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Neoadjuvant and Adjuvant Immunotherapy for Resectable Lung Cancer

SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

BLOOMBERG~KIMMEL INSTITUTE FOR CANCER IMMUNOTHERAPY

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Conflict of Interest

Research Funding (to institution): AstraZeneca, BMS, Corvus, Kyowa, Novartis, Regeneron

Consultant: Amgen, AstraZeneca, BMS, Daiichi, F-Star, G1, Genentech, Janssen, Iteos, Merck, Sanofi, Novartis, Surface, Teva,

DSMB member: Polaris

USA Lung Cancer: Mortality by Gender

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Estimated Deaths

Males

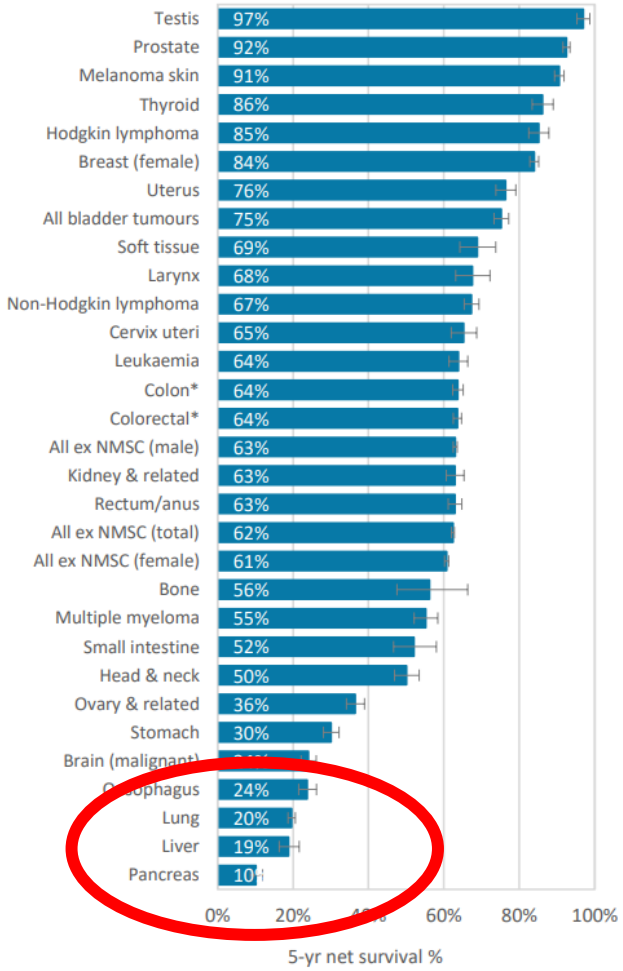
Lung & bronchus	**69,410**	**22%**
Prostate	34,130	11%
Colon & rectum	28,520	9%
Pancreas	25,270	8%
Liver & intrahepatic bile duct	20,300	6%
Leukemia	13,900	4%
Esophagus	12,410	4%
Urinary bladder	12,260	4%
Non-Hodgkin Lymphoma	12,170	4%
Brain & other nervous system	10,500	3%
All Sites	**319,420**	**100%**

Females

Lung & bronchus	**62,470**	**22%**
Breast	43,600	15%
Colon & rectum	24,460	8%
Pancreas	22,950	8%
Ovary	13,770	5%
Uterine corpus	12,940	4%
Liver & intrahepatic bile duct	9,930	3%
Leukemia	9,760	3%
Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	8,100	3%
All Sites	**289,150**	**100%**

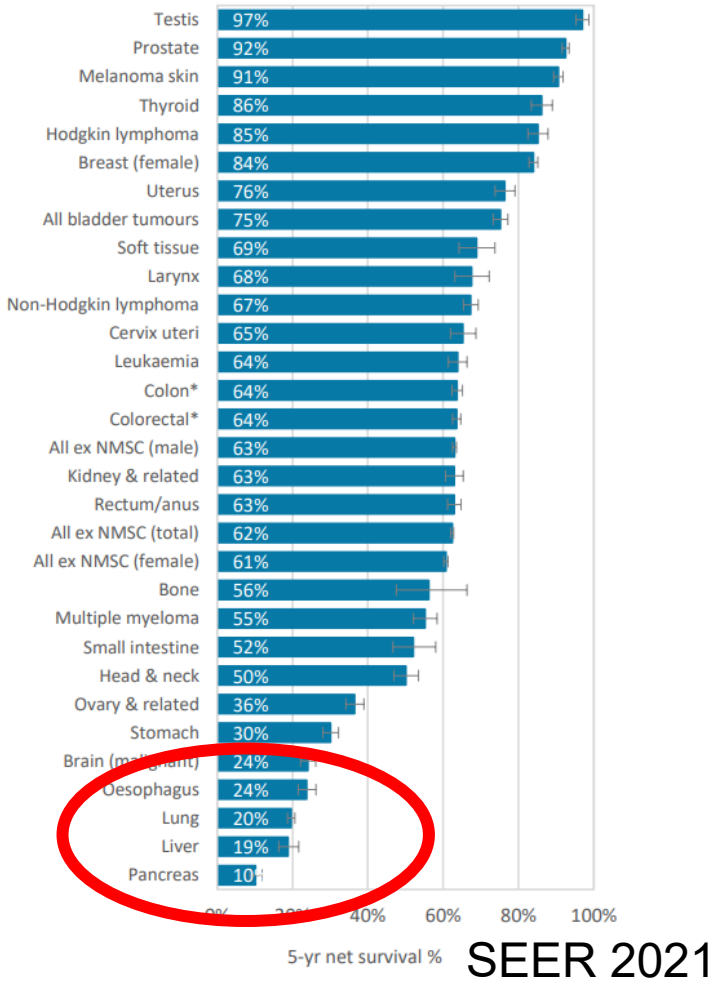
Adapted from American Cancer Society. Facts & Figures, 2021.

5 year survival from cancer 2012-2016



SEER 2021

Novel Systemic Therapy is Impacting Lung Cancer Mortality



SEER 2021

ORIGINAL ARTICLE

The Effect of Advances in Lung-Cancer Treatment on Population Mortality

Nadia Howlader, Ph.D., Gonçalo Forjaz, D.V.M., Meghan J. Mooradian, M.D., Rafael Meza, Ph.D., Chung Yin Kong, Ph.D., Kathleen A. Cronin, Ph.D., Angela B. Mariotto, Ph.D., Douglas R. Lowy, M.D., and Eric J. Feuer, Ph.D.

- 6.3% reduction in lung cancer mortality each year 2012-16
- 3.1% annual reduction in incidence over same period
- >30 new lung cancer drug approvals or indications In USA from 2015-2020

Novel Therapy Development for Earlier Stage Non-Small Cell Lung Cancer has been Slow despite Unmet Need

AJCC Stage	T (Primary Tumor)	N (Regional Lymph Nodes)	M (Distant Metastases)	5 year Survival (clinical stage)
IIA	T2b	N0	0	60%
IIB	T1a/T1b/T1c	N1	0	
	T2a/T2b	N1	0	53%
	T3	N0	0	
IIIA	T1a/T1b/T1c	N2	0	
	T2a/T2b	N2	0	36%
	T3	N1	0	
	T4	N0/N1	0	

Abbreviations: AJCC, American Joint Commission on Cancer; NSCLC, non-small cell lung cancer.

Detterbeck FC. *J Thorac Cardiovasc Surg.* 2018;155:356-359.

Novel Therapy Development for Earlier Stage Non-Small Cell Lung Cancer has been Slow despite Unmet Need

AJCC Stage	T (Primary Tumor)	N (Regional Lymph Nodes)	M (Distant Metastases)	5 year Survival (clinical stage)
IIA	T2b	N0	0	60%
IIB	T1a/T1b/T1c	N1	0	
	T2a/T2b	N1	0	53%
	T3	N0	0	
IIIA	T1a/T1b/T1c	N2	0	
	T2a/T2b	N2	0	36%
	T3	N1	0	
	T4	N0/N1	0	

Tumors ≥4cm diameter

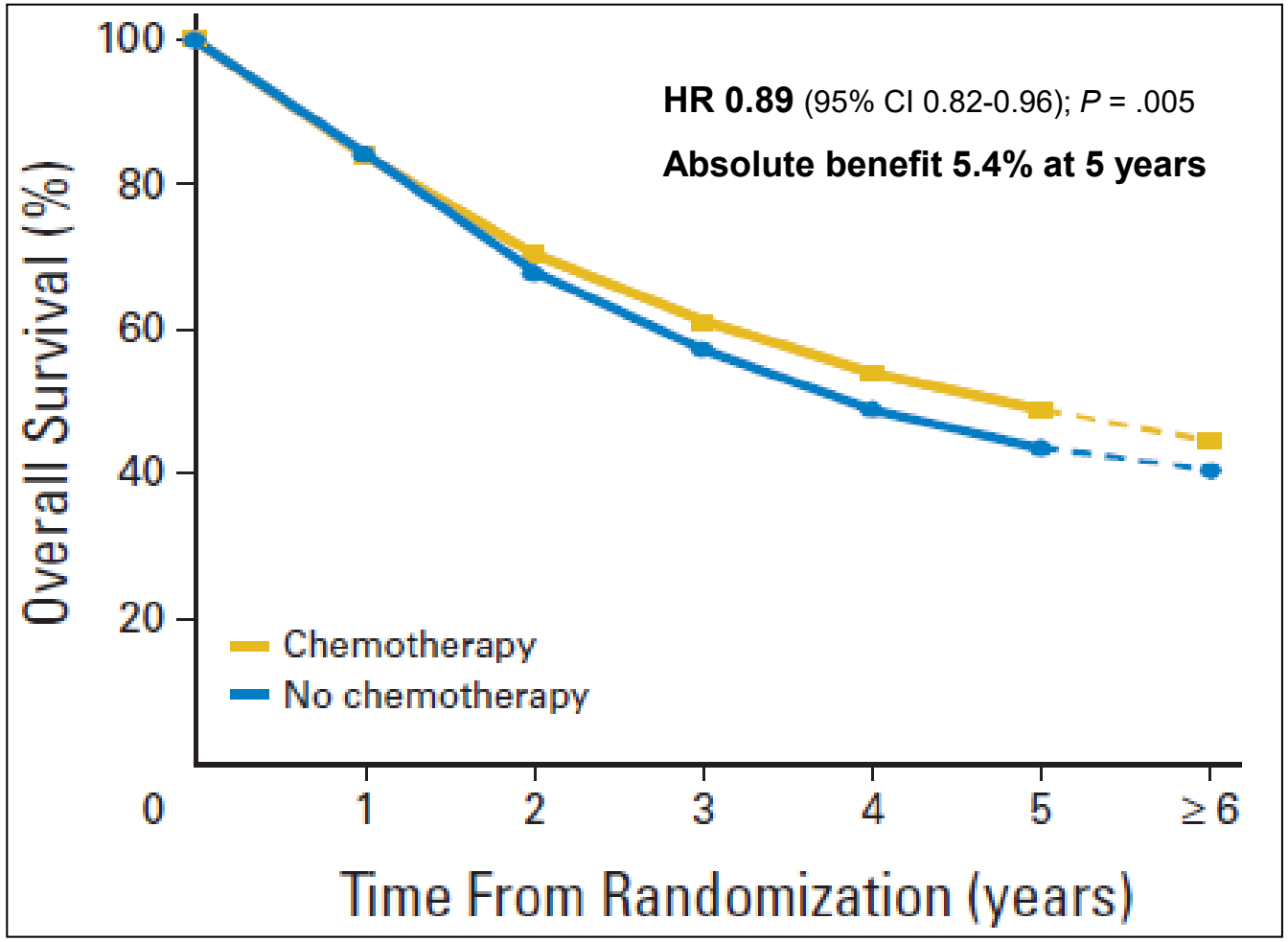
and/or

Lymph node positive

~500,000 people worldwide are diagnosed with, potentially curable, surgically resectable lung cancer each year

Abbreviations: AJCC, American Joint Commission on Cancer; NSCLC, non-small cell lung cancer.
Detterbeck FC. *J Thorac Cardiovasc Surg.* 2018;155:356-359.

LACE Meta-Analysis of Adjuvant Platinum Chemotherapy vs. no Adjuvant Chemo



Pignon J-P, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26:3552-3559.

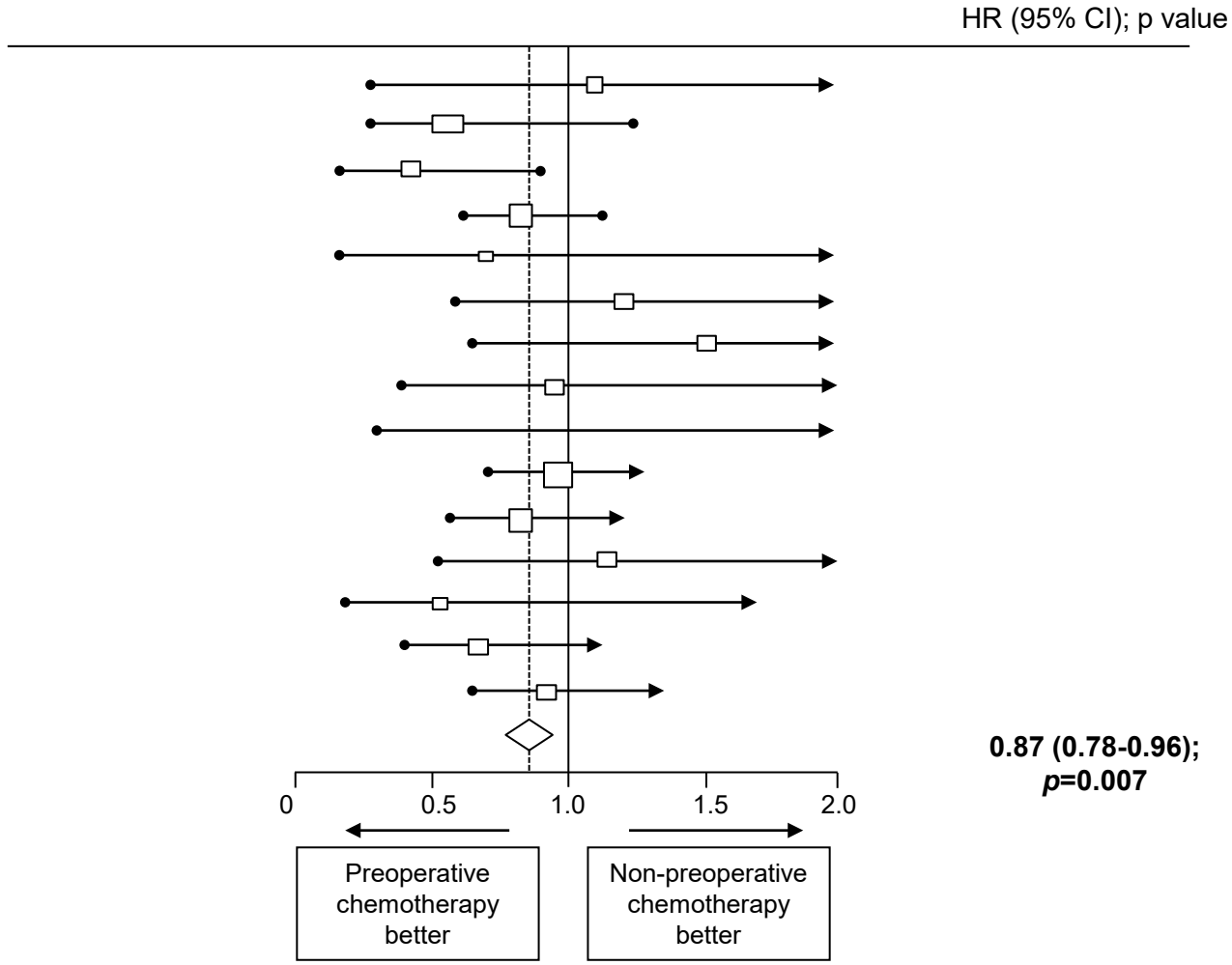
Standard of care in 2008

was still

standard of care in 2020 despite many advances in IO and Targeted Therapy for Advanced Lung Cancer

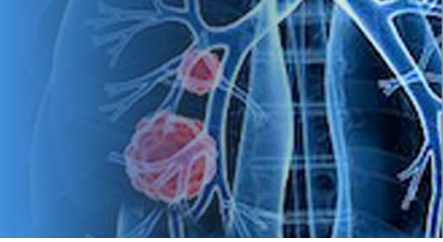
Preoperative (Neoadjuvant) Chemotherapy + Surgery vs. Surgery Alone

	Preoperative chemotherapy	Control	O-E	Variance
France 1990	8/13	8/13	0.32	3.97
MD Anderson 1994	19/28	27/32	-6.40	11.19
Spain 1994	19/29	27/30	-8.88	9.65
MIP-91	137/179	146/176	-12.99	70.22
SWOG S9015	3/5	12/16	-1.04	2.94
JCOG 9209	28/31	25/31	2.25	12.97
Netherlands 2000	23/39	15/40	3.86	9.36
Finland 2003	19/30	19/32	-0.50	9.48
MRC BLT	4/5	3/5	1.26	1.60
MRC LU22	151/258	158/261	-2.92	77.01
SWOG S9900	93/180	103/174	-9.31	48.84
China 2002	26/32	18/23	1.42	10.78
China 2005	8/19	14/21	-3.31	5.44
ChEST	45/129	61/141	-10.27	26.39
NATCH	99/201	109/212	-4.11	51.95
Total	**682/1178**	**745/1207**	**-50.62**	**351.78**



Overall HR
0.87 (0.78-0.96), *P* = .007 (fixed effect)
0.86 (0.75-0.98), *P* = .03 (random effects)
Heterogeneity; X^2 = 18.75, df = 14, *P* = .18, I^2=25%
BLT, Big Lung Trial; O–E, observed minus expected.
Adapted from NSCLC Meta-analysis Collaborative Group. *Lancet* 2014;383:1561-1571.

Considerations for Timing Systemic Treatment Options Around Surgery



Neoadjuvant

- Provides earliest opportunity to eradicate micrometastatic disease[1]
- Increased treatment initiation rate & compliance[2]
  - 97% initiated neoadjuvant vs 66% initiated adjuvant therapy
  - 90% completed neoadjuvant vs 61% completed adjuvant therapy
- Pathologic response provides early indicator of response to therapy and can guide future treatment decisions[3]
  - Immunotherapy is administered when draining lymph nodes are intact – potentially augmenting response[4]

Adjuvant

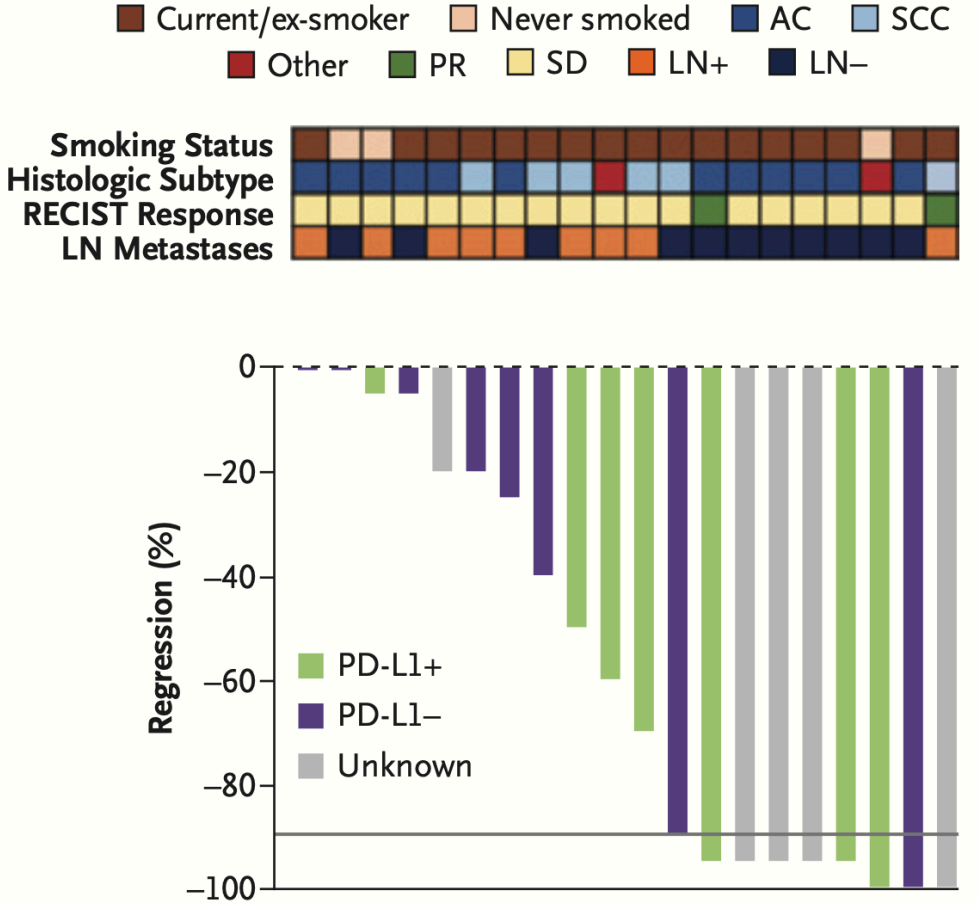
- Allows the fastest time to surgery
- No risk of presurgery complications from systemic therapy
- Enables longer treatment duration for systemic control[5]
- More flexible timing as administration postsurgery provides more recovery time for patients[5]

Perioperative treatment

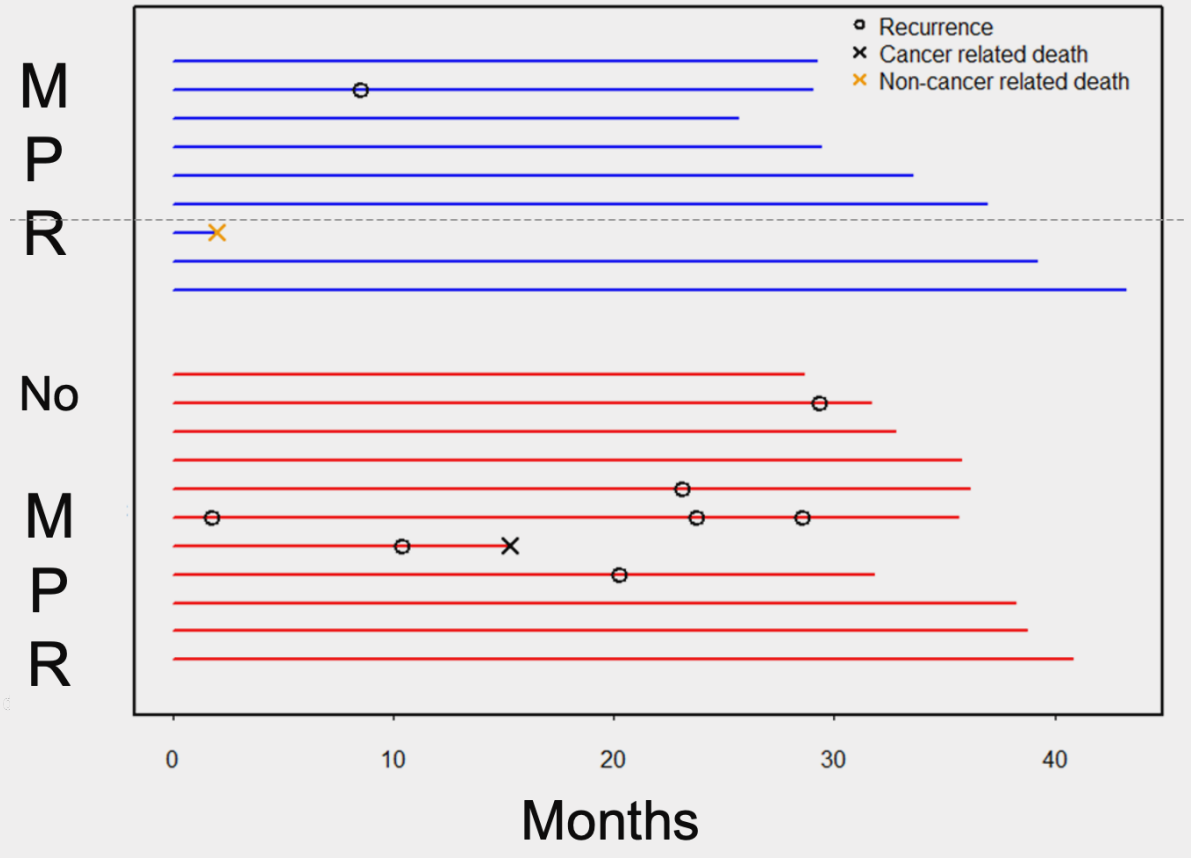
1. Blumenthal GM, et al. *J Thorac Oncol.* 2018;13:1818-1831. 2. Felip E, et al. *J Clin Oncol.* 2010;28:3138-3145. 3. Hellmann MD, et al. *Lancet Oncol.* 2014;15:e42-e50. 4. Tohme S, et al. *Cancer Res.* 2017;77:1548-1552. 5. Owen D, et al. *J Thorac Dis.* 2018;10(Suppl 3):S404-S411. Graphic courtesy of Patrick Forde, MBBCh.

