Original Article

Efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer harboring *BRAF* mutations

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Background: Despite immune checkpoint inhibitors (ICI) being widely used to treat patients with advanced non-small cell lung cancer (NSCLC), few studies examine the role of ICI in patients with proto-oncogene B-Raf, serine/threonine kinase (*BRAF*) mutations.

Methods: A retrospective study was conducted for patients with *BRAF*-mutant NSCLC who received treatment at Shanghai Pulmonary Hospital between 2014 and 2022. Primary end point was progression-free survival (PFS). Secondary end point was best response (RECIST, version 1.1).

Results: The study involved a total of 34 patients with 54 treatments recorded. The median PFS for the whole cohort was 5.8 months and the overall objective response rate (ORR) was 24%. Patients who were treated with ICI combined with chemotherapy reported a median PFS of 12.6 months and an ORR of 44%. Those who were treated with non-ICI therapy came with a median PFS of 5.3 months and an ORR of 14%. Specifically, patients had better clinical benefits with first-line ICI-combined therapy. The PFS was 18.5 months whereas that of non-ICI group was 4.1 months. The ORR was 56% in ICI-combined group and 10% in non-ICI cohort.

Conclusions: The findings observed an evidential and significant susceptibility to ICIs combined therapy in patients with *BRAF*-mutant NSCLC, especially in first-line treatment.

Keywords: *BRAF*-mutant; immune checkpoint inhibitors (ICI); non-small cell lung cancer (NSCLC); progression-free survival (PFS)

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Introduction

Globally, lung cancer is one of the most prevalent cancers and remains the predominant cause of death (1). In the past, oncogene driver-based therapies, such as those targeting epidermal growth factor receptor (*EGFR*), ROS proto-oncogene 1 (*ROS1*) or anaplastic lymphoma kinase (*ALK*), had strikingly changed the treatment of lung cancer and led up to an era of more personalized therapy. In the case of oncogenic driver mutations, driver gene inhibitors may be more beneficial than cytotoxic chemotherapy. However, drug resistance and tumor recurrence are still inevitable at this setting. In addition, targeted therapies are limited for patients who have scarce oncogenic drivers. *BRAF* alteration had been identified in 2% to 4% of non-small cell lung cancer (NSCLC) (2-5) and was even lower in Chinese patients of approximately 0.5% to 2% (6,7). Although targeting *BRAF* drugs such as vemurafenib (8) and dabrafenib (9) have shown promising efficacy in these advanced NSCLC, most of the current pivotal clinical studies on *BRAF* are phase 2 clinical studies, and validation with larger sample size is still required (10,11). Furthermore, the adverse effects during treatment and the difficulty of avoiding drug resistance still limit their therapeutic use.

In addition to molecularly targeted therapies, immune checkpoint inhibitors (ICI) have been approved as one of standard therapies for the treatment of advanced NSCLC because of their promising efficacy (12-14). However, the role of ICI in NSCLC with oncogene drivers remains uncertain because most of these clinical trials were conducted in the absence of patients carrying known oncogenic mutations. A limited number of studies have demonstrated the clinical benefits of ICI in *BRAF*-mutant NSCLC patients, whereas its efficacy for patients with *BRAF* mutation remains uncertain. Murciano-Goroff indicated that NSCLC patients with *BRAF* mutation did not receive survival benefit for ICI-monotherapy yet a subset of patients with *BRAF*-altered lung cancers achieved durable disease control with ICI. However, Dudnik and Wiesweg demonstrated that, unlike other oncogene alterations, ICI had favorable activity in *BRAF* mutant NSCLC (15). When different mutant subtypes are taken into account, especially V600E and non-V600E, recent studies show that NSCLC with V600E mutation are less likely to benefit from immunotherapy (16) whereas others suggest that immunotherapy have great performance both in V600E and non-V600E equally (15,17,18). Further, ICI combined with chemotherapy for advanced *EGFR/ALK* wild-type NSCLC patients showed more significant benefit in clinical outcomes and across PD-LI expression subgroups (19,20). National Medical Products Administration (NMPA) has approved immune combination therapy as the first-line treatment for driver-negative advanced NSCLC.

The objective of this real-world retrospective cohort study was to examine the potential benefits of ICI-combined treatment in patients with advanced NSCLC who harbored *BRAF* mutations. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-613/rc).

Highlight box

Key findings

- The findings observed an evidential and significant susceptibility to immune checkpoint inhibitors combined therapy in *BRAF*-mutant NSCLC, especially in first-line treatment.

What is known and what is new?

- Patients with *BRAF* mutation in NSCLC have a poor prognosis.
- ICI combined therapy shows a significant better PFS.

What is the implication, and what should change now?

- ICI combined therapy could be selected as first-line treatment in *BRAF*-mutant NSCLC.

