University of Colorado Cancer Center
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Neoadjuvant and adjuvant therapy for Early Stage NSCLC

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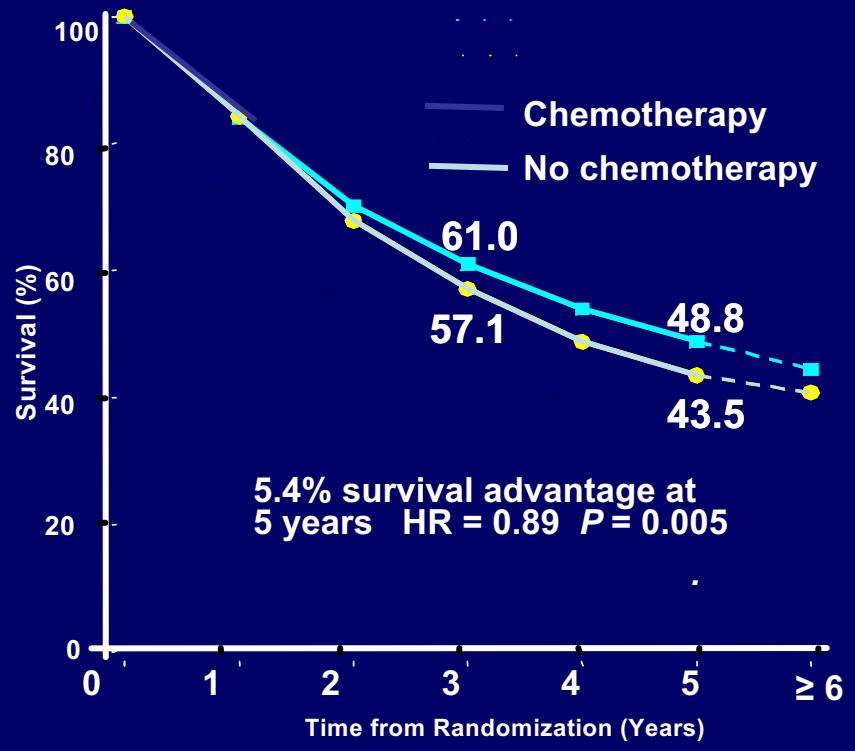
Disclosures: BOD: Verastem; DMC: BMS, Merck, Daiichi; Ad Board: Genentech, Lilly

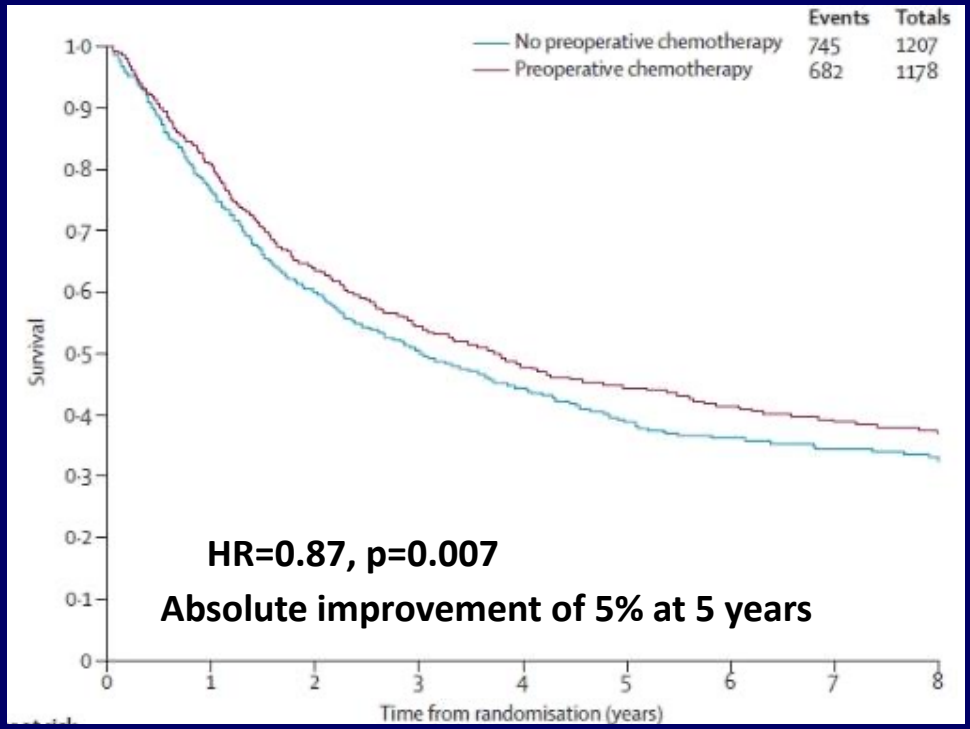
Meta-analyses of Adjuvant CT and Neoadjuvant CT

Path CR Rates <5%

LACE: Pooled Adjuvant Data Overall Survival



NSCLC Neoadjuvant Collaborative Group meta-analysis



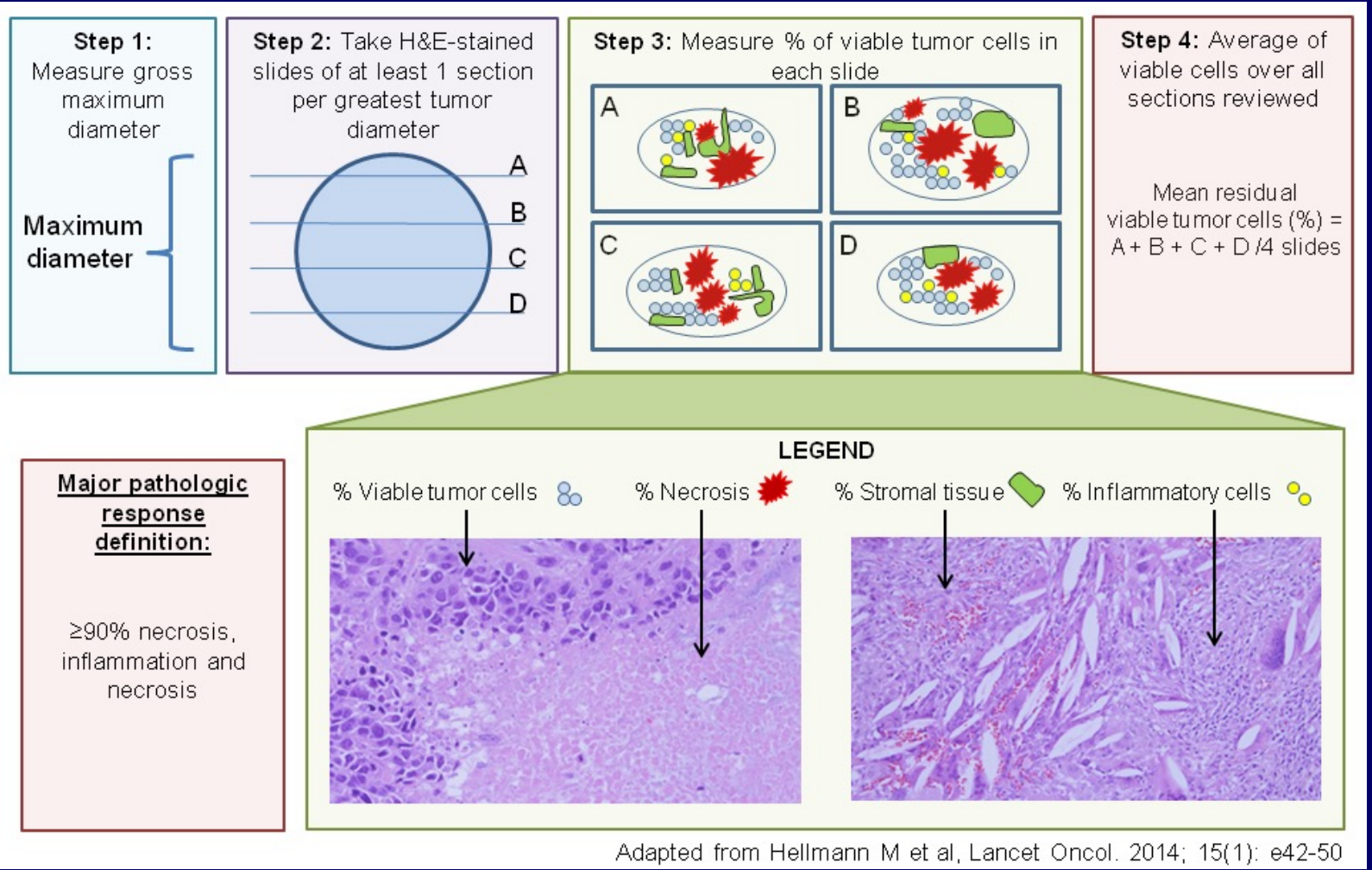
Pignon JP, et al. J Clin Oncol. 2008;26:3552-3559

