Lung Cancer: Targets and Therapy

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ORIGINAL RESEARCH

Comprehensive Survey of AACR GENIE Database of Tumor Mutation Burden (TMB) Among All Three Classes (I, II, III) of *BRAF* Mutated (*BRAF*+) NSCLC

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Background: *BRAF* mutations are generally divided into three classes based on the different altered mechanism of activation.

Methods: We queried the public AACR GENIE database (version 13.1), which includes tumor mutation burden (TMB) data, to explore potential molecular differences among the three classes of non-small cell lung cancer (NSCLC).

Results: Out of 20,713 unique NSCLC patients, 324 (1.6%) were *BRAF* mutations positive *(BRAF*+) class I, 260 (1.3%) class II, and 236 (1.1%) class III. The distribution of patient characteristics, including sex, age, and race, remains uniform across the three classes. The median TMB (mt/MB) was 6.5, 9.5, and 10.3 for class I, II, and III, respectively. The mean TMB was 61.5 ± 366.1 for class I, 40.5 ± 156.2 for class II, and 129.4 ± 914.8 for class III. About 30.5% of *BRAF* V600E+ patients had TMB ≥ 10; 47.7% of class II had TMB ≥ 10; and 52.5% of class III had TMB ≥ 10. For those patients with TMB ≥ 10, the median TMB was 45, 28.9, 18.4 for class I, II, and III, respectively. For TMB ≥ 10 patients, *TP53* mutation was the most common co-alterations across all 3 classes.

Conclusion: A substantial proportion of *BRAF*+ NSCLC patients exhibited a TMB ≥ 10, among all three classes of *BRAF* mutation classification, including *BRAF* V600E+ NSCLC. Class III mutations appeared to have the highest median TMB, followed by class II, and then class I.

Keywords: target therapy, immunocheck point inhibitor (ICI), *BRAF* mutation, tumor mutation burden (TMB), class I, II, III mutations, NSCLC

Introduction

The landscape of actionable driver mutation in NSCLC is continuously evolving.[1] Among the various actionable driver mutations that have US Food and Drug Administration (FDA) approved treatment, *BRAF* (v-Raf murine sarcoma viral oncogene homolog B1) V600E is one of these validated targets.

BRAF is an integral part of the RAS-RAF-MEK-ERK signaling cascade, a pathway central to cell differentiation, growth, and survival.[2–5] Mutations in *BRAF* disrupt this tightly regulated pathway, fostering unchecked cell proliferation and tumorigenesis.[6] *BRAF* mutations are observed in approximately 2–5% of NSCLCs.[1,4,7] Importantly, *BRAF* mutations are categorically stratified into three classes, based on their signaling mechanisms from their underlying mutations.[8–10] Class I is distinguished by its robust kinase activity that directly stimulates the MEK-ERK signaling cascade. Notably, this category encompasses the *BRAF* V600 mutation, recognized as a significant oncogenic driver in NSCLC. Class II are *BRAF* non-V600E mutations while still possessing kinase activity, they require dimerization with other RAF proteins to effectively transmit signals through the MEK-ERK pathway.[11] Class III are also *BRAF* non-V600E mutations that are characterized by impaired kinase activity. They act as scaffolds to facilitate the activation of CRAF, another member of the RAF kinase family, thereby indirectly activating the downstream MEK-ERK signaling pathway.[11] Those with *BRAF V600* mutations seems to be more likely to be found in light or never-smokers compared with those with non-V600

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mutations (42 versus 11%), and the prognosis was significantly better compared with non-V600 mutations (three-year survival rate, 24 versus 0%).[12]

