Controversies in Mesothelioma

Διονύσης Σπυράτος

Επίκ. Καθηγητής Πνευμονολογίας ΑΠΘ

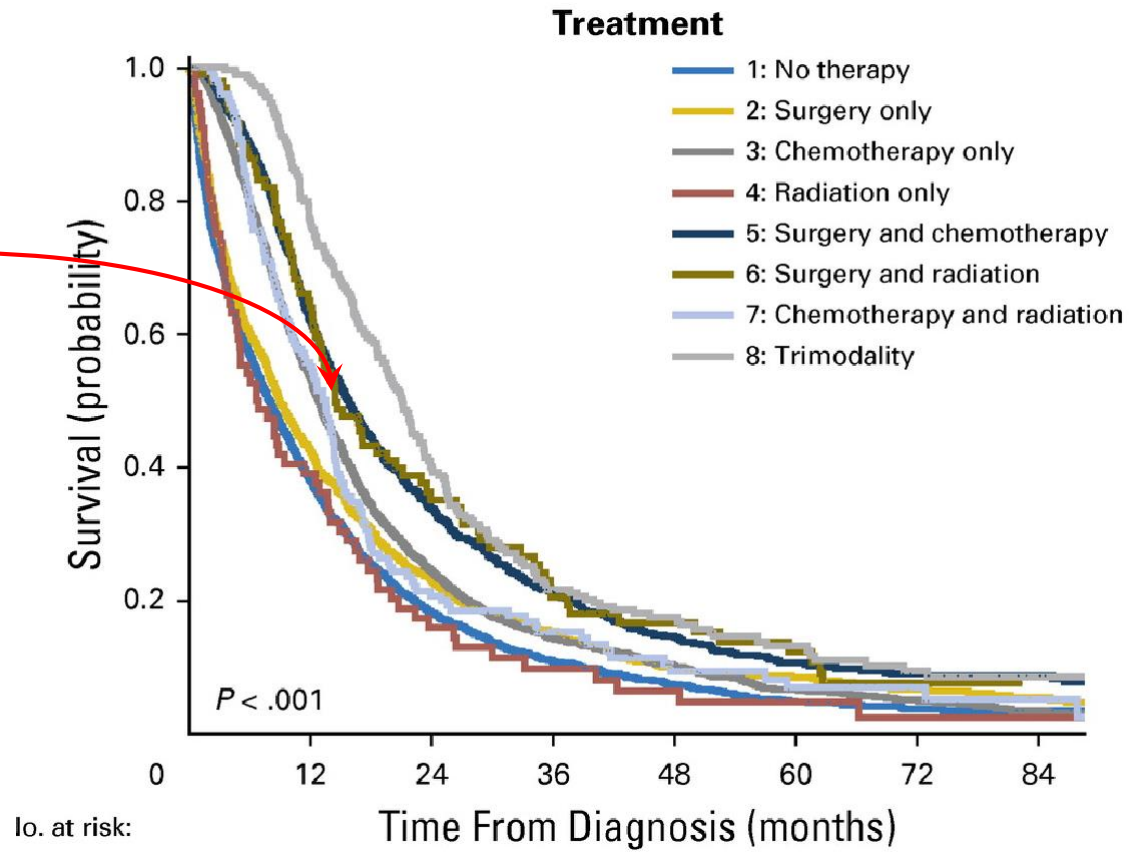
Πνευμονολογική Κλινική ΑΠΘ

ΓΝΘ «Γ. ΠΑΠΑΝΙΚΟΛΑΟΥ»

