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GRAND ROUNDS CLINICI
con il Policlinico San Matteo

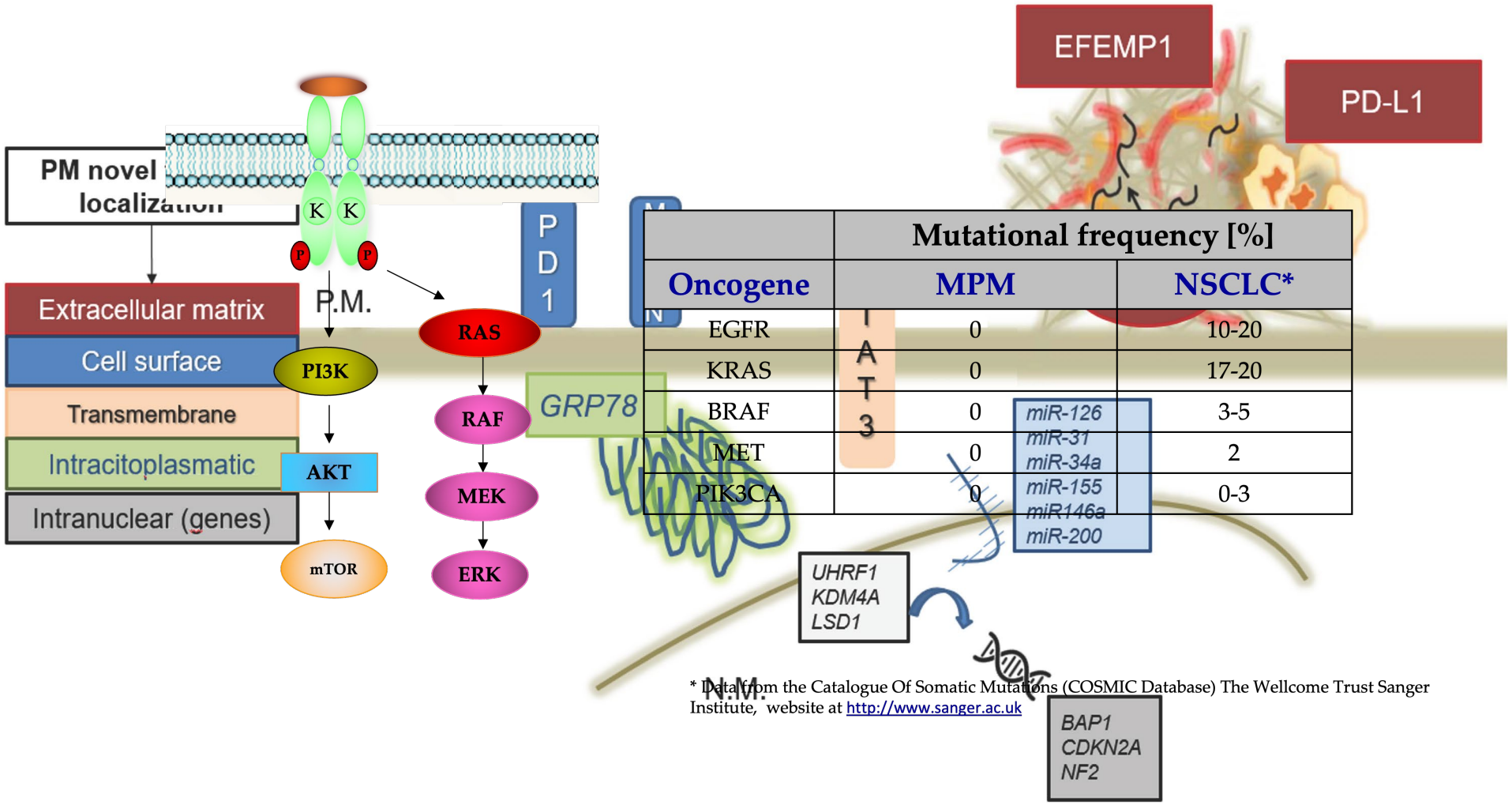
Aula Magna "C. Golgi" & WEBINAR

27 maggio

Angelo G. Corsico & Giulia M. Stella

Mesotelioma pleurico: eterogeneità clinica e suscettibilità genetica in *real-life*

Pleural mesothelioma: ***clinical*** **HETEROGENEITY and** ***genetic*** **SUSCEPTIBILITY, associated to specific immune-inflammatory reaction to asbestos,**
in ABSENCE of SOMATIC GENETIC DRIVERS



Oncogene	Mutational frequency [%] MPM	NSCLC*
EGFR	0	10-20
KRAS	0	17-20
BRAF	0	3-5
MET	0	2
PIK3CA	0	0-3

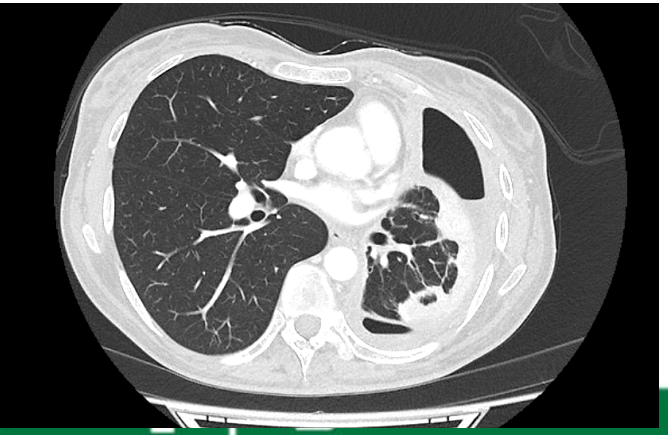
* Data from the Catalogue Of Somatic Mutations (COSMIC Database) The Wellcome Trust Sanger Institute, website at http://www.sanger.ac.uk

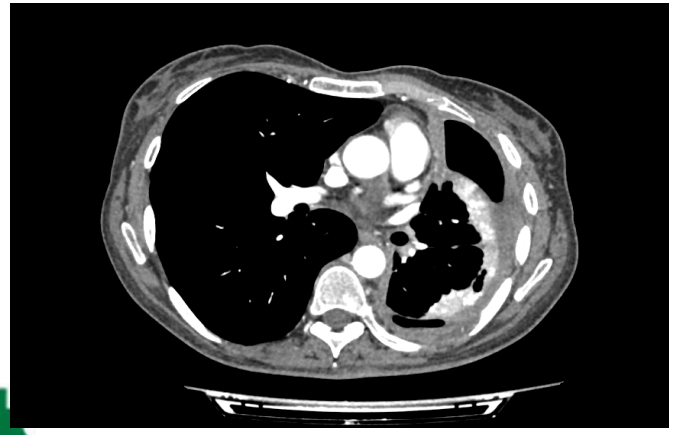
P.M.= plasma membrane
N.M.= nuclear membrane

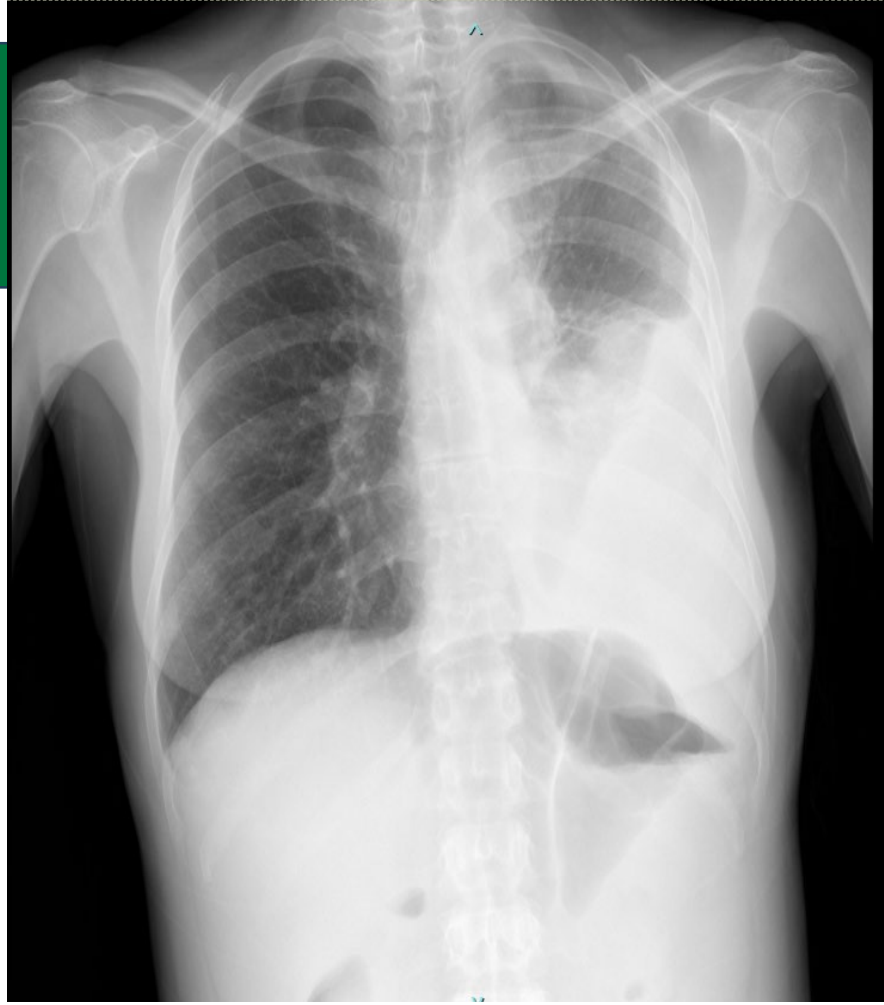
Bertuccio FR et al, 2025

Clinical case 1

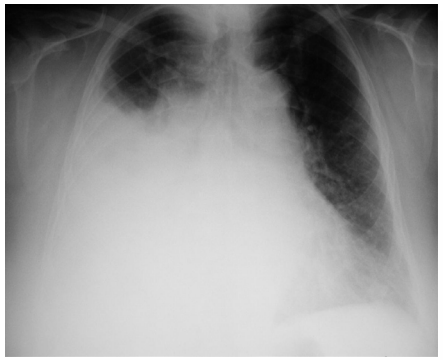
Age (yrs)	49
Gender	F
Smoking habit	No
Comorbidities	Previous local tumor of the larynx
Environemtal exposure	Partial
Work exposure	No
Other	Father deceased for PM

