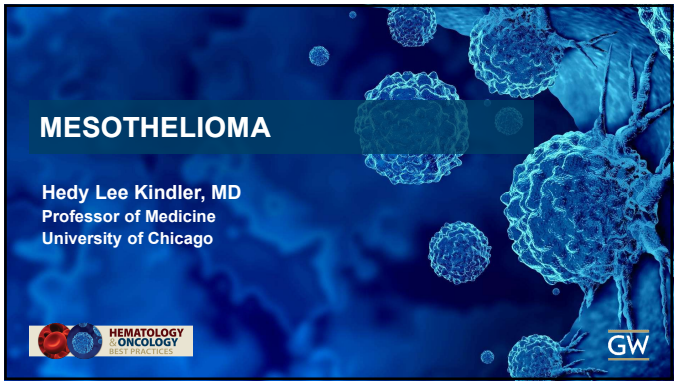
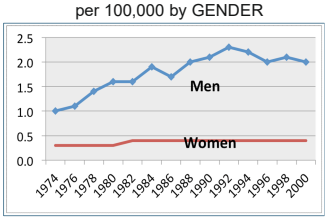


Epidemiology of Mesothelioma

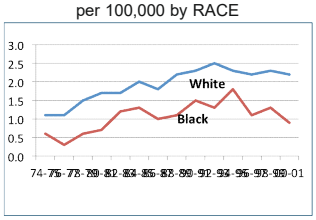
- Incidence:
  - 2,500-3,000 cases year in the US
  - 5,000 cases per year in Western Europe
  - An emerging problem in the developing world
- Onset 20 to 60 years following asbestos exposure
- Incidence has peaked:
  - US in 2000; Europe in 2018
- Male: female ratio 4:1
- In the US, a disease of the elderly
  - Median age is 74; 72% are > 65
- Less common in African-Americans

Mesothelioma Incidence by Gender and Race

Mesothelioma incidence per 100,000 by GENDER



Mesothelioma incidence per 100,000 by RACE



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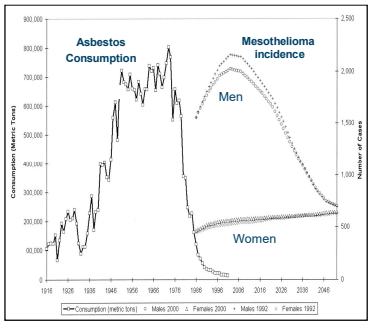
Etiology of Mesothelioma

- Asbestos (70%)
- Occupational exposure
- Para-occupational exposure
  - Occurs in homes with an occupationally exposed worker
- Environmental exposure
- Unknown (30%)

Relationship between asbestos consumption and mesothelioma incidence

There is a 20 to 50+ year latency following asbestos exposure



Asbestos, Gender, and Peritoneal Mesothelioma

- In men
  - Asbestos causes ~60% of peritoneal mesothelioma
- In women
  - The attributable risk is lower[1]
- Prolonged, heavy asbestos exposure is more likely to cause peritoneal mesothelioma
  - In asbestos miners and insulators, the highest proportion of peritoneal mesothelioma occur in those with the greatest cumulative exposure[2]

1. Spirtas, *Occup Environ Med* 1994; 2. Berry, *Br J Ca* 2012

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What is Asbestos?

- A general name for 6 types of naturally occurring minerals
- Key attributes:
  - High tensile strength, chemical/thermal stability, flexibility, low electrical conductivity, large surface area

Serpentine Asbestos:

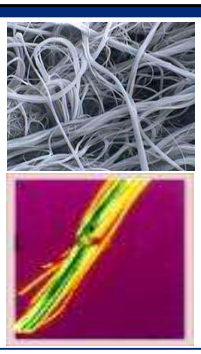
- Curly and pliable
  - Chrysotile

Amphibole Asbestos:

- Rod-like, less soluble in lung tissue
  - Actinolite, amosite, anthophyllite, crocidolite, tremolite

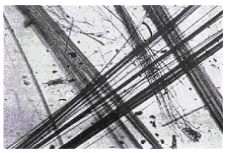
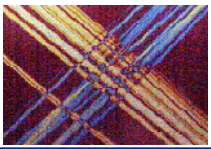
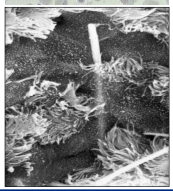
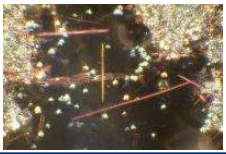
GW 7

Chrysotile: $(Mg)_6\ (OH)_8Si_4O_{10}\ (\pm Fe)$



GW 8

Crocidolite: $Na_2(Fe^{3+})_2(Fe^{2+})_3Si_8O_{22}(OH)_2\ (\pm\ Mg)$

GW 9

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Asbestos in History

Theophrastus, a student of Aristotle,
first described asbestos as:

"A substance resembling rotten wood that, when doused with oil, burns without being harmed"

On Stones, 300 B.C.E.

Asbestos: A Brief History

- Embalmed bodies of Egyptian pharaohs were wrapped in asbestos cloth
- Pliny the Elder observed, "asbestos quarry slaves die young"
- Persians burned bodies in asbestos cloth to preserve the ashes
- 1890's: Rise of asbestos as a product
- 1900's: First asbestos-related diseases
- 1930's: Johns Manville MDs document lung diseases in their workers
- 1960: Wagner observed a very high incidence of mesothelioma in South African asbestos workers
- 1964: Selikoff published study of asbestos workers with asbestosis, lung cancer and mesothelioma
- 1973: Peak consumption in US
- 2002: Last US mine closed

Asbestos in History

The causative relationship between
asbestos and malignant mesothelioma
was not recognized until 1960,
when an unusually high incidence
of the disease was noted in
South African asbestos workers

Wagner, *Br J Ind Med* 1960

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Occupational Asbestos Exposure

"Historical" asbestos occupations with ⇧ risk of MM
- Miners and millers
- Textile manufacturers
- Insulators
- Shipyard worker
- Construction
- "Secondary" or "bystander" occupations:
  - Carpenters, pipefitters, plumbers, electricians

Current: 1.3 million workers (OSHA estimate)
- Construction: abatement, demolition
- Janitors
- Brake and clutch repair (?)

