BRIEF REPORT

Patients With *BRAF*-Mutant NSCLC May Not Benefit From Immune Checkpoint Inhibitors: A Population-Based Study

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ABSTRACT

Introduction: There is no consensus on whether immune checkpoint inhibitors (ICIs) would offer comparable benefit in mutant-*BRAF* NSCLC. We, therefore, conducted a study to ascertain the role of ICIs in mutant-*BRAF* NSCLC.

Methods: Records of 4178 patients and 4462 samples from 15 studies were collected using the database from www.cbioportal.org. The role of *BRAF* mutation on the overall survival (OS) was analyzed in patients with NSCLC treated with ICIs. Kaplan-Meier analysis was used to calculate OS and the log rank test was used to compare the survival.

Results: Of the patients, 6.1% had the *BRAF* mutation. Mutations and copy numbers differed by sex. The programmed death ligand 1 expression was higher in patients with the wild-type *BRAF* compared with those with the *BRAF* mutation. *BRAF* mutation is linked with higher tumor mutational burden ($p = 0.009$). OS for patients with the ICI-treated mutant-*BRAF* and wild-type–*BRAF* NSCLC was 10 months and 11 months, respectively ($p = 0.334$). Subgroup analyses revealed that the median survival was 14 months in the non-V600E group and 5 months in the V600E group ($p = 0.017$).

Conclusions: Our results revealed that mutant-*BRAF* NSCLC was associated with high tumor mutational burden. However, for patients with NSCLC receiving ICIs, OS was prolonged in those who had no V600E mutation compared with those who had V600E mutation.

Keywords: *BRAF* mutation; Non-small cell lung cancer; Immune checkpoint inhibitor; Biomarker

Introduction

Management of patients with advanced NSCLC is currently undergoing significant transformation. It has become a clinical routine to determine precise molecular subsets to make optimized decisions. Immune checkpoint inhibitors (ICIs) now represent a promising treatment option, which could influence survival among patients with NSCLC. However, it has been generally acknowledged that ICIs would not provide significant benefit to patients with NSCLC harboring EGFR mutation.[1] Whether ICIs would offer comparable benefit in mutant-*BRAF* NSCLC remains to be checked.

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Drs. CX Zhang and CY Zhang equally contributed to this work.

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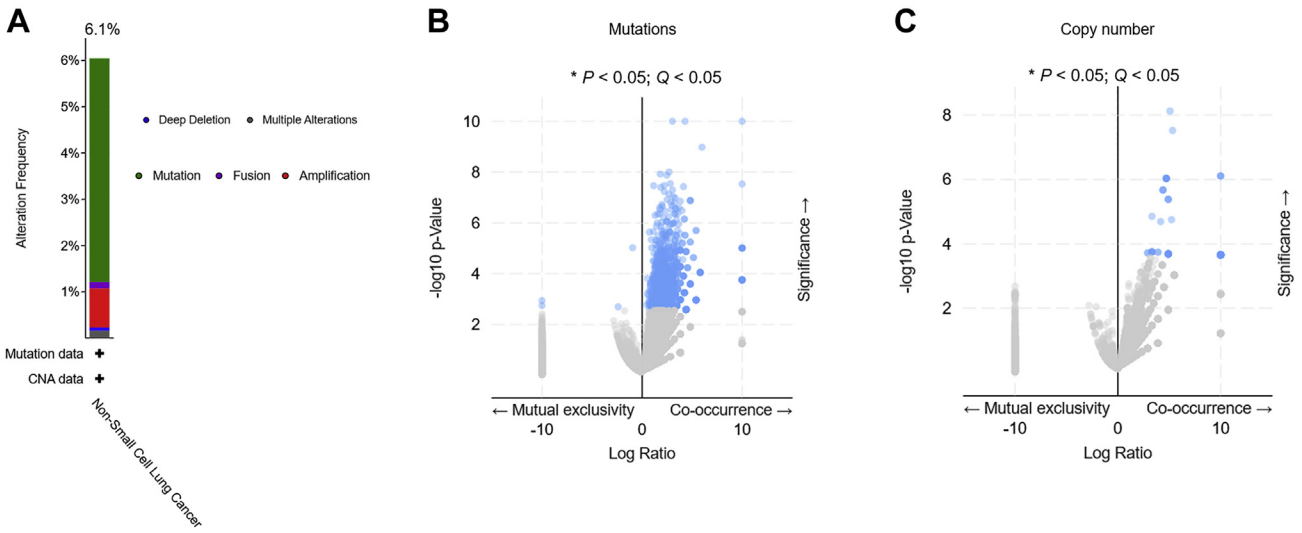

