Strahlentherapie

Prof. Dr. med. Eleni Gkika, MBA

Klinik für Strahlentherapie und Radioonkologie

ukb Klinik für Strahlentherapie und Radioonkologie

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Offenlegung Interessenskonflikte

Finanzierung wissenschaftlicher Untersuchungen:
Astra Zeneca, IntraOp, Novocure

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Stadium III NSCLC

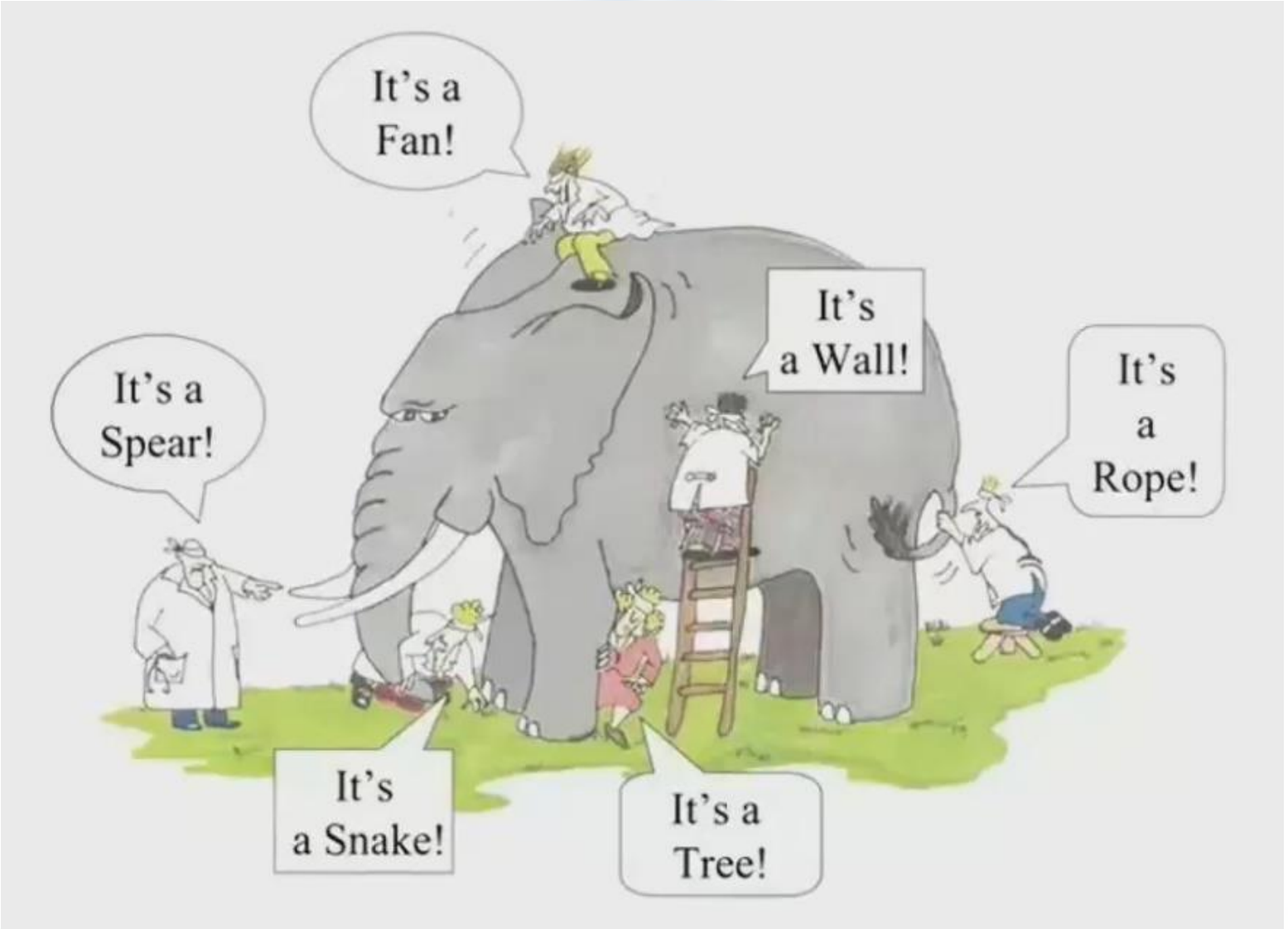
- Stadium III NSCLC ist ziemlich heterogen
- Viele Faktoren spielen eine Rolle:

Tumorspezifisch: TNM, Lokalisation, Histologie…

Patientenspezifisch: Komorbiditäten…

Therapiespezifisch: Expertise…

NSCLC Stadium III



Multidisziplinäre Therapie des ST III NSCLCs

- OP

Neoadjuvante Chemotherapie

Adjuvante Chemotherapie

Adjuvante TKI

Neoadjuvante Immuntherapie

Neoadjuvante Chemoimmuntherapie

Adjuvante Immuntherapie

Perioperative Immuntherapie

Multidisziplinäre Therapie des ST III NSCLCs

- RT

Zytoreduktiv

Neoadjuvante Radiochemotherapie gefolgt von einer Op

Zytotoxisch

Induktions- CTx gefolgt von einer definitiven RCTx

RCTx gefolgt von einer Konsolidierung mit Durvalumab

RCTx gefolgt von einer Konsolidierung mit Osimertinib

Multidisziplinäre Therapie des ST III NSCLCs

- RT

Dosis/Fraktionierungskonzepte

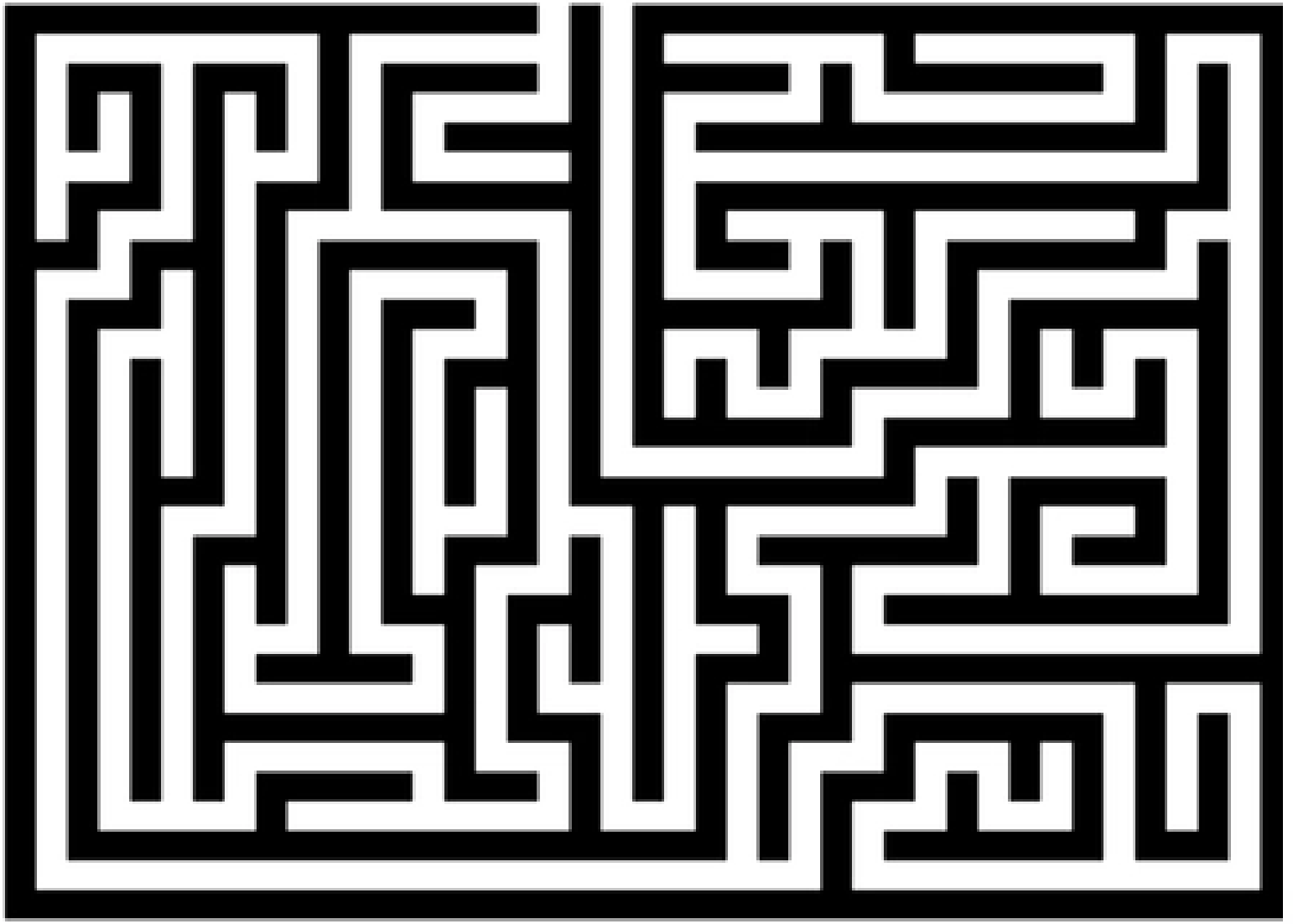
Hypofraktionierte RT

Hyperfraktionierte akzelerierte RT

Dosisekalierte RTx

Immunmodulation

Multidisziplinäre Therapie des ST III NSCLCs



Multidisziplinäre Therapie des ST III NSCLCs

- A. Neoadjuvante Radiochemotherapie

Wer ist der beste Kandidat für eine Operation?

Single level N2

Multi level N2

pCR?

Bulky ist okay

Wer ist der beste Kandidat für eine Operation?

Consensual definition of stage III NSCLC Resectability:

EORTC-Lung Cancer Group initiative with other scientific societies

A-M. Dingemans[1], J. Remon[2], L. Hendriks[3], J. Edwards[4], C. Faivre-Finn[5], N. Reguart[6], E. Smit[7], A. Levy[8], D. Sanchez[9], J.C. Trujillo[10], A. Filippi[11], K. Stathopoulos[12], T.G. Blum[13], M. Guckenberger[14], S. Popat[15], I. Opitz[14], A. Brunelli[16], R. De Angelis[12], P. Hofman[17], K. Hartemink[18], RH. Petersen[19], E. Ruffini[20], C. Dickhoff[21], E. Prisciandaro[22], J. Derks[3], I. Bahce[21], A. Mariolo[23], E. Xenophontos[24], N. Giaj Levra[25], I. Houda[21], M. Brandão[12], T. Berghmans[12]

	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY¶	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	UNCLEAR	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 size / satellite	RESECTABLE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 invasion	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE*§	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE

Keynote 671 CheckMate 816

Nicht alle Patienten werden reseziert

- KEYNOTE 671

		Pembrolizumab Group	Placebo Group
Screening	Patients screened	1364	
	Randomized (intention-to-treat population)	397	400
Neoadjuvant Treatment	Received ≥1 dose of neoadjuvant treatment (as-treated population)	396	399
	Completed 4 cycles of pembrolizumab or placebo	295 (74.5%)	297 (74.4%)
	Completed ≥3 cycles of pembrolizumab or placebo	346 (87.4%)	348 (87.2%)
	Continued to surgery and/or radiotherapy	342 (86.4%)	335 (84.0%)
	Discontinued all study therapy permanently	54 (13.6%)	64 (16.0%)
In-Study Surgery and/or In-Study Radiotherapy*	Underwent in-study surgery	325 (82.1%)	317 (79.4%)
	Underwent in-study radiotherapy	35 (8.8%)	53 (13.3%)
	Discontinued all study therapy permanently following surgery	45 (11.4%)	60 (15.0%)
	Discontinued all study therapy permanently following radiotherapy	7 (1.8%)	8 (2.0%)
Adjuvant Treatment	Received ≥1 dose of adjuvant treatment	290 (73.2%)	267 (66.9%)
	Completed adjuvant treatment	160 (40.4%)	141 (35.3%)
	Discontinued adjuvant treatment	88 (22.2%)	81 (20.3%)
	Adjuvant treatment ongoing	42 (10.6%)	45 (11.3%)

