

**Fred Hutch Cancer Center**

# Malignant Pleural Mesothelioma

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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

# Take Home Points

- Germline (not somatic) BAP1 portends improved prognosis
- Surgical resection rarely recommended
  - When done: cisplatin + pemetrexed +/- IMRT
- Unresectable disease
  - Epithelioid: multiple options
  - Non-epithelioid: include immunotherapy



# Background & Diagnosis

# Background

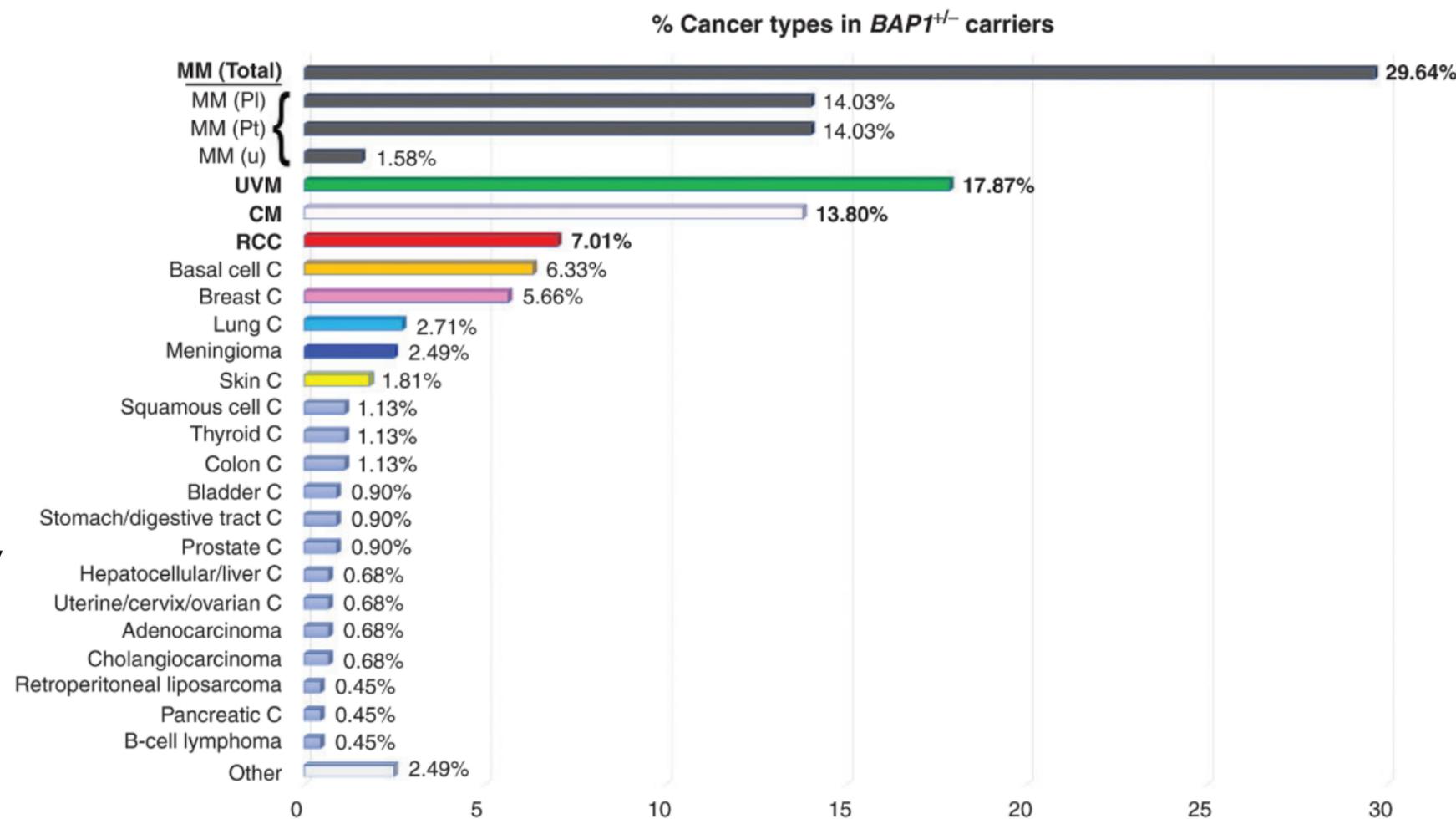
- Malignant neoplasm arising from mesothelial cells
  - ~85% pleural
  - 15% from peritoneum
  - 1% pericardium, tunica vaginalis in testes