In Place Asbestos Exposure

Products (consumers/hobbyists and workers)
- Brake work: brake pads
- Construction and maintenance: paints, vinyl floor tiles, sheeting, adhesives, pipes, gaskets
- Asbestos protective equipment: fire-proof clothing for firemen, gloves for ceramics, stage curtains
- Appliances: hair dryers, broilers, toasters, cappuccino machines

Building-related (home, work and school)
- Asbestos insulation, thermal pipes
- Schools and public buildings
  - EPA: ⅔ had damaged asbestos
  - Teachers rank high in occupations with MM cases

Building demolition/destruction
- WTC, Katrina

Asbestos and the World Trade Center

- Steel trusses supporting the Twin Towers were sprayed with hundreds of tons of asbestos-containing fire retardant
- In 1971, the New York City Council banned further use of asbestos-containing sprays
- 39 floors of WTC 1 had already been sprayed; many products containing asbestos were used

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300-400 tons of asbestos were released when the WTC collapsed

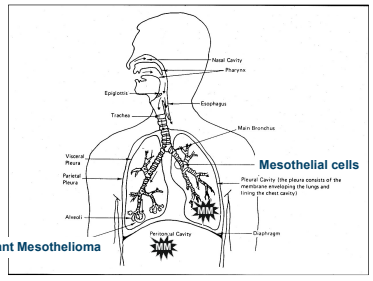
GW 16

Many WTC rescue workers had inadequate protection against asbestos

GW 17

How do we get from this:

Inhalation of asbestos fibers



MM = Malignant Mesothelioma

GW 18

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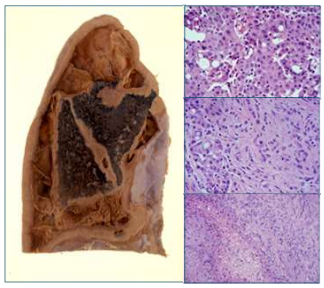
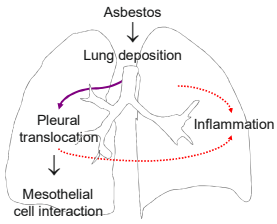
To this?



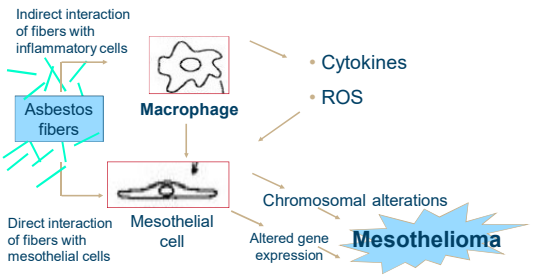
GW 19

After inhalation, asbestos fibers translocate to the pleural space



GW 20

Asbestos fibers cause persistent inflammation and cytokine production, and generate toxic oxygen and nitrogen radicals



GW 21

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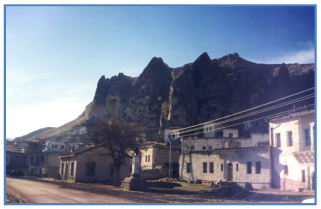
Are there any other causes of mesothelioma?

50% of the people in 3 villages in Cappadocia, in Central Anatolia, Turkey, die of mesothelioma

The cemetery in Karain

The Erionite Villages

Karain village (population ~ 600)



Tuzköy village (population ~ 1,400)

Like many other places in Cappodocia, these villages are characterized by ancient rock dwellings and caves dug into soft volcanic tuff

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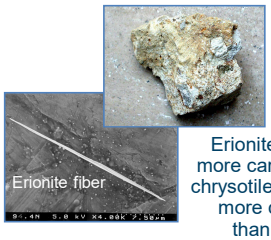
This was thought to be due to erionite in the houses. But nearby villages, built with stones from the same caves, had no mesotheliomas



Erionite is 300-800X more carcinogenic than chrysotile, and 100-500X more carcinogenic than crocidolite

GW 25

Mesothelioma cases are clustered in specific homes, called 'the houses of death'

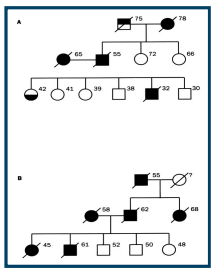
This is a house of the dead. Everyone died of mesothelioma

Next door, no one developed mesothelioma

GW 26

This suggested a genetic predisposition for mesothelioma

Analysis of a 6-generation pedigree of 526 individuals demonstrated autosomal dominant transmission of mesothelioma in these families



Hammady i-Roushdy, *Lancet* 2001

GW 27

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The Search for a Mesothelioma Genetic Susceptibility Syndrome

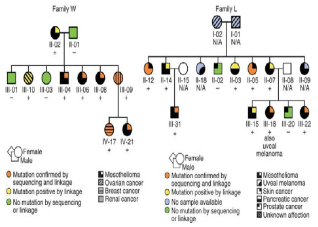
- Only a small % of people heavily exposed to asbestos will develop mesothelioma (~5%)
- Yet mesothelioma clusters in some families
  - Is there a genetic predisposing factor?
- 2 US families studied:
  - No occupational asbestos exposure
  - Modest amounts of asbestos in their homes
  - Wisconsin family: 8 cancers, 5 MM
  - Louisiana family: 13 cancers, 7 MM

Testa, *Nature Genetics* 2011

GW 28

Mesothelioma and the BAP1 Cancer Syndrome

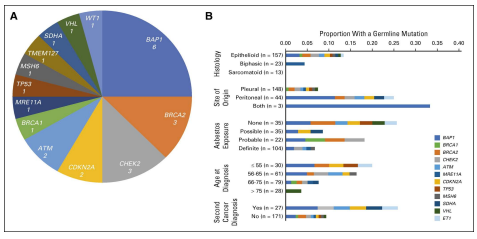
- These families have germline mutations in *BAP1*
  - BRCA1-associated protein
    - A tumor suppressor gene on 3p21
  - Predisposes to mesothelioma, uveal melanoma, cutaneous melanocytic tumors, RCC, and cholangiocarcinoma[1]
  - This is a gene-environment interaction
    - Mesothelioma is thought to predominate with asbestos exposure
- Somatic mutations of *BAP1*
  - Occur in 20-60% of MM[2]



1. Testa, *Nat Genetics* 2011 2. Bott, *Nat Genetics* 2011

GW 29

12% of mesothelioma patients carry a germline mutation in a known cancer susceptibility gene
BAP1 accounts for only 25% of the mutations found



Panou, *JCO* 2018

GW 30

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Frequency of Germline Mutations in Cancer Susceptibility Genes in Mesothelioma

Specific clinical characteristics predict the presence of germline mutations:

- Peritoneal MM (25% had germline mutations)
- Minimal asbestos exposure
- Young age
- A 2nd cancer diagnosis

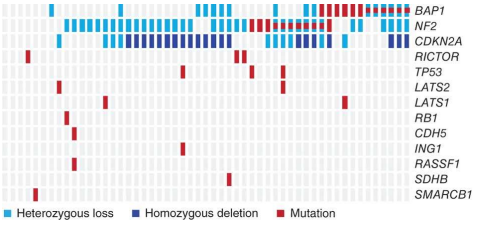
These data:

- Support clinical germline genetic testing for MM patients
- Provide a rationale for additional investigation of the homologous recombination pathway in MM
  - PARP inhibitors are being evaluated in these patients

Panou, *JCO* 2018

31

The most common somatic genetic alterations in MM are tumor suppressors: BAP1, NF2, and CDKN2A



Bott, *Nature Genetics*, 2011

32

Does the SV-40 virus cause mesothelioma?

