JOHNS HOPKINS MEDICINE

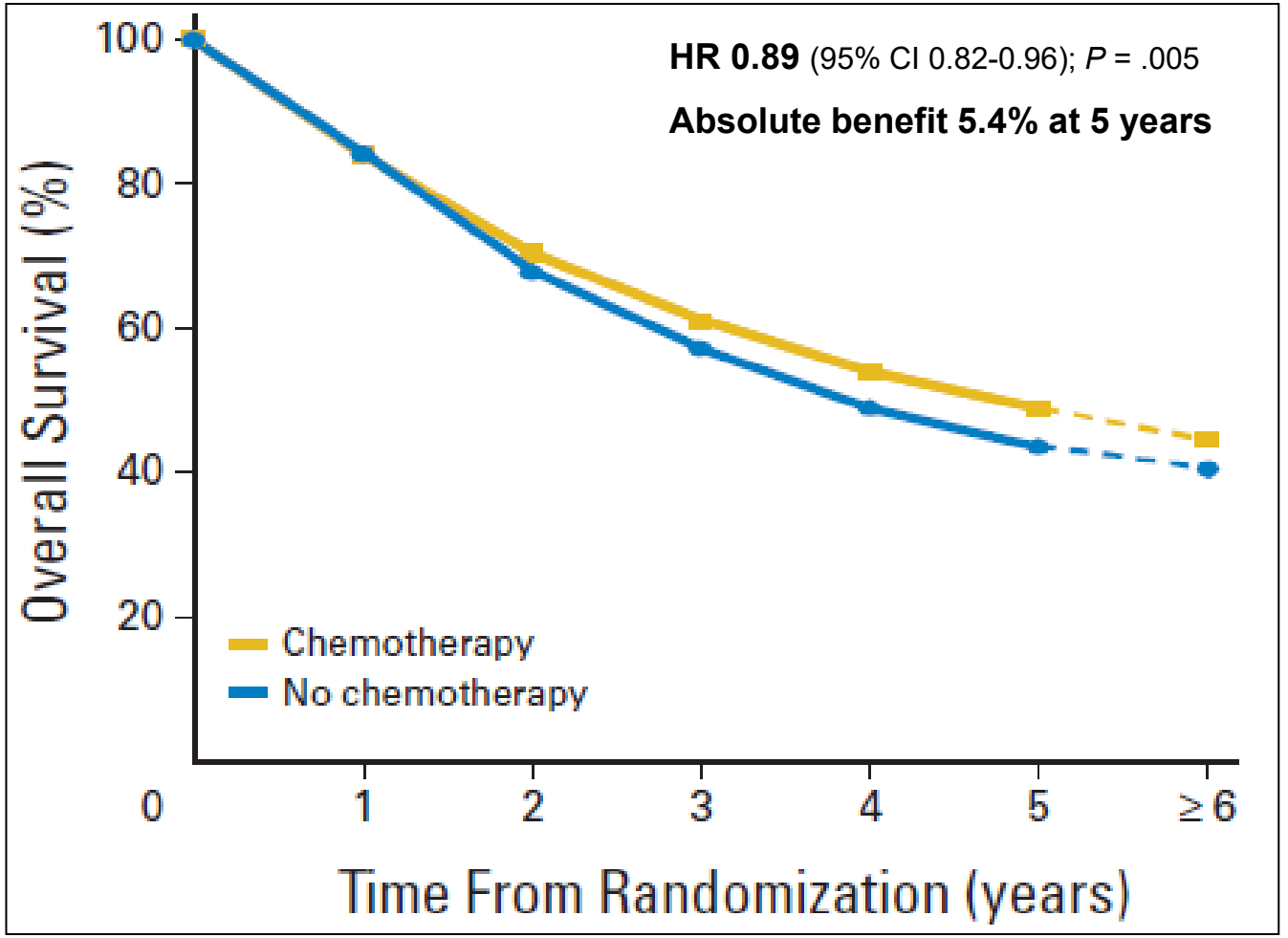
Neoadjuvant and Adjuvant Immunotherapy

SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

BLOOMBERG~KIMMEL INSTITUTE FOR CANCER IMMUNOTHERAPY

JOHNS HOPKINS MEDICINE

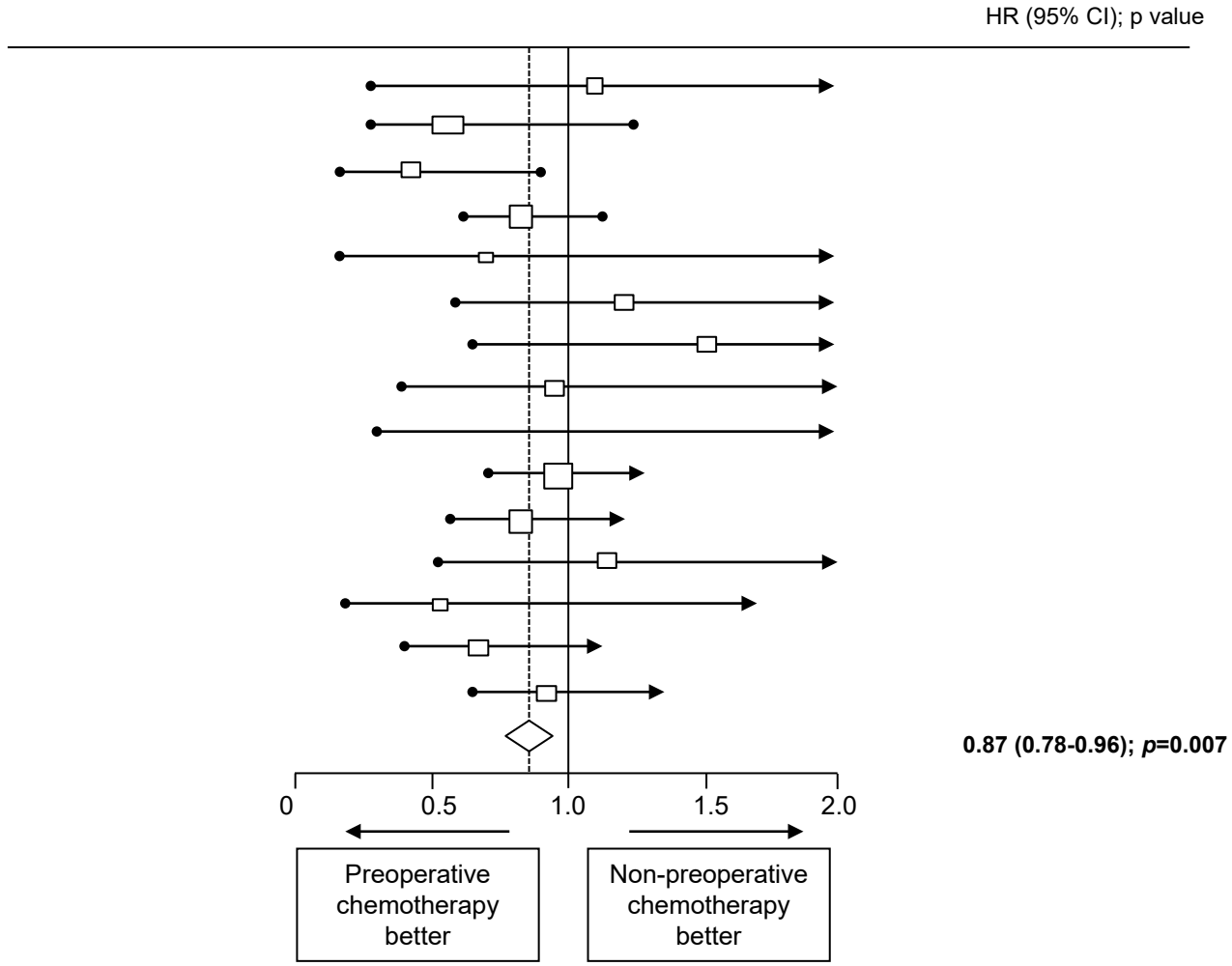
LACE Meta-Analysis of Adjuvant Platinum Chemotherapy vs. no Adjuvant Chemo



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.

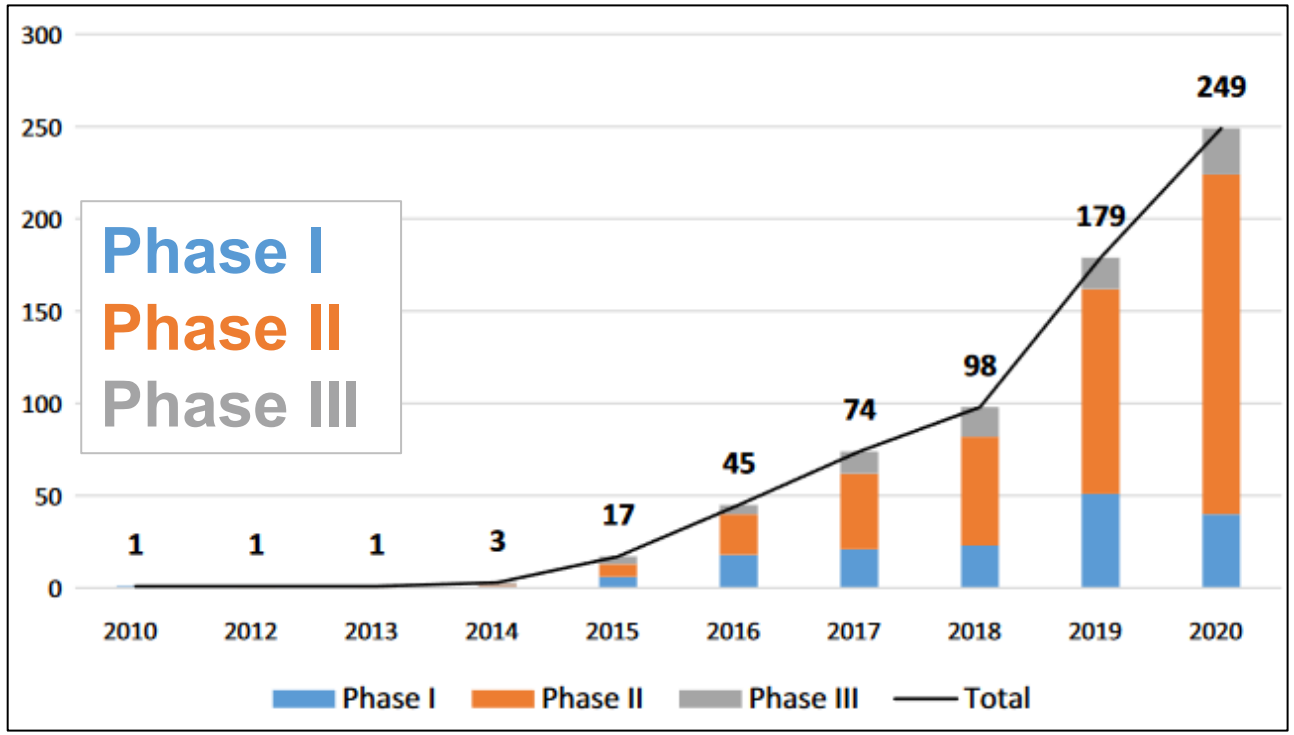
Preoperative Chemotherapy + Surgery vs. Surgery Alone

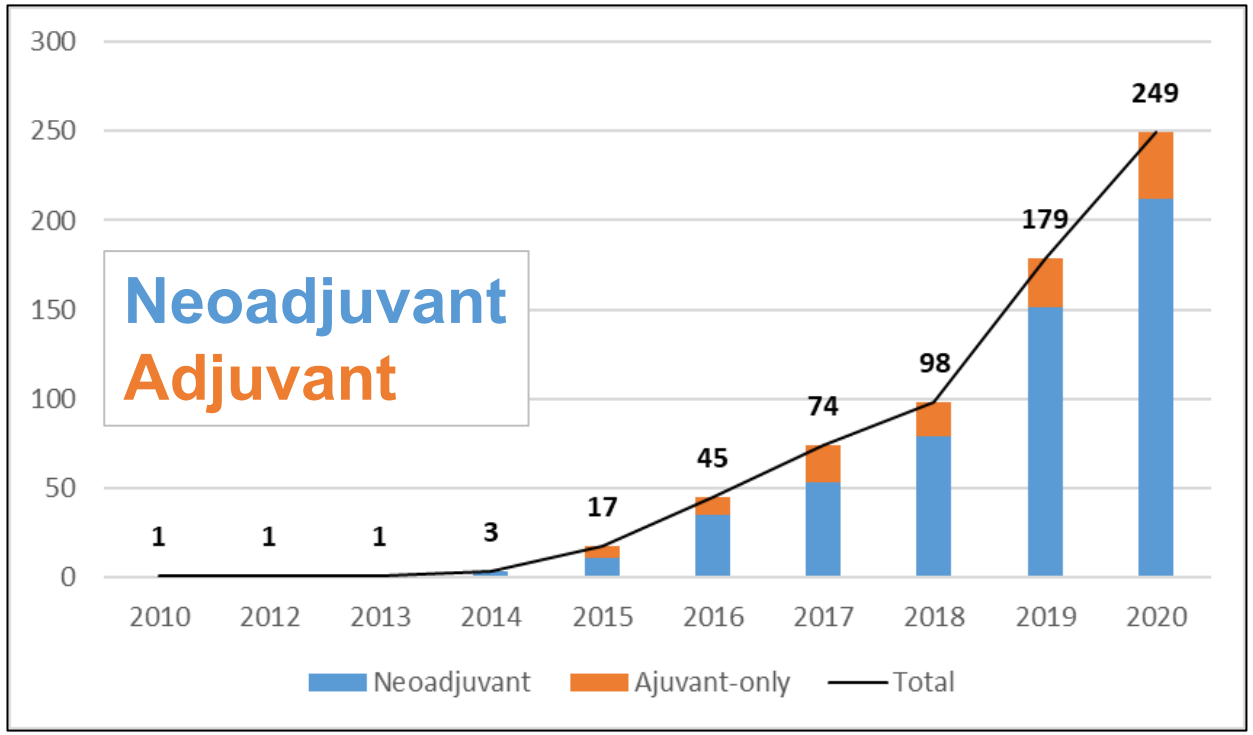
	Preoperative chemotherapy	Control	O-E	Variance
France 1990	8/13	8/13	0.32	3.97
MD Anderson 1994	19/28	27/32	-6.40	11.19
Spain 1994	19/29	27/30	-8.88	9.65
MIP-91	137/179	146/176	-12.99	70.22
SWOG S9015	3/5	12/16	-1.04	2.94
JCOG 9209	28/31	25/31	2.25	12.97
Netherlands 2000	23/39	15/40	3.86	9.36
Finland 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.

Rapid increase in Active Neoadjuvant anti-PD-1/PD-L1 Trials Worldwide





Wu et al. *J Hematol Oncol* 2022
Slide courtesy: Dr. Tricia Cottrell

Selected Neoadjuvant PD-(L)1 +/-CTLA4 Trial Data

Study	Stage/	N of subjects	Backbone	MPR/pCR
JHU/MSKCC NEJM	IB-IIIA	21	Nivo x 2 doses	45%/15% (of 20 resected)
Neostar	I-IIIA	23 21	Nivo x 2 doses (6 wks) Nivo-Ipi (6wks)	17%/9% (ITT) 33%/29% (ITT)
LCMC3	IB-IIIA/	101	Neoadj Atezo x 2 followed by adj atezo (if path response)	19%/5% (interim ITT)
Ready et al.	IB-IIIA/25	30	Neoadj pembro x 2 (6 wks) & 4 cycles of adj pembro	28%/8% (of 25 resected tumors)
Gao et al	IA-IIIA	40	Neoadj sintilimab x 2 doses (6 wks)	40.5%/16.2% (of 37 resected tumors)
PRINCEPS	I-IIIA	30	Neoadj Atezo x 1 dose (4 wks)	14%/0% (of 29 resected tumors
IONESCO	IB>4cm/IIIA	46	Neoadj durva x 3 doses (6 weeks)	17.5%/7%

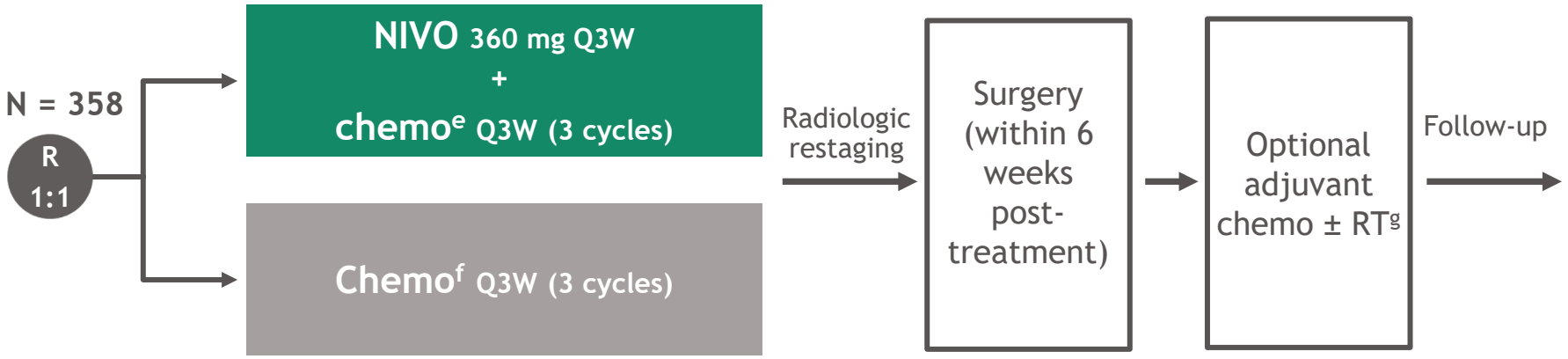
CheckMate 816 study design[a]

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.

Baseline characteristics

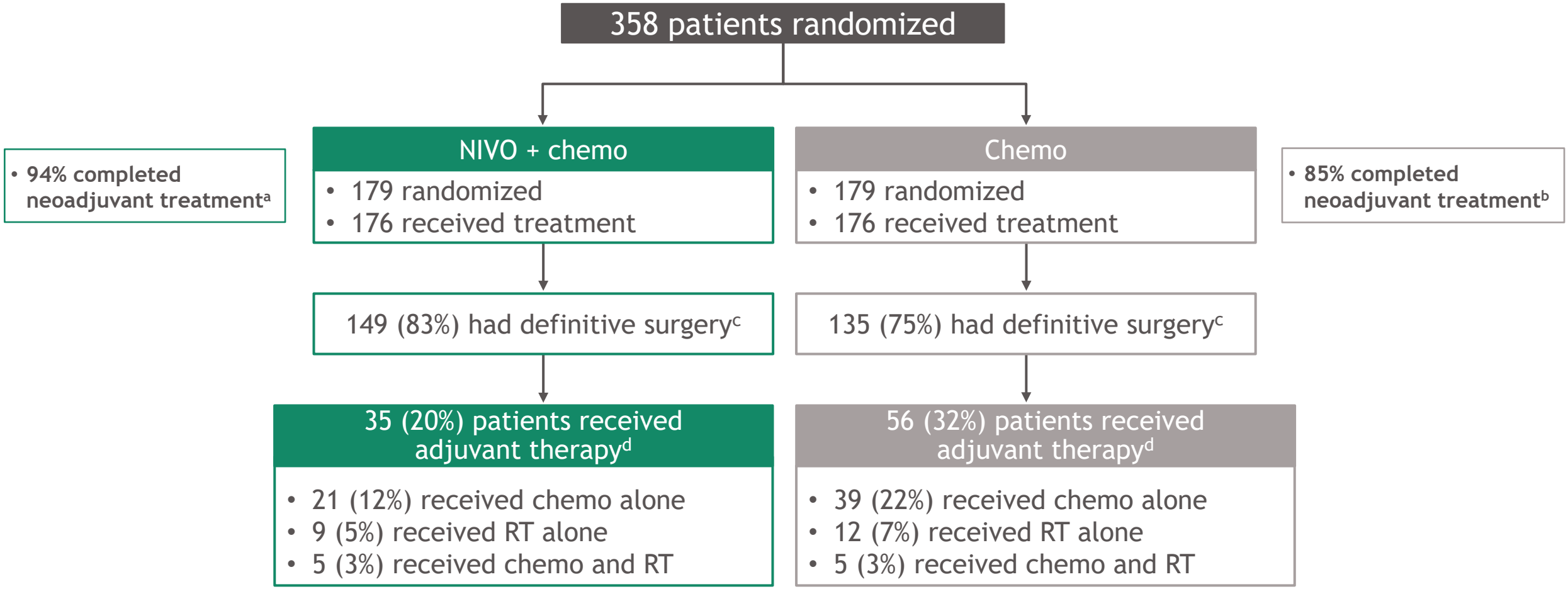
	NIVO + chemo (n = 179)	Chemo (n = 179)
Age, median (range), years	64 (41–82)	65 (34–84)
Age category, %		
< 65 years	52	46
≥ 65 years	48	54
Male, %	72	71
Region,[a] %		
North America	23	28
Europe	23	14
Asia	48	51
ECOG PS, %		
0	69	65
1	31	35
Stage,[b,c] %		
IB–II	36	35
IIIA	63	64
Histology, %		
Squamous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

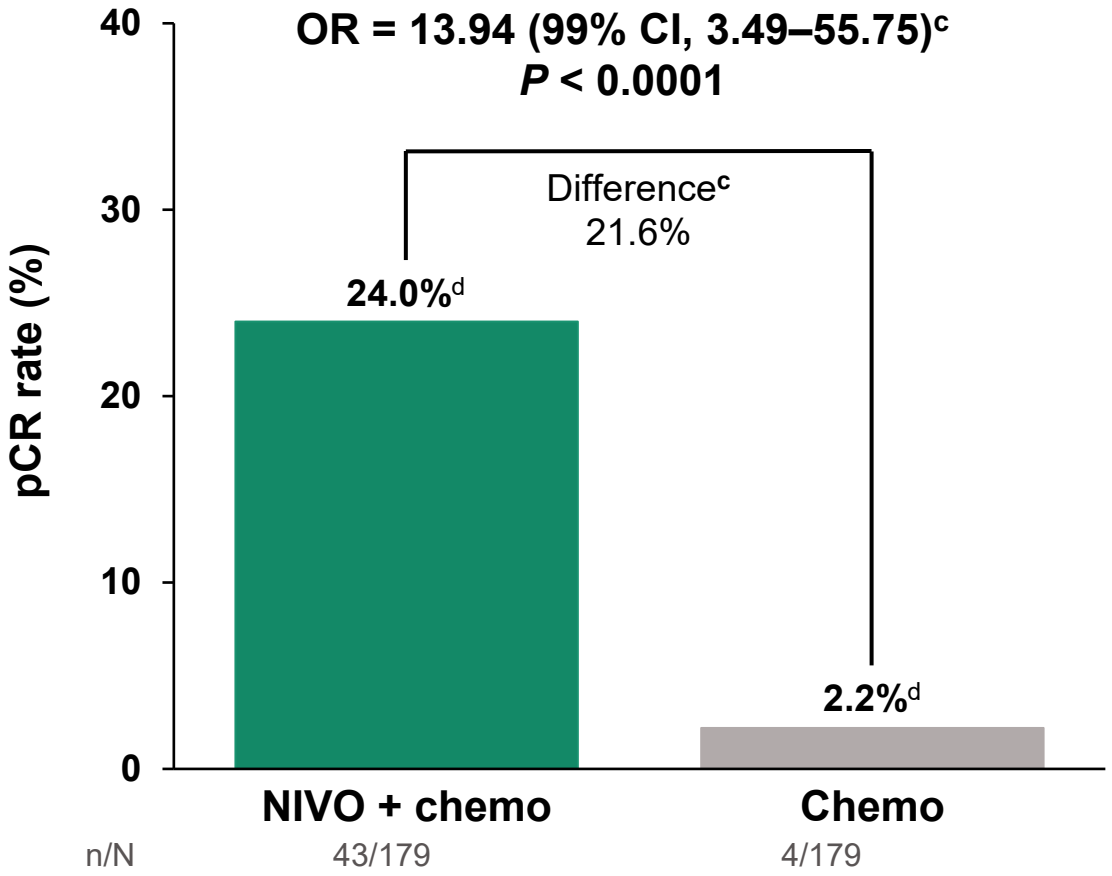


Database lock: October 20, 2021; minimum follow-up: 21 months; median follow-up, 29.5 months.

