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Should Adjuvant IO Be Given After Surgery Following Chemo-IO

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Atlanta Lung Cancer Symposium

October 26, 2024

Disclosure Information

Consultant for: AbbVie, AnHeart Therapeutics, ArriVent Biopharma, AstraZeneca, BioCurity Pharmaceuticals, BioNTech AG, Blueprint Medicines, BI, BMS, Chugai Pharmaceutical, Curio Science, DAVA Oncology, Eli Lily & Co, EMD Serono, Genentech, GlaxoSmithKline, IDEOlogy Health, Immunocore, InterVenn Biosciences, Janssen Biotech, Janssen Pharmaceuticals, Mirati Therapeutics, Moffitt Cancer Center, ModeX, Nexus Health Systems, Novartis Pharmaceuticals, OncoCyte, RefleXion, Regeneron Pharmaceuticals, Roche, Sandoz Pharmaceutical, Sanofi, Spectrum Pharmaceuticals, Takeda, uniQure

Grant/Research support from: AstraZeneca, Boehringer-Ingelheim, Spectrum, Mirati, Bristol-Myer Squibb and Takeda

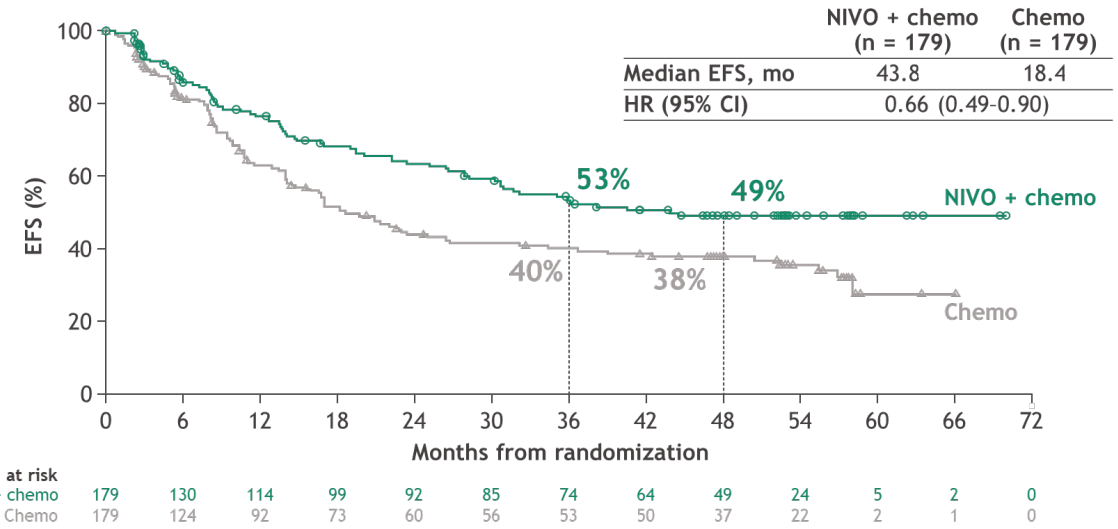
Licensing/Royalties: Spectrum

Neoadjuvant chemo-IO looks pretty good. Do we need to give adjuvant?

Perioperative IO Compared With Neoadjuvant IO

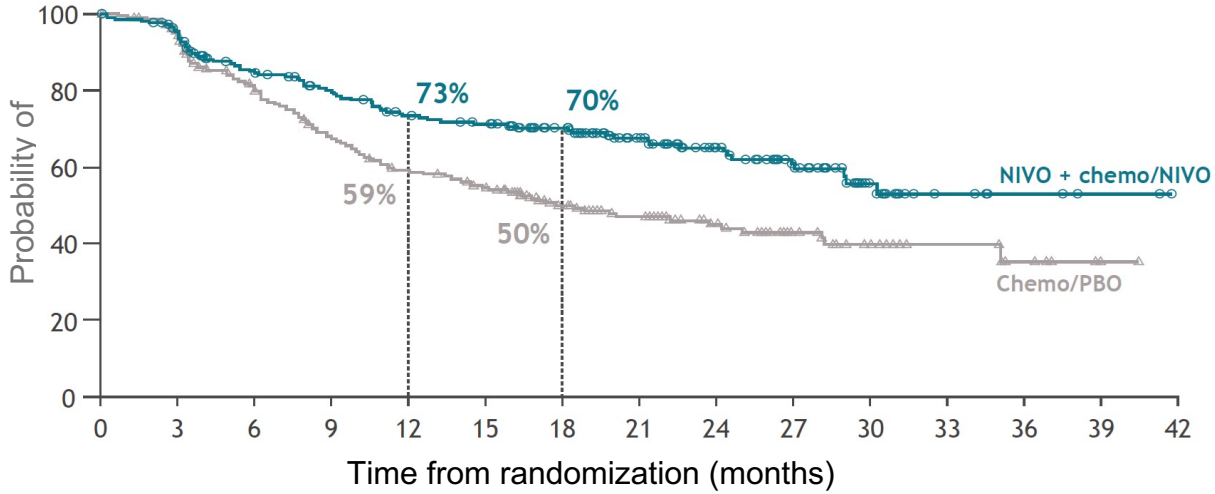
CheckMate 816 (Neoadjuvant Treatment)

HR: 0.66 (95% CI: 0.49, 0.90)



CheckMate 77T (Perioperative Treatment)

HR: 0.58 (97.36% CI: 0.42, 0.81)



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Spicer JD, et al. Neoadjuvant nivolumab plus chemotherapy vs chemotherapy in patients with resectable NSCLC: 4-year update from CheckMate 816 [oral]. Presented at 2024 ASCO Annual Meeting. ASCO 2024. Abstract LBA8010.

Forde et al NEJM 2022; Cascone et al NEJM 2024

I believe we should be greedy. For cures.

Gordon Gekko from Wall Street (1987)

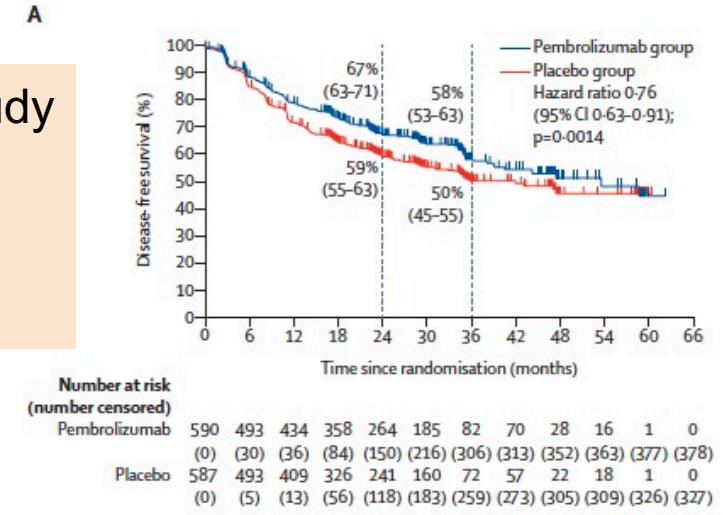
The point is, ladies and gentleman, that greed--for lack of a better word--is good

Greed is right. Greed works.

Greed clarifies, cuts through, and captures the essence of the evoluationary spirit.

Greed in all its forms– treed for life, for money, for love, knowledge- has marked the upward surge of mankind.

KN-91 adjuvant study
Stage IB-IIIA
mDFS~3 years
HR=0.76 (P=.0014,
95% CI 0.63-0.91)



O'Brien et al, Lancet Oncology 2022

Yes it's progress. But is a 50% chance of recurrence after 3 years good enough? Or should we greedier?

When the goal of treatment is **cure**, or at least to remain disease free, I believe the risk of undertreatment and missing a potential cure is greater than the risk of overtreatment and dealing with additional potential mageagable IO toxicities.

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Neoadjuvant Treatment Benefit Is Supported by a Single Small Randomized Phase 3 Trial (N=358)

Neoadjuvant

Study	**CheckMate 816[1] N=358**	
Regimen	**Nivo + Chemo**	**Chemo**
Median EFS (95% CI), mo	43.8 (30.6, NR)	18.4 (14.0, 26.7)
EFS HR (95% CI)	**0.66 (0.49, 0.90)**	
Maturity	**52% (planned)[2]**	
Median follow-up	57.6 months	

- Combined IO plus chemotherapy before surgery
- EFS includes progression precluding surgery in addition to recurrence and death
- 34% reduction in the risk of an EFS event

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Note: Most recent data from all studies (regardless of PD-L1).
Nivo=nivolumab.
1. Spicer JD, et al. ASCO 2024 [oral]. Abstract LBA8010; 2. Forde PM, et al. *N Engl J Med*. 2022;386(21):1973-1985.

