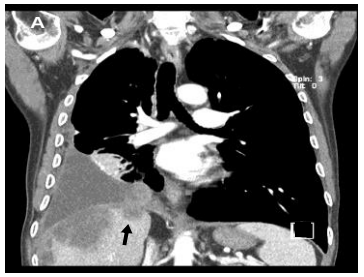
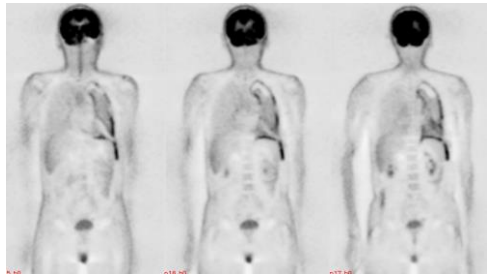




MALIGNANT PLEURAL MESOTHELIOMA: BIOLOGY & CURRENT AND FUTURE TREATMENT CONCEPTS

kristiaan.nackaerts@uzleuven.be

BSMO

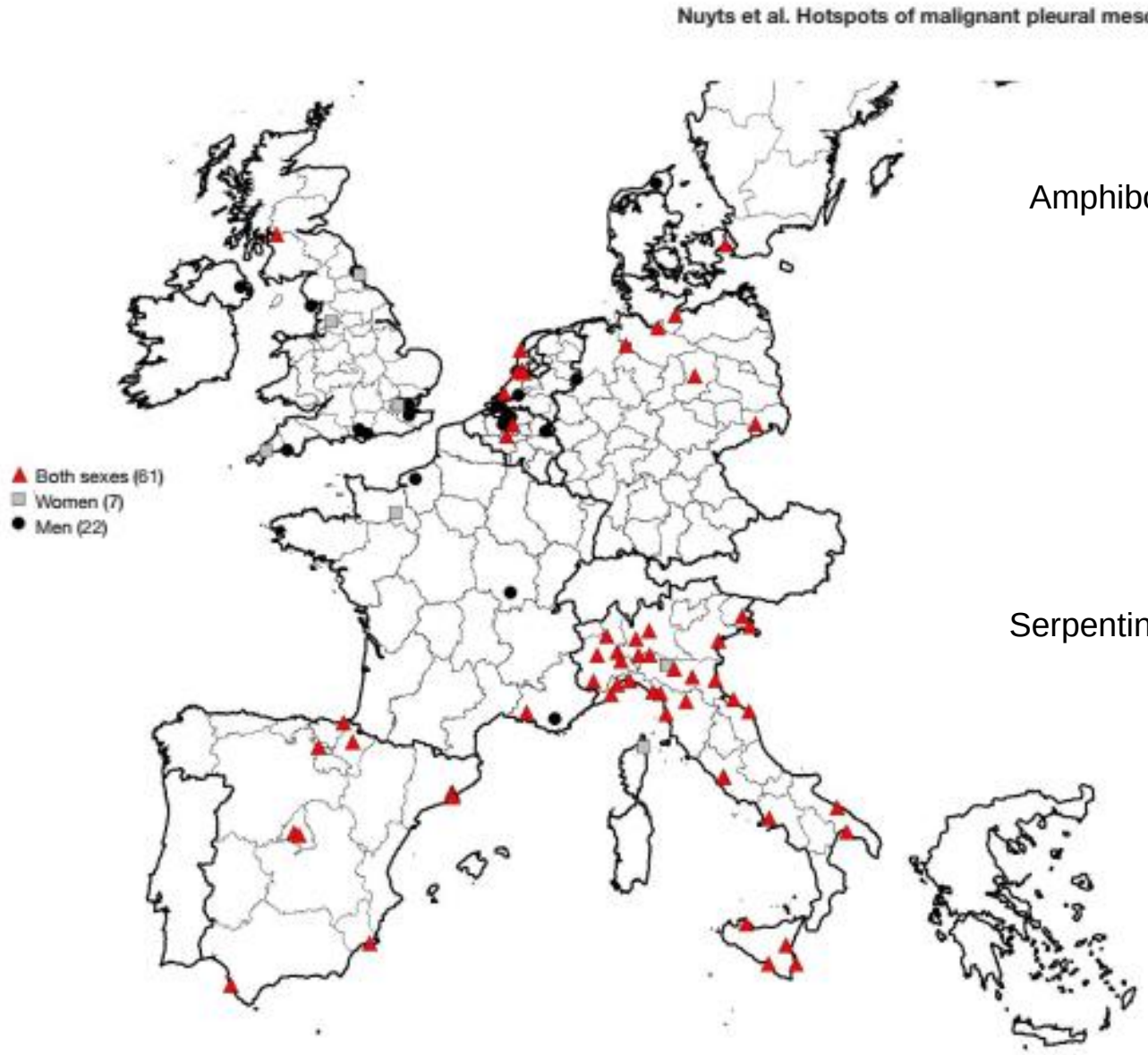
SAT 21 NOVEMBER 2020

UZ LEUVEN

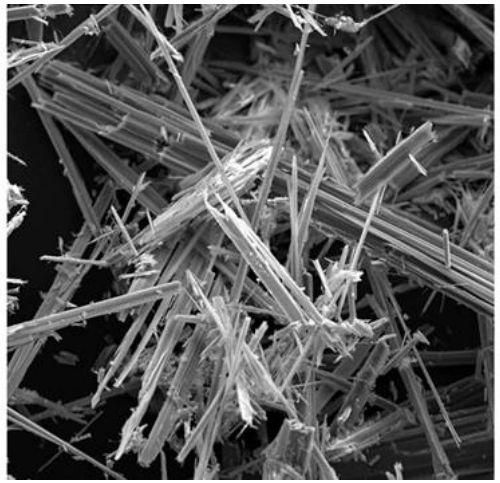
Published in 2017

KU LEUVEN

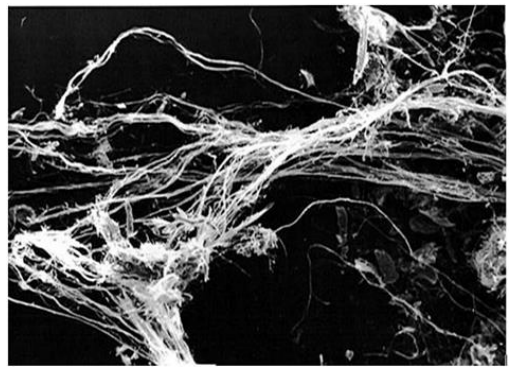
EPIDEMIOLOGY



Amphibole asbestos fibres



Serpentine asbestos fibers



Nuyts V et al. Transl Lung Cancer Res 2018;7(5):516-519

EPIDEMIOLOGY

Table 11. Epithelial Tumours of Mesothelioma: Incidence, Trends, Survival

Flemish Region 2001-2010		Incidence				Trend		Survival	
Both Sexes						EAPC		Relative Survival	
	R/C	N	CR	WSR	Avg Age	%	p-value	N at risk	5yr (%)
MALIGNANT MESOTHELIOMA	R	1,608	2.64	1.3	69	1.1	0.433	1,427	5.1
Mesothelioma of pleura and pericardium	R	1,476	2.43	1.2	69	1.3	0.334	1,310	4.5
Mesothelioma of peritoneum and tunica vaginalis	R	116	0.19	0.1	64	1.5	0.453	104	14.0
Males						EAPC		Relative survival	
	R/C	N	CR	WSR	Avg Age	%	p-value	N at risk	5yr (%)
MALIGNANT MESOTHELIOMA	R	1,343	4.48	2.35	69	0.3	0.791	1,184	4.5
Mesothelioma of pleura and pericardium	R	1,245	4.15	2.16	69	0.8	0.512	1,098	4.2
Mesothelioma of peritoneum and tunica vaginalis	R	84	0.28	0.17	64	-0.9	0.756	75	9.8
Females						EAPC		Relative survival	
	R/C	N	CR	WSR	Avg Age	%	p-value	N at risk	5yr (%)
MALIGNANT MESOTHELIOMA	R	265	0.86	0.40	69	4.4	0.162	243	7.9
Mesothelioma of pleura and pericardium	R	231	0.75	0.34	69	3.4	0.322	212	5.8
Mesothelioma of peritoneum and tunica vaginalis	R	32	0.10	0.06	65	10.1	0.077	29	*

R/C: Rare or common

CR: Crude rate (N/100,000 person years)

WSR: age-standardised rate, using the world population (N/100,000 person years)

EAPC: estimated annual percentage change

RS: relative survival

AvgAge: average age at diagnosis

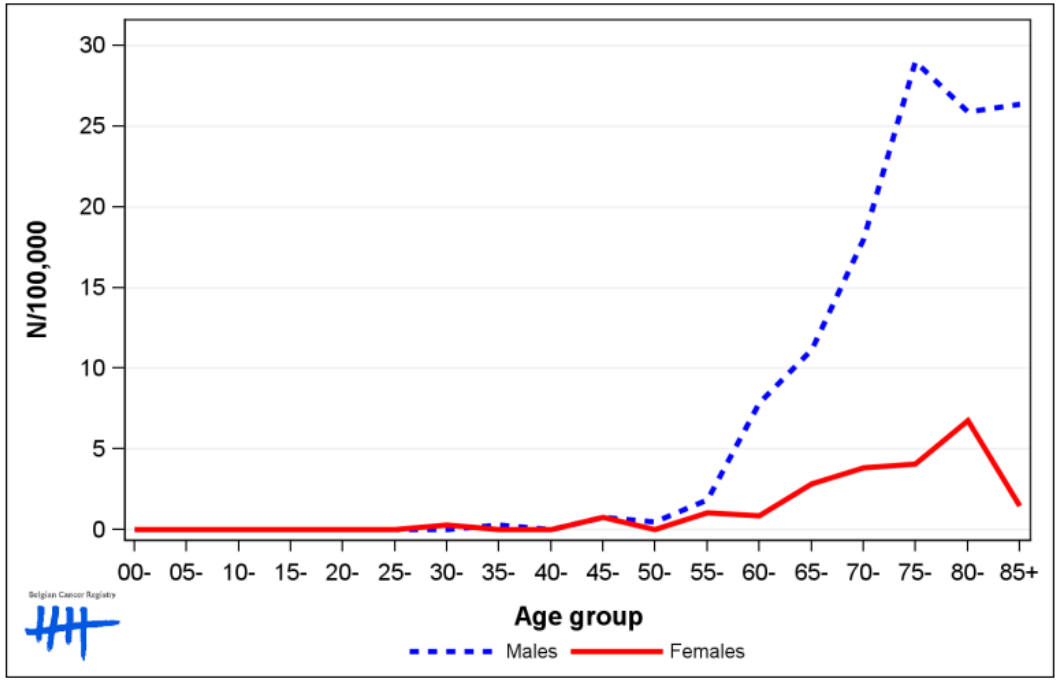
Stichting Kankerregister: Rare Thoracic Tumors 2016

EPIDEMIOLOGY

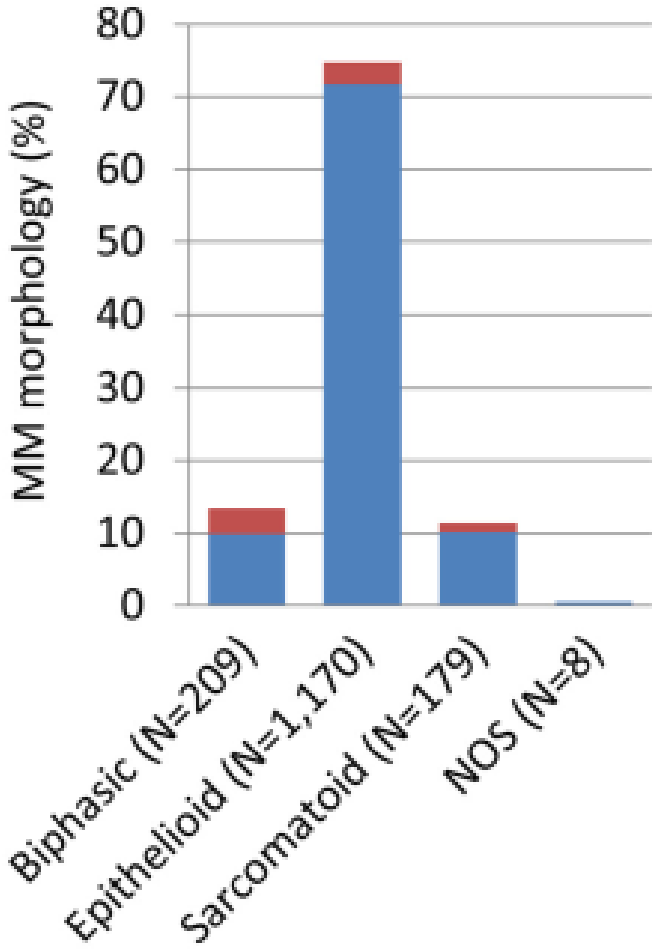
Assessing the completeness and correctness of the registration of malignant mesothelioma in Belgium

Michael Rosskamp[a,*,1], Harlinde De Schutter[a,1], Kris Henau[a], Kristiaan Nackaerts[b], Jan P. Van Meerbeeck[c], Marleen Praet[d], Liesbet Van Eycken[a]

Figure 2: Mesothelioma: Age-specific incidence rates by sex, 2016



Belgian Cancer Registry, Mesothelioma data 2016 (2018)



Lung Cancer 2018;122:38-43

EPIDEMIOLOGY

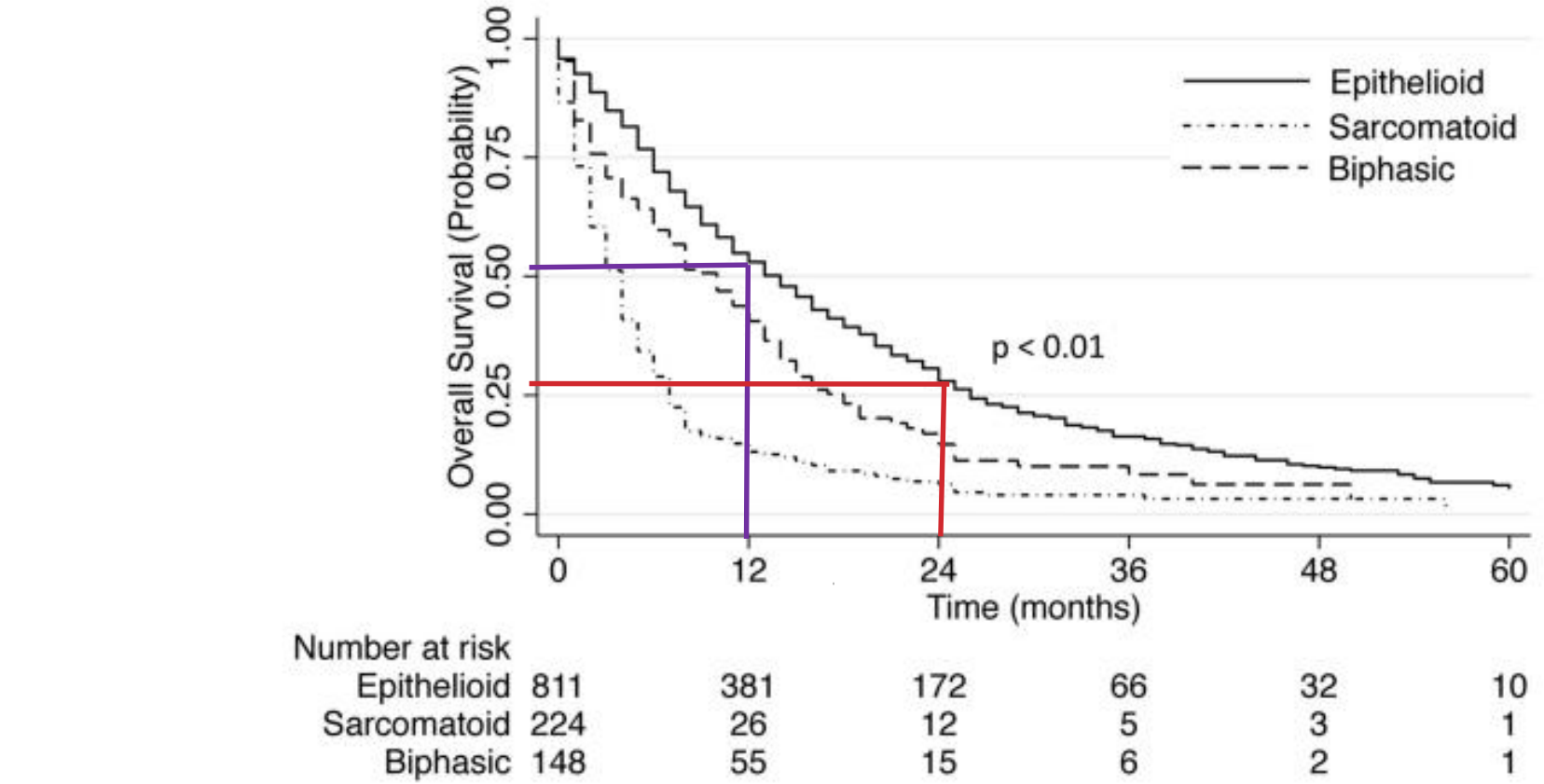
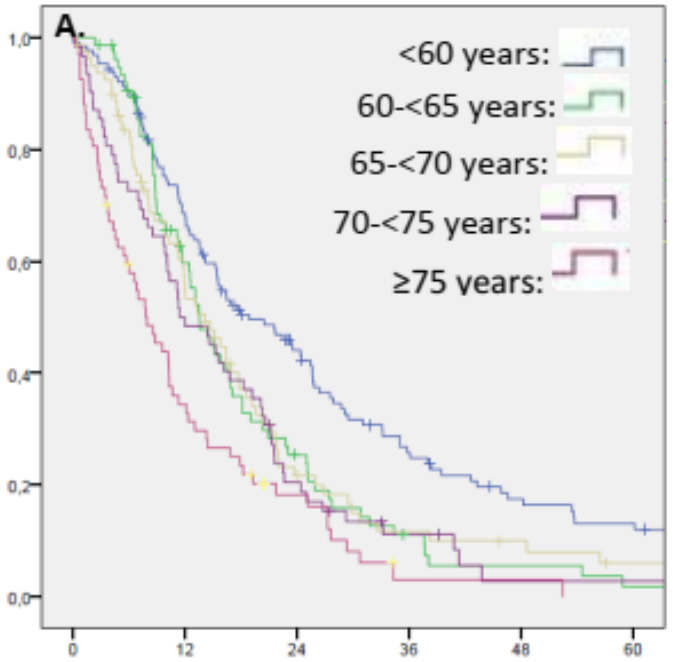
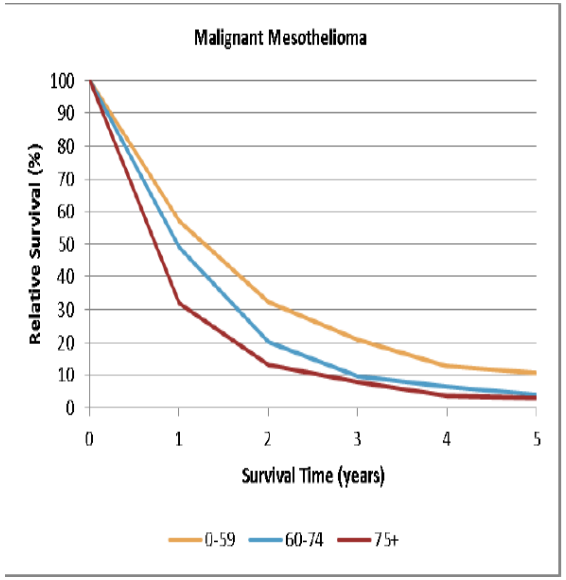


Fig. 2. Unadjusted Kaplan–Meier survival for patients with MPM, stratified by histologic subtype