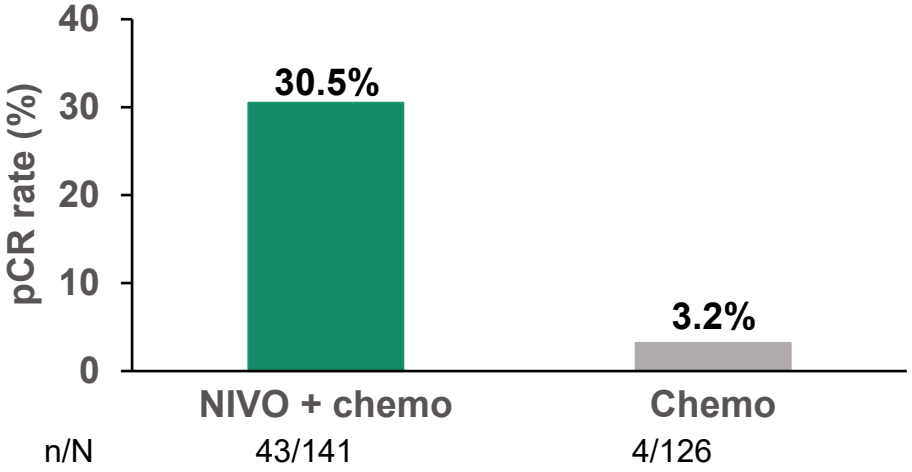
[a]Reasons for not completing neoadjuvant treatment included disease progression (1%) and study drug toxicity (6%); [b]Reasons for not completing neoadjuvant treatment included disease progression (1%), study drug toxicity (7%), and other (7%); [c]Denominator based on randomized patients. Reasons for 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: pCR rate with neoadjuvant nivo + chemo vs. chemo

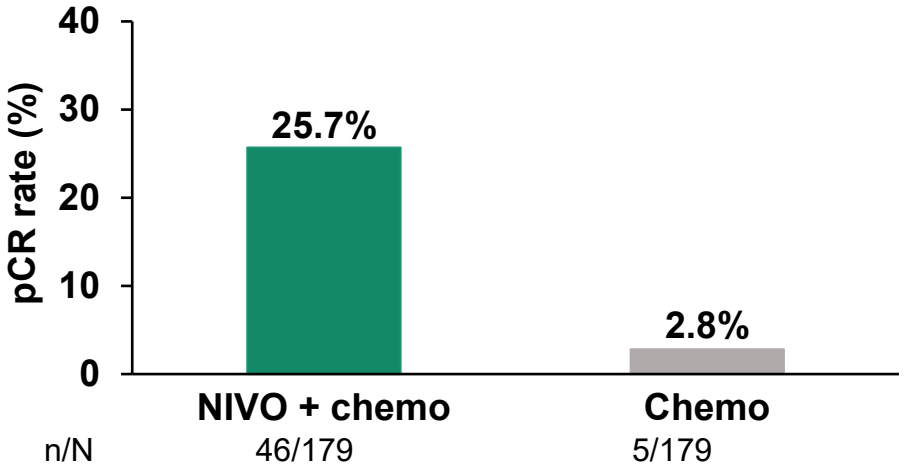
Primary endpoint: ITT (ypT0N0)[b]



Patients with resection[e] (ypT0N0)



Primary tumor only in ITT (ypT0)

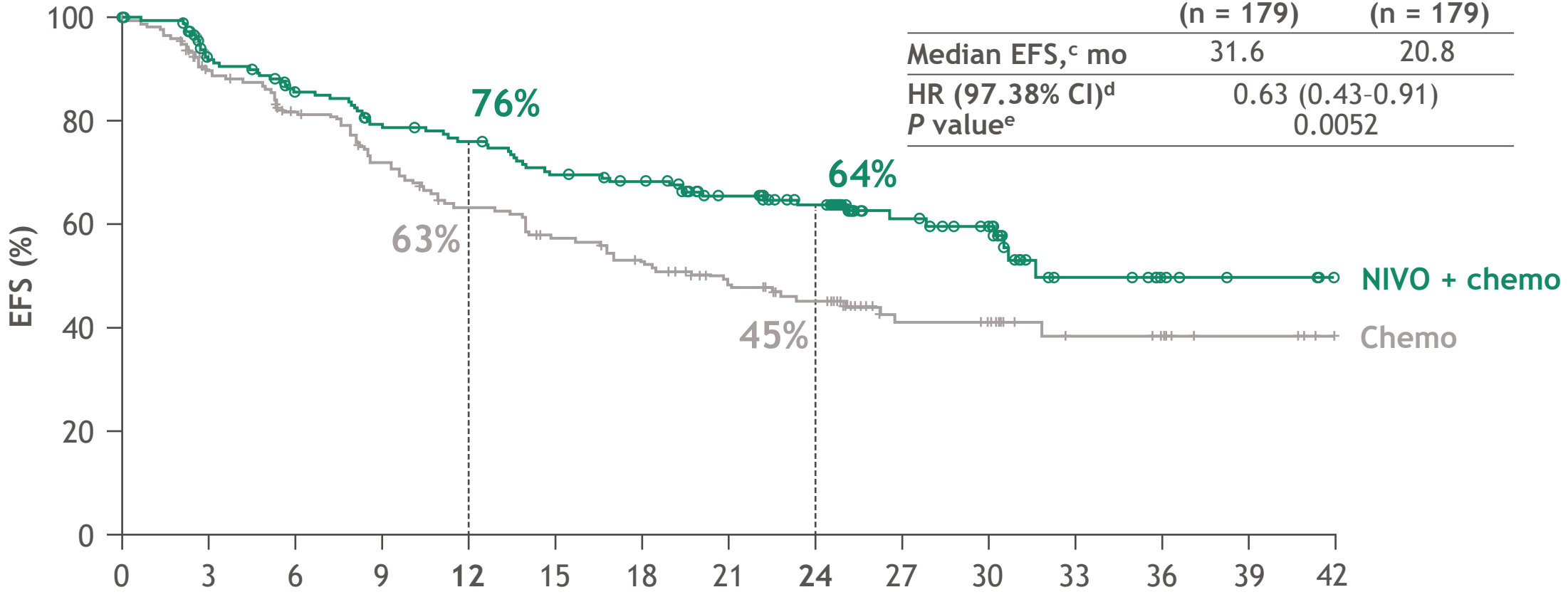


- pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4–29.0)

[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.

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	



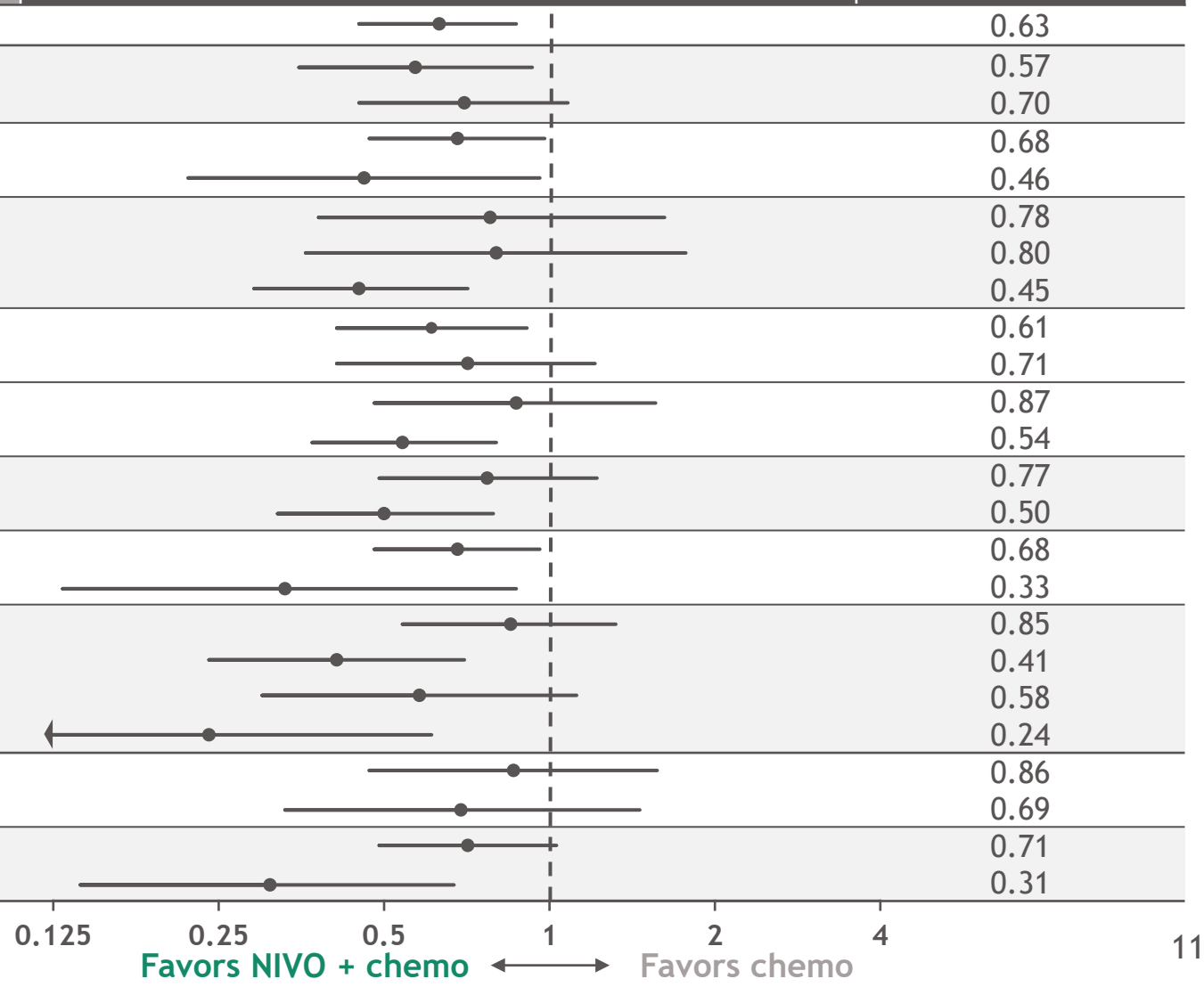
No. at risk														
NIVO + chemo	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemo	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

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

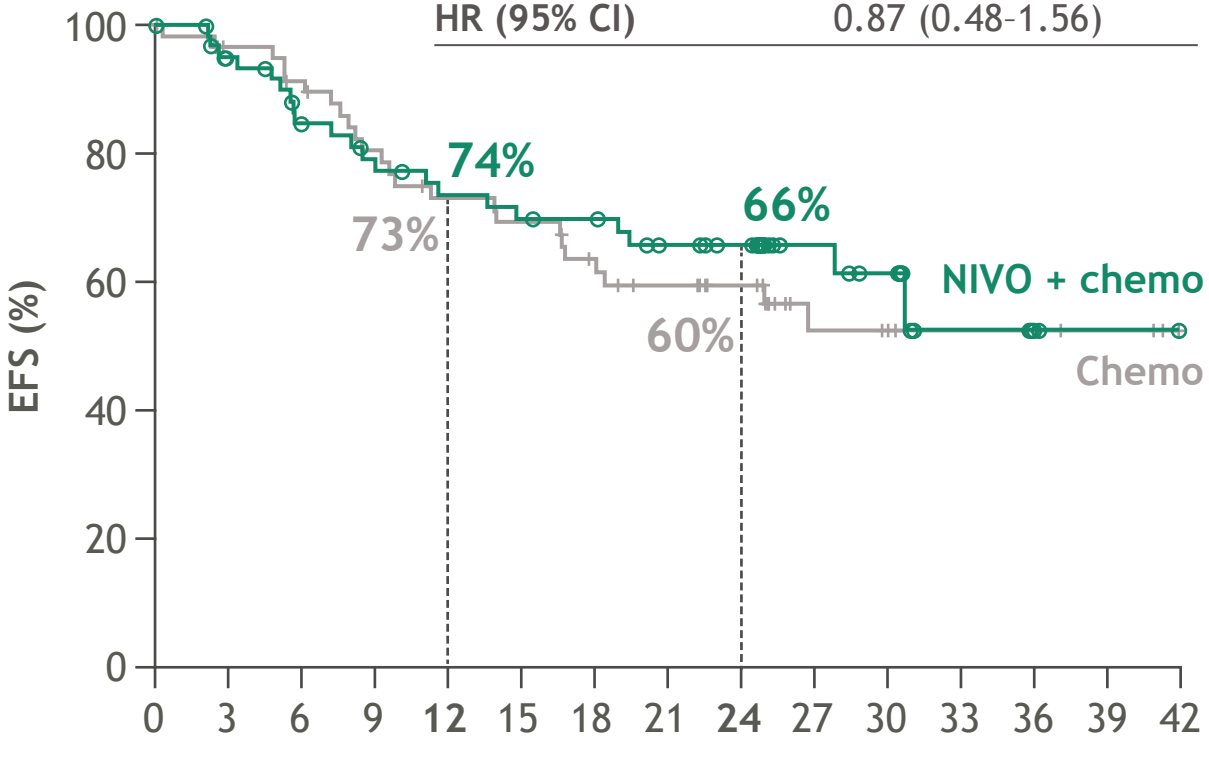


[a]Per BICR.

EFS by baseline stage of disease

Stage IB-II

	NIVO + chemo (n = 65)	Chemo (n = 62)
Median EFS,[a] mo	NR	NR
HR (95% CI)	0.87 (0.48–1.56)	

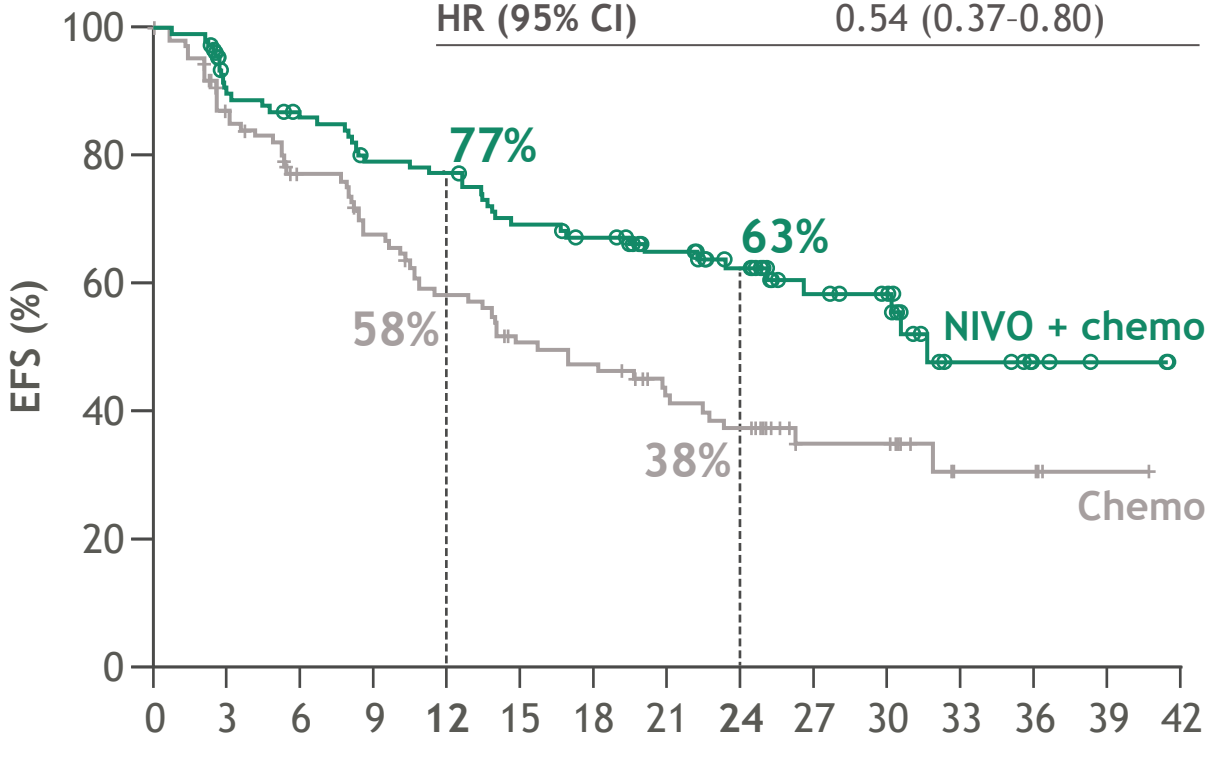


No. at risk

65	56	47	43	39	37	36	31	27	15	12	4	2	1	0
62	55	51	44	39	37	32	28	23	12	10	8	6	3	0

Stage IIIA

	NIVO + chemo (n = 113)	Chemo (n = 115)
Median EFS,[b] mo	31.6	15.7
HR (95% CI)	0.54 (0.37–0.80)	



No. at risk

113	95	89	81	79	70	66	56	47	26	22	9	4	2	0
115	89	75	65	55	46	43	33	29	14	14	5	5	1	0

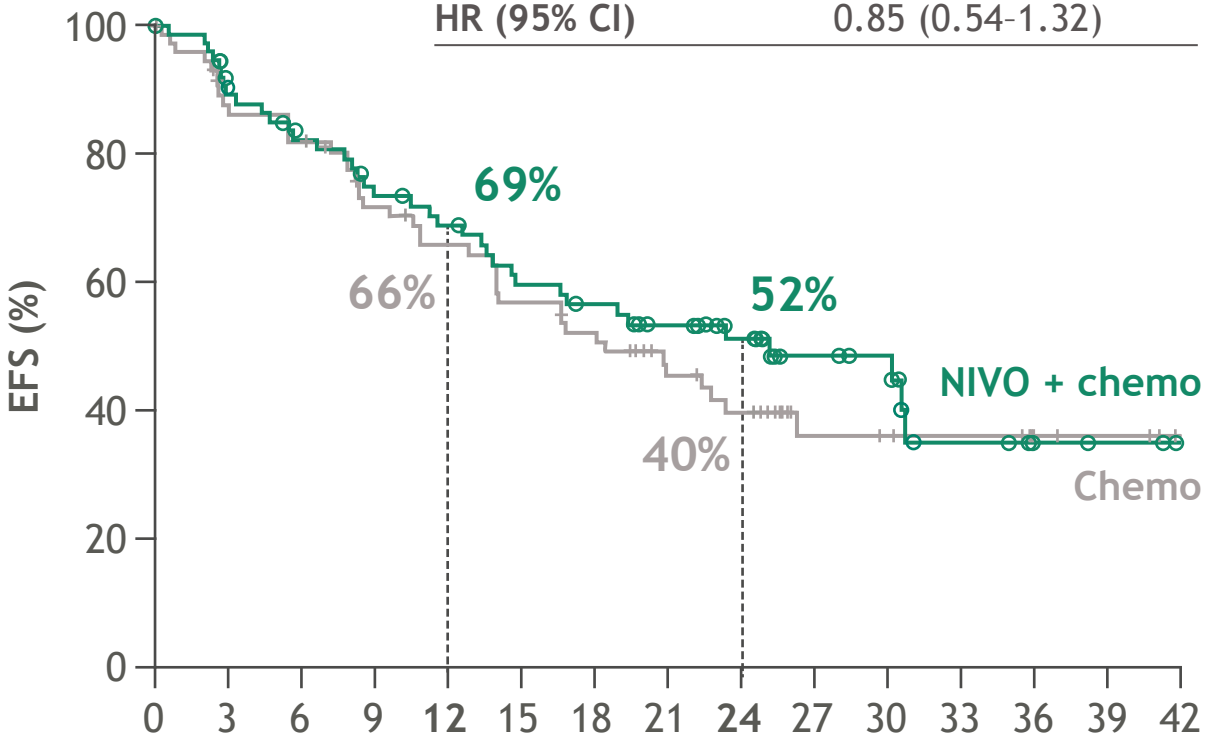
Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]95% CI = 27.8–NR (NIVO + chemo) and 16.8–NR (chemo); [b]95% CI = 26.6–NR (NIVO + chemo) and 10.8–22.7 (chemo).

