Challenges and Controversies in Perioperative Immunotherapy in Early-Stage NSCLC : Optimistic Aspect

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Challenges and Controversies in Adjuvant Immunotherapy in Early-Stage NSCLC after neoadjuvant chemoimmunotherapy

: An unavoidable yet worthwhile choice

Conflict of Interest Statement

I serve as an advisory board member for AstraZeneca, Bristol-Myers Squibb (BMS), Roche, MSD, Yuhan, Boryung, and Boehringer Ingelheim (BI). Additionally, I have received honoraria for lectures and participated in research collaborations with various pharmaceutical companies. However, these affiliations had no influence on the content, analysis, or conclusions presented in this lecture. My presentation is based on available clinical data and scientific evidence, and all statements reflect my independent professional judgment.

Disclaimer

The clinical study results on perioperative chemoimmunotherapy presented in this lecture were referenced to support my perspective. However, it should be noted that the studies discussed were not designed for a head-to-head comparison, and my intention was to describe their relationship indirectly rather than directly comparing them.

Any mention of specific drugs in this presentation does not imply their superiority or inferiority compared to others. Additionally, I have utilized presentation materials from international conferences, which were provided by the respective pharmaceutical companies conducting these studies.

The content of this presentation reflects my personal opinions, and the clinical cases used are also from my personal collection.

Perioperative Immunotherapy

In NCCN

T2a-3,N0,M0 T2a-3,N1,M0	**Surgical resection[m] + mediastinal lymph node dissection or systematic lymph node sampling after preoperative systemic therapy, if planned[q]**	**Systemic therapy after surgery**
T3(sep),N0-1,M0 T4(ips. sep),N0-1,M0	**Surgery[m] after preoperative systemic therapy, if planned[q]**	

NCCN Guidelines Version 3.2025

- **Nivolumab 360 mg and platinum-based doublet chemotherapy every 3 weeks for up to 4 cycles1,2 with the option of continuing single-agent nivolumab as adjuvant treatment after surgery (for patients with no known EGFR mutations or ALK rearrangements) (category 1)**
- **Pembrolizumab 200 mg and cisplatin-based doublet chemotherapy every 3 weeks for 4 cycles and then continued as single-agent pembrolizumab as adjuvant treatment after surgery (category 1)**
- **Durvalumab 1500 mg and platinum-based doublet chemotherapy every 3 weeks for 4 cycles and then continued as single-agent durvalumab as adjuvant treatment after surgery (for patients with no known EGFR mutations or ALK rearrangements) (category 1)**

NCCN Guidelines Version 3.2025

Outline

- The Inevitable Choice of Perioperative Immunotherapy – Uncertainty in Surgical Outcomes
- The Inevitable Choice of Perioperative Immunotherapy – Benefits in EFS and OS
- Adverse Events in Perioperative Chemoimmunotherapy
- Proposed Indications and Supporting Evidence for Optimal Patient Selection
- Summary and Key Takeaways

Uncertainty in Surgical Outcomes after neoadjuvant chemoimmunotherapy

In which stages do you primarily consider neoadjuvant or perioperative chemoimmunotherapy?

- Stage IA
- Stage IB
- Stage IIA
- Stage IIB
- Stage IIIA
- Stage IIIB
- Stage IIIC

The NCCN Guidelines(2013) state that patients with stage II or IIIA (T3,N1) disease may be treated with induction systemic therapy before surgery if they would have been candidates for adjuvant chemotherapy after surgery.

For the 2023 update (Version 1) recommended that all patients should be evaluated for neoadjuvant chemoimmunotherapy with strong consideration for those with node-positive disease or tumors 4 cm or more and no CIx for ICIs

However, neoadjuvant therapy should not be used to attempt to induce resectability in patients who do not already meet criteria for resectability on initial evaluation.

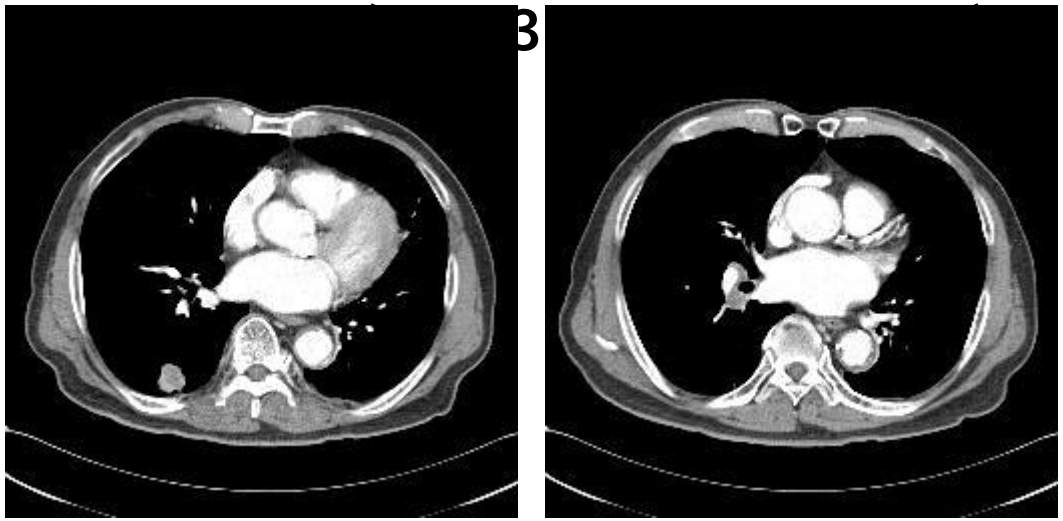
Case 1 (82/M, 60 PY)

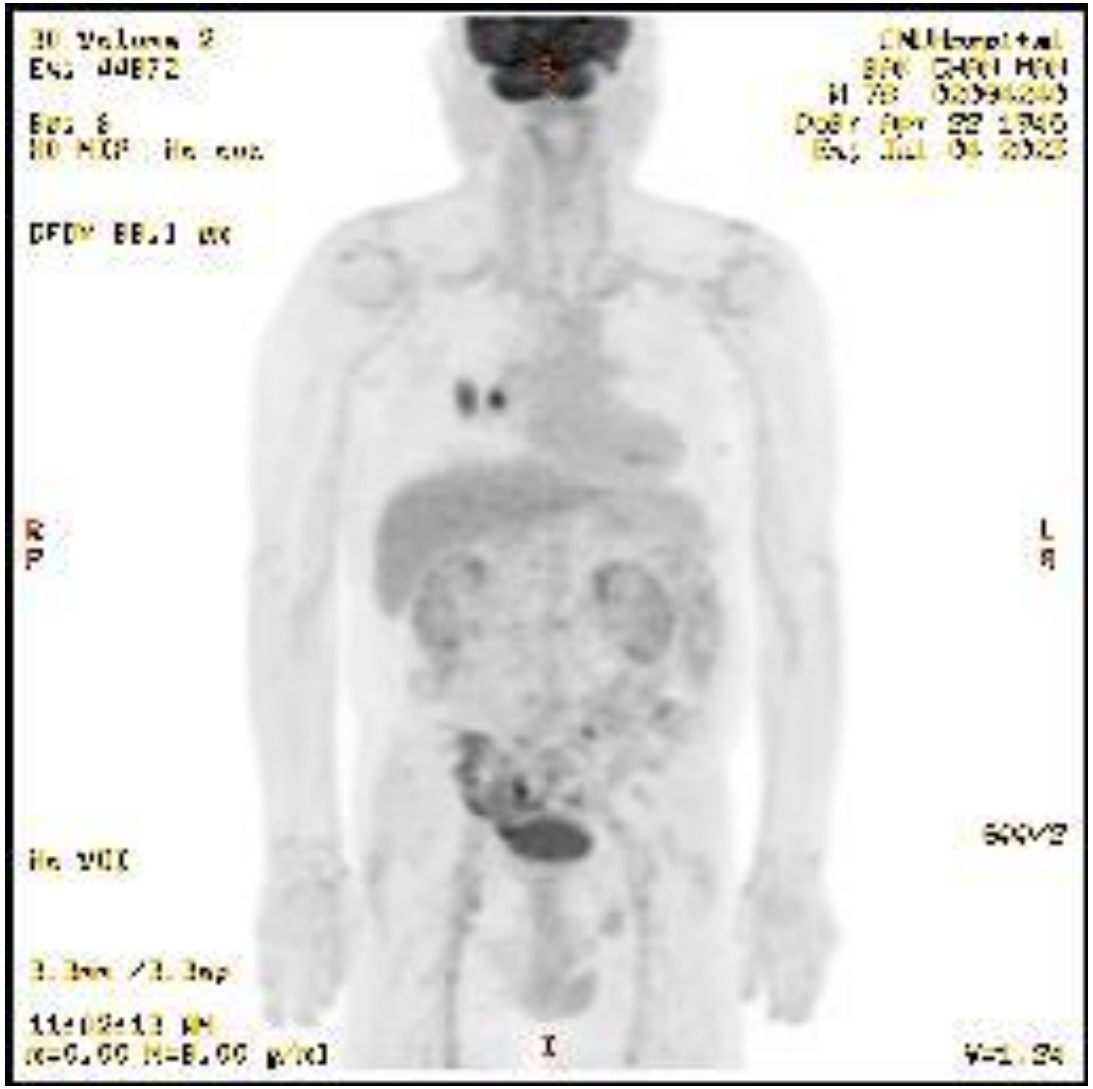
DM/HTN(+/+), Gout

NSCLC, adenocarcinoma, T1cN1M0

IIB

EGFR wild, ALK negative,





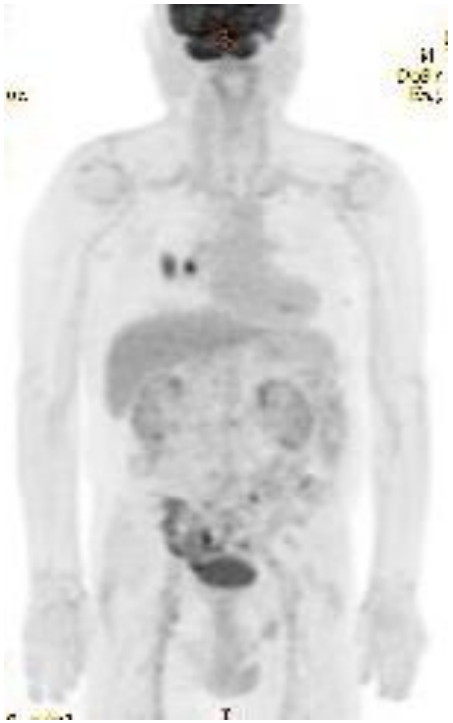
Case 1 (82/M, 60 PY)

Your Treatment Strategy?

1. Definitive Surgery and then Adjuvant chemotherapy (Platinum Doublet)
2. Concurrent chemoradiotherapy
3. Radiotherapy
4. Neoadjuvant chemoimmunotherapy and Definitive Surgery
5. Planned Perioperative chemoimmunotherapy
6. Observation and f/u

Case 1 (82/M, 60 PY)

- 2023.7.17~2023.8.31 #1~3 Neoadjuvant Carbo - Pem - Nivolumab
- 2023.9.21 Adrenal insufficiency
- 2023.11.16 RLL lobectomy with MNLD



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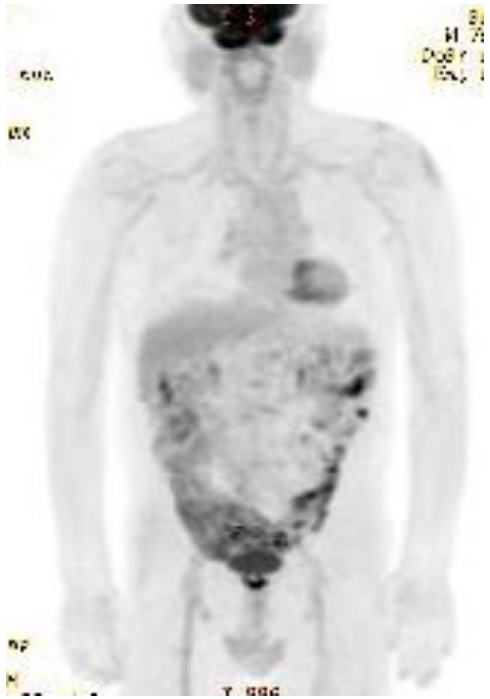

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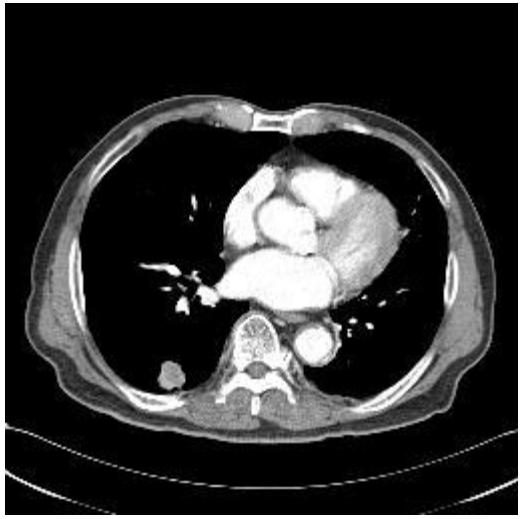

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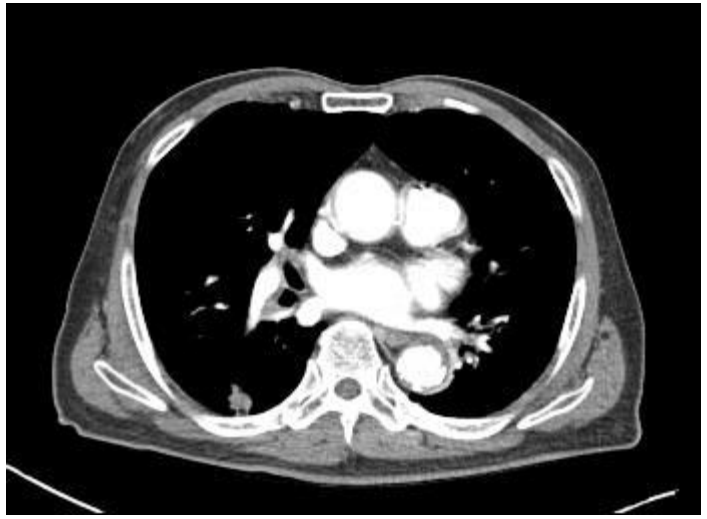

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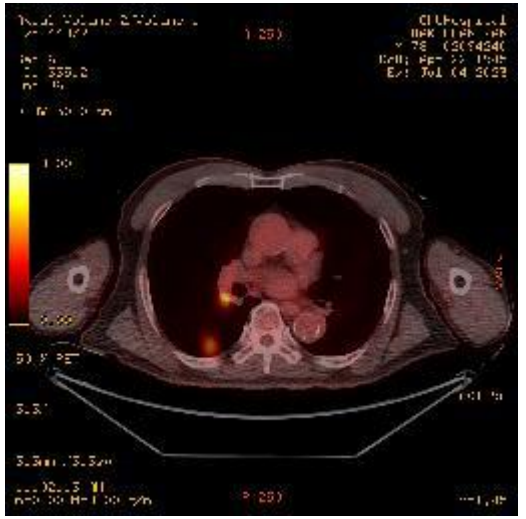

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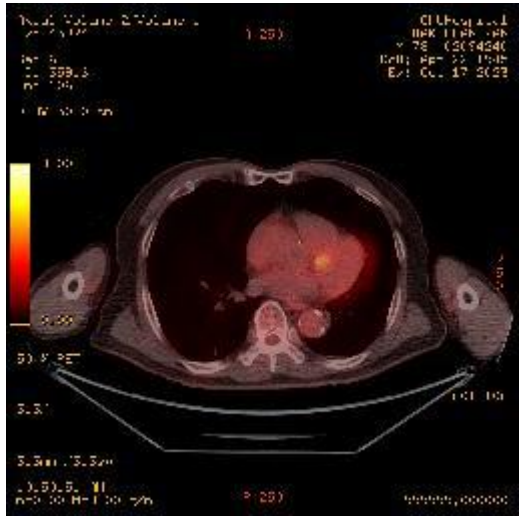


2023.9.2

Case 1 (82/M, 60 PY) 2023.11.15 chest CT : PR , 2023.11.16 RLL lobectomy with MNLD

Lung, right lower lobe, **lobectomy with lymph node dissection**:

1. **Status post neoadjuvant chemotherapy**

2. **No residual tumor** (complete pathologic response) (A2-A6)

  1) site: posterior basal segment, right lower lobe

  2) treatment effect in primary tumor

    (1) percentage of viable tumor: 0 % (no residual viable tumor identified)

    (2) percentage of necrosis: 0 %

    (3) percentage of stroma (includes fibrosis and inflammation): 100 %

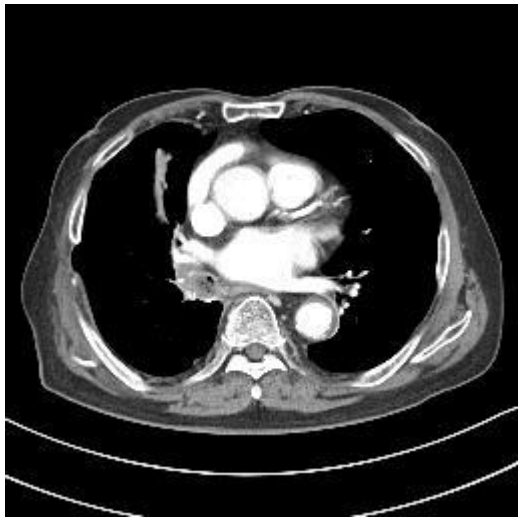
  3) background lung: unremarkable

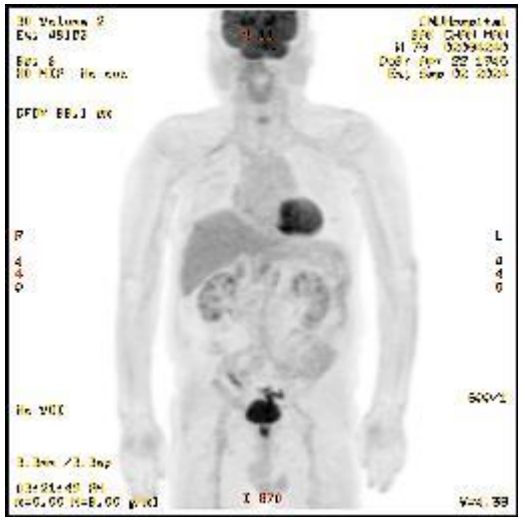
  4) ypT0 N0 by AJCC staging system **(8th edition)**

  5**) Lymph node metastasis: absent (0/11)**

    (LN 4 (B), 0/2; LN 7 (C), 0/2; LN 7-1 (D), 0/1; LN 10 (E), 0/1; LN 10-1 (F), 0/1; LN 11 (G), 0/1; LN 11-1 (H), 0/1; LN 11-2 (I), 0/1; LN 11-3 (J), 0/0; peribronchial (A), 0/1)

Case 1 (82/M, 60 PY)





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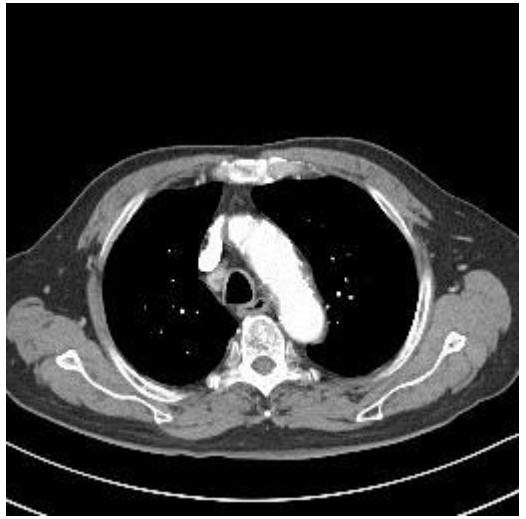
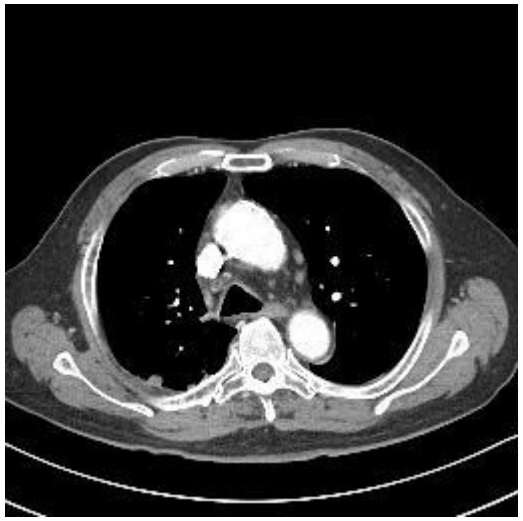
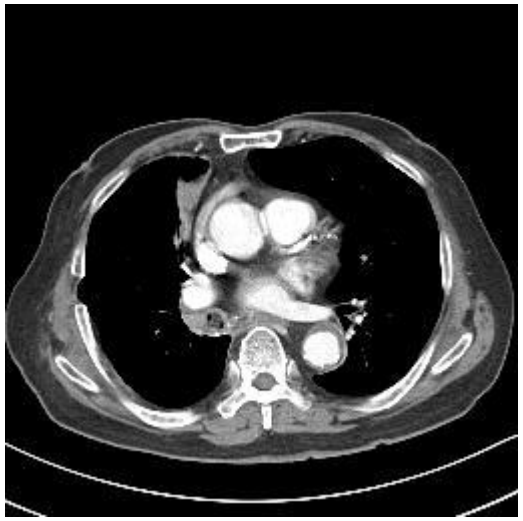
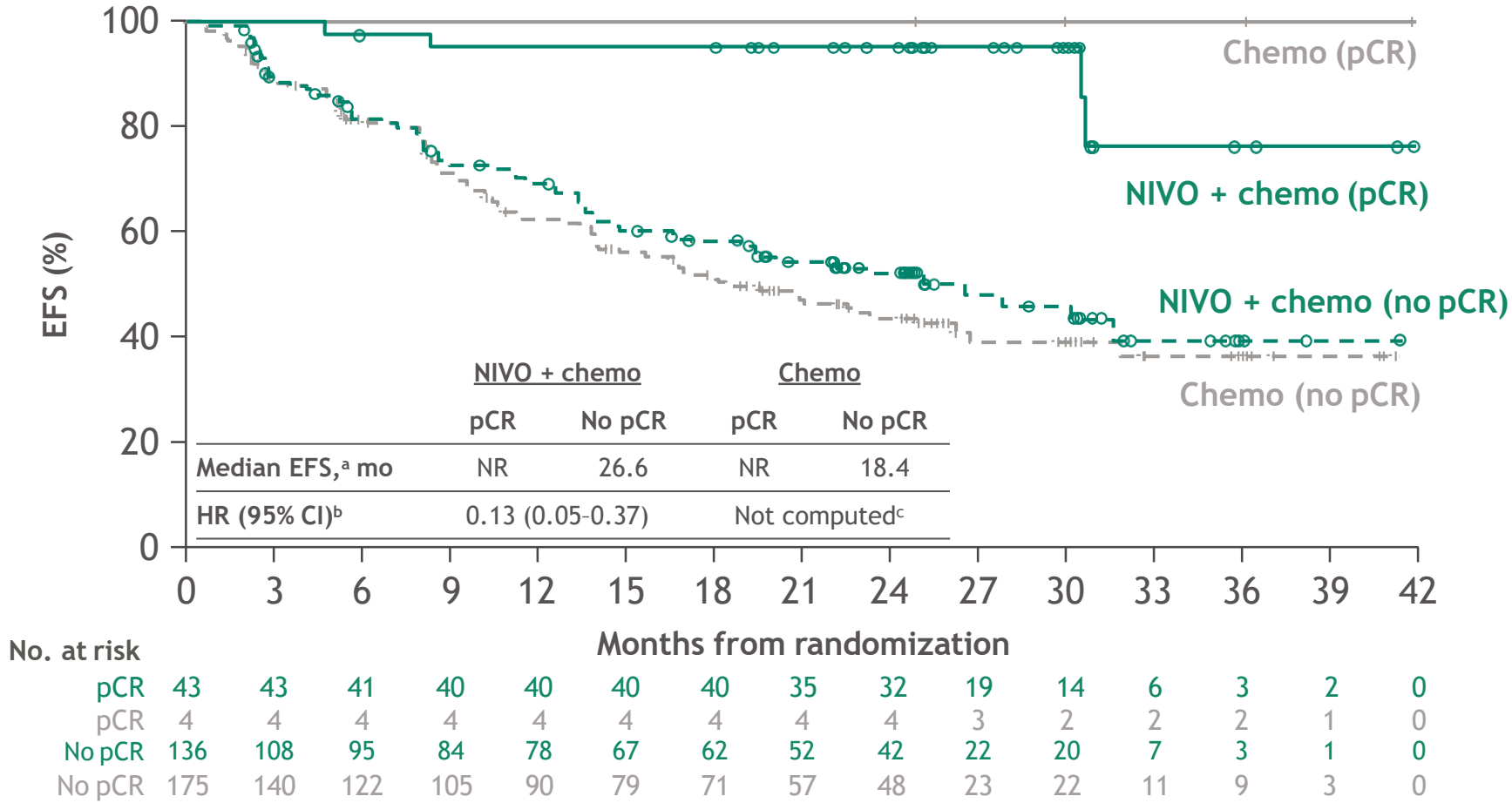






2024.10.29

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.

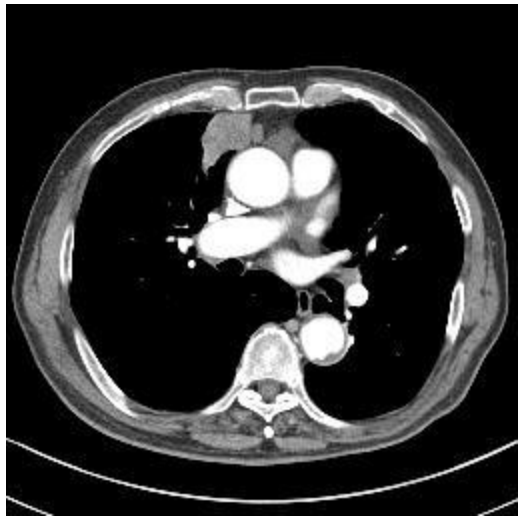
Case 2 (75/M, 55 PY)

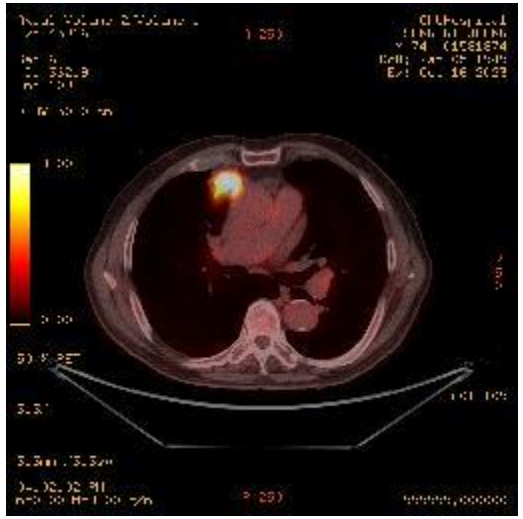
#NSCLC, squamous cell ca, T2bN0M0 IIA

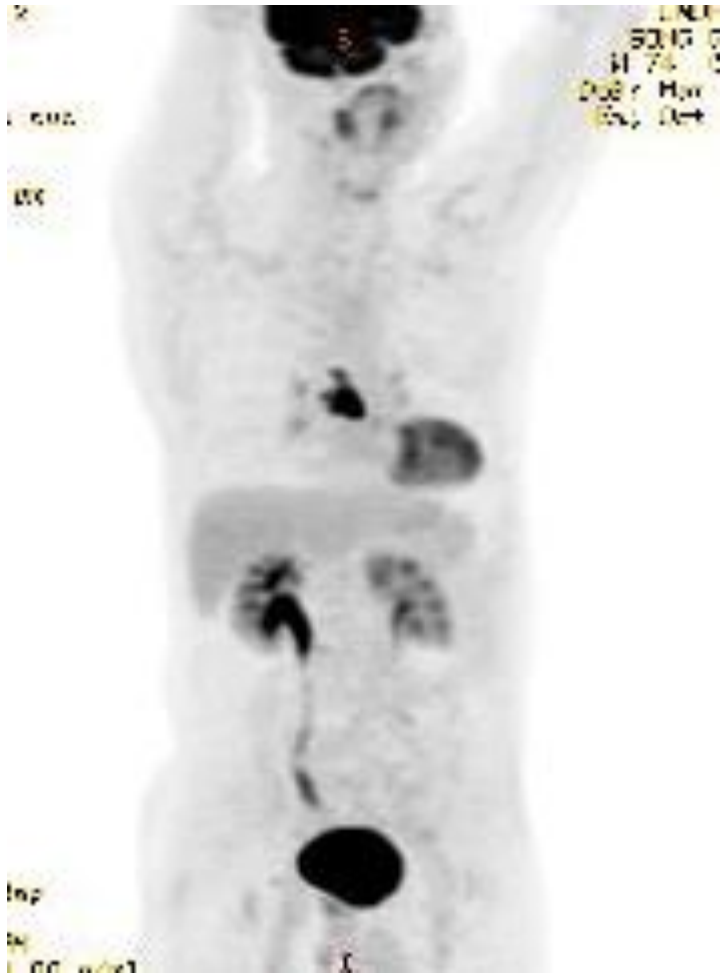
Tumor size 4.6cm

EGFR wild, ALK negative,

high PD-L1 (sp263 80%, 22C3 high)







Case 2 (75/M, 55 PY)

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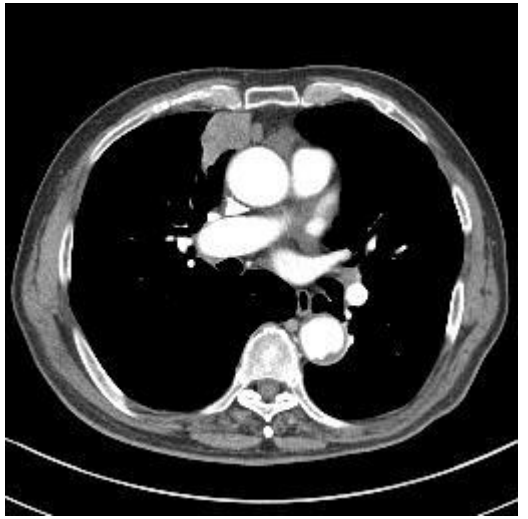
Case 2 (75/M, 55 PY)

- 2023.10.24~12.26

  Neoadjuvant Carbo-taxol-nivolumab

#1~3



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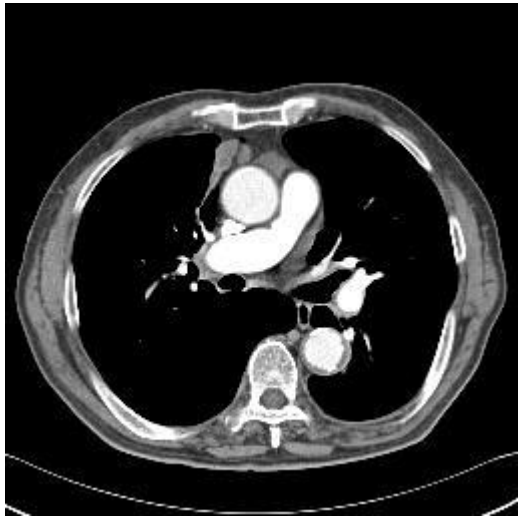
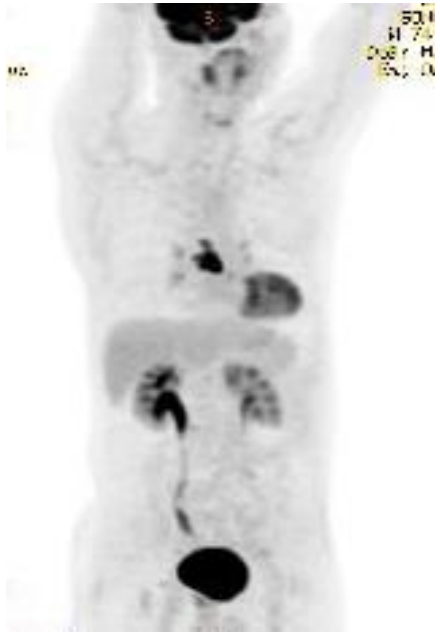


2024.2.23

#. 3VD (pRCA CTO)

#. AAA s/p EVAR(24-01-30)

#. HTN



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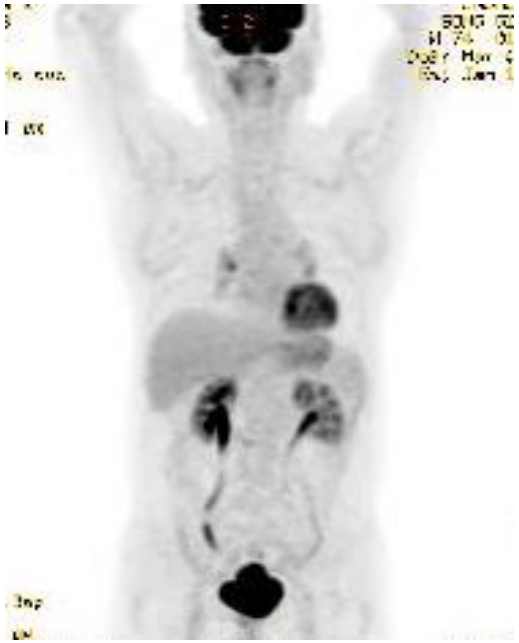