Initial Experience With Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

Percentage of Pathological Regression After Neoadjuvant Nivolumab in 20 Patients Who Underwent Surgical Resection[1]



Longer-Term Follow-Up[2]



Abbreviations: AC, adenocarcinoma; LN, lymph node; MPR, major pathologic response; PD-L1, programmed death ligand 1; PR, partial response; SCC, squamous-cell carcinoma; SD, stable disease. 1. With permission from Forde PM, et al. *N Engl J Med.* 2018;378:1976-1986.
2. Reuss JE, et al. *J Clin Oncol.* 2019;37 (suppl):Abstract 8524. Presented at: 2019 ASCO Annual Meeting; May 31–June 4, 2019; Chicago, IL. Right graphic: Graphic courtesy of Patrick Forde, MBBCh.

Neoadjuvant combines Drug Development & Translational Science to Guide Early and Late Stage Cancer Medicine

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

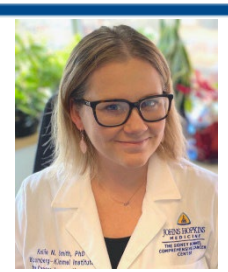
Annals of Oncology 29: 1853–1860, 2018
doi:10.1093/annonc/mdy218
Published online 6 June 2018

ORIGINAL ARTICLE

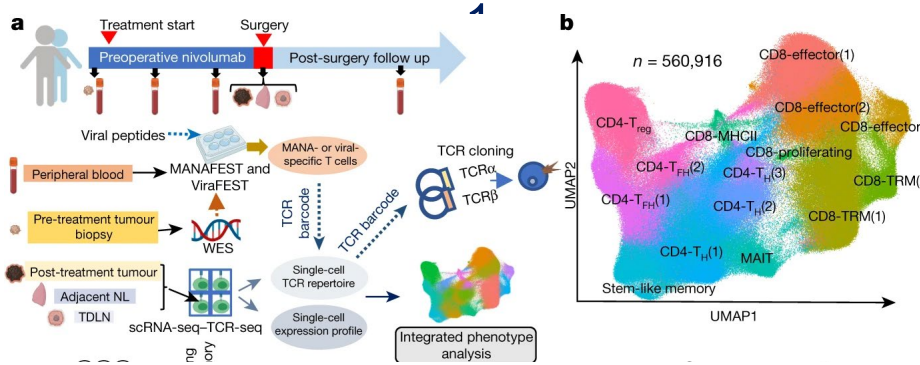
Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC)

T. R. Cottrell[1], E. D. Thompson[1,2,3], P. M. Forde[2,3], J. E. Stein[4], A. S. Duffield[1], V. Anagnostou[2], N. Rekhtman[5], R. A. Anders[1,3], J. D. Cuda[1,4], P. B. Illei[1,2], E. Gabrielson[1,2], F. B. Askin[1], N. Niknafs[2], K. N. Smith[2,3], M. J. Velez[5], J. L. Sauter[5], J. M. Isbell[6], D. R. Jones[6], R. J. Battafarano[7], S. C. Yang[7], L. Danilova[3,8], J. D. Wolchok[9,10,11], S. L. Topalian[3,7], V. E. Velculescu[2,3], D. M. Pardoll[2,3], J. R. Brahmer[2,3], M. D. Hellmann[10,11,12], J. E. Chaft[10,12], A. Cimino-Mathews[1,2] & J. M. Taube[1,2,3,4,*]

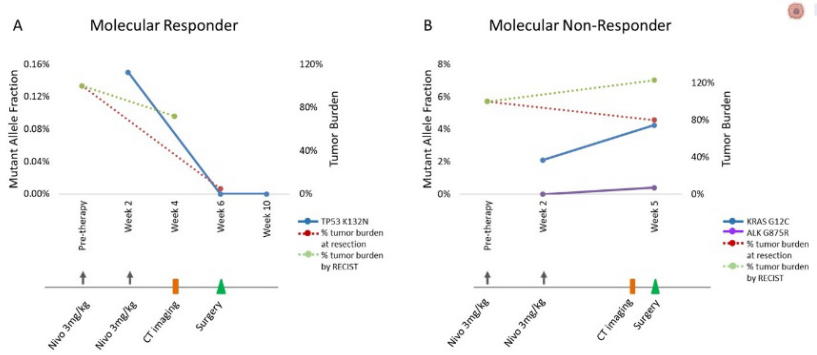
nature



Functional profiling of neoantigen-specific TIL after neoadjuvant anti-PD-



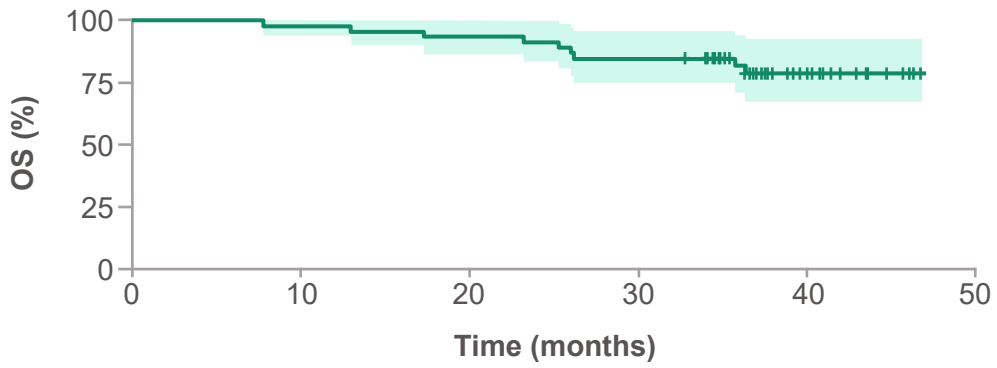
Can ctDNA Dynamics Predict Pathologic Response to Neoadjuvant Nivolumab?



Neoadjuvant and perioperative I-O combinations demonstrated activity in resectable NSCLC[1-10]

NADIM[1]

Neoadjuvant nivolumab + chemo, adjuvant nivolumab, Stage IIIA

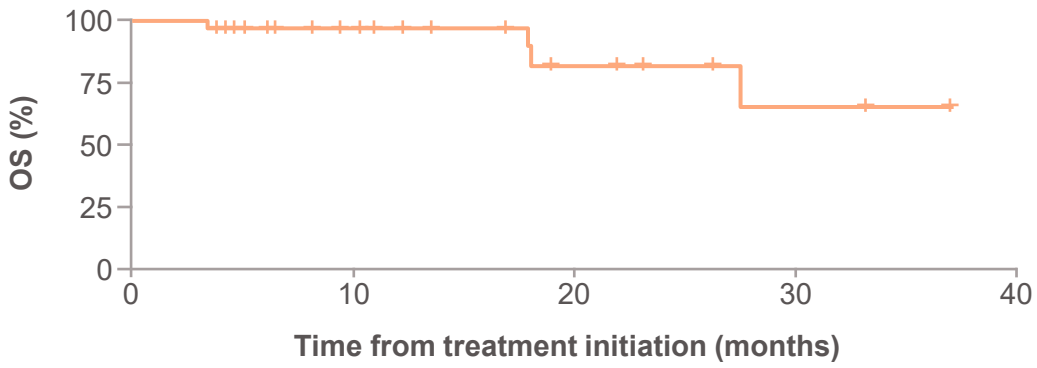


No. at risk	46	45	43	39	15	0

Type of treatment	Perioperative
Surgical patients, n (ITT)	41 (46)
MPR,* n (% of resected pts)	34 (83%)
pCR, n (% of resected pts)	26 (63%)

NCT02716038[2]

Neoadjuvant atezolizumab + chemo, Stage IB-IIIA



No. at risk (no. censored)	30 (0)	18 (11)	8 (18)	4 (22)	-

Type of treatment	Neoadjuvant
Surgical patients, n (ITT)	29† (30)
MPR,* n (% of ITT pts)	17 (57%)
pCR, n (% of ITT pts)	10 (33%)

Historic pCR rate after neoadjuvant chemotherapy for NSCLC = 2-6%

*MPR defined as 90% regression (≤10% viable tumor cells). †Including 3 patients who were taken to surgery but considered not to have resectable disease.[2]
Chemo=chemotherapy; ITT=intent-to-treat; MPR=major pathologic response; NSCLC=non-small cell lung cancer; pCR=pathologic complete response; pts=patients.

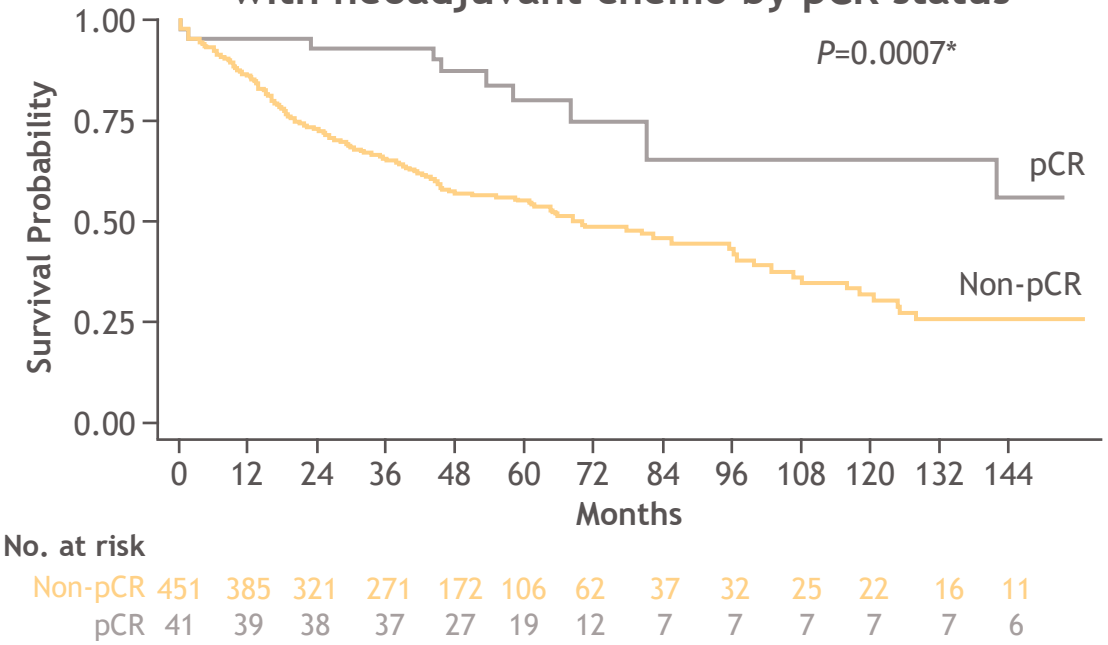
1. Provencio M et al. Oral presentation at WCLC 2021. Abstract OA20.01. 2. Shu C et al. *Lancet Oncol*. 2020;21(6):786-795. 3. Cascone T, et al. *Nat Med*. 2021;27:504-514. 4. Cascone T et al. Oral presentation at AACR 2021. Abstract SY013—03. 5. Altorki NK et al. *Lancet Oncol*. 2021;22(6):824-835. 6. Rothschild SI et al. *J Clin Oncol*. 2021;JCO2100276. doi: 10.1200/JCO.21.00276. 7. Hong MH et al. Poster presentation at WCLC 2020. Abstract FP03.02. 8. Zinner R et al. Poster presentation at ASCO 2020. Abstract 9051. 9. Reuss J et al. *J Immunother Cancer*. 2020;8:e001282. 10. Zhao Z et al. Poster presentation at ASCO 2021. Abstract 8541.

Achieving pCR or MPR may represent an early predictor of survival in resectable NSCLC

Meta-Analysis: Associations Between pCR & OS/EFS after neoadjuvant chemo(radio)therapy[1]

Association	HR (95% CI)	Range of HRs	Patients (n)	Studies (n)
OS, pCR vs no pCR	0.49 (0.42–0.57)	0.13–0.78	6474	20
EFS, pCR vs no pCR	0.49 (0.41–0.60)	0.26–0.71	2157	11

Overall Survival of NSCLC patients treated with neoadjuvant chemo by pCR status[2]



Phase 2 studies showed a trend toward improved survival outcomes in patients with pCR and/or MPR to neoadjuvant I-O-based regimens *vs* those without[3-8]

Data are presented side-by-side for ease of viewing. Cross-trial comparisons are not intended.

*Log-rank test.

EFS=event-free survival; HR=hazard ratio; I-O=immuno-oncology; MPR=major pathologic response; OS=overall survival; pCR=pathologic complete response.

1. Waser N et al. Oral presentation at ESMO 2020. Abstract 1243P. 2. Mouillet G et al. *J Thorac Oncol*. 2012;7(5):841-849. 3. Provencio M et al. *Lancet Oncol*. 2020;21(11):1413-1422. 4. Wislez M. et al. Oral presentation at ESMO 2021. Abstract 1151MO. 5. Shu CA et al. *Lancet Oncol*. 2020;21(6):786-795. 6. Cascone T et al. *Nat Med*. 2021;27:504-514. 7. Rothschild SI et al. *J Clin Oncol*. 2021;39(26):2872-2880. 8. Carbone DP, et al. Oral presentation at WCLC 2020. Abstract OA06.06.

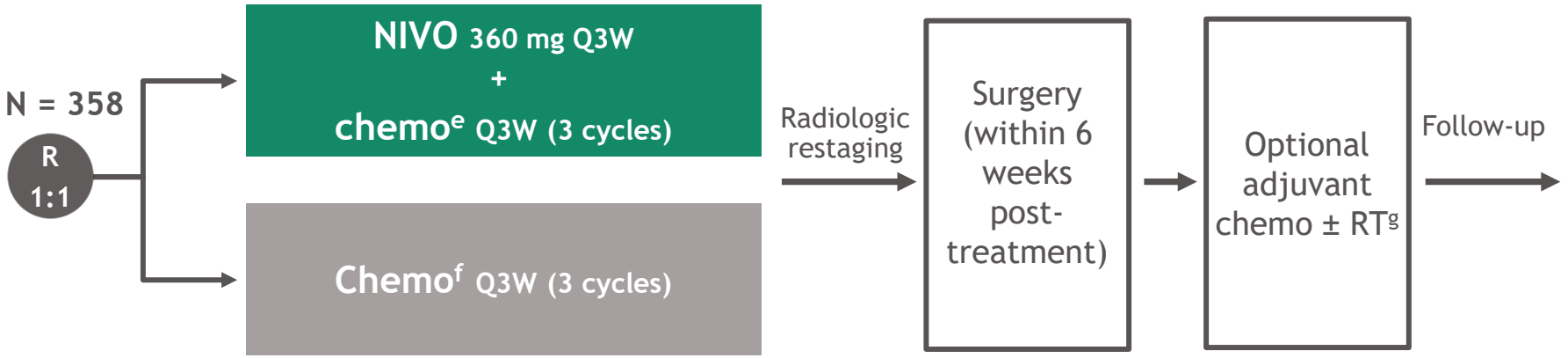
CheckMate 816 study design[a]

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)–IIIA NSCLC (per AJCC 7th edition[b])
- ECOG PS 0–1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by

Stage (IB-II vs IIIA), PD-L1[c] (≥ 1% vs < 1%[d]), and sex



Primary endpoints

- pCR by BIPR
- **EFS[h] by BICR**

Secondary endpoints

- MPR by BIPR
- **OS**
- Time to death or distant metastases

Key exploratory analysis

- **EFS by pCR status**

Database lock: October 20, 2021; minimum follow-up: 21 months for NIVO + chemo and chemo arms; median follow-up, 29.5 months.

[a]NCT02998528; [b]TNM Classification of Malignant Tumors 7th edition; [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [d]Included patients with PD-L1 expression status not evaluable and indeterminate; [e]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [f]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; [g]Per healthcare professional choice; [h]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. Ref: Forde, et al. NEJM 2022 (applies to slides 15-27)

Baseline characteristics

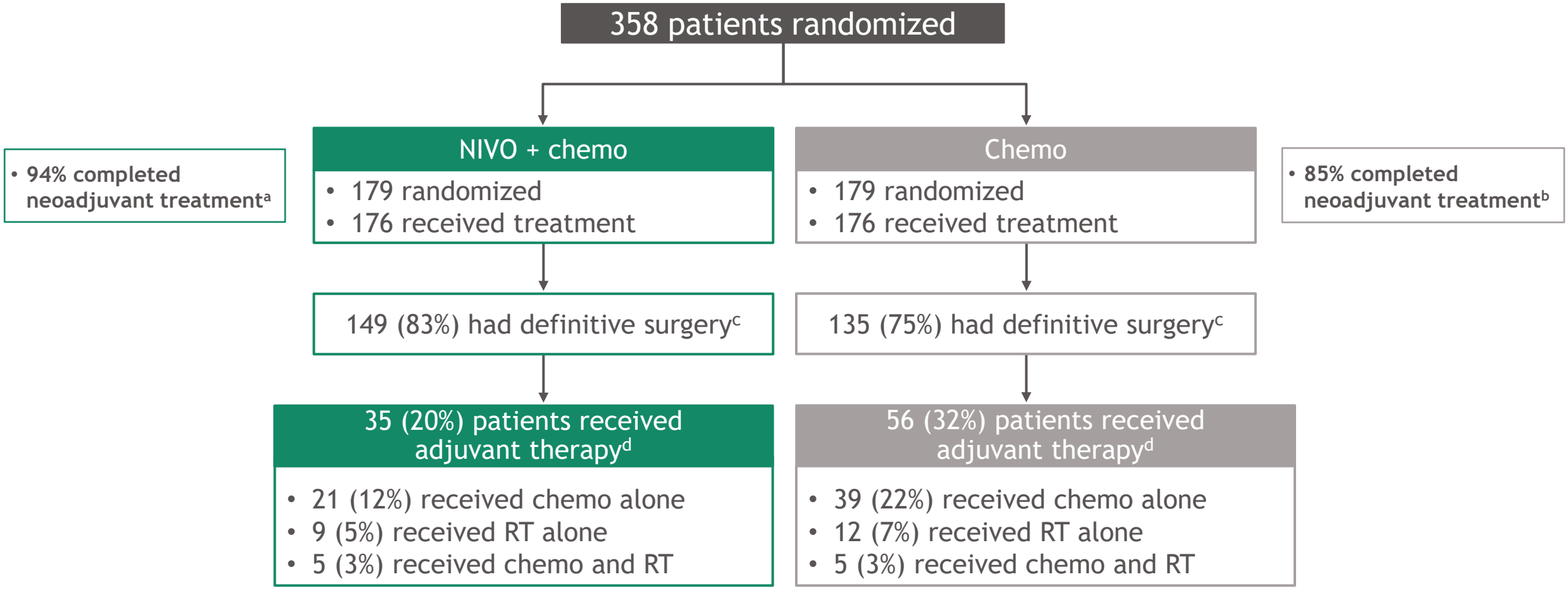
	NIVO + chemo (n = 179)	Chemo (n = 179)
Age, median (range), years	64 (41–82)	65 (34–84)
Age category, %		
< 65 years	52	46
≥ 65 years	48	54
Male, %	72	71
Region,[a] %		
North America	23	28
Europe	23	14
Asia	48	51
ECOG PS, %		
0	69	65
1	31	35
Stage,[b,c] %		
IB–II	36	35
IIIA	63	64
Histology, %		
Squamous	49	53
Non-squamous	51	47

	NIVO + chemo (n = 179)	Chemo (n = 179)
Smoking status,[d] %		
Current/former	89	88
Never	11	11
Tumor PD-L1 expression,[e] %		
Not evaluable	7	7
< 1%	44	43
≥ 1%	50	50
1–49%	28	26
≥ 50%	21	24
TMB,[f] %		
Not evaluable/not reported[g]	51	50
< 12.3 mut/Mb	27	30
≥ 12.3 mut/Mb	22	21
Type of platinum therapy, %		
Cisplatin	69	75
Carboplatin	22	18

[a]Rest of the world: 7% of patients in each of the NIVO + chemo and chemo arm; [b]Disease stage by case report form, per AJCC 7th edition; 1 patient in the chemo arm had stage IA disease and 1 patient in each arm had stage IV disease; [c]Stage IB, IIA, IIB disease: 6%, 17%, and 14% of patients in the NIVO + chemo arm and 4%, 18%, and 12% in the chemo arm, respectively; [d]One patient in the chemo arm had unknown smoking status; [e]Percentages are based on the primary analysis population; level of PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay (Dako); patients with tumor tissue that could not be assessed for PD-L1 (≤ 10% of all randomized patients) were stratified to the PD-L1 expression < 1% subgroup at randomization; [f]TMB was evaluated using the Illumina TSO500 assay. A 12.3-mut/Mb cutoff per TSO500 corresponds to 10 mut/Mb per the FoundationOne assay[1]; [g]TMB was not analyzed for patients in China and these patients are included in the 'not reported' category.

