Novel Advances in Mesothelioma

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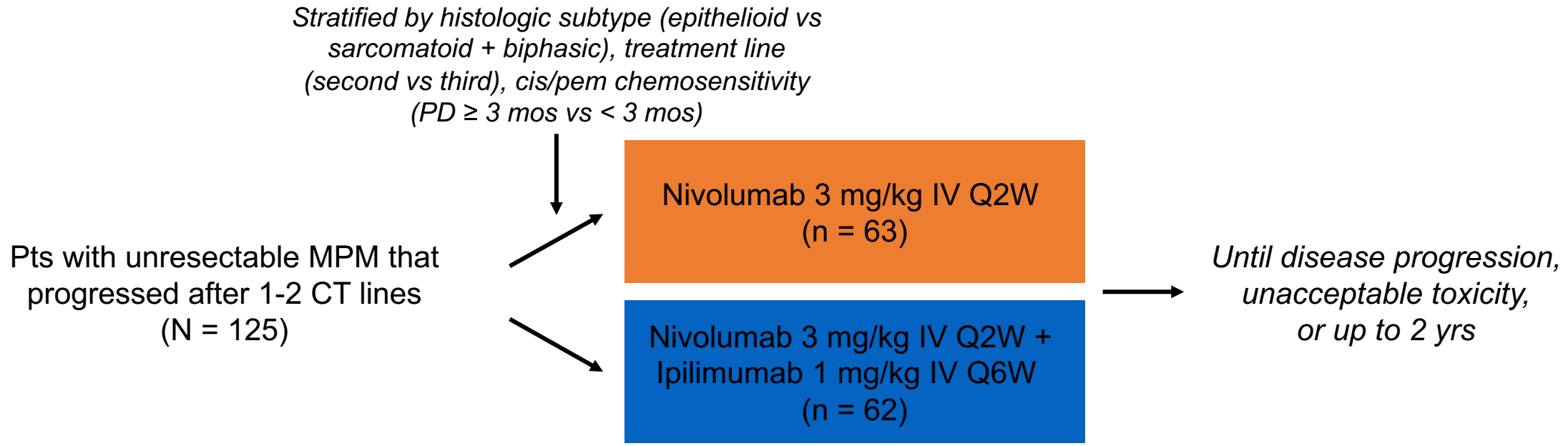
Second Line Therapy and Beyond

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

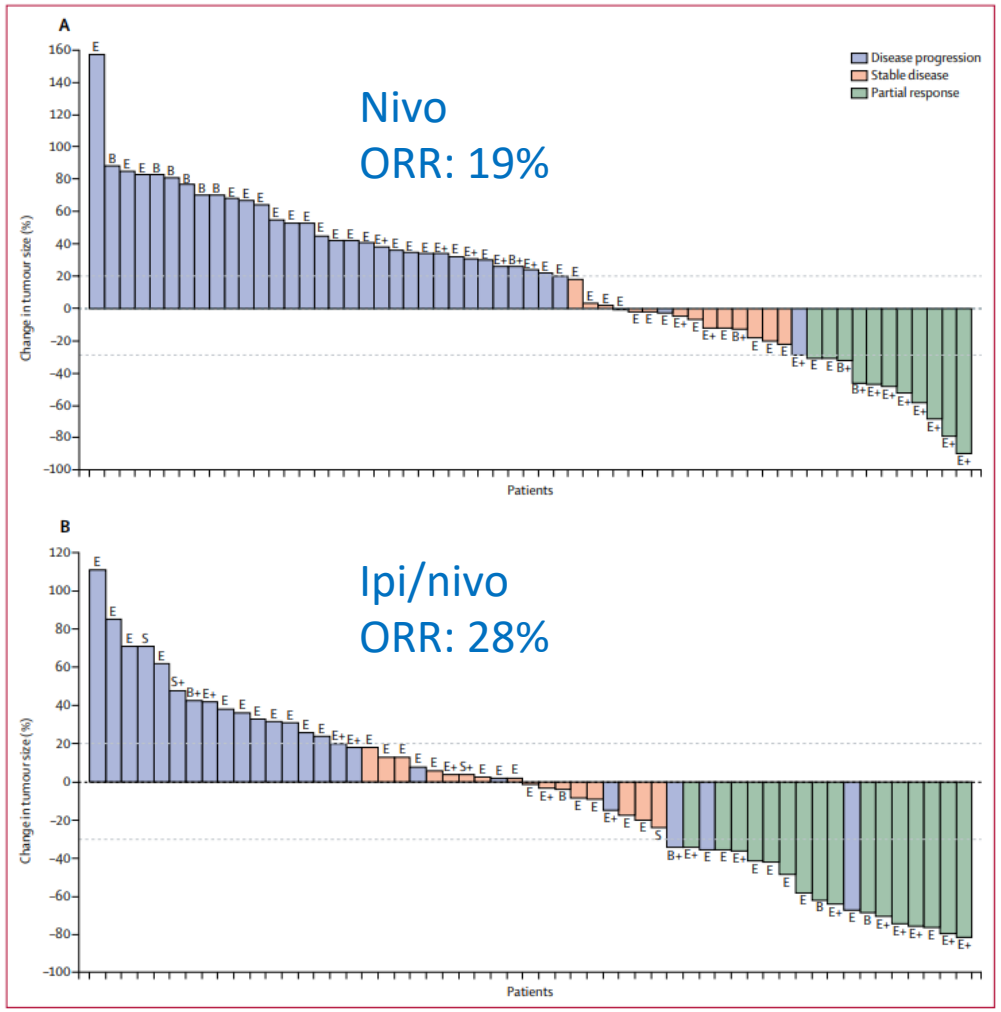


- Primary endpoint: 12-wk DCR per BICR with modified RECIST criteria for MPM
- Secondary endpoints: safety, PFS, OS, QoL, predictive utility of tumor PD-L1 score, prognostic utility of biomarkers

