Doctors of Thoracic Surgery®

Surgical Management of Pleural Malignancies

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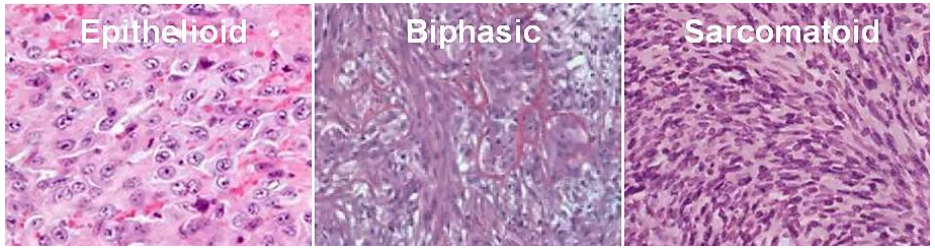
Surgery in pleural disease

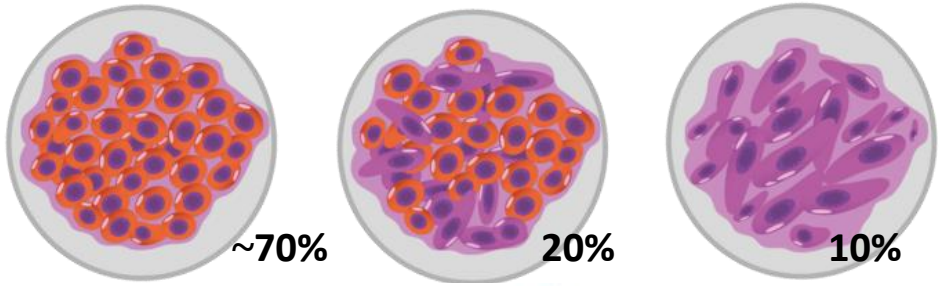
- Pleural mesothelioma
- Pleural metastasis (Thymoma, sarcoma, others)
- Rare pleural tumors (Solitary fibrous tumors, others)

This talk will focus on mesothelioma as the prototypical pleural malignancy requiring multidisciplinary approach

Histologic subtypes and EMT in mesothelioma



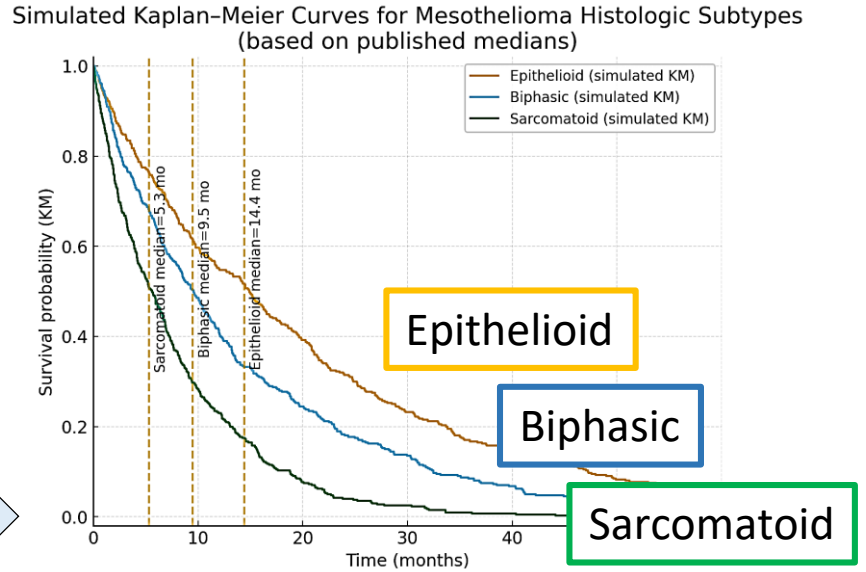
Epithelioid Biphasic Sarcomatoid







Consequences



- **Tumor progression**
- **Invasion**
- **Stemness**
- **Resistance to chemotherapy**
- **Poor prognosis**

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Some of the problems in mesothelioma

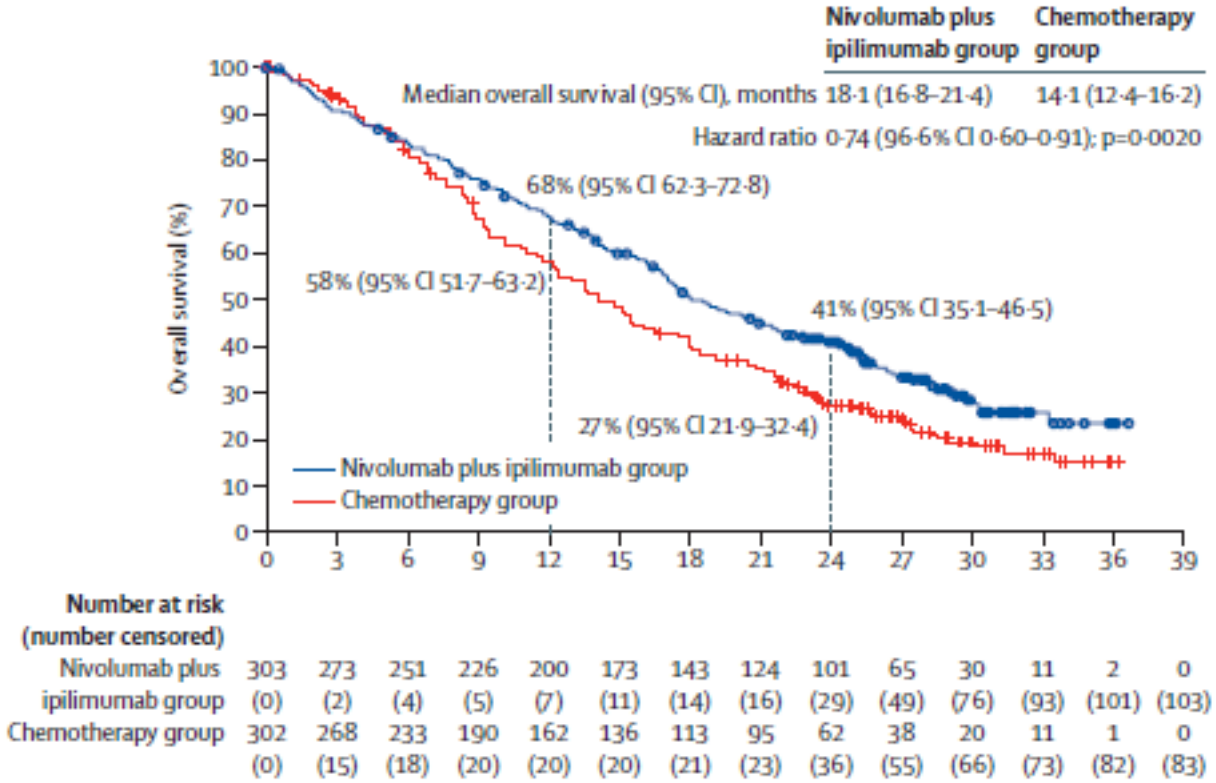
- Tumor heterogeneity
- Lack of biomarkers
- Poor clinical staging
- Lack of defined multimodality approach

Recent clinical trials impacting standard-of-care in mesothelioma

- CheckMate 743 (ipi-nivo vs chemo)
- IND-227 (chemo-pembro vs chemo)
- MARS 2 (chemo ± EPD surgery)

First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial

Paul Baas, Arnaud Scherpereel, Anna K Nowak, Nobukazu Fujimoto, Solange Peters, Anne S Tsao, Aaron S Mansfield, Sanjay Popat, Thierry Jahan, Scott Antonia, Youssef Oulkhouir, Yolanda Bautista, Robin Cornelissen, Laurent Greillier, Francesco Grossi, Dariusz Kowalski, Jerónimo Rodríguez-Cid, Praveen Aanur, Abderrahim Oukessou, Christine Baudelet, Gérard Zalcman



- 605 patients randomized to:
- Ipi-Nivo vs Cis-Pem
- MS 18.1 mo vs 14.1 mo
- Hazard ratio 0.74 (95%CI 0.6-0.9)
- *p*=0.002

Lancet 2021;397:375-386.

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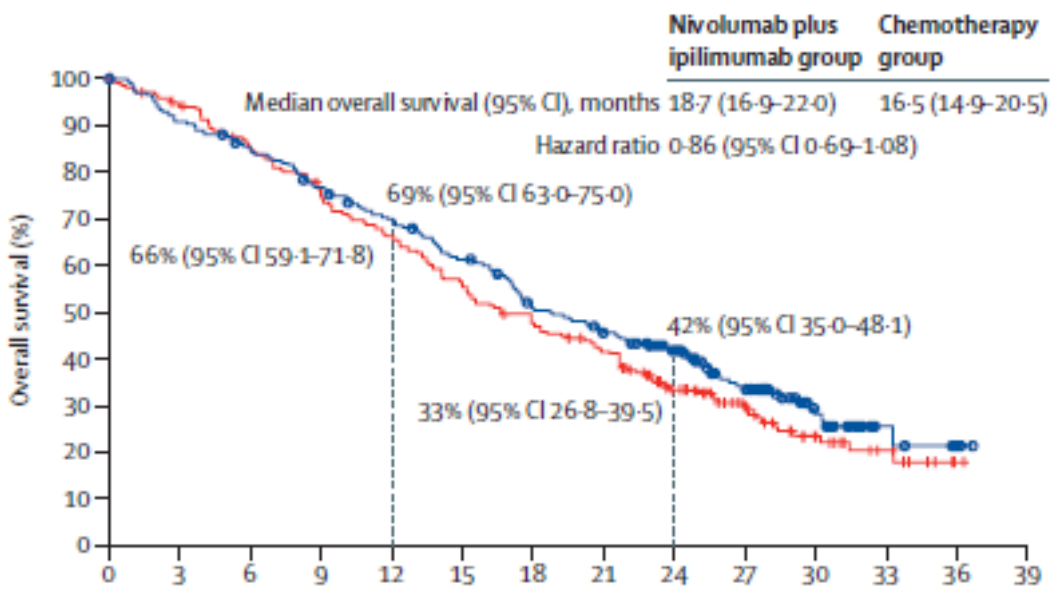
CheckMate-743: Benefit of Ipi-Nivo in non-epithelioid mesothelioma

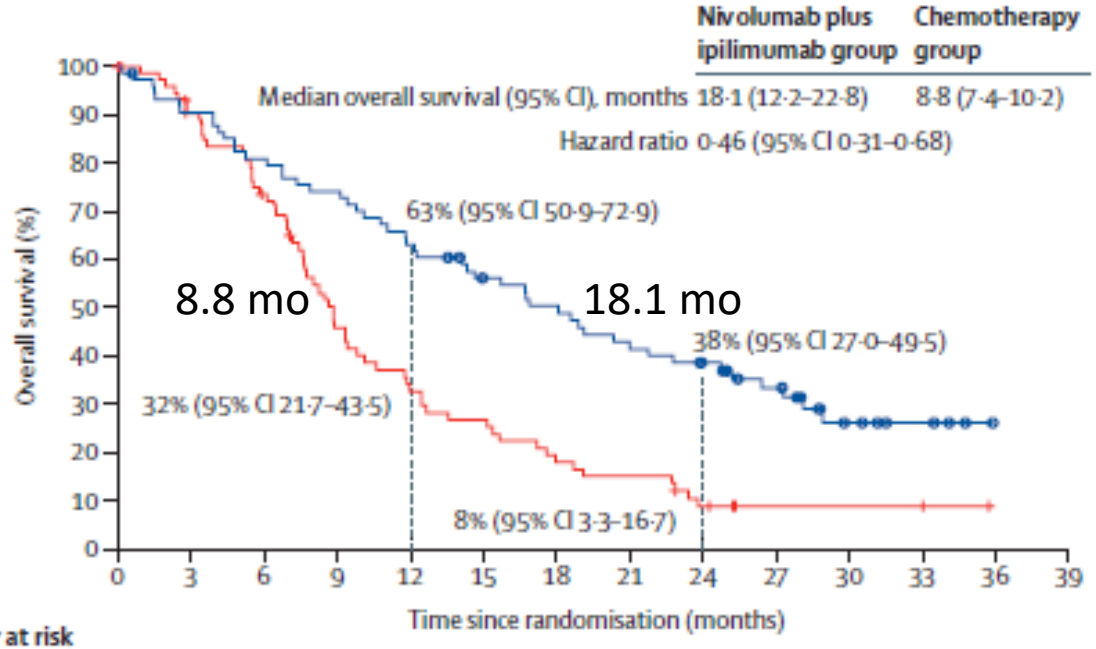
Epithelioid



Number at risk (number censored)

Nivolumab plus ipilimumab group	229 (0)	207 (1)	192 (3)	172 (4)	154 (6)	135 (7)	109 (10)	96 (12)	77 (23)	47 (40)	22 (60)	6 (74)	2 (77)	0 (79)
Chemotherapy group	227 (0)	204 (11)	182 (13)	159 (14)	140 (14)	118 (14)	101 (15)	85 (17)	57 (29)	36 (45)	18 (56)	9 (63)	1 (70)	0 (71)

Non-epithelioid



Number at risk (number censored)

Nivolumab plus ipilimumab group	74 (0)	66 (1)	59 (1)	54 (1)	46 (1)	38 (4)	34 (4)	28 (4)	24 (6)	18 (9)	8 (16)	5 (19)	0 (24)	0 (24)
Chemotherapy group	75 (0)	64 (4)	51 (5)	31 (6)	22 (6)	18 (6)	12 (6)	10 (6)	5 (7)	2 (10)	2 (10)	2 (10)	0 (12)	0 (12)

