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Original Article

Effects of chemotherapy combined with immunotherapy for non-small cell lung cancer with *BRAF*-mutations: a retrospective study

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Abstract: Objectives: To characterize the clinical features of non-small cell lung cancer (NSCLC) harboring BRAF mutations and to evaluate the effects of first-line chemotherapy combined with immunotherapy versus targeted therapy. Methods: We retrospectively reviewed patients with BRAF-mutated NSCLC diagnosed between January 2017 and June 2023 at the Affiliated Cancer Hospital of Zhengzhou University. A total of 120 patients were included, with an overall BRAF mutation frequency of 0.9%. Among the mutations detected, the Val600Glu (V600E) substitution constituted 54.2% of cases. Clinical characteristics were compared between V600E and non-V600E subgroups, and treatment efficacies were analyzed. Results: Ninety-five patients received first-line treatment. The overall median progression-free survival (mPFS) was 8.77 months, and the median overall survival (mOS) was 13.30 months. First-line chemotherapy combined with immunotherapy resulted in longer mPFS (17.17 vs. 9.03 months, P = 0.573) and mOS (17.50 vs. 16.07 months, P = 0.376) compared with targeted therapy using BRAF and MEK inhibitors. In addition, patients with V600E mutations exhibited a trend toward longer mPFS compared to those with non-V600E mutations (9.73 vs. 6.77 months, P = 0.244). Conclusions: Chemotherapy combined with immunotherapy may represent a promising first-line treatment strategy for NSCLC patients with BRAF mutations. Although the number of patients receiving subsequent lines of treatment was limited and their prognosis poor, a regimen of BRAF and MEK inhibitors appeared to offer therapeutic advantages in this setting.

Keywords: Non-small-cell lung cancer, BRAF mutations, target therapy, co-mutations, treatment outcomes

Introduction

The prognosis of non-small cell lung cancer (NSCLC) has significantly improved due to expanded treatment options, driven by the discovery of new oncogenic drivers, the development of targeted therapies, and advances in immunotherapy, all stemming from rapid progress in basic science and genetic testing. BRAF, a cytoplasmic serine/threonine kinase downstream of the Kirsten rat sarcoma viral oncogene homolog (KRAS), plays a critical role in this context [1]. Activation of KRAS promotes constitutive RAF activation, thereby enhancing mitogen-activated protein kinase (MAPK) pathway signaling and promoting tumor cell growth and proliferation [2-4].

Over 50% of BRAF mutations involve a valine-to-glutamic acid substitution at codon 600 (V600E) in exon 15 of the kinase domain [5]. BRAF mutations are classified into three functional classes based on RAF kinase activity and signaling mechanisms [6, 7]. Class I mutations, such as V600E, result in RAS-independent activation of BRAF monomers. Class II mutations activate BRAF dimers in a RAS-independent manner, while Class III mutations involve impaired kinase activity and rely on RAS for signaling activation [8].

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BRAF mutations are most frequently observed in melanoma (40-60%), papillary thyroid carcinoma (30-70%), and colorectal cancer (5-20%) [9]. Their incidence in NSCLC among Caucasians ranges from 2% to 5% [4, 10, 11]. A study on Chinese patients reported a lower prevalence of 1.7%. These mutations are more commonly found in females [10]. Most NSCLC patients with BRAF V600E mutations are current or former smokers, whereas BRAF non-V600E mutations have been reported more frequently in heavy smokers [12-14]. However, a Chinese study found a higher proportion of never-smokers among patients with BRAF mutations compared to those without BRAF mutations (78.6% vs. 56.7%, P = 0.019) [11].

Notably, BRAF mutations may influence the tumor immune microenvironment. NSCLC harboring BRAF mutations tends to exhibit higher expression of programmed cell death ligand 1 (PD-L1) and better responses to immunotherapy than tumors with other driver mutations such as EGFR or ALK alterations [15]. Conversely, existing data suggest that patients with BRAF-mutated NSCLC respond less favorably to platinum-based chemotherapy than those with wild-type BRAF [16]. Two phase II clinical trials demonstrated that BRAF and MEK inhibitor combinations yielded high objective response rates (ORR) in patients with BRAF V600E-mutant NSCLC: 64% in previously treated and 63.2% in treatment-naïve individuals [4, 16]. Consequently, dabrafenib combined with trametinib is now approved as a first-line therapy for advanced NSCLC with BRAF V600E mutations [17].

However, clinical application of such dual-target therapies in China remains limited due to high cost and poor drug accessibility. Furthermore, no approved targeted therapies currently exist for patients with non-V600E BRAF mutations, and the biological behavior and treatment responses of these subtypes remain poorly characterized [18]. To date, there is limited evidence supporting the efficacy of BRAF/MEK inhibitors in this subgroup.

Given these gaps, a comprehensive understanding of the real-world clinical features, treatment patterns, and therapeutic responses in patients with BRAF-mutated NSCLC - particularly in the Chinese population - is urgently needed. This retrospective study was therefore conducted to evaluate the clinical characteristics, treatment strategies, and outcomes of patients with BRAF-mutated NSCLC in a real-world setting.