Myerhoff et al, J Surg Res 2015

EPIDEMIOLOGY





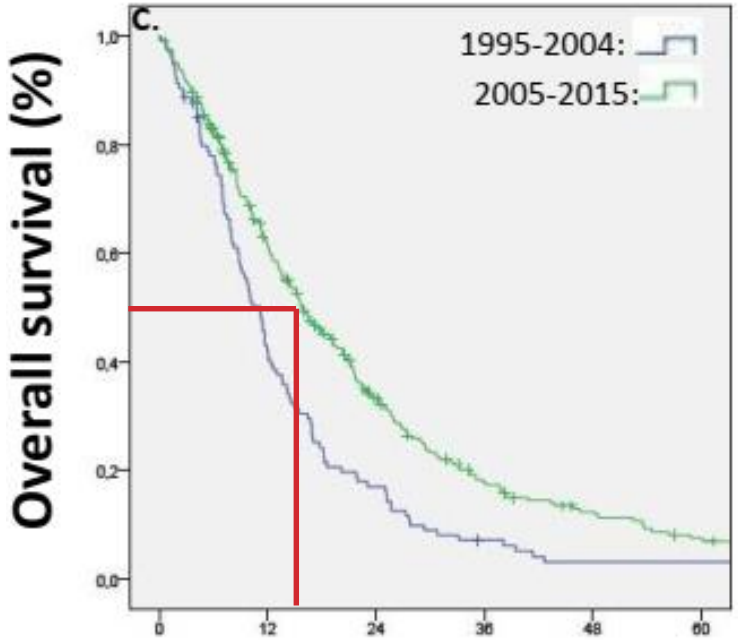
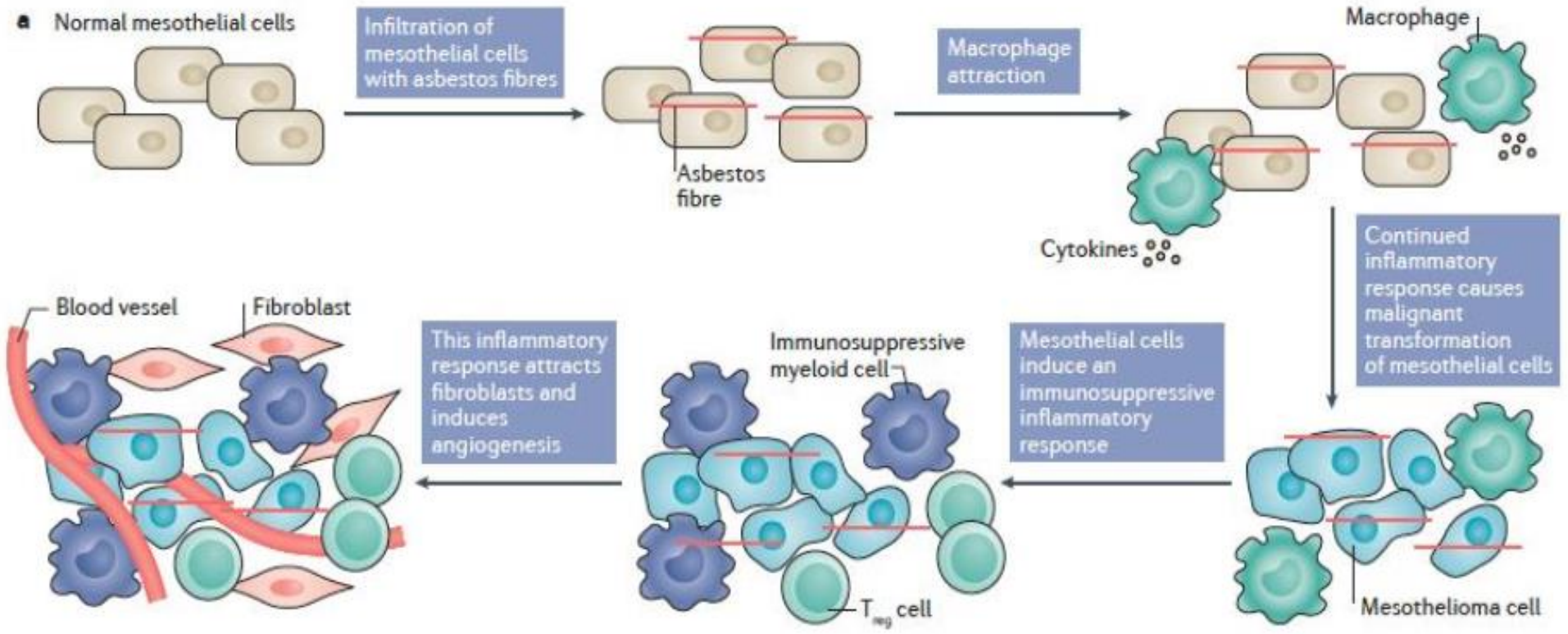


Table 1: Baseline characteristics of the whole study po mesothelioma patients. SD: standard deviation. NOS: not otherwise specified.

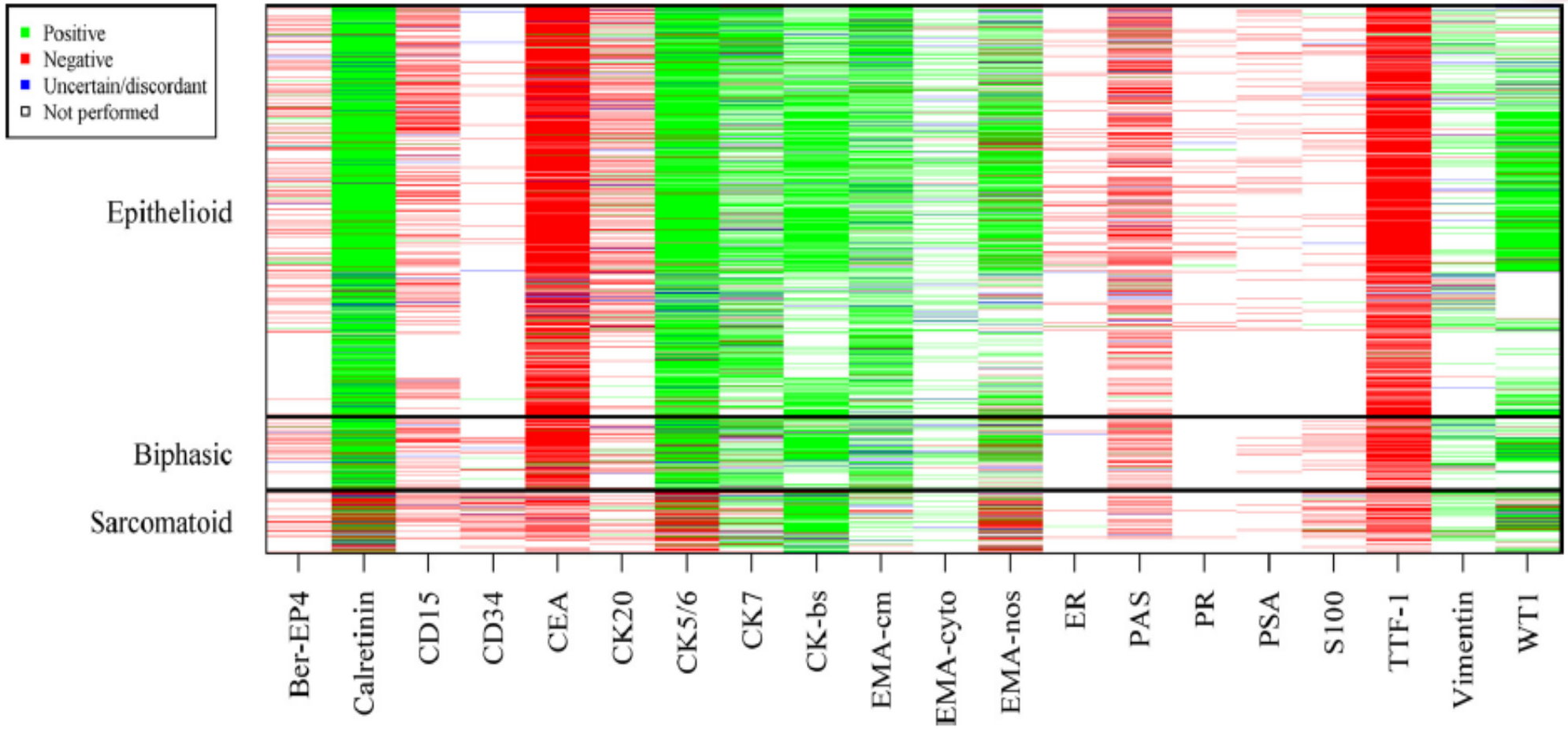
Characteristics	Total (n=414)
Gender	
Men	355 (85.7%)
Women	59 (14.3%)
Age at diagnosis years)	
< 60	128 (30.9%)
60 - < 65	77 (18.6%)
65 - < 70	80 (19.3%)
70 - < 75	62 (15.0%)
≥ 75	67 (16.2%)
Mean (±SD)	65.0 (±10.2)
Median (range)	65.3 (18.2-93.8)
Mesothelioma morphologic type	
Epithelioid	293 (70.8%)
Sarcomatoid	36 (8.7%)
Biphasic	41 (9.9%)
Desmoplastic	15 (3.6%)
NOS	29 (7.0%)
Tumour side	
Left	153 (37.0%)
Right	261 (63.0%)
Survival	
< 3 years	364 (87.9%)
≥ 3 years	50 (12.1%)

Nuyts V et al UZ Leuven data 1995-2015 - unpublished

BIOLOGY



BIOLOGY



Rosskamp M et al Lung Cancer 2018;122:38-43

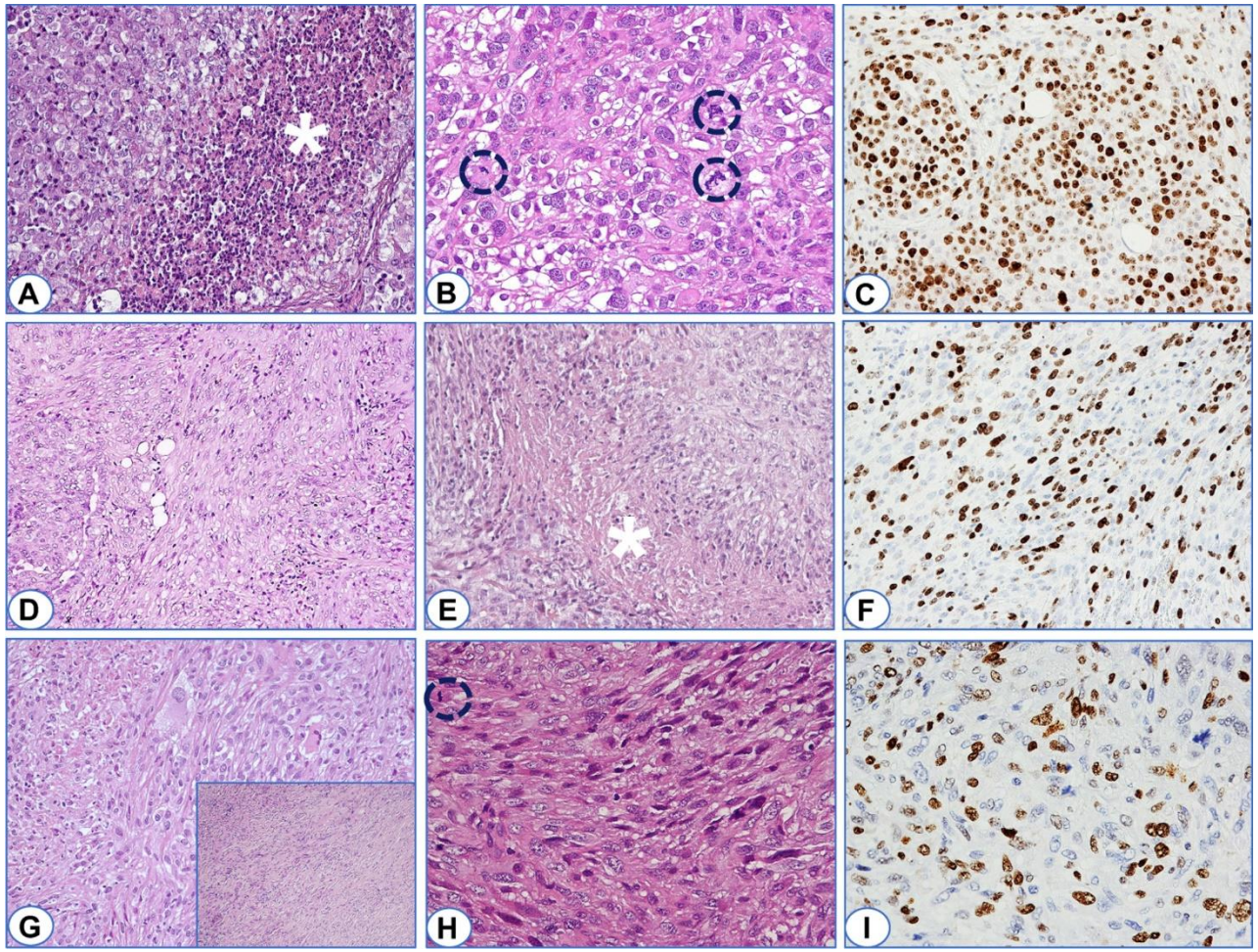
BIOLOGY

Pathologic Grading System (PGS): **necrosis foci, mitosis** **Ki67**

Epithelioid type

Bifasic type

Sarcomatoid type

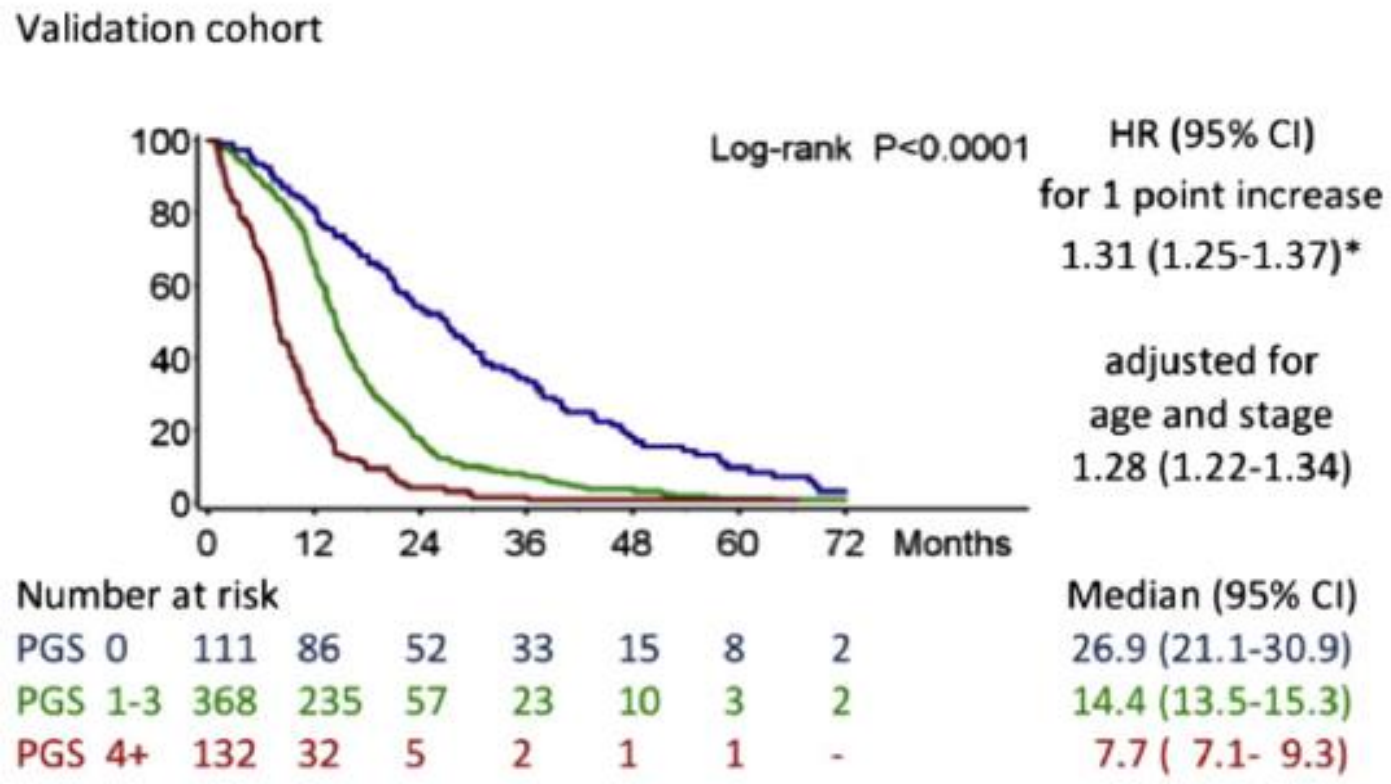


Pelosi G et al J Thor Oncol 2018

BIOLOGY

Table 2. Histopathologic Traits Associated with Overall Survival at Multivariate Analysis in the Training Cohort (n = 328 patients) and Assignation of Relative Points for Construction of Scoring of the Pathologic Grading System

Variable	Multivariable HR (95% CI)	Assignment of Points
Necrosis		
Absent	1	0
Present	1.60 (1.22-2.09)	1
Histologic variant		
Epithelioid/biphasic	1	0
Sarcomatoid	2.04 (1.39-2.99)	2
Ki-67 LI		
<30%	1	0
≥30%	1.54 (1.19-2.00)	1
Mitosis number		
1-2	1	0
3-5	1.90 (1.32-2.74)	1
6-9	2.79 (1.89-4.12)	2
≥10	4.26 (2.61-6.95)	4



Pelosi G et al J Thor Oncol 2018

BIOLOGY

BAP1 (BRCA-associated protein):

Tumor suppressor gene located on 3p21 locus

deubiquitylase, modulating activity of genes/proteins controlling:

- DNA replication
- DNA repair & metabolism
- Cell death (apoptosis)

BAP1mt cells are prone to:

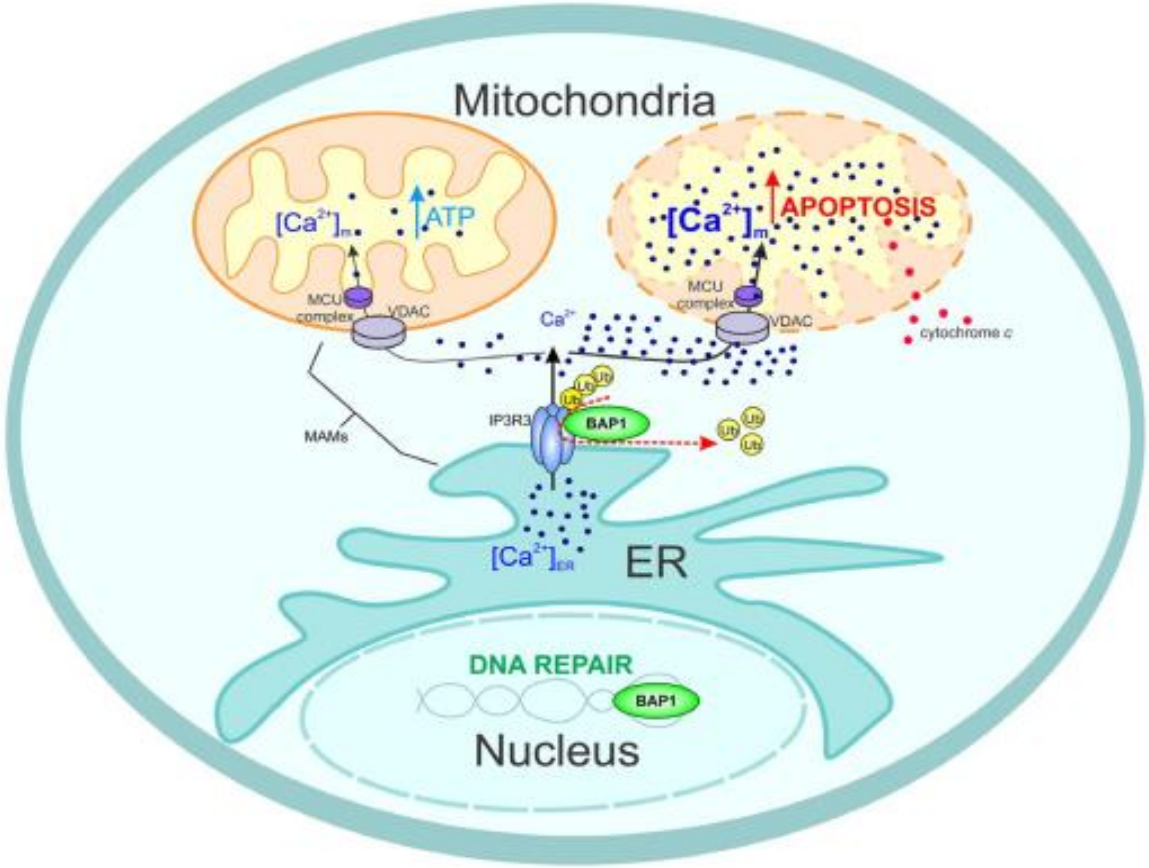
malignant transformation,

increased by asbestos exposure

Loss of BAP1 by mutation, biallelic deletion,

or deletion/insertion

Detected in 45-100% of diffuse MPM (mostly epith type)



Carbone M et al. CA Cancer J Clin 2019;69:402-29
Scherpereel A et al. Eur Respir J 2020

BIOLOGY

Young people w/o asbestos exposure (germline mutations)

- Heterozygosity for *germline BRCA-associated protein 1 (BAP1) mutations*:

BAP1 cancer syndrome (mesothelioma;uveal melanoma;skin melanoma,BCC,RCC,breast cancer)

- 'Somatically' mutated (acquired mutations) BAP1 in 60% of MPMs
- Other germline mutations in DNA repair genes (MLH1, MLH3, TP53, BRCA2)
- MPM at younger age, with M:F ratio about 1:1
- 'Germline' mutations in about 12% of patients: screening!

