UCLA Health | Jonsson Comprehensive Cancer Center

ACCELERATING DISCOVERIES
TO PREVENT AND CURE CANCER

“Perioperative Chemo/Immunotherapy and Surgical Outcomes”

Masters in Thoracic Oncology Summit

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Phase 3 IO trials in eNSCLC: Protocol Schema

Study	Neoadjuvant (CT-IO vs. CT)	N	EGFR/ALK	Adjuvant (IO 1Y vs. placebo)	Stage
Neoadjuvant only					
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	358	Excluded (if known)	None	IB-IIIA (7th ed.) II-IIIB (8th ed.)
CheckMate 816 (ESMO 2023)	Ipilimumab + Nivolumab (1 & 3 cycles)	221	Excluded (if known)	None	IB-IIIA (7th ed.) II-IIIB (8th ed.)
Perioperative (neoadjuvant + adjuvant)					
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)	802	Excluded	Durvalumab	IIA-IIIB (8th ed.)
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizumab + CT (4 cycles)	786	Included	Pembrolizumab	II-IIIB (8th ed.)
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)	461	Excluded (if known)	Nivolumab	II-IIIB (8th ed.)
Neotorch (ASCO 2023)	Toripalimab + CT (3 cycles)	500	Excluded	Toripalimab + CT (1 cycle), Toripalimab	II-III
RATIONALE-315 (ESMO 2023)	Tislelizumab + CT (3-4 cycles)	453	Excluded	Tislelizumab (8 cycles)	II-IIIA
Adjuvant only					
IMpower 010 (WCLC 2022)	N/A	1280	Included	CT mandatory Atezolizumab	II-IIIA (8th ed.)
Keynote-091 (ESMO 2022)	N/A	1177	Included	CT optional Pembrolizumab	II-IIIA (8th ed.)
BR.31 (ESMO 2024)	N/A	1415	Included	CT optional Durvalumab	IB-IIIA (7th ed.)

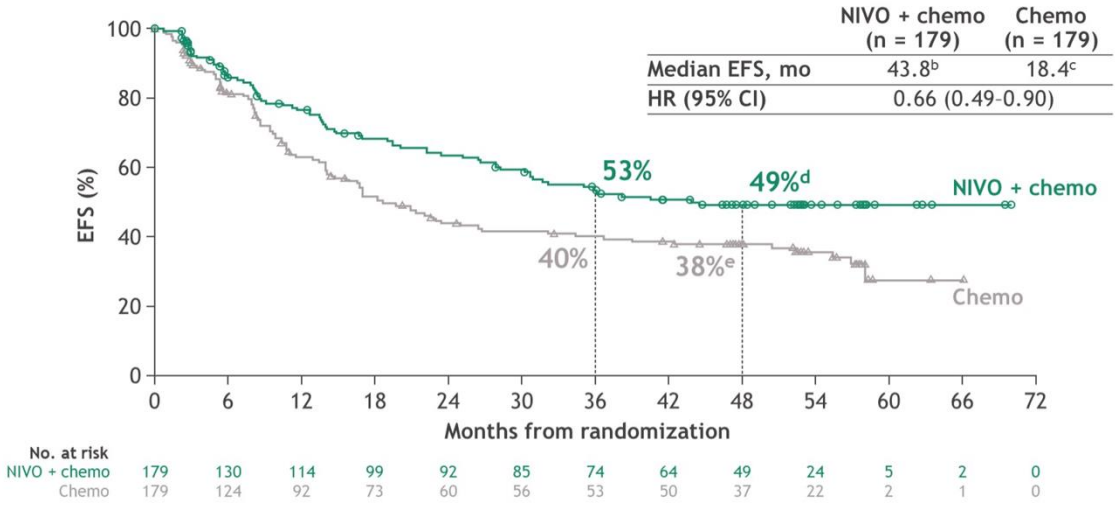
Global Trials

Study	Neoadjuvant (CT-IO vs. CT)	EGFR/ALK	Adjuvant (IO 1Y vs. placebo)	Stage	Primary Endpoint	DFS/EFS HR	OS HR	DFS/EFS	OS
Neoadjuvant									
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	Excluded (if known)	None	IB-IIIA (7th ed.) II-IIIB (8th ed.)	pCR EFS	0.68	0.62	65% 2Y	83% 2Y
Perioperative (neoadjuvant + adjuvant)									
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)	Excluded	Durvalumab	IIA-IIIB (8th ed.)	pCR EFS	0.68	NR	63% 2Y	NR
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizumab + CT (4 cycles)	Included	Pembrolizumab	II-IIIB (8th ed.)	EFS OS	0.58	0.72	62% 2Y	67% 4Y
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)	Excluded (if known)	Nivolumab	II-IIIB (8th ed.)	EFS	0.58	NR	70%1.5Y	NR
Neotorch (ASCO 2023)	Toripalimab + CT (3 cycles)	Excluded	Toripalimab + CT (1 cycle), Toripalimab	II-III	EFS MPR	0.40 (stage III)	NR	65% 2Y (stage3)	NR
RATIONALE-315 (ESMO Virtual 2024)	Tislelizumab + CT (3-4 cycles)	Excluded	Tislelizumab (8 cycles)	II-IIIA	pCR	0.56	0.62	68% 2Y	89% 2Y
Adjuvant									
IMpower 010 (WCLC 2022)	N/A	Included	CT mandatory	II-IIIA (8th ed.)	DFS	0.66	NR	75% 2Y	NR
Keynote-091 (ESMO 2022)	N								
BR.31 (ESMO 2024)	N/A	Excluded in analysis	CT optional Durvalumab	II-IIIA (8th ed.)	DFS	0.89	NR	67% 2Y	NR

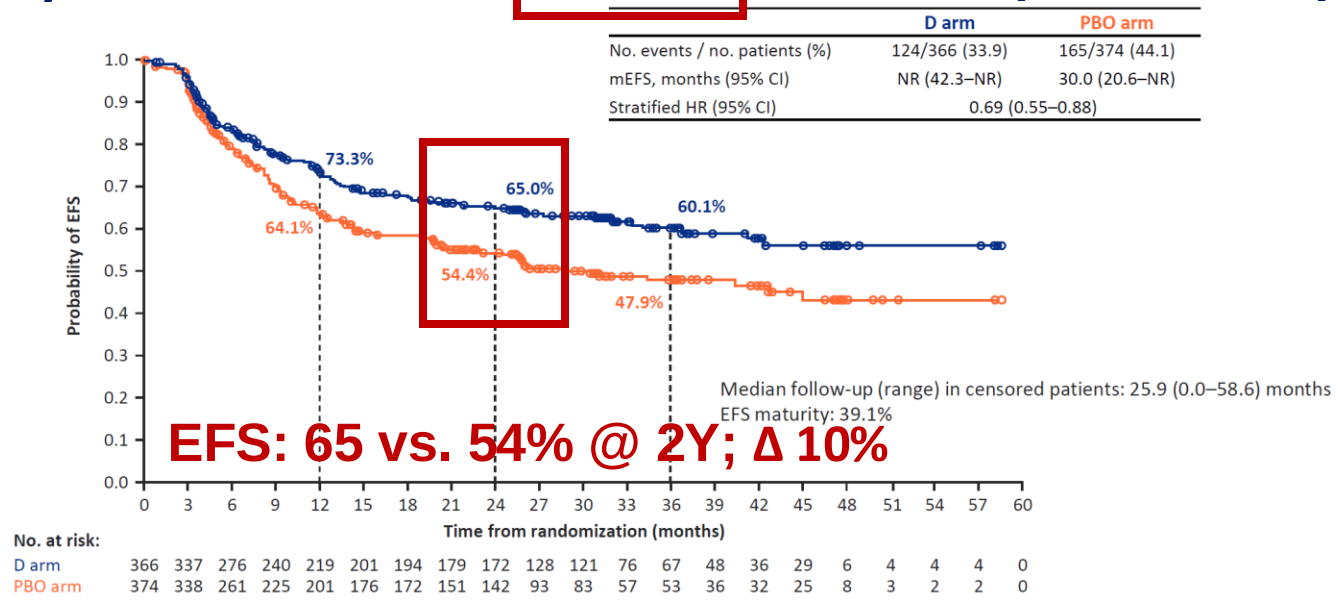
Neoadj./Periop. Trials: EFS HR (0.56-0.68) and EFS% (62-70%) are all similar in PD-L1 all-comers

Updated EFS in Ph 3 Neoadjuvant or Perioperative IO global trials

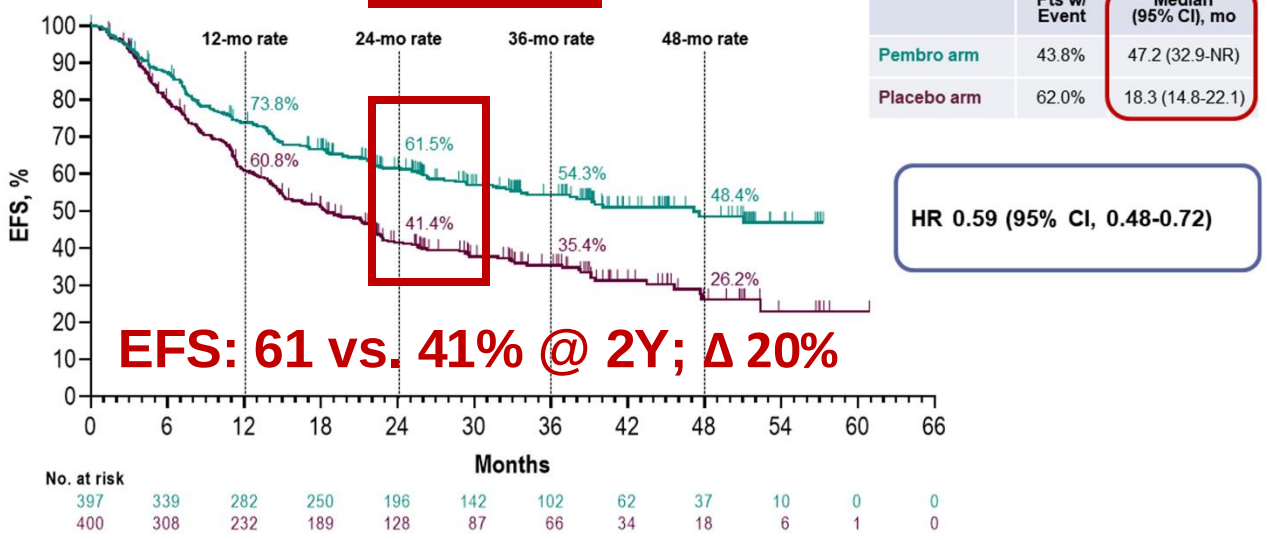
CheckMate 816: HR 0.66; 49% @4Y (ASCO 2024)