1. ΑΚΤΙΝΟΘΕΡΑΠΕΙΑ
2. ΑΝΟΣΟΘΕΡΑΠΕΙΑ
3. ΕΝΔΟΫΠΕΖΩΚΟΤΙΚΗ ΘΕΡΑΠΕΙΑ
4. ΧΕΙΡΟΥΡΓΙΚΗ ΑΝΤΙΜΕΤΩΠΙΣΗ

Survival with Trimodality Remains Poor

Surgery
Median Survival
14 Months

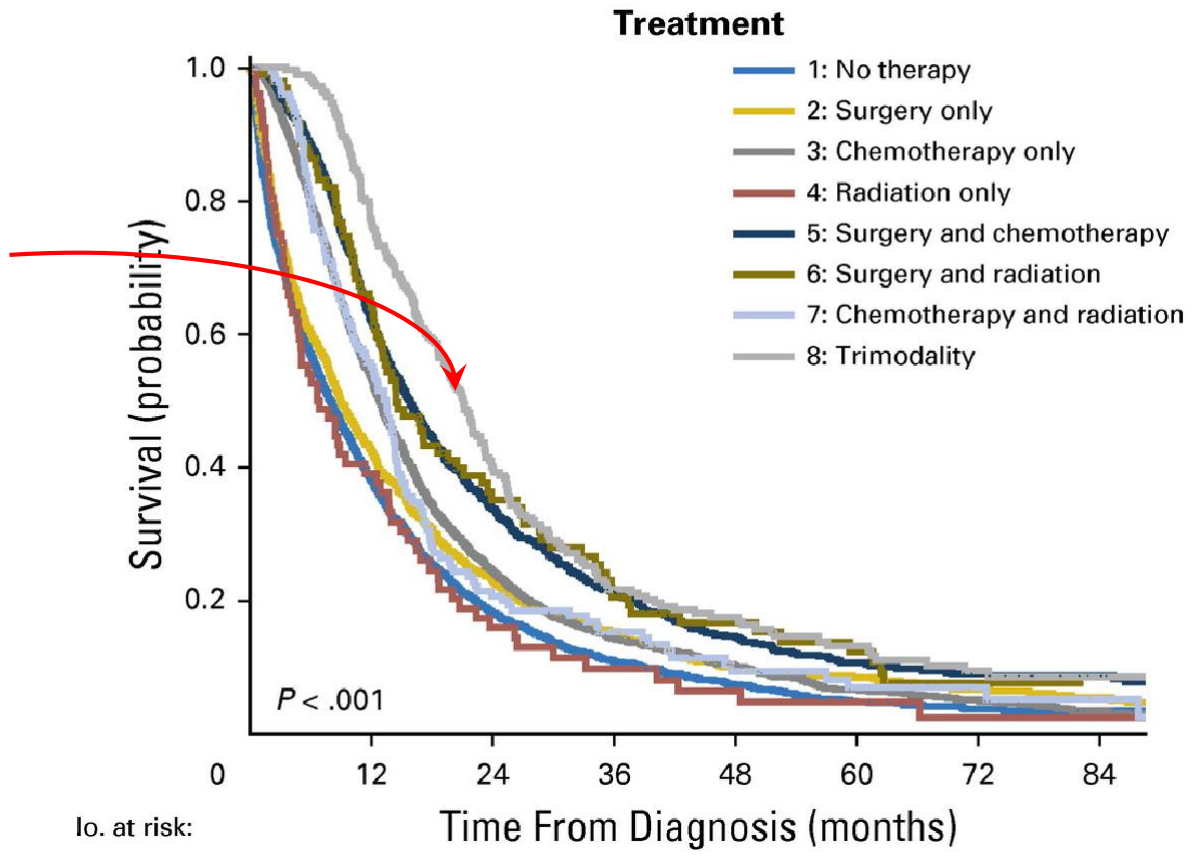


Nelson, J Clin Oncol, 2018

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

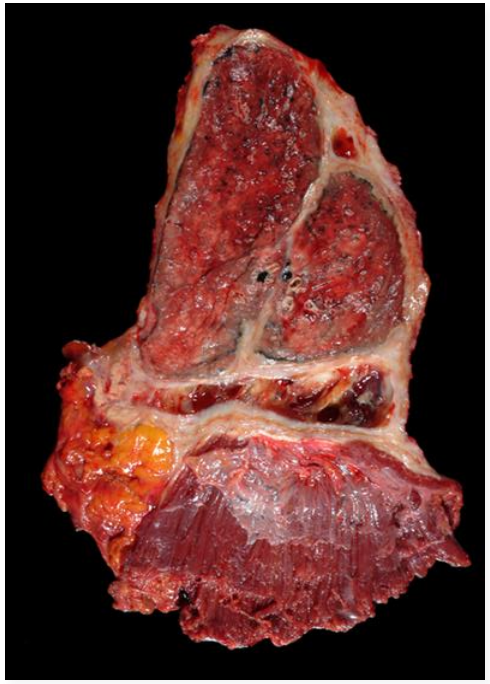
Survival with Trimodality Remains Poor

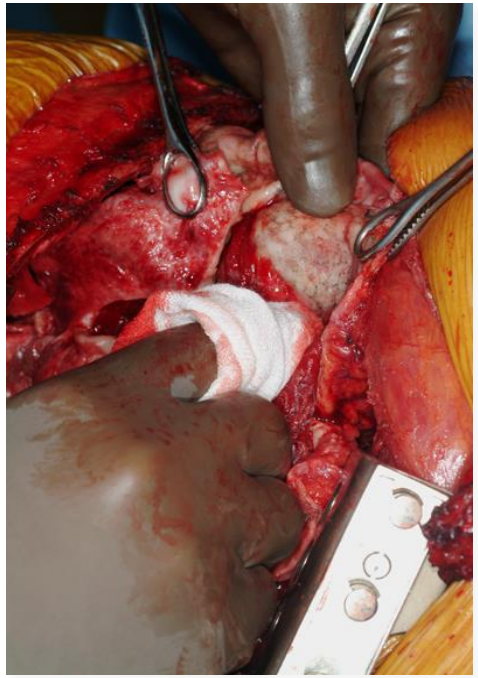
Trimodality
Median Survival
20 Months

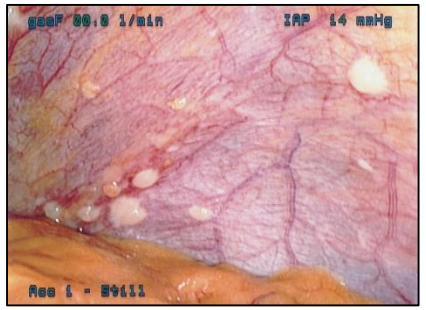


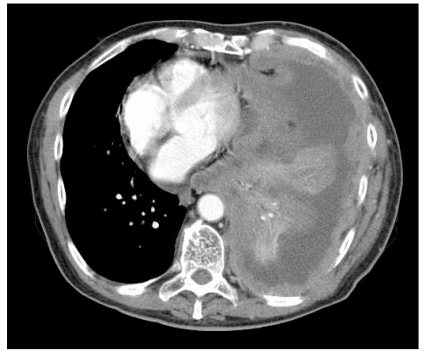
Nelson, J Clin Oncol, 2018

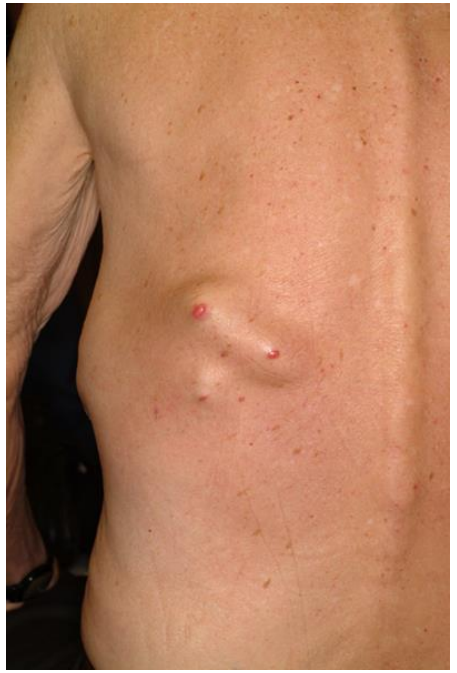
Mesothelioma is Difficult to Treat



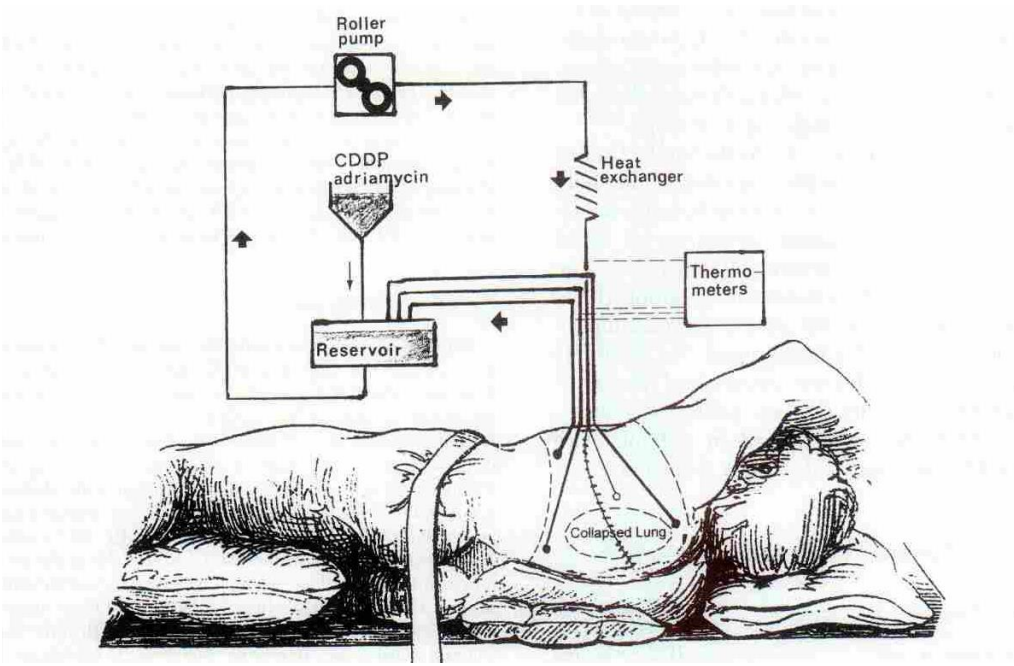


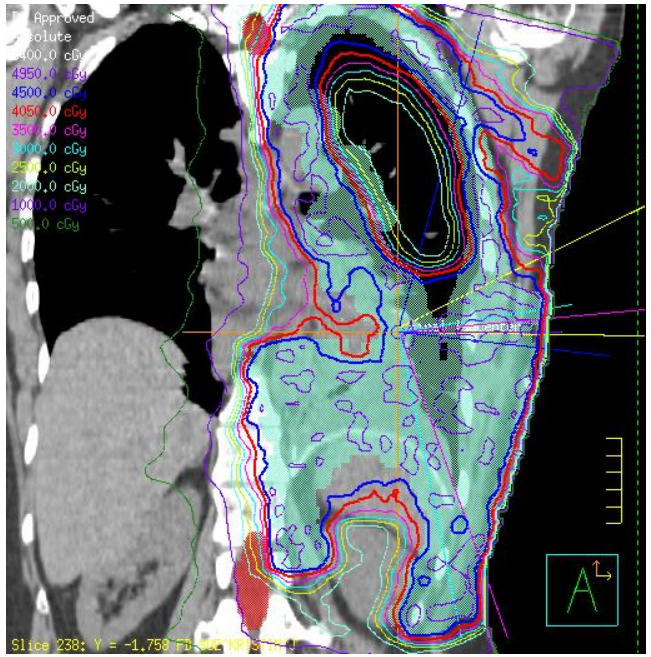






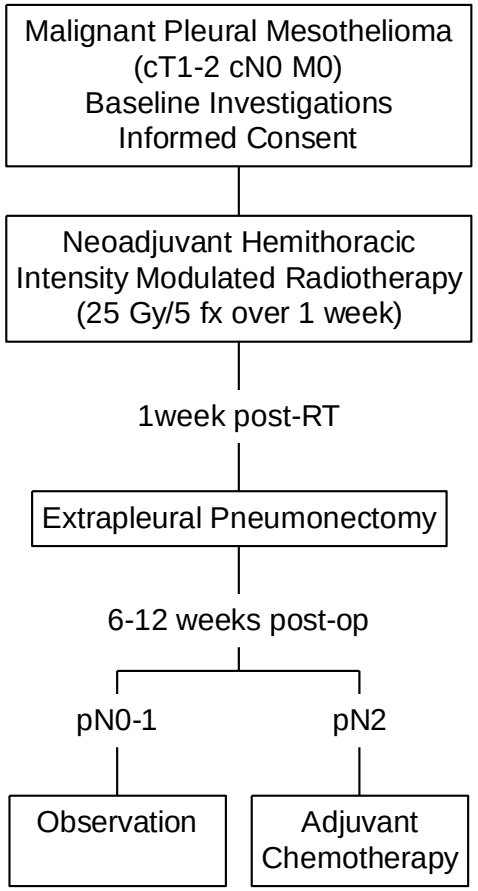
Efforts to Improve Local Control

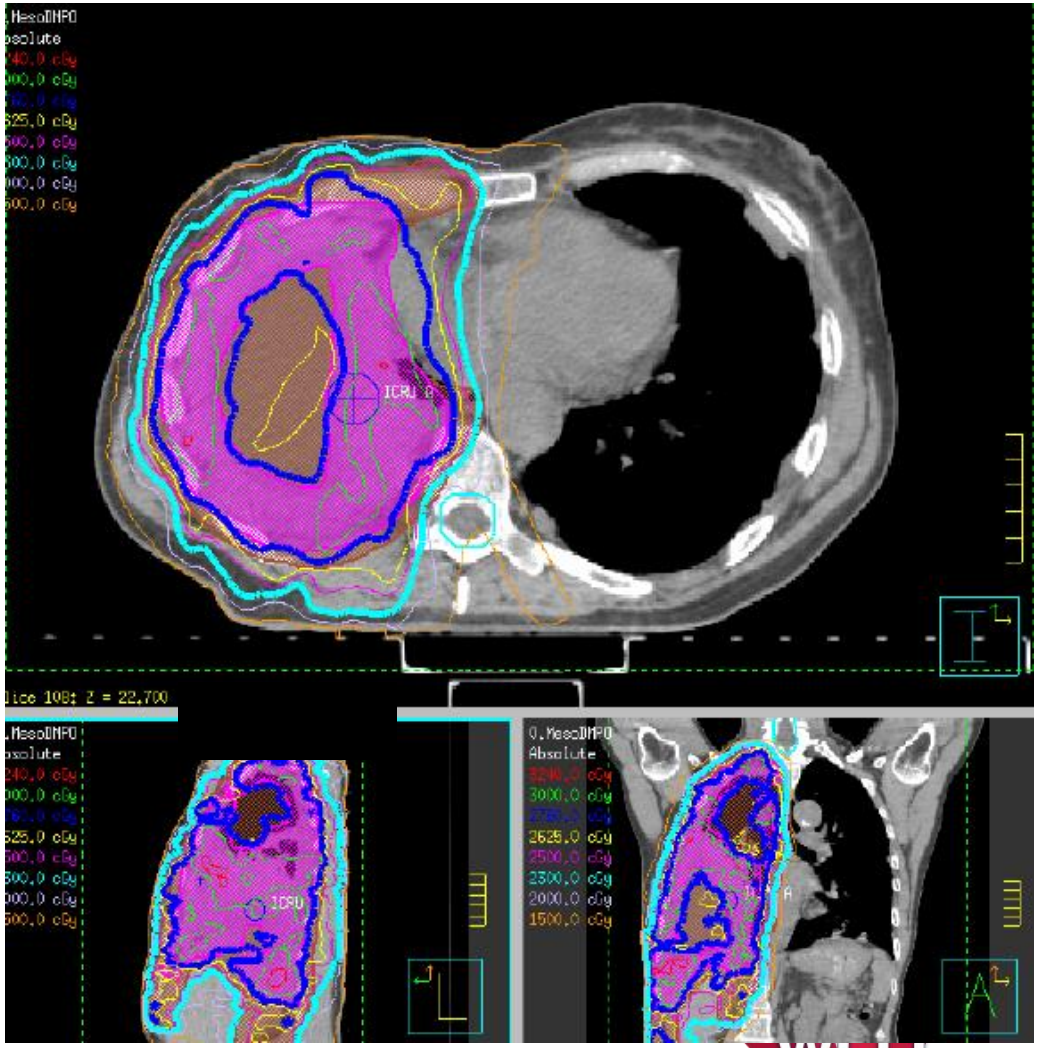




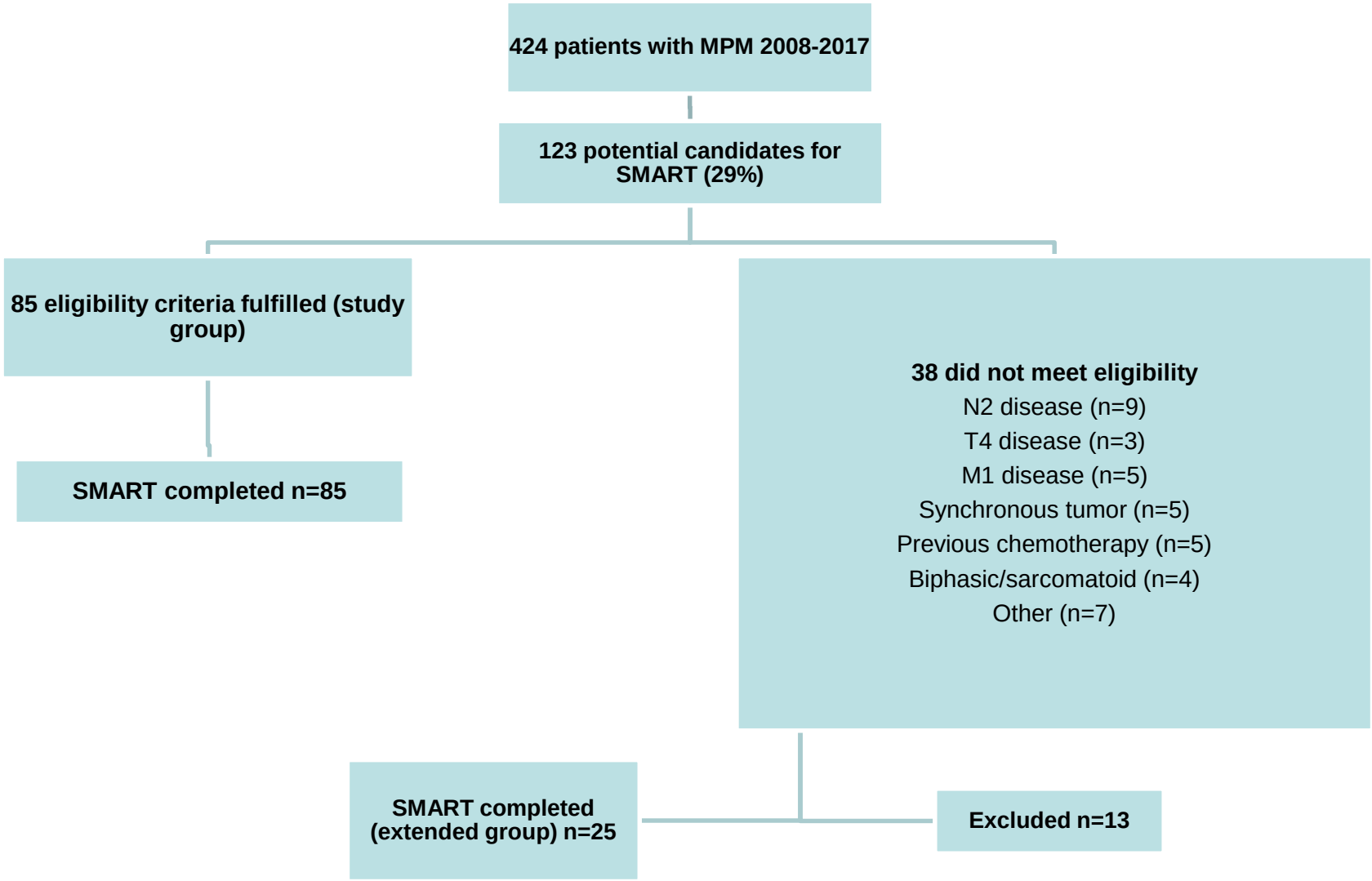
Surgery for Mesothelioma After Radiation Therapy

Study Schema



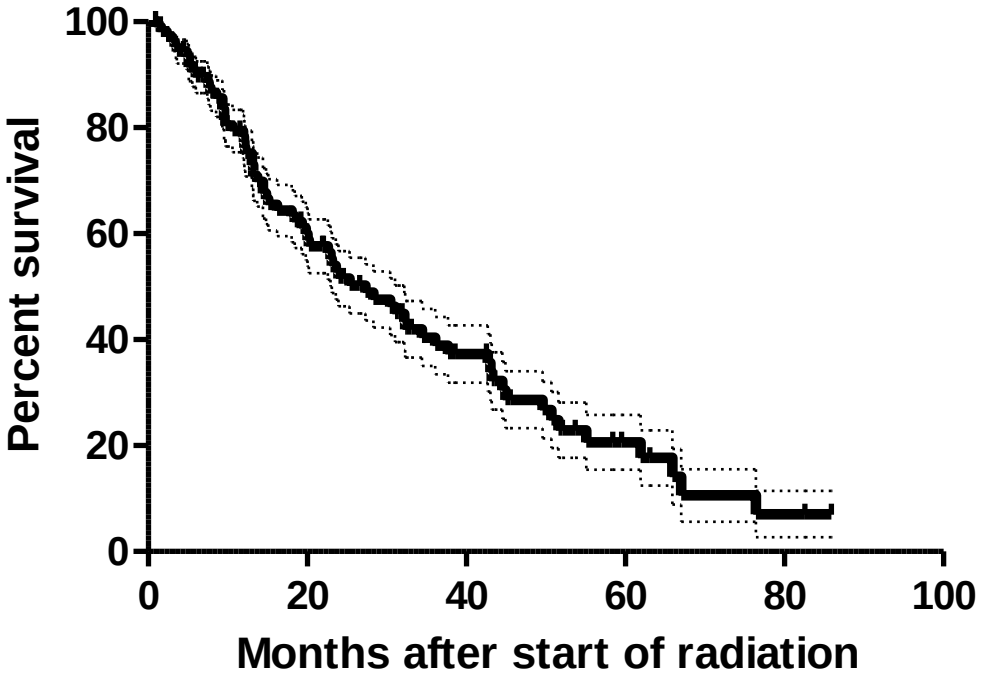


De Perrot. *J Thorac Cardiovasc Surg* 2016;151:468-75

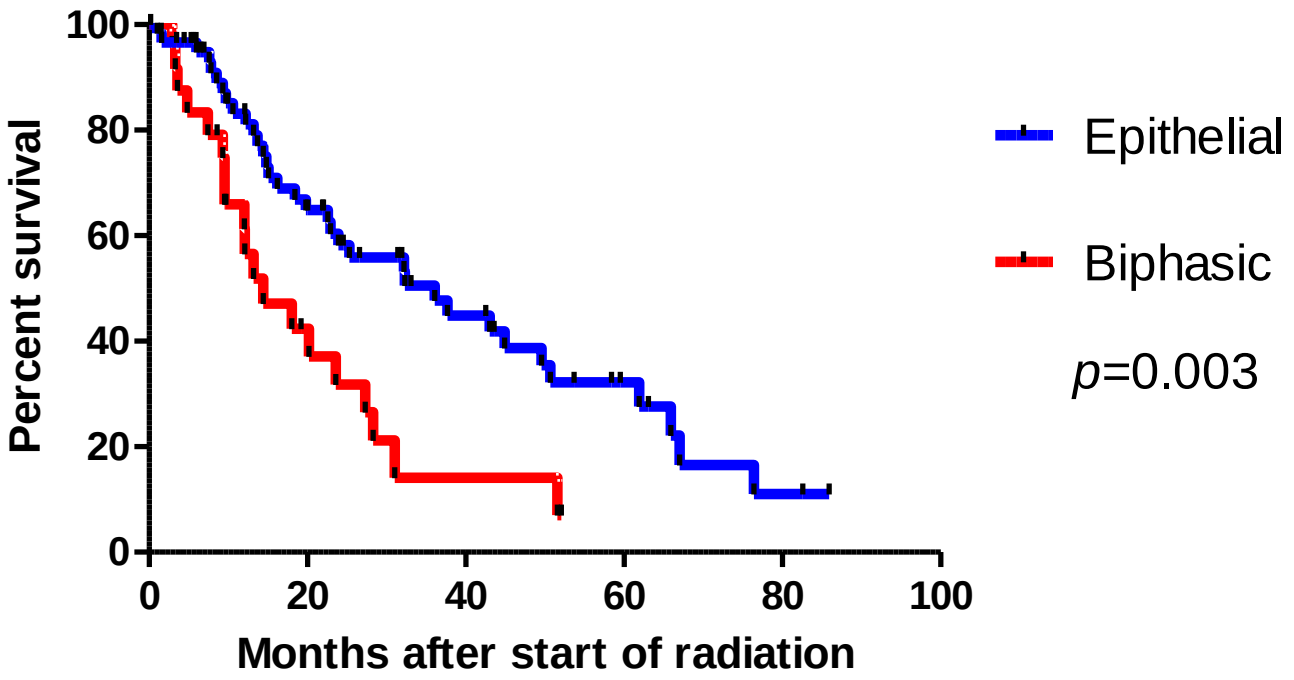

424 patients with MPM 2008-2017
123 potential candidates for SMART (29%)
85 eligibility criteria fulfilled (study group)
SMART completed n=85
38 did not meet eligibility
N2 disease (n=9)
T4 disease (n=3)
M1 disease (n=5)
Synchronous tumor (n=5)
Previous chemotherapy (n=5)
Biphasic/sarcomatoid (n=4)
Other (n=7)
SMART completed (extended group) n=25
Excluded n=13

