

# UPDATES IN MALIGNANT PLEURAL MESOTHELIOMA

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March 31, 2023

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Conquering Thoracic Cancers Worldwide

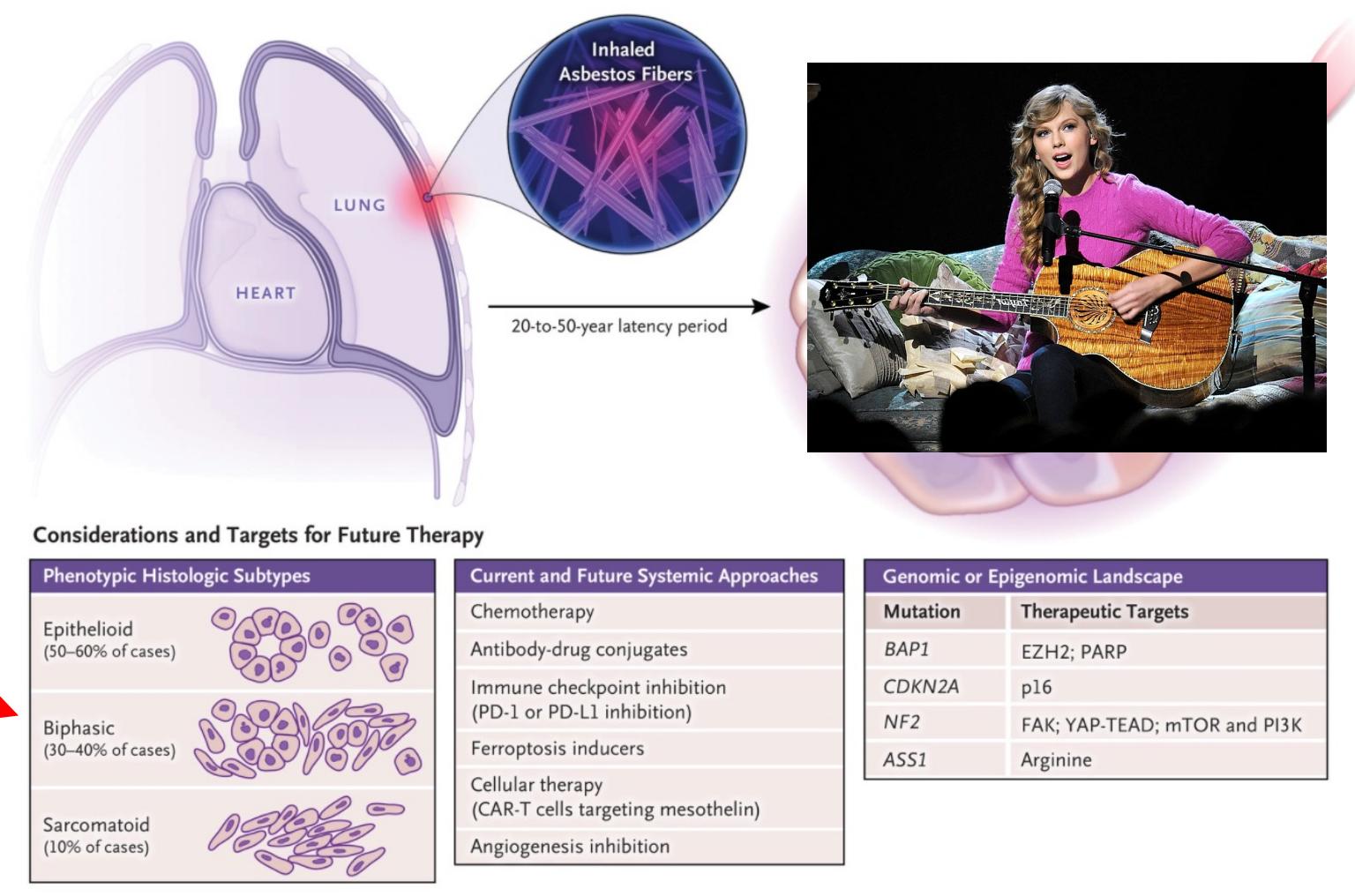
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# Malignant Pleural Mesothelioma (MPM)



**Inhaled Asbestos Fibers**

20-to-50-year latency period

**Considerations and Targets for Future Therapy**

Phenotypic Histologic Subtypes		Current and Future Systemic Approaches	Genomic or Epigenomic Landscape
Epithelioid (50–60% of cases)		Chemotherapy Antibody-drug conjugates Immune checkpoint inhibition (PD-1 or PD-L1 inhibition) Ferroptosis inducers Cellular therapy (CAR-T cells targeting mesothelin) Angiogenesis inhibition	Mutation   Therapeutic Targets  BAP1   EZH2; PARP CDKN2A   p16 NF2   FAK; YAP-TEAD; mTOR and PI3K ASS1   Arginine
Biphasic (30–40% of cases)			
Sarcomatoid (10% of cases)			