Materials and methods

Study population

Patients with BRAF-mutant NSCLC diagnosed at the Affiliated Cancer Hospital of Zhengzhou University between January 2017 and June 2023 were retrospectively enrolled. Inclusion criteria were: (1) age > 18 years; (2) histologically confirmed NSCLC with documented BRAF mutations; and (3) mutation status identified via next-generation sequencing of tumor tissue. Disease staging was performed using the 8th edition of the American Joint Committee on Cancer (AJCC) staging system.

Exclusion criteria included: (1) presence of other malignancies; (2) active or a history of severe organ dysfunction; (3) overall survival (OS) < 3 months; and (4) incomplete follow-up data for first-line treatment.

Study design and data sources

Patient data were collected after informed consent was obtained. Demographic and clinical information included age at diagnosis, sex, smoking history, tumor histology, disease stage, sites of metastasis, PD-L1 tumor proportion score (TPS), BRAF mutation subtype, and co-mutation profiles. Clinical outcomes were extracted from electronic medical records and included treatment initiation and discontinuation dates, treatment lines, therapeutic regimens, treatment responses (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD]), date of disease progression (based on RECIST v1.1), and survival endpoints.

OS was defined as the time from diagnosis of BRAF-mutated NSCLC to death or last follow-up. Progression-free survival (PFS) was defined as the time from treatment initiation to disease progression or last follow-up. The primary endpoints were median PFS (mPFS), median OS (mOS), and ORR, defined as the proportion of patients achieving CR or PR. The data cutoff for survival analysis was August 31, 2023. Disease staging was performed according to the AJCC 8th edition criteria.

Table 1. Comparison of patient characteristics

Characteristic	Overall (n = 120) (%)	V600E (n = 65) (%)	Non-V600E (n = 55) (%)	t/χ^2	*p*-Value
Age (years)	60.86 ± 8.32	60.09 ± 8.71	61.76 ± 7.82	-0.197	0.275
Sex				4.484	0.034
Male	66 (55)	30 (46.2)	36 (65.5)		
Female	54 (45)	35 (53.8)	19 (34.5)		
Smoking History				0.360	0.549
Yes	36 (30)	18 (27.7)	18 (32.7)		
No	84 (70)	47 (73.3)	37 (67.3)		
Histologic type				11.558	0.003
Adenocarcinoma	105 (87.5)	63 (96.9)	42 (76.4)		
Squamous cell carcinoma	6 (5)	1 (1.5)	5 (9.1)		
NSCLC-NOS	9 (7.5)	1 (1.5)	8 (14.5)		
Adenosquamous carcinoma	5 (4.2)	0	5 (9.1)		
Sarcomatoid carcinoma	3 (2.5)	1 (1.5)	2 (3.6)		
Neuroendocrine neoplasm	1 (0.8)	0	1 (1.8)		
Clinical stage				0.129	0.719
Early stage (I/II/IIIA)	16 (13.3)	8 (12.3)	8 (14.5)		
Advanced stage (IIIB/IIIC/IV)	104 (86.7)	57 (87.7)	47 (85.5)		
Metastatic Involvement					
Liver	11 (9.2)	8 (12.3)	3 (2.5)	1.680	0.195
Lung	53 (44.2)	33 (27.5)	20 (36.4)	2.507	0.113
Bone	36 (30)	16 (13.3)	20 (36.4)	1.958	0.116
Brain	18 (15)	10 (15.4)	8 (14.5)	0.016	0.898
Pleura	29 (24.2)	21 (32.3)	8 (14.5)	5.129	0.024
Adrenal gland	5 (4.2)	3 (4.6)	2 (3.6)	0.072	0.579
PD-L1 status				6.136	0.105
Negative (< 1%)	28 (23.3)	12 (18.5)	16 (29.1)		
Low (1%-49%)	15 (12.5)	5 (7.7)	10 (18.2)		
High (≥ 50%)	32 (26.7)	20 (30.8)	12 (21.8)		
Unknown	45 (37.5)	28(43.1)	17 (30.9)		
Type of co-mutations					0.133
EGFR	12 (10)	5 (7.7)	7 (12.7)	0.839	0.360
KRAS	5 (4.2)	0	5 (9.1)	-	0.018
TP53	35 (29.2)	16 (24.6)	19 (34.5)	1.422	0.233
PIK3CA	10 (8.3)	4 (6.2)	6 (10.9)	0.085	0.348
ERBB2	4 (3.3)	0	4 (7.3)	-	0.042
Other co-mutations	19 (15.8)	6 (9.2)	13 (23.6)	4.639	0.031
PTEN	3 (2.5)	0	3 (5.5)		
TERT	2 (1.7)	1 (1.5)	1 (1.8)		
STK11	2 (1.7)	0	2 (3.6)		
NF1	2 (1.7)	0	2 (3.6)		
AKT1	1 (0.8)	1 (1.5)	0		
ATM	1 (0.8)	1 (1.5)	0		
SMAD	1 (0.8)	1 (1.5)	0		
FGF19	1 (0.8)	1 (1.5)	0		
RET	1 (0.8)	1 (1.5)	0		
MTOR	1 (0.8)	1 (1.5)	0		

KEAP1	1 (0.8)	0	1 (1.8)		
BRCA2	1 (0.8)	0	1 (1.8)		
CDK4	1 (0.8)	0	1 (1.8)		
FGFR	1 (0.8)	0	1 (1.8)		
UGT1A	1 (0.8)	0	1 (1.8)		
RB1	1 (0.8)	0	1 (1.8)		
NRAS	1 (0.8)	0	1 (1.8)		
Acquired *BRAF* mutations	7 (5.8)	3 (4.6)	4 (7.3)	-	0.701

Notes: V600E: a glutamate-valine substitution at codon 600; NSCLC-NOS: non-small cell lung cancer, not-otherwise specified; PD-L1: programmed cell death ligand 1; EGFR: epidermal growth factor receptor; KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog; TP53: Tumor Protein 53; PIK3CA: Phosphatidylinositol 3-Kinase Catalytic Subunit Alpha; ERBB2: v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog; PTEN: phosphatase and tensin homolog deleted on chromosome ten; TERT: Telomerase Reverse Transcriptase; STK11: serine/threonine kinase 11; NF1: neurofibromatosis type 1; AKT1: v-akt murine thymoma viral oncogene homolog 1; ATM: ataxia telangiectasia-mutated gene; SMAD: drosophila mothers against decapentaplegic protein; FGF19: Recombinant Fibroblast Growth Factor 19; RET: Rearranged during Transfection; MTOR: mammalian target of rapamycin; KEAP1: kelch-like ECH-associated protein 1; BRCA2: breast cancer2; CDK4: cyclin-dependent kinase 4; FGFR: Fibroblast Growth Factor Receptor; UGT1A: uridine diphosphate-glucuronosyl-transferase 1A1; RB1: Retinoblastoma 1; NRAS: Neuroblastoma RAS viral oncogene homolog; BRAF: V-Raf murine sarcoma viral oncogene homolog B.

Statistical analysis

Statistical analyses were conducted using SPSS version 27.0 (IBM Corp., Armonk, NY, USA), and graphs were generated with GraphPad Prism version 9.5 (GraphPad Software, San Diego, CA, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages.

For continuous data, the Student's t-test was applied when the data followed a normal distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. For ranked qualitative data, the rank-sum test was used.

Survival outcomes, including mPFS and mOS, were analyzed using the Kaplan-Meier method, with group comparisons assessed by the log-rank test. Hazard ratios with 95% confidence intervals (CIs) and corresponding *p*-values were calculated. A p-value < 0.05 was considered statistically significant.

Results

Among the 13,438 lung cancer cases screened during the study period, 120 patients (0.9%) were identified as having BRAF-mutant NSCLC and were included for baseline analysis. The demographic and baseline clinical characteristics were nearly equivalent between the two groups (**Table 1**). Most patients (87.5%) had adenocarcinoma, seventy percent of the patients had no prior history of smoking and 86.7% were diagnosed as advanced stage. PDL1 expression was evaluated in a cohort of 75 patients, and the proportion of PDL1-positive individuals reached as high as 55.3%. Among the full cohort of 120 patients, 43 patients (35.8%) harbored concurrent driver gene mutations, with TP53 being the most frequently co-mutated gene. Other recurrent co-mutations included EGFR PIK3CA, KRAS, ERBB2, MET amplification, and ALK fusions. Based on mutation subtype, patients were stratified into two groups: V600E mutations (n = 65, 54.2%) and non-V600E mutations (n = 55, 45.8%). The non-V600E group included patients with class II mutations (n = 23), class III mutations (n = 6), and non-classifiable mutations (n = 26) (See **Figure 1**).

Comparison of clinicopathological features between V600E and non-V600E mutations

We next compared clinicopathological features between V600E and non-V600E mutation subgroups. No significant differences were observed in age, smoking status, disease stage at diagnosis, or incidence of secondary BRAF mutations between the two groups (all P > 0.05).

The V600E group showed a higher proportion of female patients (P = 0.034). Squamous cell carcinoma was more common in the non-

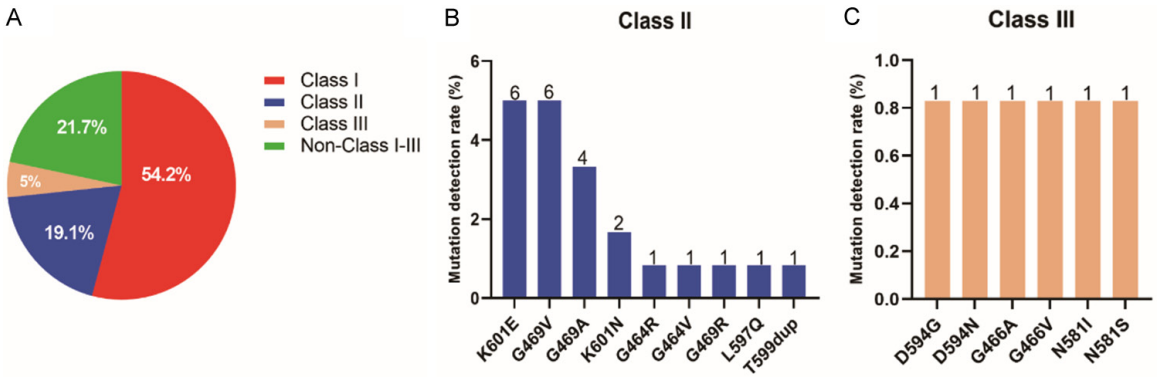

Figure 1. Distribution of BRAF mutation subtypes. A. Pie chart illustrating the distribution of *BRAF* mutations classes. B. Detection rate of each variant in class II mutations. C. Detection rate of each variant in class III mutations.

