NEOADJUVANT IMMUNOTHERAPY FOR LUNG CANCER

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Endorsed by

IASLC International Association for the Study of Lung Cancer — Conquering Thoracic Cancers Worldwide

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Overview of Reported Global Phase 3 Immunotherapy Trials in Resectable NSCLC

Neoadjuvant Immunotherapy (Approved)	
CheckMate -816	Nivolumab + chemo x 3 cycles

→ SURGERY

FDA approved

SURGERY →

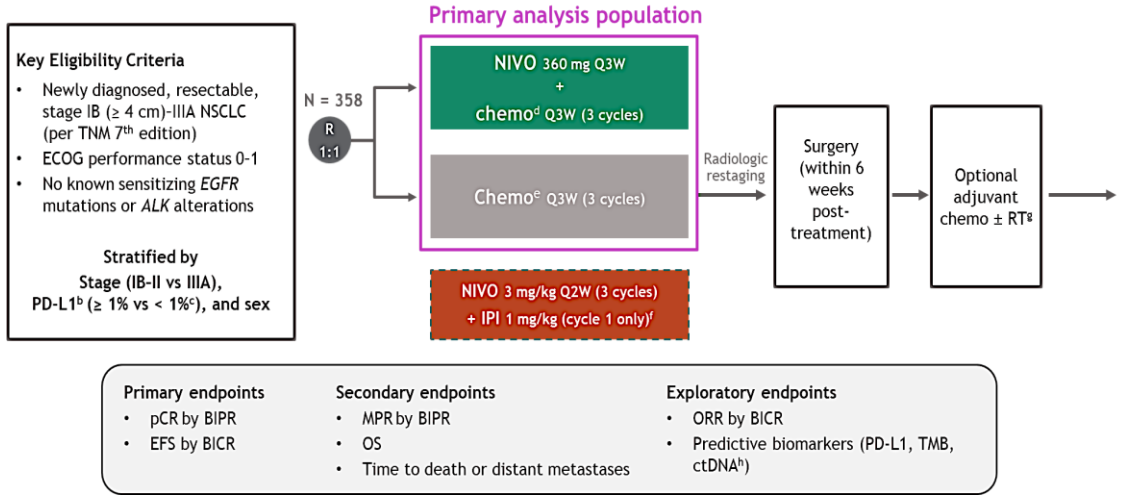
FDA approved

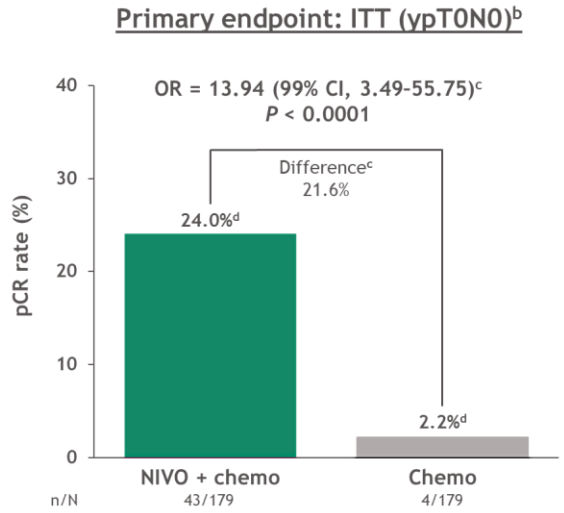
Adjuvant Immunotherapy (Approved)	
IMpower010	Chemo → atezolizumab ~1 y (PD-L1 ≥1%)
KEYNOTE-091	Chemo (trial optional but label required) → pembrolizumab ~1 year

Study	Neoadjuvant Regimen	→ SURGERY →	Adjuvant Regimen	
AEGEAN	Durvalumab + chemo x 4 cycles		Durvalumab ~1 year	
KEYNOTE-671	Pembrolizumab + chemo x 4 cycles		Pembrolizumab ~1 year	FDA approved
CheckMate -77T	Nivolumab + chemo x 4 cycles		Nivolumab ~1 year	

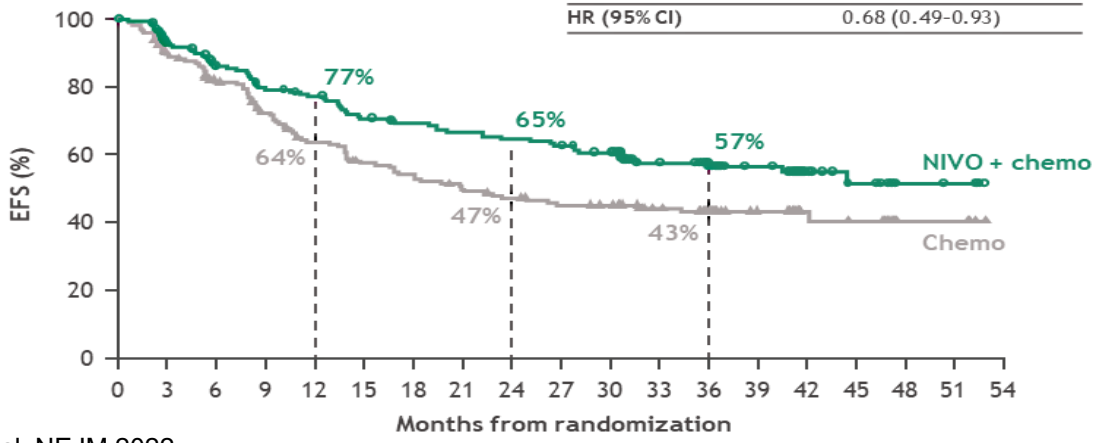
- All labels (FDA at least) require the patient to be a candidate for chemotherapy in order to receive immunotherapy
- All approvals are across disease stage (clinical or pathologic)

CheckMate-816





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



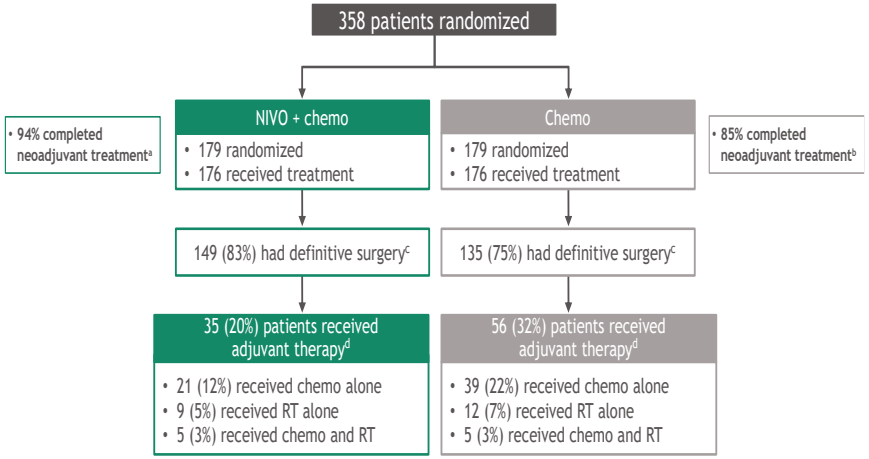
Disease stage at baseline				
IB or II	127	NR (27.8-NR)	NR (16.8-NR)	0.87 (0.48-1.56)
IIIA	228	31.6 (26.6-NR)	15.7 (10.8-22.7)	0.54 (0.37-0.80)
Geographic region				
North America	91	NR (25.1-NR)	NR (12.8-NR)	0.78 (0.38-1.62)
Europe	66	31.6 (13.4-NR)	21.1 (10.2-NR)	0.80 (0.36-1.77)
Asia	177	NR (30.2-NR)	16.5 (10.8-22.7)	0.45 (0.29-0.71)
Histologic type of tumor				
Squamous	182	30.6 (20.0-NR)	22.7 (11.5-NR)	0.77 (0.49-1.22)
Nonsquamous	176	NR (27.8-NR)	19.6 (13.8-26.2)	0.50 (0.32-0.79)
PD-L1 expression level				
<1%	155	25.1 (14.6-NR)	18.4 (13.9-26.2)	0.85 (0.54-1.32)
≥1%	178	NR (NR-NR)	21.1 (11.5-NR)	0.41 (0.24-0.70)
1-49%	98	NR (27.8-NR)	26.7 (11.5-NR)	0.58 (0.30-1.12)
≥50%	80	NR (NR-NR)	19.6 (8.2-NR)	0.24 (0.10-0.61)