AEGEAN: HR 0.69; 60% @3Y (WCLC 2024)



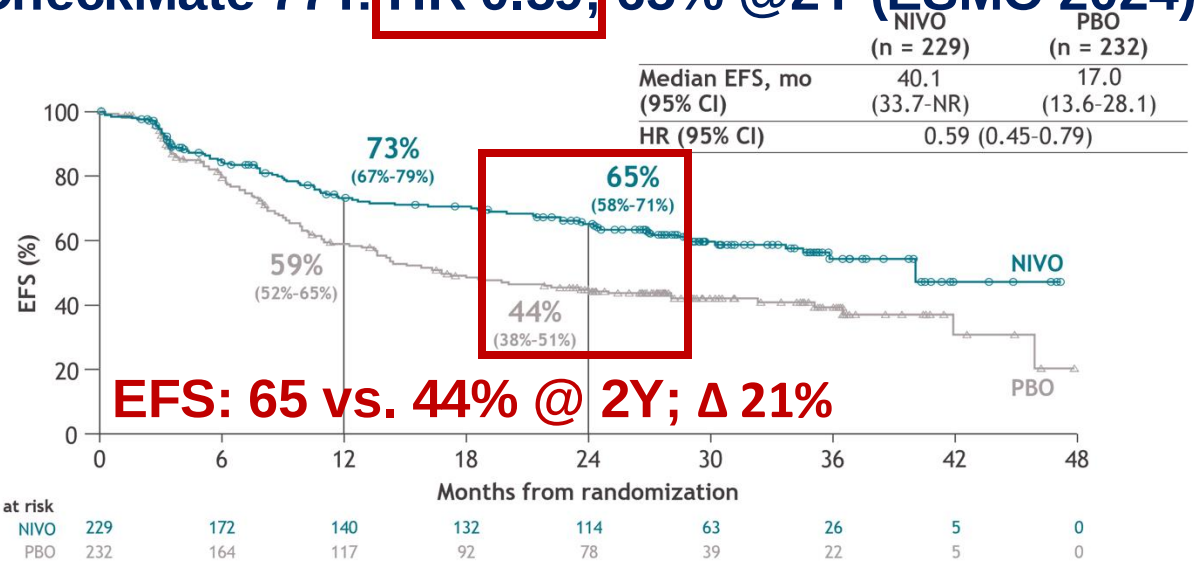
Keynote 671: HR 0.59; 48% @4Y (ESMO 2023)



	Pts w/ Event	Median (95% CI), mo
Pembro arm	43.8%	47.2 (32.9-NR)
Placebo arm	62.0%	18.3 (14.8-22.1)

HR 0.59 (95% CI, 0.48-0.72)

CheckMate 77T: HR 0.59; 65% @2Y (ESMO 2024)

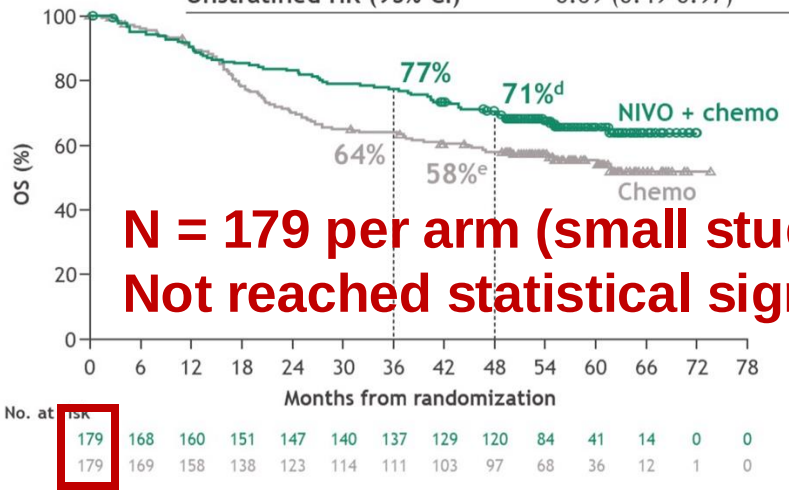


OS in Ph 3 Neoadjuvant or Perioperative IO global trials

Presenter: Jay M. Lee, M.D.

CheckMate 816: OS HR 0.69; 71% @4Y (ASCO 2024)

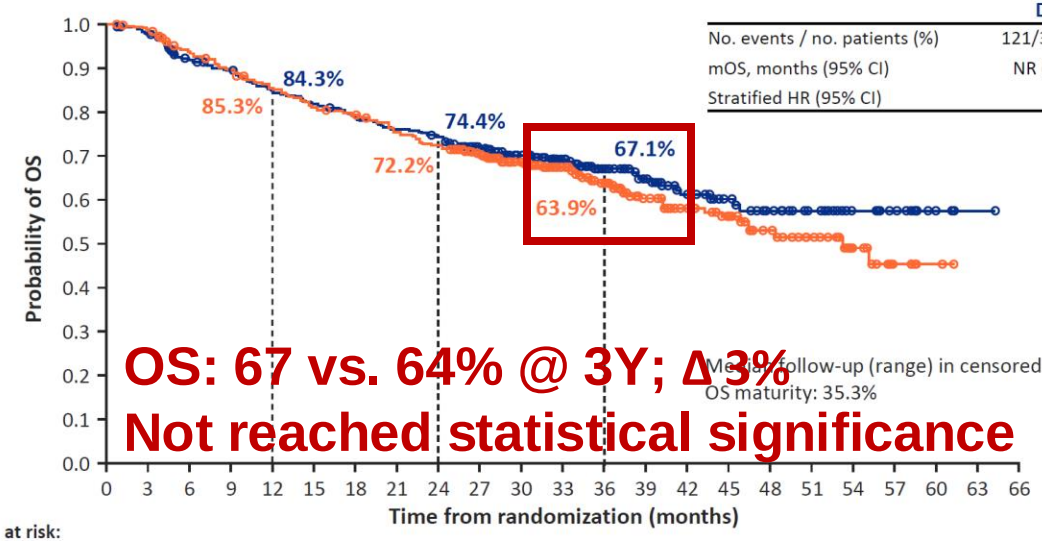
	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR[c]
HR (98.36% CI); *P* value	0.71 (0.47-1.07); 0.0451[b]	
Unstratified HR (95% CI)	0.69 (0.49-0.97)	



N = 179 per arm (small study)
Not reached statistical significance

AEGEAN: OS HR 0.89; 67% @3Y (WCLC 2024)

	D arm	PBO arm
No. events / no. patients (%)	121/366 (33.1)	140/374 (37.4)
mOS, months (95% CI)	NR (NR–NR)	53.2 (44.3–NR)
Stratified HR (95% CI)	0.89 (0.70–1.14)	

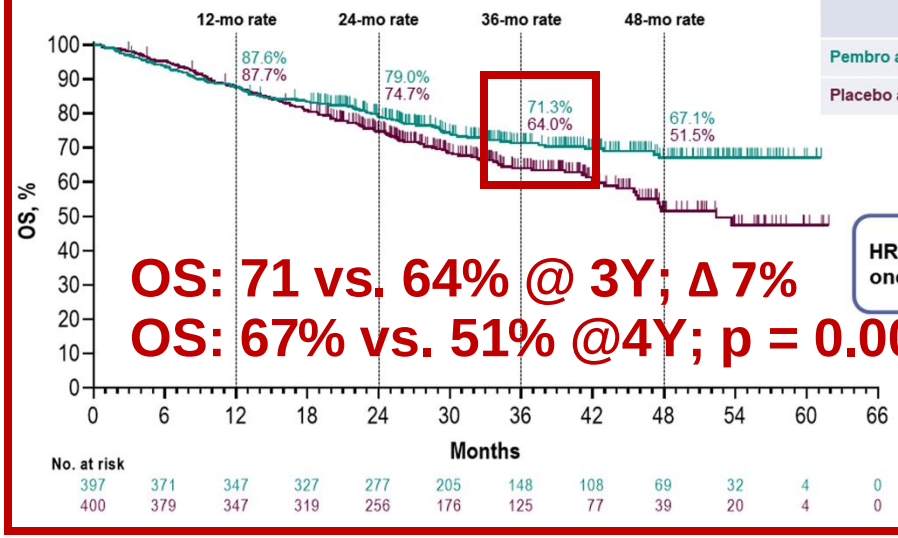


Median follow-up (range) in censored patients: 33.6 (0.7–64.3) months
OS maturity: 35.3%

OS: 67 vs. 64% @ 3Y; Δ 3%
Not reached statistical significance

Keynote 671: OS HR 0.72; 67% @4Y (ESMO 2023)

	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)



HR 0.72 (95% CI, 0.56-0.93)
one-sided *P* = 0.00517[a]