EFS by tumor PD-L1 expression < 1% or ≥ 1%

PD-L1 < 1%

	NIVO + chemo (n = 78)	Chemo (n = 77)
Median EFS,[a] mo	25.1	18.4
HR (95% CI)	0.85 (0.54-1.32)	

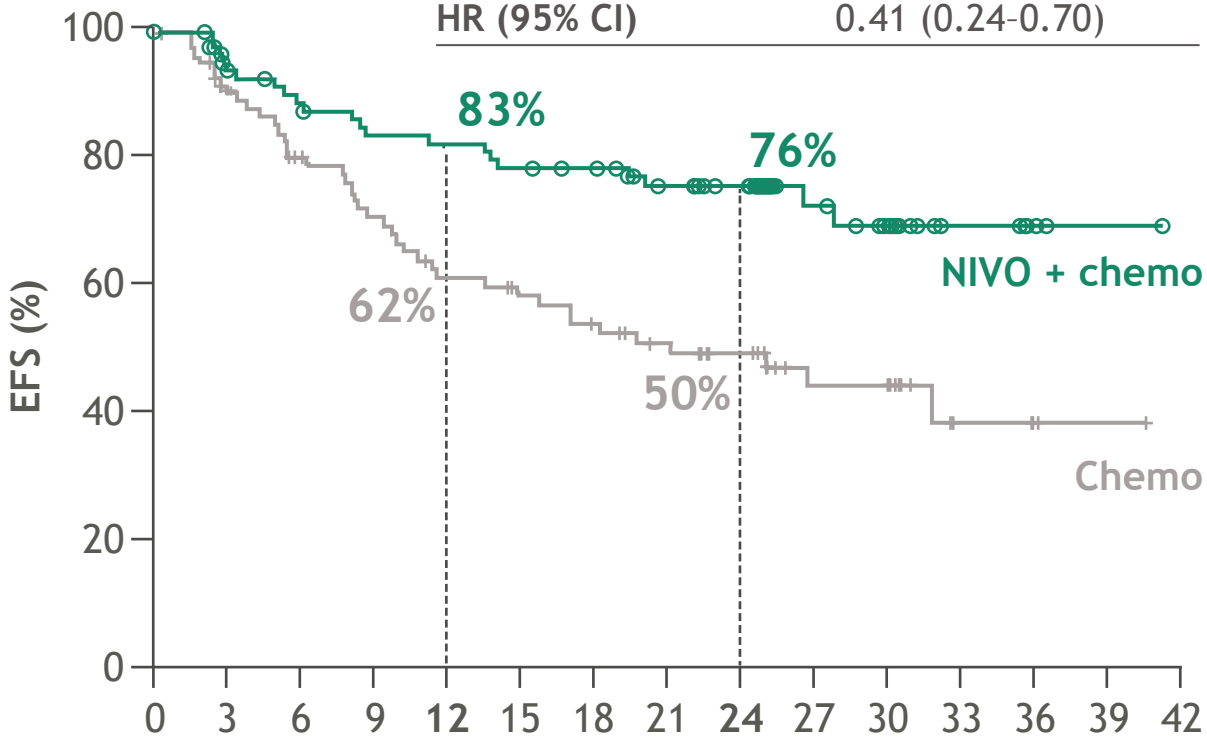


No. at risk

78	65	57	51	46	39	36	30	24	15	13	6	3	2	0
77	62	58	49	44	38	34	25	21	10	9	8	6	3	0

PD-L1 ≥ 1%

	NIVO + chemo (n = 89)	Chemo (n = 89)
Median EFS,[b] mo	NR	21.1
HR (95% CI)	0.41 (0.24-0.70)	



No. at risk

89	76	69	66	65	62	60	53	47	24	19	7	3	1	0
89	71	60	53	45	41	37	32	27	16	15	5	5	1	0

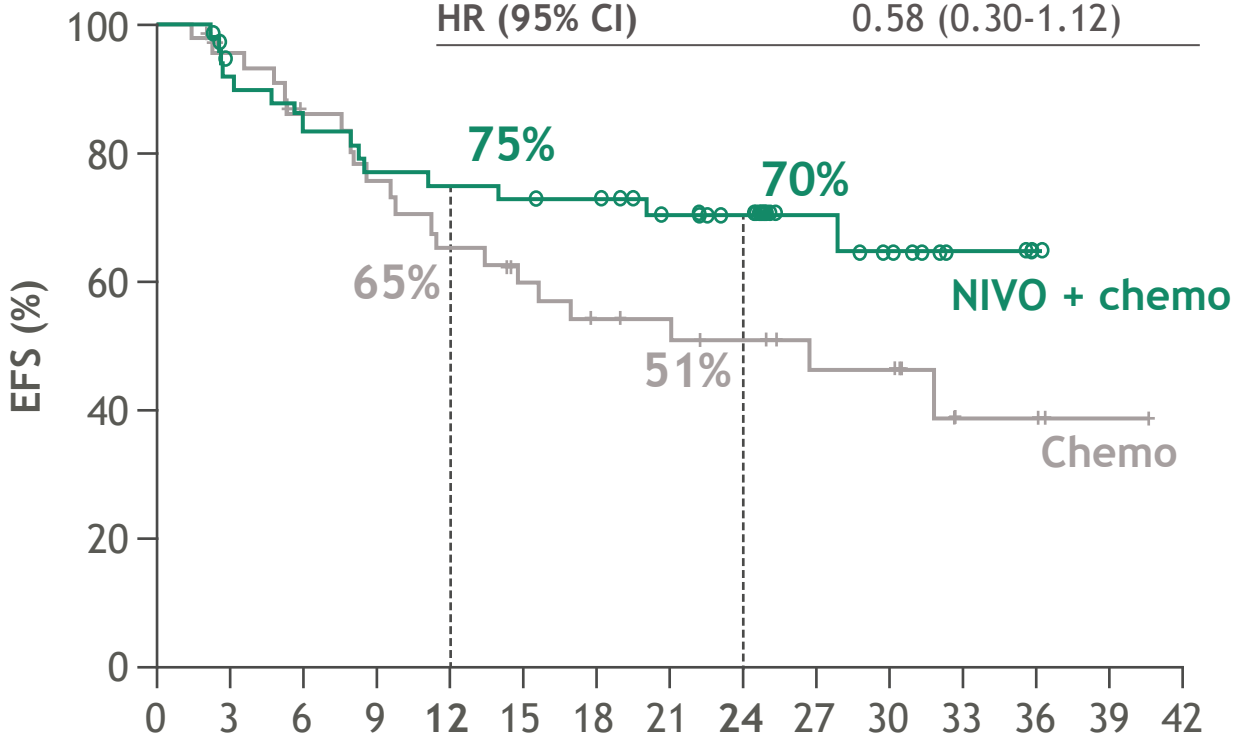
Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]95% CI = 14.6-NR (NIVO + chemo) and 13.9-26.2 (chemo); [b]95% CI = NR-NR (NIVO + chemo) and 11.5-NR (chemo).

EFS by tumor PD-L1 expression 1-49% or ≥ 50%

PD-L1 1-49%

	NIVO + chemo (n = 51)	Chemo (n = 47)
Median EFS,[a] mo	NR	26.7
HR (95% CI)	0.58 (0.30-1.12)	

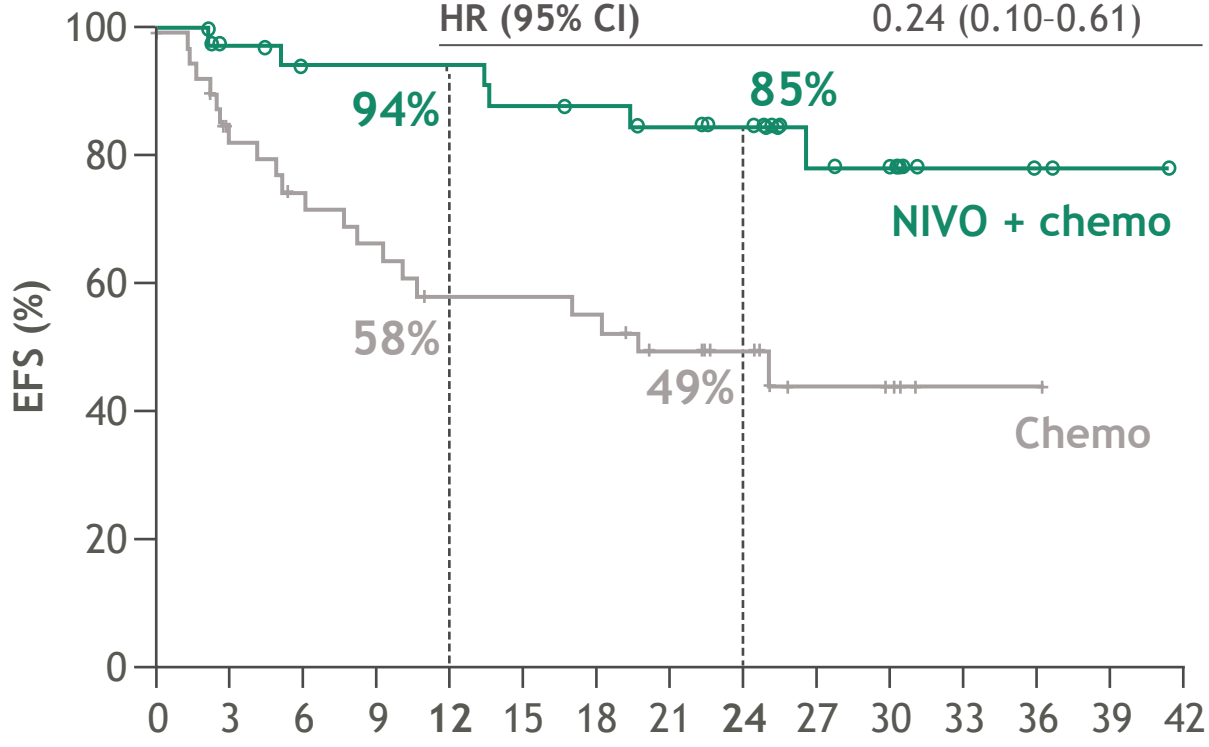


No. at risk

51	43	39	36	35	34	33	28	24	12	9	4	1	0	0
47	40	33	29	25	21	18	17	15	10	10	3	3	1	0

PD-L1 ≥ 50%

	NIVO + chemo (n = 38)	Chemo (n = 42)
Median EFS,[b] mo	NR	19.6
HR (95% CI)	0.24 (0.10-0.61)	



No. at risk

38	33	30	30	30	28	27	25	23	12	10	3	2	1	0
42	31	27	24	20	20	19	15	12	6	5	2	5	0	0

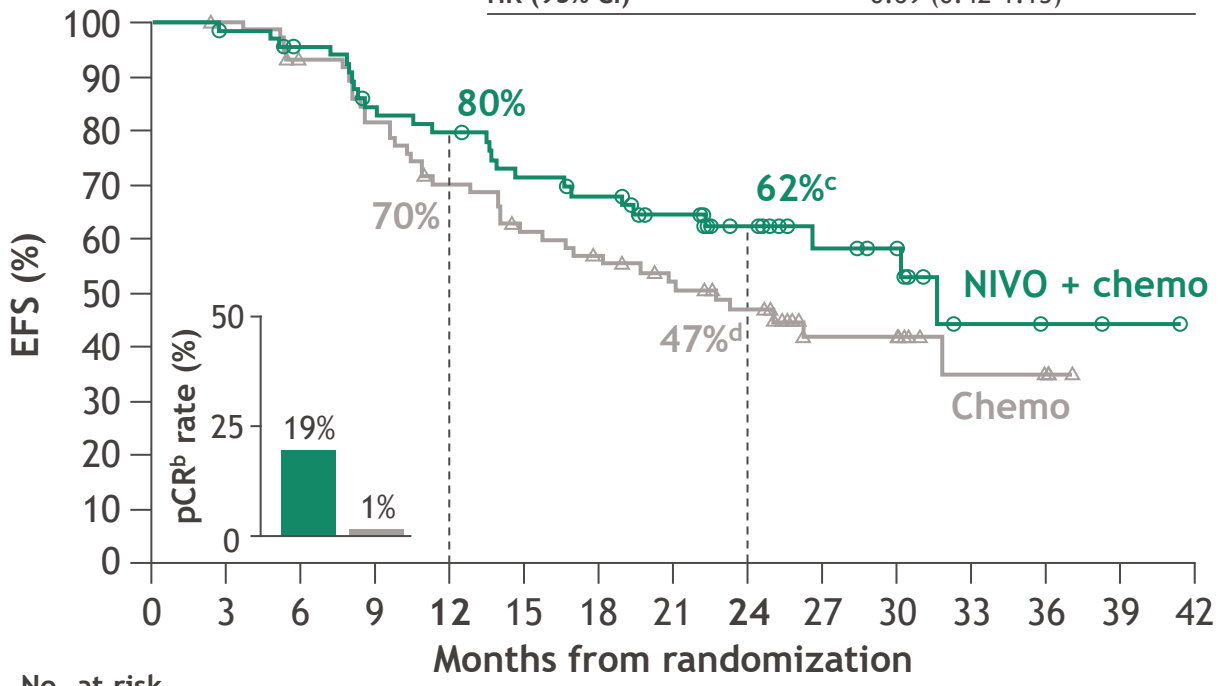
Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]95% CI = 27.8-NR (NIVO + chemo) and 11.5-NR (chemo); [b]95% CI = NR-NR (NIVO + chemo) and 8.2-NR (chemo).

Efficacy in patients with or without pathologic evidence of LN involvement[a]

With LN involvement

	NIVO + chemo (n = 68)	Chemo (n = 74)
Median EFS, mo (95% CI)	31.6 (22.2-NR)	22.7 (14.8-NR)
HR (95% CI)	0.69 (0.42-1.13)	

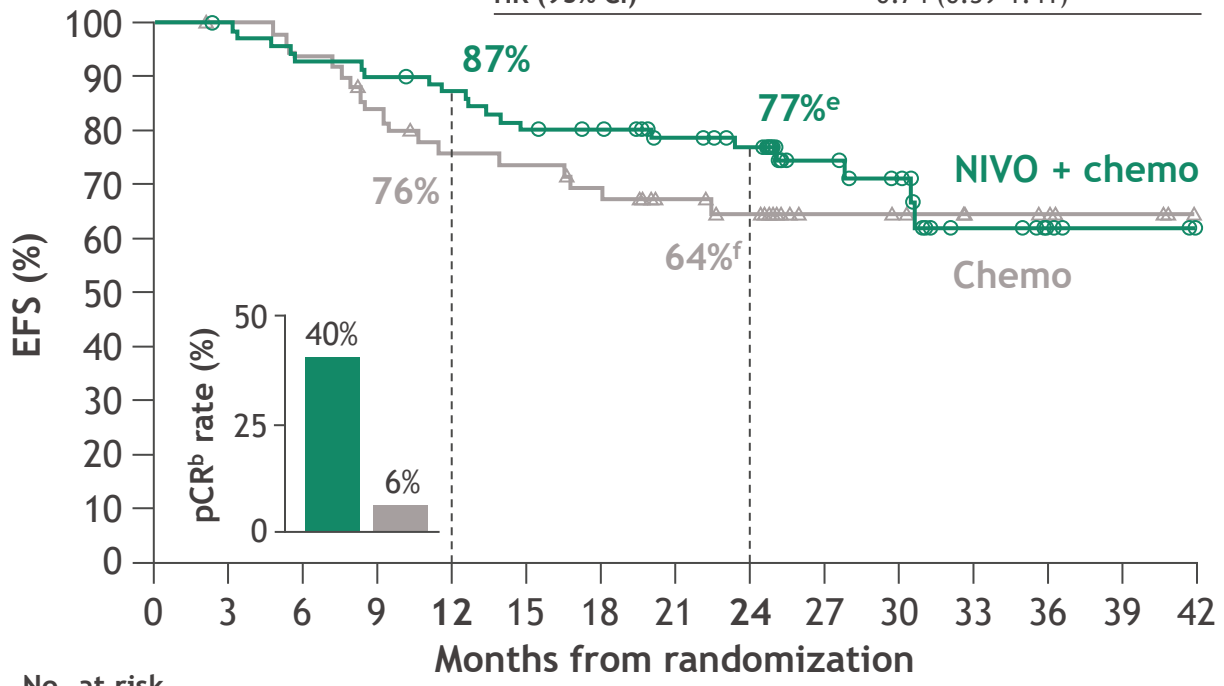


No. at risk

68	66	61	52	49	43	40	34	26	14	11	4	3	2	0
74	73	65	57	48	41	37	32	26	13	12	5	4	0	0

Without LN involvement

	NIVO + chemo (n = 72)	Chemo (n = 51)
Median EFS, mo (95% CI)	NR (30.7-NR)	NR (22.4-NR)
HR (95% CI)	0.74 (0.39-1.41)	



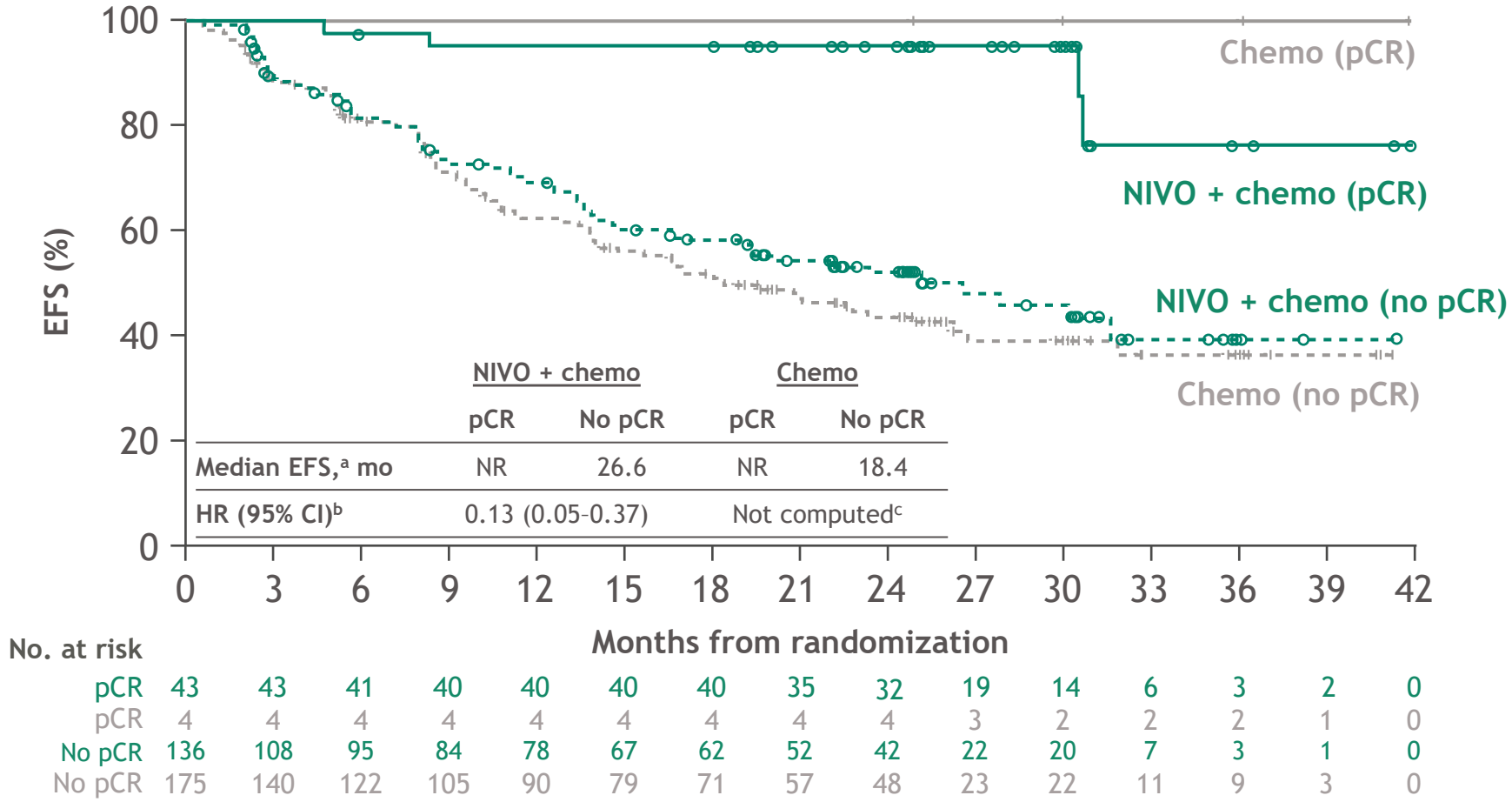
No. at risk

72	71	66	64	61	56	54	48	43	24	20	9	3	1	0
51	50	47	41	36	35	32	26	23	11	10	7	6	3	0

Minimum / median follow-up: 21 months / 29.5 months.

[a]Among 179 patients randomized to both the NIVO + chemo and chemo groups, 149 and 135 received treatment and had definitive surgery, respectively, and 140 and 125 had path-evaluable samples from both primary tumor and LN; LN involvement refers to pathologic evidence of LN disease at resection that had or had not fully regressed after neoadjuvant treatment (0% or > 0% RVT in the resected LN). [b]0% RVT in both the primary tumor and LN; MPR (≤ 10% RVT in both primary tumor and LN) with NIVO + chemo vs chemo: 29% vs 5% (patients with LN involvement) and 62% vs 24% (patients without LN involvement). 95% CI: [c]49-73, [d]34-58, [e]65-85, [f]49-76.

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]	

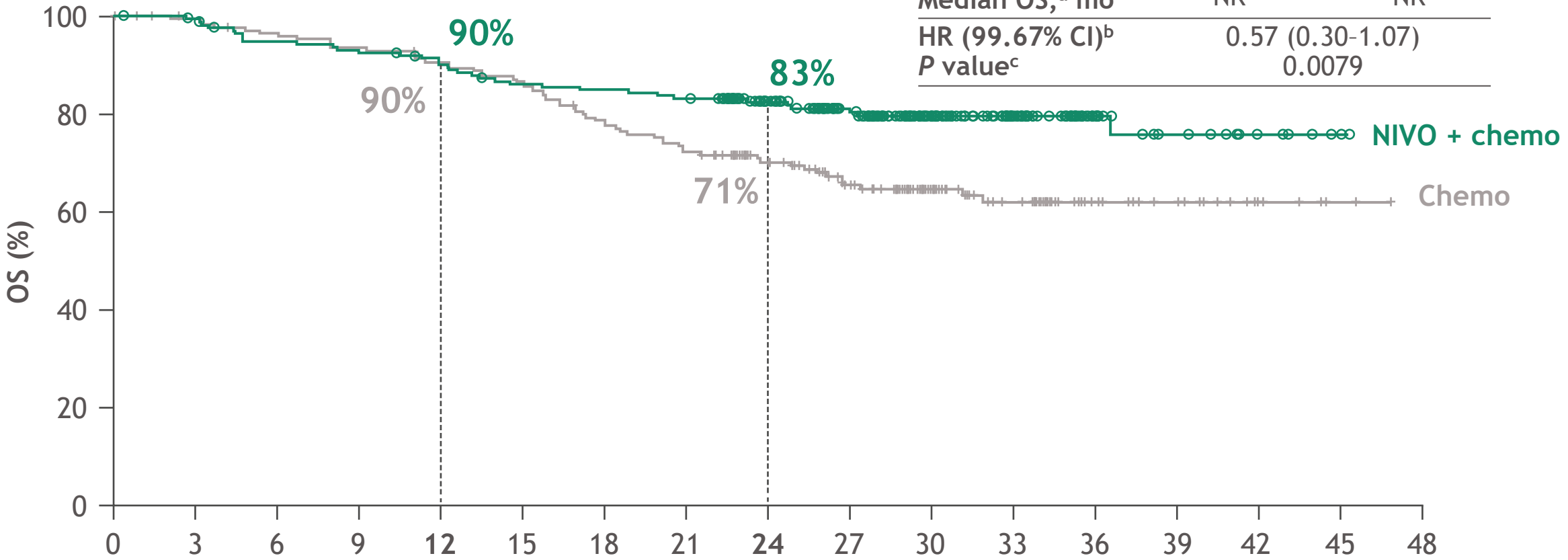
- pCR rates were significantly improved with NIVO + chemo vs chemo (24.0% vs 2.2%)
- In patients without pCR, HR (95% CI) for NIVO + chemo vs chemo was 0.84 (0.61–1.17)

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.

