Nivolumab and ipilimumab +/- UV1 vaccination as 2nd line treatment in patients with malignant mesothelioma (the NIPU-study)

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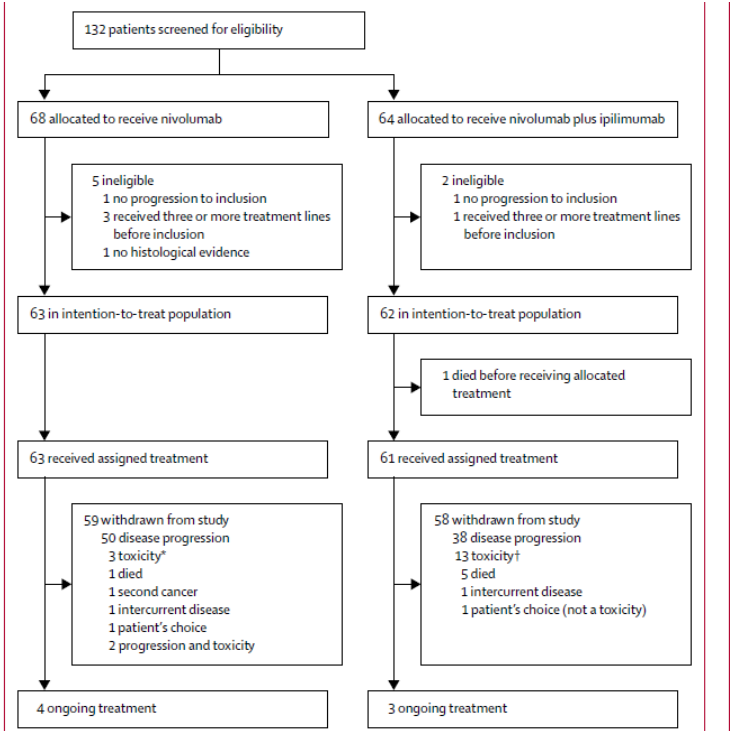
DISCLOSURES

Commercial Interest	Relationship(s)
Takeda, MSD, BMS, AstraZeneca, Roche, Bayer, Pfizer, ABBVIE,	Advisory Boards and scientific talks at meetings
Grants for research	Roche, BMS, Ultimovacs, AstraZeneca

Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial



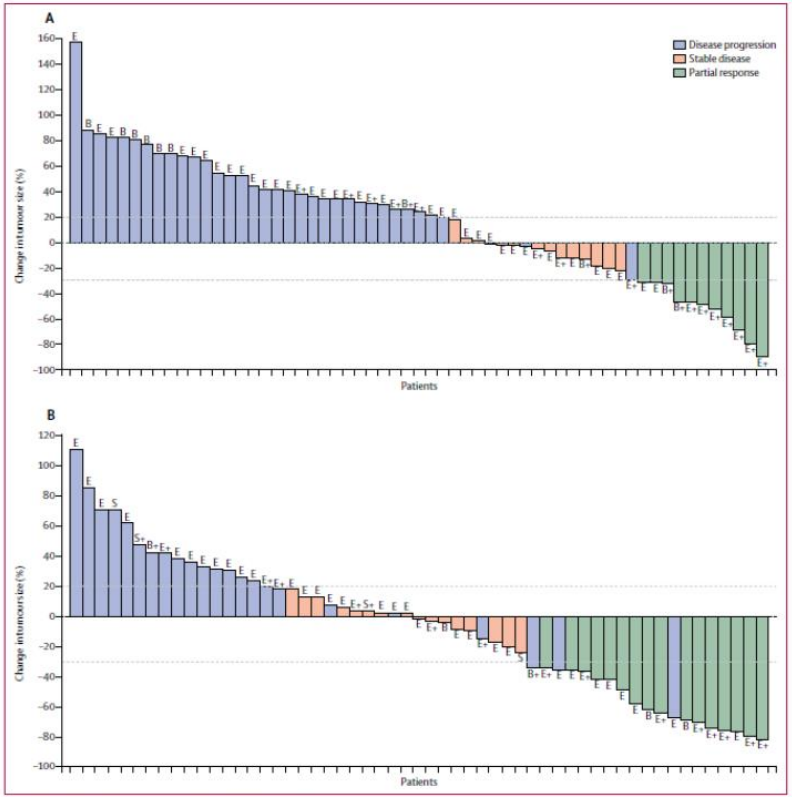


Figure 2: **Percentage changes in tumour size, baseline to week 12**
(A) Nivolumab group. Four patients were not evaluable at 12 weeks. (B) Nivolumab plus ipilimumab group. Six patients were not evaluable at 12 weeks. Positive symbol indicates patients with PD-L1 ≥1%. Negative symbol indicates patients with PD-L1 <1%. E=epithelioid. B=biphasic. S=sarcomatoid. Horizontal dashed line at −30% shows cutoff for partial response and horizontal dashed line at 20% shows cutoff for progressive disease. PD-L1=programmed cell death ligand 1.

