A Phase I Clinical Trial Investigating the Therapeutic Cancer Vaccine UV1 in Combination with Pembrolizumab as First-Line Treatment of Patients with Malignant Melanoma (ASCO2021)

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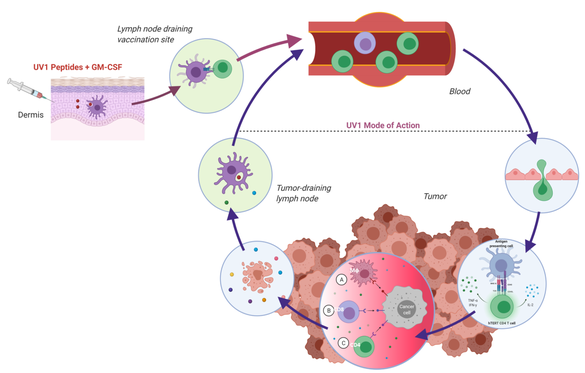
BACKGROUND AND RATIONALE

UV1 (developed by Ultimovacs ASA) consists of three peptides (15,15 and 30 amino acids) representing fragments of the human reverse transcriptase subunit of telomerase (hTERT). Telomerase activation is the major mechanism implicated in human cell immortalization and cancer cell pathogenesis [1]. Telomerase is expressed in all 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]. Thus, telomerase represents a unique cancer antigen as a basis for immunotherapy [3]. UV1 contains both CD4 and CD8 epitopes and has been shown to be immunogenic in 78% (40/52) of HLA unselected patients across three completed phase I studies. The vaccine mainly induces Th1 reactivity (i.e secretion of IFN-γ, TNFα, and IL-2), and an immune response against the UV1 peptides is associated with epitope spreading within hTERT and prolonged survival [4].

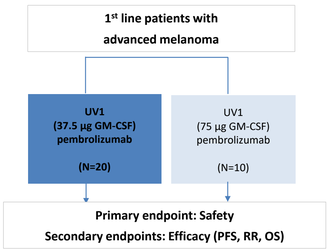
Study rationale: Efficacy of pembrolizumab depends on the presence of spontaneously induced T cell responses against relevant tumor antigens. Patients who lack or have few T cells in their tumor are less likely to obtain durable benefit from pembrolizumab alone. UV1 has the potential to increase the efficacy of pembrolizumab by amplifying the pool of hTERT-specific, tumor-reactive CD4 T cells from the naïve repertoire and has the potential to increasing the breadth and diversity of the tumor-reactive T cell response (epitope spread). Reciprocally, the efficacy of UV1 vaccination may be enhanced since the checkpoint inhibitor can augment the clonal expansion and effector activity of UV1-induced T cells that is otherwise restricted by intrinsic immune regulatory- and tumor induced suppressor mechanisms. Thus, the addition of UV1 to pembrolizumab has the potential to produce synergistic immunological activity which may transfer into increased clinical benefit compared to pembrolizumab monotherapy.

PROPOSED MECHANISM OF ACTION OF UV1



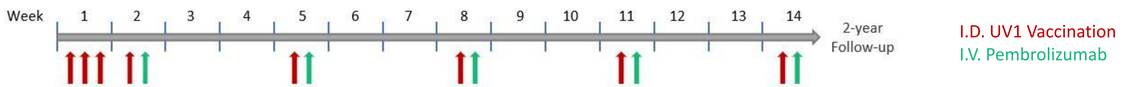
Since telomerase is continuously present, the UV1 specific CD4 T-cells may stay activated and relevant over time. Expected synergy with a PD-1 inhibitor

TRIAL DESIGN AND OBJECTIVES



- Open-label phase I study (NCT03538314), evaluating safety and tolerability of UV1 and GM-CSF in combination with standard pembrolizumab as first line treatment in patients with advanced melanoma (primary endpoint) and response rate (iRECIST), PFS and survival as secondary endpoints
- Patients received 8 UV1 vaccinations (300 µg) with GM-CSF as adjuvant. 20 patients received 37.5 µg (Cohort 1) while 10 patients received 75 µg GM-CSF (Cohort 2). Five doses of pembrolizumab were given during the UV1 treatment. Pembrolizumab continued per label after completed UV1 treatment. Results from Cohort 1 data presented

