Lung Cancer UPDATES
IASLC HIGHLIGTHS
28-31 ENERO 2021
VIRTUAL

Iniciativa científica de:
GECP lung cancer research

Mesotelioma

Manuel Dómine

Hospital Universitario Fundación Jiménez Díaz
Universidad Autónoma de Madrid

BIOMARKERS

Phosphorylated Ribosomal Protein S6, Correlation with Characteristics and Clinical Outcome in Patients with MPM: Results from ETOP Mesoscape

I. Opitz[1], J.H. Rüschoff[1], M. Haberecker[1], Z. Tsourti[2], K. Nackaerts[3], L. Ampollini[4], M. De Perrot[5], L. Brcic[6], E. Nadal[7], S. Gray[8], J. Aerts[9], E. Verbeken[10], E. Silini[4], F. Zaeimi[11], M. Samarzija[12], R. Llatjos[13], S. Tsimpoukis[14], J. Von Der Thüsen[9], S. Finn[8], K. Monkhorst[15], N. Marti[16], G. Dimopoulou[2], R. Kammler[16], S. Peters[17], P. Baas[18], R. Stahel[1], for the Mesoscape Consortium[16]

[1]University Hospital Zurich, Zurich/Switzerland, [2]Frontier Science Foundation-Hellas, Athens/Greece, [3]KU Leuven-University of Leuven, Leuven/Belgium,[4]University Hospital of Parma, Parma/Italy, [5]Toronto General Hospital, Toronto/Canada, [6]Medizinische Universität Graz, Graz/Austria, [7]Catalan Institute of Oncology, Barcelona/Spain, [8]St. James's Hospital and Trinity College Dublin, Dublin/Ireland, [9]Erasmus MC, Rotterdam/Netherlands, [10]University Hospitals Leuven, Leuven/Belgium, [11]Toronto General Hospital, Toronto, QC/Canada, [12]University Hospital Centre Zagreb, Zagreb/Croatia, [13]Hospital Universitari de Bellvitge, Barcelona/Spain, [14]Sotiria General Hospital, Athens/Greece, [15]Netherlands Cancer Institute, Amsterdam/Netherlands, [16]European Thoracic Oncology Platform (ETOP), Bern/Switzerland, [17]CHUV, Lausanne University Hospital, Switzerland/Switzerland, [18]The Netherlands Cancer Institute, Amsterdam/Netherlands

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Mesoscape 001 pS6: Clinical outcome

364 patients

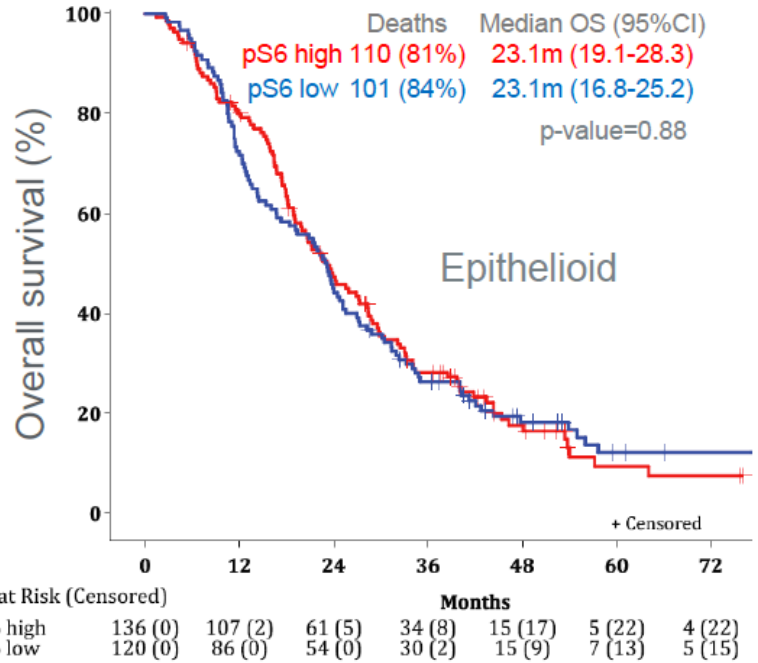
- Patient status at last follow-up (FU):
  - 86% dead (incl. 71% with disease), 14% alive
  - Median FU time: 53.8 months (IQR: 43.2 – 77.1)
  - Median OS: 19.1 months (95%CI: 17.1 - 22.2)

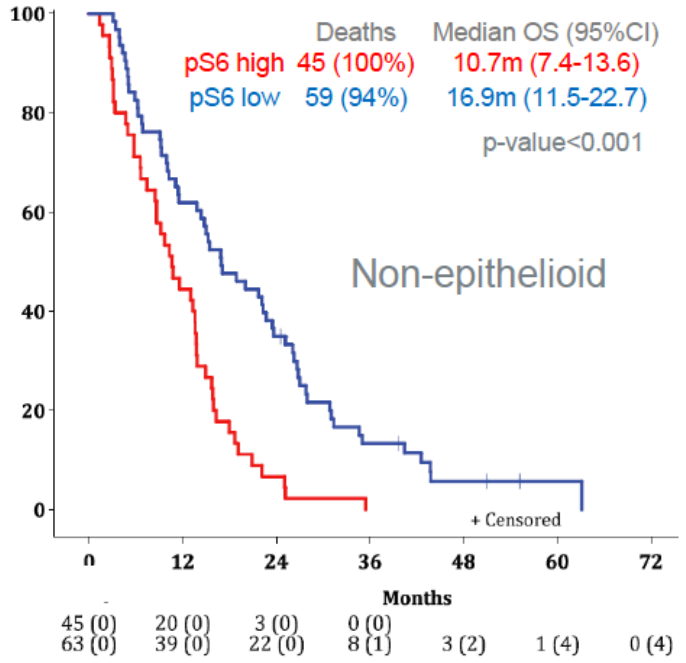
- Overall, no significant association of pS6 with outcome (OS & PFS)

- In an exploratory analysis: significant pS6 effect in the subgroup of **non-epithelioid^** patients for both OS* and PFS**

^*Mainly driven by biphasic*

* p-value<0.001
** p-value<0.001
(interaction p-values of pS6 status and histology also <0.001)





pS6 may be used as a biomarker in the future…

CHEMOTHERAPY

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CONQUERING THORACIC CANCERS WORLDWIDE

Real-World Survival Outcomes of Patients with Malignant Pleural Mesothelioma by Physician's Choice of First-line Platinum Chemotherapy

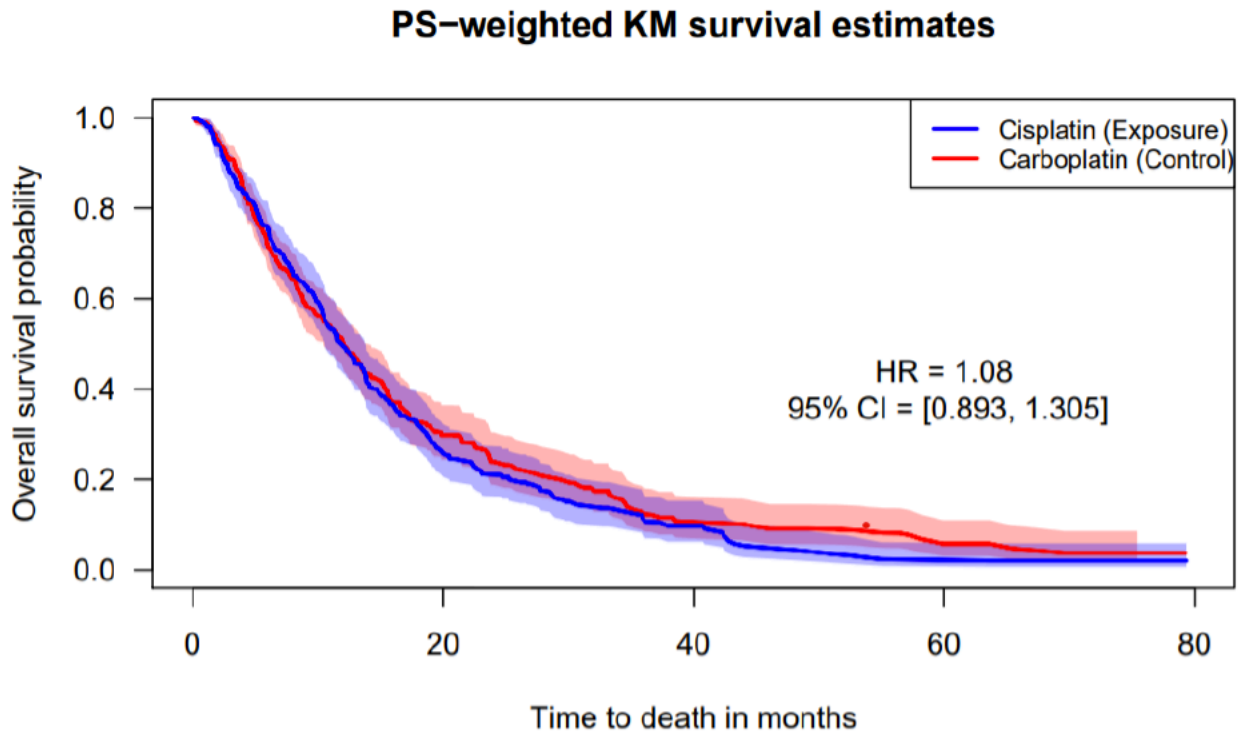
Katie Kerrigan, DO
Huntsman Cancer Institute at the University of Utah
USA

