

A PHASE II STUDY (NCT01883323) EVALUATING THE INFUSION OF AUTOLOGOUS TUMOR-INFILTRATING LYMPHOCYTES (TIL) AND LOW-DOSE INTERLEUKIN-2 (IL-2) THERAPY FOLLOWING NON-MYELOABLATIVE LYMPHODEPLETION USING CYCLOPHOSPHAMIDE AND FLUDARABINE IN PATIENTS WITH METASTATIC MELANOMA

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The first clinical trial of adoptive cell therapy using tumor-infiltrating lymphocytes (TILs) in Canada is currently accruing at the Princess Margaret Cancer Centre. The trial is a single arm phase II trial in metastatic melanoma, designed to assess safety and response. TILs are expanded *ex vivo* in an initial culture step, and then further expanded in a “rapid expansion protocol” (REP). On day 14 of the REP, the TILs are harvested for infusion. Patients first receive preparative lymphodepletion with cyclophosphamide (60mg/kg for 2 days) and fludarabine (25mg/m² for 5 days). This is followed by TIL infusion (1x10¹⁰ – 1.6x10¹¹ cells intravenously) and a moderate dose interleukin-2 (IL-2) regimen (125,000 IU/kg subcutaneous injection, daily for 2 weeks, with 2 days rest between weeks). This dose of IL-2 is lower than what is commonly used in current TIL protocols, with the aim of reducing the significant treatment-limiting toxicity associated with high-dose IL-2 therapy. The trial follows a two-stage Simon design with a maximum target of 12 evaluable patients. To date, eight patients have received investigational treatment. Cell doses ranged from 5.5x10¹⁰ – 1.6x10¹¹. Response data is pending for the two of the treated patients. For the other patients, the best overall response (RECIST v1.1) was a partial response in two patients and stable disease in four patients. TCR Vβ repertoire analysis of the TIL infusion products suggests that CD8⁺ TILs tended to be more oligoclonal than CD4⁺ TILs. Immune monitoring demonstrates peripheral oligoclonal expansion select TCR Vβ family subtypes in some patients and indicates that putative regulatory T cells did not markedly expand in peripheral blood following moderate dose IL-2 therapy. Our experience shows that TIL-based trials are feasible at our centre. Accrual will continue and data on safety, clinical responses and immune monitoring will be collected.

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