

Supplementary Materials

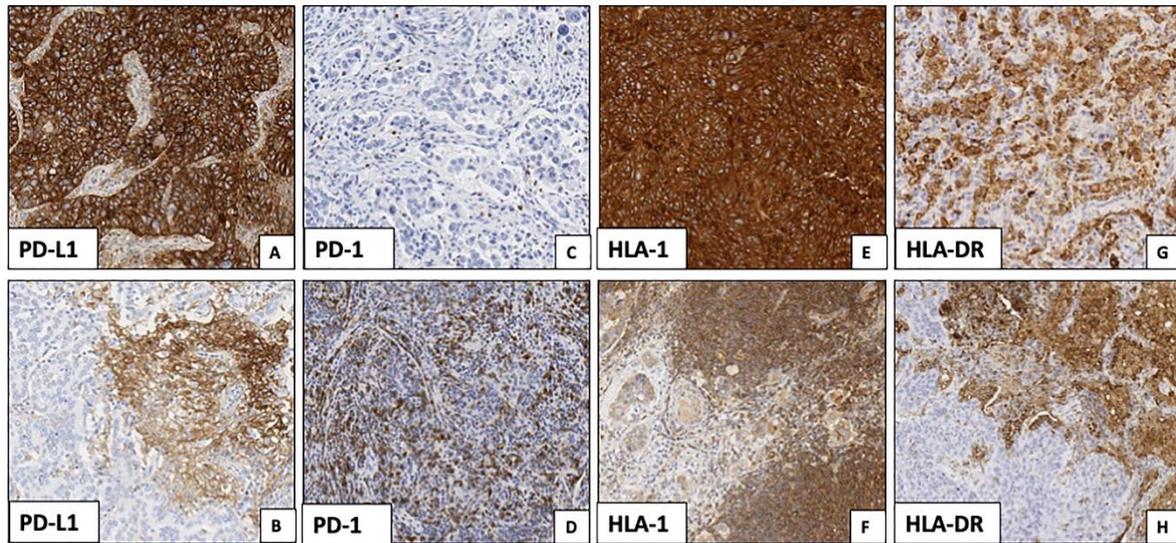


Figure S1. Representative immunohistochemical features in tumor tissue (A,C,E,G) and its microenvironment (B,D,F,H). PD-L1 staining was observed on the membrane of tumor cells (A), but not in stromal cells (B). Conversely, PD-1 signal was absent in neoplastic (C) and positive in stromal cells (D). In neoplastic cells, HLA-1 is extensively expressed in the cytoplasm (E), while HLA-DR is only focally expressed (G). Both HLA-1 and HLA-DR signals are well defined and extensively located within the tumor microenvironment (F–H).

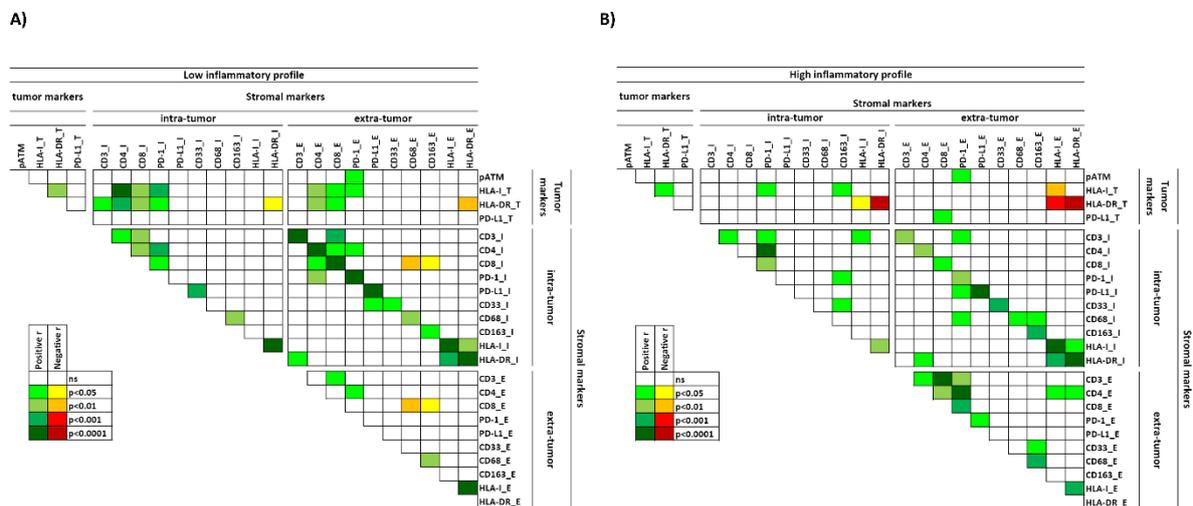


Figure S2. Heat map analysis reporting the Spearman correlation data of all possible comparisons of immune scores of all markers in LC patients with (A) low and (B) high inflammatory profile. Color coding of r and p -values: green indicates a positive correlation, while yellow-to-reds indicates a negative correlation. Color intensity is proportional to p -value, see legend.

