Fred Hutch Cancer Center

Malignant Pleural Mesothelioma

Nicholas Giustini, MD – giustini@uw.edu
Assistant Professor
Clinical Research Division FHCC
Division of Hematology/Oncology
University of Washington

I have previously received honoraria from Curio Science.

Goals and Objectives

- Review the epidemiology of MPM
- Review the clinical presentation and work-up of MPM
- Review MPM histology and staging
- Discuss treatment of resectable MPM
- Discuss treatment of unresectable MPM

Background & Diagnosis

Background

- Malignant neoplasm arising from mesothelial cells
  - 85% pleural
  - 15% from peritoneum
  - 1% pericardium, tunica vaginalis in testes

NCCN Guidelines: Malignant Pleural Mesothelioma. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf

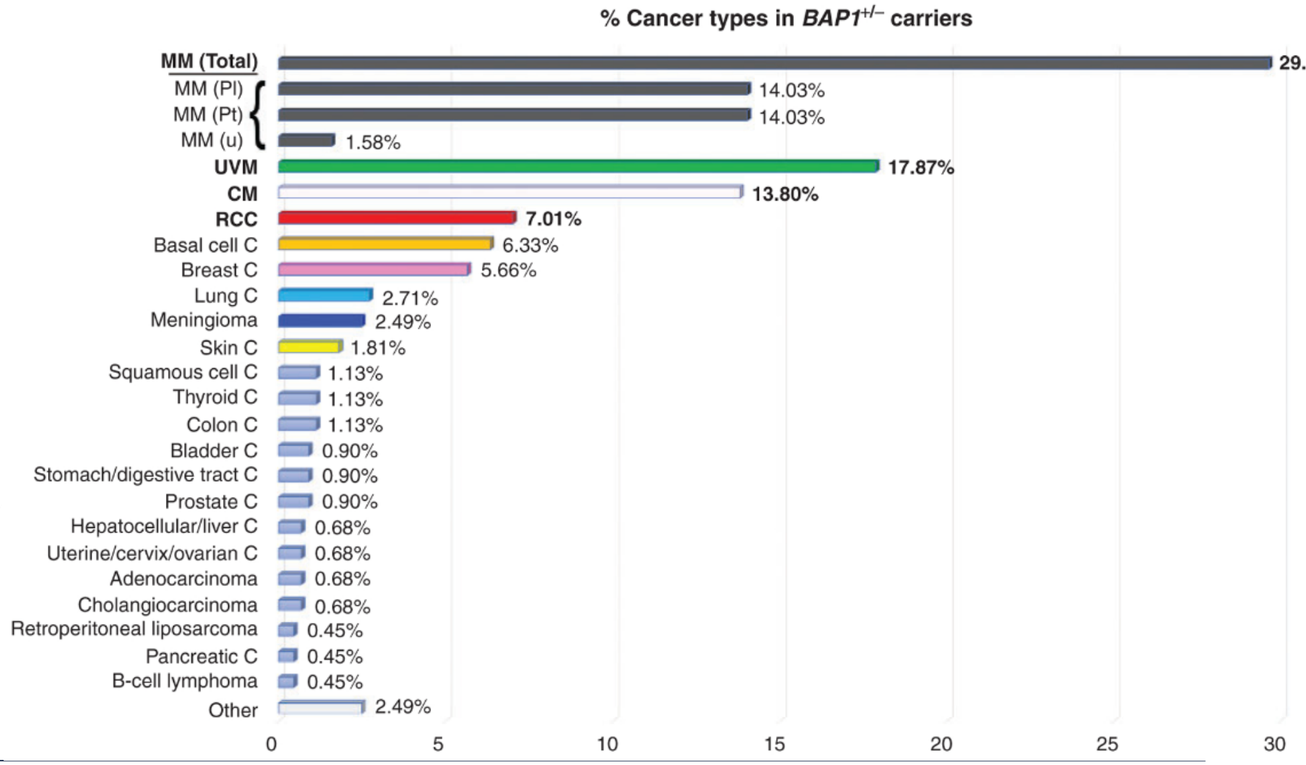
Epidemiology

- 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

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

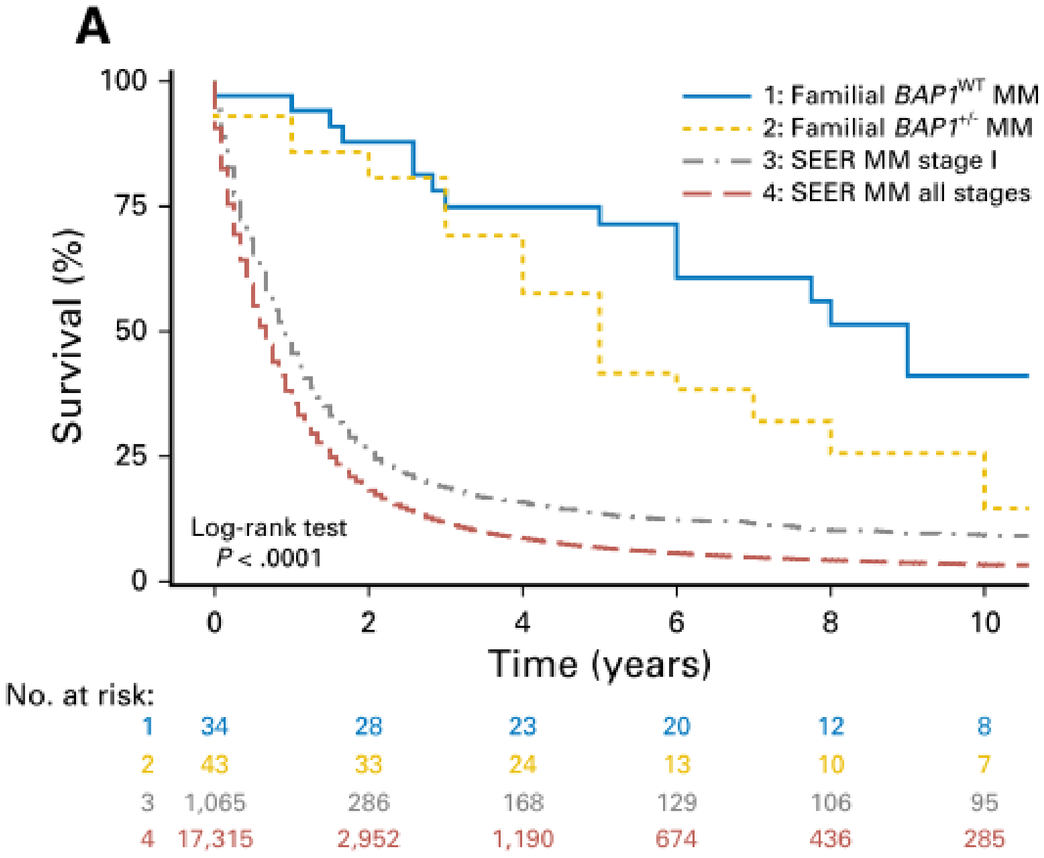
- Increased risk of:
  - Malignant pleural mesothelioma
  - Uveal & cutaneous melanoma
  - Clear cell carcinoma
  - Breast cancer
- Consider testing: young age, family history of mesothelioma and/or other associated cancers