0A0905

Overall survival

Results

- In the propensity weighted results, the median OS was 8.02 months (95% CI: 6.87, 8.90) for carboplatin treated patients
- The median OS was 8.05 months (95% CI: 6.93, 9.36) for cisplatin treated patients



Carboplatin 464 patients
Cisplatin 323 patients

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CONQUERING THORACIC CANCERS WORLDWIDE

Real world use of cisplatin and carboplatin based therapy in patients with malignant pleural mesothelioma (MPM)

Susana Cedrés, JD Assaf, P Iranzo, A Callejo, N Pardo, N Navarro, A Martinez-Marti, A Valdivia, F Filippi, V Monton, J Gonzalo, A Pedrola, S Recasens, R Madrenas, B Feliu, B Roman, R Dienstmann, E Felip

Vall d´Hebron University Hospital and Institute of Oncology
Spain

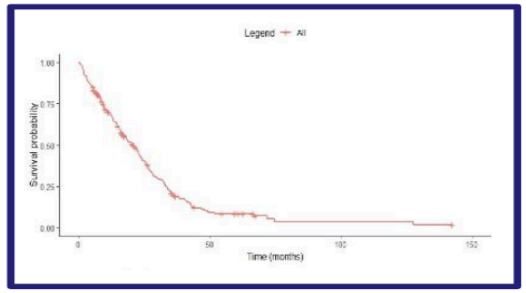
P24.06

Prognostic factors

189 patients

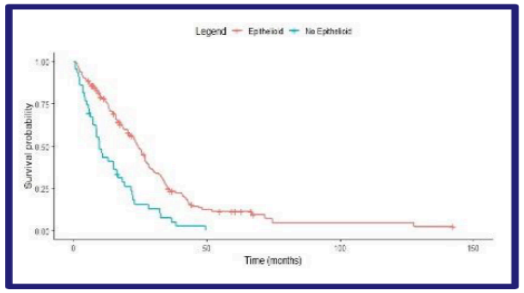
Epithelioid histology, PS 0, and treatment with cisplatin vs carboplatin were associated with significant improvements in OS

Median OS



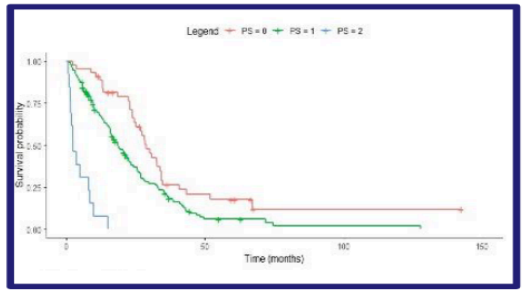
Median OS 21.3 m

OS - histology



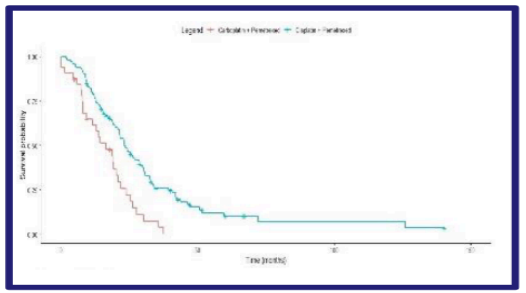
Epithelioid 21.3 m
No-epithelioid 9.6 m
HR 2.4 CI95% 1.6-3.4

OS - PS



PS0 28.8 m
PS1 18.8 m
PS2 2.4 m
HR 1.7 CI95% 1.2-2.6

OS - platinum

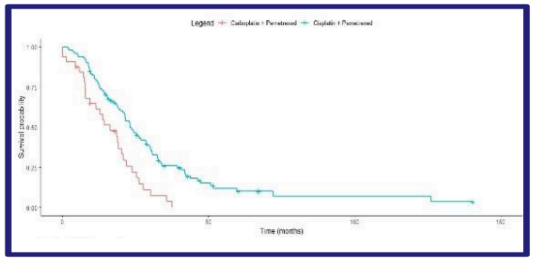


Cisplatin 23.1 m
Carboplatin 16.4 m
HR 0.4 CI95% 0.3-0.7

Survival according platinum in 1st and 2nd line

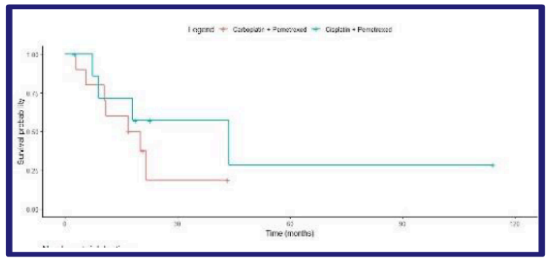
- Patients treated with cisplatin in 1st line were younger (64 vs 74 y p with carboplatin), and with more epithelioid tumors (81% vs 73%).
- No differences in median number of cycles (5 cycles for cisplatin and 5 cycles for carboplatin).
- Better survival for patients receiving cisplatin in first or second line.

OS - platinum 1st line



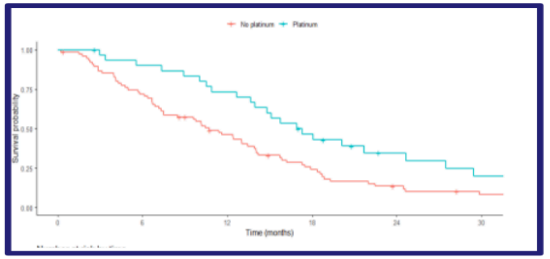
Cisplatin 23.1 m
Carboplatin 16.4 m
HR 0.4 CI95% 0.3-0.7

OS - platinum 2nd line



Cisplatin 43.7 m
Carboplatin 18.5 m
HR 0.5 CI95% 1.6-3.4

OS 2nd line - platinum vs no-platinum



Platinum 17.1 m
No-platinum 10.7 m
HR 0.5 CI95% 0.3-0.8

INMUNOTHERAPY

INMUNOTHERAPY
PRETREATED PATIENTS

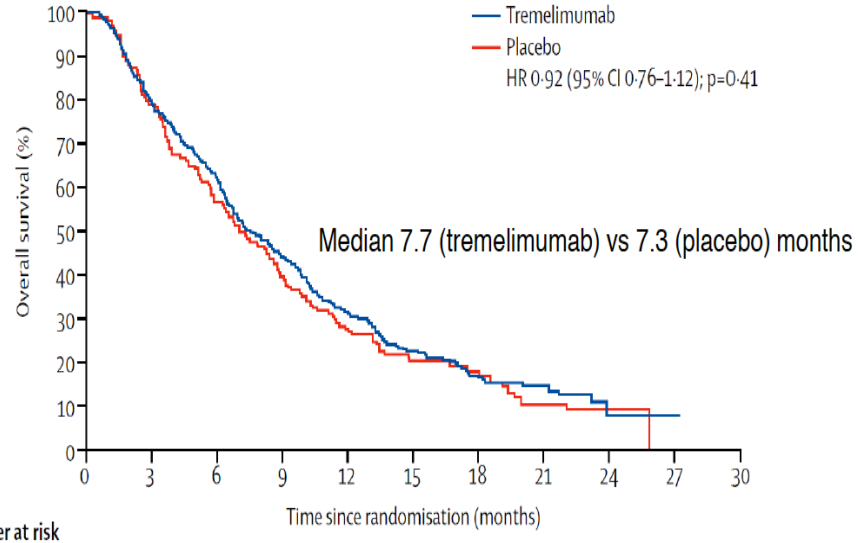
Cohort trials in relapsed mesothelioma

Trial	KN028[1]	Univ Chicago[2]	Javelin[3]	NivoMes[4]	MERIT[5]	MAPS2[6]	MAPS2[6]	INITIATE[7]	NIBIT-MESO[8]
IMP	Pembro	Pembro	Avelumab	Nivo	Nivo	Nivo	Nivo-Ipi	Nivo-Ipi	Durva-treme
PD-L1 selctn?	✓	×	×	×	×	×	×	×	×
N patients	25	64	53	34	34	63	62	35	40
Prior therapy	92%	100%	100%	100%	100%	100%	100%	100%	70%
CR	0%	0%	2%	0%	0%			0%	0%
PR	20%	22%	8%	24%	29%	ORR=17.5%	ORR=25.8%	29%	25%
SD	52%	41%	49%	24%	38%	22.2%	25.8%	38%	38%
PD	16%	20%	34%	50%	26%	54%	37.1%	32%	38%
Median PFS	5.4 mo	4.1 mo	4.1 mo	2.6 mo	6.1 mo	4.0 mo	5.6 mo	6.2 mo	5.7 mo
Median OS	18 mo	11.5 mo	10.7 mo	11.8 mo	17.3	11.9 mo	15.9 mo	NR	11.2 mo
1-year OS rate	62.6%		43.8%	50%	59%	49.2%	58.1%	64%	60%