Methods

Study design

The records of patients with advanced NSCLC harboring *BRAF*-mutation in Shanghai Pulmonary Hospital between March 2014 and March 2022 were reviewed. Patients were diagnosed with NSCLC by histology or cytology and staged according to the 8th edition of the Tumor Node Metastasis (TNM) staging system. Patients with *ALK*, *EGFR*, *ROS1*, *RET* (ret proto-oncogene), or *MET* (MET proto-oncogene, receptor tyrosine kinase) mutations, as well as those who acquired *BRAF* mutation after resisting therapies targeting another oncogenic driver gene, were ineligible. By the end of March 2022, a total of 77 patients with *BRAF* mutations were reviewed, where 38 patients loss to follow-up and 5 patients with coexisting EGFR mutations were excluded. 34 patients were ultimately included in our analysis (Figure S1). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was reviewed and approved by the Ethics Committee

of Shanghai Pulmonary Hospital (No. K22-190Y). The individual consent for this retrospective analysis was waived.

Data collection

Demographic and clinical characteristics included gender, age, smoking status, ECOG status, pathology, stage, brain metastasis, liver metastasis, bone metastasis and other distant metastasis. *BRAF* mutation was detected using Sanger sequencing or amplification refractory mutation system (ARMS) which also provided molecular profile of *EGFR*, *ALK*, *MET*, *ROS1*, *HER2* (erb-b2 receptor tyrosine kinase 2), *RET*, *KRAS* (KRAS proto-oncogene, GTPase). Complete response (CR), radiographic partial response (PR), stable disease (SD), and progression disease (PD) were defined with reference to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The objective response rate (ORR) was defined as CR plus PR. The progression-free survival (PFS) was the time from the onset of treatment to the date of disease progression or death. The clinical outcomes were independently evaluated by two physicians, and possible disputes were discussed and decided by the senior physicians. The following-up end date was March 2022.

Statistical analysis

The baseline characteristics of patients were described. Fisher's exact test and chi-squared tests were used to compare ORR between groups. Kaplan-Meier survival analysis was performed to assess PFS, and log rank tests were used to compare survival rates. A two-sided P<0.05 was considered statistically significant. Statistical analyses were performed with SPSS (V23.0) and RStudio software (V4.0.1).

Results

Patient characteristics

Thirty-four patients with *BRAF*-mutant NSCLC were included in the analysis (*Table 1*). Sixteen patients received ICI-combined chemotherapy with 18 patients never receiving ICI-based therapy. The median age of our cohort was 64 years old (range 46 to 82 years old) and the proportion of male was a bit higher (n=23, 67.6%). Among all the included patients, 44.1% (15/34) of patients had smoking history and 88.2% (30/34) were diagnosed as lung adenocarcinoma. In the cohort, 85.3% (29/34) were diagnosed as stage IV. 11.8% (4/34) of patients had brain metastasis, 5.9% (2/34) of patients had liver metastasis, 20.6% (7/34) of patients had bone metastasis, and 70.6% (24/34) of patients had other organ metastasis. All of the included patients were detected as V600E mutation. Several of these patients were treated with other regimens after disease progression, and some even received fifth-line treatment.

Clinical outcomes

Description of the study population

The 54 treatment events were recorded in 34 patients at the cutoff date. The 9 patients received ICI-combined therapy, and 20 patients received chemotherapy or targeted therapy in first-line treatment. Other 7 ICI-combined treatment was applied in later-lines. Most patients who received ICI-combined therapy are still receiving it as of the last follow-up date (*Figure 1*). The 30 out of 54 had events of PFS as of data cutoff. The median PFS for the whole cohort was 5.8 months [95% confidence interval (CI): 4.4–16.7 months] (*Figure 2A*). The 12 of these treatments achieved PR and 25 achieved SD, with an ORR of 24% (*Figure 2B*).

Patients have better outcomes in first-line therapy (P=0.027), when the median PFS of 12.6 months (95% CI: 5.3–NA months) was found in first-line and in later-line was 5.3 months (95% CI: 1.9–NA months) (*Figure 3A*). SD was 59% and 36% in first-line and later-line respectively, while the proportion of PR in first-line was 24% and in later-line was 23% (*Figure 3B*), with statistical difference not reached (P=0.16).

More patients seemed get benefits from ICI-combined therapy. In ICI-combined treatment, the median PFS was 12.6 months (95% CI: 5.8–NA months) compared with 5.3 months (95% CI: 3.4–NA months) in non-ICI treatment (P=0.083) (*Figure 3C*). Furthermore, the ORR in ICI-combined therapy was 44% compared with 14% in non-ICI therapy (P=0.06) (*Figure 3D*).

