GECP lung cancer research

16th CONGRESS Lung ON CANCER

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Systemic treatment in Mesothelioma

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GENERALITAT VALENCIANA

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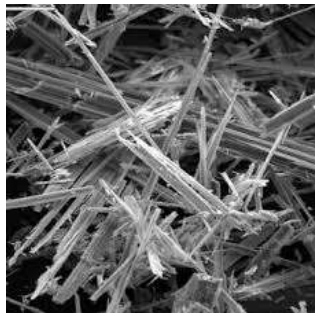
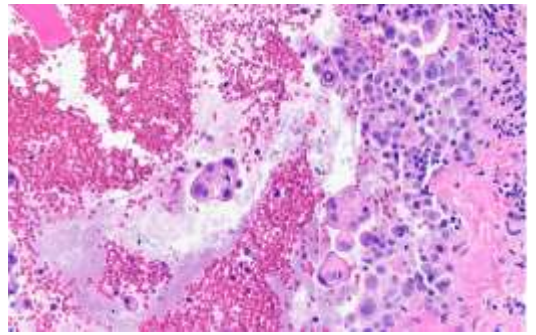
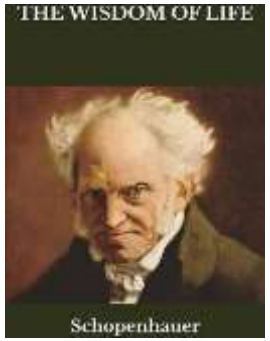
GECP
lung cancer research

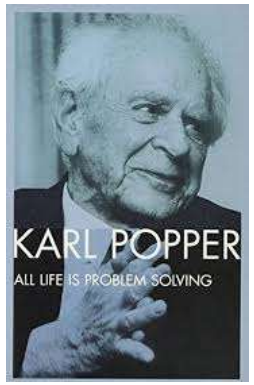
Pleural Mesothelioma: Is it possible to avoid the fate?





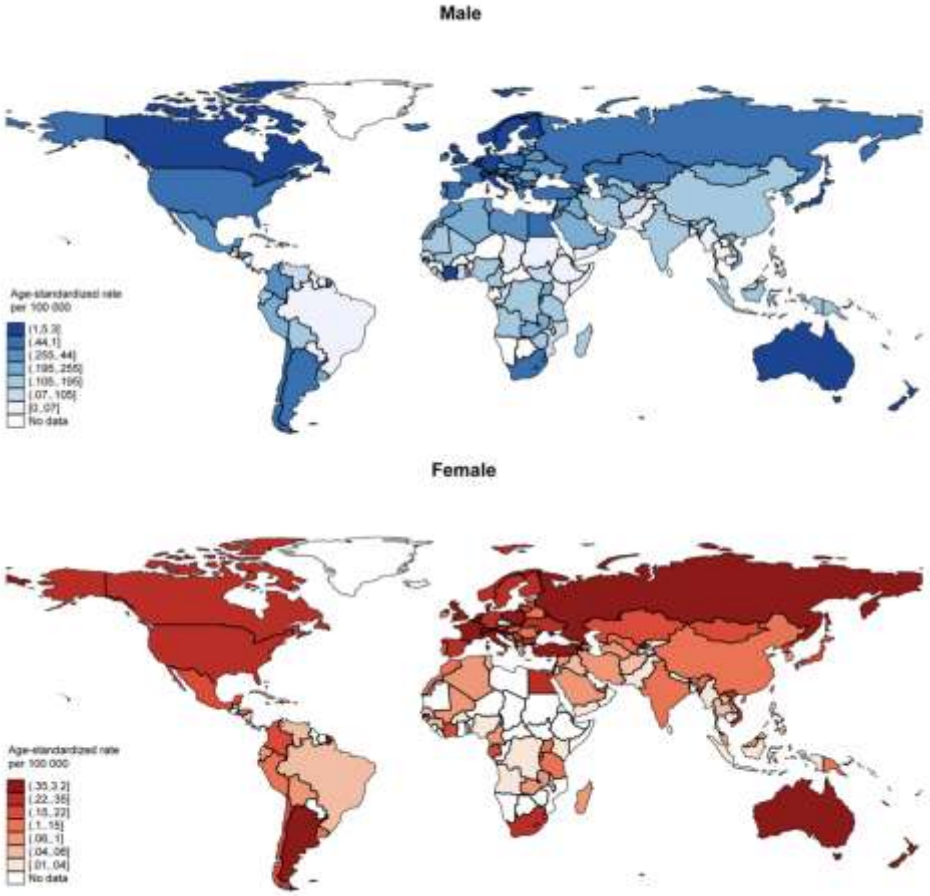


Fate is the one that shuffles the cards, but we are the ones we play



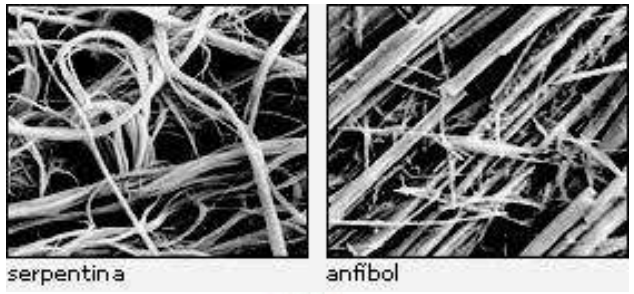
Learning embodies the same process as problem-solving

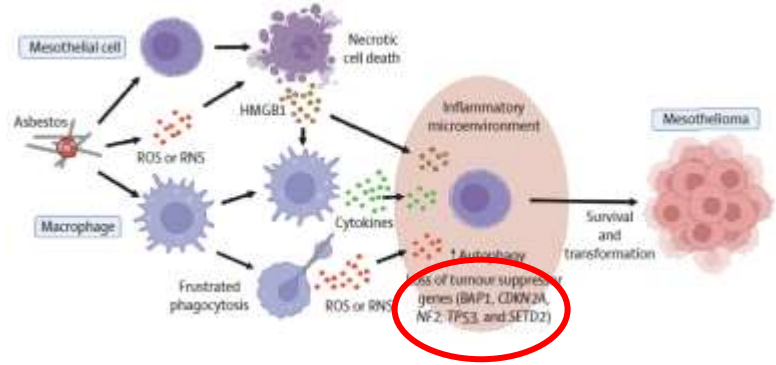
MPM: mainly an occupational disease

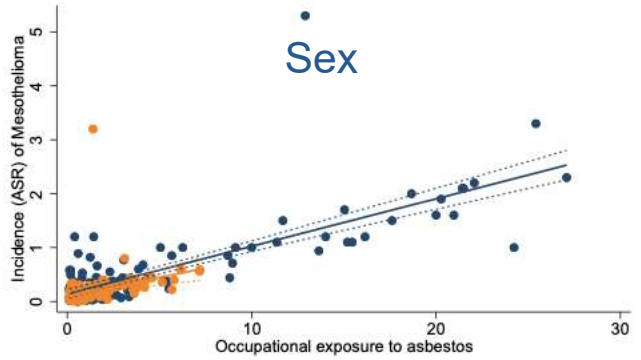


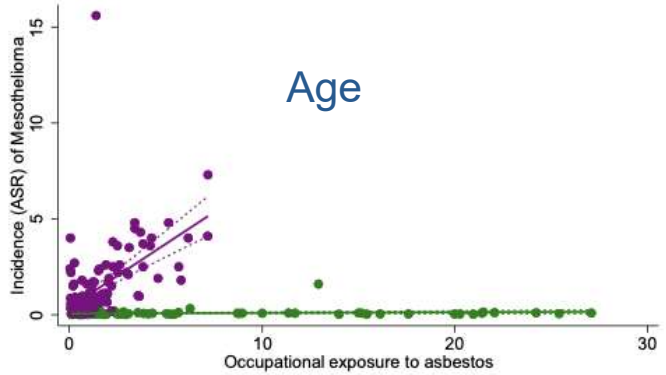
- TTR GECP 2021:
  159 patients (0.87%)
- Spain 264 death/year

91.7% deaths related to asbesto exposure









Overall incidence rate: 0.30/100.000
0.46 Males / 0.17 Females
Mean age diagnosis 75 y
(1 in > 50 years / 0.06 in < 50 years

Huang J et al: JTO 2023;18:792-203; Remon J et al Lung Cancer 147 (2020) 83-90; van Zandwijk et al Lancet Oncol 2022; Aug 30

Class I WHO carcinogen

Exposure:

- occupational
- residential
- environmental

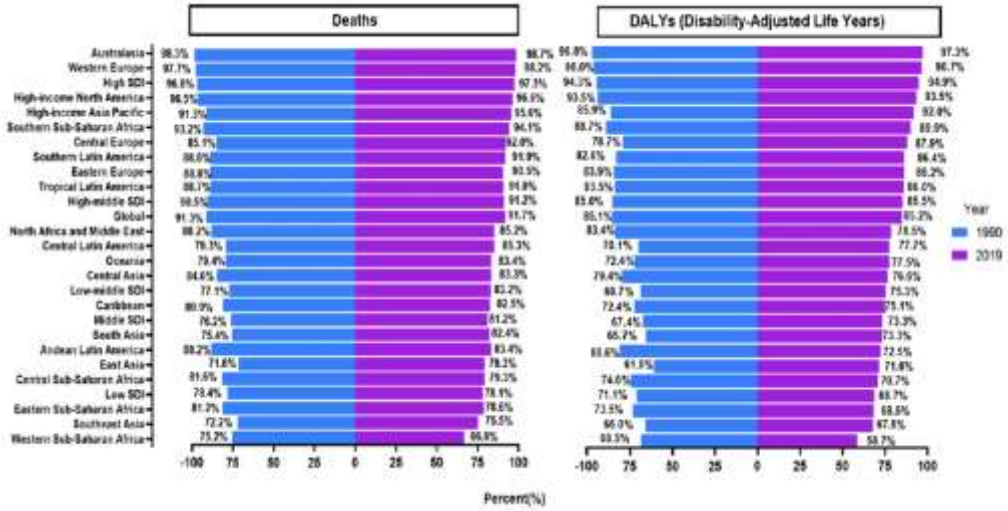
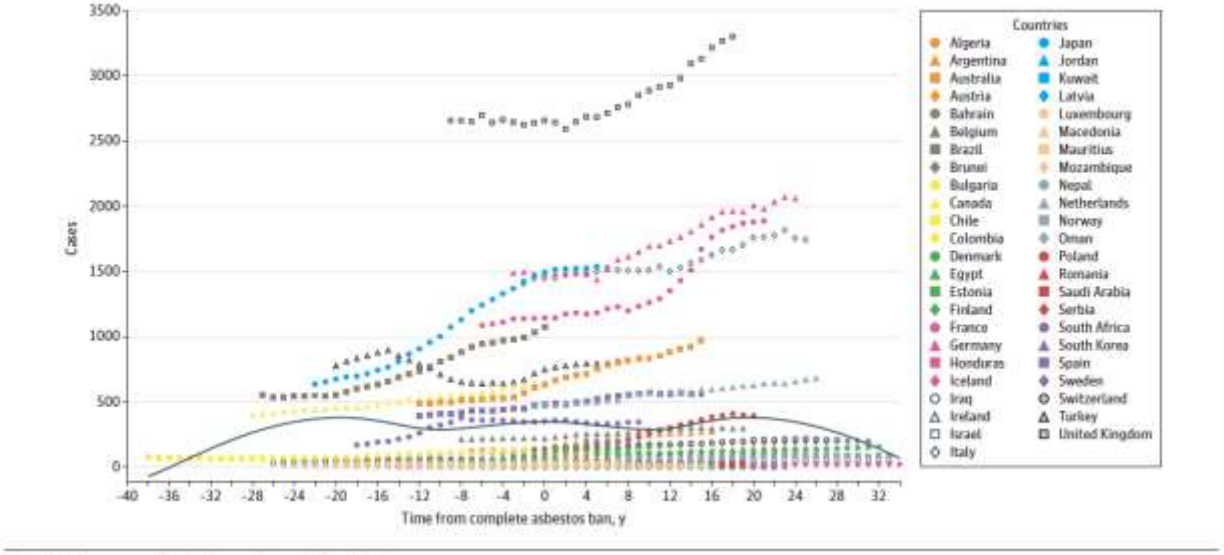
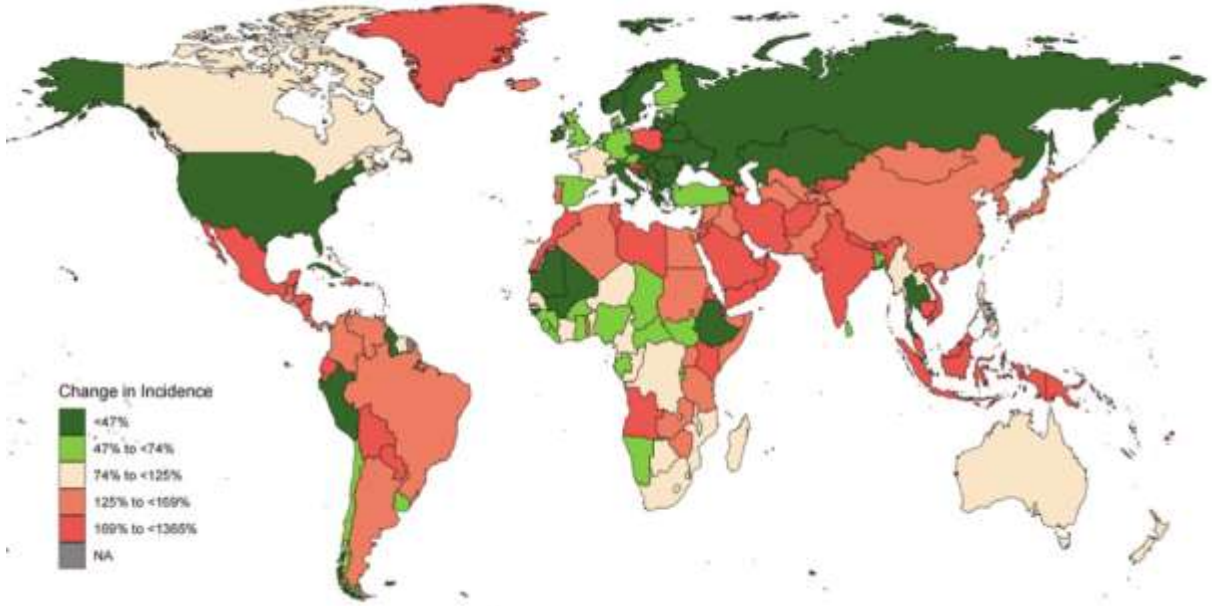


Figure 2. Temporal Trends in Mesothelioma Cases Among 47 Countries With Complete Asbestos Bans

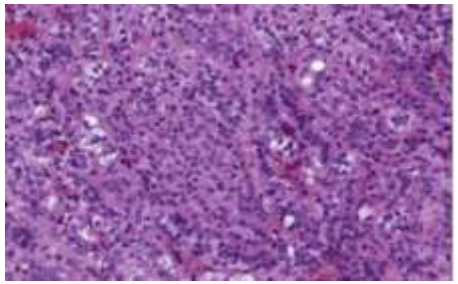


The solid blue curve reflects the overall trend of incident cases.

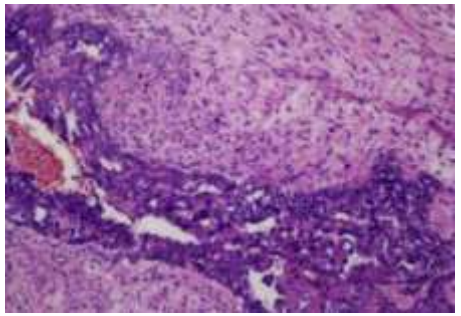


Huang J et al: JTO 2023;18:792-203; Zhai Z et al: JAMA Network Open. 2021;4(8):e2120360.
Chen Z et al: Journal of Cancer Research and Clinical Oncology (2024) 150:282

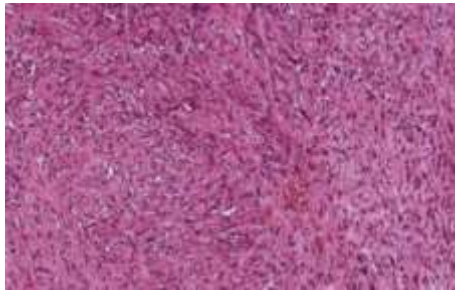
Biology of MPM



Epitelioid
50-70%

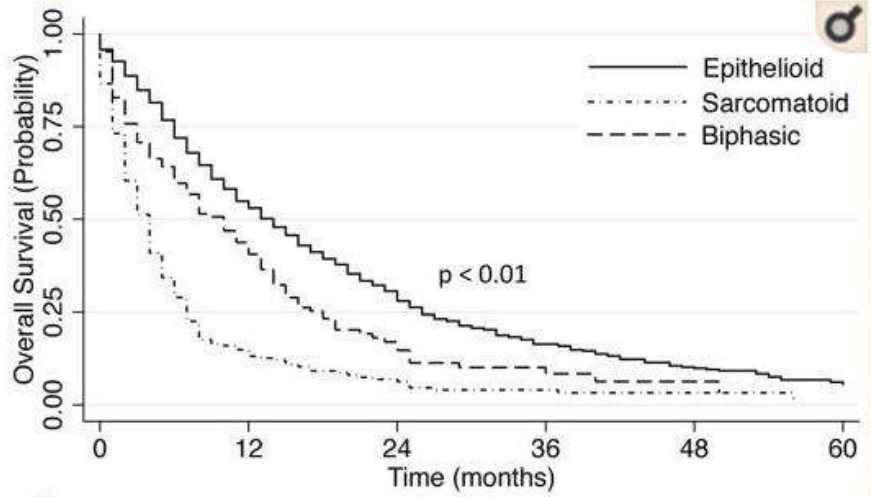


Biphasic
20-35%

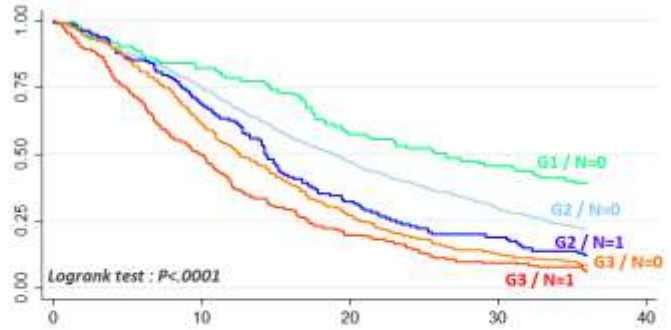


Sarcomatoid
10-20%

Diffuse malignant mesothelioma	
Epithelioid mesothelioma	Composed of rounded rather than spindle-shaped cells usually showing a cohesive architecture, although epithelioid cells can show single cell growth within fibrous stroma.
Sarcomatoid mesothelioma, including desmoplastic variant	Composed of spindle-shaped (greater than two times longer than wide). The spindle cells may lie in varying amounts of fibrous stroma, or they can form solid sheets.
Biphasic mesothelioma	Showing at least 10% of both epithelioid and sarcomatoid morphology. This rule is limited to definitive resections, namely, extended EPD and EPP. For smaller samples, until more data are collected, the group proposes that the diagnosis of "biphasic" can be rendered regardless of the percentages of each component present and that the diagnosis should be accompanied by a comment indicating the percentages of each component.
Well-differentiated papillary mesothelioma	A rare localized mesothelial neoplasm characterized by an exophytic papillary architecture lined by relatively bland mesothelium with no or only minimal areas of invasion. Diagnosis requires exclusion of diffuse malignant mesothelioma with papillary architecture.



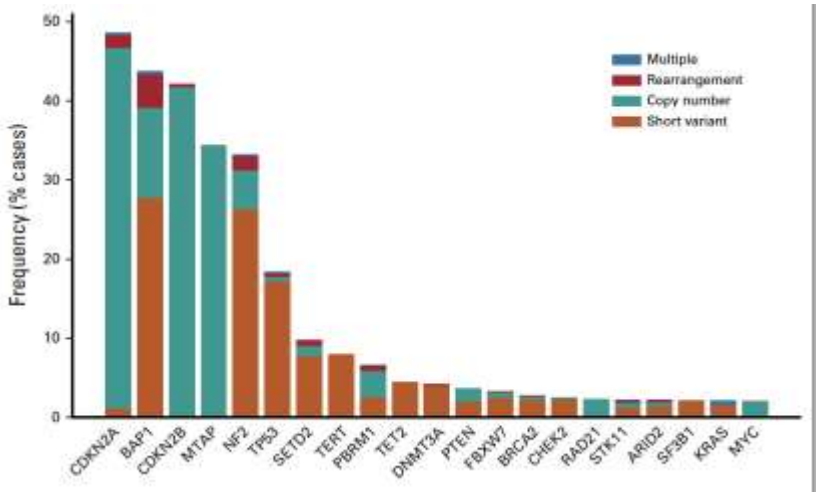
Number at risk						
Epithelioid	811	381	172	66	32	10
Sarcomatoid	224	26	12	5	3	1
Biphasic	148	55	15	6	2	1

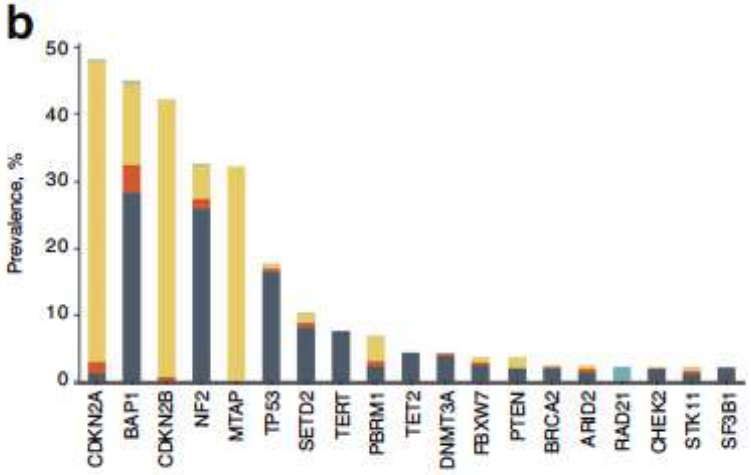


Grade / Necrosis	N	Median	1 yr-surv [95%CI]	2yr-surv [95%CI]	3yr-surv [95%CI]
G1 / N=0	115	26 mos	78% [70;85]	52% [42;61]	39% [30;48]
G2 / N=0	1079	19 mos	68% [65;71]	39% [36;42]	22% [19;25]
G2 / N=1	156	14 mos	62% [54;69]	23% [16;30]	12% [7;18]
G3 / N=0	316	12 mos	53% [47;58]	19% [15;24]	9% [5;12]
G3 / N=1	244	10 mos	39% [33;45]	14% [10;19]	6% [3;10]

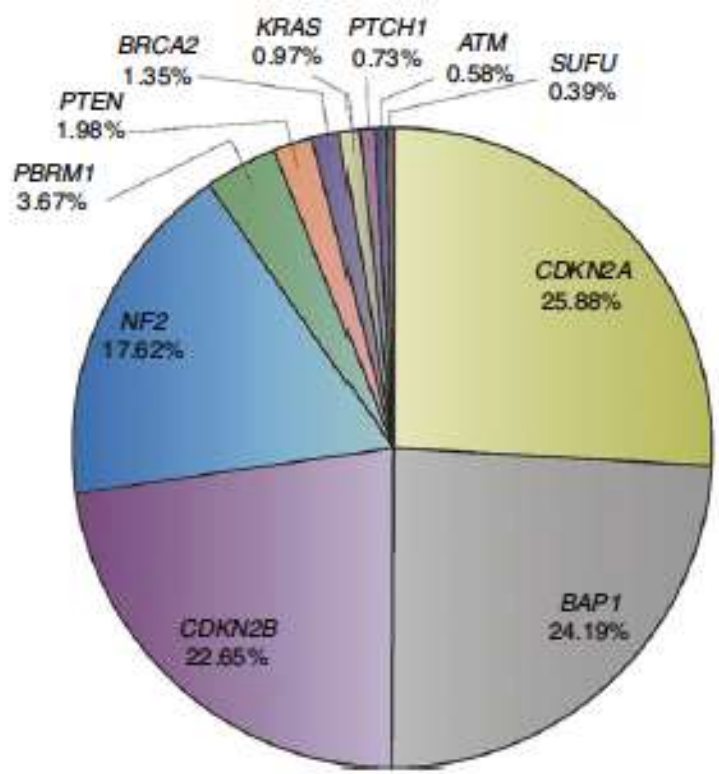
DD Adenoca BP: CK 5/6 (+) , calretinin (+) , WT-1 (+) TTF-1 (-)

Nicholson AG et al. JTO 2019;15:29-49; Galateau F et al JTO 2018;13:1189-1203; MESOPATH.