Baas et al. *Lancet* 2021;397:375-386

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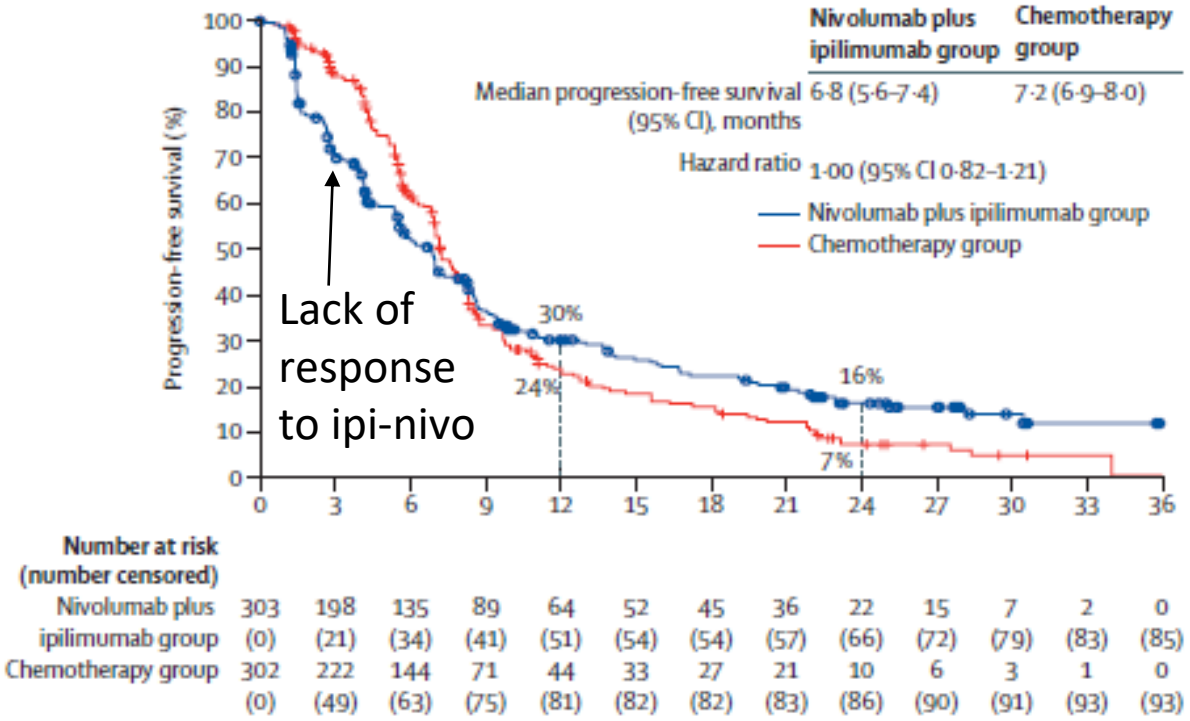
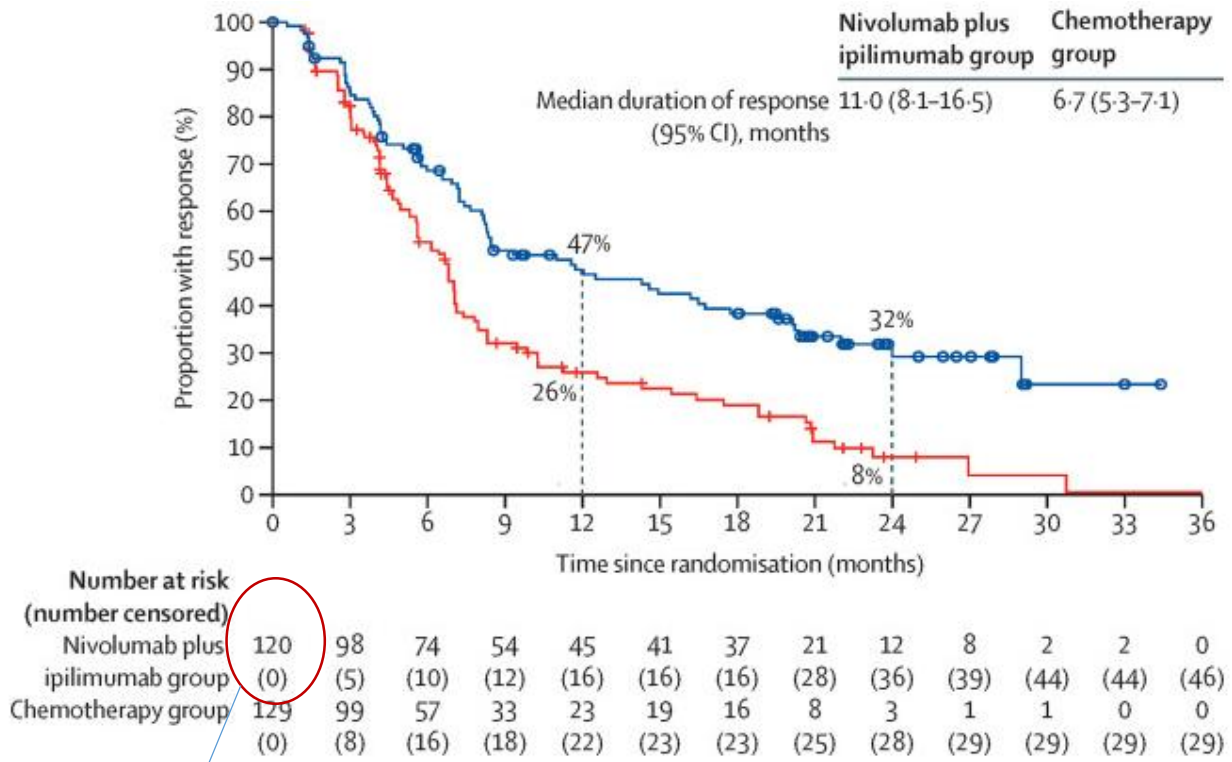
PFS in ipi-nivo *vs* chemo and duration of response in responders

PFS of 6.8 mo after IO vs 7.2 mo with chemo



Response is more durable with ipi-nivo



About 40% response rate to IO

Baas et al. *Lancet* 2021;397:375-386

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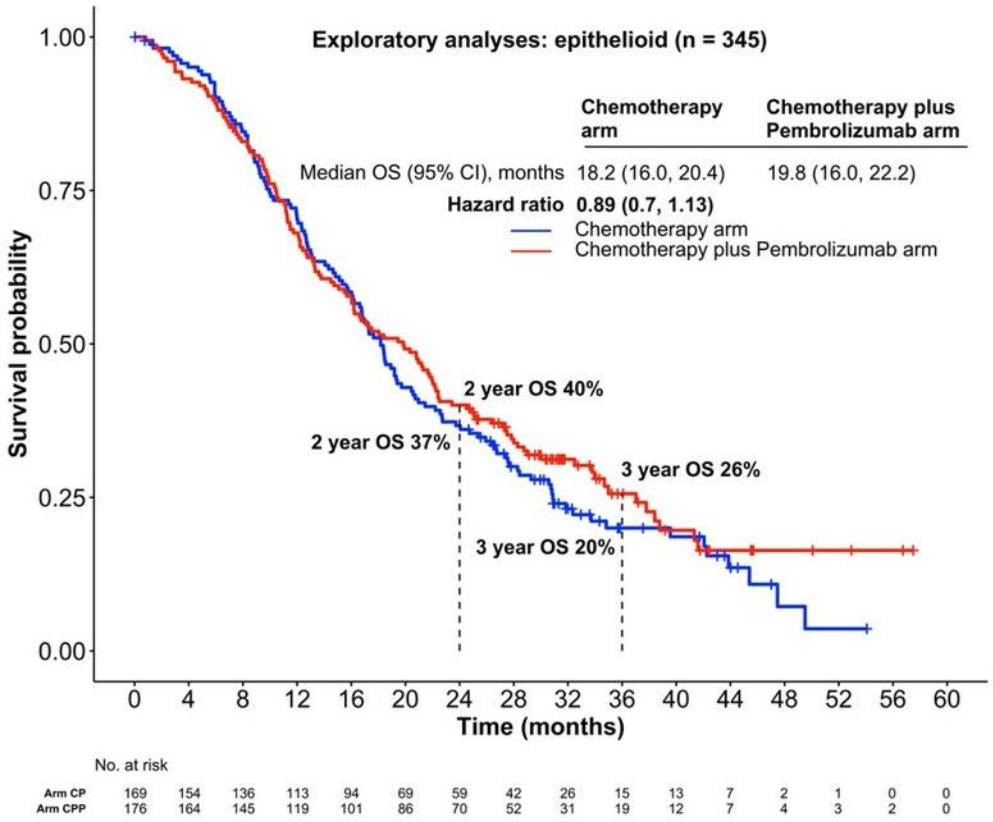
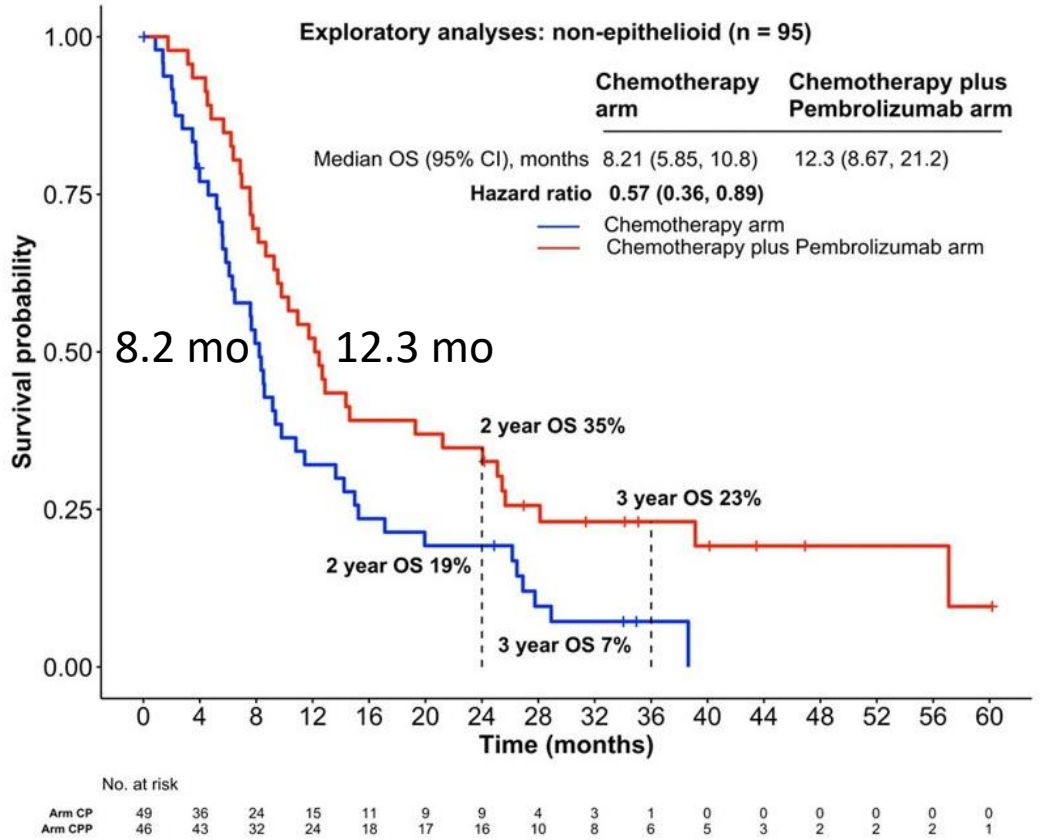
IND-227 trial: benefit of chemo-pembro in non-epithelioid meso

Epithelioid



Non-epithelioid



Chu et al, *Lancet* 2023;402:2295-2306

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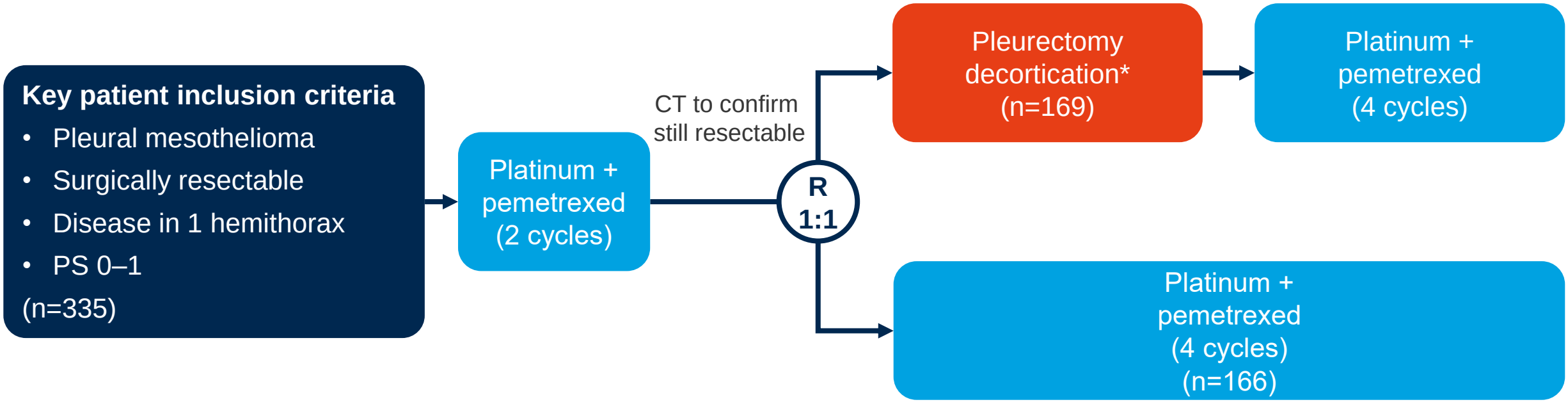
MARS 2 trial: A Multicentre Randomised Trial Comparing (Extended) Pleurectomy Decortication versus No Radical Surgery for Mesothelioma

- **Study objective**
  - To evaluate the efficacy and safety of extended pleurectomy + chemotherapy in patients with pleural mesothelioma



Primary endpoint

- OS

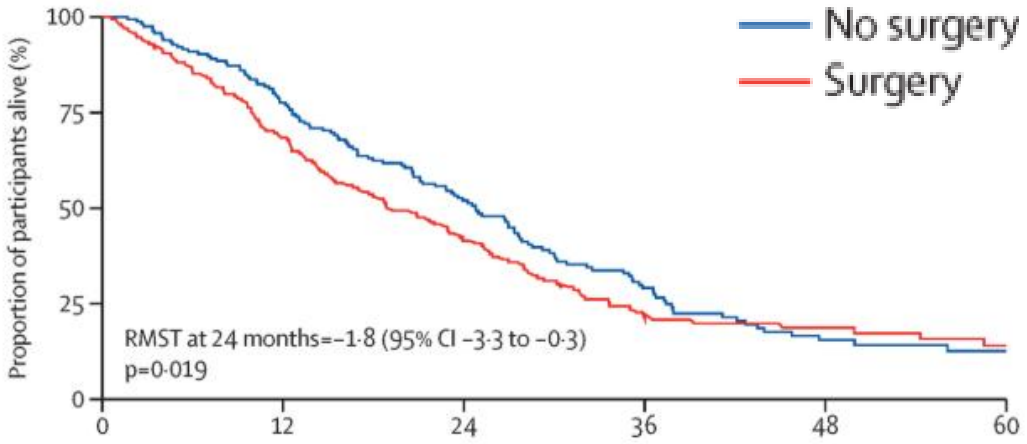
Secondary endpoints

- PFS, QoL, safety

*Removal of all visible disease in the visceral and parietal pleura and if required the ipsilateral hemidiaphragm and pericardium but sparing the lung.

