City of Hope

THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

PLEURAL & PERITONEAL MESOTHELIOMA

Surgical Management of Peritoneal Malignant Mesothelioma

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Beebe Healthcare

Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

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Malignant Peritoneal Mesothelioma

Background

- **Rare malignant neoplasm arising from the serosa of the peritoneum**
- **Approximately 15-20% of all mesothelioma arises in the peritoneum**
  - **Incidence of 600-800 new cases in the U.S. annually**
- **MPM should be considered when imaging shows a diffuse abdominal process c/w malignancy**
- **Diagnosis is made on clinical, radiographic, and histopathological criteria:**
  - **CT, biopsy, serum biomarkers (CA-125)**
  - **Ascites, omental mass, no findings c/w a primary GI source**
  - **IHC positive for calretinin, CK 5/6, mesothelin, WT-1**
  - **IHC negative for CEA, ER**

Background

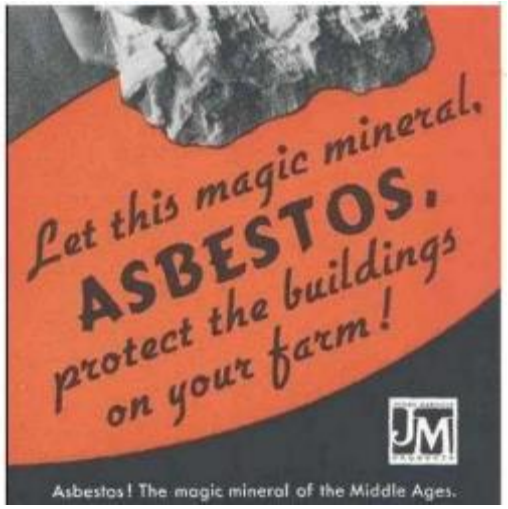
- **M:F ratio is 1:1**
- **Age at presentation 40-65 y**
- **Germline BAP-1 mutation: <10%**
  - **Increase susceptibility to MPM and other cancers**
- **Somatic BAP-1 mutation: 60% of MPM tumors**
- **Association with asbestos not firmly established (~50%)**
- **The disease is hallmarked by heterogeneity in its biological behavior**
- **Morbidity and mortality is due to regional peritoneal progression**
  - **Bloating, weight loss, pain, decreased appetite, early satiety**

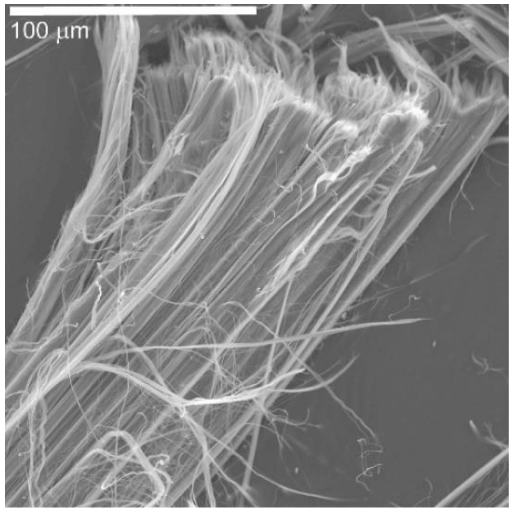
Historical Overview

- **First description of MPM**
  - **Miller and Wynn. J Pathol Bacteriol; 1908**
  - **Case report 32 y/o male with abdominal pain, “diffuse neoplastic process”**
- **Initial report of a series of 12 patients**
  - **Winslow and Taylor. Cancer; 1960**
  - **First called MPM**
- **Initial observation of an association between asbestos and mesothelioma**
  - **Irving Selikoff et al. JAMA. 1964;188:22-6.**
- **First comprehensive clinical review**
  - **Moertel, C. Gastroenterology; 1972**
- **Initial report of multimodal therapy—DFCI/UMMC**
  - **Antman et al. J Clin Oncol 1983**

Malignant Peritoneal Mesothelioma

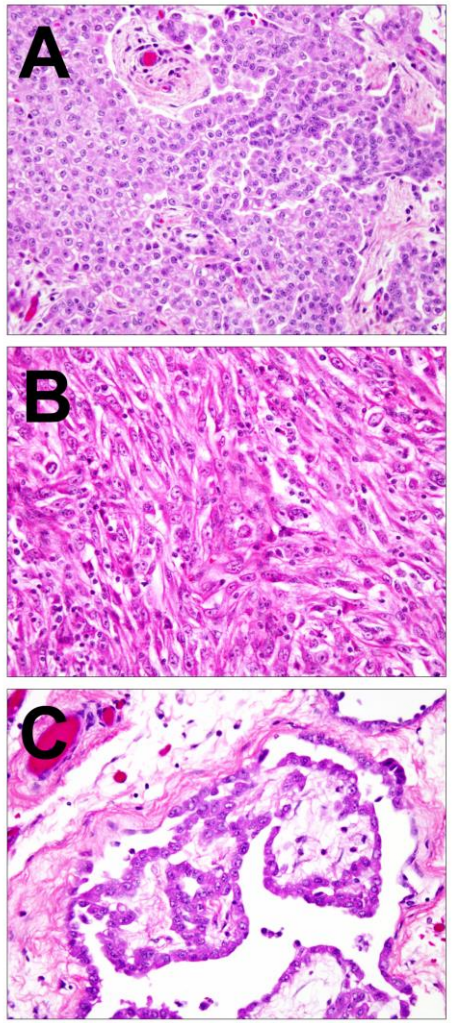
- Incidence of mesothelioma is decreasing
  - Incidence highest in the 1960s
  - Decreasing in countries where asbestos has been banned or regulated since the 1970s
  - Top world asbestos producer is currently Russia
- Asbestos is a silicate mineral (400 fibers) or which 6 are used commercially
  - Woven into a cloth with insulating and fireproofing properties





Malignant Peritoneal Mesothelioma

Histological Subtypes in MPM Have Distinct Biological Behaviors



Solid Epithelioid

Biphasic/Sarcomatoid

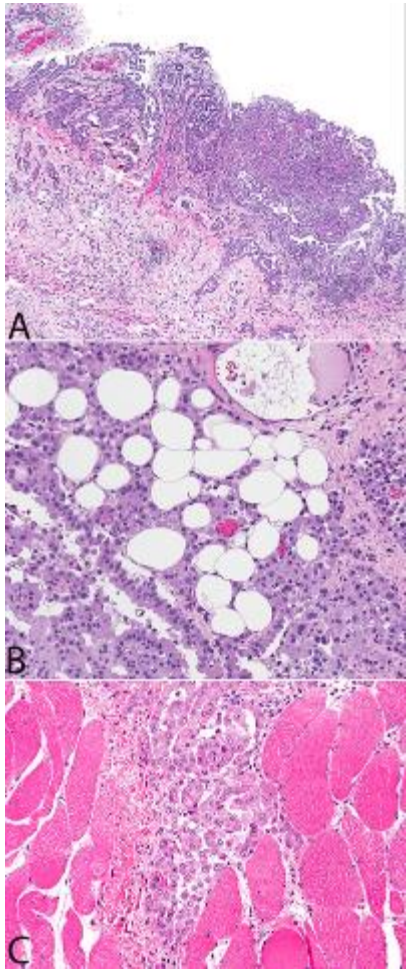
Tubulopapillary

Malignant Peritoneal Mesothelioma

Biologic Importance of Tissue Invasion: Analysis of 71 MPM Tumors

Grading System for MPM Invasion

- Grade 0: absent
- Grade 1 stroma
- Grade 2 (fat)
- Grade 3 (adjacent structures)



Liu et al. Pathology. 2014; 46:604-9.

