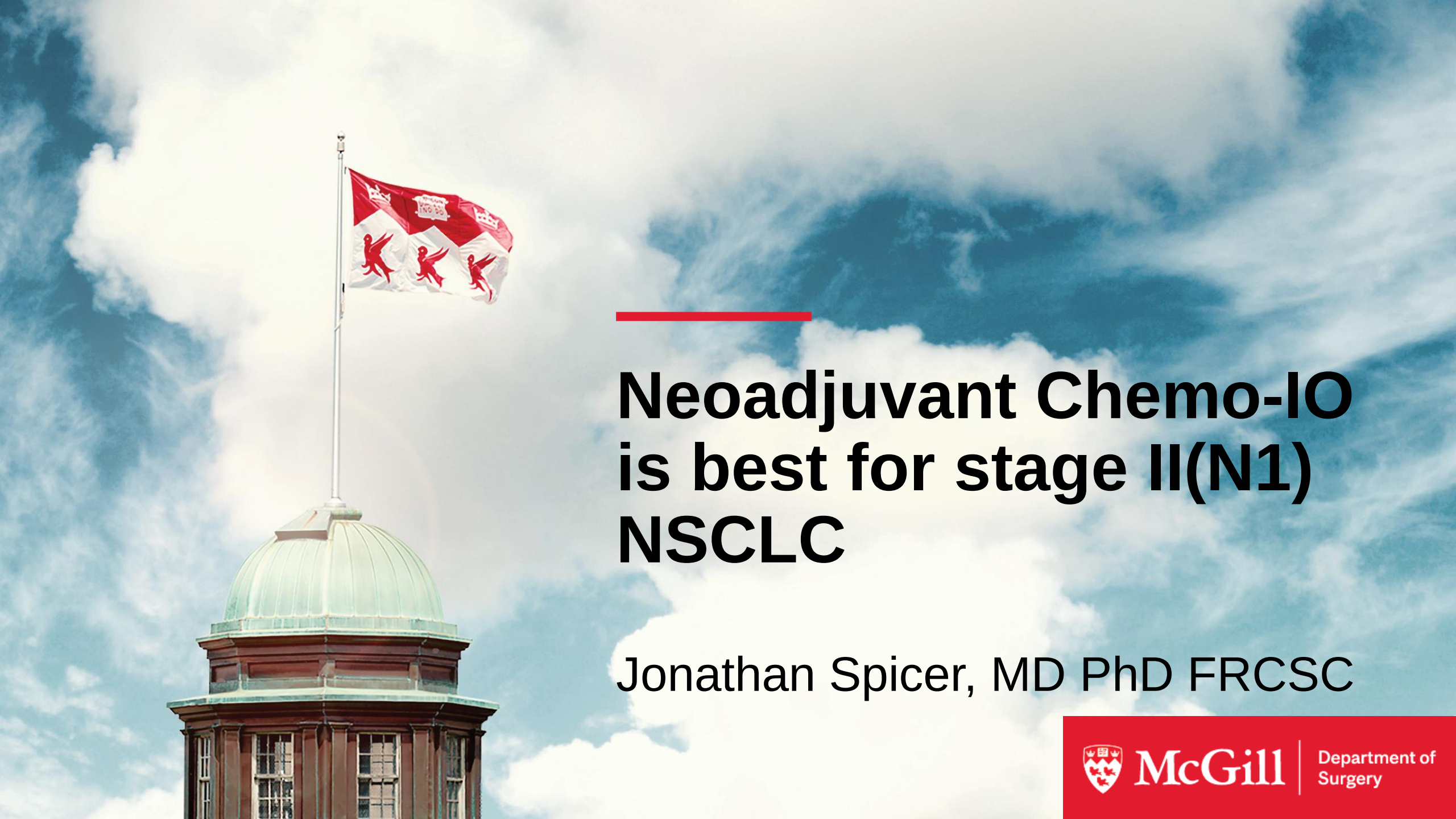


Neoadjuvant Chemo-IO is best for stage II(N1) NSCLC

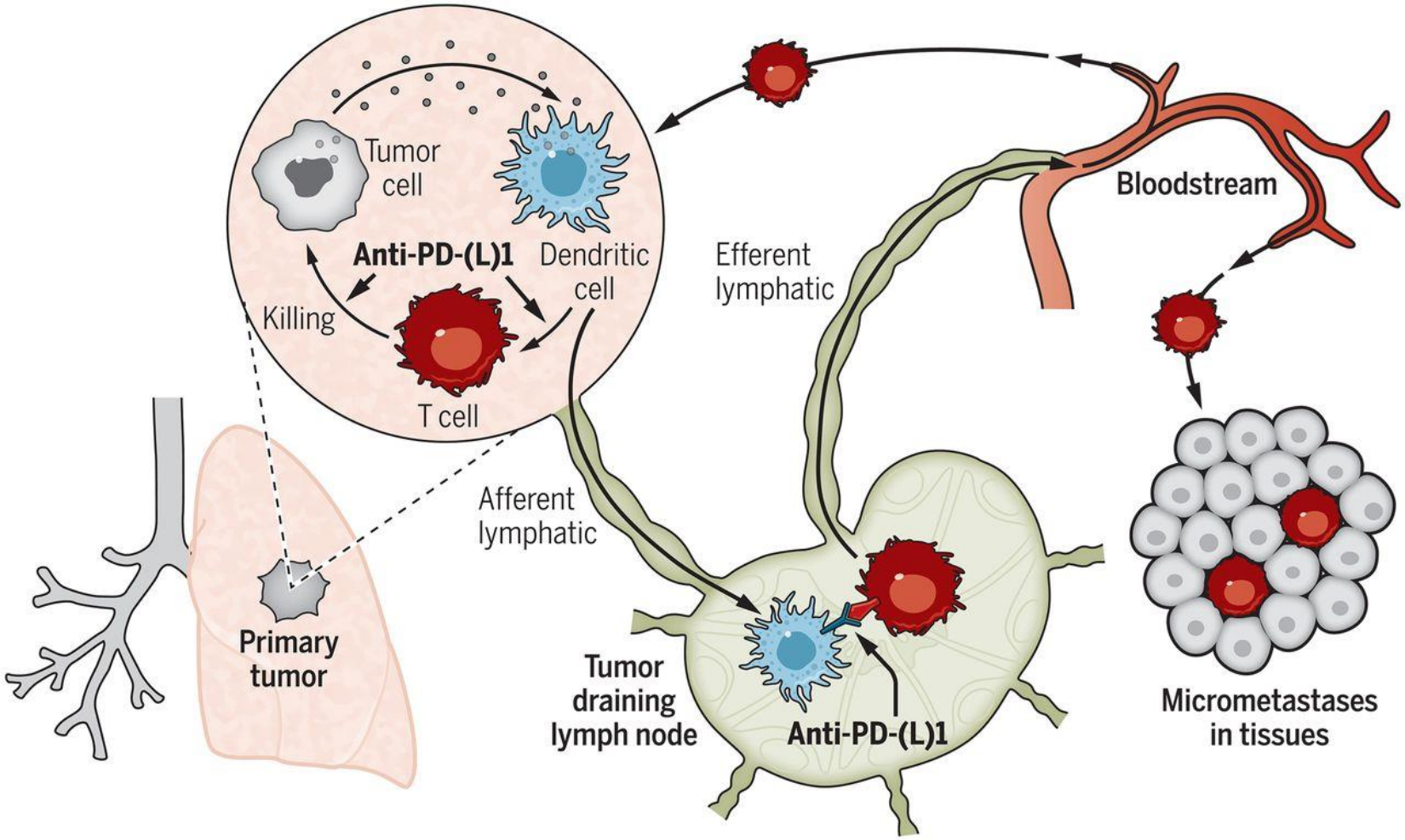
Jonathan Spicer, MD PhD FRCSC

McGill | Department of Surgery

Conflicts of interest

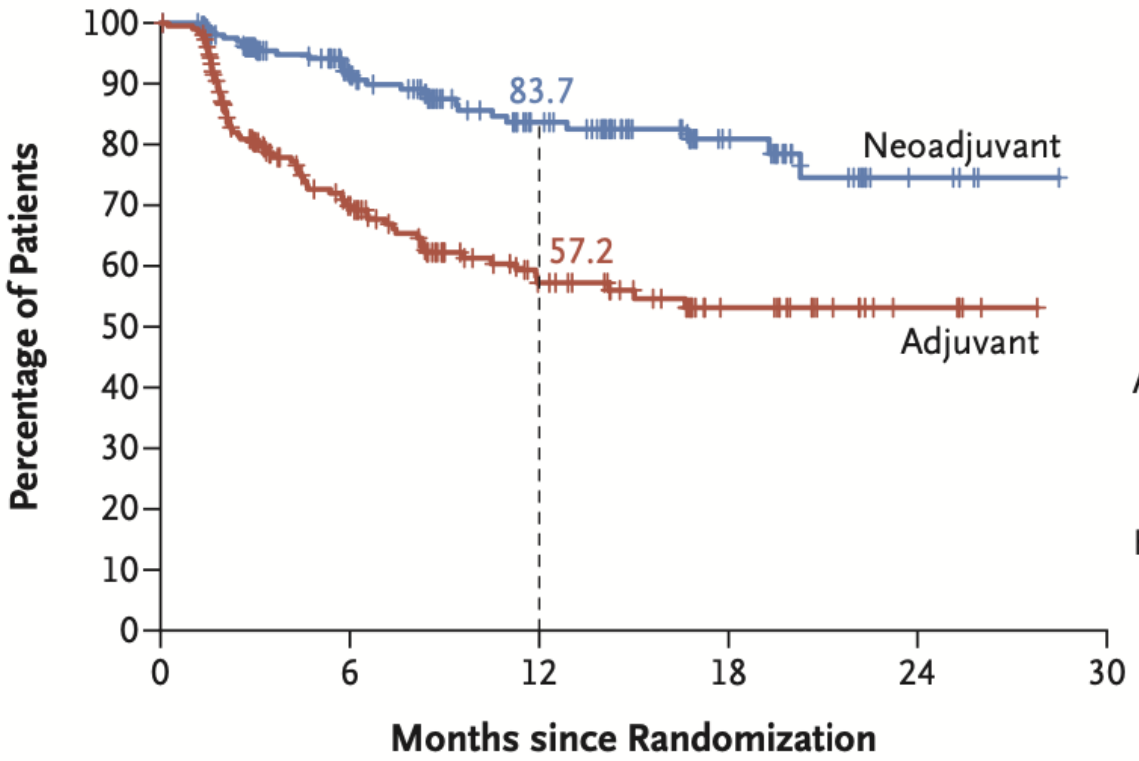
Commercial Interest	Relationship(s)
AstraZeneca, Merck, Roche, BMS, Novartis, Chemocentryx, Amgen, Protalix Biotherapeutics, Xenetic Biosciences, Regeneron, Eisai, Peerview, OncLive, Medscape, Pfizer, Foresight Diagnostics	Consulting, advisory role or honoraria
AstraZeneca, BMS, Merck, Roche, CLS Therapeutics, Protalix Biotherapeutics, Pfizer, Regeneron	Grant to institution
BMS, Novartis, Roche, Merck, AstraZeneca	Clinical trial leadership role

This is how immunotherapy works… and Dr. Sacher knows this!



Topalian et al, Science 2021

And he knows that this is why this trial was positive



	No. of Events/ Total No. of Patients
Neoadjuvant	28/212
Adjuvant	72/211

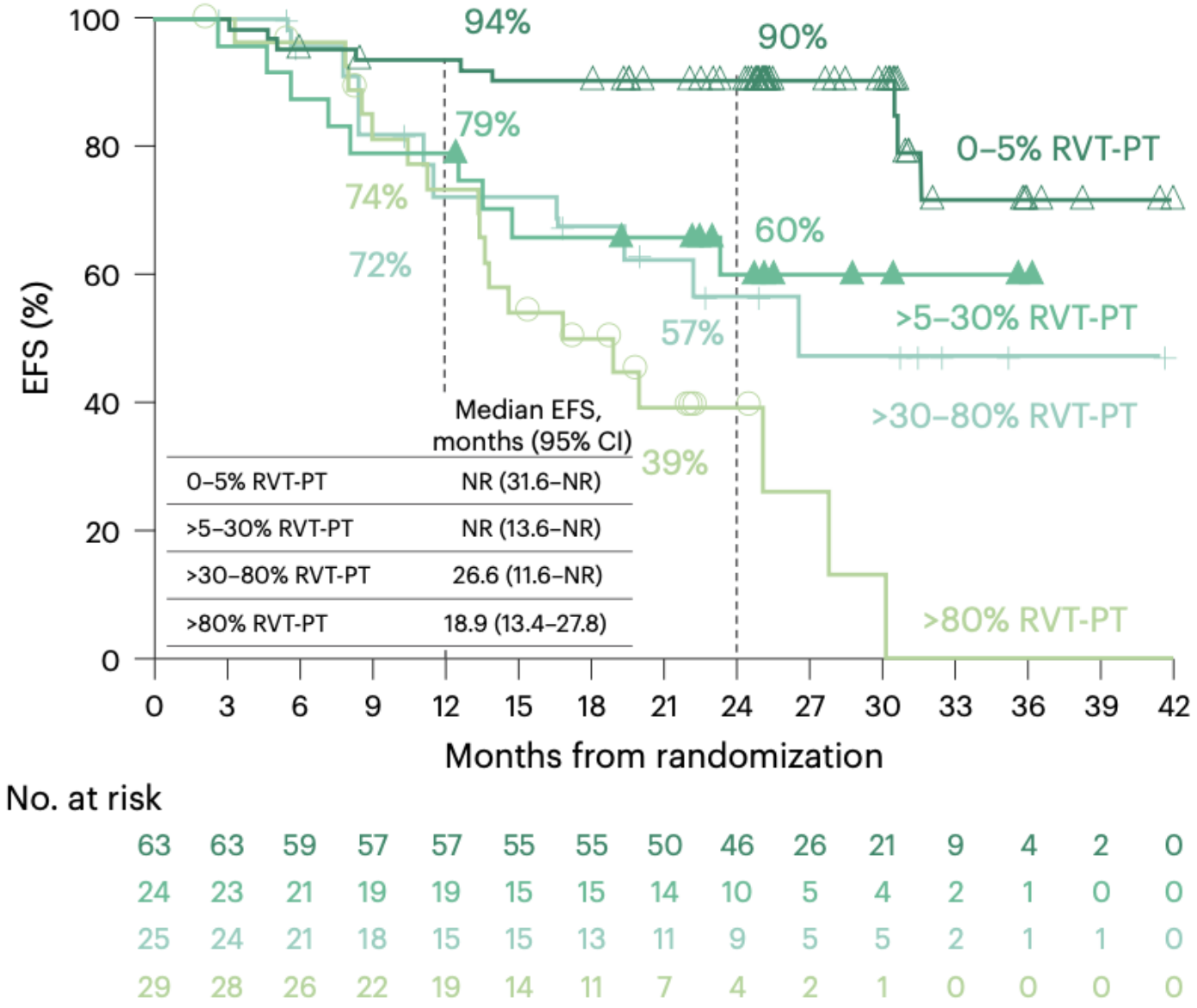
Adjusted difference in restricted mean survival time, 8.00 mo (99.9% CI, 4.94–11.05); P<0.001

Hazard ratio for progression, recurrence, or death, 0.32 (99.9% CI, 0.15–0.66)

No. at Risk (no. censored)					
Neoadjuvant	212 (0)	126 (71)	77 (111)	34 (152)	5 (179)
Adjuvant	211 (0)	100 (57)	53 (89)	23 (116)	6 (133)

