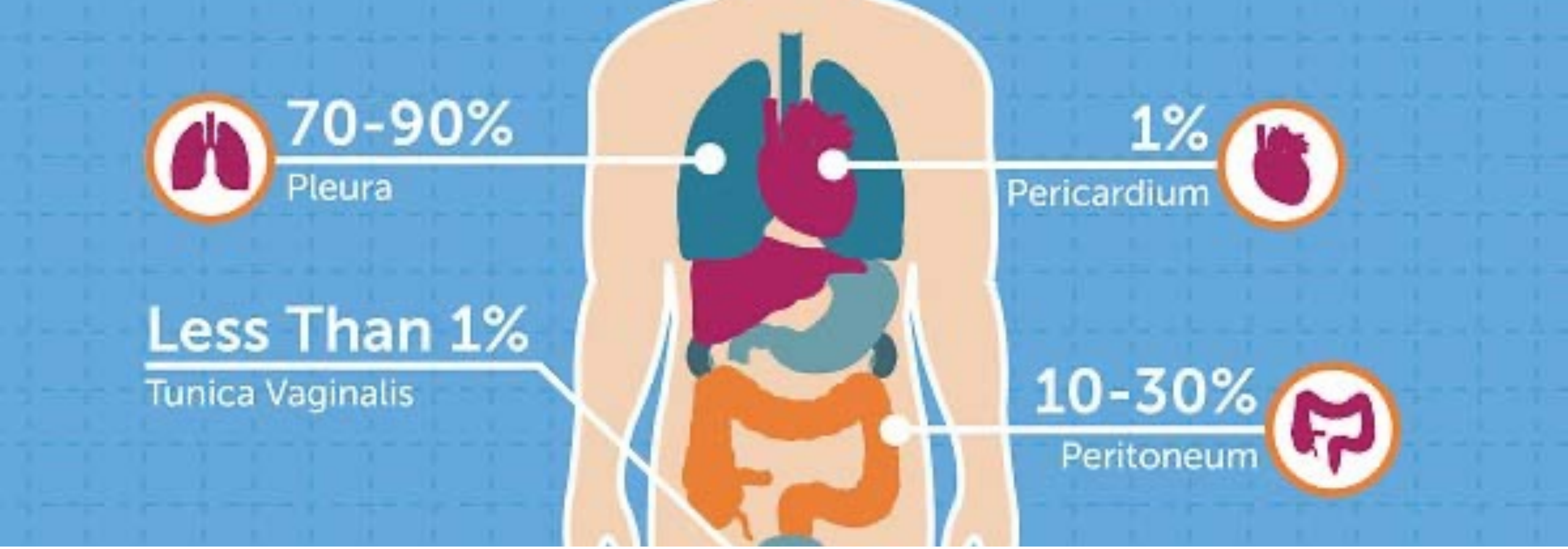
Malignt pleura mesoteliom

Bassam Hazem

Bit. Överläkare

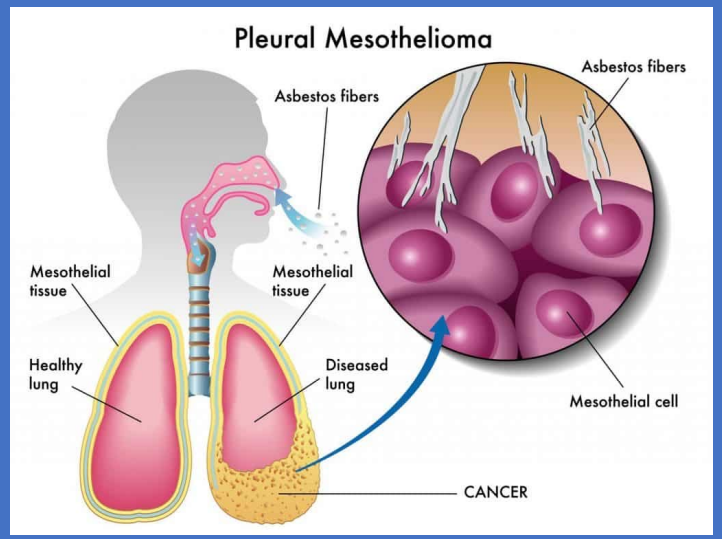
Lung & allergisektionen

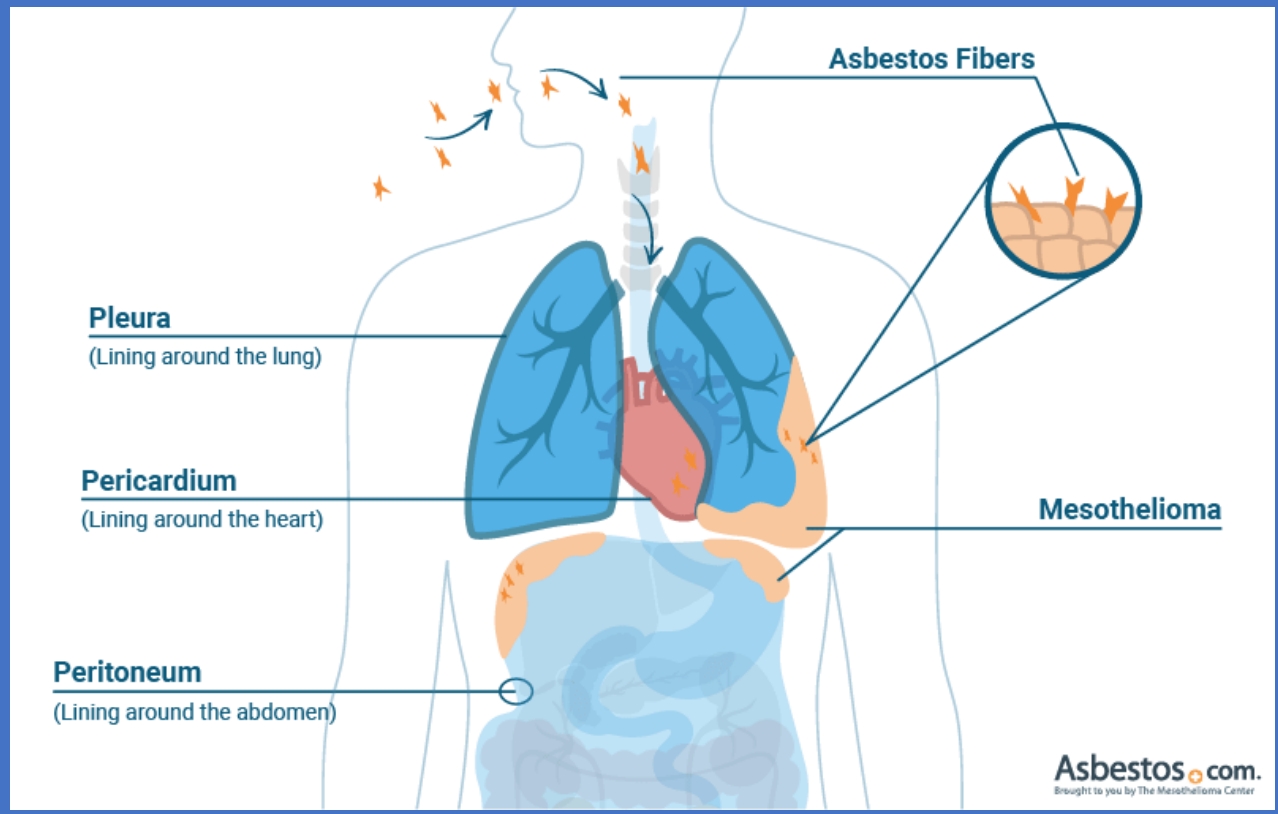
Skånes universitetssjukhus

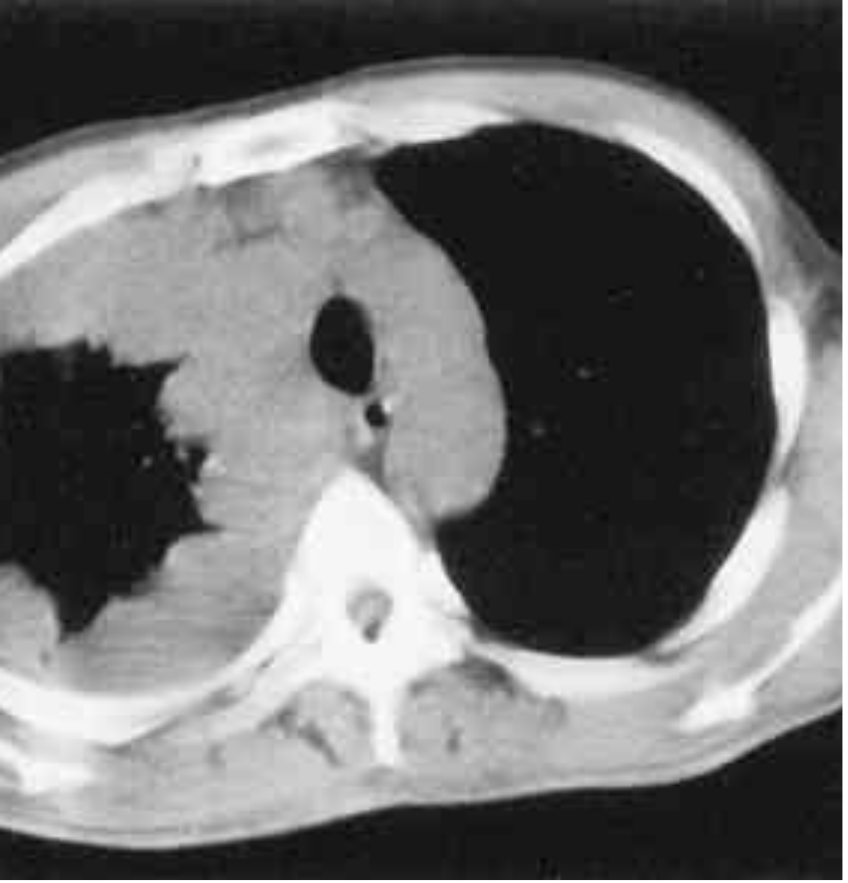
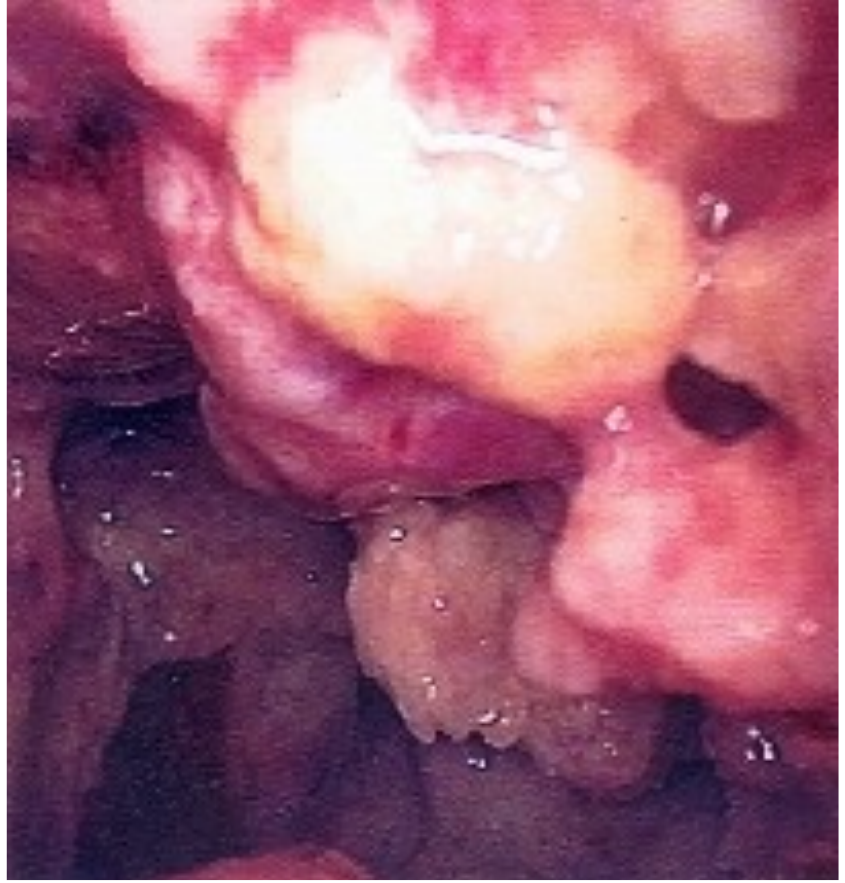
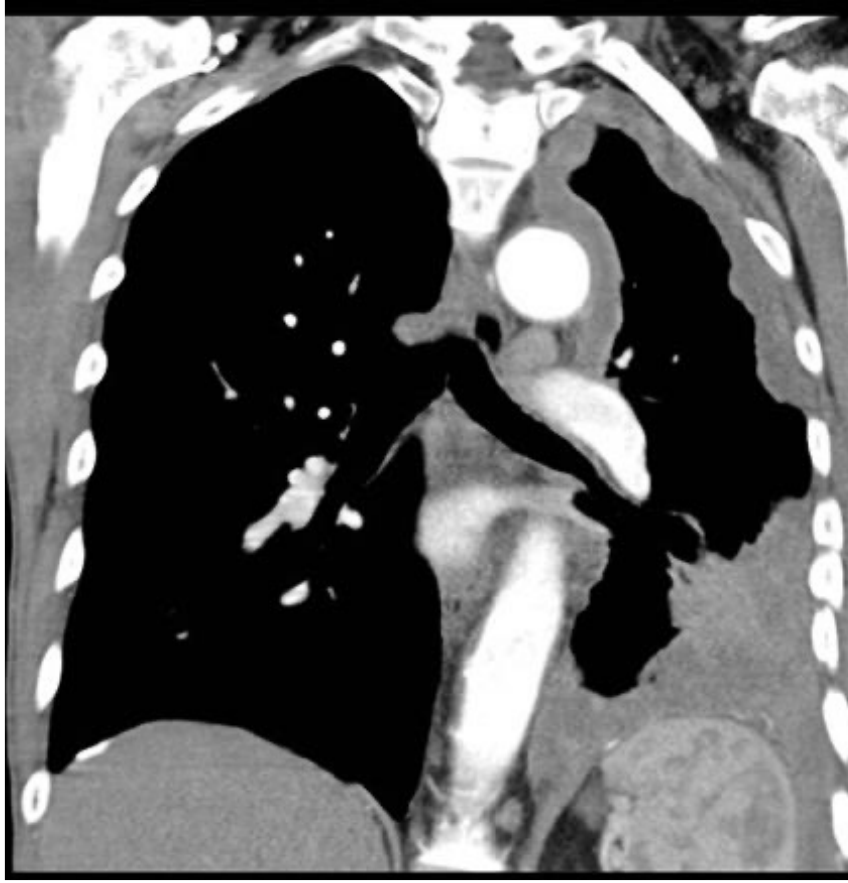


Malignt mesoteliom

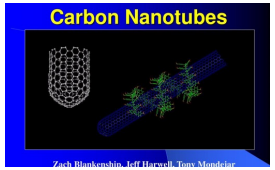
- Pleura, hjärta, buk (hinnor)
- upp till 90 % pleural mesoteliom
- Ofta avancerat stadie
- 5-år överlevnad 5-10%


Pleural Mesothelioma
Asbestos fibers
Asbestos fibers
Mesothelial tissue
Mesothelial tissue
Healthy lung
Diseased lung
Mesothelial cell
CANCER


Asbestos Fibers
Pleura
(Lining around the lung)
Pericardium
(Lining around the heart)
Mesothelioma
Peritoneum
(Lining around the abdomen)
Asbestos.com.
Brought to you by The Mesothelioma Center

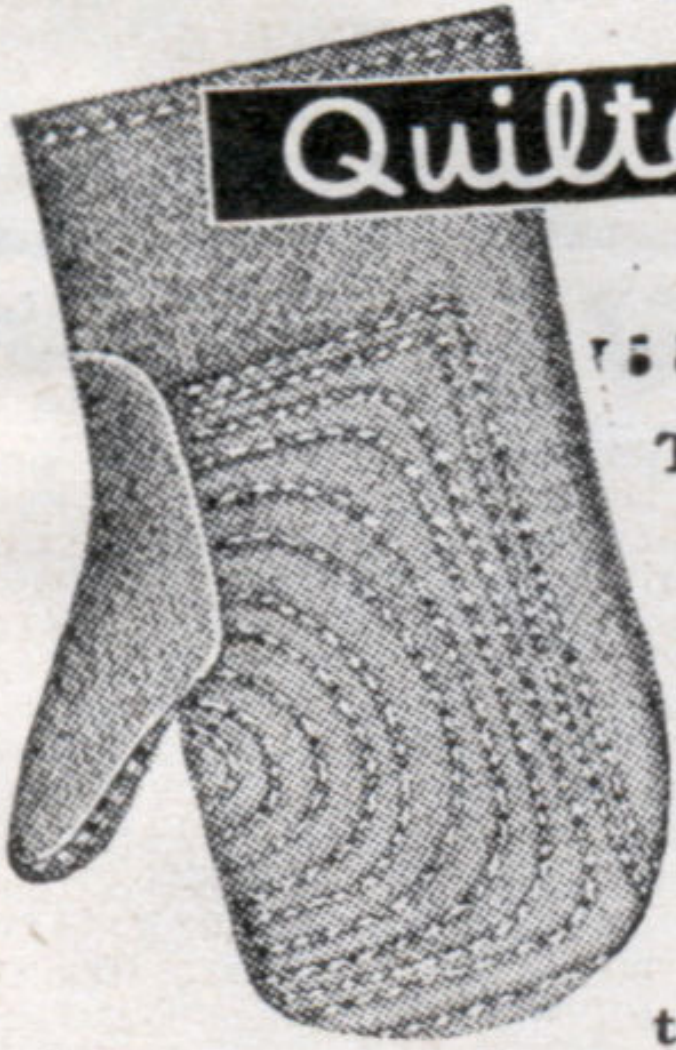




Pleuramesoteliom



Orsaker/riskfaktorer

- **Asbest exponering** (latens fas 20-50 år)
- Yrkes exponering (asbest, mineralfibrer)
- Miljö exponering (Grekland, Turkiet, Bulgarien) termolite asbestos fiber. Turkiet (Cappadocia) erionite
- Efter strålningsbehandling (bröst ca)
- Carbone nanotubes
- Viral onkogenes: Simian virus 40 (SV40)
- Genetiska faktorer(mutation in the gene BAP1. Andra är PALB2 and BRCA1/2 (DNA repair genes)
- Andra orsaker: Idiopatisk, visa geografiska områden, mineral fibers.



Quilted ASBESTOS MITTS

... they last twice as long

These asbestos mitts for handling hot metal molds and shapes are reversible to fit either hand. Both sides quilted, won't shred or fray on rough, jagged material. Double wear, double life. Wool lined. All seams double stitched. The answer to troublesome problems. $2.20 a pair. Discounts for quantities. One of 4300 production-speeding, time-saving safety gloves, aprons, sleeves, spats, etc. Write for *Free* catalog.

INDUSTRIAL GLOVES CO.

6547 Garfield Blvd., Danville, Ill.

(In Canada: Safety Supply Co., Toronto)

OLD HICKORY
STEEL GRIP
MADE IN U.S.A.
REG. U.S. PAT. OFF.

Chronology of Asbestos Bans and Restrictions[1]

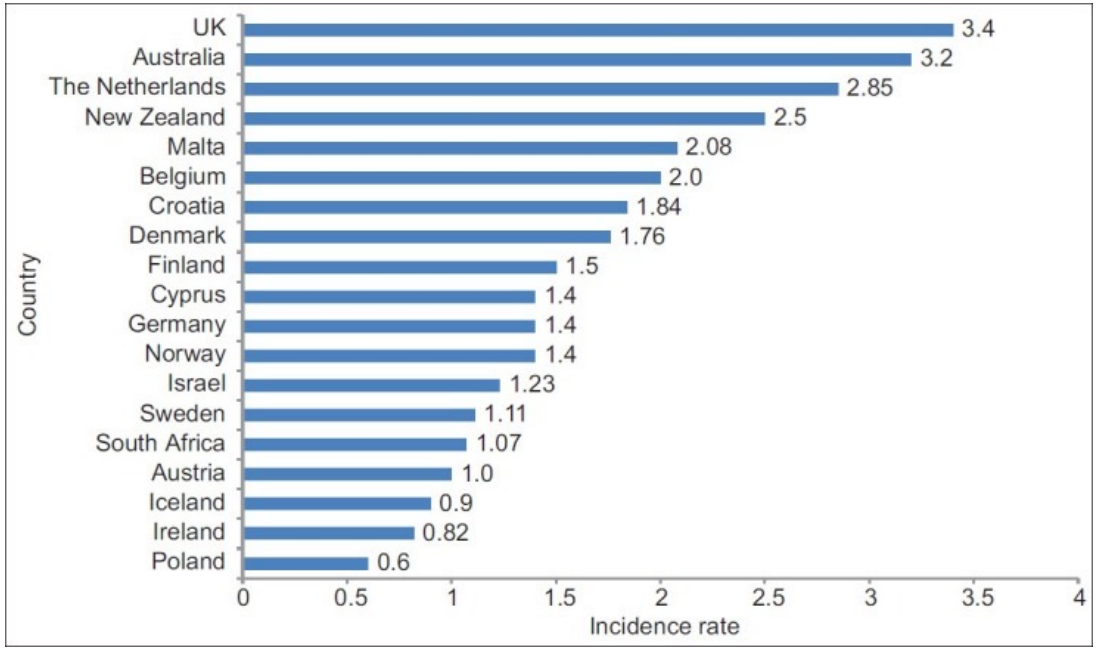
Compiled by Laurie Kazan-Allen

See also: Current Asbestos Bans

(Revised July 3, 2021)

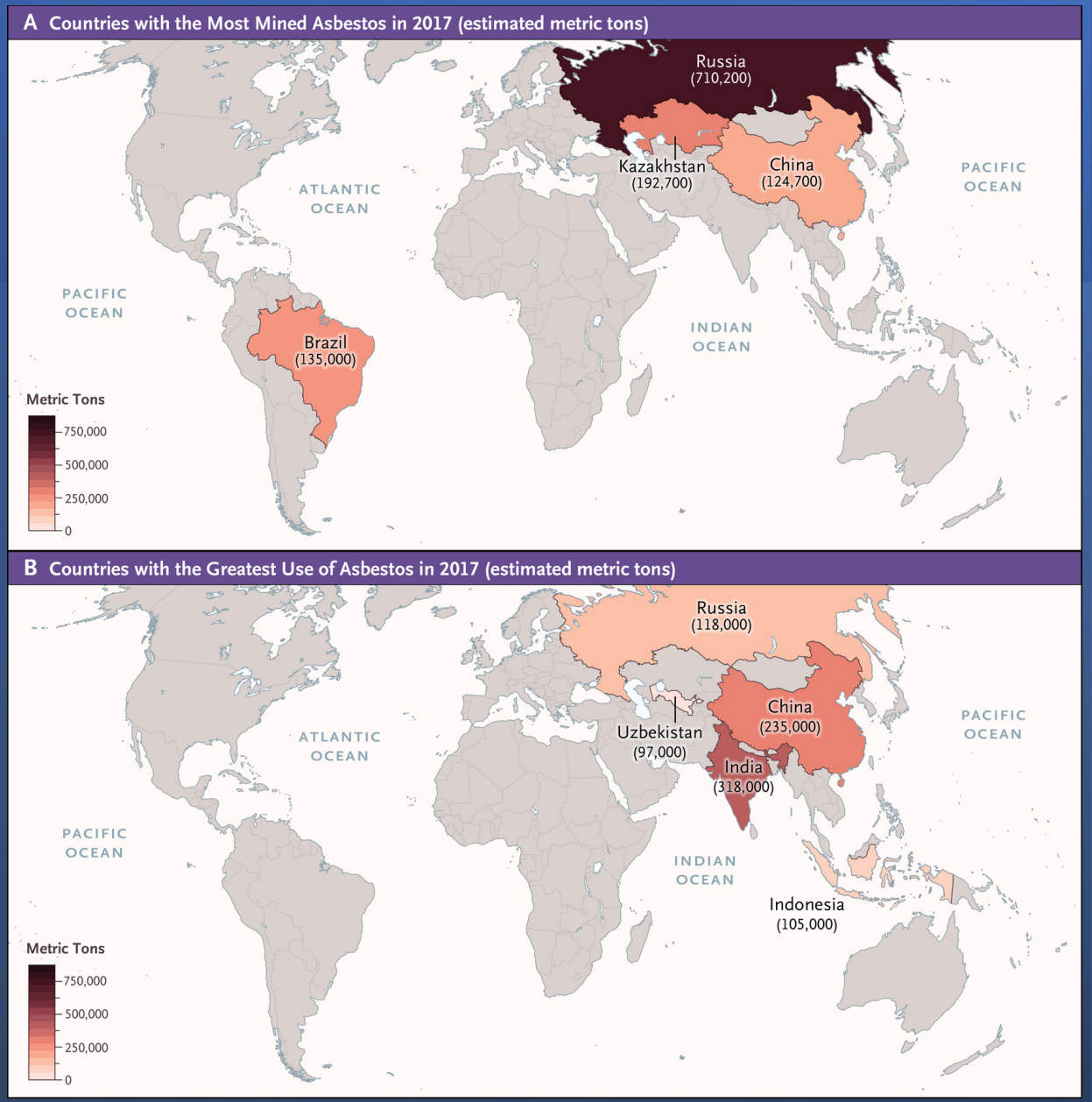
Date	Event
1972	**Denmark** bans the use of asbestos for thermal and noise insulation and waterproofing.
1973	**US** bans the use of spray-applied surfacing asbestos-containing material for fireproofing/insulating purposes (see: Federal Bans on Asbestos). **Sweden** bans asbestos spraying.
1975	**US** bans installation of asbestos pipe insulation and asbestos block insulation on facility components, such as boilers and hot water tanks, if the materials are either pre-formed (molded) and friable or wet-applied and friable after drying.
1976	**Sweden** adopts guidelines recommending a ban on crocidolite (legislation to enforce the crocidolite ban was implemented in 1982).
1977	**US** bans use of asbestos in artificial fireplace embers and wall patching compounds.
1978	**US** bans spray-applied surfacing materials for purposes not already banned.
1980	**Denmark** bans all uses of asbestos (with the exception of asbestos-cement roofing). **Israel** introduced a series of restrictions on the use of asbestos from the 1980s which eventually amounted to a de facto ban on the use of asbestos. **Indonesia**: Ministry of Manpower No 01/1980 warns the construction industry about the occupational asbestos hazard stipulating that asbestos should only be used when less dangerous materials are not available; precautions should, the regulations said, be taken to protect workers from breathing in asbestos fibers.
1982	**Sweden** enforces from July 1 the first of a series of bans on various uses of asbestos (including chrysotile).