2024.1.15

Case 2 (75/M, 55 PY)

2024.1.30 AAA s/p EVAR 2024.3.15 RUL wedge resection

RUL wedge resection pT0

Lung, right upper lobe, wedge resection (1-3):

1) No viable tumor cells (ypT0)

2) Chronic granulomatous inflammation with necrosis and cholesterol clefts

3) Lymphoid follicular inflammation

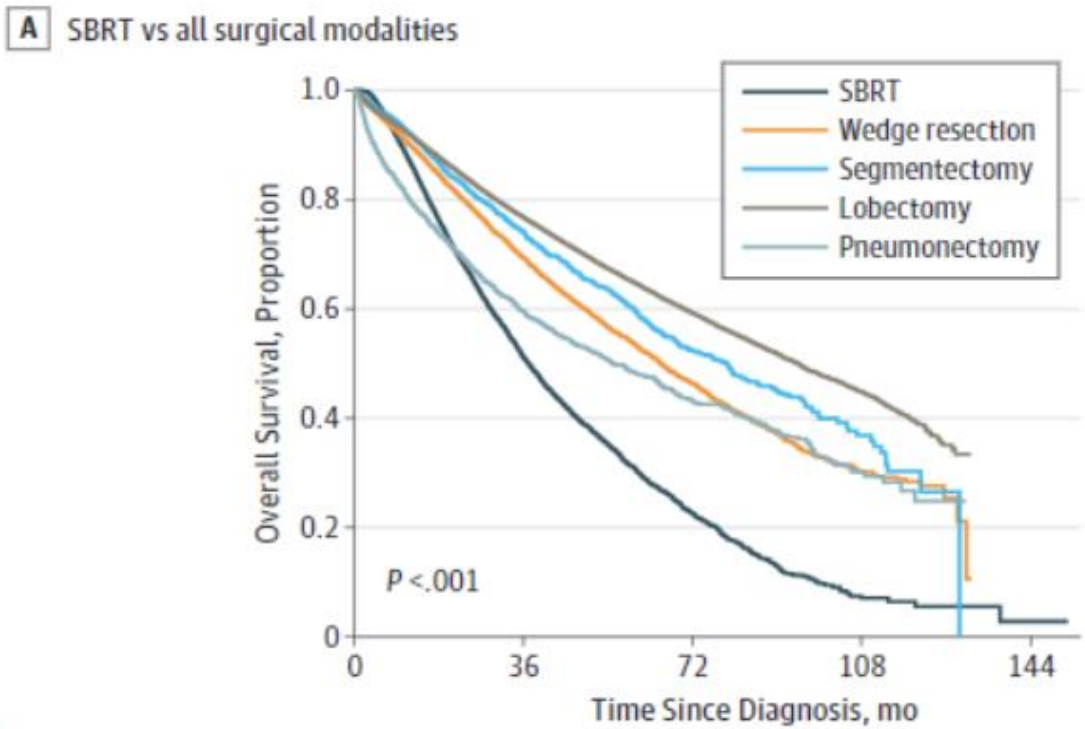
Post-Surgery Dilemmas

- Time from the last dose of Chemoimmunotherapy to Surgery
- Lobectomy with LND vs Wedge resection
- Dissected node count

Comparison of Long-term Survival of Patients With Early-Stage NSCLC After Surgery vs Stereotactic Body Radiotherapy

A. Chi et al. JAMA Network Open (2019)

- **104 709 total patients**
- **91 330 underwent surgery**
- **2004 ad 2015**



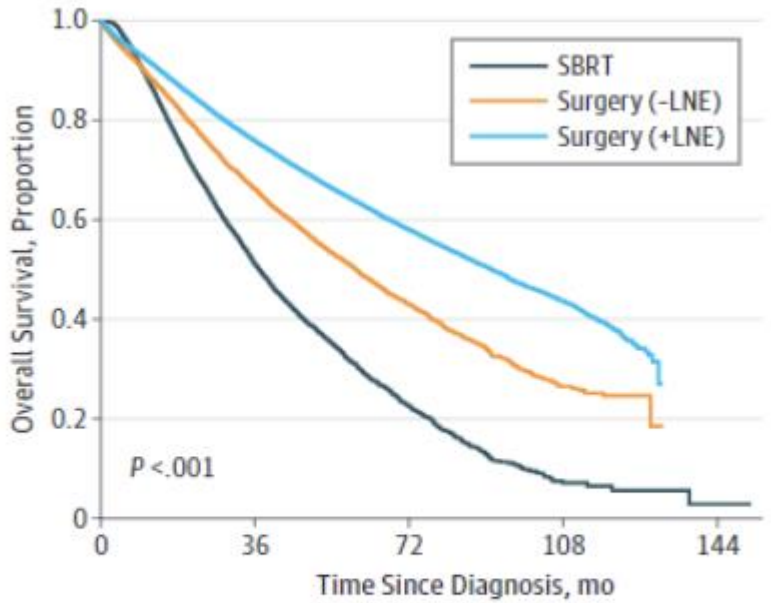
No. at risk

SBRT	13379	3334	459	21	1
Wedge resection	13377	5852	1627	173	
Segmentectomy	3146	1354	368	42	
Lobectomy	72448	35157	11546	1368	
Pneumonectomy	2359	969	315	38	

Comparison of Long-term Survival of Patients With Early-Stage NSCLC After Surgery vs Stereotactic Body Radiotherapy

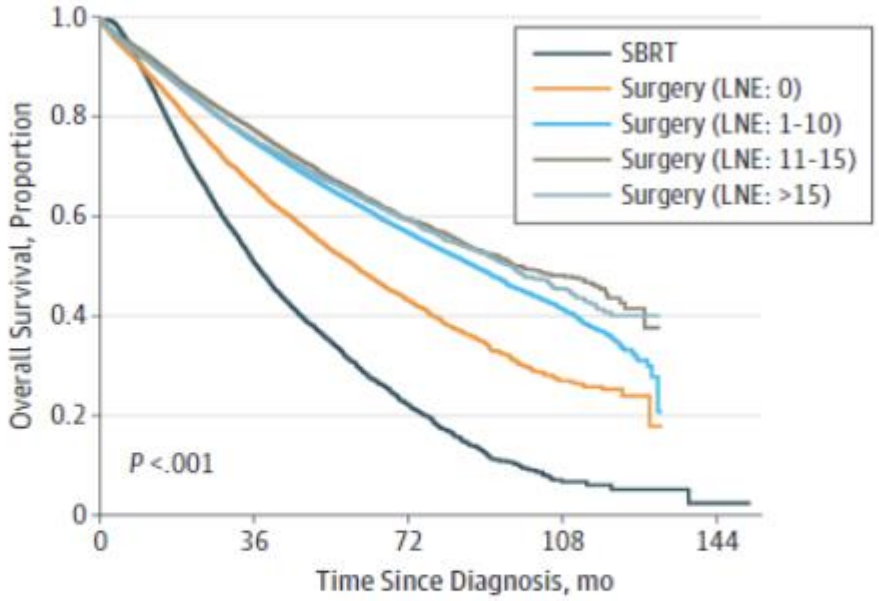
A. Chi et al. JAMA Network Open (2019)

B SBRT vs surgery with and without regional LNE



No. at risk					
SBRT	13379	3334	459	21	1
Surgery (-LNE)	7437	3333	1011	128	
Surgery (+LNE)	83573	39852	12793	1483	

C SBRT vs surgery with LNE of 0, 1-10, 11-15, and >15

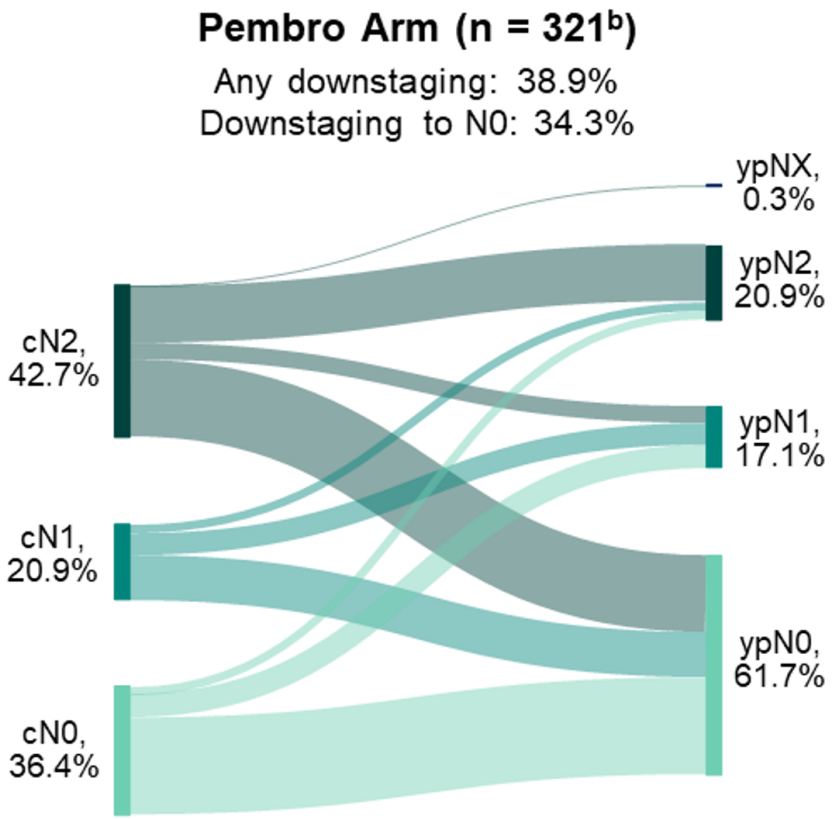


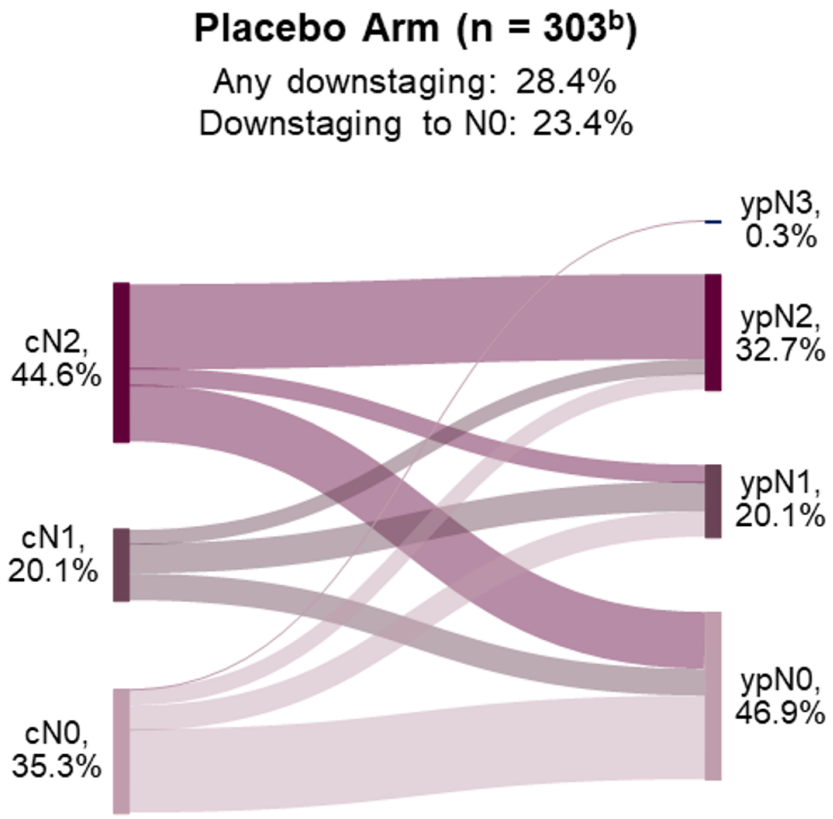
No. at risk					
SBRT	13379	3334	459	21	1
Surgery (LNE: 0)	7382	3393	1053	138	
Surgery (LNE: 1-10)	50977	24875	8140	932	
Surgery (LNE: 11-15)	14256	6547	2015	235	
Surgery (LNE: >15)	12944	5543	1685	182	

Unexpected concerns after surgery

- PL 1,2,3
- LN(+)
- Inadequate Lymph node dissection
- Insufficient safety margin
- Wedge resection or segmentectomy
- Delayed time to surgery

KN-671 : N status at baseline and post-surgery





[a]Lymph node status at baseline required pathologic confirmation unless knowledge of N status would not change the stage by which the participant was stratified; in such cases, PET scan diagnosis of N stage was sufficient. [b]Post surgery N status was missing for 4 participants in the pembro arm and for 14 participants in the placebo arm. Data cutoff date for IA2: July 10, 2023.

STS 2024

Comparison of surgical difficulty in patients with resectable non-small cell lung cancer under different neoadjuvant treatment modes: a retrospective cohort study

Fan Zhang et al. JTD (2021)

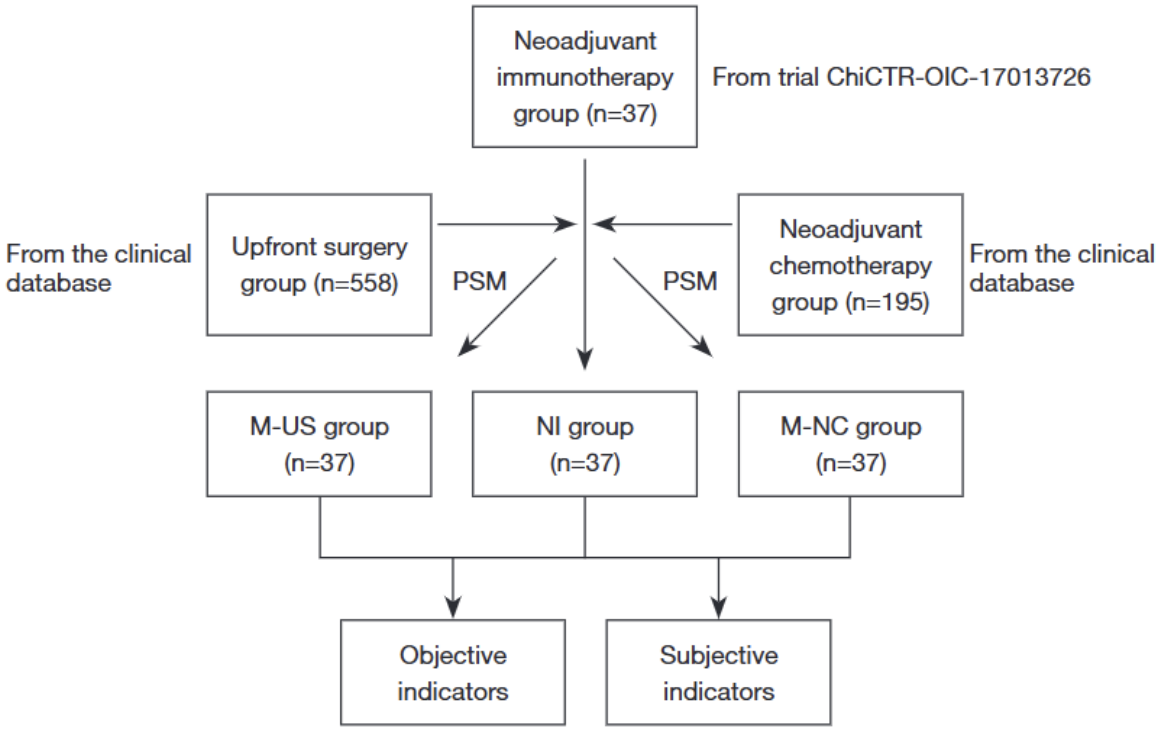


Table 3. Comparison of NI, NC, and S

Characteristics	NI	S	NC
n	37	37	37
Open procedures, %	70.3	51.4	83.8
Number of lymph nodes dissected	9	19	24
Length of stay (d)	7	6	7
Postoperative complications, %	37.8	10.8	16.2
30-d mortality, %	5.4	0	0

Modified from Zhang et al.[9]
NC, neoadjuvant chemotherapy, NI, neoadjuvant immunotherapy; S, immediate/upfront surgery.

Conclusion : The administration of neoadjuvant sintilimab increased complications but did not increase the difficulty of surgery. Fewer lymph nodes were dissected in the NI

Midpoint Summary-1

- Optimism Bias of neoadjuvant chemoimmunotherapy in all of us
- Unexpected issues after surgery
- Expected toxicities of Platinum doublet retreatment as adjuvant treatment

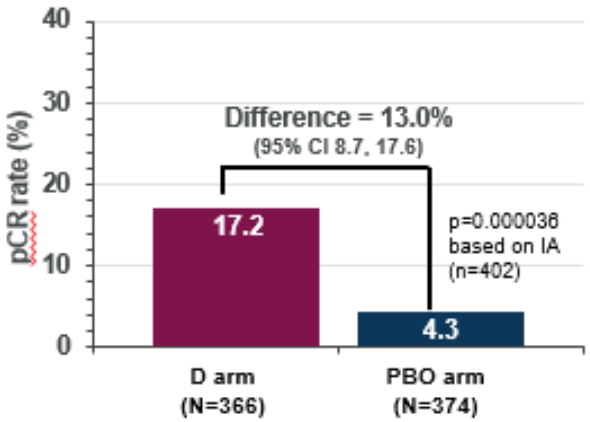
EFS and OS : Neoadjuvant chemoimmunotherapy vs Perioperative chemoimmunotherapy

	AEGEAN[1]	KEYNOTE-671[2]	CHECKMATE-77T[3,*]	CHECKMATE-816[5]
Population size	802	797 (ITT)	461	350
Study site locations	Global	Global	Global	Global
Disease stage (AJCC 8th ed)	Stage II, IIIA and IIIB (N2)	Stage II, IIIA, and IIIB (N2)	Stage II, IIIA, and IIIB (N2)	Stage IB(≥4cm)–Stage IIIA[a]
Perioperative IO regimen				
Neoadjuvant	Durvalumab + CT (Q3W x 4 cycles)	Pembrolizumab + CT (Q3W up to 4 cycles)	Nivolumab + CT (Q3W x 4 cycles)	Nivolumab + CT (Q3W x 3 cycles)
Adjuvant	Durvalumab Q4W for 12 cycles	Pembrolizumab Q3W for 13 cycles	Nivolumab Q4W for 12 cycles	N/A
Platinum-backbone	Cisplatin/carboplatin	**Cisplatin**	Cisplatin/carboplatin	Cisplatin/carboplatin
Planned pneumonectomy permitted at baseline?	No	Yes	N/A	Yes
T4 invasion	Excluded	Included	N/A	N/A
EGFRm/ALKm	Excluded from primary endpoint (mITT population)	**Included**	Excluded	Excluded patients with known EGFR/ALK alterations (molecular testing mandatory for non-squamous in Asia, at investigator's discretion in all other regions)
Primary endpoints	pCR, EFS	EFS, OS	pCR, EFS	pCR, EFS

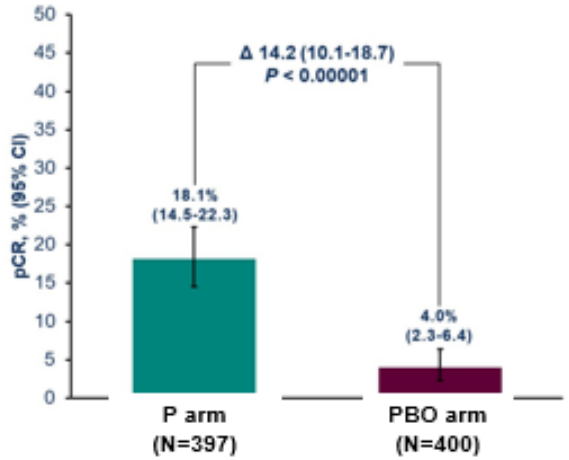
		AEGEAN[1]		KEYNOTE-671[2]		CheckMate-77T[3,*]		CheckMate-816[4]	
Characteristics		**D arm (n=366)**	**PBO arm (n=374)**	**P arm (n=397)**	**PBO arm (n=400)**	**N arm (n=229)**	**PBO arm (n=232)**	**N arm (n=179)**	**PBO arm (n=179)**
Age	Median (range), years	65.0 (30–88)	65.0 (39–85)	63 (26–83)	64 (35–81)	66 (37–83)	66 (35–86)	64 (41–82)	65 (34–84)
Sex, %	Male	68.9	74.3	70.3	71.0	73.0	69.0	72.0	71.0
	Female	31.1	25.7	29.7	29.0	27.0	31.0	28.0	29.0
ECOG PS, %	0	68.6	68.2	63.7	61.5	64.0	61.0	69.0	65.0
	1	31.4	31.8	36.3	38.5	36.0	39.0	31.0	35.0
Region, %	Asia	38.8	43.6	31.0[b]	30.2[b]	48.0	51.0	28.0	22.0
	Europe	38.5	37.4			23.0	14.0	54.0	55.0
	North America	11.7	11.5	69.0[c]	69.8[c]	23.0	28.0	10.0	9.0
	South America	10.9	7.5			-	-	8.0 (ROW)	15.0 (ROW)
Smoking status, %	Current/former	86.1	85.0	86.4	88.3	93.0	88.0	89.0	88.0
	Never	13.9	15.0	13.6	11.8	7.0	12.0	11.0	12.0
Disease stage (AJCC 8th edition)[a,d], %	II	28.4	29.4	29.7	30.3	35.0	35.0	36.0	35.0
	IIIA	47.3	44.1	54.7	56.3	65.0 (SIIIA/B)	65.0 (SIIIA/B)	64.0	65.0
	IIIB	**24.0**	**26.2**	15.6	13.5	Not separated	Not separated	Not studied	Not studied
Histology, %	Squamous	46.2	51.1	43.1	43.3	49.0	49.0	49.0	53.0
	Non-squamous	53.6	47.9	56.9	56.8	51.0	51.0	51.0	47.0
PD-L1 expression, %	TC <1%	33.3	33.4	34.8	37.8	41.0	43.0	44.0	43.0
	TC 1–49%	36.9	38.0	32.0	28.8	36.0	33.0	28.5	26.2
	TC ≥50%	29.8	28.6	33.2	33.5	20.0	22.0	21.2	23.5
Planned neoadjuvant platinum agent, %	Cisplatin	27.3	25.7	100.0	100.0	24.0	18.0	68.3	74.9
	Carboplatin	72.7	74.3	0.0	0.0	76.0	82.0	21.8	18.4

Pathologic Response

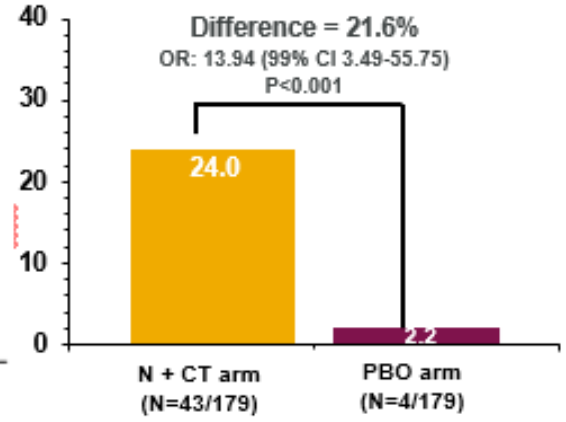
AEGEAN[1,a]



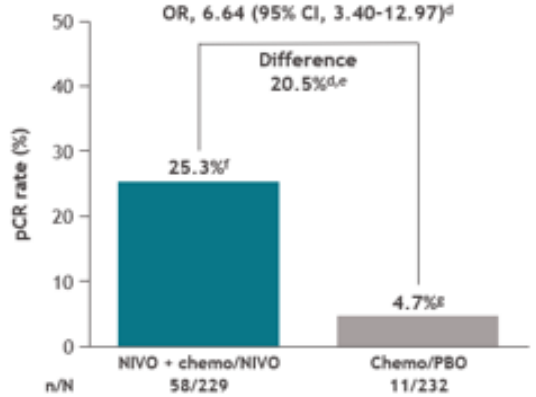
KEYNOTE-671[2,a]



CheckMate-816[4,c]

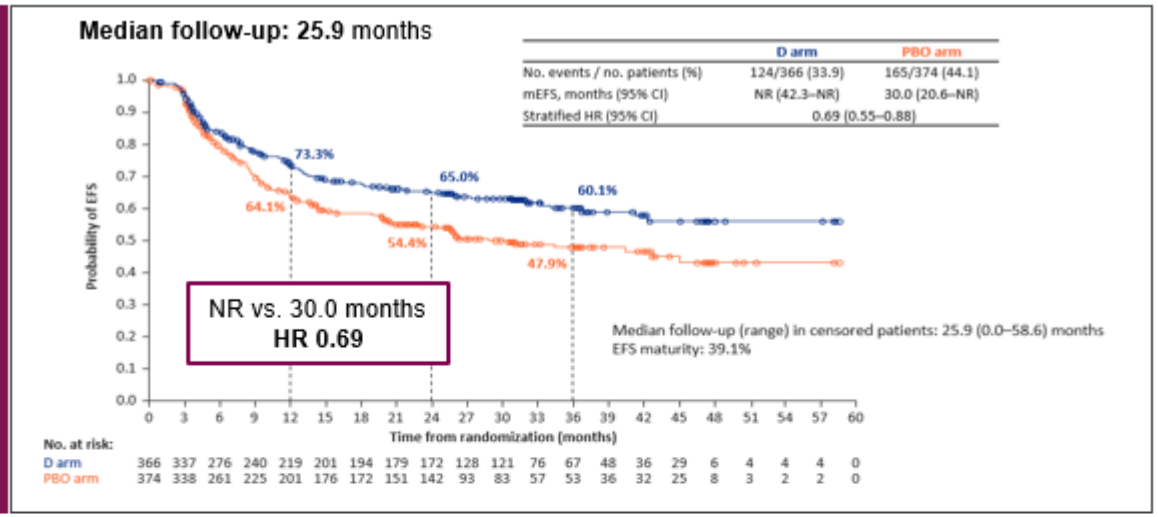


CheckMate-77T

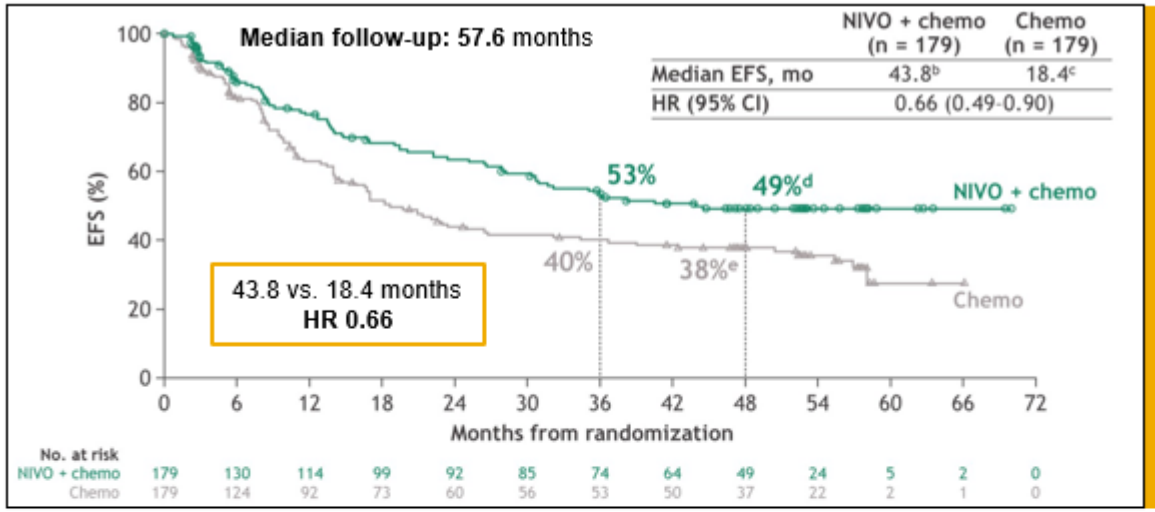


Event Free survival

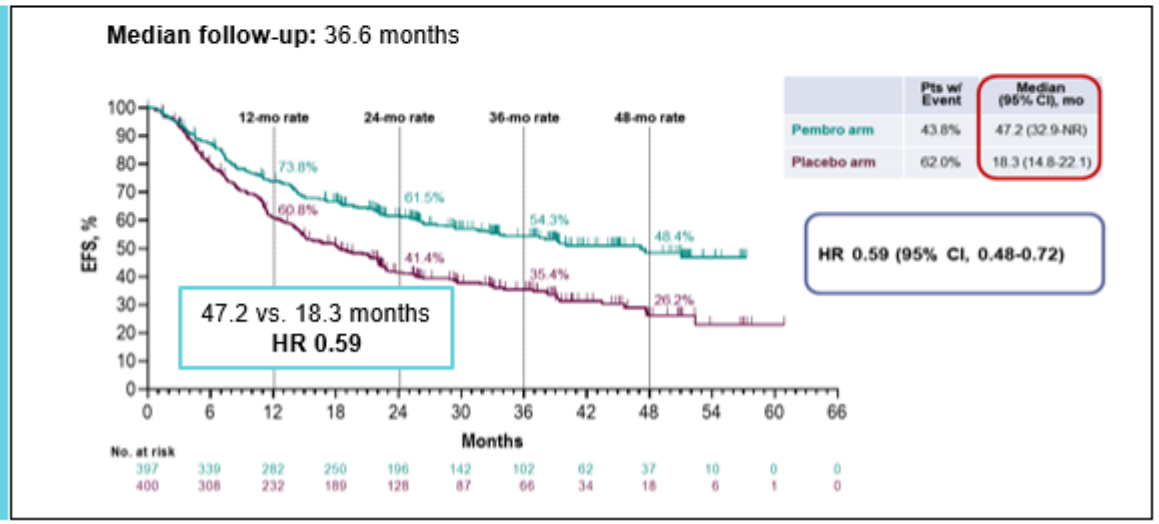
AEGEAN[1,a]



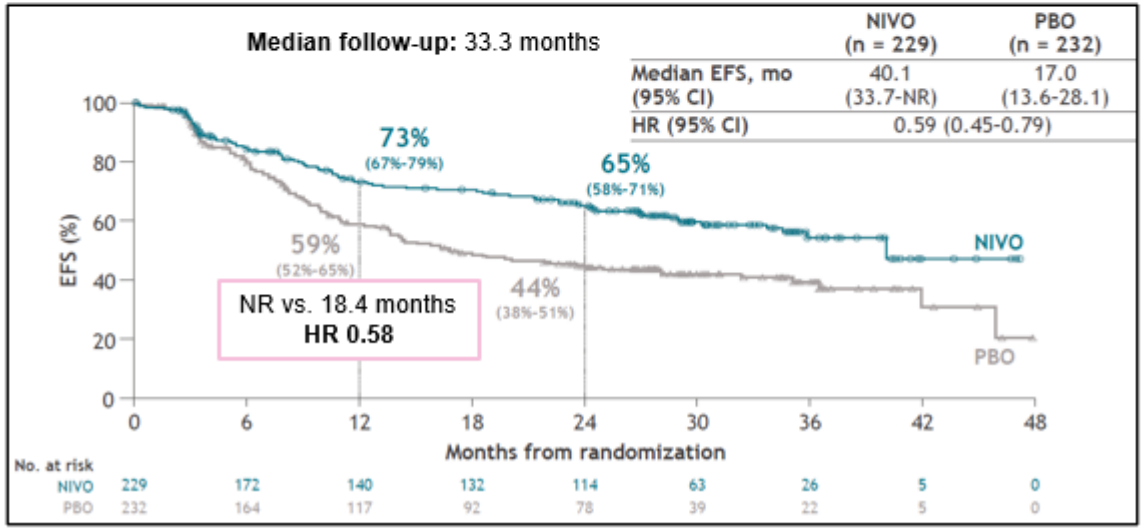
CheckMate-816[3]



KEYNOTE-671[2]



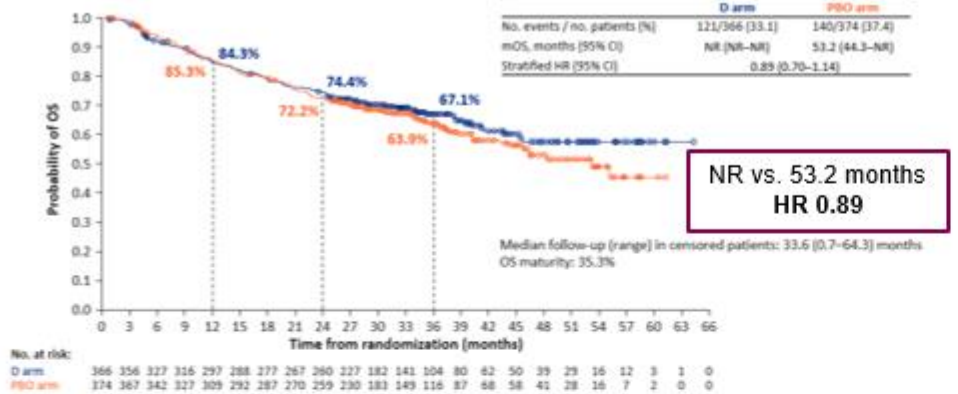
CheckMate 77T[4,*]



Overall Survival

AEGEAN[1]

