Systemic Therapies for Mesothelioma

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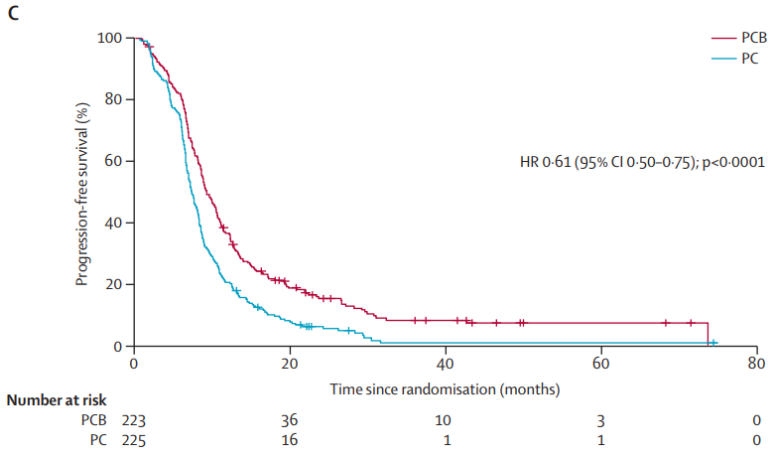
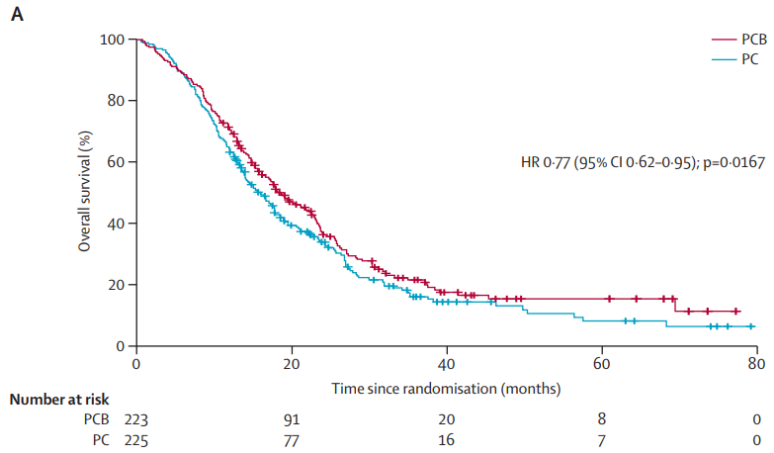
First Line Trials

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

- 448 patients randomized
- PFS: 9.2 vs 7.3 months
- OS: 18.8 vs 16.1 months





Zalcman, Lancet 2016

Tumour Treating Fields in combination with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): a multicentre, single-arm phase 2 trial

- 8o patients with unresectable mesothelioma enrolled
  - Epithelioid 53
  - Sarcomatoid or BP 21
  - Unknown 6
- Platinum plus pemetrexed every 21 days, up to 6 cycles
- TTFields at least 18 hours per day
- Only 56% of patients received subsequent treatment
- Only 9% of patients received subsequent immunotherapy

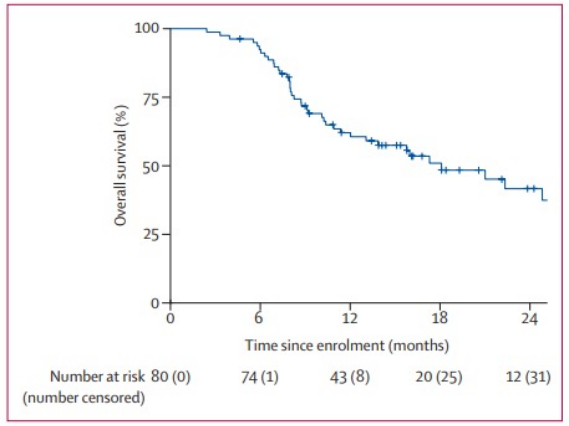


Figure 2: **Overall survival**
Kaplan-Meier analyses of overall survival in the intention-to-treat population.

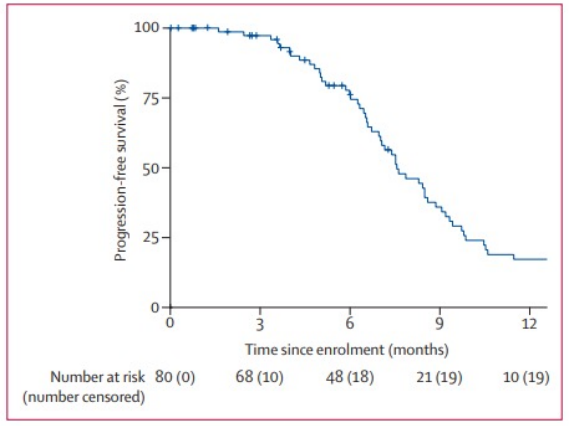


Figure 3: **Progression-free survival**
Kaplan-Meier analyses of progression-free survival in the intention-to-treat population.

Median OS	**18.2 mo**
1 yr OS	**62.2%**
2 yr OS	**41.9%**
Median PFS	**7.6 mo**

Ceresoli, Lancet Oncol 2019

Canadian Cancer Trials Group IND.227: A Phase 2 Randomized Study of Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma

	Pembro + CT (n = 222)	CT (n = 218)	HR (95% CI)	*P* Value*
Median OS, mo (95% CI)	17.28 (14.36-21.29)	16.13 (13.08-18.17)	0.79 (0.64-0.98)	.0324
Median PFS, mo (95% CI)	7.13 (6.93-8.12)	7.16 (6.83-7.69)	0.80 (0.65-0.99)	.0372

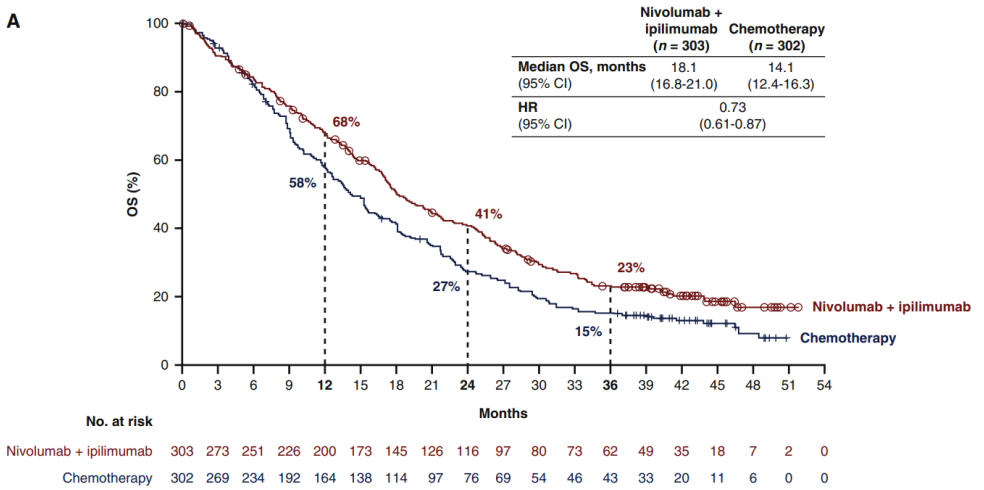
Subgroup	Pembro + CT	CT	HR (95% CI)
Epithelioid histology (n = 345) ▪ Median OS, mo (95% CI)	19.8 (16.0-22.2)	18.2 (16.0-20.4)	0.89 (0.7-1.13)
Nonepithelioid histology (n = 95) ▪ Median OS, mo (95% CI)	12.3 (8.67-21.2)	8.21 (5.85-10.8)	0.57 (0.36-0.89)
PD-L1 negative (n = 133) ▪ Median OS, mo (95% CI)	22.4 (14.4-28.0)	18.5 (13.2-23.7)	0.7 (0.47-1.03)
PD-L1 positive (n = 263) ▪ Median OS, mo (95% CI)	16.2 (12.7-20.3)	15.0 (12.0-17.0)	0.84 (0.64-1.10)