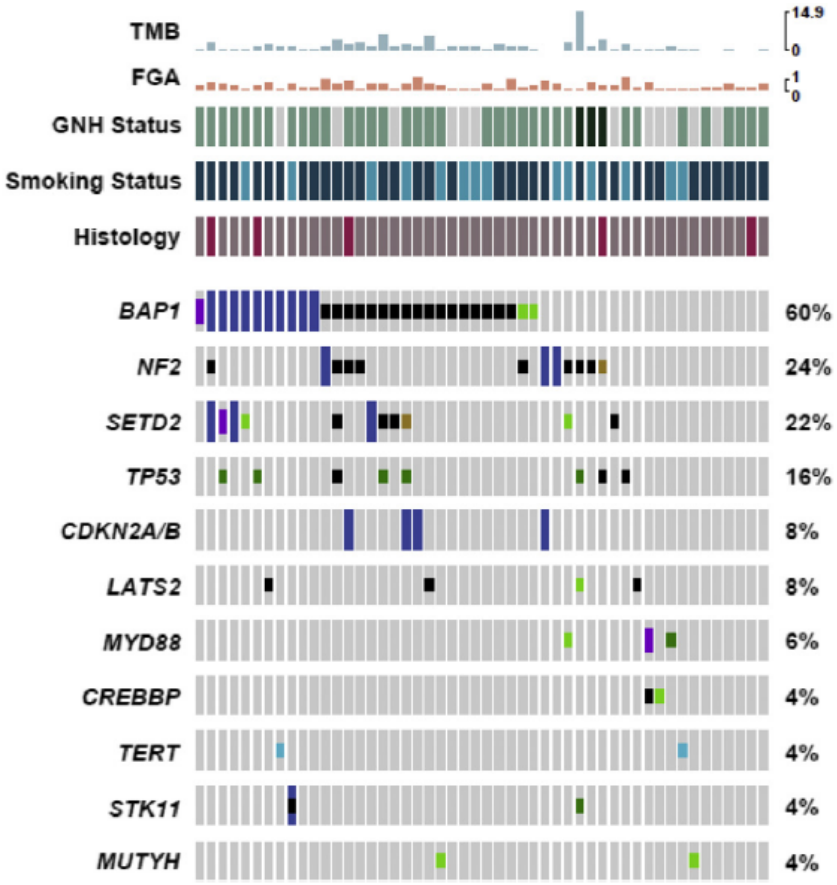
Malignant Peritoneal Mesothelioma

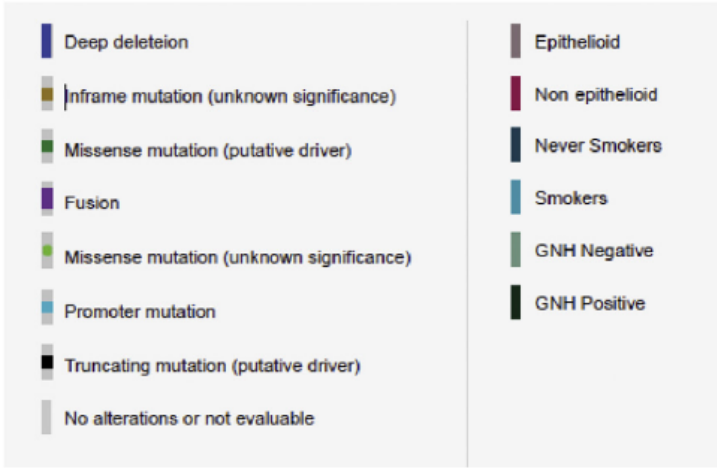
Immunohistochemical Features of MPM

Antibody	N	Positive (%)	Pattern
EGFR	32	94	Membrane, cytoplasmic
CA 125	17	94	Membrane
Calretinin	41	93	Nuclear, cytoplasmic
P16	15	80	Nuclear, cytoplasmic
Cytokeratin 5/6	21	76	Cytoplasmic
WT-1	67	70	Nuclear

Malignant Peritoneal Mesothelioma

Genomic mutational profile of MPM





Offin et al. J Thor Oncol 2021

Peritoneal Metastases

Overview of the CRS/HIPEC Technique

- **Exploratory laparotomy, lysis of adhesions, cytoreduction**
- **Insertion of cannulas and temperature probes**
- **Close fascia or skin**
- **Connect perfusion circuit**
  - **Roller pump, heat exchange coil**
- **Circulate and heat**
- **Add therapeutic agent**
- **Perfuse for 90-120 minutes**

Malignant Peritoneal Mesothelioma

HIPEC Technique

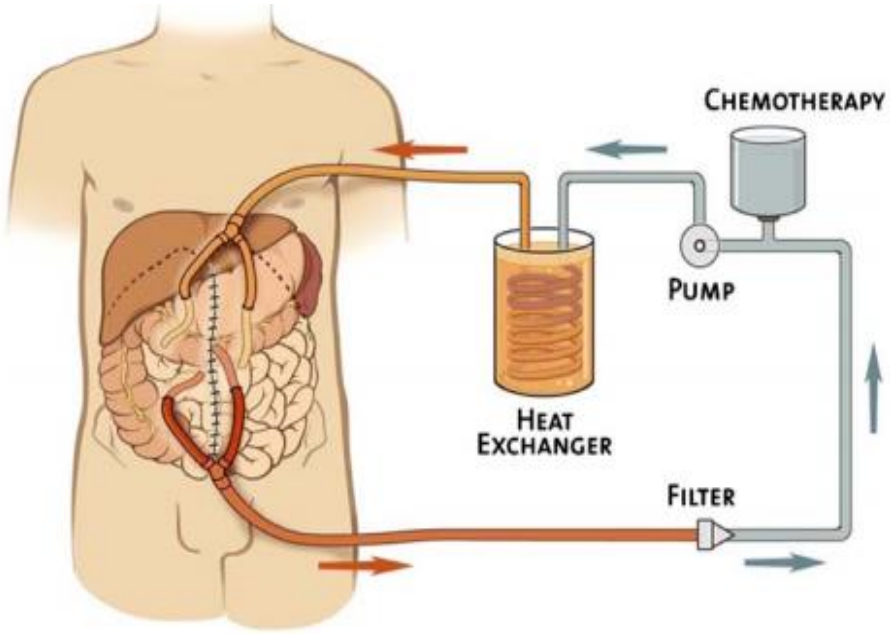
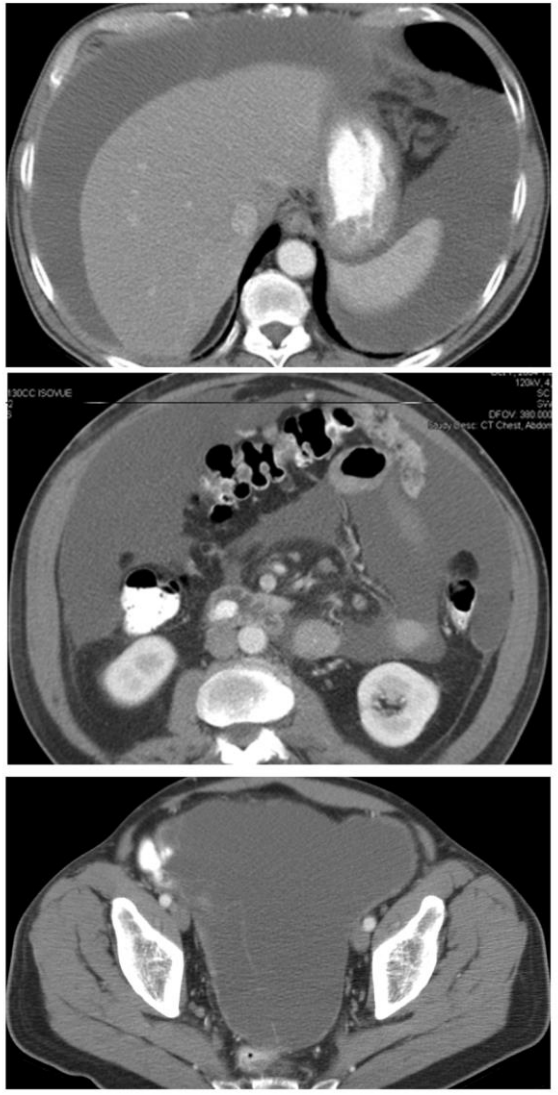
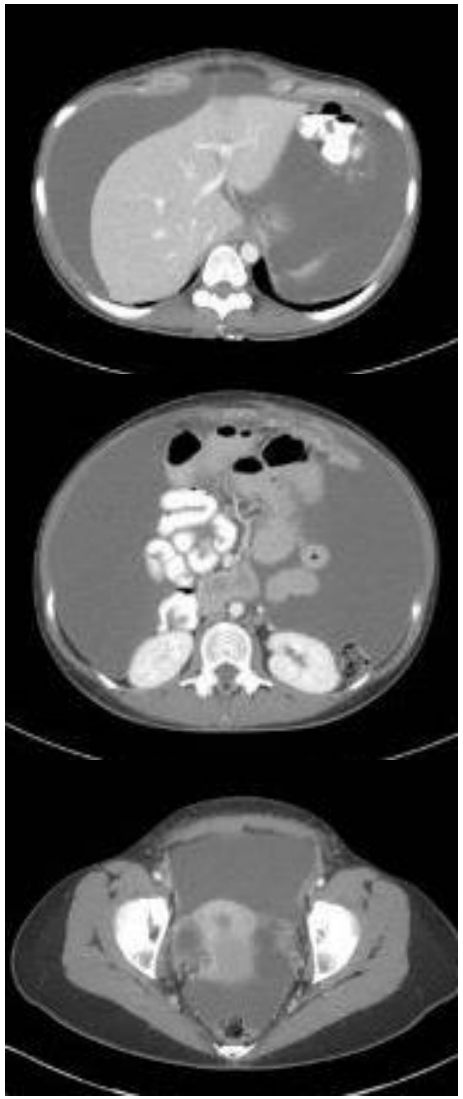