- Inactivating mutations
  - CDKN2A (49%),
  - BAP1 (44%),
  - CDKN2B (42%),
  - MTAP (34%),
  - NF2 (33%).
- BAP1 3p21 early clonal event
  - mutations
  - gene copy number variations
- BAP1 mutations germline and somátics
- CDKN, NF2 and MTAP alterations more frequent in sarcomatoid



Dagogo-Jack I et al. J Clin Oncol Precis Oncol 6:e2100422; Hithbrunner S et al: British Journal of Cancer (2022) 127:1997–2005

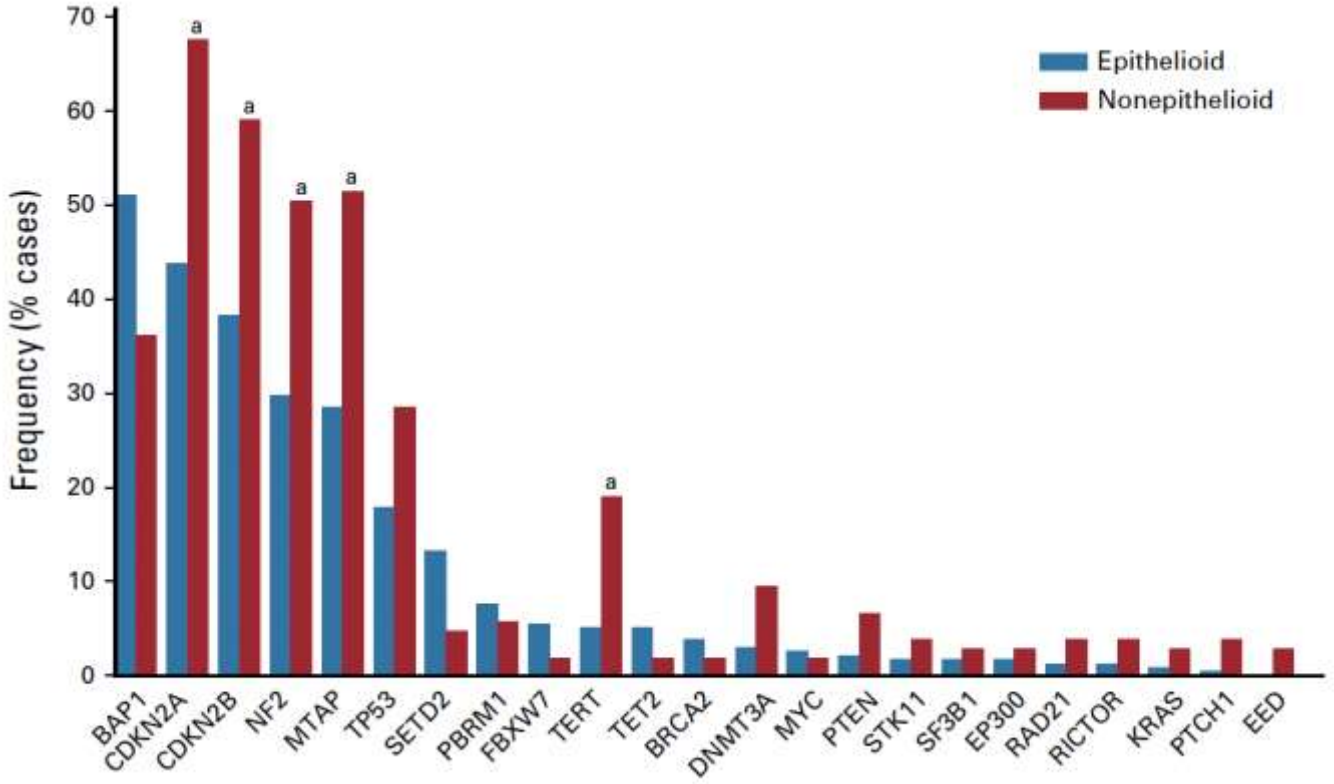


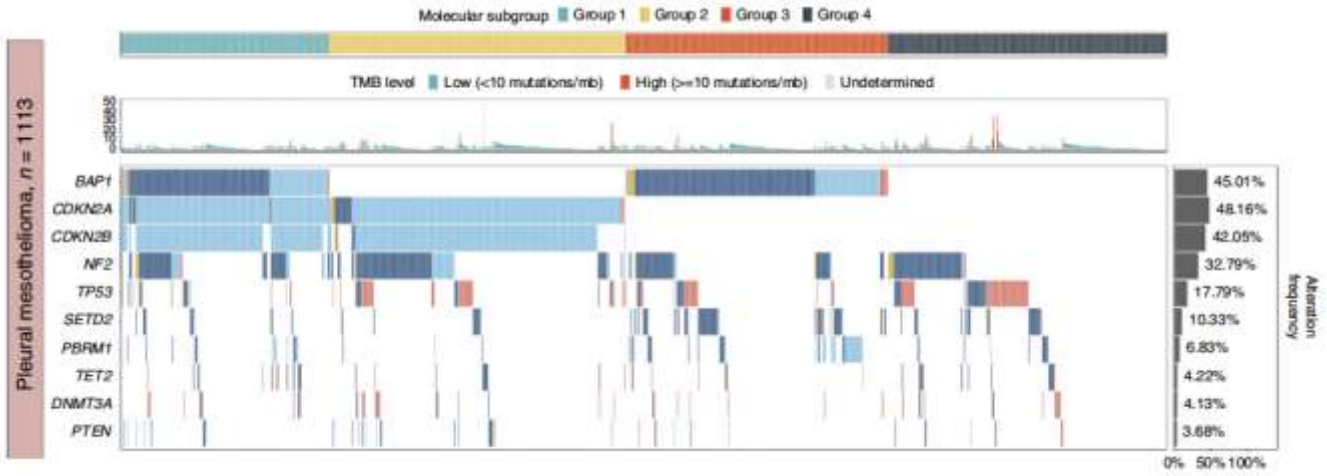
Table 1. Prevalence of Select Genetic Alterations in Mesothelioma of Different Histotypes

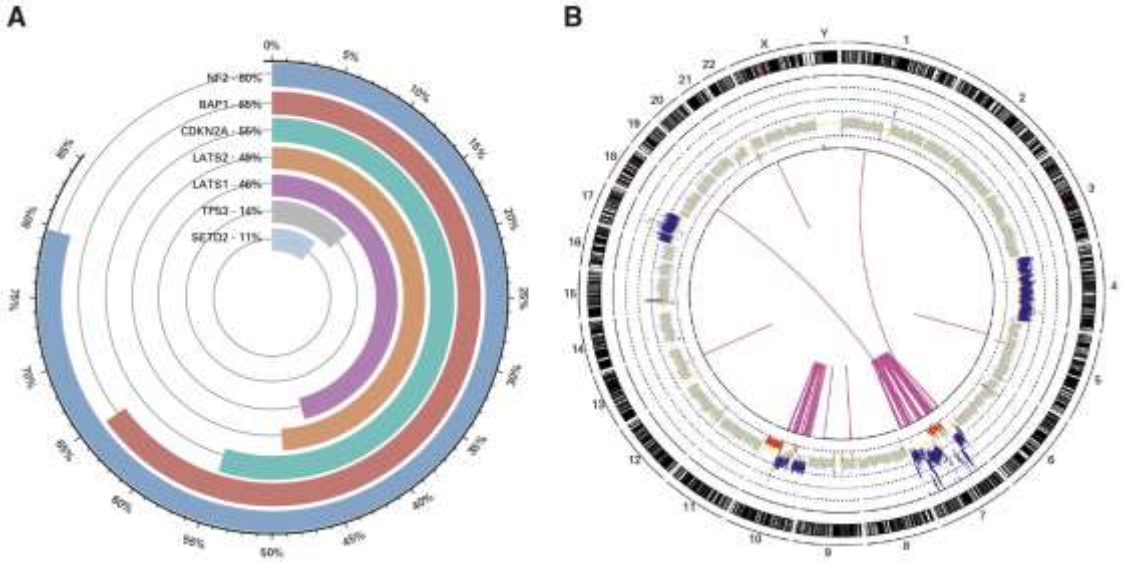
	BAP1, %	*CDKN2A*, %	*MTAP*, %	*NF2*, %
Overall[18,19,21]	44–53	25–49	27–34	21–33
Histotype				
Epithelioid[18,20,21]	51–59	22–55	28–45	20–63
Biphasic[18,20,21]	35–59	39–89	46–74	22–74
Sarcomatoid[20,21]	17–25	~80	47–83	50–83

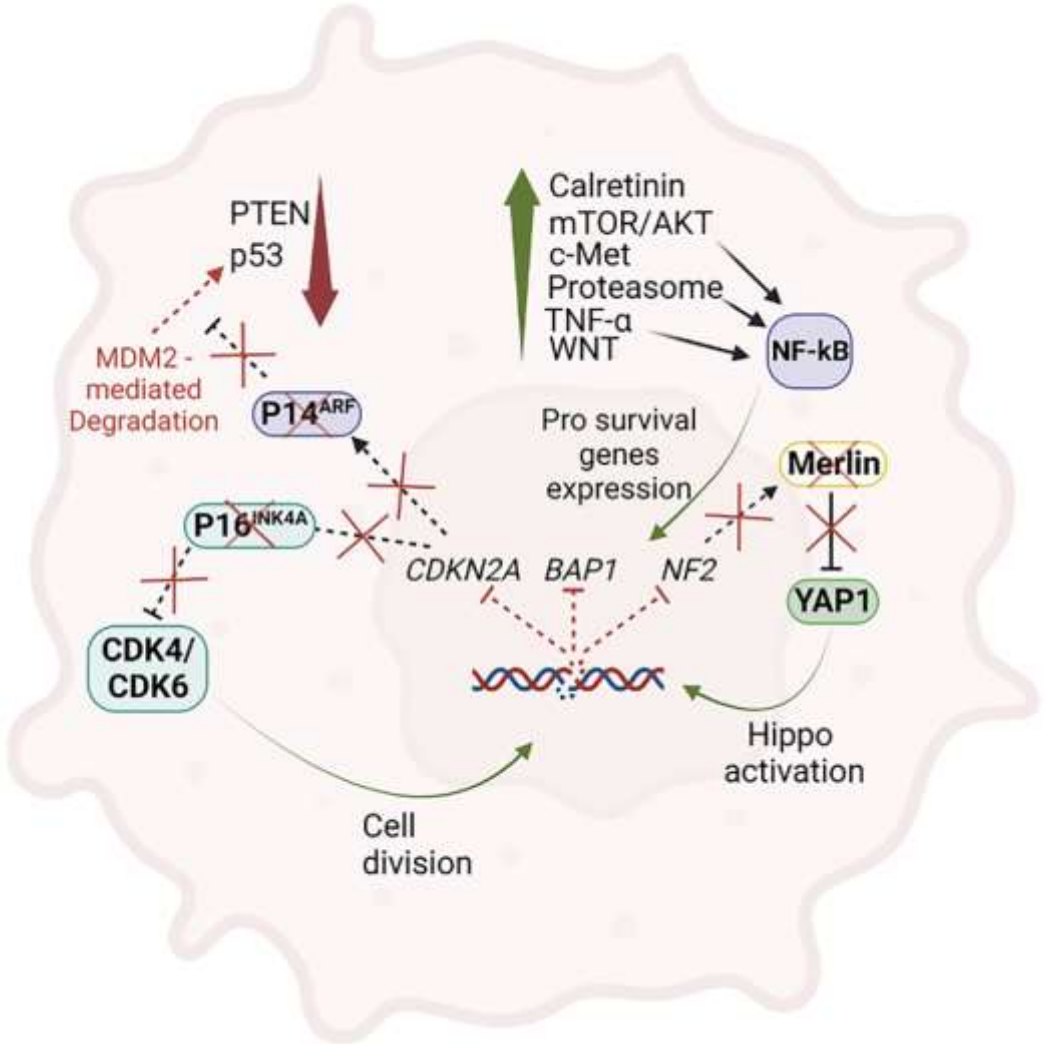
Table 3. Prevalence of Aberrant Immunohistochemical Expression of BAP1, MTAP, and Merlin in Mesothelioma of Different Histotypes

	Nuclear Loss of BAP1, %	Cytoplasmic Loss of MTAP, %	Complete Loss of Merlin, %
Overall[20,39,41]	54–66	~50	~50
Histotype			
Epithelioid[20,39,41,42,46,50]	55–70	35–65	35–41
Biphasic[20,39,41,42]	47–77	~60	~70
Sarcomatoid[20,39,41,42,47,50,51]	10–36	61–83	39–67

Dagogo-Jack I et al. J Clin Oncol Precis Oncol 6:e2100422 Hung YP, Chirieac LR *Arch Pathol Lab Med. 2024;148:e77-e89*







Hithbrunner S et al: British Journal of Cancer (2022) 127:1997–2005;Tsao AS et al: J Clin Oncol 2022;40:681-692. Rigon L e E et al Molecular Oncology 18 (2024) 797–814

MARS 2 trial

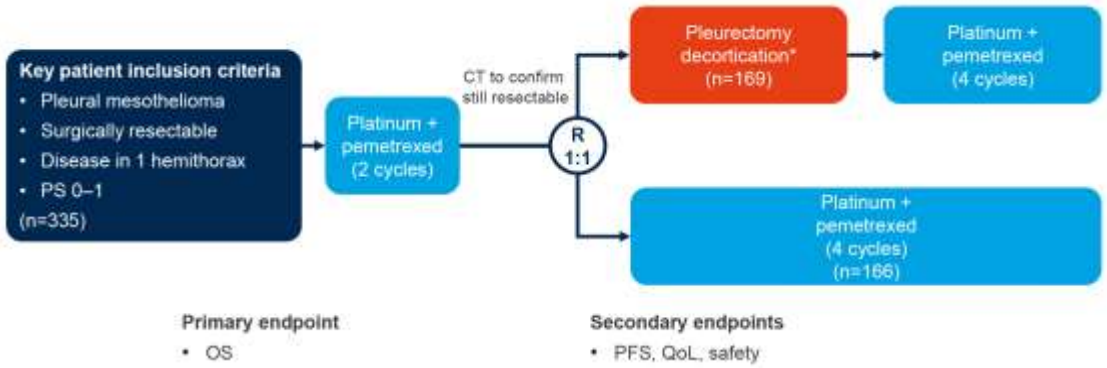
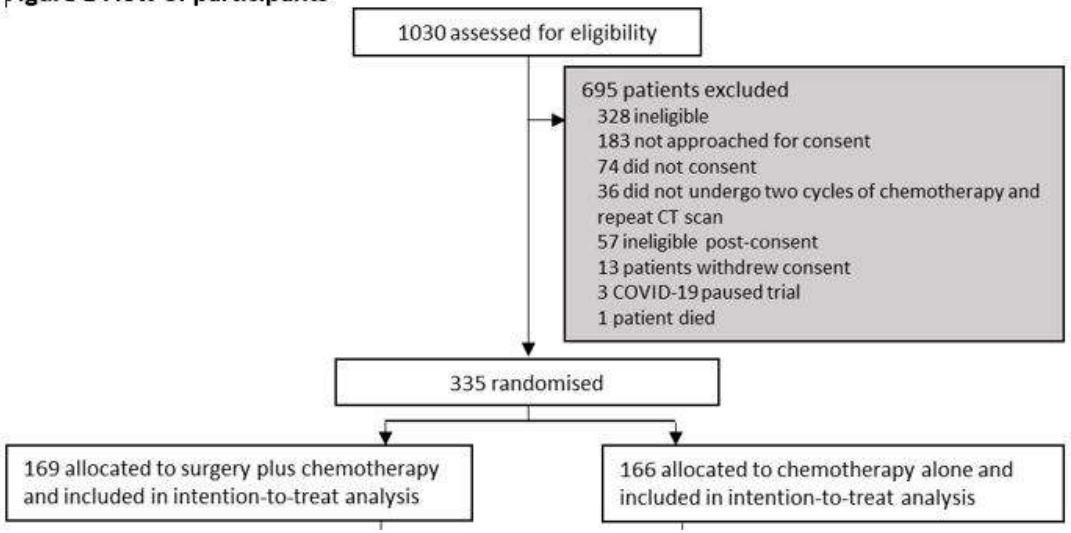
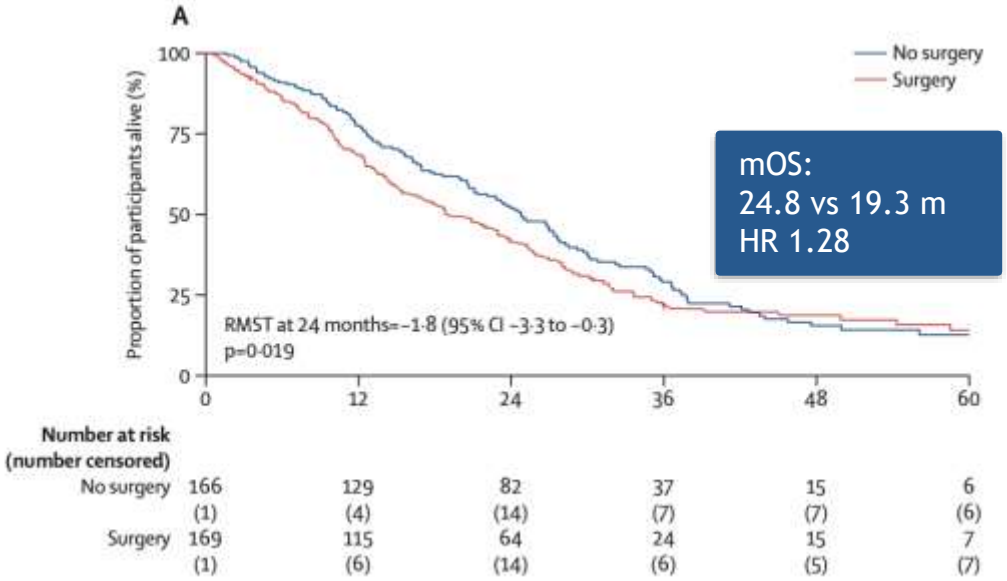
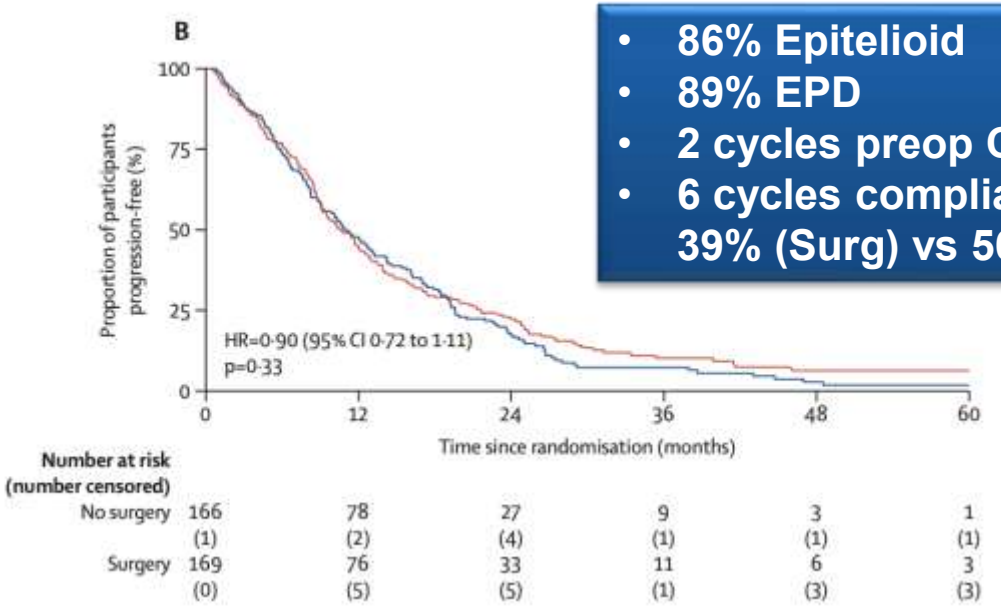


Figure 1 Flow of participants



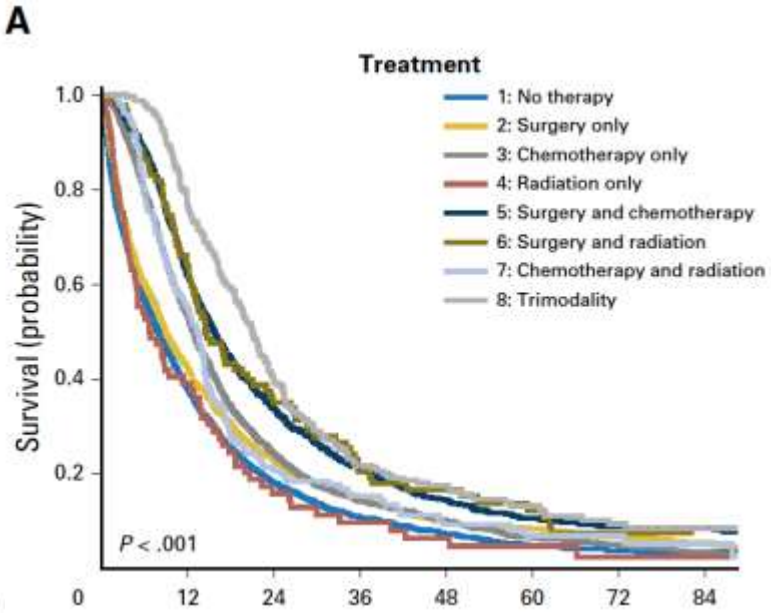


mOS:
24.8 vs 19.3 m
HR 1.28



- 86% Epitelioid
- 89% EPD
- 2 cycles preop CT: 100%
- 6 cycles compliance:
  39% (Surg) vs 56% (no Surg)

Lim E et al WCLC 2023, Lancet Respir Med 2024; 12: 457-66



Trimodality approach (chemo-EPP-rad)

Chemotherapy followed by EPD

MARS 2 trial
EORTC 1205 trial

Completed

EPD followed by Hemithoracic radiation

IMPRINT trial

Phase III trial ongoing

Hemithoracic radiation before Surgery

SMART trial (EPP)
SMARTER trial (PD)

SMARTEST trial (Rad-Sx +IO)

Popat S et al Ann Oncol 2022;33:129-142. Nelson DB et al J Clin Oncol 2017;35:3354-3362

Could radiotherapy add ?