Immune checkpoint inhibitors (ICIs), targeting the Programmed Death-1 (PD-1)/Programmed Death-Ligand 1 (PD-L1) axis, are the standard first-line therapy for most NSCLC patients without actionable mutations, either as monotherapy for high PD-L1 expression or combined with chemotherapy. While their efficacy in NSCLC with oncogenic alterations, including *BRAF* V600E mutations, is still under investigation, emerging evidence suggests potential activity in this subset.[13] Tumor Mutation Burden (TMB) is an important biomarker for the selection of the use of ICIs in solid tumors.[14–17] TMB expressed as the number of mutations per megabase (mut/Mb) of the genome examined offers a quantitative measure of the number of mutations within a tumor's DNA. The higher the TMB the higher the genomic complexity of the tumor and in lung cancer usually represents previous smoking exposure.[18] In the LC-SCRUM-Asia study, Sakai et al examined the TMB in 82 *BRAF*-mutated NSCLC samples and revealed that Class III *BRAF* mutations were associated with a higher median TMB compared to Class I (8.9 vs 3.7, $p<0.01$),[19] highlighting a potential distinct molecular profile and pathogenesis among these three classes of *BRAF* mutations.

Currently, only *BRAF* V600E+ NSCLC has the FDA approved treatment - a combination regimen of a BRAF inhibitor and MEK inhibitor (dabrafenib + trametinib and encorafenib + binimetinib respectively). The other two classes (II and III) and within the class I *BRAF* mutations, the non-*BRAF* V600E mutants have no approved targeted treatment. We investigated TMB in *BRAF* mutations positive (*BRAF*+) NSCLC patients to assess the percentage of high TMB (≥10) *BRAF*+ NSCLC patients who could then potentially benefit from treatment with ICI.

Methods

Data Source and Extraction

The American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) (https://genie.cbioportal.org) is an ongoing international pan-cancer registry that has accumulated data from more than 110,000 tumors by April 2024 making it the largest repository of publicly accessible, clinically annotated genomic data. We accessed the GENIE version 13.1's patient data, which included 148,222 patients and 167,358 samples.[20] It was publicly released in June 2023 and was accessed in August 2023. In accordance with 45 CFR 46, it was determined that the present study was exempt from institutional review board review and the requirement for informed consent because it utilized publicly available deidentified data. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for retrospective cross-sectional studies.

The database was queried for NSCLC patients exhibiting the three *BRAF* mutation classes. Class I: V600D/E/M/K/R; Class II: K601E/N/T, L597Q/V, G469A/V/R, G464V/E; Class III: D287H, V459L, G466A/E/V, S467L, G469E, N581S/I, D594A/G/H/N, F595L, G596D/R.[21,22] We extracted variables of interest from the database, including demographic data (age at sequencing, sex, and race), data sources, and tumor characteristics.

TMB

TMB is not publicly listed but obtained from the AACR GENIE database statistician. The methods of how AACR GENIC generated TMB has been previously reported.[23]

Statistical Analysis

Data organization and analysis were conducted using Microsoft Excel (version 2306) and R Project (version 4.3.3). For continuous variable group comparisons, the Wilcoxon rank-sum test was used. Two-sided $P < 0.05$ was considered statistically significant.

Results

Distribution of the *BRAF* Mutations

Of the 20,713 NSCLC patients, we identified 1173 (5.8%) *BRAF*+ NSCLC patients: 324 patients (1.6%) with class I *BRAF* mutations, 260 patients (1.3%) with class II mutations, and 236 patients (1.1%) with class III mutations. Among the *BRAF*+ NSCLC, 25.8% were class I, 20.7% class II, 18.8% class III and 34.7% non-class I–III. The distribution of

Table 1 Classification of *BRAF* Mutations

Class I (N = 324)	Class II (N = 260)	Class III (N = 236)
V600E (99.1%) V600K (0.6%) V600D (0.3%)	G469A/V/R (64.6%) K601E/N (23.5%) G464V/E (9.6%) L597Q (2.6%)	G466V/E/A (39.0%) D594N/G/A/H (29.2%) N581S/I (20.3%) G596R (8.5%) G469E (1.7%) V459L (0.85%) D287H (0.4%) S467L (0.4%)

the *BRAF* mutations in all three classes is shown in Table 1 and Figure 1A–D. All class I to class III *BRAF* mutations are missense mutations. While the majority of non-class I–III *BRAF* mutations are also missense mutations (64.9%), they include other types of alterations such as fusions (9.9%), splice region mutations (4.8%), in-frame deletions (4.5%), nonsense mutations (4.2%), in-frame insertions (3.7%), splice site mutations (3.1%), frameshift insertions (2.8%), and frameshift deletions (2%).

