MELANOMA AND MELANOCYTIC NAEVI

MELANOMA TARGETED RADIATION THERAPY BY [131I]ICF01012 INTERACTS WITH ANTITUMORAL IMMUNITY RESPONSE AND ENHANCES IMMUNE CHECKPOINT INHIBITOR EFFICACY

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Background: Our group develops radiolabelled melanin-ligands for targeted radionuclide therapy (TRT) of metastatic melanoma. Systemic injection of [131I]ICF01012 decreases tumor growth in syngeneic (B16BL6) and xenograft (SK-MEL-3) preclinical melanoma models. A clinical phase I study of our molecule will start in 2018 (MELRIV1). Simultaneously, we are pursuing the preclinical study of [131I]ICF01012: recent evolution of strategies in melanoma treatments (especially, immune checkpoints inhibitors (ICI) combination with external beam radiotherapy) lead us to focus on [131I]ICF01012 interactions with immunity. We show, using immunocompromised mice, that TRT needs an adaptative immune response to be fully efficient.

Objective: This study aims to investigate immune modifications induced by [131I]ICF01012, before considering TRT combination with ICI.

Materials and Methods: Tumor immune infiltration was explored by RT-qPCR in B16F10/C57BL6 murine melanoma model treated with 18,5MBq of [131I]ICF01012. For combination studies, B16F10-tumor bearing mice received ICI monotherapy (anti-CTLA-4, anti-PD-1, anti-PD-L1) or combination (anti-CTLA-4 + anti-PD-1, anti-CTLA-4 + anti-PD-L1) and then, they were randomized to receive either TRT or saline. Survival and mechanistical studies (TLDA, flow cytometry) were realized.

Results: We showed that TRT provokes the recruitment in the tumor of cytotoxic T cells and Natural Killer cells but also regulatory T cells. We observed a strong increase of the survival median in the anti-CTLA4 + TRT group, compared with TRT alone (41 vs 26 days). Adjunction of anti-PD-1 or anti-PD-L1 to TRT didn't modify survival. Combining TRT, anti-CTLA-4 and anti-PD-1, lengthened more survival (43.5 days). Further studies are ongoing to clarify the underlying mechanisms.

Conclusions: TRT induces two modifications within tumor immune microenvironment: anti-tumor immune response activation and immunologic tolerance induction. The importance of survival gain with anti-CTLA-4 suggests that immunologic tolerance is a preponderant mechanism in TRT-mediated immune response. Furthermore, these results underline that TRT combination with ICI could be a promising approach for melanoma treatment.