Overall Survival

MS 27.3 mo



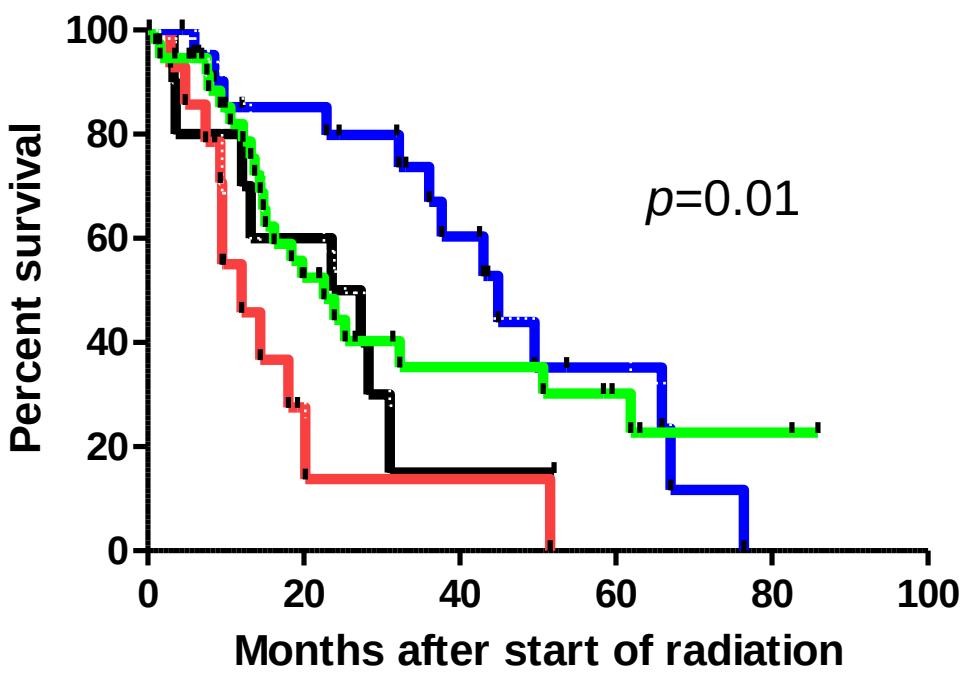
MS 36.1 mo vs 14.4 mo

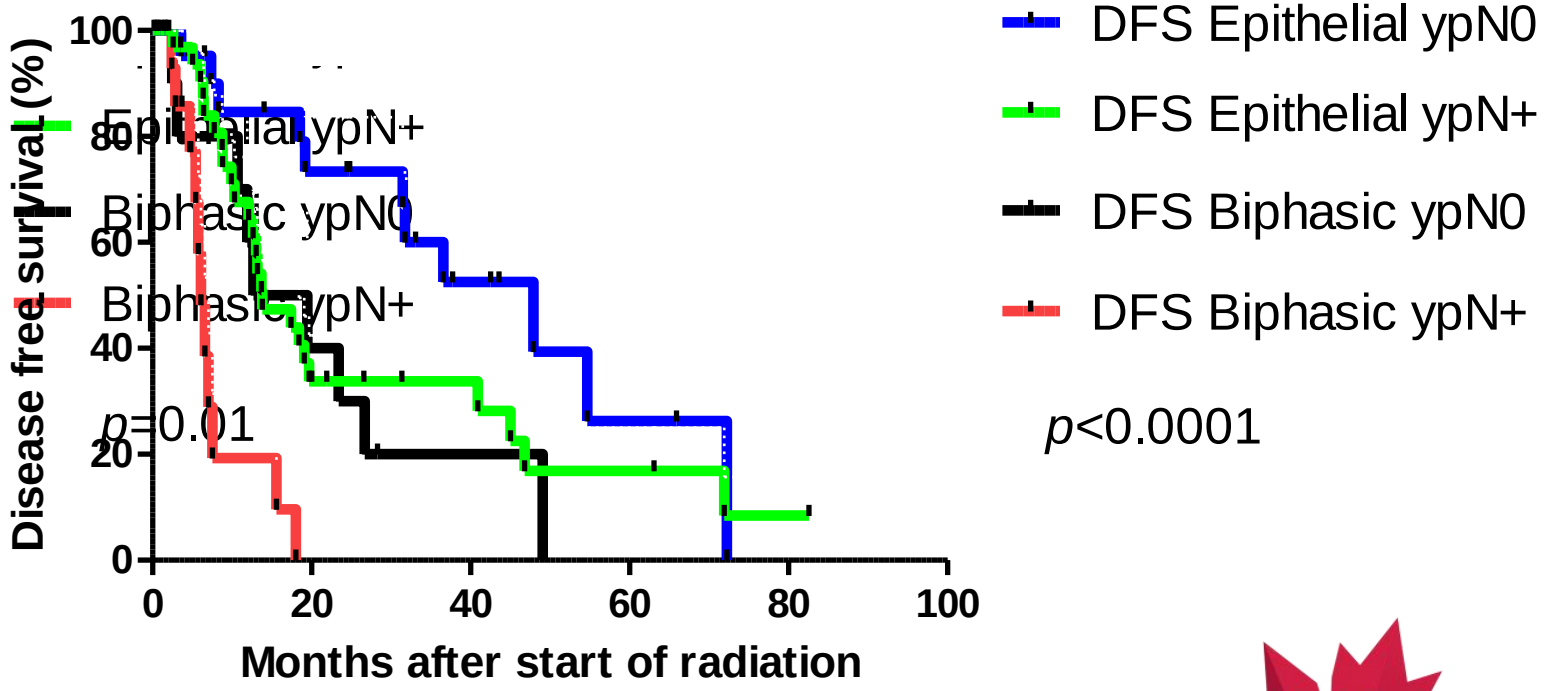


Survival by Histology and Nodal Status

MOS epithelial ypN0 44.9 mo, epithelial ypN+ 22.6 mo
MOS biphasic ypN0 25.5 mo, biphasic ypN+ 12.0 mo

MDFS epithelial ypN0 47.9 mo, epithelial ypN+ 13.8 mo,
MDFS biphasic ypN0 16.1 mo, biphasic ypN+ 6.1 mo





Conclusions

- Older radiotherapy techniques suffer from poor outcomes (tumour failure, toxicity) so newer, smarter solutions are needed
- Newer RT techniques, with better RT planning/delivery as well as better understanding of MPM, have better outcomes
- We still haven't found a cure so, in that sense, we are not yet SMART enough
- Next paradigm shift in MPM treatment will likely come from optimizing host (e.g. immunotherapy) and tumour (e.g. microenvironment) factors and finding how best to combine and sequence all these different therapeutic modalities and factors together

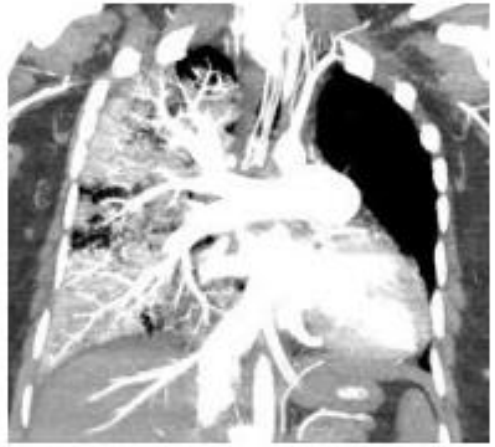
Take Home Message

Radiotherapy plays an important part in the multimodal management of MPM.

The optimal dose, volume, fractionation, and sequencing with other therapies (e.g. surgery, systemic) are still unknown and an area of active research.

Risks of Being Too SMART

- If a patient does not have surgery within 2 weeks of RT as scheduled due to:
  - Unexpected illness, trauma, early RT complication, etc
  - Surgically unresectable at the time of planned thoracotomy
- Neoadjuvant RT complications could cause a loss of a chance at a definitive surgical resection vs. upfront surgery
- Potentially FATAL pneumonitis



- Concern for lack of exportability outside of PMH or a mesothelioma center of excellence due to high complexity of the SMART approach and need for coordination and cooperation between rad onc and thoracic surgery
- More difficult ability to deliver adjuvant RT in cases of R2 resections

Potential Benefits of Lung-Sparing Surgery

- Lower perioperative mortality rate
- Lower surgical complication rates
- Better preservation of quality of life
- Better preservation of PFTs
- Better able to tolerate salvage therapies
- Better overall survival

	Pass	**Nakas**	**Lang-Lazdunski**	**Friedberg**
Number of Patients (PD/EPP)	78 (39/39)	165 (67/98)	76 (54/22)	52 (38/14)
% Stage III/IV (PD/EPP)	100%/100%	100%/100%	63%/86.5%	97%/86%
Intraoperative Adjuvant	+/- photodynamic therapy	None	Hyperthermic povidone iodine	Photodynamic therapy
Operative Mortality (PD/EPP)	0%/5%	3%/7%	0%/4.5%	0%/14%
Median Survival (PD/EPP)	14.5/9.4 mo**	13.4/14.7 mo*	23/12.8 mo*	31.7/8.4 mo**

Conclusions

- The SMART approach lead to a very impressive median OS
  - Patient population was generally earlier clinical stage, more limited tumor volume
  - Neoadjuvant RT may be difficult to generalize/export (could limit resectability, lead to fatal pneumonitis) and make adjuvant RT for gross residual disease difficult
- Adjuvant RT reduces the risk of local/pleural/nodal recurrences and can be tailored to higher risk populations
  - Gross residual disease, multi-station N2 disease, positive posterior intercostal LNs, large tumor volumes
  - Proton therapy may be a safer and more beneficial way to deliver adjuvant RT than IMRT

Controversies in Mesothelioma

PRO: IO in Mesothelioma Should Only Be Given on Clinical Trials

Penelope Bradbury
Princess Margaret Cancer Centre
University of Toronto

Trial	Checkpoint Inhibitor	Trial Design	Patient population		Endpoint
			Sample size	Line of therapy	
Keynote-028	Pembrolizumab	Phase Ib, single arm	N=25	Post SOC or unable to receive SOC, PS 0-1 PD L1≥ 1%	Safety; Objective response rate
NCT02399371	Pembrolizumab	Phase II, single arm	N=64	Pleural and peritoneal ≤2 lines; PS0-1 PD-L1 unselected	Response rate
Real world	Pembrolizumab	Retrospective	N=93	Retrospective off label use	Response, PFS, OS

SOC: standard of care

Trial	Checkpoint Inhibitor	Trial Design	Patient population		Endpoint
			Sample size	Line of therapy	
MERIT	Nivolumab	Single arm	N=34	2nd or 3rd line PS 0-1	Objective response rate
Nivo-MES	Nivolumab	Single arm	N=34	2nd or 3rd line	DCR at 12 weeks
INITIATE	Nivolumab/ Ipilimumab	Single arm	N=32	Previously treated PS 0-1, disease amenable to bx	DCR at 12 weeks
MAPS-2	Nivolumab or Nivolumab/Ipilimumab	Non-comparative randomized	N=129	2nd or 3rd Line PS 0-1	DCR at 12 weeks

Trial	Checkpoint Inhibitor	Trial Design	Patient population		Endpoint
			Sample size	Line of therapy	
JAVELIN	Avelumab	Single Arm	N=53	Pleural or peritoneal 2nd Line; PS 0-1	ORR
DREAM	Durvalumab/ pemetrexed/ cisplatin	Single arm	N=31	First line, inoperable PS 0-1	PFS at 6 months
NIBIT-MESO1	Tremelimumab/ Durvalumab	Single arm	N=40	Inoperable 2nd line or first line	Immune OR
Meso-trem 2008 (2012)	Tremelimumab (Intensified schedule)	Single arm	N=29	2nd Line	iORR
DETERMINE	Tremelimumab vs. placebo	Phase IIB randomized	N=571	Pleural or peritoneal 2nd or 3rd line	OS

What we know for PD-1 and PD-L1 inhibitors:

Response rate

- **Single agents 9-20%; 55% for chemo- durvalumab**
- **Durable responses**
- **PFS 4-7, OS 10-18 months**

What we do *not* know

- **Efficacy versus SOC in first and second line**
- **Single agent or in combination**
- **Histologic subtypes**
- **Markers of response**

Determine: Phase IIb Randomized Double Blind, Placebo Controlled Trial of Tremelimumab as 2nd or 3rd line treatment of unresectable malignant mesothelioma

Pleural or peritoneal mesothelioma
PS≤1
1 -2 prior regimens including platinum
Measurable disease

Randomize 2:1

Tremelimumab i.v
10mg/Kg q4weeks for 7 doses then q 12 weeks

Stratification factors
Pleural vs. peritoneal
2nd vs. 3rd line
EORTC low vs. high risk

Placebo i.v.

Primary endpoint: Overall survival
Secondary endpoints: 18 month OS; Progression Free Survival; ORR; Safety

Maio M et al. Lancet Oncol. 2017;18(9):1261

Determine: Phase IIb Randomized Double Blind, Placebo Controlled Trial of Tremelimumab as 2nd or 3rd line treatment of unresectable malignant mesothelioma

DETERMINE: Overall Survival (ITT Population)

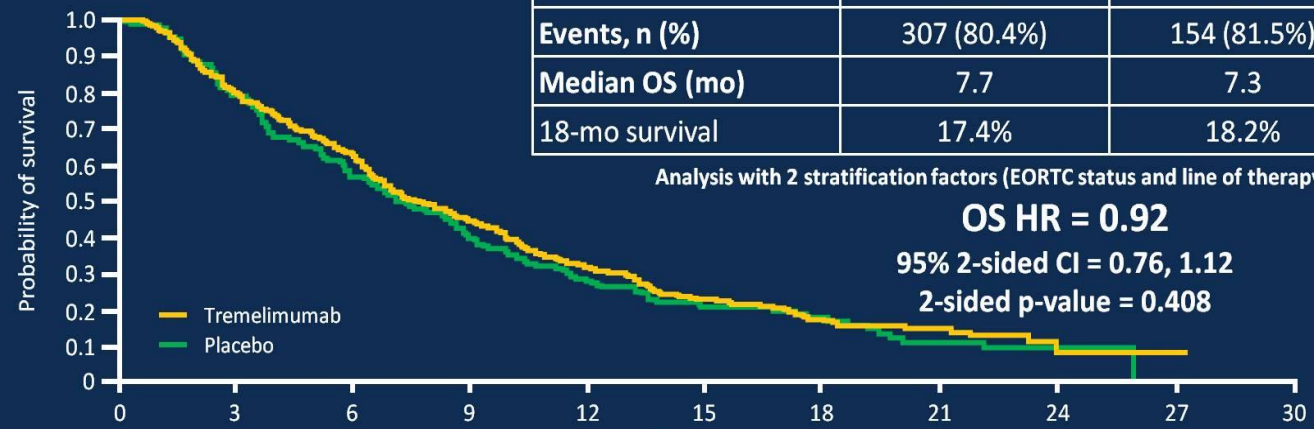
	Tremelimumab	Placebo
n	382	189
Events, n (%)	307 (80.4%)	154 (81.5%)
Median OS (mo)	7.7	7.3
18-mo survival	17.4%	18.2%

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

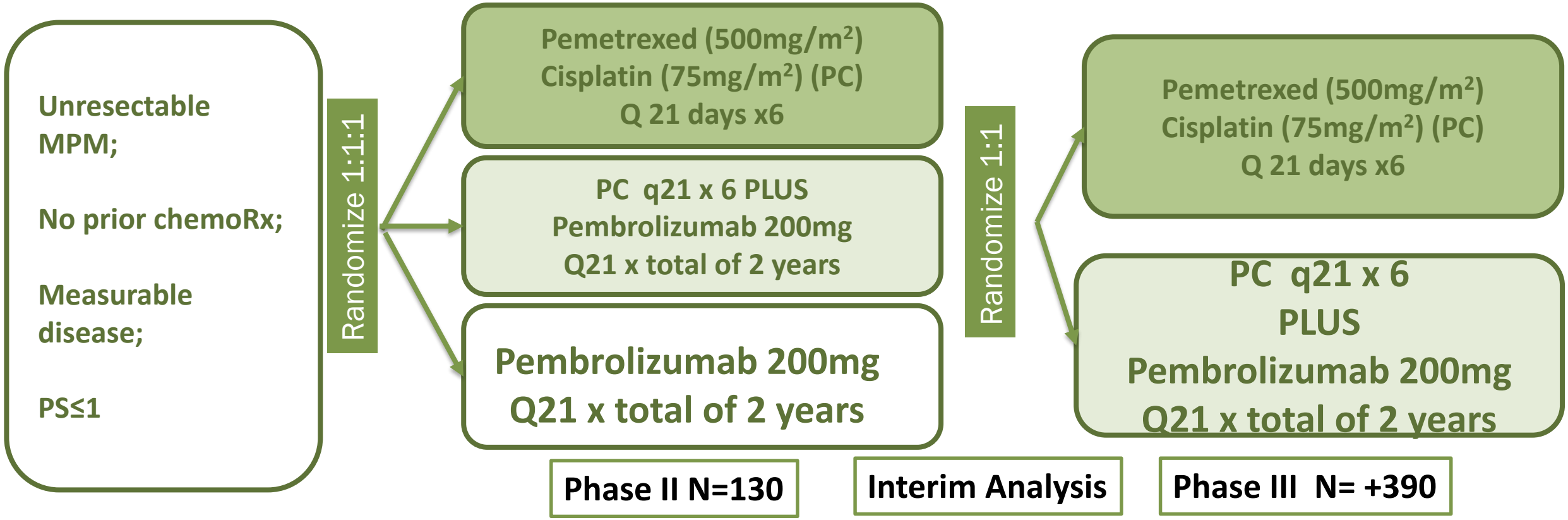


Number of patients at risk:

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.