Forde et al. NEJM 2022
Forde et al. ELCC 2023

Courtesy: Dr. S Rosner

CheckMate-816: Surgical outcomes and adjuvant therapy

Surgical/Adjuvant Outcomes



Duration of surgery‖ — min		
Median (IQR)	185.0 (133.0–260.0)	213.5 (150.0–283.0)
Surgical approach§ — no. (%)		
Thoracotomy	88 (59.1)	85 (63.0)
Minimally invasive**	44 (29.5)	29 (21.5)
Minimally invasive to thoracotomy	17 (11.4)	21 (15.6)
Type of surgery§,†† — no. (%)		
Lobectomy	115 (77.2)	82 (60.7)
Sleeve lobectomy	2 (1.3)	10 (7.4)
Bilobectomy	3 (2.0)	4 (3.0)
Pneumonectomy	25 (16.8)	34 (25.2)
Other	24 (16.1)	21 (15.6)

Adverse Events/Surgical Delays

	Nivolumab plus Chemotherapy (N = 176)		Chemotherapy (N = 176)	
Event	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Rash	15 (8.5)	3 (1.7)	1 (0.6)	0
Hypersensitivity	2 (1.1)	0	0	0
Pneumonitis	2 (1.1)	0	1 (0.6)	1 (0.6)
Endocrine				
Adrenal insufficiency	2 (1.1)	2 (1.1)	0	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0
Hypothyroidism/thyroiditis	4 (2.3)	0	0	0
Hyperthyroidism	7 (4.0)	0	0	0
Diabetes mellitus	2 (1.1)	0	0	0

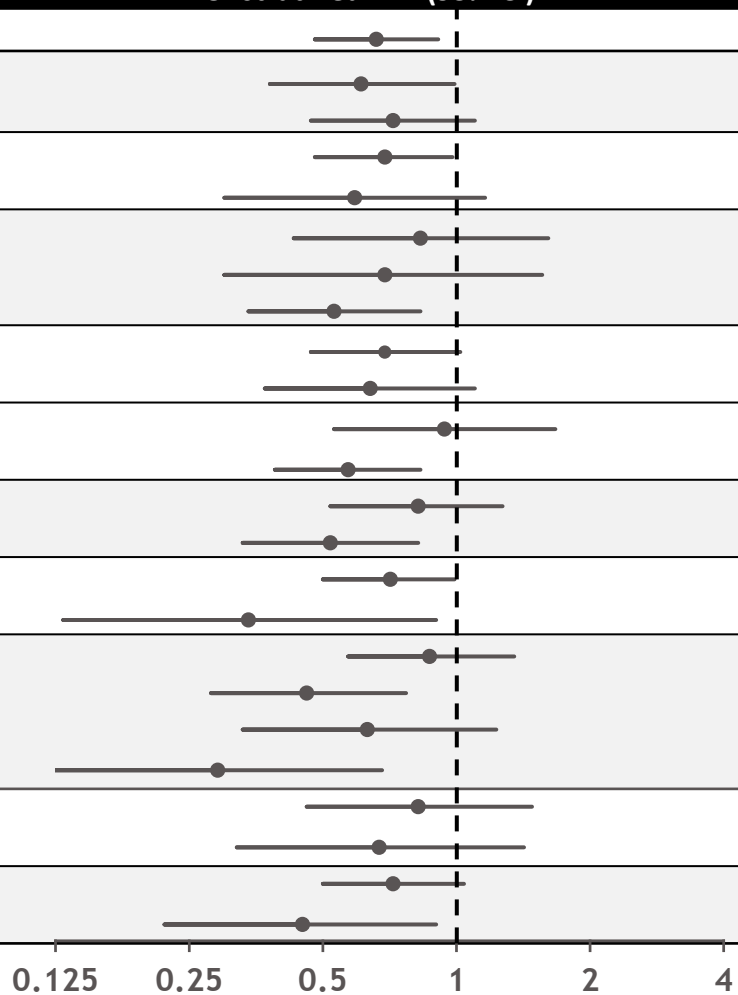
	Stage IB–II		Stage IIIA	
	Nivolumab plus Chemotherapy (N = 65)	Chemotherapy (N = 62)	Nivolumab plus Chemotherapy (N = 113)	Chemotherapy (N = 115)
Patients with definitive surgery* — no. (%)	55 (84.6)	52 (83.9)	94 (83.2)	83 (72.2)
Patients with cancelled definitive surgery — no. (%)	8 (12.3)	8 (12.9)	19 (16.8)	28 (24.3)
Disease progression	3 (4.6)	1 (1.6)	9 (8.0)	16 (13.9)
Adverse event	0	0	2 (1.8)	1 (0.9)
Other†	5 (7.7)	7 (11.1)	8 (7.1)	11 (9.6)
Patients with delayed surgery‡,§— no. (%)	9 (16.4)	13 (25.0)	22 (23.4)	11 (13.3)
Administrative reason	4 (7.3)	4 (7.7)	13 (13.8)	4 (4.8)
Adverse event	2 (3.6)	7 (13.5)	4 (4.3)	2 (2.4)
Other	3 (5.5)	2 (3.8)	5 (5.3)	5 (6.0)
Length of delay in surgery — wk				

Forde et al. NEJM 2022
Spicer et al. ASCO 2021

Courtesy: Dr. S Rosner

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.