1, Alley et al. Lancet Oncol (2107); Desai et al. WCLC (2018); Hassan et al. JAMA Oncol (2019); 4, Quispel-Janssen et al. JTO (2018);
5, Okada et al. CCR (2019); 6, Scherpereel et al. Lancet Oncol (2019); Disselhorst et al. Lancet Resp Med (2019); 8, Calabrao et al. Lancet Resp Med (2018)

Randomized trials using Inmmunotherapy

Targeting CTLA4 alone (tremelimumab): no OS benefit, DETERMINE



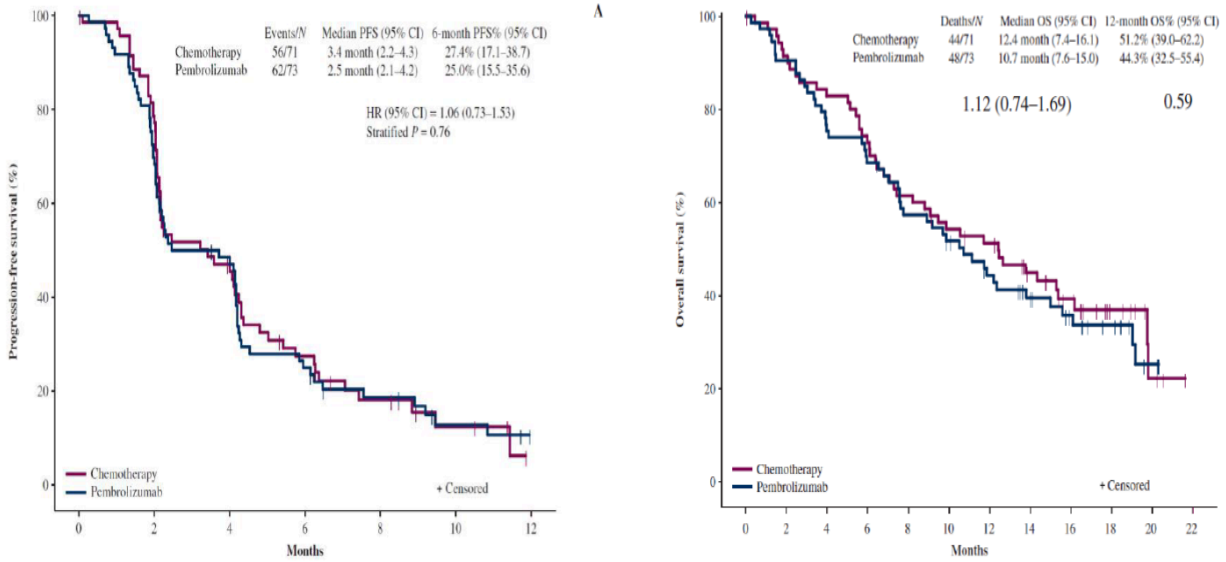
Number at risk (number censored)

Tremelimumab	382 (0)	300 (6)	232 (11)	163 (13)	116 (13)	69 (29)	36 (48)	16 (63)	3 (72)	1 (74)	0 (75)
Placebo	189 (0)	147 (3)	103 (6)	70 (9)	48 (10)	32 (14)	17 (26)	8 (29)	2 (34)	0 (35)	0 (35)

Maio et al. Lancet Oncology 2017

PROMISE: PFS & OS not improved with pembrolizumab vs chemo-monotherapy

ORR 22% (pembro) vs 6% (chemo)



Popat et al. Ann Oncol (2020)

Nivolumab Versus Placebo in Relapsed Malignant Mesothelioma: Preliminary results from the CONFIRM Phase 3 Trial

Dean Fennell[1], Christian Ottensmeier[2], Raffaele Califano[3], Gerard G Hanna[4], Sean Ewings[5], Kayleigh Hill[5], Sam Wilding[5], Sarah Danson[6], Mavis Nye[5], Nicola Steele[7], Lucy Johnson[5], Joanne Lord[8], Calley Middleton[5], Ellice Marwood[5], Peter Szlosarek[9], Sam Chan[10], Aarti Gaba[1], Liz Darlison[11], Peter Wells-Jordan[1], Cathy Richards[1], Charlotte Poile[1], Jason F Lester[12], Gareth Griffiths[5]

[1]University of Leicester, UK; [2] University of Liverpool, UK; [3]The University of Manchester, UK; [4]Peter MacCallum Cancer Centre, University Melbourne, Australia; [5]CRUK Southampton Clinical Trials Unit, University of Southampton, UK; [6]University of Sheffield, UK; [7]Beatson West of Scotland Cancer Centre, UK; [8]Southampton Health Technology Assessments Centre, University of Southampton, UK; [9]Barts Cancer Institute, UK; [10]York Teaching Hospital NHS Foundation Trust, UK; [11]Mesothelioma UK; [12]South West Wales Cancer Centre, UK.

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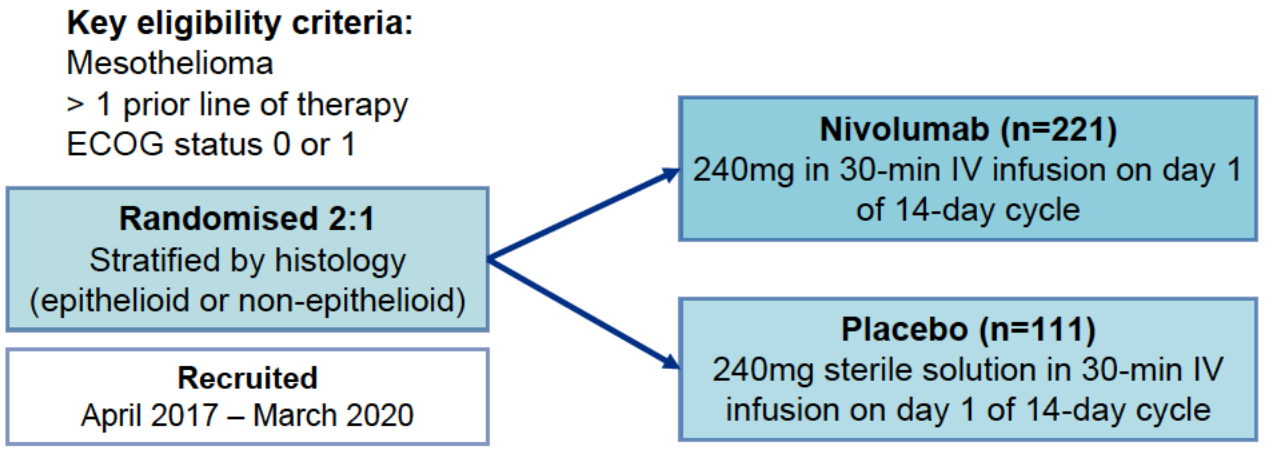
CONFIRM TRIAL DESIGN



Administered until progression, unacceptable toxicity, withdrawal or 12m

Target sample size: 336
Study halted recruitment at n=332 due to COVID-19 pandemic but sufficient event/follow-up

Co-primary outcomes:
- Overall survival
- Investigator-reported progression-free survival

Secondary outcomes:
- RECIST-determined progression-free survival
- Response rate
- EQ-5D
- Safety

Funders:
- Cancer Research UK/SU2C (C16728/A21400)
- BMS (investigator initiated)

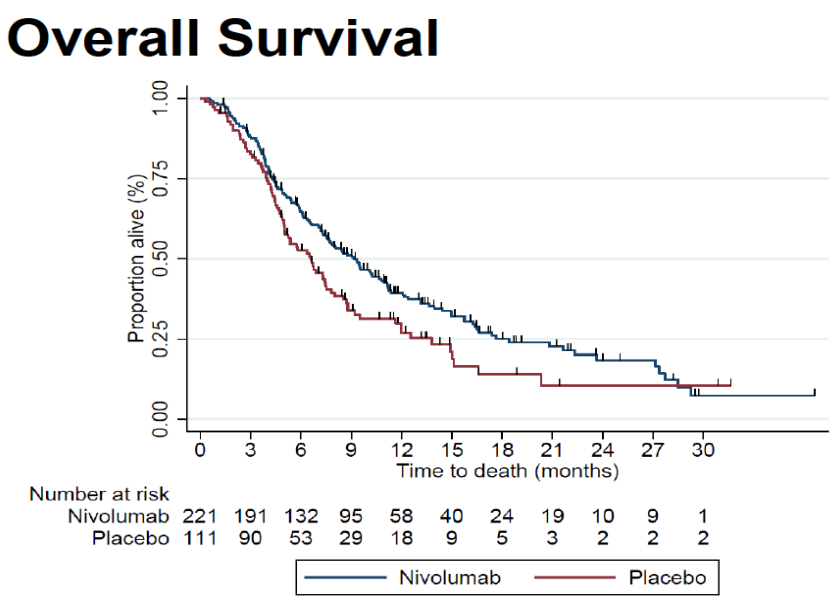
COORDINATING GROUP:
Southampton Clinical Trials Unit

