Recent Advances in Diagnosis and Treatment of ARD

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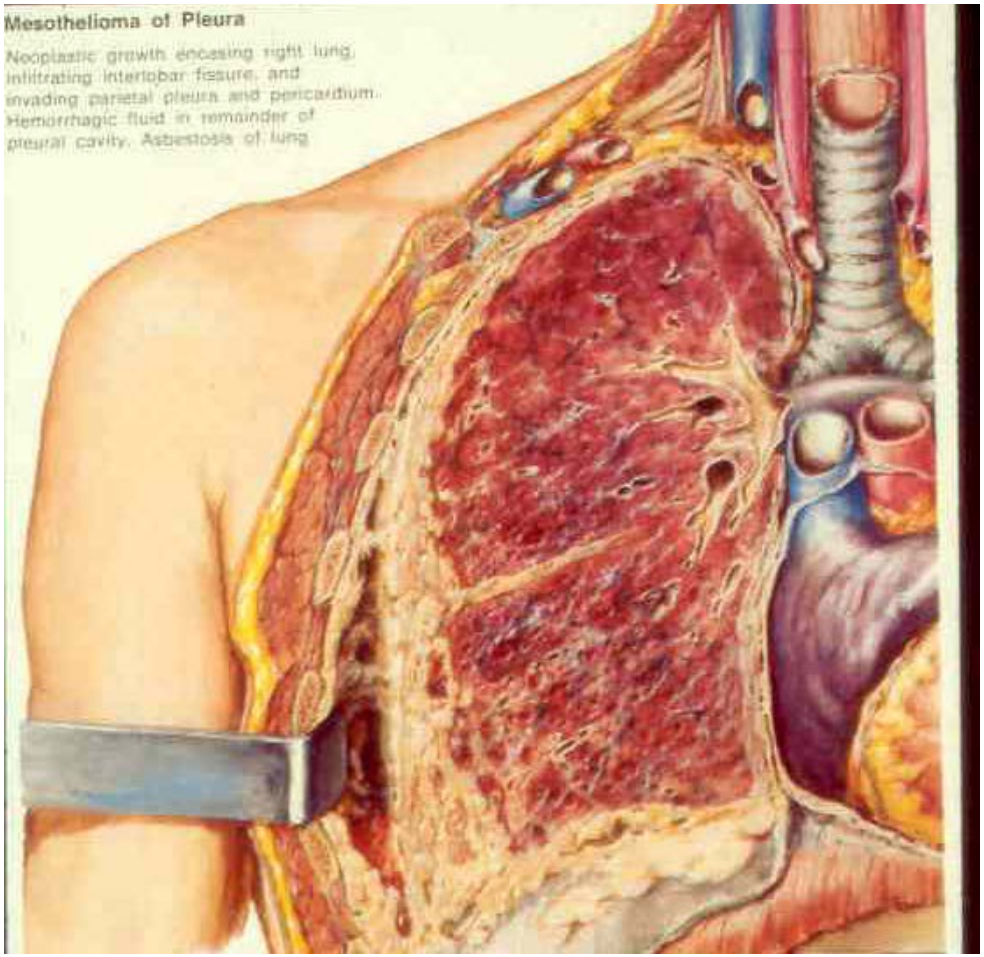
Outline

- None

Outline

- Advances and current status of biomonitoring and imaging (including CT) in diagnosis and surveillance of asbestos exposed populations.
- Recent innovations in the treatment of mesothelioma: current clinical trials of promising agents.

Mesothelioma

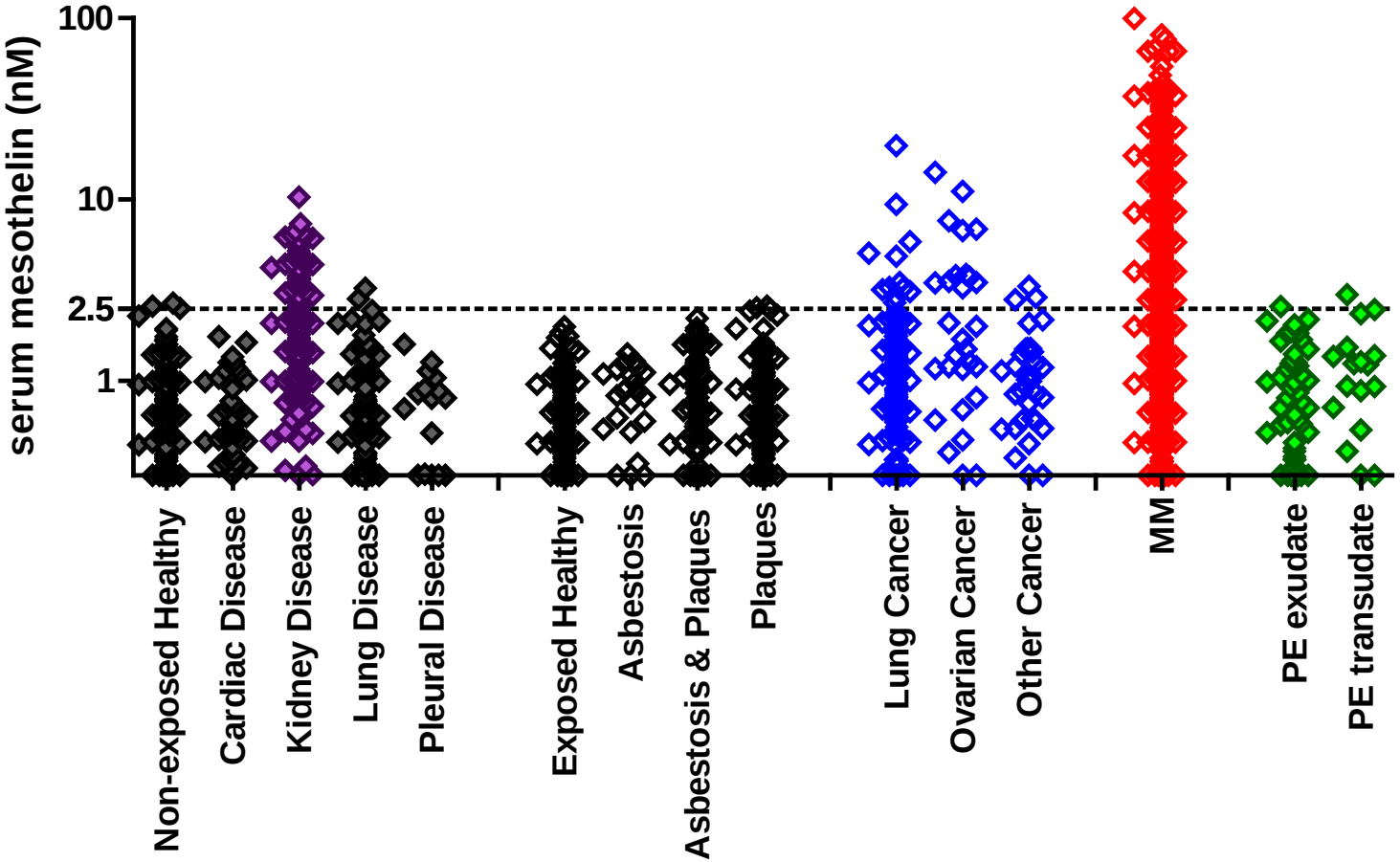


- Tumor of serosal surfaces of pleura, peritoneum, pericardium, tunica vaginalis
- Median survival is poor
  - 8-14 months
- Morbidity and mortality related to local invasion of vital structures
- Treatment options suboptimal

The Challenge of Early Detection

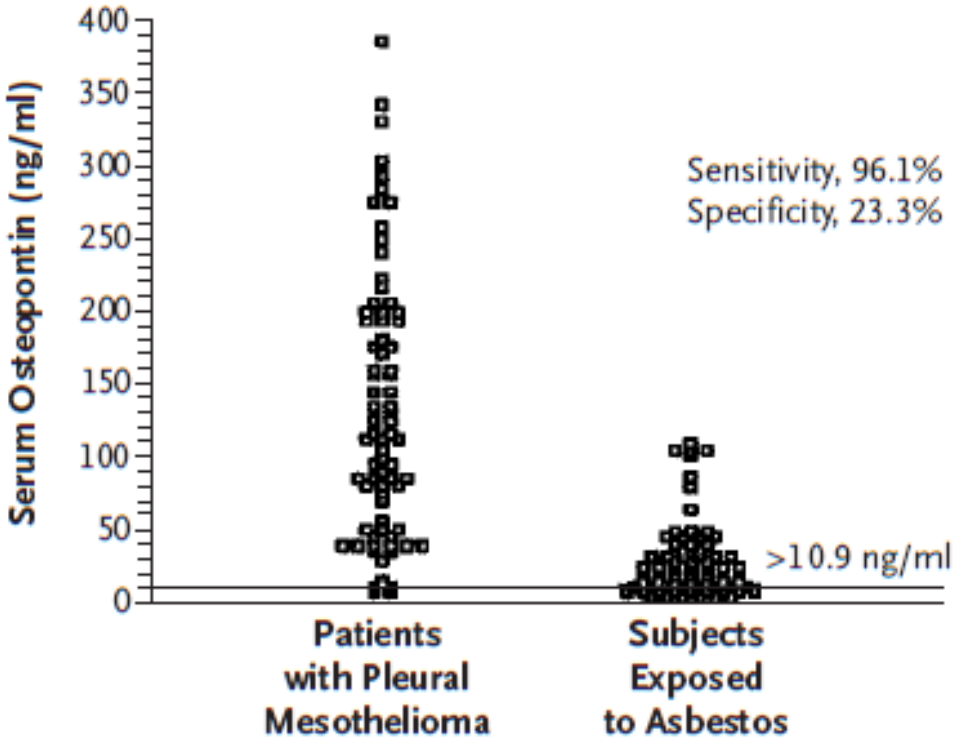
- Long period where disease is present without symptoms
- Better outcomes with treatment when early stage
- “Common” disease
  - 2000 cases
  - 10 million exposed
- Good tools for early diagnosis
  - Imaging (e.g. CXRs and Chest CT scans)
  - Blood tests

SMRP


serum mesothelin (nM)
100
10
2.5
1
Non-exposed Healthy
Cardiac Disease
Kidney Disease
Lung Disease
Pleural Disease
Exposed Healthy
Asbestosis
Asbestosis & Plaques
Plaques
Lung Cancer
Ovarian Cancer
Other Cancer
MM
PE exudate
PE transudate

Osteopontin (OPN)