V600E group, while adenosquamous carcinoma appeared exclusively in that group (P = 0.003). Pleural metastasis was more frequent in V600E-mutated patients (P = 0.024), while no significant differences in other metastatic sites were observed between the two group. Interestingly, PD-L1 expression tended to be higher in the V600E group than in the non-V600E group (P = 0.105). Co-mutations were significantly more prevalent in the non-V600E group, particularly involving KRAS and ERBB2 (P = 0.018; P = 0.042).

Comparison of treatment regimens and prognostic outcomes

After excluding 16 patients with EGFR, MET, or ALK co-mutations and 9 patients without follow-up data post-surgery, 95 patients were included in the efficacy analysis.

Allocation of treatment regimens across different phases of therapy: Among these, chemotherapy alone was the most common first-line therapy (29.5%), followed by chemotherapy combined with anti-angiogenic agents (33.7%), and chemotherapy plus immunotherapy (26.3%). A triple combination of chemotherapy, anti-angiogenic therapy, and immunotherapy was used in 5.3% of patients, while another 5.3% received BRAF and MEK inhibitor-based targeted therapy.

Second-line therapy was administered to 49.5% of patients. Among them, 6.4% received chemotherapy alone, 21.3% received chemotherapy plus anti-angiogenic therapy, and 19.1% received chemotherapy combined with immunotherapy. Furthermore, 8.5% were treated with triple-combination therapy (chemotherapy + anti-angiogenic + immunotherapy), another 8.5% with BRAF and MEK inhibitors, 14.9% with immunotherapy alone, and 21.3% with anti-angiogenic therapy combined with immunotherapy. Third- and fourth-line treatments were administered in 48.9% and 8.3% of patients, respectively (**Table 2**).

Efficacy analysis of multistage treatment regimens: The mPFS and mOS for all 95 patients receiving first-line therapy were 8.77 months and 13.30 months, respectively (**Figure 2A**). Chemotherapy plus immunotherapy yielded longer mPFS and mOS compared to chemotherapy alone (P = 0.017). Additionally, chemotherapy combined with anti-angiogenic therapy, with or without immunotherapy, resulted in shorter mPFS compared to the immunotherapy combination and reached statistical significance (P = 0.023) (**Figure 2B**).

Patients treated with BRAF and MEK inhibitors had superior ORR treated with chemotherapy alone (P = 0.018). For V600E-mutated patients, first-line chemotherapy combined with immunotherapy yielded longer mPFS and mOS than BRAF/MEK-targeted therapy, although the difference was not statistically significant (P = 0.573; P = 0.376).

In the comparison of first-line outcomes between V600E and non-V600E mutations, mPFS was 9.03 vs. 6.77 months and mOS was 14.43 vs. 12.47 months, respectively. When limited to patients not receiving targeted therapy, those with V600E mutations showed numerically longer mPFS and mOS. Among patients receiving chemotherapy or chemotherapy plus anti-

