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

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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, CD11b, CD14, CD27, CD28, CD56, CD64, CD66b, CD116, CD163 and CD206.

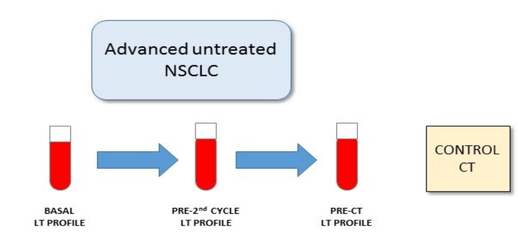
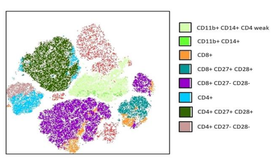


Figure 1: Scheme of the project

RESULTS



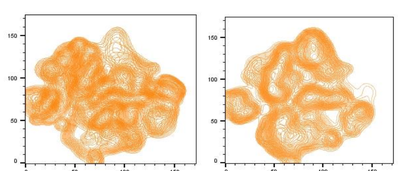
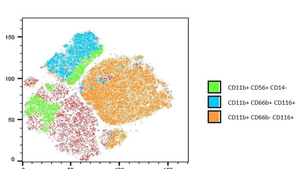


Figure 2: Up, tSNE graphic of lymphoid subpopulations represented by different colors. Left below, tSNE graph representative of 3 responders. Right below, tSNE graph representative of 3 non-responders.



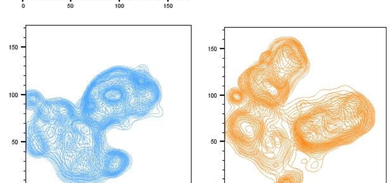


Figure 3: Up, tSNE graphic of myeloid subpopulations represented by different colors. Left below, tSNE graph representative of 3 responders. Right below, tSNE graph representative of 3 non-responders.

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).

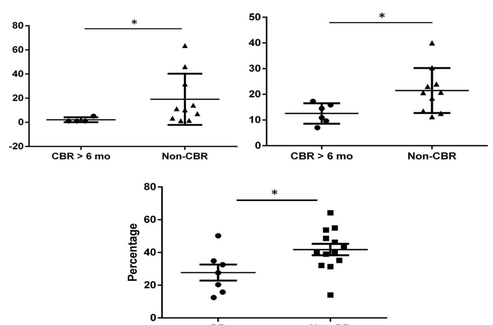
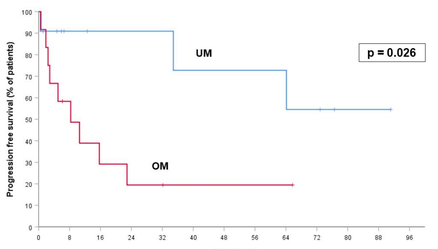
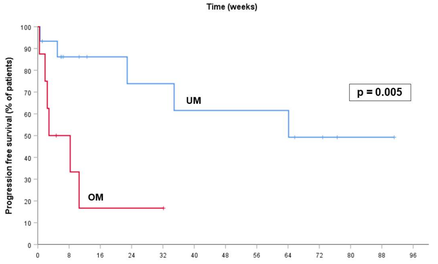


Figure 4: Upper left, basal levels of CD116+ CD66b+ neutrophils in patients with clinical benefit rate longer than 6 months compared with the rest of the patients. Upper right, same but comparing levels of CD11b+ CD56+ CD14-. Down, basal levels of CD4+ CD27- CD28- cells in responders compared to non-responders.

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).





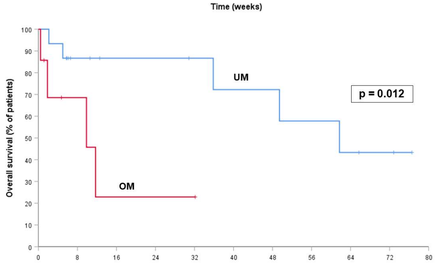
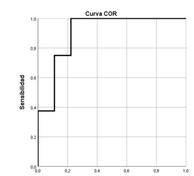


Figure 5: Up, PFS stratified by basal CD4+ CD27- CD28- cells over the mean. Middle, PFS stratified by basal CD11b+ CD56+ CD14- NK cells over the mean. Below, OS stratified by basal CD66b+ CD116+ neutrophils over the mean.

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, 2-3 = 2.86 wk; p=0.029).



AUC 0.903
p = 0.005

Threshold 6.2%
Sensitivity 87.5%
Specificity 88.9%

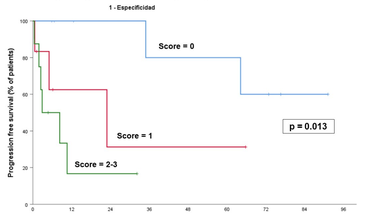


Figure 6: Up, ROC analysis of basal neutrophils as a function of progression as best response. Down, progression free survival stratified by the presence of basal neutrophils, NK cells or CD4 CD27- CD28- cells over the mean.

CONCLUSIONS

Pretreatment immune cell subpopulations in peripheral blood quantified by flow cytometry might be useful to predict immunotherapy efficacy. Myeloid and CD27- CD28- CD4 cells cells might play relevant role in primary resistance to ICI.

FUNDING

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