Piccirillo, JTO 2023

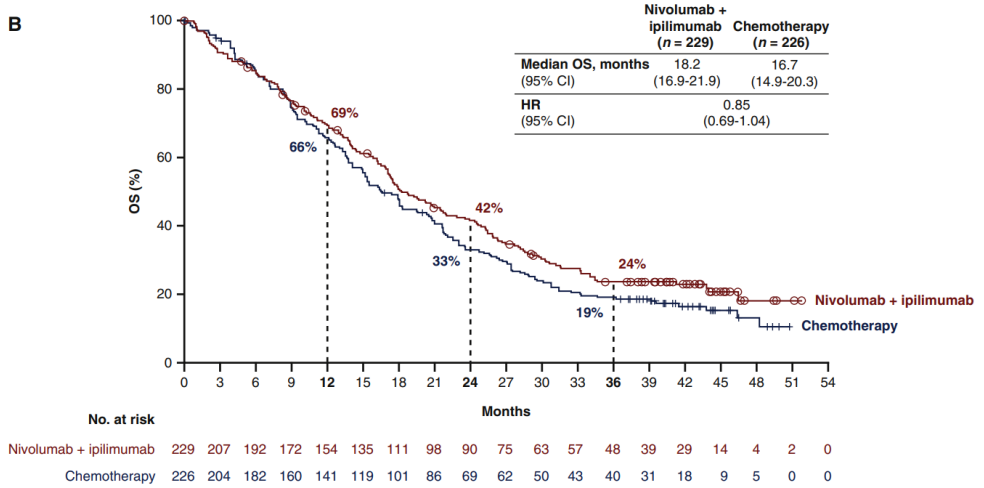
First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743

- 605 patients randomized
- OS: 18.1 vs 14.1 mo
- PFS: 6.8 vs 7.2 mo
- ORR: 40 vs 44%
- DOR: 11.6 vs 6.7 mo
- Only 21.5% of chemo patients received subsequent immunotherapy

All Patients



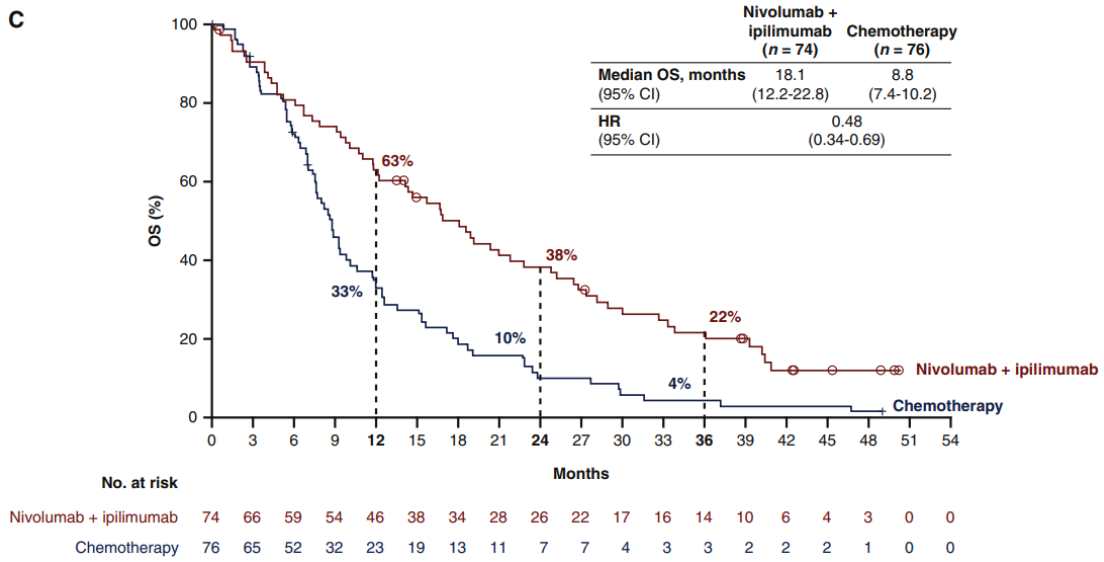
Epithelioid



Peters, Annals of Onc, 2022

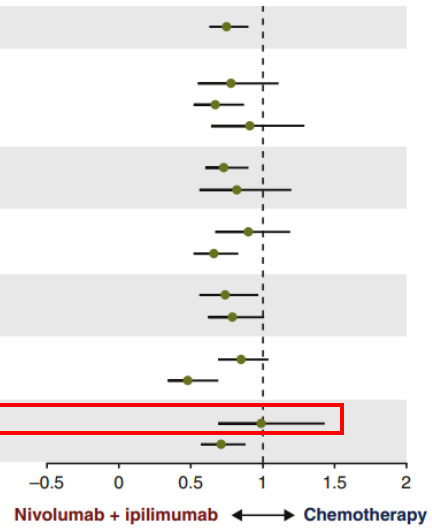
First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743

Non-epithelioid Histology



	Nivolumab + ipilimumab (*n* = 74)	Chemotherapy (*n* = 76)
Median OS, months (95% CI)	18.1 (12.2-22.8)	8.8 (7.4-10.2)
HR (95% CI)	0.48 (0.34-0.69)	

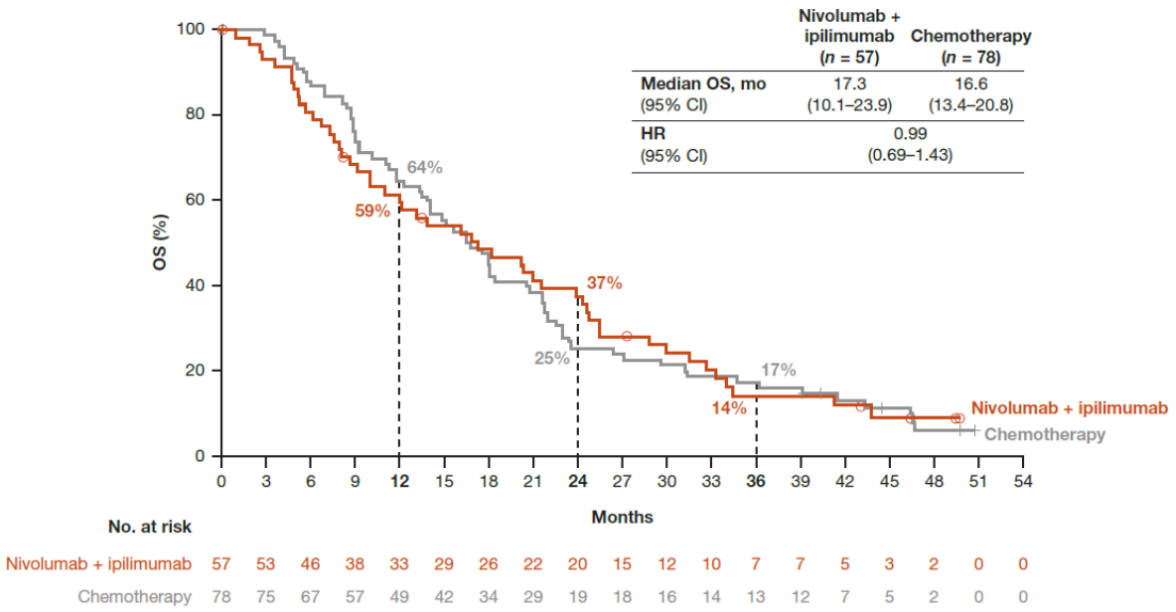
Subgroup	Median OS, months (95% CI) Nivolumab + ipilimumab (*n* = 303)	Chemotherapy (*n* = 302)	Unstratified HR (95% CI)
All randomized (*N* = 605)	18.1 (16.8-21.0)	14.1 (12.4-16.3)	0.75[a] (0.63-0.90)
Age, years			
<65 (*n* = 167)	17.2 (13.1-28.0)	13.3 (10.6-18.3)	0.78 (0.55-1.11)
≥65 to <75 (*n* = 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)