Median follow-up: 33.6 months

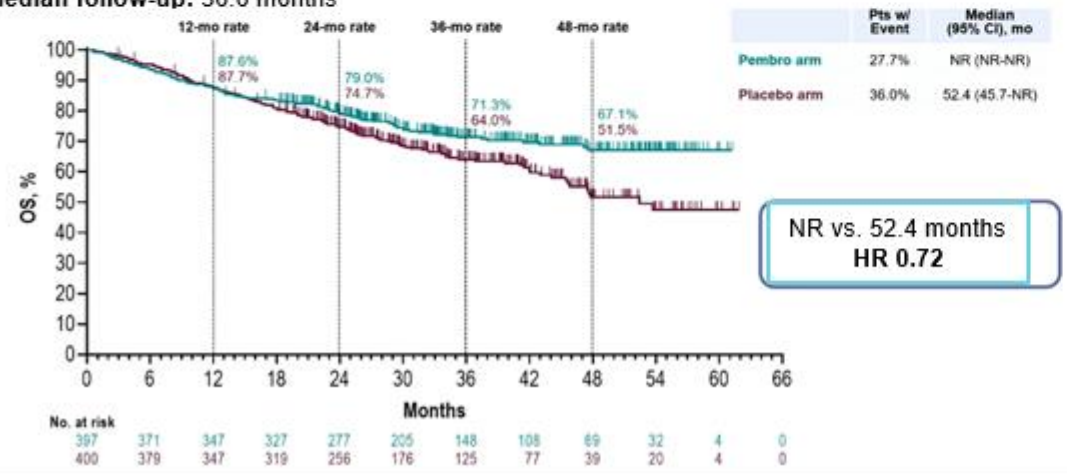


NR vs. 53.2 months
HR 0.89

Preplanned analysis censoring patients with cause of death due to COVID-19: OS HR = 0.84 (95% CI: 0.66–1.08)

KEYNOTE-671[2]

Median follow-up: 36.6 months



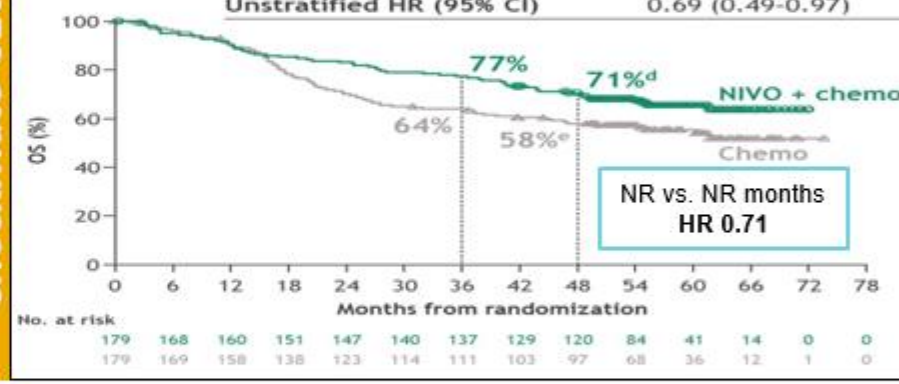
	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

NR vs. 52.4 months
HR 0.72

CheckMate-816[3]

Median follow-up: 57.6 months

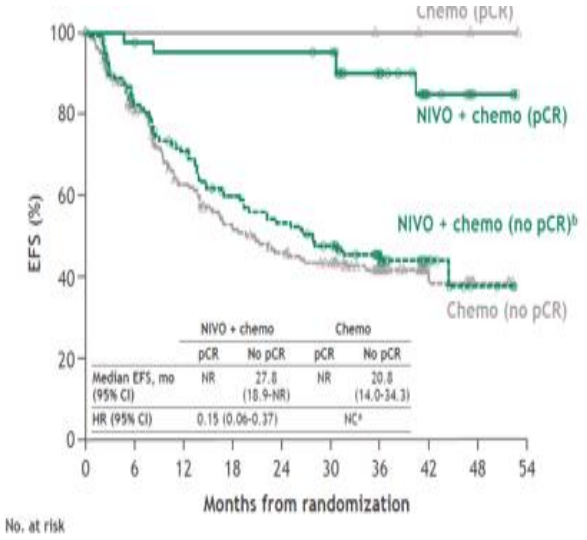
	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR[c]
HR (98.36% CI); *P* value	0.71 (0.47-1.07); 0.0451[b]	
Unstratified HR (95% CI)	0.69 (0.49-0.97)	



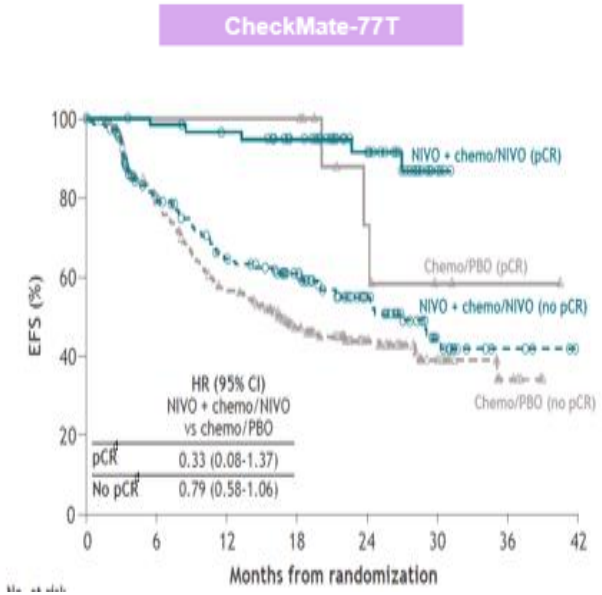
NR vs. NR months
HR 0.71

EFS by pCR

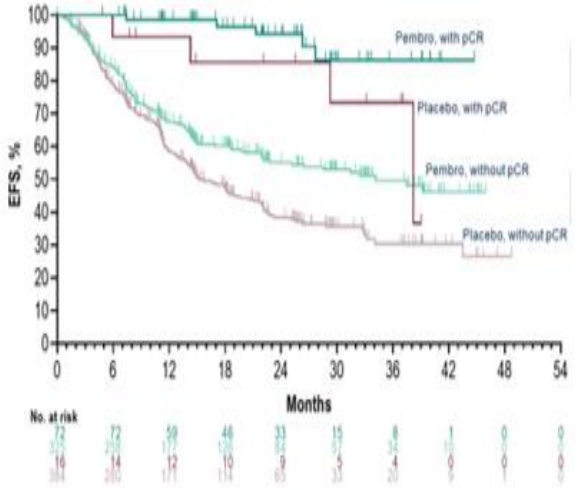
CheckMate-816[4,c]



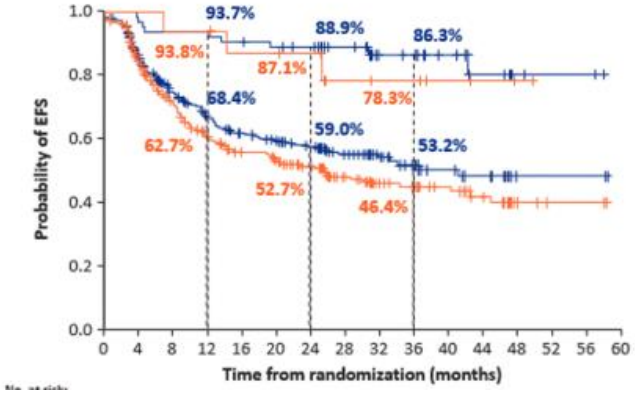
CheckMate-77T



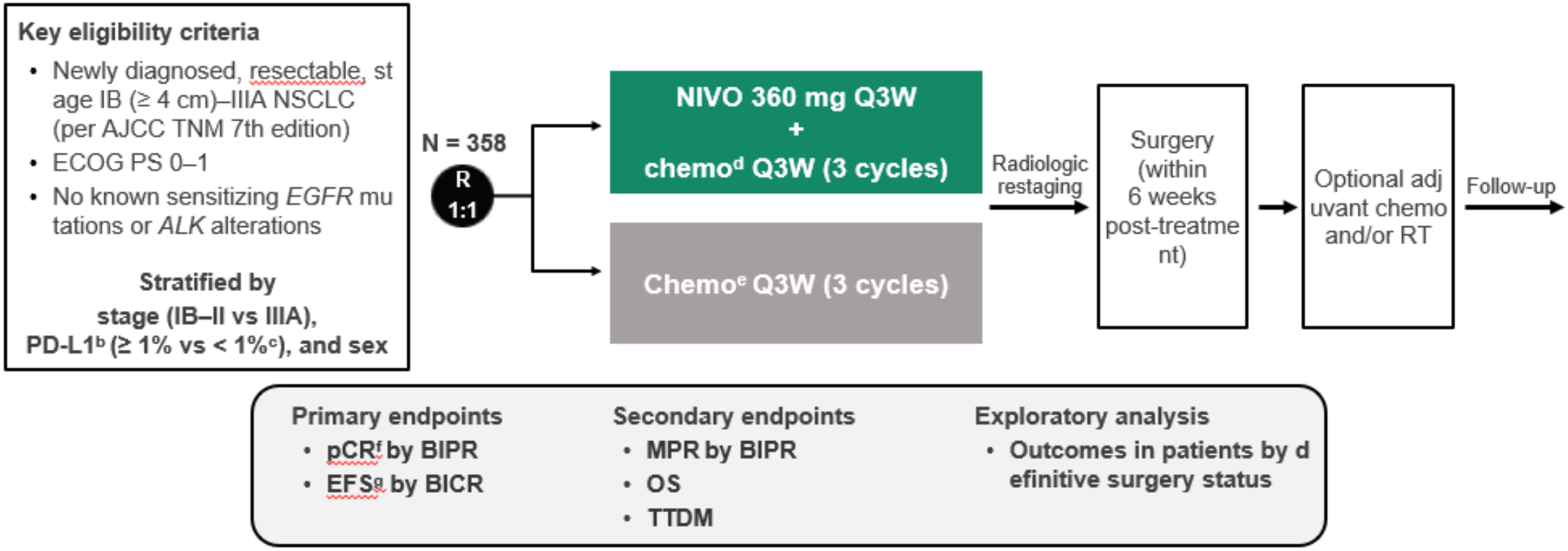
KEYNOTE-671[2,a]



AEGEAN[1,a]

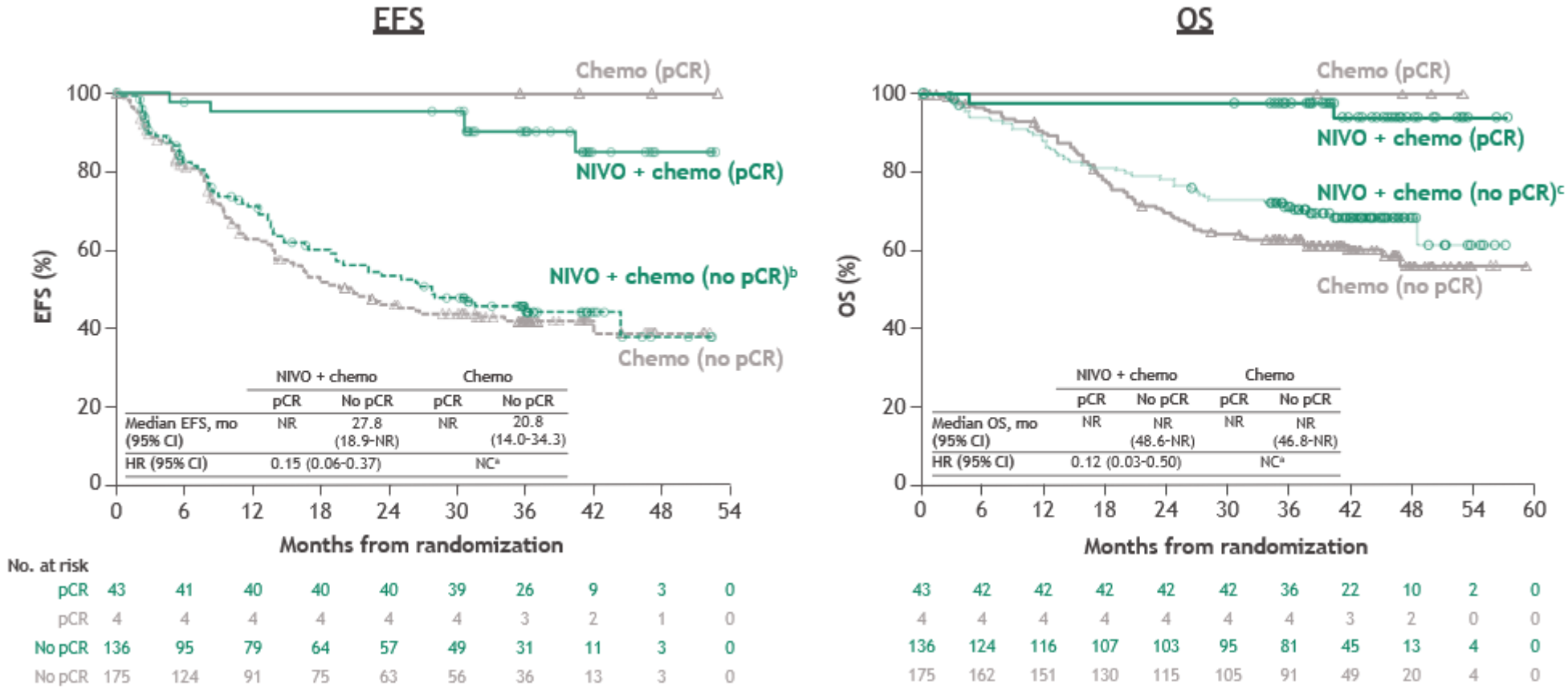


CheckMate 816 study design



ESMO 2023, CheckMate 816 (NIVO + chemo vs chemo): 3-y results by tumor PD-L1 expression

pCR after neoadjuvant chemoimmunotherapy
Is adjuvant immunotherapy necessary?



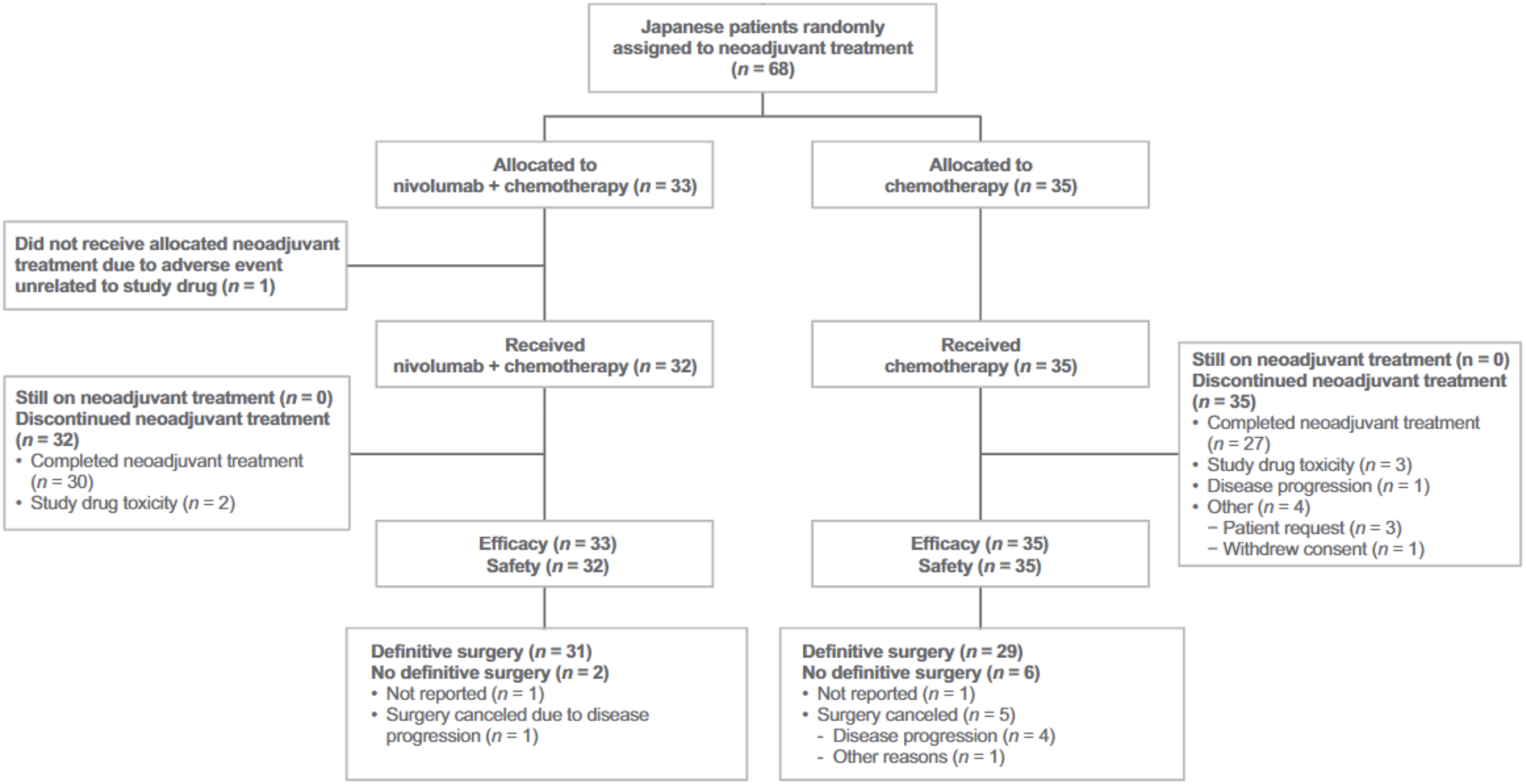
ESMO 2023, CheckMate 816 (NIVO + chemo vs chemo): 3-y results by tumor PD-L1 expression

Nearly 70% of patients do not achieve pathologic CR

Trial	No.	Stage	Systemic Regimen	No. Cycles	Primary Endpoint	pCR (%)	MPR (%)
CheckMate 816	358	IB-IIIA	Nivolumab/CTx	3	EFS, pCR	24	36.9
AEGEAN	802	IIA-IIIB	Durvalumab/CTx	4+12	EFS, pCR	17.2	33.3
Neotorch	501	IIIA-IIIB	Toripalimab/CTx	3+14	EFS, MPR	24.8	48.5
KEYNOTE-671	797	II-IIIB	Pembrolizumab/CTx	4+13	EFS, OS	18.1	30.2
CheckMate 77T	461	IIA-IIIB	Nivolumab/CTx	4+1 year	EFS	25.3	35.4
RATIONALE 315	453	IIA-IIIA	Tislelizumab/CTx	3-4+8	MPR, EFS	40.7	56.2
NADIM II	86	IIIA-B	Nivolumab/CTx	3+6 mon.	pCR	37	53

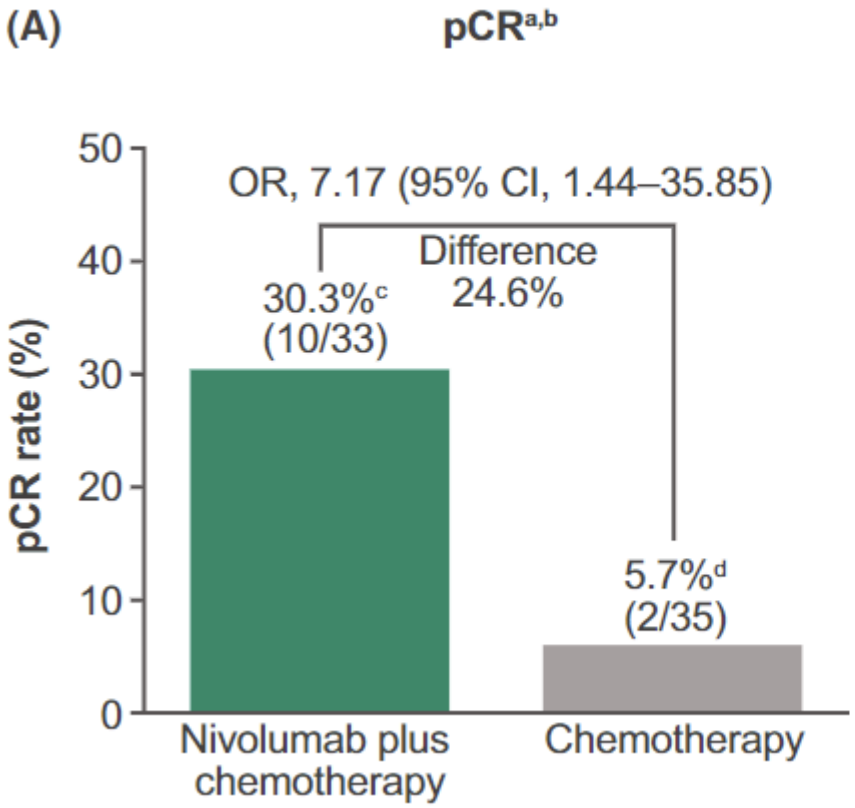
Neoadjuvant nivolumab plus chemotherapy in resectable NSCLC in Japanese patients from CheckMate 816

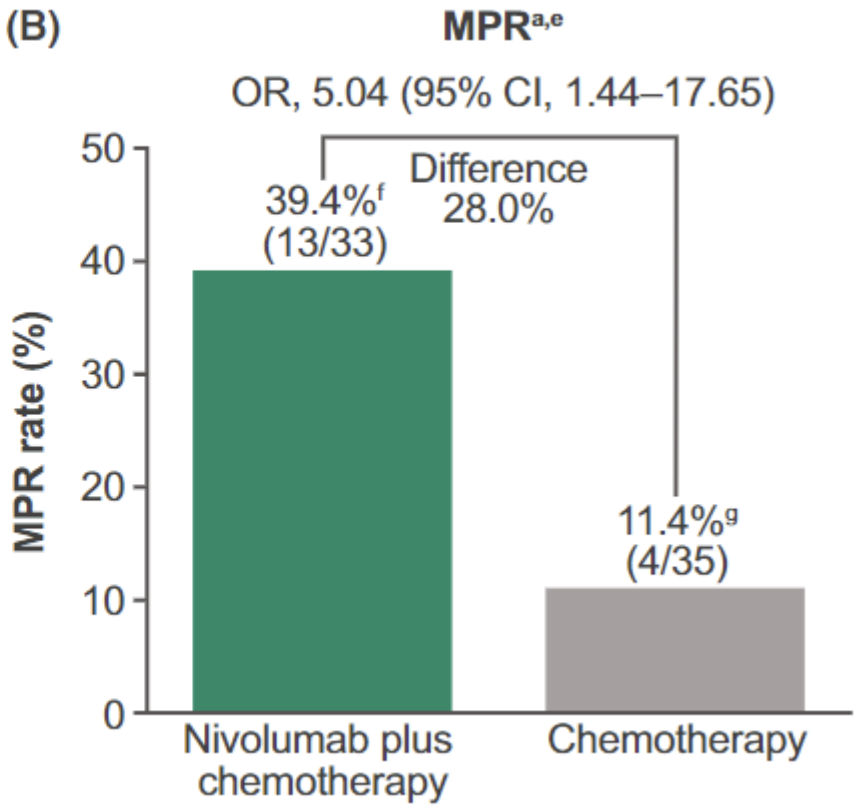
T. Mitsudomi et al Cancer Science(2024)



Neoadjuvant nivolumab plus chemotherapy in resectable NSCLC in Japanese patients from CheckMate 816

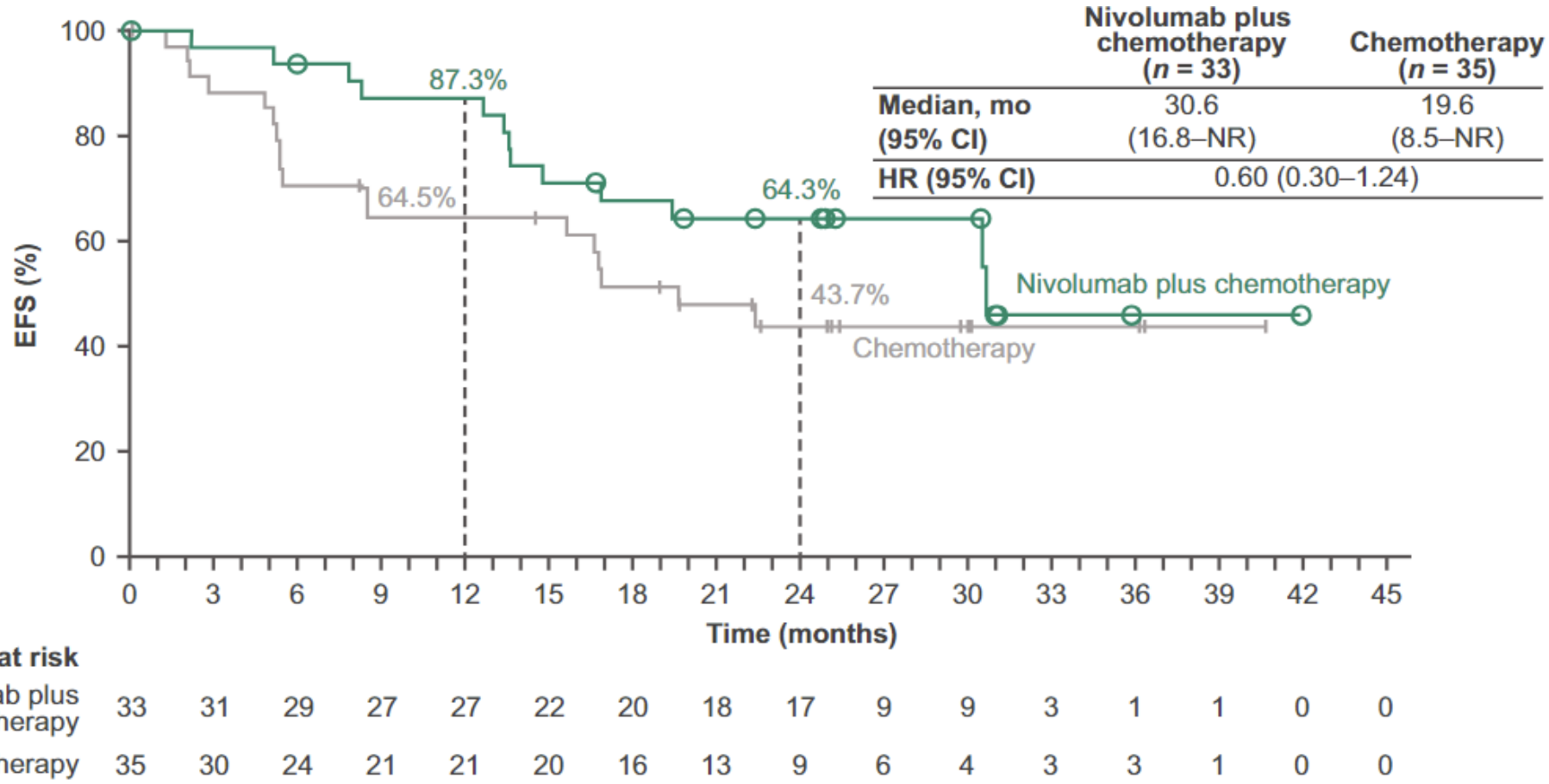
T. Mitsudomi et alCancer Science(2024)





Neoadjuvant nivolumab plus chemotherapy in resectable NSCLC in Japanese patients from CheckMate 816

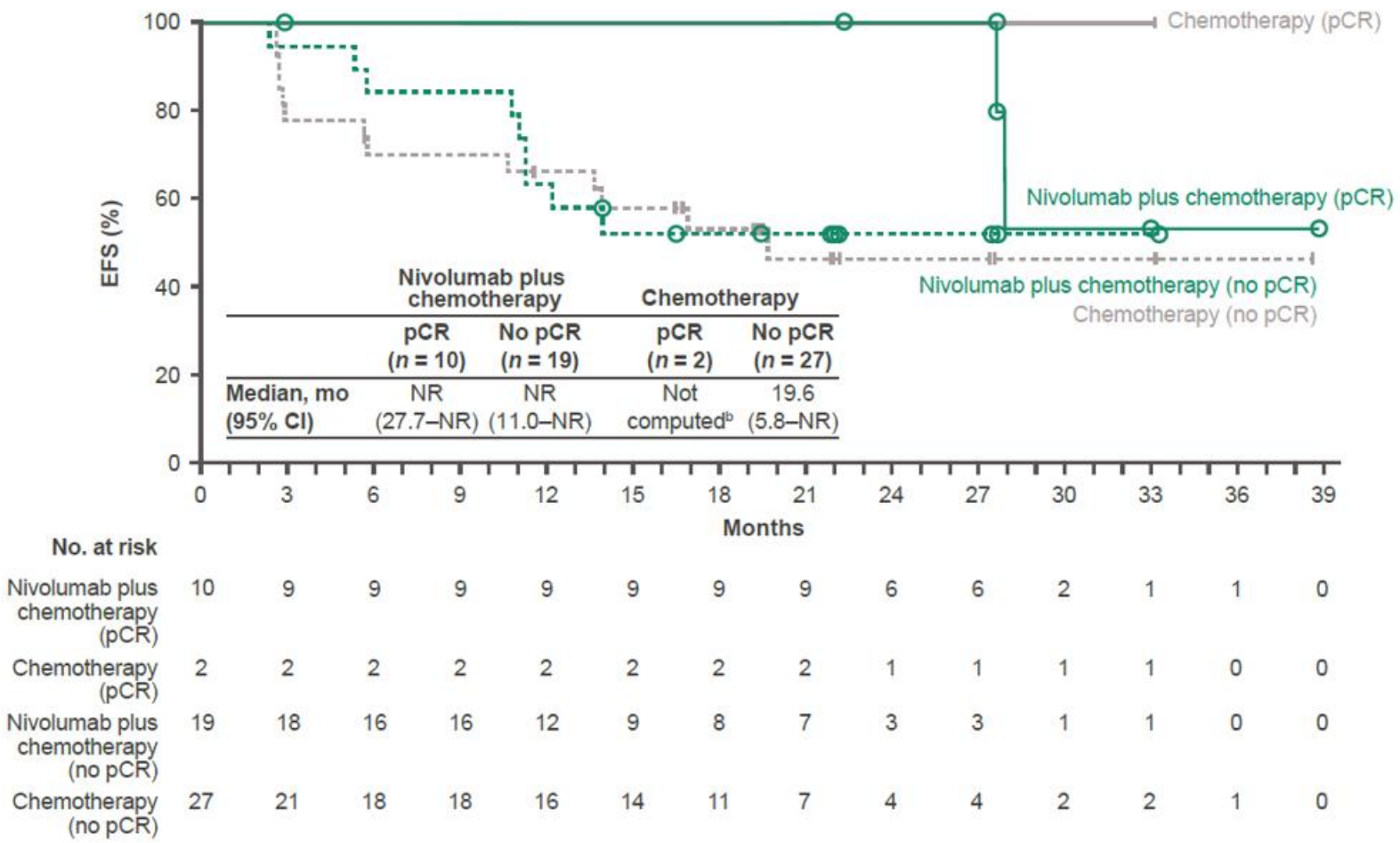
T. Mitsudomi et al Cancer Science(2024)



	Nivolumab plus chemotherapy (*n* = 33)	Chemotherapy (*n* = 35)
Median, mo (95% CI)	30.6 (16.8–NR)	19.6 (8.5–NR)
HR (95% CI)	0.60 (0.30–1.24)	

Neoadjuvant nivolumab plus chemotherapy in resectable NSCLC in Japanese patients from CheckMate 816

T. Mitsudomi et al Cancer Science(2024)



Perioperative vs neoadjuvant nivolumab for resectable NSCLC: Patient-level data analysis of CheckMate 77T vs CheckMate 816

Forde PM et al. WCLC 2024

Abstract PL02.08

CheckMate 77T vs CheckMate 816: Patient-level data analysis

CheckMate 816 (NCT02998528): A randomized open-label, phase 3 trial of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy vs platinum-doublet chemotherapy in early-stage NSCLC[1,4,5]

CheckMate 77T (NCT04025879): A phase 3 randomized, double-blind study of neoadjuvant nivolumab plus chemotherapy vs chemotherapy alone, followed by surgical resection and adjuvant treatment with nivolumab or placebo for patients with resectable stage II–IIIB NSCLC[1–3]

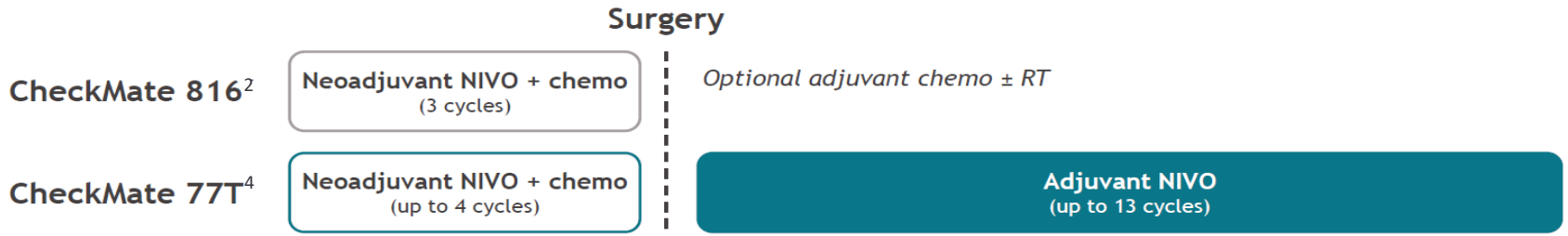


Image used with permission from: Forde et al. 2024.

