62 C9 - A Phase I/IIa Clinical Trial Investigating the Therapeutic Cancer Vaccine UV1 in Combination with Ipilimumab in Patients with Malignant Melanoma: 4-year Survival Update

E.B. Ellingsen[2,5,7], E. Aamdal [1,2,3], E. M. Inderberg [4], W. Rasch [7], P. Brunsvig [1], S. Aamdal [1,2,7], E. Hovig [5,6], M. Nyakas [1], T. K. Guren [1], G. Gaudernack [2,7]; [1] Department of Oncology, Oslo University Hospital, Oslo, Norway; [2] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway; [3] Department of Oncology, Akershus University Hospital, Lorenskog, Norway; [4] Department of Cellular Therapy, Oslo University Hospital, Oslo, Norway; [5] Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway; [6] Center for Bioinformatics, Department of Informatics, University of Oslo, Oslo, Norway; [7] Ultimovacs ASA, Oslo, Norway

BACKGROUND:

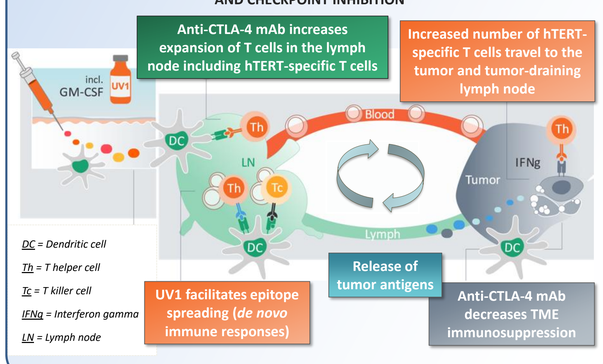
UV1

- 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.
- Thus, telomerase represents a unique cancer antigen as a basis for immunotherapy[2]. 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 [3].

Study rationale

- CPI therapy rely on spontaneous anti-tumor immune responses for their efficacy. Thus, strategies aimed at augmenting the anti-tumor immune response through therapeutic cancer vaccination against tumor-related antigens may improve outcomes with CPI therapy
- This trial explores the synergistic effect of CTLA-4 blockade and hTERT vaccination, allowing unchecked expansion of hTERT-specific T cell clones

PROPOSED MECHANISM OF SYNERGY BETWEEN IMMUNE ACTIVATION AND CHECKPOINT INHIBITION



TRIAL DESIGN:

This was an open-label, single-armed, single-center phase I/IIa clinical trial investigating UV1 in combination with ipilimumab in patients with unresectable stage III/IV metastatic cutaneous melanoma. 12 patients were enrolled.

Treatment Schedule

I.D. UV1 Vaccination
I.V. ipilimumab

Patients followed for safety up to 1 year, immune response up to 5 years, and survival up to 10 years

KEY ENTRY CRITERIA:

Key Inclusion Criteria

- Patients aged ≥ 18 years with a histologically confirmed diagnosis of unresectable stage III/IV malignant melanoma of cutaneous origin
- ECOG status of 0 or 1
- Any previous treatment was accepted

Key Exclusion Criteria

- Active brain metastases
- History of autoimmune disease

OBJECTIVES:

Primary

- Safety and tolerability of the combination of UV1 and ipilimumab

Secondary

- Immune responses to UV1 peptides
- Overall response rate (ORR)
- Overall survival (OS)
- Progression free survival (PFS)

BL CHARACTERISTICS:

Characteristics	Number of patients (%)
Sex	
Male	7 (58)
Female	5 (42)
Age (years)	
Mean	58
Range	44-73
ECOG PS	
0	11 (92)
1	1 (8)
Stage	
IV M1a	1 (8)
IV M1b	1 (8)
IV M1c	10 (83)
Tumor mutational burden	
TMB low (1-5 mut/mb)	2 (17)
TMB int. (6-19 mut/mb)	3 (25)
TMB high (>20 mut/mb)	4 (33)
BRAF V600E genotype	
Positive	3 (25)
Negative	9 (75)
LDH	
≤UNL	6 (50)
≥UNL	6 (50)
Previous treatment	
Chemotherapy	2 (17)
BRAF inhibitor	2 (17)

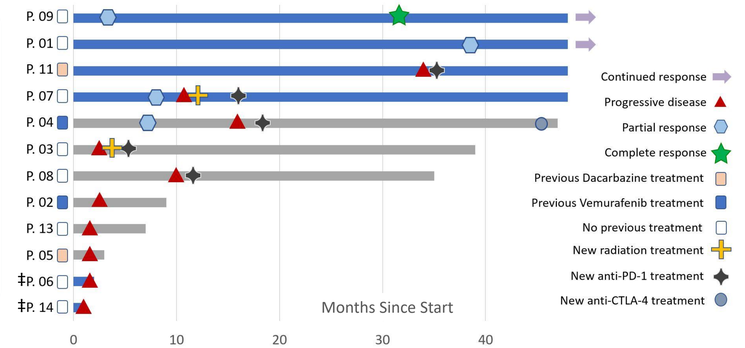
ECOG, Eastern Cooperative Oncology Group; PS, performance status; UNL, upper normal limit.