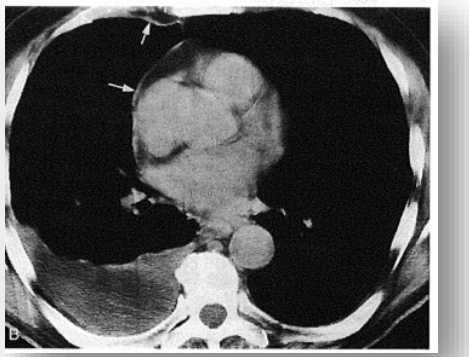






All that glisters is not…mesothelioma



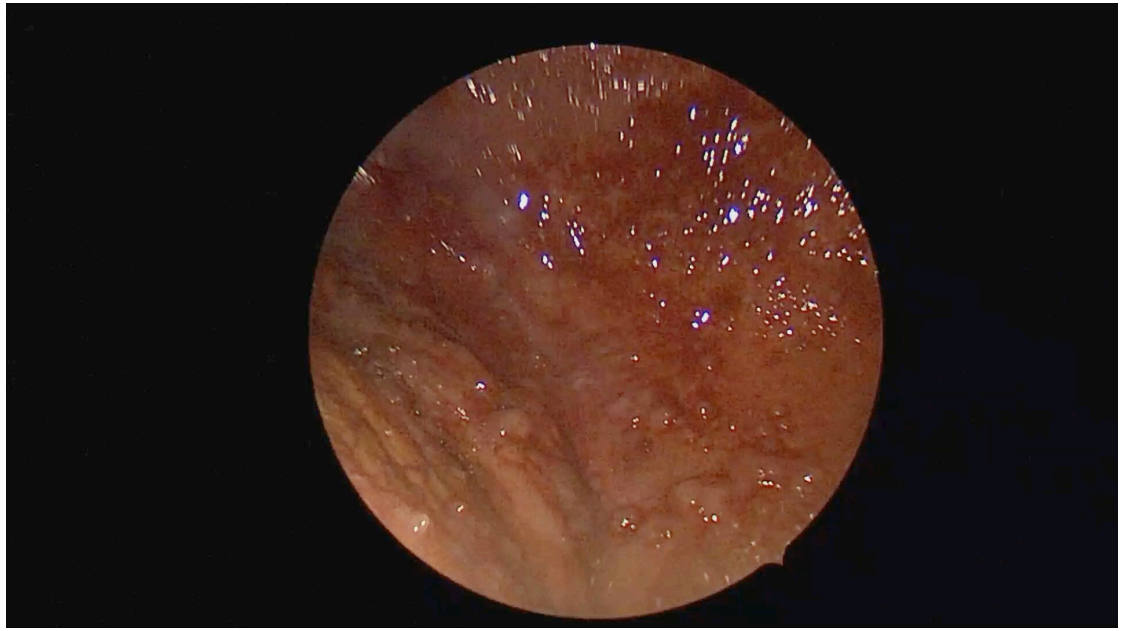


- *Is the pleural disease benign?*
- *If not, is the malignant disease primary or secondary to other distant masses?*

- The diversity of histological features in PM, combined with the pleura being a common site for metastatic disease and reactive changes showing significant atypia, makes diagnosis on ***MORPHOLOGY ALONE PROBLEMATIC*** and use of ICH is recommended

- PM histopathological diagnosis is ***STEPWISE*** , based on morphological and ICH assessment, sometimes associated with molecular tests, and supported by clinical and radiological findings.

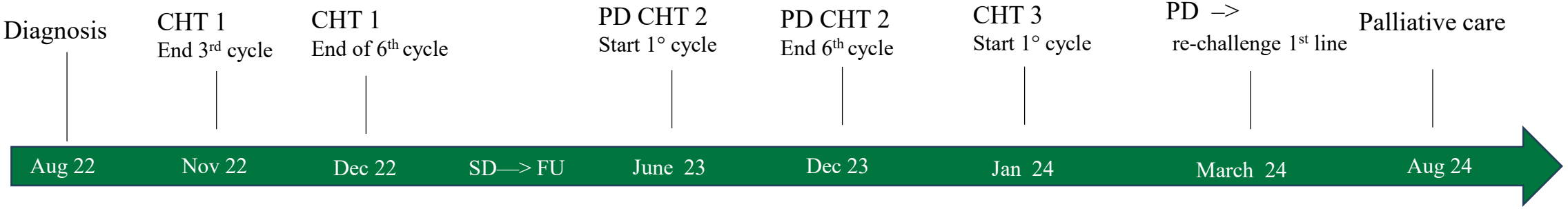
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
ANNALS OF ONCOLOGY driving innovation in oncology
SPECIAL ARTICLE
Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

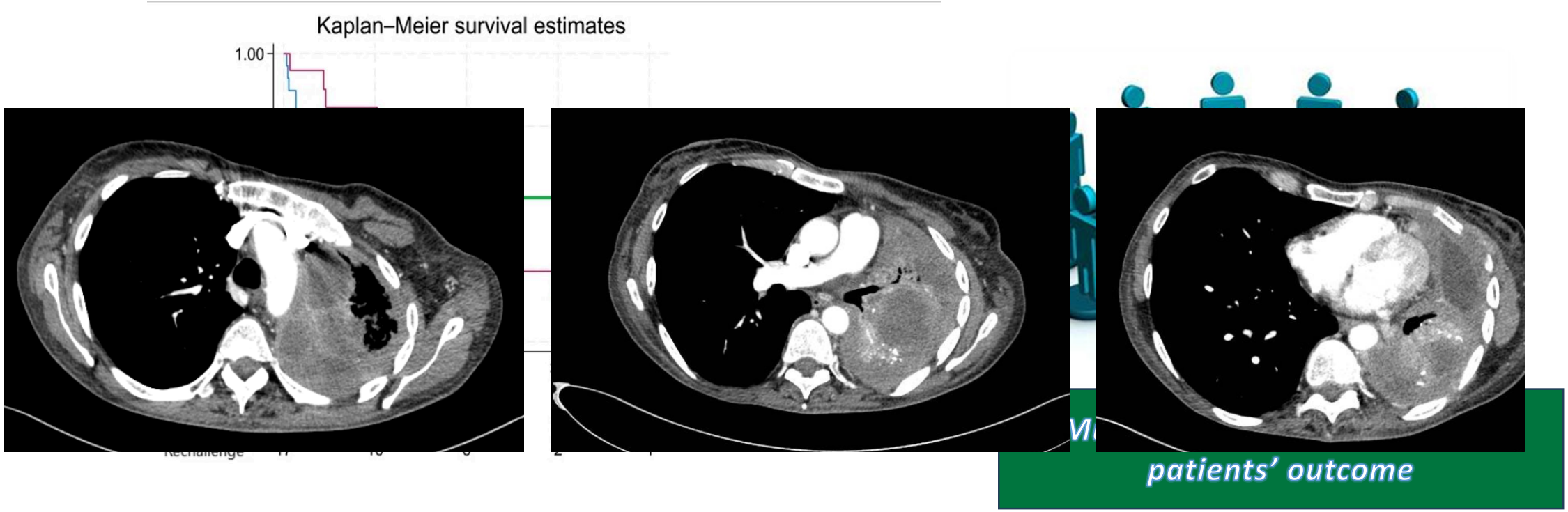


Epithelioid PM

- Previous cancer in early age in absence of risk conditions
- Familial cluster
- Absence of work exposure

Is there a role for genetic susceptibility?