FDA approved perioperative IO is supported by three large RCT with about 2000 patients

	Adjuvant[a] (N=2182)				Perioperative (N=1998)				Neoadjuvant (N=358)	
Study	**KEYNOTE-091[1] N=1177**		**IMpower010[2] N=1005**		**KEYNOTE-671[3] N=797**		**AEGEAN N=740**		**CheckMate 77T[4] N=461**		**CheckMate 816[5] N=358**	
Regimen	**Pembro**	**Placebo**	**Atezo**	**BSC**	**Pembro + Chemo →Pembro**	**Placebo + Chemo →Placebo**	**Durva + Chemo →Durva**	**Placebo + Chemo →Placebo**	**Nivo + Chemo →Nivo**	**Placebo + Chemo →Placebo**	**Nivo + Chemo**	**Chemo**
Median EFS/DFS (95% CI), mo	53.9 (46.2-67.0)	43.0 (35.0-51.6)	65.6 (NA, NA)	47.8 (NA, NA)	47.2 (32.9, NR)	18.3 (14.8, 22.1)	NR (42.3, NR)	30.0 (20.6, NR)	NR (28.9, NR)	18.4 (13.6, 28.1)	43.8 (30.6, NR)	18.4 (14.0, 26.7)
EFS/DFS HR (95% CI)	**0.81 (0.68, 0.96)**		**0.85 (0.71, 1.01)**		**0.59 (0.48, 0.72)**		**0.69 (0.55, 0.88)**		**0.58 (0.42, 0.81)**		**0.66 (0.49, 0.90)**	
Maturity	**48%**		**50%**		**53%**		**39%**		**40%**		**52% (planned)[6]**	
Median follow-up	51.7 months		65.0 months		36.6 months		25.9 months		25.4 months		57.6 months	

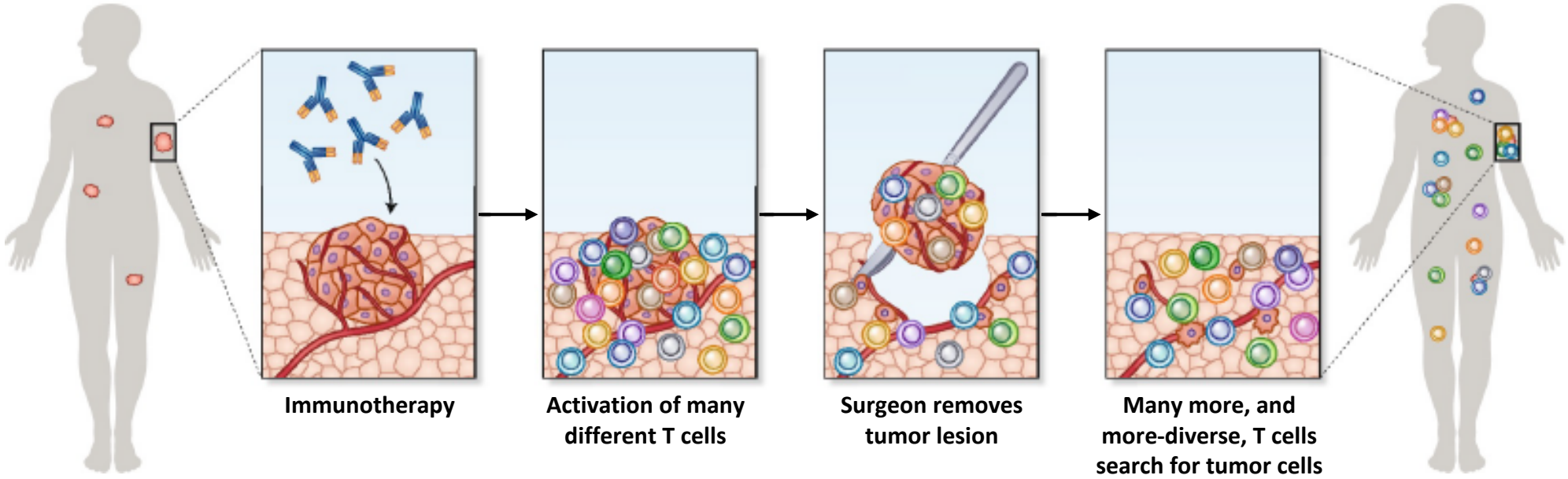
Note: Most recent data from all studies (regardless of PD-L1).

[a] For Adjuvant studies, randomization is after surgery and +/- adjuvant chemotherapy.

Atezo=atezolizumab; BSC=best supportive care; DFS=disease-free survival; Durva=durvalumab; EFS=event free survival; Nivo=nivolumab; NR=not reached/not estimable; NA=not available; Pembro=pembrolizumab.

1. Besse B, et al. ESMO-IO 2023. Abstract 120MO; 2. Wakelee HA, et al. ASCO 2024. Poster 297; 3. Spicer JD, et al. ESMO 2023. Abstract LBA56; 4. Cascone T, et al. ESMO 2023. Abstract LBA1; 5. Spicer JD, et al. ASCO 2024 [oral]. Abstract LBA8010; 6. Forde PM, et al. *N Engl J Med*. 2022;386(21):1973-1985.

Rationale for Perioperative Immunotherapy Treatment



Neoadjuvant Immunotherapy

- Optimal initial immune response stimulation (with primary tumor and LNs in situ)
- Combination with chemotherapy to induce maximal response and enhance locoregional disease control
- Early suppression/elimination of micrometastatic disease

Adjuvant Immunotherapy

- Consolidation of antitumor immunity
- Ongoing suppression of tumor PD-L1–mediated resistance to antitumor immunity
- Suppression/elimination of micrometastatic disease

LN=lymph node.

Reprinted with permission from Versluis JM, et al. Learning from clinical trials of neoadjuvant checkpoint blockade. *Nature Med*. 26:475-484, 2020, Springer Nature.

Slide courtesy of L. Horn

Rationale for adjuvant in early stage NSCLC: PD-L1 in facilitating the growth of micrometastases

nature COMMUNICATIONS

ARTICLE

Received 13 Jul 2014 | Accepted 11 Sep 2014 | Published xx xxx 2014

DOI: 10.1038/ncomms6241

Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression

Limo Chen[1,2,*], Don L. Gibbons[1,3,*], Sangeeta Goswami[1], Maria Angelica Cortez[1], Young-Ho Ahn[1,4], Lauren A. Byers[1], Xuejun Zhang[2], Xiaohui Yi[2], David Dwyer[2], Wei Lin[1], Lixia Diao[5], Jing Wang[5], Jonathon Roybal[1], Mayuri Patel[1], Christin Ungewiss[1], David Peng[1], Scott Antonia[6], Melanie Mediavilla-Varela[6], Gordon Robertson[7], Milind Suraokar[1,8], James W. Welsh[9], Baruch Erez[1], Ignacio I. Wistuba[1,8], Lieping Chen[10], Di Peng[11], Shanshan Wang[11], Stephen E. Ullrich[2], John V. Heymach[1], Jonathan M. Kurie[1] & F. Xiao-Feng Qin[1,2,11]

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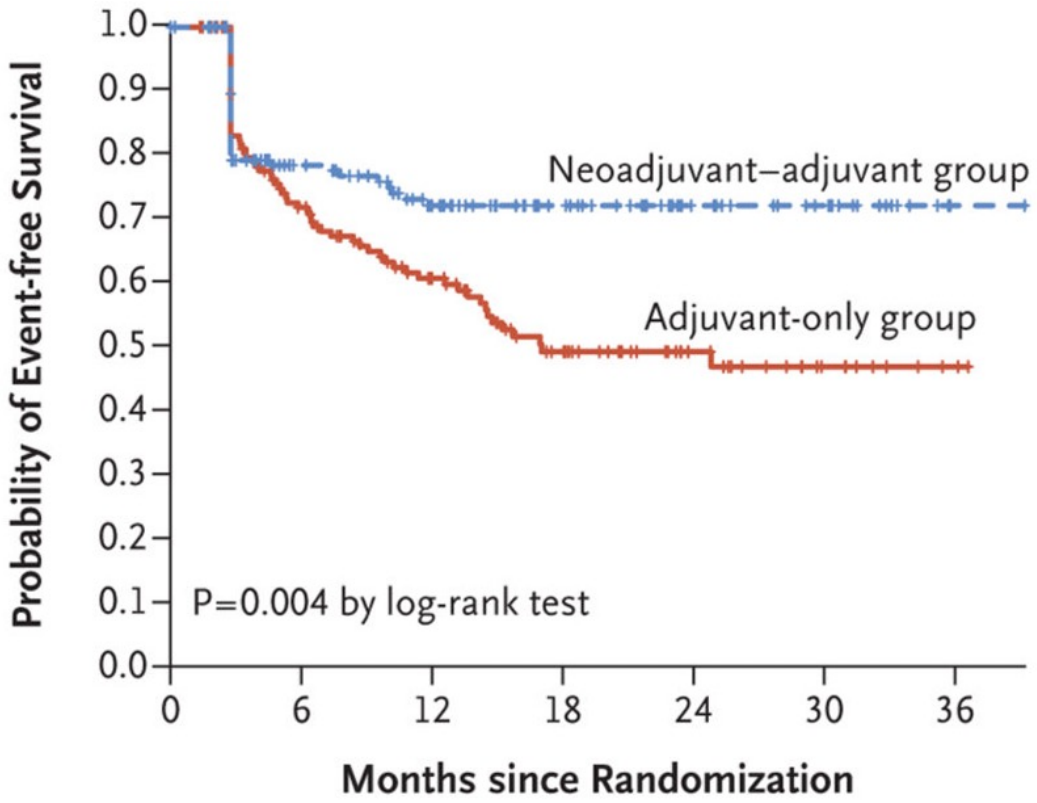
We don’t have randomized data comparing neoadjuvant chemoIO +/- adjuvant IO in NSCLC. What do we know from other diseases?