RESULTS:

Endpoint	ITT Population (n=12)
mPFS	6.7 months
1-year OS rate	75%
2-year OS rate	75%
3-year OS rate	67%
4-year OS rate	50%
mOS	Not Reached

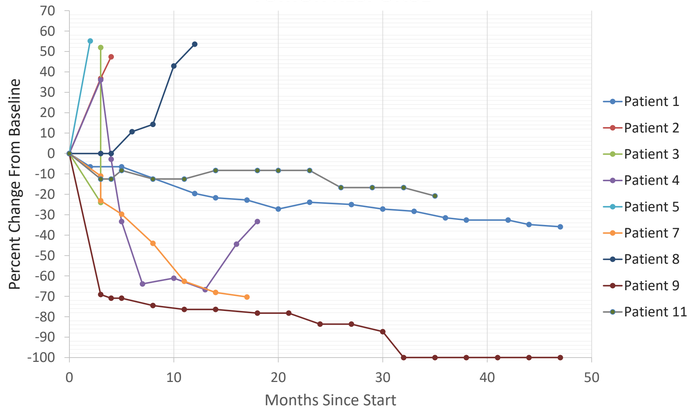
Best Overall Response (RECIST 1.1)	Evaluable patients (n=9)	
	n	%
CR	1	11.1
PR	3	33.3
SD	2	22.2
PD	3	33.3
ORR	4	44.4

SURVIVAL*

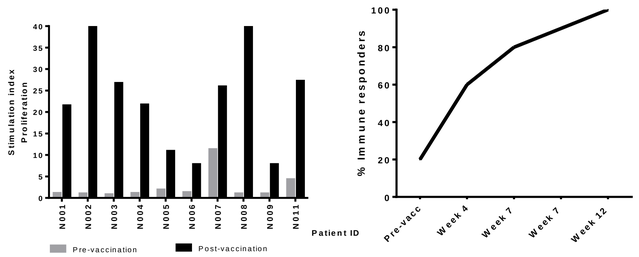


* Up to 48 months follow-up
‡ Two patients were not followed beyond progression

TUMOR RESPONSE



IMMUNE RESPONSE



Summary of pre- and post–vaccination UV1-specific T-cell responses detected. T-cell proliferation against UV1 peptides in pre- and post-vaccination blood samples from the 10 patients evaluable for immune responses. The graph shows the strongest post-vaccination T-cell responses detected against the hTERT peptide mix for each patient. Proliferation was measured in response to peptide-loaded PBMC by ^{3}H-thymidine incorporation. A stimulatory index of >3 is considered as an immune response.

CONCLUSION:

- Combining UV1 and ipilimumab is safe and induces clinical responses in melanoma
- The high proportion of immunological responders and early induction of detectable immune responses suggest synergism
- Although not directly comparable, OS in this trial compares favorably to an ipilimumab monotherapy phase IV trial conducted at our hospital (NCT02068196) with similar inclusion criteria, with a 4-year OS rate of 50 % vs 27.5 %, respectively.
- These results warrant further investigation of UV1 in combination with checkpoint blockade in melanoma

REFERENCES:

1.Hanahan, D. and R.A. Weinberg, Hallmarks of cancer: the next generation. Cell, 2011. 144(5): p. 646-74.
2.Zanetti, M., A second chance for telomerase reverse transcriptase in anticancer immunotherapy. Nat Rev Clin Oncol, 2017. 14(2): p. 115-128.
3.Inderberg-Suso, E.M., et al., Widespread CD4+ T-cell reactivity to novel hTERT epitopes following vaccination of cancer patients with a single hTERT peptide GV1001. Oncoimmunology, 2012. 1(5): p. 670-686.

E.B. Ellingsen, W. Rasch, S. Aamdal, and G. Gaudernack are employees of Ultimovacs ASA

Clinical Trial Registry Number NCT 02275416

Oslo University Hospital

Scan me