MESOTHELIOMA – RISK FACTORS, STAGING, THERAPY AND ROLE OF TARGETED AGENTS

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INTRODUCTION

- Malignant mesothelioma is a tumour arising from the mesothelial lining of the pleura, peritoneum, pericardium and tunica vaginalis
- Pleural mesothelioma is the most common of these, accounting for approximately 90% of disease
- Incidence : 1 to 2 persons per million of the general population

Robinson et al. Ann Cardiothorac Surg 2012;1(4):491-496

Rossini et al. Front Oncol. 2018 Apr 3;8:91

CLASSIFICATION OF PLEURAL TUMOURS- WHO 2015

Mesothelial tumors

- **Diffuse malignant mesothelioma**

1. Epithelioid mesothelioma
2. Sarcomatoid mesothelioma
   Desmoplastic mesothelioma
3. Biphasic mesothelioma

- **Localised malignant mesothelioma**

1. Epithelioid mesothelioma
2. Sarcomatoid mesothelioma
3. Biphasic mesothelioma

- **Well differentiated papillary mesothelioma**
- **Adenomatoid tumor**

Lymphoproliferative disorders

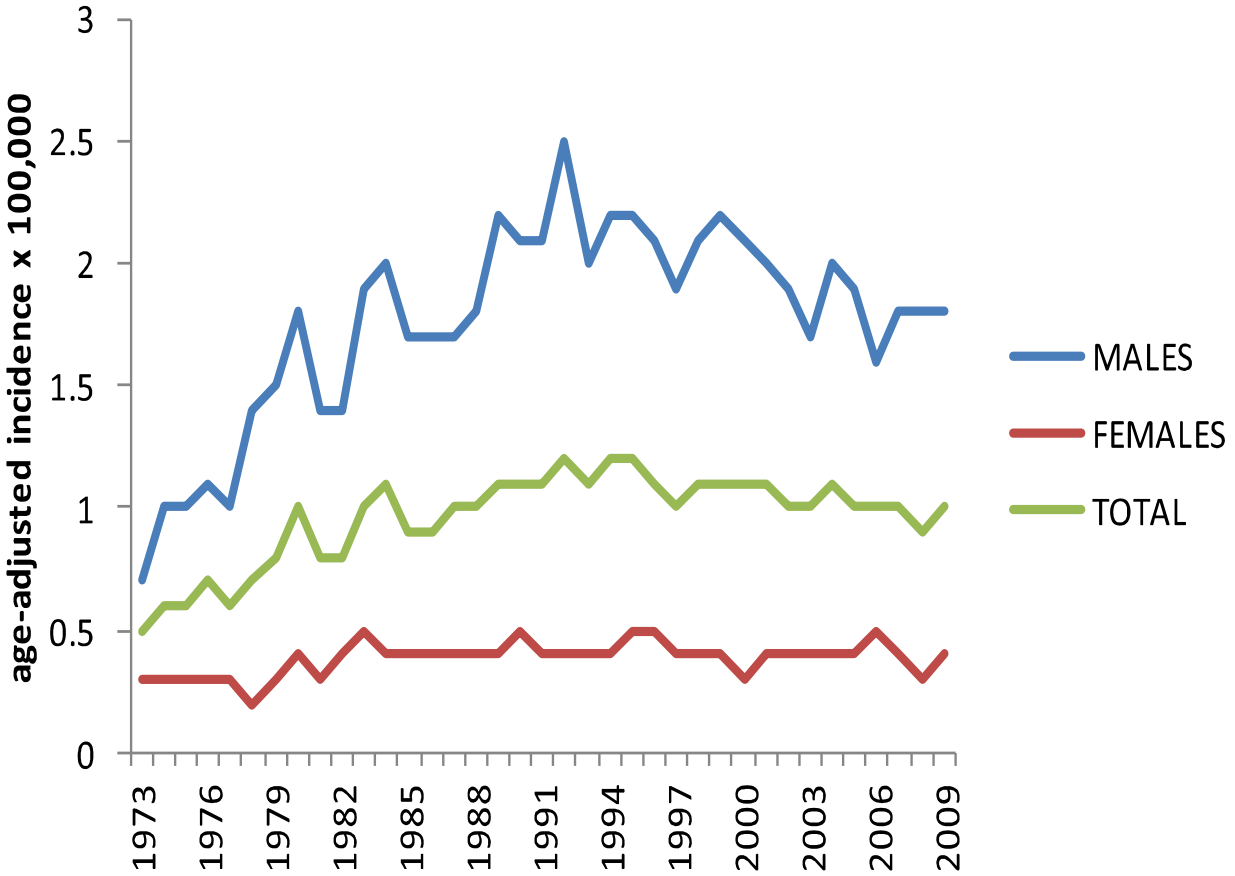
1. Primary effusion lymphoma
2. Diffuse large B-cell lymphoma associated with chronic inflammation

Mesenchymal tumors

1. Epithelioid hemangioendothelioma
2. Angiosarcoma
3. Synovial sarcoma
4. Solitary fibrous tumor
5. Malignant solitary fibrous tumor
6. Desmoid-type fibromatosis
7. Calcifying fibrous tumor
8. Desmoplastic round cell tumor

Galateau-Salle et al. Journal of Thoracic Oncology 2015. Vol. 11 No. 2: 142-154

EPIDEMIOLOGY OF MALIGNANT PLEURAL MESOTHELIOMA



- NEW MPM CASES MAXIMUM IN 1980s and 1990s
- NOW PLATEAUING

Taioli et al. Ann Thorac Surg 2014;98:1020–5

RISK FACTORS

1. Asbestos exposure (occupational and non- occupational)
2. Non asbestos minerals
3. Radiation exposure
4. Chronic inflammation
5. Simian virus 40
6. Genetic susceptibility
7. Old age
8. Male gender

Attanoos et al. Arch Pathol Lab Med. 2018 Jun;142(6):753-760

ASBESTOS

- Fibrous mineral with physical and chemical properties that make it resistant to heat and degradation
- Used extensively in factories of India
- > 80% cases of mesothelioma attributed to asbestos exposure
- Serpentine group
  - Chrysotile (95 % of worldwide used asbestos)
- Amphibole group (less commonly used but higher risk of malignancies)
  - Anthophyllite
  - Tremolite
  - Amosite
  - Crocidolite

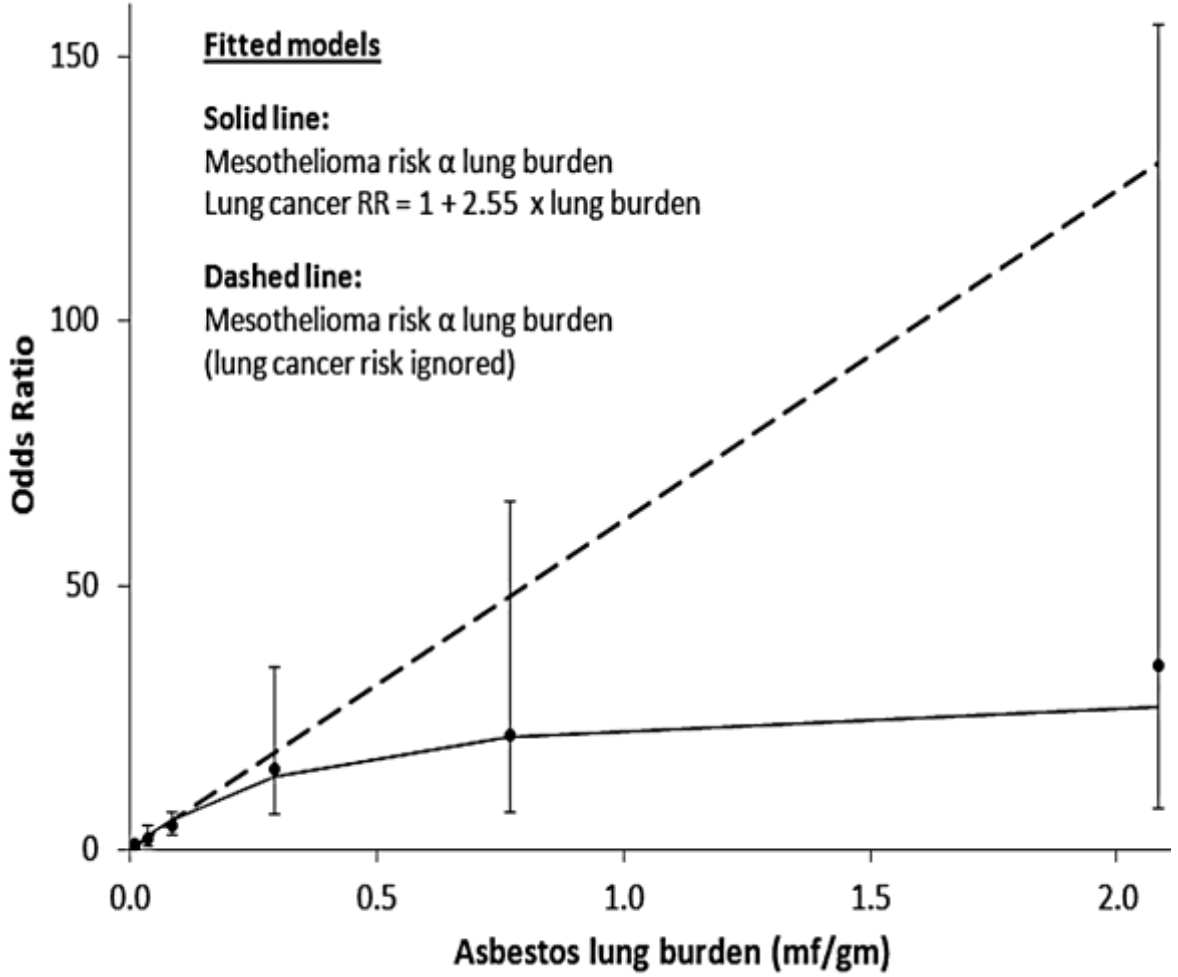
Robinson et al. Ann Cardiothorac Surg 2012;1(4):491-496

OCCUPATIONAL SOURCE

Job category and occupation	*All men* *Cases*	*Controls*	*OR (95% CIs)*
Non-construction high risk			
Metal plate worker	6	5	4.1 (1.2, 14.1)
Asbestos product manufacturer	1	0	-
Laggers & electrical, energy, boiler attendants	4	1	15.6(1.7 (142.8)
Docker, shipbuilding or working on board ship	16	13	4.1 (1.9, 8.8)
Navy	2	0	-
All non-construction high risk jobs	**29**	**19**	**5.2 (2.8, 9.6)**
Construction			
Carpenter	**57**	**21**	**10.5 (6.1, 18.1)**
Plumber	19	18	4.3 (2.2, 8.4)
Electrician	23	23	3.9 (2.1, 7.2)
Painters & decorators	17	16	4.3 (2.1, 8.7)
Plumbers, electricians & painters & decorators	**59**	**57**	**4.1 (2.7, 6.2)**
Other construction	**54**	**73**	**2.8 (1.9, 4.2)**
Medium risk industrial			
Metal working production & maintenance fitters	13	19	2.5 (1.2, 5.2)
Railway worker	1	6	0.7 (0.1, 5.6)
Chemist or industrial scientist	4	11	1.3 (0.4, 4.2)
Surveyor or inspector	14	39	1.3 (0.7, 2.6)
Metal machining & instrument makers nec.	6	13	1.8 (0.7, 5.0)
Electrical & electronic trades nec.	8	21	1.3 (0.6, 3.0)
Welding, steel erecting & fixing	5	10	1.7 (0.6, 5.2)
Metal working process operatives	0	16	-
Assemblers & routine process operatives	9	25	1.2 (0.6, 2.7)
Plant & machine operatives nec.	9	20	1.6 (0.7, 3.6)
All medium risk industrial jobs	**69**	**180**	**1.4 (1.0, 1.9)**
Low risk industrial			
Motor mechanic	7	12	2.2 (0.9, 5.9)
Draughtsmen	4	7	1.7 (0.5, 6.1)
Engineers & technologists nec.	13	23	2.2 (1.1, 4.4)
Stores & warehousemen	4	24	0.7 (0.2, 1.9)
Armed forces nec.	0	1	-
Drivers & road transport workers	30	63	1.7 (1.1, 2.8)
Other industrial not elsewhere classified	46	108	1.6 (1.0, 2.3)
All low risk industrial jobs	**104**	**238**	**1.6 (1.2, 2.2)**

Gilham C et al. Occup Environ Med 2016;73:290–299

INTENSITY OF EXPOSURE



- Transmission Electron Microscopy done on postmortem lung specimens of proven mesothelioma and lung cancer patients
- Mesothelioma 133 cases
- Lung cancer 262 cases
- P= 0.02

Gilham C, et al. Occup Environ Med 2016;73:290–299

DURATION AND TIME SINCE LAST EXPOSURE

Total duration of exposure yrs	Model 1[#]		Model 2[¶]	
	Times since last exposure yrs[+]	OR (95% CI)	Age at first exposure yrs[§]	OR (95% CI)
<30	10	1.5 (0.8–2.4)	15	1.1 (0.4–2.9)
	20	2.0 (1.0–3.9)	20	1.3 (0.4–1.3)
	30	2.4 (1.2–4.7)	25	1.0 (0.3–2.9)
	40	2.3 (1.1–4.8)	30	0.6 (0.2–2.0)
	50	1.9 (0.7–5.0)	35	0.5 (0.1–1.7)
⩾30	10	1.3 (0.72–2.4)	15	1.1 (0.3–3.8)
	20	3.1 (1.23–7.6)	20	0.7 (0.2–2.6)
	30	4.5 (0.89–22.3)	25	0.3 (0.1–1.2)
	40		30	0.2 (0.0–0.7)
	50		35	0.1 (0.0–0.5)

LONG LATENCY BETWEEN EXPOSURE AND MPM
EARLIER THE AGE OF EXPOSURE , HIGHER THE RISK
RISK DECREASES AFTER 30 YEARS SINCE LAST EXPOSURE

Lacourt et al. Eur Respir J 2012; 39: 1304–1312

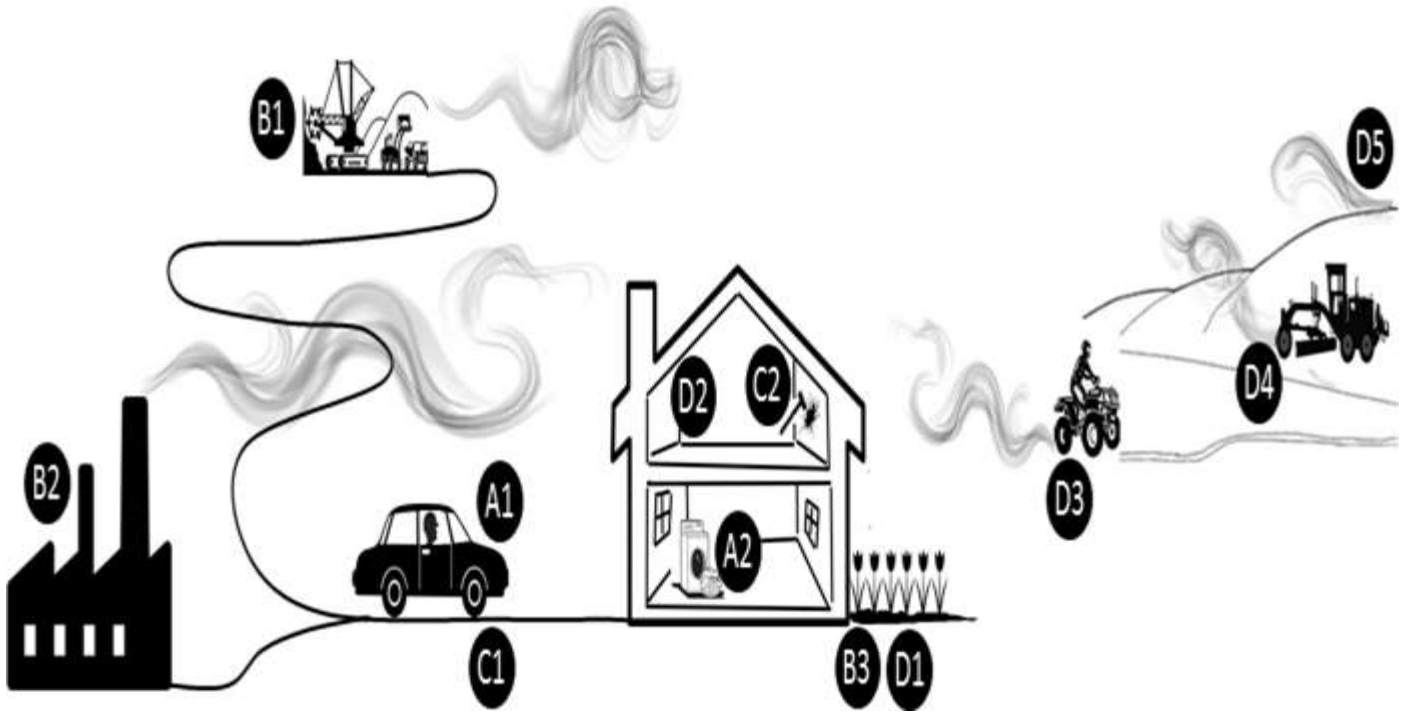
TYPE OF EXPOSURE

Highest occupational exposure category	Asbestos lung burden (million fibres per dry gram) 0–	0.025–	0.05–	0.2–	0.5–	≥1.0	Total	Meso OR vs population controls*	Mean asbestos lung burden (million fibres per dry gram) Amosite	Crocidolite	Other amphiboles	Chrysotile	All asbestos
Non-construction high-risk occupations													
Mesothelioma	5	3	11	7	6	4	36	17.5	0.375	0.094	0.014	0.005	0.487
Lung cancer	15	1	9	1	3	0	29		0.100	0.013	0.003	0.005	0.121
Carpenters													
Mesothelioma	1	2	5	3	7	5	23	34.2	0.811	0.021	0.016	0.003	0.852
Lung cancer	3	1	3	2	0	0	9		0.088	0.002	0.005	0.000	0.095
Plumbers, electricians and painter/decorators													
Mesothelioma	5	3	10	8	2	2	30	15.9	0.148	0.074	0.004	0.002	0.228
Lung cancer	12	4	5	3	1	1	26		0.095	0.040	0.006	0.001	0.143
Other construction or other reported exposure													
Mesothelioma	3	0	2	0	0	1	6	5.1	0.056	0.192	0.000	0.000	0.248
Lung cancer	28	3	13	1			45		0.027	0.004	0.002	0.002	0.036
Medium risk industrial													
Mesothelioma	3	0	2	3	0		8	4.1	0.069	0.057	0.010	0.001	0.137
Lung cancer	22	5	7	1	0	1†	36		0.078†	0.015†	0.005	0.001	0.098†
Domestic exposure													
Mesothelioma	0	0	2				2	2.1	0.035	0.060	0.000	0.000	0.094
Lung cancer	4	4	0				8		0.009	0.004	0.006	0.001	0.020
Low-risk occupations													
Mesothelioma	1	0	1				2	1.0 (ref)	0.015	0.018	0.005	0.000	0.038
Lung cancer	21	4	4				29		0.010	0.003	0.007	0.002	0.021
Total													
Mesothelioma	18	8	33	21	15	12	107		0.351	0.073	0.010	0.003	0.438
Lung cancer	105	22	41	8	4	2	182		0.058†	0.012†	0.004	0.002	0.077†

- HIGHER ASBESTOS LUNG BURDEN FOR MESOTHELIOMA THAN LUNG CANCER
- AMOSITE AND CROCIDOLITE CONTRIBUTE TO MAJORITY OF MPM

Gilham C, et al. Occup Environ Med 2016;73:290–299

NON OCCUPATIONAL ASBESTOS EXPOSURE



A. Paraoccupational exposure
B. Environmental exposure from industrial operations.
C. Exposure to commercial asbestos-containing products.
D. Naturally occurring asbestos (NOA)

Noonan et al. Ann Transl Med 2017;5(11):234

DOES BENIGN ASBESTOS RELATED PLAQUES CONFER RISK OF MALIGNANCY?