	Nivolumab + chemotherapy (149 patients)	Chemotherapy (135 patients)
Delayed surgery, number of patients (%)	31 (21)	24 (18)
Length of delay of surgery (weeks), median (IQR)	2.0 (0.6-3.0)	2.4 (1.0-3.7)
Surgical approach % of patients		
Thoracotomy	59%	63%
Minimally invasive	30%	22%
Minimally invasive → open	11%	16%
Type of surgery, % of patients		
Lobectomy	77%	61%
Pneumonectomy	17%	25%
Completeness of resection, % of patients		
R0	83%	78%
R1	11%	16%
R2	3%	3%
Rx	3%	4%
Hospital stay (days), median (IQR)	135 patients 10.0 (7.0-14.0)	124 patients 10.0 (7.0-14.5)
Surgery-related adverse events, % of patients[a]		
Any grade	41%	47%
Grades 3-4	11%	15%

Wakelee NEJM 2023, Forde NEJM 2022

CheckMate 816

Nicht alle Patienten werden reseziert

~20%, no surgery following neoadjuvant chemo/IO

CM816

	Nivolumab plus Chemotherapy (N = 179)	Chemotherapy (N = 179)
Patients with definitive surgery* — no. (%)	149 (83.2)	135 (75.4)
Time from last neoadjuvant dose to definitive surgery — wk		
Median (IQR)	5.3 (4.6–6.0)	5.0 (4.6–5.9)
Patients with cancelled definitive surgery — no. (%)	28 (15.6)	37 (20.7)
Disease progression	12 (6.7)	17 (9.5)
Adverse event	2 (1.1)	1 (0.6)
Other†	14 (7.8)	19 (10.6)

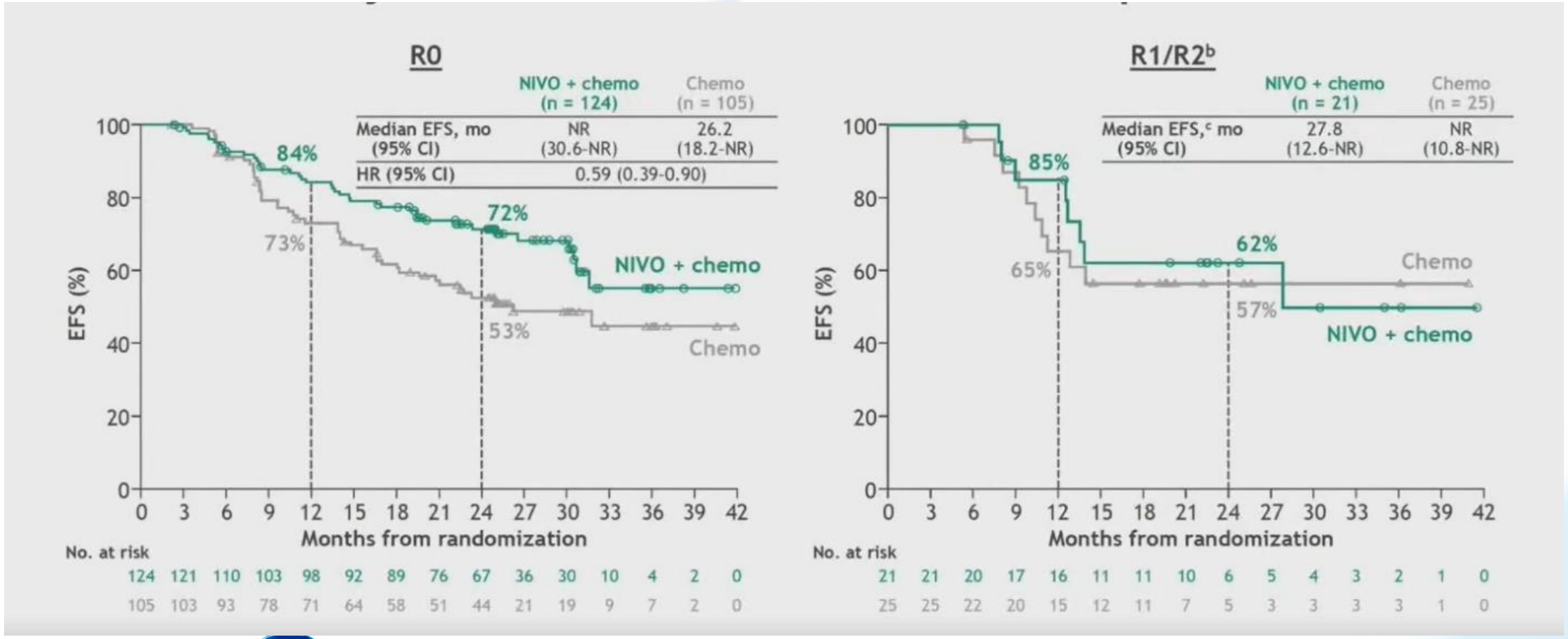
chemotherapy group.

† Other reasons were patient refusal in 9 patients in the nivolumab plus chemotherapy arm and 8 patients in the chemotherapy arm; consent withdrawal in 3 patients in the chemotherapy arm; COVID-19 in 1 patient in the chemotherapy arm; unfit for surgery due to poor lung function in 2 patients in the nivolumab plus chemotherapy arm and 4 patients in the chemotherapy arm; and unresectability in 2 patients in each arm.

‡ Time from last dose to neoadjuvant surgery >6 weeks.

CheckMate 816
Rolle der Chirurgie

Study	R0	R1	R2	p value
Gagliasso et al (N2)	59%	37%	-	0.0001
Edwards et al (N0)	82%	46%	38%	0.04
Edwards et al (N1-2)	55%	34%	22%	<0.001
Osarogiagbon et al (N0-2)	64%	33%		< 0.0001
Yun et al (N2)	55%	36%		0.043



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Broderick AATS 2022

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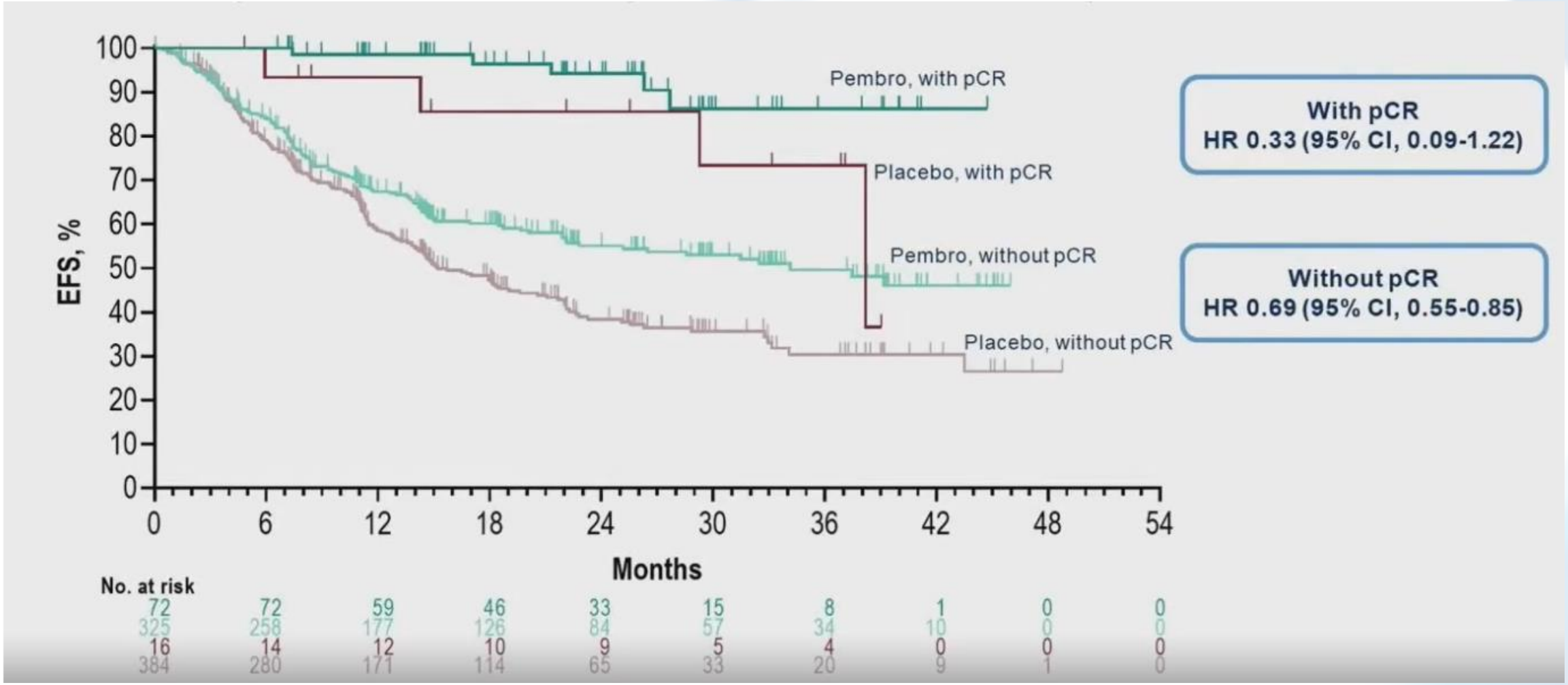
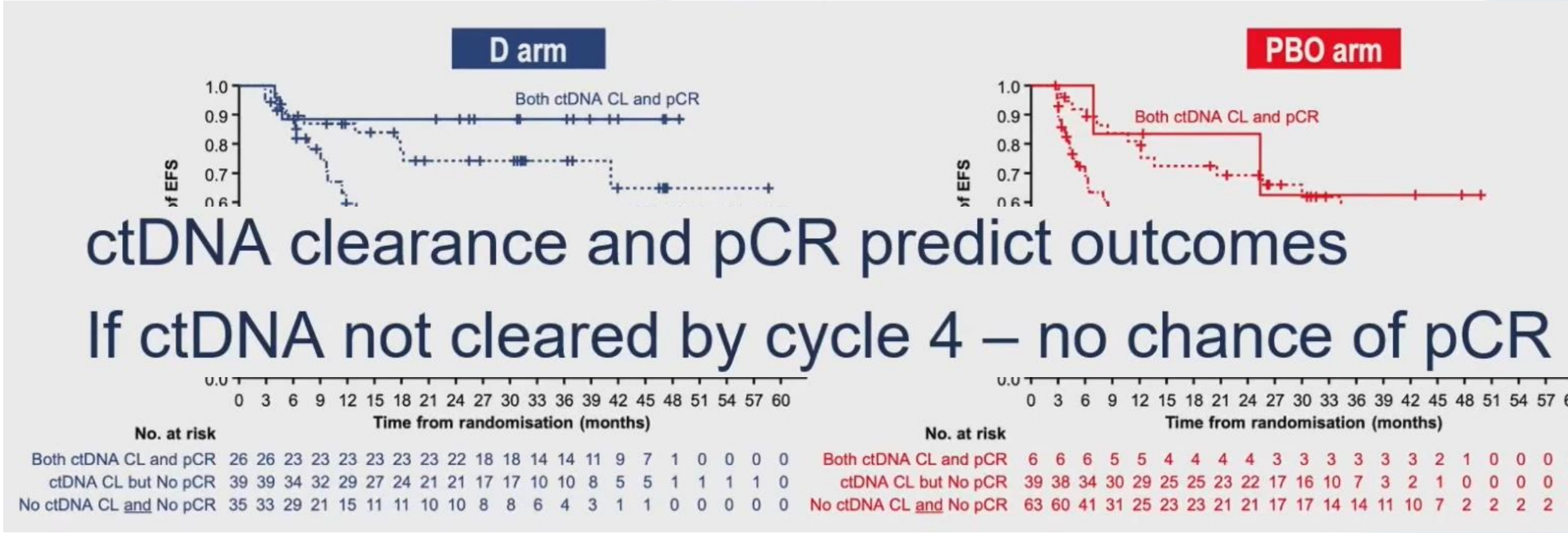
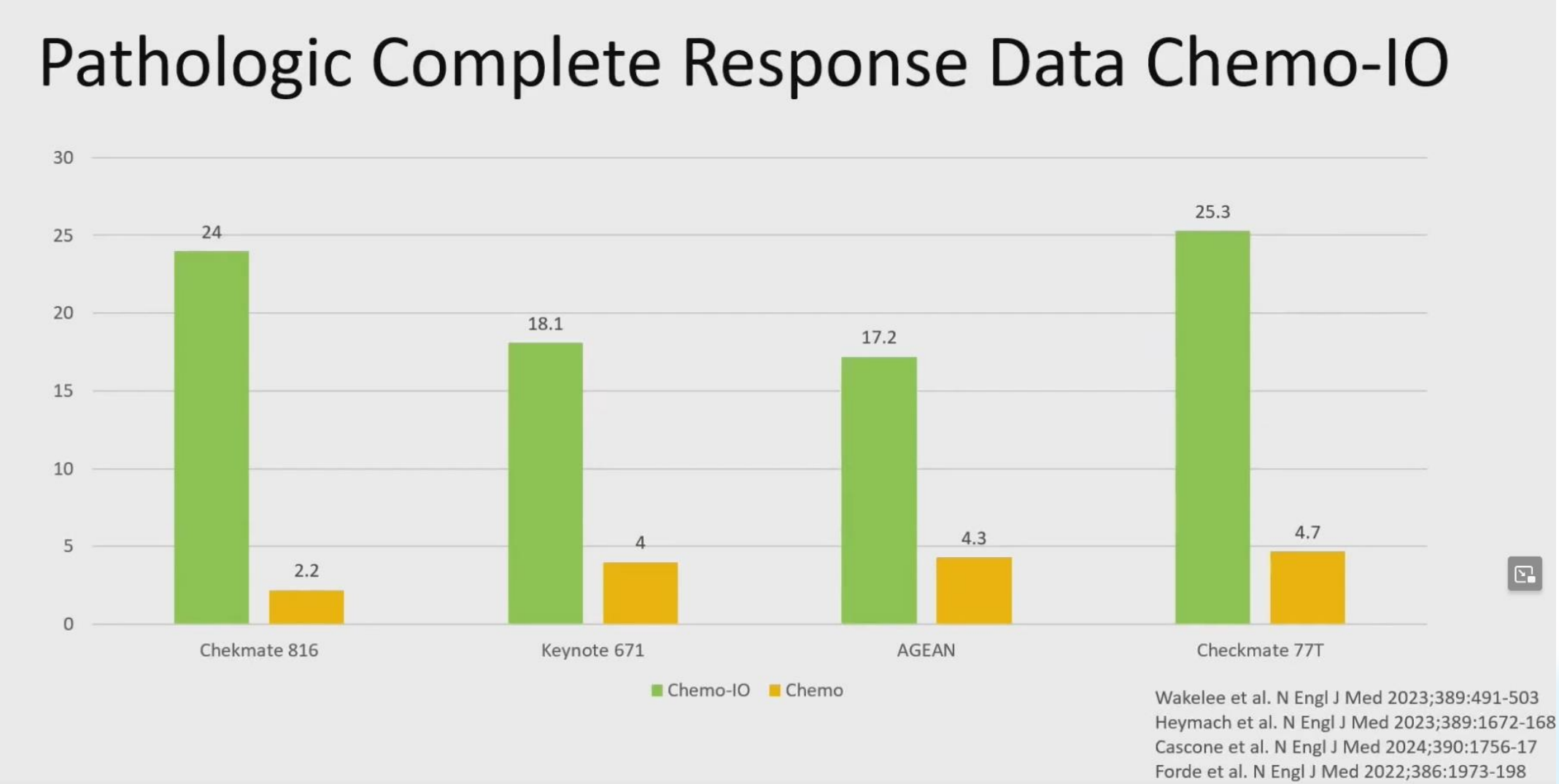
KEYNOTE 671
Rolle der pCR