SWOG S1801 (Melanoma)

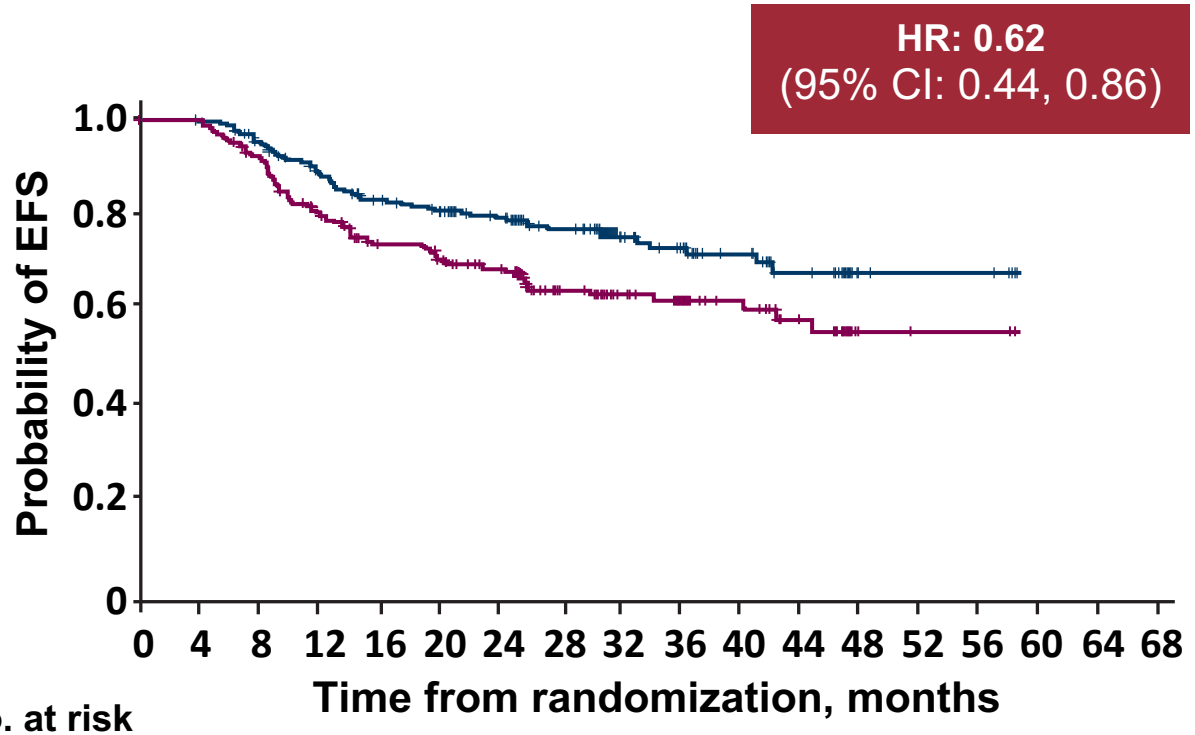


Liu J, et al. *Cancer Discov*. 2016;6(12):1382-1399; Cascone et al, unpublished; Patel SP, et al. *N Engl J Med*. 2023;388(9):813-823

What can we learn about the value of adjuvant IO after chemo-IO from patients treated in our RCTs?

In AEGEAN, patients who received adjuvant treatment had more DFS benefit than those who did not

