Malignant Pleural Mesothelioma

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2021
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I have no financial conflicts of interest to disclose.

Background & Diagnosis

Definition

- Malignant neoplasm arising from mesothelial cells
  - 80% pleural
  - 20% from peritoneum, pericardium, tunica vaginalis in testes

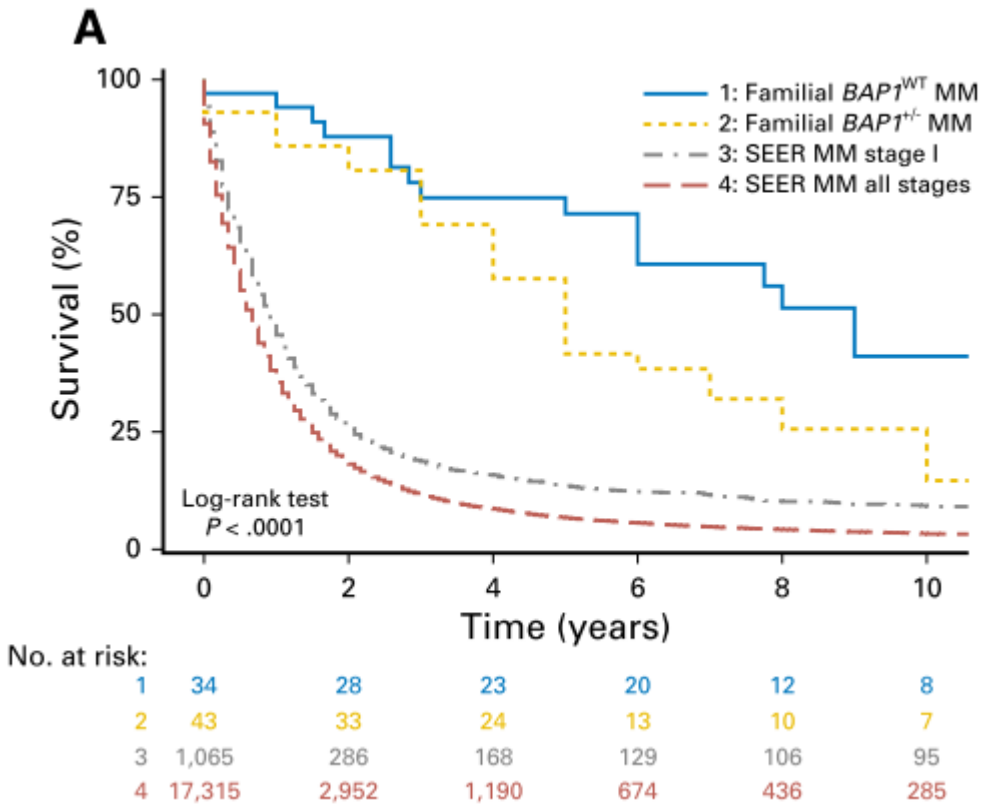
Epidemiology

- Older men
- Rare
  - Incidence ↓ in United States, but ↑ in other parts of the world
- Risk factors
  - Asbestos exposure (70-80%)
  - Erionite
  - Prior radiation
  - BRCA1-associated protein (*BAP1*) mutation
    - Somatic *BAP1* mutations in up to 60% of mesotheliomas
    - Germline *BAP1* mutation

Schumann SO, et al. *J Thorac Dis*. 2021;13(4):2510-23.
Testa JR, et al. *Nature Genetics*. 2011:43(10):1022-25.

Germline *BAP1* Cancer Syndrome

- ↑ malignant pleural mesothelioma, uveal (and cutaneous) melanoma, clear-cell renal cell carcinoma, breast cancer
- Germline *BAP1* mutations associated with improved survival
- Consider testing: young age, familial history of mesothelioma or other cancers



Pastorino S, et al. *J Clin Oncol*. 2018;36:3485-94.

Clinical Presentation

- 20-40 year latency period → often diagnosed at advanced stage
- Fatigue, chest pain, dyspnea, cough
- Pleural plaques and/or pleural effusion

Diagnosis: Recommended Work-up

- CT chest/abdomen with contrast
- Thoracentesis with pleural fluid cytology
- Pleural biopsy (thoracoscopic preferred)
- If potential surgical candidate: PET, mediastinoscopy or EBUS, PFTs
- Soluble mesothelin-related peptide

NCCN Guidelines: Malignant Pleural Mesothelioma. Version 2.2021.
https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf.

