MaTOS™
Masters in Thoracic Oncology Summit
Albuquerque, New Mexico | November 16 - 19, 2023

Neoadjuvant Immunotherapy Position

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TREATMENT STRATEGIES FOR PATIENTS WITH A RESECTABLE NSCLC IN 2023

1

NeoAdjuvant → Surgery

2

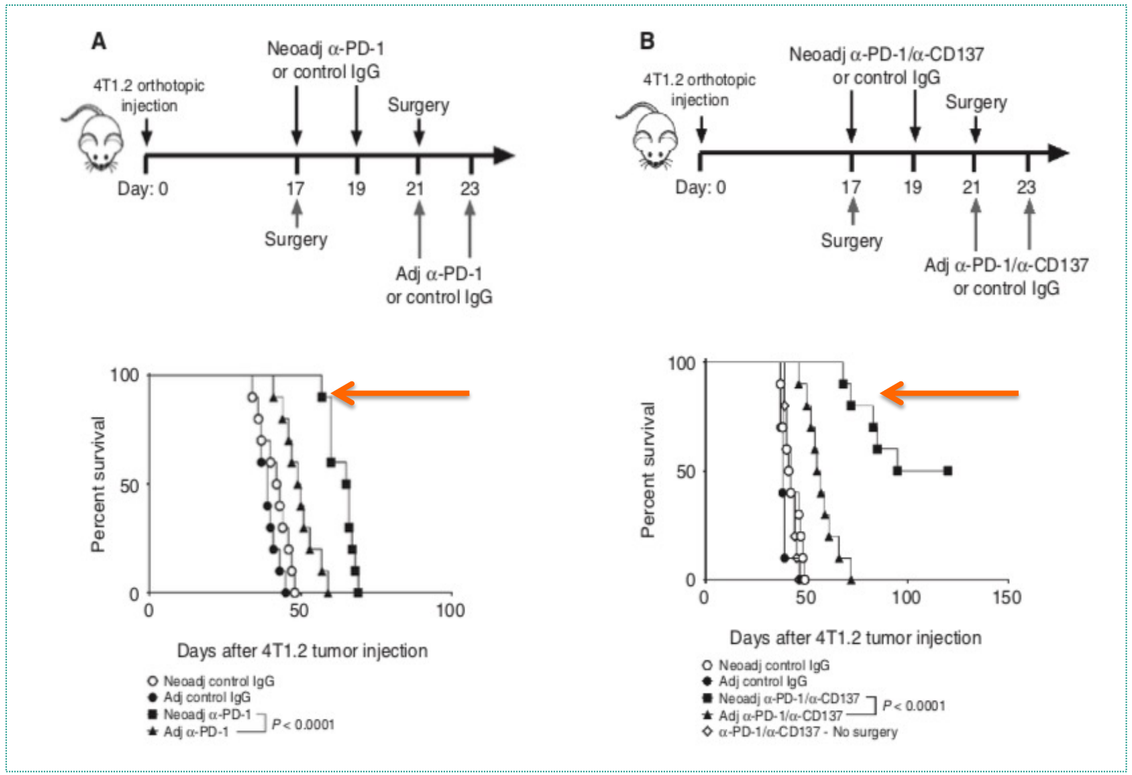
Surgery → Adjuvant

3

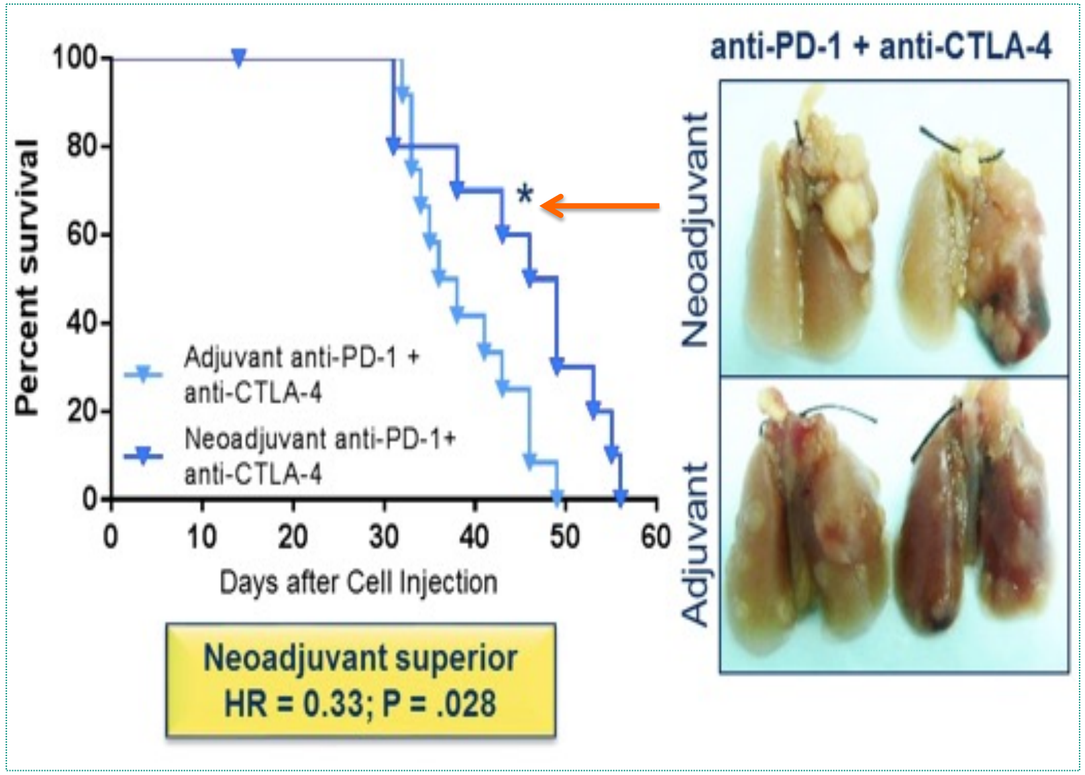
NeoAdjuvant → Surgery → Adjuvant

NEOADJ *vs.* ADJ in early stage?

Breast Model



NSCLC Model



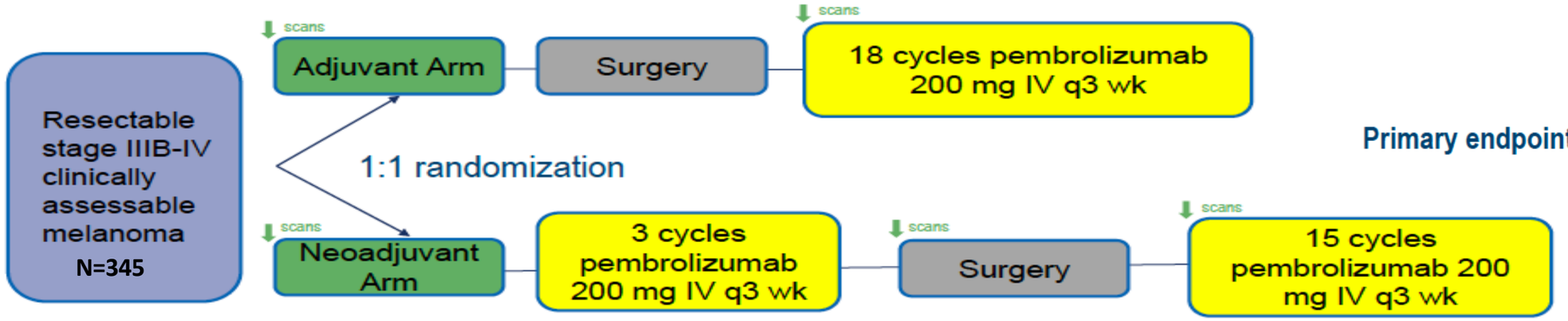
Preclinical benefit for neoadjuvant versus adjuvant immunotherapy. Do we have similar clinical data?

AT THE FOREFRONT
UChicago Medicine

Liu – Cancer Dis 2016 * Cascone – AACR 2019

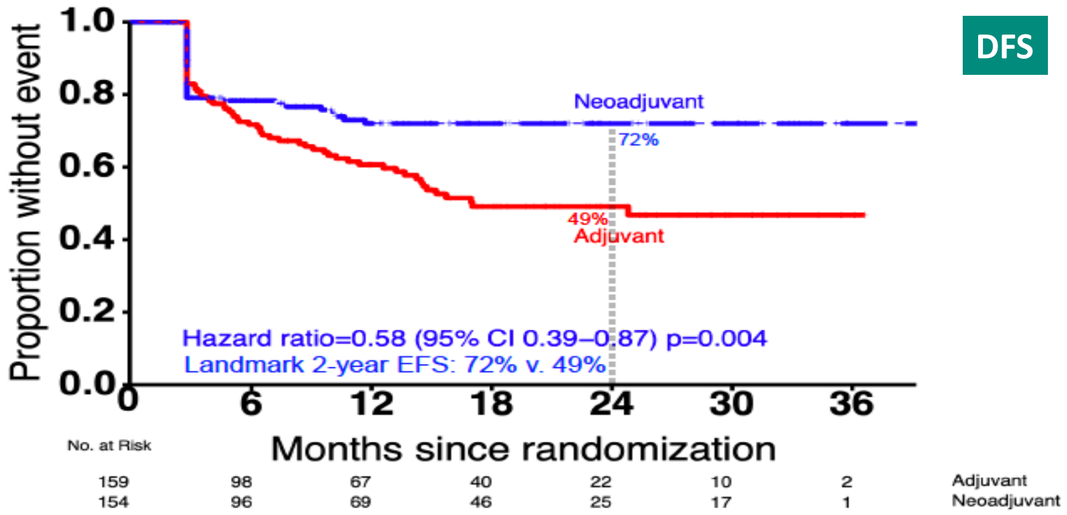
NEOADJ *vs*. ADJ in early stage?

