P342 - Long Term Outcome of a Phase I Study with UV1, a Second-Generation Telomerase Based Vaccine in Patients with Advanced Non-Small-Cell Lung Cancer

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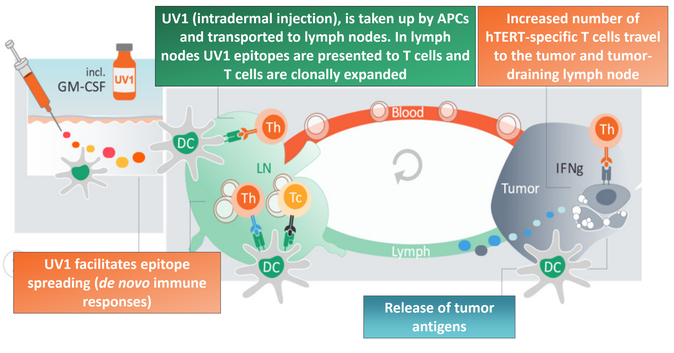
BACKGROUND

UV1 is a novel therapeutic cancer vaccine that consists of three peptides (15,15 and 30 amino acids) representing fragments of the human reverse transcriptase subunit of telomerase (hTERT). The peptides were selected based on immunological analyses of blood from long-term cancer survivors previously treated with an unrelated first generation hTERT vaccine (GV1001). Telomerase activation is the major mechanism implicated in human cell immortalization and cancer cell pathogenesis [1]. Telomerase is expressed in cancer cells at every stage of tumor evolution, from the cancer stem cell to circulating tumor cells. A CD4+ Th1 response against telomerase has recently been implicated as a positive prognostic factor in cancer [2]. Immunization with UV1 peptides predominantly aims to induce Th1 immune responses (i.e. secretion of interferon gamma (IFN-γ), tumor necrosis factor alpha (TNFα) and interleukin-2 (IL-2) to stimulate expansion of effector cells, such as cytotoxic CD8+ T cells and activate other players of the immune system. UV1 is a multiepitope vaccine and is designed to give high population coverage without the need to HLA-type patients.

TRIAL DESIGN

Patients with stage III/IV NSCLC and with no evidence of progression after prior treatments were enrolled in this single center phase I dose escalation study receiving intradermal UV1 (100 µg, 300 µg or 700 µg) + GM-CSF (75 µg) as adjuvant. Safety was assessed according to CTCAE v. 4.0 and tumor responses according to RECIST v.1.1. Immune responses (IR) against UV1 peptides were monitored in peripheral mononuclear blood cells (PBMC) by using 3H-thymidine proliferation. Patients were considered immune responders if stimulation index (SI) ≥3. IFN-γ ELISPOT assays were performed in patients with sufficient cell numbers.
UV1 and GM-CSF were given 3 times during the first week (day 1, 3, 5) and then week 2, 3, 4, 6, 8, 10, 14, 18, 22 and 26. After week 26 additional vaccinations were given every 3 months.

PROPOSED MECHANISM OF ACTION



RESULTS

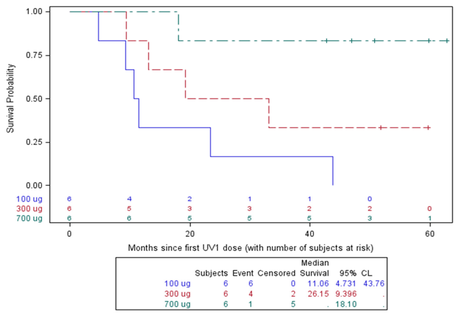
18 non-HLA-typed patients with stage III/IV NSCLC (8 squamous /10 adenocarcinoma) were enrolled; 6 on each UV1 dose level. Six patients with stage III disease, 12 with stage III/IV or IV. ECOG status was 0 or 1 (14 : 4 pts.). All patients had been treated with chemotherapy, except one (pembrolizumab) and 12 patients with radiotherapy and none had signs of progression after previous treatments. Patients were followed up for IR and new anticancer treatment for 5 years after first UV1 treatment. Survival is to be followed up for 10 years. The maximum number of UV1 and GM-CSF doses given was 18, range 9-18 for UV1 and 2-18 for GM-CSF. Treatment with UV1 was well tolerated with no serious adverse events observed. 17 patients were evaluable for tumor response; 15 patients had stable disease as best response. The median progression free survival was 12.3 months and the median overall survival (OS) was 28.2 months. The OS at 4 years was 39%. None of the 7 long-term surviving patients (median survival 4.96 years) have received checkpoint therapy after vaccination. Five of these patients are in the 700 µg dose group, two in the 300 µg dose group. UV1 induced specific T cell responses were observed in the majority (67%) of patients. Both IR response and OS were dose related. More patients in the highest UV1 dose group (700 µg) developed IRs than in the two other groups and the IRs were stronger and occurred earlier. Patients in the 700 µg group had a 4-year OS of 83%.