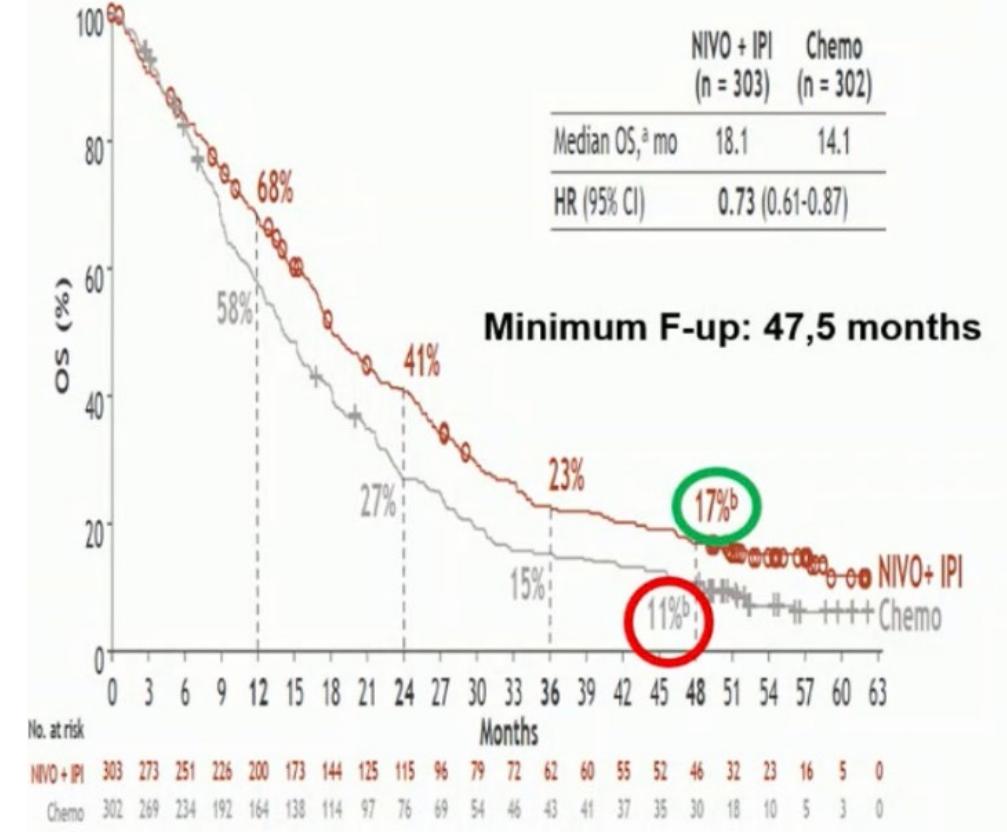
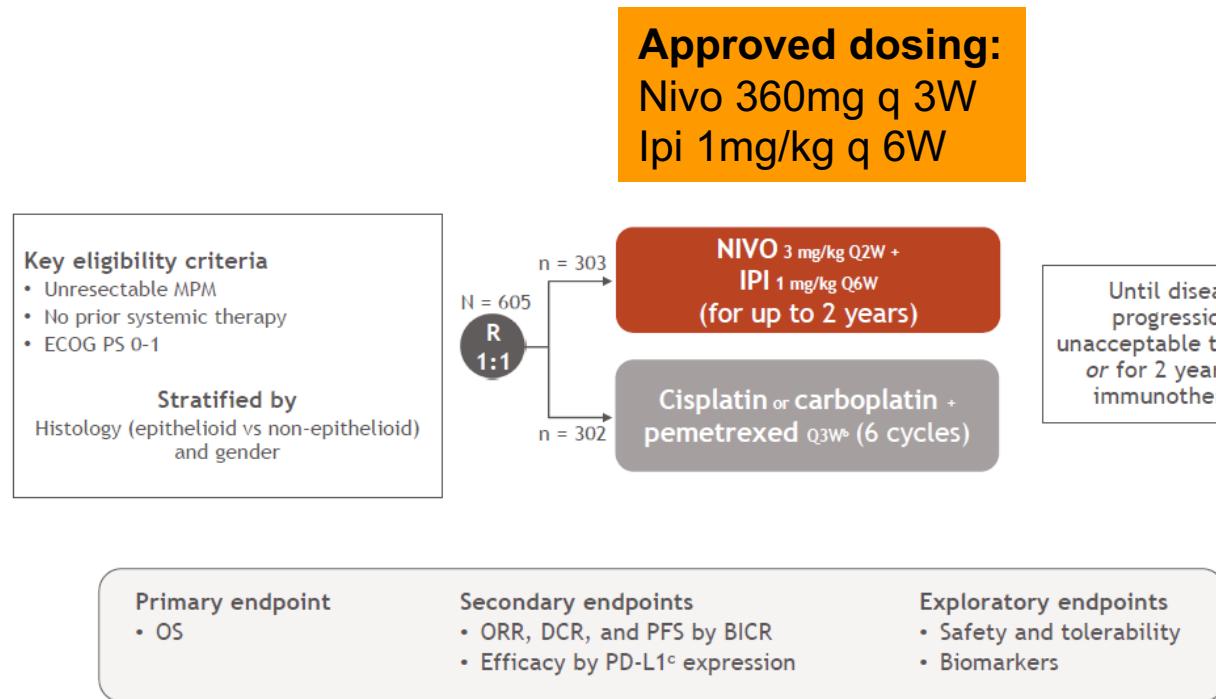
How do we use histologic subtype to guide treatment?

Sam Janes, Doraid Alrifai, Dean Fennel. NEJM, 2021; <https://www.cntraveler.com/stories/2011-11-11/country-music-travel-destinations>