Incidence rate



Mesothelioma in some countries. Age-standardized (world) incidence rates per 100,000, men

- I Sverige ca 100 fall/år, 80% män
- 2008 mindre än 100 fall (första gången på 30 år)
- 2009 siffran är högre igen.
- 2013 130 fall registrerades



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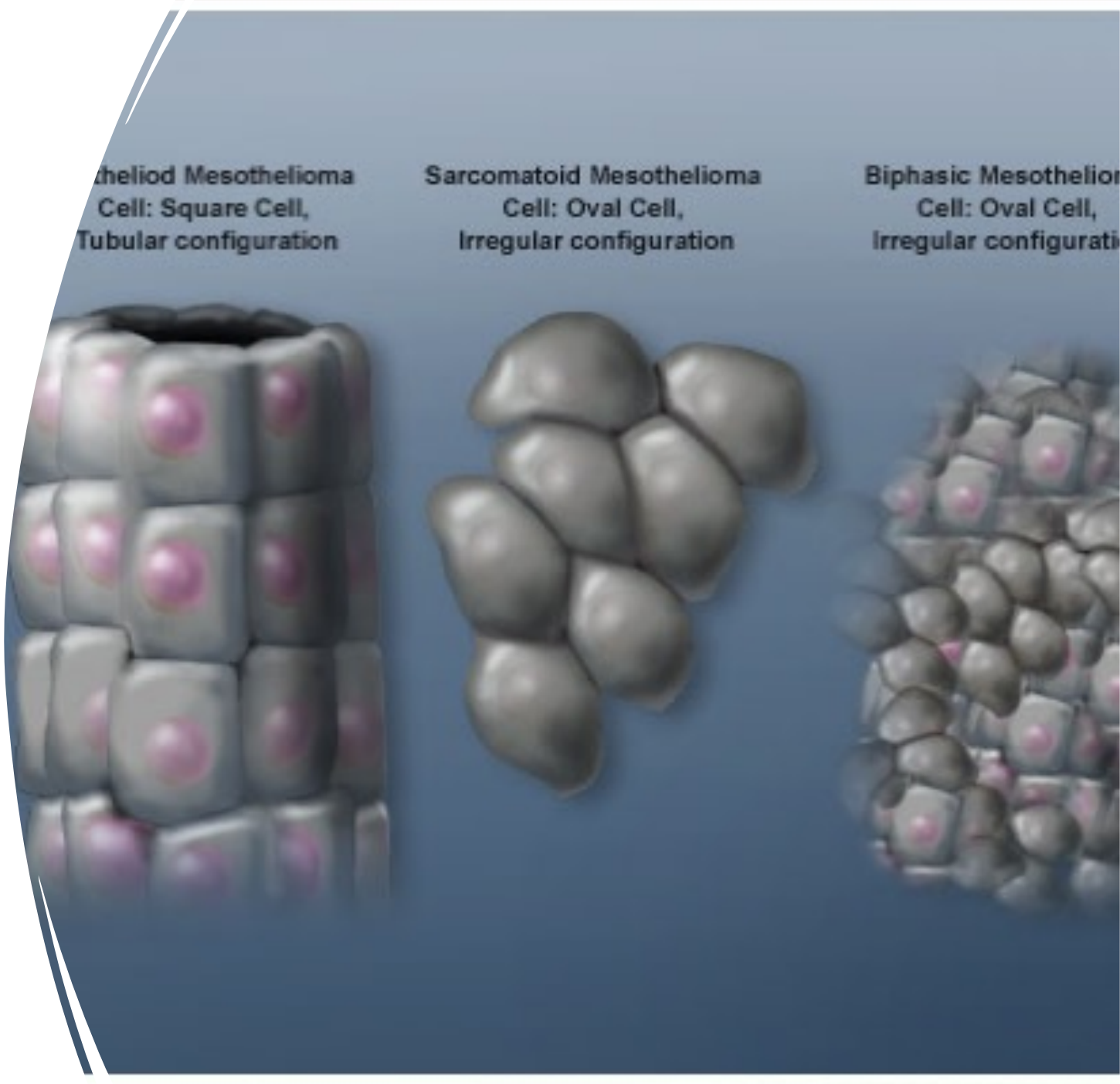
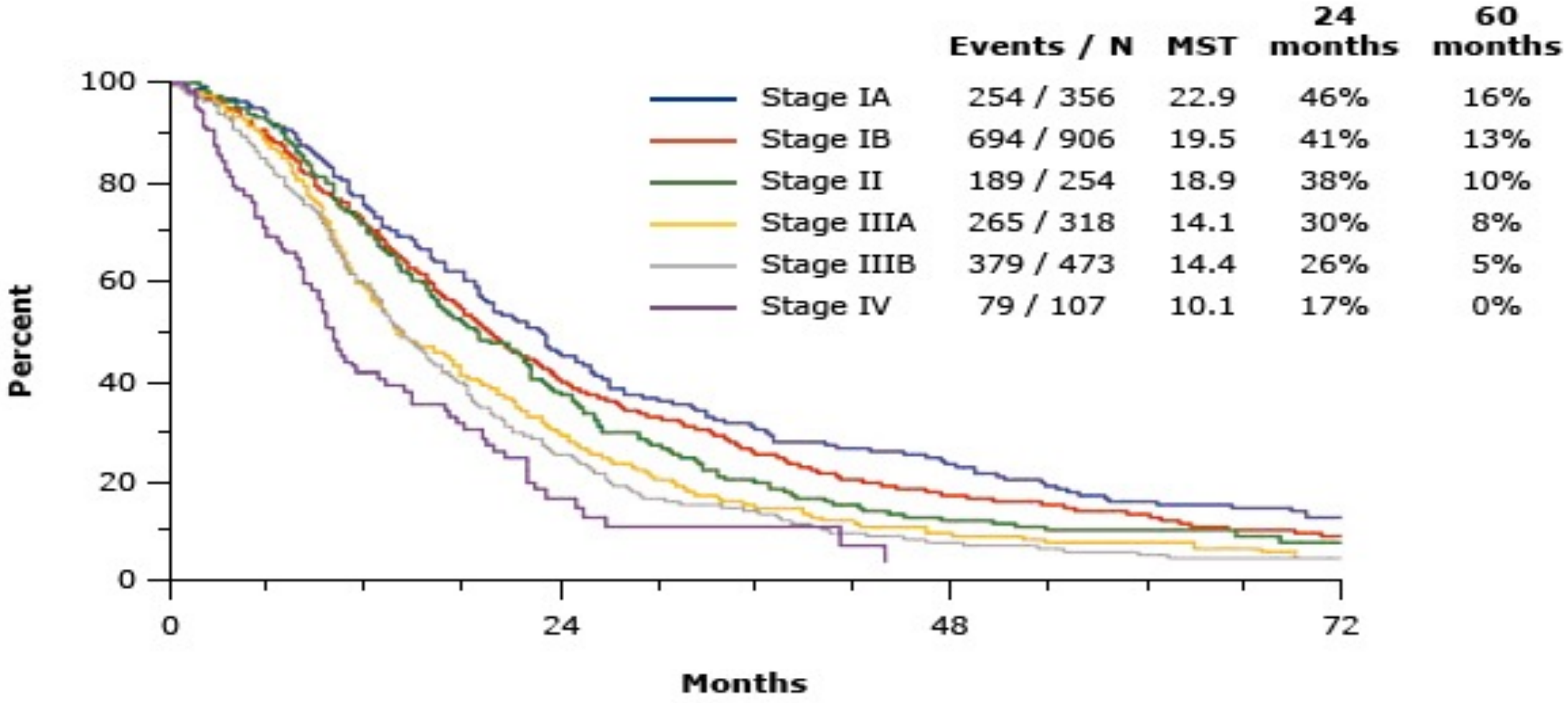
- Epiteloitt 50-60 %
- Sacromatoitt 10 %
- Bifasiskt 30-40 %

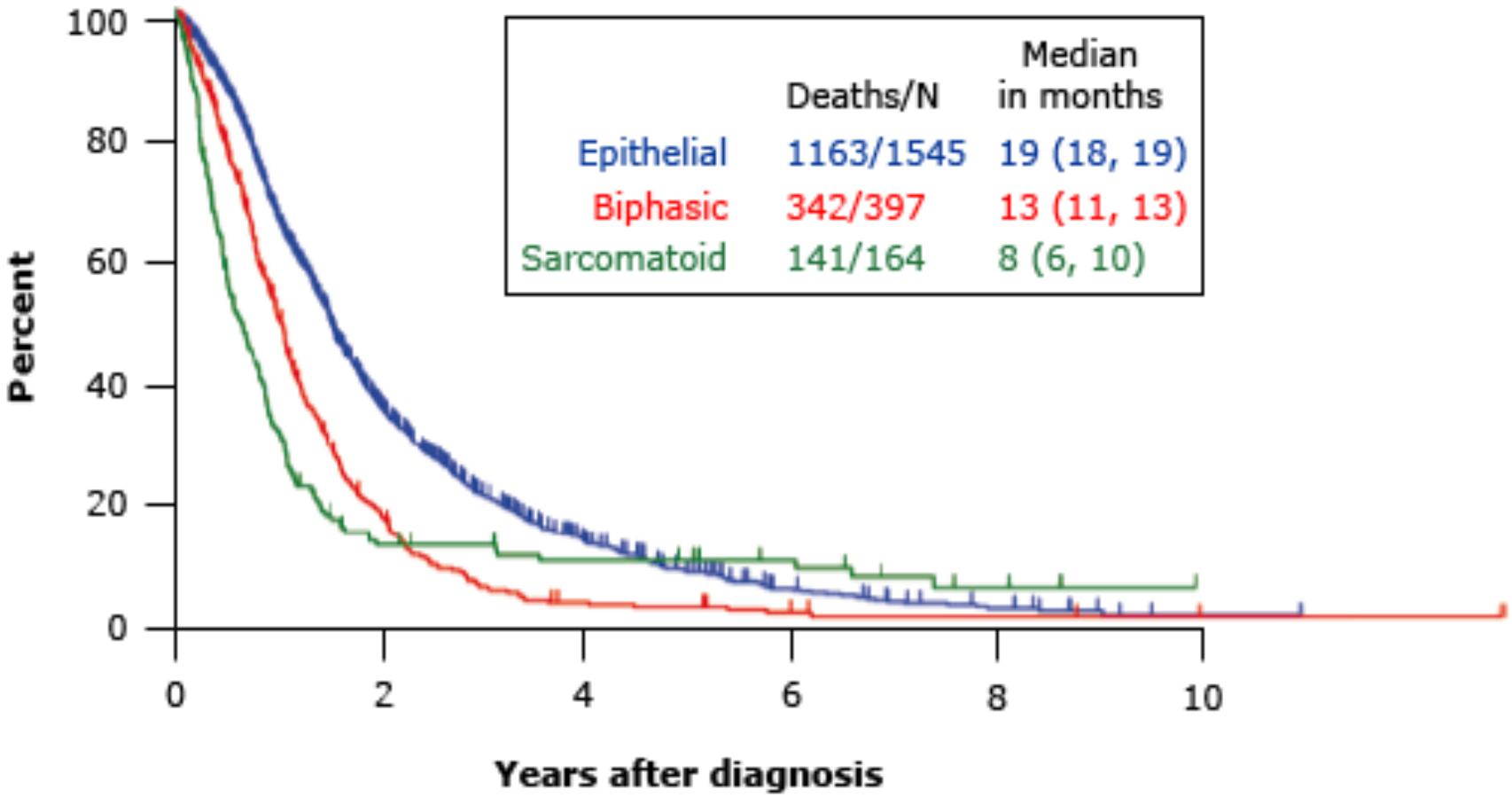


- Allmänt dålig prognos
- Median överlevnad 6-18 månader
- Selekterade patienter med lokaliserad sjukdom, aggressiv multimodalitetsbehandling lever längre

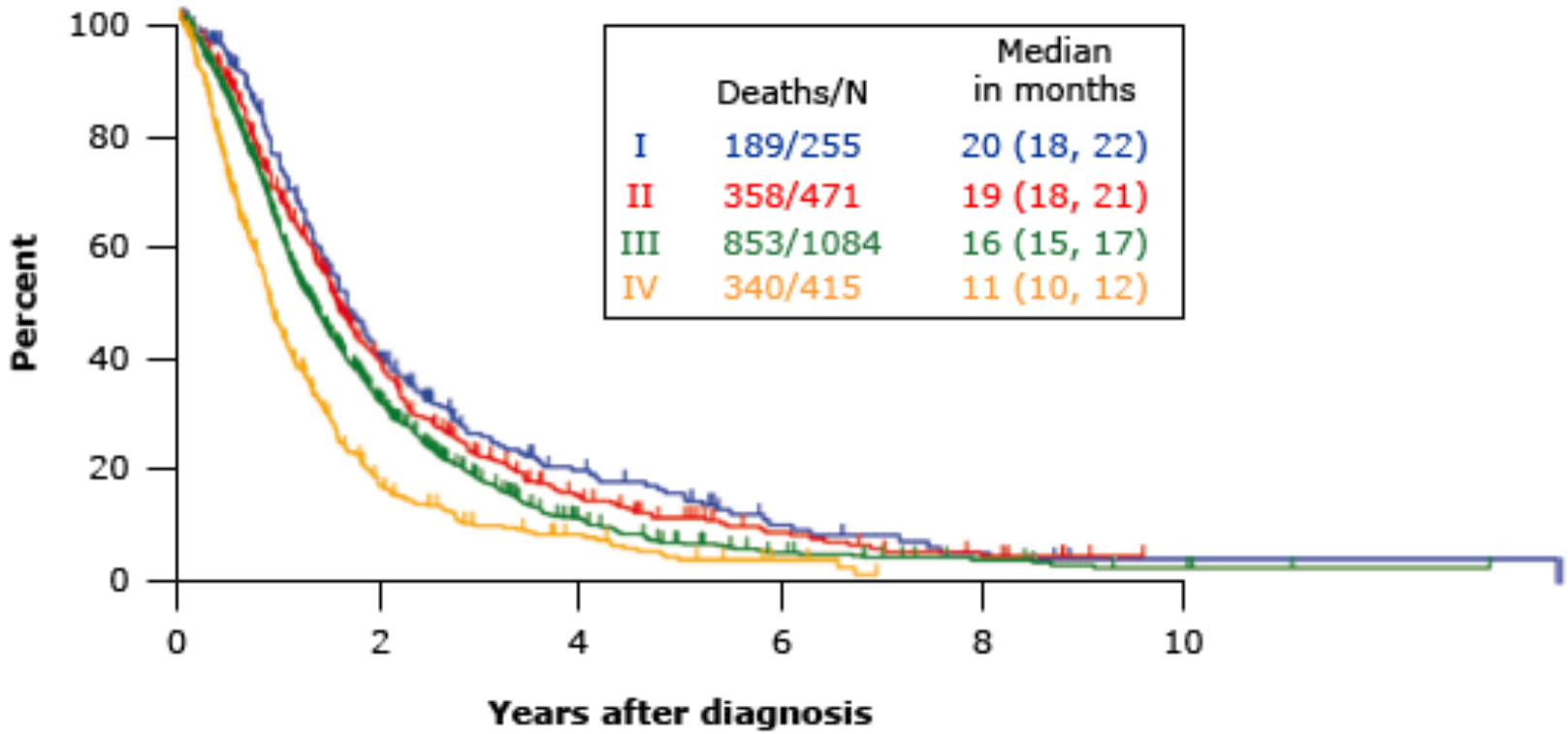
Malignant pleural mesothelioma overall survival by stage TNM AJCC 8th edition



Pleural mesothelioma survival based upon histology



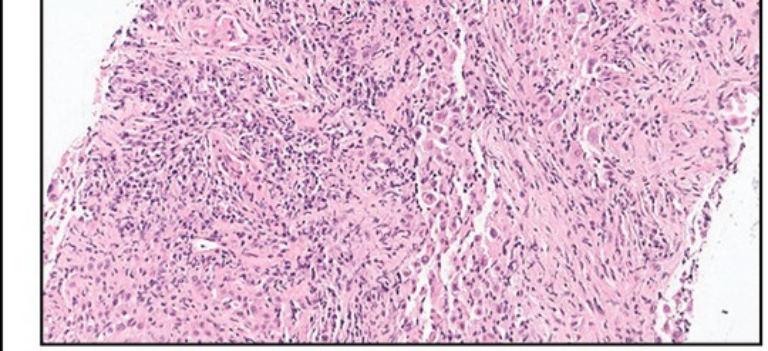
Survival following surgery for pleural mesotheliom

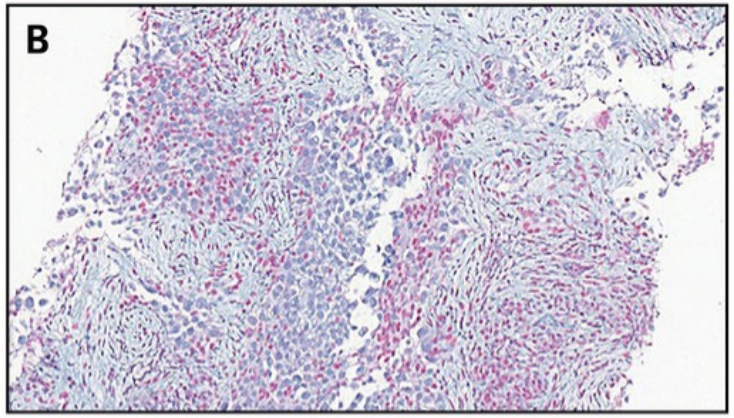


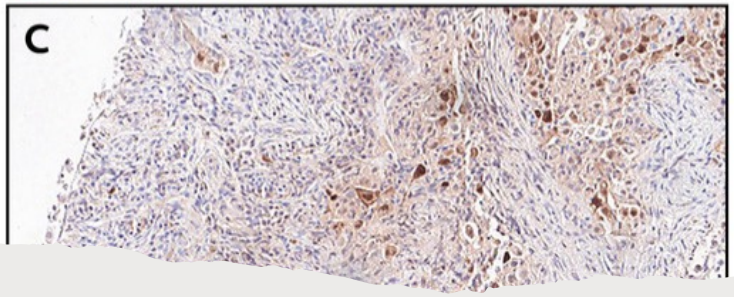
Symtom

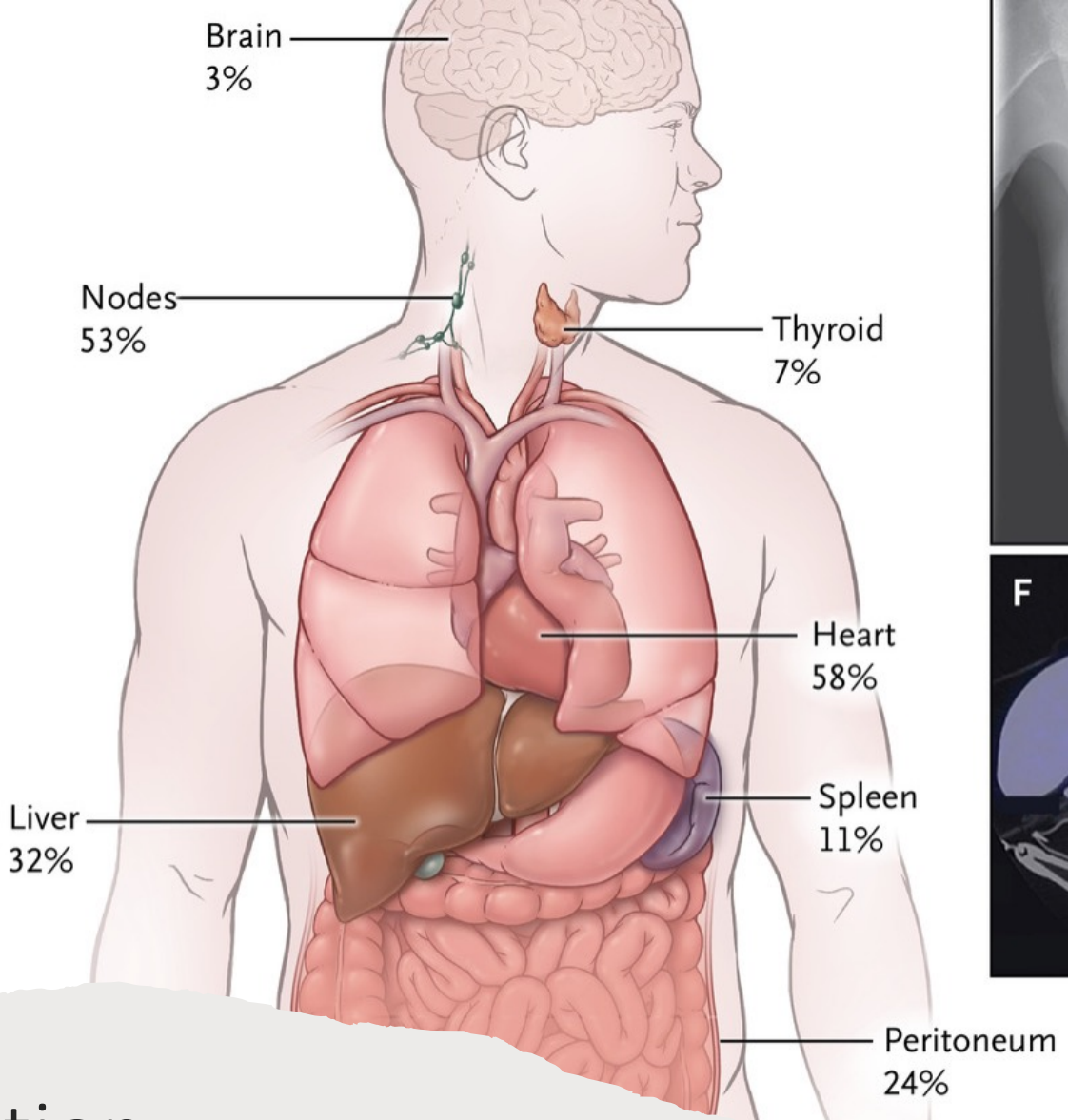
- Dyspne (pleuravätsa / restriktivitet)
- Toraxsmärta (invation av thoraxväggen)
- Fatigue
- Apetitlöshet
- Viktnedgång
- Svettningar
- trötthet

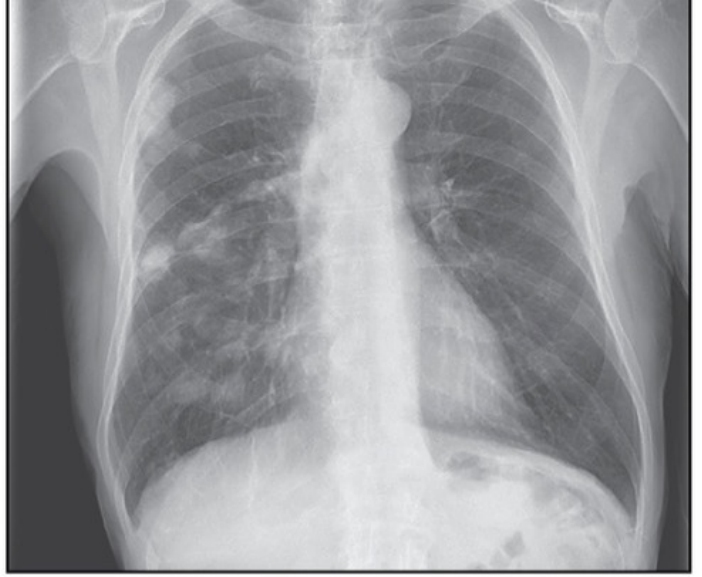
Kan komma från början, dock blir mer frekventa när sjukdomen progredierar

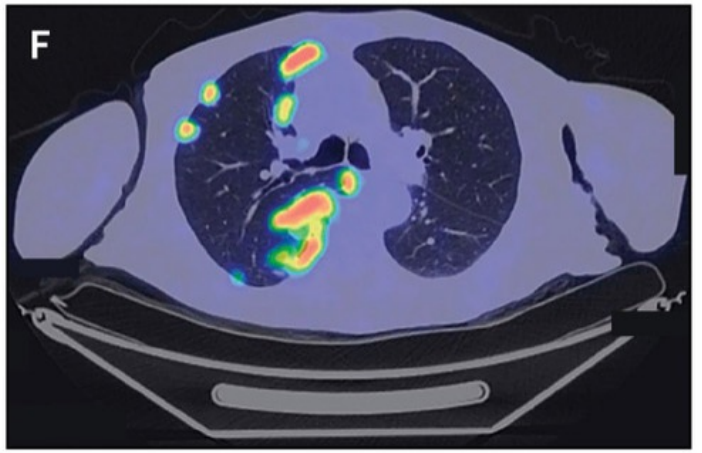












Metastas lokalisation

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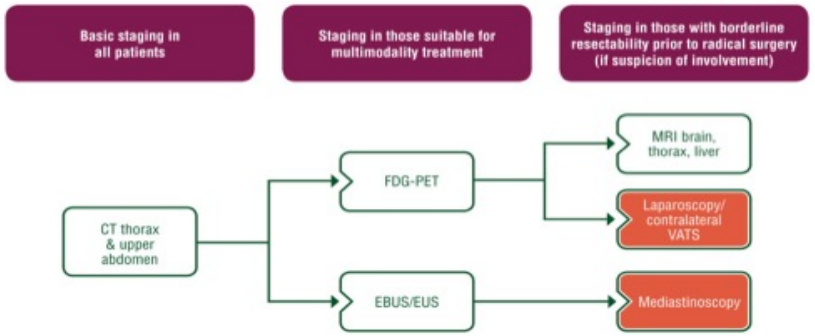
Diagnos

- CT
- PET-CT
- MR (mjukdelar, invasion/infiltration av närliggande organ, solida förändringar)
- Invasivt:
  - Madiastinoskopi
  - VATS
  - EBUS
- Cytologi i pleuravätska & IHC (epiteloitt mesoteliom!)
- Serum/ pleuravätska biomarkörer (liten evidens !)