- DNA tumor virus
- Induces MM when injected into hamsters
- Mesothelial cells are very susceptible to SV40-mediated transformation[1]
- 60% of MM have SV-40-like DNA sequences
- 100% of MM patient sera have anti-Tag Ab[2]
  - Due to lab contamination of a related virus?
- 1955-63: polio vaccines made with SV-40 contaminated monkey kidney cells
  - Did SV-40 contamination cause an ↑ in MM?
  - Institute of Medicine: this cannot be determined

1. Bochetta, *PNAS* 2000 2. Carbone, *Oncogene* 1994

33

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What is the relationship between cigarette smoking and mesothelioma?

GW 34

SMOKING DOES NOT CAUSE MESOTHELIOMA!

- Asbestos and smoking are synergistic for lung cancer, they are not synergistic for mesothelioma
- There is one exception, however…

GW 35

"What is 'Micronite'? It's a pure, dust-free, completely harmless material that is so safe, so effective, it actually is used to help filter the air in hospital operating rooms."
Kent advertisement

GW 36

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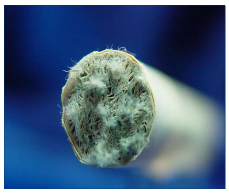
Kent Micronite Cigarette Filters

- From 1952-56, Kent sold 11.7 billion cigarettes with "micronite" crocidolite filters
- 10 mg crocidolite per filter
- 80 billion asbestos fibers per filter
- In 1 year, a person smoking 1 ppd would inhale >131 million crocidolite structures longer than 5 μm



Longo, *Cancer Research* 1995

GW 37

Uncommon Causes of Mesothelioma

- Previous Radiotherapy
  - For Hodgkin disease, breast cancer, seminoma, etc.
- Collapsotherapy
  - The induction of artificial pneumothorax or pneumoperitoneum for treatment of tuberculosis

GW 38

Mesothelioma Disease Sites

Pleural	~80%
Peritoneal	~20%
Pericardial	Rare
Tunica vaginalis	Rare

GW 39

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Clinical Presentation

Pleural
- chest pain
- dyspnea
- cough
- weight loss
- fever
- night sweats

Peritoneal
- increased abdominal girth
- abdominal pain
- constipation
- anorexia
- umbilical hernia

Clinical Presentation

Pericardial
- death (70% diagnosed post-mortem)
- dyspnea
- fever
- night sweats
- CHF
- constructive pericarditis
- pericardial effusion +/- tamponade
- acute MI

Tunica vaginalis
- unilateral testicular mass

Prognostic Factors

- Stage
- Pathologic subtype
- Chest pain
- Duration of symptoms
- Age
- Gender
- Performance status
- Weight loss
- Platelet count
- WBC
- Hemoglobin
- LDH

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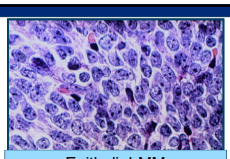
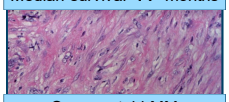
Pathologic subtype: The most important prognostic factor in mesothelioma

- Epithelial
  - 50-70% of MM
  - Best prognosis
- Sarcomatoid
  - 7-20% of MM
  - Worst prognosis
- Biphasic/mixed
  - 20-35% of MM
  - Intermediate prognosis



Epithelial MM
Median survival 17 months



Sarcomatoid MM
Median survival 6 months

43

Diagnosis is Challenging

Diagnosis of mesothelioma requires:

- An experienced pathologist
- Panel of at least 2 + and 2 - IHC stains
  - Specific panel depends on differential dx
- Common positive markers:
  - Calretinin, D2-40, CK 5/6, WT-1
- Common negative markers:
  - MOC-31, Ber-EP4, B72.3, CEA, PAX8, TTF-1, CDX-2

Cytology is usually not helpful

Husain, *Arch Pathol Lab Med* 2013

44

Sensitivity of Diagnostic Methods

	% Positive results
Fluid cytology	26%
Pleural needle biopsy	21%
Fluid cytology plus pleural needle biopsy	39%
Thoracoscopy	98%

Boutin, Cancer 1993

45

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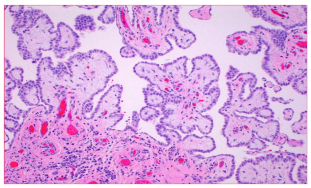
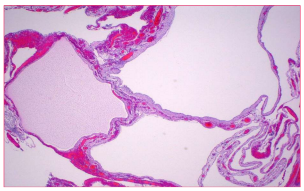
Why do we call it "malignant" mesothelioma?

- Because there are several subtypes of benign (or borderline) mesothelioma

Well-differentiated papillary mesothelioma



Benign multicystic mesothelioma



2 Pathologic Subtypes with Borderline Malignant Potential

Well-differentiated papillary mesothelioma (WDPM)

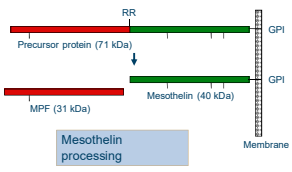
- Commonly presents as an asymptomatic incidental finding
- Often cured with resection alone

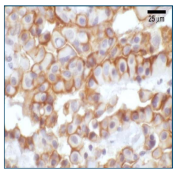
Benign multicystic mesothelioma (BMM)

- Consists of large grape-like cystic clusters
- Presents with an abdominal mass and abdominal pain, often in reproductive age women with a history of endometriosis

Biomarkers: Mesothelin

- A glycoprotein expressed on normal mesothelial cells of the pleura, pericardium and peritoneum
- Serum mesothelin-related protein (SMRP), the circulating product of mesothelin, is commercially available as MESOMARK





Hassan, *Clin Cancer Res*, 2004

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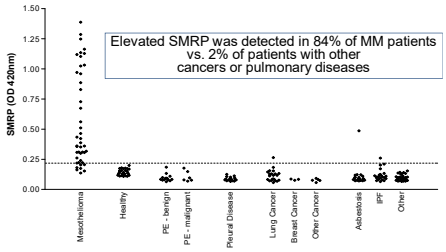
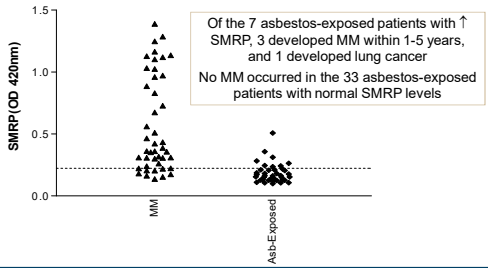
SMRP is elevated in mesothelioma, but not in other pulmonary diseases



Robinson, *Lancet* 2003

SMRP is elevated in mesothelioma, and in asbestos-exposed individuals who subsequently develop mesothelioma



Robinson, *Lancet* 2003

Potential Uses of SMRP

- Screening asbestos-exposed individuals
  - SMRP is elevated in asbestos-exposed individuals who subsequently develop MM
- Diagnosis
  - SMRP is ↑ in >60% of MM patients at presentation
- Determining prognosis
  - High SMRP levels are a poor prognostic factor
- Monitoring recurrence and treatment response
  - SMRP decreases following surgical resection and rises as the disease progresses
- Key Limitation
  - SMRP is only useful in epithelial MM

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Other Biomarkers for Mesothelioma