1. Baden J, et al. *Ann Oncol* 2019;30(suppl 5):v25–v54 (abstract 2736).

Treatment disposition and adjuvant therapy



Database lock: October 20, 2021; minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]Reasons for not completing neoadjuvant treatment included disease progression (1%) and study drug toxicity (6%); [b]Reasons for not completing neoadjuvant treatment included disease progression (1%), study drug toxicity (7%), and other (7%); [c]Denominator based on randomized patients. Reasons for cancelled surgeries in the NIVO + chemo arm (n = 28) and chemo arm (n = 37) included disease progression (NIVO + chemo, 7%; chemo, 9%), adverse event (NIVO + chemo and chemo, 1% each), other reasons (NIVO + chemo, 8% [other reasons included patient refusal (n = 9), unfit for surgery due to poor lung function (n = 2), unresectability (n = 2), not treated (n = 1)]; chemo, 11% [other reasons included patient refusal (n = 8), consent withdrawal (n = 3), COVID-19 (n = 1), unfit for surgery due to poor lung function (n = 4), unresectability (n = 2), not treated (n = 1)]; Definitive surgery was not reported in 2 patients in the NIVO plus chemo group and 7 patients in the chemo group. [d]Denominator based on patients receiving neoadjuvant treatment.

Adverse events[a] summary

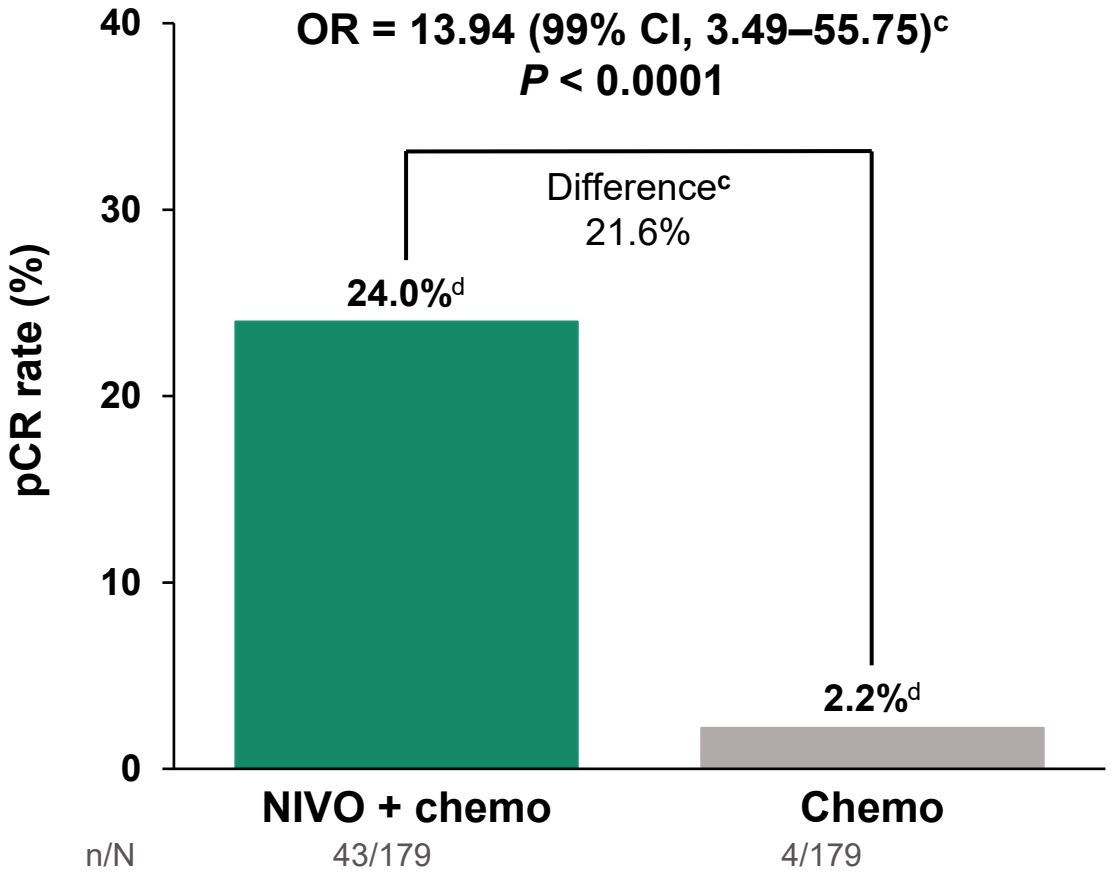
Patients (%)	NIVO + chemo (n = 176)		Chemo (n = 176)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
All AEs	93	41	97	44
TRAEs	82	34	89	37
All AEs leading to discontinuation	10	6	11	4
TRAEs leading to discontinuation	10	6	10	3
All SAEs	17	11	14	10
Treatment-related SAEs	12	8	10	8
Surgery-related AEs[b,c]	42	11	47	15
Treatment-related deaths[d]	0		2	

- Grade 5 surgery-related AEs[e] were reported in 2 patients in the NIVO + chemo arm and were deemed unrelated to study drug per investigator (1 each due to pulmonary embolism and aortic rupture)

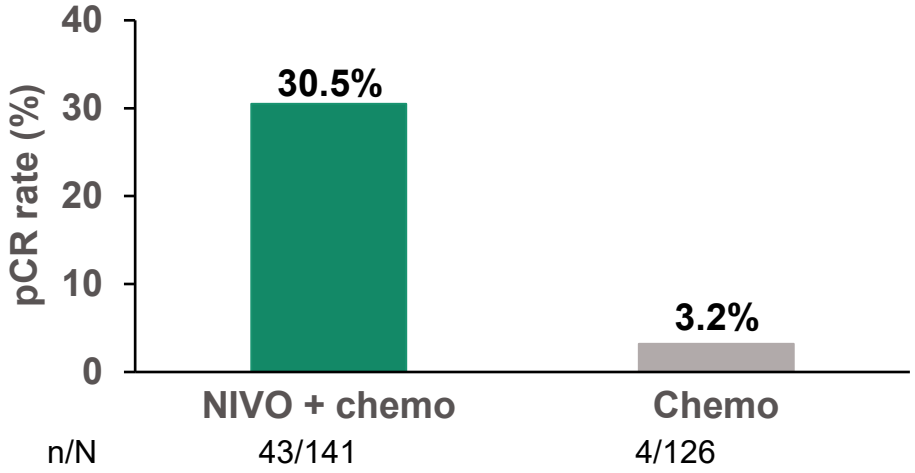
[a]Includes events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose as per CTCAE Version 4.0; MedDRA Version 24.0; [b]Includes events reported up to 90 days after definitive surgery; [c]Denominator based on patients with definitive surgery (n = 149 in the NIVO + chemo group, n = 135 in the chemo group); [d]Treatment-related deaths (not limited to 30 days window after last neoadjuvant dose) in the chemotherapy arm were due to pancytopenia, diarrhea, acute kidney injury (all in 1 patient), enterocolitis, and pneumonia; [e]Grade 5 AEs are defined as events that led to death within 24 hours of AE onset.

Primary Endpoint: pCR rate with neoadjuvant nivo + chemo vs. chemo

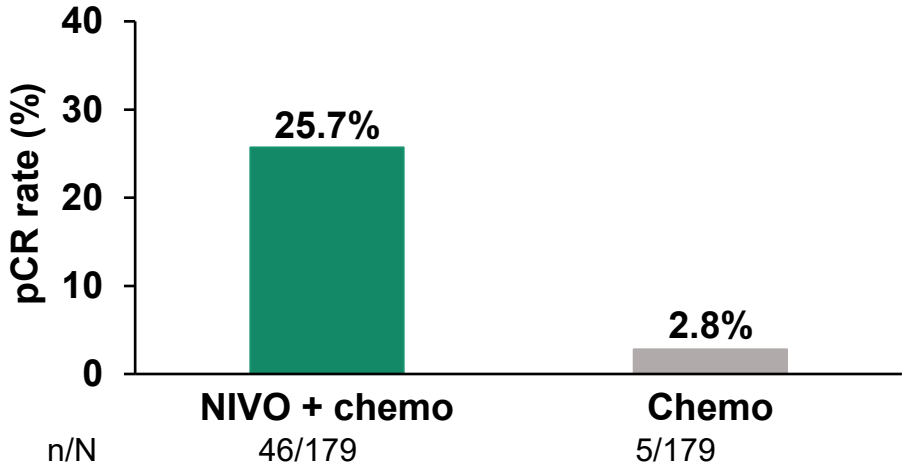
Primary endpoint: ITT (ypT0N0)[b]



Patients with resection[e] (ypT0N0)



Primary tumor only in ITT (ypT0)

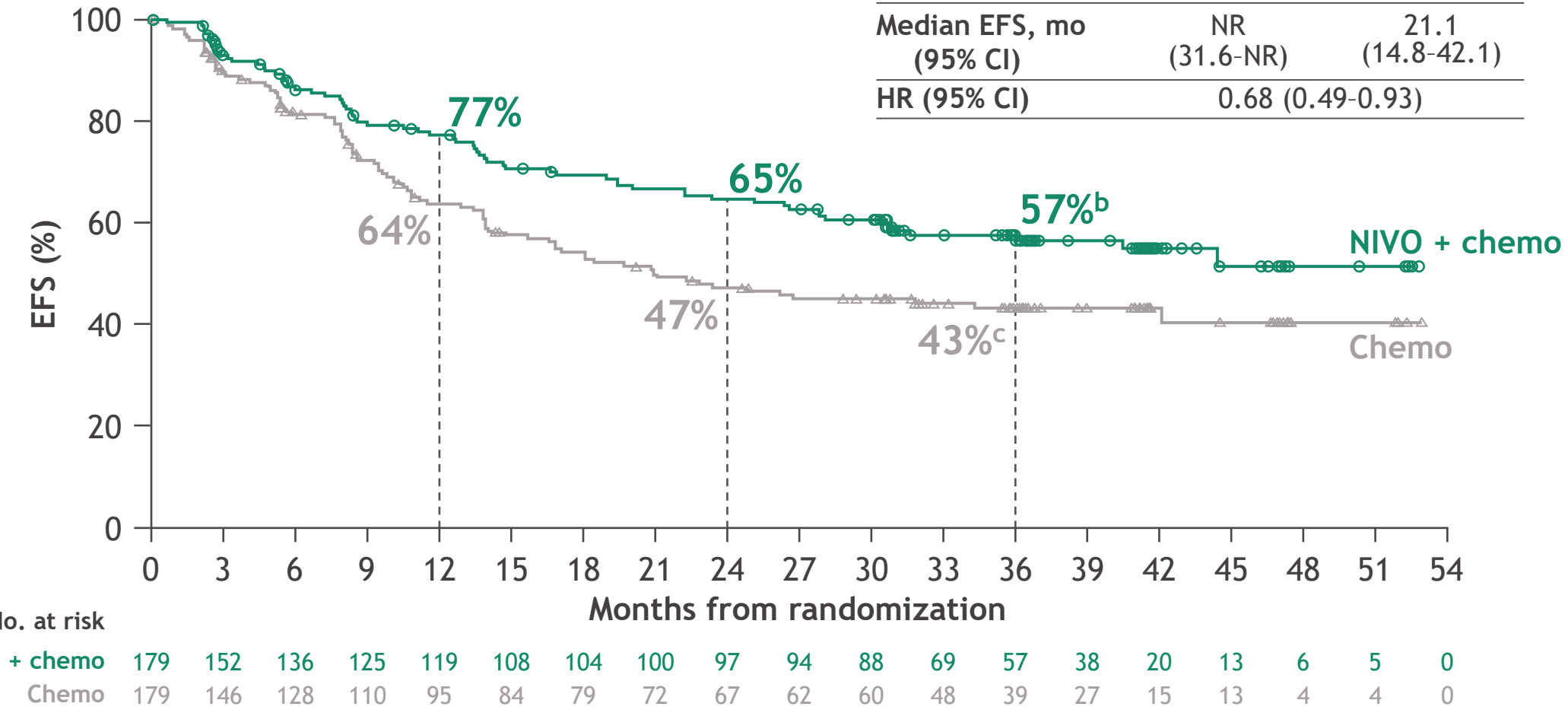


- pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4–29.0)

[a]Per BIPR; pCR: 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]ITT principle: patients who did not undergo surgery counted as non-responders for primary analysis; [c]Calculated by stratified Cochran–Mantel–Haenszel method; [d]pCR rates 95% CI: NIVO + chemo, 18.0–31.0; chemo, 0.6–5.6; [e]Patients who underwent definitive surgery with an evaluable pathology sample for BIPR.

EFS with neoadjuvant NIVO + chemo vs chemo: 3-year update[a]

	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)	

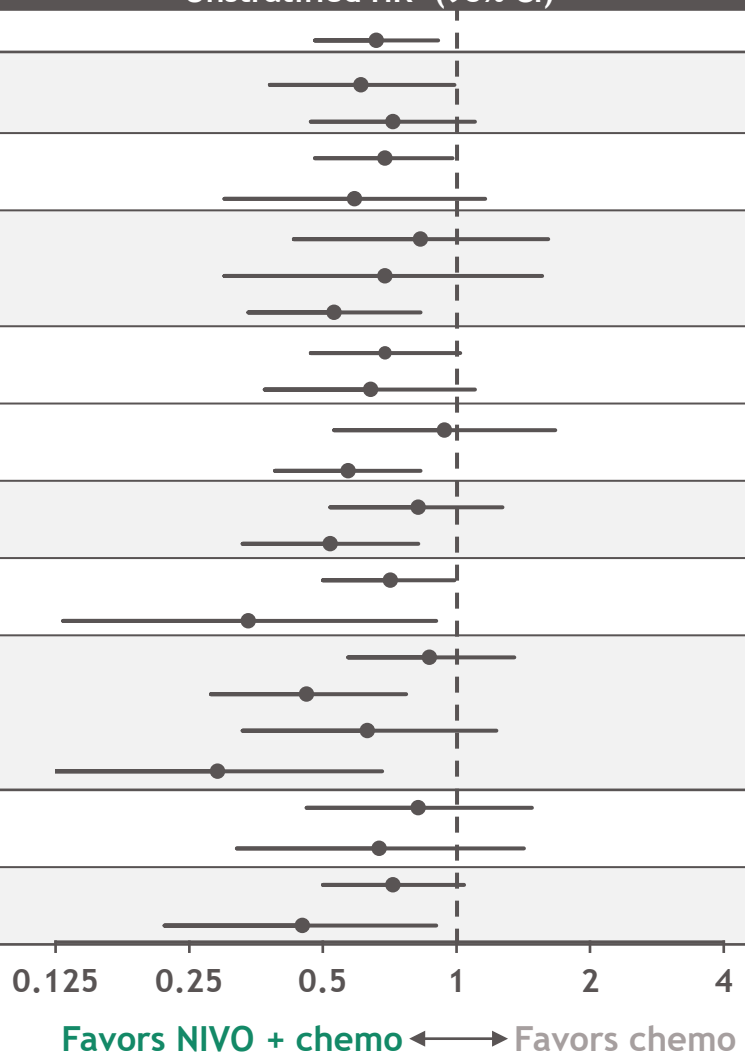


Minimum/median follow-up: 32.9/41.4 months.

[a]Exploratory analysis. Time from randomization to any disease progression precluding surgery, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause per BICR. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b,c]95% CIs for 3-year EFS rates: [b]48-64; [c]35-51.

EFS[a] subgroup analysis: 3-year update

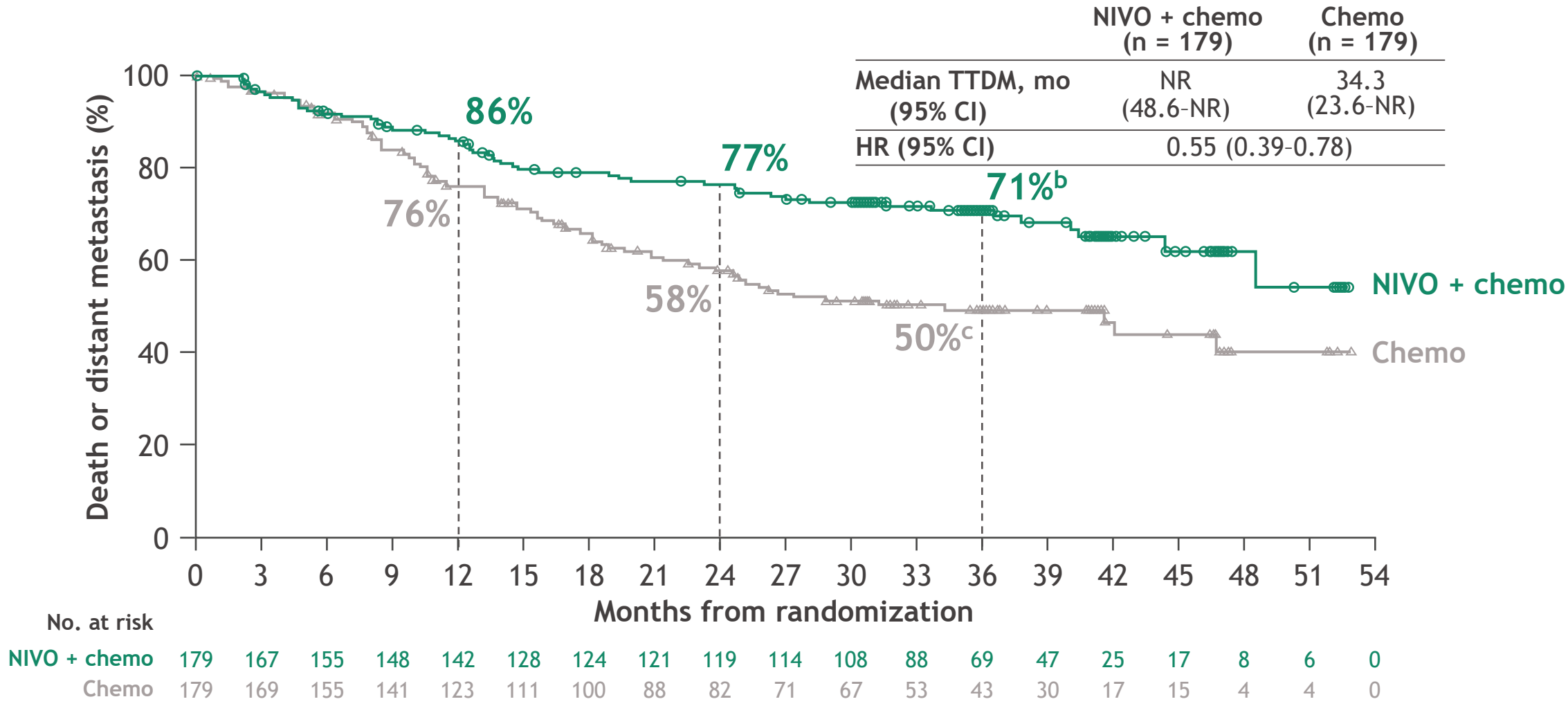
	Median EFS, mo		Unstratified HR[a] (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	NR	21.0		0.66
< 65 years (n = 176)	NR	22.4		0.61
≥ 65 years (n = 182)	40.4	20.9		0.72
Male (n = 255)	44.4	18.0		0.69
Female (n = 103)	NR	NR		0.59
North America (n = 91)	NR	42.1		0.83
Europe (n = 66)	NR	21.1		0.69
Asia (n = 177)	NR	16.5		0.53
ECOG PS 0 (n = 241)	NR	31.8		0.69
ECOG PS 1 (n = 117)	NR	14.0		0.64
Stage IB–II (n = 126)	NR	NR		0.94
Stage IIIA (n = 229)	NR	16.9		0.57
Squamous (n = 182)	40.4	22.9		0.82
Nonsquamous (n = 176)	NR	20.8		0.52
Current/former smoker (n = 318)	NR	23.3		0.71
Never smoker (n = 39)	44.4	10.4		0.34
PD-L1 < 1% (n = 155)	26.4	20.8		0.87
PD-L1 ≥ 1% (n = 178)	NR	26.7		0.46
PD-L1 1%–49% (n = 98)	NR	31.8		0.63
PD-L1 ≥ 50% (n = 80)	NR	19.7		0.29
TMB < 12.3 mut/Mb (n = 102)	44.4	31.8		0.82
TMB ≥ 12.3 mut/Mb (n = 76)	NR	NR		0.67
Cisplatin (n = 258)	44.4	21.1		0.72
Carboplatin (n = 72)	NR	10.6		0.45



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

[a]Per BICR.

