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 MHC1\textsuperscript{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\textsuperscript{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.

Results:

Our pre-clinical studies demonstrated that blocking the TNF/TNFR1 pathway potentiates the CD8\textsuperscript{+} T cell-dependent anti-melanoma immune response in mouse. Moreover, blocking the TNF/TNFR1 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\textsuperscript{+} T cell accumulation in tumors\textsuperscript{1,2}. Specifics of the clinical trial, which will begin by the end of 2017, will be presented.

Conclusion:

Our pre-clinical data support the use of TNF blocking antibodies to enhance response of melanoma patients to immune checkpoint inhibitors.

References:
