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# Tratamento Neoadjuvante no CPNPC: Como e Quando?



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**AC Camargo Cancer Center**

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## Declaração de conflitos de interesse em potencial

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- De acordo com a Resolução 1595/2000 do Conselho Federal de Medicina (CFM) e com a RDC 96/2008 da Agência Nacional de Vigilância Sanitária (ANVISA), declaro as seguintes atividades:
  - Pesquisa Clínica: Participação como investigador de ensaios clínicos patrocinados (Roche, Pfizer, MSD, BMS, AZ, Jansen, Lilly, Incyte etc);
  - Apresentações (*speaker*): MSD, Roche, Lilly, Pfizer, Takeda, BMS, Amgen, AZ, Merck
  - Advisory board e consultorias: MSD, Pfizer, Lilly, Takeda, Roche
  - Patrocínio a congressos: BMS, MSD, Pfizer, Roche, AZ, Takeda, Sanofi
  - Minha esposa trabalha na área de pesquisa clínica da AZ

## Premissa e perguntas para esta apresentação

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Dadas as opções para o tratamento de pacientes com CPNPC inicial ou localmente avançado (EGFR/ALK negativo, se não escamoso):



**Cirurgia** ⇨ Tratamento adjuvante (QT adjuvante +/- Imunoterapia)  
QT + Imunoterapia neoadjuvante ⇨ **Cirurgia** +/- Imunoterapia adjuvante)  
QT + Radioterapia ⇨ Imunoterapia de consolidação



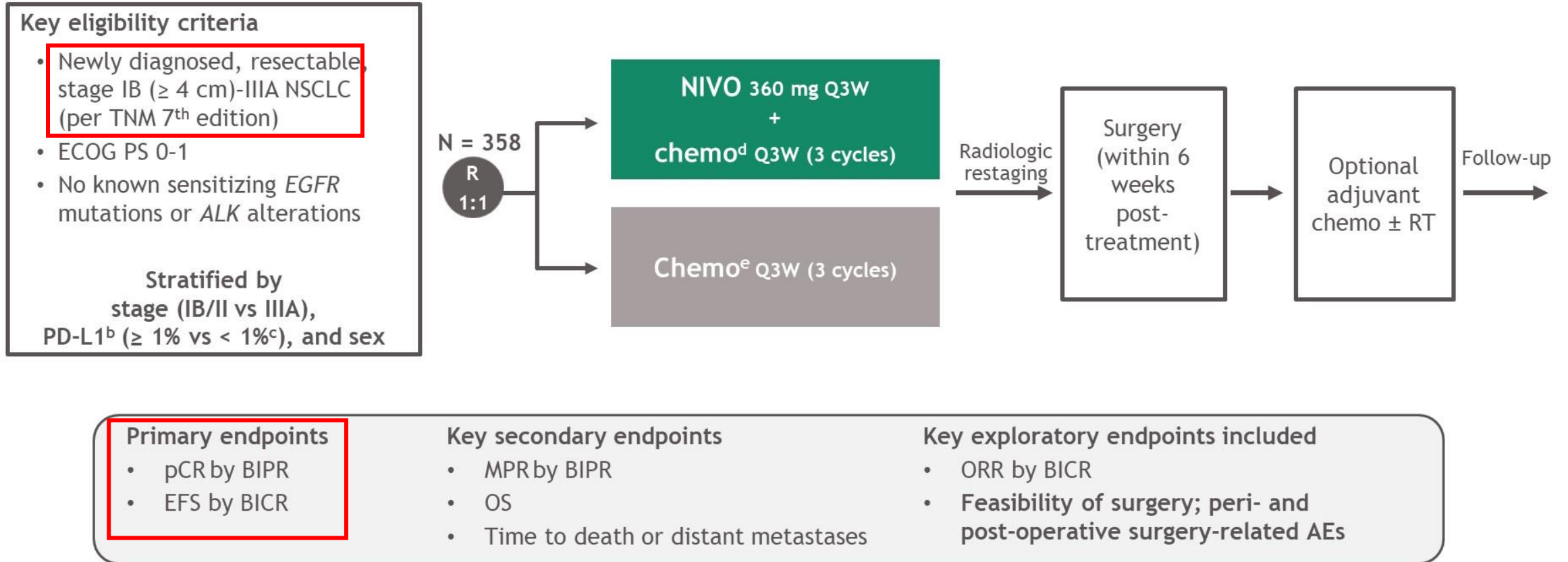
- Quando escolher o tratamento neoadjuvante?
- Como viabilizar o tratamento adjuvante?

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***Quem são os pacientes elegíveis?***

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# CheckMate 816 study design<sup>a,1</sup>



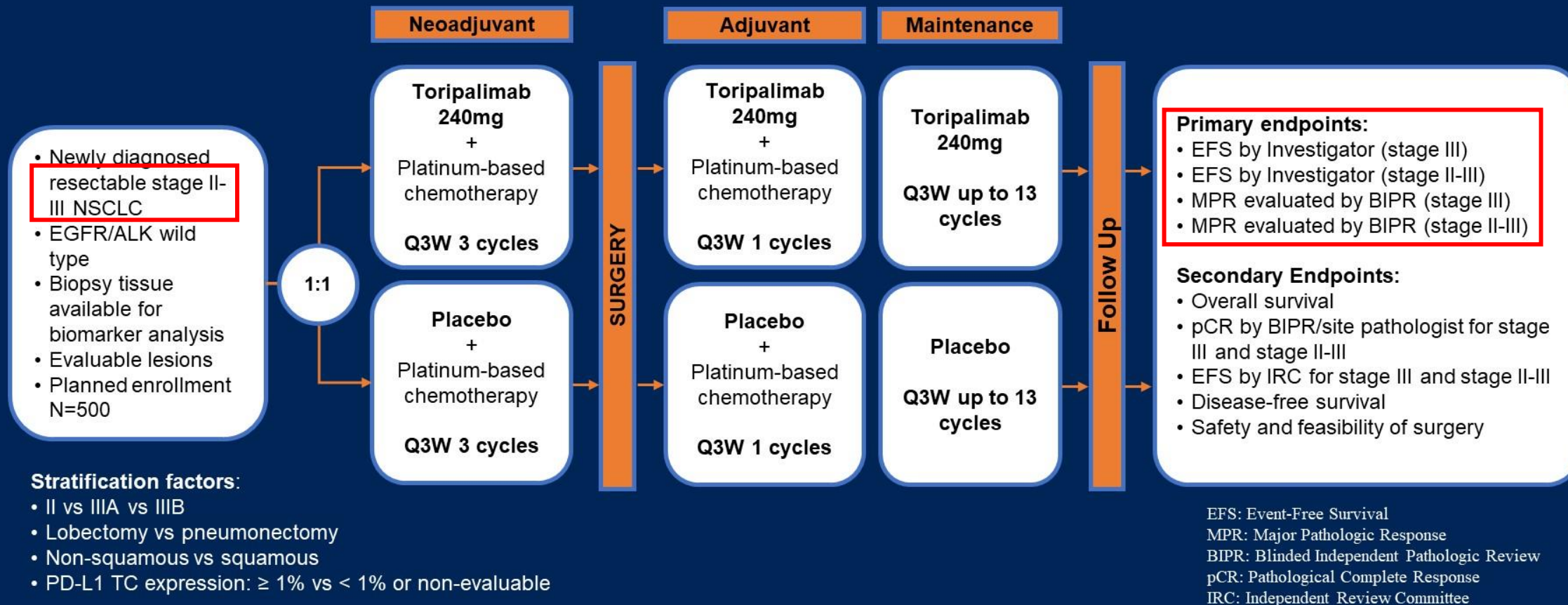
Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

<sup>a</sup>NCT02998528; this study included an exploratory arm: NIVO 3 mg/kg Q2W (3 cycles) + ipilimumab 1 mg/kg (cycle 1 only). Data from this arm are not included in this presentation; <sup>b</sup>Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); <sup>c</sup>Included patients with PD-L1 expression status not evaluable and indeterminate; <sup>d</sup>NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; <sup>e</sup>Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin.

1. Forde PM, et al. Oral presentation at the AACR Annual Meeting; April 8-10, 2021; virtual. Abstract 5218.

# Neotorch Study Design

- Neotorch is a randomized, double-blind, placebo-controlled, Phase III trial evaluating the efficacy and safety of perioperative toripalimab plus chemotherapy, followed by toripalimab maintenance vs perioperative chemotherapy alone in resectable stage II/III non-small cell lung cancer (NSCLC)

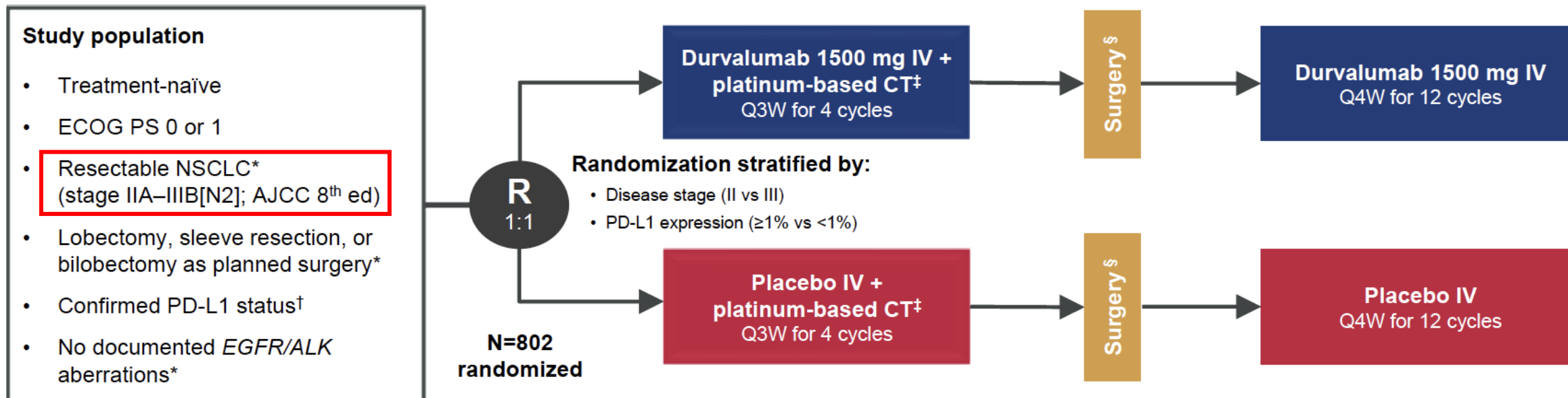


# Baseline characteristics of Stage III Patients

	Toripalimab + chemo n=202	Placebo + chemo n=202	Total n=404
<b>Median age, years (range)</b>	62 (31- 70)	61 (29 - 70)	62 (29 - 70)
<b>Age &lt; 65 years, n (%)</b>	140 (69.3)	138 (68.3)	278 (68.8)
<b>Gender, n (%)</b>			
Male	181 (89.6)	189 (93.6)	370 (91.6)
<b>Smoking status, n (%)</b>			
Non-smoker	28 (13.9)	21 (10.4)	49 (12.1)
Smoker	30 (14.9)	23 (11.4)	53 (13.1)
Former	144 (71.3)	158 (78.2)	302 (74.8)
<b>ECOG, n (%)</b>			
0	70 (34.7)	73 (36.1)	143 (35.4)
1	132 (65.3)	129 (63.9)	261 (64.6)
<b>Histology, n (%)</b>			
Non-squamous	45 (22.3)	45 (22.3)	90 (22.3)
Squamous	157 (77.7)	157 (77.7)	314 (77.7)
<b>PD-L1 expression, n (%)</b>			
TC ≥ 1%	133 (65.8)	132 (65.3)	265 (65.6)
TC < 1% or non-evaluable	69 (34.2)	70 (34.7)	139 (34.4)
<b>Stage, n (%)</b>			
IIIA	136 (67.3)	136 (67.3)	272 (67.3)
IIIB	65 (32.2)	64 (31.7)	129 (31.9)
IIIC	1 (0.5)	0	1 (0.2)
IV	0	2 (1.0)	2 (0.5)

Data cut-off date: Nov. 30, 2022

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



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

## Primary:

- pCR by central lab (per IASLC 2020<sup>1</sup>)
- EFS using BICR (per RECIST v1.1)

## Key secondary:

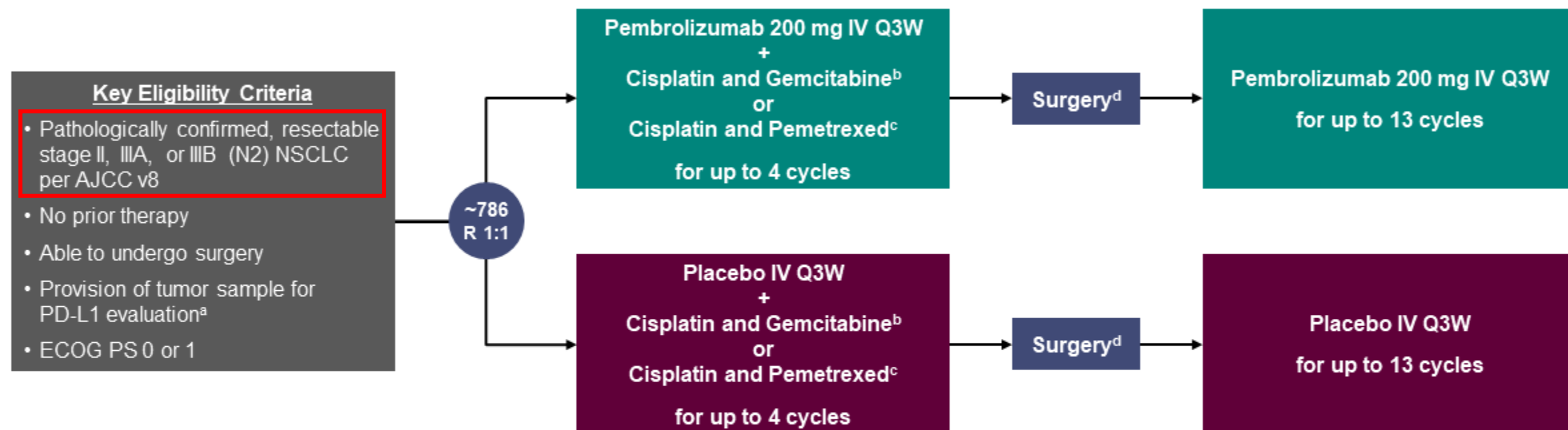
- MPR by central lab (per IASLC 2020<sup>1</sup>)
- DFS using BICR (per RECIST v1.1)
- OS

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



# KEYNOTE-671 Study Design

## Randomized, Double-Blind, Phase 3 Trial



### Stratification Factors

- Disease stage (II vs III)
- PD-L1 TPS<sup>a</sup> (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

**Dual primary end points:** EFS per investigator review and OS

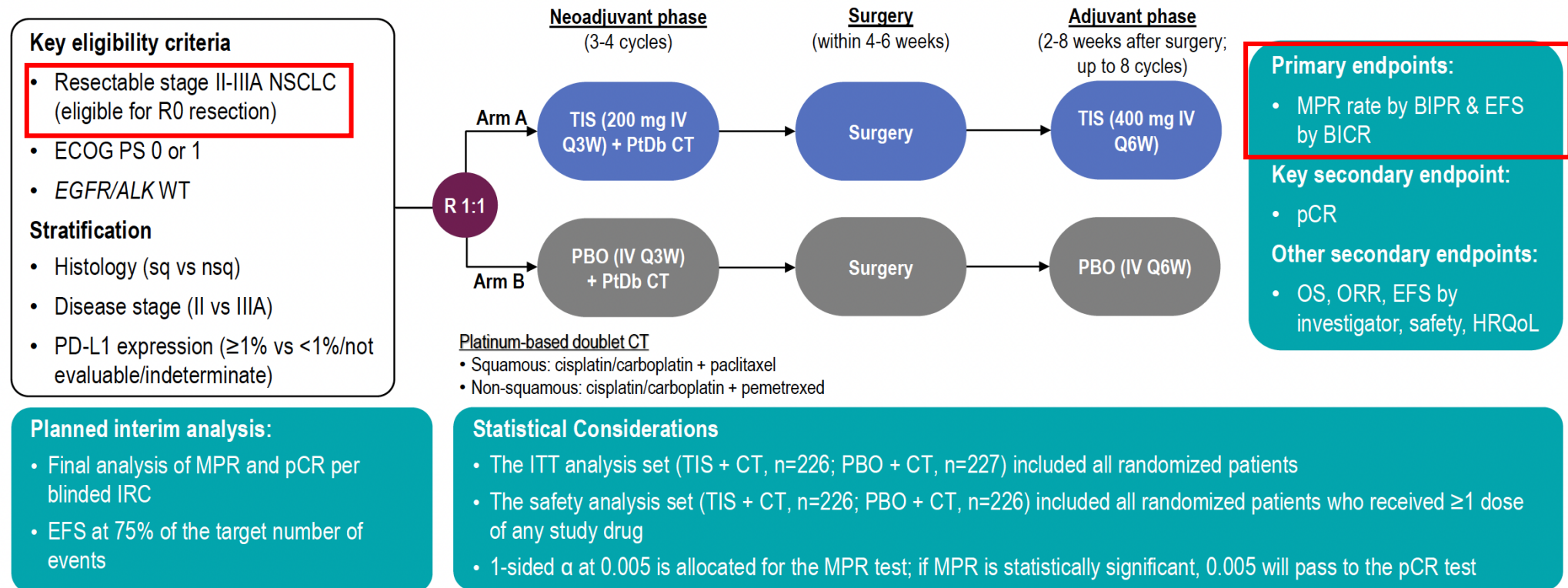
**Key secondary end points:** mPR and pCR per blinded, independent pathology review and safety

<sup>a</sup> Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. <sup>b</sup> Cisplatin 75 mg/m<sup>2</sup> IV Q3W + gemcitabine 1000 mg/m<sup>2</sup> IV on days 1 and 8 Q3W was permitted for squamous histology only. <sup>c</sup> Cisplatin 75 mg/m<sup>2</sup> IV Q3W + pemetrexed 500 mg/m<sup>2</sup> IV Q3W was permitted for nonsquamous histology only. <sup>d</sup> Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease. ClinicalTrials.gov identifier: NCT03425643.

# RATIONALE 315: Tislelizumab + QT

## Study Design

RATIONALE-315: randomized, double-blind, placebo-controlled, phase 3 study



BICR, blinded independent central review; BIPR, blinded independent pathology review; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; HRQoL, health-related quality of life; IRC, independent review committee; ITT, intention-to-treat; IV, intravenously; MPR, major pathological response; NSCLC, non-small cell lung cancer; nsq, nonsquamous; ORR, objective response rate; OS, overall survival; PBO, placebo; pCR, pathological complete response; PD-L1, programmed-death ligand 1; PtDb, platinum-based doublet; Q3W, once every 3 weeks; Q6W, once every 6 weeks; sq, squamous; R0, pathological complete resection of the primary tumor; TIS, tislelizumab; WT, wild type.

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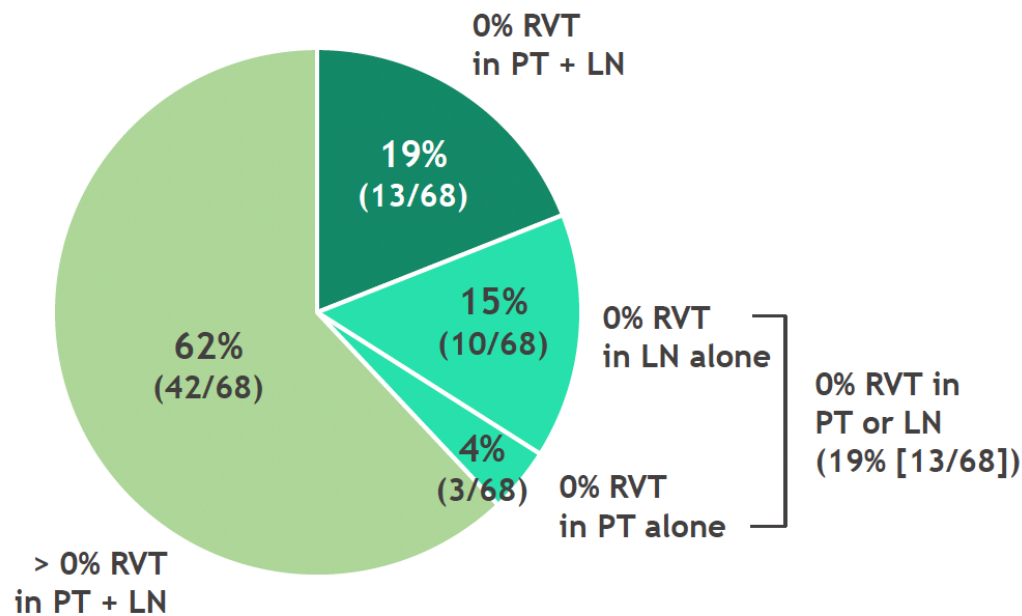
***Resposta completa patológica***

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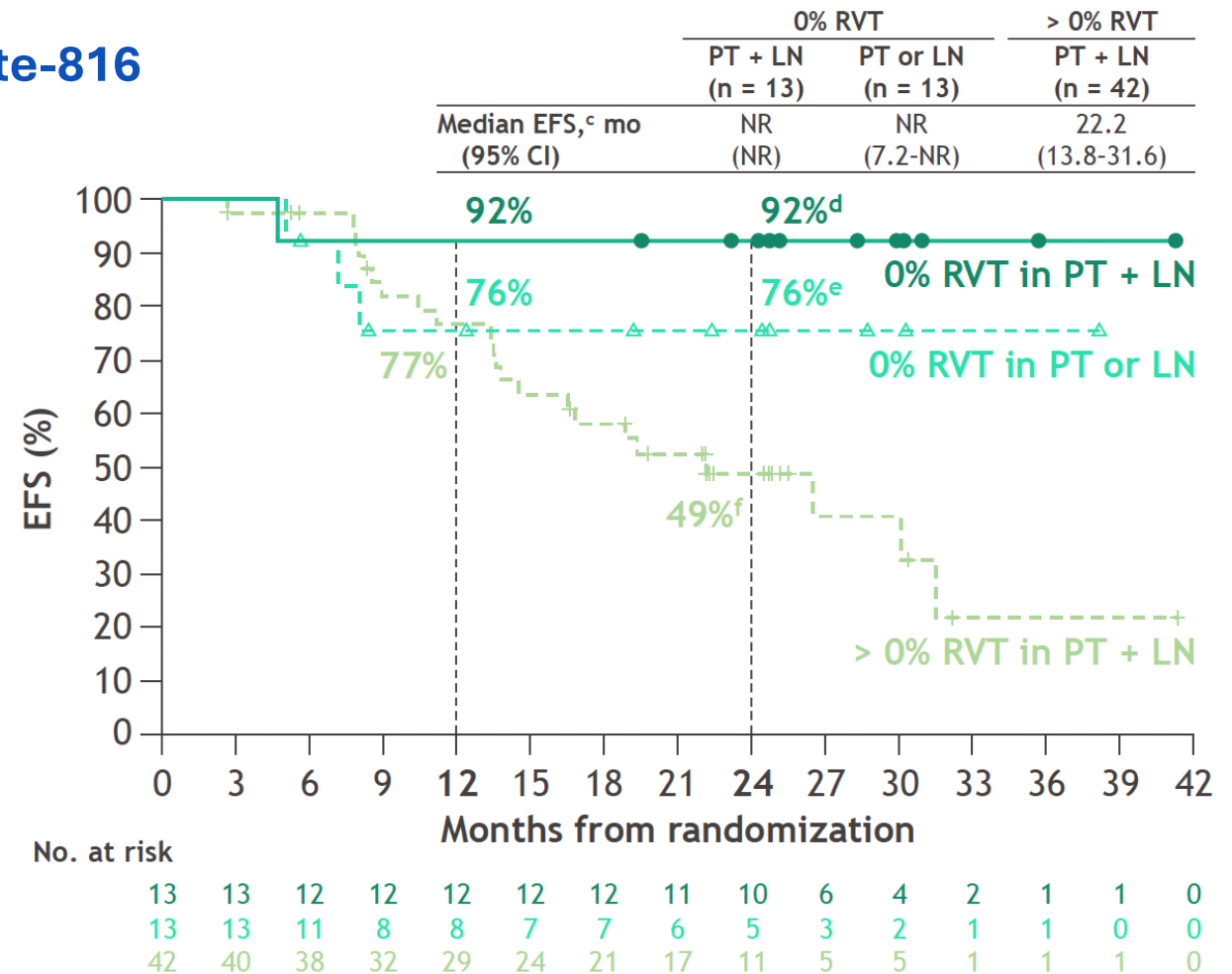
# Células tumorais viáveis no sítio primário ou nos linfonodos estão associadas a pior EFS

% RVT (primary tumor [PT] and LN)<sup>b</sup>

## Checkmate-816



EFS



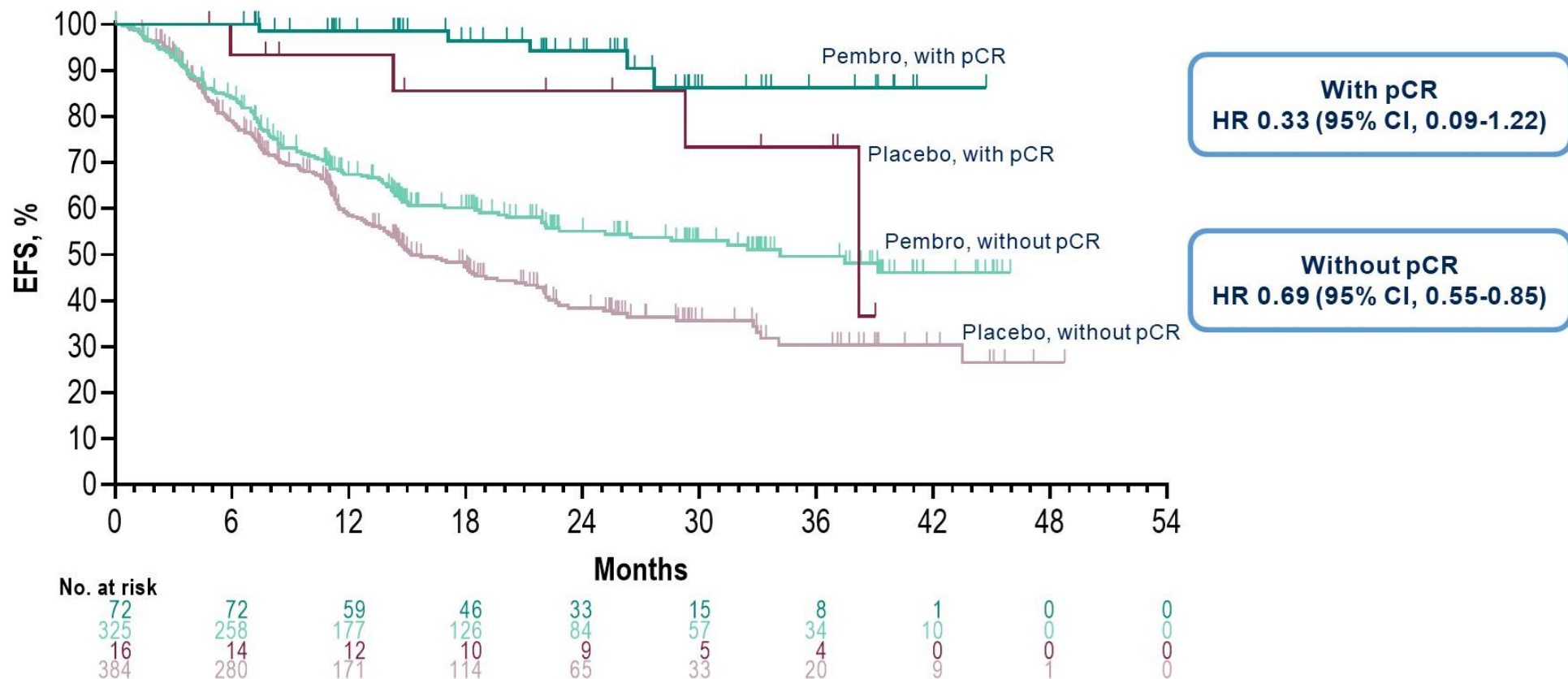
Minimum / median follow-up: 21 months / 29.5 months.

<sup>a</sup>LN involvement refers to pathologic evidence of LN disease at resection that had or had not fully regressed after neoadjuvant treatment (0% or > 0% RVT in the resected LN).

<sup>b</sup>Patients in the chemo arm with 0% RVT in both PT + LN, 1% (1/74); PT alone, 1% (1/74); LN alone, 4% (3/74); either PT or LN, 5% (4/74); > 0% RVT in PT + LN, 93% (69/74).

<sup>c</sup>HRs were not computed because of the low number of events in the 0% RVT subgroups. 95% CI: <sup>d</sup>57-99, <sup>e</sup>42-91, <sup>f</sup>32-64.

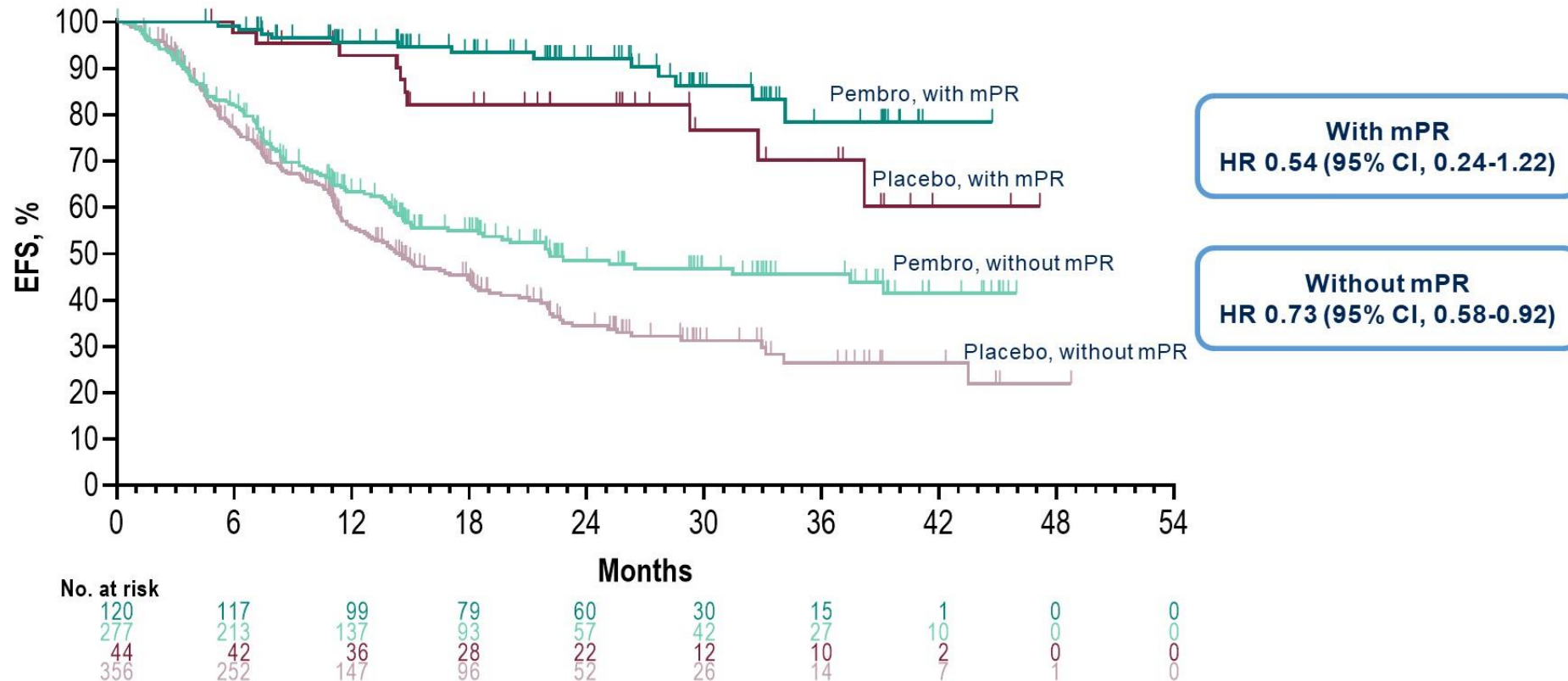
## Exploratory Analysis of EFS by pCR Status



pCR defined as absence of residual invasive cancer in resected primary tumor and lymph nodes (ypT0/Tis ypN0). EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).



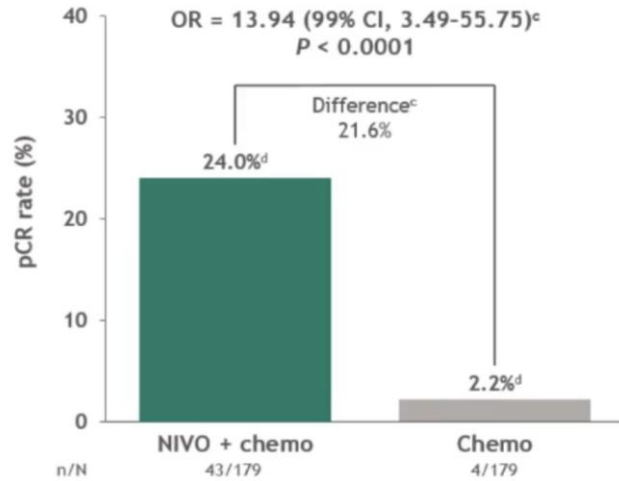
# Exploratory Analysis of EFS by mPR Status



mPR defined as  $\leq 10\%$  viable tumor cells in resected primary tumor and lymph nodes. EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

### CM-816: Nivolumabe + QT

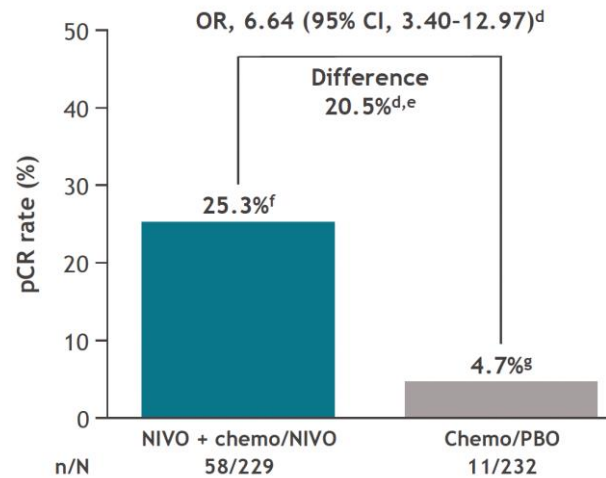
Primary endpoint: ITT (ypTONO)<sup>b</sup>



Patrick Forde et al. AACR 2021

### CM-77T: Nivolumabe + QT

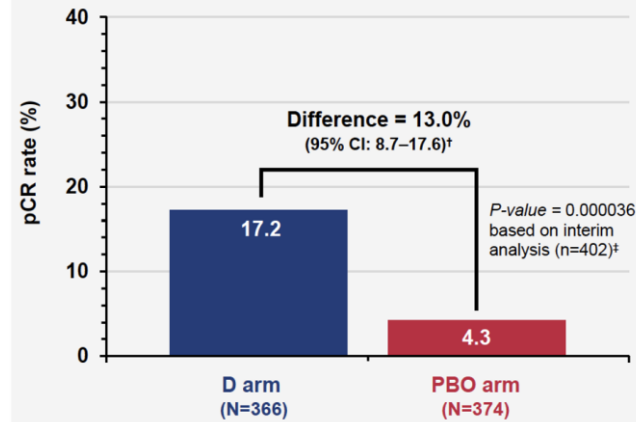
pCR<sup>c</sup>



Tina Cascone et al. ESMO 2023

### AEGEAN: Durvalumabe + QT

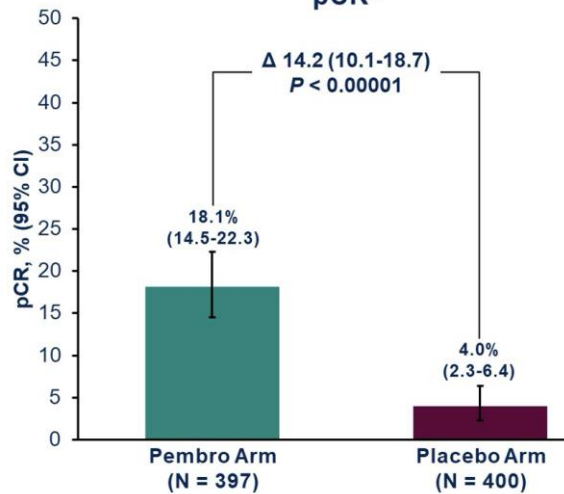
pCR (central lab)



John Heymach et al. AACR 2023

### KN-671: Pembrolizumabe + QT

pCR<sup>b</sup>



Heather Wakelee et al. ASCO 2023

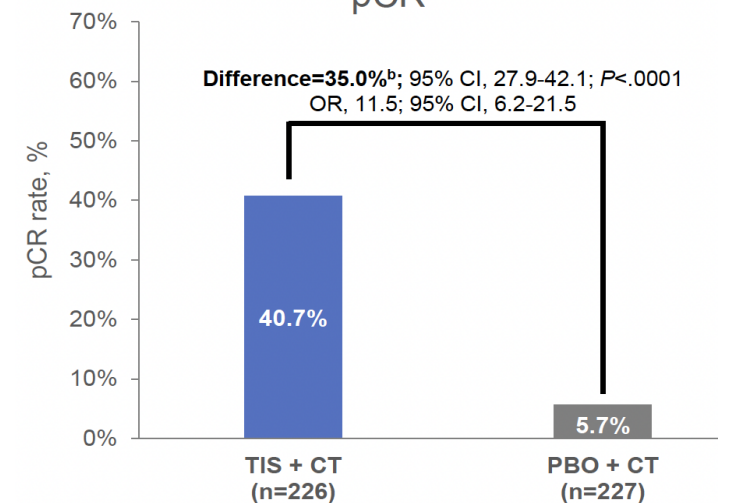
### NEOTORCH: Toripalimabe + QT

	Toripalimab + Chemo (N=202)
pCR assessed by local pathologist	
n (%)	57 (28.2)
95% CI	22.1, 35.0

Shun Lu et al. ASCO Plenary Series, 2023

### RATIONALE 315: Tislelizumabe + QT

pCR<sup>a</sup>



Dongsheng Yue et al. ESMO 2023

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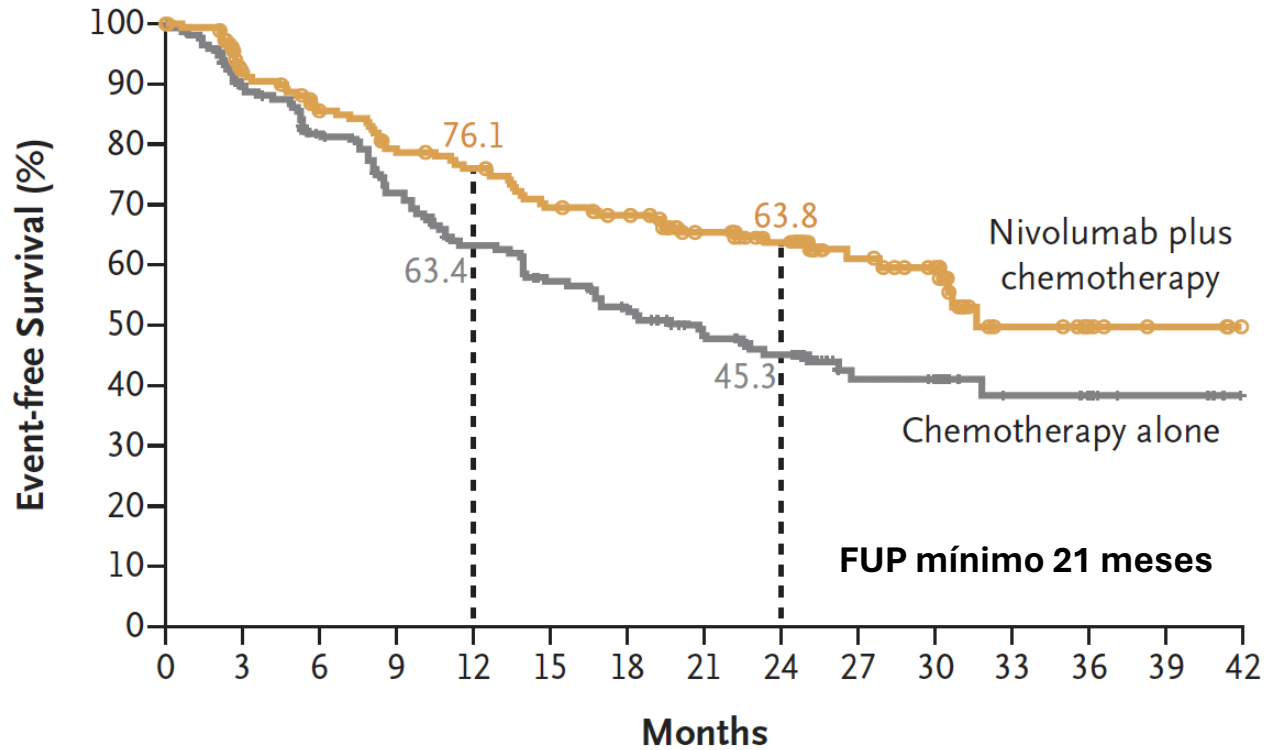
## ***Event-free survival***

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# Checkmate-816: *Event-free survival*

## Referência



	No. of Patients	Median Event-free Survival (95% CI) mo
<b>Nivolumab plus Chemotherapy</b>	179	31.6 (30.2–NR)
<b>Chemotherapy Alone</b>	179	20.8 (14.0–26.7)

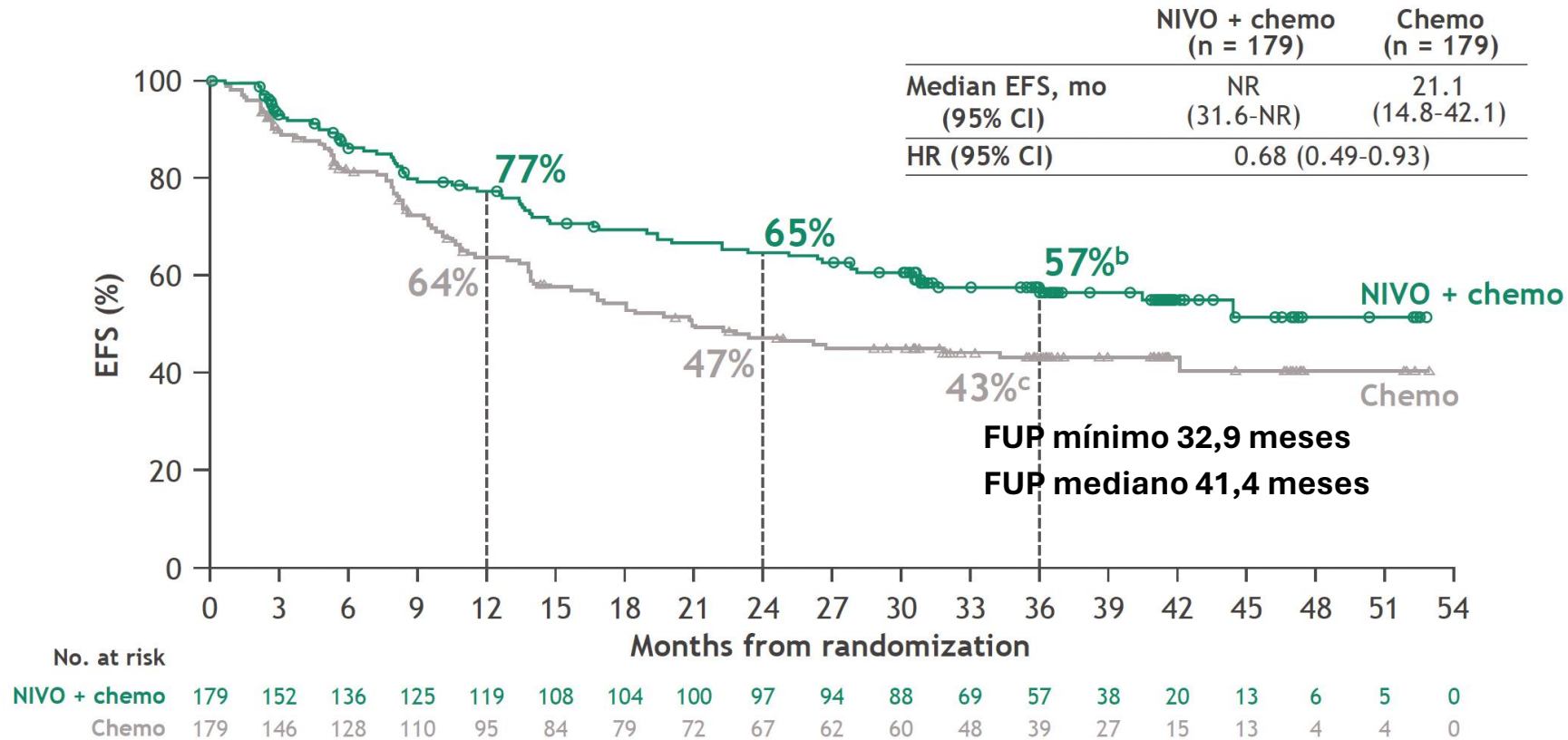
Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)  
P=0.005

### No. at Risk

Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

CheckMate 816: 3-y efficacy/safety update and biomarker analyses

## EFS with neoadjuvant NIVO + chemo vs chemo: 3-year update<sup>a</sup>



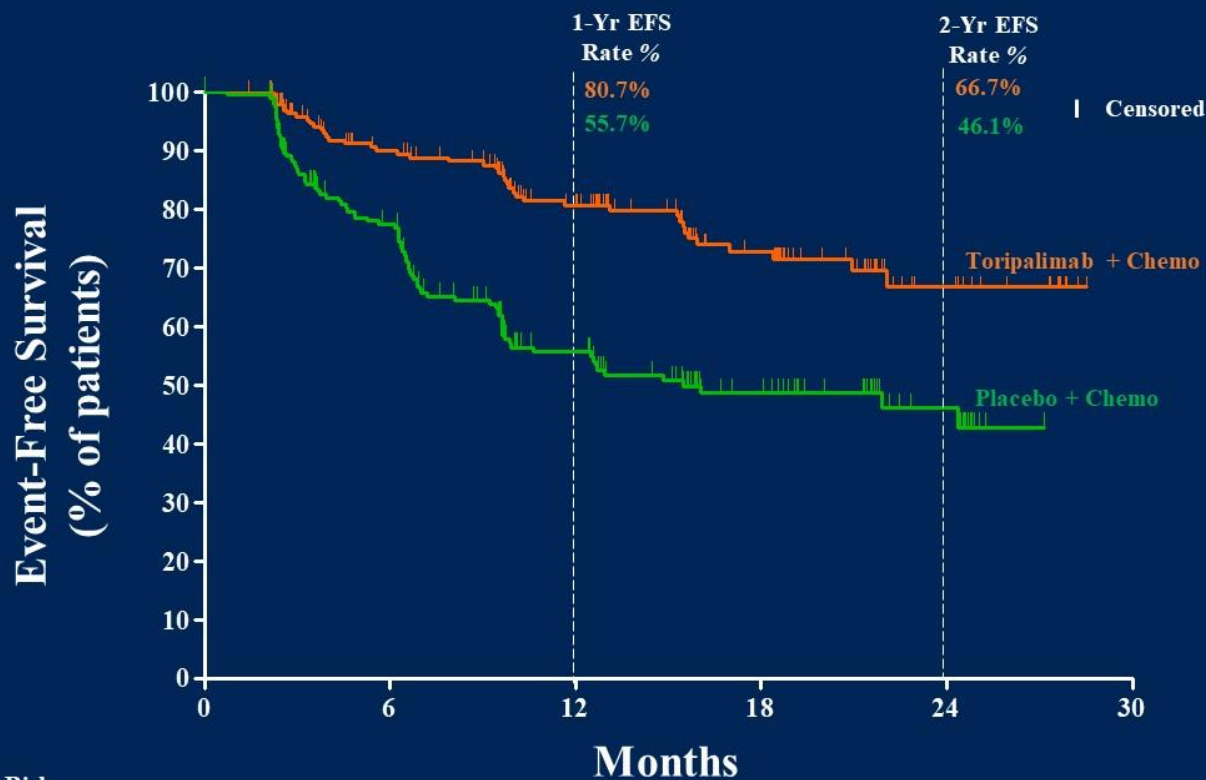
Minimum/median follow-up: 32.9/41.4 months.

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

# Event-Free Survival Analysis by IRC

**NEOTORCH: Toripalimabe + QT**

Intent-to-treat Stage III patients assessed by IRC per RECIST v1.1



	No. of Events/ No. of Patients	Median EFS mo (95% CI)
Toripalimab + Chemo	43/202	NE (NE, NE)
Placebo + Chemo	87/202	15.5 (9.9, NE)

**Median follow-up: 18.25 months**

**HR 0.40 (95%CI 0.271, 0.572)**

**nominal P<0.0001**

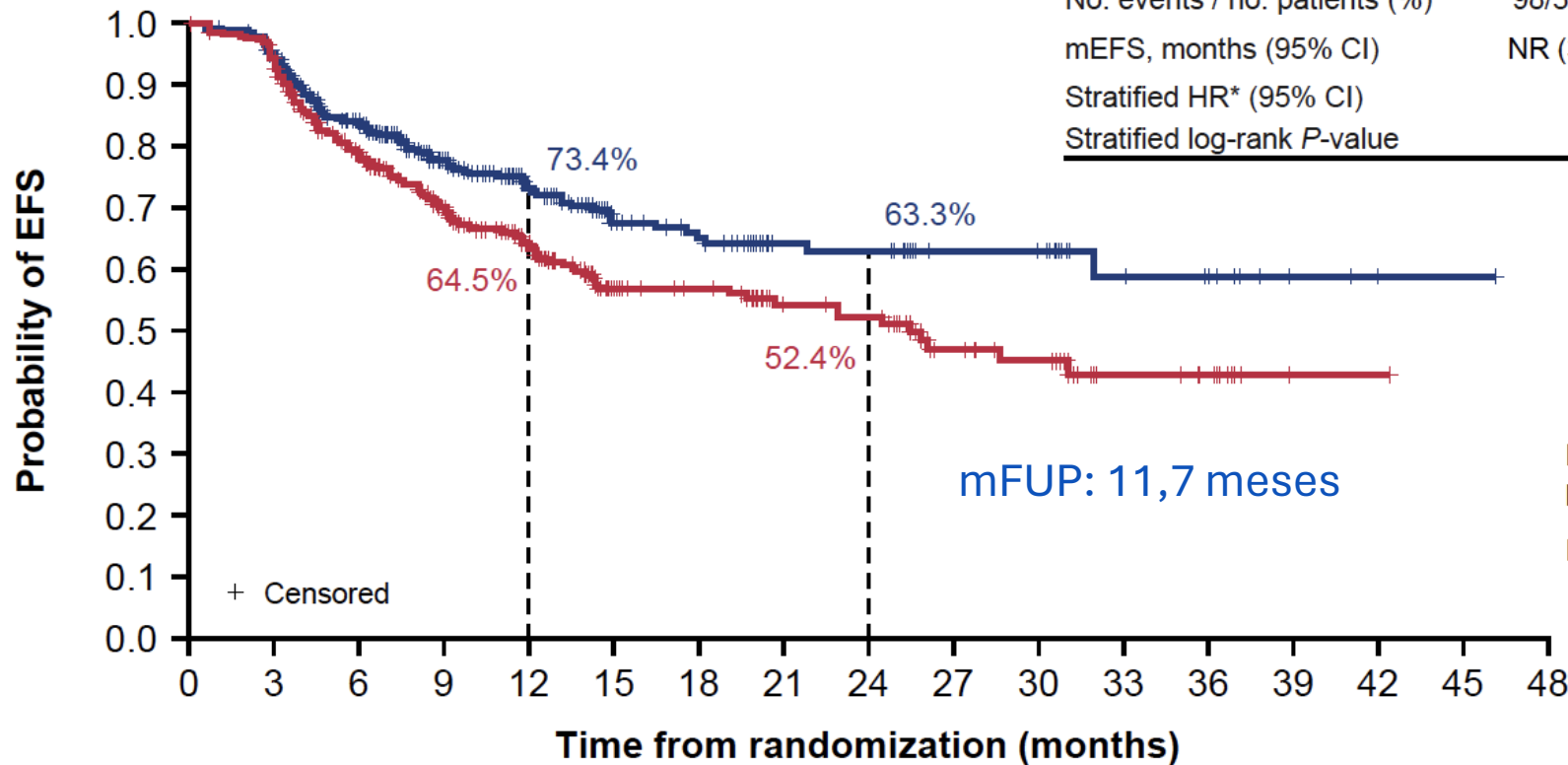
No. at Risk		0	6	12	18	24	30
Toripalimab + Chemo	202	150	107	60	17	0	
Placebo + Chemo	202	134	74	38	14	0	

Data cutoff date: Nov. 30, 2022  
 NE: not evaluable  
 HR: Hazard ratio  
 CI: confidence interval

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

## First planned interim analysis of EFS

### AEGEAN: Durvalumabe + QT



	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank P-value	0.003902	

Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

#### No. at risk:

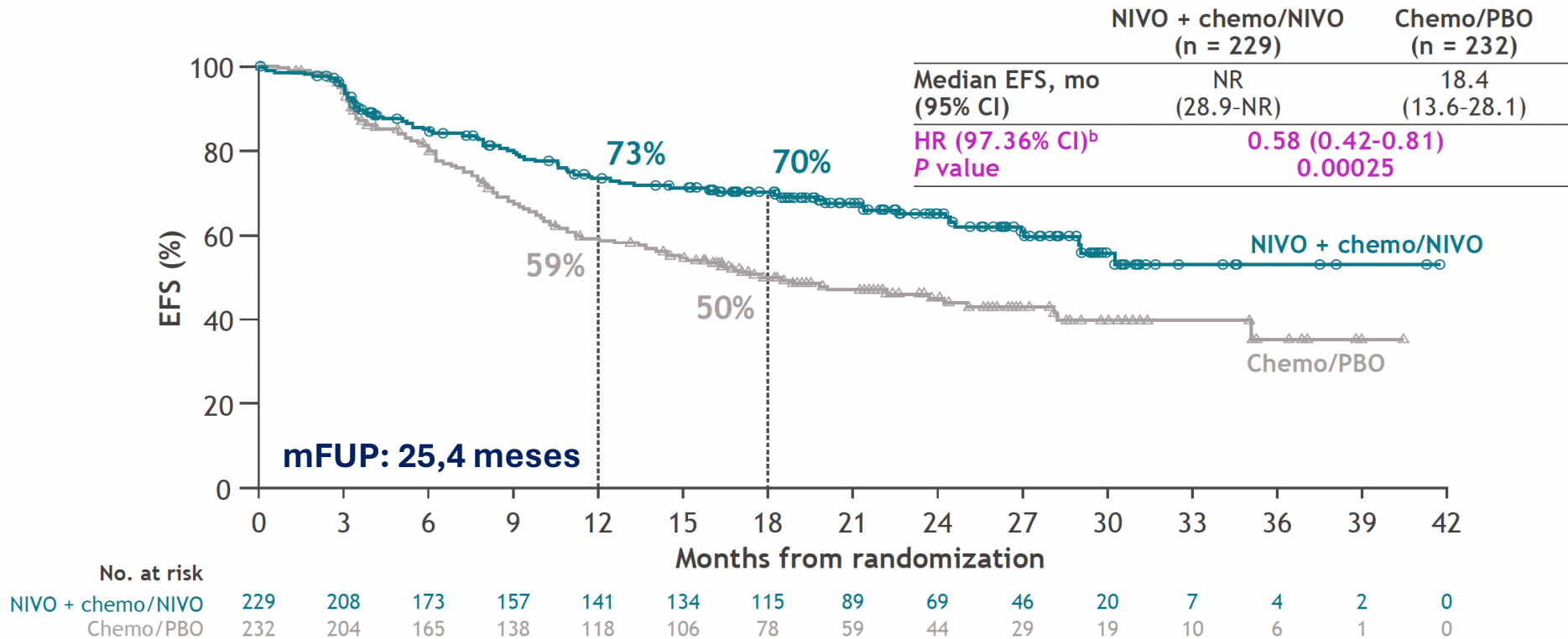
<b>D arm</b>	<b>366</b>	<b>336</b>	<b>271</b>	<b>194</b>	<b>140</b>	<b>90</b>	<b>78</b>	<b>50</b>	<b>49</b>	<b>31</b>	<b>30</b>	<b>14</b>	<b>11</b>	<b>3</b>	<b>1</b>	<b>1</b>	<b>0</b>
<b>PBO arm</b>	<b>374</b>	<b>339</b>	<b>257</b>	<b>184</b>	<b>136</b>	<b>82</b>	<b>74</b>	<b>53</b>	<b>50</b>	<b>30</b>	<b>25</b>	<b>16</b>	<b>13</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>0</b>

Presented by Dr. John Heymach

# CM-77T: Nivolumabe + QT

CheckMate 77T: perioperative NIVO in resectable NSCLC

## Primary endpoint: EFS<sup>a</sup> per BICR with neoadjuvant NIVO + chemo/adjuvant NIVO vs chemo/PBO



- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41-0.76

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

<sup>a</sup>Time from randomization to any disease progression precluding surgery, abandoned surgery due to unresectability or disease progression, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. <sup>b</sup>Unstratified HR (95% CI), 0.59 (0.44-0.79).

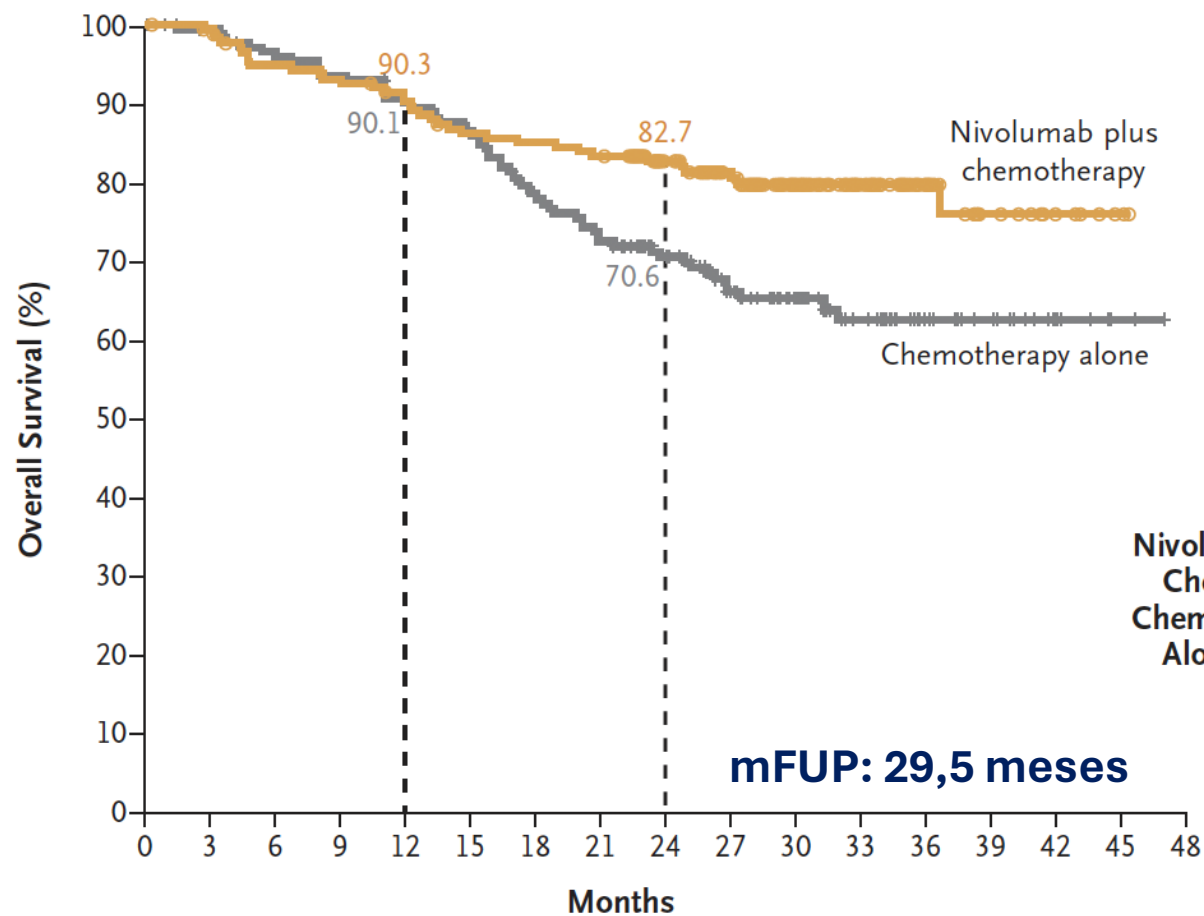
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# ***Sobrevida global***

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# Checkmate-816: Sobrevida global

**Referência**



	No. of Patients	Median Overall Survival (95% CI) mo
<b>Nivolumab plus Chemotherapy</b>	179	NR (NR–NR)
<b>Chemotherapy Alone</b>	179	NR (NR–NR)

Hazard ratio for death, 0.57 (99.67% CI, 0.30–1.07)  
P=0.008

**No. at Risk**

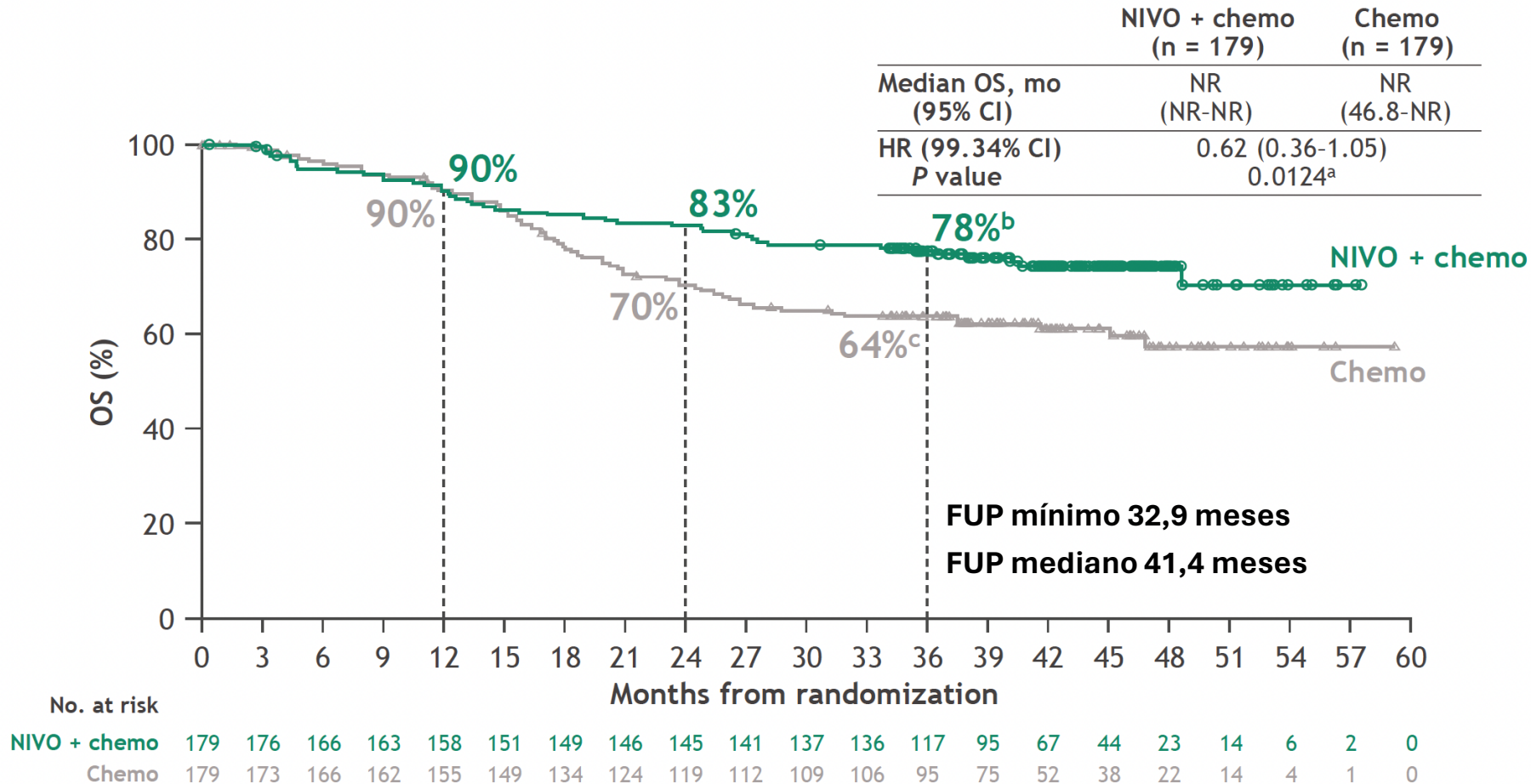
Nivolumab plus chemotherapy	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemotherapy alone	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

Forde et al. NEJM 2022

The 95% confidence interval of the hazard ratio was 0.38 to 0.87. At this first prespecified interim analysis, the P value for overall survival did not cross the boundary for statistical significance (0.003).

CheckMate 816: 3-y efficacy/safety update and biomarker analyses

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



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

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

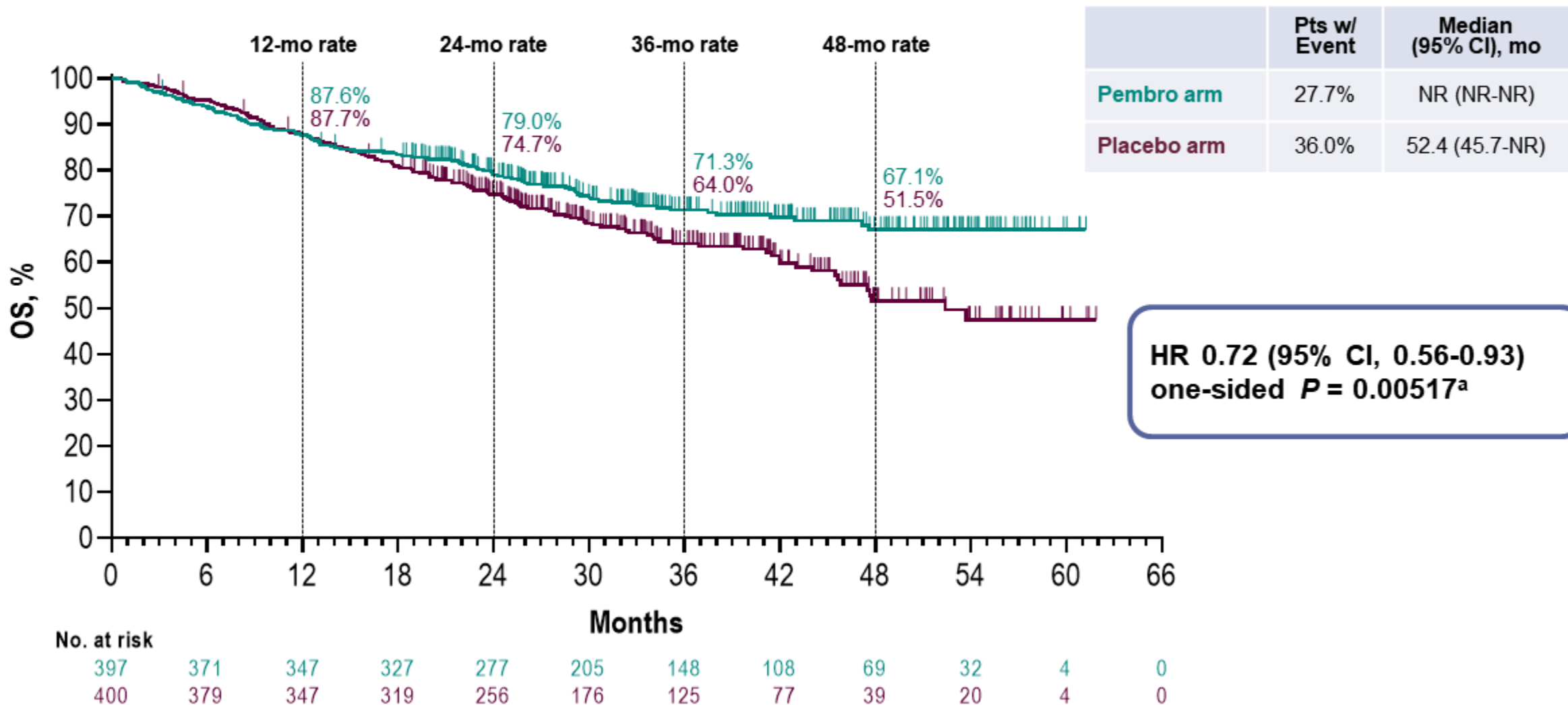


# Overall Survival, IA2

## KN-671: Pembrolizumabe + QT

Median Follow-Up: 36.6 months (range, 18.8-62.0)

Presented by Dr. Johnatan Spicer, ESMO 2023



**HR 0.72 (95% CI, 0.56-0.93)**  
**one-sided P = 0.00517<sup>a</sup>**

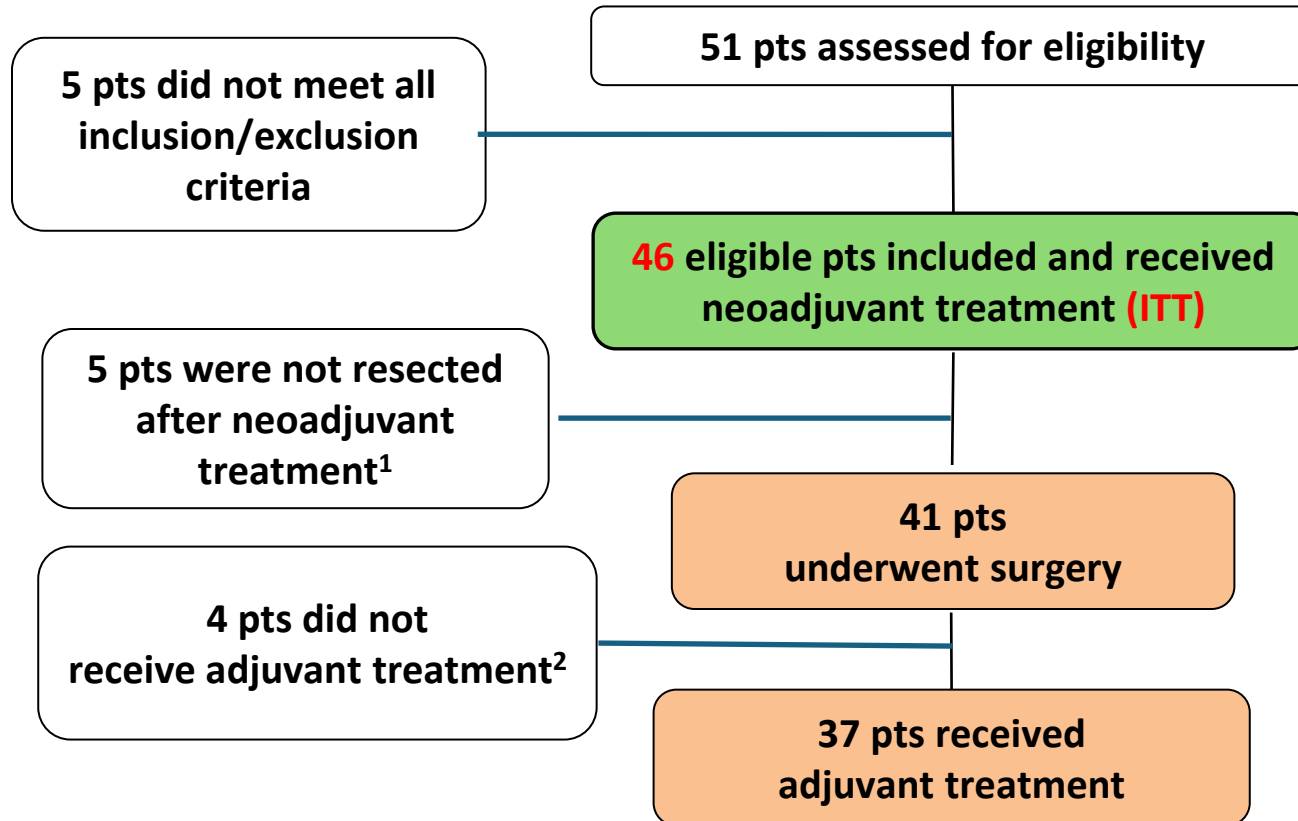
OS defined as time from randomization to death from any cause. <sup>a</sup> Significance boundary at IA2, one-sided P = 0.00543. Data cutoff date for IA2: July 10, 2023.

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***Ampliando os limites da cirurgia?***

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## Estudos NADIM 1 e 2 incluíram N2 de múltiplas cadeias



Provencio et al. Lancet Oncol 2020

<sup>1</sup> Two patients were not resected due to their own decision, 3 patients did not fulfill resectability criteria according to the protocol

<sup>2</sup> Three patients did not receive adjuvant treatment due to toxicity, 1 patient exceeded the time per protocol to start adjuvant treatment

### NADIM 1

Patient baseline characteristics	N=46 (ITT)
Age (median, range)	63(41-77)
Male, N (%)	34 (74 %)
ECOG PS	
0 N (%)	25 (54%)
1 N (%)	21 (46%)
Smoking status, N (%)	
Former/current	46 (100%)
Adenocarcinoma, N (%)	28 (61)
Co-morbidities, N (%)	43 (93,5)
N2	33 (89.2)
Multiple station	25 (75.8)

Nodal stage	NADIM 1
N0	9 (20%)
N1	3 (7%)
N2	34 (74%)
Single	9 (20%)
Multiple	25 (54%)



# 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA



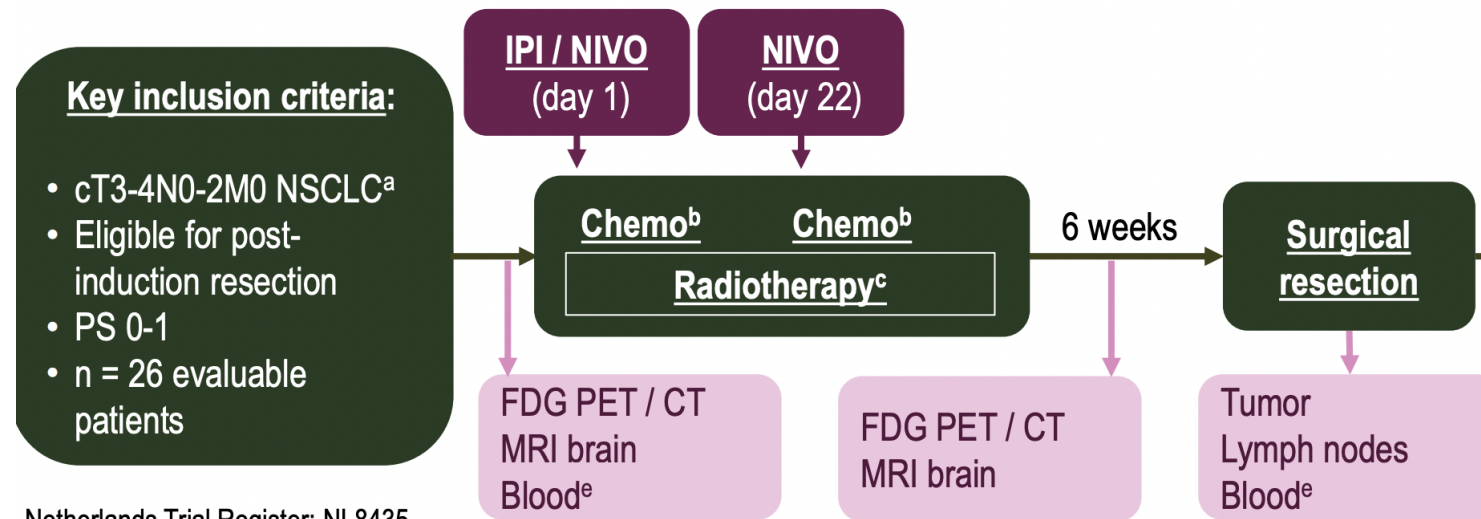
## Estudos NADIM 1 e 2 incluíram N2 de múltiplas cadeias

Characteristic	NIVO + Chemo (n = 57)	Chemo (n = 29)
Age – median (range), years	63 (58-70)	62 (57-66)
Female – No. (%)	21 (36.8)	13 (44.8)
History of tobacco use – No. (%)		
Never smoker	5 (8.7)	0 (0.0)
Former smoker	23 (40.4)	10 (34.5)
Current smoker	29 (50.9)	19 (65.5)
ECOG PS – No. (%)		
0	31 (54.4)	16 (55.2)
1	26 (45.6)	13 (44.8)
Histology – No. (%)		
Adenocarcinoma	25 (43.9)	11 (37.9)
Adenosquamous	1 (1.8)	0 (0.0)
Squamous	21 (36.8)	14 (48.3)
Large Cell Carcinoma	2 (3.5)	1 (3.5)
NOS / Undifferentiated	7 (12.3)	2 (6.9)
Other	1 (1.8)	1 (3.5)

Characteristic	NIVO + Chemo (n = 57)	Chemo (n = 29)
TNM classification (AJCC 8th Ed.)		
T1N2M0	12 (21.1)	4 (13.8)
T2N2M0	16 (28.1)	7 (24.1)
T3N1M0	2 (3.5)	1 (3.5)
T3N2M0	13 (22.8)	5 (19.3)
T4N0M0	6 (10.5)	9 (31.0)
T4N1M0	8 (14.0)	3 (10.3)
Tumor size – Median (range), mm	43 (29-54)	52 (39-75)
Nodal stage – No. (%)		
N0	6 (10.5)	9 (31.0)
N1	10 (17.5)	4 (13.8)
N2	41 (71.9)	16 (55.2)
N2 multiple station	21 (36.8)	10 (34.5)

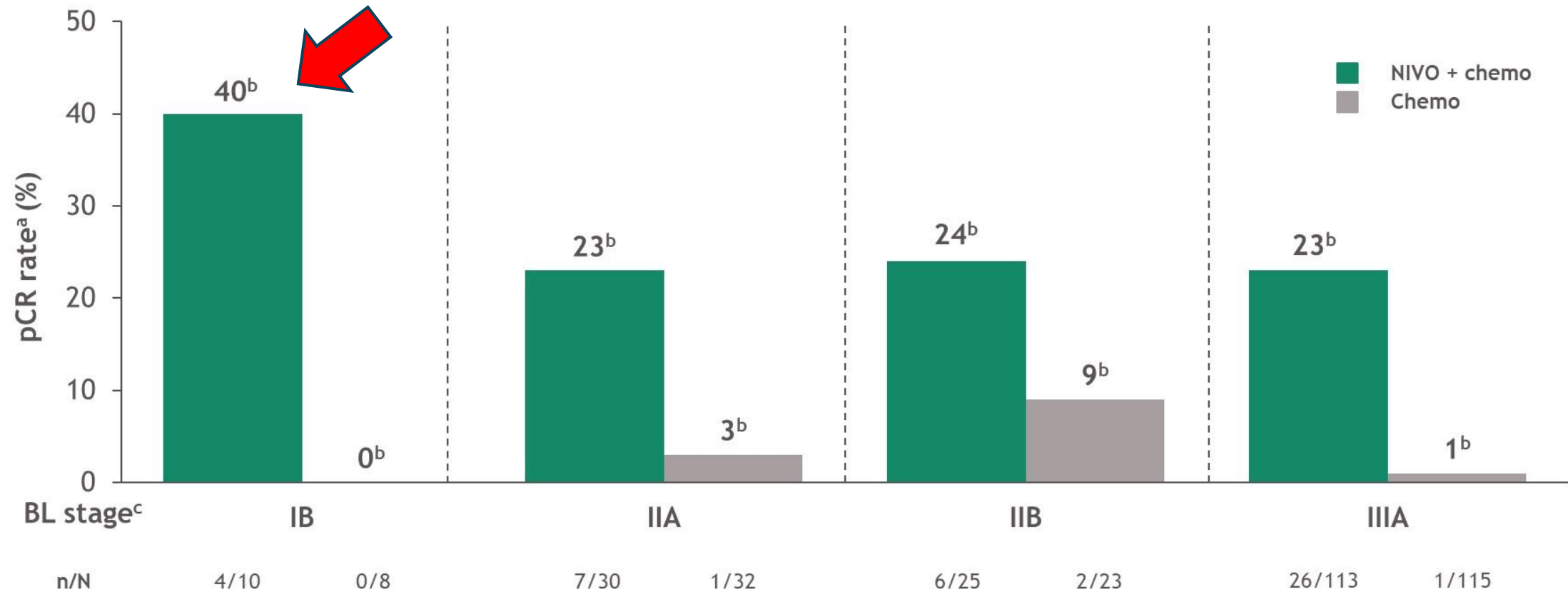
# Estudo INCREASE incluiu pacientes com doença “borderline resectable”

9500 - Ipilimumab plus nivolumab and chemoradiotherapy followed by surgery in patients with resectable and borderline resectable lung cancer: The INCREASE trial.



	pCR n (%)	MPR n (%)
Operated patients, n=24	15 (63 %) (p < 0.001) <sup>a</sup>	19 (79 %)
Received induction <sup>b</sup> , n=27	15 (55%) (p = 0.003) <sup>a</sup>	19 (70%)

# pCR by baseline stage of disease



- pCR improvement with NIVO + chemo vs chemo was observed regardless of radiologic down-staging<sup>d</sup>

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

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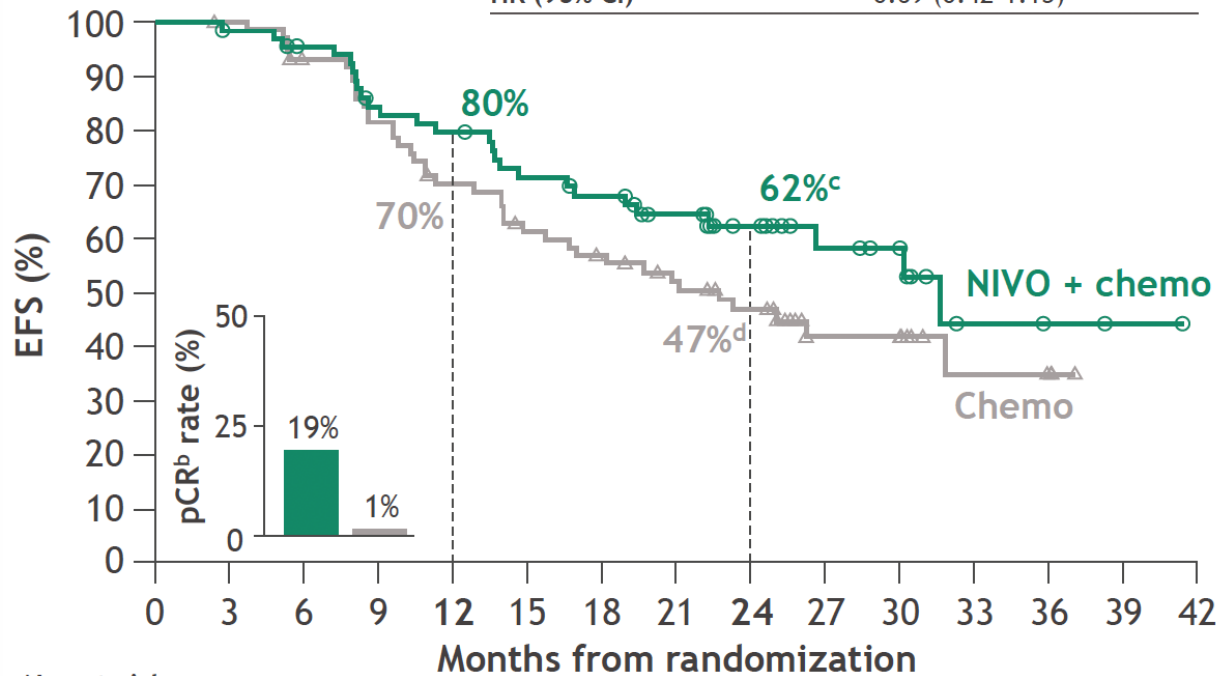
***EC I e II: Cirurgia upfront ou QT/Imuno neoadjuvante?***

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# Efficacy in patients with or without pathologic evidence of LN involvement<sup>a</sup>

## With LN involvement

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

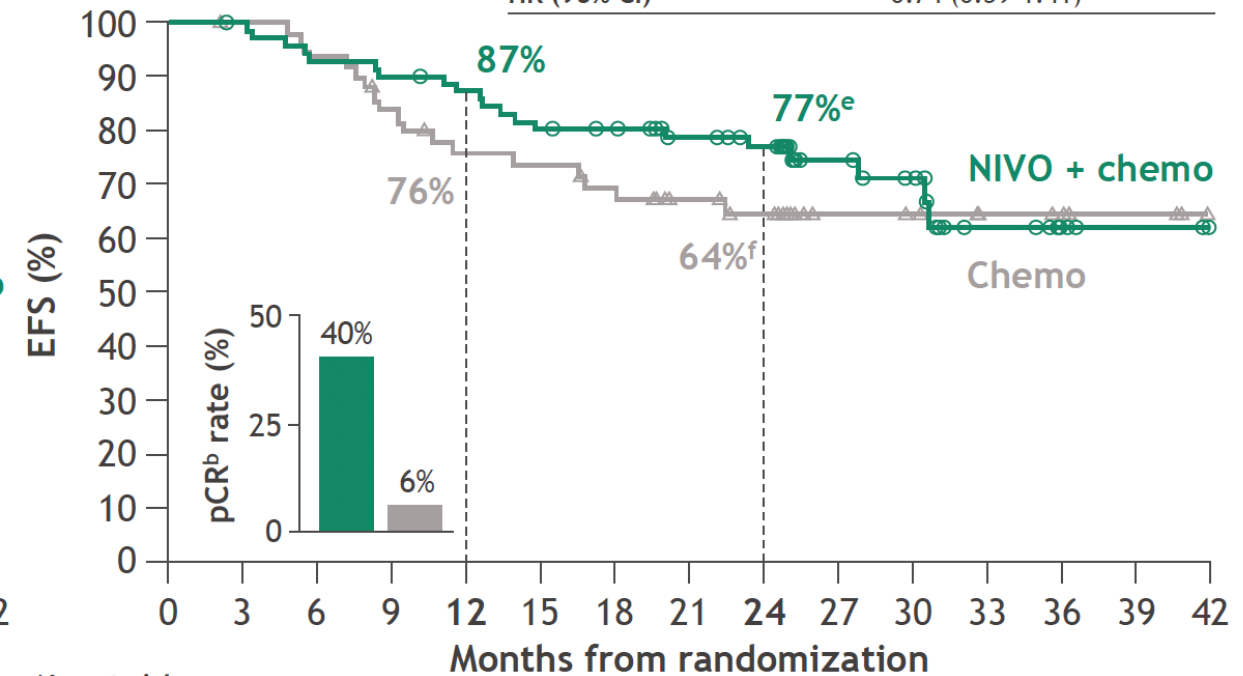


No. at risk

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

## Without LN involvement

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



No. at risk

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

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

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





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***O que pode dar errado?***

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## Checkmate-816 – Eventos adversos

**Table 2. Adverse Events.\***

Event	Nivolumab plus Chemotherapy (N=176)		Chemotherapy Alone (N=176)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Adverse events of any cause — no. (%)†				
All	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
Serious	 30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
Treatment-related adverse events — no. (%)†				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Death‡	 0	—	3 (1.7)	—
Surgery-related adverse events — no./total no. (%)§	62/149 (41.6)	17/149 (11.4)	63/135 (46.7)	20/135 (14.8)



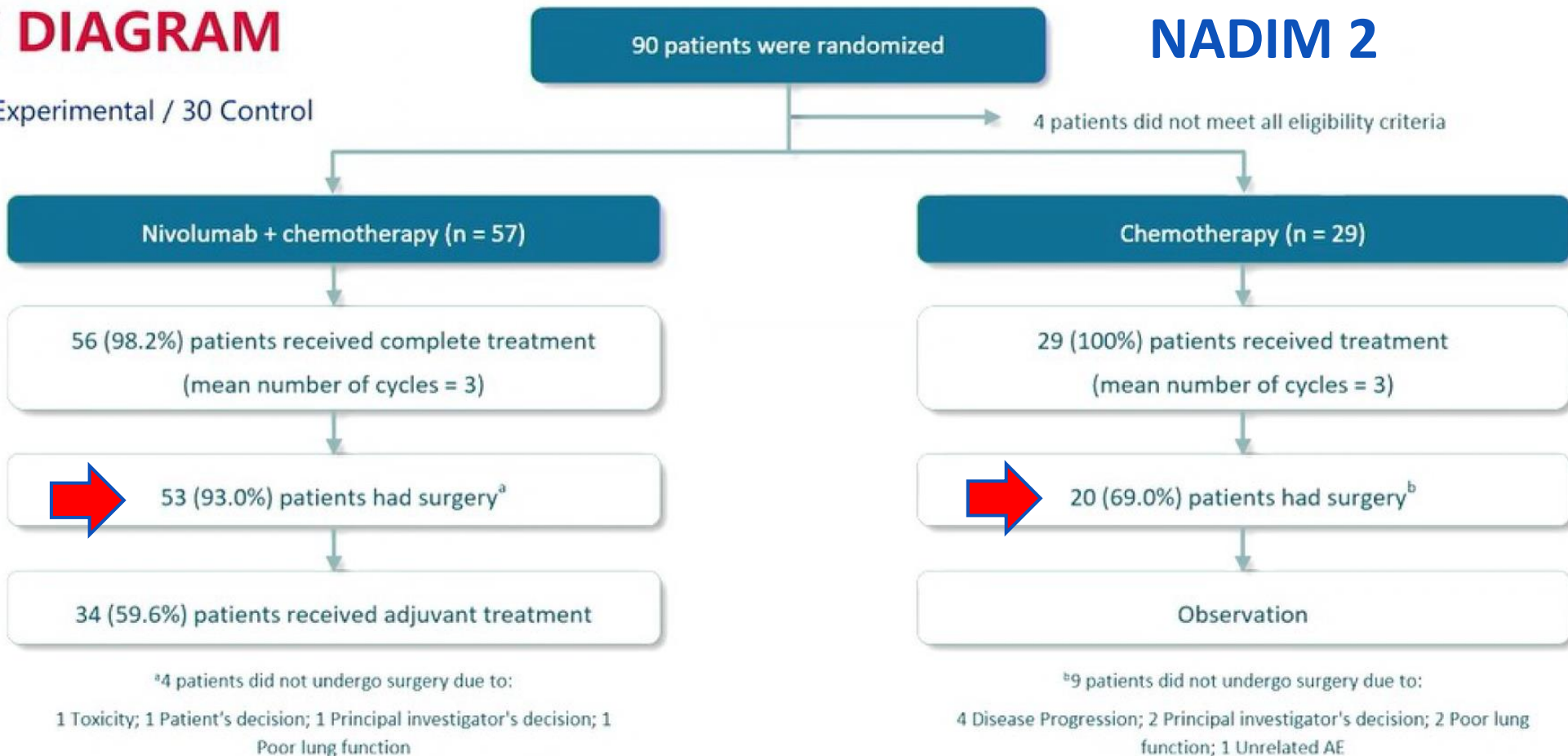
# 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

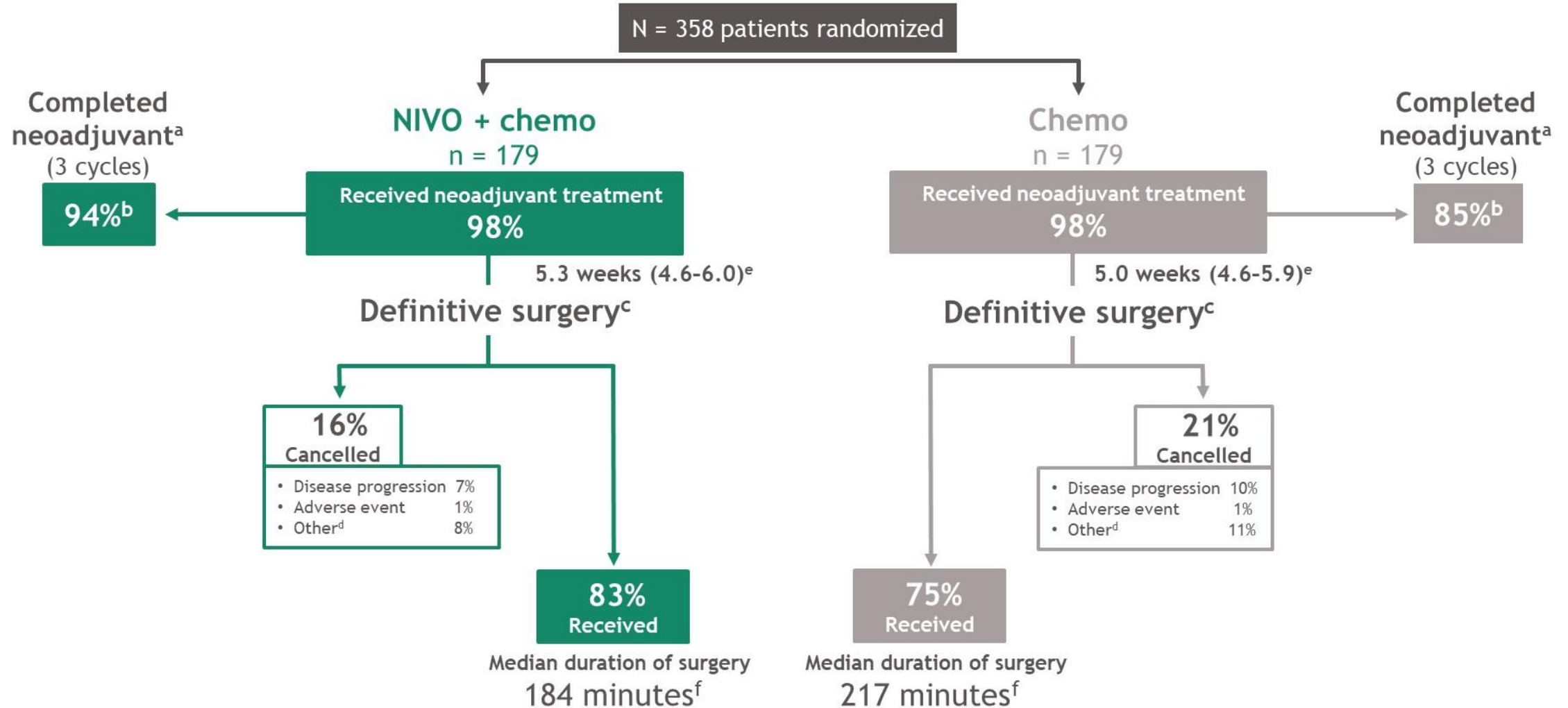


## FLOW DIAGRAM

Accrual: 60 Experimental / 30 Control

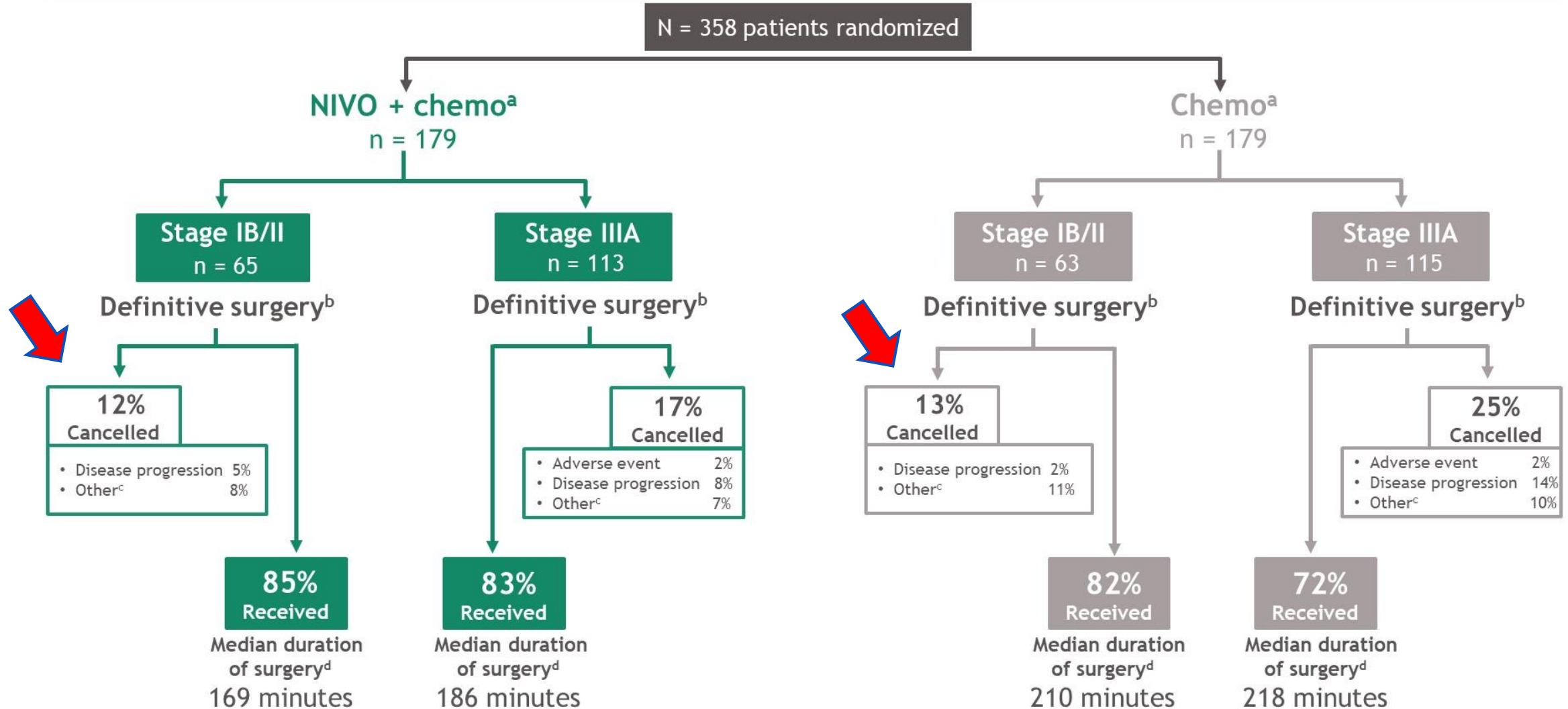


# Treatment and surgery summary: all randomized patients



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

# Surgery summary: by baseline stage of disease



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

# Summary of Surgical Procedure

**NEOTORCH: Toripalimabe + QT**

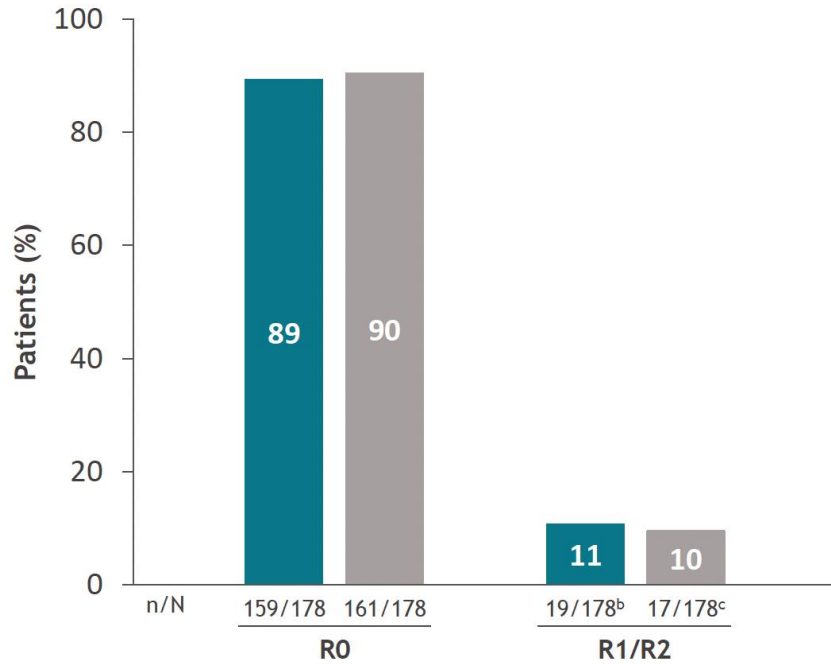
	Toripalimab +Chemo (N=202)	Placebo + Chemo (N=202)
<b>No surgery performed n(%)</b>	36 (17.8) ←	54 (26.7)
<b>Patient underwent surgery n(%)</b>	166 (82.2)	148 (73.3)
<b>R0 resection n(%*)</b>	159 (95.8)	137 (92.6)
95% CI	91.5, 98.3	87.1, 96.2
<b>Differences between arms</b>		3.2
95% CI		-2.0, 8.4

\*percent of R0 resection is based on numbers of patients underwent surgery

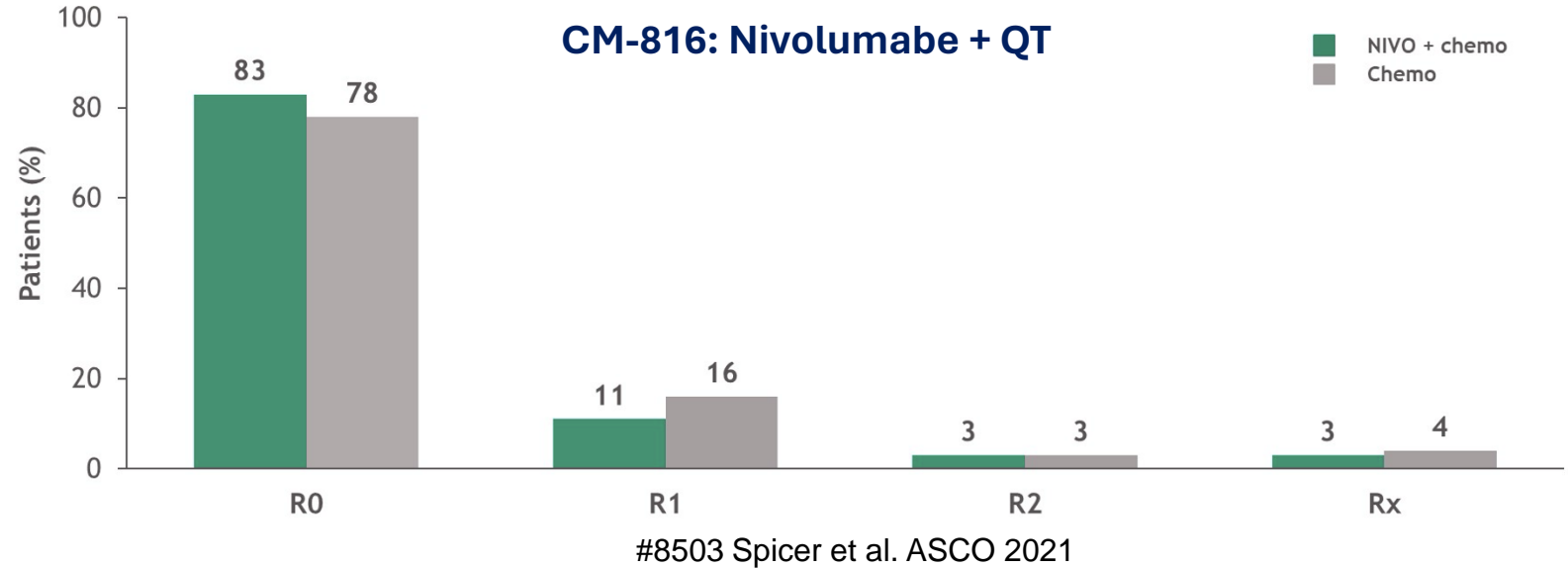
# Taxa de ressecção R0

## CM-77T: Nivolumabe + QT

### Completeness of resection



Cascone et al. ESMO 2023



## NEOTORCH: Toripalimabe + QT

	Toripalimab +Chemo (N=202)	Placebo + Chemo (N=202)
Patient underwent surgery n(%)	166 (82.2)	148 (73.3)
<b>R0 resection n(%*)</b>	<b>159 (95.8)</b>	<b>137 (92.6)</b>
95% CI	91.5, 98.3	87.1, 96.2

Shun Lu et al. ASCO Plenary Series, 2023

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# Casos clínicos

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# Casos clínicos

Mulher, 67 anos, tabagista 50 anos-maço

Comorbidades: HAS, DLP, múltiplos aneurismas cerebrais (7)

CEC de pulmão, cT2b uN0 M0

## Estadiamento:

- PET-CT, Tc tórax, RM crânio, EBUS

## Tratamento:

- Carboplatina/paclitaxel/nivolumabe x 3 ciclos
- 29/02/24 Lobectomia inferior direita + linfadenectomia RATS
- Alta no 3o PO

## 05/03/24 AP cirurgia:

- Ausência de neoplasia residual (resposta patológica completa)
- Efeito de tratamento neoadjuvante:
  - Células tumorais viáveis: 0%.
  - Necrose: 10%.
  - Estroma (incluindo fibrose e inflamação): 90%

Imagem baseline

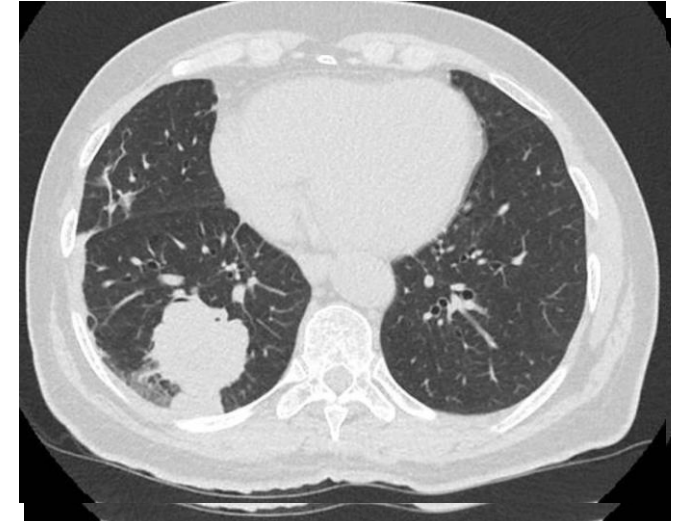
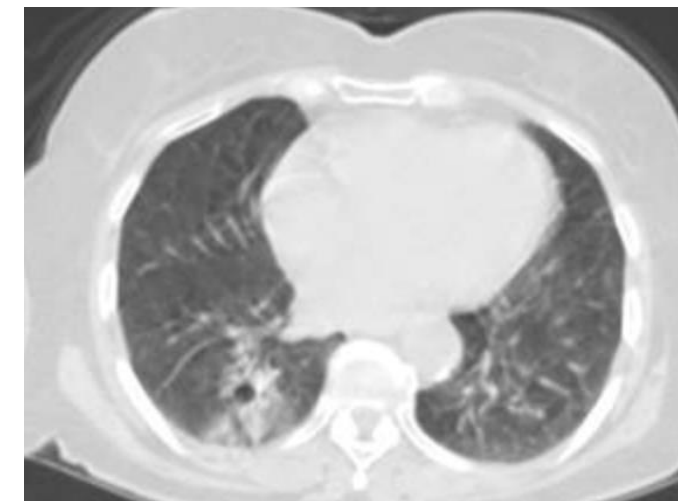


Imagem pós-C3



## Casos clínicos

Homem, 65 anos, não-tabagista

Comorbidades: HAS, DM2

Histórico de adenocarcinoma de reto (2005) e adenocarcinoma de TEG (2010)

Mutação germinativa em PMS2

CEC de pulmão

cT3 uN0\* M0 \*cadeia pré-vascular inacessível

### Estadiamento:

- PET-CT, Tc tórax, RM crânio, EBUS
- Obs: sinais de invasão da parede torácica, infiltrando o tecido adiposo extrapleural, mantendo contato com a artéria subclávia esquerda em menos que 180 graus, em íntima relação com o tronco inferior do plexo braquial

### Tratamento:

- Carboplatina/paclitaxel/nivolumabe x 3 ciclos
- 28/12/23 Lobectomia superior esquerda + pleurectomia apical + decorticação pleuropulmonar + linfadenectomia VATS
- Alta no 7o PO

### 05/03/24 AP cirurgia:

- Ausência de neoplasia residual (resposta patológica completa)
- Efeito de tratamento neoadjuvante:
  - Células tumorais viáveis: 0%.
  - Necrose: 70%.
  - Estroma (incluindo fibrose e inflamação): 30%

### Imagem baseline



### Imagem pós-C3



## Casos clínicos

- Mulher, 44 anos, não-tabagista
- Sem comorbidades
- Histórico de tumor phyllodes mama E (2021)
- Adenocarcinoma de pulmão
- Mutação ERBB2 (T772\_A775dup) , PD-L1 80%
- cT2a uN2 (2R e 4R) M0

### Estadiamento:

- PET-CT, Tc tórax, RM crânio, EBUS
- \*Lesão de retroperitônio a/e, não captante no PET-CT

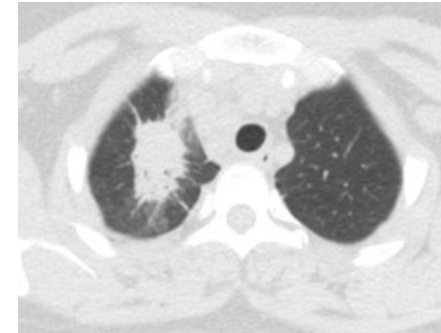
### Tratamento:

- Carboplatina/paclitaxel/nivolumabe x 3 ciclos
- 04/01/24 Lobectomia superior direita + linfadenectomia RATS
- Alta no 6o PO
- Re-internação no 9o PO para manejo de dor, alta no 13o PO

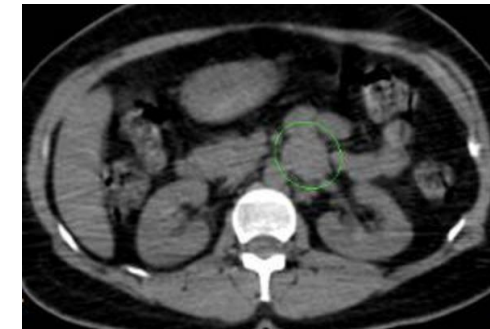
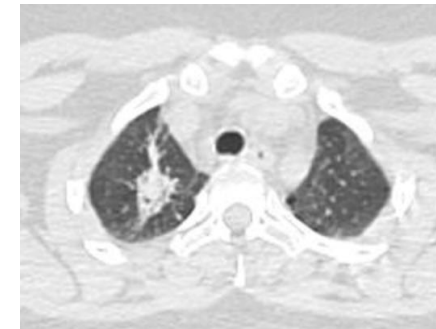
### 09/01/24 AP cirurgia:

- Adenocarcinoma pulmonar residual, predominantemente lepidico (MPR)
- Efeito de tratamento neoadjuvante:
  - Células tumorais viáveis: 2%.
  - Necrose: 0%.
  - Estroma (incluindo fibrose e inflamação): 98%

### Imagens baseline



### Imagens pós-C3



Obs: Biópsia da lesão de retroperitônio (pós tto): leiomiossarcoma de baixo grau; atualmente em avaliação para ressecção com grupo de sarcoma

## Casos clínicos

Mulher, 67 anos, não-tabagista  
Comorbidades: HAS  
Adenocarcinoma mucinoso de pulmão  
KRAS G12C, PD-L1 3%  
cT1b uN2 (4R, 7 e 10R) M0

### Estadiamento:

- PET-CT, Tc tórax, RM crânio, EBUS

### Tratamento:

- Carboplatina/paclitaxel/nivolumabe x 2 ciclos

### Evolução clínica:

- Dor em gradil costal D (fratura costela) após o C2
- Tc de tórax pós C2 com **PD óssea**

01/02/23 Imagem do PS

23/02/23 Imagem rotina pós C2

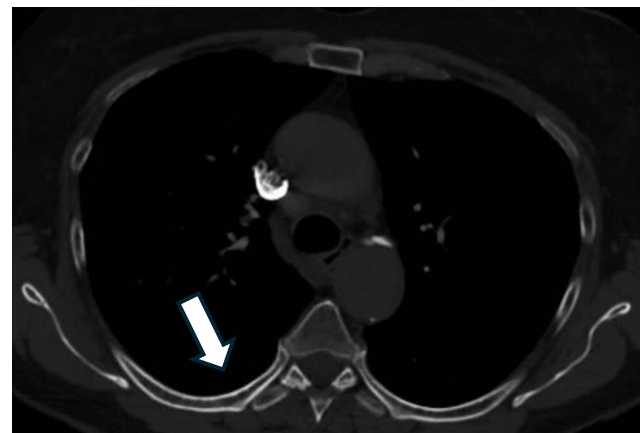


Imagem baseline

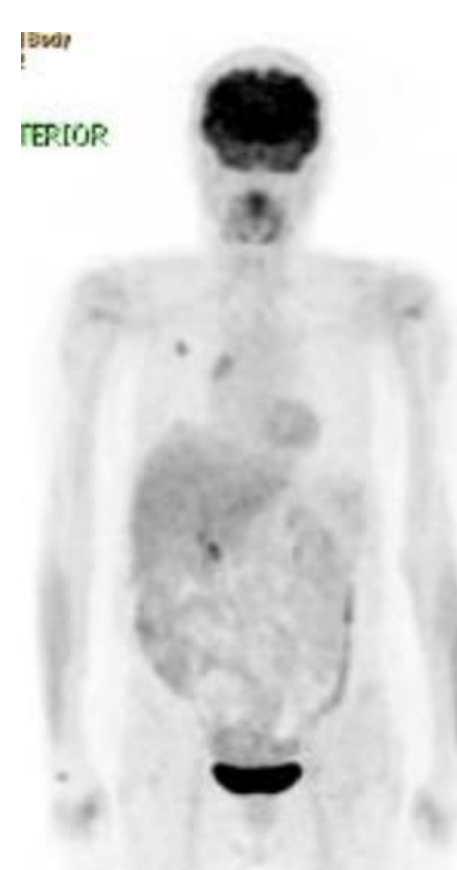
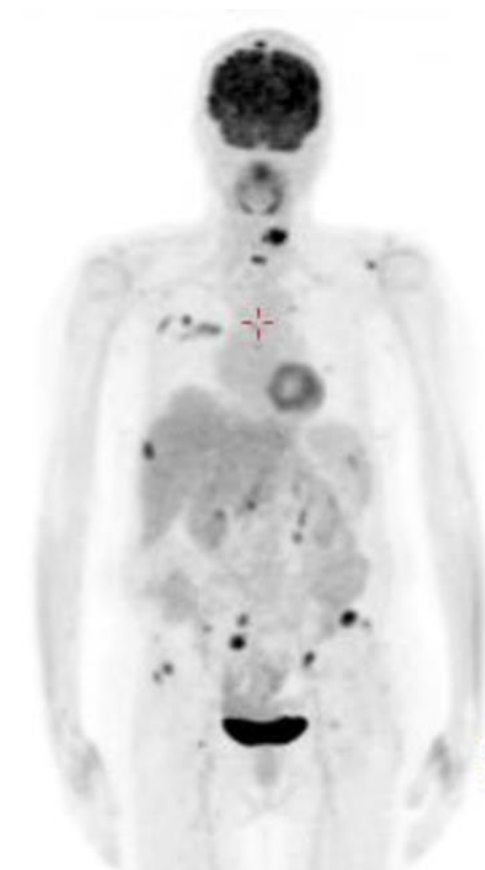


Imagem pós-C2



# Mensagens finais: Quem são os pacientes elegíveis (Quando)? *(disclaimer: minha leitura)*

**Premissa 1** Paciente apto para cirurgia

**Premissa 2** Discussão multidisciplinar

## EC I

- IA1 ⇨ <1cm N0 🟡
- IA2 ⇨ 1-2cm N0 🟡
- IA3 ⇨ 2-3cm N0 🟡 🟢
- IB ⇨ 3-4cm N0 🟡 🟢

## EC II

- 3-5cm 🟢
- Brônquio principal 🟡 🟢
- Atelectasia 🟡
- PL1/PL2 🟡
- N+ 🟢

## EC III

### • IIIA

- ⇨ T1 N2 🟡 🟡
- ⇨ T2 N2 🟡 🟡
- ⇨ T3 N1 🟡 🟡
- ⇨ T4 N0 🟡 🟡
  - > 7cm
  - Invasão de estruturas
  - Nódulo em outro lobo ipsolateral

### • IIIB

- ⇨ T1-2 N3 🟡 🟡 🟡 🟡
- ⇨ T3 N2 🟡 🟡 🟡
- ⇨ T4 N2 🟡 🟡 🟡

### • IIIC

- ⇨ T3 N3 🟡 🟡 🟡 🟡
- ⇨ T4 N3 🟡 🟡 🟡 🟡

## Mensagens finais: Como planejar o tratamento neoadjuvante? *(disclaimer: minha leitura)*

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**Premissa 1** Paciente apto para cirurgia

**Premissa 2** Discussão multidisciplinar

### **Estadiamento:**

- PET-CT e RM de crânio
- Esdiamento invasivo do mediastino
  - EBUS
  - Mediastinoscopia
- Perfil molecular
  - Mínimo: EGFR/ALK
  - Preferível: Painel NGS (todos os drivers)

## Mensagens finais: tratamento neoadjuvante ou perioperatório? *(disclaimer: minha leitura)*

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**Premissa 1** Paciente apto para cirurgia

**Premissa 2** Discussão multidisciplinar favoreceu tratamento neoadjuvante

- QT/imuno neoadjuvante (Checkmate-816) é a referência (padrão)
- Não é possível afirmar que continuar a imunoterapia após a cirurgia melhore os desfechos EFS e SG em relação à QT/imuno neoadjuvante
  - ⇒ O braço controle dos estudos de tratamento perioperatório foi QT isolada

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# Obrigado pela atenção!



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AC Camargo Cancer Center

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