OS: 71 vs. 64% @ 3Y; Δ 7%
OS: 67% vs. 51% @4Y; p = 0.005

CheckMate 77T: OS Not Reported

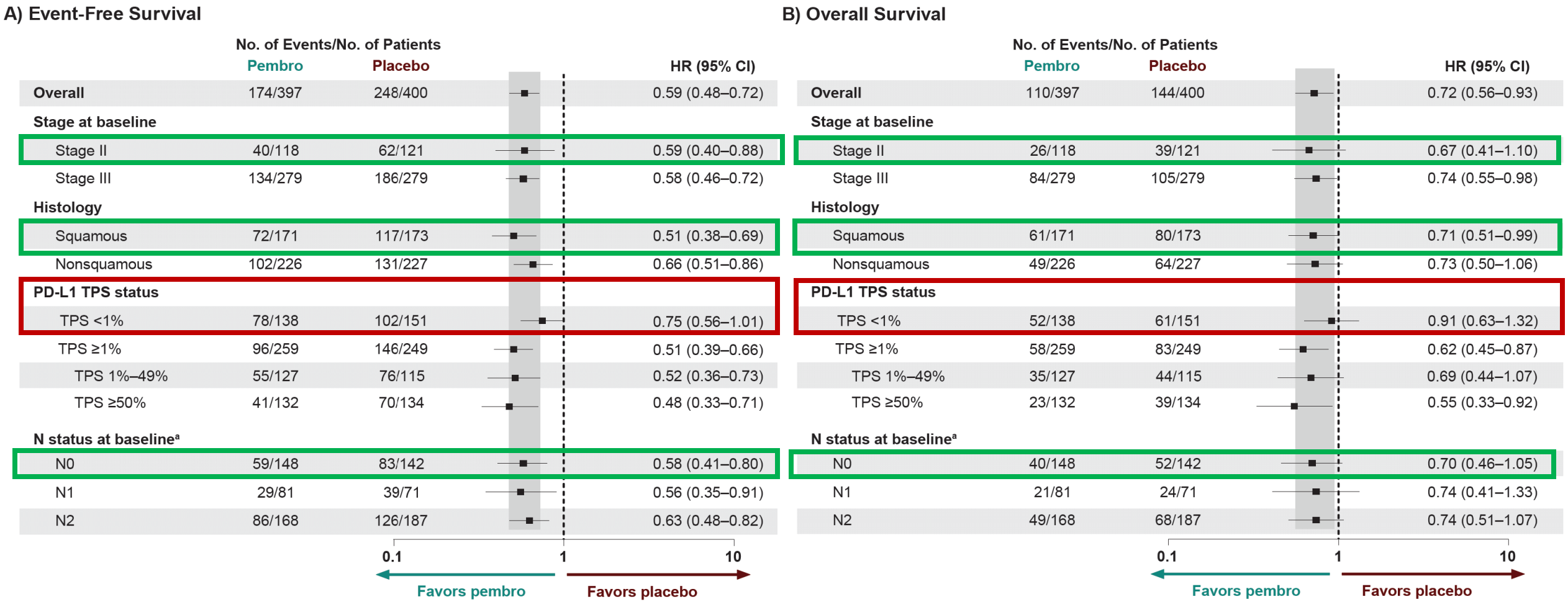
Phase 3 IO trials in eNSCLC: Subset Hazard Ratios for EFS

Study	Neoadjuvant (CT-IO vs. CT)	Stage II	Stage IIIA	Stage IIIB	PD-L1 < 1%	PD-L1 1-49%	PD-L1 ≥ 50%	SQ	Non-SQ	TMB <12.3 m/mb	TMB ≥ 12.3 m/mb
Neoadjuvant											
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	0.87 (IB/II 7th)	0.54	NA	0.85	0.58	0.24	0.77	0.50	0.86	0.69
CheckMate 816 (ESMO 2023)	Ip[illegible] Ni[illegible] (1 [illegible] cycles)										
Perioperative (neoadjuvant + adjuvant)											
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)	0.76	0.57	0.83	0.76	0.70	0.60	0.71	0.69	NR	NR
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizumab + CT (4 cycles)	0.65	0.54	0.52	0.77	0.51	0.42	0.57	0.58	NR	NR
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)	0.81	0.51		0.73	0.76	0.26	0.46	0.72	NR	NR
Neotorch (ASCO 2023)	Toripalimab + CT (3 cycles)	NA	0.40		0.59	0.31	0.31	0.35	0.54	NR	NR
RATIONALE-315 (ESMO2023; ESMOVirtual2024)	Tislelizumab + CT (3-4 cycles)	0.47	0.62	NR	0.80	0.34	0.71	0.56	0.64	NR	NR

Periop. IO improves EFS HR subsets who are poor responders to Neoadj. CT-IO only

Presenter: Jay M. Lee, M.D.

KEYNOTE-671: EFS vs. OS subgroup analyses (ESMO 2024)



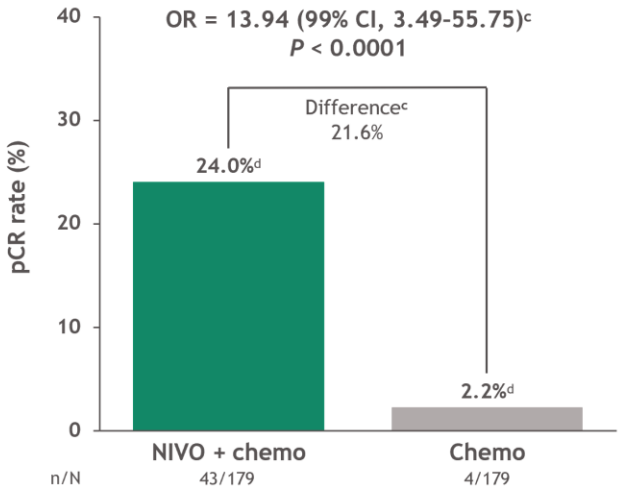
Improvement in OS HR for stage II, N0/N1, and Squamous Cell Ca but not in PD-L1 < 1% (EFS HR 0.75 vs. OS HR 0.91)

Garassino MC. ESMO 2024

pCR Is Similar in Neoadjuvant vs Perioperative Ph3 IO Trials

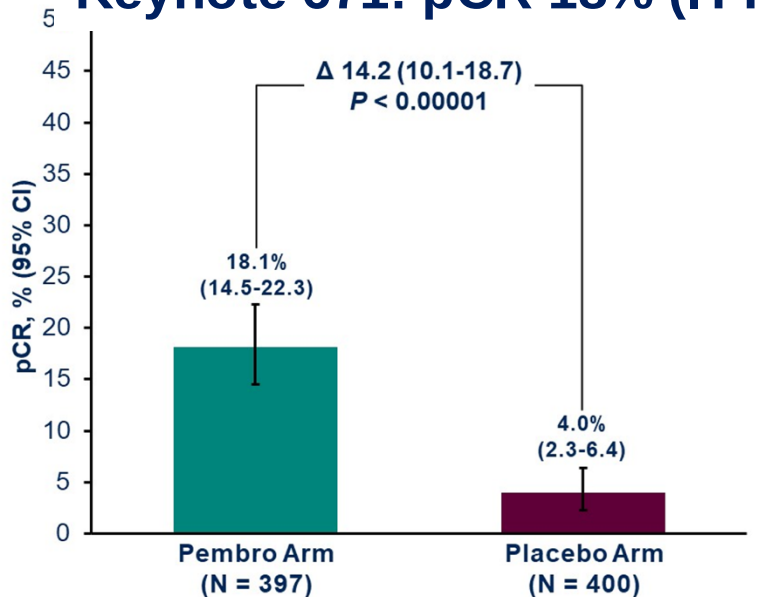
CT-IO X 3 cycles

CheckMate 816: pCR 24% (ITT)

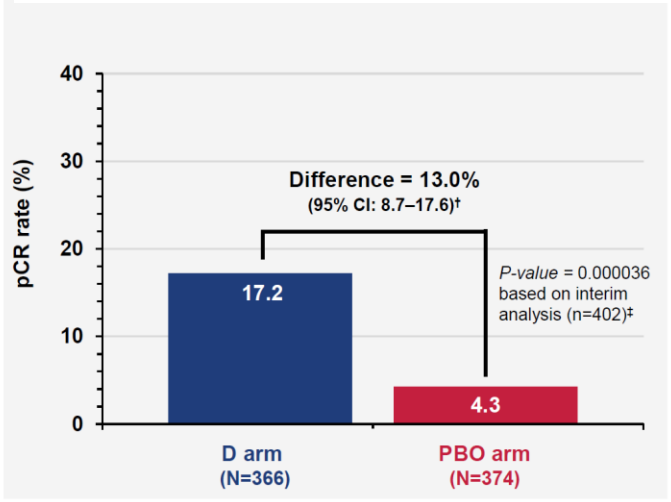


CT-IO X 4 cycles

Keynote 671: pCR 18% (ITT)



AEGEAN: pCR 17% (mITT)

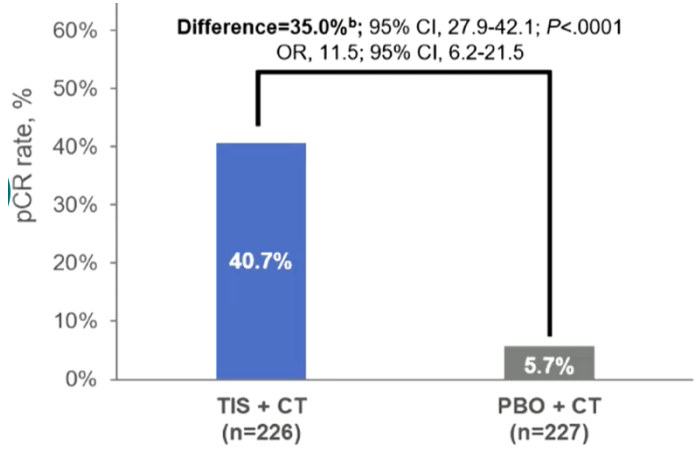


Neoadjuvant CT-IO
pCR: 17-25%

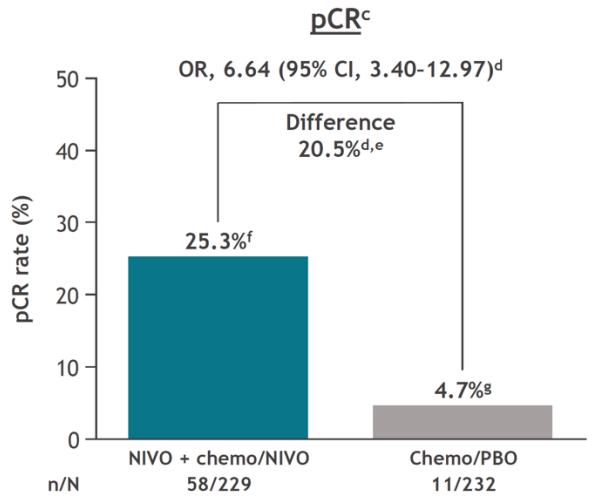
Neoadjuvant CT
pCR: 2.2-5.7%

RATIONALE-315: pCR 41% (ITT):

Stage III only; 3-4 cycles



CheckMate 77T: pCR 25% (ITT)

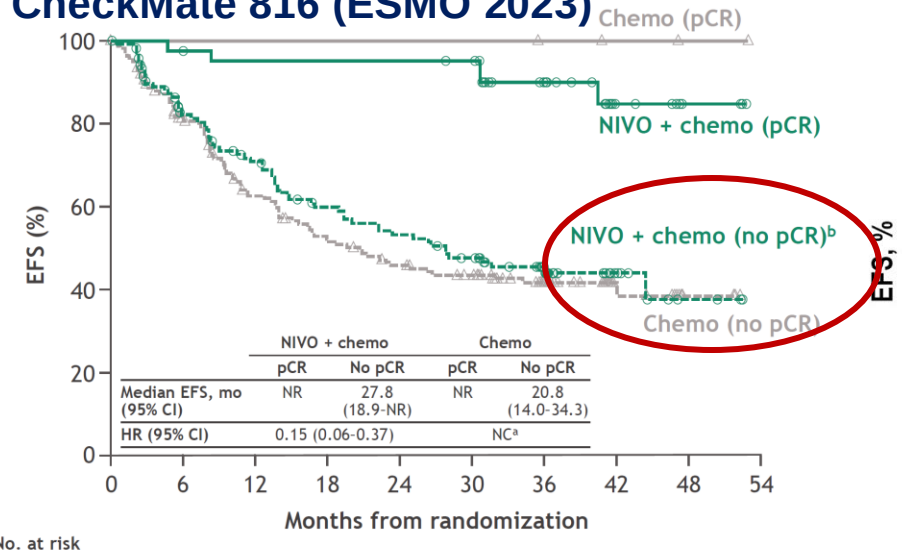


Forde PM AACR 2020. Heymach JV AACR 2023. Wakelee H ASCO 2023. Cascone T ESMO 2023. Lu S ASCO 2023.

