

Debatte

NSCLC- Neoadjuvante Therapie vs. Strahlentherapie Neoadjuvante Therapie

Klinik für Hämatologie und Onkologie, Pius-Hospital

Universitätsklinik Innere Medizin-Onkologie, Universitätsmedizin Oldenburg

Sprecher Cancer Center Oldenburg, Pius-Hospital

Sprecher CRISP Register

Sprecher NOWEL Netzwerk



Interessenskonflikte

Forschungsunterstützung:

ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer,
Roche, Takeda, Siemens, Amgen, GSK

Vortragsstätigkeit:

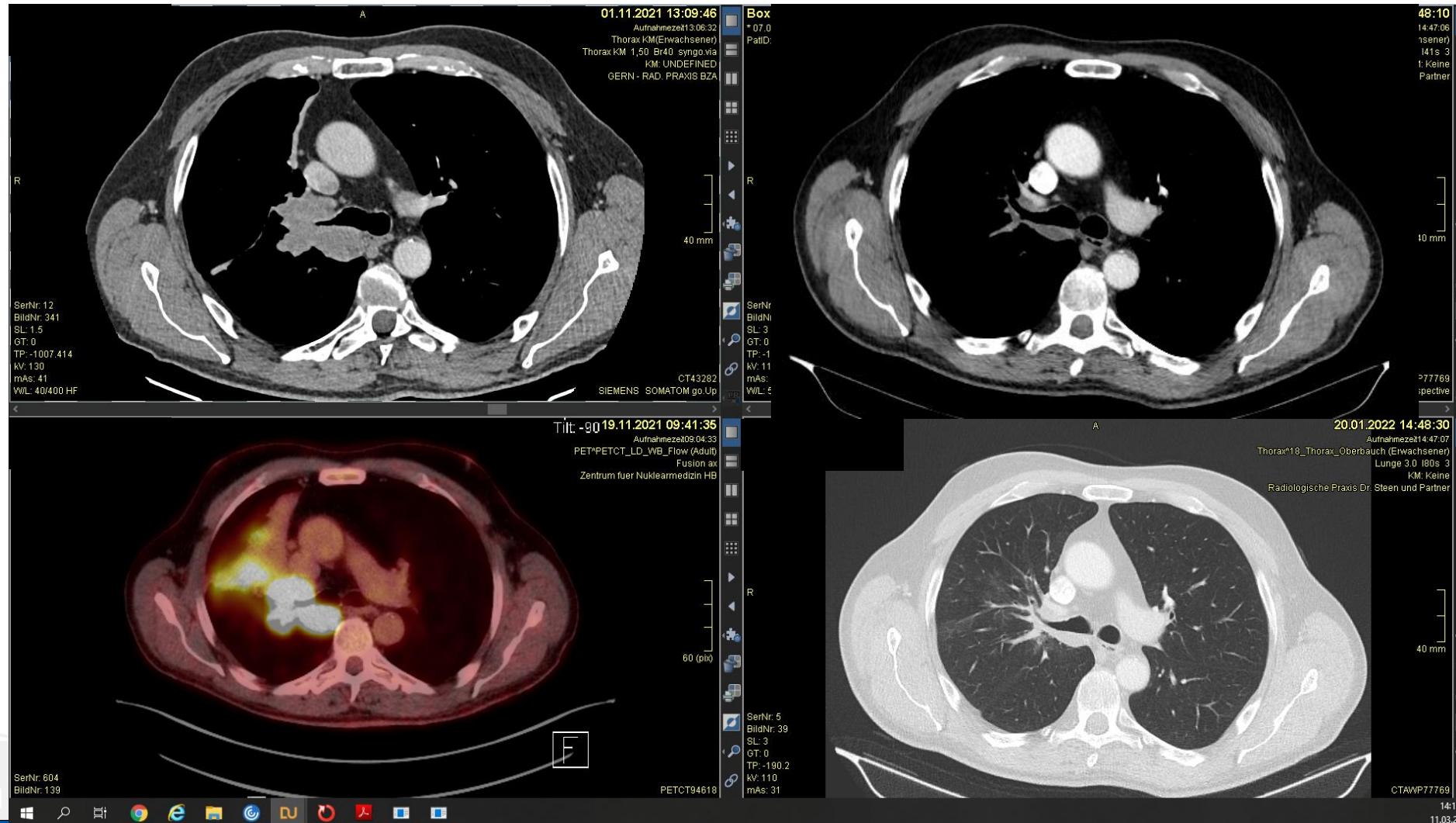
ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer,
Roche, Takeda, Ariad, Abbvie, Siemens, Amgen GSK, Sanofi

Beratertätigkeit:

ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer,
Roche, Takeda, Ariad, Abbvie, Tesaro, Siemens, Amgen, GSK, Sanofi



Fall: Fiktiver Fall



Fall: Fiktiver Fall

11/2021 Nicht-kleinzelliges Lungenkarzinom rechts zentral
Infiltration des Mediastinums
cT4 cN1 cMO; G2
Histologie: mäßig differenziertes gering verhorrendes
Plattenepithelkarzinom

Weitere Diagnosen

V. a. teilzystischen Schilddrüse-Knoten rechts
V. a. Agenesie/Hypoplasie der linken A. vertebralis
Nikotinabusus von 1972 bis 2000 (20 PY)

19.11.21 PET-CT

12/21-1/22 Induktionschemoimmuntherapie mit Carboplatin AUC6, Paclitaxel
200 mg/m² KOF, Nivolumab 240 mg absolut d1 qd22, 3 Zyklen

20.01.22 CT:
gute PR

2.3.2022 Oberlappen-Manschettenresektion
yT0NOM0, Regressionsgrad III nach Junker, keine vitalen Tumorzellen

Stadium IB-IIIA nach UICC7 (UICC 8)

	M0				M1a	M1b	M1c
	N0	N1	N2	N3	Jedes N	Jedes N	Jedes N
T1a(mi)	IA1						
T1a							
T1b	IA2						
T1c	IA3						
= 3 - >4 cm	T2a	IB				IVA	IVB
= 4 - <5 cm	T2b	IIA				IVA	
	T3	IIB					
	T4	IIIA	IIIA	IIIB	IIIC		



NSCLC Stadium II und IIIB (N2) primär operabel

Adjuvante Therapie

ADAURA	EGFR mt (e19/e21)	Osimertinib	3 Jahre	PFS	OS
ALINA	ALK Fusion	Alectinib	2 Jahre	PFS	
IMPOWER	PD-L1 >50%	Atezolizumab	1 Jahr	PFS	OS
KN91	alle PD-L1	Pembrolizuma	1 Jahr	PFS	OS

Neoadjuvante Therapie:

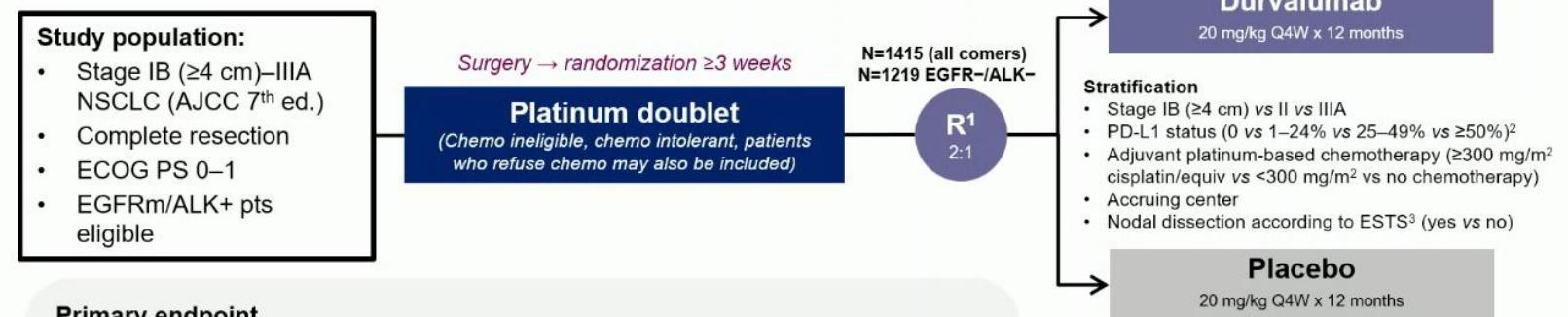
CM 816	PD-L1 ≥1%	Nivo + CTx	3 Zyklen	PFS	
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Perioperative Therapie:

KN671	alle PD-L1	Pembro +CTx	4 Zyklen	PFS	OS
77T	alle PD-L1	Nivo + CTx	4 Zyklen	PFS	
Aegean	alle PD-L1	Durva + CTx	4 Zyklen	PFS	
NeoTorch	alle PD-L1	Tisle+ CTx	3 +1 Zyklen	PFS	OS

BR31: adjuvant Durva in II-IIIB (N2) UICC 8 after R0 and adj CTx

CCTG BR.31 Trial Design



Primary endpoint

- DFS⁴ (Investigator Assessed) in patients with PD-L1 TC $\geq 25\%$ and EGFR-/ALK-

Key secondary endpoints

- DFS in patients with:
 - PD-L1 TC $\geq 1\%$ and EGFR-/ALK-
 - All PD-L1 TC $\geq 25\%$
 - All randomized patients
- OS (six patient subpopulations)
- AEs
- QoL

Today, we will present the final DFS analysis from three EGFR-/ALK- populations

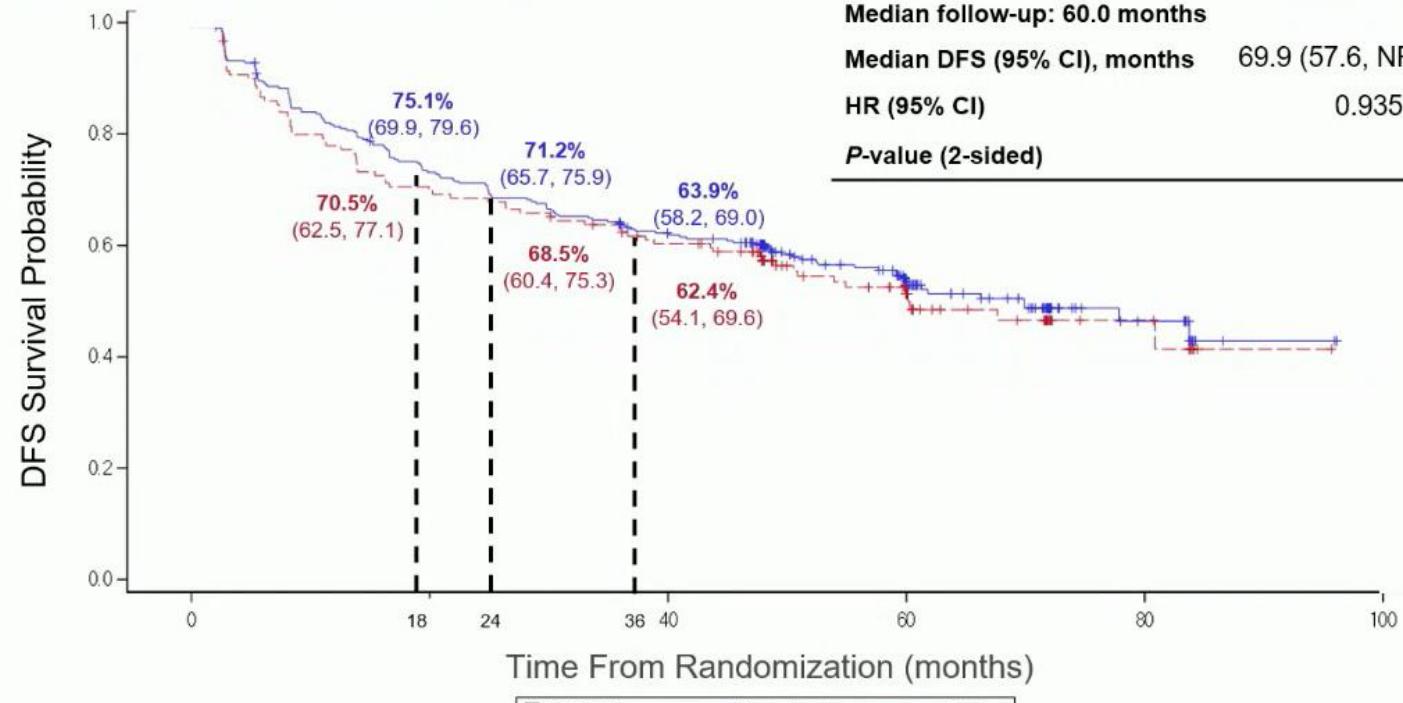
1. Patients who did not receive adjuvant CT: randomization 3–10 weeks after surgery; patients who received adjuvant CT: randomization 2–10 weeks after the last CT dose; N2 patients could receive PORT completed prior to randomization. 2. PD-L1 centrally tested using the VENTANA PD-L1 (SP263) Assay with tumour cell (TC) scoring. 3. European Society of Thoracic Surgeons Guideline for Preoperative Mediastinal Lymph Node Staging for NSCLC, De Leyn et al. (2024) Eur J Cardiothorac Surg 45(5) 787–98. 4. DFS was defined as the time from randomization to the earliest of: date of first documented evidence of disease relapse, the occurrence of a new invasive primary malignancy, or death from any cause.



BR31: adjuvant Durva in II-IIIB (N2) UICC 8 after R0 and adj CTx

CCTG BR.31 Primary Endpoint

DFS in PD-L1 \geq 25% EGFR-/ALK-



D arm n=316	PBO arm n=161
Median follow-up: 60.0 months	
Median DFS (95% CI), months	69.9 (57.6, NR) 60.2 (47.7, NR)
HR (95% CI)	0.935 (0.706, 1.247)
P-value (2-sided)	0.642

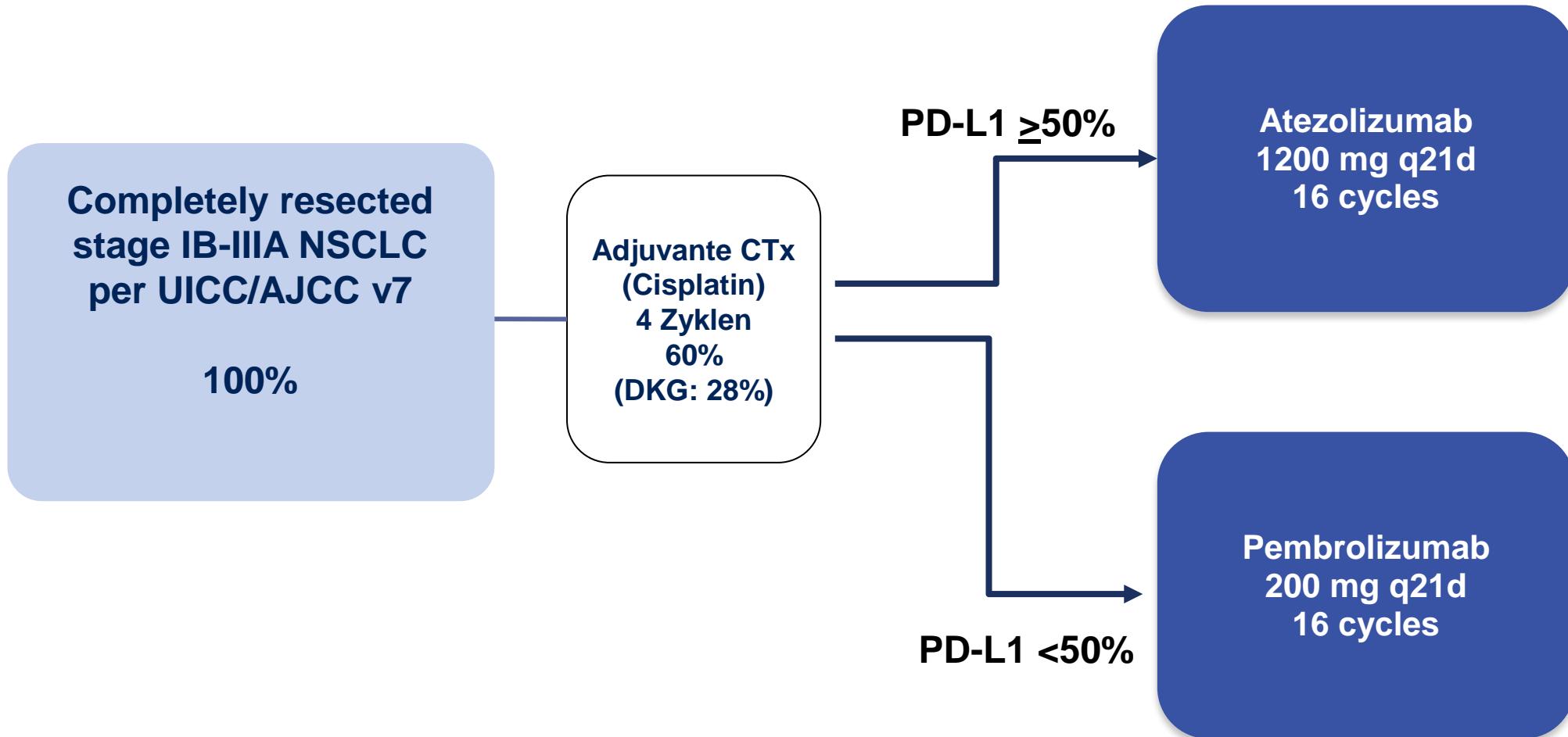
Treatment	Durvalumab	Placebo
Durvalumab	316	287
Placebo	161	136

129 273 258 248 240 228 219 216 208 202 198 190 183 179 177 149 125 119 117 86 65 62 58 39 21 19 18 7 2 2 2 1 0

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congress

Adjuvantes Setting: uneinheitliche Datenlage, 2 Zulassungen

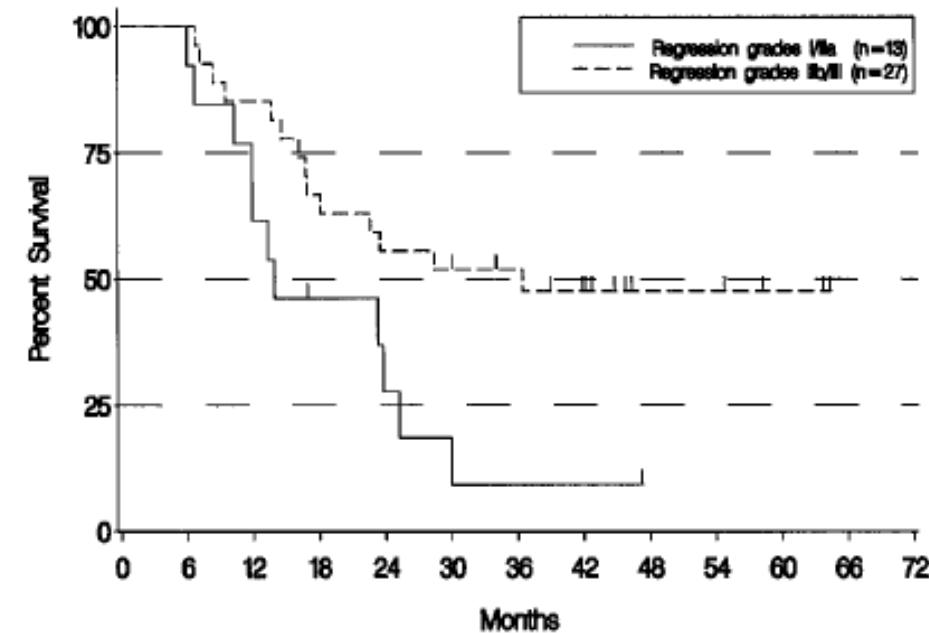
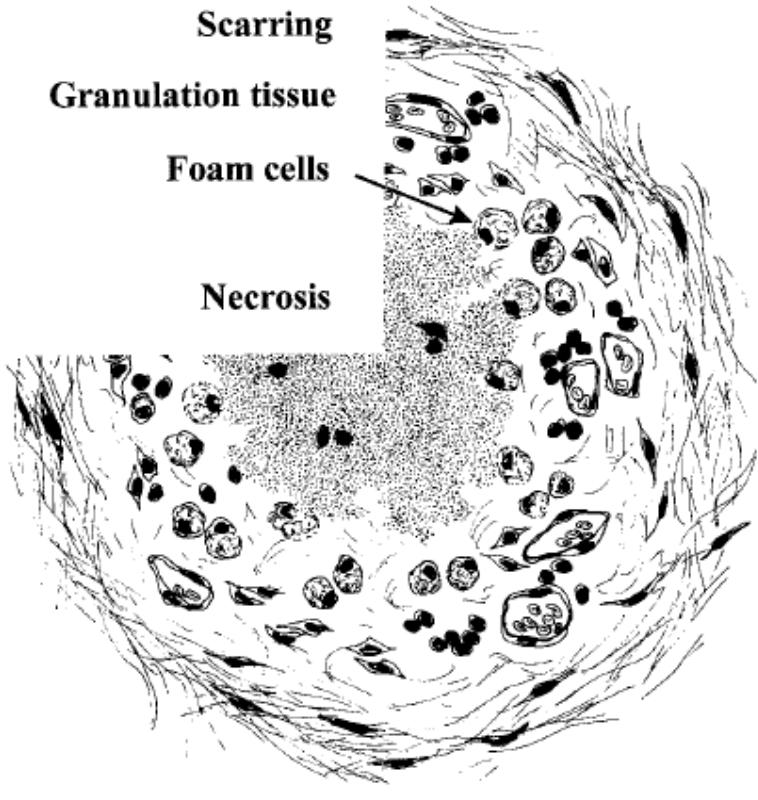
Testen auf PD-L1, EGFR und ALK (und ggf. weitere Marker)



Grading of Tumor Regression in Non-small Cell Lung Cancer*

Morphology and Prognosis

Klaus Junker, MD; Kathrin Langner, MD; Folker Klinke, MD; Ulrich Bosse, MD;
and Michael Thomas, MD (CHEST 2001; 120:1584–1591)



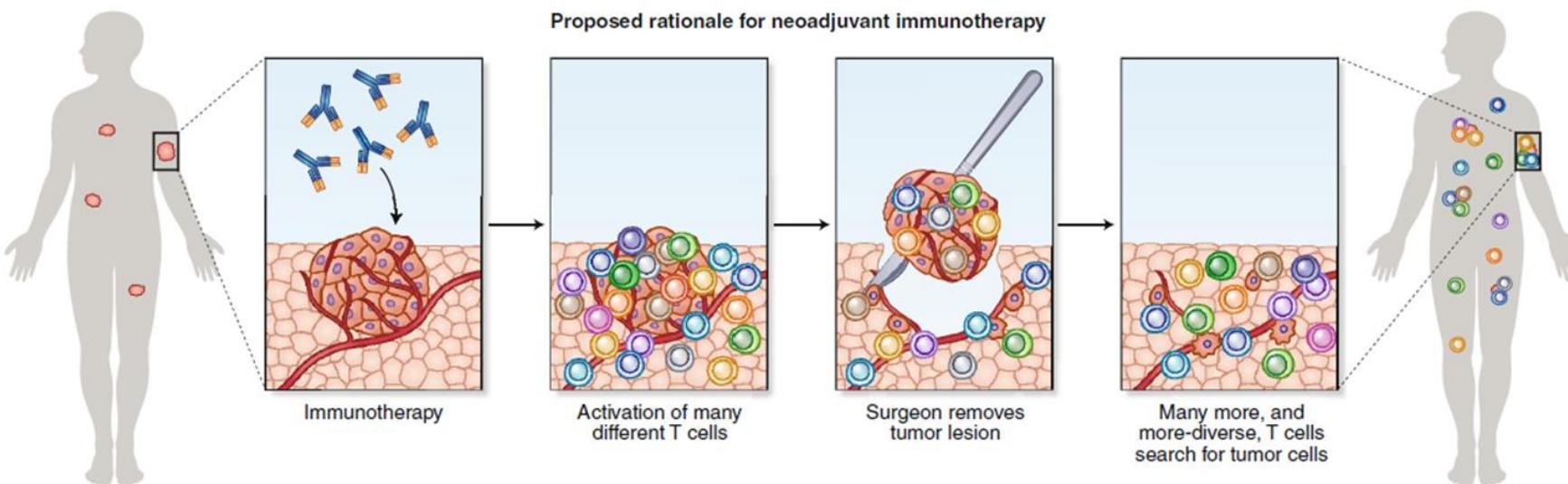
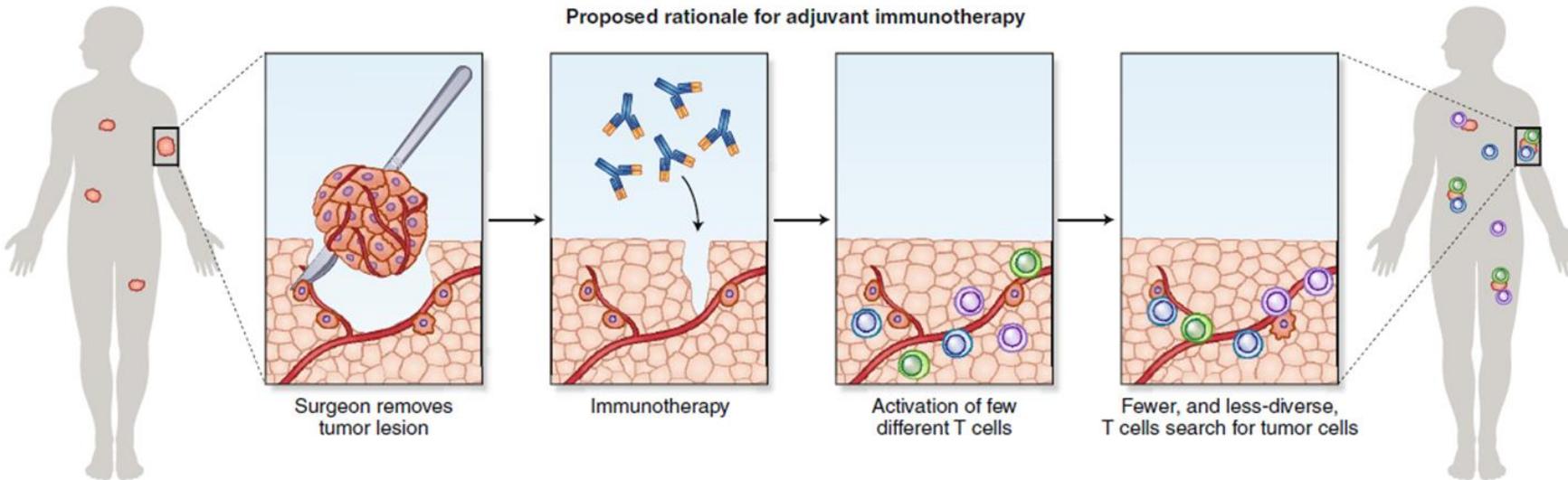
Warum Checkpoint-Inhibition vor der Operation?

Exkurs Malignes Melanom, Pembrolizumab Monotherapie

„it has been hypothesized that **neoadjuvant therapy may be able to activate more antitumor T cells and improve clinical outcomes** than administration of the same amount of drug delivered postoperatively. The presumed increase in exposure of T cells to tumor antigens may also play a role.

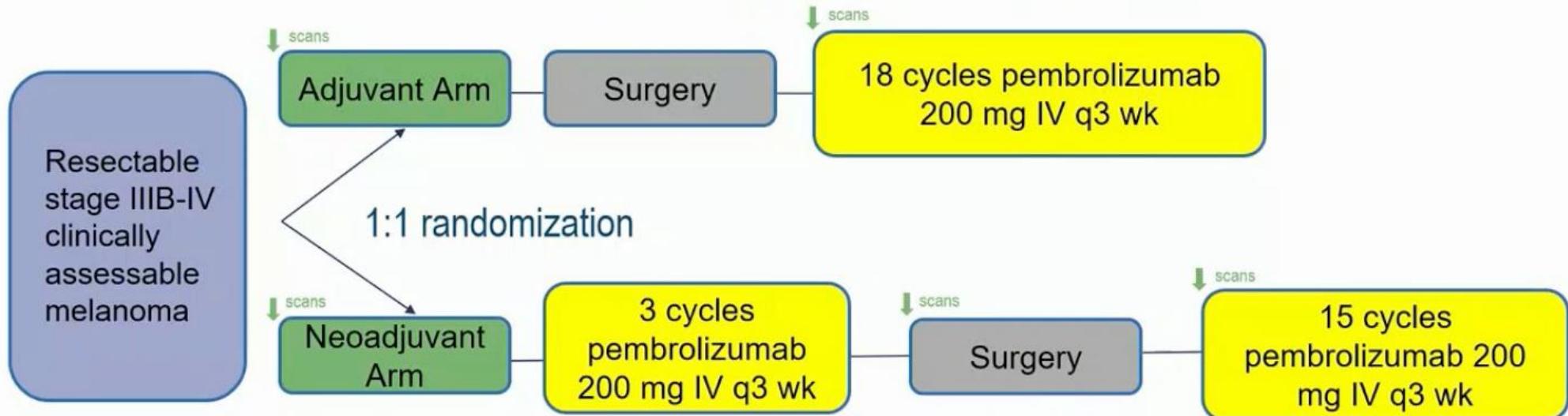
Potential flaws in this reasoning include the possibility that tumor immune escape may be independent of the timing of treatment or even more likely when bulk tumor „**and tumor draining LN**“ are present.“

Neoadjuvant vs. adjuvant: Prinzipielle Überlegungen: Biologie der Immuntherapie



S1801 Study Schema

Primary endpoint: Event-free survival



↓ radiographic assessment
(scans)

Additional criteria: strata included AJCC 8th ed. stage and LDH, adjuvant radiation allowed, concomitant radiation & pembrolizumab was not allowed, brain metastasis excluded, uveal melanoma excluded
Surgery type and extent was required to be pre-specified and carried out regardless of radiologic response to therapy

PARIS 2022 **ESMO** congress

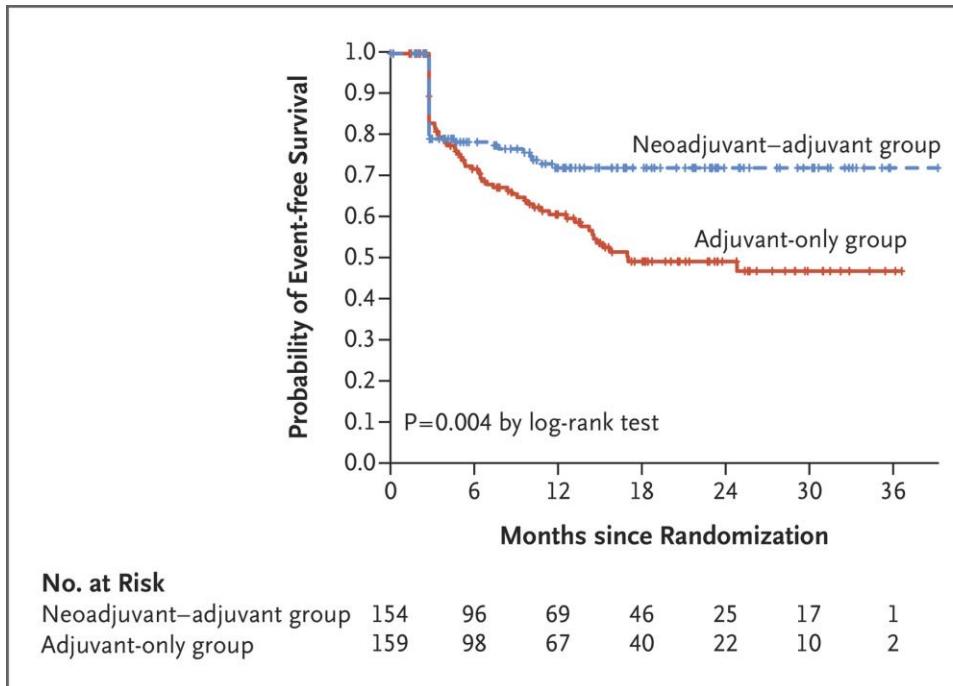
Sapna P. Patel, MD SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network NCI Community Oncology Research Program

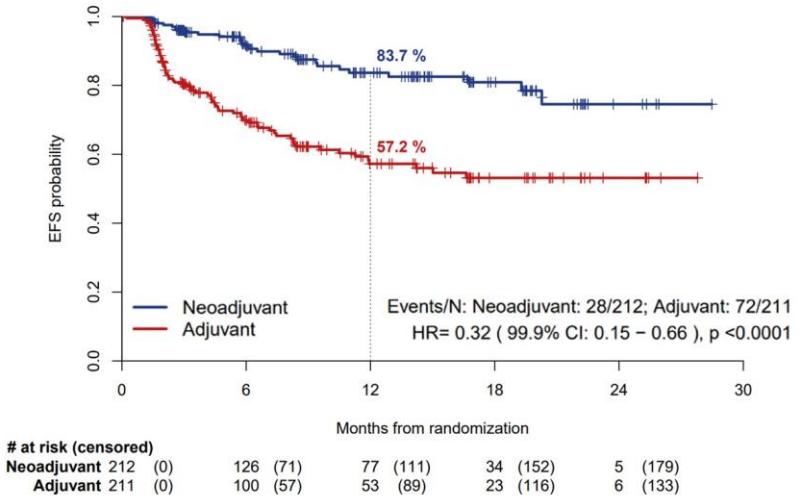
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Patel: Neoadjuvant vs. adjuvant Pembro

Blank: Neoadjuvant Ipi Nivo + Adj (non responders) vs. adjuvant Nivo



NADINA – Primary Endpoint: Event-Free Survival (EFS)



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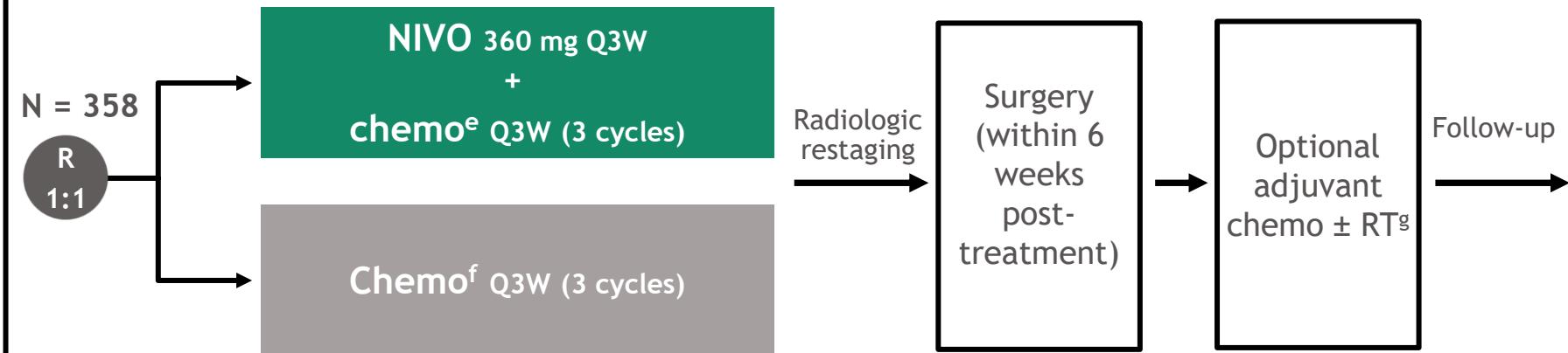
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CheckMate 816 study design^a

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per AJCC 7th edition^b)
- ECOG PS 0-1
- No known sensitizing EGFR mutations or ALK alterations

Stratified by
Stage (IB-II vs IIIA),
PD-L1^c ($\geq 1\%$ vs < 1%^d), and sex



Primary endpoints

- pCR by BIPR
- EFS^h by BICR

Secondary endpoints

- MPR by BIPR
- OS
- Time to death or distant metastases

Key exploratory analysis

- EFS by pCR status

Database lock: October 20, 2021; minimum follow-up: 21 months for NIVO + chemo and chemo arms; median follow-up, 29.5 months.