Blank et al, NEJM 2024

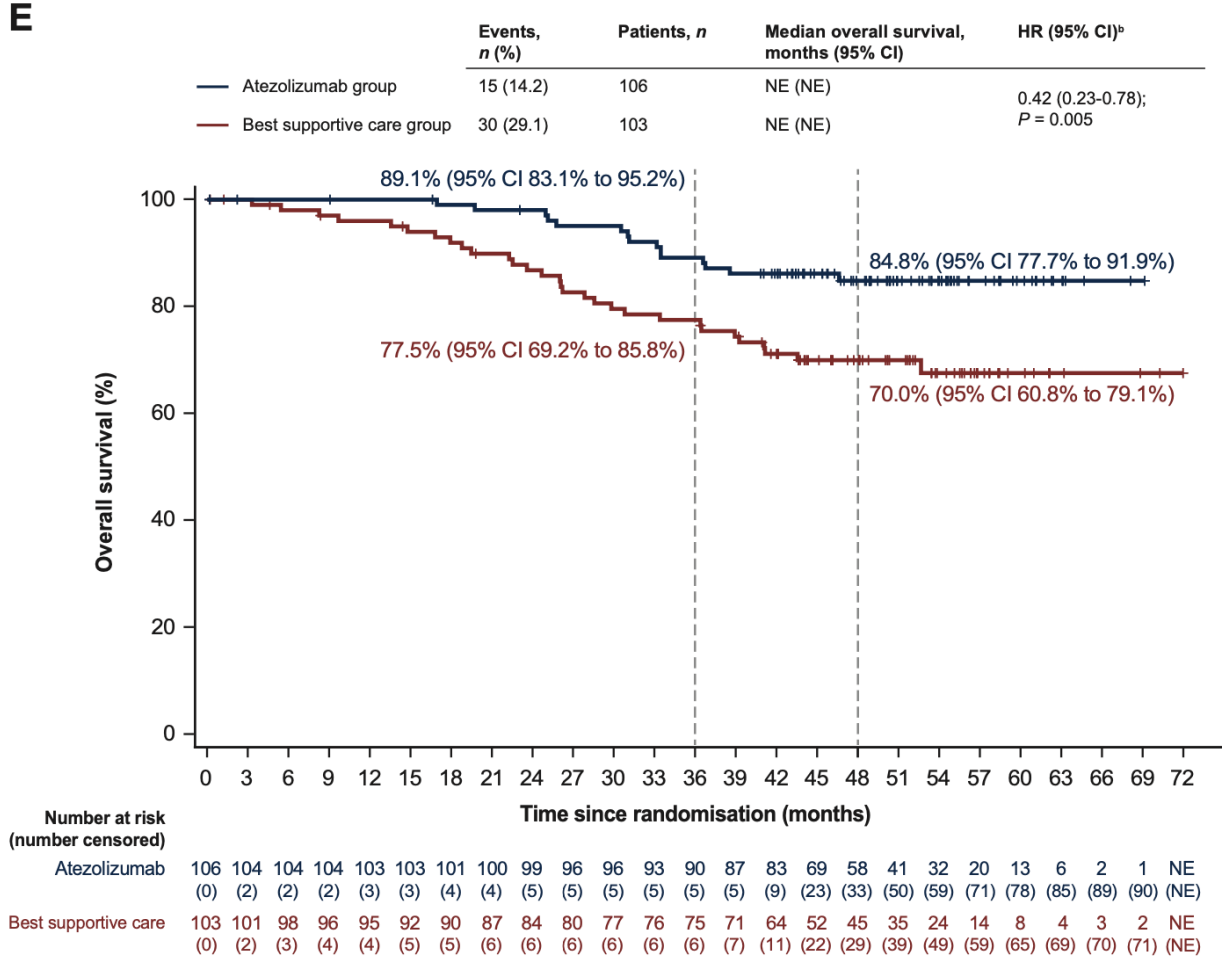
Dr. Sacher may pretend like this response data to the drugs he prescribes isn't important to the future care of his patients



Deutsch et al, Nat Med 2023

He will quote these data to support his claim (mostly because they are the only ones to quote)

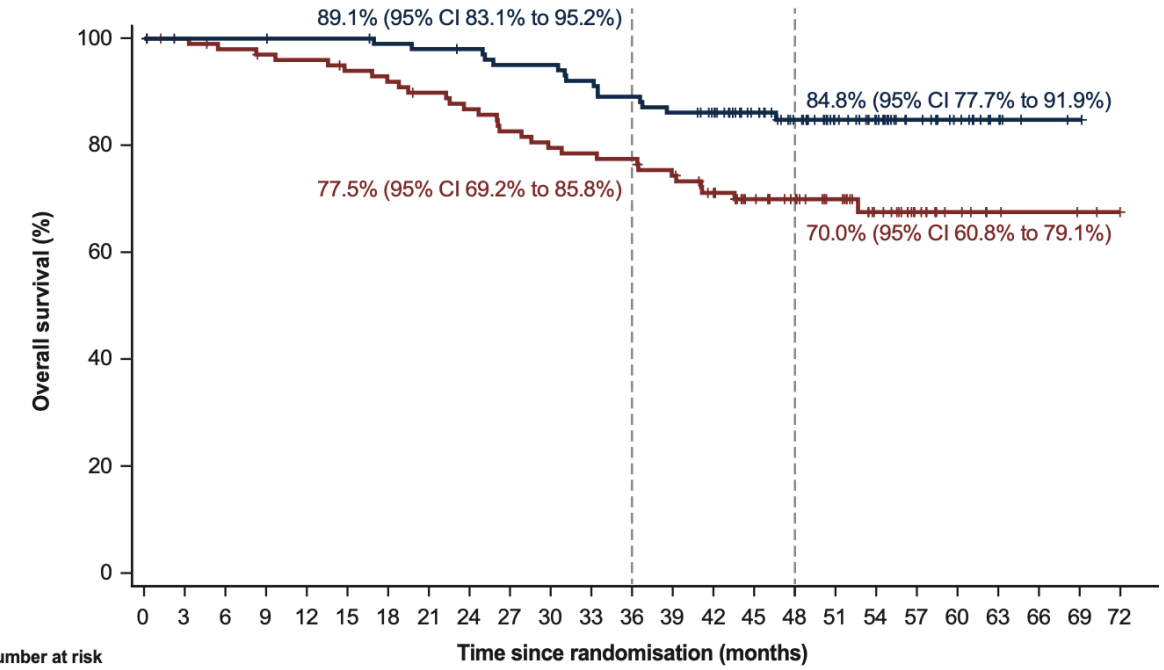
E



But he almost certainly won't show you these curves for the ITT population!

E

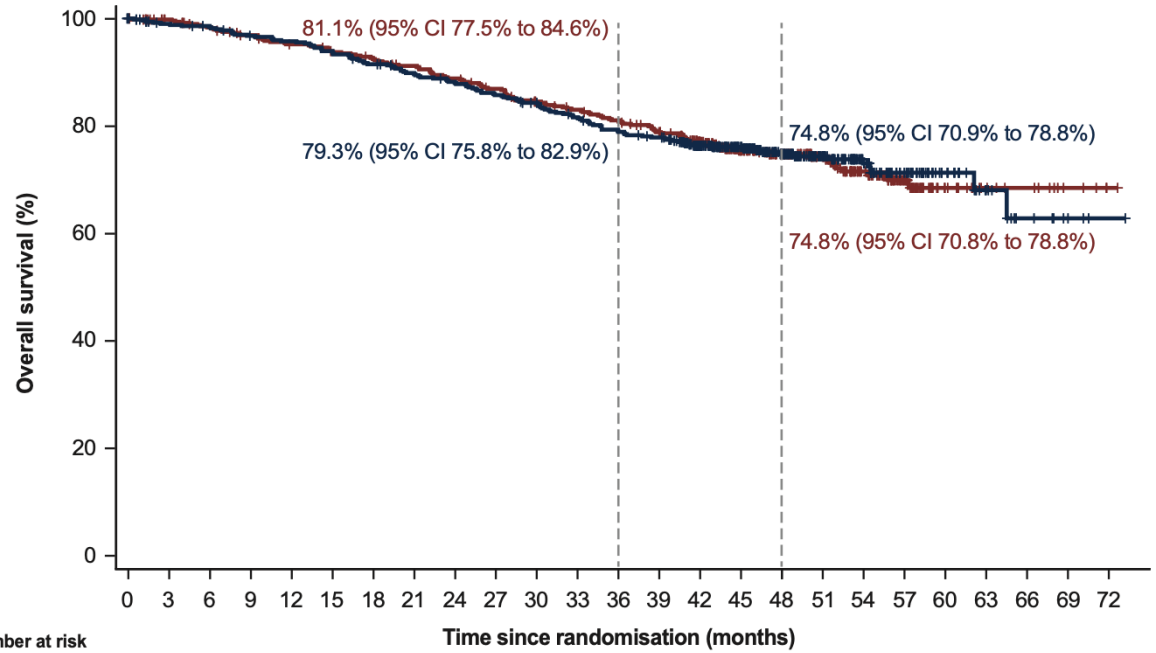
	Events, *n* (%)	Patients, *n*	Median overall survival, months (95% CI)	HR (95% CI)[b]
Atezolizumab group	15 (14.2)	106	NE (NE)	0.42 (0.23-0.78); *P* = 0.005
Best supportive care group	30 (29.1)	103	NE (NE)	



Number at risk (number censored)																								
Atezolizumab	106 (0)	104 (2)	104 (2)	104 (2)	103 (3)	103 (3)	101 (4)	100 (4)	99 (5)	96 (5)	96 (5)	93 (5)	90 (5)	87 (5)	83 (9)	69 (23)	58 (33)	41 (50)	32 (59)	20 (71)	13 (78)	6 (85)	2 (89)	1 (90)	NE (NE)
Best supportive care	103 (0)	101 (2)	98 (3)	96 (4)	95 (4)	92 (5)	90 (5)	87 (6)	84 (6)	80 (6)	77 (6)	76 (6)	75 (6)	71 (7)	64 (11)	52 (22)	45 (29)	35 (39)	24 (49)	14 (59)	8 (65)	4 (69)	3 (70)	2 (71)	NE (NE)

A

	Events, *n* (%)	Patients, *n*	Median overall survival, months (95% CI)	HR (95% CI)[a]
Atezolizumab group	127 (25.0)	507	NE (NE)	0.995 (0.78-1.28); *P* = 0.966
Best supportive care group	124 (24.9)	498	NE (NE)	



Number at risk (number censored)																								
Atezolizumab	507 (0)	492 (10)	488 (12)	478 (13)	472 (14)	463 (14)	450 (15)	439 (18)	430 (19)	419 (19)	408 (22)	393 (24)	381 (25)	372 (27)	328 (64)	262 (129)	203 (185)	144 (242)	96 (289)	61 (321)	30 (352)	17 (364)	8 (372)	4 (376)	1 (379)
Best supportive care	498 (0)	484 (13)	473 (17)	462 (21)	452 (23)	444 (25)	437 (26)	428 (28)	417 (28)	405 (31)	391 (34)	381 (37)	371 (38)	357 (42)	325 (66)	253 (132)	207 (176)	148 (234)	101 (276)	57 (318)	25 (349)	14 (360)	11 (363)	5 (369)	1 (373)

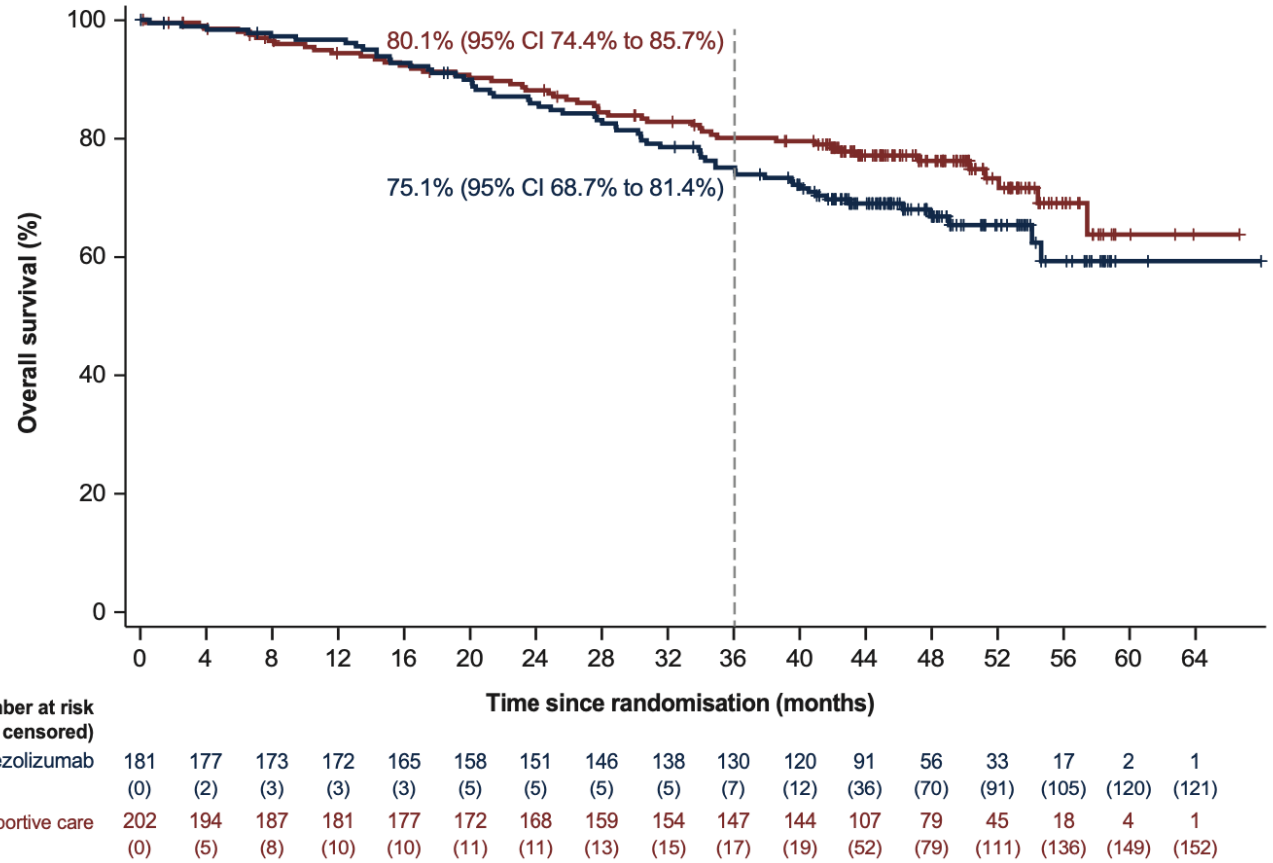
Felipe et al , Ann Onc 2023

He will be shy to show you this:

Overall survival in the PDL1<1% population, where there may be harm to adjuvant Atezo

G

	Events, *n* (%)	Patients, *n*	Median overall survival, months (95% CI)	HR (95% CI)[b]
Atezolizumab group	59 (32.6)	181	NE (54.6, NE)	1.36 (0.93-1.99); *P* = 0.109
Best supportive care group	49 (24.3)	202	NE (NE)	



Number at risk (number censored)																	
Atezolizumab	181 (0)	177 (2)	173 (3)	172 (3)	165 (3)	158 (5)	151 (5)	146 (5)	138 (5)	130 (7)	120 (12)	91 (36)	56 (70)	33 (91)	17 (105)	2 (120)	1 (121)
Best supportive care	202 (0)	194 (5)	187 (8)	181 (10)	177 (10)	172 (11)	168 (11)	159 (13)	154 (15)	147 (17)	144 (19)	107 (52)	79 (79)	45 (111)	18 (136)	4 (149)	1 (152)

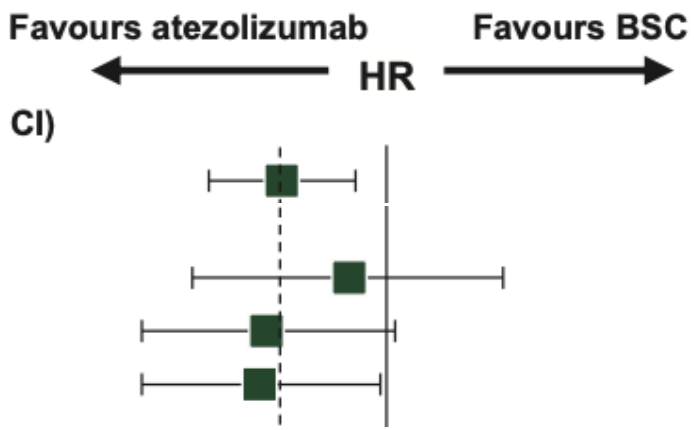
Felipe et al , Ann Onc 2023

Because he will want to show you this:

B

Stage II-IIIA PD-L1 TC ≥50%

Subgroup	N	Atezolizumab n	Atezolizumab Median OS (95% CI)	BSC n	BSC Median OS (95% CI)	HR (95% CI)
All patients	229	115	NE (NE)	114	NE (NE)	0.43 (0.24-0.78)
Regional lymph node stage (pN)						
N0	51	30	NE (NE)	21	NE (NE)	0.74 (0.21-2.55)
N1	95	43	NE (NE)	52	NE (NE)	0.38 (0.14-1.07)
N2	83	42	NE (NE)	41	NE (41.1-NE)	0.36 (0.14-0.95)



Felipe et al , Ann Onc 2023

But might forget about this…

B

Stage II-IIIA PD-L1 TC ≥50%

Subgroup	N	Atezolizumab n	Atezolizumab Median OS (95% CI)	BSC n	BSC Median OS (95% CI)	HR (95% CI)
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N1	95	43	NE (NE)	52	NE (NE)	0.38 (0.14-1.07)
N2	83	42	NE (NE)	41	NE (41.1-NE)	0.36 (0.14-0.95)
Stage						
II	119	62	NE (NE)	57	NE (NE)	0.63 (0.28-1.44)
IIIA	110	53	NE (NE)	57	NE (NE)	0.30 (0.12-0.74)

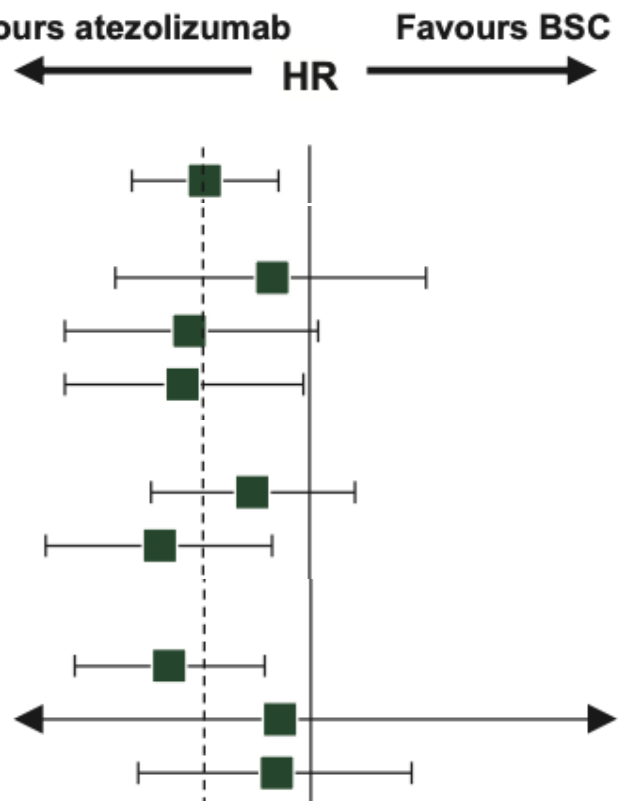
Felipe et al , Ann Onc 2023

And this…

B

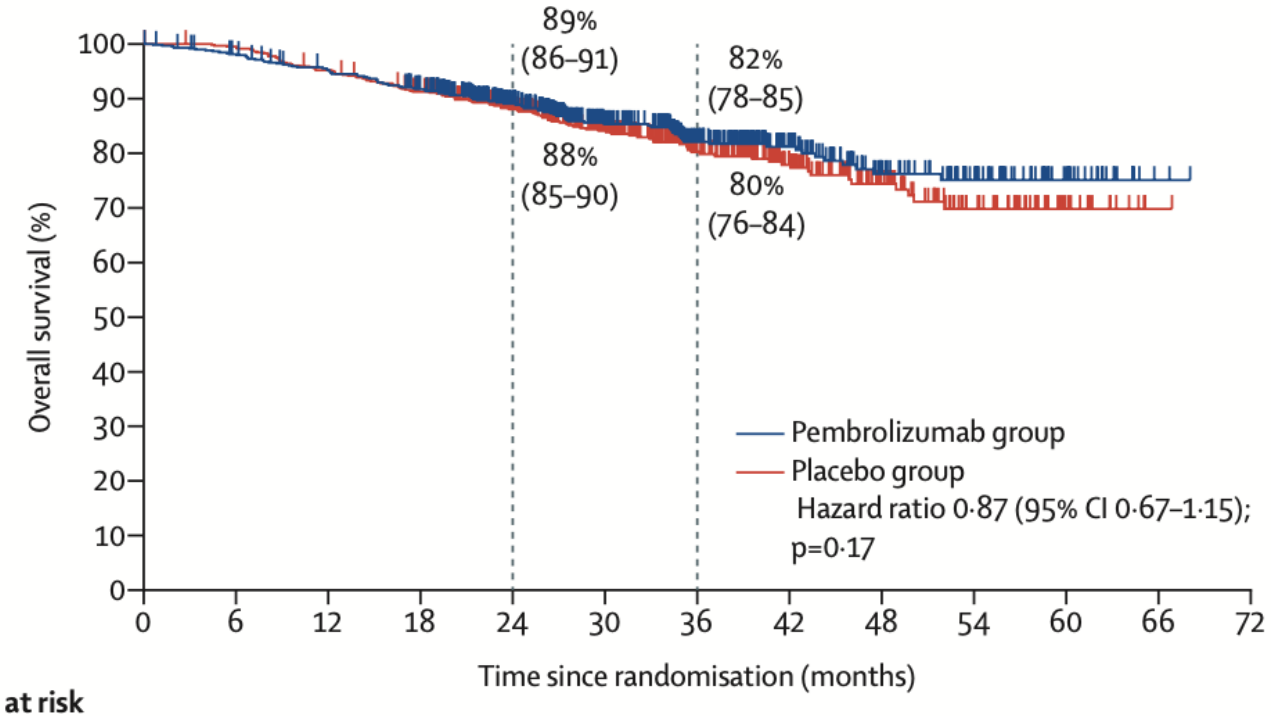
Stage II-IIIA PD-L1 TC ≥50%

Subgroup	N	Atezolizumab n	Atezolizumab Median OS (95% CI)	BSC n	BSC Median OS (95% CI)	HR (95% CI)
All patients	229	115	NE (NE)	114	NE (NE)	0.43 (0.24-0.78)
Regional lymph node stage (pN)						
N0	51	30	NE (NE)	21	NE (NE)	0.74 (0.21-2.55)
N1	95	43	NE (NE)	52	NE (NE)	0.38 (0.14-1.07)
N2	83	42	NE (NE)	41	NE (41.1-NE)	0.36 (0.14-0.95)
Stage						
II	119	62	NE (NE)	57	NE (NE)	0.63 (0.28-1.44)
IIIA	110	53	NE (NE)	57	NE (NE)	0.30 (0.12-0.74)
Type of surgery						
Lobectomy	169	84	NE (NE)	85	NE (NE)	0.32 (0.15-0.69)
Bilobectomy	14	7	NE (NE)	7	NE (NE)	0.78 (0.05-12.55)
Pneumonectomy	40	20	NE (38.5-NE)	20	NE (28.6-NE)	0.76 (0.25-2.25)

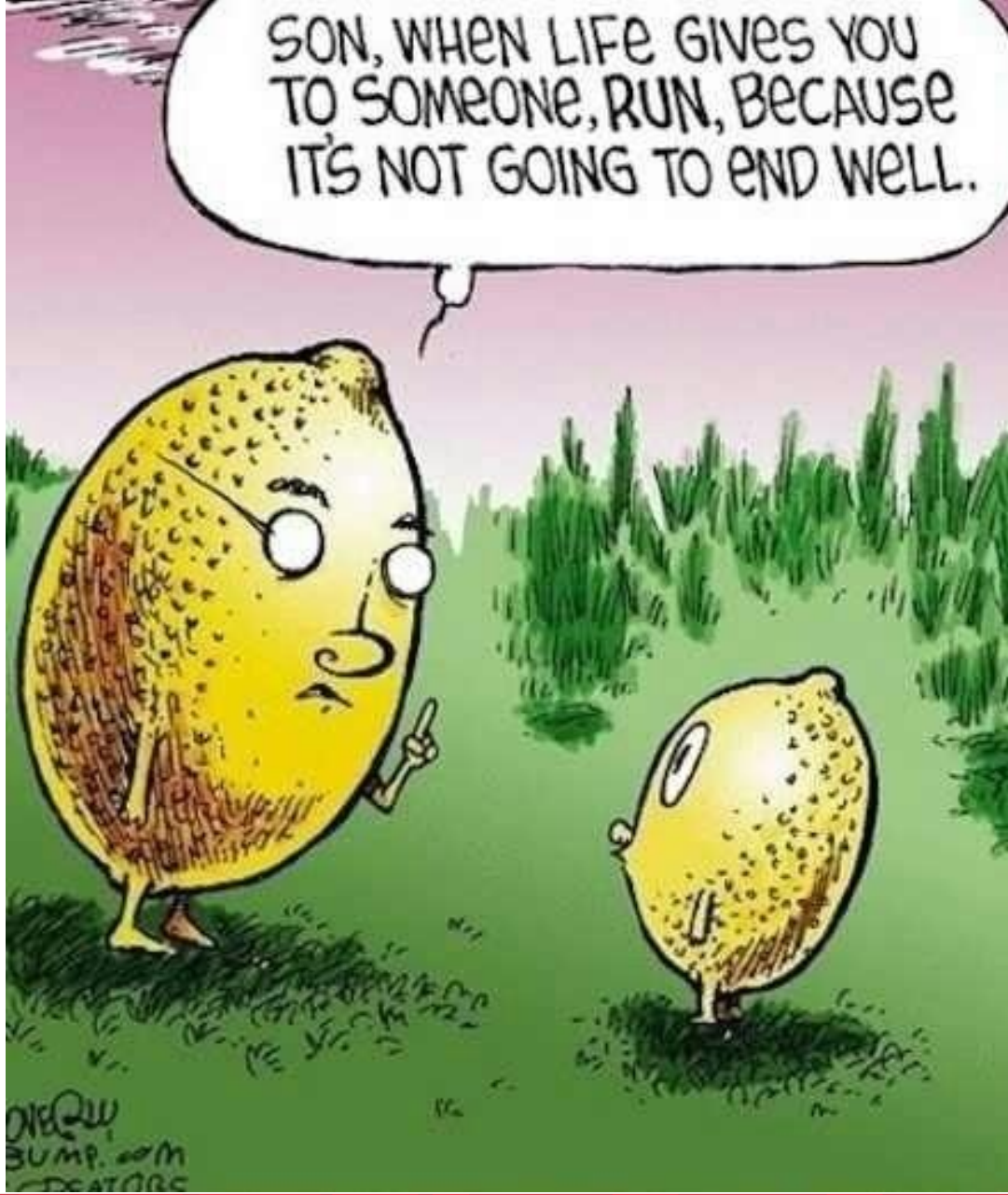


Felipe et al , Ann Onc 2023

Then he will try to make lemonade from KN091



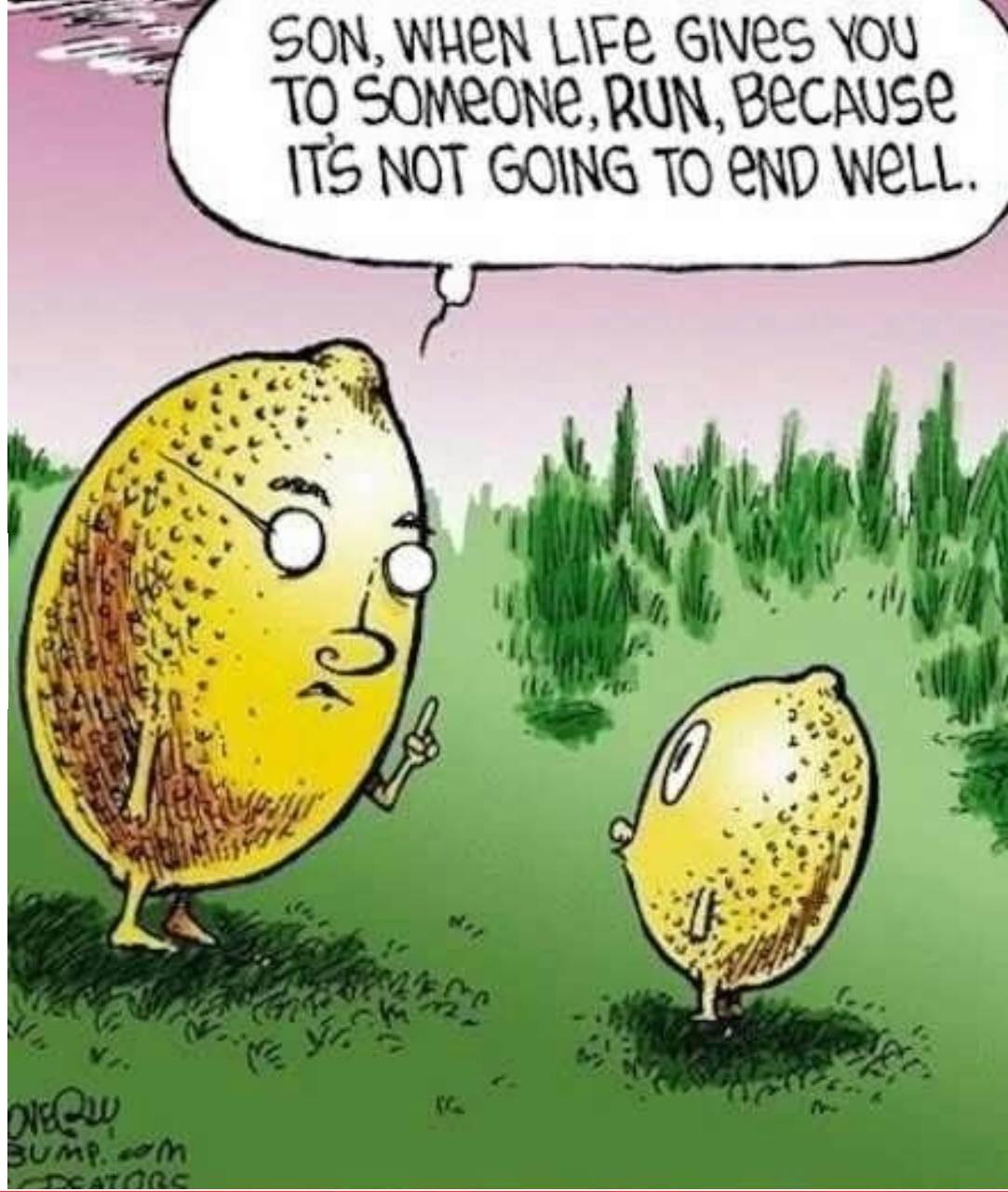
Number at risk (number censored)													
Pembrolizumab	590	572	548	520	419	318	226	143	83	52	23	2	0
	(0)	(7)	(14)	(22)	(109)	(194)	(276)	(357)	(410)	(440)	(469)	(490)	(492)
Placebo	587	582	556	524	420	309	213	135	78	44	16	1	0
	(0)	(2)	(3)	(12)	(99)	(193)	(277)	(350)	(402)	(432)	(460)	(475)	(476)



