

Diversity of peripheral CD8+PD-1+ T cells is a novel predictive biomarker for response to anti-PD-1 antibody treatment in lung cancer patients.

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Background

Anti-PD-1 antibodies (nivolumab) are effective in the treatment of many cancers, including malignant melanoma, non-small cell lung cancer (NSCLC), renal cell cancer, and head and neck squamous cell carcinoma. Immune checkpoint inhibitors (ICIs) are only effective in around 20% of patients, which saw a demand for the development of biomarkers that predict a therapeutic response before administering treatment. As the biomarkers intratumoral PD-L1 expression and tumor mutation burden (TMB) both require tumor tissue biopsy, there is now a demand for safer and less invasive biomarkers.

Peripheral and tumor CD8+PD-1+ T cells share neoantigen-specific T-cell receptors (TCRs), and are presumed to act as effector T cells with an antitumor effect at the tumor site. We analyzed the diversity in terms of TCR α and β repertoires on peripheral CD8+PD-1+ T cells and examined the relationship between this diversity and therapeutic effect of nivolumab.

Methods

This study used patients administered nivolumab after exhibiting no response to chemotherapy for recurrence following 1 surgery. Peripheral blood mononuclear cells were collected from patients before administration of nivolumab.

CD8+PD-1+ T cells were subjected to FACS sorting, NGS-based TCR repertoire analysis was performed by Repertoire Genesis Inc., and TCR diversity was evaluated statistically. CT scan was performed during week 12 of treatment and used to determine response to nivolumab. This study was approved by the Ethical Committee of Hyogo College of Medicine.

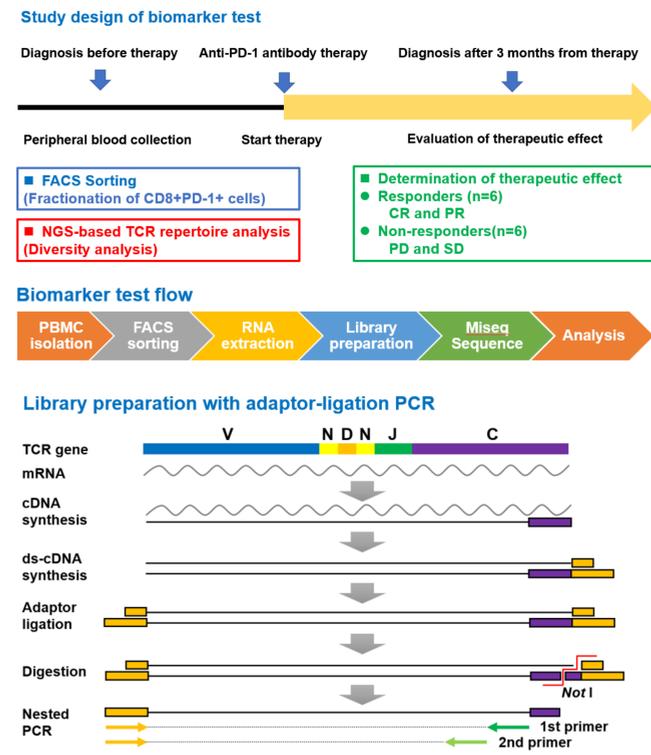


Fig1. Study design and flow of biomarker test with NGS-based TCR repertoire analysis

Results

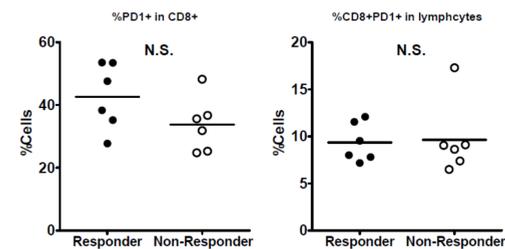


Fig.2 Comparison of PD-1 positive cell between Nivolumab responder and Non-responder

Six of 12 patients responded to treatment. Upon comparing these responders (CR, PR) with non-responders (SD, PD), there were no differences in the proportion of PD-1+ in CD8+ T cells and the proportion of CD8+PD-1+ T cells in gated lymphocytes.

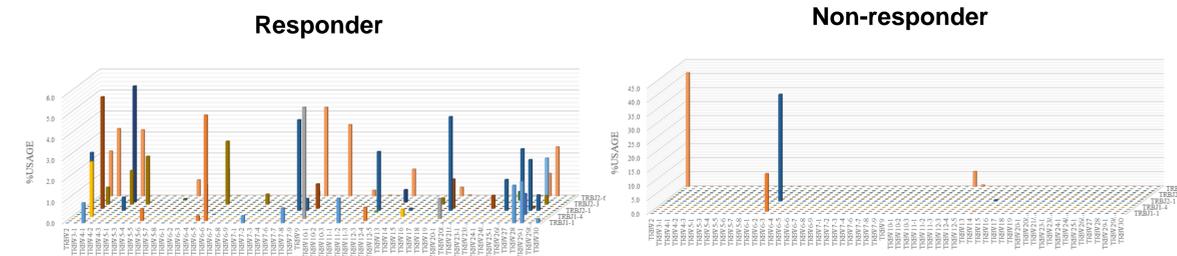


Fig.3 Representative 3D plots of TRB repertoire in Responder (left) and Non-responder (right) of lung cancer patient

Percentage usage of combinations of TRBV and TRBJ were represented by 3D plots. Responder showed diverse TCR repertoire while Non-responder had higher clonality of TCR repertoire.