Presenter: Jay M. Lee, M.D.

Non-pCR subgroup in Ph 3 Neoadjuvant or Perioperative CT-IO global trials

CheckMate 816 (ESMO 2023)

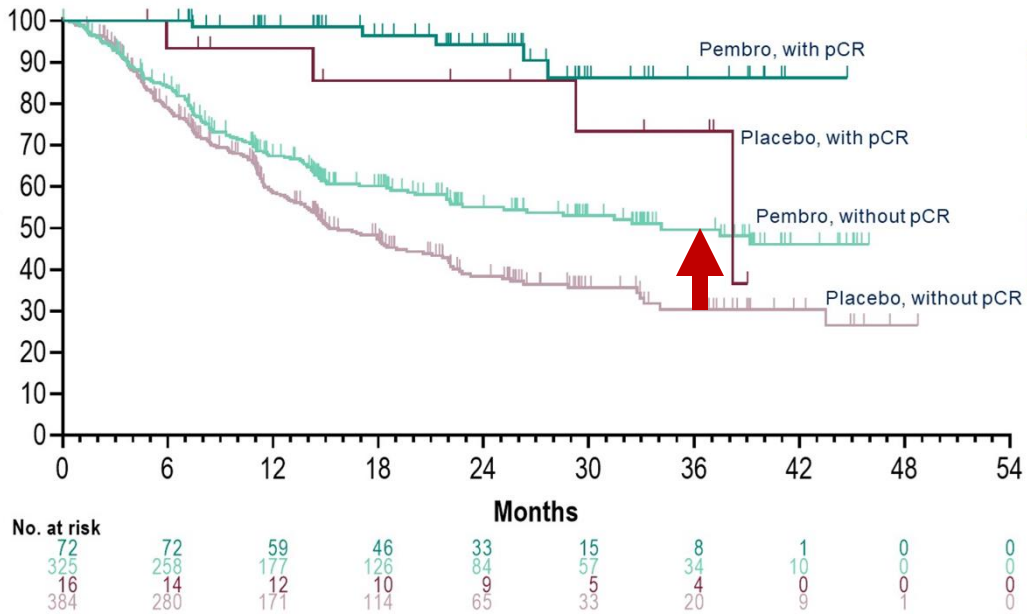


	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median EFS, mo (95% CI)	NR	27.8 (18.9-NR)	NR	20.8 (14.0-34.3)
HR (95% CI)	0.15 (0.06-0.37)		NC[a]	

No. at risk

pCR	43	41	40	40	40	39	26	9	3	0
pCR	4	4	4	4	4	4	3	2	1	0
No pCR	136	95	79	64	57	49	31	11	3	0
No pCR	175	124	91	75	63	56	36	13	3	0

KEYNOTE-671 (ASCO 2023)



With pCR
HR 0.33 (95% CI, 0.09-1.22)

Without pCR
HR 0.69 (95% CI, 0.55-0.85)

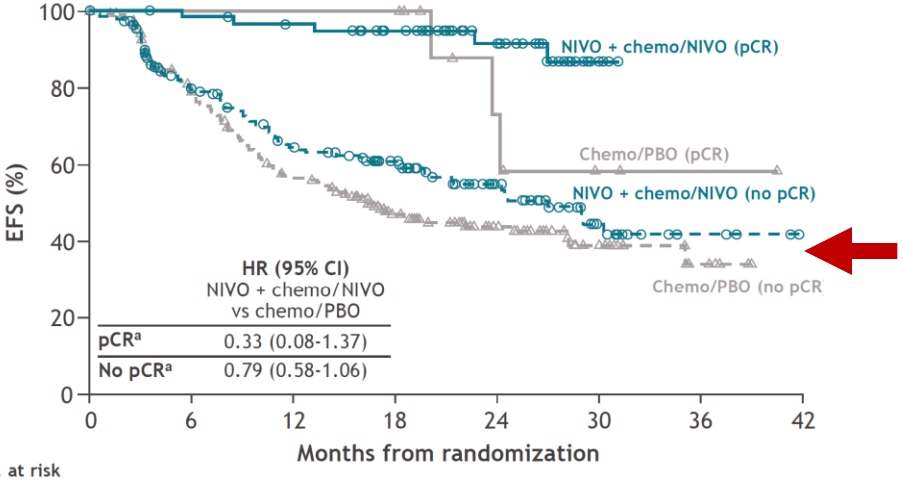
No. at risk

	72	72	59	46	33	15	8	1	0	0
	325	258	177	126	84	57	34	10	0	0
	16	14	12	10	9	5	4	0	0	0
	384	280	171	114	65	33	20	9	1	0

Improvement of EFS in no pCR (perioperative pembrolizumab) vs no pCR after CT alone in KN-671

Less apparent in CM77T and AEGEAN

CheckMate 77T (ESMO 2023)



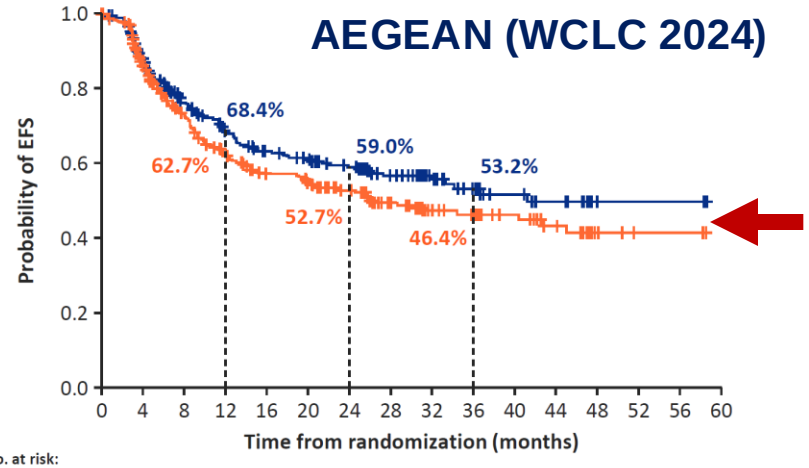
pCR[a]	0.33 (0.08-1.37)
No pCR[a]	0.79 (0.58-1.06)

No. at risk

pCR	58	56	53	45	28	4	0	0
pCR	11	11	11	11	5	2	1	0
No pCR	171	117	88	70	41	16	4	0
No pCR	221	154	107	67	39	17	5	0

AEGEAN (WCLC 2024)

	D arm	PBO arm
No. events / no. patients (%)	115/303 (38.0)	162/358 (45.3)
mEFS, months (95% CI)	41.2 (31.9–NR)	25.9 (19.8–45.0)
Unstratified HR (95% CI)	0.81 (0.64–1.03)	



No. at risk:

D arm	303	240	189	160	142	134	120	87	51	41	29	18	3	2	2	0
PBO arm	358	280	223	186	159	149	131	80	53	47	33	25	7	2	2	0

Pulla P. ESMO 2023

Wakelee H. ASCO 2023

Cascone T. ESMO 2023

Heymach JV. WCLC 2024

ITT Perioperative IO with and without Adjuvant IO: EFS

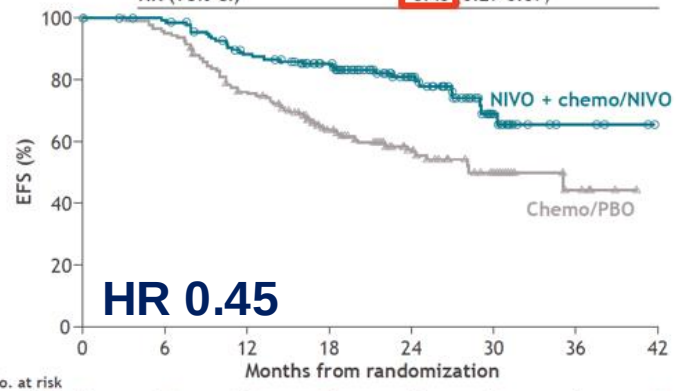
With adjuvant therapy

Without adjuvant therapy

CheckMate 77T

Adjuvant

	NIVO + chemo/NIVO (n = 142)	Chemo/PBO (n = 152)
Median EFS, mo (95% CI)	NR (NR-NR)	35.1 (22.0-NR)
HR (95% CI)	0.45 (0.29-0.69)	

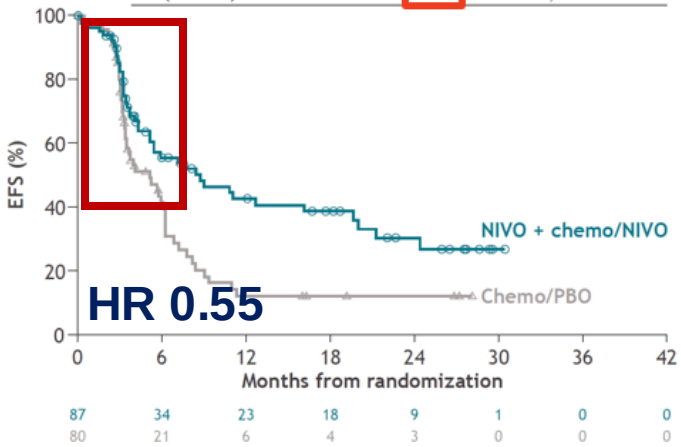


No. at risk

NIVO + chemo/NIVO	142	139	118	97	60	19	4	0
Chemo/PBO	152	144	112	74	41	19	6	0

No adjuvant

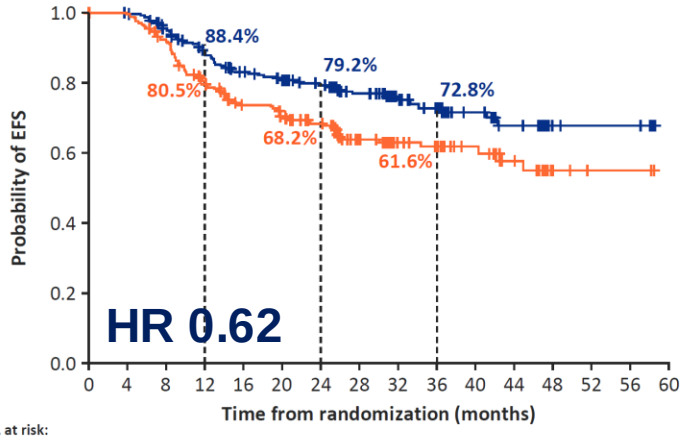
	NIVO + chemo/NIVO (n = 87)	Chemo/PBO (n = 80)
Median EFS, mo (95% CI)	8.8 (5.2-19.7)	5.2 (3.4-6.2)
HR (95% CI)	0.55 (0.37-0.83)	