FIG. 1. Schematic of intraperitoneal hyperthermic chemotherapy setup (closed technique).

Malignant Peritoneal Mesothelioma

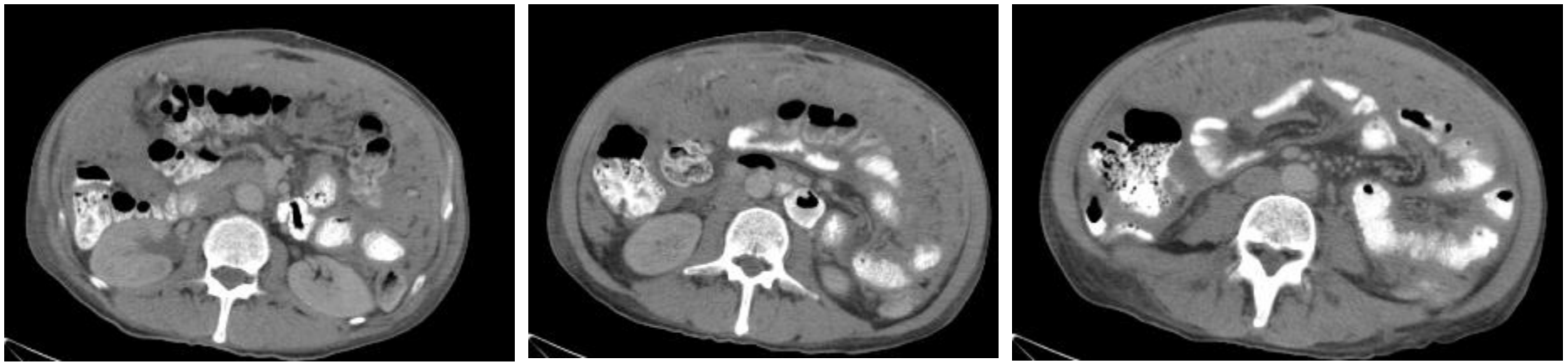
Radiographic Features Are Important in Patient Selection

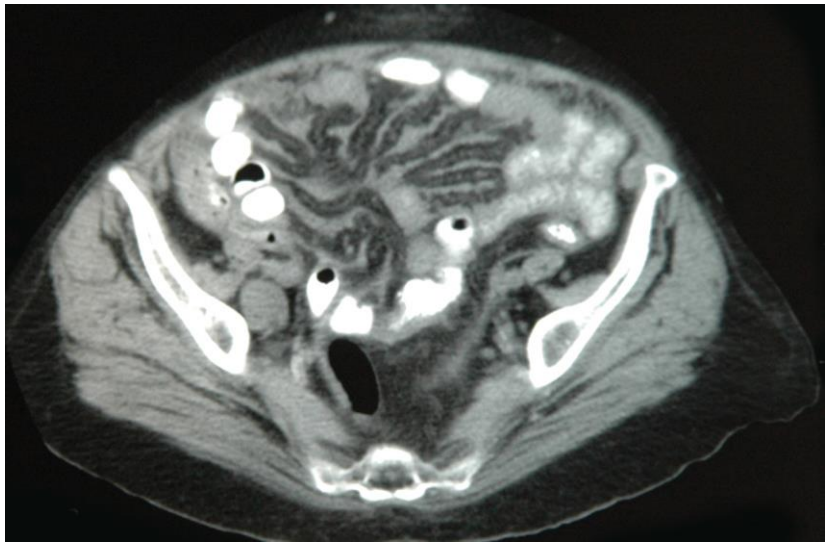




Malignant Peritoneal Mesothelioma

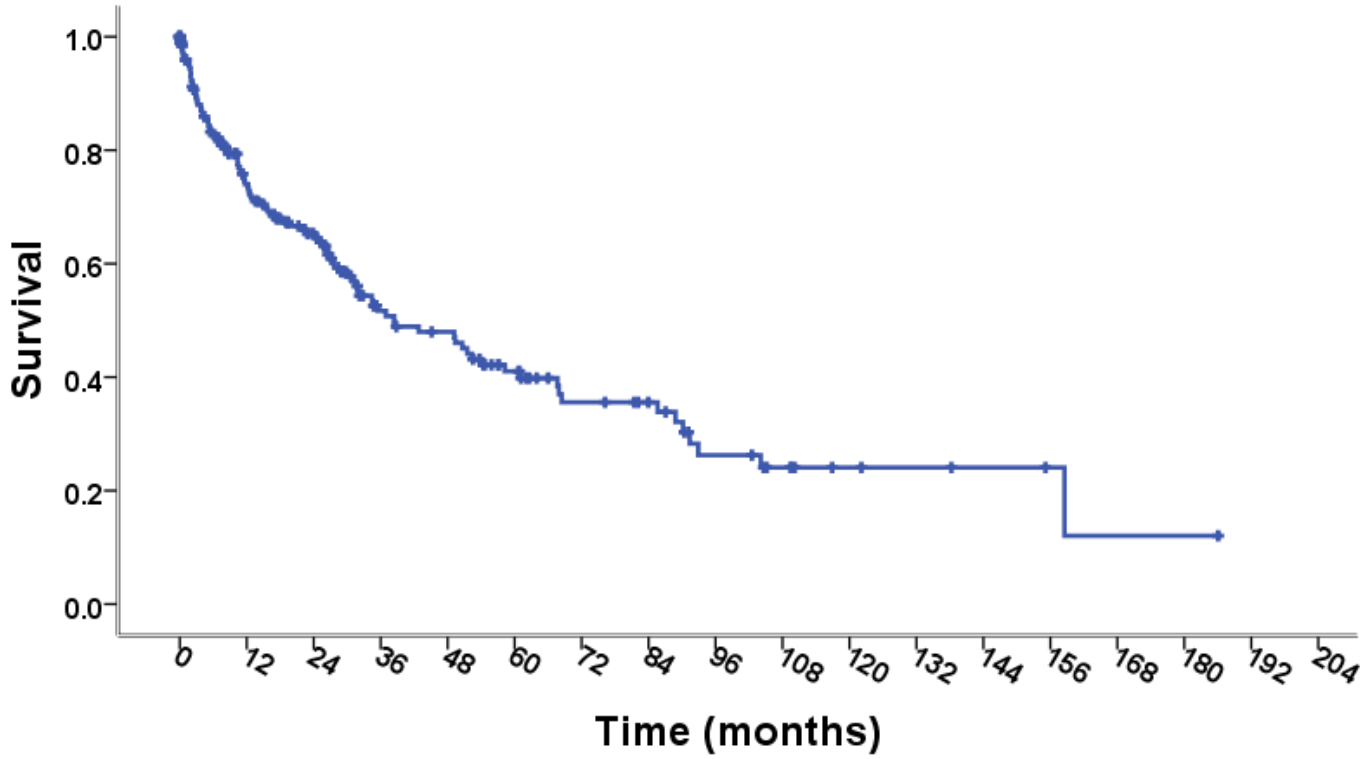
Unresectable MPM: Usually Not Amenable to CRS