2021 ASCO ANNUAL MEETING

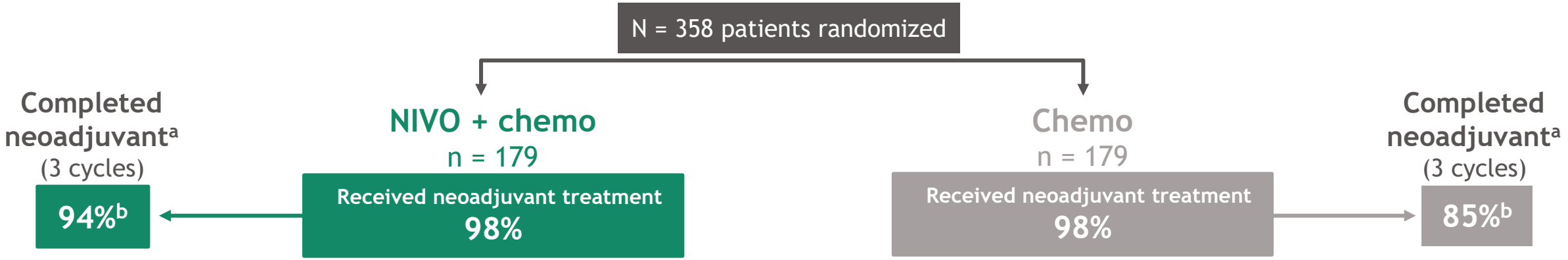
Surgical outcomes from the phase 3 CheckMate 816 trial: nivolumab + platinum-doublet chemotherapy vs chemotherapy alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer

Jonathan Spicer,[1] Changli Wang,[2] Fumihiro Tanaka,[3] Gene B. Saylors,[4] Ke-Neng Chen,[5] Moishe Liberman,[6] Everett Vokes,[7] Nicolas Girard,[8] Shun Lu,[9] Mariano Provencio,[10] Tetsuya Mitsudomi,[11] Mark M. Awad,[12] Enriqueta Felip,[13] Patrick M. Forde,[14] Scott J. Swanson,[12] Julie R. Brahmer,[14] Keith Kerr,[15] Cécile Dorange,[16] Junliang Cai,[16] Stephen Broderick[14]

[1]McGill University Health Center, Montreal, QC, Canada; [2]Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [3]University of Occupational and Environmental Health, Kitakyushu, Japan; [4]Charleston Oncology, Charleston, SC, USA; [5]Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China; [6]Centre hospitalier de l'Université de Montréal, Montréal, QC, Canada; [7]University of Chicago Medicine, Chicago, IL, USA; [8]Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France; [9]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai JiaoTong University, Shanghai, China; [10]Hospital Universitario Puerta de Hierro, Madrid, Spain; [11]Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; [12]Dana-Farber Cancer Institute, Boston, MA, USA; [13]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [14]Johns Hopkins Kimmel Cancer Center, Baltimore, MD, USA; [15]Aberdeen Royal Infirmary, Aberdeen, UK; [16]Bristol Myers Squibb, Princeton, NJ, USA

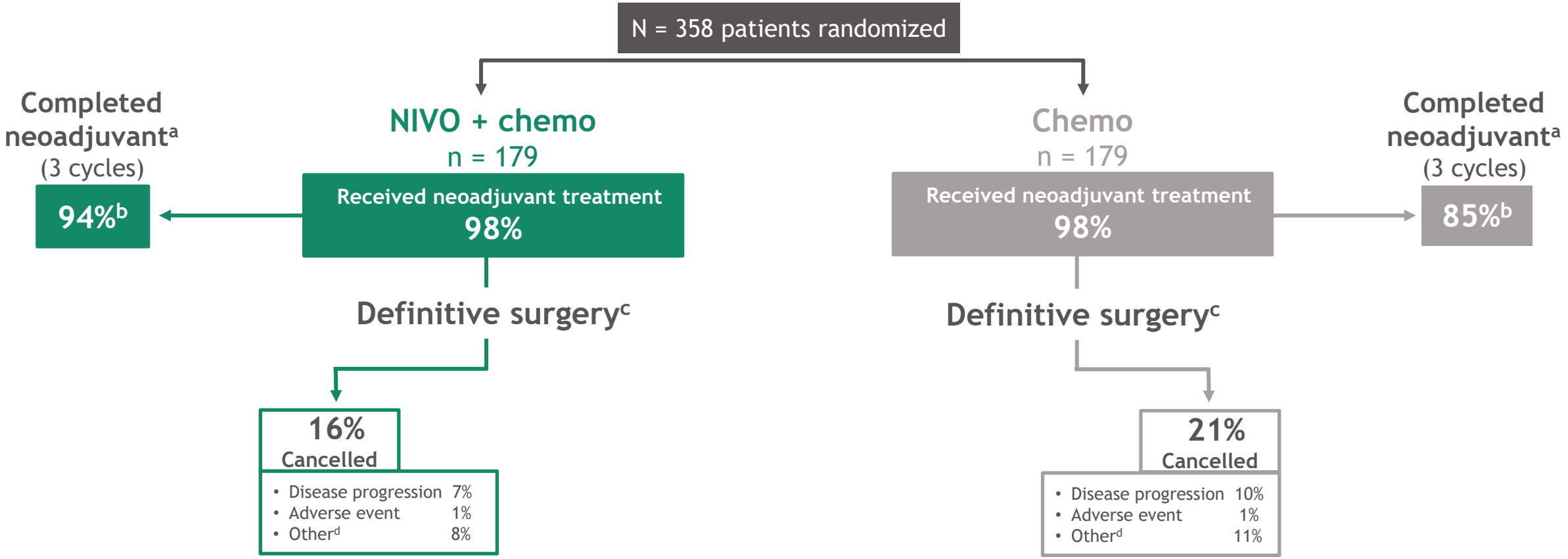
Abstract Number 8503

Treatment and surgery summary: all randomized patients



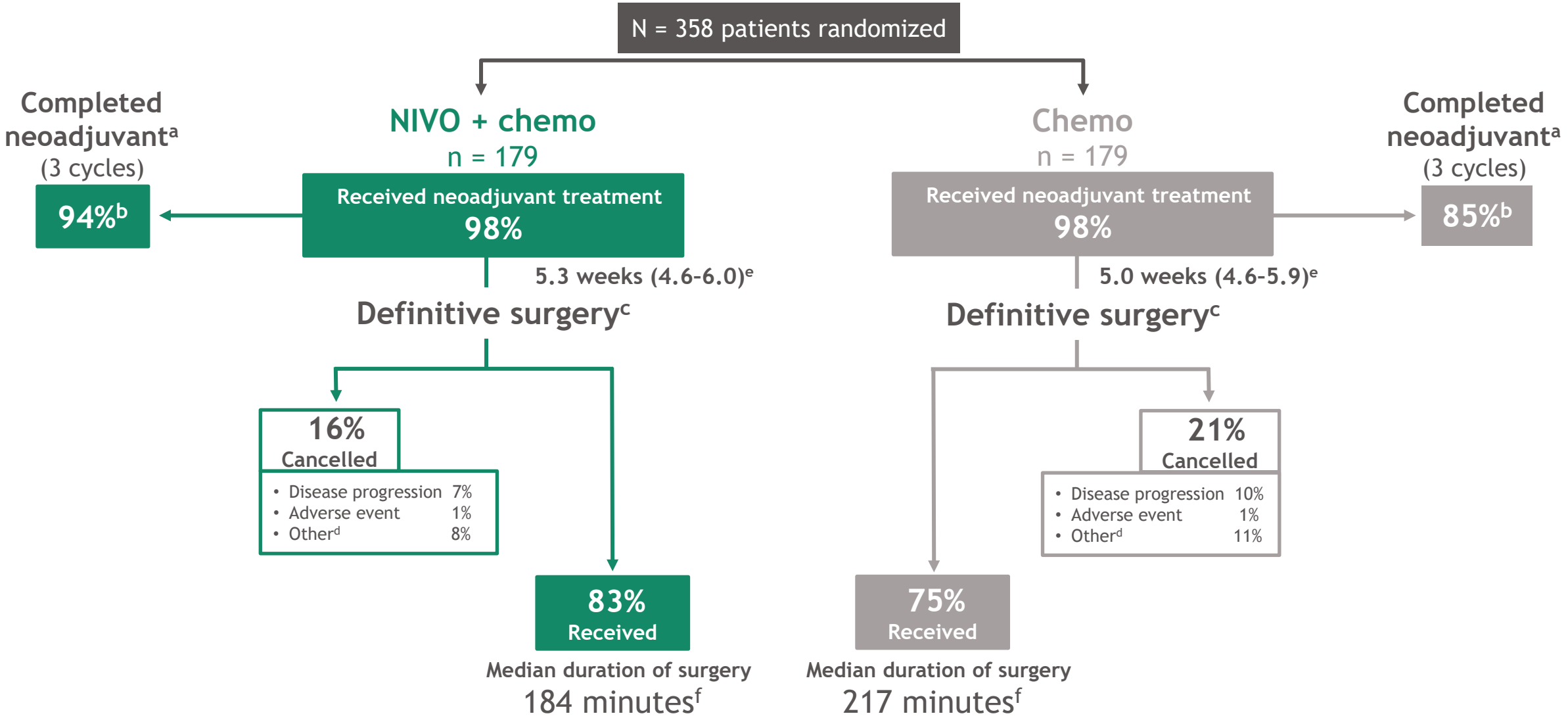
[a]Reasons for patients not completing neoadjuvant treatment: study drug toxicity (6% in the NIVO + chemo and 7% in the chemo arm), disease progression (1% in each arm), and other reasons (7% in the chemo arm only; this included AEs unrelated to study drug, patient request to discontinue treatment, patient withdrew consent, and patient no longer meeting study criteria); [b]Denominator based on patients with neoadjuvant treatment.

Treatment and surgery summary: all randomized patients



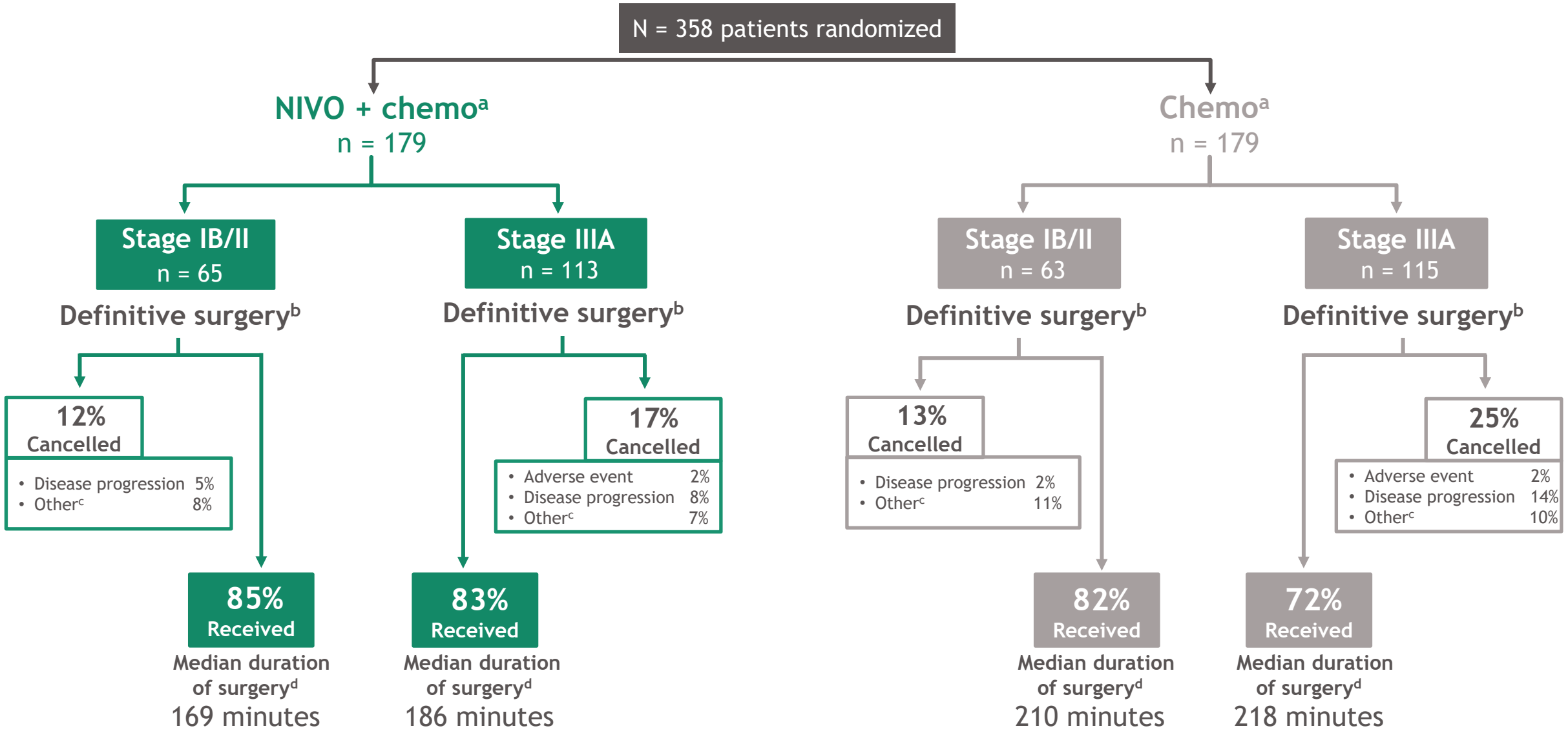
[a]Reasons for patients not completing neoadjuvant treatment: study drug toxicity (6% in the NIVO + chemo and 7% in the chemo arm), disease progression (1% in each arm), and other reasons (7% in the chemo arm only; this included AEs unrelated to study drug, patient request to discontinue treatment, patient withdrew consent, and patient no longer meeting study criteria); [b]Denominator based on patients with neoadjuvant treatment; [c]Definitive surgery not reported: NIVO + chemo, 1%; chemo, 3%; [d]Other reasons included patient refusal, unresectability, and poor lung function.

Treatment and surgery summary: all randomized patients



[a]Reasons for patients not completing neoadjuvant treatment: study drug toxicity (6% in the NIVO + chemo and 7% in the chemo arm), disease progression (1% in each arm), and other reasons (7% in the chemo arm only; this included AEs unrelated to study drug, patient request to discontinue treatment, patient withdrew consent, and patient no longer meeting study criteria); [b]Denominator based on patients with neoadjuvant treatment; [c]Definitive surgery not reported: NIVO + chemo, 1%; chemo, 3%; [d]Other reasons included patient refusal, unresectability, and poor lung function; [e]Median (IQR) time from last dose to definitive surgery; [f]Patients (n) with reported duration of surgery: NIVO + chemo, 122; chemo, 121; IQR for median duration of surgery: NIVO + chemo, 130.0-252.0 minutes; chemo, 150.0-283.0 minutes.

Surgery summary: by baseline stage of disease



[a]1 patient with stage IV in each arm; [b]Patients with definitive surgery not reported: NIVO + chemo, 3% (stage IB/II), 0 (stage IIIA); chemo, 5% (stage IB/II), 3% (stage IIIA); [c]Other reasons included patient refusal, unresectability, and poor lung function; [d]Patients (n) with reported duration of surgery: NIVO + chemo, 46 (stage IB/II), 76 (stage IIIA); chemo, 47 (stage IB/II), 74 (stage IIIA); IQR for median duration of surgery: NIVO + chemo, 126.0–275.0 (stage IB/II) and 134.5-245.5 (stage IIIA); chemo, 150.0-267.0 (stage IB/II) and 147.0-290.0 (stage IIIA).

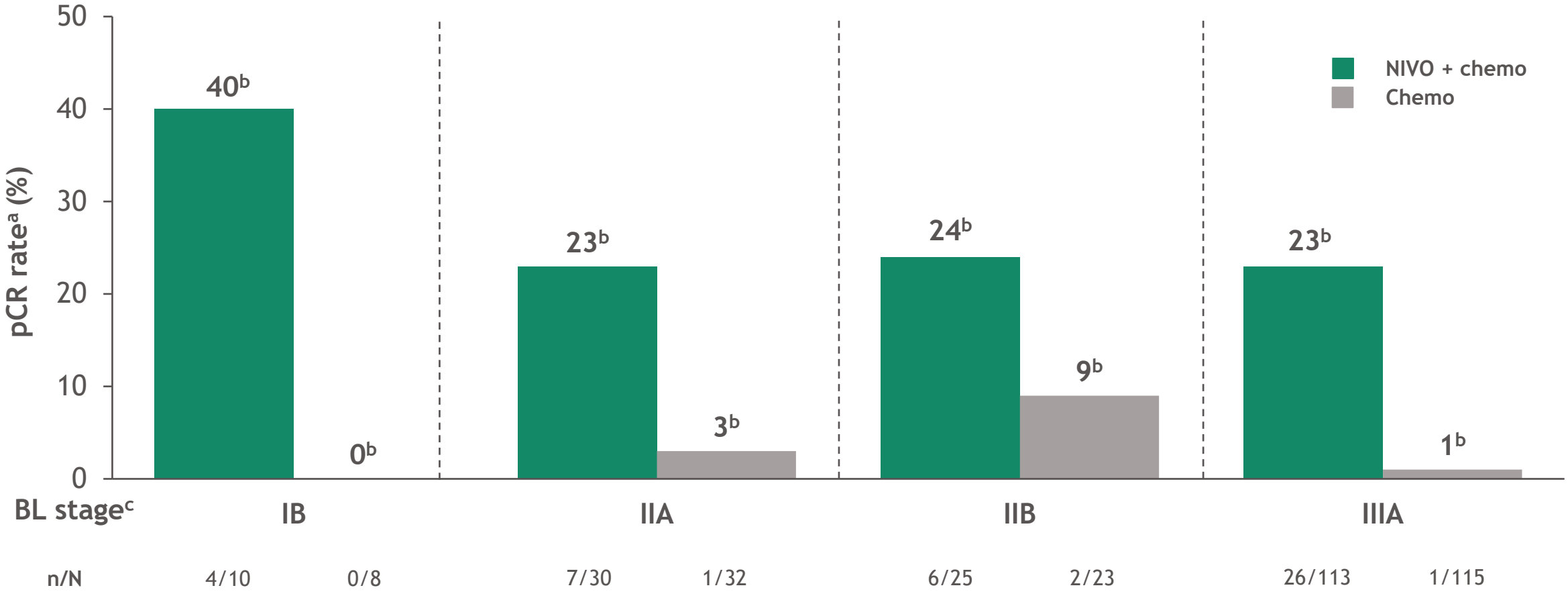
Surgery delay summary[a]

	All stages		Stage IB/II		Stage IIIA	
	NIVO + chemo (n = 149)	Chemo (n = 135)	NIVO + chemo (n = 55)	Chemo (n = 52)	NIVO + chemo (n = 94)	Chemo (n = 83)
Patients with delayed surgery,[b,c] n (%)	31 (21)	24 (18)	9 (16)	13 (25)	22 (23)	11 (13)
AE	6 (4)	9 (7)	2 (4)	7 (13)	4 (4)	2 (2)
Length of delay in surgery, weeks						
Median (IQR)	2.0 (0.6–3.0)	2.4 (1.0–3.7)	2.1 (0.9–2.9)	2.1 (1.3–3.6)	1.9 (0.6–3.0)	2.6 (0.6–4.9)
Of patients with delayed surgery, proportion n (%) with delay of[d]						
≤ 2 weeks	17 (55)	11 (46)	4 (44)	6 (46)	13 (59)	5 (46)
> 2 and ≤ 4 weeks	8 (26)	8 (33)	4 (44)	5 (38)	4 (18)	3 (27)
> 4 and ≤ 6 weeks	3 (10)	2 (8)	0	0	3 (14)	2 (18)
> 6 weeks	3 (10)	3 (12)	1 (11)	2 (15)	2 (9)	1 (9)

- Median (IQR) time from last neoadjuvant dose to definitive surgery was 5.3 (4.6–6.0) weeks with NIVO + chemo and 5.0 (4.6–5.9) weeks with chemo for all patients with definitive surgery

[a]Definitive surgery not reported: NIVO + chemo, 1%; chemo, 3%; [b]Denominator based on patients with definitive surgery; surgery was also delayed due to administration reasons (NIVO + chemo, 11% [all stages], 7% [stage IB/II], 14% [stage IIIA]; chemo, 6% [all stages], 8% [stage IB/II], 5% [stage IIIA]) and other reasons (NIVO + chemo, 5% [all stages], 5% [stage IB/II], 5% [stage IIIA]; chemo, 5% [all stages], 4% [stage IB/II], 6% [stage IIIA]); other reasons included surgeon requested additional pre-operative workup, patient request, impact of COVID-19; [c]Time from last dose of neoadjuvant treatment to surgery > 6 weeks; [d]Denominator based on patients with delayed surgery.