Diagnosis: Pathology

- 3 subtypes of diffuse malignant pleural mesothelioma
  1. Epithelioid (60%)
  2. Biphasic (20%)
  3. Sarcomatoid (20%)

Galateau-Salle F, et al. *J Thorac Oncol*. 2016;11(2):142-54.

Staging

- **T**umor
  - T1-3: resectable
  - T4: technically unresectable (multifocal masses in chest wall, peritoneal extension, contralateral pleura, spine, transmural pericardial involvement)
- **N**ode
  - N1: ipsilateral lymph nodes
  - N2: contralateral lymph nodes
- **M**etastasis
  - M0: no distant mets
  - M1: distant mets (uncommon: bone, liver, CNS)

T4 or N2 → stage IIIB

M1 → stage IV

AJCC Cancer Staging Manual, 8th Ed. 2017. Springer International Publishing.

Management

Management: Basic Principles

- Poor prognosis (median OS = 12-18 months)
- Few, if any, patients are cured
- Patients should be managed by a multidisciplinary team with experience in malignant pleural mesothelioma

Step #1: Determine resectability

Malignant pleural mesothelioma

Resectable (20%)

- Clinical stage I-IIIA

AND

- Epithelioid or biphasic histology

NOT resectable (80%)

- Clinical stage IIIB or IV

OR

- Sarcomatoid histology

OR

- Medically inoperable

Resectable Disease

- Goal: macroscopic complete resection
- Surgical approaches (both acceptable for boards)
  - Extrapleural pneumonectomy (EPP): *en bloc* resection of entire lung, visceral and parietal pleura, pericardium, diaphragm
  - Extended Pleurectomy/decortication (P/D): resection of visceral and parietal pleura, diaphragm and/or pericardium

Resectable Disease

Induction chemotherapy (cisplatin/pemetrexed) → Surgery → Hemithoracic IMRT (EPP only)

Surgery → Sequential chemotherapy, then hemithoracic IMRT (EPP only)

Unresectable Disease

- Consider observation if:
  - Minimally symptomatic
  - Low disease burden
  - Favorable prognosis (i.e. germline *BAP1* mutation)

Unresectable Disease

Epithelioid

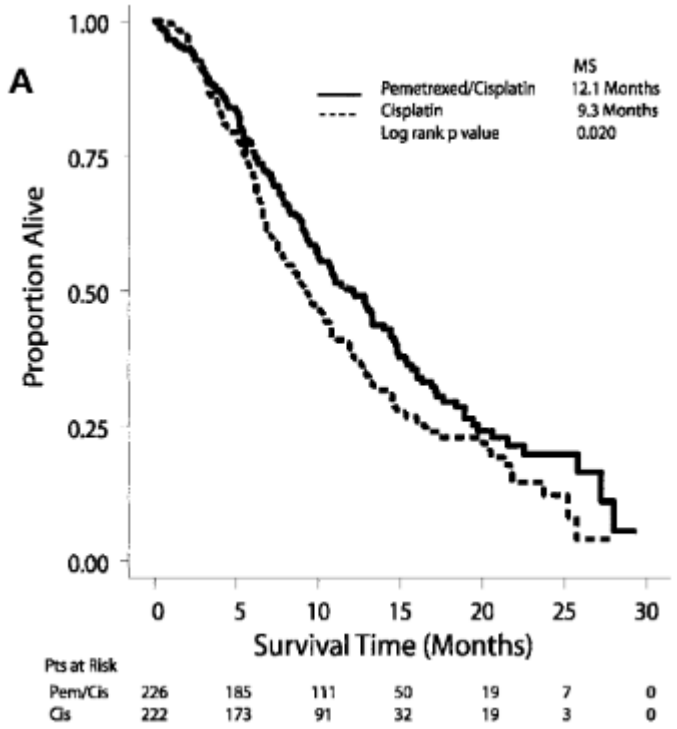
- Cisplatin/pemetrexed +/- bevacizumab
- Ipilimumab/nivolumab

