Parallel monitoring of radiomic and tissue immunophenotypic features may intercept the critical events required for immune checkpoint inhibitor (ICI) efficacy. Thus, we explored baseline radiomic features and their evolution to provide reliable predictors of IC1 response in advanced NSCLC patients.

**RESULTS**

**Baseline Tissue - Circulating Immune Microenvironment**

![Image 1](image1.png)  
**Figure 1.** Representative microscopic images of the immunohistochemical detection of CD3+ TILs, CD25+ FOXP3+ Tregs, and PD-L1 in a section of the same NSCLC sample. As our cartogram image of PD-L1 expression is shown. To define the fraction of immune-efficient (IEF), TILs, cells located in stromal (ST), peritumoral (PT), and distal (D) position with respect to cancer cells were segregated using a threshold to immune-excluded (IEE) lymphocytes (lymphocytes over dense fibrotic tissue). The presence of TILs to aggregate in clusters (defined as II) was also evaluated. While PD-L1 was differentially expressed intention to distinct subtypes, TILs from CB asking for the presence of IEF and IEE. These results were to TILs from CB (Mann-Whitney test, P<0.05). Moreover, higher CD4+ CD25+ and lower CD4- CD25- density were distinctive of CB group (P<0.05).

**Circulating Immuno-Inflammatory Score**

![Image 2](image2.png)  
**Figure 2.** We developed a multiparametric score integrating individual circulating factors. Low MIA, CD25+ FOXP3+ Tregs, GzmB+ PD-L1+ CD8+ TILs, and intermediate/advanced/ poor prognosis were considered as putative risk factors. Stratifying patients in good and poor-risk groups, we observed that 47% of low-risk IC1 cases belonged to CB (Fisher exact test, P<0.05). Kaplan-Meier survival analysis documented a significantly prolonged Progression-Free survival (PFS) in good-risk NSCLC.

**Risk Factors**

**Intermediate/ Poor LPI**

- PD-L1 levels
- CD4+ CD25+ FOXP3+
- CD8+ GzmB+
- CD8+ PD-L1+
- NK cells

**Integrated Score (IS)**

Good 1-0 risk factors

Poor 2-4 risk factors

**Delta-radioimmunological features and response to ICIs**

![Image 3](image3.png)  
**Figure 3.** We documented a direct correlation between TILs and PD-L1 as well as PD-L1 and IEF, whereas the number of PB Tregs reached directly with the incidence of ILs and inversely with that of IEF FOXP3+ lymphocytes. Progression-Free survival (PFS) in good-risk NSCLC.

**Dynamic Monitoring of Circulating and Radiomic Features**

![Image 4](image4.png)  
**Figure 4.** As illustrated by the representative Whipple graphs, mean ± SD variation of circulating NK, CD3+ CD8+PD-L1+ and CD4+ FOXP3+ Tregs were, respectively, -0.35% ± 1%, -1% ± 1%, and 1% ± 1%, in CB, which was observed a greater boost of counterregulatory Tregs (P<0.05). Values are referred to Mann-Whitney U test.

**CONCLUSION**

Static and dynamic radioimmunological signatures may discern IC1 outcome in advanced NSCLC, ultimately enabling tailored therapeutic approaches.