Both are glycoproteins that mediate cell-matrix interactions

Osteopontin

- ↑ in epithelial and sarcomatoid mesothelioma, as well as in other cancers, so less useful in discriminating mesothelioma from other diseases

Fibulin-3

- Significantly ↑ in plasma and effusions in mesothelioma patients compared with asbestos-exposed pts without mesothelioma
- Levels may correlate with mesothelioma prognosis
- May be useful in early detection

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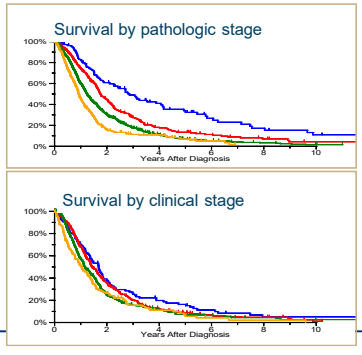
Staging for Mesothelioma is Problematic

- There are numerous staging systems for pleural MM
  - All are surgically based
  - The IMIG/IASLC staging system is most widely used
- Some staging systems may predict survival in the resected patient
  - Most are imprecise in non-surgical patients
- Chemotherapy trials usually include patients with a range of stages, and prognoses

53



IMIG staging:

Much better discrimination of survival by pathologic than clinical stage

This staging system is under revision

54

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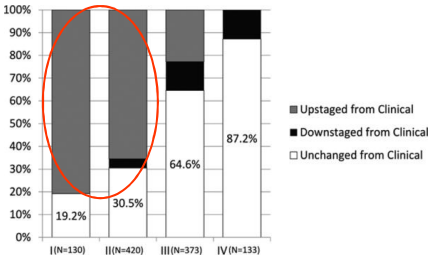
Most mesothelioma patients with an early clinical stage are upstaged at surgery

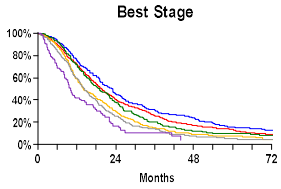


New MPM Stage Groupings

	N0		N1/2 (new N1)		N3 (new N2)	
	v7	**v8**	**v7**	**v8**	**v7**	**v8**
T1	I (A,B)	**IA**	III	**II**	IV	**IIIB**
T2	II	**IB**	III	**II**	IV	**IIIB**
T3	II	**IB**	III	**IIIA**	IV	**IIIB**
T4	IV	**IIIB**	IV	**IIIB**	IV	**IIIB**
M1	IV	**IV**	IV	**IV**	IV	**IV**

Major changes:

- T1a, T1b consolidated into T1
- All ipsilateral LN now N1
- Contralateral, supraclavicular LN now N2



Rusch, *JTO* 2016

Mesothelioma is a difficult disease to measure reproducibly

- Bi-dimensional measurement is not usually feasible
- Uni-dimensional measurements of the pleural rind should be obtained at multiple areas in multiple levels on the thoracic CT scan

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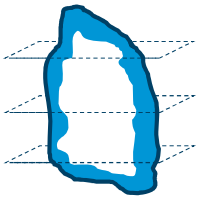
Measuring Mesothelioma: Modified RECIST

Select 3 CT sections per scan, at least 2 cm apart

2 thickness measurements per section



Byrne and Nowak, *Ann Oncol* 2004

58

Lesion Measurement in Mesothelioma

59

The role of surgery for mesothelioma is very controversial

- Surgery is rarely performed in some countries
  - In most of the US it is more widely accepted
- The goal is to remove all visible tumor
  - Surgery alone is not curative
- The optimal type of surgery is equally controversial
  - The decision is often driven more by surgeon bias than by data

Flores, *J Thor Cardiovasc Surg* 2008

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The Purpose of Surgery for Pleural Mesothelioma

- **A maximal cytoreduction,** which is able to remove the disease down to levels which, at the end of the operation, hopefully leaves only microscopic residual disease and only minimal, or preferably no macroscopic disease

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Surgical Options for Pleural Mesothelioma

Extrapleural pneumonectomy (EPP)	En bloc resection of parietal, visceral pleura, ipsilateral lung, pericardium, diaphragm
Extended pleurectomy/decortication (E-P/D)	Parietal and visceral pleurectomy to remove all gross tumor, with resection of diaphragm and/or pericardium, the lung remains in place
Pleurectomy/decortication (P/D)	Parietal and visceral pleurectomy to remove all gross tumor, without diaphragm or pericardial resection, the lung remains in place
Partial pleurectomy (palliative)	Partial removal of parietal and/or visceral pleura for diagnosis or palliation, leaves gross tumor behind, the lung remains in place

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Retrospective US analysis of 663 MM patients: No statistical difference in survival by procedure at any individual tumor stage

	EPP	P/D
Operative mortality	7%	4%
Local recurrence	33%	**65%**
Distant recurrence	**66%**	35%
Overall Survival: 14 months 5-year survival: 12%		
Stage I	38 months	
Stage II	19 months	
Stage III	11 months	
Stage IV	7 months	

Flores, *J Thor Cardiovasc Surg* 2008

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Requirements for Surgical Resection

- Able to functionally tolerate maximal cytoreduction
  - PFTs must predict adequate postop reserve
  - Cardiology workup must include assessment of ventricular function
- No disease outside ipsilateral hemithorax by "best practice" staging efforts
  - PET-CT should be performed prior to surgery to rule out extra-thoracic disease
  - Institutions vary in their staging approach, including mediastinoscopy, laparoscopy

GW 64

Prognostic Indicators for Surgical Patients

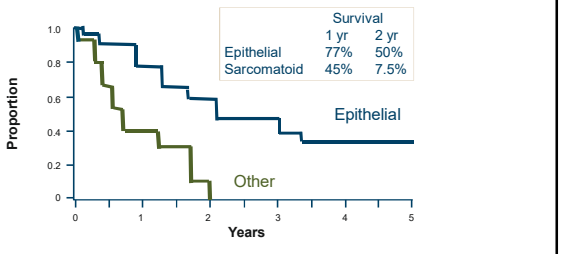
Cox regression model of survival (n = 2,107)

Variable	Hazard Ratio	p
II vs. I	1.16	0.1153
III vs. I	1.27	<0.0001
III vs. II	1.27	0.0002
IV vs. I	**1.86**	**<0.0001**
IV vs. III	1.26	0.0008
Other histology vs. epithelial	**1.70**	**<0.0001**
Male vs. Female	1.28	0.0002
Age, years 50-45 vs. <50	0.23	0.0058
65+ vs. <50	1.31	0.0006
65+ vs. 50-64	1.07	0.2500
Palliative vs. curative surgery	**1.71**	**<0.0001**

Rusch, *JTO* 2012

GW 65

Survival by Histology: Epithelial vs. Other



GW 66

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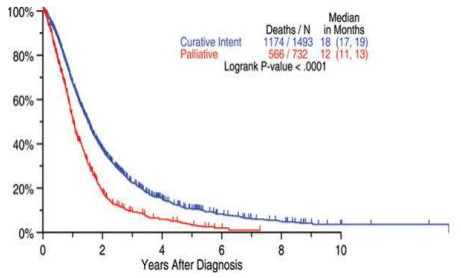
Survival by Surgical Intent: Curative vs. Palliative