Malignant pleural mesothelioma TNM staging AJCC 8th edition

Malignant pleural mesothelioma TNM staging AJCC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the ipsilateral parietal pleura with or without involvement of: ▪ Visceral pleura ▪ Mediastinal pleura ▪ Diaphragmatic pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: ▪ Involvement of diaphragmatic muscle ▪ Extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Describes locally advanced but **potentially resectable** tumor. Tumor involving all the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: ▪ Involvement of the endothoracic fascia ▪ Extension into the mediastinal fat ▪ Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall ▪ Nontransmural involvement of the pericardium
T4	Describes locally advanced **technically unresectable** tumor. Tumor involving all the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: ▪ Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction ▪ Direct transdiaphragmatic extension of tumor to the peritoneum ▪ Direct extension of tumor to the contralateral pleura ▪ Direct extension of tumor to mediastinal organs ▪ Direct extension of tumor into the spine ▪ Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion, or tumor involving the myocardium

Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in 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

Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis present

Prognostic stage groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**
T1	N0	M0	IA
T2 or T3	N0	M0	IB
T1	N1	M0	II
T2	N1	M0	II
T3	N1	M0	IIIA
T1-3	N2	M0	IIIB
T4	Any N	M0	IIIB
Any T	Any N	M1	IV

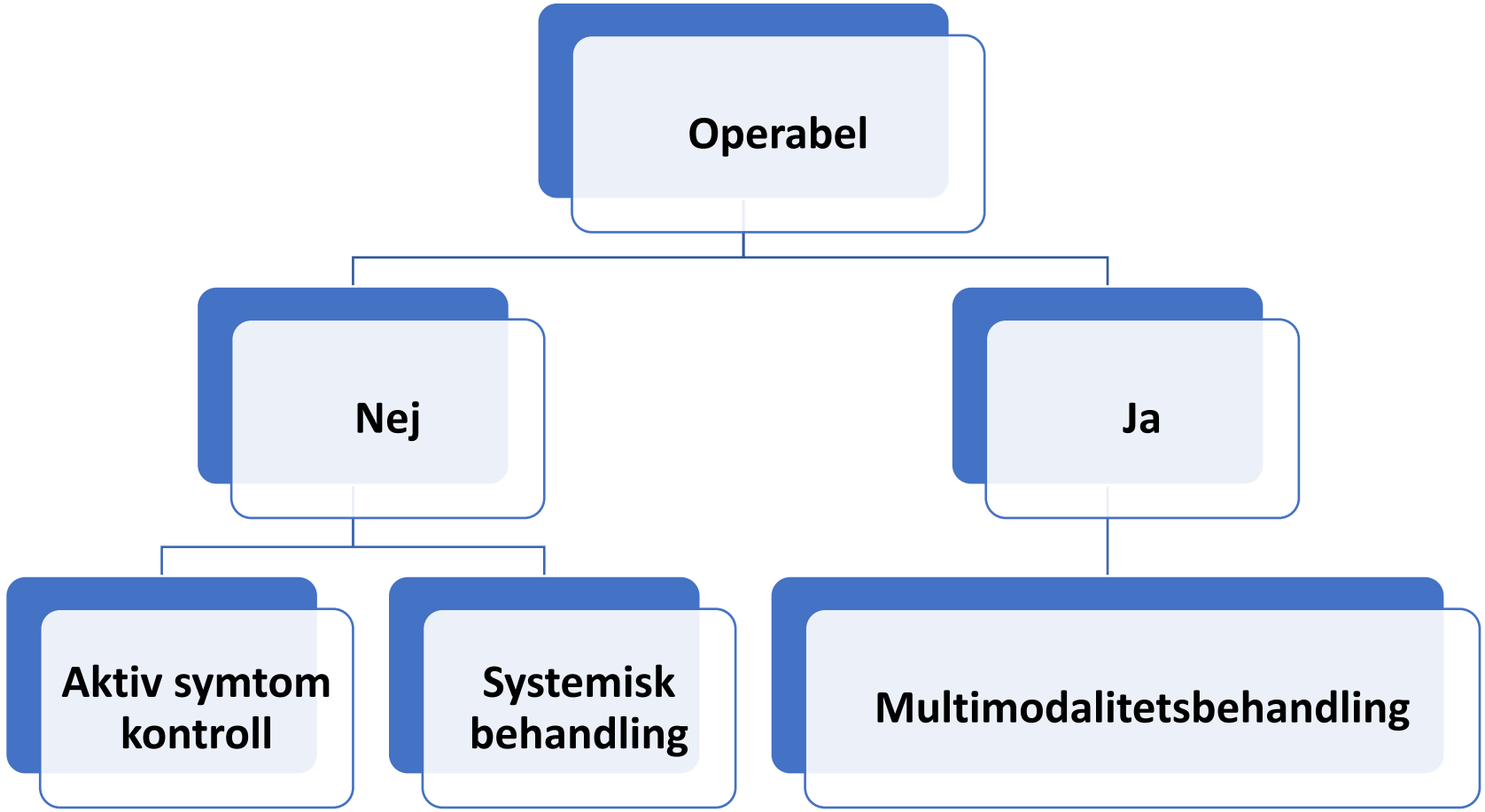
TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer.

Behandling

- MDK
- TNM staging (utbredning av sjukdomen)
- Patientens ålder, kondition, hjärt-& lungfunktion och komorbiditet
- Histopatologi
- Cytostatika är standard behandling (Platinum baserad + Pemetrexed)
- MEN! Cirka 20% av patienter kan vara kandidat för kirurgi, makroskopisk komplett resektion (en del av multimodalitet behandling Kemo/RT/Kir)

Behandlingsguide

Behandling av MPM



Nuvarande behandlingslandskap av MPM

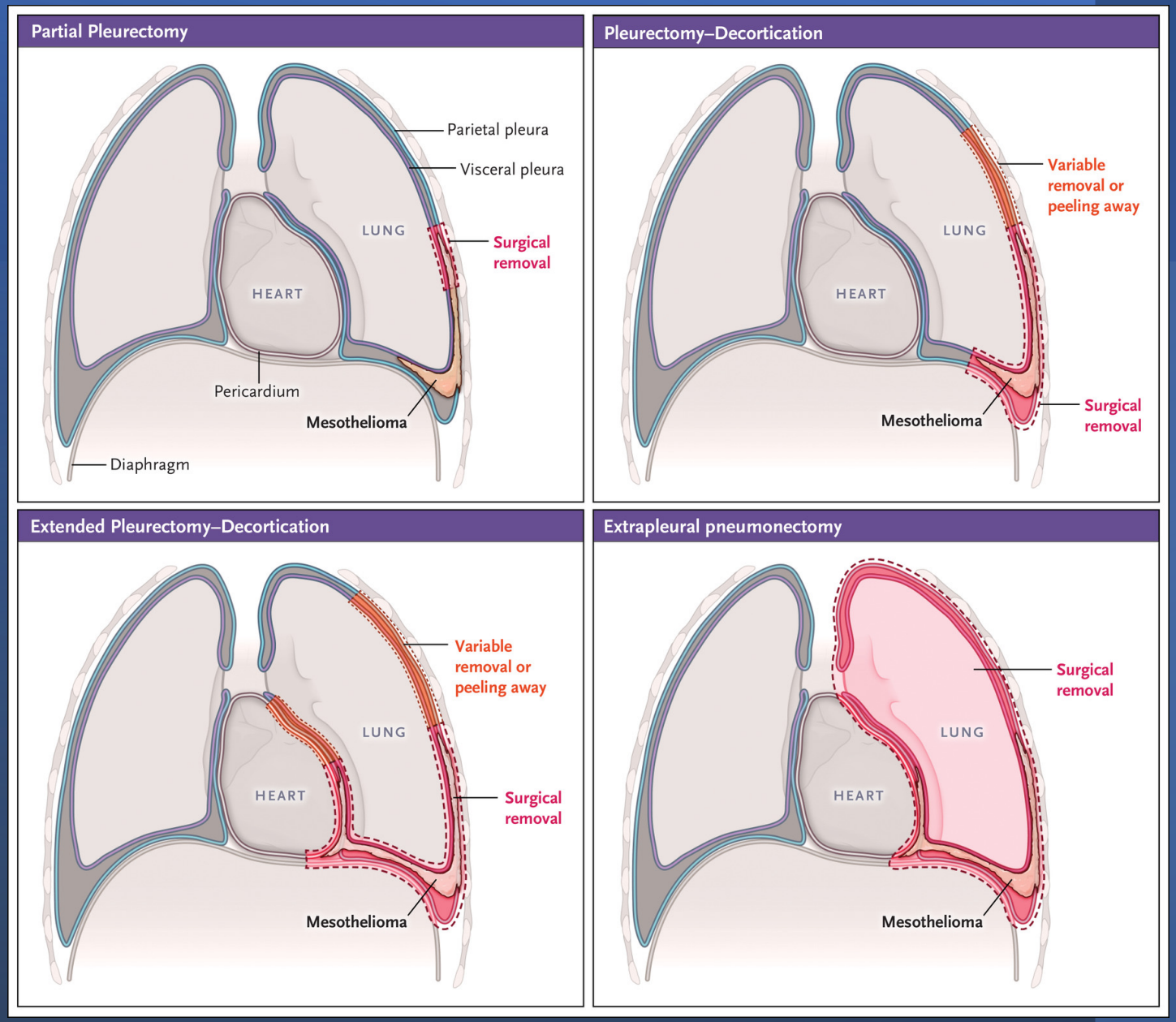
1. Hantering av pleuravätska
2. Radioterapi
3. Kirurgi
4. Tumor-treating fields
5. Systemisk behandling

Pleuravätskan

- Drän
- Medicinsk pleurodes (talk eller Mepakrin)
- Kirurgisk dekortikation/ pleurektomi plus talk pleurodes
- Samma framgång med båda procedurer, fast högre komplikationsrisk med längre vårdtid för kir procedur

Kirurgi baserad behandling

- Multimodalitets behandling (Kirurgi+ Radioterapi+ Cytostatika)
- Cytostatika kan ges preoperativ eller post operativ eller intraoperativ (reducera risken för lokal recidiv och metastaser)
- Speciella centra med erfarenhet (Rigshospitalet i Köpenhamn)
- OBS! Palliativt åtgärd, resektionen är nästan alltid inkomplett!
- Median överlevnad 18 mån, 5-års överlevnad 14%
- OS ej studerad med randomiserade studier, men visat bättre överlevnad jämfört med enbart cyto



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Randomiserad studie!
Bara en studie från England (MARS) studie

*Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery **(MARS)** randomised feasibility study.*
Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, Snee M, O'Brien M, Thomas G, Senan S, O'Byrne K, Kilburn LS, Spicer J, Landau D, Edwards J, Coombes G, Darlison L, Peto J, MARS trialists .Lancet Oncol. 2011;12(8):763. Epub 2011 Jun 30.

Hög morbiditet & mer skadligt!

MARS2 studie

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

- Fas III
- Ongoing
- UK multicentra
- Hypotes: Kir& Kemo har bättre OS vs endast kemo
- Secondary outcomes:
  - HRQL
  - PFS
  - AE

Hög morbiditet & mer skadligt!
Flera döda
Sämre QoL

Ev kirurgi kandidater

- Histologi (Epiteloitt)
- Respektabel tumör
- Faktorer med sämre prognos vid kirurgi:
  - Ålder>50 år
  - Män
  - PTK >400
  - LPK > 15,000
  - Thoraxsmärtor
  - Stort tumörvolym
- Ingen extra torakal spridning
- Bra hjärt/lungfunktion
- Inga alvarliga komorbiditeter
- PS WHO 0-1

Har vi bias här?

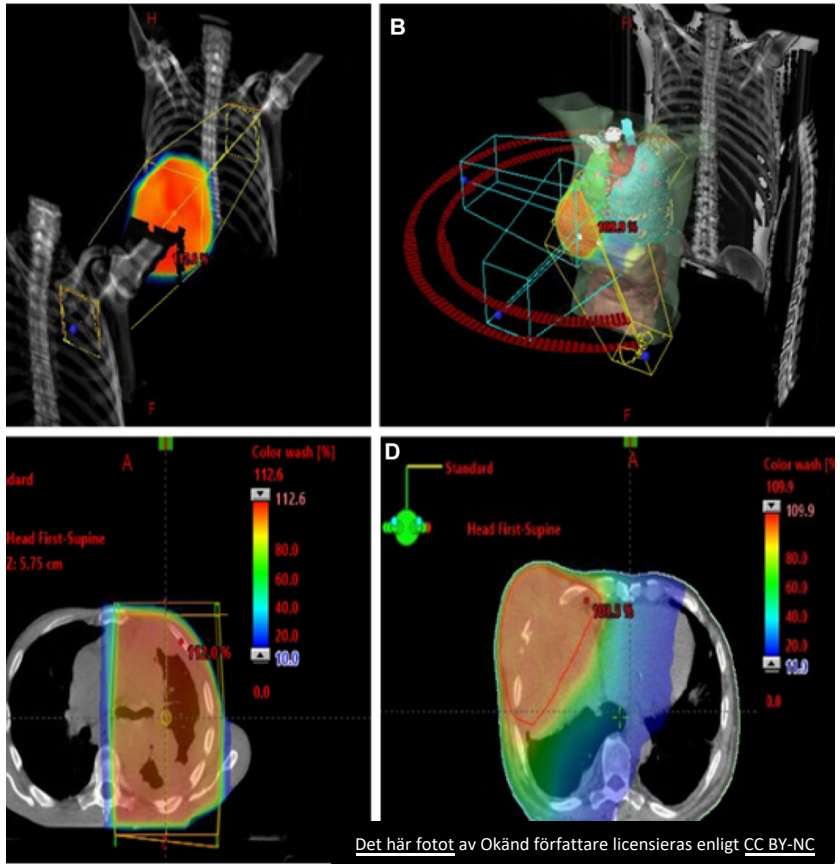
Patienter som går igenom kir lever längre!!

ESMO 2023, När ska vi operera?

- För att diagnostisera MPM
- För att kontrollera pleuravätska

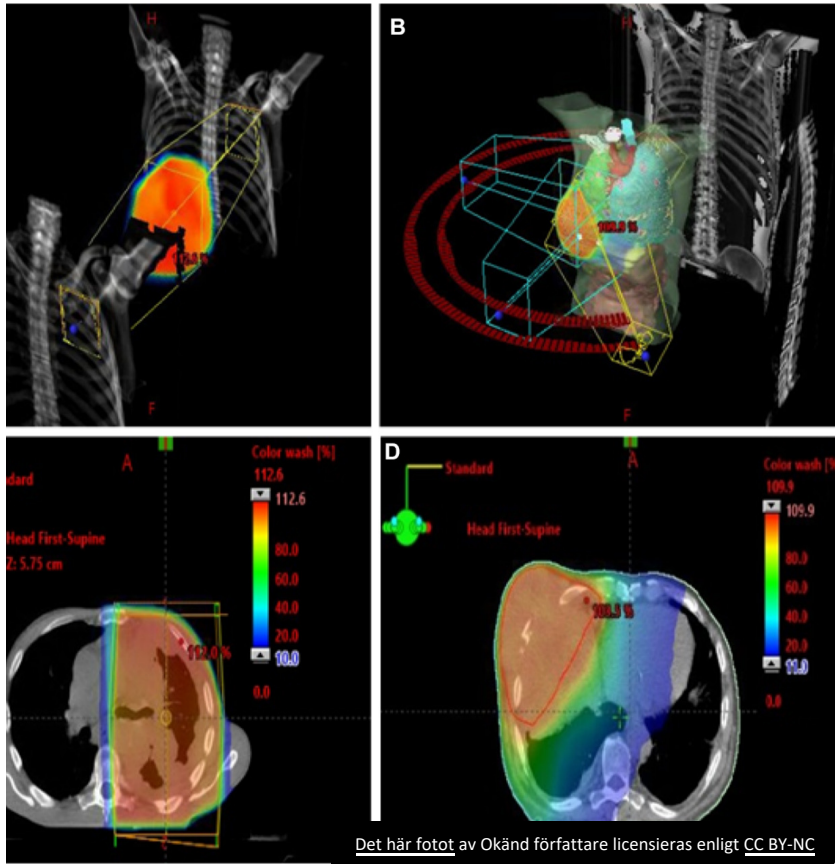
Radioterapi

- **Profylaktiskt mot bröstkorgen**(efter ingrepp) **övergiven!!**
  - Negativa resultat
  - 2 randomized, open-label fas III studier
  - **(PIT) P**rophylactic **I**rradiation of **T**racts
  - **(SMART) S**urgical and Large-Bore Procedures in **M**alignt Pleural **M**esothelioma **a**nd **R**adiotherapy **t**rial
- **Tid studier ingen förbättring i OS**



Radioterapi

- SAKK 17/04 fas II studie:
  - Primary end point: locoregional relapse-free survival: faild!
  - Slow enrollment
  - Poor macroscopic clearance
  - Only 1/3 of originally recruited patients randomly assigned to RT or obs
- Smärkontroll: SYSTEMS-2 study
  - A randomised phase II trial of radiotherapy dose escalation for pain control in MPM.
  - Comparison of 2 hypofractionated regimes (20 Gy/5# and 36 Gy/6#).
  - Highly conformal radiotherapy techniques used to aid safe dose escalation.
  - Primary outcome: pain control at week 5 at radiotherapy site.
  - Recruitment target: 112 patients from 10 to 15 UK centres.



Radioterapi, pre eller post op

- Helt beroende på typ av kirurgin
- Extrapleural pneumonektomi
  - Pre-op RT (SMART)
  - Post-op RT
    - ”lättare” , ingen underliggande lunga
    - ”svårare”, vilken toxicitet som helst på den kvarvarande lunga kan leda till fatal toxicitet!
- Pleurektomi/dekortikering
  - Pre-op (SMARTER)
  - Post-op (IMPRINT)
    - ”Svårare”, svårt att spara underliggande lunga
    - ”Lättare”, 2 lungor (toxicitet)

Hemithoracic RT *before* EPP ("SMART")

Study Schema

Histologically Proven, Previously Untreated Malignant Pleural Mesothelioma (cT1-3 N0 M0)
Baseline Investigations, Informed Consent

Neoadjuvant Hemithoracic Intensity Modulated Radiotherapy (25 Gy/5 fx +/- concomitant 5 Gy boost over 1 week)

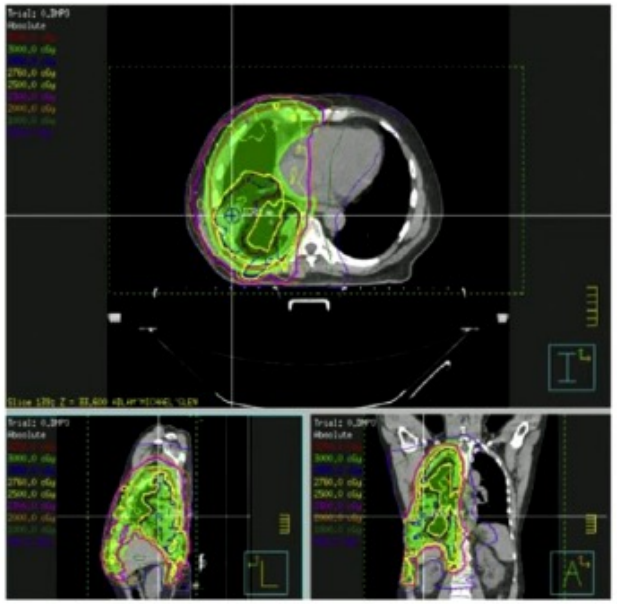
1 week post-RT

Extrapleural Pneumonectomy

<26 weeks post-op

ypN0-1 | ypN2

Observation | Adjuvant Chemotherapy



Cho, *et al.*, (de Perrot), Princess Margaret, *JTO* 2014

EPP after RT

- Cho et al., *Lancet Oncol* 2021
- 102 patients on a single center Phase 2 trial
  - Endpoint was perioperative morbidity/mortality
- All patients who had RT had surgery
- 49% had Grade 3-4 morbidity and 1% death
  - A. Fib, pneumonia, embolus, empyema, etc.
- Median overall survival was 24.4 months
- 5-year rate
  - Local recurrence 20%
  - Distal recurrence 63%

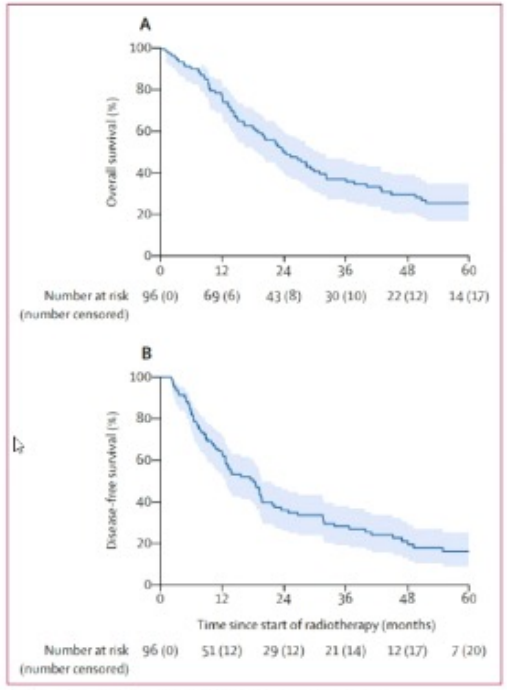


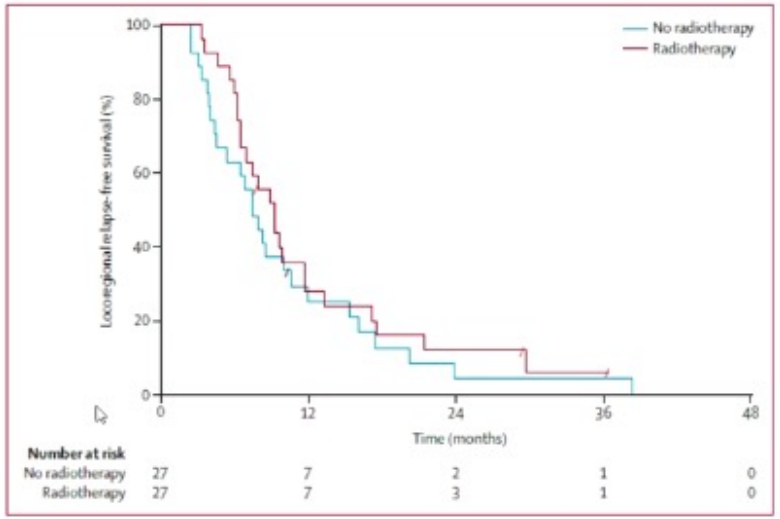
Figure 3: Overall survival (A) and disease-frees survival (B)

SMART (RT → EPP)

RT→ EPP

EPP +/- RT

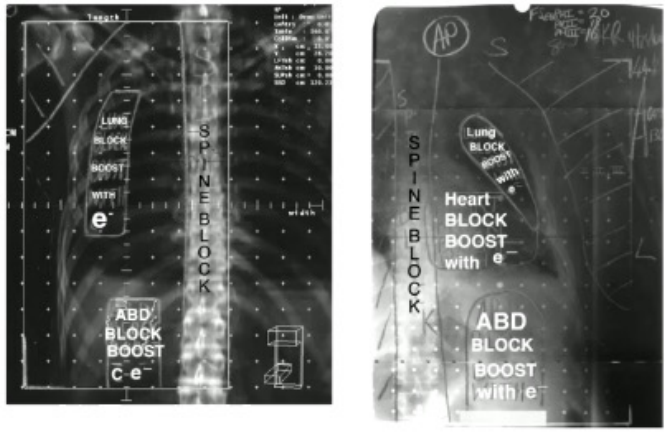
- Stahel, *et al.*, *Lancet Oncol* 2015 (SAKK 17/04)
- Induction chemo → EPP → +/- RT
- 151 patients entered
  - 113 had EPP
  - 54 patients randomized
- RT to 55.9 Gy
- One radiation toxic death out of 25 treated
- 2019 re-analysis of five local failures
  - One local only, four with distant as well
  - All in underdosed region



RT→ P/D

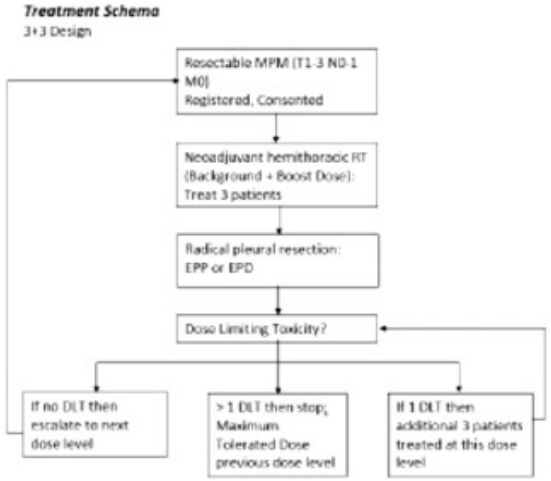
RT After P/D: 2D Experience

- Gupta, *et al.*, *IJROBP* 2005
- 123 patients : P/D and adjuvant external beam radiotherapy
- Median OS for all patients was 13.5 months (range, 1-199 months)
- 2-yr and 5-yr overall survival were 23% and 5%, respectively

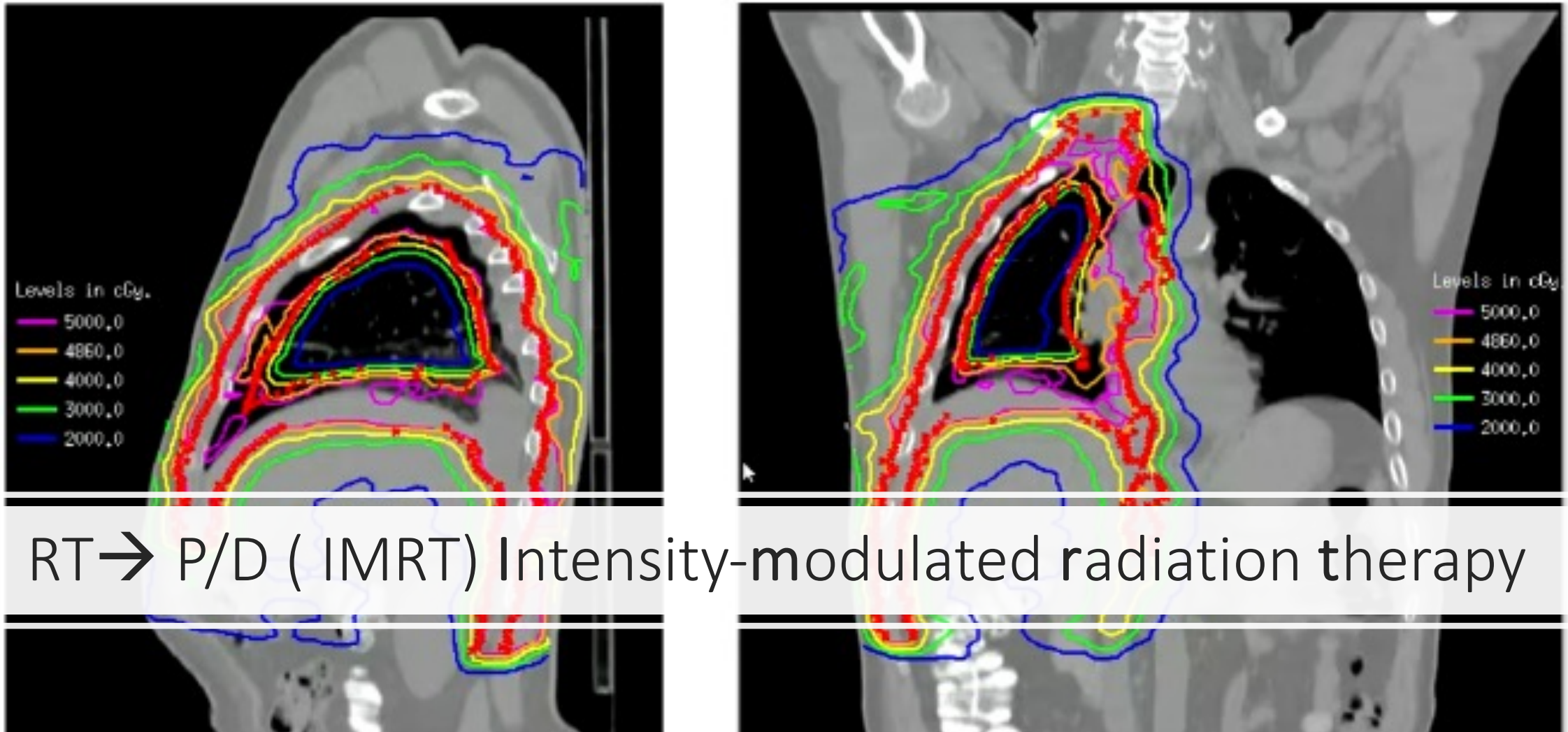


RT *before* P/D: SMARTER Trial

- Cho and de Perrot, PMH
- Ongoing trial (NCT04028570)
- RT dose escalation trial (3+3 design)
  - 2100 cGy starting dose
  - Boost by 600 cGy, then 1200 cGy, then 1800 cGy
- Hoping to exploit abscopal affect



