Debate: Is Perioperative Immunotherapy the New Standard of Care? No! (Well, Maybe)

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I could not find any embarrassing pictures of Dr. Sanborn anywhere!
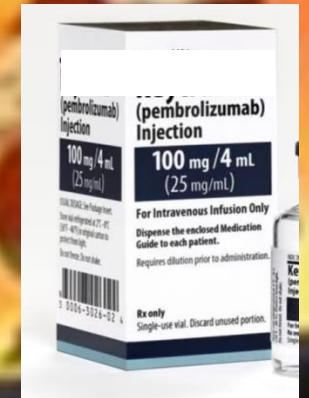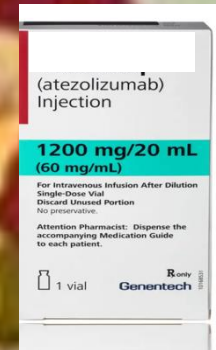
This is highly suspicious!

Is there a standard of care that applies to every tumor?

- Probably not
- Tumors with actionable genomic alterations were excluded in all trials (Except in KN-671)
- Majority of patients have stage 3 disease
- PD-L1 expression is associated with better outcomes

FDA Approved Regimens: *Resectable NSCLC*

Neoadjuvant

Trial	Stage Disease Characteristics	Regimen	Approval Endpoint
CheckMate 816 March 2022	IB-IIIA Irrespective PD-L1	Nivolumab + chemotherapy x 3 cycles	EFS HR 0.63, p = 0.005 pCR 24%

Perioperative

Trial	Stage Disease Characteristics	Regimen	Approval Endpoint
KEYNOTE-671 October 2023	II-IIIB Irrespective PD-L1	Pembrolizumab + chemotherapy x 4 cycles -> S -> pembrolizumab x ~9 months	EFS HR 0.58, p <0.00001 OS HR 0.72, p=0.00517
AEGEAN August 2024	IIA-IIIB Irrespective PD-L1	Durvalumab + chemotherapy x 4 cycles -> S -> durvalumab x 1 year	EFS HR 0.68, p=0.0039 pCR 17%
CheckMate 77T October 2024	IIA-IIIB Irrespective PD-L1	Nivolumab + chemotherapy x 4 cycles -> nivolumab x 1 year	EFS HR 0.58, p=0.00025 pCR 25%