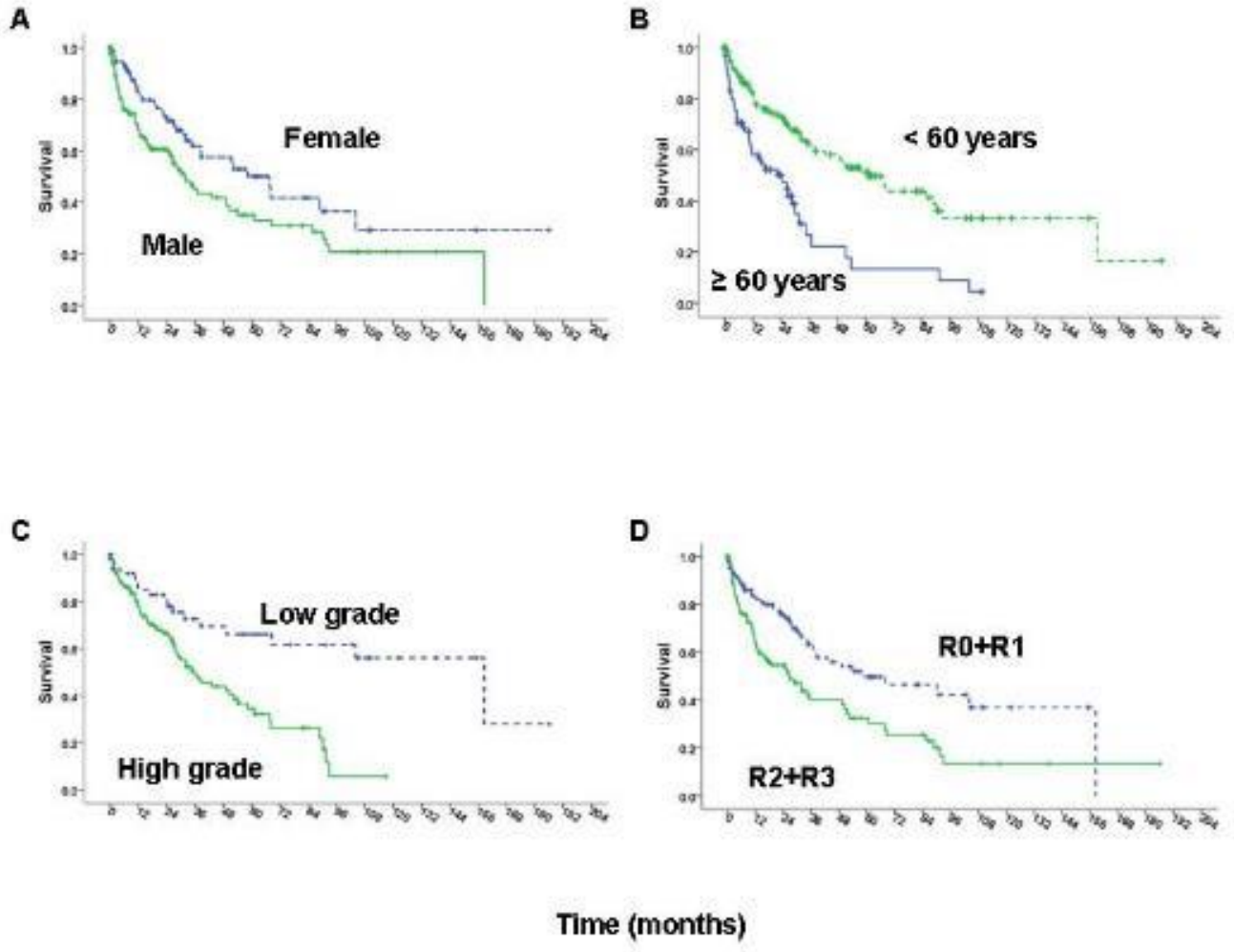
Malignant Peritoneal Mesothelioma

Actuarial Overall Survival 211 Patients with MPM



Alexander et al. Surgery 2013

Malignant Peritoneal Mesothelioma



Alexander et al. Surgery 2013

Malignant Peritoneal Mesothelioma

Multivariate analysis of factors independently associated with outcome

	Hazard ratio	95% confidence interval	Standard error	*P* value
Sex				
Male	1.62	0.85-3.07	0.33	0.14
Female	1			
Previous chemotherapy				
Yes	1.11	0.57-2.14	0.34	0.76
No	1			
Residual disease				
CCR>1	2.70	1.32-5.51	0.36	<0.01
CCR≤1	1			
PCI				
>20	2.81	1.10-7.22	0.48	0.03
≤20	1			
Platelet count				
Abnormal (>367)	2.42	1.30-4.49	0.32	<.01
Normal (≤367)	1			