TTDM[a] with neoadjuvant NIVO + chemo vs chemo: 3-year update

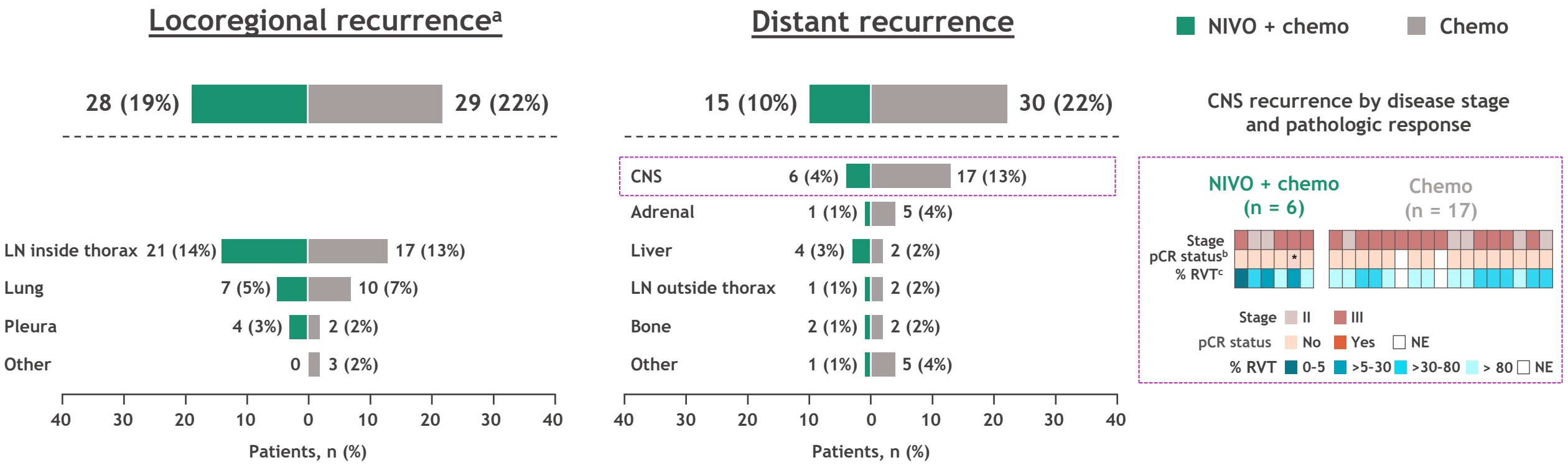


Minimum/median follow-up: 32.9/41.4 months.

[a]Time between the date of randomization and the first date of distant metastasis or the date of death in the absence of distant metastasis per BICR. [b,c]95% CI for 3-year TTDM rates: [b]63-77; [c]41-57.

Recurrence patterns in patients who underwent surgery

- 42/149 patients (28%) in the NIVO + chemo and 56/135 (42%) in the chemo arms had recurrence post surgery



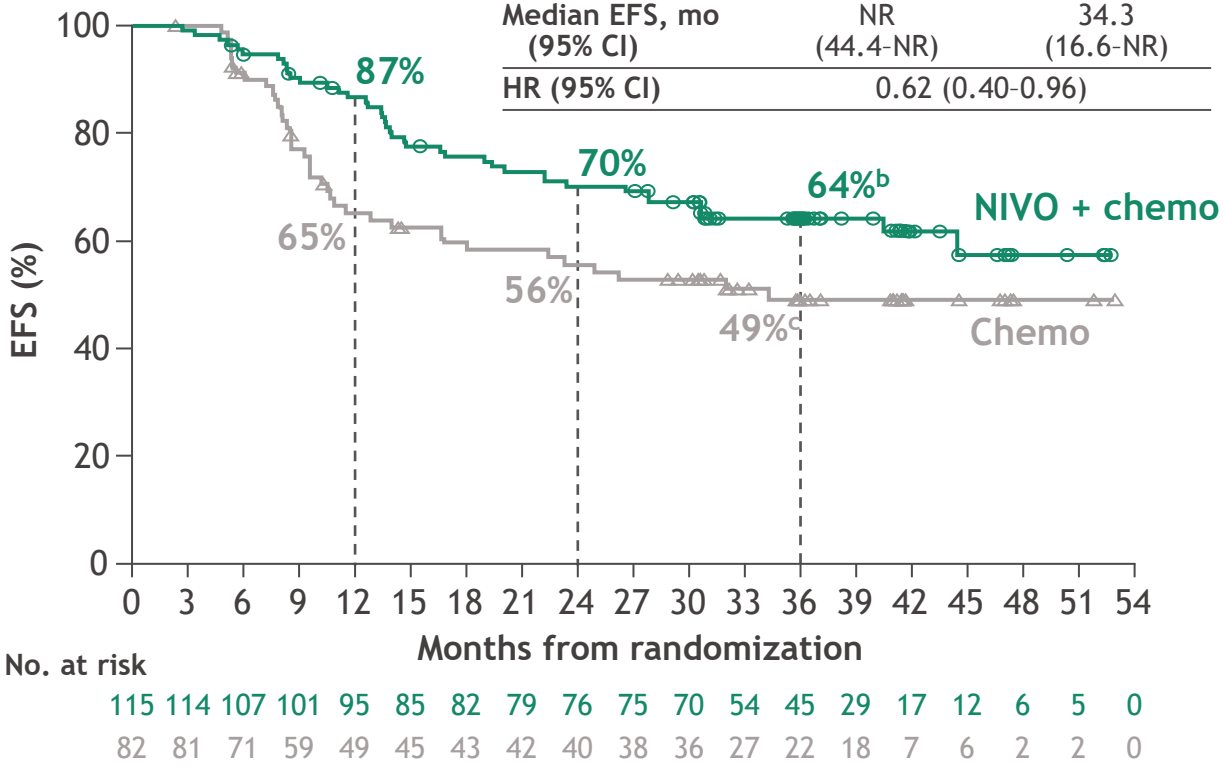
Minimum/median follow-up: 32.9/41.4 months.

[a]Some patients with locoregional recurrence may have had distant recurrence events. [b]Defined as 0% residual viable tumor cells (RVT) in both primary tumor (lung) and sampled LN (*One patient had an MPR, which was defined as ≤ 10% RVT in both primary tumor and sampled LN). [c]In the primary tumor only.

EFS by extent/completeness of resection[a]: 3-year update

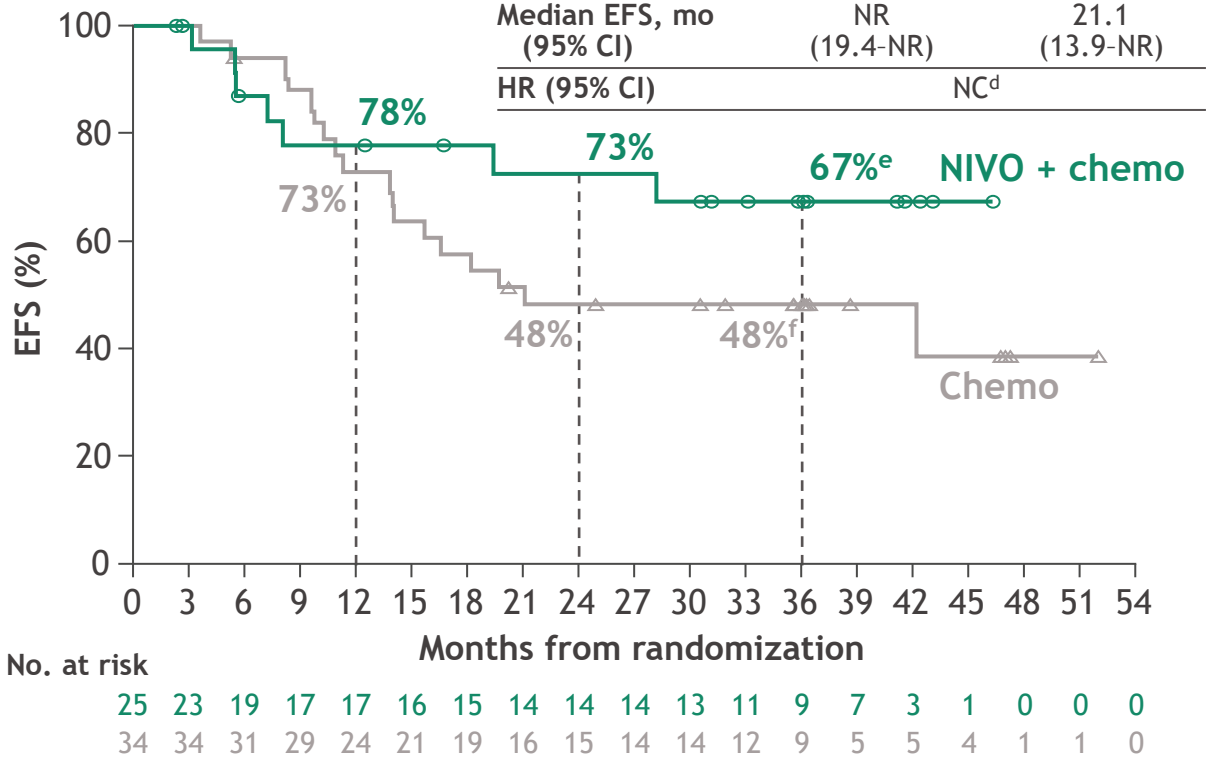
Lobectomy

	NIVO + chemo (n = 115)	Chemo (n = 82)
Median EFS, mo (95% CI)	NR (44.4-NR)	34.3 (16.6-NR)
HR (95% CI)	0.62 (0.40-0.96)	



Pneumonectomy

	NIVO + chemo (n = 25)	Chemo (n = 34)
Median EFS, mo (95% CI)	NR (19.4-NR)	21.1 (13.9-NR)
HR (95% CI)	NC[d]	

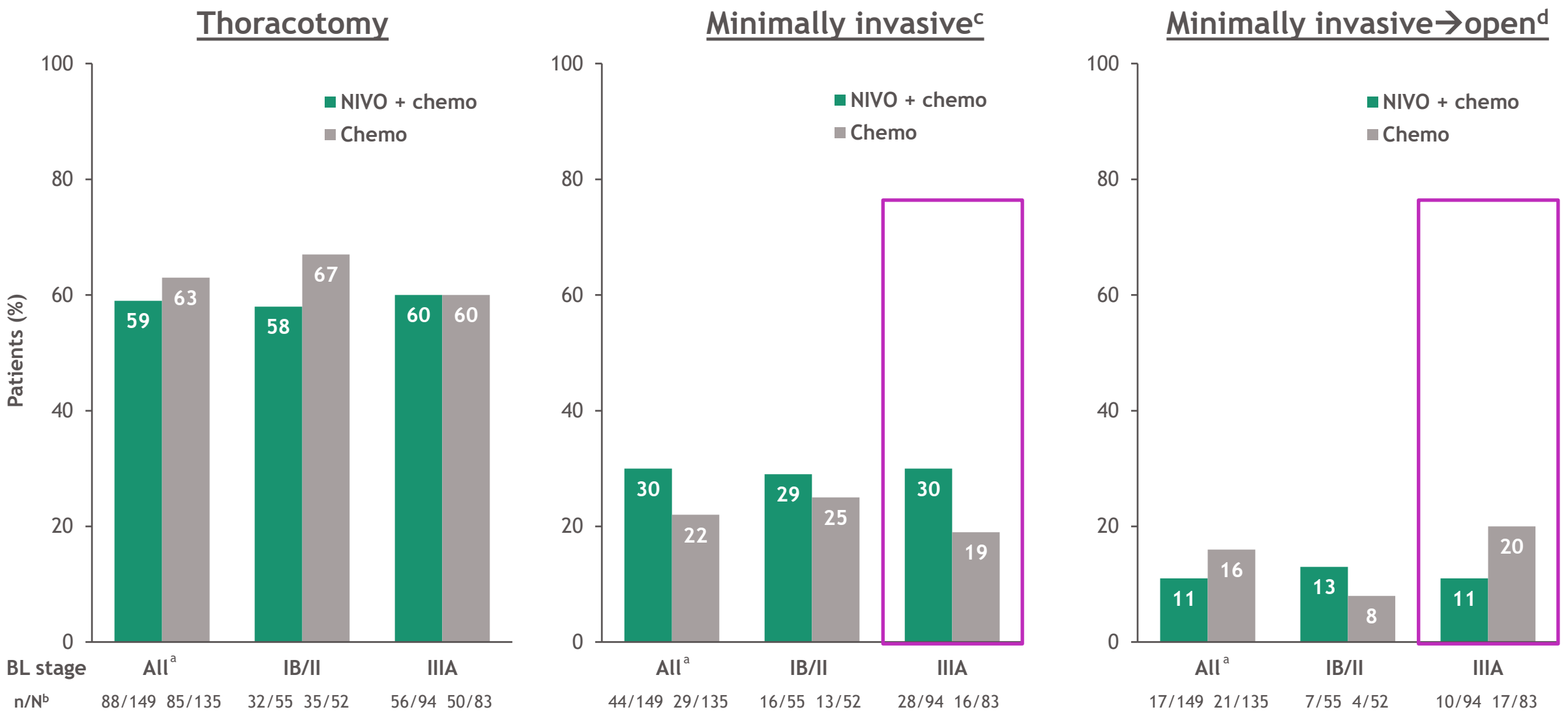


- In patients with R0 resection,[a] 3-year EFS rates were 64%[g] vs 51%[h] for NIVO + chemo vs chemo, respectively (HR, 0.65; 95% CI, 0.43–0.98)

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

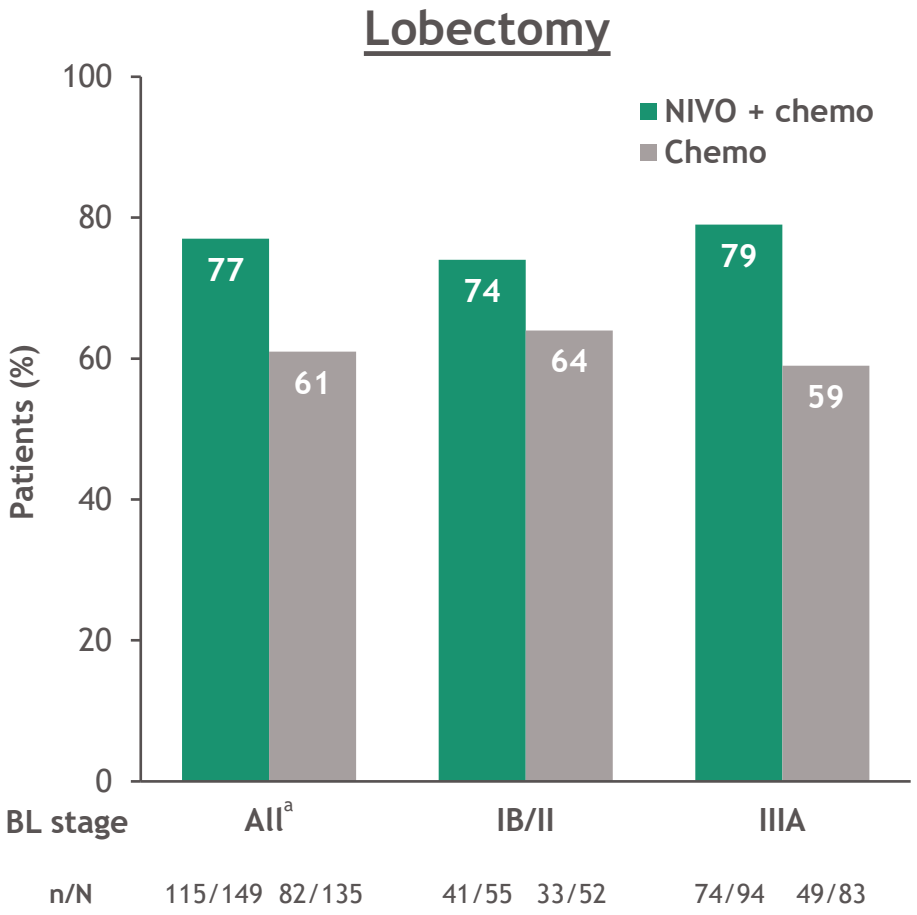
[a]Patients may have had ≥ 1 type of surgery. In the respective NIVO + chemo and chemo arms, surgery types included lobectomy (77% and 61%) and pneumonectomy (17% [11 right; 14 left] and 25% [12 right; 22 left]); patients with R0 resection: 83% and 78%. [b,c]95% CIs for 3-year EFS rates: [b]54-72; [c]37-60. [d]HR not calculated due to insufficient event numbers(< 10 per arm). [e-j]95% CIs for 3-year EFS rates: [e]43-83; [f]31-64; [g]55-72; [h]40-60. R0, no residual tumor.

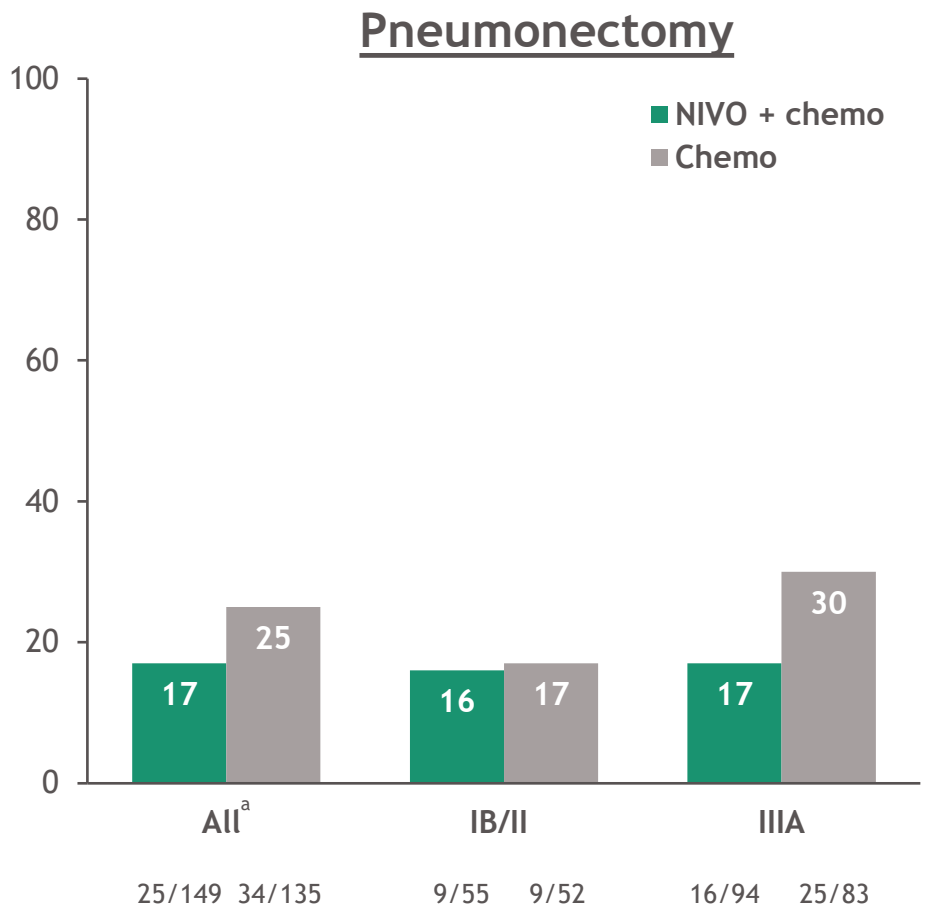
Surgical approach by baseline stage of disease



[a]Patients with all baseline stages of disease and definitive surgery; [b]Denominator based on patients with definitive surgery; [c]Thoracoscopic/robotic; [d]Minimally invasive to thoracotomy.

Type of surgery by baseline stage of disease

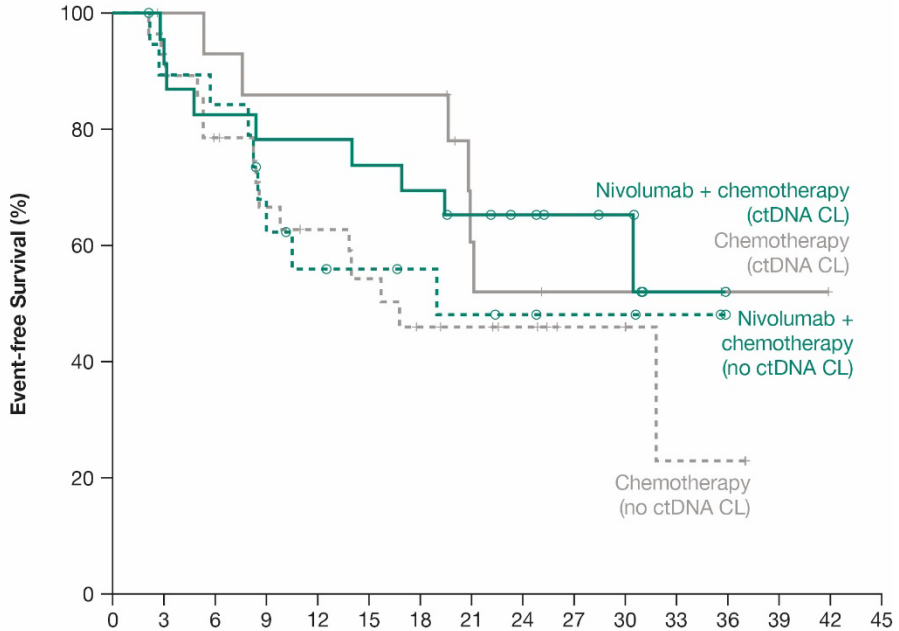




Patients may have had > 1 surgery type. Patient numbers (n/N) for stage IB/II and stage IIIA, respectively, for bilobectomy (NIVO + chemo: 1/55, 2/94; chemo: 2/52, 2/83), sleeve lobectomy (NIVO + chemo: 2/55, 0/94; chemo: 5/52, 5/83), and other (NIVO + chemo: 13/55, 11/94; chemo: 12/52, 9/83). [a]Patients with all baseline stages of disease with surgery.

Can ctDNA be used to predict clinical outcomes?

