Updated survival and vaccine response from the NIPU trial;

A randomised, phase II study evaluating nivolumab and ipilimumab with or without UV1 vaccination in patients with pleural mesothelioma (PM)

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Background

- Pleural mesothelioma (PM) has dismal prognosis despite introduction of immunotherapy
- The NIPU trial evaluated adding UV1 telomerase vaccine to double immunotherapy.
- The study did not meet the primary endpoint of improved progression-free survival by blinded, independent central review (BICR) (ESMO 2023).
- Here we present **updated survival** and analysis of **UV1-specific immune response**.

- Peripheral blood mononuclear cells (PBMC) were collected from a subset of patients.
- The cells were cultured and stimulated with UV1 peptides to identify patients with UV1-specific immune reaction.

Safety

Treatment-emergent adverse event (TEAE):
Addition of UV1 to ipilimumab and nivolumab was well tolerated

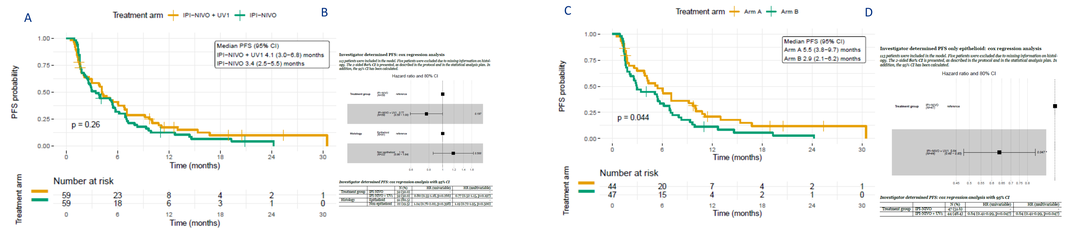
	Arm A (N=59)	Arm B (N=59)	Total (N=118)
Patients with any TEAE	59 (100.0%)	58 (98.3%)	117 (99.2%)
	TEAE 36		
Patients with any serious	(61.0%)	37 (62.7%)	73 (61.9%)
Patients with any TEAE of special interest	27 (45.8%)	25 (42.4%)	52 (44.1%)
TEAE grade			
N-Miss 0 1 1	0	1	1
Mild (grade 1)	3 (5.1%)	4 (6.9%)	7 (6.0%)
Moderate (grade 2)	24 (40.7%)	23 (39.7%)	47 (40.2%)
Severe (grade 3)	28 (47.5%)	27 (46.6%)	55 (47.0%)
Life-threatening (grade 4)	2 (3.4%)	2 (3.4%)	4 (3.4%)
Death (grade 5)	2 (3.4%)	2 (3.4%)	4 (3.4%)
Patients with any related TEAE	55 (93.2%)	50 (84.7%)	105 (89.0%)
Patients with any TEAE related to nivolumab	50 (84.7%)	50 (84.7%)	100 (84.7%)
Patients with any TEAE related to ipilimumab	47 (79.7%)	49 (83.1%)	96 (81.4%)
Patients with any TEAE related to GM-CSF	35 (59.3%)	0 (0.0%)	35 (29.7%)
Patients with any TEAE related to UV1 vaccine	37 (62.7%)	0 (0.0%)	37 (31.4%)

TEAE:
-Not present at the start of treatment OR worsened during treatment OR resolved and reappeared during treatment.
-Starting time: from the date of the first study treatment to 30 days after the last study treatment OR until the day prior to the first day of a new therapy.

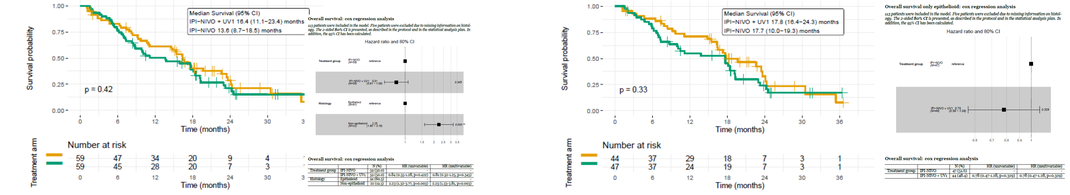
Updated progression free and overall survival

118 patients were included and randomized. With a median follow-up of 24.9 months (95% CI 21,8-31,3), investigator determined PFS events has occurred for 107 patients (91%) and OS events for 86 (73%).