Pleural IMRT

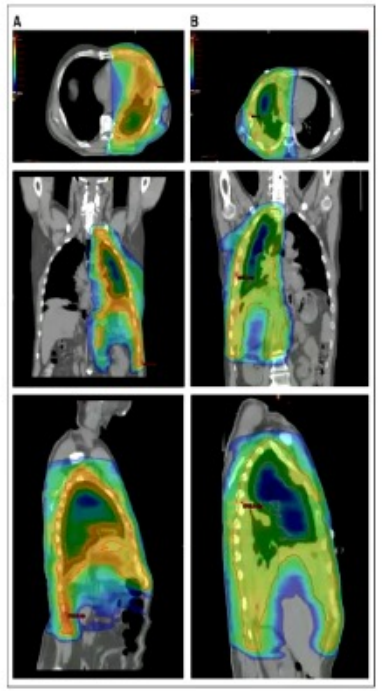


RT→ P/D (IMRT) **I**ntensity-**m**odulated **r**adiation **t**herapy

IMPRINT (**I**ntensity-**M**odulated **P**leural **R**ad**I**atio**N** **T**herapy)

IMPRINT Study (MSKCC and MDACC)

- Rimner, *et al.*, *J Clin Oncol* 2016
- IMPRINT = Intensity-Modulated Pleural RadIatioN Therapy
- 45 patients enrolled;
  - All received chemotherapy (Platinum + Pemetrexed)
  - 27 received RT
    - Goal 50.4 Gy in 28 fx (median, 46.8 Gy)
- Toxicity
  - RP: Six patients Grade 2; two patients Grade 3
  - No Grade 4 or 5
- Outcome
  - Median PFS 12.4 months
  - Median OS 23.7 months



Konklusion

- RT can be given pre-op or post-op with either EPP or P/D
- P/D followed by standard fractionation pleural IMRT is probably the most common
- Pre-op treatment in specialized centers with excellent collaboration
- Hypofraction is probably a trend that will continue to develop in the coming years

Tumor-treating fields

- Regional, antimitotic treatment for solid tumor
- Low-intensity alterating electric fields
- Aim: test the activity of TTFields delivered to the thorax in combination with chemo for front-line treatment of patients with unresectable MPM
- Encouraging OS data
- safe

Tumour Treating Fields in combination with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): a multicentre, single-arm phase 2 trial

Giovanni L Ceresoli MD, Joachim G Aerts Prof, Rafal Dziadziuszko Prof, Rodryg Ramlau MD, Susana Cedres MD, Jan P van Meerbeeck Prof, Manlio Mencoboni MD, David Planchard MD, Antonio Chella MD, Lucio Crinò MD, Maciej Krzakowski MD, Jörn Rüssel MD, Antonio Maconi MD, Letizia Gianoncelli MD and Federica Grosso MD

Systemisk behandling

- Många patienter (de flesta)
- Syfte: Förlänga livet och kontrollera symtomen
- I USA > hälften av patienterna får aldrig påbörja med sytemisk behandling (hög ålder, dålig PS, komorbiditet)

Systemisk behandling

- **Platinium (Cisplatin/Karboplatin) + Pemetrexed**
- **EMPHACIS** studie FDA approvd 2004
  - OS 12,1 mån för Cis/Pemetrexed vs 9,3 mån för enbart Cisplatin
  - Raltitrexed (Tomudex)+ Cis även bättre än enbart Cis
  - Supporting the use of antifolate treatment for MPM

Systemisk behandling

- **Chemotherapy + Bevacizumab (Avastin)**
- **MAPS study:** The mesothelioma Avastin plus Pemetrexed-Cisplatin study (franska publicerades 2016)
  - OS improved 18,8 vs 16,1 months
  - Increaced AE
  - Improvments in certain QOL such pain
  - This treatment regimen was never filed for a licens
  - Subsequent study with Nintedanib had negative results

Systemisk behandling

- Immune checkpoint inhibition
- 2 viktiga studier
- Lovande resultat

Immunterapi

- Nivolumab plus Ipilimumab 1:e linje (men kan sparas till andra linje också)
- **CheckMate 743**
  - 605 pat
  - Behandlingsnaiva
  - Nivo/ipi upp till 2 år eller Cis eller Carb plus Pemetrexed 6 kurer
  - 30 mån uppföljning
  - OS 18,1 Nivo/Ipi vs 14,1 mån for patienterna som fått cyto
  - HR 0,74
  - 2 års OS var 41 resp 27 %
  - **Subgroup analysis: Icke epit histologi OS var STATISTICLLY SIGNIFICANT för Nivp/ipi armen versus cyto (18 resp 9 månader), HR 0,46**

Immunterapi

- **CONFIRM** study: Checkpoint Blockade for Inhibition of Relapsed mesothelioma (**Nivolumab**)
  - Phase III study
  - OS 3 months improvment
  - Independent of PD-L1 expression

Systemisk behandling

- Underhålls behandling (ingen fas III studier visade förbättring i OS)
- Switch mainenance:
  - Phase II study

De Gooijer CJ, van der Noort V, Stigt JA, et al. Switch-maintenance gemcitabine after first-line chemotherapy in patients with malignant mesothelioma (NVALT19): an investigator-initiated, randomised, openlabel, phase 2 trial. Lancet Respir Med 2021; 9: 585-92.

- Rechallenge (Platinum-Pemetrexed)
- Vinorelbin show some activity

Table 1. Notable Phase 3 Clinical Trials of Immunotherapeutic Approaches to Malignant Pleural Mesothelioma (MPM).

Study Name	Description	ClinicalTrials.gov Number	Study Treatments	Status
Dendritic Cell Immunotherapy for Mesothelioma (DENIM)	Randomized, open-label phase 2–3 study of dendritic cells loaded with allogeneic tumor-cell lysate as maintenance treatment (MesoPher [Amphera]) after chemotherapy	NCT03610360	MesoPher plus best supportive care vs. best supportive care	Active but not recruiting
Pembrolizumab Immunotherapy versus Standard Chemotherapy for Advanced Pre-treated Malignant Pleural Mesothelioma (PROMISE-meso)	Multicenter, randomized phase 3 trial comparing pembrolizumab with standard chemotherapy for advanced, pretreated MPM	NCT02991482	Pembrolizumab vs. standard chemotherapy	Negative
Checkpoint Blockade for Inhibition of Relapsed Mesothelioma (CONFIRM)	Phase 3, double-blind, placebo-controlled trial to evaluate the efficacy of nivolumab in relapsed MPM	NCT03063450	Nivolumab vs. placebo	Positive
Pembrolizumab in Patients with Advanced Malignant Pleural Mesothelioma	Phase 2–3 randomized study of pembrolizumab in patients with advanced MPM	NCT02784171	Pemetrexed–cisplatin vs. pemetrexed–cisplatin plus pembrolizumab vs. pembrolizumab (phase 2 only)	Active but not recruiting
CheckMate 743*	Phase 3, randomized, open label trial of nivolumab plus ipilimumab vs. pemetrexed and platinum as first-line therapy in unresectable MPM	NCT02899299	Nivolumab plus ipilimumab vs. pemetrexed and platinum	Positive at prespecified interim analysis
INFINITE*	Phase 3, open-label, randomized, parallel group study to evaluate the efficacy and safety of intrapleural administration of adenovirus-delivered interferon alfa-2b (rAd-IFN) in combination with celecoxib and gemcitabine in patients with MPM	NCT03710876	rAd-IFN plus oral celecoxib and gemcitabine, then maintenance gemcitabine vs. oral celecoxib and gemcitabine, then maintenance gemcitabine	Active but not recruiting
Bevacizumab and Atezolizumab in Malignant Pleural Mesothelioma (BEAT-meso)	Multicenter, randomized phase 3 trial comparing atezolizumab plus bevacizumab and standard chemotherapy with bevacizumab and standard chemotherapy as first-line treatment for advanced MPM	NCT03762018	Bevacizumab plus chemotherapy vs. atezolizumab plus bevacizumab plus chemotherapy	Recruiting
Durvalumab with Chemotherapy as First Line Treatment in Advanced Pleural Mesothelioma (DREAM3R)	Phase 3 randomized trial of durvalumab with chemotherapy as first-line treatment in advanced pleural mesothelioma	NCT04334759	Durvalumab plus chemotherapy, then maintenance durvalumab vs. chemotherapy, then observation	Recruiting

* CheckMate 743 is the Study of Nivolumab Combined with Ipilimumab versus Pemetrexed and Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma Patients, and INFINITE is Efficacy and Safety of rAd-IFN Administered with Celecoxib and Gemcitabine in Patients with Malignant Pleural Mesothelioma.

The new england journal o f medicine

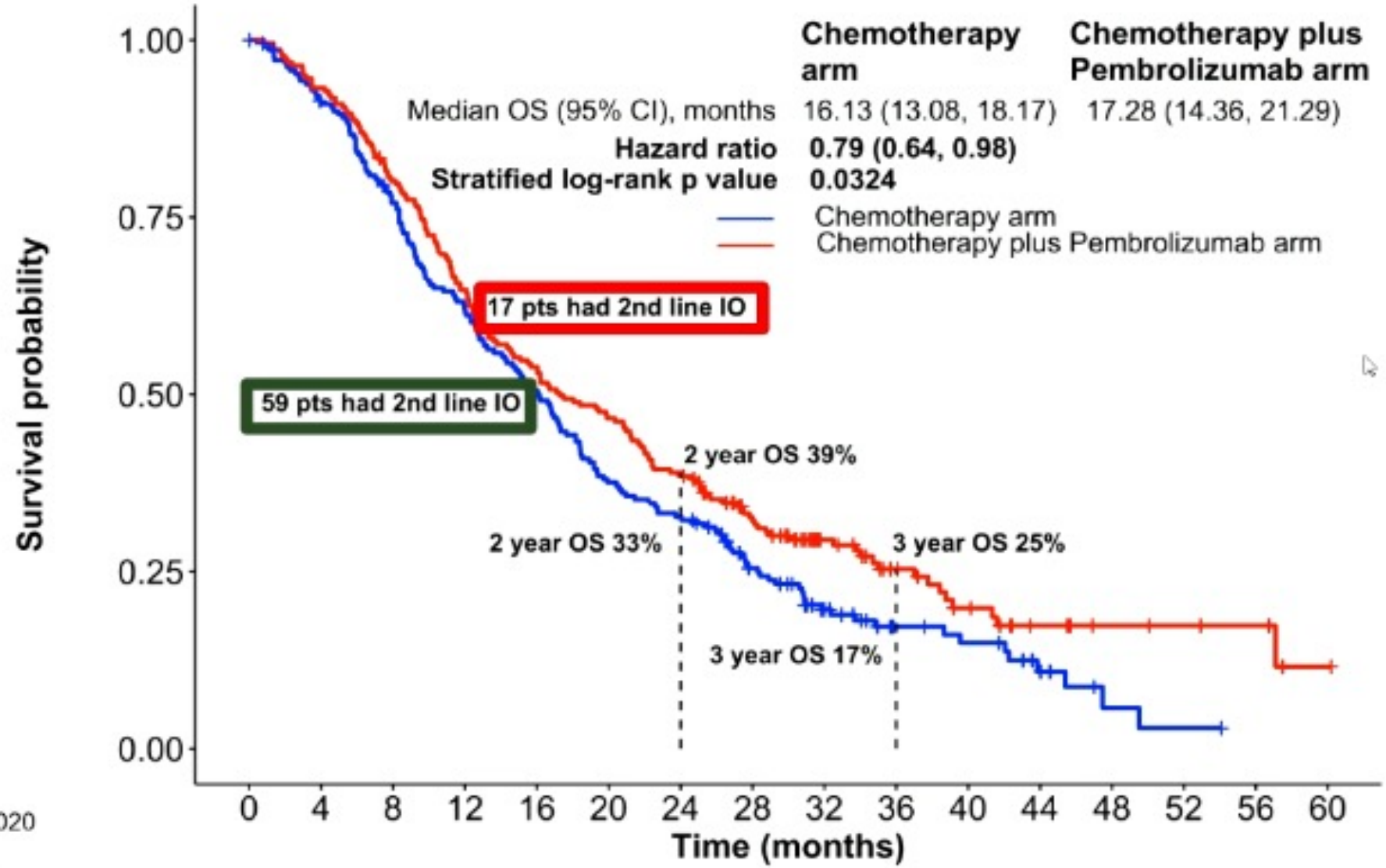
CCTG IND.227 / KN483: A Randomized Phase 3 Study of Chemotherapy *vs* Chemotherapy plus Pembrolizumab in Treatment–Naive Pleural Mesothelioma

A Collaboration of
The Canadian Cancer Trials Group (CCTG)
The National Cancer Institute of Naples (NCIN) and
The French Cooperative Thoracic Intergroup (IFCT)

Quincy Chu, Maria Carmela Piccirillo, Laurent Greillier, Federica Grosso, Giuseppe Lo Russo, Marie Florescu, Manlio Mencoboni, Penelope Bradbury, Alessandro Morabito, Fabiana Letizia Cecere, Sara Delfanti, Arnaud Scherpereel, Myriam Locatelli-Sanchez, Gerard Zalcman, David Dawe, Joana Sederias, Scott Laurie, Christopher Lee, Wei Tu, Lesley Seymour

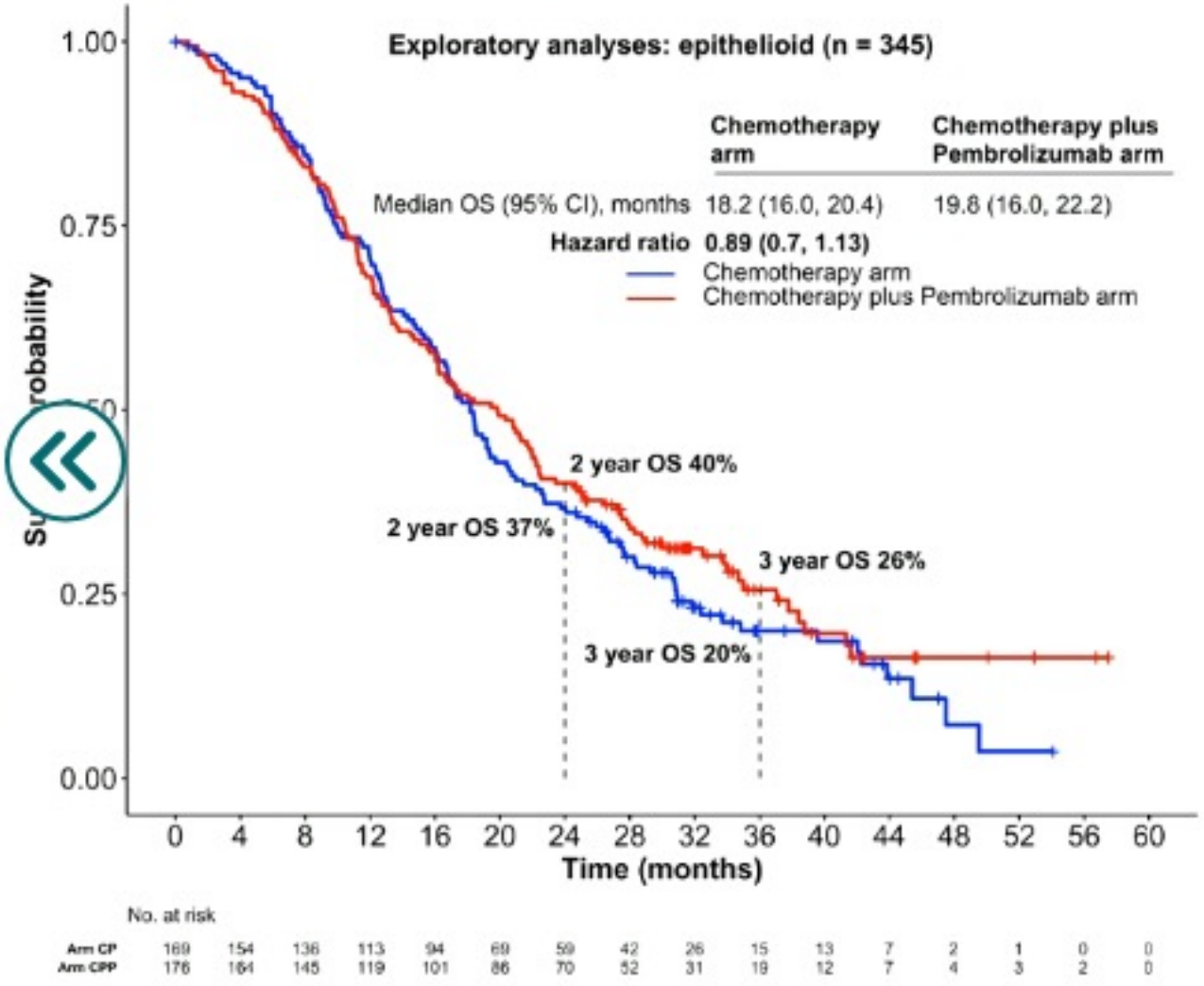
ASCO 2023; *iMig* 2023

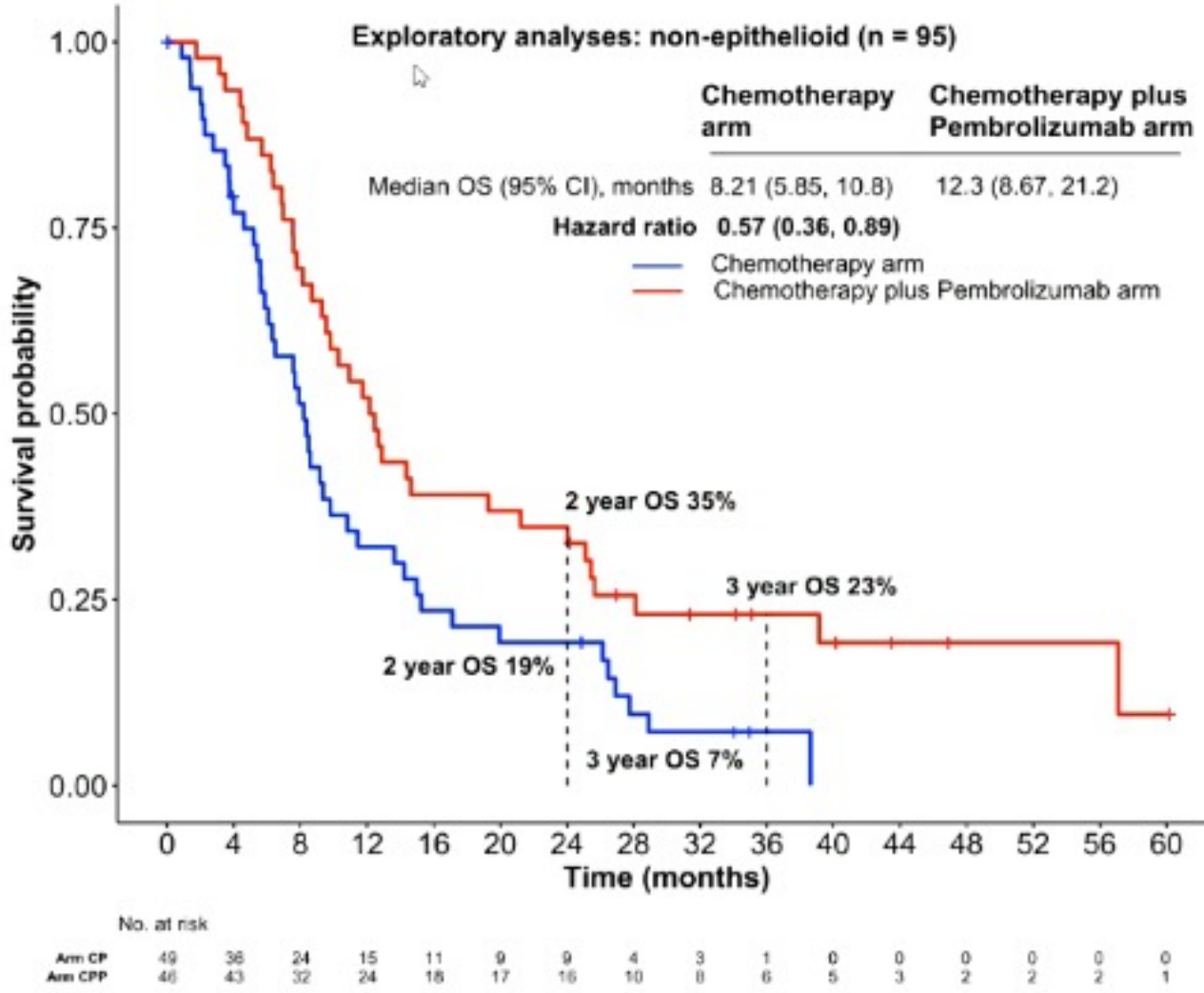
IND227 / IFCT1901 trial: Overall survival



Patients enrolled Jan 2017-Sept 2020
Median follow up 16.16 months
All pts discontinued all study drugs

IND227 / IFCT1901 trial: Exploratory OS Analyses - Histology





Conclusion

→ Adding Pembrolizumab to standard 1L chemotherapy (platinum-pemetrexed) in naive PM led to a statistically significant increase:

- Overall survival (OS): 21% reduction of death risk at 3 years: ↑ survival rate from 17% to 25%
- Objective response rate (ORR): **62% with combo** vs 38% for chemo alone
- Combo globally well tolerated (similar safety profile than in non-squamous NSCLC patients) – no new or unexpected toxicities

→ New 1L therapeutic option in unresectable MP ?

Framtidens landskap

- **Chemoimmunotherapy**
  - Bevacizumab and Atezolizumab in Malignant Pleural Mesothelioma (**BEAT-meso), phase 3**
  - Delivery of adenovirus-mediated interferonalfa-2b **INFINITE study, phase 3**
    - *Previously treated patients are randomly assigned to receive either intrapleural **adenovirus** treatment followed by treatment with **celecoxib** and then **gemcitabine** or **celecoxib and gemcitabine alone**, until disease progression or termination of treatment because of toxic effects*

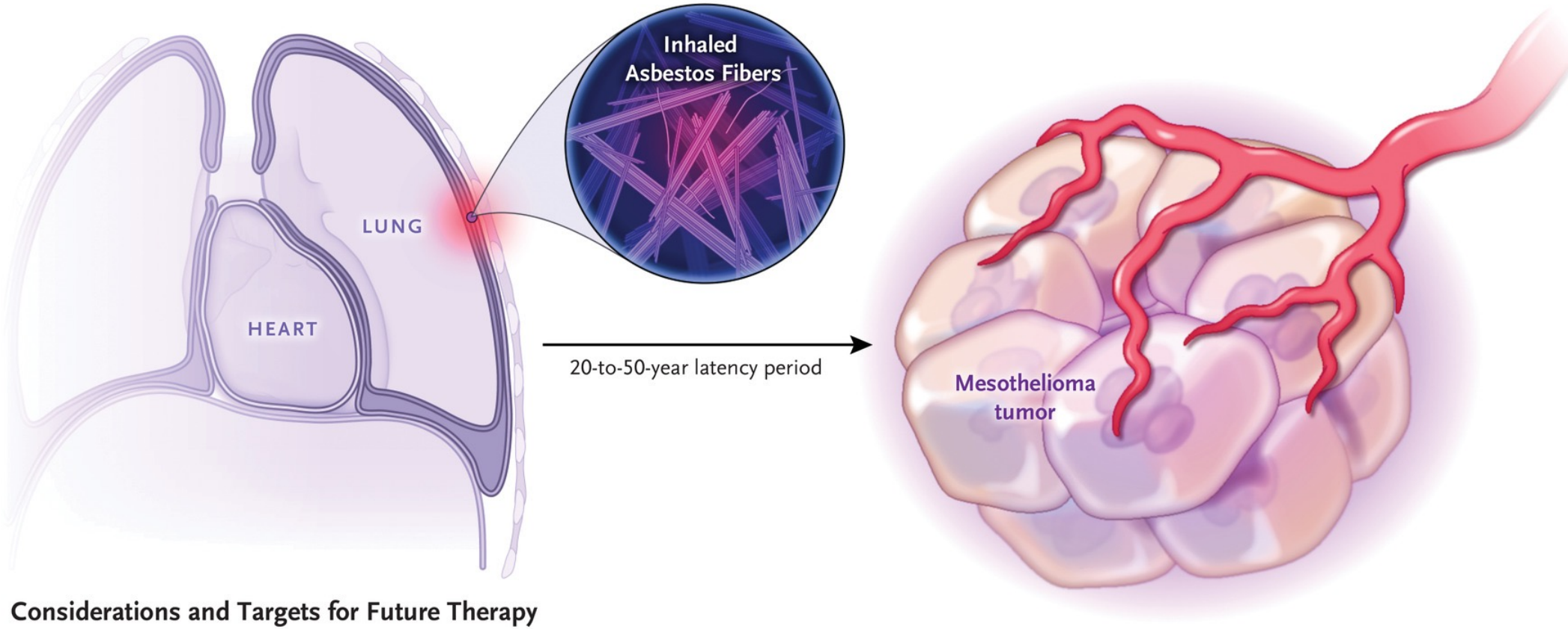
Framtidens landskap

- **Cellular Therapy**
  - Phase 1 study
  - 19 patients
  - Disease control rate 60%
  - Genetically engineered T cells called chimeric antigen receptor T (CAR-T) cells have been designed to target mesothelin
  - Combined with an immune checkpoint inhibitor

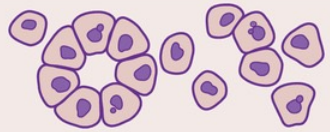
Adusumilli PS, Zauderer MG, RuschVW, et al. A phase I clinical trial of malignant pleural disease treated with regionally delivered autologous mesothelin-targeted CAR T cells: safety and efficacy. In: Proceedings of the American Association for Cancer Research Annual Meeting March 29–April 3, 2019. Atlanta: American Association for Cancer Research,2019: CT036. abstract.