SMART trial

Study Schema

Histologically Proven, Previously Untreated Malignant Pleural Mesothelioma (cT1-3 N0 M0) Baseline Investigations, Informed Consent

↓

Neoadjuvant Hemithoracic Intensity Modulated Radiotherapy (25 Gy/5 fx +/- concomitant 5 Gy boost over 1 week)

↓

1 week post-RT

↓

Extrapleural Pneumonectomy

↓

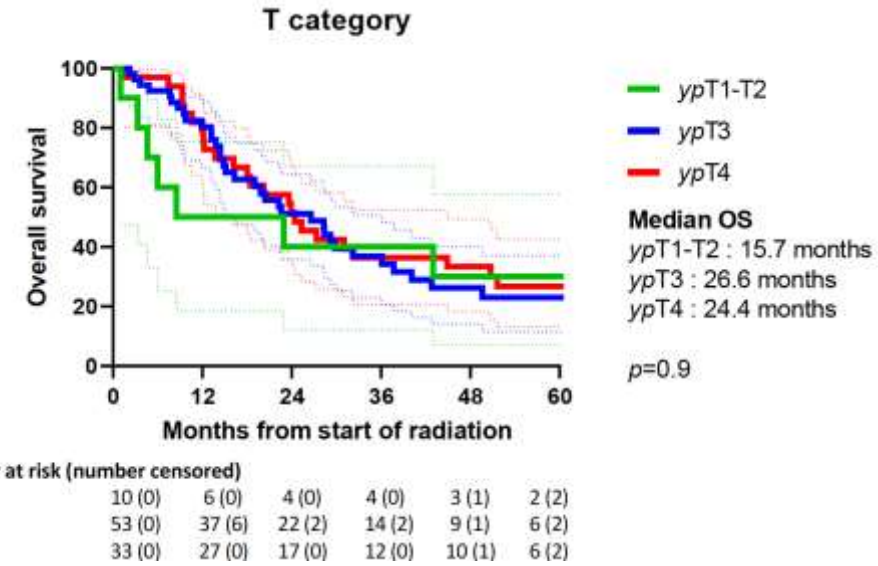
<26 weeks post-op

↓

ypN0-1 → Observation

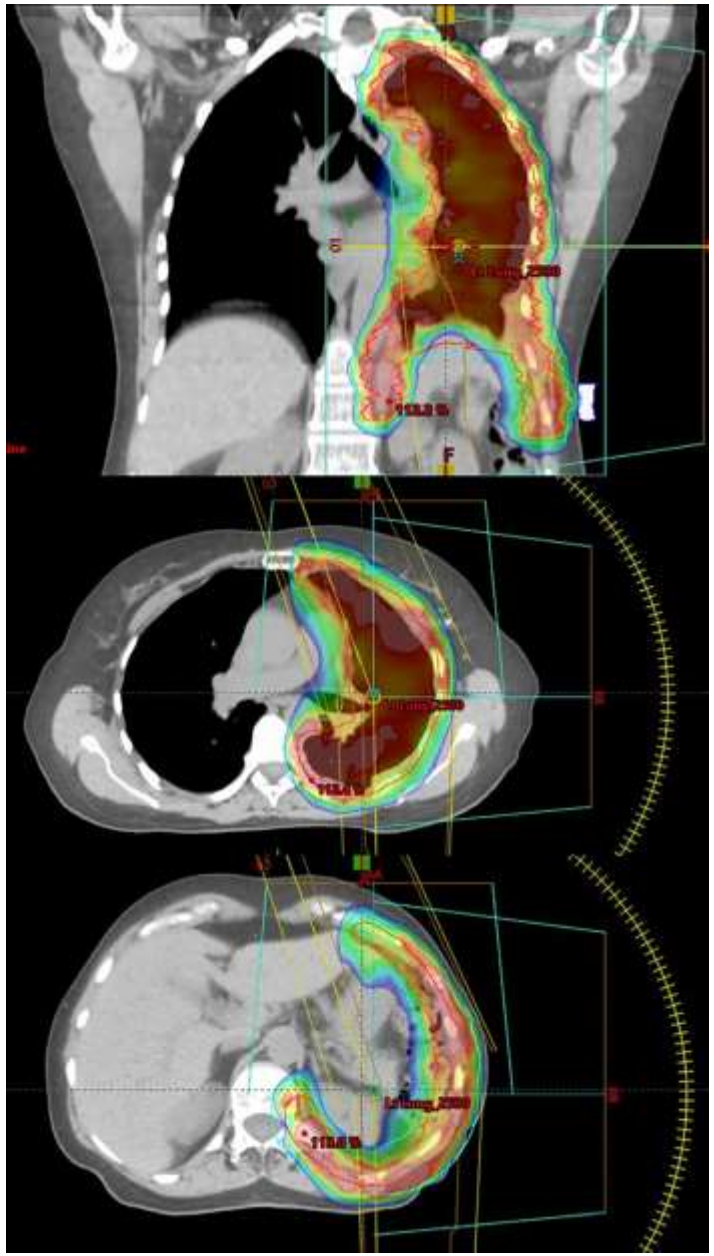
ypN2 → Adjuvant Chemotherapy

- 123 patients SMART Trial
- 96 patients received full IMRT and EPP
- 30 days mortality 1% ; 90 days mortality 3.1%
- No radiation pneumonitis



Number at risk (number censored)

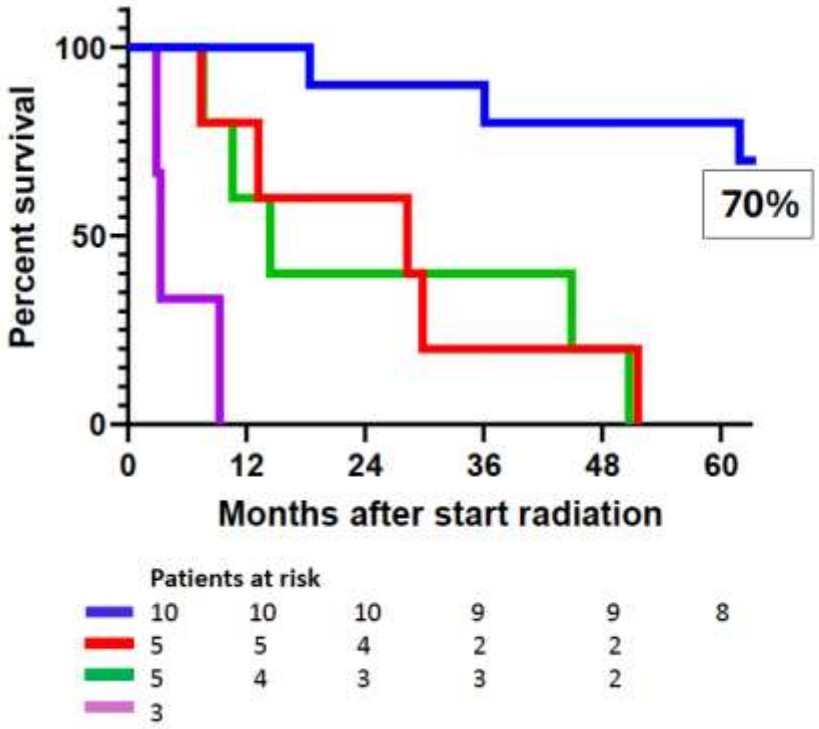
*yp*T1-T2	10 (0)	6 (0)	4 (0)	4 (0)	3 (1)	2 (2)
*yp*T3	53 (0)	37 (6)	22 (2)	14 (2)	9 (1)	6 (2)
*yp*T4	33 (0)	27 (0)	17 (0)	12 (0)	10 (1)	6 (2)



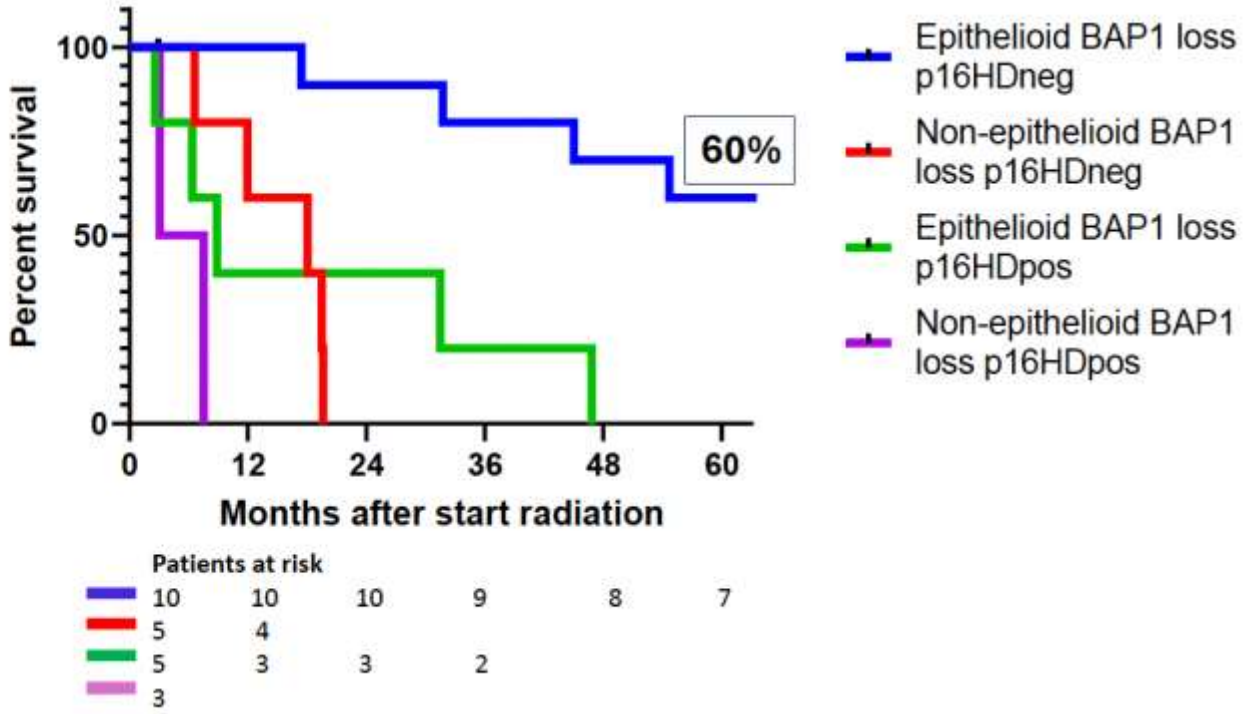
Cho BCJ et al, Lancet Oncol 2021;22:190-197

OS and DFS in epithelioid BAP1^{loss} p16^{WT} tumors after SMART

Overall survival (OS)



Disease-free survival (DFS)



Cho BCJ et al, Lancet Oncol 2021;22:190-197

Something new in MPM chemotherapy after more than 20 years?

3 Ph II CBCDA + Pem

2003 EMPHACIS

CDDP+Pem *vs* CDDP

ORR : 41 vs 17%
mPFS: 5.7 vs 3.9 m
mOS: 12.1 vs 9.3 m

2005 RALTITREXED

CDDP + Raltitrexed *vs* CDDP

ORR: 24 vs 14% (ns)
PFS: 5.3 vs 4 m (ns)
OS: 11.4 vs 8.8 m

2015 MAPS

CDDP + Pem + Bevaciz *vs* CDDP + Pem

ORR: NR
mPFS: 9.2 vs 7.3 m
mOS: 18. vs 12.1 m

Vogelzang, NJ et al. J Clin Oncol 2003; 21(14):2636-44. Van Meerbeeck JP, *et al. J Clin Oncol* 2005;23(28):6881-9. Zalcman G, *et al. Lancet* 2016;387:1405-14.

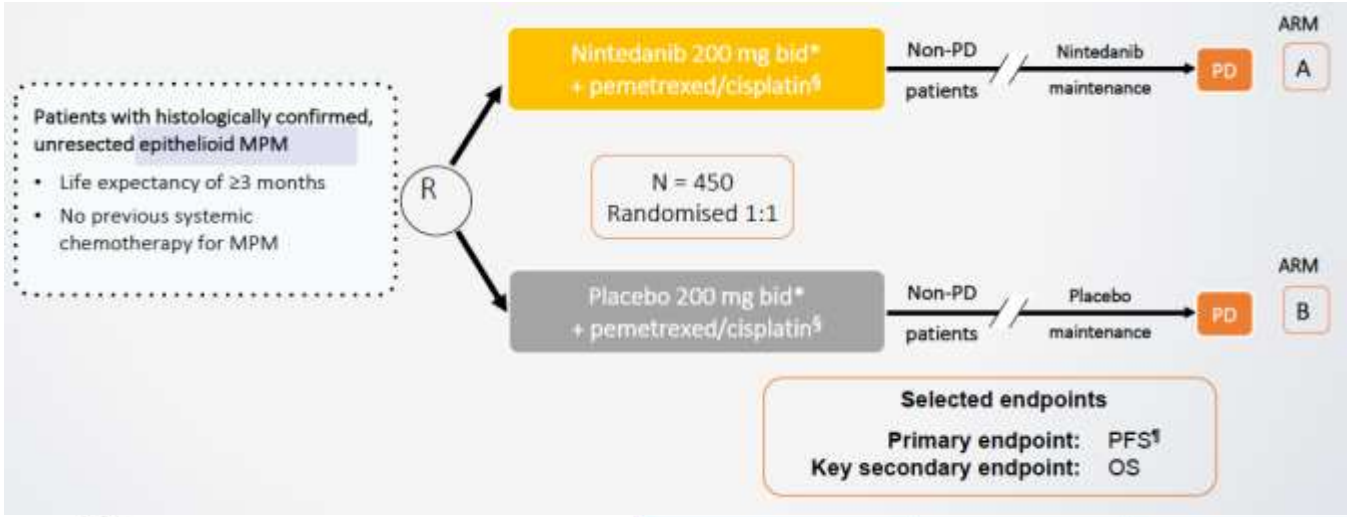
LUME Meso trial

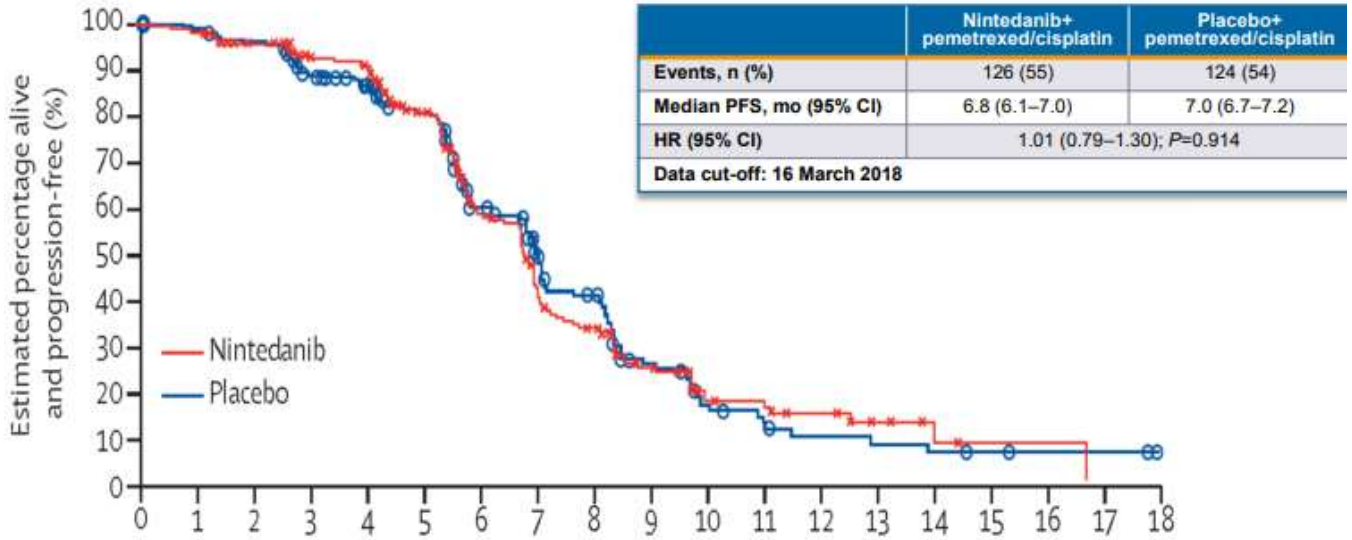
CDDP + Pem+ Nintedanib

vs

CDDP+Pem

= RR PFS OS

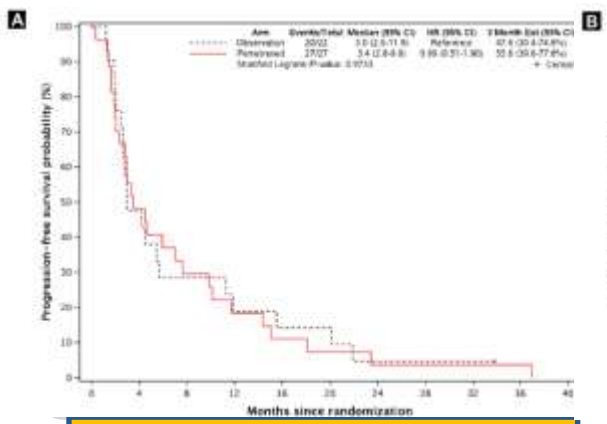




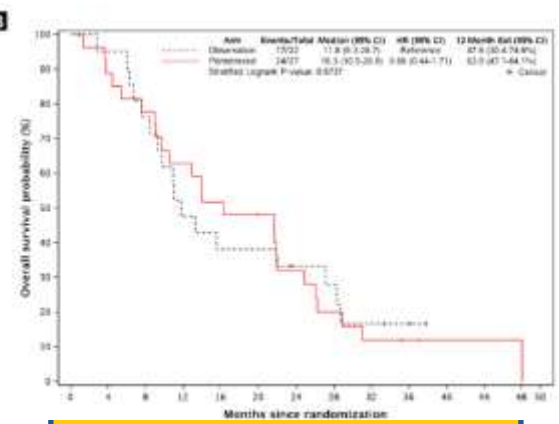
	Nintedanib+ pemetrexed/cisplatin	Placebo+ pemetrexed/cisplatin
Events, n (%)	126 (55)	124 (54)
Median PFS, mo (95% CI)	6.8 (6.1–7.0)	7.0 (6.7–7.2)
HR (95% CI)	1.01 (0.79–1.30); *P*=0.914	
Data cut-off: 16 March 2018		

Scagliotti GV, et al. Lancet Respir Med. 2019 2019;7:569-80.

Pemetrexed Maintenance(CALGB 30901)? Maintenance Switch to Gemcitabine NVALT19?



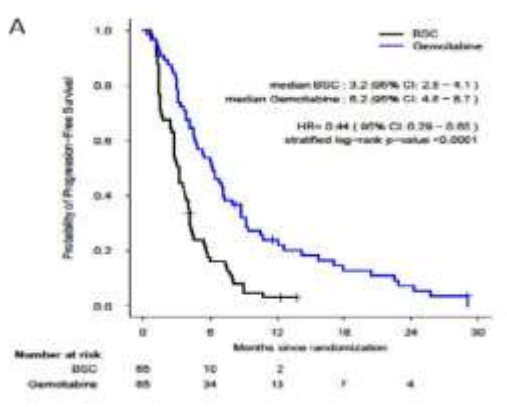
mSLP
3,4 *vs* 3m
NS



mOS
16,3 *vs* 11,8 m
NS

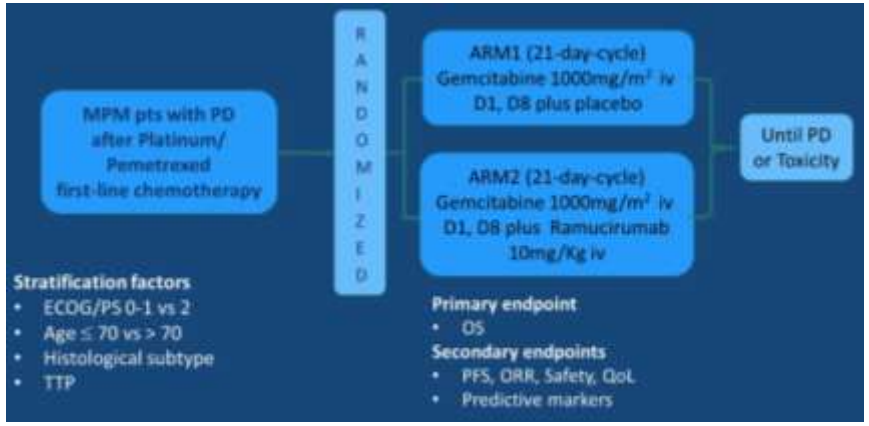
Best Response	Pemetrexed (N = 27)	Observation[a] (N = 21)	Total (N = 48)
Complete	1 (3.7%)	0 (0%)	1 (2.1%)
Partial	2 (7.4%)	0 (0%)	2 (4.2%)
Stable	12 (44.4%)	14 (66.6%)	26 (54.2%)
Progression	12 (44.4%)	6 (28.6%)	18 (37.5%)
Non CR/Non PD	0 (0.0%)	1 (4.8%)	1 (2.1%)
Response rate (95% CI)[b]	11.1 (2.4-29.2)	0 (0-0)	6.3 (1.3-17.2)

TR
11,1 *vs* 0%
NS

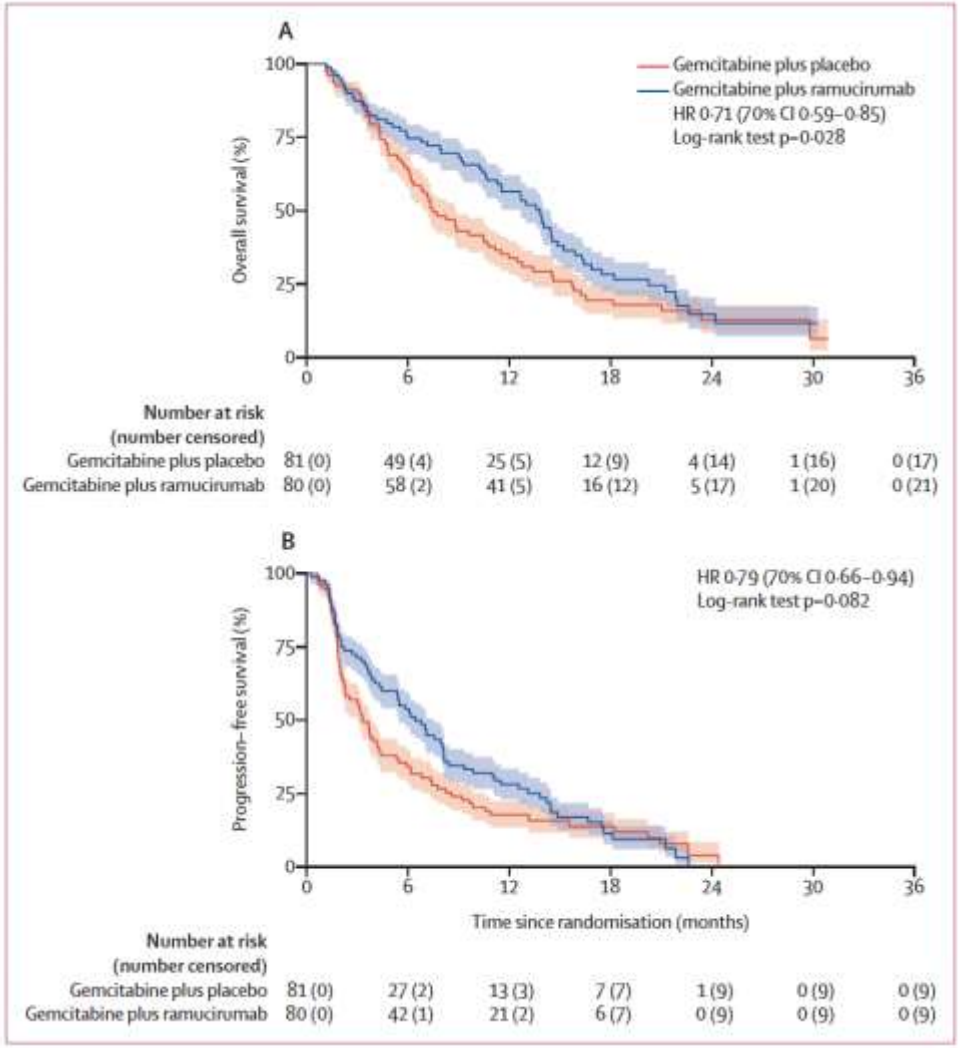


mPFS 3.2 vs 6.2 m 1
y-PFS 24 vs 3%
No survival data
Gemcitabine immunomodulatory effect?