# 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

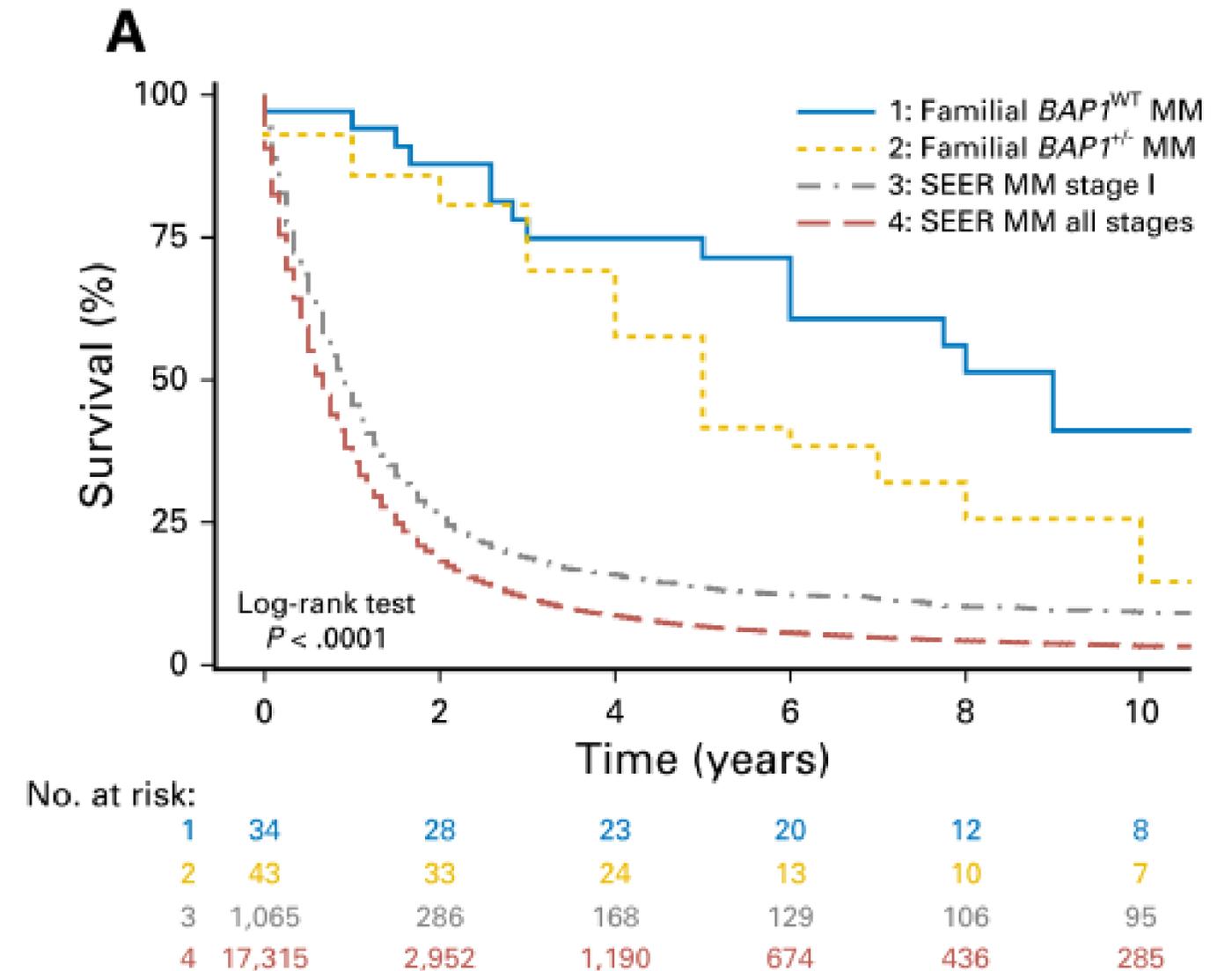
# Germline *BAP1* Cancer Syndrome

- 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



# BAP1 in Mesothelioma

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



# 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

# Diagnosis: Pathology

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

# 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

T4 or N2 → stage IIIB  
M1 → stage IV



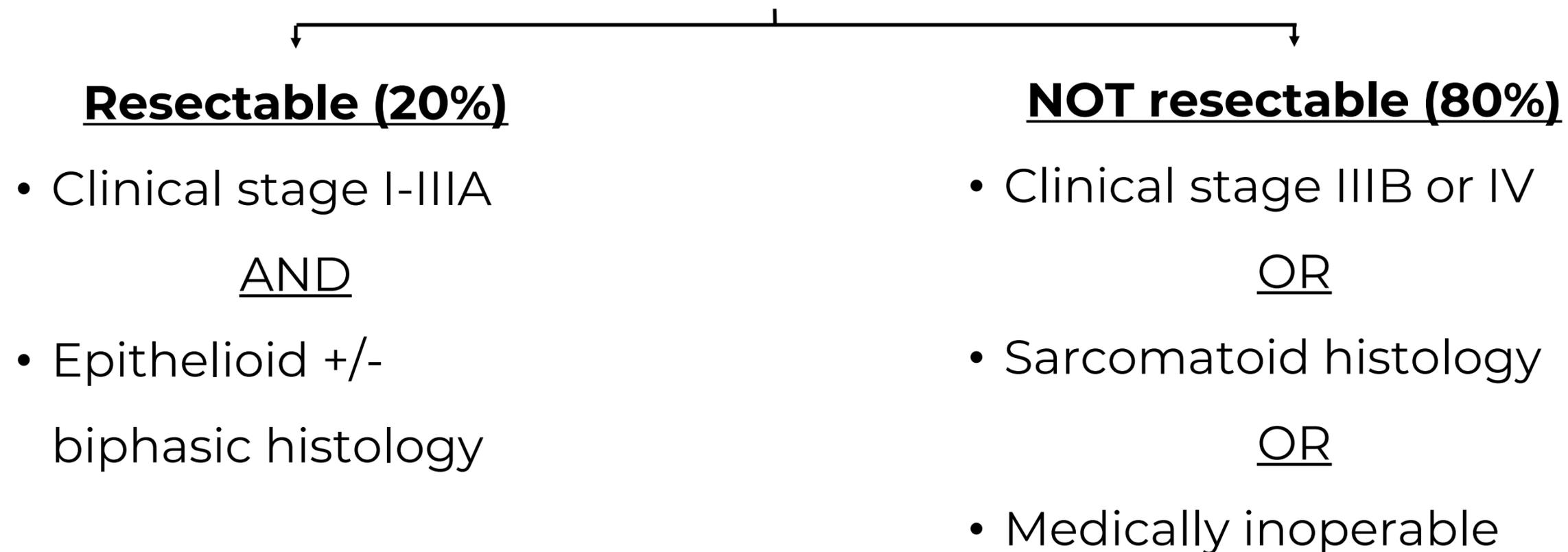
# Management

# 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



# Management: Resectable Disease

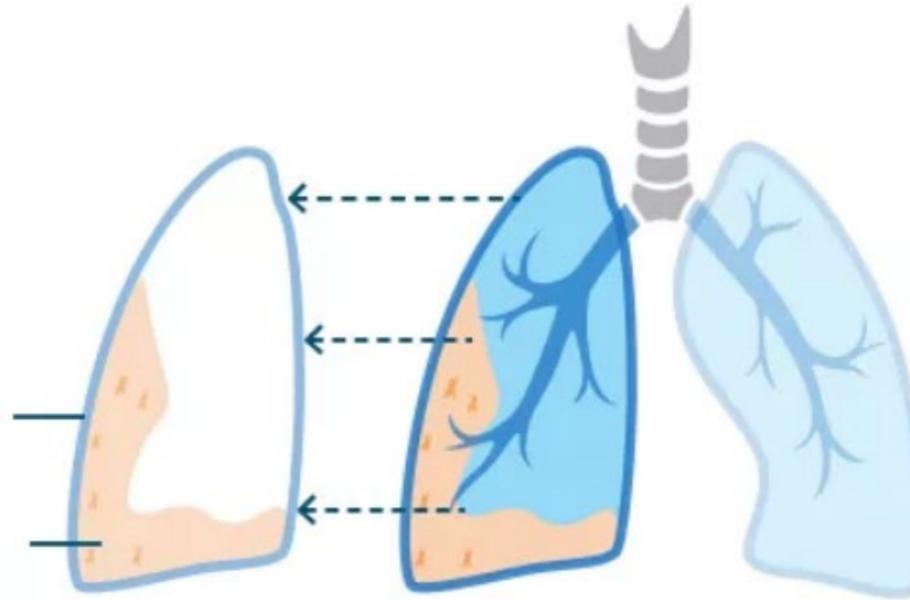
- Goal: macroscopic complete resection
- Surgical approaches (both acceptable for boards)
  - Extrapleural pneumonectomy (EPP): en bloc resection of entire lung, visceral and parietal pleura, pericardium, and diaphragm
  - Extended pleurectomy/decortication (P/D): resection of visceral and parietal pleura,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

# Pleural Mesothelioma Surgery Comparison

## Pleurectomy/ Decortication (P/D)

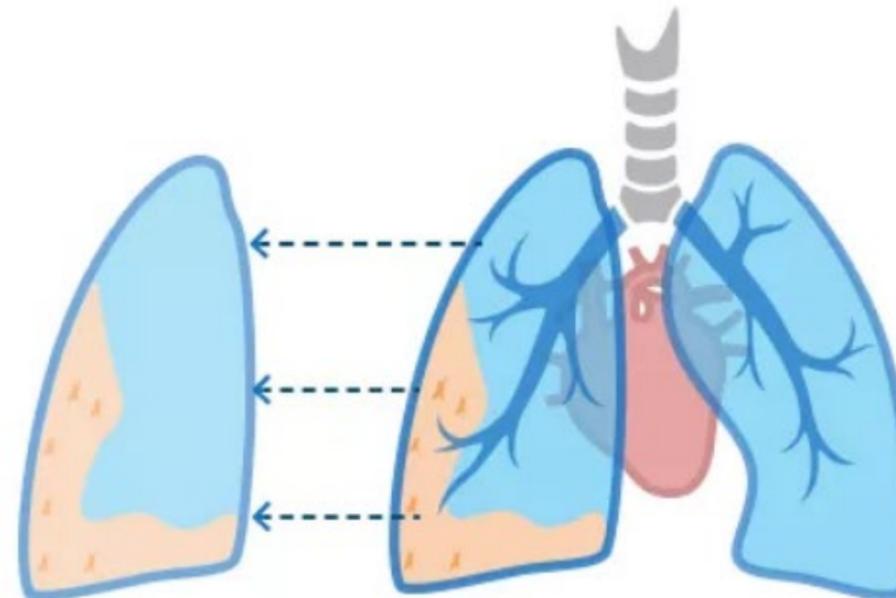
Removes the affected pleura and visible tumors on the lung and chest cavity.

**Visceral Pleura**  
(Covers Lungs)  
Plaque Forms  
in Pleura



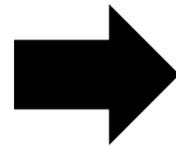
## Extrapleural Pneumonectomy (EPP):

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

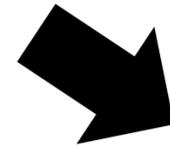


# Management: Resectable Disease

Neoadjuvant  
cisplatin +  
pemetrexed

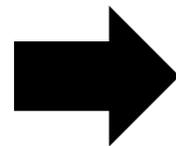


Surgery

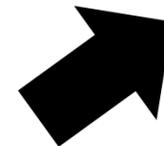


Hemithoracic IMRT  
(EPP only)