- Elevated in MM
- Less specific than mesothelin



Pass H, et al. NEJM 2005

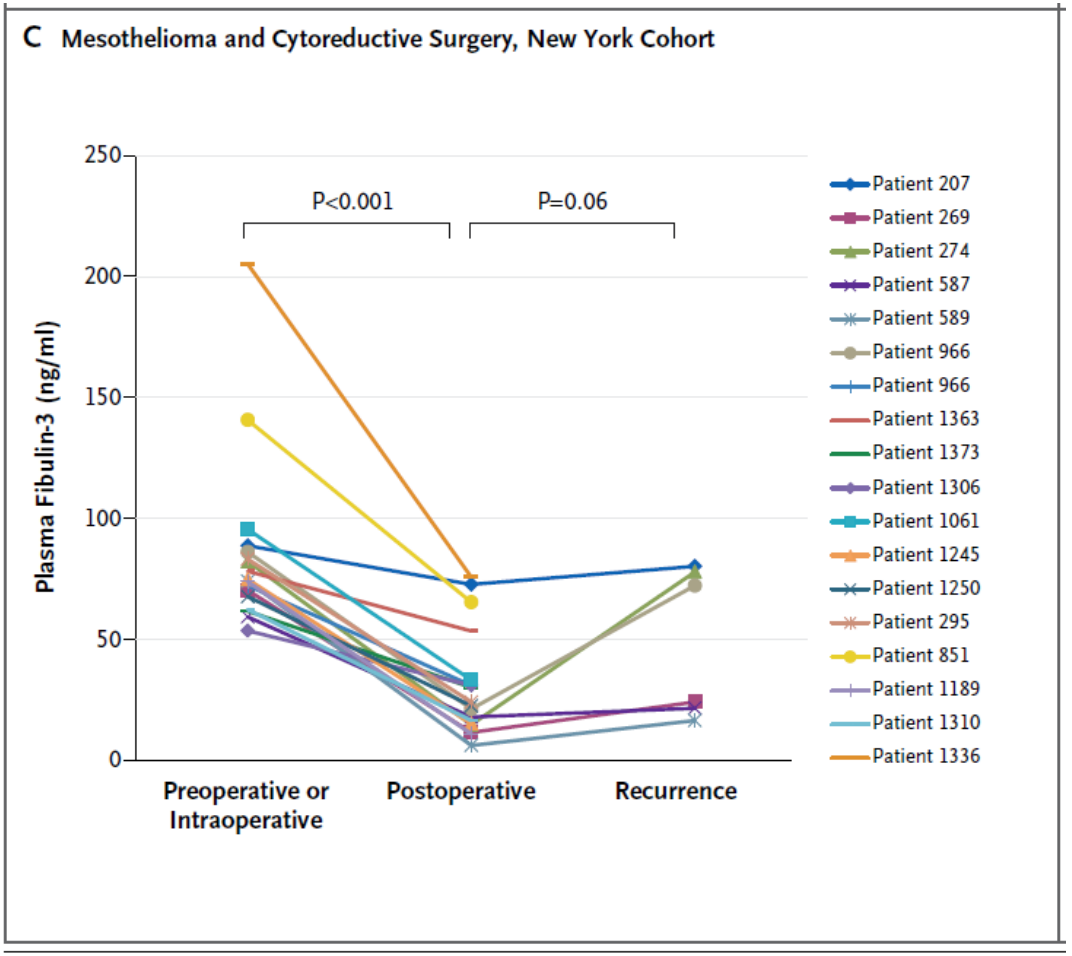
TABLE 2

COMPARISON OF MULTIPLE BIOMARKER LEVELS IN PATIENTS WITH MESOTHELIOMA

Sensitivities of biomarkers	90% specificity (threshold value)	95% specificity (threshold value)
MPF	68 (12.66)	92 (12.66)
Osteopontin	53 (12)	47 (18)
SM	78 (1.4)	73 (1.6)

MPF, megakaryocyte potentiating factor; SMRP, serum mesothelin-related proteins.

FBLN3 after Cytoreductive Surgery



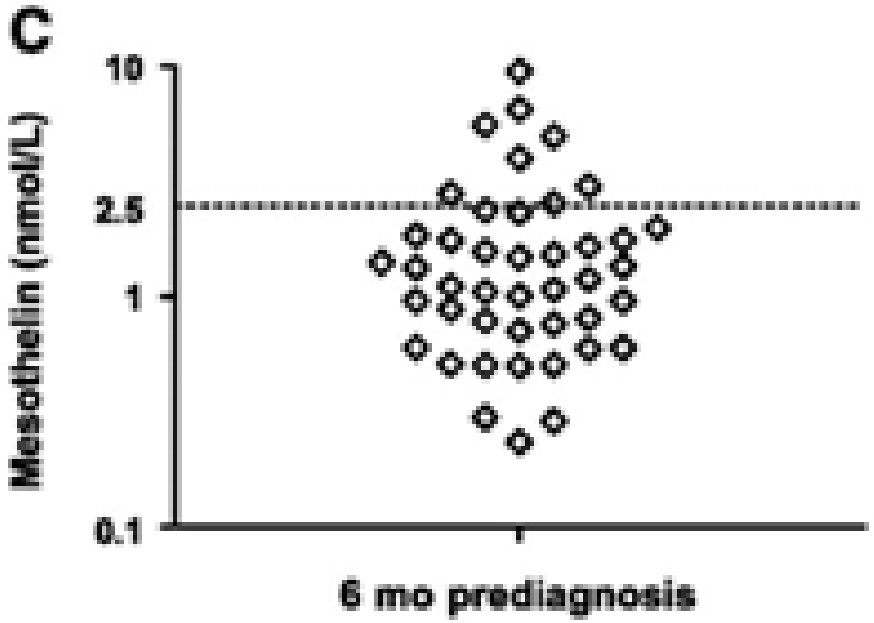
Pass H, et al. NEJM 2012

SMRP and Screening

- Wittenoom Cohort
  - ~ 7000 workers Blue Asbestos Company
  - ~ 5000 residents of township
- Lifetime MM risk of 17%
- Subset of population took part in cancer prevention program since 1991

