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Nivolumab + platinum-doublet chemotherapy vs chemotherapy as neoadjuvant treatment for resectable (IB–IIIA) non-small cell lung cancer: event-free survival results from the phase 3 CheckMate 816 trial

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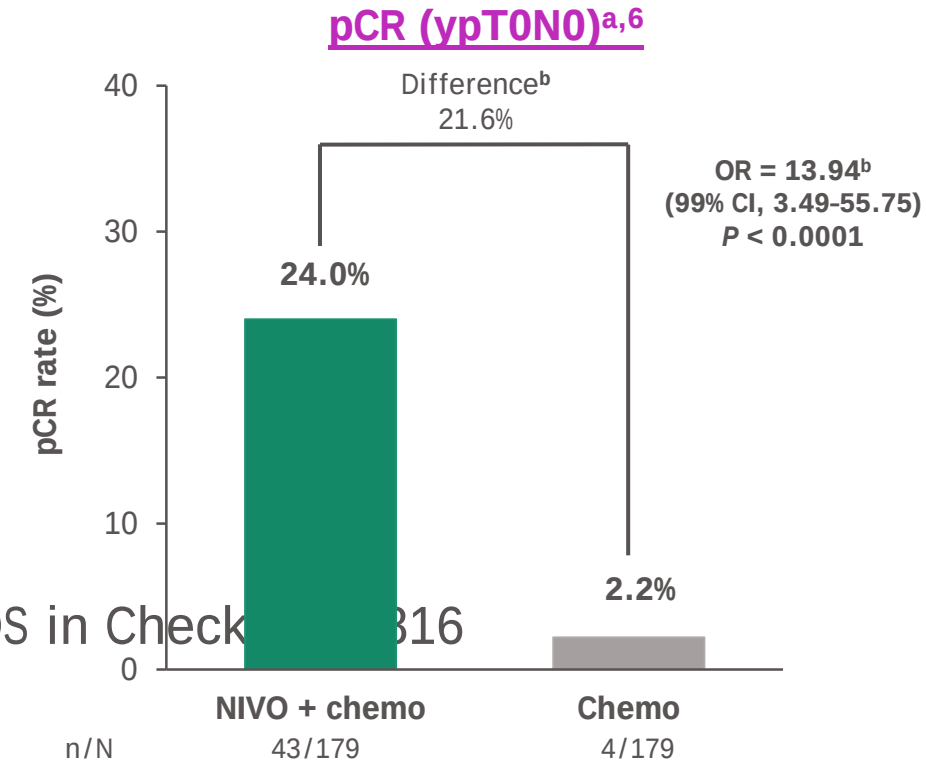
Introduction

- Despite recent advances in adjuvant therapies, improving long-term survival in patients with resectable NSCLC remains an unmet need[1-5]
- In the randomized phase 3 CheckMate 816 study, neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) significantly improved the primary endpoint of pCR vs chemo in patients with resectable NSCLC[6]
  - Tolerability was maintained and feasibility of surgery was preserved[6,7]
- NIVO + chemo is now indicated in the United States as neoadjuvant treatment for adult patients with resectable (tumors ≥4 cm or node positive) NSCLC[8]
- Here we present results from the prespecified interim analysis of EFS, the other primary endpoint, and OS in Check 816



[a]pCR: 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes in the primary analysis population (patients concurrently randomized to NIVO + chemo and chemo); [b]Calculated by stratified Cochran–Mantel–Haenszel method. 1. Wu YL, et al. *N Engl J Med* 2020;383:1711–23; 2. Felip E, et al. *Lancet* 2021;398:1344–57; 3. Forde PM, et al. *N Engl J Med* 2018;378:1976–86; 4. Provencio M, et al. *Lancet Oncol* 2020;21:1413–22; 5. Cascone T, et al. *Nat Med* 2021;27:504–14; 6. Forde PM, et al. Oral presentation at: American Association for Cancer Research; April 8–10, 2021; virtual. Abstract 5218; 7. Spicer J, et al. *J Clin Oncol* 2021;39(Suppl 15):Abstract 8503; 8. OPDIVO® (nivolumab) [package insert]. Princeton, NJ: Bristol Myers Squibb; March 2022