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

BAP1 in Mesothelioma

- Somatic *BAP1* mutations very common
  - 50-70% of epithelioid
  - <20% of sarcomatoid
- Germline *BAP1* mutations associated with improved survival (NOT somatic)



Pastorino S, et al. *J Clin Oncol*. 2018;36:3485-94.
NCCN Guidelines: Malignant Pleural Mesothelioma. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf

Clinical Presentation

- 20-60 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, cardiac stress test
- +/- soluble mesothelin-related peptide

NCCN Guidelines: Malignant Pleural Mesothelioma. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf

Diagnosis: Pathology

- Three subtypes
  1. Epithelioid (60%)
  2. Biphasic (20%)
     - Contains at least 10% of both epithelioid and sarcomatoid
  3. Sarcomatoid (20%)

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

Staging

- Tumor
  - T1-3: resectable
  - T4: technically unresectable (multifocal masses in chest wall, peritoneal extension, contralateral pleura, spine, transmural pericardial involvement)
- Node
  - N1: ipsilateral lymph nodes
  - N2: contralateral lymph nodes
- Metastasis
  - 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 = 18 months)
- Few, if any, patients are cured
- Patients should be managed by a multidisciplinary team with experience in malignant pleural mesothelioma

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

Management: 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, and diaphragm
  - Extended pleurectomy/decortication (P/D): resection of visceral and parietal pleura, diaphragm, and/or pericardium

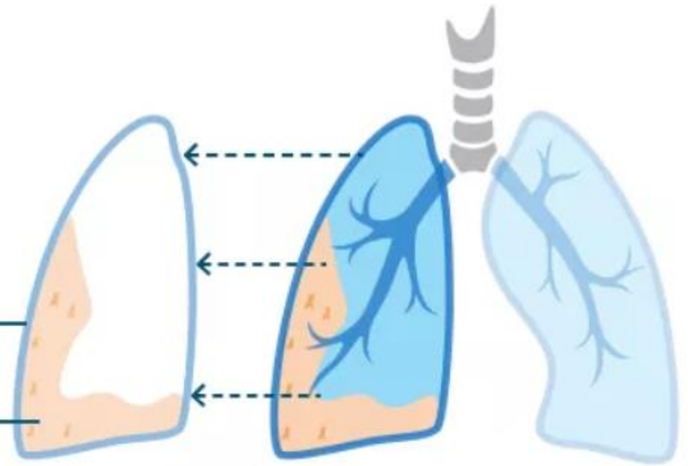
Pleural Mesothelioma Surgery Comparison

Pleurectomy/ Decortication (P/D)

Removes the affected pleura and visible tumors on the lung and chest cavity.

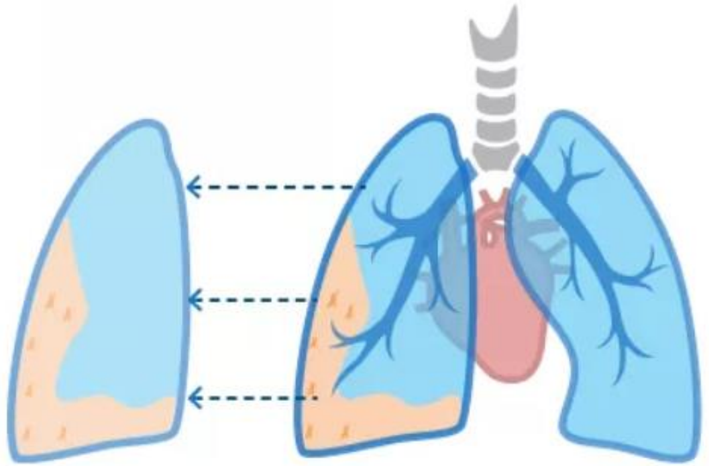
Visceral Pleura
(Covers Lungs)

Plaque Forms in Pleura



Extrapleural Pneumonectomy (EPP):

Removes the entire affected lung, linings, diaphragm and lymph nodes.