Non-Epithelioid

- Ipilimumab/nivolumab preferred

Unresectable Disease

- Cisplatin/pemetrexed



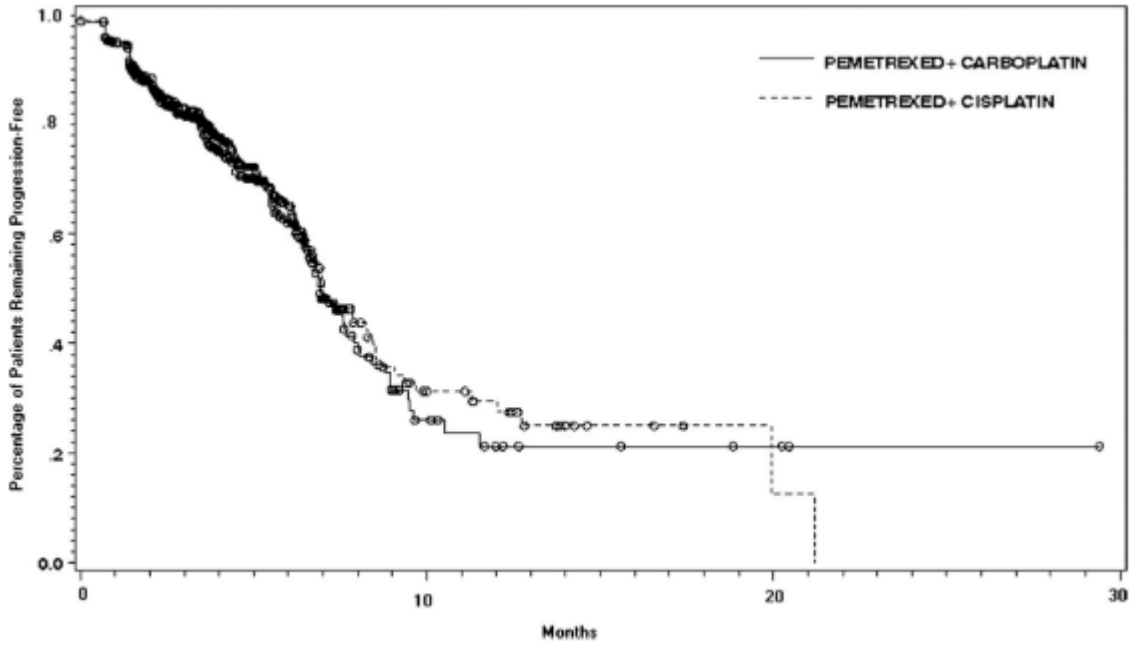
- ORR 41% (vs 17% with cisplatin alone)
- Improved median OS
- Median time to progression 5.7 months vs 3.9 months
- Major AE: fatigue, nausea/vomiting

Vogelzang NJ, et al. *J Clin Oncol*. 2003;21:2636-44.

Unresectable Disease

- If patient cannot tolerate cisplatin, may substitute carboplatin

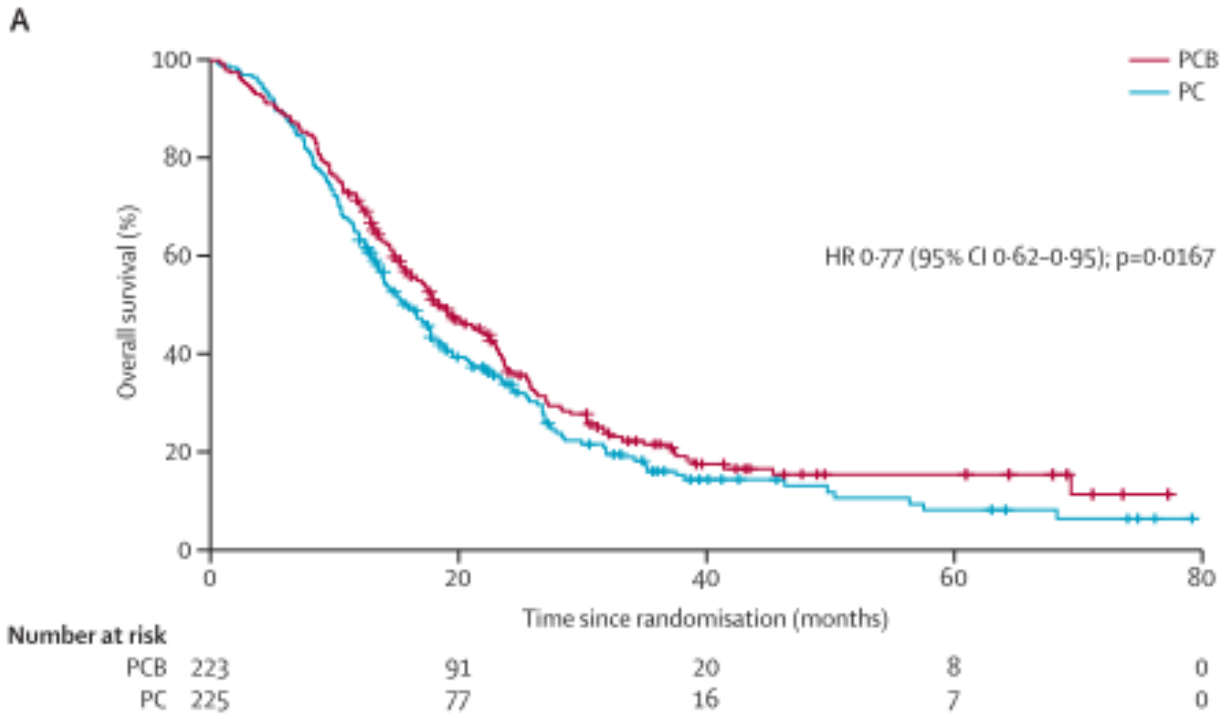
- ORR 22% (vs 26% with cisplatin)
- Similar 1-year survival (63% vs 64%)