Dudek AZ, *et al. Clinical Lung Cancer* 2020; 21(6):553-61. de Gooijer CJ et al *Lancet Resp Dis* 2021;9(6):285-92



	Gemcitabine plus placebo		Gemcitabine plus ramucirumab		Hazard ratio (90% CI)	$p_{interaction}$
	n/N	Median overall survival (90% CI), months	n/N	Median overall survival (90% CI), months		
Age at randomisation, years						
≤70	46/81	6·8 (4·8–10·5)	49/80	13·9 (11·5–16·4)	0·53 (0·36–0·79)	0·056
>70	35/81	8·9 (7·1–11·2)	31/80	11·5 (8·0–14·5)	1·08 (0·68–1·70)	
ECOG performance status						
0	46/81	8·8 (7·2–11·5)	50/80	14·5 (13·6–16·9)	0·65 (0·43–0·96)	0·29
1–2	35/81	6·8 (5·4–9·6)	30/80	5·9 (3·6–12·7)	0·95 (0·61–1·50)	
Histology						
Epithelioid	70/81	8·8 (7·1–11·2)	68/80	13·8 (11·3–15·2)	0·76 (0·55–1·05)	0·15
Non-epithelioid	11/81	3·4 (1·3–3·8)	12/80	13·0 (2·8–14·5)	0·37 (0·18–0·78)	
Time to progression during first-line treatment, months						
<6	48/81	7·1 (5·4–8·3)	47/80	13·6 (9·1–14·5)	0·59 (0·41–0·86)	0·31
≥6	33/81	11·5 (6·3–16·3)	33/80	13·9 (10·4–16·4)	0·87 (0·53–1·42)	
Overall population	81/161	7·5 (6·3–10·5)	80/161	13·8 (11·3–14·5)	0·71 (0·53–0·95)	

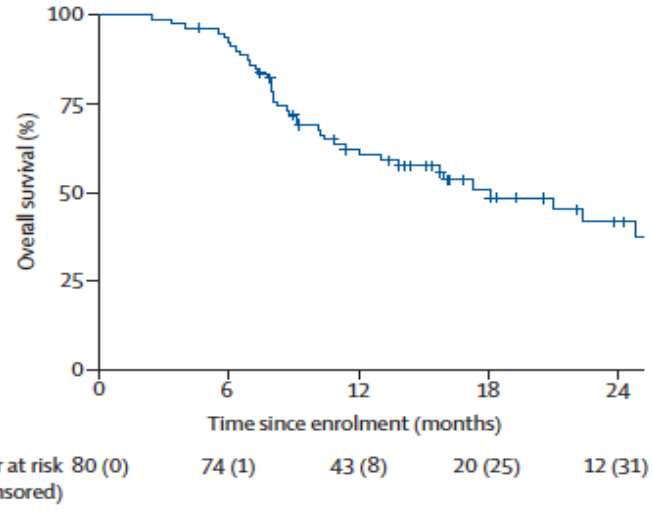


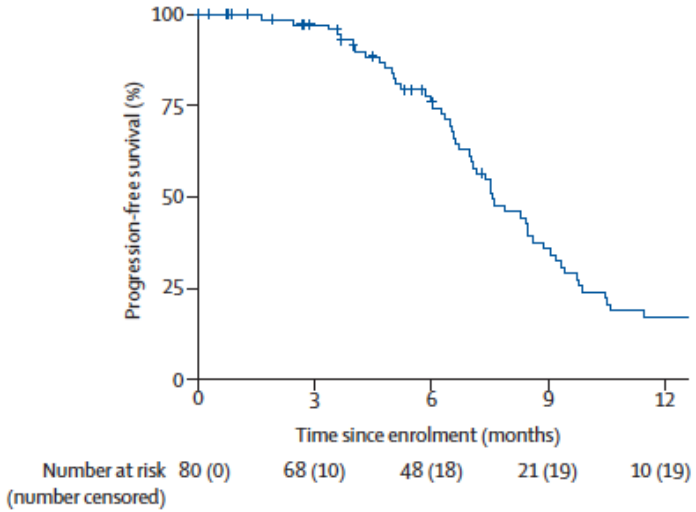
mOS:
13.8 vs 7.5 m

mPFS:
6.4 vs 3.3 m

Pinto C et al. Lancet Oncol 2021;September 6th. https://doi.org/10.1016/ S1470-2045(21)00404-6

TTFs + Platinum-Pemetrexed Ph 2 STELLAR?





	Grade 1–2	Grade 3	Grade 4	Grade 5
Patients with ≥1 adverse event	43 (54%)	24 (30%)	5 (6%)	3 (4%)
Infections and infestations	17 (21%)	0	1 (1%)	2 (3%)
Bronchopneumonia	0	0	1 (1%)	"
Candida sepsis	0	0	0	1 (1%)
Oral candidiasis	0	1 (1%)	0	"
Pneumonia	0	0	0	1 (1%)

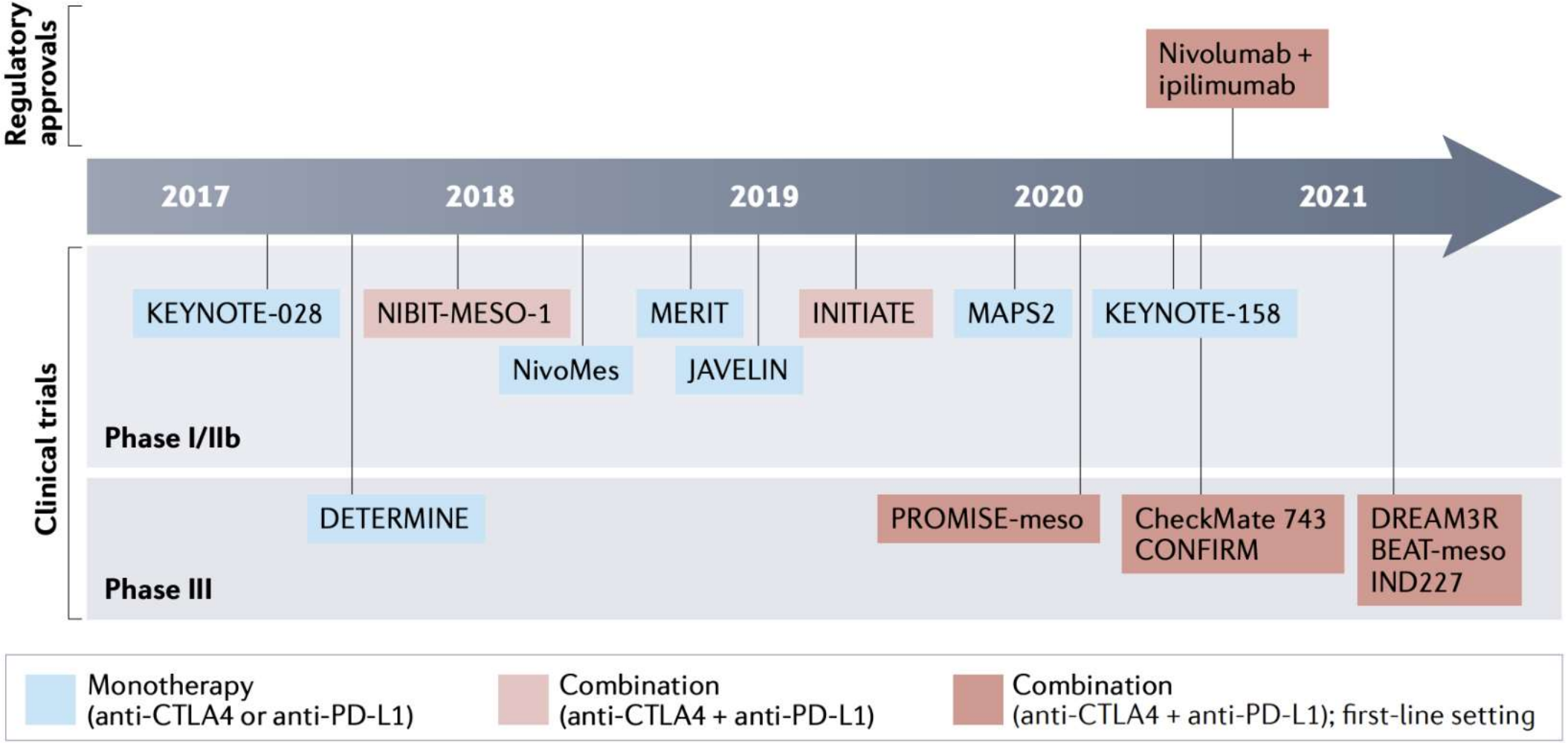
mOS 18,2m

mSLP 7,6m

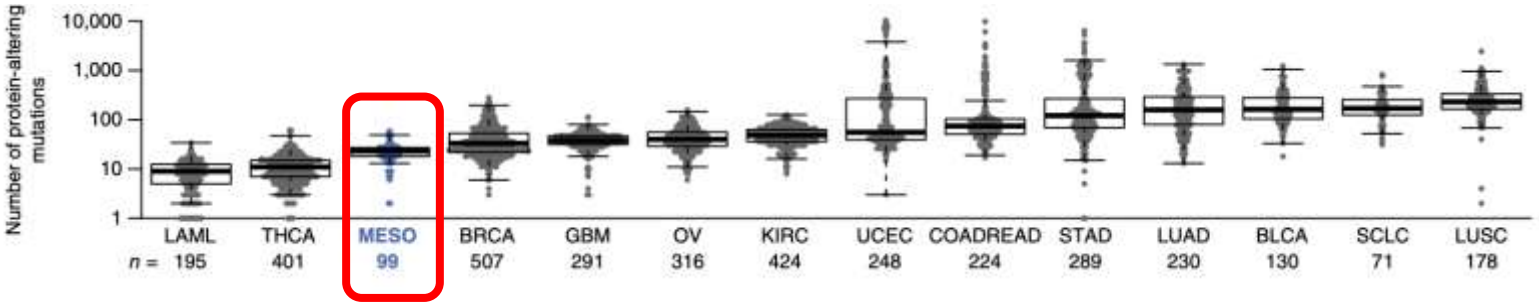
TR 40%
G5 AE 10%

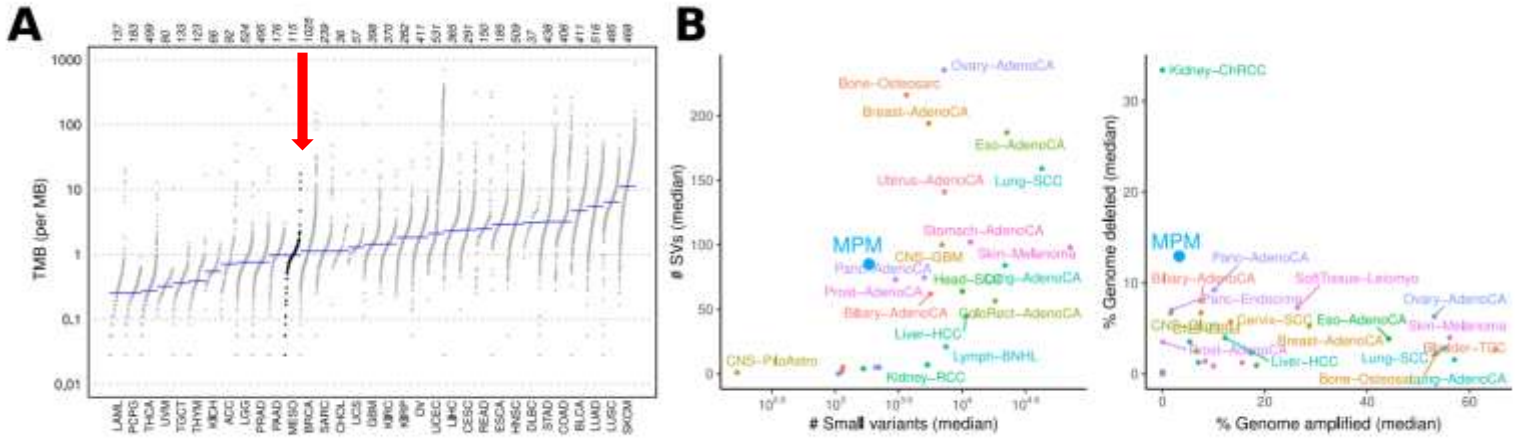
Ceresoli GL, et al. Lancet Oncol 2019;20:1702-1709.

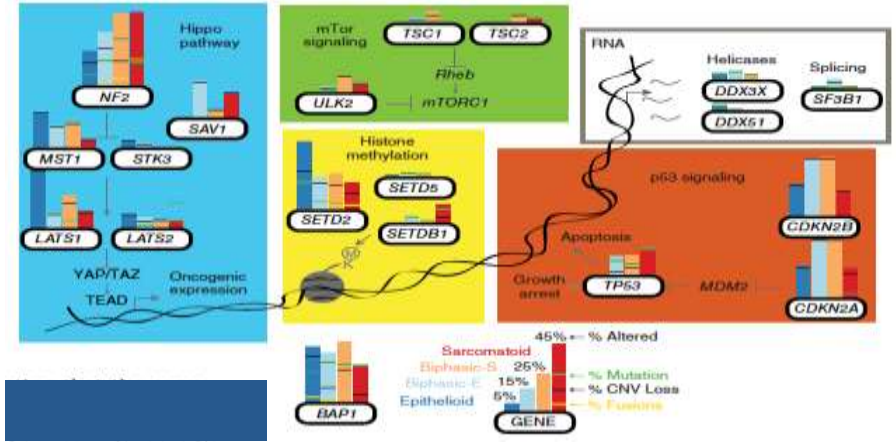
Immunotherapy the new player. A game changer?

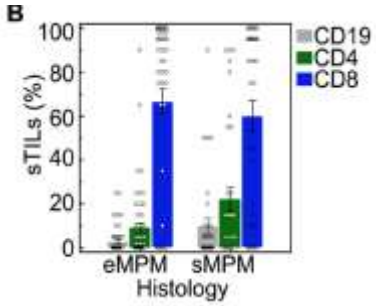


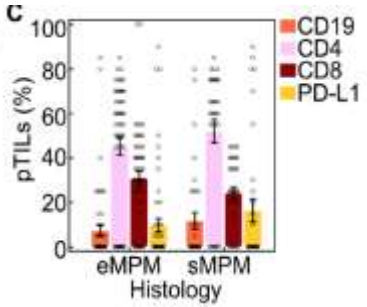
Fennell DA et al Nat Rev Clin Oncol 2022;19:573-584

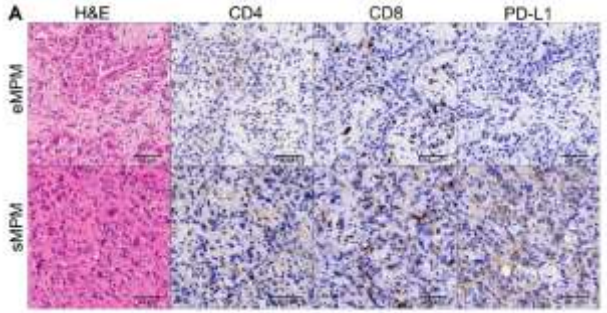




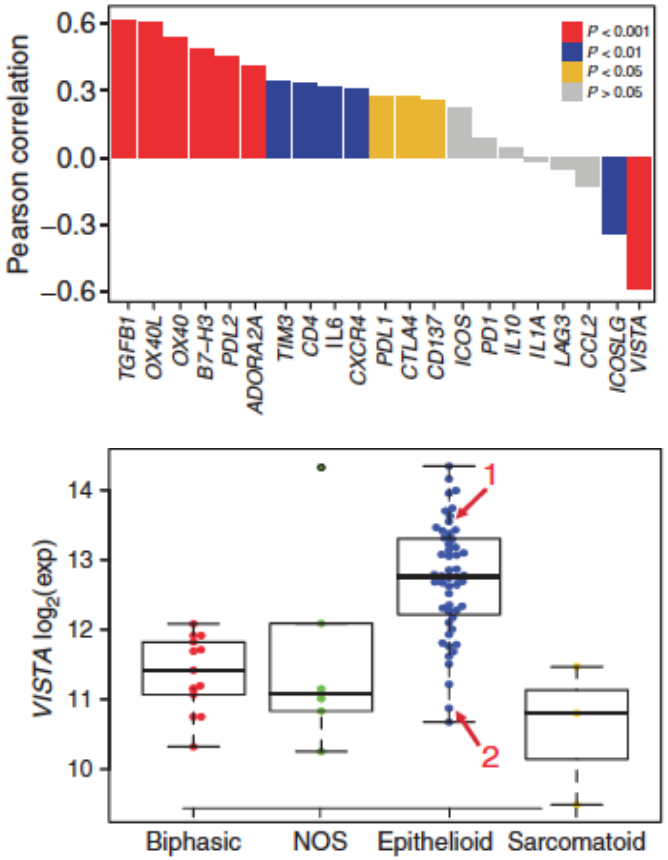


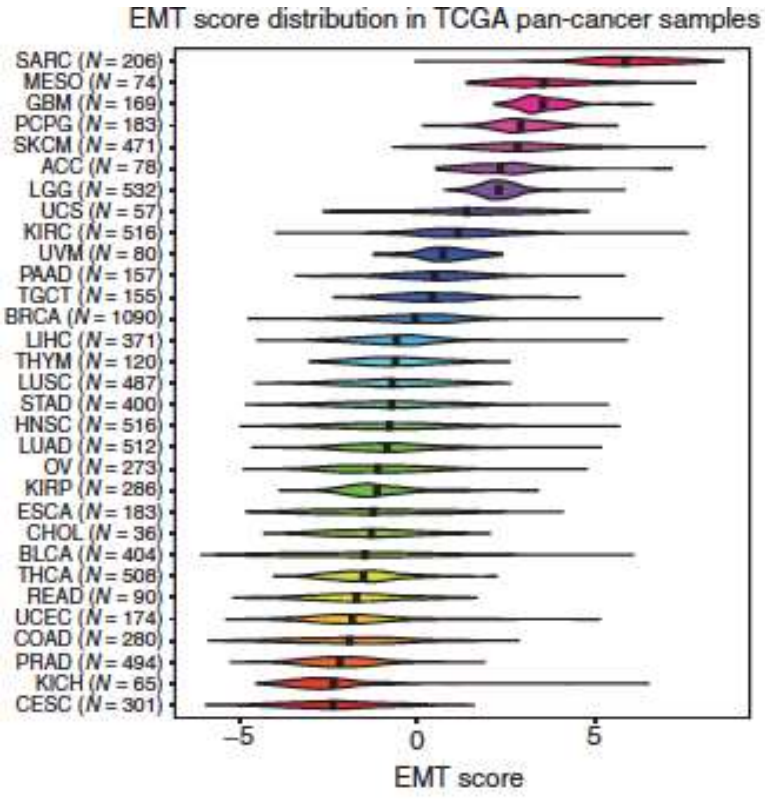


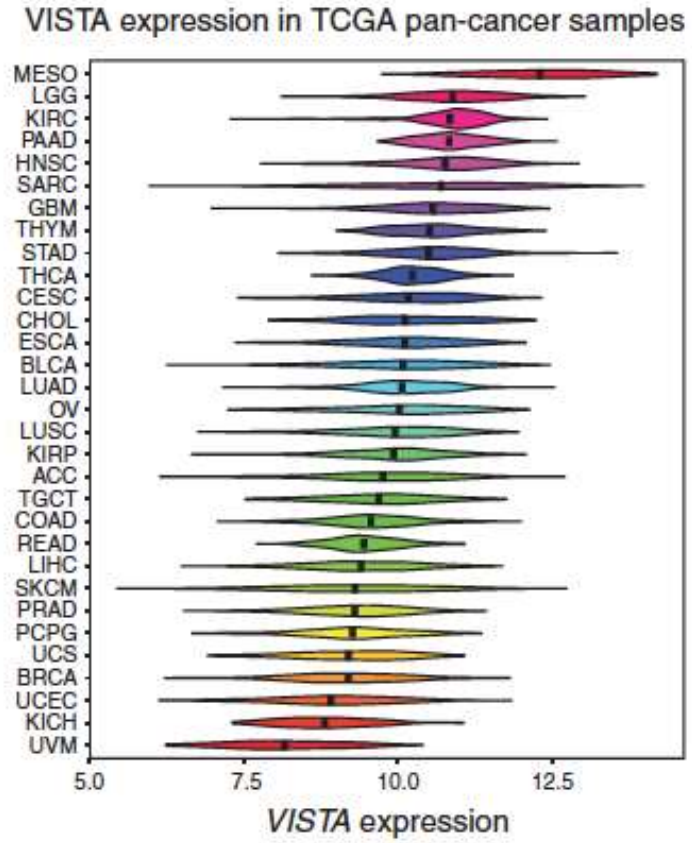




Bueno R et al Nat Genetics 2016;48:407-416; Fusco N et al Lung Cancer 2020;150:53-61







Hmeljak J et al Cancer Discov 2018:1548-1565 doi: 10.1158/2159-8290.CD-18-0804

Inmunoterapia en 2/3 L

2019 — INITIATE
Nivolumab + Ipilimumab x 4 ciclos
ORR 30%
DCR 68%

2019 — MAPS-2
Nivolumab *vs* Nivo + Ipi x 24 m,
DCR 40 vs 52%
mPFS 4 vs 5.6 m
mOS 11.9 vs 15.9 m

2017 — KEYNOTE 028
Ph Ib 2-3L Pembrolizumab x 24 m
ORR 20%
mPFS 5,4m
mOS 18m

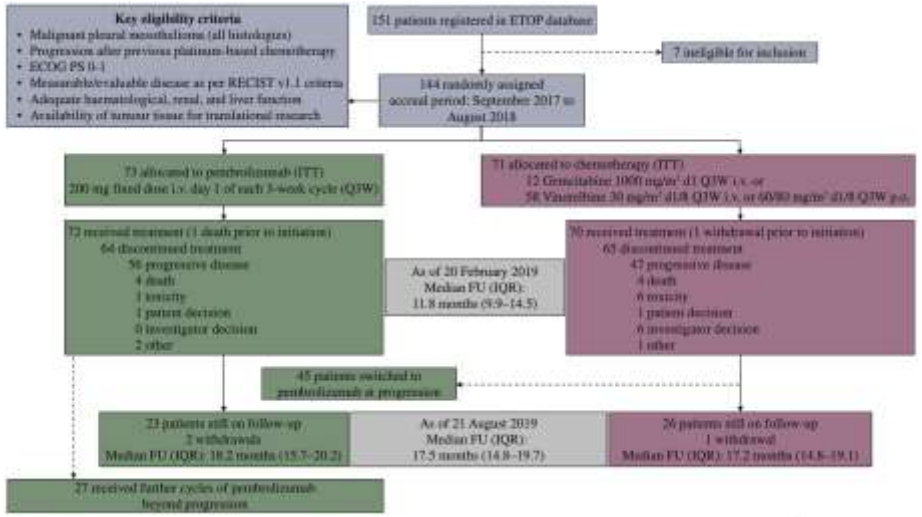
2020 — PROMISE Meso
Pembrolizumab vs CT
ORR 22 vs 6%
mPFS 2.5 vs 3.4 m
mOS 10.7 vs 12.4 m