Table 2. PFS and distribution of groups and lines of treatment regimens

Treatment regimen	Overall			V600E			Non-V600E		
	n (%)	mPFS	95% *CI*	n (%)	mPFS	95% *CI*	n (%)	mPFS	95% *CI*
1L Therapy	95	8.767	6.864-10.669	55	9.033	6.581-11.486	40	6.767	4.762-8.771
Chemotherapy	28 (29.5)	7.667	3.935-11.398	19 (34.5)	9.733	0.000-21.124	9 (22.5)	6.767	2.700-10.834
Chemotherapy + anti-angiogenic	33 (34.7)	6.033	1.287-10.779	17 (30.9)	7.600	1.678-13.522	16 (40)	3.567	0.400-6.733
Chemotherapy + immunotherapy	24 (25.3)	17.167	6.004-28.329	10 (18.2)	17.167	4.174-30.160	14 (35)	19.067	3.977-34.156
Chemotherapy + anti-angiogenic + immunotherapy	5 (5.3)	9.500	6.640-12.360	4 (7.3)	7.667	4.890-10.443	1 (2.5)	-	-
Targeted therapy	5 (5.3)	9.033	-	5 (9.1)	9.033	-	0	-	-
2L Therapy	47	5.767	3.384-8.149	25	8.133	6.458-9.809	22	3.800	2.474-5.126
Chemotherapy	3 (6.4)	8.533	0.000-19.416	3 (12)	8.267	0.000-18.722	0	-	-
Chemotherapy + anti-angiogenic	10 (21.3)	2.567	0.000-5.304	7 (28)	7.333	0.000-18.752	3 (13.6)	2.567	2.353-2.780
Chemotherapy + immunotherapy	9 (19.1)	4.300	2.990-5.610	0	-	-	9 (40.5)	4.300	2.990-5.610
Chemotherapy + anti-angiogenic + immunotherapy	4 (8.5)	3.333	0.000-8.560	2 (8)	8.133	-	2 (9.1)	2.800	-
Targeted therapy	4 (8.5)	NA	-	4 (16)	NA	-	0	-	-
Immunotherapy alone	7 (14.9)	6.267	4.984-7.550	4 (16)	5.767	0.997-10.536	3 (13.6)	10.167	2.645-17.688
Anti-angiogenic + immunotherapy	10 (21.3)	5.067	0.000-12.504	5 (20)	13.900	5.189-22.611	5 (22.7)	2.767	0.333-5.200
3L Therapy	23	4.333	1.278-7.382	11	18.600	0.000-41.327	12	2.733	1.247-4.219
Chemotherapy	4 (17.4)	1.000	0.379-1.621	3 (27.3)	1.300	0.820-1.780	1 (8.3)	0.667	-
Chemotherapy + anti-angiogenic	4 (17.4)	4.000	-	2 (18.2)	NA	-	2 (16.7)	2.600	-
Chemotherapy + immunotherapy	1 (4.3)	-	-	0	-	-	1 (8.3)	-	-
Chemotherapy + anti-angiogenic + immunotherapy	1 (4.3)	-	-	0	-	-	1 (8.3)	-	-
Targeted therapy	3 (13.0)	NA	-	3 (27.3)	NA	-	0	-	
Anti-angiogenic alone	4 (17.4)	-	-	2 (18.2)	NA	-	2 (16.7)	2.733	-
Anti-angiogenic + immunotherapy	6 (26.1)	4.333	0.000-8.814	1 (9.1)	18.600	-	5 (41.7)	4.333	0.000-10.703
4L Therapy	10	2.700	0.000-6.419	3	10.570	1.128-20.012	7	2.270	0.371-4.169
Chemotherapy + anti-angiogenic	2 (20)	2.270	-	1 (33.3)	10.570	-	1 (14.3)	2.270	-
Chemotherapy + immunotherapy	2 (20)	1.530	-	0	-	-	2 (28.6)	1.530	-
Chemotherapy + anti-angiogenic + immunotherapy	1 (10)	-	-	0	-	-	1 (14.3)	-	-
Targeted therapy	2 (20)	4.670	-	2 (66.7)	4.670	-	0	-	-
Anti-angiogenic + immunotherapy	3 (30)	1.400	0.072-2.728	0	-	-	3 (42.9)	1.400	0.072-2.728

Notes: mPFS: Median Progression-Free Survival; 95% CI: 95% Confidence Interval.