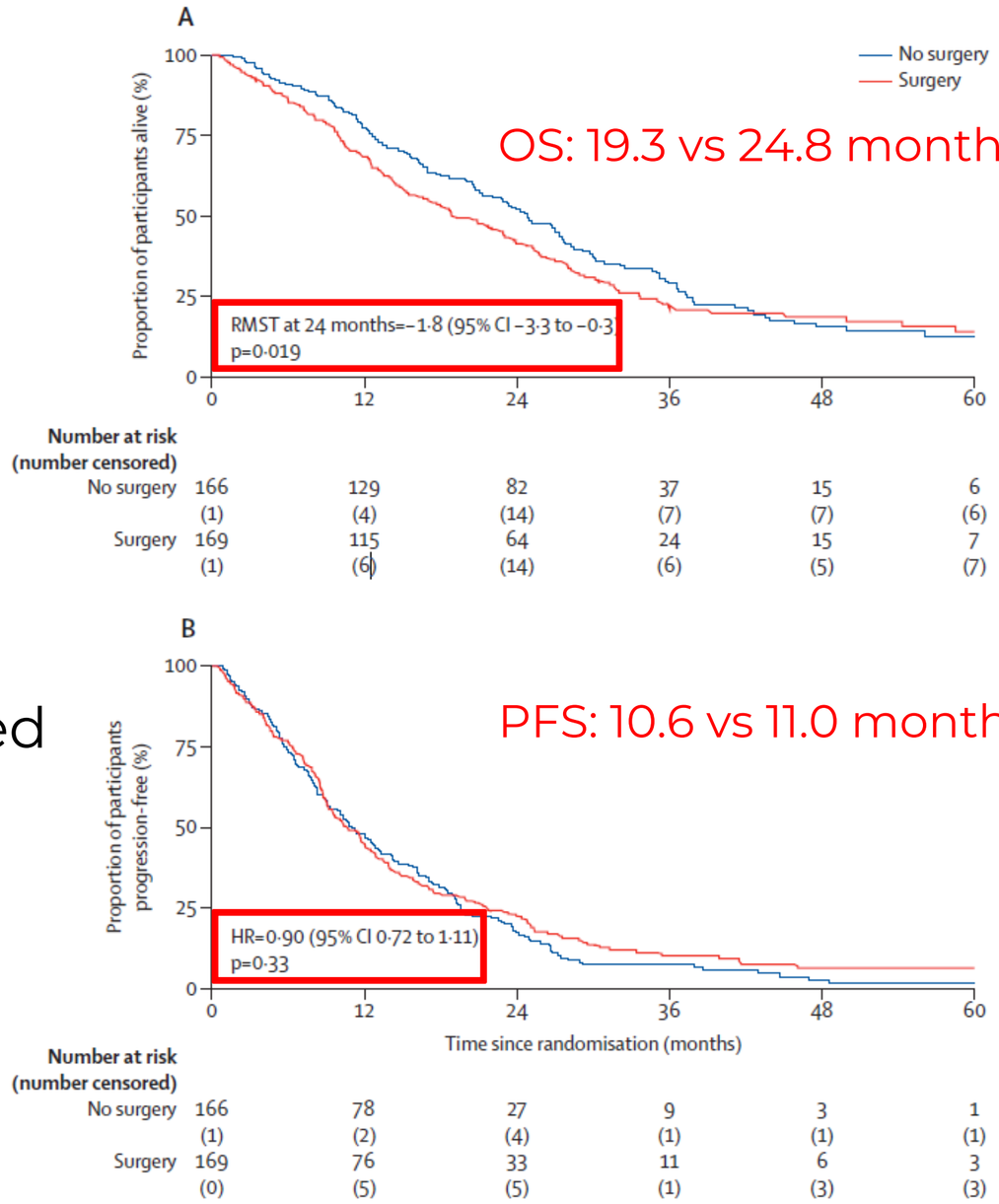
Management: Resectable Disease

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

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

MARS-2 – Phase III RCT

- Any histology surgically resectable pleural mesothelioma
- 2 cycles platinum + pemetrexed → randomized
  - Intervention: P/D → 2-4 additional cycles (169 patients)
  - Comparator: 2-4 additional cycles (166 patients)