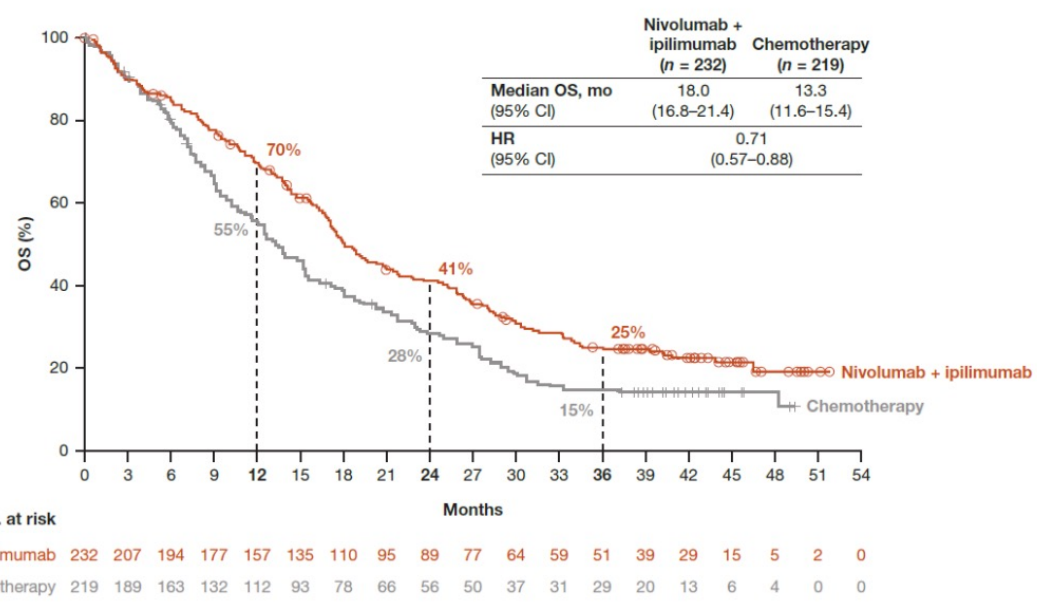
Peters, Annals of Onc, 2022

First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743

PD-L1 < 1%



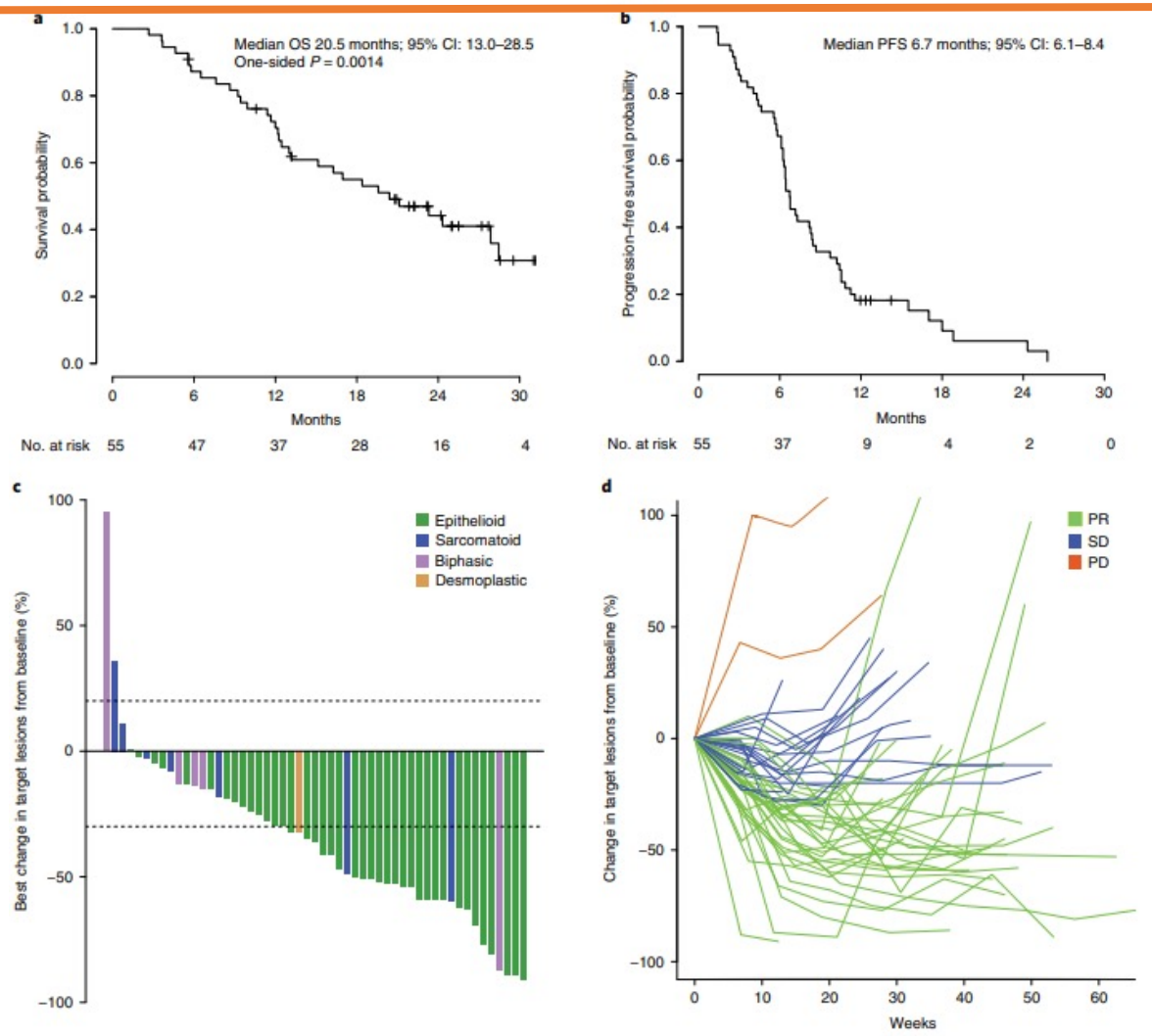
PD-L1 ≥ 1%



Peters, Annals of Onc, 2022

Durvalumab with platinum-pemetrexed for unresectable pleural mesothelioma: survival, genomic and immunologic analyses from the phase 2 PrE0505 trial