	Nivolumab + chemotherapy		Chemotherapy	
	ctDNA CL (n=24)	No ctDNA CL (n=19)	ctDNA CL (n=15)	No ctDNA CL (n=28)
Median EFS, mo (95% CI)	NR (16.8–NR)	18.9 (8.3–NR)	NR (19.6–NR)	16.8 (8.3–NR)
HR (95% CI)	0.60 (0.20–1.82)		0.63 (0.20–2.01)	

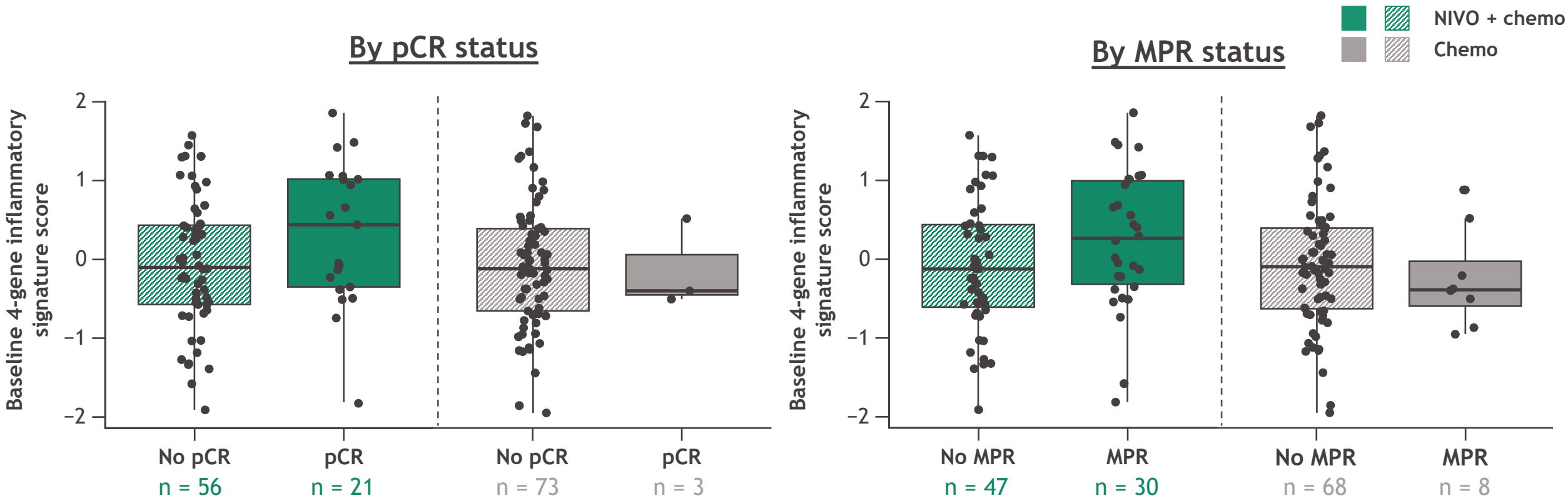


No. at Risk																
Nivolumab + chemotherapy (ctDNA CL)	24	21	19	18	18	17	16	13	11	8	7	1	0	0	0	0
Chemotherapy (ctDNA CL)	15	14	13	12	12	12	12	7	6	5	5	5	3	1	0	0
Nivolumab + chemotherapy (no ctDNA CL)	19	17	16	12	9	8	7	6	5	3	3	2	0	0	0	0
Chemotherapy (no ctDNA CL)	28	26	21	17	15	13	10	9	7	4	3	1	1	0	0	0

Subset analysis of ctDNA clearance during neoadjuvant chemo-nivo for 81/379 (23%) pts enrolled in CM816

Clearance of ctDNA during neoadjuvant treatment showed a non-significant trend toward improved EFS – HR 0.60 (0.20-1.82)

Baseline 4-gene inflammatory signature score[a] by pCR or MPR status



- The 4-gene inflammatory signature, comprised of *CD8A*, *STAT1*, *LAG3*, and *CD274* (encoding PD-L1),[1] was assessed by RNA sequencing of evaluable tumor samples at baseline (NIVO + chemo, n = 77; chemo, n = 76)

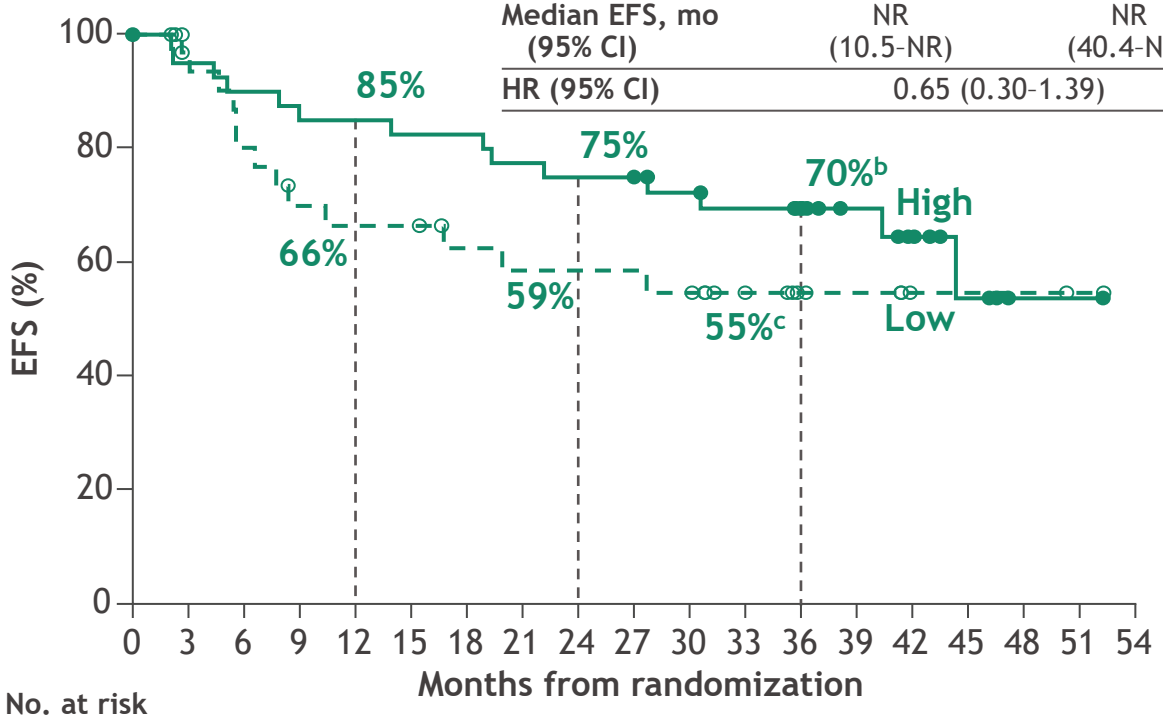
Minimum/median follow-up: 32.9/41.4 months.

[a]Z-scores were calculated using log-transformed counts per million. 1. Lei M, et al. *Clin Cancer Res* 2021:27:3926–3935.

Baseline 4-gene inflammatory signature score[a] and EFS

NIVO + chemo

	Low 4-gene inflammatory score (n = 36)	High 4-gene inflammatory score (n = 41)
Median EFS, mo (95% CI)	NR (10.5-NR)	NR (40.4-NR)
HR (95% CI)	0.65 (0.30-1.39)	

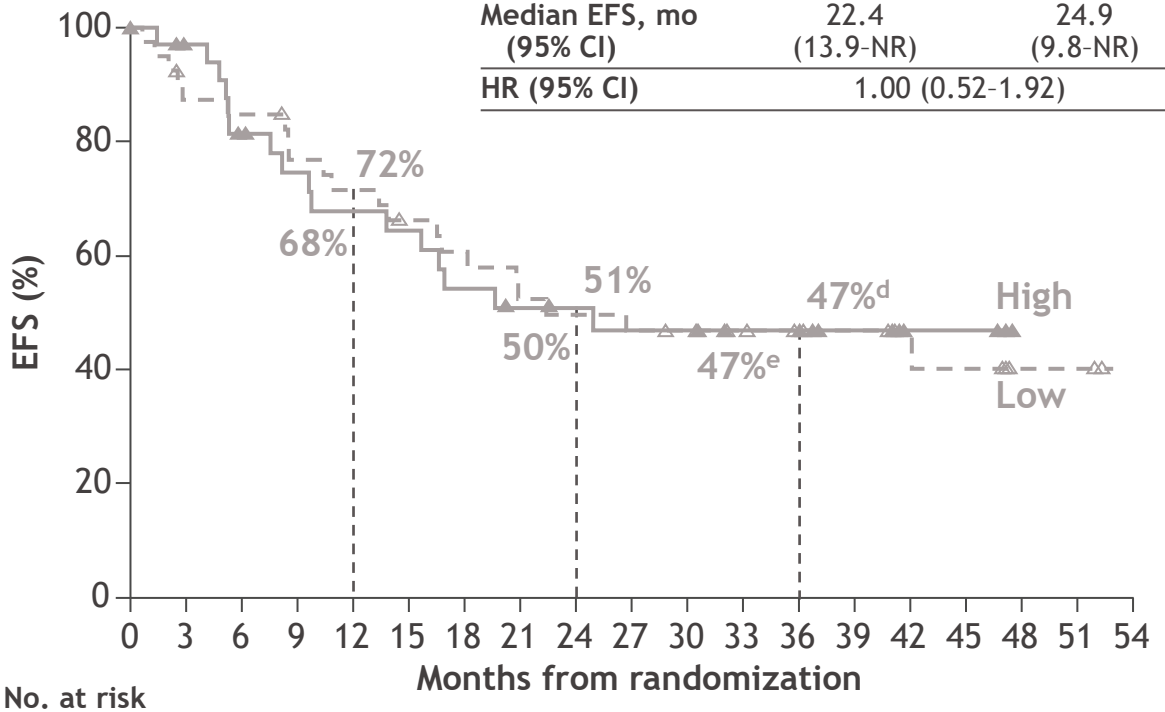


No. at risk

Low	36	29	24	20	19	19	16	15	15	15	14	10	6	5	2	2	2	1	0
High	41	38	36	35	34	33	33	31	30	30	27	25	21	14	10	5	1	1	0

Chemo

	Low 4-gene inflammatory score (n = 40)	High 4-gene inflammatory score (n = 36)
Median EFS, mo (95% CI)	22.4 (13.9-NR)	24.9 (9.8-NR)
HR (95% CI)	1.00 (0.52-1.92)	



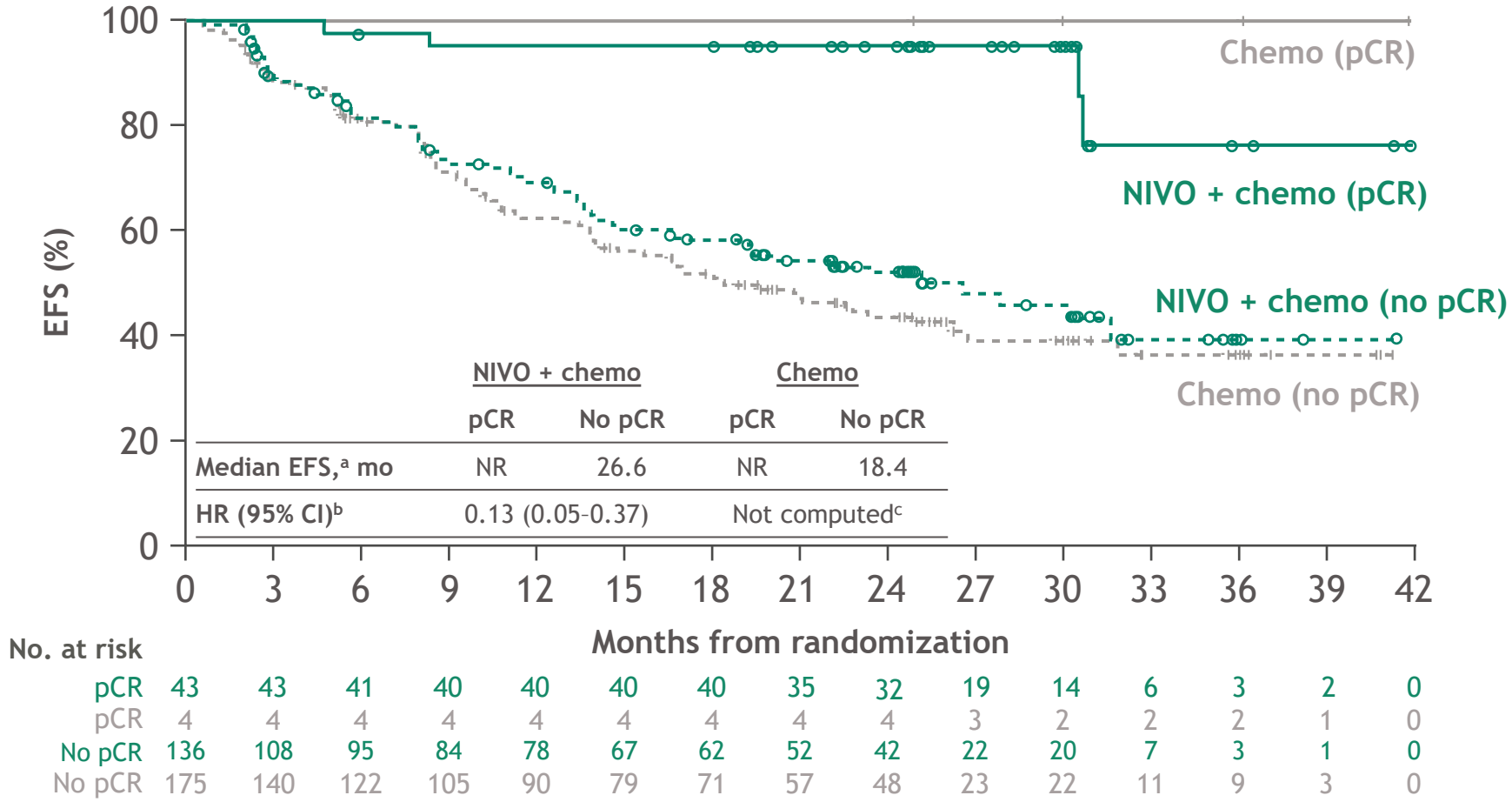
No. at risk

Low	40	34	33	29	27	24	22	19	18	17	16	13	11	9	7	6	3	3	0
High	36	31	25	22	20	19	16	14	13	12	12	9	9	6	3	3	0	0	0

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

[a]4-gene inflammatory signature scores were grouped as high or low relative to the median z-score across the dataset. [b-e]95% CI for 3-year EFS rates: [b]56-86; [c]39-77; [d]32-69; [e]33-66.

Exploratory analysis: EFS by pCR status



	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median EFS,[a] mo	NR	26.6	NR	18.4
HR (95% CI)[b]	0.13 (0.05–0.37)		Not computed[c]	

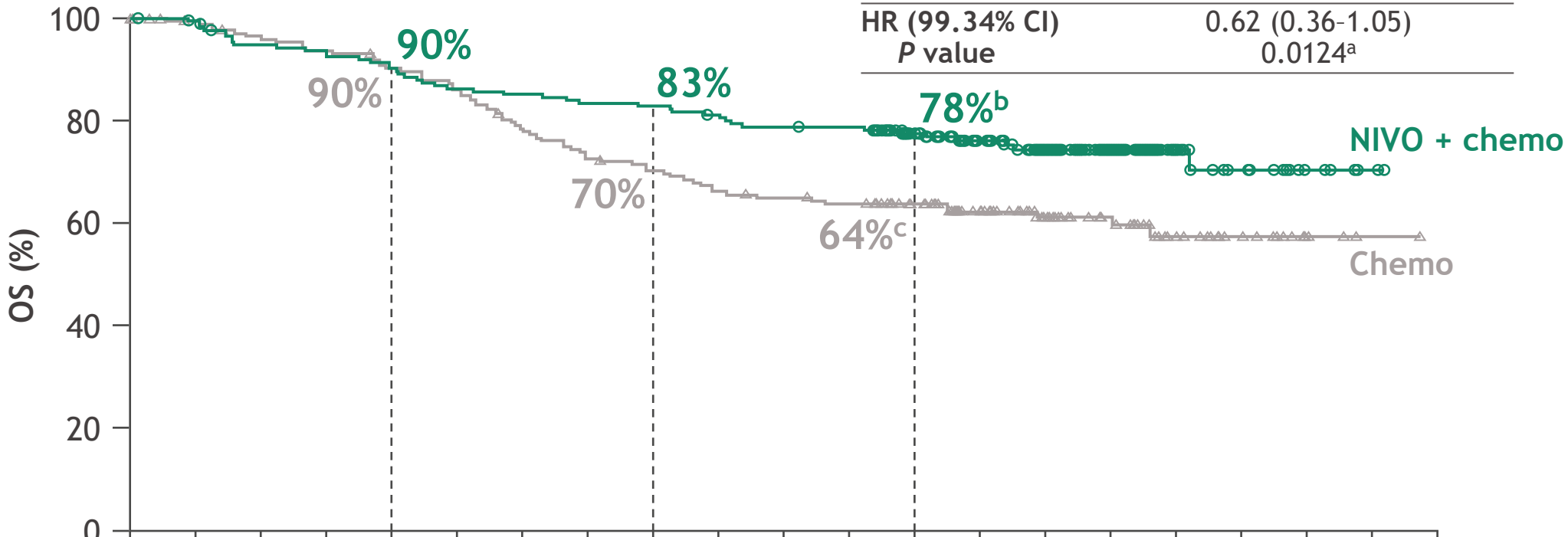
- pCR rates were significantly improved with NIVO + chemo vs chemo (24.0% vs 2.2%)
- In patients without pCR, HR (95% CI) for NIVO + chemo vs chemo was 0.84 (0.61–1.17)

Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]95% CI = 30.6–NR (NIVO + chemo, pCR), 16.6–NR (NIVO + chemo, no pCR) and NR–NR (chemo, pCR), 13.9–26.2 (chemo, no pCR); [b]In the pooled patient population (NIVO + chemo and chemo arms combined), EFS HR (95% CI) was 0.11 (0.04–0.29) for patients with pCR vs those without pCR; [c]HR was not computed for the chemo arm due to only 4 patients having a pCR.

OS with neoadjuvant NIVO + chemo vs chemo: 3-year update

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS, mo (95% CI)	NR (NR–NR)	NR (46.8–NR)
HR (99.34% CI)	0.62 (0.36–1.05)	
P value	0.0124[a]	



No. at risk

NIVO + chemo	179	176	166	163	158	151	149	146	145	141	137	136	117	95	67	44	23	14	6	2	0
Chemo	179	173	166	162	155	149	134	124	119	112	109	106	95	75	52	38	22	14	4	1	0

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

[a]Significance boundary for OS was not crossed at this interim analysis. [b,c]95% CIs for 3-year OS rates: [b]71–83; [c]56–70.

Current Status

- Neoadjuvant chemotherapy plus nivolumab FDA approved for resectable NSCLC irrespective of PD-L1 status on March 8, 2022
- Current NCCN guidelines 2023.V2 – “All patients should be evaluated for preoperative therapy, with strong consideration for nivolumab + chemotherapy for those patients with tumors ≥4cm or node positive and no contraindications to immune checkpoint inhibitors.”