Among 324 patients with class I mutations, predominantly were V600E (321 cases), with V600K and V600D found in 2 and 1 cases, respectively (Figure 1B). The class II group comprised 260 patients, including G469A (N = 114), K601E (N=50),

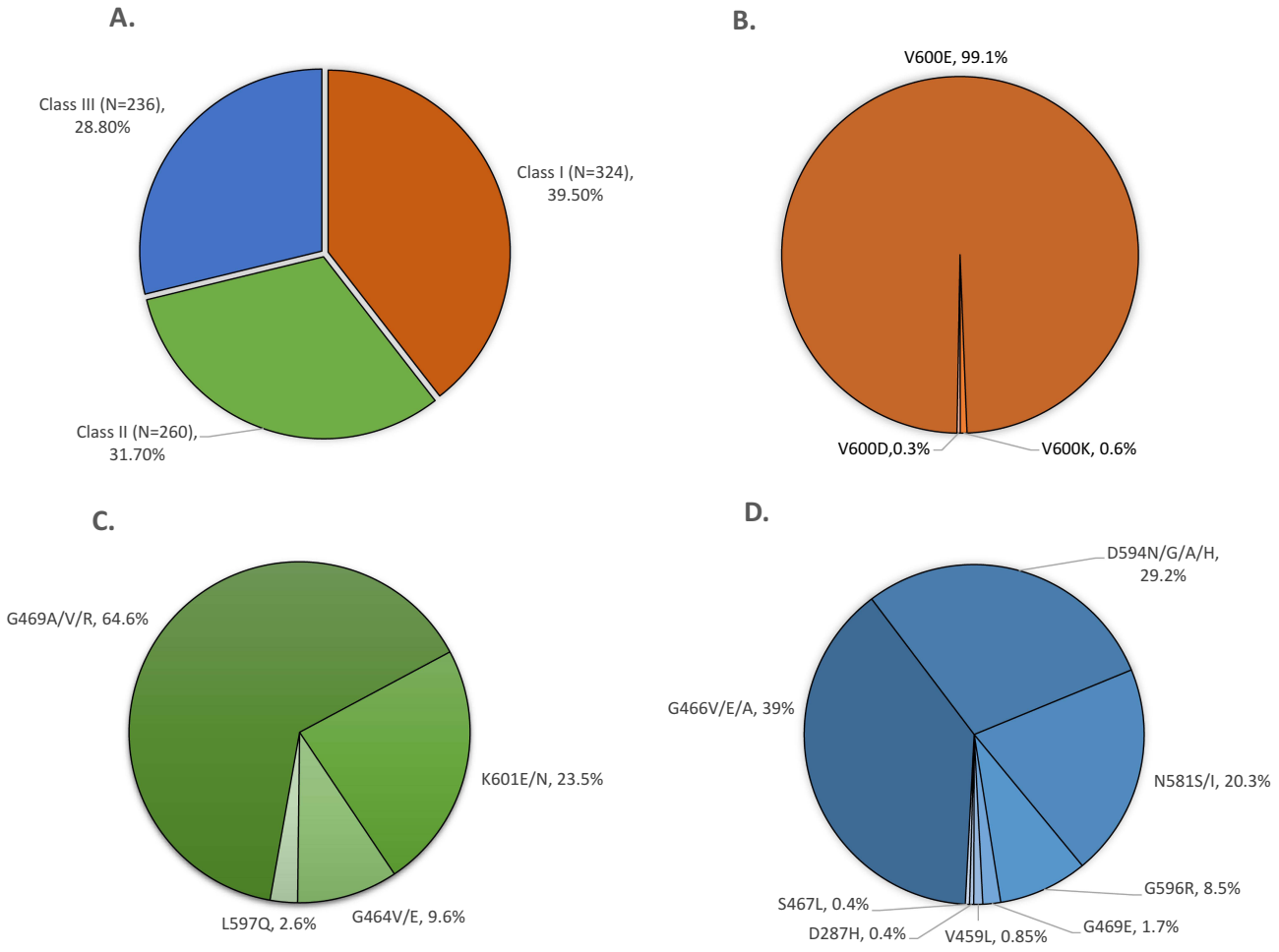

Figure 1 Pie chart on the frequency of class I, II, and III *BRAF* mutations. (**A**) Percentage of the 3 classes of *BRAF* mutations. (**B**) Frequency of individual class I *BRAF* mutations. (**C**) Frequency of individual class II *BRAF* mutations. (**D**) Frequency of individual class III *BRAF* mutations.

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Table 2 Clinical Characteristics of Patients With *BRAF*-Mutant NSCLC by Mutation Class

Clinical Characteristics	Class I (N = 324)	Class II (N = 260)	Class III (N = 236)
Age at Diagnosis, Years			
Mean (SD)	67.4 (10.5)	69.0 (8.9)	67.6 (9.6)
Sex, Number (%)			
Female	190 (58.6)	147 (56.5)	117 (49.6)
Male	134 (41.5)	113 (43.5)	119 (50.4)
Ethnicity, Number (%)			
White	229 (70.7)	209 (80.4)	183 (77.5)
Black	27 (8.3)	18 (6.9)	25 (10.6)
Asian	16 (4.9)	6 (2.3)	5 (2.1)
Unknown	52 (16)	27 (10.4)	23 (9.7)

Abbreviations: NSCLC, non-small cell lung cancer; SD, Standard deviation.