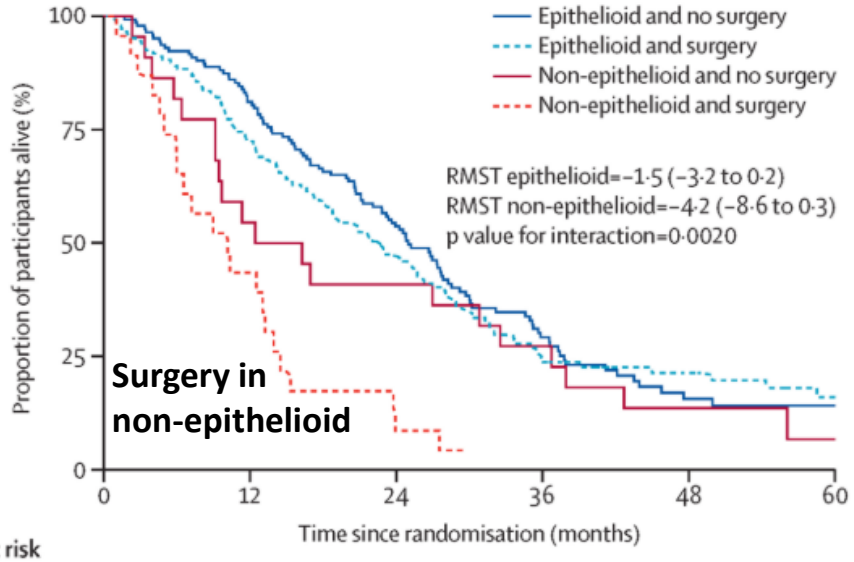
MARS 2 trial - EPD after 2 cycles of chemotherapy can be deleterious in non-epithelioid mesothelioma

Overall survival



Number at risk (number censored)						
No surgery	166	129	82	37	15	6
	(1)	(4)	(14)	(7)	(7)	(6)
Surgery	169	115	64	24	15	7
	(1)	(6)	(14)	(6)	(5)	(7)

Overall survival by histology



Number at risk (number censored)						
Epithelioid and no surgery	144 (1)	116 (4)	73 (14)	31 (7)	12 (6)	5 (5)
Epithelioid and surgery	146 (1)	105 (6)	62 (13)	24 (6)	15 (5)	7 (7)
Non-epithelioid and no surgery	22 (0)	12 (0)	9 (0)	6 (0)	3 (1)	1 (1)
Non-epithelioid and surgery	23 (0)	10 (0)	2 (1)	0 (0)	0 (0)	0 (0)

Not all resectable patients should undergo surgery – histology outweigh technical resectability

Histology is essential for both IO and surgery

Lim E, et al. *Lancet Respir Med* 2024;12:457-66

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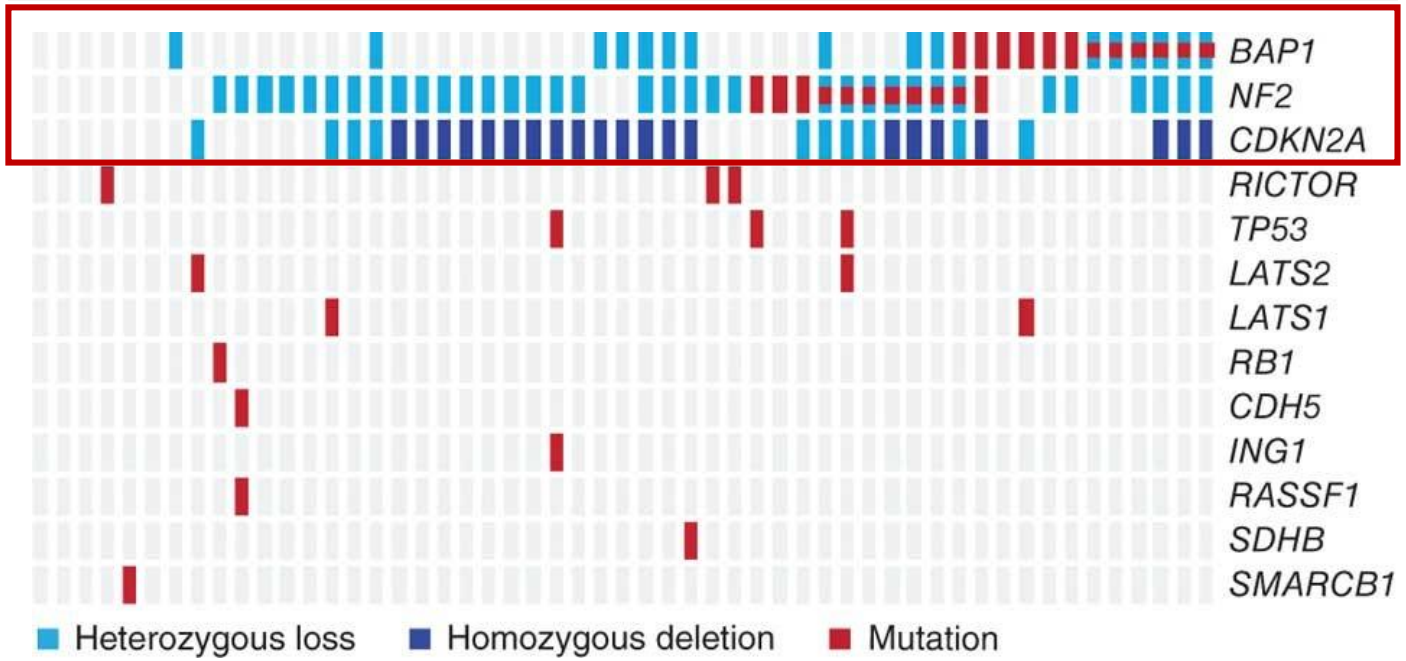
How does genetic alterations affect histology in mesothelioma?

3 main gene alterations in mesothelioma include *BAP1*, *CDKN2A*, and *NF2*



- ***BAP1* loss**
  - **Epithelioid 67%**
  - Biphasic 47%
  - Sarcomatoid 18%
- ***CDKN2A* homozygous deletion (p16HD)**
  - Epithelioid 47%
  - **Biphasic 70%**
  - **Sarcomatoid 67%**
- ***NF2* alterations**
  - Epithelioid 7%
  - Biphasic 5%
  - **Sarcomatoid 18%**

Bott et al. *Nat Genet* 2011;43:668-672
Galateau-Salle F. *WCLC* 2022

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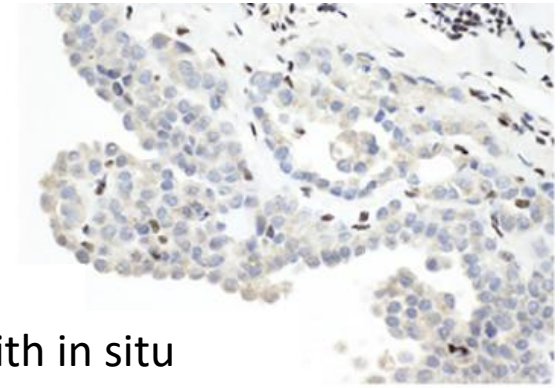
BAP1 loss can be associated with mesothelioma in situ and better prognosis

Mesothelioma in situ

- Papillary and tubulopapillary proliferation without microscopic invasion
- Tumor progress towards invasive mesothelioma
- Invasive mesothelioma with in situ component carry better prognosis

Papillary and tubulopapillary proliferation, no invasion



Pulford et al. Pathology 2020;52:635-42
Churg et al. Modern Pathology 2020;33:297-302

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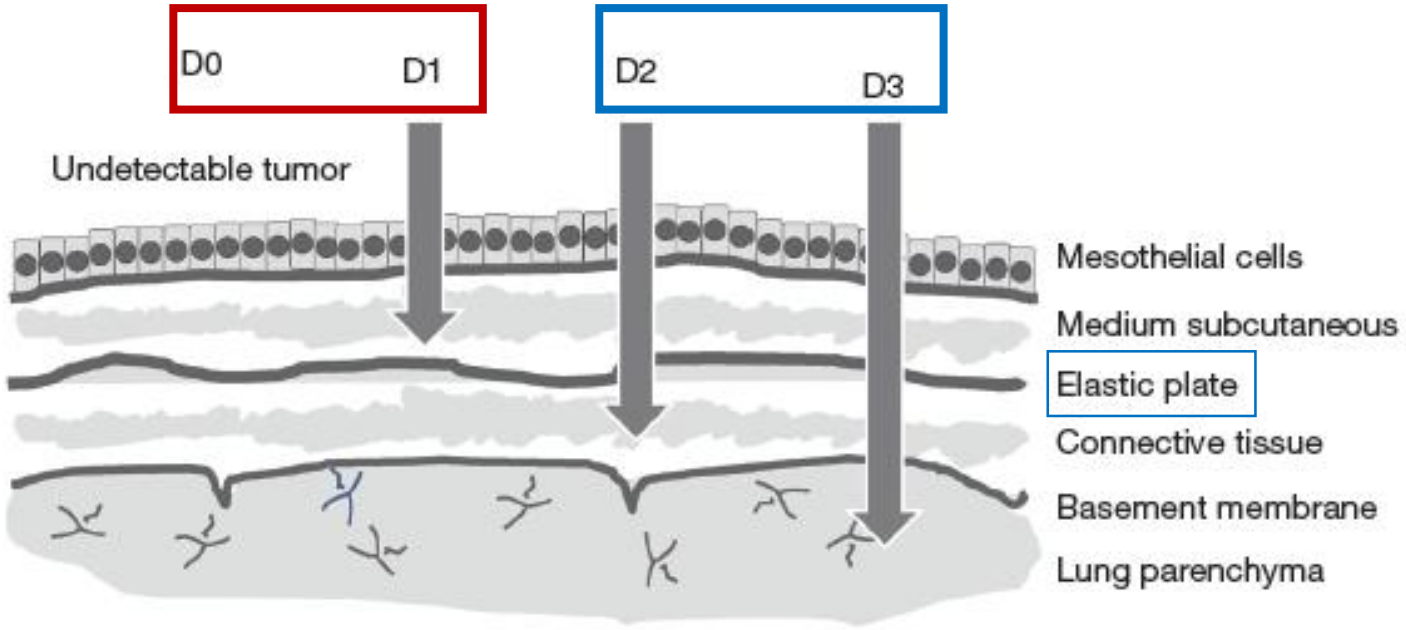
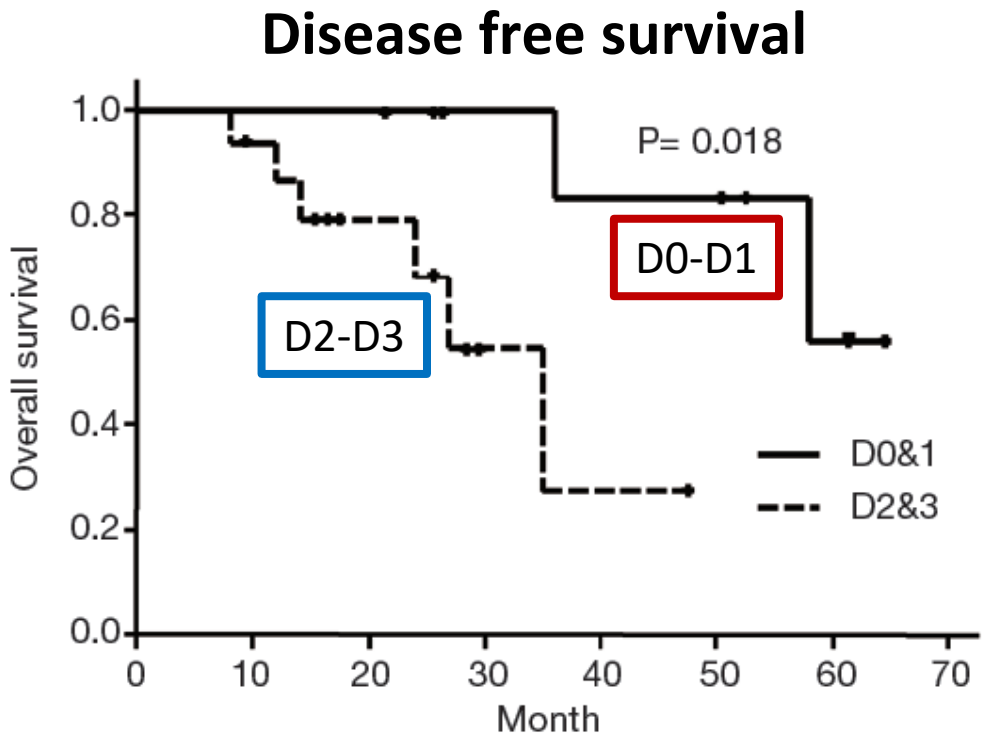
Visceral pleura invasion impacts disease-free survival



D0: No tumor involvement in the pleura
D1: Tumor involvement no reaching the elastic plate layer
D2: Tumor involvement between elastic layer and basement membrane
D3: Tumor involvement to the lung parenchyma



Kobayashi et al *J Thorac Dis* 2019;11:717-23

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Impact of T category on survival

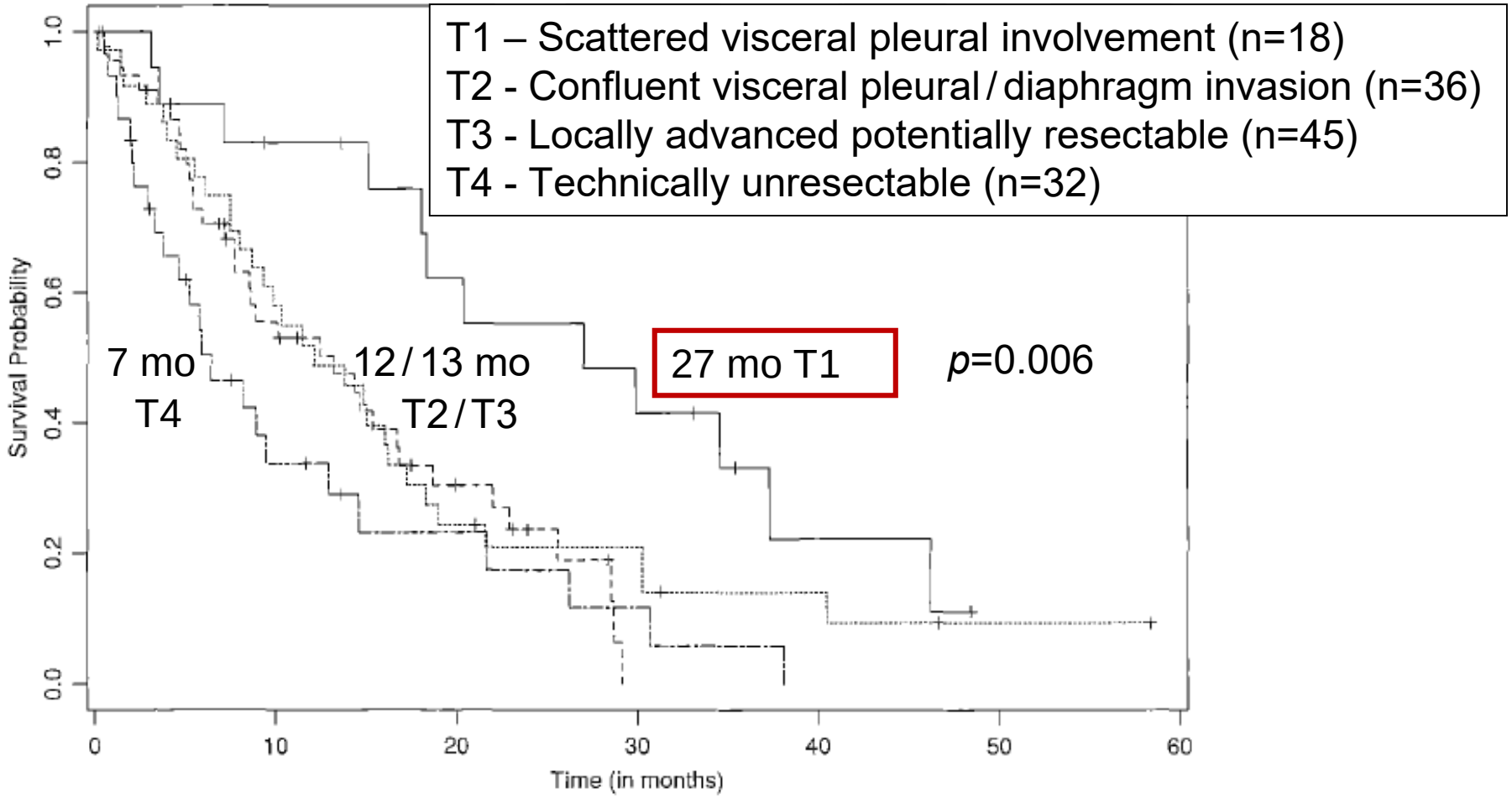
1983-1994

131 patients treated by the same surgeon (VR)