Surgery

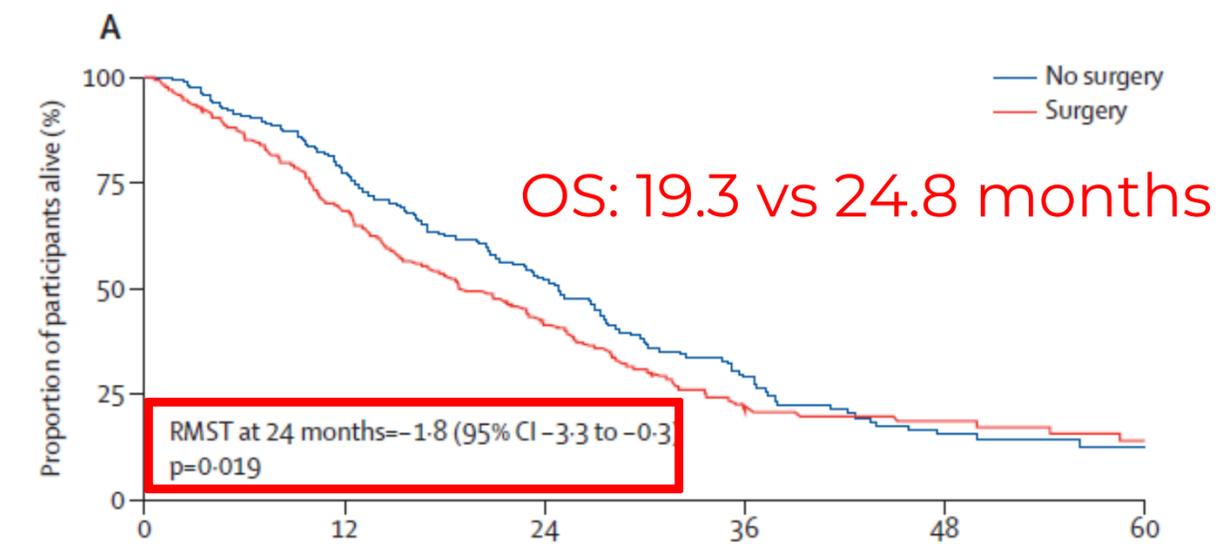


Adjuvant  
cisplatin +  
pemetrexed

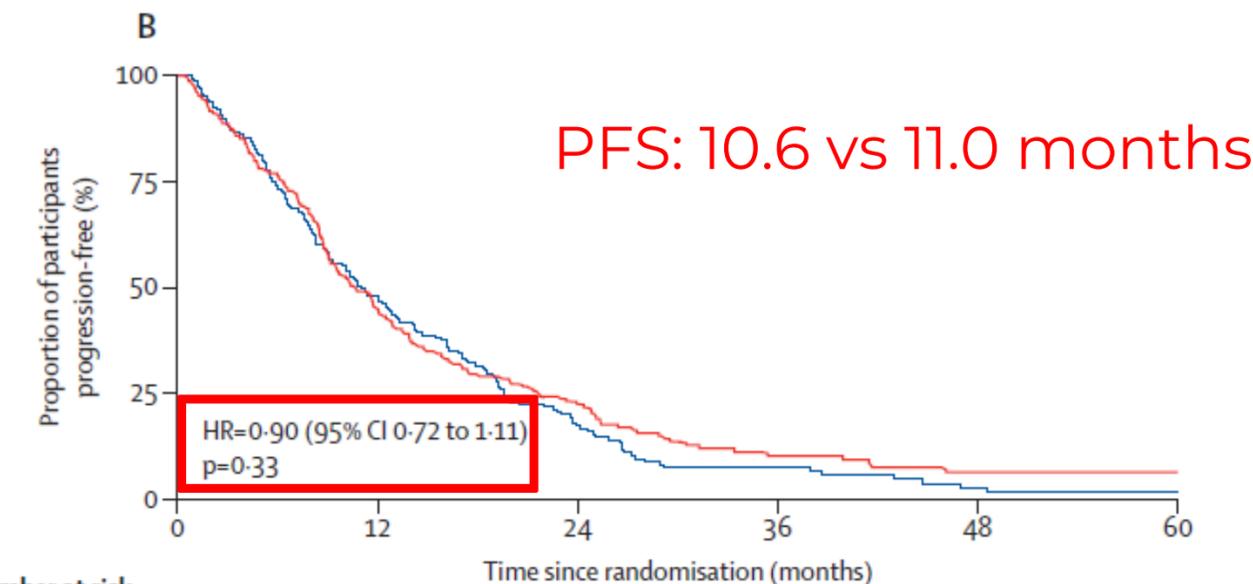


# MARS-2 – Phase III RCT

- 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)



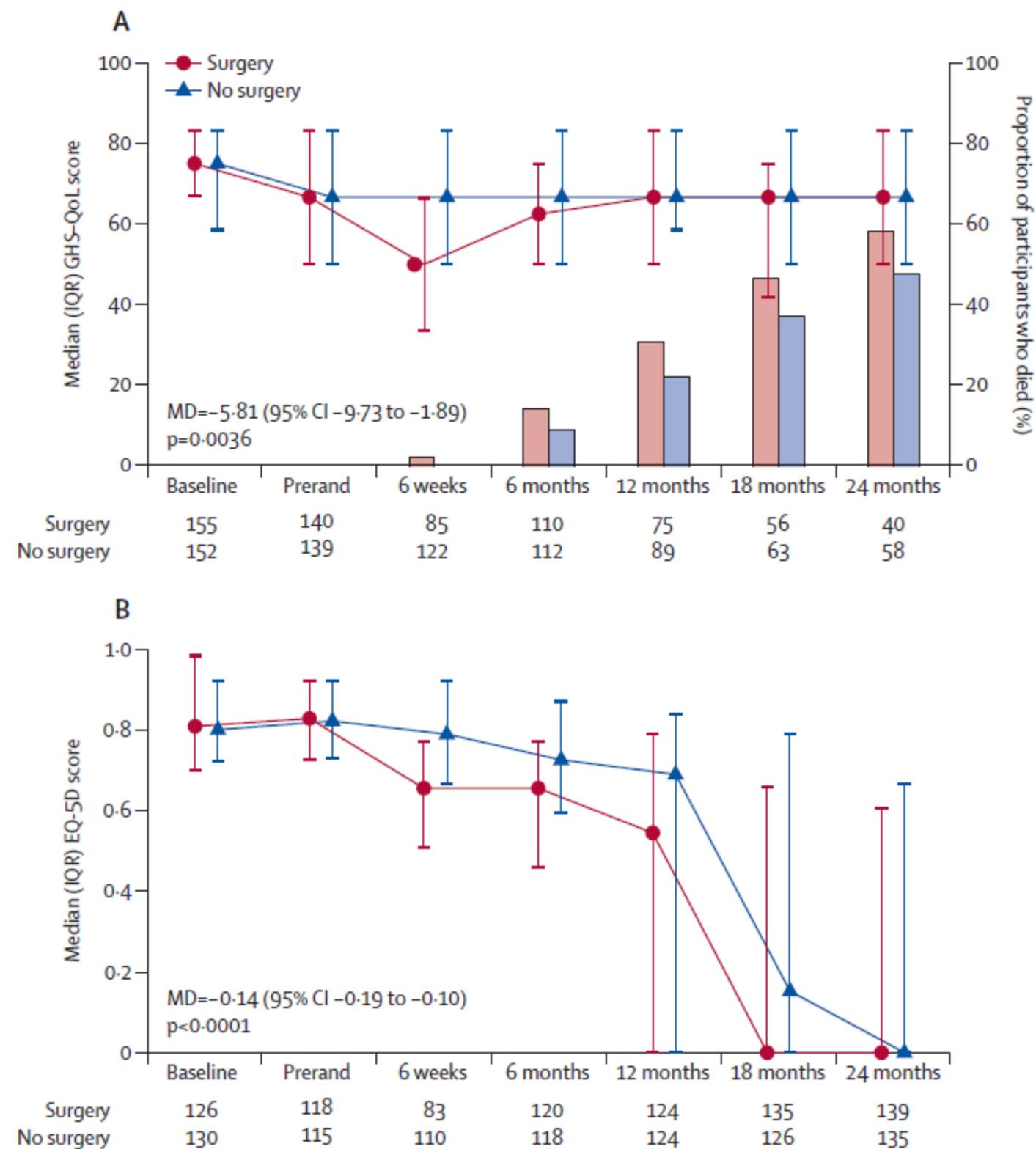
Number at risk (number censored)		0	12	24	36	48	60
No surgery	166 (1)	129 (4)	82 (14)	37 (7)	15 (7)	6 (6)	
Surgery	169 (1)	115 (6)	64 (14)	24 (6)	15 (5)	7 (7)	



Number at risk (number censored)		0	12	24	36	48	60
No surgery	166 (1)	78 (2)	27 (4)	9 (1)	3 (1)	1 (1)	
Surgery	169 (0)	76 (5)	33 (5)	11 (1)	6 (3)	3 (3)	

# MARS-2 – Outcomes

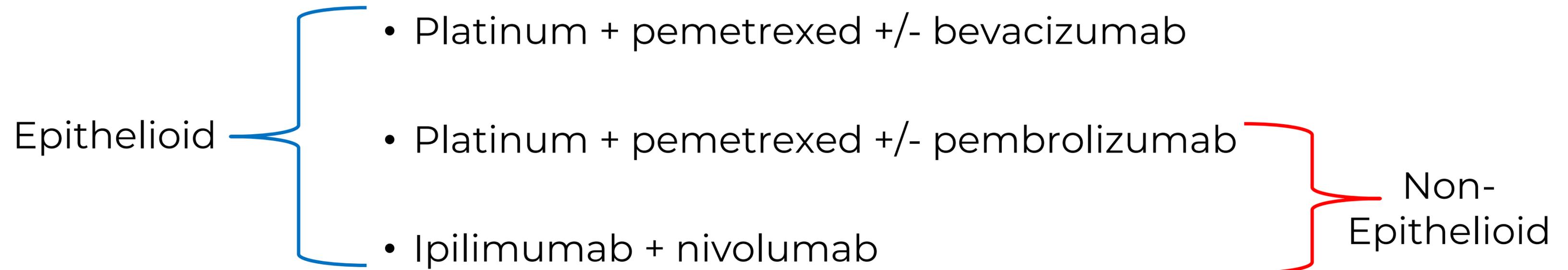
- Completeness of resection
  - R0 = 3%
  - R1 = 81%
- SAE increased with surgery
  - IRR 3.6 (95% CI 2.3-5.5)
  - Cardiac, respiratory, infection
- Worse HRQoL after surgery