Framtidens landskap

- **Molecularly Stratified Therapy**
  - Epigenetic silencing of the enzyme argininosuccinate synthetase 1 (ASS1) represents the first target to undergo molecularly stratified.
  - Phase 2 study, treatment with pegylated arginine deiminase (ADIPEG 20), decrease in arginine, efficacy in randomized phase 2 trial and can be safely combined with chemotherapy.
  - BAP1 inactivation leads to up-regulation of the oncogenic polycomb repressive complex 2. One of its subunits, enhancer of zeste homolog 2 (EZH2), has been shown to lead to cancer progression.73 A phase 2 multicenter clinical trial of the EZH2 inhibitor tazemetostat in BAP1-inactivated malignant mesothelioma met its primary end point of disease control at 12 weeks (51% of patients)

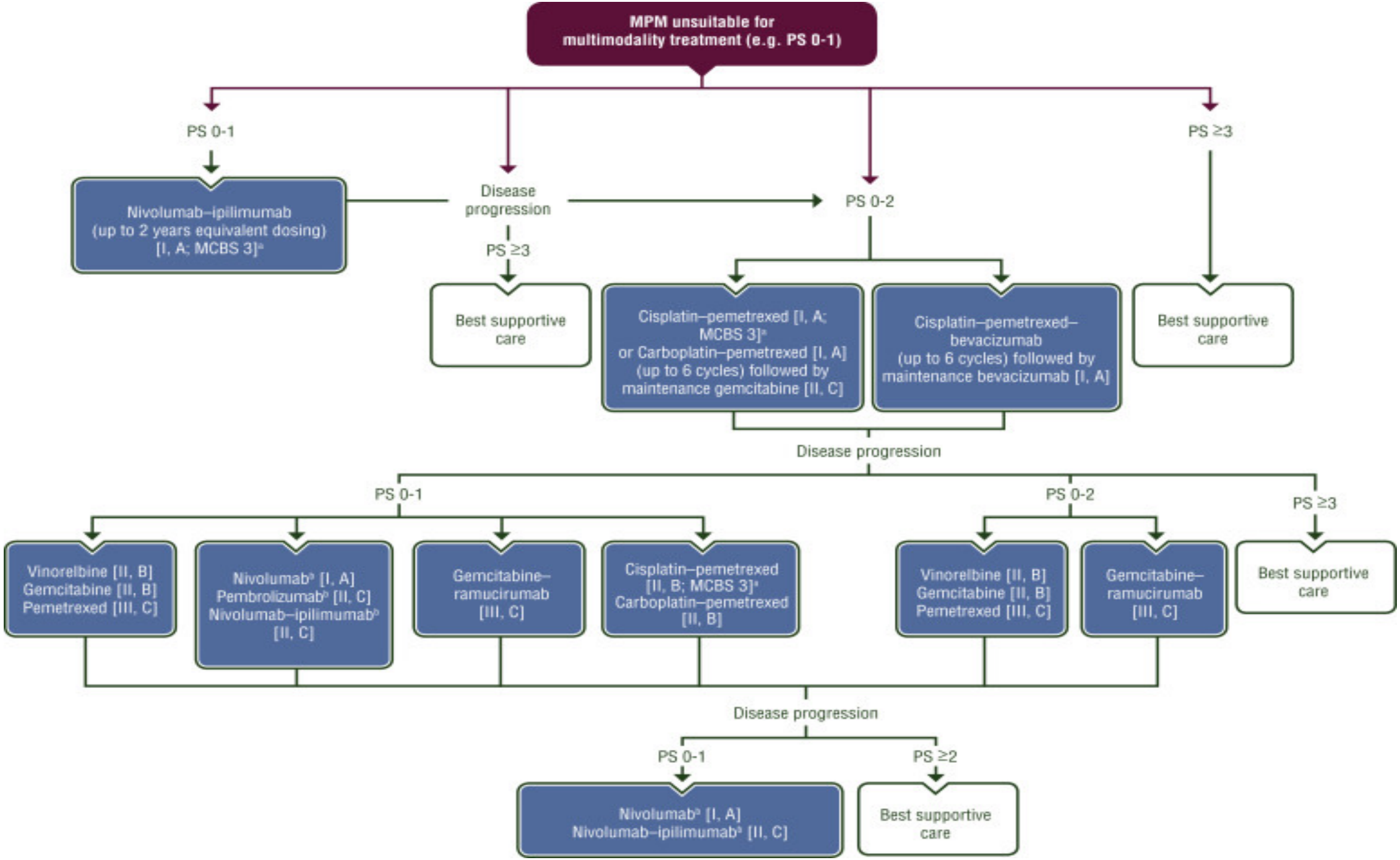


Considerations and Targets for Future Therapy

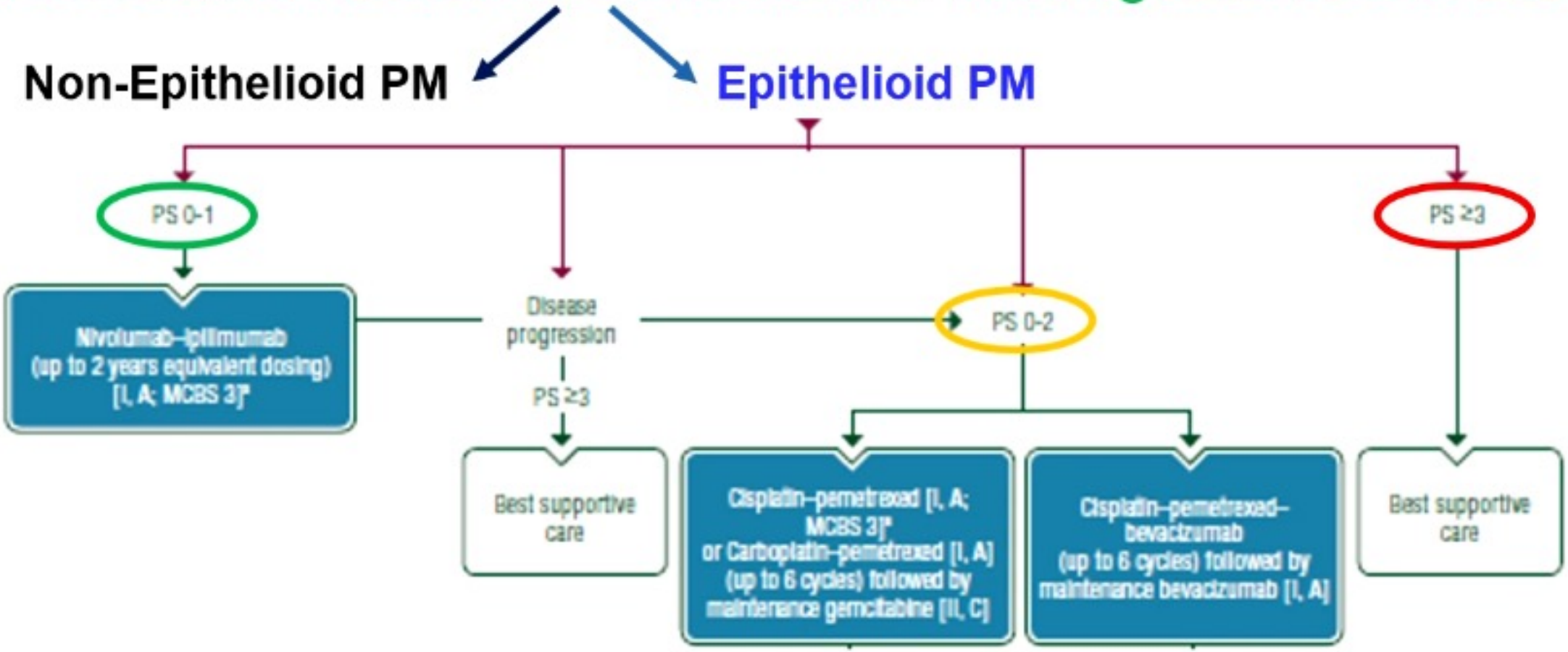
Phenotypic Histologic Subtypes	
Epithelioid (50–60% of cases)	
Biphasic (30–40% of cases)	
Sarcomatoid (10% of cases)	

Current and Future Systemic Approaches
Chemotherapy
Antibody-drug conjugates
Immune checkpoint inhibition (PD-1 or PD-L1 inhibition)
Ferroptosis inducers
Cellular therapy (CAR-T cells targeting mesothelin)
Angiogenesis inhibition

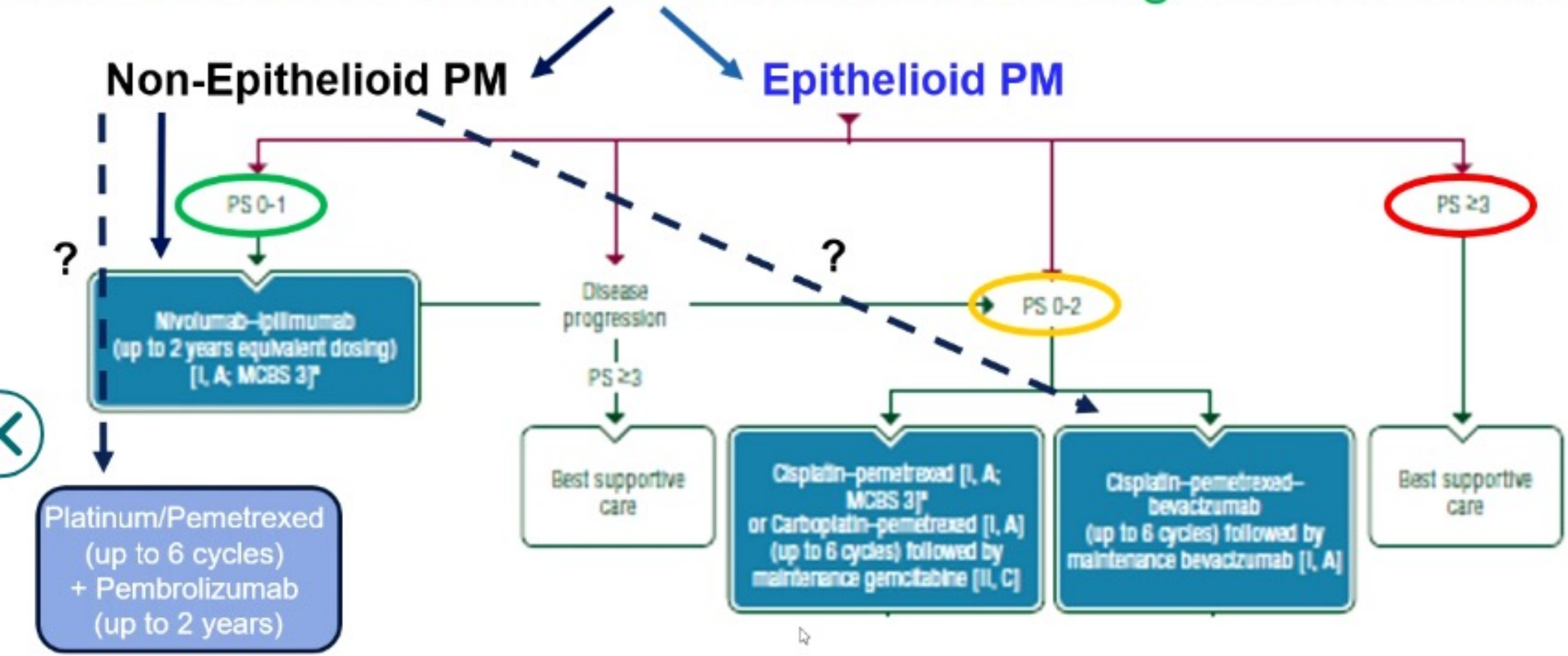
Genomic or Epigenomic Landscape	
Mutation	**Therapeutic Targets**
BAP1	EZH2; PARP
CDKN2A	p16
NF2	FAK; YAP-TEAD; mTOR and PI3K
ASS1	Arginine


MPM unsuitable for multimodality treatment (e.g. PS 0-1)
PS 0-1
PS 0-2
PS ≥3
Nivolumab–ipilimumab (up to 2 years equivalent dosing) [I, A; MCBS 3][a]
Disease progression
PS ≥3
Best supportive care
Cisplatin–pemetrexed [I, A; MCBS 3][a] or Carboplatin–pemetrexed [I, A] (up to 6 cycles) followed by maintenance gemcitabine [II, C]
Cisplatin–pemetrexed–bevacizumab (up to 6 cycles) followed by maintenance bevacizumab [I, A]
Best supportive care
Disease progression
PS 0-1
PS 0-2
PS ≥3
Vinorelbine [II, B] Gemcitabine [II, B] Pemetrexed [III, C]
Nivolumab[a] [I, A] Pembrolizumab[a] [II, C] Nivolumab–ipilimumab[a] [II, C]
Gemcitabine–ramucirumab [III, C]
Cisplatin–pemetrexed [II, B; MCBS 3][a] Carboplatin–pemetrexed [II, B]
Vinorelbine [II, B] Gemcitabine [II, B] Pemetrexed [III, C]
Gemcitabine–ramucirumab [III, C]
Best supportive care
Disease progression
PS 0-1
PS ≥2
Nivolumab[a] [I, A] Nivolumab–ipilimumab[a] [II, C]
Best supportive care

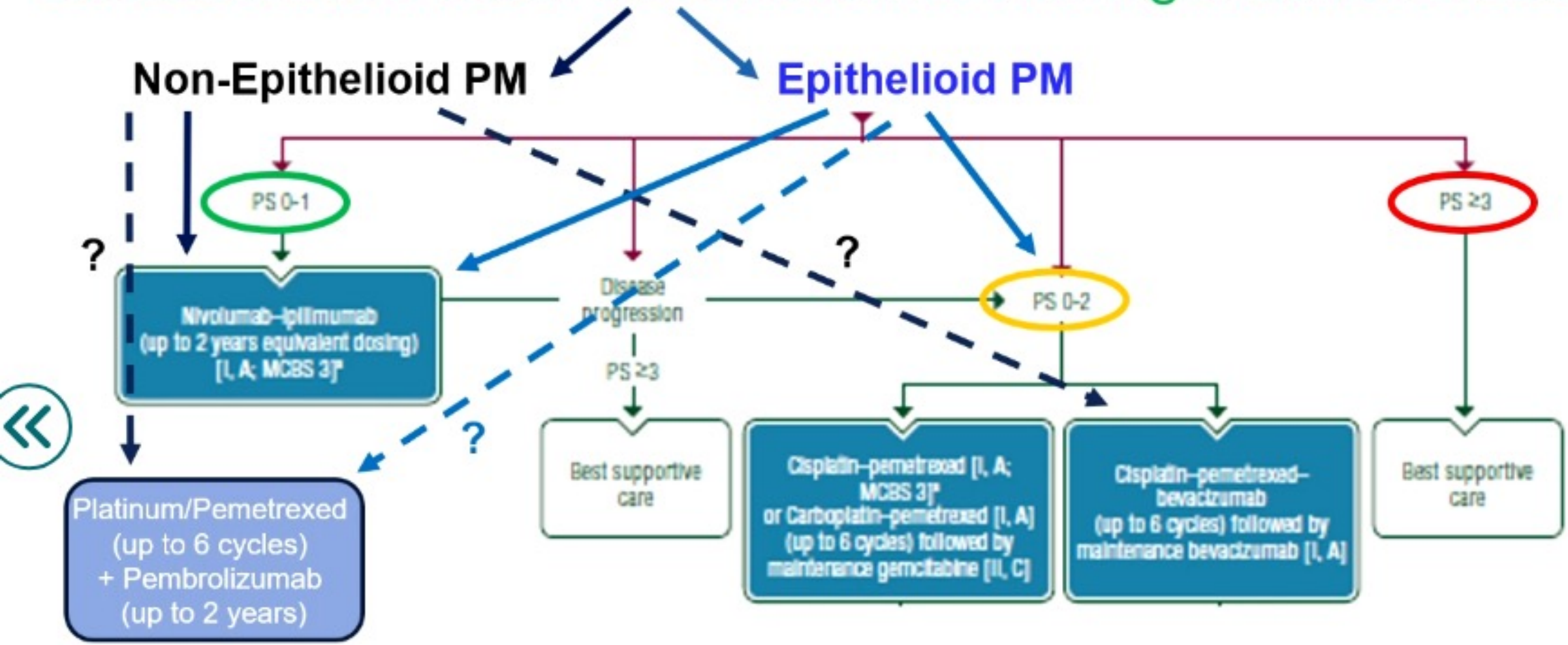
Unresectable Pleural Mesothelioma: which guidelines in 2024 ?



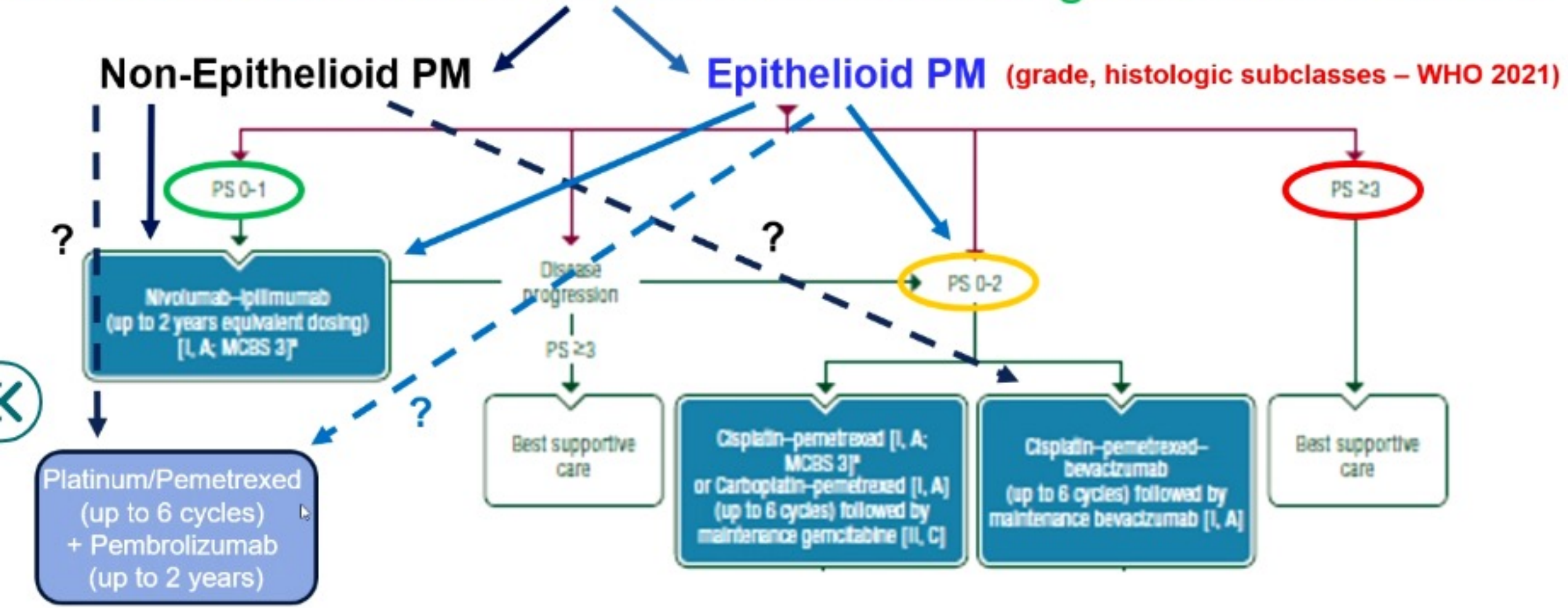
Unresectable Pleural Mesothelioma: which guidelines in 2024 ?



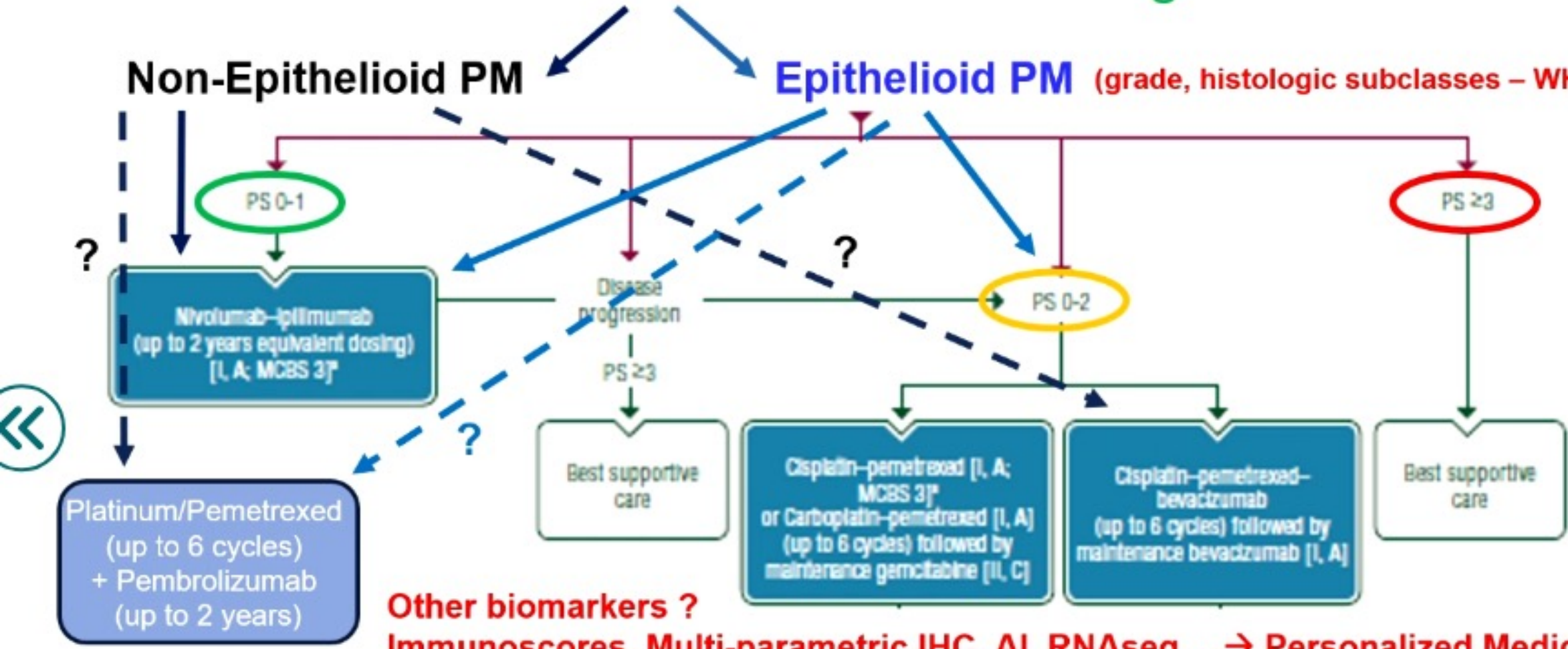
Unresectable Pleural Mesothelioma: which guidelines in 2024 ?



Unresectable Pleural Mesothelioma: which guidelines in 2024 ?



Unresectable Pleural Mesothelioma: which guidelines in 2024 ?



Other biomarkers ?
Immunoscores, Multi-parametric IHC, AI, RNAseq… → <u>Personalized Medicine</u> !

OTHER FUTURE OPTIONS ?

- Platinum/Pemetrexed + Durvalumab
- Platinum/Pemetrexed + Bevacizumab + Atezolizumab
- Targeted therapies

MORE TO COME ?

- P/P chemo + other ICB (anti-LAG-3…) or + Bispecific Ab…
- CAR T cells, PDT…

PARIS 2022 ESMO congress

First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 4-year update from CheckMate 743

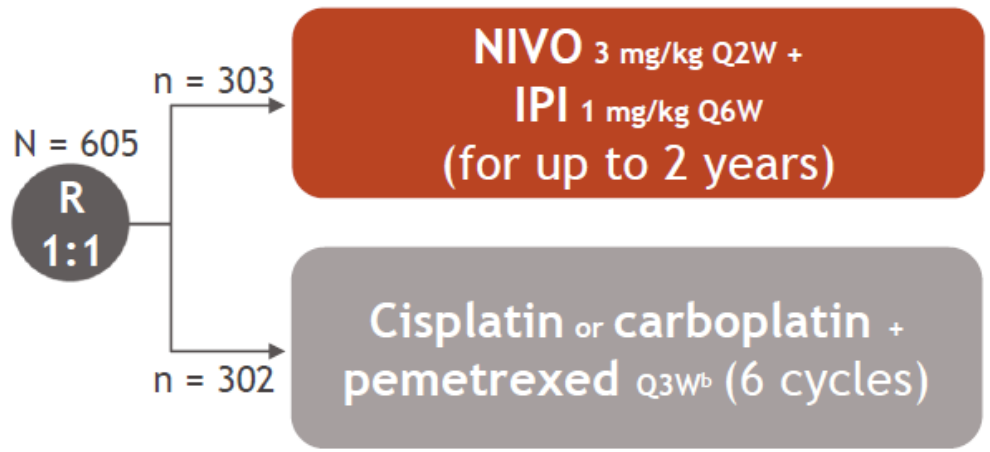
Gérard Zalcman,[1] Youssef Oulkhouir,[2] Robin Cornelissen,[3] Laurent Greillier,[4] Jerónimo Rodríguez Cid,[5] Julien Mazières,[6] Peter Briggs,[7] Anna K. Nowak,[8] Anne S. Tsao,[9] Nobukazu Fujimoto,[10] Solange Peters,[11] Aaron S. Mansfield,[12] Sanjay Popat,[13] Ayman Nassar,[14] Judith Bushong,[14] Nan Hu,[14] Thomas E. Spires,[14] David Balli,[14] Laura Eccles,[14] Paul Baas[15]

[1]Bichat-Claude Bernard University Hospital, AP-HP, Université de Paris, Paris, France; [2]Hôpital Côte de Nacre CHU Caen, Caen, France; [3]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [4]Aix Marseille University, APHM, INSERM, CNRS, CRCM, Hôpital Nord, Marseille, France; [5]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico; [6]Centre Hospitalier Universitaire de Toulouse - Hôpital Larrey, Université Paul Sabatier, Toulouse, France; [7]Monash Medical Centre, Clayton, Victoria, Australia; [8]University of Western Australia and Sir Charles Gairdner Hospital, Perth, Australia; [9]MD Anderson Cancer Center, Houston, TX, USA; [10]Okayama Rosai Hospital, Okayama, Japan; [11]Lausanne University Hospital, Lausanne, Switzerland; [12]Mayo Clinic, Rochester, MN, USA; [13]Royal Marsden Hospital and Institute of Cancer Research, London, UK; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]Netherlands Cancer Institute and Leiden University Medical Center, Amsterdam, Netherlands

Study design[a]

Key eligibility criteria
- Unresectable MPM
- No prior systemic therapy
- ECOG PS 0-1

Stratified by
Histology (epithelioid vs non-epithelioid) and sex



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

Primary endpoint
- OS

Secondary endpoints
- ORR, DCR, and PFS by BICR
- Efficacy by PD-L1[c] expression

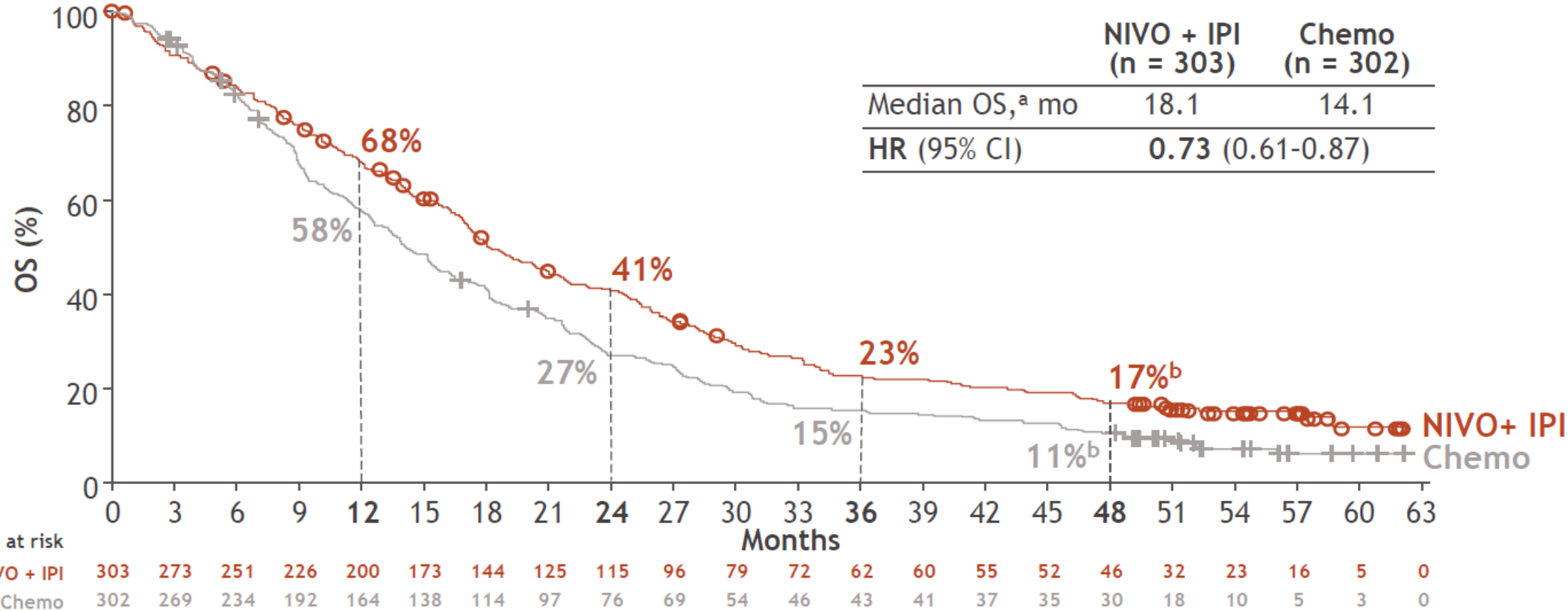
Exploratory endpoints
- Safety and tolerability
- Biomarkers

Database lock: May 6, 2022; minimum / median follow-up for OS: 47.5 months / 55.1 months.