Lancet 2014;303:1561-71

Randomized neoadjuvant trials: CT+ IO vs CT

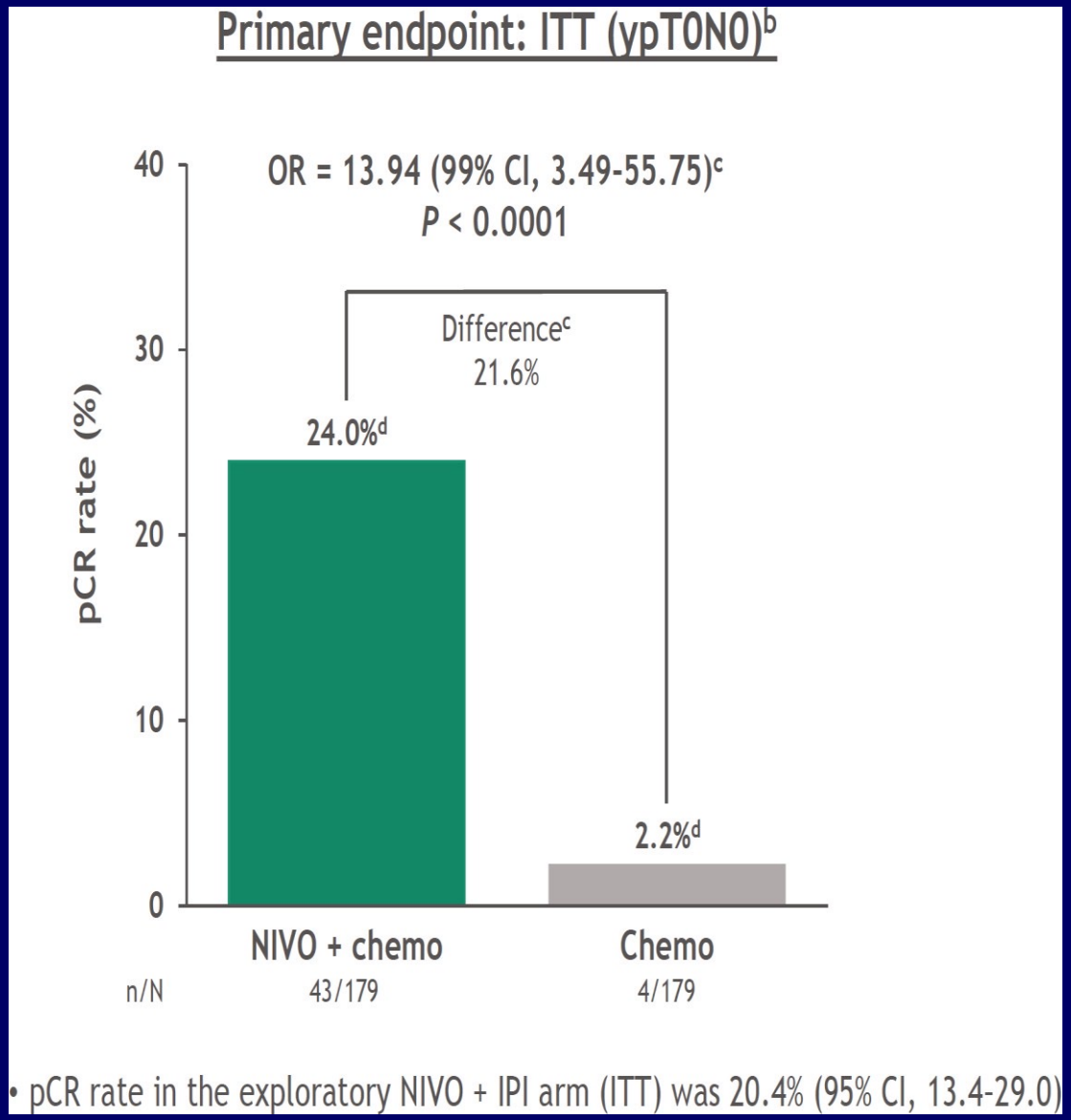
Study	PreopRX	PostopRX	Stages	#	1 Endpoint
CM 816	CT+Nivo X3	None	IB-IIIA	350	EFS,MPR
KN 617	CT+Pembrox4	Pembro x 13	IIB-IIIA	786	EFS,OS
Agean	CT+Durvax4	Durva x 12	IIA-IIIB	300	MPR
ImPower030	CT+Atezo x4	Atezo x 16	II-IIIB	374	MPR
NeoTorch	CT+toripalimab	CTx1,torix 13	II-IIIA	500	EFS,MPR
CM77T	CT+Nivox3	Nivo X13	II-IIIA	280	EFS,MPR