AUTHOR4	POPULATION	PLEURAL PLAQUES OR THICKENING	INDICATOR OF MESOTHELIOMA RISK
Hillerdal et al	General	Yes , n= 1596	RR= 11.25
Karjalainen et al	Occupational diseases registry	Yes, n=4887	RSI=5.5
Sanden and Jarvholm	Shipyard workers	Yes, n= 835 No, n= 1852	4 cases (0.5%) 7 cases (0.7%)
Koskinen et al	Construction workers	Yes, n=6563 No, n=10132	RR=0.93 RSI= 1.19
Reid et al	Crocidolite miners and non- miner residents of same town		ADJUSTED RR 1.12

- The presence of pleural plaques per se is not associated with an increased risk of pleural mesothelioma.
- However, pleural plaques reflect asbestos exposure, which is associated with pleural mesothelioma

RSI-STANDARDIZED INCIDENCE RATIO
RR- RELATIVE RISK

Ameille et al. Revue des Maladies Respiratoires (2011) 28, e11—e17

ASBESTOS IN INDIA

- Still not banned in India
- World Health Organization (WHO) -In 2014, non-communicable diseases in India accounted for 60% of total deaths. Within this 60%, asbestosis and mesothelioma comprised 13% of the total deaths in India
- In 2015, in an order of the National Green Tribunal, the legal counsel representing the Indian Bureau of Mines stated “that there is no asbestos mining presently operational anywhere in the country and the operations of the mines of associated minerals with asbestos has also been halted ”

The Occupational and Environmental Health Network of India (OEHNI), April 28, 2017

NOT MINED BUT STILL BEING IMPORTED

1: Asbestos Imports (2004-2014)

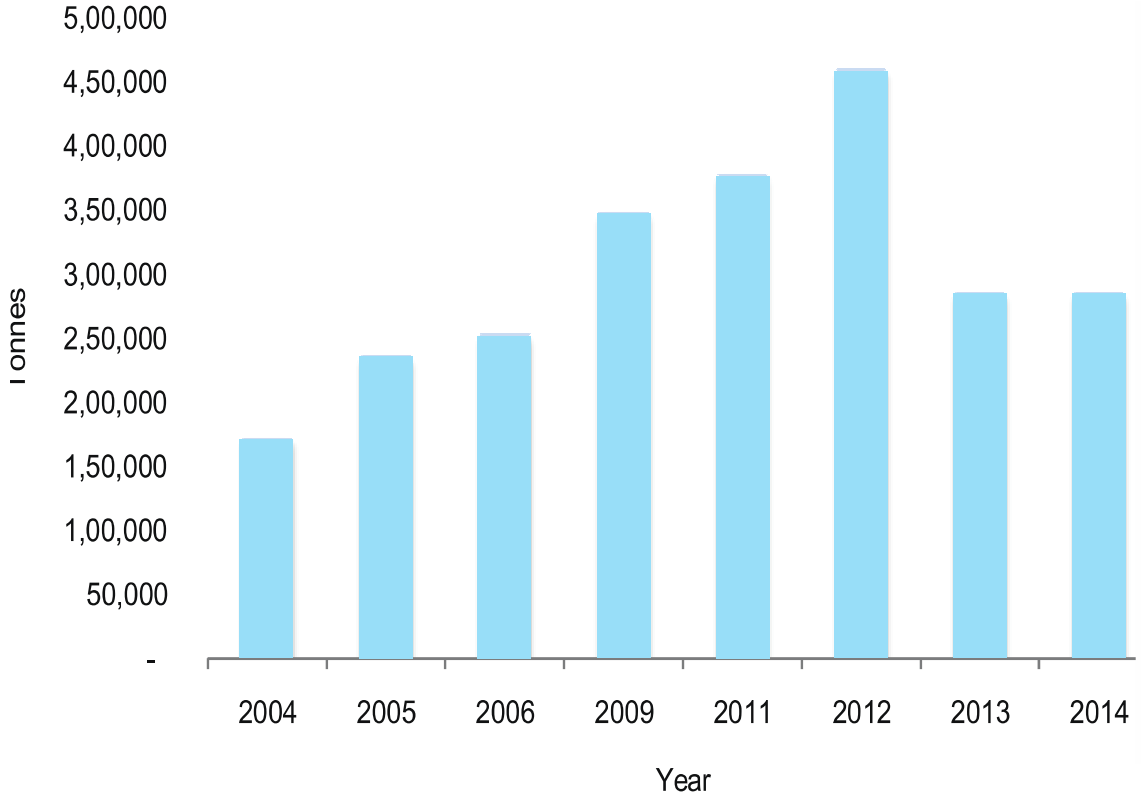
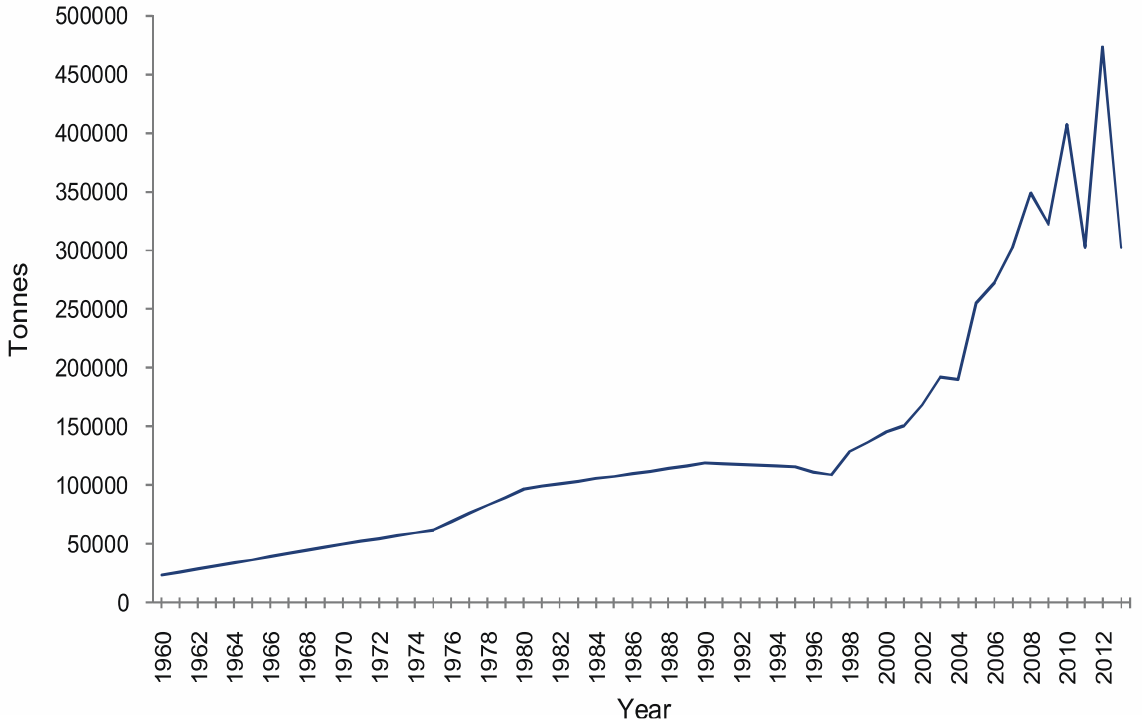


Figure 2: Indian Asbestos Consumption (tonnes)



The Occupational and Environmental Health Network of India (OEHNI), April 28, 2017

MINERALS OTHER THAN ASBESTOS

MINERAL	SOURCE	EVIDENCE
ERIONITE	VOLCANIC REGIONS	PROVEN IN MANY HUMAN STUDIES
FLUORO- EDENITE	BUILDING MATERIAL FOR ROADS AND RESIDENTIAL CONSTRUCTION	ANIMAL STUDIES
BALANGEROITE	INTERGROWN WITH CHRYSOLITE	CONTROVERSIAL HUMAN CASE REPORTS
CARBON NANOTUBES	GRAPHENE CYLINDERS	ANIMAL STUDIES

Attanoos et al. Arch Pathol Lab Med. 2018 Jun;142(6):753-760

RADIATION EXPOSURE

EVIDENCE- CASE REPORTS, CASE SERIES, RETROSPECTIVE COHORT STUDIES

SOURCES

1. Therapeutic irradiation for tumors -Hodgkin and non- Hodgkin lymphoma, germ cell neoplasms, Wilms tumor of the kidney, and breast cancer
2. Radioactive thorium dioxide contrast medium ‘‘Thorotrast’
3. Atomic energy/nuclear industry workers
4. Radiation technologists exposed to external gamma-ray emission and internal radionuclides

Attanoos et al. Arch Pathol Lab Med. 2018 Jun;142(6):753-760

CHRONIC INFLAMMATION

Case reports

- After therapeutic plombage post tuberculosis and in individuals with long- standing chronic empyema

Attanoos et al. Arch Pathol Lab Med. 2018 Jun;142(6):753-760

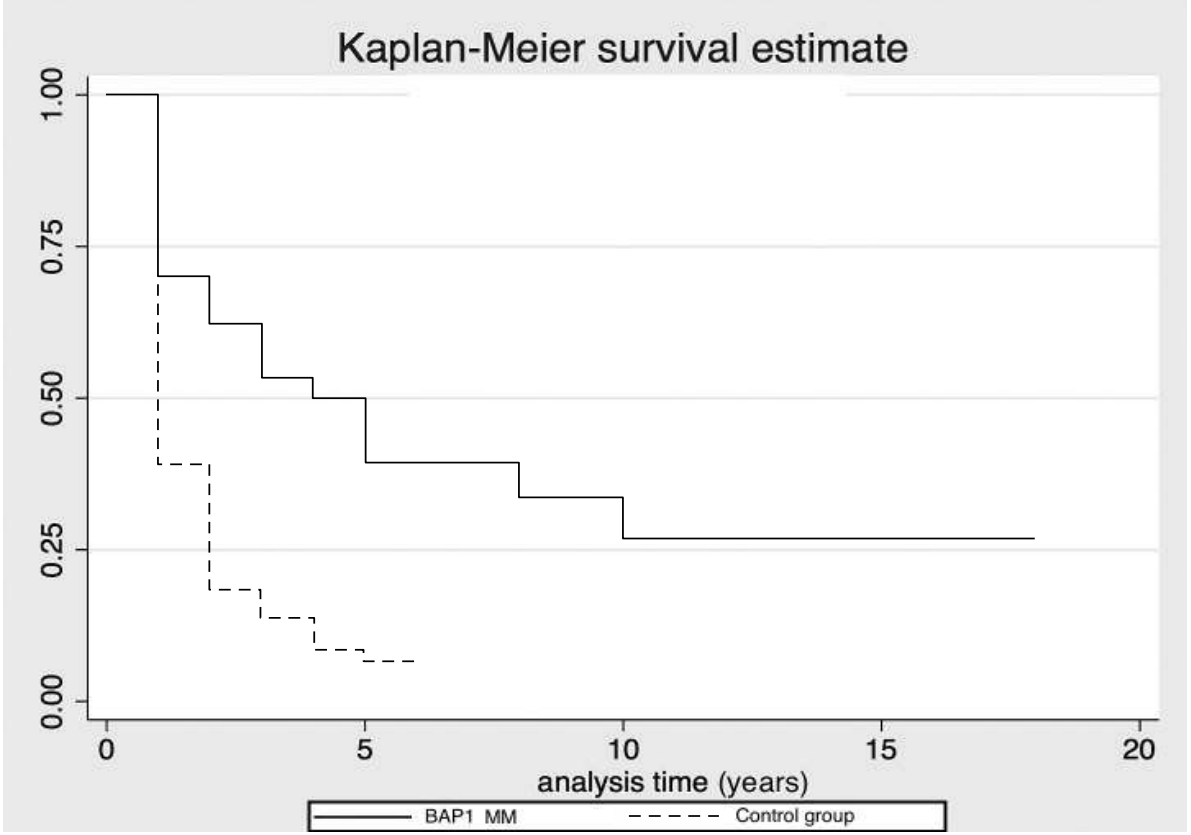
SIMIAN VIRUS 40

- SV40 is a DNA polyomavirus that commonly infects Asian macaque monkeys
- Human exposure to SV40 is believed to have largely occurred after administration of contaminated live and attenuated poliovirus vaccines, prepared from infected monkey kidney tissue culture cell lines
- Viral genome encodes several oncogenic proteins, most notably large T-antigen (Tag), which inactivate the tumor suppressor activity of p53 and p-retinoblastoma family proteins
- Detection rates of SV40 in human mesothelioma show considerable variability
- The role of SV40 as an etiologic agent in human mesotheliomas is unconvincing

Attanoos et al. Arch Pathol Lab Med. 2018 Jun;142(6):753-760

GENETIC SUSCEPTIBILITY

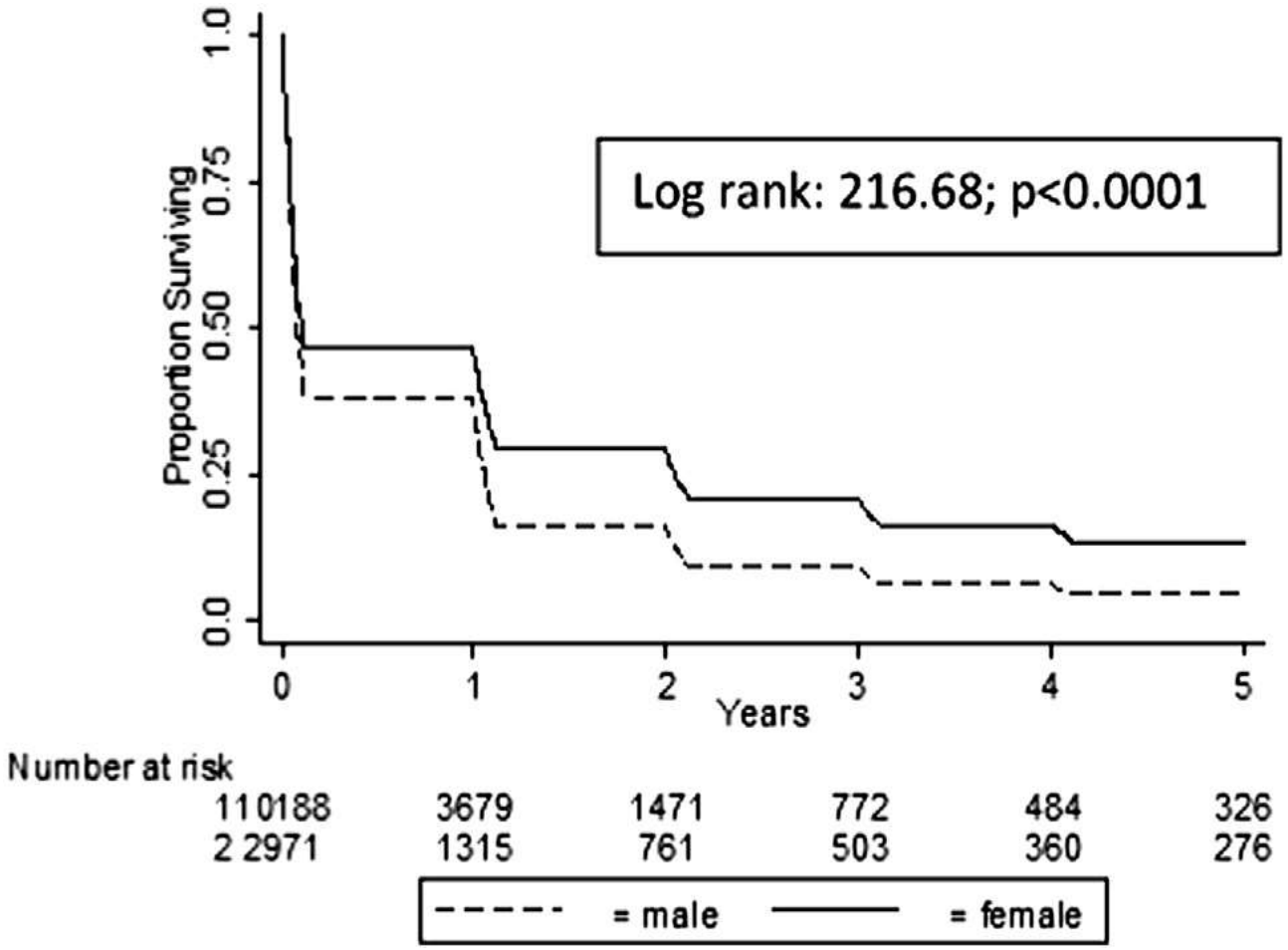
- BAP-1 (BRCA1-associated protein–1)
- Nuclear localizing deubiquitinating hydrolase enzyme
- Located on chromosome 3p
- Tumour suppressor gene
- Younger age at diagnosis (56.3 versus 72 years)
- Lower M:F ratio (0.73:1 versus 4:1
- Higher percentage of peritoneal MM (50 versus 14.2%)
- 7 fold better survival



Attanoos et al. Arch Pathol Lab Med. 2018 Jun;142(6):753-760

Baumann et al. Carcinogenesis. 2015 Jan;36(1):76-81

MALE GENDER



- PREVALENCE MORE IN MALES
- ALSO SURVIVAL LESS IN MALES

NOTE : UNTREATED CASES SURVIVAL M=F

Taioli et al. Ann Thorac Surg 2014;98:1020–5

CLINICAL MANIFESTATIONS

Symptom	No. of cases	%
Pain	62	69
Non-pleuritic	56	
Pleuritic	6	
Shortness of breath	53	59
Fever, chills or sweats	30	33
Weakness, fatigue or malaise	30	33
Cough	24	27
Weight loss	22	24
Anorexia	10	11
Sensation of heaviness or fullness in chest	6	7
Hoarseness	3	3
Early satiety	2	2
Myalgias	2	2
Others*	1 each	1

Right side predominance 1.6 : 1
Clubbing less common

Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

TNM 8 STAGING

T STAGE	PRIMARY TUMOUR
TX	Primary lesion couldn't be assessed
T0	No evidence of primary tumor
T1	Limited to the **ipsilateral parietal pleura ±** Visceral pleura/mediastinal pleura/diaphragmatic pleura
T2	**Ipsilateral pleura +** **1. Diaphragmatic muscle (or)** **2. Underlying lung parenchyma**
T3	Locally advanced but potentially resectable tumor **Ipsilateral pleura +** **1. Endothoracic fascia or** **2. Mediastinal fat or** **3. Solitary resectable chest wall involvement or** **4. Non-transmural pericardial involvement**
T4	Locally advanced technically unresectable tumor **Ipsilateral pleura +** **1. Diffuse/multifocal chest wall involvement ± rib destruction or** **2. Direct transdiaphragmatic extension into peritonium or** **3. Direct extension to contralateral pleura/mediastinal organs/spine/internal surface of pericardium/myocardium**

Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

TNM 8 STAGING

N STAGE	REGIONAL LYMPH NODES
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis to the ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal) lymph nodes
N2	Metastases in the contralateral mediastinal, ipsilateral, or contralateral supraclavicular lymph nodes

	T	N	M
IA	T1	N0	M0
IB	T2-T3	N0	M0
II	T1-T2	N1	M0
IIIA	T3	N1	M0
IIIB	T1-T3 T4	N2 Any N	M0
IV	Any T	Any N	M1

M STAGE	DISTANT METASTASIS
M0	No metastasis
M1	Metastasis

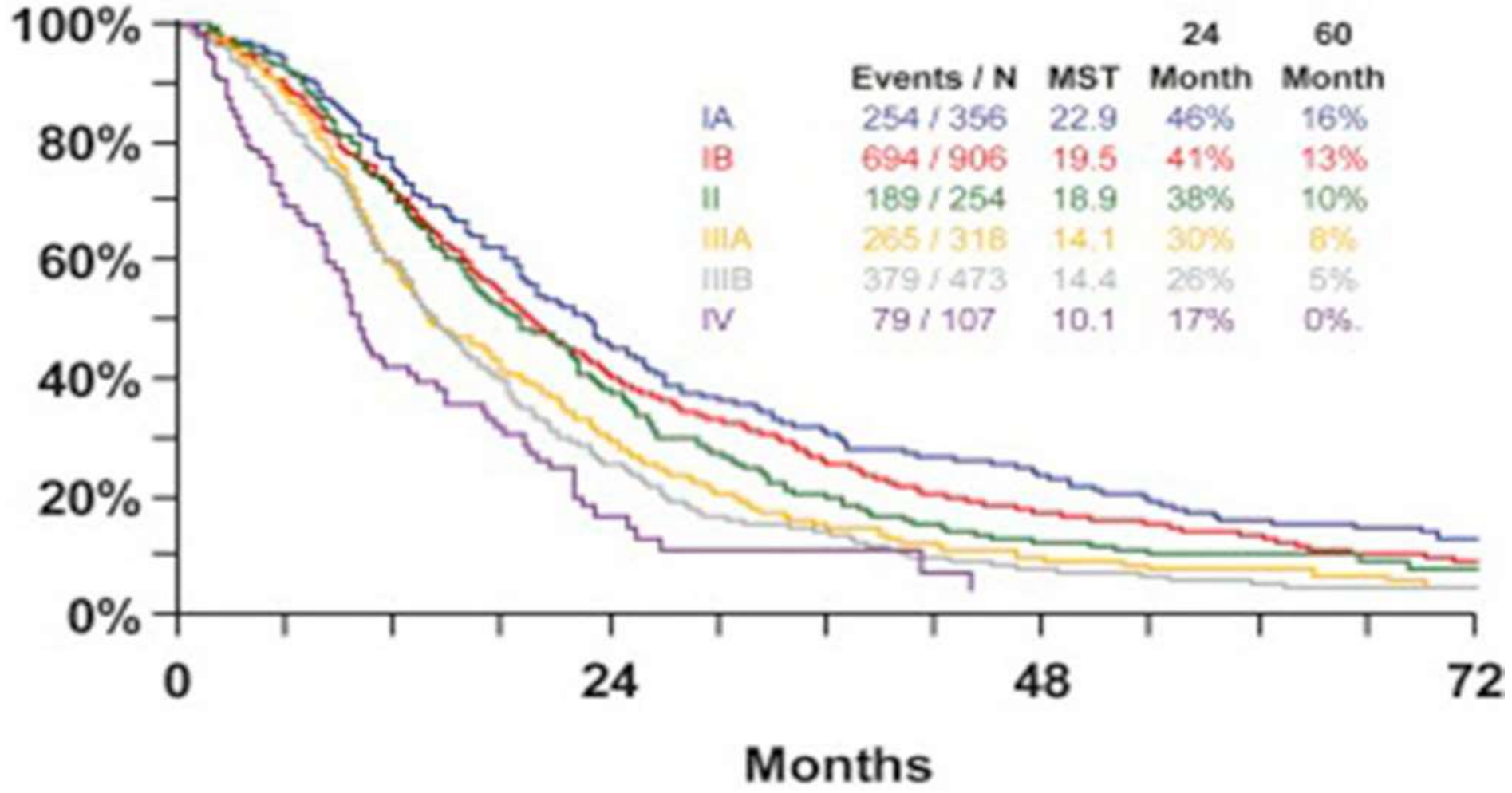
Woolhouse I, et al. Thorax 2018;73:i1–i30