SWOG 21801 in stage III-IV Melanoma



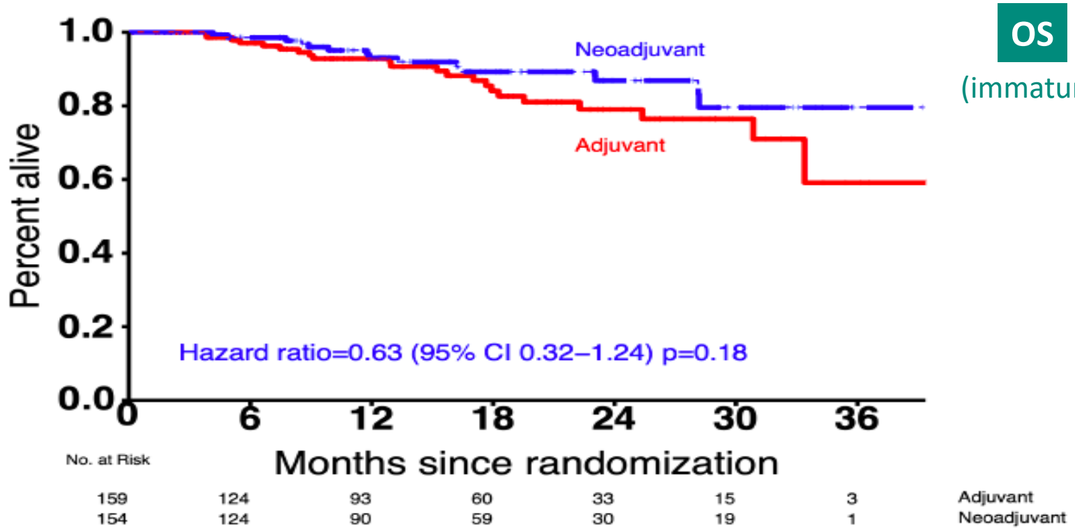
Primary endpoint: Event-free survival

DFS



OS

(immature)



Neo-adjuvant in the immunotherapy era

Checkmate 816

1

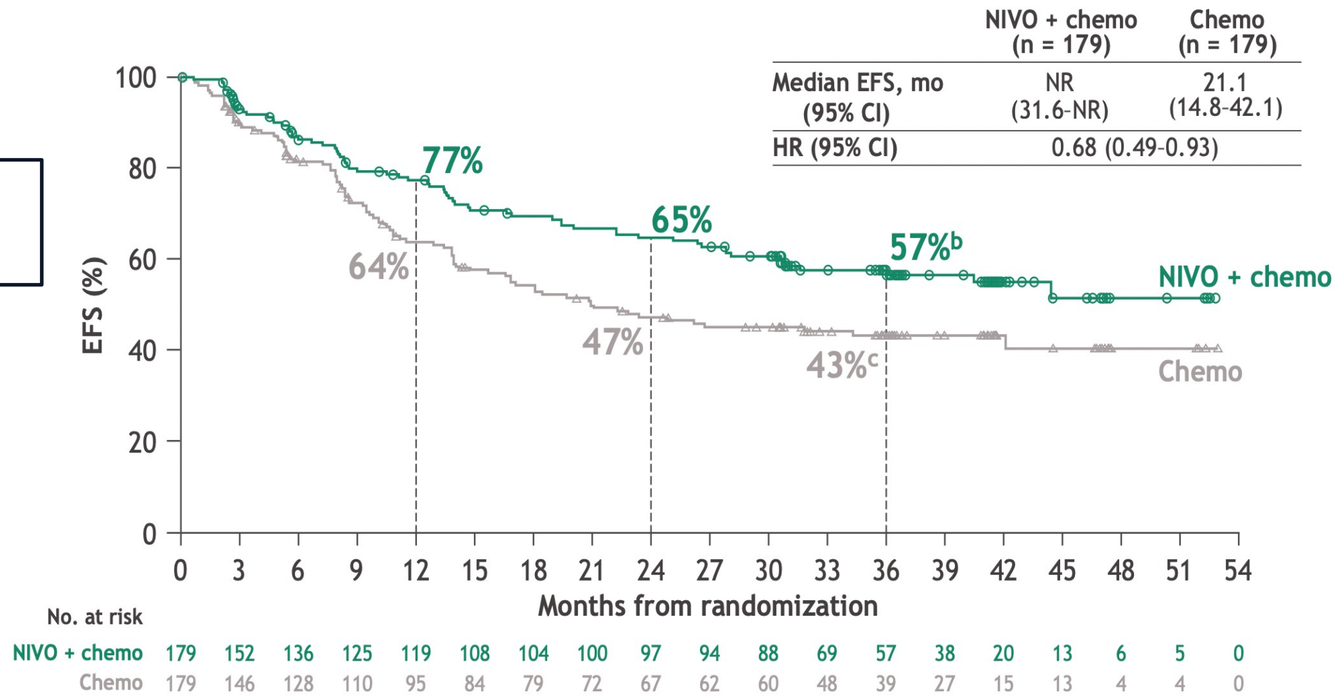
NeoAdjuvant

Surgery

HR 0.68 (0.49- 0.93)

MEDIAN FOLLOW-UP
41.4 MONTHS

EFS



Forde P, 2023 Neoadjuvant nivolumab plus platinum-doublet chemotherapy for resectable NSCLC:3-year update from CheckMate 816