Figure 1. Mutation and CNA among patients with mutant-*BRAF* NSCLC using data collected from cBioPortal. A total of 4178 patients and 4462 samples were included in the database. (*A*) Waterfall plots showing different mutational forms and their alteration frequency among mutant-*BRAF* NSCLC. (*B*) Volcano plots exhibiting the mutational disparity between female and male patients with NSCLC harboring *BRAF* mutations. (*C*) Volcano plots exhibiting the copy number disparity between female and male patients with NSCLC harboring *BRAF* mutations. Blue dots represent those with $p < 0.05$ and $q < 0.05$, whereas gray dots represent those with $p > 0.05$ and $q > 0.05$, as shown in *B* and *C*. CNA, copy number alteration; cBioPortal, cBio Cancer Genomics Portal.

Materials and Methods

We collected the records of 4178 patients and 4462 samples from the cBio Cancer Genomics Portal (cBioPortal) database. All mutation data including fusion, amplification, deep deletion, and multiple alterations in all cancer types were detected. We then analyzed the probability of mutation and copy number alteration (CNA) in the *BRAF*-mutant group. Data from the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT), including 1661 tumor-normal pairs from 1661 patients, were employed to ascertain the association between overall survival (OS) and ICIs in *BRAF*-mutant and wild-type groups. Kaplan-Meier analysis was used to calculate OS and the log rank test was used to compare the survival curves. Institutional approval and patient consent were not needed because the data came from an open-access public database.

Results

*Mutation and CNA Among Patients With Mutant-*BRAF *NSCLC*

Mutation and CNA among patients with mutant-*BRAF* NSCLC were measured using data collected from cBioPortal. A total of 4178 patients and 4462 samples were included in the study. Different mutational forms (deep deletion, multiple alterations, fusion, and amplification) and their alteration frequency among mutant-*BRAF* NSCLC are exhibited in waterfall plots (Fig. 1*A*). Furthermore, mutational disparity between female and male patients with NSCLC harboring *BRAF* mutations are displayed in Figure 1*B*. The copy number disparity between female and male patients with NSCLC harboring *BRAF* mutations are likewise exhibited in volcano plots (Fig. 1*C*).

*Programmed Death Ligand 1, Tumor Mutational Burden, and OS in Patients With Mutant-*BRAF *and Wild-Type-*BRAF *NSCLC*

Genomic and survival data were obtained from 1661 patients with various cancer types sequenced with the MSK-IMPACT assay. There were no significant differences in programmed death ligand 1 (PD-L1) expression between the *BRAF*-mutant group and the *BRAF*–wild-type group ($p = 0.198$) (Fig. 2*A*). Tumor mutational burden (TMB) was evaluated in patients with both mutant-*BRAF* and wild-type–*BRAF* NSCLC. Results revealed higher levels of TMB in the *BRAF*-mutant group ($p = 0.009$) (Fig. 2*B*). Further analyses revealed that there was no difference in OS between the *BRAF*-mutant and *BRAF*–wild-type groups treated with ICIs ($p = 0.334$) (Fig. 2*C*). We then evaluated OS in patients with *BRAF* V600E and non-V600E NSCLC administered with ICIs. For patients with *BRAF* mutation subject to ICIs, OS was 14 months in the non-V600E group, significantly longer than 5 months in the V600E group ($p = 0.017$) (Fig. 2*D*).