Carbone M et al. CA Cancer J Clin 2019;69:402-29

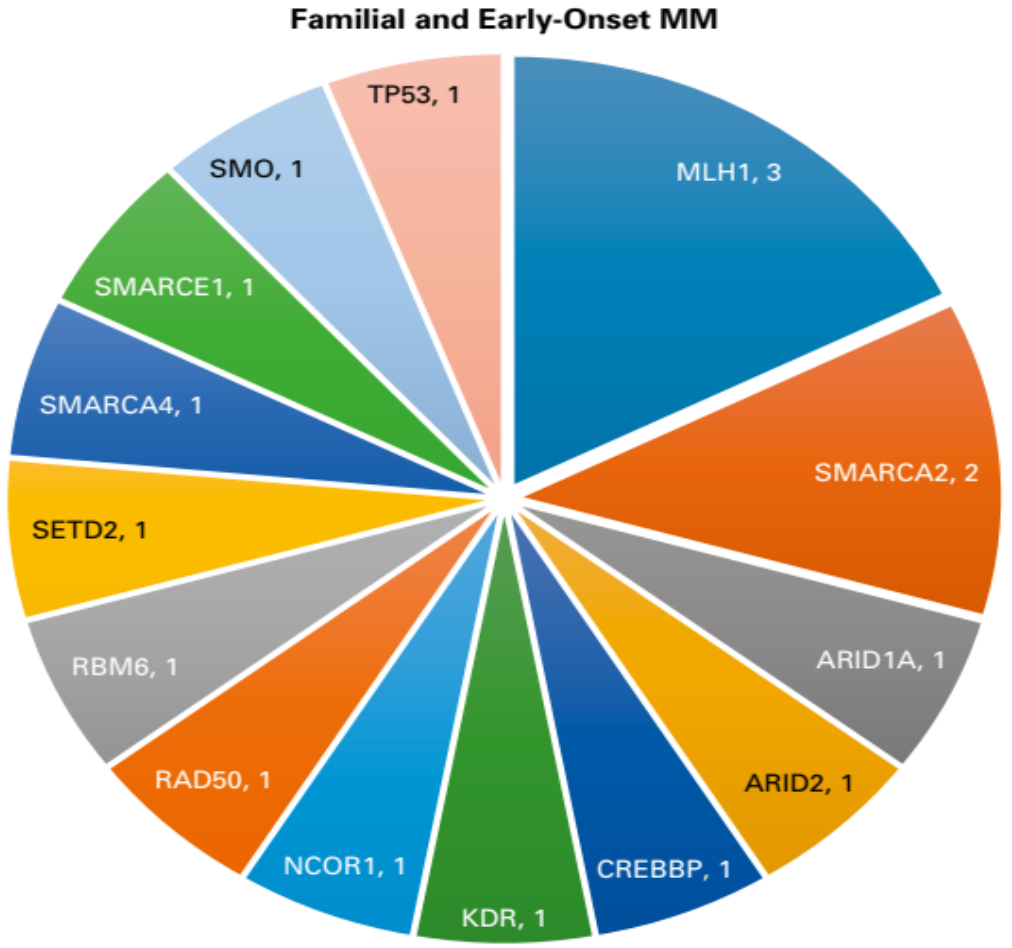
A Subset of Mesotheliomas With Improved Survival Occurring in Carriers of *BAP1* and Other Germline Mutations

Sandra Pastorino, Yoshie Yoshikawa, Harvey I. Pass, Mitsuru Emi, Masaki Nasu, Ian Pagano, Yasutaka Takinishi, Ryuji Yamamoto, Michael Minaai, Tomoko Hashimoto-Tamaoki, Masaki Ohmuraya, Keisuke Goto, Chandra Goparaju, Kavita Y. Sarin, Mika Tanji, Angela Bononi, Andrea Napolitano, Giovanni Gaudino, Mary Hesdorffer, Haining Yang, and Michele Carbone

BIOLOGY

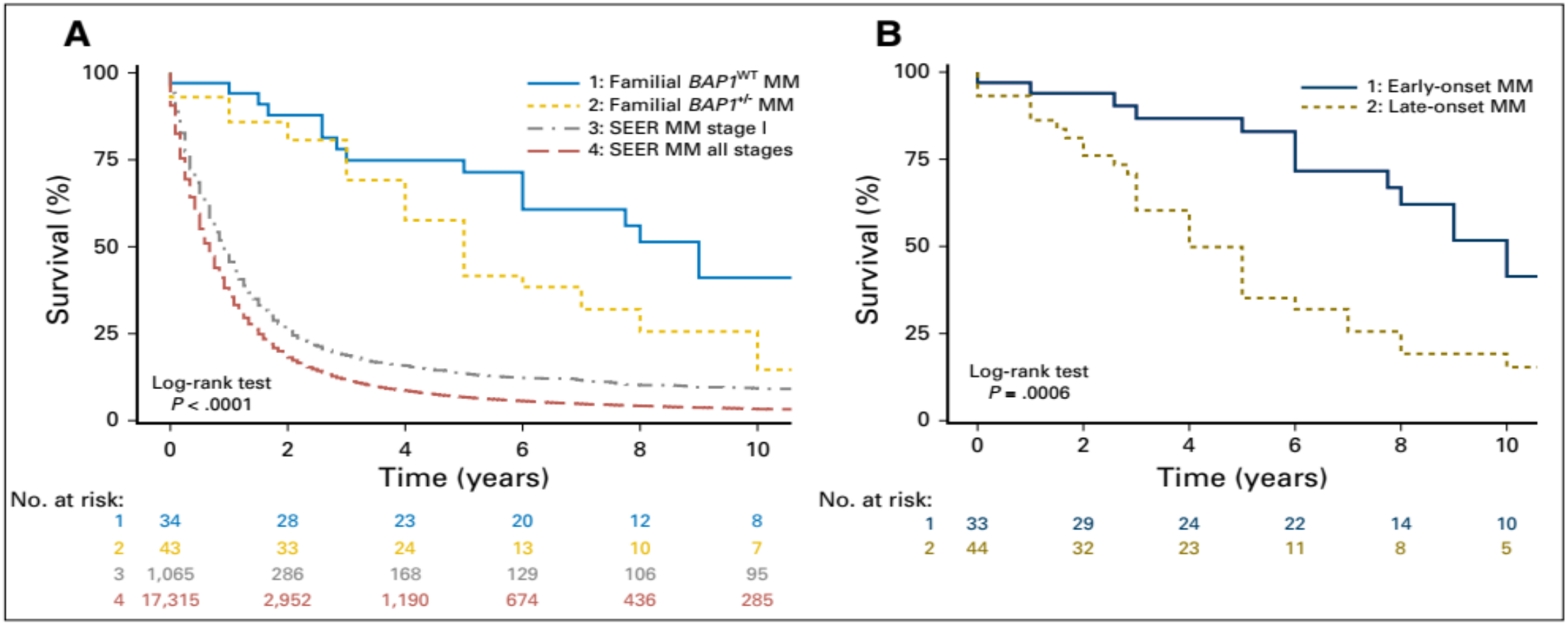
Table 4. Cancer Susceptibility Genes Identified as Mutated in Patients With Familial and Early-Onset Malignant Mesothelioma

Gene	Chromosome Location	Gene Category*
ARID1A	1	Tumor suppressor, chromatin regulation
ARID2	12	Tumor suppressor, chromatin regulation
BAP1	3	Tumor suppressor, DNA repair, chromatin regulation
CREBBP	16	Tumor suppressor, transcription regulation
KDR	4	Tyrosine kinase receptor
MLH1	3	Tumor suppressor, DNA repair
NCOR1	17	Chromatin regulation
RAD50	5	DNA repair
RBM6	3	Tumor suppressor, RNA processing
SETD2	3	Tumor suppressor, DNA repair, chromatin regulation
SMARCA2	9	Tumor suppressor, chromatin regulation
SMARCA4	19	Tumor suppressor, chromatin regulation
SMARCE1	17	Chromatin regulation
SMO	7	Oncogene, G-protein couple receptor
TP53	17	Tumor suppressor, DNA repair



Pastorino S et al J Clin Oncol 2018;36:3485-

Family history of MPM and/or other cancers
Early onset MPM (age <50yrs)
Median age at Dx **54 yrs** and median survival **5 yrs** (in familial *BAP1mt* pts)
Median age at Dx **45 yrs** and median survival **9 yrs** (in familial non*BAP1mt* pts)



Pastorino S et al J Clin Oncol 2018;36:3485-

BIOLOGY

CDKN2a (*p16*):

Homozygous deletion of CDKN2a gene

Located on 9p21 locus

In nearly 100% of sarcomatoid type MPM

VEGF:

Homozygous deletion of CDKN2a gene

Located on 9p21 locus

In nearly 100% of sarcomatoid type MPM

Loss of Nf2:

By mutation or heterozygous/homozygous deletion

Observed in 45-50% of cases

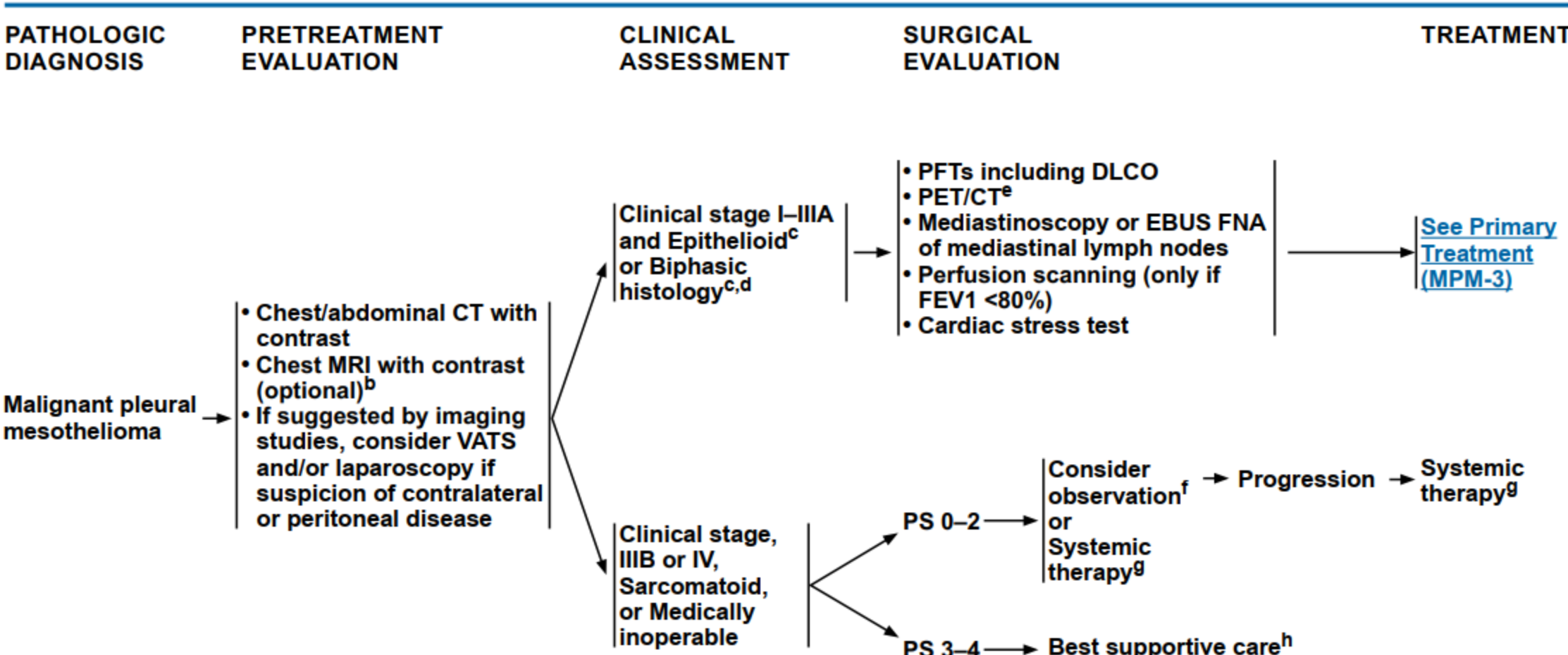
Scherpereel A et al Eur Respir J 2020

MPM TREATMENT GUIDELINES

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Malignant Pleural Mesothelioma

x
Table of Contents
Discussion



NCCN Guidelines v2.2020 15-Oct-2020 at www.nccn.org

MPM TREATMENT GUIDELINES

ESMO v2015

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Recommendation 4

The first- and second-line treatment of unresectable mesotheli

- *Anti-folate/platinum doublet is the only app* *care [I, A].*
- *Maintenance therapy (sw* *on) has not yet improved the OS and pati* *cluded in these studies [II, A].*
- *Patien* *on should be recommended to join studies in second l* *[II, A].*

New update ESMO Guideline MPM in 2021??

Baas P et al. Ann Oncol 2015;26 Suppl 5:v31-39

MPM TREATMENT GUIDELINES

ERS/ESTS/EACTS/ESTRO v2020

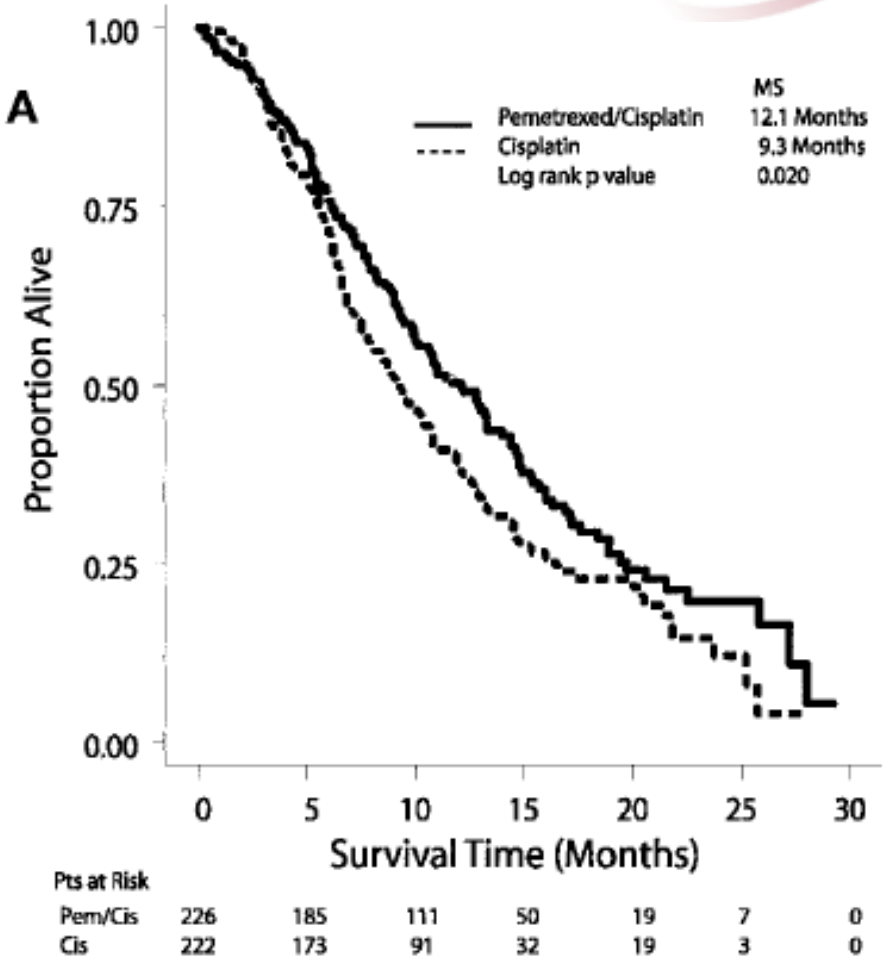
Medical treatment (PICO)

Should first line chemotherapy consisting of platinum in combination with pemetrexed be used in patients with MPM?	We recommend first-line combination (chemo)therapy consisting of platinum and pemetrexed (with folic acid and vitamin B12 supplementation) in patients fit for (chemo)therapy (good performance status, ECOG performance status 0–2, no contraindications) (strong recommendation, low quality of evidence). Research priority: patients demonstrating prolonged symptomatic and objective response with first-line pemetrexed-based (chemo)therapy may be treated again with the same regimen in the event of recurrence. In the remainder of cases, inclusion of the patients in clinical trials is highly encouraged.
Should targeted therapies be added to first line standard chemotherapy in patients with MPM? Should bevacizumab be added to first line standard chemotherapy in patients with MPM?	Recommendation: we suggest that bevacizumab, if available, be proposed in combination with cisplatin/pemetrexed as first-line treatment in patients fit for bevazucimab and cisplatin, but not for macroscopic complete resection (weak recommendation, moderate quality of evidence).
Should immunotherapy be used as salvage therapy in patients with MPM who failed first-line standard chemotherapy?	Research priority: novel insights in immunotherapy are promising, but need further development and results from ongoing or planned phase III trials before any definitive recommendations can be made for their use in the clinical routine. Inclusion of patients in these trials is highly recommended.