Analysis patient populations

- **CheckMate 816:** patients who had surgery
- **CheckMate 77T:** patients who had surgery and received ≥1 dose of adjuvant NIVO

Endpoint

- EFS (BICR) landmarked from time of surgery

Median follow-up durations

- CheckMate 816: 29.5 months
- CheckMate 77T: 33.3 months

Database locks

- CheckMate 816: 20 October 2021
- CheckMate 77T: 26 April 2024

	Unweighted[a]	
	Perioperative NIVO (n = 139), %	Neoadjuvant NIVO + chemo (n = 147), %
Age < 65 years	48	52
Male	73	69
Asian	27	50
ECOG PS ≥ 1	33	25
Disease stage		
Stage IB-II	35	37
Stage III non-N2	24	16
Stage III N2	40	47
Squamous NSCLC	50	46
Current/former smoker,[b]	94	90
Tumor PD-L1 expression ≥ 1%	58	50

Image used with permission from: Forde et al. 2024.

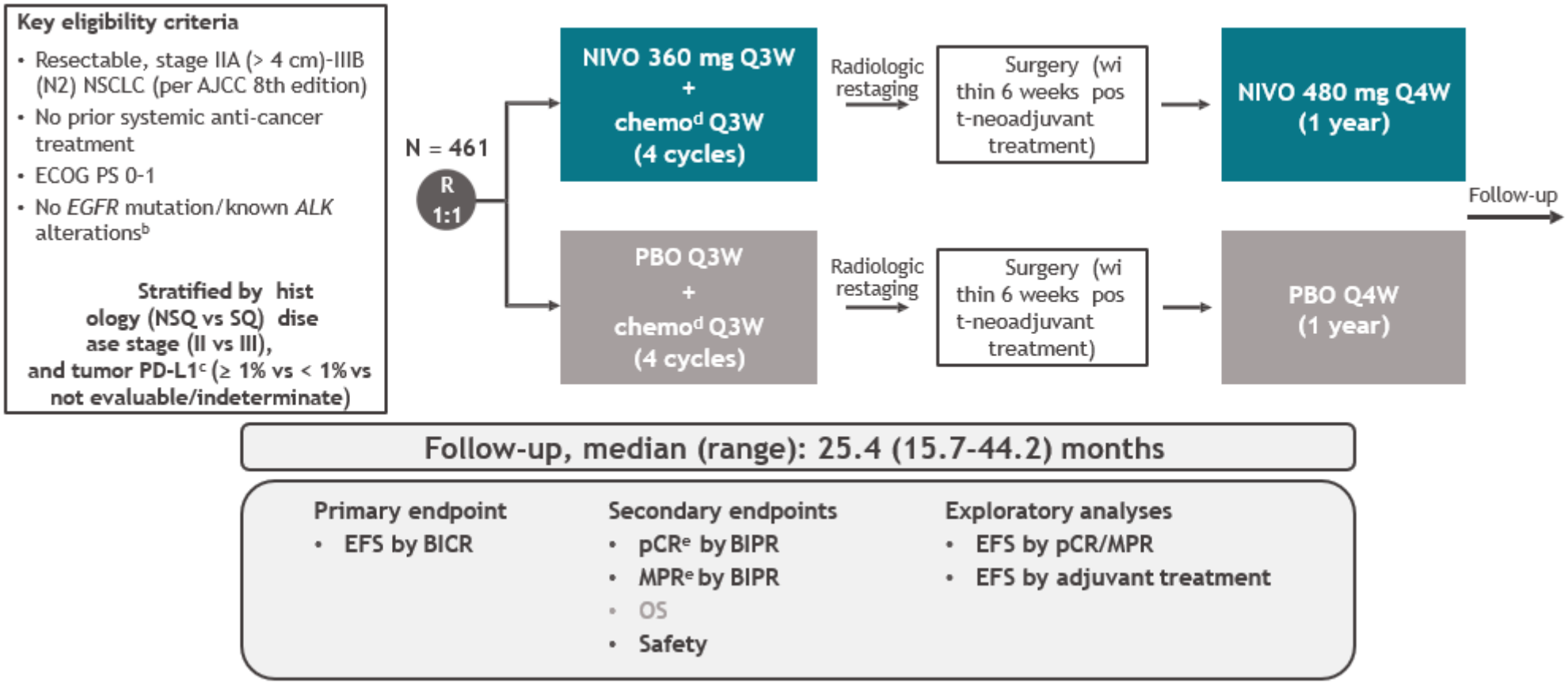
Baseline characteristics between patients who received perioperative NIVO or neoadjuvant NIVO + chemo were generally balanced after propensity score weighting (ATT and ATE)[c]

[a]Patients missing any variable used in propensity score computation were excluded from analyses; includes only patients with an EFS time at least up to the surgery; [b]Includes patients with unknown smoking status; [c]ATT: varying weights were applied to patients in the neoadjuvant NIVO + chemo arm (CheckMate 816) to make them comparable to those in the perioperative NIVO arm (CheckMate 77T). ATE: varying weights were applied to all patients in both neoadjuvant NIVO + chemo arm (CheckMate 816) and perioperative NIVO (CheckMate 77T) to make them comparable to one another.

ATE, average treatment effect; ATT, average treatment effect for the treated; chemo, chemotherapy; EFS, event-free survival; NIVO, nivolumab; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1 ; RT, radiotherapy.

1. Forde PM et al. Presented at: World Conference on Lung Cancer; 7–10 September 2024; San Diego, CA. Abstract PL02.08; 2. Cascone T et al. *N Engl J Med.* 2024;390(19):1756–1769; 3. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04025879. Accessed: 10 September 2024; 4. Forde PM et al. *N Engl J Med.* 2022;386(21):1973-1985; 5. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT02998528. Accessed: 10 September 2024.

CheckMate 77T study design



ESMO 2013 CheckMate 77T: perioperative NIVO in resectable NSCLC

CheckMate 77T vs CheckMate 816: Patient-level data analysis

Landmark EFS (BICR) from definitive surgery

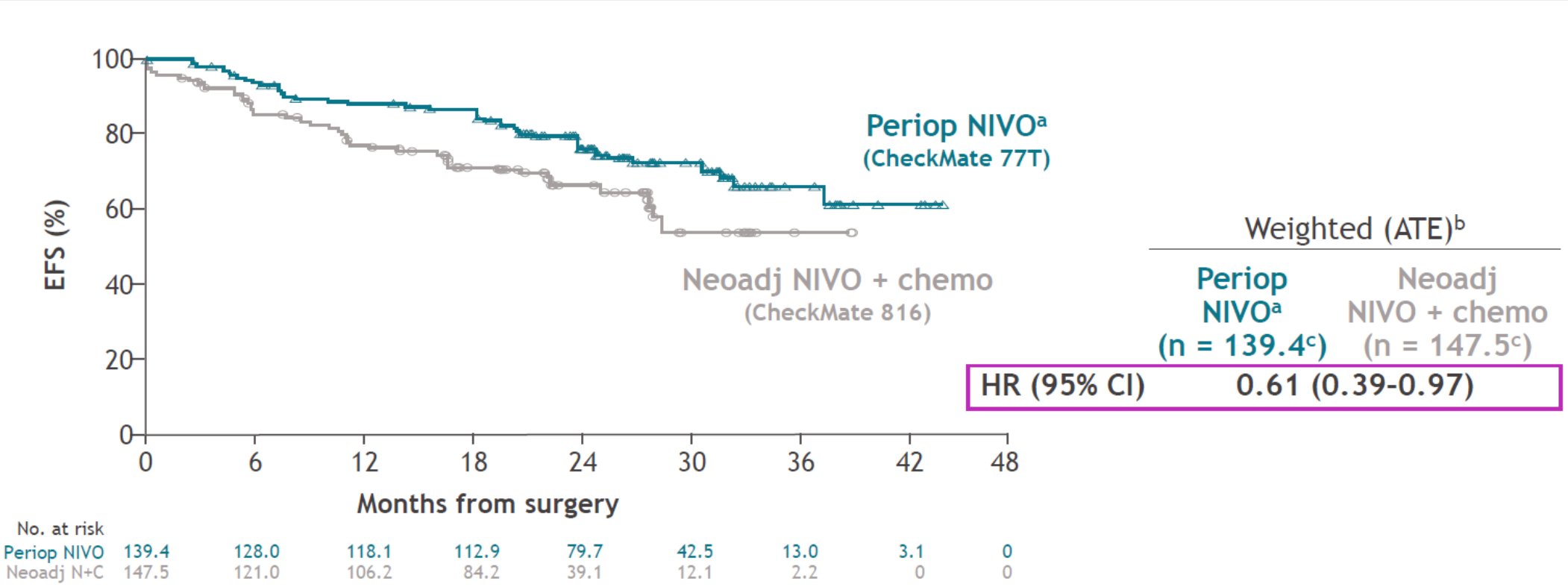


Image used with permission from: Forde et al. 2024.

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

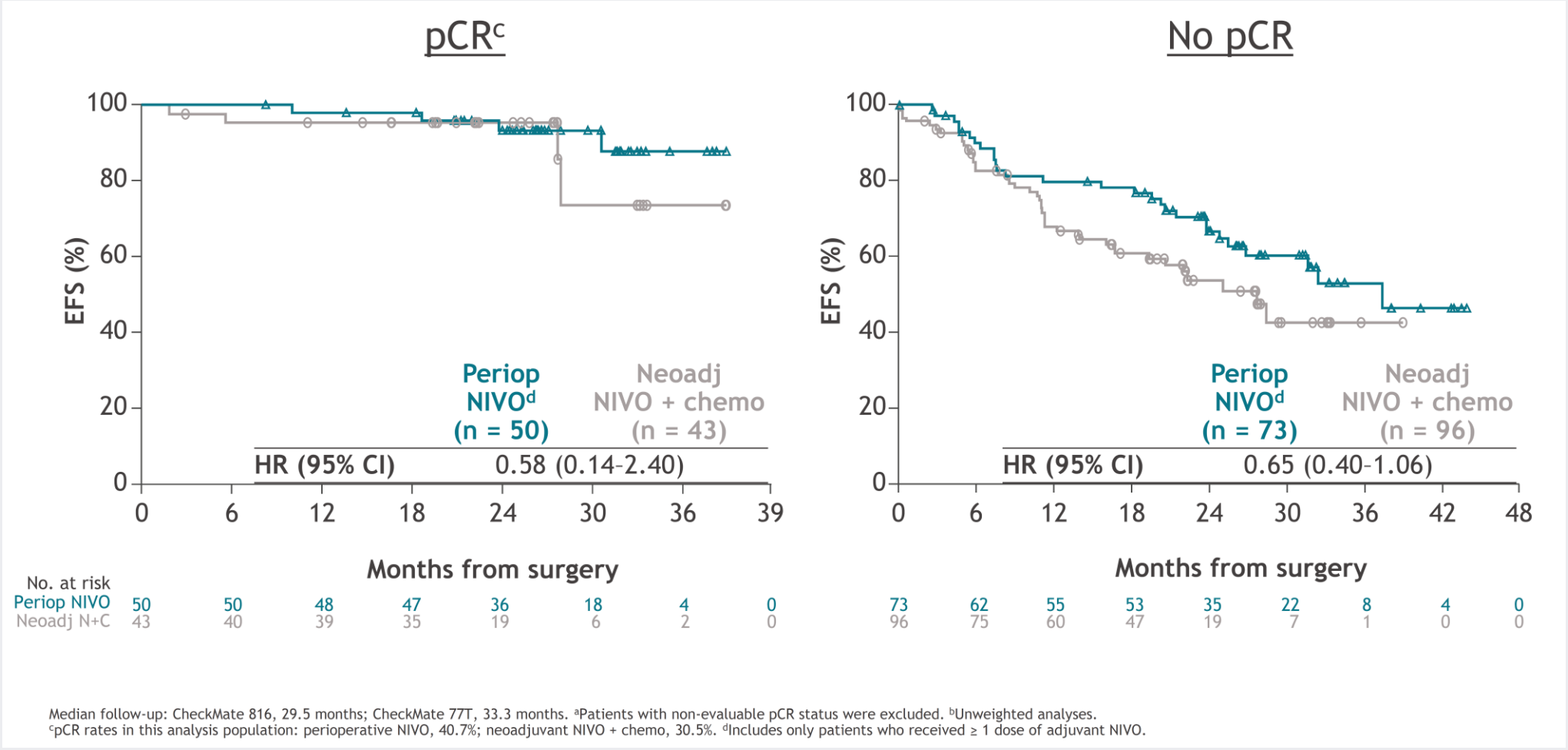
In the unweighted analysis population, 89 patients (64%) completed adjuvant therapy, and the median number (range) of doses was 13.0 (1-13). Unweighted landmark EFS from surgery among all patients who had surgery (regardless of whether they received adjuvant NIVO in CheckMate 77T) for perioperative NIVO vs neoadjuvant NIVO + chemo: HR 0.82 (95% CI 0.55–1.21).

[a]Includes only patients who received ≥1 dose of adjuvant NIVO; [b]ATE: varying weights were applied to all patients in both the neoadjuvant NIVO + chemo arm (CheckMate 816) and the perioperative NIVO (CheckMate 77T) to make them comparable to each other; [c]n values are fractional due to weighting; [d]ATT: varying weights were applied to patients in the neoadjuvant NIVO + chemo arm (CheckMate 816) to make them comparable to those in the perioperative NIVO arm (CheckMate 77T).

ATE, average treatment effect; ATT average treatment effect for the treated; chemo, chemotherapy; EFS, event-free survival; NIVO, nivolumab; NSCLC, non-small cell lung cancer; Neoadj, neoadjuvant; Periop, perioperative.

Forde PM et al. Presented at: World Conference on Lung Cancer; 7–10 September 2024; San Diego, CA. Abstract PL02.08.

CheckMate 77T vs CheckMate 816: Patient-level data analysis



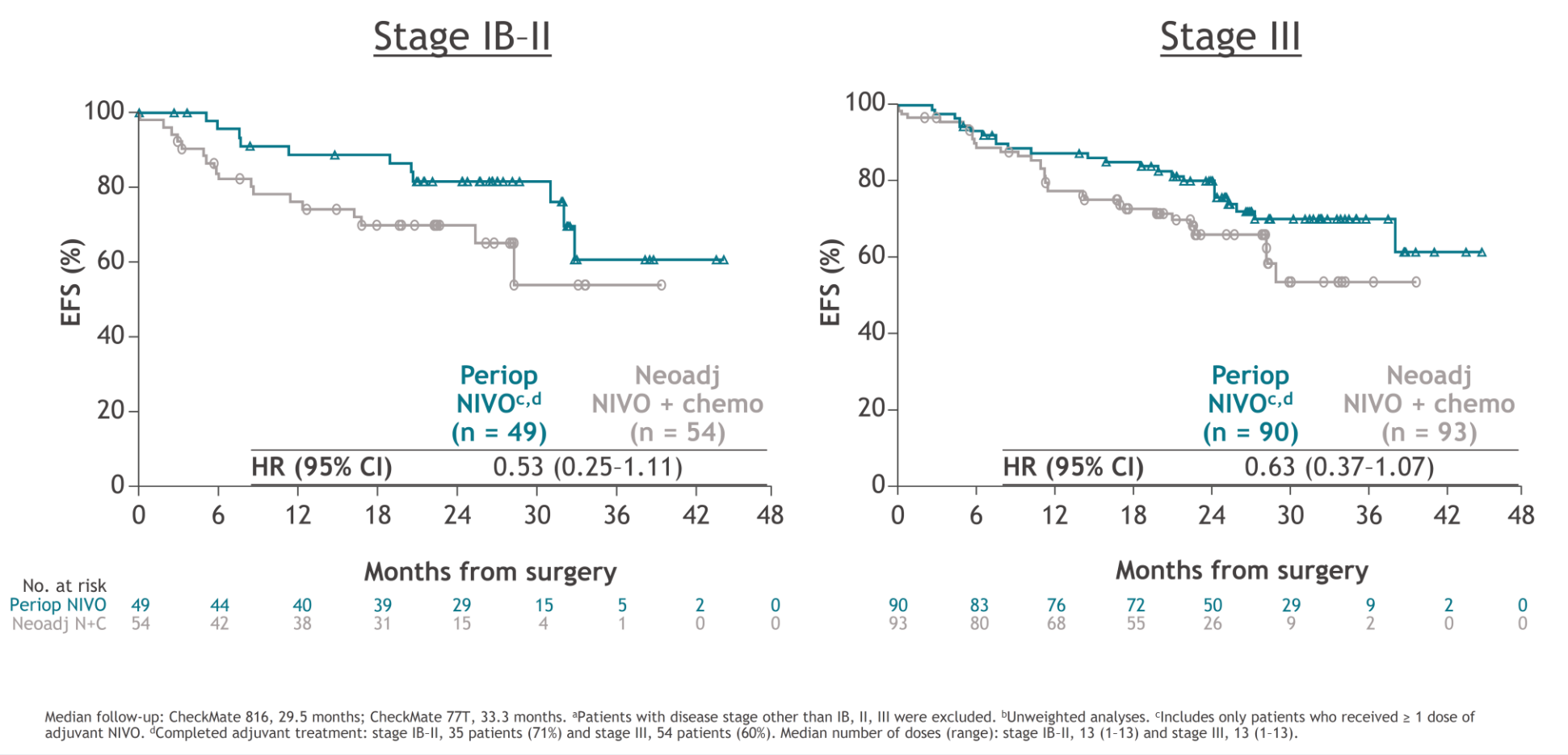
Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. [a]Patients with non-evaluable pCR status were excluded. [b]Unweighted analyses.
[c]pCR rates in this analysis population: perioperative NIVO, 40.7%; neoadjuvant NIVO + chemo, 30.5%. [d]Includes only patients who received ≥ 1 dose of adjuvant NIVO.

Image used with permission from: Forde et al. 2024.

chemo, chemotherapy; EFS, event-free survival; NIVO, nivolumab; pCR, pathologic complete response..

Forde PM et al. Presented at: World Conference on Lung Cancer; 7–10 September 2024; San Diego, CA. Abstract PL02.08.

CheckMate 77T vs CheckMate 816: Patient-level data analysis



Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. [a]Patients with disease stage other than IB, II, III were excluded. [b]Unweighted analyses. [c]Includes only patients who received ≥ 1 dose of adjuvant NIVO. [d]Completed adjuvant treatment: stage IB-II, 35 patients (71%) and stage III, 54 patients (60%). Median number of doses (range): stage IB-II, 13 (1-13) and stage III, 13 (1-13).

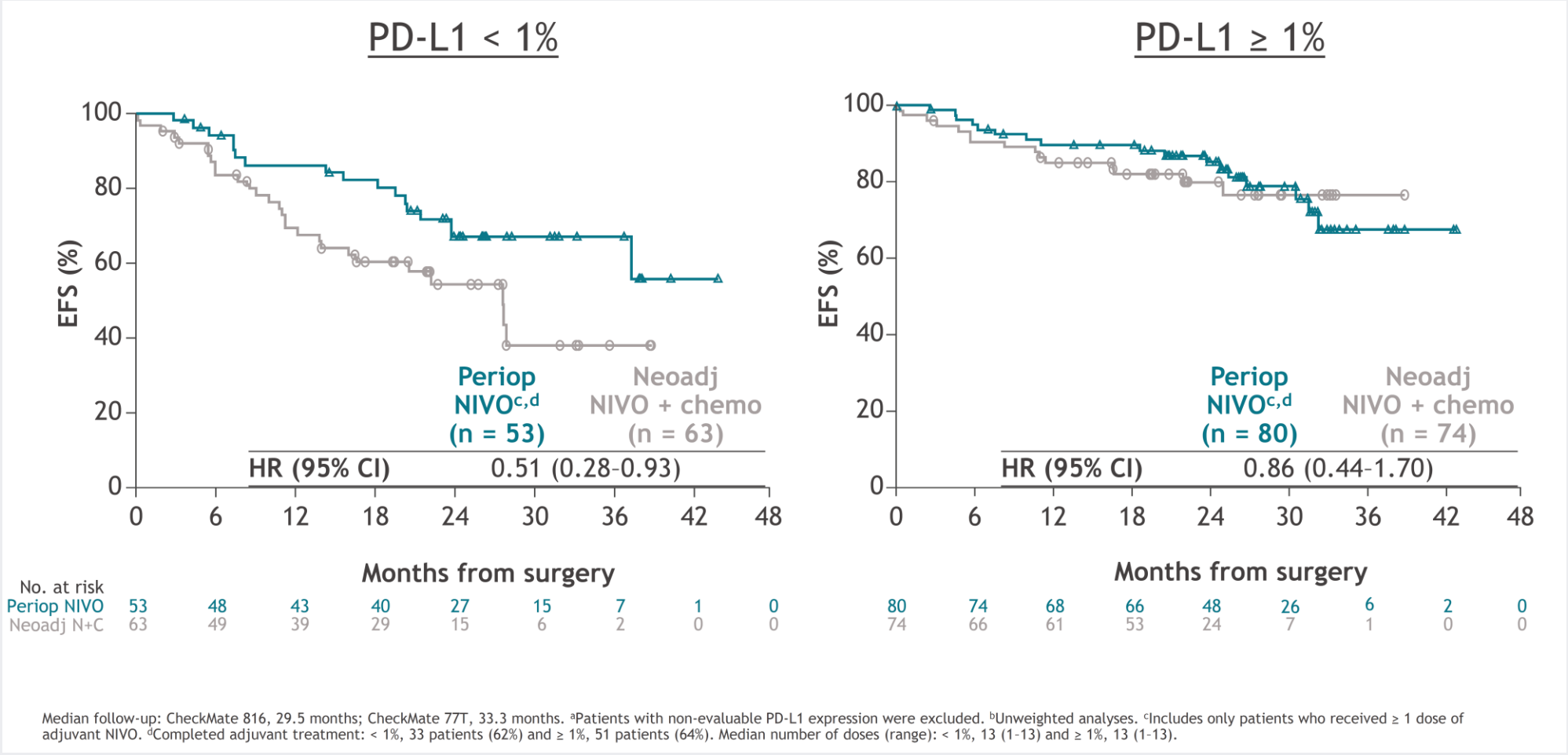
Image used with permission from: Forde et al. 2024.

chemo, chemotherapy; EFS, event-free survival; NIVO, nivolumab.

Forde PM et al. Presented at: World Conference on Lung Cancer; 7–10 September 2024; San Diego, CA. Abstract PL02.08.

CheckMate 77T vs CheckMate 816: Patient-level data analysis

Landmark EFS by tumor PD-L1 expression[a,b]



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

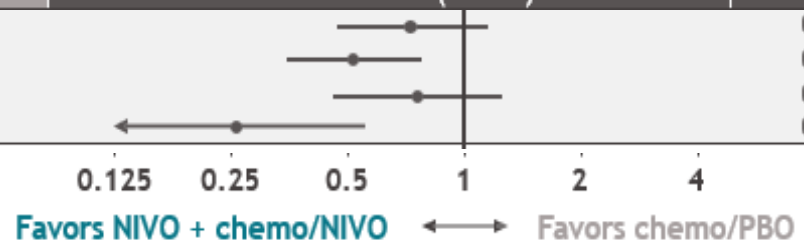
Image used with permission from: Forde et al. 2024.

chemo, chemotherapy; EFS, event-free survival; NIVO, nivolumab; PD-L1, programmed cell death-ligand 1.

Forde PM et al. Presented at: World Conference on Lung Cancer; 7–10 September 2024; San Diego, CA. Abstract PL02.08.

CheckMate 77T : EFS by PD-L1 expression

	Median EFS,[a] mo		Unstratified HR (95% CI)	Unstratified HR (95% CI)
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)		
PD-L1 < 1% (n = 186)[d]	29.0	19.8		0.73 (0.47-1.15)
PD-L1 ≥ 1% (n = 256)[d]	NR	15.8		0.52 (0.35-0.78)
PD-L1 1-49% (n = 159)[e]	30.2	28.1		0.76 (0.46-1.25)
PD-L1 ≥ 50% (n = 97)	NR	8.0		0.26 (0.12-0.55)



Median follow-up (range): 25.4 months (15.7-44.2).
[a]Per BICR. [b]Nodal status was N3 in 4 patients. [c]N2 subcategory was not reported in 1 patient.Baseline characteristics were similar across treatment arms in the N2 nodal status subgroup, which comprised ~40% of patients. [d]Tumor PD-L1 expression was not evaluable/indeterminate in 19 patients. [e]Most patients in this subgroup had low PD-L1 expression

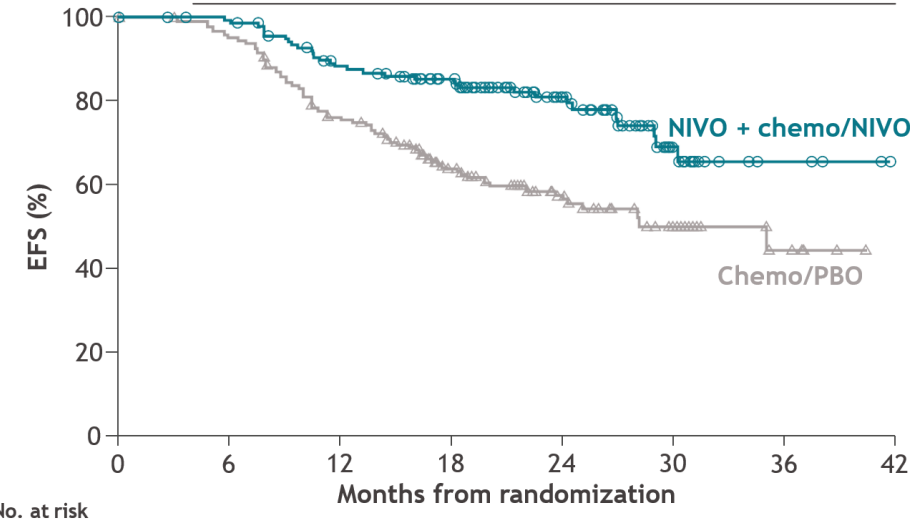
CheckMate 816 : EFS by PD-L1 expression

	Median EFS[a], mo		Unstratified HR (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
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

CheckMate-77T : Adjuvant treatment status

Adjuvant

	NIVO + chemo/NIVO (n = 142)	Chemo/PBO (n = 152)
Median EFS, mo (95% CI)	NR (NR-NR)	35.1 (22.0-NR)
HR (95% CI)	0.45 (0.29-0.69)	

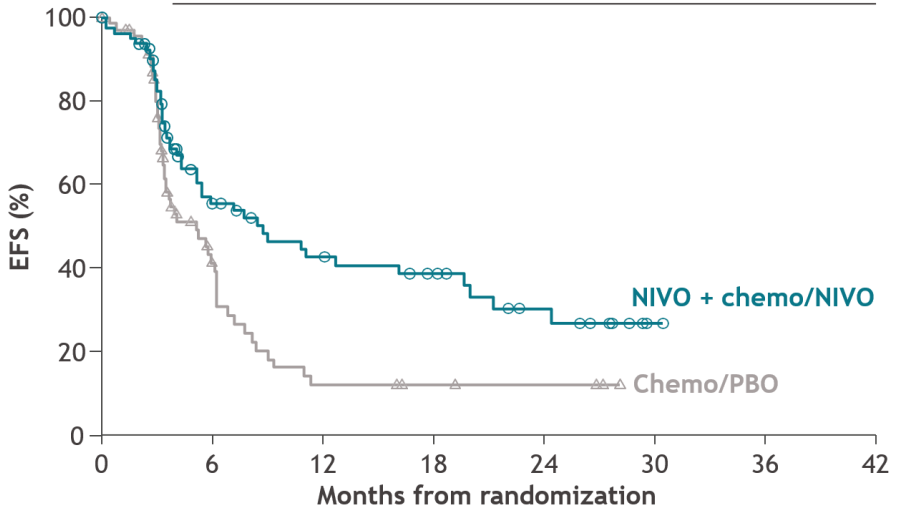


No. at risk

NIVO + chemo/NIVO	142	139	118	97	60	19	4	0
Chemo/PBO	152	144	112	74	41	19	6	0

No adjuvant

	NIVO + chemo/NIVO (n = 87)	Chemo/PBO (n = 80)
Median EFS, mo (95% CI)	8.8 (5.2-19.7)	5.2 (3.4-6.2)
HR (95% CI)	0.55 (0.37-0.83)	



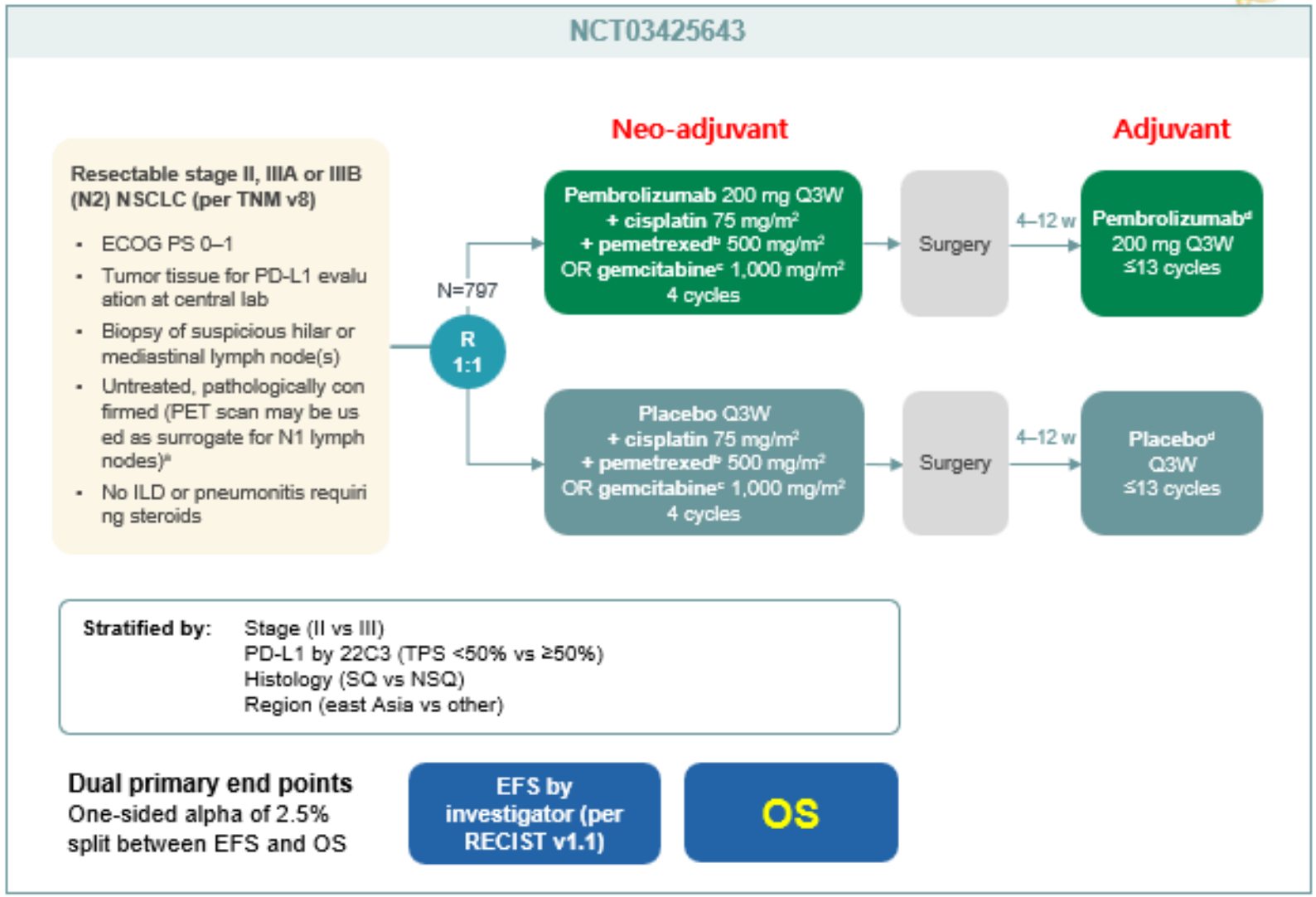
NIVO + chemo/NIVO	87	34	23	18	9	1	0	0
Chemo/PBO	80	21	6	4	3	0	0	0

- NIVO + chemo/NIVO improved EFS vs chemo/PBO with numerically higher benefit in patients who received adjuvant treatment (HR [95% CI], 0.45 [0.29-0.69]) vs those who did not (HR [95% CI], 0.55 [0.37-0.83])[a]

KEYNOTE-671 Study design

Study design

- Randomized Phase 3, placebo-controlled study **perioperative pembrolizumab**
  - Enrolled stage II–IIIB (N2) NSCLC
  - EGFR/ALKm permitted
- Up to 4 cycles neoadjuvant therapy, and up to 13 cycles of adjuvant therapy
- Dual primary end points: EFS and OS in ITT
  - EFS defined as time from randomisation to first occurrence of:
    - (i) local PD precluding surgery,
    - (ii) unresectable tumor,
    - (iii) progression or recurrence per RECIST v1.1 by investigator,
    - (iv) death from any cause



Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial

J. D. Spicer et al. The Lancet(2024)

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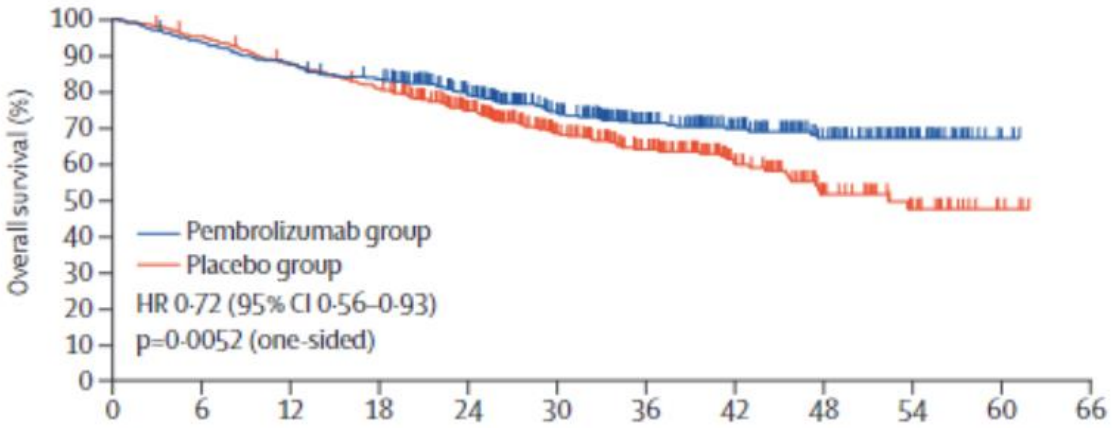
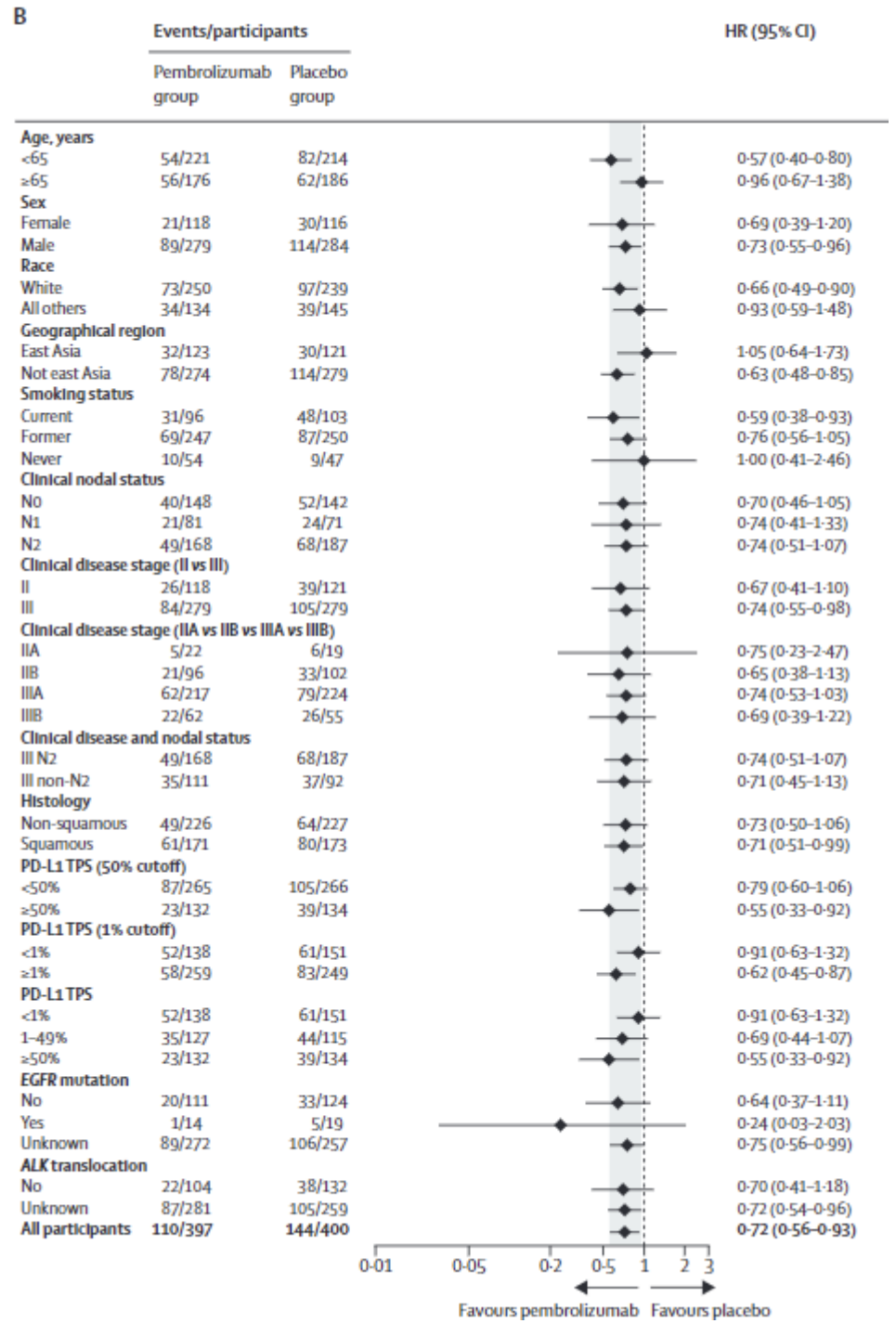


Number at risk (number censored)												
Pembrolizumab group	397	371	347	327	277	205	148	108	69	32	4	0
	(0)	(1)	(1)	(4)	(38)	(95)	(145)	(182)	(218)	(255)	(283)	(287)
Placebo group	400	379	347	319	256	176	125	77	39	20	4	0
	(0)	(2)	(4)	(5)	(45)	(106)	(147)	(190)	(219)	(236)	(252)	(256)

B



	Events/participants: Pembrolizumab group	Events/participants: Placebo group	HR (95% CI)
Age, years			
<65	54/221	82/214	0·57 (0·40–0·80)
≥65	56/176	62/186	0·96 (0·67–1·38)
Sex			
Female	21/118	30/116	0·69 (0·39–1·20)
Male	89/279	114/284	0·73 (0·55–0·96)
Race			
White	73/250	97/239	0·66 (0·49–0·90)
All others	34/134	39/145	0·93 (0·59–1·48)
Geographical region			
East Asia	32/123	30/121	1·05 (0·64–1·73)
Not east Asia	78/274	114/279	0·63 (0·48–0·85)
Smoking status			
Current	31/96	48/103	0·59 (0·38–0·93)
Former	69/247	87/250	0·76 (0·56–1·05)
Never	10/54	9/47	1·00 (0·41–2·46)
Clinical nodal status			
N0	40/148	52/142	0·70 (0·46–1·05)
N1	21/81	24/71	0·74 (0·41–1·33)
N2	49/168	68/187	0·74 (0·51–1·07)
Clinical disease stage (II vs III)			
II	26/118	39/121	0·67 (0·41–1·10)
III	84/279	105/279	0·74 (0·55–0·98)
Clinical disease stage (IIA vs IIB vs IIIA vs IIIB)			
IIA	5/22	6/19	0·75 (0·23–2·47)
IIB	21/96	33/102	0·65 (0·38–1·13)
IIIA	62/217	79/224	0·74 (0·53–1·03)
IIIB	22/62	26/55	0·69 (0·39–1·22)
Clinical disease and nodal status			
III N2	49/168	68/187	0·74 (0·51–1·07)
III non-N2	35/111	37/92	0·71 (0·45–1·13)
Histology			
Non-squamous	49/226	64/227	0·73 (0·50–1·06)
Squamous	61/171	80/173	0·71 (0·51–0·99)
PD-L1 TPS (50% cutoff)			
<50%	87/265	105/266	0·79 (0·60–1·06)
≥50%	23/132	39/134	0·55 (0·33–0·92)
PD-L1 TPS (1% cutoff)			
<1%	52/138	61/151	0·91 (0·63–1·32)
≥1%	58/259	83/249	0·62 (0·45–0·87)
PD-L1 TPS			
<1%	52/138	61/151	0·91 (0·63–1·32)
1–49%	35/127	44/115	0·69 (0·44–1·07)
≥50%	23/132	39/134	0·55 (0·33–0·92)
***EGFR* mutation**			
No	20/111	33/124	0·64 (0·37–1·11)
Yes	1/14	5/19	0·24 (0·03–2·03)
Unknown	89/272	106/257	0·75 (0·56–0·99)
***ALK* translocation**			
No	22/104	38/132	0·70 (0·41–1·18)
Unknown	87/281	105/259	0·72 (0·54–0·96)
All participants	**110/397**	**144/400**	**0·72 (0·56–0·93)**

Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial

J. D. Spicer et al. The Lancet(2024)

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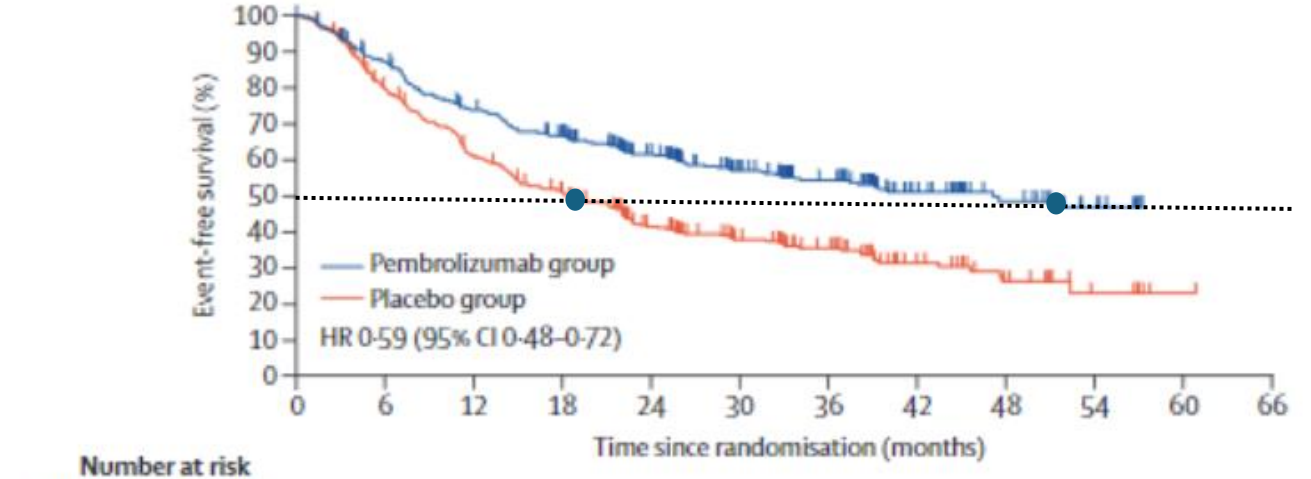
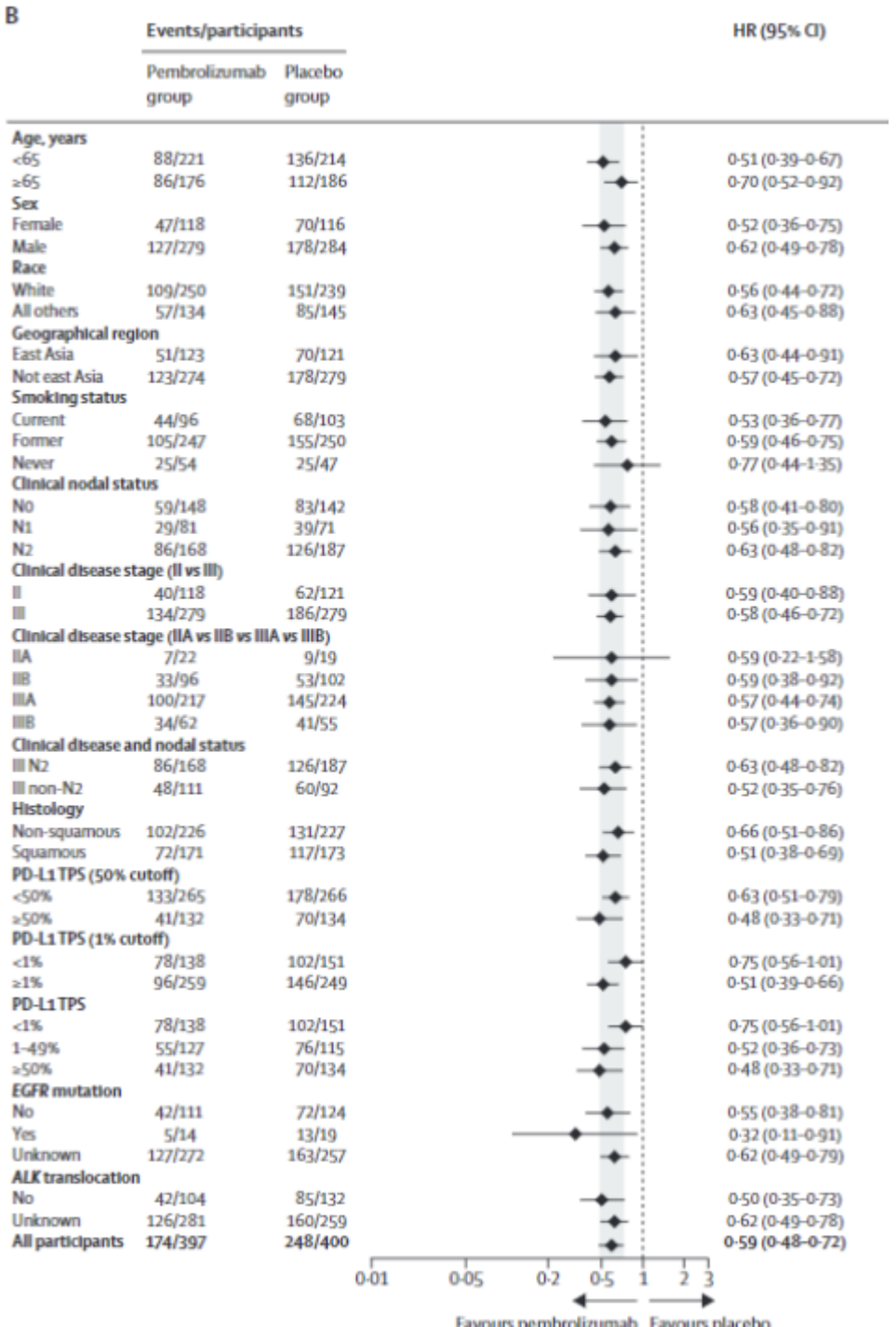


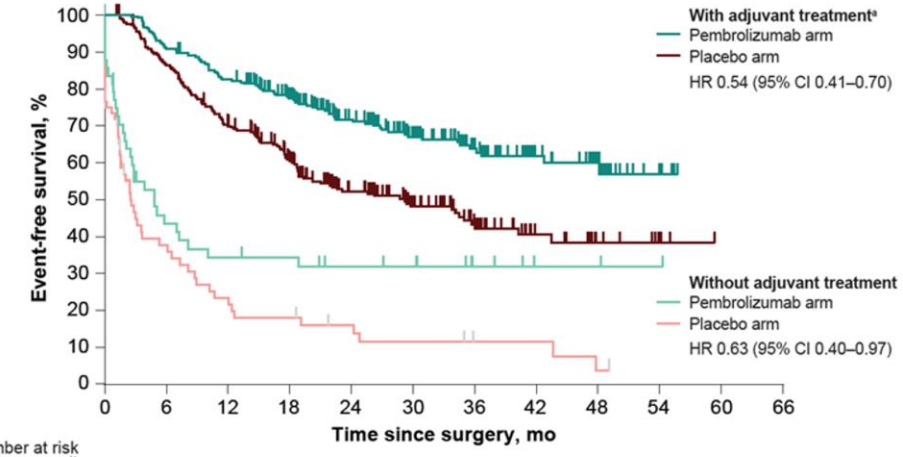
Number at risk (number censored)												
Pembrolizumab group	397 (0)	339 (8)	282 (13)	250 (18)	196 (54)	142 (95)	102 (129)	62 (164)	37 (187)	10 (213)	0 (223)	0 (223)
Placebo group	400 (0)	308 (13)	232 (16)	189 (22)	128 (50)	87 (81)	66 (97)	34 (123)	18 (135)	6 (146)	1 (151)	0 (152)

B



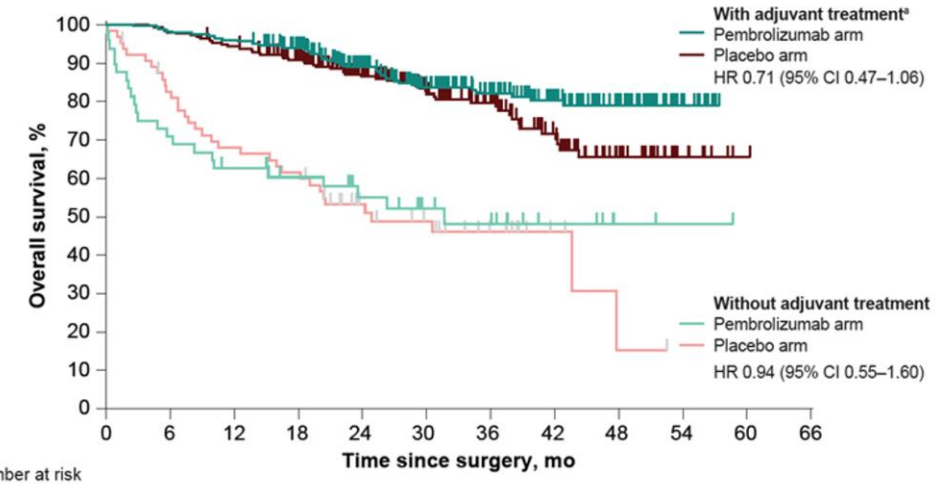
KN-671 : EFS and OS by adjuvant therapy

EFS in patients who received or did not receive adjuvant therapy



	Number at risk (number censored)												
With adjuvant treatment	Pembrolizumab arm	276 (0)	250 (1)	225 (3)	191 (24)	139 (63)	99 (95)	64 (126)	38 (150)	24 (163)	4 (182)	0 (186)	0 (186)
	Placebo arm	253 (0)	216 (3)	173 (5)	136 (21)	91 (48)	64 (69)	39 (89)	18 (108)	8 (117)	3 (122)	0 (125)	0 (125)
Without adjuvant treatment	Pembrolizumab arm	49 (0)	19 (4)	15 (4)	14 (5)	11 (7)	10 (8)	5 (13)	2 (16)	2 (16)	1 (17)	0 (18)	0 (18)
	Placebo arm	64 (0)	21 (5)	13 (5)	10 (5)	7 (7)	5 (7)	3 (9)	3 (9)	1 (9)	0 (10)	0 (10)	0 (10)

OS in patients who received or did not receive adjuvant therapy



	Number at risk (number censored)												
With adjuvant treatment	Pembrolizumab arm	276 (0)	271 (0)	265 (0)	245 (14)	183 (64)	139 (98)	102 (133)	71 (162)	45 (187)	10 (222)	0 (232)	0 (232)
	Placebo arm	253 (0)	248 (0)	238 (1)	212 (18)	158 (63)	112 (102)	85 (126)	52 (152)	26 (174)	8 (192)	1 (199)	0 (200)
Without adjuvant treatment	Pembrolizumab arm	49 (0)	34 (1)	29 (2)	25 (5)	19 (9)	14 (13)	12 (14)	6 (20)	2 (24)	1 (25)	0 (26)	0 (26)
	Placebo arm	64 (0)	51 (2)	42 (2)	38 (2)	24 (11)	18 (15)	11 (21)	4 (28)	1 (29)	0 (30)	0 (30)	0 (30)

Subsequent Therapy after disease progression or recurrence

	Pembrolizumab group (n=124)	Placebo group (n=208)
≥1 subsequent therapy	99 (80%)	178 (86%)
PD-1 or PD-L1 inhibitor-based regimen	26 (21%)	104 (50%)
Tyrosine kinase inhibitor-based regimen	23 (19%)	27 (13%)
Chemotherapy-based regimen*	55 (44%)	70 (34%)
Other antineoplastic agent	8 (6%)	3 (1%)
Surgery	9 (7%)	10 (5%)
Radiotherapy	36 (29%)	69 (33%)

Data are n (%).

*Excludes participants who received chemotherapy in combination with a PD-1 inhibitor, a PD-L1 inhibitor, or a tyrosine kinase inhibitor.

J. D. Spicer et al. The Lancet(2024)

Retreatment with Immune Checkpoint Inhibitors in the New Scenario of Immunotherapy in Non-Small Cell Lung Cancer

S. Rossi et al. Cancers(2024)

Table 2 The pooled ORR and DCR and the pooled incidence of irAEs

Reasons for discontinuation of prior ICIs	ORR	DCR	All-grade irAEs	High-grade irAEs
Retreatment (overall)	20%	54%	41%	13%
Rechallenge after PD	8%	39%	–	–
Resumption after irAEs and clinical decision	34%	71%	–	–

Grade ≥3 was defined as high-grade irAEs. ORR, objective response rate; DCR, disease control rate; PD, progression disease; irAEs, immune-related "adverse" events; ICI, immune checkpoint inhibitor.

Safety and efficacy of immune checkpoint inhibitor rechallenge in advanced non-small cell lung cancer: a retrospective study

J. Feng et al. Scientific Reports(2024)

Retrospective Study
N=111

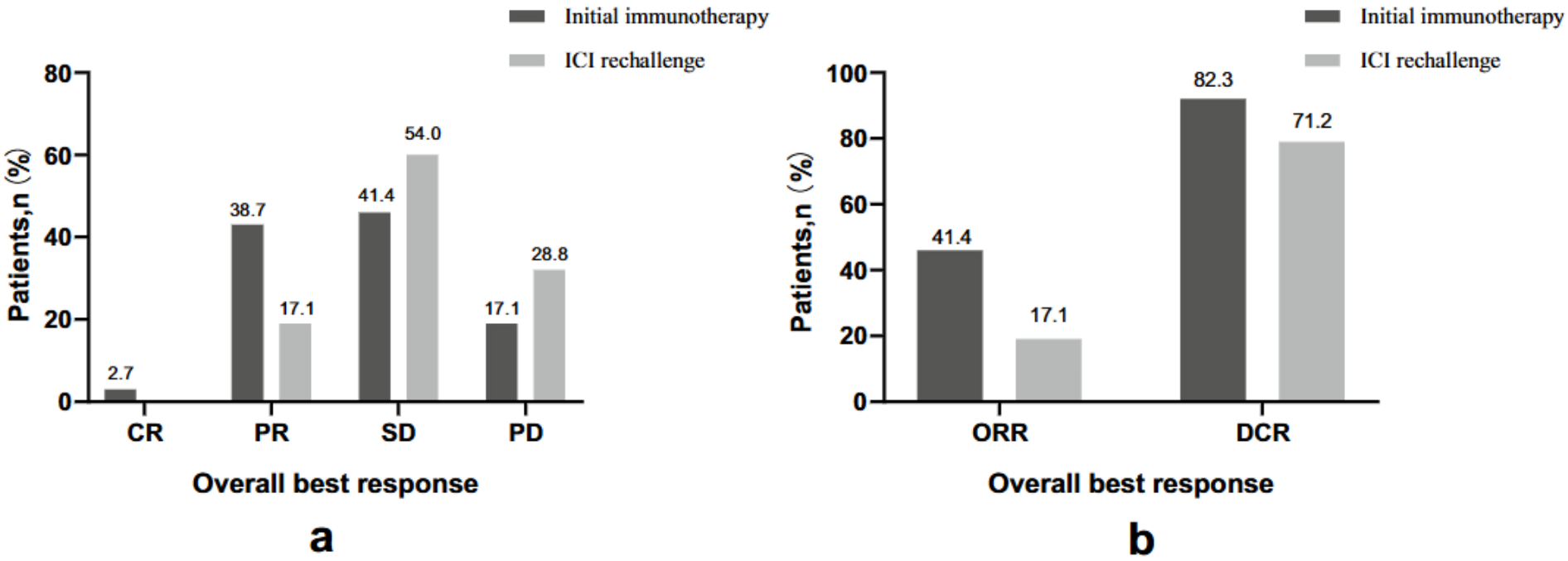
Inclusion Criteria
- Stage III B to IV
- The ICI rechallenge was started because of disease progression
- ECOG-PS ≤ 3 Points

Exclusion Criteria
- Patients who discontinued immunotherapy due to toxicity

Characteristics	Number of patients (%)
Gender	
Male	89 (80.2%)
Female	22 (19.8%)
Age	
≤63	63 (56.8%)
>63	48 (43.2%)
Smoking status	
Never-smokers	68 (61.3%)
Former or current smokers	43 (38.7%)
Histological subtype	
Adenocarcinoma	70 (63.1%)
Squamous carcinoma	41 (36.9%)
Clinical stage at ICI rechallenge initiation	
IIIB–C	13 (11.7%)
IV	98 (88.3%)
PD-L1 expression	
Number tested	47 (42.3%)
TPS < 1%	20/47 (53.3%)
1% ≤ TPS < 50%	9/47 (19.1%)
TPS ≥ 50%	18/47 (38.3%)
Unknown	64 (57.7%)

Safety and efficacy of immune checkpoint inhibitor rechallenge in advanced non-small cell lung cancer: a retrospective study

J. Feng et al. Scientific Reports(2024)



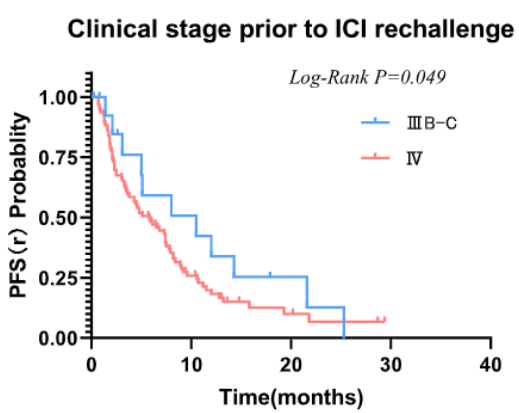
Safety and efficacy of immune checkpoint inhibitor rechallenge in advanced non-small cell lung cancer: a retrospective study

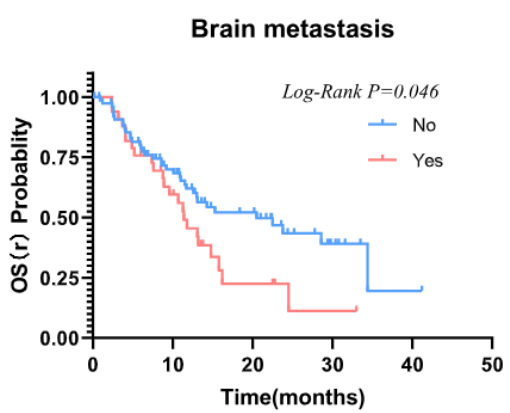
J. Feng et al. Scientific Reports(2024)

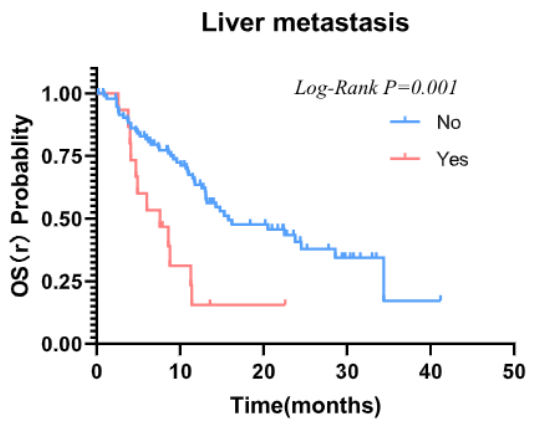
Group	PR	SD	PD	ORR	DCR
Total	19 (17.1%)	60 (54%)	32 (28.8%)	19 (17.1%)	92 (71.2%)
ICI rechallenge regimen					
ICI monotherapy	3 (20.0%)	8 (53.3%)	4 (26.7%)	3 (20.0%)	11 (73.3%)
Combination chemotherapy	3 (10.0%)	17 (56.7%)	10 (33.3%)	3 (10.0%)	20 (66.7%)
Combination angiogenesis inhibitor	6 (20.7%)	10 (34.5%)	13 (44.8%)	6 (20.7%)	16 (55.2%)
Combination chemotherapy + angiogenesis inhibitor	7 (18.9%)	25 (67.6%)	5 (13.5%)	7 (18.9%)	32 (86.5%)

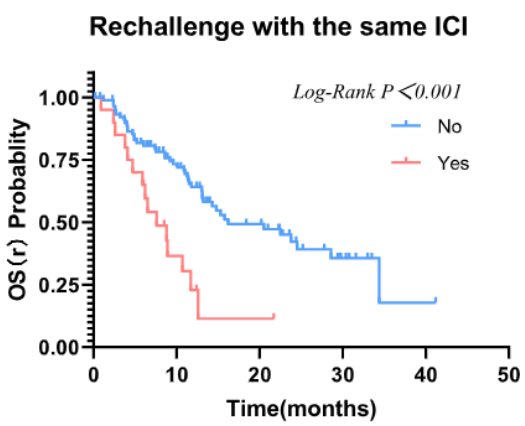
Safety and efficacy of immune checkpoint inhibitor rechallenge in advanced non-small cell lung cancer: a retrospective study

J. Feng et al. Scientific Reports(2024)



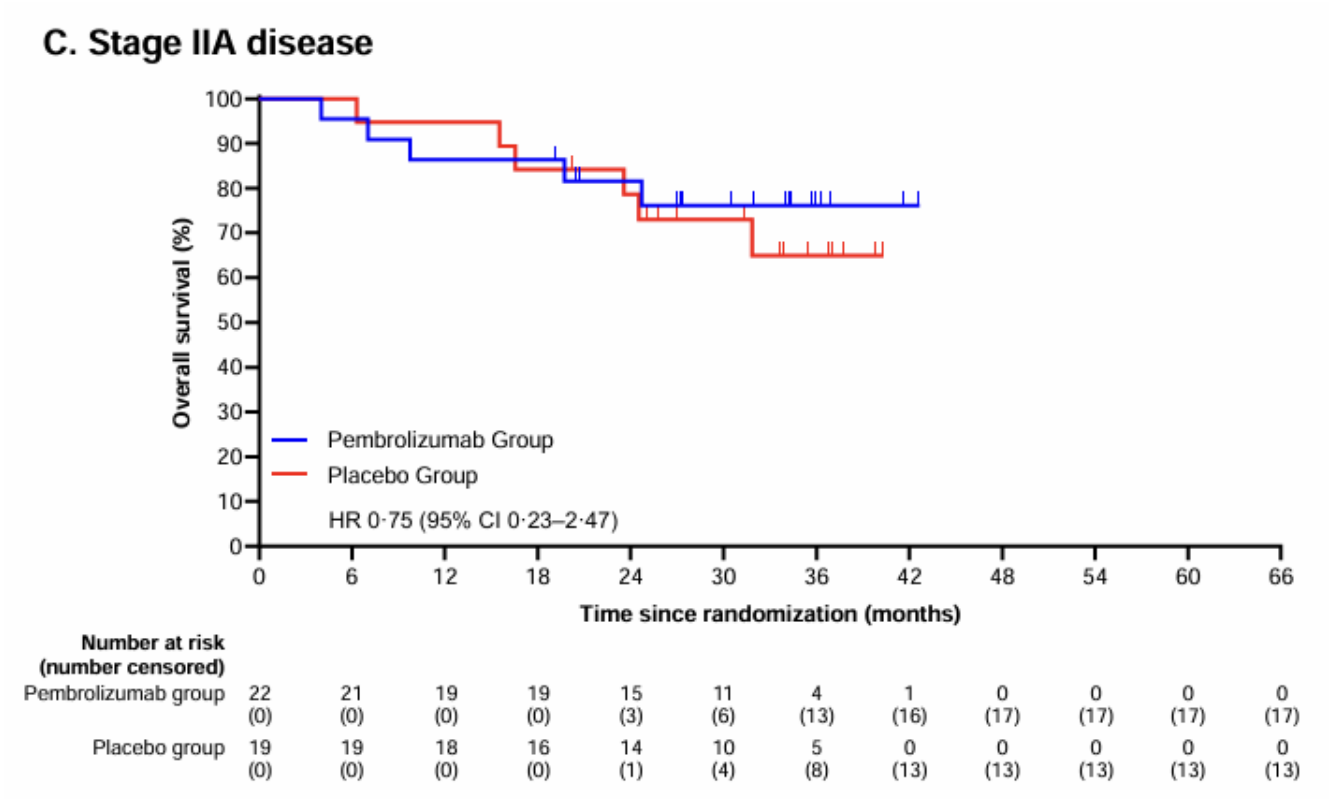






Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial

J. D. Spicer et al. The Lancet(2024)



			N0	N1	N2	N3
T1	T1a		IA1	IIB	IIIA	IIIB
	T1b		IA2	IIB	IIIA	IIIB
	T1c		IA3	IIB	IIIA	IIIB
T2	T2a	>3 cm ≤4 cm	IB	IIB	IIIA	IIIB
	T2b	>4 cm ≤5 cm	IIA	IIB	IIIA	IIIB
T3			IIB	IIIA	IIIB	IIIC
T4			IIIA	IIIA	IIIB	IIIC
M1	M1a		IVA	IVA	IVA	IVA
	M1b		IVA	IVA	IVA	IVA
	M1c		IVB	IVB	IVB	IVB

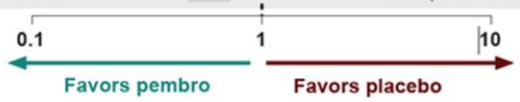
TNM 8th edition[2]