	87	34	23	18	9	1	0	0
	80	21	6	4	3	0	0	0

AEGEAN

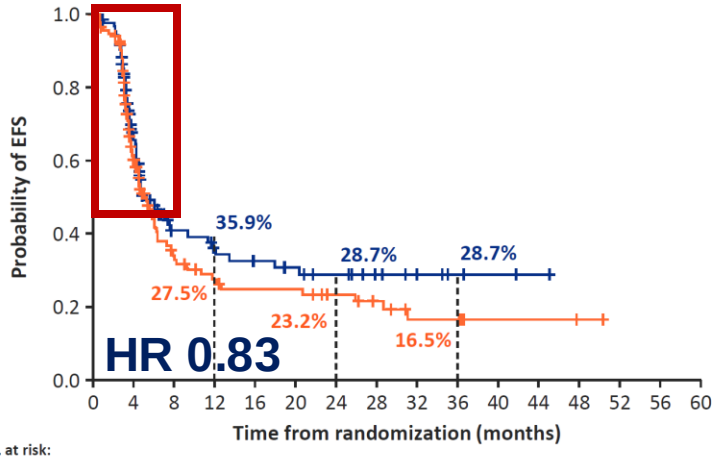
	D arm	PBO arm
No. events / no. patients (%)	58/242 (24.0)	83/237 (35.0)
mEFS, months (95% CI)	NR (NR–NR)	NR (42.6–NR)
Unstratified HR (95% CI)	0.62 (0.44–0.86)	



No. at risk:

D arm	242	239	222	198	181	173	159	118	73	64	46	29	6	4	4	0
PBO arm	237	234	212	181	155	145	129	77	53	47	33	24	7	2	2	0

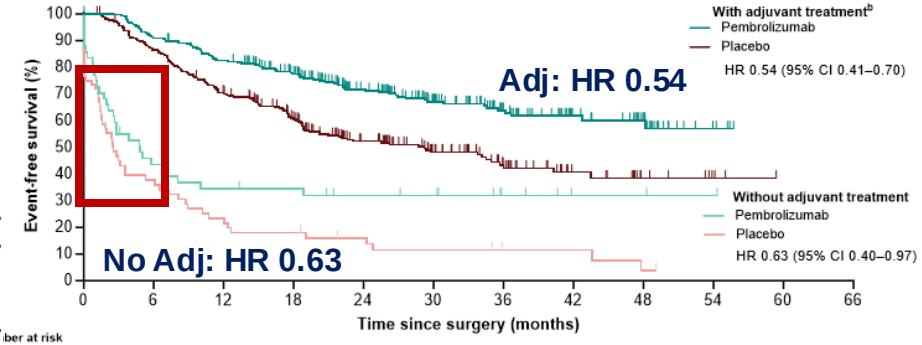
	D arm	PBO arm
No. events / no. patients (%)	66/124 (53.2)	82/137 (59.9)
mEFS, months (95% CI)	5.1 (4.5–9.3)	5.2 (4.1–6.3)
Unstratified HR (95% CI)	0.83 (0.60–1.14)	



No. at risk:

D arm	124	62	26	21	18	16	13	8	5	3	2	1	0	0	0	0
PBO arm	137	62	26	20	17	17	13	10	6	6	3	3	1	0	0	0

Keynote 671



ber at risk censored)

rolizumab	276 (0)	250 (1)	225 (3)	191 (24)	139 (63)	99 (95)	64 (126)	38 (150)	24 (163)	4 (182)	0 (186)	0 (186)
Placebo	253 (0)	216 (3)	173 (5)	136 (21)	91 (48)	64 (69)	39 (89)	18 (108)	8 (117)	3 (122)	0 (125)	0 (125)
rolizumab	49 (0)	19 (4)	15 (4)	14 (5)	11 (7)	10 (8)	5 (13)	2 (16)	2 (16)	1 (17)	0 (18)	0 (18)
Placebo	64 (0)	21 (5)	13 (5)	10 (5)	7 (7)	5 (7)	3 (9)	3 (9)	1 (9)	0 (10)	0 (10)	0 (10)

- **Steep early drop in EFS (“cliff”)**
- **Where’s the surgery?**

Cascone T, et al. ESMO 2023. Heymach JV, et al. WCLC 2024. Garassino MC, et al. ESMO 2024.

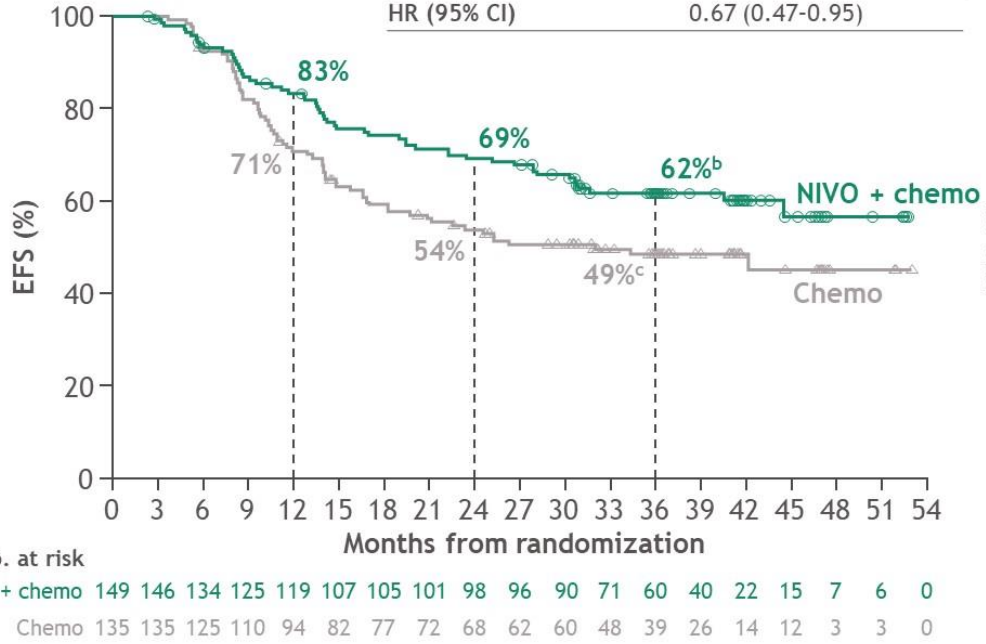
CheckMate 816 (Neoadjuvant CT and Nivolumab)

CheckMate 816 (NIVO + chemo in resectable NSCLC): 3-y efficacy and safety by definitive surgery status

EFS[a] by definitive surgery status

With definitive surgery

	NIVO + chemo (n = 149)	Chemo (n = 135)
Median EFS, mo (95% CI)	NR (44.4-NR)	31.8 (18.0-NR)
HR (95% CI)	0.67 (0.47-0.95)	

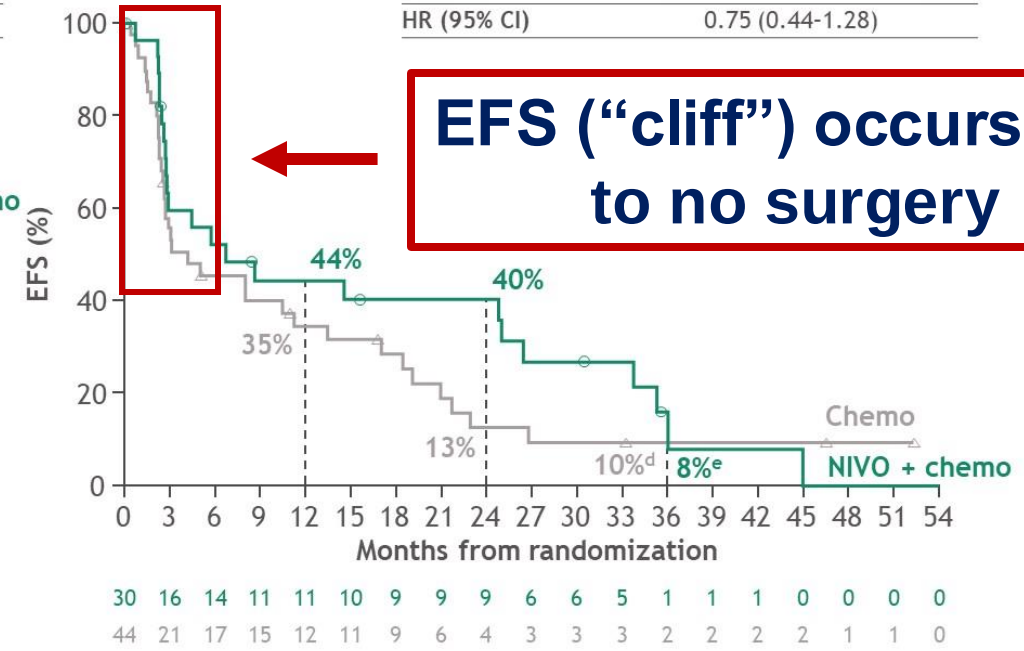


No. at risk

NIVO + chemo	149	146	134	125	119	107	105	101	98	96	90	71	60	40	22	15	7	6	0
Chemo	135	135	125	110	94	82	77	72	68	62	60	48	39	26	14	12	3	3	0

Without definitive surgery

	NIVO + chemo (n = 30)	Chemo (n = 44)
Median EFS, mo (95% CI)	6.7 (2.7-24.9)	4.1 (2.5-11.2)
HR (95% CI)	0.75 (0.44-1.28)	



NIVO + chemo	30	16	14	11	11	10	9	9	9	6	6	5	1	1	1	0	0	0	0
Chemo	44	21	17	15	12	11	9	6	4	3	3	3	2	2	2	2	1	1	0

EFS ("cliff") occurs due to no surgery

Minimum/median follow-up, 32.9/41.4 months.