Discussion

Dudnik et al.[2] recently conducted a retrospective study using a database encompassing seven

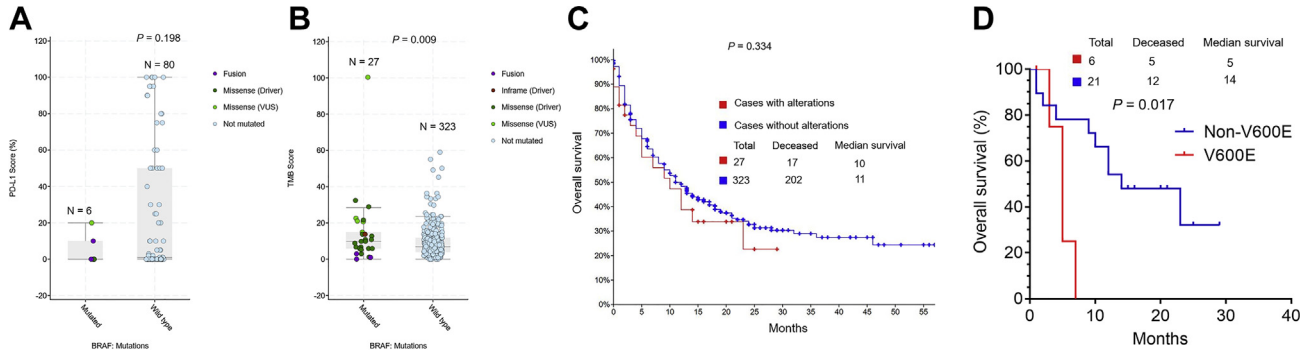

Figure 2. PD-L1, TMB, and OS were evaluated in patients with mutant-*BRAF* and wild-type-*BRAF* NSCLC using data collected from cBioPortal. Genomic and survival data were obtained from 1661 patients with various cancer types sequenced with the MSK-IMPACT assay. (*A*) PD-L1 expressions were evaluated in patients with mutant-*BRAF* and wild-type-*BRAF* NSCLC. (*B*) TMB was evaluated in patients with mutant-*BRAF* and wild-type-*BRAF* NSCLC. (*C*) OS was measured in patients with mutant-*BRAF* and wild-type-*BRAF* NSCLC treated with ICIs. (*D*) OS were tested in patients with *BRAF* V600E and non-V600E NSCLC treated with ICIs. cBioPortal, cBio Cancer Genomics Portal; ICIs, immune checkpoint inhibitors; MSK-IMPACT, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets; OS, overall survival; PD-L1, programmed death ligand 1; TMB, tumor mutational burden.

participating Israeli cancer centers. A total of 39 patients with mutant-*BRAF* NSCLC were enrolled, 22 of whom were exposed to ICIs. They were divided into either the V600E and non-V600E group, or the PD-L1–high and PD-L1–low or intermediate group. Results revealed that progression-free survival and OS were associated with either the *BRAF*-mutant subtype or PD-L1 expression. The study also revealed that patients with mutant-*BRAF* NSCLC treated with ICIs had more favorable benefits than those not exposed to ICIs. The results were consistent with previous studies reporting that *BRAF*-mutant patients benefited more from ICIs than patients harboring EGFR and MET mutation.[3,4]

A large amount of data has confirmed that immunotherapy markers such as PD-L1 expression, TMB, and microsatellite instability are potentially helpful markers for predicting response to ICIs.[5–7]

In the study Efficacy of ICI in patients with NSCLC Harboring Activating Molecular Alterations (Immuno-Target),[8] results revealed that progression-free survival was correlated with smoking status among 43 patients with mutant-*BRAF* NSCLC receiving ICIs, whereas the association between outcomes and PD-L1 expression was not elucidated. Therefore, it is possible that ICIs may be an optional strategy after targeted therapy and chemotherapy.

