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Myeloid-derived suppressor cell quantity prior to treatment with ipilimumab at 10mg/kg to predict for overall survival in patients with metastatic melanoma.

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Background: Ipilimumab, an antibody that blocks the function of the immune inhibitory molecule cytotoxic T lymphocyte antigen 4 (CTLA-4), significantly prolongs survival in patients with metastatic melanoma. Approximately 30% of patients derive clinical benefit from therapy. Defining biomarkers of response to ipilimumab therapy would enable selection of patients more likely to respond and is relevant for both practicing clinicians and for clinical trial design. We performed a pilot correlative study evaluating myeloid derived suppressor cells (MDSC), a population of immune suppressive monocytic cells, as a biomarker of clinical outcome.
Methods: Peripheral blood from 26 patients with stage IV melanoma treated with ipilimumab 10mg/kg every 3 weeks for 4 doses at our center, as part of an expanded access program (BMS CA184-045) was assessed for MDSC quantity (%$CD14^{+}$,HLA-$DR^{low/-}$ cells) pre-treatment, at week 7, week 12, and week 24 by flow cytometry. MDSC ability to inhibit T cell proliferation was tested using an in vitro suppression assay.

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Results: We found that lower MDSC quantity pre-treatment predicted for improved overall survival (Hazard ratio 1.07 (1.03, 1.11) p=0.002) and trended toward associating with clinical benefit measured at week 24 imaging (p=0.09). This effect was independent of pre-treatment or week 7 absolute lymphocyte counts (ALC) and pre-treatment LDH when evaluated in a multivariate model with ALC and MDSC quantity HR 1.10; 95% CI 1.04, 1.17 p=0.0006 and LDH and MDSC quantity HR 1.06; 95% CI 1.01, 1.11 p = 0.013. Furthermore, a general trend of increasing MDSC number by week 24 from the pre-treatment baseline was associated with patients that did not achieve clinical benefit. MDSC suppressed peripheral blood T cell proliferation as measured by CFSE dilution in response to anti-CD3 antibody stimulation.
Conclusions: Pre-treatment MDSC quantity may predict clinical response following ipilimumab therapy. Further studies evaluating MDSC as a biomarker of ipilimumab therapy are warranted both retrospectively and prospectively in a broader group of patients.

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