Santoro A, et al. *J Thorac Oncol*. 2008;3:756-63.

Unresectable Disease

- Cisplatin/pemetrexed + bevacizumab (MAPS trial)

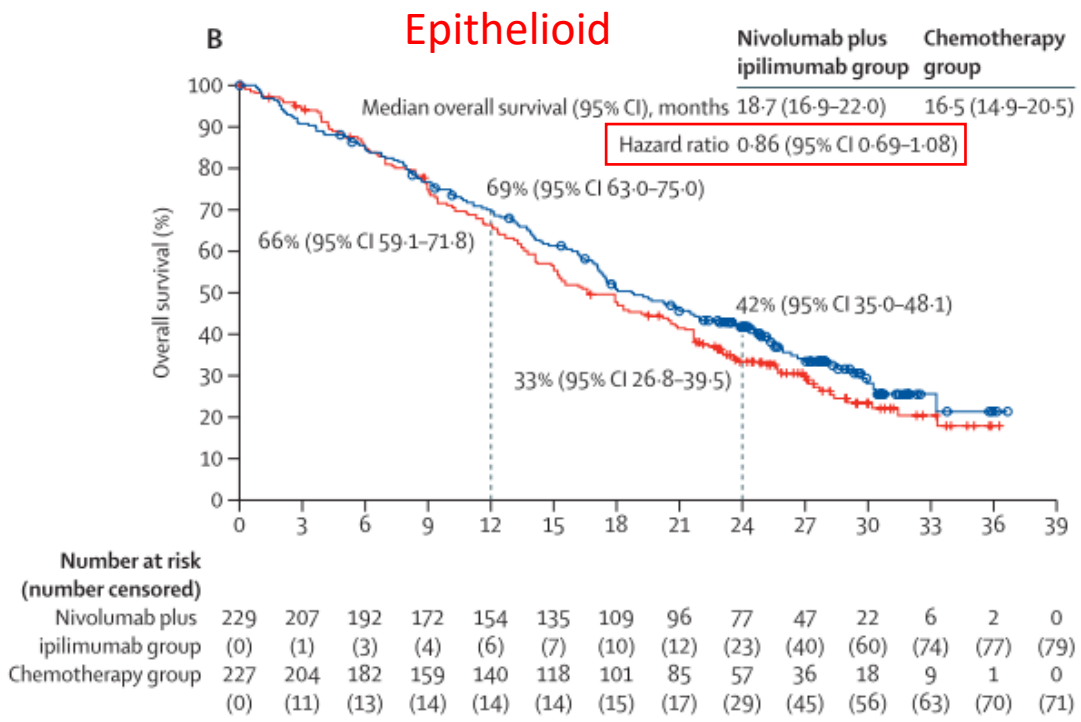


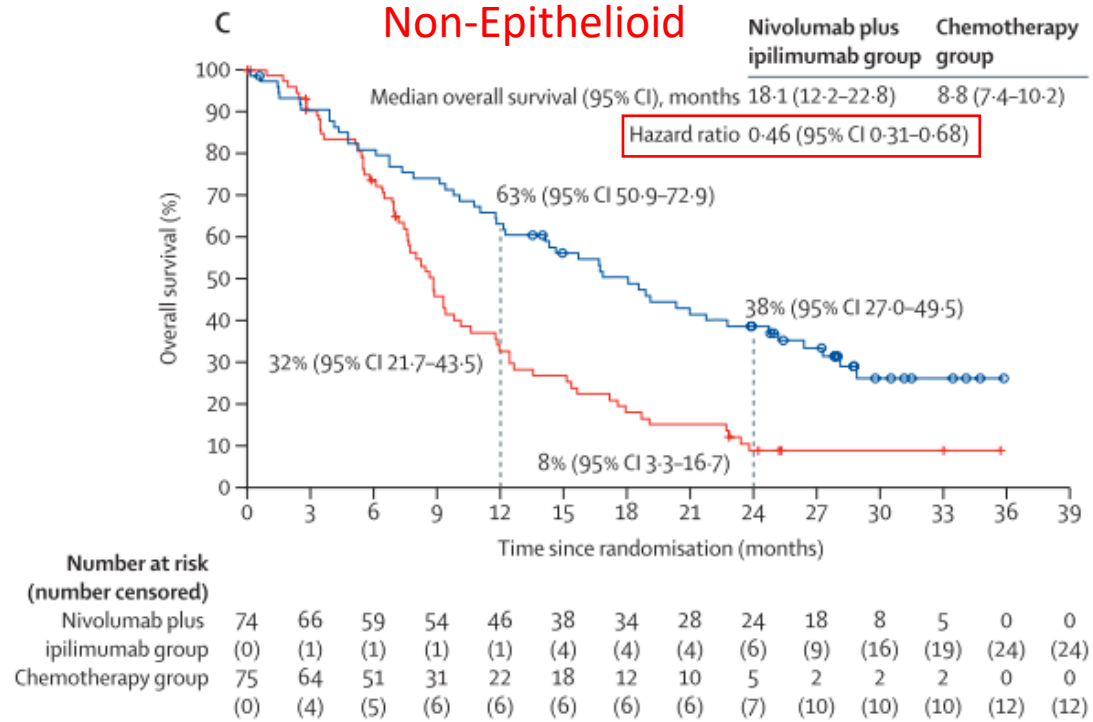
- Improved median OS (18.8 vs 16.1 months)
- AE: hypertension, thrombotic events

Zalcman G, et al. *Lancet*. 2016;387:1405-14.

Unresectable Disease

- Ipilimumab/nivolumab (Checkmate 743)