50 EPP, 51 PD

Median survival

- T1 had a MS of 27 mo
- T2, T3 MS of 12-13 mo
- T4 MS 7 mo



Rusch and Venkatraman *J Thorac Cardiovasc Surg* 1996;111:815-26

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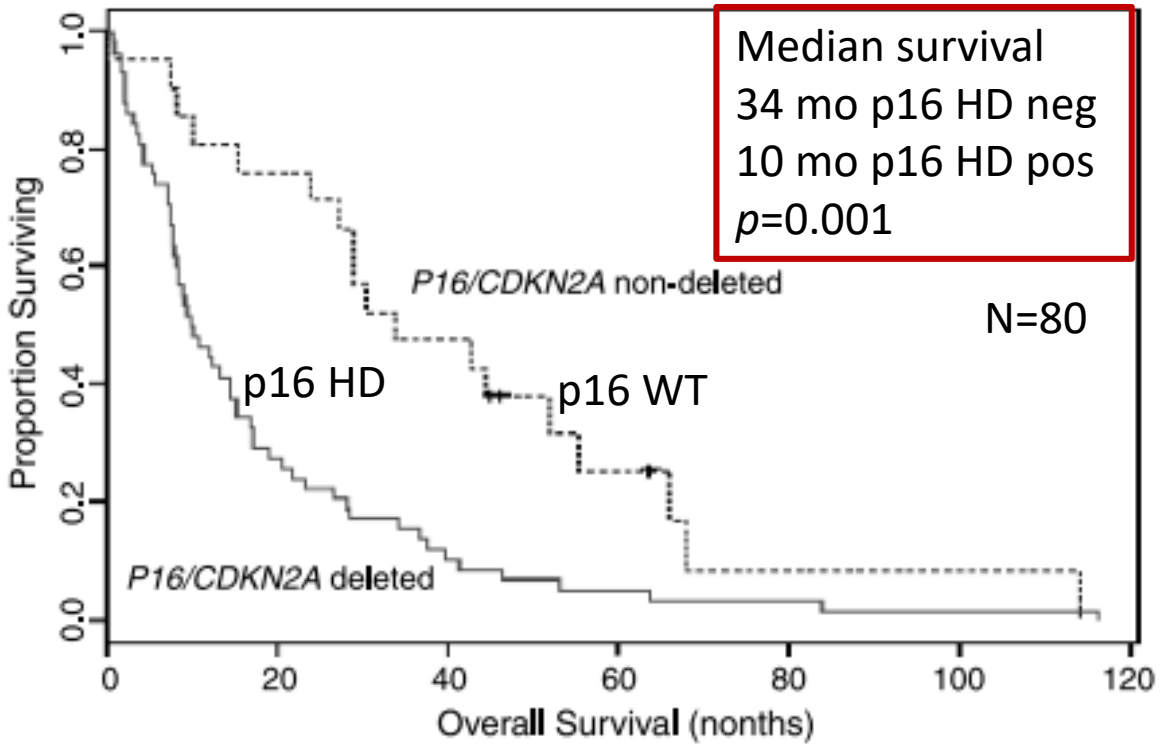
p16 homozygous deletion (p16HD) is an independent factor of worse prognosis



Factors	Multivariate hazard ratio (95% confidence interval)	Multivariate *P*
Sex: female vs male	1.43 (0.77, 2.66)	0.26
T status: T_3/T_4 vs T_1/T_2	1.03 (0.60, 1.78)	0.92
Stage: III/IV vs I/II	2.23 (1.18, 4.22)	0.01
Histology: B/S vs E	1.84 (1.08, 3.16)	0.03
P16 deletion status: D vs ND	0.49 (0.27, 0.88)	0.02

Histology, stage and genomic profile are independently impacting survival

Lopez-Rios et al. *Cancer Res* 2006;66:2970-9

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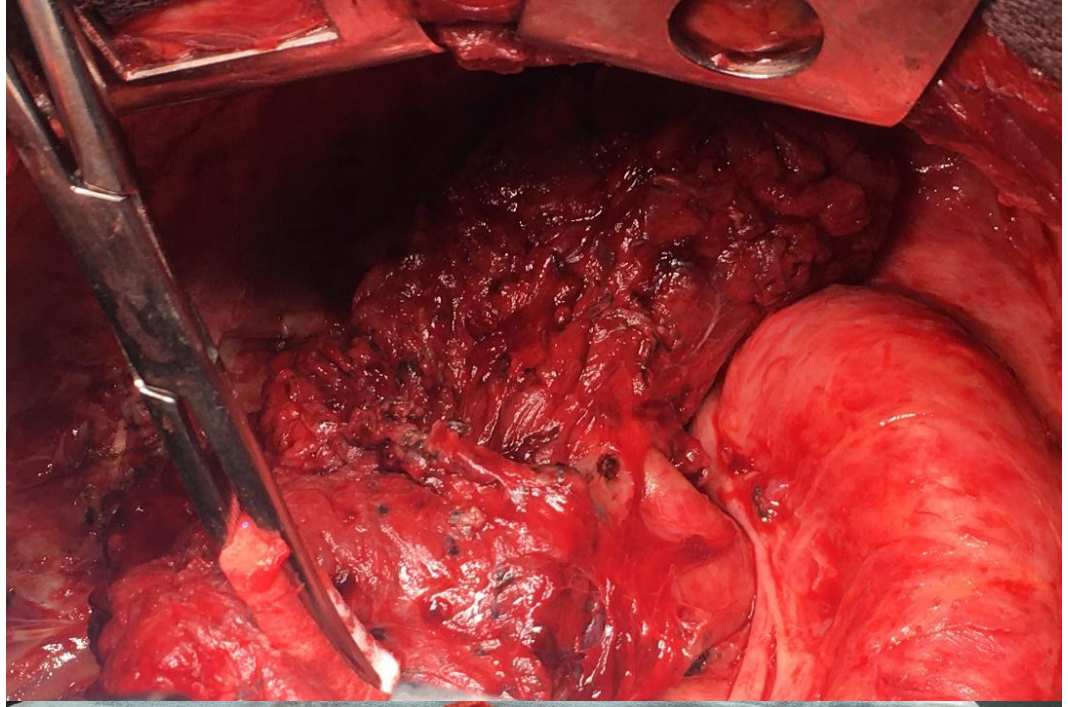
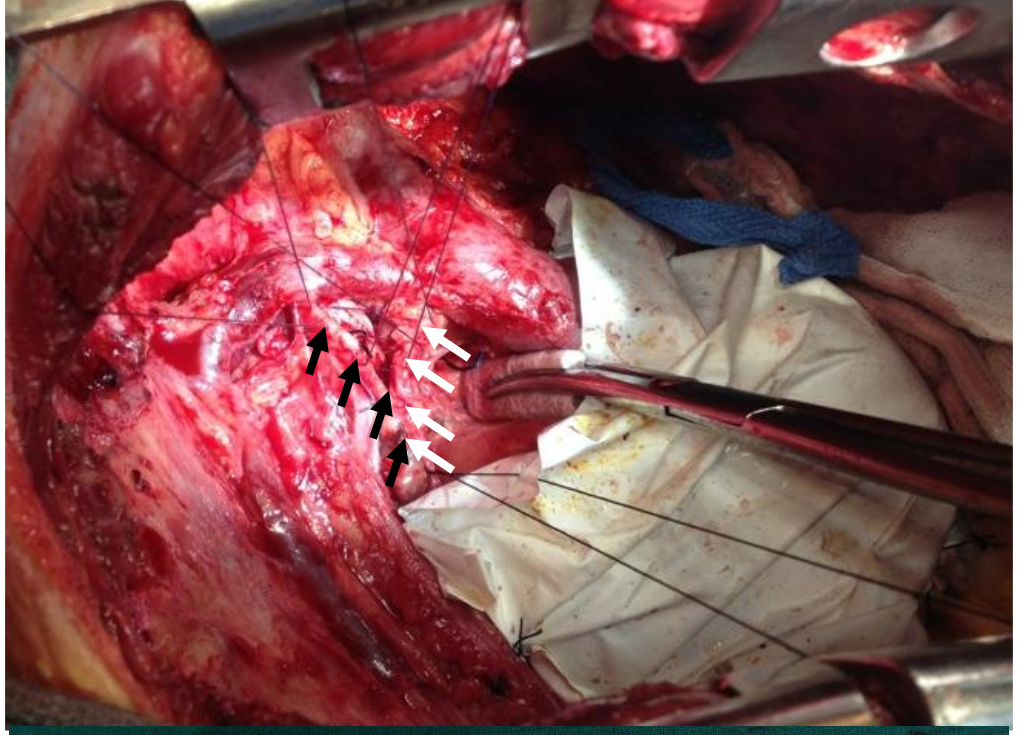
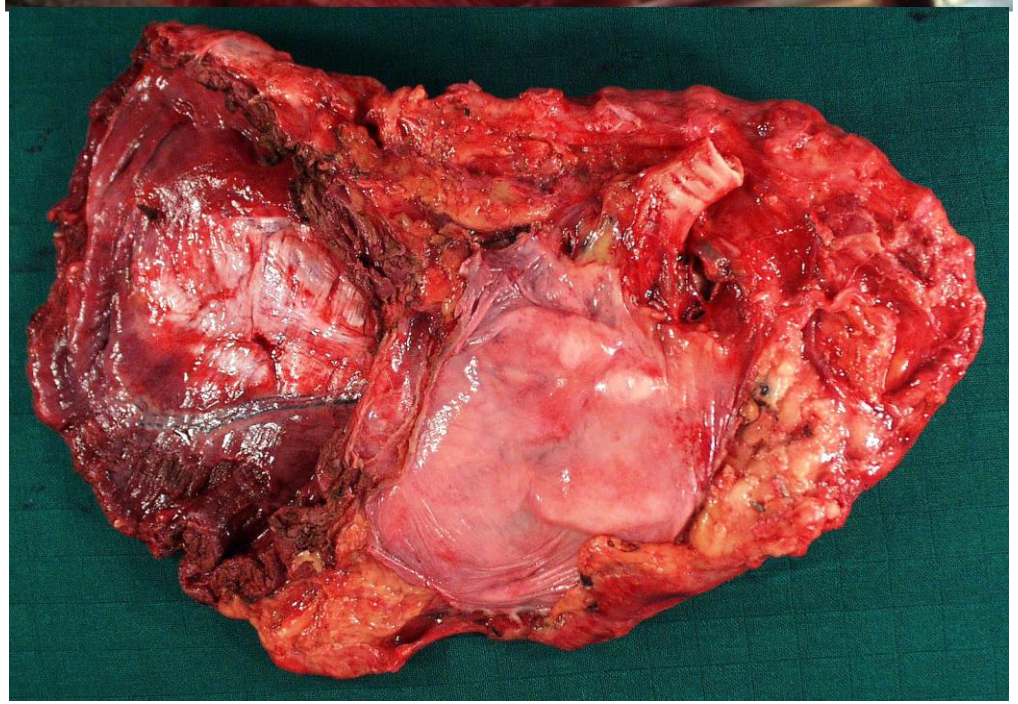
EPD





EPP





How do I choose between EPD and EPP?

- Goal: macroscopic complete resection (MCR)
- PD/EPD preferred if there is limited visceral pleural involvement
- Favor EPP preferred if there is :
  - Confluent visceral disease
  - Invasion into the lung parenchyma

Conversion from EPD to EPP with increased tumor thickness

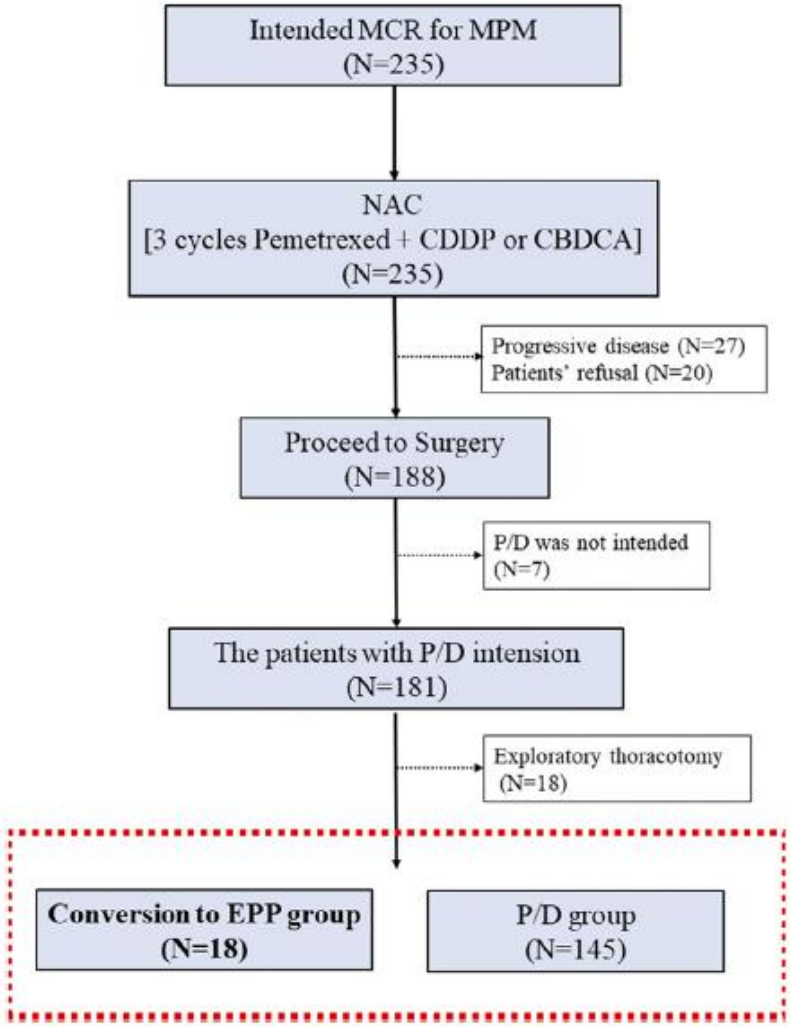


Table 4. Univariable Regression Analysis of Preoperative Factors for Conversion to EPP

Variable	Univariable	
	Odds Ratio (95% Confidence Interval)	*P* Value
Sex (male vs female)	0.8 (0.6–1.1)	0.3
Age (≥65 y vs <65 y)	1.0 (0.6–1.4)	1.0
Laterality (right vs left)	1.0 (0.6–1.5)	1.0
Pleurodesis history	0.6 (0.2–1.9)	0.6
FEV1 (<2000 mL vs ≥2000 mL)	1.5 (0.9–2.5)	0.3
FEV1% (<70% vs ≥70%)	1.2 (0.5–2.6)	1.0
SUVmax (≥5 vs <5)	1.8 (0.9–3.7)	0.3
Preoperative pleural thickness		
max (≥5.1 mm vs <5.1 mm)	1.9 (1.4–2.6)	0.006
sum (≥13 mm vs <13 mm)	2.5 (1.7–3.5)	<0.001
Clinical T stage (3 or 2 vs 1)	2.8 (1.8–4.4)	<0.001

EPP, extrapleural pneumonectomy; FEV1, force expiratory volume in 1 second; P/D, pleurectomy/decortication; SUVmax, standardized uptake value.

