Association of immune checkpoint inhibitor with survival in patients with cancers with protein tyrosine phosphatase receptor T mutation

Dear Editor,

We and others have shown that the tumor mutation burden (TMB) and several underlying oncogenic alterations could provide clinically predictive implications for immune checkpoint inhibitor (ICI).\textsuperscript{1–3} Protein tyrosine phosphatases (PTPs) consist of a variety classes, and most of them are highly mutated in multiple cancers and are closely interact with innate and acquired immunity regulating immune cell activation and differentiation.\textsuperscript{4,5} PTP receptor T (\textit{PTPRT}) has been found to be the most frequently mutated PTP gene in cancers and could predict poor prognosis;\textsuperscript{4,6} however, the association of \textit{PTPRT} mutation with clinical outcomes of ICI remains unknown. Here, we performed a comprehensive pancancer investigation to clinically validate \textit{PTPRT} mutation as a predictive biomarker for ICI therapy.

We collected clinical and \textit{PTPRT} mutational data quantified by whole exome sequencing of 2129 cancer patients treated with ICI and 10,814 cancer patients without receiving ICI from the cBioPortal, PubMed, and The Cancer Genome Atlas. The study protocol was approved by the ethics committee of the Sun Yat-sen Memorial Hospital of Sun Yat-sen University. The requirement for informed consent of study participants and the permission to use the patient data were waived because the human data were obtained from publicly available datasets. All analyses were performed according to the STROBE guideline from September 18 through October 1, 2019. Overall survival (OS) were primary outcomes, which were computed using the Kaplan-Meier method and were assessed with the log-rank test and the hazard ratio (HR) calculated by the Cox regression model. The TMB in \textit{PTPRT} wild-type versus mutant groups were compared with Wilcoxon rank-sum tests. All analyses were performed using R (version 3.4.4) and were considered statistically significant if \( P \) values < .05.

Among 2129 ICI-treated patients (250 [11.7%] \textit{PTPRT} mutant; Figure 1A), 596 (28.0%) patients had melanoma, 510 (24.0%) patients had non-small cell lung cancer (NSCLC), and 1023 (48.1%) patients had 12 other cancer types. Patients treated with ICI showed significantly higher TMB in \textit{PTPRT} mutant group versus \textit{PTPRT} wild-type group (\( P < .001; \) Figure 1B). Thirty-five (6.9%) of 510 NSCLC patients and 151 (25.3%) of 596 melanoma patients harbored \textit{PTPRT} mutation, who analogously displayed remarkably higher TMB than patients with \textit{PTPRT} wild-type tumors (\( P < .001; \) Figure 1C and D). \textit{PTPRT} mutations were identified in 687 (6.4%) out of 10,814 patients without receiving ICI across 33 cancer types, among which the mutation frequency was 28.4% in melanoma, 11.1% in esophagogastic adenocarcinoma, 10.9% in endometrial carcinoma, 8.6% in colorectal adenocarcinoma, and 8.0% in NSCLC (Figure 2A). Missense mutations were most commonly observed (82.6%), followed by truncating mutations (15.5%) (Figure 2B).

\textit{PTPRT} mutation resulted in significantly longer OS in 2129 pancancer patients treated with ICI compared with \textit{PTPRT} wild-type (HR 0.63, 95% CI 0.52-0.77, \( P < .001; \) Figure 3A). We further found the clinical usefulness of \textit{PRPRT} mutation status was most prominent in ICI-treated patients with NSCLC and melanoma. Compared with \textit{PTPRT} wild-type group, \textit{PTPRT} mutation group had substantially longer OS in patients with NSCLC and melanoma (HR 0.61, 95% CI 0.48-0.77, \( P < .001; \) Figure 3B). However, among ICI-treated patients with cancers except NSCLC and melanoma, no significant difference in OS between \textit{PTPRT} mutation and wild-type patients was observed (HR 0.95, 95% CI 0.64-1.43; \( P = .810).\)

We also assessed \textit{PTPRT} mutation in patients without receiving ICI. Among 10,814 pancancer patients, there was no difference in OS between \textit{PTPRT} mutant and wild-type (HR 1.00, 95% CI 0.87-1.14; \( P = .980; \) Figure 3C). Among 986 NSCLC patients (101 [10.2%] \textit{PTPRT} mutant)
and 431 melanoma patients (126 [29.2%] PTPRT mutant), no difference in OS between PTPRT mutant and wild-type patients was observed, either (HR 0.83 95% CI 0.67-1.03; \( P = .097 \); Figure 3D). These findings indicated that the status of PTPRT mutation was particularly predictive of ICI treatment.

To the best of our knowledge, this is the first study to identify the mutation status of PTPRT as a key predictor of ICI efficacy. We found that PTPRT mutation conferred an elevated TMB and better survival during ICI therapy in pancancer and specifically in melanoma and NSCLC, which collaborated with our previous research\(^1\) showing a pronounced survival and response benefits of ICI among cancer patients with high TMB. PTPRT has not been suggested to be screened for mutations in current widely used gene panels such as Memorial Sloan Kettering...
Cancer Center’s Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) and FDA-approved FoundationOne CDx (FICDx). Therefore, *PTPRT* should be considered together with other known essential genes to expand the landscape of immuno-oncological genomic panel, and should be integrated into multionomics to more fully realize the precision immunotherapy. In-depth characterization of PTP expression pattern could be informative for understanding patterns of immune escape and the selection of candidates for immunotherapy.

Moreover, PD-L1 inhibitor atezolizumab plus VGFR inhibitor bevacizumab plus platinum-based chemotherapy was shown to have an encouraging survival benefit in recent randomized IMpower 150 trial.\textsuperscript{7} We hypothesized that the efficacy of this strategy probably further enhanced through concurrently targeting *PTPRT*, since *PTPRT* mutation was demonstrated to be promisingly predictive of immunotherapy efficacy in our study and has been found to determine bevacizumab resistance in the study conducted by Hsu et al.\textsuperscript{8} The study limitations included a potential random variability in the context of an exploratory analysis contributed by NSCLC and melanoma, our inability to assess the heterogeneity of other treatment between ICI and non-ICI groups and
FIGURE 3 Association of PTPRT mutation with survival benefit of immune checkpoint inhibitor. (A) Overall survival of patients treated with immune checkpoint inhibitor in PTPRT mutant versus wild-type in pancancer. (B) Same as (A) but describing patients with NSCLC and melanoma. (C) Overall survival of patient without receiving ICI in PTPRT mutant versus wild-type in pancancer. (D) Same as (C) but describing patients with NSCLC and melanoma. HR, hazard ratio; CI, confidence interval; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PTPRT, protein tyrosine phosphatase receptor T.

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.

ACKNOWLEDGMENTS
This work was supported by the National Science and Technology Major Project (grant number 2020ZX09201021); the Medical Artificial Intelligence Project of Sun Yat-Sen Memorial Hospital (grant number...
ETHICS APPROVAL AND CONSENT TO PARTICIPATE
The study protocol was approved by the ethics committee of the Sun Yat-sen Memorial Hospital of Sun Yat-sen University. The requirement for informed consent of study participants and the permission to use the patient data were waived because the human data were obtained from publicly available datasets.

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