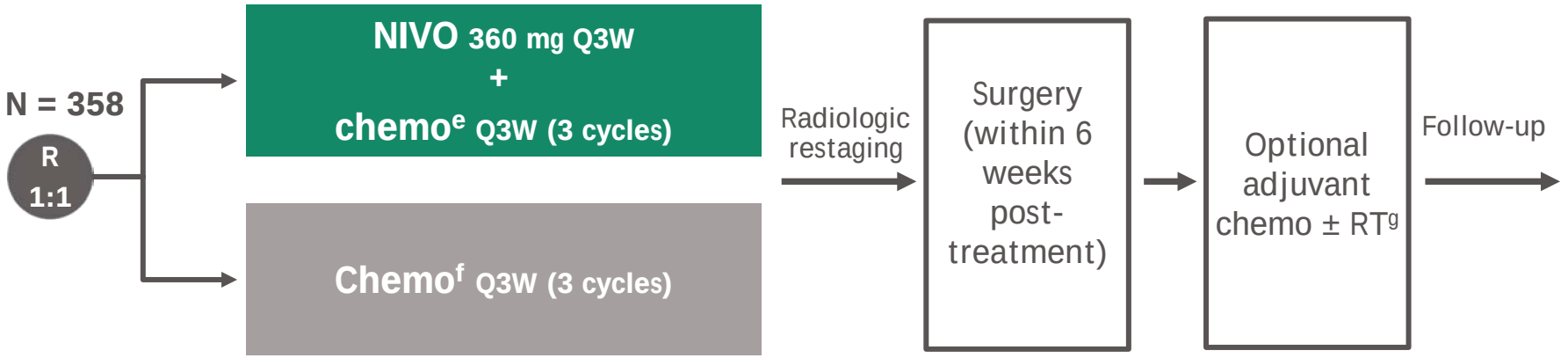
CheckMate 816 study design[a]

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.

Statistical analysis plan

- The overall sample size of ~350 patients was calculated based on the primary endpoint of EFS, and accounted for the two independent primary endpoint comparisons
  - pCR and EFS for NIVO + chemo vs chemo in the primary analysis population[a] were to be tested with 1% and 4% type I error (2-sided), respectively[b]
- If pCR was statistically significant, EFS was to be tested with a 2-sided type I error of 5%[c]
- OS was to be tested hierarchically if EFS was statistically significant[d]
- Data presented here are from the first prespecified interim analysis for EFS and OS

[a]Patients concurrently randomized to NIVO + chemo and chemo. For the primary pCR analysis, patients who did not undergo surgery or have evaluable tissue samples were to be counted as non-responders; [b]Comparison between treatment arms using stratified Cochran-Mantel-Haenszel test for pCR and stratified log-rank test for EFS; [c]Approximately 185 EFS events would provide 82% power to detect an HR of 0.65, with a 5% type I error (2-sided) considering 2 interim analyses; [d]Significance boundaries for EFS and OS at interim analysis were calculated based on Lan–DeMets alpha spending function with the O'Brien–Fleming type of boundary.