[a]NCT02899299; [b]Cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2), Q3W for 6 cycles; [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako).

Baas P, et al. *Lancet* 2021;397:375-386.

4-year update: overall survival in all randomized patients



	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS,[a] mo	18.1	14.1
HR (95% CI)	**0.73** (0.61-0.87)	

- 4-year PFS rates were 9% vs 0% with NIVO + IPI vs chemo[c]
- ORR and DOR were consistent with previous database lock[d]; rate of ongoing responders at 4 years was 16% vs 0%, respectively

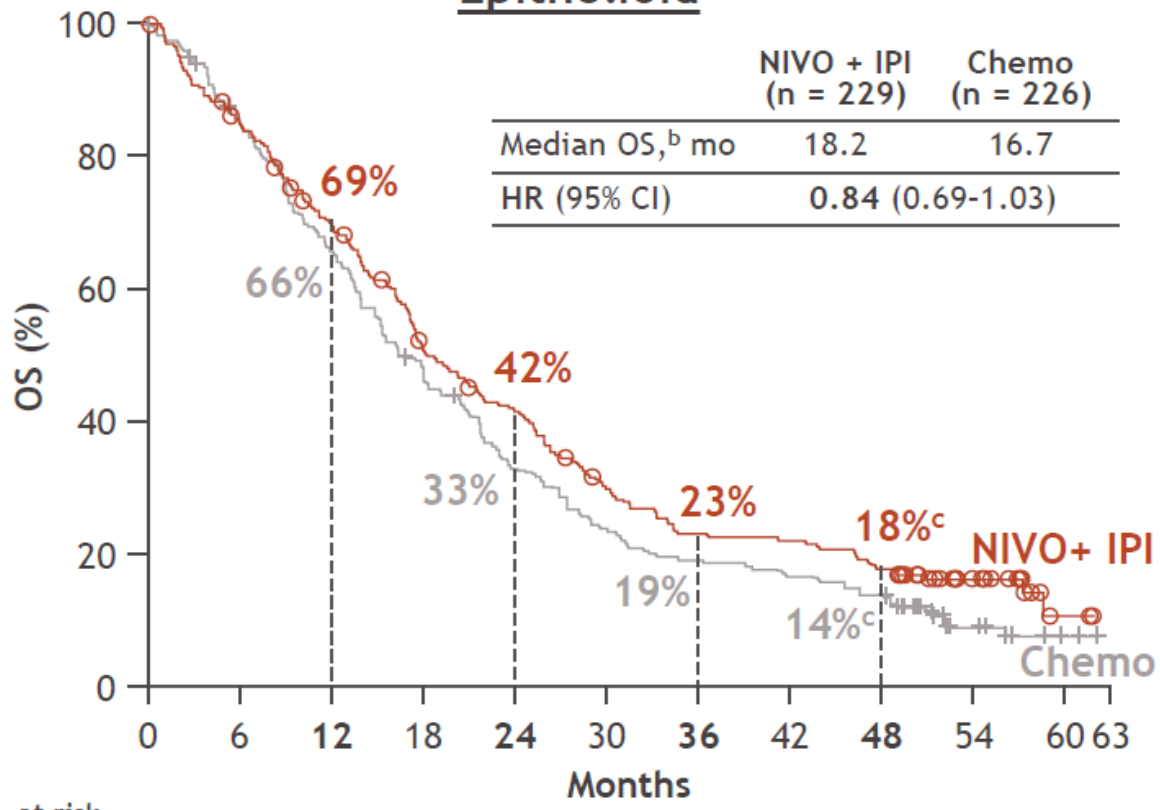
Minimum / median follow-up for OS: 47.5 months / 55.1 months.

Subsequent systemic therapy was received by 46% of patients in the NIVO + IPI arm and 43% in the chemo arm; subsequent immunotherapy was received by 5% and 23%; subsequent chemotherapy was received by 44% and 34%, respectively.

[a]95% CIs were 16.8-21.0 (NIVO + IPI) and 12.4-16.3 (chemo); [b]95% CIs were 12.7-21.5 (NIVO + IPI) and 7.5-14.7 (chemo); [c]Median PFS was 6.8 vs 7.2 months with NIVO + IPI vs chemo (HR, 95% CI: 0.93, 0.77-1.13); [d]ORR was 39.3% vs 44.4%, and median DOR was 11.6 vs 6.8 months.

4-year update: OS by histology[a]

Epithelioid

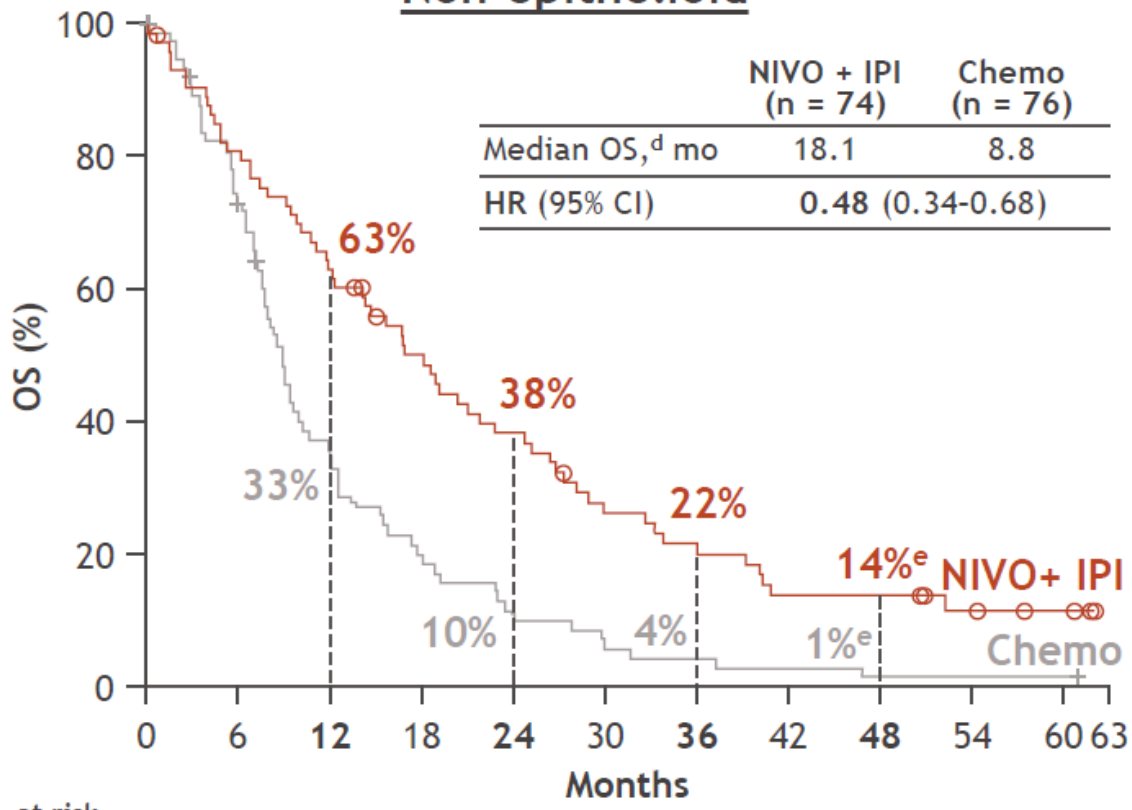


	NIVO + IPI (n = 229)	Chemo (n = 226)
Median OS,[b] mo	18.2	16.7
HR (95% CI)	0.84 (0.69-1.03)	

No. at risk

NIVO + IPI	229	192	154	110	89	62	48	46	37	18	2	0
Chemo	226	182	141	101	69	50	40	35	29	9	2	0

Non-epithelioid



	NIVO + IPI (n = 74)	Chemo (n = 76)
Median OS,[d] mo	18.1	8.8
HR (95% CI)	0.48 (0.34-0.68)	

No. at risk

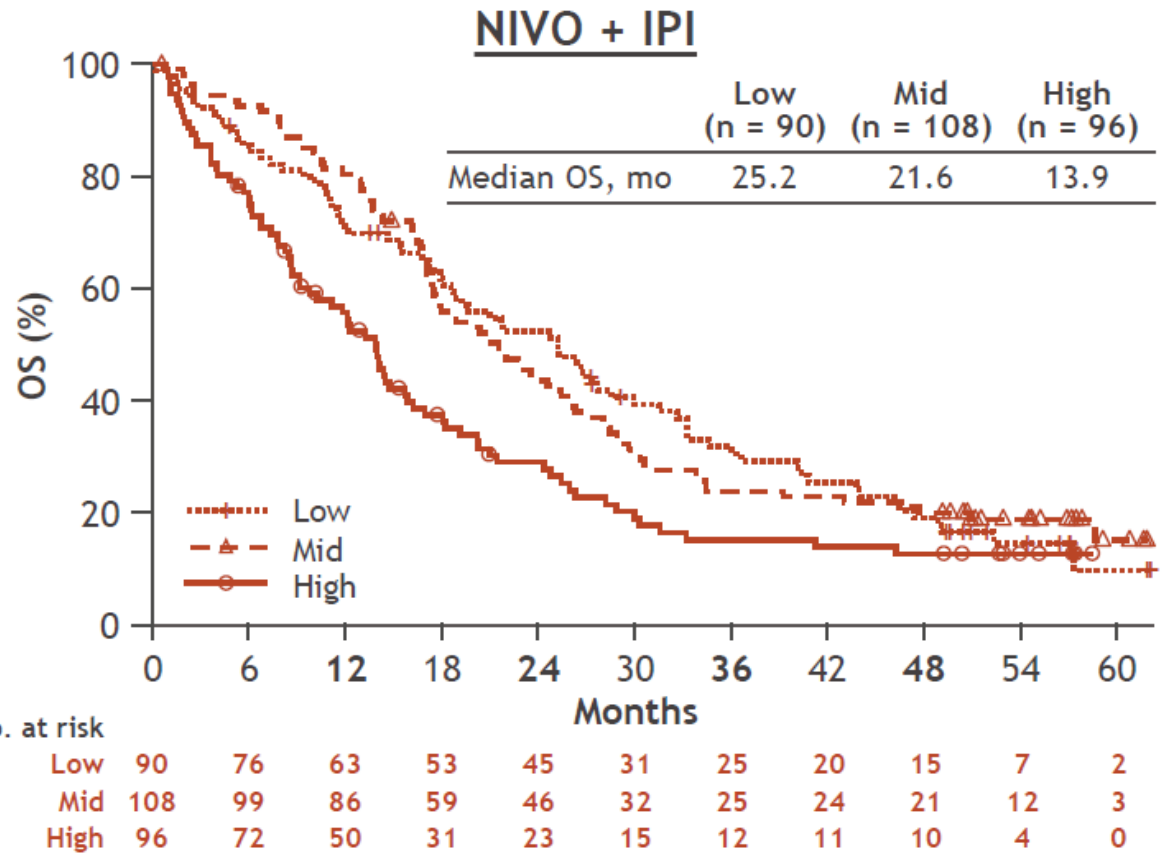
NIVO + IPI	74	59	46	34	26	17	14	9	9	5	3	0
Chemo	76	52	23	13	7	4	3	2	1	1	1	0

Minimum / median follow-up for OS: 47.5 months / 55.1 months.

In patients with epithelioid histology, subsequent systemic therapy was received by 48% in the NIVO + IPI arm vs 45% in the chemo arm; subsequent immunotherapy was received by 4% vs 24%; subsequent chemotherapy was received by 46% vs 37%, respectively. In patients with non-epithelioid histology, subsequent systemic therapy was received by 40% in the NIVO + IPI arm vs 37% in the chemo arm; subsequent immunotherapy was received by 7% vs 20%; subsequent chemotherapy was received by 38% vs 26%, respectively.

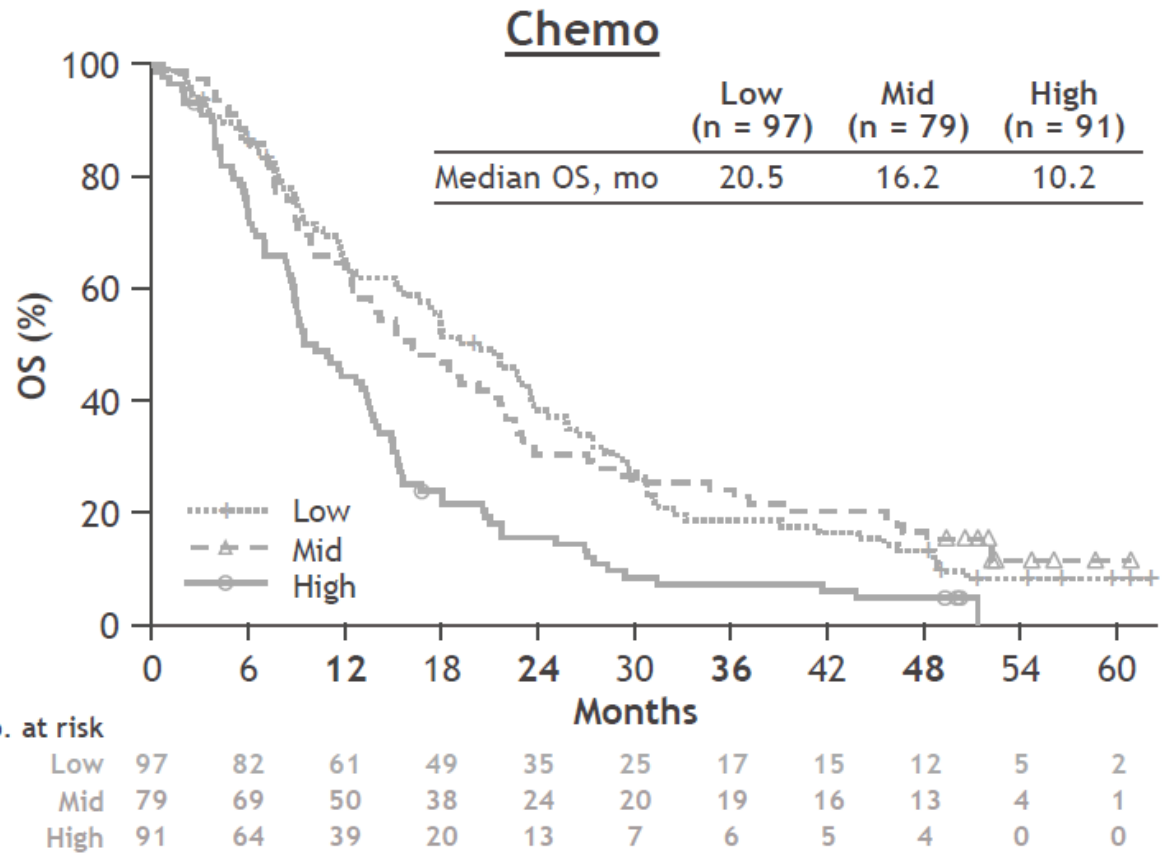
[a]Histology per CRF; [b]95% CIs were 16.9-21.9 (NIVO + IPI) and 14.9-20.3 (chemo); [c]95% CIs were 13.0-23.2 (NIVO + IPI) and 9.6-18.9 (chemo); [d]95% CIs were 12.2-22.8 (NIVO + IPI) and 7.4-10.2 (chemo); [e]95% CIs were 6.9-23.3 (NIVO + IPI) and 0.1-6.8 (chemo).

Exploratory analysis: OS by baseline soluble mesothelin level[a,b]



No. at risk

Low	90	76	63	53	45	31	25	20	15	7	2
Mid	108	99	86	59	46	32	25	24	21	12	3
High	96	72	50	31	23	15	12	11	10	4	0



No. at risk

Low	97	82	61	49	35	25	17	15	12	5	2
Mid	79	69	50	38	24	20	19	16	13	4	1
High	91	64	39	20	13	7	6	5	4	0	0

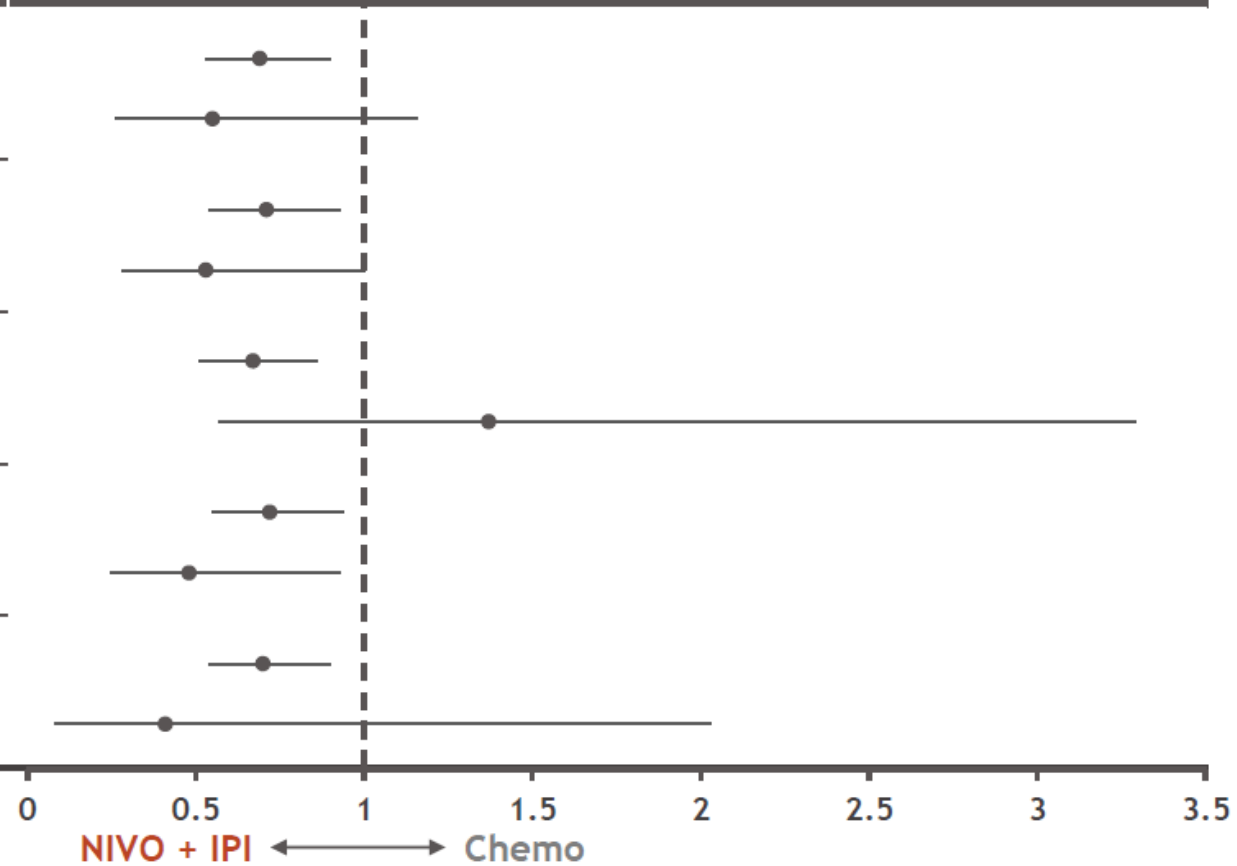
- Similar trends in OS were seen in patients with epithelioid[c] and those with non-epithelioid histology,[d] although the non-epithelioid histology subgroups were small

Minimum / median follow-up for OS: 47.5 months / 55.1 months.

[a]Quantified using an ELISA-based methodology on patient serum samples; low, mid, and high subgroups were split by tertile median soluble mesothelin levels; [b]97% (n/N = 294/303) and 88% (267/302) of patients had evaluable baseline soluble mesothelin levels in the NIVO + IPI and chemo arms, respectively; [c]Epithelioid histology: median OS for low, mid, and high soluble mesothelin level: 27.7 (n = 50), 21.7 (n = 86), and 13.9 (n = 85) months for the NIVO + IPI arm, respectively, and 25.9 (n = 61), 20.8 (n = 57), and 11.6 (n = 79) for the chemo arm, respectively; [d]Non-epithelioid histology: median OS for low, mid, and high soluble mesothelin level were 18.6 (n = 40), 20.3 (n = 22), and 12.3 (n = 11) months for the NIVO + IPI arm, respectively, and 8.6 (n = 36), 9.3 (n = 22), and 8.4 (n = 12) for the chemo arm, respectively.

Exploratory analysis: OS by MPM-specific tumor suppressor gene mutations[a,b]

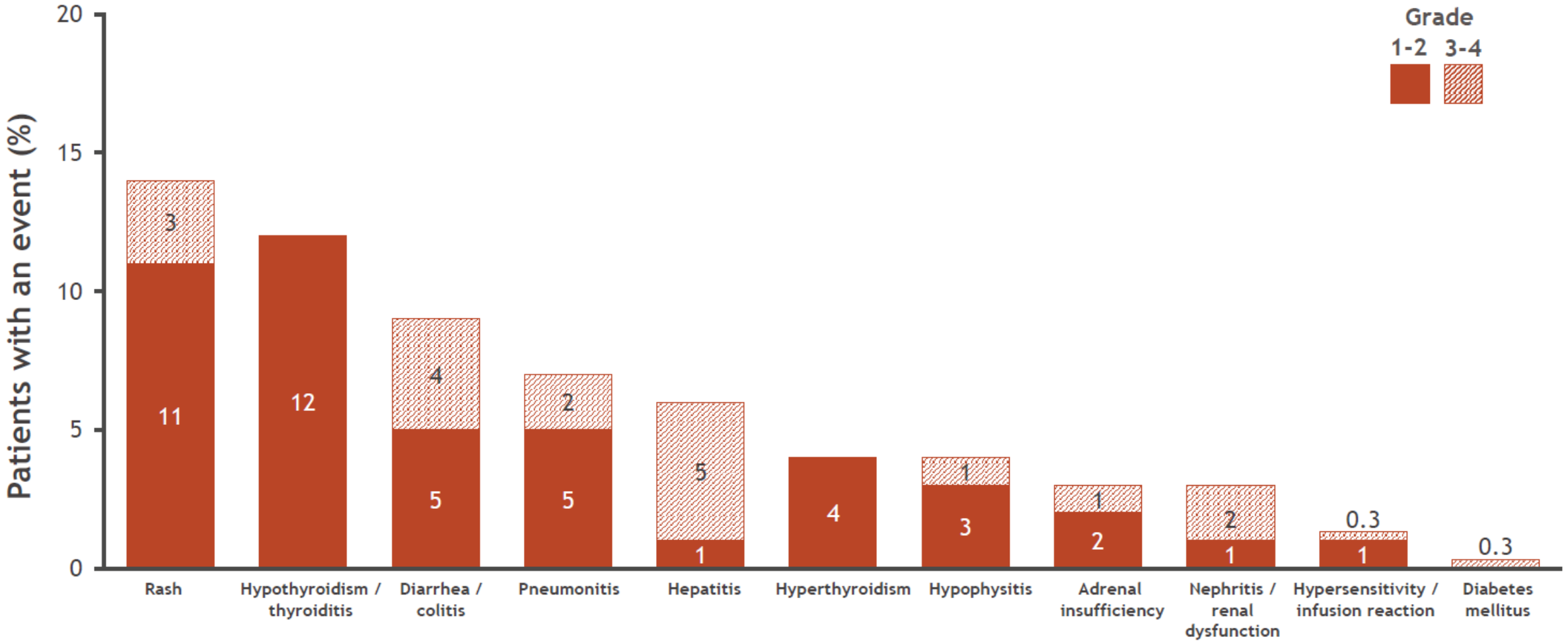
Subgroup (n)[c]	Unstratified HR (NIVO + IPI vs chemo)
TP53wt (n = 262)	0.69
TP53mut (n = 34)	0.55
Total *BAP1wt* (n = 246)[d]	0.71
Total *BAP1mut* (n = 47)[d]	0.53
SETD2wt (n = 269)	0.67
SETD2mut (n = 26)	1.37
NF2wt (n = 250)	0.72
NF2mut (n = 46)	0.48
LATS2wt (n = 282)	0.70
LATS2mut (n = 11)	0.41



Minimum / median follow-up for OS: 47.5 months / 55.1 months.

[a]Tumor mutations in *TP53*, *BAP1*, *SETD2*, *NF2*, and *LATS2* were evaluated by whole-exome sequencing; deleterious mutations were defined as SNVs, INDELs, or copy number alterations with likely or known deleterious impact to protein function; [b]Samples were available for 48% of the study population (52% in the NIVO + IPI arm; 44% in the chemo arm); [c]Indicates total number of patients in each subgroup across both arms; [d]Includes germline and somatic mutations.