TREATMENT AND KEY INC/EXC CRITERIA



Key Inclusion Criteria

- Unresectable histological confirmed malignant melanoma (Stage IIIB-C, IV)
- Measurable and evaluable disease per RECIST v.1.1
- Previous untreated and eligible for pembrolizumab (prior BRAF and MEK inhibitors permitted)
- ECOG 0-1

Key Exclusion Criteria

- Uveal or ocular melanoma
- Prior therapy with anti-CTLA4, anti-PD-L1/L2 or oncolytic virus
- Active brain metastases (MRI)

RESULTS (Cohort 1)

Demographic and UV1/GM-CSF

Patients	N=20
Male/Female	13/7
Median age (range)	70 (31-82)
ECOG 0/1	15/5
Stage IIIb, IIIc, IV	2 /8 /10
Elevated LDH	5
UV1 and GM-CSF doses (pts.)	8 (17) 7 (2) 6 (1)

Safety

	UV1 + pembrolizumab (N=20)		
Adverse Events, N (%)	Any grade	Grade ≤ 2	Grade 3
Fatigue	10 (50)	10	
Injection site reactions	5 (25)	5	
Hypothyroidism	5 (25)	5	
Diarrhoea	4 (20)	3	1
Pyrexia	4 (20)	4	
Dyspnoea	4 (20)	3	1
Colitis	4 (20)	3	1
Arthritis	2 (10)	0	2

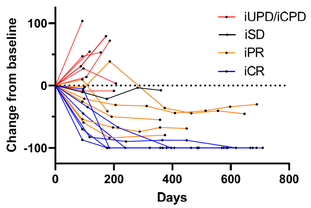
- All except one patient reported an AE
- A total 150 AEs were reported
- Majority of AEs were grade 1 or 2 (48%, 41%)
- 18% and 30% of AEs were possibly/definitely related to UV1 or pembrolizumab, respectively
- Three patients experienced a SAE, one SAE (inflammatory arthritis) was considered possibly related to UV1
- No severe allergic reactions were observed

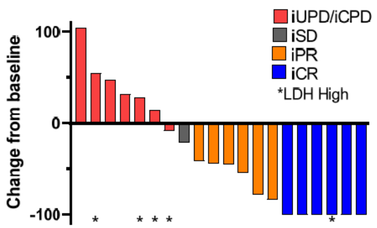
Clinical Response

Patients	N=20
Response rate	6 iCR (30%) 6 iPR (30%) 1 iSD (5%) 7 iUPD/iCPD (35%)
Survival°	80%
mPFS	18.9 months

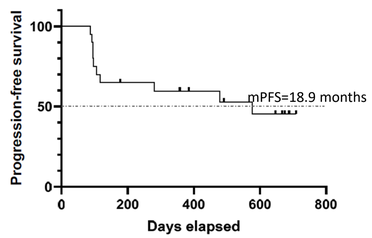
°Median follow-up is 21.2 months

Change in tumor by patient





Progression free survival



CONCLUSION

- UV1 in combination pembrolizumab is very well tolerated as first line treatment in patients with advanced melanoma (N=20), with fatigue and injection site reactions as the most frequent reported AEs. Majority of AEs were grade 1 or 2.
- The survival was 80% and mPFS was 18.9 months after a median follow-up of 21.2 months. The response rate (RR) was 60%, with 6CRs and 6PRs.
- The presented results are encouraging and support further validation
- Cohort 2 (N=10) will be presented after 1 year follow-up reached
- UV1 is currently evaluated in a phase II study in combination with ipilimumab and nivolumab in advanced melanoma

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Clinical Trial Registry Number NCT 03538314
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