O'Brien et al, Lancet Oncol 2022

Then he will try to make lemonade from KN091

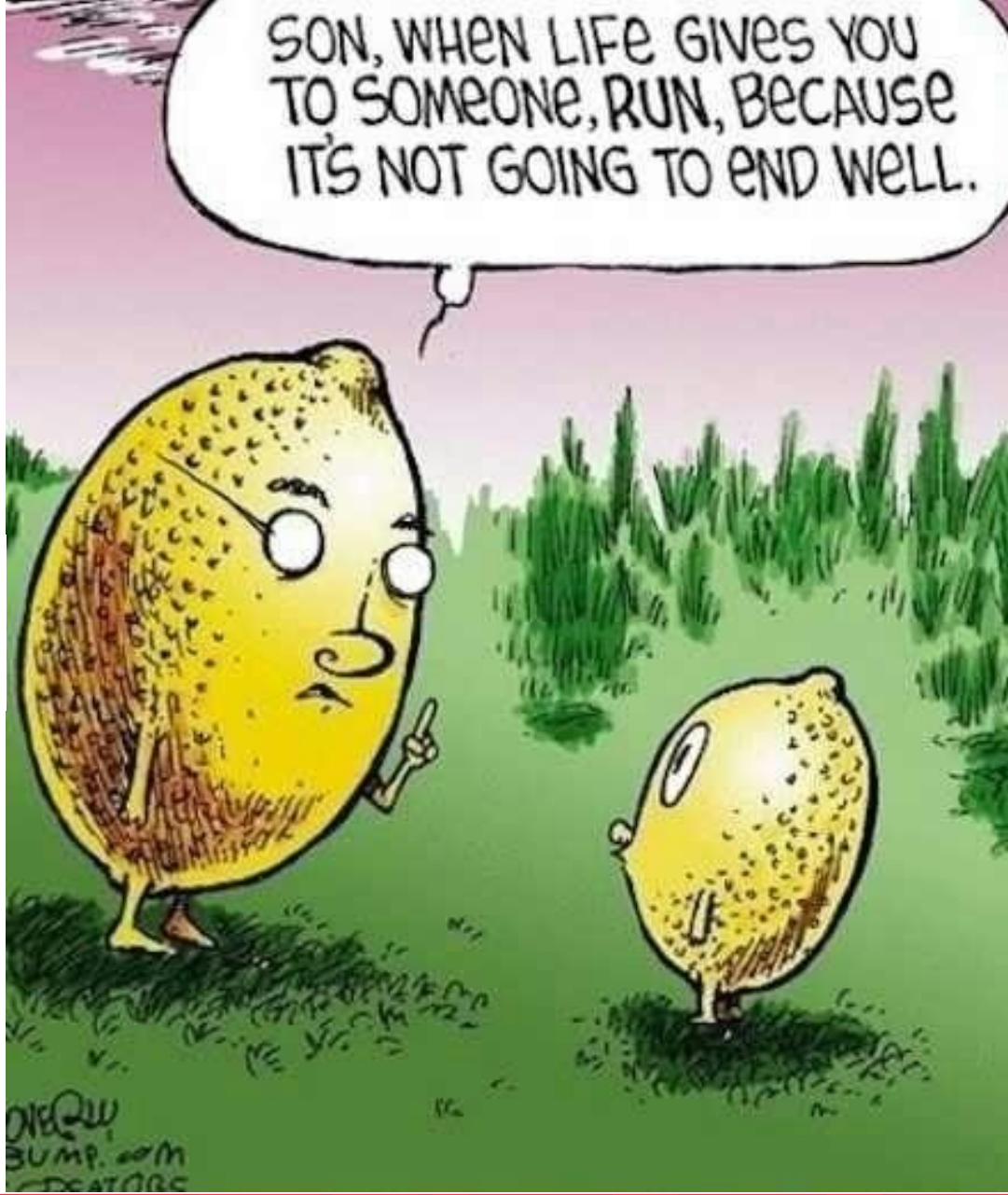
	Events/participants		Hazard ratio (95% CI)
	Pembrolizumab	Placebo	
Disease stage			
IB	21/84	25/85	0·76 (0·43–1·37)
II	102/329	144/338	0·70 (0·55–0·91)
IIIA	89/177	89/162	0·92 (0·69–1·24)



O'Brien et al, Lancet Oncol 2022

Then he will try to make lemonade from KN091

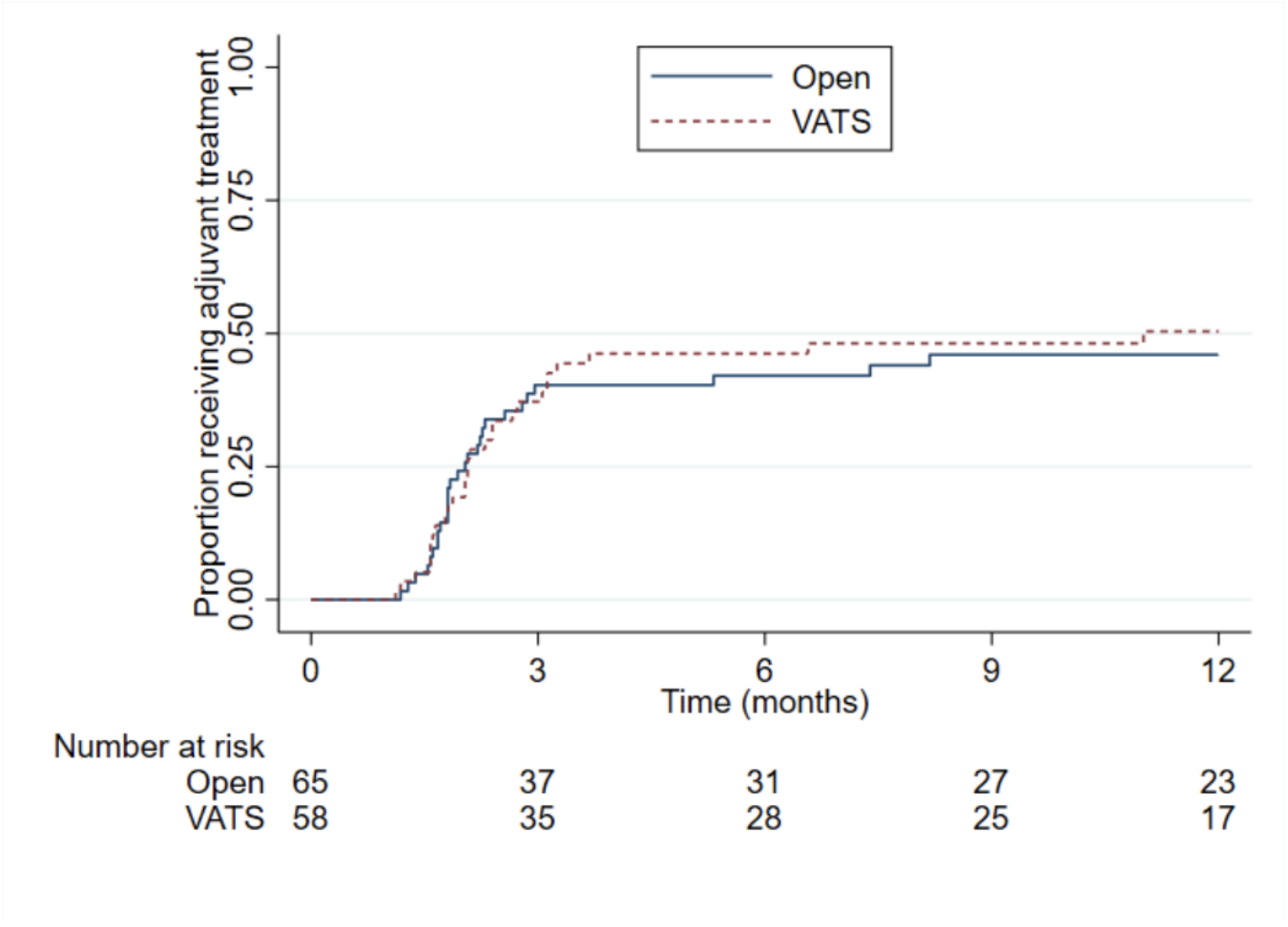
	Events/participants		Hazard ratio (95% CI)
	Pembrolizumab	Placebo	
Disease stage			
IB	21/84	25/85	0·76 (0·43–1·37)
II	102/329	144/338	0·70 (0·55–0·91)
IIIA	89/177	89/162	0·92 (0·69–1·24)
Received adjuvant chemotherapy			
No	35/84	29/83	1·25 (0·76–2·05)
Yes	177/506	231/504	0·73 (0·60–0·89)

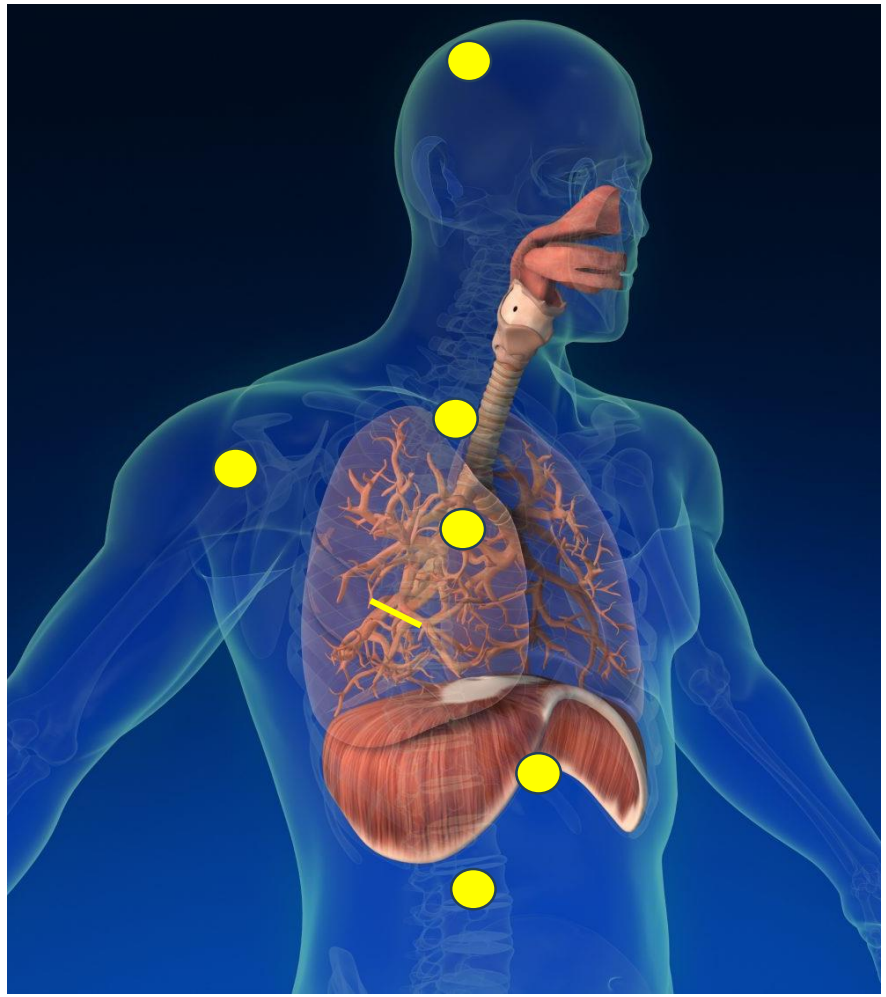


O'Brien et al, Lancet Oncol 2022

Indicated adjuvant therapy is inconsistently delivered…

Supplementary Figure S29 Uptake of adjuvant treatment: eligible cohort

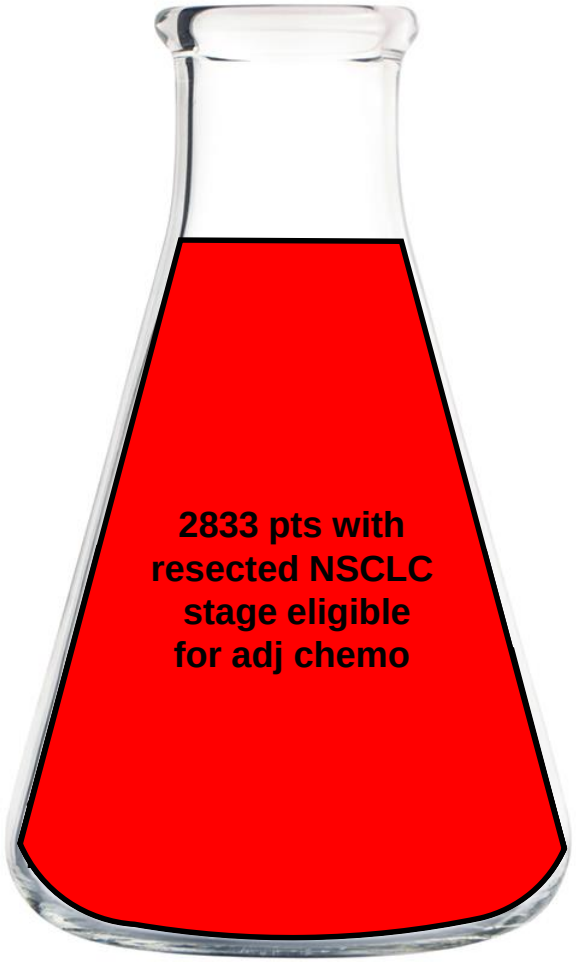




Lim et al, NEJM Evidence 2022

Russian roulette of adjuvant therapy

- ALCHEMIST trial results on guideline concordant surgery and adjuvant chemotherapy



Galina et al, under review

If asked what the SoC is for metastatic NSCLC PDL1 < 50%, Dr. Sacher would say:

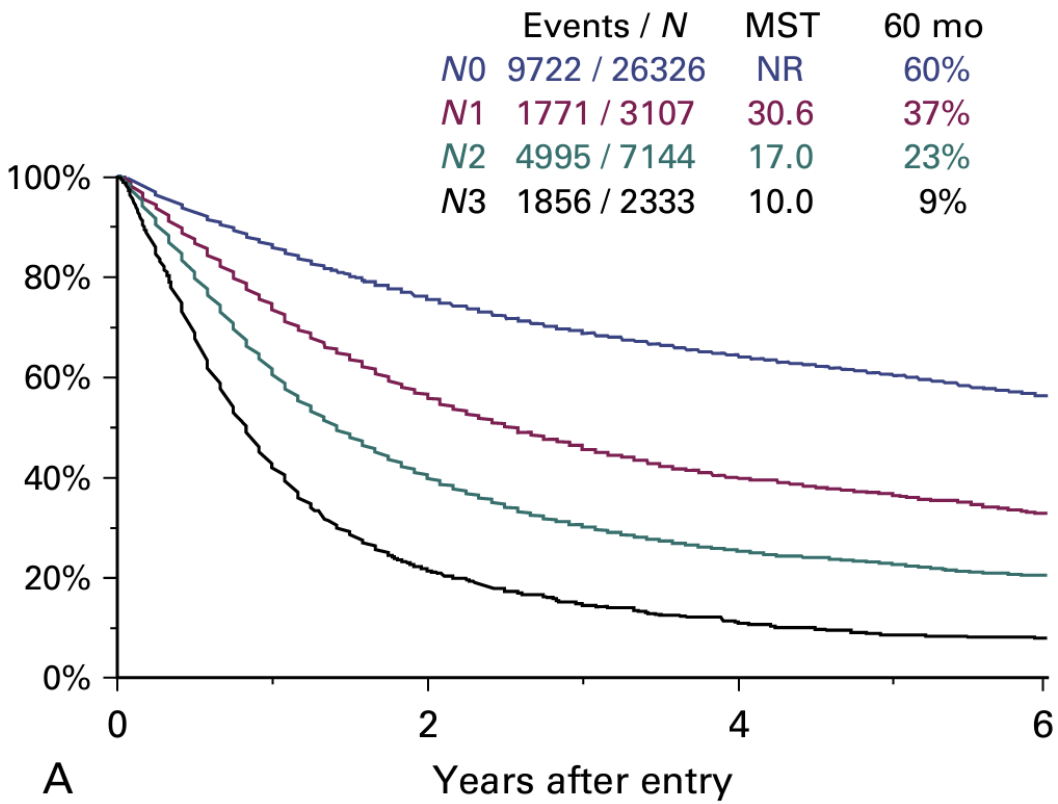
If asked which regimen has the highest objective response rate in metastatic PDL1 >50%, he would say:

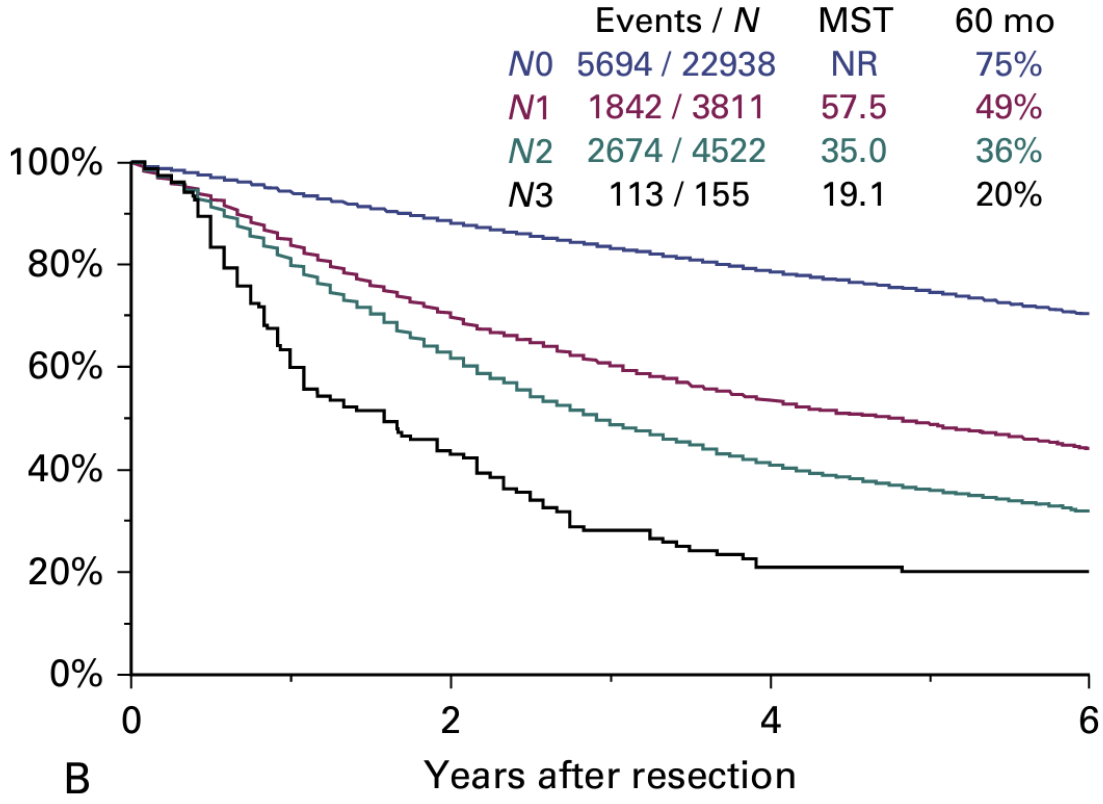
If asked how many meta-analyses there are about the survival benefits of adjuvant IO, Dr. Sacher would say:

So why would he agree to defend this indefensible position?