Scherpereel A et al. Eur Respir J 2020

CHEMOTHERAPY

- 1L Platin-pemetrexed
- MORE Line treatment
- Combination CHEMO + Targeted Therapy
- *Combination CHEMO + IO*



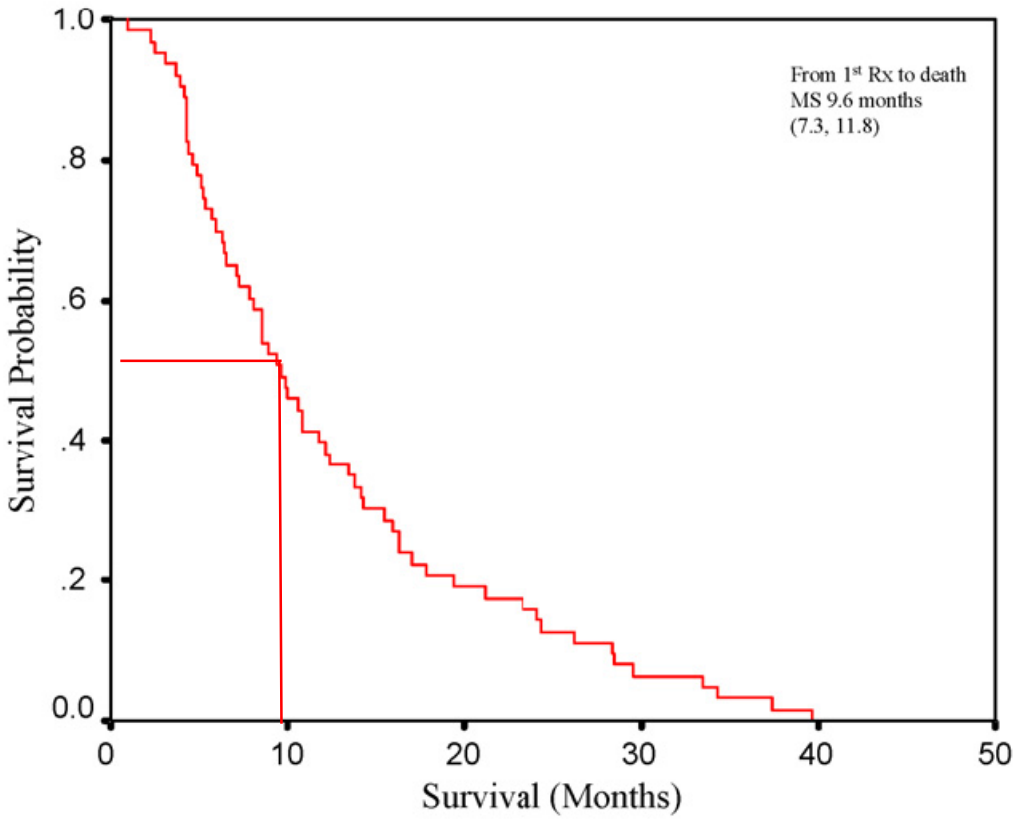
Vogelzang NJ et al J Clin Oncol 2003

MPM 1L CHEMOTHERAPY

1L MPM	schedule	RR (%)	PFS (m)	OS (m)	Phase
Vogelzang 2003	Cis-pemetrexed Control arm	41,3 16,7	5,7 (TTP) 3,9 (TTP)	12,1 9,3	3
Van Meerbeeck 2005	Cis-raltitrexed Control arm	23,6 13,6	5,3 4,0	11,4 8,8	3
Santoro 2008	Cis-pemetrexed Carbo-pemetrexed	26,3 21,7	7,0 (TTP) 6,9 (TTP)	na na	EAP
Kartitzoglou 2009	Carbo-pemetrexed	29	7	14 Ep:16 > Sarc:11	2

MORE LINE CHEMOTHERAPY

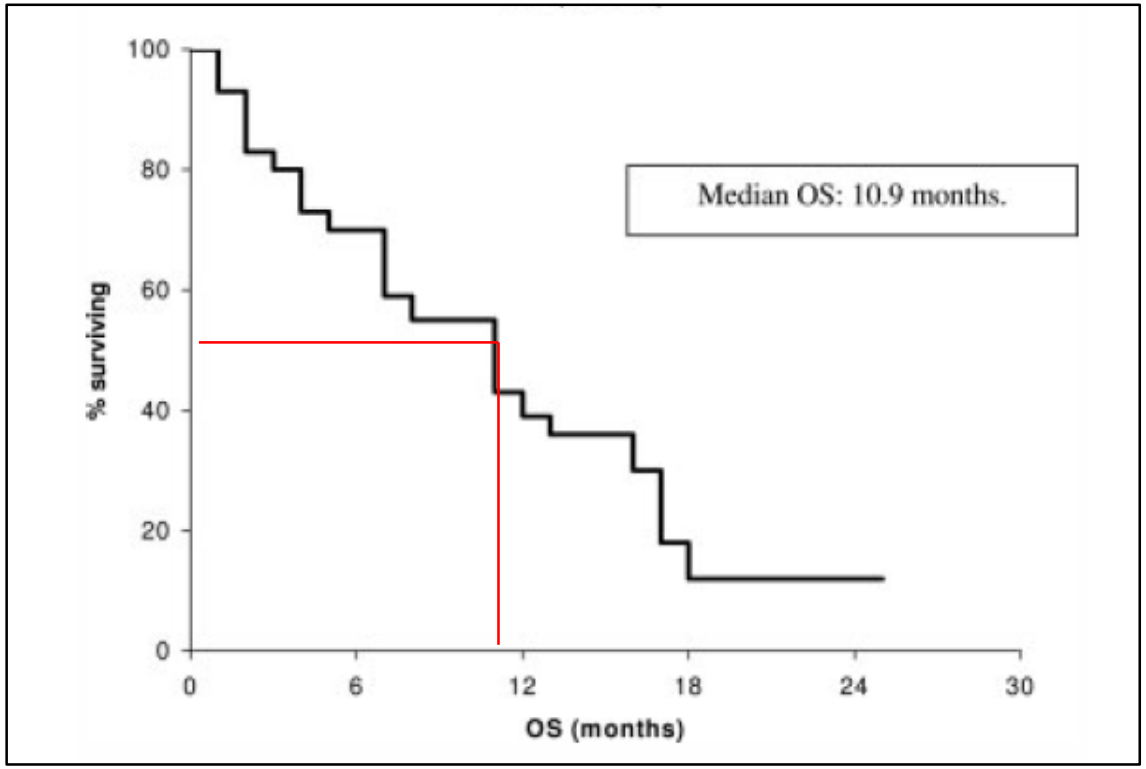
The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma



Mediane overleving vinorelbine: 9,6m

Stebbing J et al Lung Cancer 2009;63:94-7;

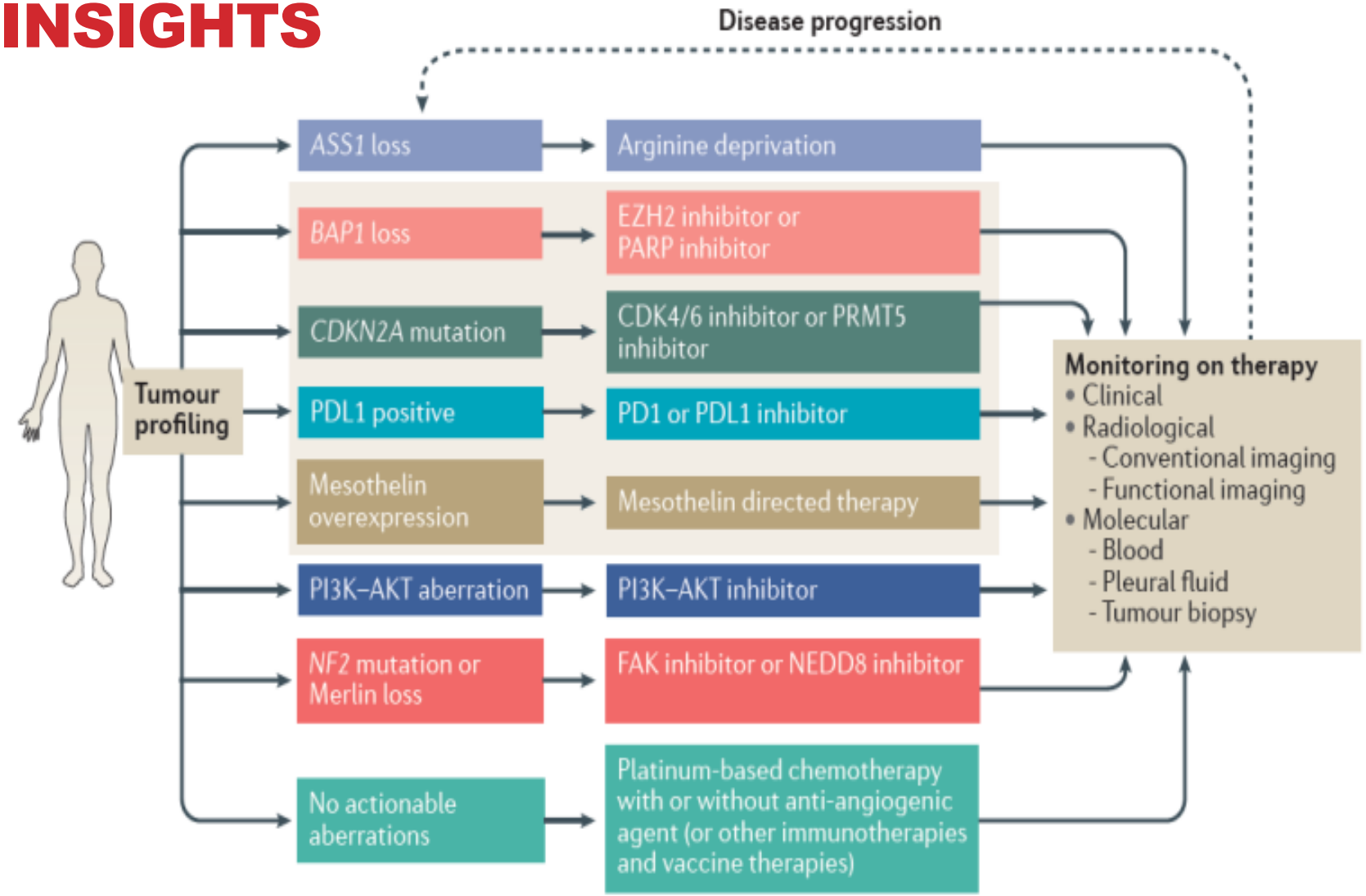
Gemcitabine and Vinorelbine in Pemetrexed-Pretreated Patients With Malignant Pleural Mesothelioma



Mediane overleving gemci-vino: 10,9m

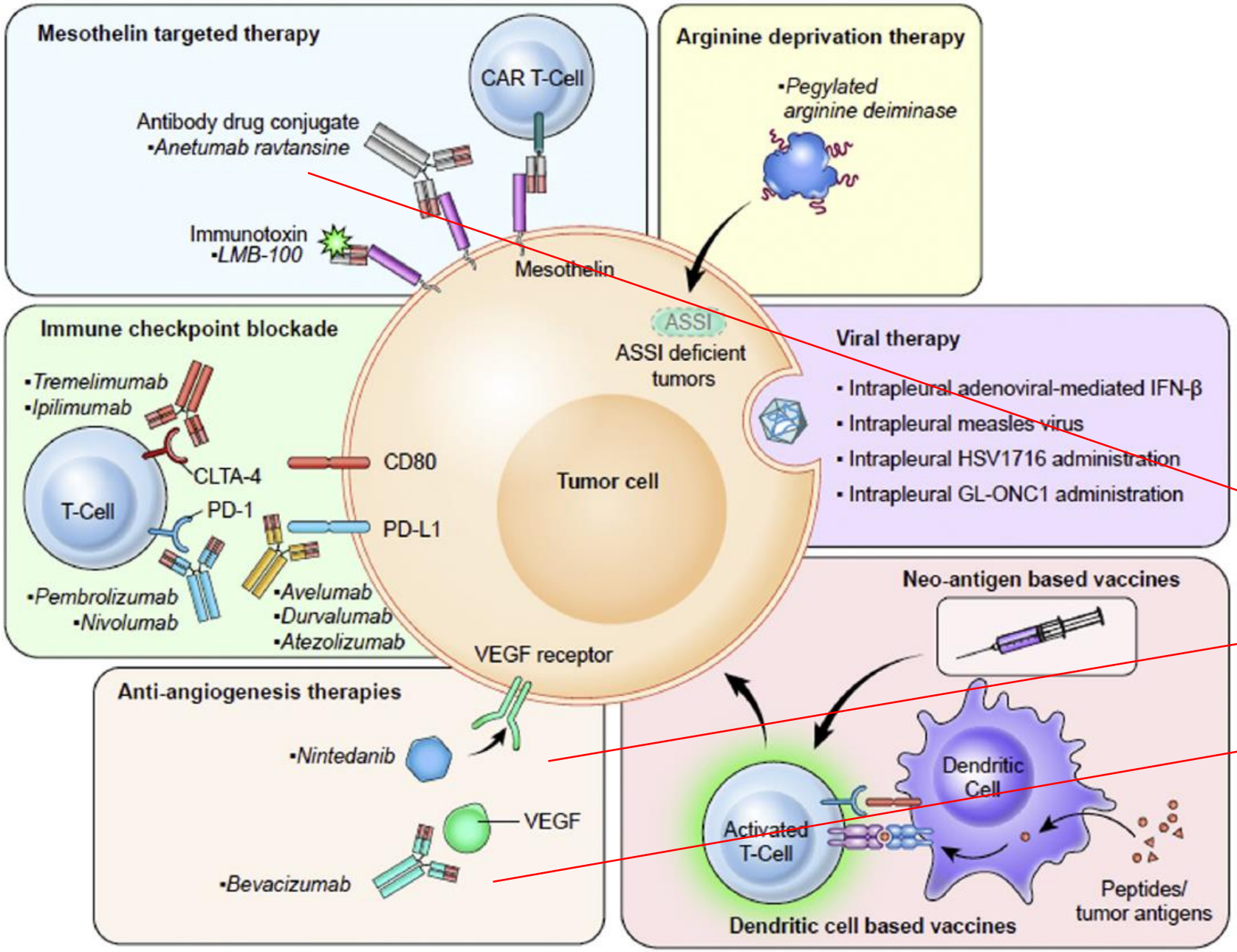
Zucali PA et al Cancer 2008;112:1555-61

NEW INSIGHTS



No oncogene driver has yet been detected in MPM

Aerts J ESMO E Learning 2020; Bueno R et al, J Thorac CVS 2020



Tremelimumab

Anti-PD-1
Anti-PD-L1

Anetumab-ravtansin

Nintedanib

Bevacizumab

Mutti L et al J Thorac Oncol 2018;9:1269-83

1L MPM	schedule	RR (%)	PFS (m)	OS (m)	Phase
Zacman 2016	cis+pem+beva cis-+pem	NR NR	9,2 7,3	18,8 16,1	3 MAPS
Grosso 2016	cis+pem+ninte cis+pem	59 44	9,4 5,7	18,3 14,2	2
Scagliotti 2018	Cis+pem+ninte Cis+pem		6,8 7,0	14,4 16,1	3
2L MPM	**schedule**	**RR (%)**	**PFS (m)**	**OS (m)**	**Phase**
Kindler 2017	Anetumab-ravtansine vino	8 6	4,3 4,5	10,1 11,6	2
Pagano 2020	Gem vs Gem+Ramucirumab	DCR 51,86 DCR 72,50	3,3 6,2	7,5 13,8	2

1L DOUBLET CHEMOTHERAPY + TT

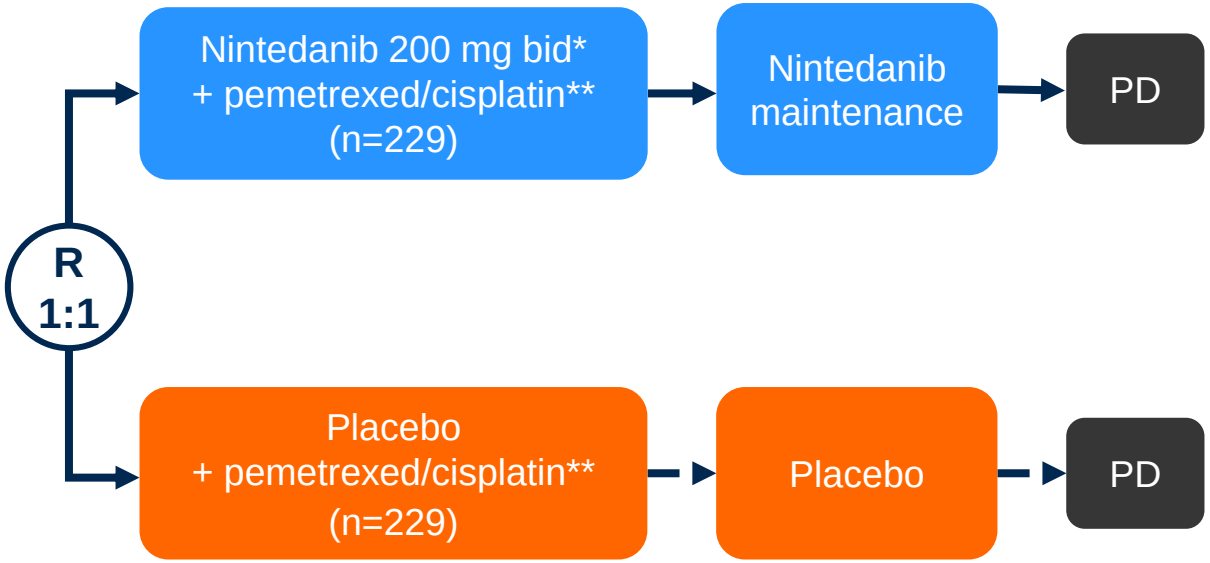
Nintedanib

PL02.09: Nintedanib + Pemetrexed/Cisplatin in Patients with Unresectable MPM: Phase III Results from the LUME-Meso Trial – Scagliotti GV, et al

Key patient inclusion criteria

- Histologically confirmed unresectable epithelioid MPM
- Life expectancy ≥3 months
- No previous systemic chemotherapy

(n=458)



Primary endpoint

Investigator-assessed PFS

Secondary endpoints

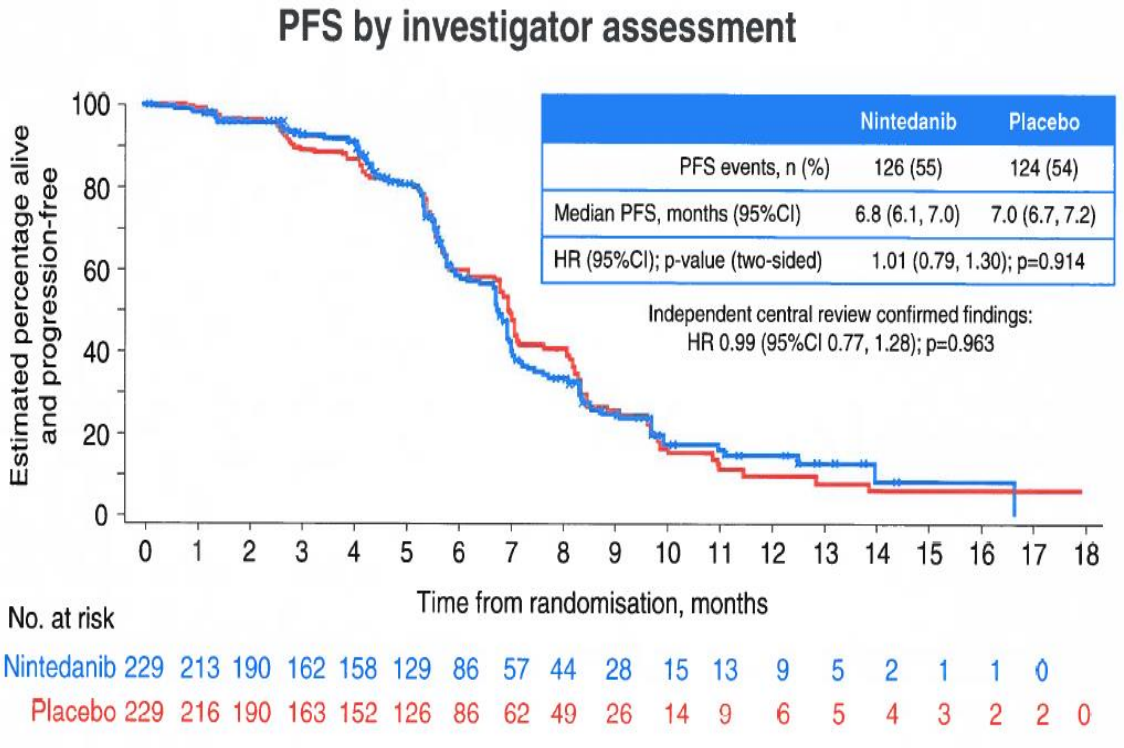
OS, safety

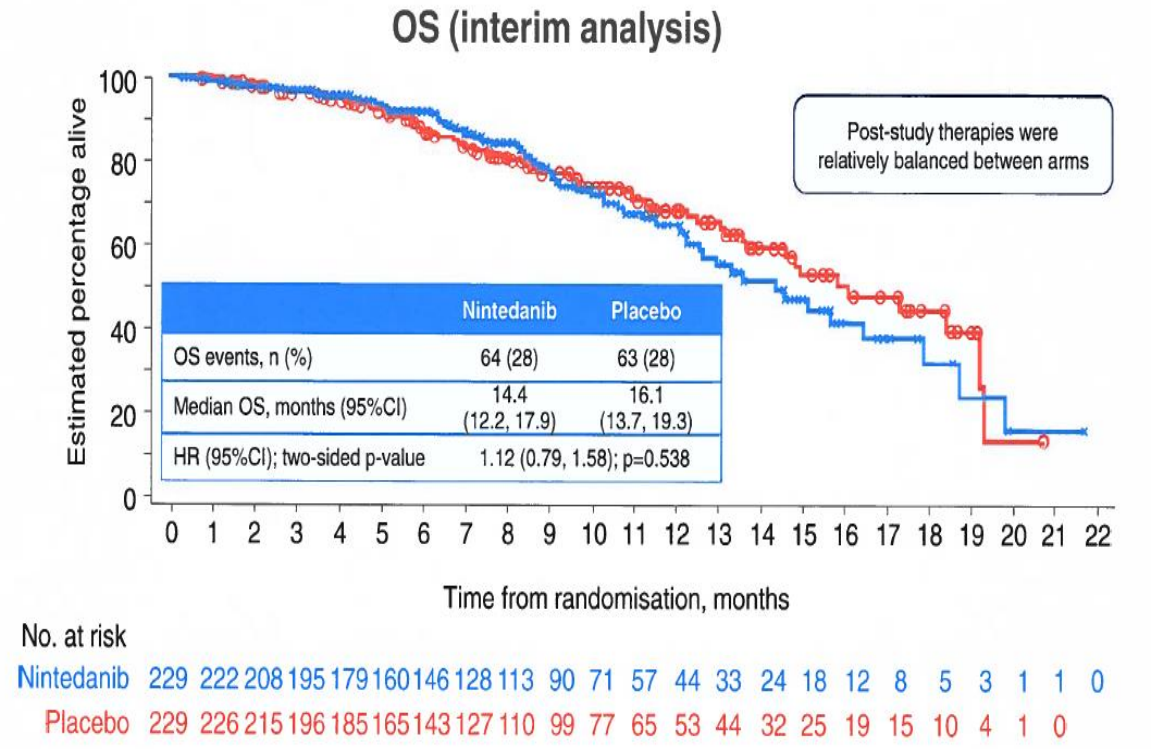
Scagliotti GV et al. J Thorac Oncol 2018;13(suppl):Abstr PL02.09

1L DOUBLET CHEMOTHERAPY + TT

Nintedanib

PL02.09: Nintedanib + Pemetrexed/Cisplatin in Patients with Unresectable MPM: Phase III Results from the LUME-Meso Trial – Scagliotti GV, et al





NEGATIVE TRIAL !