TNM 7 VS TNM 8

	N0		N1/N2	N1	N3	N2
Stage	Seventh edition	Eighth edition	Seventh edition	Eighth edition	Seventh edition	Eighth edition
T1	I (A, B)	IA	III	II	IV	IIIB
T2	II	IB	III	II	IV	IIIB
T3	II	IB	III	IIIA	IV	IIIB
T4	IV	IIIB	IV	IIIB	IV	IIIB
M1	IV	IV	IV	IV	IV	IV

Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

OVERALL SURVIVAL AS PER TNM 8



Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

DIAGNOSIS

1. CT
2. MRI
3. PET CT
4. TISSUE DIAGNOSIS AND IHC

BENIGN VS MPM

Morphology	Imaging modality	Sensitivity (%)	Specificity (%)
Pleural thickening > 1 cm	CT	35 – 47	64 – 94
	Ultrasound (US)	42 (95% CI 26% to 61%)	95 (95% CI 74% to 99%)
Pleural nodularity	CT	37–48	86–97
	MRI	48	86
	US	42 (95% CI 26% to 61 %)	100 (95% CI 82% to 100 %)
Infiltration of the chest wall and/or diaphragm	CT	17–29	100
	MRI	44	100
Mediastinal pleural involvement	CT	70–74	83–93
	MRI	77	93
Interlobar fissure nodularity	CT	10	100

Overall reported diagnostic accuracy of CT in the detection of pleural malignancy is 68%–97%, with

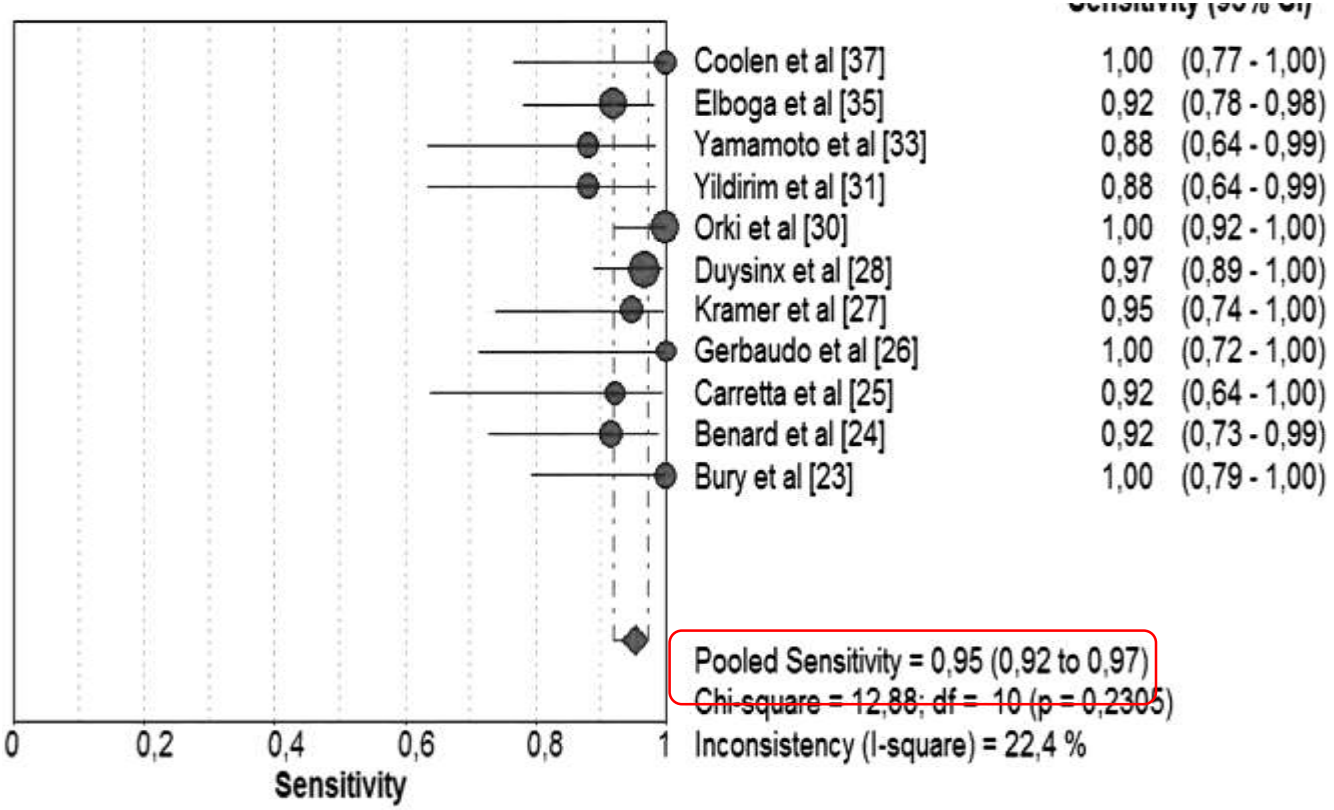
Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

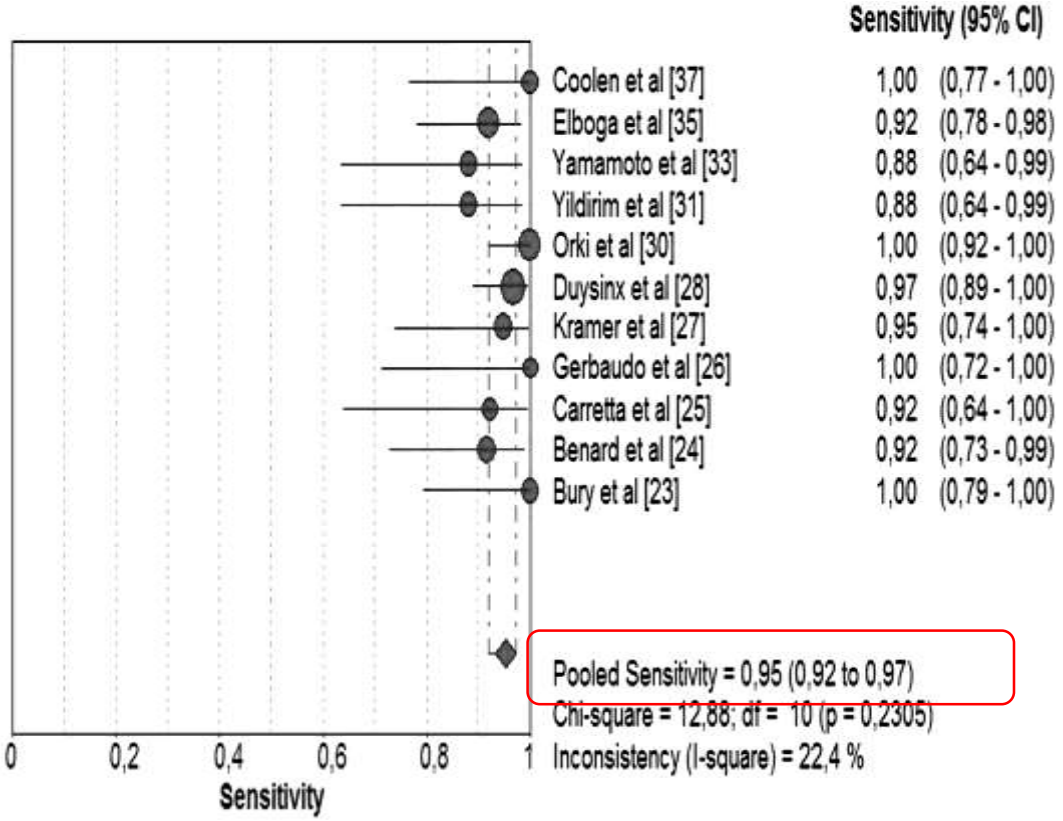
CT vs MRI

Imaging modality	Stage II		Stage III	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
CT	100	69.20	75	100
MRI	87.50	87.50	91	100
PET-CT	100	100	100	100

Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

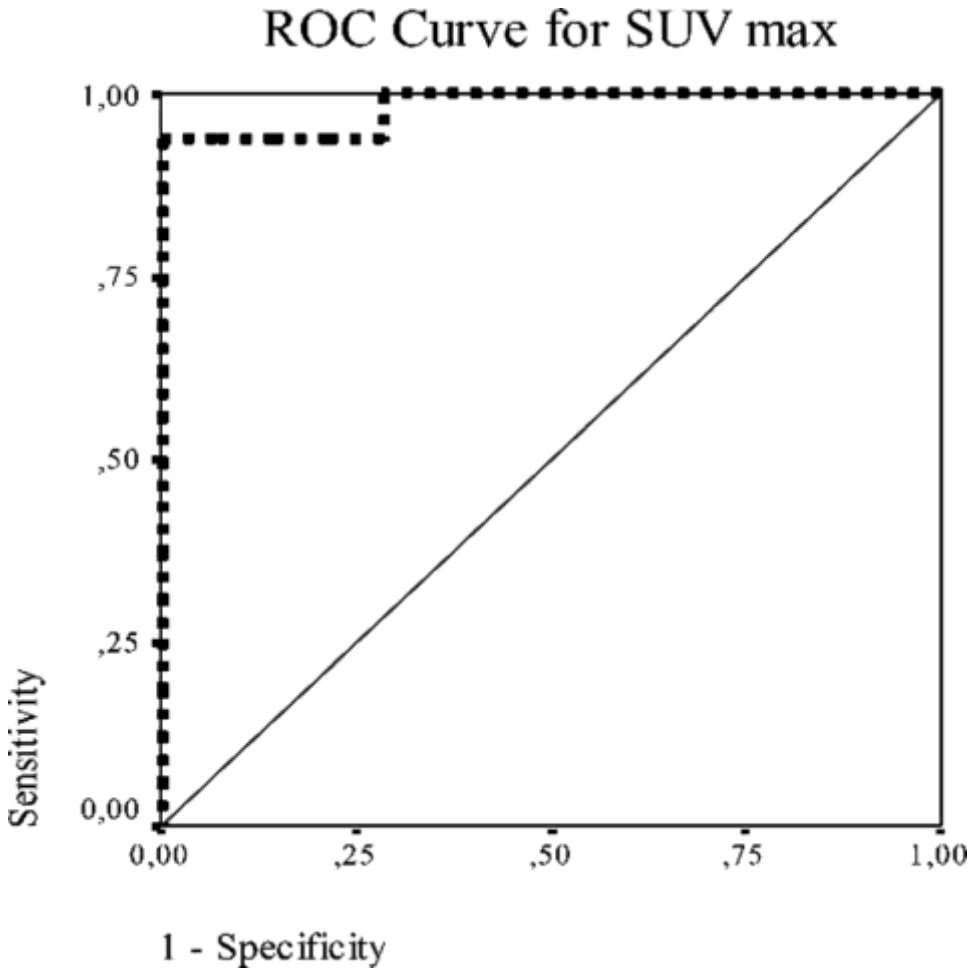
ROLE OF PET CT





Treglia G et al. Acad Radiol. 2014 Jan;21(1):11-20

PET CT IN DIAGNOSING MPM



AUC for SUV max 0.983

- 40 patients with undiagnosed pleural effusion underwent PET/CT followed by tissue diagnosis
- Mean SUVmax **6.5 ± 3.4 vs 0.8 ± 0.6** (p < 0.001) for MPM vs Benign pleural disease
- **At a SUV > 2.2**

Sensitivity 94.1 %

Specificity. 100 %

PPV 100 %

NPV 93.3 %

Yildirim et al. *J Thorac Oncol.* 2009;4: 1480–1484

IMMUNO HISTOCHEMISTRY

Marker	Sensitivity	Specificity
Calretinin	89-100	61-95
CK 5/6	89-100	58-97
CAM 5.2	97-100	0-1.5
EMA	74.5-90	7-87
WT 1	72-91	88-100
Vimentin	60-85	64-98
Desmin	45-90	85-100
p53	45-95	47-100
GLUT 1	58-100	100
D-240	72.5	93.5

Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

BIOMARKERS

Several biomarkers studied

1. Osteopontin
2. Fibulin 3
3. Megakaryocyte potentiating factor
4. Hyaluronic acid
5. VEGF
6. SMRP (Soluble Mesothelin Related Peptide) –
   - Most extensively studied
   - Only FDA approved biomarker for mesothelioma and marketed as MESOMARK®
   - Monitoring of patients diagnosed with epithelioid or biphasic mesothelioma

Woolhouse I, *et al*. *Thorax*. 2018;73:i1–i30

Arnold DT et al. Ann Clin Biochem. 2018 Jan;55(1):49-58

BIOMARKERS

BIOMARKER	SPECIMEN	POOLED SENSITIVITY	POOLED SPECIFICITY
SMRP	PLASMA	60 (95% CI 56 to 64)	81 (95% CI 78 to 83)
	PLEURAL FLUID	75 (95% CI 69 to 80)	76 (95% CI 71 to 82)
OSTEOPONTIN	SERUM+PLASMA	65 (95% CI 60 to 70)	81 (95% 78 to 85)
	SERUM+PLASMA	57 (95% CI 52 to 61)	81 (95% 79 to 84)
FIBULIN – 3	SERUM + PLASMA	62 (95% CI 0.45-0.77)	82 (95% CI 0.73-0.89)

Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

Pei et al. Oncotarget. 2017 Feb 21; 8(8): 13030–13038

Ahmadzada et al. *J Thorac Dis* 2018;10(Suppl 9):S1003-S1007

BIOMARKERS- JUST REMEMBER

- None has be validated for screening purposes in view of low sensitivity
- SMRP can be used to monitor response to therapy especially epitheloid and biphasic subtypes
- Fibulin -3 levels and pleural fluid HA levels at baseline inversely correlate with prognosis and outcome
- SMRP can be used in special circumstances with high pre-test probability to diagnose when tissue diagnosis is not possible

  (eg Elderly male with history of Asbestos exposure and typical symptoms and CT findings)

NCCN guidelines 2018
Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

GUIDELINES ON DIAGNOSIS

PARAMETER	ASCO (2018)	BTS (2018)	NCCN (2018)
Screening	No mention	No mention	**Not recommended (No benefit)**
Diagnosis	Cytology - for screening **Biopsy - for confirmation** (Gold standard)	Same	Same
Method	**Surgical** (thoracoscopic or open) preferred > CT guided core biopsy	No mention	No mention
IHC	**Mandatory** with positive and negative markers (number not specified) **NEGATIVE MARKERS :** CEA, EPCAM, Claudin 4, TTF-1	**Mandatory** with atleast 2 positive and 2 negative markers	**Mandatory**
Cell Block	Not stressed upon	same	No mention
Benign vs Malignant	Loss of BAP-1 found by IHC and homozygous deletion of *p16* FISH recommended	No mention	No mention

Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

GUIDELINES ON DIAGNOSIS

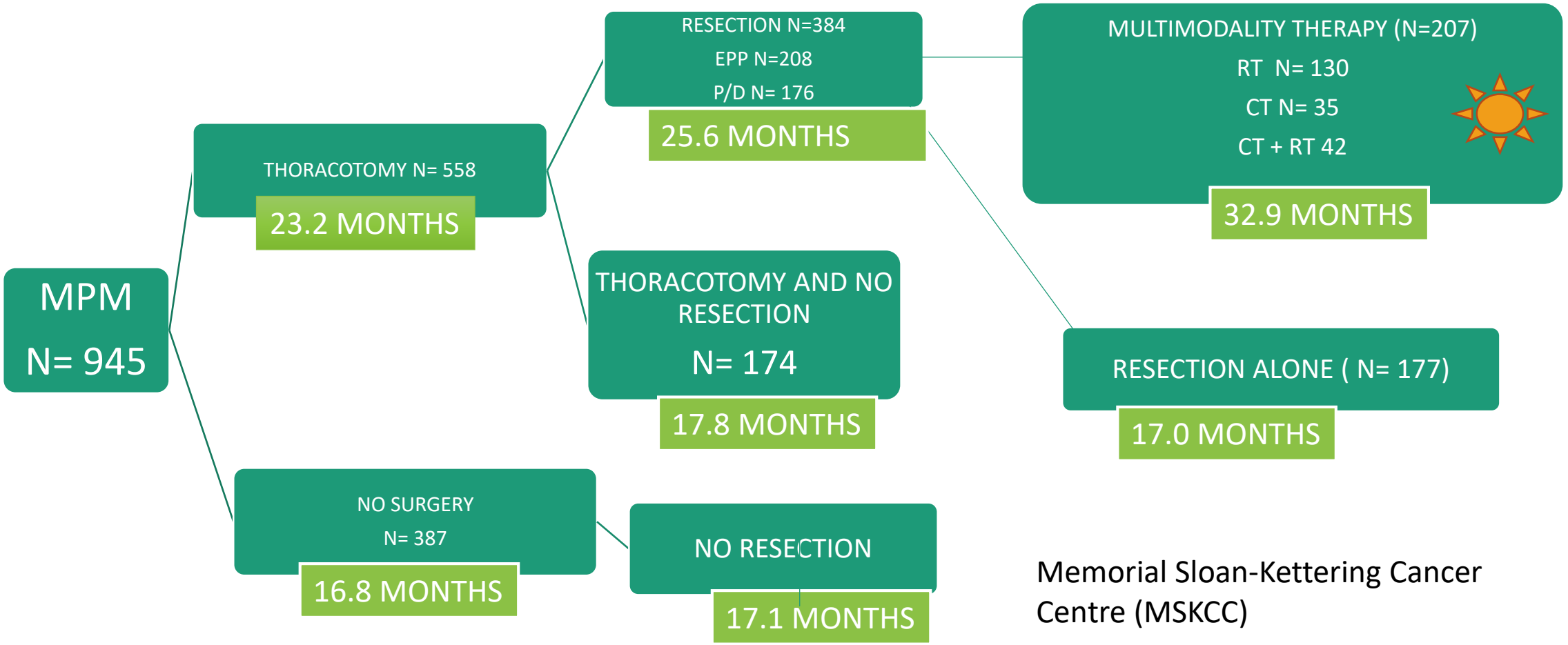
PARAMETER	ASCO (2018)	BTS (2018)	NCCN (2018)
Subtype classification	Epitheloid vs Sarcomatoid vs biphasic – Should be done	Same	Same
Biomarkers	Not recommended – low sensitivity and specificity in predicting response to therapy and prognosis	Not routinely used but in **cases where tissue diagnosis is difficult**	**SMRP (Soluble mesothelin related peptide) - optional**
Initial Staging	CECT chest with upper abdomen	same	Same
MRI	Not recommended routinely but useful for T stage evaluation	Same	Same
PET CT	Recommended for staging to **look for metastases in surgical candidates PET CT- Not to be used after TALC pleurodesis (false positive)**	Same	Same
Additional procedures	Positive imaging w/u for staging to be confirmed by EBUS/EUS/Thoracoscopy/laparoscopy	No mention	EBUS-FNA and mediastinoscopy recommended before surgery

Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

THERAPEUTIC OPTIONS

- Surgery
- Chemotherapy
- Radiotherapy
- Palliation
- Observation

MULTIMODALITY APPROACH



Memorial Sloan-Kettering Cancer Centre (MSKCC)

MEDIAN SURVIVAL

M. Utley et al. European Journal of Cardio-thoracic Surgery 38 (2010) 241—244

ROLE OF SURGERY

"Macroscopic complete Resection ***(MCR)-***
removal of ALL visible or palpable tumors"

ASCO 2018
NCCN 2018

SURGICAL OPTIONS

1. Partial pleurectomy (PP): partial removal of parietal and/ or visceral pleura for diagnostic or palliative purposes but leaving gross tumour behind
2. Pleurectomy/Decortication (PD): Resection of parietal + visceral pleura
3. Extended Pleurectomy/Decortication (EPD): Resection of parietal pleura + visceral pleura + diaphragm ± pericardium
4. Extrapleural pneumonectomy (EPP): Resection of the parietal pleura + visceral pleura + lung + diaphragm + pericardium

1- PALLIATIVE PROCEDURE

1, 2 and 3 – LUNG SPARING SURGERIES

2, 3 and 4 - MCR surgeries

ANY ROLE OF VATS – PARTIAL PLEURECTOMY

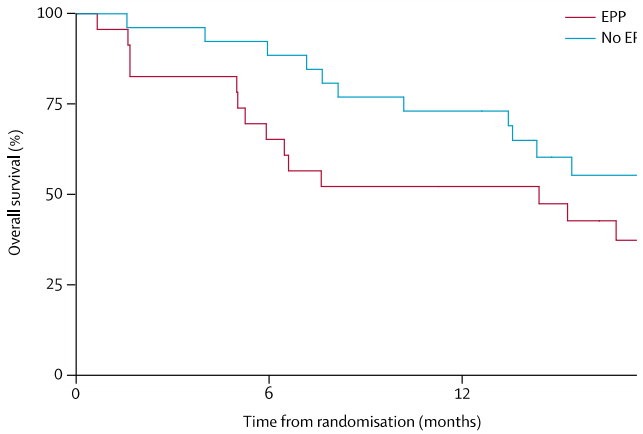
TRIAL	MesoVATS TRIAL
STUDY	OPEN LABEL RCT
PERIOD	Oct 24, 2003, - Jan 24, 2012
SUBJECTS	N= 175 , confirmed mesothelioma cases
METHOD	1: 1 randomization to either VATS PP vs TALC pleurodesis (VATS / ICTD)
OUTCOME	**Overall survival at 1 year : 52% (95% CI 41–62) vs 57% (46–66) (p = 0.81)** **Surgical complications : 24 (31%) of 78 patients vs 10 (14%) of 73 patients (p = 0.019)** **Median hospital stay : 7 days vs 3 days (p < 0.0001)** **Total Cost : 14252 Euros vs 10 436 Euros**
VERDICT	**VATS – NOT AN MCR** **PARTIAL PLEURECTOMY NOT RECOMMENDED**

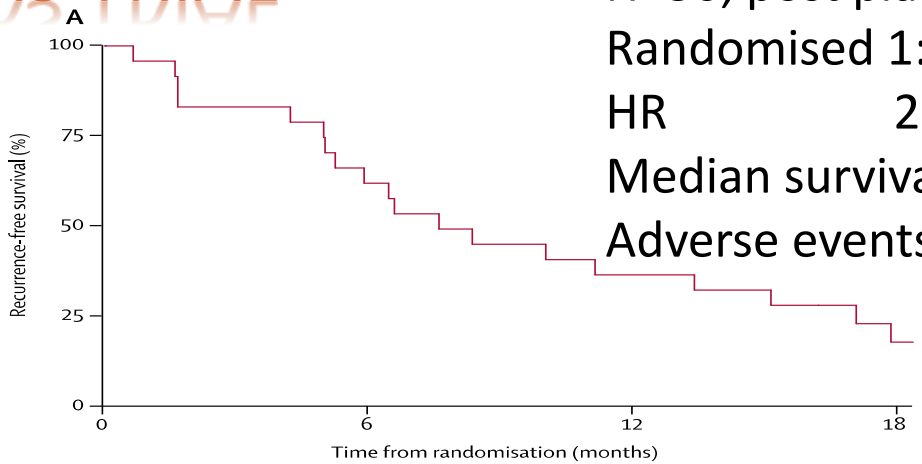
Rintoul et al. *Lancet* 2014;384:1118–27.