Adjuvant

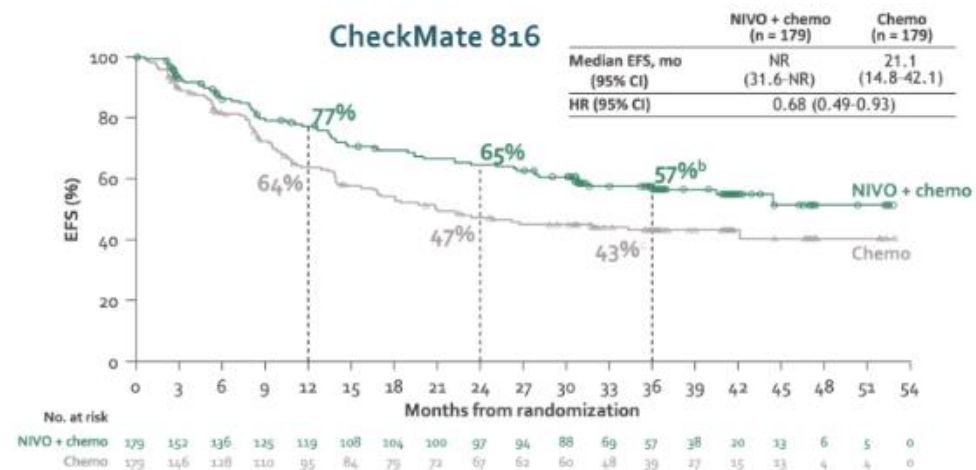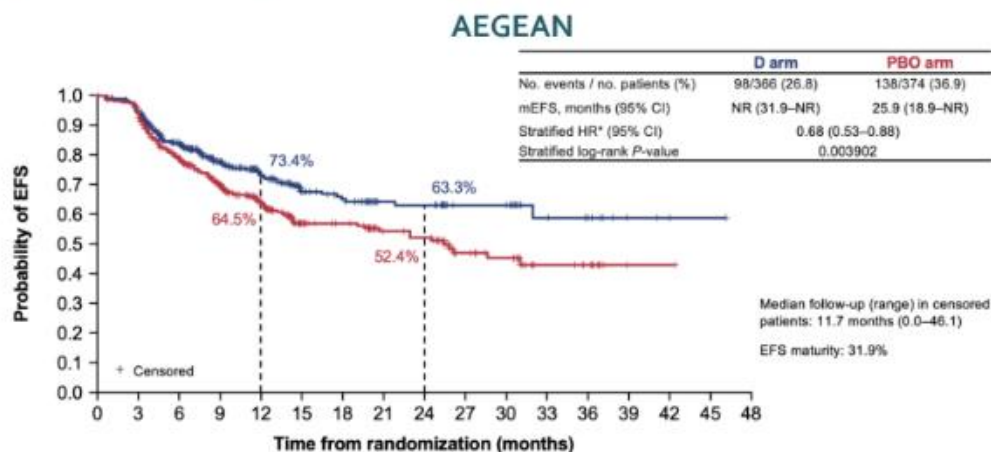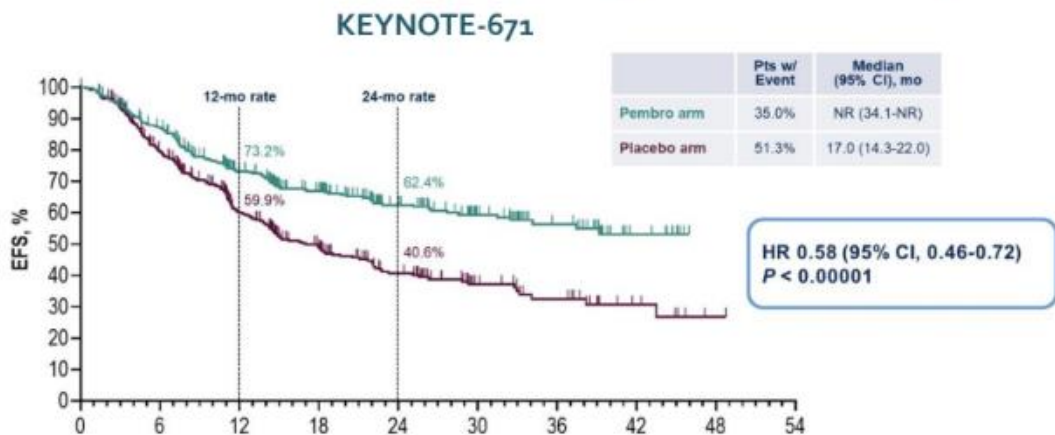| Trial	Stage Dz characteristics	Regimen	Approval Endpoint
IMpower010 October 2021	II-IIIA PD-L1 positive (>/=1%)	Adjuvant chemotherapy -> atezolizumab x 1 year	DFS HR 0.66; p = 0.004
PEARLS/ KEYNOTE-091 January 2023	IB-IIIA Irrespective PDL1	Adjuvant chemotherapy -> pembrolizumab x 1 year	DFS HR 0.73
ADAURA December 2020	IB-IIIA EGFR exon 21 L858R or exon 19 deletion positive	Osimertinib x 3 years (regardless of adjuvant chemotherapy)	DFS HR 0.20; p < 0.0001 OS HR 0.49; p <0.001
ALINA April 2024	IB-IIIA ALK-positive	Alectinib x 2 years	DFS HR 0.24; p<0.0001