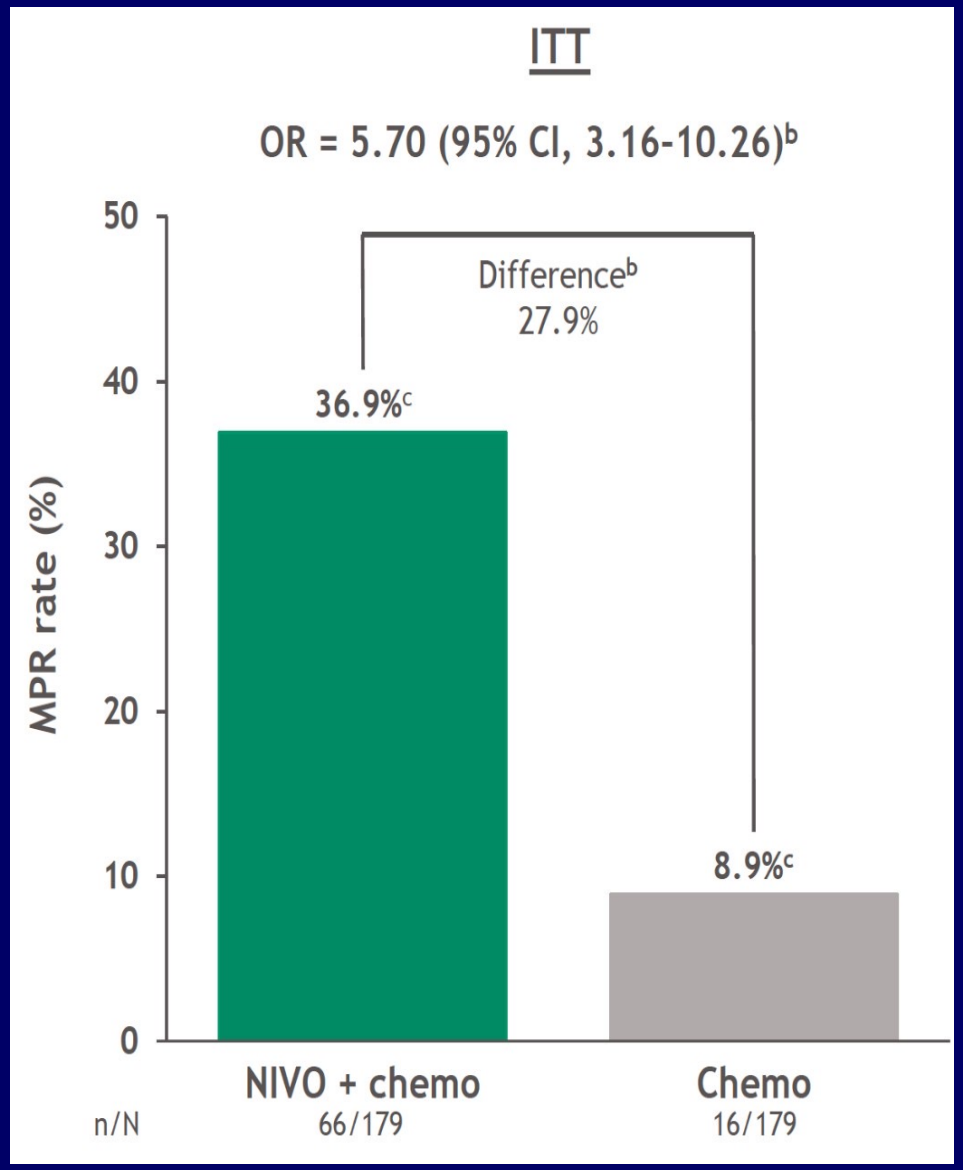
Pathologic response assessment



Adapted from Hellmann M et al, Lancet Oncol. 2014; 15(1): e42-50

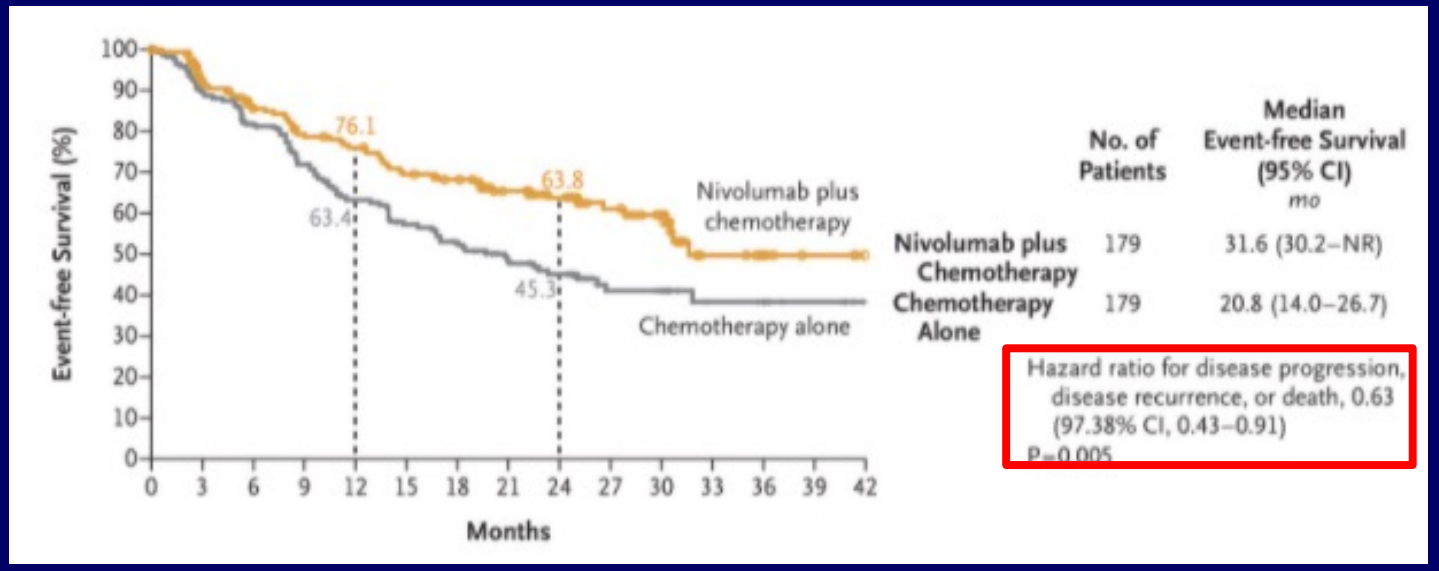
CM816 – pCR and MPR in ITT population





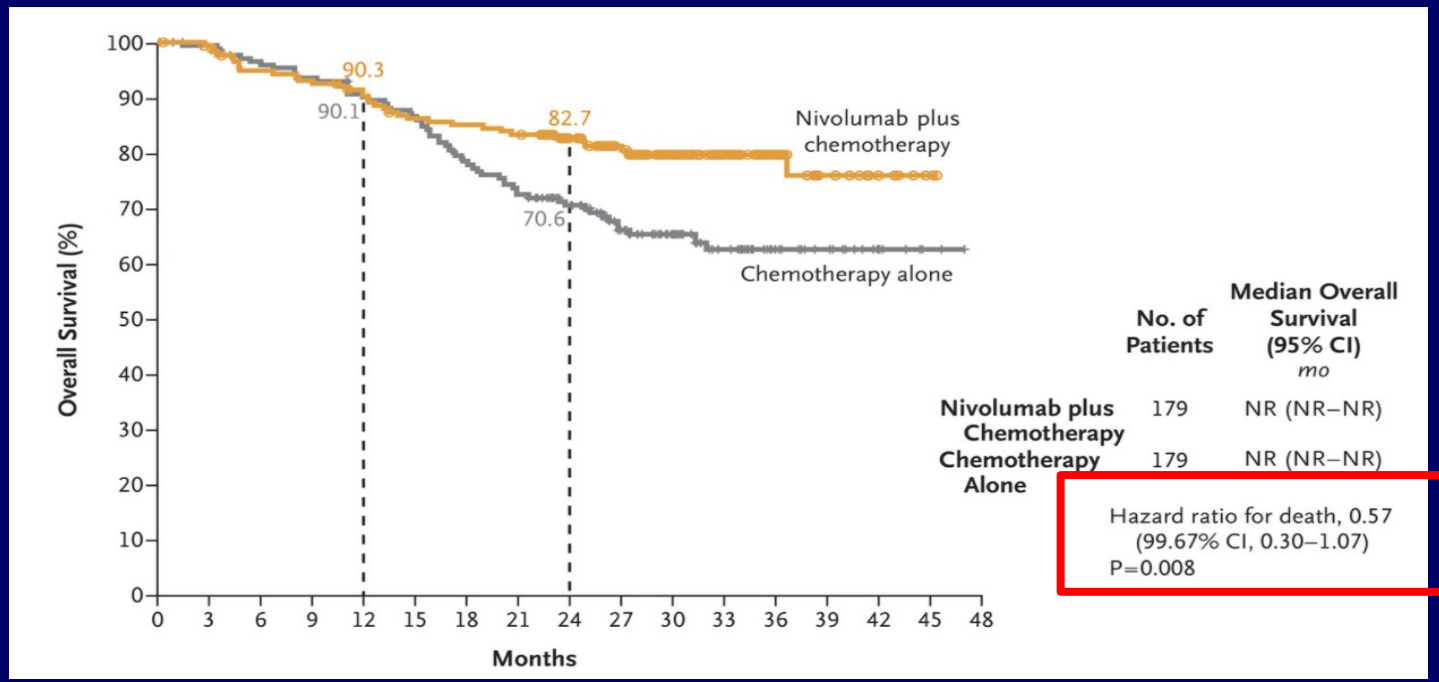
Forde CM816, AACR2021

CM816:Neoadjuvant Nivo +CT in Early Stage NSCLC



	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

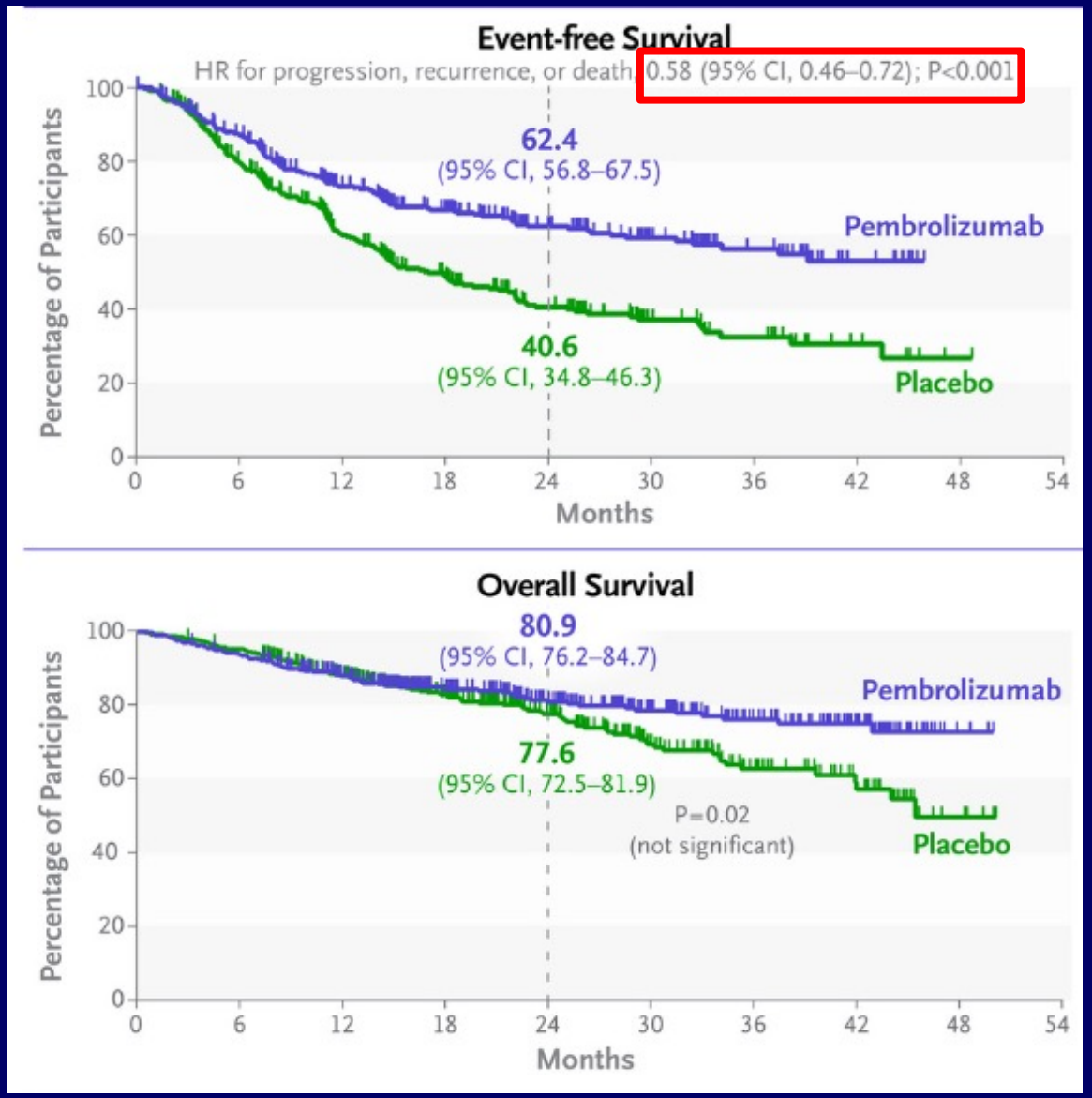


	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57 (99.67% CI, 0.30–1.07)
P=0.008

Forde PM et al: Neoadjuvant Nivolumab plus Chemotherapy in resectable lung cancer. NEJM2022

KN671 Perioperative Pembro/CT vs CT

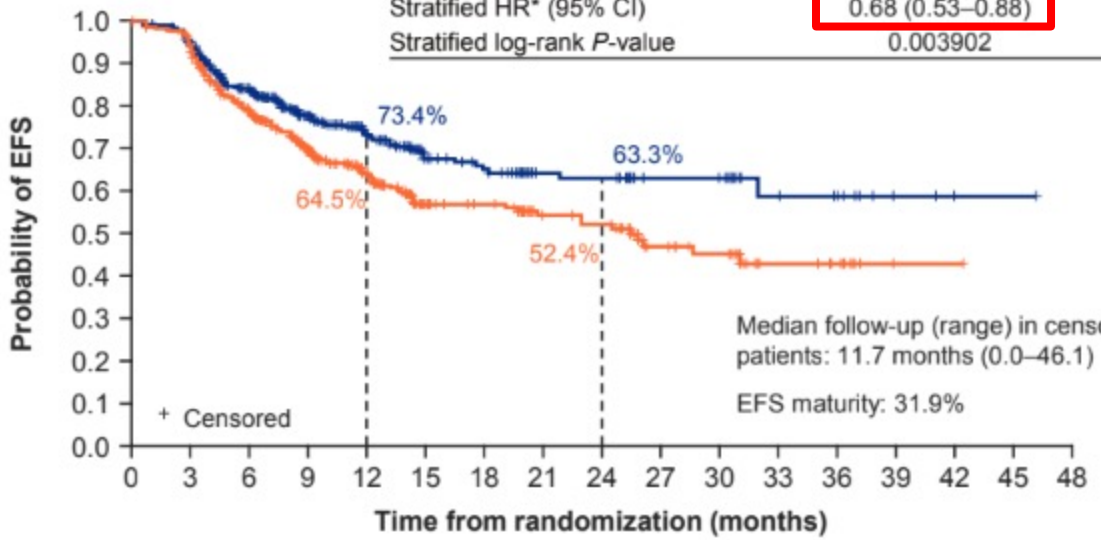


Wakelee H et al;NEJM 2023;389:491-503

Aegean Trial
Primary endpoints: EFS and pCR (mITT)[1]

First planned interim analysis

	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	



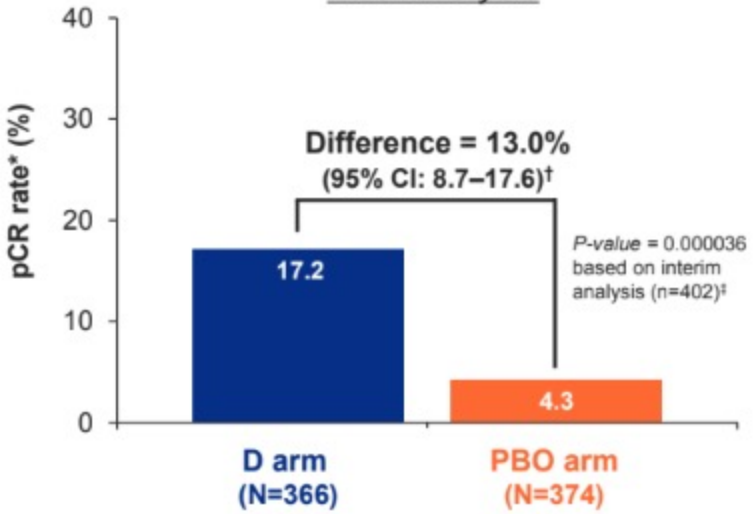
No. at risk:

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

EFS is defined as time from randomization to the earliest of: (A) 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 favors the D arm versus the PBO arm. Median and landmark estimates calculated using the Kaplan–Meier method; HR calculated using a stratified Cox proportional hazards model; and *P*-value calculated using a stratified log rank test. Stratification factors: disease stage (II vs III) and PD-L1 expression status (<1% vs ≥1%). Significance boundary = 0.009899 (based on total 5% alpha), calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary. mEFS, median EFS; NR, not reached; PD, progressive disease.