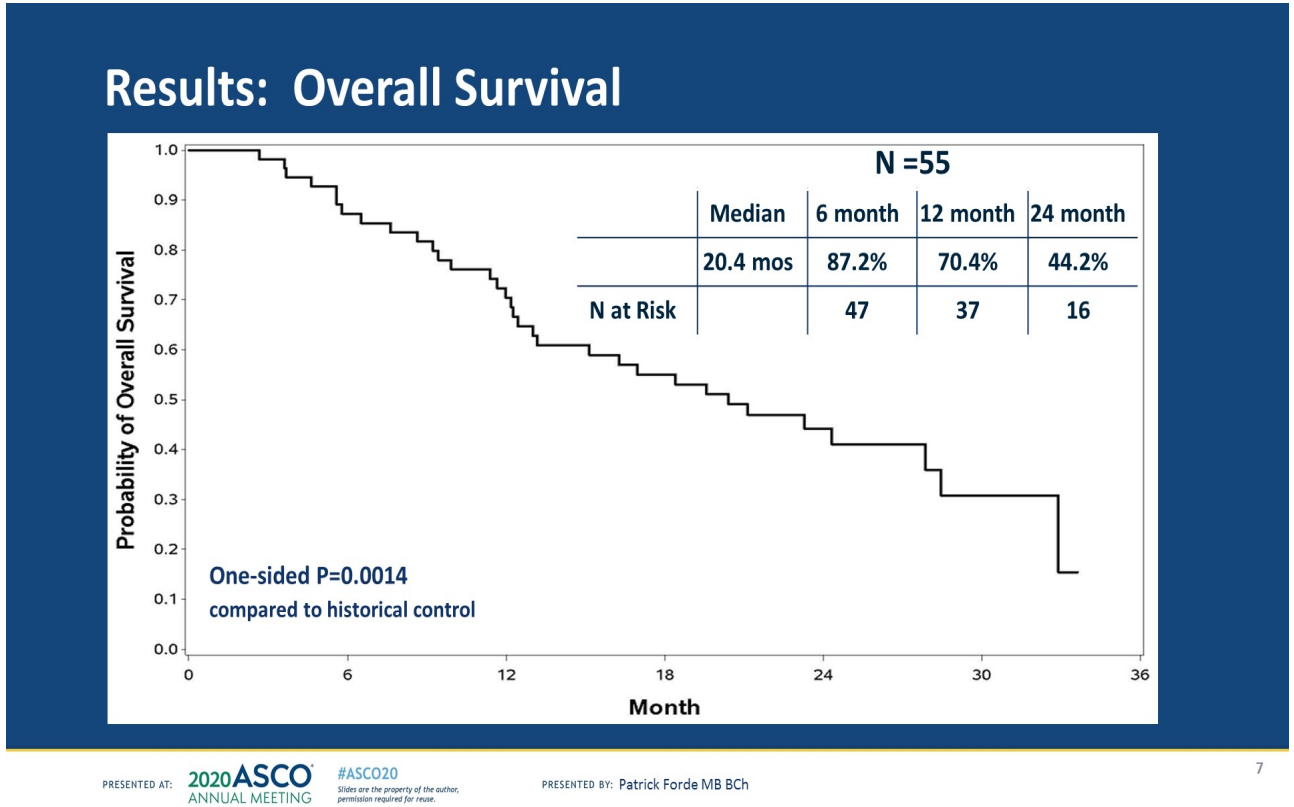




Baas P, et al. *Lancet*. 2021;397:375-86.

Unresectable Disease: Upcoming

- DREAM3R: Cisplatin/pemetrexed +/- durvalumab



PrE0505 trial presented at 2020 ASCO Annual Meeting: promising preliminary data on OS

ClinicalTrials.gov: DREAM3R. https://clinicaltrials.gov/ct2/show/NCT04334759.

