

POSTER PRESENTATION

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# Combination immunotherapy with Interleukin-2 and CTLA-4 blockade decreases tumor growth and improves overall survival

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## Background

Combination immunotherapy is quickly gaining attention in the field of cancer treatment. IL-2, a cytokine which activates T cells, and ipilimumab, a monoclonal antibody that blocks CTLA-4, are both approved as monotherapy for metastatic melanoma. To date, combination immunotherapy with IL-2 and anti-CTLA-4 has not been adequately investigated. We hypothesized that this combination may work synergistically owing to its distinct but complementary mechanisms of T cell activation.

## Methods

C57BL/6 mice (10 per group) were challenged with B16-F10 melanoma (via intradermal injection with 120,000 cells) on day 0. Four groups were treated via intraperitoneal injection: -Group 1 (combination): IL-2 (100,000 units in 100  $\mu$ l) every 12 h on days 4-8 and anti-CTLA-4 (100  $\mu$ g in 100  $\mu$ l) on days 3, 6, and 9; -Group 2 (IL-2 only): IL-2 (100,000 units in 100  $\mu$ l) every 12 h on days 4-8 and IgG (100  $\mu$ g in 100  $\mu$ l) on days 3, 6, and 9; -Group 3 (anti-CTLA-4 only): PBS (100  $\mu$ l) every 12 h on days 4-8 and anti-CTLA-4 (100  $\mu$ g in 100 $\mu$ l) on days 3, 6, and 9; -Group 4 (placebo): PBS (100  $\mu$ l) every 12 h on days 4-8 and IgG (100  $\mu$ g in 100  $\mu$ l) on days 3, 6, and 9. Tumor area (length\*width) was measured every other day until death of the animal or until tumors reached 100mm<sup>2</sup>, when animals were sacrificed as per institutional protocols. Primary outcomes included tumor size and overall survival.

## Results

Tumor growth was significantly reduced with combination IL-2 and anti-CTLA-4. Specifically, on day 14, the

mean tumor area with combination IL-2 and anti-CTLA-4 was 2mm<sup>2</sup>, while in the anti-CTLA-4 only, IL-2 only, and placebo groups it was 14, 29, and 68 mm<sup>2</sup>, respectively ( $P < 0.01$  for all comparisons, except IL-2 only versus anti-CTLA-4 only [not significant]). At day 30, the overall survival with combination IL-2 and anti-CTLA-4 was 50%, while with IL-2 only and anti-CTLA-4 only it was 10% and 20%, respectively ( $P < 0.01$  for all comparisons). All animals treated in the placebo group succumbed to their tumors by day 19. These findings were confirmed in a second experiment with similar results.

## Conclusions

Combination immunotherapy with IL-2 activation and CTLA-4 blockade significantly decreases tumor growth and increases overall survival when compared to IL-2 or anti-CTLA-4 monotherapy or placebo. The role of CD8+ effector versus CD4+ regulatory T cells in the success of this immunotherapy is ongoing and will be included in our formal presentation. Ultimately, we aim to translate this work into a combination immunotherapy clinical trial.

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