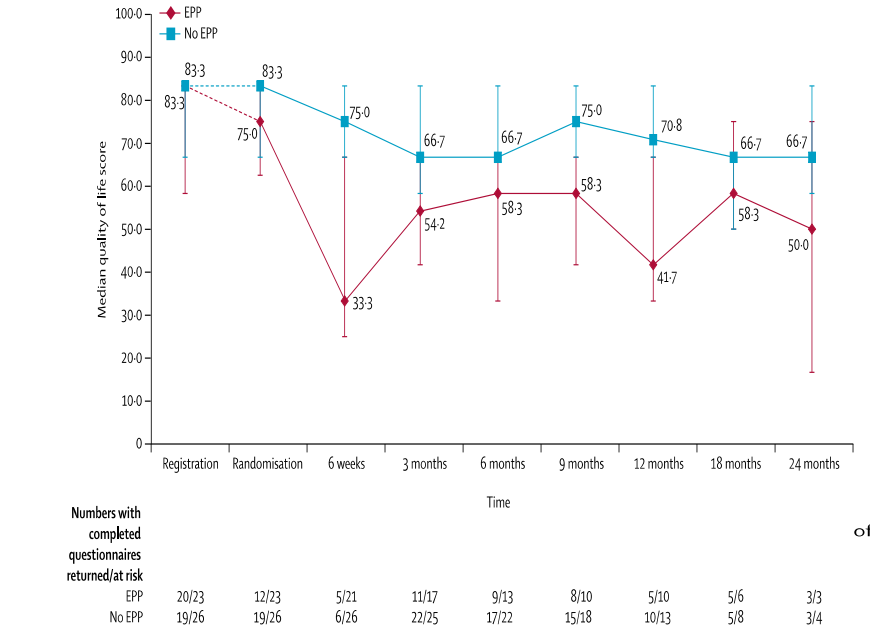
EXTRAPLEURAL PNEUMONECTOMY - IS IT REALLY INDICATED ?

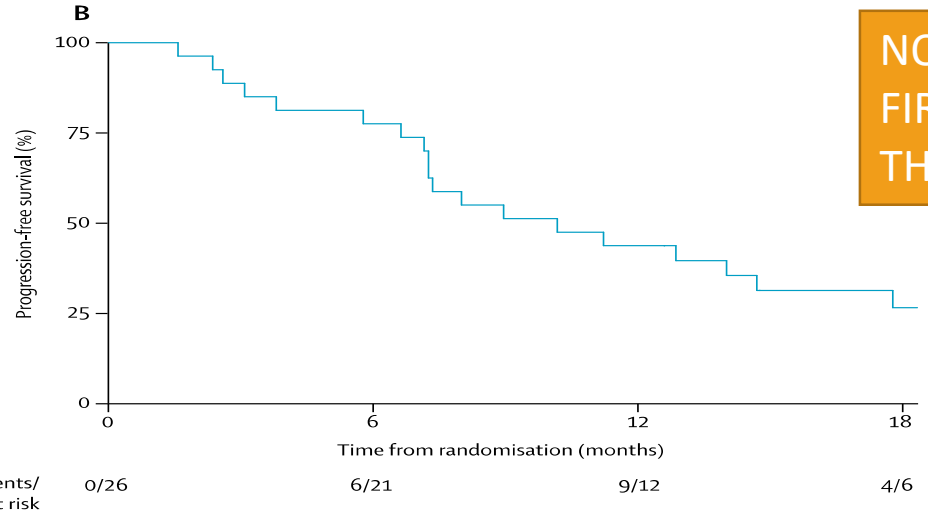
MARS TRIAL

N=50, post platinum based chemo status
Randomised 1:1 to EPP vs No EPP
HR 2.75
Median survival 14.4 vs 19.5 months
Adverse events 10 vs 2







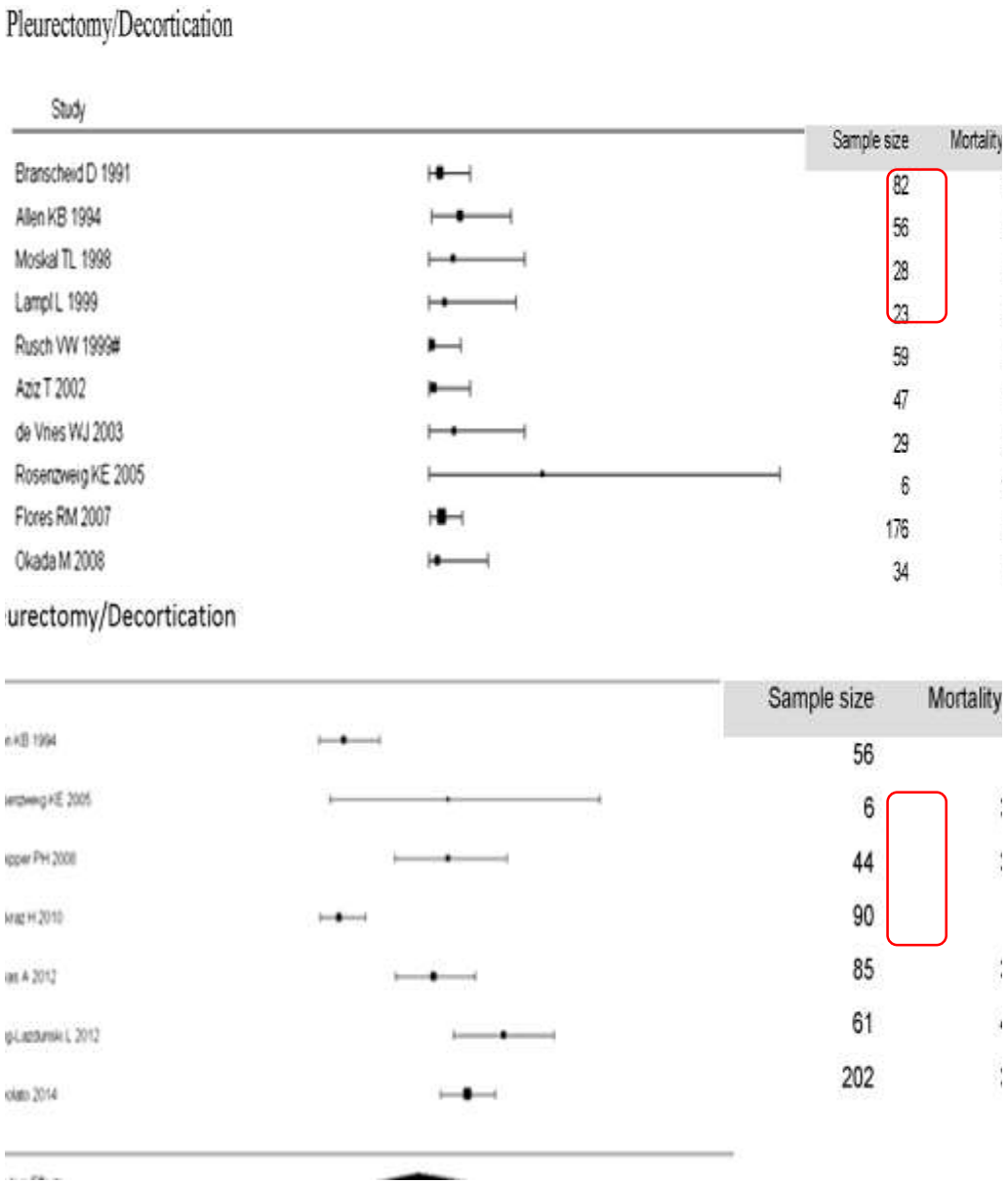


NOT RECOMMENDED AS A FIRST CHOICE THERAPEUTIC OPTION

BUT, HERE EPP COMPARED WITH CHEMOTHERAPY ALONE

Treasure et al. *Lancet Oncol* 2011;12:763–72.

HOW DOES EPP FARE AGAINST P/D?



METANALYSIS

19 STUDIES (JAN 1990 TO JAN 2014)

SHORT TERM MORTALITY MORE WITH EPP

17 STUDIES

2 YEAR SURVIVAL POST EPP VS P/D SIMILAR

MOST OF THE STUDIES HETEROGENOUS

Taioli et al. Ann Thorac Surg 2015;99:472–81

EPP VS P/D

AUTHOR (YEAR)	TOTAL PATIENTS	(EPP/PD)	EPP/PD-MORBIDITY	EPP/PD MORTALITY	MEDIAN SURVIVAL (months)
Flores (2008)	663	385/278	10/6.4	7/4	12/16 (p < 0.001)
Burt (2014)	225	95/130	Higher in EPP	10.5/3.1	NOT STATED
Batirel (2016)	130	42/66	20/5	7/2	18.3/14.6
Sharkey (2016)	362	133/229	Higher in EPP	6/3.5	12.9/12.3

- Early and late reoperation, bleeding, bronchopleural fistula, ARDS, Sepsis, atrial arrhythmias, right heart failure and ileus were significantly higher in EPP patients,

- Prolonged air leak was higher in P/D patients

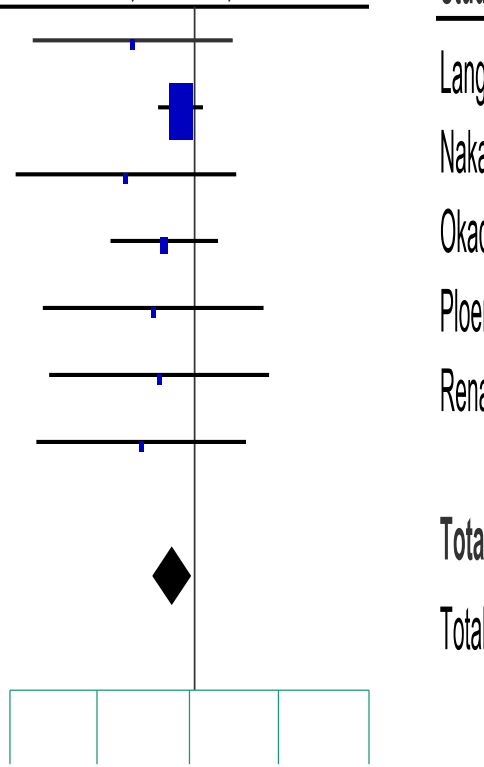
SIMILAR LONGTERM OUTCOME WITH HIGHER SHORT TERM MORBIDITY AND MORTALITY WITH EPP

Batirel et al. Ann Trans Med. 2017 Jun; 5(11): 232.

EPP VS EPD

Study or Subgroup	Extended P/D Events	Extended P/D Total	EPP Events	EPP Total	Weight	Risk Ratio M-H, Random, 95% CI
Bedirhan 2013	0	20	4	31	3.6%	0.17 [0.01, 2.98]
Flores 2008	13	278	27	385	71.7%	0.67 [0.35, 1.27]
Lang-Lazdunski 2012	0	54	1	22	3.0%	0.14 [0.01, 3.30]
Nakas 2012	2	67	7	98	12.5%	0.42 [0.09, 1.95]
Okada 2008	0	34	1	31	3.0%	0.30 [0.01, 7.22]
Ploenes 2013	0	23	1	25	3.0%	0.36 [0.02, 8.45]
Rena 2012	0	37	2	40	3.3%	0.22 [0.01, 4.35]
Total (95% CI)		513		632	100.0%	0.53 [0.31, 0.91]
Total events	15		43			

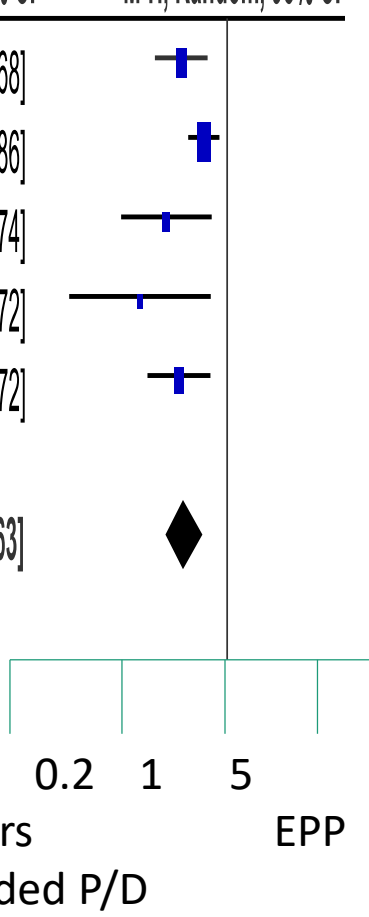
Risk Ratio M-H, Random, 95% CI



- EPP NOT BETTER THAN EPD
- RATHER HARMFUL

Study or Subgroup	Extended P/D Events	Extended P/D Total	EPP Events	EPP Total	Weight	Risk Ratio M-H, Random, 95% CI
Lang-Lazdunski 2012	15	54	15	22	24.7%	0.41 [0.24, 0.68]
Nakas 2012	29	67	67	98	36.5%	0.63 [0.47, 0.86]
Okada 2008	5	34	15	31	12.5%	0.30 [0.13, 0.74]
Ploenes 2013	2	23	12	25	6.0%	0.18 [0.05, 0.72]
Rena 2012	9	37	25	40	20.3%	0.39 [0.21, 0.72]
Total (95% CI)		215		216	100.0%	0.44 [0.30, 0.63]
Total events	60		134			

Risk Ratio M-H, Random, 95% CI



Cao et al. *Lung Cancer* 2014;83:240–5

195 **A feasibility study comparing (extended) pleurectomy decortication versus no pleurectomy decortication in the multimodality management of patients with malignant pleural mesothelioma: the MARS 2 study**

E. Lim, on behalf of Mars 2 Investigators. *Thoracic Surgery, Royal Brompton Hospital, London, United Kingdom*

Introduction: The aim of the MARS 2 study is to determine if it is feasible to recruit patients with malignant pleural mesothelioma with disease amenable to surgical resection into a randomised trial of (extended) pleurectomy decortication (lung sparing surgery) versus no surgery. The feasibility ~~component will also assess if there~~ is any evidence of harm associated with (extended) pleurectomy decortication.

Methods: Patients with a histological confirmation of mesothelioma with disease confined to one hemi-thorax are eligible for enrolment. Patients are ineligible if they are unable to give informed consent or are unwilling to be randomised or if they have disease that is not deemed to be surgically resectable, an ECOG status 2 or more, a predicted pre-operative FEV1 or TLco less than 20%, severe heart failure, end stage kidney failure, liver failure or are already participating in another interventional clinical trial. All patients will receive the usual standard of care chemotherapy. After 2 cycles, participants will be reassessed by CT to screen for progressive disease. Patients with no evidence of disease progression beyond the limits of surgical resection will be randomised to either: A) (Extended) pleurectomy decortication, or B) No surgery. All patients will then receive the remaining 4 cycles of chemotherapy.

Results: Two lead surgical centres: Leicester and Sheffield are authorised to recruit patients. Approximately 20 medical centres will also join the study. To date 7 patients have been enrolled and 3 patients randomised.

Conclusion: The results from the MARS 2 feasibility study will determine if it is possible to recruit patients with malignant pleural mesothelioma with disease amenable to surgical resection into a randomised trial of (extended) pleurectomy decortication (lung sparing surgery) versus no surgery. The feasibility study will also assess if there is any evidence of harm.

ClinicalTrials.gov Identifier: NCT02040272; Funded by Cancer Research UK: CRUK/12/030.

Disclosure: All authors have declared no conflicts of interest.

MARS 2 STUDY

MARS 2 STUDY
Post 2 cycles chemotherapy (If no progression)
Randomised to EPD vs No surgery
Results awaited

Lim et al: the MARS 2 study. *Lung Cancer* 2016;91((Suppl 1: S71)):S71.