Because I'm a such a nice guy!

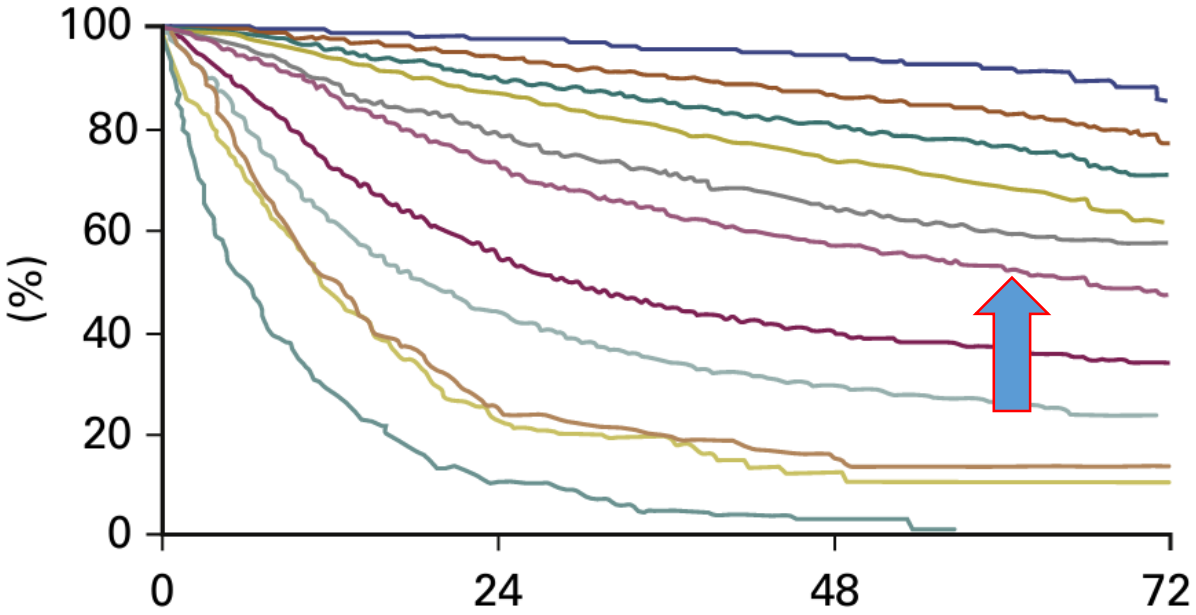
N1 disease is associated with at least 50% mortality at 5 years

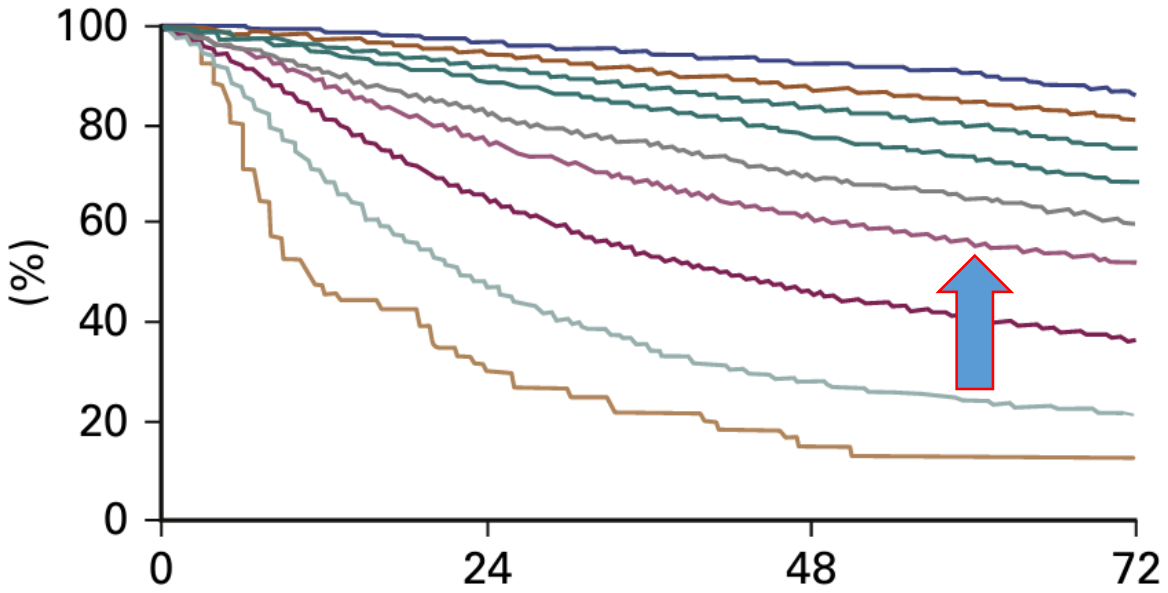




Rami-Porta et al, IASLC Thorac Onc 2018

Stage IIB disease is also associated with at least 50% mortality at 5 years





Months

	Events/N	MST	24 mo (%)	60 mo (%)
IA1	68/781	NR	97	92
IA2	505/3105	NR	94	83
IA3	546/2417	NR	90	77
IB	560/1928	NR	87	68
IIA	215/585	NR	79	60
IIB	605/1453	66.0	72	53
IIIA	2052/3200	29.3	55	36
IIIB	1551/2140	19.0	44	26
IIIC	831/986	12.6	24	13
IVA	336/484	11.5	23	10
IVB	328/398	6.0	10	0

A

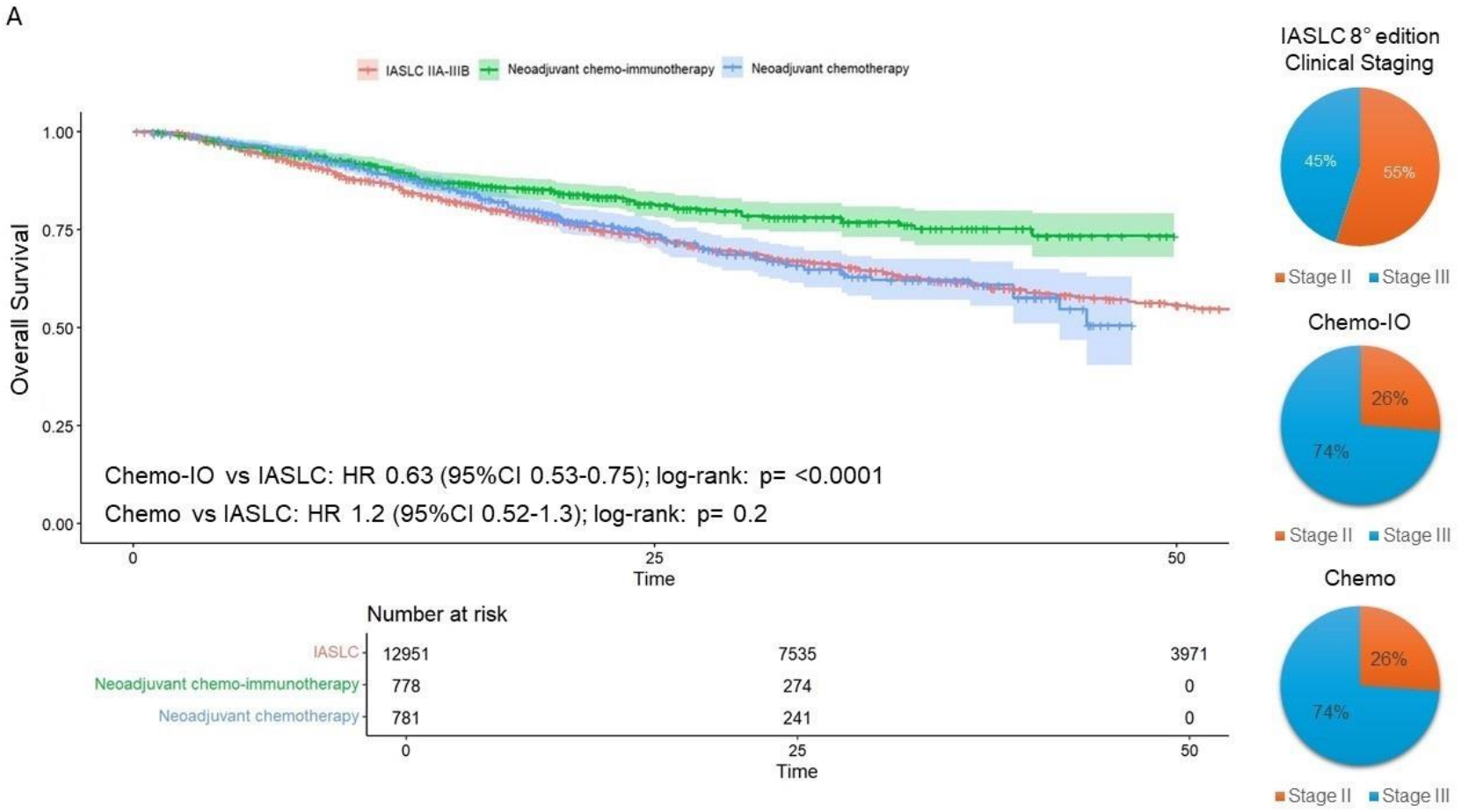
Months

	Events/N	MST	24 mo (%)	60 mo (%)
IA1	139/1389	NR	97	90
IA2	823/5633	NR	94	85
IA3	875/4401	NR	92	80
IB	1618/6095	NR	89	73
IIA	556/1638	NR	82	65
IIB	2175/5226	NR	76	56
IIIA	3219/5756	41.9	65	41
IIIB	1215/1729	22.0	47	24
IIIC	55/69	11.0	30	12

B

Rami-Porta et al, IASLC Thorac Onc 2018

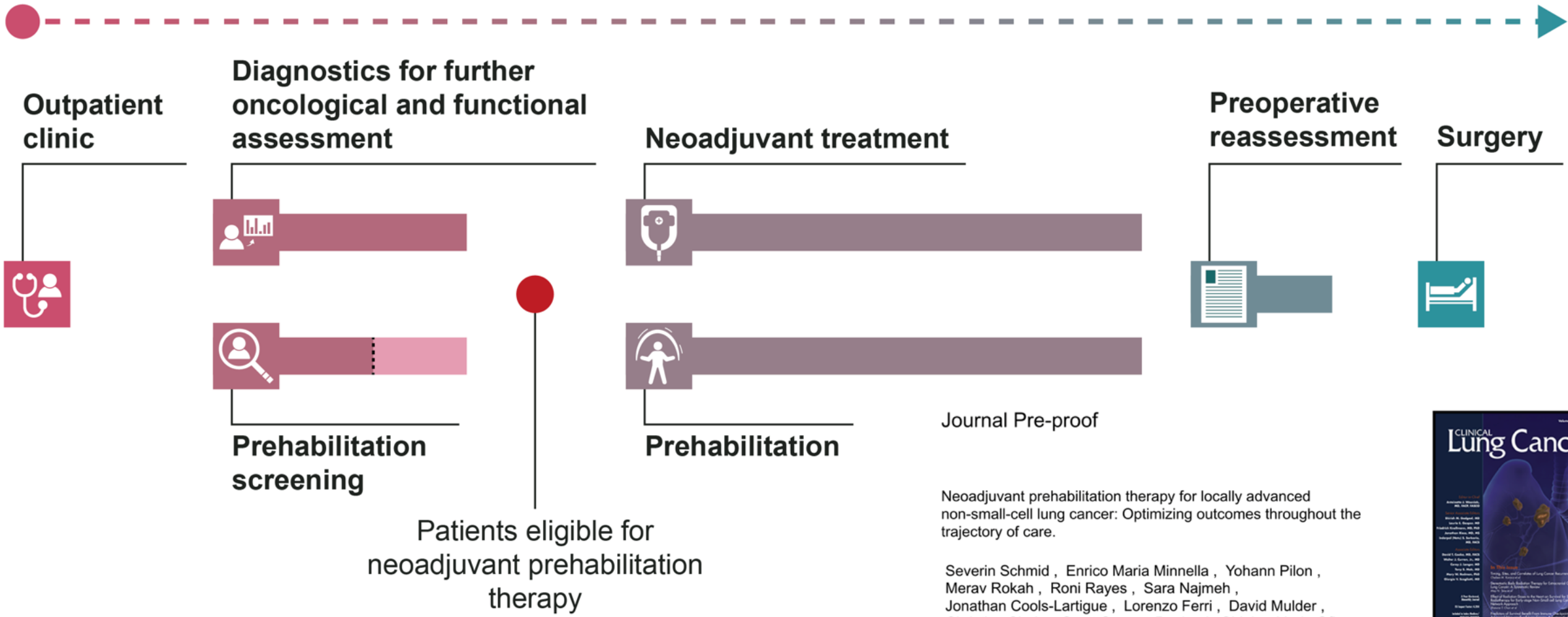
How well would adjuvant IO have to work to catch up to neaodj/periop chemoIO on OS?



Galina et al, under review

So, why is neoadj/periop so much better?