Rihawi et al.[9] carried out a retrospective study on the Italian expanded-access program comprising patients with advanced nonsquamous NSCLC treated with second-line nivolumab. They divided a total of 1588 patients into three subgroups: (1) *BRAF*-mutated (n = 11), (2) *BRAF*–wild-type (n = 199), and (3) *BRAF* not evaluated (n = 1378), with OS being 10.3 months, 11.2 months, and 11.0 months, respectively. They also reported that only one patient had partial response; the overall response rate was slightly lower than that obtained by Dudnik et al.[2] and Mazieres et al.[8] Unfortunately, PD-L1 and TMB were not assessed in the study.

To overcome the shortcomings in the studies performed by Dudnik et al.[2] and Rihawi et al.,[9] we, therefore, conducted a study encompassing 4178 patients and 4462 samples from 15 studies using the www.cbioportal.org database to ascertain the role of ICIs in NSCLC.[10] Of the patients, 6.1% were found to have the *BRAF* mutation in different forms (deep deletion, multiple alterations, mutation, fusion, and amplification), as exhibited in Figure 1*A*. We next sought to analyze the mutational and copy number status in mutant-*BRAF* NSCLC. Results revealed that most mutations that were detected differed by sex, as seen in Figure 1*B*. Figure 1*C* exhibits the copy number status among male and female patients.

One of the major flaws in the study conducted by Dudnik et al.[2] was the lack of patients with wild-type–*BRAF* NSCLC treated with ICIs as controls. We therefore incorporated patients with wild-type–*BRAF* NSCLC into our analysis. Of the 86 tumors that had tissue evaluated for PD-L1 expression, six were found to have the *BRAF* mutation. The mutant types were fusion, in-frame (driver), missense (driver), and missense (variants of uncertain significance). The results revealed that PD-L1 expression was higher in patients with the wild-type *BRAF* compared with those with *BRAF* mutation (p = 0.198) (Fig. 2*A*). To assess the association between TMB and *BRAF* mutation status, we used the TMB and Immunotherapy database.[11] This database contains genomic and survival data from 1661 tumor-normal pairs of 1661 patients with various cancer types sequenced with the MSK-IMPACT assay. A total of 350 patients with NSCLC were included in this database. *BRAF* mutation was linked

with higher TMB compared with the wild-type *BRAF* ($p = 0.009$), as exhibited in Figure 2*B*. OS for patients with mutant-*BRAF* NSCLC treated with ICIs was 10 months, whereas OS in patients with wild-type–*BRAF* NSCLC exposed to ICIs was 11 months ($p = 0.334$) (Fig. 2*C*).

To further ascertain the impact of ICIs on different subsets of mutant-*BRAF* NSCLC, the 27 patients were divided into V600E and non-V600E groups. Five of the six patients in the V600E group died, the median survival being 5 months, and 12 of the 21 patients in the non-V600E group died, the median survival being 14 months ($p = 0.017$) (Fig. 2*D*).

In summary, our results revealed that mutant-*BRAF* NSCLC was associated with high TMB, which is consistent with the results reported by Dudnik et al.[2] However, for patients with NSCLC subjected to ICIs, we found that OS was prolonged in patients with *BRAF* non-V600E compared with patients with *BRAF* V600E, which was contradictory to what Dudnik et al.[2] had previously reported. The observation that OS was improved among patients with *BRAF* non-V600E NSCLC compared with patients with *BRAF* V600E NSCLC is generally in line with the study conducted by Rihawi et al.[9] Nevertheless, it has to be noted that the patients enrolled had nonsquamous NSCLC, which was distinguished from NSCLC in our study cohort.

Smith et al.[12] reported that a durable benefit to PD-1 blockade could be seen in a 76-year-old patient harboring a *BRAF* N581I mutation. The underlying mechanisms could possibly be attributed to the T-cell responses to oncogenic driver mutations.

To the best of our knowledge, we have conducted the largest series study to explore the possible impact of ICIs on the particular subset of patients with NSCLC harboring *BRAF* mutations. Interestingly, we have found that this subtype of *BRAF* mutations could possibly determine the survival because of ICIs. In summary, ICI treatment for *BRAF*-mutant subgroups deserves careful evaluation in large prospective cohorts, the adoption of which should be considered with discretion.

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