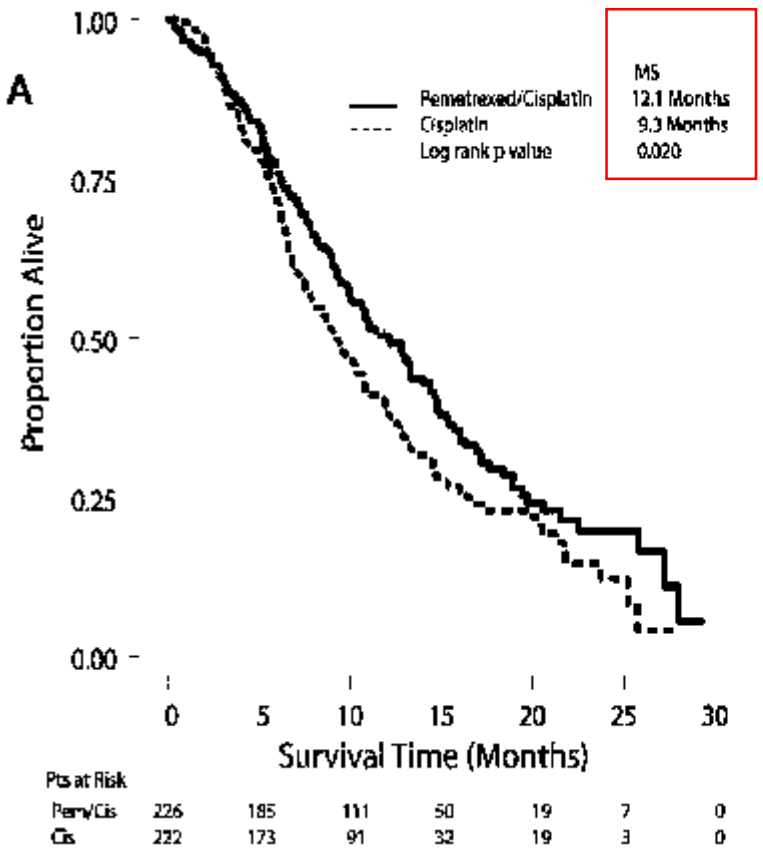
SURGERY GUIDELINES

GUIDELINES	ASCO (2018)	BTS (2018)	NCCN (2018)
Surgery (Maximum surgical cytoreduction)- **Indications**	Recommended in Epitheloid /biphasic + early stage (no N3 disease / metastases) + PS ≤ 1 + no comorbidities (**N3 disease - C/L hilar or C/L mediastinal or I/L or C/L Supraclavicular LN)** **However Neoadjuvant chemo f/b surgery – option**	Surgery not recommended usually Only in trials	Recommended in stage (I to III) + epitheloid subtype + PS ≤ 2
Adjuvant or neoadjuvant chemo ± radiotherapy	Required	No mention	Required
Type of surgery	Lung sparing (P/D and Extended P/D) > EPP	Both P/D and EPP not recommended	PD > EPP
Palliative therapies- **Indications**	PS ≥ 2 or Symptomatic pleural effusion or surgery couldn't be performed **Non thoracoscopic TALC pleurodesis and VATS pleurodesis preferred over VATS partial pleurectomy**		No mention

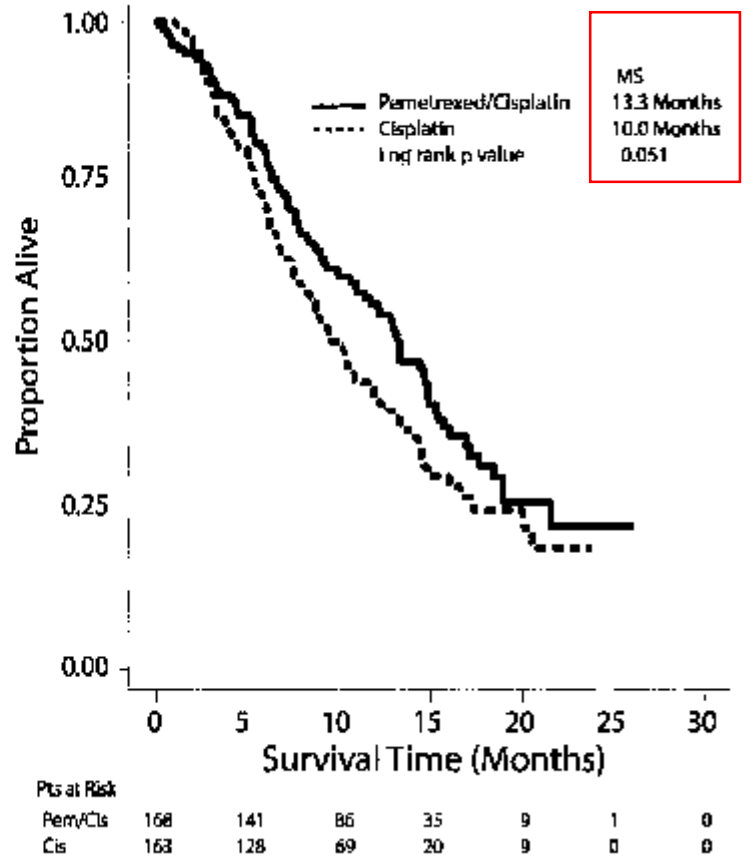
ROLE OF CHEMOTHERAPY

- 1ST LINE SINGLE AGENT VS COMBINATION REGIMEN
- 2nd LINE THERAPY OPTIONS

1ST LINE CHEMOTHERAPY- EMPHASIS TRIAL



ALL PATIENTS



VITAMIN B12 + FOLATE SUPPLEMENTED PATIENTS

- N= 456
- KPS $\geq$ 70
- Multi centre RCT
- Intervention arm :
- Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2(3 weekly)
- +Inj Vit B12 1000 once every 9 weeks i.m + Oral folate 350 to 1000 micro OD + Dexa
- Control Arm : Cisplatin 65mg/m^2 3 weekly + Vit B12 + folate + Dexa

Vogelzang et al *J Clin Oncol* 2003;21:2636–44.

1ST LINE CHEMOTHERAPY- EMPHASIS TRIAL

	Full Supplementation (n = 168)		Partial Supplementation + Never Supplemented (n = 58)			Full Supplementation + Partial Supplementation (n = 194)		Never Supplemented (n = 32)		
	No. of Patients	%	No. of Patients	%	P*	No. of Patients	%	No. of Patients	%	P*
Hematologic Laboratory Toxicity										
Hemoglobin	7	4.2	4	6.9	.479	8	4.1	3	9.4	.192
Leukocytes	25	14.9	15	25.9	.072	29	14.9	11	34.4	.012
Neutrophils	39	23.2	24	41.4	.011	51	26.3	12	37.5	.205
Platelets	9	5.4	4	6.9	.744	10	5.2	3	9.4	.403
Nonlaboratory Toxicity										
Nausea	20	11.9	13	22.4	.082	23	11.9	10	31.3	.012
Fatigue	17	10.1	6	10.3	.999	18	9.3	5	15.6	.338
Vomiting	18	10.7	12	20.7	.071	20	10.3	10	31.3	.003
Diarrhea	6	3.6	4	6.9	.284	7	3.6	3	9.4	.154
Dehydration	7	4.2	2	3.4	.999	7	3.6	2	6.3	.619
Stomatitis	5	3.0	4	6.9	.240	8	4.1	1	3.1	.999
Anorexia	2	1.2	3	5.2	.108	3	1.5	2	6.3	.148
Febrile neutropenia	1	0.6	3	5.2	.053	1	0.5	3	9.4	.009
Infection with G3 or G4 neutropenia	0	0	3	5.2	.016	1	0.5	2	6.3	.053
Rash	1	0.6	2	3.4	.163	3	1.5	0	0.0	.999

PEMETREXED + CISPLATIN
+ DEXA + VIT B12 + FOLATE
APPROVED AS 1ST LINE THERAPY

Vogelzang et al *J Clin Oncol* 2003;21:2636–44.

OTHER 1ST LINE CHEMOTHERAPY DRUGS STUDIED

AUTHOR	YEAR	TREATMENT ARM	OS (MONTHS)	P VALUE
Van Meerbeeck et al	2005	R/C vs C	11.4 vs 8.8	0.048
Santoro et al	2008	P/CAR vs P/C	1 year survival 64 % vs 63.1% TTP. - 6.9 vs 7.0	-
Zalcman et al(MAPS TRIAL)	2015	P/C/B vs P/C	18.8 vs 16.1	0.017

R- RALTITREXED (THYMIDYLATE SYNTHASE INHIBITOR)
B- BEVACIZUMAB
P- PEMETREXED
C- CISPLATIN
CAR- CARBOPLATIN
TTP- TIME TO PROGRESSION

1. P/CAR
2. R/C
3. P/C/B

ALTERNATE 1ST LINE CHEMOTHERAPY REGIMENS

Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

2ND CHEMOTHERAPY OPTIONS STUDIED

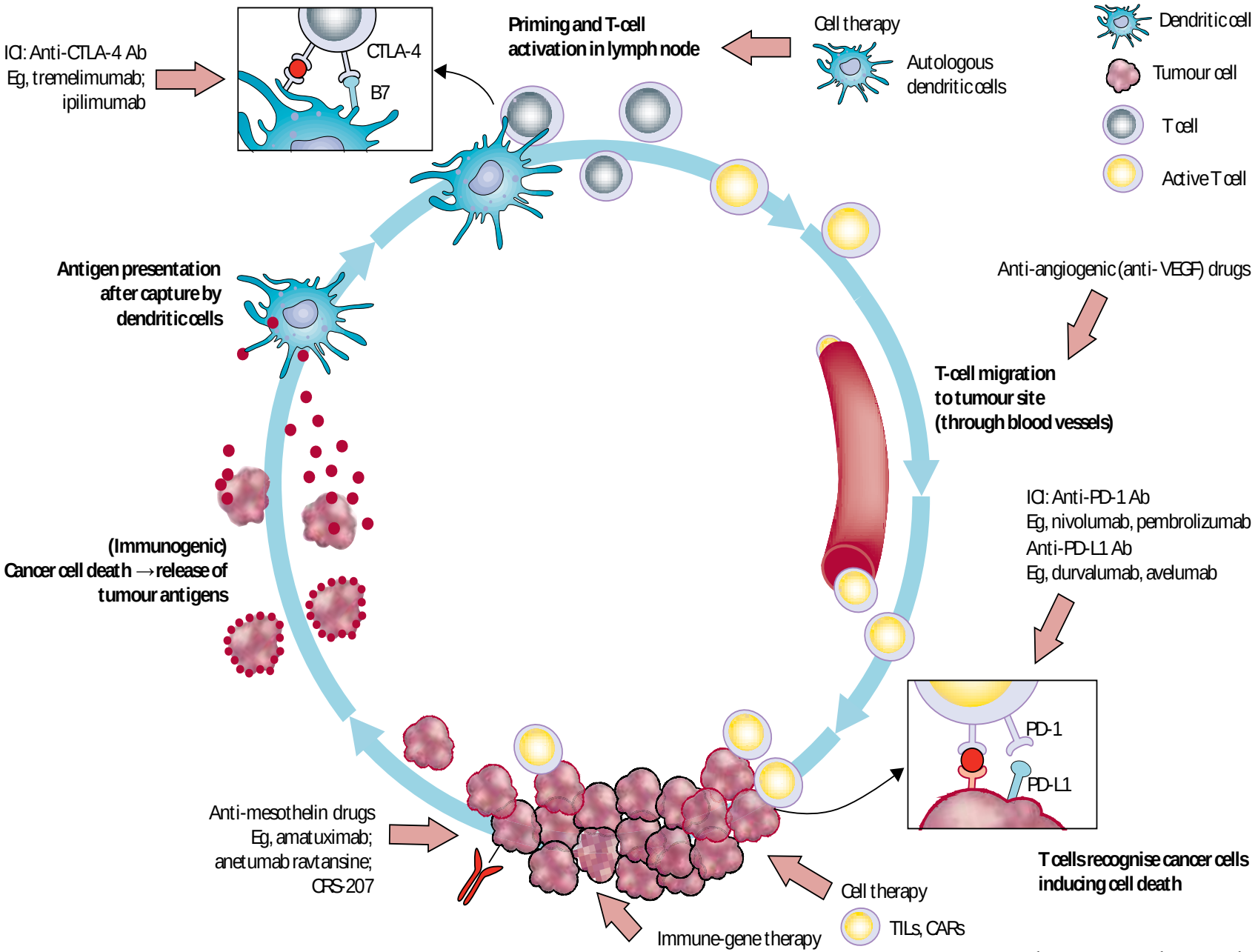
DRUG REGIMEN	AUTHOR	NUMBER OF SUBJECTS	PFS	OS	TOXICITY
Raltitrexed + oxaliplatin	Fazizi et al	70	6.2	10.1	NA
Raltitrexed + oxaliplatin	Porta et al	14	2	3.5	CNS GI Hemotoxocity
Vinorelbine	Stebbing et al.	63	NA	9.6	CNS, GI, Hemotoxicity
Gemcitabine + docetaxel	Tourkantonis et al	37	7	16.2	Same
Pemetrexed + BSC vs BSC	Jassem et al	243	3.6	8.4	Hemotoxicity, GI, Respiratory
Pemetrexed vs pemetrexed + carboplatin	Sorensen et al	39	6.1	NA	NA
Pemetrexed	Taylor et al	493	4.9	9.5	Hemotoxicity
Pemetrexed vs pemetrexed + cisplatin	Janne et al	187	Na	NA	

W.A. Buikhuisen et al. Lung Cancer 89 (2015) 223–231

TARGETED THERAPIES BEING STUDIED

- Anti angiogenic factors
- Immune check point inhibitors
- EGFR Inhibitors (TKIs and antibodies)
- Other targeted therapies
- Immune therapy targeting mesothelin
- Vaccine and Novel therapies

NONE FDA APPROVED



TARGETED THERAPIES

Scherpereel et al. Lancet Oncol 2018; 19: e161–72

	Target	Developmental phase and trial design	Number of patients	Primary endpoint	Results or trial status
Anti-angiogenic therapies					
Bevacizumab (NCT00651456)[9]	VEGF	Phase 3; bevacizumab plus cis/pem *vs* cis/pem alone	448	OS	Positive
Thalidomide (ISRCTN13632914)[22]	VEGF; FGF	Phase 3; single-arm: thalidomide maintenance therapy after frontline cis/pem	222	PFS	Negative
Axitinib (NCT01211275)[1]	VEGFR	Phase 1/2; single-arm: axitinib plus cis/pem	25	PFS	Negative
Cediranib (NCT0024307)[23]	VEGFR; PDGFR	Phase 2; beyone firstline; single-arm: cediranib alone	54	ORR	Negative
Cediranib (NCT01064648)	VEGFR; PDGFR	Phase 2 ; cediranib plus cis/pem *vs* cis/pem alone	116	PFS	Active, not recruit
Nintedanib[24]	VEGFR; PDGFR; FGFR	Phase 2; nintedanib plus cis/pem followed by nintedanib (maintenance) *vs* placebo plus cis/pem followed by placebo (maintenance)	87	PFS	Positive
Nintedanib (NCT01907100)	VEGFR; PDGFR; FGFR	Phase 3; nintedanib plus cis/pem followed by nintedanib (maintenance) *vs* placebo plus cis/pem followed by placebo (maintenance)	537	PFS	Active, not recruiting
Sorafenib (NCT00794859)[25]	VEGFR2/VEGFR3; PDGFR; RAF; c-KIT	Phase 2; beyond first-line; single-arm: sorafenib alone	53	6-month PFS	Negative
Sorafenib (NCT00107432)	VEGFR2/VEGFR3; PDGFR; RAF; c-KIT	Phase 2; beyond first-line; single-arm: sorafenib alone	51	PFS	Negative
Sorafenib (NCT00703638)	VEGFR2/VEGFR3; PDGFR; RAF; c-KIT	Phase 1; sorafenib plus cis/pem	16	ORR	Negative
Imatinib mesylate (NCT00402766)[26]	BCR-ABL; c-KIT; RAF; PDGFR	Phase 1; imatinib plus cis/pem	17	Safety ORR	Negative
Imatinib mesylate (NCT02303899)	BCR-ABL; c-KIT; RAF; PDGFR	Phase 2; single-arm: imatinib plus gemcitabin in pemetrexed-pretreated patients	22	PFS	Active, not recruiting

(Table 1 continues on next page)

MAPS TRIAL

LUME MESO TRIAL

ANTI ANGIOGENIC FACTORS – ROLE AS ADD ON IN 1ST LINE?

Scherpereel et al. Lancet Oncol 2018; 19: e161–72

	Target	Developmental phase and trial design	Number of patients	Primary endpoint	Results or trial status
Immune checkpoint inhibitors					
Tremelimumab (NCT01649024)[51]	Anti-CTLA-4 mAb	Phase 2; second-line	29	ORR	Negative
Tremelimumab (NCT01843374)[52]	Anti-CTLA-4 mAb	Phase 2; second-line and third-line; tremelimumab *vs* placebo	564	OS	Negative
Nivolumab (NCT02497508)	Anti-PD-1 mAb	Phase 2; second-line and third-line; nivolumab *vs* placebo	33	3 months-DCR	Active, not recruiting
Nivolumab (NCT03063450)	Anti-PD-1 mAb	Phase 3; relapse after 2 previous lines; nivolumab *vs* placebo	336	OS	Currently recruiting
Pembrolizumab (NCT02054806)[53]	Anti-PD-1 mAb	Phase 1b; beyond frontline mesothelioma expressing PD-L1	25	ORR; safety	Positive
Pembrolizumab (NCT02784171)	Anti-PD-1 mAb	Phase 2; pembrolizumab plus cis/pem *vs* cis/pem alone	126	PFS	Curre
Pembrolizumab (NCT02991482)	Anti-PD-1 mAb	Phase 3; pembrolizumab *vs* gemcitabine or vinorelbine in pre-treated mesothelioma	142	PFS	Not yet recruiting
Durvalumab (NCT02899195)	Anti-PD-L1 mAb	Phase 2; single-arm: durvalumab plus cis/pem maintenance durvalumab	55	OS	Currently recruiting
Tremelimumab and durvalumab (NCT02588131)	Combination; anti-CTLA-4 mAb; anti-PD-L1 mAb	Phase 2; single-arm: tremelimumab plus durvalumab	40	ORR	Currently recruiting
Ipilimumab and nivolumab (NCT02716272)[54,55]	Combination; anti-CTLA-4 mAb; anti-PD-1 mAb	Phase 2; ipilimumab and nivolumab *vs* nivolumab alone; second and third-line	125	3-months DCR	Positive
Ipilimumab and nivolumab (NCT02899299)	Combination; anti-CTLA-4 mAb; anti-PD-1 mAb	Phase 3; ipilimumab and nivolumab *vs* cis/pem in frontline	600	PFS; OS	Currently recruiting

CHECK MATE 028

NIBIT MESO 1 TRIAL

MAPS 2 TRIAL

IMMUNE CHECK POINT INHIBITORS- IN 2ND LINE?

Scherpereel et al. Lancet Oncol 2018; 19: e161–72

IMMUNE CHECK POINT INHIBITORS

	Target	Setting	Number of patients	Objective response rate	Disease control rate	Median PFS (months)	Median OS	PD-L1 IHC status
Pembrolizumab (KEYNOTE-028) (NCT02054806)[53]	PD-1	Second-line	25	20%	72%	5·4	18 months	All patients were PD-L1 IHC positive
Pembrolizumab (NCT02399371)[59]	PD-1	Second-line	35	21%	77%	6·2	NR	Did not correlate to response
Nivolumab (NivoMES trial) (NCT02497508)[60]	PD-1	Beyond first-line	33	24%	50%	3·6	NR	Trend for correlation with OR
Avelumab (JAVELIN) (NCT01772004)[61]	PD-L1	Salvage, any line	53	9·4%	57%	4·3	NR	Trend for correlation with median PFS
Nivolumab and ipilimumab vs nivolumab alone (MAPS-2) (NCT02716272)[54,55]	PD-1 ± CTLA-4	Second-line or third-line	125 (62 vs 63)	25·9%; 18·5%	50%; 44·1%	5·6; 4	NR; 13·6 months	Correlation with OR (p=0·003 if ≥1%)

PDL1 TESTING LIKELY USEFUL

Scherpereel et al. Lancet Oncol 2018; 19: e161–72

	Target	Developmental phase and trial design	Number of patients	Primary endpoint	Results or trial status
(Continued from previous page)					
EGFR TKI					
Gefitinib (NCT00025207)	EGFR	Phase 2; frontline; single-arm: gefitinib	43	3-month PFS	Negative
Erlotinib (NCT00039182)	EGFR	Phase 2; frontline; single-arm: erlotinib	63	ORR	Negative
Erlotinib plus bevacizumab (NCT00137826)	EGFR; VEGF	Phase 2; single-arm: erlotinib plus bevacizumab in previously treated mesothelioma	24	ORR	Negative
Anti-EGFR antibodies					
Cetuximab (NCT00996567)	EGFR	Phase 2; single-arm: cetuximab plus platinum-based chemotherapy	18	18-week PFS	Negative
Pro-apoptotic and other targeted therapies					
Vorinostat (NCT00128102)[19]	HDAC inhibitors	Phase 2/3: vorinostat *vs* placebo	661	OS	Negative
Valproate (NCT00634205)[27]	HDAC inhibitors	Phase 2: valproate plus doxorubicin	45	ORR	Positive
Defactinib (NCT01870609)	FAK inhibitor	Phase 2: defactinib maintenance after first-line cis/pem	372	OS; PFS	Negative, stopped
Everolimus (NCT00770120)	PI3K/AKT/mTOR	Phase 2; single-arm: everolimus as second-line and third-line treatment	59	4-month PFS	Negative
Tazemetostat[28]	EZH2 inhibitors; BAP-1	Phase 1; beyond first-line, non-Hodgkin lymphoma and solid tumours	58	DCR	Positive
Tazemetostat (NCT02860286)	EZH2 inhibitors; BAP-1	Phase 2; beyond first-line, mesothelioma with BAP-1 loss of function	67	DCR	Active, completed accrual
Pegylated arginine deiminase (ADI-PEG 20) (NCT01279967)[29]	ASS-1	Phase 1; ADI-PEG 20 plus cis/pem	20	Safety ORR	Positive
Pegylated arginine deiminase (ADI-PEG 20) (NCT02709512)	ASS-1	Phase 2/3; ADI-PEG 20 plus cis/pem *vs* cis/pem plus placebo; biphasic or sarcomatoid mesothelioma	386	ORR	Currently recruiting
Tivantinib (NCT02049060)	Met	Phase 1/2: single-arm: tivantinib plus carbo/pem	31	Safety	Active, not recruiting
Ganetespib (NCT01590160)	Molecular chaperone HSP90	Phase 1/2: single-arm: ganetespib plus cis/pem or carbo/pem	27	Safety PFS	Active, not recruiting
NGR-hTNF (NCT01098266)	CD13	Phase 3; second-line	390	OS	Negative
NGR-hTNF (NCT01358084)	CD13	Phase 2; NGR-hTNF maintenance after frontline	100	PFS	Currently recruiting

EGFR TKIs – NO ROLE

POTENTIAL TARGET BAP – 1 MUTATION + CASES

AKT=RAC-alpha serine/threonine-protein kinase.
EZH2=enhancer of zeste homolog 2.
BAP-1=BRCA1 associated protein-1.
DCR=disease control rate.