X: @lungoncdoc

Trial	IMpower010	KEYNOTE-091	CheckMate -816	AEGEAN	Neotorch	KEYNOTE-671	CheckMate -77T	RATIONALE-315
Timing	Adjuvant	Adjuvant	Neoadjuvant	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative
Size	1005	1177	358	802	500	786	461	453
Agent I/O	Atezolizumab (PD-L1)	Pembrolizumab (PD-1)	Nivolumab (PD-1)	Durvalumab (PD-L1)	Toripalimab (PD-1)	Pembrolizumab (PD-1)	Nivolumab (PD-1)	Tislelizumab (PD-1)
No. cycles	16	18	3	16	17	13	16	12
Inclusion	Completely resected IB (>4cm)-IIIA (7th)	Completely resected IB (>4cm)-IIIA (7th)	Resectable IB (>4cm)-IIIA (7th)	Resectable II-IIIB (8th) by lobectomy	Resectable II-IIIB (8th)	Resectable II-IIIB (8th)	Resectable II-IIIB (8th)	Resectable II-IIIA
Stage II/III, %	59 / 41	72 / 28	36 / 64	27 / 73	20 / 80*	30 / 70	35 / 65	
Primary endpoint	DFS hierarchical	DFS, DFS (PD-L1 ≥50%)	pCR, EFS	MPR, EFS	MPR, EFS	EFS, OS	EFS	EFS, pCR
Chemotherapy	Cisplatin doublet	Platinum doublet encouraged	Platinum doublet	Platinum-based	Platinum-based	Cisplatin doublet	Platinum doublet	Platinum doublet
EGFR/ALK	Included (15%)	Included (7.5%)	No documented mutation (WT: Asia)	No documented mutation	WT	No documented mutation (7%)	No EGFR, no documented ALK	Excluded

Forde P, NEJM 2022, Heymach J, AACR 2023, Lu S, ASCO 2023, Wakelee H, NEJM 2023, Cascone T, ESMO 2023, Felipe E, Lancet 2021, O'Brien M, Lancet Onc 2022; Yue D, ESMO 2024.
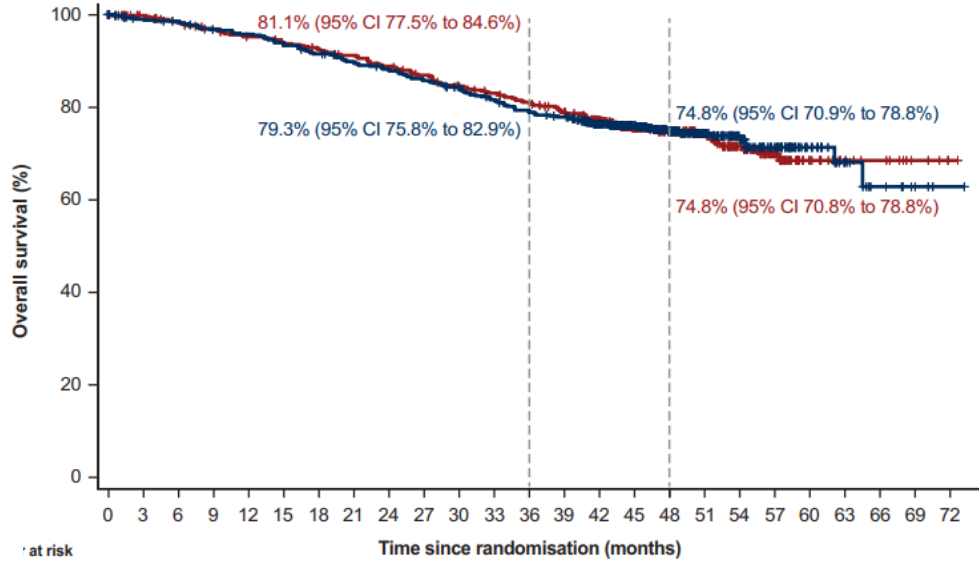
Table Credit: Jessica Donington