Patients no longer wait for surgery - they have a strategic plan

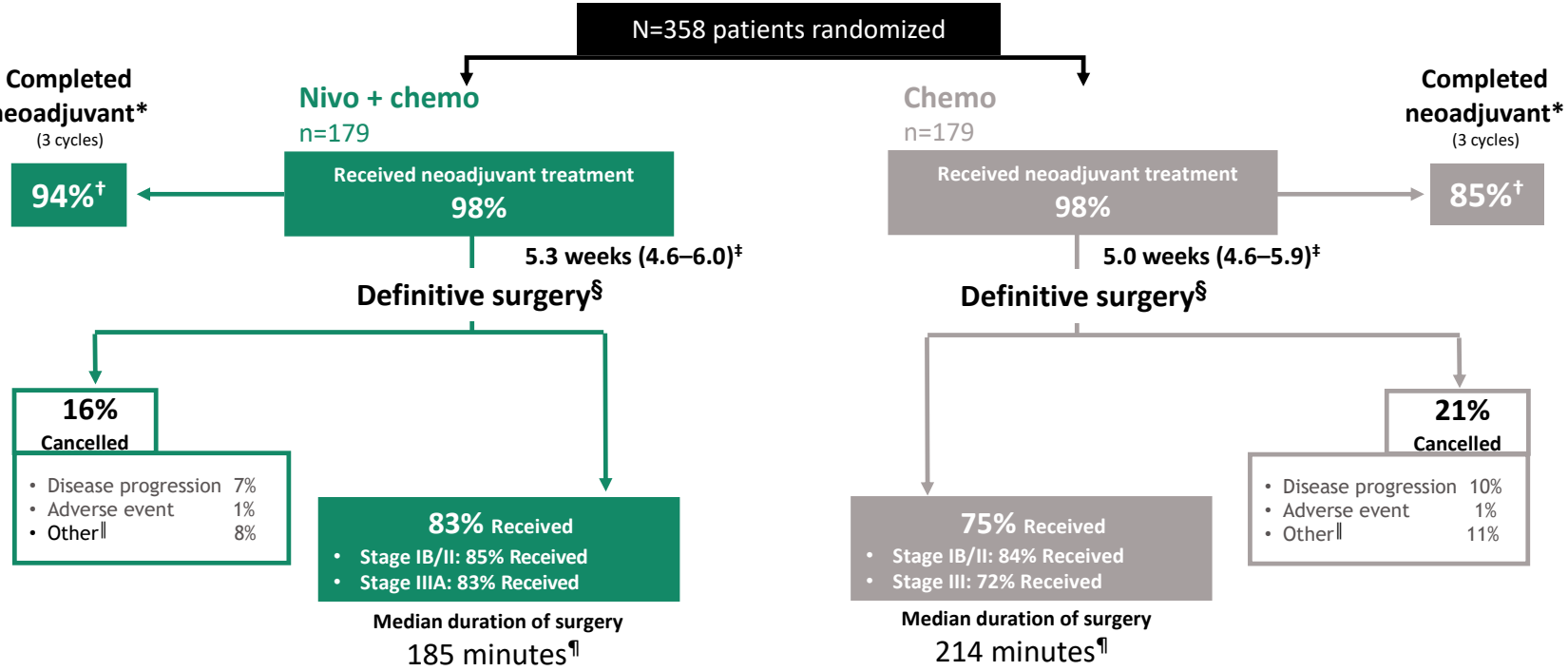


Journal Pre-proof

Neoadjuvant prehabilitation therapy for locally advanced non-small-cell lung cancer: Optimizing outcomes throughout the trajectory of care.

Severin Schmid , Enrico Maria Minnella , Yohann Pilon , Merav Rokah , Roni Rayes , Sara Najmeh , Jonathan Cools-Lartigue , Lorenzo Ferri , David Mulder , Christian Sirois , Scott Owen , Benjamin Shieh , Linda Ofiara , Annick Wong , Shelly Sud , Gabriele Baldini , Francesco Carli , Jonathan Spicer

94% completed all cycles of systemic tx



35 (20%) patients received adjuvant therapy[d]	56 (32%) patients received adjuvant therapy[d]
• 21 (12%) received chemo alone • 9 (5%) received RT alone • 5 (3%) received chemo and RT	• 39 (22%) received chemo alone • 12 (7%) received RT alone • 5 (3%) received chemo and RT

Forde et al, AACR 2022

Chemotherapy is important for these patients: Canadian data!

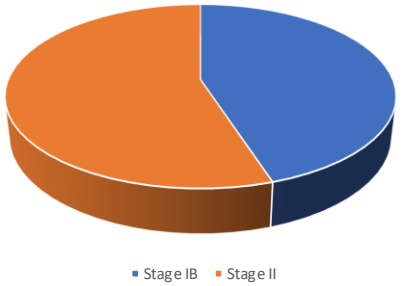
VOLUME 28 · NUMBER 1 · JANUARY 1 2010

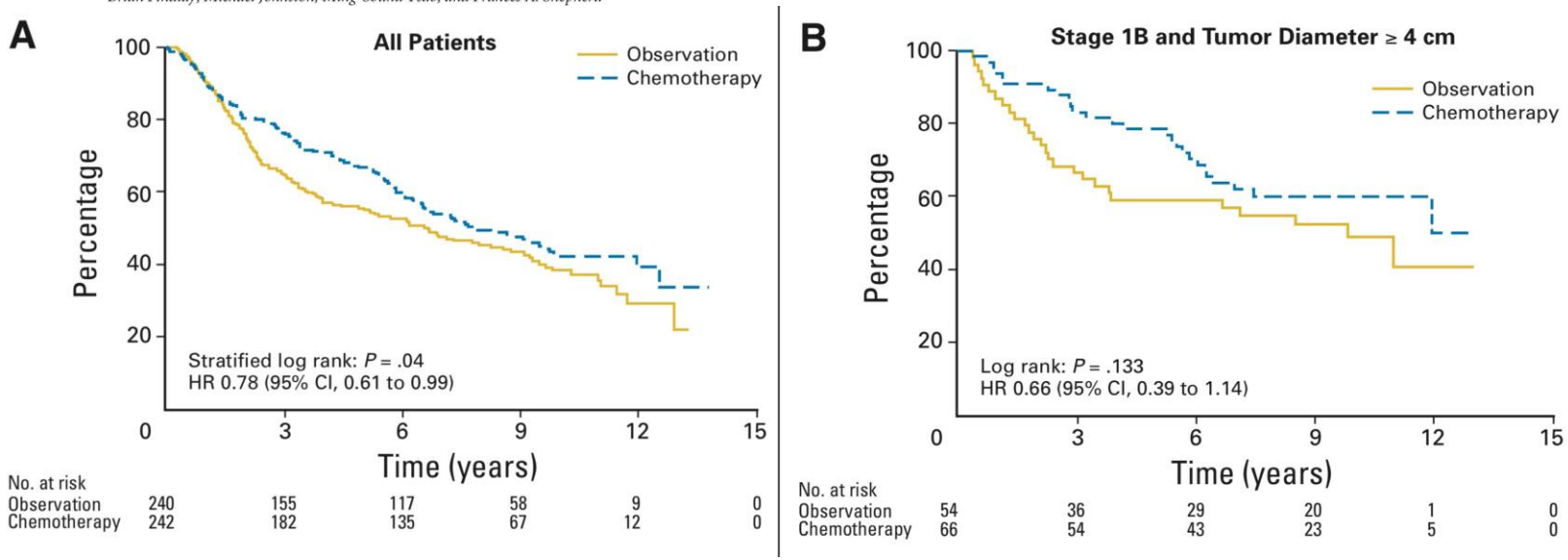
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Randomized Phase III Trial of Vinorelbine Plus Cisplatin Compared With Observation in Completely Resected Stage IB and II Non–Small-Cell Lung Cancer: Updated Survival Analysis of JBR-10

Charles A. Butts, Keyue Ding, Lesley Seymour, Philip Twumasi-Ankrah, Barbara Graham, David Gandara, David H. Johnson, Kenneth A. Kesler, Mark Green, Mark Vincent, Yvon Cormier, Glenwood Goss, Brian Findlay, Michael Johnston, Ming-Sound Tsao, and Frances A. Shepherd

Stage distribution in JBR.10





CheckMate 816: First subsequent therapy in patients with canceled definitive surgery due to disease progression[1]

Sex	Region	ECOG PS	Stage	Smoking status	Tumor PD-L1	First subsequent therapy
NIVO + chemo (n=11)						
						Chemotherapy
						Chemotherapy
						Chemotherapy
						Radiotherapy
						Radiotherapy
						Radiotherapy*
						None recorded
						None recorded
						None recorded
						None recorded
						None recorded
Chemo (n=17)						
						Chemotherapy
						Chemotherapy
						Radiotherapy
						Radiotherapy
						Radiotherapy
						Radiotherapy
						Radiotherapy*
						Radiotherapy + immunotherapy (pembrolizumab)
						Chemoradiotherapy + immunotherapy (durvalumab)
						Chemoradiotherapy + immunotherapy (durvalumab)
						Chemotherapy + immunotherapy (toripalimab)
						Chemotherapy + immunotherapy (pembrolizumab)
						Immunotherapy (nivolumab)
						Immunotherapy (nivolumab)
						Immunotherapy (nivolumab)
						Immunotherapy (pembrolizumab)
						None recorded

Sex
- Male
- Female

Region
- North America
- Asia
- Europe
- ROW†

ECOG PS
- 0
- 1

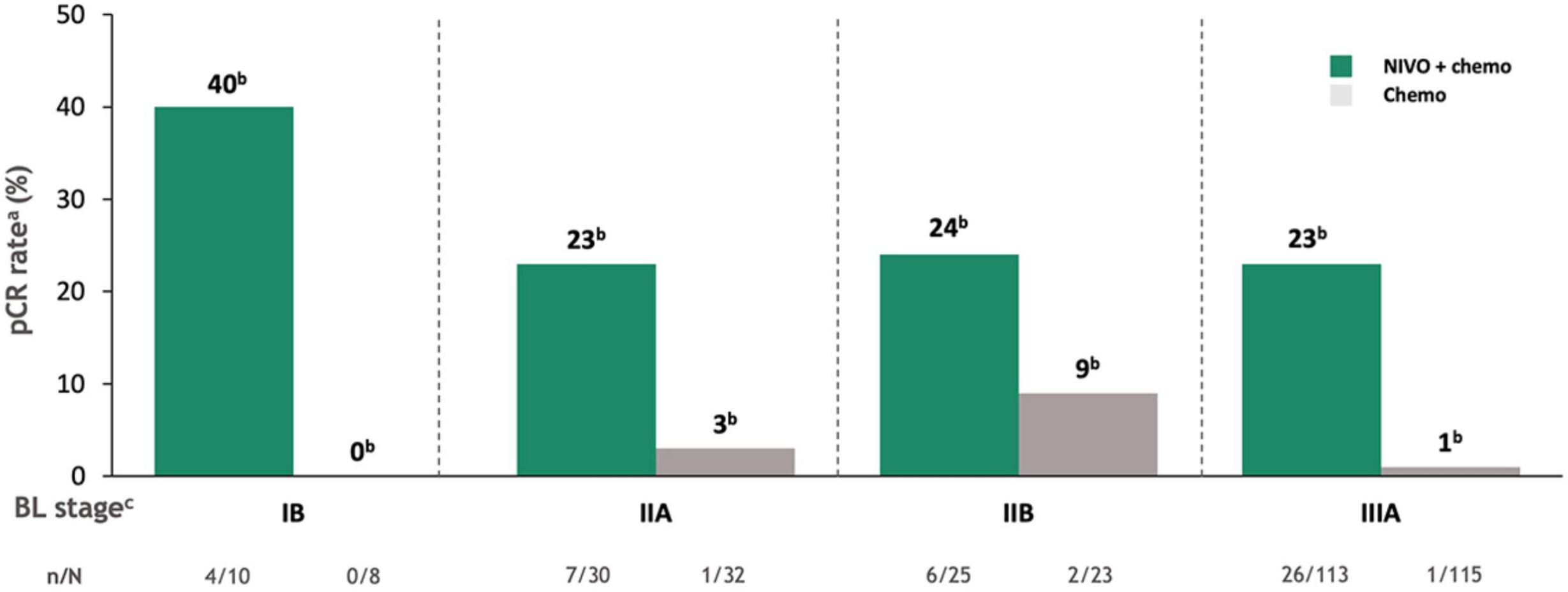
Stage
- IIA
- IIB
- IIIA

Smoking status
- Current/former
- Never

Tumor PD-L1
- ≥1%
- <1%‡

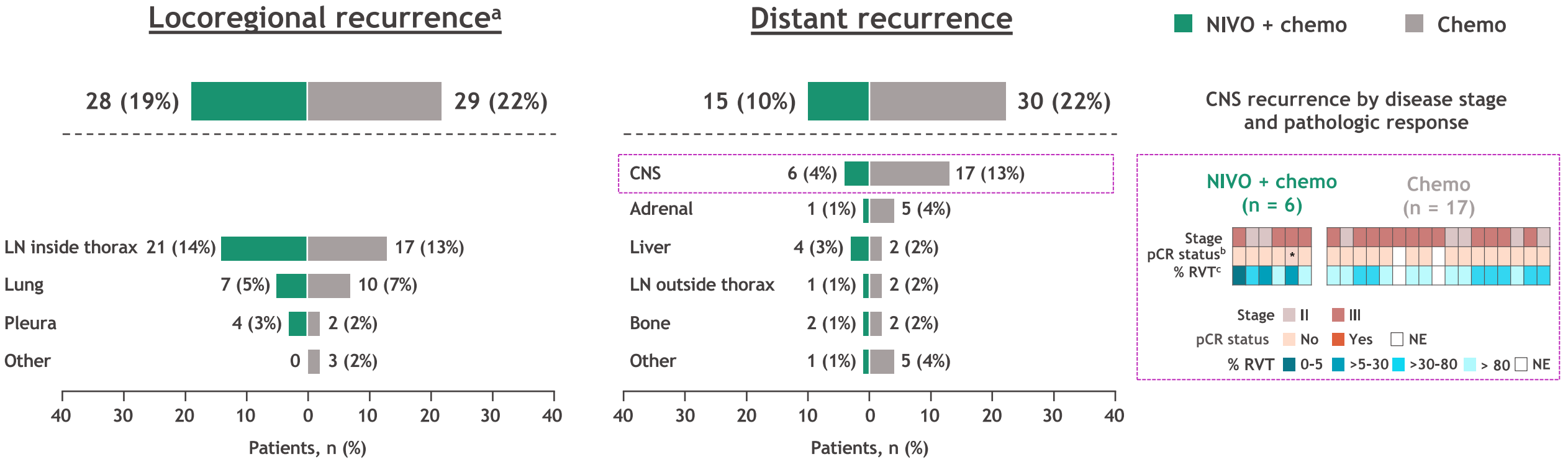
- Of the patients who canceled definitive surgery due to reasons other than disease progression (19, nivo + chemo; 27, chemo), some of the patients received definitive radiotherapy-based treatment modalities as an alternative to surgery, while no subsequent therapies were recorded for other patients[1]

Pathological response by cTNM in CM816



Forde et al, AACR 2022

Three doses of neoadj chemo-IO reduce distant recurrence by more than 50%

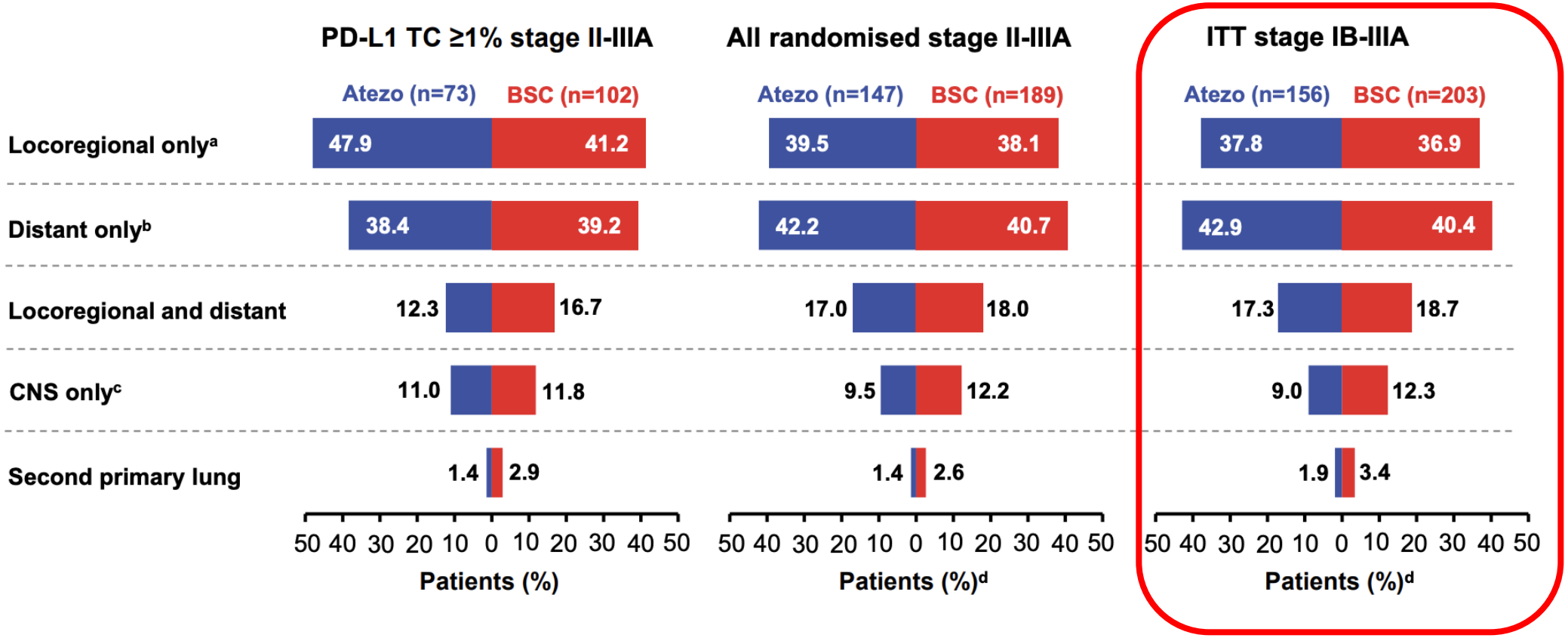


Forde et al, ELCC 2023

16 doses of IO impact on distant recurrence?