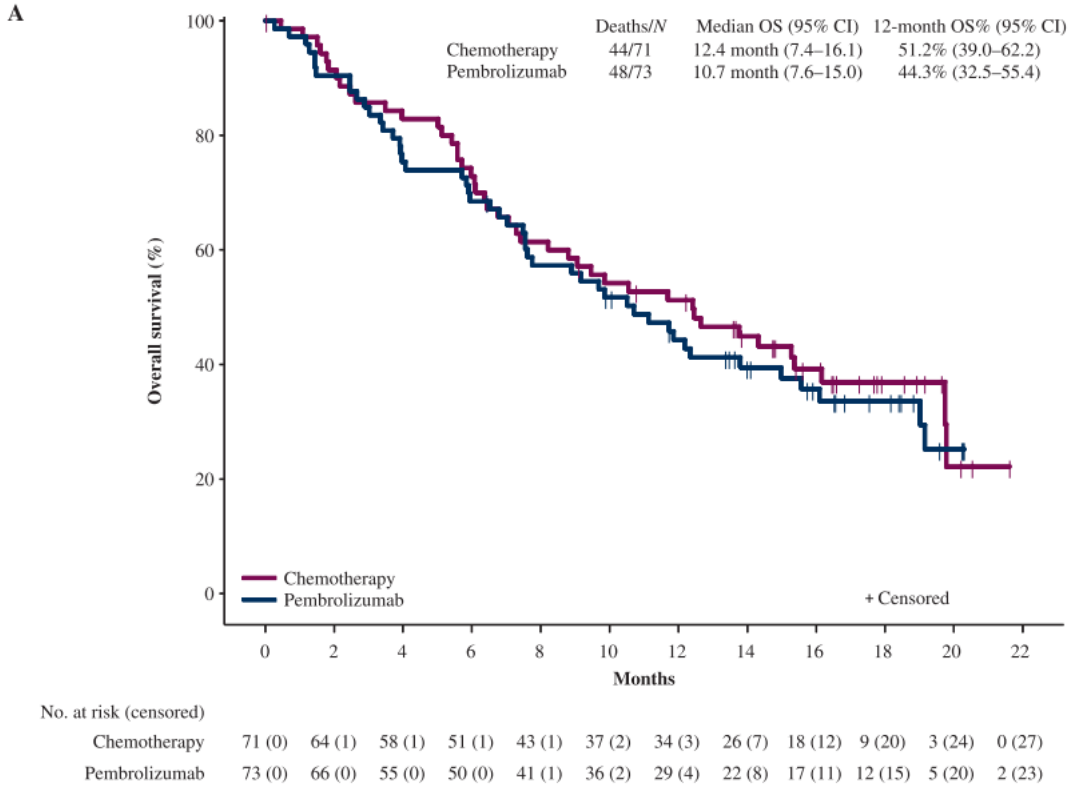
Relapse

- No FDA approved second line regimens

Chemotherapy (RR ~10%)	Immunotherapy	Anti-VEGF
• Vinorelbine • Gemcitabine • Pemetrexed rechallenge	• Pembrolizumab • Nivolumab +/- ipilimumab	• Gemcitabine + ramucirumab

Relapse

- Pembrolizumab (PROMISE-meso trial)