Prognostic Indicators for Surgical Patients

Covariate	Hazard Ratio	95%CI	*p*
Tumor volume >500 cm^3	2.02	1.18-3.47	0.0109
Anemia	1.99	1.19-3.33	0.0089
Adjuvant chemotherapy or radiotherapy	0.30	0.18-0.52	<0.0001

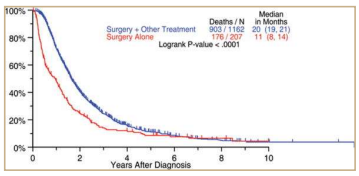
Gill, *AJR* 2012

Rationale for Multimodality Therapy in MM

- Maximal debulking surgery for MM rarely achieves a complete resection
- Retrospective IASLC database: longer survival with surgery + another treatment modality

Surgery alone:
- 11 months

Surgery + another treatment modality:
- 20 months



No adequately powered randomized trials have been completed to evaluate this approach

Rusch, *JTO* 2012

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Prospective multimodality trials in pleural mesothelioma

N	Chemotherapy	Surgery	PFS (months)	Median survival (months)
19	Neo-adjuvant Gemcitabine/Cisplatin x 3	EPP	16.5	23
21	Neo-adjuvant Gemctabine/Cisplatin x 4	EPP	NR	19
61	Neo-adjuvant Gemcitabine/Cisplatin x 3	EPP	13.5	19.8
21	Neo-adjuvant Gemcitabine/Carboplatin x 3-4	EPP	16.3	25.5
77	Neo-adjuvant Pemetrexed/Cisplatin x 4	EPP	10.1	16.8
58	Neo-adjuvant Pemetrexed/Cisplatin x 3	EPP	13.9	18.4
35	Adjuvant Pemetrexed/Cisplatin x 3	P/D	15.8	30

The Roles of Radiation for Mesothelioma

Curative	Limited by tumor volume and normal tissue toxicity
Palliative	40-50 Gy effective for painful masses
Prophylactic	21 Gy in 3 fractions may prevent seeding from biopsy tracks (controversial)
Adjuvant after EPP	Hemi-thoracic RT decreases local recurrence
Adjuvant after P/D	Not generally feasible b/c pulmonary toxicity IMRT is being evaluated in clinical trials
Neoadjuvant before EPP	Pre-operative hemi-thoracic RT is highly experimental

Peritoneal Mesothelioma Outcomes: Past and Present

Historical series: Untreated
- Median survival ~6 months

1980s-90s: Systemic chemotherapy or palliative surgery
- Median survival <1 year

Contemporary series: Aggressive locoregional treatment
- Median survival approaches 5 years

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Rationale for aggressive loco-regional treatment of peritoneal mesothelioma

- Natural history
  - Remains confined to abdomino-pelvic cavity
  - Little invasion of underlying organs
  - No metastatic spread until advanced
- Aggressive loco-regional treatment is a preferred strategy
  - No level 1 evidence
  - Appears to improve survival over historical controls

GW 73

Locoregional Treatment for Peritoneal Mesothelioma

- Cytoreductive surgery (CRS)
  - Removes gross peritoneal disease
- Hyperthermic intraperitoneal chemotherapy (HIPEC)
  - Delivers high drug concentrations intra-operatively to microscopic residual tumor
  - Cisplatin, mitomycin, carboplatin, doxorubicin are most commonly used
- Additional modalities may include
  - Early post-operative intraperitoneal chemotx (EPIC)
  - (Whole abdominal radiation)
  - Adjuvant or neo-adjuvant systemic chemotherapy

GW 74

Most (~90%) of peritoneal mesothelioma patients obtain durable palliation of malignant ascites with CRS + HIPEC

Before CRS + HIPEC

18 months after CRS+ HIPEC

GW 75

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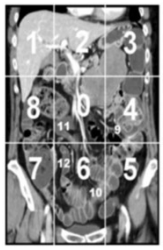
Determining extent of disease pre-operatively: The peritoneal cancer index (PCI)

PCI divides:
- Abdomen into a grid of 9 squares
- Small bowel mesentery into 4 quadrants

Tumor in each area is scored:
- Scale 0-3 (none to extensive)
- Up to a score of 39

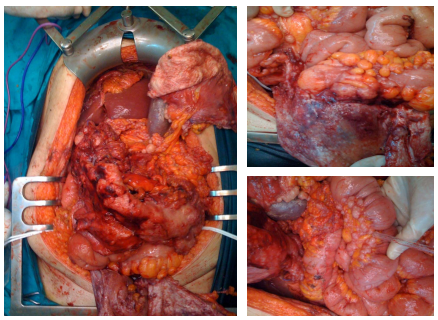
PCI: a key prognostic indicator

Pre-op CT findings that predict adequate cytoreduction:
- No epigastric mass > 5 cm
- No loss of normal architecture of small bowel and its mesentery



REGIONS
0 = Central
1 = Right upper
2 = Epigastrium
3 = Left upper
4 = Left flank
5 = Left lower
6 = Pelvis
7 = Right lower
8 = Right flank

9 = Upper jejunum
10 = Lower jejunum
11 = Upper ileum
12 = Lower ileum



Courtesy of Marcello Deraco, Milan NCI

Determining the extent of disease post-operatively: Completeness of cytoreduction (CC) score

Quantifies residual disease after resection
based on the size of the remaining tumor nodules

CC score	Size of remaining tumor nodules
CC-0	None
CC-1	< 2.5 mm
CC-2	2.5 mm- 2.5 cm
CC-3	> 2.5 cm, or a confluence of tumor nodules at any site

The CC score is a key prognostic indicator for survival

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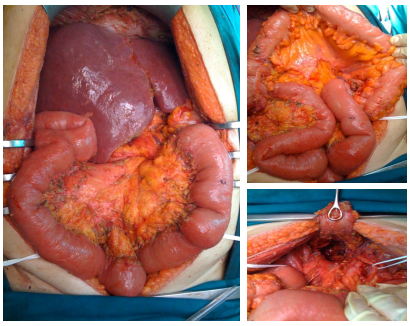

Courtesy of Marcello Deraco, Milan NCI

Multivariate Analysis of Prognostic Factors in Peritoneal Mesothelioma

Covariate	P
Gender	0.003
Pathologic subtype	< 0.001
Completeness of cytoreduction	< 0.001

Proposed TNM Staging System Derived from Multi-institutional Registry

7 prognostic variables identified on univariate analysis from registry		
Age ≤ 50	Intrinsic	Not considered for preoperative staging
Female gender		
Epithelial subtype		
CC 0/1	Post-operative variable	
PCI	T	Useful for preoperative staging
No LN metastases	N	
No extra-abdominal metastases*	M	

*defined as penetrating the diaphragm or invading an abdominal wall scar

T stage	PCI
T1	1-10
T2	11-20
T3	21-30
T4	31-39
N stage	0/1
M stage	0/1

Yan, *Cancer* 2011

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Proposed TNM System Stratifies Survival by Stage