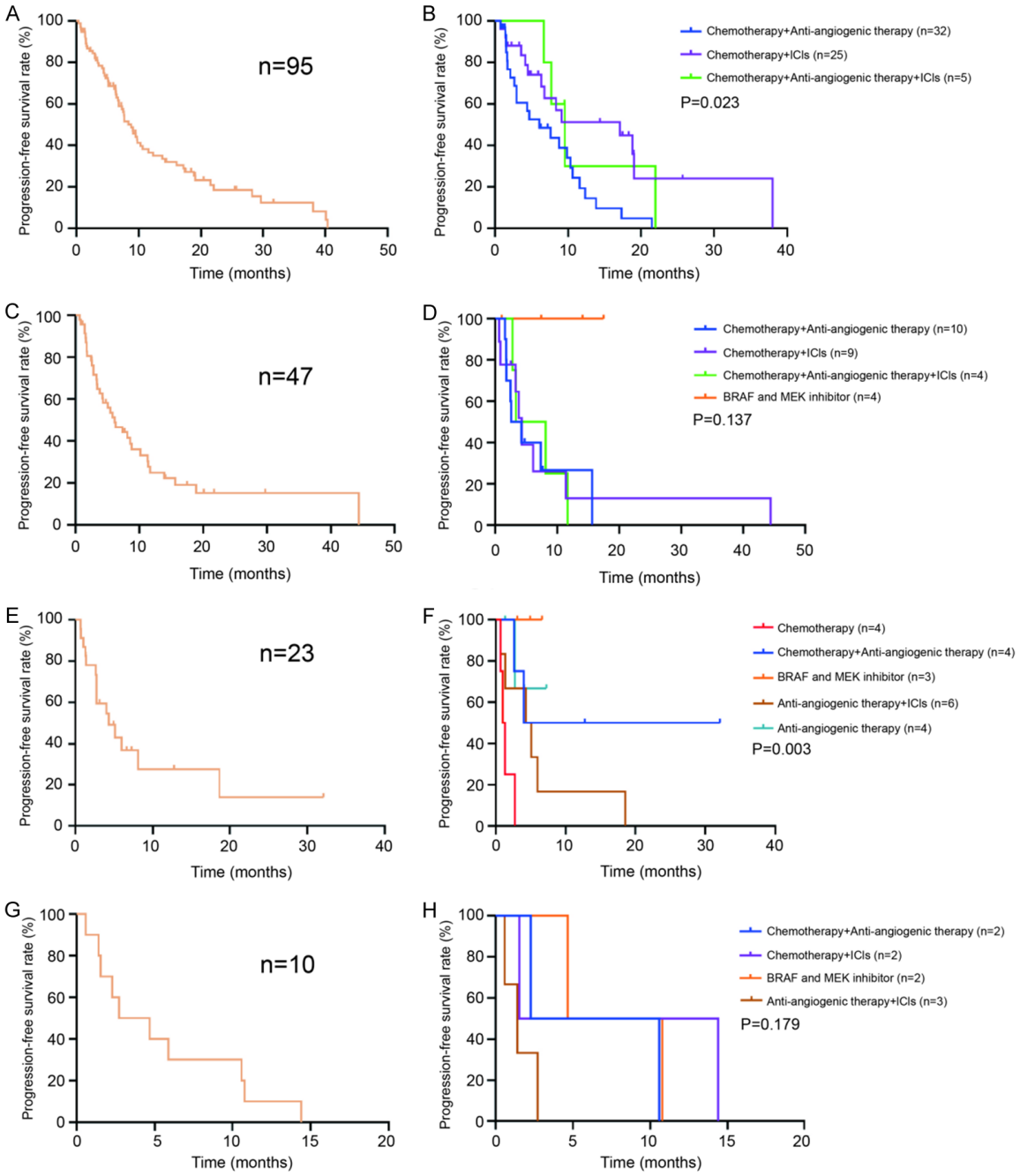

Figure 2. Evaluation of Progression-Free Survival (PFS) according to treatment regimens treatment regimens. A. PFS of all first-line patients. B. PFS comparisons among first-line regimens: chemotherapy combined with immunotherapy, chemotherapy combined with anti-angiogenic therapy, and triple combination therapy (chemotherapy combined with anti-angiogenic and immunotherapy). C. PFS by second line treatment regimen. D. PFS of patients receiving BRAF and MEK inhibitor therapy, chemotherapy plus anti-angiogenic therapy, chemotherapy plus immunotherapy, and triple combination therapy in the second-line setting. E. PFS of all patients receiving third-line therapy. F. PFS by treatment modality in the third-line setting. G. PFS of all patients receiving fourth-line therapy. H. PFS by treatment modality in the fourth-line setting.

angiogenic therapy as first-line treatment, those with V600E mutations again showed longer mPFS (9.73 vs. 6.77 months, P = 0.244; 7.60 vs. 2.10 months, P = 0.314).

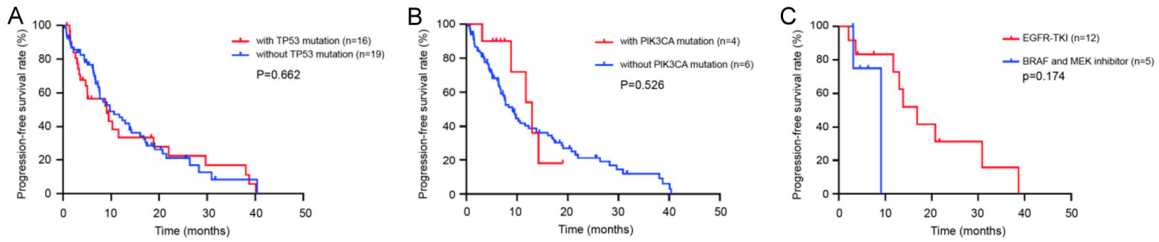

Figure 3. Prognosis of co-mutated gene types. A. PFS in patients with and without Tumor Protein 53 (*TP53)* mutations. B. PFS in patients with and without Phosphatidylinositol 3-Kinase Catalytic Subunit Alpha (*PIK3CA)* mutations. C. PFS in patients treated with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (*EGFR-TKIs)* and those treated with targeted *BRAF* and *MEK* inhibitors.

In the 47 patients receiving second-line treatment, the overall mPFS was 5.77 months (**Figure 2C**). Among the seven patients receiving second-line immunotherapy alone, those with V600E mutations had shorter mPFS compared to patients with non-V600E mutations. Combination therapy with anti-angiogenic agents and immunotherapy yielded longer mPFS than anti-angiogenic therapy with chemotherapy (4.30 vs. 2.57 months, P = 0.335) (**Figure 2D**).

Among the 23 patients who received third-line treatment, the mPFS was 4.3 months (**Figure 2E**). One patient receiving chemotherapy plus immunotherapy had a PFS of 2.73 months; another receiving triple combination therapy achieved a PFS of 8.10 months. Notably, BRAF/MEK inhibitor therapy did not reach mPFS (P = 0.003) (**Figure 2F**).

For the 10 patients receiving fourth-line treatment, mPFS was only 2.70 months (**Figure 2G**). One patient on triple-combination therapy had a PFS of 5.87 months. Among those receiving BRAF/MEK inhibitors, mPFS was 4.67 months, indicating a trend toward superior outcomes over other regimens (P = 0.179) (**Figure 2H**).

Comparison of PFS based on co-mutation status

Patients harboring concurrent TP53 mutations had a shorter mPFS after first-line treatment than those without TP53 mutations (P = 0.662) (**Figure 3A**). Conversely, patients with PIK3CA co-mutations showed longer mPFS than non-mutated counterparts (P = 0.526) (**Figure 3B**). Interestingly, 12 patients with EGFR co-mutations achieved longer mPFS than those who received first-line BRAF and MEK inhibitor therapy (P = 0.174) (**Figure 3C**).