# Management: Unresectable Disease

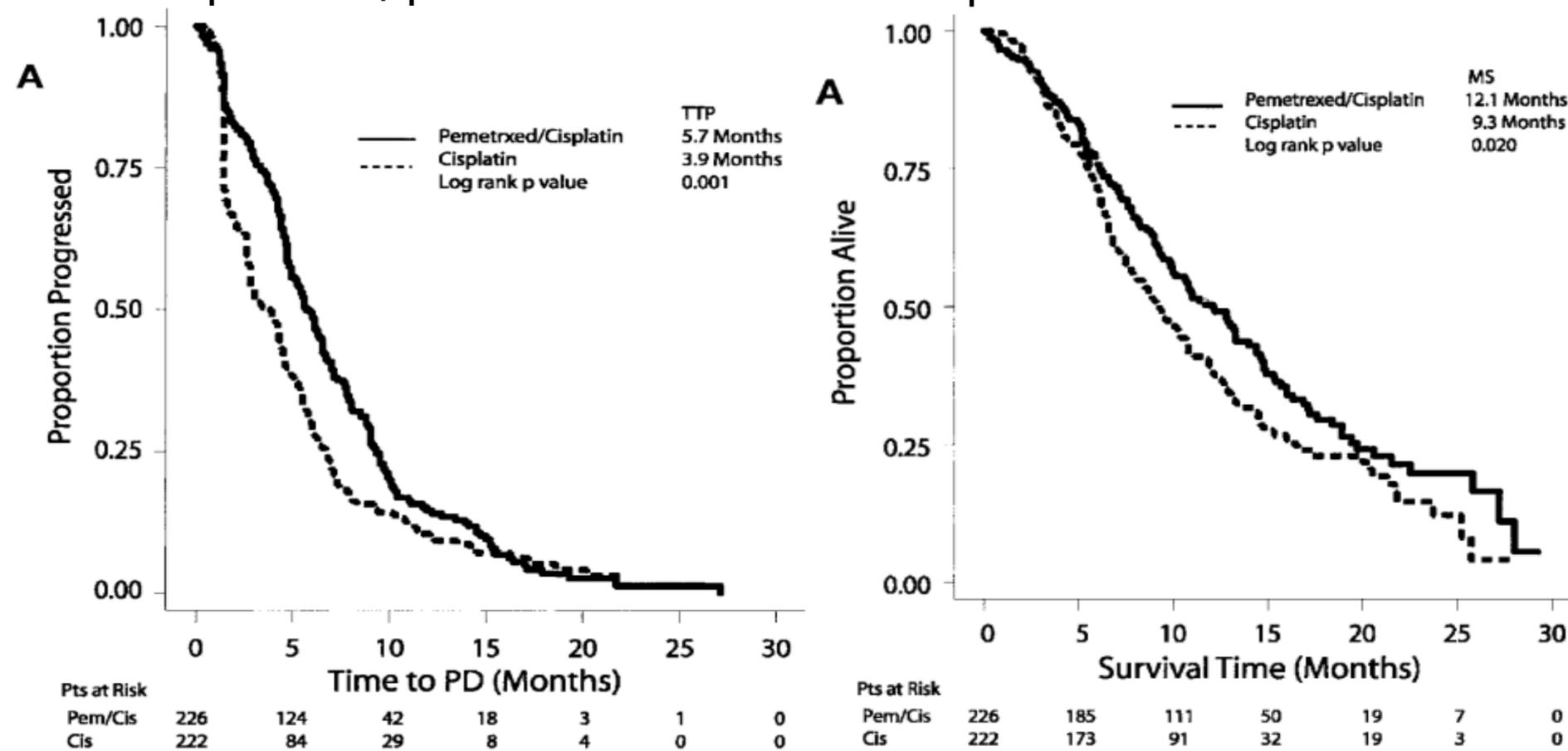
- Consider observation if:
  - Minimally symptomatic
  - Low disease burden
  - Favorable prognosis (i.e. germline *BAP1* mutation)

# Management: Unresectable Disease



# Management: Unresectable Disease

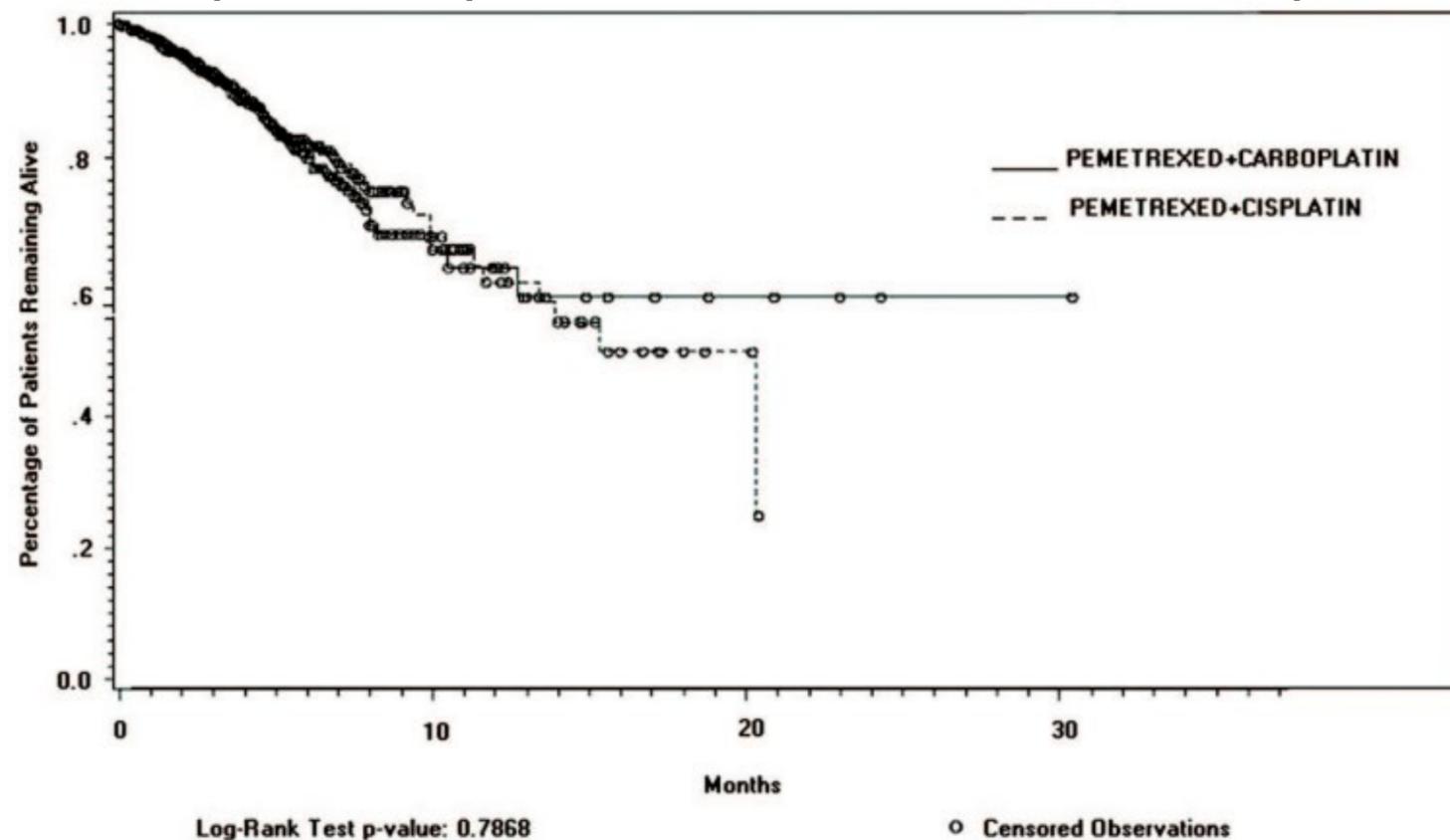
- Cisplatin/pemetrexed vs cisplatin alone