Scagliotti GV et al. J Thorac Oncol 2018;13(suppl):Abstr PL02.09

1L DOUBLET CHEMOTHERAPY + TT

Bevacizumab

The primary outcome of OS was significantly extended with PCB (median OS 18·8 months [95% CI 15·9–22·6]; . months [14·0–17·9];

PCB
PC

HR 0·77 (95% CI 0·62–0·95); p=0·0167

Section 11: Systemic anticancer treatment

Recommendations

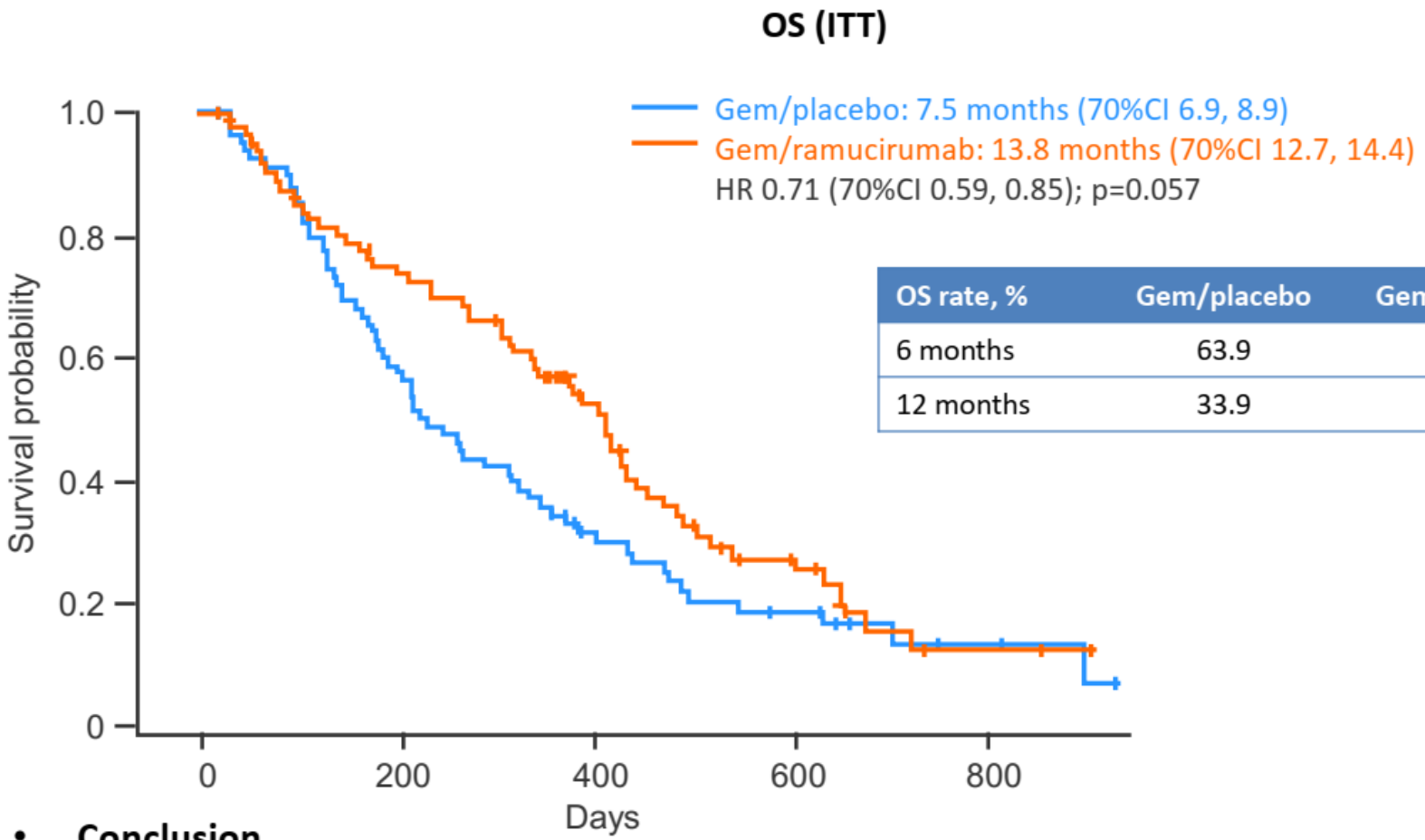
- Offer patients with MPM with good PS (WHO 0-1) first-line therapy with cisplatin and pemetrexed. Where licensed (not presently in the UK), bevacizumab should be added to this regime. Raltitrexed is an alternative to permetrexed. Grade A.

Recommendation 3.1: The addition of bevacizumab to pemetrexed-based chemotherapy improves survival in select patients and therefore may be offered to patients with no contraindications to bevacizumab. The randomized clinical trial demonstrating benefit with bevacizumab used cisplatin/pemetrexed; data with carboplatin/pemetrexed plus bevacizumab are insufficient for a clear recommendation (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: moderate)

PC	225	77	16	7	0

Zalcman et al Lancet Oncol 2017;6:319-30; Woolhouse I et al BTS Guideline MPM Thorax 2018;73:i1-i30;
Kindler HJ et al ASCO Clin Practice Guideline Mesothelioma J Clin Oncol 2018;36:1343-1373,

2L CHEMOTHERAPY VS TT

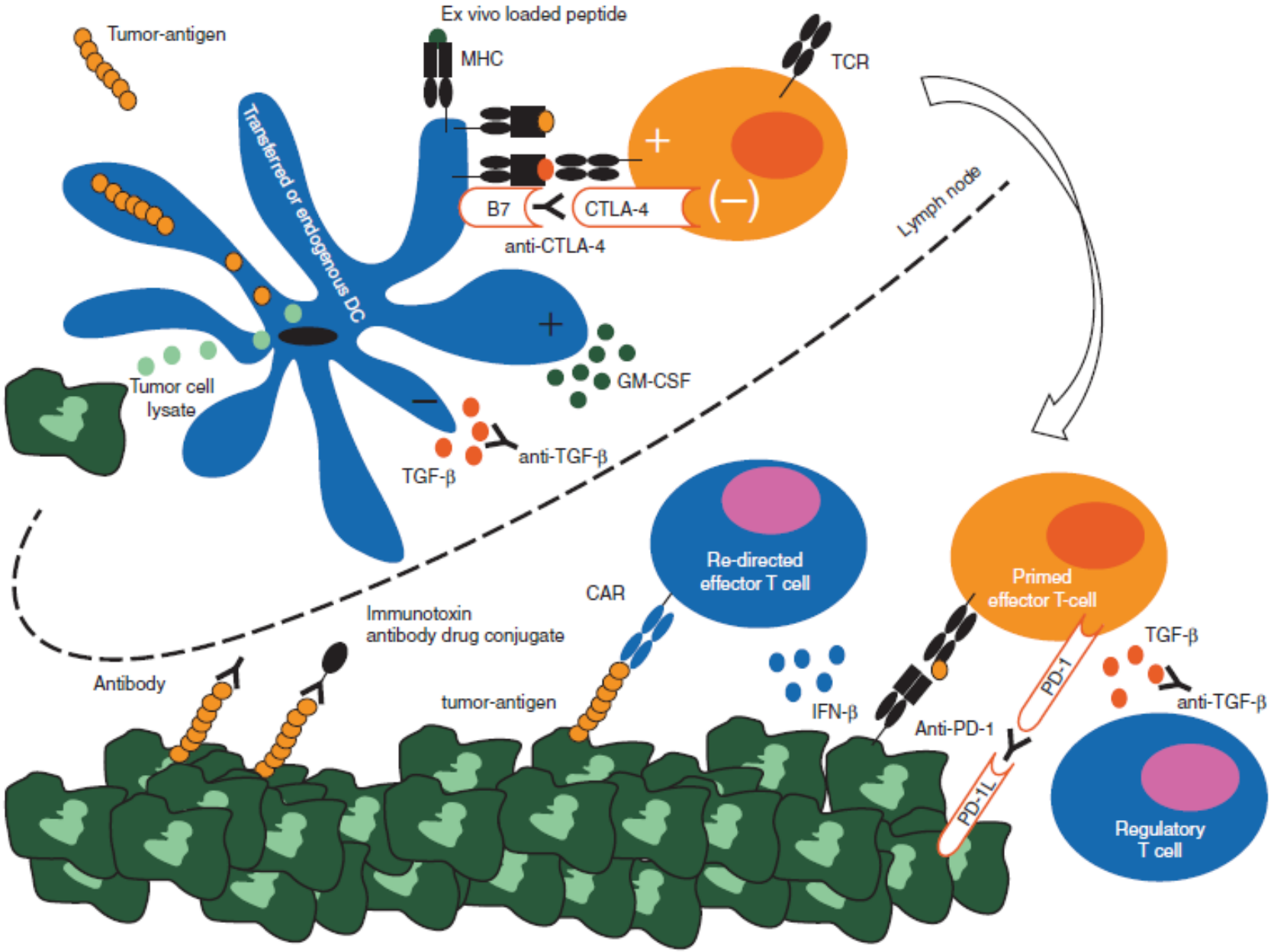


OS rate, %	Gem/placebo	Gem/ramucirumab
6 months	63.9	74.7
12 months	33.9	56.5

- **Conclusion**
  - In patients with MPM, phase 2 data suggest that ramucirumab added to gemcitabine as a 2L therapy can improve OS, with an expected safety profile
  - Comparable survival benefit was seen in epithelioid and non-epithelioid mesothelioma

ASCO 2020

Pagano M, et al. J Clin Oncol 2020;38(suppl):Abstr 9004



Stahel RA et al Ann Oncol 2015;26:1649-60

DETERMINE: Overall Survival (ITT Population)

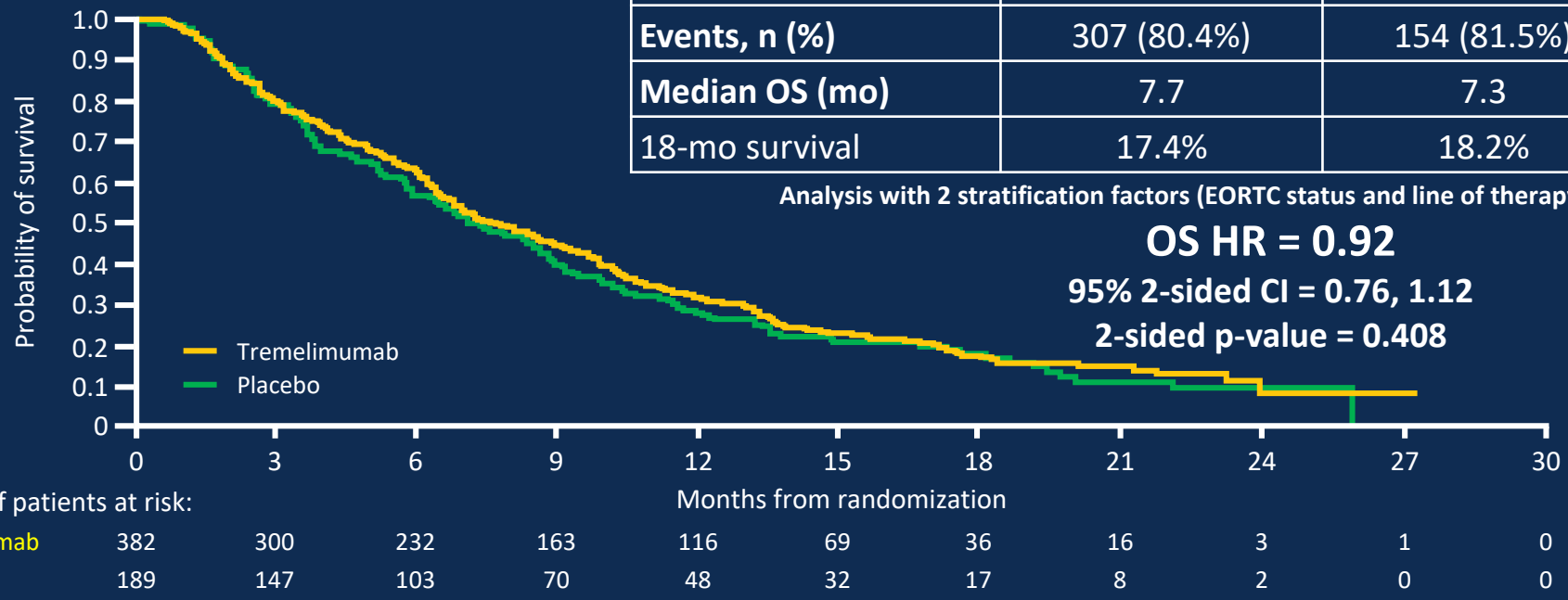
	Tremelimumab	Placebo
n	382	189
Events, n (%)	307 (80.4%)	154 (81.5%)
Median OS (mo)	7.7	7.3
18-mo survival	17.4%	18.2%

Analysis with 2 stratification factors (EORTC status and line of therapy)[a]

OS HR = 0.92

95% 2-sided CI = 0.76, 1.12

2-sided p-value = 0.408



Number of patients at risk:											
Tremelimumab	382	300	232	163	116	69	36	16	3	1	0
Placebo	189	147	103	70	48	32	17	8	2	0	0

[a]p-value for OS derived from stratified Log-rank test; HR and its CI derived from stratified Cox regression. HR<1 implies a lower risk of death with tremelimumab.

Presented by: H. L. Kindler

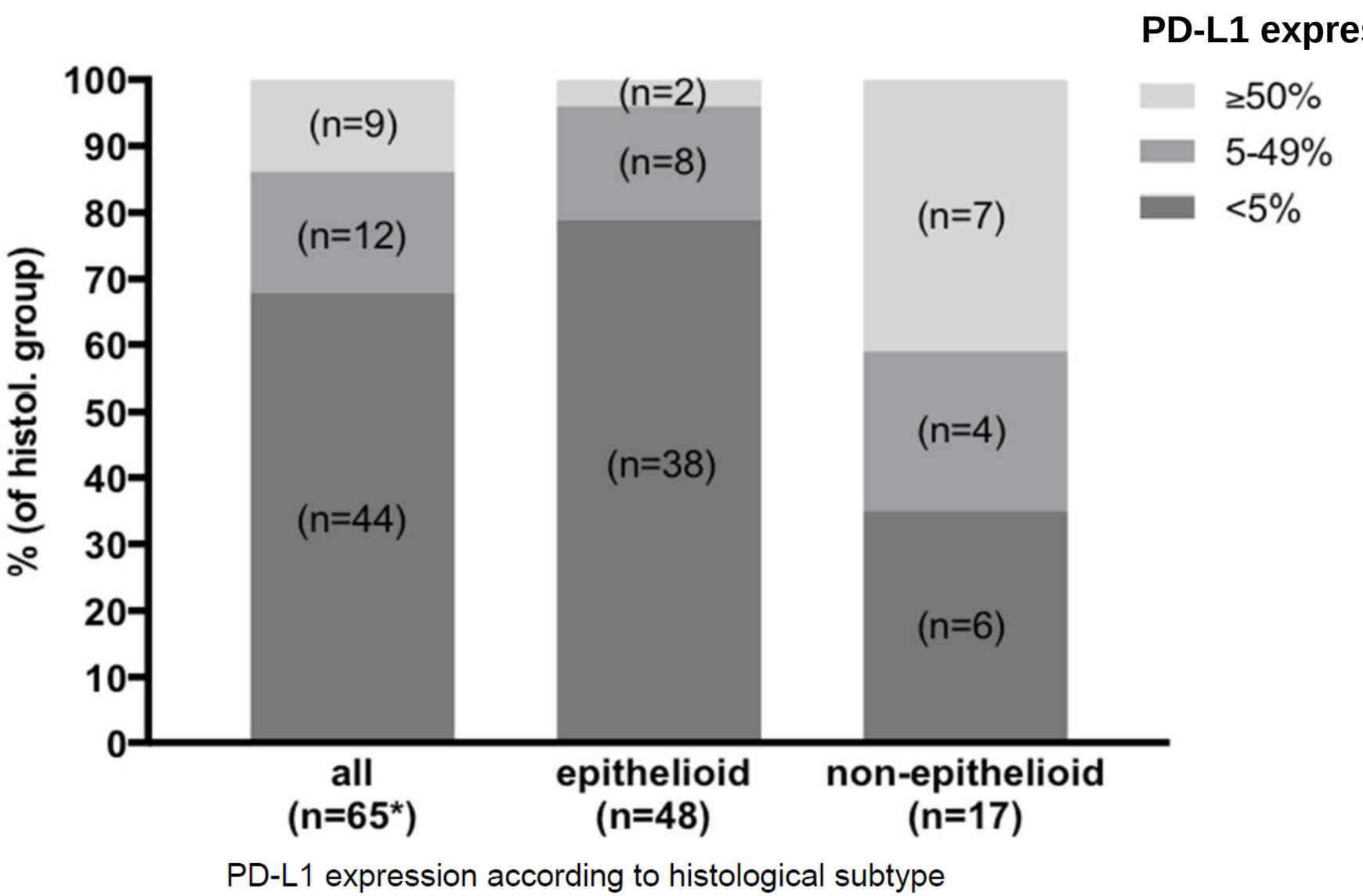
Rationale to target PD-1/PD-L1 in MPM

- Anti-tumor effect of anti-PD-1/anti-PD-L1 mAb in melanoma, NSCLC…
- Inflammatory phenotype (T cells) and **tumor expression of PD-L1 by MPM cells** (and stroma): at least 20-40% **(but « cold tumor » ?!)**
  (Mansfield et al, JTO 2014; Khanna et al, JTO 2016…)
- **PD-L1 expression associated with bad prognosis in MPM**:
  (Cedrés et al, PLoS One 2015)
  - mOS: 5.0 months if PD-L1+ vs 14.5 months if PD-L1-
  - PD-L1+ = independent risk factor for OS: RR 1.71
- MPM : a tumor with a rather **low protein-altering mutation rate**

  (Bueno R et al, Nature Genetics 2016)

Slide adapted from A Scherpereel

IMMUNOTHERAPY



PD-L1 expression according to histological subtype

Metaxas Y et al J Thorac Oncol 2018;accepted for publication

IMMUNOTHERAPY

- IO mono more line
- IO combinations more line

>1L MPM PD(L)1	schedule	RR (%)	DCR (%)	PFS (m)	Phase
Alley EW 2017	pembrolizumab	24	76		Keynote-028 1b
Hassan R 2017	avelumab	PDL1+ 14,3 PDL- 8	47,2 (all)	PDL1+ 17,1(wks) PDL1- 7,4	Javelin 1b
Kindler H 2017	pembrolizumab	21	80	6,2	2
Baas P 2017	nivolumab	15	50 (12w)	3,6	Nivo Mes 2
Desai A 2018	pembrolizumab	22 Higher in PD-L1 high	63	4,1	2
Zacman G 2017	Nivolumab Nivo+Ipi	17,5 25,8	39,7 51,6	4,0 5,6	MAPS2 2
Baas P 2019	Nivo+Ipi	29	68	6,2	2
Calabria L 2017	Durvalumab+ Tremelimumab	27,5 (ir-ORR)	65 (ir-DCR)	NR	NIBIT-MESO-1 1b