# Checkmate 743: 4-year update



'Long Live the walls we crashed through.'  
-Taylor Swift, Long Live



Solange Peters, ESMO 2021+2022



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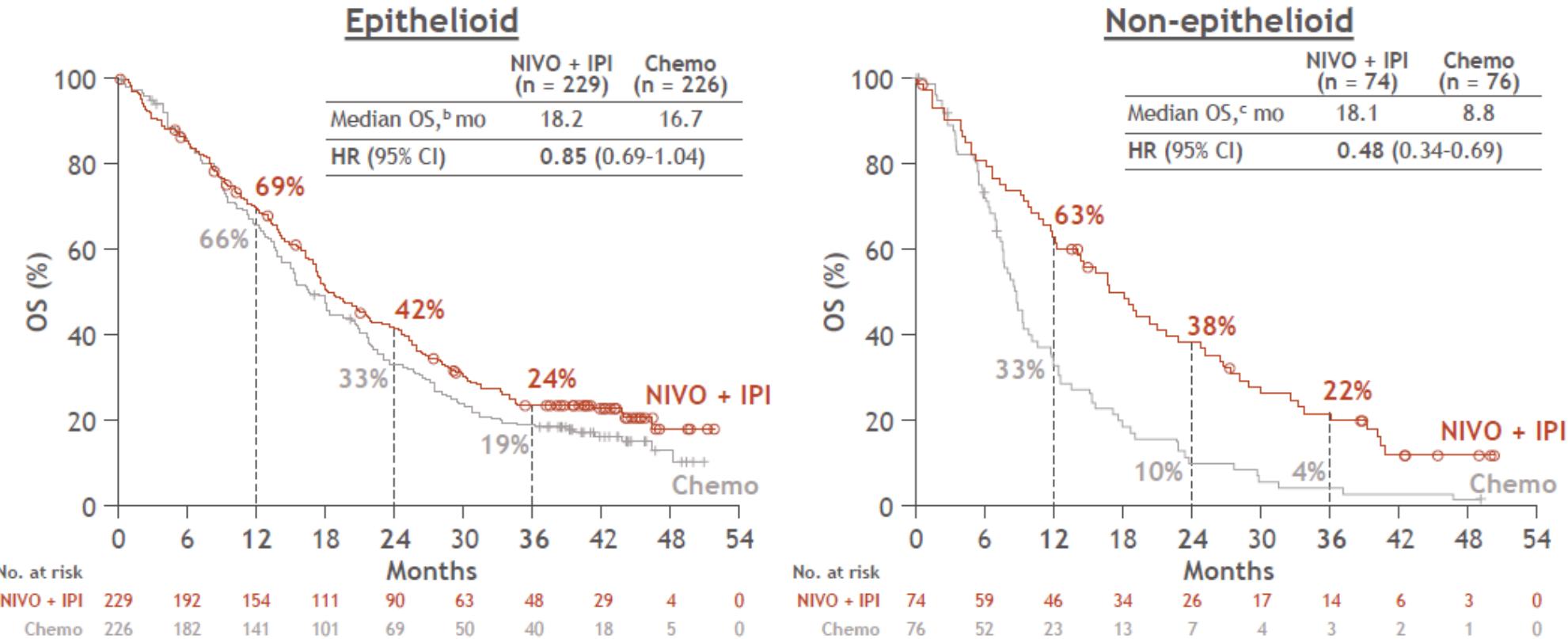
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# Non-epithelioid benefits most from Ipi/Nivo



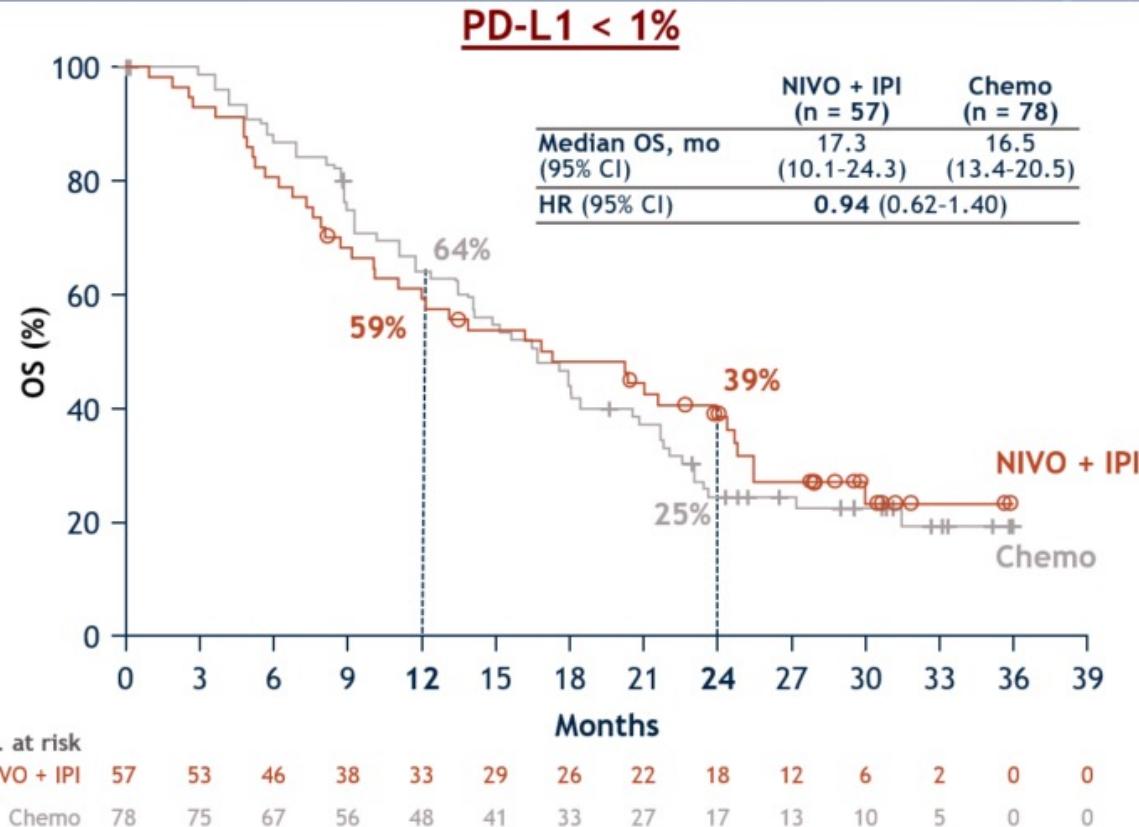
'With you I'd dance in a storm.  
In my best dress.  
Fearless.'  
-Taylor Swift, End Game