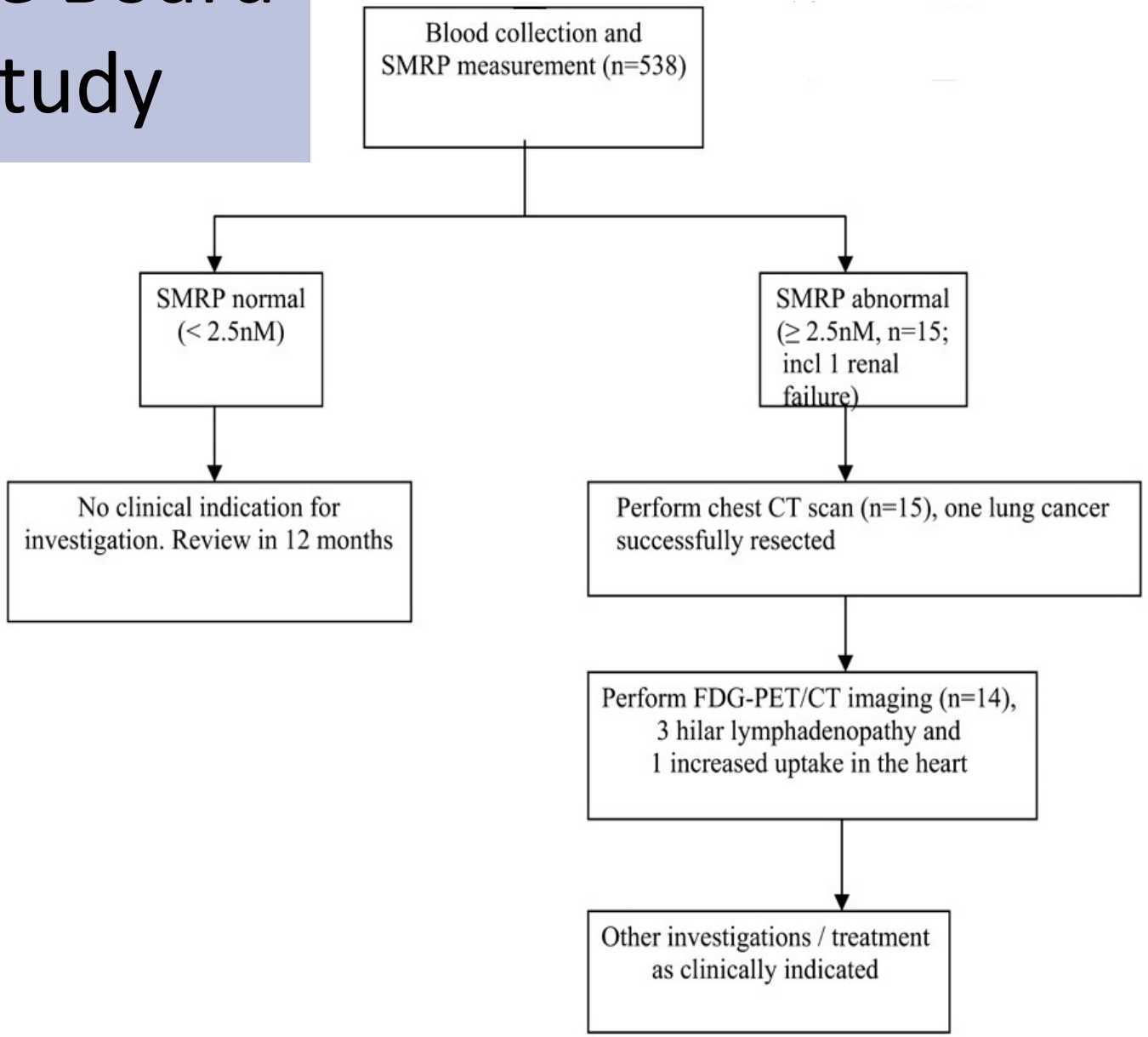
Serum Mesothelin

- 6 months before Mesothelioma Diagnosis



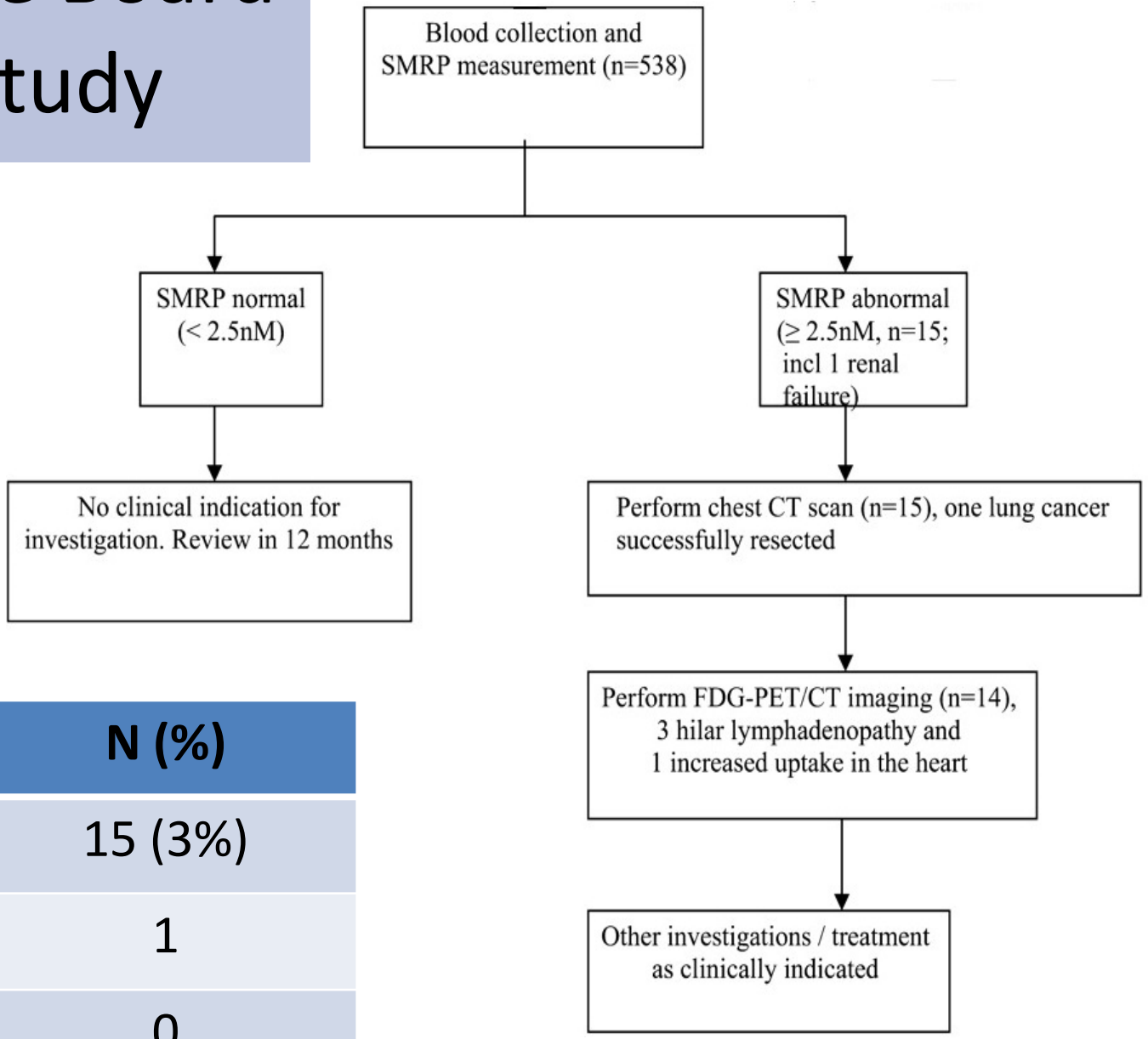
Creaney J et al. Cancer Epidemiol Biomarkers Prev 2010;19:2238-2246