2021 ESMO congress

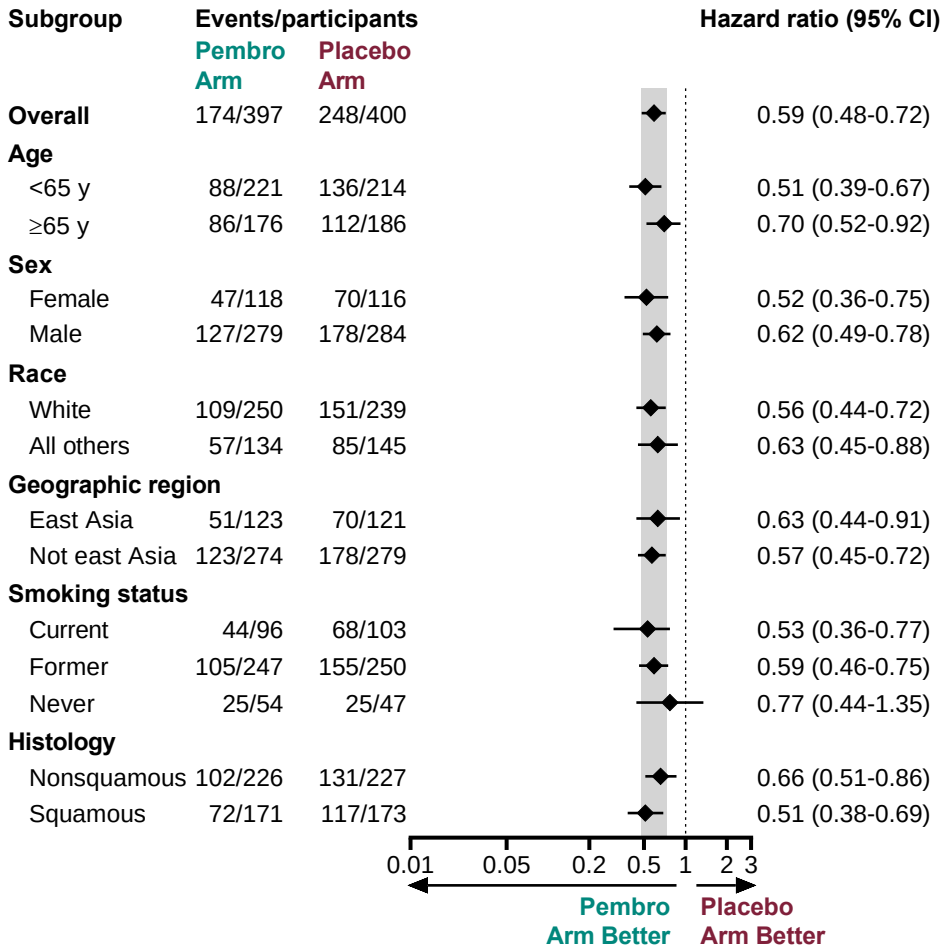
Patterns of relapse

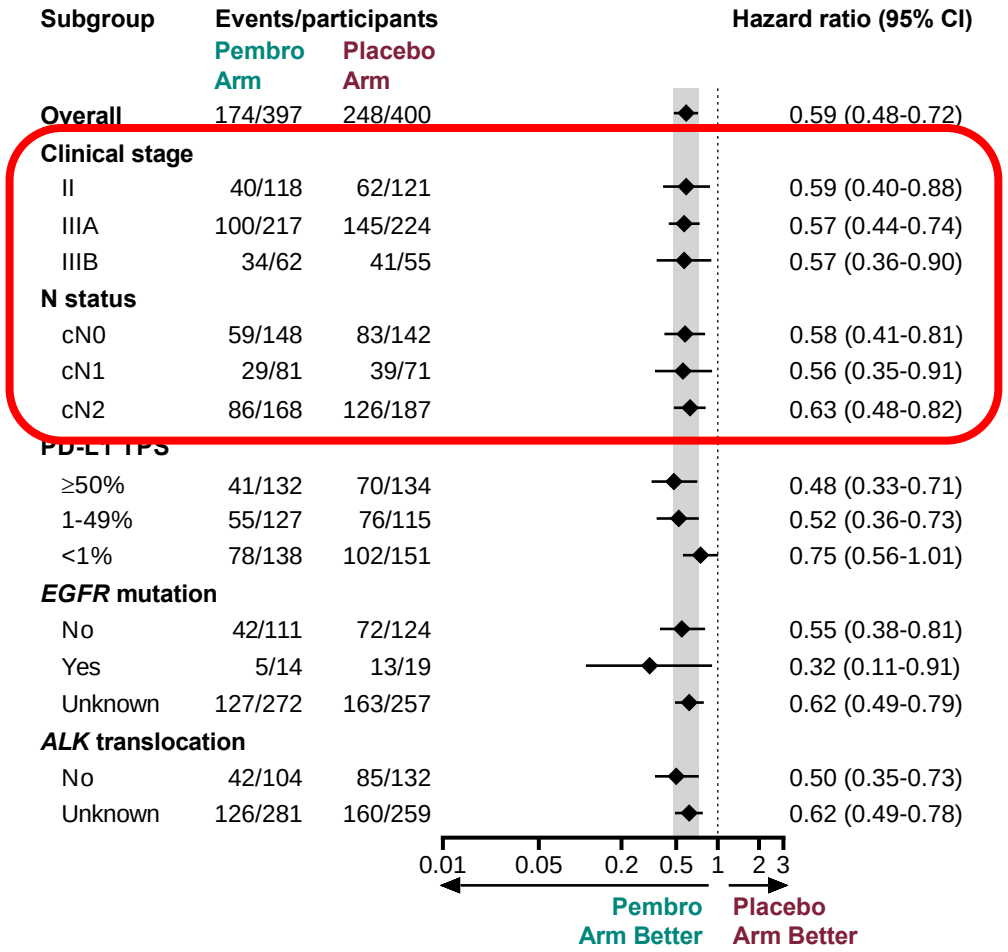


Clinical cutoff: 21 January 2021. [a] Includes patients with 'local' and/or 'regional' recurrence only. [b] Includes patients with distant sites only; patients could have >1 distant site. [c] Subset of the Distant only category; includes patients with only distant CNS site. Patients with recurrence in CNS and other sites are not included. [d] One patient in the BSC arm had distant + second primary non-lung sites.

Felip et al. IMpower010 Relapse Patterns. https://bit.ly/3mNMSAi

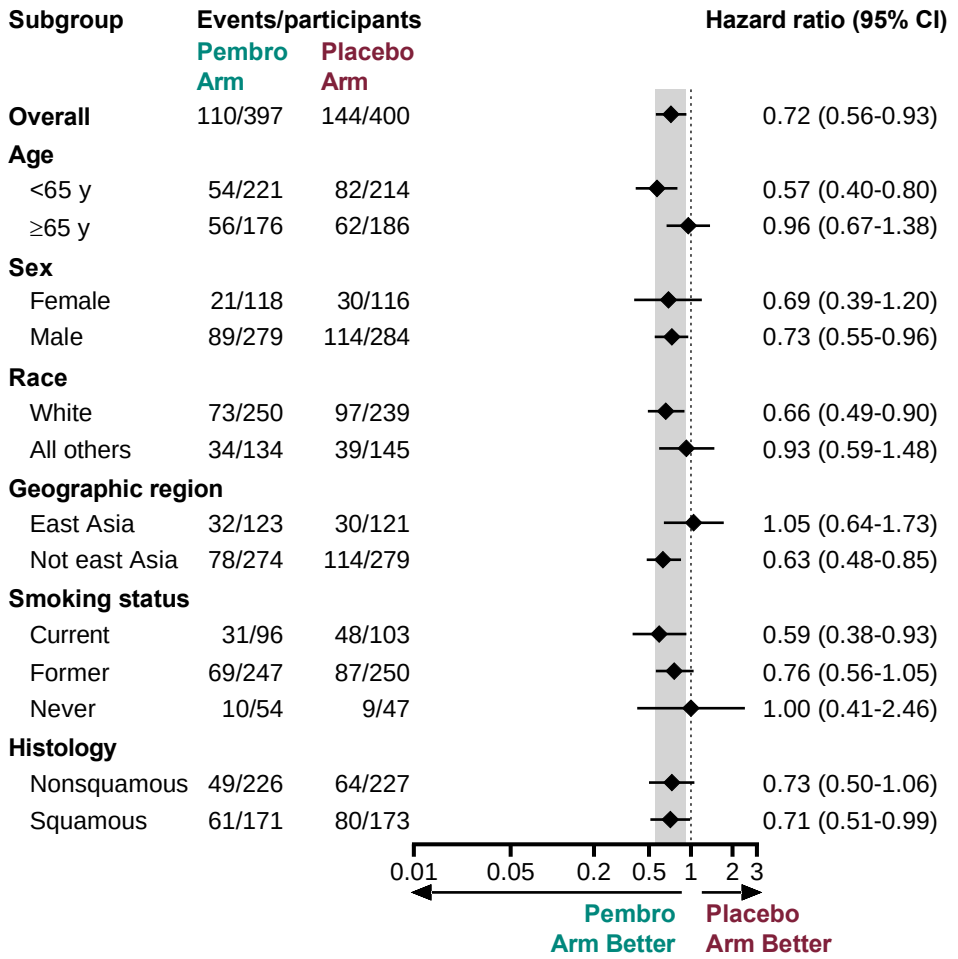
Event-Free Survival in Subgroups, IA2

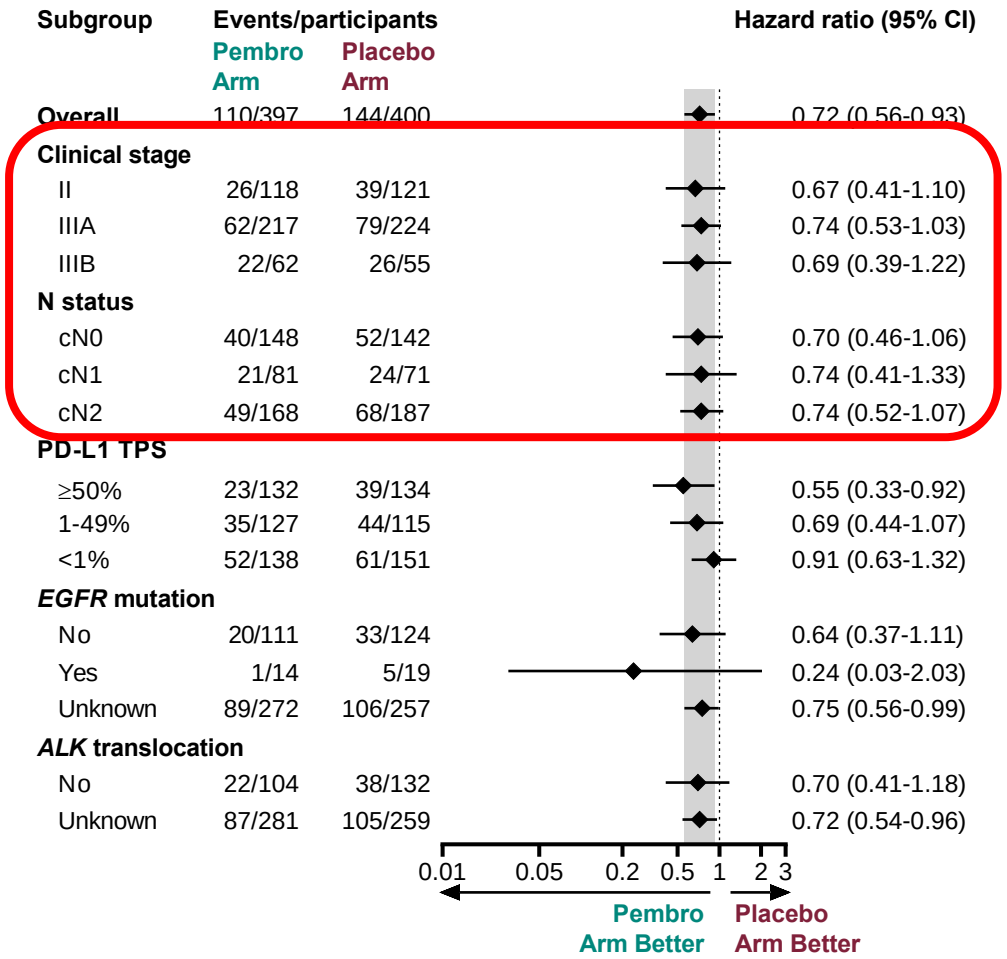




Per the prespecified analysis plan, subgroups with <30 participants are excluded from the forest plot. Subgroups for stage IIIA and IIIB and pN status were post hoc; all other subgroups were prespecified.
Data cutoff date for IA2: July 10, 2023.

Overall Survival in Subgroups, IA2



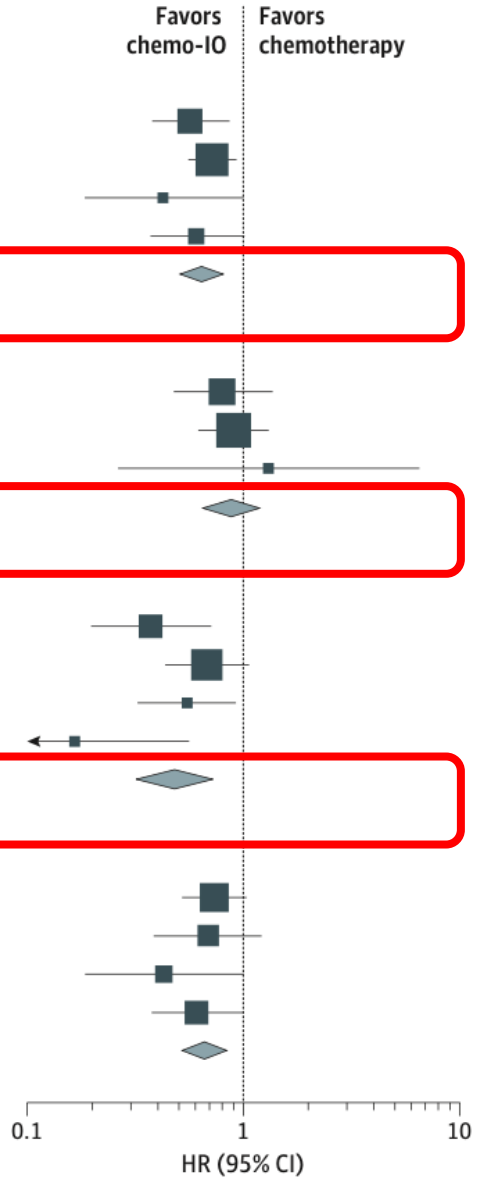


Per the prespecified analysis plan, subgroups with <30 participants are excluded from the forest plot. Subgroups for stage IIIA and IIIB and pN status were post hoc; all other subgroups were prespecified.
Data cutoff date for IA2: July 10, 2023.