Scherpereel et al. Lancet Oncol 2018; 19: e161–72

IMMUNOTHERAPY TARGETING MESOTHELIN

Immunotherapy targeting mesothelin

Amatuximab (MORab-009) (NCT02357147)	Anti-mesothelin chimeric antibody	Phase 2: plus cis/pem *vs* cis/pem plus placebo	560 (planned)	OS	Stopped enrolment
Anetumab ravtansine (NCT02485119)	Anti-mesothelin mAb and anti-tubulin	Phase 1: second-line and third-line	16	ORR; safety	Positive
Anetumab ravtansine (NCT02610140)	Anti-mesothelin mAb and anti-tubulin	Phase 2; second and third-line; anetumab ravtansine *vs* vinorelbine	248	PFS	Active, not recruiting
CRS-207 (NCT01675765)[56]	Anti-mesothelin and attenuated live *Listeria* toxin	Phase 1; CRS-207 plus cis/pem	34	ORR; safety	Positive
CRS-207 plus pembrolizumab (NCT03175172)	Anti-mesothelin and attenuated live *Listeria* toxin plus anti-PD-1 mAb	Phase 2; second-line and third-line; CRS-207 plus pembrolizumab	35	ORR	Active, not recruiting

Mesothelin is a glycoprotein that is physiologically expressed by mesothelial cells

Scherpereel et al. Lancet Oncol 2018; 19: e161–72

	Target	Development phase and trial design	Number of patients	Primary endpoint	Results or trial status
(Continued from previous page)					
Vaccine					
WT-1 vaccine galinpepimut-S (NCT01265433)	Anti-WT-1	Phase 2; WT-1 montanide plus GM-CSF *vs* adjuvant montanide plus GM-CSF after multimodal treatment	41	1-year PFS	Completed
Cell therapy					
WT-1-targeted dendritic cell vaccination (NCT02649829)	Autologous dendritic cell vaccination	Phase 1/2; WT-1-targeted dendritic cell vaccination plus chemotherapy	20	Safety feasibility	Currently recruiting
Tumour lysate-loaded dendritic cells (NCT01241682)[57]	Autologous dendritic cell vaccination	Phase 1; beyond frontline associated with cyclophosphamide	10	Safety feasibility	Positive
TILs (NCT02414945)	Autologous TILs	Phase 1/2; autologous TILs infusion after cyclophosphamide plus fludarabine,and low dose interleukin-2 therapy	10	Safety; clinical response rate	Currently recruiting
CAR T meso cells (NCT02159716)	CARs	Phase 1; intravenously administered lentiviral transduced CAR T meso cells with and without cyclophosphamide	19	Safety feasibility	Completed Study
FAP-specific T cells (NCT01722149)	CARs	Phase 1; adoptive transfer of re-directed FAP specific T cells in the pleural effusion	6	Safety	Currently recruiting

OTHER NOVEL THERAPIES

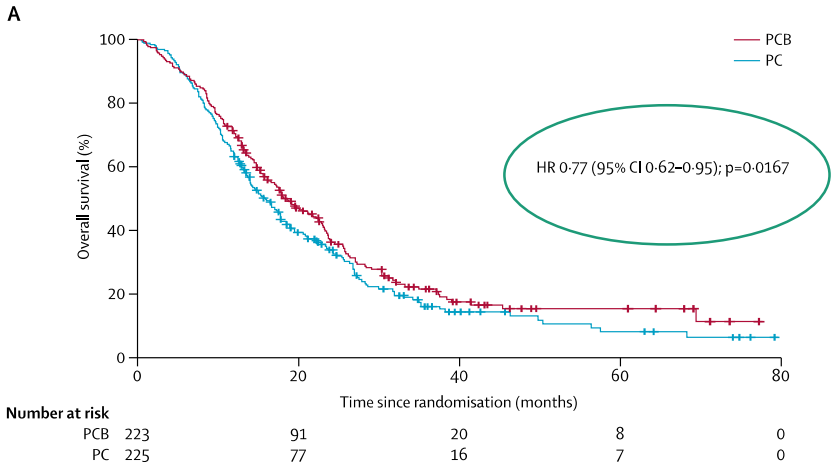
Scherpereel et al. Lancet Oncol 2018; 19: e161–72

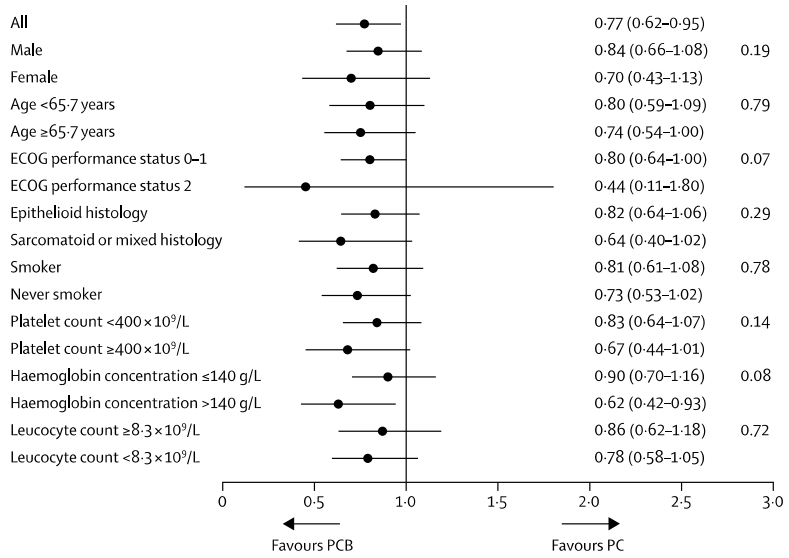
ROLE OF TARGETED AGENTS IN MPM

- AS ADD ON TO CHEMO IN FIRST LINE
- 2ND LINE MONOTHERAPY/COMBINATION

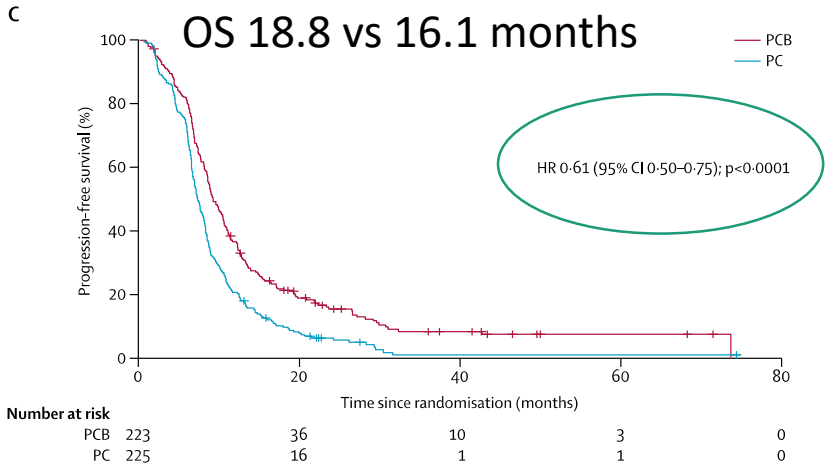
MAPS TRIAL

ADD ON BEVACIZUMAB TO CHEMO IN 1ST LINE





Phase 3 Multicentre RCT
N=448
ECOG ≤ 2
1:1 to P/C/B vs P/C
VEGF mutation status not teste



OS BENEFIT 2.7 MONTHS

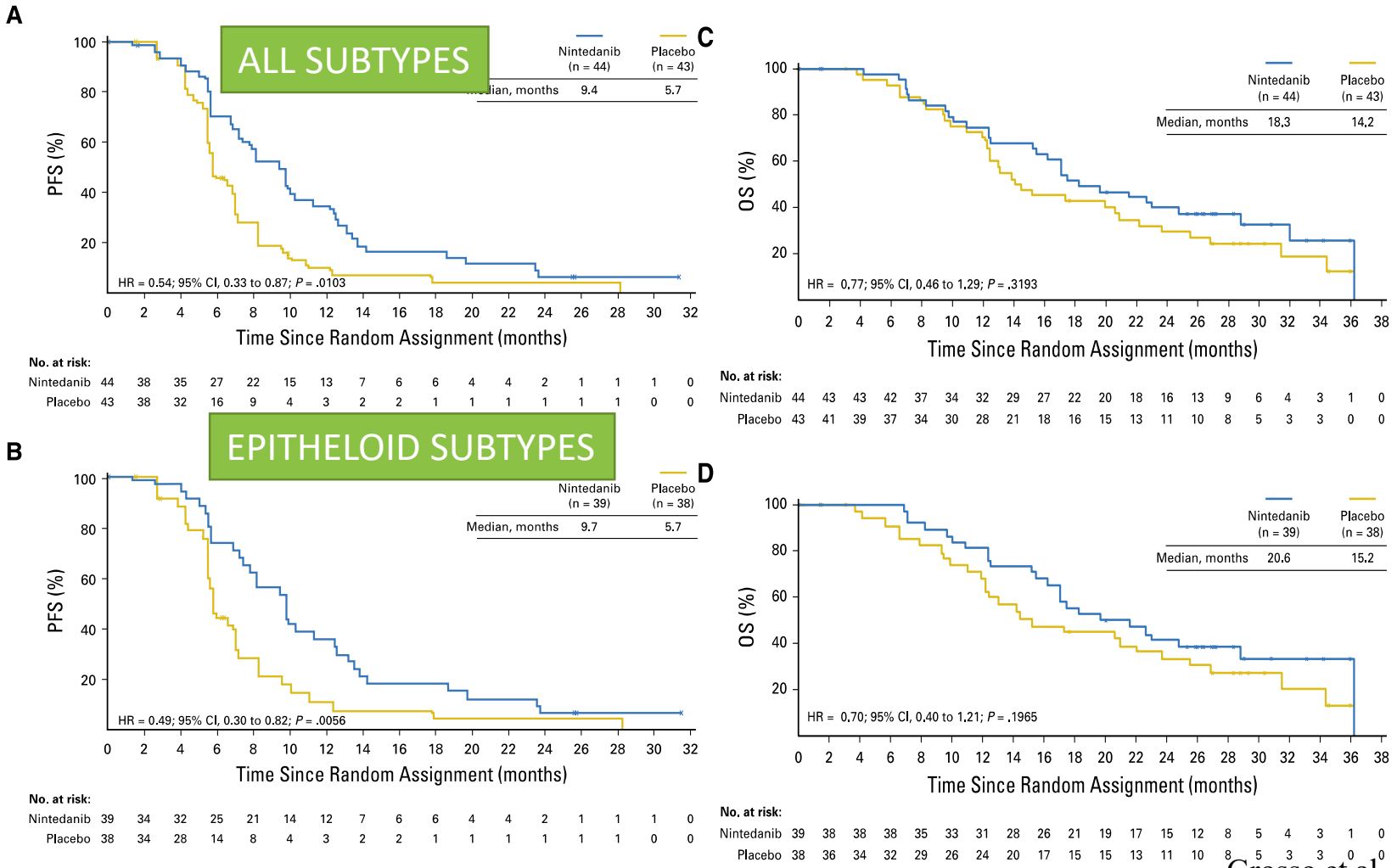
ADVERSE EVENTS : Hemorrhage, Thromboembolism, hypertension, Raised Creatinine, Proteinuria More In The Bevacizumab Arm

BEVACIZUMAB CAN BE ADDED TO 1ST LINE C + P

Zalcman et al. *J of Clinical Oncology* 2015;33(15 SUPPL. 1):7500.

LUME-MESO TRIAL

ADD ON NINTEDANIB TO CHEMO IN 1ST LINE

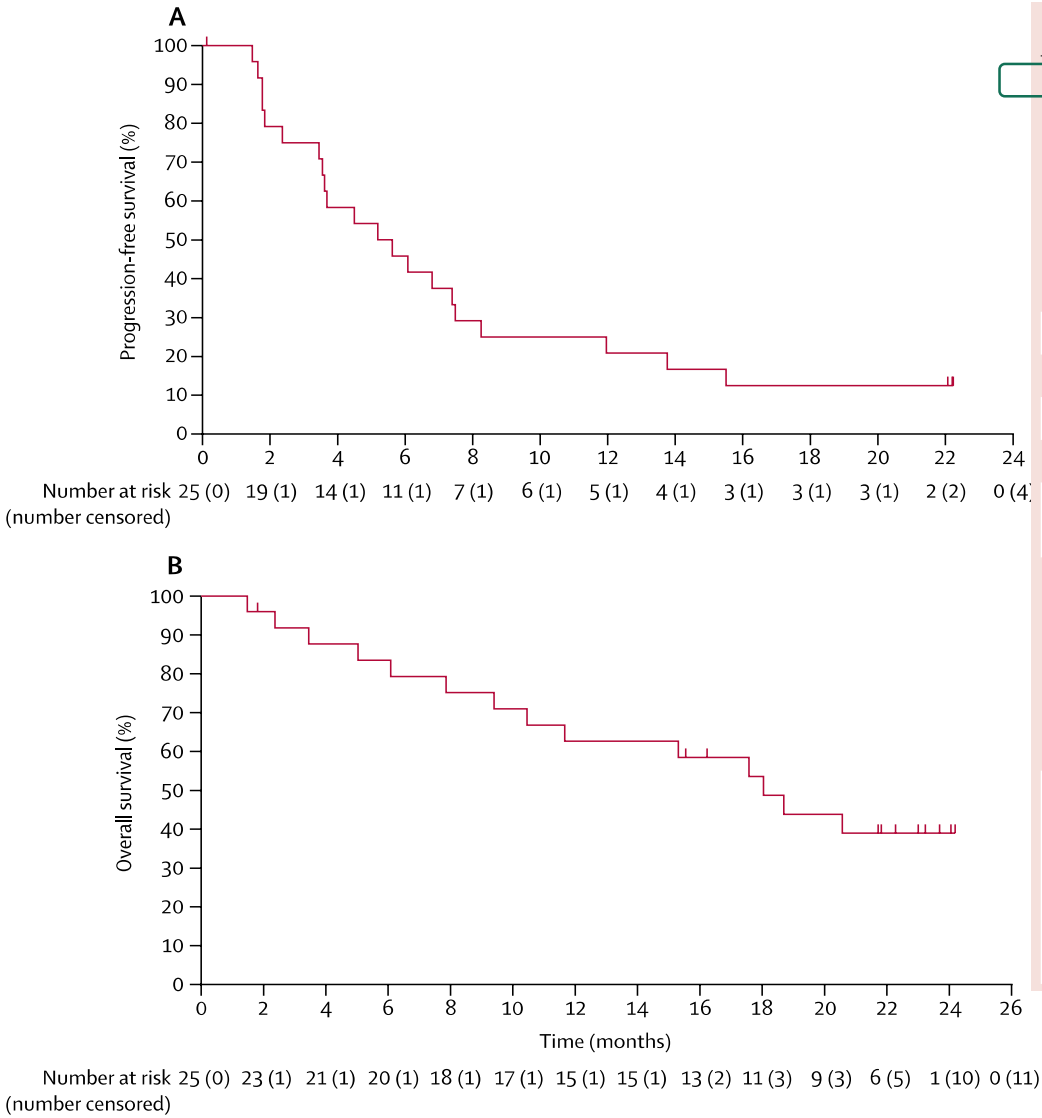


- Phase II/III randomized, double-blind trial
- Chemotherapy-naive patients with unresectable, non sarcomatoid MPM
- N= 86, 1 : 1 to N/C/P vs C/P

median OS [nintedanib v placebo] 20.6 months v 15.2 months)
median PFS [nintedanib v placebo], 9.7 v 5.7 months) in epitheloid subtype
Neutropenia 43.2 % vs 12.2 %

Grosso et al. J Clin Oncol. 2017 Nov 1;35(31):3591-3600

PD1 INHIBITION IN 2ND LINE –KEYNOTE 028 TRIAL



	Full-analysis set (n=25)
Objective response	5 (20%; 95% CI 6·8–40·7)
Complete response	0
Partial response	5 (20%)
Stable disease	13 (52%)
Progressive disease	4 (16%)
Not evaluable or no assessment*	3 (12%)
Duration of follow-up (months)	18·7 (10·4–24·0)
Time to response (months)	1·9 (1·7–3·8)
Duration of response (months)	12 (3·7–NR)
Duration of stable disease (months)	5·6 (3·6–12·0)
Clinical benefit (complete response + partial response + stable disease ≥6 months)	40% (21·1–61·3)
Progression-free survival	
Events	21 (84%)
Median (months)	5·4 (3·4–7·5)
6 months	45·8% (25·6–64·0)
12 months	20·8% (7·6–38·5)
Overall survival	
Deaths	14 (56%)
Median (months)	18 (9·4–NR)
6 months	83·5% (61·7–93·5)
12 months	62·6% (40·4–78·5)

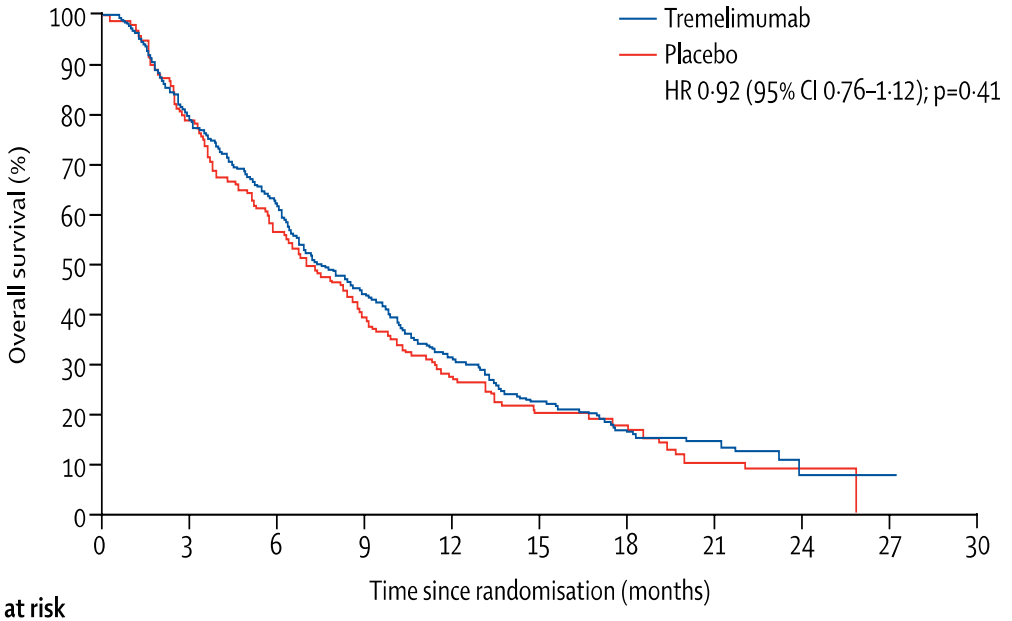
- PHASE 1b trial
- Previously treated PDL-1 +ve (≥ 1% by IHC) MPM pts
- ECOG 0-1

- RHABDOMYOLYSIS
- IRIDOCYCLITIS
- HYPOTHYROIDISM

WELL TOLERATED OVERALL AS A 2ND LINE THERAPY

Alley et al. Lancet Oncol. 2017 May;18(5):623-630

CTLA -4 INHIBITION IN 2ND LINE - DETERMINE TRIAL



- **Double-blind, placebo-controlled, phase 2b trial**
- **Multi centre RCT**
- **May 17, 2013 to Dec 4, 2014**
- **N= 571**
- **I.V tremelimumab (10 mg/kg) or placebo every 4 weeks for 7 doses and every 12 weeks thereafter**

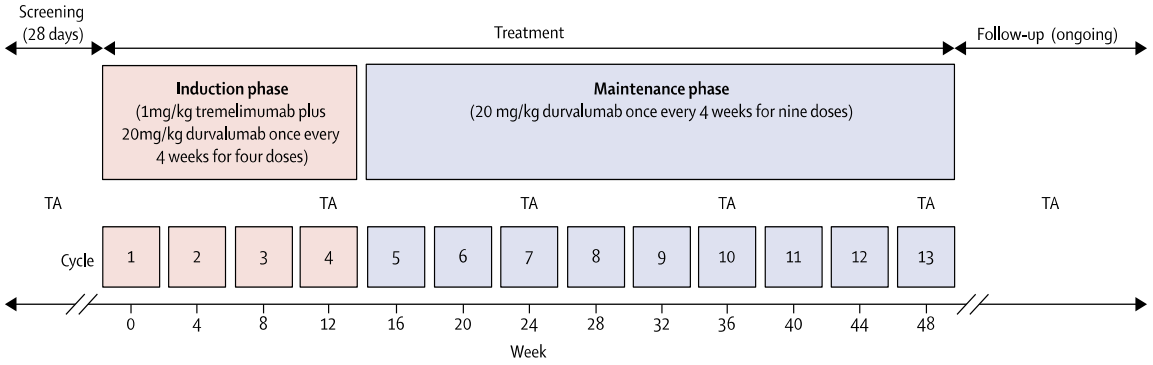
NO BENEFIT OF CTLA - 4 AS A MONOTHERAPY
MORE ADVERSE EVENTS

MEDIAN OS 7.7 vs 7.3 months
ADVERSE EVENTS ≥ Grade 3 65 % vs 48%

Maio et al. Lancet Oncol. 2017 Sep;18(9):1261-1273.