- 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

# Management: Unresectable Disease

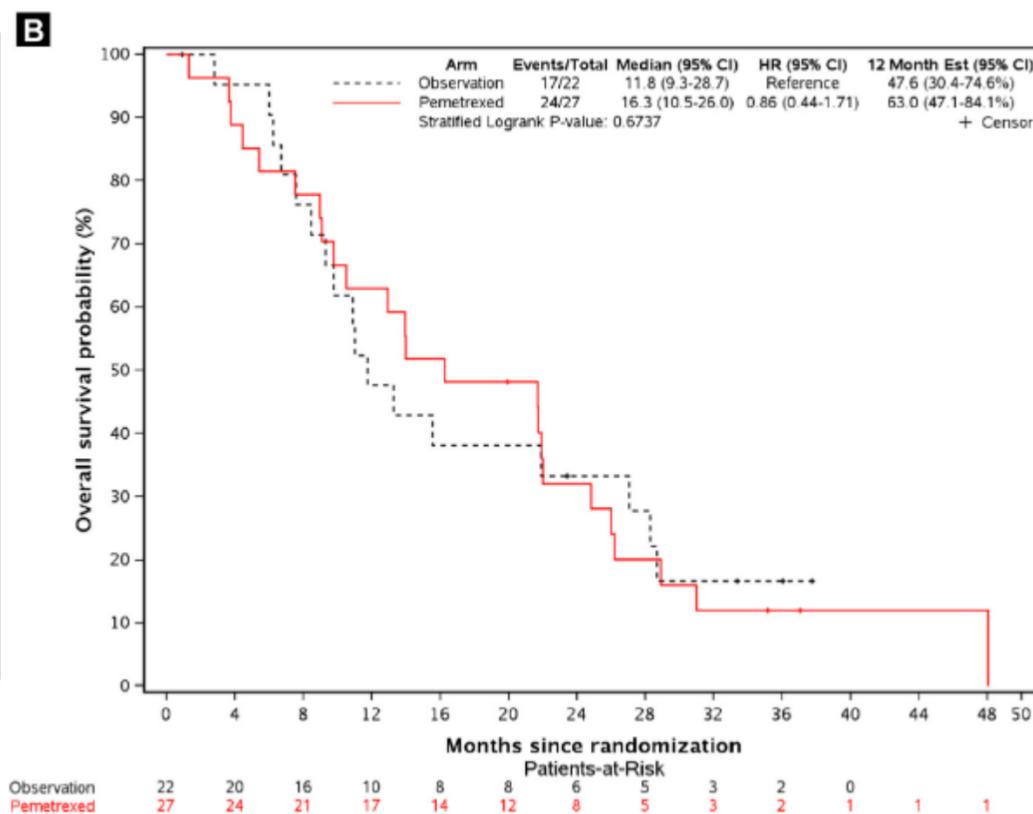
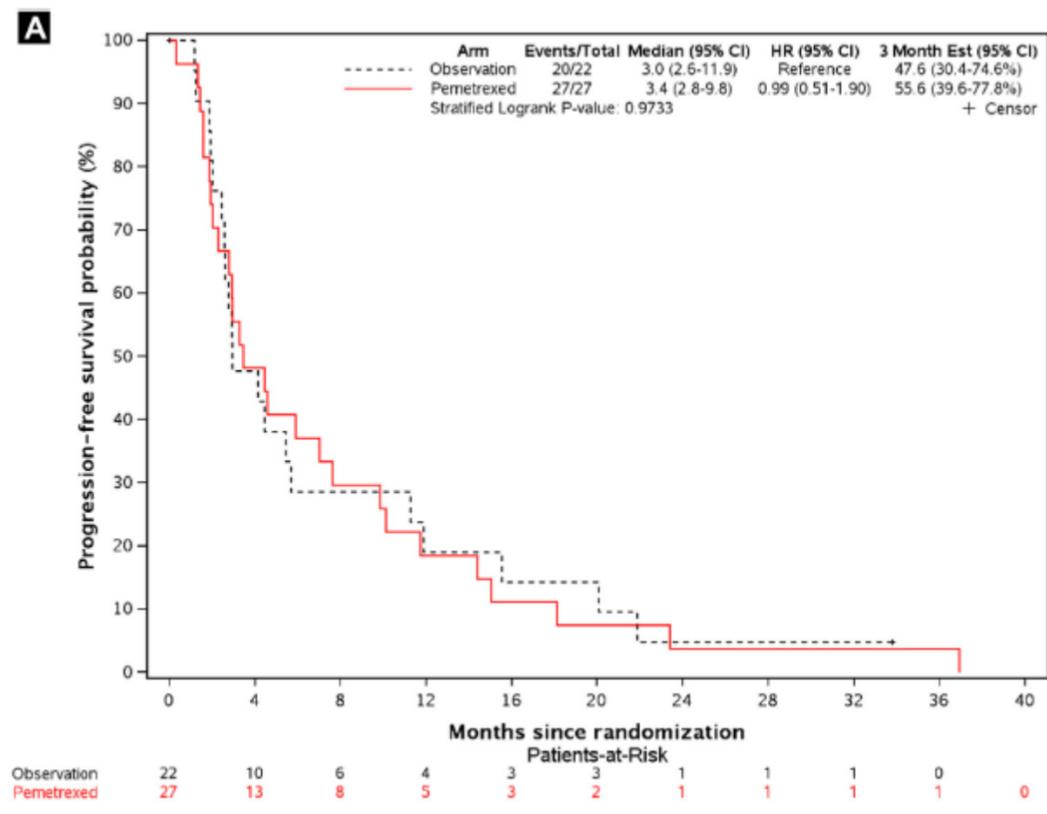
- Cisplatin/pemetrexed vs carboplatin/pemetrexed – can substitute



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

# Management: Unresectable Disease

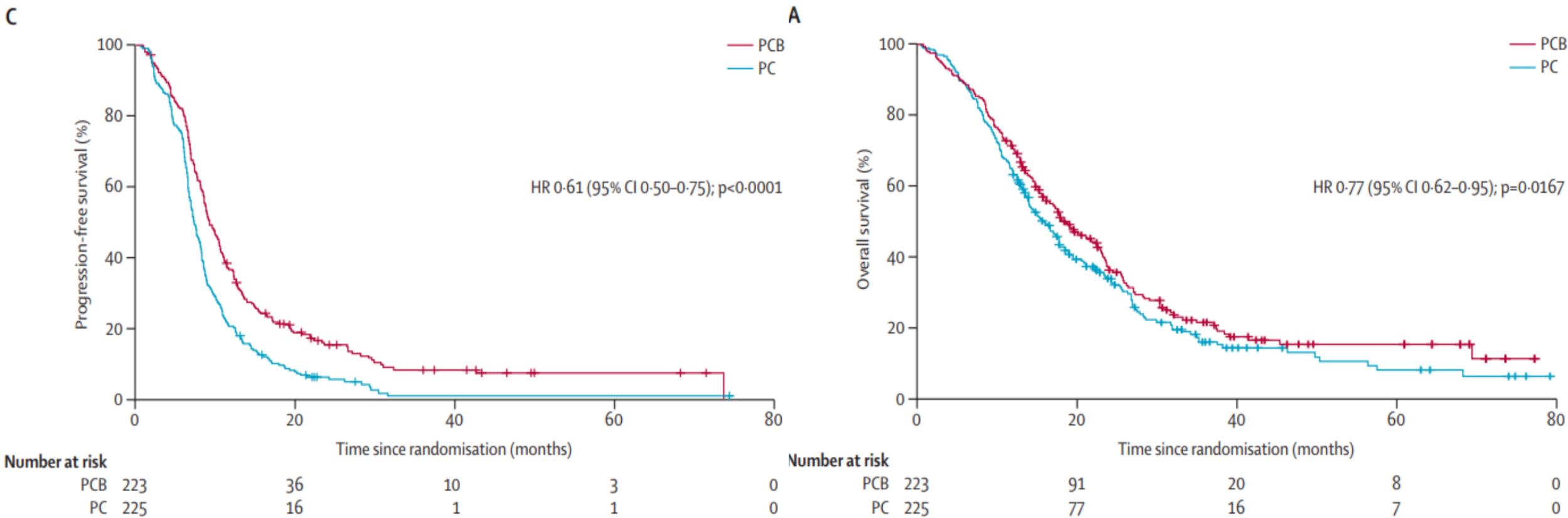
- Pemetrexed maintenance after platinum/pemetrexed? → **NO**



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

# Management: Unresectable Disease

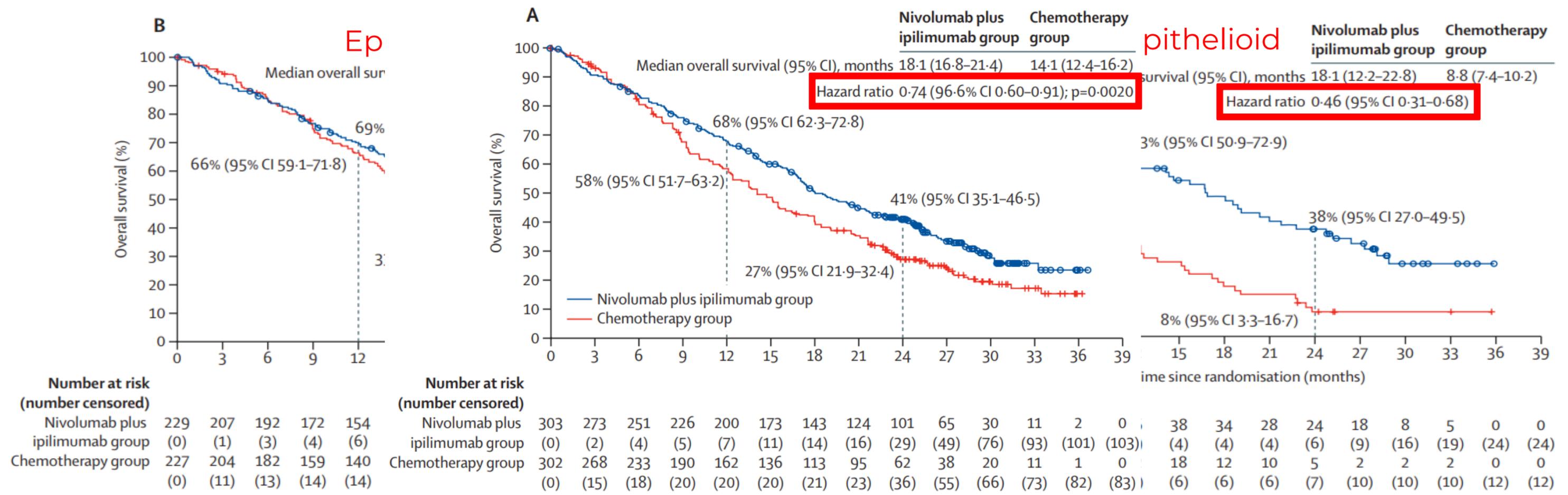
- Cisplatin/pemetrexed +/- bevacizumab (MAPS trial)