Select Phase III Neoadjuvant Chemo plus PD-(L)1 antibody studies in NSCLC

Trial Identifier	Study Title (accrual)	Stage (ed)	Backbone	Intervention	Adjuvant IO Treatment	Primary Endpoints
NCT02998528	Checkmate 816 (n=360)	IB-IIIA (7^{th})	3 cycles of Cis or Carbo + Vin/Peme/Gem/Doce/Pacli	+/- Nivo I+N closed	No	pCR* EFS*
NCT03425643	Keynote 671 (n=786)	IIA-IIIA (8^{th})	4 cycles of Cis + Peme or Gem	+ Pembro or placebo	Pembro/placebo for one year	EFS** OS
NCT03456063	IMPOWER 030 (n=450)	II-IIIB (8^{th})	4 cycles of Cis/Carbo + nab-pac/peme/gem	+/- Atezo	Atezo or BSC for one year	MPR EFS
NCT03800134	AEGEAN (n=800)	IIA-IIIB (8^{th})	4 cycles Cis + gem or peme Carbo + peme or pacli	+ Durva or placebo	Durvalumab or placebo for 1 year	pCR*** EFS
NCT04025879	CheckMate 77T (n=452)	II-IIIB (8^{th})	3-4 cycles Cis/Carbo + pemetrexed/docetaxel or paclitaxel	+ Nivo or placebo	Adj nivo or placebo	EFS

*positive for pCR and EFS endpoints **reportedly positive for EFS endpoint ***positive for pCR and EFS endpoints

IMpower010: Adjuvant Atezolizumab

N = 1280

Key Eligibility Criteria

- Completely resected stage IB (≥4cm)–IIIA NSCLC (per TNM 7th edition)
- ECOG performance status 0–1
- PD-L1 all-comers

Stratified by

Sex, histology, stage of disease (IB vs II vs IIIA), PD-L1 expression*

Up to 4 cycles of:
Cisplatin 75 mg/m²
+
Vinorelbine 30 mg/m²
or
Docetaxel 75 mg/m²
or
Gemcitabine 1250 mg/m²
or
Pemetrexed 500 mg/m²

N = 1005

R
1:1

No crossover permitted

Atezolizumab 1200 mg
Q3W, 16 cycles

Best supportive care

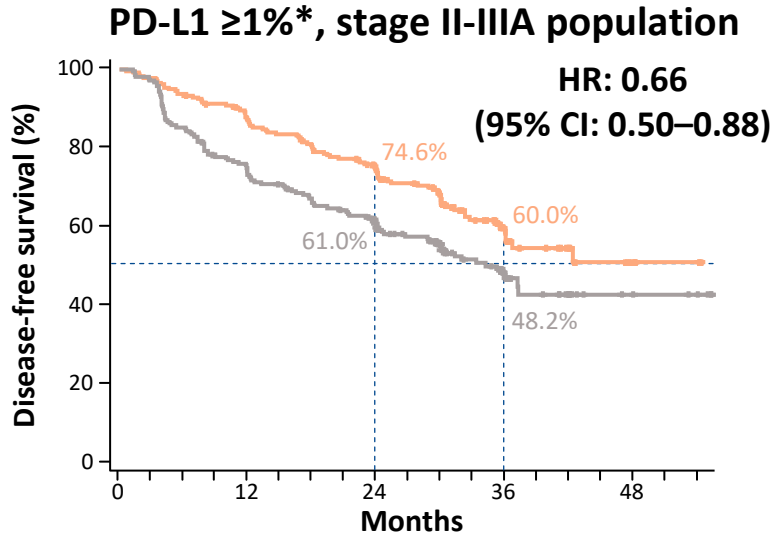
Primary endpoints

- DFS tested hierarchically
  - PD-L1 ≥1%†, stage II–IIIA population
  - All-randomized stage II–IIIA population
  - ITT population IB–IIIA

Secondary endpoints

- OS in ITT population
- DFS in patients with PD-L1 ≥50%‡ and stage II–IIIA disease
- 3- and 5-year DFS in all populations

IMpower010: DFS benefit observed among patients with PD-L1+ stage II-IIIA disease



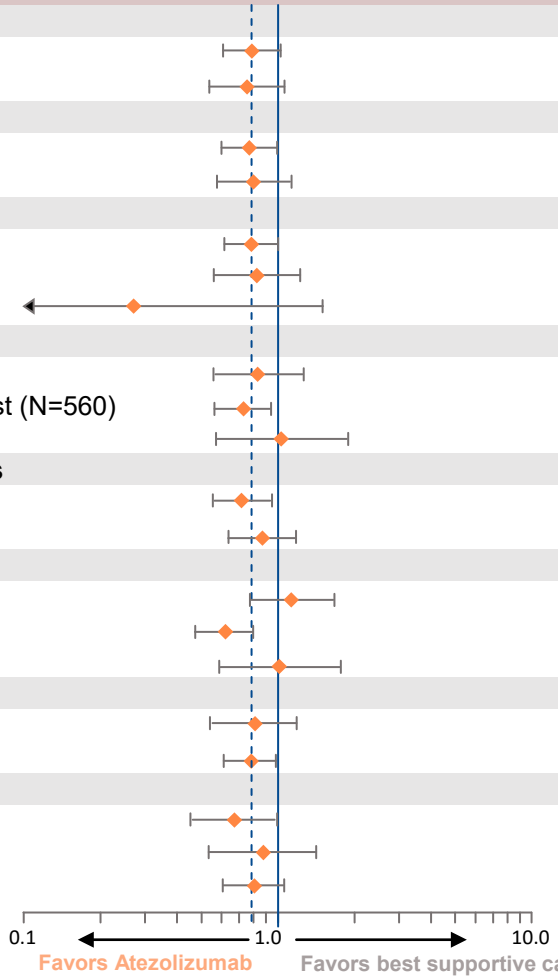
	Atezo (n=248)	BSC (n=228)
Median DFS, mo	NR	35.3
HR (95% CI), *P* value	0.66 (0.50–0.88), 0.004[†]	

Median follow-up: 32.8 mo

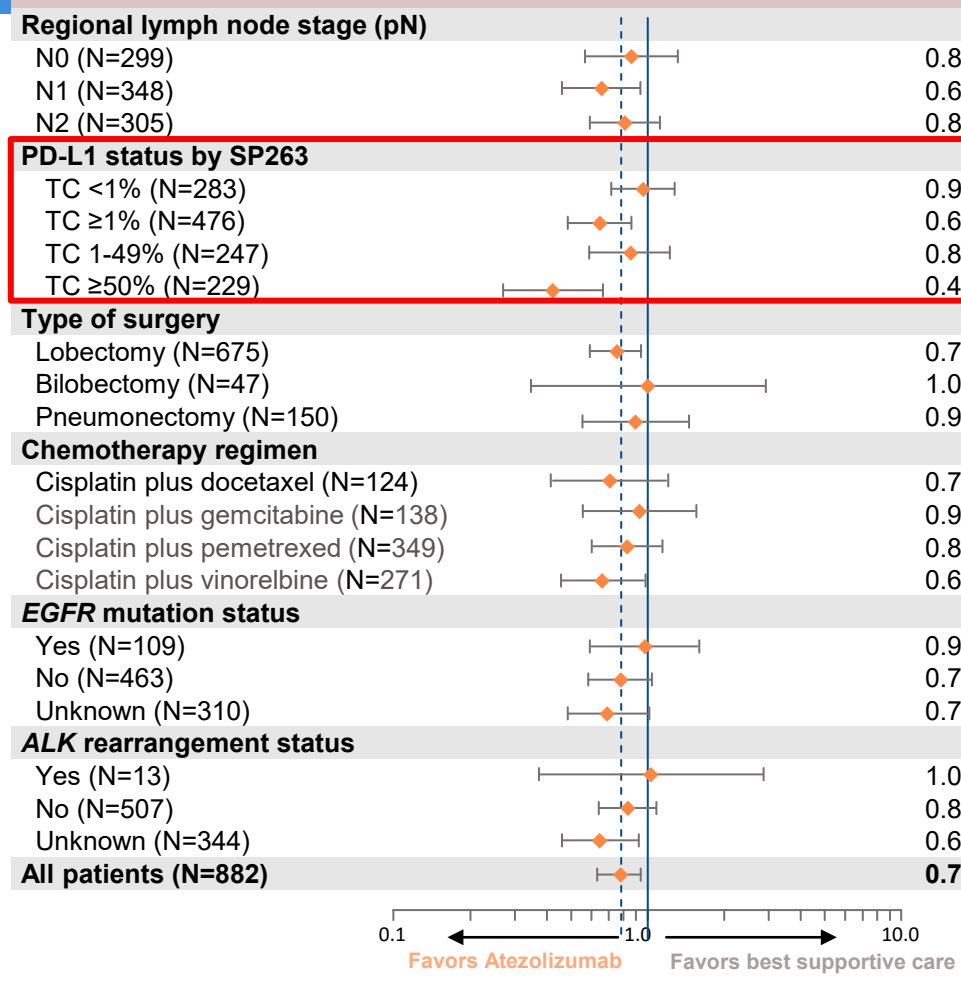
- Median DFS in the ITT population (IB-IIIA) was not reached with atezolizumab and 37.2 months with BSC (HR: 0.81; 95% CI: 0.67–0.99) after median follow-up of 32.2 months; this endpoint did not cross the significance boundary and analysis is ongoing

Felip E et al. *Lancet*. 2021;398(10308):1344-1357.

IMpower010: Adjuvant atezolizumab shows enriched benefit with increased PD-L1 expression



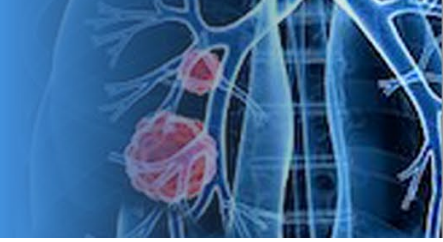
	HR (95% CI)
Age	
<65 years (N=544)	0.79 (0.61-1.03)
≥65 years (N=388)	0.76 (0.54-1.05)
Sex	
Male (N=589)	0.76 (0.59-0.99)
Female (N=293)	0.80 (0.57-1.13)
Race	
White (N=631)	0.78 (0.61-1.00)
Asian (N=277)	0.82 (0.55-1.22)
Unknown (N=16)	0.27 (0.05-1.50)
Region	
Asia-Pacific (N=219)	0.83 (0.55-1.25)
Europe and the Middle East (N=560)	0.73 (0.56-0.94)
North America (N=101)	1.03 (0.57-1.89)
ECOG performance status	
0 (N=491)	0.72 (0.55-0.95)
1 (N=388)	0.87 (0.64-1.18)
Tobacco use history	
Never (N=196)	1.13 (0.77-1.67)
Previous (N=547)	0.62 (0.47-0.81)
Current (N=139)	1.01 (0.58-1.75)
Histology	
Squamous (N=294)	0.80 (0.54-1.18)
Non-squamous (N=588)	0.78 (0.61-0.99)
Stage	
IIA (N=295)	0.68 (0.46-1.00)
IIB (N=174)	0.88 (0.54-1.42)
IIIA (N=413)	0.81 (0.61-1.06)



	HR (95% CI)
Regional lymph node stage (pN)	
N0 (N=299)	0.88 (0.57-1.35)
N1 (N=348)	0.67 (0.47-0.95)
N2 (N=305)	0.83 (0.61-1.13)
PD-L1 status by SP263	
TC <1% (N=283)	0.97 (0.72-1.31)
TC ≥1% (N=476)	0.66 (0.49-0.87)
TC 1-49% (N=247)	0.87 (0.60-1.26)
TC ≥50% (N=229)	0.43 (0.27-0.68)
Type of surgery	
Lobectomy (N=675)	0.77 (0.61-0.97)
Bilobectomy (N=47)	1.02 (0.35-2.98)
Pneumonectomy (N=150)	0.91 (0.56-1.47)
Chemotherapy regimen	
Cisplatin plus docetaxel (N=124)	0.72 (0.42-1.23)
Cisplatin plus gemcitabine (N=138)	0.94 (0.56-1.57)
Cisplatin plus pemetrexed (N=349)	0.84 (0.61-1.16)
Cisplatin plus vinorelbine (N=271)	0.67 (0.46-0.99)
***EGFR* mutation status**	
Yes (N=109)	0.99 (0.60-1.62)
No (N=463)	0.79 (0.59-1.05)
Unknown (N=310)	0.70 (0.49-1.01)
***ALK* rearrangement status**	
Yes (N=13)	1.04 (0.38-2.90)
No (N=507)	0.85 (0.66-1.10)
Unknown (N=344)	0.66 (0.46-0.93)
All patients (N=882)	**0.79 (0.64-0.96)**

Felip E et al. *Lancet*. 2021;398(10308):1344-1357.

PEARLS/KEYNOTE-091 Study Design



Randomized, Triple-Blind, Phase 3 Trial

Eligibility for Registration

- Confirmed stage IB (T ≥4 cm), II, or IIIA NSCLC per AJCC v7
- Complete surgical resection with negative margins (R0)
- Provision of tumor tissue for PD-L1 testing

PD-L1 testing
done centrally using PD-L1 IHC 22C3 pharmDx

Eligibility for Randomization

- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemotherapy
  - Considered for stage IB (T ≥4 cm) disease
  - Strongly recommended for stage II and IIIA disease
  - Limited to ≤4 cycles

R
1:1

Pembrolizumab 200 mg Q3W for ≤18 administrations (~1 yr)

Placebo Q3W for ≤18 administrations (~1 yr)

Stratification Factors

- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points

- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points

- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

Courtesy: Dr. Luis Paz-Ares

Baseline Characteristics: Overall and PD-L1 TPS ≥50% Populations

	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 590)	Placebo (N = 587)	Pembro (N = 168)	Placebo (N = 165)
Age, median (range)	65.0 y (31-87)	65.0 y (37-85)	64.5 y (38-82)	65.0 y (37-85)
Male	68.0%	68.7%	72.0%	70.3%
Geographic region				
Asia	18.0%	17.9%	17.3%	17.6%
Eastern Europe	19.7%	19.3%	18.5%	18.2%
Western Europe	51.4%	51.3%	53.6%	53.9%
Rest of world	11.0%	11.6%	10.7%	10.3%
ECOG PS 1	35.6%	41.6%	31.0%	38.8%
Current/former smoker	85.3%	88.8%	91.7%	92.1%
***EGFR* mutation**[a]	6.6%	5.8%	3.6%	3.0%
***ALK* translocation**[b]	1.2%	1.2%	1.8%	0.0%

[a] *EGFR* status unknown for 56.4% in pembro arm and 57.4% in placebo arm in overall population and 62.5% and 56.4%, respectively, in the TPS ≥50% population.
[b] *ALK* status unknown for 60.5% in pembro arm and 66.4% in placebo arm in overall population and 65.5% and 64.8%, respectively, in the TPS ≥50% population.

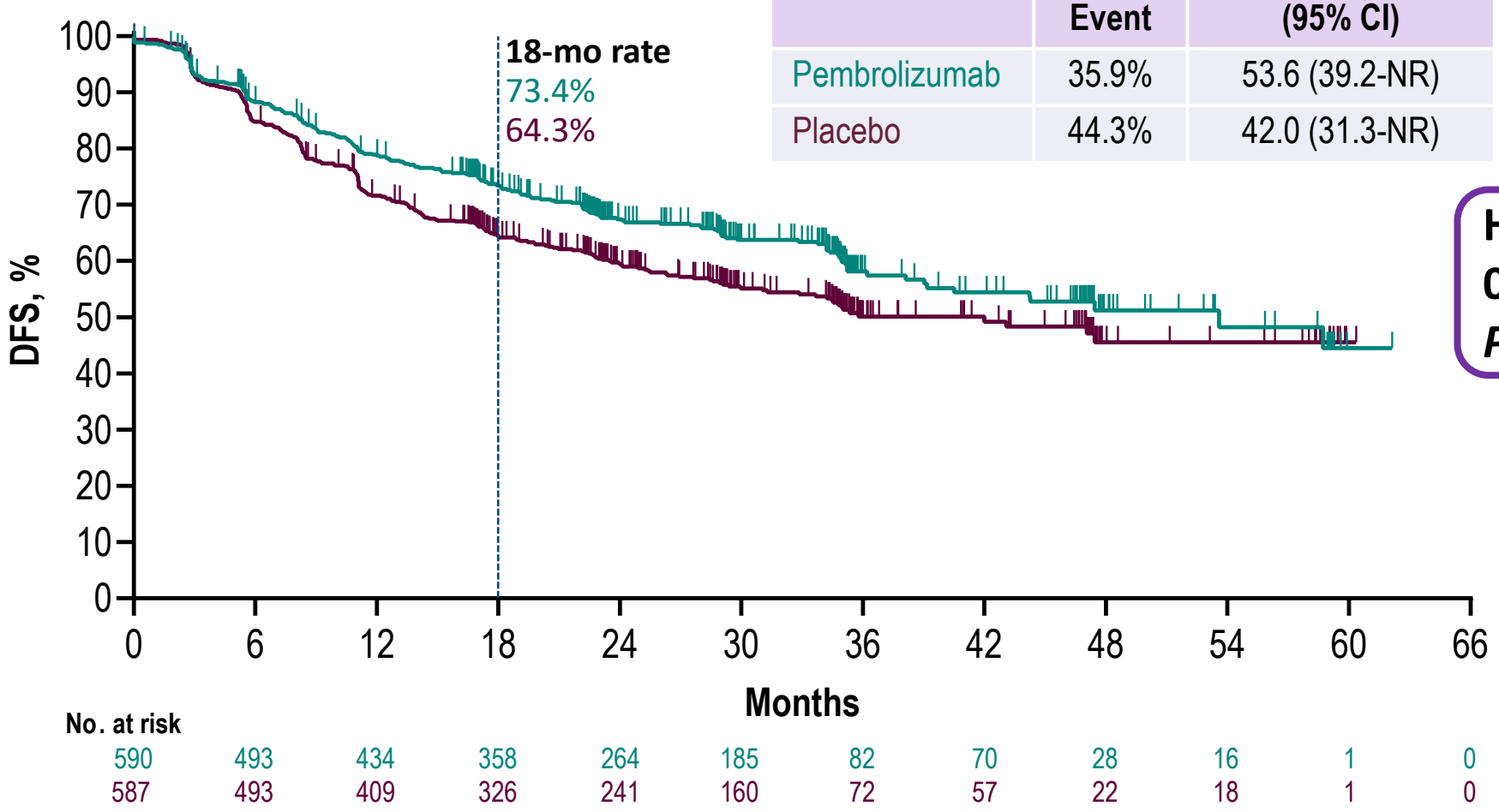
	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 590)	Placebo (N = 587)	Pembro (N = 168)	Placebo (N = 165)
Nonsquamous histology	67.5%	61.8%	61.3%	63.6%
Received adjuvant chemotherapy	85.8%	85.9%	85.1%	85.5%
Pathologic stage[c]				
IB	14.2%	14.5%	12.5%	13.3%
II	55.8%	57.6%	56.5%	56.4%
IIIA	30.0%	27.6%	31.0%	30.3%
Regional lymph node stage (pN)				
N0	39.5%	43.8%	28.0%	35.8%
N1	39.5%	38.0%	50.0%	43.6%
N2	21.0%	18.2%	22.0%	20.6%
PD-L1 TPS				
<1%	39.5%	39.5%	0.0%	0.0%
1-49%	32.0%	32.4%	0.0%	0.0%
≥50%	28.5%	28.1%	100%	100%

[c] 2 (0.3%) participants in the placebo group had stage IV disease; neither had TPS ≥50%.

Data cutoff date: September 20, 2021

DFS, Overall Population

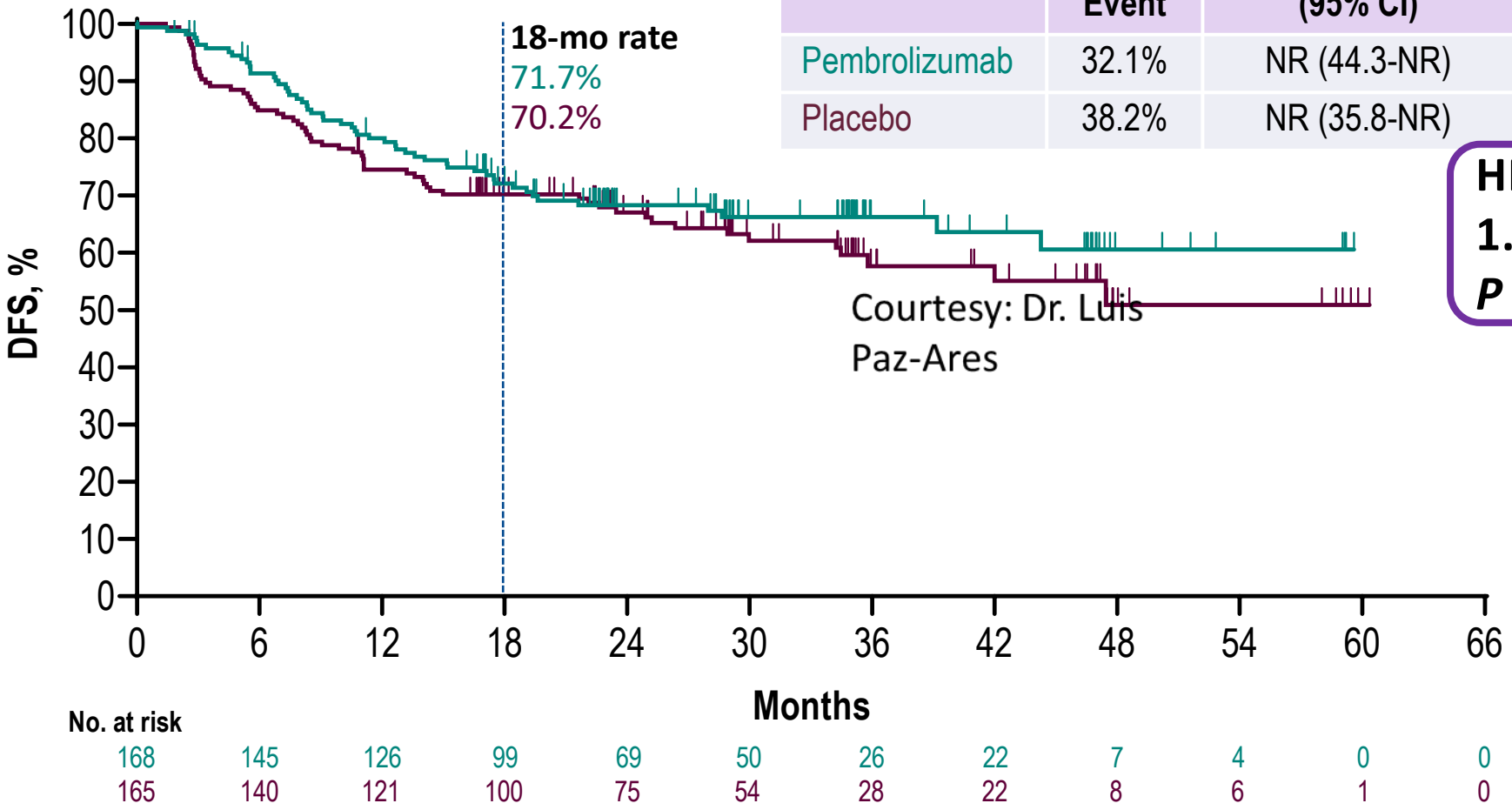
	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)