Markers	All patients n=68			Low Inflammatory subset n=34			High Inflammatory subset n=34		
	CRP0	CRP3	CRP _{MAX}	CRP0	CRP3	CRP _{MAX}	CRP0	CRP3	CRP _{MAX}
HLA-I_T									
HLA-DR_T									
PD-L1_T	r= 0.388 p=0.0011	r= 0.4382 p=0.0002	r= 0.397 p=0.0009						
CD3_I									r= -0.514 p=0.0022
CD4_I	r= -0.285 p=0.0186								
CD8_I							r= -0.372 p=0.03		
PD-1_I									
PD-L1_I		r= 0.286 p=0.0183							
CD33_I									
CD68_I									
CD163_I									
HLA-I_I	r= -0.416 p=0.0004	r= -0.422 p=0.0003	r= -0.440 p=0.0002						
HLA-DR_I	r= -0.35 p=0.0035	r= -0.368 p=0.002	r= -0.360 p=0.0028						
CD3_E	r= -0.243 p=0.0463		r= -0.288 p=0.0181						
CD4_E	r= -0.395 p=0.0008	r= -0.335 p=0.0052	r= -0.268 p=0.028						
CD8_E	r= -0.348 p=0.0037	r= -0.312 p=0.0095	r= -0.340 p=0.0049						
PD-1_E	r= -0.366 p=0.0022	r= -0.309 p=0.01	r= -0.287 p=0.019						r= -0.429 p=0.0127
PD-L1_E									
CD_33_E									
CD68_E									
CD163_E							r= 0.5163 p=0.002		
HLA-I_E	r= -0.476 p<0.0001	r= -0.446 p=0.0001	r= -0.460 p<0.0001						
HLA-DR_E	r= -0.406 p=0.0006	r= -0.399 p=0.0007	r= -0.386 p=0.0013						

Figure S3. Spearman correlation analysis for association of all immune markers evaluated in the tumor lesions by IHC with the CRP₀, CRP₃ and CRP_{max} values in the whole set of patients ($n = 68$) and in the two subsets defined by low and high inflammatory profile. Positive and negative r values are highlighted in green and red respectively. Only significant correlations are shown.