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%

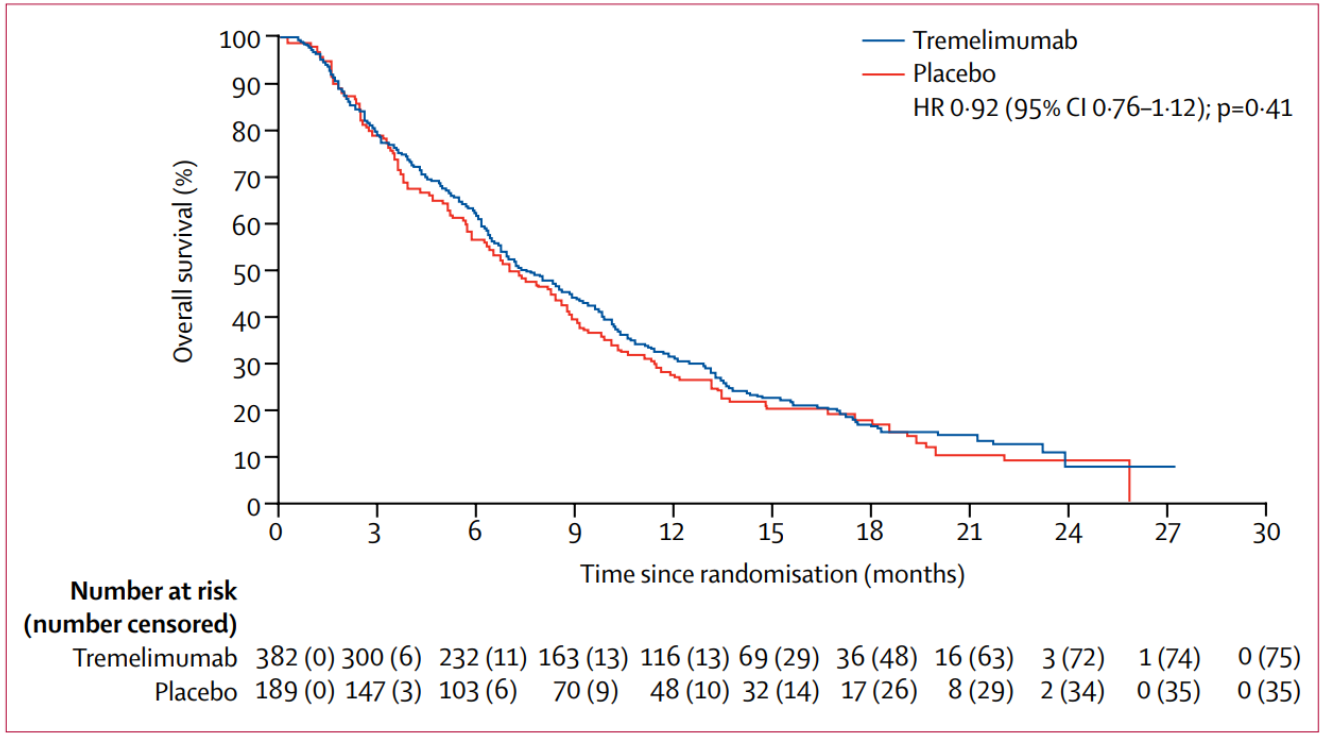
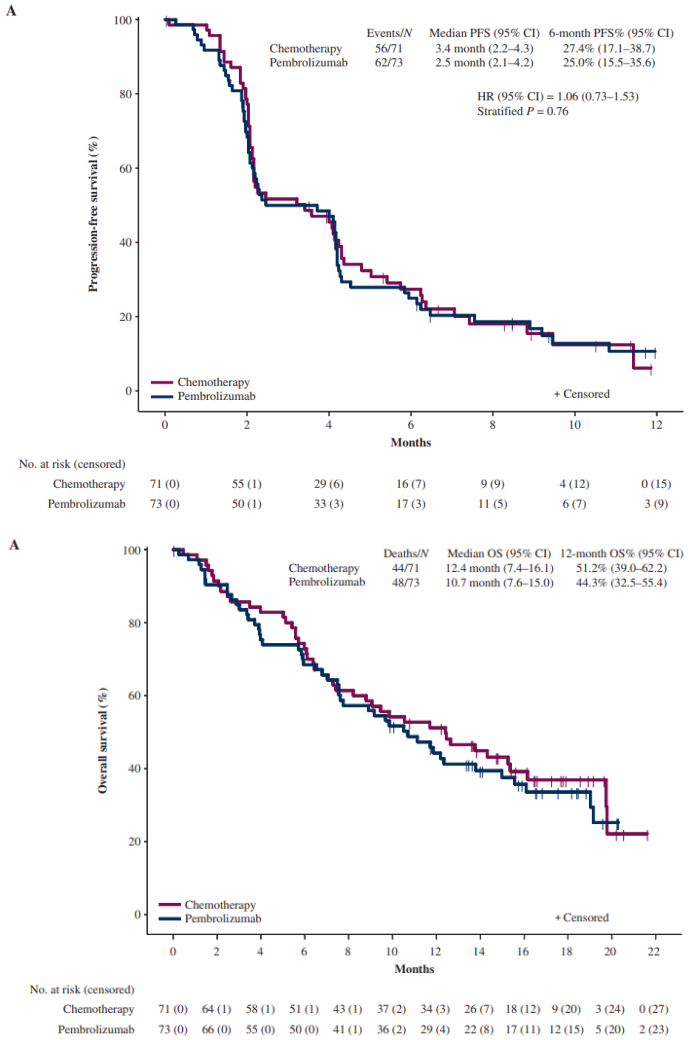


Figure 2: **Overall survival**

Maio, Lancet 2017

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

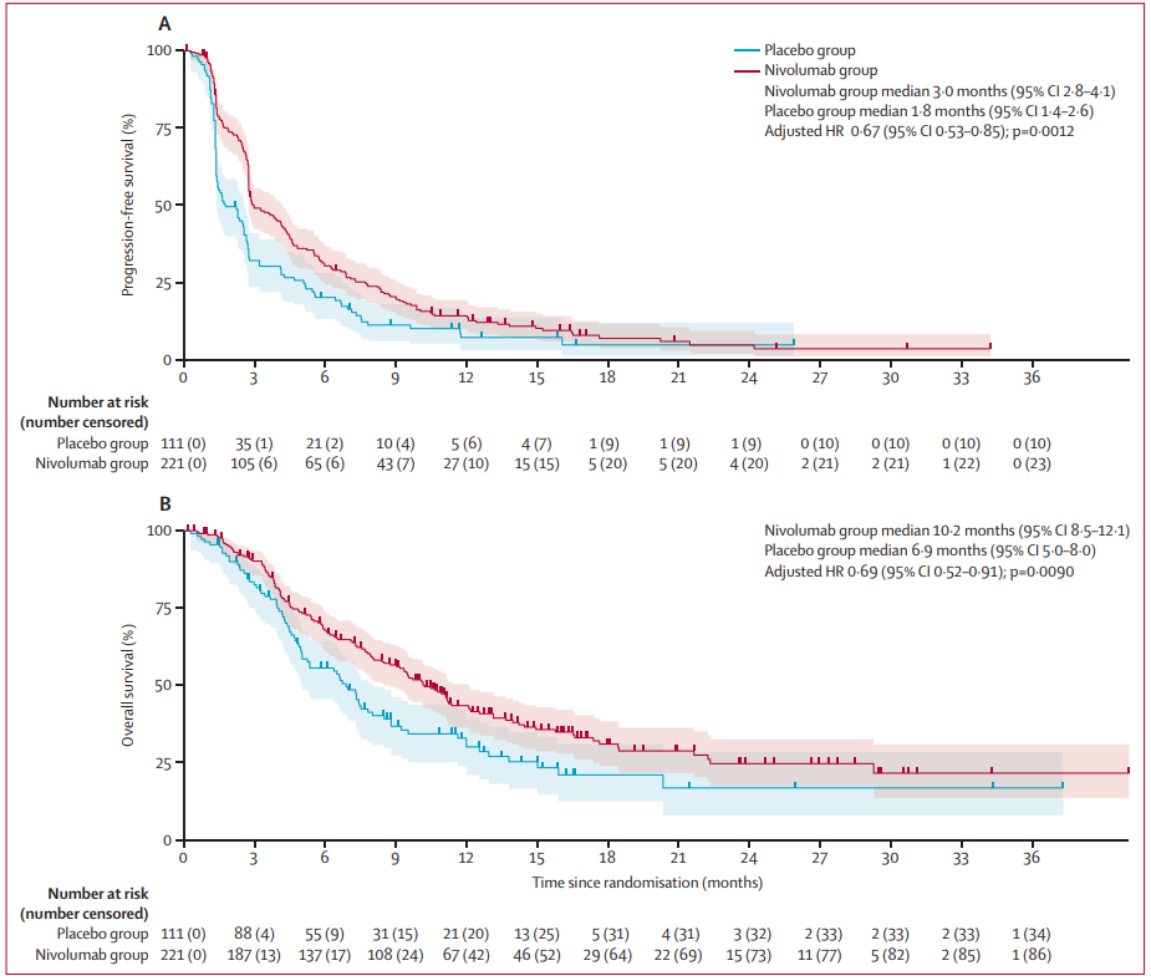
- 144 patients randomized:
  - Pembrolizumab
  - Chemotherapy
    - Gemcitabine
    - Vinorelbine
- ORR: 22% vs 6% favoring pembrolizumab
- 63% of chemotherapy patients crossed over to pembrolizumab upon progression