Dust Disease Board Cohort Study



Park, et al AJRCCM 2008

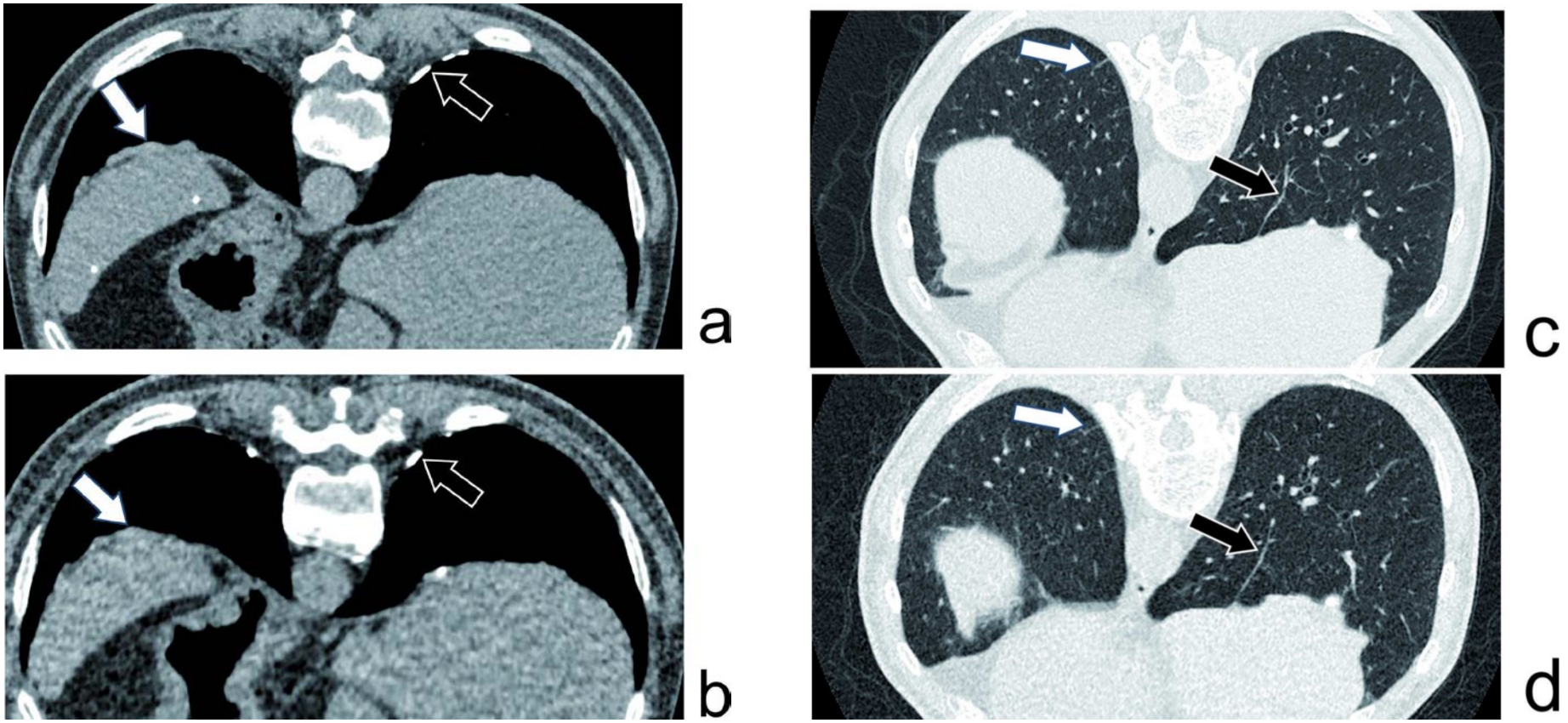
Dust Disease Board Cohort Study



Outcome	N (%)
Positive SMRP	15 (3%)
Lung Cancer	1
MM	0

Park, et al AJRCCM 2008

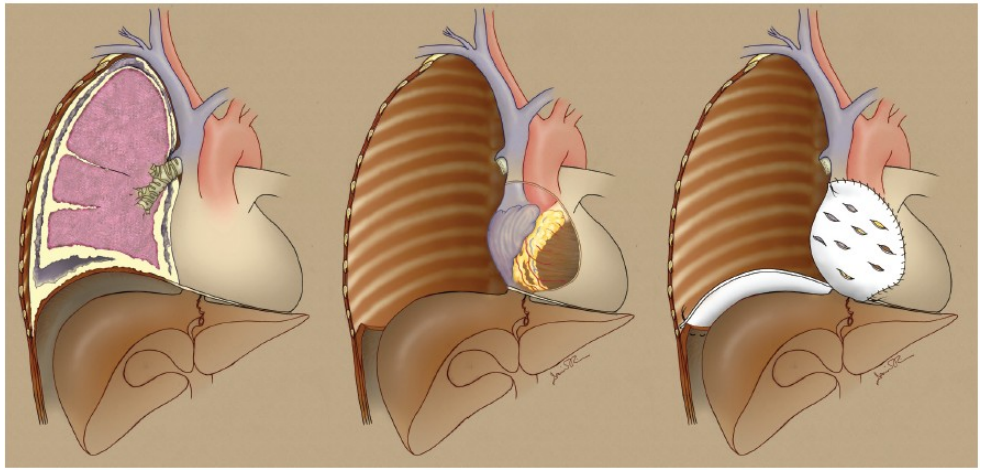
Imaging- Ultra low dose CT



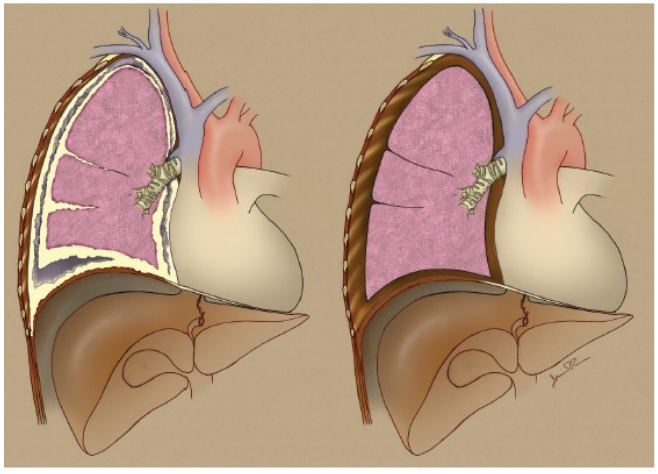
Schaal, et al. PLOS ONE; Dec 2016

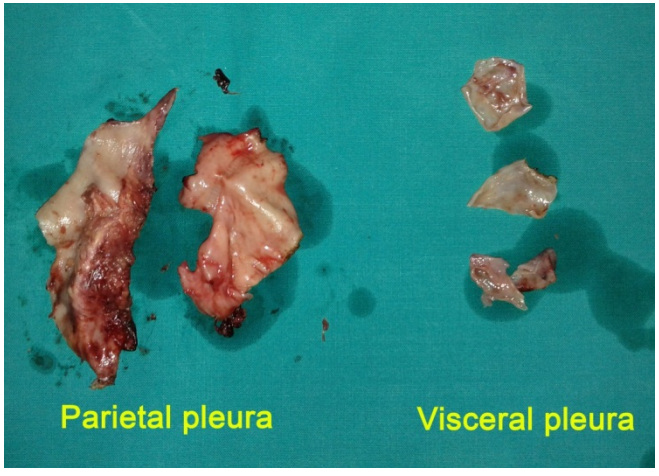
Mesothelioma Treatment
Surgery

Extrapleural pneumonectomy



Radical pleurectomy & decortication



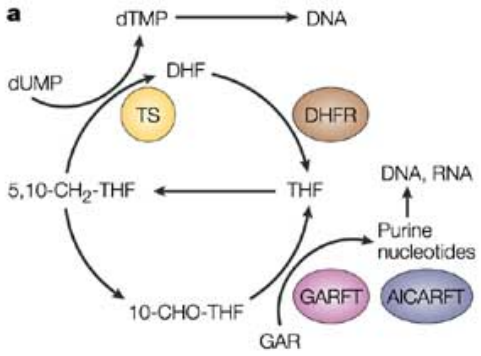


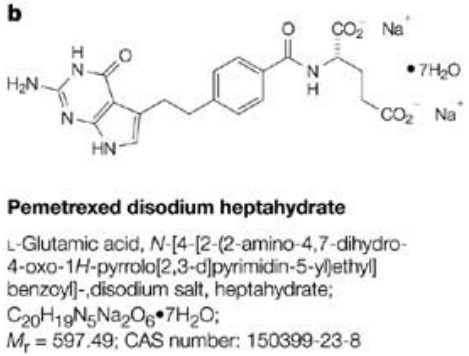
EPP vs Pleurectomy

	EPP N=385	P/D N=278
Operative mortality	7%	4%
Local recurrence	33%	**65%**
Distant recurrence	**66%**	35%
Overall Survival (both groups) 14 months 5 year survival 12%		
Stage I	38 months	
Stage II	19 months	
Stage III	11 months	
Stage IV	7 months	

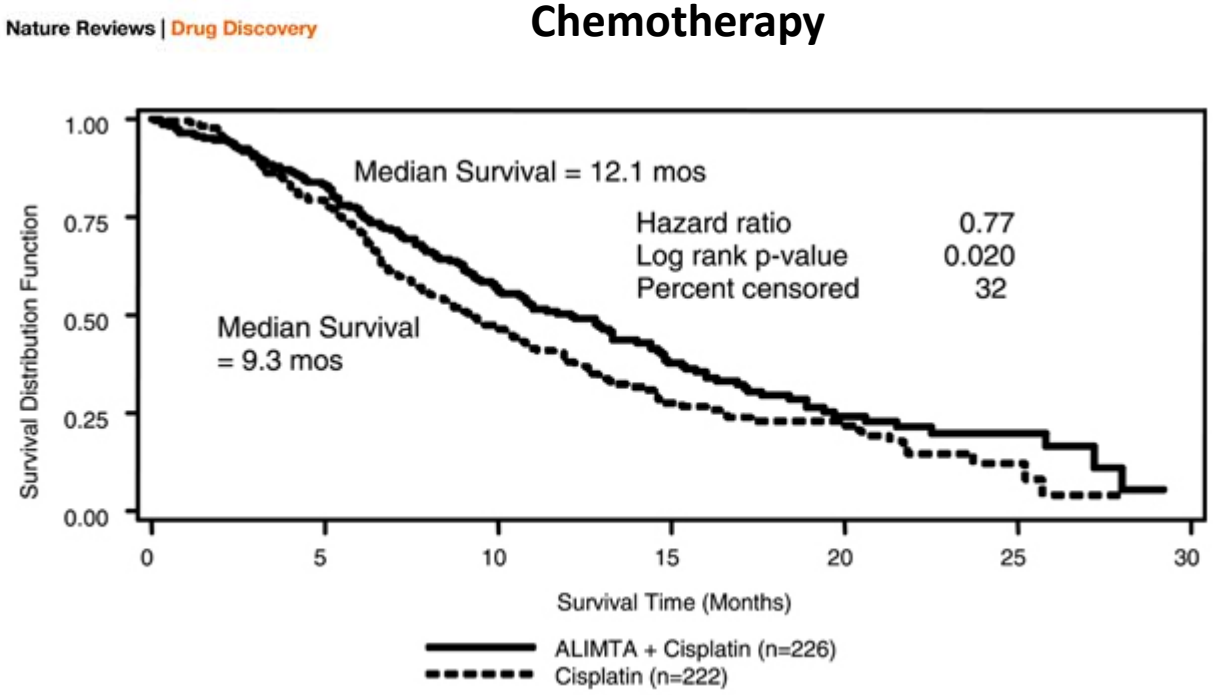
Flores, *J Thor Cardiovasc Surg* 2008

Chemotherapy





Folate antimetabolite that inhibits three enzymes used in purine/pyrimidine sythesis



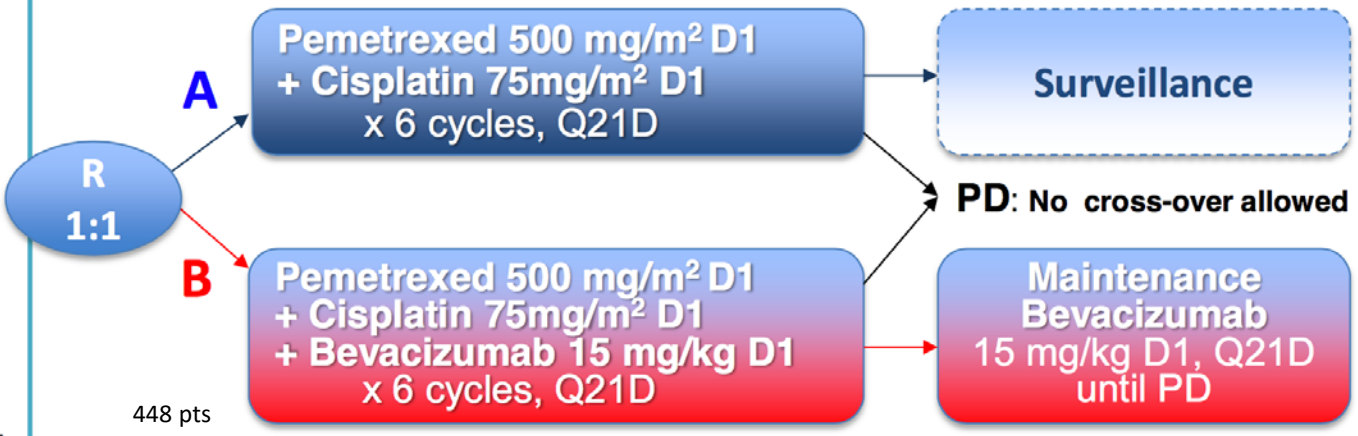
IFCT-GFPC-0701 trial: MAPS

Mesothelioma **A**vastin cisplatin **P**emetrexed **S**tudy

- MPM proved by pleural biopsies (thoracoscopy...)
- Written informed consent
- Age ≥18 - <75 years
- PS 0 - 2
- Chemonaïve patients
- not candidate to curative intent surgery according to Multidisciplinary Board
- At least 1 evaluable or measurable lesion by CT
- Weight loss <10% within 3 months prior to enrolment
- No significant cardio-vascular comorbidity and/or other usual chemo or beva contra-indications (HTA, GI perforation…)
- Prophylactic radiotherapy (3 x 7 Gy) before chemo

IFCT-sponsored, open-label, multi-centre randomized phase II-III trial

(bevacizumab supplied by Roche)



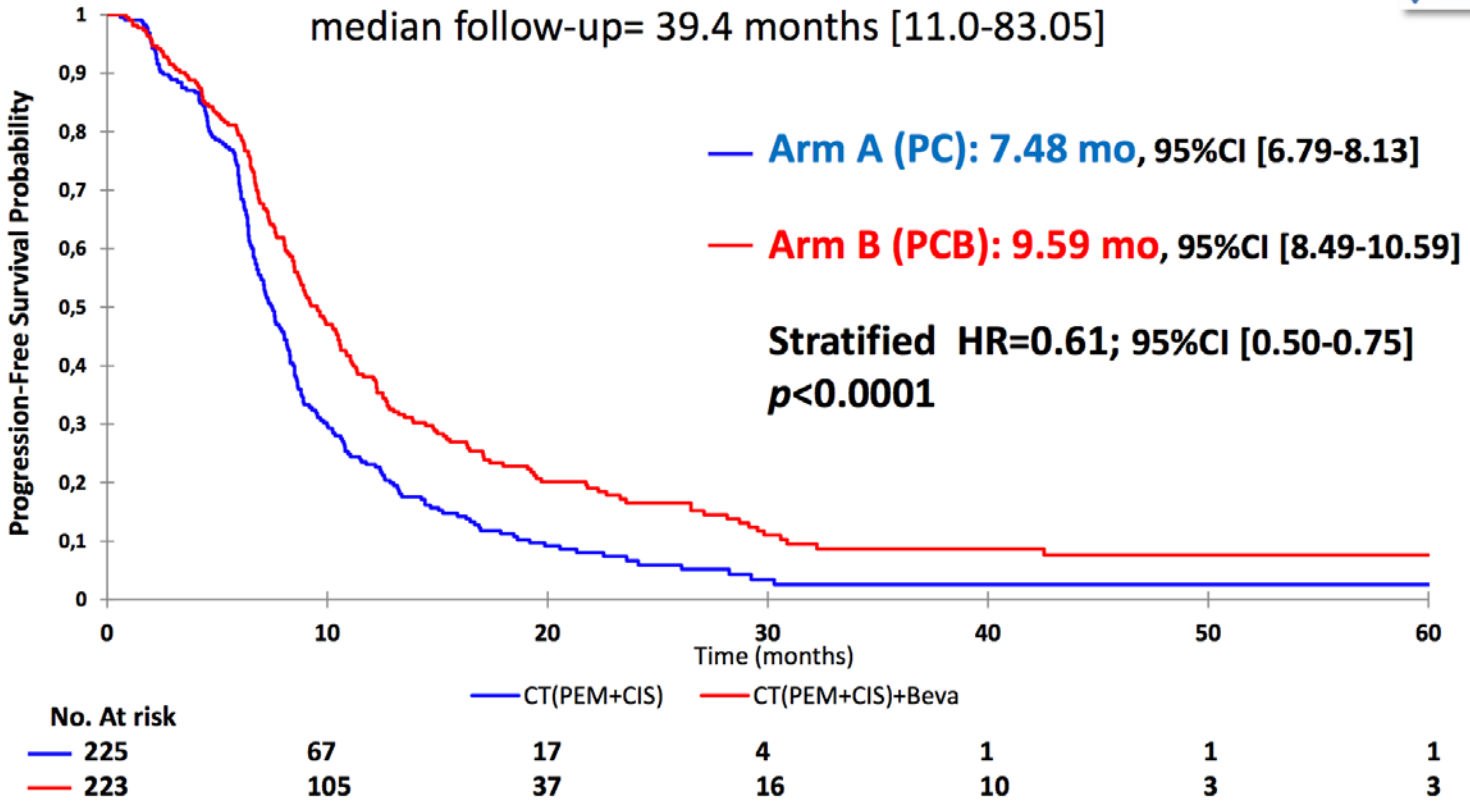
CT-scan Q 3 cycles in both arms; Response assessed with modified RECIST criteria for MPM

