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CITN11-02 interim trial results: subcutaneous administration of recombinant human IL-15 (rhIL- 15) is associated with expansion of peripheral blood CD56+ NK cells and CD8+ T cells

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Background

The Cancer Immunotherapy Trials Network is conducting a Phase I, dose-escalation study of subcutaneous (SQ) rhIL-15 in advanced melanoma, renal cell, non-small cell lung (NSCLC) and squamous cell head and neck carcinoma patients. IL-15 has been identified as a high priority agent for immunotherapy development because it is a homeostatic factor for both NK cells and CD8+ T cells and, unlike IL-2, has little effect on suppressive regulatory T cells.

Methods

Each cycle consists of 5 daily SQ injections of rhIL-15 (E.coli-derived, NCI) administered Monday-Friday for two weeks, followed by 2 weeks observation. The absolute lymphocyte count is tested every injection day, and whole blood flow cytometric analysis of T and NK cell frequencies is conducted on Days 1, 11 and 15 of each cycle.

Results

Three patients have been enrolled in each of the 0.25, 0.5, 1.0 and 3.0 mcg/kg dose cohorts and six at 2.0 mcg/kg (N=18). Fourteen patients completed ≥2 cycles, three completed one cycle, and one patient (3 mcg/kg) received only 2 doses due to dose limiting toxicity (DLT). This last patient had NSCLC and developed grade 3 chest pain, hypoxia and dyspnea leading to hospitalization and discontinuation of rhIL-15. One serious adverse event, grade 2 pancreatitis, was observed in a metastatic melanoma patient 3 days after completing Cycle 1 (at 2.0 mcg/kg). Flow cytometric data indicate a consistent increase in the frequency of CD56+CD3-NK cell frequencies peaking at Day 15 of Cycle 1 (3 days after the last dose), with lesser increases in subsequent cycles. The mean fold-increase in circulating NK cells during Cycle 1 was 2.3, 3.3, 4.4, 9.6, and 11.8-fold for the 0.25, 0.5, 1.0, 2.0 and 3.0 mcg/kg dose cohorts respectively, demonstrating dose responsiveness. By contrast, the mean fold-increase in circulating CD8+ T cells was relatively modest at 1.1, 0.9, 1.2, 3.3, and 3.2-fold for the 0.25, 0.5, 1.0, 2.0 and 3.0 mcg/kg dose cohorts respectively.

Conclusions

SQ rhIL-15 was well tolerated through 2.0 mcg/kg/dose and may be the maximum tolerated dose. One of 3 patients treated with 3.0 mcg/kg rhIL-15 experienced a DLT; this cohort will be expanded. Higher doses of rhIL-15 were associated with profound increases in circulating NK cells with smaller but still significant increases in CD8+ T cells. Outpatient use of subcutaneous rhIL-15 is safe and will likely emerge as a key agent for combination with other cancer immunotherapies.

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Trial registration

ClinicalTrials.gov identifier NCT01727076.

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