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

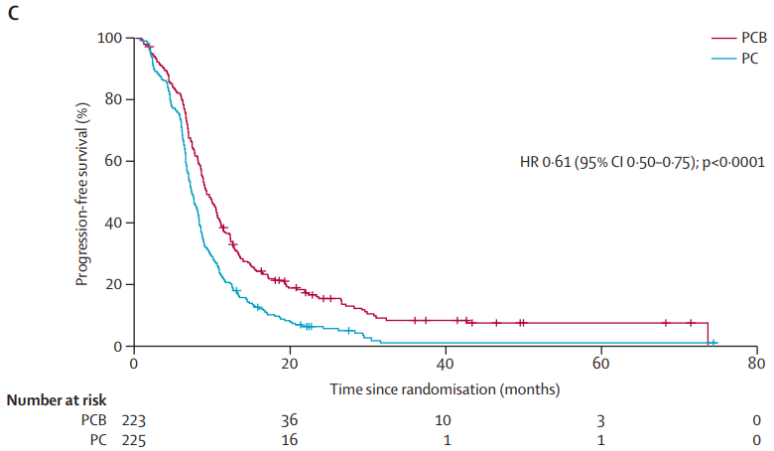


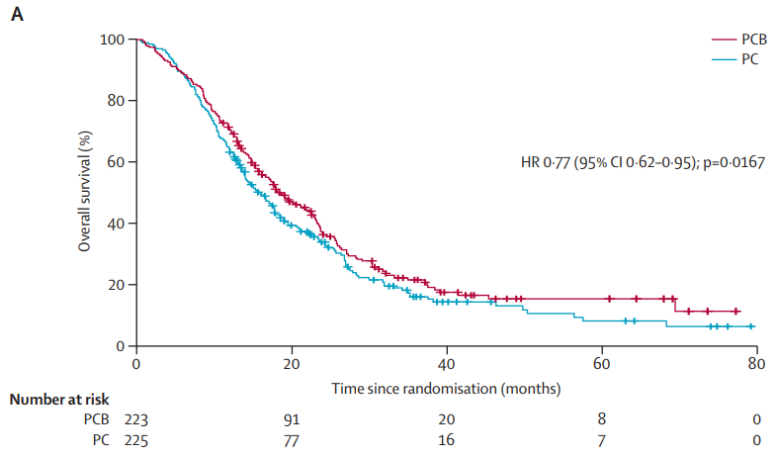
Fennell, Lancet 2021

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

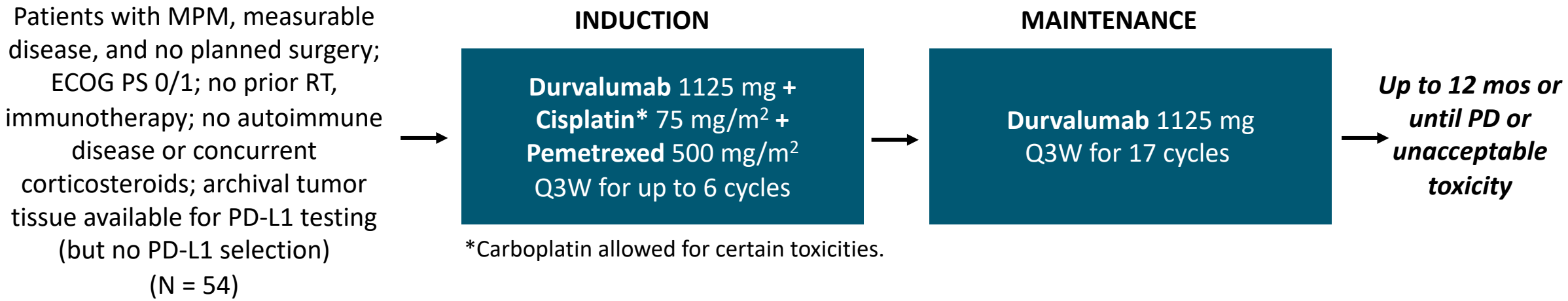




Zalcman, Lancet 2016

DREAM: Study Design

- Multicenter, single-arm, open-label phase II trial
  - 2-stage Simon's design (stage 1, n = 31; stage 2, n = 23) with initial 3 + 3 safety run-in



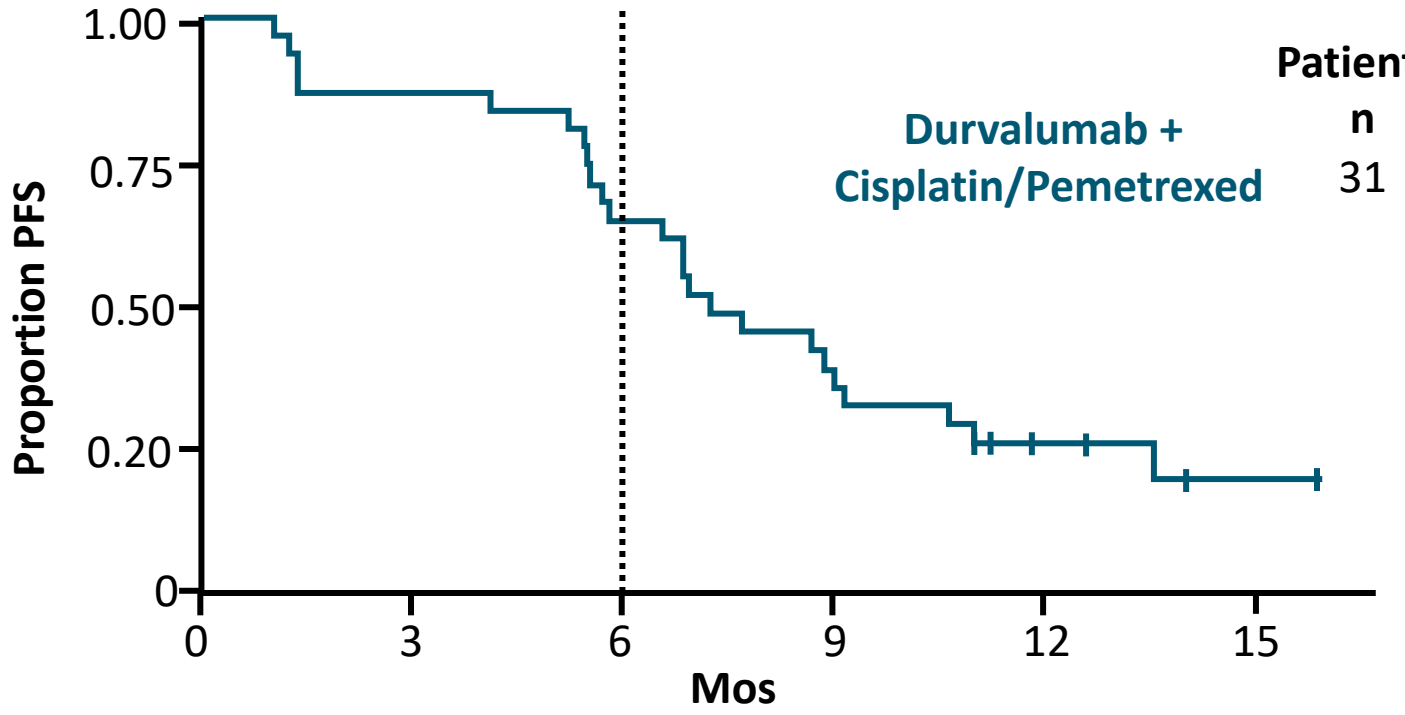
*Carboplatin allowed for certain toxicities.