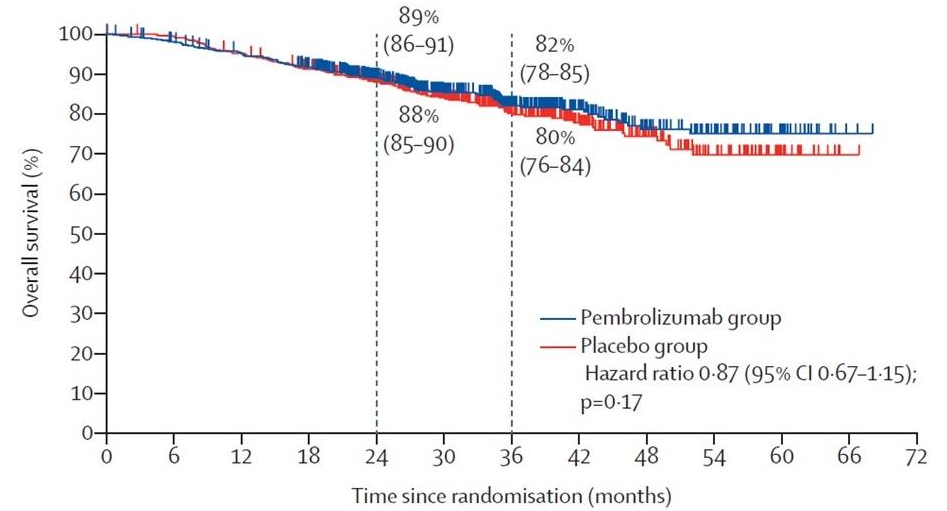# Similar EFS signal across perioperative/neoadjuvant trials

Overall survival

IMpower 010
ITT population stage IB-IIIA

81.1% (95% CI 77.5% to 84.6%)

79.3% (95% CI 75.8% to 82.9%)

74.8% (95% CI 70.9% to 78.8%)

74.8% (95% CI 70.8% to 78.8%)

KEYNOTE-091/PEARLS

89% (86–91)

88% (85–90)

82% (78–85)

80% (76–84)

Pembrolizumab group
Placebo group
Hazard ratio 0·87 (95% CI 0·67–1·15);
p=0·17

CheckMate 816

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS, mo (95% CI)	NR (NR-NR)	NR (46.8-NR)
HR (99.34% CI)	0.62 (0.36-1.05)	
P value	0.0124ᵃ	

90%

90%

83%

78%ᵇ

NIVO + chemo

70%

64%ᶜ

Chemo

No. at risk
NIVO + chemo 179 176 166 163 158 151 149 146 145 141 137 136 117 95 67 44 23 14 6 2 0
Chemo 179 173 166 162 155 149 134 124 119 112 109 106 95 75 52 38 22 14 4 1 0

KEYNOTE-671

Pembrolizumab group

Placebo group

No. at Risk
Pembrolizumab group 397 370 313 232 170 118 76 41 5 0
Placebo group 400 379 316 225 153 91 54 30 6 0

Felip E, et al. Ann Oncol 2023
O'Brien M, et al. Lancet Oncol 2022
Forde P, et al. ELCC 2023
Wakelee H et al. N Engl J Med 2023

Comparing the Neoadjuvant Only and Perioperative Trials - Study Populations

CM816

64% Stage III

50% PD-L1+

CM77T

64% Stage III

56% PD-L1+

AEGEAN

71% Stage III

67% PD-L1+

KN671

70% Stage III

65% PD-L1+

Across all these trials, who is doing the heavy lifting?