SPONSOR:
University of Southampton

Patient Characteristics

Characteristic	Nivolumab (n=221)	Placebo (n=111)
Age (median, IQR)	70 (65-74)	71 (65-76)
Male	167 (76%)	86 (77%)
ECOG Status 0	44 (20%)	22 (20%)
PD-L1 TPS ≥ 1%*	56 (37%)	24 (29%)
Epithelioid	195 (88%)	98 (88%)
Pleural site	211 (95%)	105 (95%)
Line of treatment		
2nd line	63 (29%)	37 (33%)
3rd line	124 (56%)	66 (59%)
>3L	15%	8%

Overall Survival

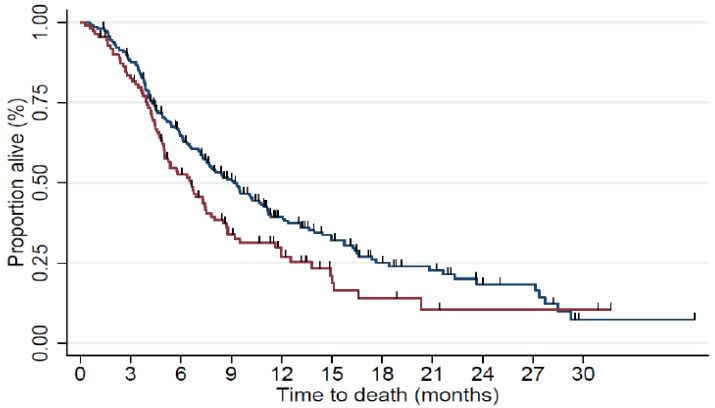


	Nivolumab (n = 221)	Placebo (n = 111)
Median OS, mo (95% CI)	9.2 (7.5–10.8)	6.6 (5.0–7.5)
12m survival, % (95% CI)	39.5 (32.5–46.3)	26.9 (18.2–36.4)
HR (95% CI)	**0.72** (0.55–0.94)	
P value	0.018	

Median follow-up Nivolumab: 17.1 months, Placebo: 14.2 months:
Number of events Nivolumab: n=151, Placebo: n=81

Overall Survival

Overall Survival



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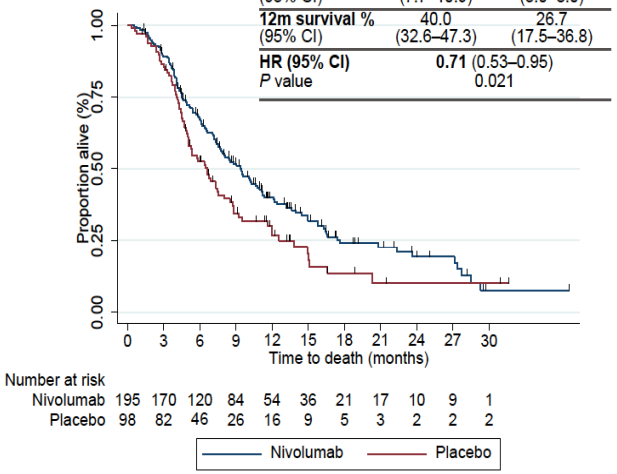
Overall Survival by Histology

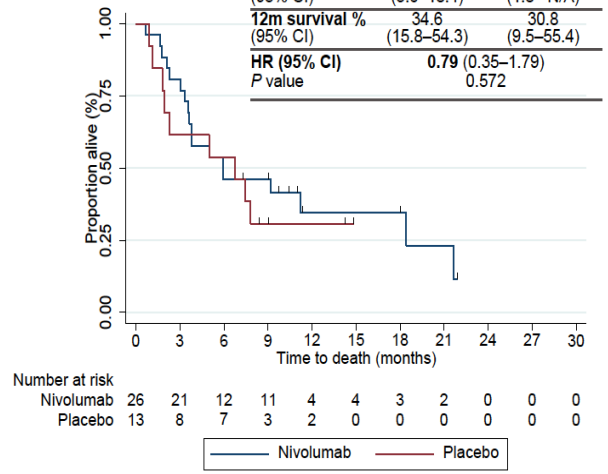
Epithelioid

	Nivolumab (n = 195)	Placebo (n = 98)
Median OS, mo (95% CI)	9.4 (7.7–10.9)	6.6 (5.0–8.0)
12m survival % (95% CI)	40.0 (32.6–47.3)	26.7 (17.5–36.8)
HR (95% CI)	**0.71** (0.53–0.95)	
P value	0.021	



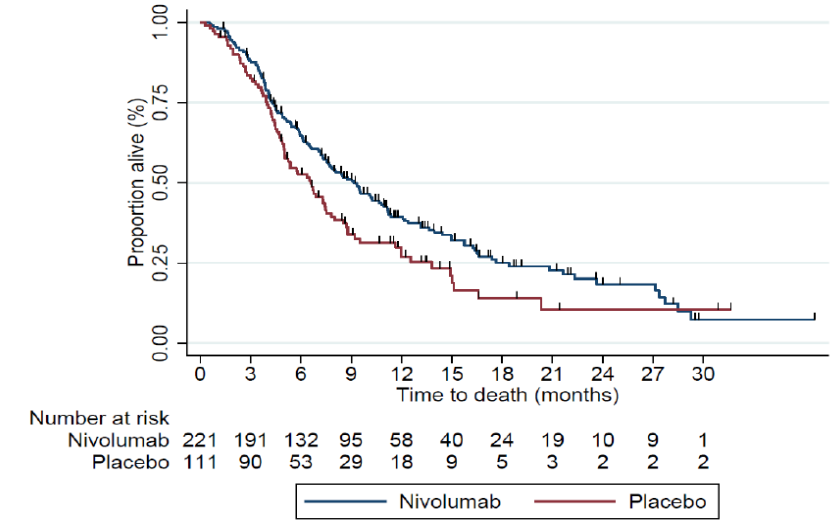
Non-Epithelioid

	Nivolumab (n = 26)	Placebo (n = 13)
Median OS, mo (95% CI)	5.9 (3.6–18.4)	6.7 (1.8– N/A)
12m survival % (95% CI)	34.6 (15.8–54.3)	30.8 (9.5–55.4)
HR (95% CI)	**0.79** (0.35–1.79)	
P value	0.572	



Overall Survival

Overall Survival



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Overall Survival by Histology

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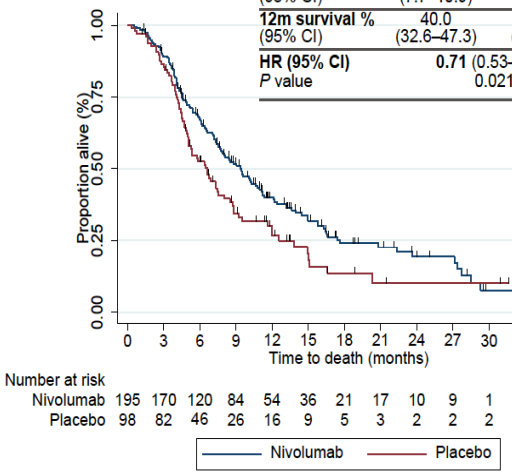
P value	0.021	



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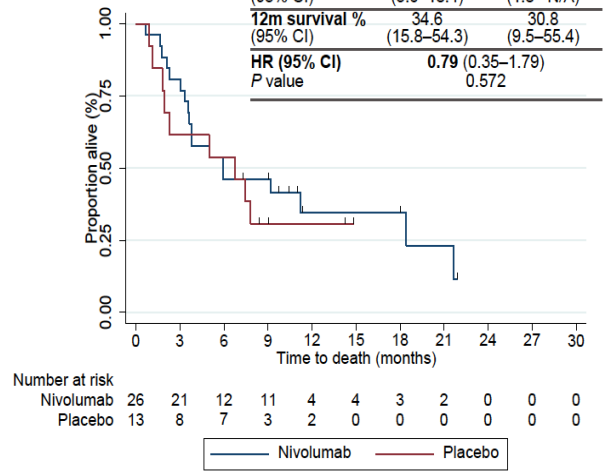
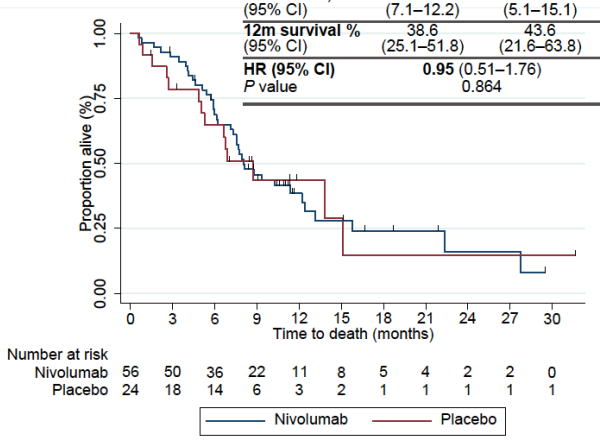