Red line indicates KN-671 eligibility

KN-671 : EFS and OS by PD-L1 expression

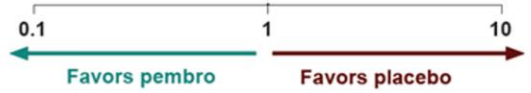
EFS

	No. of Events/No. of Patients		HR (95% CI)
	Pembro	Placebo	
Overall	174/397	248/400	0.59 (0.48–0.72)
Stage at baseline			
Stage II	40/118	62/121	0.59 (0.40–0.88)
Stage III	134/279	186/279	0.58 (0.46–0.72)
Histology			
Squamous	72/171	117/173	0.51 (0.38–0.69)
Nonsquamous	102/226	131/227	0.66 (0.51–0.86)
PD-L1 TPS status			
TPS <1%	78/138	102/151	0.75 (0.56–1.01)
TPS ≥1%	96/259	146/249	0.51 (0.39–0.66)
TPS 1%–49%	55/127	76/115	0.52 (0.36–0.73)
TPS ≥50%	41/132	70/134	0.48 (0.33–0.71)
N status at baseline[a]			
N0	59/148	83/142	0.58 (0.41–0.80)
N1	29/81	39/71	0.56 (0.35–0.91)
N2	86/168	126/187	0.63 (0.48–0.82)



OS

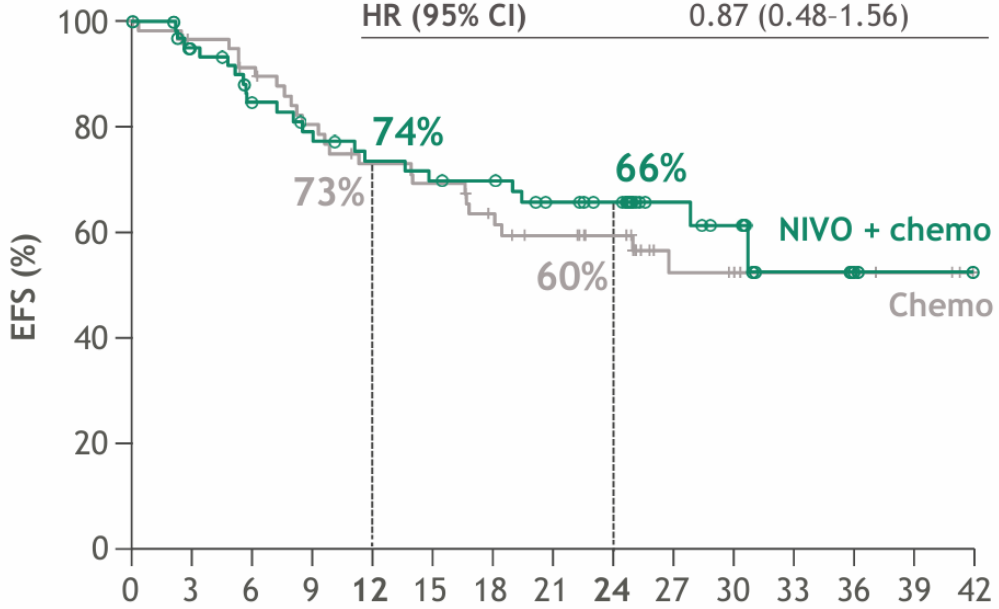
	No. of Events/No. of Patients		HR (95% CI)
	Pembro	Placebo	
Overall	110/397	144/400	0.72 (0.56–0.93)
Stage at baseline			
Stage II	26/118	39/121	0.67 (0.41–1.10)
Stage III	84/279	105/279	0.74 (0.55–0.98)
Histology			
Squamous	61/171	80/173	0.71 (0.51–0.99)
Nonsquamous	49/226	64/227	0.73 (0.50–1.06)
PD-L1 TPS status			
TPS <1%	52/138	61/151	0.91 (0.63–1.32)
TPS ≥1%	58/259	83/249	0.62 (0.45–0.87)
TPS 1%–49%	35/127	44/115	0.69 (0.44–1.07)
TPS ≥50%	23/132	39/134	0.55 (0.33–0.92)
N status at baseline[a]			
N0	40/148	52/142	0.70 (0.46–1.05)
N1	21/81	24/71	0.74 (0.41–1.33)
N2	49/168	68/187	0.74 (0.51–1.07)



CheckMate-816 : EFS by stage

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)	

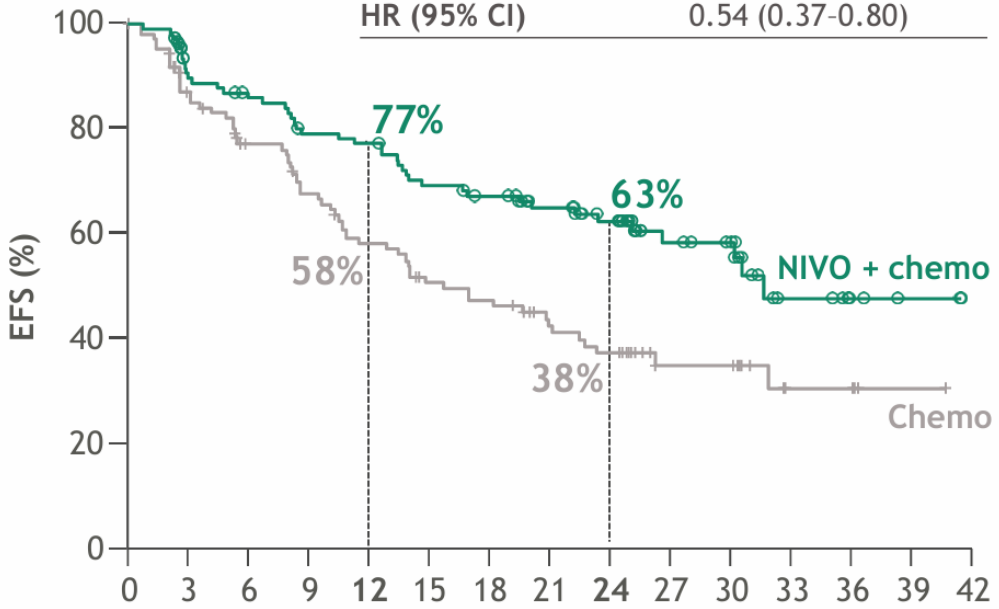


No. at risk

NIVO + chemo	65	56	47	43	39	37	36	31	27	15	12	4	2	1	0
Chemo	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

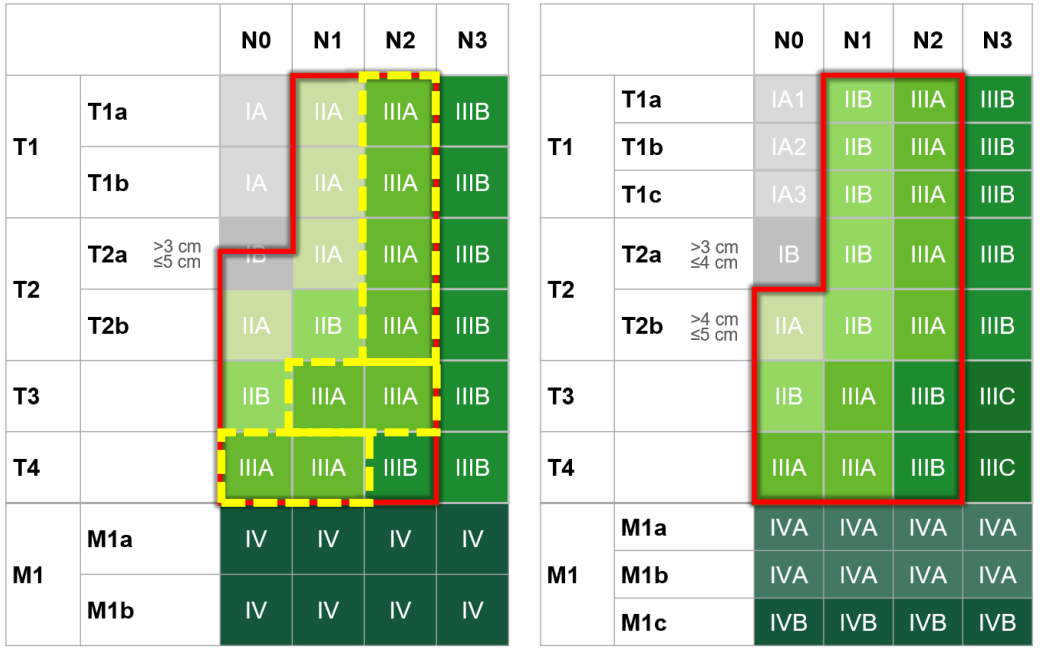
NIVO + chemo	113	95	89	81	79	70	66	56	47	26	22	9	4	2	0
Chemo	115	89	75	65	55	46	43	33	29	14	14	5	5	1	0

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).

Midpoint Summary-2

- Perioperative chemo-IO is superior to neoadjuvant chemo-IO in terms of EFS and OS, regardless of pCR status.
- Reassumption of ICIs : Available option for the future
- Stage IIA is a homogeneous group with a specific phenotype



		N0	N1	N2	N3
T1	T1a	IA	IIA	IIIA	IIIB
	T1b	IA	IIA	IIIA	IIIB
T2	T2a >3 cm ≤5 cm	IB	IIA	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3		IIB	IIIA	IIIA	IIIB
T4		IIIA	IIIA	IIIB	IIIB
M1	M1a	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

TNM 7th edition[3]

		N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a >3 cm ≤4 cm	IB	IIB	IIIA	IIIB
	T2b >4 cm ≤5 cm	IIA	IIB	IIIA	IIIB
T3		IIB	IIIA	IIIB	IIIC
T4		IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

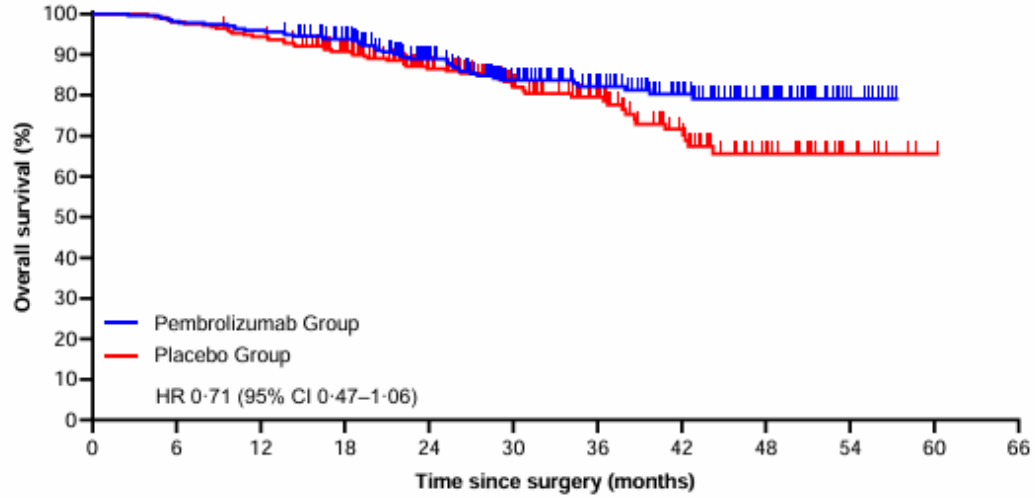
TNM 8th edition[2]

When Do Serious AEs Occur in Perioperative Chemoimmunotherapy, and What Do They Mean

J. D. Spicer et al. The Lancet(2024)

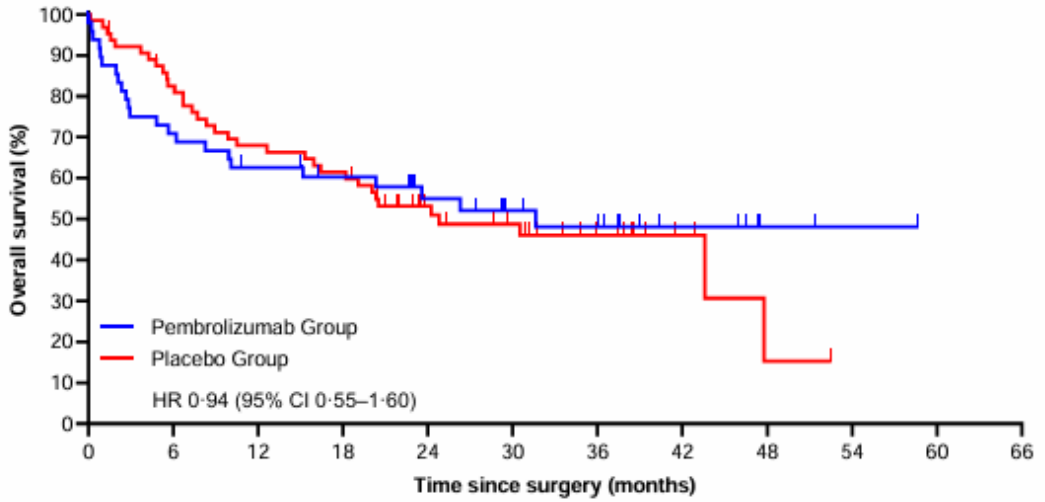
KN-671: OS from surgery by Adjuvant therapy

A. Participants who received adjuvant therapy



Number at risk (number censored)												
Pembrolizumab group	276 (0)	271 (0)	265 (0)	245 (14)	183 (64)	139 (98)	102 (133)	71 (162)	45 (187)	10 (222)	0 (232)	0 (232)
Placebo group	253 (0)	248 (0)	238 (1)	212 (18)	158 (63)	112 (102)	85 (126)	52 (152)	26 (174)	8 (192)	1 (199)	0 (200)

B. Participants who did not receive adjuvant therapy



Number at risk (number censored)												
Pembrolizumab group	49 (0)	34 (1)	29 (2)	25 (5)	19 (9)	14 (13)	12 (14)	6 (20)	2 (24)	1 (25)	0 (26)	0 (26)
Placebo group	64 (0)	51 (2)	42 (2)	38 (2)	24 (11)	18 (15)	11 (21)	4 (28)	1 (29)	0 (30)	0 (30)	0 (30)

KN-671: **Events that contributed to event-free survival**

Event	Pembrolizumab group (n=397)	Placebo group (n=400)
No event	223 (56%)	152 (38%)
Event	174 (44%)	248 (62%)
Categorization A		
Death	50 (13%)	40 (10%)
Disease progression or recurrence	118 (30%)	187 (47%)
Local disease progression preventing surgery	1 (<1%)	6 (2%)
Inability to resect the tumour	5 (1%)	15 (4%)
Categorization B		
Death	50 (13%)	40 (10%)
Locoregional progression or recurrence only	66 (17%)	111 (28%)
Distant metastasis*	57 (14%)	95 (24%)
Unknown†	1 (<1%)	2 (1%)

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KN-671 : All cause Mortality

	Pembro Arm	Placebo Arm
All participants who underwent surgery	**n = 325**	**n = 317**
Within 30 days	6 (1.8%)[a]	2 (0.6%)[b]
Within 90 days	13 (4.0%)[c]	5 (1.6%)[d]
Participants who underwent lobectomy or bilobectomy	**n = 282**	**n = 264**
Within 30 days	4 (1.4%)	2 (0.8%)
Within 90 days	10 (3.5%)	4 (1.5%)
Participants who underwent pneumonectomy	**n = 37**	**n = 39**
Within 30 days	2 (5.4%)[e]	0
Within 90 days	3 (8.1%)[e]	1 (2.6%)[f]

[a]Pulmonary embolism (n = 2) and pulmonary hemorrhage due to arterial injury during surgery, pulmonary sepsis, respiratory failure, and septic shock (n = 1 each); all attributed to surgery. [b]Pneumonia and respiratory failure (n = 1 each); both attributed to surgery. [c]Additional deaths that occurred from days 31-90: malignant neoplasm progression (n = 3) and cardiac arrest, pulmonary hemorrhage, immune-mediated lung disease, and unexplained death (n = 1 each); none attributed to surgery; immune-mediated lung disease attributed to study drug. [d]Additional deaths that occurred from days 31-90: acute respiratory failure, malignant neoplasm progression, and septic shock (n = 1 each); none attributed to surgery or study drug. [e]Deaths within 30 days occurred in 1 of 23 participants with a left-sided tumor and 1 of 14 participants with a right-sided tumor; within 90 days, 1 additional participant with a right-sided tumor died. [e]Death occurred in 1 of 24 participants with a right-sided tumor.
Data cutoff date for IA2: July 10, 2023.

KN-671: **Treatment-related adverse events**

	Neo-Surgery Any TRAE		Surgery Any adverse events		Adjuvant Any TRAE		Immune related Or infusion R. Any adverse events	
n	396	399	325	317	290	267	396	399
Events	378(95%)	376(94%)	233(72%)	229(72%)	164(57%)	91(34%)	103(26%)	36(9%)
Grade 3-5	161(41%)	147(37%)	83 (26%)	68 (21%)	34 (12%)	16 (6%)	26 (7%)	6 (2%)
Serious	56 (14%)	52 (13%)	60 (18%)	54 (17%)	19 (7%)	8 (3%)	24 (6%)	6 (2%)
Led to death	3 (1%)	3 (1%)	10 (3%)	5 (2%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Led to discontinuation			18 (6%)	7 (2%)			23 (6%)	3 (1%)

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Table S10. Causes of All-Cause Mortality in the Post-Operative Period (Participants Who Underwent In-Study Surgery)

	Pembrolizumab Group (N = 325)	Placebo Group (N = 317)
	no. (%)	
Any death within 30 days of surgery[a]	6 (1.8)	2 (0.6)
Pulmonary embolism	2 (0.6)	0
Pulmonary hemorrhage due to arterial injury during surgery	1 (0.3)	0
Pulmonary sepsis	1 (0.3)	0
Respiratory failure	1 (0.3)	1 (0.3)
Septic shock	1 (0.3)	0
Pneumonia	0	1 (0.3)
Any death within 31-90 days of surgery[b]	7 (2.2)	3 (0.9)
Malignant neoplasm progression	3 (0.9)	1 (0.3)
Cardiac arrest	1 (0.3)	0
Pulmonary hemorrhage	1 (0.3)	0
Immune-mediated lung disease	1 (0.3)	0
Unexplained death[c]	1 (0.3)	0
Acute respiratory failure	0	1 (0.3)
Septic shock	0	1 (0.3)

[a]All deaths were attributed by the investigator to the surgery and not any study drug.
[b]None of the deaths were attributed by the investigator to the surgery. One death (immune-mediated lung disease in the pembrolizumab group) was attributed by the investigator to study drug.
[c]Participant's family declined to provide additional details and no autopsy was performed.

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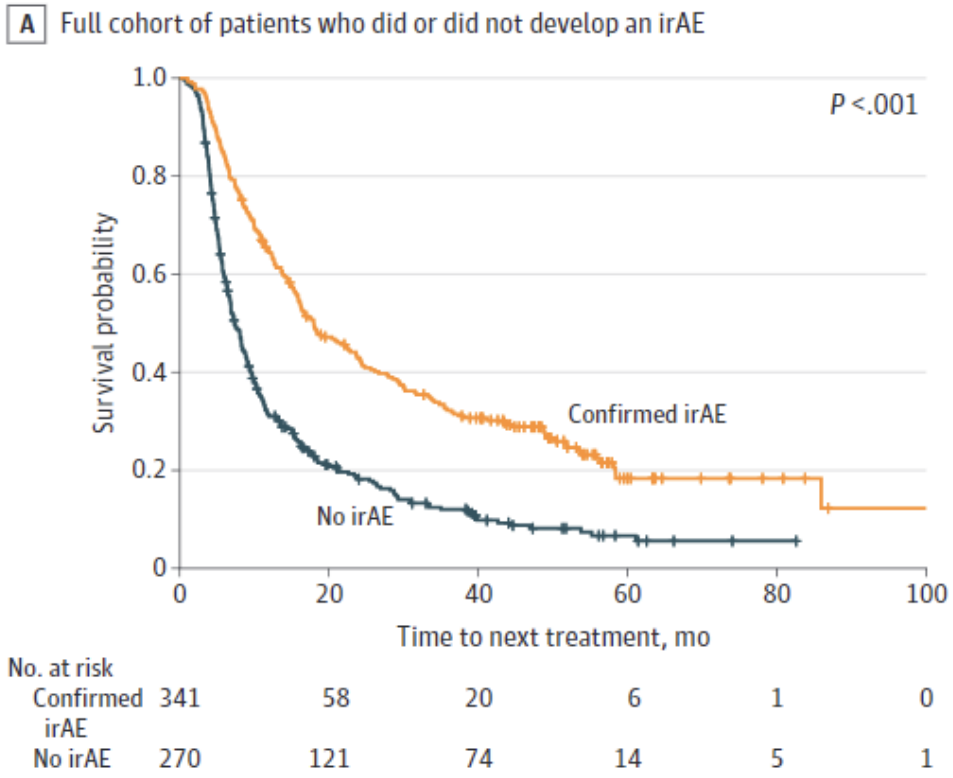
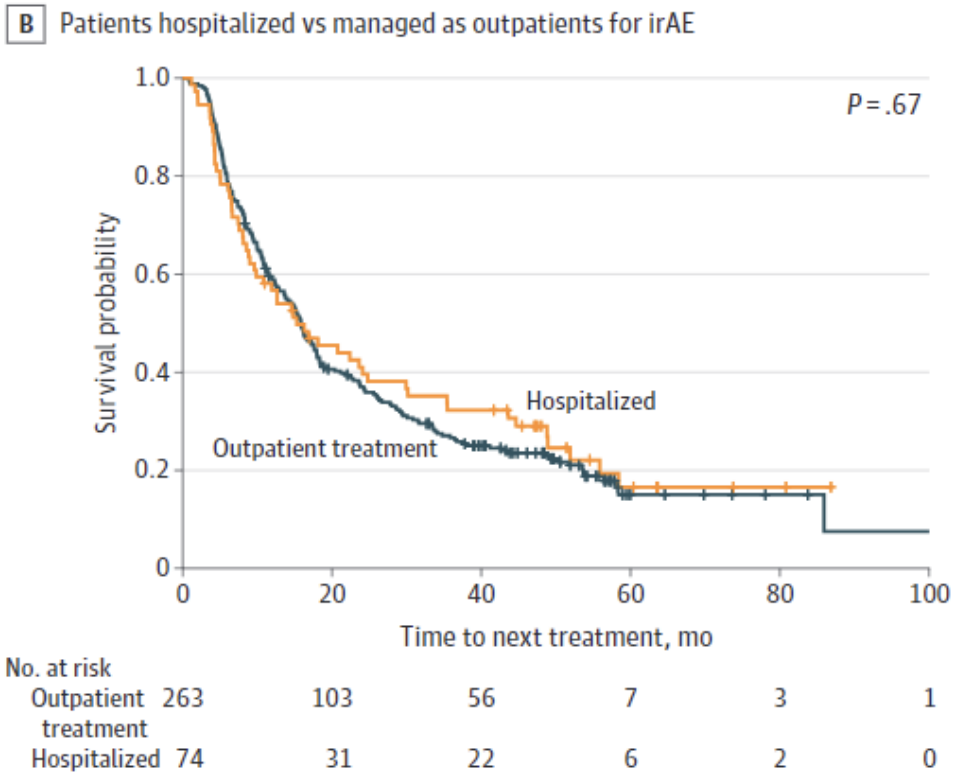
Immune-Related Adverse Events and Survival Among Patients With Metastatic NSCLC Treated With Immune Checkpoint Inhibitors

S. Cook et al. *JAMA Network Open*(**2024**)

Figure 3. Median Time to Next Treatment for Patients With Metastatic Non–Small Cell Lung Cancer



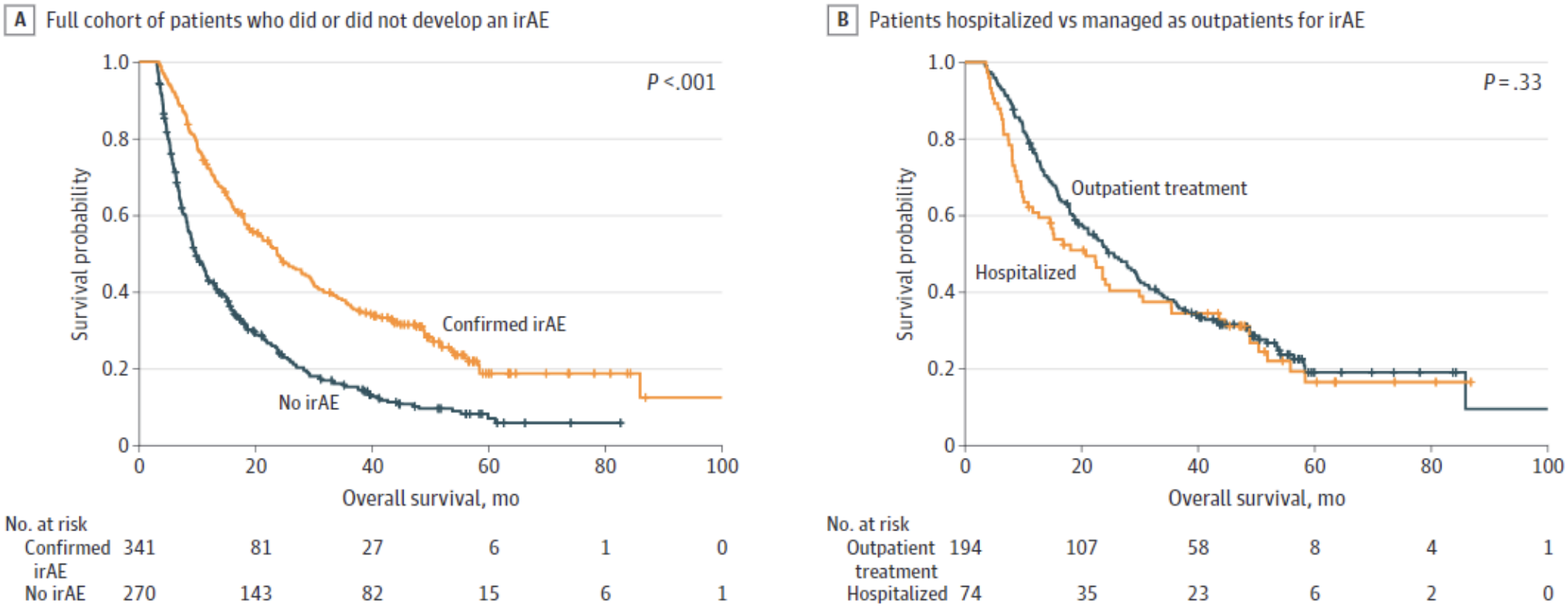


Analysis includes patients who survived to at least 12 weeks. A, Full cohort of patients who did or did not develop an immune-related adverse event (irAE) (median time to next treatment, 18.0 [95% CI, 15.6-22.9] vs 7.3 [95% CI, 6.6-8.4] months; $P < .001$). B, Patients hospitalized compared with those treated as outpatients for irAEs (median time to next treatment, 15.3 [95% CI, 9.6-24.8] vs 15.9 [95% CI, 13.6-18.0] months; $P = .67$).

Immune-Related Adverse Events and Survival Among Patients With Metastatic NSCLC Treated With Immune Checkpoint Inhibitors

S. Cook et al. *JAMA Network Open*(**2024**)

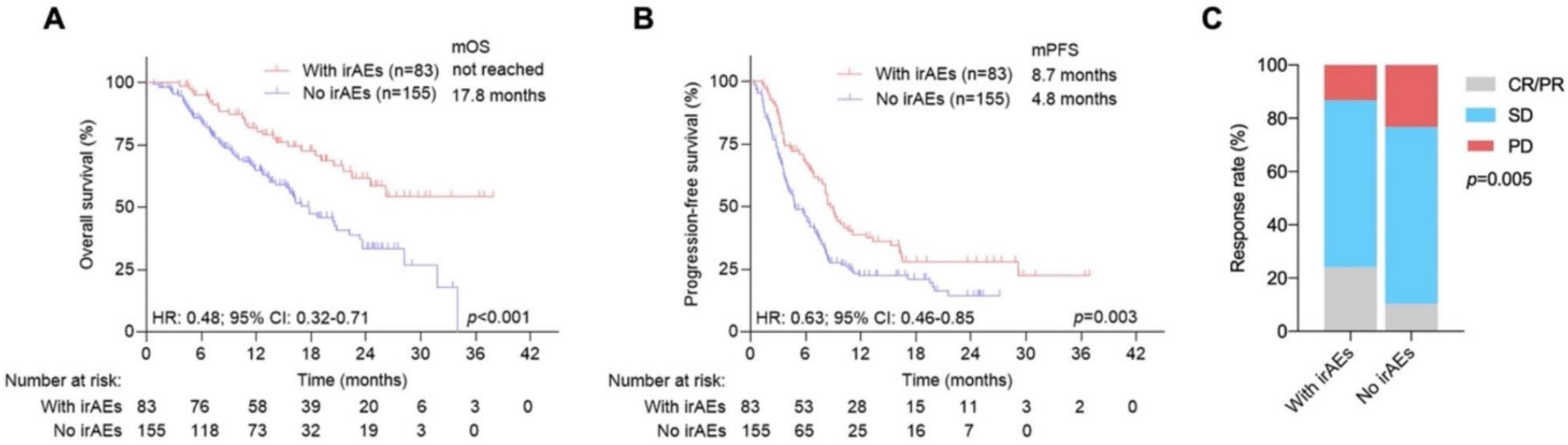
Figure 2. Median Overall Survival for Patients With Metastatic Non–Small Cell Lung Cancer



Analysis includes patients who survived to at least 12 weeks. A, Full cohort of patients who did or did not develop an immune-related adverse event (irAE) (median OS, 23.7 [95% CI, 19.3-29.1] vs 9.8 months [95% CI, 8.7-11.4 months]; $P < .001$). B, Patients hospitalized compared with those treated as outpatients for irAEs (median OS, 20.8 [95% CI, 11.7-30.6] vs 25.6 [95% CI, 20.1-29.8] months; $P = .33$).