- Primary endpoint: PFS at 6 mos (mRECIST for MPM)
  - Stage 1: 90% power with 5% 1-sided type 1 error rate to test hypothesis that regimen is worthy of pursuit if 6-mo PFS is ≥ 65%, but not if ≤ 45% as expected with SoC
- Secondary endpoints: ORR (CR + PR), PFS, OS, safety
- Tertiary endpoints: predictive/prognostic biomarker analysis, including tumor PD-L1 expression

Nowak AK, et al. ASCO 2018. Abstract 8503.

Slide credit: clinicaloptions.com

DREAM: PFS



	Patients, n	Median PFS, Mos (95% CI)	6-Mo PFS, %
Durvalumab + Cisplatin/Pemetrexed	31	7.3 (5.8-11.0)	65

Patients at Risk, n	31	25	20	12	5	2

- With 6-Mo PFS of 65%, stage 1 met criteria to proceed to stage 2 of trial

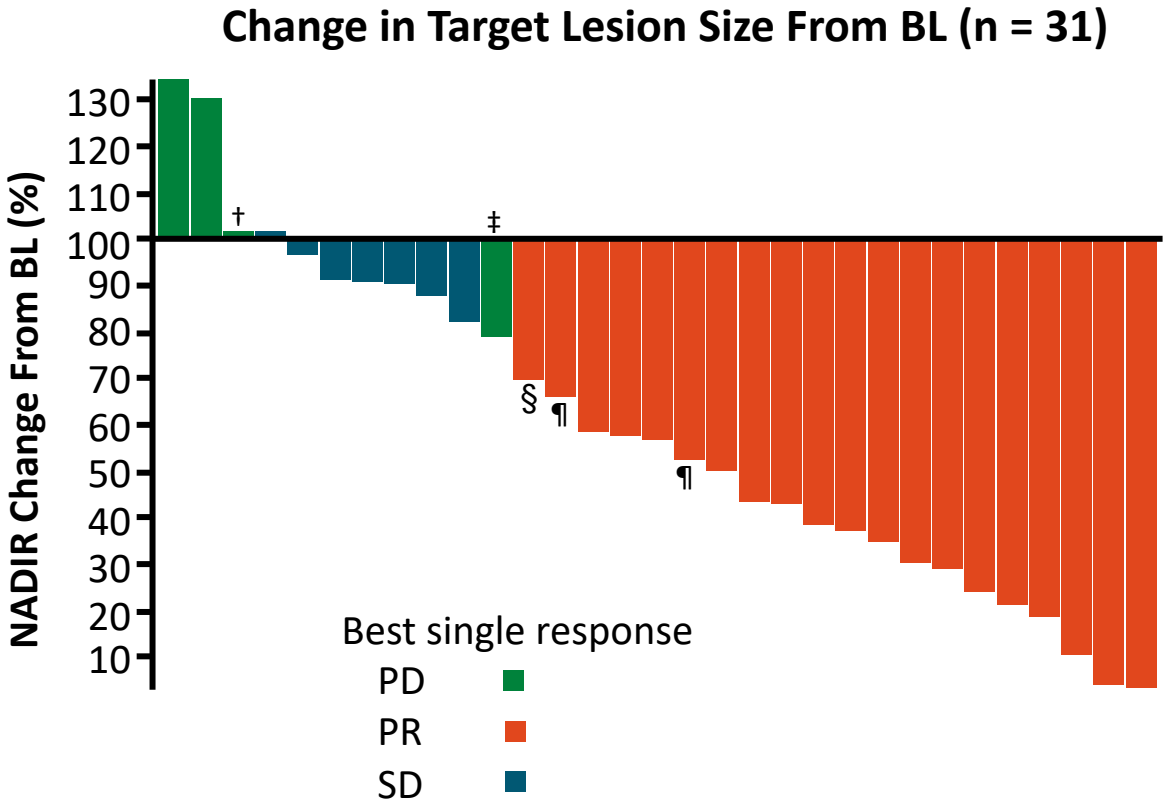
Nowak AK, et al. ASCO 2018. Abstract 8503.

Slide credit: clinicaloptions.com

DREAM: Response

Response, n (%)	Stage 1 Patients (n = 31)		
	Best Single Response	Confirmed Response by mRECIST	Confirmed Response by iRECIST
CR	0	0	0
PR*	20 (65)	17 (55)	18 (58)
SD	7 (23)	9 (29)	9 (29)
PD	4 (13)	5 (16)	14 (3)

*2 patients with PR after pseudoprogression.



- Despite the presence of CT, 2 patients exhibited pseudoprogression within first 10-15 wks of therapy, followed by PR

Nowak AK, et al. ASCO 2018. Abstract 8503.

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

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

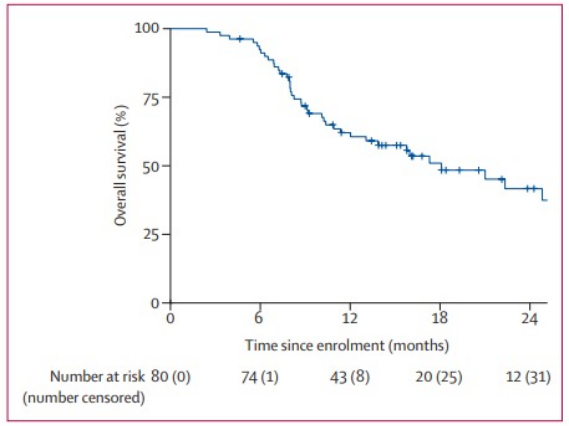


Figure 2: **Overall survival**
Kaplan-Meier analyses of overall survival in the intention-to-treat population.

