy's use in ordinary clinical practice. However, study limitations must be acknowledged. The study's retrospective nature and selection bias may limit generalizability. In the absence of centralised imaging evaluation, disease assessment may vary. Prospective studies and larger patient cohorts are needed to confirm and expand these findings and better understand the long-term efficacy and safety of dabrafenib plus trametinib in BRAF V600E-mutant NSCLC patients.

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