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1

NeoAdjuvant

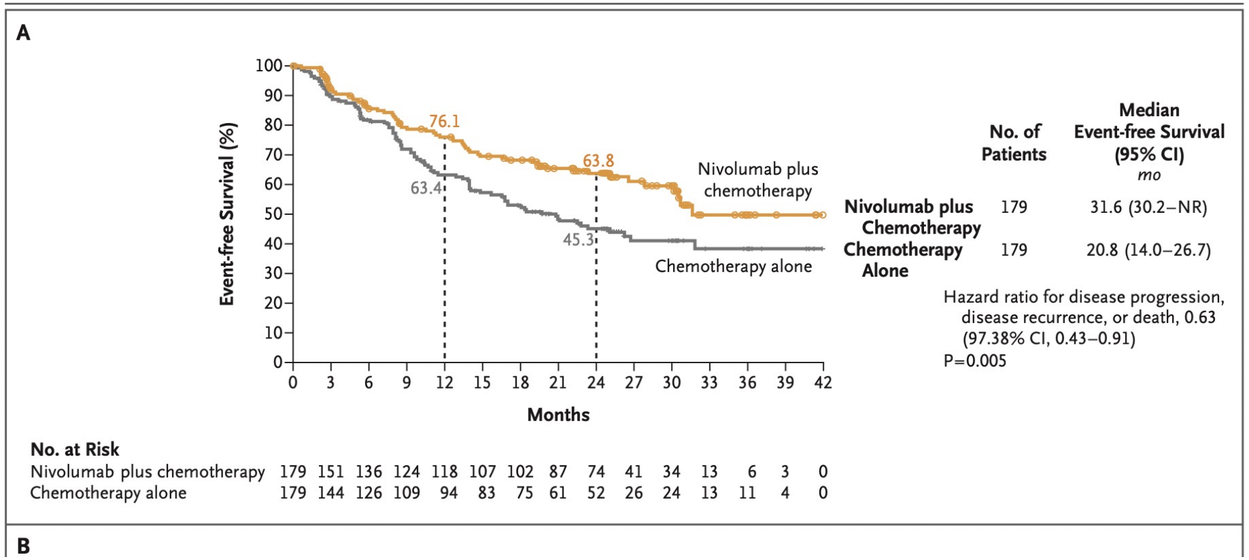
Surgery

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2022 VOL. 386 NO. 21

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*



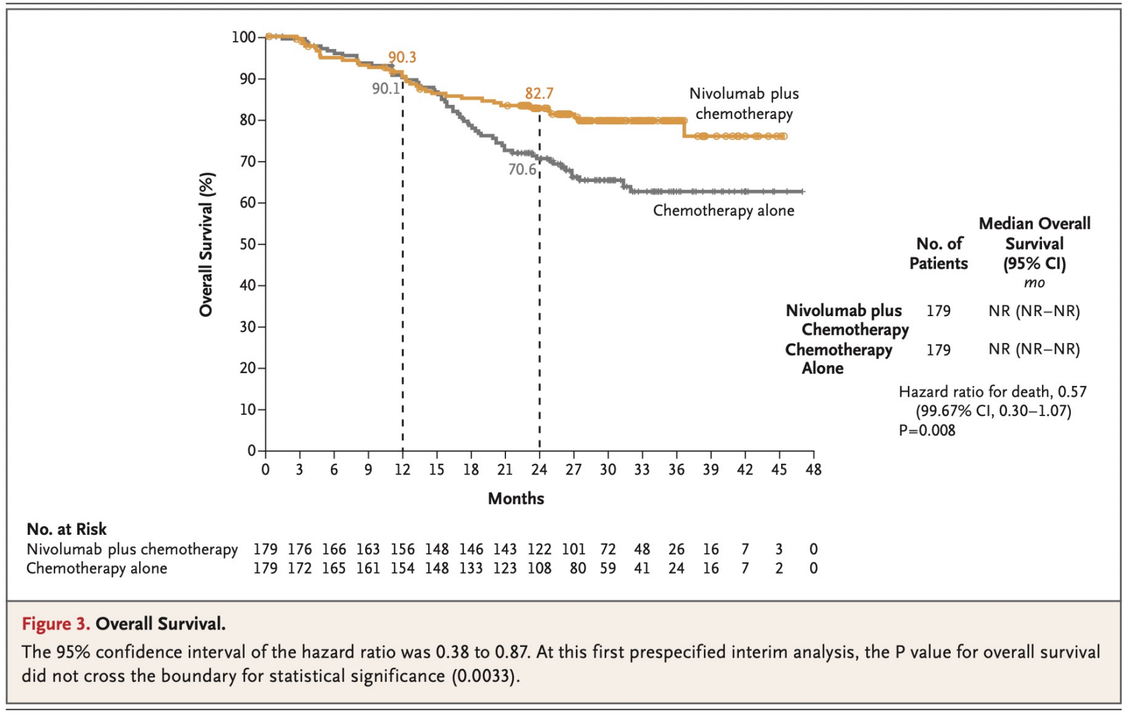


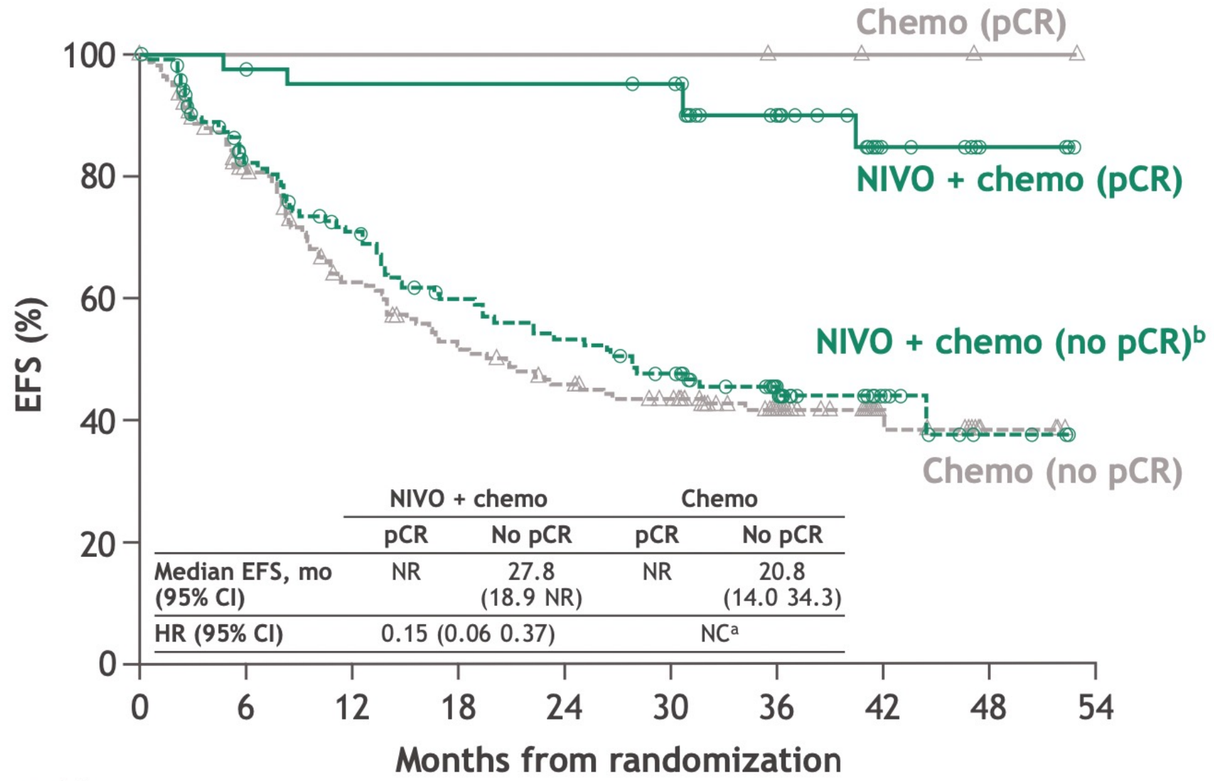
Figure 3. Overall Survival.

The 95% confidence interval of the hazard ratio was 0.38 to 0.87. At this first prespecified interim analysis, the P value for overall survival did not cross the boundary for statistical significance (0.0033).

AT THE FOREFRONT UChicago Medicine

Efficacy outcomes by pCR status in concurrently randomized patients

EFS

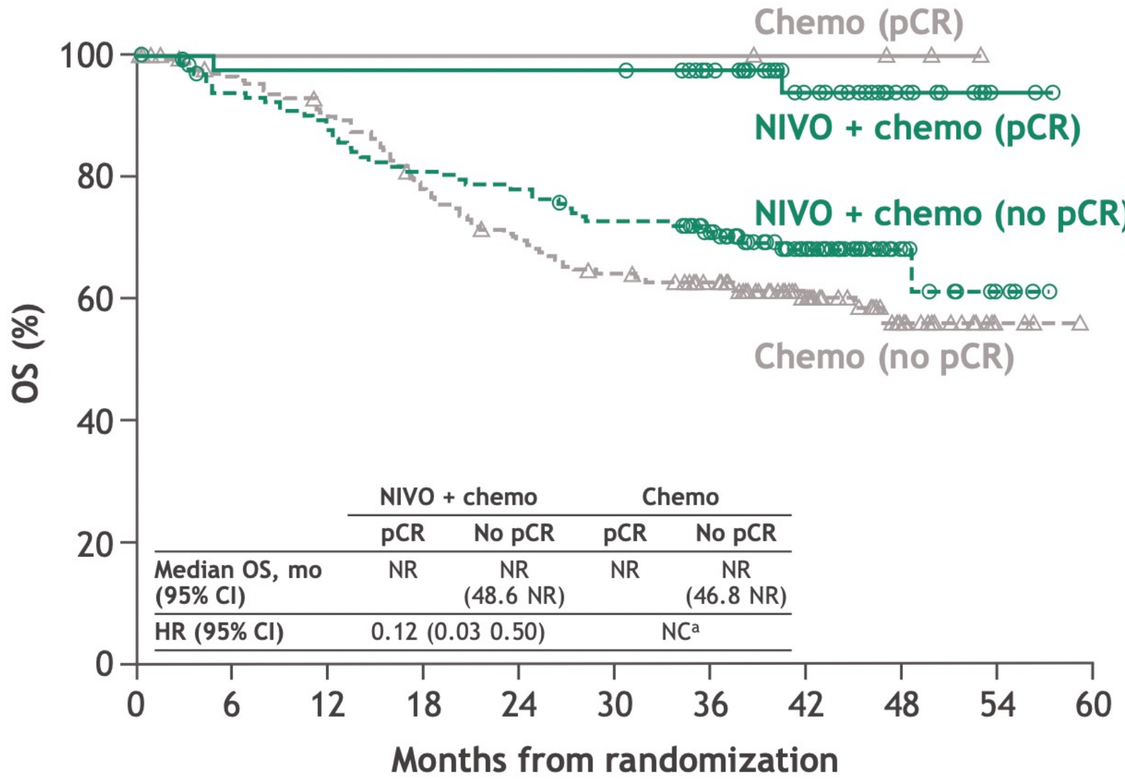


	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median EFS, mo (95% CI)	NR	27.8 (18.9 NR)	NR	20.8 (14.0 34.3)
HR (95% CI)	0.15 (0.06 0.37)		NC[a]	

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

OS



	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

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

[a]HR was NC for the chemo arm due to few patients having a pCR (n = 4). [b]EFS HR was 0.89 (95% CI, 0.64 1.22) for patients with NIVO + chemo vs chemo without pCR. [c]OS HR was 0.77 (95% CI, 0.52 1.14) for patients with NIVO + chemo vs chemo without pCR.