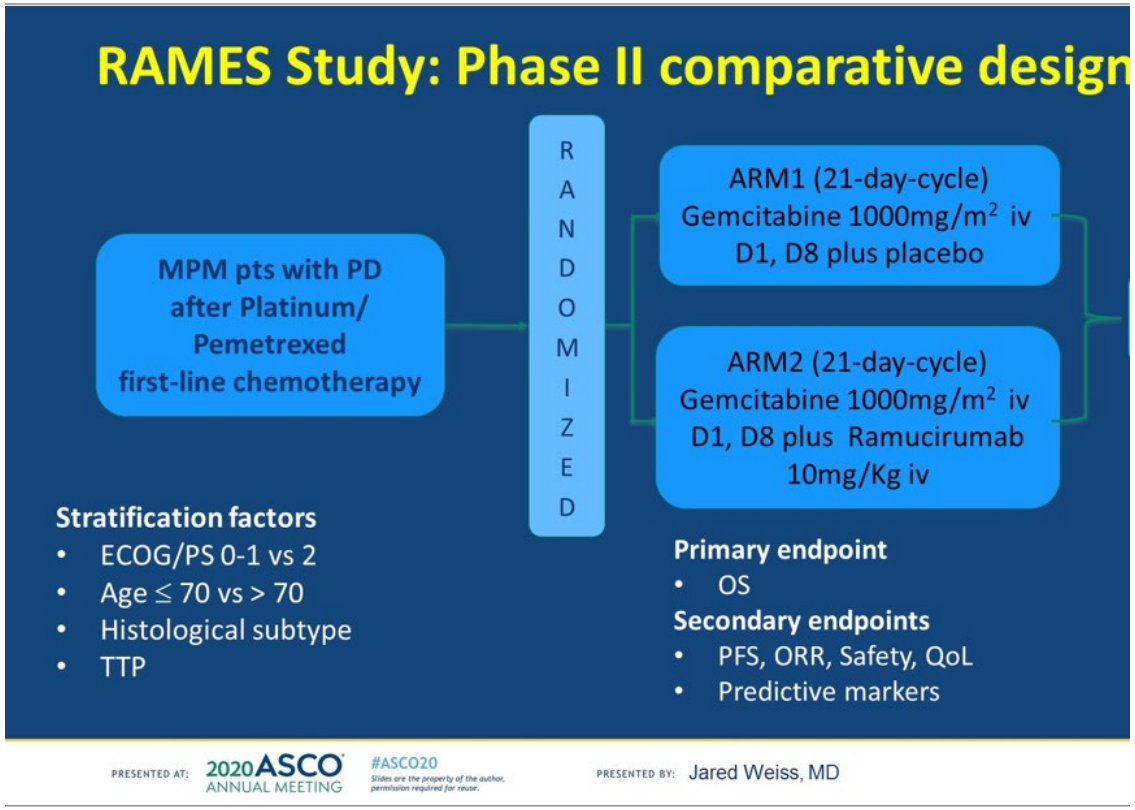


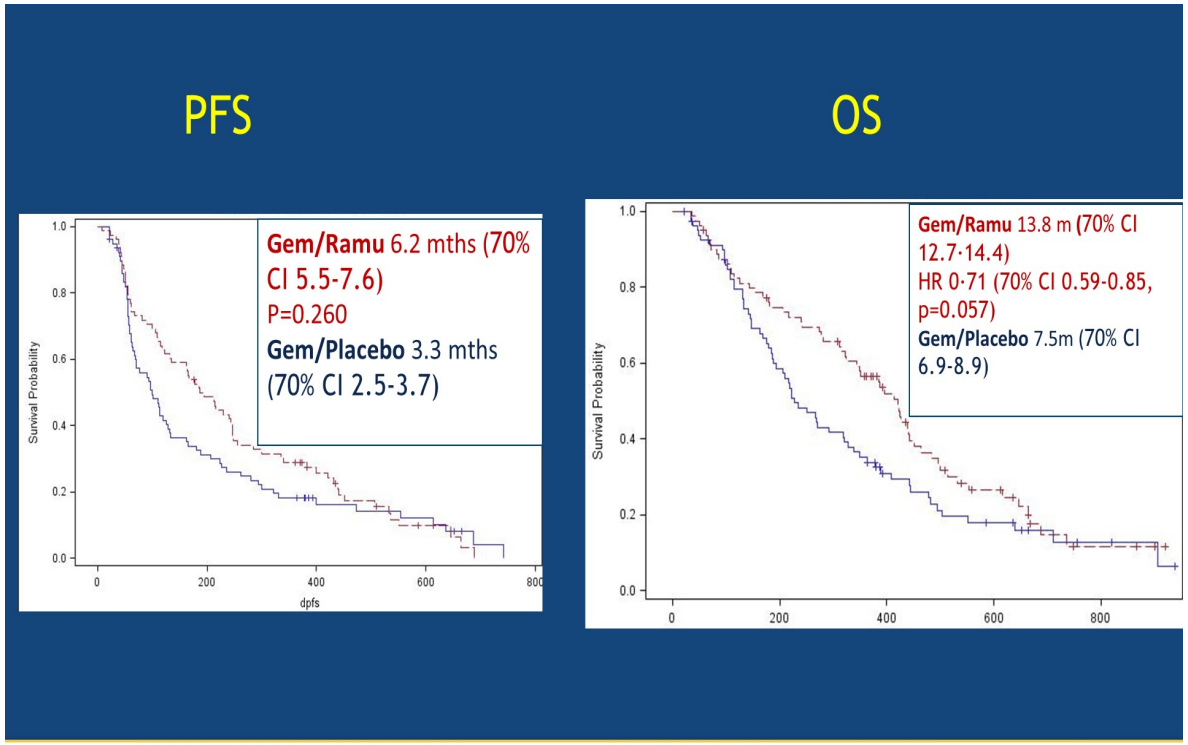
- ORR 12% (vs 6% with single-agent gemcitabine or vinorelbine)
- No difference in PFS or OS

Popat S, et al. *Ann Oncol*. 2020;31(12):1734-45.

Relapse

- Gemcitabine + ramucirumab (RAMES trial presented at 2020 ASCO Annual Meeting)





Summary

- Germline *BAP1* mutation associated with improved prognosis
- First step with a new diagnosis: determine resectability
- Resectable disease
  - Cisplatin/pemetrexed = regimen of choice in neoadjuvant and adjuvant settings
  - Surgery: both EPP or P/D acceptable
- Unresectable disease
  - First line: ipilimumab/nivolumab vs cisplatin/pemetrexed +/- bevacizumab
  - Second line: no FDA approved therapies

Question #1

A 70 year-old male with a history of HTN, COPD, right lower extremity DVT on rivaroxaban presents with a new diagnosis of unresectable epithelioid malignant pleural mesothelioma. Which of the following would NOT be an acceptable first line therapy?

a) Cisplatin/pemetrexed

b) Cisplatin/pemetrexed + bevacizumab

c) Carboplatin/pemetrexed

d) Ipilimumab/nivolumab

Explanation: Cisplatin/pemetrexed + bevacizumab would not be a recommended first line therapy in this patient with a known history of DVT. All other options would be reasonable.

Question #2

Which of the following is FALSE?

a) Cisplatin/pemetrexed is the regimen of choice for both the neoadjuvant and adjuvant settings in resectable mesothelioma.

b) There are no FDA approved second line therapy regimens for mesothelioma.

c) Somatic *BAP1* mutations are associated with improved prognosis in mesothelioma.

d) It is unclear whether EPP or P/D is the preferred surgical approach in mesothelioma.

Explanation: Germline *BAP1* mutations are associated with improved prognosis in mesothelioma. While somatic *BAP1* mutations are more common, there is not a demonstrated association with overall survival.