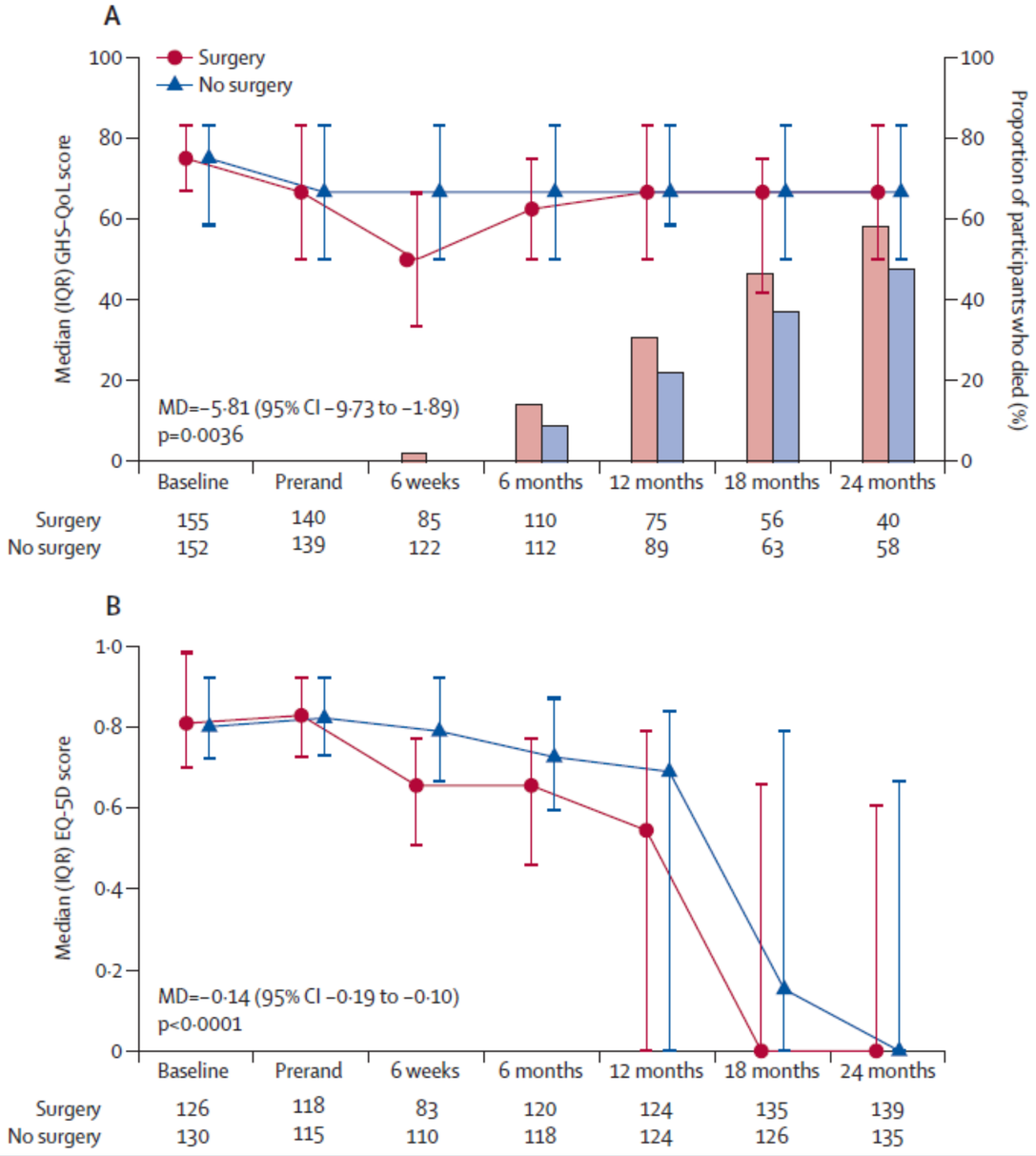
OS: 19.3 vs 24.8 months

PFS: 10.6 vs 11.0 months

Lim E, et al. *Lancet*. 2024;12:457-66.

MARS-2 – Outcomes

- Completeness of resection
  - R0 = 3%
  - R1 = 81%
- SAE increased with surgery
  - IRR 3.6 (95% CI 2.3-5.5)
  - Cardiac, respiratory, infection
- Worse HRQoL after surgery



Lim E, et al. *Lancet*. 2024;12:457-66.

Management: Unresectable Disease

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

Management: Unresectable Disease

<u>Epithelioid</u>

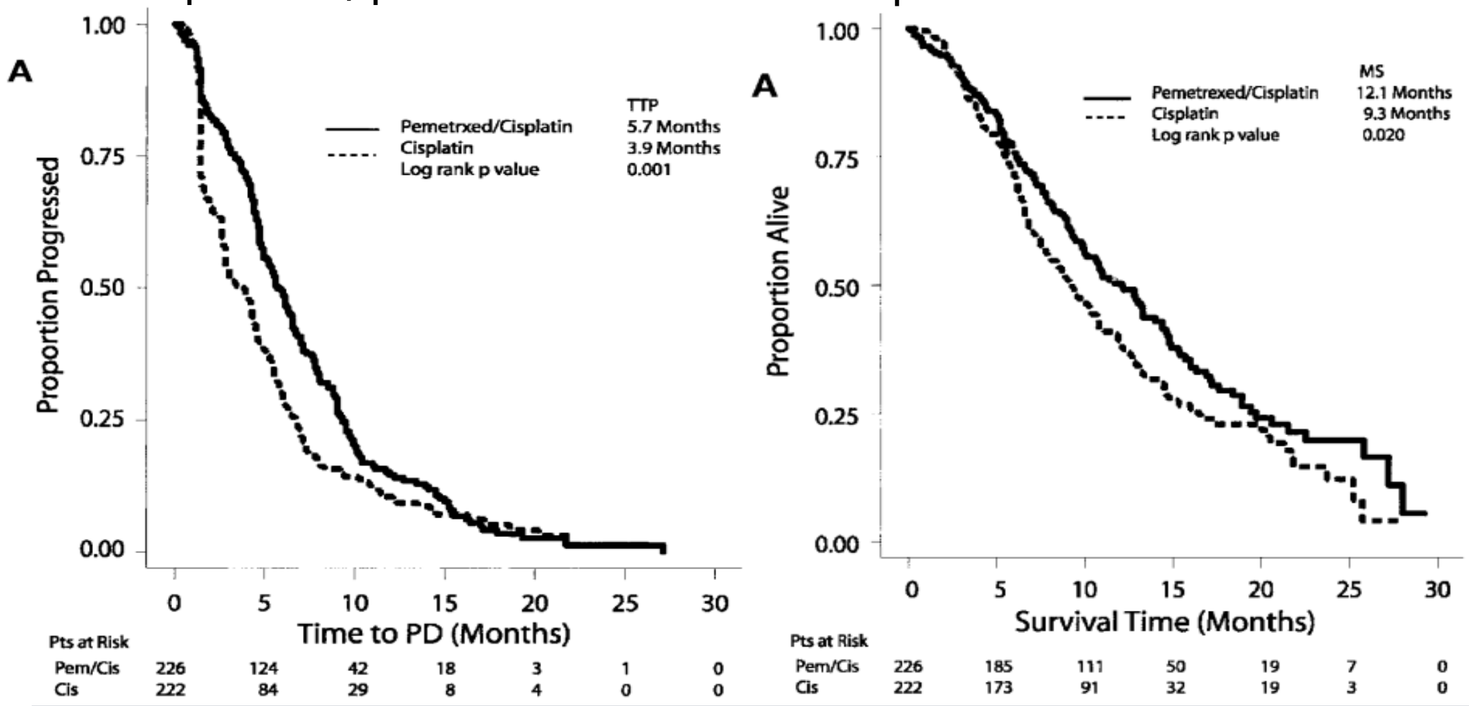
- Cisplatin/pemetrexed +/- bevacizumab
- Ipilimumab/nivolumab