DCO = Nov 10, 2022. D, Durvalumab; PBO, placebo.

Final analysis



*Using IASLC recommendations for pathologic assessment of response to therapy, including gross assessment and processing of tumor bed (Travis WD, et al. *J Thorac Oncol* 2020;15:709-40). †CI calculated by stratified Miettinen and Nurminen method. ‡No formal statistical testing was performed at the pCR final analysis (DCO: Nov 10, 2022; N=740 [data shown]). Statistical significance was achieved at the interim pCR analysis (DCO: Jan 14, 2022; n=402; *P*-value for pCR/MPR calculated using a stratified Cochran-Mantel-Haenszel test with a significance boundary = 0.000082 calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary).

[1]Heymach JV, et al. *Cancer Res* 2023; 83 (8_Supplement):CT005.

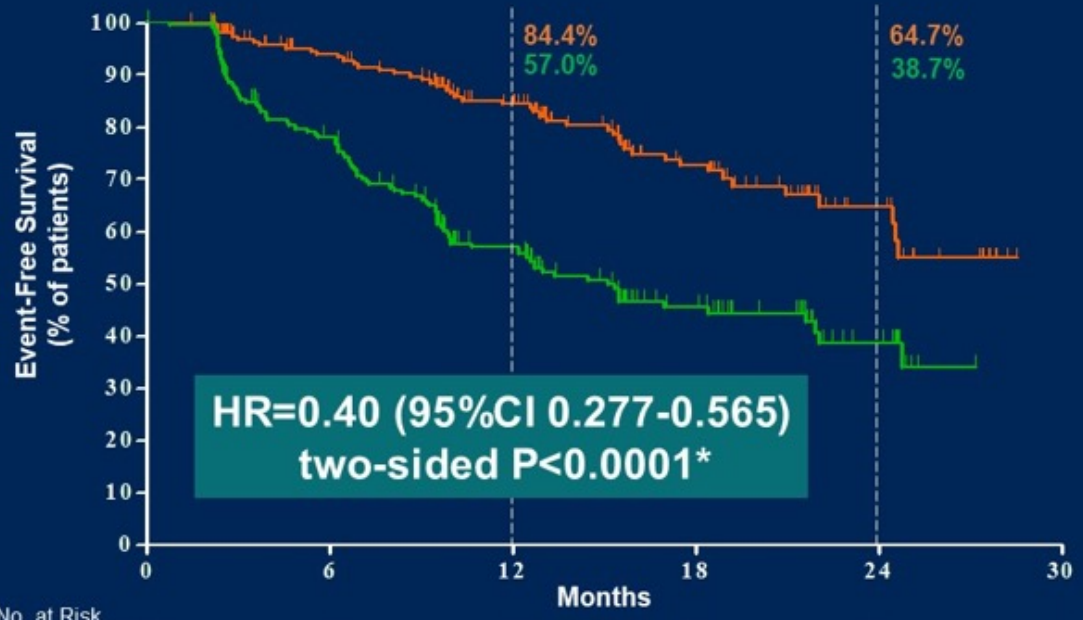
Event-Free Survival Analysis: Neo-TORCH

Intent-to-treat Stage III patients assessed by investigator per RECIST v1.1

EFS by investigator

	No. of Events/ No. of Patients	Median EFS *mos.* (95% CI)
Toripalimab + chemo	47/202	NE (24.4, NE)
Placebo + chemo	97/202	15.1 (10.6, 21.9)

Median follow-up: 18.25 months



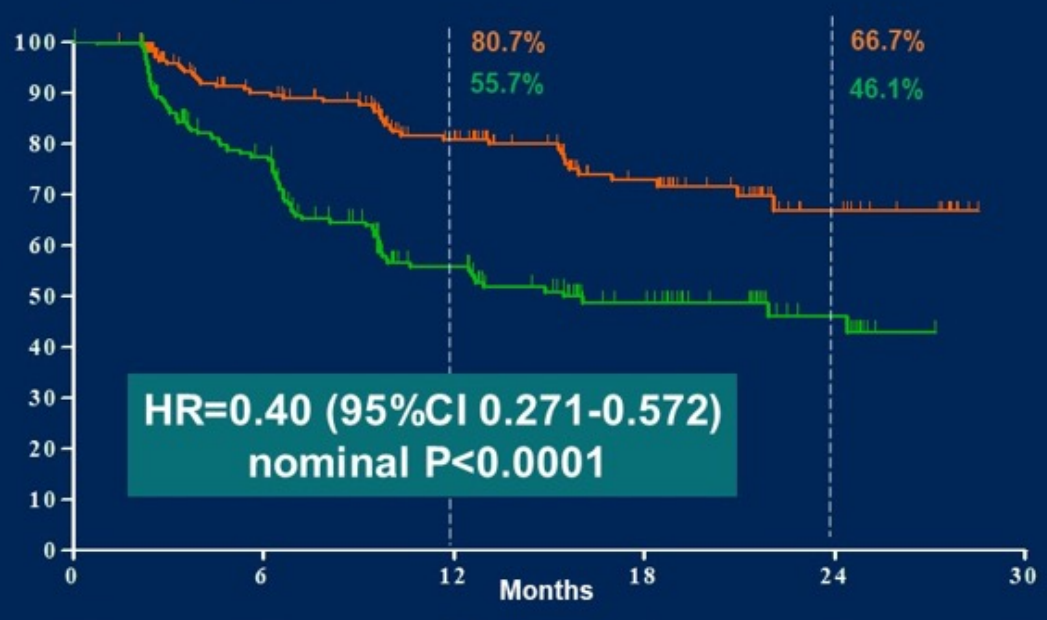
No. at Risk						
Toripalimab + chemo	202	156	116	66	23	0
Placebo + chemo	202	139	86	43	15	0

*2-sided efficacy boundary: 0.01683

EFS by IRC

	No. of Events/ No. of Patients	Median EFS *mos.* (95% CI)
Toripalimab + chemo	43/202	NE (NE, NE)
Placebo + chemo	87/202	15.5 (9.9, NE)

Median follow-up: 18.25 months



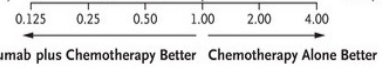
	202	150	107	60	17	0
	202	134	74	38	14	0

NE: not evaluable
HR; Hazard ratio
CI: confidence interval
Data cutoff date: Nov. 30, 2022

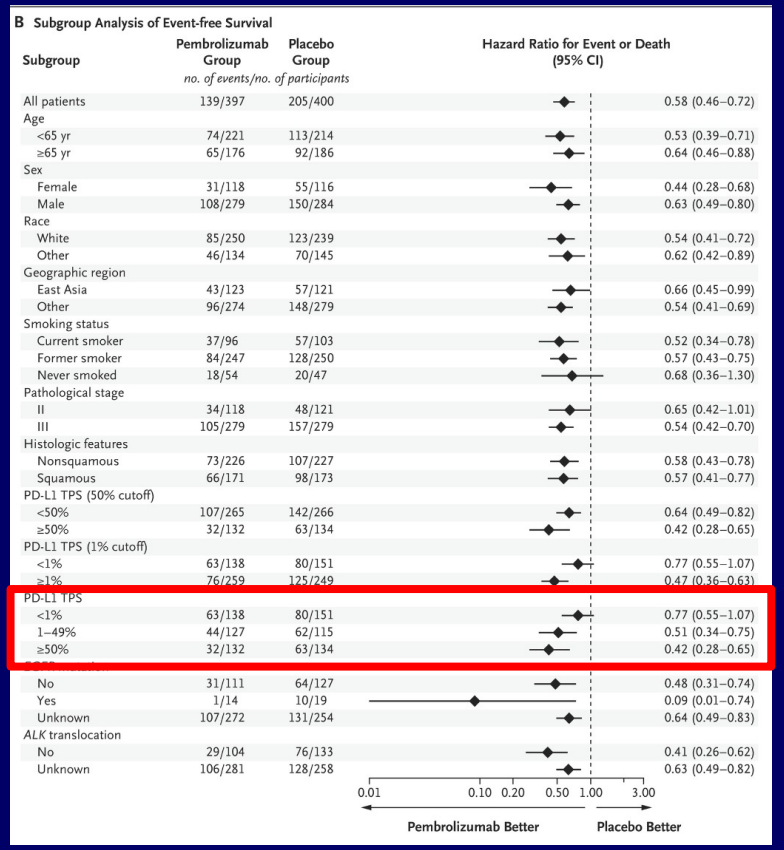
Forest plot of EFS in CM816, KN671 & Aegean

CM 816

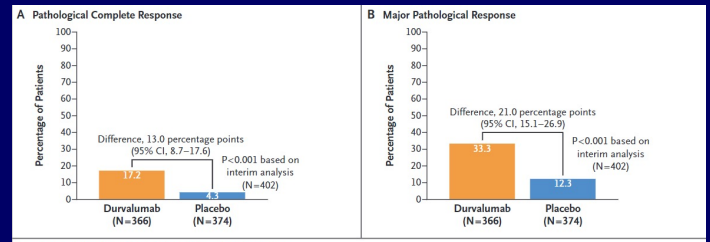
Subgroup	No. of Patients	Median Event-free Survival (95% CI): Nivolumab plus chemotherapy (N=179)	Median Event-free Survival (95% CI): Chemotherapy alone (N=179)	Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
		mo		
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)	0.63 (0.45–0.87)
Age				
<65 yr	176	NR (31.6–NR)	20.8 (14.0–NR)	0.57 (0.35–0.93)
≥65 yr	182	30.2 (23.4–NR)	18.4 (10.6–31.8)	0.70 (0.45–1.08)
Sex				
Male	255	30.6 (20.0–NR)	16.9 (13.8–24.9)	0.68 (0.47–0.98)
Female	103	NR (30.5–NR)	31.8 (13.9–NR)	0.46 (0.22–0.96)
Geographic region				
North America	91	NR (25.1–NR)	NR (12.8–NR)	0.78 (0.38–1.62)
Europe	66	31.6 (13.4–NR)	21.1 (10.2–NR)	0.80 (0.36–1.77)
Asia	177	NR (30.2–NR)	16.5 (10.8–22.7)	0.45 (0.29–0.71)
ECOG performance-status score				
0	241	NR (30.2–NR)	22.7 (16.6–NR)	0.61 (0.41–0.91)
1	117	30.5 (14.6–NR)	14.0 (9.8–26.2)	0.71 (0.41–1.21)
Disease stage at baseline				
IB or II	127	NR (27.8–NR)	NR (16.8–NR)	0.87 (0.48–1.56)
IIIA	228	31.6 (26.6–NR)	15.7 (10.8–22.7)	0.54 (0.37–0.80)
Histologic type of tumor				
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)	0.77 (0.49–1.22)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)	0.50 (0.32–0.79)
Smoking status				
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)	0.68 (0.48–0.96)
Never smoked	39	NR (5.6–NR)	10.4 (7.7–20.8)	0.33 (0.13–0.87)
PD-L1 expression level				
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)	0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)	0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)	0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)	0.24 (0.10–0.61)
TMB				
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)	0.86 (0.47–1.57)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)	0.69 (0.33–1.46)
Type of platinum therapy				
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)	0.71 (0.49–1.03)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)	0.31 (0.14–0.67)