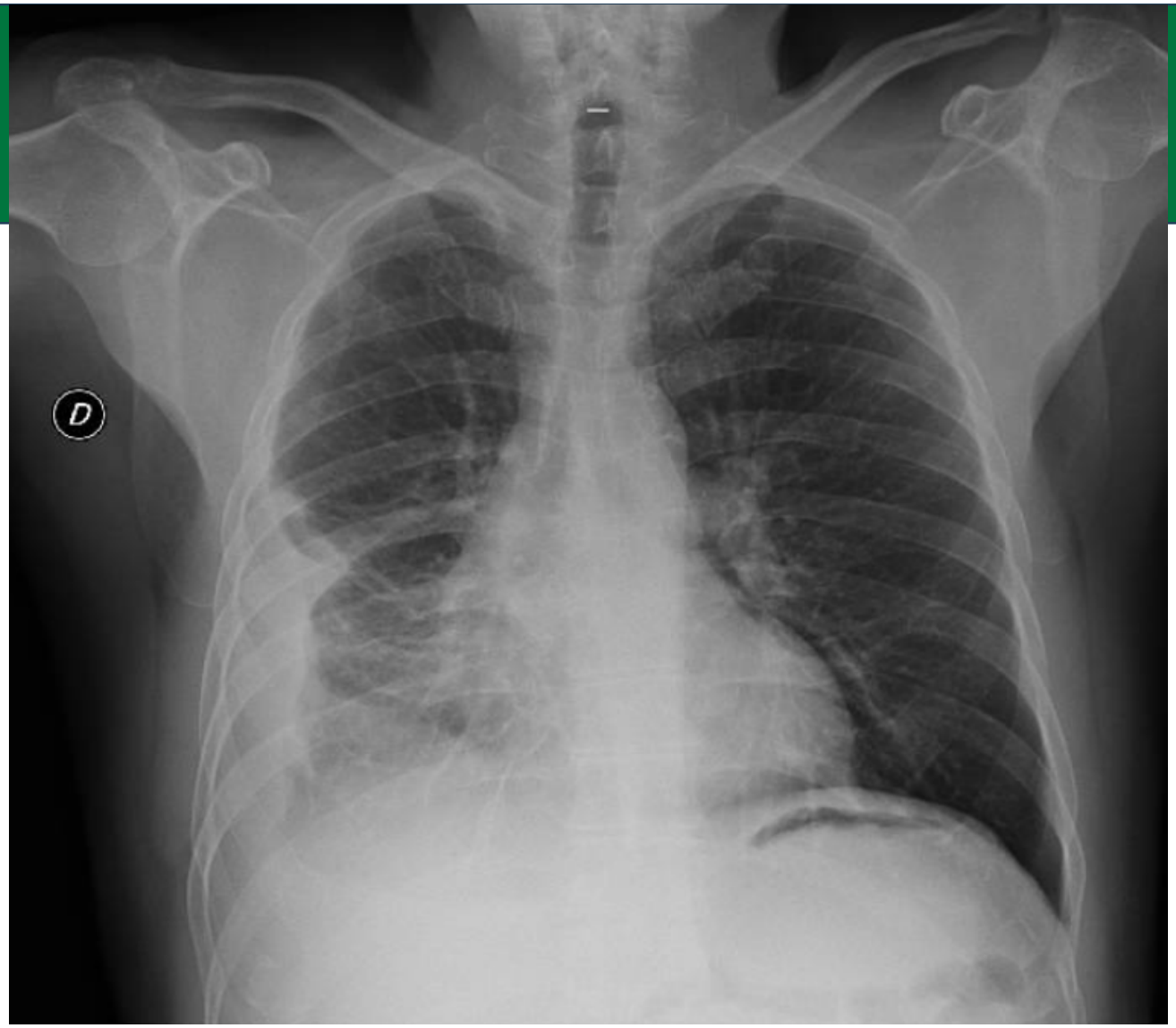


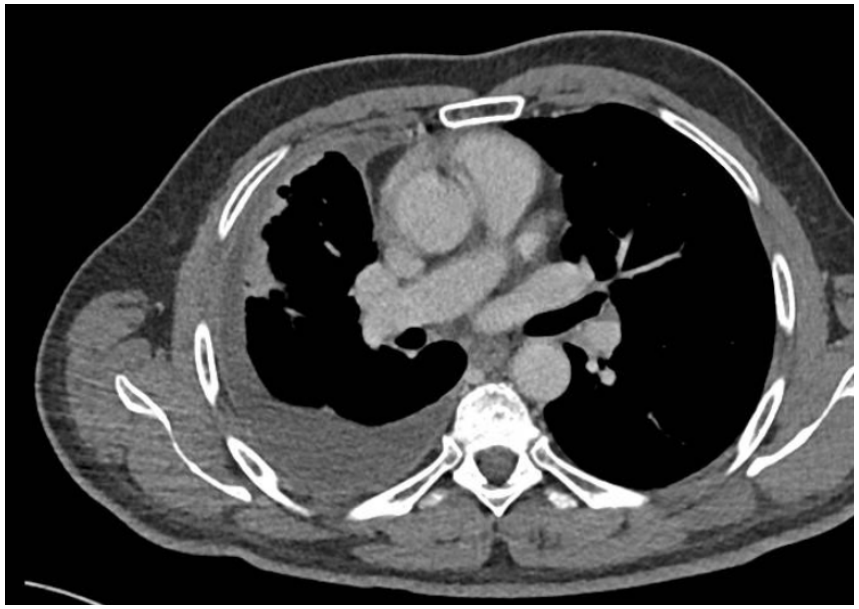


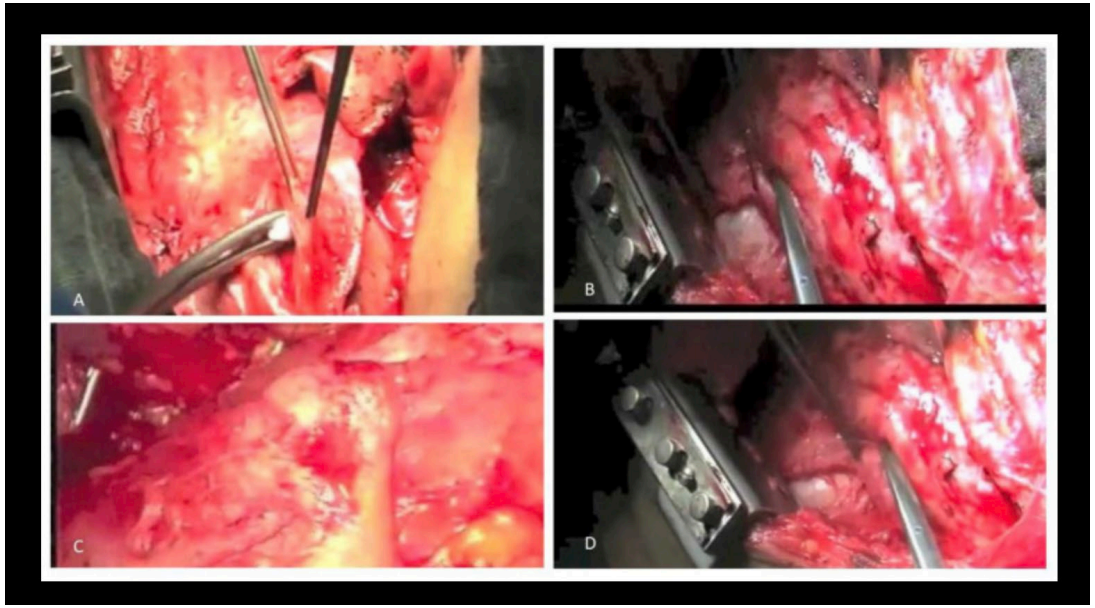
Kaplan-Meier curves related to survival after initiation of rechallenge or palliative care pathway with median survival. Ferrari G *et al*. Under review

Clinical case2

Age (yrs)	62
Gender	M
Smoking habit	Past
Comorbidities	None
Environemtal exposure	None
Work exposure	Partial