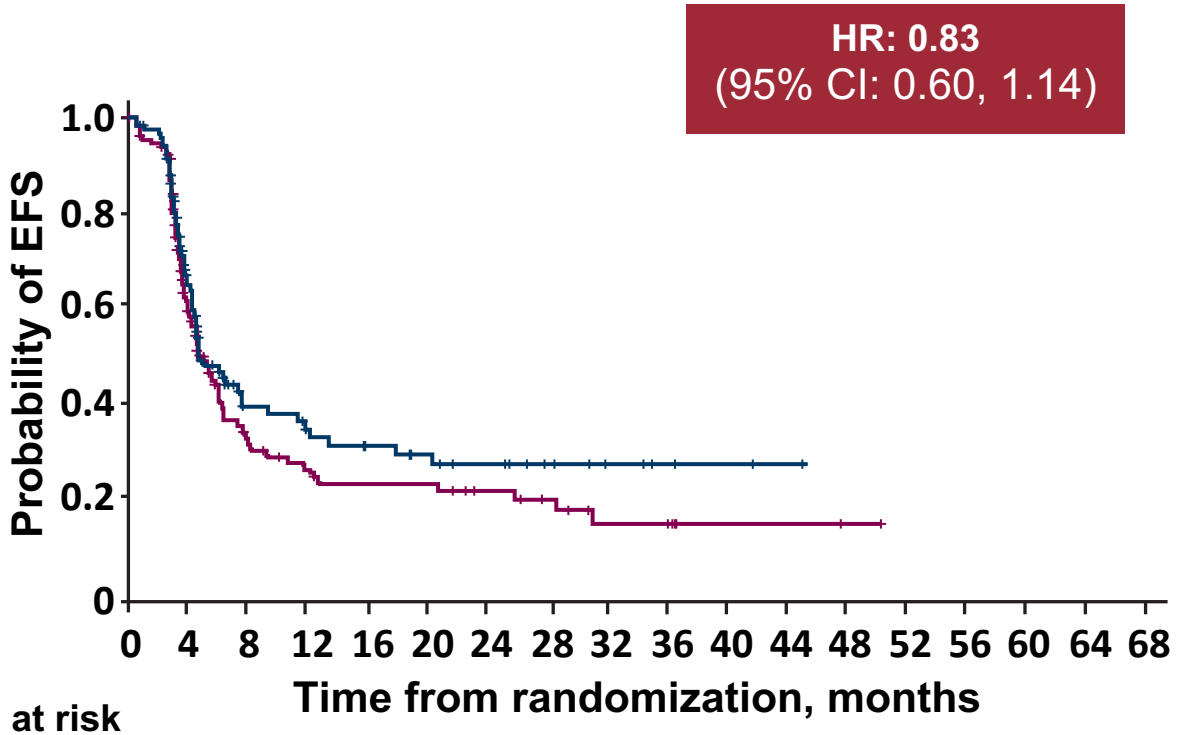
Received Adjuvant Treatment



No. at risk

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

Did Not Receive Adjuvant Treatment

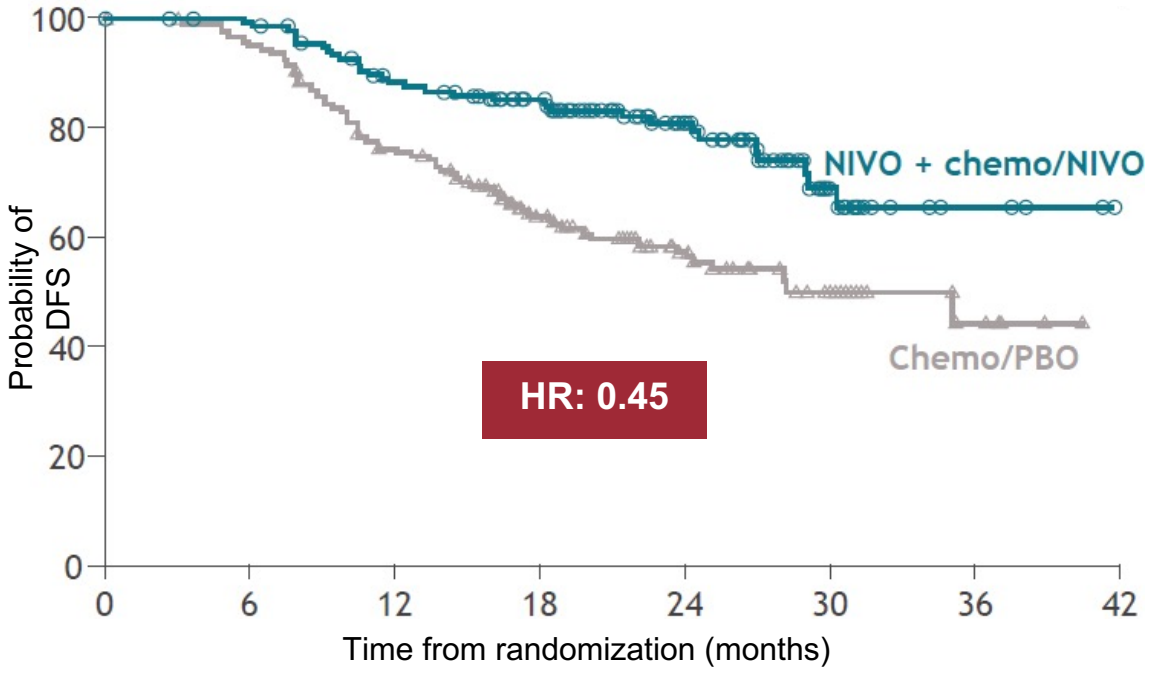


No. at risk

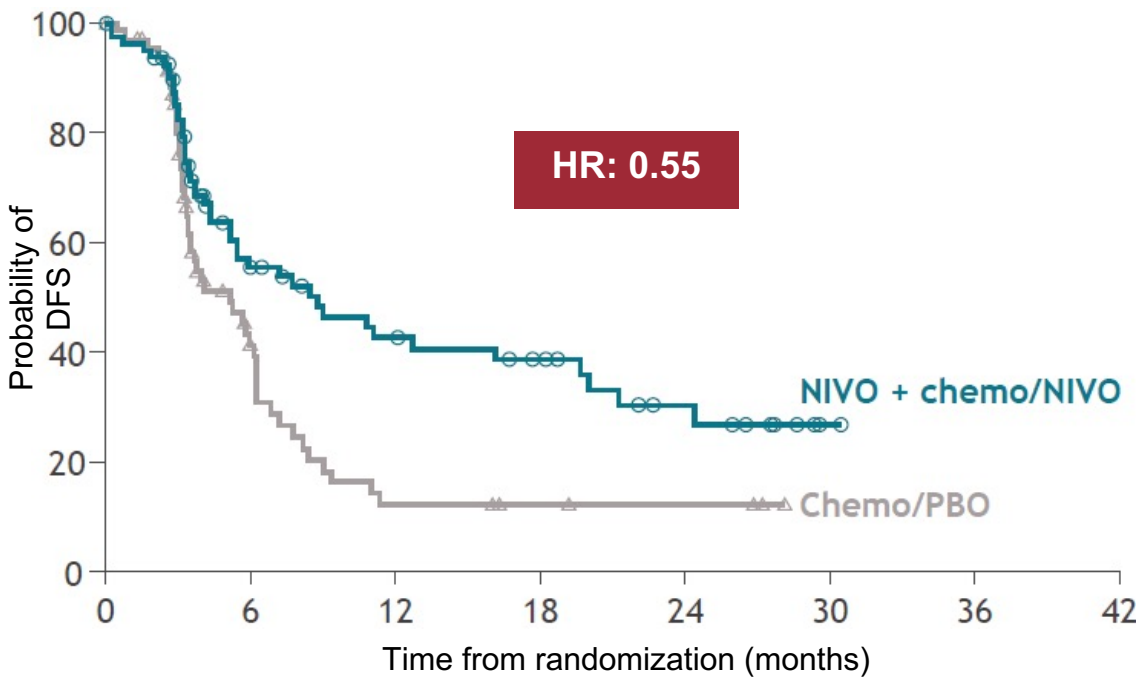
D + CTx	124	62	26	21	18	16	13	8	5	3	2	1	0
PBO + CTx	137	26	20	17	17	17	13	10	6	6	3	3	1	0

In AEGEAN, patients who received adjuvant treatment had more DFS benefit than those who did not

CheckMate-77T
(Received adjuvant treatment)



CheckMate-77T
(Did not received adjuvant treatment)



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Cascone T, et al. *N Engl J Med*. 2024;390(19):1756-1769

2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

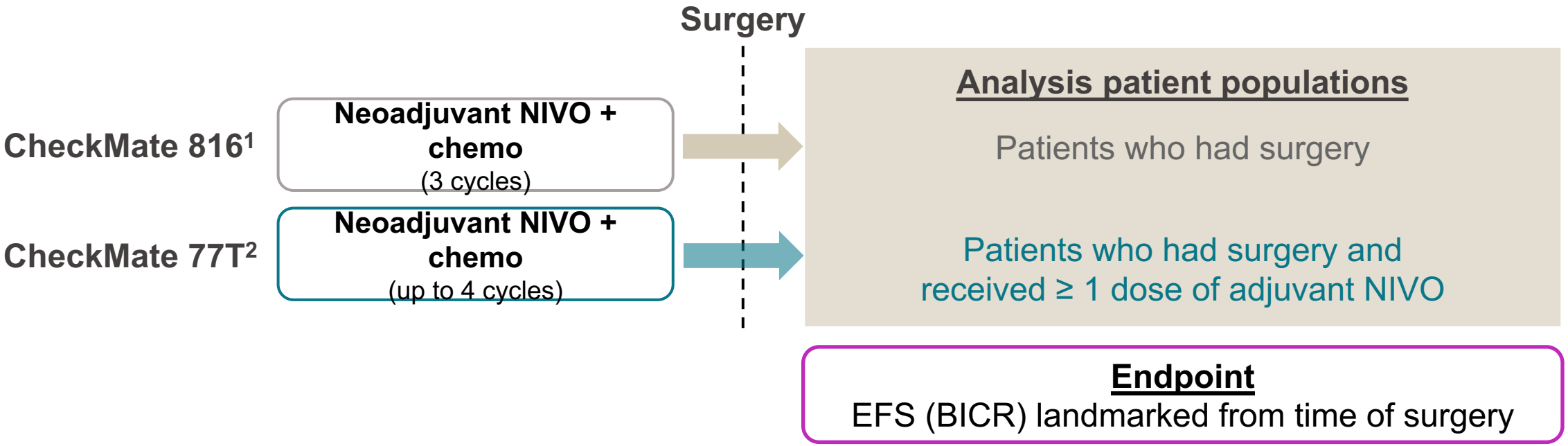
Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816

Patrick M. Forde,[1] Solange Peters,[2] Jessica Donington,[3] Stephanie Meadows-Shropshire,[4] Phuong Tran,[4] Stefano Lucherini,[5] Cinthya Coronado Erdmann,[6] Hong Sun,[6] Tina Cascone[7]

[1]The Bloomberg–Kimmel Institute for Cancer Immunotherapy, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medicine, Baltimore, MD, USA; [2]Lausanne University Hospital, Lausanne, Switzerland; [3]The University of Chicago, Chicago, IL, USA; [4]Bristol Myers Squibb, Princeton, NJ, USA; [5]Bristol Myers Squibb, Uxbridge, UK; [6]Bristol Myers Squibb, Boudry, Switzerland; [7]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Presentation number 3589

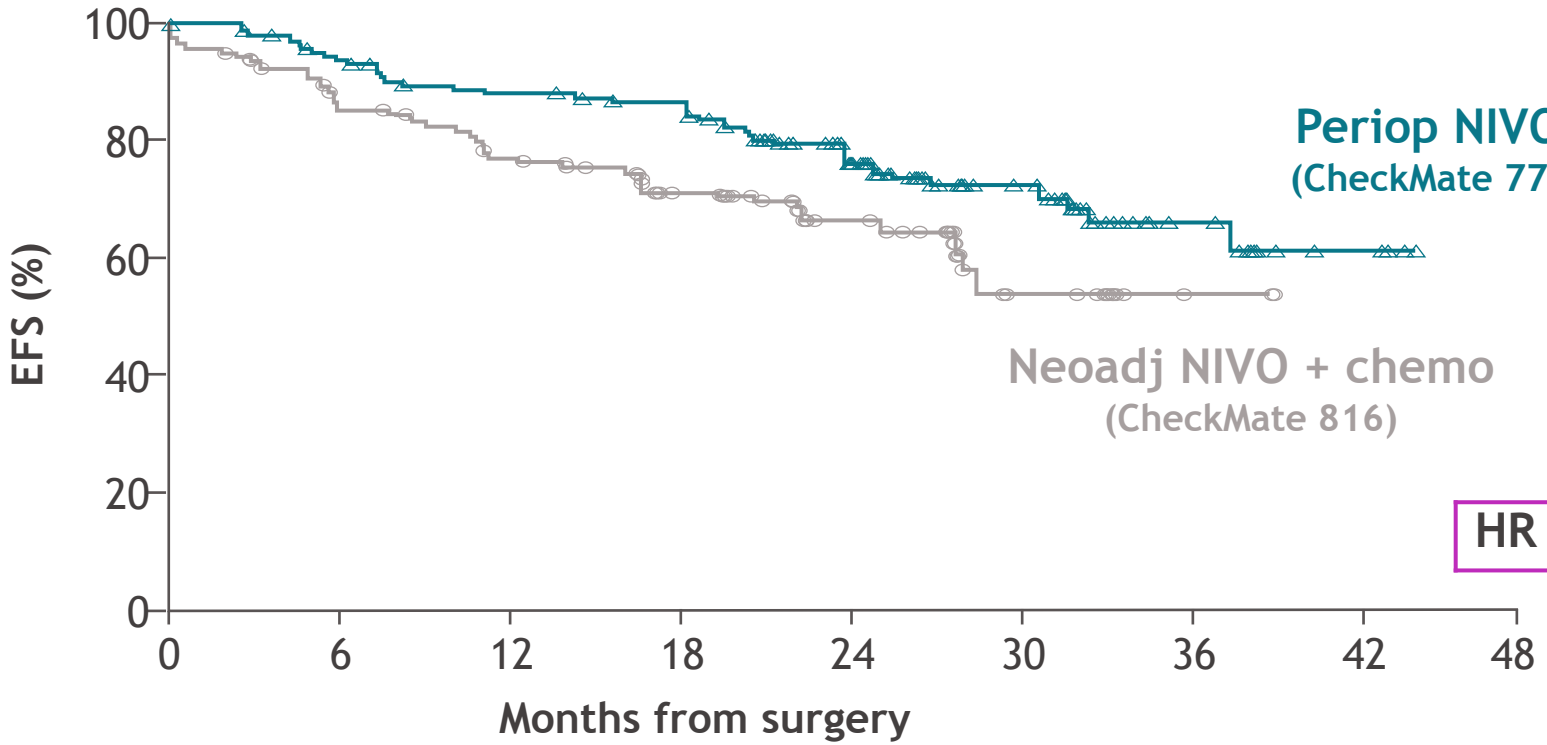
Methods: perioperative NIVO vs neoadjuvant NIVO + chemo