Calabro L et al Cytokine Growth Fact Rev 2017;36:25-31; WCLC 2017; WCLC 2018

IMMUNOTHERAPY

OA08.03: Phase II Trial of Pembrolizumab (NCT02399371) In Previously-Treated Malignant Mesothelioma (MM): Final Analysis – Desai A, et al

- **Key results**

	Unselected (n=64)
PR, n (%)	14 (22)
SD, n (%)	26 (41)
DCR, n (%)	40 (63)
Median DoR, months	11.7
Median PFS, months	4.1
Median OS, months	11.5

Outcomes by PD-L1 expression (PD-L1 TPS)	None (0%) (n=28)	Low (1–49%) (n=20)	High (≥50%) (n=14)	p-value
Response rate, %	7	25	43	0.021
Median PFS, months	2.8	4.1	4.9	0.034
Median OS, months	9.9	10	12.5	0.50

- **Conclusions**
  - In patients with mesothelioma responses to pembrolizumab were observed regardless of PD-L1 expression
  - A higher response rate and longer PFS were seen in patients with high (≥50%) PD-L1 expression
  - PD-L1 expression may be a biomarker for predicting response to pembrolizumab in patients with mesothelioma

Desai A et al. J Thorac Oncol 2018;13(suppl):Abstr OA08.03

IMMUNOTHERAPY

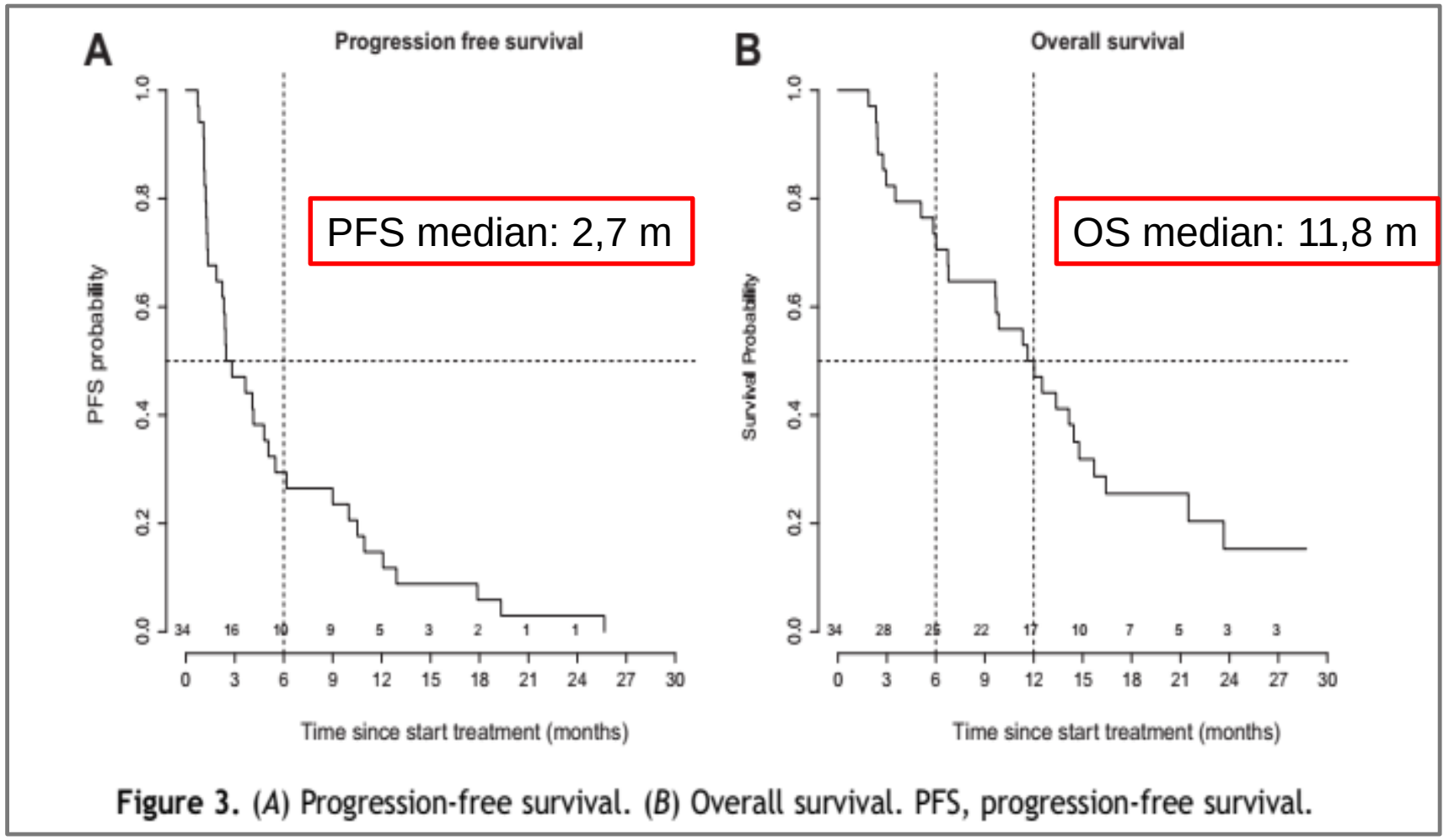


Figure 3. (*A*) Progression-free survival. (*B*) Overall survival. PFS, progression-free survival.

Conclusions: Single-agent nivolumab has meaningful clinical efficacy and a manageable safety profile in pre-treated patients with mesothelioma. PD-L1 expression does not predict for response in this population.

Quispel-Janssen et al. NIVO MES J Thorac Oncol 2018

IMMUNOTHERAPY

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

Arnaud Scherpereel, Julien Mazieres, Laurent Greillier, Sylvie Lantuejoul, Pascal Dô, Olivier Bylicki, Isabelle Monnet, Romain Corre, Clarisse Audigier-Valette, Myriam Locatelli-Sanchez, Olivier Molinier, Florian Guisier, Thierry Urban, Catherine Ligeza-Poisson, David Planchard, Elodie Amour, Franck Morin, Denis Moro-Sibilot, Gérard Zalcman, on behalf of the French Cooperative Thoracic Intergroup

Multicentre
Non-comparative
Open-label
Phase 2 trial

WHO 0-1
After 1L or 2L Rx
N = 125 pts

IV nivolumab 3mg/kg q2wks

IV nivolumab 3mg/kg q2wks plus
IV ipilimumab 1mg/kg q6wks

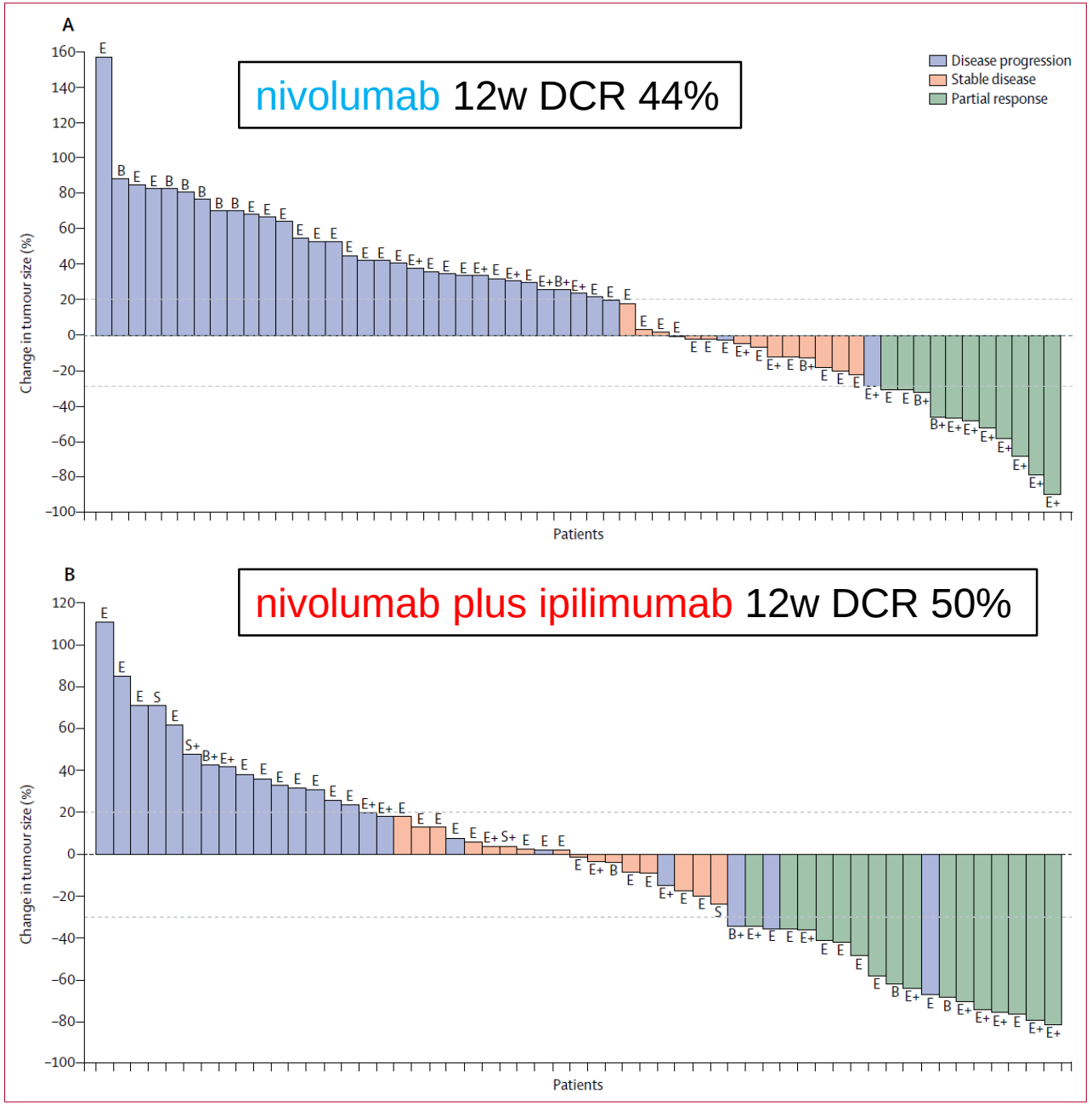
Randomisation:
Ep vs non-Ep
2nd L vs 3rd L
PD ≥3m or ≤3m after Pem

Primary Endpoint:
12 wks disease control
1ry EP met if ≥ 40%

Scherpereel A et al. Lancet Oncol 2019

IMMUNOTHERAPY

	Nivolumab group (n=63)	Nivolumab plus ipilimumab group (n=62)
Sex		
Female	16 (25%)	9 (15%)
Male	47 (75%)	53 (85%)
Age, years		
Mean (SD)	71·2 (9·5)	70·4 (9·0)
Median (IQR)	72·3 (32·5–87·2)	71·2 (48·1–88·1)
Histological subtype		
Epithelioid	52 (83%)	53 (85%)
Sarcomatoid or biphasic	11 (17%)	9 (15%)
PD-L1 status available (28-8 monoclonal antibody, Dako PharmDx)		
Negative	31 (49%)	27 (44%)
≥1%	19 (30%)	22 (35%)
≥25%	2 (3%)	5 (8%)
≥50%	0	3 (5%)
Data not available	13 (21%)	13 (21%)



Scherpereel A et al. Lancet Oncol 2019

IMMUNOTHERAPY

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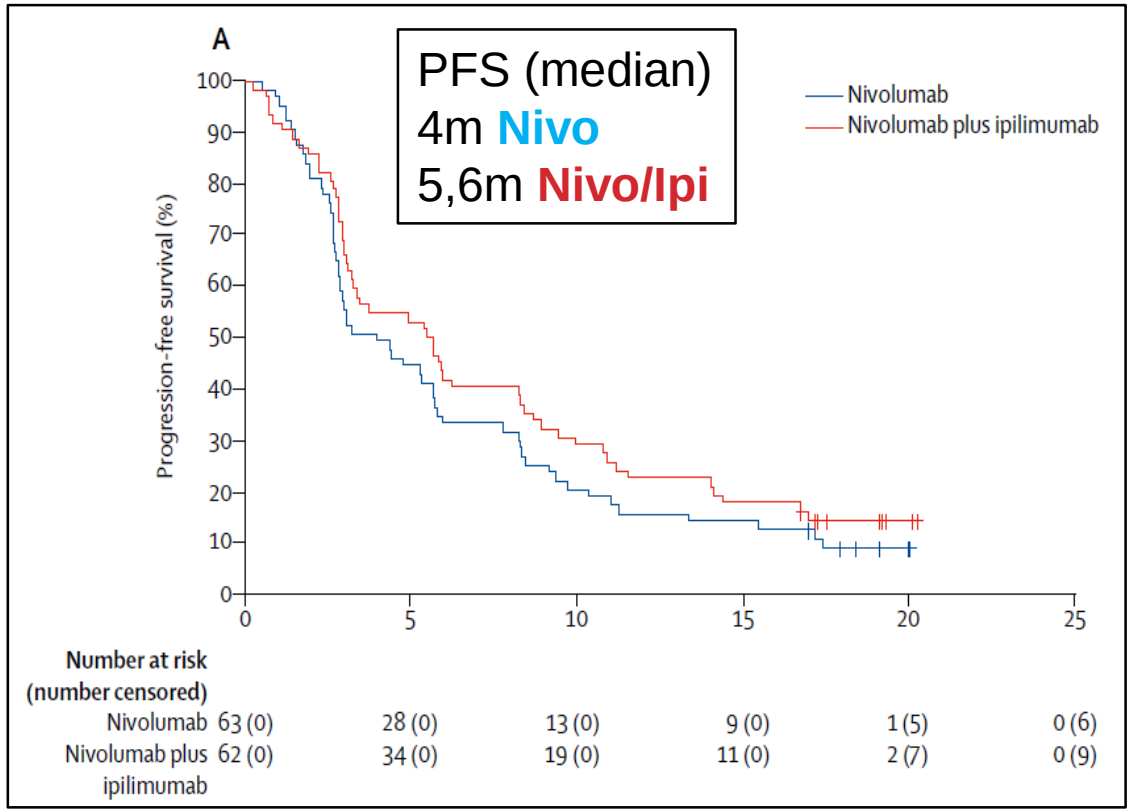
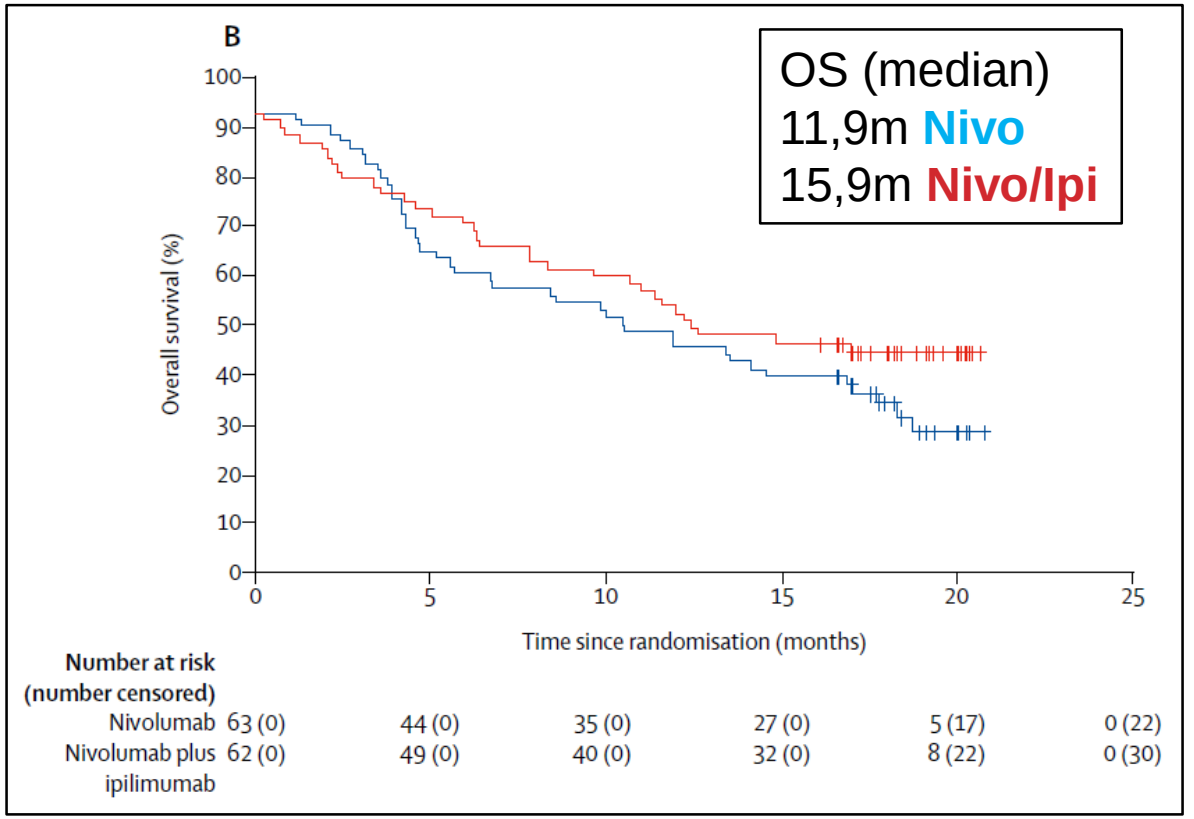




Scherpereel A et al. Lancet Oncol 2019

IMMUNOTHERAPY

	Nivolumab group (n=63)			Nivolumab plus ipilimumab group (n=61)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	47 (75%)	8 (13%)	1 (2%)	38 (62%)	14 (23%)	2 (3%)
Serious adverse event	1 (2%)	2 (3%)	0	7 (11%)	6 (10%)	1 (2%)
Led to discontinuation	2 (3%)	1 (2%)	0	4 (7%)	7 (11%)	2 (3%)
Led to death	0	0	0	0	0	0
Immune-related adverse events						
Stomatitis	4 (6%)	1 (2%)	0	4 (7%)	0	0
Arthritis	3 (5%)	0	0	7 (11%)	0	0
Aspartate aminotransferase increase	2 (3%)	0	0	3 (5%)	4 (7%)	0
Alanine aminotransferase increase	1 (2%)	0	0	4 (7%)	4 (7%)	0
Lipase increase	1 (2%)	2 (3%)	1 (2%)	2 (3%)	1 (2%)	1 (2%)
Oedema peripheral	4 (6%)	0	0	3 (5%)	1 (2%)	0
γ-Glutamyltransferase increased	1 (2%)	0	0	3 (5%)	3 (5%)	0
Amylase increased	1 (2%)	1 (2%)	0	3 (5%)	0	0
General physical health deterioration	3 (5%)	0	0	0	2 (3%)	0
Acute kidney failure	0	0	0	0	0	1 (2%)
Blood alkaline phosphatase increased	0	0	0	2 (3%)	2 (3%)	0
Colitis	1 (2%)	0	0	1 (2%)	1 (2%)	0
Pneumonitis	1 (2%)	0	0	1 (2%)	1 (2%)	0
Polyneuropathy	0	0	0	0	1 (2%)	0
Acute respiratory distress syndrome	0	0	0	0	1 (2%)	0
Cardiac failure	0	0	0	0	1 (2%)	0
Dermatitis bullous	0	0	0	0	1 (2%)	0
Encephalitis	0	0	0	0	0	0
Hepatitis	0	0	0	0	2 (3%)	0
Hyperbilirubinaemia	0	0	0	0	1 (2%)	0
Hyponatraemia	0	0	0	0	1 (2%)	0
Hypophysitis	0	0	0	0	1 (2%)	0
Interstitial lung disease	0	0	0	0	1 (2%)	0
Pericardial effusion	0	1 (2%)	0	0	0	0
Pleural effusion	0	1 (2%)	0	0	0	0

All grade 3 and 4 events are shown as well as grade 1 and 2 occurrences of these events. For other grade 1–2 events, only events occurring in more than ten people are included. Three serious grade 5 events (deaths) occurred in the nivolumab plus ipilimumab group: one acute kidney failure, one fulminant hepatitis, and one encephalitis.