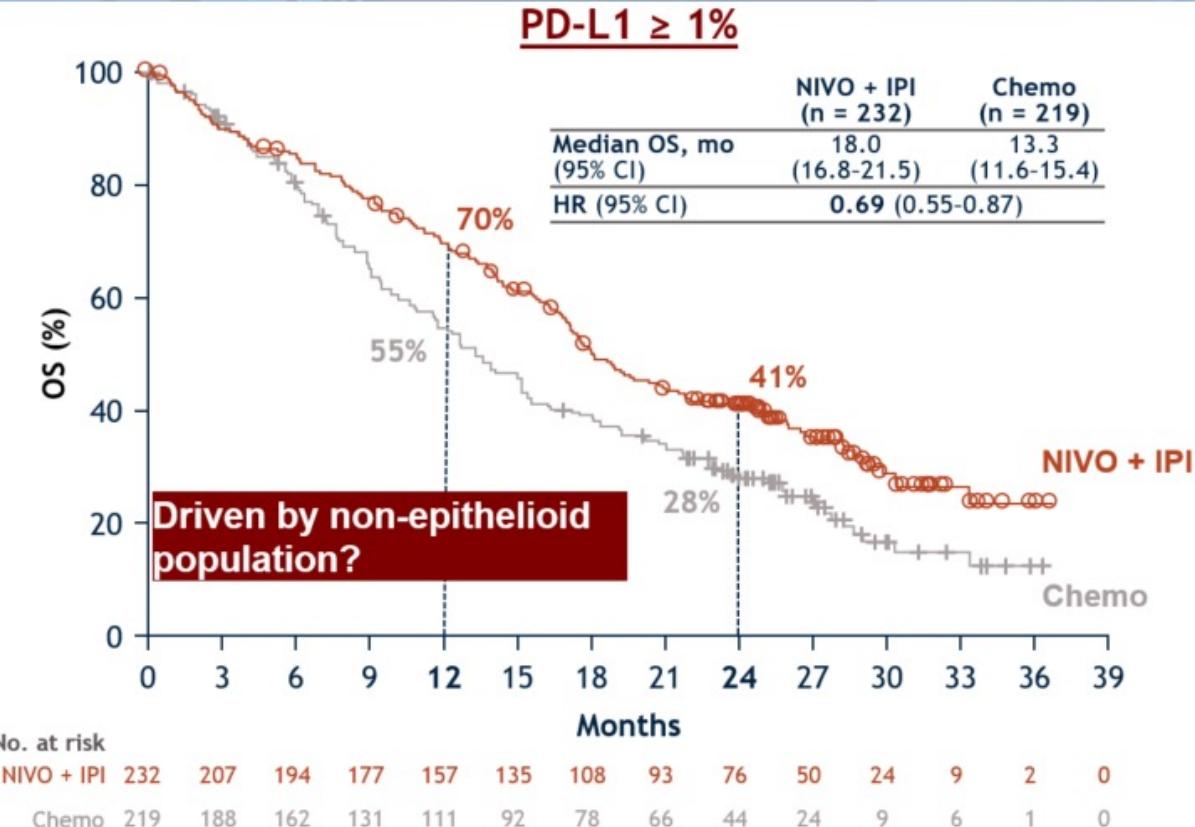
Solange Peters, ESMO 2021

# Does PD-L1 level predict response to Ipi/Nivo?

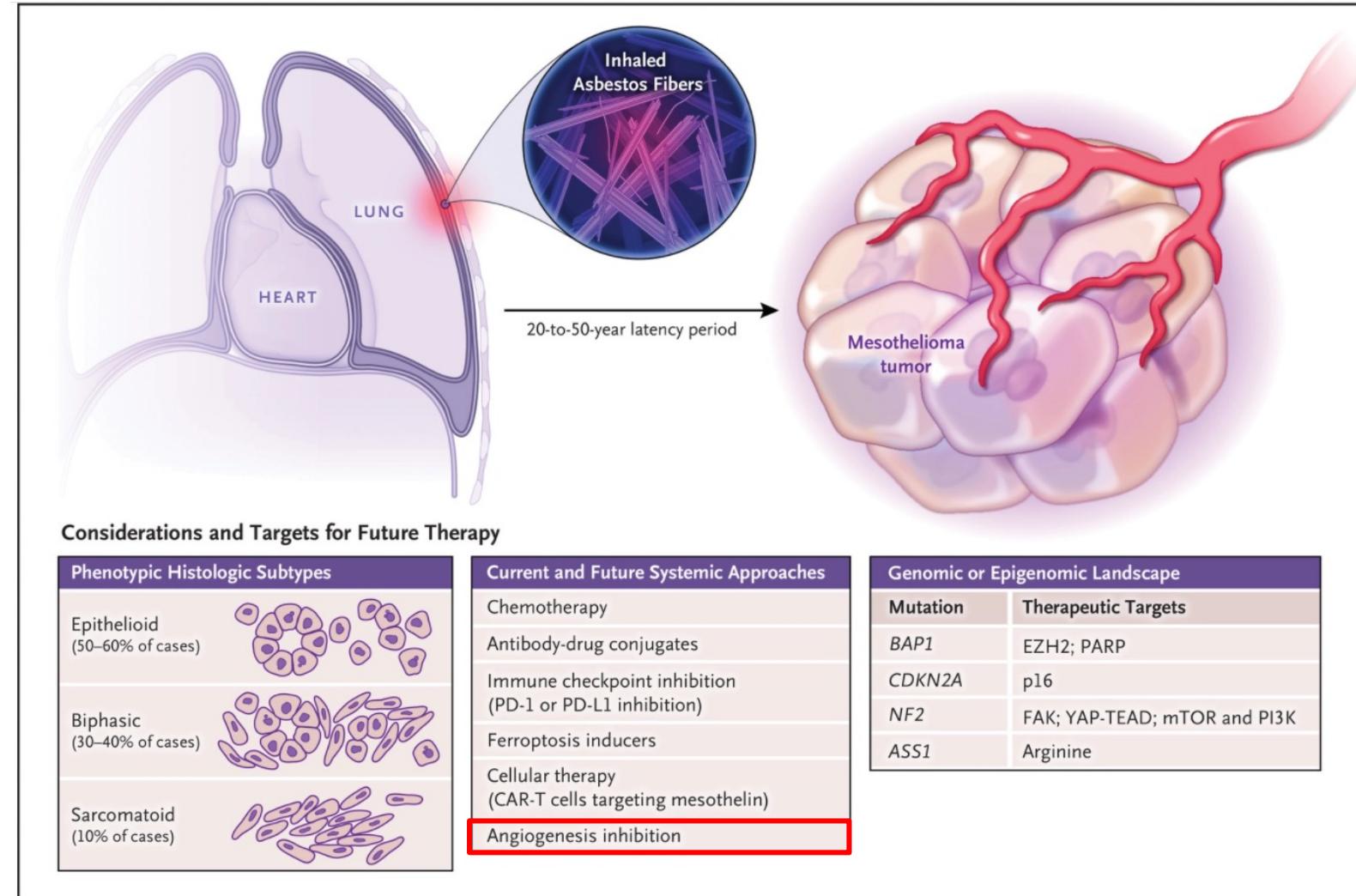
'I wanna be your endgame. I wanna be your first string.  
I wanna be your A-Team...Big reputation.'  
-Taylor Swift, End Game