Malignant Peritoneal Mesothelioma

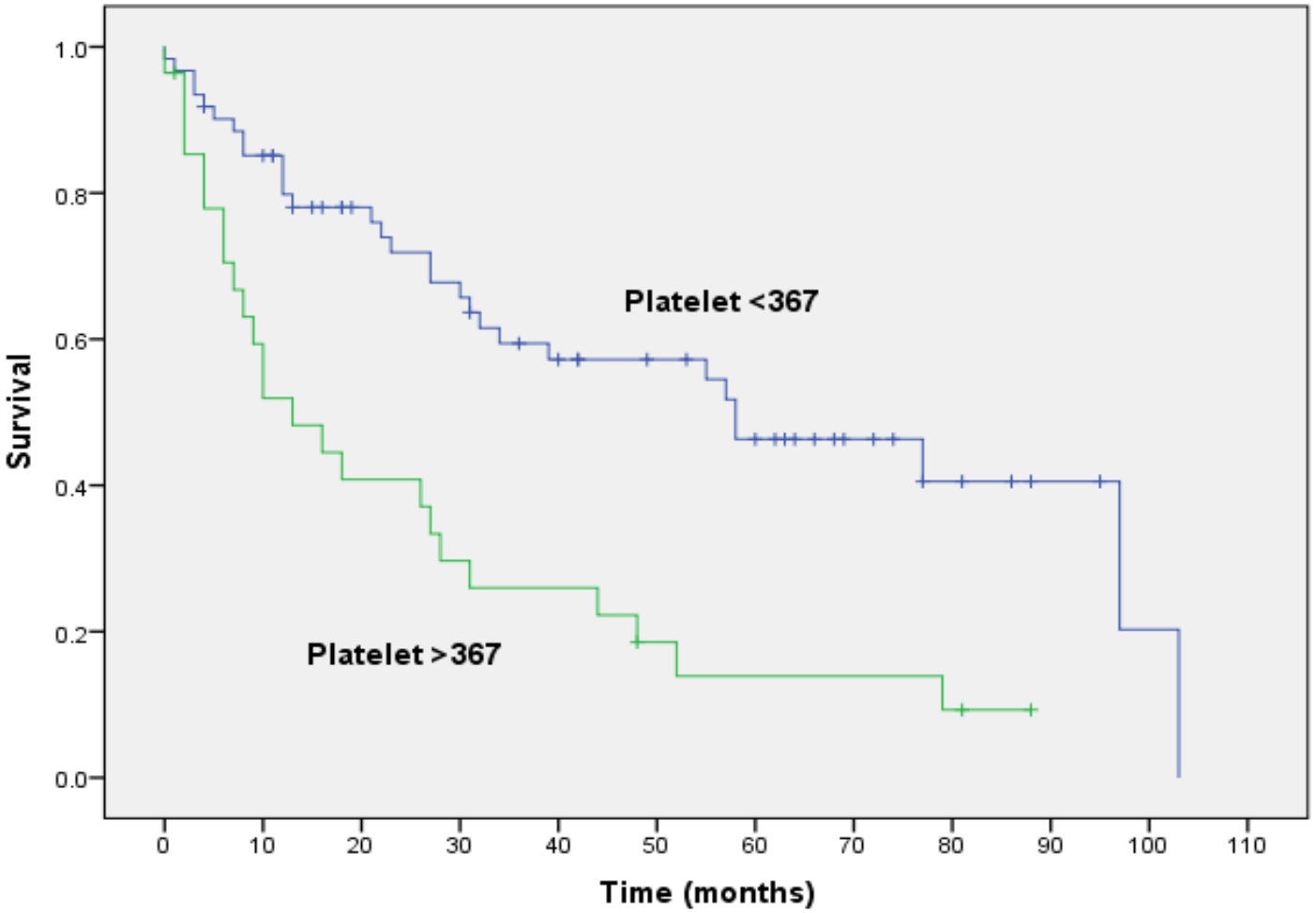
Baseline thrombocytosis is an important surrogate for aggressive biological behavior: Clinicopathologic Factors of 100 MPM patients

	N		Percentage (%)
Sex			
Male	**53**		**53**
Female	**47**		**47**
Age (yrs)			
Mean		**54**	
Median		**57**	
Range		**17-81**	
Race			
White	**85**		**85**
Non-white	**15**		**15**
Previous chemotherapy			
Yes	**29**		**29**
No	**71**		**71**
Residual Disease			
CCR≤1	**80**		**80**
CCR>1	**17**		**17**
Unknown	**3**		**3**
Peritoneal cancer index			
≤20	**29**		**29**
>20	**65**		**65**
Unknown	**6**		**6**
Platelet count			
Mean		**351**	
Median		**305**	
Range		**109-1362**	

Li et al. Ann Surg Oncol. 2017;24:2259.

Malignant Peritoneal Mesothelioma

Thrombocytosis is an Important Prognostic Factor in MPM Patients



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Malignant Peritoneal Mesothelioma

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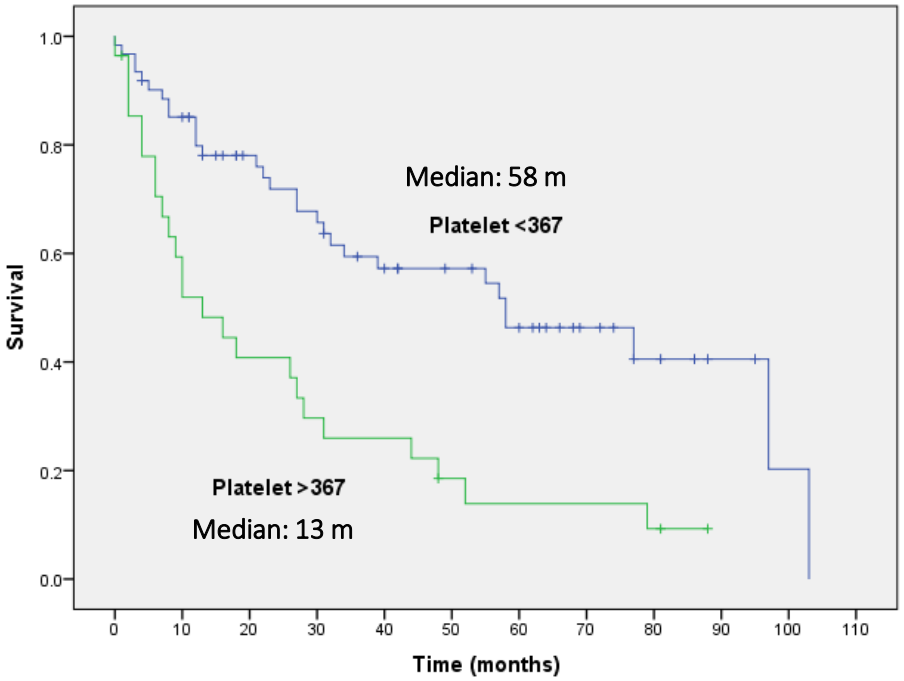
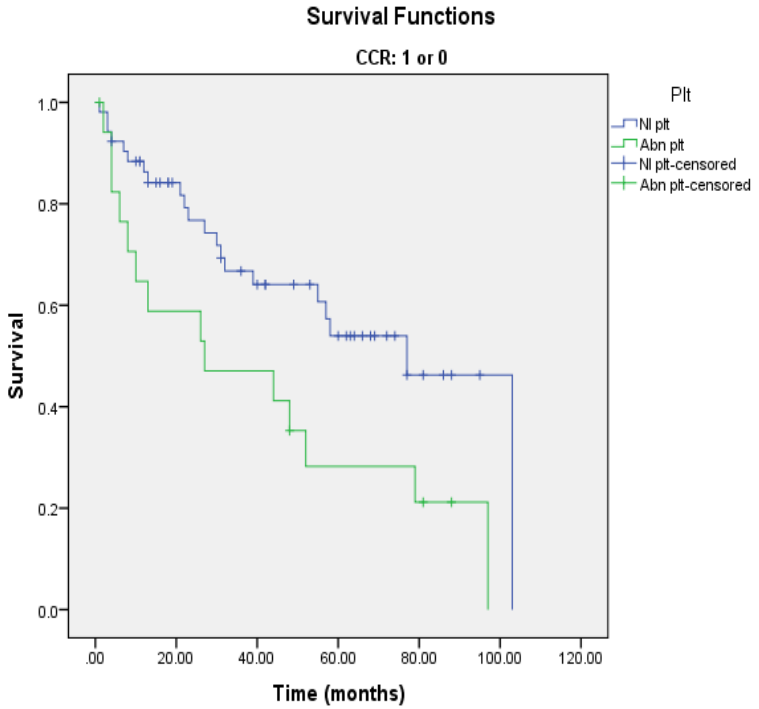




