Overview of Mesothelioma

Raffit Hassan, M.D.

Mesothelioma

- **Is an aggressive tumor that arises from the serosal surfaces of body cavities**
- **In 1960, Wagner reported increased incidence of mesothelioma in asbestos miners of South Africa**
- **Asbestos is the primary cause of mesotheliomas**
- **Long latency from the time of asbestos exposure to onset of disease**
- **No history of asbestos exposure in 30-50% of cases of mesothelioma**

Mesothelioma

- **Endemic erionite exposure in Cappadocia, Turkey**
- **Simian virus 40 (SV40) has been implicated in the etiology of some mesotheliomas**
- **Some cases have been reported following therapeutic radiation**
- **Patients with Hodgkin's disease may have an increased risk of developing mesothelioma**
- **Approx. 2200 new cases of mesothelioma are diagnosed each year in the United States**

Global Burden of Mesothelioma

Table 1. Worldwide Trends in the Epidemiologic Features of Malignant Mesothelioma.*

Country or Region	Incidence	Predicted Peak Year	Predicted No. of Deaths in Next 40 Yr†	Predicted Cost‡
	cases/million population			*billions of U.S. dollars*
United States	15	2004	72,000	200
Europe	18§	2015–2020	250,000	80
Japan	7	2025	103,000	—
Australia	40	2015	30,000	5–10

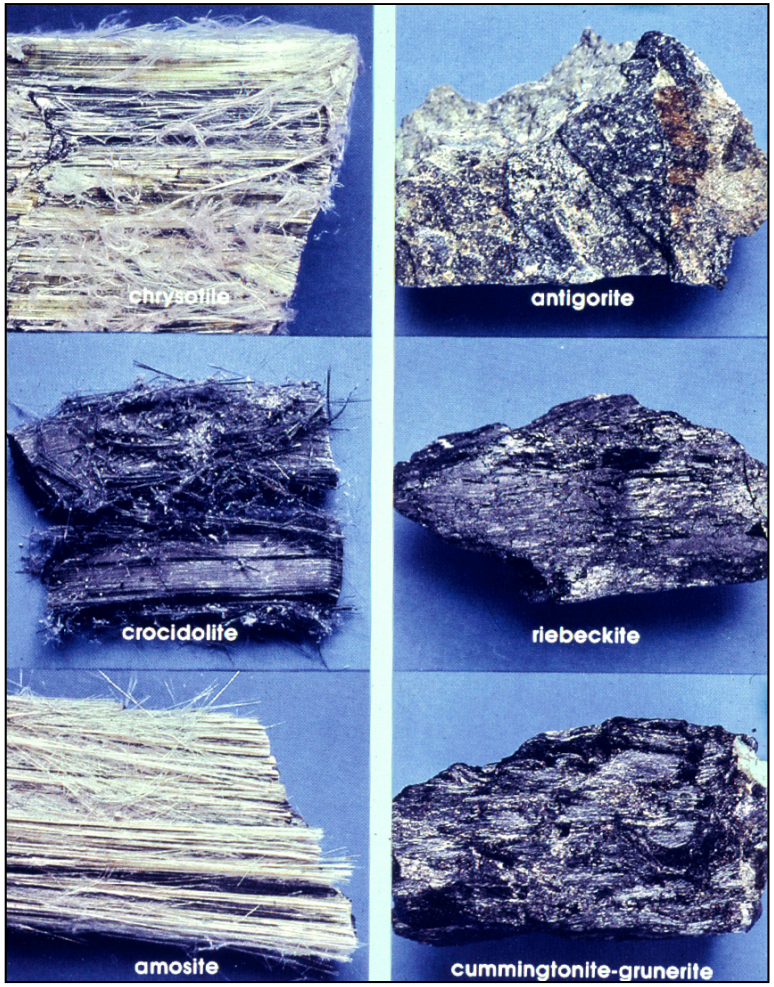
Asbestos Fibers

CHRYSOTILE (Serpentine)

AMPHIBOLES (Rod-like)

Crocidolite

Amosite



Asbestos Fibers

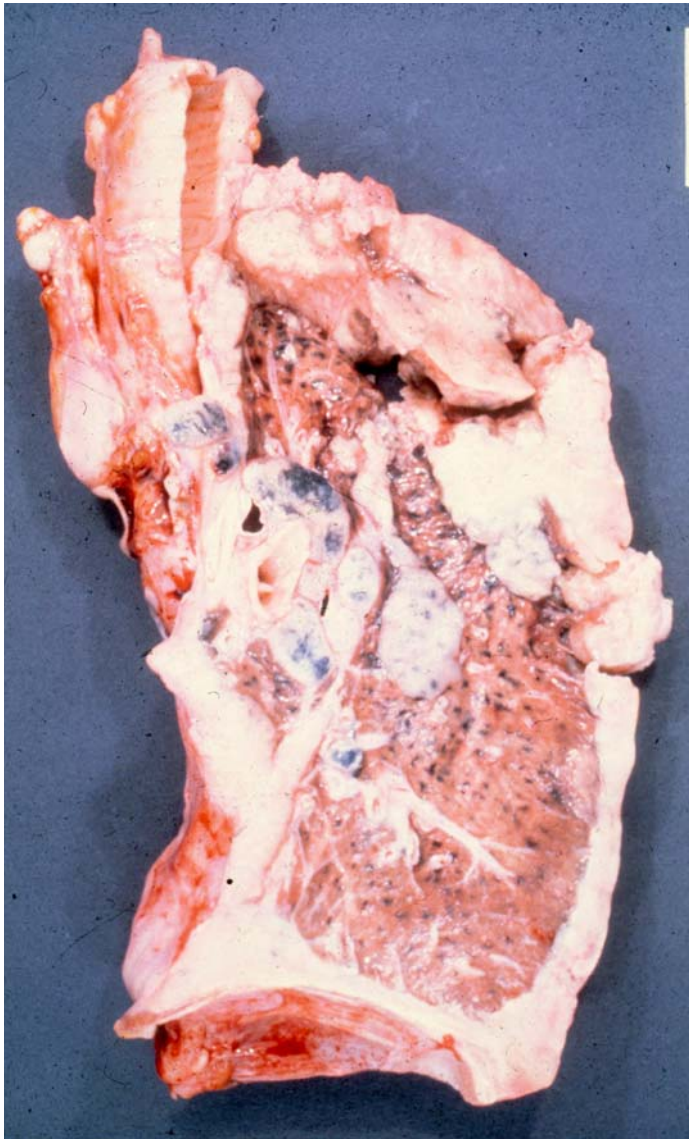
CHRYSOTILE

AMOSITE

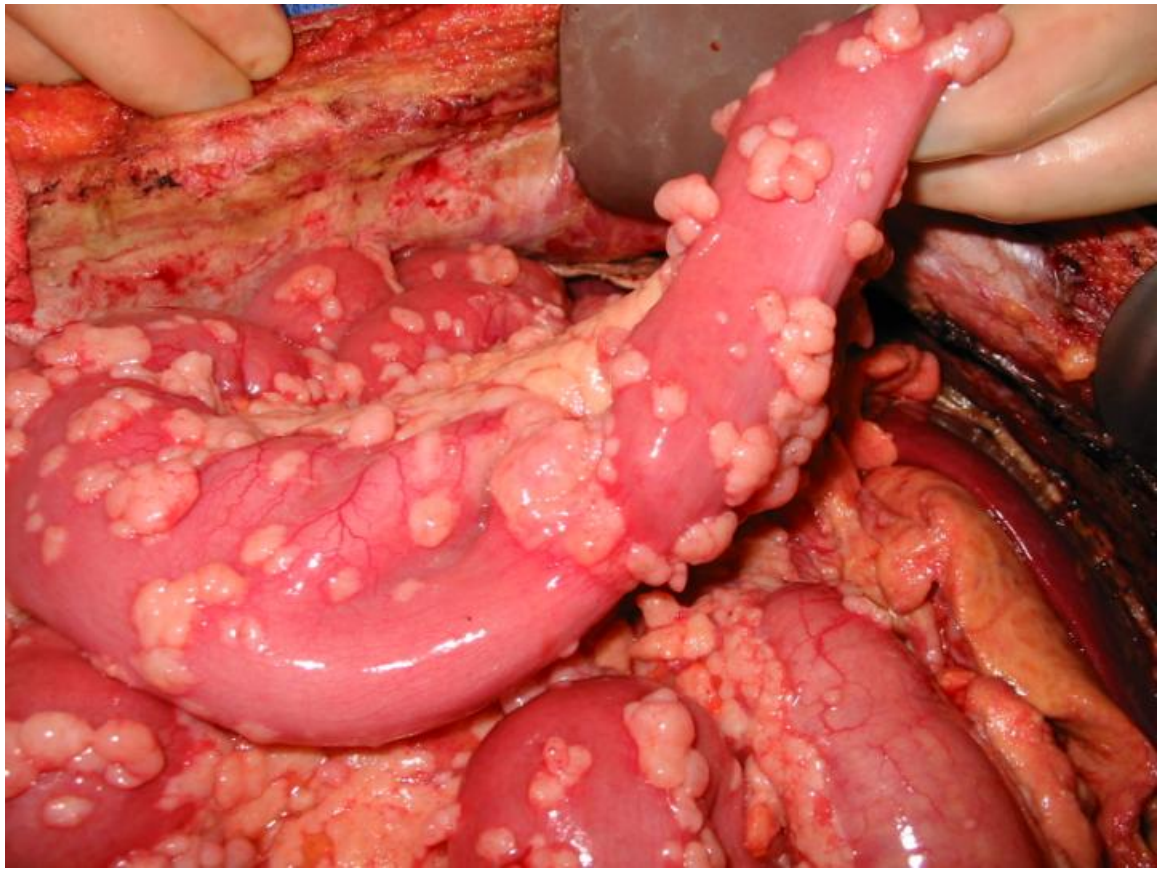
Occupations associated with asbestos exposure

- Miners (blue asbestos mine in Wittenoom, Australia)
- Family members of miners and others
- Asbestos insulators
- Plumbers
- Carpenters
- Defense personnel

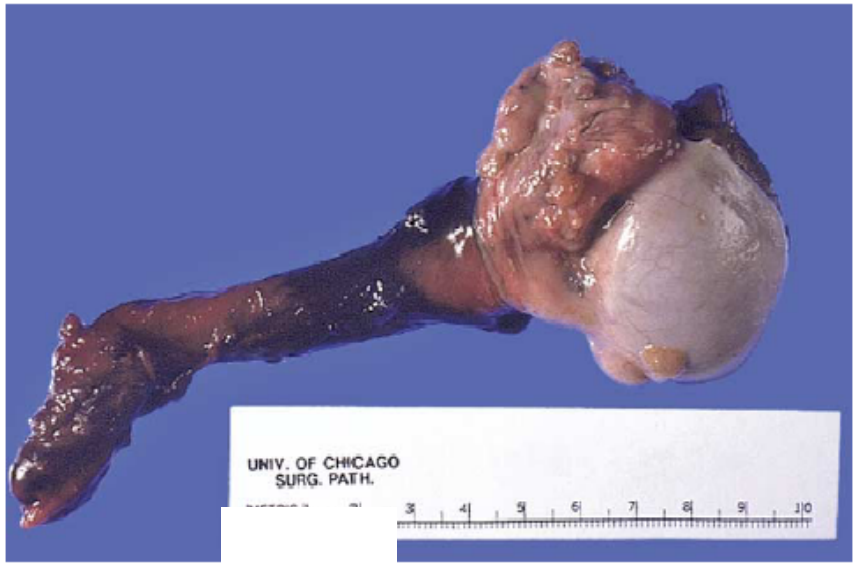
Pleural Mesothelioma



Peritoneal Mesothelioma

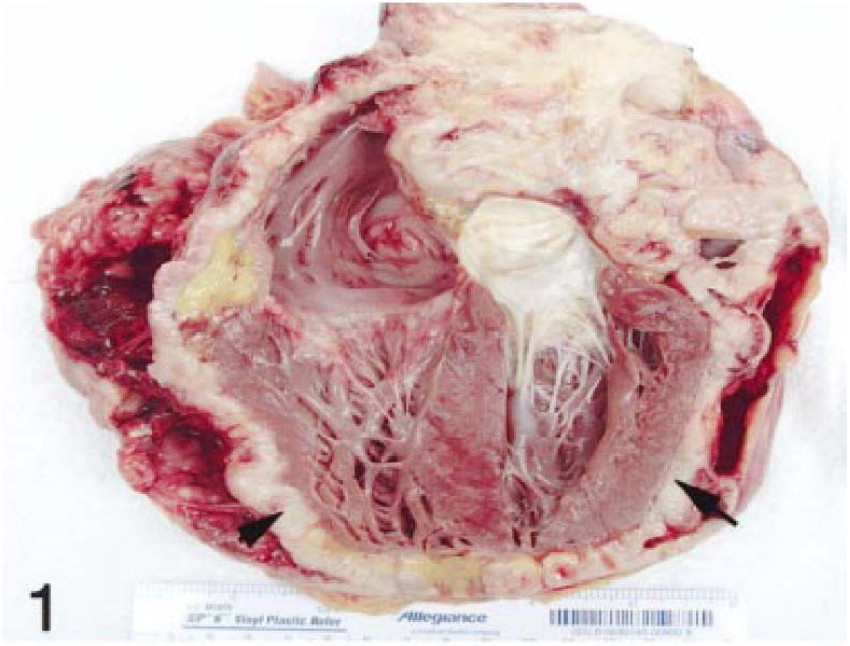


Tunica Vaginalis Mesothelioma



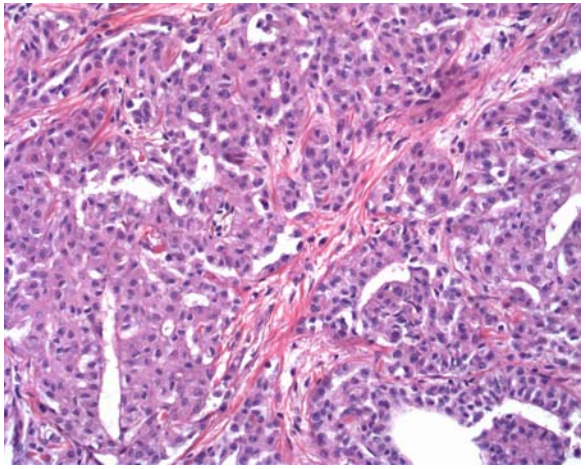
Tolhurst et al *Urologic Oncology*, 2006

