(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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Abstract

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. Persistent (up to 5 years) vaccine-induced immune responses were demonstrated in 91% of evaluable patients (10/11) (**Figure 1**). Vaccine-specific T cell clones were polyfunctional CD4+ Th1 cells, expressing ICOS and producing both IFN-γ and TNF-α upon in vitro peptide stimulation (**Figure 2**). Clinical responses were observed irrespective of TMB and neoantigen load. 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. (**Figure 3**).

Conclusion: UV1 in combination with ipilimumab leads to robust and long-lasting CD4+ Th1 anti-hTERT immune responses sculpting the local tumor microenvironment. These mechanistic data, together with the promising clinical read-out previously reported [1], support further development of UV1 in combination with checkpoint inhibitors.

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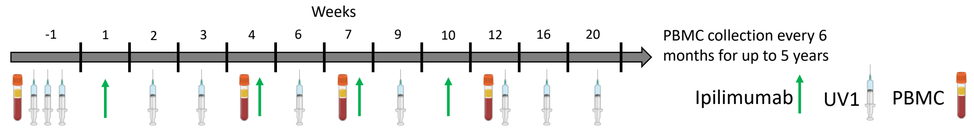
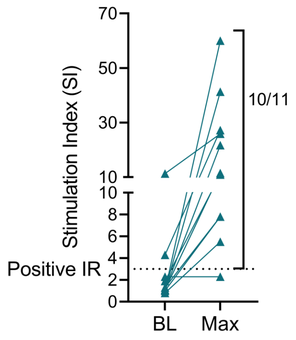
1: Aamdal E. et al (2021). Combining a Universal Telomerase Based Cancer Vaccine With Ipilimumab in Patients With Metastatic Melanoma - Five-Year Follow Up of a Phase I/IIa Trial. *Frontiers in Immunology, 12, 1278*

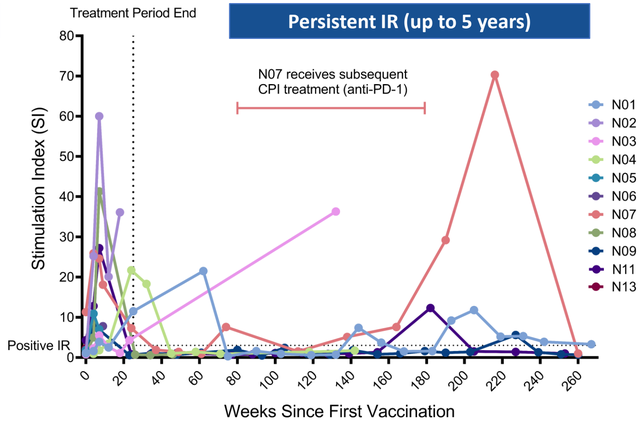
1. UV1 Vaccination Schedule and Immune Responses (IR)



Highest IR within treatment period

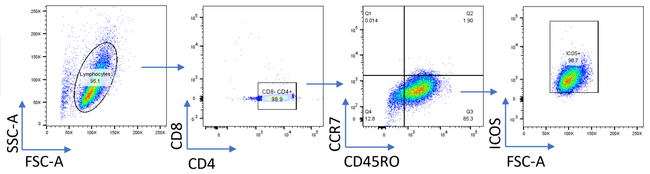


Persistent IR (up to 5 years)

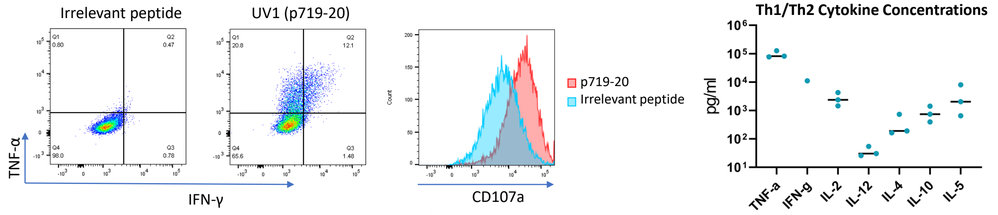


2. Characterization of Vaccine-Specific T Cell Clones

UV1 Induced T Cells Have Effector Memory Phenotype



UV1 Induced T Cells Produce Inflammatory Cytokine Responses Upon *In Vitro* Vaccine-Peptide Stimulation



Cytokine concentration (pg/ml)

