Unveiling the Immune Key: HLA-I and CD73 as a Catalyst for Long-Term Triumph in Non-Small Cell Lung Cancer Patients Undergoing Immunotherapy

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1 BACKGROUND

Advancements in therapeutic strategies involving Immune checkpoint inhibitors (ICIs), which focus on disrupting the programmed cell death-1 (PD-1)–programmed cell death ligand-1 (PDL1) axis, have brought about a significant shift in the management of Non Small Cell Lung Cancer (NSCLC) patients. Among these patients, a subset exhibits enduring responses, earning them the distinction of being Long-Term Responders (LTR) to ICIs. Nonetheless, it is imperative to uncover the predictive elements linked to prolonged response in these individuals .

2 METHODS

We conducted an assessment of the immunophenotype in a group of 145 patients with metastatic Non-Small Cell Lung Cancer (NSCLC) who were administered immune checkpoint inhibitor (ICI)-based treatments in the metastatic setting at the Catalan Institute of Oncology in Badalona, covering the years 2014 to 2019. To identify Long-Term Responders (LTR), we investigated the influence of progression-free status on extended survival. An exploratory landmark analysis was carried out to determine the 5-year Overall Survival (OS) rates based on progression-free status concerning ICIs at the 6, 12, and 24-month marks. We examined the levels of expression, using immunohistochemistry, of HLA-I and other immune-related markers, including CD73, CD8+ tumor-infiltrating lymphocytes (TILs), and PD-L1 (Ventana SP263), using formalin-fixed paraffin-embedded human tissue samples. Our evaluation included an assessment of responses and clinical outcomes linked to ICIs. We employed the Chi-Square test for categorical variables and the Kaplan-Meier method for survival analysis. Significance was determined with a threshold of $p < 0.05$.

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4 CONCLUSIONS

The identification and development of predictive biomarkers for long-term benefit with ICIs is required. In our cohort, we characterized a subset of LTR to ICIs (22% of patients). This subgroup of patients was enriched with HLA-I expression and higher levels of CD73, which are emerging biomarkers in NSCLC and predictors of LTR to ICIs.

5 ACKNOWLEDMENT

Patients and their families , Ulises Ferrándiz. Medical Oncology Department ICO Badalona. Pathology Department Germans Trias i Pujol Hospital

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3 RESULTS

Within our group of 145 patients, comprising 86% males and 14% females, lung adenocarcinomas made up 63%, with squamous cell carcinomas accounting for 37%. The median age at the time of diagnosis was 63 years. They underwent ICI treatment as the first line (29%), second line (46%), or third and beyond (25%). Notably, PD-L1 levels greater than or equal to 50% were present in 25% of the cases.

The five-year survival rates for patients achieving progression-free survival (PFS) at 6, 12, 18, and 24 months following ICI initiation were 25% (with a 95% confidence interval (CI) of 18-35), 30% (95% CI: 22-41), 36% (95% CI: 26-50), and 43% (95% CI: 31-59), respectively. As a result, we established the cutoff for defining Long-Term Responders (LTR) as those with at least 2 years of PFS, which encompassed 32 patients (22%) in our cohort. When examining clinical attributes, LTR were notably six years younger than non-LTR (59 years vs. 65 years; $p < 0.013$) and exhibited a significantly superior overall response rate (comprising complete and partial responses) compared to non-LTR (75% vs. 36%; $p < 0.001$). The five-year overall survival (OS) rate for LTR stood at 74% (with a 95% CI ranging from 60% to 93%), whereas for non-LTR, it was a mere 4% (with a 95% CI ranging from 1% to 11%; $p < 0.001$).

Molecular characterization was achievable for 107 patients, but KRAS mutation, TILS score, and PD-L1 expression were not linked to LTR. In 88 patients who were assessable for HLA-I at the time of the analysis, LTR patients displayed higher HLA-I expression (68%) compared to non-LTR (35%) ($p = 0.013$). Median CD73 expression was also noticeably elevated in LTR at 35% (95% CI: 10-57.5) in contrast to non-LTR at 5% (95% CI: 0-23.8; $p = 0.007$).

Table 1: Demographics

	Total	Non-LT responders	LT responders	p
	N=145	*N=113*	*N=32*	
Age at diagnosis (years), Median [IQR]	63.6 [56.5;69.5]	65.1 [58.0;70.8]	59.3 [52.8;62.9]	0.011
Gender, n (%):				1.000
Female	20 (13.8%)	16 (14.2%)	4 (12.5%)	
Male	125 (86.2%)	97 (85.8%)	28 (87.5%)	
Date of birth, Median [IQR]	16-Feb-1952 [10-Feb-1946;07-Apr-1958]	02-Mar-1950 [24-Nov-1945;23-Sep-1956]	05-Apr-1957 [01-Aug-1951;14-Oct-1963]	0.022
Smoking status, n (%):				0.286
Current	80 (56.7%)	59 (53.2%)	21 (70.0%)	
Former	49 (34.8%)	42 (37.8%)	7 (23.3%)	
Never	12 (8.5%)	10 (9.0%)	2 (6.7%)	
Pack/y, Median [IQR]	50.0 [35.0;62.0]	50.0 [36.5;67.8]	45.0 [32.5;60.0]	0.347

Figure 1: Overall Survival by HLA and CD73