G469V (N = 43), G464V (N = 24), K601N (N = 11), G469R (N = 11), L597Q (N = 6), and G464E (N = 2) (Figure 1C). Class III mutations were observed in 236 patients, including G466V (N = 66), N581S (N = 34), D594N (N = 34), D594G (N = 25), G596R (N = 20), G466A (N = 16), N581I (N = 14), G466E (N = 10), D594H (N = 6), G469E (N = 4), D594A (N = 3), V459L (N = 2), D287H (N = 1), S467L (N = 1), and F595L (N = 1) (Figure 1D).

Sex and Ethnicity Distribution

There were 190 female (58.6%) and 134 male (41.5%) in class I, with an average age of 67.4 ± 10.5. There were 147 female (56.5%) and 113 male (43.5%) in class II, with an average age of 69.0 ± 8.9. There were 117 female (49.6%), and 119 male (50.4%) in class III, with an average age of 67.6 ± 9.6 (Table 2). Smoking status was not captured in the database.

TMB Analysis

The median TMB (mt/MB) were 6.5, 9.5, and 10.3 for class I, II, and III *BRAF*+ NSCLC, respectively (Figure 2). Significant differences per Wilcoxon testing were observed between class I and II ($p<0.001$) in addition to class I and class III ($p<0.001$). The mean TMB was 61.5 ± 366.1 for class I, 40.5 ± 156.2 for class II, and 129.4 ± 914.8 for class III. About 30.5% of *BRAF* V600E had TMB ≥ 10; 47.7% of class II had TMB ≥ 10; and 52.5% of class III had TMB ≥ 10. For those patients with TMB ≥ 10, the median TMB was 45, 28.9, 18.4 for class I, II, and III, respectively.