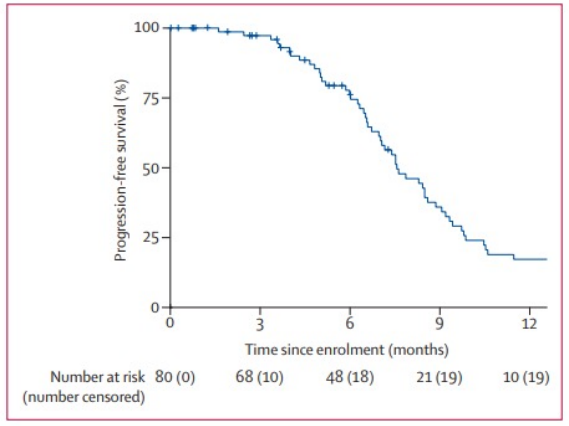


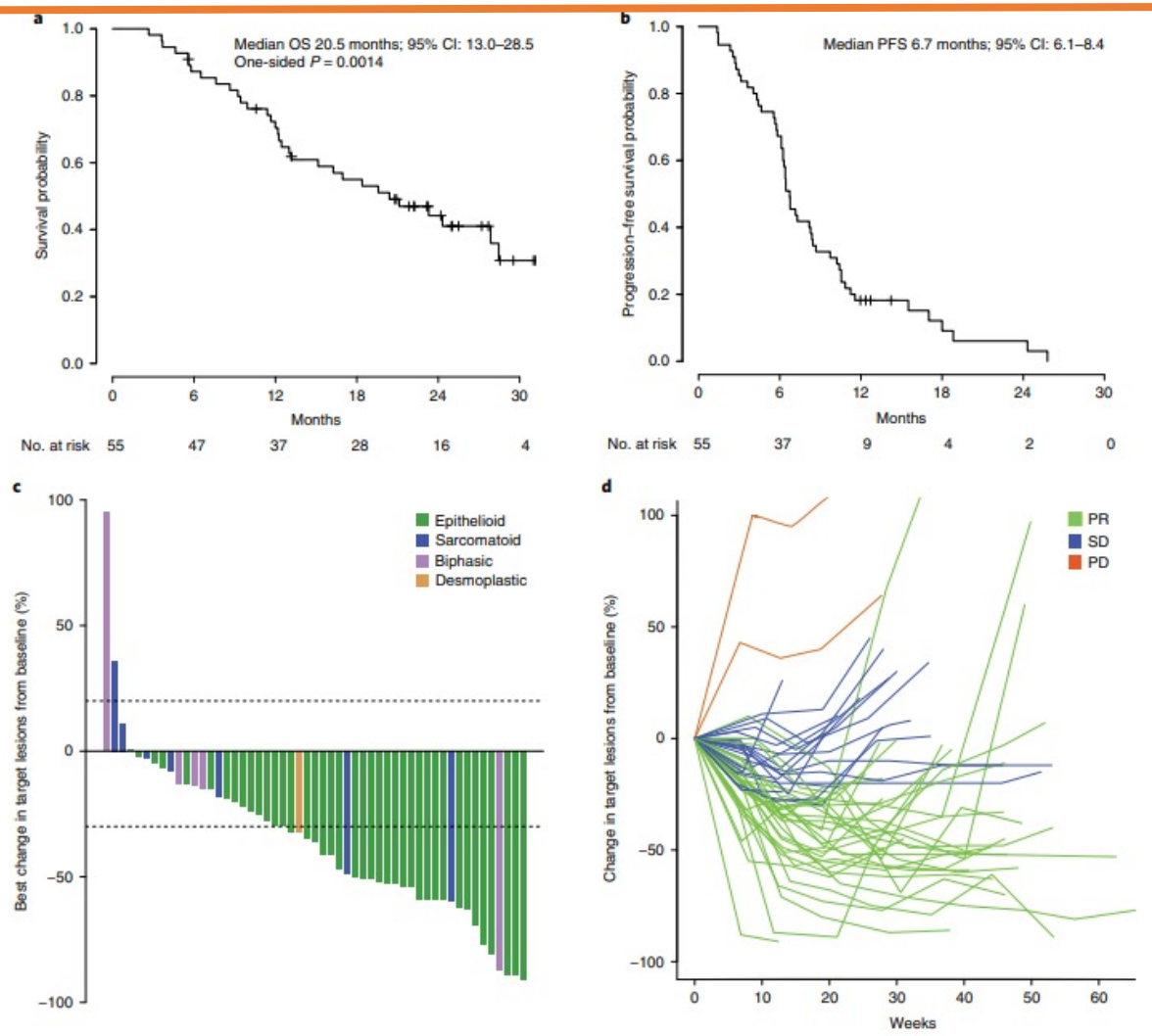
Figure 3: **Progression-free survival**
Kaplan-Meier analyses of progression-free survival in the intention-to-treat population.

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

Ceresoli, Lancet Oncol 2019

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%

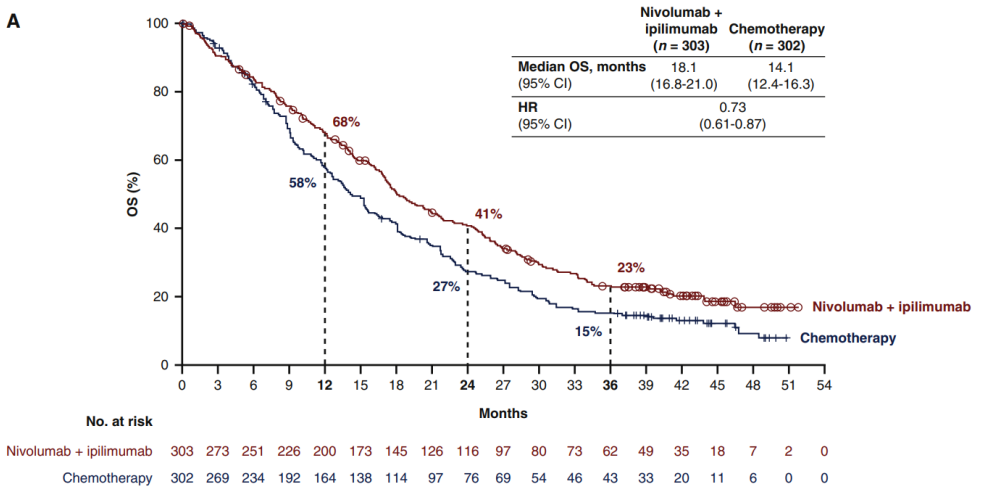


Forde, Nature Medicine 2021

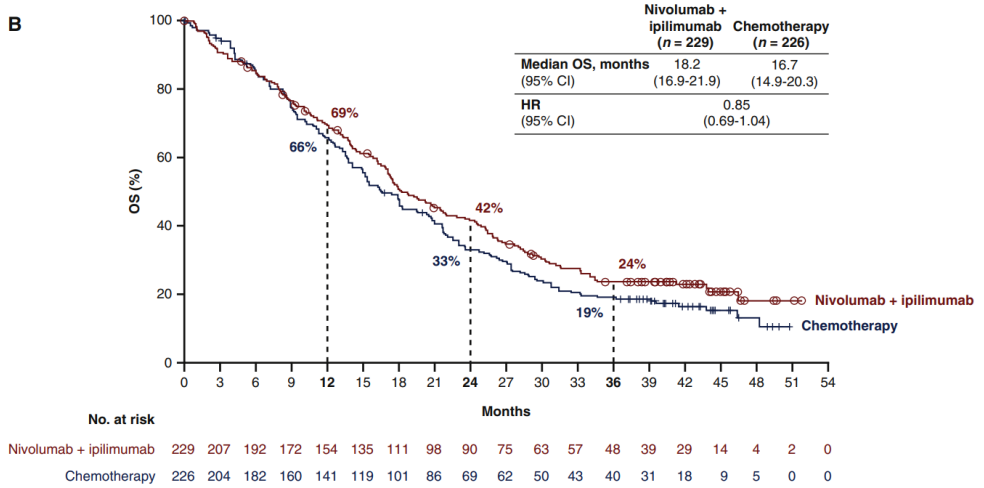
First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743