HR 0.76 (95% CI, 0.63-0.91)
***P* = 0.0014**

Courtesy: Dr. Luis Paz-Ares

DFS, PD-L1 TPS ≥50% Population

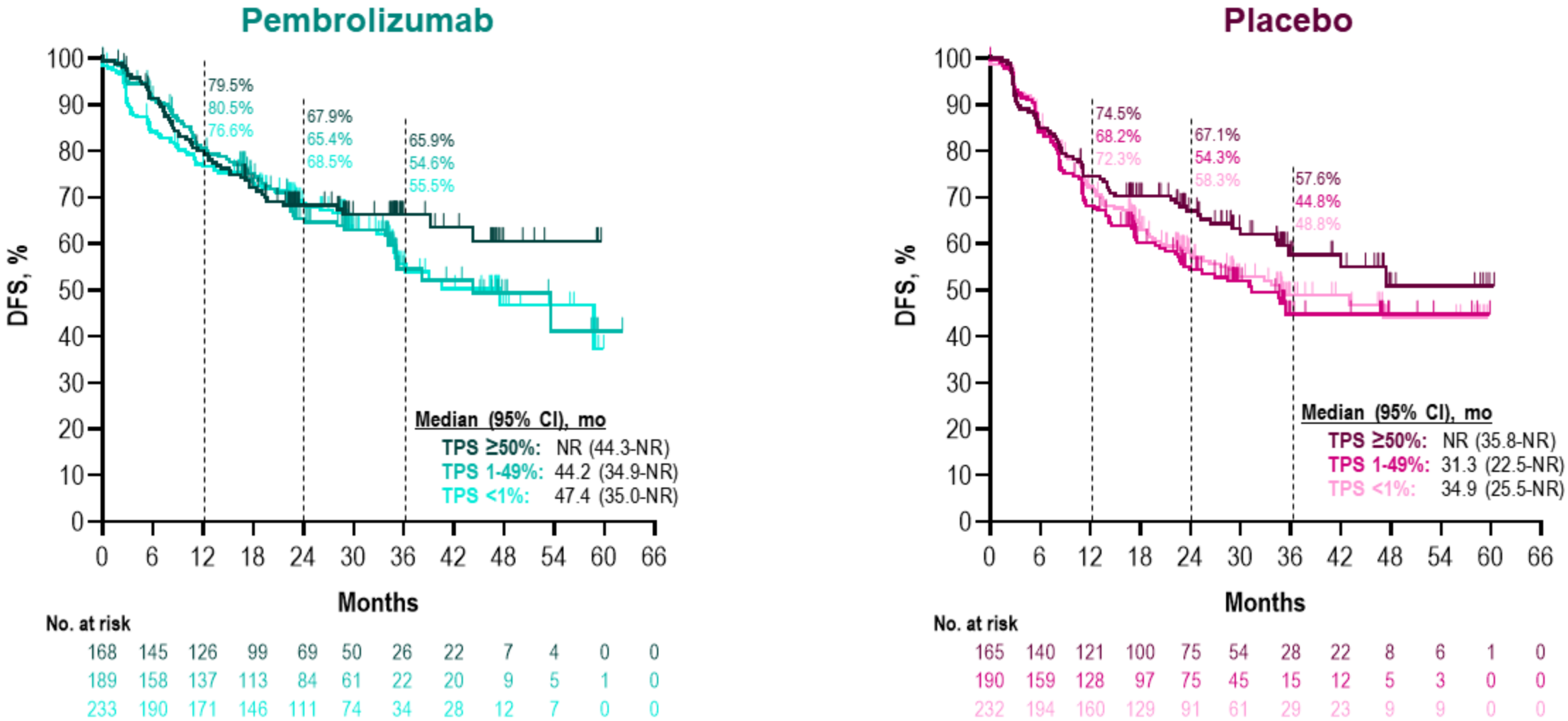


	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	32.1%	NR (44.3-NR)
Placebo	38.2%	NR (35.8-NR)

HR 0.82 (95% CI, 0.57-1.18)
***P* = 0.14**

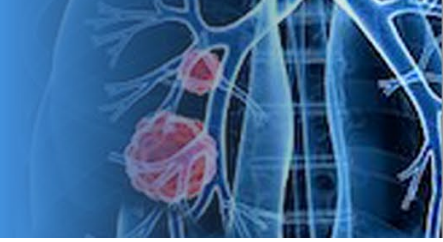
Courtesy: Dr. Luis Paz-Ares

DFS: Pembrolizumab and Placebo by PD-L1 TPS



Data cutoff date: September 20, 2021

Summary of Adverse Events



	Pembrolizumab (N = 580)	Placebo (N = 581)
Any	556 (95.9%)	529 (91.0%)
Grade 3-5	198 (34.1%)	150 (25.8%)
Led to death	11 (1.9%)	6 (1.0%)
Treatment-related	4 (0.7%)[a]	0 (0.0%)
Serious	142 (24.5%)	90 (15.5%)
Led to treatment discontinuation	115 (19.8%)	34 (5.9%)
Led to treatment interruption	221 (38.1%)	145 (25.0%)

[a] 1 participant each with myocarditis + cardiogenic shock, myocarditis + septic shock, pneumonia, and sudden death.

Courtesy: Dr. Luis Paz-Ares

AEGEAN: A Phase 3 Trial of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab in Patients with Resectable NSCLC

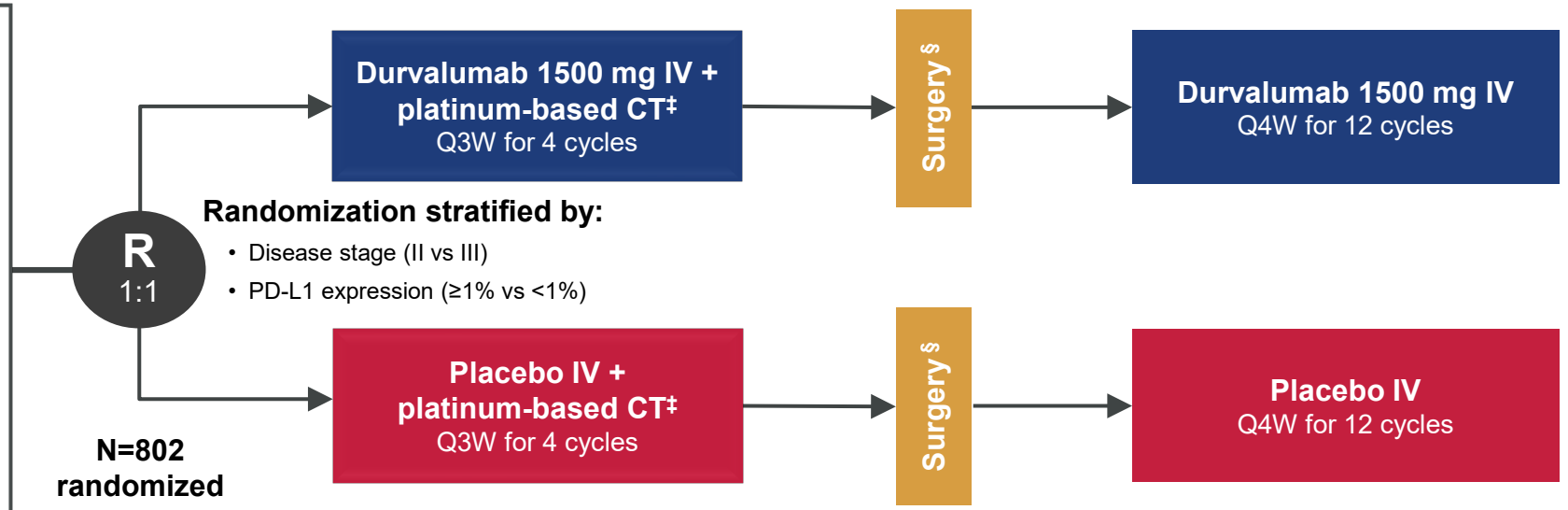
John V. Heymach[1], David Harpole[2], Tetsuya Mitsudomi[3], Janis M. Taube[4], Gabriella Galffy[5], Maximilian Hochmair[6], Thomas Winder[7], Ruslan Zukov[8], Gabriel Garbaos[9], Shugeng Gao[10], Hiroaki Kuroda[11], Jian You[12], Kang-Yun Lee[13], Lorenzo Antonuzzo[14], Mike Aperghis[15], Gary J. Doherty[15], Helen Mann[15], Tamer M. Fouad[16], Martin Reck[17]

[1]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas, USA; [2]Department of Surgery, Duke University Medical Center, Durham, North Carolina, USA; [3]Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan; [4]Bloomberg–Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Kimmel Cancer Center, Baltimore, Maryland, USA; [5]Pest County Pulmonology Hospital, Törökbálint, Hungary; [6]Department of Respiratory and Critical Care Medicine, Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Klinik Floridsdorf, Vienna, Austria; [7]Department of Hematology, Oncology, Gastroenterology and Infectiology, Landeskrankenhaus Feldkirch, Feldkirch, Austria; [8]Krasnoyarsk State Medical University, Krasnoyarsk, Russia; [9]Fundación Estudios Clínicos, Santa Fe, Argentina; [10]Thoracic Surgery Department, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [11]Department of Thoracic Surgery, Aichi Cancer Center Hospital, Aichi, Japan; [12]Department of Lung Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, China; [13]Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; [14]Clinical Oncology Unit, Careggi University Hospital, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [15]AstraZeneca, Cambridge, UK; [16]AstraZeneca, New York, NY, USA; [17]Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany

AEGEAN: a phase 3, global, randomized, double-blind, placebo-controlled study

Study population

- Treatment-naïve
- ECOG PS 0 or 1
- Resectable NSCLC* (stage IIA–IIIB[N2]; AJCC 8th ed)
- Lobectomy, sleeve resection, or bilobectomy as planned surgery*
- Confirmed PD-L1 status†
- No documented *EGFR/ALK* aberrations*



Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented *EGFR/ALK* aberrations¶

Primary:

- pCR by central lab (per IASLC 2020[1])
- EFS using BICR (per RECIST v1.1)

Key secondary:

- MPR by central lab (per IASLC 2020[1])
- DFS using BICR (per RECIST v1.1)
- OS

*The protocol was amended while enrollment was ongoing to exclude (1) patients with tumors classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with documented *EGFR/ALK* aberrations. †Ventana SP263 immunohistochemistry assay. ‡Choice of CT regimen determined by histology and at the investigator's discretion. For non-squamous: cisplatin + pemetrexed or carboplatin + pemetrexed. For squamous: carboplatin + paclitaxel or cisplatin + gemcitabine (or carboplatin + gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment). §Post-operative radiotherapy (PORT) was permitted where indicated per local guidance. ¶All efficacy analyses reported in this presentation were performed on the mITT population, which includes all randomized patients who did not have documented *EGFR/ALK* aberrations. AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; DFS, disease-free survival; EFS, event-free survival; mITT, modified intent-to-treat; MPR, major pathologic response; pCR, pathologic complete response.

[1]Travis WD, et al. *J Thorac Oncol* 2020;15:709-40.

Statistical analysis*

- A pCR interim analysis (IA) was planned once ~400 mITT patients had the opportunity to undergo surgery (actual N=402), and final analysis was performed once all mITT patients (actual N=740) had the opportunity to undergo surgery
  - pCR and MPR rates were compared between the study arms using a stratified CMH test
  - CIs for the difference between arms were estimated using MN confidence limits
- The first interim EFS analysis (presented here) was planned at ~30% maturity (actual EFS maturity: 31.9%)
  - Comparisons between the study arms were analyzed using stratified log-rank tests
  - HRs and 95% CIs were estimated from stratified Cox PH models
  - EFS medians and landmarks were estimated using the KM method

Population	Definition	D arm	PBO arm	Total
ITT	All randomized patients	400	402	802
mITT	ITT excluding patients with documented *EGFR/ALK* aberrations	366	374	740
pCR IA cohort†	First ~400 patients in the mITT	196	206	402
Safety analysis set	ITT patients who received ≥1 dose of study Tx	400	399	799

*A hierarchical testing procedure was employed for the primary and key secondary efficacy endpoints. †The pCR IA cohort is a subset of the mITT population used for efficacy analyses at the pCR IA.
CMH, Cochran-Mantel-Haenszel; D, durvalumab; KM, Kaplan–Meier; MN, Miettinen and Nurminen; PBO, placebo; PH, proportional hazards.

Baseline characteristics and planned treatment (mITT)

- Baseline characteristics were largely balanced between the study arms
- The planned neoadjuvant CT doublet regimen was carboplatin-based for >70% of patients

TNM classification†		D arm (N=366)	PBO arm (N=374)
Primary tumor, %	T1	12.0	11.5
	T2	26.5	28.9
	T3	35.0	34.5
	T4	26.5	25.1
Regional lymph nodes, %	N0	30.1	27.3
	N1	20.5	23.3
	N2	49.5	49.5

Characteristics*		D arm (N=366)	PBO arm (N=374)
Age	Median (range), years	65.0 (30–88)	65.0 (39–85)
	≥75 years, %	12.0	9.6
Sex, %	Male	68.9	74.3
	Female	31.1	25.7
ECOG PS, %	0	68.6	68.2
	1	31.4	31.8
Race‡, %	Asian	39.1	43.9
	White	56.3	51.1
	Other	4.6	5.1
Region, %	Asia	38.8	43.6
	Europe	38.5	37.4
	North America	11.7	11.5
	South America	10.9	7.5
Smoking status, %	Current	26.0	25.4
	Former	60.1	59.6
	Never	13.9	15.0
Disease stage (AJCC 8th ed.), %	II	28.4	29.4
	IIIA	47.3	44.1
	IIIB	24.0	26.2
Histology, %	Squamous	46.2	51.1
	Non-squamous	53.6	47.9
PD-L1 expression, %	TC <1%	33.3	33.4
	TC 1–49%	36.9	38.0
	TC ≥50%	29.8	28.6
Planned neoadjuvant platinum agent, %	Cisplatin	27.3	25.7
	Carboplatin	72.7	74.3

DCO = Nov 10, 2022. *Characteristics with missing/other responses are histology (0.3% in the D arm and 1.1% in PBO arm had 'other' histology) and disease stage (0.3% in D arm had stage IV disease, and 0.3% in the PBO arm had stage III [NOS] disease, as reported per the electronic case report form [eCRF]). †All patients were M0 except one patient in the D arm who was classified as M1 (NOS). ‡Race was self-reported per the eCRF. NOS, not otherwise specified; TC, tumor cells.

Patient disposition and treatment summary (mITT)

- Patients were randomized between January 2, 2019 and April 19, 2022 (minimum follow-up: 6.7 months)
- At the first planned interim analysis of EFS (DCO: Nov 10, 2022), median EFS follow-up in censored patients was 11.7 months (range: 0.0–46.1)

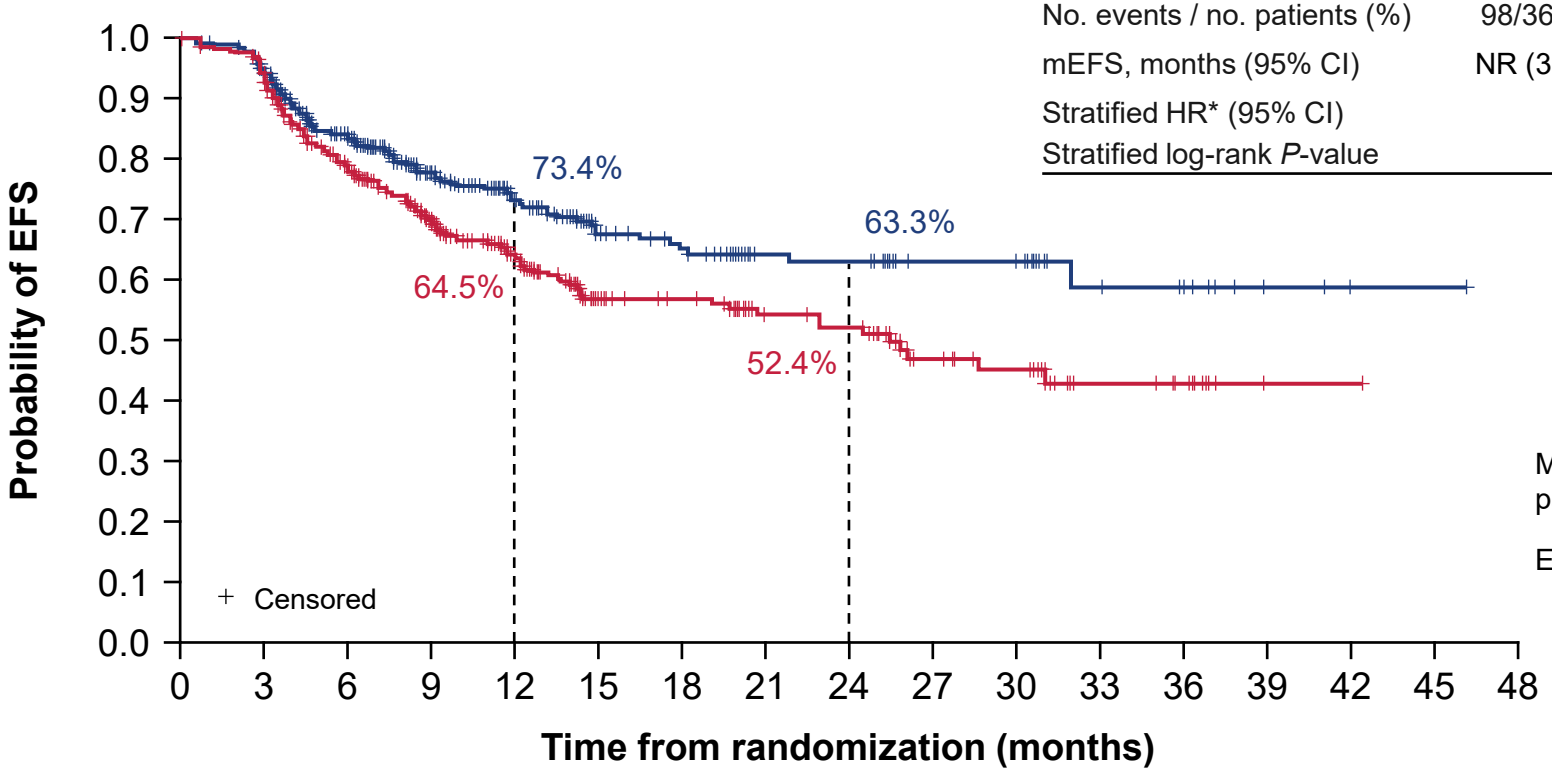
Study phase*		D arm (N=366)	PBO arm (N=374)
Neoadjuvant phase	Randomized, n (%)	366 (100)	374 (100)
	Received Tx, n (%)	366 (100)	371 (99.2)
	Completed 4 cycles of both CT agents, n (%)	310 (84.7)	326 (87.2)
	Completed 4 cycles of D / PBO, n (%)	318 (86.9)	331 (88.5)
Surgery	Underwent surgery†, n (%)	295 (80.6)	302 (80.7)
	Did not undergo surgery†‡, n (%)	71 (19.4)	72 (19.3)
	Completed surgery†, n (%)	284 (77.6)	287 (76.7)
	− R0 resection, n (% of completed surgery)	269 (94.7)	262 (91.3)
	Did not complete surgery†, n (%)	11 (3.0)	15 (4.0)
Adjuvant phase (*ongoing*)	Started D / PBO§, n (%)	241 (65.8)	237 (63.4)
	Completed D / PBO, n (%)	88 (24.0)	79 (21.1)
	Discontinued D / PBO, n (%)	68 (18.6)	70 (18.7)
	Ongoing D / PBO, n (%)	85 (23.2)	88 (23.5)

DCO = Nov 10, 2022. *Except where specified otherwise, percentages were calculated using the full mITT population as the denominator. †As per investigator assessment. Patients who 'underwent' surgery were those for whom curative-intent thoracic surgery was attempted regardless of whether it was completed. Patients who 'completed' surgery were those for whom curative-intent thoracic surgery was completed (assessed at the time of surgery). ‡Includes patients who had surgery outside of the study. §For patients to be eligible for adjuvant D / PBO, surgery must have been completed with R0/R1 margins and no evidence of disease on post-surgical RECIST assessment. DCO, data cutoff.

EFS using RECIST v1.1 (BICR) (mITT)

First planned interim analysis of EFS

	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

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 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.

EFS using RECIST v1.1 (BICR) by subgroup (mITT)

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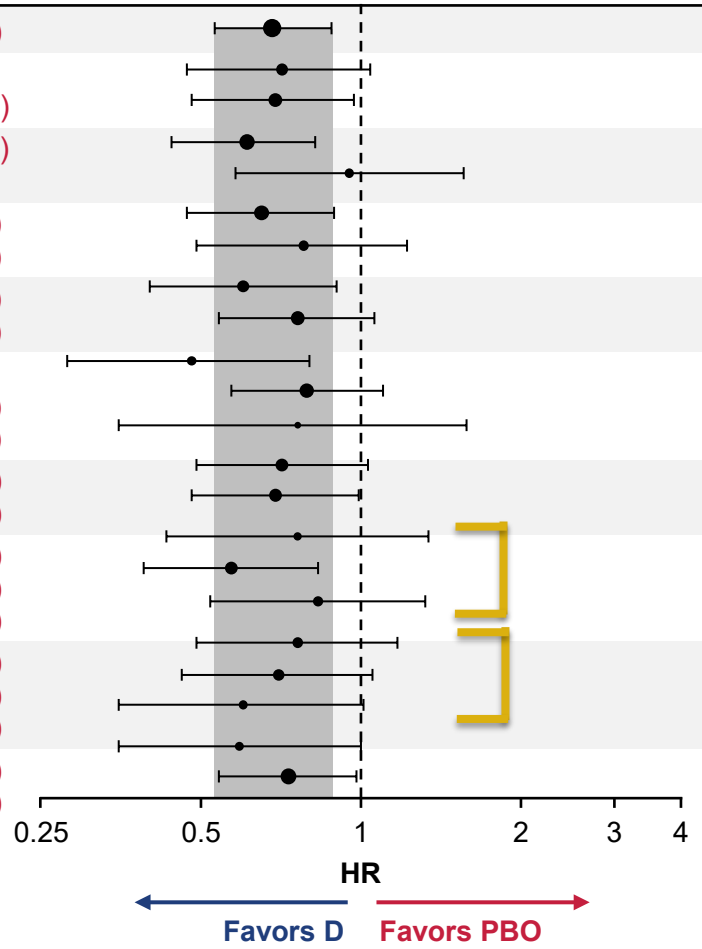
Subgroup		n	Median EFS, months (95% CI) D arm (N=366)	Median EFS, months (95% CI) PBO arm (N=374)	HR (95% CI)
All patients		740	NR (31.9–NR)	25.9 (18.9–NR)	0.68 (0.53–0.88)
Age at randomization	<65 years	358	NR (NR–NR)	NR (18.9–NR)	0.71 (0.47–1.04)
	≥65 years	382	NR (17.9–NR)	24.5 (13.6–31.1)	0.69 (0.48–0.97)
Sex	Male	530	NR (31.9–NR)	22.9 (14.3–31.1)	0.61 (0.44–0.82)
	Female	210	NR (17.5–NR)	NR (13.6–NR)	0.95 (0.58–1.56)
ECOG PS	0	506	NR (31.9–NR)	25.4 (14.3–NR)	0.65 (0.47–0.89)
	1	234	NR (21.8–NR)	25.9 (14.3–NR)	0.78 (0.49–1.22)
Race*	Asian	307	NR (NR–NR)	25.4 (13.9–NR)	0.60 (0.40–0.90)
	Non-Asian	433	31.9 (21.8–NR)	26.2 (14.3–NR)	0.76 (0.54–1.06)
Smoking	Current	190	NR (NR–NR)	14.3 (8.1–NR)	0.48 (0.28–0.80)
	Former	443	NR (31.9–NR)	25.9 (19.5–NR)	0.79 (0.57–1.10)
	Never	107	NR (NR–NR)	24.5 (14.3–NR)	0.76 (0.35–1.58)
Histology	Squamous	360	NR (31.9–NR)	26.2 (13.0–NR)	0.71 (0.49–1.03)
	Non-squamous	375	NR (NR–NR)	25.4 (14.3–NR)	0.69 (0.48–0.99)
Disease stage (AJCC 8th ed.)	Stage II	214	NR (NR–NR)	31.1 (25.4–NR)	0.76 (0.43–1.34)
	Stage IIIA	338	NR (NR–NR)	19.5 (11.7–NR)	0.57 (0.39–0.83)
	Stage IIIB	186	31.9 (11.7–NR)	18.9 (11.8–NR)	0.83 (0.52–1.32)
PD-L1 expression at baseline†	TC <1%	247	NR (14.9–NR)	20.6 (13.9–NR)	0.76 (0.49–1.17)
	TC 1–49%	277	NR (31.9–NR)	25.4 (12.2–NR)	0.70 (0.46–1.05)
	TC ≥50%	216	NR (NR–NR)	26.2 (14.3–NR)	0.60 (0.35–1.01)
Planned neoadjuvant platinum agent	Cisplatin	196	NR (NR–NR)	31.1 (14.3–NR)	0.59 (0.35–1.00)
	Carboplatin	544	NR (31.9–NR)	25.4 (14.3–NR)	0.73 (0.54–0.98)