AEGEAN
ctDNA



Rolle der pCR



pCR nach RCTx

Neoadjuvant chemoradiotherapy						
Albain *et al* PMID19632716	Stage IIIA(N2)	III	396	OS	CT/RT/S vs CT/RT	pCR: 18%
Epithor PMID37156211	T3-4 tumors	RS	688	OS	S vs CT+S vs CT/RT/S	CRT: pCR: 18.5% CT: pCR: 6%
ESPATUE PMID26527789	Stage IIIA-B	III	246	OS	CT/RT/S vs CT/RT	pCR 33%
Cerfolio *et al* PMID19233668	Stage III	RS	216	DES	CT/RT/S	pCR 33%

Bahce et al JITC 2024

Behandlung des NSCLCs im St. III

Table 1: Randomized studies comparing induction treatment followed by surgery with definitive radio(chemo)therapy.

Trial (Period of Recruitment)	Inclusion Criteria	**Treatment**	median OS [mo]	long-term OS	Hazard Ratio	*P*
RTOG 89-01 (1990-1994)	IIIA N2	[R]* (1) 2x CDDP/VBL (MMC) → S (2) 2x CDDP/VBL (MMC) → RT [64 Gy]	19.4 17.4	22.0% [4Y] 22.0%	n.g.	0.46
NCI Canada (closed 1995)	IIIA N2	[R] (1) 2x CDDP/VBL → S (2) ---------- → RT [60 Gy]	18.7 16.2	n.g.	n.g.	NS
MRC (1995-1999)	IIIA	[R] (1) 4x CDDP/MMC/IFO or VBL → S (2) ---------- → RT [40-60 Gy]	13.8 11.2	n.g.	0.91 [0.49-1.72]	0.78
EORTC 08941 (1994-2002)	IIIA N2	(1) 3x CDDP/ 3rd gen drug →[R]° → S [+PORT 56 Gy] (2) 3x CDDP/ 3rd gen drug → RT [60-62.5 Gy]	16.4 17.5	15.7% [5Y] 14.0%	1.06 [0.84-1.35]	0.596
Nordic TOG (1998-2009)	IIIA N2	[R] (1) 3x carboplatin/paclitaxel → S [+PORT 60 Gy] (2) 3x carboplatin/paclitaxel → RT [60 Gy]	17.3 14.9	19.0% [5Y] 17.0%	0.866	0.218
INT 0139 (1994-2001)	IIIA N2	[R] (1) 2x CDDP/ETOII45 Gy/1.8 Gy qd → S → 2x CDDP/ETO (2) 2x CDDP/ETOII45 Gy/1.8 Gy qd → RT [61 Gy]→2x CDDP/ETO	23.6 22.2	27.0% [5Y] 20.0%	0.87 [0.7-1.1]	0.24
ESPATUE (2004-2012)	IIIA N2 selected IIIB	(1) 3x CDDP/paclitaxel→CDDP/VINII45 Gy (AHF)→[R]→ S (2) 3x CDDP/paclitaxel→CDDP/VINII45 Gy (AHF) → RT [20-26 Gy→65-71 Gy] +CDDP/VIN	49.3 34.8	44.0% [5Y] 40.0%	0.81 [0.5-1.3]	0.34

Abbreviations: [R]: randomisation timepoint, [R]*: only 45 of 73 patients randomised, [R]°: only responders randomised, OS: overall survival, (1): arm 1 – induction treatment plus surgery, (2): arm 2 – conservative treatment: combined radio(chemo)therapy without resection, mo: months, --: no chemotherapy, S: surgery, RT: radiotherapy, CDDP: cisplatin, VBL: vinblastin, IFO: ifosfamide, MMC: mitomycin, ETO: etoposide, VIN: vinorelbine, n.g.: not given, NS: not significant, PORT: postoperative radiotherapy, qd: once daily, II: concurrent, AHF: accelerated hyperfractionation.

Pöttgen et al. Oncotarget 2017

RCTx vs OP Stadium III

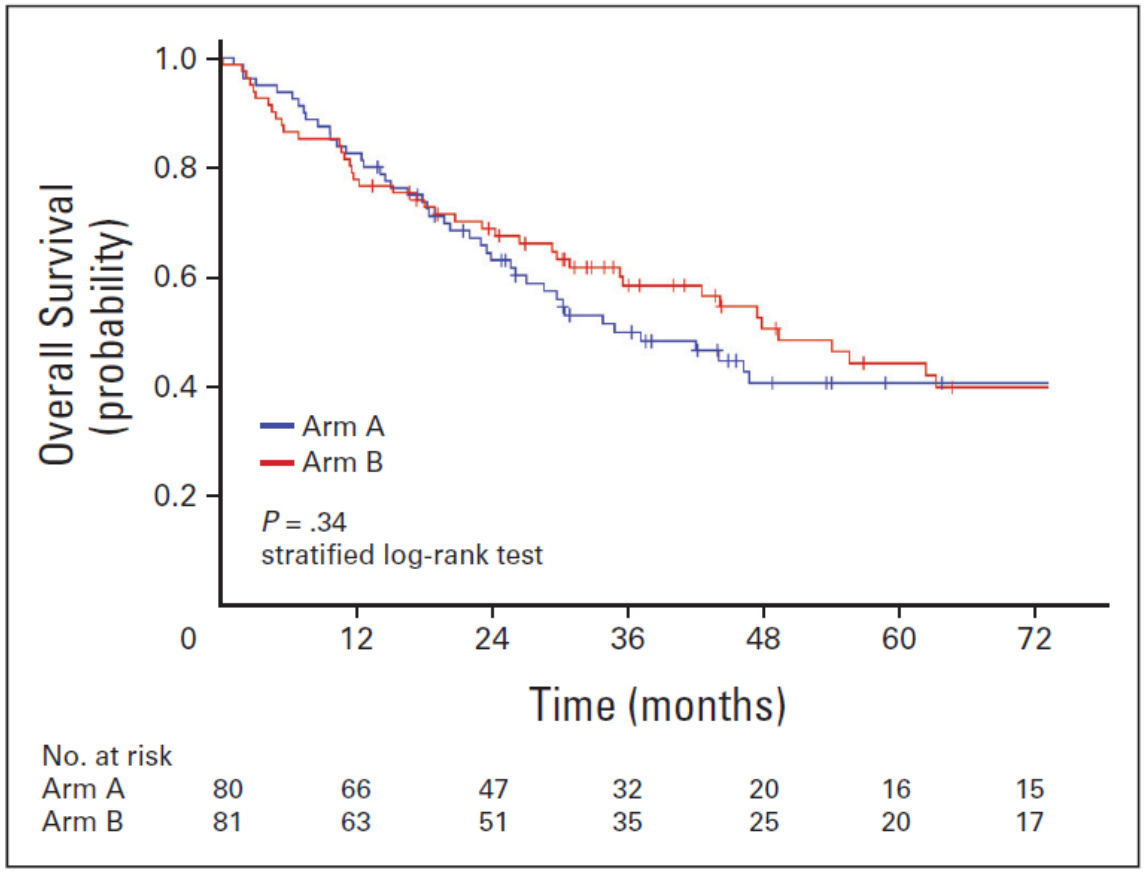


Fig 2. Overall survival of randomly assigned arms.

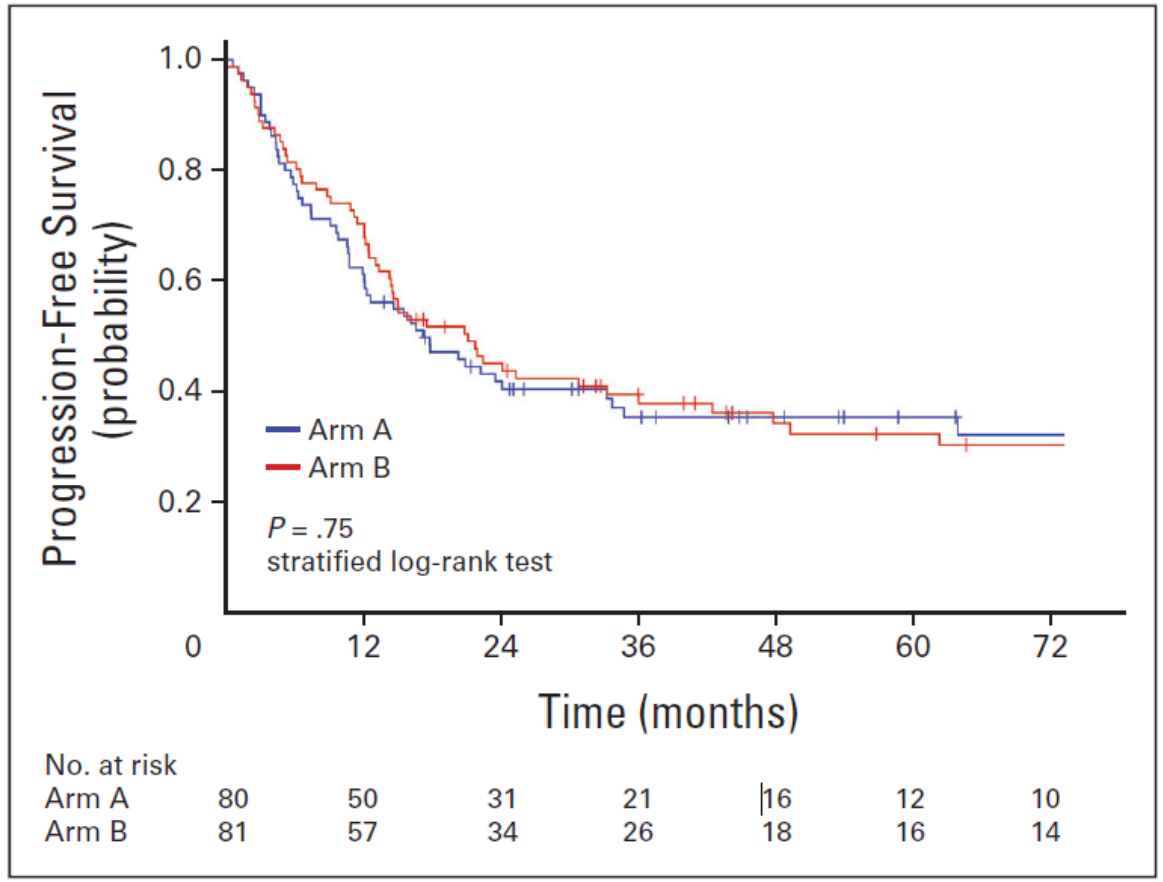


Fig 3. Progression-free survival of randomly assigned arms.