First-line treatment ICI *vs.* non-ICI

Moreover, we analyzed the clinical outcomes in first-line treatment, respectively. The benefits of ICI-combined therapy only appeared in first-line treatment. The median PFS in ICI-combined group was 18.5 months (95% CI: 12.63–NA months) when in non-ICI group was 4.1 months (95% CI: 3.03–NA months) among the first-line cohort (P=0.0098) (*Figure 4A*). The ORR was 56% in ICI-combined and 10% in non-ICI therapy (P=0.02)

Table 1 Clinical and biological description of entire patients

Characteristics	Overall (N=34)	Non-ICI group (N=18)	ICI-combined group (N=16)	P
Age				
Median [95% CI]	64 [57, 69]	67 [58, 70]	62 [54, 66]	0.207
Gender (%)				
Male	23 (67.6)	12 (66.7)	11 (68.8)	1.000
Smoke (%)				
Ever	15 (44.1)	7 (38.9)	8 (50.0)	0.760
Never	19 (55.9)	11 (61.1)	8 (50.0)	
ECOG (%)				
0	6 (27.3)	4 (33.3)	2 (20.0)	0.118
1	9 (40.9)	6 (50.0)	3 (30.0)	
2	3 (13.6)	2 (16.7)	1 (10.0)	
Pathology (%)				
Ad	30 (88.2)	15 (83.3)	15 (93.8)	0.684
Non-Ad	4 (11.8)	3 (16.7)	1 (6.3)	
Stage (%)				
III	5 (14.7)	2 (11.1)	3 (18.8)	0.887
IV	29 (85.3)	16 (88.9)	13 (81.3)	
Brain metastasis (%)	4 (11.8)	0 (0.0)	4 (25.0)	0.085
Liver metastasis (%)	2 (5.9)	1 (5.6)	1 (6.3)	1.000
Bone metastasis (%)	7 (20.6)	4 (22.2)	3 (18.8)	1.000
Other metastasis (%)	24 (70.6)	13 (72.2)	11 (68.8)	1.000

ICI, immune checkpoint inhibitors; Ad, adenocarcinoma.

(*Figure 4B*). Especially, no patients get progressive disease in ICI-combined treatment.

Later-line ICI *vs.* non-ICI

However, during the later-line, ICI-combined treatment did not have a significant survival benefit compared with non-ICI treatments (P=0.087) (*Figure 4C*). The median PFS in ICI-combined group was 1.9 months (95% CI: 1.23–NA months) whereas in non-ICI group was 5.3 months (95% CI: 4.4–NA months). The ORR in ICI-combined group was 29% with 20% in non-ICI group (P=0.429) (*Figure 4D*). It indicates that ICI-combined therapy in front line shows more benefits compared with chemotherapy and targeted therapy, while in later-line, ICI-combined therapy may not be the preferable choice.

First-line ICI *vs.* later-line ICI

Interestingly, when taking the treatment lines into consideration, we found that the effect of immunotherapy in first-line treatment was much better than that of later-line treatment contrast to non-ICI therapy which showed no significant difference in clinical benefits. In ICI-combined group, the median PFS was 18.5 months (95% CI: 12.63–NA months) in first-line treatment and 1.9 months (95% CI: 1.23–NA months) in later-line treatment (P=0.009) (*Figure 5A*). Also, the ORR in first-line was 56% while in later-line was 29% (P=0.03) (*Figure 5B*). However, the median PFS was 4.1 months (95% CI: 3.03–NA months) in first-line treatment while in later-line treatment was 5.3 months (95% CI: 4.4–NA months) in non-ICI treatment (P=0.62) (*Figure 5C*). The ORR in first-line was

