382 THE SYNTHETIC LONG PEPTIDE CANCER VACCINE UV1 IN COMBINATION WITH IPILIMUMAB INDUCES A CD4+ TH1 ANTI-HTERT IMMUNE RESPONSE AND AN INFLAMMATORY TUMOR MICROENVIRONMENT IN PATIENTS WITH MELANOMA

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Background Checkpoint inhibitors (CPIs) have revolutionized the treatment of malignant melanoma. Although melanoma patients may experience deep and durable clinical responses to CPI treatment, the majority develop disease progression requiring additional therapy. Combining CPIs with therapeutic cancer vaccines may augment the anti-tumor immune response and thus improve clinical outcomes. UV1 is a therapeutic cancer vaccine based on synthetic antigens derived from the tumor-associated antigen telomerase reverse transcriptase (hTERT). hTERT is activated in 85–90% of all cancers and leads to replication of telomeric DNA, an essential mechanism for increased proliferation, immortality, and invasiveness of cancer cells. In this phase I/IIa study combining UV1 with ipilimumab in patients with melanoma (NCT02275416), we hypothesized that UV1 and ipilimumab might provide synergy in the expansion of vaccine-induced T cells. Furthermore, an augmented CD4+ Th1 immune response targeting a shared tumor antigen may increase T cell infiltration in the tumor microenvironment, promoting immune-mediated cancer cell death.

Methods The immune response dynamics were assessed by longitudinal immunomonitoring for up to 5 years using a standard proliferation assay. The phenotype and functionality of vaccine-induced T cells were assessed by patient-derived T cell cloning and subsequent in vitro characterization by flow cytometry, peptide stimulation, and cytokine release assays. On available biopsies harvested at baseline and 12 weeks after treatment initiation, the tumor microenvironment was assessed based on whole-exome sequencing, RNA sequencing, and immunohistochemistry.

Results Twelve patients with metastatic melanoma were enrolled in the study and received up to 9 vaccine doses over a 20-week period. A persistent (up to 5 years) vaccine-induced immune responses were demonstrated in 91% of evaluable patients (10/11). Vaccine-specific T cell clones were polyfunctional CD4+ Th1 cells, producing both IFN-γ and TNF-α upon in vitro peptide stimulation. Differential gene expression analysis and immunohistochemical characterization of biopsies at baseline and 12 weeks showed induction of an inflammatory ”hot” tumor microenvironment in clinical responders with available paired biopsies.

Conclusions UV1 in combination with ipilimumab leads to robust and long-lasting CD4+ Th1 anti-hTERT immune responses sculpting the local tumor microenvironment.

Trial Registration NCT02275416

Ethics Approval The study was approved by Regional Ethical Committee South East (ID number 25 165). The patients provided their written informed consent to participate in the study.

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