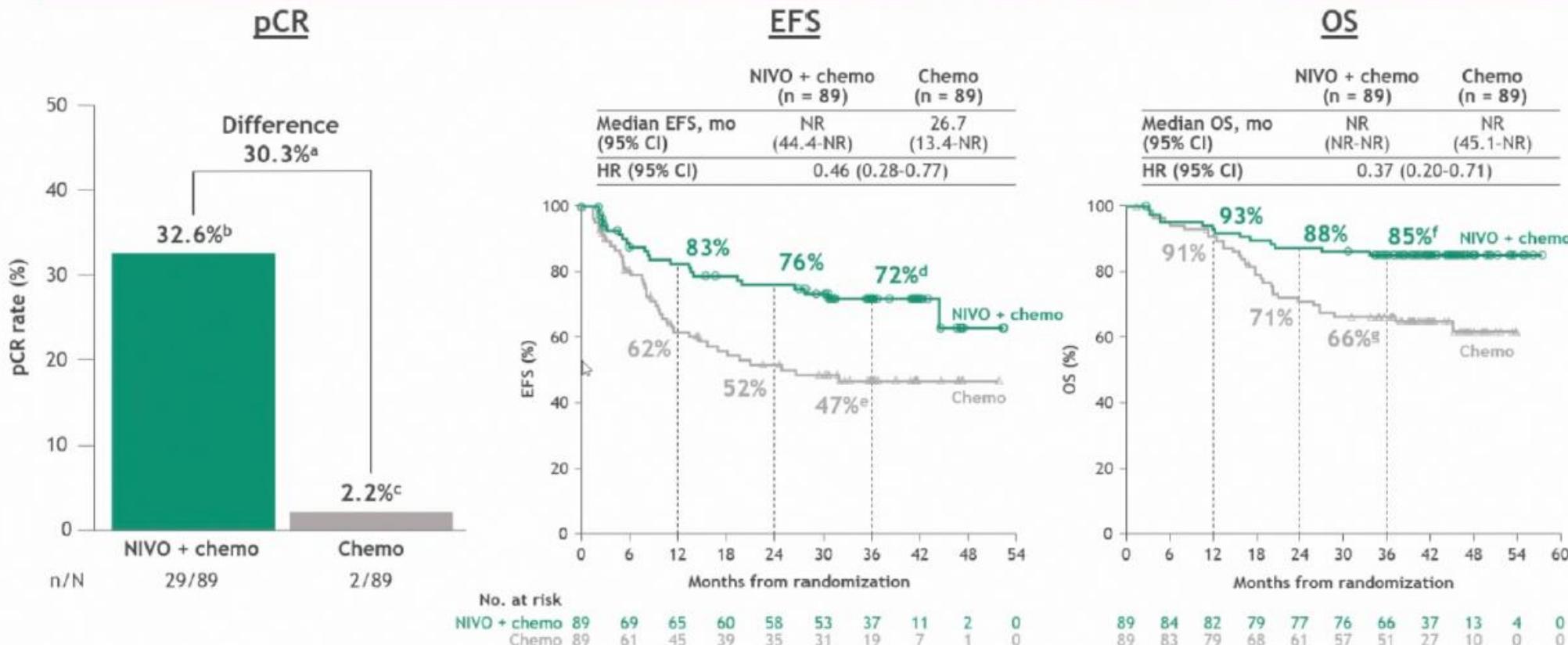
^aNCT02998528; ^bTNM Classification of Malignant Tumors 7th edition; ^cDetermined by the PD-L1 IHC 28-8 pharmDx assay (Dako); ^dIncluded patients with PD-L1 expression status not evaluable and indeterminate;

^eNSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; ^fVinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), etoposide + carboplatin; ^gPer healthcare professional choice; ^hEFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, or progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy.

CM 816: zulassungsrelevante Population PD_L1>1%

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

Efficacy outcomes in patients with tumor PD-L1 $\geq 1\%$

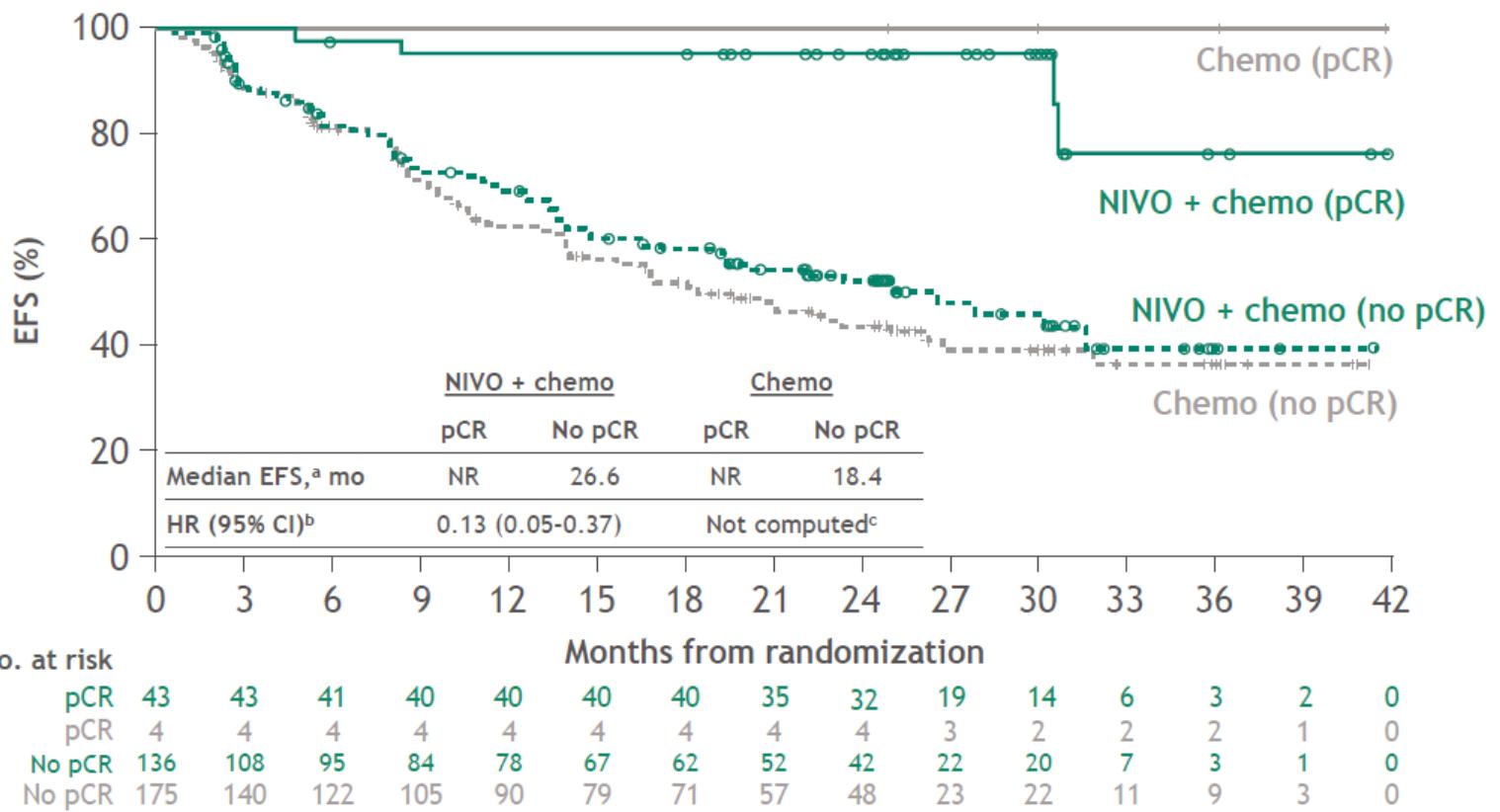


- Median TTDM (95% CI) in months was NR vs NR (18.8-NR) for NIVO + chemo vs chemo (HR, 0.35; 95% CI, 0.19-0.62); 3-year TTDM rates were 82%^h vs 53%ⁱ

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

MPR rates were 44.9% (95% CI, 34.4-55.9) with NIVO + chemo and 5.6% (95% CI, 1.8-12.6) with chemo (difference, 39.3%; 95% CI, 27.3-50.1). Unweighted differences in pCR and MPR rates between treatment arms were calculated using the Newcombe method. ^a=95% CI: ^b=19.9-40.7; ^c=23.0-43.3; ^d=0.3-7.9; ^e=61-81; ^f=35-58; ^g=76-91; ^h=56-75; ⁱ=71-88; ^j=41-63.

Exploratory analysis: EFS by pCR status



- 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)

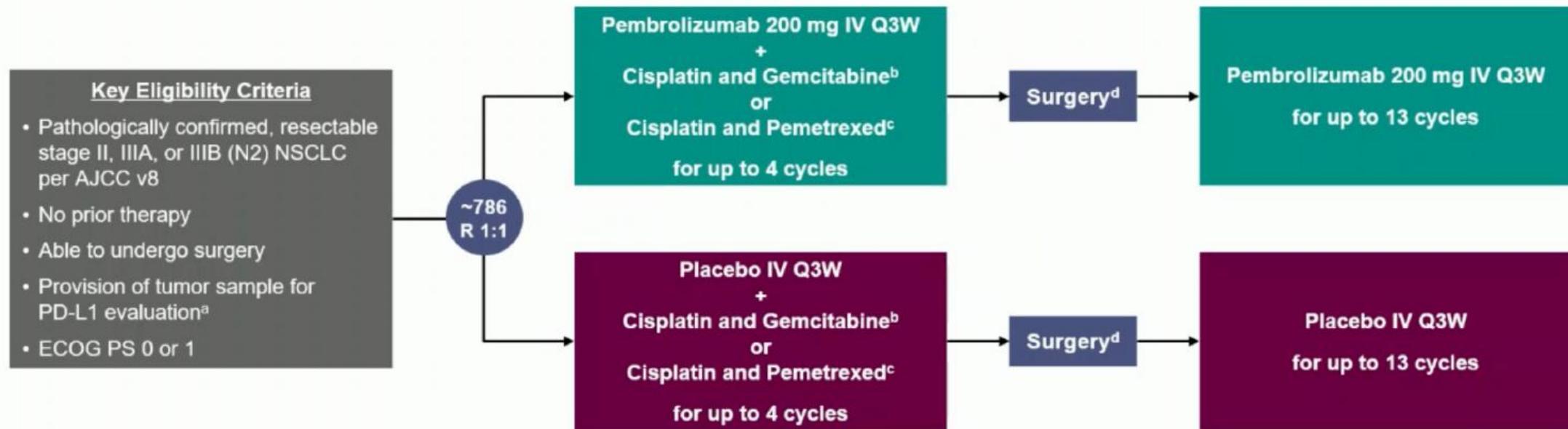
Minimum follow-up: 21 months; median follow-up, 29.5 months.

^a95% 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); ^bIn 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; ^cHR was not computed for the chemo arm due to only 4 patients having a pCR.

KEYNOTE-671 Study Design

Randomized, Double-Blind, Phase 3 Trial

IS



Stratification Factors

- Disease stage (II vs III)
- PD-L1 TPS^a (<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

^a Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. ^b Cisplatin 75 mg/m² IV Q3W + gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W was permitted for squamous histology only.

^c Cisplatin 75 mg/m² IV Q3W + pemetrexed 500 mg/m² IV Q3W was permitted for nonsquamous histology only. ^d 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.

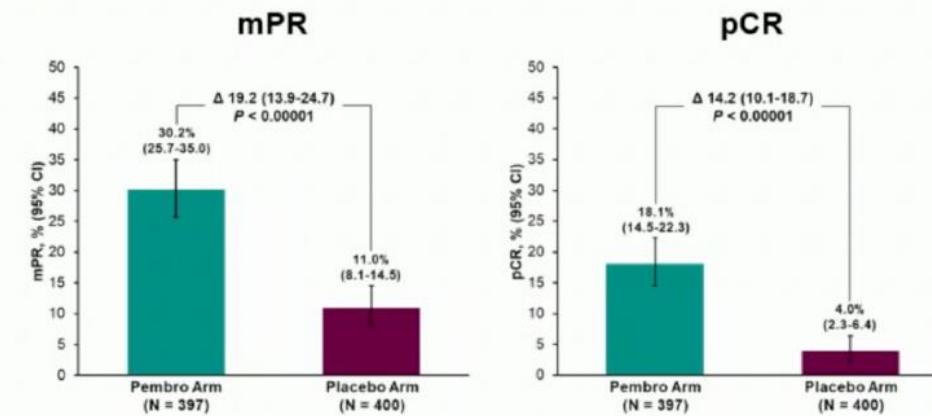
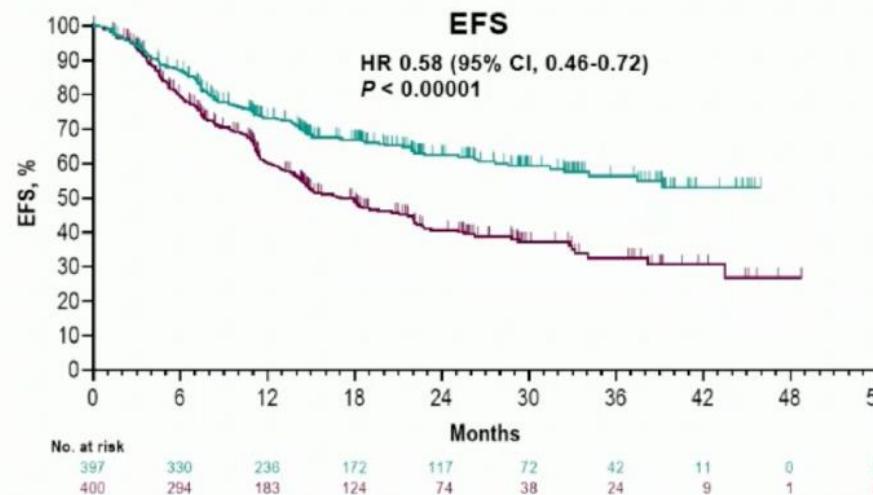
ClinicalTrials.gov identifier: NCT03425643.

KN 671: PFS und pCR

KEYNOTE-671 Results: Interim Analysis 1

Median Follow-Up^a: 25.2 months (range, 7.5-50.6)

- Neoadjuvant pembrolizumab + chemotherapy followed by surgery and adjuvant pembrolizumab significantly improved EFS, mPR, and pCR compared with neoadjuvant chemotherapy and surgery alone
- AE profile was as expected based on the known profiles of the individual treatment components

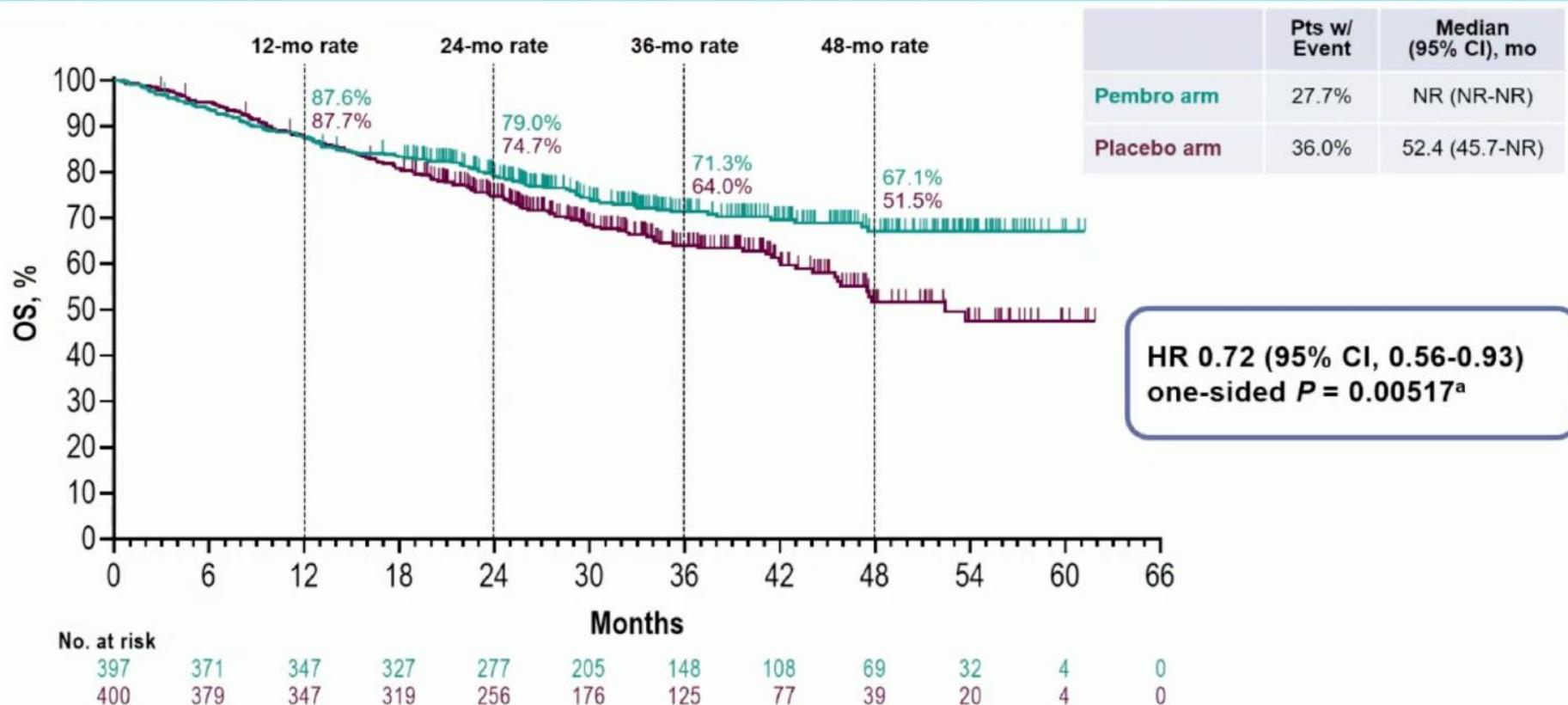


^a Defined as time from randomization to data cutoff date of July 29, 2022.

