Nivolumab and ipilimumab +/- UV1 vaccine as 1st line treatment in patients with malignant melanoma (INITIUM-trial)

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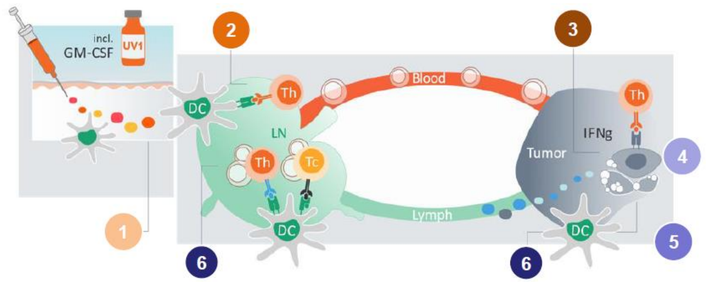
BACKGROUND:

UV1: (developed by Ultimovacs ASA, Oslo, Norway) 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 at least 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 the combined treatment of ipilimumab and nivolumab depends on the presence of a spontaneously induced T cell response against relevant tumor antigens. Patients who lack or have few tumor-specific T cells in their tumor are less likely to obtain durable benefit from combination therapy with nivolumab and ipilimumab. UV1 vaccination has the potential to increase the efficacy of the combination therapy in patients where the immune response spontaneously primed by tumor antigens is insufficient for induction of long-term clinical benefit. Vaccination with UV1 amplifies the pool of hTERT specific tumor-reactive CD4 T cells from the naïve repertoire and has the potential to increase 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 inhibitors 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. The addition of UV1 vaccination to checkpoint inhibitors thus have the potential to produce synergistic immunological activity which may transfer into increased clinical benefit compared to dual CTLA-4 and PD-1 checkpoint inhibitor therapy.

PROPOSED MECHANISM OF SYNERGY BETWEEN IMMUNE ACTIVATION AND CHECKPOINT INHIBITION



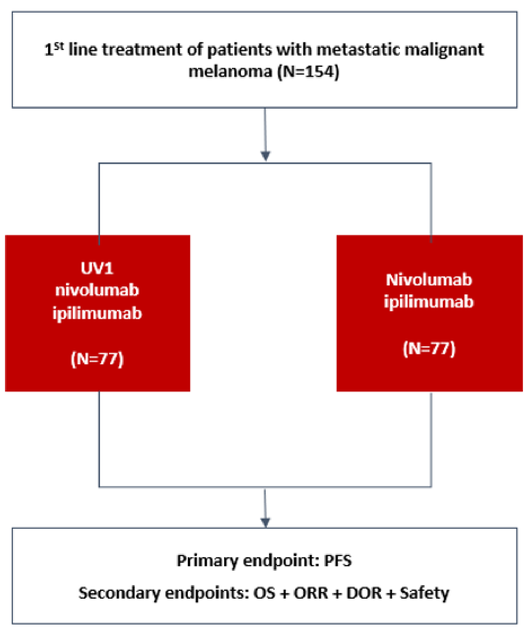
UV1 mechanism of action

1. Skin: UV1 is taken up by dendritic cells and transported to the lymph node
2. Lymph node: UV1 peptides are presented to näive T cells, and telomerase-specific CD4 T cells are expanded
   - Expected synergy with a-CTLA-4
3. UV1 induced CD4 T cells enter the tumor and the tumor-draining lymph node if the tumor microenvironment is permissive

Relevance of anti-telomerase T cells

4. CD4 T cells produce pro-inflammatory cytokines (TNF-a, IFN-g) stimulating other cells of the immune system against the tumor
5. Since telomerase is continuously present, the vaccine-specific CD4 T cells may stay activated and relevant over time
   - Expected synergy with a-PD-1
6. The inflammatory environment induced by the CD4 T cells optimize for *de novo* immune responses against other antigens

STUDY DESIGN



TRIAL DESIGN:

The INITIUM study (EudraCT no: 2019-002026-75) is an ongoing Ultimovacs sponsored, randomized, open-label, multi-center study comparing the efficacy and safety of nivolumab and ipilimumab per label with or without UV1 vaccination in 1st line metastatic MM patients. Patients receive 8 UV1 vaccinations (300 µg) with GM-CSF as adjuvant. A substudy is conducted with additional biological sampling for an extensive translational research program.

KEY ENTRY CRITERIA:

Key Inclusion Criteria

- Unresectable histological confirmed malignant melanoma (Stage IIIB-C, IV)
- Measurable and evaluable disease per RECIST v.1.1
- ECOG 0-1

Key Exclusion Criteria

- Previous non-melanoma malignancies unless curatively treated and complete remission was achieved at least 2 years prior to randomization.
- Prior systemic treatment for unresectable stage IIIB-D or unresectable stage IV malignant melanoma.
- Prior systemic BRAF/MEK inhibitors or immunotherapy as neoadjuvant or adjuvant if patient progressed earlier than 6 months after last dose of such treatment.
- Known brain metastases or leptomeningeal metastases

OBJECTIVES:

Primary

- Progression free survival

Secondary

- Overall survival
- Objective response rate
- Duration of response
- Safety
- Translational endpoint (see translational research objectives)

TRANSLATIONAL RESEARCH OBJECTIVES:

- Correlation between UV1 specific immune responses in vitro (proliferation/ELISPOT) and in vivo (delayed type hypersensitivity)
- Correlation between exploratory biomarkers and clinical response
- Whole-exome and RNA sequencing for tumor gene mutation and expression analysis
- T cell receptor (TCR) sequencing to generate TCR repertoire and evaluate changes in response to treatment
- Cell-free DNA analysis (liquid biopsy) for tumor-specific mutation tracking over time
- Correlation of fecal microbiome and response to treatment

SUMMARY:

- The study is open and actively accruing at sites in the US, UK, Belgium and Norway
- Accrual is expected to be completed 4Q2021
- For additional information please contact jens.bjorheim@ultimovacs.com

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

Clinical Trial Registry Number NCT04382664

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