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Meeting Abstract

Potential biomarkers of immune activation in ipilimumab-treated patients with advanced melanoma

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Abstract

Ipilimumab is a fully human, monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4) – a key negative regulator of T-cell responses to tumor-associated antigens.

Ipilimumab treatment results in durable disease control in patients with advanced melanoma. The most common adverse events are mechanism-based (immune-related adverse events [irAEs]) and primarily affect the gastrointestinal (GI) system. In a randomized, double-blind, placebo-controlled, multicenter, phase II study (CA184-007), patients with unresectable stage III or IV melanoma received ipilimumab induction dosing 10 mg/kg every 3 weeks (Q3W) X 4 + placebo/prophylactic budesonide, an oral steroid with minimal systemic exposure hypothesized to reduce GI irAEs. Objectives of the biomarker analyses were to assess the effect of ipilimumab on peripheral T-cell populations during the induction phase (i.e., to Week 12) and to evaluate potential biomarkers of irAEs, particularly GI. Absolute lymphocyte count (ALC) captured in study CA184-007 was combined with data from 2 other phase II studies of advanced melanoma patients who received ipilimumab 10 mg/kg Q3W X 4 (CA184-008 and CA184-022). Response was assessed by modified World Health Organization (mWHO) criteria; the first efficacy assessment was at Week 12. Flow cytometric analysis on pre- and post-treatment blood and serum samples from 115 treated patients (CA184-007) showed that ipilimumab increased the frequency of activated CD4+ and CD8+ T cells during the first 4 weeks of treatment (96% increase each) which was maintained to Week 12 (an additional 33% and 57% increase, respectively). Ipilimumab decreased naïve T cells by Week 12 (91% and 81% decrease for CD4+ and CD8+ T cells, respectively). There was a small, overall mean increase in the frequency of central memory CD4+ and CD8+ T cells from baseline at Weeks 4 and 12, but no meaningful changes in effector memory T cells. In the multi-study analysis ($n = 329$), responding patients had higher ALC levels, and no patient with an ALC decrease over the induction period responded; these results were highly statistically significant ($P = 6 \times 10^{-4}$). These results suggest that ipilimumab activates the immune system, and that ALC may predict response to treatment. No predictive biomarkers of irAEs were identified.