

# Immunologic impact of anti-CTLA-4 antibody

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## Abstract

**Background:** Significant anti-tumor responses have been reported in a small subset of approximately 10% of cancer patients treated with a novel immunotherapeutic agent, anti-CTLA-4 antibody. All clinical trials to date, comprising over 3000 patients, have been conducted in the metastatic disease setting, which allows for correlation of drug administration with clinical outcome but has limited analyses of intermediate biomarkers to indicate whether the drug has impacted human immune responses within the tumor microenvironment. Knowledge of biomarkers that correlate with drug administration and/or clinical outcome is essential to developing immunotherapeutic strategies with anti-CTLA-4 therapy to provide clinical benefit to a greater number of patients.

**Methods:** We designed and conducted a pre-surgical clinical trial to administer 3 mg/kg of anti-CTLA-4 antibody for 2 doses ( $n = 6$ ) and 10 mg/kg of anti-CTLA-4 antibody for 2 doses ( $n = 6$ ) to patients with localized bladder cancer, which allows for correlation of drug administration with biomarkers in both blood and tumor tissues. Immunologic analyses were conducted on blood and tumor samples.

**Results:** We found that CD4 T cells from treated patients had markedly increased expression of inducible costimulator (ICOS). These CD4<sup>+</sup> ICOS<sup>hi</sup> T cells produced interferon-gamma (IFN- $\gamma$ ) and could recognize the tumor antigen NY-ESO-1. Changes in expression of the transcription factor FOXP3 were also analyzed and found to be variable; however, there was increased expression of FOXP3 observed in T cells from the systemic circulation of patients treated with higher doses of antibody. These immunological markers are being examined in a cohort of patients with metastatic disease to determine whether these changes correlate with clinical outcome.

**Conclusions:** The role of ICOS-expressing T cells remains enigmatic and our results raise the possibility that ICOS-expressing T cells may play a role in antitumor responses mediated by CTLA-4 blockade. In addition, although FOXP3 serves as a hallmark of regulatory T cells in murine models, our studies suggest that subsets of effector T cells in humans may have increased expression of FOXP3 as a result of activation. Increased expression of ICOS and FOXP3 may serve as predictive biomarkers of clinical outcome for cancer patients treated with anti-CTLA-4 therapy.