- 55 Patients with untreated, unresectable mesothelioma
  - Epithelioid 41
  - Sarcomatoid 7
  - Biphasic 6
- Median OS: 20.5 mo
- Median PFS: 6.7 mo
- ORR: 56.4%



Forde, Nature Medicine 2021

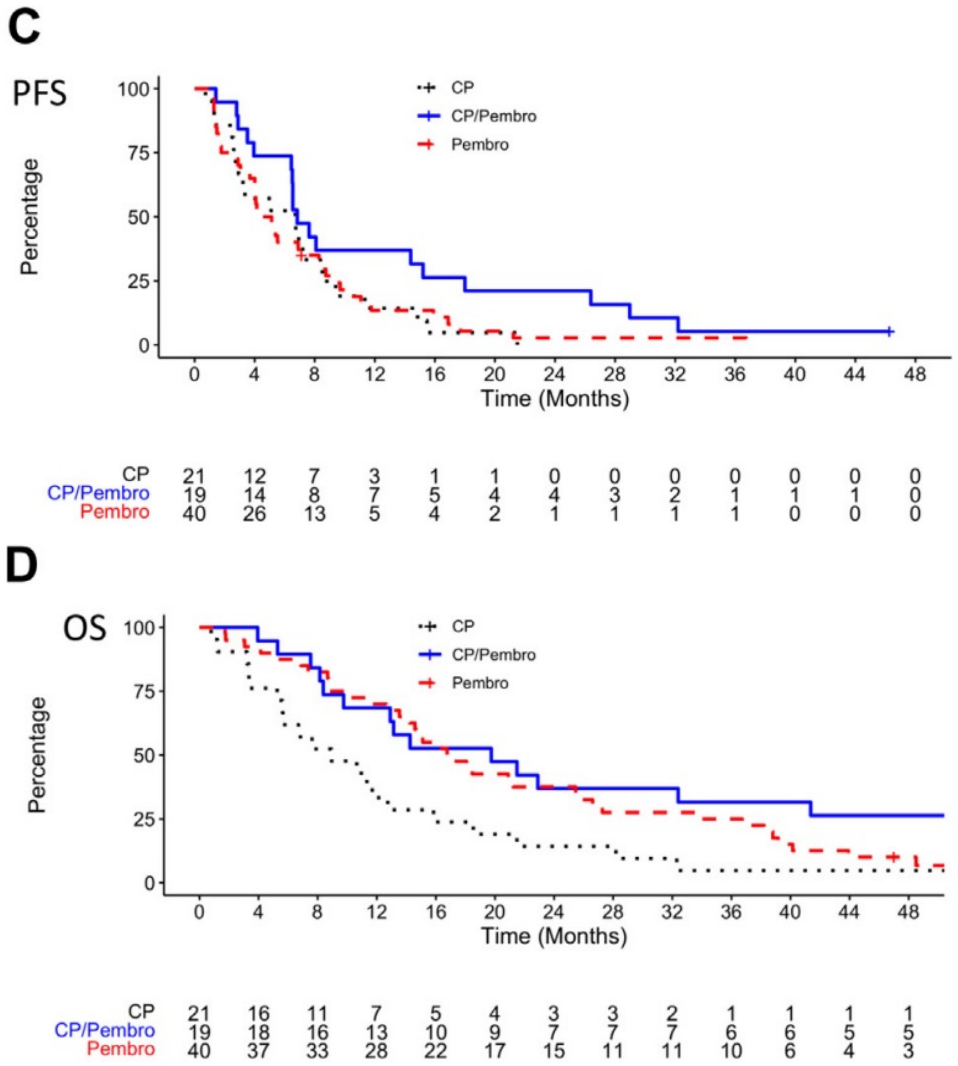
Brief Report: Canadian Cancer Trials Group IND.227: A Phase 2 Randomized Study of Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma

- 80 patients randomized to
  - Pemetrexed, platinum (21)
  - Pemetrexed, platinum, pembrolizumab (19)
  - Pembrolizumab (40)
- PFS

CP	**6.7 mo**
CPP	**6.8 mo**
P	**5.3 mo**

- OS

CP	**8.9 mo**
CPP	**19.8 mo**
P	**17.5 mo**



Piccirillo, J Thorac Onc 2023

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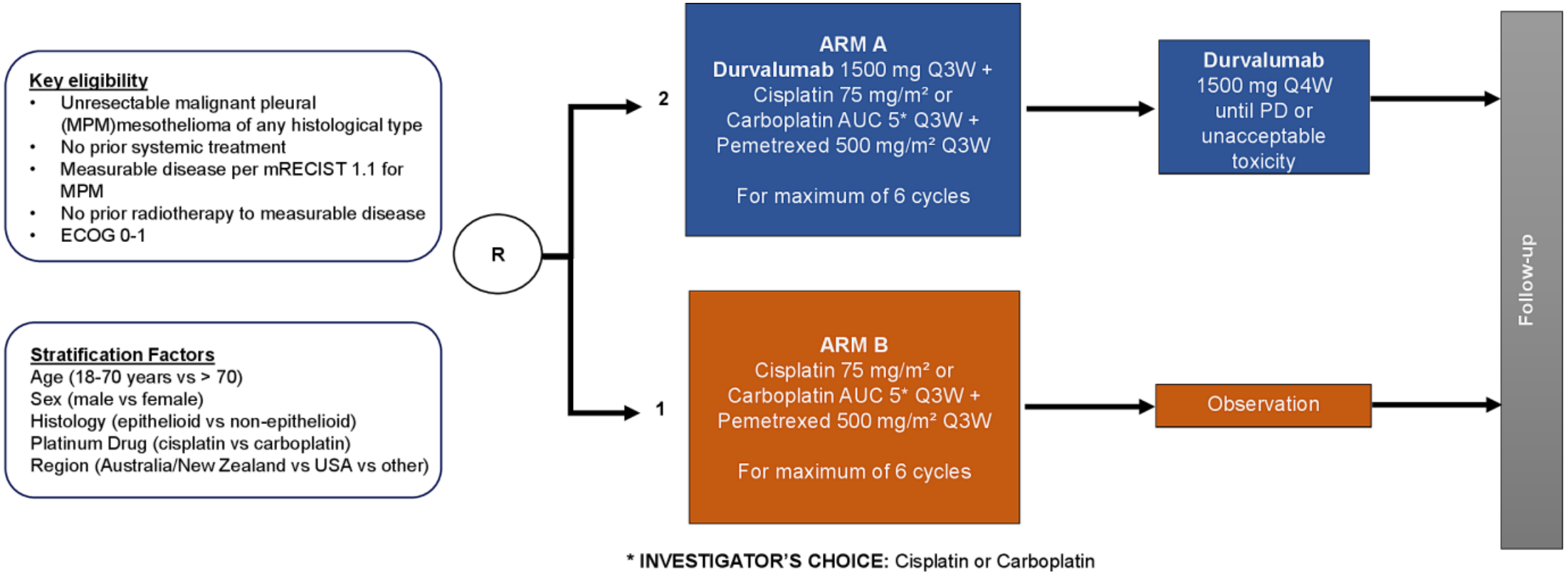