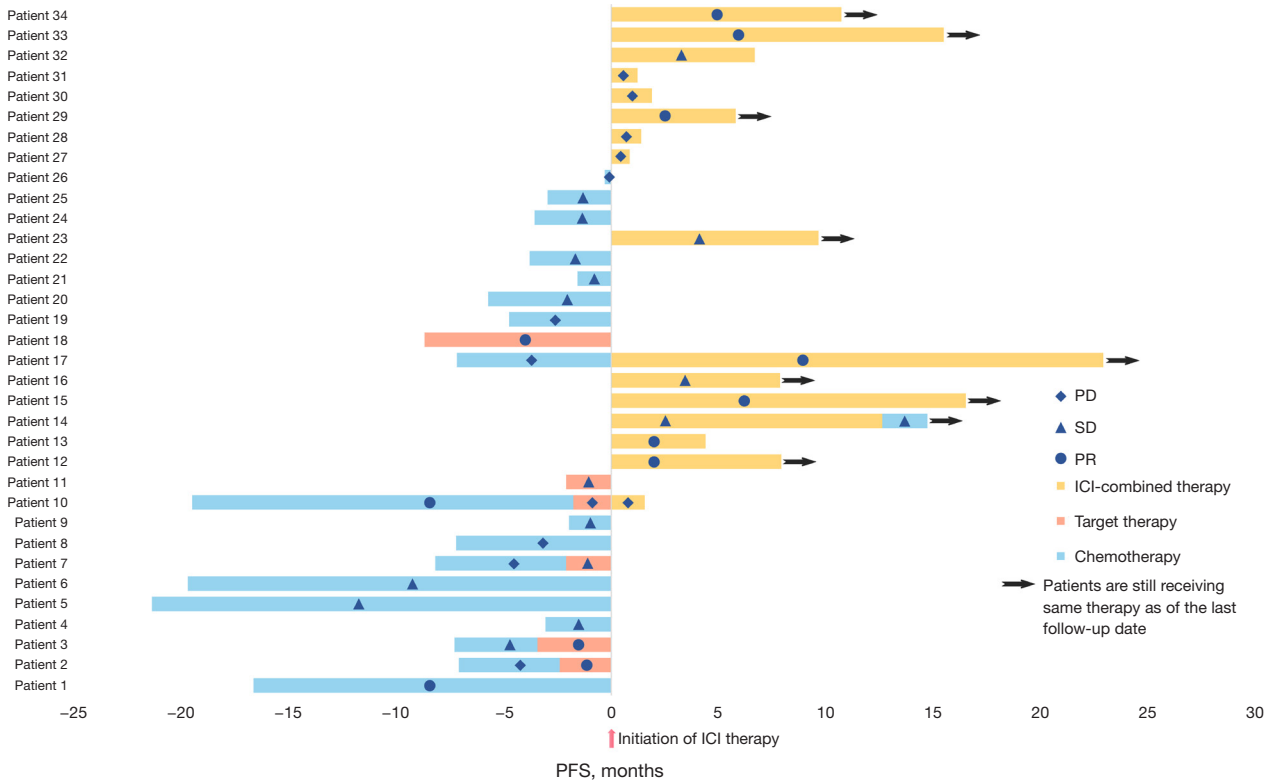

Figure 1 Progression-free survival of all *BRAF* mutant patients receiving different therapies. *BRAF*, proto-oncogene B-Raf, serine/threonine kinase; PFS, progression-free survival; ICI, immune checkpoint inhibitors; PR, partial response; SD, stable disease; PD, progression disease.

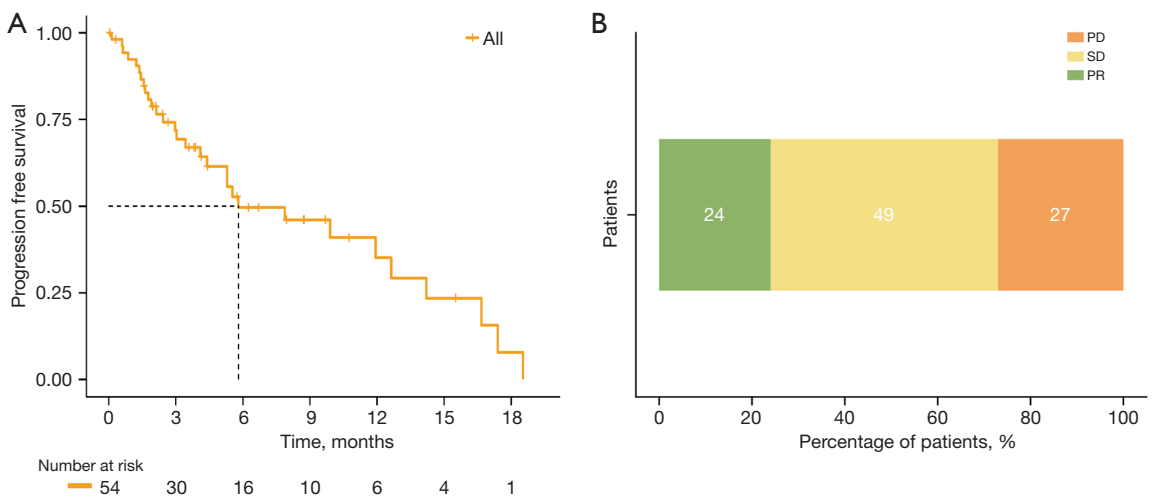

Figure 2 Progression-free survival (on the left) and objective response rate (on the right) in the whole cohort. PR, partial response; SD, stable disease; PD, progression disease.