NIBIT-MESO-1 Trial

PDL1 inh + CTLA-4 inh- 1st /2nd line



Phase 2 Non randomized study Open label

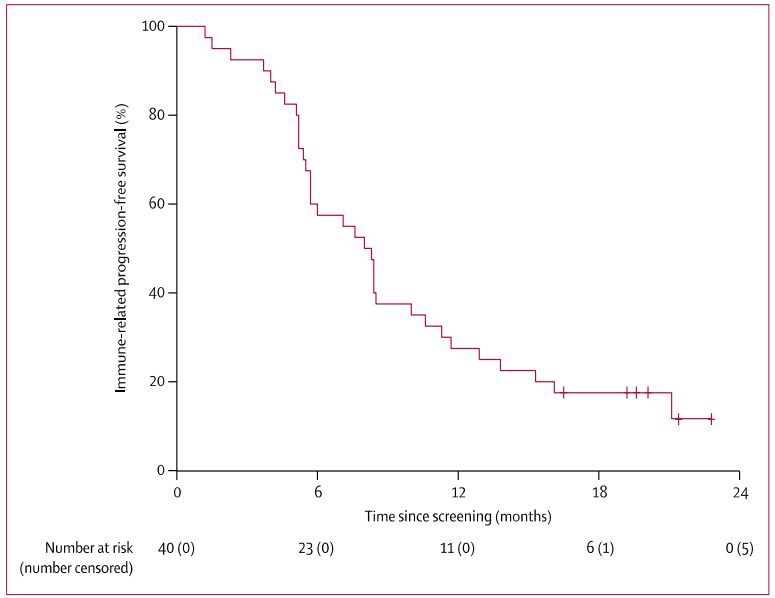
Oct 30, 2015, to Oct 12, 2016, 40 patients

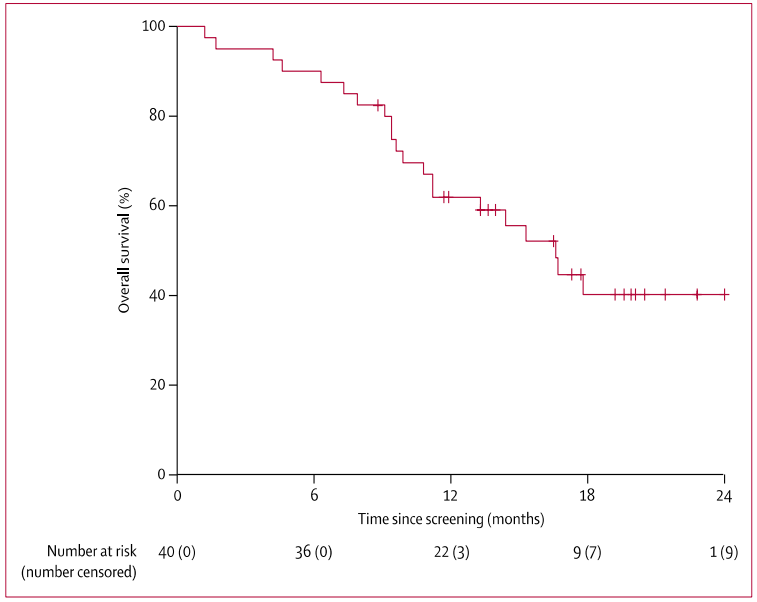
1st line or 2nd line

ECOG ≤ 1

	Immune-related modified RECIST (n=40)	Modified RECIST (n=40)
Objective response	11 (28%; 15–44)	10 (25%; 13–41)
Complete response	0 (0%)	0 (0%)
Partial response	11 (28%)*	10 (25%)†
Stable disease	15 (38%)	15 (38%)
Disease progression	14 (35%)	15 (38%)
Disease control	26 (65%; 48–79)	25 (63%; 46–77)
Duration of objective response (months)‡	16·1 (11·5–20·5)	13·8 (11·5–20·5)
Duration of disease control (months)	10·6 (8·2–16·5)	10·6 (8·2–16·0)

Data are n (%), n (%; 95% CI), or median (IQR). RECIST=Response Evaluation Criteria in Solid Tumors. *Confirmed in 10 patients; histological types included epithelioid (n=9) and biphasic (n=2). †Confirmed in nine patients; histological types included epithelioid (n=8) and biphasic (n=2). ‡Includes only patients with a confirmed partial response.





Calabro et al. Lancet Respir Med 2018; 6: 451–60

Median PFS 8 months

Median OS 16.6 months

NIBIT-MESO-1 TRIAL
PDL1 INH + CTLA-4 INH

	0%	≥1%	≥5%	≥10%	≥25%	≥50%
Patients without PD-L1 expression	15	18	21	27	31	34
Patients with PD-L1 expression	23	20	17	11	7	4
Immune-related objective response						
Patients without PD-L1 expression	4 (27%; 3–69)	4 (22%; 3–61)	5 (24%; 4–59)	8 (30%; 8–61)	8 (26%; 7–55)	10 (29%; 10–57)
Patients with PD-L1 expression	7 (30%; 7–64)	7 (35%; 9–71)	6 (35%; 7–74)	3 (27%; 2–76)	3 (43%; 3–92)	1 (25%; 0–94)
p value	0·80	0·39	0·44	0·88	0·37	0·85
1-year overall survival (%)						
Patients without PD-L1 expression	44% (16–72)	42% (16–68)	51% (27–75)	55% (35–75)	44% (24–64)	42% (24–60)
Patients with PD-L1 expression	62% (40–84)	66% (44–88)	59% (33–85)	55% (20–90)	62% (24–100)	66% (22–100)
p value	0·86	0·37	0·78	0·56	0·86	0·36
Immune-related progression-free survival (months)						
Patients without PD-L1 expression	5·2 (4·5–5·8)	5·2 (4·5–5·8)	5·7 (4·9–6·4)	5·7 (2·9–8·1)	5·2 (2·8–7·3)	5·2 (2·4–7·9)
Patients with PD-L1 expression	8·5 (7·8–9·0)	11·7 (6·9–16·5)	8·5 (7·7–9·1)	8·5 (7·5–9·4)	8·5 (8·2–8·7)	11·7 (8·9–14·5)
p value	0·38	0·13	0·51	0·75	0·87	0·99
Immune-related disease control						
Patients without PD-L1 expression	8 (53%; 16–88)	9 (50%; 16–84)	12 (57%; 24–86)	16 (59%; 29–85)	18 (58%; 30–83)	21 (62%; 34–85)
Patients with PD-L1 expression	16 (70%; 36–93)	15 (75%; 38–96)	12 (71%; 31–95)	8 (73%; 24–98)	6 (86%; 24–100)	3 (75%; 6–100)
p value	0·31	0·11	0·39	0·43	0·17	0·60

Data are n, n (%; 95% CI), % (95% CI), or median (IQR). Data are shown for 38 patients who had sufficient archival tumour tissue for analysis. p values are for the differences between patients with and without PD-L1 expression for each cutoff.

	Grade 1–2	Grade 3–4
Any treatment-related adverse event	27 (68%)	7 (18%)
Dermatological (rash, pruritus, erythema multiforme, psoriasis)	22 (55%)	0
Gastrointestinal (diarrhoea, nausea, vomiting)	10 (25%)	1 (3%)
Pancreatic (amylase or lipase increase)	3 (8%)	2 (5%)
Endocrine disorders (hypothyroidism, hyperthyroidism, diabetes insipidus)	4 (10%)	0
Hepatic (AST or ALT increase)	1 (3%)	2 (5%)
Haematological (anaemia, neutropenia, thrombocytopenia)	1 (3%)	2 (5%)
Neuropathy (limbic encephalitis, peripheral neuropathy)	1 (3%)	1 (3%)
Renal disorders (acute kidney injury)	1 (3%)	0

Data are number of patients (%). Safety population included 40 patients.
AST=aspartate aminotransferase. ALT=alanine aminotransferase.

TREMELIMUMAB + DURVALUMAB – WELL TOLERATED

Calabro et al. Lancet Respir Med 2018; 6: 451–60

MAPS 2 TRIAL

PD1 INH + CTLA 4 INH IN 2ND LINE

STUDY	MAPS 2 TRIAL (RCT)
SUBJECTS	Histologically proved MPM relapsing after 1 or 2 prior lines including pemetrexed/platinum doublet N=125, April 2016 to August 2016, 1:1
INTERVENTION	Nivo 3 mg/kg q2w, or Nivo 3 mg/kg q2w plus Ipi 1 mg/kg q6w, until progression or unacceptable toxicity
RESULTS	PFS 4 months vs 5.6 months ORR 18.5% vs 27.8% Grade 3/4 toxicities 12.7 % vs 22.9% Positive PD-L1 IHC did not predict longer PFS or OS PDL $\geq$ 1 % response seen Nivolumab arm, PDL $\geq$ 25% response seen in combination arm

NCCN guidelines 2018 recommend this combination as 2nd line therapy

Scherpereel et al. . *Proc Am Soc Clin Oncol* 2017; **35** (suppl 18)**:** LBA8507.

CHEMOTHERAPY GUIDELINES

GUIDELINES	ASCO (2018)	BTS (2018)	NCCN (2018)
Indications	• Non surgical candidates with good PS • **Adjuvant or neo adjuvant therapy** with surgery	Recommended (same)	Recommended (same)
1st line Regimens	1. Cisplatin + pemetrexed 2. Carboplatin + pemetrexed (Only for intolerable cases)	1. Cisplatin + pemetrexed 2. Carboplatin+ pemetrexed(intolerable cases) 3. Raltitrexed (alternative to pemetrexed)	**1. Cisplatin + pemetrexed** **2. carboplatin + pemetrexed (both equal)** 3. Cisplatin + Gemcitabine 4. Pemetrexed + vinorelbine 5. Single agent pemetrexed 6. Single agent vinorelbine
Bevacizumab	Can be added to Cisplatin + pemetrexed in those with PS $\leq$ 1 + age < 75 years + no cardiovascular disease/uncontrolled HTN/bleeding/thrombosis risk	Same	Same
Effect of PS on chemo	PS 1 – dual chemo PS 2 – Single agent chemo vs palliation PS $\geq$ 3 – only supportive care and palliation	PS 0-1 - dual chemotherapy PS 2-4 - supportive care	PS 0-2 – Dual chemo PS 3-4 – supportive care and palliation

CHEMOTHERAPY GUIDELINES

GUIDELINES	ASCO (2018)	BTS (2018)	NCCN (2018)
2nd line chemo for PD	1. Pemetrexed 2. Vinorelbine 3. Enrollment in clinical trials	Clinical trials needed	1. Pemetrexed (if not used as 1st line) or good sustained response before interruption 2. Vinorelbine 3. Pembrolizumab 4. Nivolumab +Ipilimumab 5. Gemcitabine
Maintenance therapy after PR/SD	No	No	Bevacizumab can be used (if used in 1st line)
Intracavitory therapies	chemotherapy or photodynamic therapy **may be considered in an experimental basis**	No	same
Number of cycles	4 to 6	-	4 To 6

RADIOTHERAPY GUIDELINES

INDICATIONS	ASCO (2018)	BTS (2018)	NCCN (2018)
Prophylaxis to sites of intervention	No	No	May be used
Adjuvant therapy to resected tracts (histology proven)	Yes	No	No mention
Adjuvant therapy to hemithorax after surgery	**May be Given (Decreases local recurrence)**	No	**After EPP - Yes** **After P/D - Optional** and not routinely recommended
Neo Adjuvant radiotherapy	Before EPP- YES **Before P/D – NO (Increased lung toxicity)**	No	Not recommended
Small isolated localized asymptomatic Recurrence	Yes (sole therapy)	No	No mention
Palliation to metastatic sites	Yes	Yes	Yes

ADJUVANT RADIOTHERAPY

❖**All critera to be met**

- ECOG PS ≤1
- Good functional pulmonary status
- Good function of contralateral kidney confirmed by renal scan
- Absence of disease in abdomen, contralateral chest, or elsewhere
- Not on supplemental oxygen

❖ **IMRT – Intensity Modulated Radiotherapy preferred**

ASCO 2018
NCCN 2018

ROLE OF PROPHYLACTIC RADIOTHERAPY

STUDY	SUBJECTS (N)	INTERVENTION	NODULES IN INTERVENTION GROUP	NODULES IN CONTROL GROUP	P VALUE	COMMENTS
Boutin et al 1995	40	21G in 3 F	0/20	8/20	P<0.001	Prechemotherapy era
Bydderet al 2004	43 (58 sites)	10G in 19Mev	2/28	3/30	Not significant	Chemotherapy patients excluded
O'Roukeet al 2007	61	21G in 3F	4/31	3/30	Not significant	Chemotherapy patients excluded
Clive et al 2016	203	21G in 3F	9/102	16/101	Not significant	Chemotherapy included

NO BENEFIT OF PROPHYLACTIC RADIOTHERAPY

Woolhouse I, *et al*. *Thorax* 2018;73:i1–i30

RADIOTHERAPY DOSING

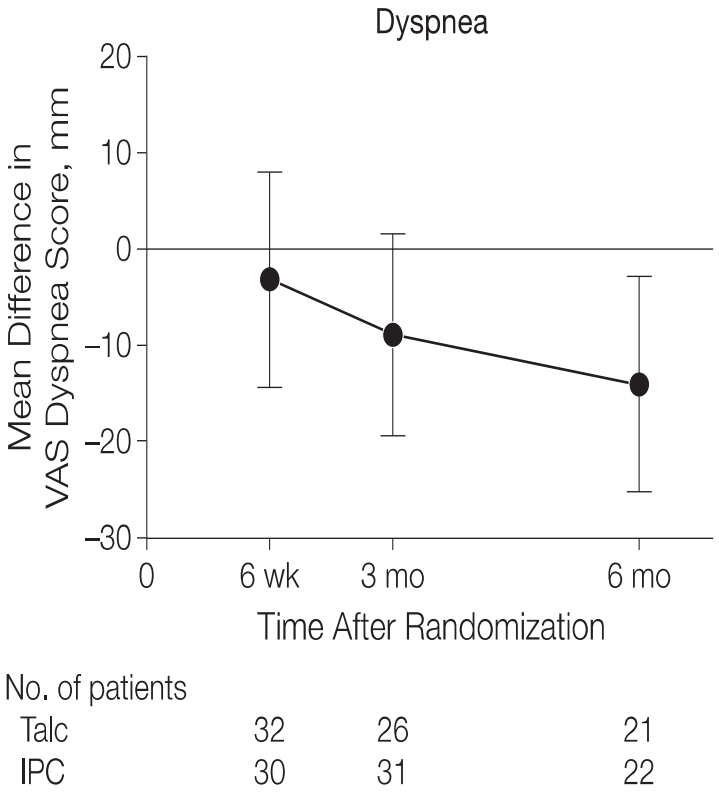
Treatment type	Total dose (Gy)	Fraction size (Gy)	Duration (weeks)
• **Postoperative after EPP** 1. Negative margins 2. Microscopic-macroscopic positive margins	 50-54 54-60	 1.8-2 1.8-2	 5-6 6-7
• **Palliatiion**	30	3	2
• **Post pleurectomy/decortication** 1. Negative margins 2. Microscopic positive margins	 45-50.4 50-54	 1.8 - 2 1.8 - 2	 5-6 5-6

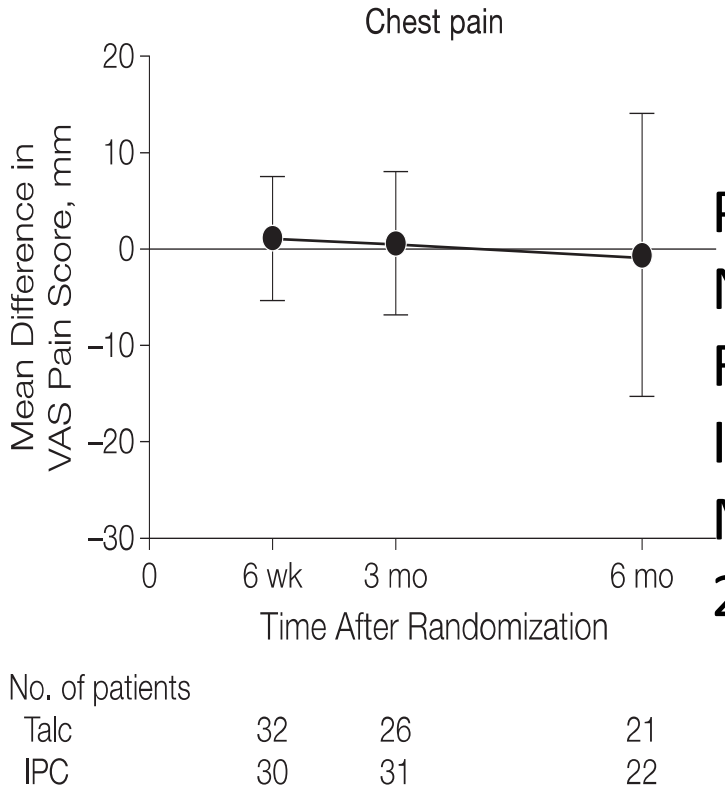
The mean lung dose should be kept as low as possible, preferably <8.5 Gy

NCCN 2018

PALLIATION

INDWELLING PLEURAL CATHETER *VS* PLEURODESIS





Proven malignant pleural effusion

N=106

Randomised IPC 52: 54 TP (via ICTD)

Mean VAS Dyspnoea (1st 42 days)

24.7 vs 24.4 (p=0.96)

Davies et al.. *JAMA* 2012;307:2383–9.

PALLIATION

SURGICAL VS ICTD PLEURODESIS

	Overall (n=165)	Surgical pleurodesis (n=78)	Bedside pleurodesis (n=87)	p Value
Pleurodesis outcome				
Complete success	29.7%	28.2%	31.0%	p=0.82
Partial success	38.8%	39.7%	37.9%	p=0.94
Failure	31.5%	32.1%	31.0%	p=0.98
Demographics				
Mean (SD) age	69.9 (10.5)	67.1 (10.4)	72.3 (10.5)	p=0.00
Male	86.7%	83.3%	89.7%	p=0.34
Survival in days (diagnosis to death)	443 (197–743)	410 (186–753)	455 (197–743)	p=0.52
Days from diagnosis to pleurodesis	17 (0.0–63.0)	0.0 0.0–29.5)	54.0 (9.0–121.0)	p<0.00
Subtype				
Epithelioid	86	40	46	p=0.21
Sarcomatoid	9	8	1	
Biphasic	30	19	11	
Unclassified*	40	11	29	
Hospital admissions (episodes)	6.0 (2.0–9.0)	5.0 (2.0–9.0)	6.0 (2.5–9.0)	p=0.51
Hospital admissions (total days from diagnosis)	20.0 (12.0–31.0)	19.0 (12.0–28.0)	23.0 (13.0–35.0)	p=0.36
Hospital admissions (total days expressed as % of remaining lifespan spent)	5.1% (2.1–10.9%)	4.9% (2.1–12.1%)	5.1% (2.1–10.3%)	p=0.96

Fysh ETH, et al. Thorax 2013;68:594–596.

PALLIATION

BTS 2018 STATEMENT ON PALLIATION

1. No single fluid control technique (surgical including pleurectomy and VATS, thoracoscopic talc poudrage, talc slurry or IPC) has been shown to be superior in terms of patient symptoms or pleurodesis success in MPM
2. VATS-PP has been shown to be more expensive, associated with greater complications and longer hospital stay than talc slurry pleurodesis
3. Indwelling pleural catheters and talc slurry pleurodesis have similar patient-related outcomes in malignant effusion and MPM.