Neoadj/periop strategy: Overall Survival

Figure 1. Pooled Hazard Ratios (HRs) of Overall Survival Across Randomized Clinical Trials

Study	Patients, No. Chemo-IO	Patients, No. Chemotherapy	HR (95% CI)
All patients			
Forde et al,[8] 2022; Forde et al,[64] 2023; Provencio Pulla et al,[65] 2023; Provencio Pulla et al,[66] 2023	179	179	0.57 (0.38-0.87)
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023	397	400	0.72 (0.56-0.93)
Provencio et al,[21] 2023	57	29	0.43 (0.19-0.98)
Lu et al,[63] 2023; Lu et al,[68] 2023	202	202	0.62 (0.38-1.00)
Random-effects model	835	810	0.65 (0.54-0.79)
Heterogeneity: $I^2=0\%$; $\tau^2 \leq 0.1$; $P=.57$			
PD-L1 <1%			
Forde et al,[8] 2022; Forde et al,[64] 2023; Provencio Pulla et al,[65] 2023; Provencio Pulla et al,[66] 2023	78	77	0.81 (0.48-1.36)
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023	138	151	0.91 (0.63-1.32)
Provencio et al,[21] 2023	20	8	1.31 (0.27-6.41)
Random-effects model	236	236	0.89 (0.66-1.19)
Heterogeneity: $I^2=0\%$; $\tau^2 \leq 0.1$; $P=.83$			
PD-L1 ≥1%			
Forde et al,[8] 2022; Forde et al,[64] 2023; Provencio Pulla et al,[65] 2023; Provencio Pulla et al,[66] 2023	89	89	0.38 (0.20-0.71)
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023[a]	127	115	0.69 (0.44-1.07)
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023[b]	132	134	0.55 (0.33-0.57)
Provencio et al,[21] 2023	30	15	0.17 (0.05-0.57)
Random-effects model	378	353	0.49 (0.33-0.73)
Heterogeneity: $I^2=48.5\%$; $\tau^2 \leq 0.1$; $P=.12$			
Stage III			
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023[c]	217	224	0.74 (0.53-1.03)
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023[d]	62	55	0.69 (0.39-1.22)
Provencio et al,[21] 2023	57	29	0.43 (0.19-0.98)
Lu et al,[63] 2023; Lu et al,[68] 2023	202	202	0.62 (0.38-1.00)
Random-effects model	538	510	0.67 (0.53-0.85)
Heterogeneity: $I^2=0\%$; $\tau^2 \leq 0.1$; $P=.67$			

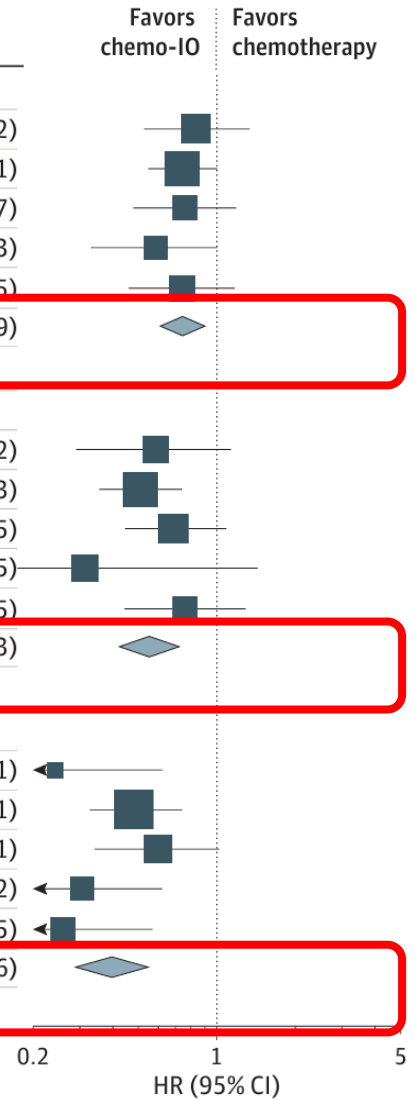


Sorin et al, JAMA Onc 2024

Neoadj/periop strategy and EFS

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

Study	Patients, No. Chemo-IO	Patients, No. 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: $I^2 = 32.1\%$; $\tau^2 \leq 0.1$; $P = .21$			

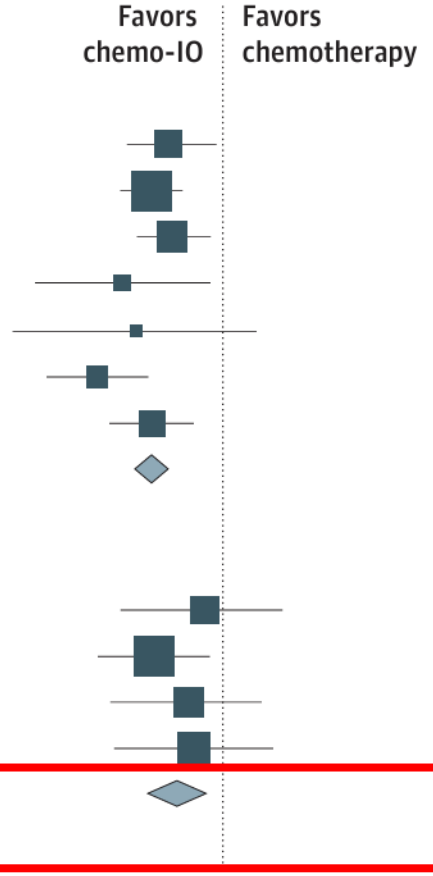


Sorin et al, JAMA Onc 2024

Neoadj/periop strategy: EFS for stage II

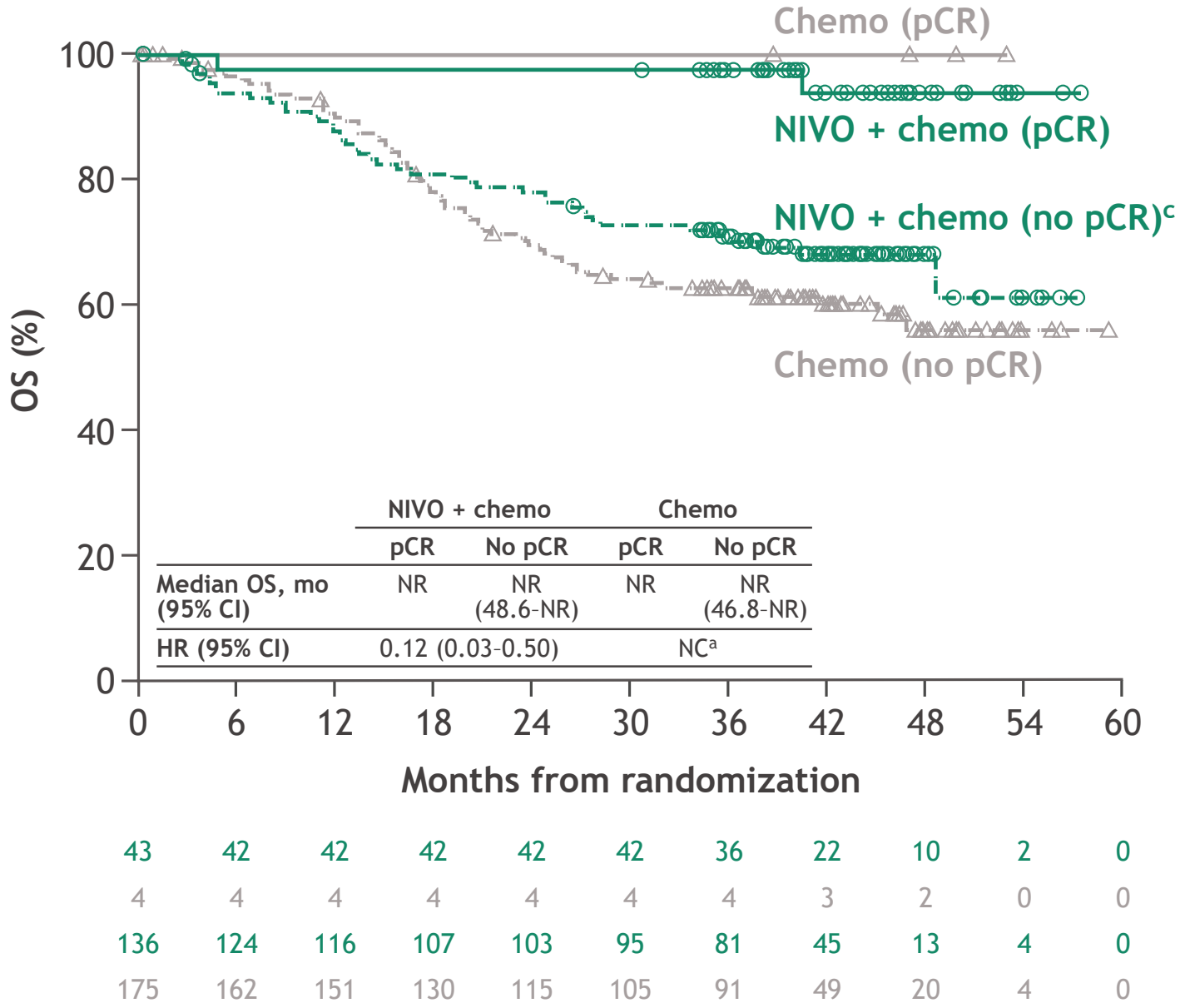
Figure 2. Pooled Hazard Ratios (HRs) of Event-Free Survival Across Randomized Clinical Trials

Study	Patients, No. Chemo-IO	Patients, No. Chemotherapy	HR (95% CI)
All patients			
Forde et al,[8] 2022	179	179	0.68 (0.49-0.93)
Wakelee et al,[10] 2023	397	400	0.59 (0.48-0.72)
Heymach et al,[41] 2023	366	374	0.68 (0.53-0.88)
Provencio et al,[21] 2023	57	29	0.47 (0.25-0.88)
Lei et al,[23] 2023	43	45	0.52 (0.21-1.29)
Lu et al,[63] 2023	202	202	0.40 (0.27-0.57)
Cascone et al,[61] 2023	229	232	0.59 (0.44-0.79)
Random-effects model	1473	1461	0.59 (0.52-0.67)
Heterogeneity: $I^2 = 14.9\%$; $\tau^2 \leq 0.1$; $P = .32$			
Stage II			
Forde et al,[8] 2022	65	62	0.87 (0.48-1.56)
Wakelee et al,[10] 2023	118	121	0.59 (0.40-0.88)
Heymach et al,[41] 2023	104	110	0.76 (0.43-1.34)
Cascone et al,[61] 2023	81	81	0.81 (0.46-1.43)
Random-effects model	368	374	0.71 (0.55-0.92)
Heterogeneity: $I^2 = 0\%$; $\tau^2 \leq 0.1$; $P = .68$			



Sorin et al, JAMA Onc 2024

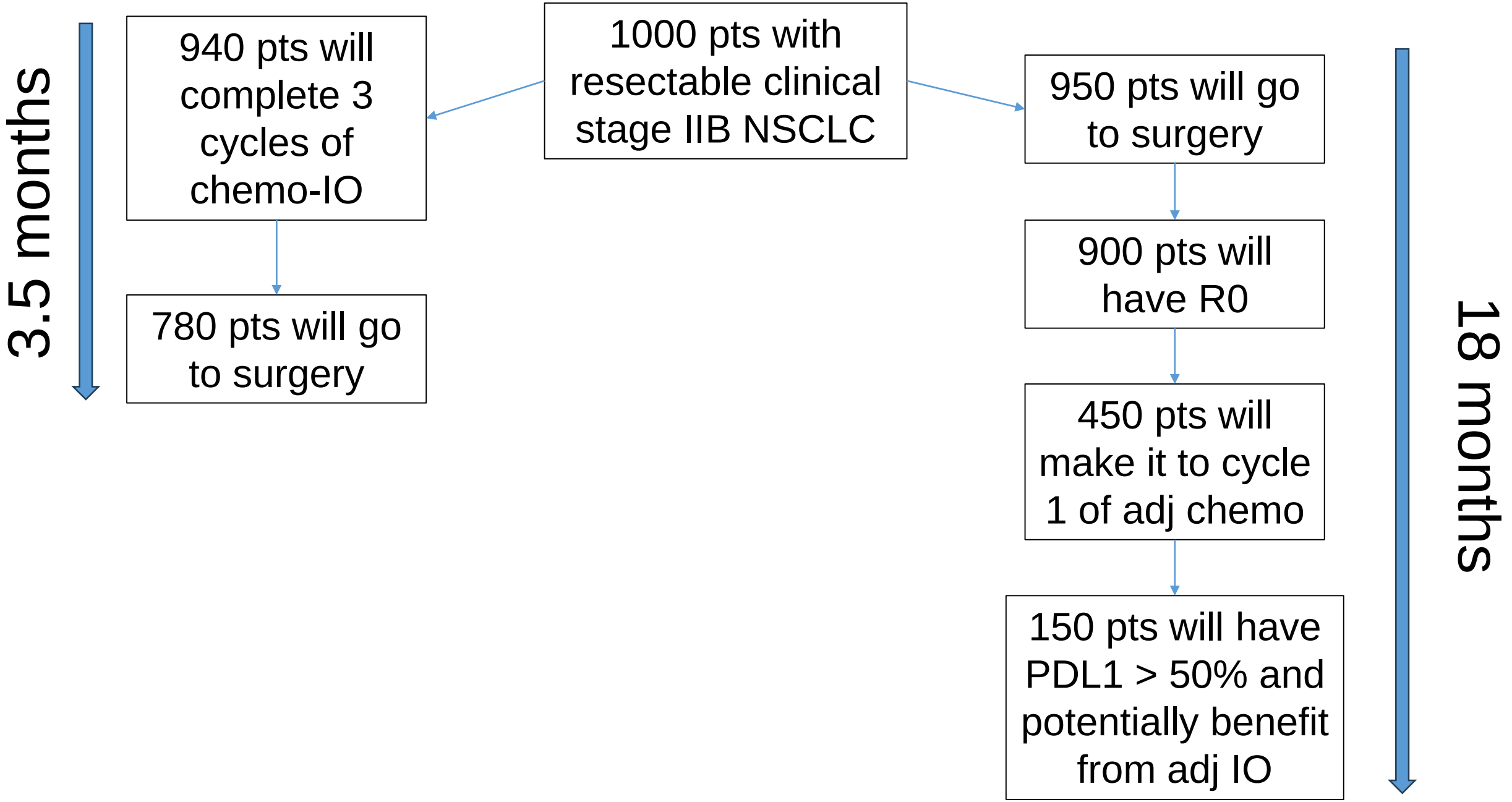
Providing a roadmap for Dr. Sacher and the patient



	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median OS, mo (95% CI)	NR	NR (48.6-NR)	NR	NR (46.8-NR)
HR (95% CI)	0.12 (0.03-0.50)		NC[a]	

43	42	42	42	42	42	36	22	10	2	0
4	4	4	4	4	4	4	3	2	0	0
136	124	116	107	103	95	81	45	13	4	0
175	162	151	130	115	105	91	49	20	4	0

Provencio et al, ESMO 2024


3.5 months
940 pts will complete 3 cycles of chemo-IO
780 pts will go to surgery
1000 pts with resectable clinical stage IIB NSCLC
950 pts will go to surgery
900 pts will have R0
450 pts will make it to cycle 1 of adj chemo
150 pts will have PDL1 > 50% and potentially benefit from adj IO
18 months

Up front surgery for N1 disease is not a plan! It's wishful thinking

It's like bringing these kids to the museum with no snacks.

Don't do it!

Final take home points

- Melanoma has proven that neoadj for resectable disease is vastly preferable
- Progression or death occurs in 50% of resectable cIIB NSCLC @ 5 years
- Until we can predict which 50% is cured with surgery, we need to consider that systemic progression is highest risk for cause of death in these patients
- Neoadjuvant chemo-IO is the most optimal way to address this risk
- Most robust survival data favour neoadjuvant/perioperative chemo-IO