Univariate and multivariate analyses of the impact of clinicopathological characteristics on clinical outcomes

Univariate analysis revealed that brain metastasis, secondary BRAF mutations, and adrenal metastasis were significantly associated with shorter PFS in the overall cohort (all $P < 0.05$). These factors also showed significant prognostic relevance in patients with BRAF V600E mutations, although similar trends were observed in the non-V600E subgroup. Variables with P < 0.2 were subsequently included in the multivariate analysis, which confirmed that brain metastasis, adrenal metastasis, and secondary BRAF mutations were independently associated with worse PFS in patients with BRAF-mutant NSCLC (**Tables 3** and **4**).

Discussion

Apart from differences in sex and co-mutation patterns, no significant clinicopathological differences were found between the V600E and non-V600E subgroups, consistent with prior studies. BRAF mutations were more frequently observed in females and non-smokers, aligning with findings reported by Marchetti et al. [2]. As previously described, adenocarcinoma was the predominant histologic type among V600E-mutant patients [11, 19]. We also observed a higher proportion of patients with high PD-L1 expression (TPS > 50%) in the V600E group, in line with findings by Gibson et al. [20]. In contrast, Dudnik et al. reported a weaker association between non-V600E mutations and elevated PD-L1 expression (42% vs. 50%; P = 0.051) [21].

Table 3. Univariate analysis of PFS

Variable	Overall			V600E			Non-V600E		
	95% *CI*	χ^2	*p*-Value	95% *CI*	χ^2	*p*-Value	95% *CI*	χ^2	*p*-Value
Age		3.745	0.053		1.895	0.169		1.758	0.185
≤ 65	7.081-10.986			7.040-11.027			3.580-11.020		
> 65	1.515-11.152			1.070-11.597			-		
Sex		1.167	0.280		0.474	0.491		0.129	0.720
Male	5.287-9.913			6.438-11.095			4.976-8.557		
Female	3.621-11.513			3.972-15.495			0.000-41.933		
Smoking History		2.260	0.133		0.001	0.972		3.536	0.060
Yes	5.350-9.695			6.648-10.885			2.907-10.627		
No	4.193-14.553			6.781-12.219			0.000-31.487		
Histologic type		4.535	0.421		1.132	0.519		1.929	0.587
Adenocarcinoma	6.949-11.318			7.483-11.517			2.389-15.878		
Squamous cell carcinoma	0.666-8.067			-			0.000-10.522		
NSCLC-NOS									
Adenosquamous carcinoma	-			-			/		
Sarcomatoid carcinoma	-			/			-		
Clinical stage		1.323	0.339		0.111	0.739		2.649	0.104
Early stage (I/II/IIIA)	0.000-21.903			5.344-9.656			-		
Advanced stage (IIIB/IIIC/IV)	6.473-10.193			6.656-11.410			4.244-9.289		
Metastatic Involvement									
Liver	3.925-8.675	1.640	0.200	3.269-9.331	0.748	0.387	-	2.573	0.109
Lung	6.355-11.912	0.005	0.942	5.980-13.620	0.262	0.609	4.675-8.859	0.562	0.453
Bone	5.729-7.804	1.719	0.190	4.104-11.096	0.527	0.468	4.739-8.794	0.911	0.34
Brain	0.000-15.388	4.493	0.034	0.520-12.080	4.501	0.034	0.000-11.302	0.961	0.327
Pleura	0.902-16.631	0.070	0.792	6.831-10.703	0.051	0.822	0.000-22.043	0.036	0.849
Adrenal gland	0.000-4.934	8.616	0.003	1.167-2.233	17.783	< 0.001	-	0.168	0.682
PD-L1 status		1.824	0.610		7.021	0.071		5.671	0.129
Negative (< 1%)	5.448-12.819			6.981-21.419			2.091-11.442		
Low (1%-49%)	4.824-13.243			7.597-10.469			2.978-9.088		
High (≥ 50%)	5.993-6.941			3.593-9.073			0.000-39.803		
Unknown	5.986-11.548			5.592-13.874			2.221-11.312		
Co-mutations	3.885-14.182	0.088	0.767	1.072-16.461	1.326	0.250	1.966-18.634	1.778	0.182
Acquired *BRAF* mutations	-	4.073	0.045	-	8.429	0.004	-	0.553	0.457

Note: PFS: Progression-Free Survival.

Table 4. Multivariate cox regression models associated with PFS

Variable	Overall			V600E			Non-V600E		
	HR	95% *CI*	*p*-Value	*HR*	95% *CI*	*p*-Value	*HR*	95% *CI*	*p*-Value
Age	1.023	0.984-1.063	0.251	1.022	0.976-1.069	0.358	1.009	0.922-1.105	0.841
Brain metastatic	0.394	0.191-0.814	0.012	0.281	0.097-0.815	0.020	0.563	0.200-1.587	0.277
Adrenal metastasis	0.196	0.067-0.567	0.003	0.089	0.022-0.354	0.001	0.536	0.064-4.492	0.566
BRAF secondary mutationss	0.153	0.033-0.703	0.016	0.032	0.003-0.341	0.004	0.374	0.039-3.629	0.397

Notes: HR: Hazard Ratio; PFS: Progression-Free Survival.