Wakelee H et al. *N Engl J Med* 2023;389:491-503.

Overall Survival, IA2

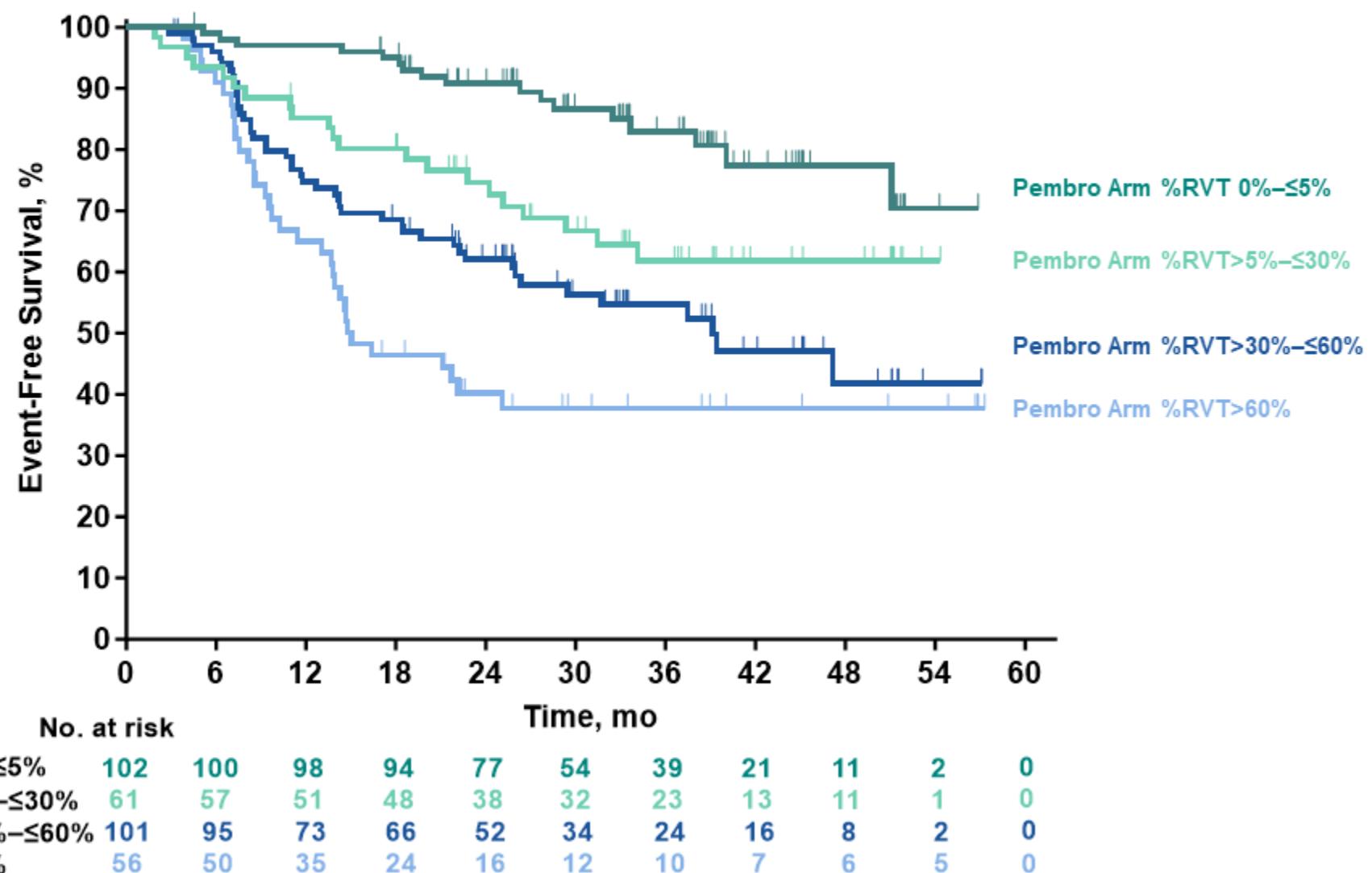
Median Follow-Up: 36.6 months (range, 18.8-62.0)



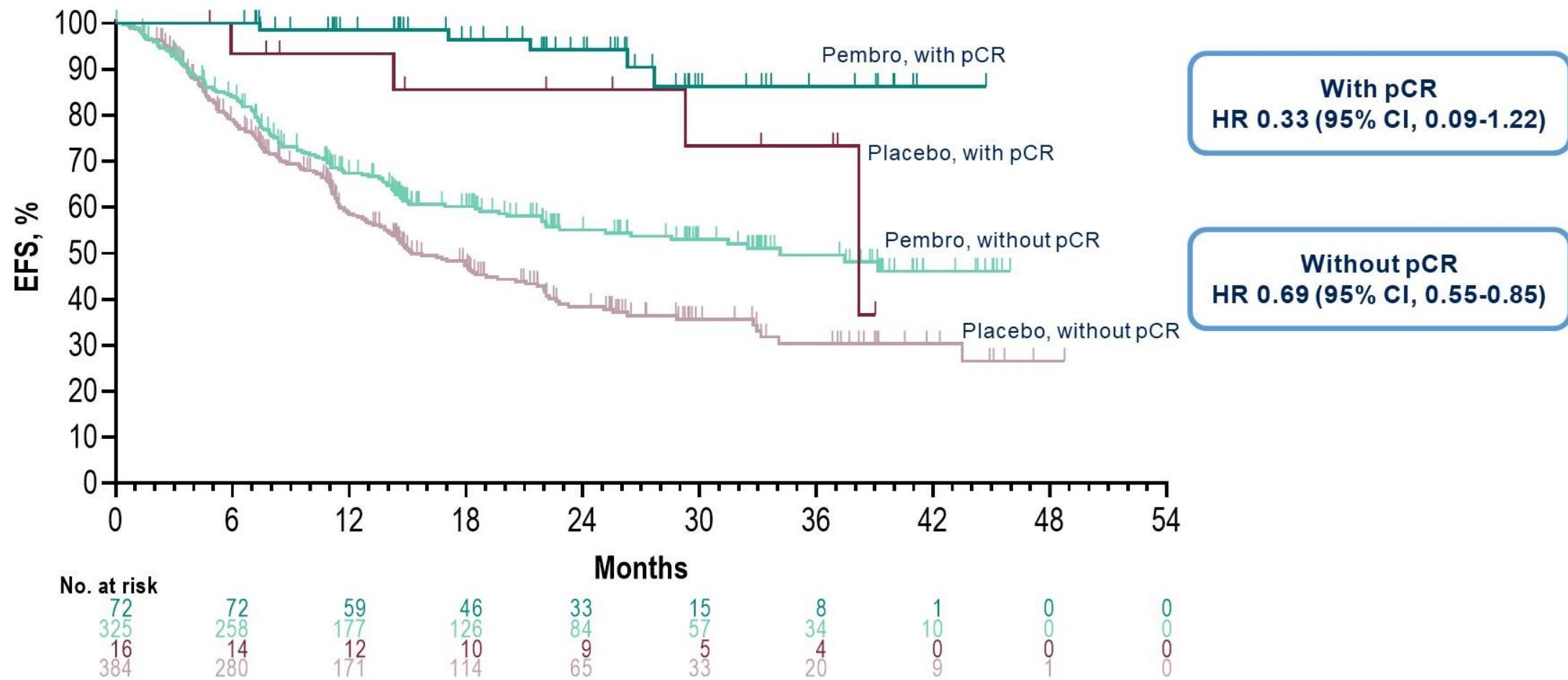
^aS defined as time from randomization to death from any cause. ^a Significance boundary at IA2, one-sided $P = 0.00543$.
ata cutoff date for IA2: July 10, 2023.

Event-Free Survival

According to %RVT Categorization in the Pembrolizumab Arm



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]).

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PRESENTED BY: Dr. Heather Wakelee

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Zusammenfassung

EFS und OS bei Patienten im Stadium II bis IIIB (N2) durch ICI verbessert

Non-pCR Patienten profitieren vermutlich von einer adjuvanten ICI Therapie

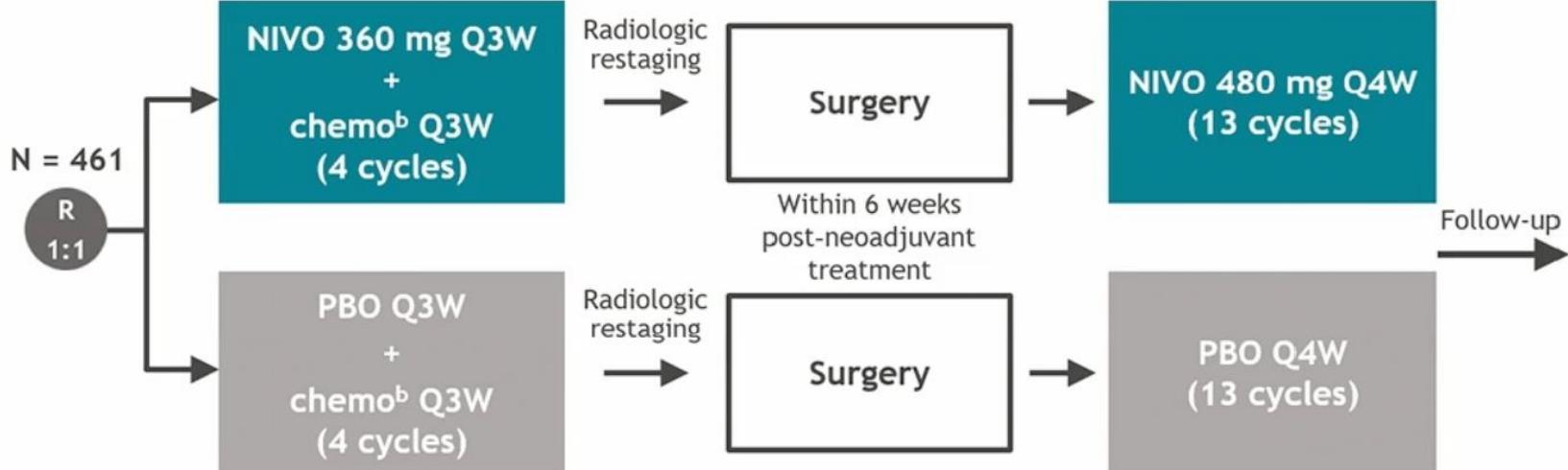
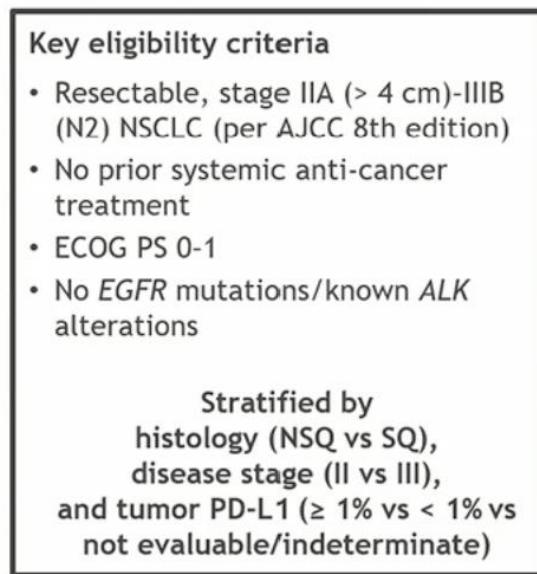
Bei pCR ist der Stellenwert der adjuvanten Therapie unklar

Diese Fragestellungen sollten prospektiv randomisiert geprüft werden

Non-pCR Ergebnis ist Tumorübergreifend (TNBC)



CheckMate 77T^a study design



Primary endpoint

- EFS by BICR

Secondary endpoints

- pCR by BIPR
- MPR by BIPR
- OS
- Safety

Exploratory analyses

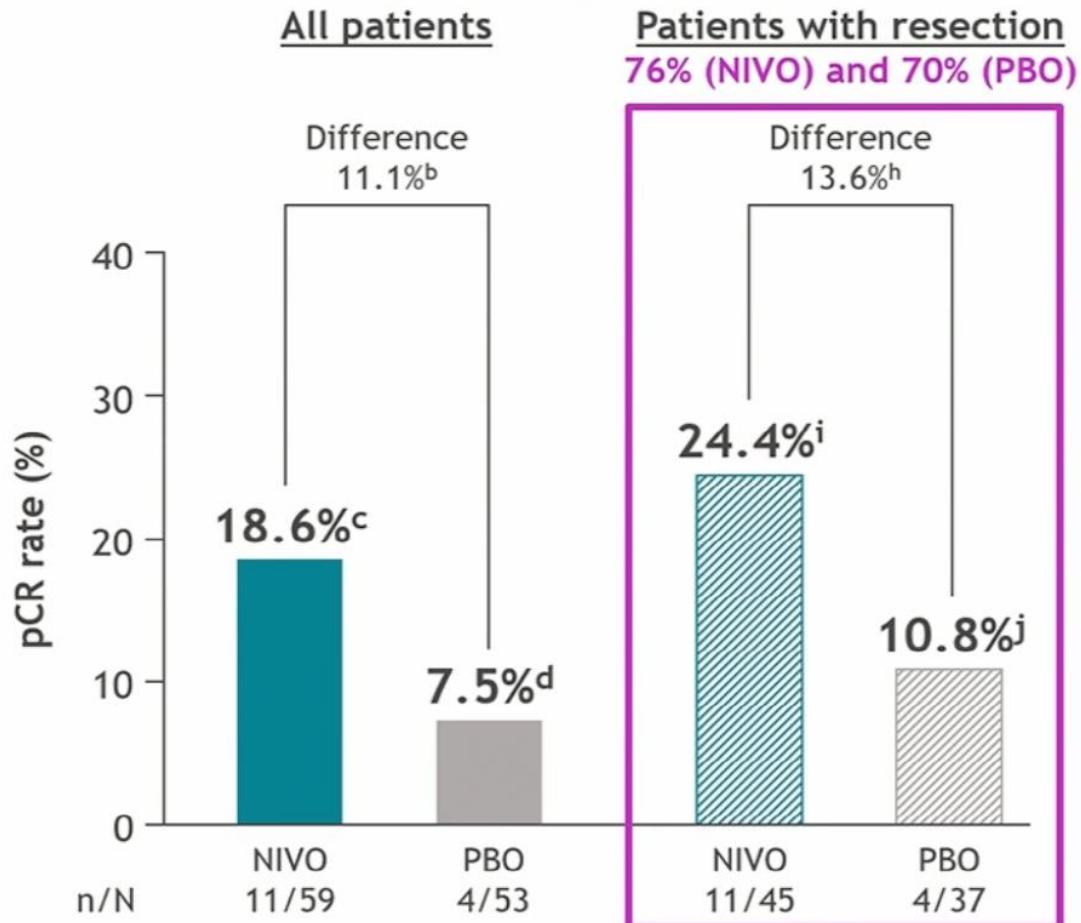
- Clinical outcomes by clinical stage III N2 or non-N2 status

Database lock date: September 6, 2023; median follow-up (range): 25.4 months (15.7-44.2).