Nakamura, Hasegawa et al *Semin Thorac Cardiovasc Surg* 2021 Feb 18

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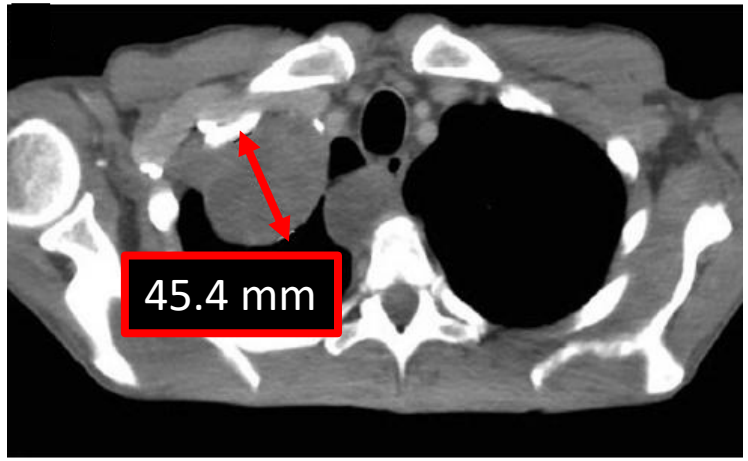
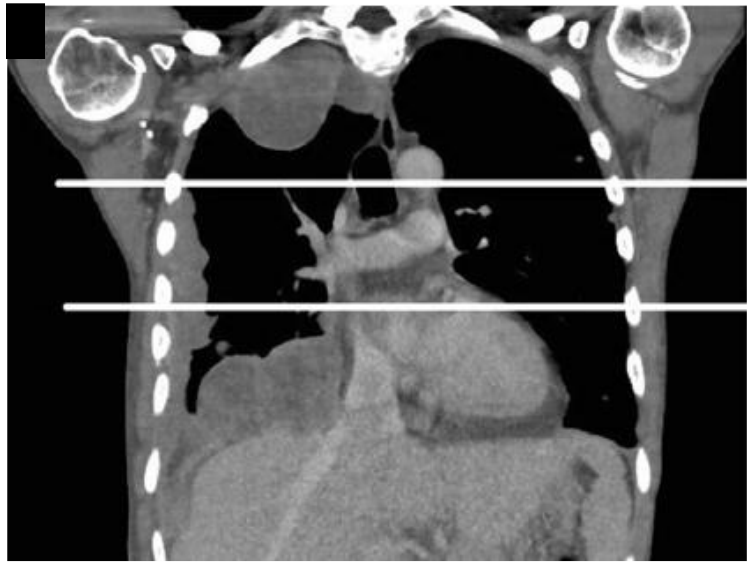
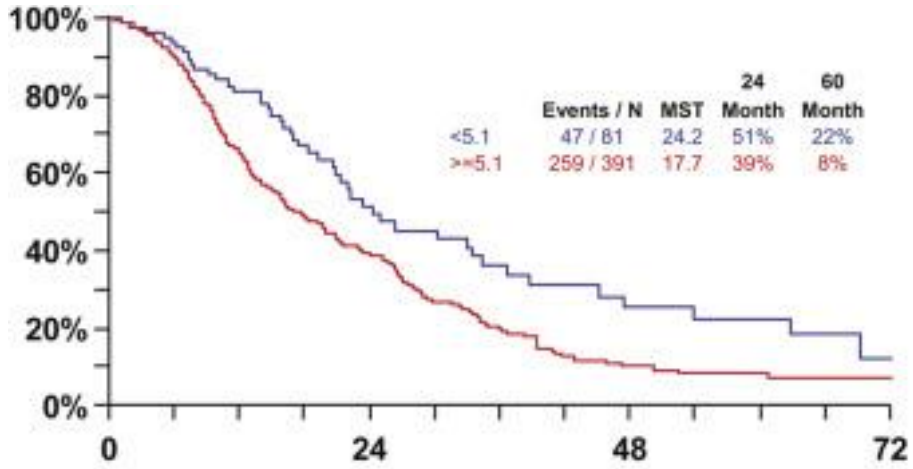
Tumor thickness (TT) is part of the new TNM staging classification to evaluate the T category

Tumor thickness

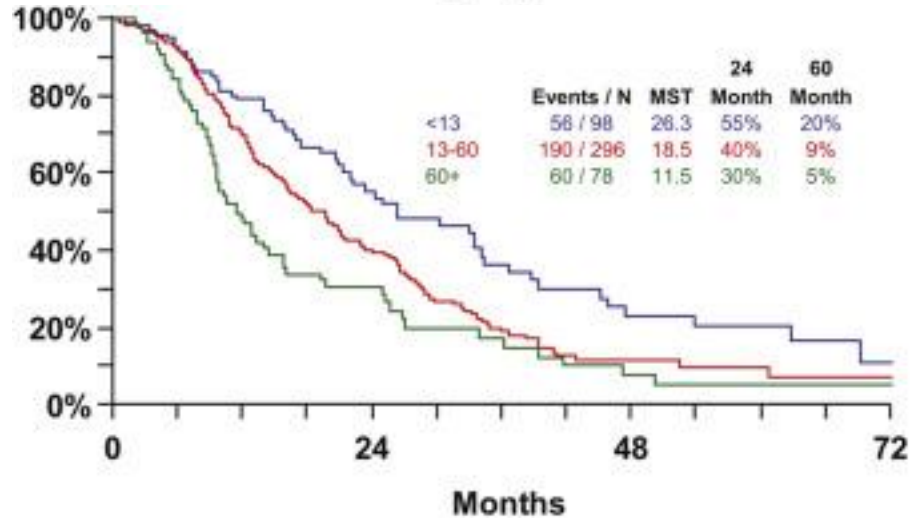


3 levels





Max TT
<5.1 mm



Sum of 3 TT
<13 mm

Novak et al J Thorac Oncol 2016;11:2089-99

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Surgery for mesothelioma: multimodal strategy

Trimodality approach (chemo-EPP-radiation)

Chemotherapy combined with EPD	EPD followed by Hemithoracic radiation	Hemithoracic radiation before surgery
MARS 2 trial **EORTC 1205 trial**	**IMPRINT trial** (Phase III ongoing)	**SMART trial** **SMARTER trial** **SMARTEST trial**

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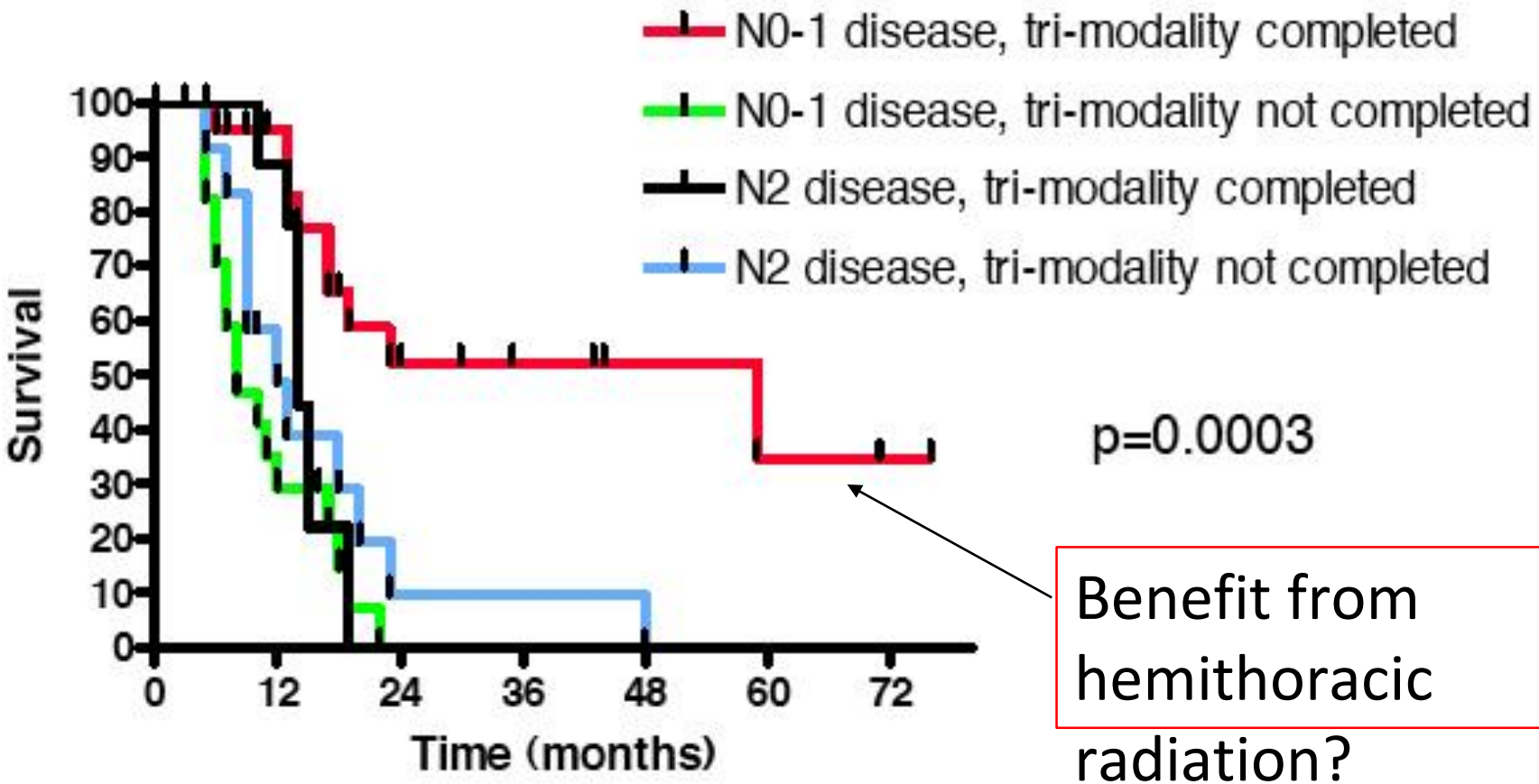
Toronto experience with trimodality therapy



Benefit from hemithoracic radiation?

de Perrot et al *J Clin Oncol* 2009;27:1413-8

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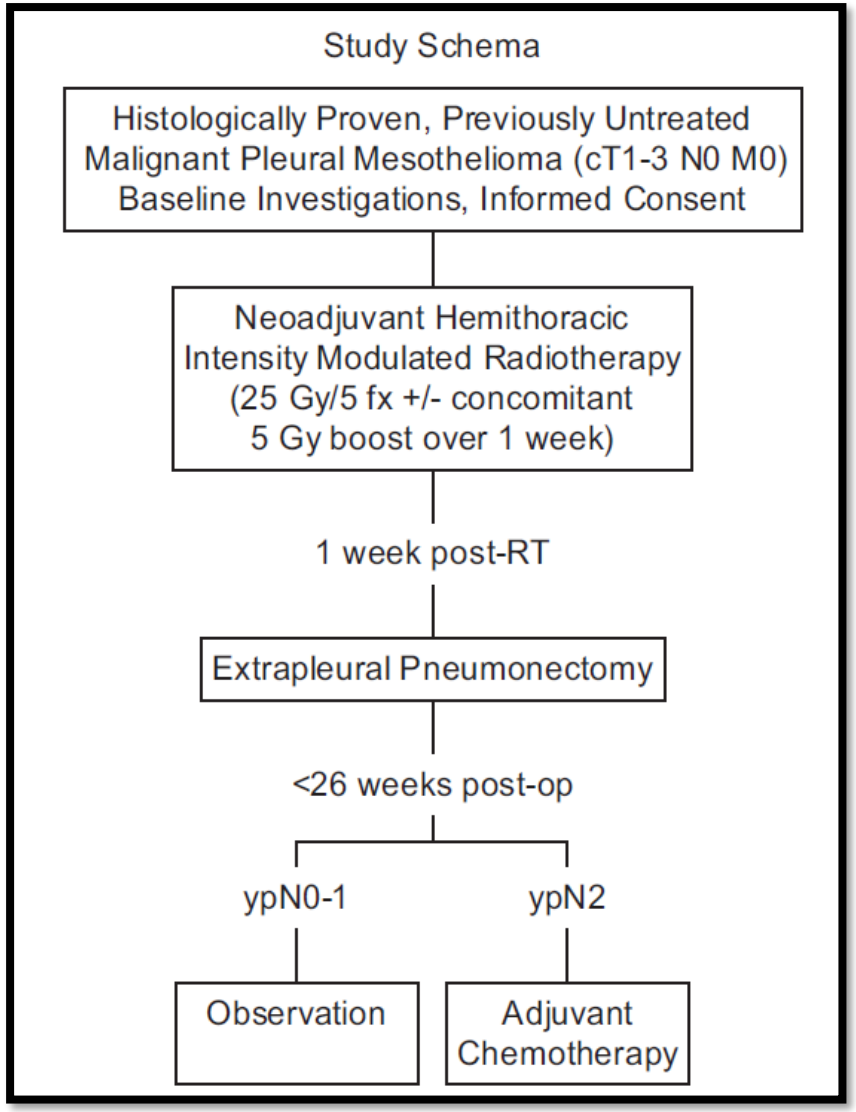
Designing the SMART approach – change of paradigm