PALLIATION- BTS 2018 GUIDELINES

SYMPTOM	THERAPY
BREATHLESSNESS	1. Pleural fluid control 2. Sustained release morphine 3. Breathing control
Pain	1. Opioids 2. Amitriptyline, duloxetine, gabapentin or pregabalin for neuropathic pain 3. Radiotherapy for refractory localised pain
Fatigue	Aerobic exercises
Anorexia	Megestrol acetate

NCCN 2018 GUIDELINES

Malignant pleural mesothelioma

- Chest/abdominal CT with contrast
- Chest MRI with contrast (optional)
- Consider VATS and/or laparoscopy if suspicion of contralateral or peritoneal disease

Clinical stage I-III + Epithelial histology + PS ≤ 2

- PFTs including DLCO
- PET CT
- Mediastinoscopy
- EBUS-FNA
- Perfusion scan (if FEV1 < 80%)
- Cardiac stress test

Trimodality therapy (Surgery + chemo ± radiotherapy)

Clinical stage IV or Sarcomatoid or Mixed histology or Medically inoperable

PS 0-2

1. Observation for progression (especially epitheloid type and minimal symptom burden) or
2. Chemotherapy

PS 3/4

Best supportive care

NCCN 2018 GUIDELINES

Clinical stage I-III + Medically operable + Epitheloid histology

Surgical exploration

Resectable

P/D

Chemotherapy f/b Observation or RT

EPP

Chemo f/b Hemithoracic RT

Unresectable

Chemotherapy

Induction chemotherapy with pemetrexed and cisplatin or carboplatin

Chest CT with contrast
PET/CT for mediastinal assessment

Surgical exploration

Resectable

P/D

Observation or RT

EPP

Hemithoracic RT

Unresectable

Chemotherapy

RESPONSE ASSESSMENT FOLLOWING THERAPY

PARAMETERS	MODIFIED RECIST (2004)	MODIFIED RECIST 1.1 (2018)
How to measure	Perpendicular to a tangent at pleural surface	Perpendicular to a tangent at pleural surface
Where to measure	2 sites at 3 different CT levels ≥ 1 cm apart (**6 sites required**)	Upto a **maximum of 6 sites at 3 different CT levels ≥ 1 cm apart**
Minimal measurable pleural lesion	**≥ 10 mm**	**≥ 7 mm**
Non pleural sites	NOT ADDRESSED	**≥ 10 mm**
Bilateral pleural disease	NOT ADDRESSED	Considered a single organ with total upto 6 lesions distributed across both hemithoraces
Pleural effusion	NOT ADDRESSED	Not included in measurement
Follow up of lesions (initially measurable) which reduce to below the measurable limit	NOT ADDRESSED	Default value of 2 mm for non measurable follow up lesions

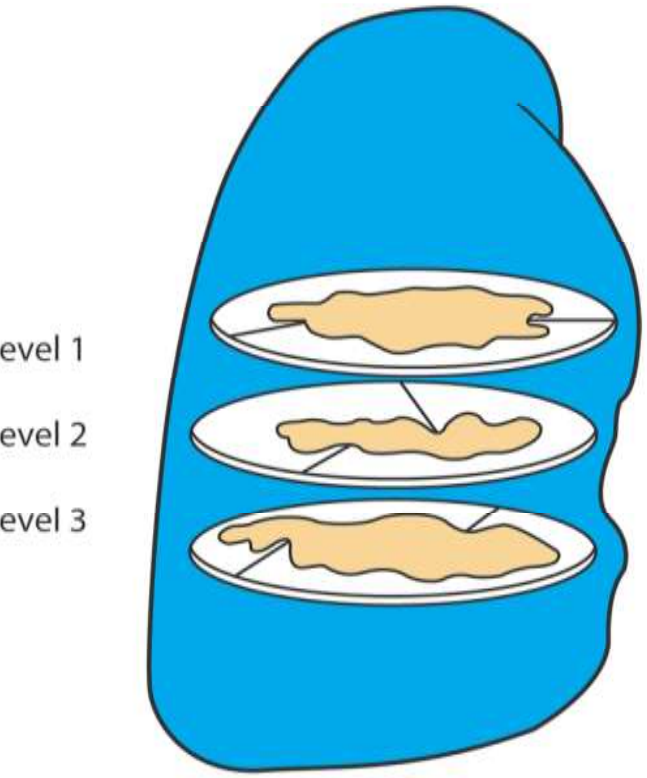
Armato et al. J Thorac Oncol 2018. Jul;13(7)

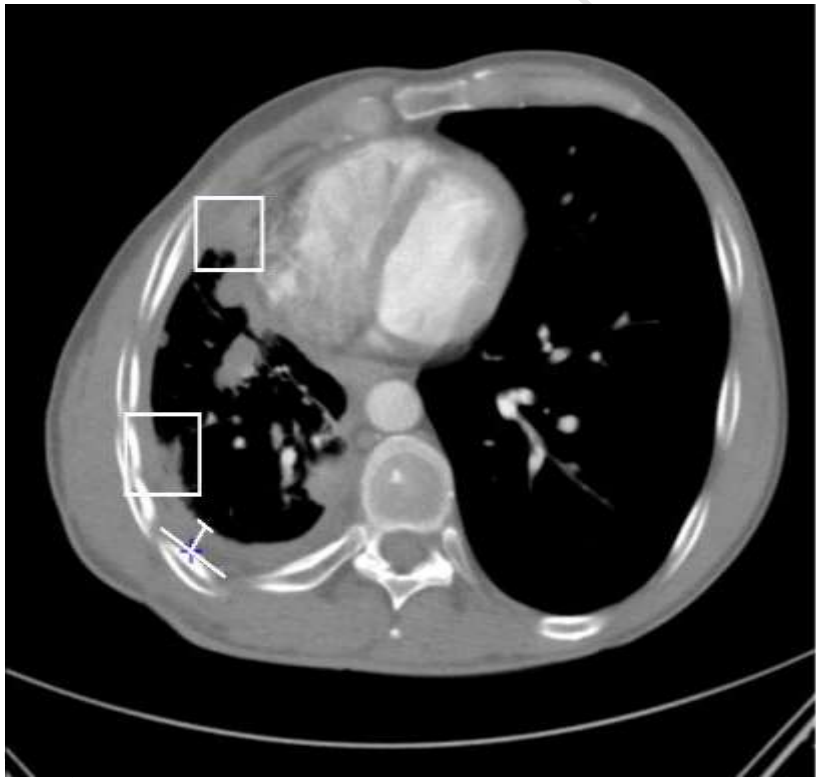
RESPONSE ASSESSMENT FOLLOWING THERAPY

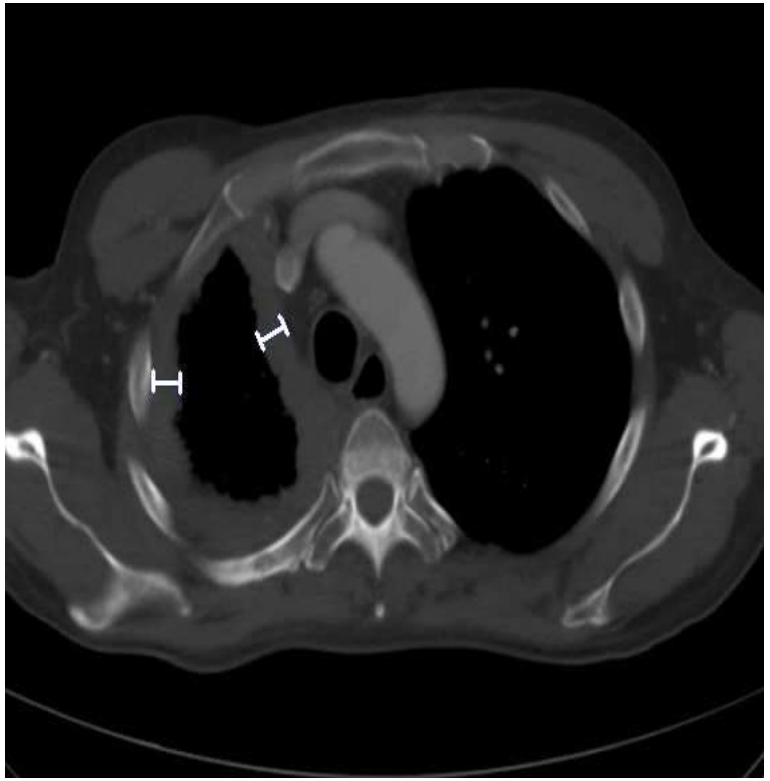
PARAMETERS	MODIFIED RECIST (2004)	MODIFIED RECIST 1.1 (2018)
Total number of lesions to measure	NOT MENTIONED	Maximum of 5 target lesions with a maximum of 2 from each organ
Non target lesions	NOT MENTIONED	• Non measurable lesions • Measurable lesions not that are not measured • Circumferential pleural thickening and pleural nodularity
Lymphnodes	≥ 15 mm SAD considered significant	≥ 10 mm < 15 mm – non target lesions ≥ 15 mm – target lesions < 10 mm – non pathological
Measurement	Same observer and same display parameters	same
PET CT	Not mentioned	Not recommended to use

Armato et al. J Thorac Oncol 2018 Jul;13(7)

MEASURING THE TARGET LESIONS







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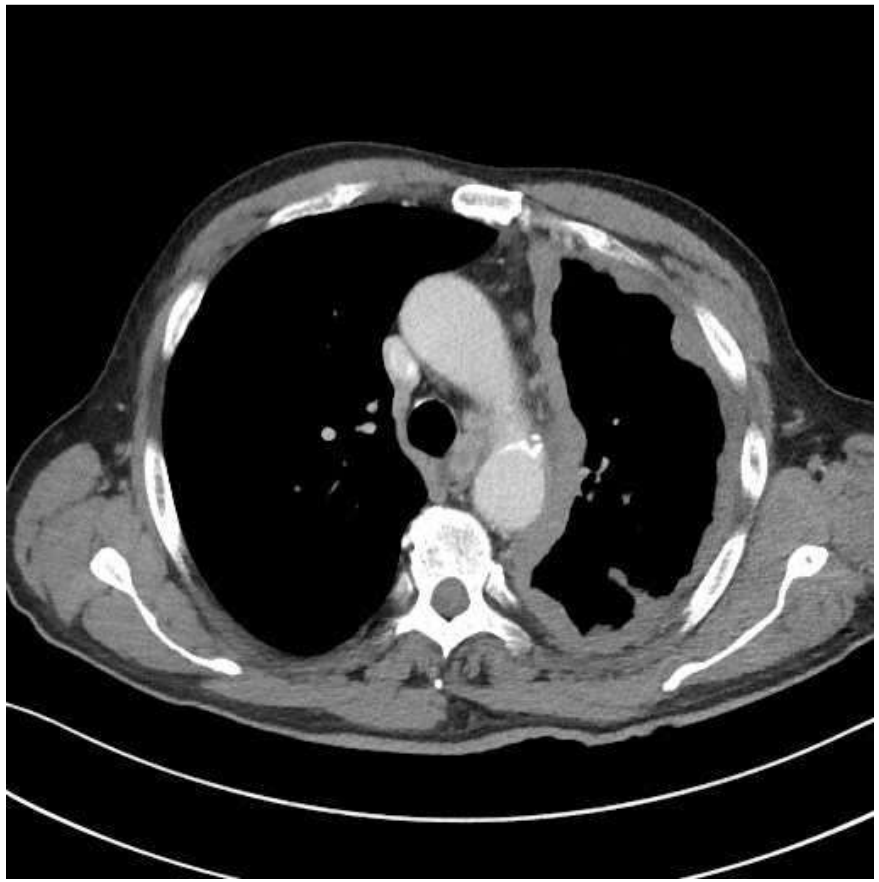
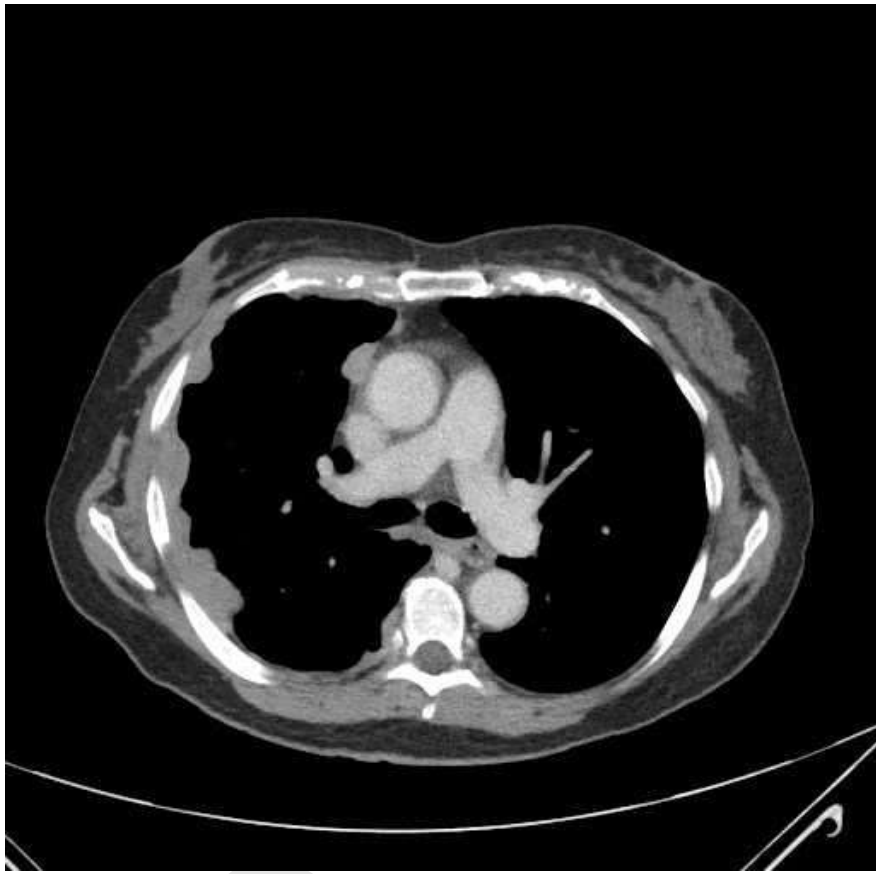
NON TARGET LESIONS



CIRCUMFERENTIAL PLEURAL THICKENING



PLEURAL NODULARITY

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OBJECTIVE RESPONSE

Complete response (CR) :

Disappearance of all pleural and non-pleural disease (including pleural thickening considered to represent tumor)

Partial response (PR):

- Summed measurement ≥ 30 % decrease
- Confirmed by a follow-up scan at least 4 weeks later

Progressive disease (PD) :

- Summed measurement ≥ 20 % increase from the nadir of the summed measurements from all prior scans (up to and including the baseline scan) + ≥ 5 mm absolute increase
- An unequivocal new non-pleural lesion
- Unequivocal new focus of pleural thickening that exceeds the minimum measurable size

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PROGNOSTIC SCORES

- Validated
  - The EORTC Prognostic Score
  - Decision tree analysis
  - LENT score
  - CALGB score
- Not Validated
  - The Neutrophil-to-Lymphocyte ratio (NLR)

EORTC PROGNOSTIC SCORE

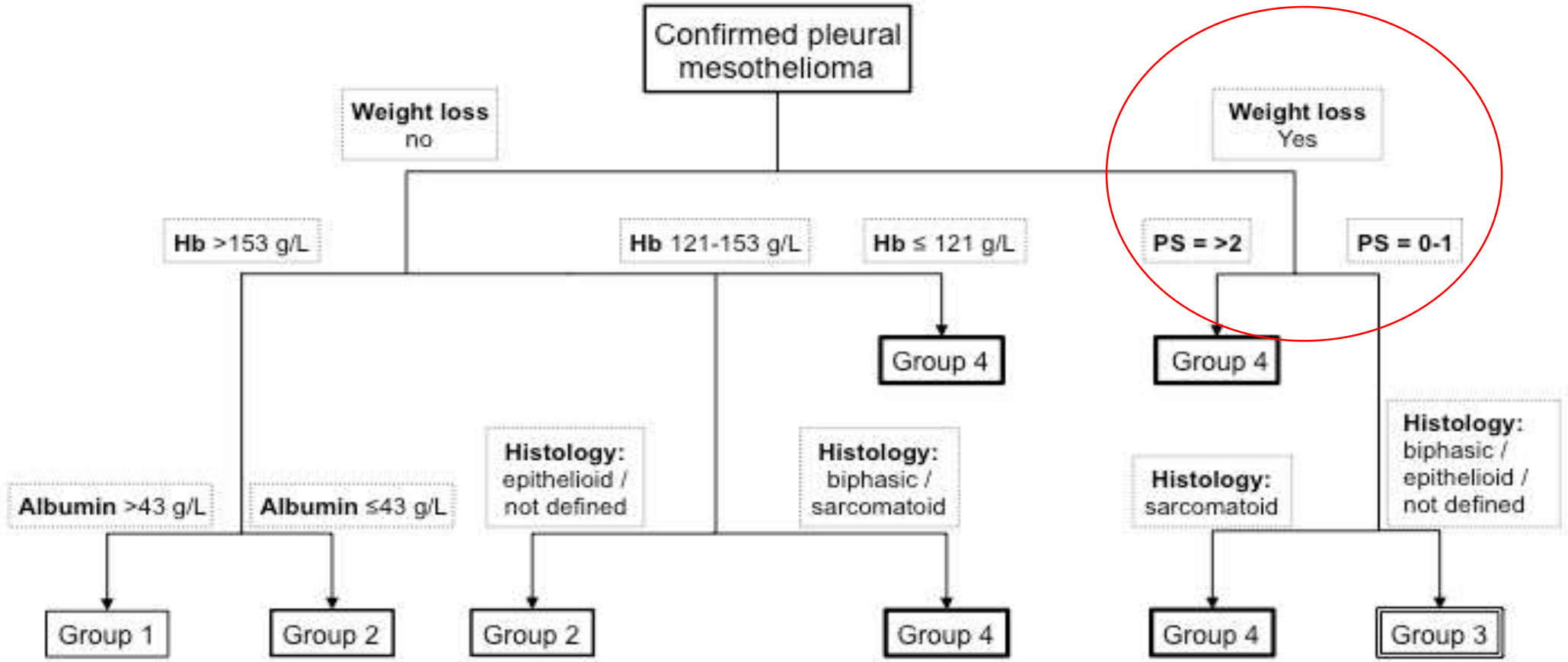
- EPS = 0.55 (if WBC>8.3 x 109/L) + 0.6 (if PS=1 or 2) + 0.52 (if histological diagnosis probable or possible) + 0.67 (if histology=sarcomatoid) + 0.6 (if male)

❑EPS < 1.27 - Good prognosis

❑EPS > 1.27 - Poor prognosis

Curran et al. the European Organization for Research and Treatment of Cancer experience. *J Clin Oncol* 1998;16:145–52.

DECISION TREE ANALYSIS



PS = ECOG Performance Status
Hb = haemoglobin
IQR = interquartile range

Risk group median (IQR) survival:
1. 34.0 (22.9-47.0) months
2. 17.7 (11.6-25.9) months
3. 12.0 (6.0-20.6) months
4. 7.4 (3.3-11.1) months

Brims FJ et al. J Thorac Oncol. 2016 Apr;11(4):573-82

CALGB SCORE STUDY

pain, platelet count >400,000/μL, and increasing age >75 years are predictive of a greater risk of dying early.

Exponential survival trees were used in an effort to define patient subgroups with similar prognoses using all patient data. The results formed the regression tree shown in Figure 1. The first and most significant prognostic split was by PS category (0 vs 1, 2). Age, hemoglobin, WBC, presence of chest pain, and weight loss defined further splits of the tree. The resulting tree included 10 terminal nodes (note: the terminal nodes are rectangular boxes in Fig 1) that were not split into smaller subgroups owing to their homogeneity of prognosis. A Cox

Multivariate Analyses With Adjustment for Study Arm

The analyses presented have considered the prognostic importance of patient characteristics unrelated to treatment. A natural question is whether the assigned study arm had any impact on survival beyond that predicted by nontreatment factors. In multivariate analysis limited to variables collected in all studies (N=309), there was no significant difference among the 10 treatment regimens. However, when study arm is considered in the analysis limited to studies collecting all variables (N=195), the prognosis with treatment on 9031 (cisplatin plus dihydroazacytidine [DHAC]) and 9234 (paclitaxel) is

Herndon et al. *Chest* 1998;113:723–31.

LENT SCORE

Mnemonic	variable	score
L	Pleural fluid (IU/L)	0
	< 1500	1
	> 1500	
E	ECOG performance status	
	0	0
	1	1
	2	2
	3-4	3
NLR	< 9	0
	> 9	1
T	Tumor type	
	Low risk (mesothelioma , hematological malignancy)	
	Moderate risk(breast , renal, gynaecological cancers)	
	High risk(lung cancer, other cancer types)	

RISK	TOTAL SCORE	MEDIAN (IQR) SURVIVAL
LOW	0-1	319 days
MODERATE	2-4	130 days
HIGH	5-7	44 days

Clive et al. *Thorax* 2014;69:1098-104.

NEUTROPHIL LYMPHOCYTE RATIO

	Kao *et al* (2010)	Kao *et al* (2011)	Pinato *et al* (2012)	Kao *et al* (2013)	Meniawy *et al* (this study)
Total no. of study patients	173	85	171	148	274
No. in multivariate model	NR	NR	NR	130	274
No. with NLR available	168 (97%)	84 (99%)	159 (94%)	79 (53%)	274 (100%)
Treatments received	Chemotherapy First line (69%) Second line (31%)	Extrapleural pneumonectomy (EPP)	Chemotherapy (41%) Supportive Care (42%) Unknown (17%)	Chemotherapy (53%) Radiotherapy (34%) EPP (5%)	Chemotherapy (62%) Supportive Care (38%) EPP (1%)
Median baseline NLR	NR	3	NR	3.5	3.5
Cutoff used in analysis	< 5 vs ≥ 5	< 3 vs ≥ 3	< 5 vs 5 ≥	< 3 vs 3 ≥	< 5 vs 5 ≥

TAKE HOME MESSAGE

- Mesothelioma is a rare malignancy with extremely poor prognosis
- Traditionally attributed to asbestos exposure
- Many new risk factors have been identified recently including genetic mutations
- Clinical staging is less reliable than other solid malignancies
- Multimodality therapy including surgery, chemotherapy and radiotherapy is the current standard of care with best outcome
- However most patients present with advanced unresectable stage disease
- Maximal cytoreductive surgery is the goal of resection
- Surgery usually considered in early stage, epitheloid subtype
- Pleurectomy/Decortication is the surgery of choice with less morbidity and mortality

TAKE HOME MESSAGE

- However Extrapleural pneumonectomy can be considered in experienced centres to achieve tumour free margin
- Platinum based doublet chemotherapy is the standard 1st line regimen
- Growth factor inhibitors can be added to platinum doublet chemotherapy in selected patients in 1st line setting
- Also newer immunotherapy drugs (PD1/PDL1/ CTLA-4 inhibitors)have been studied alone or in combination for 2nd line settings
- Newer targeted therapies are being studied