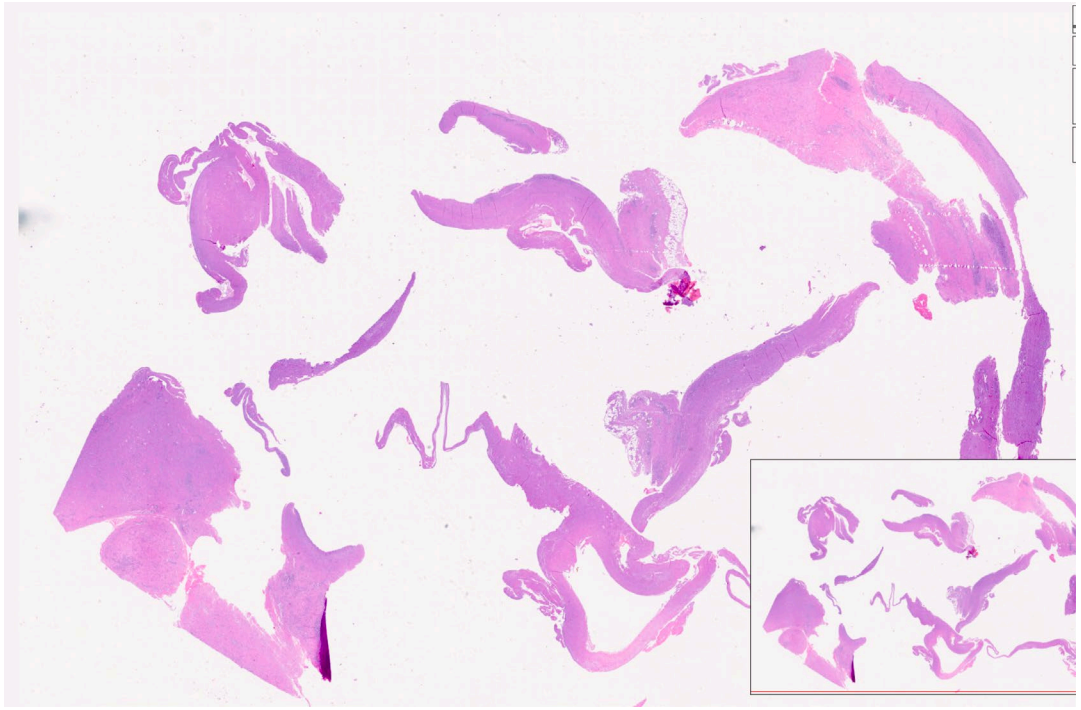


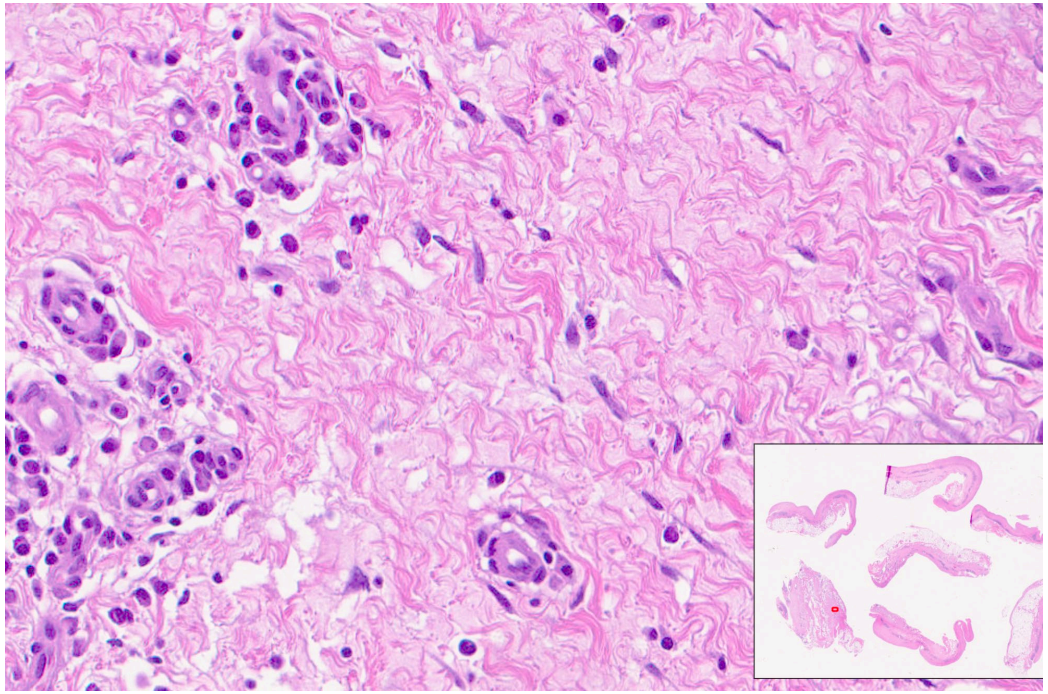


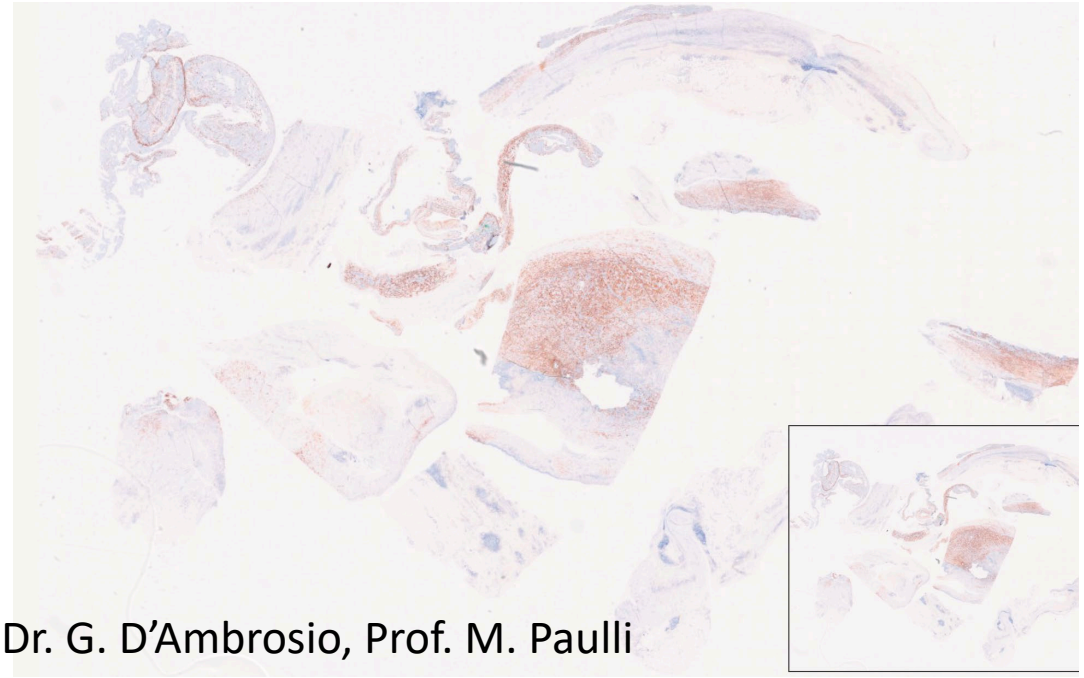
Lembi di tessuto pleurico con discreto ispessimento fibroso, iperplasia microvascolare (con sparsi granulociti perivascolari) e diffusa flogosi cronica 'a banda' costituita da linfociti B (CD20+) e T (CD3+); i lembi sono completamente disepitelizzati con depositi di detrito fibrino-ematico. In alcuni lembi le immunoreazioni con CKcam e Calretinina hanno evidenziato elementi mesoteliali fusati disposti nel tessuto fibroso superficiale, con atipie indeterminate ed apparente conservazione dell'espressione nucleare di BAP1.