2019 — MERIT
Nivolumab 2-3L Japan 34 p
ORR 29%
mPFS 5,9m
mOS 17,3m
3 y OS 23.5%

2020 — CONFIRM
2-3L Nivolumab vs Placebo x 12 m
DCR 11 vs 1%
mPFS 3 vs 1.8 m
mOS 10.2 vs 6.9 m
HR 0.69

Disselhorst MJ, et al. Lancet Respir Med. 2019;7:260-270. Scherpereel A et al. Lancet Oncol. 2019;20:239-53. Alley EW, et al. Lancet Oncol. 2017;18:623-630. Popat S et al Ann Oncol 2020; 31:1734-45. Okada M et al: Clin Cancer Res 2019;25:5485-5492. Fennell DA Lancet Oncol 2021;22: 1530-1540

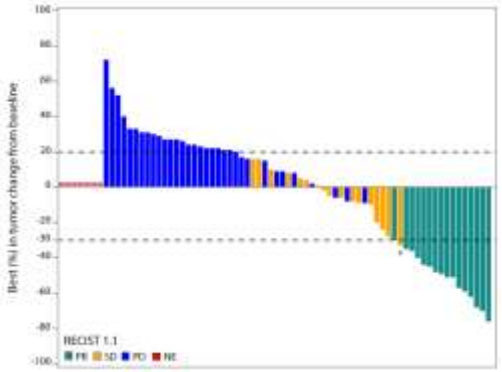
PROMISE-Meso: Pembrolizumab vs CT in pretreated MPM

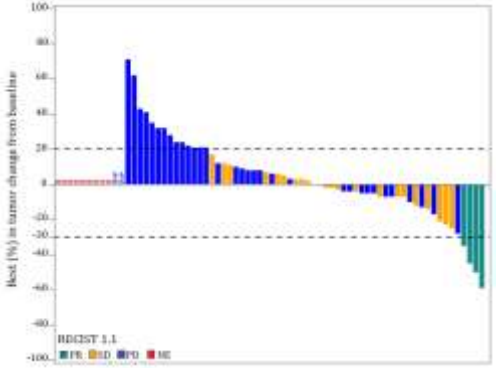


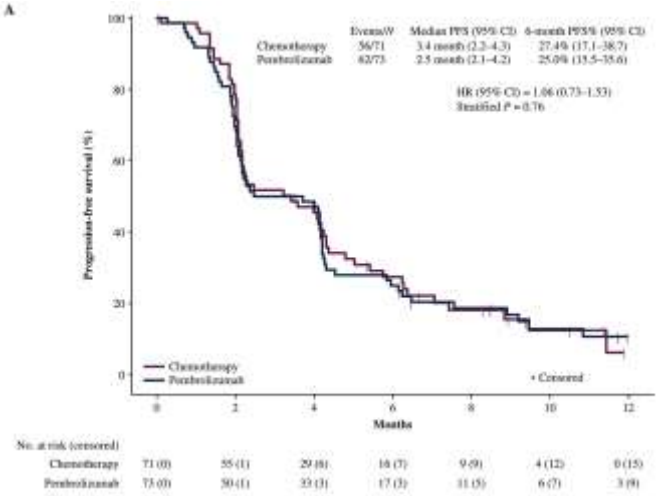
88.9% Epitelioid

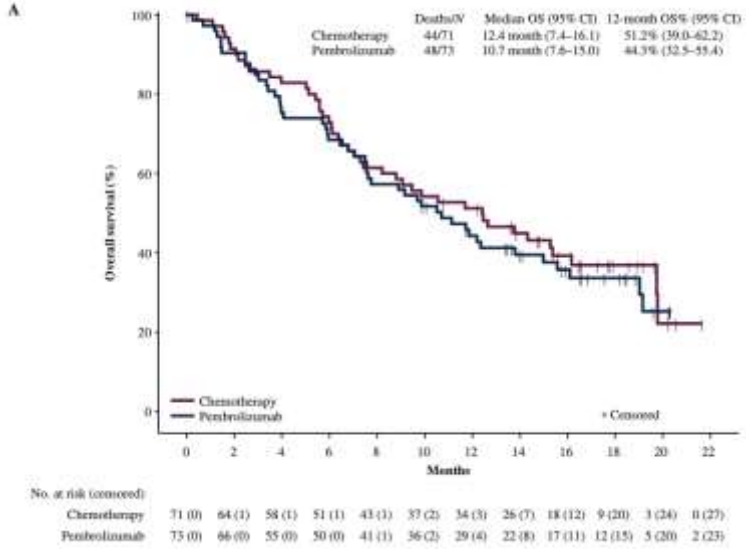
48.9% PD-l1 < 1%

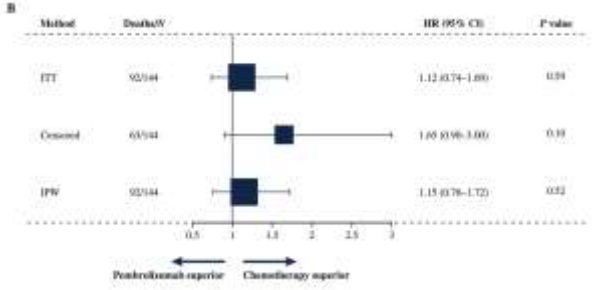
PR 22% vs 6%
P = 0.004











Popat S et al. Ann Oncol 2020;31: 1734-1741

CONFIRM: Nivolumab vs Placebo after Platinum based CT

88% Epitelioid

Key eligibility criteria:
Mesothelioma
> 1 prior line of therapy
ECOG status 0 or 1

Randomised 2:1
Stratified by histology
(epithelioid or non-epithelioid)

Nivolumab (n=221)
240mg in 30-min IV infusion on day 1 of 14-day cycle

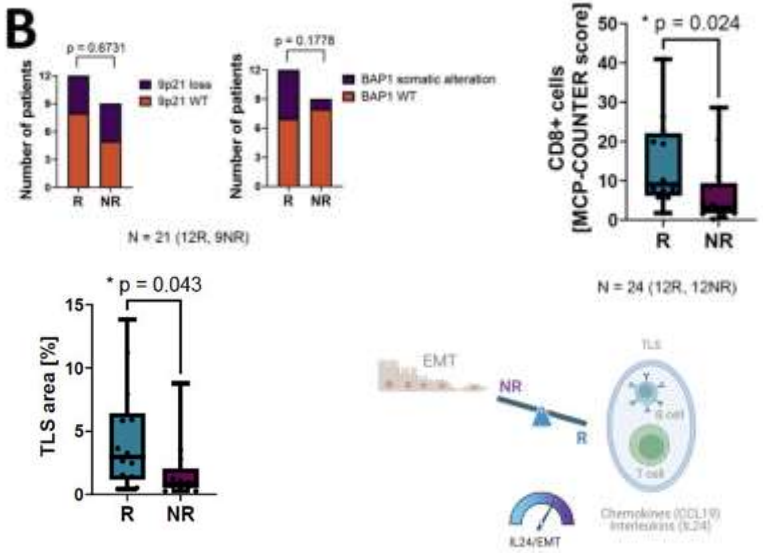
Placebo (n=111)
240mg sterile solution in 30-min IV infusion on day 1 of 14-day cycle

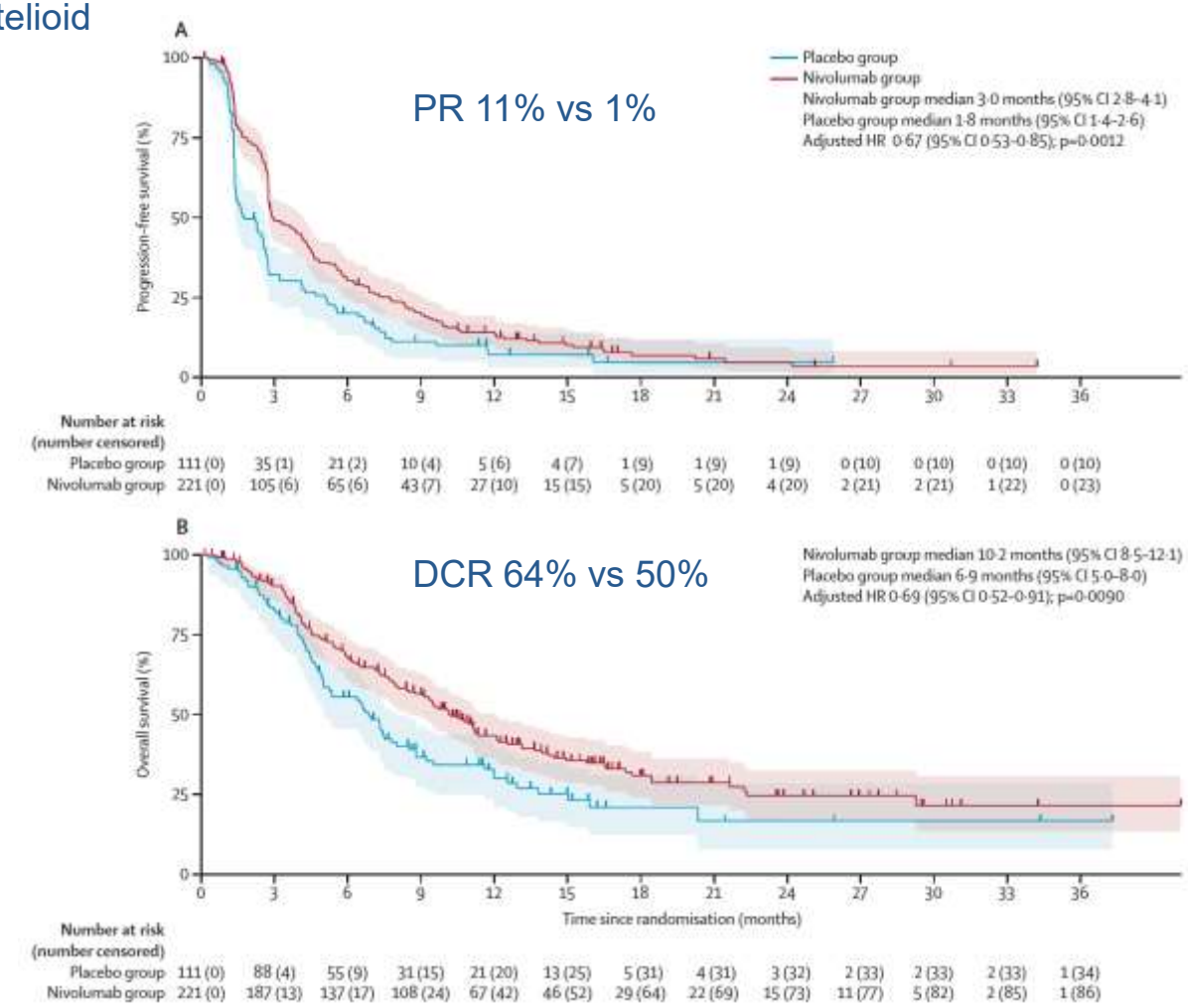
Recruited
April 2017 – March 2020

Target sample size: 336
Study halted recruitment at n=332 due to COVID-19 pandemic but sufficient event/follow-up

Co-primary outcomes:
- Overall survival
- Investigator-reported progression-free survival

Secondary outcomes:
- RECIST-determined progression-free survival
- Response rate
- EQ-5D
- Safety





PR 11% vs 1%

DCR 64% vs 50%

Fennell DA et al. Lancet Oncol 2021; 22: 1530–40. Fennell DA et al *Nature Communications* | (2025) 16:6688

Nivolumab-Ipilimumab en 1 L CheckMate 743

Key eligibility criteria
- Unresectable MPM
- No prior systemic therapy
- ECOG PS 0-1

Stratified by
Histology (epithelioid vs non-epithelioid) and sex

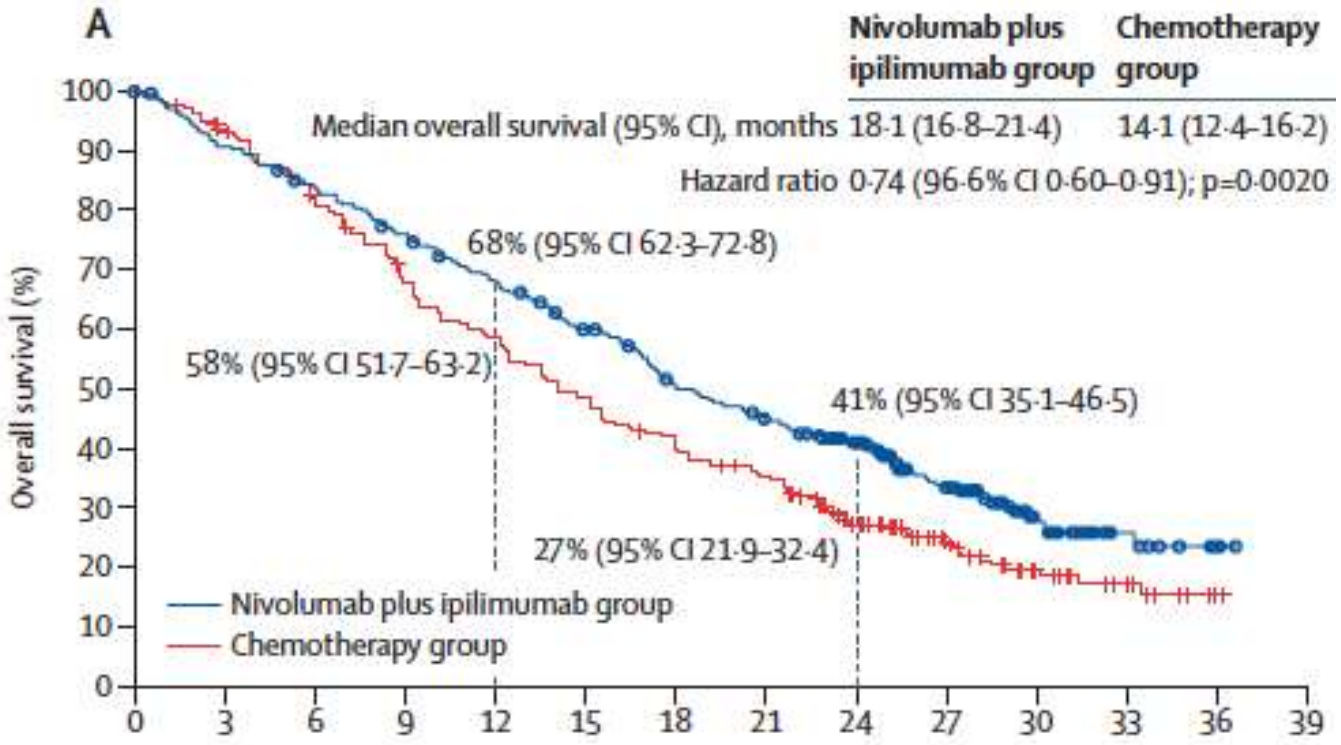
N = 605 → R 1:1
- n = 303 → NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W (for up to 2 years)
- n = 302 → Cisplatin or carboplatin + pemetrexed Q3W (6 cycles)

Until disease progression, unacceptable toxicity, or for 2 years for immunotherapy

Primary endpoint
- OS

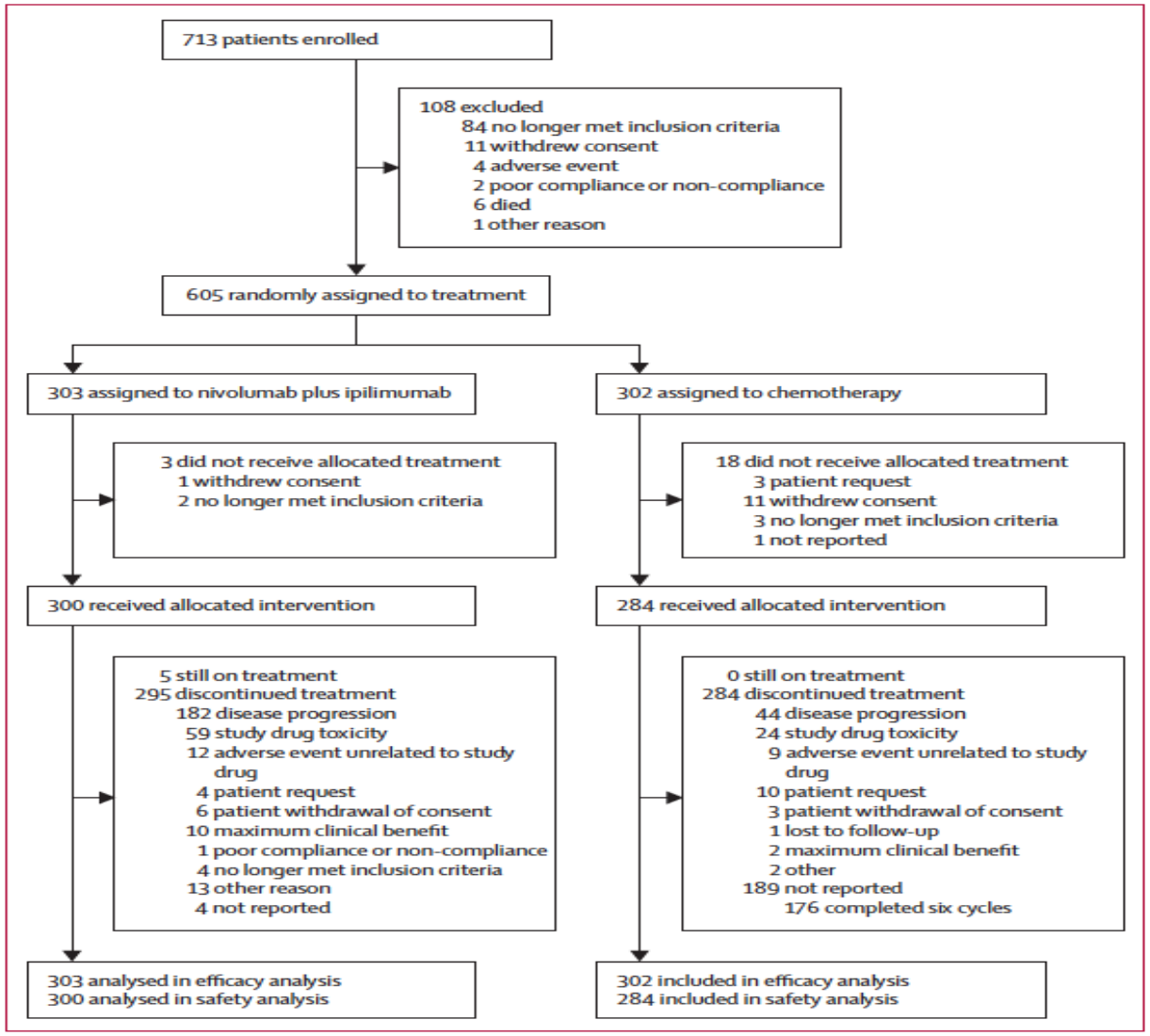
Secondary endpoints
- ORR, DCR, and PFS by BICR
- Efficacy by PD-L1[c] expression

Exploratory endpoints
- Safety and tolerability
- Biomarkers



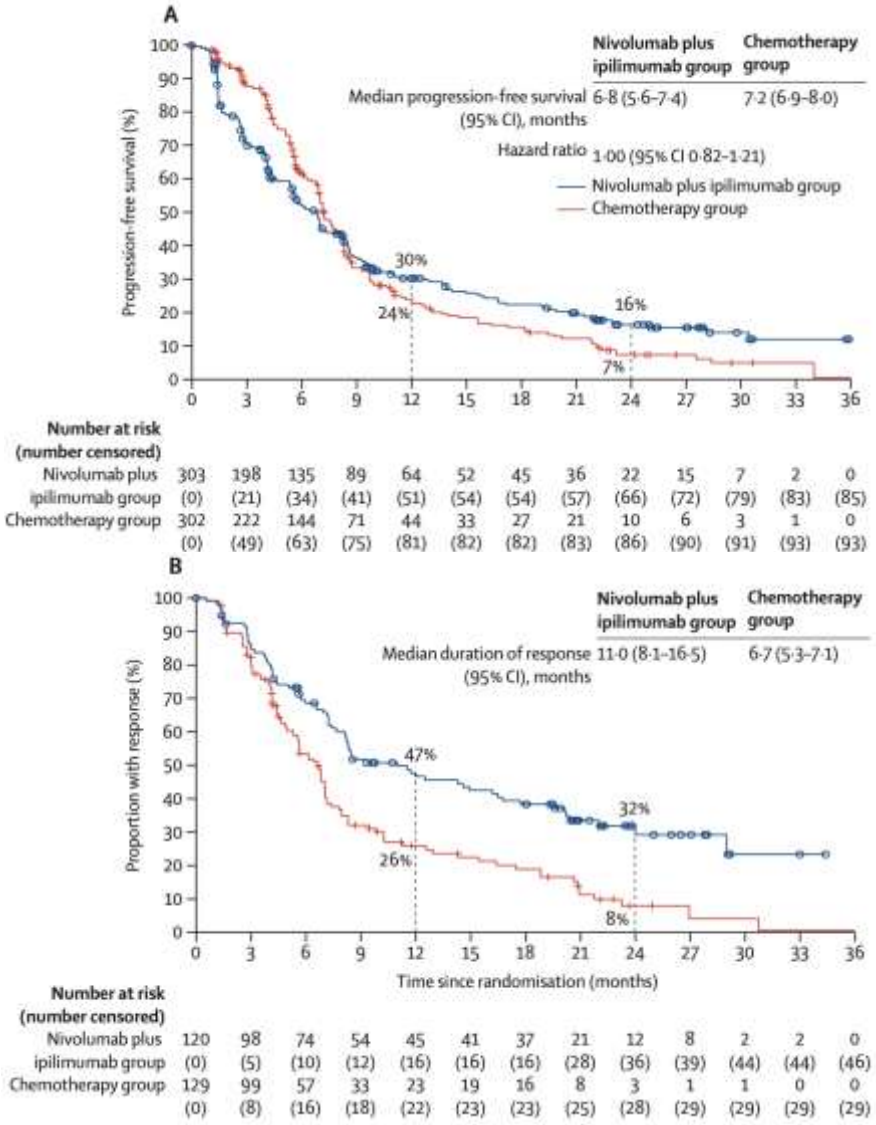
Baas P et al. Lancet. 2021;397:375-386

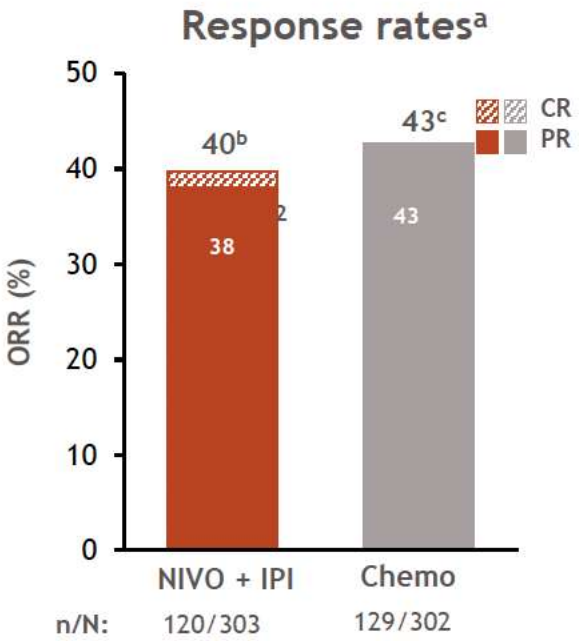
Hospital General Universitario Dr. Balmis