- Stage III
- PD-L1 >1%

Pooled Clinical Trial Meta-analysis Data in <u>Stage III</u>

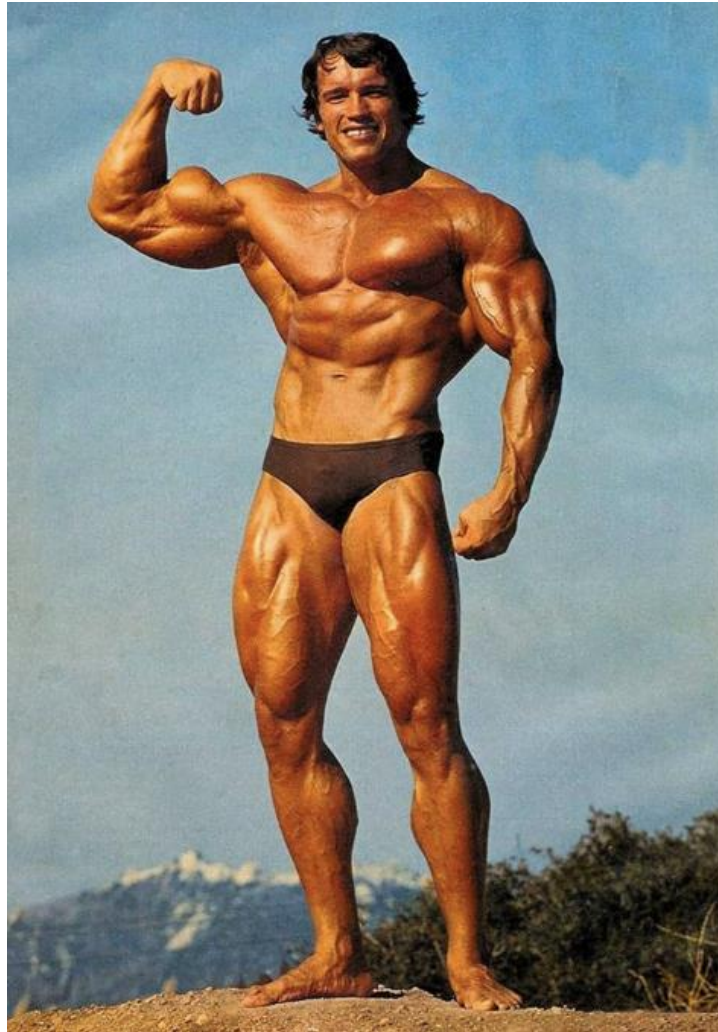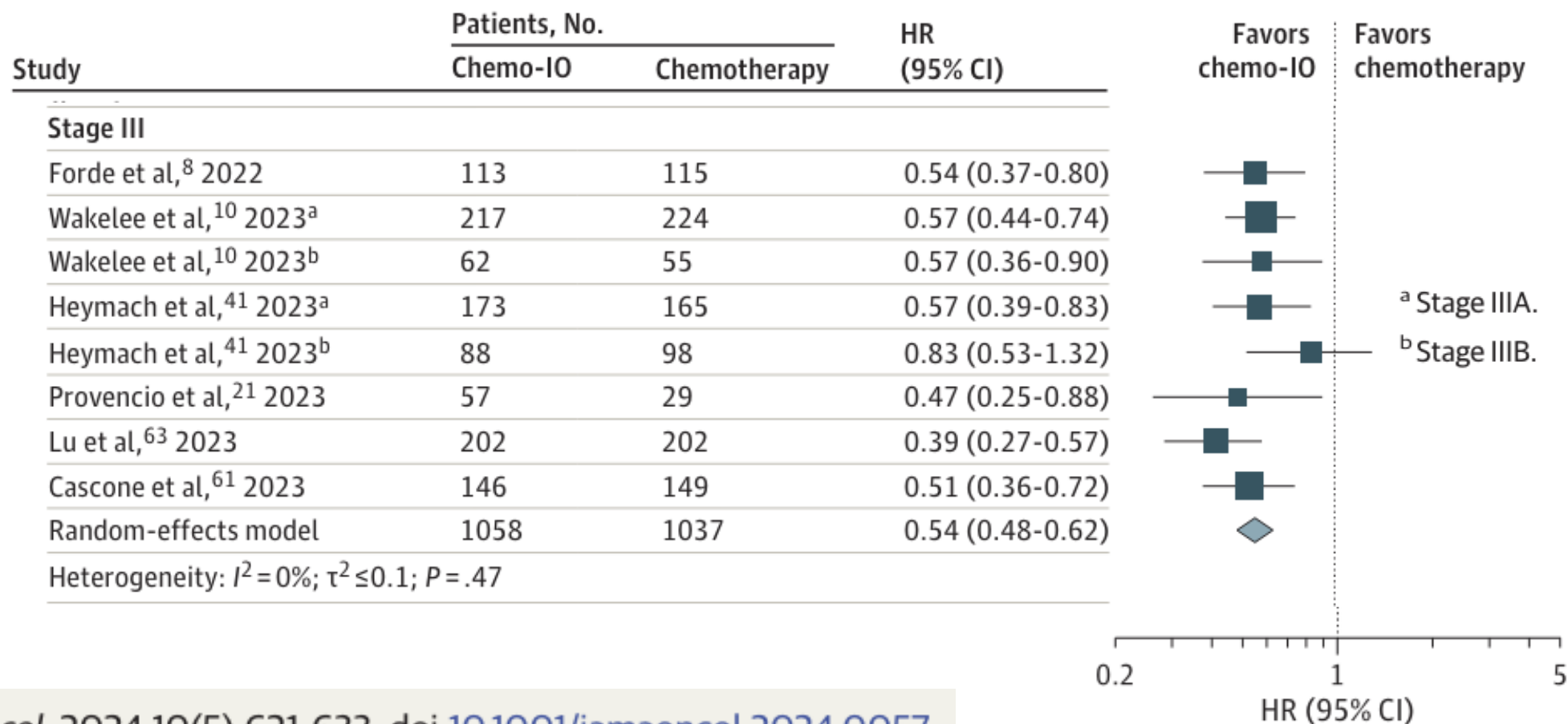## Figure 2. Pooled Hazard Ratios (HRs) of Event-Free Survival Across Randomized Clinical Trials