→ ***Phase 3 primary goal* = OS;** *Secondary goals:* PFS, QoL, ancillary studies

Stratification: center, histology (epithelioid vs sarcomatoid/mixed), PS (0-1 vs 2), smoking status

Efficacy: ITT median Progression-free Survival (PFS)

median follow-up= 39.4 months [11.0-83.05]



Arm A (PC): 7.48 mo, 95%CI [6.79-8.13]

Arm B (PCB): 9.59 mo, 95%CI [8.49-10.59]

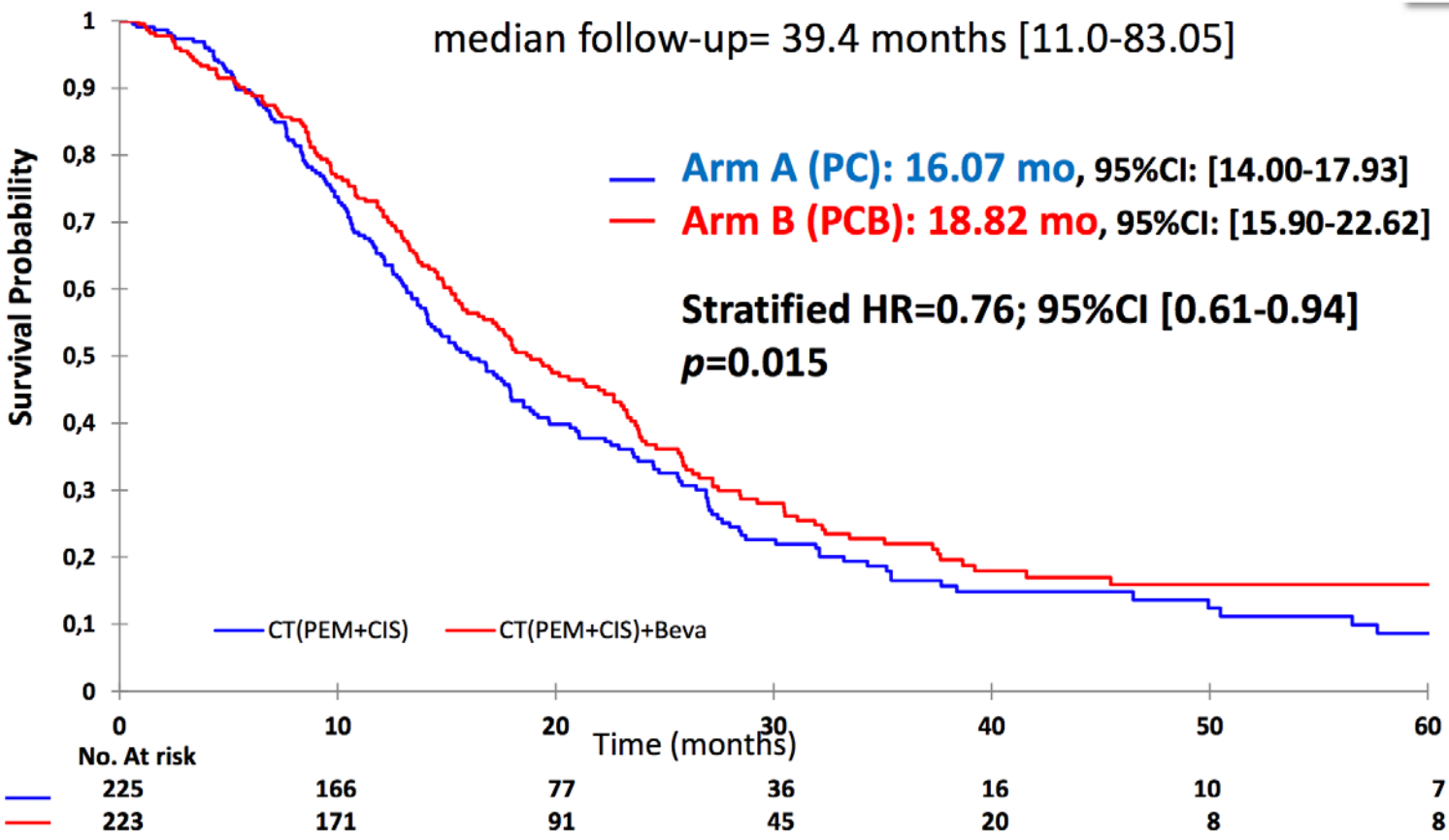
Stratified HR=0.61; 95%CI [0.50-0.75]

***p*<0.0001**

IFCT 0701 'MAPS' randomized phase 3 trial

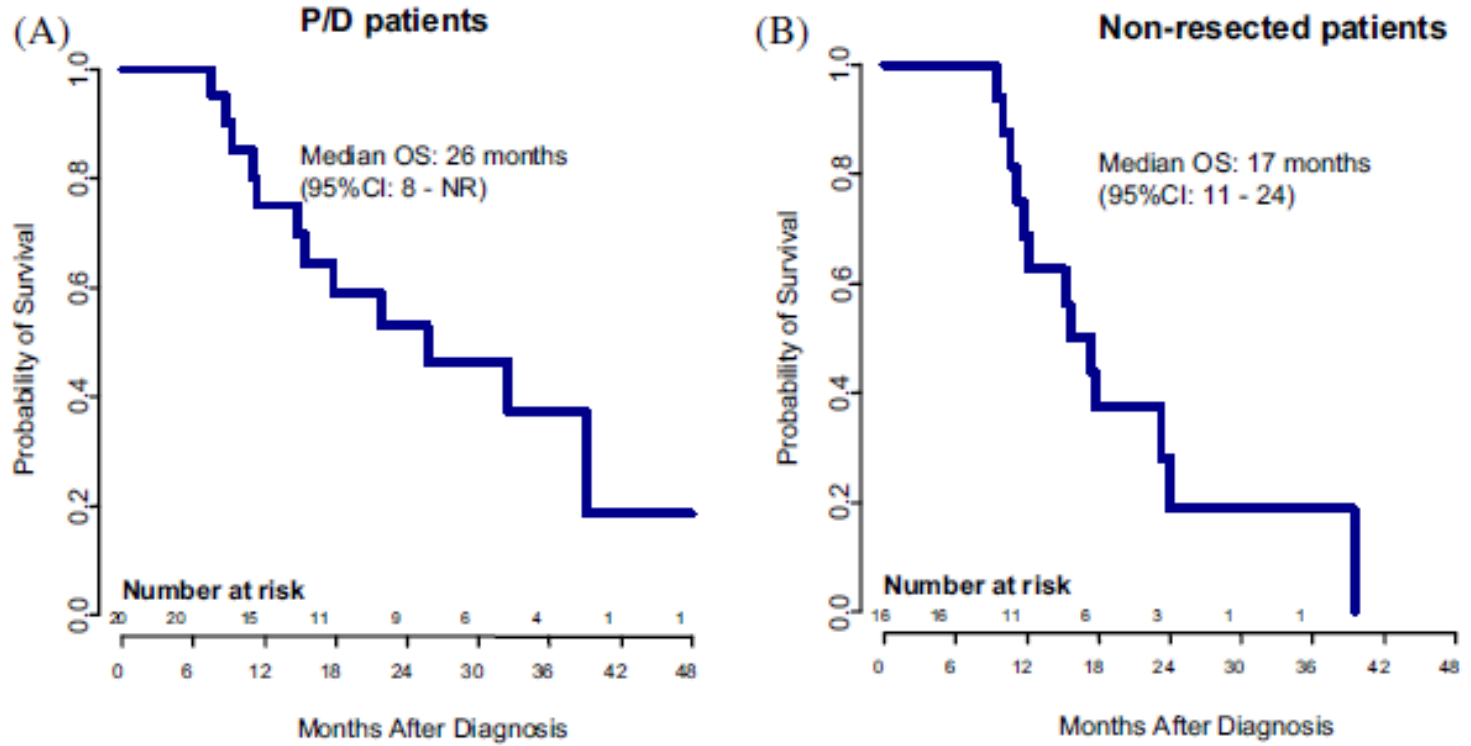
PRESENTED AT: ASCO Annual '15 Meeting

Efficacy: ITT median Overall Survival (OS)