Kok, BMJ 2021

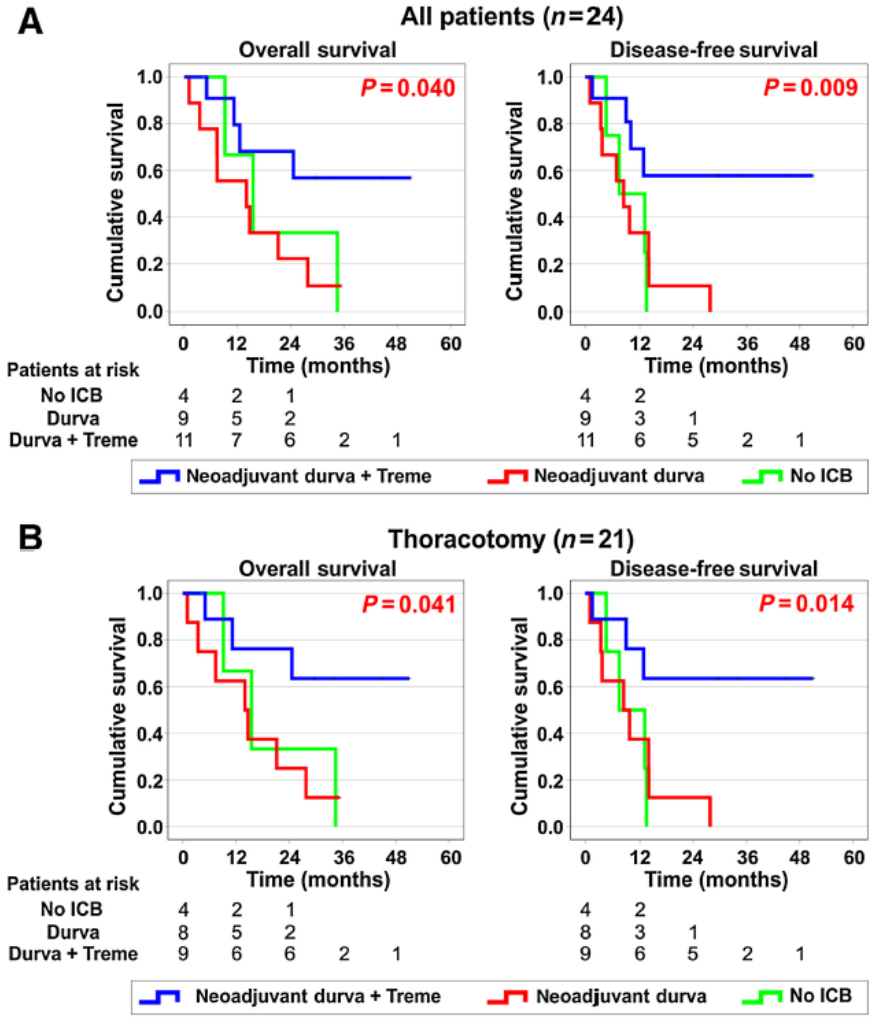
Perioperative Immunotherapy in Mesothelioma

NCT04177953	**Adjuvant platinum/pemetrexed/nivolumab**	**Nicita**	**Phase II, 92 Patients.**
NCT04996017	**Adjuvant atezolizumab**	**AtezoMeso**	**Phase III**
NCT03228537	**Neoadjuvant platinum/pemetrexed/atezolizumab**	**NCI**	**PPA + surgery +/- radiation, 29 patients**
NCT02592551	**Neoadjuvant Durvalumab vs durva/treme vs placebo**	**Baylor**	**See Below**
NCT02707666	**Neoadjuvant pembrolizumab**	**U of Chicago**	**Phase II, 15 patients**
NCT05647265	**Neoadjuvant ipi/nivo for sarcomatoid mesothelioma**	**Alliance**	**Phase II, 26 patients**
NCT03918252	**Neoadjuvant Nivolumab vs ipi/nivo**	**Hopkins**	**Phase II 30 patients**

A Phase II Window of Opportunity Study of Neoadjuvant PD-L1 versus PD-L1 plus CTLA-4 Blockade for Patients with Malignant Pleural Mesothelioma

- 24 patients randomized 2:2:1 to neoadjuvant
  - 9 Durvalumab
  - 11 Durva/Treme
  - 4 no ICI
- 16 epithelioid
- 8 non-epithelioid
- Chemotherapy allowed
- Surgery 3-6 weeks after ICI

- Increase In tertiary lymphoid structures
- Increased cytotoxic T-cell activation
- Increased effector memory T-cells



Lee et al. Clinical Cancer Research 2023

Gemcitabine and cisplatin plus nivolumab as organ-sparing treatment for muscle-invasive bladder cancer: a phase 2 trial