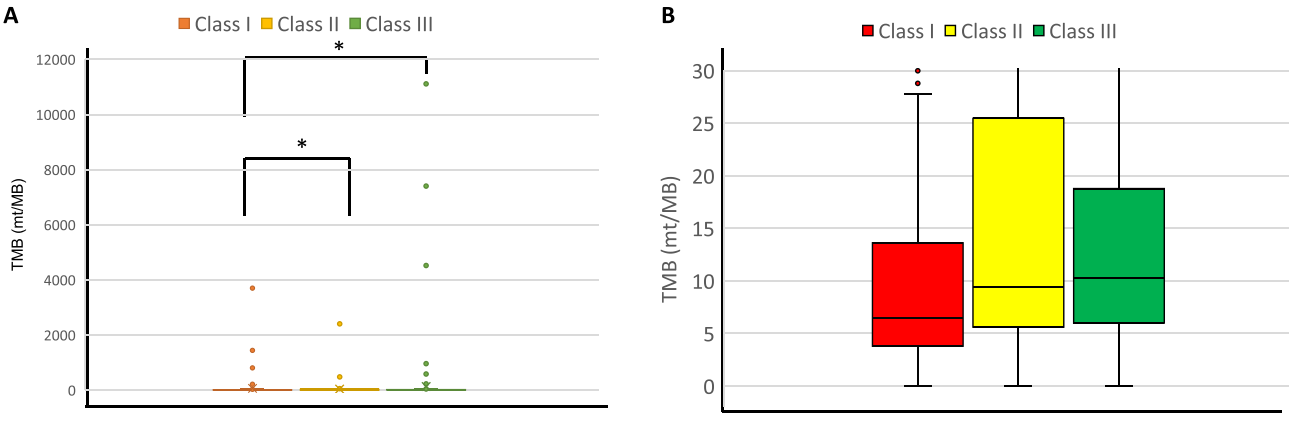

Figure 2 Box and whiskers plot of tumor mutation burden (TMB) in *BRAF*+ NSCLC by mutation class. (**A**) Median TMB (mut/Mb) values were 6.5, 9.5, and 10.3 for class I, II, and III *BRAF*+ NSCLC, respectively. Significant differences were observed between class I and class II (p = 2.092e-05) as well as class I and class III (p = 2.604e-07) based on Wilcoxon testing. (**B**) Zoomed-in view of the TMB range (0–30 mut/Mb) from (**A**), providing a detailed visualization of the data distribution within this range. Asterisk represents significant difference between classes.
Abbreviations: NSCLC, non-small cell lung cancer; TMB, tumor mutation burden.

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The median TMB for *TP53* mutations positive (*TP53*-mut)/*BRAF*+ class I NSCLC patients was 7.15, compared to a median of 6 for *TP53* mutations negative (*TP53*-wt) class I NSCLC patients (P=0.009). In class II, the median TMB for *TP53*-mut was 12.7, compared to a median of 7.65 for *TP53*-wt patients (P=0.002). In class III, the median TMB for *TP53*-mut was 12.6, compared to a median of 7.9 for *TP53*-wt patients (P=0.007) (Figure 3). Among *TP53*-mut patients, both class II and class III demonstrated significantly higher median TMB compared to class I ($P < 0.05$).

Major Genomic Alteration Associated With High TMB in *BRAF* Class I-III mutations

The most common co-currence mutation with *BRAF*+ NSCLC was *TP53* (49.4%), *KRAS* (17.7%) and *STK11* (17.4%). In patients with a TMB≥ 10 within *BRAF* class I, the predominant concurrent alteration was observed in *TP53* (42.6%), followed by *SETD2* (13.8%). Among *BRAF* class II with a TMB ≥10, the most common co-alteration was *TP53* (62.6%), followed by *STK11* (20%) and *EPHA3* (17.4%). For TMB ≥10 *BRAF* class III patients, the most common co-alteration was *TP53* (71.2%), followed by *KEAP1* (22.9%) and *STK11* (20.3%) (Figure 4). The percentage of *TP53* co-mutations increased progressively across the classes, from 42.6% in class I to 62.6% in class II, and 71.2% in class III.