pCR 33% nach einer neoadjuvanten RCTx

Eberhardt et al. JCO 2025

Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial

Nasser K Altorki, Timothy E McGraw, Alain C Borczuk, Ashish Saxena, Jeffrey L Port, Brendon M Stiles, Benjamin E Lee, Nicholas J Sanfilippo, Ronald J Scheff, Bradley B Pua, James F Gruden, Paul J Christos, Cathy Spinelli, Joyce Gakuria, Manik Uppal, Bhavneet Binder, Olivier Elemento, Karla V Ballman, Silvia C Formenti

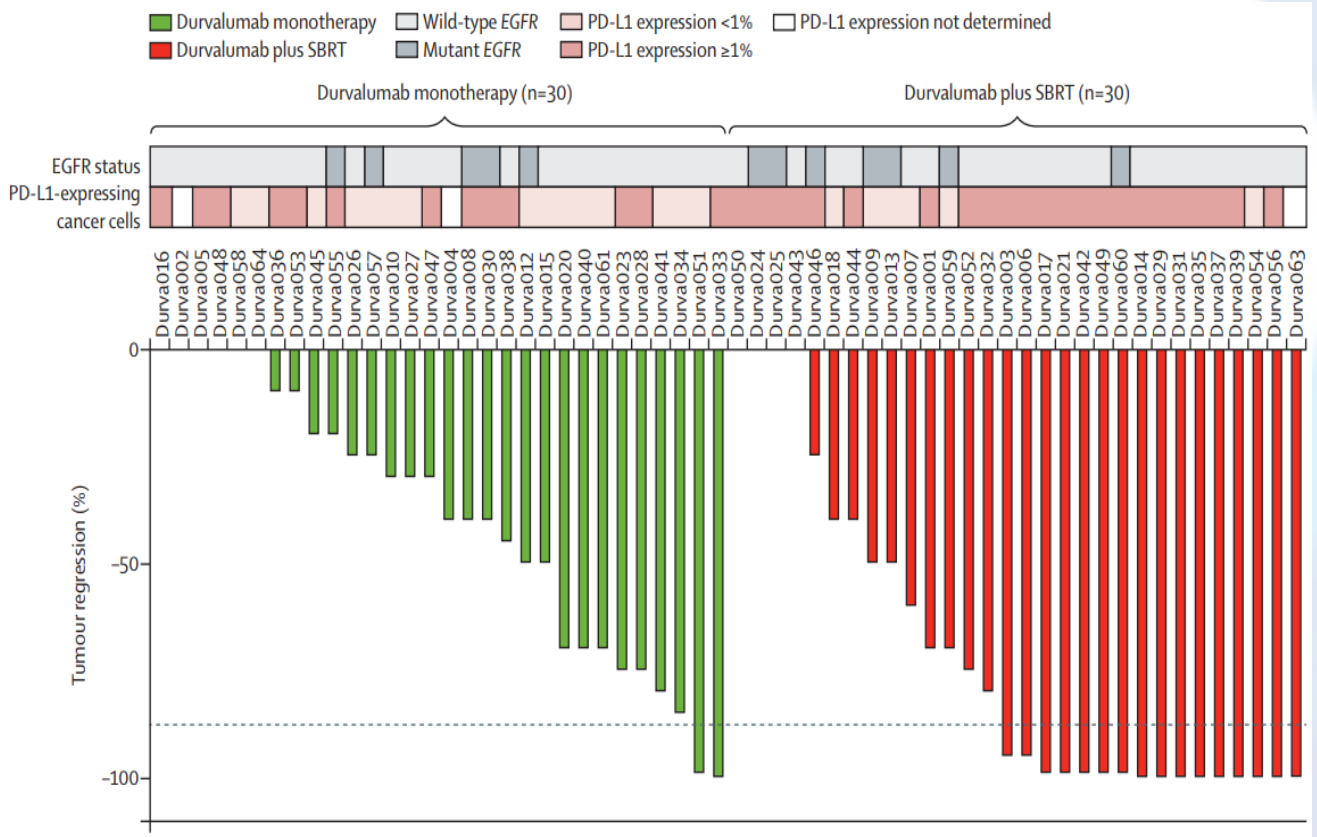
MPR 53 % nach RTx+Durva vs 6% nach Durva

3x8 Gy ca 30 Gy EQD2 auf den Primarius

	Major pathological response*	Complete pathological response
Durvalumab monotherapy (n=30)		
IB	1 (3%)	0
IIIA	1 (3%)	0
Durvalumab plus SBRT (n=30)		
IA	1 (3%)	0
IB	0	1 (3%)
IIA	1 (3%)	2 (7%)
IIB	2 (7%)	2 (7%)
IIIA	4 (13%)	3 (10%)

Data are n (%). SBRT=stereotactic body radiotherapy. *Excluding patients with complete pathological response.

Table 2: **Clinical stages in major and complete pathological responders**



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Altroki et al. Lancet Oncol 2021

UNIVERSITÄTS KLINIKUM FREIBURG

dkfz. Deutsches Konsortium für Translationale Krebsforschung Partnerstandort Freiburg

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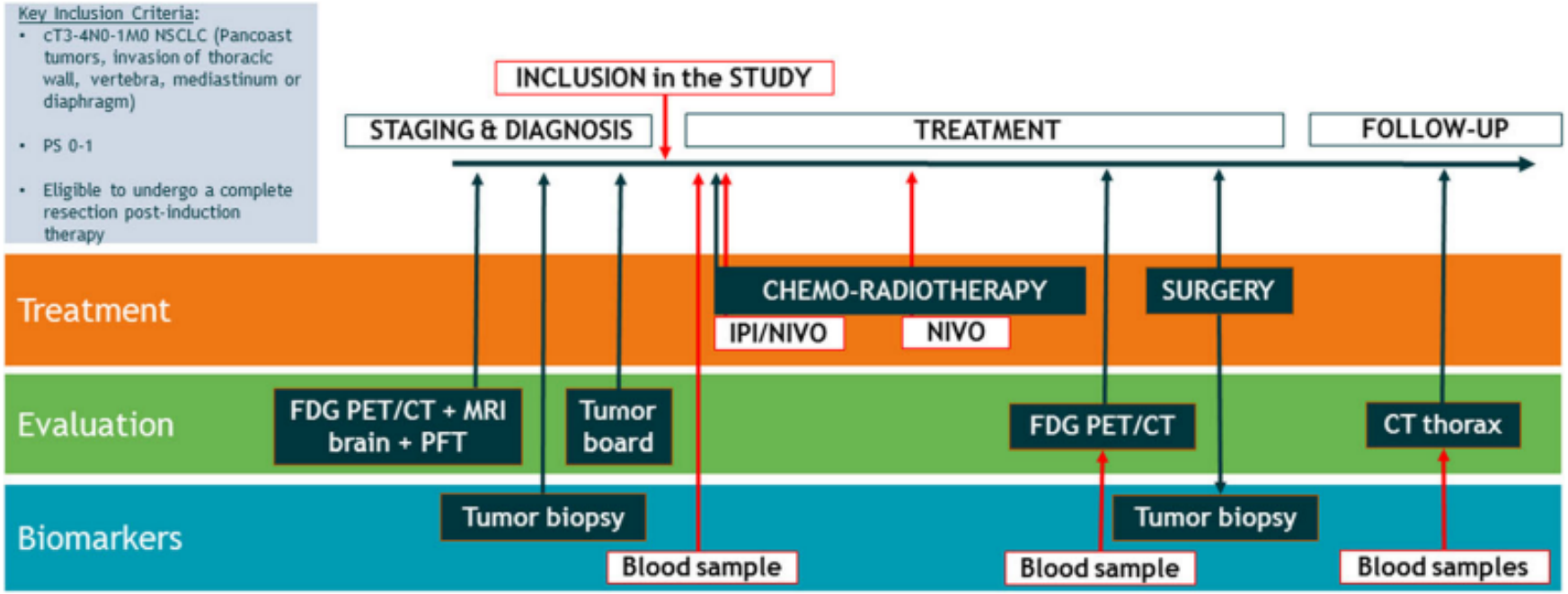
Neoadjuvant Chemo-Immuno-Radiotherapy