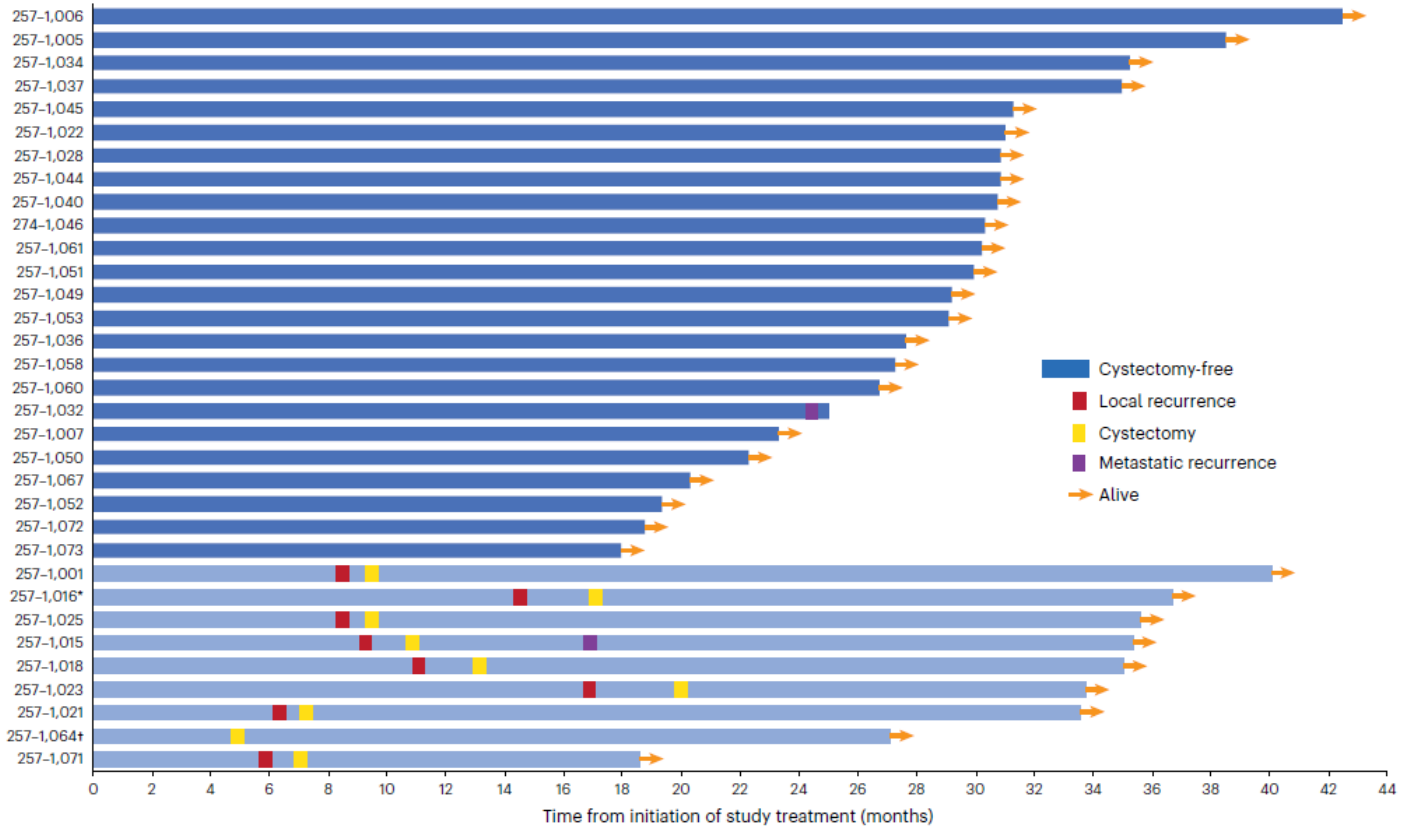


Fig. 2 | Clinical outcomes of patients enrolled on HCRN GU16-257 achieving a cCR. * Patient underwent cystectomy for radiographic changes concerning for local recurrence without evidence of cancer on biopsy or final cystectomy specimen. † Patient opted for immediate cystectomy.

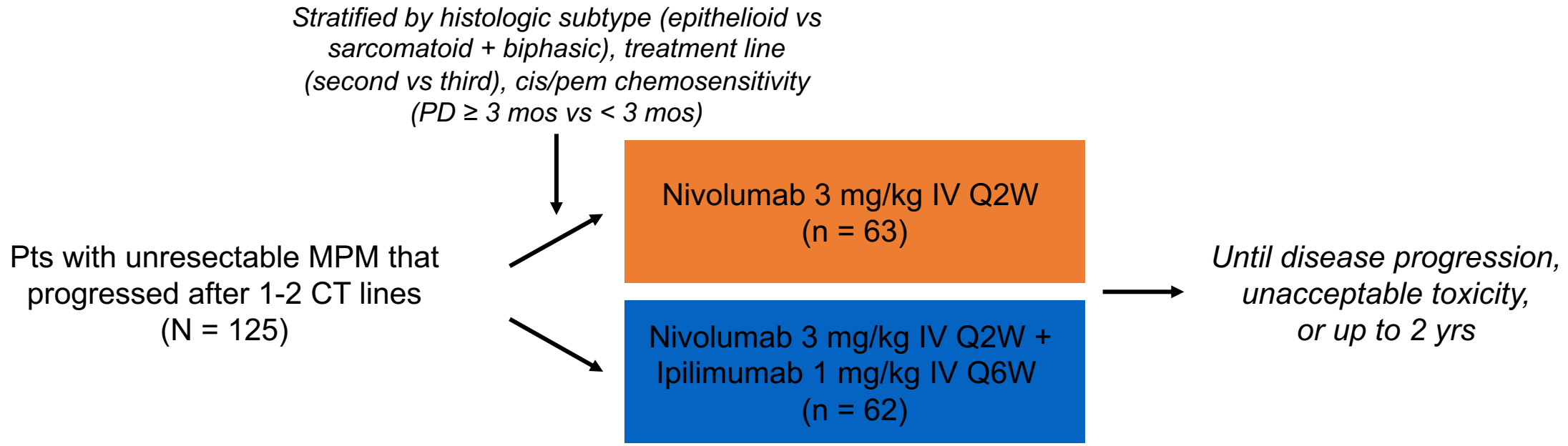
Galsky et al, Nature Medicine 2023

Second Line Therapy and Beyond

Therapeutic Targets

- CAR T
- Antiangiogenic drugs
- Mesothelin ADC
- AXL/PD-1 inhibition
- Vaccines
- Arginine
- PARP
- EGFR
- MEK
- MTOR
- CDK4/6

Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial

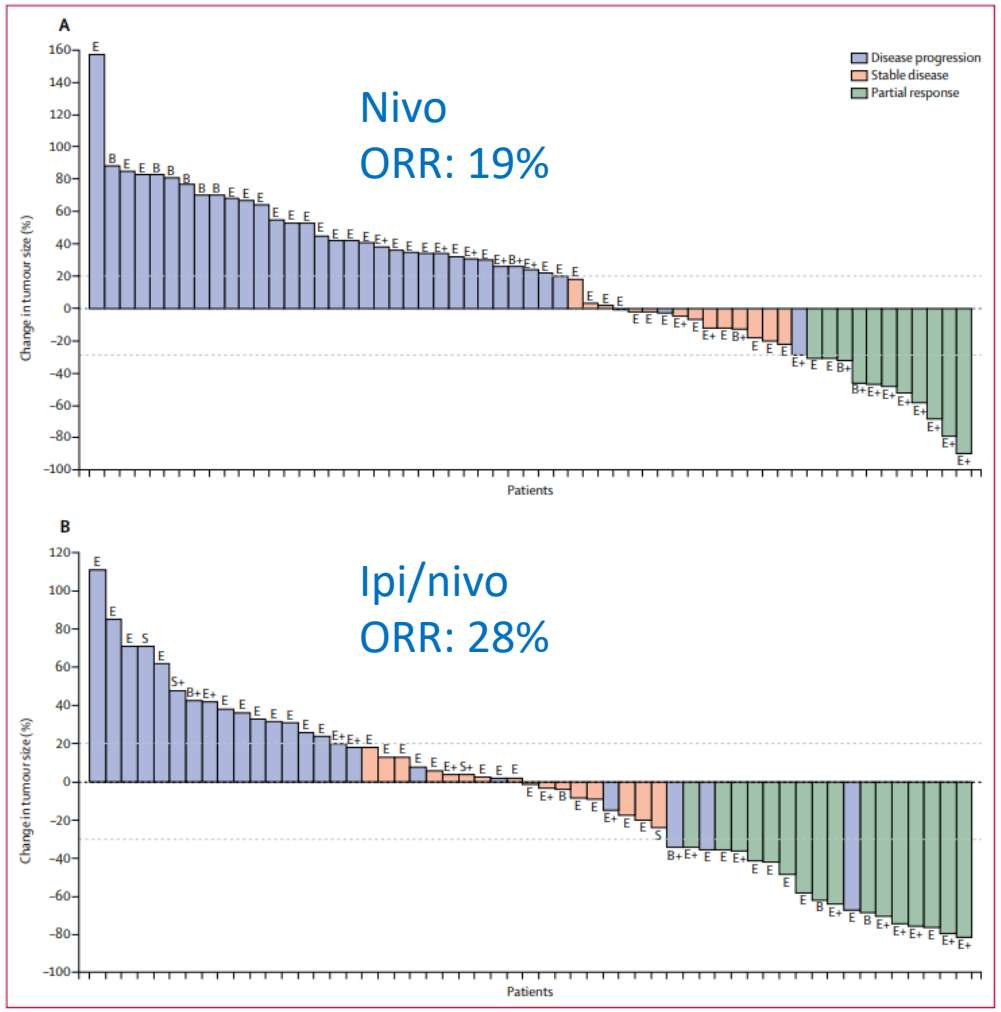


- Primary endpoint: 12-wk DCR per BICR with modified RECIST criteria for MPM
- Secondary endpoints: safety, PFS, OS, QoL, predictive utility of tumor PD-L1 score, prognostic utility of biomarkers

Scherpereel, Lancet Oncol 2019

Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial

125 patients randomized
12 week DCR: 40% and 52%
Median OS: 11.9 vs 15.9 mo
Serious AE: 5% vs 28%