It is worth noting that due to the frequent use of fine-needle aspiration for diagnosis at our center, some biopsy samples were insufficient for both molecular and PD-L1 testing, limiting the scope of PD-L1 analysis. Larger studies are needed to validate these findings.

Regarding mutation distribution, class I mutations (primarily V600E) were significantly more prevalent than class II or III. The frequency of class I mutations in our cohort was comparable to that reported in Caucasian populations but higher than the previously documented 30% in Chinese patients [22, 23]. No statistically significant differences in PFS were observed across different mutation classes in our study.

While previous studies have demonstrated that BRAF mutation class may influence chemotherapy response and PFS [24, 25], the lack of observed differences in our cohort may be attributable to small subgroup sizes and intergroup heterogeneity.

Interestingly, co-mutations were more common in the non-V600E group. Prior studies have shown frequent co-occurrence of BRAF mutations with other driver genes such as EGFR, TP53, KRAS, and PIK3CA [26]. Specifically, co-mutations involving TP53 and PIK3CA have been associated with more aggressive disease and poorer prognosis [14, 27], which is consistent with our findings. These results highlight the need for comprehensive genomic profiling in NSCLC, as co-altered driver genes may substantially impact prognosis and therapeutic decisions.

Among the 12 patients with concurrent BRAF and EGFR mutations, those treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) had longer mPFS than those receiving BRAF or MEK inhibitor-based therapy as first-line treatment. This suggests that EGFR-TKIs may be the preferred option in the context of BRAF and EGFR co-mutations. Similarly, two patients with concurrent BRAF mutations and ALK fusions achieved longer mPFS than those treated with BRAF/MEK inhibitors. In contrast, two patients with BRAF and MET co-mutations treated with savolitinib had worse outcomes. However, due to the small number of patients in each subgroup, the observed differences should be interpreted with caution. Larger cohorts are needed to characterize the clinical behavior and therapeutic responses in patients with concurrent mutations.

In our study, first-line chemotherapy combined with immunotherapy resulted in the longest mPFS. Notably, patients with high PD-L1 expression and a smoking history may benefit more from immunotherapy as a frontline treatment [28]. For instance, Mazieres et al. reported that immune checkpoint inhibitor monotherapy yielded significantly longer mPFS in smokers compared to non-smokers) [15]. The inconsistencies observed in our study may be attributable to the small sample size and the relatively high proportion of non-smokers. Furthermore, BRAF and MEK inhibitor-based therapy was superior to chemotherapy alone, consistent with previous evidence from a study involving 46 patients with advanced NSCLC harboring BRAF V600E mutations [29]. Overall, combination therapies incorporating immunotherapy may serve as viable alternatives, particularly in patients with high PD-L1 expression or limited access to targeted agents due to financial constraints.

Additionally, patients with V600E mutations had longer mPFS and OS than those with non-V600E mutations. A retrospective study also found that patients with V600E mutations had better prognoses than those with non-V600E variants [30]. In a cohort of 380 patients with BRAF-mutant NSCLC, Sakai et al. similarly

reported improved survival in the V600E subgroup [31], further corroborating our findings [32].

We also observed that 5.8% of patients acquired BRAF mutations after progression following multiple lines of systemic therapy. Among these, 41.8% developed the V600E mutation, and notably, 71.4% of these cases occurred after resistance to EGFR-TKIs. In these patients, EGFR mutations were no longer detectable at the time of BRAF mutation emergence. This aligns with data from the AURA3 clinical trial, which reported BRAF mutations in 3% of patients with resistance to third-generation EGFR inhibitors (e.g., osimertinib) [33]. These findings suggest that acquired BRAF mutations may represent a resistance mechanism to EGFR-TKIs. Importantly, patients with secondary BRAF mutations had significantly shorter mPFS than those with primary BRAF mutations (2.63 vs. 8.77 months, P = 0.045). In this unique subgroup, combination therapy with EGFR-TKIs and BRAF/MEK inhibitors was more effective than chemotherapy-based regimens [34]. However, the mechanisms driving the emergence of secondary BRAF mutations remain poorly understood, and further research is needed to guide treatment strategies for this population.

This study has several limitations. First, due to the relatively small sample size, our findings require validation in larger, multicenter cohorts. Second, as a retrospective study, our analysis was limited to clinical efficacy data, without assessment of treatment-related toxicities or tolerability. With the increasing use of targeted and immune-based therapies, future studies should incorporate safety profiles into treatment evaluations. Moreover, as access to targeted therapies improves in China, further investigations are needed to optimize first-line and sequential treatment strategies for patients with both primary and acquired BRAF mutations.

In summary, we investigated the clinical characteristics and treatment outcomes of Chinese patients with BRAF-mutated NSCLC. Our findings suggest that PD-L1 expression is relatively high in this population, and that chemotherapy combined with immunotherapy is an effective first-line treatment option in real-world settings. While targeted therapy may offer benefits, particularly for patients with high tumor burden, its use is often limited by drug accessibility and cost. Clinical trials have reported high rates of grade 3/4 adverse events with BRAF-targeted therapies, emphasizing the need to balance efficacy with patient tolerability [17]. Therefore, chemotherapy plus immunotherapy remains a viable treatment approach, especially when tailored to the patient's physical status, molecular subtype, tumor burden, and treatment tolerance.

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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