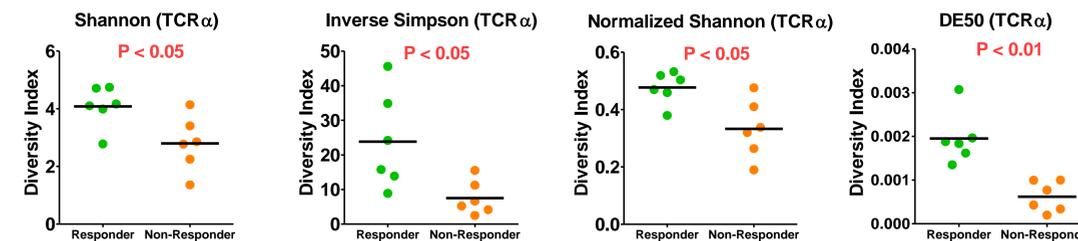


Fig.4 Comparison of diversity between Nivolumab responder and Non-responder (TCR α diversity)

TCR α diversity was significantly higher among responders (n=6) than non-responders (n=6) based on Shannon index, Simpson index and DE50 ($P < 0.05$, $P < 0.05$, $P < 0.01$, respectively).

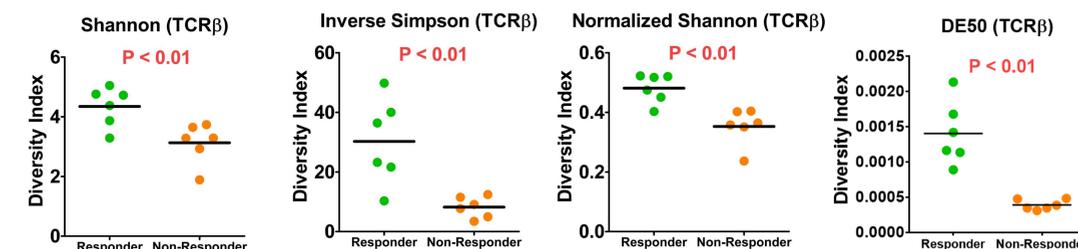


Fig.5 Comparison of diversity between Nivolumab responder and Non-responder (TCR β diversity)

TCR β diversity was also significantly higher among responders (n=6) than non-responders (n=6) based on Shannon index, Simpson index and DE50 (all $P < 0.01$).

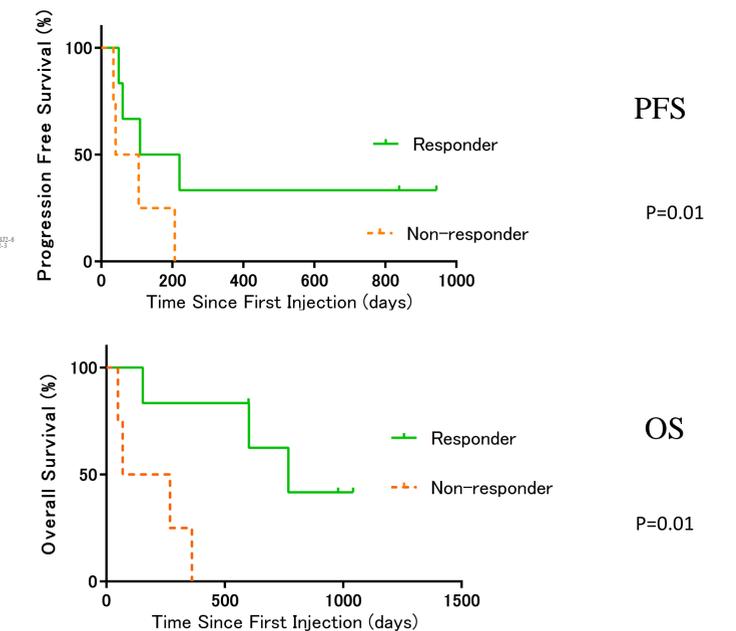


Fig. 6 PFS and OS

Kaplan-Meier curves of PFS and OS comparing Responder with Non-responder.

Conclusions

TCR repertoire analysis was performed on CD8+PD-1+ T cells in easily-obtainable peripheral blood before nivolumab treatment in patients with NSCLC, and nivolumab was observed to be effective in patients with high TCR diversity. This result indicates the TCR diversity of peripheral CD8+PD-1+ T cells is effective as a predictive biomarker for response to ICI therapy. In the future, we intend to analyze TMB and neoepitopes using surgical specimens of these patients and determine the efficacy of this biomarker for cancers other than NSCLC.

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