THE VARIATION OF T-CELL RECEPTORS (TCR) DIVERSITY AND GENOMIC HUMAN LEUKOCYTE ANTIGEN (HLA-I) AMONG NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS EXPRESSING HIGH PDL-1 (≥50%) VERSUS THOSE WITH LOW OR NO PDL1 (<50%)

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**Background**

NSCLC patients with PDL1≥50% are more likely to respond to single agent anti-PD1 comparing to those who are expressing PDL1 in less than 50% of their cancer cells. This suggest that there might be biological differences among high PDL1 (≥50%) NSCLC comparing to low PDL1 (<50%) NSCLC. We aim to investigating the presence of differences between those two groups in terms of pre-treatment T-Cell Receptor (TCR) repertoire and genomic Human Leukocyte Antigen-I (HLA-I).

**Methods**

We prospectively collected baseline blood from 90 NSCLC; 50 patients with high PDL1 and 40 patients with low PDL1. High quality DNA was extracted. Genomic HLA-I typing and TCR sequencing was performed. TCR diversity variables were represented by number of unique clones, evenness, Shannon diversity, clonality and convergence. TCR gene usage has been compared between both groups as well. Mann-Whitney test was used to perform the comparison analysis. HLA-I homozygosity at one or more loci versus maximal heterozygisty was compared between the two groups using Fisher’s exact test to calculate relative risk. HLA-A and -B supertypes was compared between the two groups as well. All analysis was conducted using GraphPad Prism version 9.3.1.

**Results**

We had TCR results for 84 patients (47 high PDL1 and 37 low PDL1). We had to repeat the analysis for 6 patients. We found that patients with high PDL1 NSCLC are more likely to have higher TCR evenness and lower clonality comparing to those with low or no PDL1 (median = 0.887 vs 0.845, P=0.013) and (median = 0.110 vs 0.155, P=0.008) respectively. No statistically significant results were found with other TCR variables. Moreover, certain TCR-genes are found more frequent among patients with high PDL1 comparing to those with low PDL1 like: TRBV3-1 (P=0.012), TRBV5-3 (P=0.029), TRBV9 (P=0.029), TRBV18 (P=0.019). Other TCR genes are found less frequent among patients with high PDL1 comparing to those with low PDL1 like: TRBV6-2 (P=0.040), TRBJ1-5 (P=0.032) and TRBJ2-7 (P=0.049). HLA typing was available for the 90 patients. No statistically significant result was found among both groups in terms of homozygosity versus heterozygosity. However, patients with high PDL1 are less likely to express HLA-A24 (RR=0.47, 95%CI 0.19-0.94, P=0.027) and more likely to express HLA-A03 (RR=1.87, 95%CI 1.24-2.98, P=0.002) on their cell surfaces.

**Conclusions**

High PDL1 NSCLC is biologically differ from low or no PDL1 expressing NSCLC. This is reflected by their different response to immunotherapy treatment and confirmed by different pre-treatment TCR repertoire and HLA-I supertypes.

**Ethics Approval**

Patients were recruited from two major teaching hospitals in Western Australia. All procedures were approved by the Human Research Ethics Committees at Edith Cowan University (ECU) (No. 18957) and Sir Charles Gairdner Hospital (No. 2013-246 and RGS0000003289) in compliance with the Declaration of Helsinki.

Consent All participants signed a consent form which is saved at ECU research database.