Study	Patients, No. Chemo-IO	Chemotherapy	HR (95% CI)
Stage III			
Forde et al,[8] 2022	113	115	0.54 (0.37-0.80)
Wakelee et al,[10] 2023[a]	217	224	0.57 (0.44-0.74)
Wakelee et al,[10] 2023[b]	62	55	0.57 (0.36-0.90)
Heymach et al,[41] 2023[a]	173	165	0.57 (0.39-0.83)
Heymach et al,[41] 2023[b]	88	98	0.83 (0.53-1.32)
Provencio et al,[21] 2023	57	29	0.47 (0.25-0.88)
Lu et al,[63] 2023	202	202	0.39 (0.27-0.57)
Cascone et al,[61] 2023	146	149	0.51 (0.36-0.72)
Random-effects model	1058	1037	0.54 (0.48-0.62)

Heterogeneity: $I^2 = 0\%$; $\tau^2 \leq 0.1$; $P = .47$

Favors chemo-IO | Favors chemotherapy

[a] Stage IIIA.
[b] Stage IIIB.

0.2 — 1 — 5
HR (95% CI)

Sub-groups Based on PD-L1 Expression

Figure 2. Pooled Hazard Ratios (HRs) of Event-Free Survival Across Randomized Clinical Trials

Study	Patients, No. Chemo-IO	Chemotherapy	HR (95% CI)
PD-L1 <1%			
Forde et al,[8] 2022	78	77	0.84 (0.54-1.32)
Wakelee et al,[10] 2023	138	151	0.75 (0.56-1.01)
Heymach et al,[41] 2023	122	125	0.76 (0.49-1.17)
Lu et al,[63] 2023	69	70	0.59 (0.33-1.03)
Cascone et al,[61] 2023	93	93	0.73 (0.47-1.15)
Random-effects model	500	516	0.74 (0.62-0.89)
Heterogeneity: $I^2 = 0\%$; $\tau^2 \leq 0.1$; $P = .91$			
PD-L1 1%-49%			
Forde et al,[8] 2022	51	47	0.58 (0.30-1.12)
Wakelee et al,[10] 2023	127	115	0.52 (0.36-0.73)
Heymach et al,[41] 2023	135	142	0.70 (0.46-1.05)
Lu et al,[63] 2023	69	68	0.31 (0.18-0.55)
Cascone et al,[61] 2023	83	76	0.76 (0.46-1.25)
Random-effects model	465	448	0.56 (0.42-0.73)
Heterogeneity: $I^2 = 41.3\%$; $\tau^2 \leq 0.1$; $P = .15$			
PD-L1 ≥50%			
Forde et al,[8] 2022	38	42	0.25 (0.10-0.61)
Wakelee et al,[10] 2023	132	134	0.48 (0.33-0.71)
Heymach et al,[41] 2023	109	107	0.60 (0.35-1.01)
Lu et al,[63] 2023	64	64	0.31 (0.15-0.62)
Cascone et al,[61] 2023	45	52	0.26 (0.12-0.55)
Random-effects model	388	399	0.40 (0.28-0.56)
Heterogeneity: $I^2 = 32.1\%$; $\tau^2 \leq 0.1$; $P = .21$			