- 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



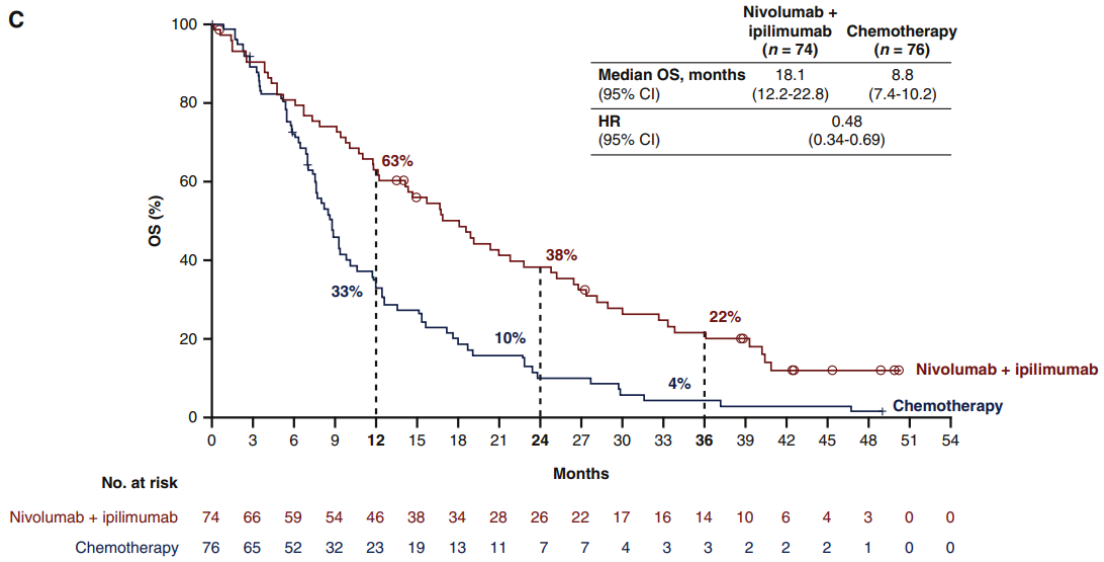
Epithelioid



Peters, Annals of Onc, 2022

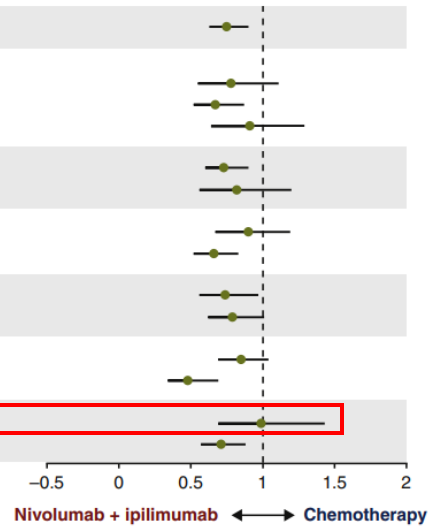
First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743

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)	

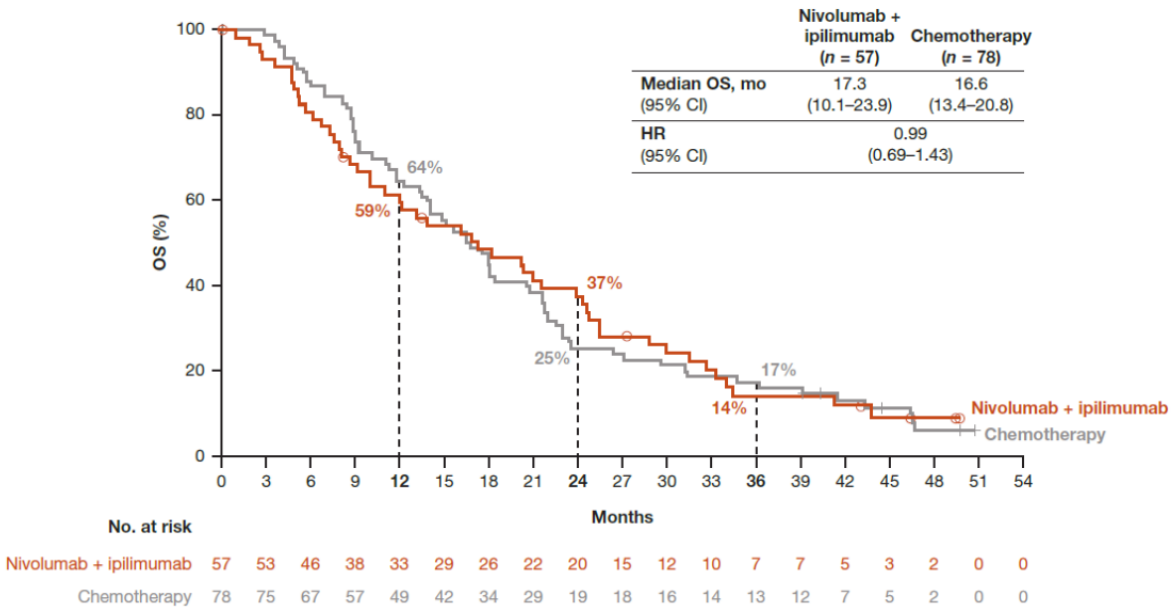
Subgroup	Median OS, months (95% CI) Nivolumab + ipilimumab (*n* = 303)	Chemotherapy (*n* = 302)	Unstratified HR (95% CI)
All randomized (*N* = 605)	18.1 (16.8-21.0)	14.1 (12.4-16.3)	0.75[a] (0.63-0.90)
Age, years			
<65 (*n* = 167)	17.2 (13.1-28.0)	13.3 (10.6-18.3)	0.78 (0.55-1.11)
≥65 to <75 (*n* =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