<u>Non-Epithelioid</u>

- Ipilimumab/nivolumab

Management: Unresectable Disease

- Cisplatin/pemetrexed vs cisplatin alone

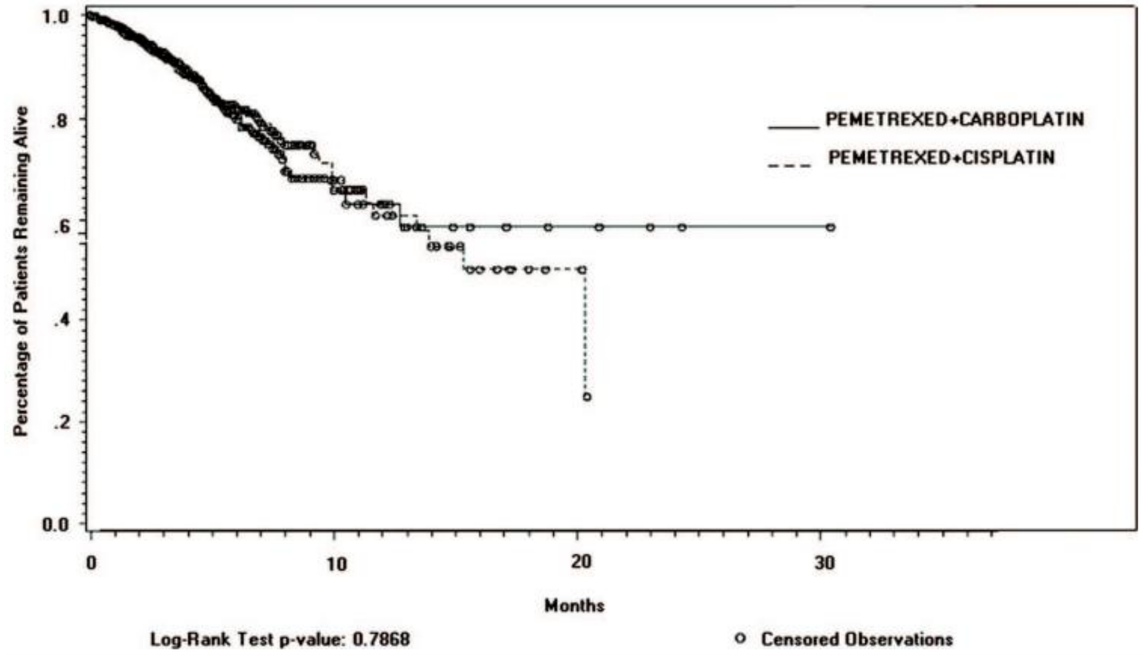


- Median cycles given: 6
- ORR 41% vs 17%
- PFS 5.7 vs 3.9 months
- OS 12.1 vs 9.3 months
- Major AE: fatigue, nausea/vomiting, hematologic

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

Management: Unresectable Disease

- Cisplatin/pemetrexed vs carboplatin/pemetrexed – can substitute

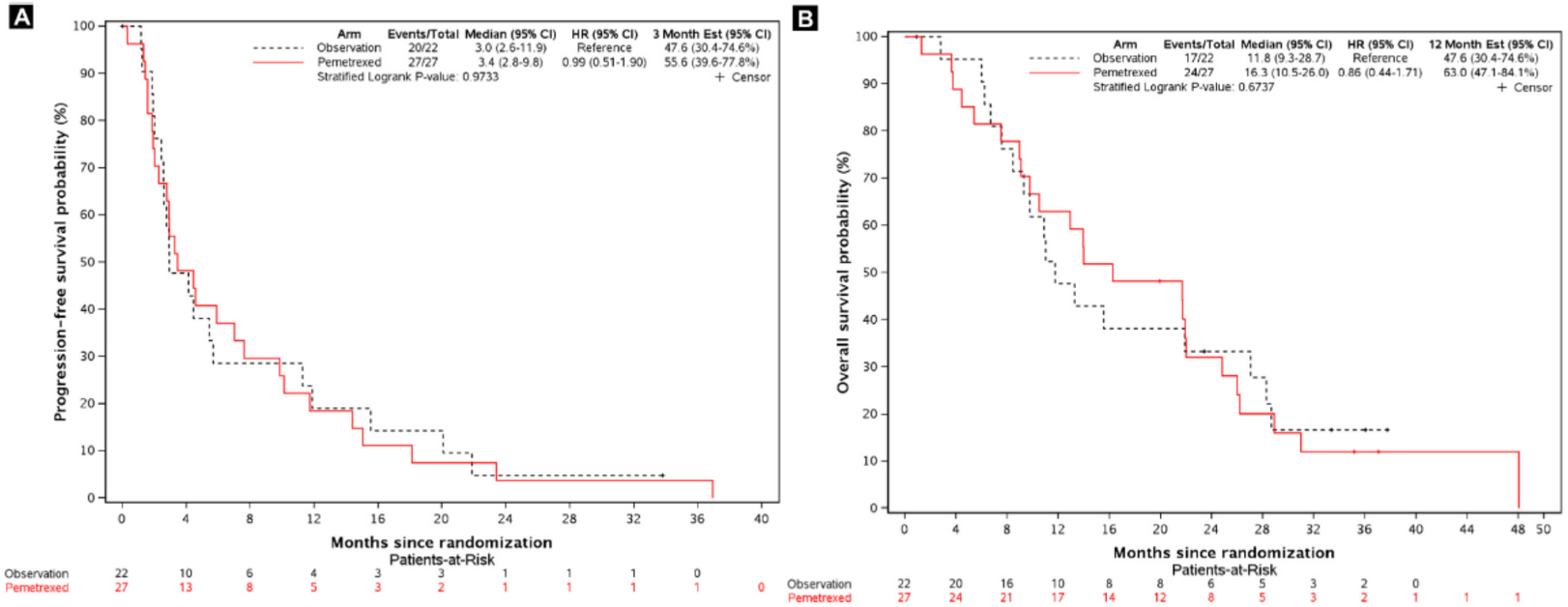


- ORR 26 vs 22%
- PFS 7 vs 6.9 months
- 1 year OS: 63 vs 64%
- AE: increased myelosuppression with carboplatin