Baas, WCLC, 2020



# Malignant Pleural Mesothelioma (MPM)



Sam Janes, Doraid Alrifai, Dean Fennel. NEJM, 2021

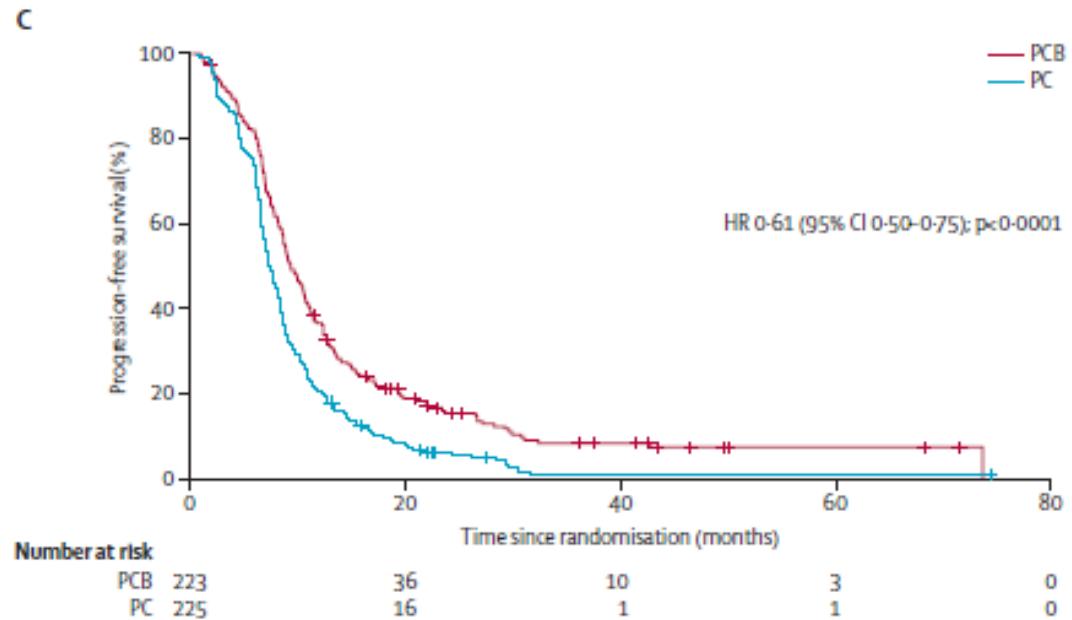
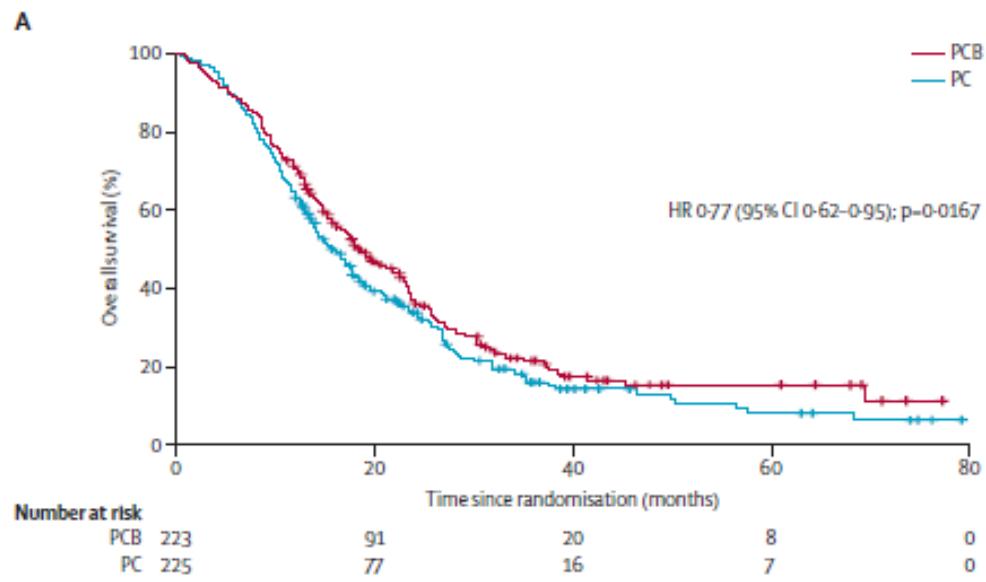
# Bevacizumab in Pleural Mesothelioma: Where We Started