KN 671

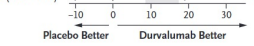


AEGEAN



C Subgroup Analysis for Pathological Complete Response

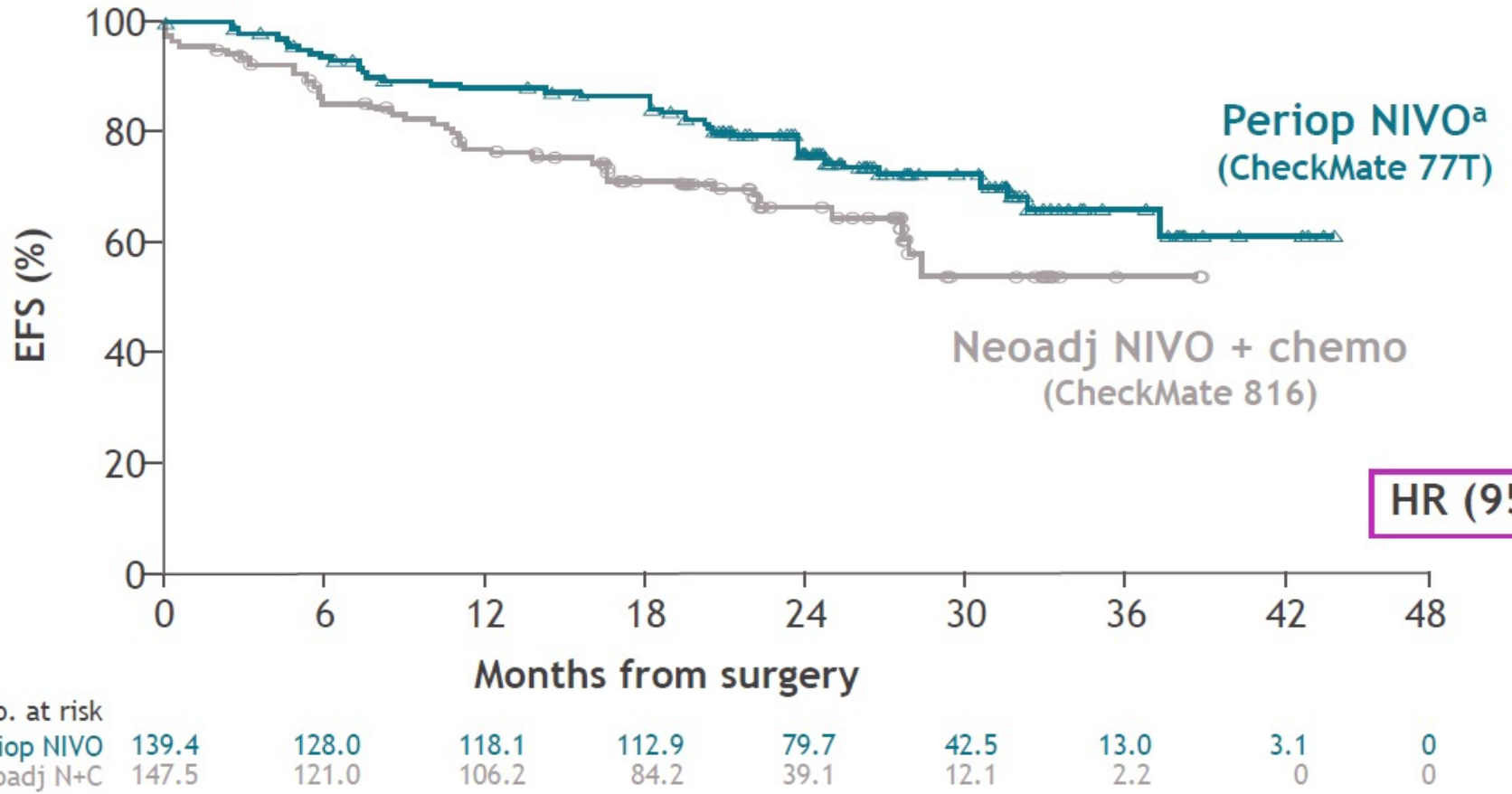
Subgroup	No. of Patients	Pathological Complete Response (95% CI): Durvalumab	Pathological Complete Response (95% CI): Placebo	Difference in Pathological Complete Response (95% CI)
		percent		*percentage points*
All patients	740	17.2 (13.5 to 21.5)	4.3 (2.5 to 6.9)	13.0 (8.7 to 17.6)
Age at randomization				
<65 yr	358	18.3 (12.9 to 24.8)	3.8 (1.6 to 7.7)	14.5 (8.3 to 21.3)
≥65 yr	382	16.2 (11.3 to 22.2)	4.7 (2.2 to 8.8)	11.5 (5.6 to 17.9)
Sex				
Male	530	19.4 (14.7 to 24.9)	4.7 (2.5 to 7.9)	14.8 (9.5 to 20.5)
Female	210	12.3 (6.9 to 19.7)	3.1 (0.6 to 8.9)	9.2 (2.0 to 16.9)
ECOG performance-status score				
0	506	16.7 (12.3 to 21.9)	5.1 (2.7 to 8.6)	11.6 (6.4 to 17.3)
1	234	18.3 (11.7 to 26.5)	2.5 (0.5 to 7.2)	15.7 (8.6 to 24.1)
Race				
Asian	307	18.2 (12.2 to 25.5)	4.3 (1.7 to 8.6)	13.9 (7.2 to 21.5)
Non-Asian	433	16.6 (12.0 to 22.1)	4.3 (2.0 to 8.0)	12.3 (6.8 to 18.2)
Geographic region				
Asia	305	18.3 (12.3 to 25.7)	4.3 (1.7 to 8.6)	14.0 (7.2 to 21.7)
Europe	281	19.9 (13.6 to 27.4)	5.0 (2.0 to 10.0)	14.9 (7.5 to 22.8)
North America	86	14.0 (5.3 to 27.9)	2.3 (0.1 to 12.3)	11.6 (0.0 to 25.4)
South America	68	7.5 (1.6 to 20.4)	3.6 (0.1 to 18.3)	3.9 (−11.2 to 17.1)
Smoking status				
Current smoker	190	24.2 (16.0 to 34.1)	4.2 (1.2 to 10.4)	20.0 (10.7 to 30.1)
Former smoker	443	17.3 (12.5 to 22.9)	5.4 (2.8 to 9.2)	11.9 (6.2 to 18.0)
Never smoked	107	3.9 (0.5 to 13.5)	0.0 (0.0 to 6.4)	3.9 (−2.7 to 13.3)
Histology				
Squamous	360	21.3 (15.4 to 28.3)	5.2 (2.5 to 9.4)	16.1 (9.3 to 23.4)
Nonsquamous	375	13.3 (8.9 to 18.8)	3.4 (1.2 to 7.2)	9.9 (4.6 to 15.8)
Disease stage				
II	214	21.2 (13.8 to 30.3)	4.5 (1.5 to 10.3)	16.6 (8.1 to 26.0)
IIIA	338	18.5 (13.0 to 25.1)	4.8 (2.1 to 9.3)	13.6 (7.1 to 20.7)
IIIB	186	10.2 (4.8 to 18.5)	3.1 (0.6 to 8.7)	7.2 (0.1 to 15.7)
Lymph node station				
N2 single	273	18.4 (12.4 to 25.8)	4.5 (1.7 to 9.6)	13.9 (6.6 to 21.7)
N2 multi	74	8.8 (1.9 to 23.7)	5.0 (0.6 to 16.9)	3.8 (−9.2 to 18.8)
PD-L1 expression at baseline				
Tumor cell <1%	247	9.0 (4.6 to 15.6)	3.2 (0.9 to 8.0)	5.8 (−0.2 to 12.7)
Tumor cell 1–49%	277	16.3 (10.5 to 23.6)	4.9 (2.0 to 9.9)	11.4 (4.3 to 19.1)
Tumor cell ≥50%	216	27.5 (19.4 to 36.9)	4.7 (1.5 to 10.6)	22.9 (13.7 to 32.5)
Planned neoadjuvant platinum agent				
Cisplatin	196	12.0 (6.4 to 20.0)	2.1 (0.3 to 7.3)	9.9 (3.1 to 18.0)
Carboplatin	544	19.2 (14.6 to 24.4)	5.0 (2.8 to 8.3)	14.1 (8.9 to 19.8)
EGFR-mutation positive	51	3.8 (0.1 to 19.6)	0.0 (0.0 to 13.7)	3.8 (−10.0 to 19.1)