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

Management: Unresectable Disease

- Pemetrexed maintenance after platinum/pemetrexed? → NO

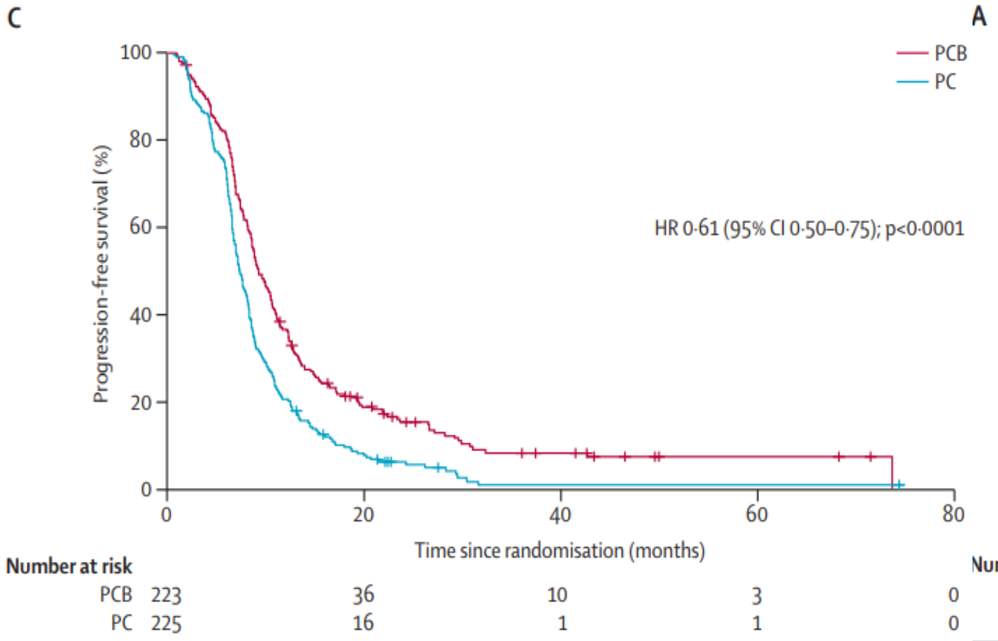


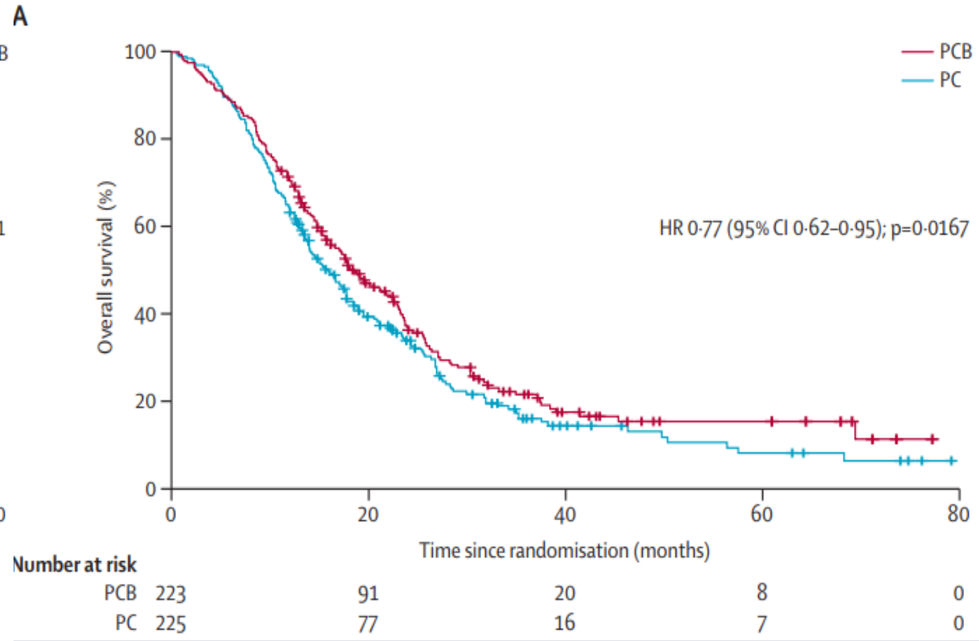
- Trial closed early
- PFS 3.4 vs 3 months
- OS 16.3 vs 11.8 months (nonsignificant)

Dudek, A., et al. *Clinical Lung Cancer*. 2020;21:553-561.

Management: Unresectable Disease

- Cisplatin/pemetrexed +/- bevacizumab (MAPS trial)