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

# Management: Unresectable Disease

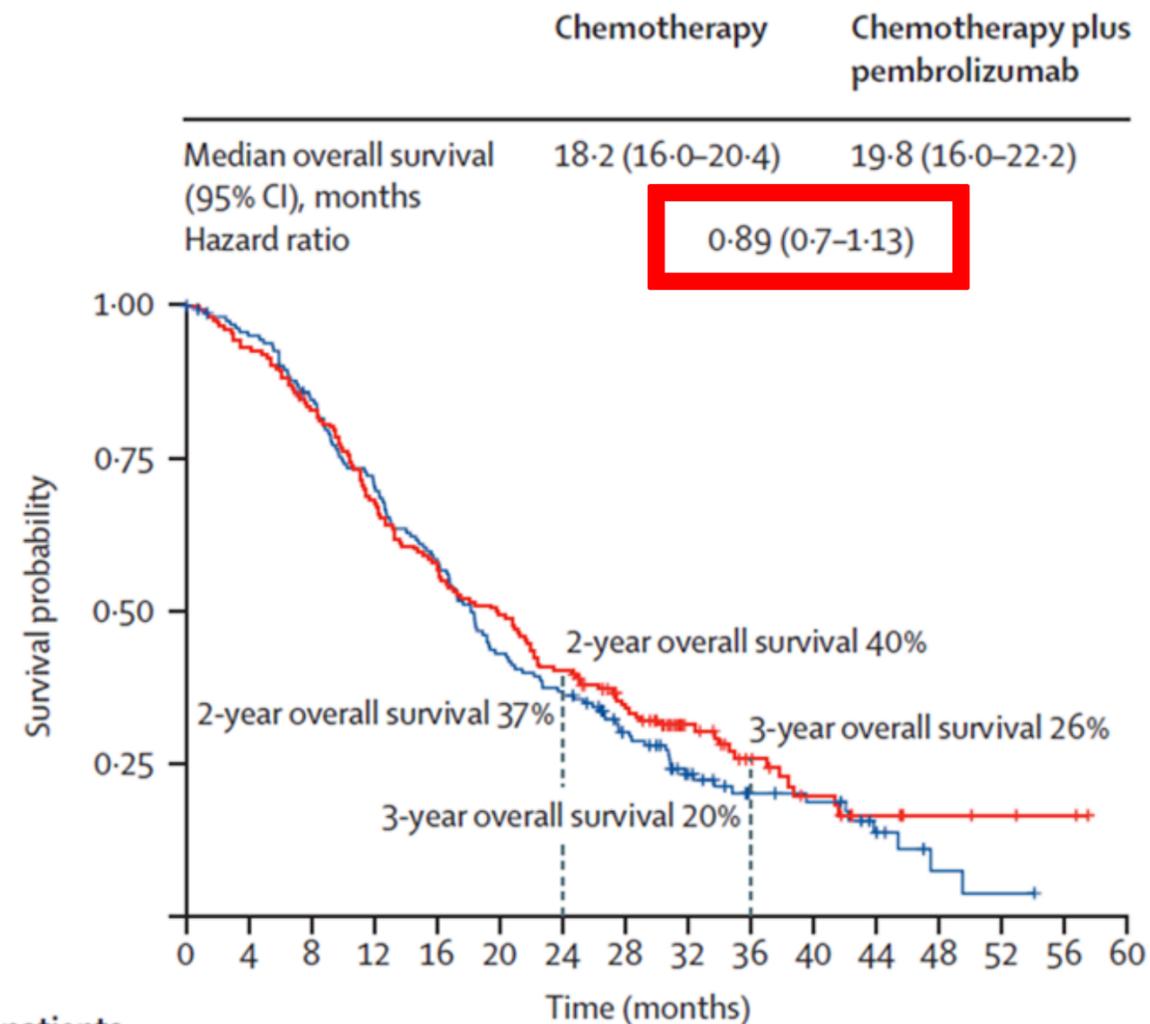
- Ipilimumab/nivolumab vs platinum/pemetrexed (CheckMate 743)



# Management: Unresectable Disease

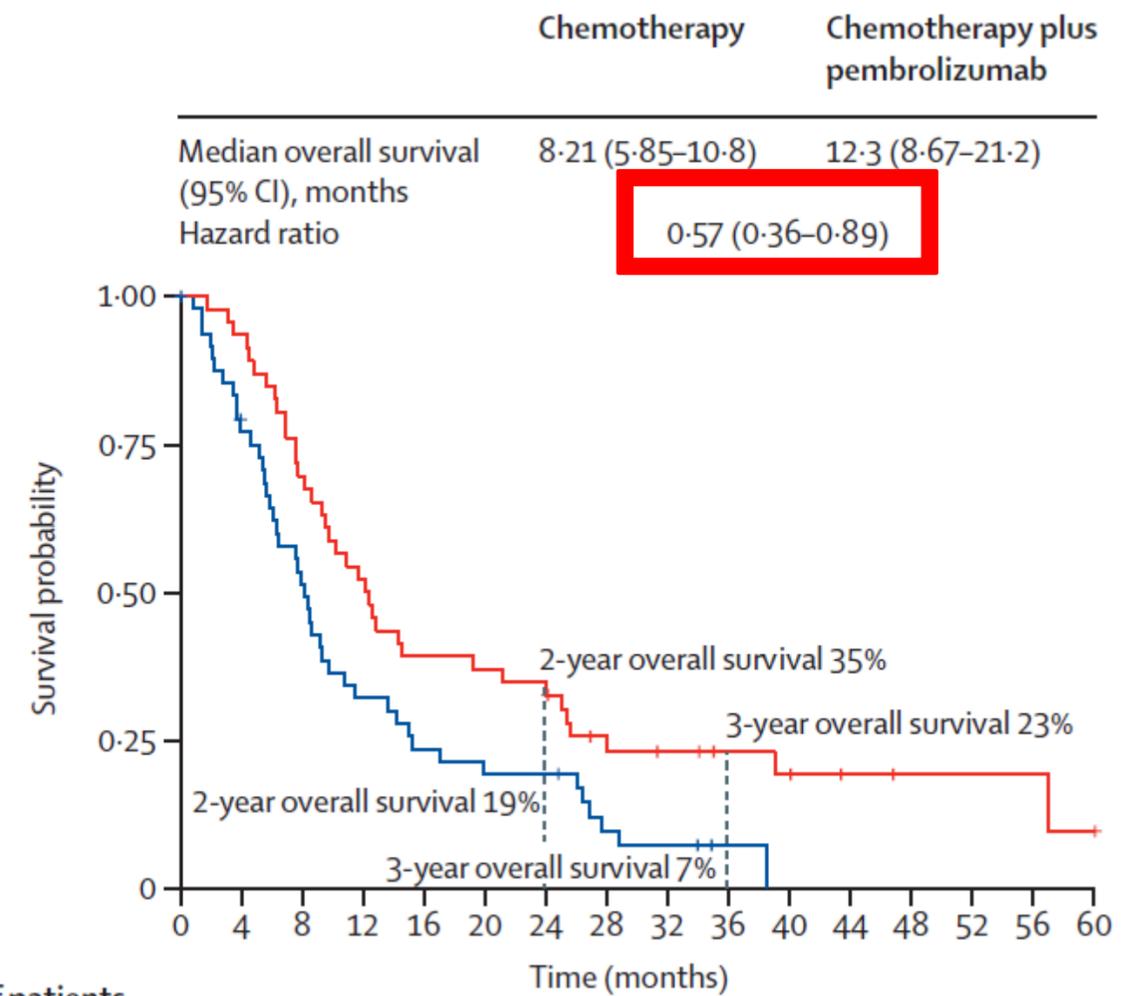
- Platinum + pemetrexed +/- pembrolizumab (IND227)

D Exploratory analyses: epithelioid (n=345)



Number of patients	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
Chemotherapy	169	154	136	113	94	69	59	42	26	15	13	7	2	1	0	0
Chemotherapy plus pembrolizumab	176	164	145	119	101	86	70	52	31	19	12	7	4	3	2	0

C Exploratory analyses: non-epithelioid (n=95)