Li et al. ASO 2017

Selected Series of Outcomes After CRS +/- HIPEC/EPIC in MPM Patients

Study	N	Median OS (months)	5-y OS	Prognostic Factors
Yan 2009 Multi-center international	405	53	47 %	Epithelioid histology Negative LNs, Optimal CCR Use of HIPEC
Baratti 2013 Single institution	108	63	N/A	Low Mitotic count (Ki-67) Epithelioid histology, Optimal CCR
Alexander 2013 Multi-center U.S.	211	38	41%	Histologic grade, Optimal CCR Age < 60 y Use of Cisplatin
Magge 2014 Single institution	65	46	39%	Young age, Female gender Optimal CCR Operative complications (-)
Li 2017 Single institution	100	33	36%	Thrombocytosis (-) Optimal CCR, PCI ≤20
Schaub 2012 Single institution	104	N/A	46%	Low PCI Histologic grade Low pre-op CA-125
Helm 2014 Muira 2014 SEER database	1,047 1,591	N/A 38	42% N/A	Use of Surgery Use of Cisplatin Use of EPIC
Naffouje 2018 NCDB	1,740	52-57	N/A	No change in OS with surgery alone v neoadjuvant v adjuvant chemotherapy. OS: Surgery> chemotherapy>BSC
Kepenekian 2016 RENAPE	126	61	53%	PCI<30, ASA Score ≤2 CCR 0/1 OS: No chemo or PO>NA

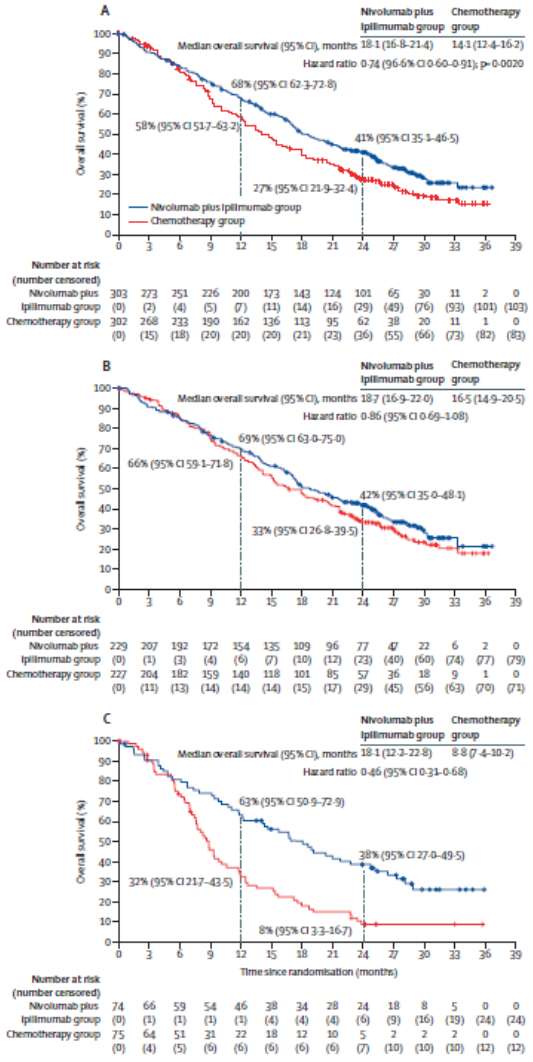
Systemic Agents for Patients with MPM

Agent	Level of Evidence	Efficacy	Toxicities	
Cisplatin Pemetrexed (EAP)	Phase II	26% RR 45% SD 13 mo OS	Dehydration N/V	
Carboplatin Pemtrexed (EAP)	Phase II	24% RR 52% SD	Neutropenia Anemia	
Chemo +/- Bevacizumab (MAPS)	1st line RCT	18.8 vs 16.1 months OS	Hypertension Thrombotic events	
HDAC Inhibitor (Vantage-014)	RCT	30.7 vs 27.1 wks	Fatigue Malaise	
Tremelimumab v placebo (DETERMINE)	2nd or 3rd line RCT	7.7 vs 7.3 months OS	Diarrhea colitis	
PI3K/mTOR Inhibitor	Phase I	PR: 2.4% SD: 43%	Fatigue	
Dual CPB v Chemo (Checkmate-743)	1st line RCT	18.1 vs 14.1 months OS	Diarrhea Pruritis	

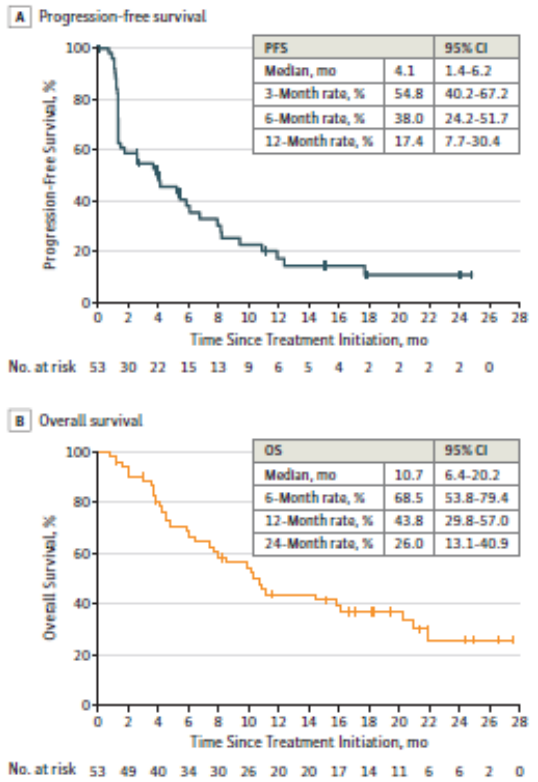
Malignant Peritoneal Mesothelioma

Is there a Role for CPB in MPM?

Checkmate 743 (Nivo/Ipi)



JAVELIN Solid Tumor Trial (Avelumab)



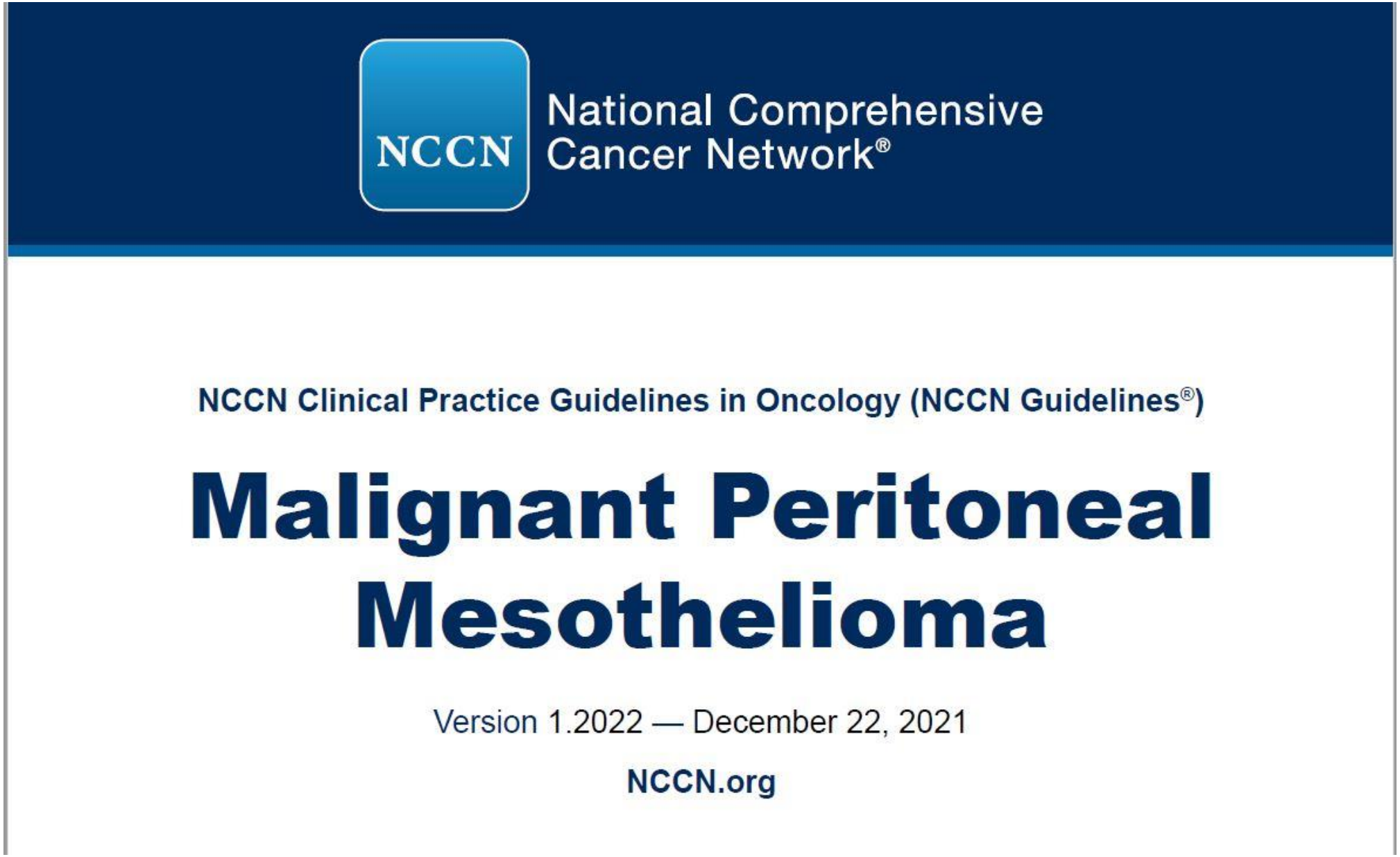
Hassan et al. JAMA Oncol 2019
Baas et al. Lancet 2021