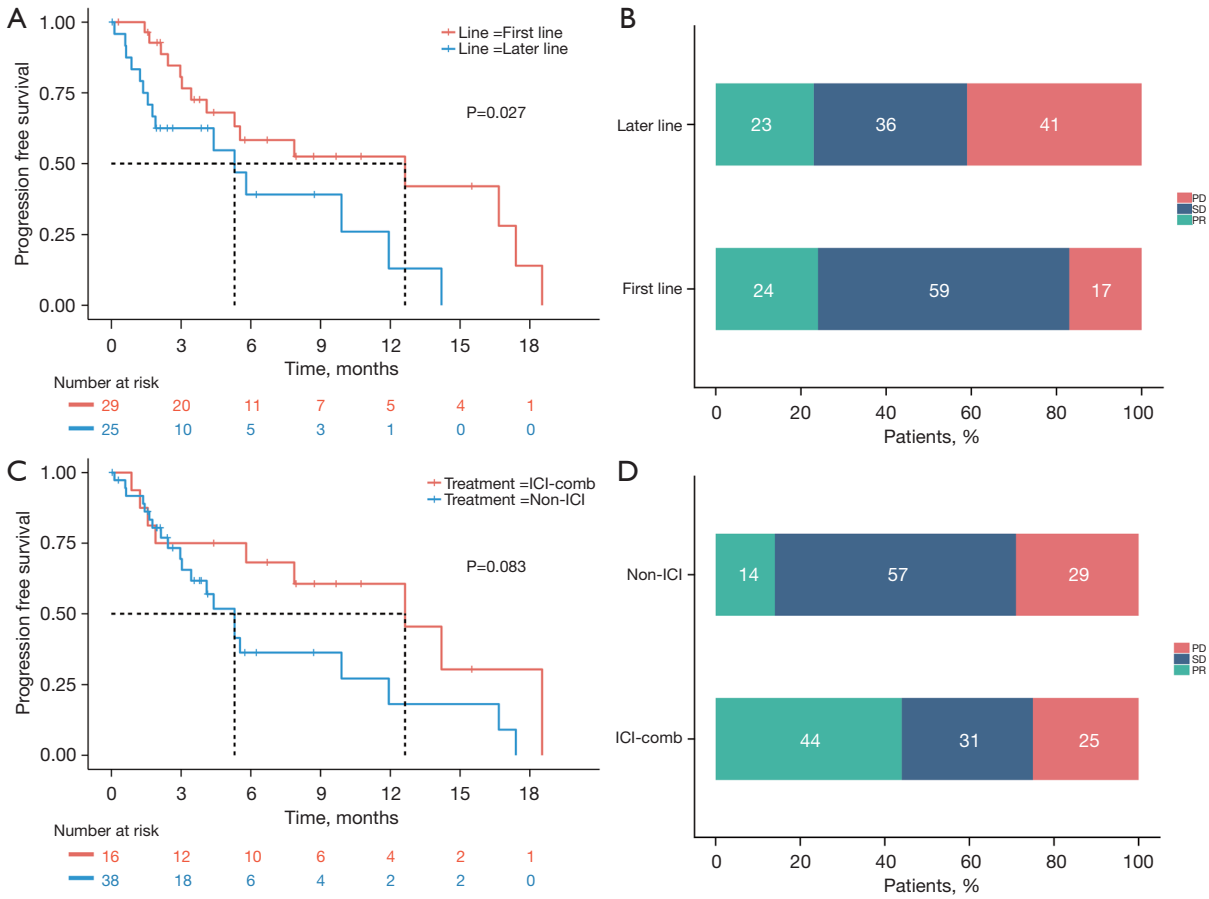

Figure 3 Progression-free survival (on the left) and objective response rate (on the right) in different therapy lines (upper figures) and different treatment strategies (lower figures). ICI, immune checkpoint inhibitors; PR, partial response; SD, stable disease; PD, progression disease.

10% while in later-line was 20% (P=0.52) (*Figure 5D*). It also indicated that ICI-combined therapy would be more available in front line treatment on the other hand.

Discussion

In this study, data from the cohort of patients with *BRAF*-mutant lung cancers reported to date were analyzed. The study found that immune combination chemotherapy had better treatment outcomes than chemotherapy and targeted therapy alone. PFS for ICI combination therapy was 12.6 months (95% CI: 5.8–NA months) compared with 5.3 months (95% CI: 3.4–NA months) for non-ICI therapy. In addition, the ORR for ICI combination therapy was 44% compared with 14% for non-ICI therapy. Considering the lines of treatment, patients treated with ICI combination therapy in first-line had better effects and that combination therapy did not show an advantage over chemotherapy and targeted therapy in the later-line of treatment. Also, first-line ICI combination therapy was more effective than later-line. In contrast, little difference was observed in clinical outcomes among patients receiving chemotherapy or targeted therapy. This study suggests that in NSCLC patients with *BRAF* mutation, a treatment strategy using immune-combination chemotherapy in the first-line and chemotherapy or targeted therapy after disease progression may be a better treatment modality.