Pericardial Mesothelioma

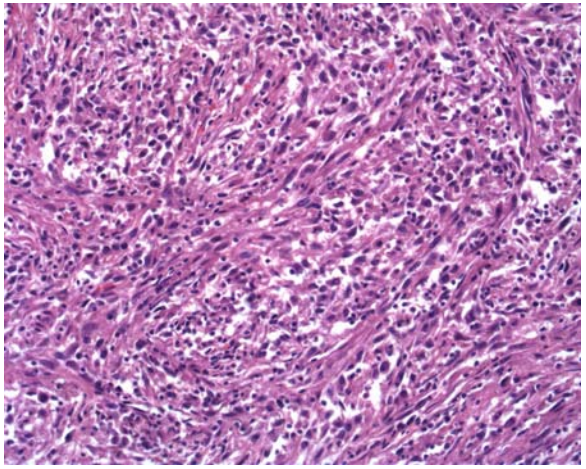


Sharaf El-Dean et al Arch Pathol Lab Med, 2004

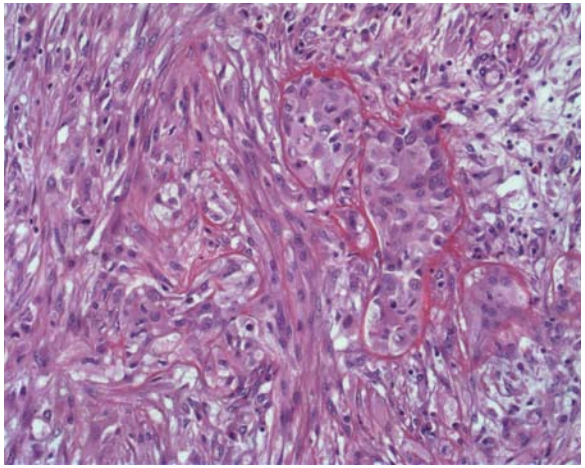
Histological Sub-types of Mesothelioma



Epithelial

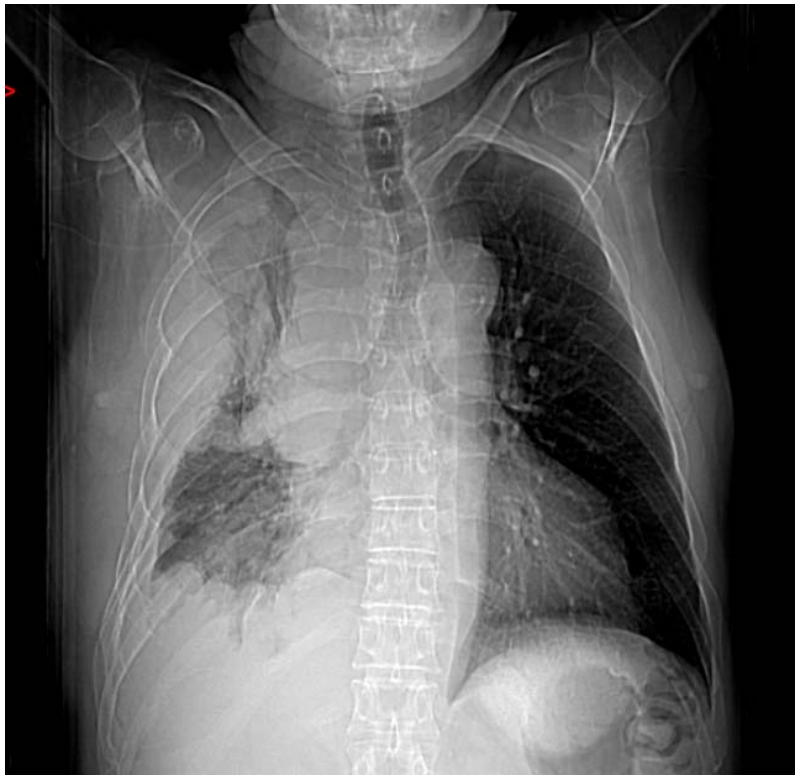


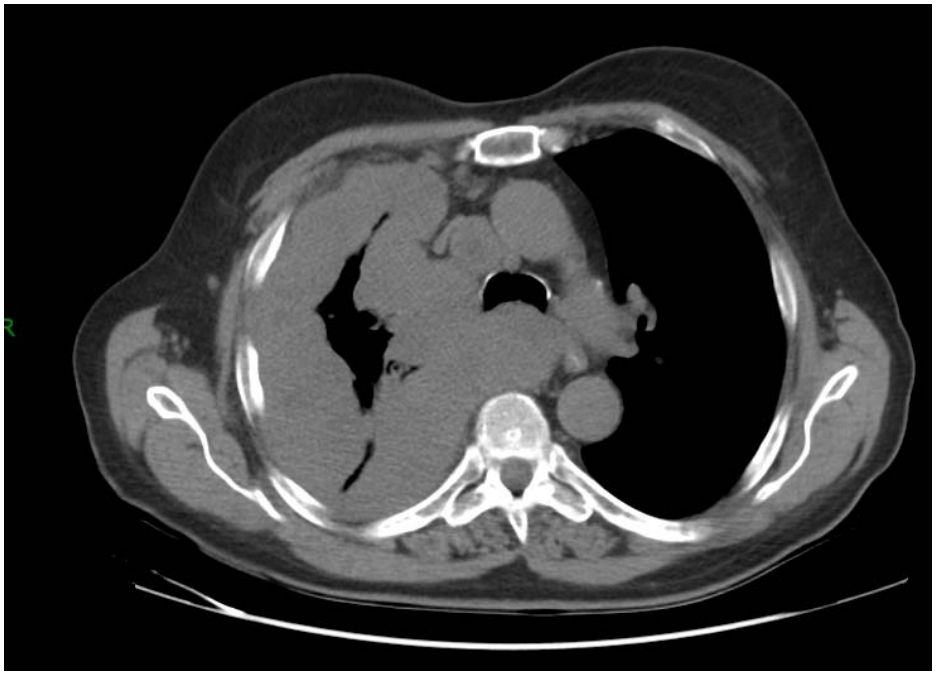
Sarcomatoid



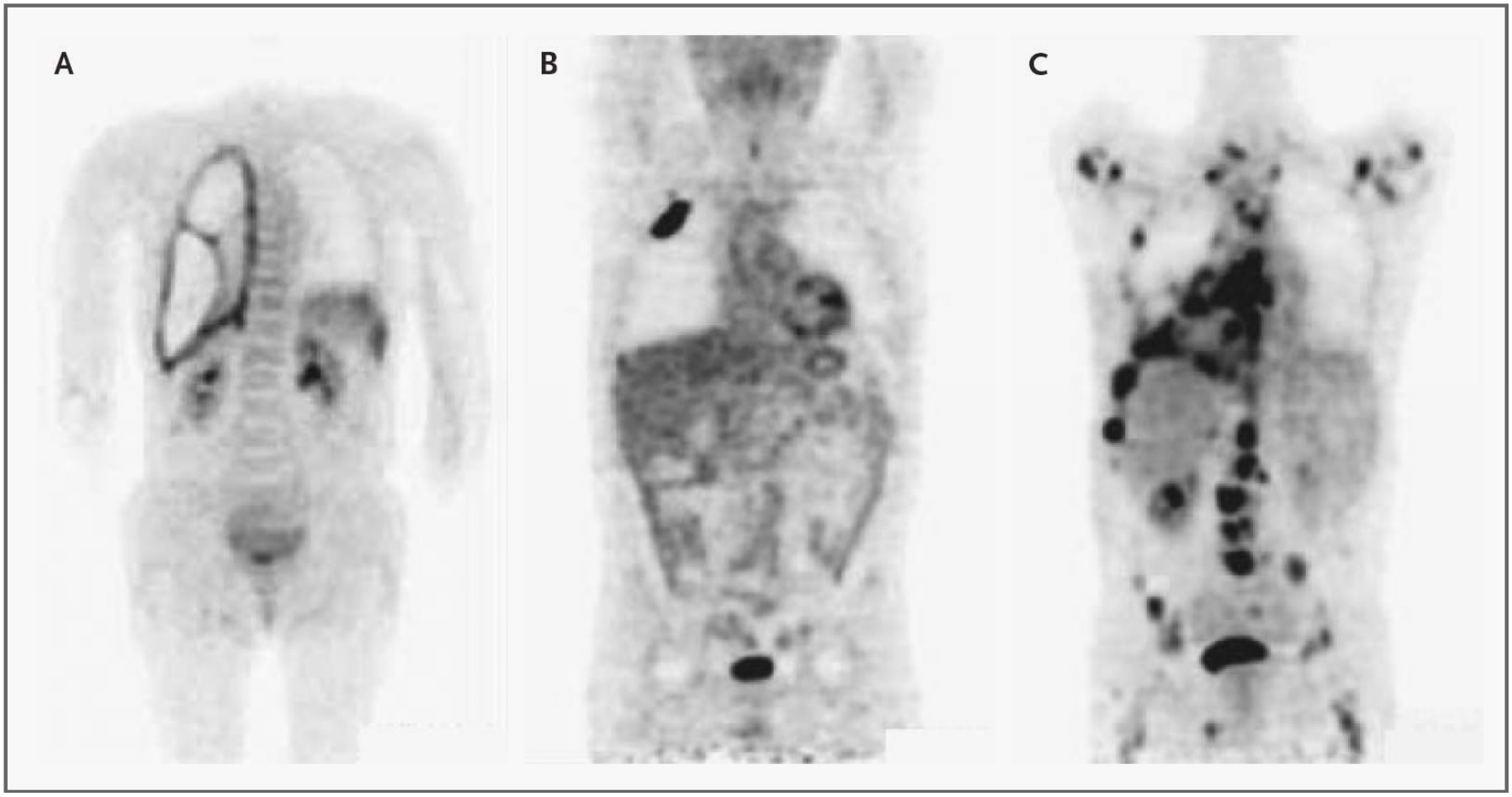
Biphasic

Pleural Mesothelioma





Pleural Mesothelioma



Presentation

- **Pleural effusion (cytology often negative)**
- **Chest wall pain**
- **Constitutional symptoms**
- **Asymptomatic**
- **Distant metastasis uncommon at presentation**

Staging

New international staging system for diffuse malignant pleural mesothelioma

T1

T1a Tumor limited to the ipsilateral parietal including mediastinal and diaphragmatic pleura

No involvement of the visceral pleura

T1b Tumor involving the ipsilateral parietal including mediastinal and diaphragmatic pleura

Scattered foci of tumour also involving the visceral pleura

T2 Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features:
— involvement of diaphragmatic muscle
— confluent visceral pleural tumour (including the fissures), or extension of tumour from visceral pleura into the underlying pulmonary parenchyma