Overall Survival by PD-L1* Tumour Proportion Score

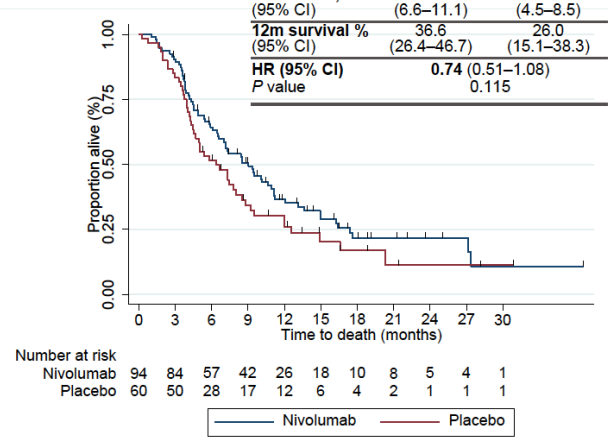
PD-L1 Positive

	Nivolumab (n = 56)	Placebo (n = 24)
Median OS, mo (95% CI)	8.0 (7.1–12.2)	8.7 (5.1–15.1)
12m survival % (95% CI)	38.6 (25.1–51.8)	43.6 (21.6–63.8)
HR (95% CI)	**0.95** (0.51–1.76)	
P value	0.864	



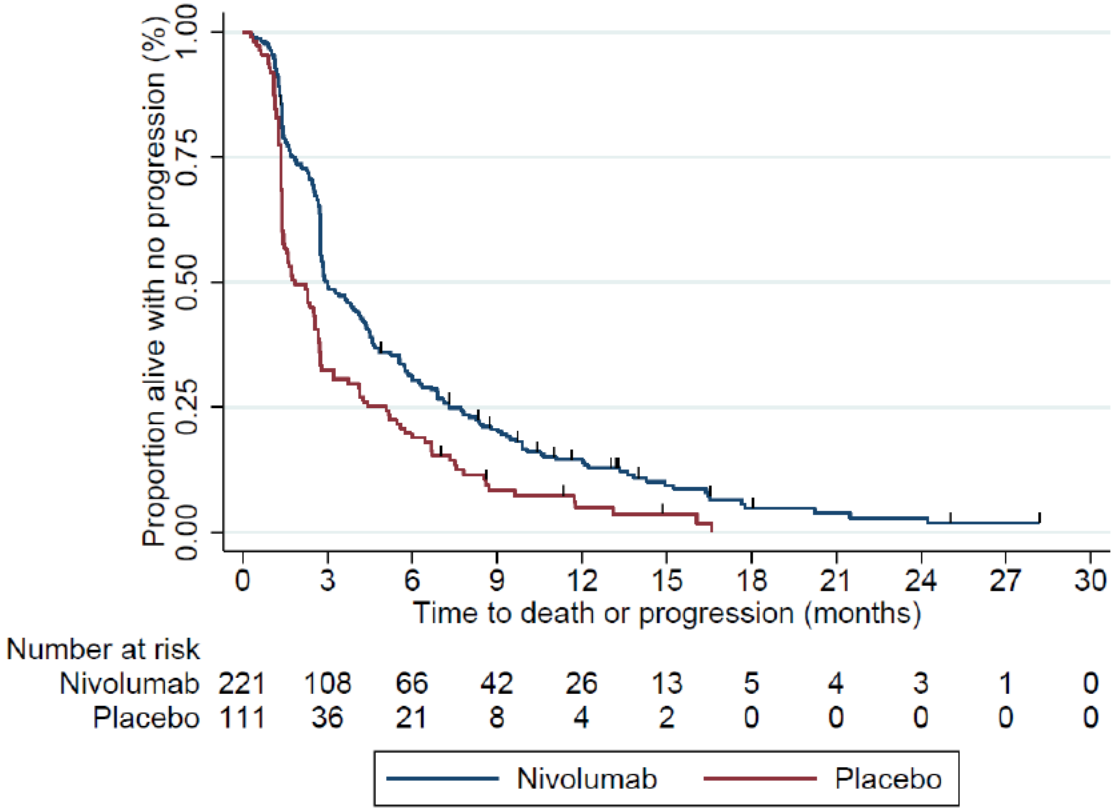
PD-L1 Negative

	Nivolumab (n =94)	Placebo (n = 60)
Median OS, mo (95% CI)	9.0 (6.6–11.1)	6.4 (4.5–8.5)
12m survival % (95% CI)	36.6 (26.4–46.7)	26.0 (15.1–38.3)
HR (95% CI)	**0.74** (0.51–1.08)	
P value	0.115	



*PD-L1 tumour proportion score (TPS). Immunochemistry was assessed using Dako 22C3 PD-L1 antibody: negative < 1% TPS, positive ≥1%TPS

Investigator Progression-free Survival



	Nivolumab (n = 221)	Placebo (n = 111)
Median PFS, mo (95% CI)	3.0 (7.5–10.8)	1.8 (5.0–7.5)
12m PFS, % (95% CI)	14.5 (10.2–19.7)	4.9 (1.8–10.6)
HR (95% CI)	**0.61** (0.48–0.77)	
P value	<0.001	

Treatment

- Median (IQR) duration of treatment was 84 (30-168) days in the Nivolumab arm and 43 (29-88) days in the Placebo arm

- Number of participants receiving IO as further treatment was 3 (1.4%) on the Nivolumab arm and 14 (12.6%) on the Placebo arm

Safety

Adverse events (AE), number of patients (%)	Nivolumab (n = 221)		Placebo (n = 111)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	207 (94%)	99 (45%)	104 (94%)	47 (42%)
Serious AE	90 (41%)	80 (36%)	49 (44%)	43 (39%)

- Number (%) of deaths related to a Serious AE was 5 (3.6%) in the Nivolumab arm and 4 (5.3%) in the Placebo arm

Immunotherapy Studies in Relapsed Mesothelioma

Study	Phase	Agent (s)	n	ORR	mPFS (m)	mOS (m)
KN 028	Ib	Pembrolizumab	25 (PD-L1 pos)	20%	5.4m	18m
JAVELIN	Ib	Avelumab	53	9%	4.1m	10.7m
Treme (Italy)	II	Tremelimumab	29	14%	6.2m	11.3m
MERIT	II	Nivolumab	34	29%	6.1m	17.3m
Pembro (Chicago)	II	Pembrolizumab	64	22%	4.1m	11.5m
NIBIT-meso1	II	Treme / Durva	40 (30% 1L)	28%	5.7m	16.6m
INITIATE	II	Nivo / Ipi	34	29%	NR: >6.2m	NR: >12.7m
MAPS2	II	Nivo or Nivo/Ipi	63 & 62	19% & 28%	4.0m & 5.6m	11.9m & 15.9m
DETERMINE	IIb	Treme vs placebo	571 (2:1)	4.5%	2.8m	7.7m
PROMISE-meso	III	Pembro vs Chemo	144	22%	2.5m	10.7m
CONFIRM	III	Nivo vs placebo	332	10.4%	3.0m	9.2m

- CONFIRM met its endpoint of statistically improved investigator-reported PFS and OS with Nivolumab versus placebo in relapsed malignant mesothelioma
- There was no evidence to support PDL-1 TPS as being predictive
- Significant clinical benefit was observed in the epithelioid subtype
- First phase III trial demonstrating a significant Overall survival with IO in relapse setting
- Nivolumab is a safe and effective treatment and should be considered a new treatment option for patients with relapsed mesothelioma

INMUNOTHERAPY
UNTREATED PATIENTS

NO PRIOR SYSTEMIC THERAPY

CM743: nivo-ipi vs platinum-pemetrexed

Key Eligibility Criteria
- Unresectable pleural mesothelioma
- No prior systemic therapy
- ECOG performance status 0-1

Stratified by:
histology (epithelioid vs non-epithelioid) and gender

N = 605
R 1:1

n = 303: **NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W (for up to 2 years)**

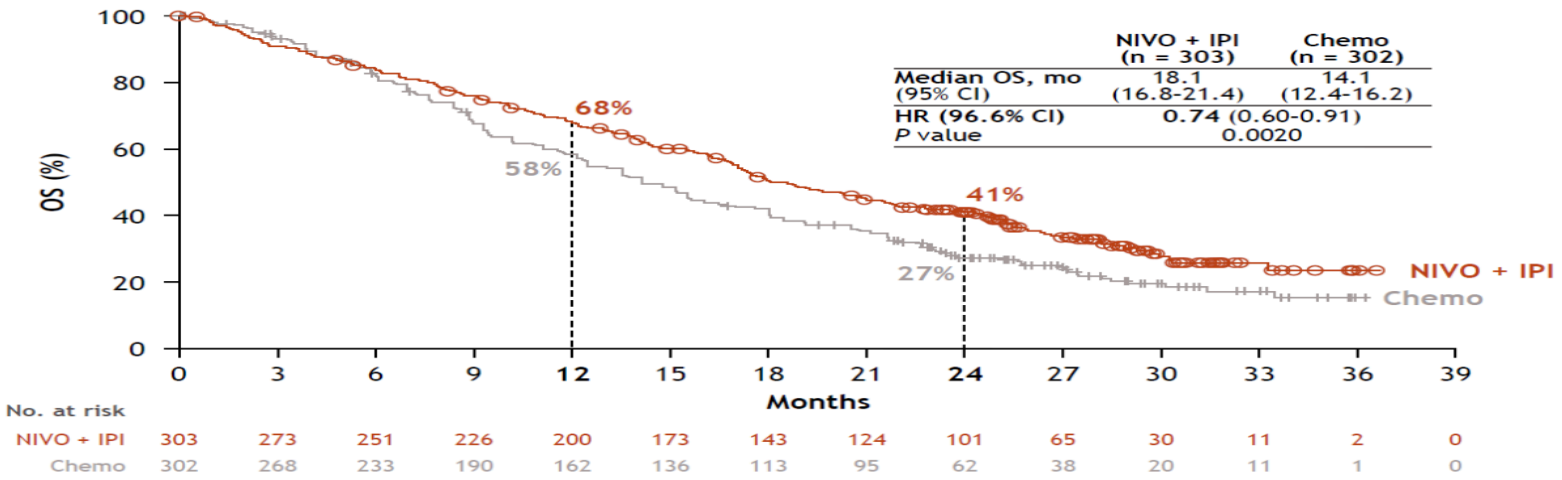
n = 302: **Cisplatin or carboplatin + pemetrexed Q3W[b] (6 cycles)**