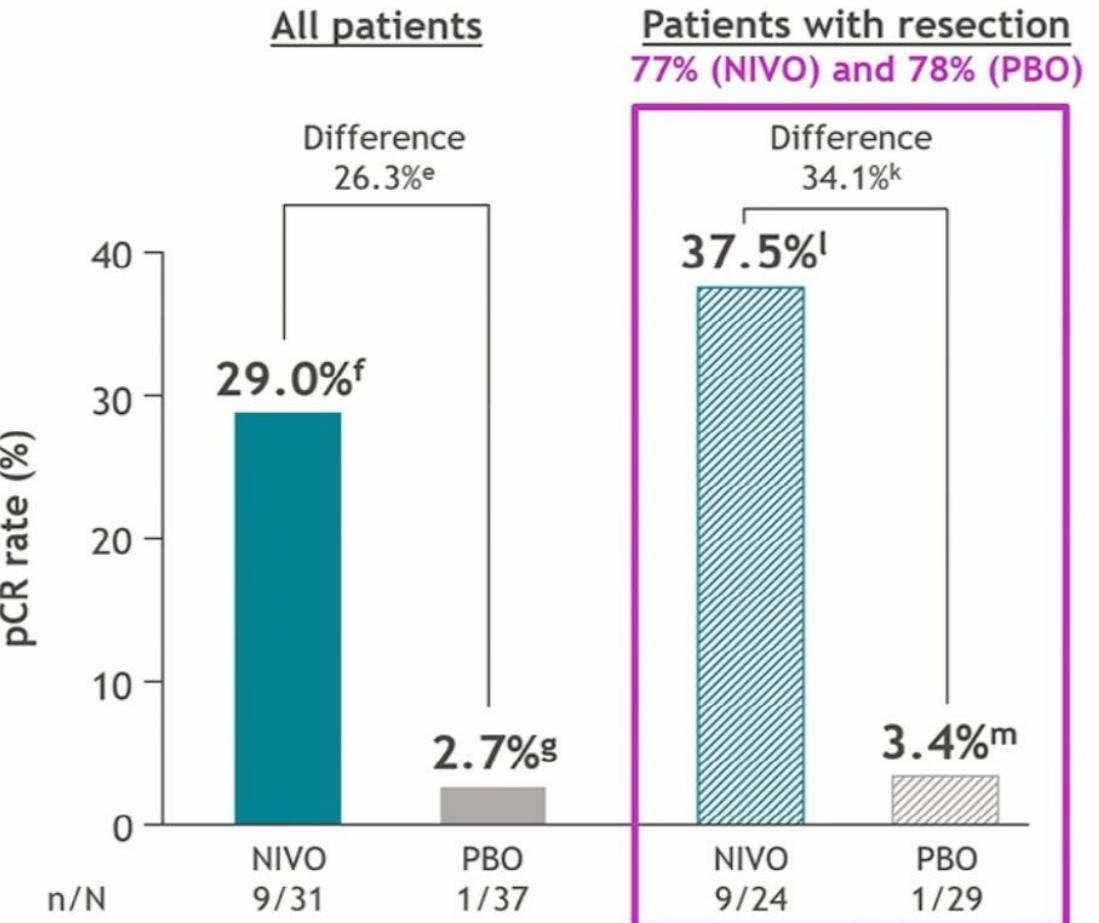
^aNCT04025879. ^bNSQ: cisplatin + pemetrexed, carboplatin + pemetrexed, or carboplatin + paclitaxel; SQ: cisplatin + docetaxel or carboplatin + paclitaxel.

pCR

Stage III single-station N2^a

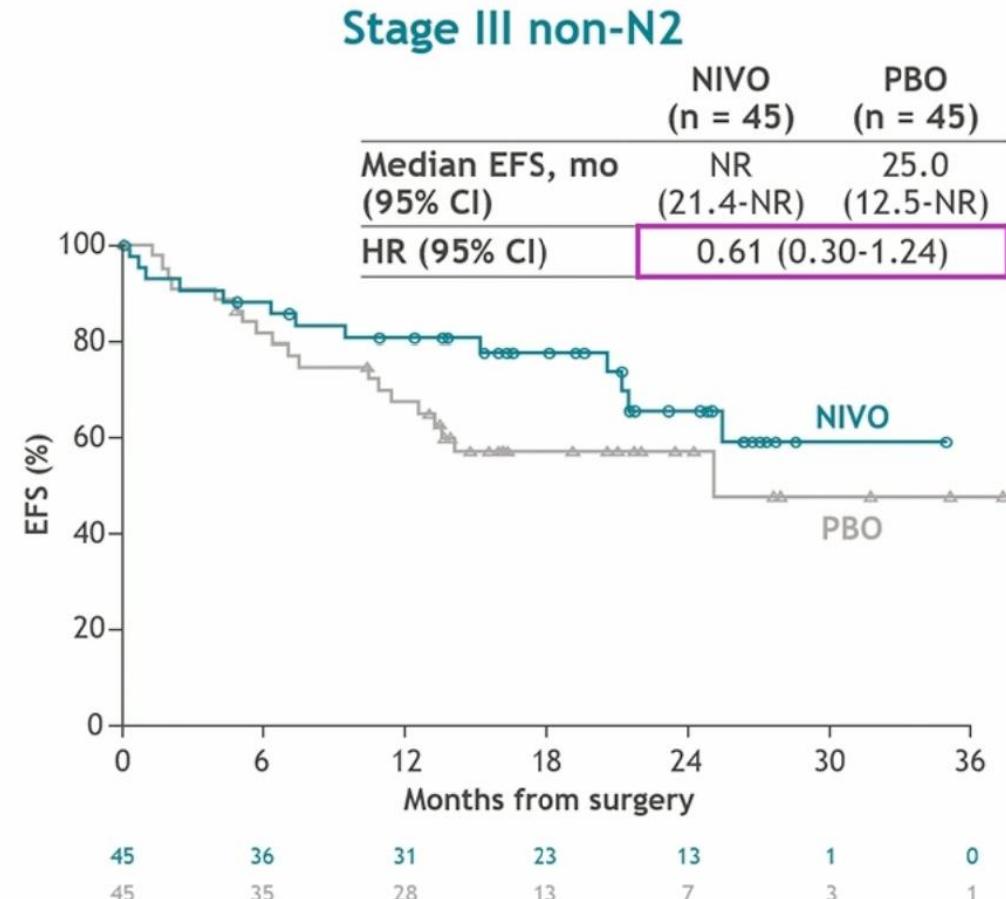
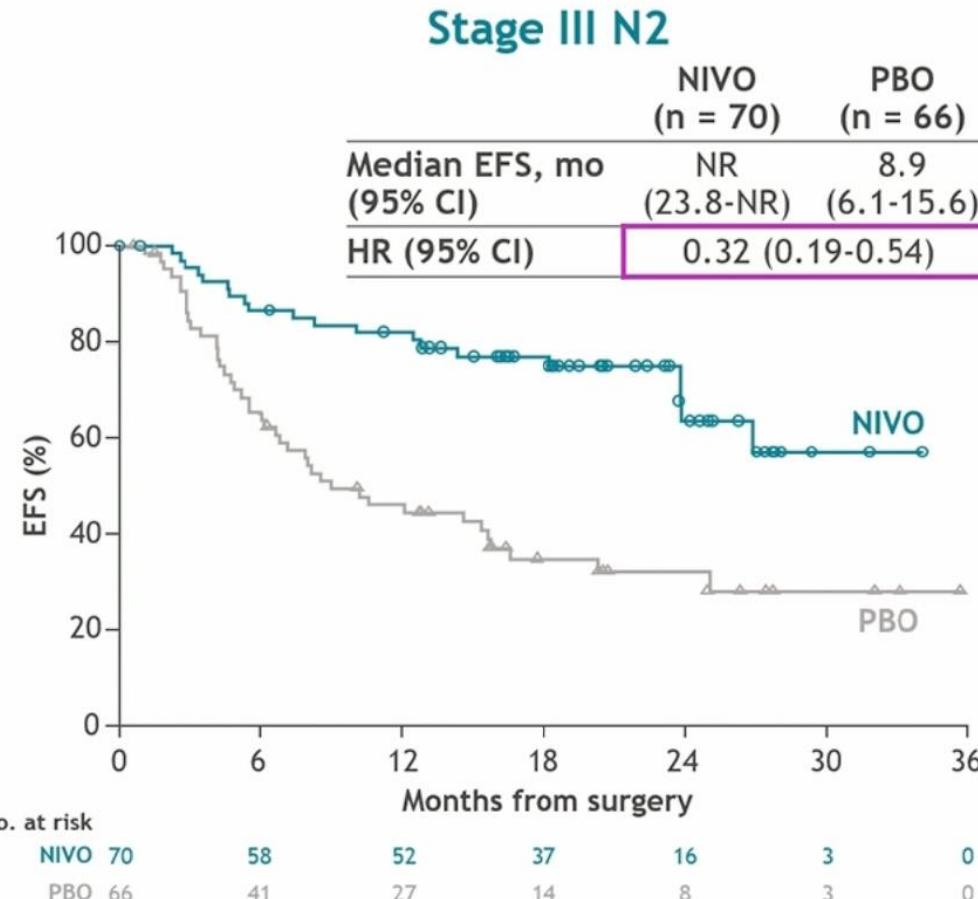


Stage III multi-station N2^a



^aN2 subcategory was not reported in 1 patient in the NIVO arm. ^{b-m}95% CI: ^b-1.9-23.7; ^c9.7-30.9; ^d2.1-18.2; ^e9.3-44.0; ^f14.2-48.0; ^g0.1-14.2; ^h-3.6-29.3; ⁱ12.9-39.5; ^j3.0-25.4; ^k12.7-54.0; ^l18.8-59.4; ^m0.1-17.8.

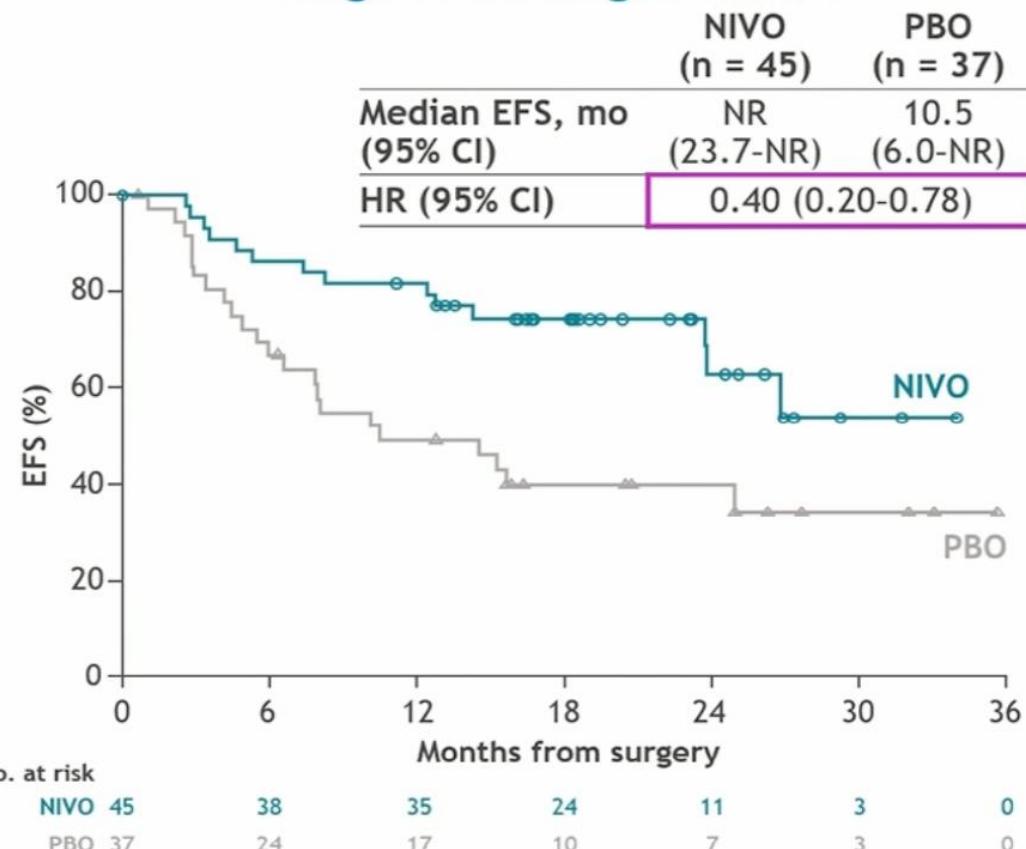
Landmark EFS from definitive surgery



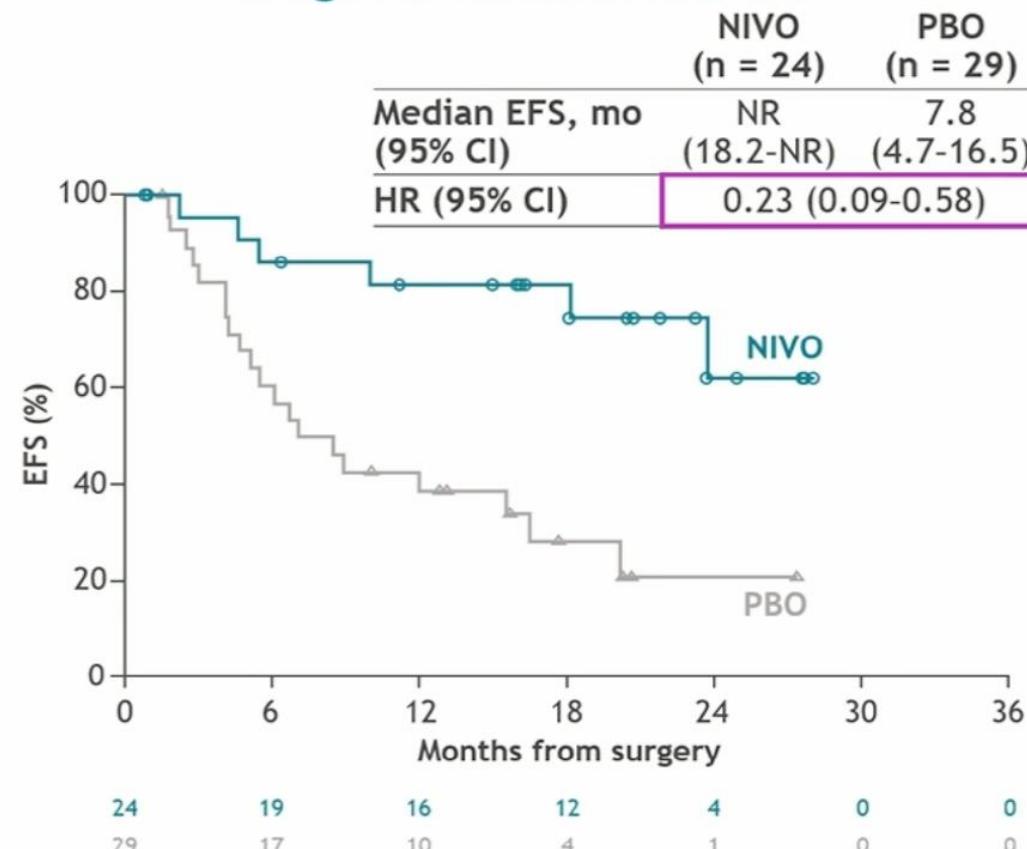
Median follow-up (range): 25.4 months (15.7-44.2).

Landmark EFS from definitive surgery

Stage III N2 single-station^a

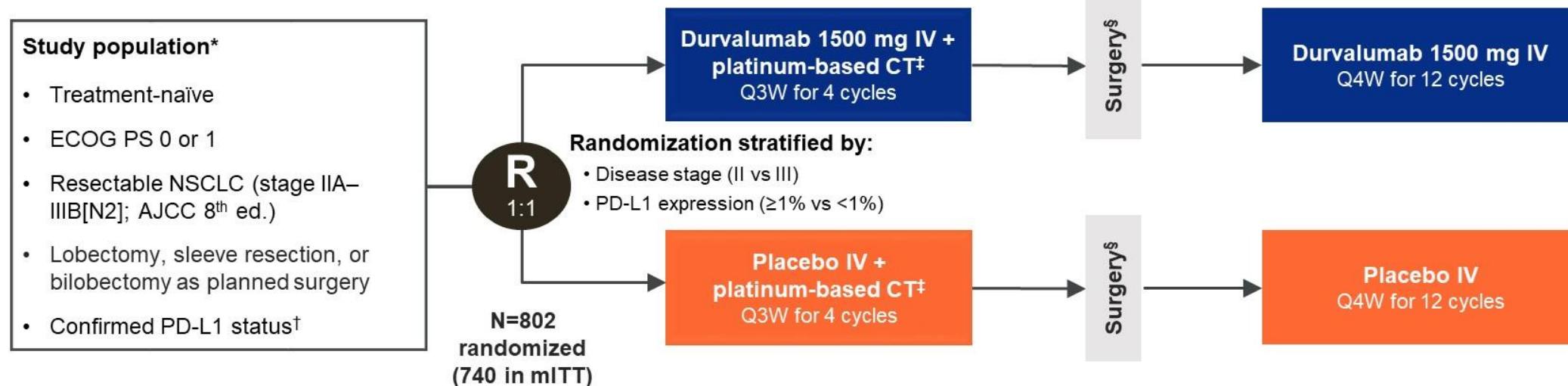


Stage III N2 multi-station^a



Median follow-up (range): 25.4 months (15.7-44.2). ^aN2 subcategory was not reported in 1 patient in the NIVO arm.

AEGEAN study design



Primary endpoints: pCR by central lab (per IASLC 2020¹) and EFS using BICR (per RECIST v1.1)

Key secondary endpoints: MPR by central lab (per IASLC 2020¹), DFS using BICR (per RECIST v1.1)[¶] and OS[¶]

All efficacy analyses were performed on the mITT population (N=740), which included all randomized patients without documented EGFR/ALK aberrations

- Efficacy was assessed in the mITT subpopulation with baseline N2 nodal status per the investigator (i.e., the ‘baseline N2 subgroup’)
 - FDG-PET was recommended for investigation of baseline nodal status, with specific recommendations for invasive staging when scans showed a positive mediastinum or negative mediastinum with T >3 cm, central tumor, or clinical N1 disease[£]
- Safety was assessed in all patients in the baseline N2 subgroup who had ≥ 1 treatment dose (i.e., the ‘N2 safety analysis subset’)

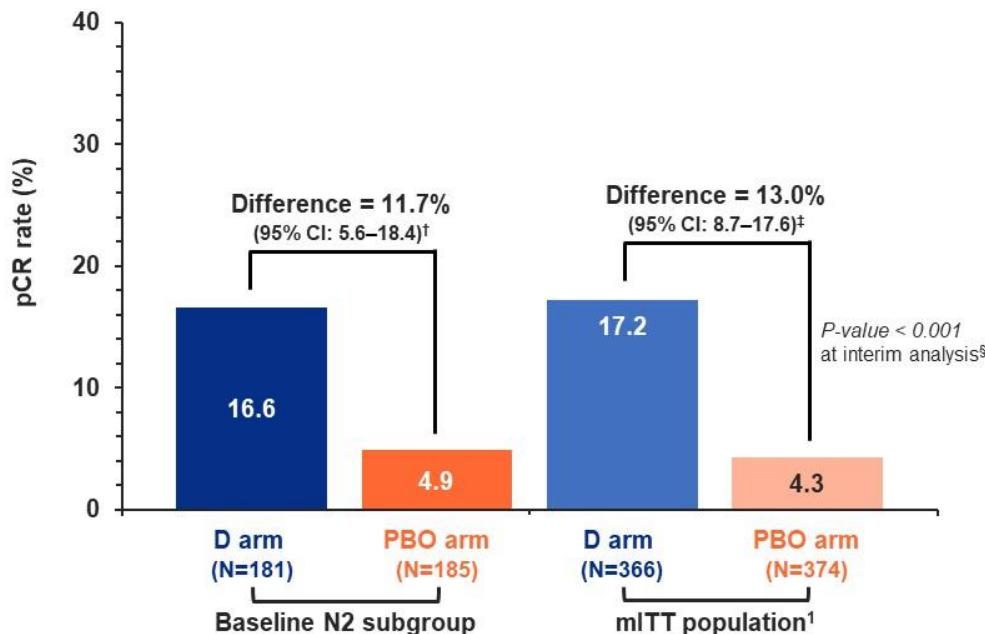
*The protocol was amended while enrollment was ongoing to exclude (1) patients with tumors classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with EGFR/ALK aberrations. [†]Ventana PD-L1 (SP263) immunohistochemistry assay. [‡]Choice of CT regimen was 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 had comorbidities or who were unable to tolerate cisplatin per the investigator’s judgment). [¶]Post-operative radiotherapy was permitted where indicated per local guidance. [§]AEGEAN continues for assessment of DFS and OS. [£]Using biopsy by endobronchial ultrasound, mediastinoscopy, or thoracoscopy. AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG-PET, ¹⁸F-fluoro-deoxyglucose positron emission tomography; IASLC, International Association for the Study of Lung Cancer; IV, intravenously; mITT, modified intent-to-treat; MPR, major pathologic response; OS, overall survival; PD-L1, programmed cell death-ligand 1; QXW, every X weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; T, tumor.