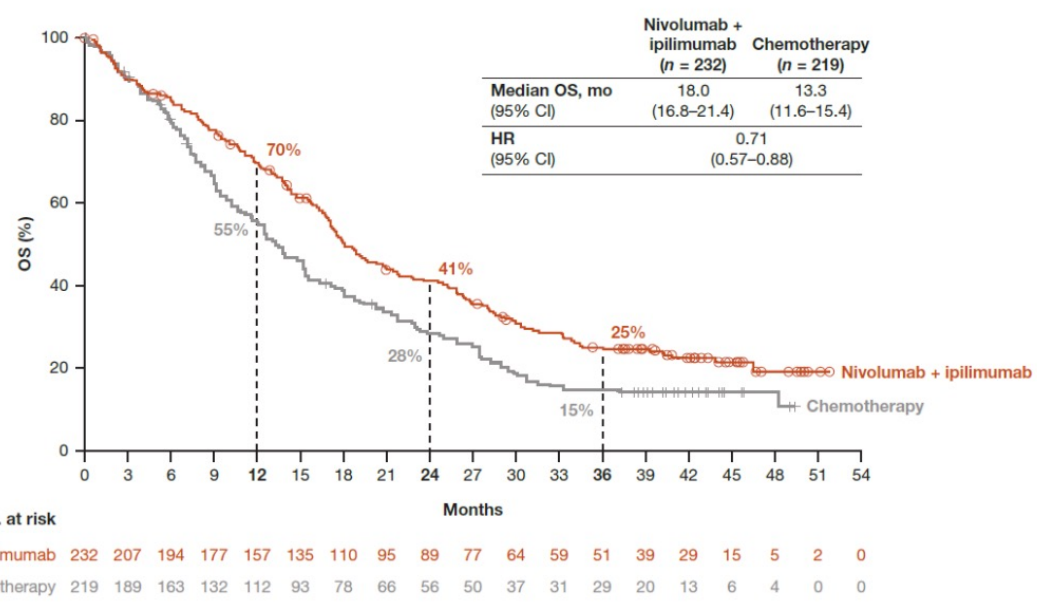
Peters, Annals of Onc, 2022

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

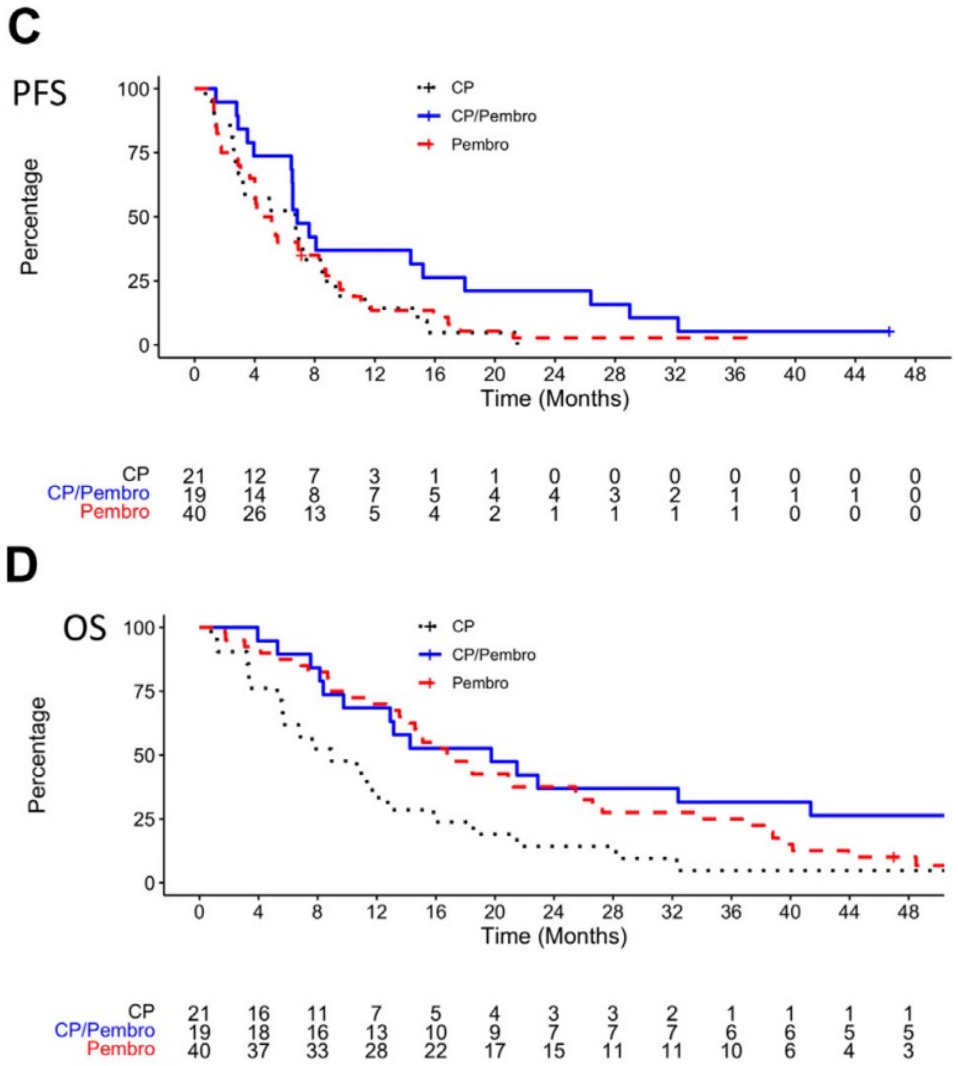
Brief Report: Canadian Cancer Trials Group IND.227: A Phase 2 Randomized Study of Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma

- 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

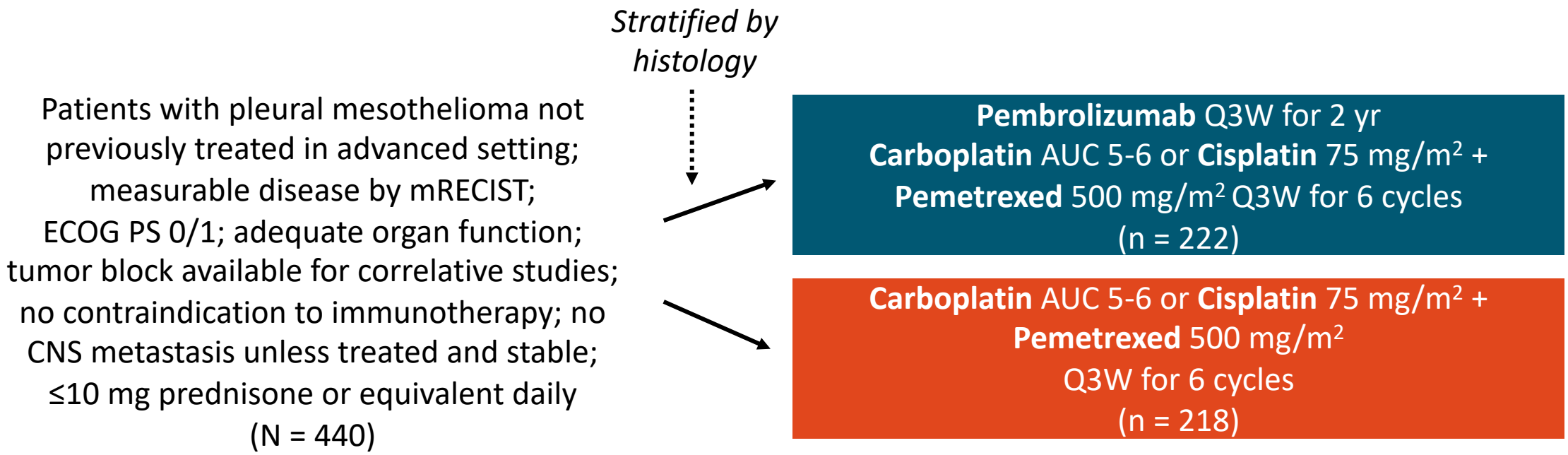
CP	**8.9 mo**
CPP	**19.8 mo**
P	**17.5 mo**



Piccirillo, J Thorac Onc 2023

CCTG IND.227: Study Design

- Multicenter, randomized, double-blind phase III trial



- **Primary endpoint:** OS
- **Secondary endpoints:** tolerability, response, PFS, QoL, health economics; exploratory correlative analyses

CCTG IND.227: Efficacy

Parameter	Pembro + CT (n = 222)	CT (n = 218)	HR (95% CI)	*P* Value*
OS				
Median OS, mo (95% CI)	17.28 (14.36-21.29)	16.13 (13.08-18.17)	0.79 (0.64-0.98)	.0324
2-yr OS, %	39	33	--	--
3-yr OS, %	25	17	--	--
PFS				
Median PFS, mo (95% CI)	7.13 (6.93-8.12)	7.16 (6.83-7.69)	0.80 (0.65-0.99)	.0372
1-yr PFS, %	26	17	--	--
2-yr PFS, %	9	4	--	--

*Stratified log-rank *P* value.

- At final analysis, 17 patients in the pembro + CT arm and 59 patients in the CT arm received second-line immunotherapy
- OS, PFS benefit with Pembro was observed across most subgroups (except age <65 yr and EORTC prognostic score ≤1.27)

Chu. ASCO 2023. Abstr LBA8505.

CCTG IND.227: Exploratory OS Analyses

Outcome by 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)
▪ 2-yr OS, %	40	37	
▪ 3-yr OS, %	26	20	
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)
▪ 2-yr OS, %	35	19	
▪ 3-yr OS, %	23	7	
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)
▪ 2-yr OS, %	47	37	
▪ 3-yr OS, %	28	18	
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)
▪ 2-yr OS, %	35	30	
▪ 3-yr OS, %	23	16	

Chu. ASCO 2023. Abstr LBA8505.