- In lieu of a head-to-head trial, exploratory propensity score weighting analyses (ATT[a] and ATE[b]) were performed to allow simplified reproduction of a randomized trial by adjusting for clinically relevant baseline demographics and disease characteristics[c] between study populations and reducing the confounding effects of these factors
- Subgroup analyses were not weighted due to smaller sample sizes
- Median duration of follow-up[d]: 29.5 months (CheckMate 816) and 33.3 months (CheckMate 77T)

[a]Average treatment effect for the treated (ATT): a weight of 1 was applied to patients in the perioperative NIVO arm of CheckMate 77T; varying weights were applied to patients in the CheckMate 816 NIVO + chemo arm to make them comparable to those in the perioperative NIVO arm in CheckMate 77T based on propensity scores. [b]Average treatment effect (ATE): varying weights were applied to all patients in the populations of interest from CheckMate 77T and CheckMate 816 to make them comparable to one another based on propensity scores. [c]Sex, race, clinical stage, tumor histology, PD-L1 expression, age, ECOG PS, and smoking status. [d]Database locks: CheckMate 816, October 20, 2021; CheckMate 77T, April 26, 2024. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973–1985. 2. Cascone T, et al. *N Engl J Med* 2024;390:1756–1769.

Landmark EFS (BICR) from definitive surgery



No. at risk									
Periop NIVO	139.4	128.0	118.1	112.9	79.7	42.5	13.0	3.1	0
Neoadj N+C	147.5	121.0	106.2	84.2	39.1	12.1	2.2	0	0

	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 et al WCLC 2024

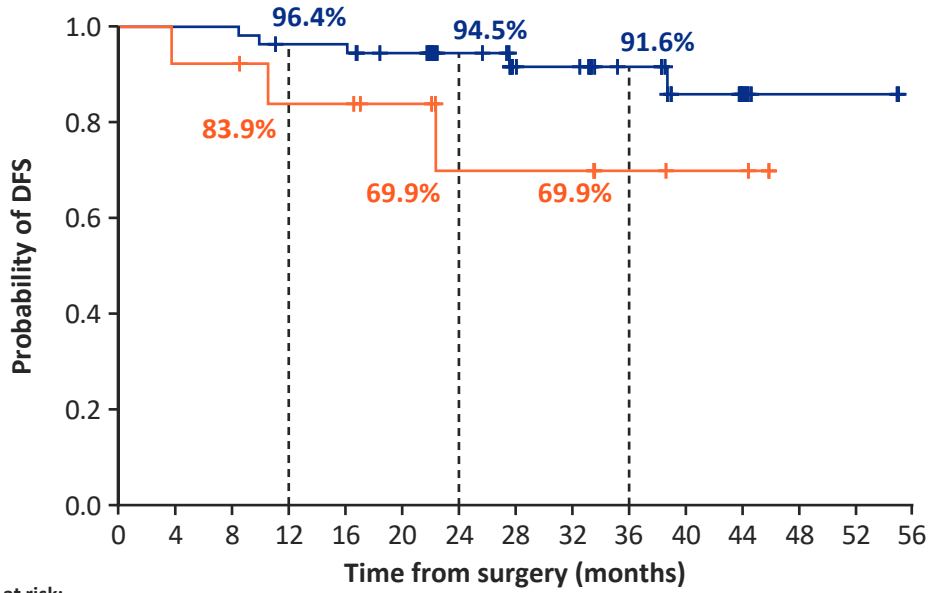
Ok, maybe adjuvant IO helps some people, but we can probably spare people who had a complete path CR since they don’t have any tumor left, right?

DFS by pCR status (exploratory analysis; modified resected subpopulation)

- Larger magnitude of DFS benefit with durvalumab was observed in patients with pCR

Patients with pCR

	D arm	PBO arm
No. events / no. patients (%)	5/55 (9.1)	3/13 (23.1)
mDFS, months (95% CI)	NR (NR–NR)	NR (10.5–NR)
Unstratified HR (95% CI)	0.31 (0.07–1.51)	

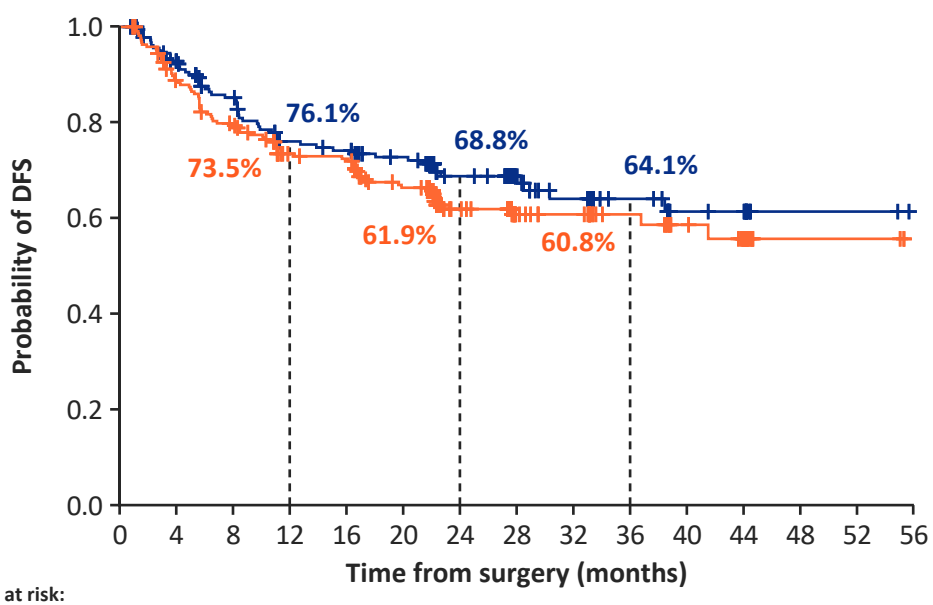


No. at risk:

D arm	55	55	55	52	52	48	36	27	26	19	12	8	2	2	0
PBO arm	13	12	12	10	10	8	5	5	5	3	2	2	0	0	0

Patients without pCR

	D arm	PBO arm
No. events / no. patients (%)	55/187 (29.4)	78/218 (35.8)
mDFS, months (95% CI)	NR (NR–NR)	NR (41.5–NR)
Unstratified HR (95% CI)	0.82 (0.58–1.15)	



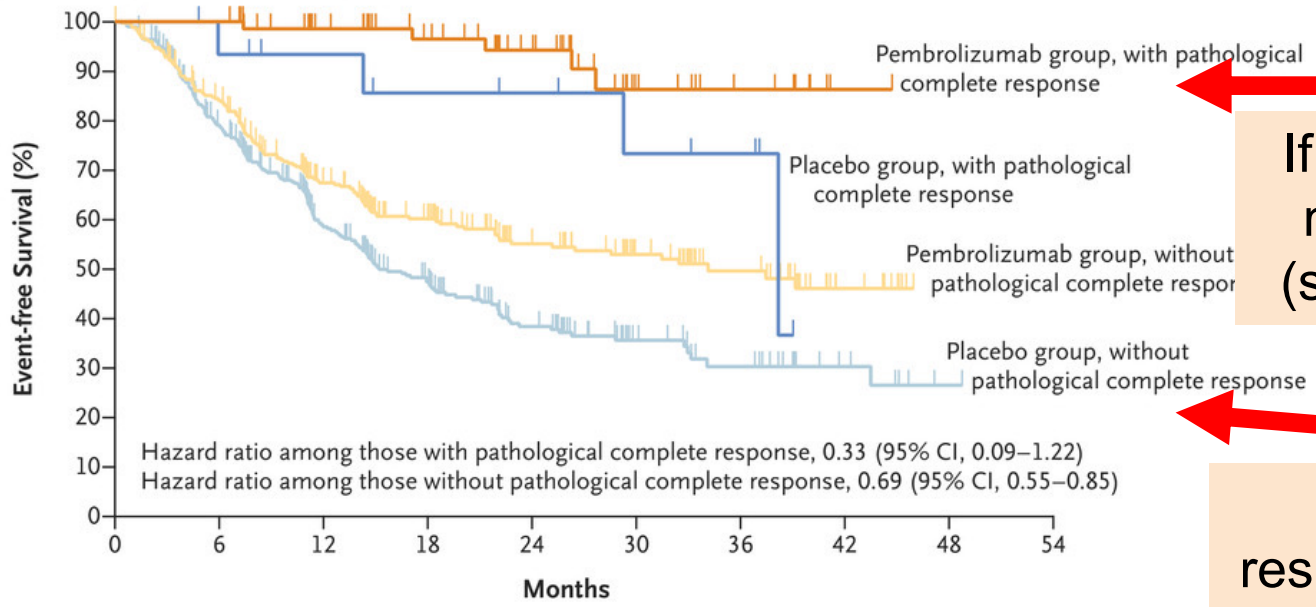
No. at risk:

D arm	187	164	142	119	115	104	77	48	37	26	15	14	2	2	0
PBO arm	218	188	167	142	139	114	69	46	41	28	21	13	2	2	0

DCO = May 10, 2024. The small number of patients and events in the pCR subgroup results in greater uncertainty in the point estimate and confidence intervals.