	Nivolumab plus ipilimumab group (n=303)	Chemotherapy group (n=302)
Age, years	69 (65–75)	69 (62–75)
<65	71 (23%)	96 (32%)
≥65 to <75	154 (51%)	127 (42%)
≥75	78 (26%)	79 (26%)
Sex		
Male	234 (77%)	233 (77%)
Female	69 (23%)	69 (23%)
Region		
North America	32 (11%)	27 (9%)
Europe	177 (58%)	175 (58%)
Asia	26 (9%)	39 (13%)
Rest of the world*	68 (22%)	61 (20%)
Eastern Cooperative Oncology Group performance status†		
0	114 (38%)	128 (42%)
1	189 (62%)	173 (57%)
Smoking status		
Current or former	173 (57%)	171 (57%)
Never	127 (42%)	122 (40%)
Unknown	3 (1%)	9 (3%)
Histology		
Epithelioid	229 (76%)	227 (75%)
Non-epithelioid	74 (24%)	75 (25%)
Sarcomatoid	35 (12%)	36 (12%)
Mixed or other	39 (13%)	39 (13%)
Stage		
1	12 (4%)	20 (7%)
2	23 (8%)	22 (7%)
3	103 (34%)	106 (35%)
4	160 (53%)	149 (49%)
Not reported	5 (2%)	5 (2%)
Previous cancer therapy		
Radiotherapy‡	29 (10%)	28 (9%)
Systemic therapy§	1 (<1%)	0
PD-L1 status		
Quantifiable	289 (95%)	297 (98%)
<1%¶	57/289 (20%)	78/297 (26%)
≥1%¶	232/289 (80%)	219/297 (74%)

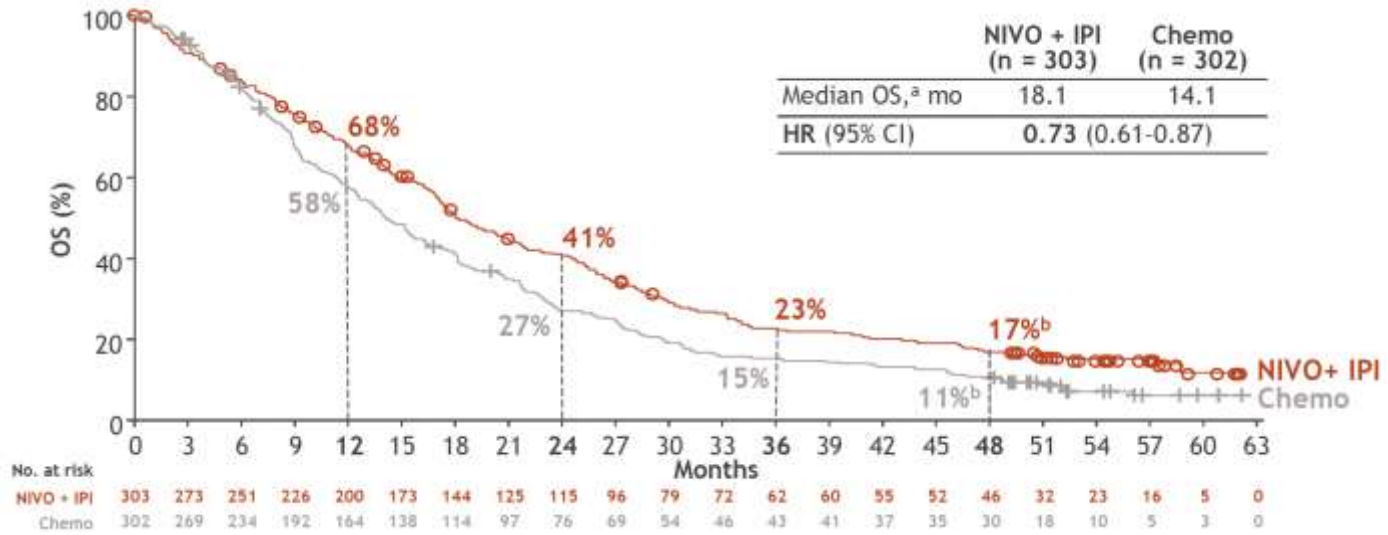
Baas P et al. Lancet. 2021;397:375-386





	Nivolumab plus ipilimumab group (n=303)	Chemotherapy group (n=302)
Objective response rate		
n (%)	120 (40%)	129 (43%)
95% CI	34·1–45·4	37·1–48·5
Best overall response		
Complete response	5 (2%)	0
Partial response	115 (38%)	129 (43%)
Stable disease	112 (37%)	125 (41%)
Non-complete response and non-progressive disease	0	3 (1%)
Progressive disease	55 (18%)	14 (5%)
Unable to determine	4 (1%)	5 (2%)
Not reported	12 (4%)	26 (9%)
Disease control rate		
n (%)	232 (77%)	257 (85%)
95% CI	71·4–81·2	80·6–88·9
Time to response, months		
Median	2·7	2·5
IQR	1·45–3·27	1·41–3·02
Duration of response, months		
Median	11·0	6·7
95% CI	8·1–16·5	5·3–7·1
Proportion of patients with a response of at least 1 year or 2 years*		
At 1 year	47%	26%
95% CI	37–56	18–34
At 2 years	32%	8%
95% CI	23–41	3–15

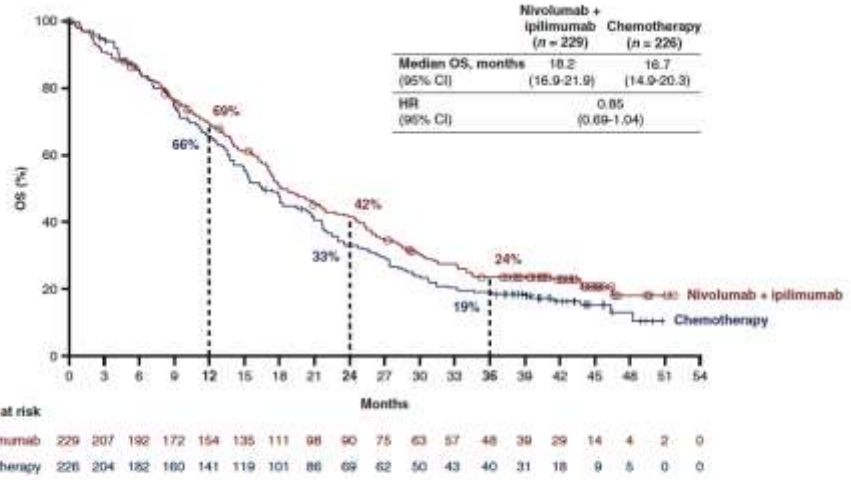
Baas P et al. Lancet. 2021;397:375-386



	CheckMate 743	Netherlands 1L	Australia 1L,2L	Switzerland 1L, 2L
Patients	303	126	119	109
Epitelioid	76%	55%	50%	75%
mPFS	6.8 m	6.2 m	6.7 m	5.6 m
mOS	18.1 m	15.0 m	14.5 m	16.6 m
EA G3-4	30%	25%	22%	23%
EA G5	1.0%	2.4%	3%	3%

Zalcman G et al. ESMO 2022

B



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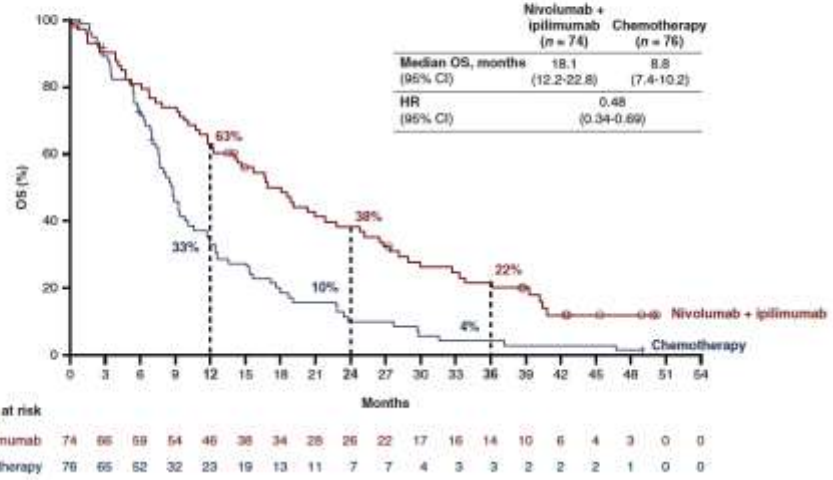
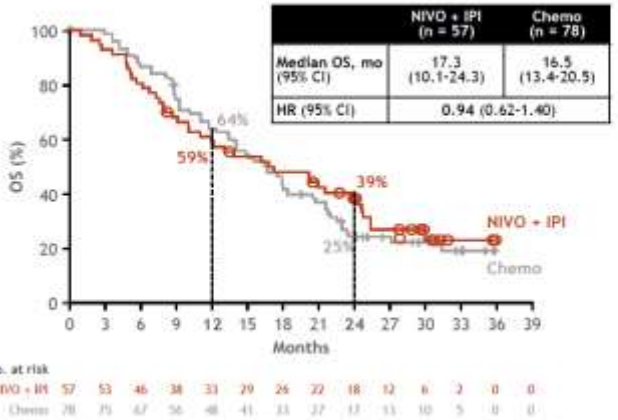
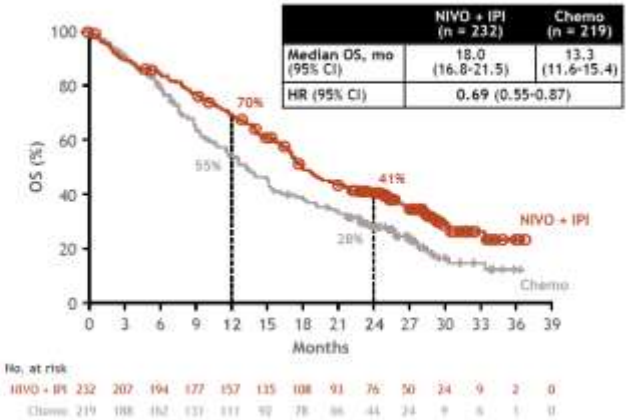


PD-L1 < 1%

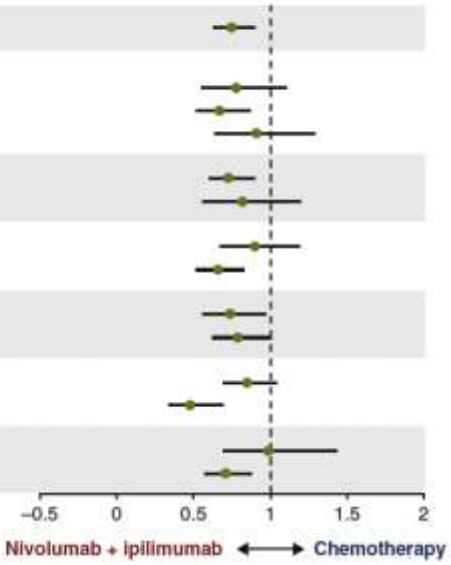


PD-L1 ≥ 1%



Minimum follow-up: 22.1 months; median follow-up: 29.7 months.

Subgroup	Median OS, months (95% CI): Nivolumab + ipilimumab (*n* = 303)	Chemotherapy (*n* = 302)	Unstratified HR (95% CI)
All randomized (*N* = 605)	18.1 (16.8-21.0)	14.1 (12.4-16.3)	0.75[a] (0.63-0.90)
Age, years			
<65 (*n* = 167)	17.2 (13.1-28.0)	13.3 (10.6-18.3)	0.78 (0.55-1.11)
≥65 to <75 (*n* = 281)	20.3 (17.3-24.9)	14.5 (11.6-17.4)	0.67 (0.52-0.87)
≥75 (*n* = 157)	16.9 (11.0-21.8)	15.5 (11.7-19.1)	0.91 (0.64-1.29)
Male (*n* = 467)	**17.5 (16.2-20.7)**	**13.7 (11.7-15.5)**	**0.73 (0.60-0.90)**
Female (*n* = 138)	**21.1 (15.7-25.9)**	**18.0 (12.6-23.8)**	**0.82 (0.56-1.20)**
ECOG PS 0 (*n* = 242)	20.7 (17.5-25.9)	19.5 (15.2-22.8)	0.90 (0.67-1.19)
ECOG PS ≥1[b] (*n* = 363)	17.0 (14.1-20.3)	11.6 (9.0-13.9)	0.66 (0.52-0.83)
Never smoker (*n* = 249)	17.9 (14.1-25.2)	14.1 (11.8-17.6)	0.74 (0.56-0.97)
Former smoker[c] (*n* = 318)	17.6 (15.5-20.3)	14.9 (11.6-17.9)	0.79 (0.62-1.01)
Epithelioid (*n* = 455)	**18.2 (16.9-21.9)**	**16.7 (14.9-20.3)**	**0.85 (0.69-1.04)**
Non-epithelioid[d,e] (*n* = 150)	**18.1 (12.2-22.8)**	**8.8 (7.4-10.2)**	**0.48 (0.34-0.69)**
PD-L1 <1% (*n* = 135)	17.3 (10.1-23.9)	16.6 (13.4-20.8)	0.99 (0.69-1.43)
PD-L1 ≥1%[f] (*n* = 451)	18.0 (16.8-21.4)	13.3 (11.6-15.4)	0.71 (0.57-0.88)



LCSS-Meso ASBI: Symptom burden

- Scale: 0-100
- MID: ≥ 10 points

Higher scores indicate **greater** symptom burden

LCSS-Meso 3-IGI: Symptom burden and QoL

- Scale: 0-300
- MID: ≥ 30 points

Higher scores indicate **lesser** symptom burden and impact on QoL

EQ-5D-3L UI: Health status and QoL

- Range: -0.59 to 1
- MID: ≥ 0.08

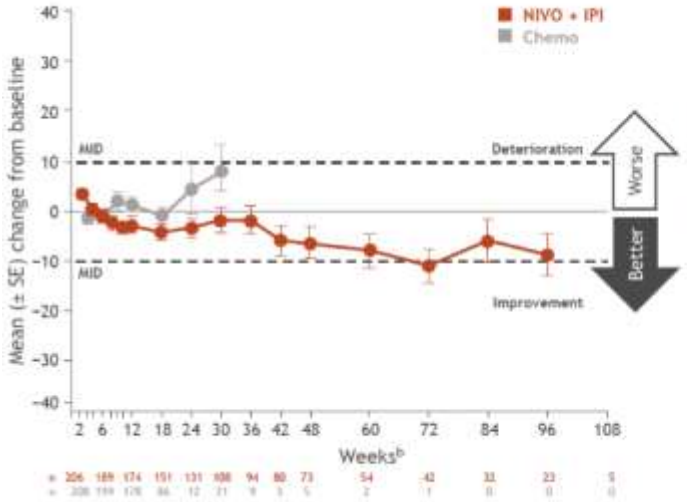
Higher scores indicate **better** health status

EQ-5D-3L VAS: Generic measure of health status

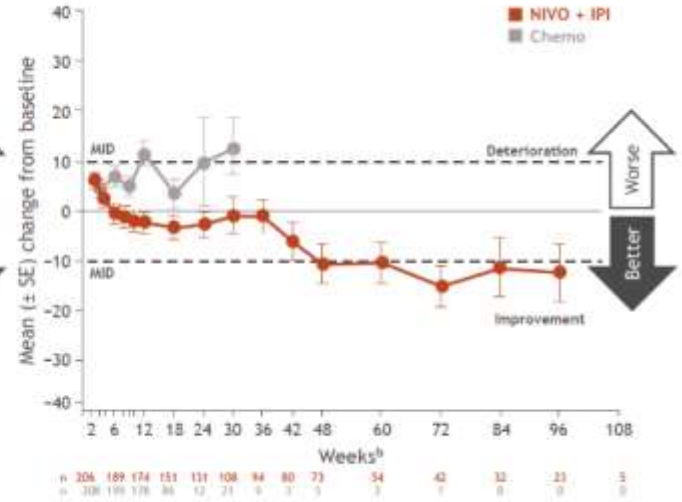
- Scale: 0-100
- MID: ≥ 7 points

Higher scores indicate **better** health status

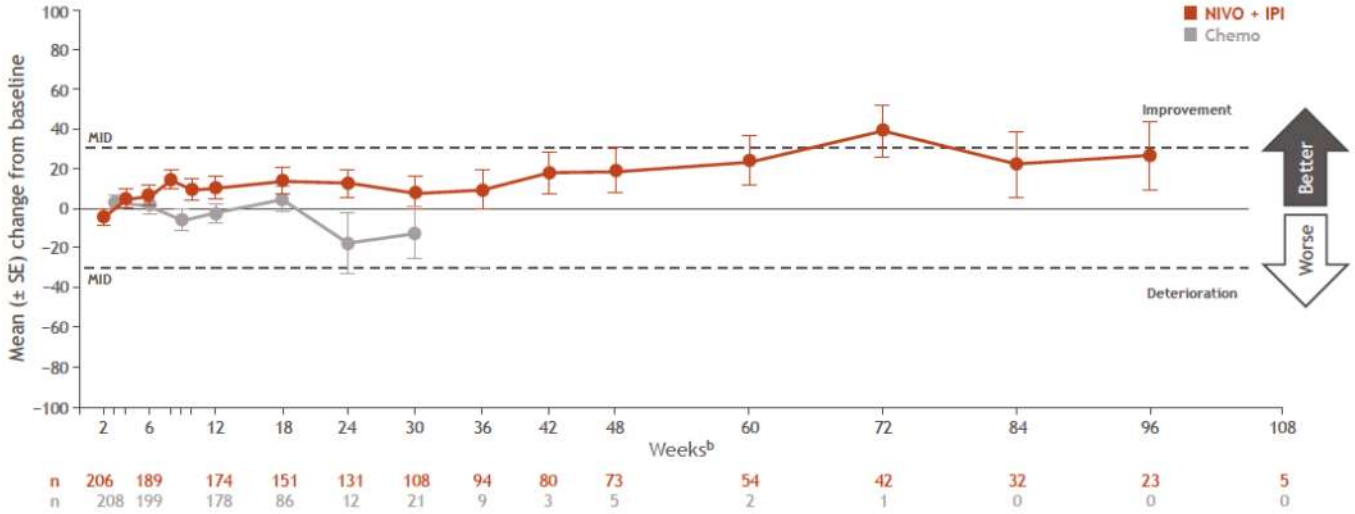
LCSS-Meso ASBI[a]



LCSS-Meso ASBI Item 2 (Fatigue)

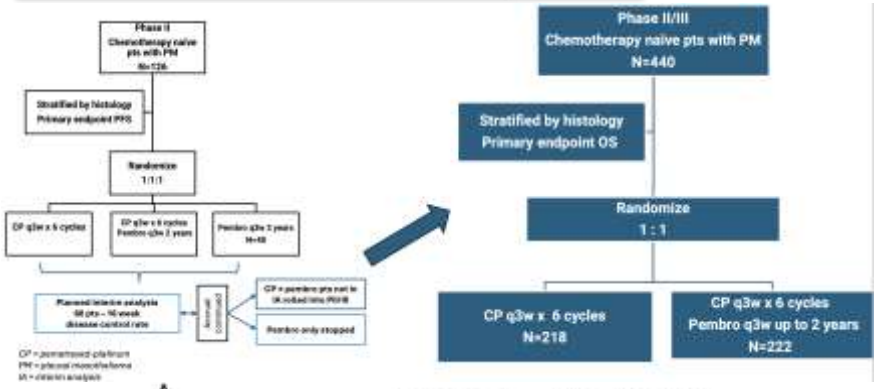


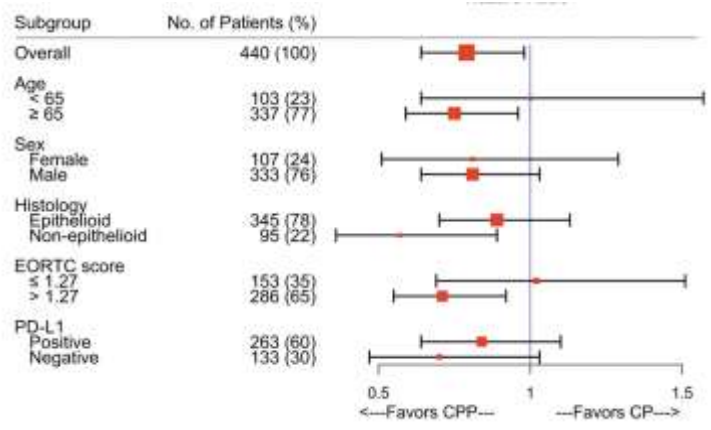
LCSS-Meso 3-IGI[a]



Scheerpereel A et al ESMO-IO 2020

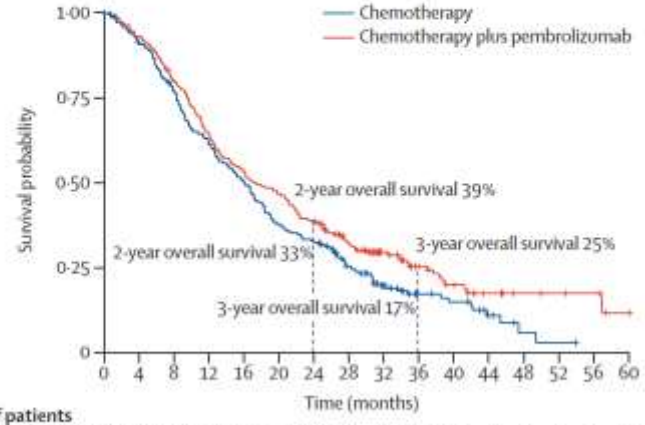
CT+Pembrolizumab IND227





A

	Chemotherapy	Chemotherapy plus pembrolizumab
Median overall survival (95% CI), months	16·13 (13·08–18·17)	17·28 (14·36–21·29)
Hazard ratio	0·79 (0·64–0·98)	
Stratified log-rank p-value	0·0324	

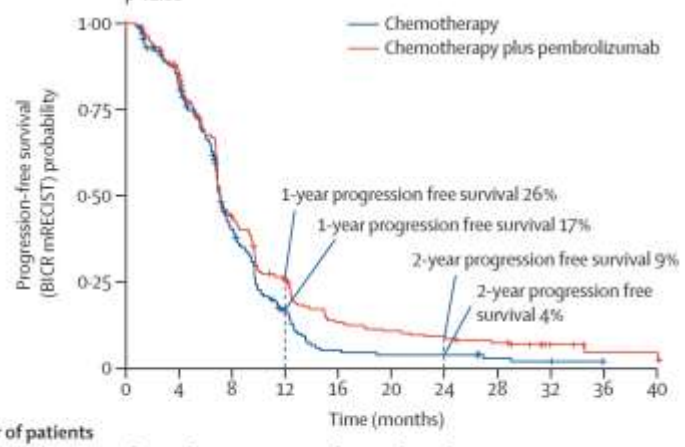


Number of patients

Chemotherapy	218	190	160	128	105	78	68	46	29	16	13	7	2	1	0	0
Chemotherapy plus pembrolizumab	222	207	177	143	119	103	86	62	39	25	17	10	6	5	4	1