Adjuvant in the immunotherapy era

IMPOWER 010, KEYNOTE 091

Surgery

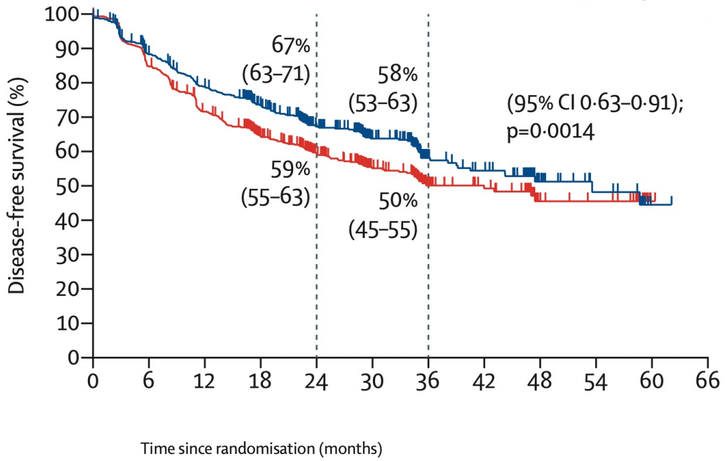
Adjuvant

HR 0.76 (0.63-0.91)

MEDIAN FOLLOW-UP
35.6 MONTHS

A

EFS



Number at risk number censored)												
Pembrolizumab	590	493	434	358	264	185	82	70	28	16	1	0
	(0)	(30)	(36)	(84)	(150)	(216)	(306)	(313)	(352)	(363)	(377)	(378)
Placebo	587	493	409	326	241	160	72	57	22	18	1	0
	(0)	(5)	(13)	(56)	(118)	(183)	(259)	(273)	(305)	(309)	(326)	(327)

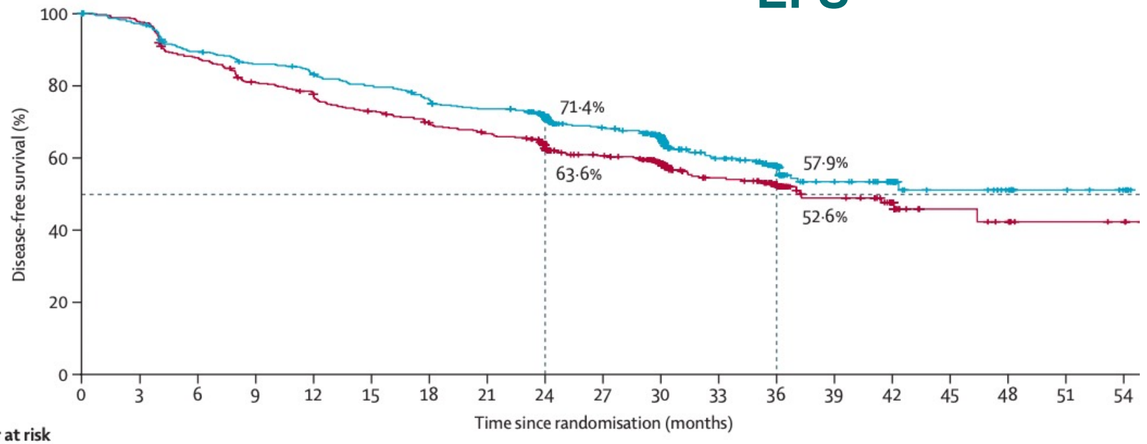
O'Brien M, Lancet Oncol 2022

HR 0.79 (0.64-0.96)

MEDIAN FOLLOW-UP
45.3 MONTHS

C

EFS



Number at risk (number censored)																			
Atezolizumab	507	478	437	418	403	387	367	353	306	257	212	139	97	53	38	19	14	8	4
	(0)	(15)	(18)	(20)	(21)	(22)	(23)	(25)	(62)	(99)	(135)	(192)	(230)	(268)	(283)	(301)	(306)	(312)	(316)
Best supportive care	498	467	418	383	365	342	324	309	269	219	173	122	90	46	30	13	10	5	4
	(0)	(19)	(21)	(24)	(26)	(27)	(30)	(31)	(57)	(95)	(134)	(175)	(203)	(243)	(258)	(274)	(276)	(281)	(282)

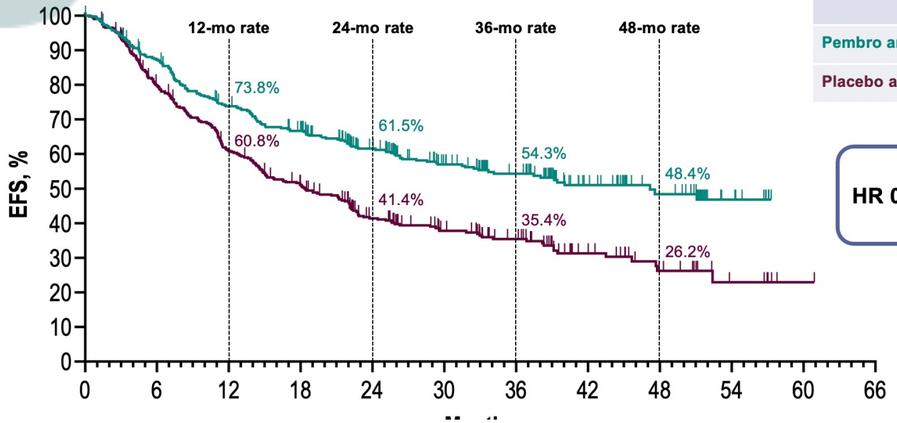
Wakelee H, Lancet 2021

Perioperative in the immunotherapy era

KEYNOTE671, AEGEAN, NEOTORCH, CHECKMATE 77T (EFS)

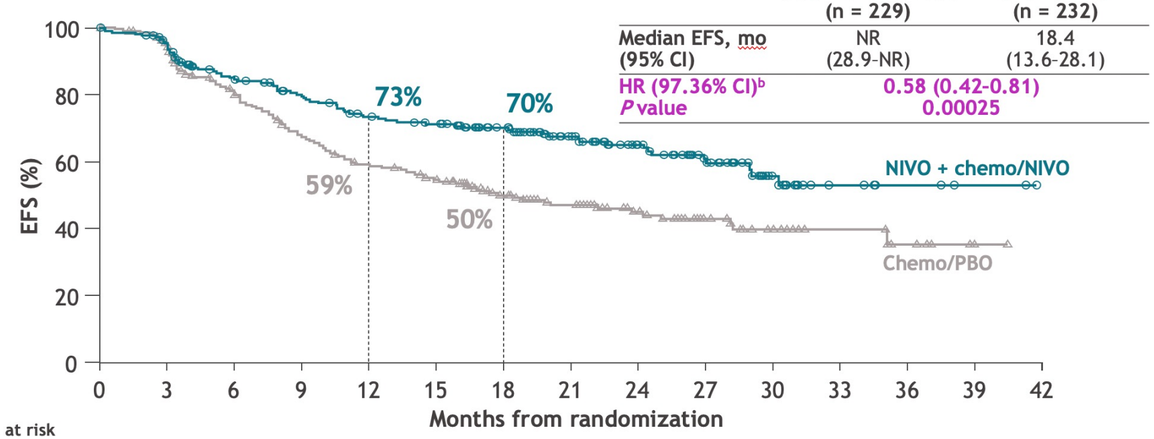
3

NeoAdjuvant | **Surgery** | **Adjuvant**



	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)

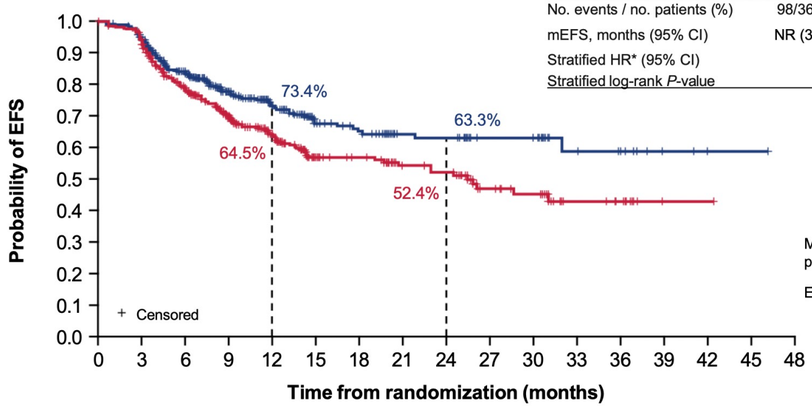
HR 0.59 (95% CI, 0.48-0.72)



	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)
Median EFS, mo (95% CI)	NR (28.9-NR)	18.4 (13.6-28.1)
HR (97.36% CI)[b]	0.58 (0.42-0.81)	
P value	0.00025	

No. at risk														
NIVO + chemo/NIVO	229	208	173	157	141	134	115	89	69	46	20	7	4	2	0
Chemo/PBO	232	204	165	138	118	106	78	59	44	29	19	10	6	1	0

- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41–0.76

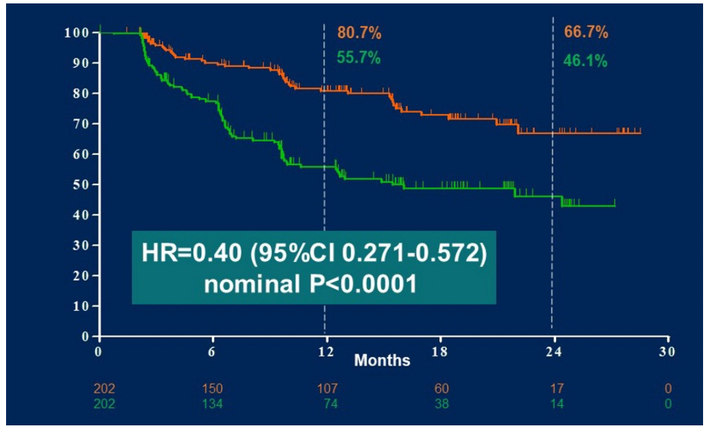


	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9 NR)	25.9 (18.9 NR)
Stratified HR* (95% CI)	0.68 (0.53 0.88)	
Stratified log-rank *P*-value	0.003902	

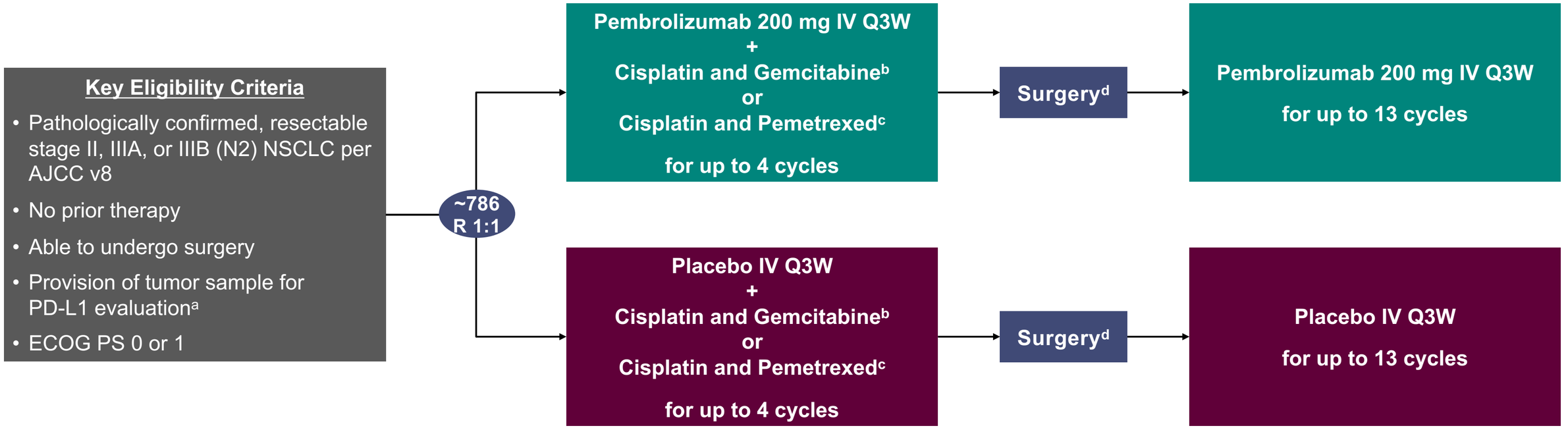
Median follow-up (range) in censored patients: 11.7 months (0.0 46.1)

EFS maturity: 31.9%

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



KEYNOTE-671 Study Design
Randomized, Double-Blind, Phase 3 Trial



Stratification Factors
- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

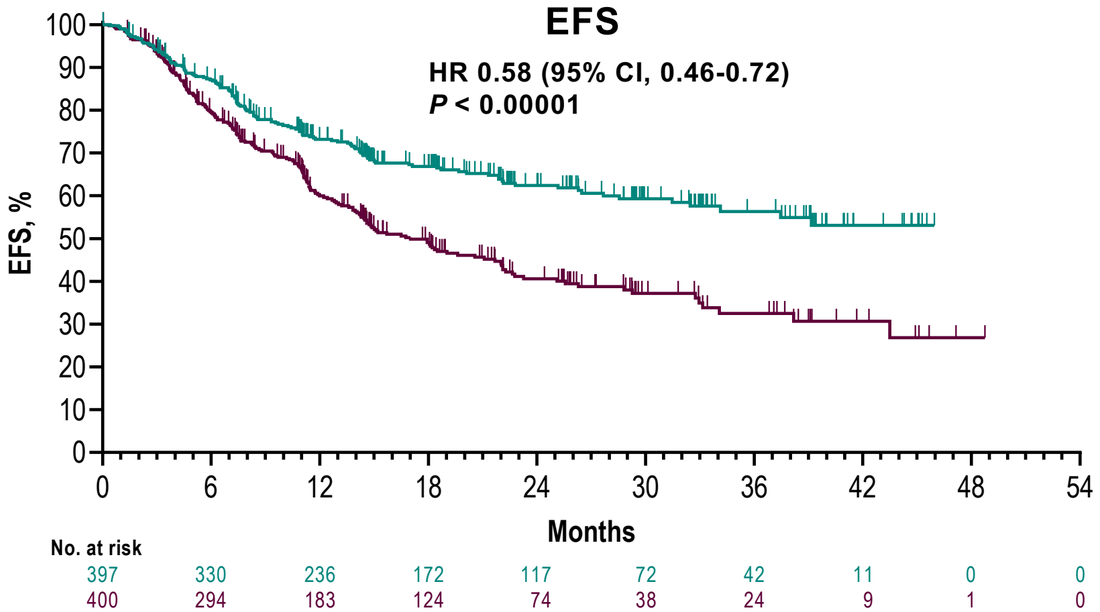
Key secondary end points: mPR and pCR per blinded, independent pathology review and safety

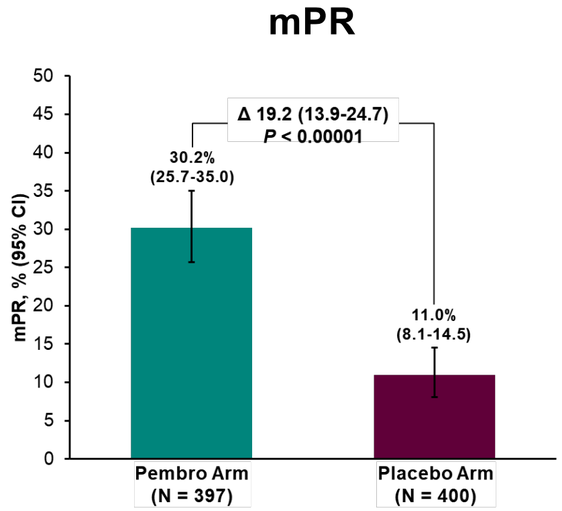
[a] Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. [b] Cisplatin 75 mg/m^2 IV Q3W + gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W was permitted for squamous histology only. [c] Cisplatin 75 mg/m^2 IV Q3W + pemetrexed 500 mg/m^2 IV Q3W was permitted for nonsquamous histology only. [d] Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease.
ClinicalTrials.gov identifier: NCT03425643.

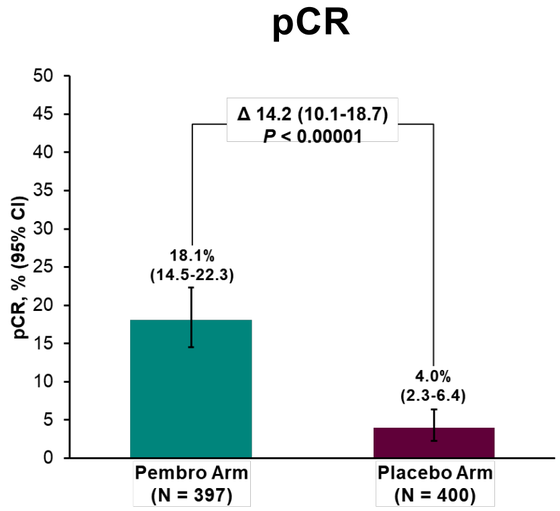
KEYNOTE-671 Results: Interim Analysis 1

Median Follow-Up[a]: 25.2 months (range, 7.5-50.6)

- Neoadjuvant pembrolizumab + chemotherapy followed by surgery and adjuvant pembrolizumab significantly improved EFS, mPR, and pCR compared with neoadjuvant chemotherapy and surgery alone
- AE profile was as expected based on the known profiles of the individual treatment components