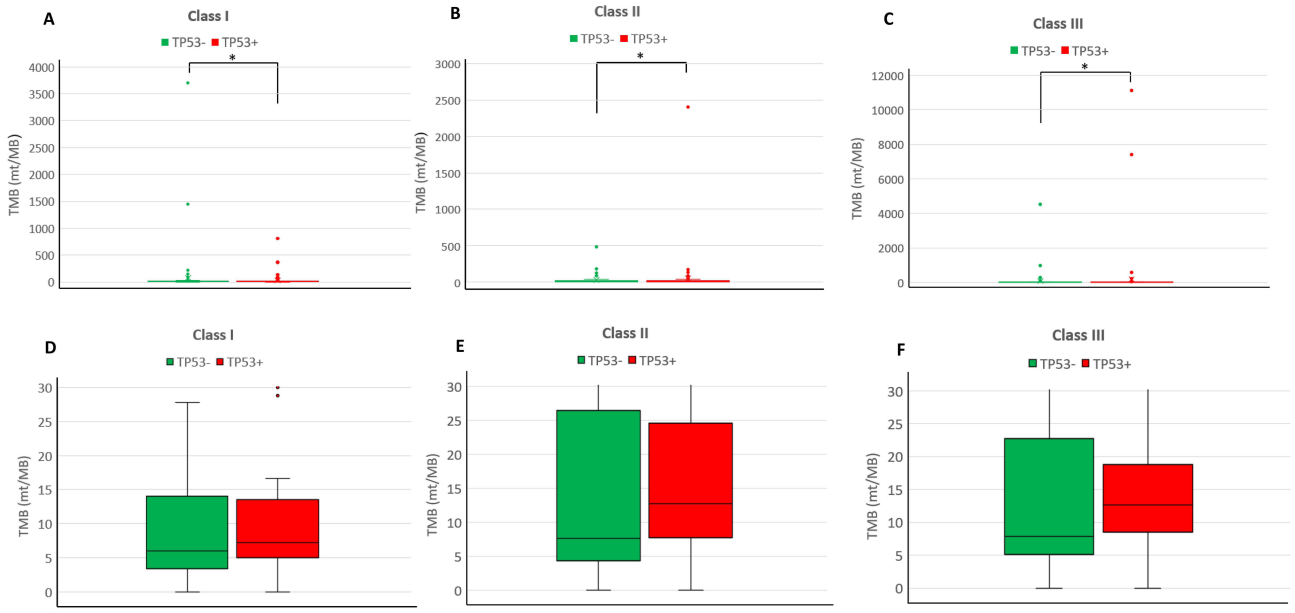

Figure 3 Box and whiskers plot of tumor mutation burden (TMB) in *BRAF*-mutant NSCLC by *TP53* mutation status. (**A**) In Class I, the median TMB for *TP53*-mut patients was 7.15, compared to a median of 6 for *TP53*-wt patients. Significant differences were observed (P = 0.009, Wilcoxon test). (**B**) In Class II, the median TMB for *TP53*-mut was 12.7, compared to 7.65 for *TP53*-wt patients. Significant differences were observed (P = 0.002, Wilcoxon test). (**C**) In Class III, the median TMB for *TP53*-mut was 12.6, compared to 7.9 for *TP53*-wt patients. Significant differences were observed (P = 0.007, Wilcoxon test). (**D**–**F**) Detailed view of the TMB range (0–30 mut/Mb) as zoomed-in sections from (**A**–**C**) respectively. Asterisk represents significant difference between classes.
Abbreviations: NSCLC, non-small cell lung cancer; TMB, tumor mutation burden; *TP53*-mut, *TP53* mutations positive; *TP53*-wt, *TP53* wild-type.