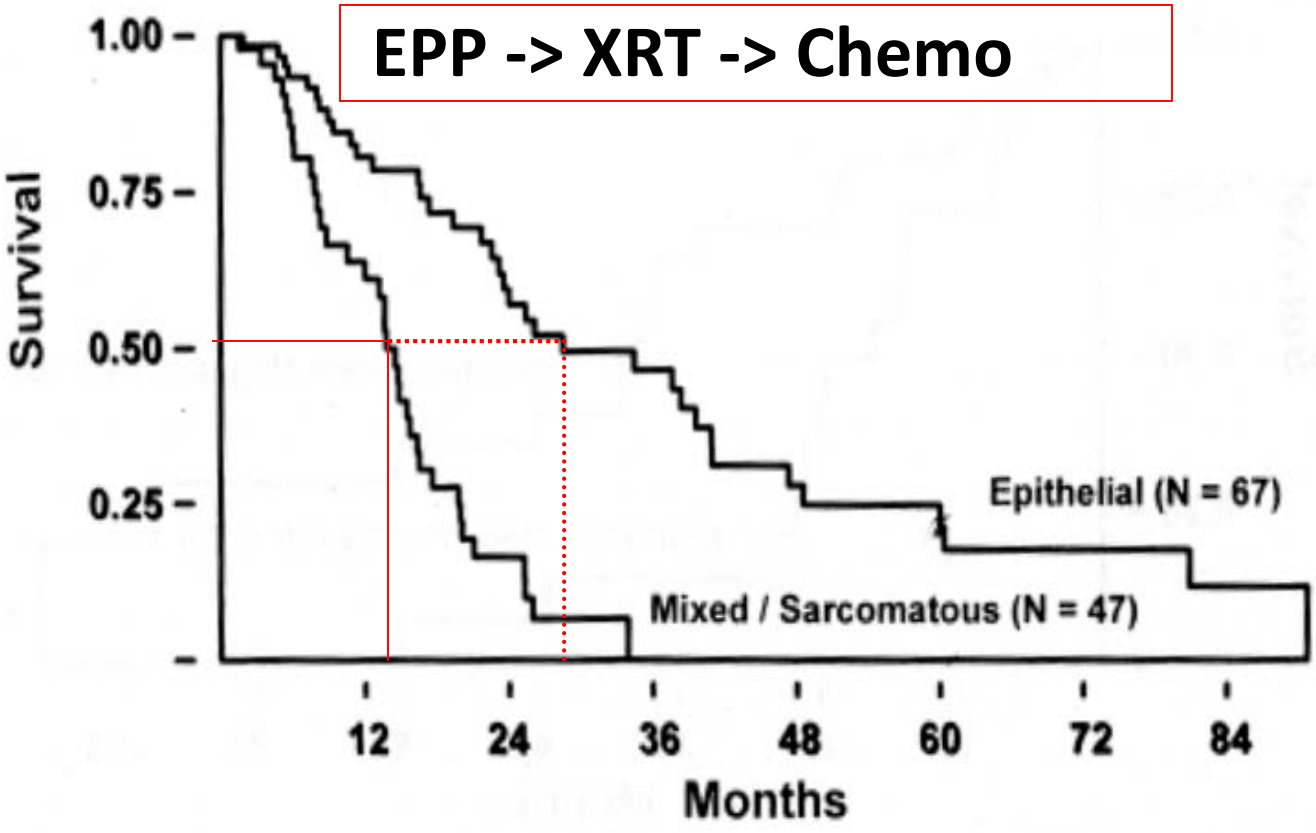
IFCT 0701 'MAPS' randomized phase 3 trial

IMRT After Chemotherapy



Int J Radiation Oncol Biol Phys, Vol. 83, No. 4, pp. 1278-1283, 2012

Paradigm of Multimodality Therapy



- 183 Pts through 1999
- **Overall Median Survival –19 mos.**
- 5-year survival -15%