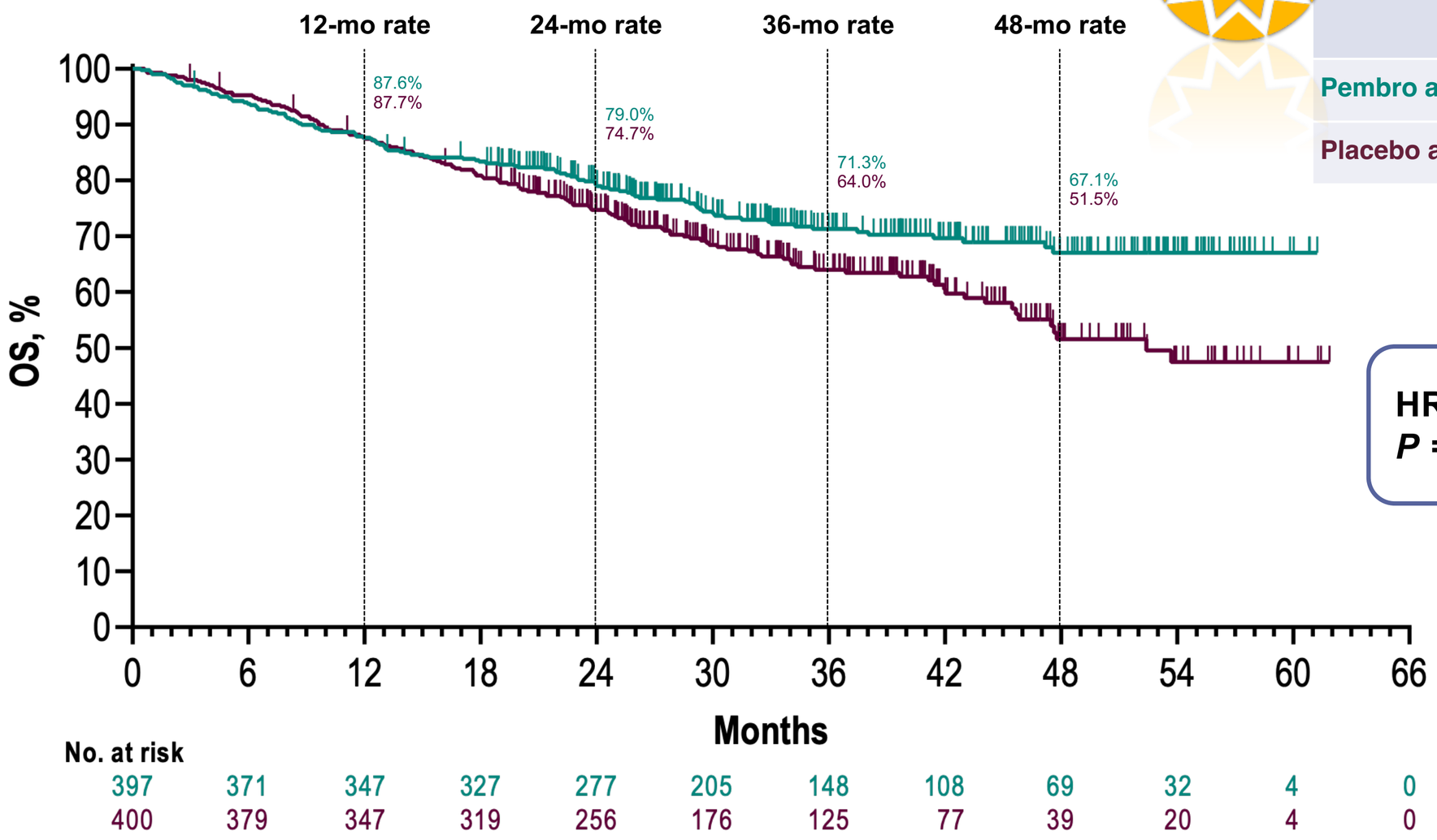


[a] Defined as time from randomization to data cutoff date of July 29, 2022.

Wakelee H et al. *N Engl J Med* 2023;389:491-503.

Overall Survival, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)



	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)
P = 0.00517[a]

OS defined as time from randomization to death from any cause. [a] Significance boundary at IA2, *P* = 0.00543.
Data cutoff date for IA2: July 10, 2023.

Open questions

1. Are all the perioperative combos similar in terms of efficacy?
2. Should we give perioperative/neoadjuvant to Stage II?
3. Should we give perioperative/neoadjuvant to PD-L1 negative?
4. Is perioperative superior to Neoadjuvant only?

Differences among perioperative trials

	KN671 (N=786) %	AEGEAN (N=802) %	NEOTORCH (N=404) %	CM 77T (N=358) %
MALE	70.3	68.9	89.6	73
SQUAMOUS	43.1	46.2	77.7	51
STAGE II	29.7	28.4	NA	35
STAGE IIIA	54.7	47.3	NA	64
STAGE IIIB	15.6	24.0	NA	-
PNEUMONECTOMY ALLOWED	YES	NO	YES	YES
EGFR/ALK	YES	NO	YES	NO
REGIMEN	CIS ONLY	INVESTIGATOR CHOICE	INVESTIGATOR CHOICE	INVESTIGATOR CHOICE
N CYCLES	UP to 4 CYCLES	4	3	4
PRIMARY ENDPOINT	EFS & OS	pCR, EFS	EFS, MPR	EFS
FOLLOW UP (MOs)	36.6	11.7	NA	25.4

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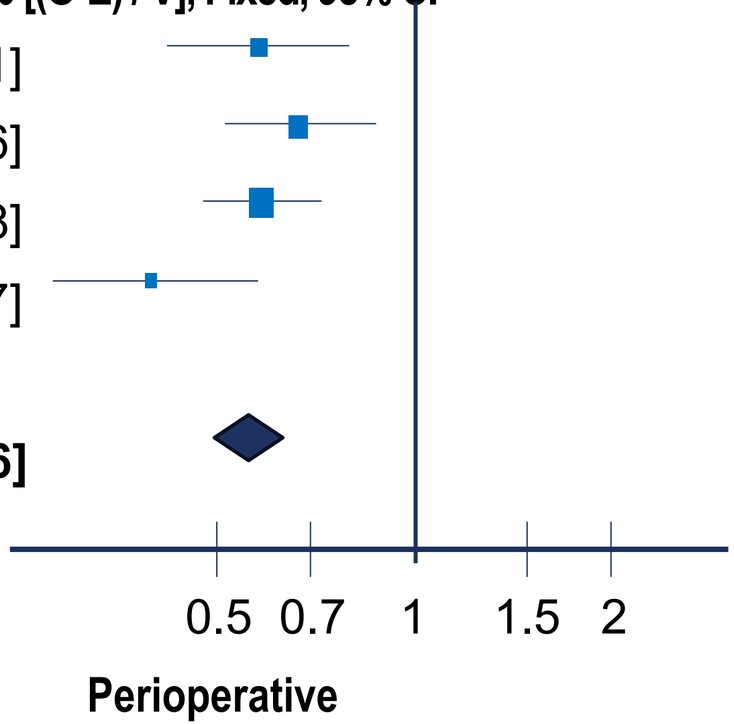
Are all the perioperative trials the same?

YES!

			Placebo		Hazard Ratio
	Events	Total	Events	Total	Exp [(O-E) / V], Fixed, 95% CI
77T	52	229	90	232	0.58 [0.42, 0.81]
Aegean	98	366	138	374	0.67 [0.51, 0.86]
Keynote671	174	397	248	400	0.68 [0.53, 0.88]
Neotorch	47	202	97	202	0.40 [0.28, 0.57]
Total (95% CI)		**1194**		**1208**	**0.58 [0.50, 0.66]**
Total events	371		573		

Heterogeneity: $Chi^2 = 5.31$, df = 3 (P = 0.15); $I^2 = 43\%$

Test for overall effect: Z = 8.15 (P < 0.00001)



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Should we treat also stage II?

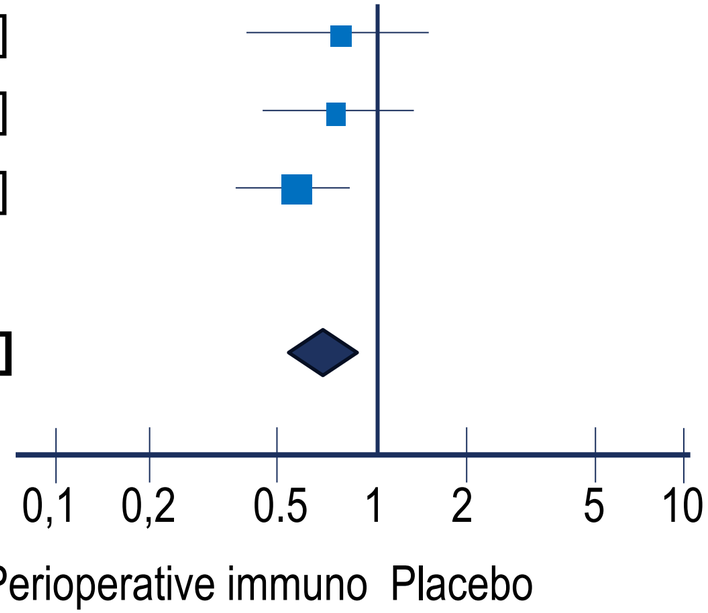
(20% cancelled surgeries across trials)

YES!