Until disease progression, unacceptable toxicity *or* for 2 years for immunotherapy arm

Primary Endpoint
- OS

Secondary Endpoints
- ORR, DCR, and PFS by BICR
- PD-L1[c] expression as a predictive biomarker

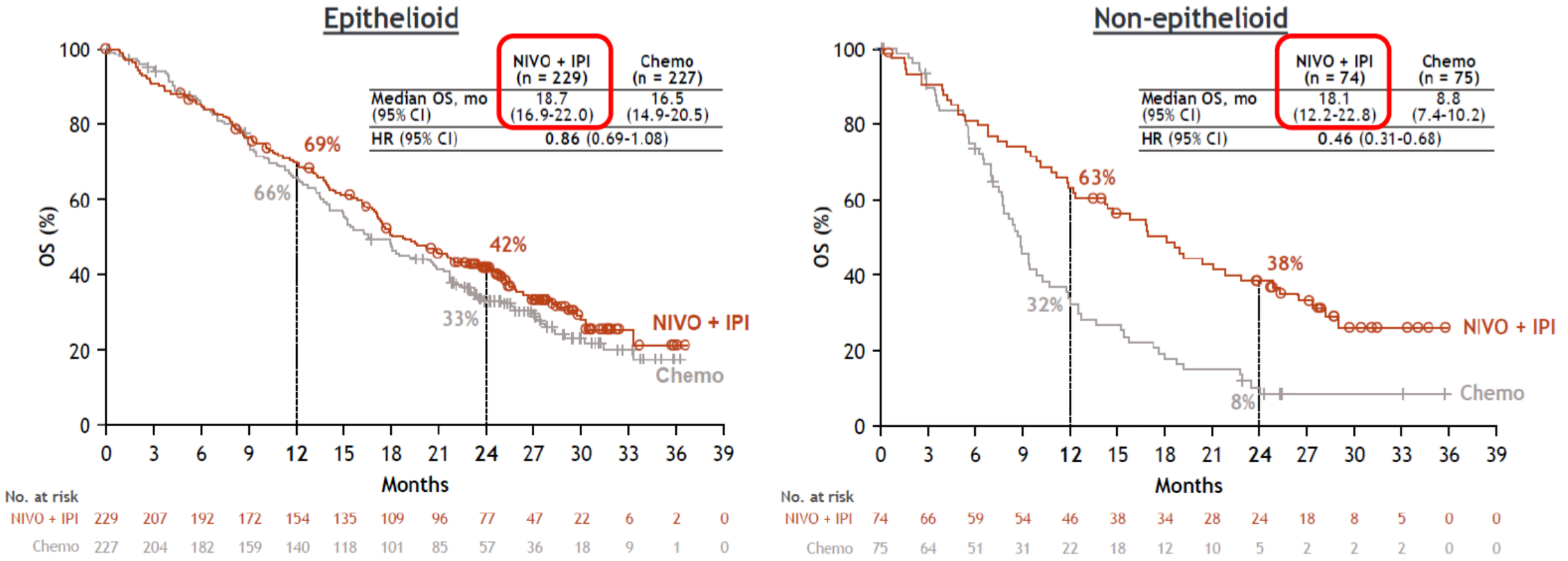
CM743: nivo-ipi improves OS



	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	

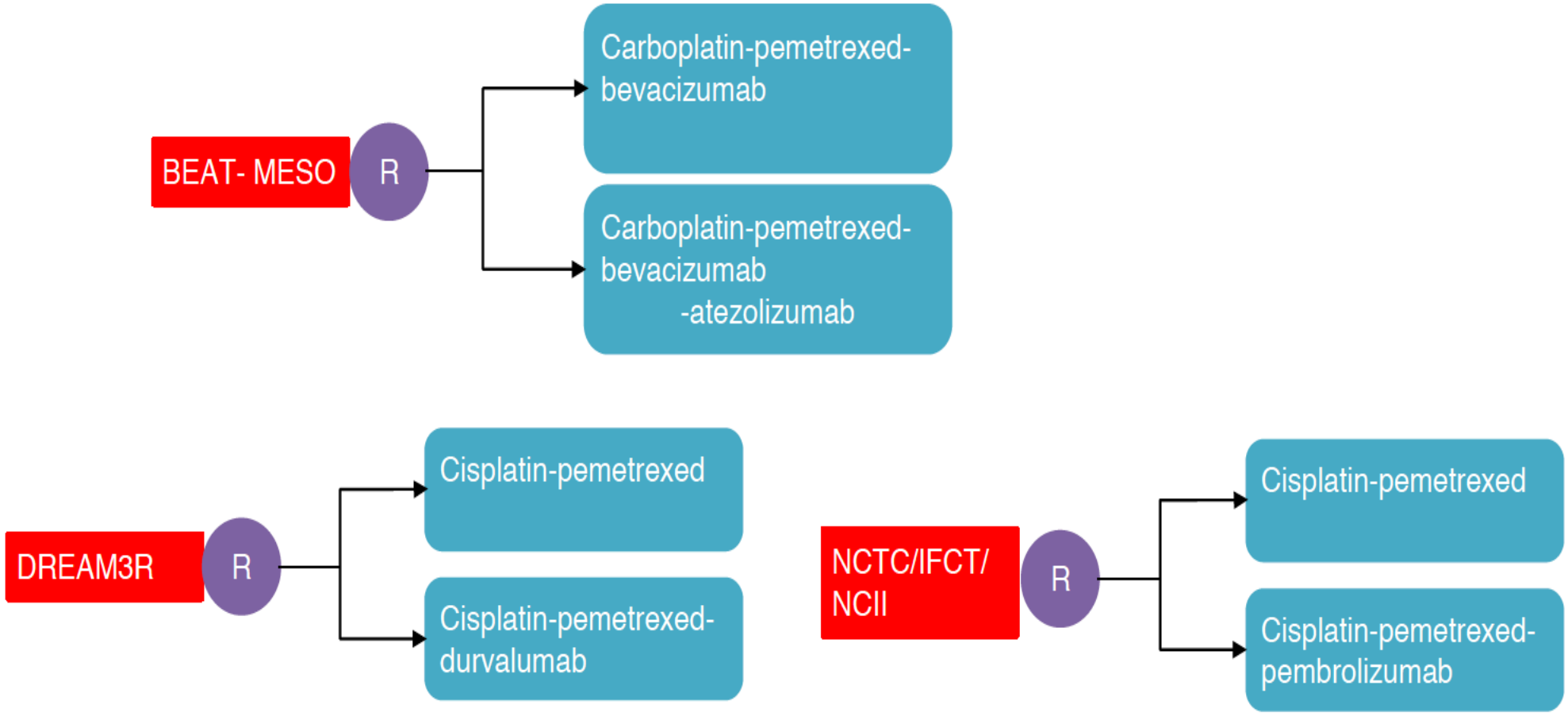
Bass P, et al. Lancet Oncol 2021

CM743: nivo-ipi consistent benefit

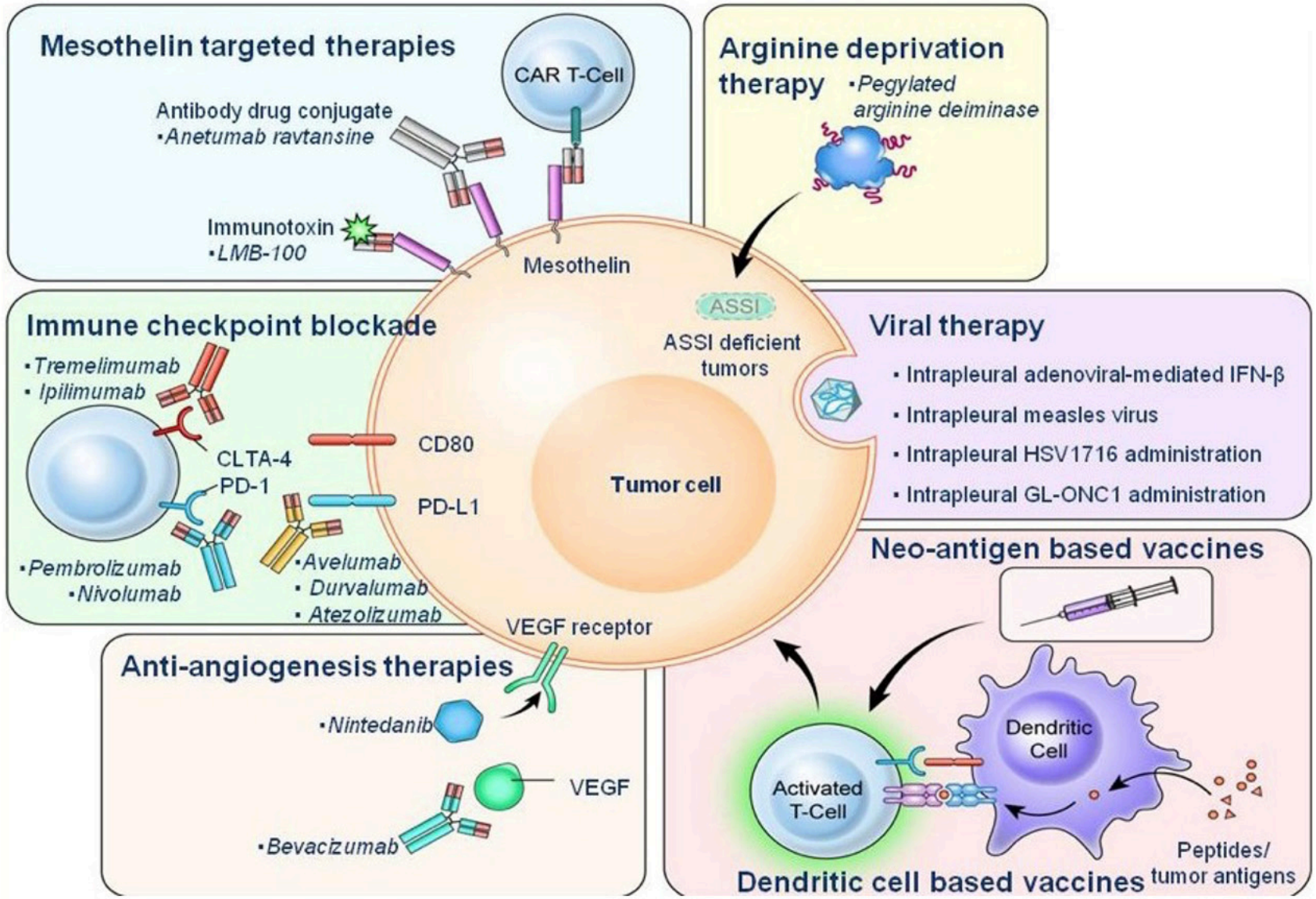


Bass P, et al. Lancet Oncol 2021

Ongoing front line Chemo-IO trials



NEW STRATEGIES



Intra-pleural mesothelin-directed CARs: MSKCC experience

iCasM28z CAR

Fully human mesothelin CAR to reduce immunogenicity

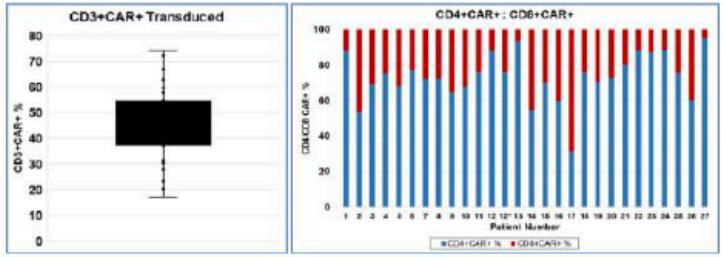
No adverse events >Grade 2
No on-target, off-tumor toxicity

Monitored by	Method
Clinical	Pleuritis Pericarditis Peritonitis
Laboratory	Serum Troponin level
Cardiac	EKG, Echocardiogram
Imaging	CXR, CT, PET