The precision medicine model for advanced NSCLC relies on the targeted drugs acting on their oncogenic gene mutations. During clinical validation, a high response rate should be achieved in patients with advanced or metastatic NSCLC, leading to more durable responses than with classical cytotoxic chemotherapy. Targeted agents as first-line therapy for patients with EGFR-mutated or ALK-

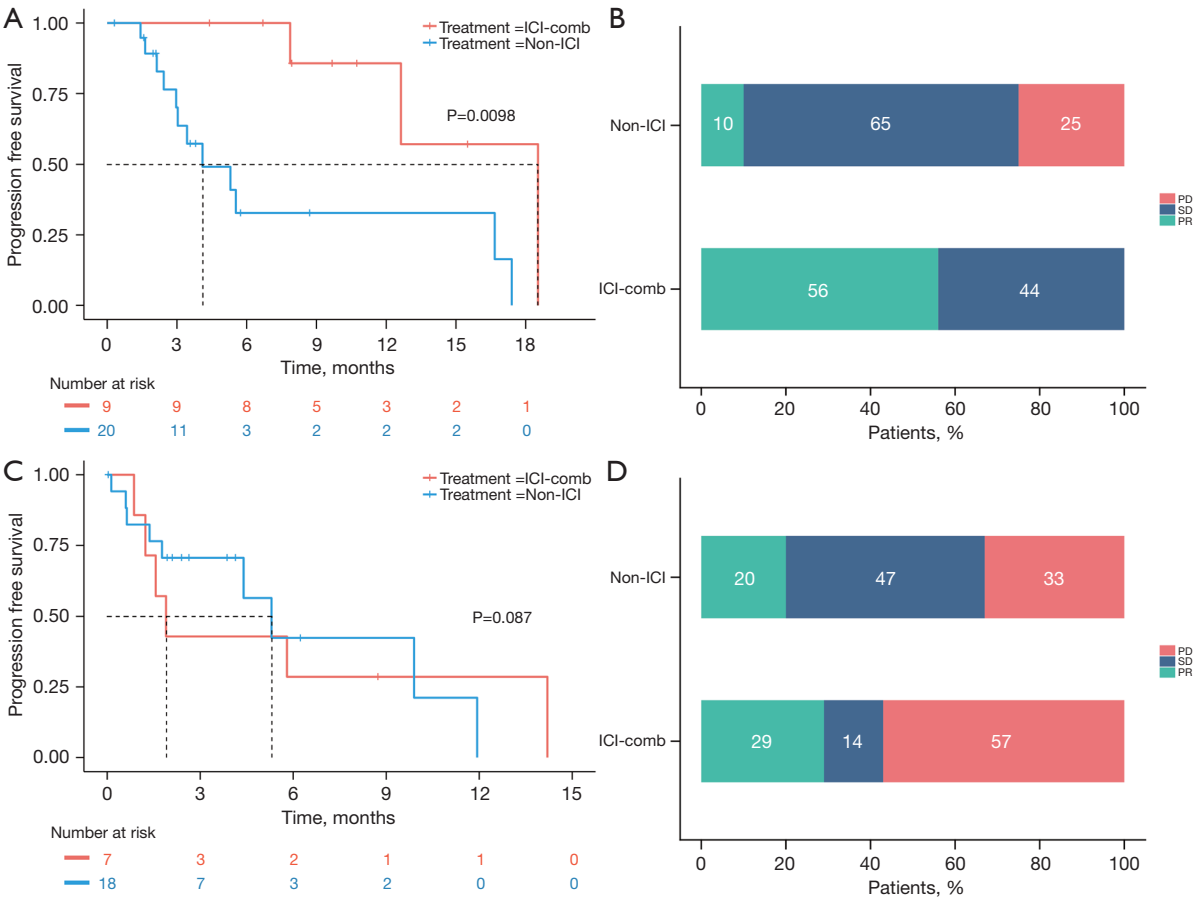

Figure 4 Progression-free survival (on the left) and objective response rate (on the right) of different treatment strategies in first-line (upper figures) and later-line (lower figures). ICI, immune checkpoint inhibitors; PR, partial response; SD, stable disease; PD, progression disease.

positive NSCLC have been demonstrated to be superior to platinum-based chemotherapy in a number of randomized studies, and have achieved worldwide acceptance (16,21-24). In the context of this impressive proof-of-concept clinical demonstration, other precision drugs targeting very rare NSCLC entities such as *NTRK* fusions, *MET* 14 exon mutations, *ROS1* rearrangements or *BRAF* V600E mutations were developed (9,25-28). All of these drugs were approved on the basis of single-arm studies. While patients and physicians are glad to have these additional and highly effective therapy options, using these agents requires extra caution and attention to as much clinical evidence as possible.