Chemotherapy EPP Hemithoracic radiation	→	Hemithoracic radiation Surgery ± Systemic therapy

Rational:

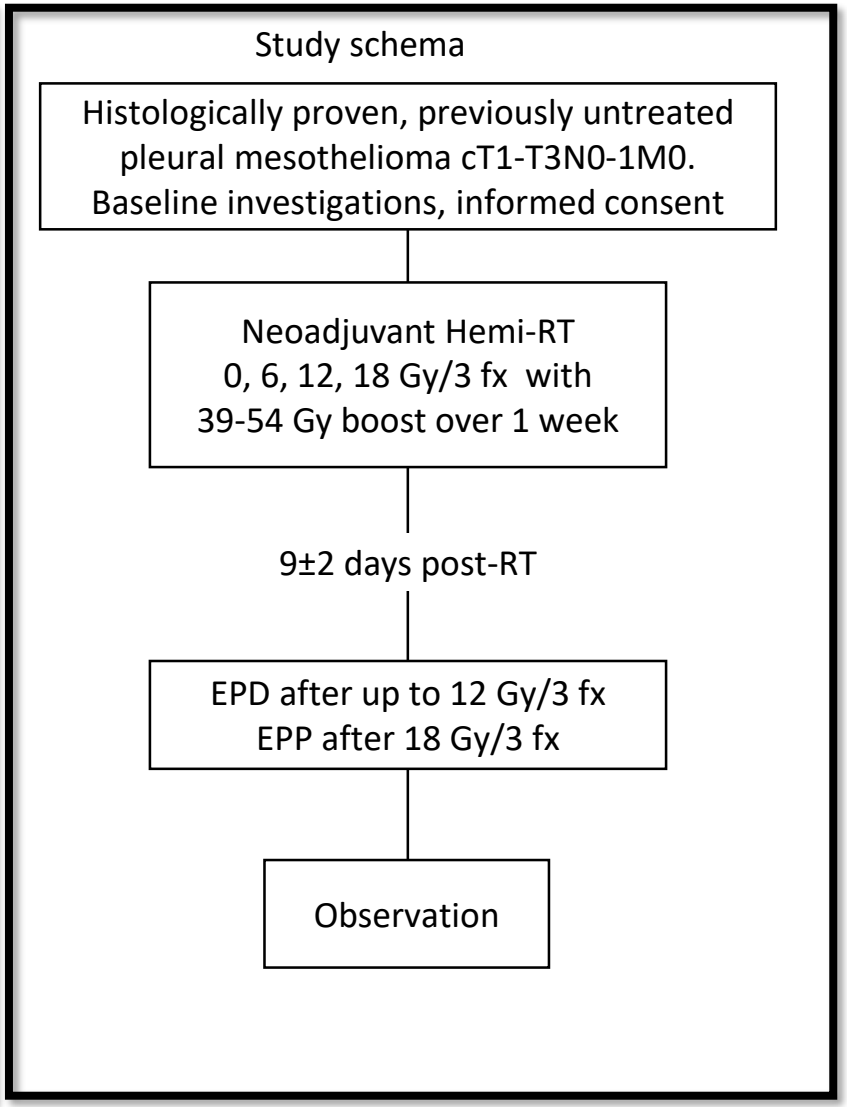
- Optimal delivery of radiation based on PET and CT findings
- Sterilization of the tumor before surgery with less risk of seeding
- Shorter treatment
- Potentially immunogenic

SMART trial



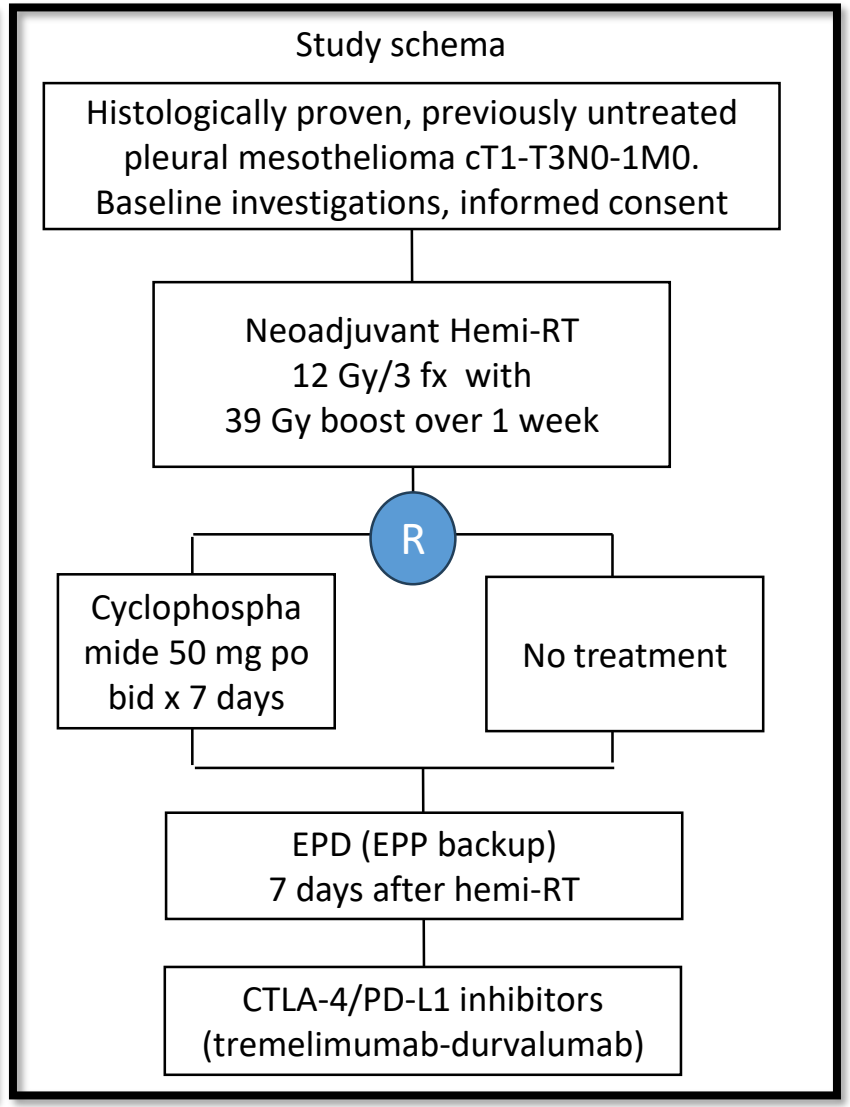
RT (25 Gy/5) → EPP (pneumonectomy)

SMARTER trial



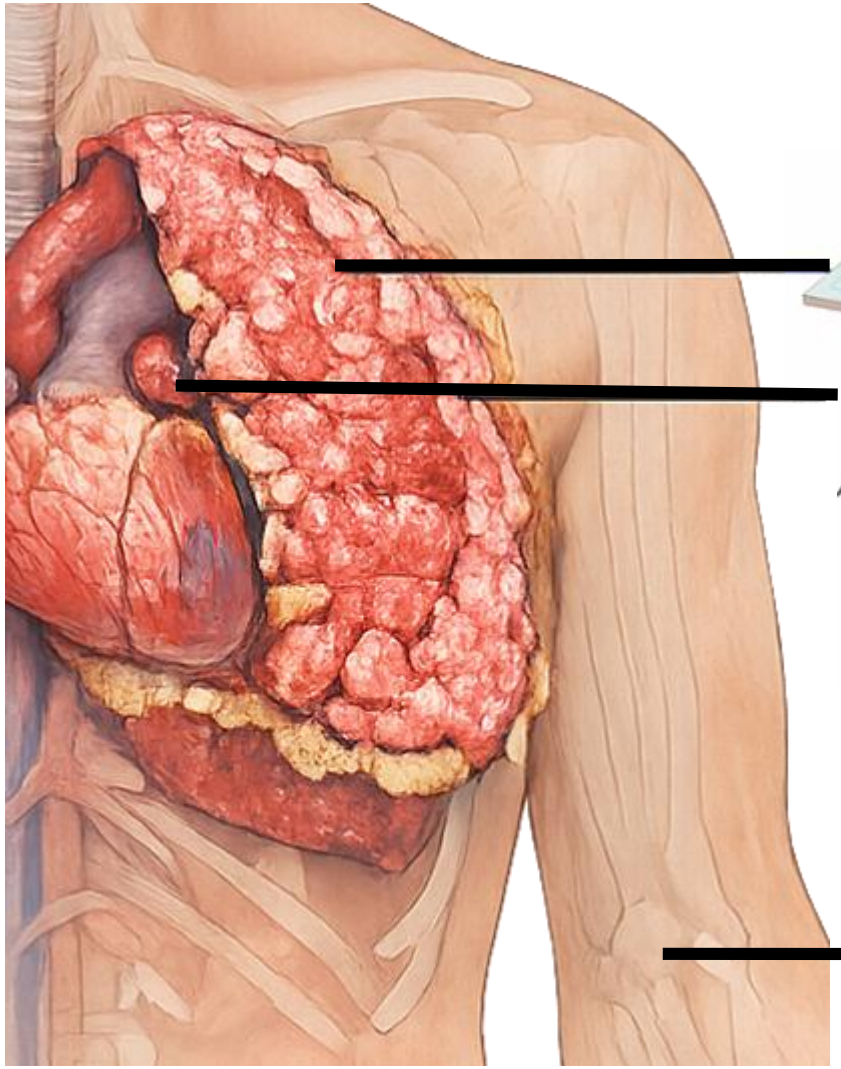
RT (12 Gy/3) → Lung-sparing surgery

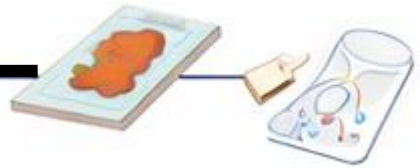
SMARTEST trial



RT → Surgery → immunotherapy

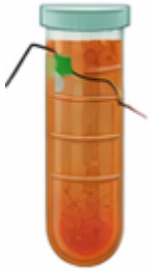
Translational Research: Moving Toward Personalized Therapy





Tumor (baseline, post-low/high dose RT)

- Single cell RNA sequencing
- RNA quantification (NanoString)
- Imaging mass cytometry
- CyTOF



Tumor draining lymph nodes (post-RT)

- Single cell RNA sequencing
- CyTOF



Blood (baseline, post-RT, follow-up)

- Luminex
- CyTOF
- Cap-TCR
- cell-free DNA

Pleural mesothelioma

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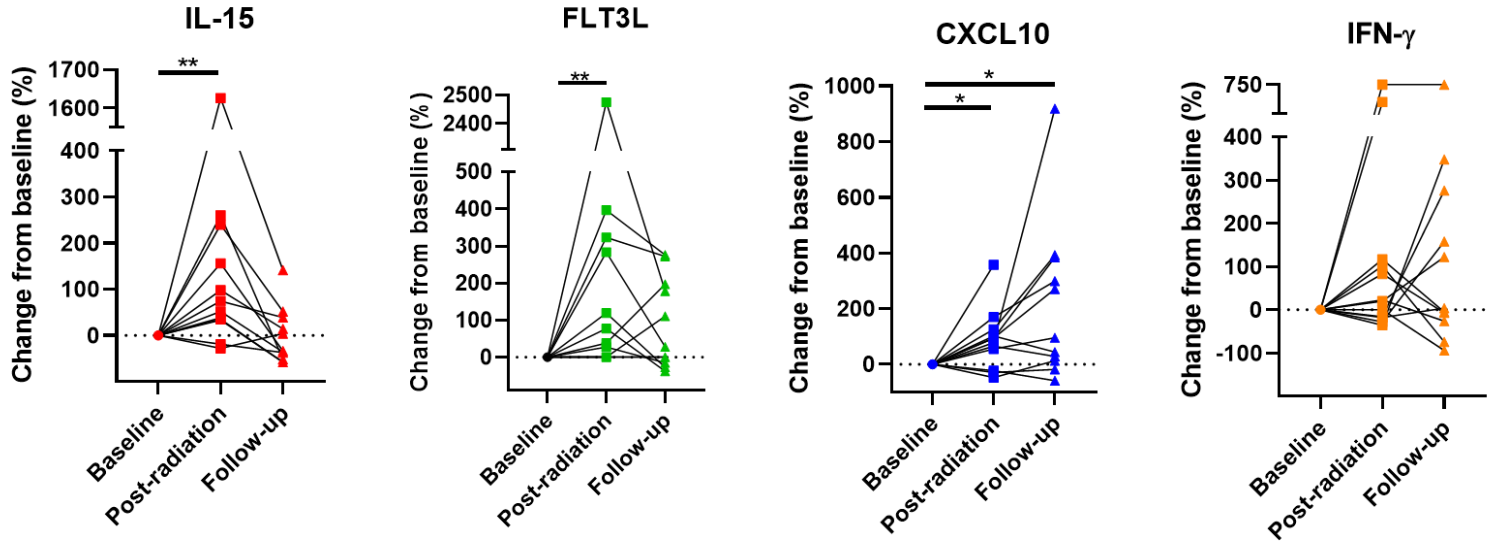
Systemic and intra-tumoral immune response to sub-ablative radiation in the SMARTER trial