IND227: A Randomized Study of Pembrolizumab in Patients with Advanced Malignant Pleural Mesothelioma. NCT02784171



Primary Endpoint: Overall Survival

Secondary Endpoints: Progression Free Survival; Response Rate; Quality of Life; Incremental Cost Effectiveness; Tolerability; Predictive/prognostic value of PD-L1

Canadian Cancer Trials Group

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

Study of Nivolumab Combined With Ipilimumab Versus Pemetrexed and Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma Patients (CheckMate743) NCT02899299

Malignant pleural mesothelioma
Inoperable
ECOG 0-1
No prior chemotherapy
Measurable disease

N=600

Nivolumab; Ipilimumab

Pemetrexed; platin

Primary endpoints: OS and PFS; secondary endpoints: objective response rate; disease control rate; PD-L1 expression and efficacy

- Promising *preliminary* signal of activity
- Preliminary results of efficacy are not always maintained when tested in larger randomized trials
- Insufficient data to recommend checkpoint inhibitors outside of clinical trial
- Enrol patients on randomized trials to determine the role of checkpoint inhibitors in mesothelioma

Trial design – Single-arm, multicentre phase II trial with a safety run-in, N= 54

Population

- 1st line MPM
- Non-surgical
- No prior RT to measurable disease
- ECOG PS 0-1
- No PD-L1 selection

Induction

Cisplatin 75mg/m² + Pemetrexed 500mg/m² + Durvalumab 1125mg q3w

6 cycles

Maintenance

Durvalumab 1125mg q3w x 52 w

To total 17 cycles durvalumab including induction period (12 months from treatment start)

Outcomes

PFS6*

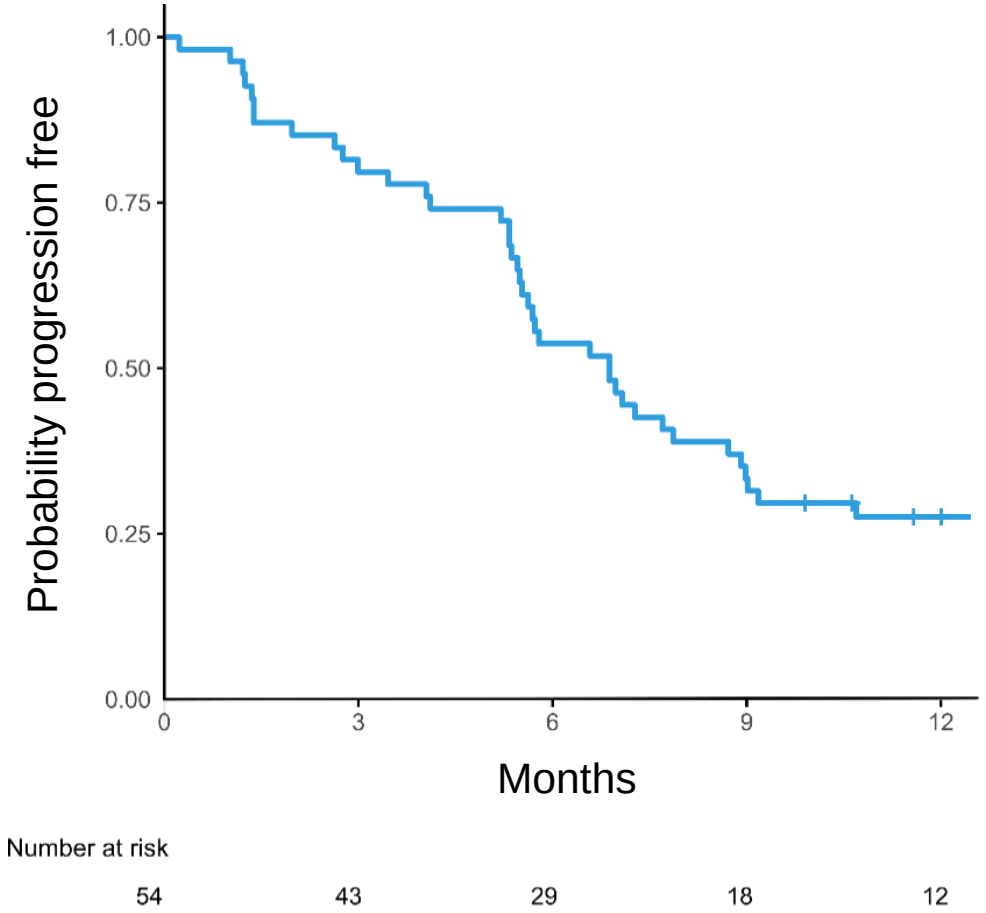
ORR (CR + PR)*
Toxicity
PFS*
OS

* mRECIST for MPM, mirRC

Statistical considerations

- 2-stage Simon's design: 31 in stage 1, additional 23 in stage 2, for total n= 54
- 6 patient initial safety run-in using a 3+3 design
- Null hypothesis: PFS6 = 45%
- Alternate hypothesis: PFS6 = 65%
- Required 31 of 54 patients to be progression free at 6 months (by mRECIST) to meet primary endpoint
- 90% power with a one-sided type 1 error rate of 5%

Progression Free Survival (mRECIST)



Median PFS, mo (95% CI)	
Chemotherapy + Durvalumab	6.2 (5.5-9.0)
PFS6	31/54 (57%)

Rejected null hypothesis

Take home message

- The regimen of durvalumab, cisplatin and pemetrexed was active and tolerable as first line treatment in advanced mesothelioma
- Progression free survival at 6 months was 57% - met primary endpoint
- PFS6 used mRECIST not iRECIST
- Objective tumour response rate (mRECIST) was 46%
- Adverse events comparable to chemotherapy and immunotherapy alone; chemotherapy dose intensity maintained
- This supports evaluation in a randomised phase 3 trial of the regimen

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
#WCLC2018

Phase II Trial of Pembrolizumab (NCT02399371) in Previously Treated Malignant Mesothelioma: Final Analysis

A Desai, T Karrison, B Rose, E Pemberton, B Hill, A Mendoza, CM Straus, Y-H Carol Tan, TY Seiwert, HL Kindler

University of Chicago, Chicago, IL, USA

Trial Design

Single institution, single arm, phase II trial

WCLC 2016

Part A (N=35)

- RR of pembrolizumab in PD-L1 **unselected** pts
- **Optimal PD-L1 cutoff**

Part B Expansion Cohort (N=30)

If ≥ 3 responses and a cutoff is determined in Part A:

- Part B would use a **biomarker enrichment** strategy for PD-L1
- At WCLC 2016* we reported 7 responses in Part A. No PD-L1 cutoff was established. Thus, Part B recruited patients unselected for PD-L1.

WCLC 2018

Today's presentation reports the final results of this study

*Kindler, *WCLC* 2016

Statistics

- Single-stage binomial design (Parts A and B separately). Type I error rate of 0.1, power of 80%
- Part A: 35 patients, null RR: 2%, alternative RR: 12%
    - If ≥3 responses, null hypothesis is rejected; if identified, PD-L1 threshold is used for Part B
    - Should no threshold be identified, study proceeds without PD-L1 prescreening
- Part B: 30 patients, null RR: 10%, alternative RR: 25%
  - If ≥6 responses, null hypothesis is rejected

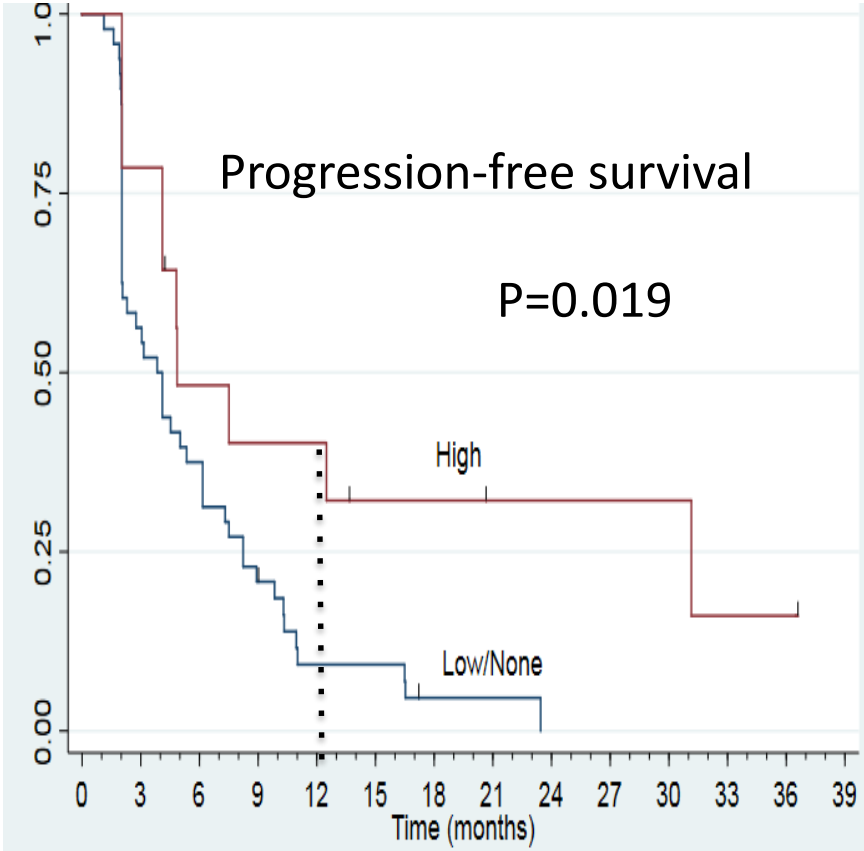
Treatment outcomes (N=64)

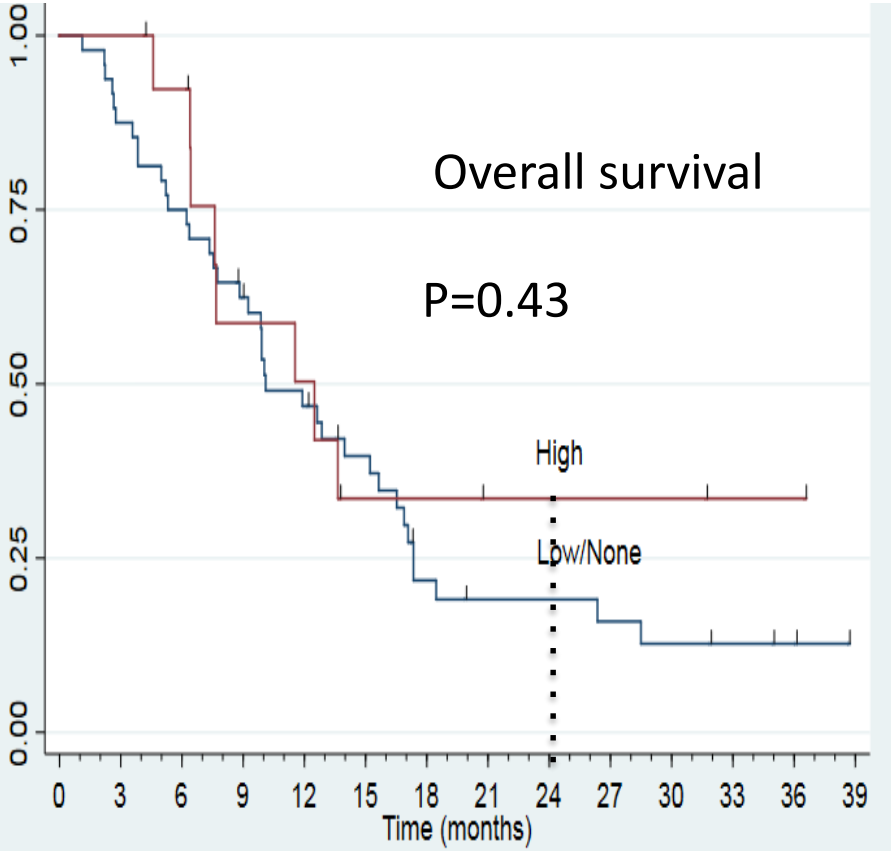
	N (%)
Partial response	14 (22%)
Stable disease	26 (41%)
Disease control rate	40 (63%)
Median duration of response	11.7 months
Median progression-free survival	4.1 months
Median overall survival	11.5 months

Response rate and PD-L1 expression by histology and disease site

	Number of patients	Response rate (N=64)	PD-L1 expression (N=62)		
			No (0%)	Low (1-49%)	High (≥50%)
Histology					
Epithelioid	49	22%	46%	40%	**14%**
Sarcomatoid	5	**40%**	20%	0%	**80%**
Biphasic	10	10%	70%	10%	20%
Disease site					
Pleural	56	**23%**	49%	29%	22%
Peritoneal	8	13%	25%	50%	25%

PFS and OS by PD-L1 expression





PD-L1	Low/None	High
Median PFS	3.8 mo	4.9 mo
1 year PFS	9.3%	40.2%

PD-L1	Low/None	High
Median OS	10.1 mo	12.5 mo
2 year OS	19.1%	33.6%

Conclusions

- Pembrolizumab has robust activity in PD-L1 unselected mesothelioma patients:
  - Response rate: 22%
  - Disease control rate: 63%
  - Responses were observed in patients with no, low, and high PD-L1 expression
- Patients with high (≥ 50%) PD-L1 expression achieved:
  - A higher response rate (p=0.021)
  - Longer progression-free survival (p=0.034)
- PD-L1 can be used as a biomarker to predict response in mesothelioma patients treated with pembrolizumab

Study Design of MERIT

- Single-arm, open-label, phase 2 trial (JapicCTI-No.163247)

Key Eligibility Criteria
- Second- or third-line advanced or metastatic MPM
- Prior platinum-based combination therapy with pemetrexed
- No prior surgery for MPM
- ECOG PS 0-1
- Available tumor tissue for PD-L1 analysis
- PD-L1 all comers

→ Nivolumab
240 mg IV, Q2W
(N=34)

→ Until disease progression or unacceptable toxicity

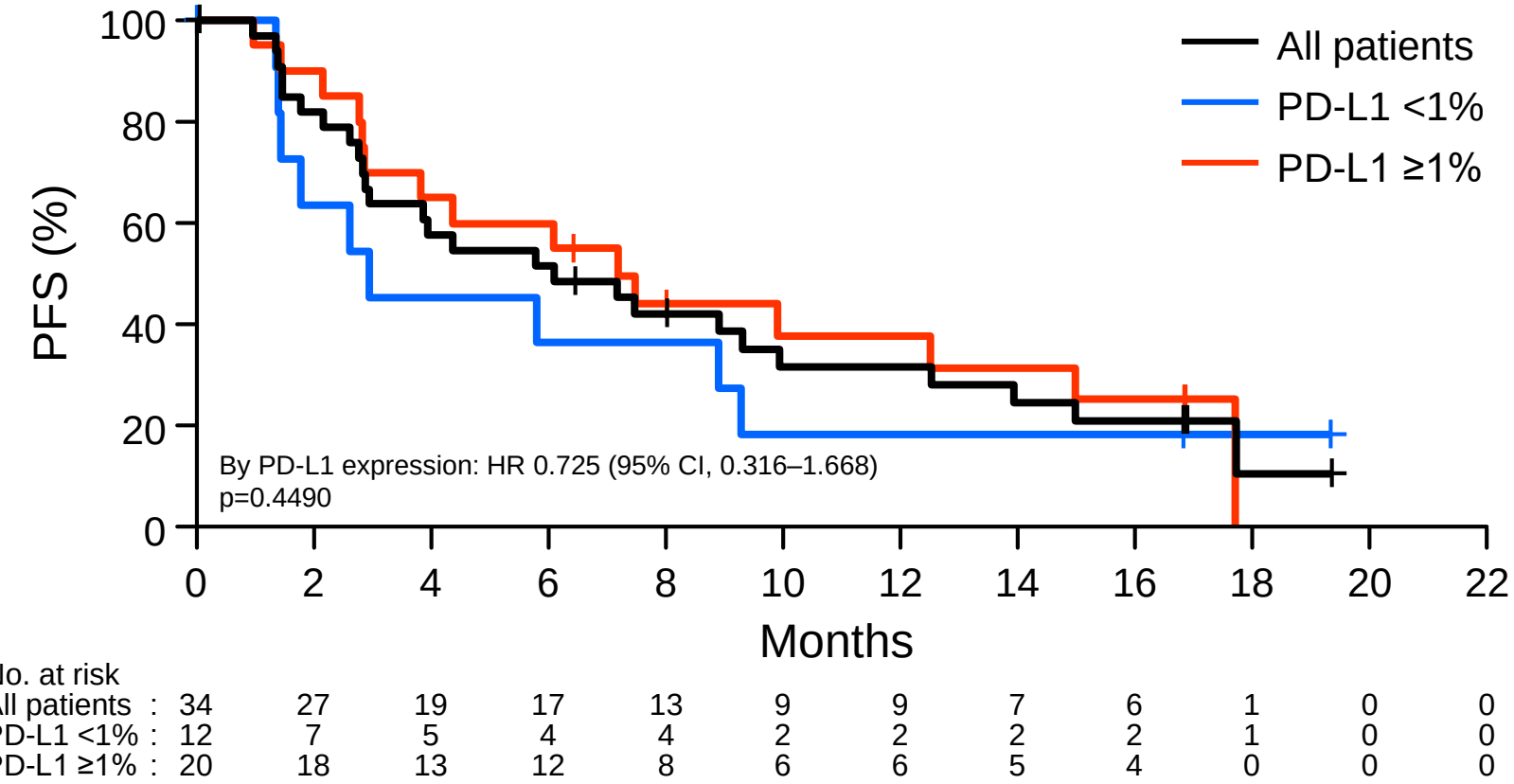
Primary endpoint: ORR*
Select secondary endpoints:
• PFS and OS • Safety

- Data cut-off: March 14, 2018 (median follow-up: 16.8 months [min. 1.8–max. 20.2])

*Efficacy analyses by central assessment according to mRECIST criteria, Statistical analysis α: 5%, power: 80%, expected response rate: 19.2%

PFS by PD-L1 Expression (≥1% and <1%)

Data cut-off: March 14, 2018

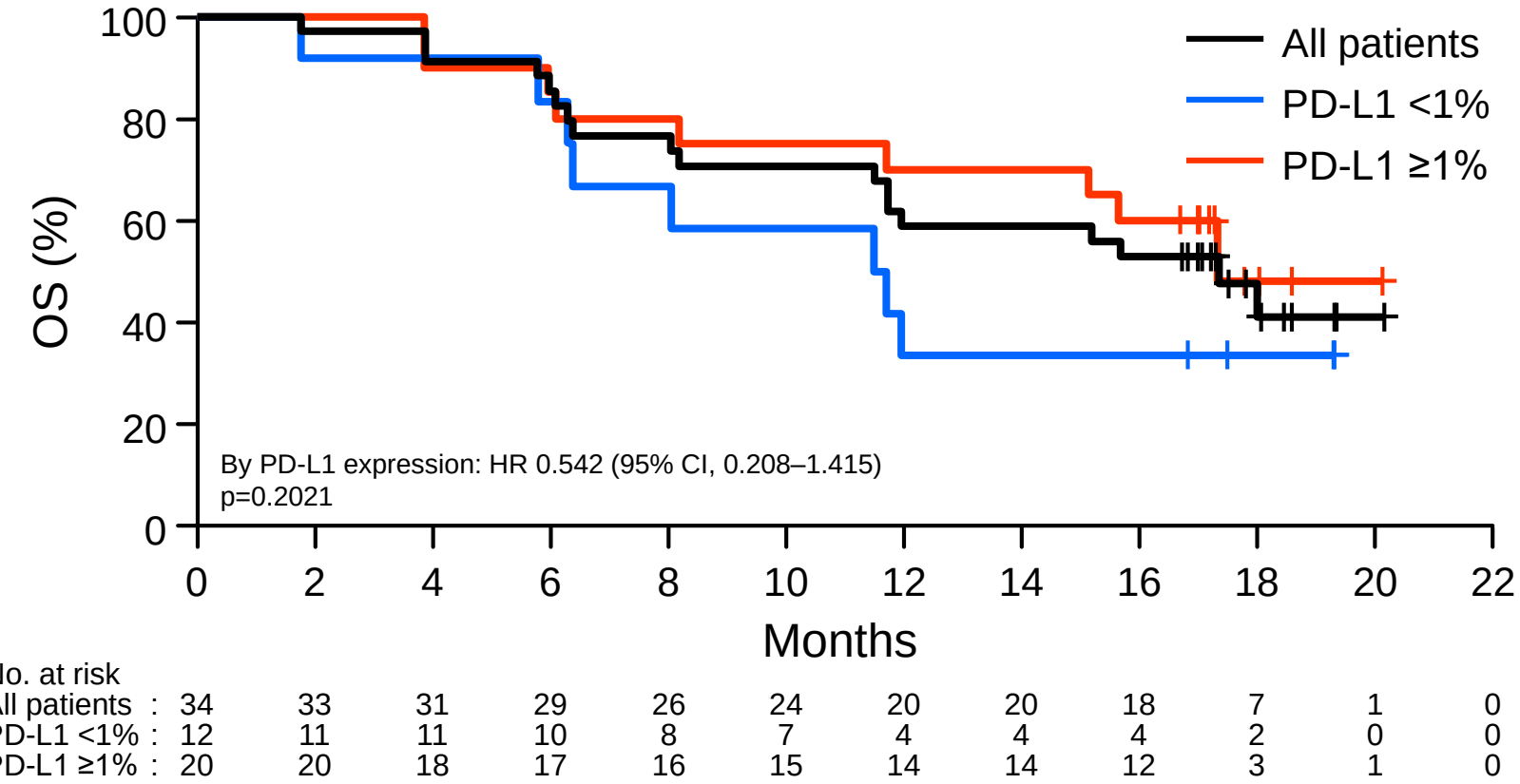


Median PFS, months (95% CI)	
All patients	6.1 (2.9, 9.9)
PD-L1 ≥1%	7.2 (2.8, 15.0)
PD-L1 <1%	2.9 (1.4, 9.3)

Median follow-up: 16.8 months (min. 1.8–max. 20.2)

OS by PD-L1 Expression (≥1% and <1%)

Data cut-off: March 14, 2018



Median OS, months (95% CI)	
All patients	17.3 (11.5, NR)
PD-L1 ≥1%	17.3 (8.2, NR)
PD-L1 <1%	11.6 (5.8, NR)

Median follow-up: 16.8 months (min. 1.8–max. 20.2)

Summary and Conclusions

- Nivolumab showed substantial clinical activity with ORR of 29.4% in second- or third-line MPM patients, which met the primary endpoint.
- Median PFS and OS were 6.1 months and 17.3 months, respectively.
- Nivolumab was efficacious regardless of histological subtype especially in sarcomatoid histology.
- PD-L1 expression (≥1%) in the tumor could favor better response.
- Longer follow-up did not identify any safety concerns.

Based on the results of the MERIT study,
nivolumab was approved on Aug 21st in Japan for
unresectable advanced or recurrent MPM which has progressed after chemotherapy.

PRO Intrapleural Chemotherapy - Is It the Future?

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On behalf of Isabelle Opitz

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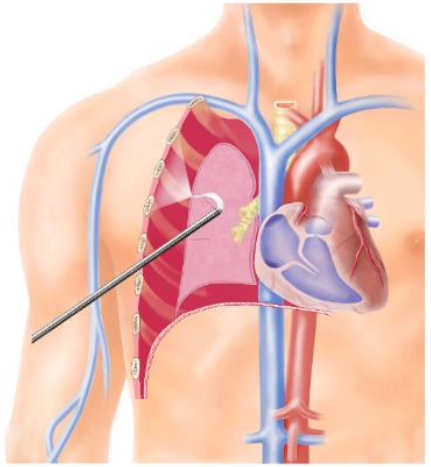
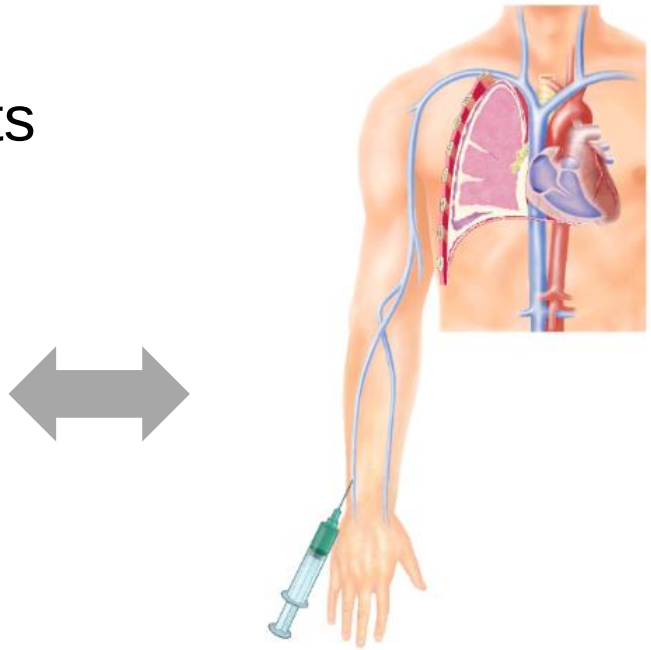
WCLC 2018

Rationale of Intraoperative/ Localized / Intracavitary Treatment

- To eliminate microscopic residual disease (MRD) after macroscopic complete resection (MCR)
- Enhance local effects
- Decrease systemic effects of therapeutic agents

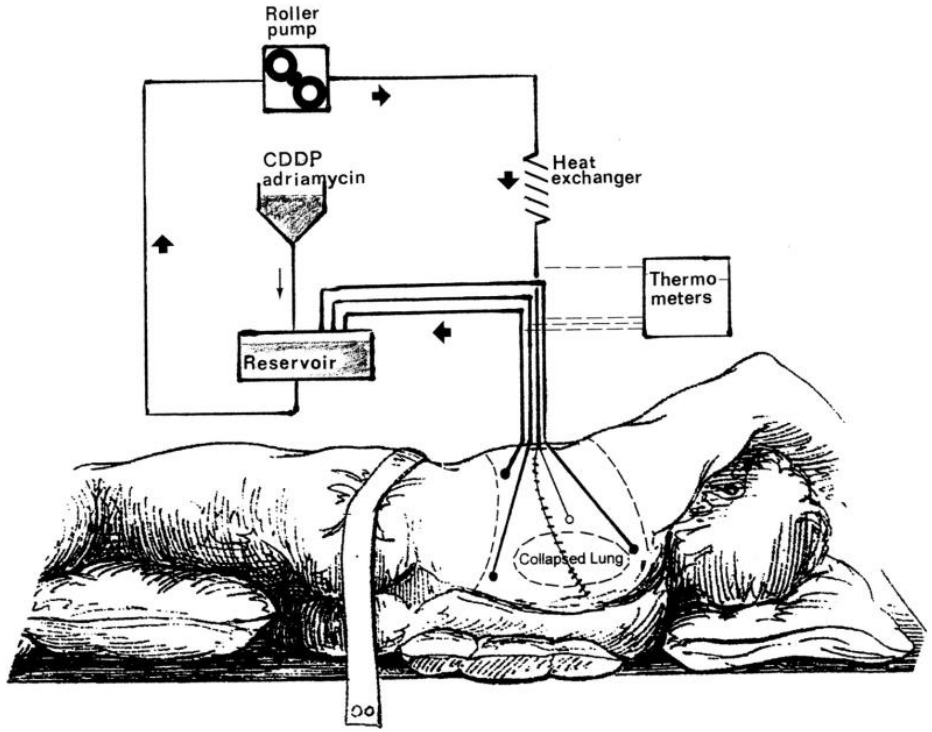




Treatment approaches

- Intracavitary chemotherapy

- Intracavitary immunotherapy



de Bree, Chest 2002

Intracavitary Chemotherapy

- Mostly platinum-based, combined to EPP and (e)P/D

- Hyperthermic (HIPEC) or not

Rice, Ann Thorac Surg 1994; Rusch, J Clin Oncol 1994; Lee, J Surg Oncol 1995; Colleoni, Tumori 1996; Pinto, Am J Clin Oncol 2001; Van Ruth, Ann Surg Oncol 2003; Monneuse, Br J Cancer 2003; Richards, J Clin Oncol 2006; Tilleman, J Thorac Cardiovasc Surg 2009 Ried, Chirurg 2012; Surgarbaker, J Thorac Cardiovasc Surg 2013

HIPEC after P/D or EPP

- Maximum tolerated dose of cisplatin 225 - 250 mg/m^2

- Dose-limiting toxicity: renal insufficiency, other common AE: atrial fibrillation

Reviewed in Gomez, Current Treatment Options in Oncology 2014

- Median OS: 9 – 35.3 months

De Bree, Chest 2002; Sugarbaker, JTCVS 2013

- Median PFS: 4.5 – 27.1 months

Ried, Eur J Cardiothoracic Surg 2013; Sugerbaker, JTCVS 2013

Intracavitary Chemotherapy - HIPEC

	n	Histology	N2 or Nx	IMIG stage	intraoperative regimen	Surgery type	Peri-op Mortality	Morbidity / Toxicity	Adjuvant systemic CTX	Adjuvant RT	Median OS (months)	Median PFS (months)
Sugarbaker 2013	72	63 epithelioid 9 biphasic	46	I-II: 14 III-IV: 60	cisplatin	P/D or EPP	4.2%	NR	57%	57%	35.3	27.1
Tilleman 2009	92	53 epithelioid 39 non-epithelioid	NR	I-II: 14 III-IV: 78	cisplatin	EPP	4.3%	49%	NR	NR	13.1	15.3
Zellos 2009	29	24 epithelioid 5 non-epithelioid	9	I-II: 18 III: 11	cisplatin	NR	7%	NR	NR	NR	20	16
Richards 2006	44	24 epithelioid 17 biphasic 3 sarcomatoid	33	I-II: 27 II-III: 17	cisplatin	P/D	11%	25%	None	None	13	7.2
Chang 2004	50	NR	31	I-II: 19 III: 31	cisplatin	EPP	2%	60%	Unknown	Unknown	NR	NR
Monneuse 2003	17	NR	NR	I-II: 10 III-IV: 7	mitomycin C and/or cisplatin	P/D or pleurectomy	6%	29%	NR	NR	18	NR
Van Ruth 2003	20	16 epithelioid 4 biphasic	0	NR	cisplatin + doxorubicin	12 P/D 8 EPP	0%	65%	None	Thoracotomy scar and drainage ducts	11	8
Ratto 1999	10	4 epithelioid 6 biphasic	0	I-II: 10	cisplatin	P/D or EPP	0%	20%	None	55 Gy to chest wall incision	NR	NR

Adapted from Tsao, Clin Lung Cancer 2009

Intracavitary Immunotherapy

- Historically:
  - Patients with postoperative empyemas after lung cancer resection had improved survival rates
  - Intrapleural BCG instillation after surgery w/o clear clinical benefit.
- Intracavitary application of cytokines: IL-2, IFN-α, IFN-γ
- Toxicity (fever, but can be empyema also)
- Good control of malignant pleural effusion

Astoul, Chest 1993; Antoniou, Chest 2003;
Bone BMJ 1973, Bakker Cancer Immunol Immunozhrt 1986, Boutin Cancer 1994;
Sterman, Clin Cancer Res 2007; Sterman, Mol Ther 2010

Summary

- Excellent strategy to attack the minimal residual disease after MCR
- The therapeutic agents can be delivered directly to the chest cavity and the desired local effect may be enhanced while the **systemic side effects are rare**
- Largest experience and **best survival data exist** with intracavitary chemotherapy (OS up to 35 months, PFS up to 27months)
- It is not recommended to perform these procedures unless on a clinical trial and in experienced hands, and precise pharamockinetic evaluation.
- Mesothelioma is ideal as „local disease“

Intrapleural Chemotherapy, Is It The Future?

The con side of the argument

David Rice, MB, BCh

IASLC 19th World Conference on Lung Cancer, Sept 23-26, Toronto, Canada

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Cytoreduction & Intrapleural ChemoRx

Author	Year	n	Study Type	Route	EPP	PD
Rusch	1994	27	Phase I	PICT		27 (100%)
Rice	1994	19	Phase I	PICT	10 (53%)	9 (47%)
Colleoni	1996	14	Phase I	PICT		14 (100%)
Ratto	1999	10	Phase I	HIOC	4 (40%)	6 (60%)
deBree	2002	8	Phase I	HIOC	4 (50%)	7 (88%)
van Ruth	2006	20	Phase I	HIOC	8 (40%)	12 (60%)
Richards	2006	44	Phase I/II, dose escalation	HIOC		44 (100%)
Zellos	2008	29	Phase I, dose escalation	HIOC	29 (100%)	
Tilleman	2009	92	Phase II	HIOC	92 (100%)	
Tokunaga	2011	11	Phase I	PICT	11 (100%)	
Ried	2013	8	Phase I	HIOC		8 (100%)

Cytoreduction & Intrapleural ChemoRx

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Tilleman	2009	92	Phase II	HIOC	92 (100%)	
Tokunaga	2011	11	Phase I	PICT	11 (100%)	
Ried	2013	8	Phase I	HIOC		8 (100%)

Morbidity 50%

Morbidity 67%

Intrapleural ChemoRx: Survival

Author	Year	OS	1-yr	2-yr	3-yr	4-yr
Rusch	1994	18	69%	40%		
Rice	1994	13	63%*	24%*		
Colleoni	1996	nr				
Ratto	1999	nr				
deBree	2002	nr				
van Ruth	2006	11	42%			
Richards	2006	13	50%	30%	20%	14%
Zellos	2008	20	83%	48%	31%	28%
Tilleman	2009	13	60%*	25%*	20%*	
Tokunaga	2011	19	64%	18%		
Ried	2013	18	88%	50%		

* Survival data imputed from published KM curves

Comparative Data: Trimodality Trials

	Survival (mo)					Morbidity	
	ITT	NC+EPP	TMT	DFS (mo)	Mortality	Overall	Major
Treasure, 2011	14.4			7.6	12.5	69%	42%
van Schil, 2010	18.4	NR	33	13.9	6.5	82.6	NR
Krug, 2009	16.8	21.9	29.1	10.2	3.7	NR	NR
Rea, 2007	25.5	27.5	NR	16.3	0	52.4	23.8
Weder, 2007	19.8	23	NR	13.5	2.2	NR	35

Predictors of Survival

Disease Free Survival

	Univariate		Multivariate	
	HR	p	HR	p
Sex (Female)	**0.32 (0.13-0.81)**	**0.016**	**0.35 (0.14-0.92)**	**0.03**
Age	1.02 (0.99-1.06)	0.216		
Procedure (PD/EPP)	1.41 (0.63-3.17)	0.405		
HIOC	0.53 (0.24-1.17)	0.105		
Periop ChemoRx	0.84 (0.37-1.89)	0.671		
Adjuvant XRT	0.93 (0.21-4.24)	0.927		
Stage	1.05 (0.48-2.31)	0.9		
SMRP	**1.16 (1.01-1.11)**	**0.029**	**1.06 (1.00-1.11)**	**0.04**

Overall Survival

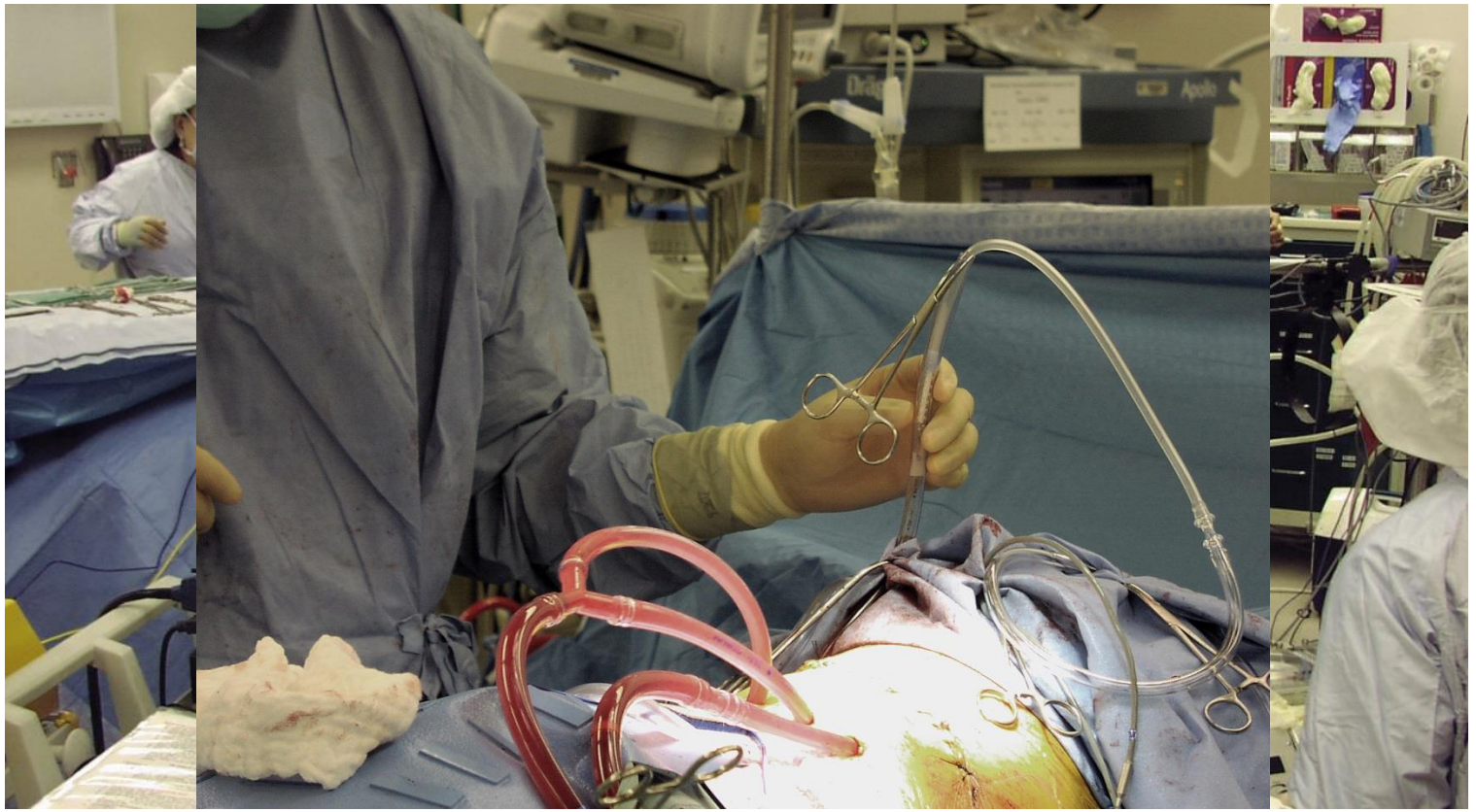
	Univariate		Multivariate	
	HR	p	HR	p
Sex (Female)	0.15 (0.02-1.19)	0.07	**0.11 (0.01-0.9)**	**0.04**
Age	1.04 (0.97-1.10)	0.3		
Procedure (PD/EPP)	0.60 (0.18-2.06)	0.4		
HIOC	0.83 (0.24-2.87)	0.8		
Periop ChemoRx	**0.25 (0.07-0.86)**	**0.03**	**0.17 (0.04-0.68)**	**0.01**
Adjuvant XRT	1.34 (0.17-11.04)	0.8		
Stage	1.54 (0.65-5.07)	0.5		
SMRP	**1.07 (0.01-1.12)**	**0.02**		

Burt, Ann Thorac Surg, 2017

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Potential Issues with HIOC

- Coordination
- Space
- Potential Errors
- Health Risk
- Time



Conclusions

- Preclinical data support efficacy in vitro and in vivo in rodent models
- Drug penetrance may be enhanced by hyperthermia (controversial) but is limited to <5mm
- There is no consensus on ideal drug(s), dose or hyperthermic conditions
- Data from clinical studies show feasibility with cisplatin, but risk of renal toxicity and thromboembolic events appears elevated
- The data do not support superiority in terms of either overall survival or local control compared to other combined modality approaches.

MTE06: SYMPTOM MANAGEMENT IN MESOTHELIOMA

07:00 MTE06.01: Role of Pleurectomy in Palliation of Symptoms
John G. Edwards, Sheffield Teaching Hospitals NHS Foundation Trust, UK

07:30 MTE06.02: How to Register Toxicity and Guide Patients
Liz Darlison, University Hospitals of Leicester NHS Trust, UK

Justification for Surgery

Palliative Surgery

- Improve Quality of Life
- May (or may not) improve Survival

Radical Surgery

- Improve Survival
- May (or may not) improve Quality of Life

Surgical Options:

Extrapleural Pneumonectomy (EPP)

- *en bloc* resection of lung, pericardium, diaphragm

Extended Pleurectomy / Decortication (eP/D)

- with diaphragm / pericardium resection

Pleurectomy / Decortication (P/D)

- without diaphragm / pericardium resection

Partial Pleurectomy

- palliative R2 resection

IASLC Staging Article

Recommendations for Uniform Definitions of Surgical Techniques for Malignant Pleural Mesothelioma

A Consensus Report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group

David Rice, MB, BCh, Valerie Rusch, MD,† Harvey Pass, MD,‡ Hisao Asamura, MD,§ Takashi Nakano, MD,‖ John Edwards, MB, ChB, PhD,¶ Dorothy J. Giroux, MS,# Seiki Hasegawa, MD,** Kemp H. Kernstine, MD, PhD,†† David Waller, MD,‡‡ and Ramon Rami-Porta, MD§§, on behalf of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group*

Introduction: Extrapleural pneumonectomy has been well defined; however, surgeons vary regarding the surgical extent and goals of "pleurectomy/decortication" (P/D). We explored mesothelioma surgeons' concepts of P/D with the aim of unifying surgical nomenclature.
Methods: A web-based survey was administered to surgeons who operated on malignant pleural mesothelioma (MPM) for diagnosis, staging, palliation, or cytoreduction. One hundred thirty surgeons from 59 medical centers were included. Surgeons who did not perform surgery for MPM within the last year were excluded.
Results: There were 62 (48%) respondents from 39 medical centers in 14 countries. The mean number of patients with MPM seen annually at each medical center was 46, and the mean annual number of cytoreductive procedures performed per surgeon was 8. Most (88%) agreed that the goal of cytoreductive surgery should be macroscopic complete resection of tumor. P/D was defined as resection of parietal and visceral pleura with the aim of achieving macroscopic complete resection by 72% of respondents. If the diaphragm or pericardium required resection, 64% preferred the term "radical P/D," whereas "P/D" (40%) or "total pleurectomy" (39%) was preferred if these structures were not removed. Most surgeons believed that extrapleural pneumonectomy (90%) or "radical P/D" (68%) could provide adequate cytoreduction, whereas only 23% thought that P/D could.
Conclusions: There was significant variation regarding surgical nomenclature for procedures for MPM. The International Staging Committee of the International Association for the Study of Lung Cancer and the International Mesothelioma Interest Group recommend that P/D should aim to remove all macroscopic tumor involving the parietal and visceral pleura and should be termed "extended" P/D when the diaphragm or pericardium is resected.

Key Words: Mesothelioma, Pleural neoplasm, nomenclature, Surgery.
(*J Thorac Oncol.* 2011;6: 1304–1312)

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Disclosure: The authors declare no conflicts of interest.
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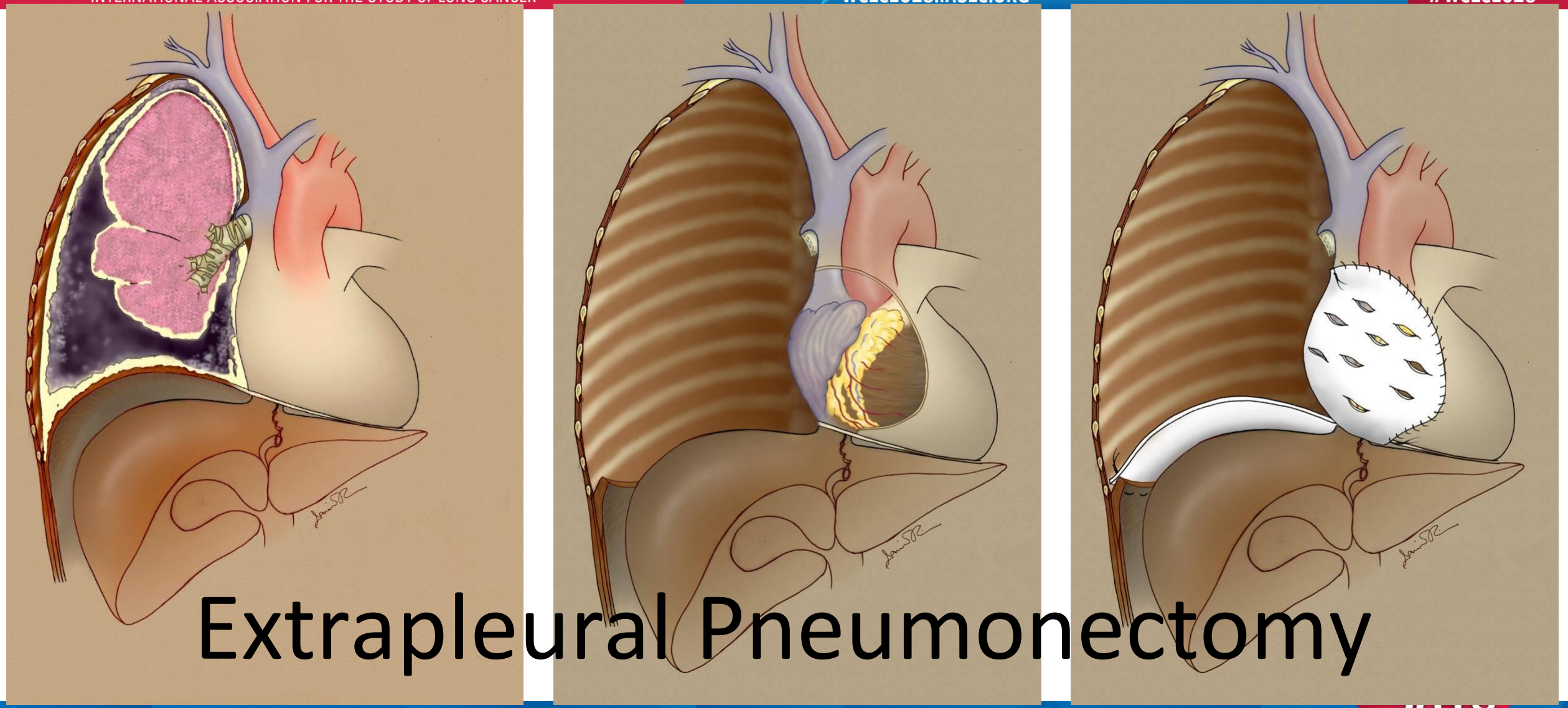
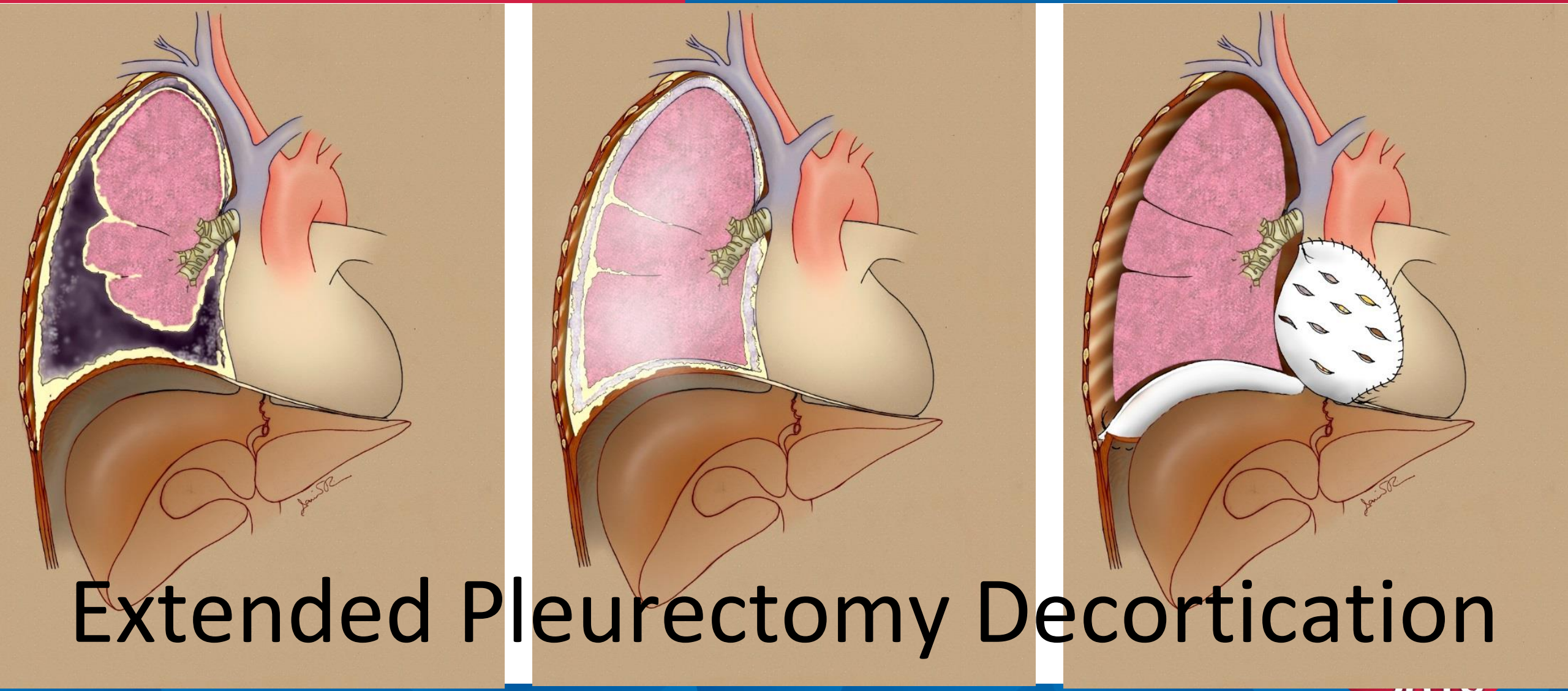
ISSN: 1556-0864/11/0608-1304

Surgery for malignant pleural mesothelioma (MPM) may include relatively minor procedures for diagnosis and staging, more involved debulking operations for palliation, and extensive cytoreductive procedures where the goal is to lengthen survival by reducing the intrathoracic tumor burden to microscopic levels. The latter is usually accomplished either by extrapleural pneumonectomy (EPP) or by a procedure that is presently classified as "pleurectomy/decortication" (P/D), generally as part of a multimodality treatment regimen. Although the surgical technique of EPP has been standardized, there is a variation among surgeons with respect to what is involved in P/D.[1–5] For some mesothelioma surgeons, P/D refers to a surgical procedure that aims to remove all macroscopic tumor from the affected hemithorax.[6] This typically includes resection of the entire parietal and

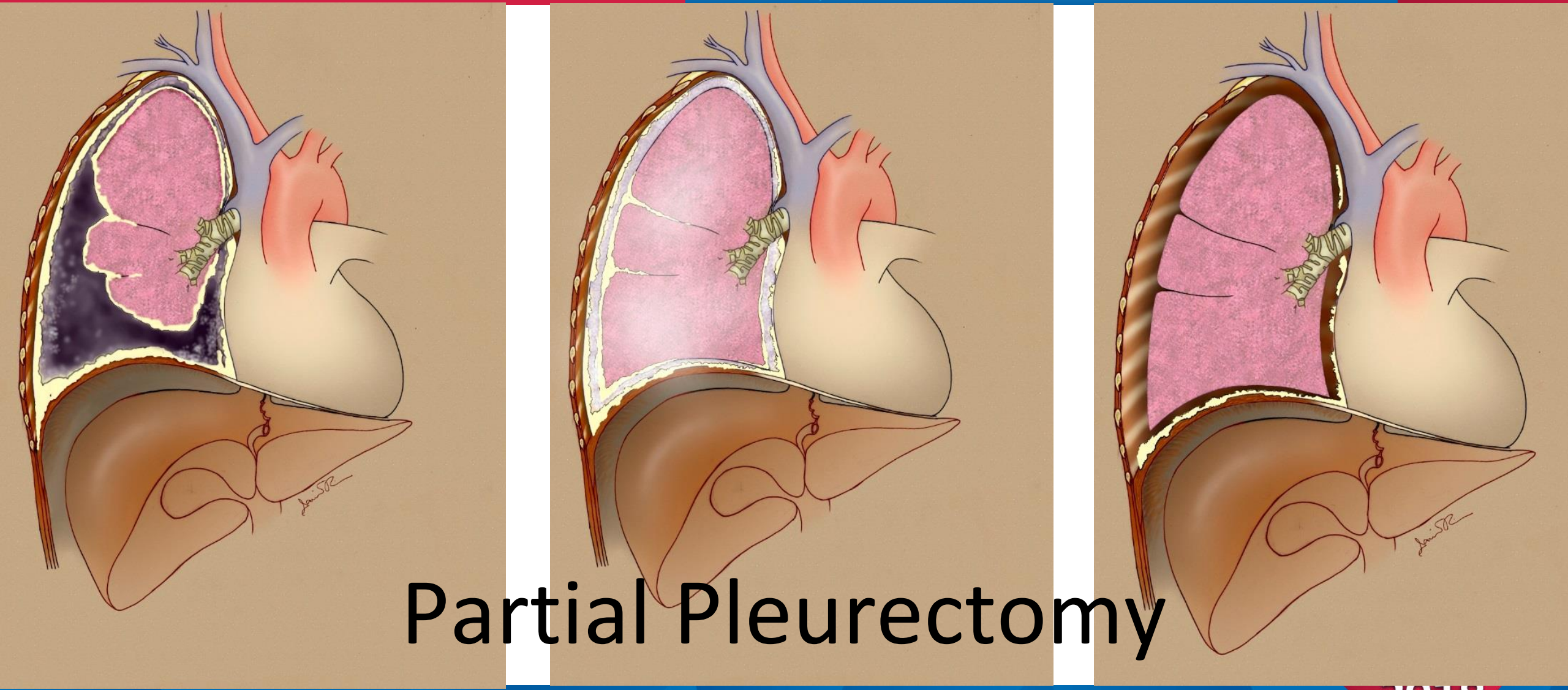
J Thorac Oncol. 2011;6: 1304–1312)



Extrapleural Pneumonectomy



Extended Pleurectomy Decortication



Partial Pleurectomy

Partial Pleurectomy

Surgical Technique:

- Thoracotomy
- VATS
- Multiport VATS ?
- Singleport VATS ?

Randomised controlled trial of video-assisted thoracoscopic partial pleurectomy compared to talc pleurodesis in patients with confirmed or suspected malignant pleural mesothelioma: the MesoVATs trial

Robert Rintoul

Papworth Hospital, Cambridge, UK

On behalf of the MesoVATs investigators

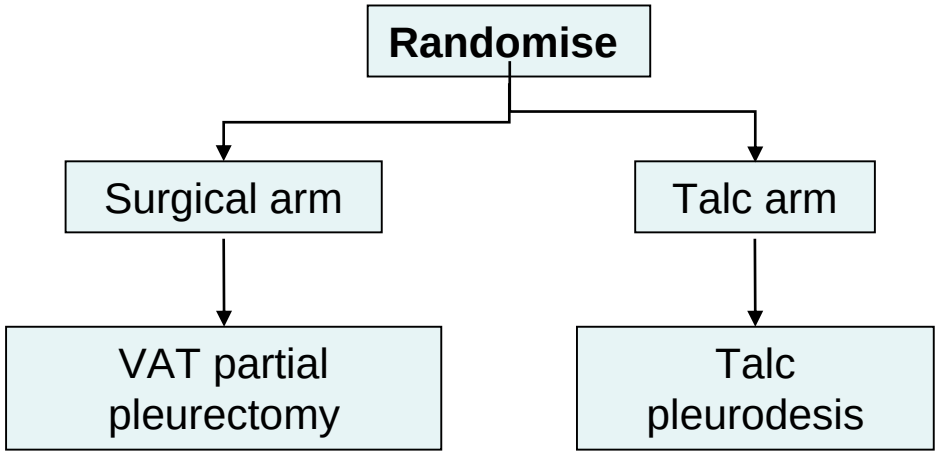
BUPA foundation THE MEDICAL RESEARCH CHARITY

Lancet 2014; 384(9948):1118-1127.