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2020 Presidential Symposium
AUGUST 8, 2020 | WORLDWIDE

First-line nivolumab + ipilimumab vs chemotherapy in unresectable malignant pleural mesothelioma: CheckMate 743

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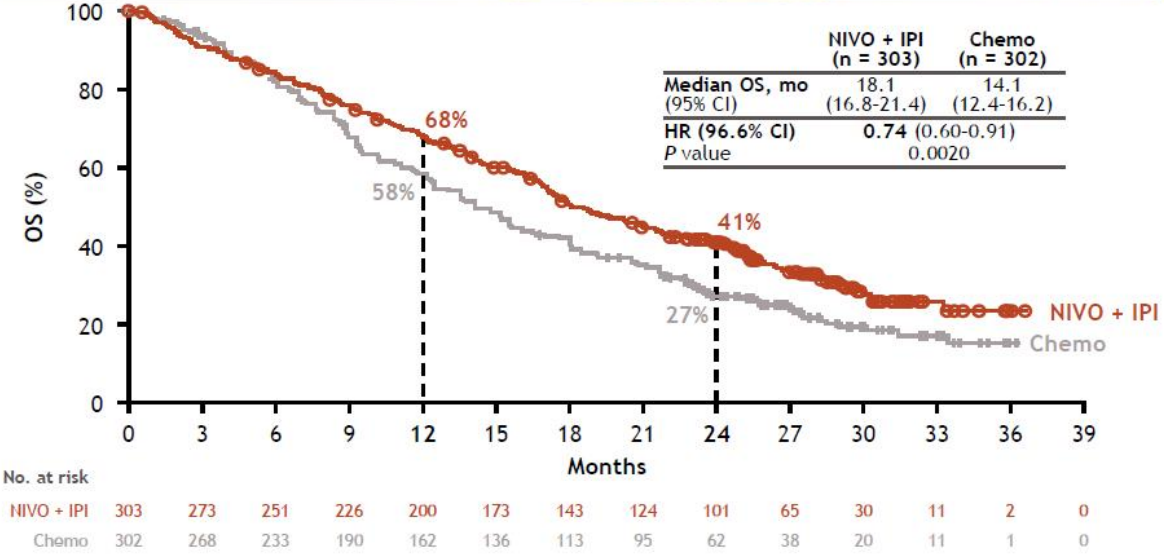
Primary endpoint: Overall survival