EFS[a] subgroup analysis: 3-year update

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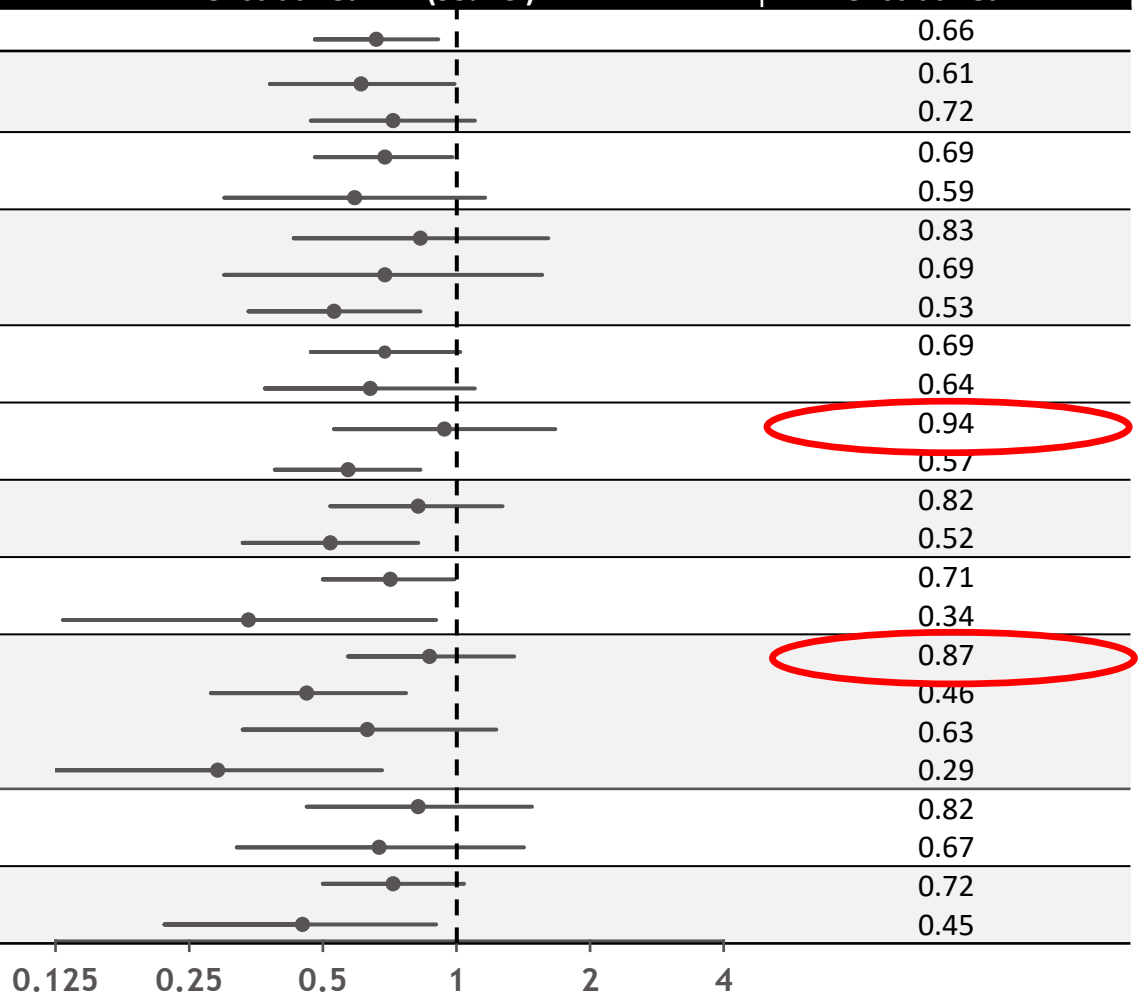
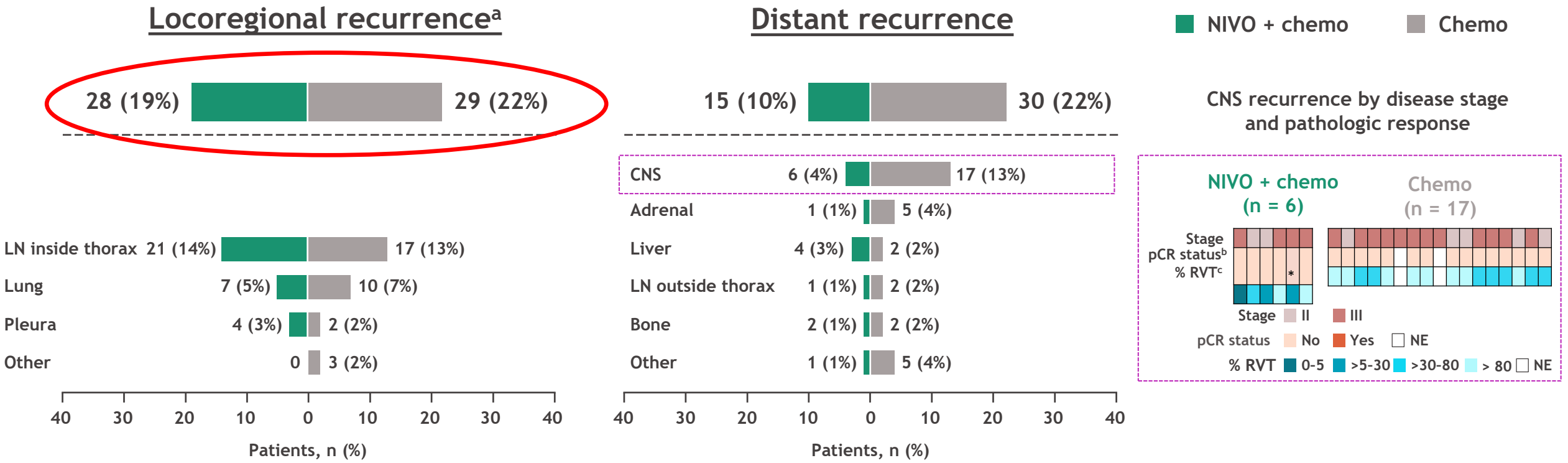


Minimum median follow-up: 32.9/41.4 months.
[a]Per BICR.