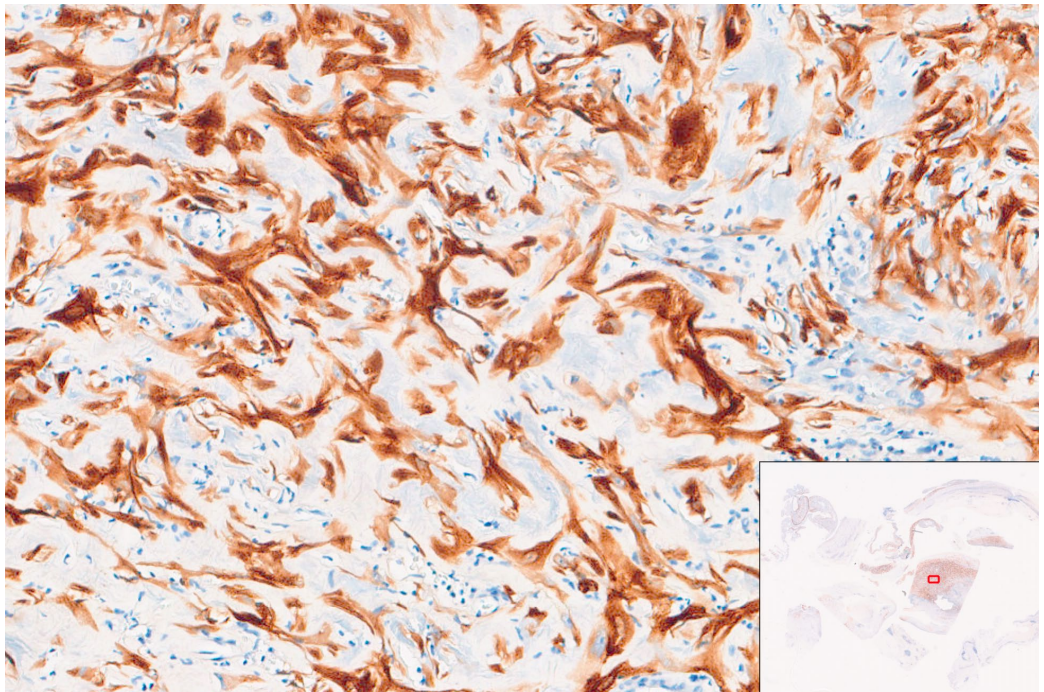
DIAGNOSIS NOT SOLVED
FIBROUS PLEURITIS vs SARCOMATOID PM

CDKN2A copy number





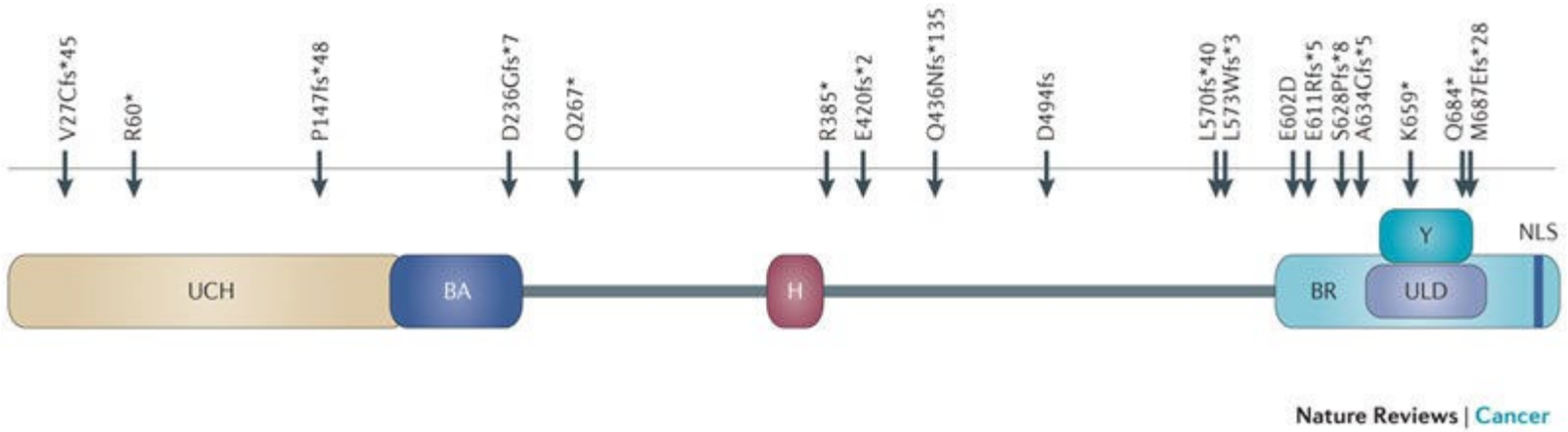




Courtesy Dr. G. D’Ambrosio, Prof. M. Paulli

The *BAP1* gene & PM

Carbone M et al, 2013

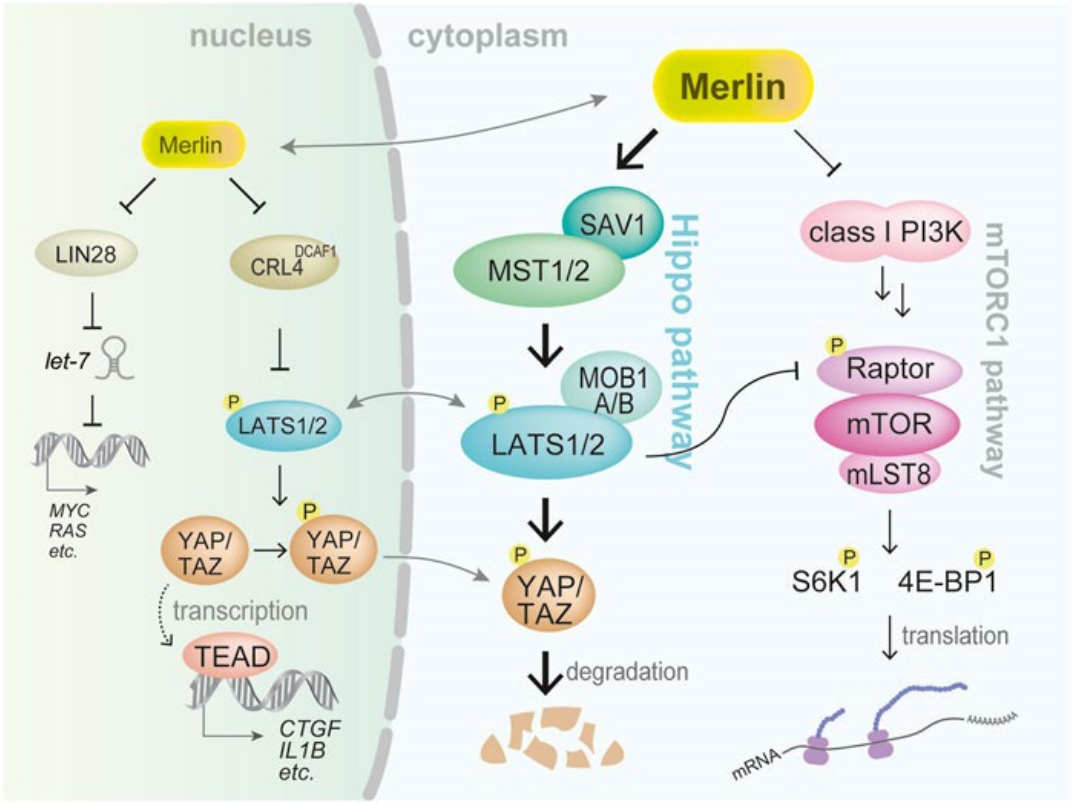


- ✓ *BAP1* gene encodes for a deubiquitylase that is found associated with multiprotein complexes that regulate key cellular pathways, including the cell cycle, cellular differentiation, cell death, gluconeogenesis and the DNA damage response
- ✓ *BAP1* is a tumor suppressor gene whose mutations predispose to PM onset
- ✓ Low doses of asbestos are sufficient to trigger PM in the presence of genetic predisposition
- ✓ Germline *BAP1* mutations are rare events : 1-5% of unselected cases, 18-20 after careful
- ✓ **Loss of BAP1 protein expression is documented in > 50% of cases**
- ✓ **Somatic *BAP1* changes are frequently reported, followed by mutations in *NF2* (encoding for merlin) and *CDKN2A* (encoding for $p16^{INK4A}$ and $p14^{ARF}$)**

PM + uveal melanoma (+ basal cell carcinoma+ clear cell carcinoma**)**
= BAP1-related cancer syndrome

PM within the BAP1-related cancer sd: better prognosis *(Baumann F et al, 2015)*

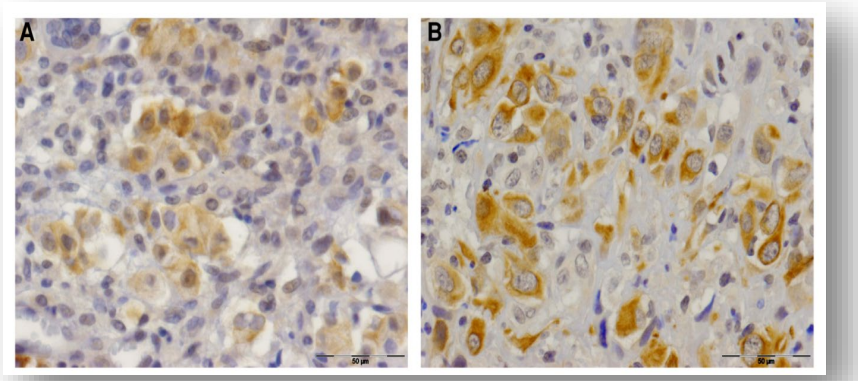
Merlin (encoded by *NF2 gene)*



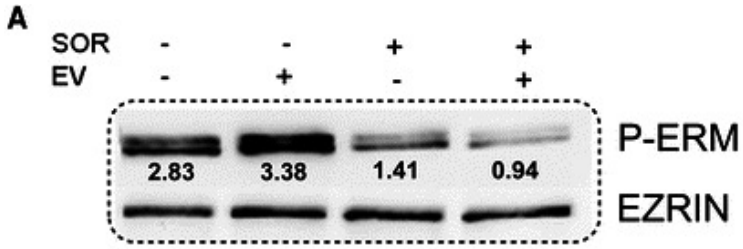
Sato T, Sekido Y 2023

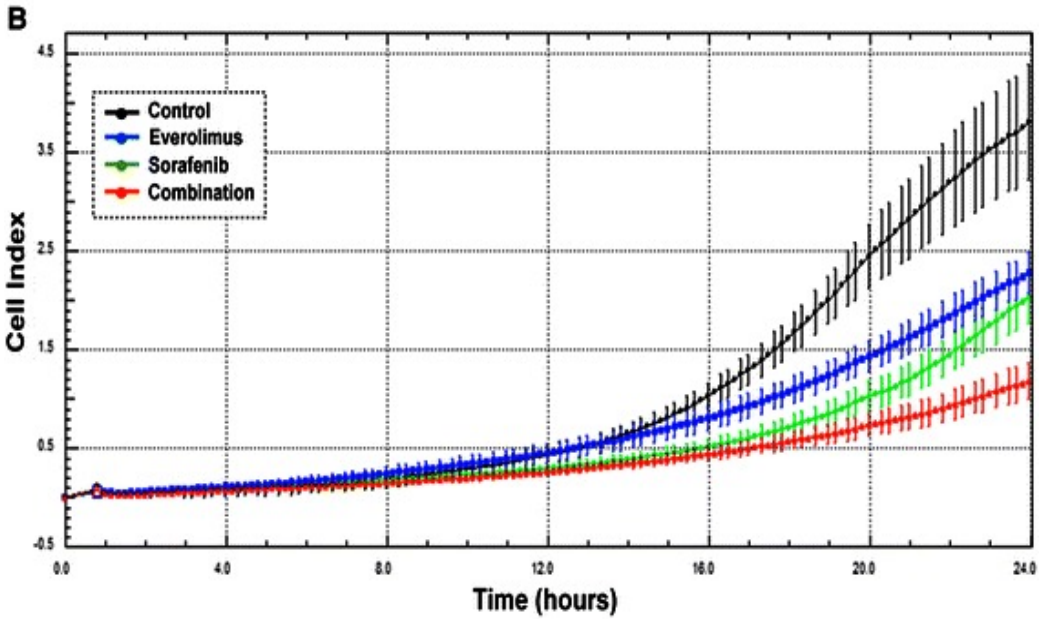
- Important tumor suppressor, mutated in ~ 50% of PM
- Its loss results in upregulation of 3 targets: mTOR, FAK, Hippo signaling pathways
- It promotes Hippo signaling without stimulating the kinase activity of Hpo/Mst
- mTORC1 is a mediator of merlin's tumor suppressor activity