Baseline characteristics

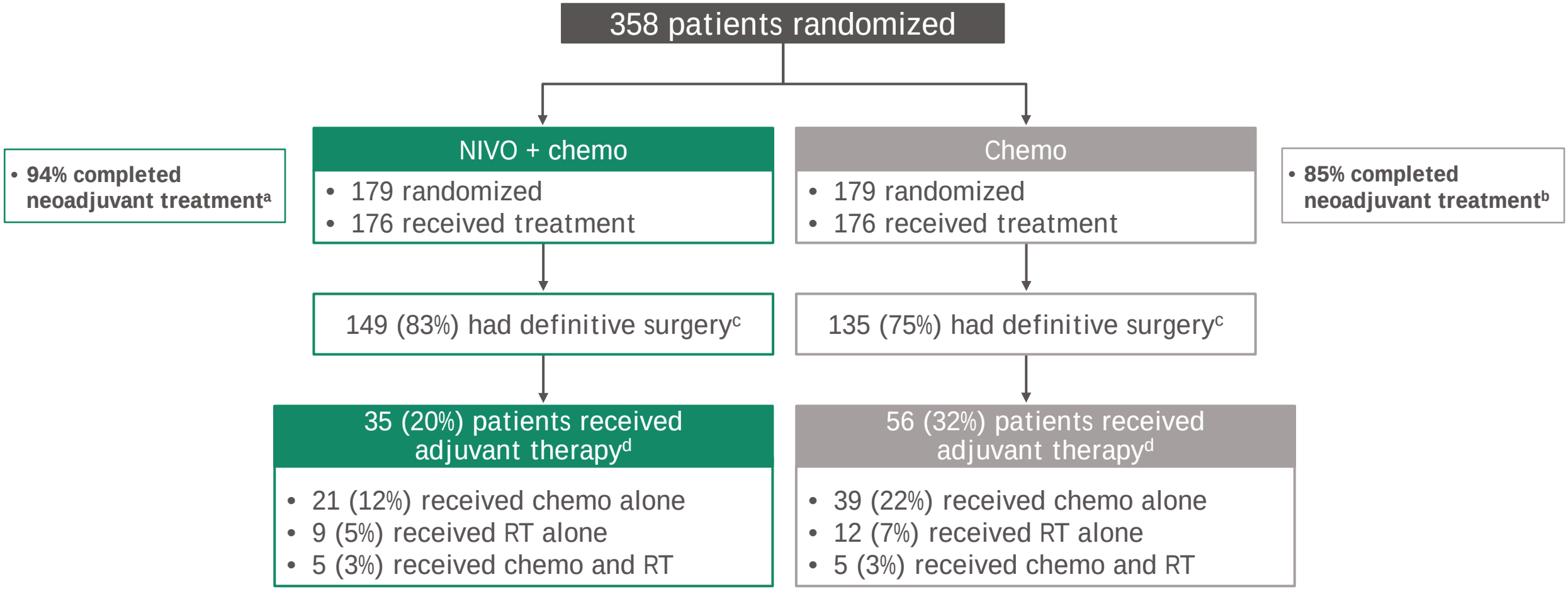
	NIVO + chemo (n = 179)	Chemo (n = 179)
Age, median (range), years	64 (41–82)	65 (34–84)
Age category, %		
< 65 years	52	46
≥ 65 years	48	54
Male, %	72	71
Region,[a] %		
North America	23	28
Europe	23	14
Asia	48	51
ECOG PS, %		
0	69	65
1	31	35
Stage,[b,c] %		
IB–II	36	35
IIIA	63	64
Histology, %		
Squamous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