Speaker: Patrick Forde, MD

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

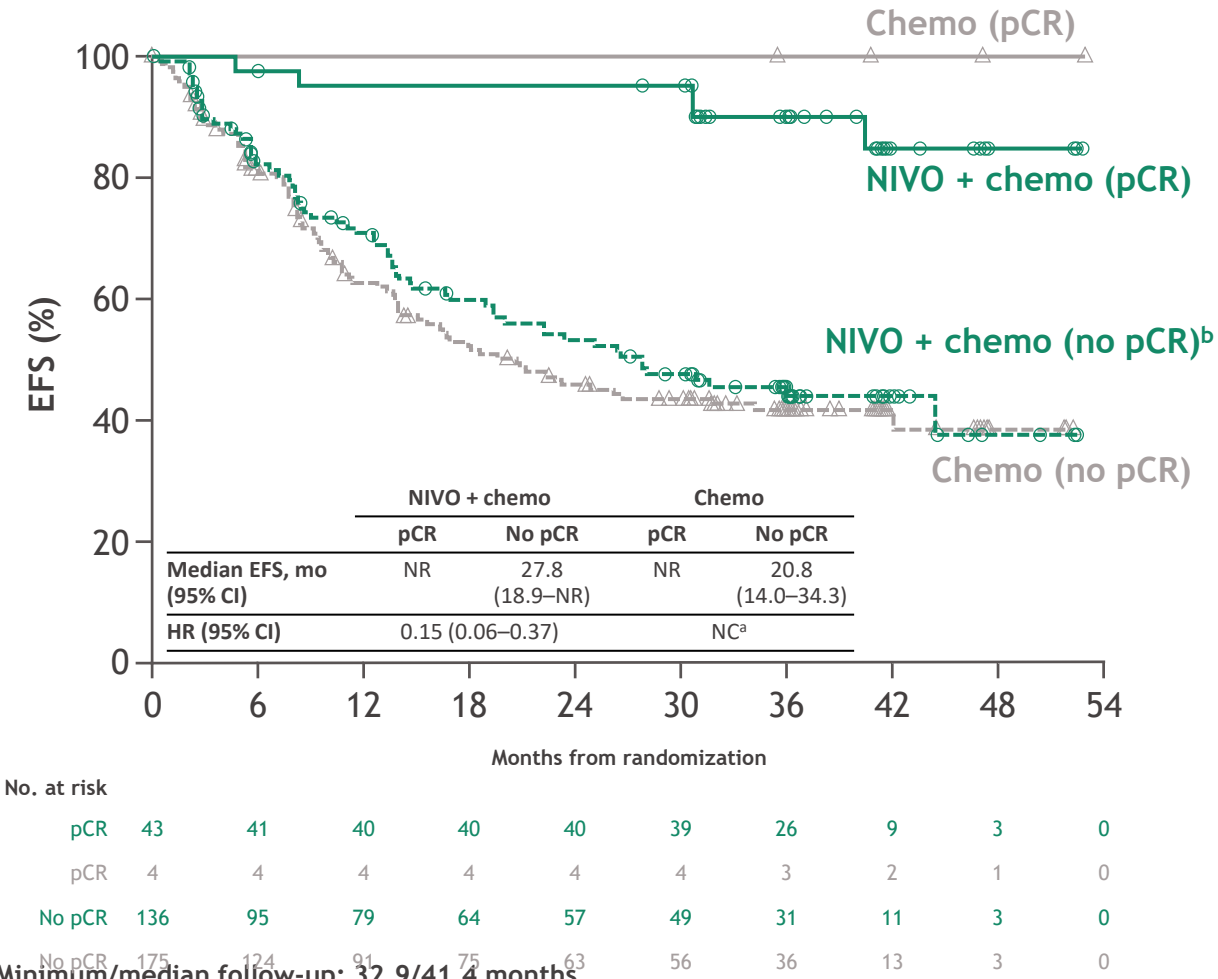


Minimum/median follow-up: 32.9/41.4 months.

[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.

Efficacy outcomes by pCR status in concurrently randomized patients

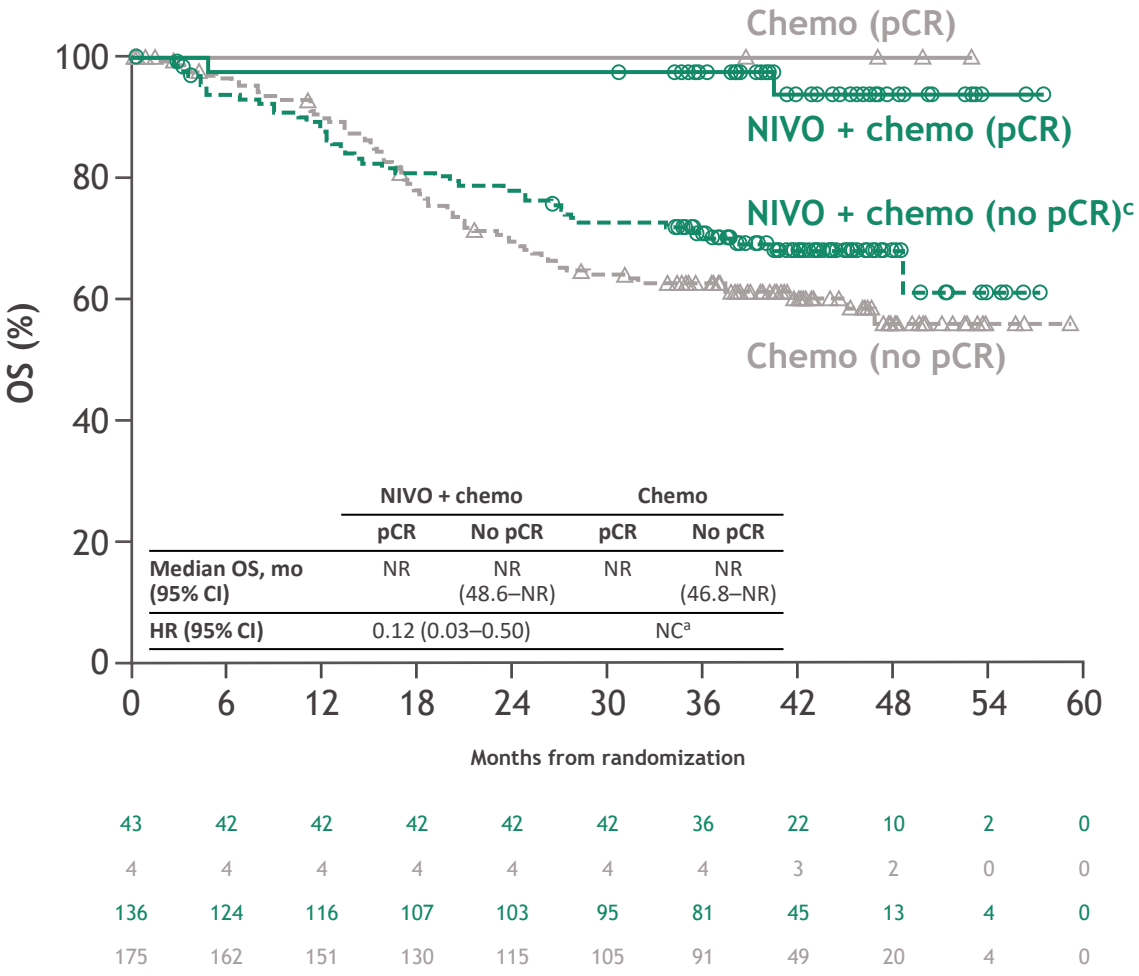
EFS



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

No. at risk										
pCR	43	41	40	40	40	39	26	9	3	0
pCR	4	4	4	4	4	4	3	2	1	0
No pCR	136	95	79	64	57	49	31	11	3	0
No pCR	175	124	91	75	63	56	36	13	3	0