Table 2: Drug-related adverse events

Scherpereel A et al. Lancet Oncol 2019

CLINICAL TRIALS

- New combinations: chemotherapy + immunotherapy in 1L
- Combination immunotherapy in 1L
- New compounds

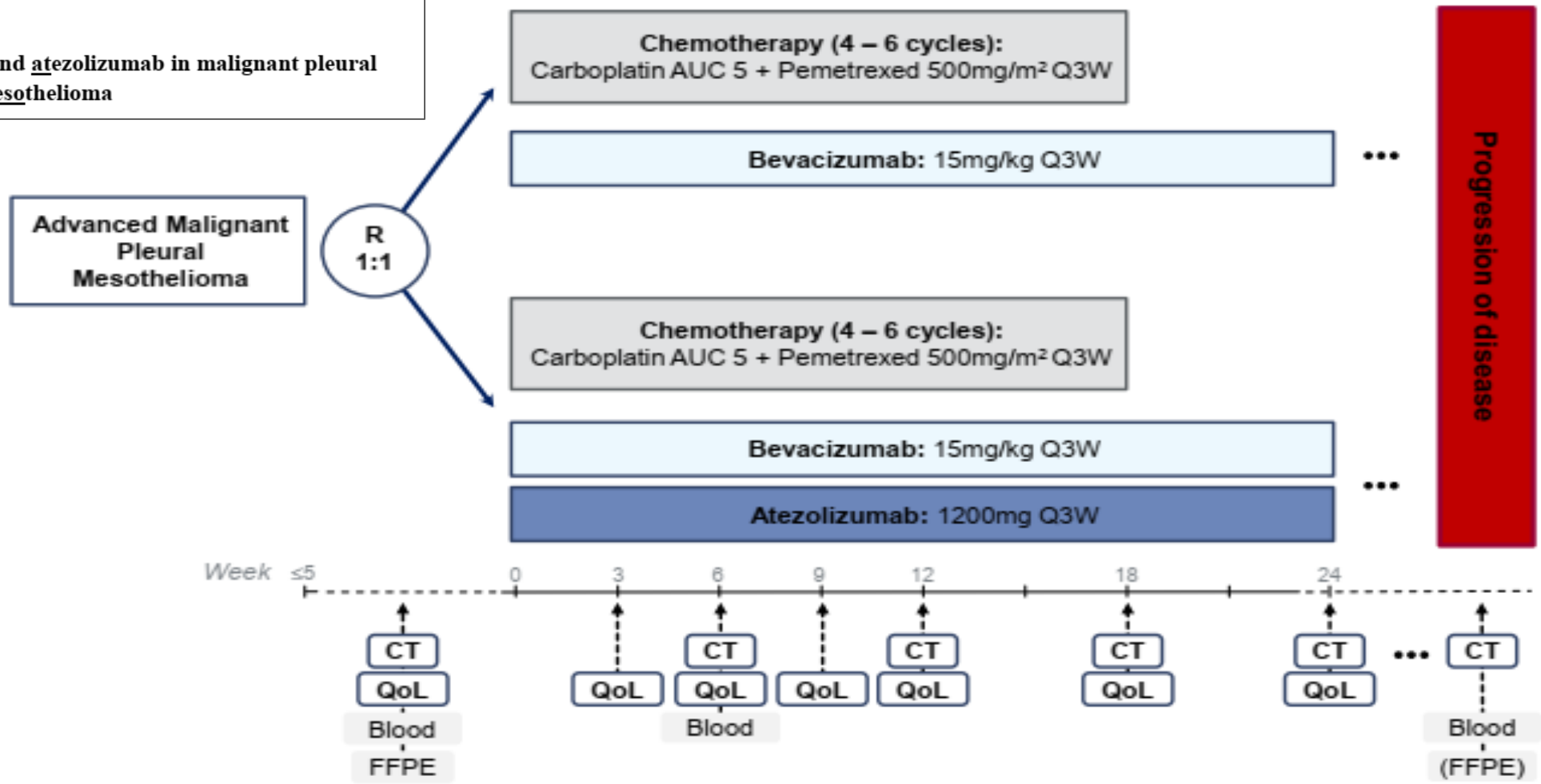
1L MPM PD(L)1	Schedule	RR (%)	DCR (%)	PFS (m)	OS (m)	Phase
Hayashi H 2020	nivolumab	29,4	68	5,9	17,3	MERIT 2
Nowak 2018	Cis-pem-Durvalumab	48		57 6 months		DREAM 2
Forde P 2020	Cis-pem-durvalumab	56,4	96,4	6,7	20,4	USPrE0505 2
Chemo-IO IO Combo's						
BEAT Trial	Cb-Pem-Beva Cb-Pem-Beva-IO	running				3
CM743	Nivo-Ipi Platin-Pem	40 43	76,6 85,1	7,2 6,8	14,1 18,1	3

Hayashi H et al Abstract 1895MO ESMO Virtual Congress 2020; Nowak et al Lancet Oncol 2020;
Forde P et al ASCO 2020 A9003: BEAT ETOP Phase 3 trial ClinicalTrials.gov Identifier: NCT03762018; Baas P et al Presidential Symposium IASLC 2020

ETOP 13-18 BEAT-meso

A multicentre randomised phase III trial comparing atezolizumab plus bevacizumab and standard chemotherapy versus bevacizumab and standard chemotherapy as first-line treatment for advanced malignant pleural mesothelioma

BEAT-meso: Bevacizumab and atezolizumab in malignant pleural mesothelioma



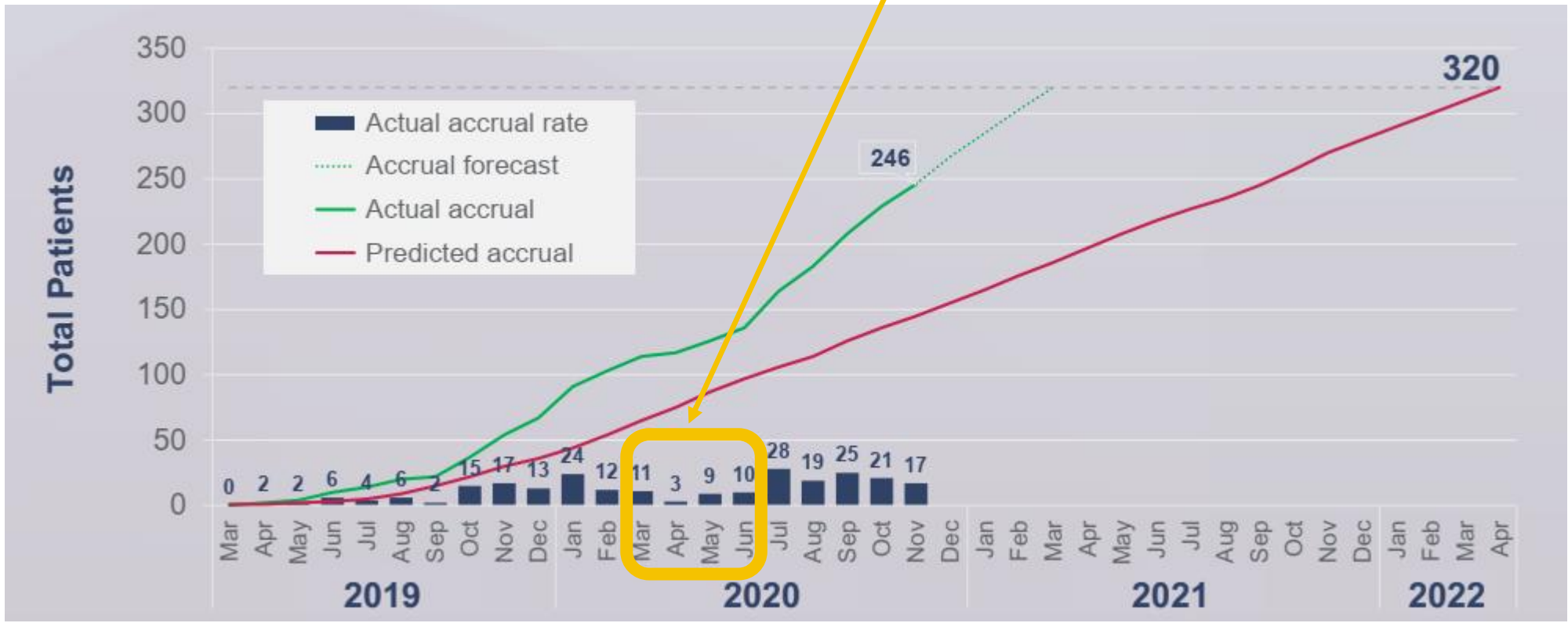
ETOP BEAT-MESO 1L MPM Trial protocol 2018

ETOP 13-18 BEAT-meso

A multicentre randomised phase III trial comparing atezolizumab plus bevacizumab and standard chemotherapy versus bevacizumab and standard chemotherapy as first-line treatment for advanced malignant pleural mesothelioma

BEAT-meso: Bevacizumab and atezolizumab in malignant pleural mesothelioma

COVID-19 EFFECT



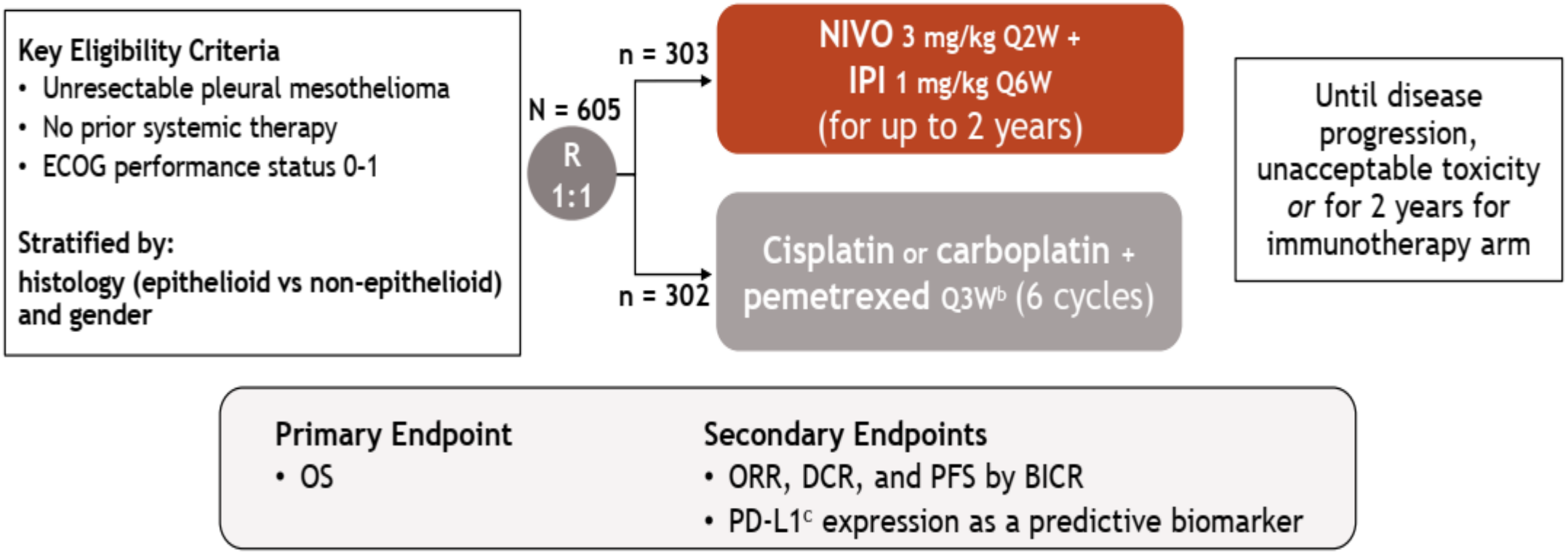
ETOP BEAT-MESO 1L MPM Trial protocol 2018

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

CheckMate 743 is a phase 3, randomized, open-label study evaluating NIVO + IPI versus standard of care chemotherapy in 1L unresectable MPM

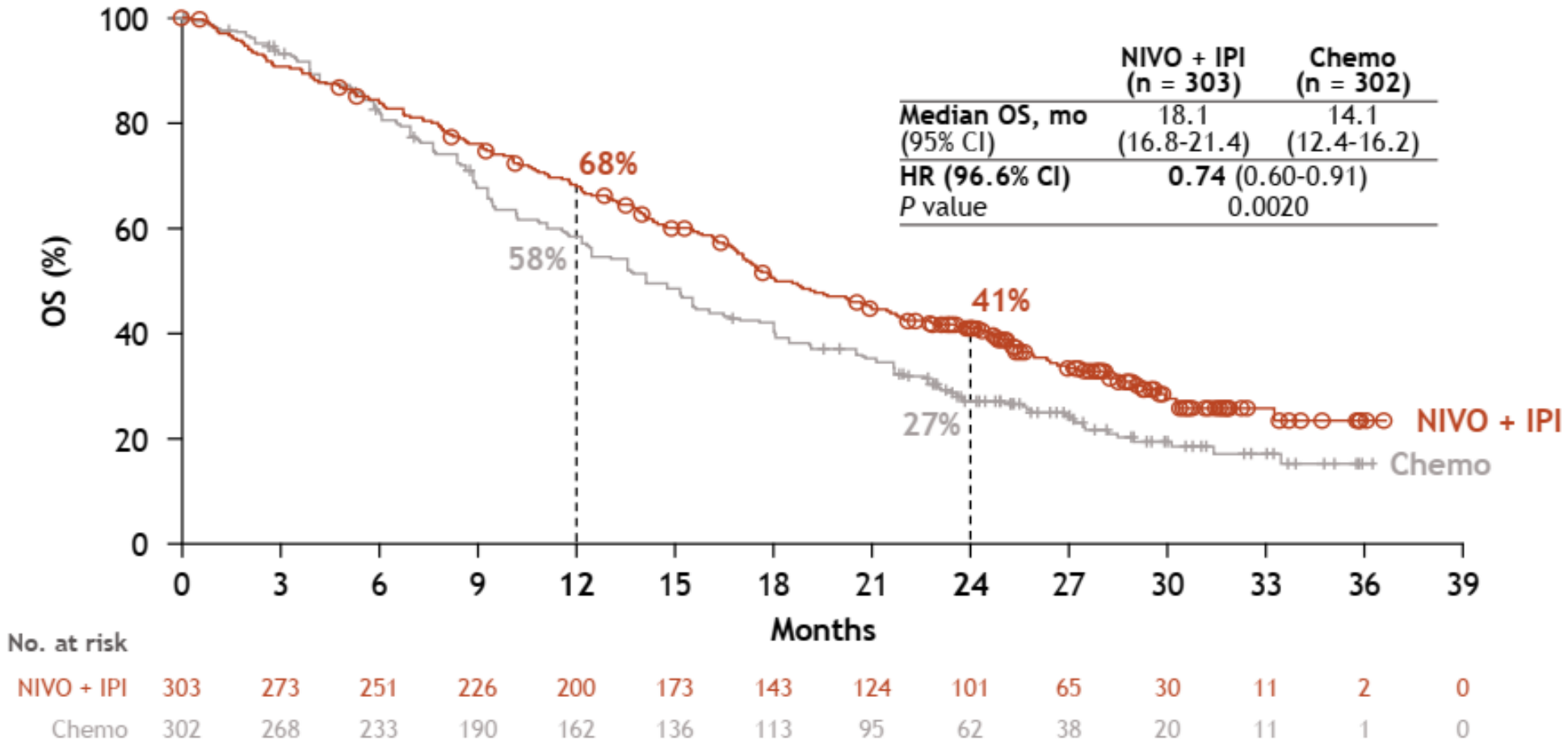
Paul Baas,[1] Arnaud Scherpereel,[2] Anna K. Nowak,[3] Nobukazu Fujimoto,[4] Solange Peters,[5] Anne Tsao,[6] Aaron S. Mansfield,[7] Sanjay Popat,[8] Thierry Jahan,[9] Scott Antonia,[10] Youssef Oulkhouir,[11] Yolanda Bautista,[12] Robin Cornelissen,[13] Laurent Greillier,[14] Francesco Grossi,[15] Dariusz Kowalski,[16] Jerónimo Rodriguez-Cid,[17] Praveen Aanur,[18] Christine Baudelet,[18] Gérard Zalcman[19]

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



P Baas et al IASLC Presidential Symposium 2020

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	

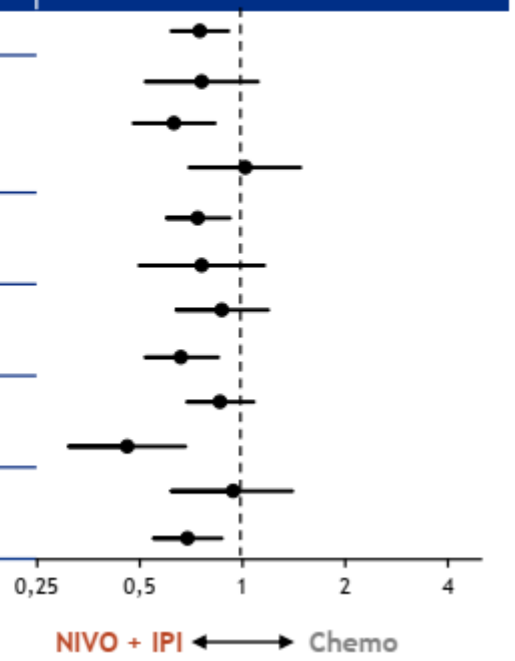
Minimum follow-up: 22.1 months; median follow-up: 29.7 months.

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.