KN 671: Exploratory analysis of EFS in path CR and non-path CR groups

B Event-free Survival According to Pathological Complete Response



No. at Risk										
With pathological complete response										
Pembrolizumab group	72	72	59	46	33	15	8	1	0	0
Placebo group	16	14	12	10	9	5	4	0	0	0
Without pathological complete response										
Pembrolizumab group	325	258	177	126	84	57	34	10	0	0
Placebo group	384	280	171	114	65	33	20	9	1	0

pCR group: HR 0.33

If the pCR group is benefitting so much, shouldn't they continue? (still >20% chance of recurrence)

Non-pCR group: HR 0.69

If the no pCR group hasn't responded as well, should they get a different type of, or intensified, therapy?

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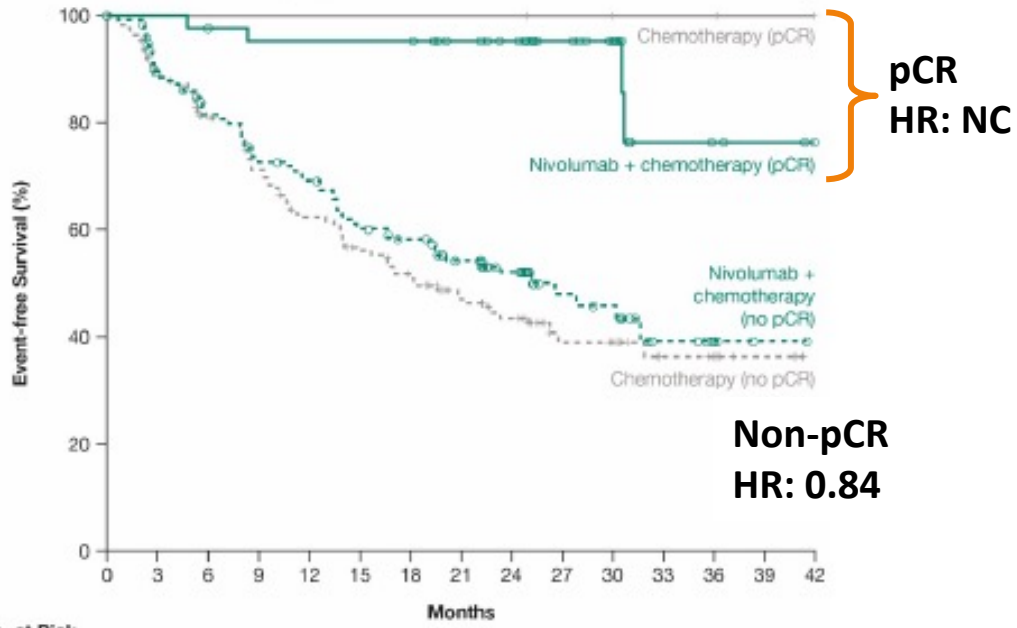
Wakelee et al, NEJM 2023

CM 816 and CM 77T: EFS Analysis (pCR vs non-pCR)

CheckMate 816 (Neoadjuvant Treatment)

	Nivolumab + chemotherapy		Chemotherapy	
	pCR (n=43)	No pCR (n=136)	pCR (n=4)	No pCR (n=175)
Median EFS, mo (95% CI)	NR (30.6–NR)	26.6 (16.6–NR)	NR (NR–NR)	18.4 (13.9–26.2)
HR (95% CI)*	0.13 (0.05–0.37)		Not computed†	



pCR
HR: NC

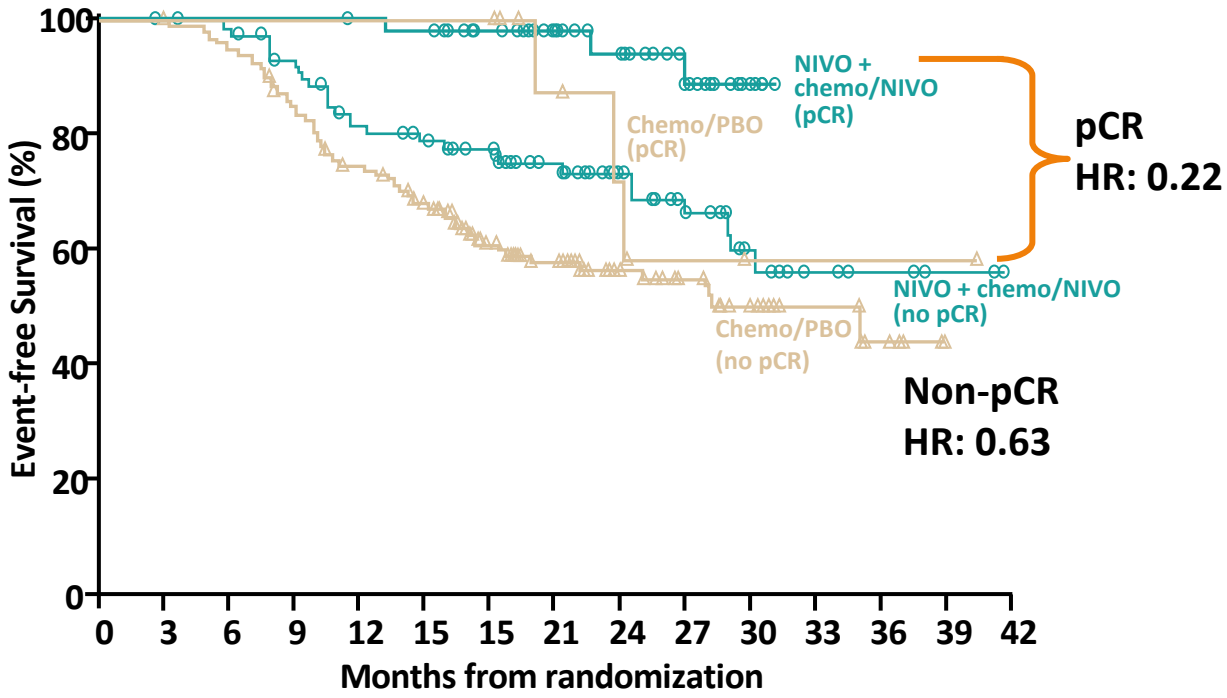
Non-pCR
HR: 0.84

No. at Risk															
Nivolumab + chemotherapy (pCR)	43	43	41	40	40	40	40	35	32	19	14	6	3	2	0
Chemotherapy (pCR)	4	4	4	4	4	4	4	4	4	3	2	2	2	1	0
Nivolumab + chemotherapy (no pCR)	136	108	95	84	78	67	62	52	42	22	20	7	3	1	0
Chemotherapy (no pCR)	175	140	122	105	90	79	71	57	48	23	22	11	9	3	0

NC=not computed.

Left figure reprinted with permission from Girard N, et al. Nivolumab + platinum-doublet chemotherapy vs chemotherapy as neoadjuvant treatment for resectable (IB–IIIA) non-small cell lung cancer: event-free survival results from the phase 3 CheckMate 816 trial [oral]. Presented at AACR 2022; CT012.