Role of adjuvant Nivo: Comparison of 816 and 77T

Perioperative vs neoadjuvant NIVO: Patient-level analy

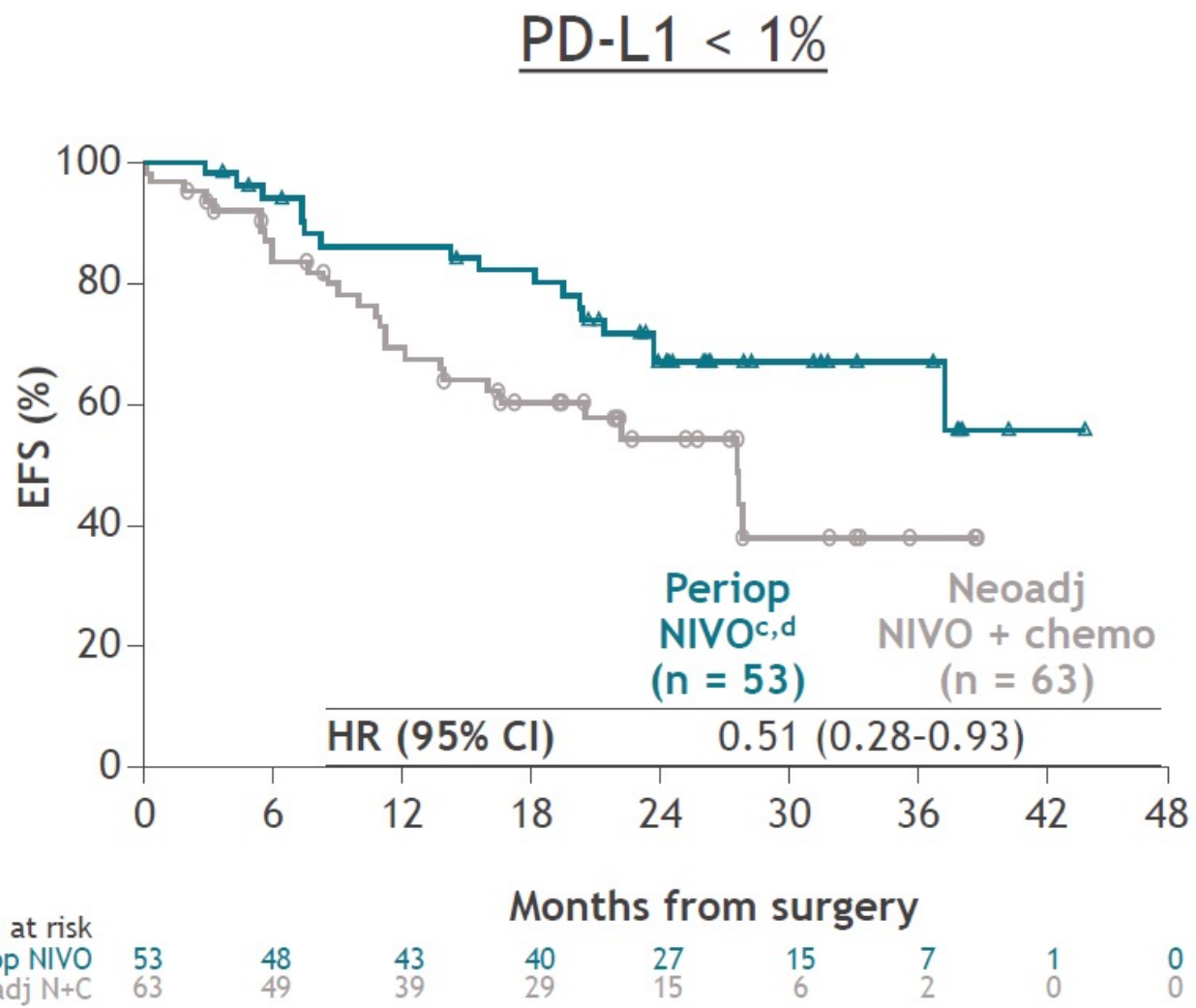
Landmark EFS (BICR) from definitive surgery

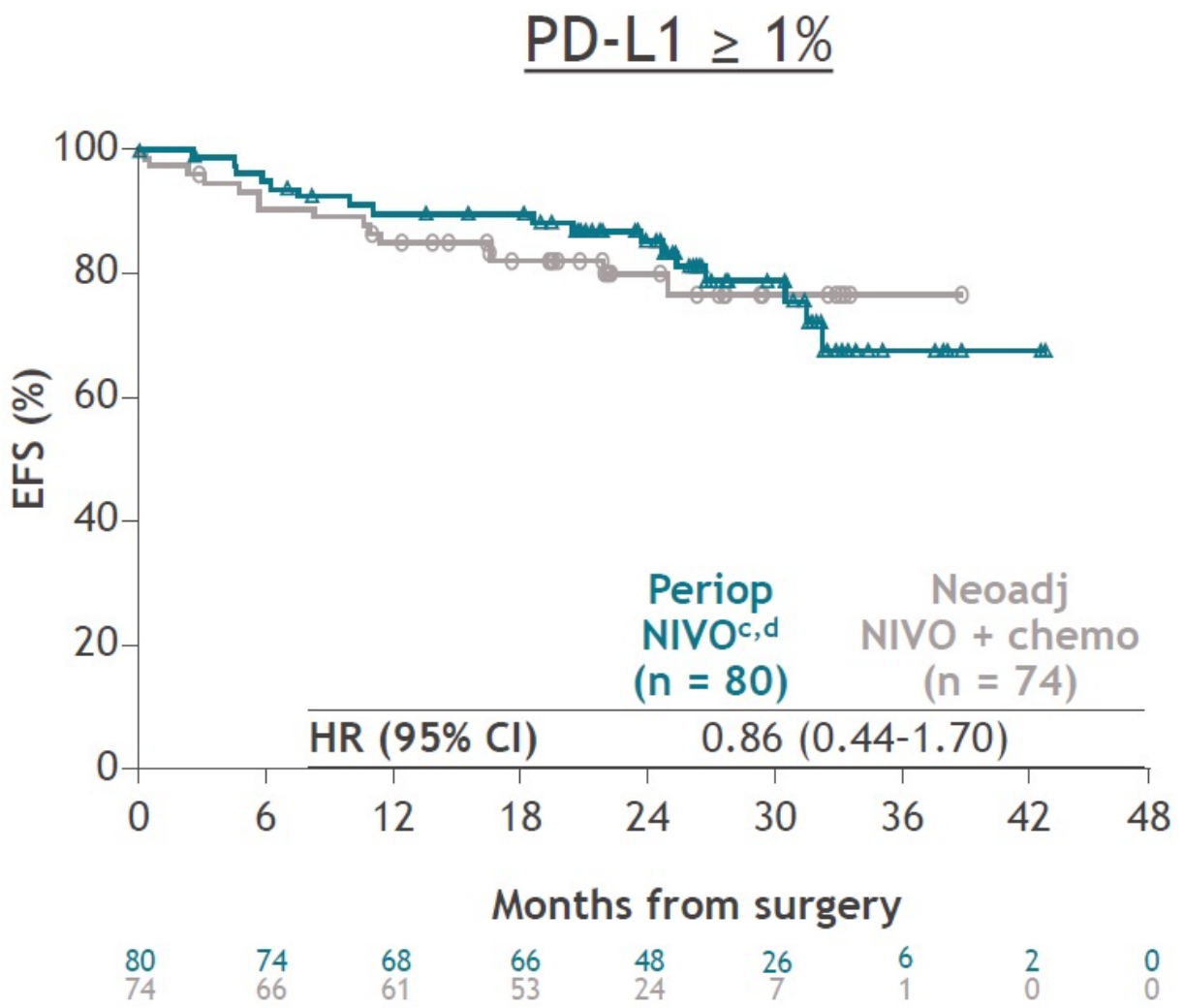


	Weighted (ATE)[b]	
	Periop NIVO[a] (n = 139.4[c])	Neoadj NIVO + chemo (n = 147.5[c])
HR (95% CI)	0.61 (0.39-0.97)	

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

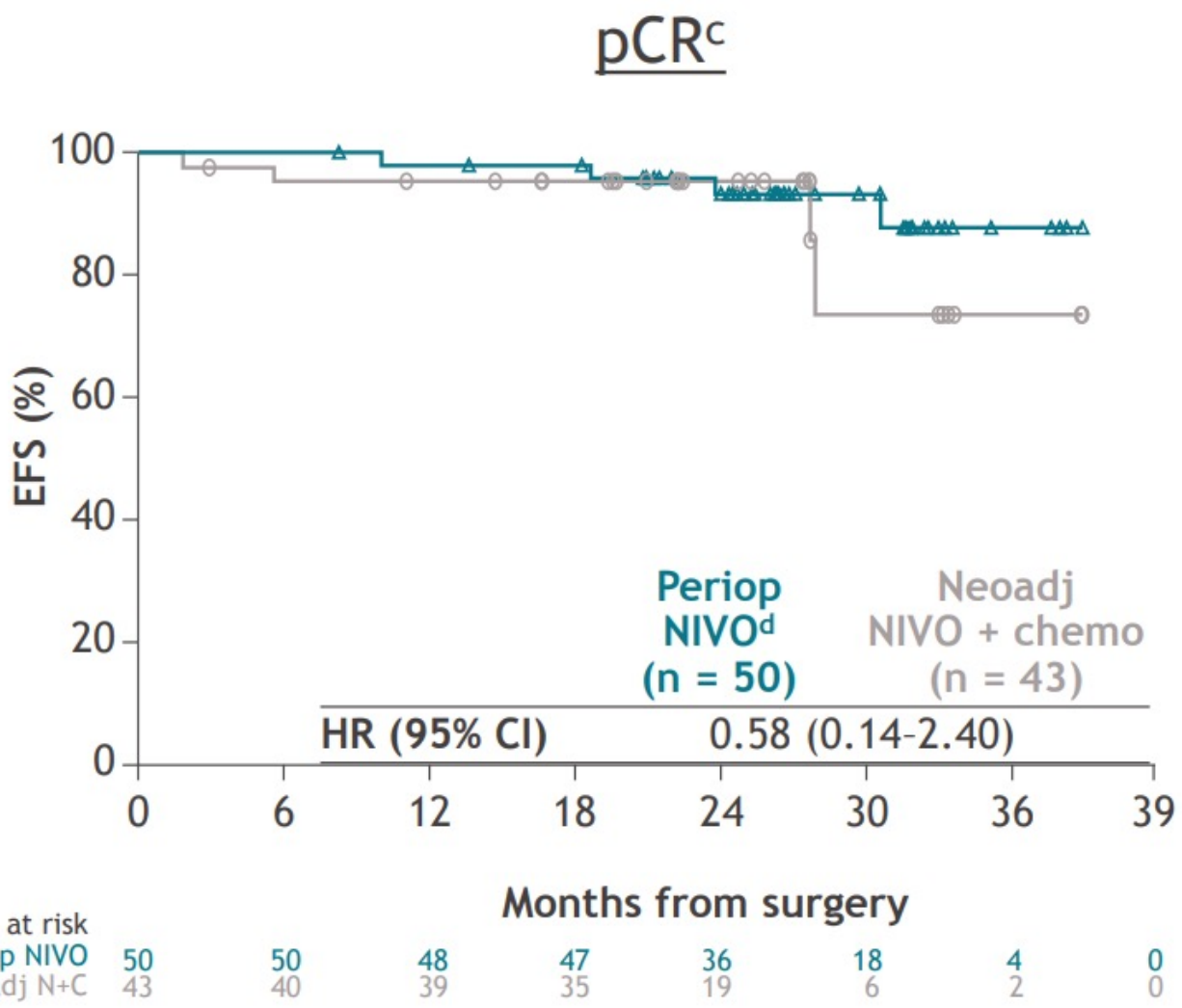
Landmark EFS (analysis population) by tumor PD-L1 expression[a,b]