T3 Describes locally advanced but potentially resectable tumour
Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features:
— involvement of the endothoracic fascia
— extension into the mediastinal fat
— solitary, completely resectable focus of tumour extending into the soft tissues of the chest wall
— non-transmural involvement of the pericardium

T4 Describes locally advanced technically unresectable tumour
Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral) with at least one of the following features:
— diffuse extension or multifocal masses of tumour in the chest wall, with or without associated rib destruction
— direct transdiaphragmatic extension of tumour to the peritoneum
— direct extension of tumour to the contralateral pleura
— direct extension of tumour to one or more mediastinal organs
— direct extension of tumour into the spine
— tumour extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumour involving the myocardium

N — Lymph nodes

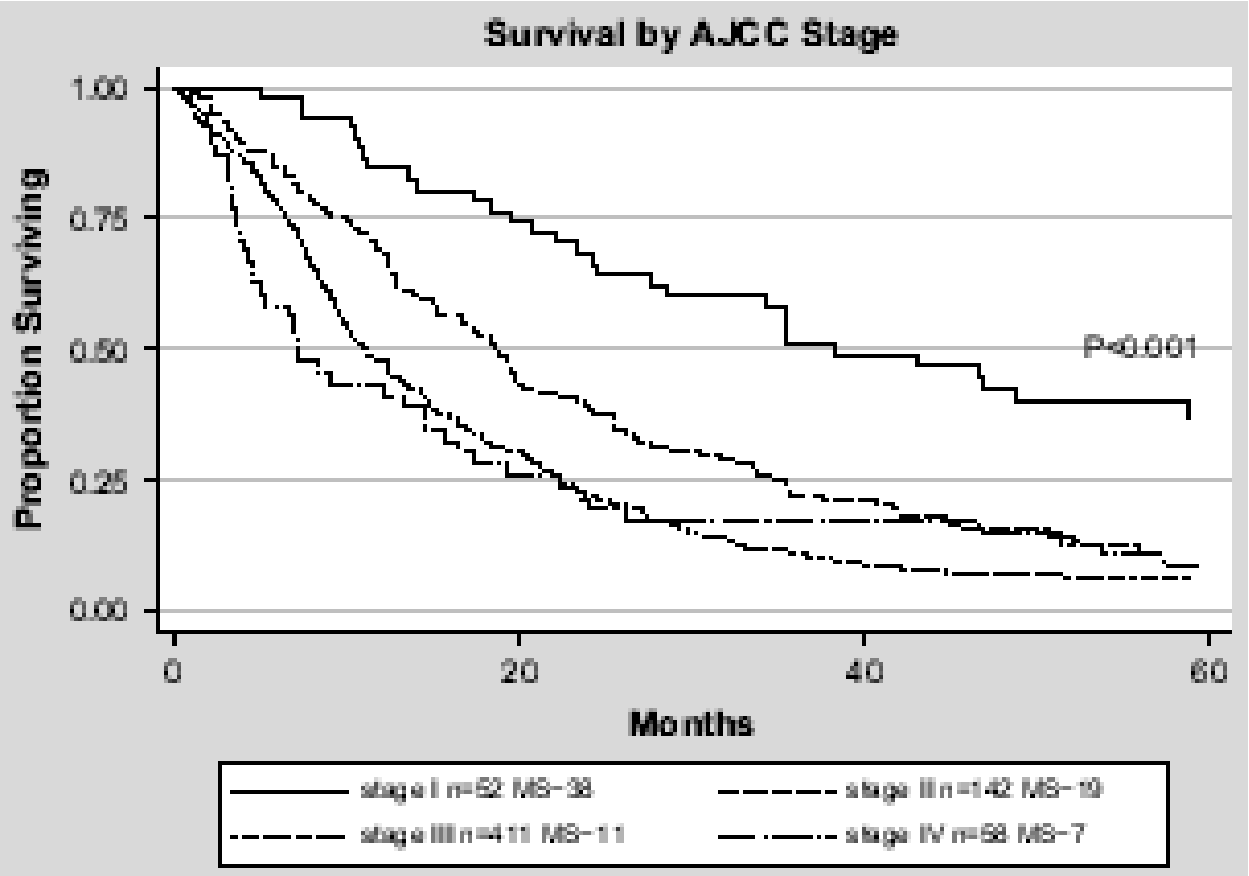
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2 Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary nodes
N3 Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

M — Metastases

MX Presence of distant metastases cannot be assessed
M0 No distant metastasis
M1 Distant metastasis present

Stage I	
Ia	T_{1a} N_0 M_0
Ib	T_{1b} N_0 M_0
Stage II	T_2 N_0 M_0
Stage III	Any T_3 M_0
	Any N_1 M_0
	Any N_2 M_0
Stage IV	Any T_4
	Any N_3
	Any M_1

Overall Survival by Stage



Surgical Management

Has a role in patients with stage I and II mesothelioma

Pleurectomy / decortication

- **Minimal bulk disease confined to parietal pleura**
- **Resection of the parietal and visceral pleura, pericardium ± diaphragm**

Extrapleural pneumonectomy (EPP)

- **Bulky disease or disease that involves the fissures**
- **En bloc removal of lung, pleura, pericardium and diaphragm**
- **Post-operative XRT and Chemotherapy**

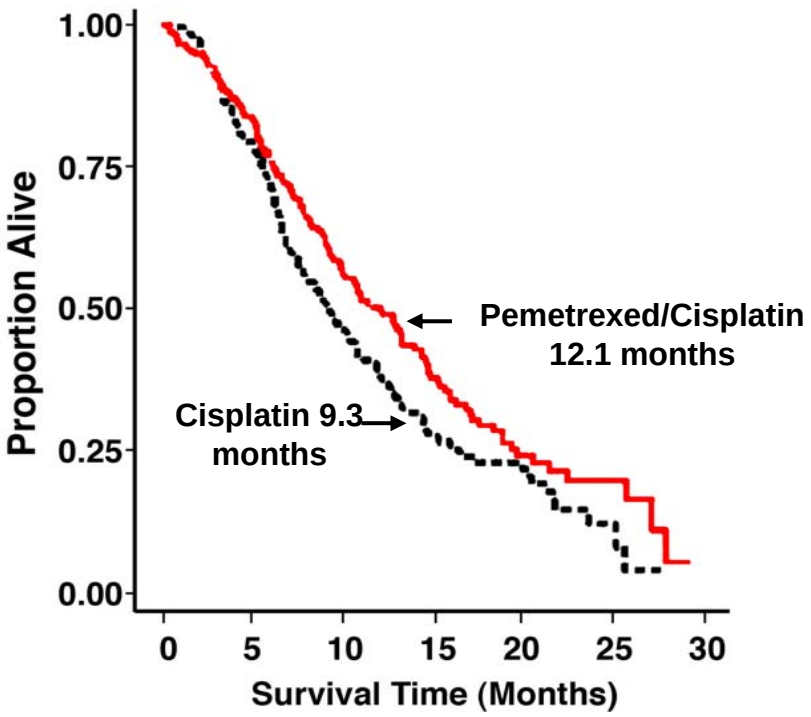
Chemotherapy for mesothelioma

- **Chemotherapy results in improved survival and quality of life**
- **Anti-folates are the most active agents**
- **Activity of anti-folates is markedly increased when given in combination with platinum compounds**

Phase III clinical trials of antifolates

Author	Study arms	No. of patients	Response rate	Median survival (months)
Vogelzang et al	Pemetrexed + Cisplatin	226	41%	12.1
	Cisplatin	222	17%	9.3
Van Meerbeeck et al	Raltitrexed + Ciplatin	110	24%	11.2
	Cisplatin	103	14%	8.8

Pemetrexed / Cisplatin Phase III Study

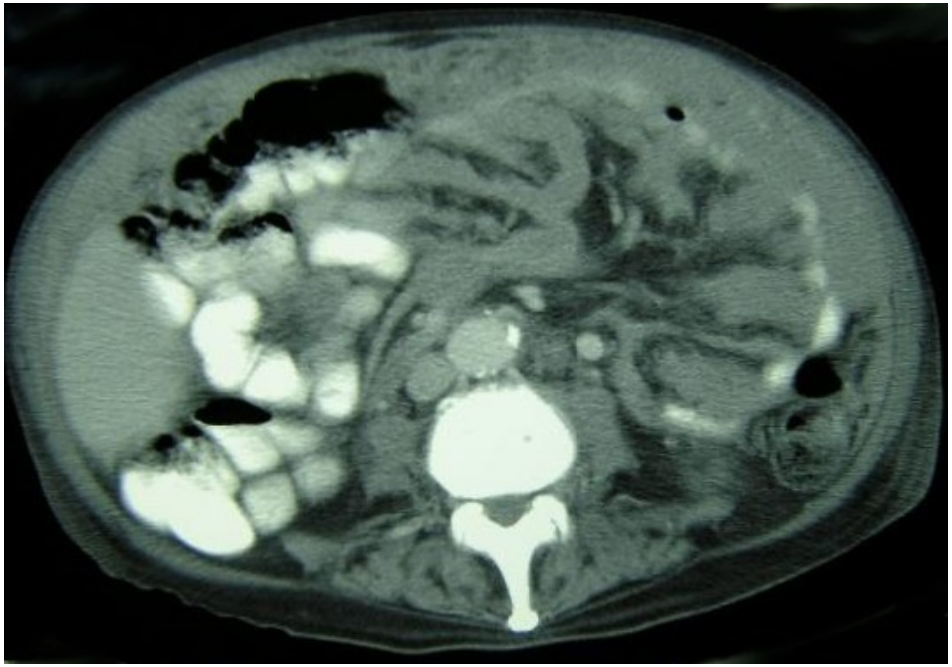


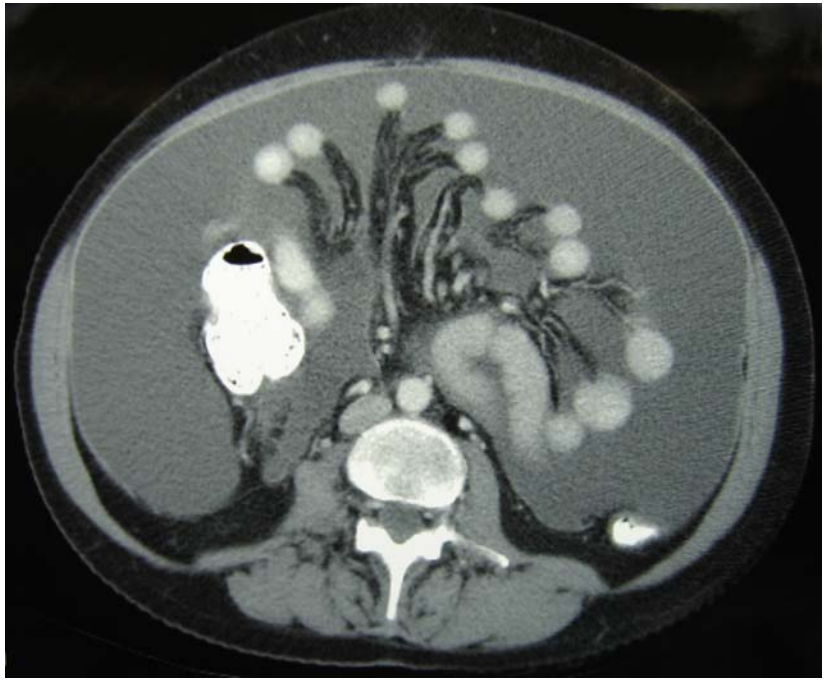
Vogelzang et al., JCO 2003

Second line agents for pleural mesothelioma

- **Gemcitabine**
- **Gemcitabine plus carboplatin**
- **Navelbine**

Peritoneal Mesothelioma





Median Overall Survival

Pleural mesothelioma	**12 months**
Peritoneal mesothelioma	**> 60 months**

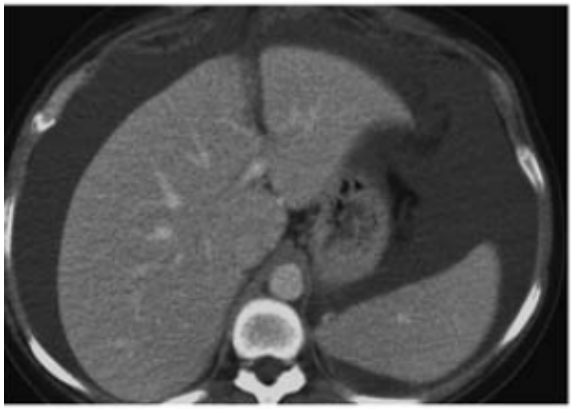
Surgical debulking improves survival

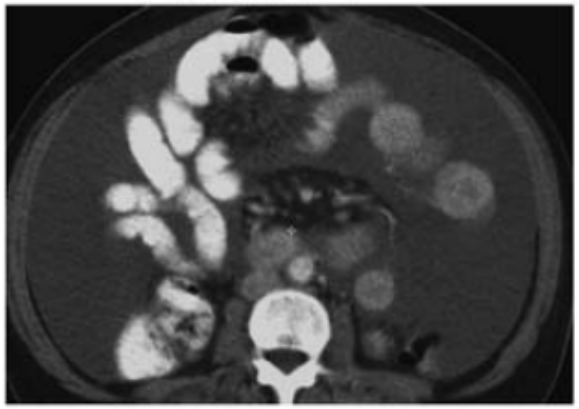
Table 1
Studies of operative cytoreduction and continuous hyperthermic peritoneal perfusion for treatment of peritoneal mesothelioma