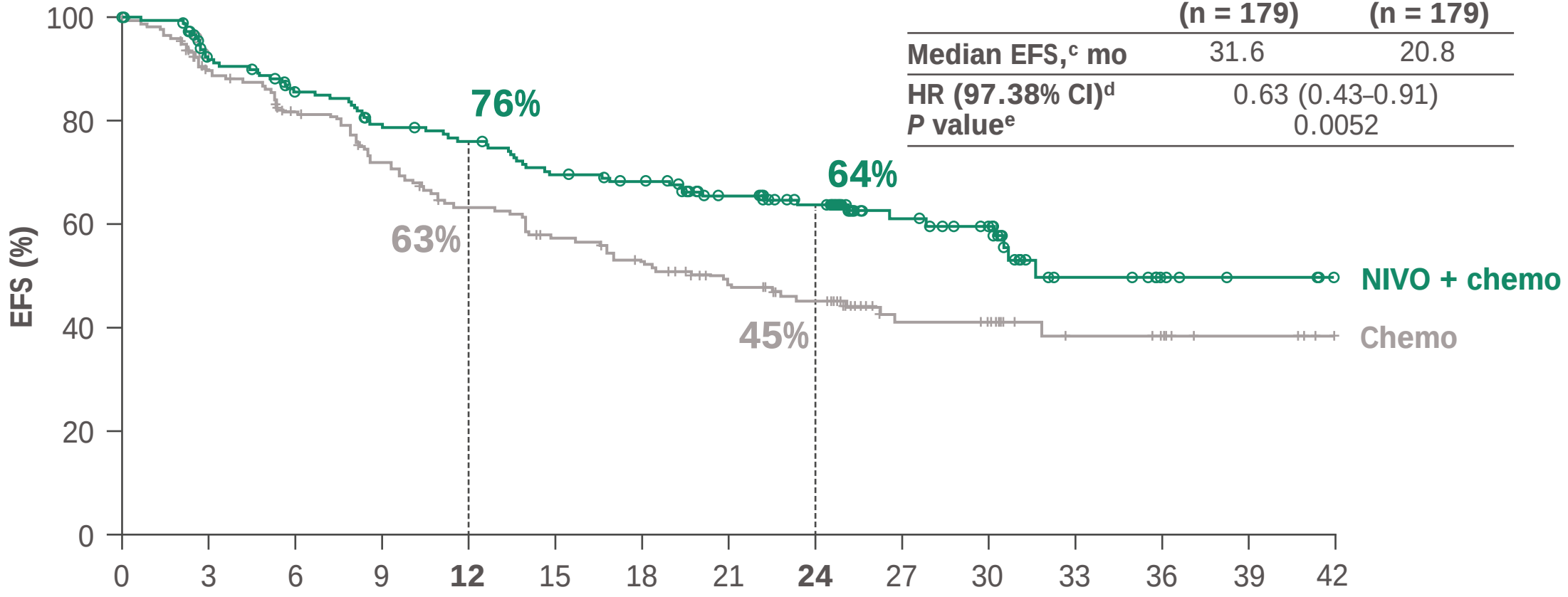


Database lock: October 20, 2021; minimum follow-up: 21 months; median follow-up, 29.5 months.

[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.

Primary endpoint: EFS[a,b] with neoadjuvant NIVO + chemo vs chemo