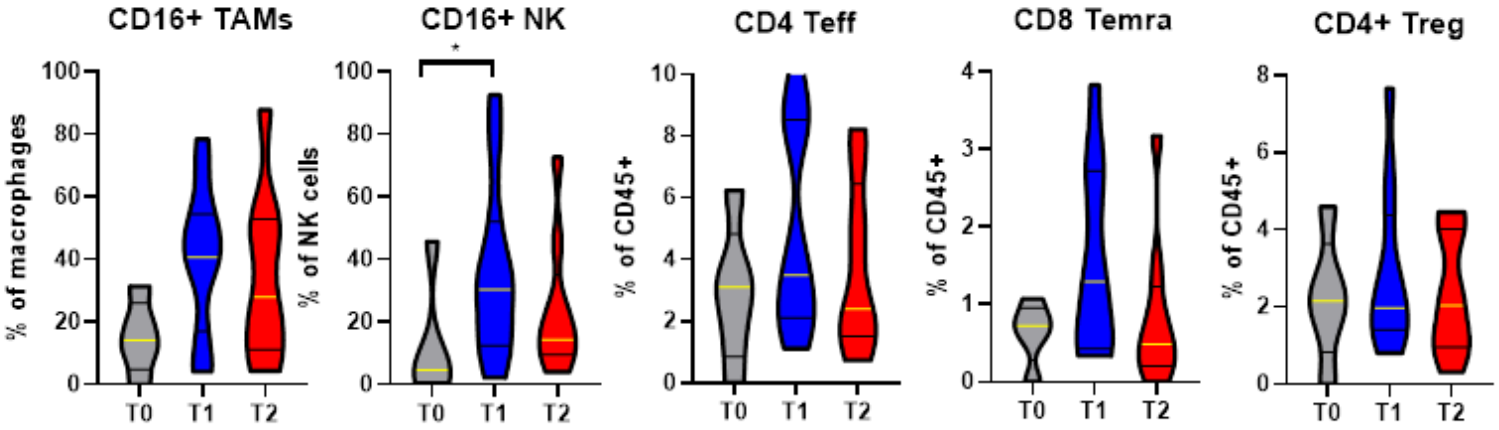
Systemic response

- Baseline
- Post-RT
- 6 weeks follow-up



Intra-tumoral response

- T0: baseline
- T1: sub-ablative RT
- T2: ablative RT



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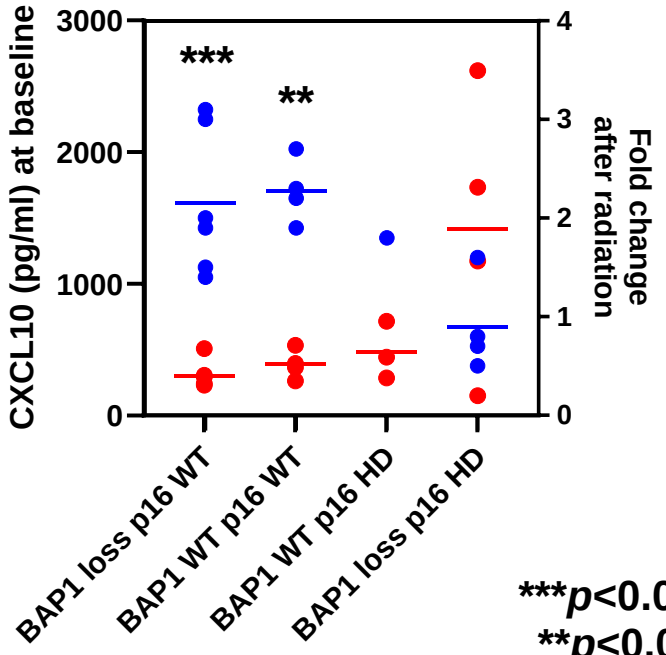
BAP1 loss p16 WT tumors respond to RT, whereas BAP1 loss p16HD tumors are immunogenic at baseline

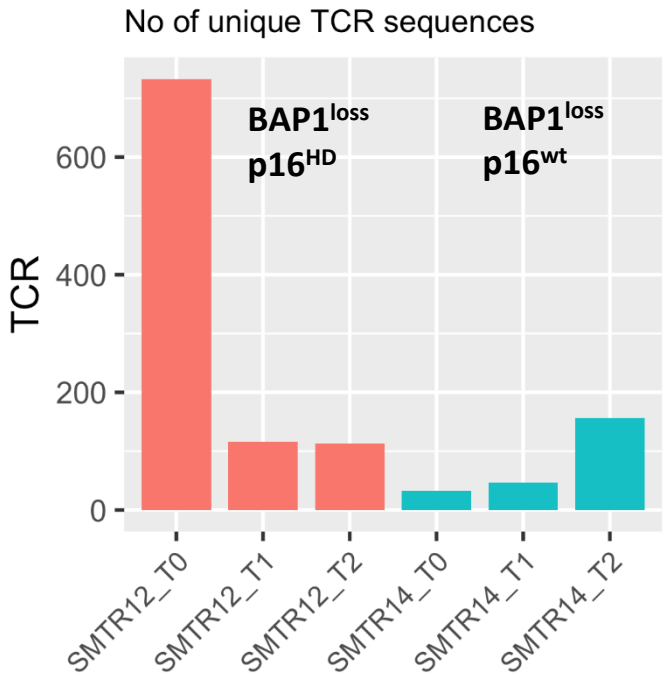
Circulating CXCL10

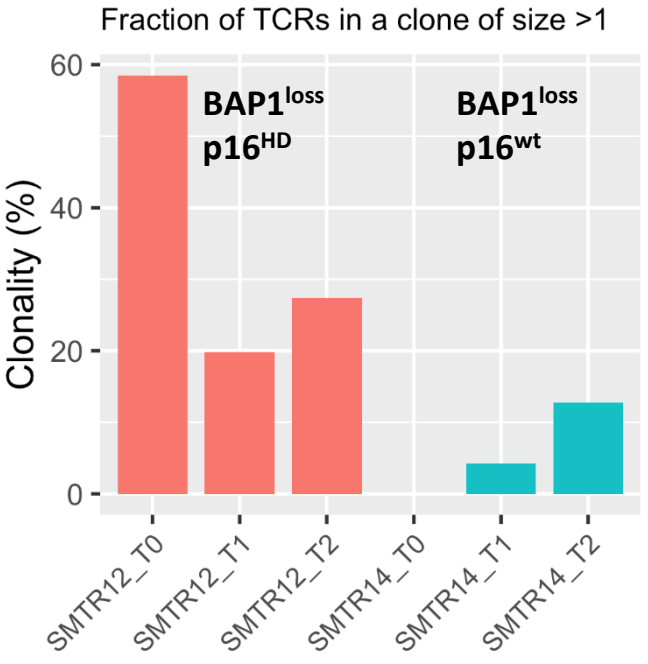


***p<0.001
**p<0.01

● Baseline level ● Fold change after radiation

T cell clonality in the tumor





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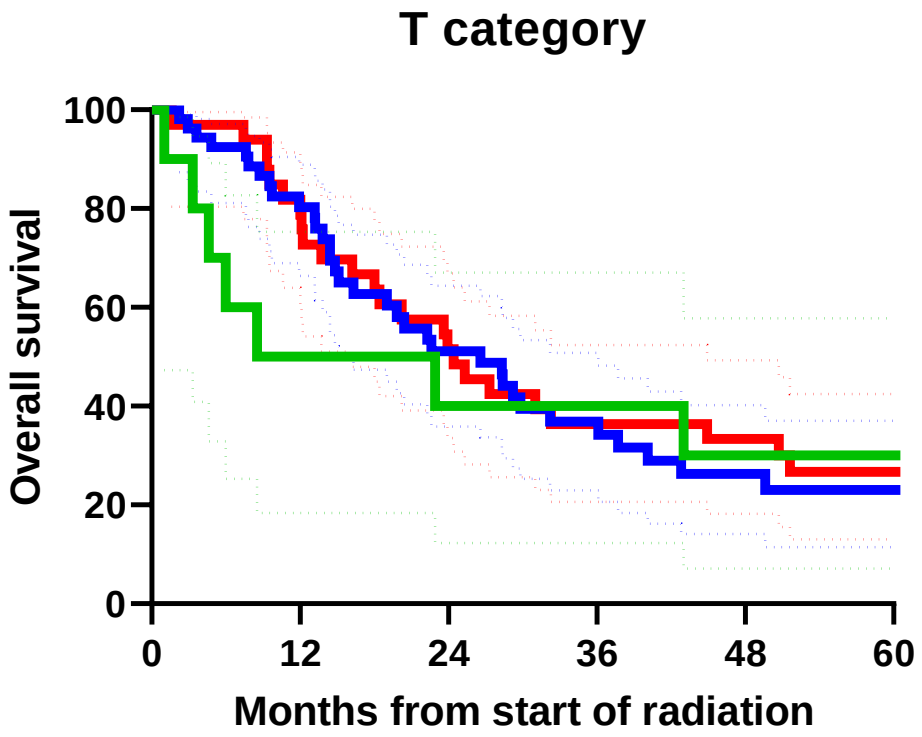
Surgery for malignant pleural mesothelioma after radiotherapy (SMART): final results from a single-centre, phase 2 trial

B C John Cho, Laura Donahoe, Penelope A Bradbury, Natasha Leighl, Shaf Keshavjee, Andrew Hope, Prodipto Pal, Michael Cabanero, Kasia Czarnecka, Karen McRae, Ming-Sound Tsao, Marc de Perrot

- 123 patients underwent SMART
- 96 patients completed SMART on study
- 27 performed off-protocol
- All patients had IMRT and EPP as planned
- 30-day mortality of 1% and 90-day mortality of 3.1%
- No radiation pneumonitis

Cho, de Perrot et al. *Lancet Oncol.* 2021;22:190-197

SMART trial – Overall survival based on T category



*yp*T1-T2
*yp*T3
*yp*T4

Median OS
*yp*T1-T2 : 15.7 months
*yp*T3 : 26.6 months
*yp*T4 : 24.4 months

p=0.9

Number at risk (number censored)

*yp*T1-T2	10 (0)	6 (0)	4 (0)	4 (0)	3 (1)	2 (2)
*yp*T3	53 (0)	37 (6)	22 (2)	14 (2)	9 (1)	6 (2)
*yp*T4	33 (0)	27 (0)	17 (0)	12 (0)	10 (1)	6 (2)

Cho, de Perrot et al. *Lancet Oncol.* 2021;22:190-197

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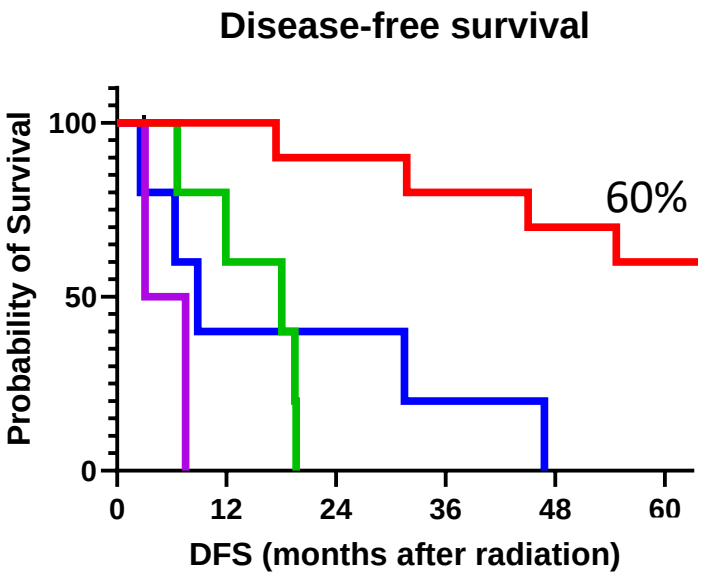
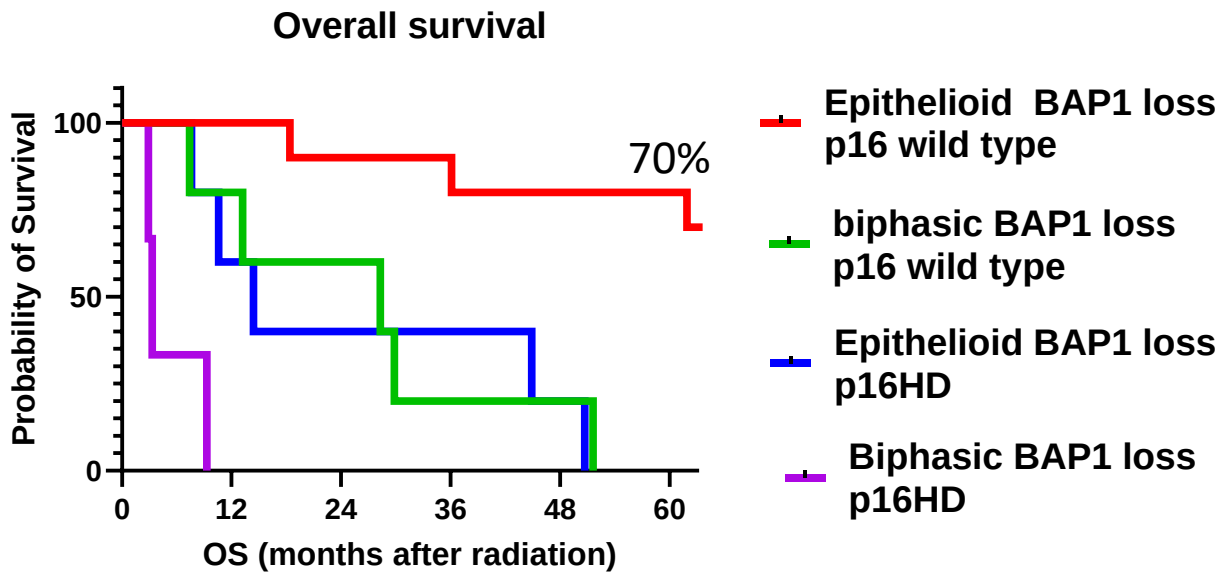
Survival by histology and genetic alterations



p=0.0002



p<0.0001

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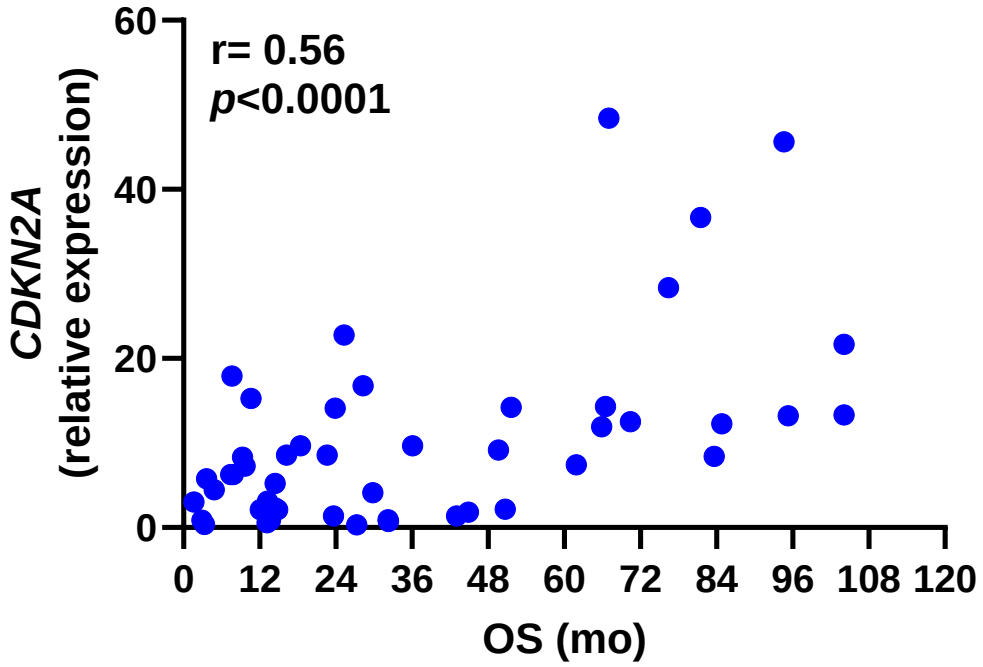
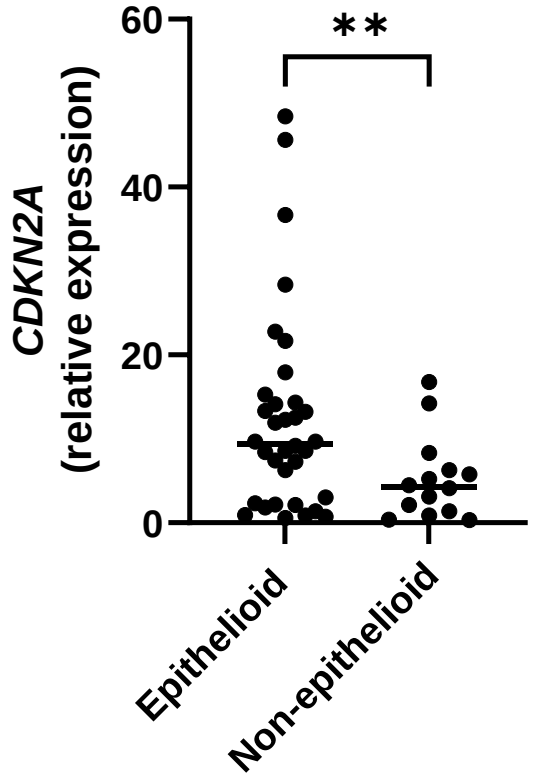
Importance of CDKN2A (p16) on survival