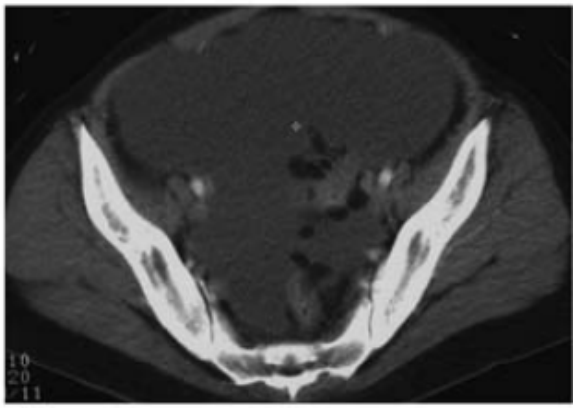
Study [reference]	No. of patients	CHPP agents	Residual disease status	Median survival	Comments
Washington Cancer Institute, 2003 [58]	68	Cisplatin + doxorubicin	60% <2.5 cm	67 mo	OS greater for women than men
National Cancer Institute, 2003 [62]	49	Cisplatin	88% <1 cm	92 mo	OS better for patients ≤60 y Minimal residual disease History of previous debulking
Wake Forest University Baptist Medical Center, 2001 [61]	12	MMC	66% <2 cm	34.2 mo	86% ascites palliated
National Cancer Institute of Milan, 2003 [60]	19	Cisplatin + MMC or cisplatin + doxorubicin	75% <2.5 mm	NR	94% ascites palliated

Abbreviations: MMC, mitomycin C; NR, not reported; OS, overall survival.

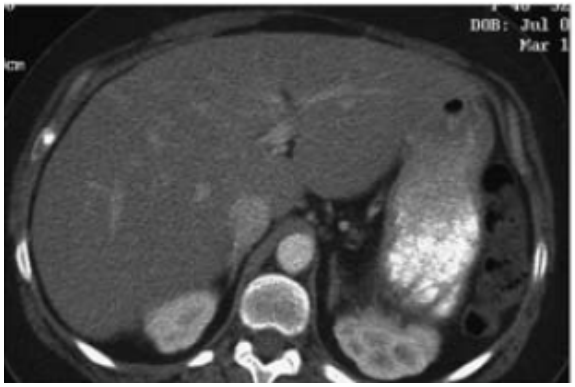
Pre-CHPP

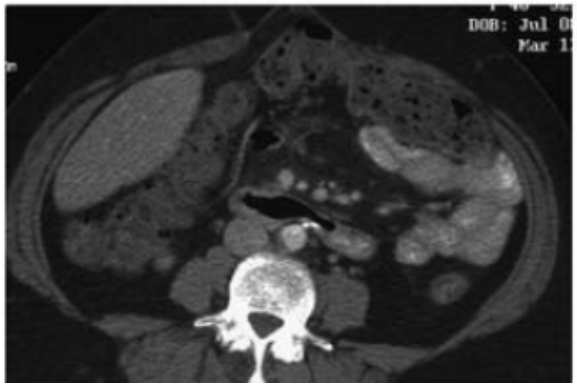


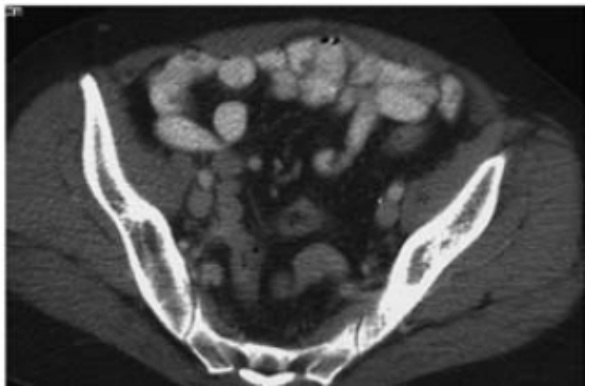




54 months S/P CHPP







Pemetrexed for peritoneal mesothelioma

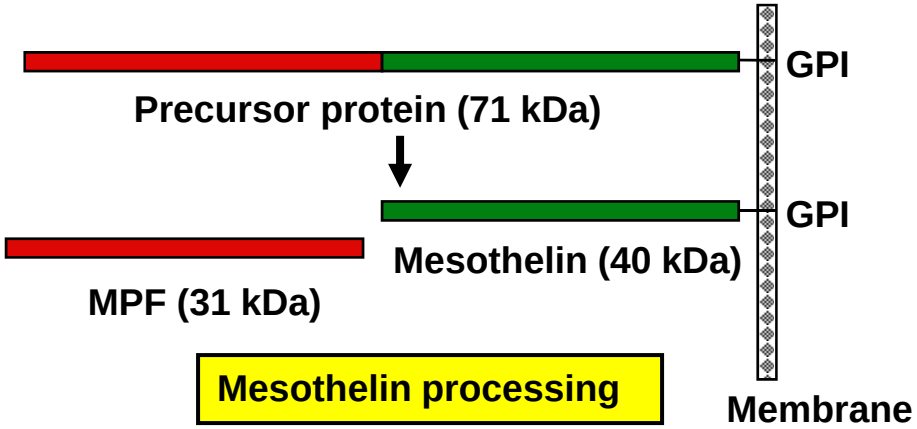
- **Pemetrexed in combination with cisplatin or carboplatinum is now the first line treatment for patients who are not surgical candidates**
- **?Neoadjuvant therapy, could make some patients resectable**
- **?Adjuvant therapy after cytoreduction and intraperitoneal chemotherapy or use at time of recurrence**

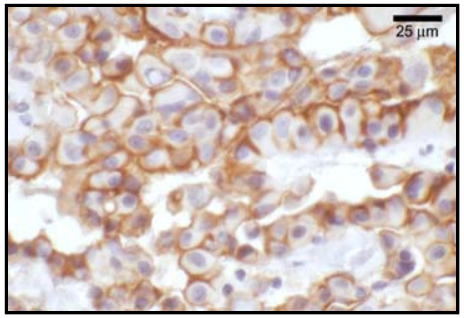
Novel Targets for Mesothelioma

- **Mesothelin**
- **IGF-1R**

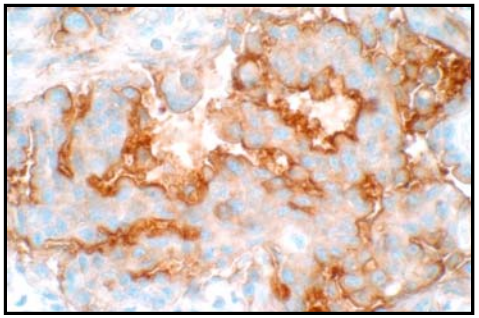
Mesothelin

- Cell surface glycoprotein
- Normal expression in human tissues is limited to mesothelial cells of pleura, peritoneum & pericardium
- Mesothelin is highly expressed in many cancers

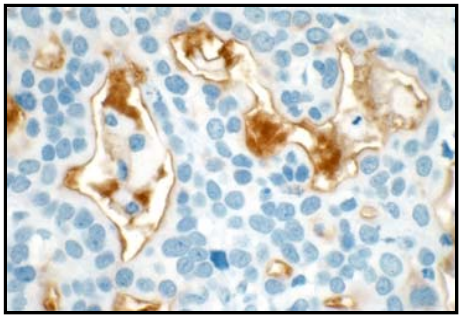




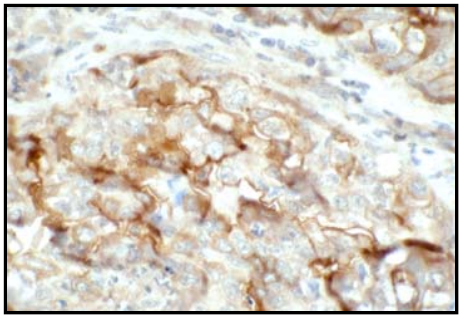
Mesothelioma



Ovarian Cancer



Pancreatic Cancer



Lung Cancer

Hassan et al. Clin. Cancer Res., 2004

Mesothelin

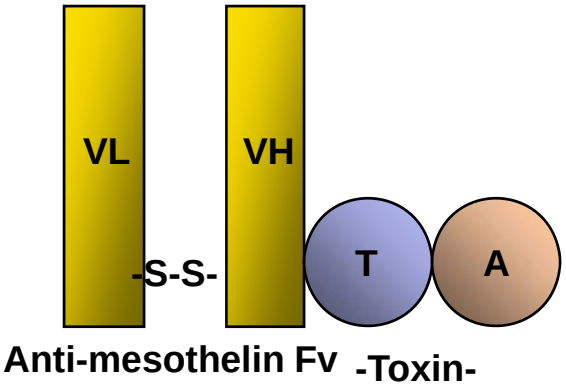
- **Biological function of mesothelin is not known**
- **Mesothelin is a novel CA125 binding protein and may play a role in tumor metastasis**
- **Shed into the serum and is elevated in patients with mesothelioma**

Targeting mesothelin for cancer therapy

- **The limited expression of mesothelin in normal tissues and high expression in many common cancers makes it a good target for antibody based therapies**

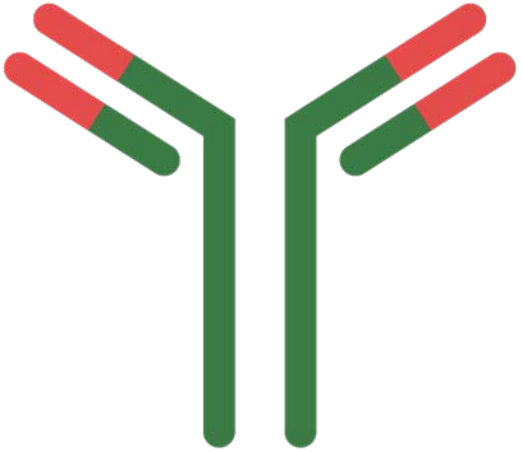
Targeting mesothelin for cancer therapy

Recombinant immunotoxin



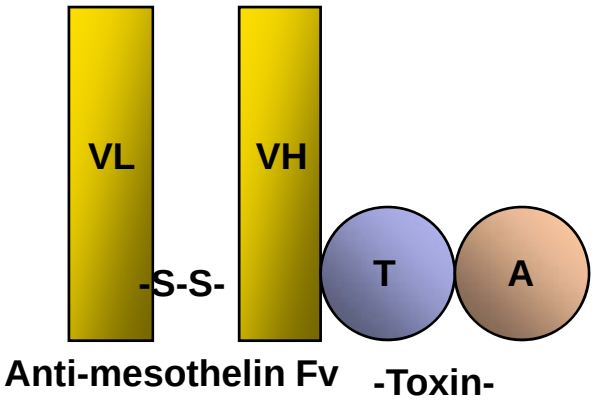
SS1P

Chimeric mAb

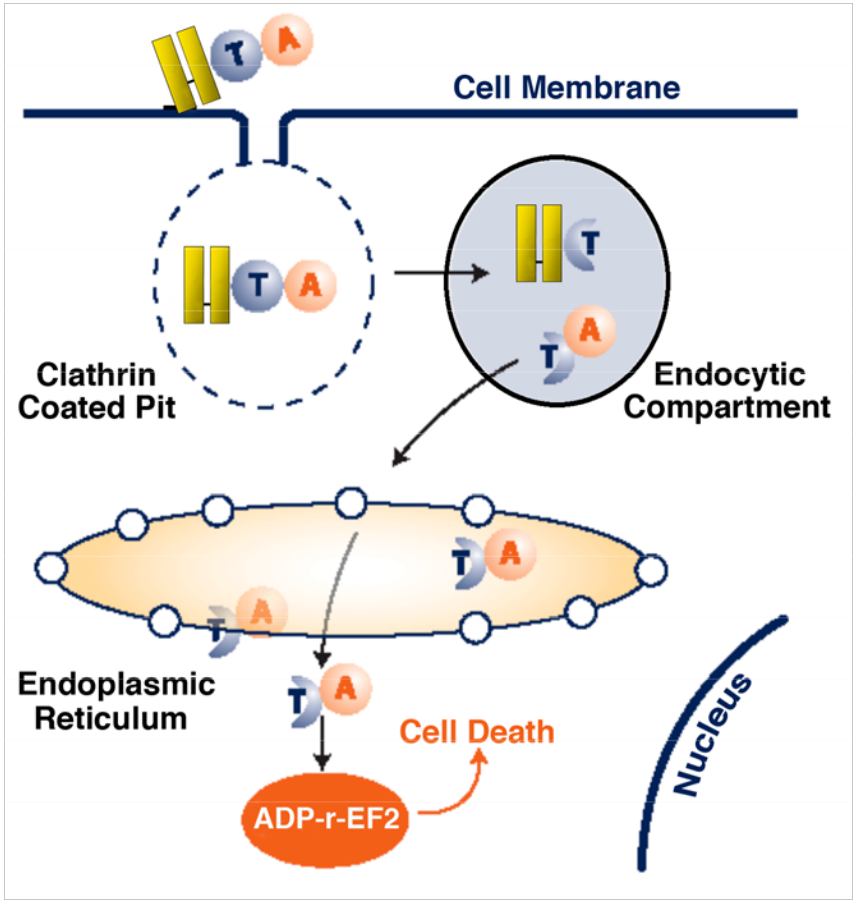


MORAb-009

SS1P, anti-mesothelin immunotoxin



- High affinity for mesothelin
- Cytotoxic to mesothelin expressing tumor cells obtained from patients
- Regression of mesothelin positive tumors in mice