SAFETY

UV1 dose (µg)	100	300	700	All
Number of patients	6	6	6	18
Injection site erythema	2	0	3	5
Fatigue	0	1	3	4
Injection site pruritus	2	0	2	4
Injection site reaction	2	1	0	3
Influenza like illness	1	1	0	2
Arthralgia	0	0	1	1
Blood pressure decreased	0	1	0	1
Erythema	0	1	0	1
Headache	0	1	0	1
Hypersensitivity	0	1	0	1
Injection site hyperaesthesia	1	0	0	1
Injection site pain	1	0	0	1
Injection site rash	1	0	0	1
Musculoskeletal pain	0	1	0	1
Pruritus	0	1	0	1
Tongue movement disturbance	0	1	0	1

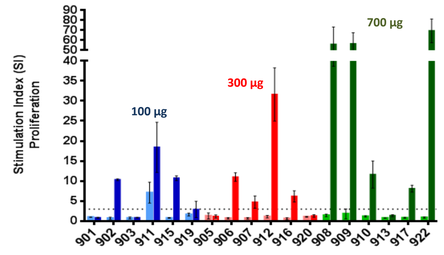
Number of patients with one or more treatment related AEs

SURVIVAL

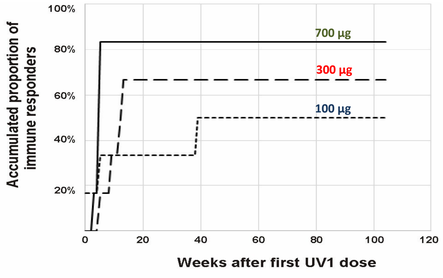


Overall survival. KM plot of OS for patients in the three UV1 dose groups

IMMUNE RESPONSES



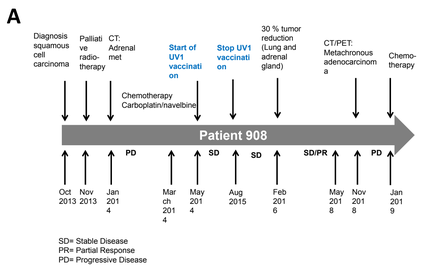
T-cell proliferation against UV1 peptides in pre- and post-vaccination blood samples (PBMC). The graph shows the strongest post-vaccination T-cell responses detected against the UV1 peptide mix for each patient at each dose level



The time-to-response and accumulated proportion of immune responders per UV1 dose group

CASE REPORT

700 µg dose group patient



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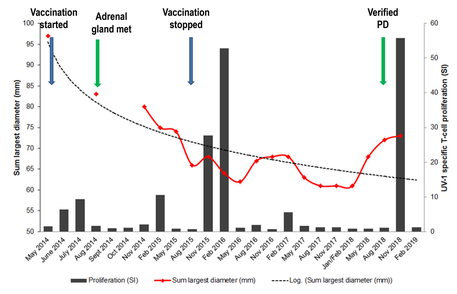

Timeline for diagnosis, treatment and disease progression in patient 908 (A). Summary of pre- and post-vaccination UV1-specific T-cell responses and tumor reduction measured in patient 908 (B). T-cell proliferation was measured in response to peptide-loaded PBMC by 3H-thymidine incorporation. A stimulation index (SI) of ≥3 is considered as an immune response. Dotted line is the logarithmic trend line for tumor diameter

CONCLUSION

The highest dose of UV1 resulted in the highest proportion of immune responses, associated with long survival. This together with the safety and clinical outcome data, favors 700 µg as the preferred UV1 dose in this patient population. We believe that the true potency of UV1 and other hTERT vaccines can only be explored in combinations with immune checkpoint inhibitors, where the role of the vaccine is to prime a meaningful T cell response and the role of the checkpoint inhibitors will be to enhance the response and to facilitate the activity of the T cells in the tumor microenvironment. The results provide a rationale for further clinical studies in NSCLC with UV1 vaccination in combination with immune checkpoint blockade.

1.Hanahan, D. and R.A. Weinberg, Hallmarks of cancer: the next generation. Cell, 2011. 144(5): p. 646-74.
2.Laheurte, C., et al., Distinct prognostic value of circulating anti-telomerase CD4(+) Th1 immunity and exhausted PD-1(+)/TIM-3(+) T cells in lung cancer. Br J Cancer, 2019. 121(5): p. 405-416.

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ultimovacs