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS,[c] mo	31.6	20.8
HR (97.38% CI)[d]	0.63 (0.43–0.91)	
P value[e]	0.0052	



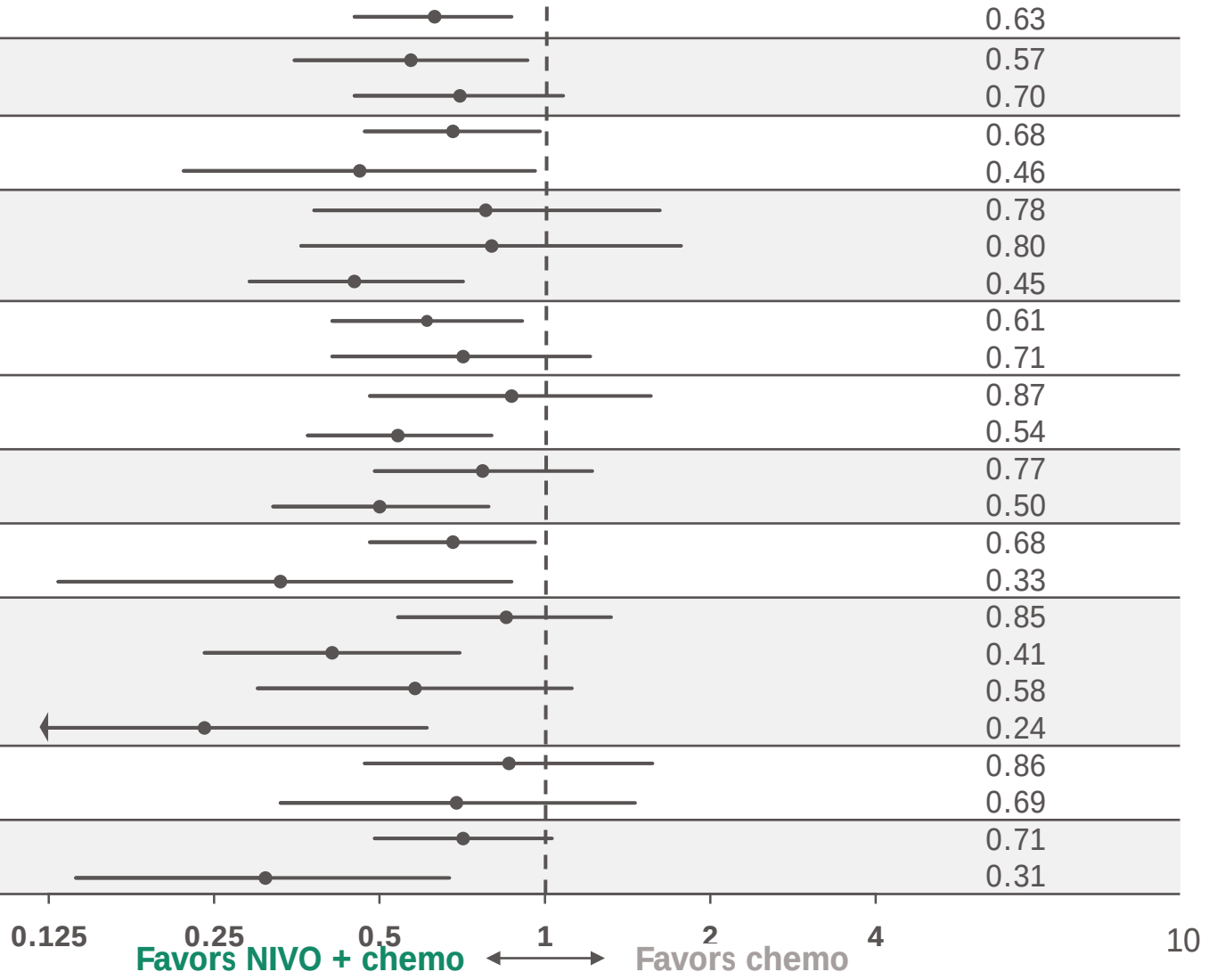
No. at risk														
NIVO + chemo	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemo	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