Scherpereel, Lancet Oncol 2019

Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial

- 571 patients with unresectable pleural or peritoneal malignant mesothelioma who had progressed after one or two previous systemic treatments for advanced disease
- Randomized to tremelimumab or placebo
- Median OS: 7.7 vs 7.3 mo
- No difference in PFS
- ORR: 4.5 vs 1.1%

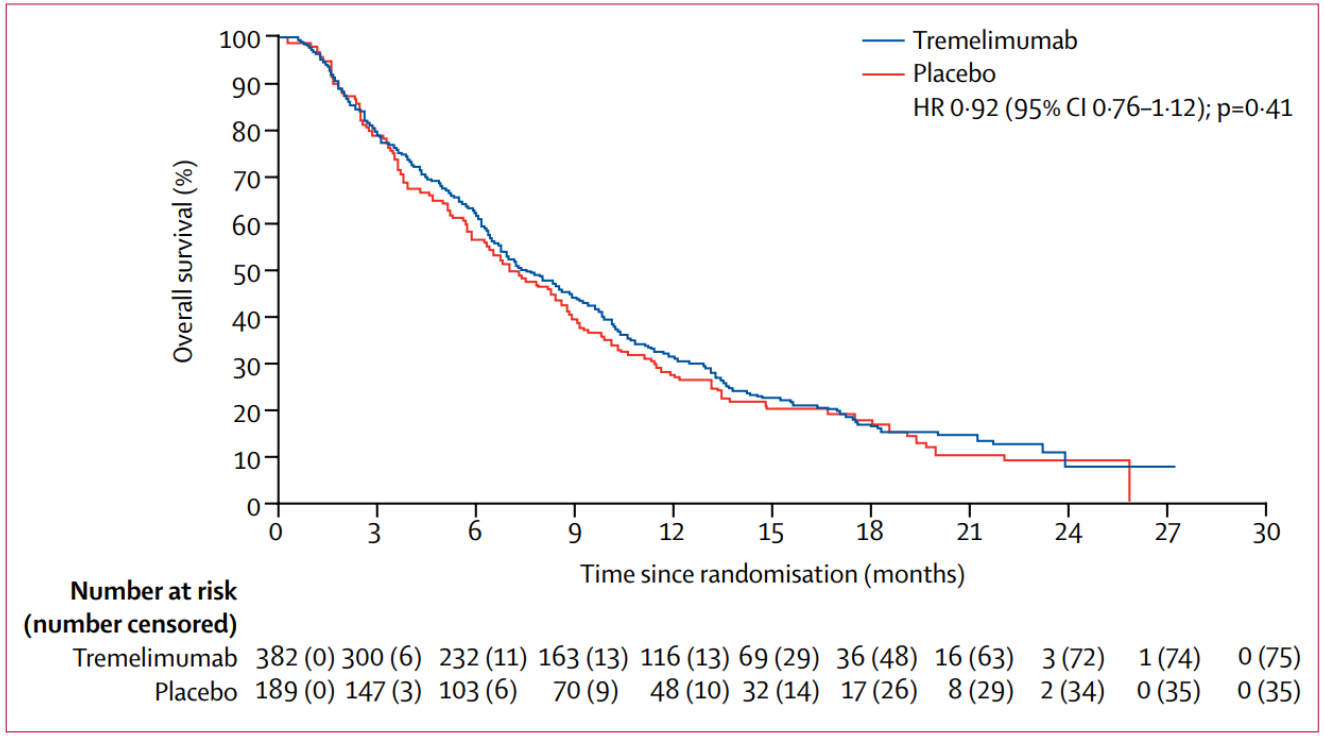
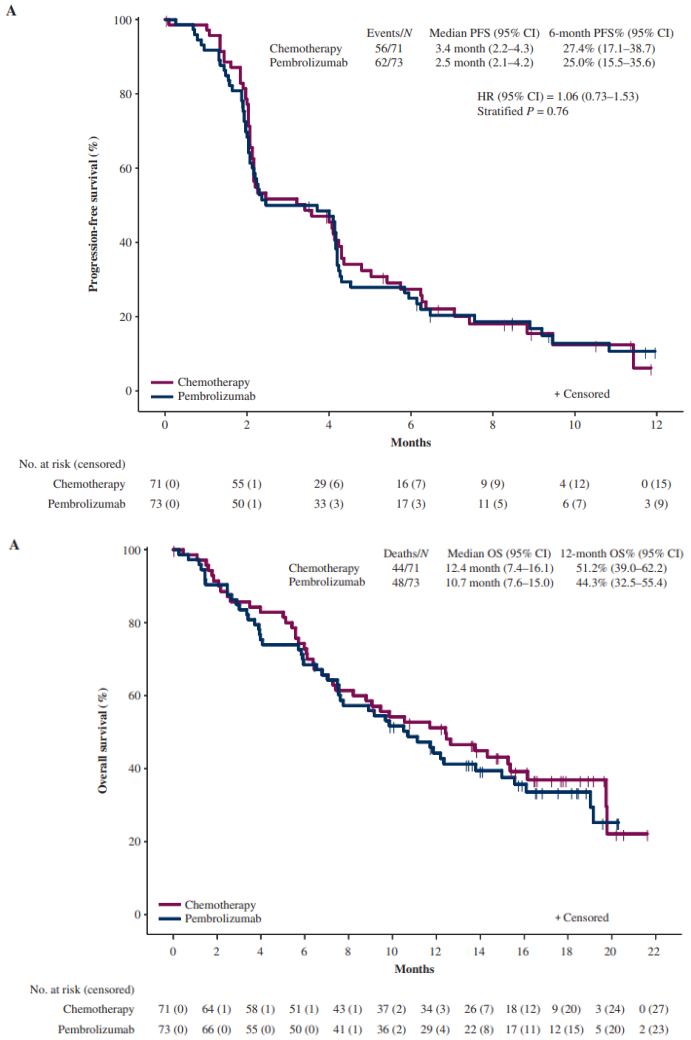


Figure 2: **Overall survival**

Maio, Lancet 2017

A multicentre randomised phase III trial comparing pembrolizumab versus standard chemotherapy for advanced pre-treated malignant pleural mesothelioma (PROMISE-meso)