Organ-specific immune-related adverse events and prognosis in cancer patients receiving immune checkpoint inhibitors

X. Han et al. BMC Cancer(2025)



Organ-specific immune-related adverse events and prognosis in cancer patients receiving immune checkpoint inhibitors

X. Han et al. BMC Cancer(2025)

Table 3 Cox proportional hazards regression models for OS and PFS in the entire study population with organ-specific irAEs

Toxicity	OS, Univariable		OS, Multivariable		PFS, Univariable		PFS, Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Skin toxicity	0.33 (0.13–0.81)	0.016	0.39 (0.16–0.96)	0.040	0.43 (0.24–0.80)	0.008	0.43 (0.23–0.80)	0.008
Endocrine toxicity	0.20 (0.05–0.79)	0.022	0.18 (0.04–0.74)	0.018	0.52 (0.26–1.06)	0.073	0.48 (0.24–0.99)	0.046
Bone and joint and muscle toxicity	1.89 (0.60–5.96)	0.279	2.40 (0.74–7.80)	0.147	1.59 (0.59–4.30)	0.359	1.92 (0.70–5.22)	0.204
Pulmonary toxicity	0.89 (0.45–1.77)	0.738	0.65 (0.30–1.41)	0.279	1.10 (0.67–1.82)	0.706	0.95 (0.56–1.62)	0.841
Cardiotoxicity	0.78 (0.25–2.47)	0.677	0.72 (0.22–2.31)	0.575	0.76 (0.34–1.72)	0.506	0.67 (0.29–1.55)	0.351
Digestive system toxicity	0.65 (0.21–2.05)	0.461	0.68 (0.21–2.16)	0.511	0.83 (0.39–1.76)	0.618	0.84 (0.39–1.79)	0.649
Renal toxicity	1.88 (0.46–7.63)	0.379	2.50 (0.60-10.42)	0.208	0.83 (0.21–3.34)	0.790	0.99 (0.24–4.04)	0.987

OS: overall survival; PFS: progression-free survival; HR: hazard ratio; irAEs: immune-related adverse events

- **Skin toxiciy**
- **Endocrine Toxicity**

Organ-specific immune-related adverse events and prognosis in cancer patients receiving immune checkpoint inhibitors

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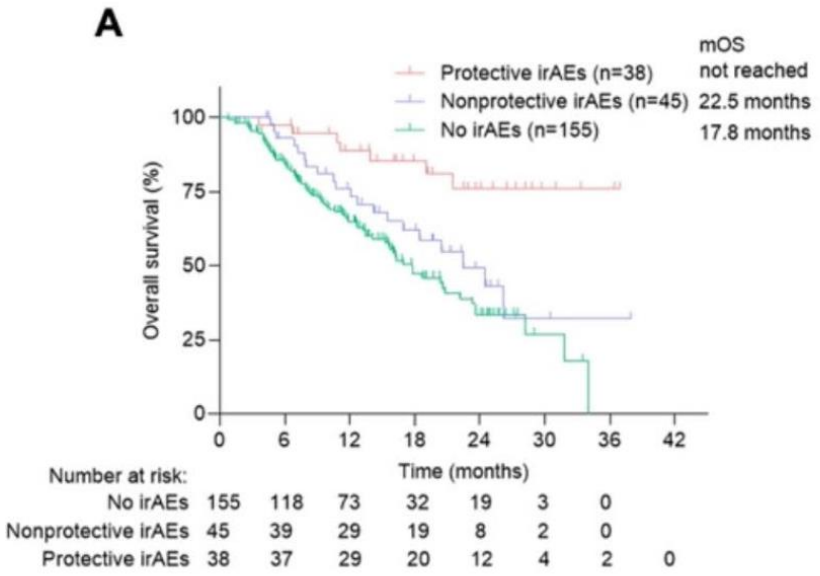
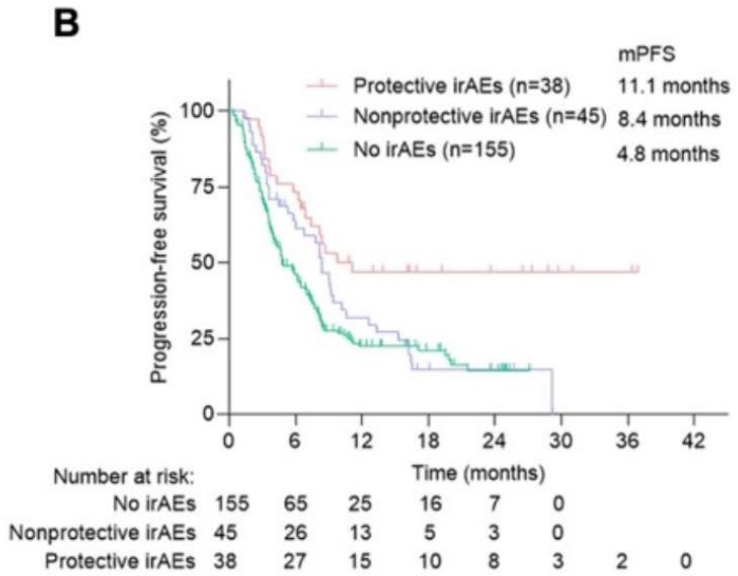
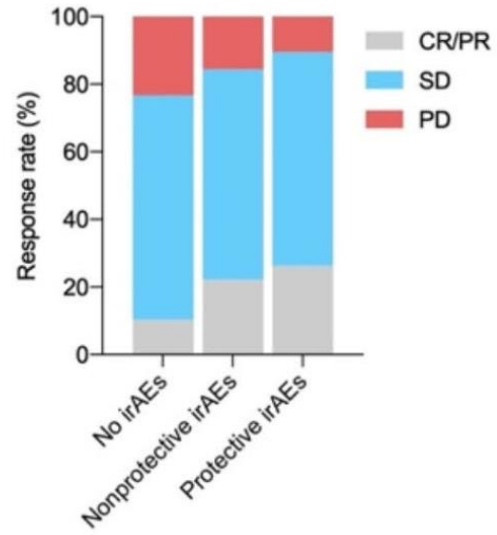




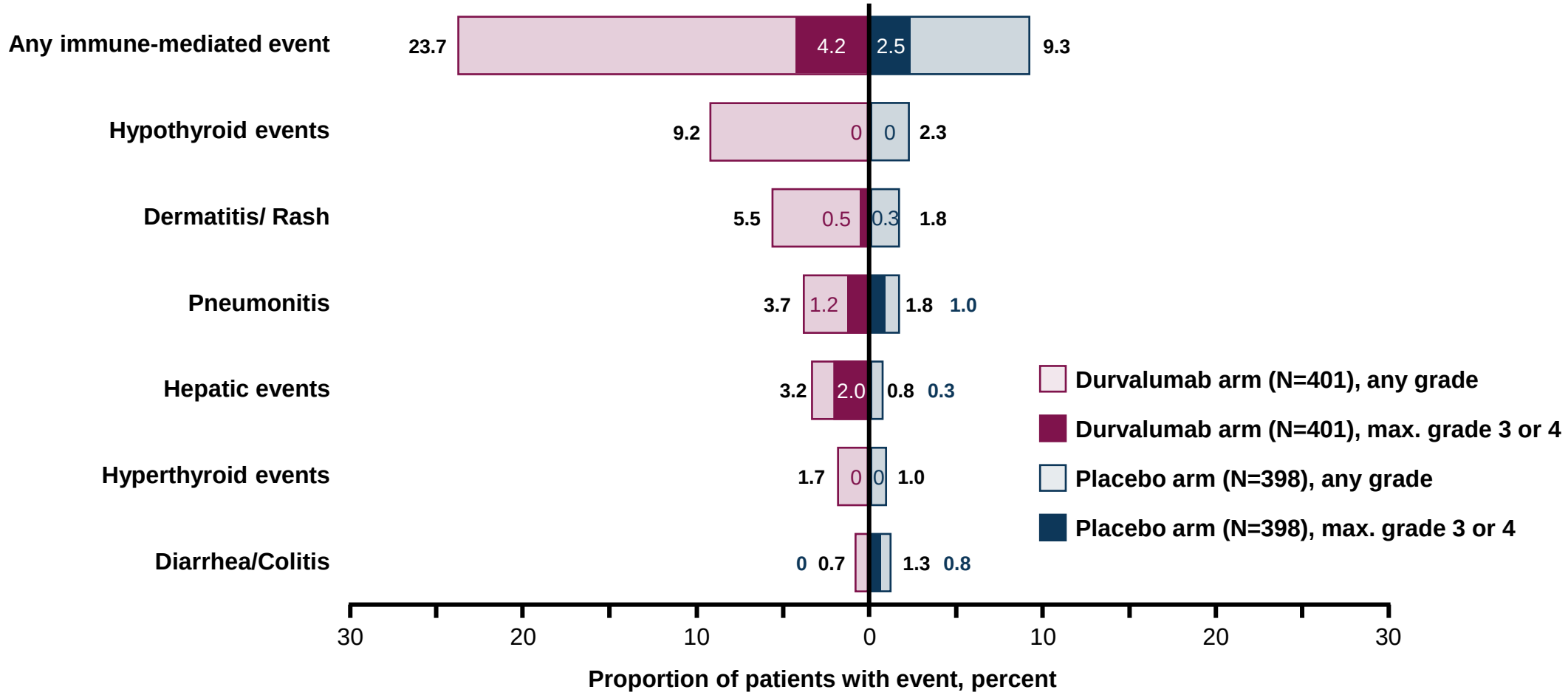


	HR (95% CI)	*p* value
Nonprotective irAEs vs No irAEs	0.71 (0.45-1.11)	0.133
Protective irAEs vs No irAEs	0.23 (0.14-0.38)	<0.001
Protective irAEs vs Nonprotective irAEs	0.33 (0.16-0.71)	0.008

	HR (95% CI)	*p* value
Nonprotective irAEs vs No irAEs	0.81 (0.57-1.16)	0.246
Protective irAEs vs No irAEs	0.51 (0.35-0.75)	<0.001
Protective irAEs vs Nonprotective irAEs	0.51 (0.30-0.87)	0.013

	OR	*p* value
Nonprotective irAEs vs No irAEs	2.15	0.037
Protective irAEs vs No irAEs	2.55	0.010
Protective irAEs vs Nonprotective irAEs	1.18	0.664

Immune-mediated Adverse Events (Grouped Terms) Occurring in >1% of Patients in Either Treatment Arm (Safety Analysis Set)[a]

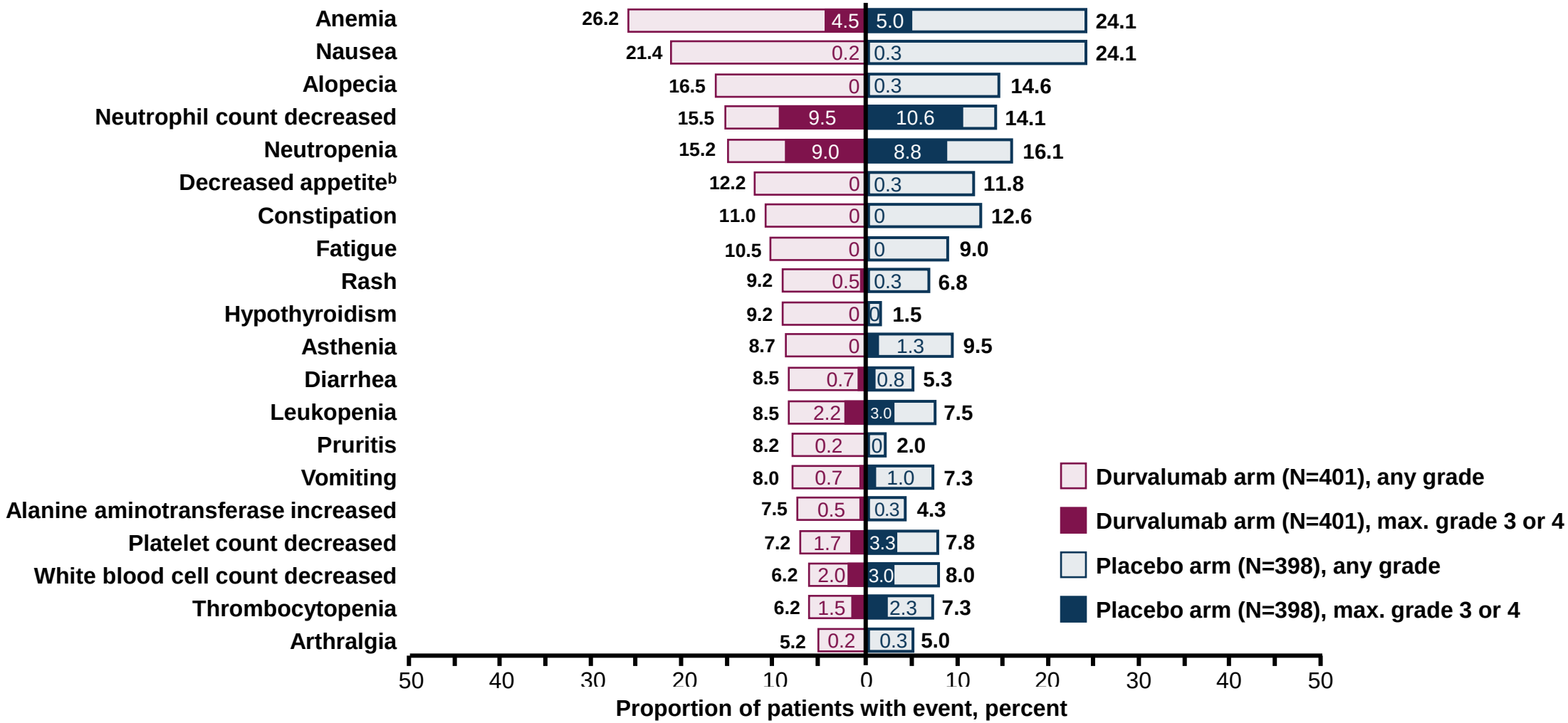


Data cut-off of November 10, 2022 (N=799). [a]The safety analysis set includes all randomized patients who received ≥1dose of study Tx; one patient assigned to the placebo arm erroneously received a single cycle of durvalumab (in the adjuvant phase) and was included in the durvalumab arm for the safety analysis set; AEs were graded using CTCAE v5.0. An immune-mediated AE was defined as 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.

AE = adverse event; CI = confidence interval; D = durvalumab; CTCAE v5.0 = Common Terminology Criteria for Adverse Events version 5.0; PBO = placebo; Tx = treatment.

Heymach JV, et al. *N Engl J Med*. 2023; 389:1672-1684.

Most Common Adverse Events Possibly Related to Study Treatment (Safety Analysis Set)[a]



Data cut-off of November 10, 2022 (N=799). [a]The safety analysis set includes all randomized patients who received at least one dose of study treatment; one patient assigned to the placebo arm erroneously received a single cycle of durvalumab (in the adjuvant phase) and was included in the durvalumab arm for the safety analysis set; adverse events were graded using Common Terminology Criteria for Adverse Events version 5.0. Included are adverse events assessed by the investigator as possibly related to any study treatment (durvalumab or placebo or chemotherapy) reported with an any-grade incidence of at least 5% in the durvalumab arm during the overall study period, which spans from the first dose of study treatment until the earliest of: the last dose of study treatment or surgery + 90 days (taking the latest dose of durvalumab or placebo or chemotherapy or the date of surgery, + 90 days); the data cut-off date; or the date of the first dose of subsequent anti-cancer treatment. [b]One patient in the durvalumab arm had decreased appetite with an outcome of death (grade 5) that was assessed as possibly related to study treatment by the investigator.

Heymach JV, et al. *N Engl J Med.* 2023; 389:1672-1684.

KN-671:Treatment-related adverse events

Table S11: Treatment-related adverse events that occurred during the adjuvant treatment phase in the as-treated population

	Pembrolizumab group (n=290)		Placebo group (n=267)	
Any treatment-related adverse event	164 (57%)		91 (34%)	
Grade 3-5	34 (12%)		16 (6%)	
Serious	19 (7%)		8 (3%)	
Led to death	1 (<1%)*		0 (0%)	
Treatment-related adverse events with incidence ≥5% in either group	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Pruritus	25 (9%)	2 (1%)	7 (3%)	0 (0%)
Rash	19 (7%)	1 (<1%)	8 (3%)	0 (0%)
Diarrhoea	15 (5%)	3 (1%)	12 (4%)	0 (0%)
Hypothyroidism	15 (5%)	0 (0%)	2 (1%)	0 (0%)

Data are n (%). The adjuvant phase began with the first dose of adjuvant therapy. Treatment-related adverse events were adverse events considered to be related to pembrolizumab or placebo by the investigator.

J. D. Spicer et al. The Lancet(2024)

Midpoint Summary-3

- Patient selection is crucial for surgery-related Aes
- Critical immune-related AEs are rare, but irAE can be an optimistic marker

Proposed Indications and Supporting Evidence for Optimal Patient Selection

NCCN Guidelines Version 3.2025

Neoadjuvant Systemic Therapy

• Tumors ≥4 cm or node positive NSCLC should be evaluated for preoperative therapy, with strong consideration for an ICI+ chemotherapy.

Adjuvant Chemotherapy

- For stage IB and IIA (T2b, N0) and negative margins (R0), adjuvant chemotherapy is recommended for high-risk features.
- For stage IIB (T1 abc–T2a, N1), stage IIB (T3, N0; T2b, N1), stage IIIA (T1–2, N2; T3, N1; T4, N0–1), stage IIIB (T3–4, N2) and negative margins (R0), adjuvant chemotherapy is recommended as a category 1.

NCCN Guidelines Version 3.2025

- Patients with completely resected tumors ≥4 cm or node positive NSCLC should be evaluated for additional systemic therapy

- Systemic Therapy Following Surgical Resection

  Adjuvant atezolizumab : PD-L1 (+)

  Adjuvant pembrolizumab : PD-L1 (+)

  Perioperative pembrolizumab

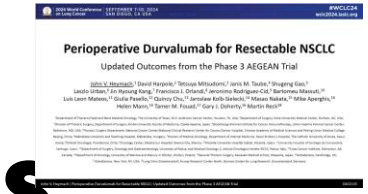
  Perioperative nivolumab

  Perioperative durvalumab

NCCN Guidelines Version 3.2025

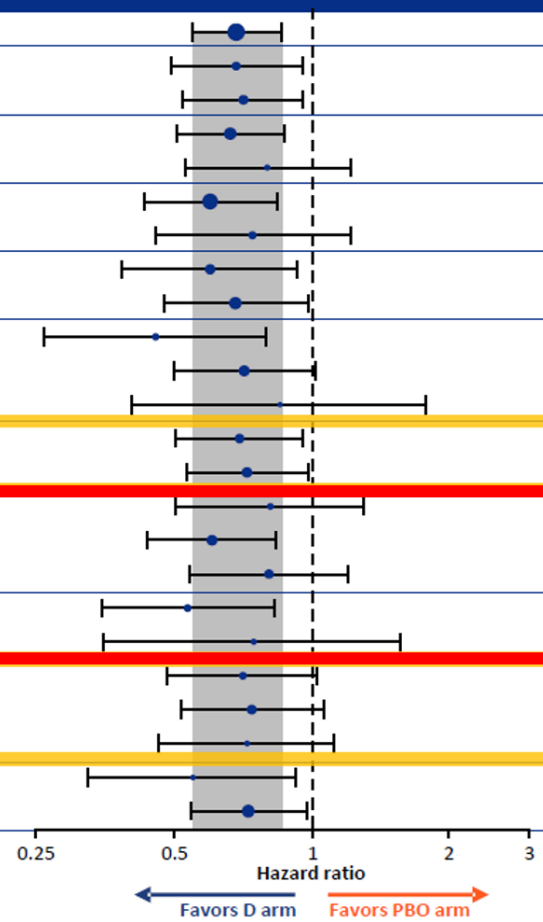
Systemic Therapy Following Surgical Resection

- Adjuvant atezolizumab : PD-L1 (+)
- Adjuvant pembrolizumab : PD-L1 (+)
- Perioperative pembrolizumab
- Perioperative nivolumab
- Perioperative durvalumab



AGEAN : EFS by stage and LN status

Subgroup		n	Median EFS, months (95% CI) D arm (N=366)	PBO arm (N=374)	HR (95% CI)
All patients		740	NR (42.3–NR)	30.0 (20.6–NR)	0.69 (0.55–0.88)
Age at randomization	<65 years	358	NR (NR–NR)	34.4 (19.8–NR)	0.69 (0.48–0.97)
	≥65 years	382	NR (31.9–NR)	25.9 (15.1–NR)	0.71 (0.52–0.97)
Sex	Male	530	NR (41.2–NR)	25.9 (19.8–NR)	0.66 (0.50–0.88)
	Female	210	NR (33.2–NR)	40.4 (15.1–NR)	0.80 (0.52–1.23)
ECOG PS	0	506	NR (42.3–NR)	31.1 (19.5–NR)	0.66 (0.50–0.88)
	1	234	NR (21.8–NR)	28.6 (18.9–NR)	0.79 (0.52–1.20)
Race*	Asian	307	NR (42.3–NR)	25.9 (19.5–NR)	0.66 (0.45–0.95)
	Non-Asian	433	NR (33.2–NR)	31.1 (15.7–NR)	0.73 (0.54–0.99)
Smoking	Current	190	NR (33.2–NR)	20.4 (8.1–NR)	0.52 (0.32–0.82)
	Former	443	NR (41.2–NR)	30.0 (20.7–NR)	0.75 (0.56–1.02)
	Never	107	NR (13.0–NR)	34.4 (14.7–NR)	0.88 (0.47–1.61)
Histology	Squamous	360	NR (41.2–NR)	40.4 (15.1–NR)	0.70 (0.49–0.98)
	Non-squamous	375	NR (36.6–NR)	28.6 (19.8–NR)	0.73 (0.53–1.00)
Disease stage (AJCC 8th ed.)	Stage II	214	NR (41.2–NR)	NR (34.4–NR)	0.82 (0.49–1.34)
	Stage IIIA	338	NR (42.3–NR)	25.8 (11.7–45.0)	0.60 (0.42–0.84)
	Stage IIIB	186	36.6 (12.7–NR)	19.8 (11.7–42.6)	0.81 (0.53–1.23)
Lymph node station	N2 single	273	NR (NR–NR)	22.8 (13.9–42.6)	0.58 (0.39–0.85)
	N2 multi	74	31.9 (9.3–NR)	12.2 (7.2–NR)	0.78 (0.40–1.49)
PD-L1 expression at baseline†	TC <1%	247	NR (24.7–NR)	20.6 (14.3–NR)	0.69 (0.46–1.02)
	TC 1–49%	277	NR (31.9–NR)	25.9 (12.3–NR)	0.73 (0.50–1.05)
	TC ≥50%	216	NR (41.2–NR)	NR (24.5–NR)	0.71 (0.44–1.12)
Planned neoadjuvant platinum agent	Cisplatin	196	NR (NR–NR)	45.0 (13.9–NR)	0.58 (0.35–0.93)
	Carboplatin	544	NR (36.6–NR)	26.2 (20.6–NR)	0.75 (0.57–0.97)



DCO = May 10, 2024; median EFS follow-up in censored patients: 25.9 months; EFS maturity: 39.1%. *Race was self-reported per the electronic case report form. †Determined using the Ventana SP263 immunohistochemistry assay.

CheckMate-77T : EFS by stage and LN status


MADRID ESMO congress 2023

CheckMate 77T: Phase 3 study comparing neoadjuvant nivolumab plus chemotherapy with neoadjuvant placebo plus chemotherapy followed by surgery and adjuvant nivolumab or placebo for previously untreated, resectable stage II-IIIB NSCLC

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Presentation number LBA1

	Median EFS,[a] mo		Unstratified HR (95% CI)
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)	
Overall (N = 461)	NR	18.4	0.59 (0.44-0.79)
< 65 years (n = 202)	NR	16.7	0.55 (0.36-0.85)
≥ 65 years (n = 259)	NR	20.1	0.61 (0.41-0.91)
Male (n = 327) F	NR	16.7	0.53 (0.37-0.75)
emale (n = 134)	30.2	18.8	0.71 (0.41-1.20)
North America (n = 44)	30.2	9.4	0.59 (0.25-1.38)
Europe (n = 250)	NR	23.7	0.61 (0.40-0.92)
Asia (n = 115)	NR	13.9	0.47 (0.26-0.86)
ECOG PS 0 (n = 288)	NR	20.1	0.57 (0.39-0.83)
ECOG PS 1 (n = 173)	29.0	17.3	0.61 (0.39-0.97)
Stage II (n = 162)	NR	NR	0.81 (0.46-1.43)
Stage III (n = 297)	30.2	13.4	0.51 (0.36-0.72)
N0 (n = 167)[b]	NR	NR	0.80 (0.48-1.32)
N1 (n = 108)[b]	NR	28.1	0.58 (0.29-1.16)
N2 (n = 182)[b,c]	30.2	10.0	0.46 (0.30-0.70)
Single-station (n = 112)	30.2	10.0	0.49 (0.29-0.84)
Multi-station (n = 69)	NR	10.0	0.43 (0.21-0.88)
Squamous (n = 234)	NR	17.0	0.46 (0.30-0.72)
Non-squamous (n = 227)	28.9	18.4	0.72 (0.49-1.07)
Current/former smoker (n = 417)	NR	17.0	0.54 (0.40-0.74)
Never smoker (n = 44)	19.7	25.0	1.32 (0.54-3.20)
PD-L1 < 1% (n = 186)[d]	29.0	19.8	0.73 (0.47-1.15)
PD-L1 ≥ 1% (n = 256)[d]	NR	15.8	0.52 (0.35-0.78)
PD-L1 1-49% (n = 159)[e]	30.2	28.1	0.76 (0.46-1.25)
PD-L1 ≥ 50% (n = 97)	NR	8.0	0.26 (0.12-0.55)
Cisplatin (n = 97) Ca	27.0	15.8	0.61 (0.35-1.08)
rboplatin (n = 347)	NR	17.3	0.53 (0.37-0.75)

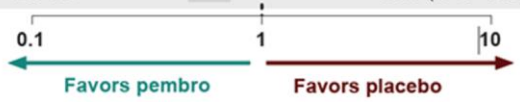
Median follow-up (range): 25.4 months (15.7-44.2).

[a]Per BICR. [b]Nodal status was N3 in 4 patients. [c]N2 subcategory was not reported in 1 patient. Baseline characteristics were similar across treatment arms in the N2 nodal status subgroup, which comprised ~40% of patients. [d]Tumor PD-L1 expression was not evaluable/indeterminate in 19 patients. [e]Most patients in this subgroup had low PD-L1 expression (median 10% across both arms).

KN-671 : EFS and OS by stage

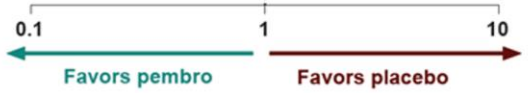
EFS

	No. of Events/No. of Patients		HR (95% CI)
	Pembro	Placebo	
Overall	174/397	248/400	0.59 (0.48–0.72)
Stage at baseline			
Stage II	40/118	62/121	0.59 (0.40–0.88)
Stage III	134/279	186/279	0.58 (0.46–0.72)
Histology			
Squamous	72/171	117/173	0.51 (0.38–0.69)
Nonsquamous	102/226	131/227	0.66 (0.51–0.86)
PD-L1 TPS status			
TPS <1%	78/138	102/151	0.75 (0.56–1.01)
TPS ≥1%	96/259	146/249	0.51 (0.39–0.66)
TPS 1%–49%	55/127	76/115	0.52 (0.36–0.73)
TPS ≥50%	41/132	70/134	0.48 (0.33–0.71)
N status at baseline[a]			
N0	59/148	83/142	0.58 (0.41–0.80)
N1	29/81	39/71	0.56 (0.35–0.91)
N2	86/168	126/187	0.63 (0.48–0.82)



OS

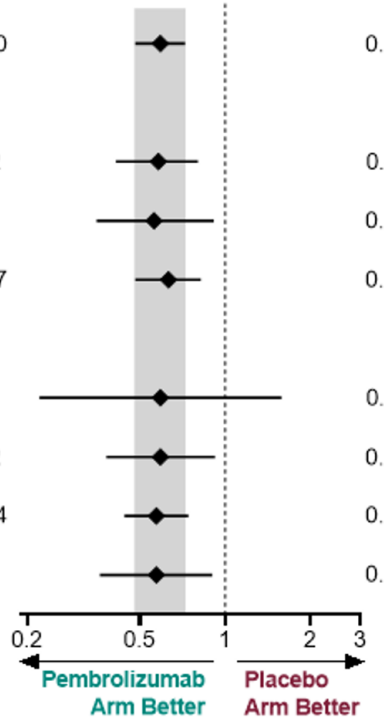
	No. of Events/No. of Patients		HR (95% CI)
	Pembro	Placebo	
Overall	110/397	144/400	0.72 (0.56–0.93)
Stage at baseline			
Stage II	26/118	39/121	0.67 (0.41–1.10)
Stage III	84/279	105/279	0.74 (0.55–0.98)
Histology			
Squamous	61/171	80/173	0.71 (0.51–0.99)
Nonsquamous	49/226	64/227	0.73 (0.50–1.06)
PD-L1 TPS status			
TPS <1%	52/138	61/151	0.91 (0.63–1.32)
TPS ≥1%	58/259	83/249	0.62 (0.45–0.87)
TPS 1%–49%	35/127	44/115	0.69 (0.44–1.07)
TPS ≥50%	23/132	39/134	0.55 (0.33–0.92)
N status at baseline[a]			
N0	40/148	52/142	0.70 (0.46–1.05)
N1	21/81	24/71	0.74 (0.41–1.33)
N2	49/168	68/187	0.74 (0.51–1.07)



Stage IIA : Surgically relevant subgroup

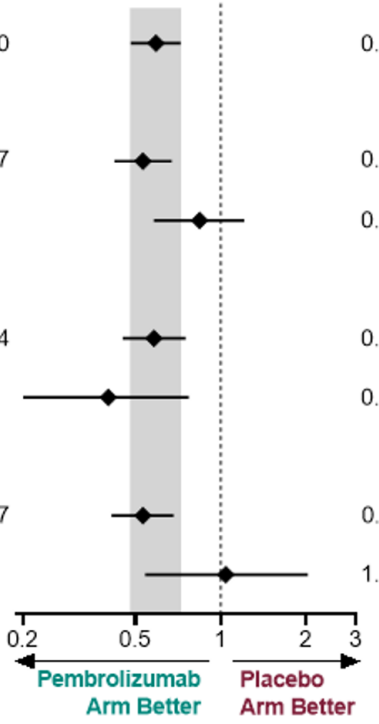
Baseline Characteristics

Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	174/397	248/400	0.59 (0.48-0.72)
N status			
cN0	59/148	83/142	0.58 (0.41-0.80)
cN1	29/81	39/71	0.56 (0.35-0.91)
cN2	86/168	126/187	0.63 (0.48-0.82)
Clinical stage			
IIA	7/22	9/19	0.59 (0.22-1.58)
IIB	33/96	53/102	0.59 (0.38-0.92)
IIIA	100/217	145/224	0.57 (0.44-0.74)
IIIB	34/62	41/55	0.57 (0.36-0.90)



Post Randomization Factors

Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	174/397	248/400	0.59 (0.48-0.72)
Surgery performed			
Yes	121/325	182/317	0.53 (0.42-0.67)
No	53/72	66/83	0.84 (0.58-1.21)
Type of surgery			
Lobectomy or bilobectomy	102/282	142/264	0.58 (0.45-0.75)
Pneumonectomy	14/37	26/39	0.40 (0.20-0.77)
Surgical completeness			
R0	102/299	144/267	0.53 (0.41-0.68)
R1 or R2	14/21	23/35	1.04 (0.54-2.03)



Data cutoff date for IA2: July 10, 2023.

STS 2024

PRINCIPLES OF SURGICAL THERAPY

The Role of Surgery in Patients with N2 NSCLC

A questionnaire was submitted to the NCCN Member Institutions in 2024 regarding their approach to patients with N2 disease. Their responses indicate the patterns of practice when approaching this difficult clinical problem.

- **All NCCN Member Institutions treat select N2 patients with multimodality therapy that includes surgery.**
- **All NCCN Member Institutions consider surgery for single-station non-bulky N2 disease.**
  - **100% consider surgery after neoadjuvant therapy**
  - **33% consider upfront surgery for single-station non-bulky N2 disease**
  - **None consider upfront surgery for multi-station or bulky (≥3 cm) N2 disease**
- **After neoadjuvant therapy, 100% consider surgery for single-station non-bulky N2 disease**
  - **76% consider surgery for single-station bulky (≥3 cm) disease**
  - **67% consider surgery for multi-station non-bulky disease**
  - **27% consider surgery for multi-station bulky (≥3 cm) disease**
- **All NCCN Member Institutions prefer neoadjuvant chemotherapy ± immunotherapy most of the time.**
  - **None use chemoradiotherapy most of the time.**
- **85% require at least stable disease on imaging after induction neoadjuvant therapy for consideration of surgery.**
  - **None require imaging complete response in mediastinal lymph nodes.**
  - **94% do not require pathologic complete response in mediastinal lymph nodes.**
  - **82% do not use pathologic evaluation of mediastinal lymph nodes to make a final decision regarding surgery.**
- **76% would consider pneumonectomy after neoadjuvant chemotherapy.**
- **54% would consider adjuvant RT for positive residual N2 disease, but only 9% would consider RT for N2 pathologic complete response.**
- **For a resected stage III tumor, adjuvant immunotherapy is given for 30% of patients and considered for another 24% of patients if PD-L1 negative.**
  - **Given for 81% and considered for another 13% if PD-L1 ≥1%–49%**
  - **Given for 91% and considered for another 9% if PD-L1 ≥50%**
- **If neoadjuvant chemo-immunotherapy is given and there is a pathologic complete response, adjuvant therapy is recommended about a quarter of the time (24%) and considered another 27% of the time.**

Opinion on Surgical Feasibility

Single Station non-bulky N2 disease

All NCCN Member Institutions consider surgery for single-station non-bulky N2 disease.

