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Combination of LAG3 and HVEM as a predictive biomarker to second-line immunotherapy treatment in advanced Non-Small Cell Lung Cancer (NSCLC) patients

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Introduction: Immune checkpoint blockade (ICB) therapy has become the second-line standard treatment for most advanced Non-Small Cell Lung Cancer (NSCLC) patients.

However, not all patients benefit from this treatment, and therefore, identification of reliable biomarkers to expand the therapeutic efficacy of ICB is a current priority.

Goals: To asses the utility of 17 immuno-related soluble biomarkers for predicting response to immunotherapy with anti-PD1 antibodies in NSCLC patients.

Materials and methods: Blood samples were collected from advanced 57 NSCLC patients before treatment with Nivolumab in second-line. Plasma protein levels were measured by the multiplexed bead-based immunoassay MILLIPLEX® HCKP1 (Merck. Non-parametric tests were employed for correlating analytical variables with clinico-pathological characteristics, using median as cut-off. For survival analysis (progression-free survival, PFS or overall survival, OS), Cox Regression and Kaplan Meier curves were performed.

Results: High plasma levels of sHVEM or sLAG3 were associated with clinical benefit –CB- (SD/PR/CR) (p=0.042 both), improved PFS (sHVEM, p=0.046), or prolonged OS (sLAG3, p=0.015). According to the circulating levels of these 2 markers, two groups of patients were established: G1, patients with low levels of both markers (sLAG3↓ and sHVEM ↓); and G2, patients with high levels of at least one of these 2 markers or both (sLAG3↑ and sHVEM↑, sLAG3↓ and sHVEM↑, sLAG3↑ and sHVEM↓). Interestingly, the CB was 61.9% in G2 patients, and 20% in G1 patients (p=0.005). In the same way, G2 exhibited better overall response rate (ORR) than G1 (47.6% vs 13.3%; p= 0.019). Moreover, G2 patients showed prolonged PFS (HR=0.406; 95% CI, 0.193-2.59; 6.67 vs. 2.7, p=0.037) and OS (HR=0.432; 95% CI, 0.212-0.881; 11.03 vs 6.270, p=0.015), in comparison with G1 patients. Multivariate analysis revealed this combination as an independent prognostic biomarker for PFS [HR=0.432; 95% CI,0.212-0.881; p= 0.021] and OS [HR=0.344; 95% CI,0.159-0.745; p=0.007] in our patient cohort.

Conclusions: Circulating immune markers can be reliably detected in plasma. The combination of sLAG3 and sHVEM might be used as a predictive and prognostic factor for improved survival in NSCLC patients treated with nivolumab in second-line.

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