IMMUNE CELL SUBSETS IN PERIPHERAL BLOOD ARE ASSOCIATED WITH PRIMARY RESISTANCE TO IMMUNOTHERAPY AS FRONTLINE TREATMENT IN NSCLC


BACKGROUND
Kagamu H et al and our group recently reported the association between high levels of effector and highly differentiated CD4 T cells in peripheral blood and response to ICI in pretreated NSCLC (Zuazo M, EMBO Mol Med 2019, Kagamu H, Cancer Immunol Res 2020). After having observed that our findings are not applicable to first line patients we have evaluated the dynamics of immune cell populations in this clinical context.

METHODS
PBMCs from 25 patients with advanced NSCLC receiving pembrolizumab alone or concomitant with chemotherapy were obtained from peripheral blood before treatment. Cell subpopulations have been studied by flow cytometry according to the expression of CD3, CD4, CD8, CD316, CD14, CD27, CD28, CD56, CD64, CD66b, CD116, CD163 and CD206.

RESULTS
Higher levels of CD116+ CD66b+ neutrophils (21.1% vs 3.8%, p=0.045) and CD11b+ CD56+ CD14- NK cells (22.6% vs 12.7%, p=0.003) were associated with progression, while responders had lower levels of CD4+ CD27- CD28- cells (p = 0.032).

Over the mean (OTM) CD4+ CD27- CD28- and NK cell levels were associated with shorter PFS [NR vs 8.3 wk, p = 0.026 and 64.1 vs 2.9 wk, p = 0.005]. OTM neutrophils were associated with shorter OS (71.7 vs 9.9 wk, p = 0.012).

CONCLUSIONS
Pretreatment immune cell subpopulations in peripheral blood quantified by flow cytometry might be useful to predict immunotherapy efficacy. Myeloid and CD27- CD28- cells might play relevant role in primary resistance to ICI.

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ROC analysis showed an association between OTM neutrophils and progression as best response (AUC 0.903, p=0.005), with a threshold of 6.2% for a 90% specificity and 75% sensitivity. A score based on OTM neutrophils, NK and CD4+ CD27- CD28- cells discriminates patients according to their mPFS (0 = 64 wk, 1 = 22.9 wk, 2 = 2.3 = 2.86 wk; p=0.029).

Figure 1: Scheme of the project.

Figure 2: UU, DMM graphic of lymphoid subpopulations, represented by different colors. Left below, DMM graph representative of 2 non-responders. Right below, DMM graph representative of 2 non-responders.

Figure 3: UU, DMM graphic of myeloid subpopulations, represented by different colors. Left below, DMM graph representative of 2 non-responders. Right below, DMM graph representative of 3 non-responders.

Figure 4: Upper, left, basal levels of CD116+ CD66b neutrophils in patients with clinical benefit rate lower than 6 months compared with the rest of the patients. Upper, right, same but comparing levels of CD11+ CD56+ CD14- Down, basal levels of CD4+ CD27- CD28- cells in responders compared to the non-responders.

Figure 5: UU, PFS stratified by basal CD4+ CD27- CD28- cells over the mean. Middle, PFS stratified by basal CD116+ CD66b+ NK cells over the mean. Left, UU stratified by basal CD64- CD66b+ neutrophils over the mean.