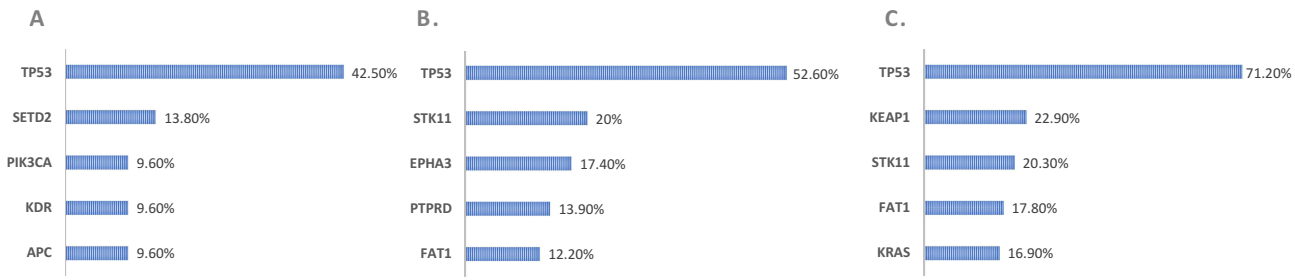

Figure 4 Common co-alterations in *BRAF*+ NSCLC by mutation class. (**A**) Common co-alterations in Class I. (**B**) Common co-alterations in Class II. (**C**) Common co-alterations in Class III.
Abbreviation: NSCLC, non-small cell lung cancer.

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Discussion

Our exploration into the TMB across the three classes of *BRAF*+ NSCLC unveils genomic complexity unique to each class of *BRAF* mutations. The median TMB values for all three classes were relatively low, which aligns with findings from previous research.[19] However, a significant proportion of *BRAF*+ NSCLC across all classes harboring a TMB of 10 or higher underscores TMBs as a biomarker for additional treatment with ICIs. High TMB is linked to increased neoantigen load, rendering tumors more recognizable to the immune system, and enhances the effectiveness of ICIs, as they work by unleashing the immune system's ability to target and destroy cancer cells.[15] Clinical studies have demonstrated that patients with high TMB (≥10) solid tumors experience better response rates and improved survival outcomes when treated with ICIs compared to those with lower TMB.[24] This practical implication of these results is that many *BRAF*+ NSCLC patients could benefit from ICI. Our observation could potentially elucidate why *BRAF*+ NSCLC (both V600 and non-V600) demonstrates a more favorable response to immunotherapy than most driver oncogene NSCLC.[13] While there were no differences in the progression free survival (PFS) for immunotherapy among the three subgroups,[19,25,26] Bracht et al reported that treatment with chemotherapy plus immunotherapy resulted in lower PFS in class I *BRAF*+ NSCLC (median 1.8 months, N=3) compared to class II (6.1 months, N=3) and class III (5.0 months, N=3; one patient received osimertinib).[27]

The divergent TMB profiles across classes emphasize that a "one-size-fits-all" approach may be inadequate. The elevated TMB in class III, in particular, hints at underlying genomic instability or increased mutagenic processes and potentially a different underlying pathogenic pathways. Interestingly, our study also highlighted the significant variability within each class, particularly in class III, as evidenced by the high standard deviation in mean TMB. This suggests that even within each class, there is substantial molecular heterogeneity that could impact disease behavior and treatment responses. The use of next-generation sequencing is important not just to diagnose *BRAF* mutations but to determine the TMB.

Recent research has aimed at developing therapies for tumors with *BRAF* non-V600E mutations.[28] A small retrospective series including patients with class II or III *BRAF*+ NSCLC found limited response to monotherapy with BRAF inhibitors, consistent with preclinical studies suggesting that these inhibitors are less effective against dimer-promoting *BRAF* variants. This observation is supported by clinical reports in melanoma where resistance to BRAF inhibitors has been linked to genetic alterations that promote RAF dimerization.[29] Another study involving 3 patients with NSCLC harboring Class III *BRAF* mutations found that treatment with MEK inhibitors led to progressive disease in 2 patients, with only 1 patient achieving short-term disease stabilization.[29] This underscores the complexity of these mutations and the imperative need for larger, prospective studies to evaluate the potential of MAPK-directed therapies and other novel treatment strategies for these specific molecular subsets. Hence, it is even more important to assay for TMB to provide potentially more than half of these patients with ICIs.