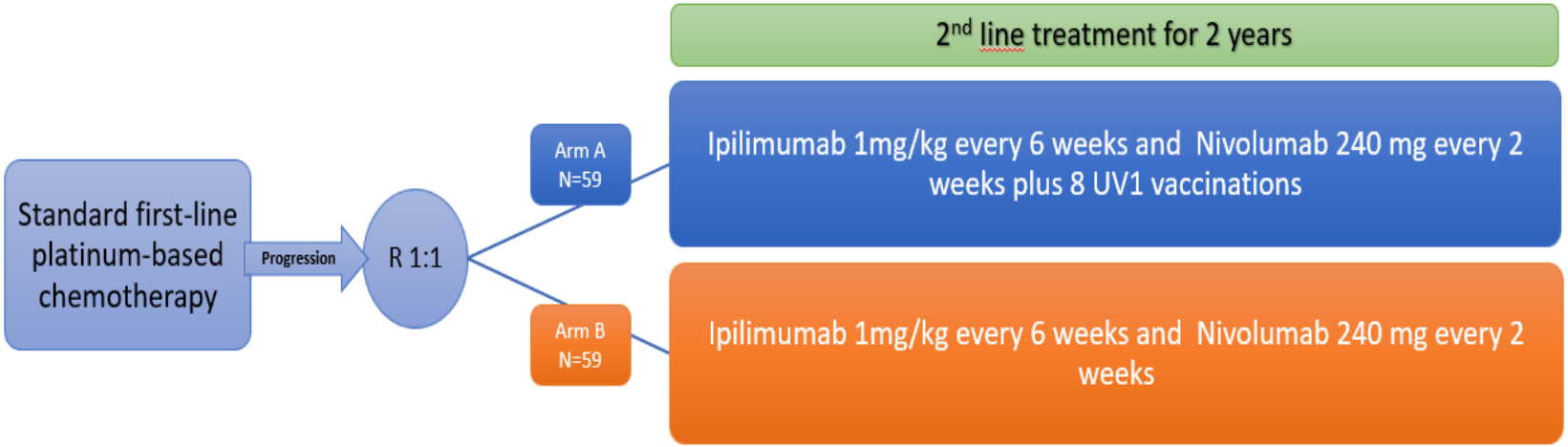


	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS, mo (95% CI)	18.1 (16.8-21.4)	14.1 (12.4-16.2)
HR (96.6% CI)	0.74 (0.60-0.91)	
P value	0.0020	

Minimum follow-up: 22.1 months; median follow-up: 29.7 months.
Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm and 41% in the chemo arm; subsequent immunotherapy was received by 3% and 20%, and subsequent chemotherapy by 43% and 32%, respectively.

Paul Baas, Netherlands Cancer Institute and The University of Leiden, The Netherlands

NIPU trial


Standard first-line platinum-based chemotherapy
Progression
R 1:1
Arm A N=59
Arm B N=59
2nd line treatment for 2 years
Ipilimumab 1mg/kg every 6 weeks and Nivolumab 240 mg every 2 weeks plus 8 UV1 vaccinations
Ipilimumab 1mg/kg every 6 weeks and Nivolumab 240 mg every 2 weeks

Primary objective and endpoints (protocol v3.0)

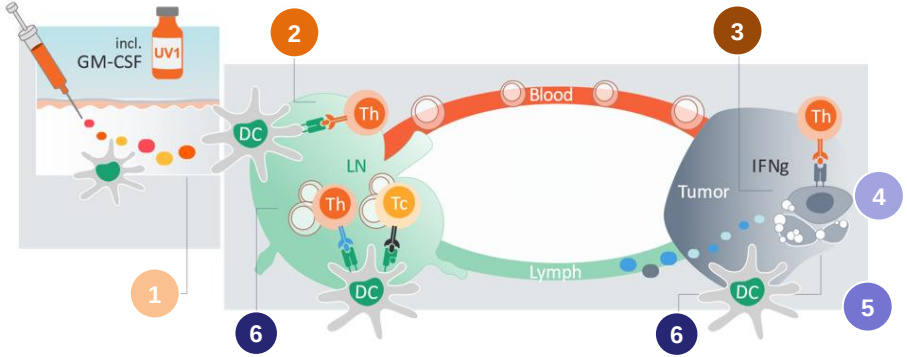
Objective / Hypothesis	Endpoint	Assessment
Primary		
Objective: To evaluate and compare the efficacy of nivolumab and ipilimumab with or without UV1-vaccine in patients with inoperable malignant pleural mesothelioma progressing after first-line platinum-based chemotherapy. Hypothesis (H1): When UV1 is used in combination with nivolumab and ipilimumab, the combination does improve progression-free survival (PFS) compared to nivolumab and ipilimumab alone.	Progression-free survival (PFS) per Modified Response Evaluation Criteria in Solid Tumors (RECIST) as determined by blinded independent central review (BICR)	Radiographic assessment

Scientific rationale for therapeutic vaccination against telomerase

Induction of hTERT-specific CD4 T lymphocytes

Telomerase in cancer

- Telomerase is an essential enzyme for the immortality, invasiveness, and tumorigenic potential of cancer[1]
- 90-95% of all tumors over-express telomerase[2]
- Tumor telomerase expression is associated with poor prognosis[3]
- Spontaneous anti-telomerase immune responses have been reported as a positive prognostic factor in lung cancer[4]



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

1 Hannen R, Bartsch JW. Essential roles of telomerase reverse transcriptase hTERT in cancer stemness and metastasis. FEBS Lett. 2018
2 Kim NW et al. Specific association of human telomerase activity with immortal cells and cancer. Science. 1994
3 Bertorelle, R. et al. Telomerase is an independent prognostic marker of overall survival in patients with colorectal cancer. Br J Cancer. 2013
4 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

Translational studies

Immune profiling

TMB

PET

Microbiome

Transcriptomics

Serial
- Biopsies
- Blood samples
- PET
- CT
- Urine/faeces

Update

- Participation from centres in Australia, Spain, Sweden, Denmark and Norway
- 16 included patients (of planned 118)
- No unexpected toxicities