- 448 patients randomized
- Cisplatin, Pemetrexed +/- Bevacizumab
- OS longer with bevacizumab
- mOS 18.8 mo vs 16.1 mo

'I bet you think about me'  
-Taylor Swift, I bet you think about me

**Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial**

Gérard Zalcman, Julien Mazieres, Jacques Margery, Laurent Greillier, Clarisse Audigier-Valette, Denis Moro-Sibilot, Olivier Molinier, Romain Corre, Isabelle Monnet, Valérie Gounant, Frédéric Rivière, Henri Janicot, Radj Gervais, Chrystèle Locher, Bernard Milleron, Quan Tran, Marie-Paule Lebitay, Franck Morin, Christian Creveuil, Jean-Jacques Parienti, Arnaud Scherpereel, on behalf of the French Cooperative Thoracic Intergroup (IFCT)

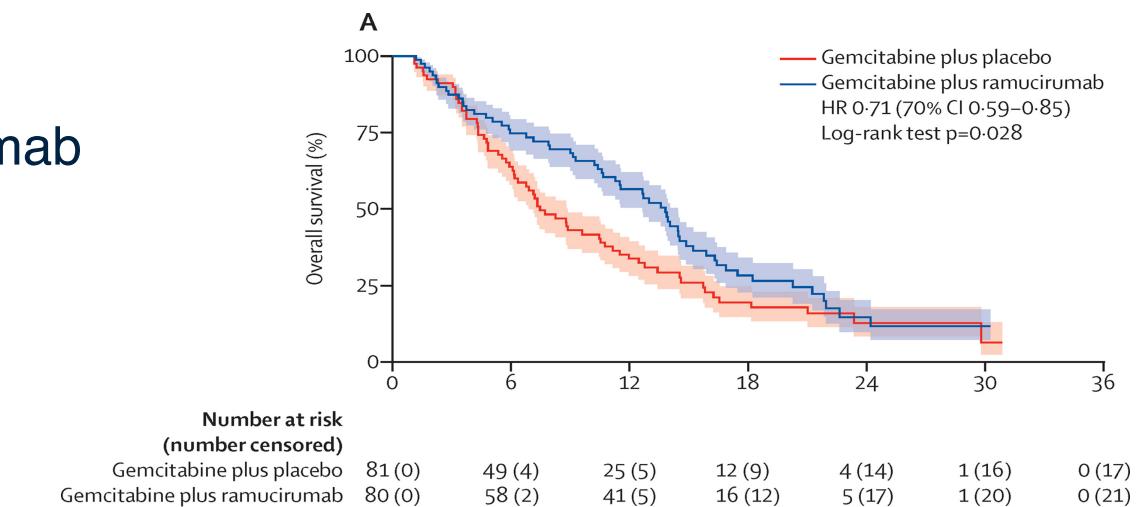


Zalcman, The Lancet, 2016

# RAMES Study: Gemcitabine +/- Ramucirumab

- ▶ Malignant pleural mesothelioma
- ▶ Disease progression after 1L pemetrexed + platinum
- ▶ Randomized, double-blind, placebo controlled trial
- ▶ 26 centers in Italy
  
- ▶ 161 patients treated
- ▶ Improved overall survival in group with Ramucirumab
  - 13.8 mo vs 7.5 mo (HR 0.71, p= 0.028)

'But if I showed up at your party  
Would you have me?  
Would you want me?'  
-Taylor Swift, Betty



Pinto, The Lancet, 2021

# What is next?

'Can I go where you go? Can we always be this close forever and ever?'  
-Taylor Swift, Lover



## Immunotherapy and anti-VEGF

### ► PEMMELA Study (WCLC 2022)

- **Pembrolizumab + lenvatinib** (20mg daily) in 2L
- Single-arm, phase 2
- 38 patients
- 15/38 had confirmed PR (**ORR 39.5%**)
- 26/38 patients with grade 3-4 AEs (hypertension and anorexia most common)
  - 76% of patients requires dose reduction or stopping lenvatinib due to toxicity

Douma, JTO, WCLC 22 abstract

## All together?

### Chemotherapy + Immunotherapy in 1L

- DREAM Trial
- Cisplatin, pemetrexed and durvalumab
- mPFS 6.9 mo, ORR 48%
- mOS 18.4 months
- Phase III DREAM3R study ongoing

### Chemotherapy + Immunotherapy + anti-VEGF in 1L

- BEAT-meso (ongoing)
  - Chemotherapy + Bevacizumab
  - Chemotherapy + Bevacizumab + Atezolizumab