P Baas et al IASLC Presidential Symposium 2020

Primary endpoint: Overall survival

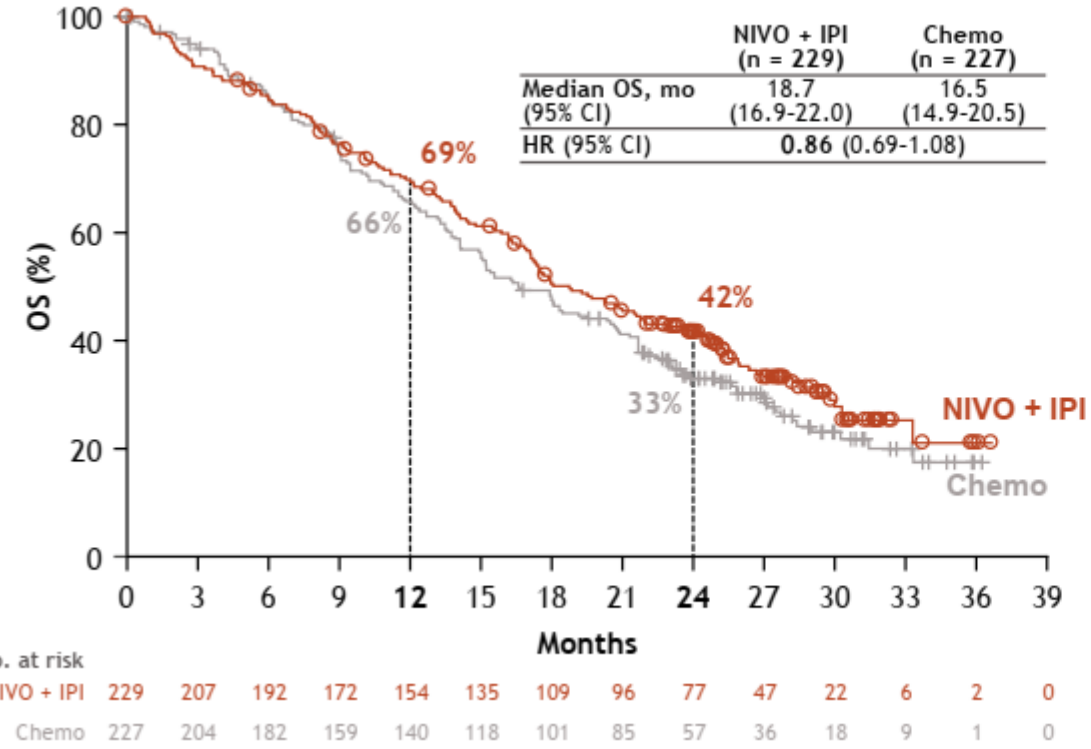
Subgroup	Median OS, mo		Unstratified HR	Unstratified HR (95% CI)
	NIVO + IPI n = 303	Chemo n = 302		
All randomized (N = 605)	18.1	14.1	0.75[a]	
< 65 years (n = 167)	17.2	13.3	0.76	
≥ 65 to < 75 years (n = 281)	20.3	14.9	0.63	
≥ 75 years (n = 157)	16.9	15.4	1.02	
Male (n = 467)	**17.5**	**13.7**	**0.74**	
Female (n = 138)	**21.4**	**18.0**	**0.76**	
ECOG performance status 0 (n = 242)	20.7	19.5	0.87	
ECOG performance status ≥ 1 (n = 363)	17.0	11.6	0.66	
Epithelioid (n = 456)	**18.7**	**16.5**	**0.86**	
Non-epithelioid (n = 149)	**18.1**	**8.8**	**0.46**	
PD-L1 < 1% (n = 135)	17.3	16.5	0.94	
PD-L1 ≥ 1% (n = 451)	18.0	13.3	0.69	



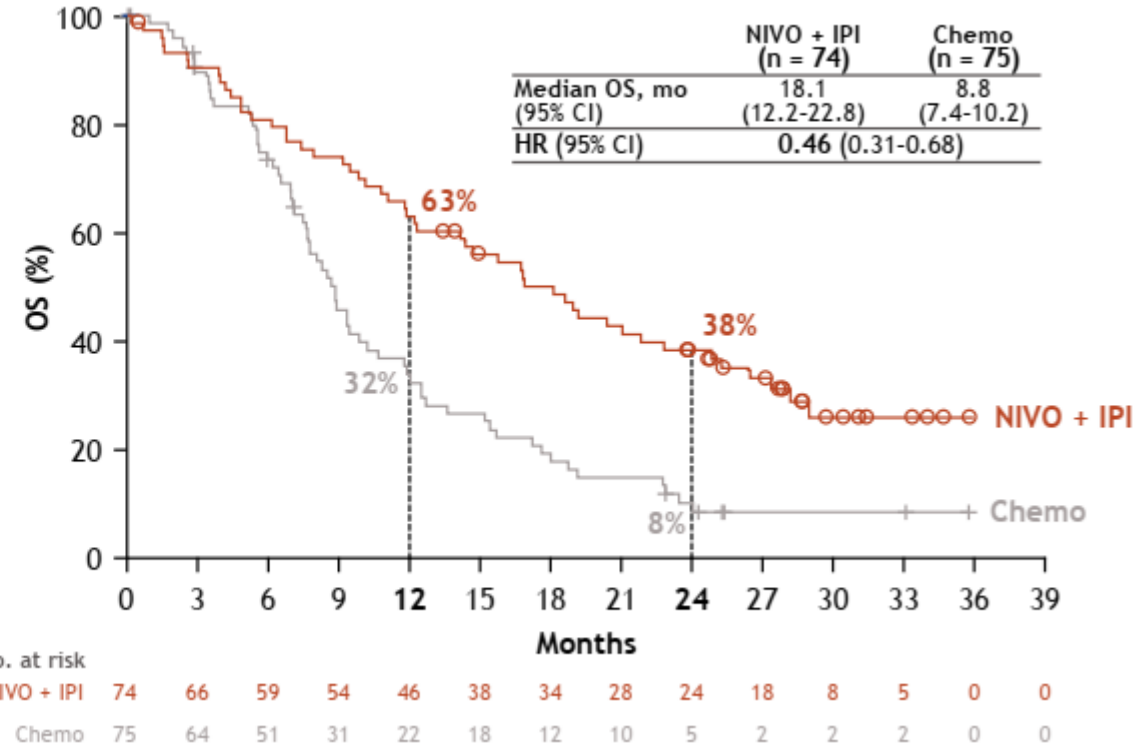
P Baas et al IASLC Presidential Symposium 2020

Overall survival by histology[a]

Epithelioid



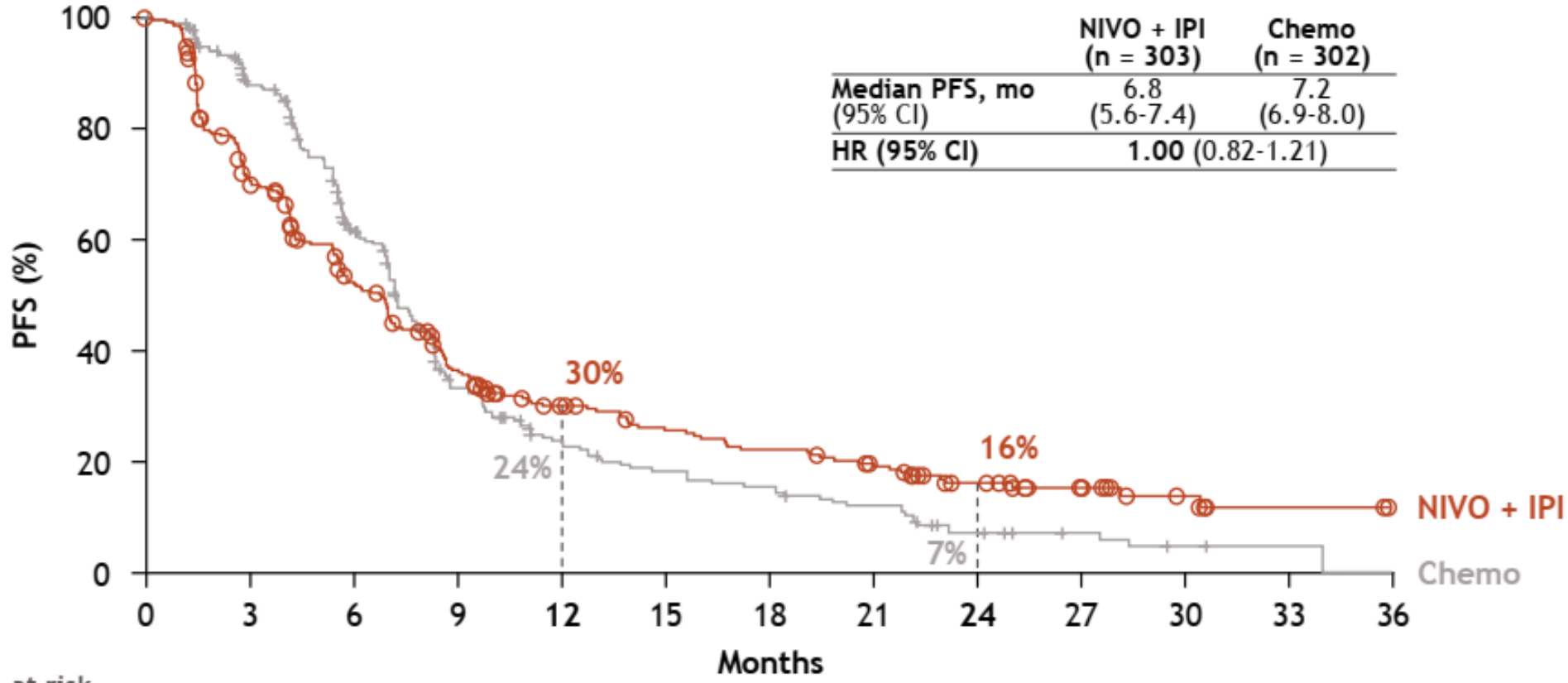
Non-epithelioid



P Baas et al IASLC Presidential Symposium 2020

Progression-free survival by BICR[a]

	NIVO + IPI (n = 303)	Chemo (n = 302)
Median PFS, mo (95% CI)	6.8 (5.6-7.4)	7.2 (6.9-8.0)
HR (95% CI)	1.00 (0.82-1.21)	

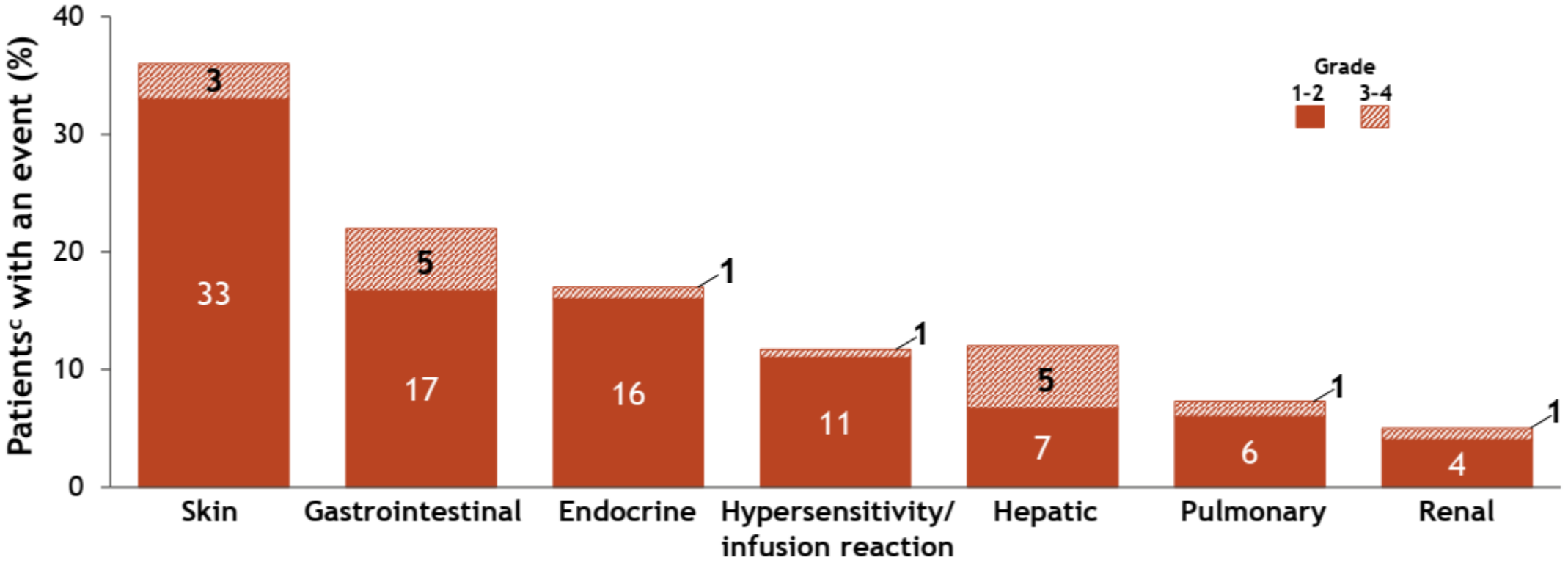


No. at risk

NIVO + IPI	303	198	135	89	64	52	45	36	22	15	7	2	0
Chemo	302	222	144	71	44	33	27	21	10	6	3	1	0

P Baas et al IASLC Presidential Symposium 2020

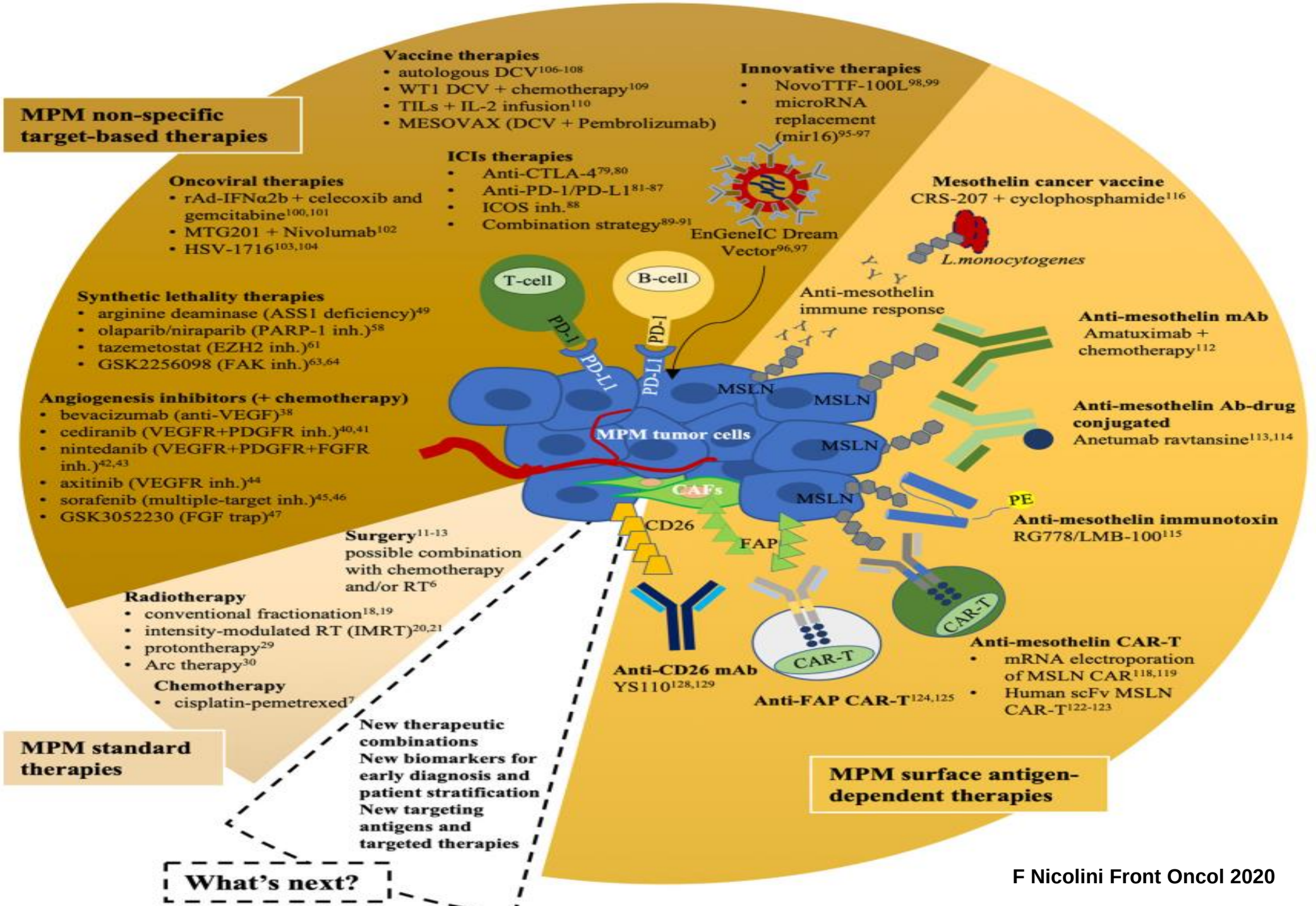
Treatment-related select AEs with NIVO + IPI[a,b]



- This is the first positive randomized trial of dual immunotherapy in first line treatment of patients with unresectable MPM and therefore NIVO+ IPI should be considered as a new standard of care

FDA approval on 02 Oct 2020

P Baas et al IASLC Presidential Symposium 2020



F Nicolini Front Oncol 2020

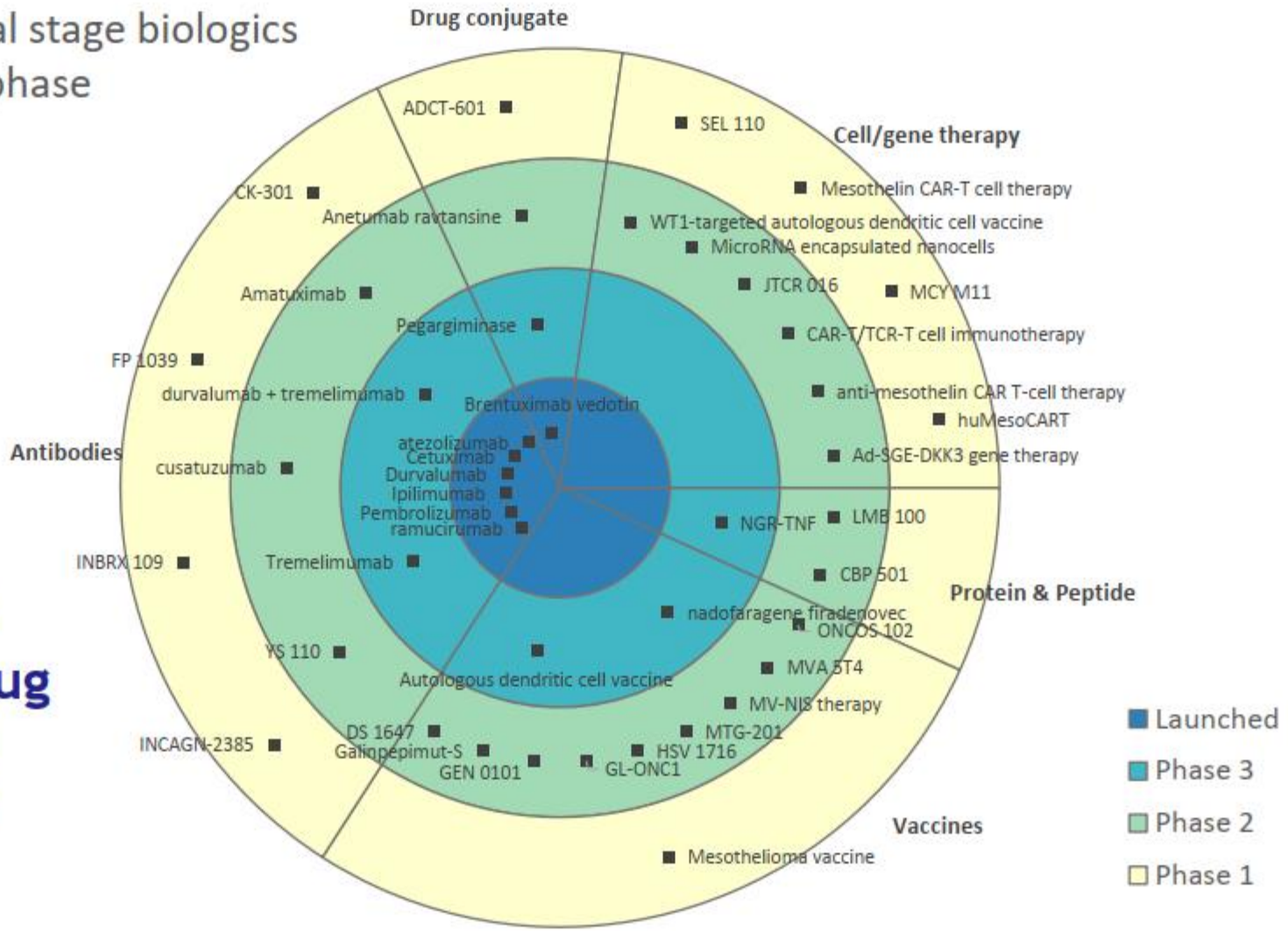
IO studies in MPM

VEGF-R 1–3, FGF-R 1–4, and PDGF-R α

Study	Phase	# pts	location	
Pembrolizumab Plus Lenvatinib In Second Line and Third Line Malignant Pleural mesotheLioma Patients	2	36	Netherlands	NCT04287829
Pembrolizumab With or Without Anetumab Ravtansine in Treating Patients With Mesothelin-Positive Pleural Mesothelioma	2	134	USA	NCT03126630
Phase II Nivolumab and Ramucirumab for Patients With Previously-Treated Mesothelioma	2	35	USA	NCT03502746
MTG201 + nivolumab	2	12	USA	NCT04013334
BEAT-meso: Bevacizumab and Atezolizumab in Malignant Pleural Mesothelioma	3	320	ETOP	NCT03762018
Autologous Dendritic Cell Vaccination in Mesothelioma	1/2	12	Belgium	NCT02649829
Phase 1/2 Trial of TC-210 T Cells in Patients With Advanced Mesothelin-Expressing Cancer	1/2	70	USA	NCT03907852

Slide adapted from Baas P ESMO Preceptorship 2020 Manchester

Mesothelioma – Clinical stage biologics by highest phase



You need a single phase for each drug for visualizations like the bullseye!

http://www.bizint.com/pdfs/Pipeline_TownHall_Webinar_2020April.pdf

CONCLUSIONS

1/ Mesothelioma incidence is still increasing in many (also European) countries

2/ Treating MPM patients is a challenging task but …

3/ … new treatment options (IO; TT; combinations) are being evaluated in clinical trials

4/ Need for good predictive biomarkers in IO treatment (also in combined therapies)

5/ New immunologic therapies, dendritic cell vaccination, … being studied

6/ Advise your MPM patients to take part in clincical trials