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

[a]Per BICR; [b]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; [c]95% CI = 30.2–NR (NIVO + chemo) and 14.0–26.7 (chemo); [d]95% CI = 0.45-0.87; [e]The significance boundary at this interim analysis was 0.0262.

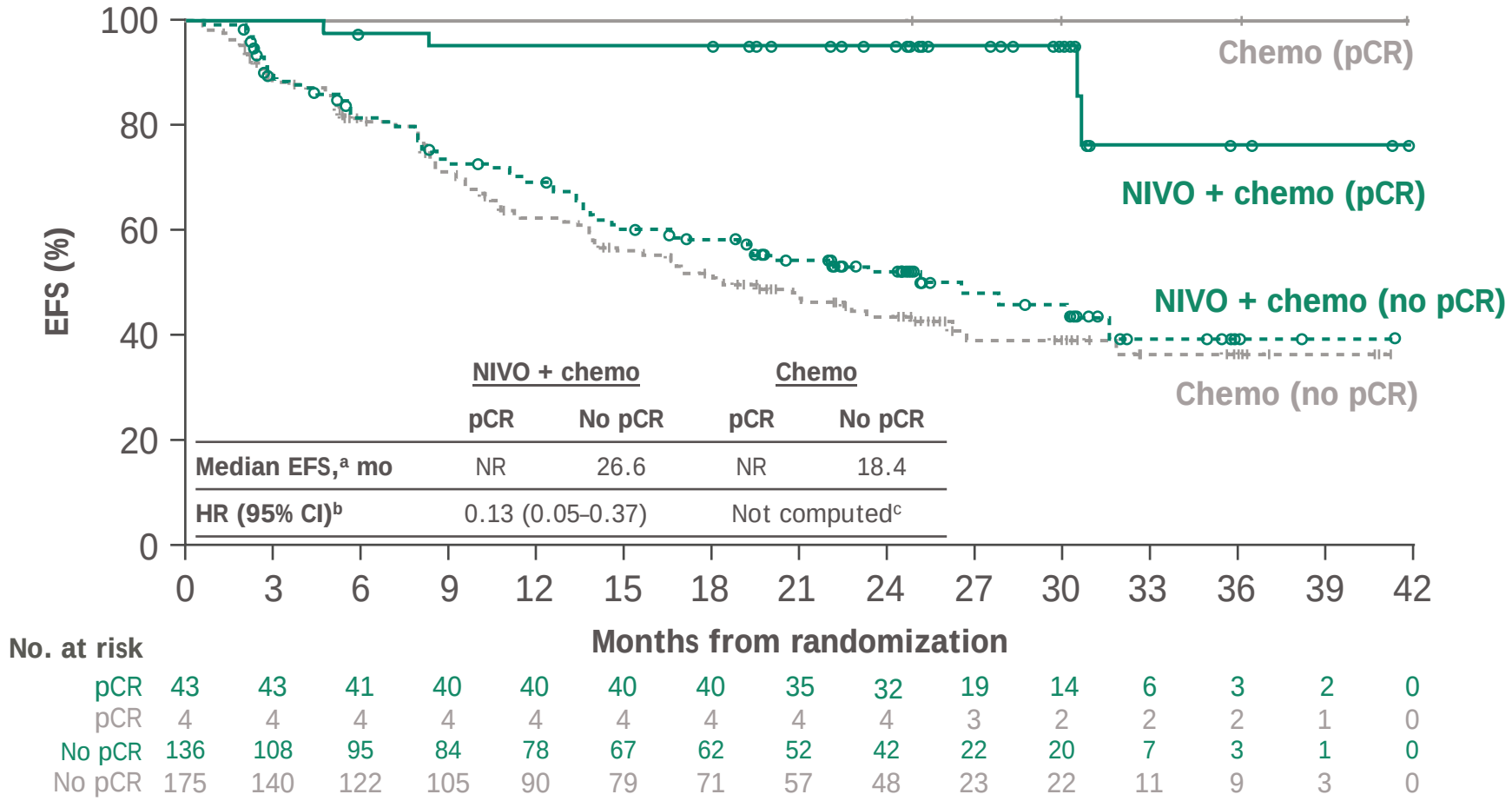
EFS subgroup analysis

	Median EFS[a], mo		Unstratified HR (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	32	21		0.63
< 65 years (n = 176)	NR	21		0.57
≥ 65 years (n = 182)	30	18		0.70
Male (n = 255)	31	17		0.68
Female (n = 103)	NR	32		0.46
North America (n = 91)	NR	NR		0.78
Europe (n = 66)	32	21		0.80
Asia (n = 177)	NR	16		0.45
ECOG PS 0 (n = 241)	NR	23		0.61
ECOG PS 1 (n = 117)	30	14		0.71
Stage IB–II (n = 127)	NR	NR		0.87
Stage IIIA (n = 228)	32	16		0.54
Squamous (n = 182)	31	23		0.77
Non-squamous (n = 176)	NR	20		0.50
Current/former smoker (n = 318)	32	22		0.68
Never smoker (n = 39)	NR	10		0.33
PD-L1 < 1% (n = 155)	25	18		0.85
PD-L1 ≥ 1% (n = 178)	NR	21		0.41
PD-L1 1–49% (n = 98)	NR	27		0.58
PD-L1 ≥ 50% (n = 80)	NR	20		0.24
TMB < 12.3 mut/Mb (n = 102)	30	27		0.86
TMB ≥ 12.3 mut/Mb (n = 76)	NR	22		0.69
Cisplatin (n = 258)	NR	21		0.71
Carboplatin (n = 72)	NR	11		0.31



[a]Per BICR.

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]	