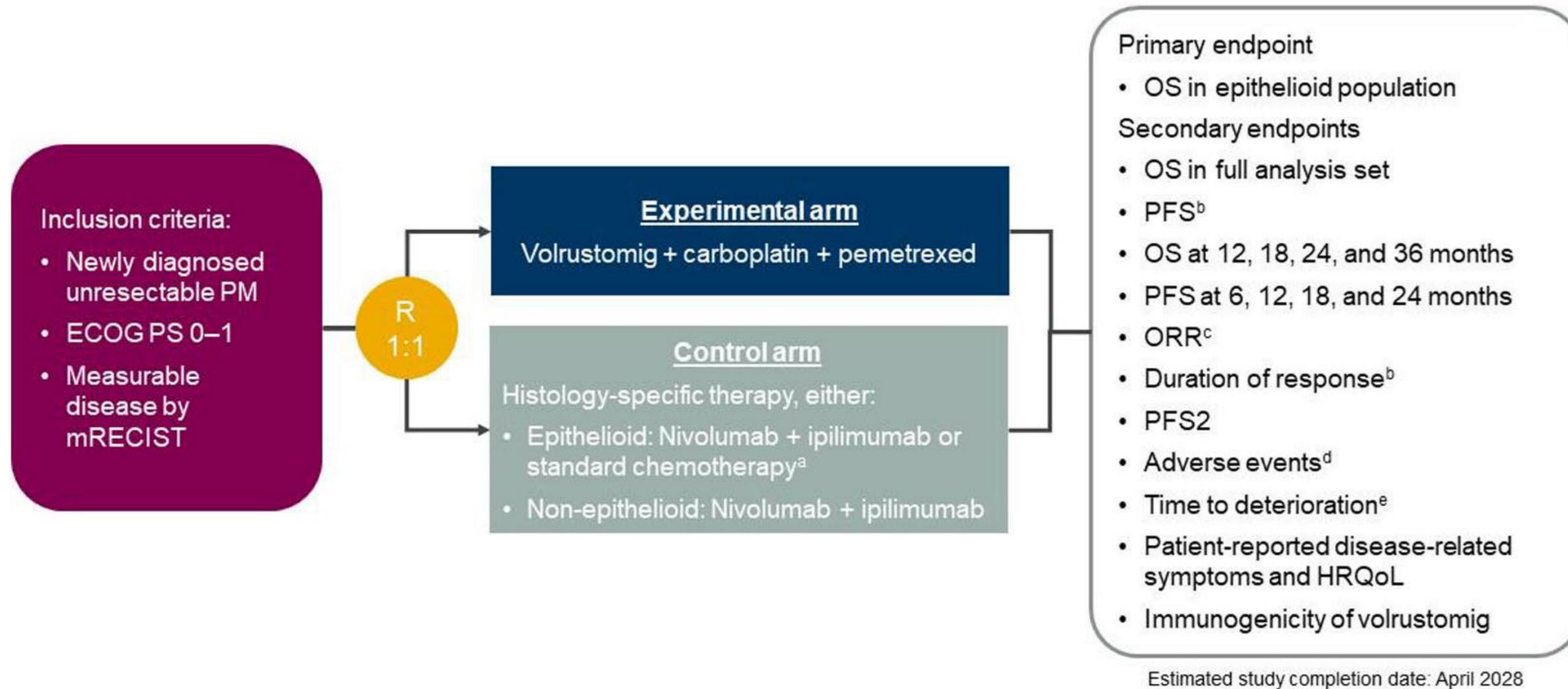


Number of patients	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
Chemotherapy	49	36	24	15	11	9	9	4	3	1	0	0	0	0	0	0
Chemotherapy plus pembrolizumab	46	43	32	24	18	17	16	10	8	6	5	3	2	2	2	1

# Management: Unresectable Disease

	ORR	DCR	Time to Rx
• Checkmate 743			
• Ipilimumab + nivolumab	40%	77%	2.7 mo
• Platinum + pemetrexed	43%	84%	2.5 mo
• IND227			
• Platinum + pemetrexed + pembro	62%	93%	2.6 mo
• Platinum + pemetrexed	38%	85%	2.6 mo

# Management: Upcoming Unresectable Disease



# Management: Relapse

- No FDA approved 2<sup>nd</sup> line regimens

## Chemotherapy (RR ~10%)

- **Vinorelbine**
- **Gemcitabine**
- **Pemetrexed  
rechallenge**

## Immunotherapy

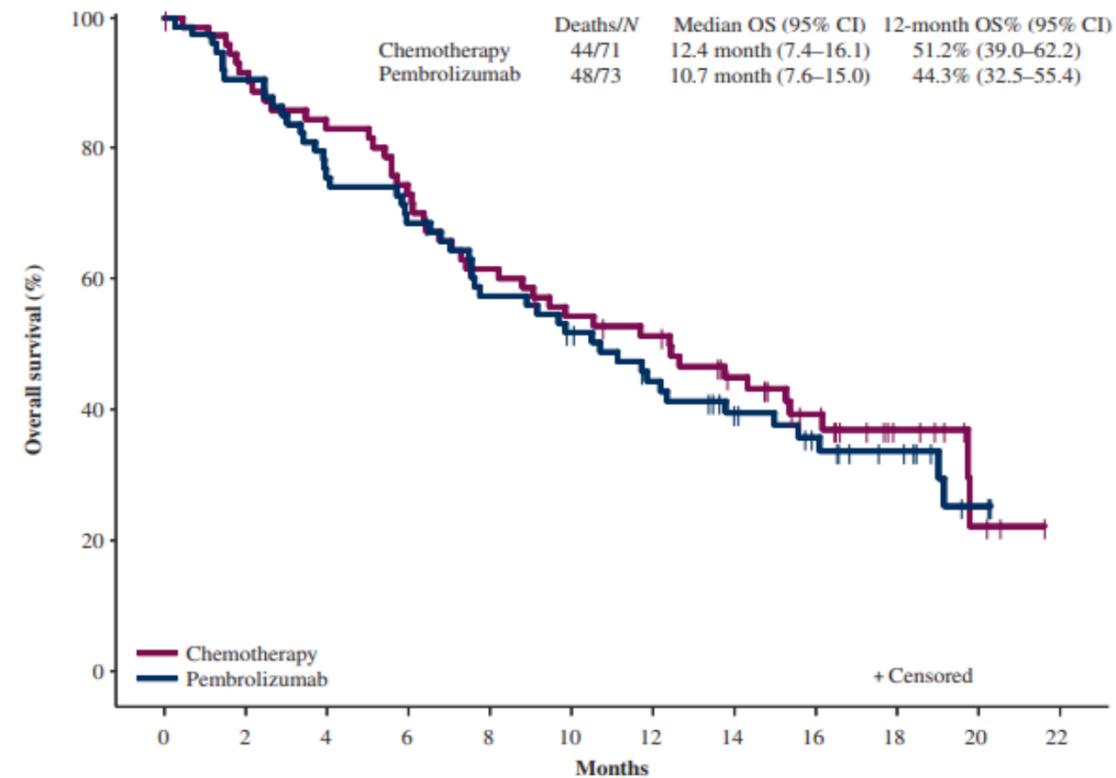
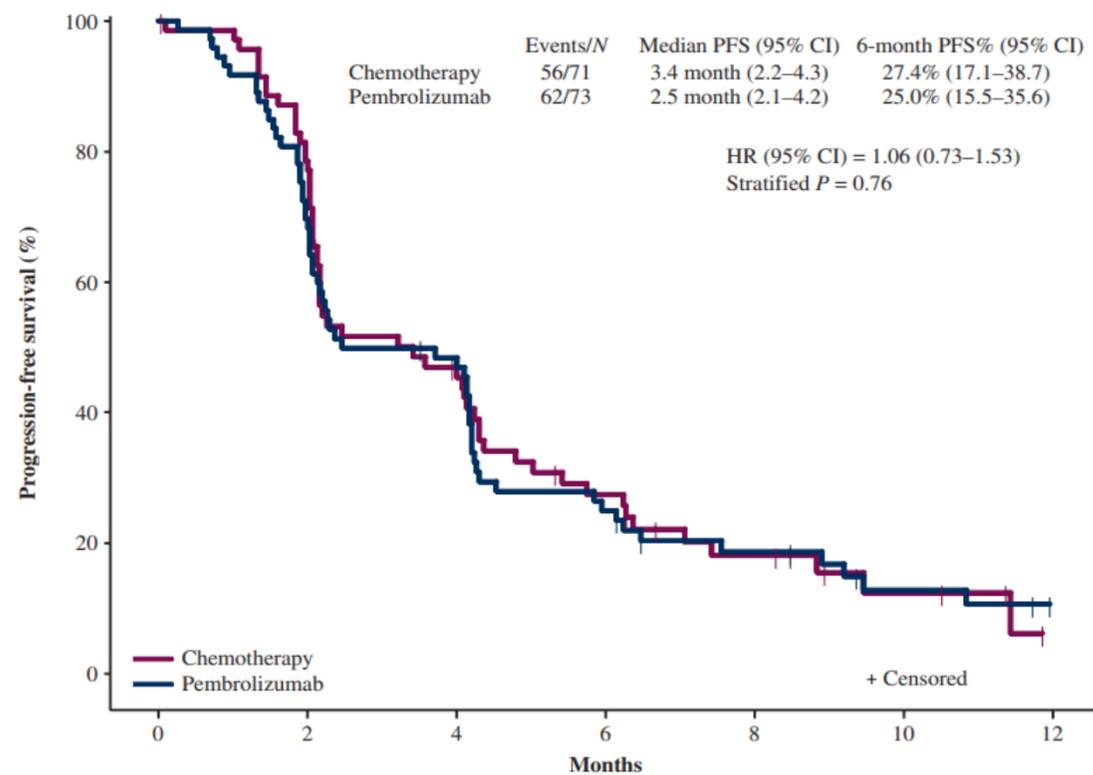
- Pembrolizumab
- Nivolumab +/-  
ipilimumab