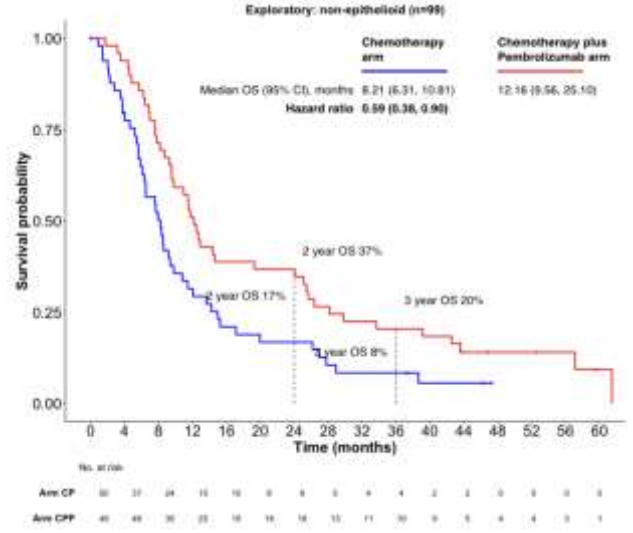
A

	Chemotherapy	Chemotherapy plus pembrolizumab
Median progression-free survival (95% CI), months	7·16 (6·83–7·69)	7·13 (6·93–8·12)
Hazard ratio	0·80 (0·65–0·99)	
Stratified log-rank p-value	0·0372	

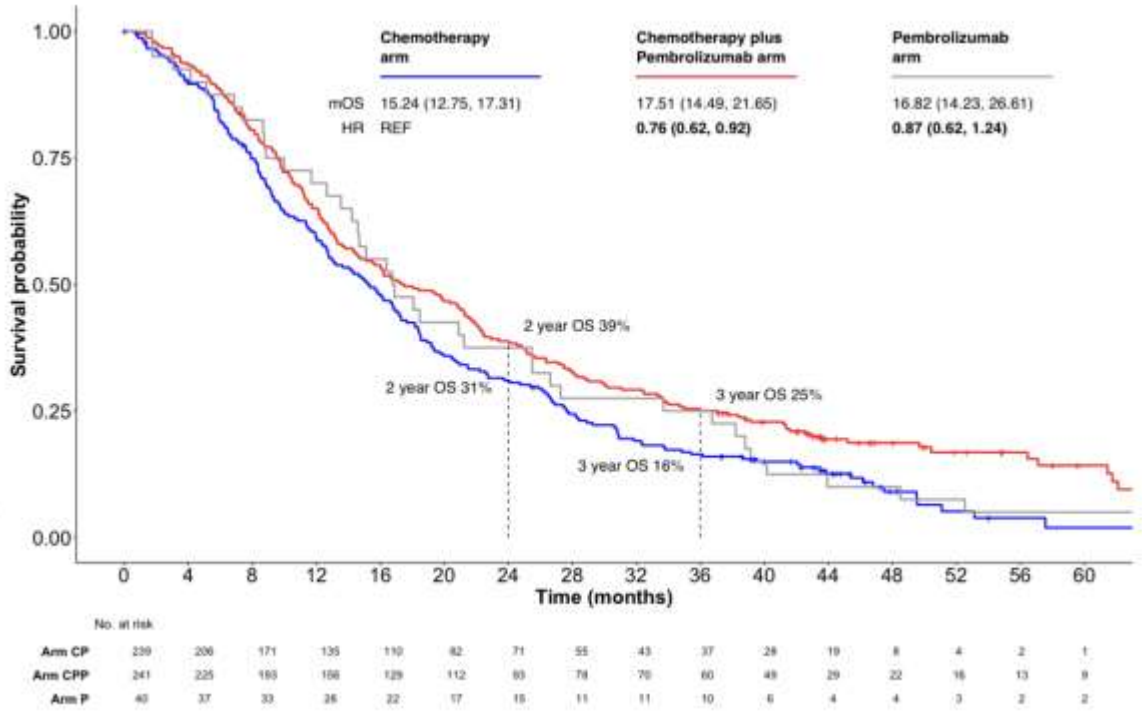


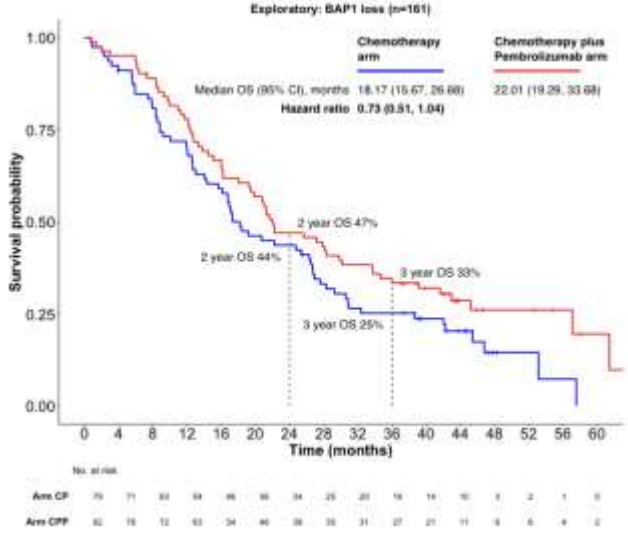
Number of patients

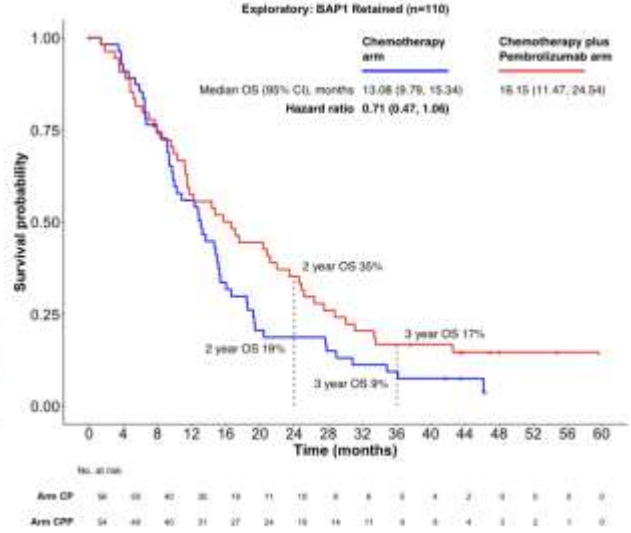
Chemotherapy	218	156	70	25	8	6	6	3	2	0	0
Chemotherapy plus pembrolizumab	222	187	91	50	25	20	17	13	5	2	2

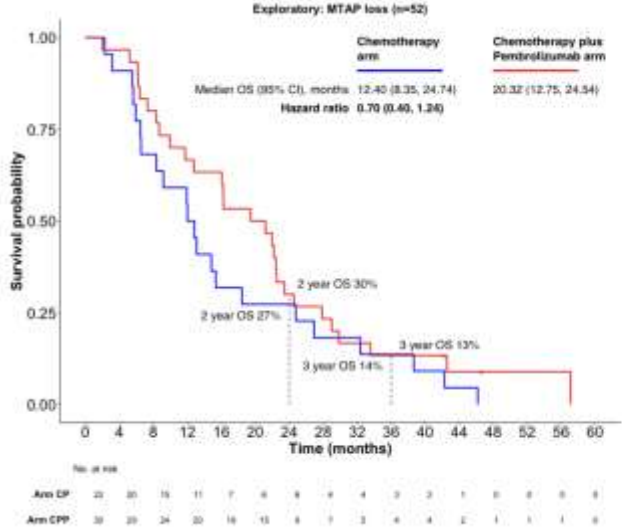


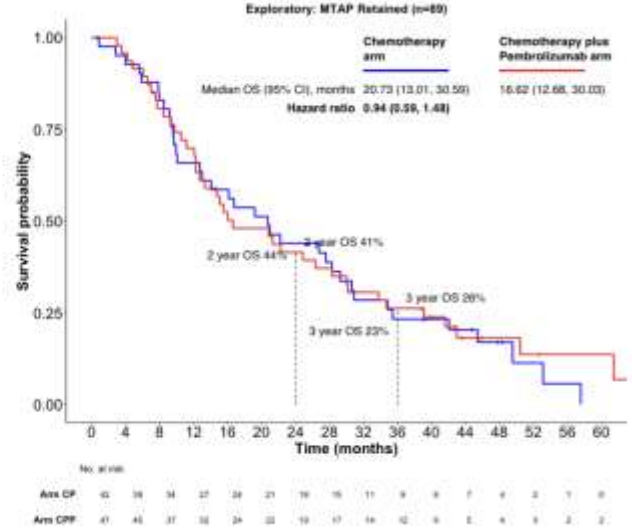
Chu Q et al Lancet 2023;405:2293-2306. Laurie SA et al WCLC 2025











Laurie SA et al WCLC 2025

EC BEAT-Meso 1L Fase III

Protocol amendment (v3.1): Primary endpoint **PFS & OS → OS only**
Sample size from **320 → 400 patients**

Key eligibility criteria

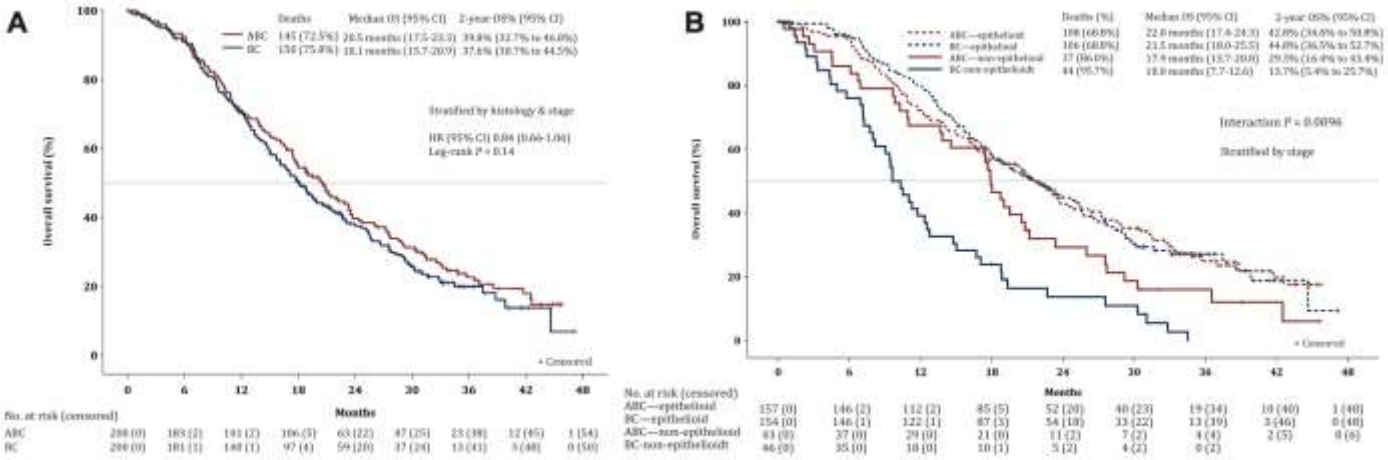
- ECOG PS 0-1
- Histologically confirmed advanced malignant pleural mesothelioma
- Not amenable for radical surgery
- Evaluable/measurable disease assessed by mRECIST v1.1

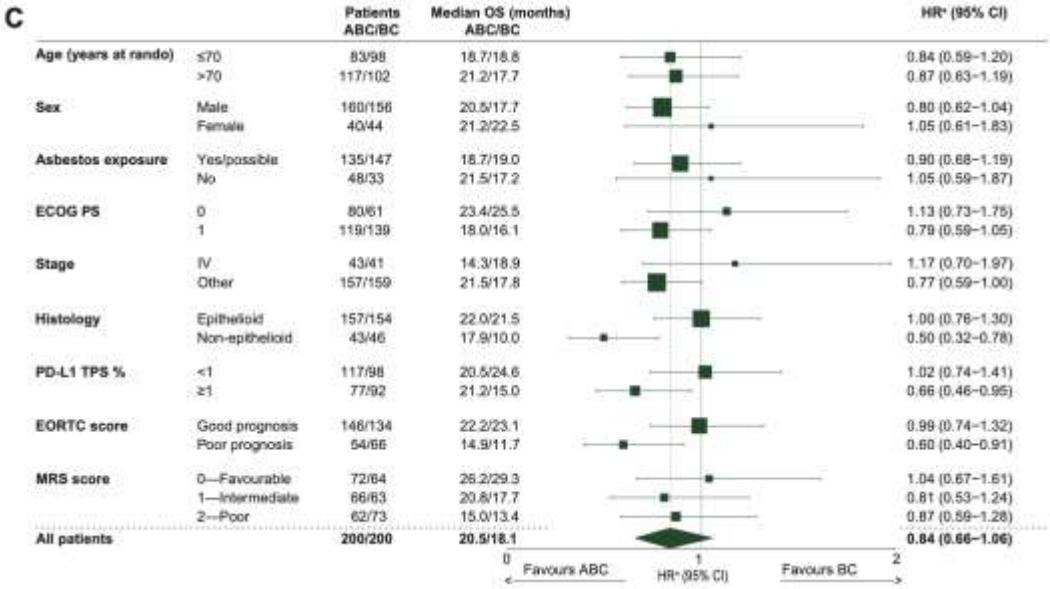
R* 1:1

ABC (n=200)
Atezolizumab: 1200mg Q3W
Bevacizumab: 15mg/kg Q3W
until PD or unacceptable toxicity
Chemotherapy (4 - 6 cycles):
Carboplatin AUC 5 + Pemetrexed 500mg/m² Q3W

BC (n=200)
Bevacizumab: 15mg/kg Q3W until PD or unacceptable toxicity
Chemotherapy (4 - 6 cycles):
Carboplatin AUC 5 + Pemetrexed 500mg/m² Q3W

*__Stratified by__: Histology (Epithelioid vs Not) & Stage (IV vs Other)

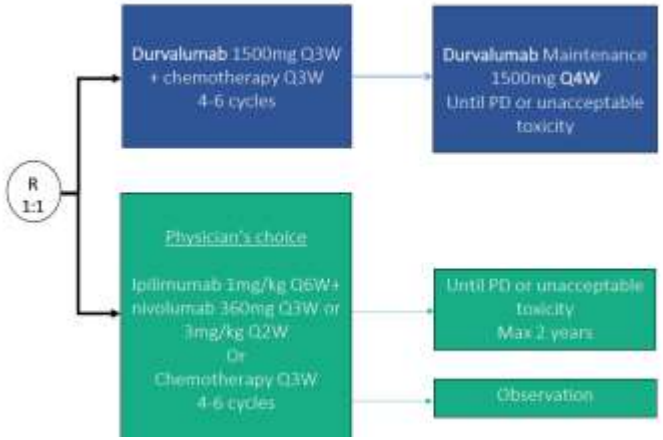




- AEs ≥ 3: 55.3 % vs 47.2 %
- AEs treatment-related: 31.2 % vs 15.1 %
- Mortality: 3.5 % vs 0.5 %
- Treatment discontinuation: 27.1 % vs 14.6 %

Felip E et al. Ann Oncol 2025:36:548-560

CT+Durvalumab DREAM3R

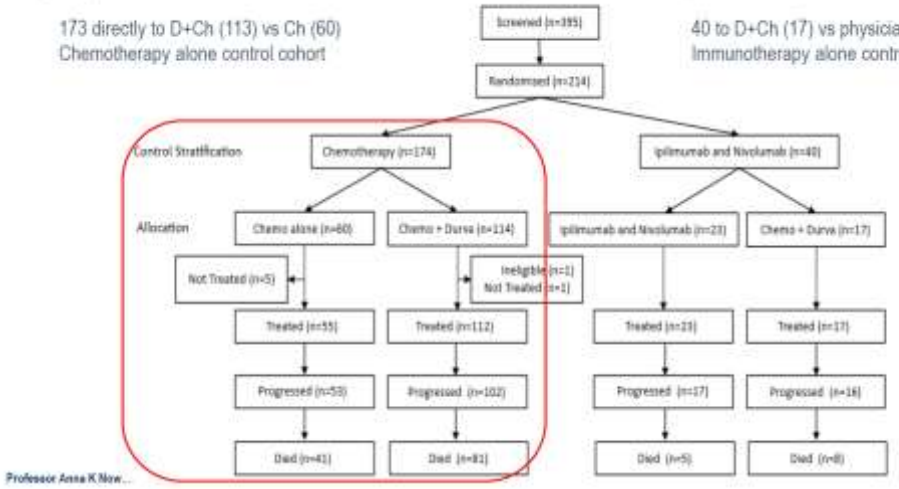


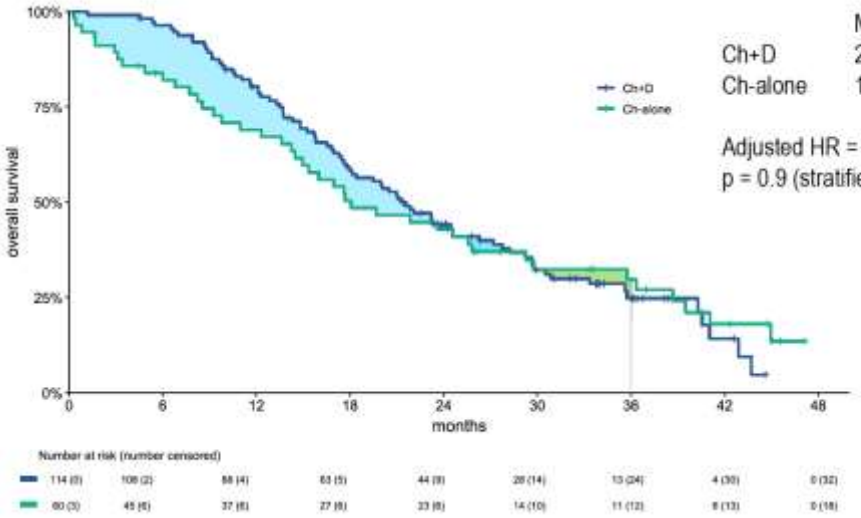
93% Epitelioid

214 participants were randomised from 3 Feb 2021 to 30 Nov 2023 (Australia 147, USA 67)

173 directly to D+Ch (113) vs Ch (60)
Chemotherapy alone control cohort

40 to D+Ch (17) vs physician's choice of Ch or NI (23)
Immunotherapy alone control stratum

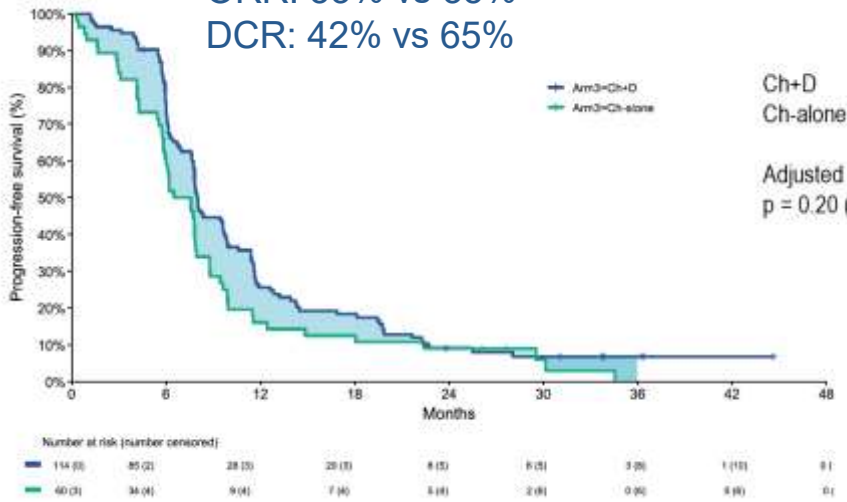




	Median OS in months	RMST
Ch+D	21 (95% CI 18, 27)	23 mo
Ch-alone	18 (95% CI 14, 30)	21 mo

Adjusted HR = 0.92 (95% CI 0.63, 1.36)
p = 0.9 (stratified log-rank test)

ORR: 53% vs 35%
DCR: 42% vs 65%



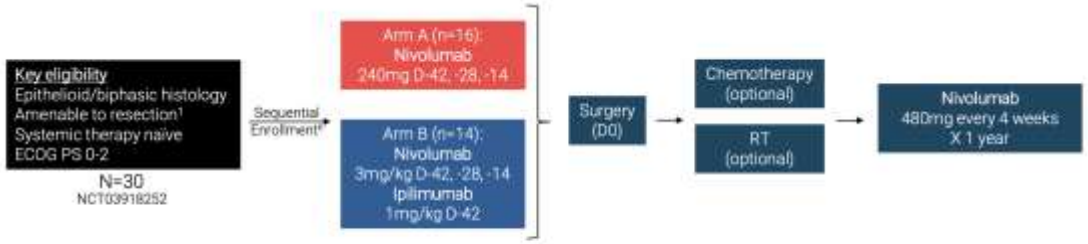
	Median PFS in months
Ch+D	8 (95% CI 8, 10)
Ch-alone	7 (95% CI 6, 8)

Adjusted HR = 0.70 (95% CI 0.5, 0.98)
p = 0.20 (stratified log-rank test)

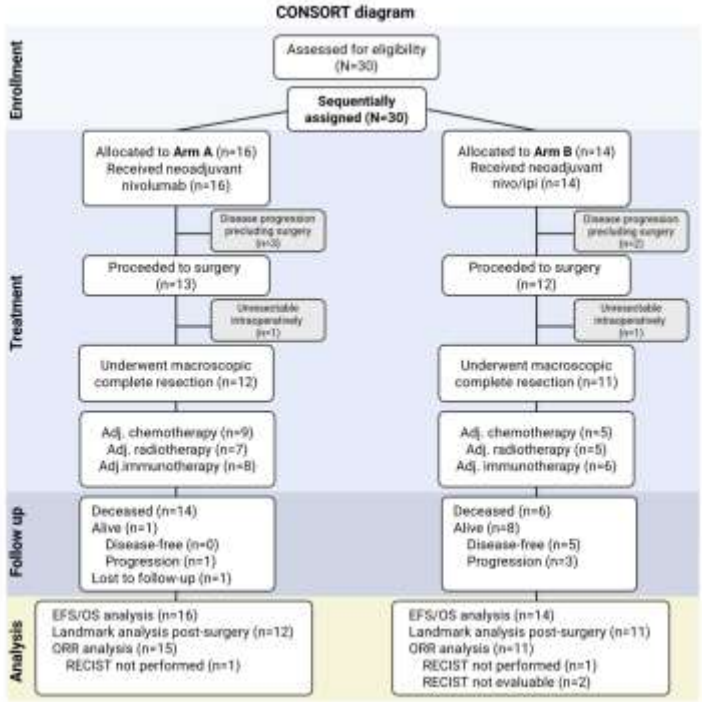
Nowak AK et al ESMO 2025

Trial	Schedule	Patients	ORR	mPFS	mOS
CM 743	Nivo-Ipi	303	40 %	6.8 m	18.1 m
DREAM	Cis-Pem-Durvalumab	55	48 %	6.9 m	18.4 m
PrE0505	Cis-Pem-Durvalumab	55	56.%	6.7 m	20.5 m
JME-001	Cis-Pem-Nivolumab	18	78 %	8 m	20.8 m
CCTG IND227	Cis-Pem-Pembrolizumab	222	61 %	7.1 m	17.2 m
BEAT-Meso	Atezo-Bevaciz-Carb-Pem	200	55%	9.2 m	20.5 m
DREAM3R	Cis/Carb-Pem-Durvalumab	114	53%	8 m	21 m