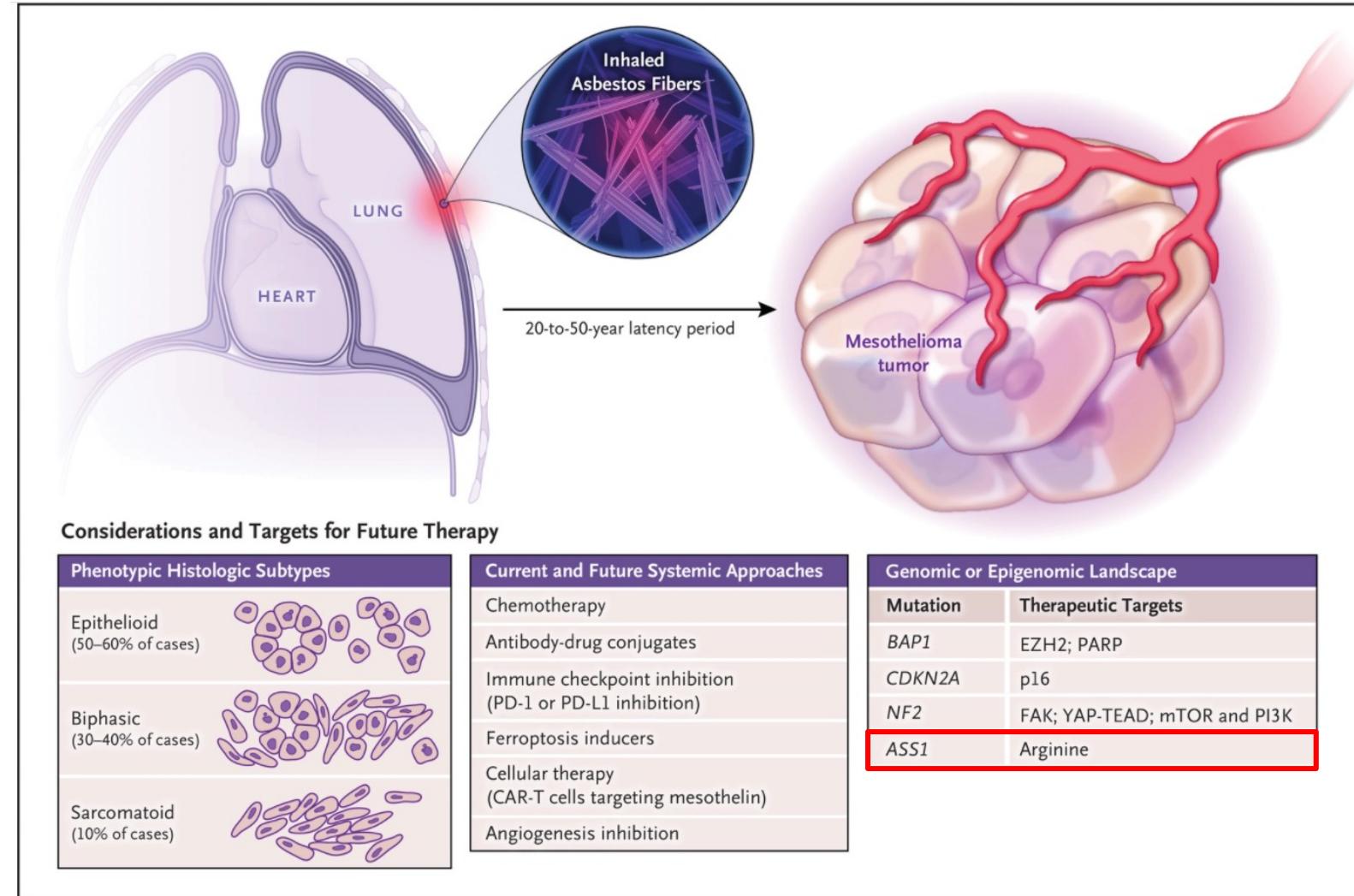
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Sam Janes, Doraid Alrifai, Dean Fennel. NEJM, 2021



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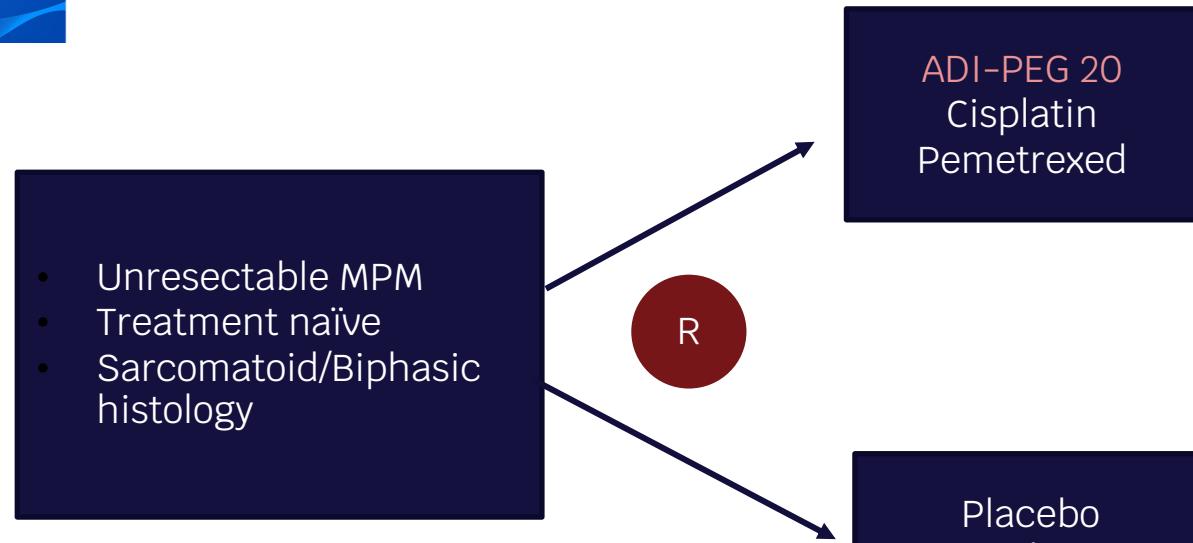
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# ATOMIC-Meso shows OS and PFS benefit for ADI-PEG 20