4-year update: immune-mediated AEs[a] with NIVO + IPI



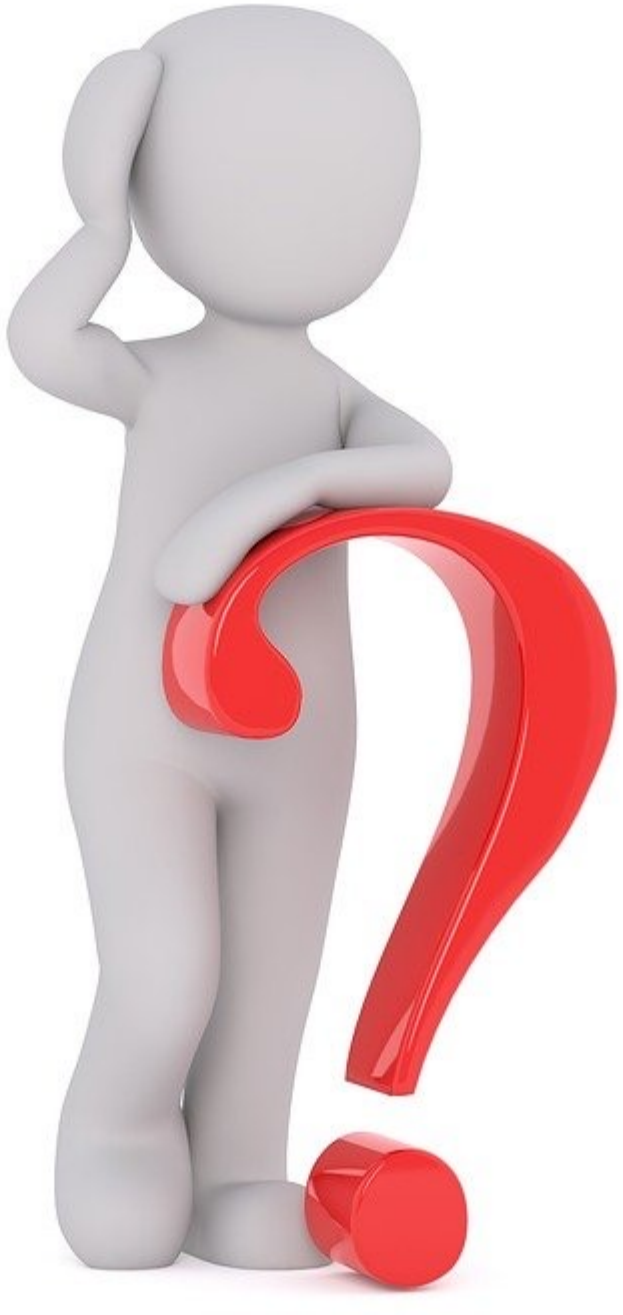
[a]Includes AEs considered as potential immune-mediated events by investigator occurring within 100 days of last dose regardless of causality and treated with immune-modulating medication, with the exception of endocrine events (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus), which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. CTCAE Version 4.0; MedDRA Version: 25.0.

Summary

- These results from CheckMate 743 represent the longest reported follow-up with immunotherapy in 1L unresectable MPM; NIVO + IPI continued to provide long-term, durable benefit versus chemo
  - **4-year OS rates:** 17% vs 11%, respectively
  - **4-year PFS rates:** 9% vs 0%, respectively
  - **16% of responders** in the NIVO + IPI arm have ongoing response at 4 years vs none in the chemo arm
- In exploratory biomarker analyses:
  - High baseline soluble mesothelin levels were correlated with a poor OS
  - OS showed a consistent trend for benefit with NIVO + IPI vs chemo across most MPM-specific tumor suppressor mutation subgroups, with some subgroups being small in size and limiting data interpretation
- No new safety signals were observed with longer follow-up; rates of grade 3-4 IMAEs were ≤ 5%
- **With a 4-year minimum follow-up, these data from CheckMate 743 continue to confirm NIVO + IPI as a standard of care for unresectable MPM regardless of histology**

Nationella vårdprogrammet

- **Kirurgi**: selekterade fall, kontakta Köpenhamn! **Experimentell behandling**
- **Radioterapi**: Ingen profylaktisk, ingen roll för sjukdomskontroll, palliativ mot smärta!
- **Cytostatika**:
  - Cis/Karb + Pemetrexed
  - Cis+ Pemetrexed+ Bevacizumab kan övervägas! (2 mån förbättring i OS)
  - Vid progress: Rechallenge, Pemetredex, Vinorelbin singel eller kombination med platinum.
- Nya behandlingar: **IT** Nivo/Ipi- Sakramatoitt MPM



Frågor

- Hur gör Ni hor Er?
- Vad säger vårdprogrammet?
- Mer nationell samarbete och kunskapsdelning?

Fall

Anamnes

- Man född 1989
- 2018 s aureus sepsis/ endokardit/ op mekanisk aortaklaff
- Waran beh
- Fö frisk
- Icke rökare
- 0 herdiditet för malignitet
- Ensamboende. Har en hund
- Arbetar som rörläggare, möjligen asbest exponering vid 16 års åldern

Aktuellt

- Sökte VC, pga thorax smärta i revbenskurvatur, tolkades som revbensfraktur! , konservativ hållning!
- Söker akut 2021-04-13 pga förvärring av symtomen ffa dyspne
- Mer thorax smärta
- Nattliga svettningar

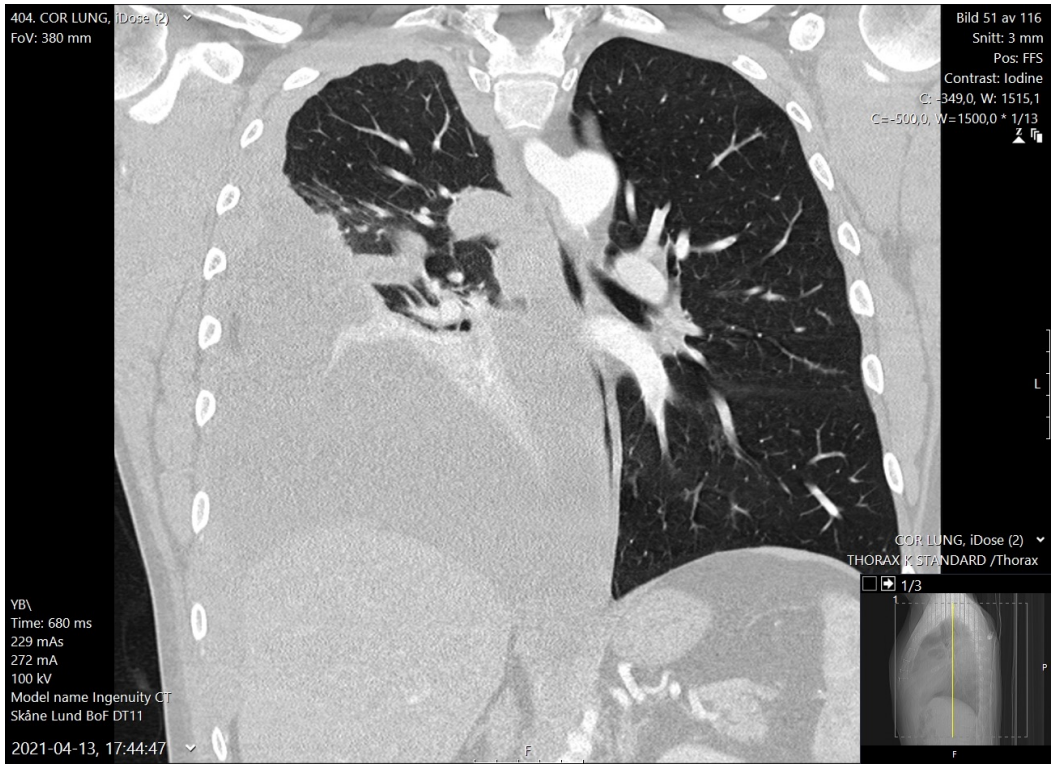
Status& Fynd!

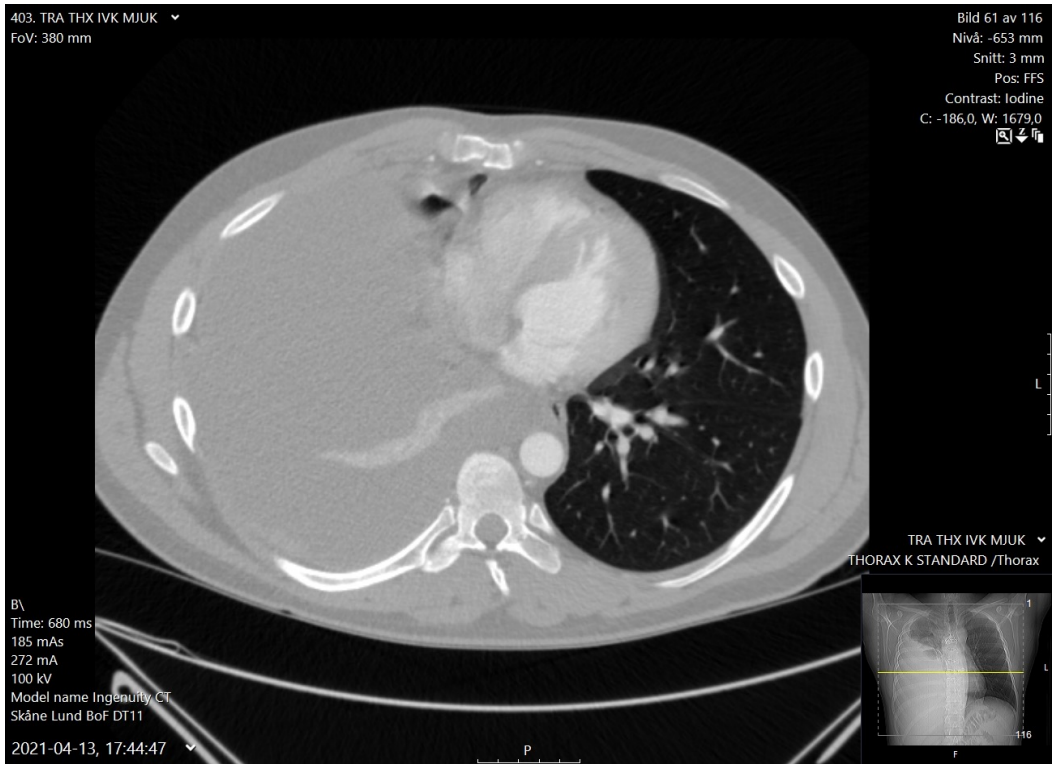
- Samtals dyspné
- Saturation 98% (Vila), AF 20/min
- Dämpning basalt hö vid auskultation och perkussion
- Lab: CRP 109, LPK 9,9, PK 6,5
- COVID-19 negativ

Åtgärd

- Blododlingar
- IV ab (Cefotaxim)
- Inläggning
- CT-thorax

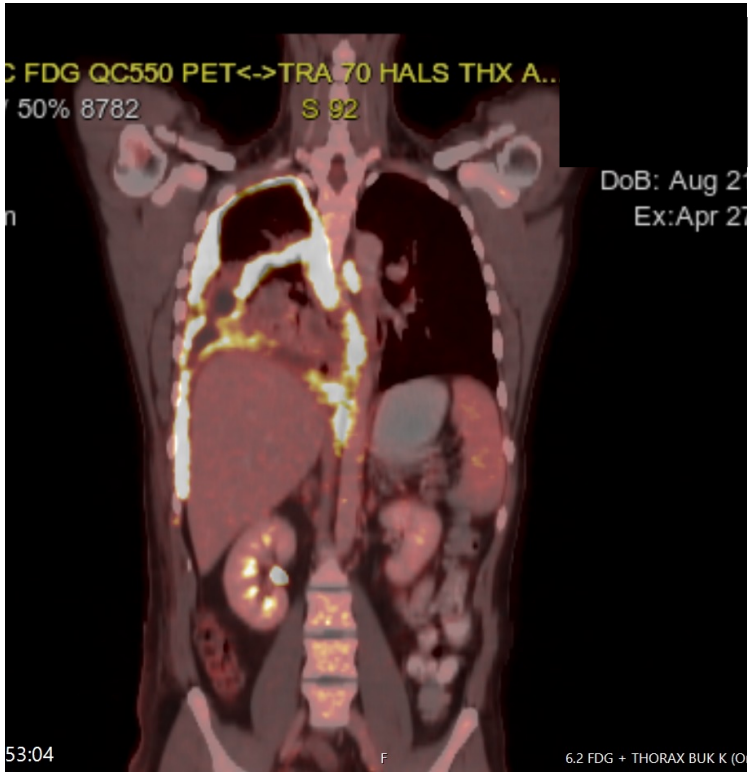
CT-thorax

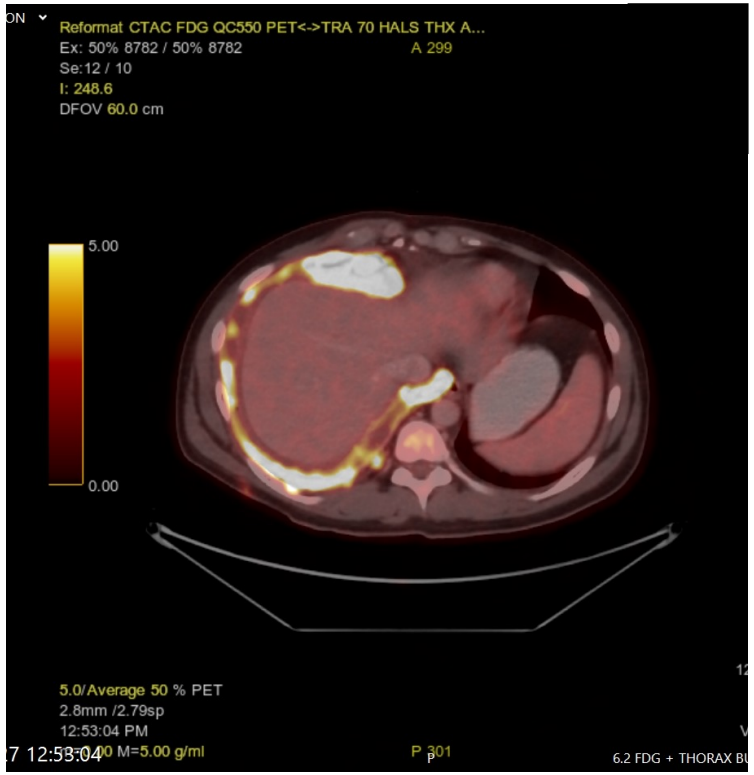

404. COR LUNG, iDose (2)
FoV: 380 mm
Bild 51 av 116
Snitt: 3 mm
Pos: FFS
Contrast: Iodine
C: -349,0, W: 1515,1
C=-500,0, W=1500,0 * 1/13
COR LUNG, iDose (2)
THORAX K STANDARD /Thorax
1/3
YB\
Time: 680 ms
229 mAs
272 mA
100 kV
Model name Ingenuity CT
Skåne Lund BoF DT11
2021-04-13, 17:44:47

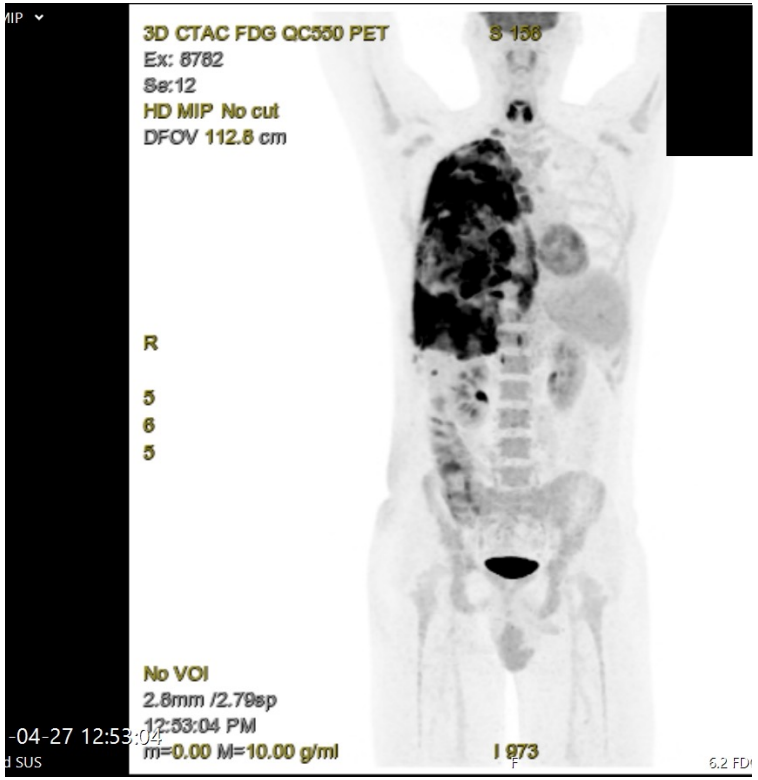

403. TRA THX IVK MJUK
FoV: 380 mm
Bild 61 av 116
Nivå: -653 mm
Snitt: 3 mm
Pos: FFS
Contrast: Iodine
C: -186,0, W: 1679,0
TRA THX IVK MJUK
THORAX K STANDARD /Thorax
B\
Time: 680 ms
185 mAs
272 mA
100 kV
Model name Ingenuity CT
Skåne Lund BoF DT11
2021-04-13, 17:44:47

Förlopp

- Thorax drän X 2
- Odlingar & cytologi på vätskan
- Odlingar negativa, ab utsatt, CRP kring 200, SR 100
- Cytologi 1: reaktiva mesotelceller, inget malign
- Cytologi 2: Benignt
- PET CT!


FDG QC550 PET<->TRA 70 HALS THX A..
50% 8782
S 92
DoB: Aug 2
Ex:Apr 2
53:04
6.2 FDG + THORAX BUK K (O


Reformat CTAC FDG QC550 PET<->TRA 70 HALS THX A...
Ex: 50% 8782 / 50% 8782
A 299
Se:12 / 10
I: 248.6
DFOV 60.0 cm
5.00
0.00
5.0/Average 50 % PET
2.8mm /2.79sp
12:53:04 PM
P 301
6.2 FDG + THORAX BU


3D CTAC FDG QC550 PET
S 156
Ex: 8782
Se:12
HD MIP No cut
DFOV 112.8 cm
R
5
6
5
No VOI
2.8mm /2.79sp
12:53:04 PM
m=0.00 M=10.00 g/ml
I 973
SUS

PET CT

Torakoskopisk pleurabiopsi 28/4

- Rikligt med pleuravätska
- Förtjockning med septering
- 3-4 ställen med kraftig förtjockning (tumör?)
- Biopsi tagits från diafragmalpleura, lateralt och apikalt.

PAD: Epiteloitt mesoteliom

Utbredd tumörväxt, N2-N3

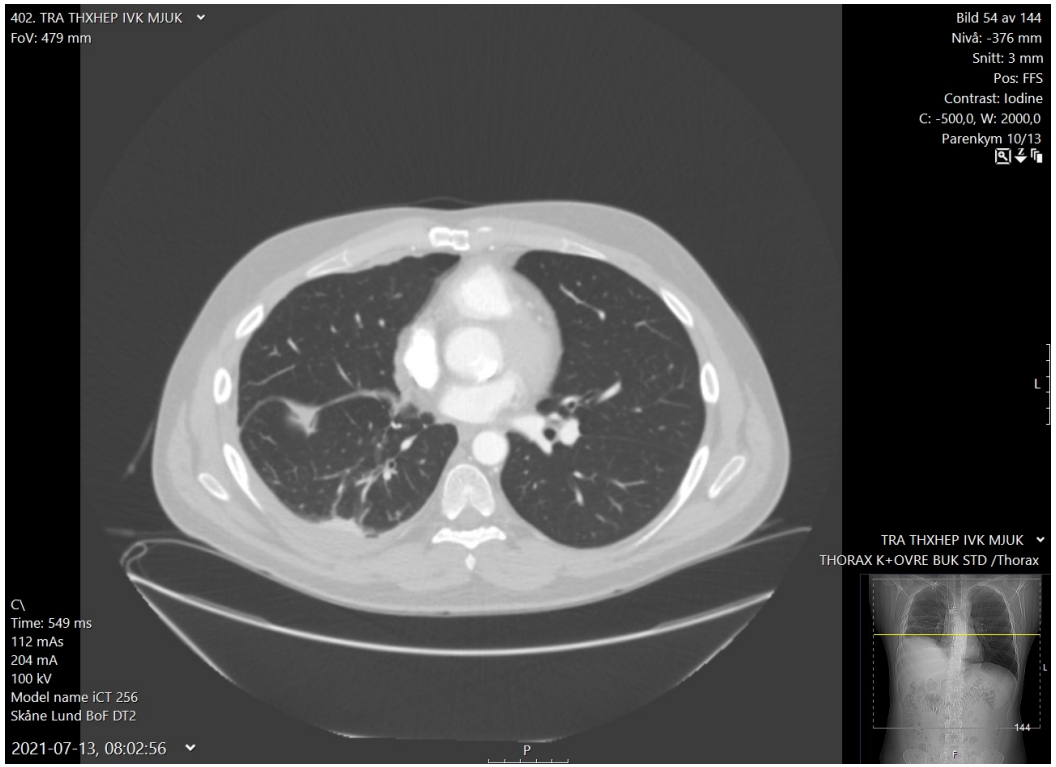
Cisplatin/Pemetrexed

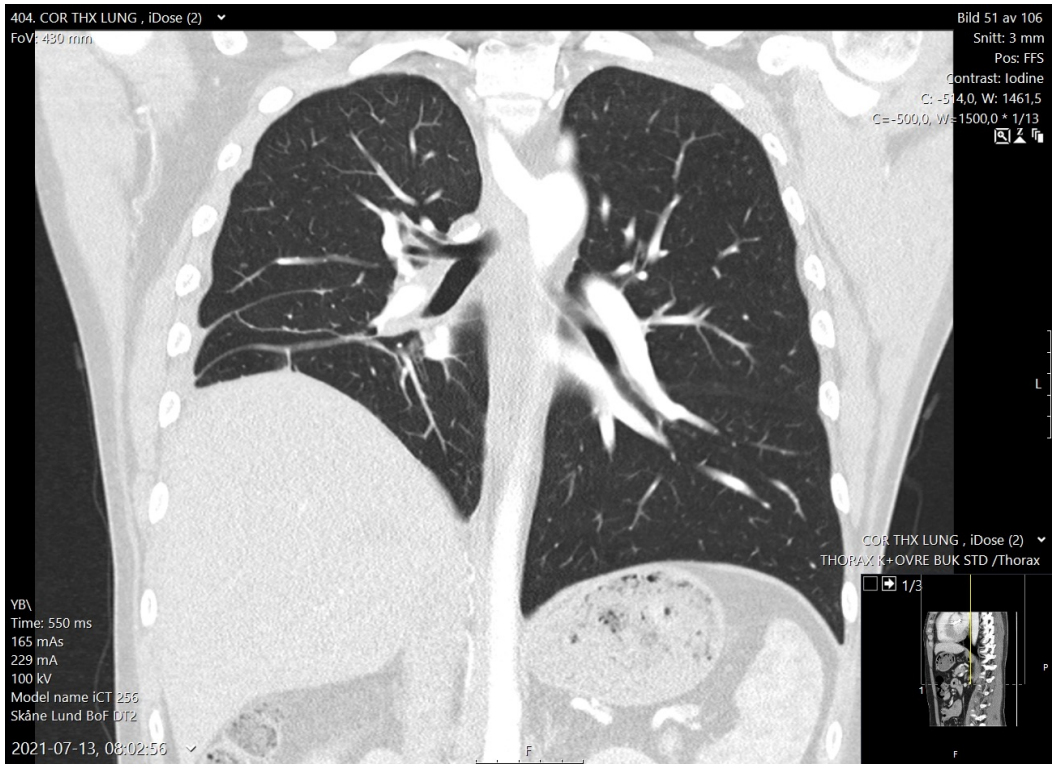
Efter diskussion tillägg av Immunterapi

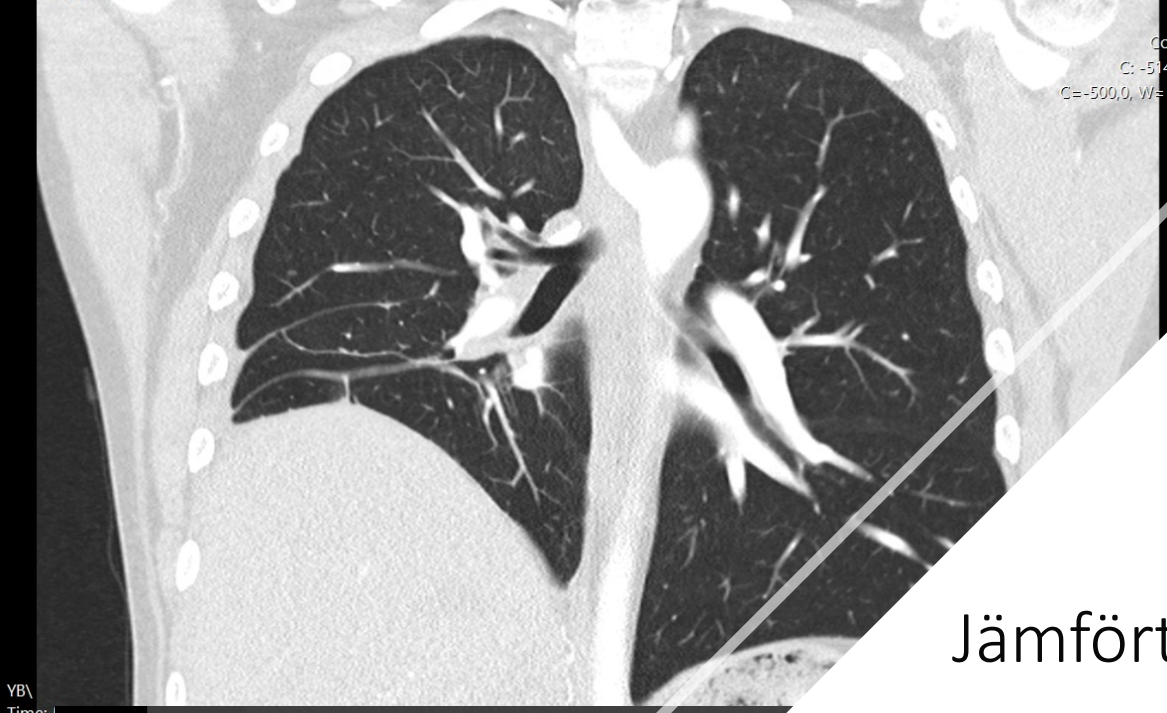
Behandlingsresan!