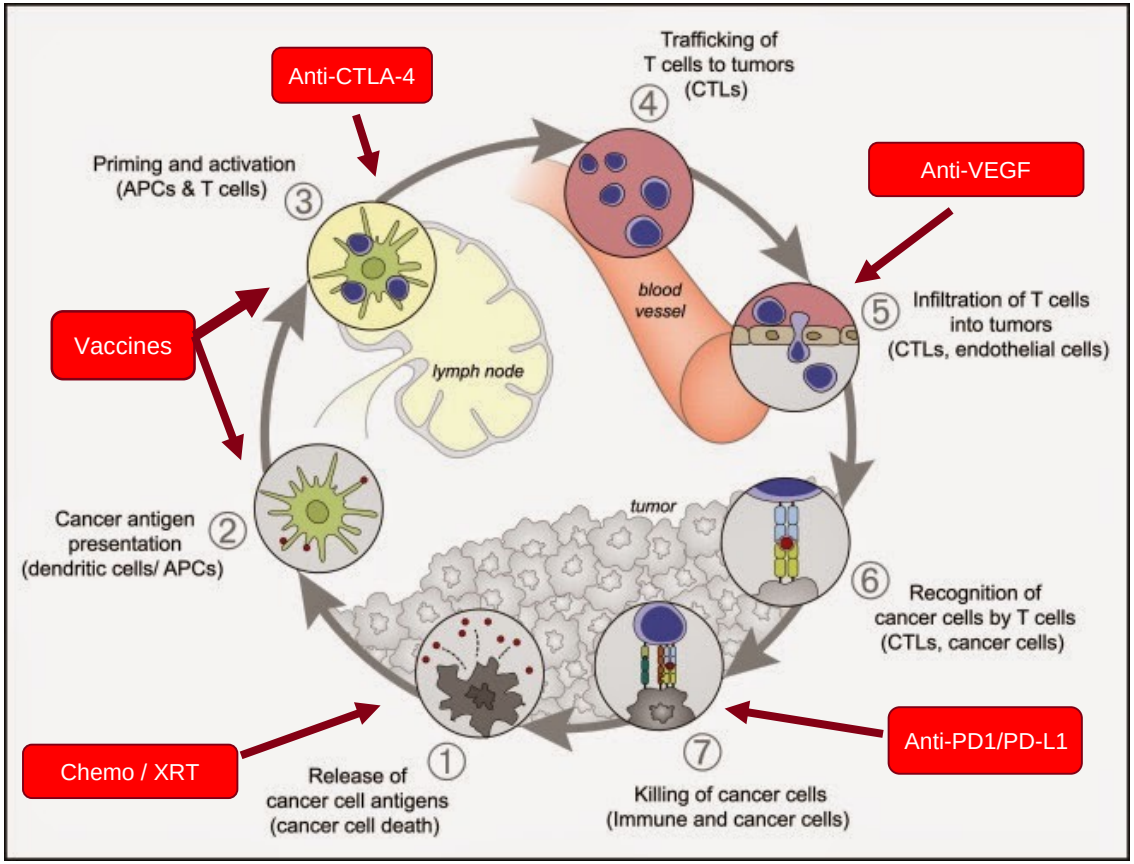
Highly selected

Non-randomized

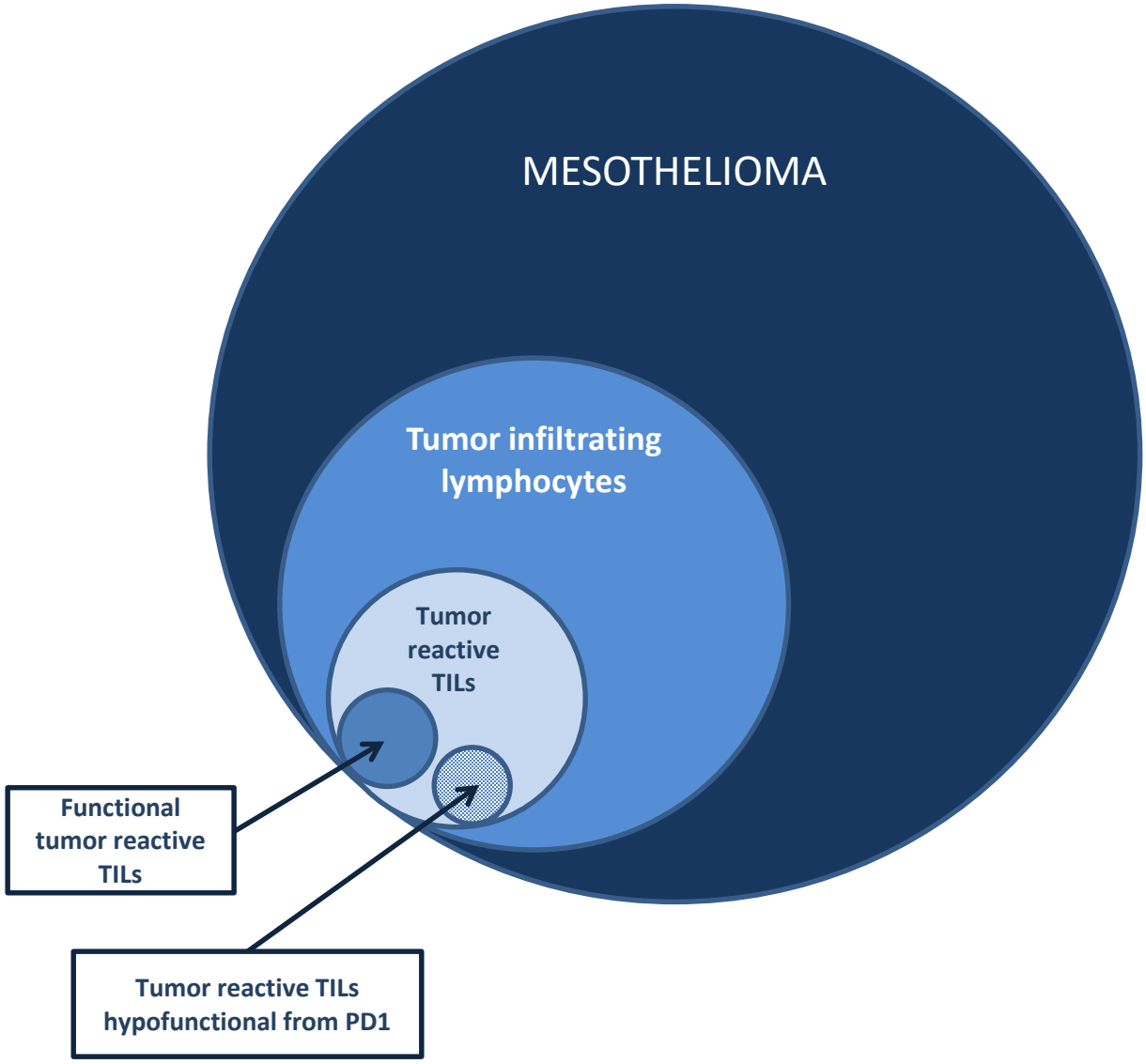
Non-controlled

Sugarbaker, et al., JTCVS, 1999

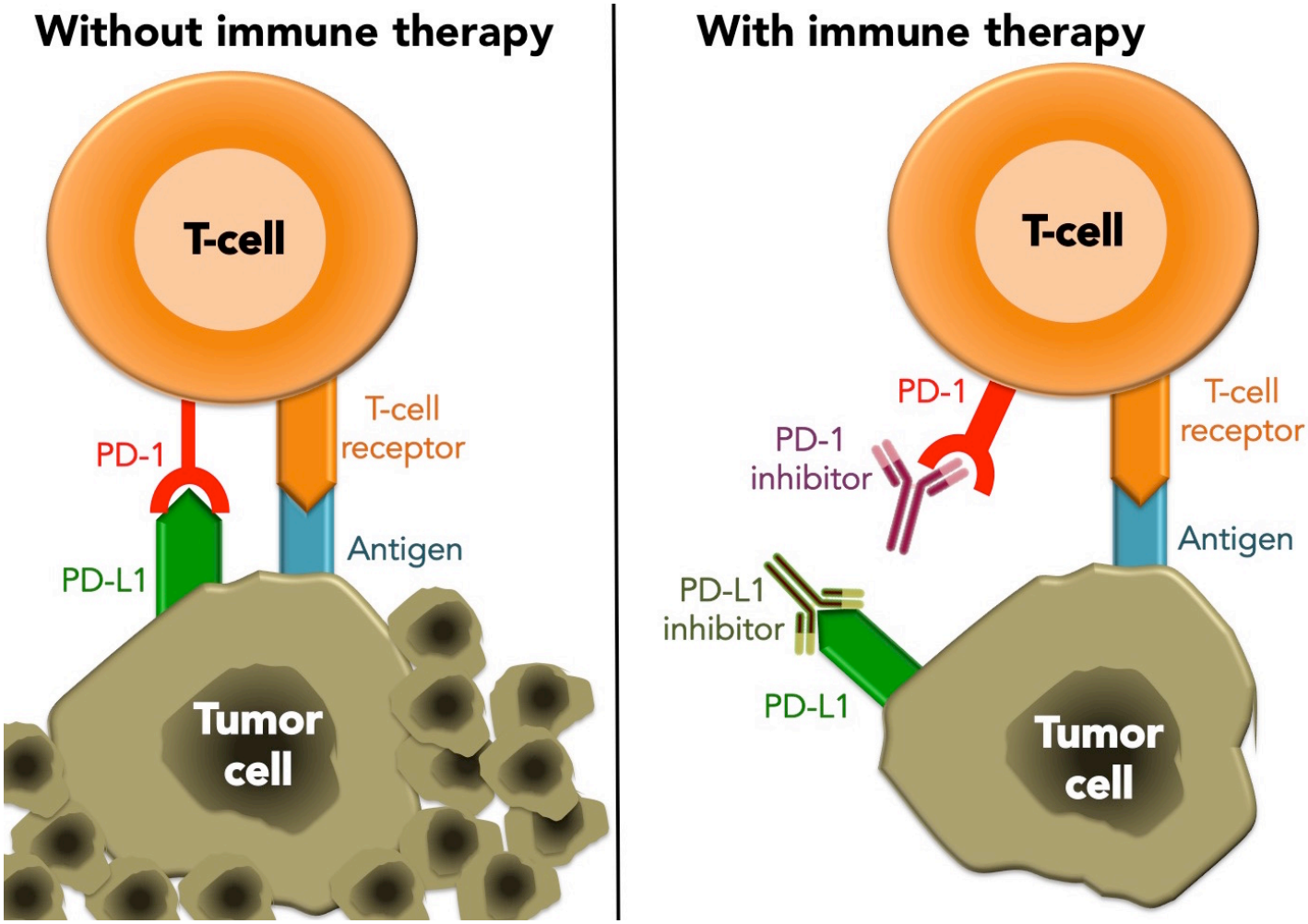
The Cancer Immunity Cycle



Scientific Rationale

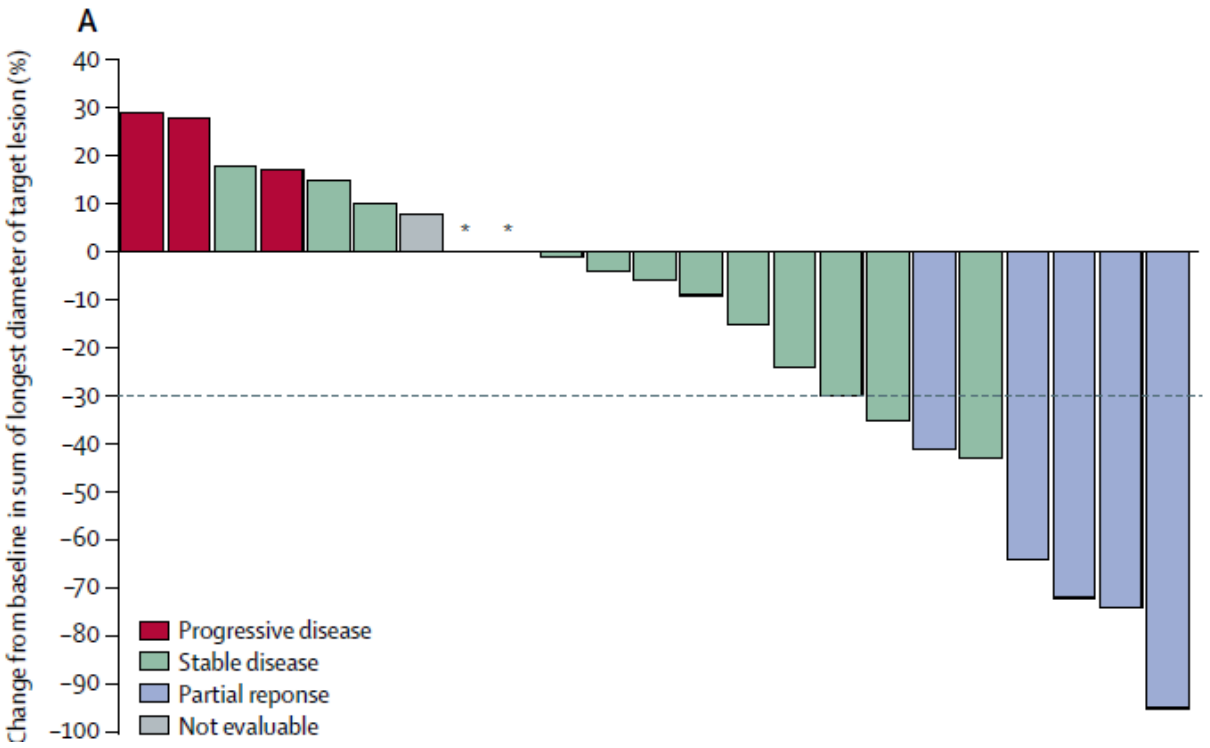


Blockade of T cell Checkpoints



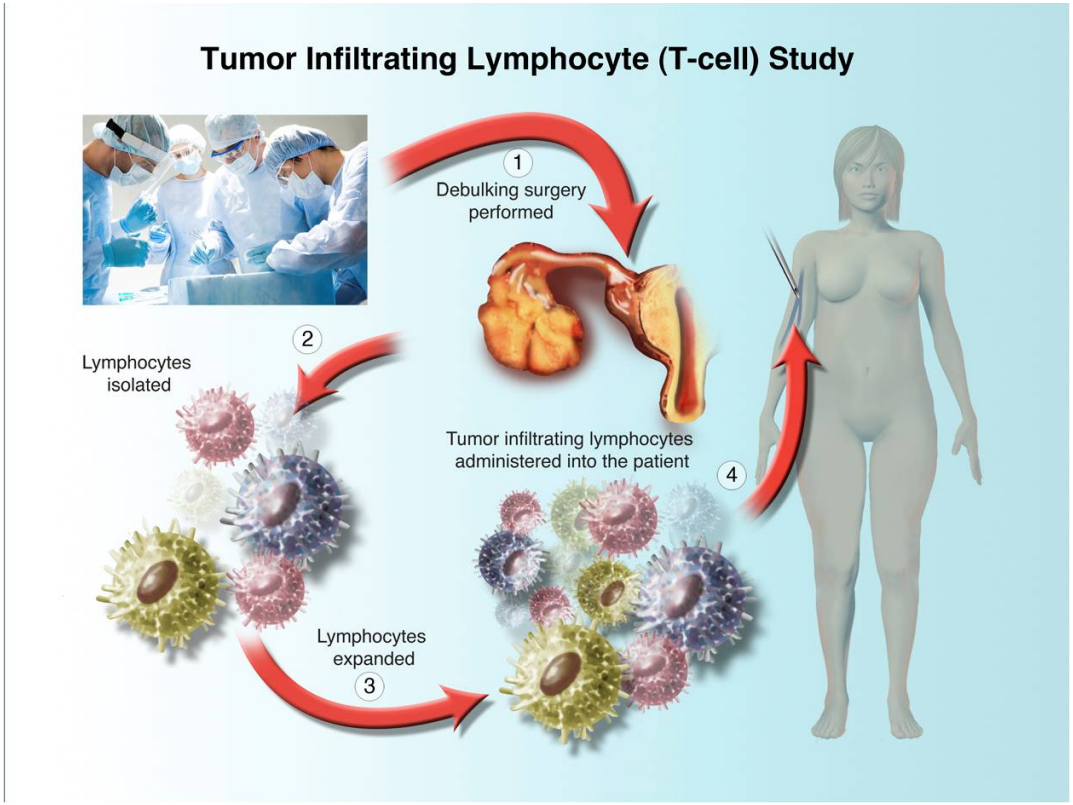
Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial

Evan W Alley, Juanita Lopez, Armando Santoro, Anne Morosky, Sanatan Saraf, Bilal Piperdi, Emilie van Brummelen