INCREASE

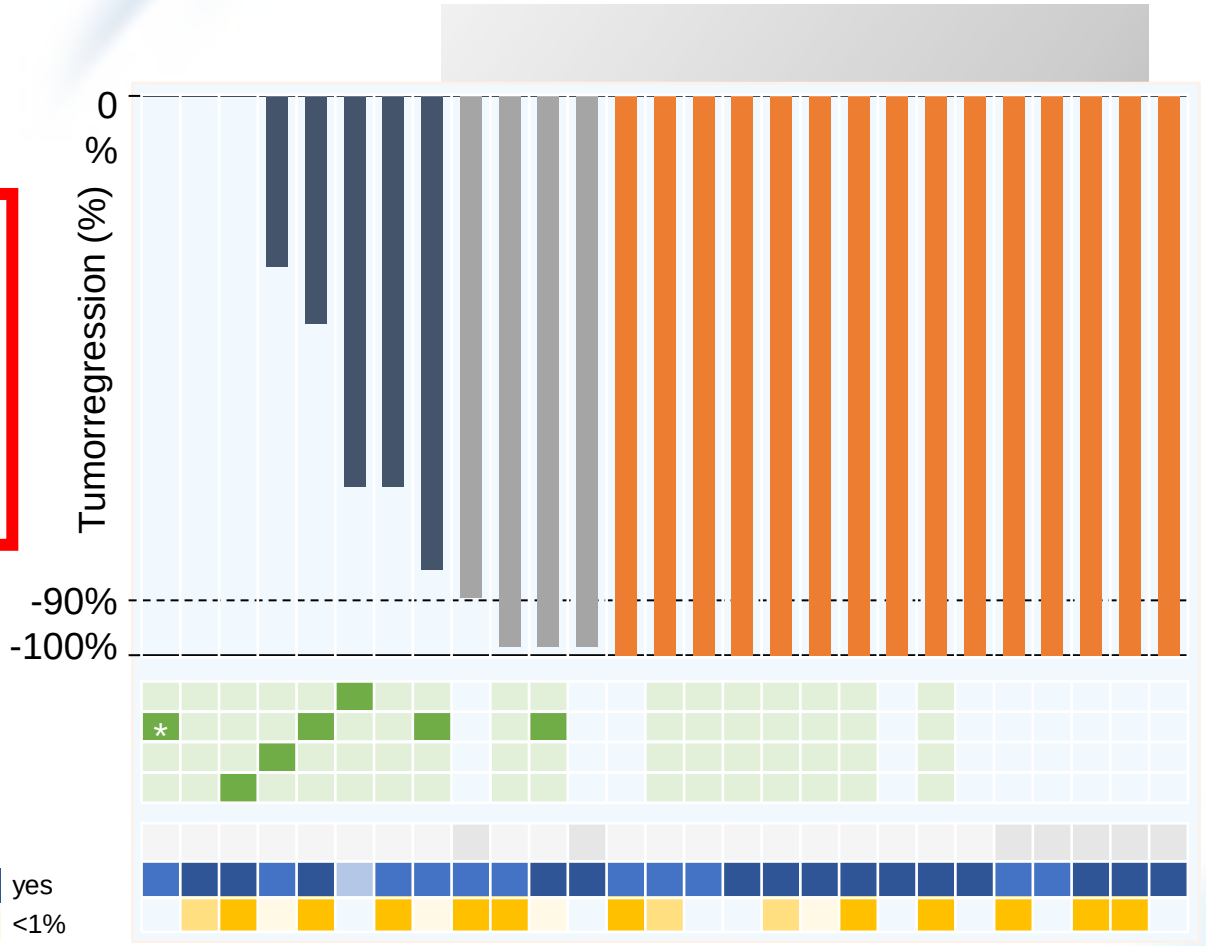


- Primary Endpoint: pCR / MPR, Safety
- Secondary Endppint: EFS^{g}, OS

Neoadjuvant Chemo-Immuno-Radiotherapy

INCREASE

	pCR (%)	MPR (%)
ITT	**50 %**	**63%**
Resected	**58%**	**73%**



Multidisziplinäre Therapie des ST III NSCLCs

- B. Definitive Radiochemotherapie

Multidisziplinäre Therapie des ST III NSCLCs

- B. Definitive Radiochemotherapie

RCTx vs OP als lokale Therapie

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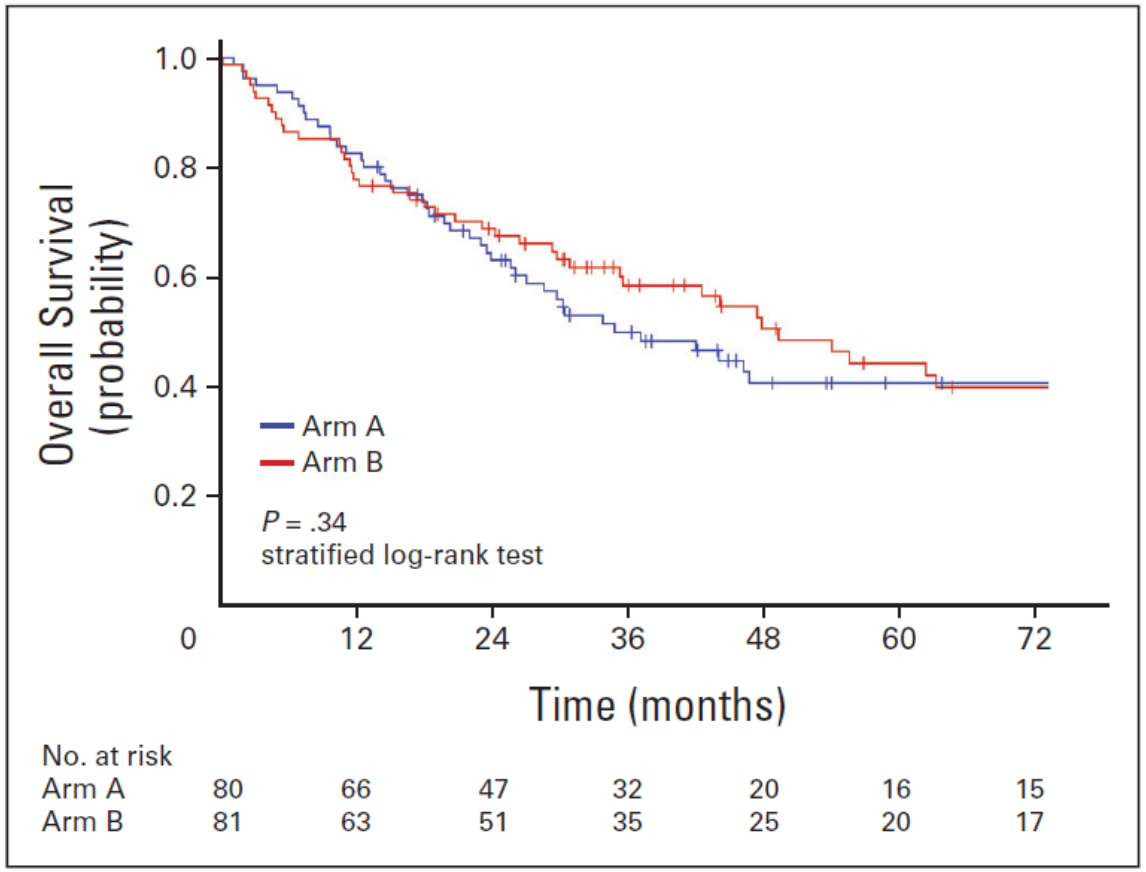
Abbreviations: [R]: randomisation timepoint, [R]*: only 45 of 73 patients randomised, [R]°: only responders randomised, OS: overall survival, (1): arm 1 – induction treatment plus surgery, (2): arm 2 – conservative treatment: combined radio(chemo)therapy without resection, mo: months, --: no chemotherapy, S: surgery, RT: radiotherapy, CDDP: cisplatin, VBL: vinblastin, IFO: ifosfamide, MMC: mitomycin, ETO: etoposide, VIN: vinorelbine, n.g.: not given, NS: not significant, PORT: postoperative radiotherapy, qd: once daily, II: concurrent, AHF: accelerated hyperfractionation.

Pöttgen et al. Oncotarget 2017

RCTx vs OP Stadium III



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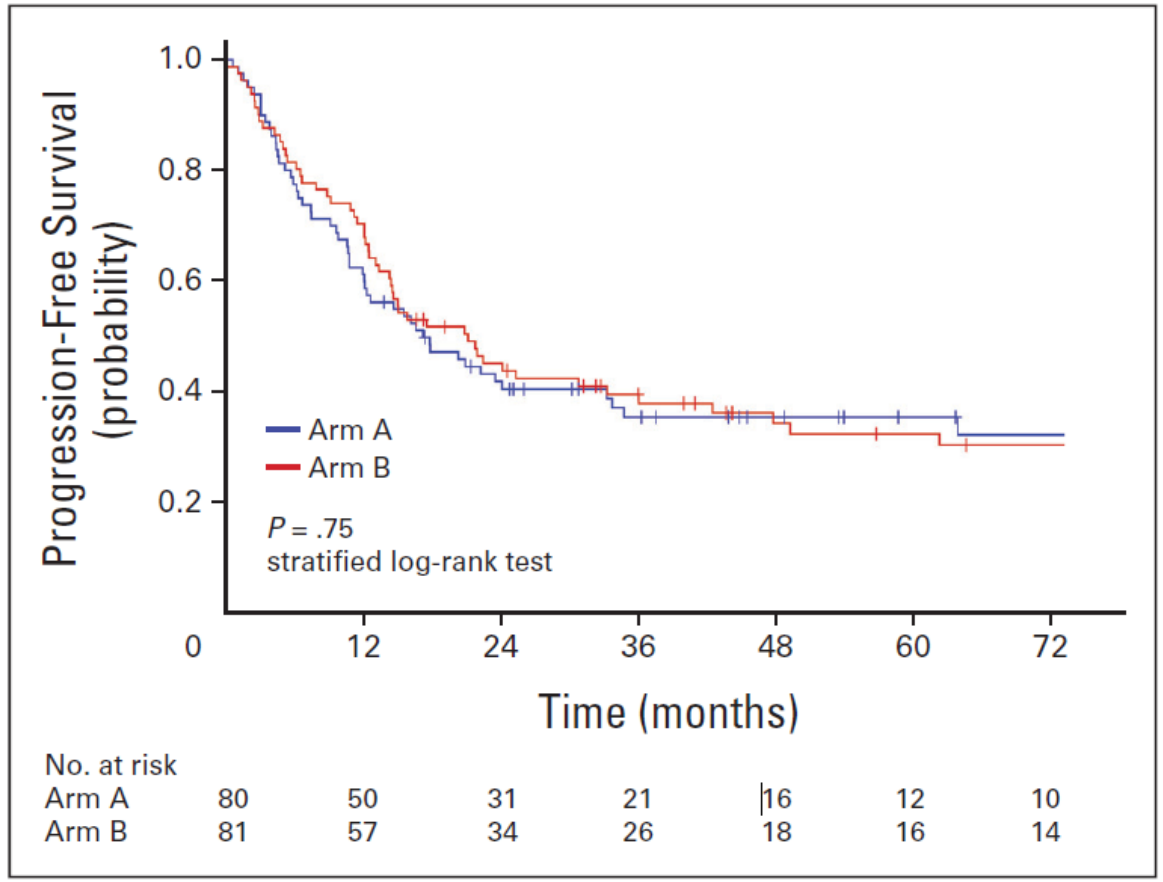


Fig 3. Progression-free survival of randomly assigned arms.