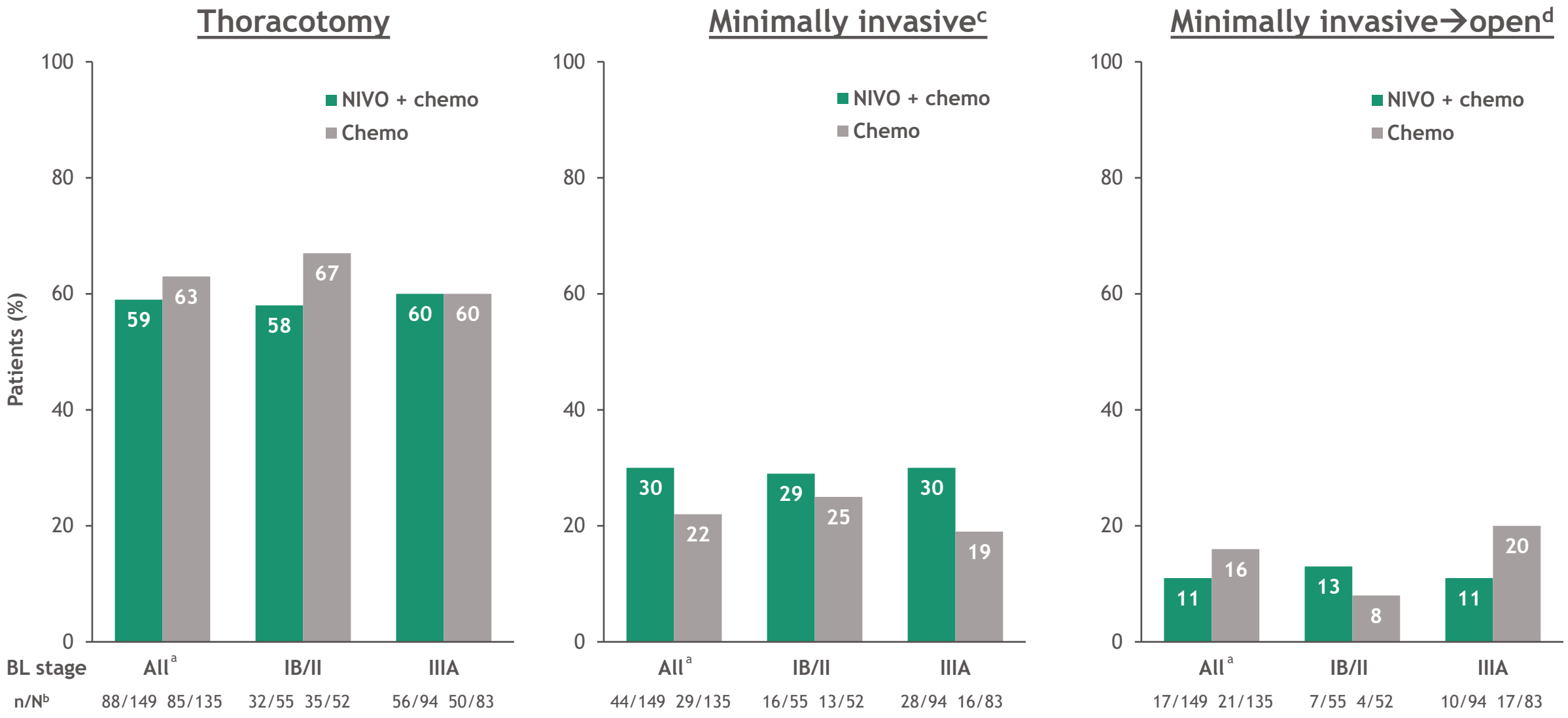
pCR by baseline stage of disease



- pCR improvement with NIVO + chemo vs chemo was observed regardless of radiologic down-staging[d]

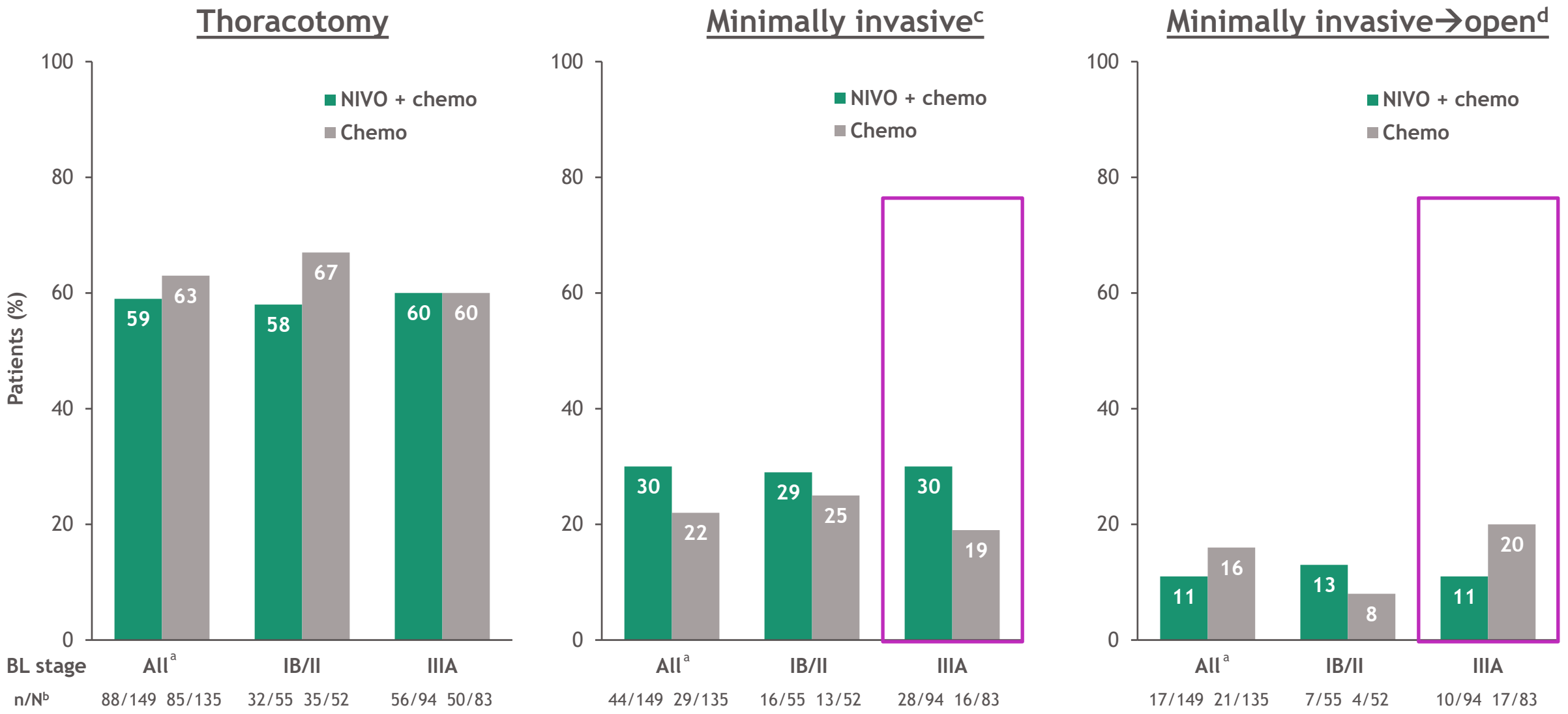
[a]Per BIPR in the ITT population; neither of the 2 patients with stage IV disease (1 in each arm) achieved pCR; [b]95% CI: NIVO + chemo, chemo (stage): 12.2–73.8, 0.0–36.9 (IB); 9.9–42.3, 0.1–16.2 (IIA); 9.4–45.1, 1.1–28.0 (IIB); 15.6–31.9, 0.0–4.7 (IIIA); [c]Baseline stage of disease by CRF, TNM 7th edition used for classification; [d]pCR rate in patients with radiographic down-staging: 31% with NIVO + chemo vs 7% with chemo; pCR rate in patients without radiographic down-staging: 22% with NIVO + chemo vs 1% with chemo.

Surgical approach by baseline stage of disease



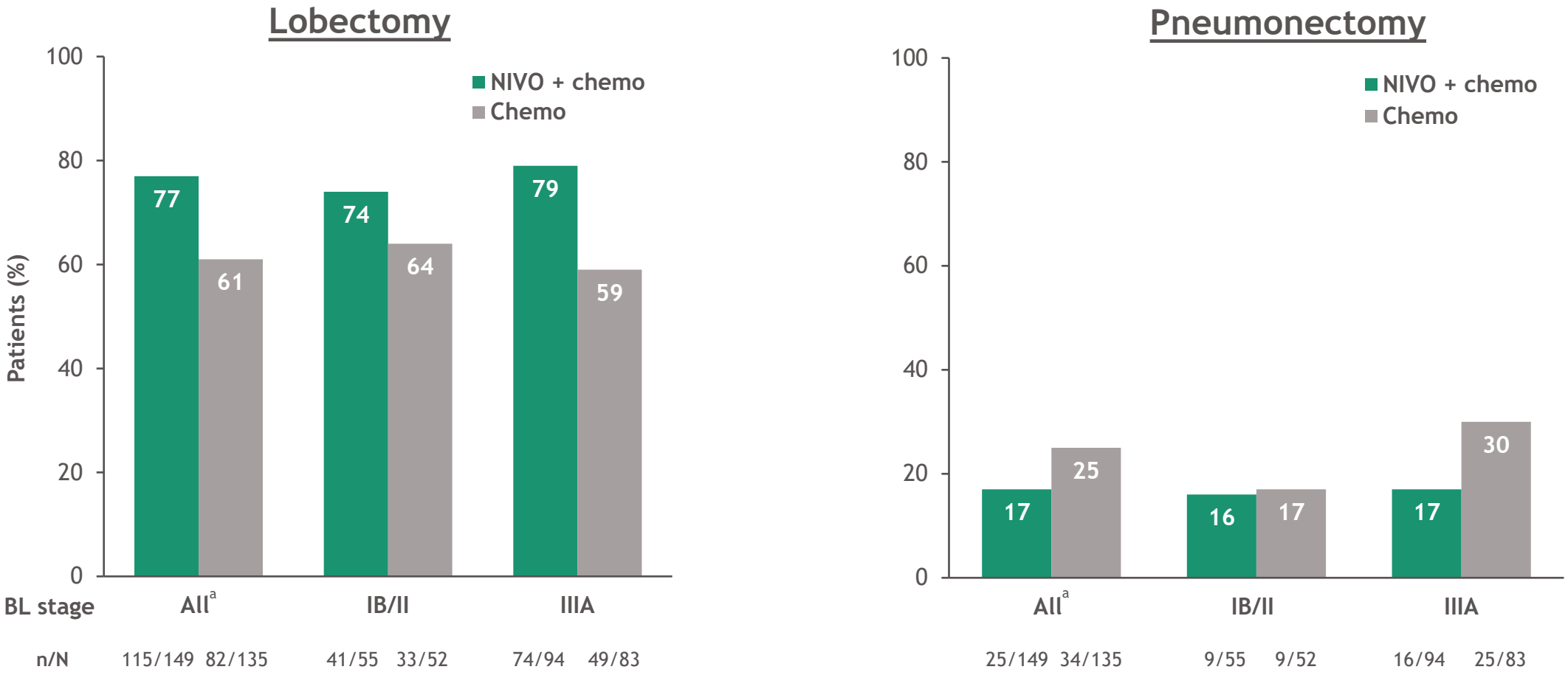
[a]Patients with all baseline stages of disease and definitive surgery; [b]Denominator based on patients with definitive surgery; [c]Thoracoscopic/robotic; [d]Minimally invasive to thoracotomy.

Surgical approach by baseline stage of disease



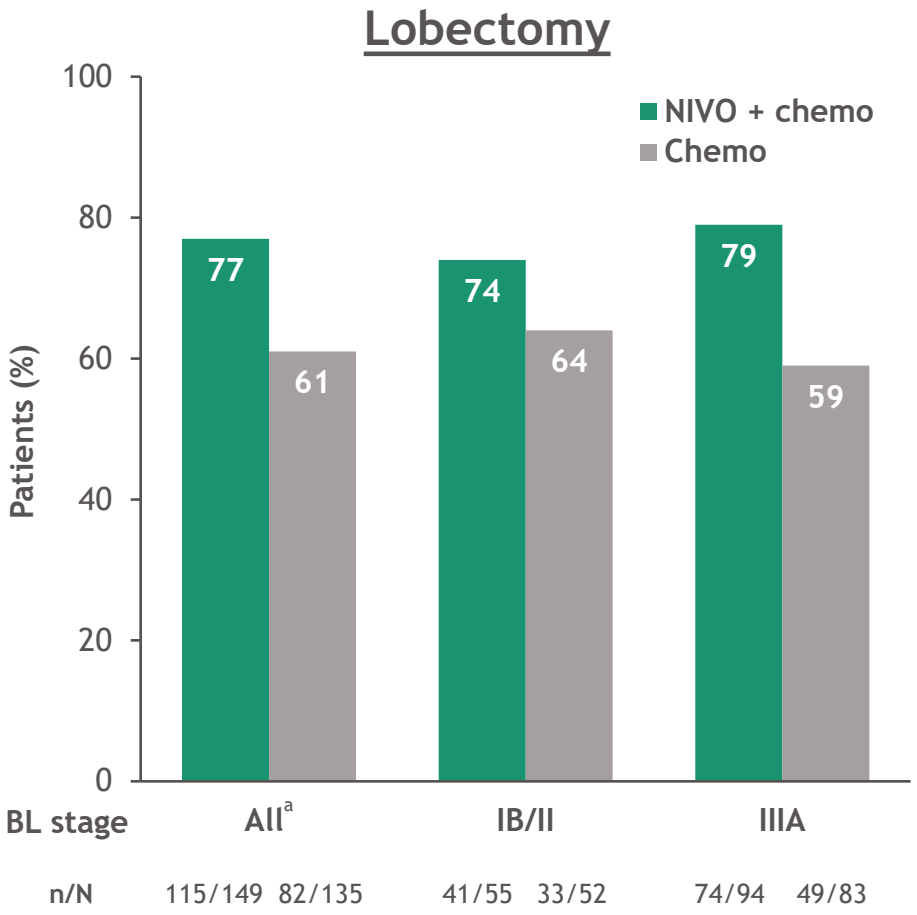
[a]Patients with all baseline stages of disease and definitive surgery; [b]Denominator based on patients with definitive surgery; [c]Thoracoscopic/robotic; [d]Minimally invasive to thoracotomy.

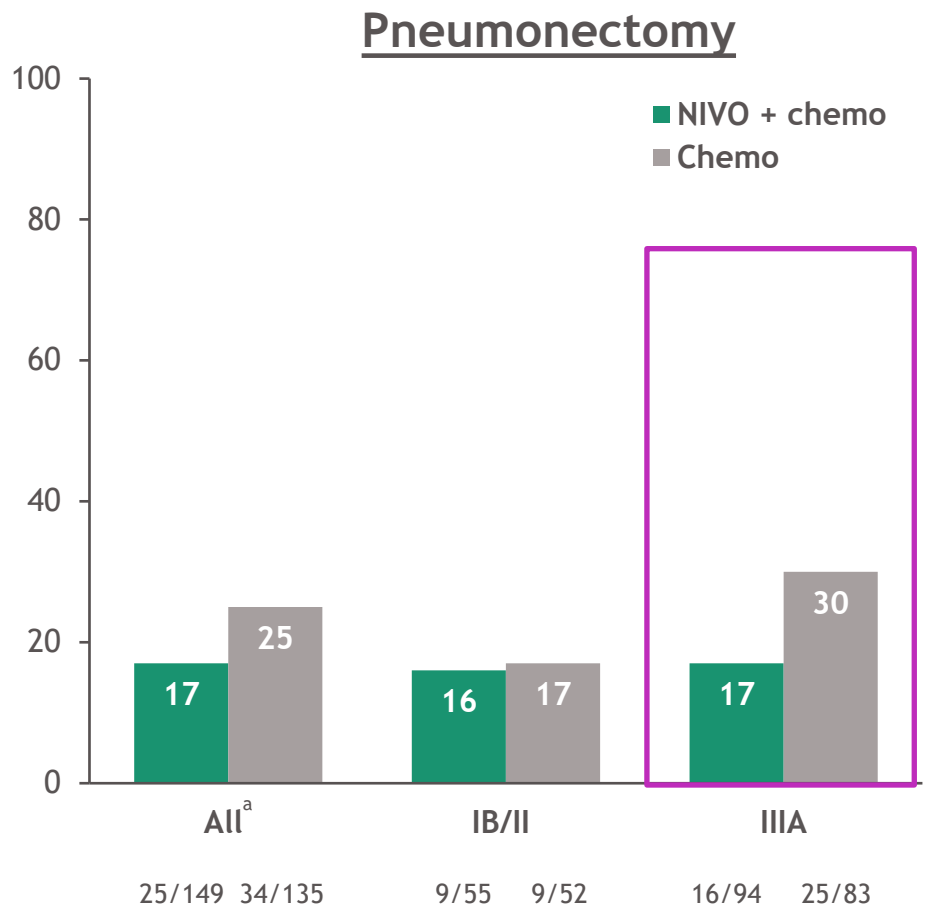
Type of surgery by baseline stage of disease



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.

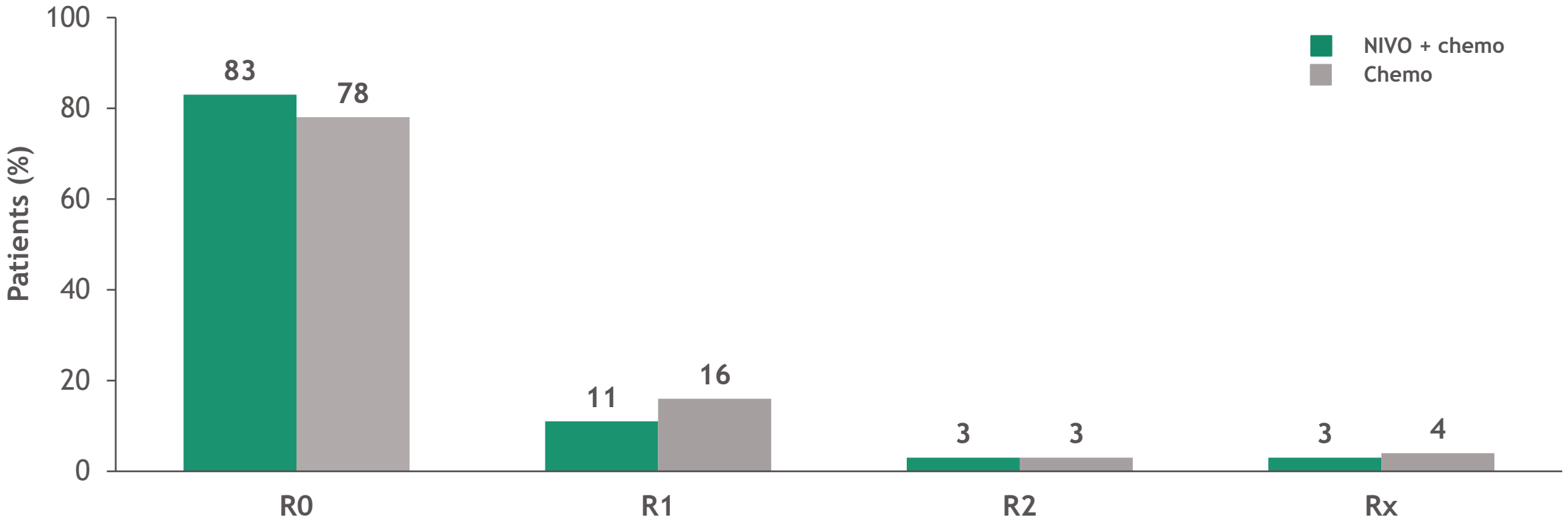
Type of surgery by baseline stage of disease





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.

Completeness of resection: all randomized population



- R0, R1, and R2 rates of resection were similar regardless of baseline stage of disease in both treatment arms[a]
- Median (IQR) number of lymph nodes dissected was similar between treatment arms: 19.0 (12–25) for NIVO + chemo and 18.5 (10–26) for chemo

[a]Patient numbers (%) for stage IB/II and stage IIIA, respectively, R0 (NIVO + chemo: 84, 83; chemo: 77, 78), R1 (NIVO + chemo: 9, 12; chemo: 15, 16), and R2 (NIVO + chemo: 4, 3; chemo: 6, 1).

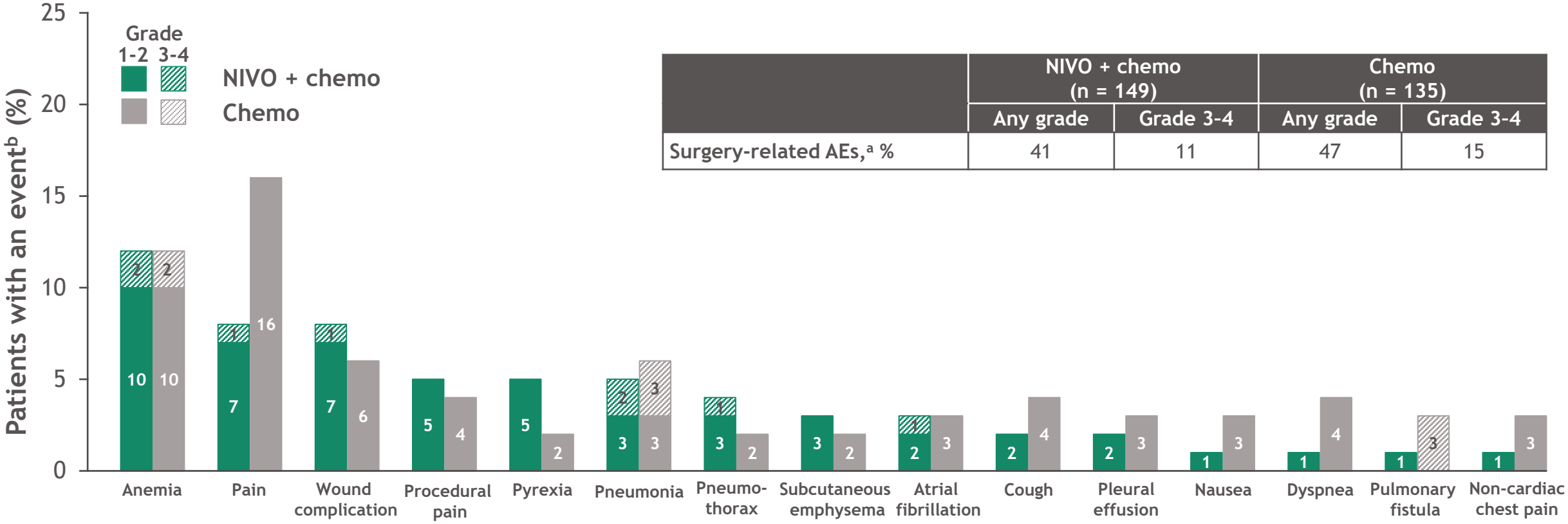
Hospital stay summary

	NIVO + chemo (n = 135)	Chemo (n = 124)
Length of hospital stay, median (IQR), days	10.0 (7.0–14.0)	10.0 (7.0–14.5)
Length of hospital stay by surgery type,[a] median (IQR), days		
Lobectomy	10.0 (7.0–15.0)	9.0 (6.0–14.0)
Pneumonectomy	10.0 (8.0–13.0)	11.0 (9.0–16.0)
Other[b]	8.5 (4.0–13.0)	9.0 (7.0–14.0)
Length of hospital stay per region,[c,d] median (IQR), days		
North America	4.0 (4.0–7.0)	6.0 (4.0–8.0)
Europe	9.5 (8.0–14.0)	13.0 (7.0–18.0)
Asia	11.0 (9.0–16.0)	13.0 (10.0–16.0)

- Length of hospital stay was similar regardless of baseline stage of disease in both the NIVO + chemo and chemo arms

[a]Patient numbers (n) for NIVO + chemo and chemo for lobectomy: 104, 77; pneumonectomy: 23, 29; other: 26, 32; [b]Includes bilobectomy, sleeve lobectomy, and other. Patients may have had more than one surgery type; [c]Median length of hospital stay in the rest of world was 6.0 days (IQR, 4.0–9.0) with NIVO + chemo, and 30.0 days (IQR, 8.0–42.0) with chemo; [d]Patient numbers (n) for NIVO + chemo and chemo for North America: 31, 38; Europe: 26, 11; Asia: 73, 70; rest of world: 5, 5.

90-Day surgery-related complications summary[a]



	NIVO + chemo (n = 149)		Chemo (n = 135)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Surgery-related AEs,[a] %	41	11	47	15

- Grade 5 surgery-related AEs (within 24 hours of AE onset) 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)[c]
- 30-day and 90-day mortality rates are planned to be evaluated when survival endpoints are available

[a]Includes events reported up to 90 days after definitive surgery; denominator based on patients with definitive surgery; CTCAE Version 4.0; MedDRA Version 23.0. Two intra-operative complications occurred in the NIVO + chemo arm (1 each of intraoperative hemorrhage and aortic rupture, not study treatment related); [b]Surgery-related AEs with an incidence of ≥ 3%; [c]Grade 5 AEs are defined as events that led to death within 24 hours of AE onset; only aortic rupture in NIVO + chemo arm was confirmed to occur within 24 hours of AE onset post-database lock.