Malignant Peritoneal Mesothelioma

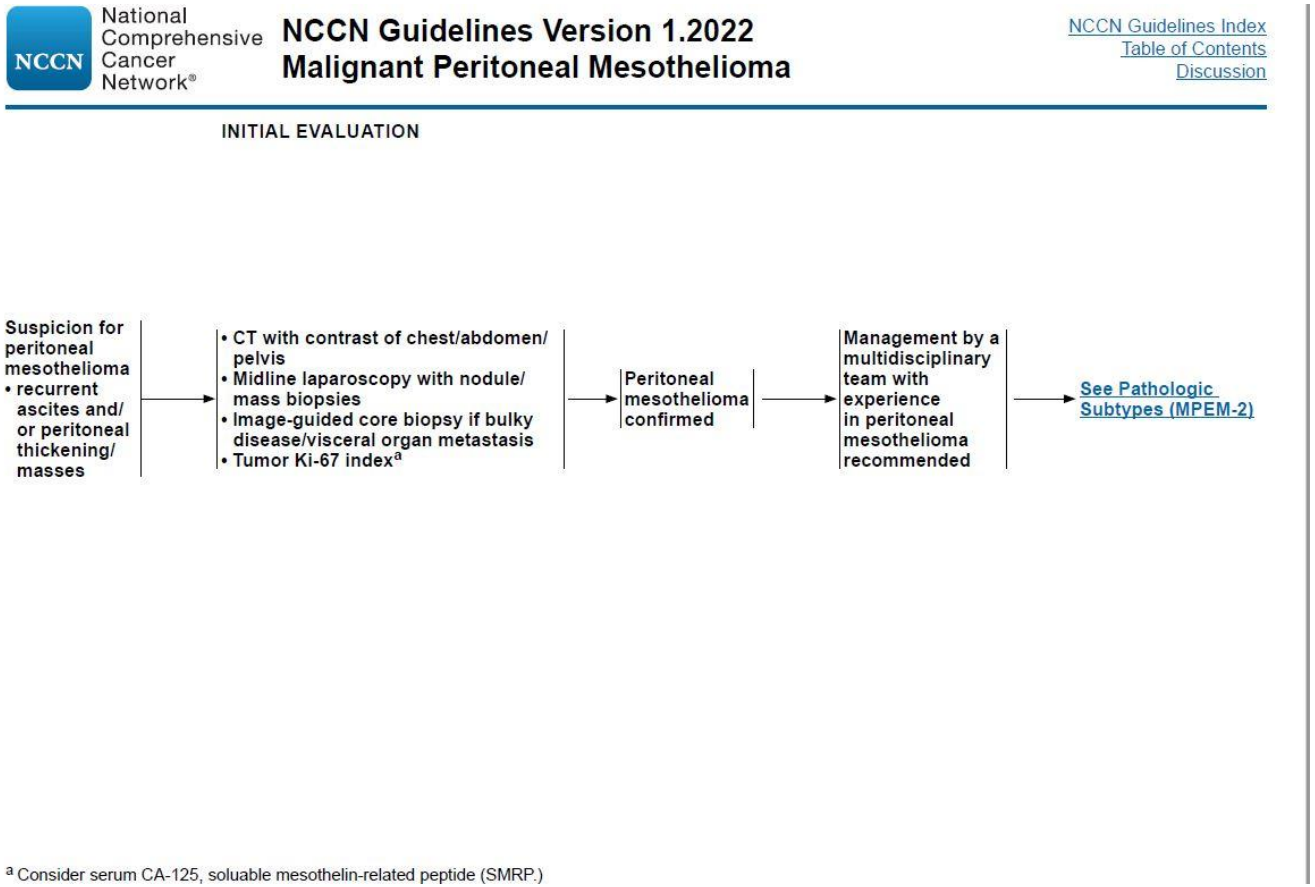
PD L-1 Expression is Frequent (79%) in MPM

Cohort Characteristics	
Age (median, IQR)	57.5 (46.5-70)
Sex (M : F)	12 : 8
Recurrent Disease	n = 6
Histology	Epithelioid: 21
	Epithelioid/Sarcomatoid: 3