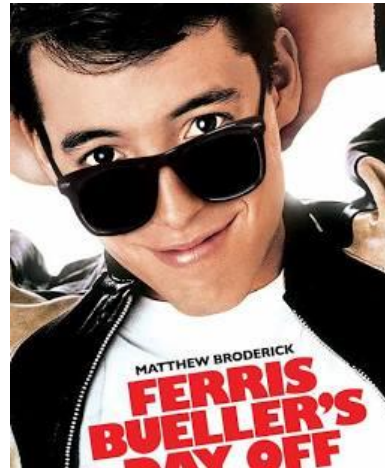Favors chemo-IO — Favors chemotherapy

HR (95% CI): 0.2 — 1 — 5

Mild benefit when PD-L1 =0%

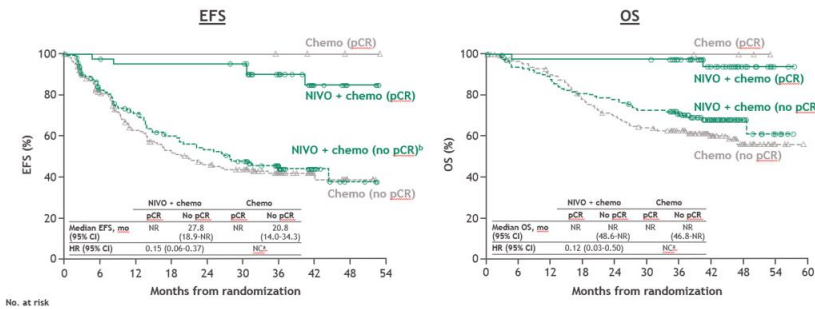Greatest benefit in PD-L1 >50%

Are patients with PD-L1 negative tumors or those with lower than stage III really benefiting form peri-op chemo-IO?

Bueller? Bueller?

What does adjuvant IO add after neoadjuvant IO?

If pCR occurs it portends a >90% 3 yr EFS and >95% likelihood of being alive at 3 years - *without* adjuvant IO
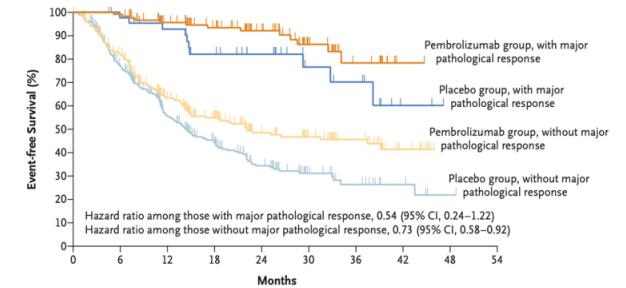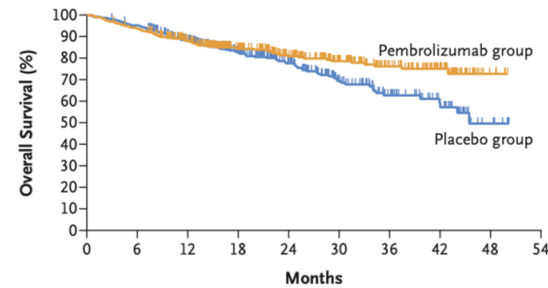
CheckMate 816 - 3 year outcomes by pCR status

After neoadj IO, added benefit of additional adjuvant IO is unknown

KEYNOTE-671 (Pembro 4 cycles preop, 13 cycles postop)

Data show that even patients without major pathologic response, some exposure to IO better

Trial not designed to show improved outcomes from <u>addition</u> of adjuvant IO in any group

N Engl J Med 2023;389:491-503.

pCR is a good indicator of longterm efficacy.
If we could only predict pCR upfront.....

Is Perioperative Immunotherapy the New Standard of Care?

- Maybe not in every patient who is diagnosed with early stage lung cancer
- Stage and PD-L1 expression play a role in benefit seen across all trials
- Tumors with actionable alterations need more investigation
- Predictive biomarkers of long term efficacy are lacking

Basics of Small Cell Lung Cancer

Rachel Sanborn, MD
Medical Oncologist and Co-Director
Providence Thoracic Oncology Program

Global Resource for Advancing Cancer Education
LUNG Cancer Video Library