CCTG IND.227: Response Rates by Central Review

Best Overall Response*	Pembro + CT (n = 222†)	CT (n = 218‡)	*P* Value
CR, n (%)	2 (1)	0	<.0001
PR, n (%)	136 (61)	83 (38)	
SD, n (%)	70 (32)	103 (47)	
PD, n (%)	11 (5)	11 (5)	
Median duration of CR/PR, mo (95% CI)	5.8 (5.5-7.0)	5.5 (4.2-6.0)	.185

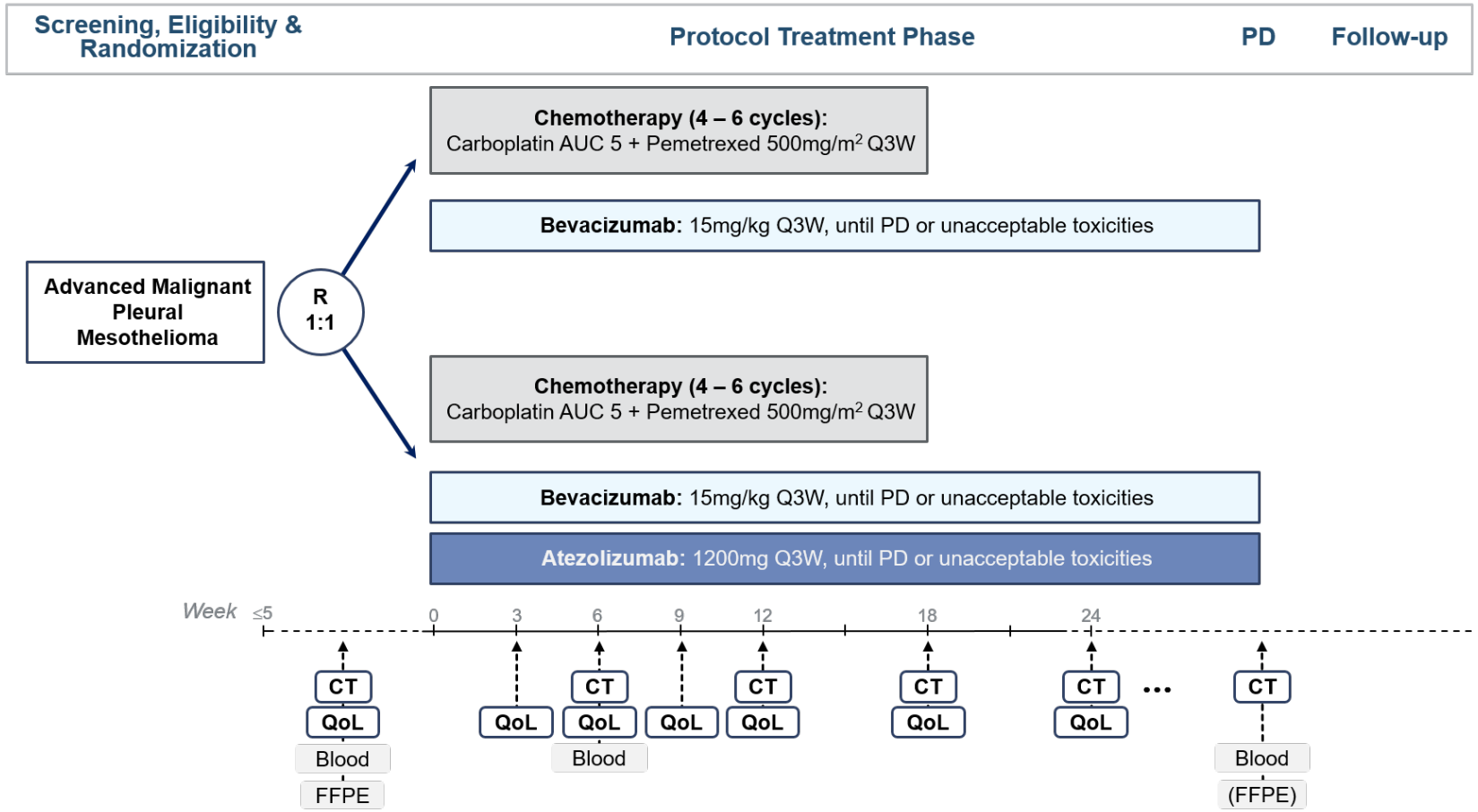
Best Overall Response, %	Pembro + CT	CT
Best overall response by histology		
▪ Epithelioid	67	47
▪ Nonepithelioid	47	13
Best overall response by PD-L1 status		
▪ Positive	64	39
▪ Negative	59	48

*Using modified RECIST criteria. †5 patients without response assigned (no baseline image, n = 2; other reason, n = 3).
‡21 patients without response assigned (never treated or withdrawal of consent, n = 7; no baseline image, n = 5; other reason, n = 9).

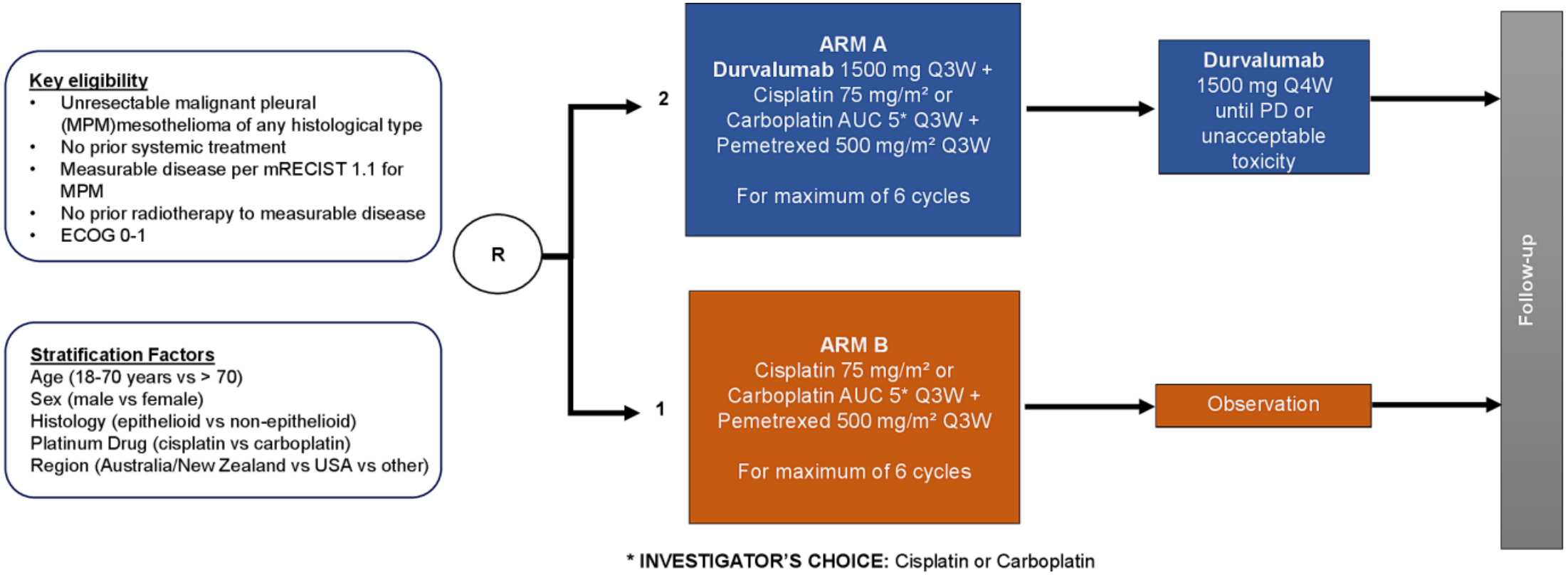
Chu. ASCO 2023. Abstr LBA8505.

Slide credit: clinicaloptions.com

A multicentre randomised phase III trial comparing atezolizumab plus bevacizumab and standard chemotherapy versus bevacizumab and standard chemotherapy as first-line treatment for advanced malignant pleural mesothelioma (BEAT-meso)



Dream3r



Kok, BMJ 2021

Perioperative Immunotherapy in Mesothelioma

NCT04177953	Adjuvant platinum/pemetrexed/nivolumab
NCT04996017	Adjuvant atezolizumab
NCT03228537	Neoadjuvant platinum/pemetrexed/atezolizumab
NCT02592551	Neoadjuvant Durvalumab vs durva/treme vs placebo
NCT02707666	Neoadjuvant pembrolizumab
NCT05647265	Neoadjuvant ipi/nivo for sarcomatoid mesothelioma
NCT03918252	Neoadjuvant Nivolumab vs ipi/nivo