¹Travis WD, et al. J Thorac Oncol 2020;15:709–40.

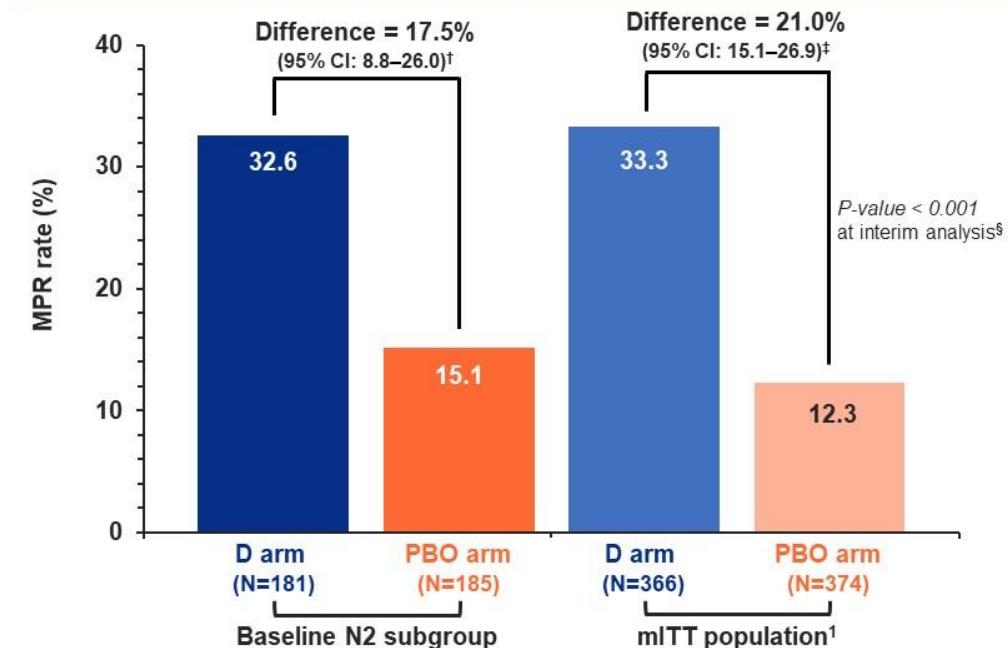
pCR and MPR (baseline N2 subgroup and mITT)*

- pCR and MPR benefit in this subgroup was consistent with the mITT population

pCR (central lab)



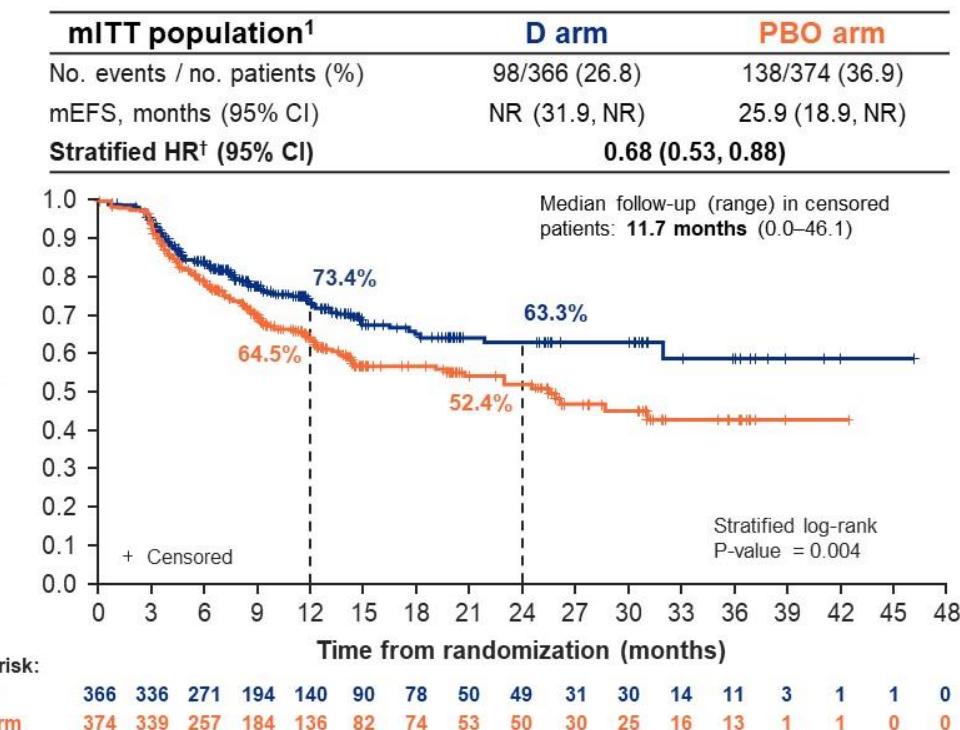
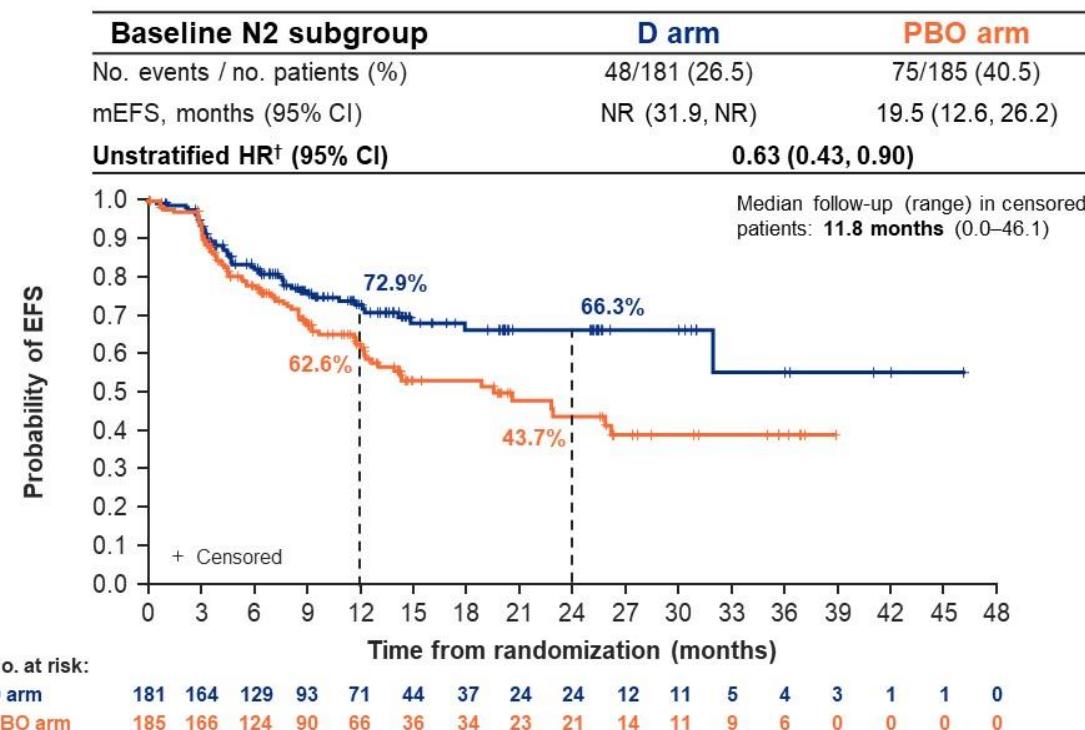
MPR (central lab)



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).

EFS using RECIST v1.1 (BICR) (baseline N2 subgroup and mITT)*

- EFS benefit in this subgroup was consistent with the mITT population and similar among patients with single- and multi-station N2 disease
 - N2 single-station (n=273) HR[†] (95% CI): 0.61 (0.39–0.94)¹
 - N2 multi-station (n=74) HR[†] (95% CI): 0.69 (0.33–1.38)¹



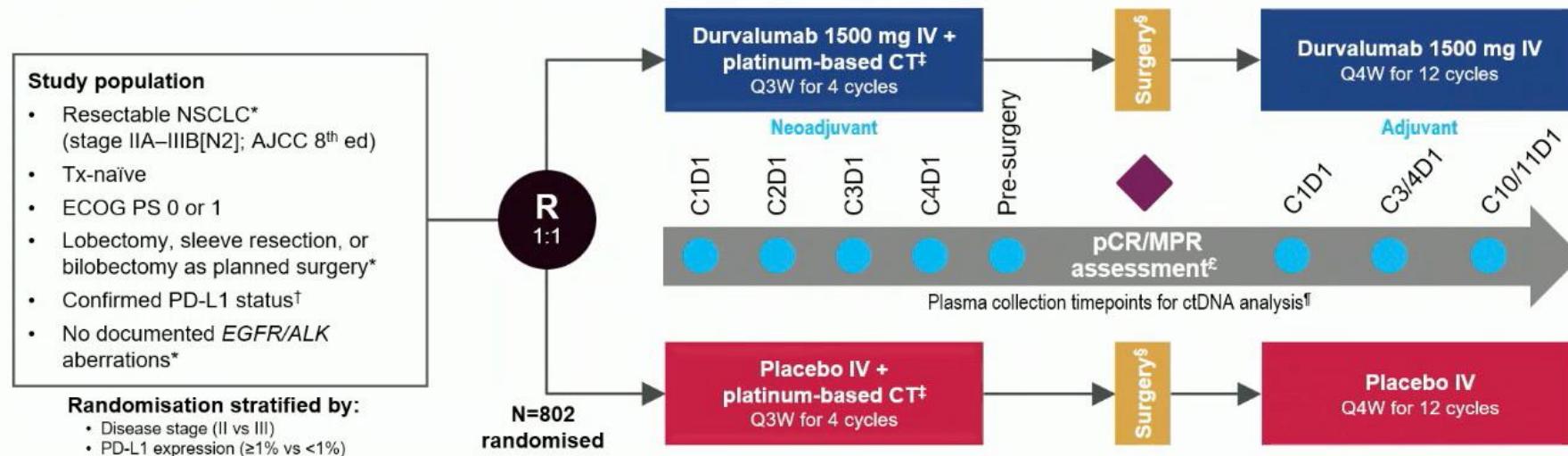
DCO = Nov 10, 2022. *EFS is defined as time from randomization to the earliest of: (A) progressive disease (PD) that precludes surgery; (B) PD discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; (C) local/distant recurrence using BICR per RECIST v1.1; or (D) death from any cause. HR <1 favours the D arm versus the PBO arm. Median and landmark EFS estimates calculated using the Kaplan-Meier method. [†]HR for the baseline N2 subgroup calculated from an unstratified Cox proportional hazards model; HR for the mITT population calculated using a stratified Cox proportional hazards model. CI, confidence interval; D, durvalumab; HR, hazard ratio; mEFS, median EFS; NR, not reached; PBO, placebo.

¹From Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer, Heymach JV, et al, N Engl J Med 2023;389:1672–84, Copyright © (2023) Massachusetts Medical Society. Reproduced with permission.

AEGEAN

AEGEAN Study Design

Phase 3, global, randomised, double-blind, placebo-controlled study



- Plasma samples were collected at protocol-specified timepoints, including prior to each neoadjuvant Tx cycle, surgery, and adjuvant Tx at select cycles
- ctDNA analysis was performed using Invitae Personalized Cancer Monitoring,™ a tumour-informed MRD assay,^{€1} with the exploratory analyses reported here based on data from the second EFS interim analysis
 - Patient-specific tumour-informed panels were designed to include 16-50 variants, identified by whole exome sequencing of Tx-naïve diagnostic biopsies only (rather than on-study surgical resections) to avoid selection bias

*The protocol was amended while enrolment was ongoing to exclude (1) patients with tumours classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with documented EGFR/ALK aberrations. †Ventana SP263 immunohistochemistry assay. ‡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). §Post-operative radiotherapy was permitted where indicated per local guidance.

¶Not all patients had samples available at all timepoints. †pCR and MPR were evaluated centrally per IASLC recommendations.² The lower limit of detection for the assay was 0.008% VAF (80 parts per million). AJCC, American Joint Committee on Cancer; CXDX, cycle X day X; ECOG PS, Eastern Cooperative Oncology Group performance status; IASLC, International Association for the Study of Lung Cancer; IV, intravenous; PD-L1, programmed cell death-ligand 1; QXW, every X weeks; R, randomisation; VAF, variant allele fraction.

1. Zhao J, et al. Mol Diagn Ther 2023;27:753-768.
 2. Travis WD, et al. J Thorac Oncol 2020;15:709-40.

Association of ctDNA Clearance* with pCR/MPR and Its Predictive Utility

- Among patients who were ctDNA-positive at baseline (neoadjuvant C1D1) in both arms (89.6%), all patients who had pCR and >93% who had MPR had ctDNA clearance at neoadjuvant C4D1†
- Absence of early ctDNA clearance may identify patients unlikely to have pCR
 - In both arms, lack of early ctDNA clearance identified patients with a low probability of having pCR (NPV: ≥89% at C2D1; 100% at C4D1)
 - Patients who had ctDNA clearance were more likely to have pCR in the D vs PBO arm (PPV: 49% vs 11% at C2D1)

Predictive Value of ctDNA Clearance at Different Timepoints for pCR‡

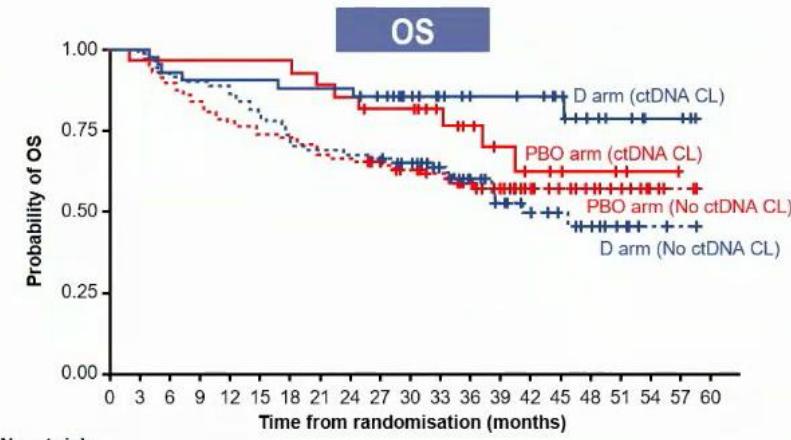
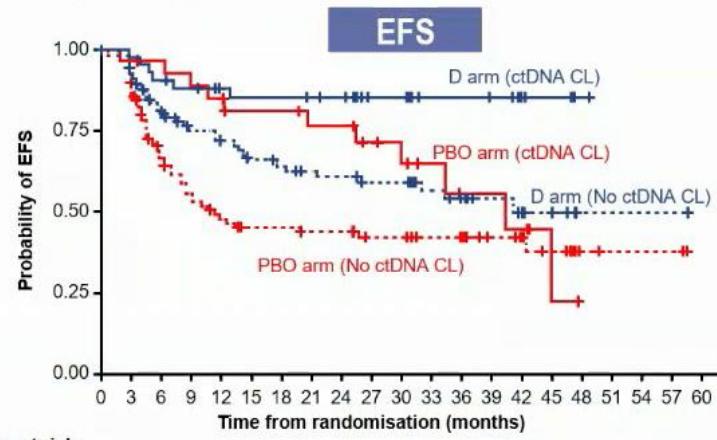
D arm	pCR		PBO arm	pCR	
	PPV	NPV		PPV	NPV
C2D1	49%	89%	C2D1	11%	98%
C3D1	39%	94%	C3D1	12%	100%
C4D1	40%	100%	C4D1	12%	100%
Pre-surgery	40%	100%	Pre-surgery	13%	100%

Second EFS interim analysis DCO = 10 May 2024. *ctDNA clearance was defined as a change from ctDNA detected at baseline (neoadjuvant C1D1) to undetectable at the specified on-Tx timepoint. ctDNA non-clearance was defined as ctDNA-positive at the specified timepoint (where baseline could be either evaluable or non-evaluable). †In the BEP, pCR (23% vs 4%) and MPR (42% vs 14%) rates were higher in the D vs PBO arm. ‡Assessed in patients who were ctDNA-positive at baseline (neoadjuvant C1D1). In the D arm, the number of patients analysed at each timepoint (had ctDNA clearance, were pCR-positive) were as follows: C2D1 (41, 29), C3D1 (62, 27), C4D1 (63, 25) and Pre-surgery (65, 26). In the PBO arm, the number of patients analysed at each timepoint (had ctDNA clearance, were pCR-positive) were as follows: C2D1 (27, 5), C3D1 (50, 6), C4D1 (51, 6) and Pre-surgery (45, 6). NPV, negative predictive value; PPV, positive predictive value.