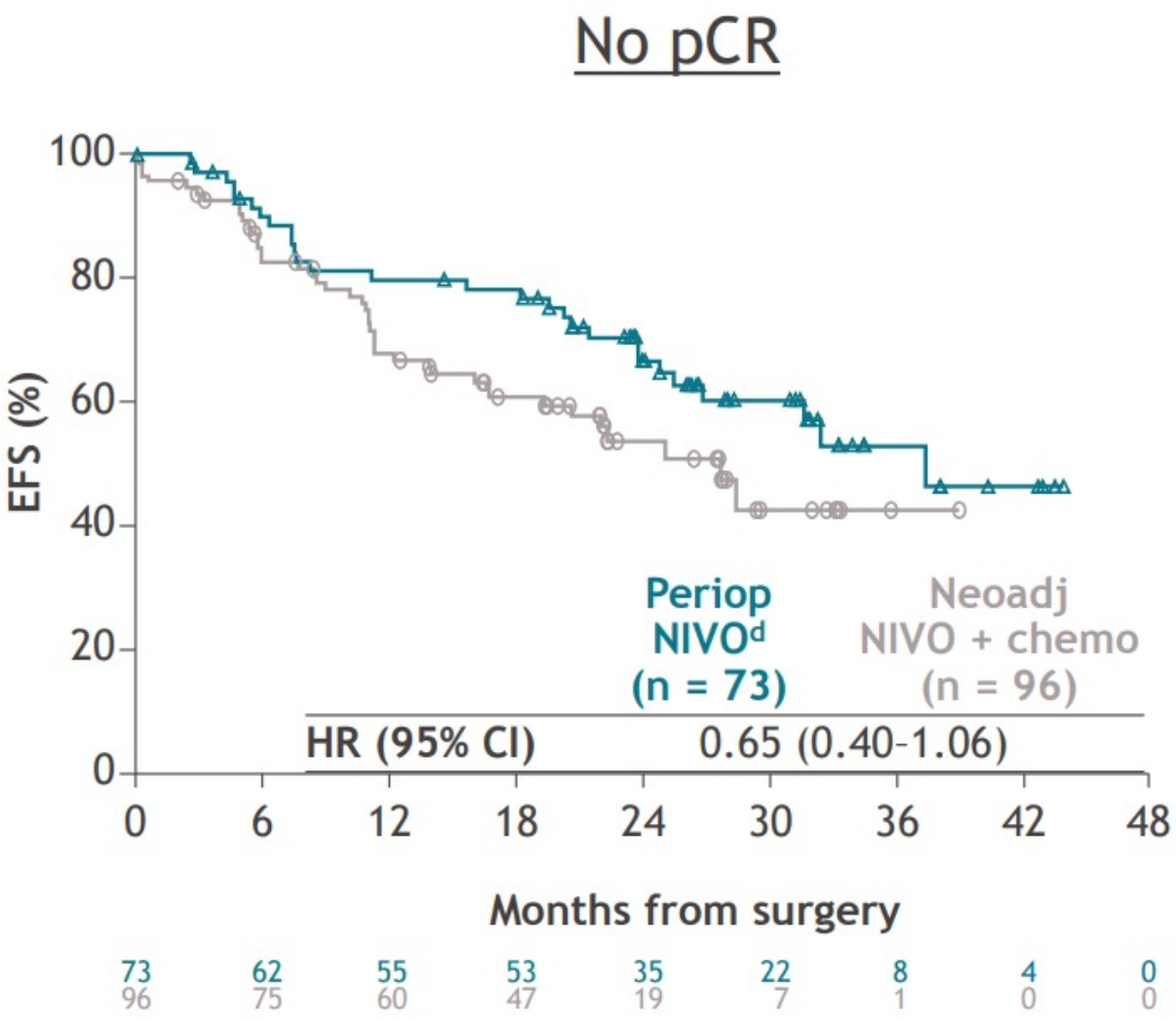




Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. [a]Patients with non-evaluable PD-L1 expression were excluded. [b]Unweighted analyses. [c]Includes only patients who received ≥ 1 dose of adjuvant NIVO. [d]Completed adjuvant treatment: < 1%, 33 patients (62%) and ≥ 1%, 51 patients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

Landmark EFS[a] (analysis population) by pCR status[a,b]





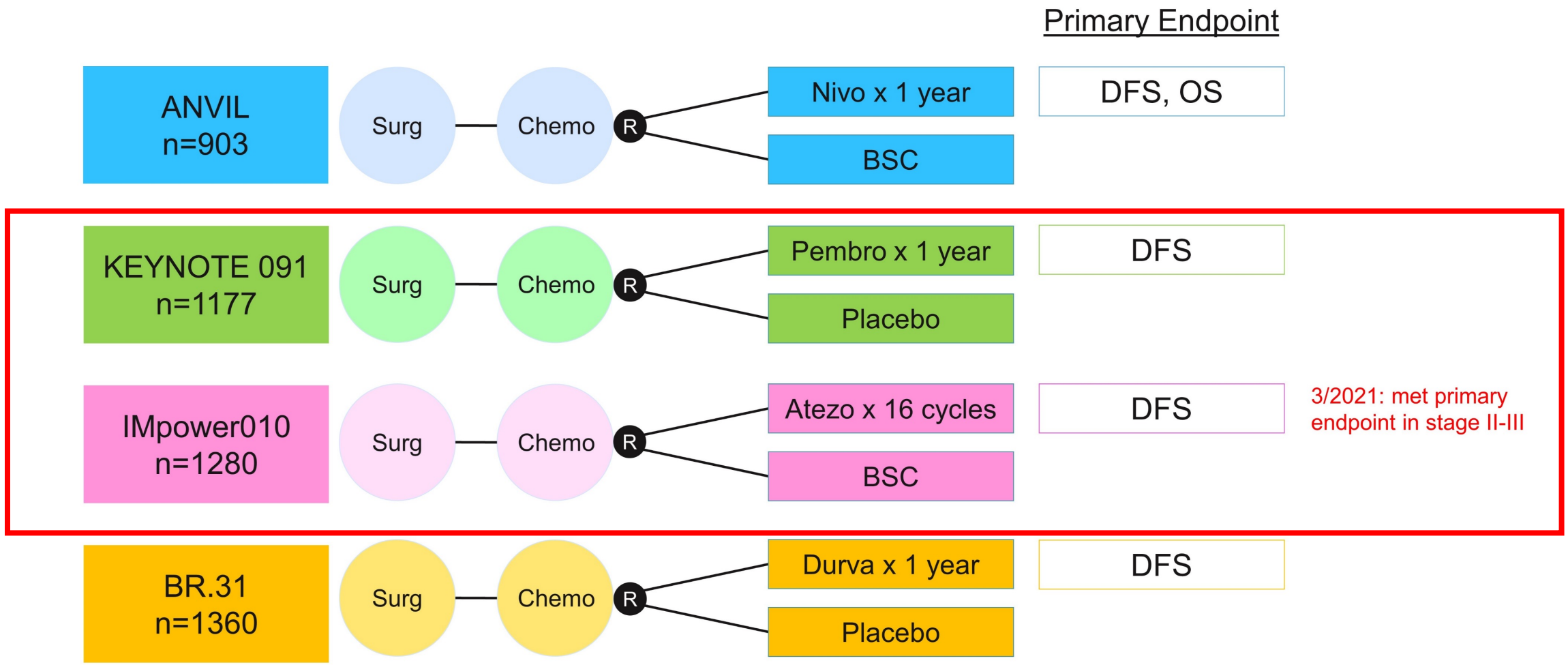
Summary

- In the absence of a randomized-controlled trial, this analysis represents the only comparison of perioperative vs neoadjuvant-only immunotherapy treatments for patients with resectable NSCLC, using individual patient-level data from 2 randomized phase 3 trials
- Approximately 40% reduction in risk of disease recurrence or death after surgery was observed in patients who received ≥ 1 dose of adjuvant NIVO following neoadjuvant NIVO + chemo treatment and surgery compared with those who did not receive adjuvant NIVO
  - Similar benefit was seen regardless of baseline stage, with a greater magnitude of benefit in patients with tumor PD-L1 expression < 1%
  - Perioperative NIVO improved EFS benefit vs neoadjuvant NIVO + chemo for patients without a pCR
- Perioperative NIVO had a generally manageable safety profile
- These results help inform the potential benefit of adjuvant NIVO following neoadjuvant NIVO + chemo treatment and surgery and further support perioperative NIVO as a treatment option for eligible patients with resectable NSCLC