mTOR protein is an actionable PM target



Pignochino Y et al, 2015



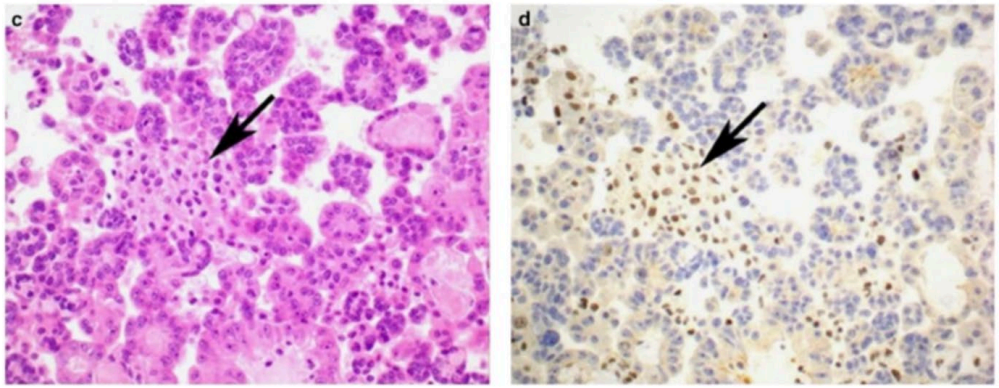


Antiproliferative synergistic effect of sorafenib and everolimus against PM *in vitro* based **on NF2/Merlin-related protein ERM**

Pignochino Y et al, 2015

EPITHELIOD PM *vs* MESOTHELIAL HYPERPLASIA

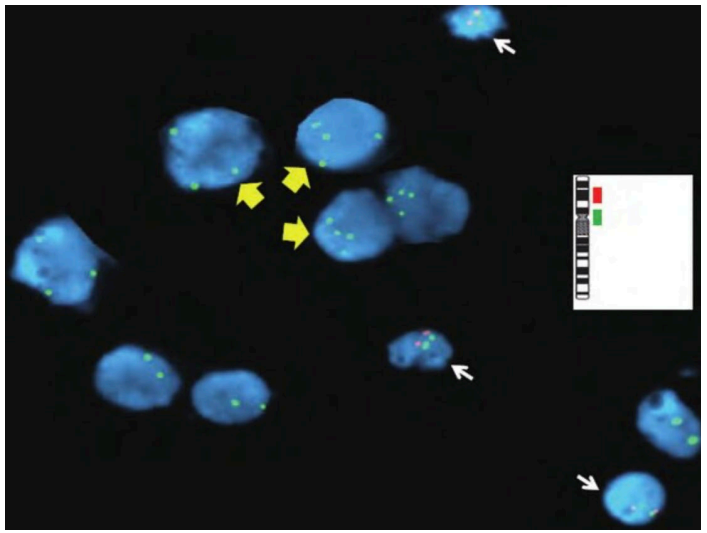
LOSS BAP1	IHC



Andrici J et al. 2015

SARCOMATOID PM *vs* REACTIVE FIBROUS PLURITIS

LOSS CDKN2A (9p21.3)	FISH/molecular analysis	LOSS MTAP (9p21.3)	IHC

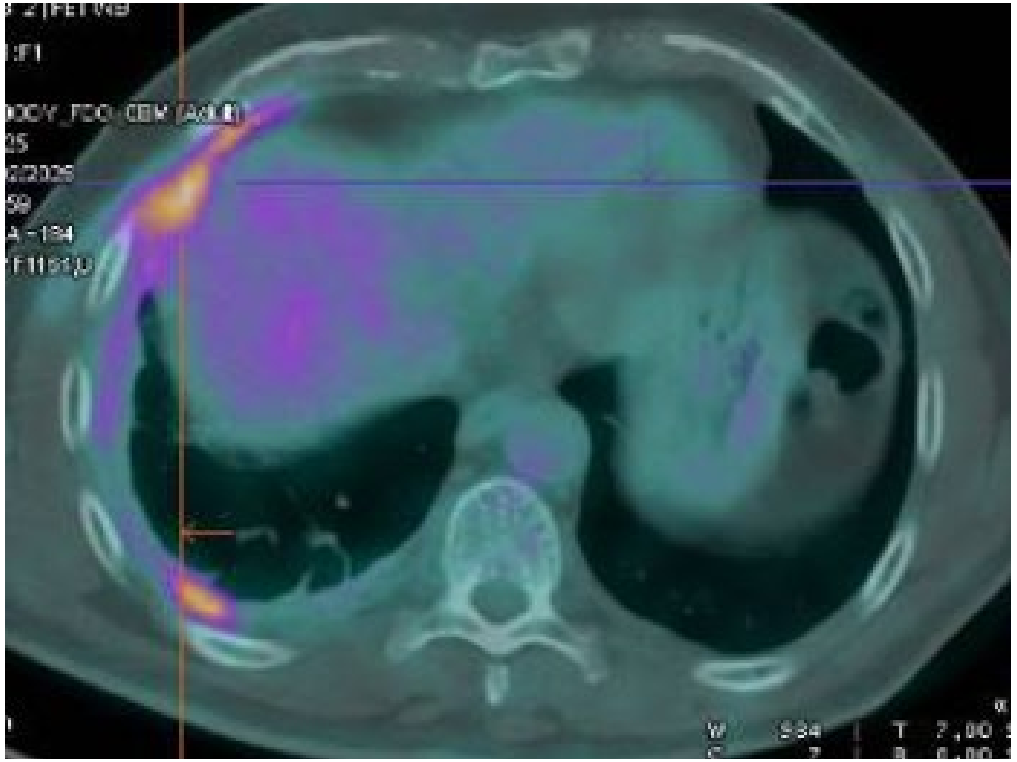


From diagnosis to personalized therapeutic approach

Gene	Primary Function	Alteration Frequency	Mechanism of Action	Therapeutic Implications
BAP1	DNA repair, transcription regulation, and cell cycle control	1–7% (germline), 20–64% (somatic)	Point mutations, copy number loss, rearrangements	Increased sensitivity to platinum-based therapy, potential target for PARP inhibitors (PARPi) and EZH2 inhibitors, possible response to immune checkpoint inhibitors (ICPi)
CDKN2A	Cell cycle regulation (encodes p16INK4A and p14ARF)	61–88%	Homozygous/hemizygous deletion (most common), promoter hypermethylation	CDK4/6 inhibitors (e.g., Abemaciclib), potential synergy with immune checkpoint blockade
NF2	Hippo signaling pathway regulation (encodes Merlin)	30–40%	Nonsense/missense mutations, deletions, rearrangements	Targeting YAP/TAZ within the Hippo pathway, TEAD inhibitors under clinical investigation

Bertuccio FR et al, 2025

Clinical case 2



MORPHOLOGY INCONCLUSIVE

LOSS BAP1?	NO
Altered *CDKN2A* copy number ?	NO

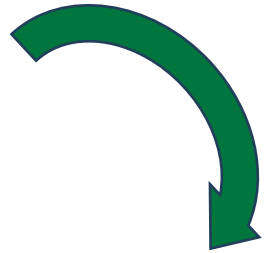
REACTIVE FIBROUS PLURITIS

FU due to 10-40% risk of malignant transformation

UNMET *CLINICAL* NEEDS

To uncover potential genetic predispositions that contribute to PM susceptibility
→ genetic signature of **RISK for PM**

To distinguish individuals at higher risk despite similar environmental exposures
→ genetic signature of **PROTECTION from PM**



Genetic susceptibility in MAlignant pleural mesothelioma: clinical implication of GermliNE variaTionS. The MAGNETS project.

R.C.