BRAF is a member of the RAF family of serine/threonine kinases and is part of the mitogen-activated protein kinase (MAPK) pathway, which is essential for regulating cell growth, proliferation and survival (29). In papillary thyroid cancers, colorectal cancers, and melanoma, *BRAF* mutations have been well documented, but not in NSCLCs, due to their low incidence. In melanoma, both ICI and targeted therapies are considered first-line options for patients with V600E mutation based on robust overall response rates (30-32). The general consensus in melanoma (33-36) is that *BRAF*/*MEK* inhibitors are recommended prior to ICI for patients with symptoms, significant organ involvement, or high tumor burden to achieve rapid tumor shrinkage and symptom improvement. Given the favorable safety profile of PD-1 inhibitors (37), they are recommended as first-line therapy over targeted therapies when rapid efficacy is not a concern. For non-V600E patients, few targeted therapies are being used, and immunotherapy continues to show good promise in this group. Regarding to NSCLC with *BRAF* mutation, this issue is further complicated by the efficacy of chemotherapy, as well as that of PD-L1 and TMB biomarkers for first-line immunotherapy. The therapy of non-V600E mutation refers to patients with negative driver

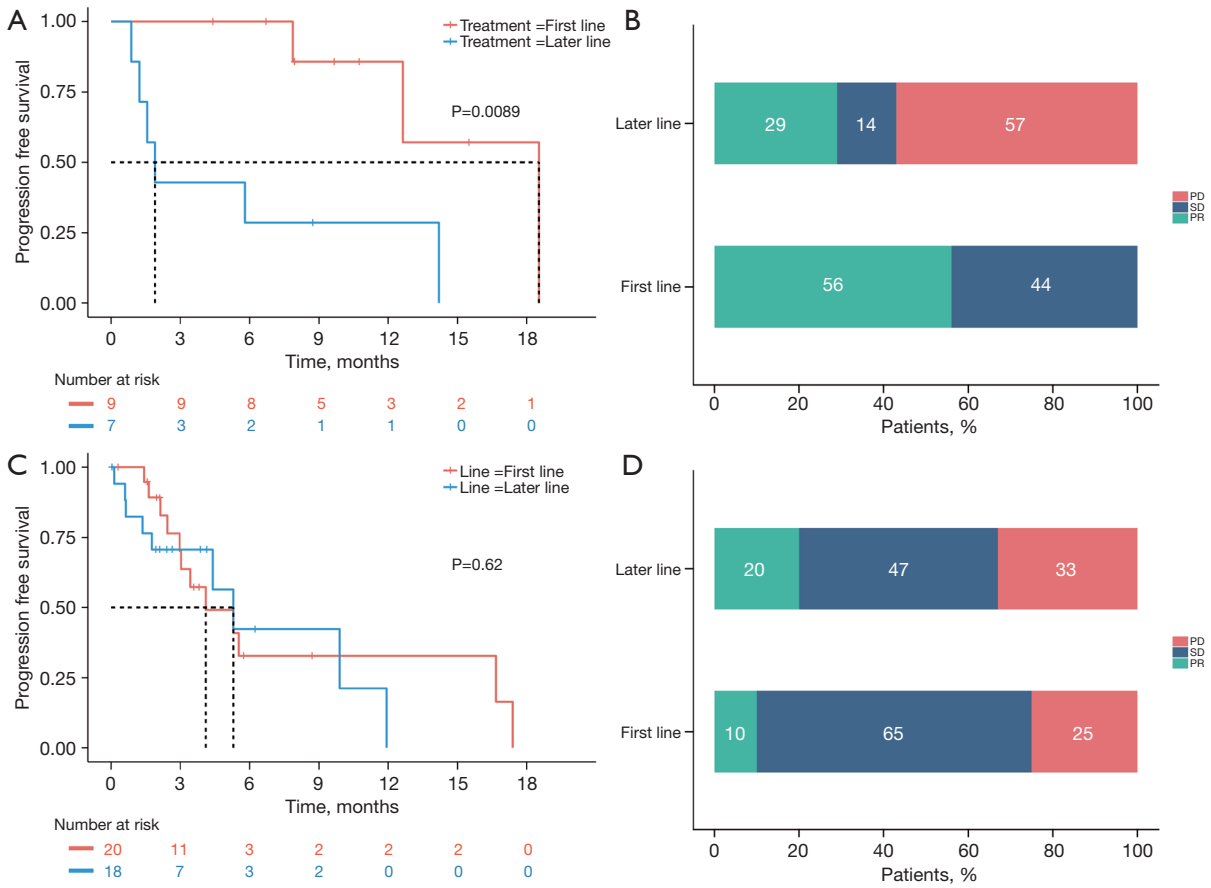

Figure 5 Progression-free survival (on the left) and objective response rate (on the right) of different therapy lines in ICI-combined group (upper figures) and non-ICI group (lower figures). ICI, immune checkpoint inhibitors; PR, partial response; SD, stable disease; PD, progression disease.

genes. In *BRAF* V600E mutant NSCLC, dabrafenib in combination with trametinib is efficient, but toxicity is a concern (especially fever and gastrointestinal dysfunction), whereas anti-PD-1/PD-L1 inhibitors are generally better tolerated. The efficacy of *BRAF/MEK* inhibitor therapy for V600E mutation is not affected by the number of lines of therapy and can be reserved as a follow-up treatment (9,38).