Hassan et al. Clin. Cancer Res., 2002

Li et al. Anticancer Res., 2004

SS1P Phase I Study

- Patients with advanced mesothelin positive cancers
- SS1P given as IV infusion every other day x 3 doses
- Thirty four patients treated (20 mesothelioma, 12 ovarian and 2 pancreatic cancer)
- Maximum tolerated dose - 45 µg/kg
- Dose-limiting toxicity was self limited pleuritis
- Tumor response
  - Minor response 4
  - Stable disease 18
  - Progressive disease 11

Hassan et al. Clin. Cancer Res., 2007

SS1P in combination with chemotherapy results in increased anti-tumor activity

- **Marked synergy between SS1P and chemotherapy in mice**
- **Synergy observed with several chemotherapeutic agents including taxol, cisplatin and gemcitabine**
- **Chemotherapy decreases mesothelin concentration in the tumor extracellular fluid leading to increased cell killing by SS1P**

Zhang et al. Clin. Cancer Res., 2006
Zhang et al. PNAS, 2007
Hassan et al. Clin. Cancer Res., 2007

Phase I, dose-escalation study of SS1P plus Pemetrexed (P) and Cisplatin (C) for front line therapy of malignant pleural mesothelioma

Primary Objectives

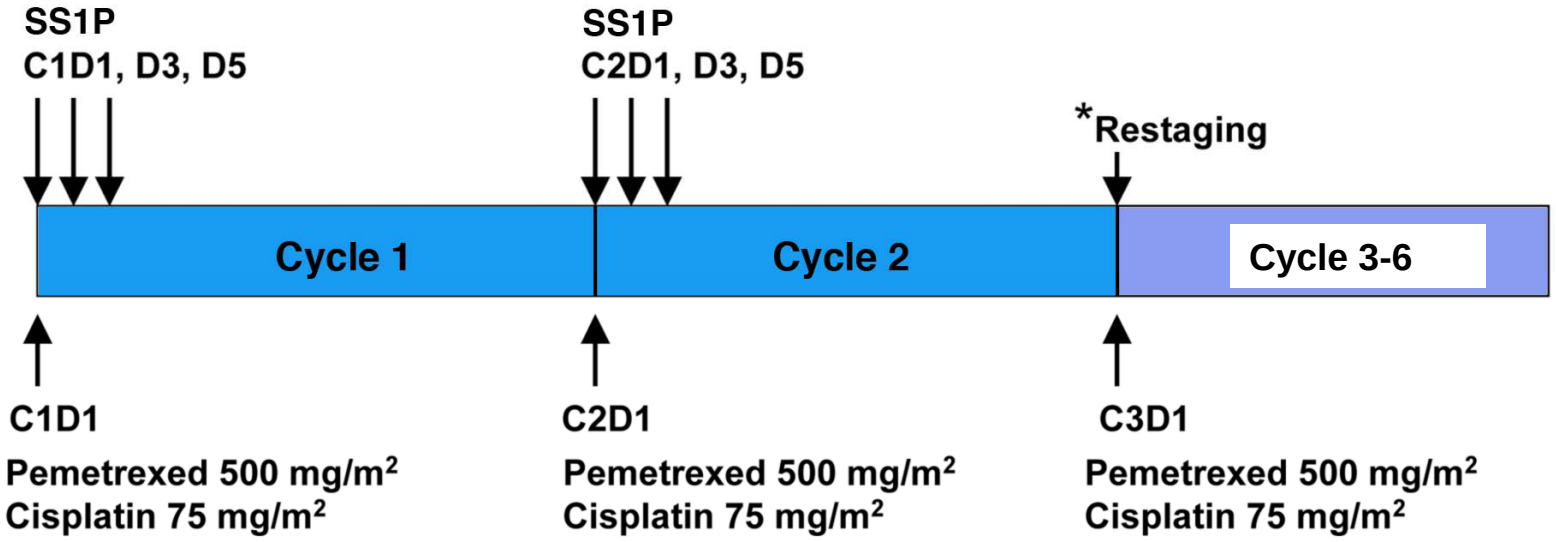
- To determine MTD of SS1P that be safely given with P + C
- Anti-tumor activity of SS1P with chemotherapy
- SS1P toxicity and pharmacokinetics

Secondary Objective

- Serum mesothelin as a predictor of therapeutic response

SS1P plus Pemetrexed and Cisplatin Mesothelioma Study

Clinical trial design



Patient	SS1P dose level (µg/kg)	Response	PFS (months)	Overall survival (months)
002	25	SD	35+	35+
004	25	PR	11	30+
005	25	PR	16	29+
006	35	PD	1	4
007	35	PD	3	15
008	35	SD	6	7
009	45	PR	6	9
010	45	PR	6	9
011	45	PR	13	22+
013	45	PD	3	14+
015	45	PR	7	10+
016	45	SD	7+	7+
018	45	PR	6	6+
019	45	SD	4+	4+
012	55	PD	4	14

+ Response Ongoing

Anti-tumor Response (all dose levels)

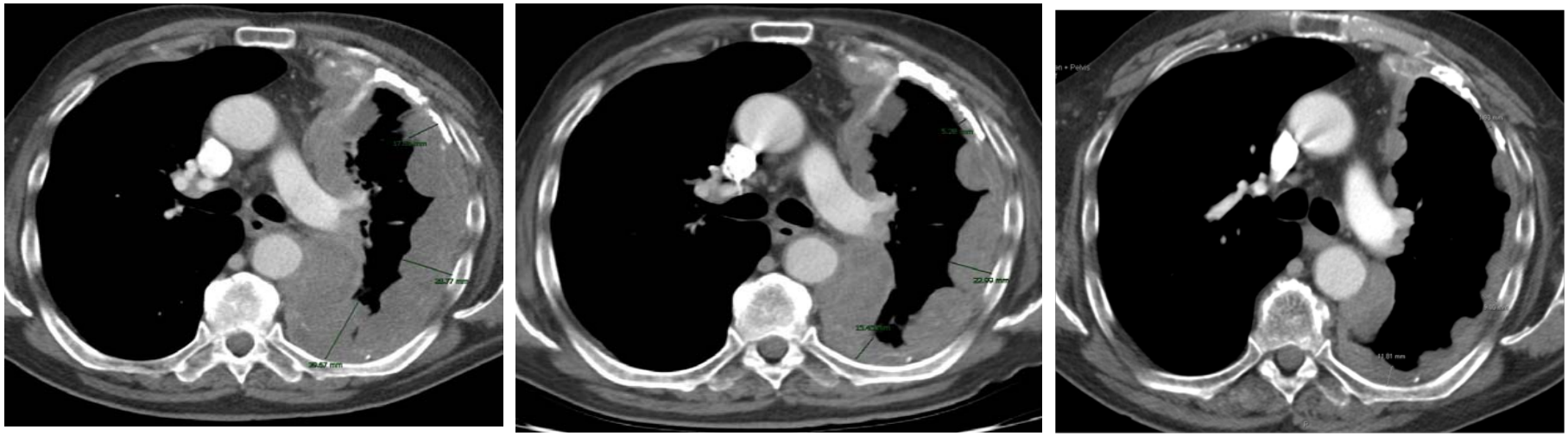
	n = 15
Complete Response	0
Partial Response	7
Stable Disease	4
Progressive Disease	4

Anti-tumor Response (at MTD dose-level)

	n = 8
Complete Response	0
Partial Response	5
Stable Disease	2
Progressive Disease	1

Patient 009 (45 µg/kg dose level)

Baseline **After Cycle 2** **After Cycle 6**

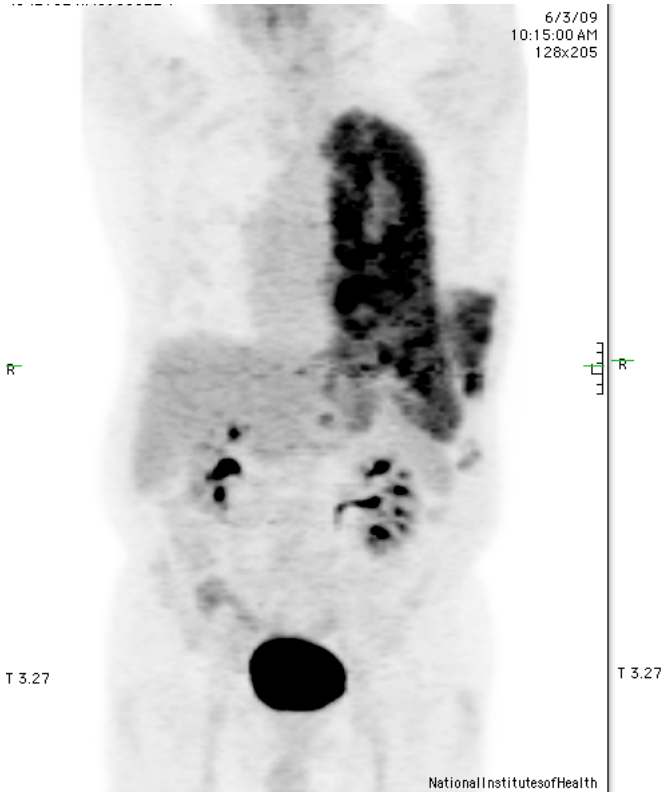


↓33% **↓61%**

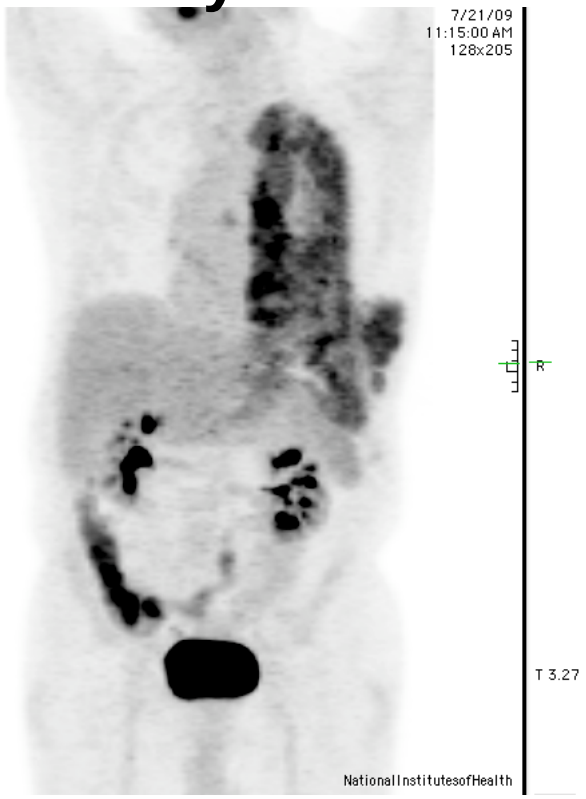
Decrease in tumor area

Patient 009 (45 µg/kg dose level)