## Anti-VEGF

- Gemcitabine +  
ramucirumab

# Management: Relapse

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



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

No. at risk (censored)

	0	2	4	6	8	10	12
Chemotherapy	71 (0)	55 (1)	29 (6)	16 (7)	9 (9)	4 (12)	0 (15)
Pembrolizumab	73 (0)	50 (1)	33 (3)	17 (3)	11 (5)	6 (7)	3 (9)

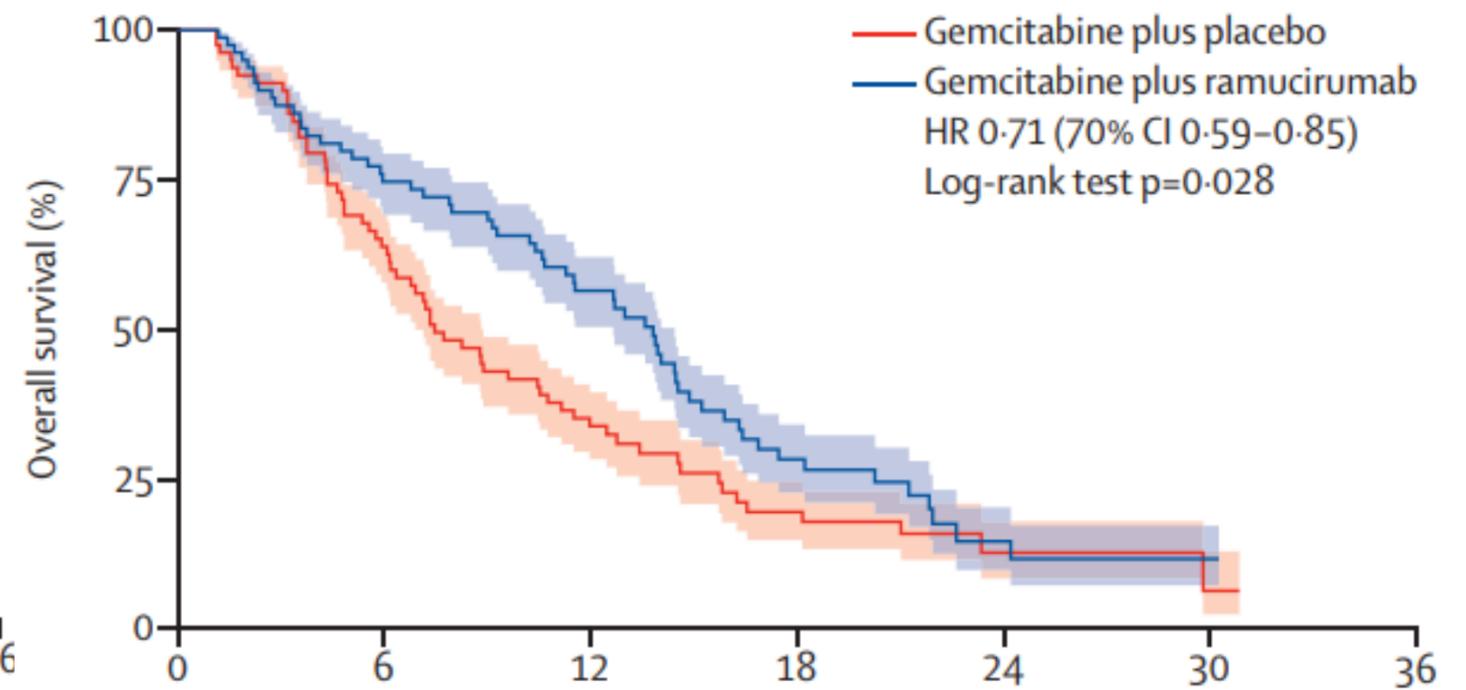
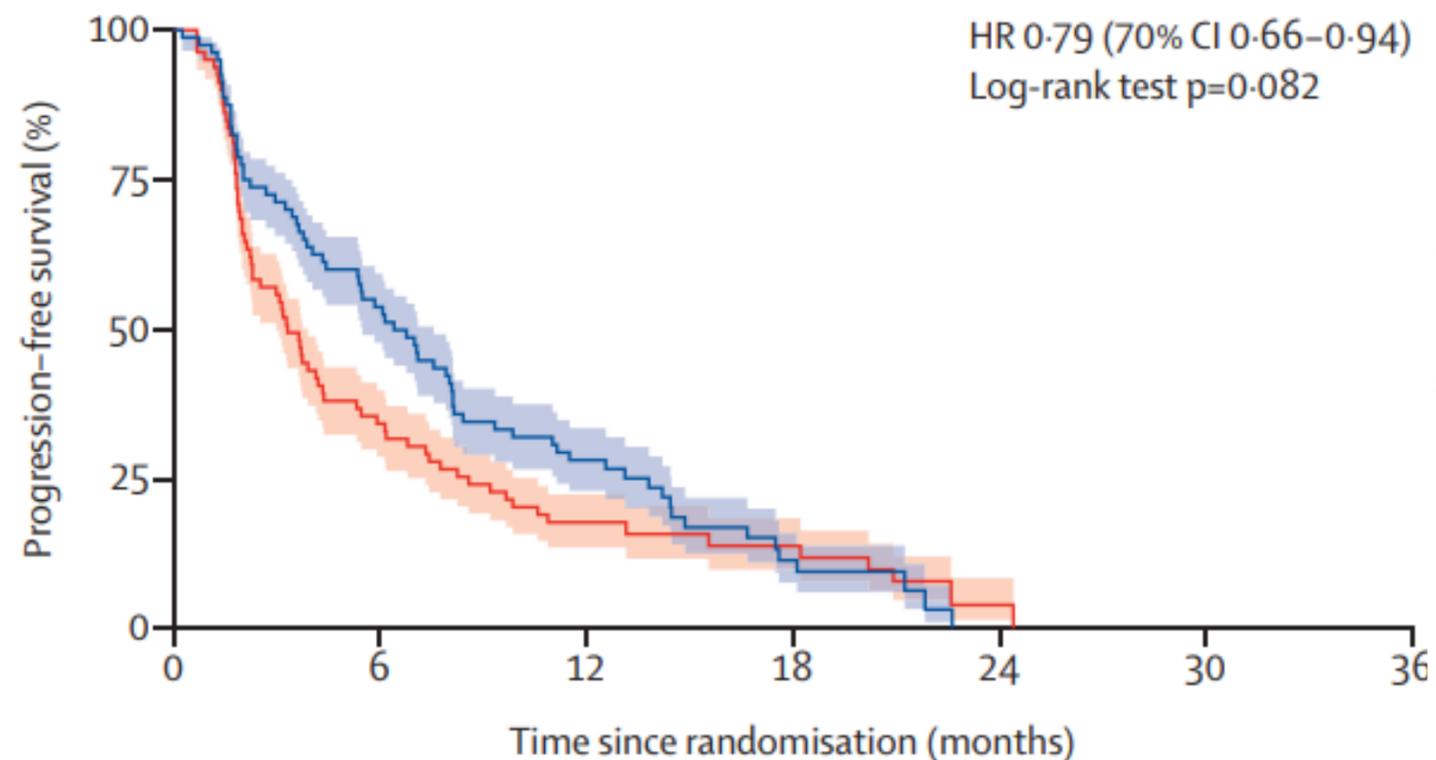
No. at risk (censored)

	0	2	4	6	8	10	12	14	16	18	20	22
Chemotherapy	71 (0)	64 (1)	58 (1)	51 (1)	43 (1)	37 (2)	34 (3)	26 (7)	18 (12)	9 (20)	3 (24)	0 (27)
Pembrolizumab	73 (0)	66 (0)	55 (0)	50 (0)	41 (1)	36 (2)	29 (4)	22 (8)	17 (11)	12 (15)	5 (20)	2 (23)

# 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



# Summary

- Germline *BAP1* mutation associated with improved prognosis
- Goal of surgery = macroscopic complete resection
- Resectable disease (in question due to MARS 2 data)
  - Neoadjuvant/adjuvant cisplatin/pemetrexed w/ either P/D or EPP +/- IMRT
- Unresectable disease
  - First line
    - Epithelioid: platinum + pemetrexed (+/- bev) (+/- pembro); ipi + nivo
    - Non-epithelioid: immunotherapy regimen
  - Second line: no FDA approved therapies

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**Thank You.**

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