Summary: neoadjuvant NIVO + chemo vs chemo for resectable NSCLC

- In CheckMate 816, neoadjuvant NIVO + chemo significantly improved pCR rates and had greater depth of pathological response vs chemo regardless of disease stage
  - The study continues to mature for the other primary endpoint of EFS
- Numerically, a greater percentage of patients treated with neoadjuvant NIVO + chemo vs chemo had definitive surgery and complete resection while fewer patients underwent pneumonectomy
  - The majority of patients in both arms had surgery within the protocol-specified time window
- Neoadjuvant NIVO + chemo treatment was tolerable and addition of NIVO to chemo did not increase post-surgical complications
- The safety and surgical outcome data reported thus far from CheckMate 816, along with significant improvement in pCR, support NIVO in combination with chemo as a potential neoadjuvant option for patients with resectable NSCLC

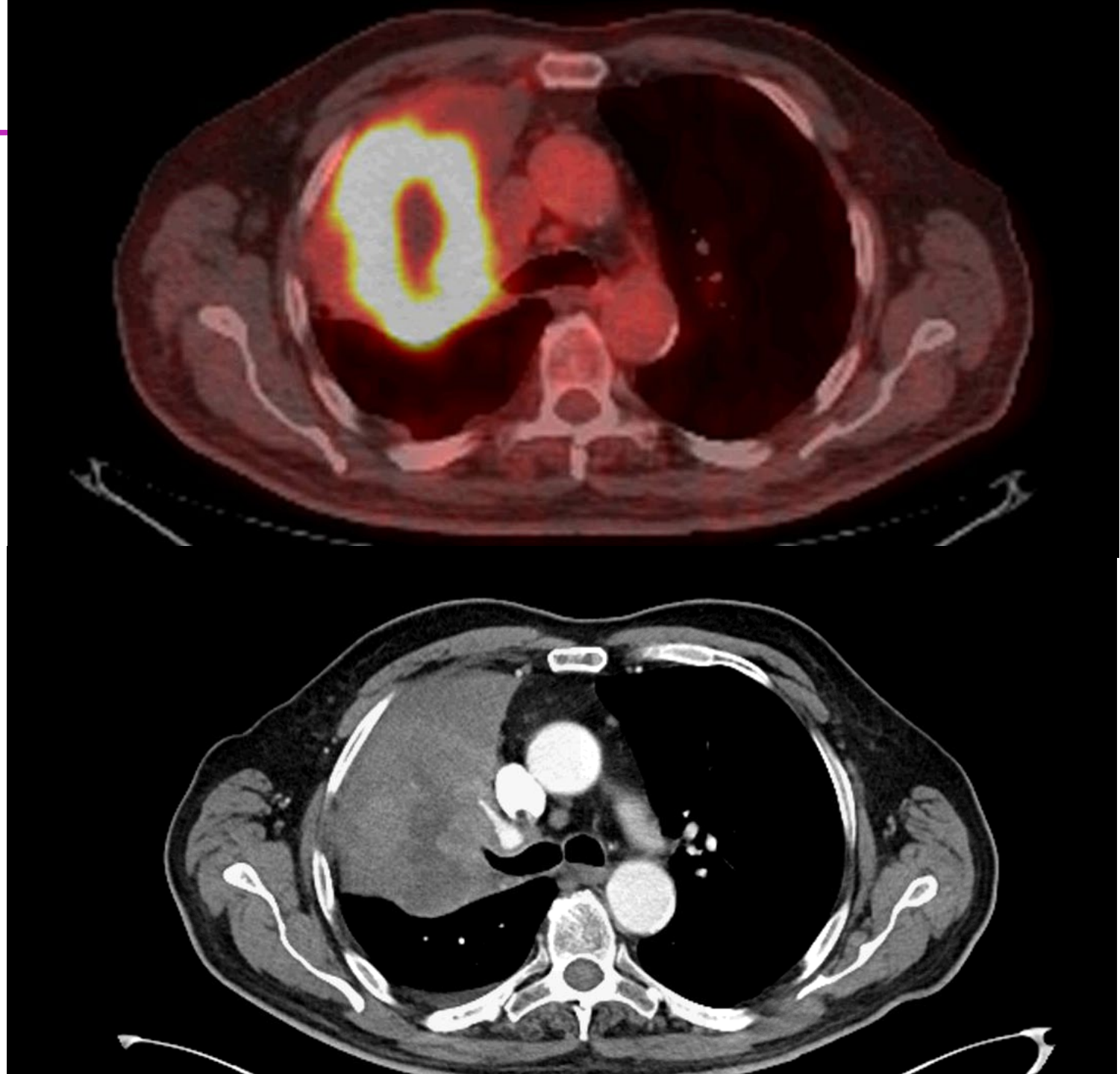
Resectable?

75M active smoker cT4N1, adenocarcinoma, no driver mutations on 52 gene NGS panel, PDL1 30%

CAD, HTN, COPD

FEV1 76%
DLCO 63%

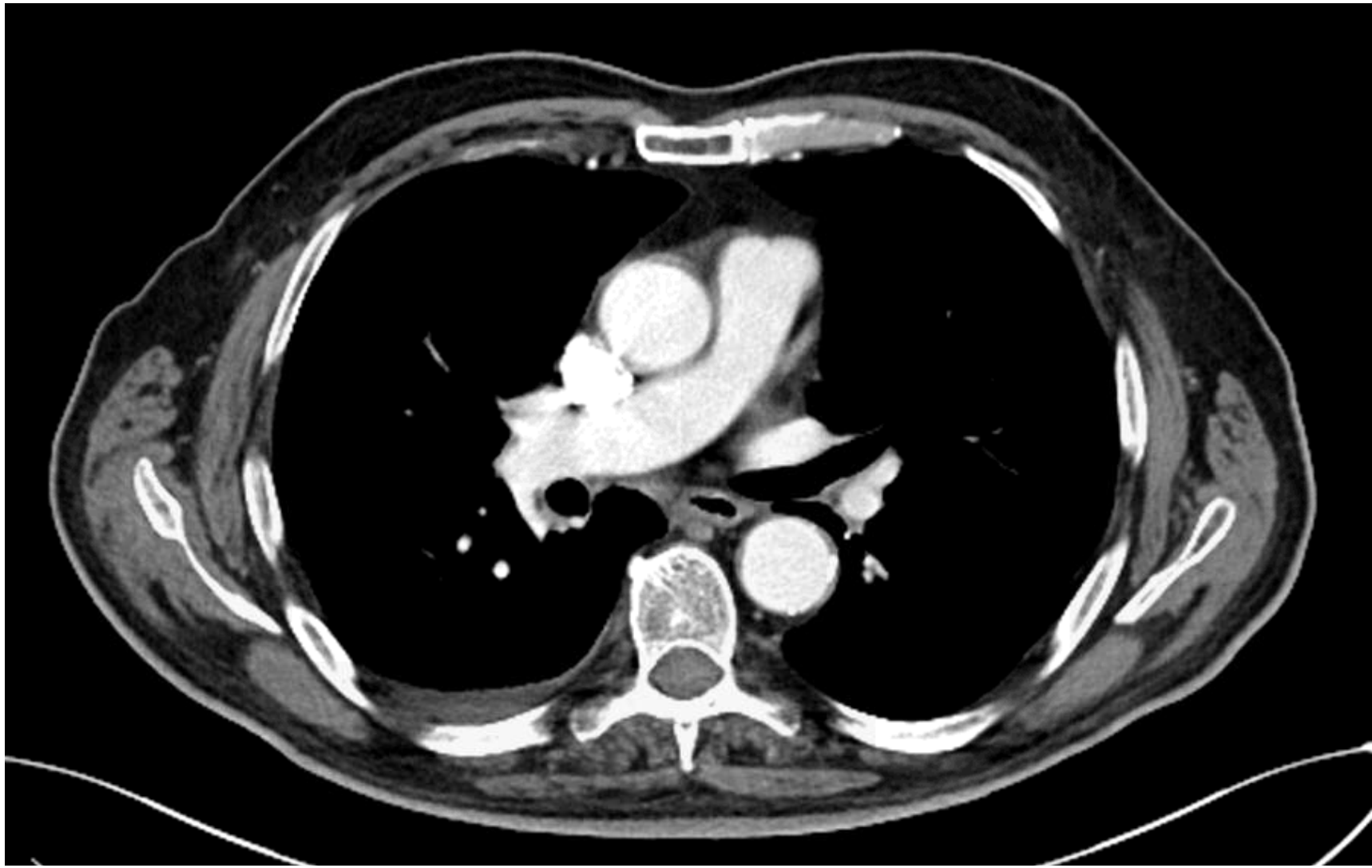
ECOG 1



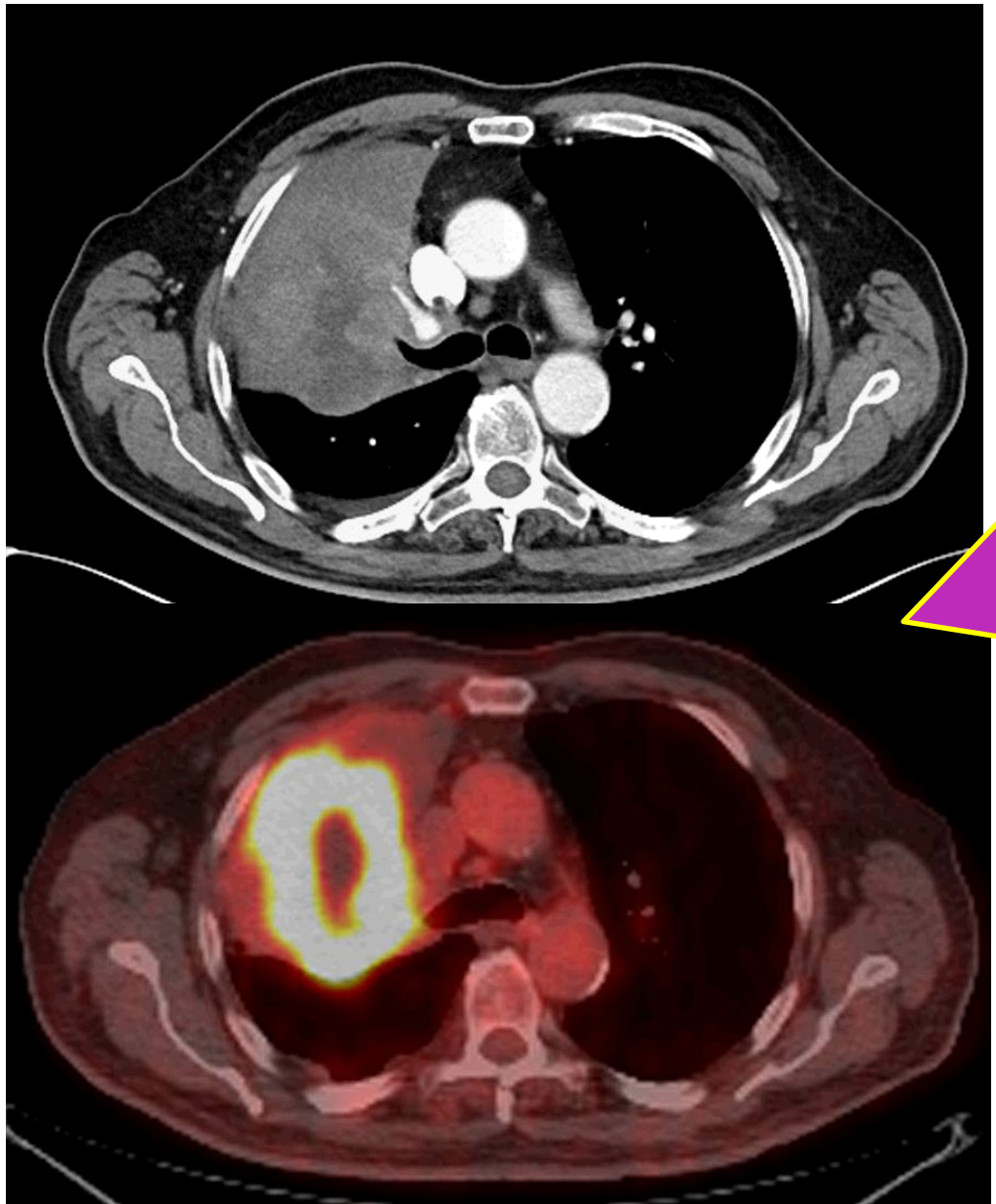
Probably!

Proposed operation:

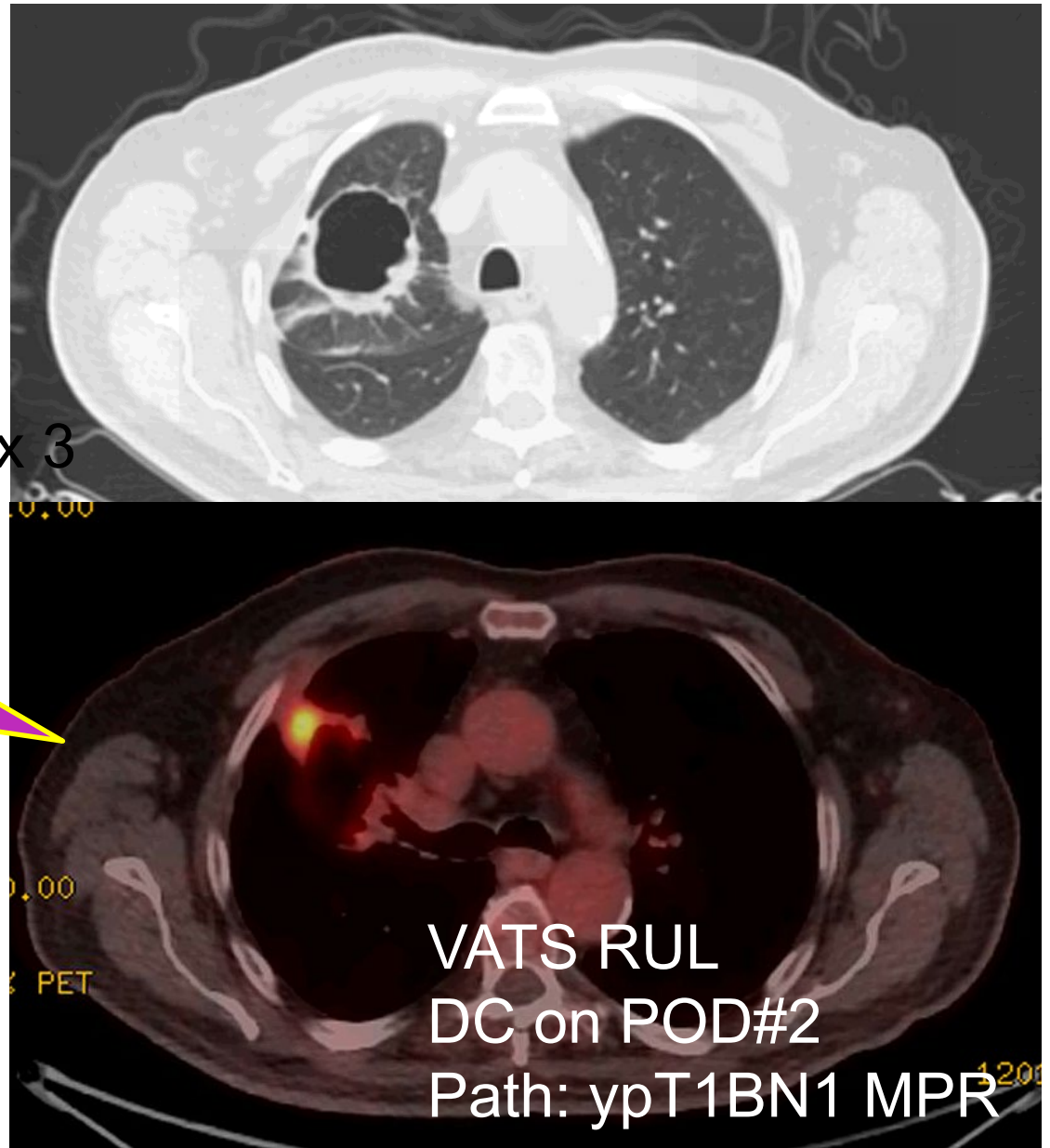
Open thoracotomy, upper lobectomy with bronchial sleeve resection, possible pulmonary artery angioplasty



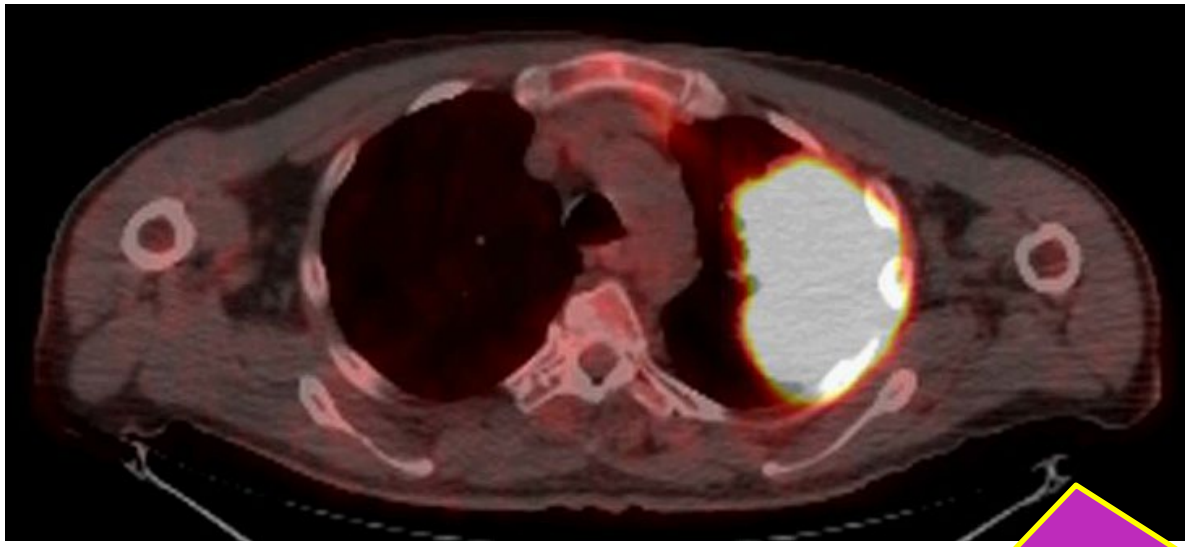
But seeing is believing…



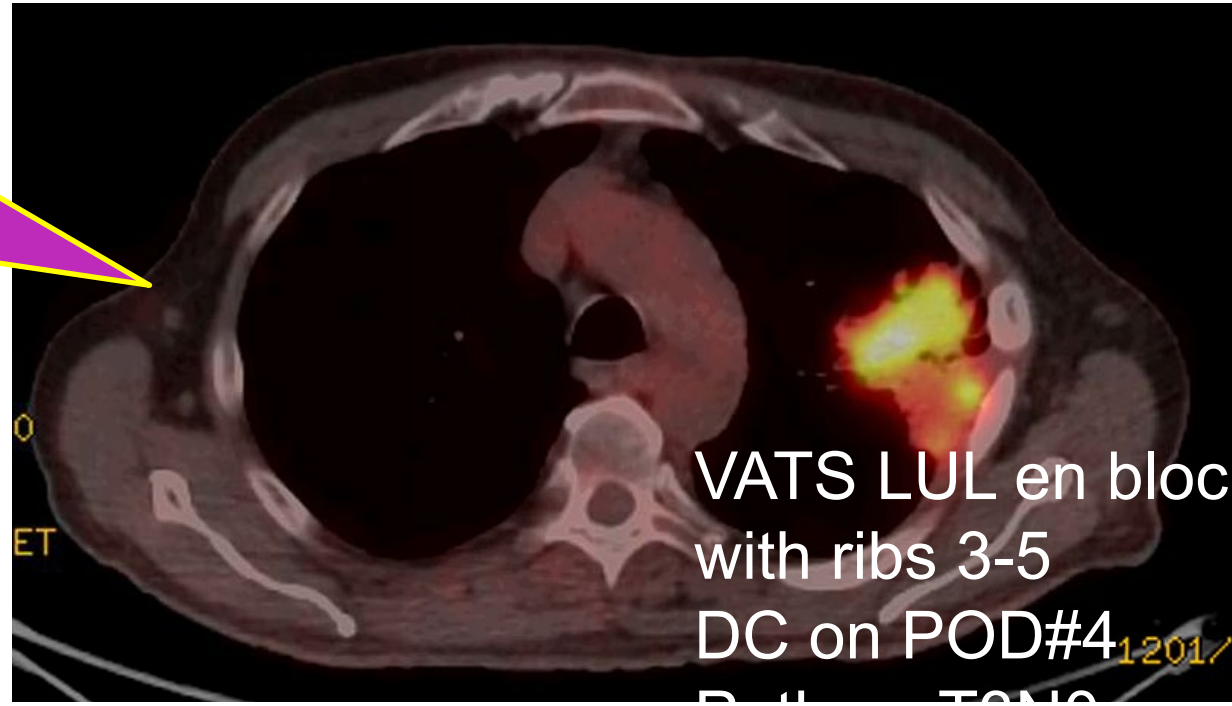
Chemo-IO x 3



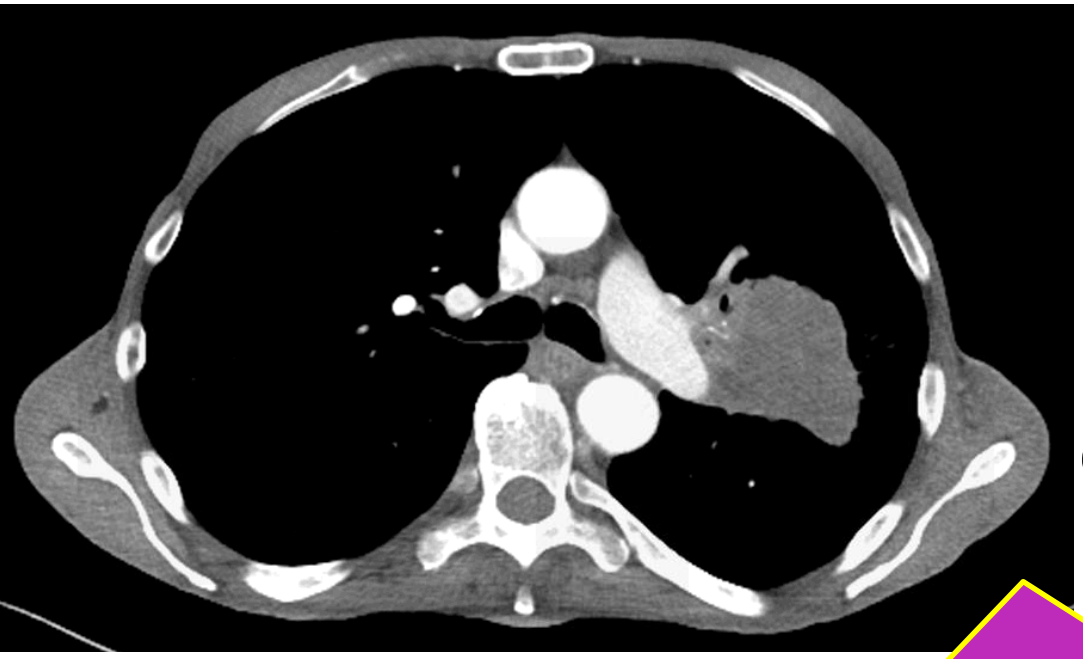
But seeing is believing… (cont.)



