Combining TNF-targeting antibodies to immune checkpoint inhibitors in melanoma

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Purpose:
Anti-PD-1 therapy has significantly improved the care of melanoma patients. However, more than 50% of them do not display optimal response to treatment and a significant proportion of responders relapse. In addition, about 50% of patients will experience mild to severe immune-related adverse events (irAEs). Our goal is to evaluate, both in pre-clinical and clinical settings, the impact of combining immune checkpoint inhibitors (ICI) to TNF blockade in the treatment of melanoma.

Experimental Design:
In pre-clinical analyses using the B16K1 (B16F10 MHC\(^{1}\)\(^{\text{high}}\)) mouse melanoma model we studied the impact of TNF deficiency/blockade on response to αPD-1. The parameters assessed included tumor growth, overall survival (OS) of mice as well as analyses of the immune contexture of tumors\(^{1,2}\).

Clinical analyses will be performed as a phase 1b clinical trial (TICIMEL: NCT03293784) assessing the safety and tolerance of combining ICI (Nivolumab + Ipilimumab) to anti-TNF (Infliximab or Certolizumab) for the treatment of metastatic melanoma patients. Additional translational research will be carried out in human samples (blood and melanoma biopsies) to identify biomarkers of resistance to ICI associated with TNF (MELANF\(\alpha\): NCT03348891) and evaluate the anti-melanoma specific immune response (MELANIC\(\alpha\)).

Results:
Our pre-clinical studies demonstrated that blocking the TNF/TNFRI pathway potentiates the CD8\(^{+}\) T cell-dependent anti-melanoma immune response in mouse. Moreover, blocking the TNF/TNFRI pathway synergizes with anti-PD-1 treatment to impair tumor growth in mouse. In this context, anti-TNF prevent the anti-PD-1-dependent upregulation of TIM-3 on Tumor-infiltrating T cells as well as activation-induced cell death thus favoring CD8\(^{+}\) T cell accumulation in tumors\(^{1,2}\).

Specifics of the clinical trial, which began in January 2018, will be presented.

Conclusion:
Our pre-clinical data support the use of TNF blocking antibodies to enhance response to immune checkpoint inhibitors and constitute the scientific rationale of clinical trials in melanoma patients. This project illustrates the great advantages the oncopole structure provides to transfer basic findings to the Clinic and back.

References: