

## LIFE AFTER MARS 2

Wird das resektable maligne Pleuramesotheliom nicht mehr operiert?

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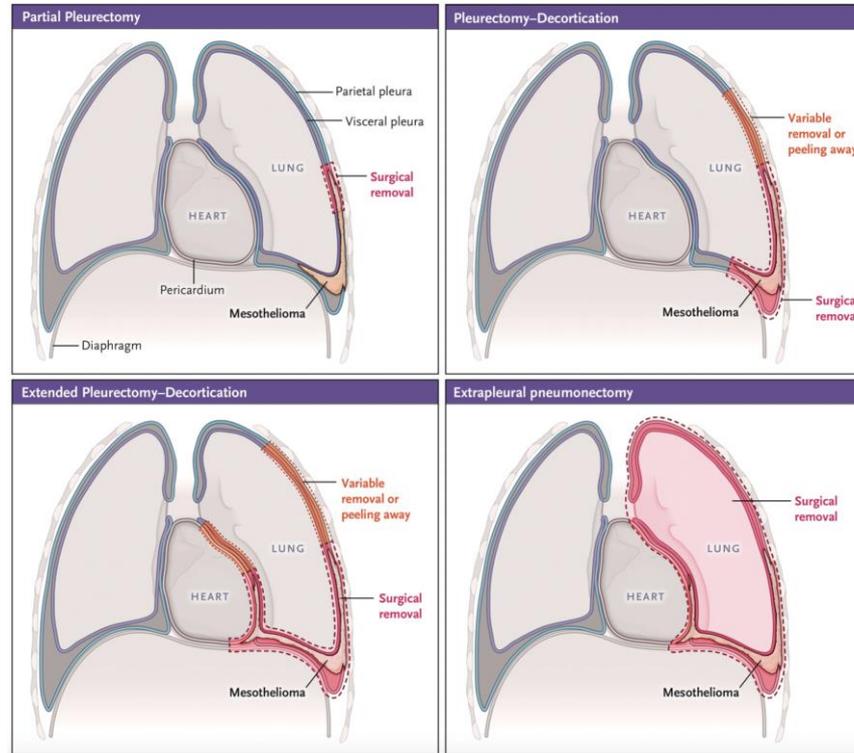
# (A THORACIC SURGEON´S) LIFE AFTER MARS 2

## Wird das resektable maligne Pleuramesotheliom nicht mehr operiert?

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# Chirurgie des Pleuramesothelioms

## Viele Fragen: Selektion, Technik, Begleittherapie....

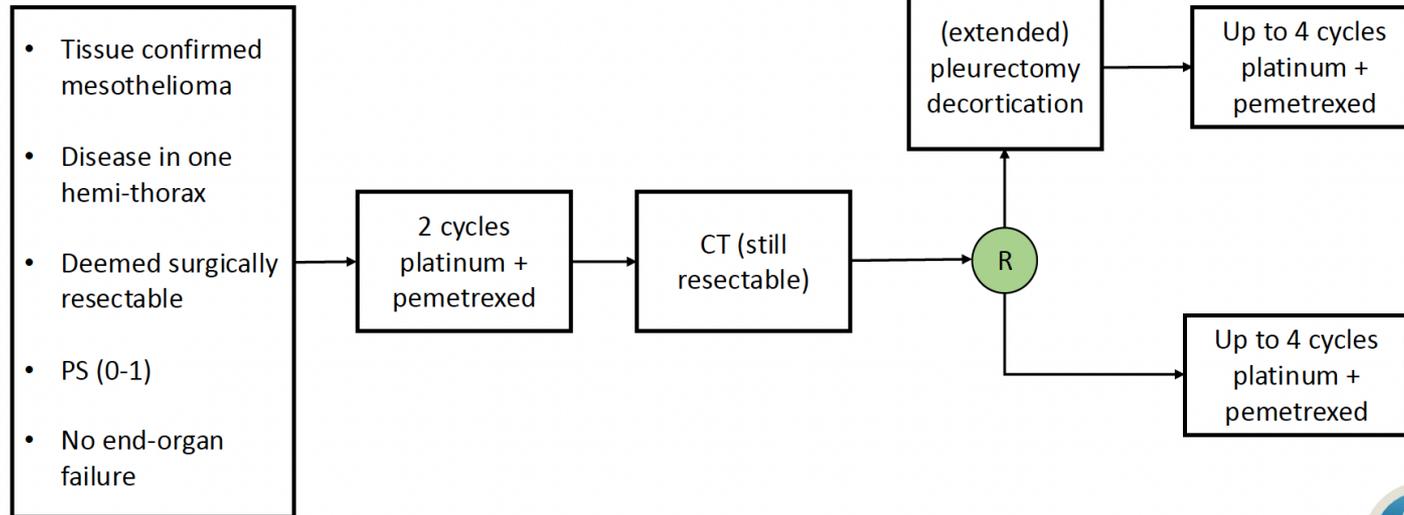


# Chirurgie des Pleuramesothelioms

## Ist jetzt alles klar?

### MARS 2

#### MARS 2 trial schema



# Chirurgie des Pleuramesothelioms

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### MARS 2

	Randomised to surgery (n=169)	Randomised to no surgery (n=166)	Overall (n=335)
<b>Baseline characteristics</b>			
<b>Demographics and bloods</b>			
Age (years)	69 (7.0)	69 (6.5)	69 (6.8)
Male	152/169 (89.9%)	139/166 (83.7%)	291/335 (86.9%)
ECOG status			
0	82/169 (48.5%)	69/166 (41.6%)	151/335 (45.1%)
1	87/169 (51.5%)	97/166 (58.4%)	184/335 (54.9%)
CRP (mg/L)	16 (7.0, 57.0)	10 (5.0, 44.0)	12 (6.0, 49.5)
White cell count (x10 <sup>9</sup> /L)	8 (6.7, 9.5)	8 (6.7, 9.8)	8 (6.7, 9.7)
Platelets (x10 <sup>9</sup> /L)	315 (265.0, 405.0)	314 (251.5, 397.5)	315 (259.0, 400.0)
Albumin (g/dL)	4 (3.6, 4.3)	4 (3.6, 4.3)	4 (3.6, 4.3)
Haemoglobin (g/dL)	14 (12.6, 14.7)	14 (12.9, 14.8)	14 (12.7, 14.8)
<b>Histological breakdown</b>			
Stratification cell type			
Epithelioid only	145/169 (85.8%)	142/166 (85.5%)	287/335 (85.7%)
Other	24/169 (14.2%)	24/166 (14.5%)	48/335 (14.3%)
Histological type/subtype			
Epithelioid mesothelioma	145/169 (85.8%)	143/166 (86.1%)	288/335 (86.0%)
Sarcomatoid mesothelioma	8/169 (4.7%)	3/166 (1.8%)	11/335 (3.3%)
Biphasic mesothelioma	13/169 (7.7%)	16/166 (9.6%)	29/335 (8.7%)
Other (desmoplastic or not specified) mesothelioma	2/169 (1.2%)	3/166 (1.8%)	5/335 (1.5%)
Unable to classify	1/169 (0.6%)	1/166 (0.6%)	2/335 (0.6%)

Data are median (IQR), mean (SD) or n/N (%)

# Chirurgie des Pleuramesothelioms

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### MARS 2

	Randomised to surgery (n=169)	Randomised to no surgery (n=166)	Overall (n=335)
<b>Clinical TNM stage</b>			
cT			
T1	75/169 (44.4%)	81/166 (48.8%)	156/335 (46.6%)
T2	36/169 (21.3%)	36/166 (21.7%)	72/335 (21.5%)
Involvement of diaphragmatic muscle	9/36 (25.0%)	21/36 (58.3%)	30/72 (41.7%)
Extension of tumour into underlying pulmonary parenchyma	30/36 (83.3%)	18/36 (50.0%)	48/72 (66.7%)
T3	58/169 (34.3%)	49/166 (29.5%)	107/335 (31.9%)
Involvement of endothoracic fascia	20/58 (34.5%)	17/50 (34.0%)	37/108 (34.3%)
Extension into mediastinal fat	30/58 (51.7%)	30/50 (60.0%)	60/108 (55.6%)
Solitary, completely resectable focus of tumour extending into soft tissues of chest wall	18/58 (31.0%)	14/50 (28.0%)	32/108 (29.6%)
Nontransmural involvement of pericardium	16/58 (27.6%)	10/50 (20.0%)	26/108 (24.1%)
cN			
N0	122/169 (72.2%)	119/166 (71.7%)	241/335 (71.9%)
N1	34/169 (20.1%)	36/166 (21.7%)	70/335 (20.9%)
N2	13/169 (7.7%)	11/166 (6.6%)	24/335 (7.2%)
cM			
M0	163/169 (96.4%)	162/166 (97.6%)	325/335 (97.0%)
M1	6/169 (3.6%)	4/166 (2.4%)	10/335 (3.0%)

Data are n/N (%)

# Chirurgie des Pleuramesothelioms

## Ist jetzt alles klar?

### MARS 2

## Surgery

	Received surgery (n=158*)
<b>Surgical procedure</b>	
Extended pleurectomy/decortication	139/157 (88.5%)
Pleurectomy decortication	13/157 (8.3%)
Partial pleurectomy	3/157 (1.9%)
Exploration, no pleurodesis	1/157 (0.6%)
Other	1/157 (0.6%)
<b>Resection and reconstruction</b>	
Diaphragm resection	130/157 (82.8%)
Diaphragm reconstructed	128/157 (81.5%)
Pericardium resection	105/157 (66.9%)
Pericardium reconstructed	84/157 (53.5%)
Chest wall resection	19/157 (12.1%)
Chest wall reconstructed	9/157 (5.7%)
Other ipsilateral lung resection	67/157 (42.7%)
Wedge resection	64/67 (95.5%)
Bilobectomy	1/67 (1.5%)
Lobectomy	2/67 (3.0%)

Completeness of resection	
R0 (no residual tumour)	5/157 (3.2%)
R1 (microscopic residual tumour)	127/157 (80.9%)
R2 (macroscopic residual tumour)	25/157 (15.9%)
Length of hospital stay (days) §	
	13 (12, 14)
In-hospital mortality	
30 day mortality	6/157 (3.8%)
90 day mortality	14/157 (8.9%)

Data are n/N (%)

\* 1 patient withdrew to receive surgery privately and operative details were unable to be obtained. § in-hospital deaths censored at maximum length of stay

# Chirurgie des Pleuramesothelioms

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### MARS 2

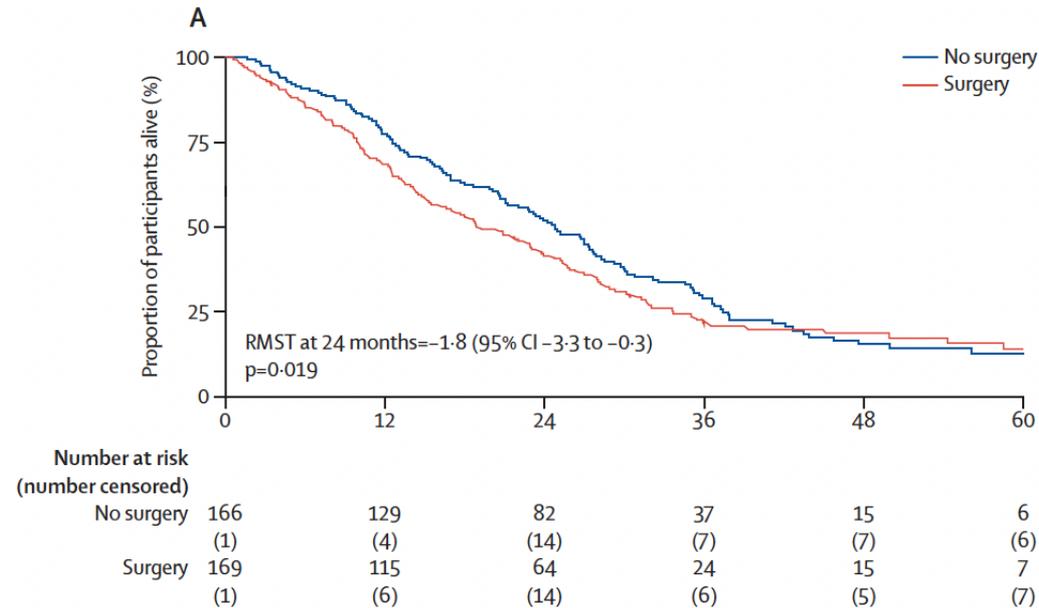
## Systemic treatments

	Randomised to surgery (n=169)	Randomised to no surgery (n=166)	Overall (n=335)
<b>Systemic treatments</b>			
<b>First-line chemotherapy cycles</b>			
Completed 2 cycles	169/169 (100.0%)	166/166 (100.0%)	335/335 (100.0%)
Completed 3 cycles	101/169 (59.8%)	154/166 (92.8%)	255/335 (76.1%)
Completed 4 cycles	96/169 (56.8%)	147/166 (88.6%)	243/335 (72.5%)
Completed 5 cycles	76/169 (45.0%)	111/166 (66.9%)	187/335 (55.8%)
Completed 6 cycles	66/169 (39.1%)	93/166 (56.0%)	159/335 (47.5%)
<b>Additional treatments</b>			
<b>Any additional treatment reported during trial participation</b>	<b>90/169 (53.3%)</b>	<b>115/166 (69.3%)</b>	<b>205/335 (61.2%)</b>
Immunotherapy or other treatment known to improve overall survival ††	37/169 (21.9%)	64/166 (38.6%)	101/335 (30.1%)
Additional chemotherapy	35/169 (20.7%)	65/166 (39.2%)	100/335 (29.9%)
Radiotherapy	32/169 (18.9%)	30/166 (18.1%)	62/335 (18.5%)
Further surgery	4/169 (2.4%)	6/166 (3.6%)	10/335 (3.0%)
Other systemic treatment	10/169 (5.9%)	19/166 (11.4%)	29/335 (8.7%)

# Chirurgie des Pleuramesothelioms

## Ist jetzt alles klar?

### MARS 2



# Chirurgie des Pleuramesothelioms

## Ist jetzt alles klar?

### MARS 2

## Safety

	Randomised to surgery (n=169)	Randomised to no surgery (n=166)	Effect (95% CI)	P value
Number of CTCAE grade 3+ events	1 (0, 3)	0 (0, 2)	IRR=3.6 (2.3, 5.5)	<0.001
0	62/169 (36.7%)	86/166 (51.8%)		
1	33/169 (19.5%)	38/166 (22.9%)		
2	22/169 (13.0%)	17/166 (10.2%)		
3	21/169 (12.4%)	12/166 (7.2%)		
4+	31/169 (18.3%)	14/166 (7.8%)		

Data are median (interquartile range) or n/N (%). CI=confidence interval, IRR=incidence rate ratio

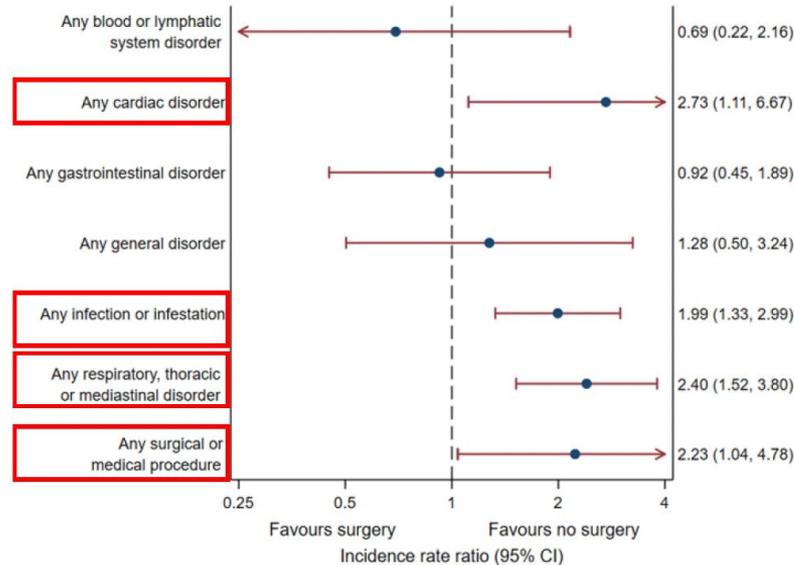
# Chirurgie des Pleuramesothelioms

## Ist jetzt alles klar?

### MARS 2

#### Safety

Any CTCAE grade 3+ event within each MedDRA system organ class



# Chirurgie des Pleuramesothelioms

## Ist jetzt alles klar?

### MARS 2

- Extended pleurectomy decortication for mesothelioma had:
  - higher risk of death
  - more serious complications
  - poorer quality of life
  - at higher cost of £14,631 (\$20,102 USD)

...compared to those who were randomised to chemotherapy alone

# Chirurgie des Pleuramesothelioms

## MARS 2 - Kritikpunkte

### Imbalance der Studienarme

	Randomised to surgery (n=169)	Randomised to no surgery (n=166)	Overall (n=335)
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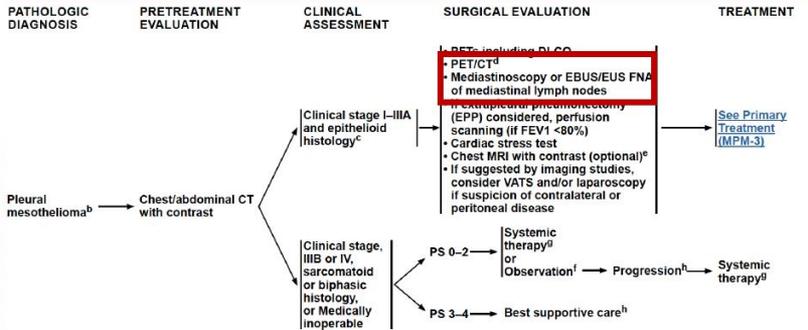
# Chirurgie des Pleuramesothelioms

## MARS 2 - Kritikpunkte

### Suboptimales Staging

NCCN National Comprehensive Cancer Network  
**NCCN Guidelines Version 1.2023**  
**Mesothelioma: Pleural**

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)



SPECIAL ARTICLE

Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up<sup>1\*</sup>

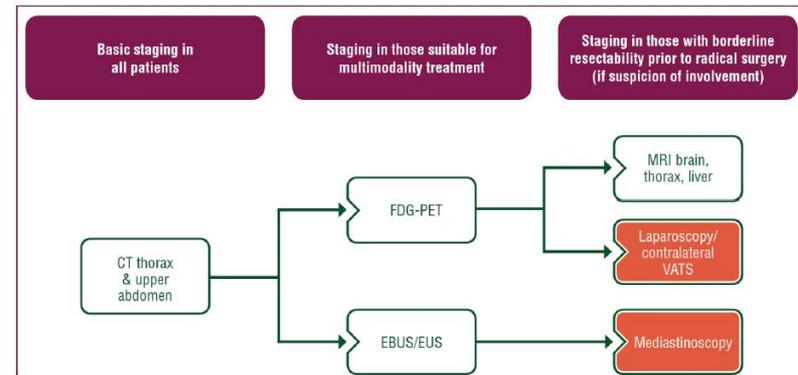


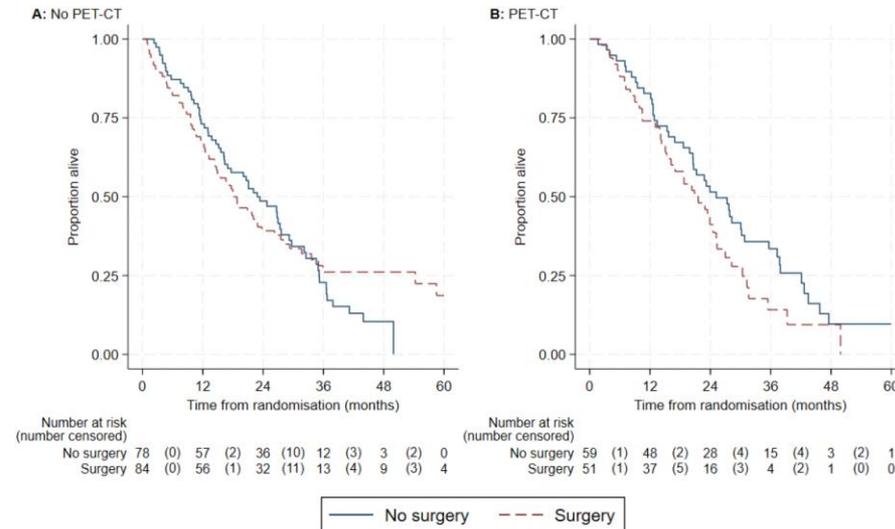
Figure 1. A staging summary for MPM.

# Chirurgie des Pleuramesothelioms

## MARS 2 - Kritikpunkte

### Suboptimales Staging

Figure S17 Overall survival by PET-CT subgroups

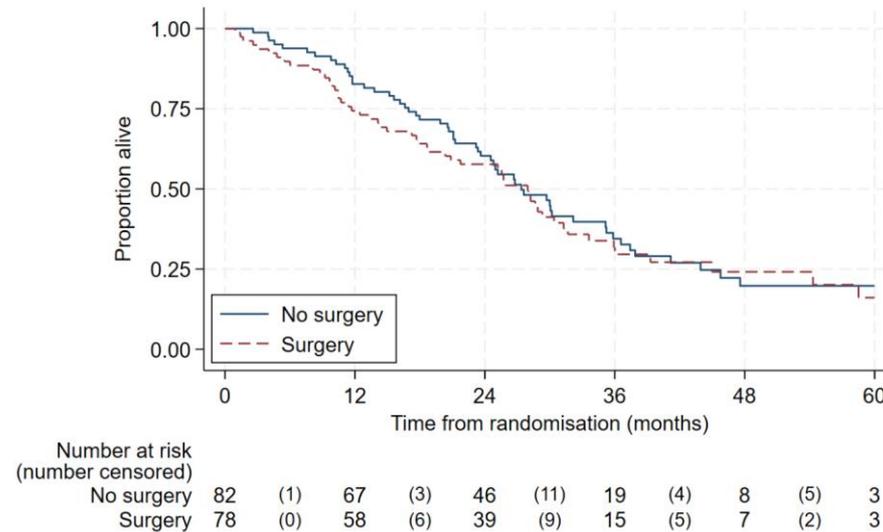


# Chirurgie des Pleuramesothelioms

## MARS 2 - Kritikpunkte

### Suboptimale Patienten-Selektion

Figure S19 Overall survival for T1-2 N0 epithelioid only cohort



# Chirurgie des Pleuramesothelioms

## MARS 2 - Kritikpunkte

### Suboptimale Chirurgie – Low Volume Center

- Nur 5 Studienzentren haben die Operationen durchgeführt
- Nur eines davon wurde als Low-Volume-Center eingestuft
- Qualitäts-Sicherungs-Programm in Studie inkludiert

**Table S16 Exploratory analysis of surgical site experience level**

	HR (95% CI)	p-value for three level factor
Expert surgical site vs chemotherapy alone	HR=1.18 (0.95, 1.47)	0.29
Non-expert surgical site vs chemotherapy alone	HR=1.83 (0.49, 6.85)	
Expert surgical site vs non-expert surgical site	HR=0.65 (0.17, 2.40)	

CI=confidence interval, HR=hazard ratio

# Chirurgie des Pleuramesothelioms

## MARS 2 - Kritikpunkte

### Imbalance der systemischen Therapiezyklen

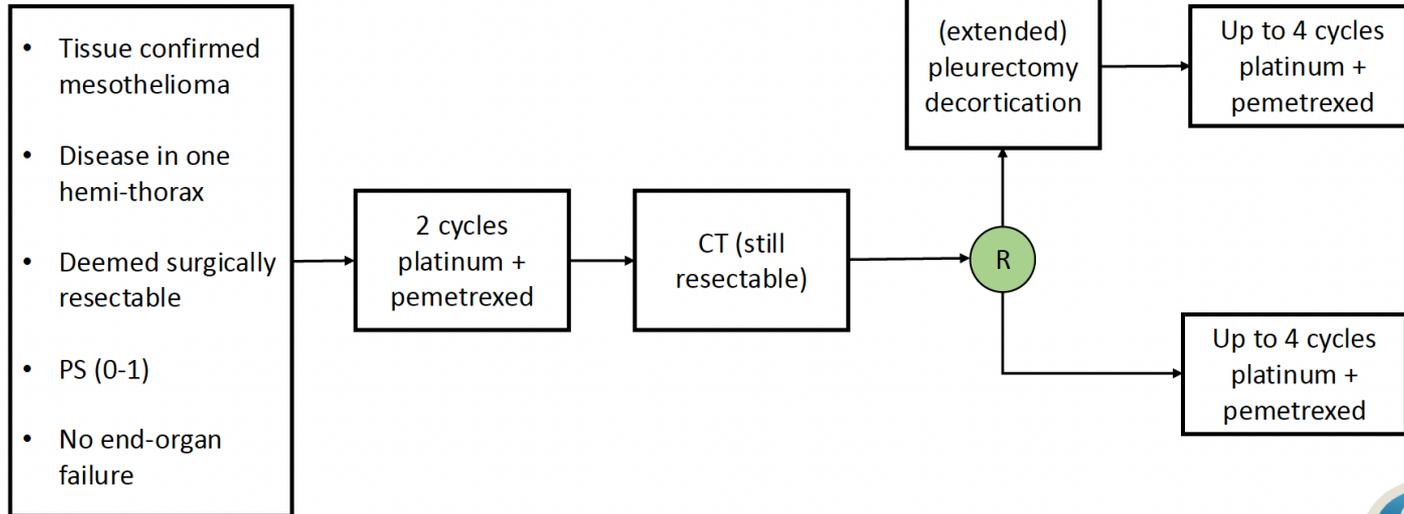
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# Chirurgie des Pleuramesothelioms

## MARS 2 - Kritikpunkte

### Präselektion von CTX-responsiven Fällen

### MARS 2 trial schema



# Chirurgie des Pleuramesothelioms

## Aktuelle NCCN-Guidelines

CLINICAL STAGE I AND  
EPITHELIOID HISTOLOGY  
SURGICAL EVALUATION<sup>g</sup>

TREATMENT<sup>h</sup>

- PFTs including DLCO
- FDG-PET/CT<sup>i</sup>
- Mediastinoscopy or EBUS/EUS FNA of mediastinal lymph nodes
- Cardiac stress test
- Chest MRI with contrast (optional)<sup>j</sup>
- If suggested by imaging studies, consider VATS and/or laparoscopy if suspicion of contralateral or peritoneal disease

Induction  
systemic therapy<sup>d</sup>

or

Surgical  
exploration<sup>k</sup>

Surgical  
exploration<sup>k</sup>

Resectable

Unresectable

Resectable

Unresectable

Pleurectomy/  
decortication  
(P/D)<sup>k</sup>

Consider  
sequential  
pleural IMRT<sup>e</sup>

Systemic  
therapy<sup>d</sup> and  
consider  
sequential  
pleural IMRT<sup>e</sup>

Systemic therapy<sup>d</sup>  
and consider  
sequential pleural  
IMRT<sup>e</sup>

Consider  
sequential  
pleural IMRT<sup>e</sup>

Progression

Progression

Progression

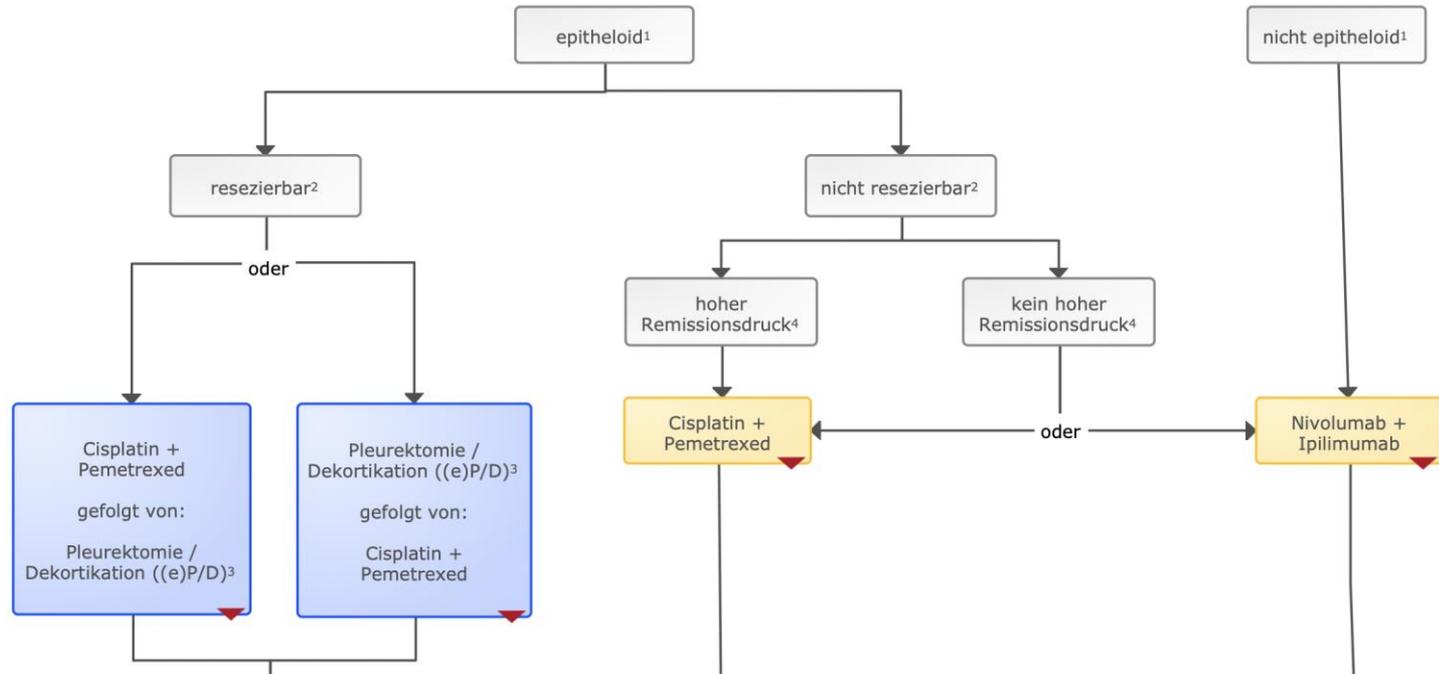
Systemic  
therapy<sup>d,h</sup>

Systemic  
therapy<sup>d,h</sup>

Systemic  
therapy<sup>d,h</sup>

# Chirurgie des Pleuramesothelioms

## „Aktuelle“ Onkopedia-Guidelines



# Life after MARS 2

## Wird das resektable maligne Pleuramesotheliom nicht mehr operiert?

### TAKE HOME MESSAGES

- MARS 2 = Phase III-Evidenz
- Klar negative Studie, ohne Hinweise für einen Nutzen der OP
- Berechtigte Kritikpunkte (Staging, Histologie, etc.)
- Aber Subgruppen- und Sensitivitäts-Analysen ohne Tendenz zur Bestätigung der Kritikpunkte
- Wird also das Pleuramesotheliom nicht mehr operiert? Doch, nämlich in Studien!

## LIFE AFTER MARS 2

Wird das resektable maligne Pleuramesotheliom nicht mehr operiert?

**Danke für die Aufmerksamkeit!**

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