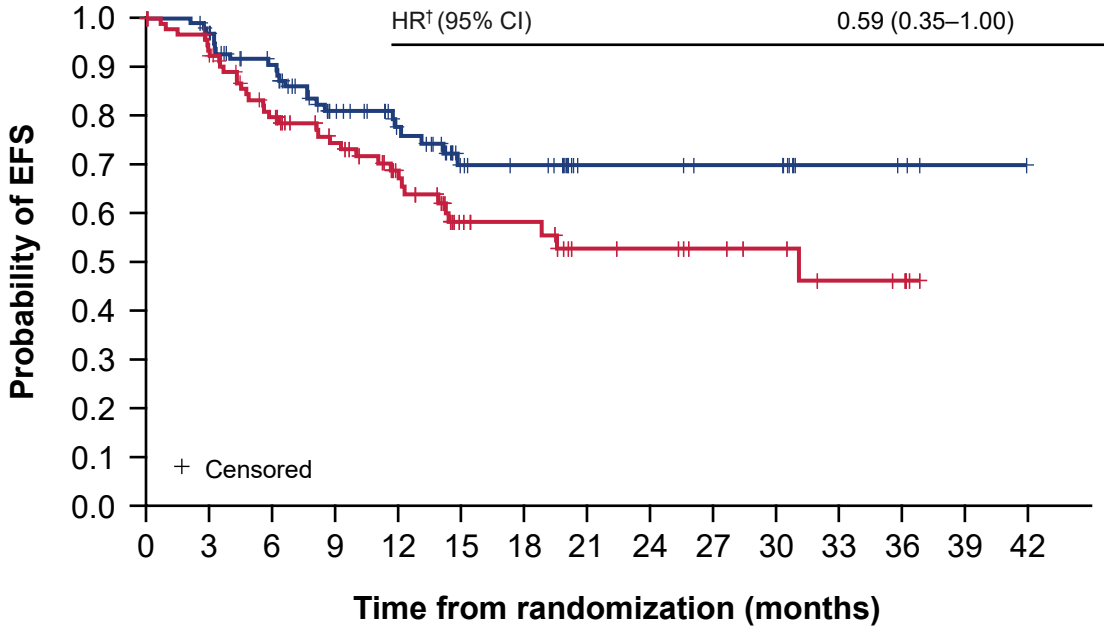


DCO = Nov 10, 2022; median EFS follow-up in censored patients: 11.7 months (range: 0.0–46.1); EFS maturity: 31.9%. Median calculated using the Kaplan–Meier method; HR for all patients (mITT) calculated using a stratified Cox proportional hazards model. HRs for subgroups calculated using unstratified Cox proportional hazards models. The size of circles is proportional to the number of events for each subgroup, and the horizontal bars represent the 95% CIs. *Race was self-reported per the electronic case report form. †Determined using the Ventana SP263 immunohistochemistry assay.

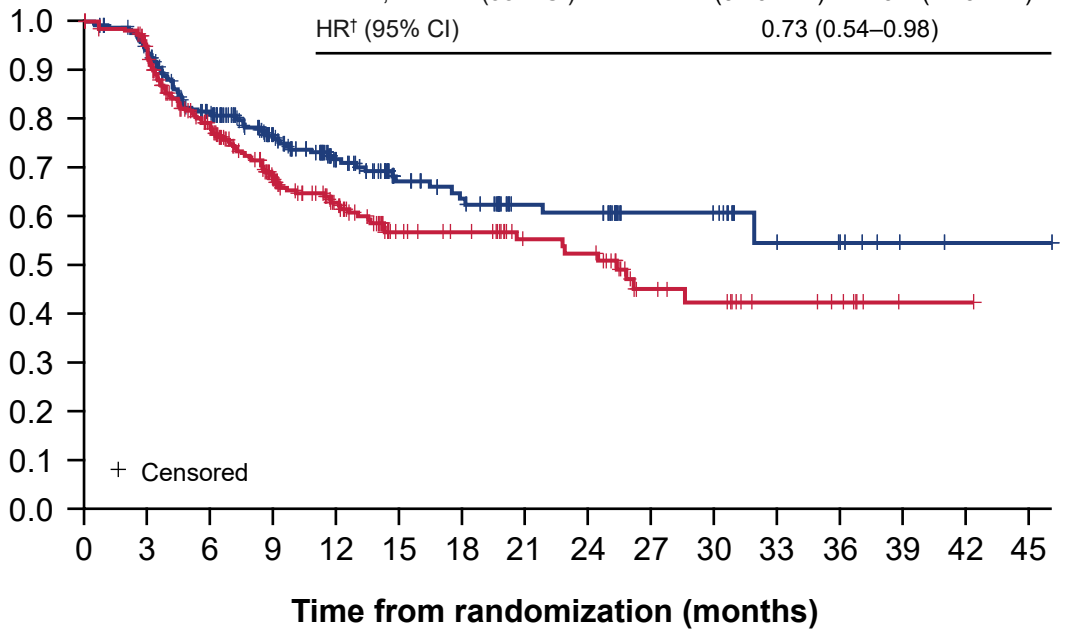
EFS using RECIST v1.1 (BICR) by planned neoadjuvant platinum agent (mITT) – *prespecified subgroup analysis*

- A clear and consistent EFS benefit was observed regardless of the planned platinum agent*

Cisplatin	D arm	PBO arm
No. events / no. patients (%)	23/100 (23.0)	35/96 (36.5)
mEFS, months (95% CI)	NR (NR–NR)	31.1 (14.3–NR)
HR† (95% CI)	0.59 (0.35–1.00)	



Carboplatin	D arm	PBO arm
No. events / no. patients (%)	75/266 (28.2)	103/278 (37.1)
mEFS, months (95% CI)	NR (31.9–NR)	25.4 (14.3–NR)
HR† (95% CI)	0.73 (0.54–0.98)	



No. at risk:

D arm	100	95	81	59	45	28	25	14	14	12	12	5	4	1	0
PBO arm	96	86	68	55	42	25	22	15	14	11	9	6	5	0	0

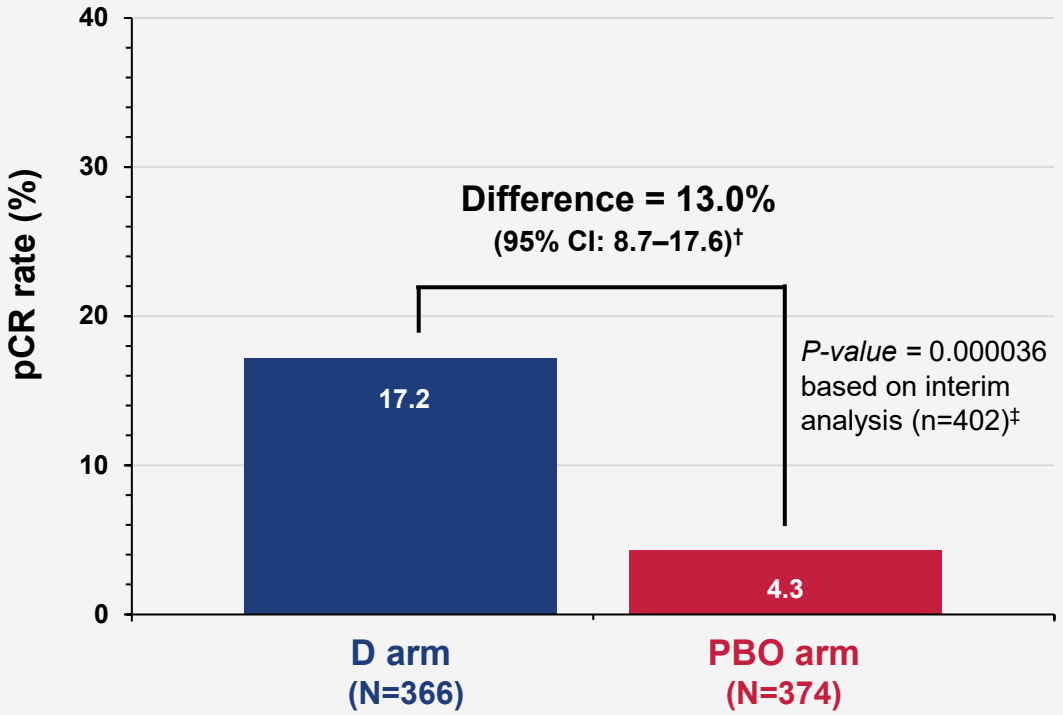
D arm	266	241	190	135	95	62	53	36	35	19	18	9	7	2	1	1
PBO arm	278	253	189	129	94	57	52	38	36	19	16	10	8	1	1	0

DCO: Nov 10, 2022; median EFS follow-up in censored patients: 11.7 months (range: 0.0–46.1); EFS maturity: 31.9%. Median and landmark estimates calculated using the Kaplan–Meier method. HRs calculated using an unstratified Cox proportional hazards model. *Choice of CT regimen determined by histology and at the investigator's discretion. For non-squamous: cisplatin + pemetrexed or carboplatin + pemetrexed. For squamous: carboplatin + paclitaxel or cisplatin + gemcitabine (or carboplatin + gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment). †HR <1 favors the D arm versus the PBO arm.

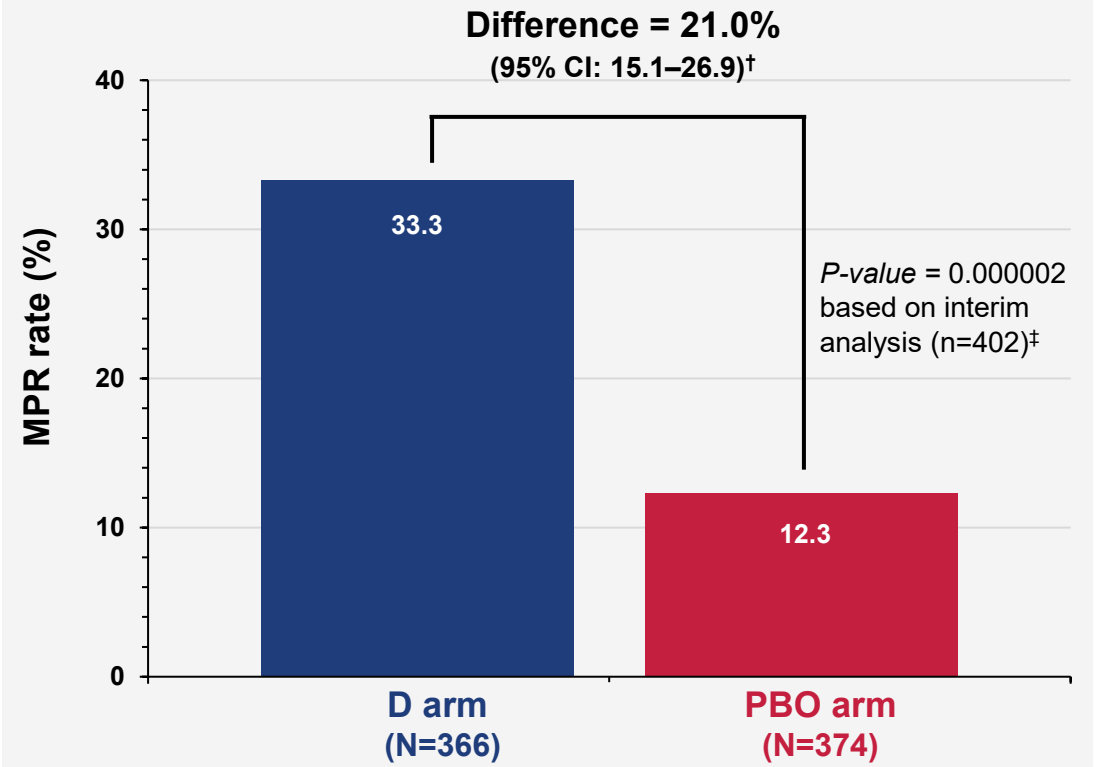
Pathologic response per IASLC 2020 methodology* (mITT)

Final analysis

pCR (central lab)



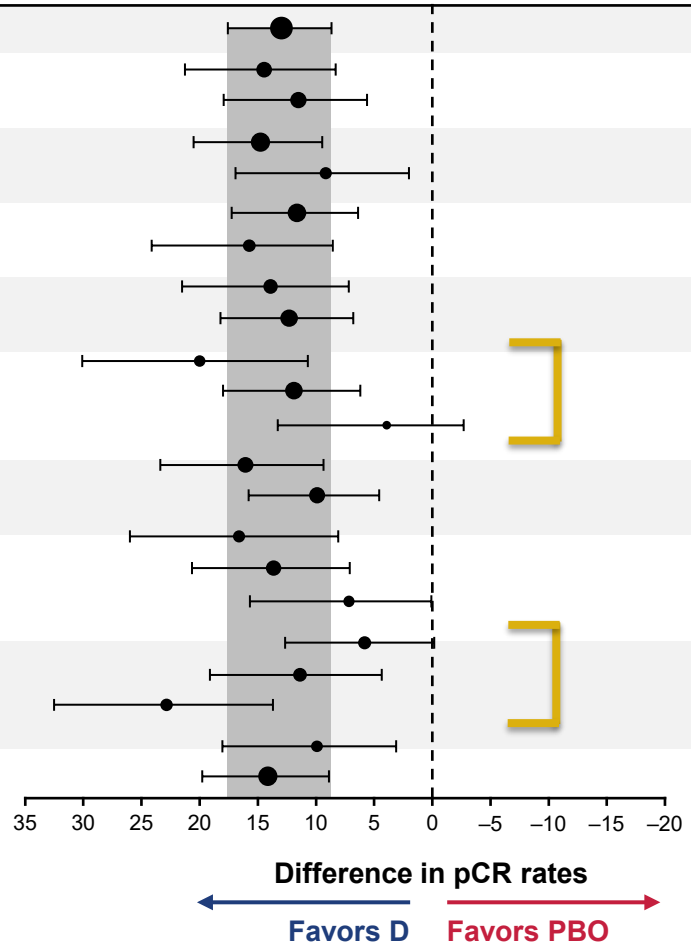
MPR (central lab)



*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). pCR = a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes. MPR = less than or equal to 10% viable tumor cells in lung primary tumor after complete evaluation of the resected lung cancer specimen. To be eligible for pathologic assessment, patients needed to have received three cycles of neoadjuvant study Tx per protocol. Patients who were not evaluable were classified as non-responders. †CIs 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).

pCR by subgroup (mITT)

Subgroup		n	pCR rate, % (95% CI) D arm (N=366)	pCR rate, % (95% CI) PBO arm (N=374)	Difference in pCR rates (95% CI)
All patients		740	17.2 (13.5–21.5)	4.3 (2.5–6.9)	13.0 (8.7–17.6)
Age at randomization	<65 years	358	18.3 (12.9–24.8)	3.8 (1.6–7.7)	14.5 (8.3–21.3)
	≥65 years	382	16.2 (11.3–22.2)	4.7 (2.2–8.8)	11.5 (5.6–17.9)
Sex	Male	530	19.4 (14.7–24.9)	4.7 (2.5–7.9)	14.8 (9.5–20.5)
	Female	210	12.3 (6.9–19.7)	3.1 (0.7–8.9)	9.2 (2.0–16.9)
ECOG PS	0	506	16.7 (12.3–21.9)	5.1 (2.7–8.6)	11.6 (6.4–17.3)
	1	234	18.3 (11.7–26.5)	2.5 (0.5–7.2)	15.7 (8.6–24.1)
Race*	Asian	307	18.2 (12.2–25.5)	4.3 (1.7–8.6)	13.9 (7.2–21.5)
	Non-Asian	433	16.6 (12.0–22.1)	4.3 (2.0–8.0)	12.3 (6.8–18.2)
Smoking	Current	190	24.2 (16.0–34.1)	4.2 (1.2–10.4)	20.0 (10.7–30.1)
	Former	443	17.3 (12.5–22.9)	5.4 (2.8–9.2)	11.9 (6.2–18.0)
	Never	107	3.9 (0.5–13.5)	0.0 (0.0–6.4)	3.9 (-2.7–13.3)
Histology	Squamous	360	21.3 (15.4–28.3)	5.2 (2.5–9.4)	16.1 (9.3–23.4)
	Non-squamous	375	13.3 (8.9–18.8)	3.4 (1.2–7.2)	9.9 (4.6–15.8)
Disease stage (AJCC 8th ed.)	Stage II	214	21.2 (13.8–30.3)	4.5 (1.5–10.3)	16.6 (8.1–26.0)
	Stage IIIA	338	18.5 (13.0–25.1)	4.8 (2.1–9.3)	13.6 (7.1–20.7)
	Stage IIIB	186	10.2 (4.8–18.5)	3.1 (0.6–8.7)	7.2 (0.1–15.7)
PD-L1 expression at baseline†	TC <1%	247	9.0 (4.6–15.6)	3.2 (0.9–8.0)	5.8 (-0.2–12.7)
	TC 1–49%	277	16.3 (10.5–23.6)	4.9 (2.0–9.9)	11.4 (4.3–19.1)
	TC ≥50%	216	27.5 (19.4–36.9)	4.7 (1.5–10.6)	22.9 (13.7–32.5)
Planned neoadjuvant platinum agent	Cisplatin	196	12.0 (6.4–20.0)	2.1 (0.3–7.3)	9.9 (3.1–18.0)
	Carboplatin	544	19.2 (14.6–24.4)	5.0 (2.8–8.3)	14.1 (8.9–19.8)



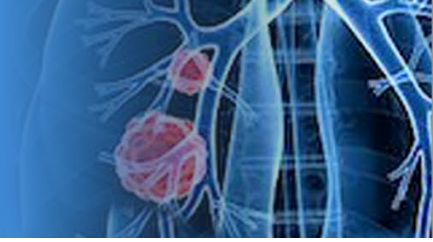
DCO = Nov 10, 2022. The 95% CIs were estimated using a stratified Miettinen and Nurminen method for all patients (mITT) and an unstratified Miettinen and Nurminen method for subgroups. The size of the circles is proportional to number of patients for each subgroup, and the horizontal bars represent the 95% CIs.
*Race was self-reported per the electronic case report form. †Determined using the Ventana SP263 immunohistochemistry assay.

AE summary (safety analysis set)*

Overall study period (inclusive of the neoadjuvant, surgical, and adjuvant Tx phases)†	**D arm (N=400)**	**PBO arm (N=399)**
Any-grade all-causality AEs, n (%)	386 (96.5)	378 (94.7)
Max. grade 3 or 4	169 (42.3)	173 (43.4)
SAE	150 (37.5)	126 (31.6)
Outcome of death	23 (5.8)	15 (3.8)
Leading to discontinuation of D / PBO	48 (12.0)	24 (6.0)
Leading to cancellation of surgery	7 (1.8)	4 (1.0)
Any-grade AEs possibly related to D / PBO / CT, n (%)	346 (86.5)	322 (80.7)
Max. grade 3 or 4	129 (32.3)	132 (33.1)
Outcome of death‡	7 (1.8)	2 (0.5)
Any-grade immune-mediated AEs§, n (%)	94 (23.5)	39 (9.8)
Grade 3 or 4	16 (4.0)	10 (2.5)
Pneumonitis (any grade)¶	15 (3.8)	7 (1.8)

DCO = Nov 10, 2022. *The safety analysis set includes all randomized patients who received ≥1 dose of study Tx; AEs were graded using Common Terminology Criteria for Adverse Events v5.0. †First dose of study Tx (D / PBO / CT) until the earliest of: the last dose of study Tx or surgery + 90 days (taking the latest dose of D / PBO / CT / date of surgery, + 90 days); the DCO date; or the date of the first dose of subsequent anti-cancer Tx. ‡Included interstitial lung disease (n=2) and immune-mediated lung disease, pneumonitis, hemoptysis, myocarditis, and decreased appetite (n=1 each) in the D arm and pneumonia and infection (n=1 each) in the PBO arm. §An AE of special interest consistent with an immune-mediated mechanism of action, where there is no clear alternate etiology, and requiring the use of systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy. ¶Pneumonitis is summarized as a grouped term comprising the 'pneumonitis', 'interstitial lung disease', and 'immune-mediated lung disease' preferred terms. AE, adverse event; SAE, serious AE.

My approach to resectable stage II-IIIA NSCLC?



- Chemo-eligible?
- PD-L1 status + EGFR/ALK (for non-squamous)
- If chemo-eligible + EGFR/ALK negative
  - Stage III irrespective of PD-L1 – neoadjuvant chemo-nivo
  - Stage II PD-L1≥50% - neoadjuvant chemo-nivo or adj chemo→atezo
  - Stage II PD-L1 1-49% - neoadjuvant chemo-nivo or adj chemo→pembro
  - Stage II PD-L1 0% - neoadjuvant chemo-nivo or adj chemo→pembro

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