OS



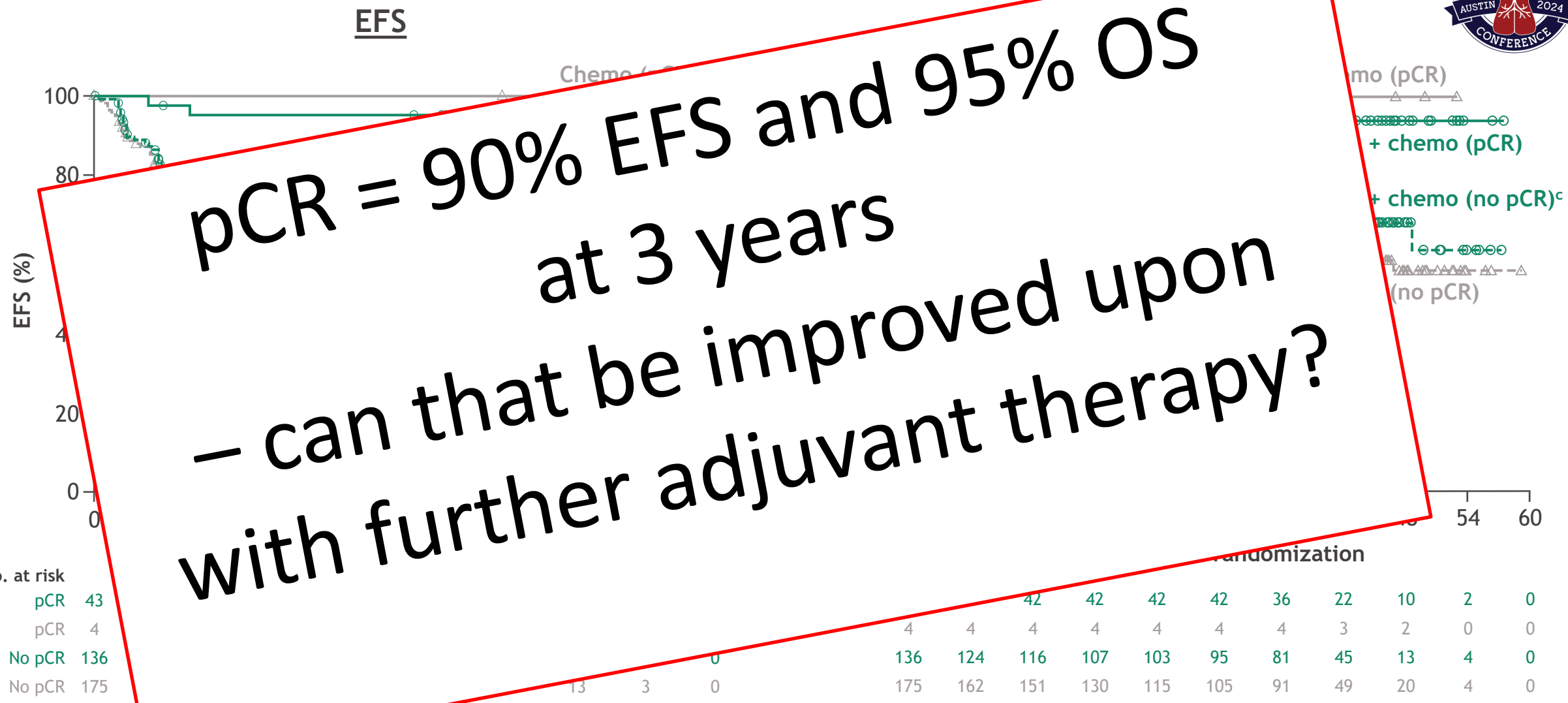
	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median OS, mo (95% CI)	NR	NR (48.6–NR)	NR	NR (46.8–NR)
HR (95% CI)	0.12 (0.03–0.50)		NC[a]	

	43	42	42	42	42	42	36	22	10	2	0
	4	4	4	4	4	4	4	3	2	0	0
	136	124	116	107	103	95	81	45	13	4	0
	175	162	151	130	115	105	91	49	20	4	0

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

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

Efficacy outcomes by pCR status in concurrently randomi- -tients



pCR = 90% EFS and 95% OS at 3 years

– can that be improved upon with further adjuvant therapy?

Minimum/median f

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

FDA officials raise concerns with immunotherapy overuse for early-stage cancer patients: #AACR24

In lung cancer, for instance, Singh pointed to six Phase 3 studies of different combinations of immune checkpoint therapy, chemo and surgery, where the addition of immunotherapy reduced the risk of disease progression, relapse or death compared to placebo.

But comparing the trial results, immunotherapy before surgery only — versus also adding it after surgery — seemed to "have a similar impact on event-free survival," Singh said. "This is a topic that crosses all solid tumors."

"Unless we address this question, we're going to be prolonging drug development without the consideration for generations of patients to come — and exposing generations and thousands and thousands of patients to unnecessary therapy," Pazdur added. "So although we could say, 'Well, this is a home run,

CheckMate 816[a] study design

Key Eligibility Criteria

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

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

R

NIVO 360 mg Q3W (3 cycles) + chemo[d] Q3W (3 cycles)

Chemo[e] Q3W (3 cycles) (n = 108)

NIVO 3 mg/kg Q2W (3 cycles) + IPI 1 mg/kg (cycle 1 only)[f] (n = 113)

Exploratory analysis population[g]

Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo ± RT → Follow-up

Primary analysis (NIVO + chemo vs chemo)

Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- TTDM

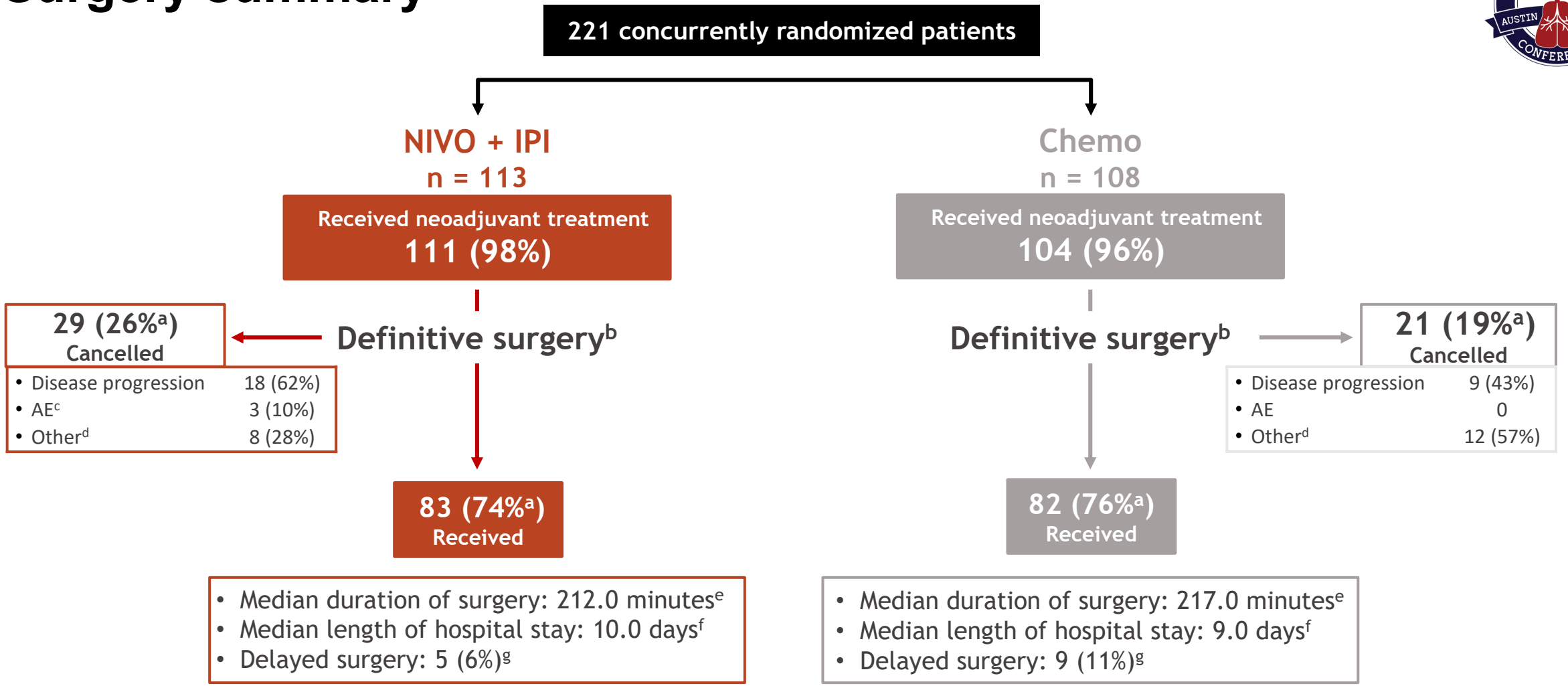
Exploratory analysis (NIVO + IPI vs chemo)

- **EFS by BICR**
- **pCR and MPR by BIPR**
- **OS**
- **EFS, pCR, and MPR by 4-gene inflammatory signature score**

Database lock date: October 14, 2022. Minimum/median follow-up: 37.1/49.2 months.