Baas P et al. Lancet. 2021;397:375-386. Nowak AC et al Lancet Oncol 2020;21:1213-1223. Forde PM et al Nat Med 2021;27:1910-1920.
Miyamoto Y et al JITC 2021 11:e003288. doi:10.1136/jitc-2021-003288. Chu Q et al Lancet 2023;405:2293-2306 Nowak AK et al ESMO 2025



Primary Endpoints: Feasibility, Safety
Secondary Endpoints: ORR[2], Safety of adjuvant nivo[3]
Exploratory Endpoints: PFS[4], OS[5], Longitudinal ctDNA assessment, genomic/immunologic analyses, gut microbiome



Nivo
n=16
Median f/u 43.2mo

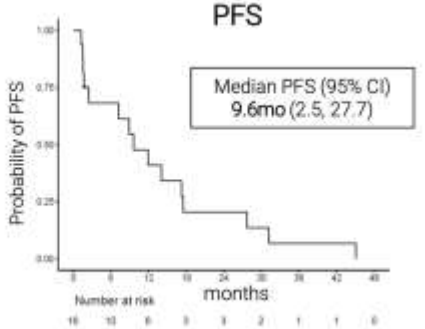
Nivo plus Ipi
n=14
Median f/u 24.1mo

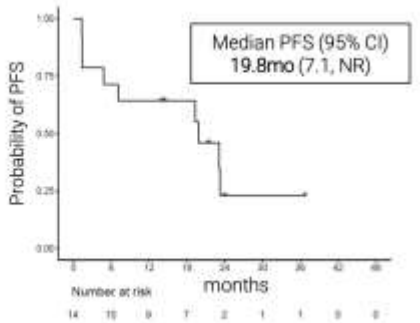
Surgical Feasibility

	Arm A Nivo (n=16)	Arm B Nivo/Ipi (n=14)
Proceeded to Surgery, n(%)	13 (81.3%)	12 (85.7%)
Completed Surgery, n(%)	12 (75%)	11 (78.6%)
- P/D	- 10 (83.3%)	- 9 (81.8%)
- EPP	- 2 (16.7%)	- 2 (18.2%)
Posterior mean [90% credible interval]	0.78 [0.60, 0.92]	0.81 [0.64, 0.94]

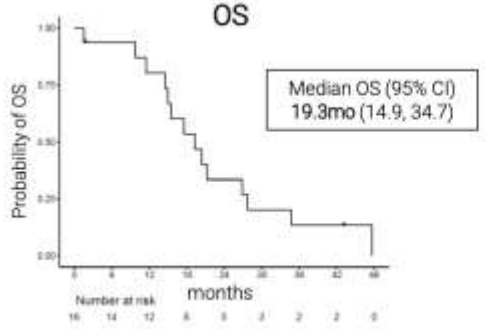
P/D: pleurectomy/decortication
EPP: extrapleural pneumonectomy

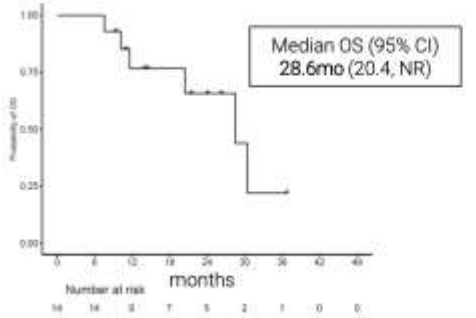
PFS





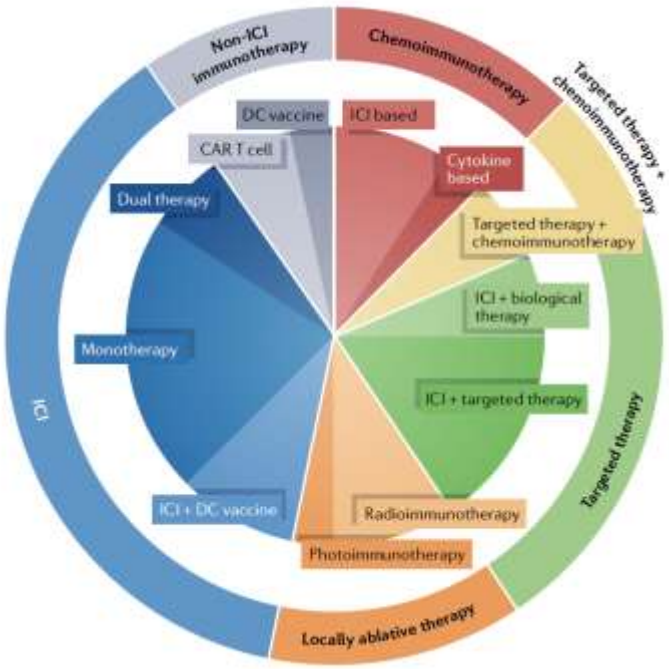
OS





Patient Disposition
Deceased – 14 (88%)
Alive – 1 (6%)
Disease-free – 0 (0%)
Progression – 1 (100%)
Lost to f/u – 1 (6%)

Patient Disposition
Deceased – 6 (43%)
Alive – 8 (57%)
Disease-free – 5 (63%)
Progression – 3 (38%)



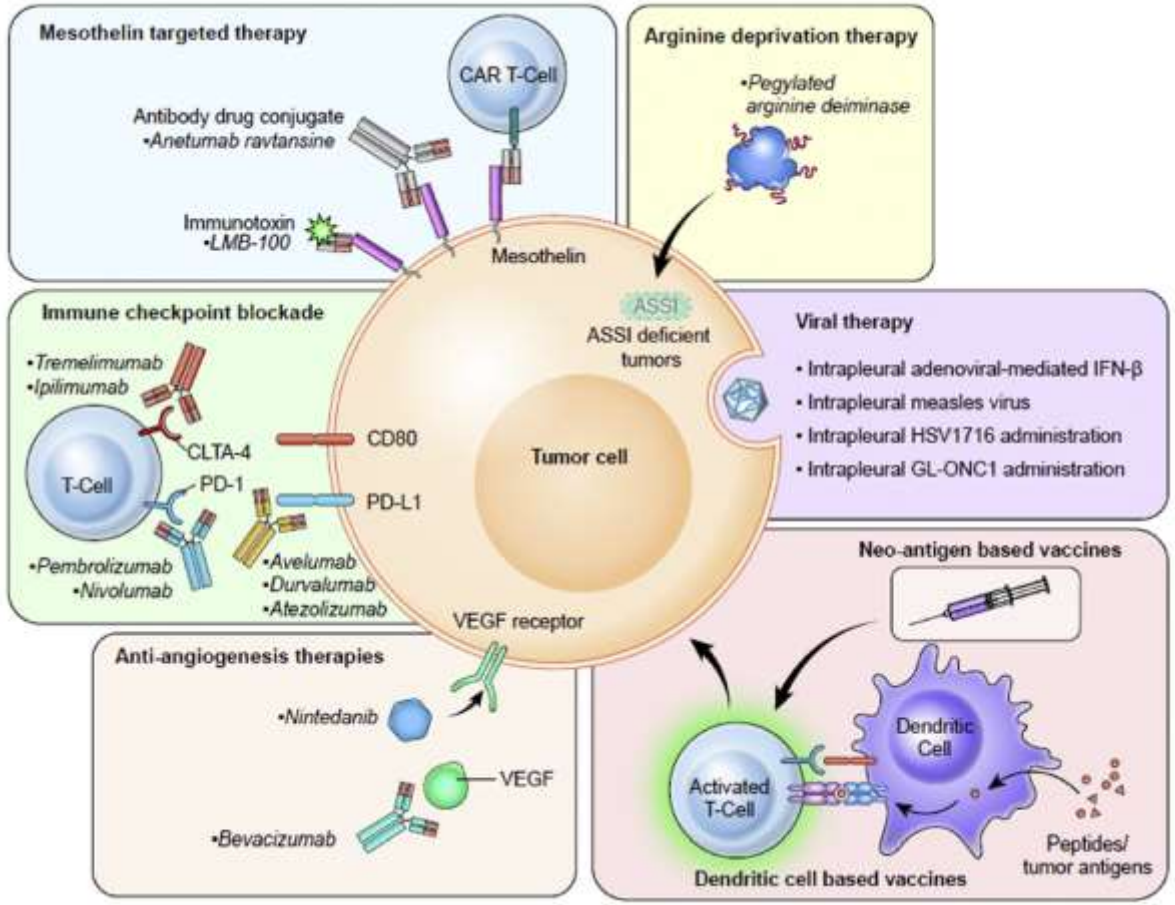
Surface targets:
Mesotelin
FAP

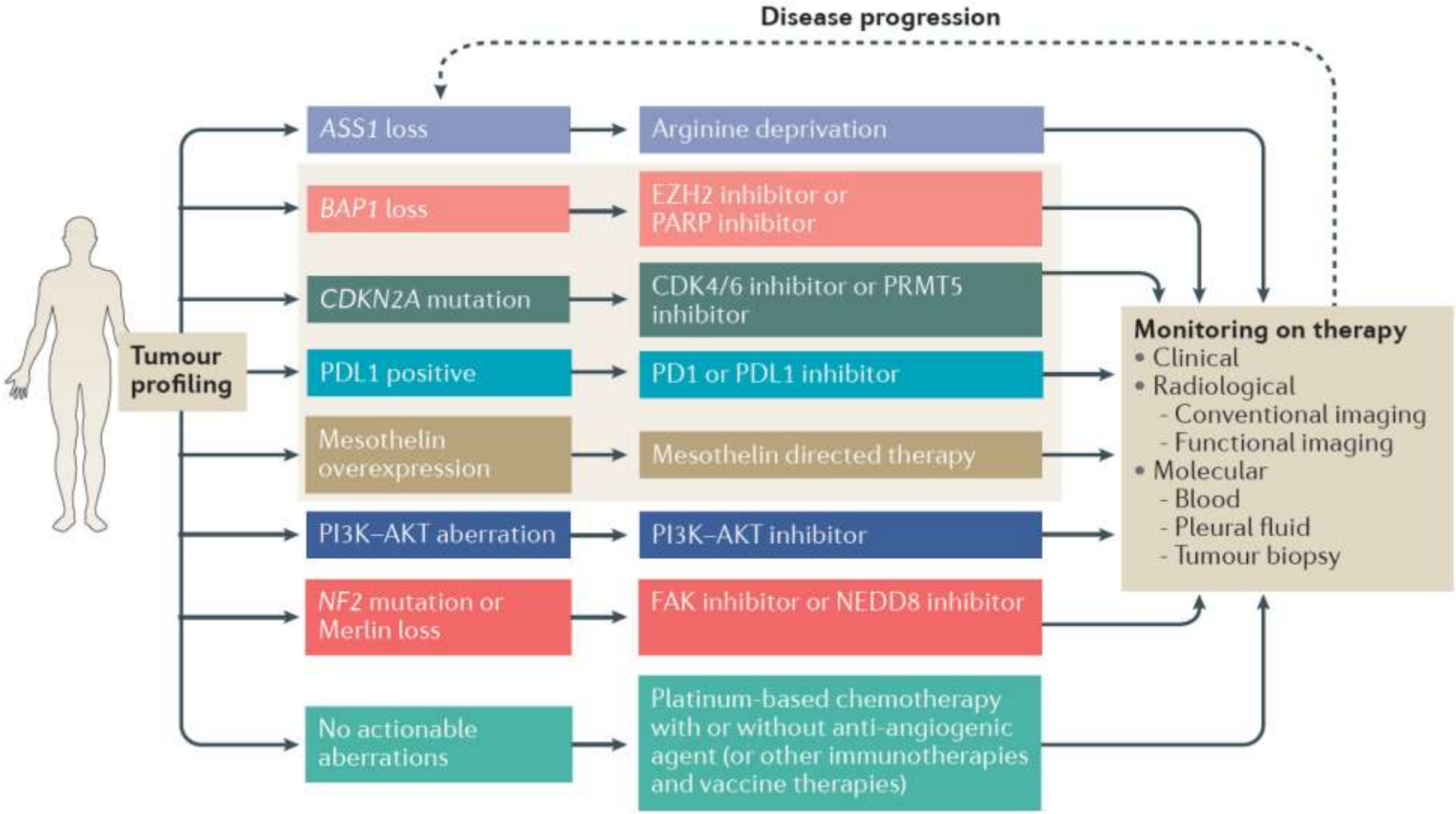
ADCs

Genomic alterations:
BAP1
CDKN2
p16
Hedgehog
NF2
MTAP

Metabolism interference:
Deprivación Arginina

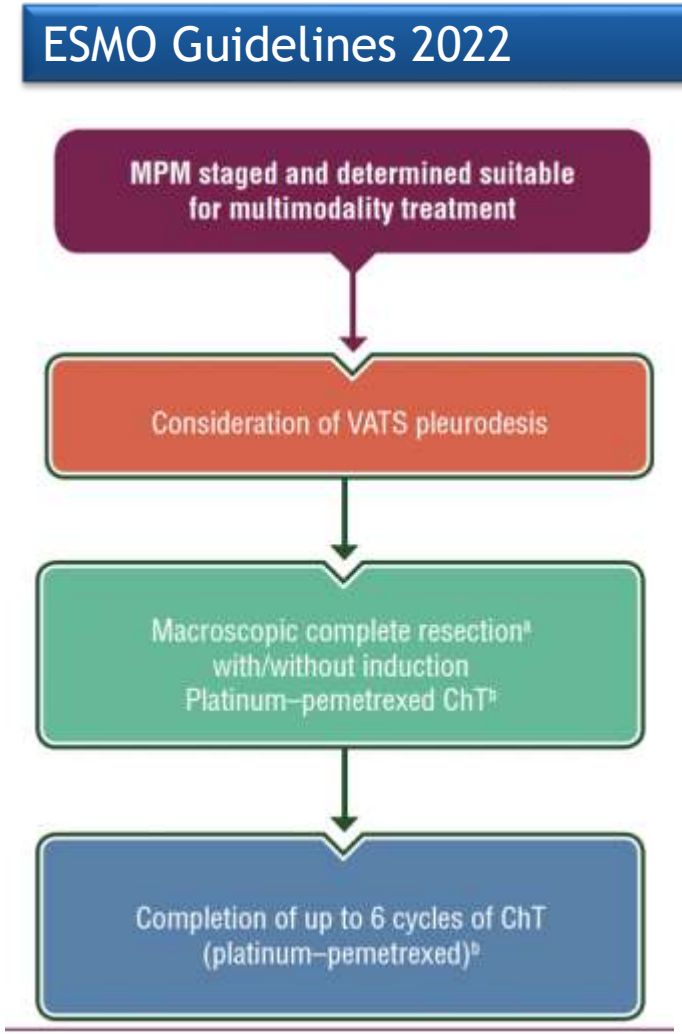
Intrapleural therapies

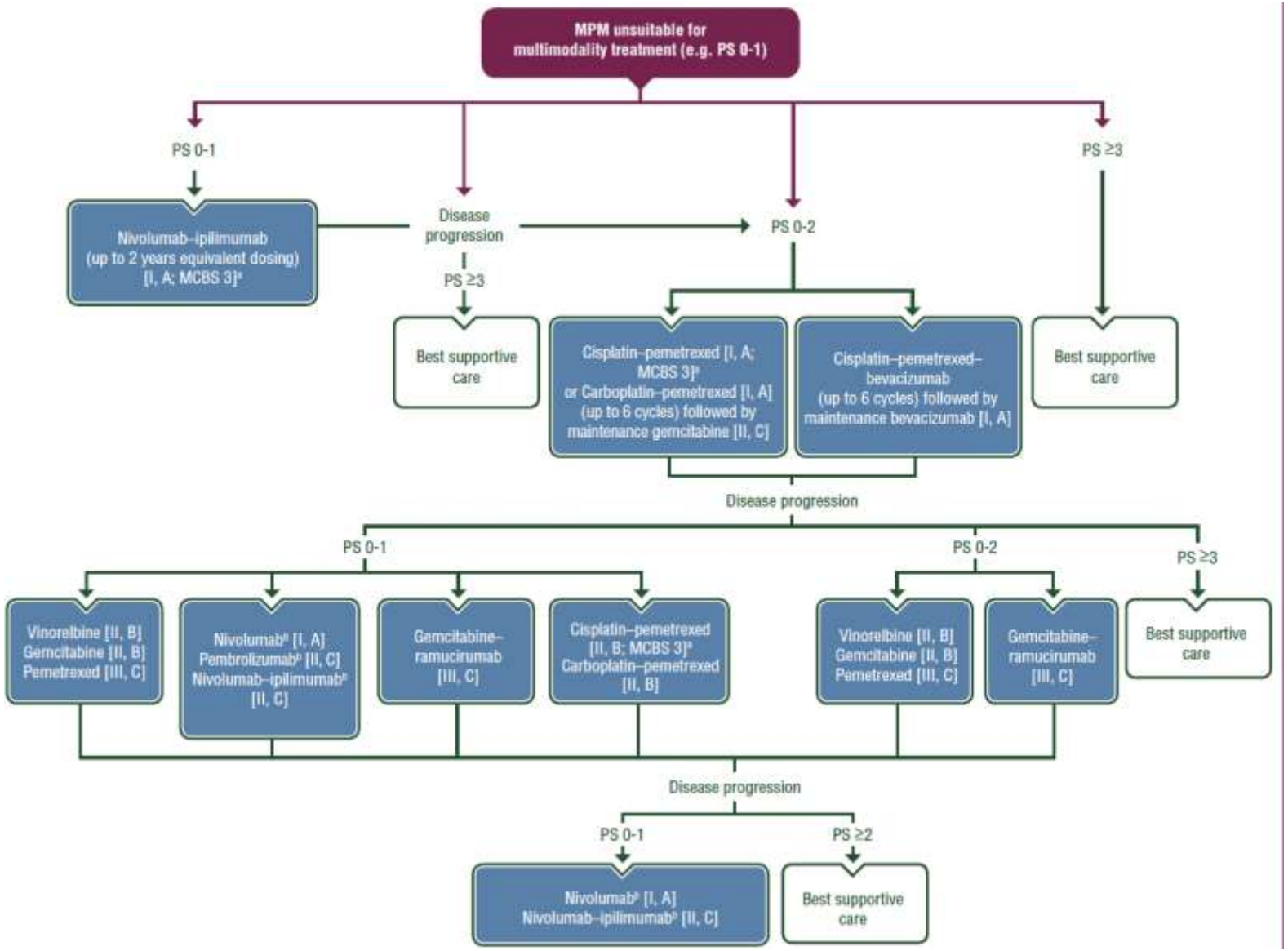




YAP TA et al. Nat Rev Cancer 2017;475-488

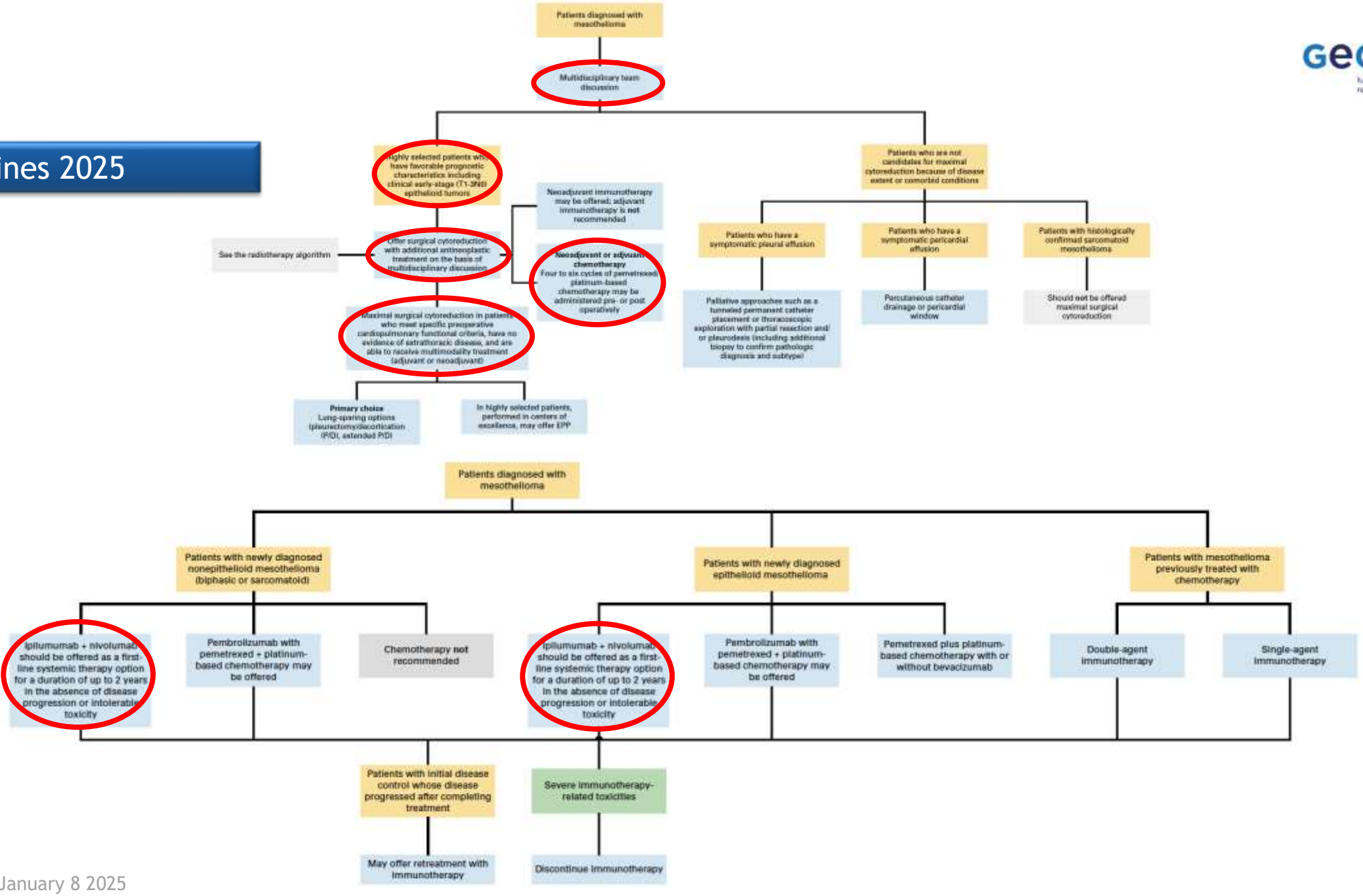
ESMO Guidelines 2022





Popat S et al. Ann Oncol 2022;33:129-142

ASCO Guidelines 2025



Kindler H et al. JCO January 8 2025

To wrap up in MPM treatment

- MPM predominantly treated with systemic treatment even in early stage
- CT with Platinum and antifolates achieved therapeutic ceilinge
- Nivolumab plus Ipilimumab superior to CT but mainly in sarcomatoid
- CT + Pembrolizumab superior to CT but mainly in sarcomatoid
- Benefit of 2L Nivolumab after CT in epitelioid subtype
- Priority of clinical research: ADCs, MTAP, BAP1, intrapleural approach

16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

THANK YOU!!

Gracias!!

Ben agraït!!

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GECP lung cancer research