BRIEF COMMUNICATION

**PBRM1** mutation and preliminary response to immune checkpoint blockade treatment in non-small cell lung cancer

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Polybromo-1 (**PBRM1**) gene is a promising biomarker for immunotherapy in clear cell renal cell carcinoma. But to our knowledge, the frequency and clinical relevance of **PBRM1** mutation in lung cancer remain unknown. We conducted a retrospective study to evaluate the prevalence of **PBRM1** mutation and its correlation with preliminary response to immunotherapy in non-small cell lung cancer (NSCLC). Our results indicated that **PBRM1** mutation was more likely to be a negative predictive biomarker for immunotherapy in NSCLC.

**INTRODUCTION**

Immune checkpoint blockade (ICB) therapy has been a pivotal treatment for lung cancer1,2. However, the response rate of cancer immunotherapy among lung cancer patients is still limited. Although several predictive biomarkers have been identified, such as PD-L1 expression, tumor mutation burden (TMB), and microsatellite instability, additional biomarkers should be found out to cover more patients who may benefit most from ICB therapy3-5.

**RESULTS**

In the 2767 patients included in our study (Supplementary Fig. 1), **PBRM1** mutation was identified in 84 NSCLC patients (3.04%, Supplementary Table 1). Fifty-one patients were found to have **PBRM1** loss-of-function (LOF) mutation, accounting for 60.17% of the mutated patients (Supplementary Fig. 2). Among the 84 mutated patients, 56 (66.7%) had lung adenocarcinoma, and 23 (27.38%) had lung squamous cell carcinoma. The ratio of gender was most from ICB therapy3-5.

The baseline characteristics of 441 ICB-treated patients are shown in Table 1. Most of the patients received anti-PD1/PD-L1 therapy (Table 1, Therapy). As shown in Table 1, there was no significant difference in the distribution of gender, age, smoking status, and pathology between the two groups (P > 0.05). Most of the patients received anti-PD1/PD-L1 therapy (Table 1, Therapy).

**DISCUSSION**

**PBRM1** mutation predicts worse response to immunotherapy in NSCLC

A combined cohort of 441 ICB-treated patients (385 from Memorial Sloan Kettering Cancer Center (MSKCC), 56 from Dana Farber Cancer Institute (DFCI)) were further analyzed to access the association between **PBRM1** mutation and response to ICB therapy. As shown in Table 1, there was no significant difference in the distribution of gender, age, smoking status, and pathology between the two groups (P > 0.05). Most of the patients received anti-PD1/PD-L1 therapy (Table 1, Therapy).

**Table 1.** The baseline characteristics of 441 ICB-treated patients.

| Characteristics | **PBRM1** wild type (N = 415) | **PBRM1** mutant (N = 26) | P value |
|-----------------|------------------------------|--------------------------|---------|
| Sex (%)         |                              |                          | 0.207   |
| Male            | 194 (46.7)                   | 16 (61.5)                |         |
| Female          | 221 (53.3)                   | 10 (38.5)                |         |
| Age (%)         |                              |                          | 0.199   |
| <31             | 1 (0.3)                      | 0 (0)                    |         |
| 31-50           | 36 (9.9)                     | 1 (4.3)                  |         |
| 50-60           | 80 (22.1)                    | 2 (8.7)                  |         |
| 61-70           | 124 (34.3)                   | 7 (30.4)                 |         |
| >71             | 121 (33.4)                   | 13 (56.5)                |         |
| NA              | 53                           | 3                        |         |
| Smoke (%)       |                              |                          | 0.133   |
| Never           | 60 (21.4)                    | 0 (0)                    |         |
| Ever            | 208 (74.0)                   | 14 (93.3)                |         |
| Current         | 13 (4.6)                     | 1 (6.7)                  |         |
| NA              | 134                          | 11                       |         |
| Pathology (%)   |                              |                          | 0.697   |
| LUAD            | 323 (77.8)                   | 21 (80.8)                |         |
| LUSC            | 54 (13.0)                    | 2 (7.7)                  |         |
| Other           | 38 (9.2)                     | 3 (11.5)                 |         |
| Therapy (%)     |                              |                          | 0.210   |
| Mono            | 377 (90.8)                   | 26 (100)                 |         |
| Combo           | 38 (9.2)                     | 0 (0)                    |         |
| Lines of treatment (mean (SD)) | 2.24 (1.15) | 2.33 (0.89) | 0.775   |