[a]Secondary definition: time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, or death due to any cause; patients receiving subsequent therapy were not censored. [b-e]95% CI: [b]53-69; [c]40-57; [d]2-22; [e]1-28.

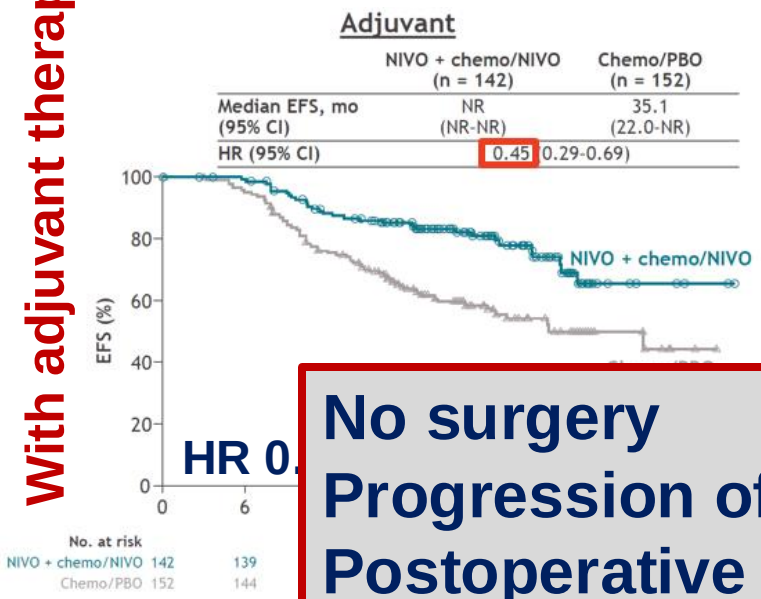
Spicer J, et al. ASCO 2023.

ITT Perioperative IO with and without Adjuvant IO: EFS

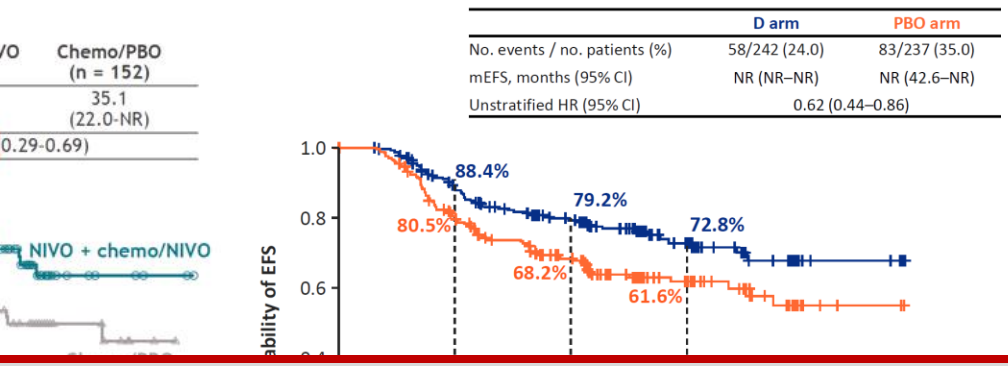
With adjuvant therapy

Without adjuvant therapy

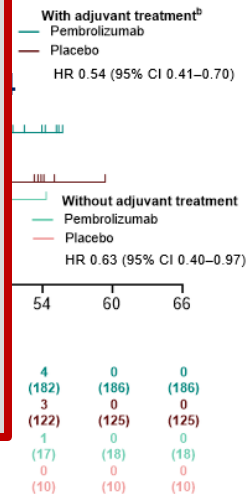
CheckMate 77T



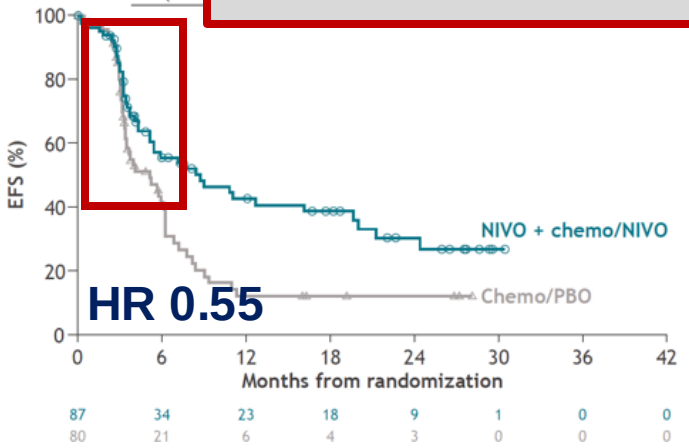
AEGEAN

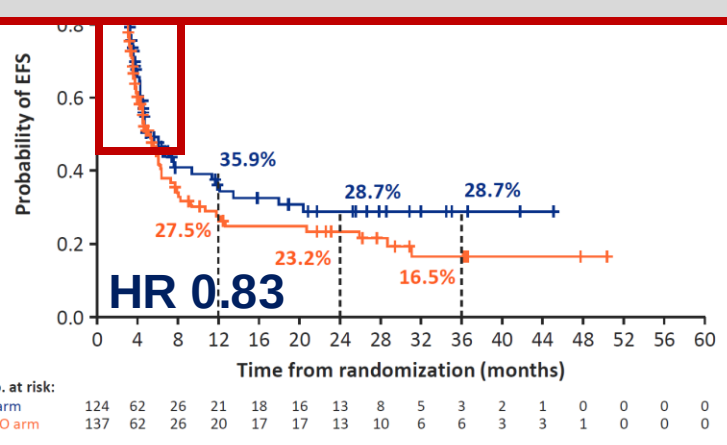


Keynote 671



No surgery
Progression of disease
Postoperative complications = **no adjuvant therapy**
Postoperative mortality
IRAE
TRAE



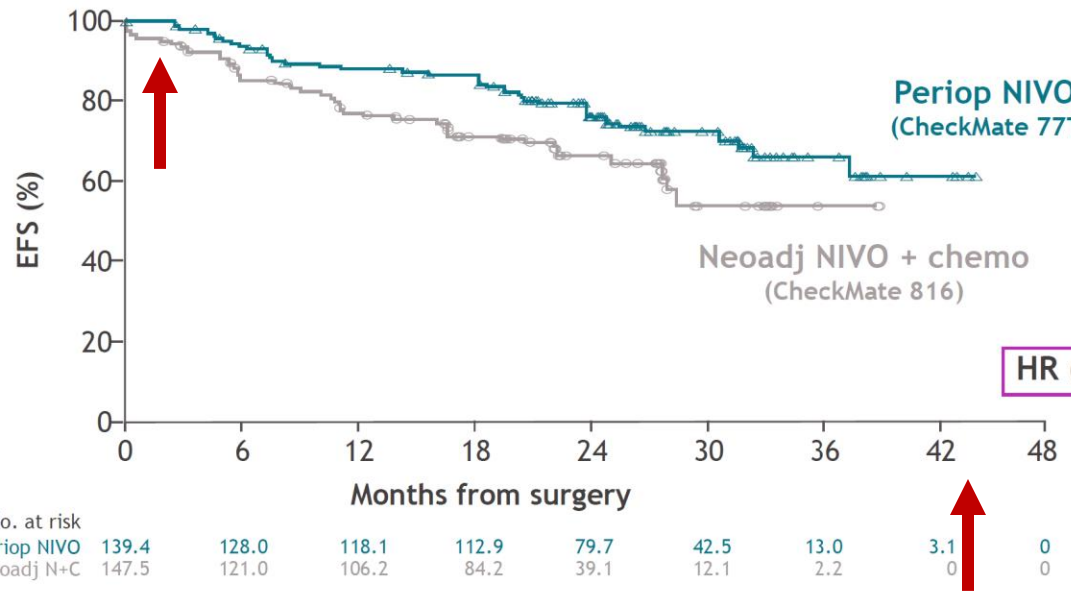


- **Steep early drop in EFS (“cliff”)**
- **What are the reasons for this?**

Cascone T, et al. ESMO 2023. Heymach JV, et al. WCLC 2024. Garassino MC, et al. ESMO 2024.

CheckMate 77T vs. CheckMate 816

Landmark EFS (BICR) from definitive surgery



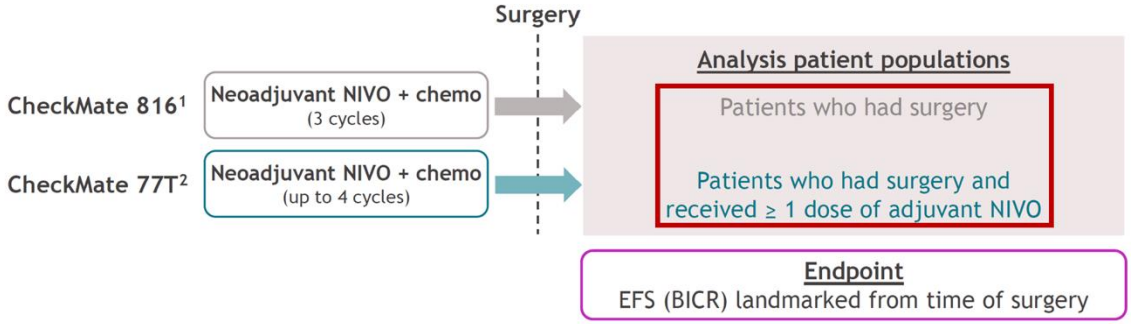
- No EFS drop in neoadjuvant-only arm
- Where is 4Y and 5Y EFS for CM816?
- What about ITT analysis?

	Weighted (ATE)[b]	
	Periop NIVO[a] (n = 139.4[c])	Neoadj NIVO + chemo (n = 147.5[c])
HR (95% CI)	0.61 (0.39-0.97)	

- HR (95% CI): ATT[d] weighted analysis, 0.56 (0.35-0.90); unweighted analysis, 0.59 (0.38-0.92)

Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. [a]Includes only patients who received ≥ 1 dose of adjuvant NIVO. [b]ATE: varying weights were applied to all patients in both neoadjuvant NIVO + chemo arm (CheckMate 816) and perioperative NIVO (CheckMate 77T) to make them comparable to one another. [c]N values fractional due to weighting. [d]ATT: varying weights were applied to patients in the neoadjuvant NIVO + chemo arm (CheckMate 816) to make them comparable to those in the perioperative NIVO arm (CheckMate 77T).