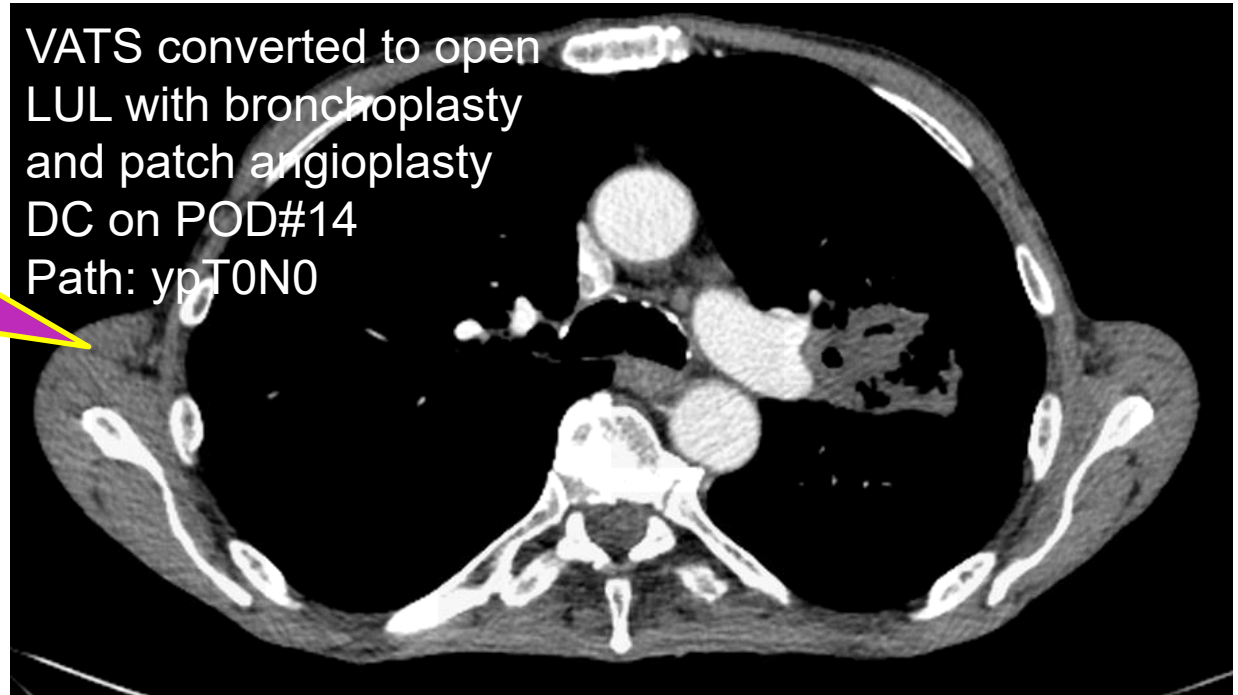
Chemo-IO x 3



But seeing is believing… (cont.)



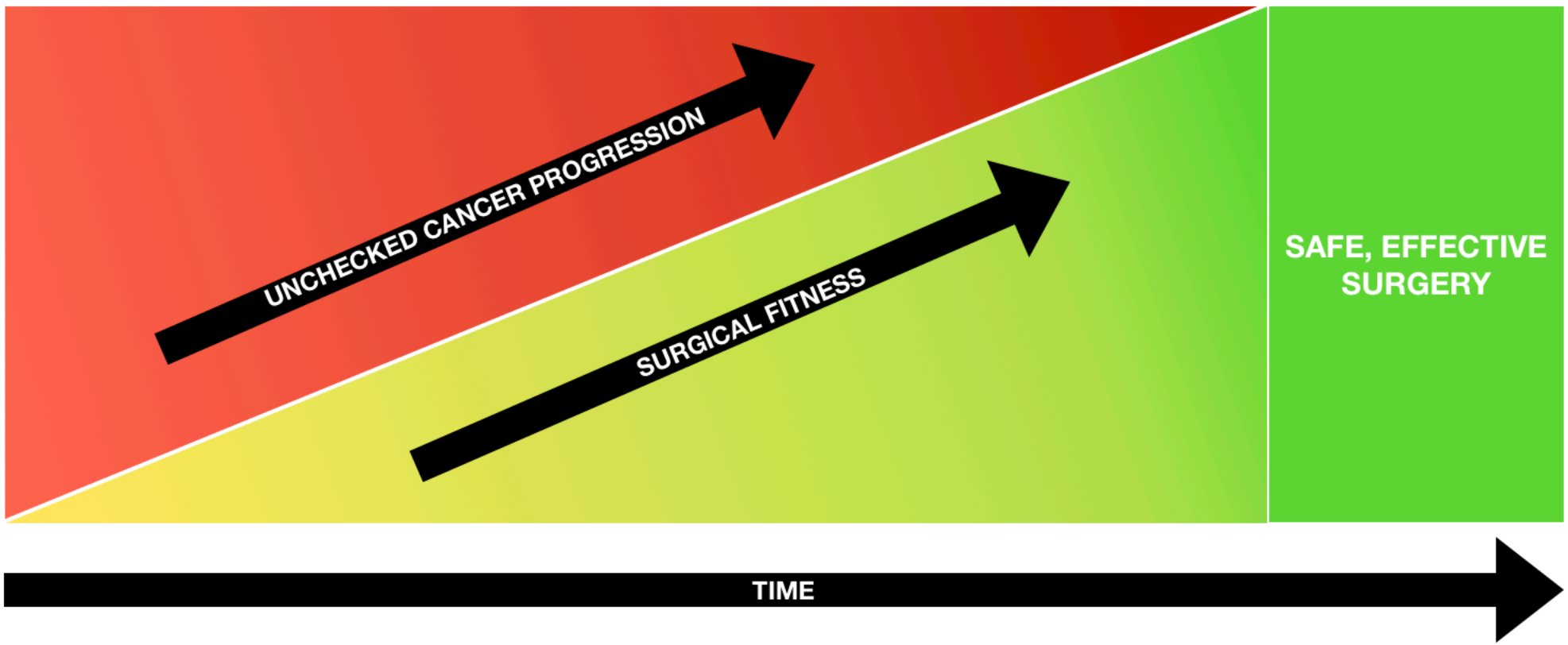
Chemo-IO x 3



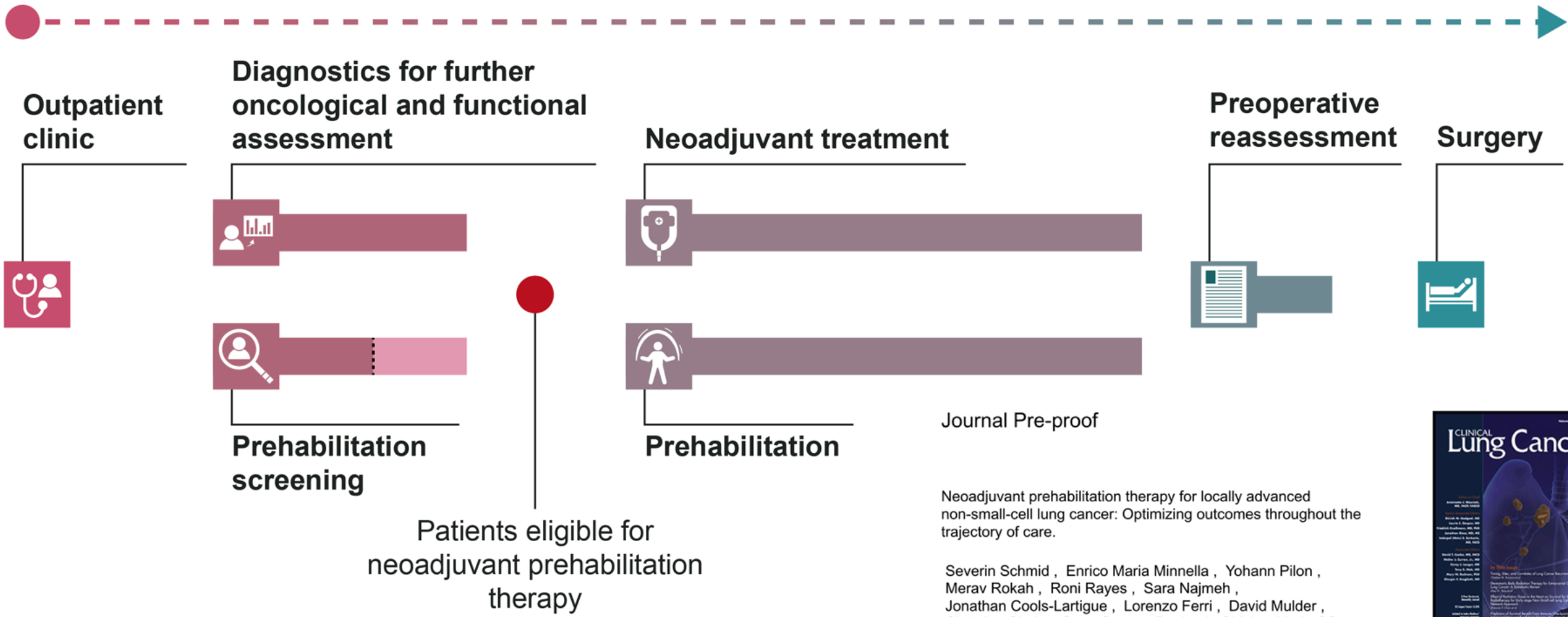
Notes from neoadj IO trials @McGill

- Current peri-adj trial portfolio (N=54 over 5 years):
  - CM816 - closed to accrual (N=24)
  - KN671 - closed to accrual (N= 19)
  - NeoCOAST - closed to accrual (N=2)
  - J1414 - closed to accrual (N=10)
  - MERMAID1/2 - Closed to accrual (N=1)
  - NeoADAURA - pending activation
  - McGill MK-A74 - active and recruiting
  - NeoCOAST2 - active and recruiting
  - ADAURA2 - pending activation
- 100% of patients enrolled on neoadj studies went on to surgery
- 1 operative mortality in a patient who became COVID19 + post-op in March 2020

How to reach optimal surgical outcomes and mitigate cancer progression?



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



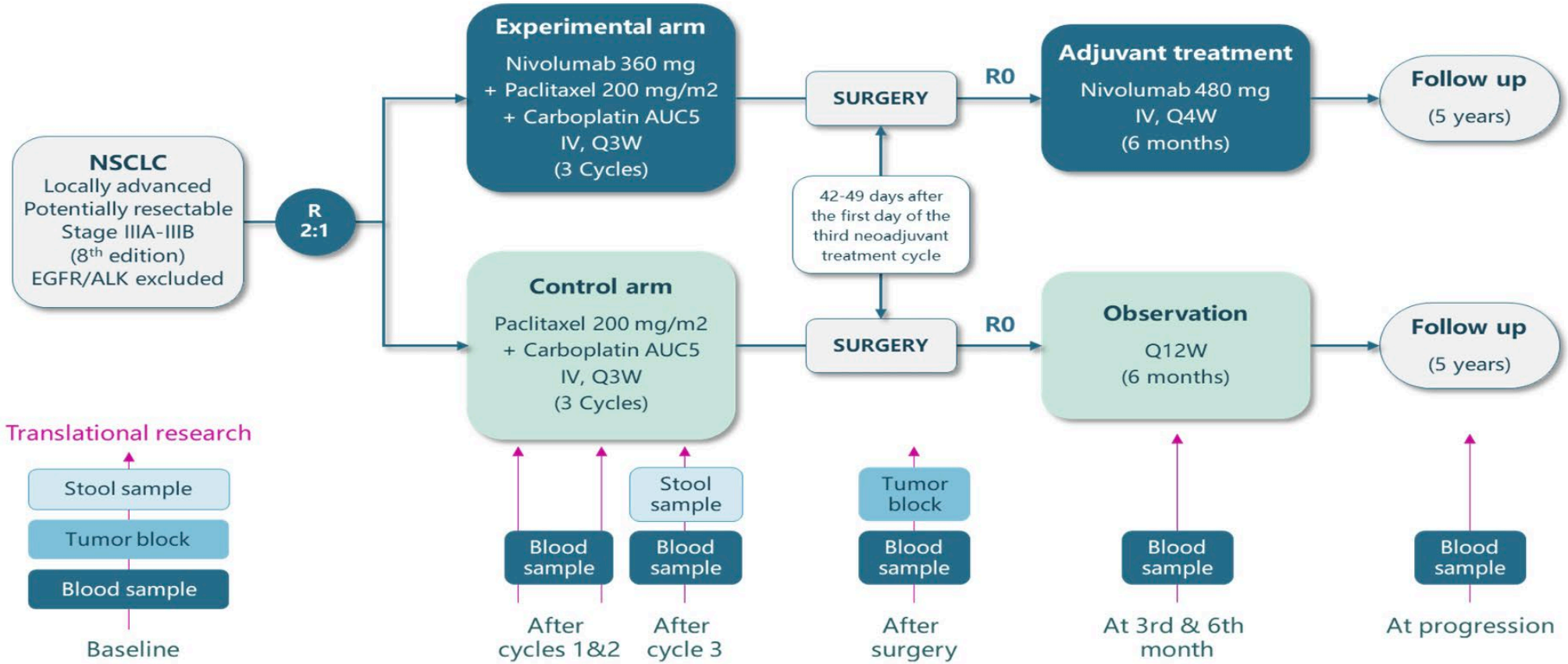
Journal Pre-proof

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

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

NADIM II

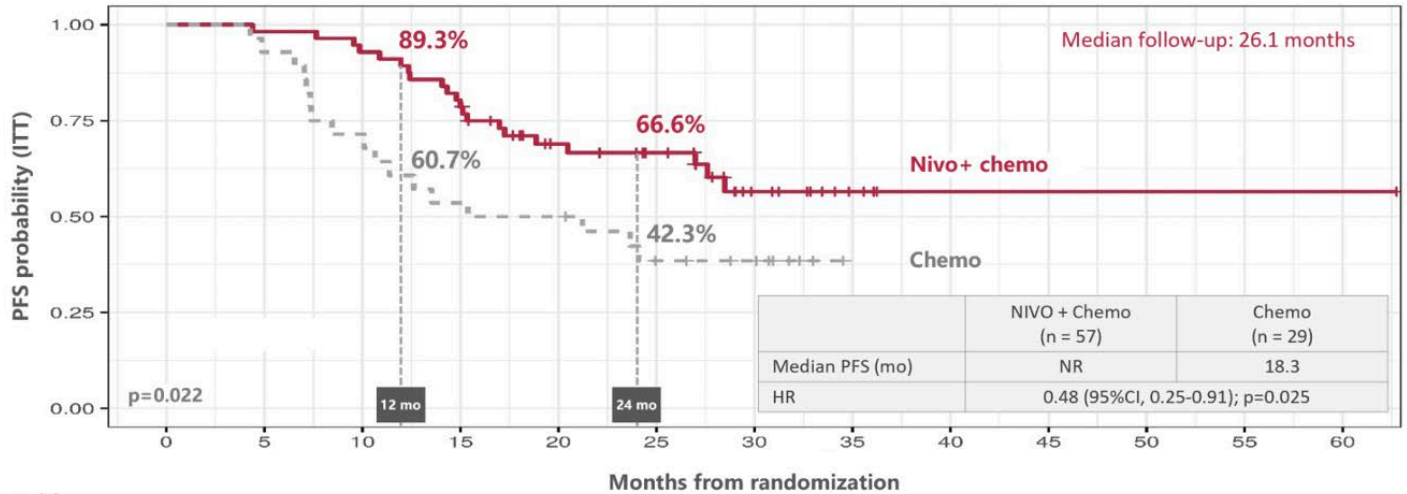
Perioperative nivolumab + chemotherapy



Presented by Dr. Mariano Provencio at IASLC WCLC 2022, PL03.12

NADIM II

Perioperative nivolumab + chemotherapy improves PFS and OS

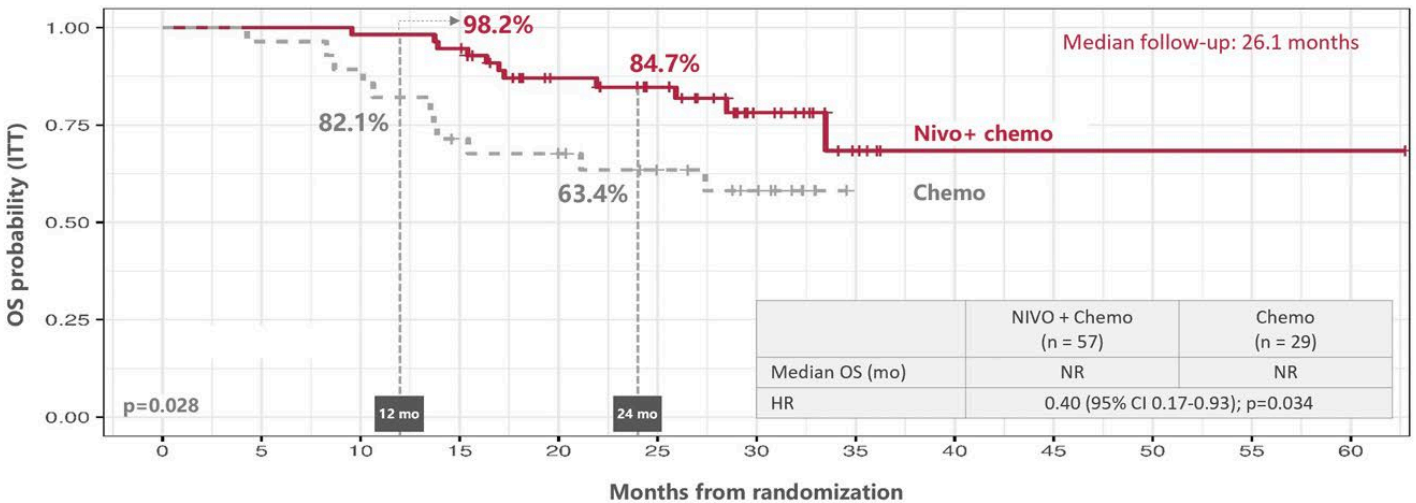


	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median PFS (mo)	NR	18.3
HR	0.48 (95%CI, 0.25-0.91); p=0.025	

Progression free survival

18.3 months → NR

HR 0.48 (0.25-0.91)



	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median OS (mo)	NR	NR
HR	0.40 (95% CI 0.17-0.93); p=0.034	

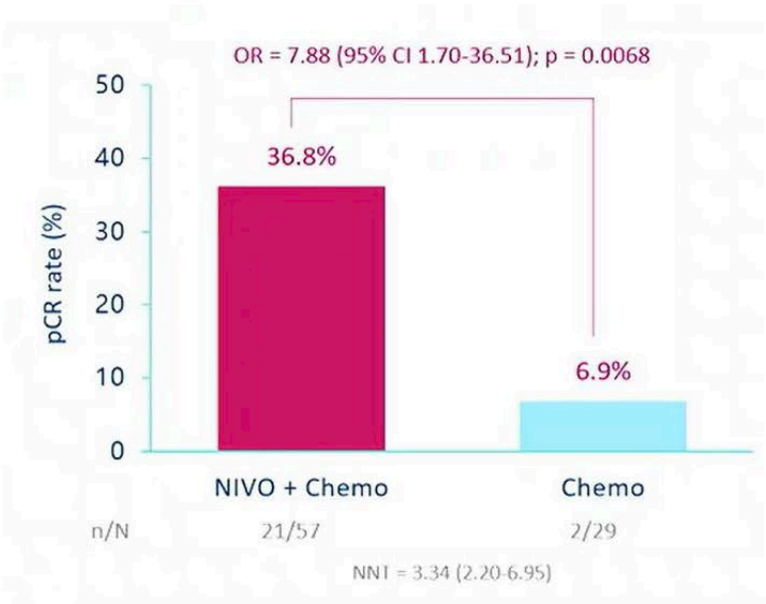
24 Month overall survival

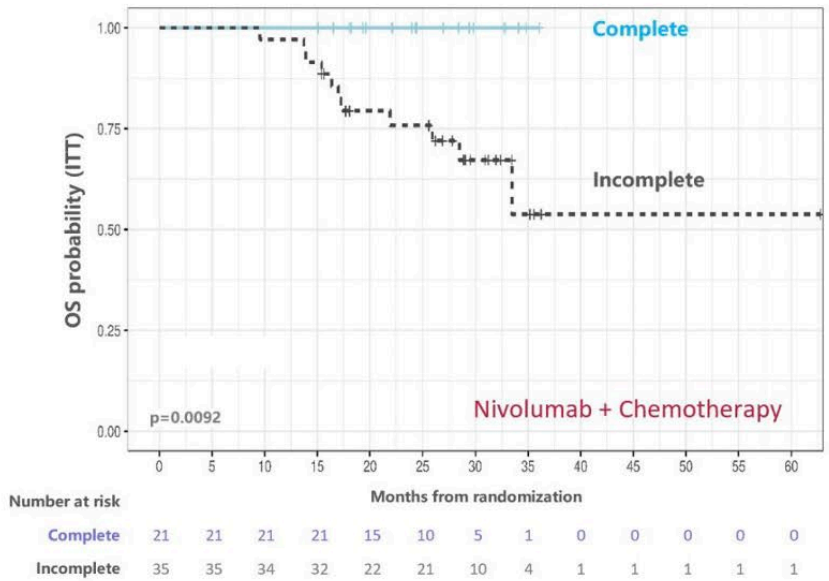
63.4% → 84.7%

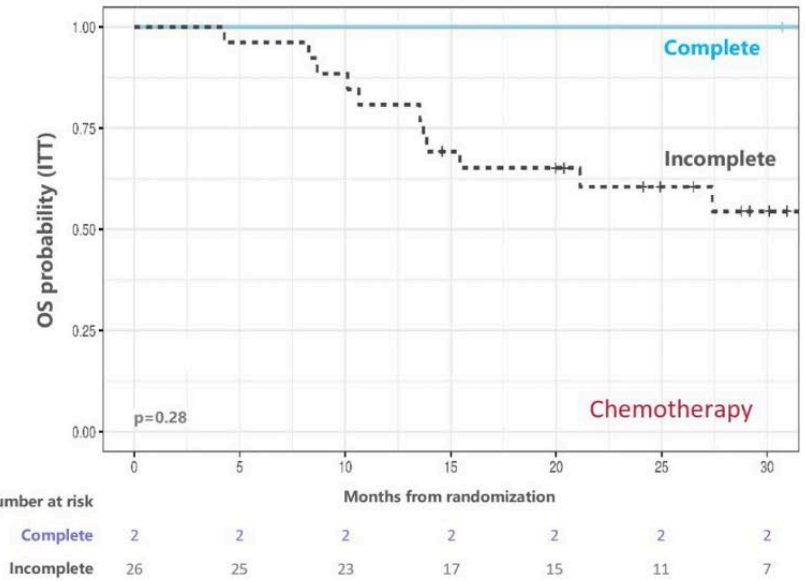
Median NR, HR 0.4 (0.17-0.93)