AEGEAN: Correlation ctDNA mit EFS und OS

Associations of ctDNA Clearance at Neoadjuvant C2D1 with EFS and OS

- As early as neoadjuvant C2D1, patients in the D arm with ctDNA clearance had longer EFS and OS compared to patients without clearance, and versus the PBO arm*



No. at risk

No. at risk

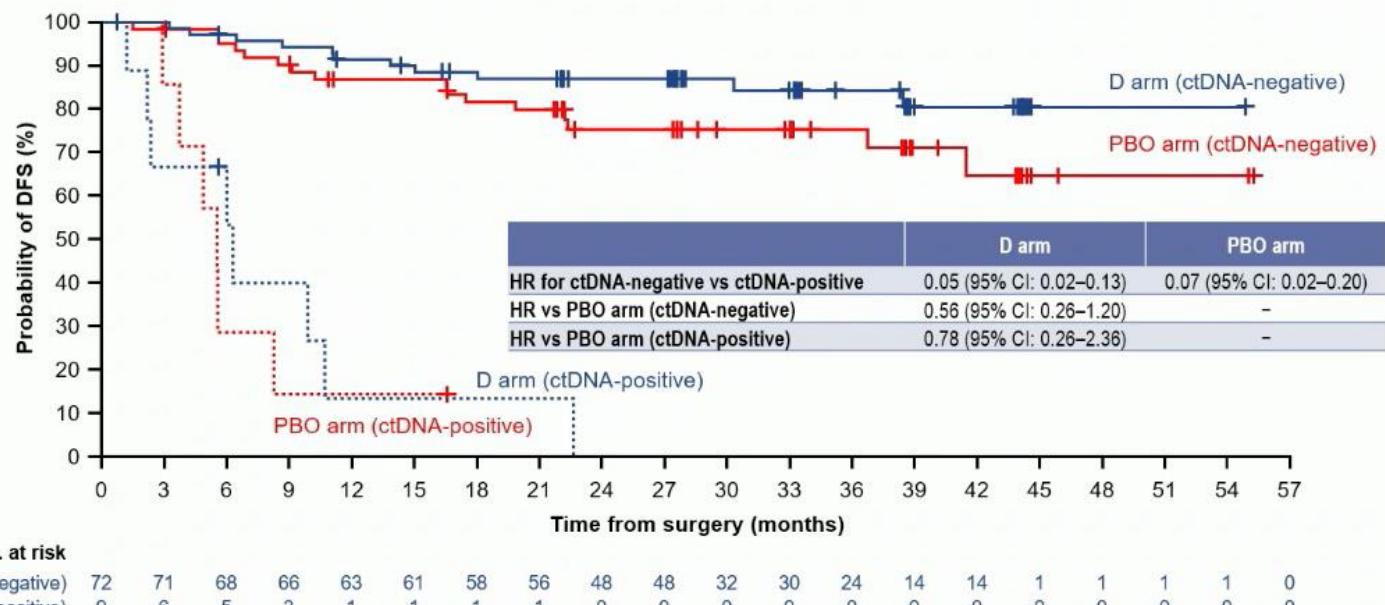
	D arm	PBO arm
EFS HR for ctDNA CL vs No ctDNA CL	0.30 (95% CI: 0.12–0.71)	0.53 (95% CI: 0.27–1.02)
EFS HR for the D vs PBO arm (ctDNA CL)	0.31 (95% CI: 0.11–0.85)	-
EFS HR for the D vs PBO arm (No ctDNA CL)	0.62 (95% CI: 0.40–0.97)	-

	D arm	PBO arm
OS HR for ctDNA CL vs No ctDNA CL	0.32 (95% CI: 0.14–0.72)	0.61 (95% CI: 0.28–1.31)
OS HR for the D vs PBO arm (ctDNA CL)	0.55 (95% CI: 0.20–1.52)	-
OS HR for the D vs PBO arm (No ctDNA CL)	1.07 (95% CI: 0.68–1.69)	-

AEGEAN: postoperative ctDNA Ergebnisse

Association of MRD at the Post-surgical Landmark (Adjuvant C1D1) with DFS*

- Among patients who completed Sx, patients with ctDNA detected at adjuvant C1D1 had the poorest DFS outcomes compared to ctDNA-negative patients in both Tx arms
- DFS trends favoured the D arm versus the PBO arm



Second EFS interim analysis DCO = 10 May 2024. HRs were calculated using an unstratified Cox proportional hazard model using the Efron method to adjust for ties and Wald confidence intervals. *DFS (assessed per BICR using RECIST v1.1) was analyzed in patients who had tumour resection with R0/R1 margins and no evidence of disease in the first post-Sx scan. The landmark MRD timepoint was a median 6.9 weeks (range, 2.3–19.4) post-Sx at adjuvant C1D1.



2024 World Conference on Lung Cancer

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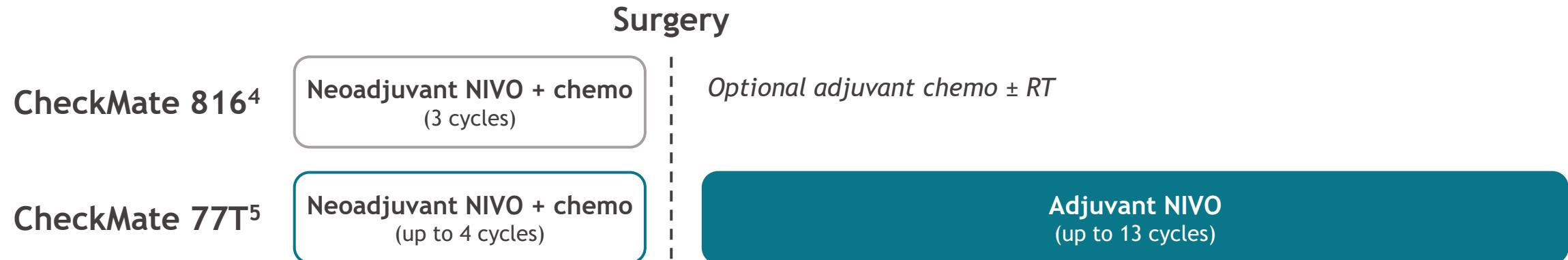
Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816

Patrick M. Forde,¹ Solange Peters,² Jessica Donington,³ Stephanie Meadows-Shropshire,⁴ Phuong Tran,⁴ Stefano Lucherini,⁵ Cinthya Coronado Erdmann,⁶ Hong Sun,⁶ Tina Cascone⁷

¹The Bloomberg-Kimmel Institute for Cancer Immunotherapy, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medicine, Baltimore, MD, USA; ²Lausanne University Hospital, Lausanne, Switzerland; ³The University of Chicago, Chicago, IL, USA; ⁴Bristol Myers Squibb, Princeton, NJ, USA; ⁵Bristol Myers Squibb, Uxbridge, UK; ⁶Bristol Myers Squibb, Boudry, Switzerland; ⁷The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Introduction

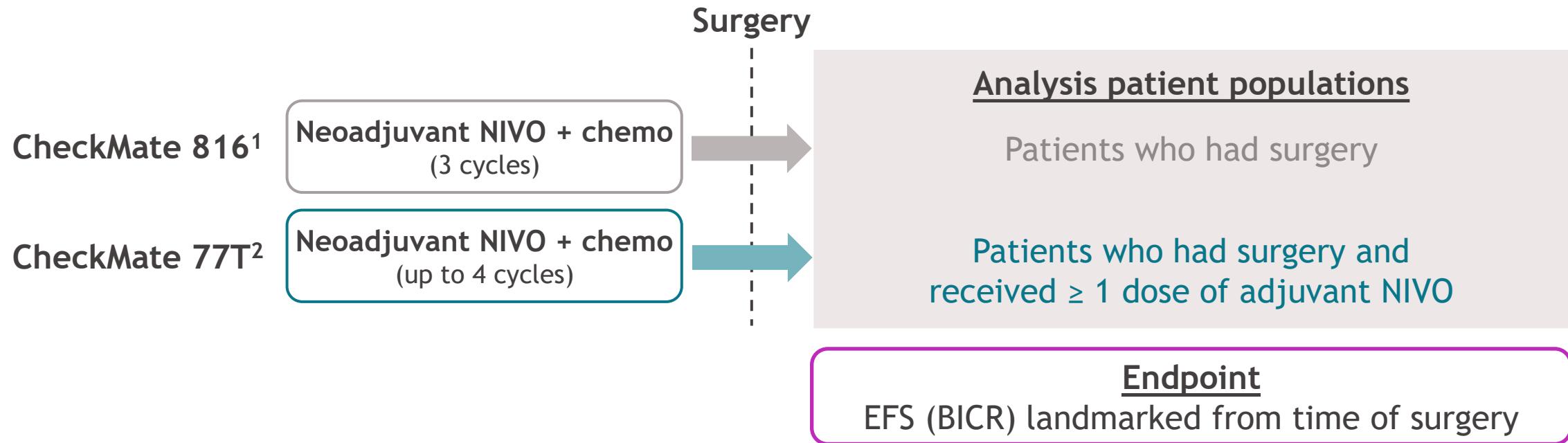
- NIVO + chemo is an approved and guideline-recommended neoadjuvant-only immunotherapy-containing regimen for eligible patients with resectable NSCLC¹⁻³
 - EFS benefit was demonstrated vs neoadjuvant chemo (HR = 0.63^a)⁴
- Perioperative NIVO built on neoadjuvant NIVO + chemo and demonstrated significant EFS benefit vs placebo (HR = 0.58^b)⁵
- pCR rates with neoadjuvant NIVO + chemo were 24%-25%^{4,5}



^a97.38% CI, 0.43-0.91. ^b97.36% CI, 0.42-0.81.

1. OPDIVO® (nivolumab) [package insert]. Princeton, NJ, USA: Bristol Myers Squibb; February 2023. 2. OPDIVO® (nivolumab) [summary of product characteristics]. Dublin, Ireland: Bristol Myers Squibb Pharma EEIG; July 2023. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V7.2024. ©National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed August 19, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 4. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985. 5. Cascone T, et al. *N Engl J Med* 2024;390:1756-1769.

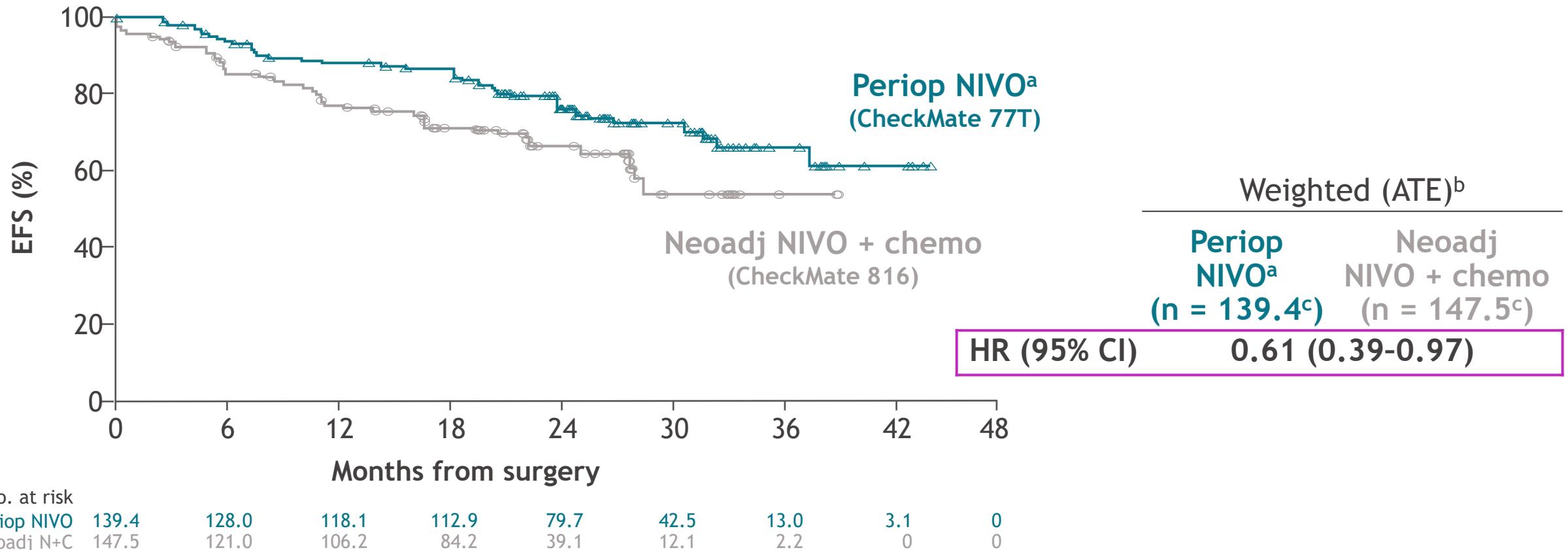
Methods: perioperative NIVO vs neoadjuvant NIVO + chemo



- In lieu of a head-to-head trial, exploratory propensity score weighting analyses (ATT^a and ATE^b) were performed to allow simplified reproduction of a randomized trial by adjusting for clinically relevant baseline demographics and disease characteristics^c between study populations and reducing the confounding effects of these factors
 - Subgroup analyses were not weighted due to smaller sample sizes
- Median duration of follow-up^d: 29.5 months (CheckMate 816) and 33.3 months (CheckMate 77T)

^aAverage treatment effect for the treated (ATT): a weight of 1 was applied to patients in the perioperative NIVO arm of CheckMate 77T; varying weights were applied to patients in the CheckMate 816 NIVO + chemo arm to make them comparable to those in the perioperative NIVO arm in CheckMate 77T based on propensity scores. ^bAverage treatment effect (ATE): varying weights were applied to all patients in the populations of interest from CheckMate 77T and CheckMate 816 to make them comparable to one another based on propensity scores. ^cSex, race, clinical stage, tumor histology, PD-L1 expression, age, ECOG PS, and smoking status. ^dDatabase locks: CheckMate 816, October 20, 2021; CheckMate 77T, April 26, 2024. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985. 2. Cascone T, et al. *N Engl J Med* 2024;390:1756-1769.

Landmark EFS (BICR) from definitive surgery

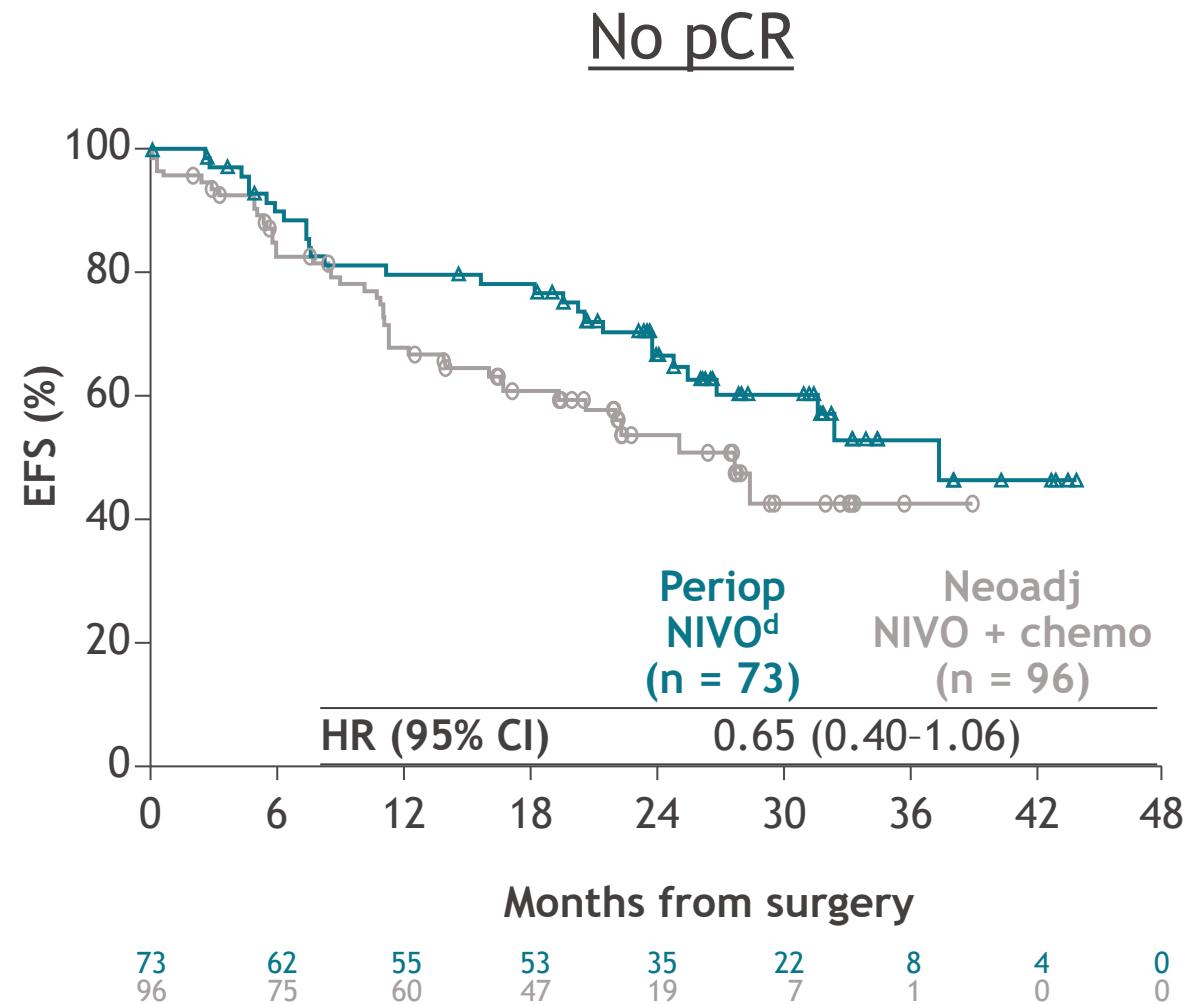
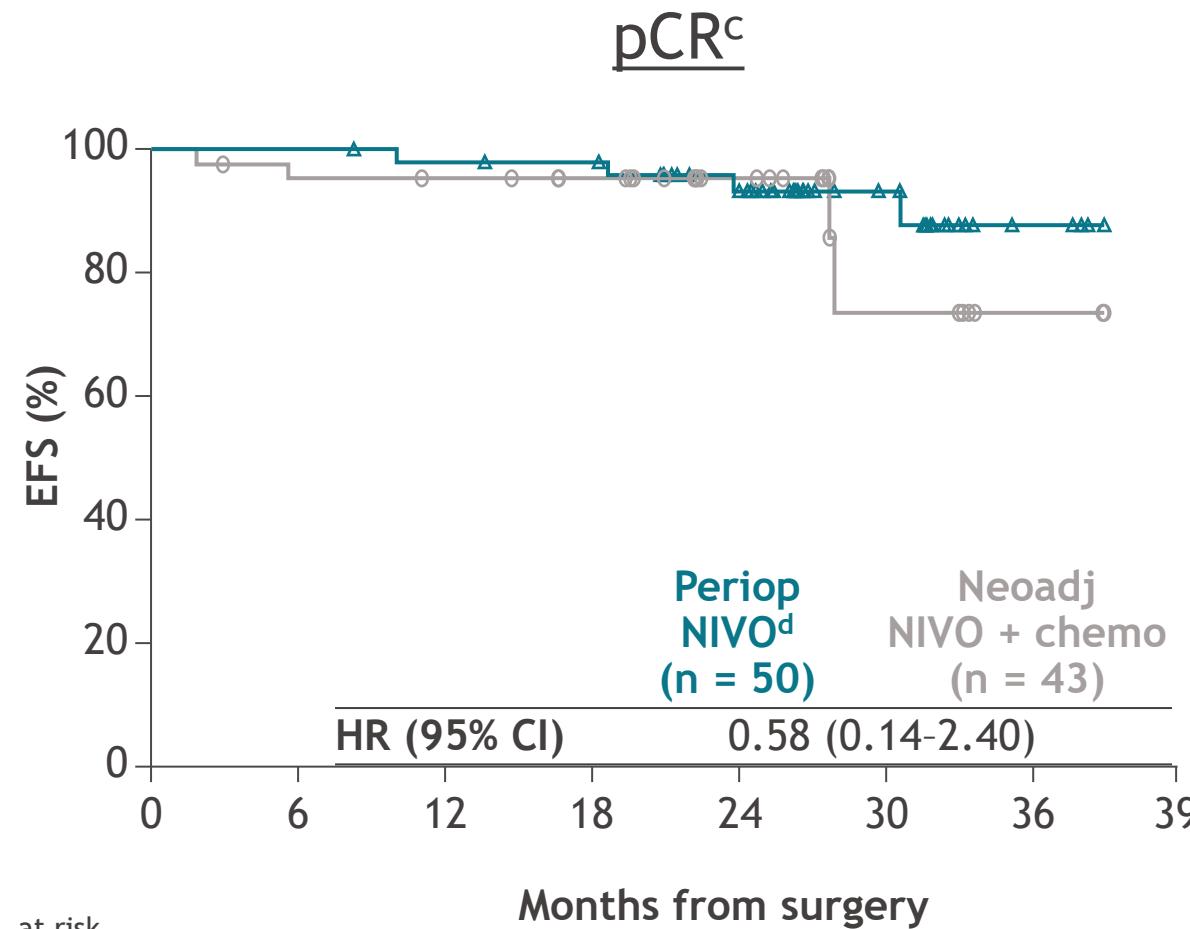