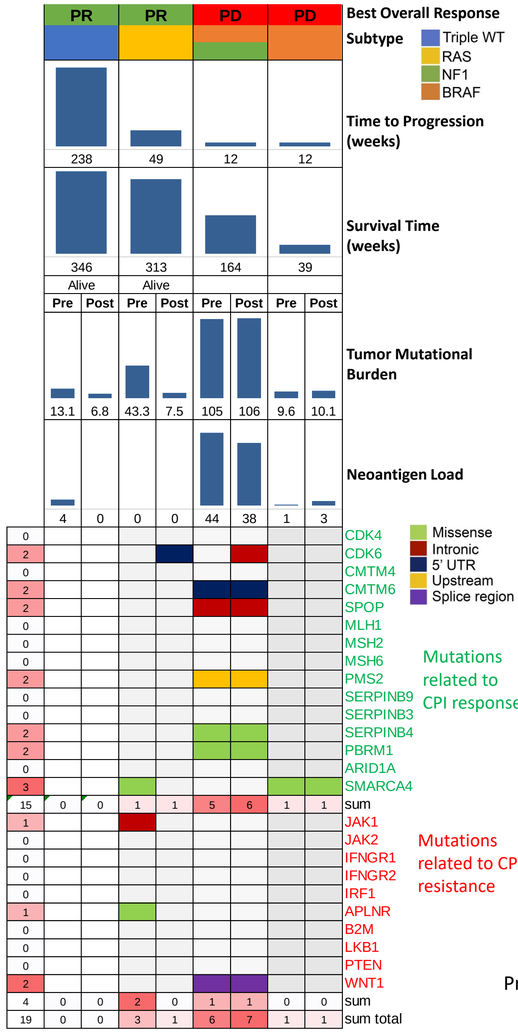
Ratio between Th1/Th2 cytokines

Patient	TCC #	IL-2	IL-4	IL-5	IL-10	IL-12	IL-13	GM-CSF	IFN-γ	TNF-α	IFN-g / IL-10	TNF-a / IL-4	IFN-g / IL-4	IFN-g / IL-5	IFN-g / IL-13	Polarization
N02	7	2359	190	2035	395	54	>5407	>7683	11118	76864	28.2	404.8	58.6	5.5	<2.1	Th1
	13	1460	164	654	738	26	>3996	>6868	>7242	127638	>9.8	778.6	>44.2	>11.1		Th1
	28	4284	728	8037	1425	30	>1910	>6849	>7228	81535	>5.1	112.1	>9.9	>0.9		Th1

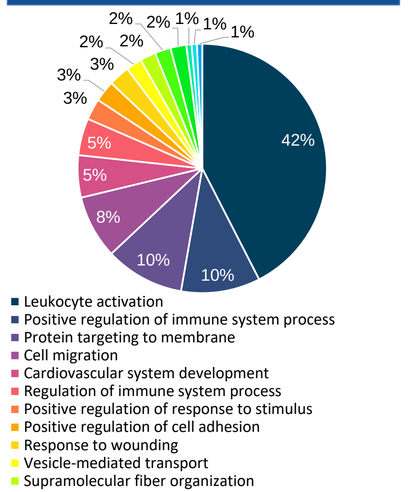
Concentrations from negative control subtracted.
Cytokine ratios written in blue refer to Th1 polarization (IFNγ/IL10 > 5; TNFγ/IL4 > 10; IFNα/IL4 > 20; IFNγ/IL5 > 5; IFNγ/IL13 > 1)

3. Modulation of the Tumor Microenvironment

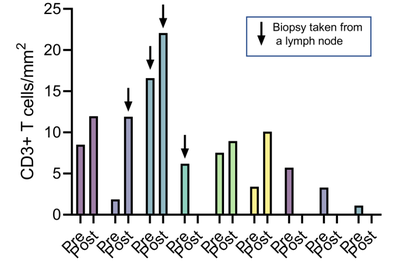
Clinical and Genomic Characterization

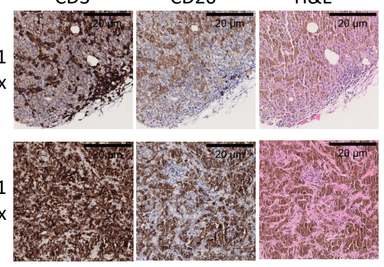


Gene Set Enrichment Analysis (ClueGO) on Differentially Expressed Genes in Tumor at Week 12 (N01)



Tumor Infiltrating Lymphocytes





Overlapping SNVs Pre and Post Treatment