Stage	TNM	Median survival (months)	1-year survival	5-year survival
I	T1 N0 M0	Not reached	94%	87%
II	T2-3 N0 M0	67	87%	53%
III	T4 or N1 or M1	26	66%	29%

Yan, *Cancer* 2011

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Outcomes of CRS + HIPEC in Peritoneal MM

Center	Pts	Survival				Operative mortality (%)	Major morbidity (%)
		Overall (mo)	1-yr (%)	3-yr (%)	5-yr (%)		
Multi-institutional[1]	401	53	81	60	47	2.2	31
Milan[2]	83	44	78	56	50	2.4	28
DC[3]	62	79	84	58	50	2.9	27
Bethesda[4]	49	92	86	59	59	0	25

1. Yan 2009 2. Baratti 2010 3. Yan 2007 4. Feldman 2003

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International Peritoneal Mesothelioma Surgical Registry

# of patients	405
Median age	50
Male	56%
Epithelial	79%
Mean PCI	20
CC 0/1	23%/21%
Mean surgical duration	8 hours
Median LOS	22 days
Perioperative complications	46% (grade 3 31%)
Perioperative mortality	2%
Median survival (range)	53 months (1-235)
Median survival women	**119 months**
Median survival men	**36 months**
3-year survival	60%
5-year survival	47%

Yan, *JCO* 2009

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Key Milestones in the Development of Systemic Therapy for Mesothelioma

Year	Trial	Phase	Drugs
2003	EMPHACIS*	3	Cisplatin +/- **Pemetrexed**
2016	MAPS	3	Pemetrexed/cisplatin +/- **Bevacizumab**
2020	RAMES	2	Gemcitabine +/- **Ramucirumab**
2020	Checkmate 743*	3	**Ipilimumab/nivolumab** vs. Pemetrexed/platinum
2021	CONFIRM	3	**Nivolumab** vs. placebo
2021	NVALT19	2	Switch maintenance **gemcitabine** vs. BSC
2021	VIM	2	Oral **vinorelbine** vs. BSC

*Trial led to an FDA approval

The five positive randomized trials in the past year have transformed the treatment paradigm and will affect the design of all future mesothelioma studies

Pemetrexed + Cisplatin
A long-standing benchmark regimen for mesothelioma

456 patients

RANDOMIZE

Pemetrexed 500 mg/m^2
Cisplatin 75 mg/m^2 Q 21D

Primary endpoint: OS (HR 0.67)

Placebo
Cisplatin 75 mg/m^2 Q 21D

For many years, pemetrexed was the only FDA-approved drug for MM

Vogelzang, *JCO* 2003

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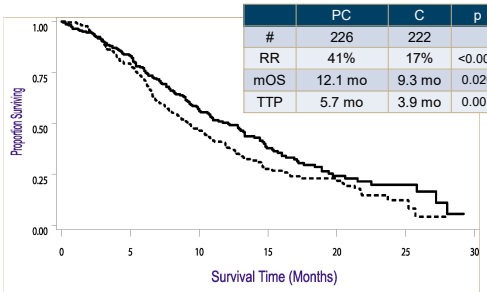
Pemetrexed + Cisplatin vs. Cisplatin



	PC	C	p
#	226	222	
RR	41%	17%	<0.001
mOS	12.1 mo	9.3 mo	0.020
TTP	5.7 mo	3.9 mo	0.001

Vogelzang, *JCO* 2003

Cisplatin or Carboplatin?

Cisplatin is the regulatory standard

Carboplatin (AUC 5) + Pemetrexed:

- Commonly used in older patients
- No randomized trials compare these regimens in MM
  - Non-randomized data from the Extended Access Database and single-arm phase II trials demonstrate that cis- and carboplatin have similar activity

	Pem Cis	Pem Carbo
#	843	861
RR	26%	22%
DCR	78%	76%
TTP	7.0 mo	6.9 mo
1-yr OS	63%	64%
Gr ¾ neutropenia	24%	36%

CALGB 30901: There is no role for maintenance pemetrexed in MM

63 pts
Pemetrexed
+
Cisplatin or Carboplatin
x 4-6 cycles

SD, PR or CR

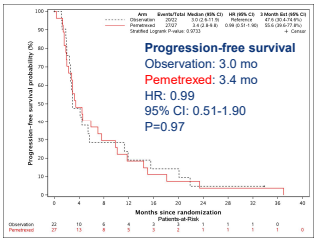
RANDOMIZE

Pemetrexed until progression

Stratification:
- Cisplatin vs. carboplatin
- Epithelial vs. other
- # cycles

Observation until progression

Primary endpoint: PFS



Dudek, *Clin Lung Ca* 2020

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NVALT 19 Randomized phase 2 trial: There may be a role for switch maintenance gemcitabine in mesothelioma

130 pts
Pemetrexed + Platinum ≥ 4 cycles
No disease progression

RANDOMIZE

Gemcitabine until progression

Stratification:
- Response to 1st-line treatment
- Histology

Best supportive care until progression

Primary endpoint: PFS

	Gem N=65	BSC N=65
PFS	6.2 months	3.2 months
	HR 0.48 95% CI 0.33-0.71; P=0.0002	
OS	13.4 months	16.4 months
	HR 0.90 95% CI 0.6-1.34; P=0.6	

De Gooijer, *Lancet Resp Med*, 2021

GW 91

The first positive randomized trial since pemetrexed was approved

MAPS: Open-label, randomized phase II/III trial of pemetrexed/cisplatin +/- bevacizumab

448 pts
Pleural MM
PS: 0-2
Chemo-naive
Age < 75

Pemetrexed Cisplatin Bevacizumab → Bevacizumab

x 6 cycles

Pemetrexed Cisplatin → Surveillance

Primary endpoints:
Phase II: 6 mo PFS
Phase III: OS

CT q 3 cycles—modified RECIST for MM

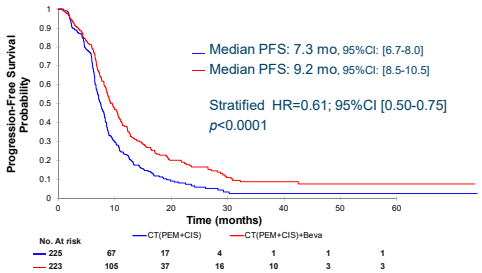
Stratification:
- Center
- Histology (epithelioid vs. non-epithelioid)
- PS (0-1 vs. 2)
- Smoking status

Statistics
Ph II: >25/50 non-PD at 6 mo to proceed to Ph III
Ph III: ↑median OS 13 to 17.3 mo, 3 yr OS 14.7 to 23.6%

Zalcman, *Lancet* 2016

GW 92

MAPS: Progression-free Survival



Zalcman, *Lancet* 2016

GW 93

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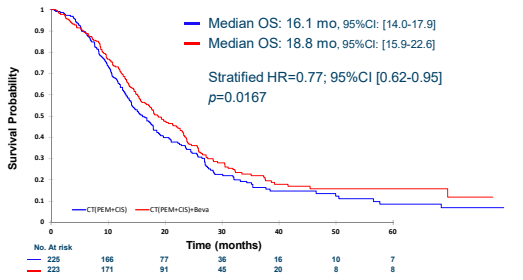
MAPS: Overall Survival



