

Meeting Abstract: 2013 ASCO Annual Meeting I

FREE ACCESS Developmental Therapeutics—Immunotherapy May 20, 2013



Peripheral and tumor immune correlates in patients with advanced melanoma treated with combination nivolumab (anti-PD-1, BMS-936558, ONO-4538) and ipilimumab.

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Publication: Journal of Clinical Oncology Volume 31, Number 15 suppl https://doi.org/10.1200/jco.2013.31.15_suppl.3003

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Abstract

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Background: Nivolumab and ipilimumab are fully human monoclonal antibodies that block the immune checkpoint receptors PD-1 and CTLA-4, respectively. In a multi-cohort, phase I study of nivolumab/ipilimumab combination therapy in melanoma patients (pts), objective response rates up to 47% were observed (NCT01024231). Putative predictive biomarkers from peripheral blood (PB) or tumor, including tumor PD-L1 expression, absolute lymphocyte count (ALC) and PB myeloid derived suppressor cells (MDSC) were evaluated. Pharmacodynamic changes in activated and effector T cells were also assessed. **Methods:** Tumor PD-L1 membrane expression was assessed in archival FFPE specimens by immunohistochemistry (28-8 PD-L1 antibody). ALC was measured in serial PB samples; changes in the percentage, number and phenotype of activated CD4⁺ and CD8⁺T cells and MDSC were characterized by flow cytometry. **Results:** PD-L1 expression was seen in 37% (10/27) of pts, using a cut-off of 5% tumor cell membrane staining. Objective responses (OR) were seen in pts with both PD-L1 negative (8/17) and PD-L1 positive (4/10) tumors. Relative to baseline, a rise in ALC was not detected, but phenotypic changes in PB T-cell subsets, including increases in the percentage of CD4 and CD8 expressing HLA-DR, ICOS and/or Ki67 were seen with combination therapy. Low ALC (<1.0 at wk 6-7) did not preclude OR as 3 of 12 pts with low ALC responded. Of pts evaluated, OR with ≥80% reduction in tumor burden at 12 wk were seen in pts with a low frequency of pretreatment PB MDSC (3/7) but no OR were seen in pts with high MDSC (0/6). **Conclusions:** In this small subset of pts, OR were seen independent of PD-L1 or ALC status in contrast to prior observations with nivolumab or ipilimumab, respectively. Thus, the immune response generated by combination therapy may have unique features compared to either monotherapy. The relationship between frequency of PB MDSC and reduction in tumor burden will be further explored. Further efforts in this study and in future phase III randomized studies will investigate these and other phenotypic changes in immune

cell populations and their relationship to patterns of clinical activity. [Clinical trial information: NCT01024231.](#)

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