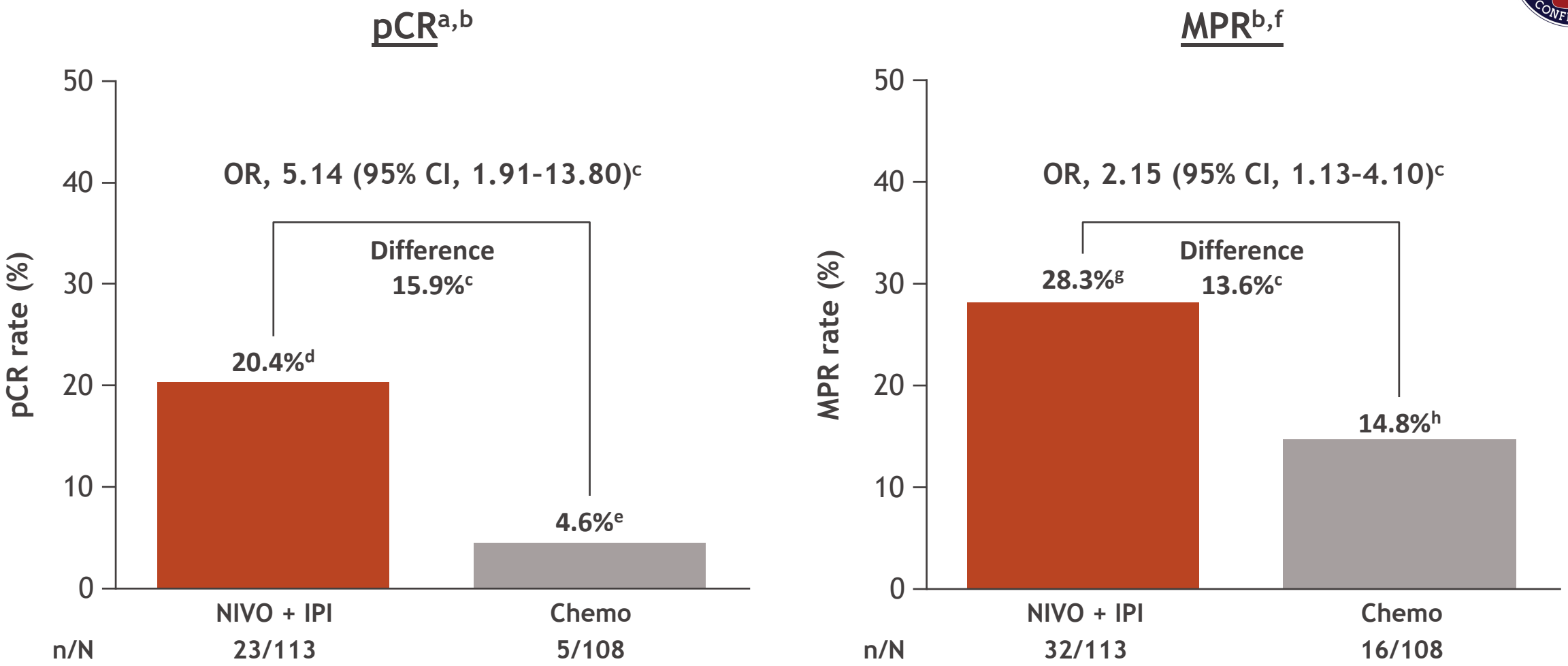
1. Cascone T, et al. *Nat Med* 2021;27:504–514. 2. Provencio M, et al. *Lancet Oncol* 2020;21:1413–1422.

Surgery summary



[a]Out of the number of randomized patients in each arm. [b]Definitive surgery not reported: NIVO + IPI, 1 (1%); chemo, 5 (5%). [c]Includes grade 2 pneumonitis, grade 3 pulmonary thromboembolism, and grade 3 diarrhea. [d]Includes refusal of surgery or withdrawal of consent (4 per arm), unresectable tumor (1 per arm), randomized but never treated (1 per arm), unfit for surgery (NIVO + IPI, 2; chemo, 5), and achieved a complete response (chemo, 1). [e]IQR for median duration of surgery: NIVO + IPI, 152.0-273.0 minutes; chemo, 151.0–307.0 minutes. [f]IQR for median length of hospital stay: NIVO + IPI, 6.0–16.0 days; chemo, 6.0–15.0 days. [g]Median length of delay: 2.1 weeks (both NIVO + IPI and chemo).

pCR and MPR with neoadjuvant NIVO + IPI vs chemo

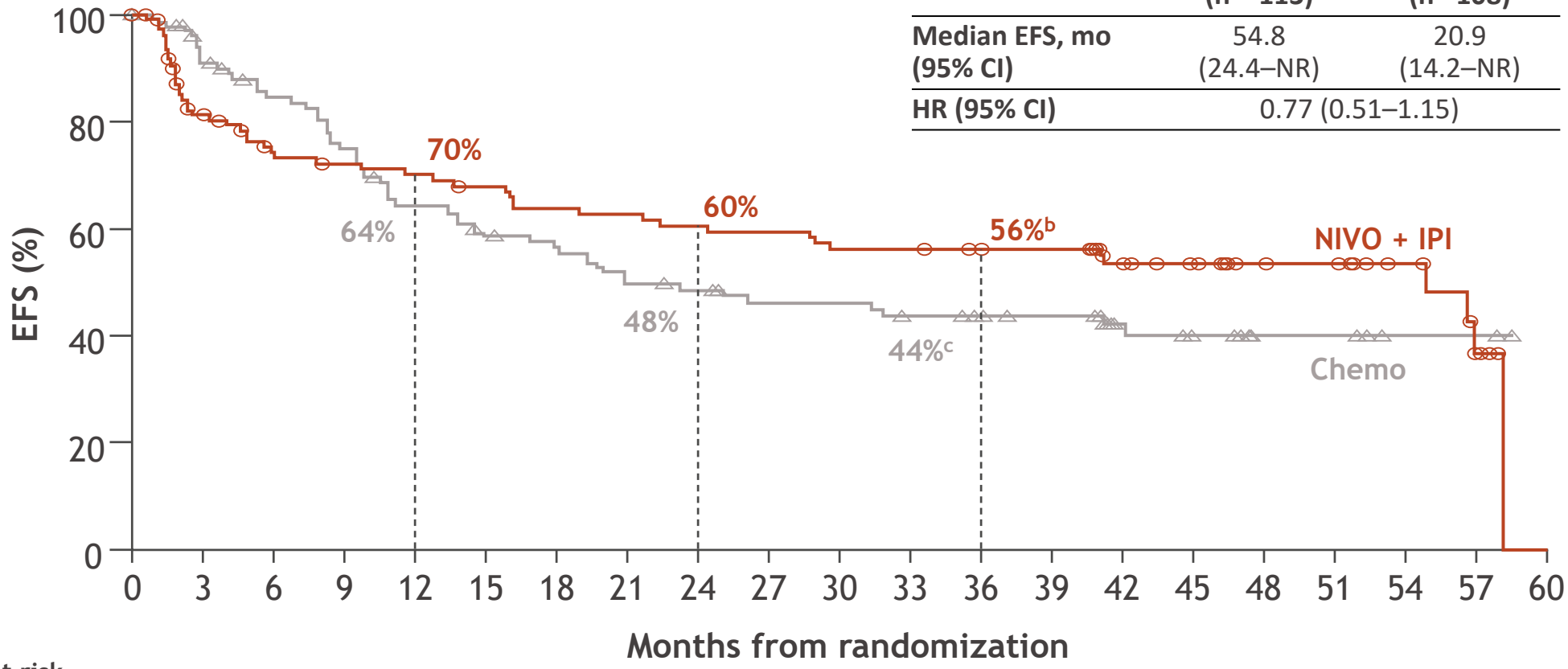


Database lock date: September 16, 2020.