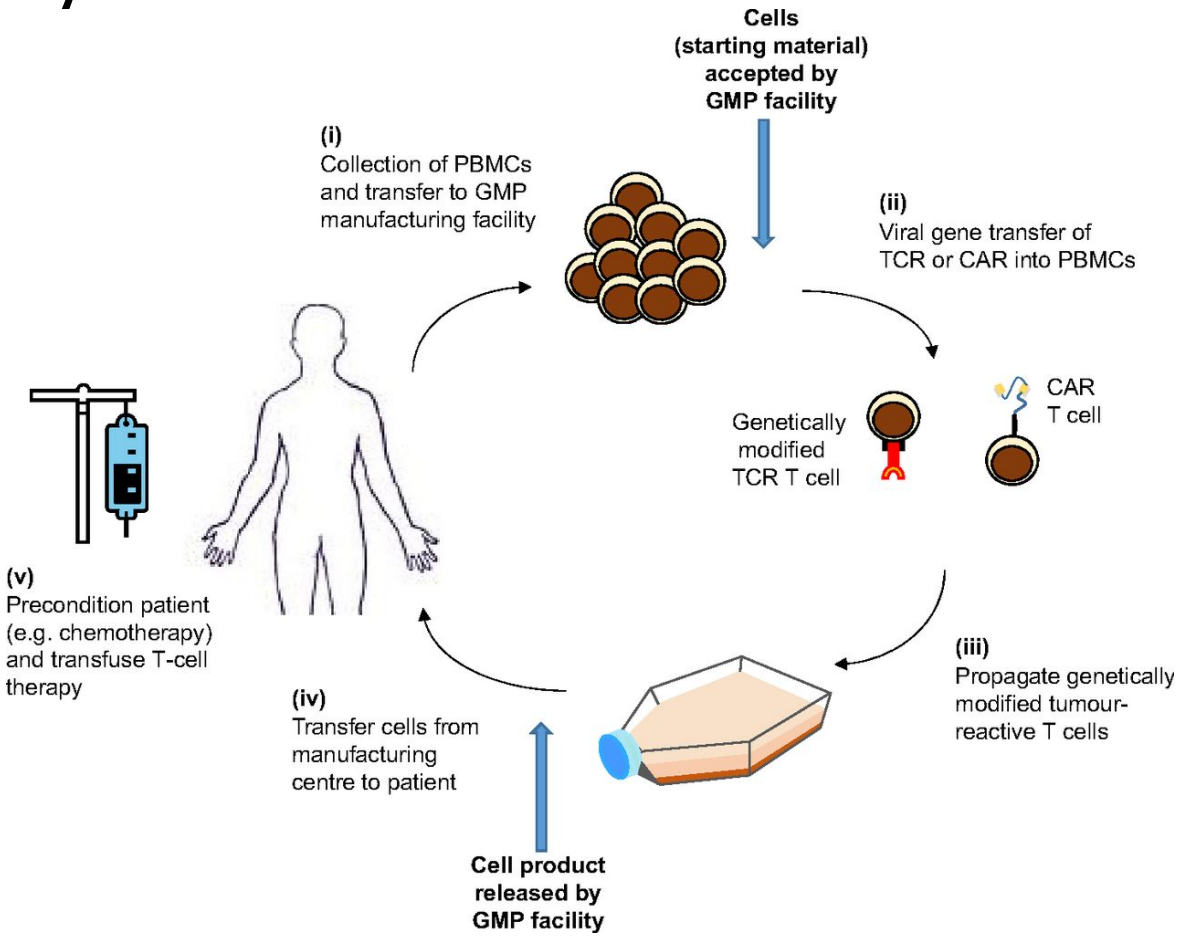
Methods to Increase T-cells

- Isolate tumor infiltrating lymphocytes (TILs) and grow to them to large numbers outside the patient before injecting them back in
- Has worked for certain tumors (e.g. melanoma, renal cancer)
- Difficult strategy for many tumors
  - Low numbers of TILs
  - Even lower numbers of TILs that bear reactivity to the tumor (i.e. many "bystander" TILs
  - Methods to break apart tough tumors to release the T cells can be harsh on them

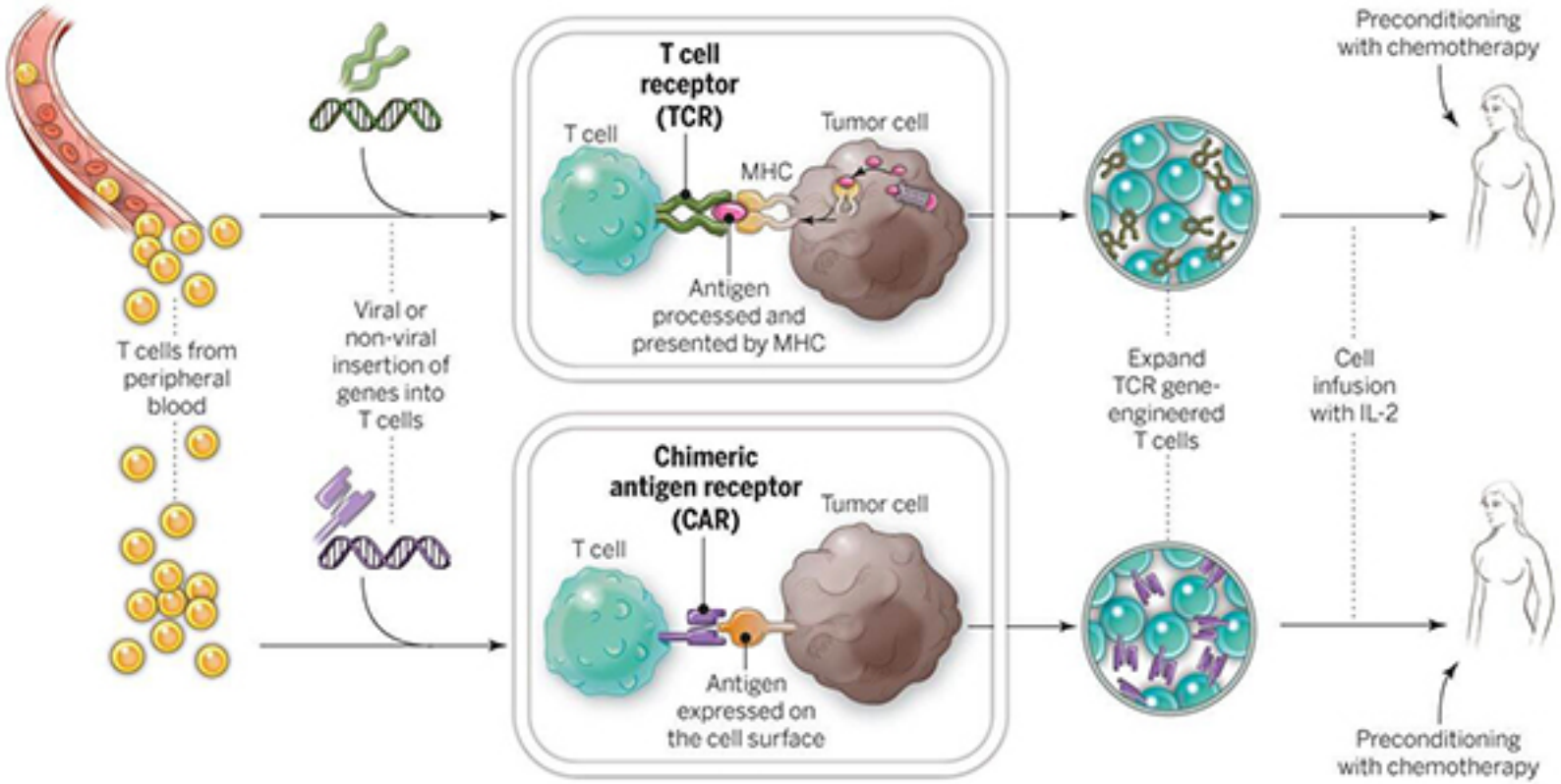


Methods to Increase T-cells

- Engineering T cells isolated from the bloodstream can overcome many of these hurdles
  - No need to expose T cells to harsh digestion methods to isolate them
  - Non-reactive T cells can be made reactive by engineering them to express receptors that recognize proteins (aka “antigens”) expressed on the tumor surface
  - Has achieved remarkable cures in lymphoma and leukemia



CARs

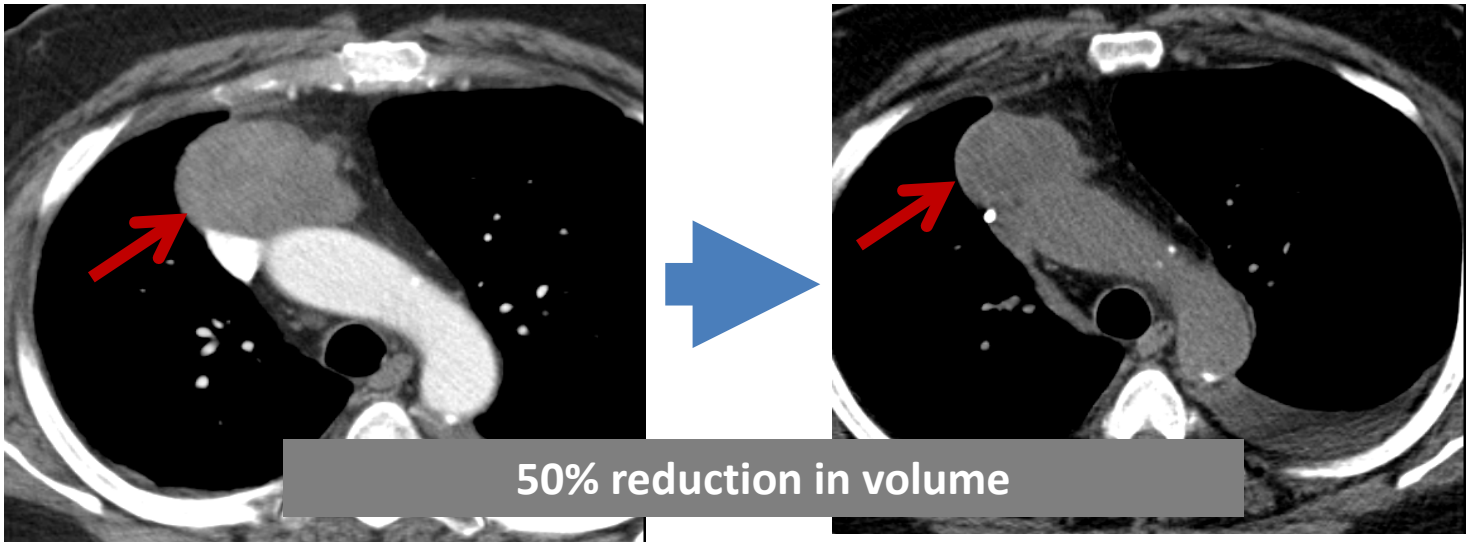

T cells from peripheral blood
Viral or non-viral insertion of genes into T cells
T cell receptor (TCR)
T cell
Tumor cell
MHC
Antigen processed and presented by MHC
Chimeric antigen receptor (CAR)
T cell
Tumor cell
Antigen expressed on the cell surface
Expand TCR gene-engineered T cells
Cell infusion with IL-2
Preconditioning with chemotherapy
Preconditioning with chemotherapy

Mesothelin-specific Chimeric Antigen Receptor mRNA-Engineered T cells Induce Anti-Tumor Activity in Solid Malignancies

Gregory L. Beatty[1,3,*,†], Andrew R. Haas[1,2,†], Marcela V. Maus[1,3], Drew A. Torigian[1,5], Michael C. Soulen[1,5], Gabriela Plesa[1], Anne Chew[1], Yangbing Zhao[1,4], Bruce L. Levine[1,4,6], Steven M. Albelda[1,2], Michael Kalos[1,4,†], and Carl H. June[1,4,6,*,†]

Pre-Rx

3 months post- Rx



No major toxicities

CAR T cells detected transiently in the blood (mRNA)

One patient with a dramatic response

UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center


DANGER
ASBESTOS HAZARD