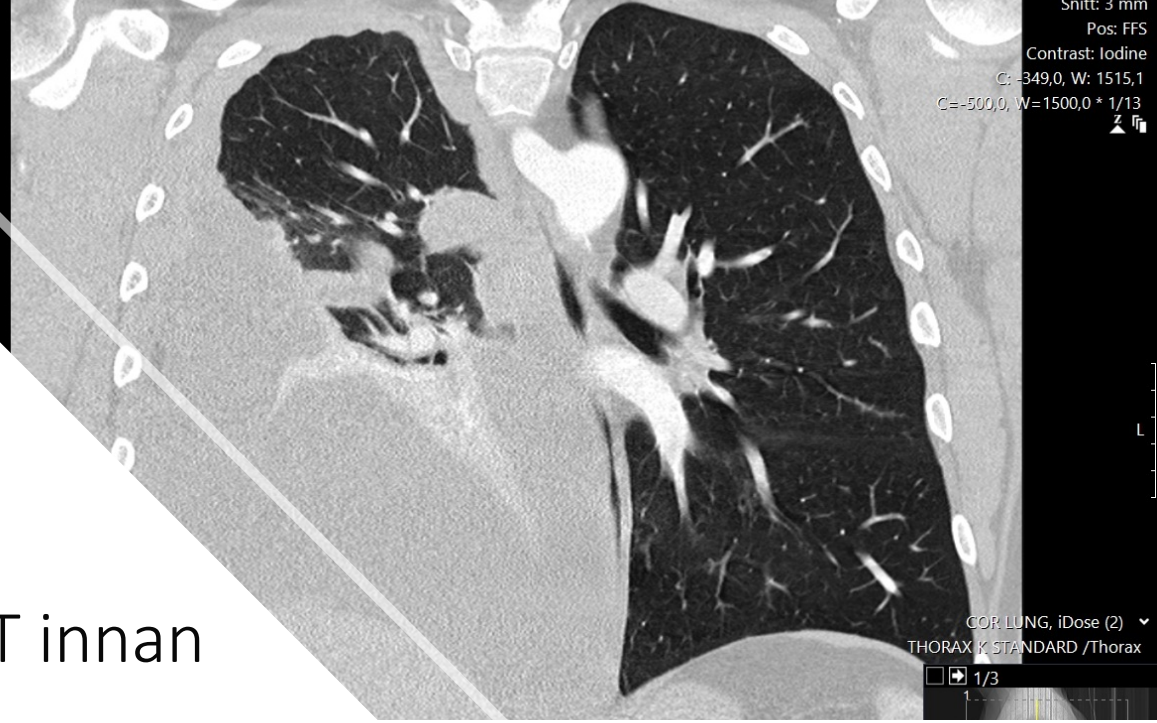
- Cytostatika Cis/Pem/Pembro 2021-05-14

Första utvärdering efter 3 kurer

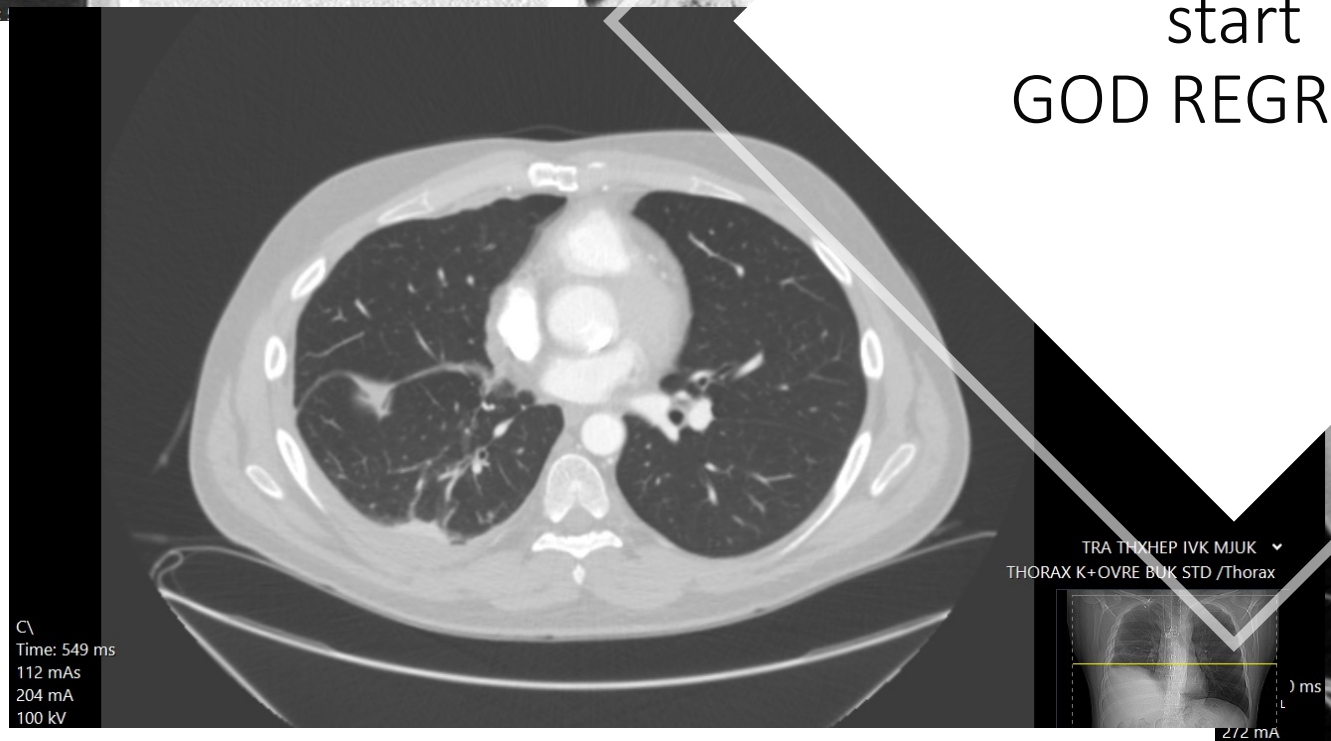


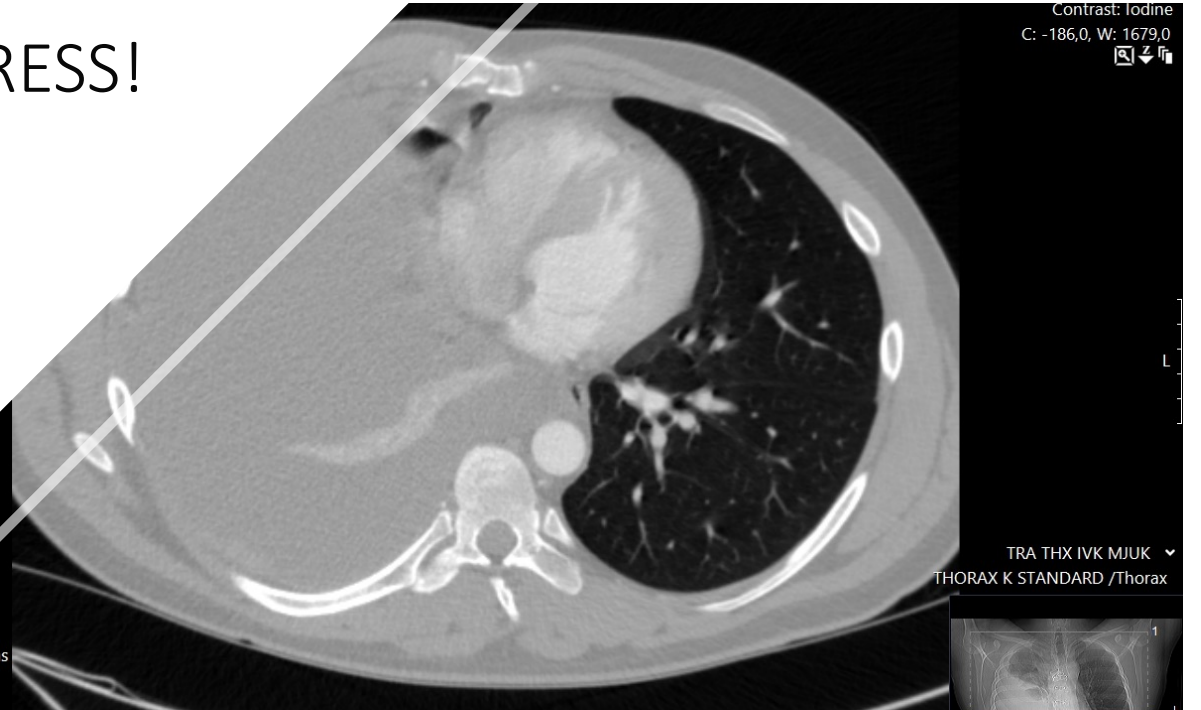


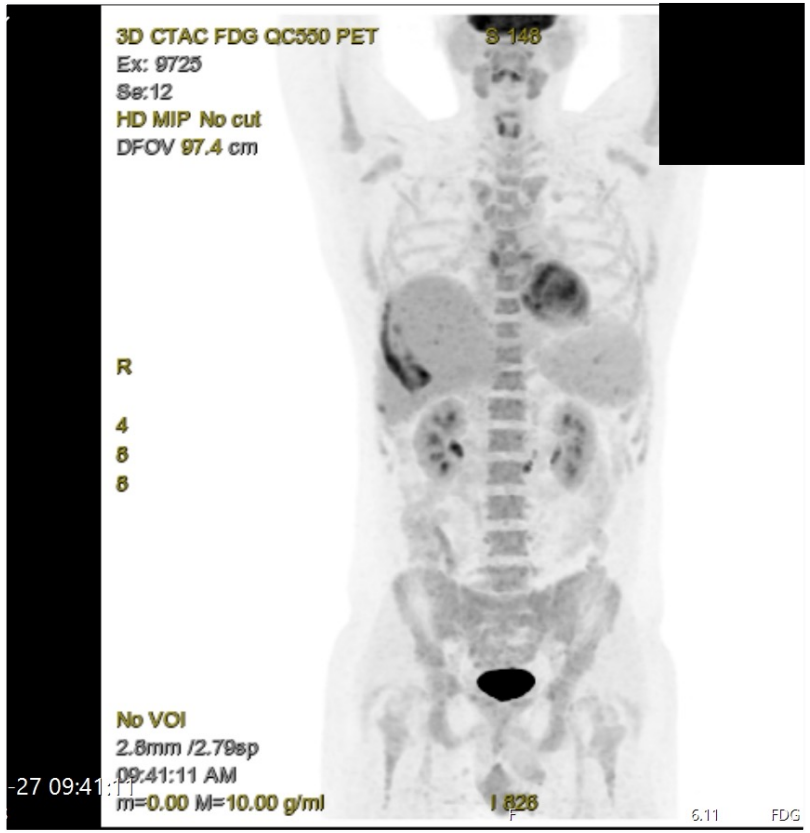


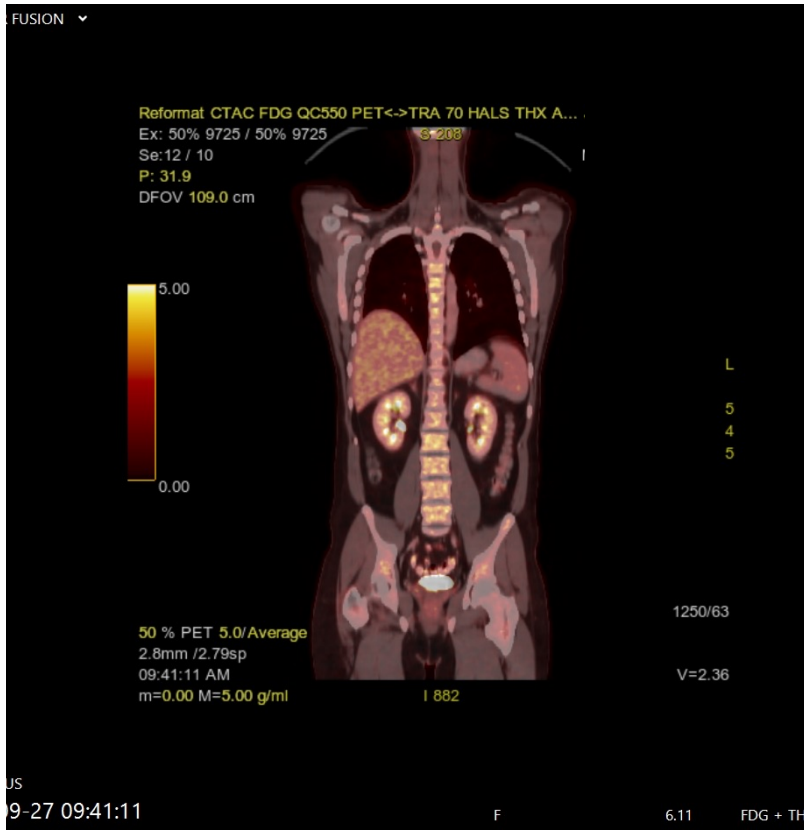


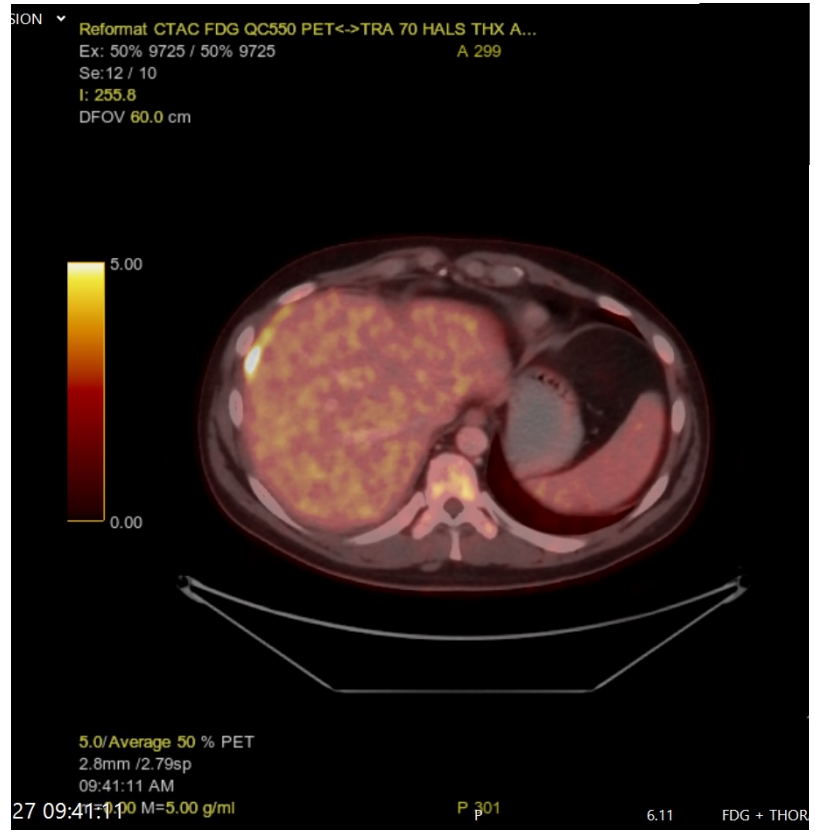
Jämfört med CT innan start
GOD REGRESS!





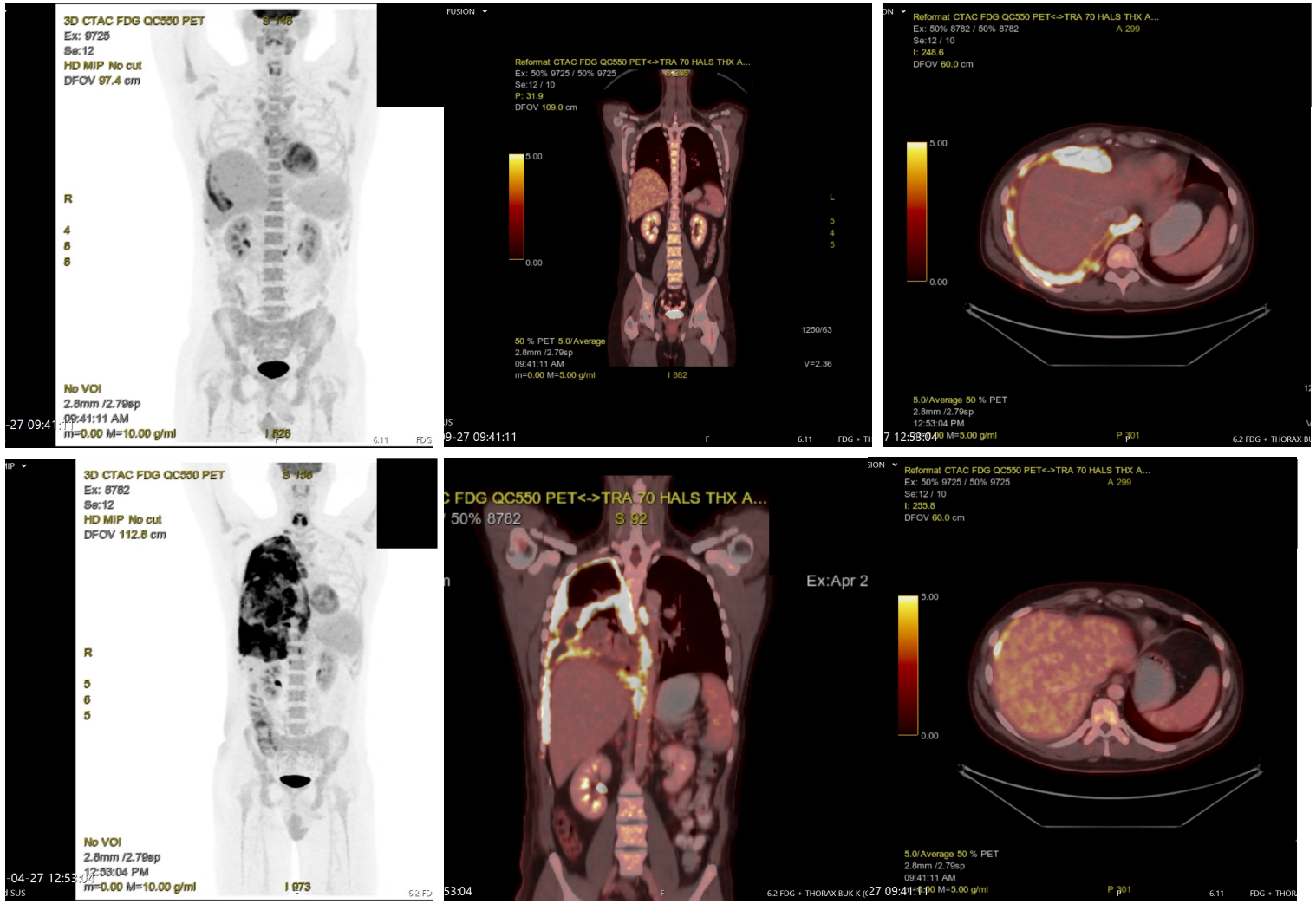




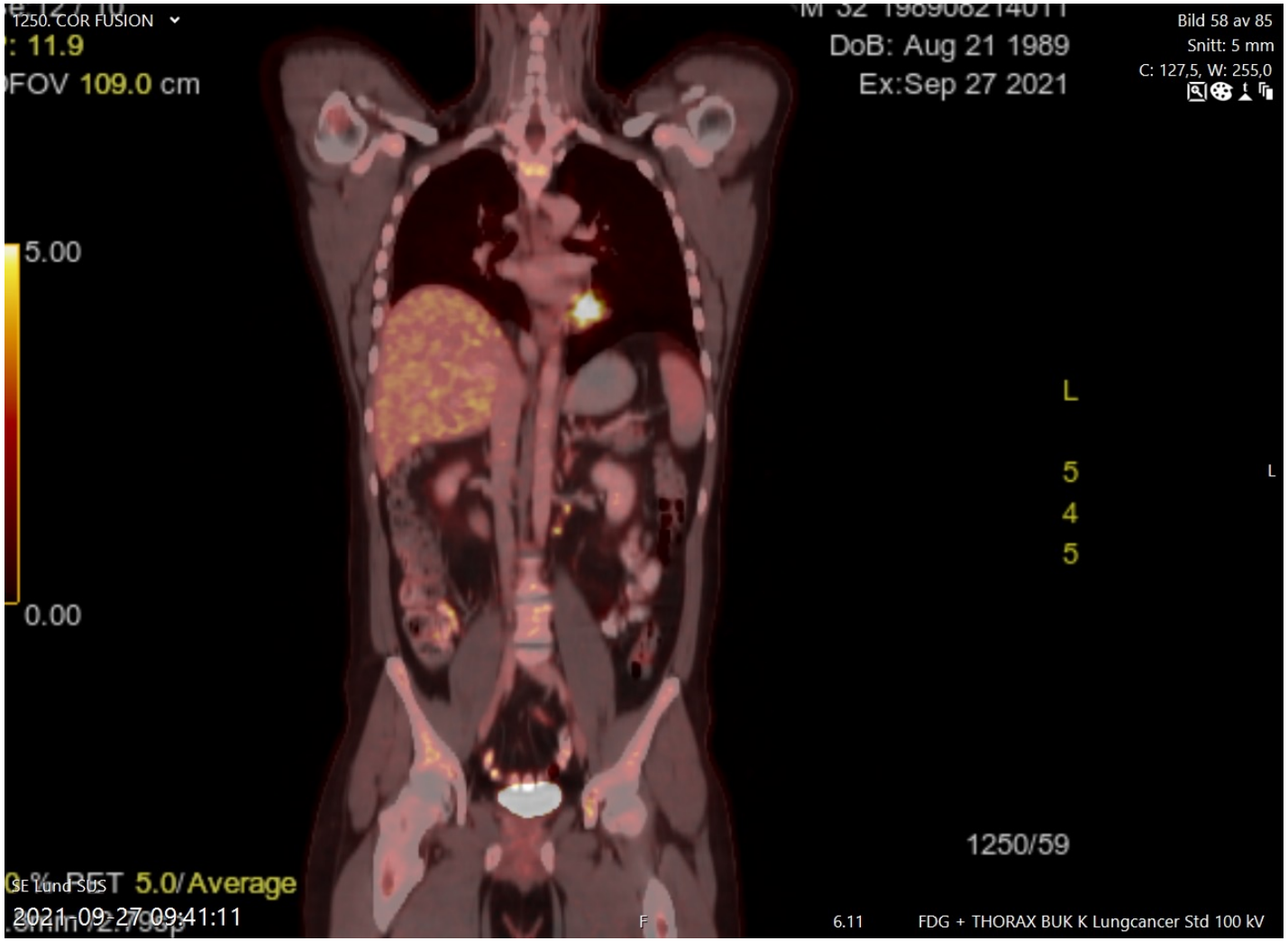


PET efter totalt 6 kurer!

Jämförelse med PET innan start



MEN!


1250. COR FUSION
: 11.9
FOV 109.0 cm
DoB: Aug 21 1989
Ex:Sep 27 2021
Bild 58 av 85
Snitt: 5 mm
C: 127,5, W: 255,0
5.00
0.00
L
5
4
5
L
1250/59
% PET 5.0/Average
SE Lund SUS
2021-09-27 09:41:11
F
6.11
FDG + THORAX BUK K Lungcancer Std 100 kV

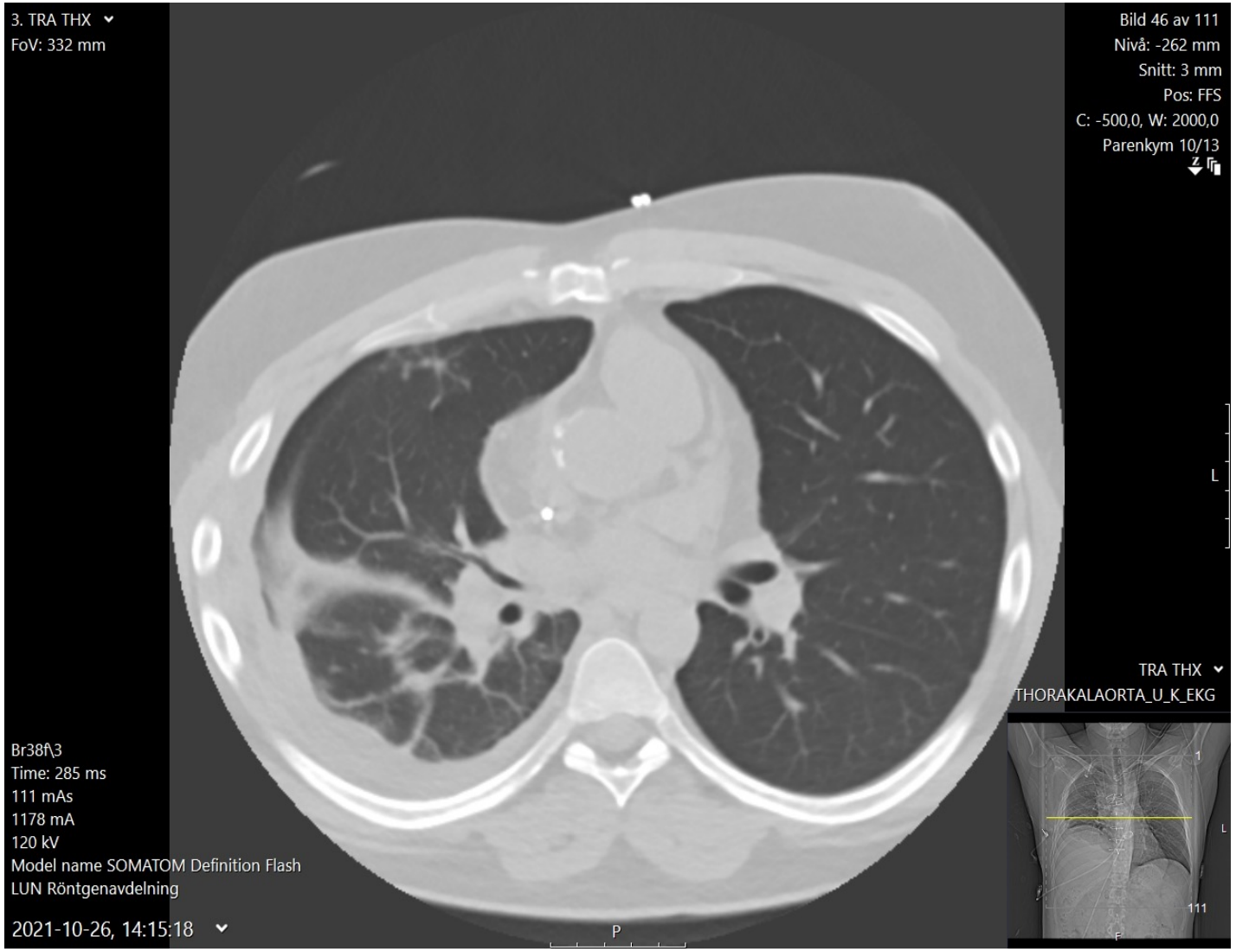
Remiss till thoraxkirurger i Köpenhamn!

- PET positiva retroperitoneala och subdiafragmala körtlar
- T3N1M1
- Ej kandidat för kirurgiskt ingrepp

Ny MDK

- **Beslut om underhålls behandling med Pemetrexed/Pembrolizumab**
- Fått 1 kur 2021-10-13
- Inlagd 25/10-2/11 pga feber & CRP Stegring’
- Fått ab iv, oklar inf!
- CT visade **progress!**

CT 2021-10-26


3. TRA THX
FoV: 332 mm
Bild 46 av 111
Nivå: -262 mm
Snitt: 3 mm
Pos: FFS
C: -500,0, W: 2000,0
Parenkym 10/13
L
TRA THX
THORAKALAORTA_U_K_EKG
Br38f\3
Time: 285 ms
111 mAs
1178 mA
120 kV
Model name SOMATOM Definition Flash
LUN Röntgenavdelning
2021-10-26, 14:15:18
P
1
L
111
F

Åb 8/11

- Trött, andfåd, takykard
- Inlagd 8/11
- Iv ab
- **CT**
- **Beslut om andra linje Nivi /Ipi**

Tack för uppmärksamhet!

Egyptians would wrap bodies in asbestos cloth to preserve them

Women working at an asbestos mattress factory in the early 1900's