Study or Subgroup	Perioperative Immunothery Events	Total	Placebo Events	Total	Hazard Ratio Exp [(O-E) / V], Fixed, 95% CI
77T	22	81	26	81	0.81 [0.46, 1.43]
Aegean	21	104	27	110	0.76 [0.43, 1.34]
Keynote671	37	118	62	121	0.59 [0.40, 0.88]
Total (95% CI)		**303**		**312**	**0.68 [0.51, 0.90]**
Total events	80		115		

Heterogeneity: $Chi^2 = 1.01$, df = 2 (P = 0.60); $I^2 = 0\%$

Test for overall effect: Z = 2.70 (P = 0.007)



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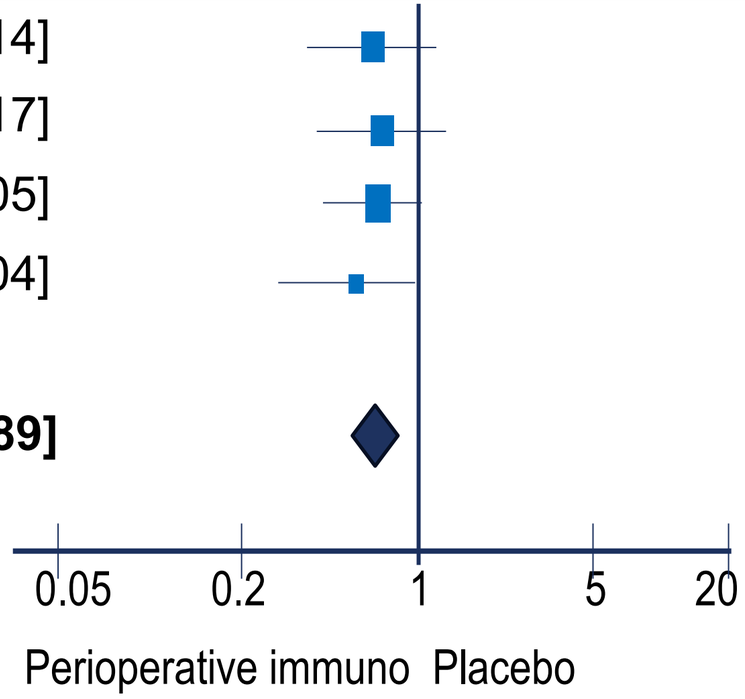
Should we treat also PD-L1 negative?

YES!

Study or Subgroup	Perioperative immuno		Placebo		Hazard Ratio
	Events	Total	Events	Total	Exp [(O-E) / V], Fixed, 95% CI
77T	33	93	44	93	0.73 [0.47, 1.14]
Aegean	35	122	46	125	0.76 [0.49, 1.17]
Keynote671	58	138	77	151	0.75 [0.54, 1.05]
Neotorch	17	69	30	70	0.59 [0.33, 1.04]
Total (95% CI)		**422**		**439**	**0.72 [0.58- 0.89]**
Total events	143		197		

Heterogeneity: $Chi^2 = 0.59$, df = 3 (P = 0.90); $I^2 = 0\%$

Test for overall effect: Z = 2.99 (P = 0.003)



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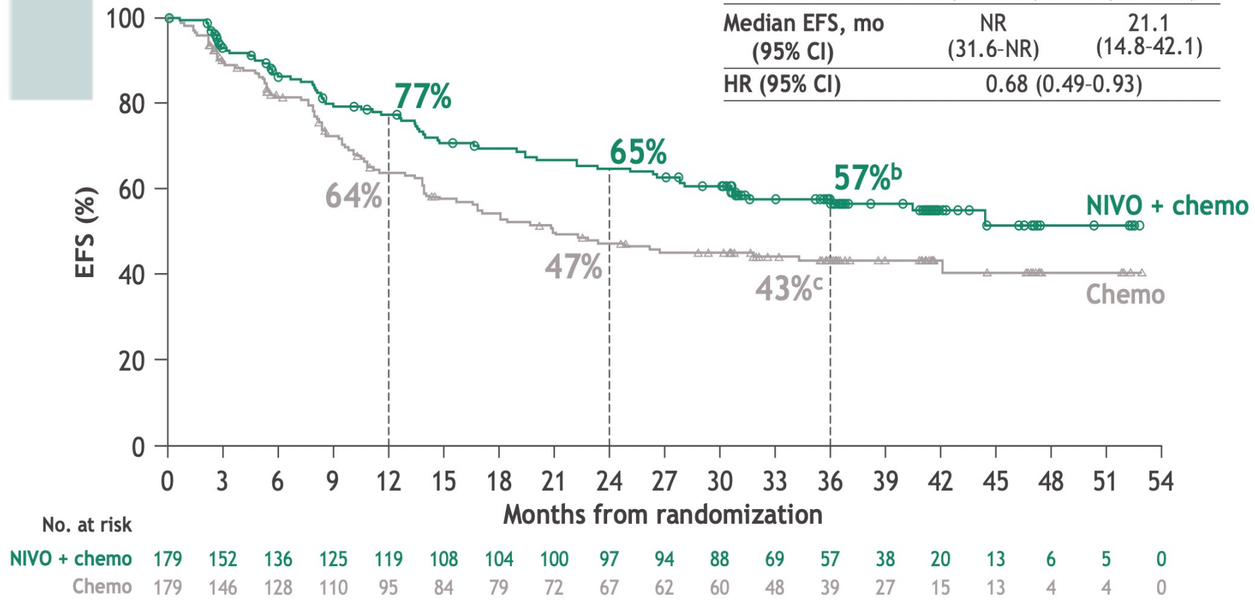
Is the perioperative superior to neoadjuvant only?

1

NeoAdjuvant | Surgery

CM 816



	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo (95% CI)	NR (31.6-NR)	21.1 (14.8-42.1)
HR (95% CI)	0.68 (0.49-0.93)	

No. at risk

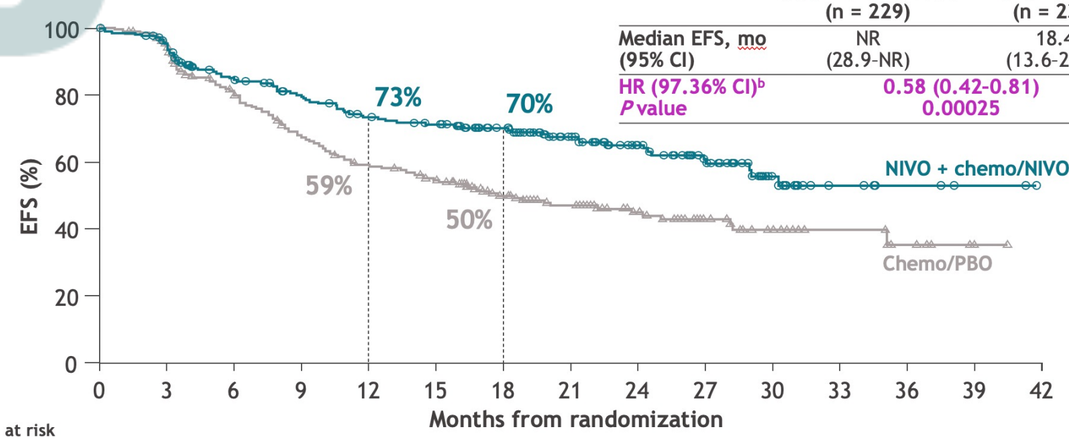
NIVO + chemo	179	152	136	125	119	108	104	100	97	94	88	69	57	38	20	13	6	5	0
Chemo	179	146	128	110	95	84	79	72	67	62	60	48	39	27	15	13	4	4	0

HR 0.68 (0.49-0.93)

3

NeoAdjuvant | Surgery | Adjuvant

77T



	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)
Median EFS, mo (95% CI)	NR (28.9-NR)	18.4 (13.6-28.1)
HR (97.36% CI)[b]	0.58 (0.42-0.81)	
P value	0.00025	

No. at risk

NIVO + chemo/NIVO	229	208	173	157	141	134	115	89	69	46	20	7	4	2	0
Chemo/PBO	232	204	165	138	118	106	78	59	44	29	19	10	6	1	0

- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41-0.76

HR 0.58 (0.42-0.81)

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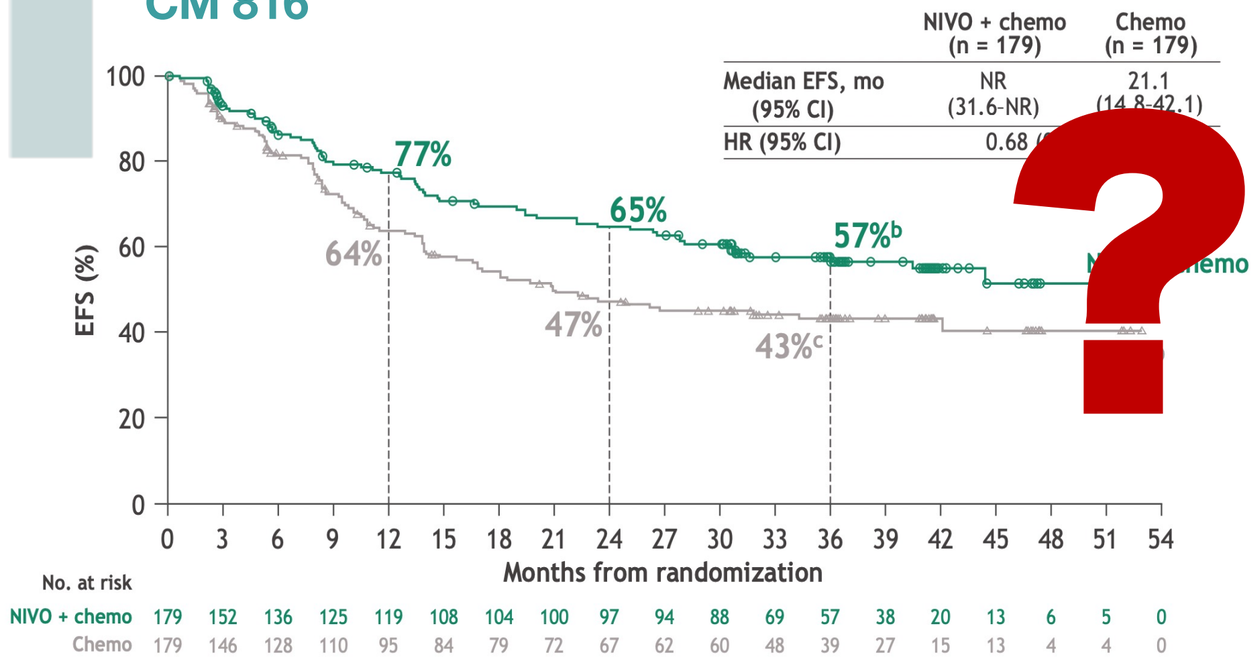
Is the perioperative superior to neoadjuvant only?