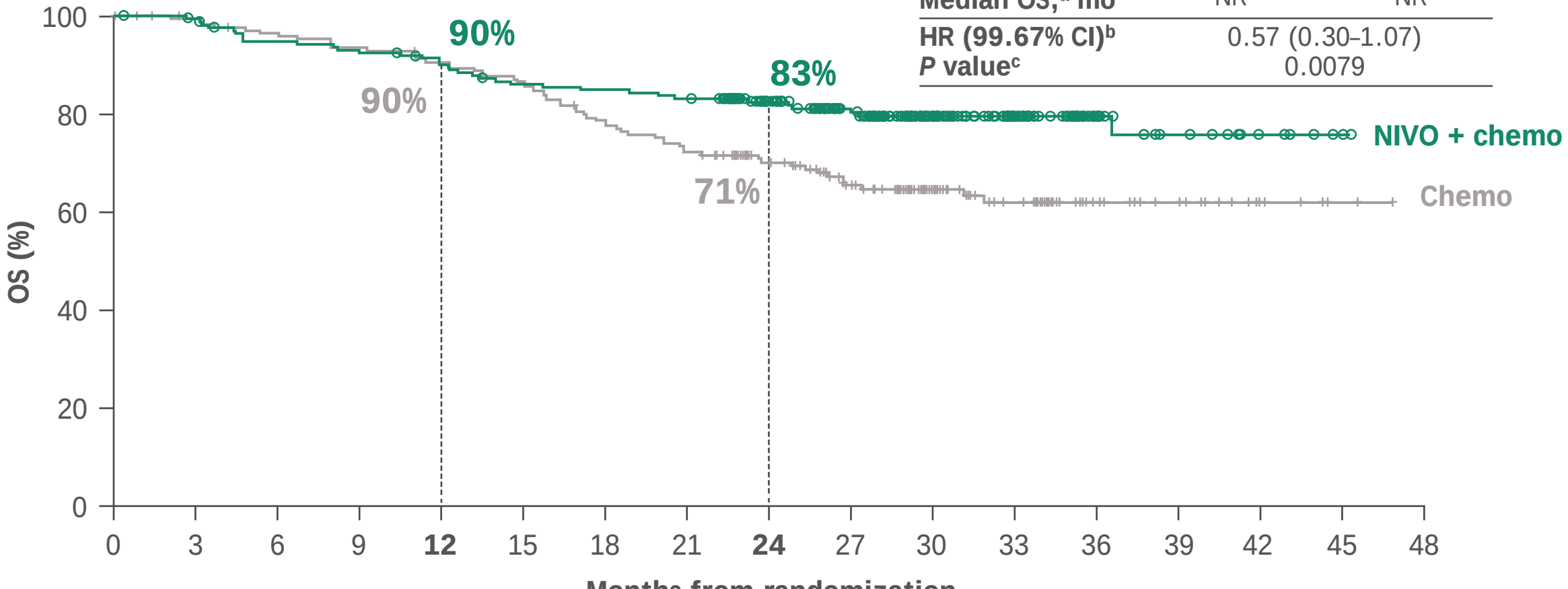
- pCR rates were significantly improved with NIVO + chemo vs chemo (24.0% vs 2.2%)
- In patients without pCR, HR (95% CI) for NIVO + chemo vs chemo was 0.84 (0.61–1.17)

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.

Overall survival: interim analysis

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR
HR (99.67% CI)[b]	0.57 (0.30–1.07)	
***P* value[c]**	0.0079	



No. at risk

NIVO + chemo	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemo	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

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

[a]95% CI = NR-NR (NIVO + chemo) and NR-NR (chemo); [b]95% CI = 0.38-0.87; [c]Significance boundary for OS (0.0033) was not met at this interim analysis.

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.

Summary

- In CheckMate 816, neoadjuvant NIVO + chemo showed a statistically significant and clinically meaningful improvement in EFS vs chemo (HR = 0.63 [97.38% CI, 0.43–0.91]; *P* = 0.0052)
  - EFS benefit favored NIVO + chemo across most subgroups
- Preliminary OS analysis showed a trend of improvement with NIVO + chemo vs chemo (HR = 0.57 [99.67% CI, 0.30–1.07]); the study continues to mature
- EFS was improved in patients with a pCR compared with those without, suggesting pCR as an early indicator of therapeutic benefit with NIVO + chemo
- Neoadjuvant NIVO + chemo showed a safety profile consistent with previous reports and did not impact the feasibility of surgery vs chemo alone
- CheckMate 816 is the first phase 3 study with a neoadjuvant immunotherapy–based combination for resectable NSCLC to show improved EFS and pCR, along with promising OS results
- These results support neoadjuvant NIVO in combination with chemo as a new standard of care for patients with resectable NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

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Abbreviations

AE = adverse event

AJCC = American Joint Committee on Cancer

ALK = anaplastic lymphoma kinase

BICR = blinded independent central review

BIPR = blinded independent pathological review

chemo = chemotherapy

CI = confidence interval

CTCAE = Common Terminology Criteria for Adverse Events

ECOG PS = Eastern Cooperative Oncology Group performance status

EFS = event-free survival

EGFR = epidermal growth factor receptor

HR = hazard ratio

IHC = immunohistochemistry

MedDRA = Medical Dictionary for Regulatory Activities

MPR = major pathological response

mut/Mb = mutations per megabase

NIVO = nivolumab

NSCLC = non-small cell lung cancer

NR = not reached

NSQ = non-squamous

OR = odds ratio

OS = overall survival

pCR = pathological complete response

PD-L1 = programmed death ligand 1

PS = performance status

Q3W = every 3 weeks

R = randomized

RT = radiotherapy

SAE = serious adverse event

SQ = squamous

TMB = tumor mutational burden

TNM = Tumor Node Metastasis

TRAE = treatment related adverse event

ypT0N0 = absence of tumor cells in surgical specimen