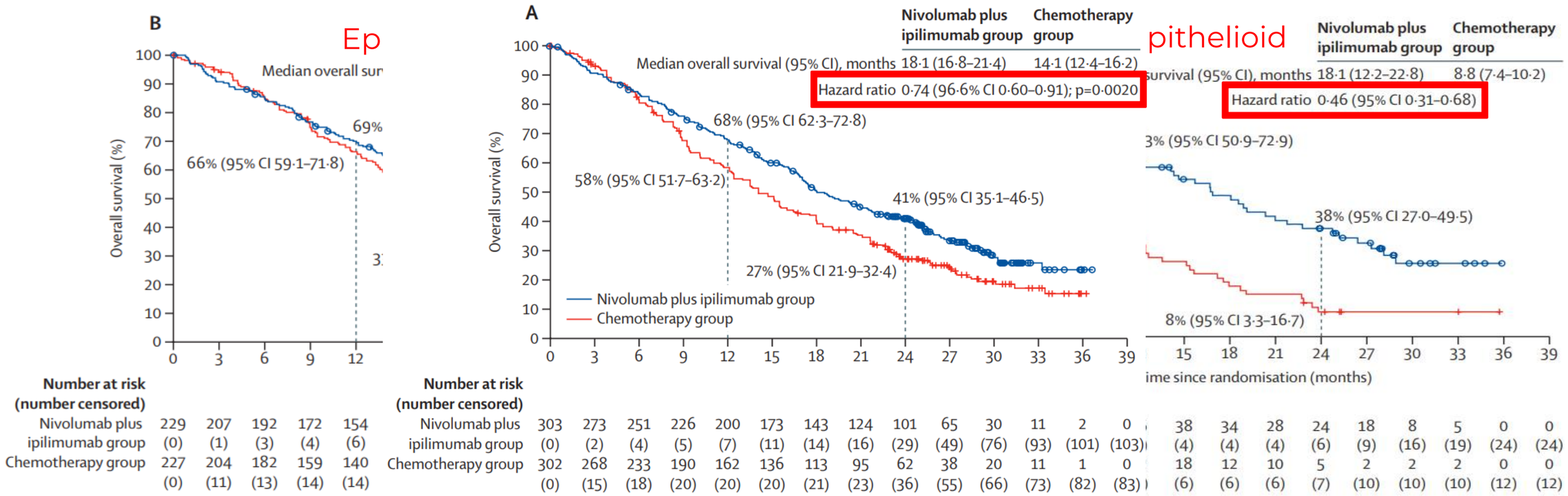


- PFS
  - 9.2 vs 7.3 months
- OS
  - 18.8 vs 16.1 months
- AE: HTN, bleeding, thrombotic events

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

Management: Unresectable Disease

- Ipilimumab/nivolumab vs platinum/pemetrexed (CheckMate 743)



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

Management: Upcoming Unresectable Disease

- DREAM3R: platinum/pemetrexed +/- durvalumab
- CCTG IND 227 (ASCO 2023): platinum/pemetrexed +/- pembrolizumab
  - ~78% epithelioid
  - ORR 63% vs 40%
  - mPFS 7.13 mo vs 7.16 mo
  - mOS 17.3 mo vs 16.1 mo (HR 0.79, 95% CI 0.64-0.98, p = 0.0324)
- eVOLVE-Meso: platinum/pemetrexed + volrustomig vs SOC

ClinicalTrials.gov: DREAM3R. https://clinicaltrials.gov/ct2/show/NCT04334759.
Chu, Q., et al. *J Clin Oncol*. 2023; 41: LBA8505 10.1200/JCO.2023.41.17_suppl.LBA8505.

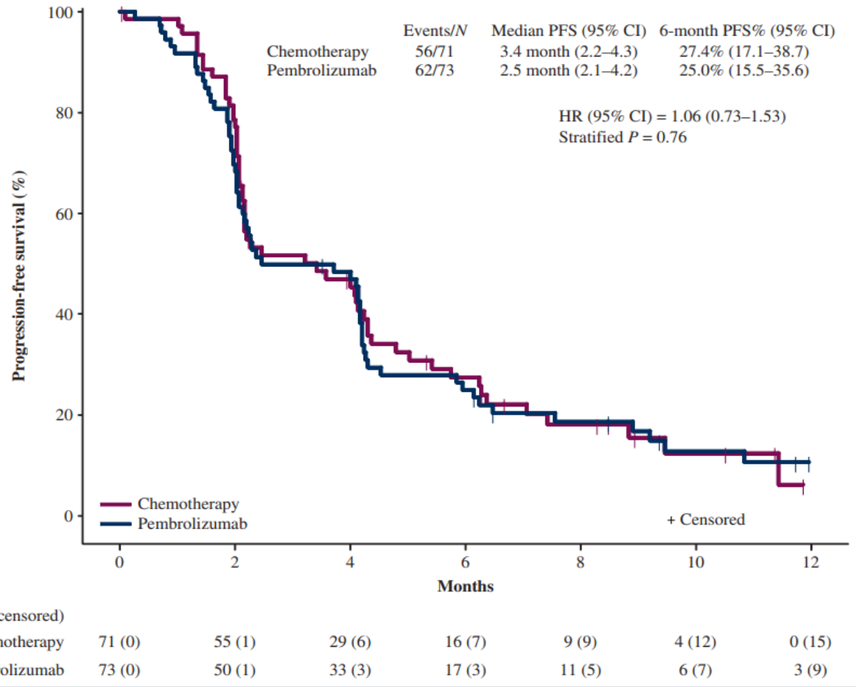
Management: Relapse

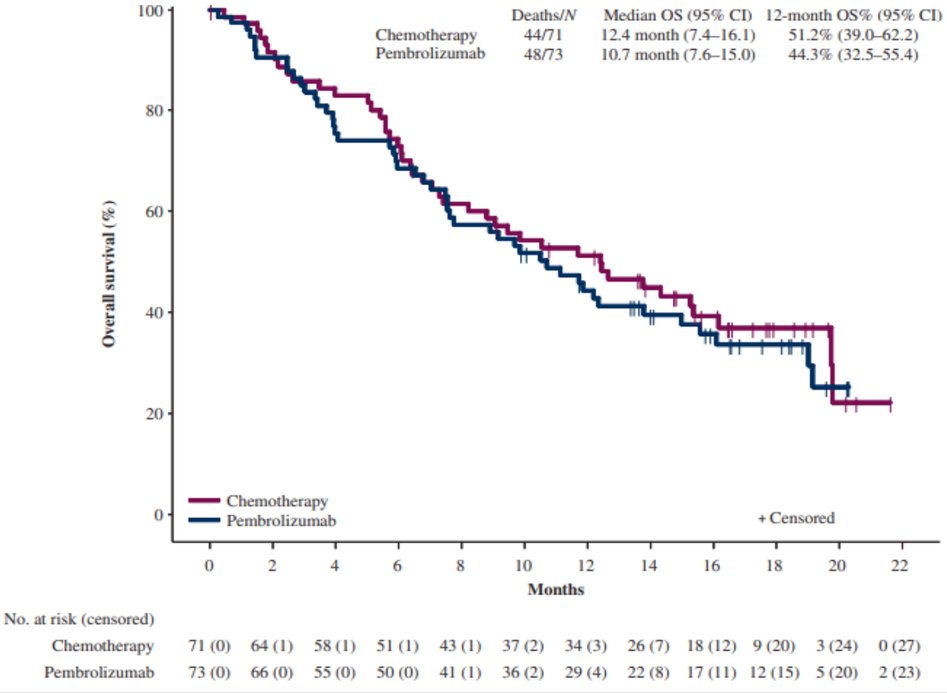
- No FDA approved 2nd line regimens

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

Management: Relapse

- Pembrolizumab vs gemcitabine or vinorelbine (PROMISE-meso trial)