## ADI-PEG 20

- ASS-1 deficiency present in ~60% of MPM
- ASS-1 deficient MPM is sensitive to arginine deprivation therapy
- ADI-PEG 20 depletes arginine

**mOS 9.3 mo** (95% CI 7.85-11.79)  
**HR 0.71** (95% CI 0.55-0.93)

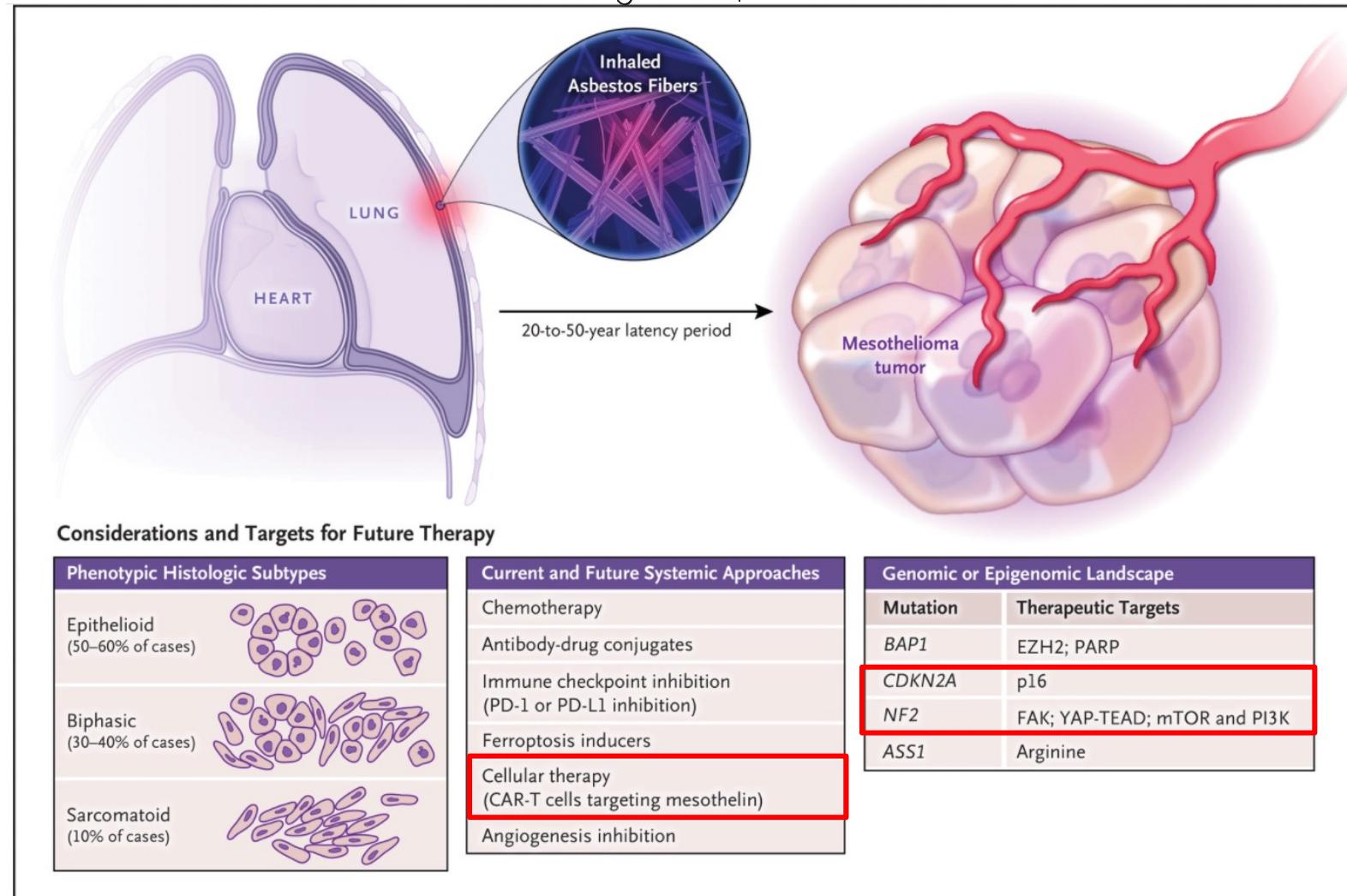
**mPFS 6.11 mo** (95% CI 5.75-7.43)  
**HR 0.65** (95% CI 0.47-0.9)

**mOS 7.66 mo** (95% CI 6.14-9.53)

**mPFS 5.59 mo** (95% CI 4.14-5.85)

# Malignant Pleural Mesothelioma (MPM)

'I could build a castle  
Out of all the bricks they threw at me and every day is like a battle'  
-Taylor Swift, New Romantics



Sam Janes, Doraid Alrifai, Dean Fennel. NEJM, 2021



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# Emerging therapies in Malignant Pleural Mesothelioma



## ► Mesothelin targeted therapies

- CART-meso with or without immunotherapy
- HPN536 (mesothelin + CD3), NCT03872206

## ► TEAD inhibitors

- Targets Hippo pathway in NF2 deficient mesothelioma, NCT05228015
- Also targets YAP1 or TAZ fusions

## ► PRMT5 inhibition

- Targets CDKN2A or MTAP loss, NCT05245500, NCT05275478, NCT04794699

'Thank you for everything. I wouldn't be here without you. Thank you'  
-Taylor Swift, Thank you

Castelletti, Biomarker Research, 2021; <https://www.curemeso.org/2022/10/04/news-positive-results-reported-from-mesothelioma-phase-2-3-trial-for-sarcomatoid-biphasic-patients/>