1

NeoAdjuvant | Surgery

CM 816

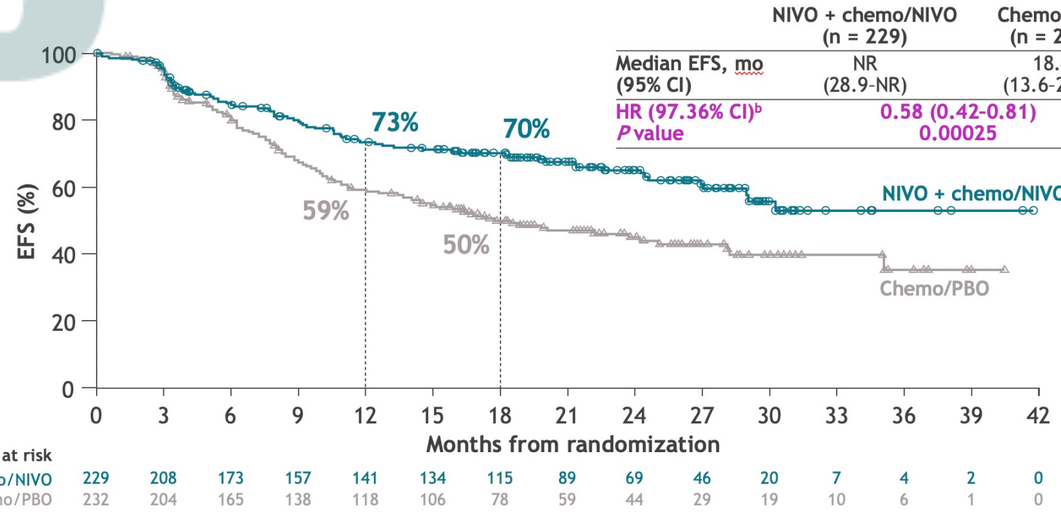


HR 0.68 (0.49-0.93)

3

NeoAdjuvant | Surgery | Adjuvant

77T



- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41-0.76

HR 0.58 (0.42-0.81)

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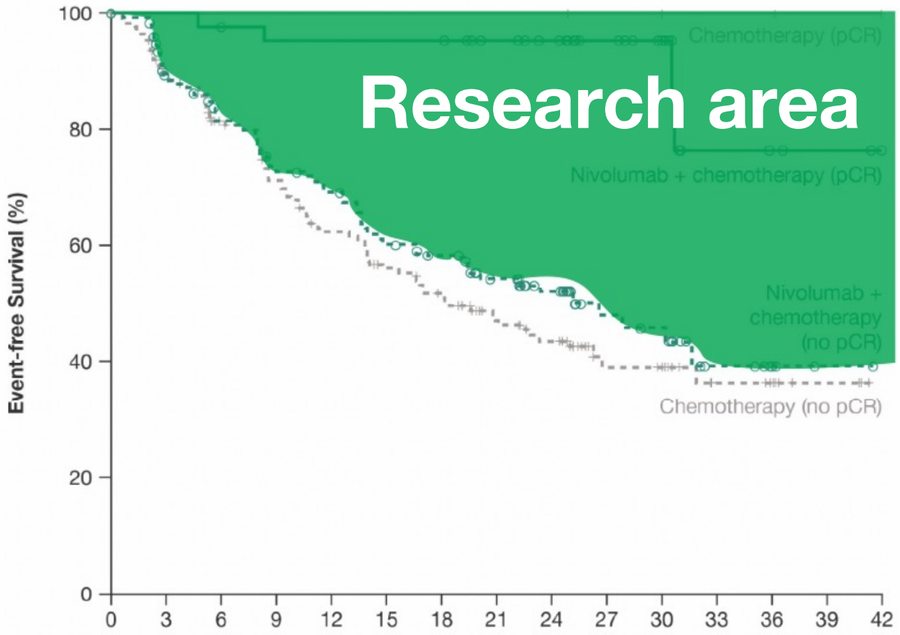
For non pCR more research is needed
Biomarkers, ctDNA, new drugs

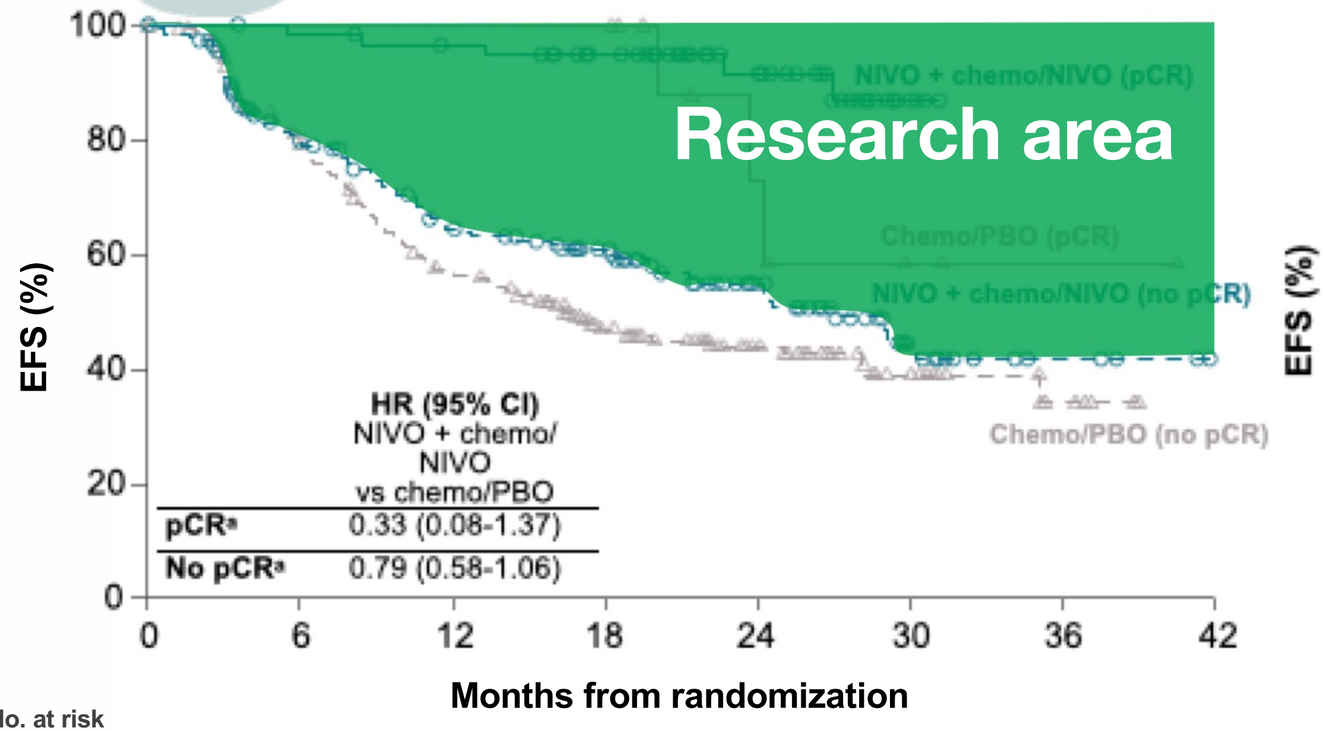
1 CHECKMATE 816

	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†	



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

3 77T



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 MPR
No pCR	221	154	107	67	39	17	5	0	No MPR

Conclusions

- Strong rationale for the use of a neoadjuvant strategy over adjuvant
- 20% cancelled surgeries among trials
- All patients with resectable Stage II and III should be offered 3-4 cycles neoadjuvant chemo IO treatment
- Benefit independent by PD-L1, but stronger in PD-L1>50%
- cPR is the most relevant prognostic factor
- Perioperative showed with KN671an OS benefit
- Benefit of adjuvant after neoadjuvant is still debatable