[a]0% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per BIPR. [b]Patients who did not undergo surgery were classified as nonresponders. [c]Calculated using stratified Cochran-Mantel-Haenszel method. [d,e]95% CI: [d]13.4-29.0; [e]1.5-10.5. [f]≤ 10% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per BIPR. [g,h]95% CI: [g]20.2-37.6; [h]8.7-22.9.

EFS[a] with neoadjuvant NIVO + IPI vs chemo

	NIVO + IPI (n = 113)	Chemo (n =108)
Median EFS, mo (95% CI)	54.8 (24.4–NR)	20.9 (14.2–NR)
HR (95% CI)	0.77 (0.51–1.15)	



No. at risk

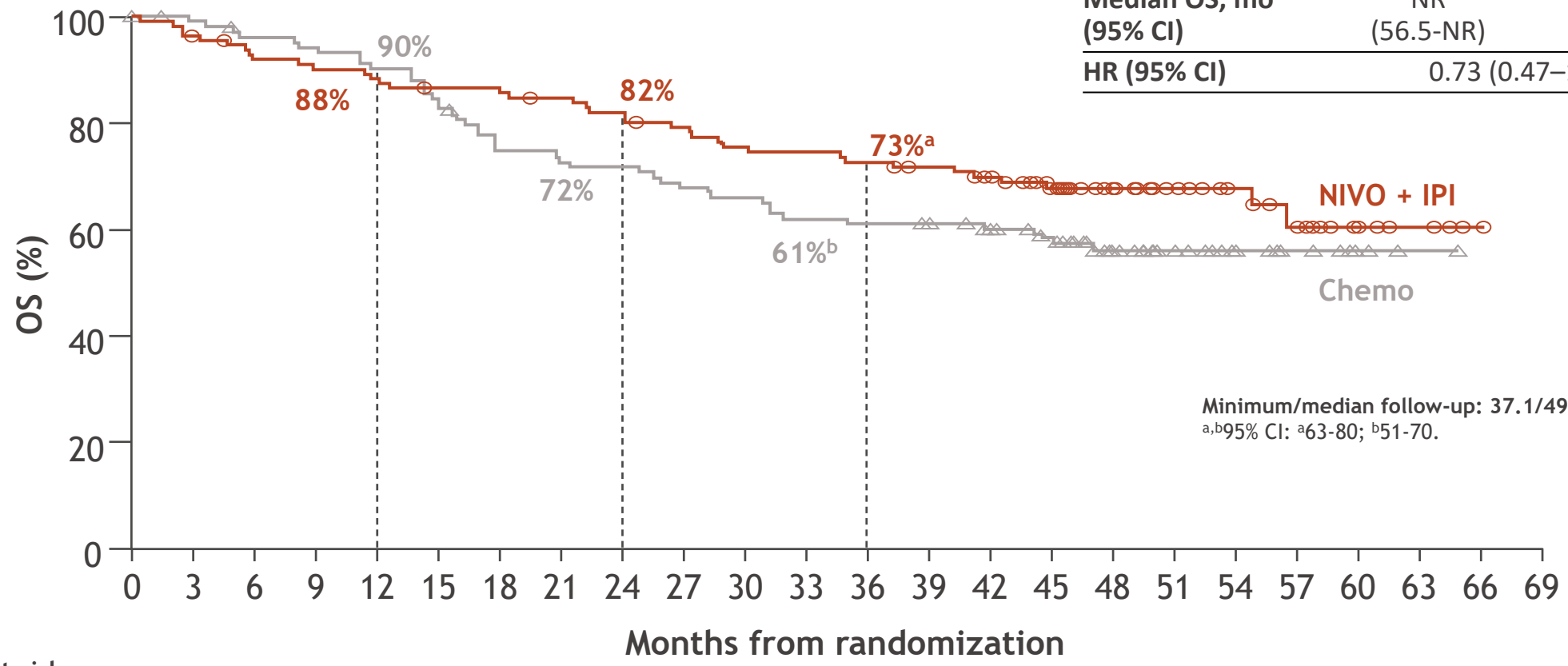
NIVO + IPI	113	83	71	69	67	64	60	59	57	56	53	53	51	50	34	31	18	17	11	6	0
Chemo	108	90	79	70	59	53	51	44	42	38	38	35	33	31	19	16	6	6	2	2	0

Minimum/median follow-up: 37.1/49.2 months.

[a]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% CI: [b]46-65; [c]33-54.

OS with neoadjuvant NIVO + IPI vs chemo

	NIVO + IPI (n = 113)	Chemo (n =108)
Median OS, mo (95% CI)	NR (56.5-NR)	NR (41.8-NR)
HR (95% CI)	0.73 (0.47–1.14)	



Minimum/median follow-up: 37.1/49.2 months.
[a,b]95% CI: [a]63-80; [b]51-70.

No. at risk

NIVO + IPI	113	108	102	100	98	95	95	92	89	85	81	80	78	75	70	60	41	30	22	14	8	4	1	0
Chemo	108	103	99	97	93	87	77	74	73	69	67	63	62	61	57	50	31	22	11	7	3	1	0	0

LBA37: A randomized, multicentric phase II study of preoperative nivolumab plus relatlimab or nivolumab in patients with resectable non-small-cell lung cancer (NEOpredict-Lung) – Schuler MH, et al

Study objective

To evaluate the efficacy of nivolumab or nivolumab + relatlimab (a LAG-3 targeting mAb) prior to surgery in patients with NSCLC in the phase 2 NEOpredict-Lung study

Key patient inclusion criteria

- Stage IB–IIIA NSCLC (UICC 8th edition)
- Adequate organ function

(n=60)

R

Nivolumab 240 mg q2w (n=30)

Nivolumab 240 mg + relatlimab 80 mg q2w (n=30)

SURGERY

SoC adjuvant therapy

Primary endpoint

- Feasibility (surgery ≤D43)

Secondary endpoints

- Histopathological response, radiological response, DFS, OS, safety

Schuler MH, et al. Ann Oncol 2022;33(suppl):Abstr LBA37

LBA37: A randomized, multicentric phase II study of preoperative nivolumab plus relatlimab or nivolumab in patients with resectable non-small-cell lung cancer (NEOpredict-Lung) – Schuler MH, et al

Key results

	Nivolumab (n=30)	Nivolumab + relatlimab (n=30)
Feasibility (surgery ≤D43), %	100	100
ORR (RECIST v1.1), %	10	27
ORR (PERCIST v1.0), %	38	38
Complete/major pathological response*, %	27	30
12-mo DFS rate, % (95%CI)	92 (70, 98)	91 (66, 98)
12-mo OS rate, % (95%CI)	92 (70, 98)	100
R0 resection rate, %	100	97