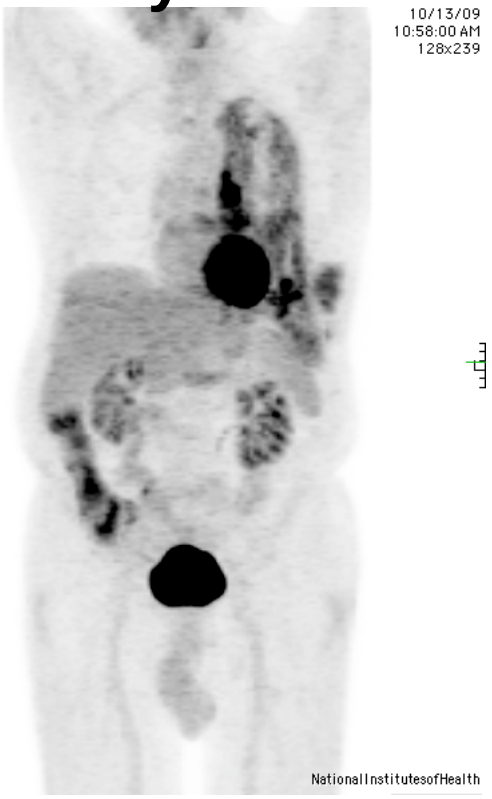
Baseline



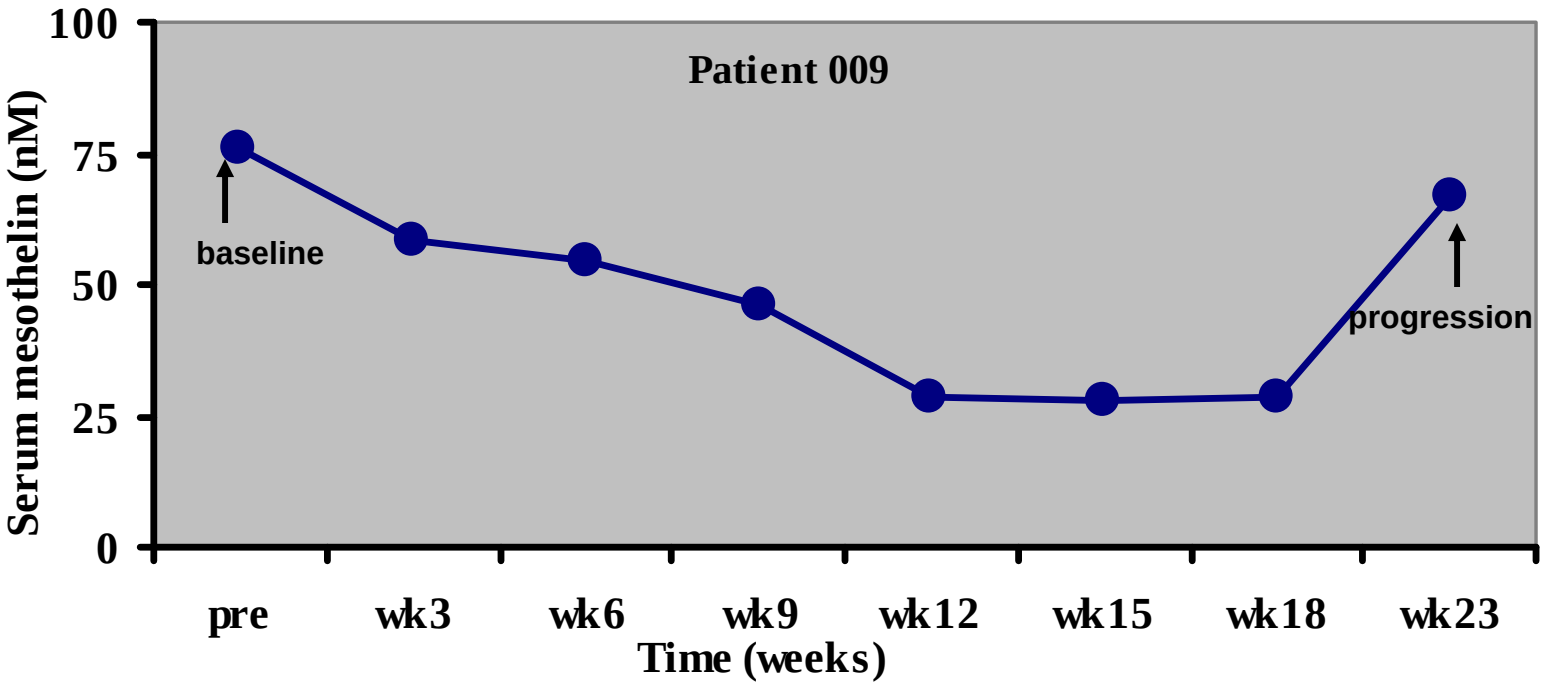
After cycle 2



After cycle 6

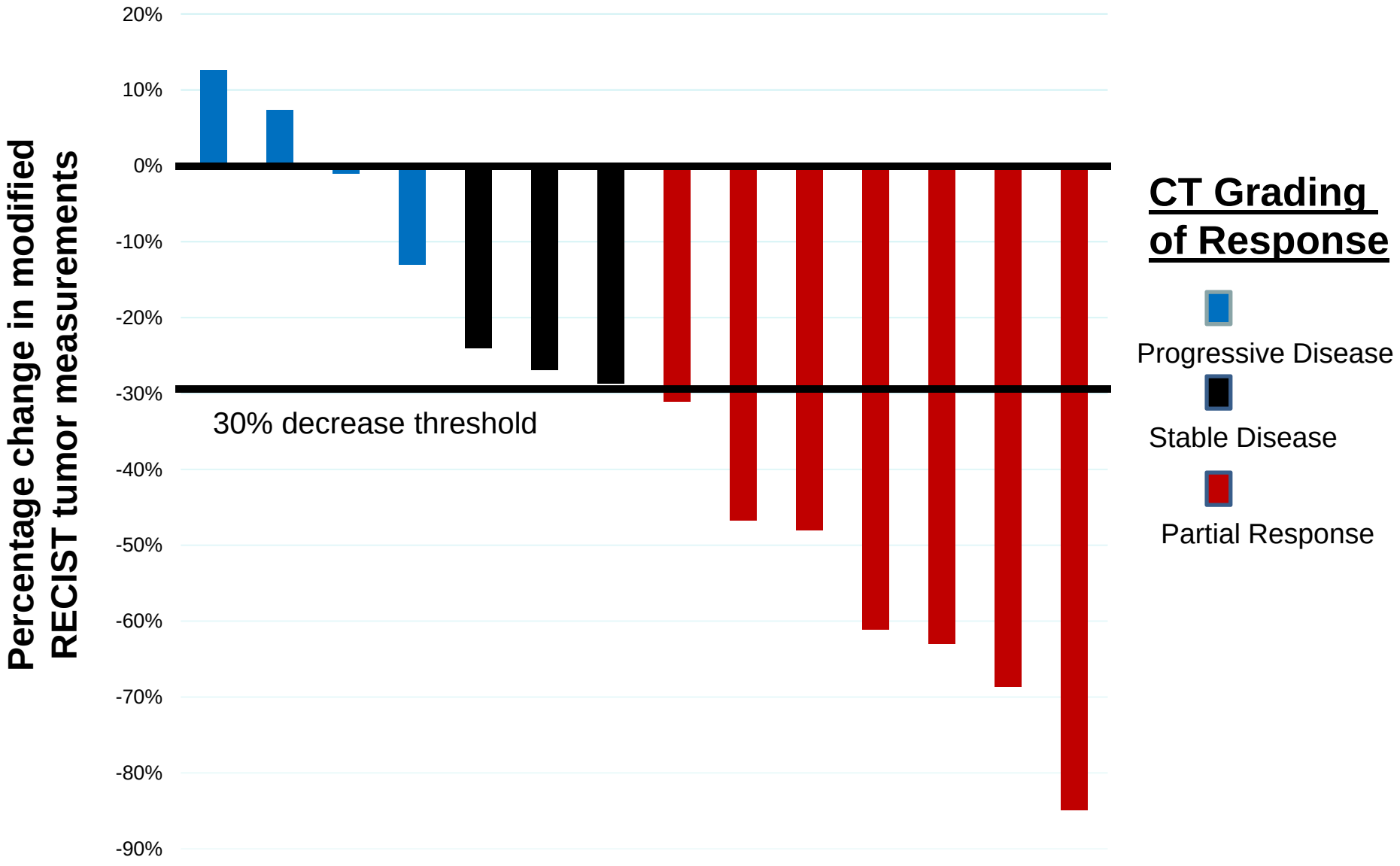


Patient 009 (45 µg/kg dose level)



Serum mesothelin

Tumor Response (Modified RECIST)*



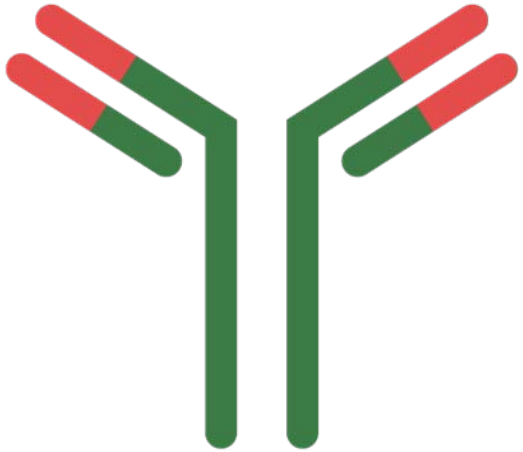
*** Tumor response at end of 2 cycles or best response**

SS1P plus Pemetrexed and Cisplatin Mesothelioma Study: Conclusions

- **Chemotherapy plus SS1P well tolerated**
- **Dose expansion ongoing at 45 µg/kg dose level**
- **Out of 15 evaluable patients: 7 PRs and 4 SD**
- **Serum mesothelin levels may predict response**
- **If we continue to see this anti-tumor activity in the cohort expansion phase, will consider a randomized study of pemetrexed and cisplatin with and without SS1P**

MORAb-009, anti-mesothelin monoclonal antibody

- **Chimeric IgG1 antibody**
- **Same Fv as SS1P**
- **Kills mesothelin expressing cell lines by ADCC**
- **Inhibits mesothelin CA-125 interaction in vitro**



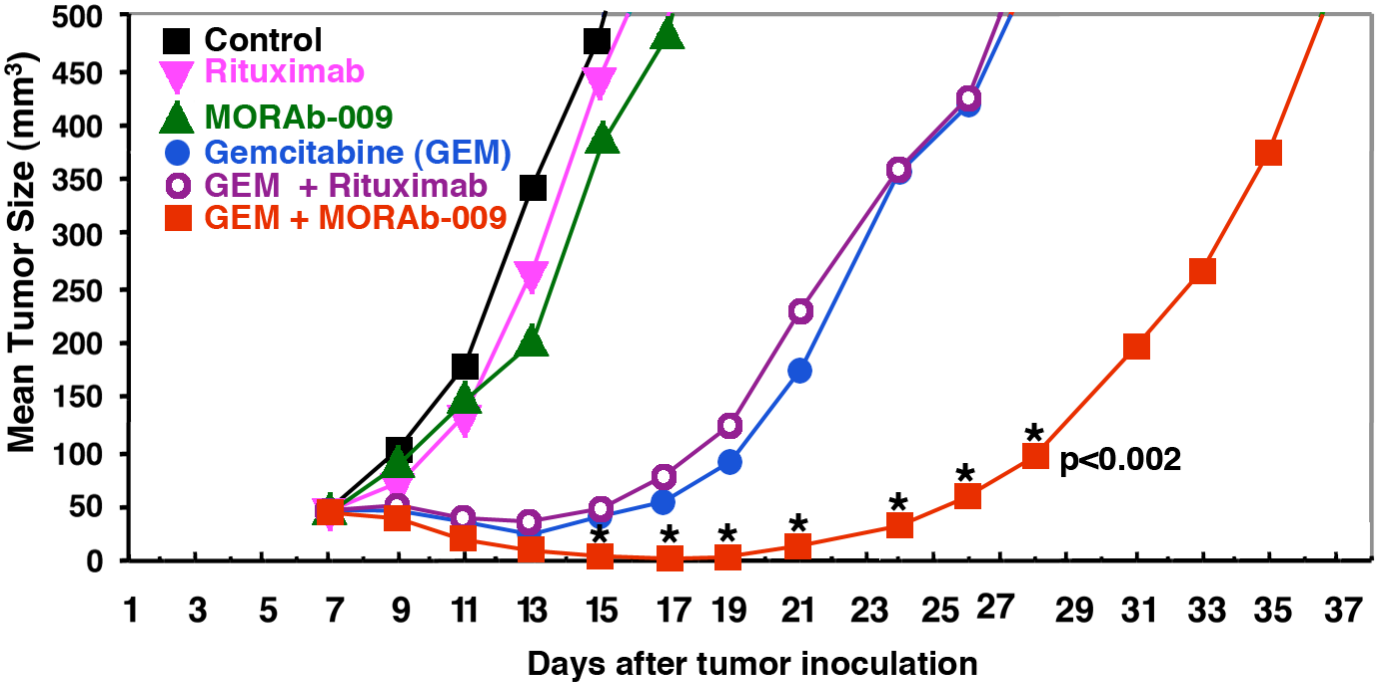
Morphotek Inc.