Zalcman, *Lancet* 2016

94

MAPS: Results

	PC (N=225)	PCB (N=223)	HR
Response	Not reported		
PFS (mo)	7.3	9.2	HR 0.61
OS (mo)	16.1	18.8	HR 0.77
Grade ¾ toxicity	62%	71%	
Treatment discontinuation due to toxicity	6%	24%	P< 0.0001
QoL	No difference		

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The MAPS Trial in Context

The addition of bevacizumab to pemetrexed + cisplatin:

- Significantly improves PFS: 7.3 vs. 9.2 months, HR 0.61, p<0.0001
- Significantly improves OS : 16.1 vs. 18.8 months HR 0.77, p=0.0167
- Yields an expected, manageable increase in toxicity
- Does not produce a detrimental effect on QOL
- Response: data not provided

OS in the pem/cis control arm of MAPS was 4 months longer than in the pivotal Vogelzang trial (16.1 vs. 12.1 months)

- Likely reflects patient selection for bevacizumab and the impact of subsequent pemetrexed/platinum retreatment
- Bevacizumab is not FDA-approved for MM

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On October 2, 2020, the FDA approved the combination of nivolumab plus ipilimumab as first-line treatment for patients with unresectable malignant pleural mesothelioma

This was the first new drug approval for mesothelioma in seventeen years!

GW 97

The CheckMate 743 trial has transformed first-line treatment of mesothelioma

N= 603

Key Eligibility criteria
- Unresectable pleural MM
- No prior systemic therapy
- PS 0-1

Stratification:
- Histology (Epithelioid vs. non-epithelioid)
- Gender

R A N D O M I Z E

Nivolumab
3 mg/kg Q 2 weeks
Ipilimumab
1 mg/kg Q 6 wks
x 2 years

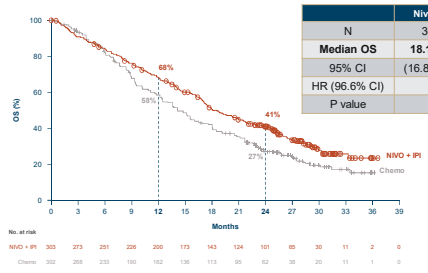
Pemetrexed +
Cisplatin or Carboplatin x 6 cycles

Primary endpoint: Overall survival
Secondary endpoints:
ORR, DCR, and PFS by BICR
PD-L1 expression as a predictive biomarker

Baas, *Lancet* 2021

GW 98

CheckMate 743: Overall Survival



	Nivo-Ipi	Chemo
N	303	302
Median OS	**18.1 mo**	**14.1 mo**
95% CI	(16.8-21.4)	(12.4-16.2)
HR (96.6% CI)	**0.74** (0.60-0.91)	
P value	0.0020	

GW 99

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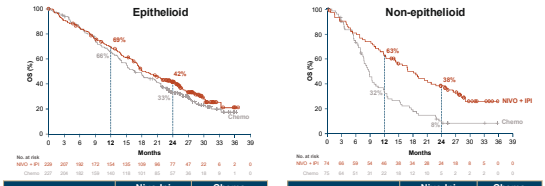
CheckMate 743
Overall Survival by Histology

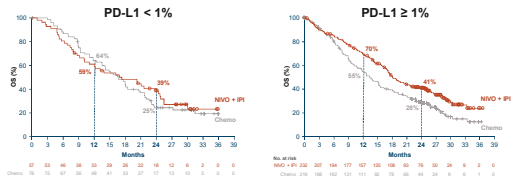


	Nivo-Ipi	Chemo
N	229	227
Median OS (mo)	**18.7**	**16.5**
(95% CI)	(16.9-22.0)	(14.9-20.5)
HR (95% CI)	**0.86** (0.69-1.08)	

	Nivo-Ipi	Chemo
N	74	75
Median OS (mo)	**18.1**	**8.8**
(95% CI)	(12.2-22.8)	(7.4-10.2)
HR (95% CI)	**0.46** (0.31-0.68)	

100

CheckMate 743
Overall Survival by PD-L1 Expression



	Nivo-Ipi	Chemo
N	57	78
Median OS (mo)	**17.3**	**16.5**
(95% CI)	(10.1-24.3)	(13.4-20.5)
HR (95% CI)	**0.94** (0.62-1.40)	

	Nivo-Ipi	Chemo
N	232	219
Median OS (mo)	**18.0**	**13.3**
(95% CI)	(16.8-21.5)	(11.6-15.4)
HR (95% CI)	**0.69** (0.55-0.87)	

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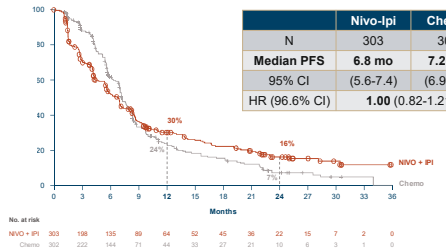
CheckMate 743: Progression-free Survival



	Nivo-Ipi	Chemo
N	303	302
Median PFS	**6.8 mo**	**7.2 mo**
95% CI	(5.6-7.4)	(6.9-8.0)
HR (96.6% CI)	**1.00** (0.82-1.21)	

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CheckMate 743: Summary of Results

		Nivo-Ipi	Chemo	HR
Survival	Median overall	18.1	14.1	0.74
	1-year	68%	58%	
	2-year	41%	27%	
Median overall survival	Epithelioid	18.7	16.5	0.86
	Non-epithelioid	18.1	8.8	0.46
	PD-L1 < 1%	17.3	16.5	0.94
	PD-L1 ≥ 1%	18.0	13.3	0.69
Progression-free survival (months)		6.8	7.2	1.00
Response rate		40%	43%	
Duration of response (months)		11.0	6.7	
Disease control rate		76.6%	85.1%	

GW 103

CheckMate 743: Author's Conclusions

- CheckMate 743 met its primary endpoint of statistically improved OS with NIVO + IPI vs. chemo at the pre-specified interim analysis
  - HR 0.74, *P* = 0.002; 2-year OS rates were 41% vs. 27%
- Survival benefit with NIVO + IPI vs. chemo was observed regardless of histology
- NIVO + IPI performed similarly in both histologies while chemo performed better in epithelioid histology, as expected
- PD-L1 data was descriptive in nature, precluding firm conclusions
- No new safety signals were observed
- This is the first positive randomized trial of dual immunotherapy in first-line treatment in MPM
- **NIVO+ IPI should be considered a new standard of care**