Pathology	Biopsy

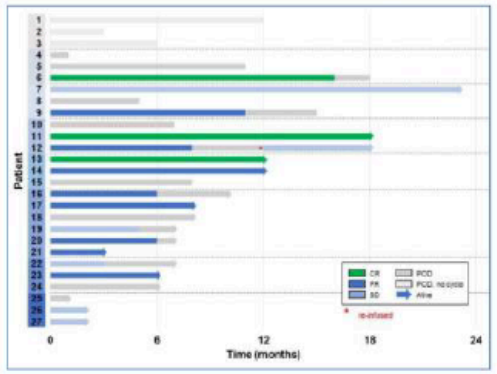
NCT02414269
Intrapleural administration
29 patients treated
(3 patients re dosed)

Mesothelioma, pleural metastatic lung and breast cancers

CAR transduction is successful in all patients in both CD4 and CD8 T cells



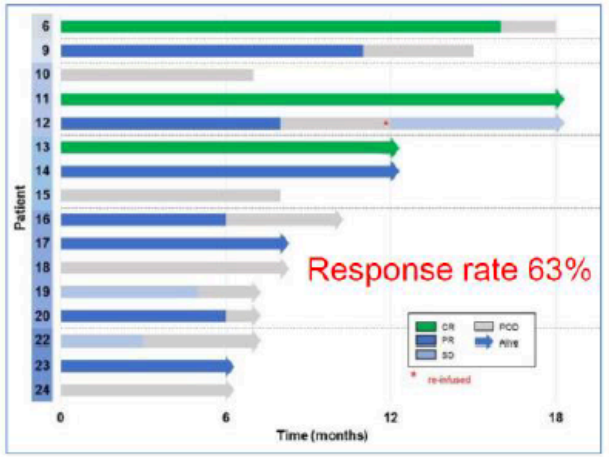
Responses of all patients (n=27)



PD-L1: 0-5% in 22 patients,
≥10% in 4 patients

CR – Complete response
PR – Partial response
SD – Stable disease
POD – Progression of disease

Responses of mesothelioma patients (n=16) that received Cyclophosphamide and CAR T-cells and at least 3 doses of anti-PD1 antibody with minimum 3 months follow-up



Adusumilliet al. AACR (2019), ASCO (2019), WCLC (2109)

DENdritic cell Immunotherapy for Mesothelioma (DENIM) trial

R.A. Belderbos

On behalf of:

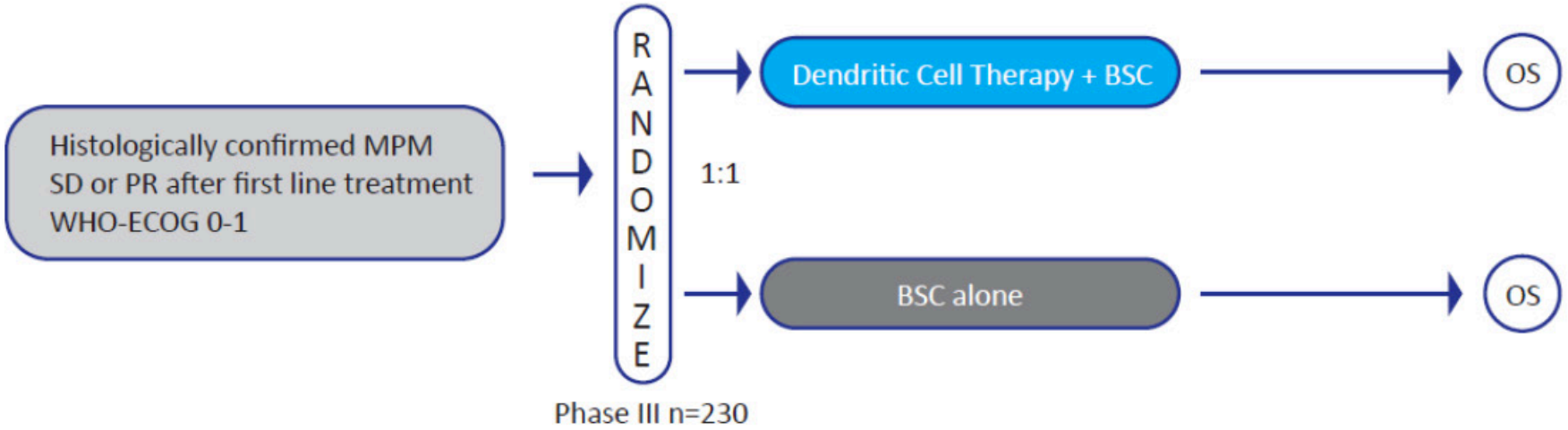
Baas P., Berardi R., Cornelissen R., Fennell D.A., Van Meerbeeck J.P., Scherpereel A., Aerts J.G.J.V.