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monotherapy, and the mean lines of treatment was about 2.3. In the cohort of ICB-treated patients (\(N_{\text{os}} = 412, \text{PBRM1 MT} = 24\)), the OS of the PBRM1-mutant patients was worse than that of those without the mutation in the cohort of ICB-treated patients. No survival difference between PBRM1 mutation types (LOF mutation and non-LOF mutation) were observed in the cohort of ICB-treated (c) and non-ICB-treated (d) patients. OS overall survival, ICB immune checkpoint blockade, LOF loss of function.

**DISCUSSION**

In this retrospective study, we combined data from three institutions to investigate the clinical efficacy of ICB therapy in NSCLC patients with or without PBRM1 mutation. Unlike ccRCC, NSCLC seemed to follow a different PBRM1 mutation pattern. The prevalence of PBRM1 mutation (NSCLC: 84/2767, 3.04%; ccRCC: 31/454, 6.85%) was lower than that in ccRCC. In the NSCLC cohort, the PBRM1 mutation was associated with worse OS (hazard ratio 2.16, 95% confidence interval 1.03–4.51, \(P = 0.041\)) after adjusting these covariates. In the TMB-high and TMB-low subgroup analysis, we still observed the worse OS in the PBRM1-mutant patients treated with ICB therapy (\(P < 0.05\), Fig. 2c, d).

TMB was significantly higher in PBRM1-mutated patients compared with that in PBRM1 WT patients (median 12.79 and 5.9, respectively, \(P < 0.05\), Fig. 2b). In the TMB-high and TMB-low subgroup analysis, we still observed the worse OS in the PBRM1-mutant patients treated with ICB therapy (\(P < 0.05\), Fig. 2c, d).

**Fig. 1** Kaplan–Meier curve comparing overall survival of patients whose tumors did or did not harbor PBRM1 mutations. a The OS of the PBRM1-mutant patients was worse than that of those without the mutation in the cohort of ICB-treated patients. b There is marginally significant difference in OS between the PBRM1 mutation subgroup and the PBRM1 wild type subgroup in the cohort of non-ICB-treated patients. No survival difference between PBRM1 mutation types (LOF mutation and non-LOF mutation) were observed in the cohort of ICB-treated (c) and non-ICB-treated (d) patients. OS overall survival, ICB immune checkpoint blockade, LOF loss of function.
162/402, 40.30% in The Cancer Genome Atlas (TCGA)) and the proportion of truncating mutation (NSCLC: 51/84, 60.17%; ccRCC: 144/162, 93.51% in TCGA) were relatively low in NSCLC (Supplementary Fig. 2). Our findings suggested that PBRM1-mutant NSCLC patients might get less survival benefit from ICB therapy, unlike previously reported data in ccRCC. Interestingly, PBRM1-mutant patients tended to have higher TMB. But no matter in TMB-high subgroup or in TMB-low subgroup, PBRM1-mutant patients who received ICB therapy had worse survival than those without PBRM1 mutation. Besides, PBRM1 mutation was not a remarkable prognostic factor in NSCLC patients according to our analysis in non-ICB-treated patients. Taken together, our results indicated that PBRM1 was more likely to be a negative predictive biomarker for ICB therapy in NSCLC.