Keine Immutherapie

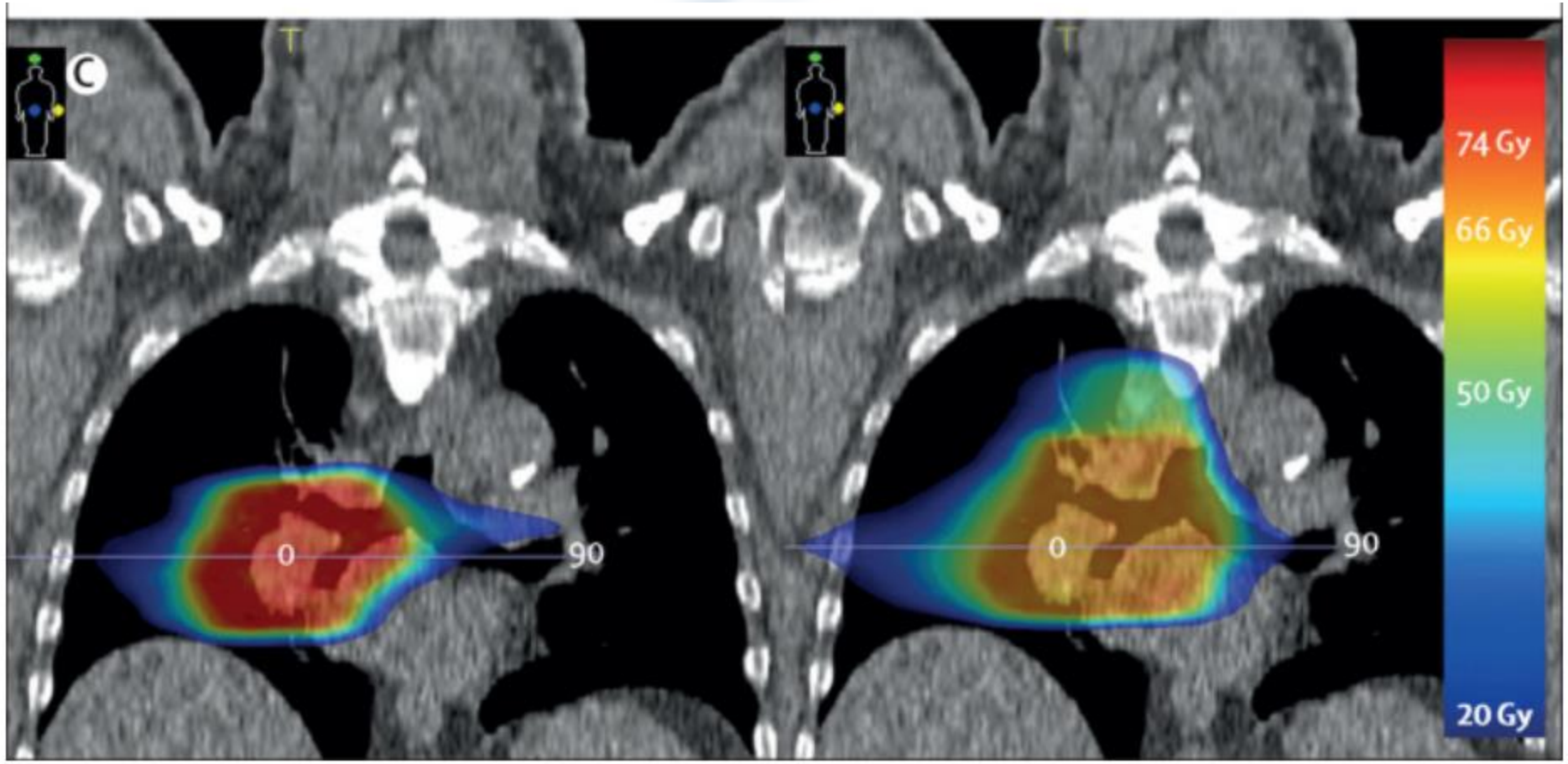
Eberhardt et al. JCO 2025

Multidisziplinäre Therapie des ST III NSCLCs

- B. Definitive Radiochemotherapie

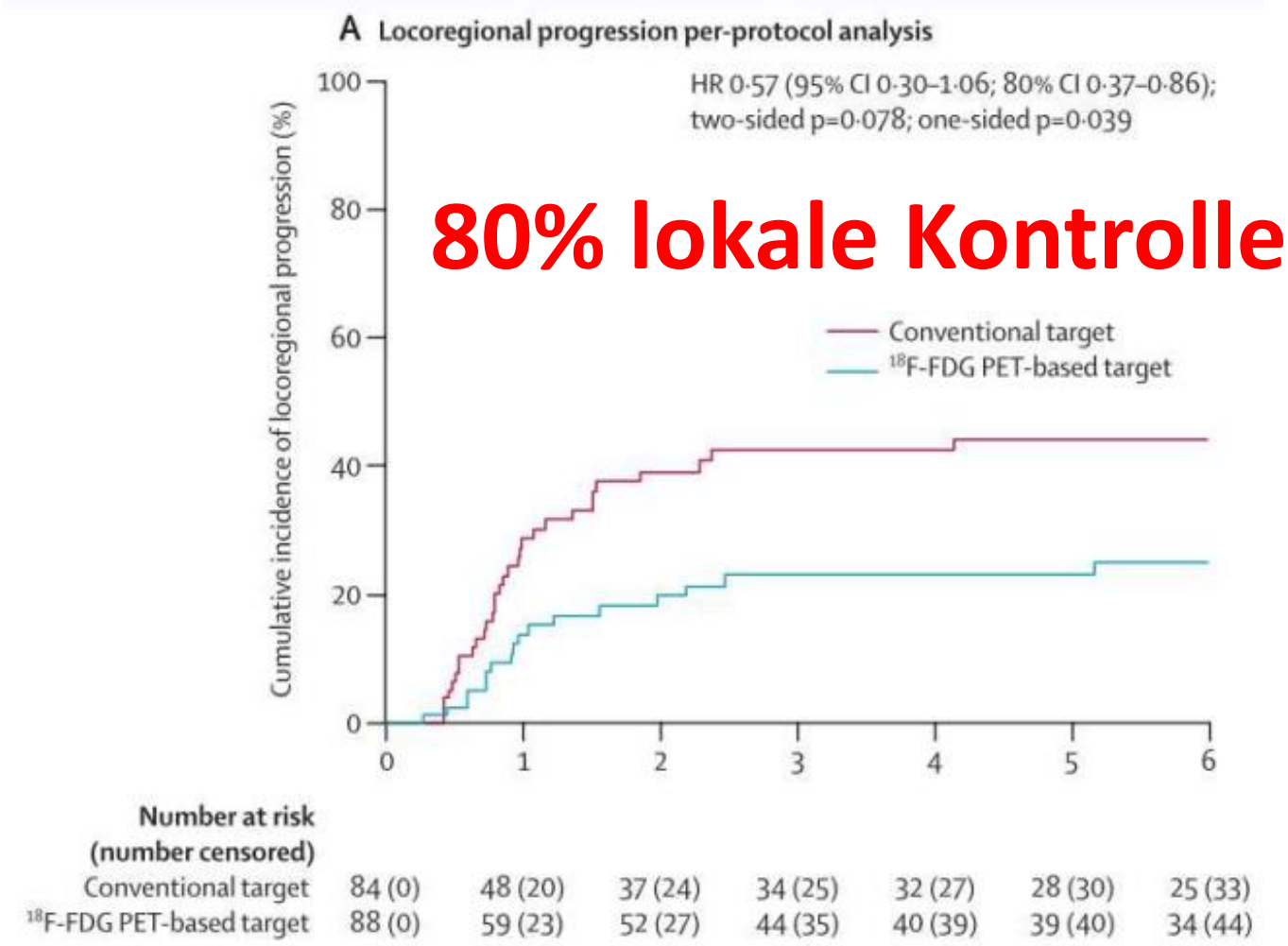
Dosiseskalation

Dosiseskalation



Nestle et al. Lancet Oncol 2021

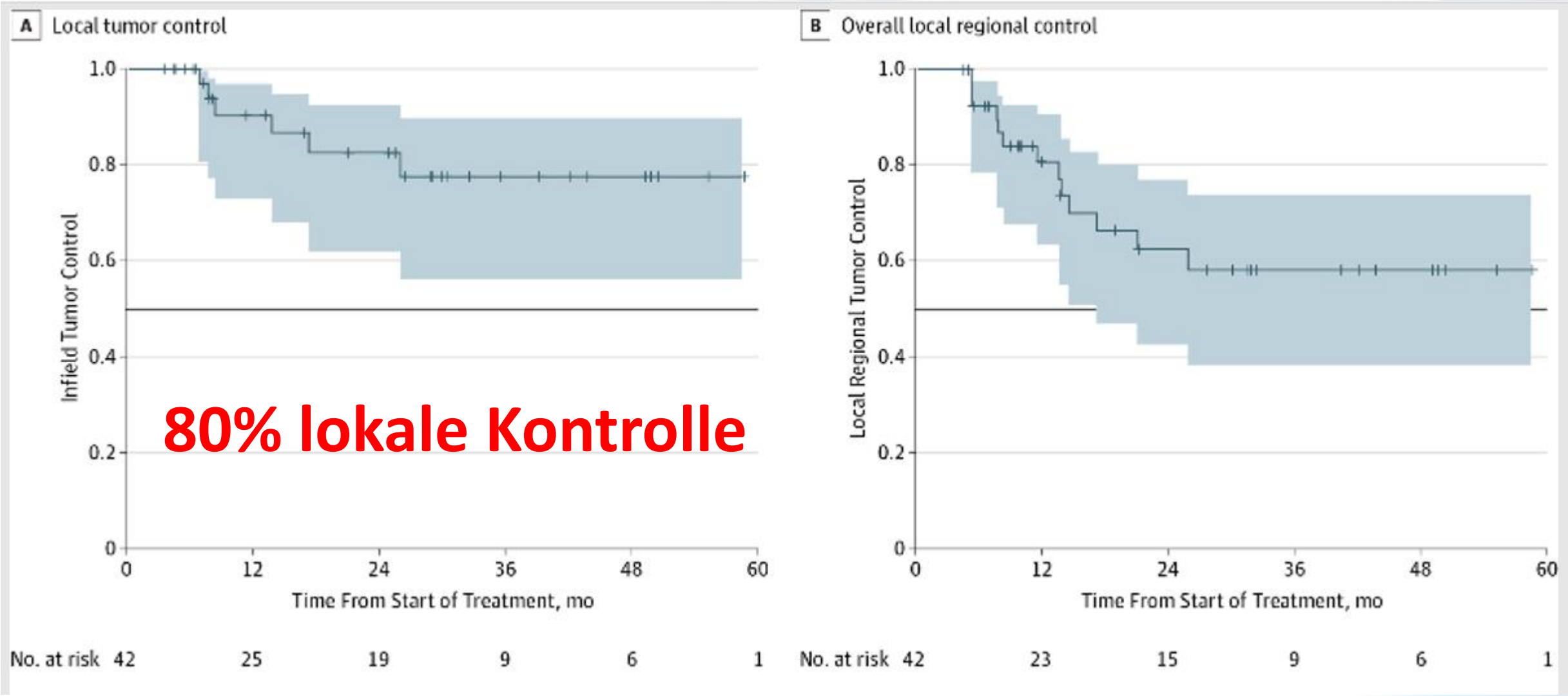
FDG PET/CT basierte Dosiseskalation



80% lokale Kontrolle

Nestle et al. Lancet Oncol. 2021

FDG PET/CT basierte Dosiseskalation



80% lokale Kontrolle

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Kong et al. JAMA Oncol. 2017

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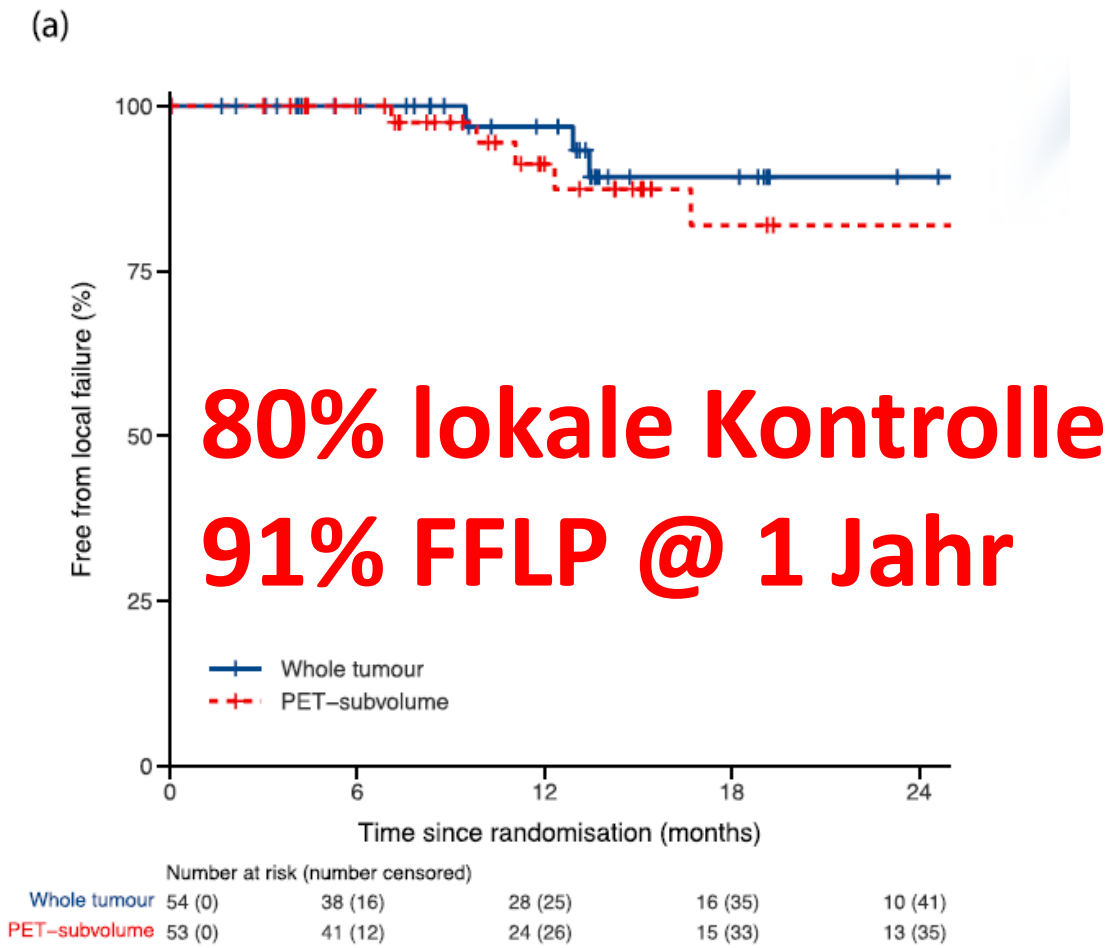
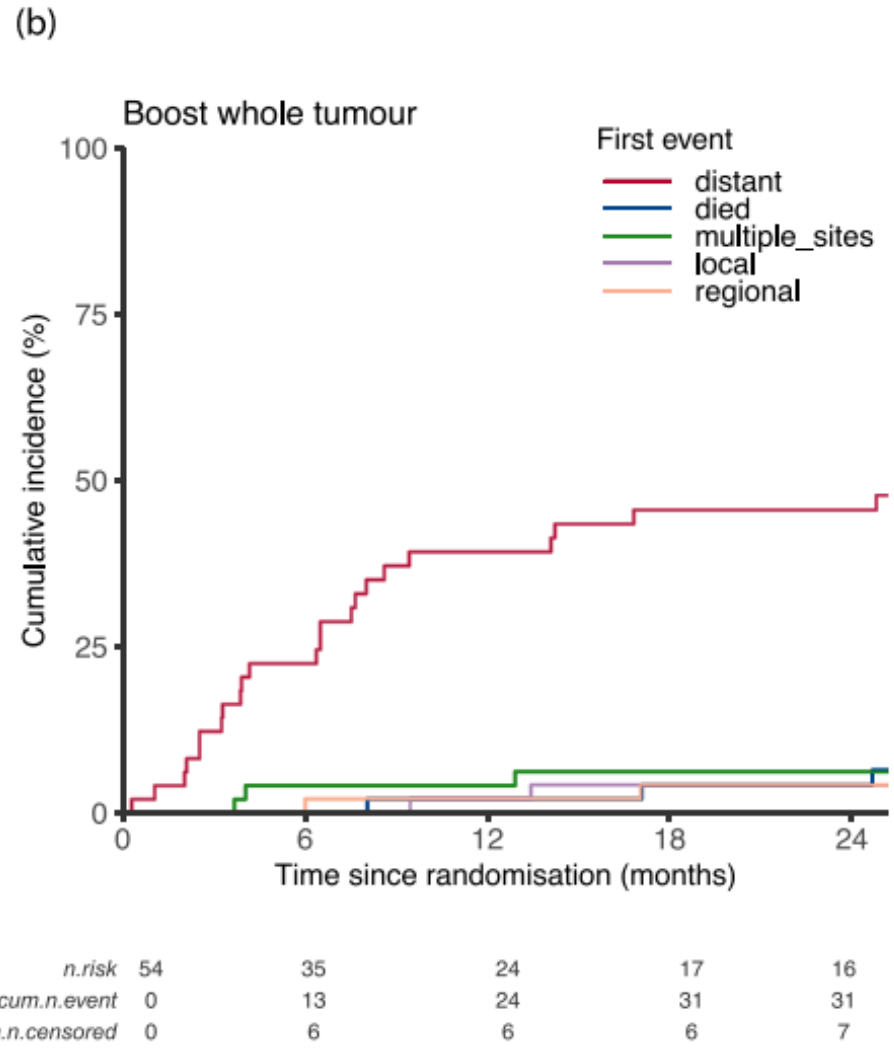
FDG PET/CT basierte Dosiseskalation