Provencio et al. IASLC WCLC 2022, PL03.12

NADIM II:
Overall survival by pathologic response







Povencio et al. J Clin Oncol. 2022;40(16_suppl):8501; Provencio et al. IASLC WCLC 2022, PL03.12

17

PARIS 2022 ESMO congress

Take home messages

- Survival endpoints have different meanings when time ZERO is at presentation versus later in therapeutic course neoadj vs adj (Similar to 1L vs 2L in metastatic disease)
- Surgery remains unparalleled in terms of achieving cure with 90-day mortality comparable to CRT
- Neoadjuvant chemo-IO has untapped potential to improve the surgical experience for patients
- Neoadjuvant chemo-IO is well suited to improve outcomes for a large proportion of the inherent heterogeneity of resectable stage III NSCLC
- Benefits of neoadjuvant chemo-IO come with an excellent pharmacoeconomic and safety profile
- Neoadjuvant chemo-IO + surgery is the most parsimonious approved approach to the management of locally advanced NSCLC

IMpower010: Study design

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

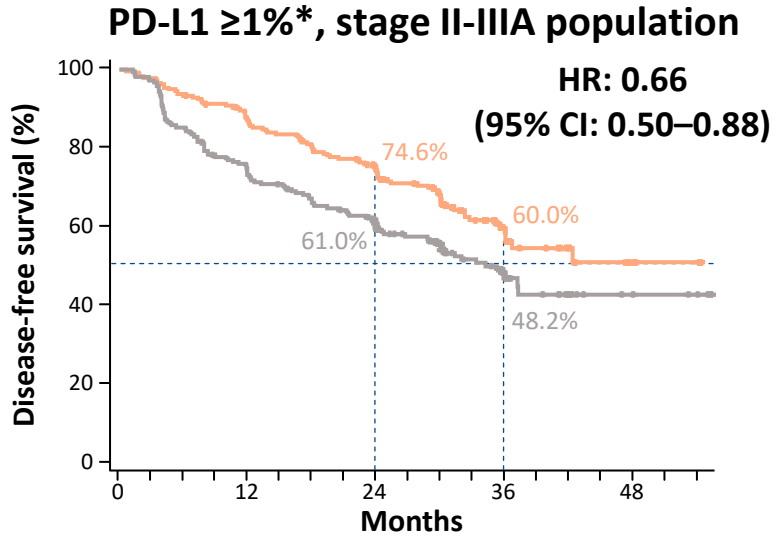
Primary endpoints

- 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



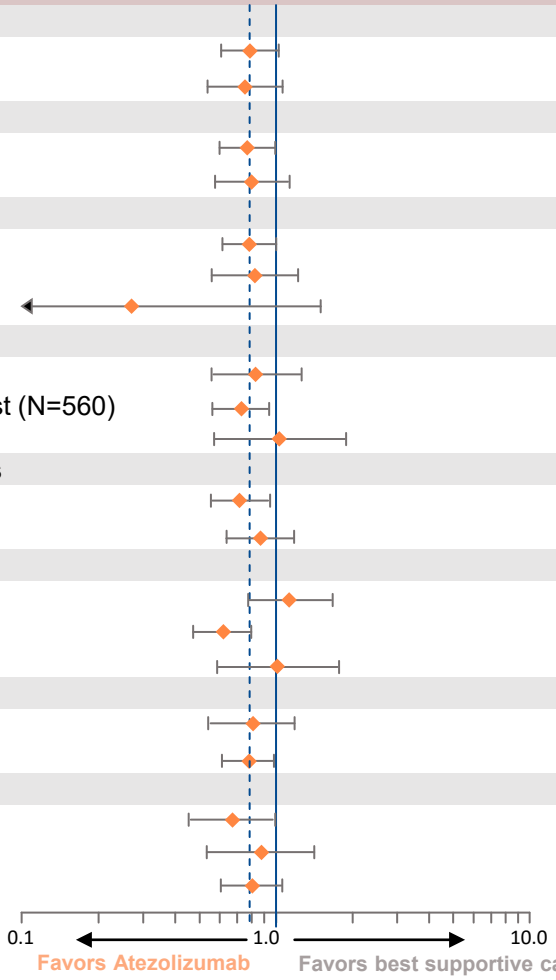
	Atezo (n=248)	BSC (n=228)
Median DFS, mo	NR	35.3
HR (95% CI), *P* value	0.66 (0.50–0.88), 0.004[†]	

Median follow-up: 32.8 mo

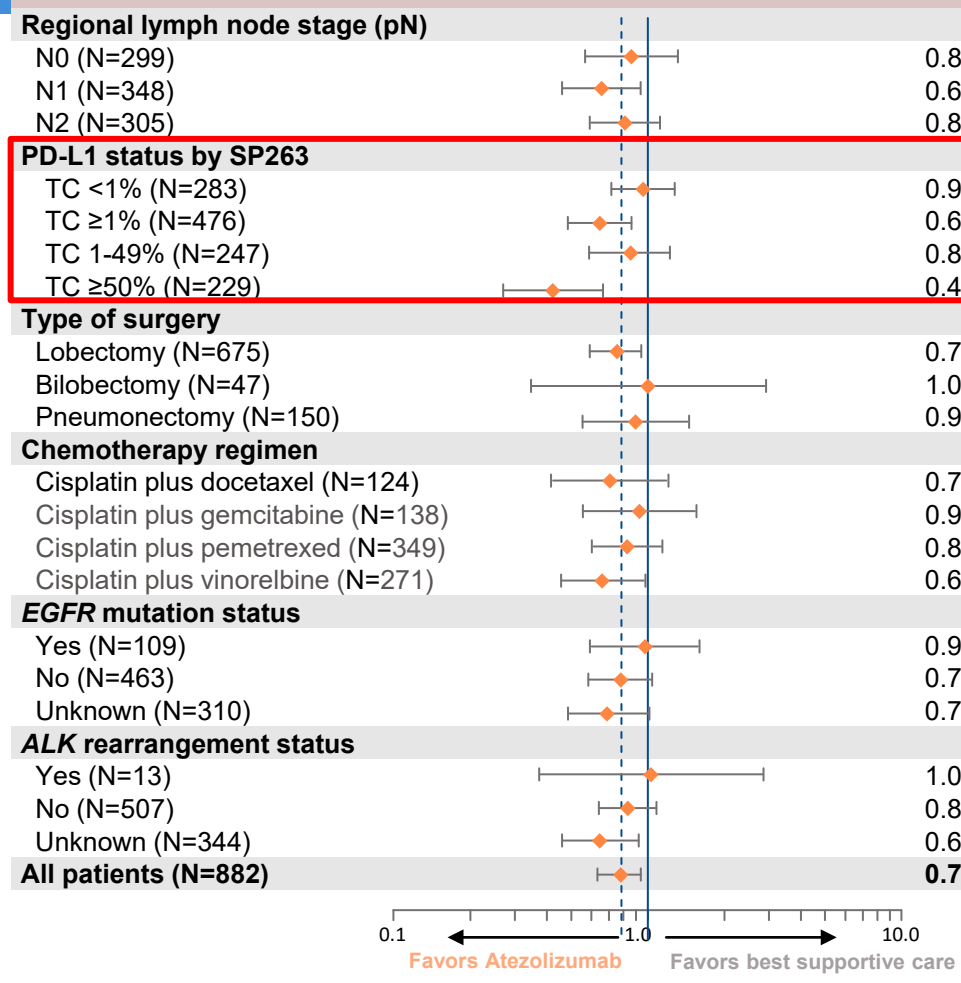
- Median DFS in the ITT population (IB-IIIA) was not reached with atezolizumab and 37.2 months with BSC (HR: 0.81; 95% CI: 0.67–0.99) after median follow-up of 32.2 months; this endpoint did not cross the significance boundary and analysis is ongoing

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)



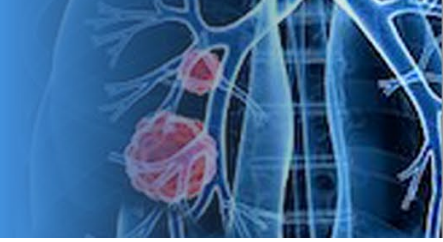
	HR (95% CI)
Regional lymph node stage (pN)	
N0 (N=299)	0.88 (0.57-1.35)
N1 (N=348)	0.67 (0.47-0.95)
N2 (N=305)	0.83 (0.61-1.13)
PD-L1 status by SP263	
TC <1% (N=283)	0.97 (0.72-1.31)
TC ≥1% (N=476)	0.66 (0.49-0.87)
TC 1-49% (N=247)	0.87 (0.60-1.26)
TC ≥50% (N=229)	0.43 (0.27-0.68)
Type of surgery	
Lobectomy (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.

Nothing an oncologist likes more than a questionable cross-trial comparison

	CM-816 EFS HR by PD-L1	IMpower 010 DFS HR by PD-L1
PD-L1 <1%	0.85	0.97
PD-L1 1-49%	0.41	0.87
PD-L1 ≥50%	0.24	0.43

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

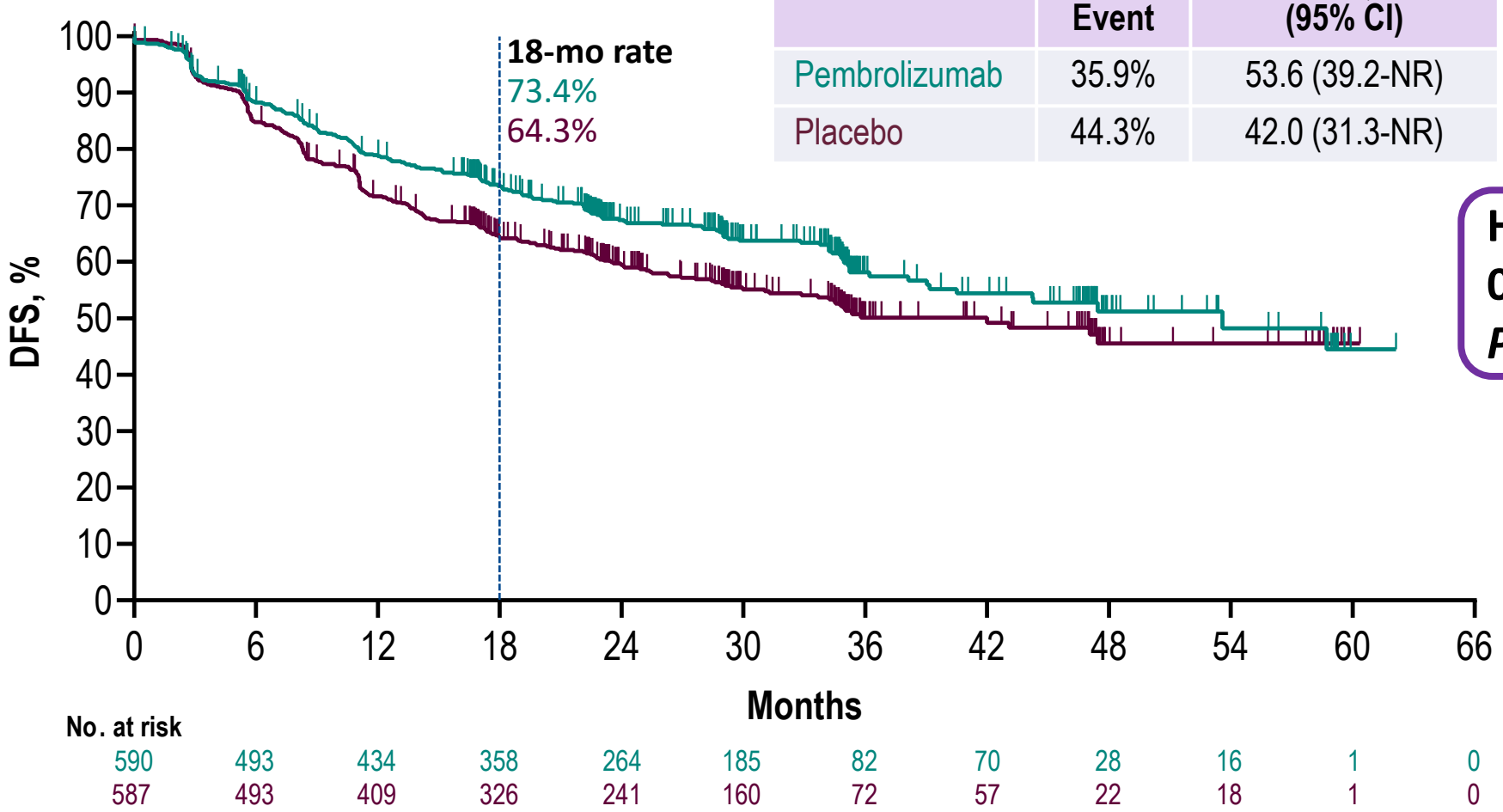
Secondary End Points

- 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

DFS, Overall Population

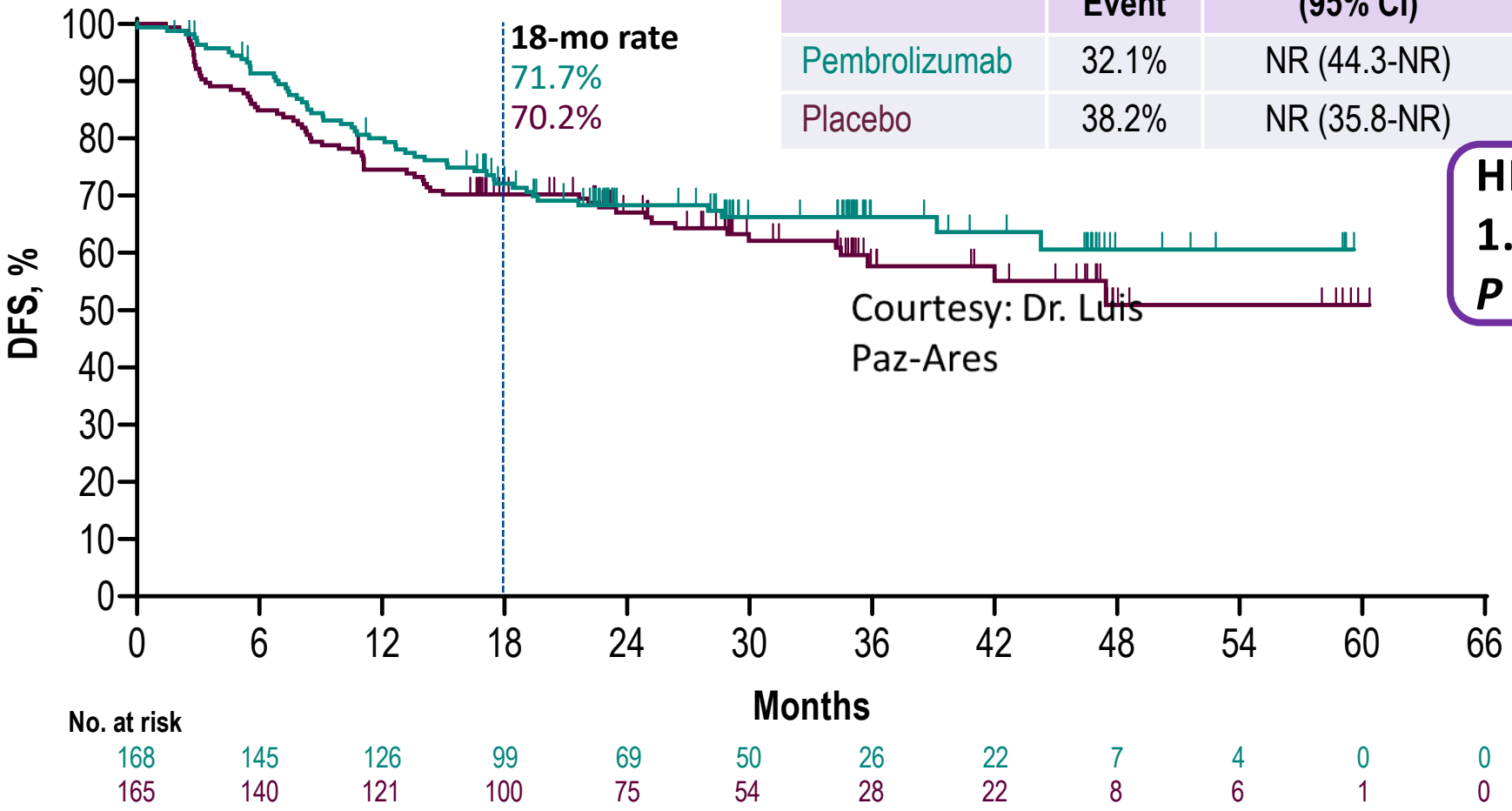
	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)



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

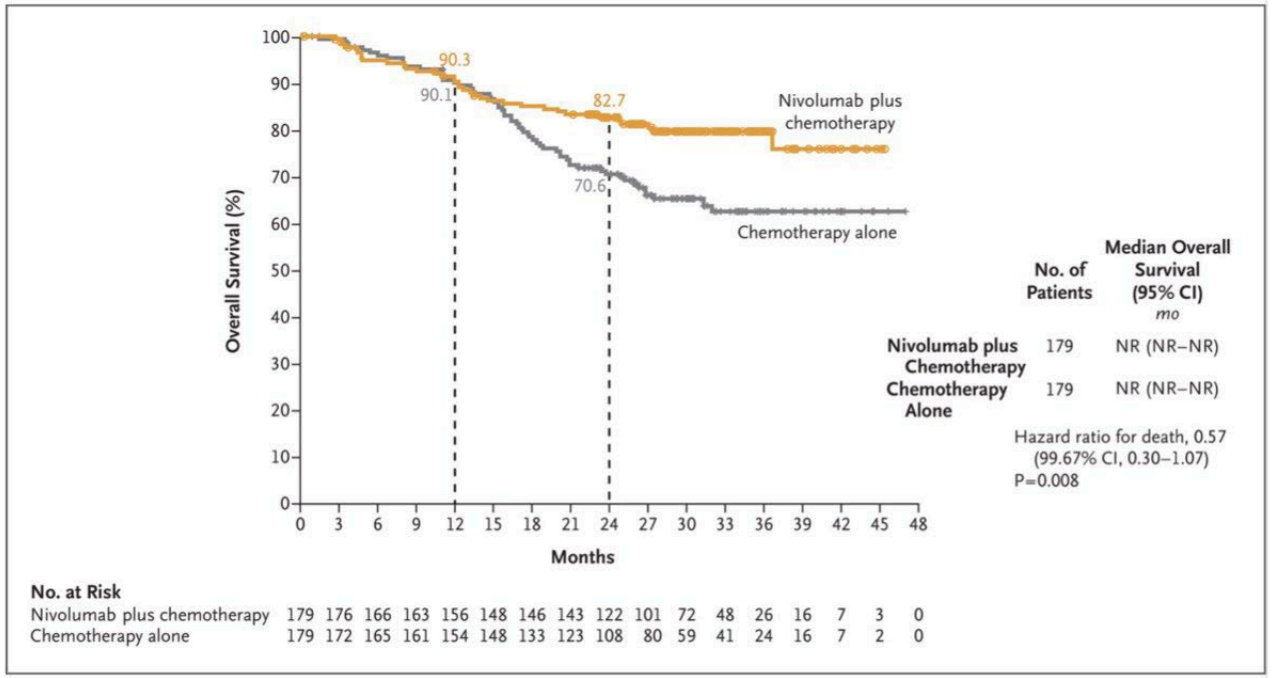
Summary of Adverse Events

	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%)

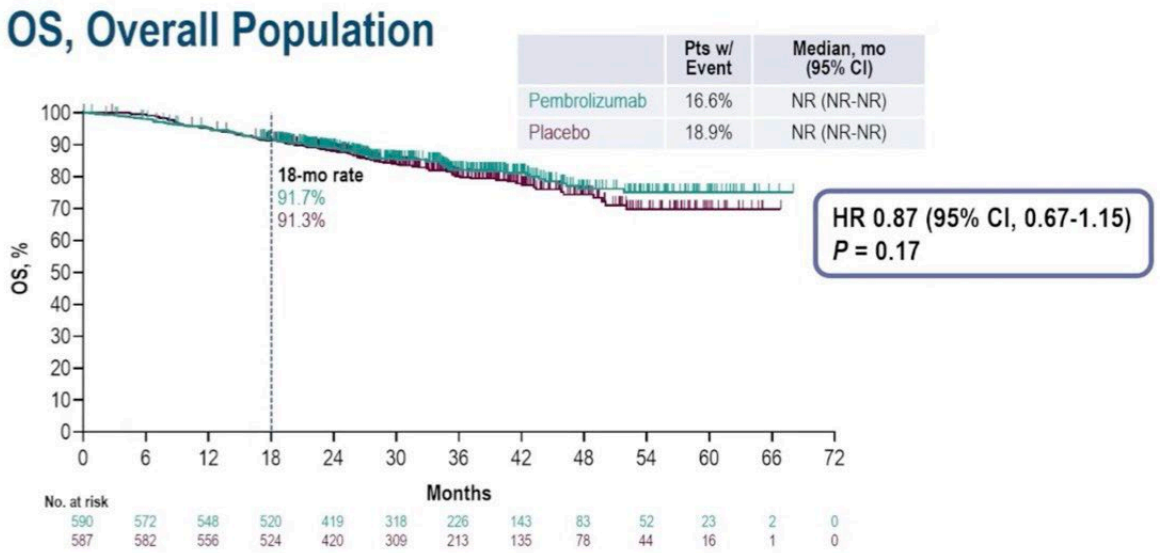
[a] 1 participant each with myocarditis + cardiogenic shock, myocarditis + septic shock, pneumonia, and sudden death.

Courtesy: Dr. Luis Paz-Ares

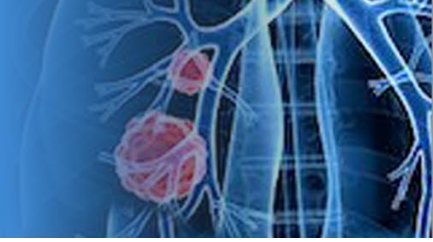
Neoadjuvant chemo-IO
CheckMate-816



Adjuvant IO
PEARLS



Conclusion



- Adding PD-1 blockade to neoadjuvant chemotherapy increases pCR and Event-Free Survival without increased toxicity
- Adjuvant anti-PD-L1 improves disease-free survival for pts with resected PD-L1+ NSCLC after adjuvant cisplatin-based chemotherapy
- PD-L1 status, pCR after neoadjuvant and potentially ctDNA clearance all enrich for benefit

- Neoadjuvant nivolumab-chemotherapy (non-EGFR/ALK, regardless of PD-L1)

  or adjuvant chemotherapy followed by atezolizumab (non-EGFR/ALK, PD-L1+ tumors)

  are now standard of care for patients with resectable NSCLC

Abbreviations: DFS, disease-free survival; NSCLC, non-small cell lung cancer. PD-L1, programmed death ligand 1; pCR, pathologic complete response.