To our knowledge, our study was the first study to estimate the role of PBRM1 mutation in both ICB and non-ICB-treated NSCLC cohorts. However, due to data restrictions, not all patients have the full record of clinical data. There was discrepancy in the patients when performing different analysis. We were also not able to include PD-L1 level, microsatellite instability and other factors that might influence the response to ICB therapy in our analysis. In addition, the number of PBRM1-mutated patients was limited, this low frequency may limit the utility of PBRM1 mutation as a predictive biomarker, and we still have to interpret the results with caution. Moreover, PBRM1 mutation did not help predict benefit from the first-line ICB treatment for ccRCC. Most patients received ICB therapy as second or later-line therapy in our cohort. It is still unknown whether PBRM1 mutation can be a predictive biomarker for the first-line ICB therapy. Therefore, further prospective research is warranted to confirm the negative predictive role of PBRM1 in NSCLC ICB therapy.

**METHODS**

**Patients**

We analyzed the combined NSCLC cohort of 2767 patients, from three sources: (1) TCGA (N = 1144), (2) MSKCC (N = 1567), and (3) DFCI (N = 56)\textsuperscript{5,11-14}.
PBRM1 mutation

We first estimated the prevalence of PBRM1 mutation in the whole NSCLC cohort. PBRM1 mutation was defined as any SNV or indel, including putative truncating mutations (nonsense mutations, frameshift, insertions and deletions, and splice-site mutations) and other alterations presumed not to be truncating (In-frame insertions and deletions, missense mutations etc.). Notably, homozygous deletion was also calculated in the PBRM1 mutation. Moreover, we classified PBRM1 mutations into two types: LOF (any truncating mutation and homozygous deletion) and non-LOF.

PBRM1 mutation and response to immunotherapy

A subset of ICB-treated patients (N = 441, 385 from MSKCC, 56 from DFCI) with annotated clinical records were further analyzed for the association between PBRM1 mutation and response to ICB therapy. The OS, PFS (calculated from the date of first ICB infusion) and response to ICB therapy (ORR, DCR, and DCB) were evaluated among these 441 ICB-treated patients. We also calculated the OS (calculated from the date of first chemotherapy infusion) of 454 non-ICB-treated patients from MSKCC cohort. The results of subgroup analysis were also displayed according to the status of PBRM1 LOF mutations. In addition, we investigated the relationship between TMB and PBRM1 mutation status (804 available patients, 454 non-ICB; 350 ICB). In order to further clarify the role of PBRM1 mutation, we classified the ICB-treated patients into two groups (TMB-High and TMB-low, cut-off data: TMB = 10 mut/Mb), and compared their OS. We also showed the PBRM1 mutation landscape of 402 patients with ccRCC from the TCGA database. Institutional review board approval and informed consent were waived because all data were de-identified and publicly available.

Statistical analysis

Patients’ characteristics at baseline and response to therapy were compared by T test or Mann–Whitney U test (continuous variables) and Pearson chi-squared test (categorical variables). Kaplan–Meier curve was used to describe the OS and PFS, and the differences between groups were tested by log-rank method. All statistical analyses were performed using R version 3.5.3 software (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org). Statistical significance was set at two-sided P < 0.05.

DATA AVAILABILITY

The data that support the findings of this study are available from the website [cBioPortal for Cancer Genomics] (https://www.cbioportal.org/), and are also available from the corresponding author on reasonable request. TCGA: Pan-Lung Cancer" [https://www.cbioportal.org/study/?summaryId=mslc_tcga_broad_2016] MSKCC: MSK-IMPACT Clinical Sequencing Cohort [https://www.cbioportal.org/study/summaryId=msk_impact_2017] DFCI: MSS Mixed Solid Tumors [https://www.cbioportal.org/study/summaryId=mixed_allen_2018].

CODE AVAILABILITY

The code that support the findings of this study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

H.Z., J.L., Y.Z., Y.H., and J.S. contributed equally to this work and should be considered as co-first authors. Study concept and design: W.F., H.Z., Y.Z., Y.H., and L.Z. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: H.Z., J.L., and L.Z. Critical revision of the manuscript for important intellectual content: W.F., Y.Z., Y.Y., Y.H., and L.Z. Statistical analysis: H.Z., J.L., and Y.Z. Obtained funding: W.F., Y. H., L.Z. Study supervision: L.Z.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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