*2 patients excluded at surgery

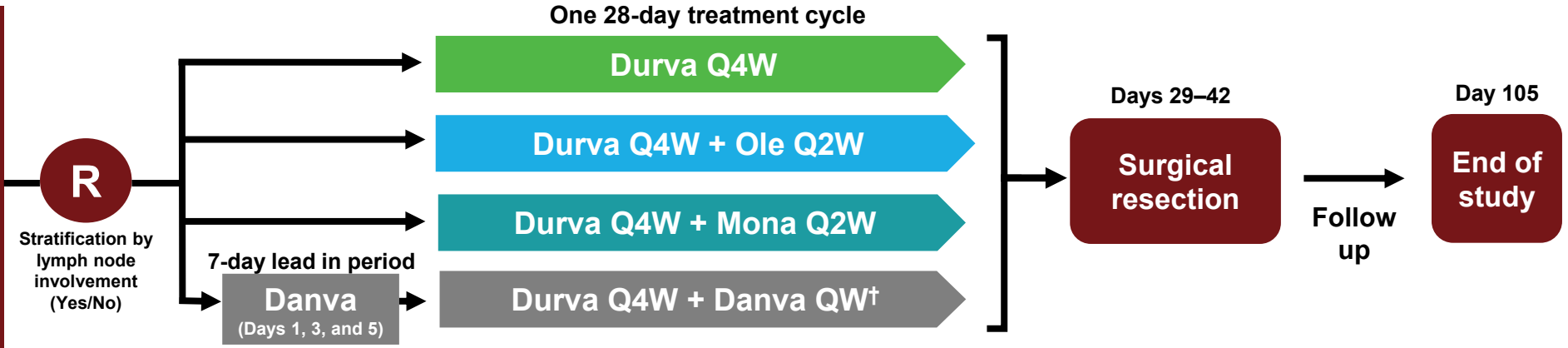
Schuler MH, et al. Ann Oncol 2022;33(suppl):Abstr LBA37

NeoCOAST: Study design and objectives

Key eligibility criteria:

- Stage I (>2cm) to IIIA NSCLC*
- Fully resectable
- ECOG PS 0 or 1
- No prior systemic therapy
- Adequate organ and marrow function

N=84



Endpoints:

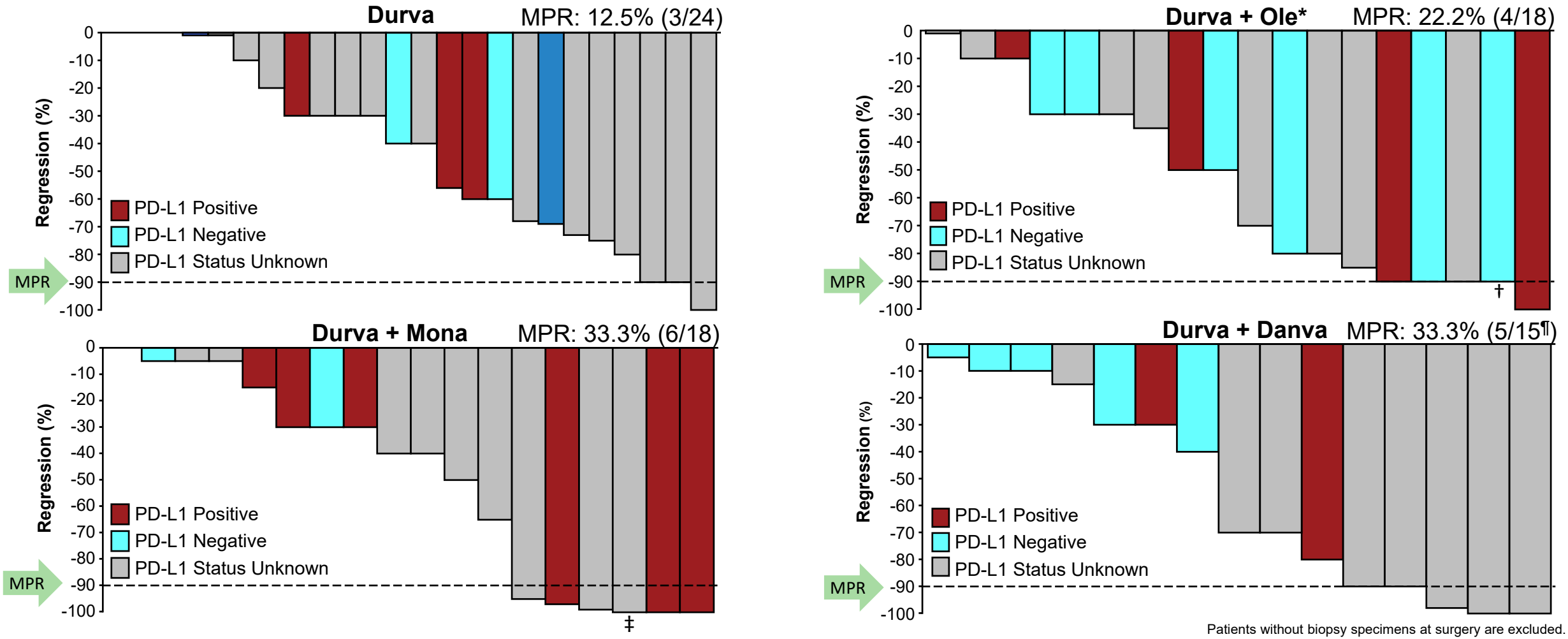
- **Primary: MPR rate (proportion of patients with ≤10% residual viable tumor cells in resected tumor specimen and sampled nodes at surgery) per investigator assessment.**
- **Secondary: pCR rate (no viable tumor cells in resected tumor specimen or sampled nodes at surgery), safety and tolerability, feasibility of planned surgery, pharmacokinetics, and immunogenicity.**
- **Exploratory: Tumor, blood, and stool microbiome biomarkers; investigator-assessed best overall response and ORR (per RECIST v1.1).**

Statistical analysis:

- Continuous variables were summarized using descriptive statistics; this study was not statistically powered to make explicit conclusions for any hypothesis test. The primary intent was to look for preliminary efficacy signals by calculating MPR rates and their confidence intervals.

*Per American Joint Committee on Cancer Staging, 8th edition.
†Danvatirsen arm was stopped early as the program was discontinued.

NeoCOAST: Pathological regression at surgery



Patients without biopsy specimens at surgery are excluded.

*One patient initially reported to have 10% viable tumor cells in primary tumor later determined by the investigator to have pCR;.†Patient determined not to have MPR after local evaluation of primary tumor and lymph nodes; ‡Patient reported to have 0% residual viable tumor cells in primary tumor but was later determined by investigator not to have pCR; ¶Of the 16 patients who underwent surgery, 1 patient was reclassified following a retrospective change in diagnosis.
MPR, major pathological response; PD-L1, programmed cell death ligand-1.

Conclusion

Addition of anti-PD-1 to neoadjuvant chemotherapy confers a lot of benefit over chemotherapy alone at minimal/no additional toxicity cost

So far novel neoadjuvant IO-IO combinations have not been clear advances in terms of efficacy

Neoadjuvant chemotherapy plus CTLA4-PD1 is worthy of investigation

Future perioperative approvals will likely require a contribution of components (neoadjuvant vs adjuvant) assessment