80% lokale Kontrolle

91% FFLP @ 1 Jahr



Cooke et al. Green J. 2023

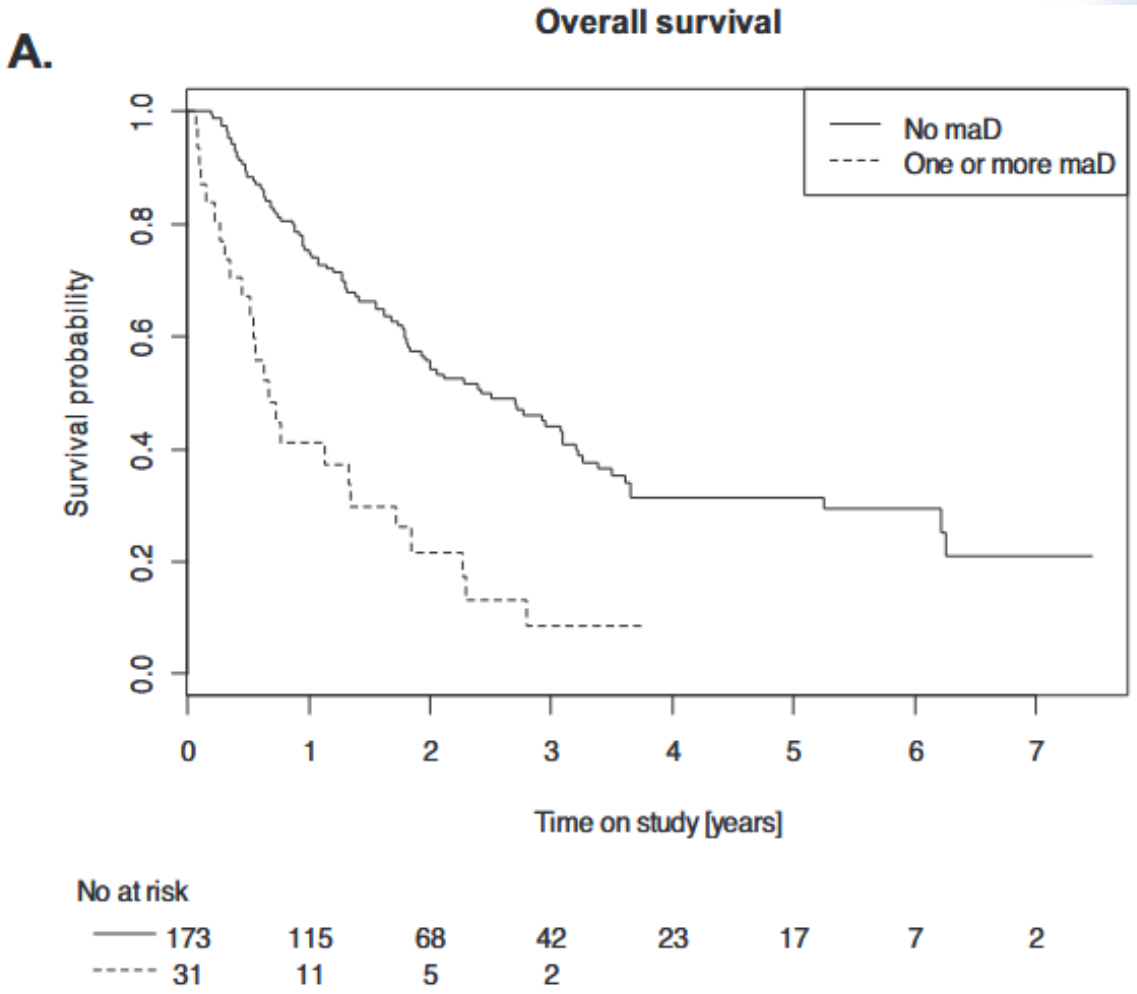
Multidisziplinäre Therapie des ST III NSCLCs

- B. Definitive Radiochemotherapie

Qualitätssicherung

Qualitätssicherung bei der Radiotherapie korreliert mit dem Gesamtüberleben- Ergebnisse aus der PET Plan Studie

Rolle der Dosis und Therapie-Abweichungen



	Overall survival			Local progression		
All patients	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Any maD (yes vs no)	2.87	1.80 – 4.41	<0.0001	5.74	2.74 – 11.13	<0.0001
maD in treatment planning (yes vs no)±	2.16	1.25 – 3.52	0.0075	5.63	2.53 – 11.26	0.00012
maD in TV definition (yes vs no) *	1.62	0.68 – 3.23	0.25	4.34	1.30 – 10.81	0.021
maD concerning OAR (yes vs no) †	3.62	1.52 – 7.28	0.0059	8.34	1.95 – 24.58	0.0078
maD concerning dose (yes vs no) §	1.15	0.45 – 2.39	0.75	6.25	2.14 – 14.60	0.0021
maD in treatment execution (yes vs no)#	2.30	1.23 – 3.95	0.011	9.19	3.60 – 20.63	<0.0001