5x1000

Inizio progetto: 01/01/2023
Fine progetto: 30/12/2024

Fondazione IRCCS Policlinico San Matteo

Sistema Socio Sanitario
Regione Lombardia

Istituti Clinici Scientifici Maugeri

MEDICINA del LAVORO

MAGNETS STUDY DESIGN: CASE (PM patients)-CONTROL (ASBESTOS EXPOSED WORKERS WITHOUT PM)

Study start

Blood samples from MPM patients

Central database

Blood samples from biobank

Sequencing analysis

Germilne changes in genes involved in inflammatory infiltration, drug response, cancer predisposition

Result interpretation

Data validation and integration

- Identification of of germline signaures with prognostic and predictive value
- Start of *in vitro* assays

Hypothesis validation

1. Identification of novel host actionable pathwyas
2. Definition of effective screening programs for asbestos exposed subjects

NCT06886672 Recruiting New

Genetic Susceptibility in MAlignant Pleural **Mesothelioma**: Clinical Implication of GermliNE VariaTionS

Conditions

Mesothelioma, Malignant Pleural

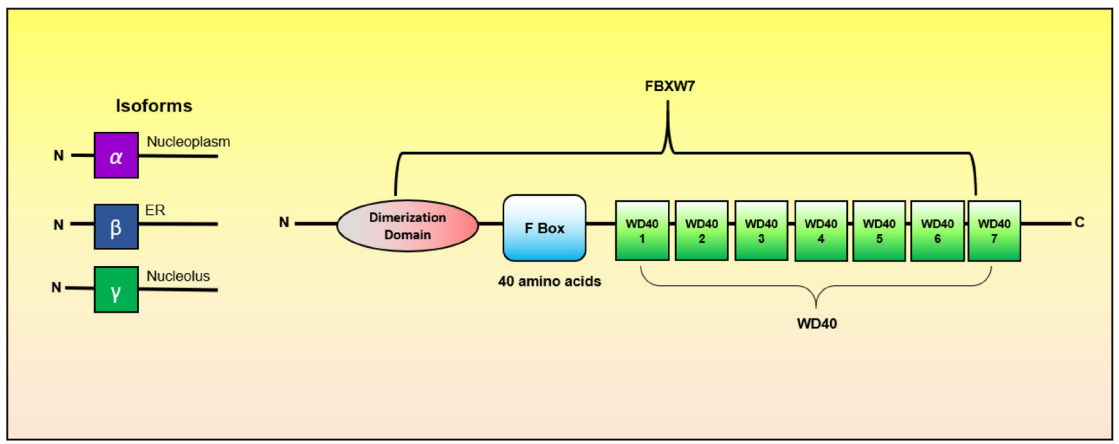
Locations

Pavia, Italy (2)

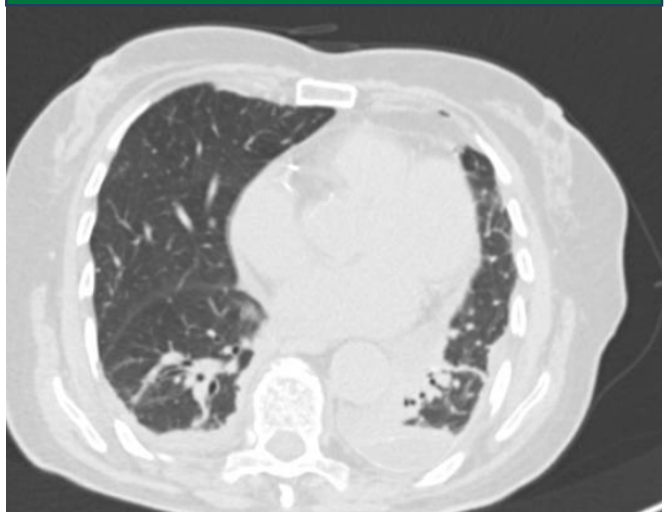
	PM	Exposed workers
Cases (n)	**21**	**31**
Gene	%	%
FBXW7 *Deletion*	75 62.5	50 41
ATM	56	41
BRACA2	19	41
PBRM1	12	34
FAT1	12.5	25

Clinical case 3

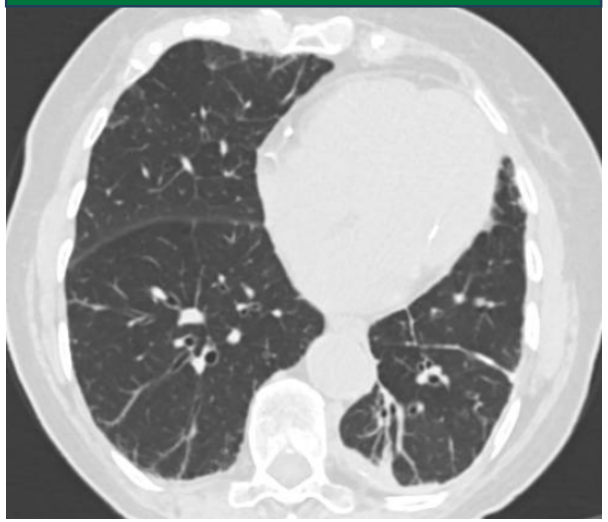
- **FBXW7:**c.585-5del; chr4-153268227 C>C; NM_001349798.2
- **FBXW7:**c.585-5dup; chr4-153268227 C>CA; NM_001349798.2



Diagnosis : Epithelioid PM



Stable response to ICI



Sailo BL et al, 2019

frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 14 March 2023
DOI 10.3389/fonc.2023.1147239

Check for updates

OPEN ACCESS

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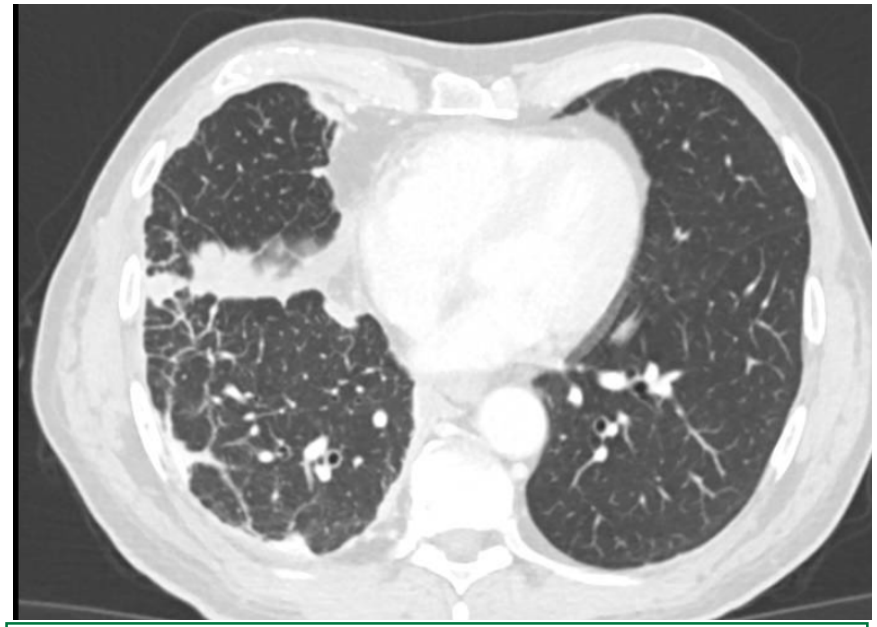
REVIEWED BY
Zhi-Wei Wang,

FBXW7 attenuates tumor drug resistance and enhances the efficacy of immunotherapy

Shimin Chen[1,2,3†], Jichun Lin[1,2,3†], Jiaojiao Zhao[1,2,3†], Qian Lin[1], Jia Liu[4], Qiang Wang[5], Ryan Mui[6] and Leina Ma[1,2*]

Clinical case 4

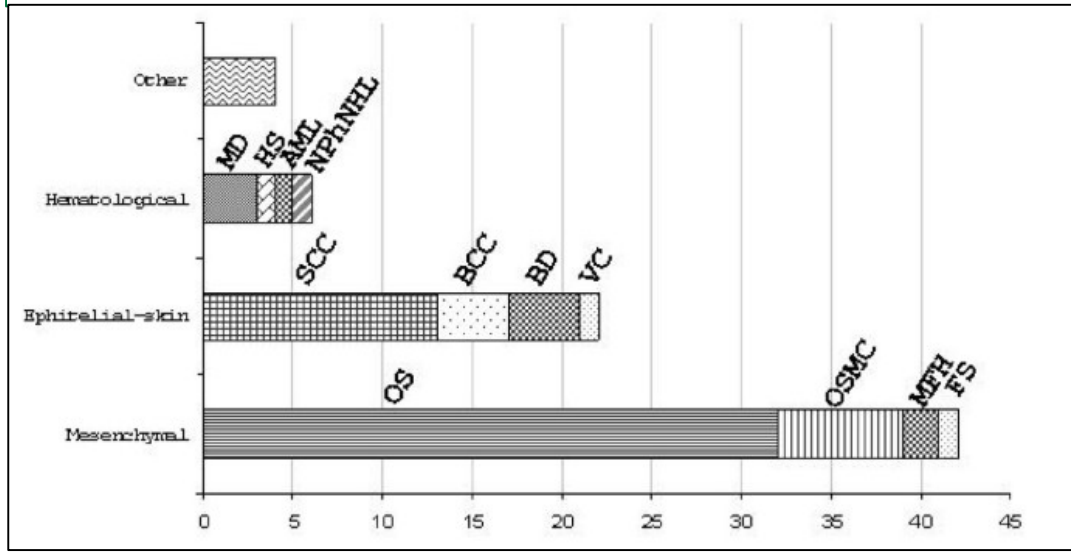
BAP1: c.1034G>C; chr3-52439208 C>G p.Gly345Ala NM_004656.4
FBXW7:c.585-5del; chr4-153268227 C>C; NM_001349798.2
RECQL4: c.2987T>C; chr8-145737843 A>G p.Met996Thr NM_004260.4



Epitheliod PM and Prostate Cancer

BAP1 related cancer sd?