CheckMate 77T (Perioperative Treatment)



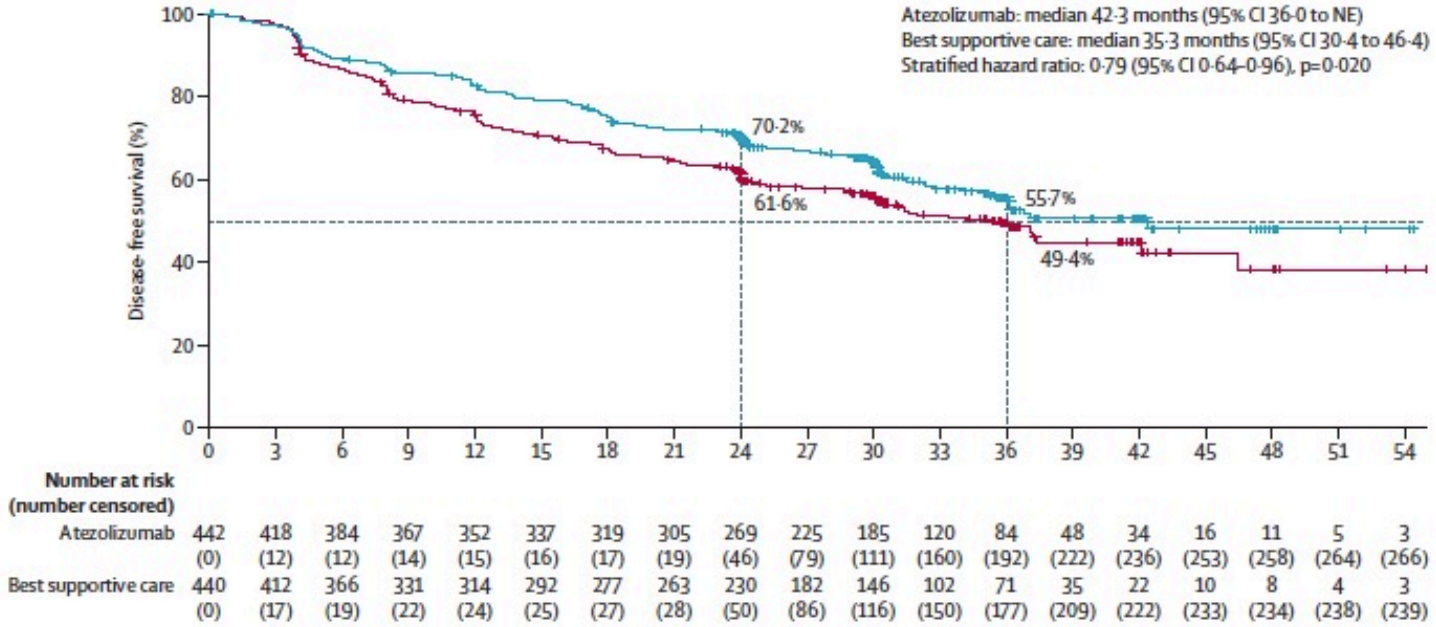
pCR
HR: 0.22

Non-pCR
HR: 0.63

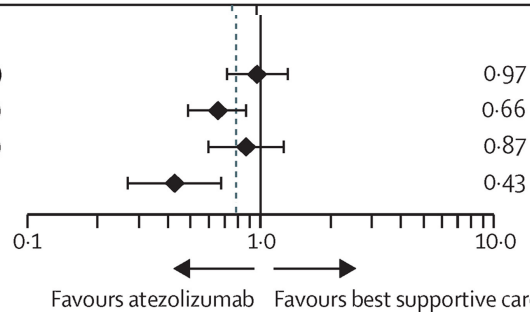
Right figure reprinted with permission from Cascone T, et al. CheckMate 77T: Phase 3 study comparing neoadjuvant nivolumab plus chemotherapy with neoadjuvant placebo plus chemotherapy followed by surgery and adjuvant nivolumab or placebo for previously untreated, resectable stage II–IIIB NSCLC. Presented at ESMO 2023; LBA1.

Can we at least spare the patients who are PD-L1 negative, since they don’t get any benefit from adjuvant IO?

Impower-010 randomized study of adjuvant atezolizumab vs BSC: DFS (all stage II-IIIA)



	Atezolizumab group		Best supportive care group		Hazard ratio (95% CI)
	Events/patients, n/N	Median DFS (95% CI), months	Events/patients, n/N	Median DFS (95% CI), months	
PD-L1 status by SP263					
TC <1%	181/383	36·1 (30·2–NE)	202/383	37·0 (28·6–NE)	0·97 (0·72–1·31)
TC ≥1%	248/476	NE (36·1–NE)	228/476	35·3 (29·0–NE)	0·66 (0·49–0·87)
TC 1–49%	133/247	32·8 (29·4–NE)	114/247	31·4 (24·0–NE)	0·87 (0·60–1·26)
TC ≥50%	115/229	NE (42·3–NE)	114/229	35·7 (29·7–NE)	0·43 (0·27–0·68)



Felip et al, Lancet 2021

All stage II-IIIA:
HR 0.79 (p=.0039)
8.6% improvement in 2Y DFS

TC<1%:
no benefit
(HR 0.97)

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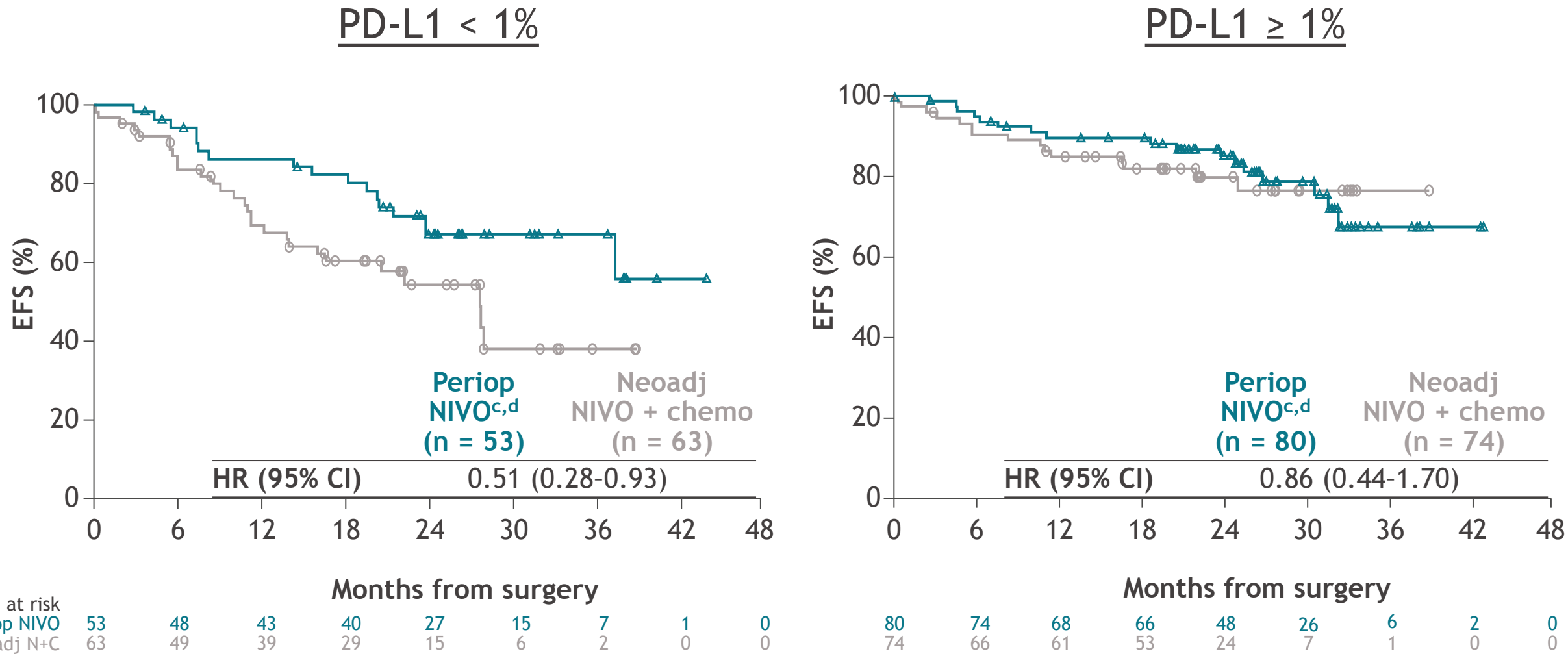
CM77T vs CM816: Landmark EFS (analysis population) by tumor PD-L1 expression[a,b]