Hassan et al., Cancer Immunity, 2007

Results of MORAb-009 Phase I study

- **Dose-escalation study of MORAb-009 as weekly iv infusion to determine safety and maximum tolerated dose**
- **Twenty four pts. treated including 13 mesothelioma, 7 pancreatic and 4 ovarian cancer pts.**
- **Well tolerated with most common AE, infusion reaction**
- **Phase II dose established as 200 mg/m2**
- **Out of 20 evaluable patients 11 with stable disease and 9 with progressive disease**

MORAb-009 with chemotherapy

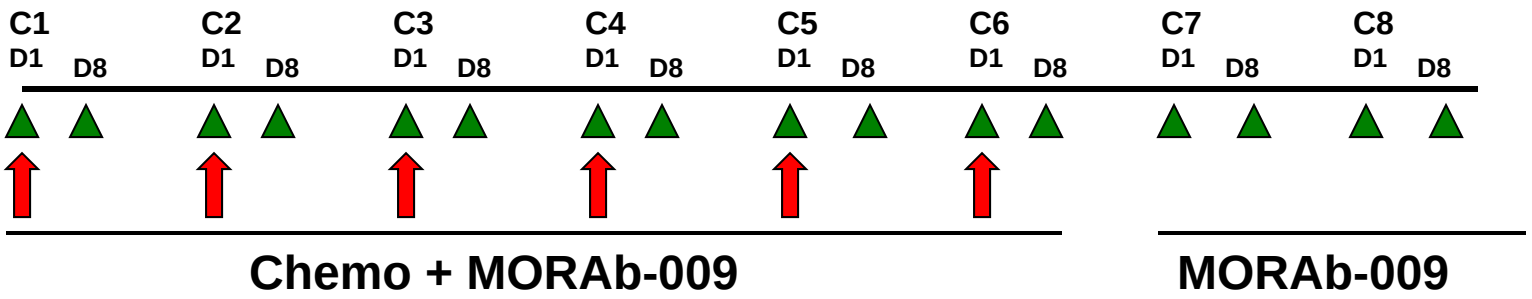


Anti-tumor activity of MORAb-009 with gemcitabine

Hassan et al., Cancer Immunity, 2007

Phase II study of MORAb-009 plus pemetrexed and cisplatin for pleural mesothelioma

- **Front line therapy in newly diagnosed patients**
- **Progression-free survival as primary end-point**
- **Translational endpoints - CA-125 kinetics**



Cisplatin 75 mg/m^2
Pemetrexed 500 mg/m^2

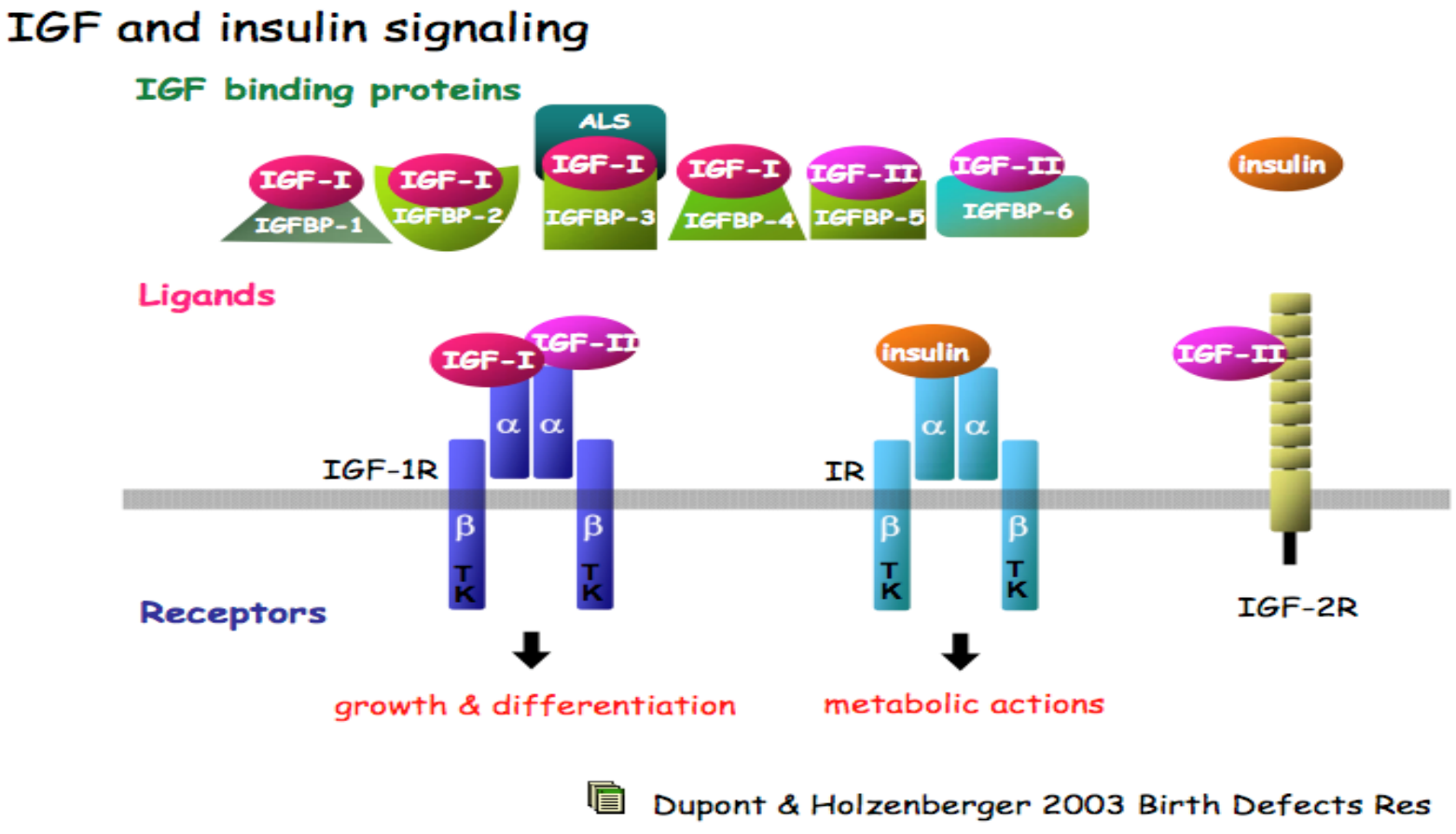
MORAb-009 5 mg/kg

Phase II study of MORAb-009 plus pemetrexed and cisplatin for pleural mesothelioma

- **Multi-institutional study with NCI as lead site**
- **1st patient treated 2/11/09**
- **n = 89 patients treated (last patient treated 10/14/10)**
- **49 patients still receiving treatment**
- **Data analysis planned for early 2011**

Insulin Growth Factor 1 Receptor (IGF-1R) as Target for Mesothelioma Treatment

Insulin Growth Factors and IGF-1R



Dupont & Holzenberger 2003 Birth Defects Res

IGF Pathway and Cancer

- **The IGF pathway is a stimulatory signaling system that is integral to the growth of many tissues**
- **Stimulates cellular differentiation and proliferation**
- **Inhibits cancer cell apoptosis**
- **Associated with resistance to cytotoxic agents**

Pollak et al. Nat Rev Cancer 2004

IGF Pathway and Mesothelioma

- **IGF-1R is highly expressed in mesothelioma**
- **Activation of IGF-1R pathway may play a role in mesothelioma tumorigenesis**
- **In a hamster mesothelioma model an antisense plasmid to IGF-1R inhibited tumor growth**
- **IGF-1R inhibitors decrease viability of mesothelioma cell lines in vitro**

Lee TC et al. Cancer Research, 1993
Pass HI et al. Cancer Research, 1996
Whitson BA & Kratzke, et al. Ann Thorac Surg., 2006

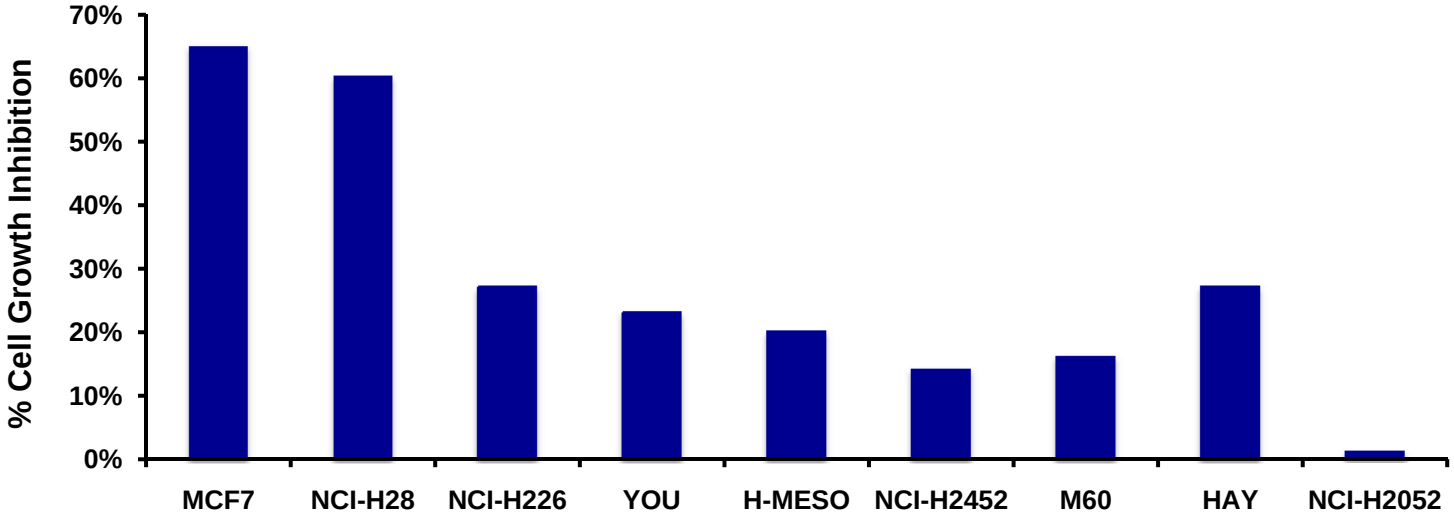
IMC-A12

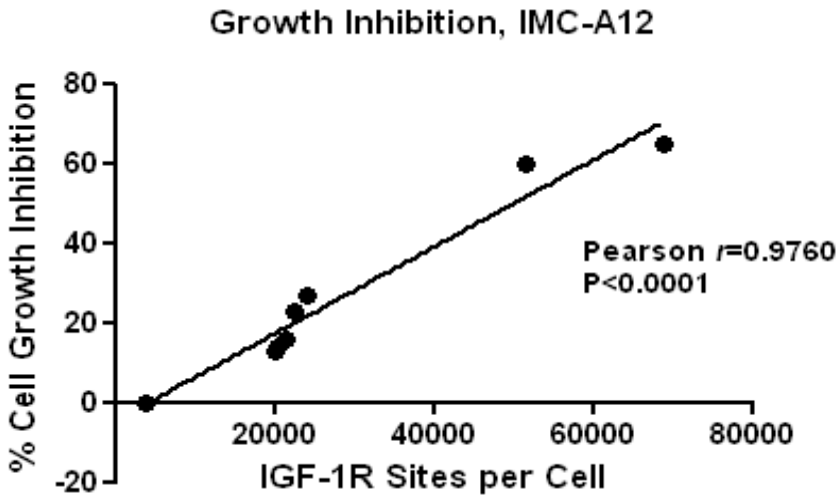
- **Fully human IgG1 high affinity monoclonal antibody that selectively binds IGF-1R**
- **Inhibits ligand binding to IGF-1R**
- **Induces rapid receptor internalization and degradation**
- **Anti-tumor activity against different tumor cell types in vitro as well as against tumor xenografts**
- **Phase I clinical trials using different scheduling regimens have been completed**