Rothmund-Thomson syndrome (RTS) is a genodermatosis presenting with a characteristic facial rash (poikiloderma) associated with short stature, sparse scalp hair, sparse or absent eyelashes and/or eyebrows, juvenile cataracts, skeletal abnormalities, radial ray defects, premature aging and a predisposition to cancer.
It is transmitted in an autosomal recessive manner and is genetically heterogeneous

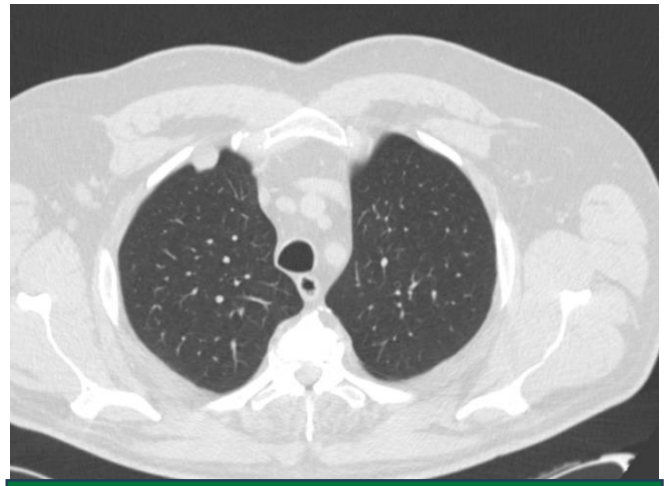


Martin-Giacalone BA et al, 2022.

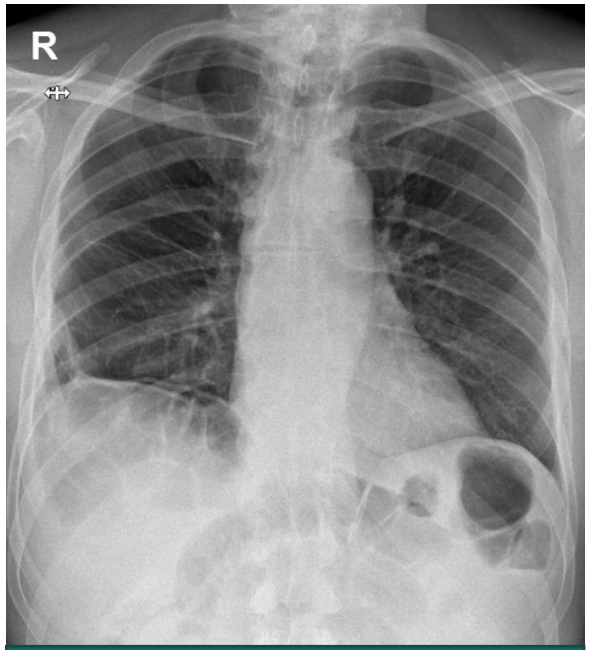
Clinical case 5

- **FBXW7**:c.585-5del; chr4-153268227 C>C; NM_001349798.2;
- **ATM**:c.4437-14dup; chr11-108163323 G>GT; NM_000051.4;
- **WT1**:c.337T>C; chr11-32456570 A>G; p.Phe113Leu; NM_024426.6;

WT-1 expression is associated with survival in PM patients

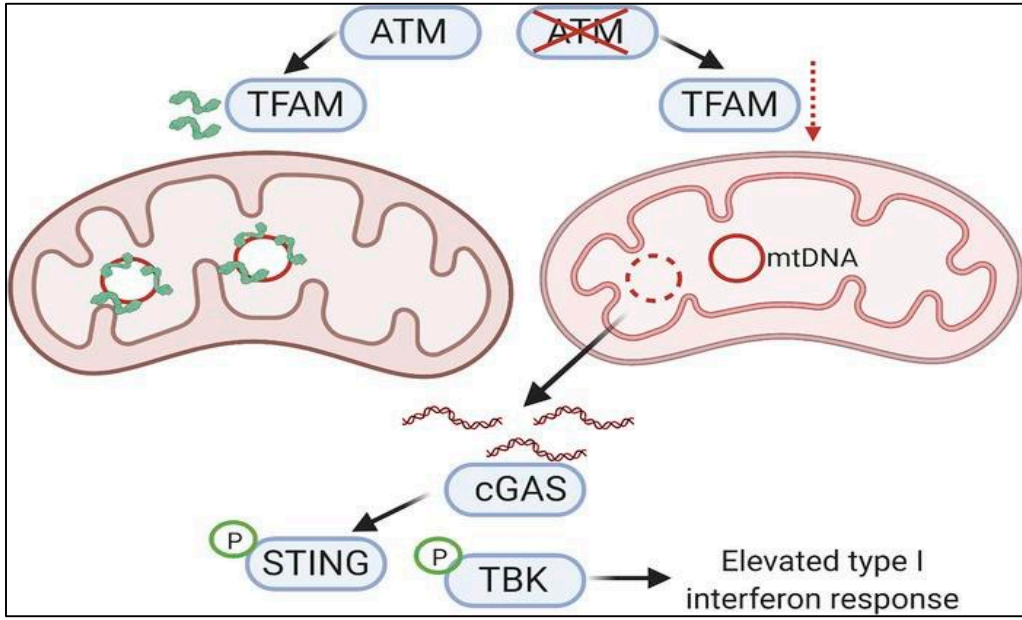


Diagnosis :early stage biphasic PM in previous myastenia



Stable response after surgery and ICI, onset of motor neuron disease

ATM : protein product of the gene mutated in ataxia-telangiectasia (A-T), characterized by neuronal degeneration, immunodeficiency, sterility, genomic instability, cancer predisposition, and radiation sensitivity.
ATM inhibition ↑ cancer immunotherapy by promoting mtDNA leakage and cGAS/STING activation



Hu M et al, 2020

ASCO Publications

Journal of Clinical Oncology
An American Society of Clinical Oncology Journal

Treatment of Pleural Mesothelioma: ASCO Guideline Update

Authors: Hedy L. Kindler, MD, Nofisat Ismaila, MD, Lyudmila Bazhenova, MD, Quincy Chu, MD, Jane E. Churpek, MD, MS, Ibiayi Dagogo-Jack, MD, Darren S. Bryan, MD, ... SHOW ALL ... , and Raffit Hassan, MD | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 43, Number 8 • https://doi.org/10.1200/JCO-24-02425

Clinical Question	Recommendation
	6.8. The non–tissue-based biomarkers that are under evaluation at this time do not have the sensitivity or specificity to predict outcome or monitor tumor response and are therefore not recommended. (Evidence quality: Moderate; Strength of recommendation: Strong)
Germline testing	
Should genetic testing for pathogenic germline mutations be routinely performed in patients with mesothelioma?	**7.1. All patients with mesothelioma should be offered germline testing. (Evidence quality: High; Strength of recommendation: Strong)**
	7.2. Actionable cancer risk genes that have been identified in patients with mesothelioma or that are appropriate based on the patient's personal or family history should be evaluated. (Evidence quality: Moderate; Strength of recommendation: Strong)
	7.3. Because patients with P/LP *variant* germline variants in *BAP1* are likely to have superior survival, individualized treatment including surveillance, platinum-based systemic therapy, and/or resection of multicavitary disease may be offered. (Evidence quality: Low; Strength of recommendation: Conditional)
	7.4. For patients with mesothelioma and a P/LP germline variant in *BAP1* P/LP variant, screening should be offered to detect secondary cancers based on age, sex, and *BAP1* tumor predisposition syndrome cancer risks. (Evidence quality: Low; Strength of recommendation: Strong)
	7.5. Relatives of patients with known P/LP germline P/LP variants may be at increased risk of developing cancers associated with hereditary syndromes and should be offered genetic counseling regarding the potential risks and benefits of germline genetic testing. (Evidence quality: High; Strength of recommendation: Strong)
	7.6. All patients who are offered germline testing should be offered pretest genetic counseling with a qualified health professional. (Evidence quality: Low; Strength of recommendation: Strong)

«…Il grigio polverone d'asbesto della cava che dove arriva brucia, foglie e polmoni…»

La Fabbrica nella Montagna.
I. Calvino 1954.

La legge italiana avrebbe messo al bando l'asbesto 38 anni dopo

«C'era amianto dappertutto, come una neve cenerina…».
Il sistema Periodico-Nichel. P.Levi, 1975

THANKS TO

Pneumology Lab.
I Campo (CO-PI MAGNETS Study)
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A. Grosso

Gruppo Interdisciplinare Neoplasie del Torace (GINT)

U.O. Pneumologia
AG Corsico

L. Saracino
G.M. Stella
S. Tomaselli

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PREDICT-Meso

European Reference Network
for rare or low prevalence complex diseases
Network Respiratory Diseases (ERN-LUNG)