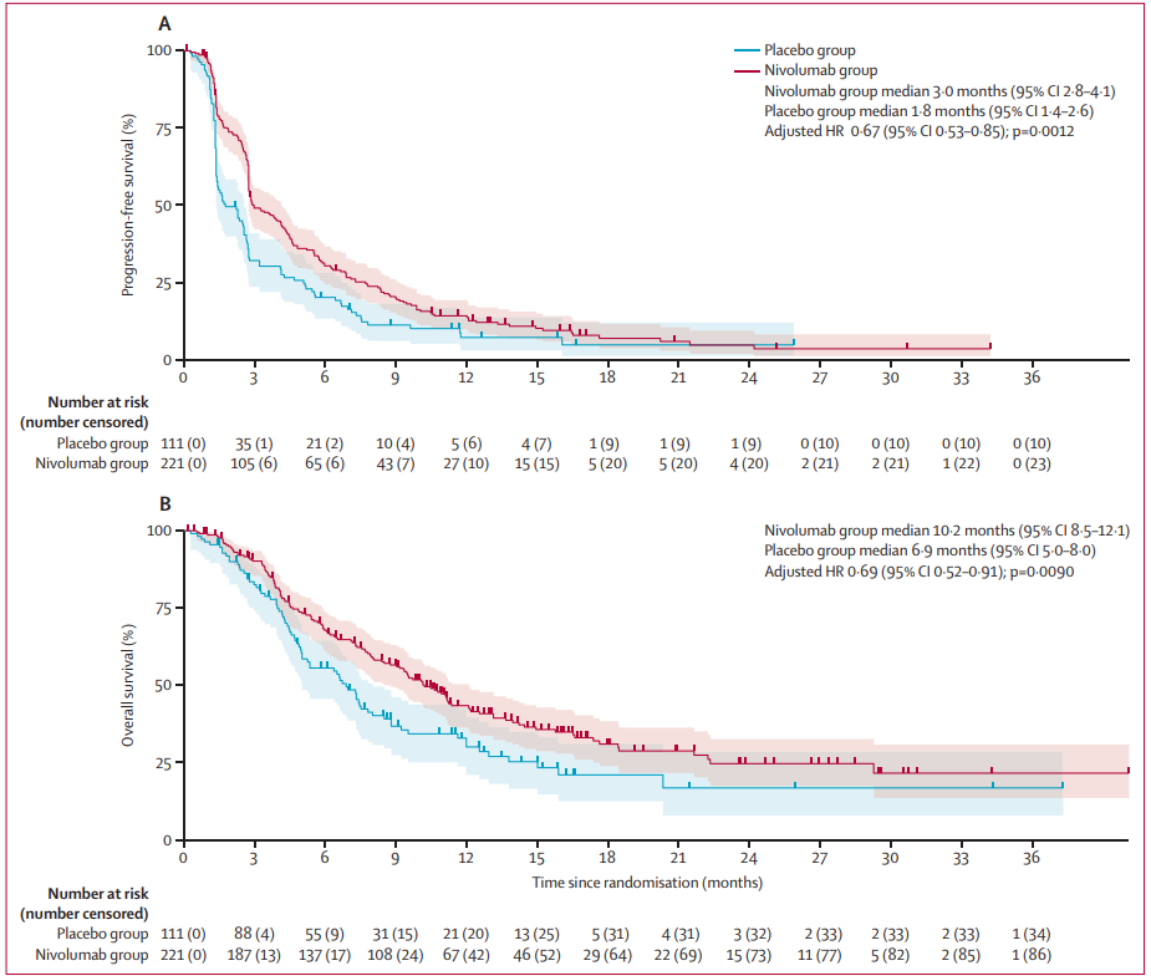
- 144 patients randomized:
  - Pembrolizumab
  - Chemotherapy
    - Gemcitabine
    - Vinorelbine
- ORR: 22% vs 6% favoring pembrolizumab
- 63% of chemotherapy patients crossed over to pembrolizumab upon progression



Popat, Annals of oncol 2020

Nivolumab versus placebo in patients with relapsed malignant mesothelioma (CONFIRM): a multicentre, double-blind, randomised, phase 3 trial

- 332 patients randomized (2:1) to nivolumab vs placebo after progression on first-line chemotherapy
- ORR 11% vs 1%
- SD 53% vs 49%
- Median PFS: 3 vs 1.8 mo
- Median OS: 10.2 vs 6.9 mo
- ASCO 2023 report unchanged



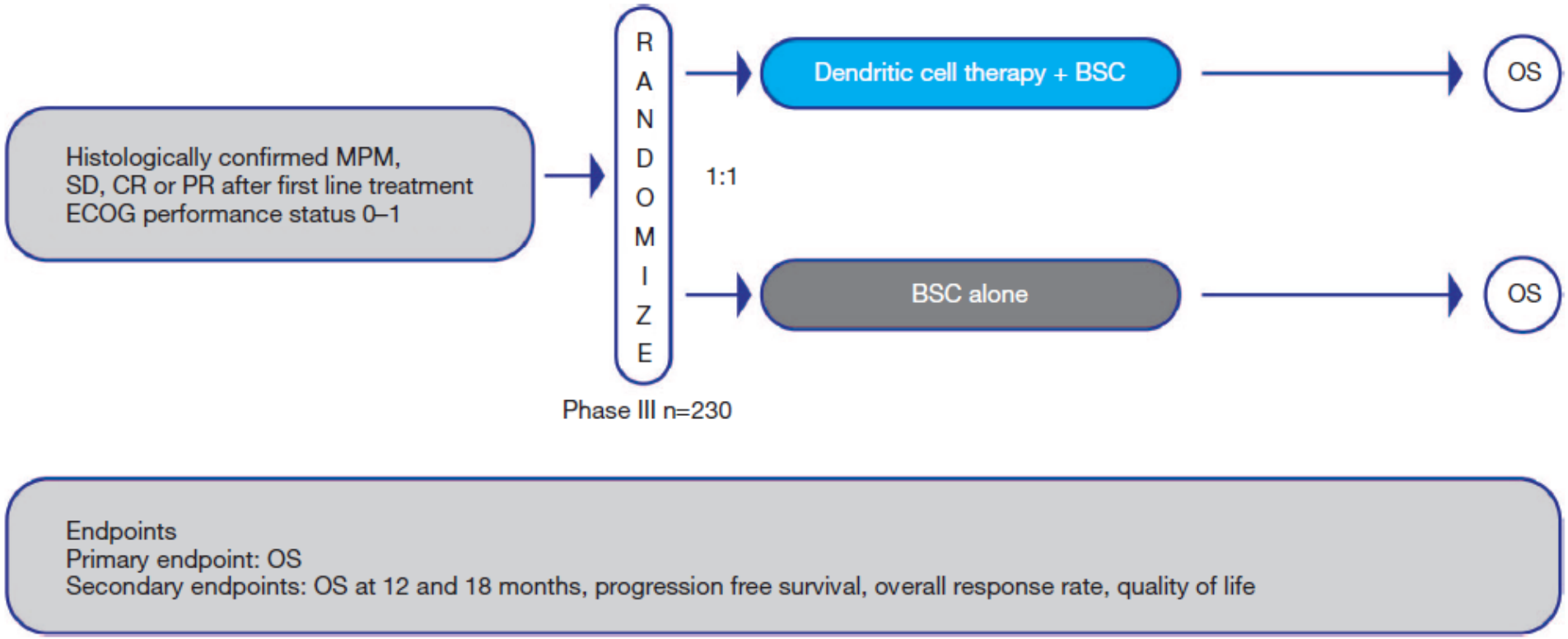
Fennell, Lancet 2021

ATOMIC-Meso: A randomized phase 2/3 trial of ADI-PEG20 or placebo with pemetrexed and cisplatin in patients with argininosuccinate synthetase 1-deficient non-epithelioid mesothelioma

- 249 chemonaive patients with MPM randomized
  - Pemetrexed/Cisplatin/Pegargiminase
  - Pemetrexed/Cisplatin
- Median OS: 9.3 vs 7.7 mo (p=0.023)
- Median PFS: 6.2 vs 5.6 mo (p=0.019)
- ORR: 13.8 vs 13.5

Szlosarek, AACR 2023

A multicenter, randomized, phase II/III study of dendritic cells loaded with allogeneic tumor cell lysate (MesoPher) in subjects with mesothelioma as maintenance therapy after chemotherapy: DENdritic cell Immunotherapy for Mesothelioma (DENIM) trial



Personal Thoughts

- Many Targets, many trials, little collaboration.
- ICI can be very effective in some patients. Who and why?