IDENTIFICATION OF SUPER-EXHAUSTED T CELLS: A NOVEL POPULATION PREDICTIVE OF RESPONSE TO IMMUNOTHERAPY

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Background Given that most of cancer patients treated with anti-PD1/PD-L1 immune checkpoint blockers (ICB) do not derive benefit, there is a crucial need to identify reliable predictive biomarker of responses. Besides PD-1, several key immune checkpoints, such as CTLA4, LAG3, TIM3 and TIGIT, are associated with a T cell exhausted phenotype and play a crucial role in leading to cancer immune evasion. The impact of simultaneous expression by T cells of distinct inhibitory receptors on outcome of patients treated with ICB is still unknown.

Methods We analyzed the tissue samples, collected before ICB initiation, from patients with solid tumors and included in an institutional molecular profiling program (NCT02534649). We used multiplexed-immunohistofluorescence with the following panel CD3/PD1/TIM3/LAG3/TIGIT/CTLA4, and performed immune cell characterization using multispectral images analysis. We then investigated the correlation between coexpression of T cell-associated exhaustion markers, clinical response rate, progression-free survival (PFS) and overall survival (OS) by Cox proportional hazards models.

Results Four hundred thirty five patients were included in the analysis (NSCLC: n=207, 47.6%; sarcoma: n=42, 9.7%; urothelial: n=30, 6.9%; others: n=156, 35.9%). Digital pathology analysis allowed us to identify a population of ‘super-exhausted’ T cells characterized by the co-expression of PD1, LAG3, TIGIT and TIM3 which was enriched in 125 cases (28.7%), and was significantly associated with better PFS (HR 1.60, CI95 1.26–2.04, p<0.001) and OS (HR 1.42, CI95 1.07–1.89, p=0.016) in the whole cohort. Patients with super-exhausted high tumors had higher objective response rate (38.4%) compared to super-exhausted low tumors (19.7%, p<0.001). The presence of super-exhausted T cells was significantly higher in responders (10%) versus non responders (4%, p<0.001). Correlation with better outcome was observed whatever the subgroup considered (NSCLC vs other tumors, CD8 T cells density and presence of tertiary lymphoid structure [TLS]). In multivariate analysis (n=372, 85.5%), increased tumor infiltration by super-exhausted T cells (>1%) was significantly associated with better PFS (HR 0.61, CI95 0.46–0.81, p<0.001) and OS (HR 0.68, CI95 0.48–0.97, p=0.033).

Conclusions The presence of super-exhausted T cells may represent a new predictive biomarker of response to ICB and pave the way for the development of effective ICB combinations. Data from an independent validation cohort will be presented at the meeting.