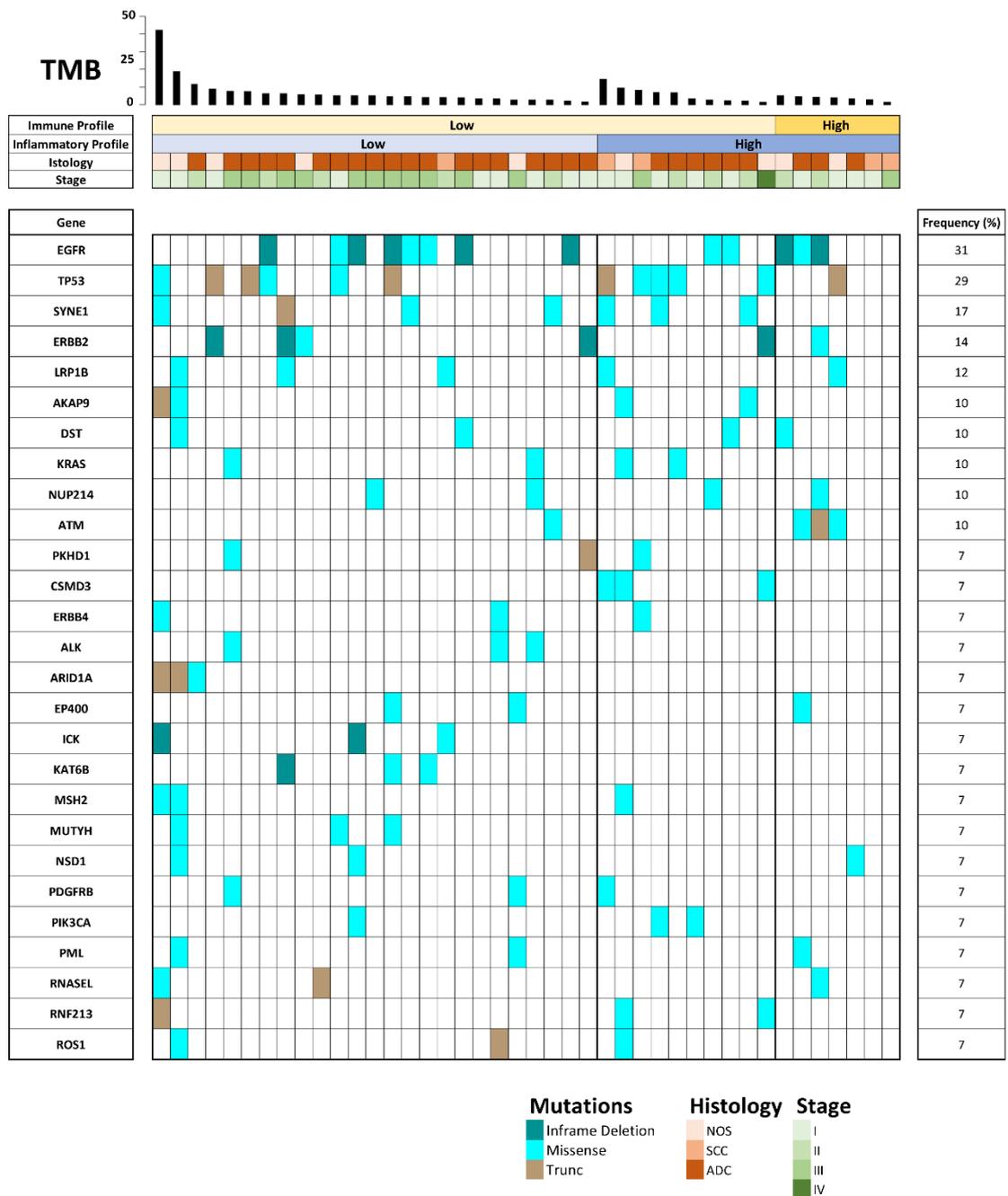


Figure S4. Mutation plot of 42 lung tumors resected from never-smokers lung cancer patients. Co-mutation plot of genes mutated in at least 3 samples and clinico-pathological characteristics of patients. Genes are ranked according to the mutation frequency. Samples are ranked according to the tumor mutational burden (TMB) in the three groups of patients: low inflammatory and low immune profile; high inflammatory and low immune profile; and high inflammatory and high immune profile.

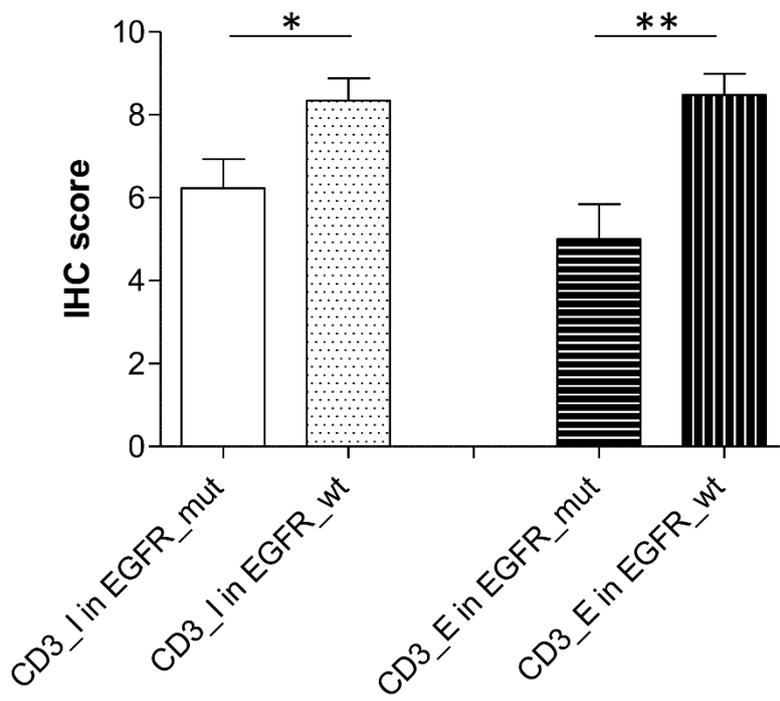


Figure S5. Distribution of CD3 IHC score in intra- and extra-tumor stromal cells in patients with *EGFR* mutated (mut) and *EGFR* wild type (wt). * and ** indicate p -values $p < 0.05$, $p < 0.01$, respectively