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S48. Biomarker development for ipilimumab and prostate GVAX treatment

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Background

Immunotherapeutic approaches such as vaccination or immune checkpoint blockade have proven to be clinically active in prostate cancer, but only in fractions of treated patients; this calls for personalized application of these novel therapies based on predictive biomarkers.

Methods

Our own research over the past years has focused on the clinical efficacy in patients with castration-resistant prostate cancer of the combination of an allogeneic cell line-based vaccine (Prostate GVAX) and an anti-CTLA4 checkpoint inhibitor (ipilimumab) in a Phase-I/II dose escalation/expansion trial. We carried out an extensive immune monitoring programme comprising flowcytometric profiling of lymphoid and myeloid subsets in peripheral blood (PB) and T cell and serological reactivity to a panel of known tumor antigens, all before and after treatment.

Results

On-treatment PSA declines of more than 50% were observed in 5, and PSA stabilizations in 12 of 28 patients. Regressing bone and lymph node metastases were observed in 2/5 responding patients. Significantly prolonged overall survival (OS) was observed for patients with high pre-treatment frequencies of CD4+CTLA-4+, CD4+PD-1+, or differentiated CD8+ T cells, or low pre-treatment frequencies of regulatory T cells. Treatment-induced activation of PB Dendritic Cell subsets was similarly associated with significantly prolonged OS. In contrast, high pre-treatment frequencies of monocytic Myeloid-Derived Suppressor Cells (MDSC) were associated with reduced OS. Th2/Th17 cytokine profiles were induced. Indeed, profound up-regulation of CD4+IL-5+ T cell frequencies was associated with improved OS (p=0.03) and correlated significantly with the breadth of the induced antibody response. IgG antibody responses against 11 (prostate) tumor-associated antigens were determined and increased seroreactivity to prostate-specific membrane antigen (PSMA), pyridoxamine 5'-phosphate oxidase (PNPO) and/or Neuropilin-2 (NRP2) was significantly correlated with improved OS (p=0.002 for combined upregulated seroreactivity to all three). Finally, patients with pre-existing NY-ESO-1 T cell reactivity also demonstrated a significantly prolonged OS (p=0.044).

Conclusion

Together these data provide an immune profile to predict clinical outcome. Importantly, cluster analysis revealed pre-treatment expression of CTLA-4 by circulating CD4+ T cells and an immune-stimulatory myeloid profile to be dominant predictors for OS after Prostate GVAX/ipilimumab therapy. These flowcytometry-based parameters may thus provide potentially useful and easy-to-use biomarkers for patient selection.

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