

Immunotherapy of advanced melanoma by intra-tumoral injections of autologous, purified dendritic cells transduced with gene construct of interleukin-12, with dose-dependent expression under the control of an oral activator ligand

Category: Translational

Topic, primary: Developmental Therapeutics, Clinical Pharmacology & Immunotherapy; Experimental Immunotherapy and biologic therapy

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Abstract:

Background: RTS-IL12 is a novel synthetic gene construct in an adenovirus vector, with IL-12 expression only turned on when an oral small molecule activator ligand (AL) interacts with the promoter of the gene. Syngeneic dendritic cells (DC) transduced with RTS-IL-12 injected intra-tumorally + oral AL induced IL-12 and associated genes only locally, triggering systemic, specific anti-tumor cytotoxic T cells and regression of B16 melanoma and other mouse tumors. A Phase 1 trial was initiated to evaluate safety, mechanism of action (MOA) and clinical activity of DC-RTS-IL12 in patients with advanced melanoma. **Methods:** Autologous immature DC-RTS-IL-12s (5×10^7) are injected intra-tumorally, in combination with 14 days of AL (0.6, 20, 60 or 200 mg /day), for ≤ 5 treatment cycles. Safety, MOA (genomic and immunologic) and clinical responses (CT evaluation by RECIST) are being assessed. **Results:** Among 7 patients treated, partial or complete regression of injected and some uninjected lesions was observed by CT in 2 patients, with 1 patient having RECIST PR of >11 months. These 2 patients had intratumoral changes in IL-12 associated gene expression, and circulating CD8⁺ and/or CD4⁺T cells reactive against several melanoma-associated peptides by ELISPOT. Treatment was generally well tolerated and MTD has not yet been reached.

Conclusions: This phase I trial in patients with advanced melanoma has confirmed key findings from mouse tumor models: regression of some uninjected as well as injected tumor lesions, induction of systemic, specific anti-tumor T cell immunity even at dose levels of AL that do not trigger increases in circulating IL-12 or its associated cytokines.