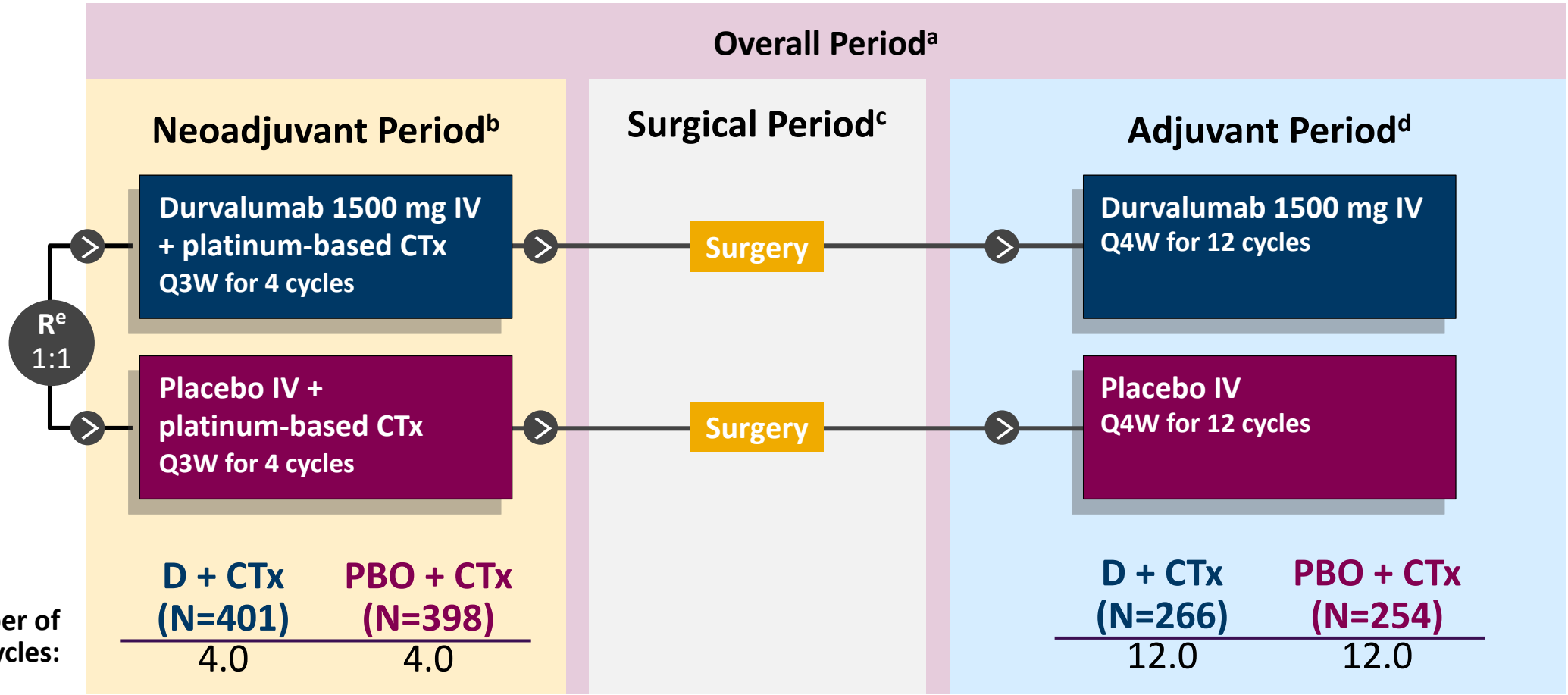


Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. [a]Patients with non-evaluable PD-L1 expression were excluded. [b]Unweighted analyses. [c]Includes only patients who received ≥ 1 dose of adjuvant NIVO. [d]Completed adjuvant treatment: < 1%, 33 patients (62%) and ≥ 1%, 51 patients (64%). Median number of doses (range): < 1%, 13 (1–13) and ≥ 1%, 13 (1–13).

Forde et al. WCLC 2024

But what about the toxicity? And won't a year of adjuvant IO impact QOL?

AEGEAN: Exposure and Safety Periods



[a] AEs occurring between the first dose of study treatment and the earliest or maximum of (last dose of study treatment or surgery) + 90 days, tne date of the DCO, or start of subsequent anticancer therapy.
[b] AEs occurring between the date of first dose of study treatment and the day before surgery, or for patients without surgery up to the 90 days post last dose of neoadjuvant treatment or start of subsequent anticancer therapy.
[C] AEs occurring between the date of surgery (including day of surgery) and the earliest of date of surgery + 90 days, or first dose of subsequent anticancer therapy.
[d] AEs occurring after the first dose of study treatment post surgery and the earliest of 90 days following the last dose adjuvant or first dose of subsequent anticancer therapy.
[e] N=802 randomized.

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Summary of AEs by Category and Treatment Period
DCO4

Event	Overall		Neoadjuvant Period		Surgical Period		Adjuvant Period	
	D + CTx (N=401)	PBO + CTx (N=398)	D + CTx (N=401)	PBO + CTx (N=398)	D + CTx (N=325)	PBO + CTx (N=326)	D + CTx (N=266)	PBO + CTx (N=254)
Any-grade AEs, n (%)	**387 (96.5)**	**379 (95.2)**	**365 (91.0)**	**357 (89.7)**	**239 (73.5)**	**227 (69.6)**	**224 (84.2)**	**195 (76.8)**
Max. grade 3-4	175 (43.6)	172 (43.2)	131 (32.7)	145 (36.4)	56 (17.2)	43 (13.2)	41 (15.4)	27 (10.6)
Serious adverse events (SAEs)	157 (39.2)	126 (31.7)	83 (20.7)	66 (16.6)	61 (18.8)	51 (15.6)	41 (15.4)	26 (10.2)
Leading to discontinuation of any study treatment	78 (19.5)	39 (9.8)	54 (13.5)	30 (7.5)	2 (0.6)	2 (0.6)	26 (9.8)	10 (3.9)
Outcome of death[a]	23 (5.7)	15 (3.8)	8 (2.0)	4 (1.0)	13 (4.0)	9 (2.8)	4 (1.5)	2 (0.8)
Any-grade imAEs	102 (25.4)	41 (10.3)	33 (8.2)	19 (4.8)	19 (5.8)	2 (0.6)	61 (22.9)	21 (8.3)
Grade 3-4	18 (4.5)	10 (2.5)	6 (1.5)	5 (1.3)	6 (1.8)	1 (0.3)	6 (2.3)	4 (1.6)

[a] Two events; ILD and aortic aneurysm rupture (1 patient each) were captured in both the surgical and adjuvant periods.
ILD=interstitial lung disease; max=maximum.

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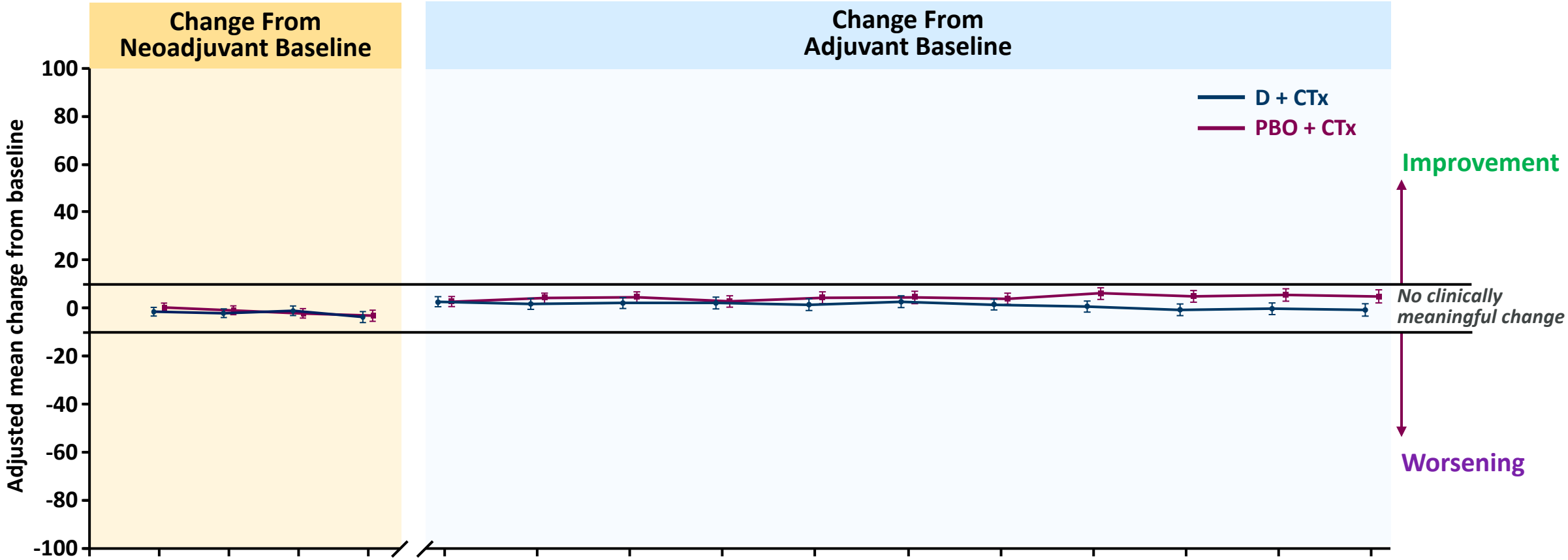
Minimal Impact on Patient-Reported **Global Health Status/QoL**

EORTC QLQ-C30, MMRM, DCO4



Patients, n															
D + CTx	304	273	252	184	174	167	163	155	152	148	139	139	137	135	128
PBO + CTx	293	276	256	199	160	161	153	152	143	139	128	131	128	117	117

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Who can you trust?

As they say in Texas, you can always trust a man (or a medical oncologist) in a cowboy hat!

Cascone ✓
Heymach ✓

Garassino ✗

Gentzler ✗

Gentzler and colleagues ✗

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Bottom line

- Multiple large RCTs support perioperative chemo-IO (~2000 patients); one small RCT supports neoadjuvant chemo-IO
- In RCTs, DFS benefit was larger in patients who received adjuvant than those who did not and detailed comparison of CM77T vs CM816 supports benefit
- Outcomes favored perioperative IO arm for both path CR and non-path CR patients
- Adjuvant IO adds little toxicity and no detriment to QOL
- We should be greedy for even incremental gains in cures
- Trust issues