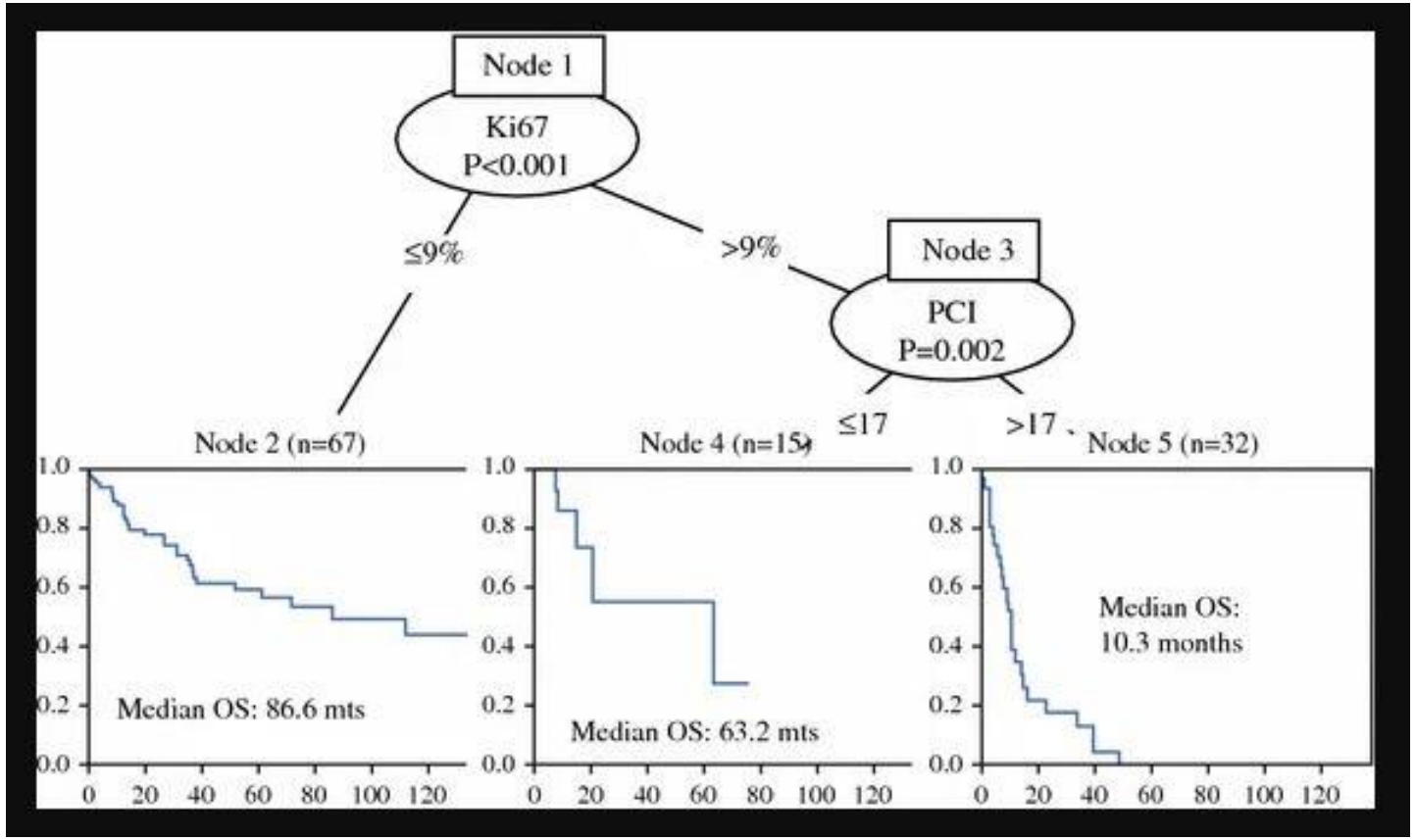
CPS Threshold 1%	CPS (+) n = 19	CPS (-) n = 5	P value
Age (median, IQR)	57 (45-68)	65 (47.5-77)	0.419
Sex (M : F)	9 : 6	3 : 2	0.849
Recurrent Disease	n = 5	n = 1	0.627
Histology	Epithelioid: 16	Epithelioid: 5	
Median OS	73.6	57.3	


NCCN
National Comprehensive Cancer Network®
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Malignant Peritoneal Mesothelioma
Version 1.2022 — December 22, 2021
NCCN.org

Initial Evaluation

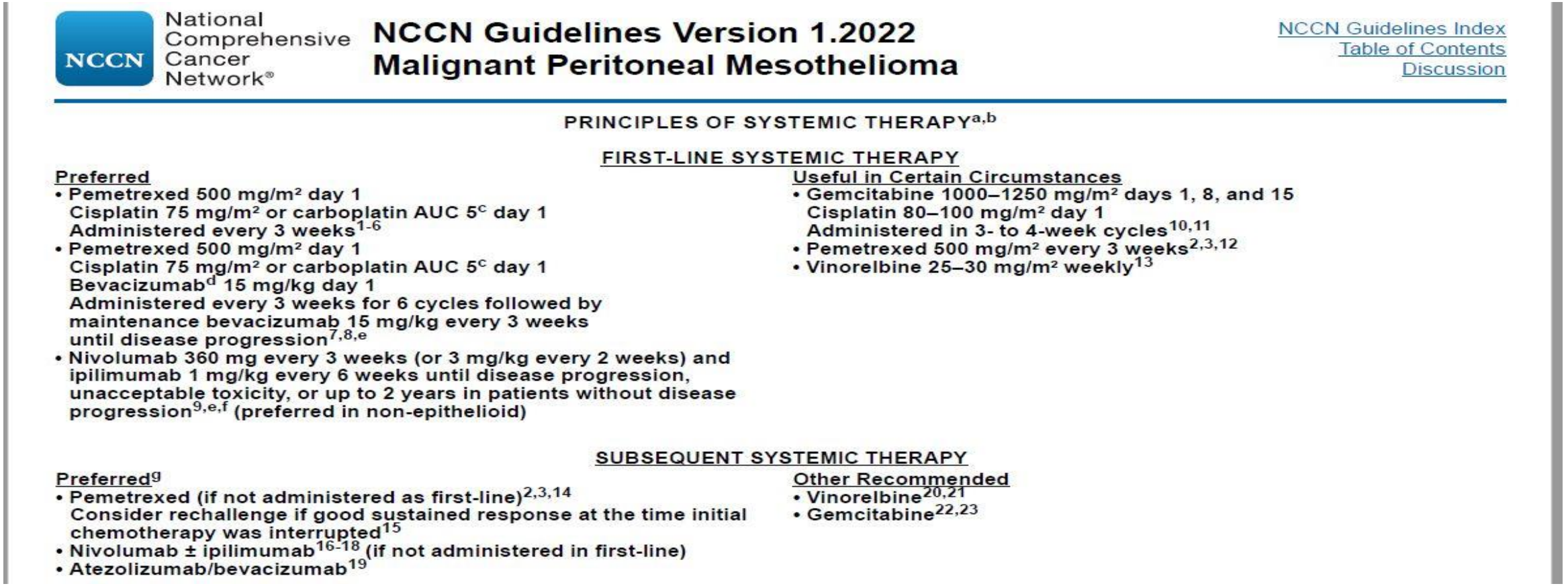


National Cancer Institute of Milano, Italy



Marcello Deraco, MD

Systemic Therapy Options



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NCCN Guidelines Version 1.2022
Malignant Peritoneal Mesothelioma

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY[a,b]

FIRST-LINE SYSTEMIC THERAPY

Preferred

- Pemetrexed 500 mg/m² day 1
  Cisplatin 75 mg/m² or carboplatin AUC 5[c] day 1
  Administered every 3 weeks[1-6]
- Pemetrexed 500 mg/m² day 1
  Cisplatin 75 mg/m² or carboplatin AUC 5[c] day 1
  Bevacizumab[d] 15 mg/kg day 1
  Administered every 3 weeks for 6 cycles followed by maintenance bevacizumab 15 mg/kg every 3 weeks until disease progression[7,8,e]
- Nivolumab 360 mg every 3 weeks (or 3 mg/kg every 2 weeks) and ipilimumab 1 mg/kg every 6 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression[9,e,f] (preferred in non-epithelioid)

Useful in Certain Circumstances

- Gemcitabine 1000–1250 mg/m² days 1, 8, and 15
  Cisplatin 80–100 mg/m² day 1
  Administered in 3- to 4-week cycles[10,11]
- Pemetrexed 500 mg/m² every 3 weeks[2,3,12]
- Vinorelbine 25–30 mg/m² weekly[13]

SUBSEQUENT SYSTEMIC THERAPY

Preferred[g]

- Pemetrexed (if not administered as first-line)[2,3,14]
  Consider rechallenge if good sustained response at the time initial chemotherapy was interrupted[15]
- Nivolumab ± ipilimumab[16-18] (if not administered in first-line)
- Atezolizumab/bevacizumab[19]

Other Recommended

- Vinorelbine[20,21]
- Gemcitabine[22,23]

Malignant Peritoneal Mesothelioma

Summary and Conclusions

- **CRS and HIPEC has been broadly acknowledged as the first line approach for properly selected patients with MPM**
- **CRS and HIPEC is associated with long-term survival in selected patients but is still underutilized nationally**
- **Patient and tumor factors associated with tumor biology should be used to guide therapeutic decision making**
- **Improvements in selection, operative technique, and post-op management have resulted in reduction in morbidity and mortality**
- **MPM has an unpredictable tumor biology related to molecular features of the tumor and independent of other known prognostic histopathological factors**
- **CPB or regional immunotherapy (+/- CRS and HIPEC) are a high priority continued clinical research**