- HR (95% CI): ATT^d weighted analysis, 0.56 (0.35-0.90); unweighted analysis, 0.59 (0.38-0.92)

Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. ^aIncludes only patients who received ≥ 1 dose of adjuvant NIVO. ^bATE: 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. ^cN values fractional due to weighting. ^dATT: 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).

In the unweighted analysis population, 89 patients (64%) completed adjuvant therapy, and median number of doses (range) 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 periop NIVO vs neoadj NIVO + chemo: HR = 0.82 (95% CI, 0.55-1.21).

Landmark EFS^a (analysis population) by pCR status^{a,b}



Median follow-up: CheckMate 816, 29.5 months; CheckMate 77T, 33.3 months. ^aPatients with non-evaluable pCR status were excluded. ^bUnweighted analyses.

^cpCR rates in this analysis population: perioperative NIVO, 40.7%; neoadjuvant NIVO + chemo, 30.5%. ^dIncludes only patients who received ≥ 1 dose of adjuvant NIVO.

Zusammenfassung

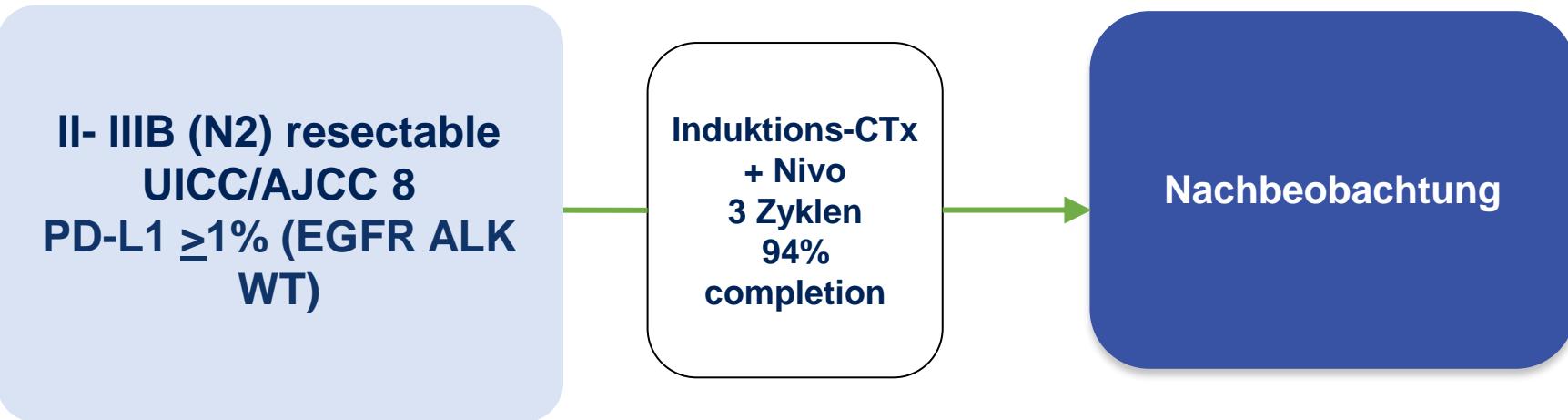
- Bei Fehlen von prospektiv randomisierten Studien
- Post-hoc inter-Studienvergleich erlaubt: IPD: ausschließlich Patienten mit mindestens 1 Zyklus Nivo
- 40% Reduktion des Risikos für Rezidiv durch adjuvante Therapie
- Untergruppen: kleine Gruppen, daher eingeschränkte Aussage:
- Vorteil unabhängig vom Stadium, unklar, ob Abhängig von der PD-L1 Expressi0n



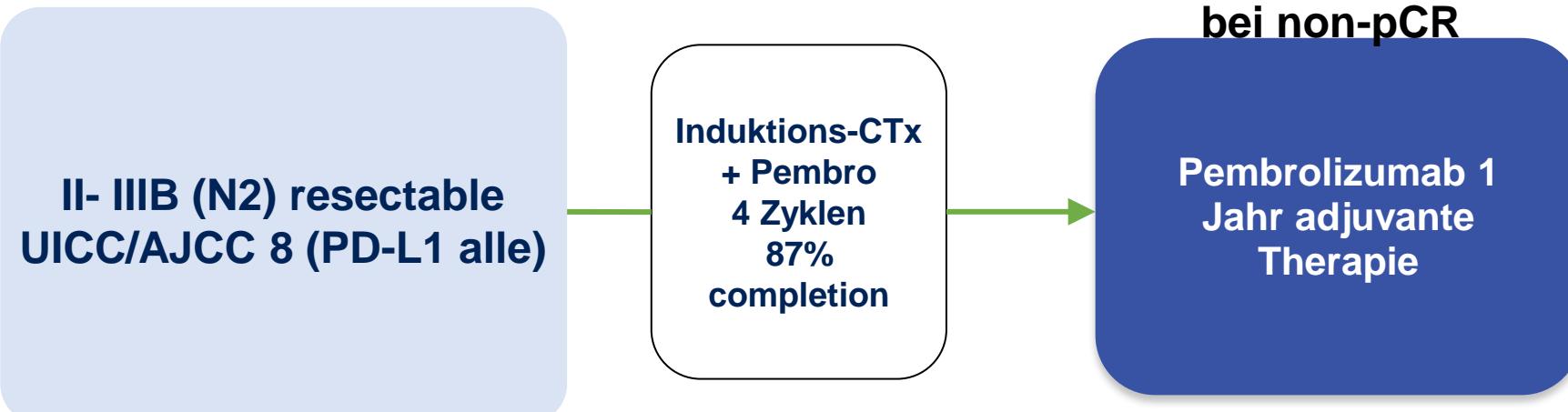
Neoadjuvantes Therapie oder perioperative Therapie

Zulassung 06/24

Prä-interventionelles Tumorboard:
Kategorisierung: primär, potentiell
operabel



Perioperatives Konzept: KN 671



Neoadjuvantes Therapie vs. Strahlentherapie

Prä-interventionelles Tumorboard: Kategorisierung: potentiell operabel

Primär operabel

inoperabel

Einschlußkritierien alle
Studien
**Neoadjuvant und
perioperativ**

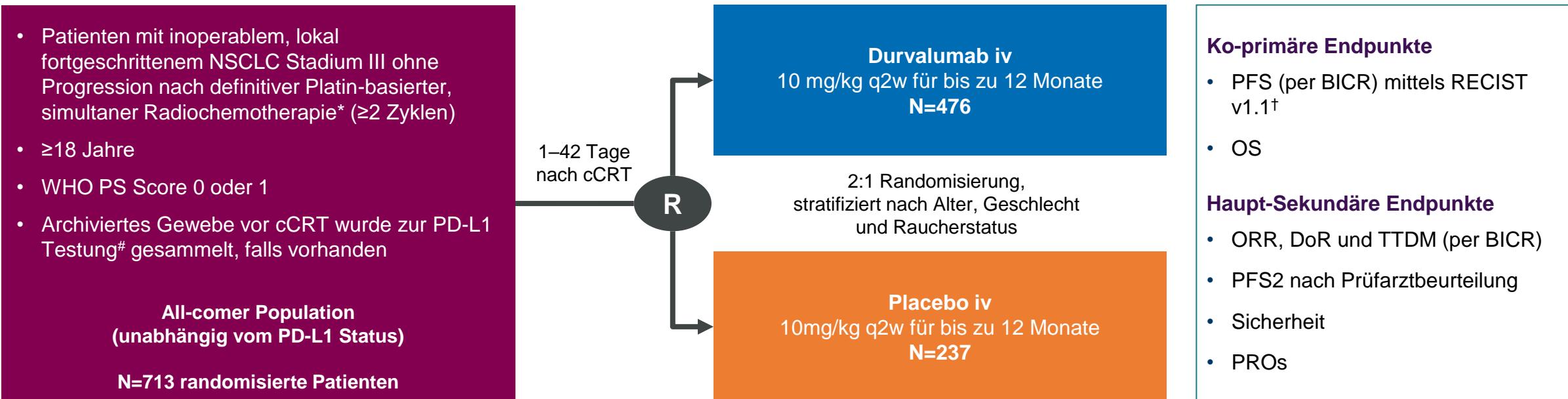
N1 und N2 Situation
T3N0 und T4N0

**Keine einheitlichen
Kriterien:**
wenn Tumorbord keine
primäre Operabilität
und STR keine
Bestrahlbarkeit
beschließt, Induktion
dann je nach
Ansprechen Op oder
RTx-CTx + Durva

Einschlußkritierien
PACIFIC, PACIFIC 9 etc.
N3
**Inoperabilität
technisch oder
funktionell**

Studiendesign

Randomisierte, doppel-blinde, placebo-kontrollierte, multi-zentrische, globale Phase-III-Studie

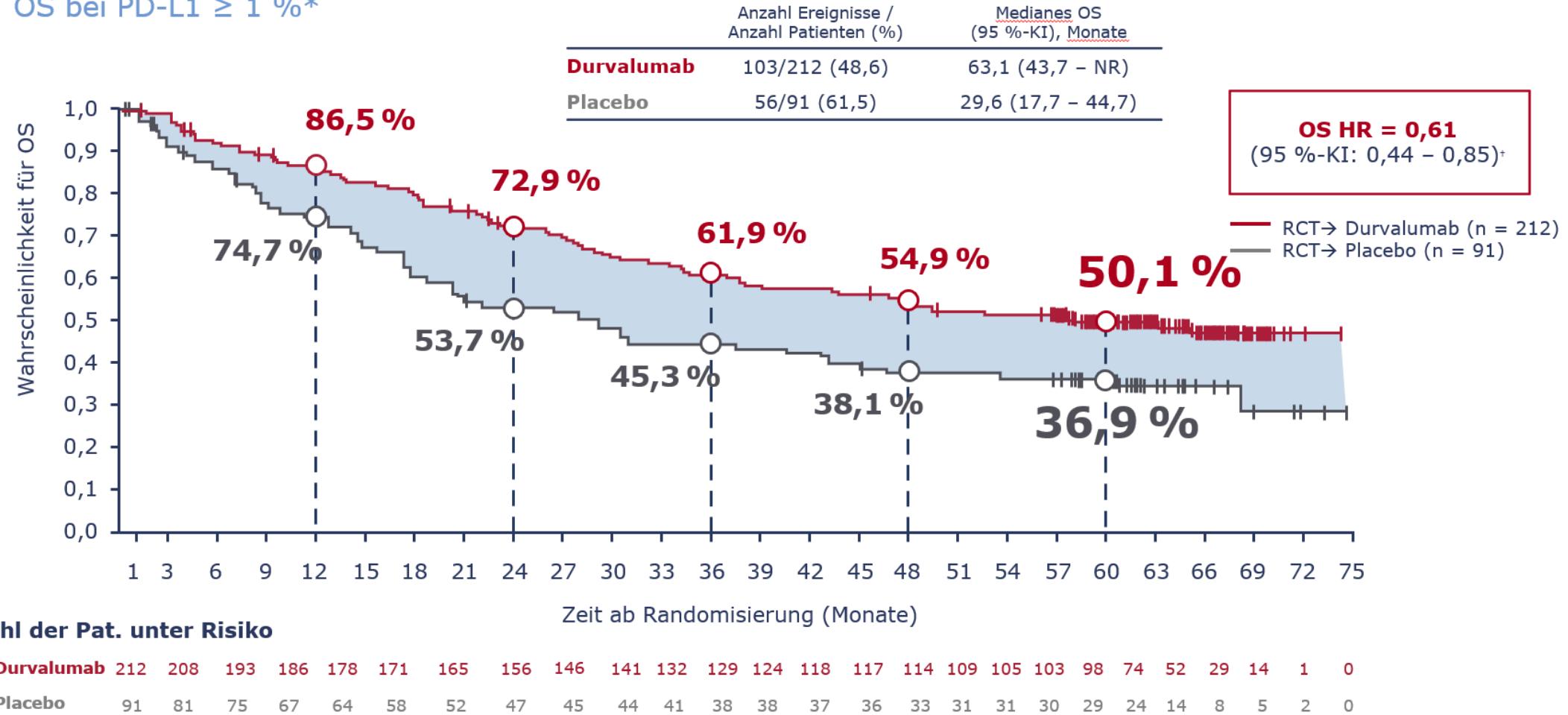


- Aktualisierte Analysen OS und PFS (~4 Jahre, nachdem der letzte Patient randomisiert wurde; geplantes exploratives Update)
 - Die Behandlungseffekte für die ITT-Population wurden unter Verwendung eines stratifizierten Log-Rank-Ansatzes (inkl. Studien-Stratifika-tionsfaktoren) geschätzt
 - Die Behandlungseffekte für Patienten-Subgruppen wurden anhand unstratifizierter Cox-Proportional-Hazard-Modelle (Behandlung als einzige Kovariate) geschätzt.

NCT02125461. *Strahlungsdosis typischerweise 60-66 Gy in 30-33 Fraktionen. Durchgeführt mittels Ventana SP263 Immunhistochemie-Assay [†] Definiert als Zeit seit Randomisierung bis zum ersten dokumentierten Ereignis von Progression oder Tod jeglicher Ursache ohne Progression; BICR: blinded independent central review, verblindeter unabhängiger Zentralreview; cCRT: concurrent chemoradiotherapy, simultane Radiochemotherapie; DoR: duration of response, Ansprechdauer; NSCLC: non-small cell lung cancer, nicht kleinzelliges Lungenkarzinom; ORR: objective response rate, objektive Ansprechraten; OS: overall survival, Gesamtüberleben; PD-L1: programmed death-ligand 1; PFS: progression-free survival, progressionsfreies Überleben; PFS2: Zeit bis zur zweiten dokumentierten Krankheitsprogression; PROs: patient-reported outcomes, Patienten-berichtete Ereignisse; q2w: every 2 weeks, alle 2 Wochen; R: Randomisierung; RECISTv1.1: Response Evaluation Criteria In Solid Tumorsv1.1; TTDM: time to death or distant metastasis, Zeit bis zum Tod oder Fernmetastasierung; WHO PS: World Health Organization Performance Status

OS bei PD-L1 $\geq 1\%$

OS bei PD-L1 $\geq 1\%*$





**Vielen Dank für die
Aufmerksamkeit!**



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frank.griesinger@uol.de**