TP53, a gene commonly associated with tumor suppression, appears as the top co-alteration across all *BRAF* classes, with its prevalence increasing from class I to class III. The presence of *TP53* mutations in a significant majority may potentially negatively modulate the response to targeted therapy and warrants further investigation. For class II, the co-alteration in *STK11* (20%) may influence response to immunotherapy, as *STK11* mutations have been associated with resistance to ICIs in lung cancer.[30,31] *BRAF* class III harbors the highest percentage of *TP53* co-mutations (71.2%), indicating a potential for a more aggressive tumor profile. *KRAS* mutations (16.9%) in this group could imply a subset of tumors that may not respond to standard therapies targeting BRAF alone due to the involvement of KRAS in alternate proliferative signaling pathways.

Within each class of *BRAF* mutations, *TP53* positivity exhibited a higher median TMB than those with *TP53* negativity. Especially in class II and III *BRAF* mutations, where the median TMB of *TP53* positivity was greater than 10, a threshold for use of ICIs. This may suggest that *TP53* mutations are linked to an increased TMB, as reported in the previous study[32] or potential a positive smoking history which was not systemically captured in the AACR GENIE database.

Limitations

First, TMB was calculated from different sequencing platforms used by the reporting institutions which may explain the large range of TMB reported. Second, the smoking history was not captured as this is important etiology and prognostic factor in NSCLC. High TMB and/or *TP53*-mut may refelct a smoking history which would add further confidence in the anticipated efficacy of ICIs. Third, the lack of treatment outcome data limited further insight into how TMB and the three classes of mutations interact. Finally, the study is constrained by the lack of reported PD-L1 expression levels within the GENIE dataset, which is another predictive factor for the efficacy of ICIs.

Conclusion

Our analysis of the AACR GENIE database reveals a complex and heterogeneous molecular landscape of *BRAF* + NSCLC. A large proportion of *BRAF*+ NSCLC harbored a high TMB (≥10) regardless of the classification of the mutations. Class I *BRAF*+ NSCLC may benefit from additional ICI if the TMB ≥10. For class II and III *BRAF*+ NSCLC, given the lack of approved targeted therapies, ICIs are likely the standard of care. However, future targeted therapies, such as a pan-RAS inhibitor, may potentially be combined with ICIs.

Abbreviations

AACR, American Association for Cancer Research; BRAF, V-Raf Murine Sarcoma Viral Oncogene Homolog B; *BRAF+, BRAF* mutations positive; FDA, Food and Drug Administration; GENIE, Genomics Evidence Neoplasia Information Exchange; ICI, Immunocheck Point Inhibitor; MSI/MMR, Microsatellite Instability/Mismatch Repair; NSCLC, Non-Small Cell Lung Cancer; PD-L1, Programmed Death-Ligand 1; PFS, Progression Free Survival; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TMB, Tumor Mutation Burden; TP53-mut, TP53 mutations positive; TP53-wt, TP53 wild-type.

Data Sharing Statement

The data utilized in this research is publicly available except for the tumor mutation burden (TMB) which was obtained from the AACR GENIE database statistician.

Ethics Approval and Consent to Participate

In accordance with 45 CFR 46, it was determined that the present study was exempt from institutional review board review and the requirement for informed consent because it utilized publicly available deidentified data. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for retrospective cross-sectional studies.

Consent for Publication

This is an observational study involving analysis of secondary data only. All data were deidentified. There was no direct interaction with human subjects for this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dr. Ou has received speaker bureau honoraria from Pfizer, Janssen/JNJ, DAVA Oncology LLP, and OncLive. He also holds advisory board roles with AnHeart Therapeutics, Pfizer, Janssen/JNJ, Daiichi Sankyo, BMS, and Elevation Oncology, for which he receives honoraria. Additionally, he serves on the scientific advisory boards for Elevation Oncology and AnHeart Therapeutics and has ownership in MBrace Therapeutics, Nuvalent, Nuvation, and BlossomHill Therapeutics. Dr Nagasaka has received consulting fees from Caris Life Sciences, honoraria from AstraZeneca, Daiichi Sankyo, Novartis, Lilly, Pfizer, EMD Serono, Genentech, Regeneron and BMS. She is a speaker for Mirati, Takeda, Janssen, and Blueprint Medicine and has received travel support from AnHeart Therapeutics. The authors report no other conflicts of interest in this work.

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