ICI monotherapy may be equally effective for patients with *BRAF*-mutant NSCLC of all functional classes as those with *BRAF* wild-type NSCLC, according to emerging evidence (15,17,18). This is significantly different from the findings in NSCLC patients with oncogenic drivers such as *EGFR*, *ALK* or *ROS1* aberrations (17,39). However, the efficacy in these patients treated with monotherapy is still not very satisfactory (40). With the increasingly widespread use of immune combination chemotherapy, we are also considering whether combination therapy has also shown great efficacy in this subgroup of *BRAF* mutations. Our data strongly support this scenario, which again raises questions about the choice of *BRAF*-targeted therapy, chemotherapy, or ICI-combined therapy as the most appropriate first-line option.

Due to the retrospective nature of our analysis, several limitations must be acknowledged. First, the small number of patients reviewed may lead to a potential selection bias. Second, before 2019, the test kit could only detect V600E mutation. After 2019, the multigene test kits could detect *BRAF* V600 mutations but cannot distinguish the specific subtype. Of the 34 cases we enrolled, 25 were detected as V600E directly. 9 were detected as *BRAF* V600 mutation and then confirmed as V600E by sanger sequence. Because only V600E mutation was detected, we were not able to specifically explore the role of each mutant subtype in ICI-combined therapy. Third, although the guidelines

had previously recommended targeted therapy, it was not approved in China until March 25, 2022 for V600-mutated non-small cell lung cancer (NSCLC). Therefore, only 6 of our patients received targeted therapy, so we grouped targeted therapy and chemotherapy together as non-ICI treatment and lacked data on direct comparisons of targeted therapy with ICI combination therapy. As more patients will be treated with targeted therapy or immunotherapy, we expect that a clear requirement for further research, preferably in randomized trials, to determine the better treatment modality in the future.

Conclusions

In summary, the findings observed an evidential and significant susceptibility to ICI combined chemotherapy in patients with *BRAF*-mutant NSCLC, especially in first-line treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-613/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-613/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-613/coif). CZ serves as the Editor-in-Chief of *Translational Lung Cancer Research*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was reviewed and approved by the Ethics Committee of Shanghai Pulmonary Hospital (No. K22-190Y) and was conducted in accordance with the Helsinki Declaration (as revised in 2013). The individual consent for this retrospective analysis was waived.

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Supplementary

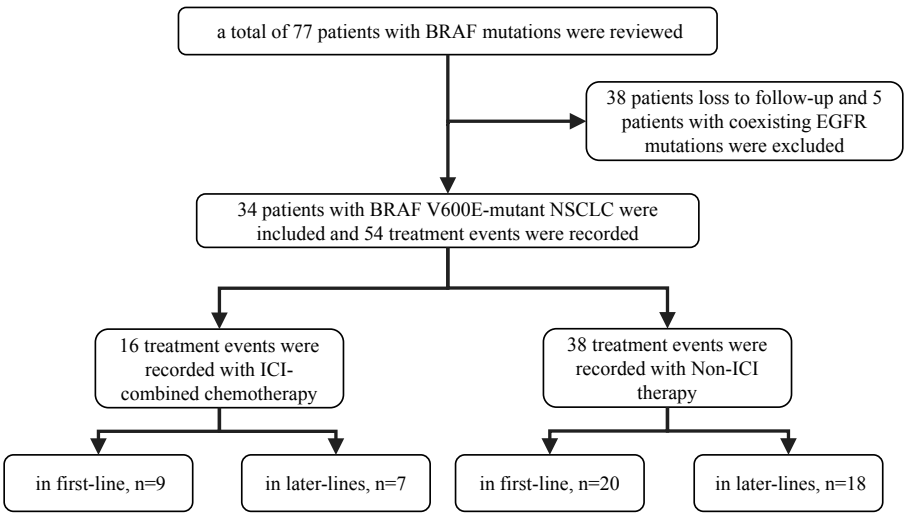

Figure S1 A flowchart of patients inclusion. BRAF, proto-oncogene B-Raf serine/threonine kinase; ICI, immune checkpoint inhibitors.

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