Murine peripheral blood prognostic biomarkers for tumor survival following combination aCTLA-4 and aPD-1 treatment

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From 30th Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer (SITC 2015) National Harbor, MD, USA. 4-8 November 2015

Background
Immune checkpoint inhibitors, particularly those targeting CTLA-4 and PD-1, are transforming the way cancer is treated. However, these therapies do not benefit all patients and frequently cause significant immune-related adverse events. Therefore, prognostic biomarkers that identify positively-responding patients, early in the course of therapy, are essential for guiding treatment decisions and improving patient outcomes.

Methods
In this study, we present evidence that shortly after initiating combination PD-1/CTLA-4 blockade, there is a transient increase in the frequency of pro-inflammatory and cytotoxic lymphocytes in peripheral blood, and the dynamics of this shift correlate with survival outcomes in multiple murine models.

Results
Specifically, we observed that 1) the relative frequency of cytotoxic CD8 T cells among peripheral lymphocytes and 2) the pro-inflammatory capacity of peripheral lymphocytes are both predictive for outcomes at an early time point. Surprisingly, robust correlations between peripheral lymphocyte markers and outcomes were limited to CD8 T cell populations. In general, the expression of potential biomarkers on peripheral CD4 T cells, including ICOS and FoxP3, were poorly correlated with outcomes in this study.

Conclusions
Overall, these findings suggest that elements of the near-term peripheral immune response to dual anti-PD-1/anti-CTLA-4 therapy associated with cytotoxic lymphocyte function may provide unique prognostic biomarkers for therapeutic outcomes.

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Published: 4 November 2015

doi:10.1186/2051-1426-3-S2-P91
Cite this article as: Hilgart-Martiszus et al. Murine peripheral blood prognostic biomarkers for tumor survival following combination aCTLA-4 and aPD-1 treatment. Journal for Immunotherapy of Cancer 2015 3 (Suppl 2):P91.
Figure 1

A

CD4 T cells

FoxP3

ICOS

GzmB

CT26 (colon)

4T1 (TNBC, mammary carcinoma)

3LL (lung)

MCA-205 (sarcoma)

TUBO (HER2+, mammary carcinoma)

r² = 0.08

p = 0.01

r² < 0.01

p = 0.61

r² = 0.01

p = 0.32

Avg tumor growth (mm²/day)

Avg tumor growth (mm²/day)

% expressing marker

% expressing marker

r² = 0.04

p = 0.06

r² = 0.02

p = 0.19

B

CD8 T cells

GzmA

GzmB

Ki-67

CD44

r² = 0.14

p < 0.01

r² = 0.14

p < 0.01

r² = 0.21

p < 0.01

r² = 0.15

p < 0.01

Avg tumor growth (mm²/day)

Avg tumor growth (mm²/day)

% expressing marker

% expressing marker