GW 104

CheckMate 743 in Context

- Compared with pemetrexed/platinum, NIVO + IPI yields superior median, 1 and 2-year survival regardless of histology or PD-L1 expression
- CheckMate 743 clearly changes the standard of care for MPM patients with non-epithelioid histology
  - Median survival is dramatically improved: 18.1 vs. 8.8 months, HR 0.46
  - Now, with doublet IO, epithelioid and non-epithelioid patients can achieve an equivalent survival of about 18 months
- For epithelioid histology and PD-L1 negative tumors, though NIVO + IPI is still favorable, the choice is more nuanced
  - OS from NIVO + IPI is comparable to the bevacizumab arm of the MAPS trial (18.8 months).
  - Would PCB have been a better control arm and a treatment option?
  - Ongoing chemo-immunotherapy trials may identify regimens better suited to these patient subsets
- Further analyses are eagerly awaited

GW 105

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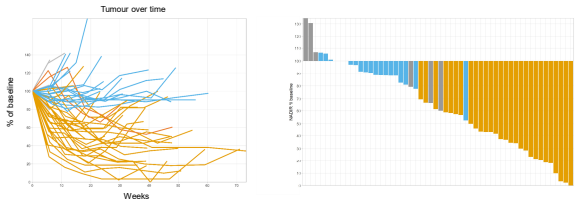
The phase 2 DREAM trial: substantial activity of chemo-immunotherapy in pleural mesothelioma



Nowak, *Lancet Oncol* 2020

DREAM3R/PrE0506: DuRvalumab with chEmotherapy as first line treAtment in advanced pleural Mesothelioma. A phase III open-label, randomized trial

480 pts
Untreated MPM
PS 0-1
2:1 randomization

Durvalumab
Pemetrexed
Cisplatin
→ **Durvalumab**

Pemetrexed
Cisplatin
→ Observation

Stats:
85% power to detect HR 0.70

Stratification:
- Age (< > 70)
- Gender
- Histology (epithelioid vs. non-epithelioid)
- Region (Australia/NZ vs. USA vs other)

Primary endpoint:
Overall Survival

What about previously-treated MM?

No drugs are FDA-approved

Pemetrexed/platinum re-treatment:
- Durable disease control in pemetrexed-sensitive patients

Treatment options include:
- Gemcitabine
- Gemcitabine-ramucirumab
- Vinorelbine
- Nivolumab
- Nivolumab/ipilimumab

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RAMES: Randomized phase II study of gemcitabine with or without ramucirumab as 2nd-line treatment for MPM

N=164
- MPM with PD after platinum/pemetrexed 1st -line chemotherapy
- No prior VEGF

Stratification:
- ECOG PS 0-1 vs. 2
- Age ≤ 70 vs. > 70
- Histologic subtype
- TTP

RANDOMIZE

Gemcitabine 1000 mg/m²
Placebo
D1, D8, Q 21 D

Gemcitabine 1000 mg/m²
Ramucirumab 10 mg/kg
D1, D8, Q 21 D

Primary endpoint: Overall survival

Pagano, *ASCO 2020*

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RAMES: Results

		Gemcitabine-Placebo	Gemcitabine-Ramucirumab	HR
N		81	80	
Survival	**Median overall**	**7.5 M**	**13.8 M**	**0.71**
	6-month	63.9%	74.7%	
	12-month	33.9%	56.5%	
	Epithelioid	8.8 M	13.8 M	
	Non-epithelioid	3.4 M	13 M	
	1st-line PFS ≤ 6 M	11.5 M	13.6 M	
	1st-line PFS > 6 M	7.1 M	13.9 M	
Progression-free survival		3.3 M	6.2 M	
Response rate		10%	6%	
Disease control rate		52%	73%	

Pagano, *ASCO 2020*

110

CONFIRM: Phase 3 trial of nivolumab vs. placebo in previously-treated mesothelioma

332 pts
ECOG 0-1
> 1 line of therapy

RANDOMIZE 2:1

Nivolumab

Stratification: Histology

Placebo

Dual primary endpoints: PFS and OS

		Nivo	Placebo	HR
Survival	**Median overall**	**9.2 M**	**6.6 M**	**0.72**
	12 month	39.5%	26.9%	
Investigator reported PFS	**Median overall**	**3.0 M**	**1.8 M**	**0.61**
	12 month	14.5%	4.9%	
Histology	**Epithelioid**	**9.4**	**6.6**	**0.71**
	Non-epithelioid	5.9	6.7	0.79
PD-L1 TPS	Positive	8.0 M	8.7 M	0.95
	Negative	9.0 M	6.4 M	0.74

- CONFIRM met its endpoint of statistically improved PFS and OS
- There was no evidence to support PDL-1 TPS being predictive
- Significant clinical benefit observed in the epithelioid subtype

Fennell, Proc WCLC 2020

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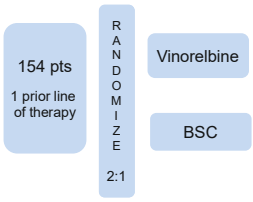
VIM: Randomized phase 2 trial of oral vinorelbine vs. BSC in previously-treated mesothelioma



	Vinorelbine	BSC
N	98	56
Median PFS	4.2 M	2.8 M
	HR 0.60 P=0.002	
Median OS	9.3 M	9.1 M
	HR 0.79 P=0.24	
Response rate	3.1%	1.8%
Stable disease	62.2%	46.4%

Primary endpoint: PFS

Fennell, Proc ASCO 2021

GW 112

Moving Treatment Forward in Mesothelioma: Key Challenges

Mesothelioma is rare and regional
- Trials can be challenging to accrue
- Small market: less pharma and research funding

Disease management fundamentals are unresolved
- Controversies re: roles of surgery, RT, screening
- Staging, radiologic measurement are problematic
- Recent guidelines address some of these issues:
  - Staging (IASLC)[1-3]
  - Imaging (mRECIST 1.1)[4]
  - Diagnosis and treatment (ASCO)[5]

1. Nowak, *JTO* 2016 2. Rice, *JTO* 2016 3. Rusch, *JTO* 2016 4. Armato, *JTO* 2018 5. Kindler, *JCO* 2018

GW 113

Mesothelioma: Where do we go from here?

Prevention and screening
- World-wide regulation of asbestos
- Utilize current biomarkers, develop new ones
- More thorough understanding of the role of germline mutations in the development of mesothelioma

Systemic therapy
- Combination IO has just changed the standard of care
- After years of negative trials, we are finally beginning to make progress against this terrible disease

GW 114

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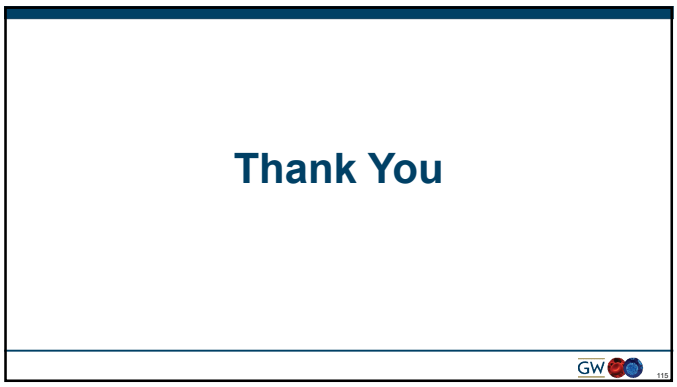

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