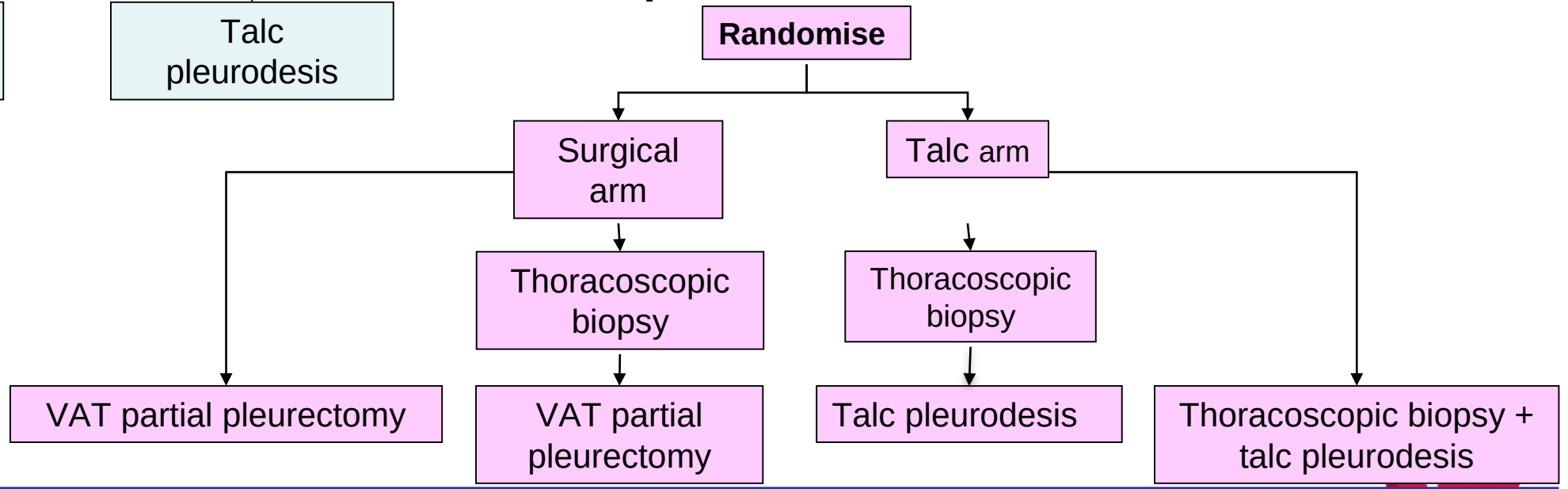
Study Procedures

Confirmed mesothelioma

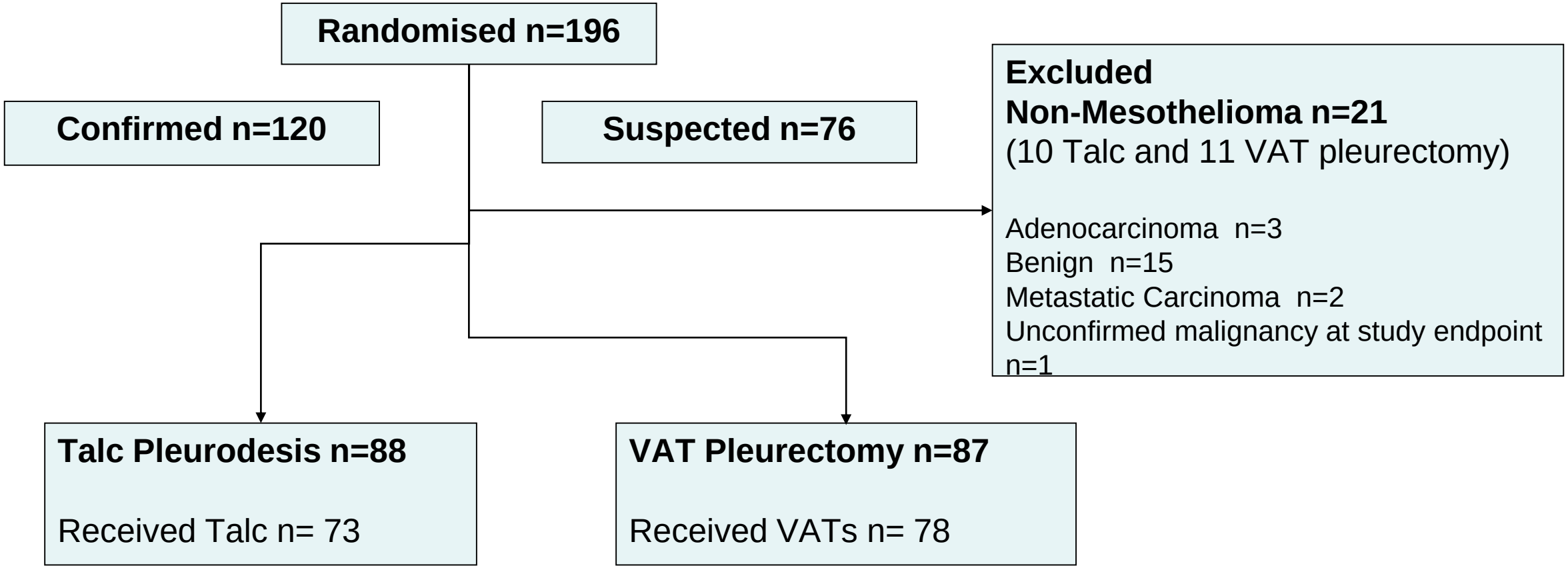
Lancet 2014; 384(9948):1118-1127.



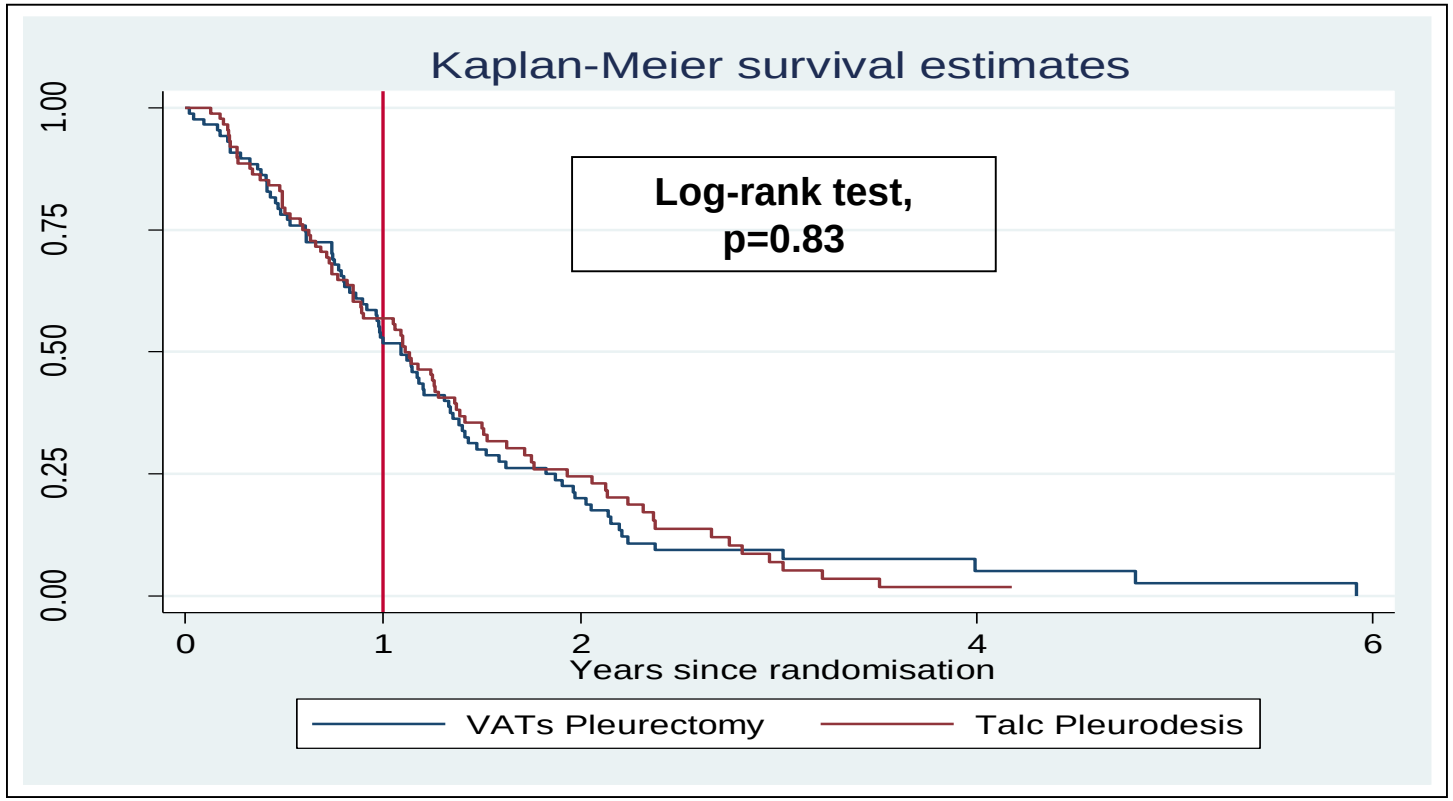
Suspected mesothelioma



Randomisation



Overall survival



6m survival

Talc 80% VATs 78%

12m survival

Talc 57% VATs 52%

Number at risk over time

Months	0	6	12	24	48
VAT Pleurectomy	87	68	45	16	2
Talc Pleurodesis	88	70	50	17	1

MesoVATS trial: Summary

There was no difference in overall survival between VATS partial pleurectomy and Talc pleurodesis

VATS partial pleurectomy improved control of pleural effusion and quality of life

Should VAT partial pleurectomy be considered in patients with mesothelioma for symptom control?

Lancet 2014; 384(9948):1118-1127.

VATS Partial Pleurectomy

MesoTRAP Trial

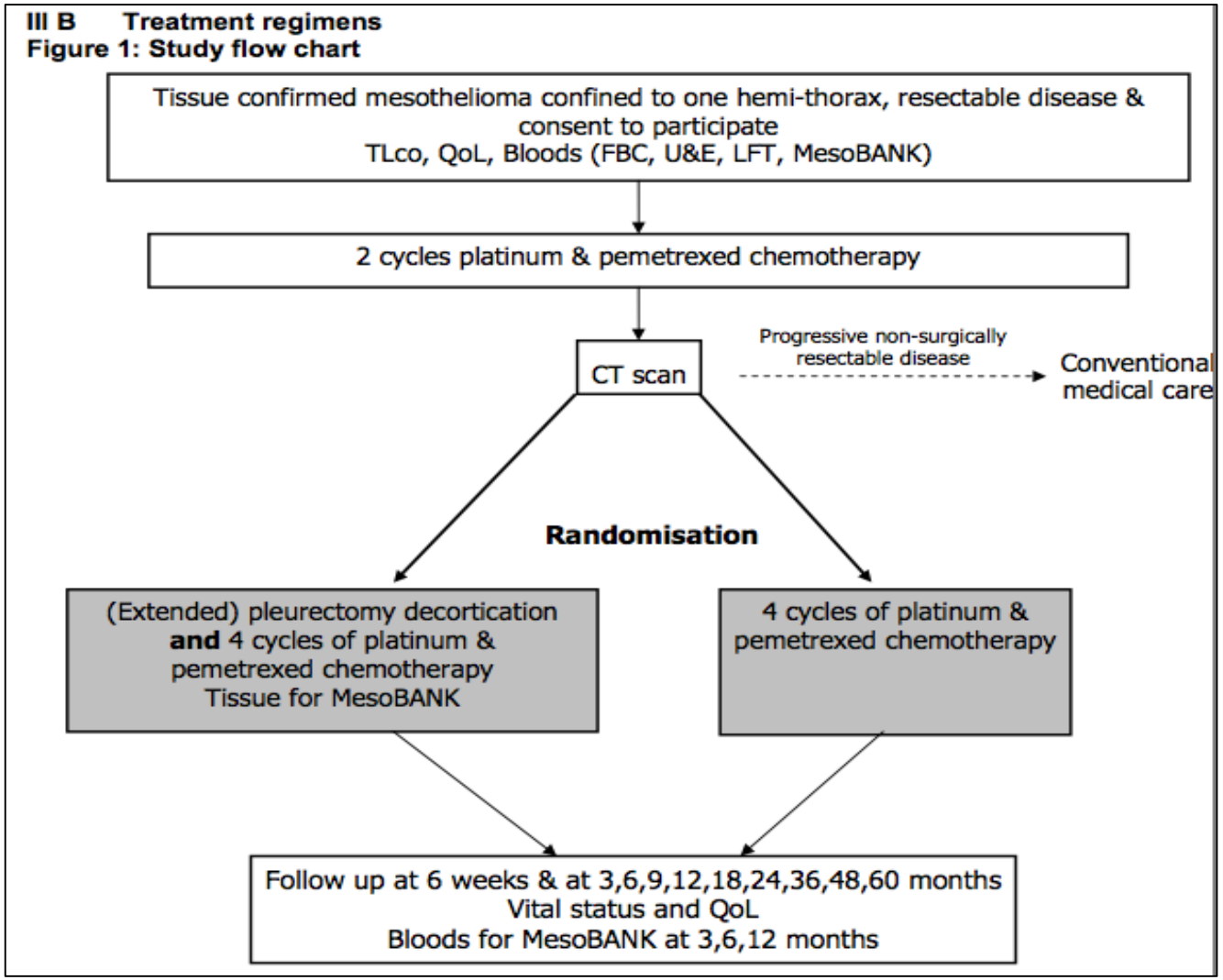
MesoTRAP recruitment update

Patients screened for trapped lung	**501**
Patients with trapped lung assessed for eligibility	67 (13%)
Still in screening	2
Excluded	65
(2 site not opened, 14 declined, 49 met exclusion criteria)	
Randomised	**8**
(4 IPC, 4 VAT-PD)	

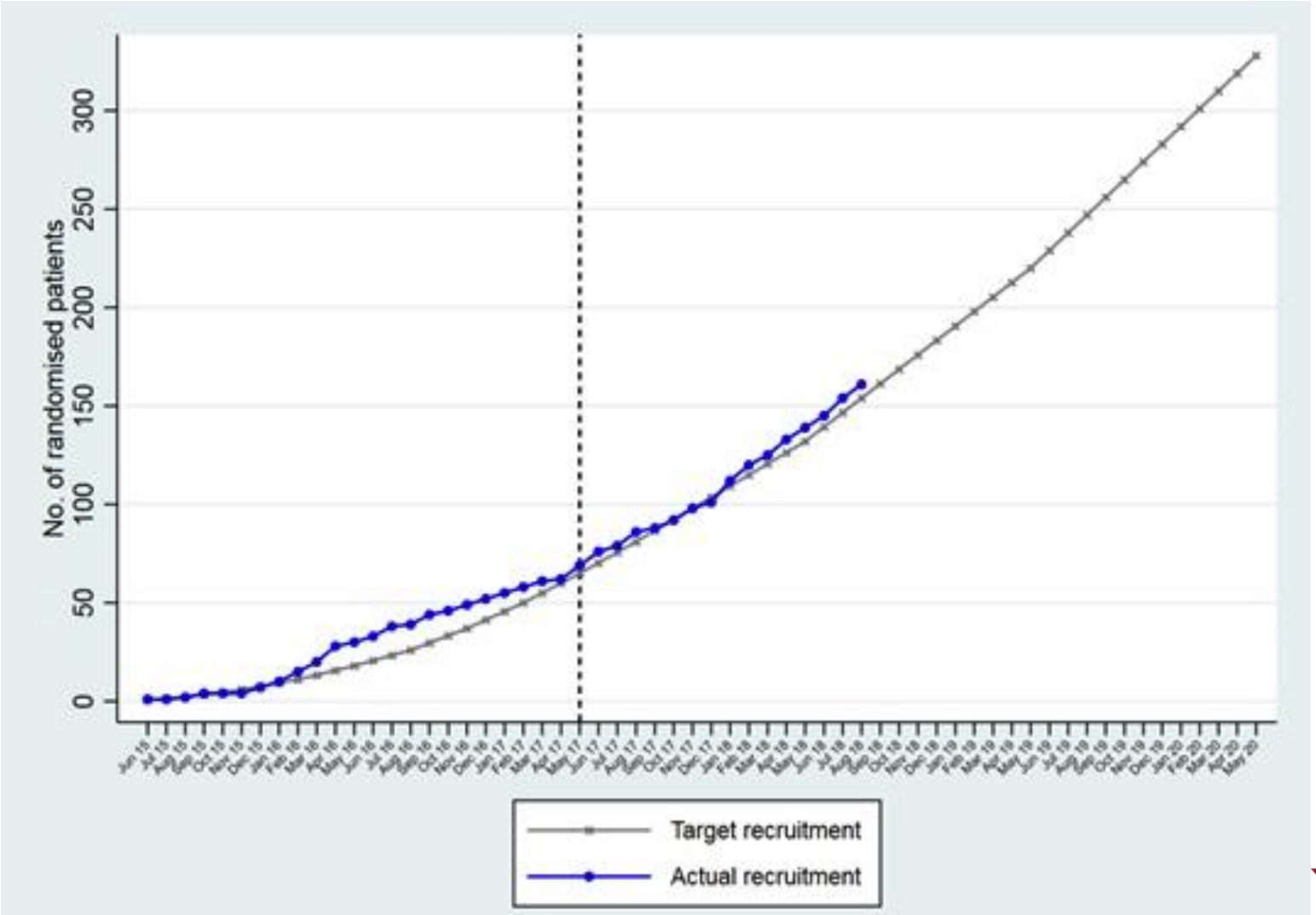
Mesothelioma and Radical Surgery 2: a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma

III B Treatment regimens

Figure 1: Study flow chart



TRIAL MARS 2


No. of randomised patients
0
50
100
150
200
250
300
Target recruitment
Actual recruitment

TAKE HOME MESSAGES:

- (VATS) Partial Pleurectomy or Pleurectomy Decortication is feasible and safe in selected patients
- An R2 resection <u>will not extend life</u>
- Survival may be *worse* in patients with a poor prognosis
- Partial Pleurectomy *may* improve symptoms in selected patients, at the risk of complications
- Hopefully, MesoTRAP will inform about the role of VATS-PP when there is a trapped lung
- MARS-2 will yield Quality of Life data after eP/D