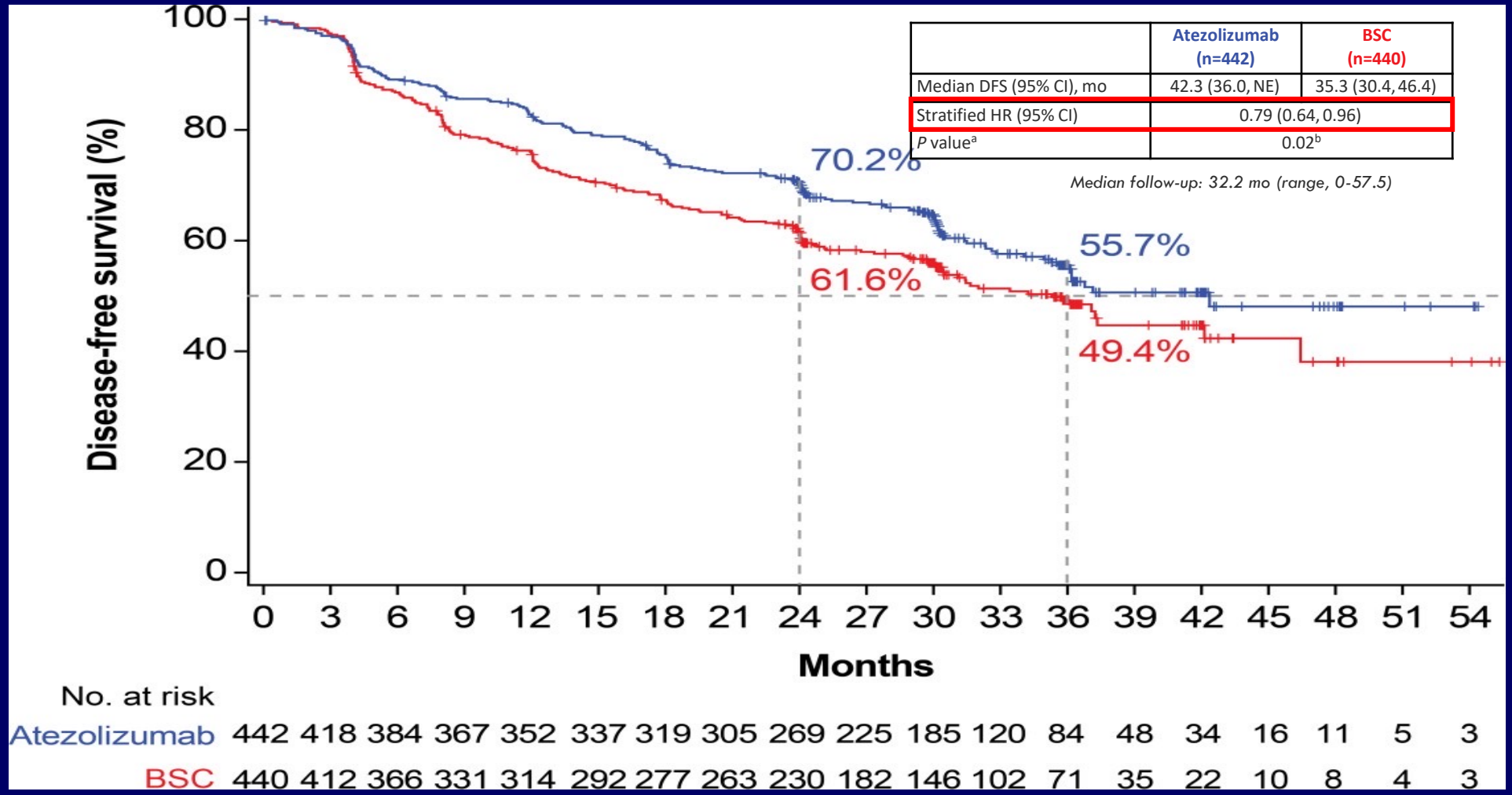
Major Remaining Questions: Neoadjuvant IO+CT & TKI Rx

- How many pre-op cycles? 2 vs 3
- Need for post-op adjuvant IO?
  - Does pCR matter?
  - Does ctDNA matter?
- Stage 1B included?
- Does PD-L1 status matter?
- Should patients with genetic alterations receive neoadjuvant TKI or CT/IO?

Phase III Studies Exploring Adjuvant Checkpoint Inhibitors



IMpower010: DFS in the all-randomized stage II-IIIA population (primary endpoint)

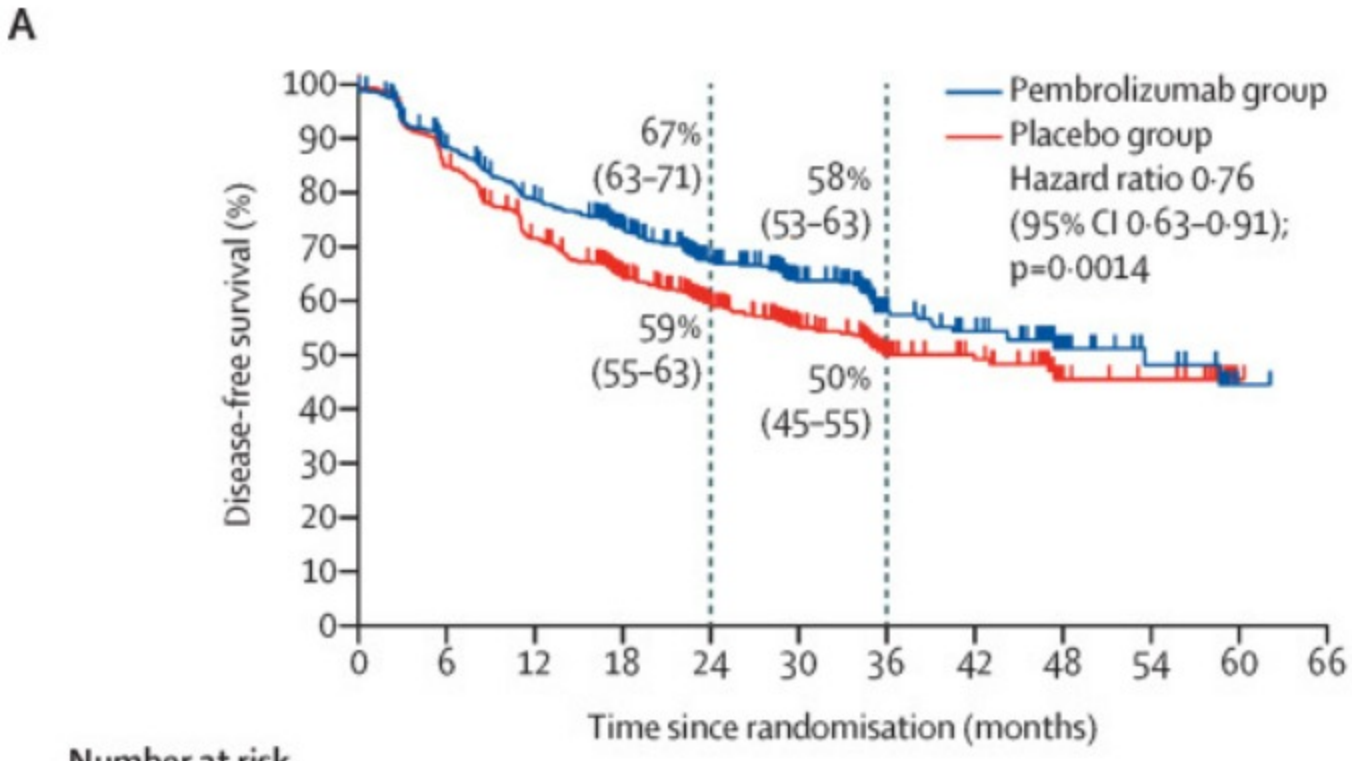


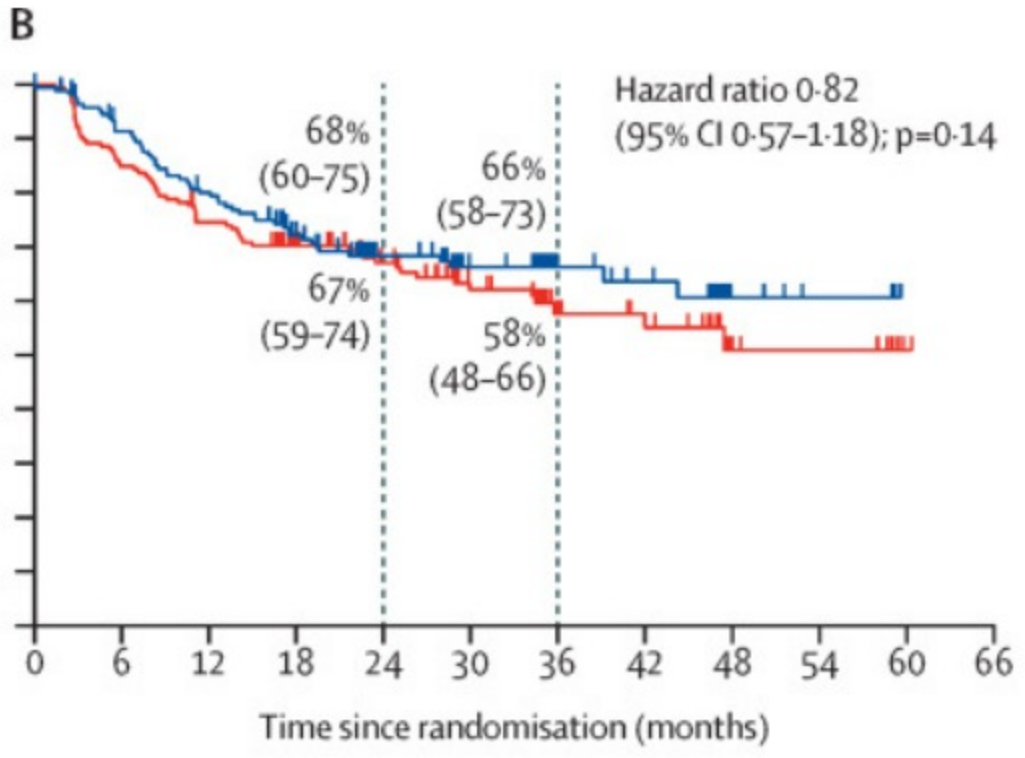
	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

Dr. Heather A. Wakelee ASCO 2021, abstr 8500 IMpower010 Interim Analysis https://bit.ly/33t6JJP

Clinical cutoff: January 21, 2021. [a] Stratified log-rank. [b] Crossed the significance boundary for DFS.

PEARLS 091: Adjuvant pembro vs placebo





Overall Survival

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)

Pembrolizumab	168	145	126	99	69	50	26	22	7	4	0	0
	(0)	(8)	(9)	(24)	(49)	(66)	(90)	(93)	(107)	(110)	(114)	(114)
Placebo	165	140	121	100	75	54	28	22	8	6	1	0
	(0)	(0)	(2)	(16)	(37)	(53)	(76)	(81)	(94)	(96)	(101)	(102)