Pre-clinical studies of IMC-A12 for treatment of mesothelioma

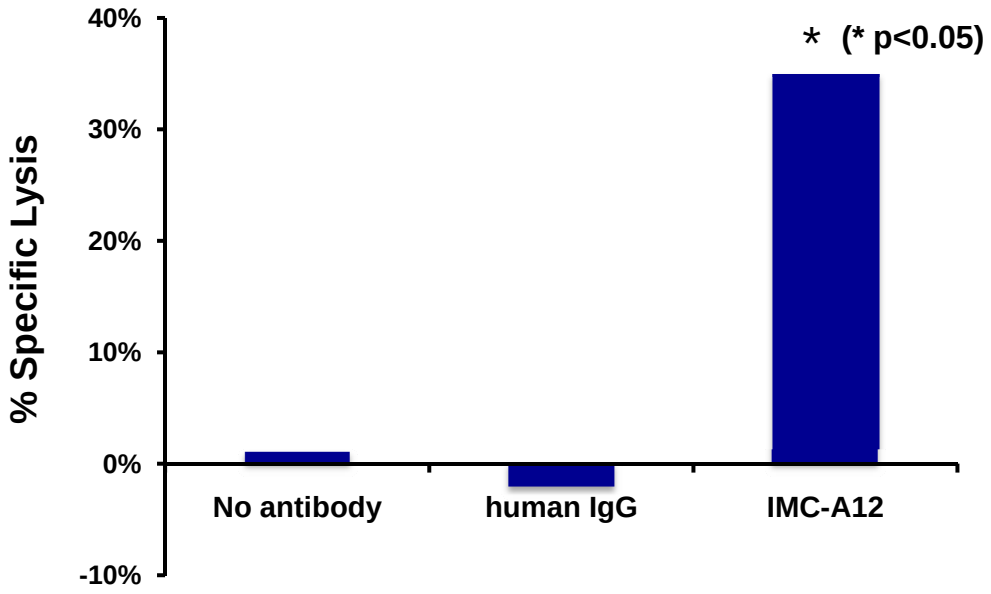
- **Characterize IGF-1R expression in established mesothelioma cell lines as well as early passage tumor cells obtained from patients**
- **In vitro activity of IMC-A12 and correlation with IGF-1R expression**
- **In-vivo activity of IMC-A12 against mesothelioma tumor xenografts**

IMC-A12 : Growth Inhibition against established cell lines





IMC-A12 : ADCC



NCI-H28 cell line

Intraperitoneal Model to Evaluate Anti-tumor Activity of IMC-A12

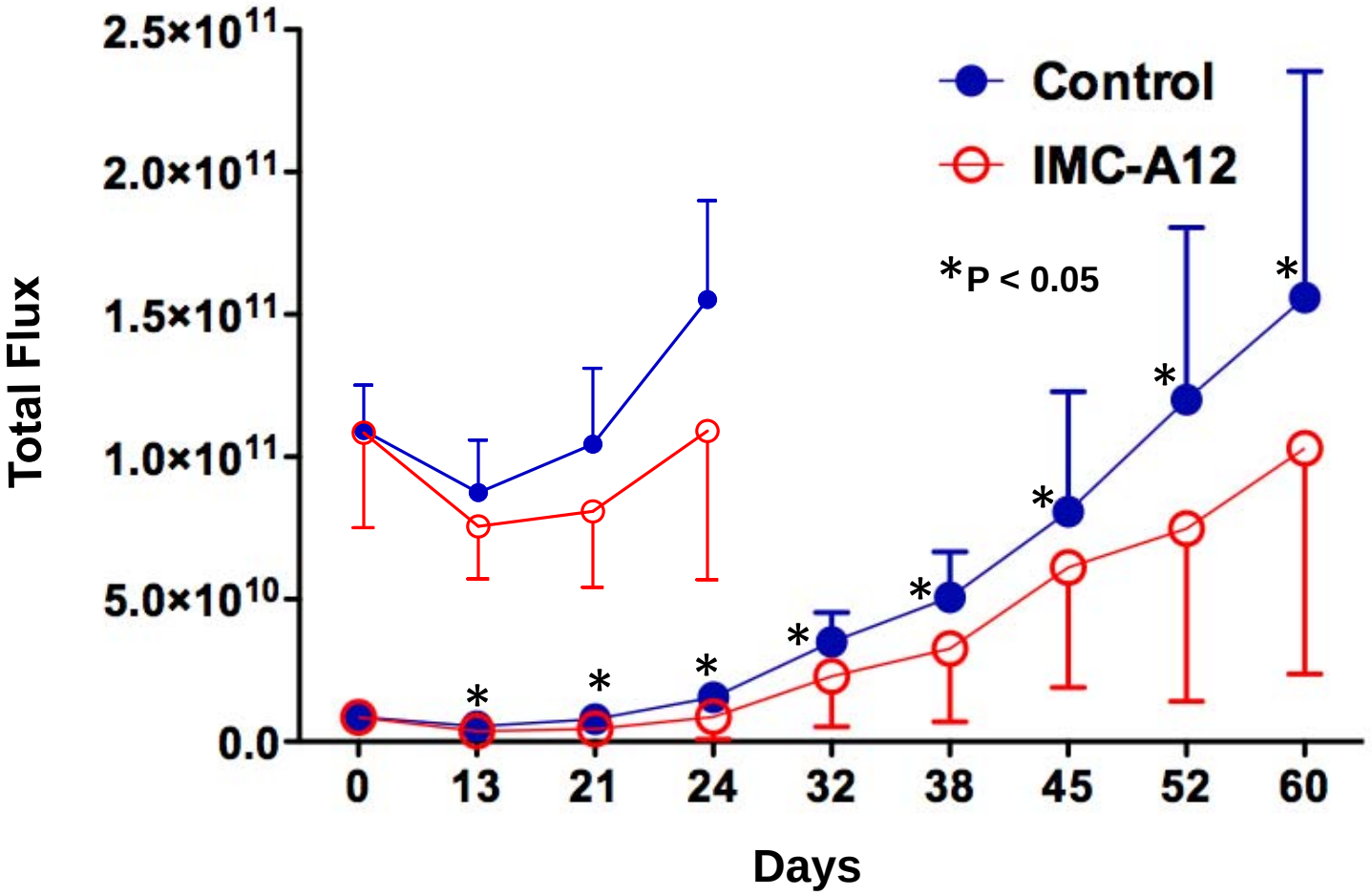
- **NCI-H226 cells were stably transfected with pFUGW-mPol2- fLuc2/eGFP vector containing both GFP and Luciferase genes**

- **$5x10^6$ cells injected i.p. into athymic nude mice**

- **Mice were randomized into two groups and received either saline or IMC-A12 (5 mg/kg twice a week x 60 days)**

- **Analysis was done weekly and total luminescence flux was analyzed for each mouse**

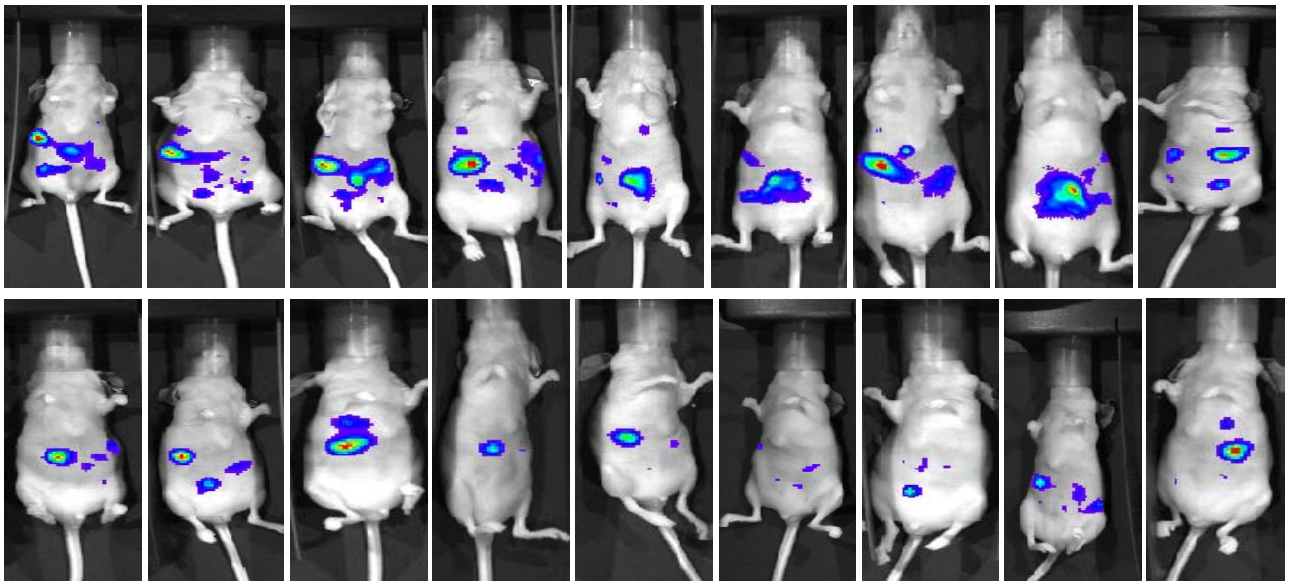
IMC-A12: Anti-tumor activity against NCI-H226 i.p. tumor model



Day 24

Control

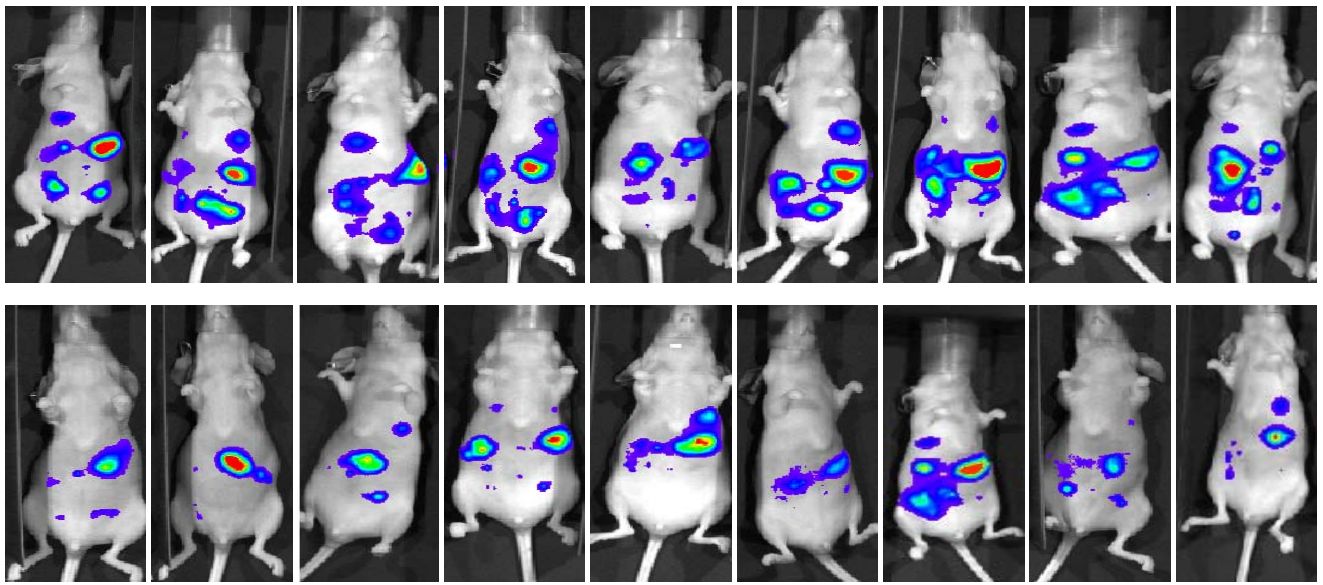
IMC-A12



Day 60

Control

IMC-A12



IMC-A12 Preclinical Studies: Conclusions

- **IGF-1R is expressed in mesothelioma cell lines and early passage tumor cells.**
- **However, IGF-1R sites per cell variable**
- **ADCC and inhibition of cell proliferation correlate with IGF-1R sites per cell**
- **Significant anti-tumor activity seen in mesothelioma i.p. tumor model**

Phase II Clinical Trial of IMC-A12 in patients who have failed front line mesothelioma therapy

Primary Objective

- **To determine the clinical response rate (PR + CR)**

Secondary Objectives

- **Progression free survival**
- **Overall survival**

Exploratory Objectives

- **Tumor expression of IGF-1R**
- **Serum mesothelin as a marker of tumor response**

IMC-A12 : Phase II Mesothelioma trial

- **Patients who have failed front line therapy**
- **IMC-A12 dose of 20mg/kg every 3 weeks**
- **Tumor restaging after every 2 cycles**
- **Separate cohort of pleural and peritoneal mesothelioma patients**
- **Trial opened in July 2010 and 20 pts. enrolled thus far**

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