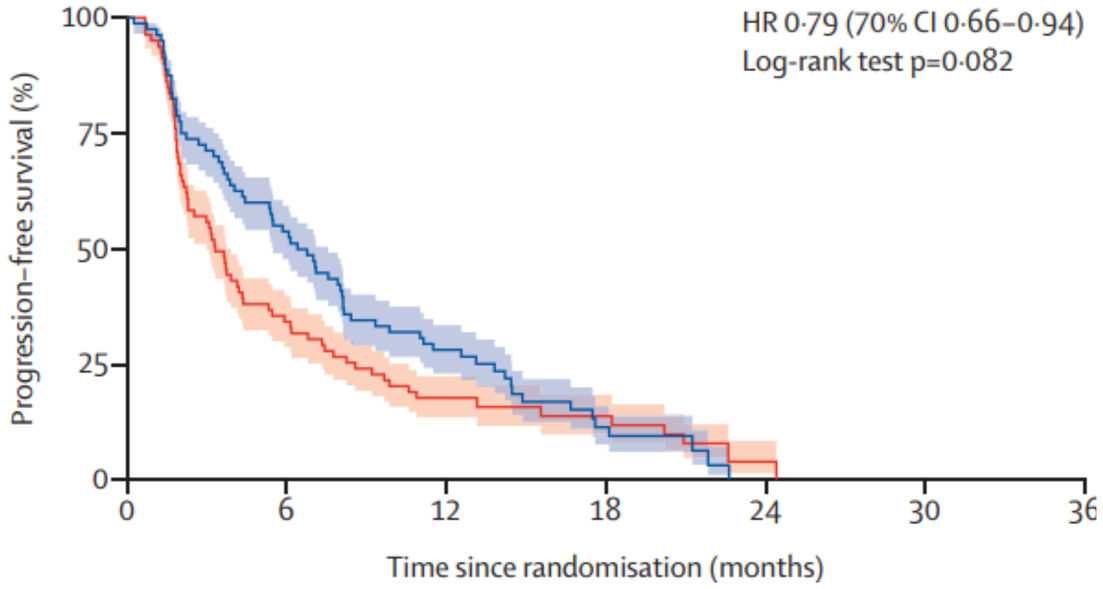
- ORR 22% vs 6%
- No difference in PFS or OS

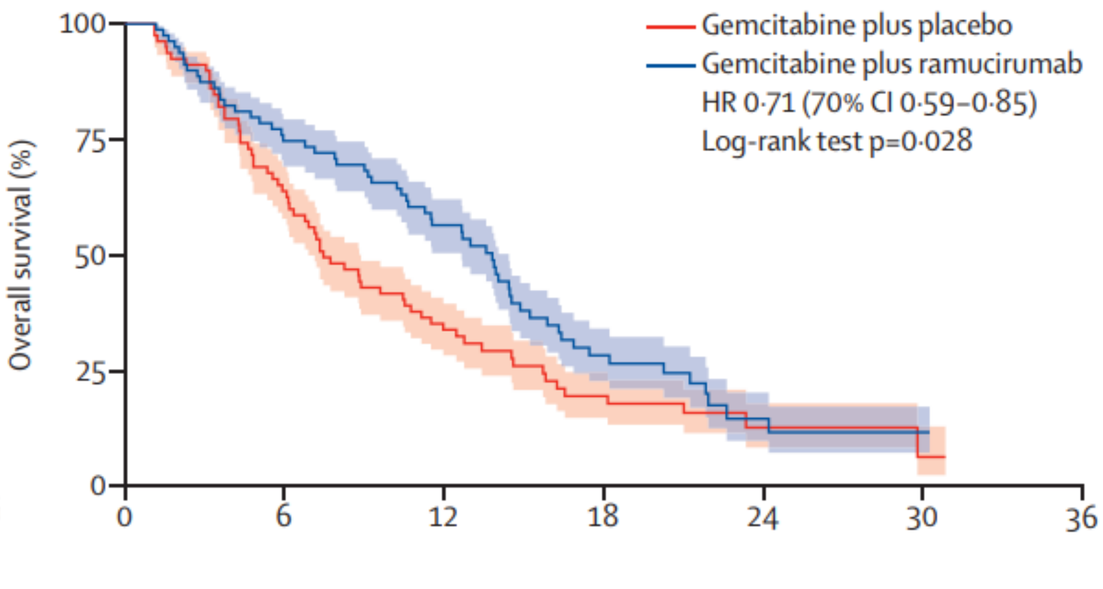
Popat S, et al. *Ann Oncol*. 2020;31(12):1734-45

Management: Relapse

- Gemcitabine +/- ramucirumab (RAMES)

- ORR 10% vs 6%
- DCR 73% vs 52%
- PFS 6.4 vs 3.3 months (NS)
- OS 13.8 vs 7.5 months





Pinto, C. et al. *Lancet Oncol*. 2021;22:1438-1447.

Summary

- Germline *BAP1* mutation associated with improved prognosis
- Goal of surgery = macroscopic complete resection
- Resectable disease (in question due to MARS 2 data)
  - Cisplatin/pemetrexed = regimen of choice in neoadjuvant and adjuvant settings
  - Surgery: both EPP or P/D acceptable though EPP more morbid
- Unresectable disease
  - First line: ipilimumab/nivolumab vs cisplatin/pemetrexed +/- bevacizumab
  - Second line: no FDA approved therapies

Fred Hutch Cancer Center

Thank You.