1378TiP - A Phase I Clinical Trial Investigating the Therapeutic Cancer Vaccine UV1 in Combination with Pembrolizumab as First-Line Treatment of Patients with Malignant Melanoma (ID3996)

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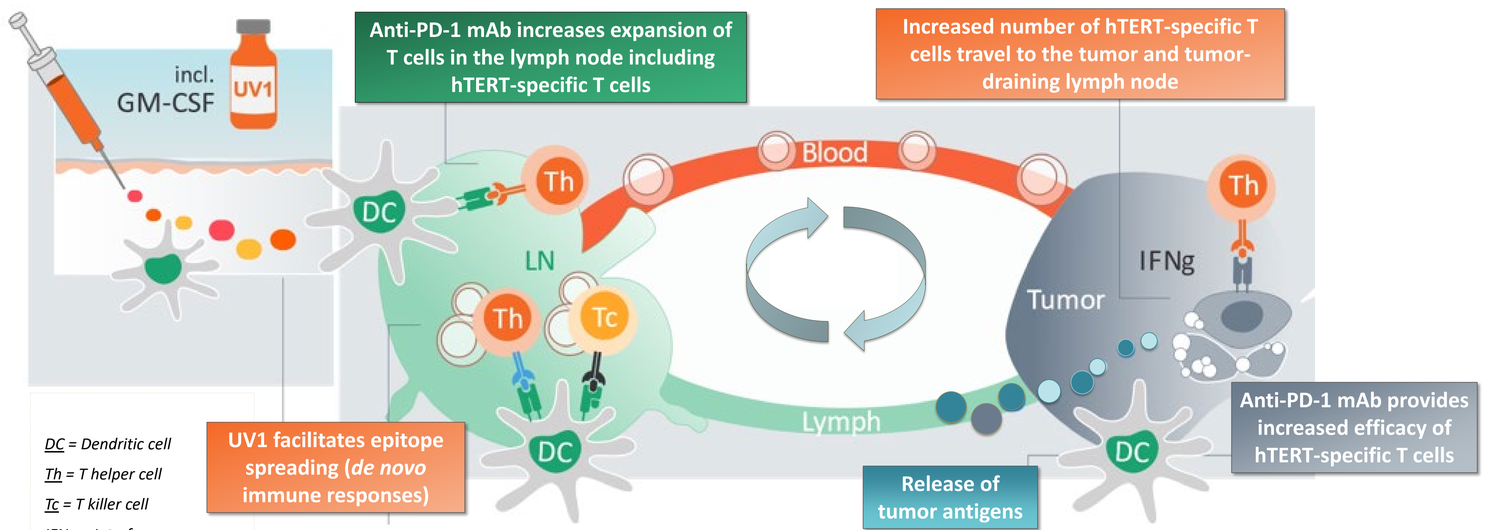
BACKGROUND:

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 and by increasing the breadth and diversity of the tumor-reactive T cell response (epitope spread). Reciprocally, the efficacy of UV1 vaccination may be enhanced since pembrolizumab augment the effector activity of UV1 induced T cells that are 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 SYNERGY BETWEEN IMMUNE ACTIVATION AND CHECKPOINT INHIBITION



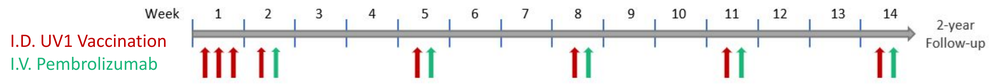
DC = Dendritic cell
Th = T helper cell
Tc = T killer cell
IFNg = Interferon gamma
LN = Lymph node

Relevance of the hTERT-specific CD4 cells

- hTERT is present throughout the tumorigenesis and the tumor cannot escape from dependence on telomerase.
- Due to the temporo-spatial presence of the target, the CD4 T cells induced by UV1 can provide a pro-immunological environment in the tumor and tumor-draining lymph node, continuously and over time, regardless of the genetic makeup of the individual tumor cell.
- The vaccine mediated CD4-immune response optimize for priming of de novo immune responses (epitope spreading) and tumor cell killing in an otherwise highly dynamic tumor.

TRIAL DESIGN:

This is an ongoing Phase I, open-label, multicenter study investigating UV1 vaccination in combination with pembrolizumab in 30 patients with untreated unresectable or metastatic melanoma. Patients receive 8 UV1 vaccinations (300 µg) with GM-CSF as adjuvant. 20 patients will receive 37.5 µg while 10 patients will receive 75 µg GM-CSF. Five doses of pembrolizumab are given during the UV1 treatment. Pembrolizumab continues per label after completed UV1 treatment.



KEY ENTRY 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)

TRANSLATIONAL RESEARCH OBJECTIVES:

- Correlation between UV1 specific immune responses in vitro (proliferation/ELISPOT) and in vivo (DTH*)
- Correlation between exploratory biomarkers and clinical response
- Whole-exome sequencing for TMB estimation and neoantigen prediction
- Evolution of the TCR repertoire in response to treatment by TCR sequencing of PBMCs
- Correlation of mutations seen on liquid and solid tissue biopsies**
- Correlation of fecal microbiome and response to treatment

OBJECTIVES:

Primary

- Safety and tolerability of the combination of UV1 and pembrolizumab

Secondary

- Immunological response against the vaccine
- Progression Free Survival (PFS) (RECIST1.1 and iRECIST)
- Overall Survival (OS)
- Duration of pembrolizumab treatment
- Time to subsequent anticancer therapies

SUMMARY:

- The study is open and actively accruing at sites in the US
- Accrual is expected to be completed early Q12020
- For additional information please contact wenche.rasch@ultimovacs.com

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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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*DTH = Delayed type hypersensitivity ** Cell-free DNA in blood will be sequenced and analyzed for tumor-specific mutations

None of the authors have any Conflicts of Interest to disclose with regards to Ultimovacs ASA

Clinical Trial Registry Number NCT 03538314

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