Investigator determined PFS
Kaplan-Meier plots with log-rank test for (A) all patients and (C) patients with epithelioid histology only.
Cox regression for investigator determined PFS for (B) all patients and (D) patients with epithelioid histology only



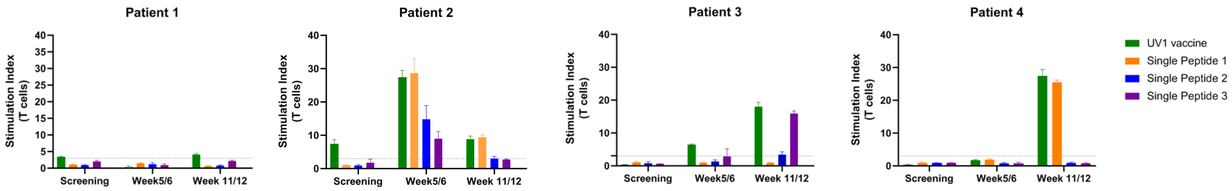
Overall survival
Kaplan-Meier plots with log-rank test for (E) all patients and (G) patients with epithelioid histology only.
Cox regression for investigator determined OS for (F) all patients and (G) patients with eithelioid histology only



UV1 specific immunity

Successful vaccine-specific T-cell proliferation analysis was possible for 8 patients in arm A and 9 patients in arm B, analysed at baseline and 6 and 12 weeks after randomisation. Peripheral blood mononuclear cells (PBMC) were stimulated *in vitro* with the UV1 vaccine for 14 days, then specific T-cell proliferation against the vaccine and its single peptide components was measured in a thymidine incorporation assay. The response is shown as Stimulation Index (SI), or fold-stimulation above background without peptides. A positive control, superantigen, SEC-3, was included. A stimulation index of ≥3 is a positive response.

Of the evaluable patients, 3 showed UV1 vaccine-induced response in arm A (patients 2-4) and one in arm B. One patient in arm B had a non-vaccine induced UV1-reaction at baseline and week 11/12 (patient 1).



A positive response against the UV1 vaccine UV1 both at baseline and at week 11/12, but non-vaccine induced.
The patient had radiological progression at week 6, but stable disease at week 12 until week 31 when the pt died of other causes (not progression or side effect).

A vaccine-induced response against the UV1 vaccine and against single peptides was seen at week 5/6 and at week 11/12. This response is >3 times higher than, and/or with additional peptides compared to baseline.
Patient has progression at week 5/6 and 11/12, but then stabilized until week 35 and continued treatment until week 67.

A vaccine-induced response was detected at week 5/6 and 11/12 against the UV1 vaccine and single peptides. No response was seen at baseline.
Patient has stable disease on these two evaluations, but progressed on week 19.
Judged to have clinical benefit and continued treatment until week 65.

A vaccine-induced response was detected at week 11/12 against the UV1 vaccine and one of the single peptides.
The patient had stable disease at week 5/6, but had radiological progression at week 11/12. Judged to have clinical benefit and continued treatment until week 53.

Discussion/conclusions

- There is no significant survival benefit of adding UV1 to ipilimumab and nivolumab for patients with pleural mesothelioma who have progressed after platinum chemotherapy
- Further immunological characterisation may indicate the resistance mechanisms and subgroups with increased effect, particularly subgroups of the epithelioid histology
- The effect of UV1 can be explored further in the epithelioid subgroup
- UV1 stimulation assay was technically suboptimal for several patients, leading to insufficient results for final conclusions.
- Of the 3 patients in the UV1-arm that developed UV1-specific T-cell response, one had an early radiological progression at week 6 and 12 before experiencing radiological stable disease. All three were considered to have clinical benefit after radiological progression and continued treatment thereafter

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Conflicts of interest
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