In the unweighted analysis population, 89 patients (64%) completed adjuvant therapy, and median number of doses (range) was 13.0 (1-13). Unweighted landmark EFS from surgery among all patients who had surgery (regardless of whether they received adjuvant NIVO in CheckMate 77T) for periop NIVO vs neoadj NIVO + chemo: HR = 0.82 (95% CI, 0.55-1.21).



Forde PM, et al. WCLC 2024.

	Neoadjuvant Therapy				Adjuvant Therapy					
	Received		Completed		Received		Completed		Ongoing	
Study	**CT-IO**	**CT**	**CT-IO**	**CT**	**IO**	**PBO**	**IO**	**PBO**	**IO**	**PBO**
Neoadjuvant only										
CheckMate 816 (NEJM 2022)	98%	98%	94% (C3)	85% (C3)	NA	NA	NA	NA	NA	NA
CheckMate 816 (ESMO 2023)	98% (Ipi/Nivo)	96%	91% (Ipi/Nivo)	86%	NA	NA	NA	NA	NA	NA
Perioperative (neoadjuvant + adjuvant)										
AEGEAN (AACR 2023)	100%	99%	87%	89%	66%	64%	24%	21%	23%	24%
Keynote 671 (ASCO 2023)	99%	99%	75%	74%	73%	67%	40%	35%	11%	11%
CheckMate 77T (ESMO 2023)	99%	99%	85%	89%	62%	66%	37% (ITT)	40% (ITT)	3% (ITT)	3% (ITT)
Neotorch (ASCO 2023)	100%	100%	87% (C3)	92% (C3)	71%	65%	44%	33%	12%	10%
RATIONALE-315 (ESMO 2023; ESMO Virtual 2024)	100%	99%	93%	93%	74%	65%	47%	45%	5%	4%
Adjuvant only										
IMpower 010 (Lancet 2021)					98%	99%	64%	75%	0%	0%
Keynote 091 (Lancet 2022)					98%	99%	51%	65%	0%	0%
BR.31 (ESMO 2024)	NA	NA	NA	NA	99%	99%	59%	68%	68%	68%

Periop. trials:
26-38% of patients do not start intended adjuvant therapy

Phase 3 IO trials in eNSCLC: Preoperative Attrition to Surgery

Study	Neoadjuvant (CT-IO vs. CT)	N	Preop. Attrition (Rx arm)	Preop. Attrition (Control arm)	Time from last dose neoadj. Rx to surgery
Neoadjuvant only					
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	358	16%	21%	5.3 (4.6-6) weeks
CheckMate 816 (ESMO 2023)	Ipilimumab + Nivolumab (3 cycles)	221	26%	19%	Not reported
Perioperative (neoadjuvant + adjuvant)					
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)	802	19%	19%	Not reported
Keynote-671 (ASCO 2023) (ESMO 2023)	Pembrolizumab + CT (4 cycles)	786	18%	21%	5.9 (2.6-19.7) weeks (STS 2024)
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)	461	22%	23%	Not reported
Neotorch (ASCO 2023)	Toripalimab + CT (3 cycles)	500	18%	27%	Not reported
RATIONALE-315 (ESMO 2023)	Tislelizumab + CT (3-4 cycles)	453	16%	24%	Not reported

Preoperative attrition to surgery after Neoadj. CT-IO: 16-26%

Reasons for attrition to surgery following preoperative CT-IO:
Adverse events (AE), progression of disease (PD), and other reasons (ITT analysis)

Study	Neoadjuvant (CT-IO vs. CT)	N	Adjuvant (IO 1Y vs. placebo)	AE (Rx arm)	AE (Control)	PD (Rx arm)	PD (Control)	Other (Rx arm)	Other (Control)
Neoadjuvant									
CheckMate 816 (ELCC2023)(ASCO2021)	Nivolumab + CT (3 cycles)	358	None	1%	1%	7%	10%	8%	11%
CheckMate 816 (ESMO 2023)	Ipilimumab + Nivolumab (1 & 3 cycles)	221	None	3%	8%	16%	8%	7%	11%
Perioperative (neoadjuvant + adjuvant)									
AEGEAN (AACR2023)(NEJM2023)	Durvalumab + CT (4 cycles)	802	Durvalumab	2%	1%	7%	7%	11%	10%
Keynote-671 (ASCO 2023)(ESMO 2023) (STS 2024)	Pembrolizumab + CT (4 cycles)	786	Pembrolizumab	6%	4%	4%	8%	7%	8%
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)	461	Nivolumab	3%	2%	6%	10%	12%	10%
Neotorch (ASCO 2023)	Toripalimab + CT (3 cycles)	500	Toripalimab + CT (1 cycle), Toripalimab	3%	0%	3%	10%	12%	11%
RATIONALE-315 (ESMO Virtual 2024)	Tislelizumab + CT (3-4 cycles)	453	Tislelizumab (8 cycles)	3%	1%	3%	8%	11%	15%

Study	Neoadjuvant (CT-IO vs. CT)	N	Adjuvant (IO 1Y vs. placebo)	Lx (Rx arm)	Lx (Control)	Px (Rx arm)	Px (Control)	Bi-Lx (Rx arm)	Bi-Lx (Control)
Neoadjuvant									
CheckMate 816 (ELCC 2023)	Nivolumab + CT (3 cycles)	358	None	77%	61%	17%	25%	2%	3%
CheckMate 816 (ESMO 2023)	Ipilimumab + Nivolumab (1 & 3 cycles)	221	None	66%	67%	11%	21%	7%	5%
Perioperative (neoadjuvant + adjuvant)									
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)	802	Durvalumab	65%	59%	7%	8%	4%	5%
Keynote-671 (ASCO 2023)(ESMO 2023) (STS 2024)	Pembrolizumab + CT (4 cycles)	786	Pembrolizumab	79%	75%	11%	12%	8%	8%
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)	461	Nivolumab	80%	72%	9%	14%	NR	NR
Neotorch (ASCO 2023)	Toripalimab + CT (3 cycles)	500	Toripalimab + CT (1 cycle), Toripalimab	81%	83%	9%	10%	NR	NR
RATIONALE-315 (ESMO Virtual 2024)	Tislelizumab + CT (3-4 cycles)	453	Tislelizumab (8 cycles)	NR	NR	NR	NR	NR	NR
Adjuvant									
IMpower 010 (WCLC 2022)	N/A	1280	CT mandatory Atezolizumab	75%	76%	17%	18%	6%	4%
Keynote-091 (ESMO2022)(ASCO2022)	N/A	1177	CT optional Pembrolizumab	79%		11%		8%	
BR.31 (ESMO 2024)	N/A	1415	CT optional Durvalumab	81%	79%	10%	15%	NR	NR

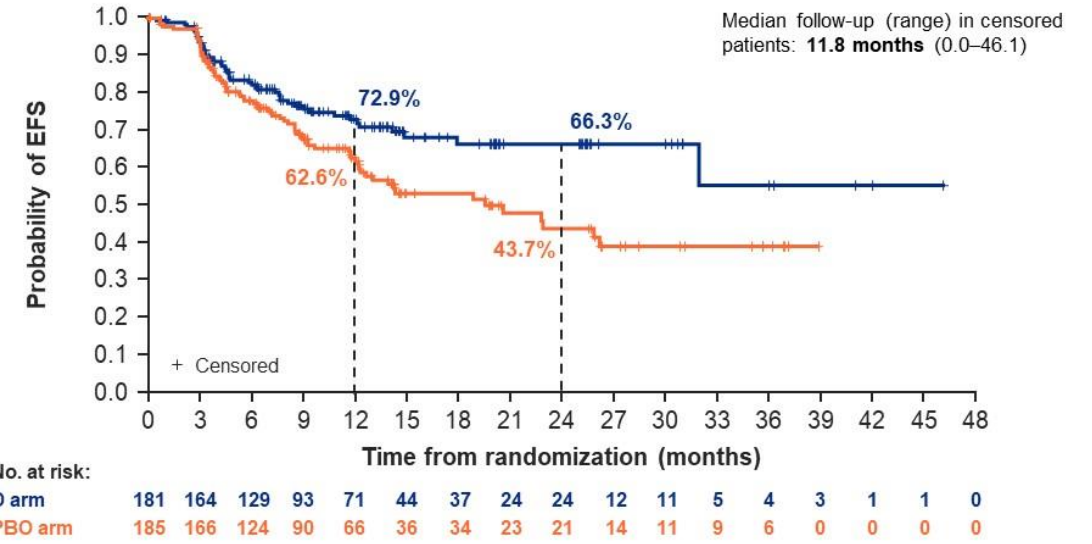
Study	Neoadjuvant (CT-IO vs. CT)	N	Adjuvant (IO 1Y vs. placebo)	R0 (Rx arm)	R0 (Control)	R1 (Rx arm)	R1 (Control)	R2 (Rx arm)	R2 (Control)
Neoadjuvant									
CheckMate 816 (ELCC 2023)(NEJM2022)	Nivolumab + CT (3 cycles)	358	None	83%	78%	11%	16%	3%	3%
CheckMate 816 (ESMO 2023)	Ipilimumab + Nivolumab (1 & 3 cycles)	221	None	80%	71%	14%	17%	4%	7%
Perioperative (neoadjuvant + adjuvant)									
AEGEAN (AACR 2023)	Durvalumab + CT (4 cycles)	802	Durvalumab	95%	91%	4%	8%	NR	NR
Keynote-671 (ASCO 2023)(ESMO 2023) (STS 2024)	Pembrolizumab + CT (4 cycles)	786	Pembrolizumab	92%	84%	5%	10%	1%	1%
CheckMate 77T (ESMO 2023)	Nivolumab + CT (4 cycles)	461	Nivolumab	89%	90%	11% R1/R2	10% R1/R2	11% R1/R2	10% R1/R2
Neotorch (ASCO 2023)	Toripalimab + CT (3 cycles)	500	Toripalimab + CT (1 cycle), Toripalimab	96%	93%	4% R1/R2	7% R1/R2	4% R1/R2	7% R1/R2
RATIONALE-315 (ESMO Virtual 2024)	Tislelizumab + CT (3-4 cycles)	453	Tislelizumab (8 cycles)	NR	NR	NR	NR	NR	NR
Adjuvant									
IMpower 010 (WCLC 2022)	N/A	1280	CT mandatory Atezolizumab	100%	100%	NA	NA	NA	NA
Keynote-091 (ESMO 2022)	N/A	1177	CT optional Pembrolizumab	100%	100%	NA	NA	NA	NA
BR.31 (ESMO 2024)	N/A	1415	CT optional Durvalumab	100%	100%	NA	NA	NA	NA