Erasmus Medical Center
The Netherlands

P24.03

Methods

Figure 1 DENIM Study Design

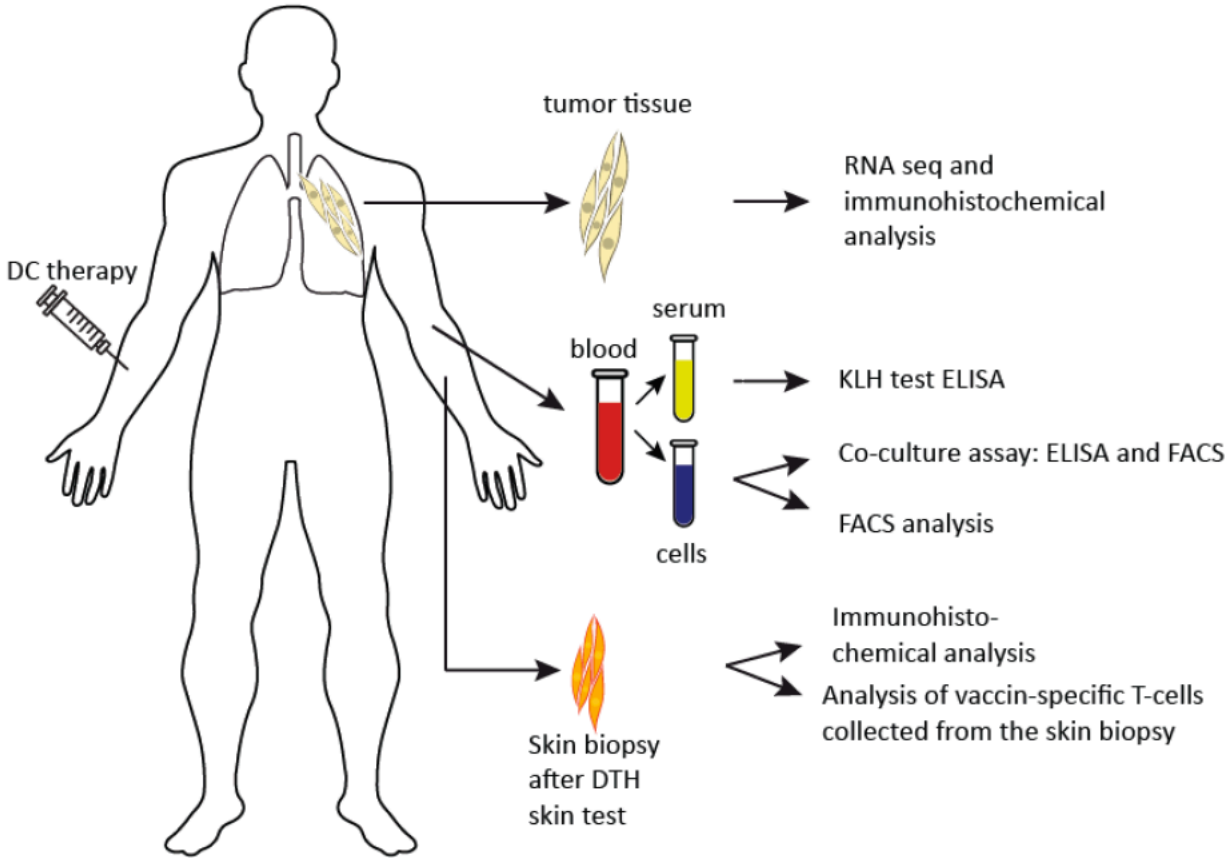


Endpoints
Primary Endpoint: OS
Secondary Endpoints: OS at 12 and 18 months, Progression Free Survival, Overall response rate, Quality of Life

Abbreviations: MPM = Malignant Pleural Mesothelioma; SD = Stable disease; PR = Partial response, BSC = Best Supportive Care, OS = Overall Survival

Belderbos RA, et al.: DENdritic cell Immunotherapy for Mesothelioma (DENIM) trial. Transl Lung Cancer Res. 2019 Jun;8(3):280-285. doi: 10.21037/tlcr.2019.05.05. PMID: 31367541; PMCID: PMC6626859.

Exploratory objectives



151 patients included

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

Authors: Vilde D Haakensen[1], Anna Nowak[2], Espen Basmo Ellingsen[1,3], Oscar Grundberg[4], Saima Farooqi[1], Tine McMulloch[5],, Susana Maria Cedres[6], Maria M Bjaanæs[1], Åslaug Helland[7]

[1]Oslo University Hospital, Oslo/Norway, [2]University of Western Australia, Crawley, ACT/Australia, [3]Ultimovacs ASA, Oslo/Norway, [4]Karolinska Institutet, Stockholm/Sweden, [5]Aalborg University Hospital, Ålborg/Denmark, [6]Vall d´Hebron Institute of Oncology (VHIO), Vall d´Hebron Barcelona Hospital Campus, Barcelona/Spain, [7]University of Oslo and Oslo University Hospital, Oslo/Norway-presenting author

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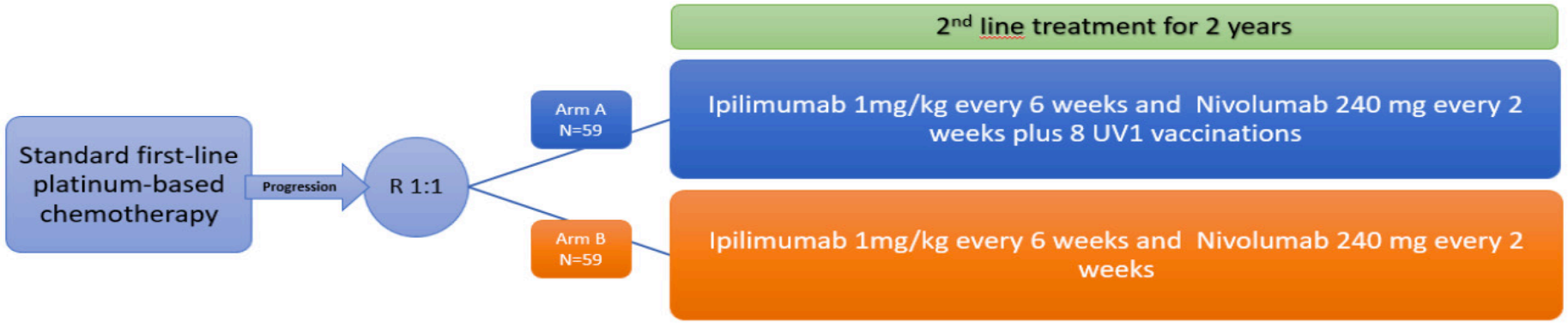
NIPU trial



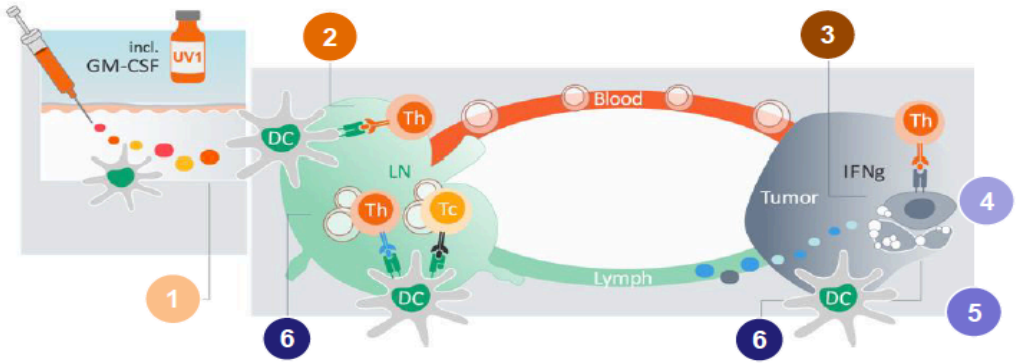
P24.07

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 naïve 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

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Update

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

Ongoing combination trials

NCT03393858	Pembrolizumab	DC immunotherapy	Hyperthermia
NCT04400539	Nivolumab	Intrapleural photodynamic therapy	
NCT03399552	Avelumab	Radiotherapy	
NCT04480372	Atezolizumab	Gemcitabine	
NCT04040231	Nivolumab	Galinpepimut-S	
NCT04056026	Pembrolizumab	Fecal microbiota transplant	
NCT03126630	Pembrolizumab	Anetumab Ravtansine	
NCT02959463	Pembrolizumab	Radiotherapy	
NCT03710876	rAd-IFN	Gemcitabine	Celecoxib
NCT02758587	Pembrolizumab	Defactinib	
NCT03228537	Atezolizumab	Chemotherapy	Radiotherapy

TAKE HOME MESSAGES

- pS6 may be used as a biomarker in the future mainly in non-epitheliod
- Cisplatin-pemetrexed probably better option that carboplatin-pemetrexed, but carboplatin iaalso effective preferably in frail and elderly patients
- For the pretreated setting: immune checkpoint inhibitors have modest activity overall. Did not improve PFS or OS compared to second line chemotherapy.
- Nivolumab should be considered a new treatment option for patients with relapsed mesothelioma
- For the first line setting: nivolumab-ipilimumab improves OS over chemotherapy alone, markedly so in non-epithelioid subtypes
- Many trials are ongoing investigating first line checkpoint inhibitor-chemo combinations
- Novel approaches such as cellular therapies are in development