- **100% consider surgery after neoadjuvant therapy**
- **33% consider upfront surgery for single-station non-bulky N2 disease**
- **None consider upfront surgery for multi-station or bulky (≥3 cm) N2 disease**

NCCN Guidelines Version 1.2025

Opinion on Surgical Feasibility

After neoadjuvant therapy, 100% consider surgery for single-station non-bulky N2 disease

- **76% consider surgery for single-station bulky (≥3 cm) disease**
- **67% consider surgery for multi-station non-bulky disease**
- **27% consider surgery for multi-station bulky (≥3 cm) disease**

NCCN Guidelines Version 1.2025

For a resected stage III tumor…

- **For a resected stage III tumor, adjuvant immunotherapy is given for 30% of patients and considered for another 24% of patients <u>if PD-L1 negative</u>.**

Given for 81% and considered for another 13% if PD-L1 ≥1%–49%

Given for 91% and considered for another 9% if PD-L1 ≥50%

NCCN Guidelines Version 1.2025

For patients with pCR, adjuvant therapy is…

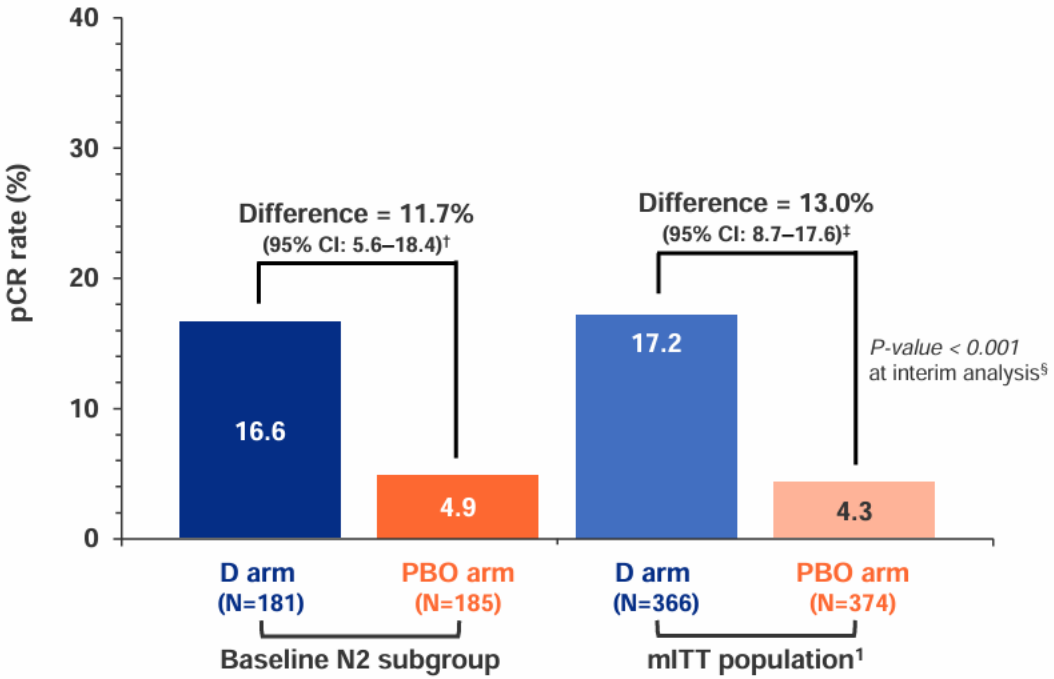
- **If neoadjuvant chemo-immunotherapy is given and there is a pathologic complete response, adjuvant therapy is recommended about a quarter of the time (24%) and considered another 27% of the time**

NCCN Guidelines Version 1.2025

pCR and MPR (baseline N2 subgroup and mITT)*

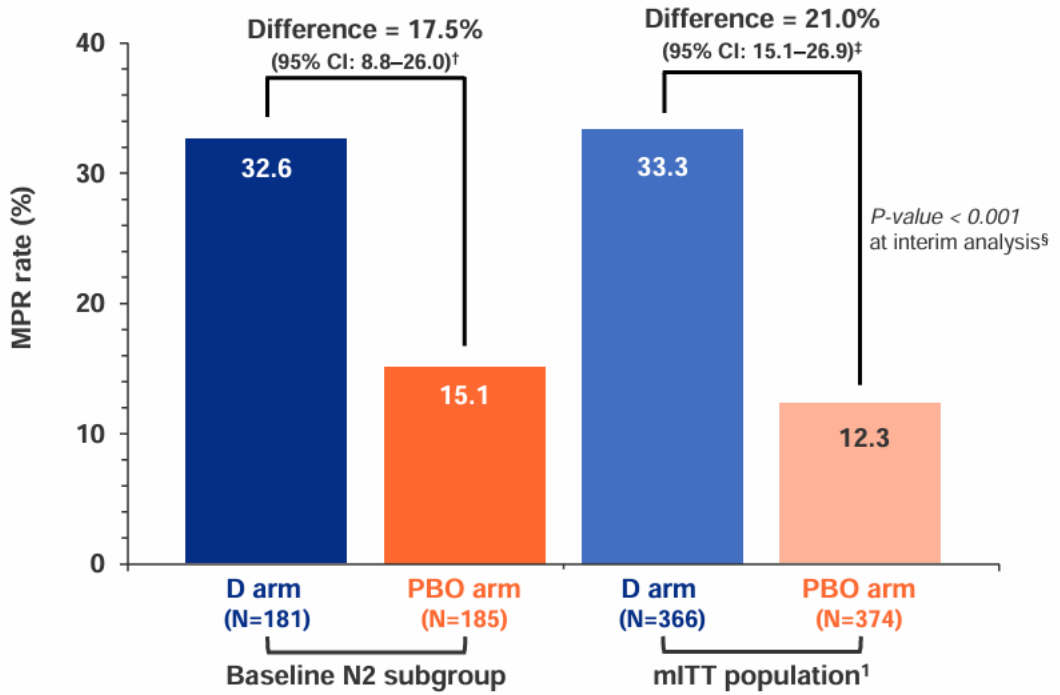
- pCR and MPR benefit in this subgroup was consistent with the mITT population and driven by patients with single-station N2 disease; note that pCR/MPR could only be achieved in eligible patients with an evaluable surgical sample

pCR (blinded central review)



	Difference in pCR rates (95% CI)¹
N2 single-station (n=273)	13.9% (6.6–21.7)
N2 multi-station (n=74)	3.8% (-9.2–18.8)

MPR (blinded central review)



	Difference in MPR rates (95% CI)¹
N2 single-station (n=273)	20.9% (10.5–31.0)
N2 multi-station (n=74)	1.8% (-13.5–18.2)

DCO = Nov 10, 2022. *Pathological response assessed using IASLC recommendations for pathologic assessment of response to therapy, including gross assessment and processing of tumor bed.[2] pCR = a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes. MPR = ≤10% viable tumor cells in lung primary tumor after complete evaluation of the resected lung cancer specimen. Patients were classified as non-responders if they were not eligible for assessment (including those with R2 resection margins by local assessment) or they did not have a surgical specimen. †CIs calculated by unstratified Miettinen and Nurminen method. ‡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 in the mITT population 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).

[1]Heymach JV, et al. N Engl J Med 2023;389:1672–84;
[2]Travis WD, et al. J Thorac Oncol 2020;15:709-40.

AGEAN
:Operability After Neoadjuvant Chemoimmunotherapy


2024 ASCO ANNUAL MEETING

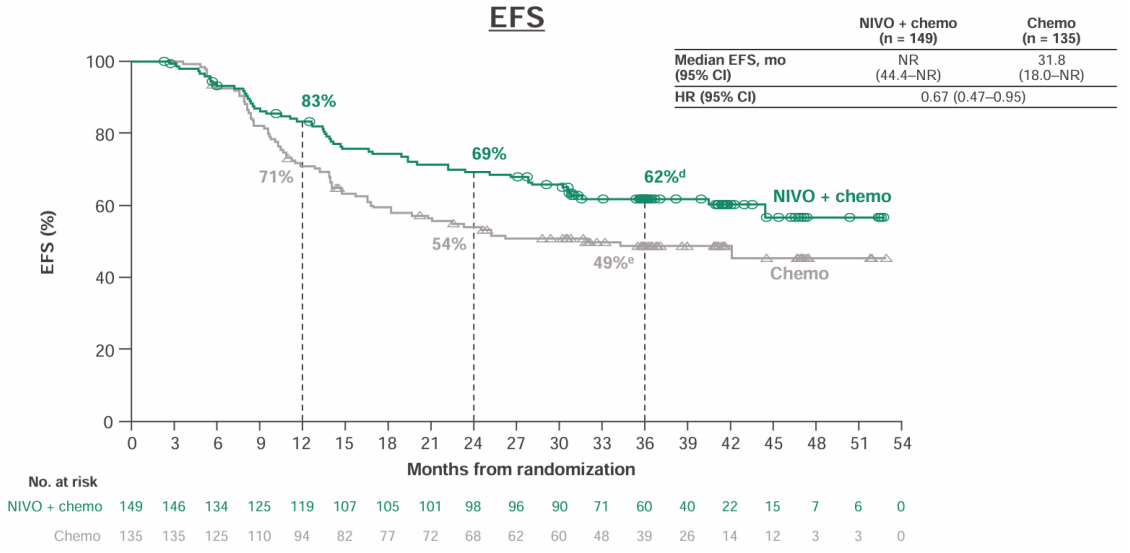
Abstract 8011

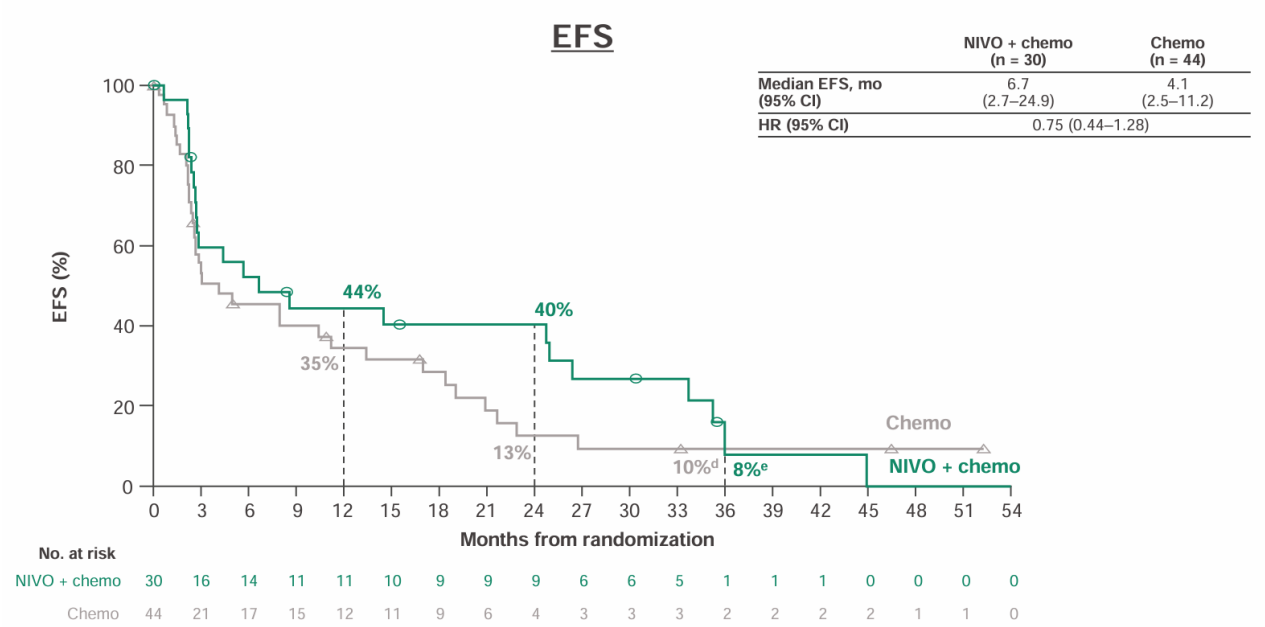
Outcomes with Perioperative Durvalumab in Patients with Resectable NSCLC and Baseline N2 Lymph Node Involvement (N2 R-NSCLC)

An Exploratory Subgroup Analysis of AEGEAN

Study phase		Baseline N2 subgroup		mITT population[1]	
		D arm (n=181)	PBO arm (n=185)	D arm (N=366)	PBO arm (N=374)
Neoadjuvant phase	Randomized, n (%)	181 (100)	185 (100)	366 (100)	374 (100)
	Received Tx, n (%)	181 (100)	182 (98.4)	366 (100)	371 (99.2)
	Completed 4 cycles of both CT agents, n (%)	151 (83.4)	157 (84.9)	310 (84.7)	326 (87.2)
	Completed 4 cycles of durvalumab / placebo, n (%)	153 (84.5)	159 (85.9)	318 (86.9)	331 (88.5)
Surgery	Underwent surgery,* n (%)	141 (77.9)	144 (77.8)	295 (80.6)	302 (80.7)
	Did not undergo surgery,*† n (%)	40 (22.1)	41 (22.2)	71 (19.4)	72 (19.3)
	Completed surgery,* n (%) *– R0 resection, n (% of completed surgery)*	133 (73.5) *126 (94.7)*	133 (71.9) *122 (91.7)*	284 (77.6) *269 (94.7)*	287 (76.7) *262 (91.3)*
	Did not complete surgery,* n (%)	8 (4.4)	11 (5.9)	11 (3.0)	15 (4.0)
Adjuvant phase *(ongoing)*	Started durvalumab / placebo,‡ n (%)	116 (64.1)	114 (61.6)	241 (65.8)	237 (63.4)
	Completed durvalumab / placebo, n (%)	41 (22.7)	36 (19.5)	88 (24.0)	79 (21.1)
	Discontinued durvalumab / placebo, n (%)	38 (21.0)	34 (18.4)	68 (18.6)	70 (18.7)
	Ongoing durvalumab / placebo, n (%)	37 (20.4)	44 (23.8)	85 (23.2)	88 (23.5)

CheckMate 816
EFS in patients with or without definitive surgery





CheckMate 816 (NIVO + chemo in resectableNSCLC): 3-y efficacy and safety by definitive surgery status (ASCO 2023)

Midpoint Summary-4

- Survival benefit of perioperative Tx.

  : Stage IIIA> stage IIB stage IIIB>Stage IIA
- Single station N2 vs Multi station N2
- PD-L1 expression >1%

The goal of Treatment

Lung Cancer

- Lung Cancer Basics
- Saved By The Scan
- Screening Resources
- Symptoms & Diagnosis
- Treatment
  - Types of Lung Cancer Treatment
  - Manage Side Effects
  - Stay Healthy
  - Treatment Assistance
  - Your Lung Cancer Team
  - **Your Lung Cancer, Your Goals**
  - When To Call Your Doctor
- Living with Lung Cancer
- Support for Family & Friends
- Get Involved
- Healthcare Professionals
- Resource Library

When making lung cancer treatment goals, ask yourself two questions:

1. What do I want out of lung cancer treatment?
2. Is this a realistic goal with my type of lung cancer?

You will work with your lung cancer care team to decide if the goal of treatment should be curing your lung cancer, controlling your lung cancer or being comfortable.

Cure. Every doctor, patient and caregiver hope that treatment will get rid of the cancer completely. This is a more realistic goal for some lung cancer patients than for others. It depends on your lung cancer profile—the type and stage of your cancer and what treatment options you are eligible for. When a lung cancer cure is your goal, you may be willing to endure more intense side effects in return for the chance at a cure.

Control. Sometimes when your cancer is at a later stage or previous lung cancer treatments have been unsuccessful, your treatment goal might change to controlling your lung cancer. This might mean choosing treatments that try to shrink or stop your cancer from growing. If this is your goal, you might not want to choose harsher lung cancer treatments and the side effects they may cause.

Comfort. If you have advanced-stage lung cancer or one that hasn't responded to treatments, you might consider treatment that focuses on symptom management that allows you to be comfortable and enjoy your life instead of treatment that will continue to address the cancer but might make you suffer. You and your doctor will work together to manage your lung cancer symptoms and help you maintain a good quality of life.

The goals listed above are broad lung cancer treatment goals. Sometimes your goals are short-term and specific. Maybe you want to feel well enough to attend a family event, or maybe you want to make sure you can be with your family and friends during a holiday. Lung cancer treatment is not perfect, but often doctors and nurses can adapt the delivery of your treatment to meet your short-term and long-term goals.

Download the Treatment Decision-Making Worksheet and Plan to fill out with your doctor.

When discussing your goals with your doctors and family members, the conversation likely will turn to your lung cancer prognosis. You may wonder:

Treatment priorities in oncology: do we want to live longer or better?

Marta GN et al. Clinics. 2014

- Between January and September 2010
- 214 people were interviewed
- 101 patients
- 44 health-care professionals
- 69 laypersons

Treatment priorities in oncology: do we want to live longer or better?

Marta GN et al. Clinics. 2014

Table 1 - Responses to the question about who should be involved in treatment decisions for a fictitious cancer patient (the responses did not add up to 100%).

Who should be involved?	Patients	Health-care professionals	Laypersons
The physician	74.7%	75.7%	50.7%
The patient	58.2%	75.7%	44.9%
Relatives	35.4%	48.6%	33.3%
Others members of the health-care team	2.5%	13.5%	14.5%
All	21.5%	21.6%	46.4%

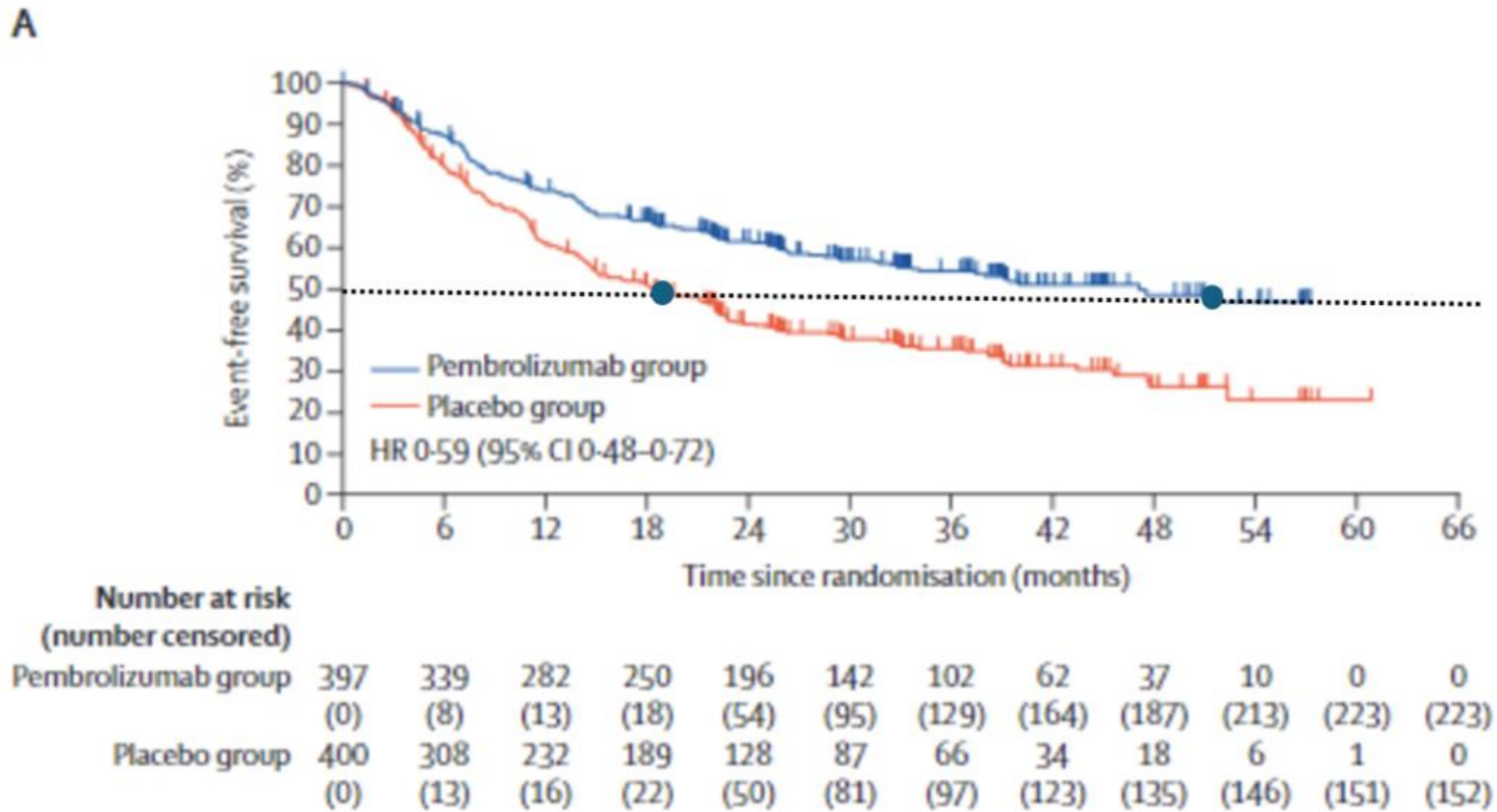
Treatment priorities in oncology: do we want to live longer or better?

Marta GN et al. Clinics. 2014

Table 4 - Treatment aggressiveness for fictitious cancer patients in four age groups, according to participant group (see Appendix for complete definitions of treatment types).

Fictitious Patient's age	Treatment type	Patients	Health-care professionals	Laypersons
5 years old	Very toxic, with high chance of cure	84.7%	93.2%	72.5%
	Toxic but able to prolong survival	10.2%	4.5%	14.5%
	Low toxicity but less effective than others	5.1%	2.3%	13.0%
16 years old	Very toxic, with high chance of cure	89.9%	97.7%	78.3%
	Toxic but able to prolong survival	7.1%	2.3%	18.8%
	Low toxicity but less effective than others	3.0%	0%	2.9%
50 years old	Very toxic, with high chance of cure	78.6%	81.0%	64.7%
	Toxic but able to prolong survival	16.3%	11.9%	27.9%
	Low toxicity but less effective than others	5.1%	7.1%	7.4%
70 years old	Very toxic, with high chance of cure	44.3%	18.6%	35.3%
	Toxic but able to prolong survival	23.7%	30.2%	17.6%
	Low toxicity but less effective than others	32.0%	51.2%	47.1%

Chance of Cure



Treatment priorities in oncology: do we want to live longer or better?

Marta GN et al. Clinics. 2014

Table 5 - Prioritization between survival time and quality of life (QOL) using weights.

Scenario	Weight for lifespan	Weight for QOL	Patients	Health-care professionals	Laypersons
A	10	0	11.6%	2.3%	6.0%
B	8	2	13.7%	11.6%	6.0%
C	6	4	28.4%	14.0%	23.9%
D	4	6	26.3%	53.5%	37.3%
E	2	8	14.7%	16.3%	19.4%
F	0	10	5.3%	2.3%	7.5%

Table 6 - Prioritization between survival time and quality of life using weights and grouping scenarios (see Appendix for definitions).

Scenario	Patients	Health-care professionals	Laypersons
A, B or C	53.7%	27.9%	35.8%
D, E or F	46.3%	72.1%	64.2%

Case 3 (56/M, 20 PY. Ex)

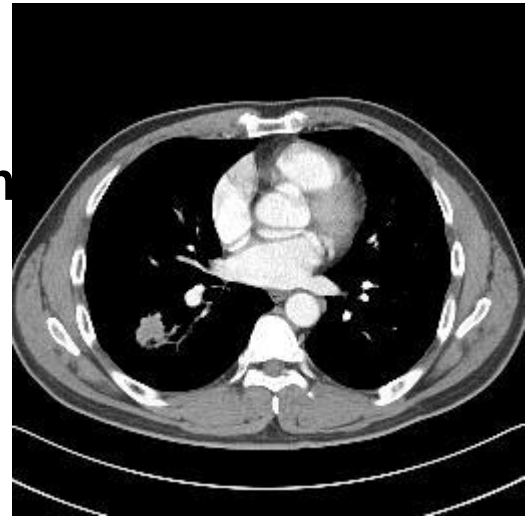
#2024.3.18

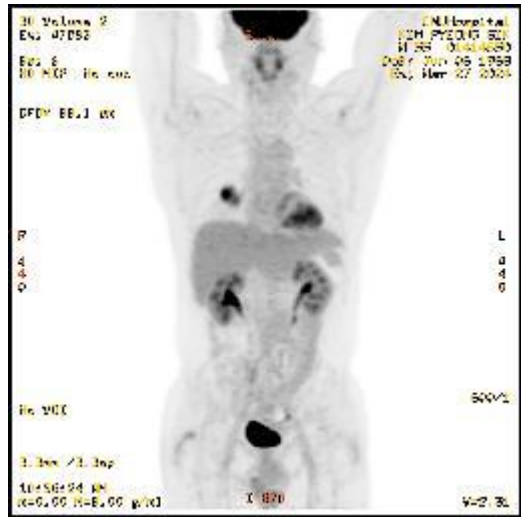
NSCLC adenocarcinomaT2bN0M0 IIA (4.9cm

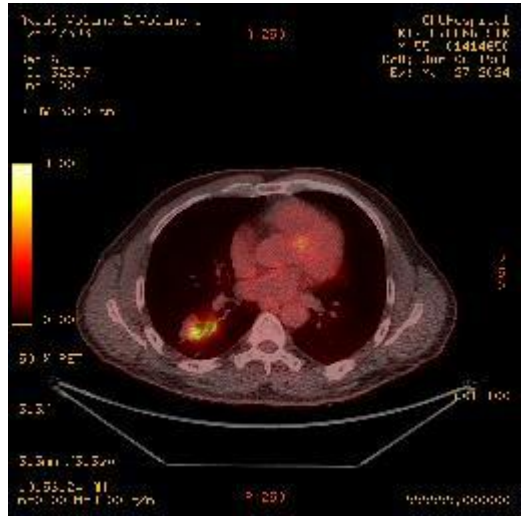
EGFR wild, ALK negative

MET Exon 14 deletion

1% PD-L1 22c3







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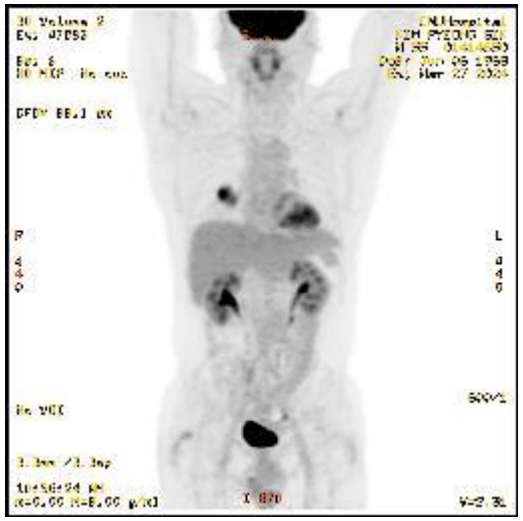
Case 3 (56/M, 20 PY. Ex)



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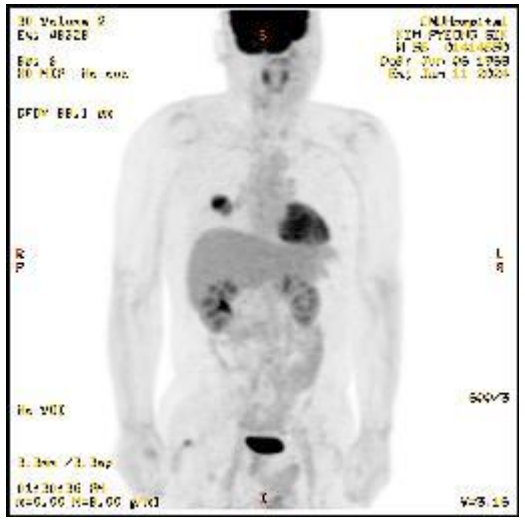

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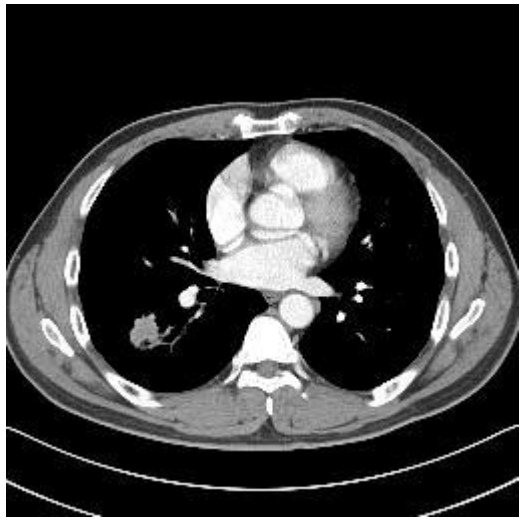

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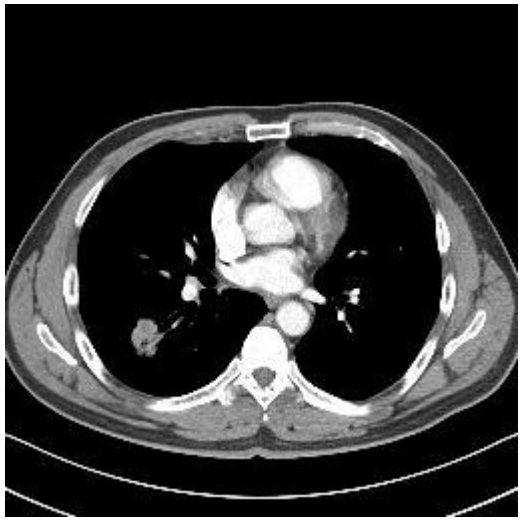

2024.06.13

Patholog
y

◎ 병 리 진 단　　등록일시: 2024-08-02 15:55:12

A-O) Lung, right lobe, lobectomy:
INVASIVE ADENOCARCINOMA, non-mucinous type, micropapillary and papillary predominant (A2-A7), with
1) invasive tumor size: 4cmx3.3cmx2.5cm
2) tumor focality: single focus, right lower lobe
3) pleura invasion: absent (PL 0)
4) lymphovascular invasion: Present
5) perineural invasion: not identified
6) micropapillary pattern: Present
7) spread through air spaces: Present
8) lymphoplasmacytic reaction: Present
9) necrosis: absent
10) bronchial resection margin: free from the tumor (distance from margin: 2cm)
11) No tumor, labled "RML1" and "RML2" (B1-B2, C)
12) Lymph node metastasis: Positive (8/20) (LN4:0/5; LN7:0/3; LN7-1:2/4; LN10:1/1; LN10-1:1/1; LN10-2:0/1; LN11R:1/2; LN11-1:1/1; LN11-2:1/1; LN11-3:1/1; LN11-4:0/0; LN11-5:0/0) (D-O)

* pT2a, pN2 (by AJCC staging system, 8th edition)

<Special stain results> (A6)
1) Elastic stain: Negative for pleural tumor invasion
2,3) Alcian blue and D-PAS: negative

<Immunohistochemical stain results> (A6)
1) CD31: positive for lympphovascular tumor invasion
2) p40: negative

What treatment would you choose next?

Residual viable tumor

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Association of Pathologic Regression With Event-Free Survival in the KEYNOTE-671 Study of Perioperative Pembrolizumab for Early-Stage NSCLC

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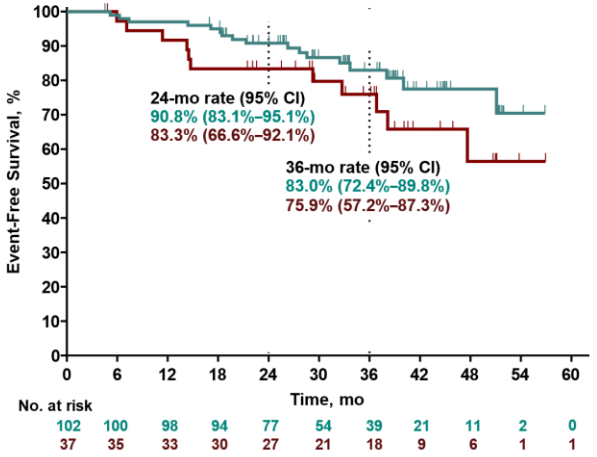
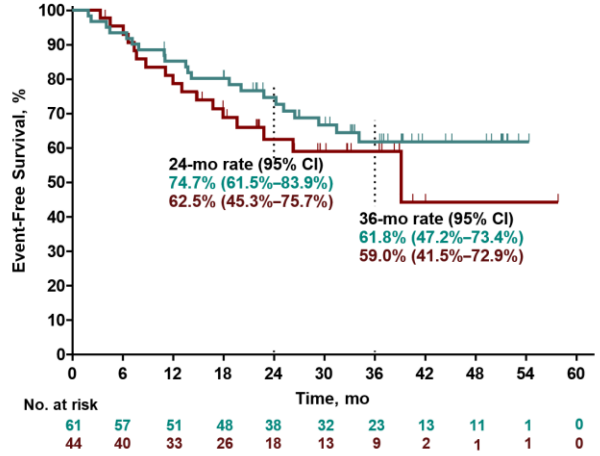
%RVT 0%–≤5%

	Pts w/ Event	Median, mo (95% CI)	HR (95% CI)
Pembro Arm	16.7%	NR (NR–NR)	0.58 (0.27–1.23)
Placebo Arm	29.7%	NR (38.2–NR)	



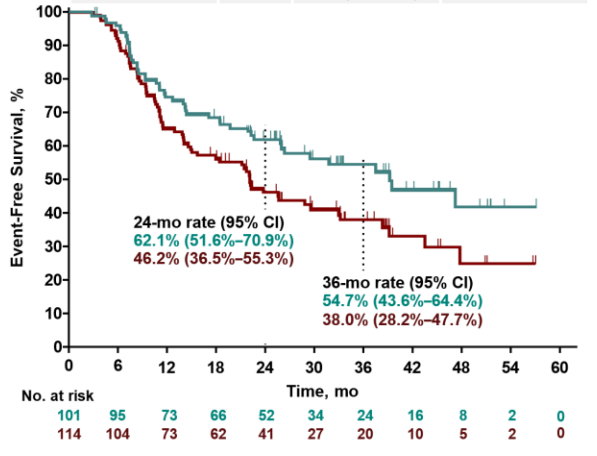
%RVT >5%–≤30%

	Pts w/ Event	Median, mo (95% CI)	HR (95% CI)
Pembro Arm	34.4%	NR (34.1–NR)	0.73 (0.38–1.38)
Placebo Arm	38.6%	39.1 (19.6–NR)	



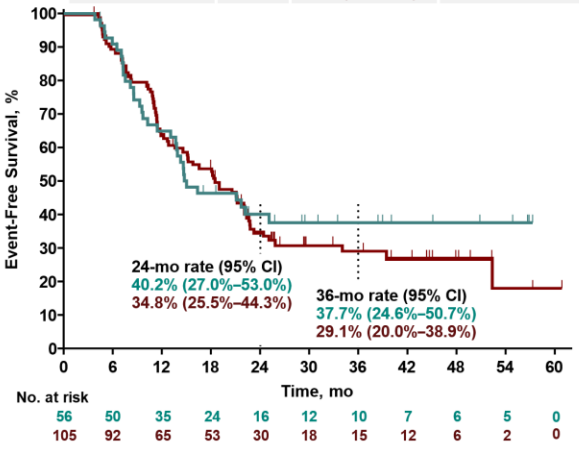
%RVT >30%–≤60%

	Pts w/ Event	Median, mo (95% CI)	HR (95% CI)
Pembro Arm	45.5%	39.2 (26.0–NR)	0.65 (0.45–0.94)
Placebo Arm	60.5%	22.1 (14.9–33.0)	



%RVT >60%

	Pts w/ Event	Median, mo (95% CI)	HR (95% CI)
Pembro Arm	58.9%	15.0 (13.1–NR)	0.90 (0.60–1.36)
Placebo Arm	67.6%	18.5 (13.6–22.1)	



Summary and Key Takeaways

- Adjuvant immunotherapy should always be considered after neoadjuvant chemoimmunotherapy in stage II–IIIB patients.
- Patient selection is crucial to ensure they can tolerate surgery after neoadjuvant chemoimmunotherapy.
- Multi-station N2 and perioperative chemoimmunotherapy
- High PD-L1 expression is a key predictor not only for pCR but also for the efficacy of adjuvant immunotherapy.

Thank you for your attentions