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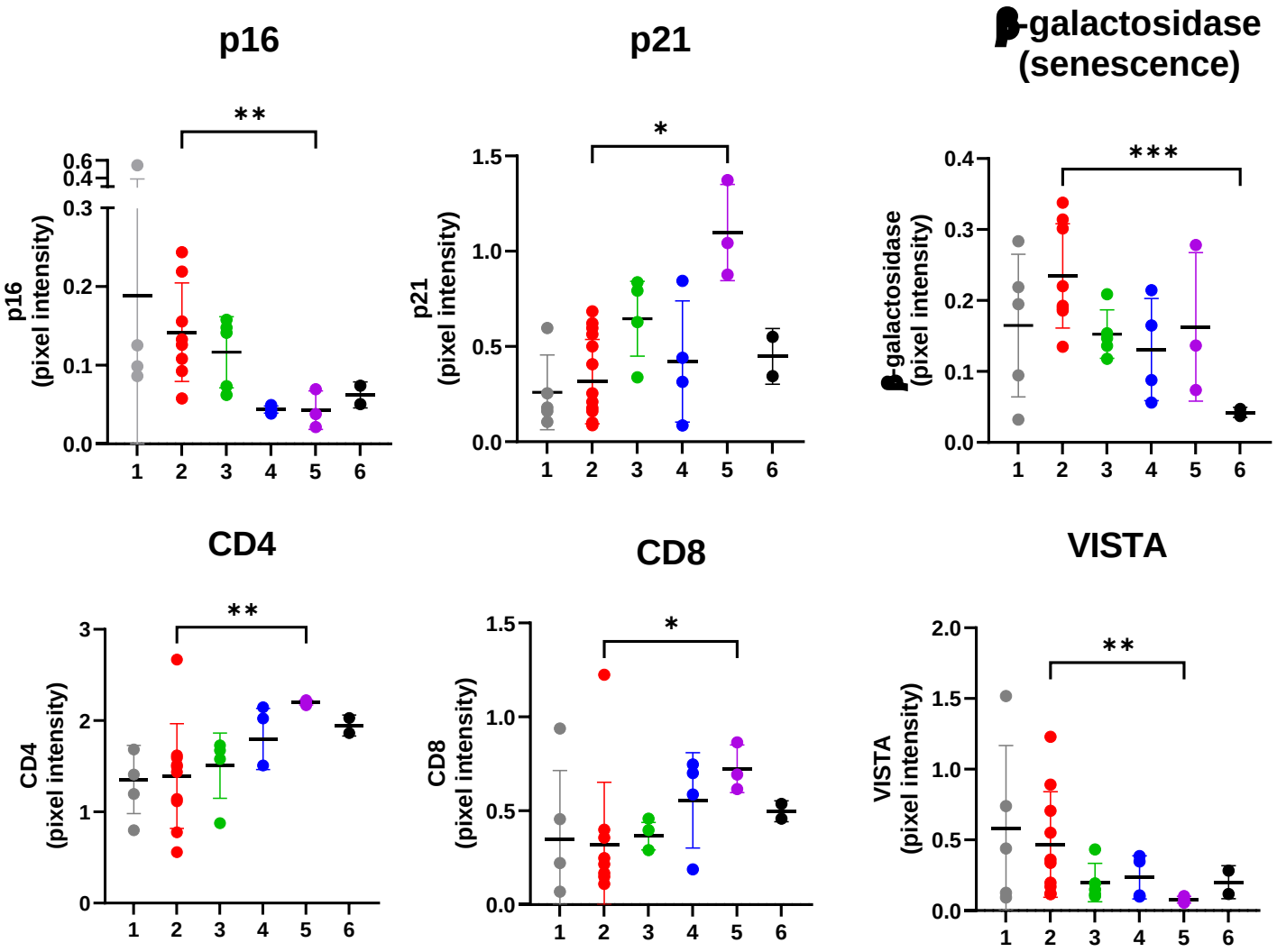
Survival by histology and genetic alterations



1. Epith BAP1 WT p16 WT
2. Epith BAP1 loss p16 WT
3. Biphasic BAP1 loss p16 WT
4. Epith BAP1 loss p16HD
5. Biphasic BAP1 loss p16HD
6. Biphasic BAP1 WT p16HD

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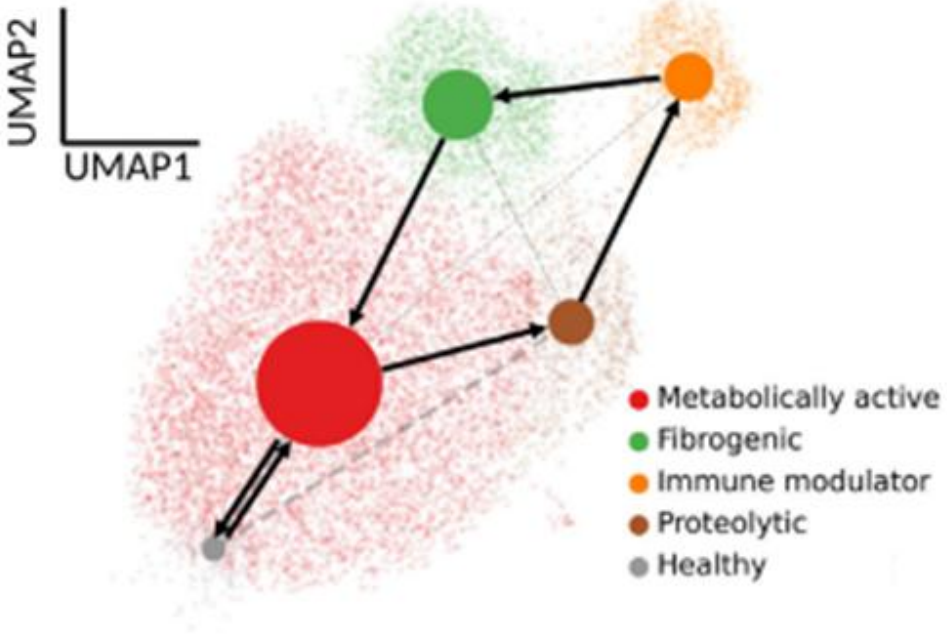
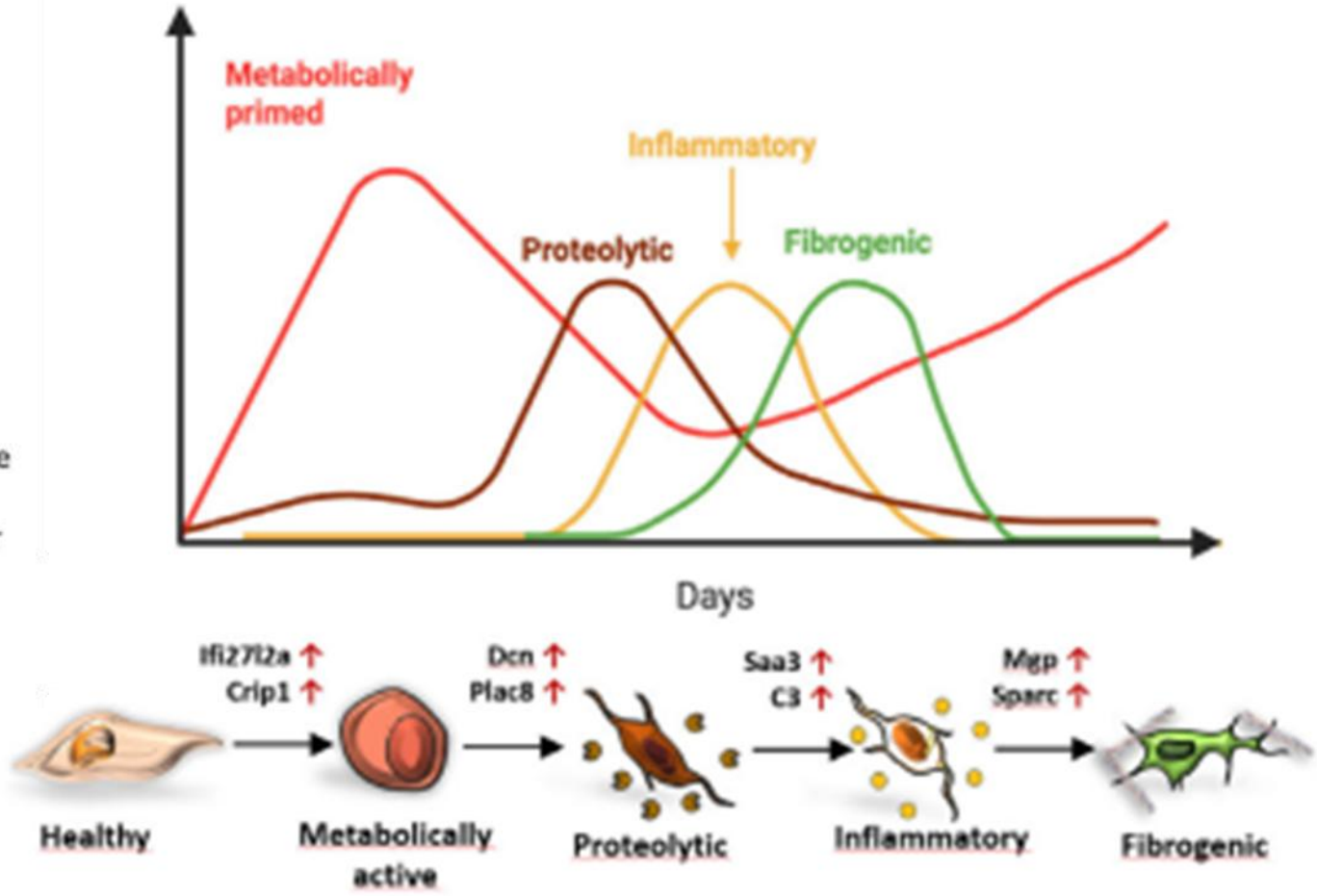
Mesothelial cells are physiogically important for tissue repair



Single cell analysis
mouse model, 11952 cells



Tumors evolve within a constrained biological program related to tissue repair

Kadri et al. Nat Commun. 2025 Sep 16;16:8295.

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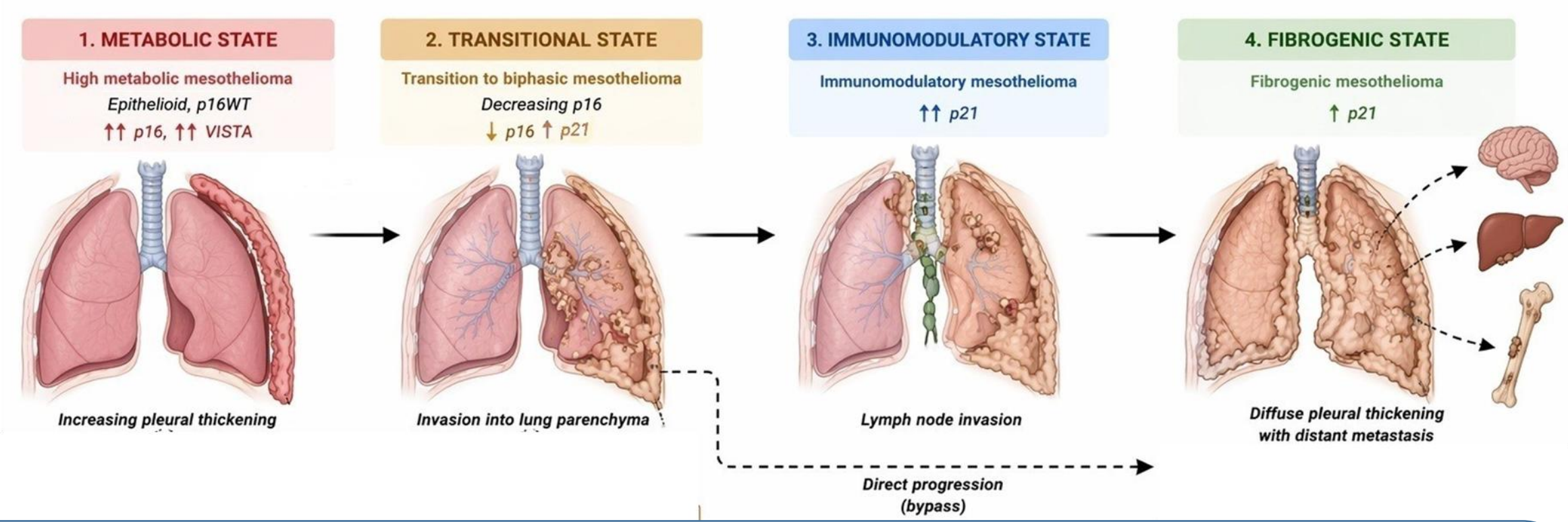
Mesothelioma as a dysregulated repair process shaped by genetics



Biological stage	Stage I (localized)	Stage II (mobile)	Stage III (nodal extension)	Stage IV (proliferative)
Gene profile	Epithelioid BAP loss p16 WT	Non-epithelioid p16 WT	Non-epithelioid BAP1 loss p16HD	Non-epithelioid BAP1 WT p16HD
Potential treatment	RT-Surgery	RT-ICB-Surgery?	Dual ICB	RT-Dual ICB-Vaccine?

Conclusions

- Immunotherapy (ipi–nivo) is standard-of-care for non-surgical patients, with greatest benefit in non-epithelioid mesothelioma
- Surgery remains a key component of multimodality therapy in carefully selected, resectable patients, ideally in experienced centres and within clinical trials
- Histology and biomarkers (BAP1, p16) can guide selection between systemic vs locoregional strategies
- SMART (25 Gy/EPP) and SMARTER (12 Gy/EPD) are most beneficial in p16 WT tumors and can provide a platform to integrate immunotherapy in transitional tumor state
- Future progress will depend on a more personalized approach and should integrate radiation, immunotherapy, and surgery to address tumor heterogeneity

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Mesothelioma Applied® Research Foundation
research - education - support - advocacy

CMF Canadian Mesothelioma Foundation

OICR Ontario Institute for Cancer Research

FNSNF Swiss National Science Foundation

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