AEGEAN (Perioperative Durvalumab)

EFS using RECIST v1.1 (BICR) (baseline N2 subgroup and mITT)*

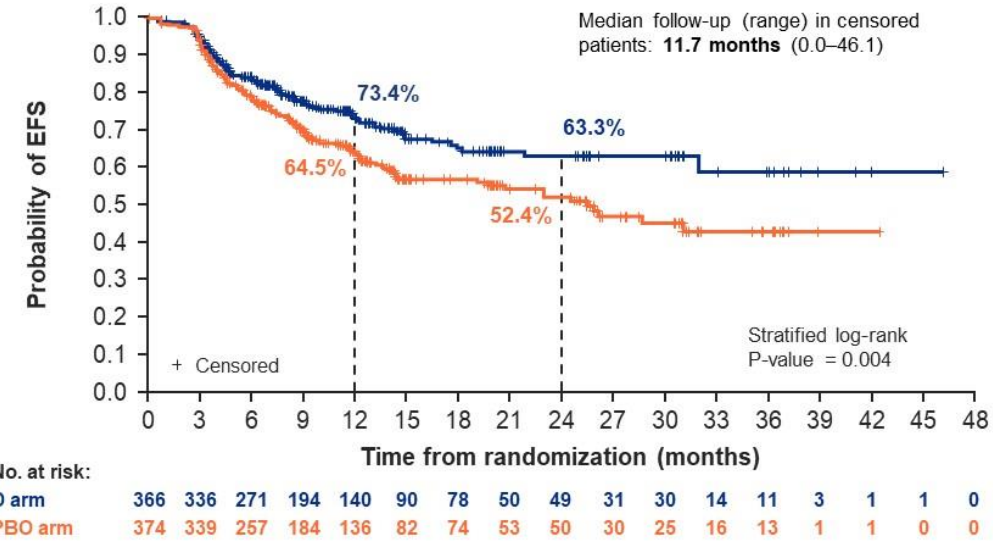
- EFS benefit in this subgroup was consistent with the mITT population and similar among patients with single- and multi-station N2 disease
  - N2 single-station (n=273) HR† (95% CI): 0.61 (0.39–0.94)[1]
  - N2 multi-station (n=74) HR† (95% CI): 0.69 (0.33–1.38)[1]

Baseline N2 subgroup	D arm	PBO arm
No. events / no. patients (%)	48/181 (26.5)	75/185 (40.5)
mEFS, months (95% CI)	NR (31.9, NR)	19.5 (12.6, 26.2)
Unstratified HR† (95% CI)	**0.63 (0.43, 0.90)**	



No. at risk:																	
D arm	181	164	129	93	71	44	37	24	24	12	11	5	4	3	1	1	0
PBO arm	185	166	124	90	66	36	34	23	21	14	11	9	6	0	0	0	0

mITT population[1]	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9, NR)	25.9 (18.9, NR)
Stratified HR† (95% CI)	**0.68 (0.53, 0.88)**	



No. at risk:																	
D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

DCO = Nov 10, 2022. *EFS is defined as time from randomization to the earliest of: (A) progressive disease (PD) that precludes surgery; (B) PD discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; (C) local/distant recurrence using BICR per RECIST v1.1; or (D) death from any cause. HR <1 favours the D arm versus the PBO arm. Median and landmark EFS estimates calculated using the Kaplan–Meier method. †HR for the baseline N2 subgroup calculated from an unstratified Cox proportional hazards model; HR for the mITT population calculated using a stratified Cox proportional hazards model. CI, confidence interval; D, durvalumab; HR, hazard ratio; mEFS, median EFS; NR, not reached; PBO, placebo.

PRESENTED BY: John V. Heymach, MD, PhD; Professor and Chair

[1]From Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer, Heymach JV, et al, N Engl J Med 2023;389:1672–84, Copyright © (2023) Massachusetts Medical Society. Reproduced with permission.

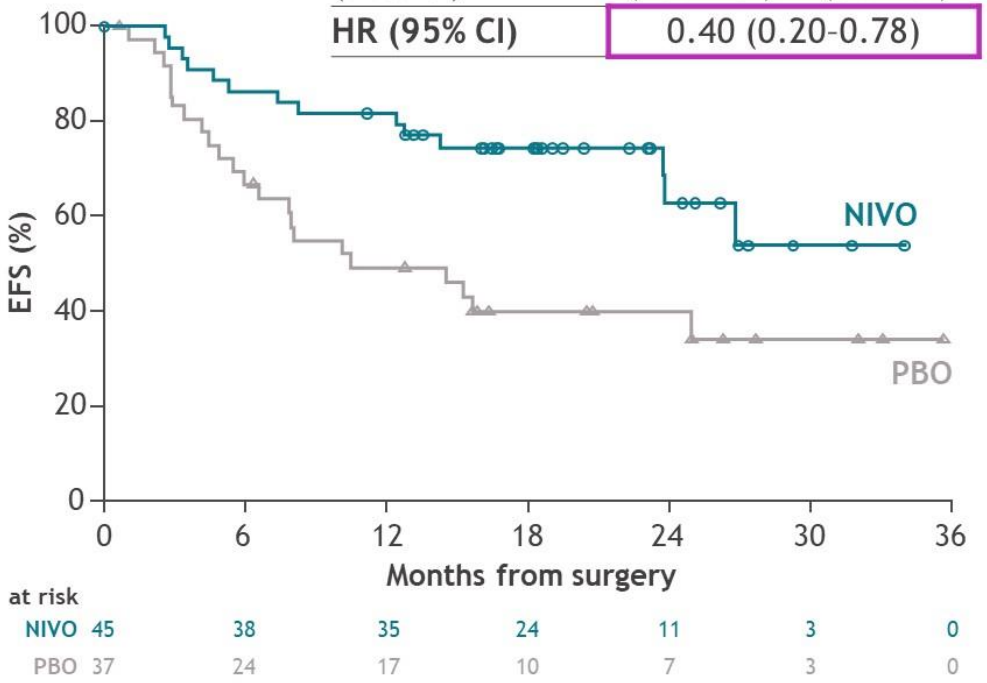
CheckMate 77T (Perioperative Nivolumab)

CheckMate 77T: clinical outcomes with perioperative NIVO by nodal status

Landmark EFS from definitive surgery

Stage III N2 single-station[a]

	NIVO (n = 45)	PBO (n = 37)
Median EFS, mo (95% CI)	NR (23.7-NR)	10.5 (6.0-NR)
HR (95% CI)	0.40 (0.20-0.78)	

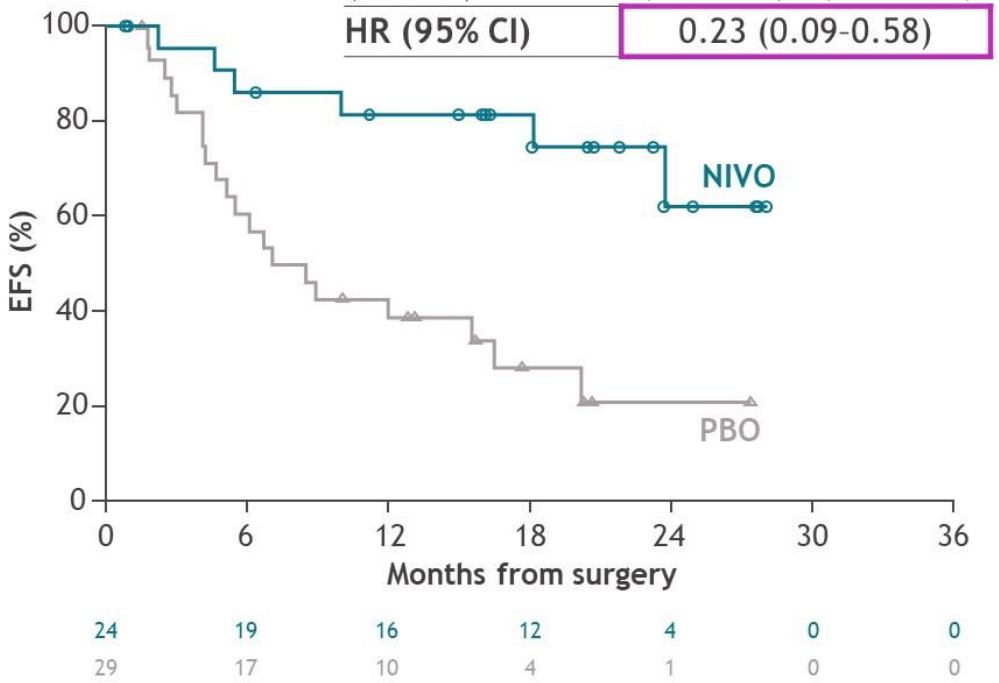


No. at risk

NIVO	45	38	35	24	11	3	0
PBO	37	24	17	10	7	3	0

Stage III N2 multi-station[a]

	NIVO (n = 24)	PBO (n = 29)
Median EFS, mo (95% CI)	NR (18.2-NR)	7.8 (4.7-16.5)
HR (95% CI)	0.23 (0.09-0.58)	



	24	19	16	12	4	0	0
	29	17	10	4	1	0	0

Median follow-up (range): 25.4 months (15.7-44.2). [a]N2 subcategory was not reported in 1 patient in the NIVO arm.

Pulla, MP et al. ASCO 2024

Conclusions

- Neoadjuvant, perioperative, and adjuvant IO approaches are all approved and acceptable standards of care
- Head-to-head trials are needed to determine most efficacious approach
- Following neoadjuvant CT-IO, the benefit of adjuvant IO remains controversial
- However, there are efficacy signals that support the superiority of a perioperative IO approach
  - Poor-responding EFS subsets from neoadjuvant CheckMate 816 improve with perioperative approach (AEGEAN, Keynote 671, and CheckMate 77T)
  - Survival analysis of neoadjuvant CT-IO (no pCR) with adjuvant IO improves compared to CT alone (no pCR)
  - Survival benefit with adjuvant vs without adjuvant IO after neoadjuvant IO (CheckMate 77T vs CheckMate 816)
- Preoperative attrition to surgery occurs in neoadjuvant and adjuvant approaches
- Defining resectability remains controversial; but most trials include pneumonectomy patients, invasive T4 tumors, and multi-station N2 disease