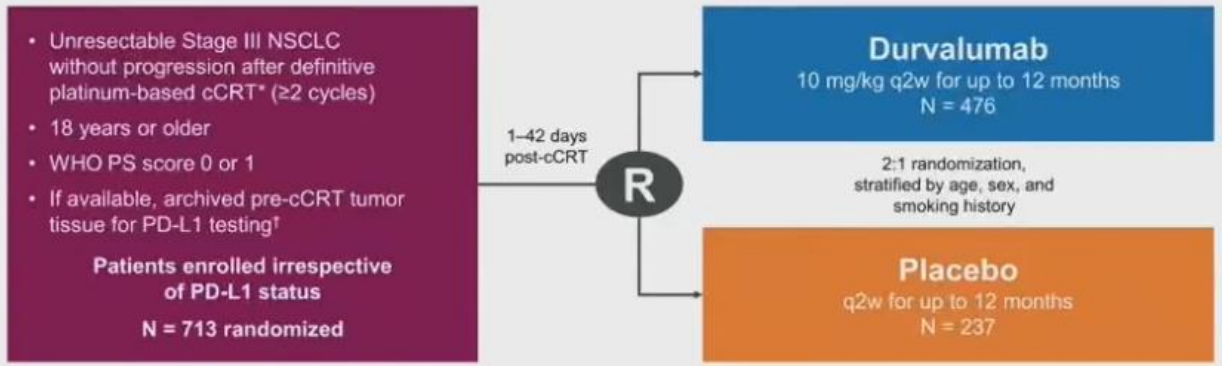
Gkika green J. 2022

Multidisziplinäre Therapie des ST III NSCLCs

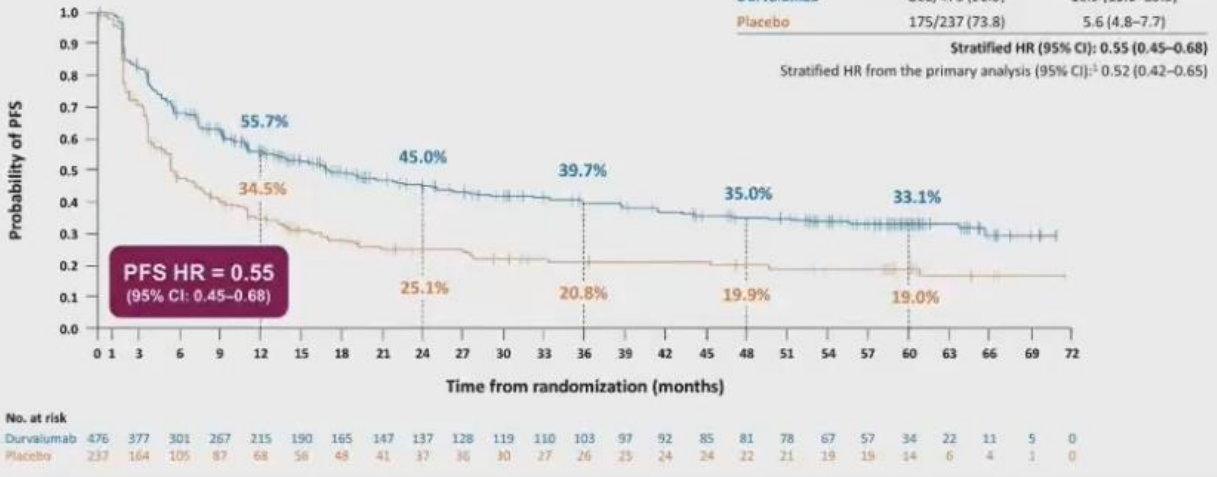
- B. Definitive Radiochemotherapie

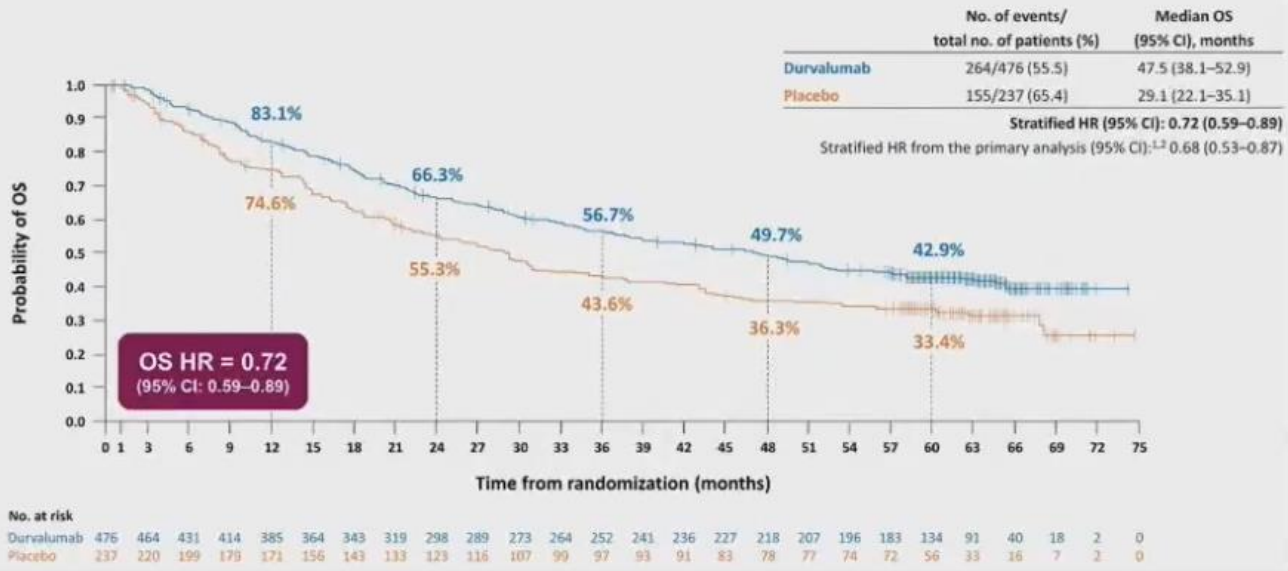
Immuntherapie

PACIFIC : Immuntherapie Konsolidierung



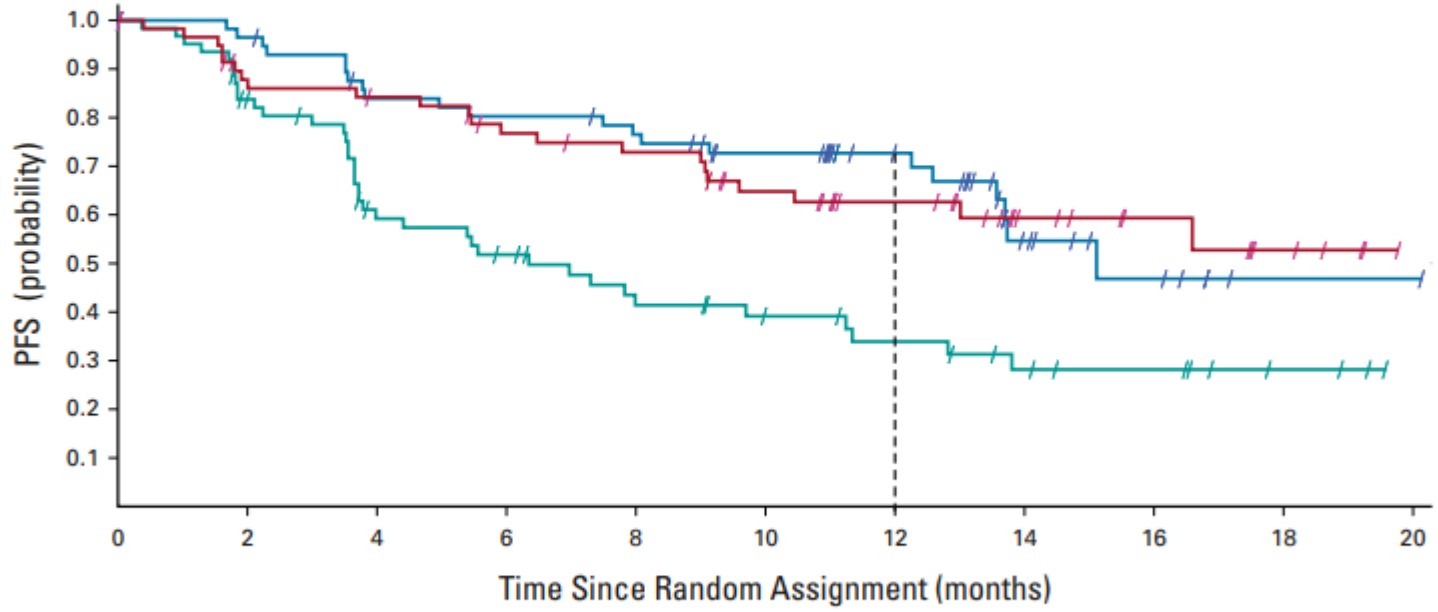
- PFS HR 0.55
  - 5y PFS rate 33.1% vs 19.0%
- OS HR 0.72
  - 5y OS rate 42.9% vs 33.4%
- FDA approved 2/16/18





Immuntherapie nach Radiochemotherapie beim inoperablen NSCLC

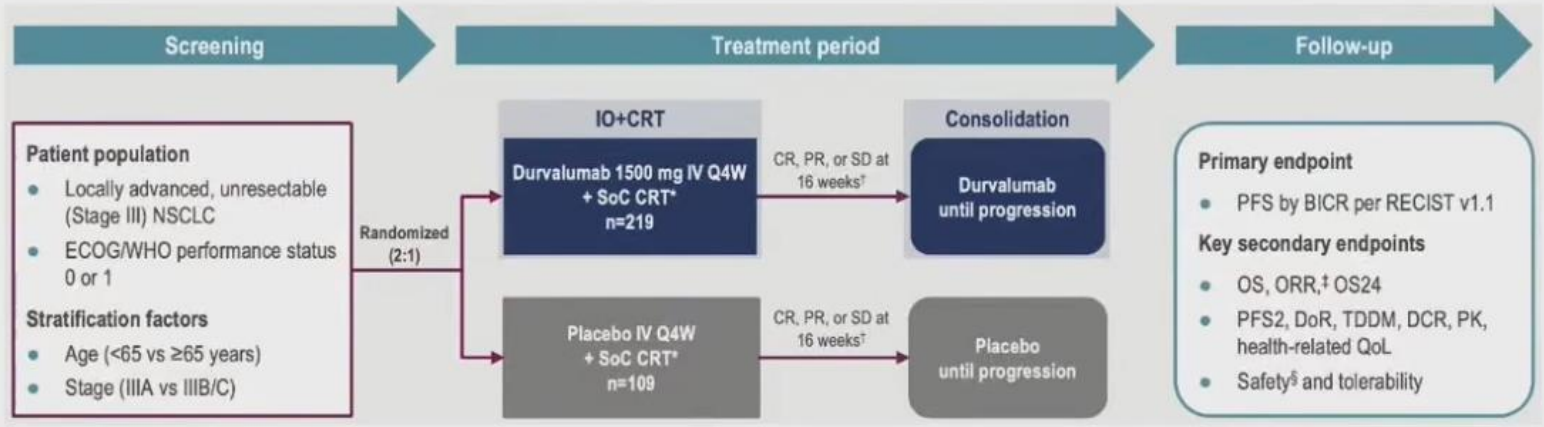
Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–



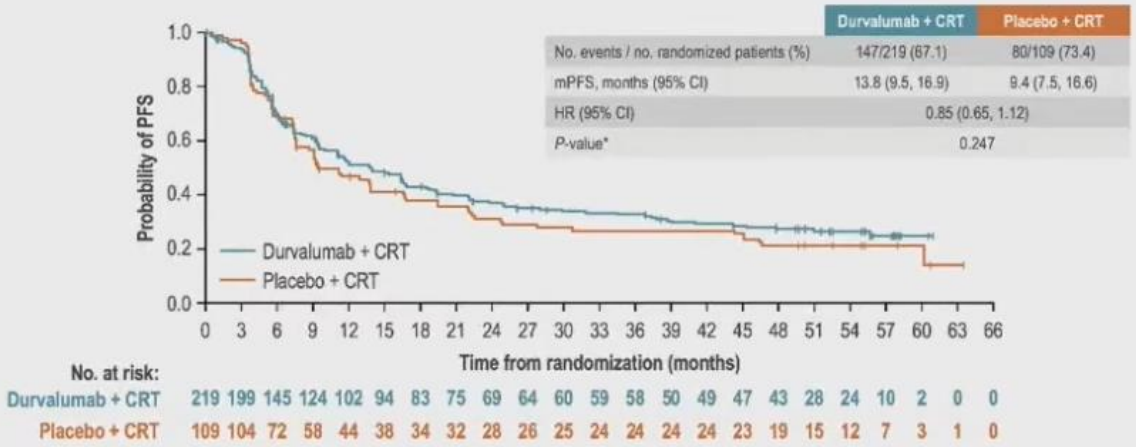
No. at risk:											
Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab	67	50	32	27	20	16	13	9	7	3	0

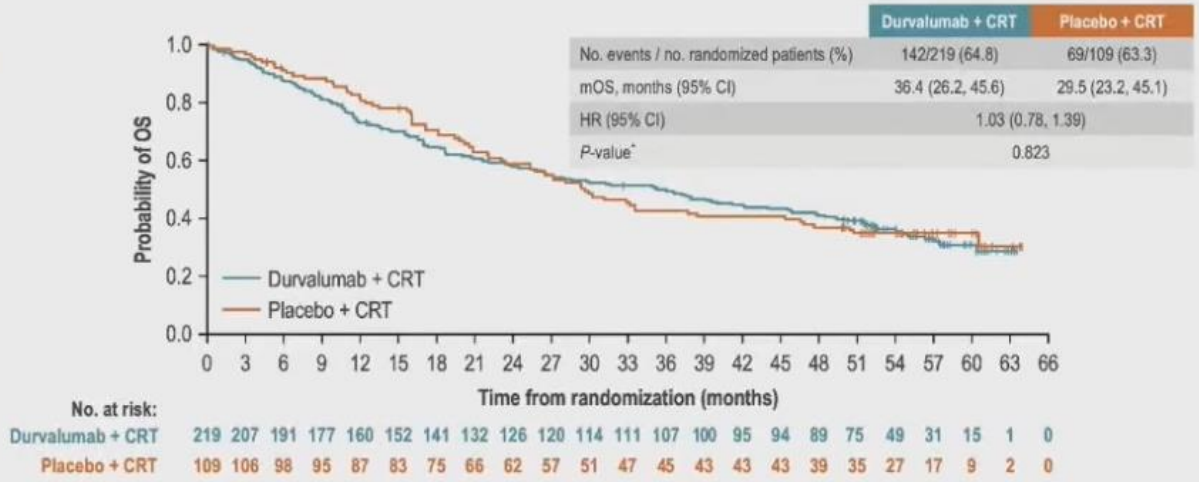
Herbst et al., JCO 2023

PACIFIC 2: Immuntherapie Simultan + Konsolidierung



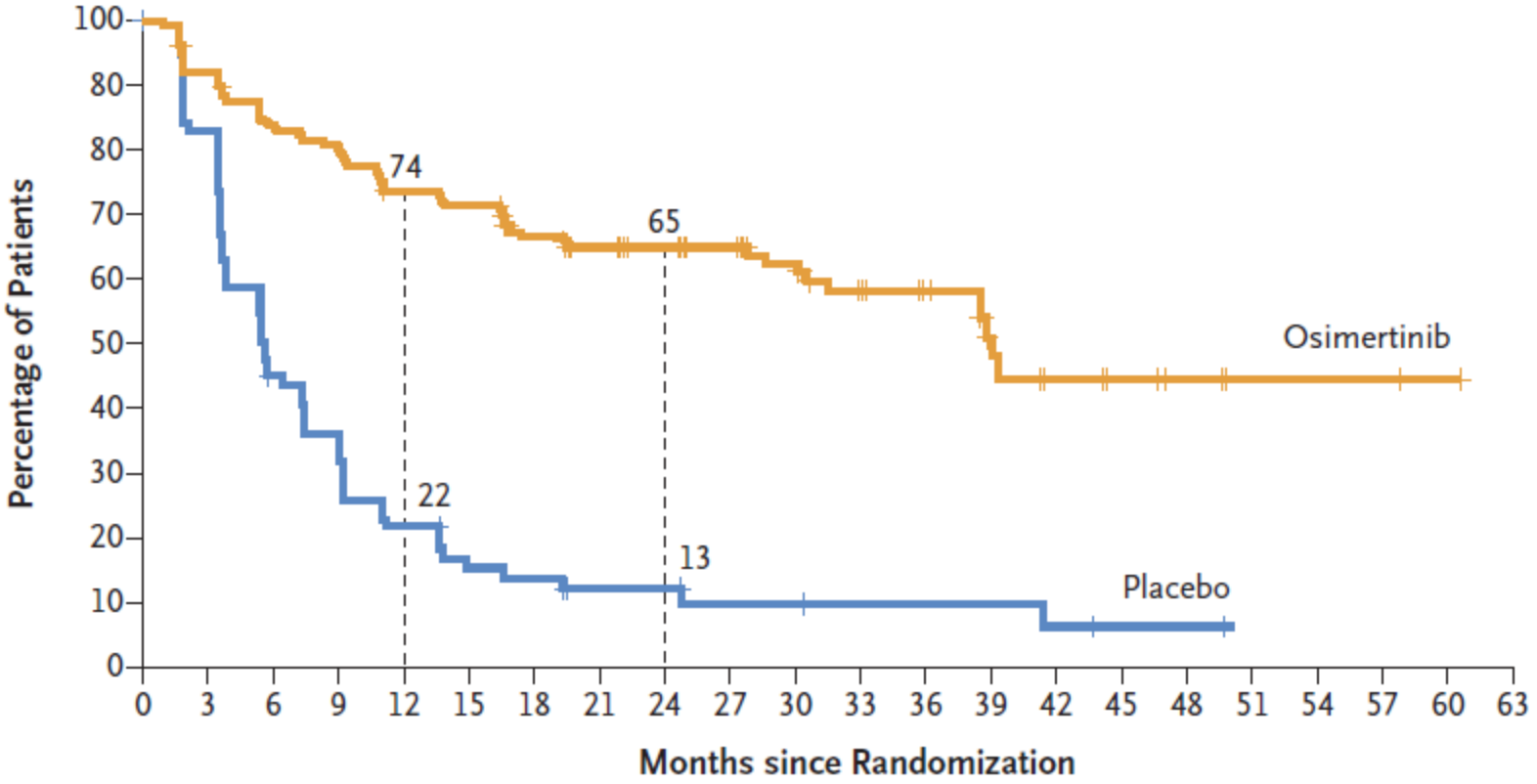
- PFS HR 0.85
  - mPFS 13.8m vs 9.4m
- OS HR 1.03
  - mOS 36.4m vs 29.5m





Bradley et al., ELCC 2024

LAURA Radiochemotherapie gefolgt von Osimertinib



Median Progression-free Survival (95% CI)

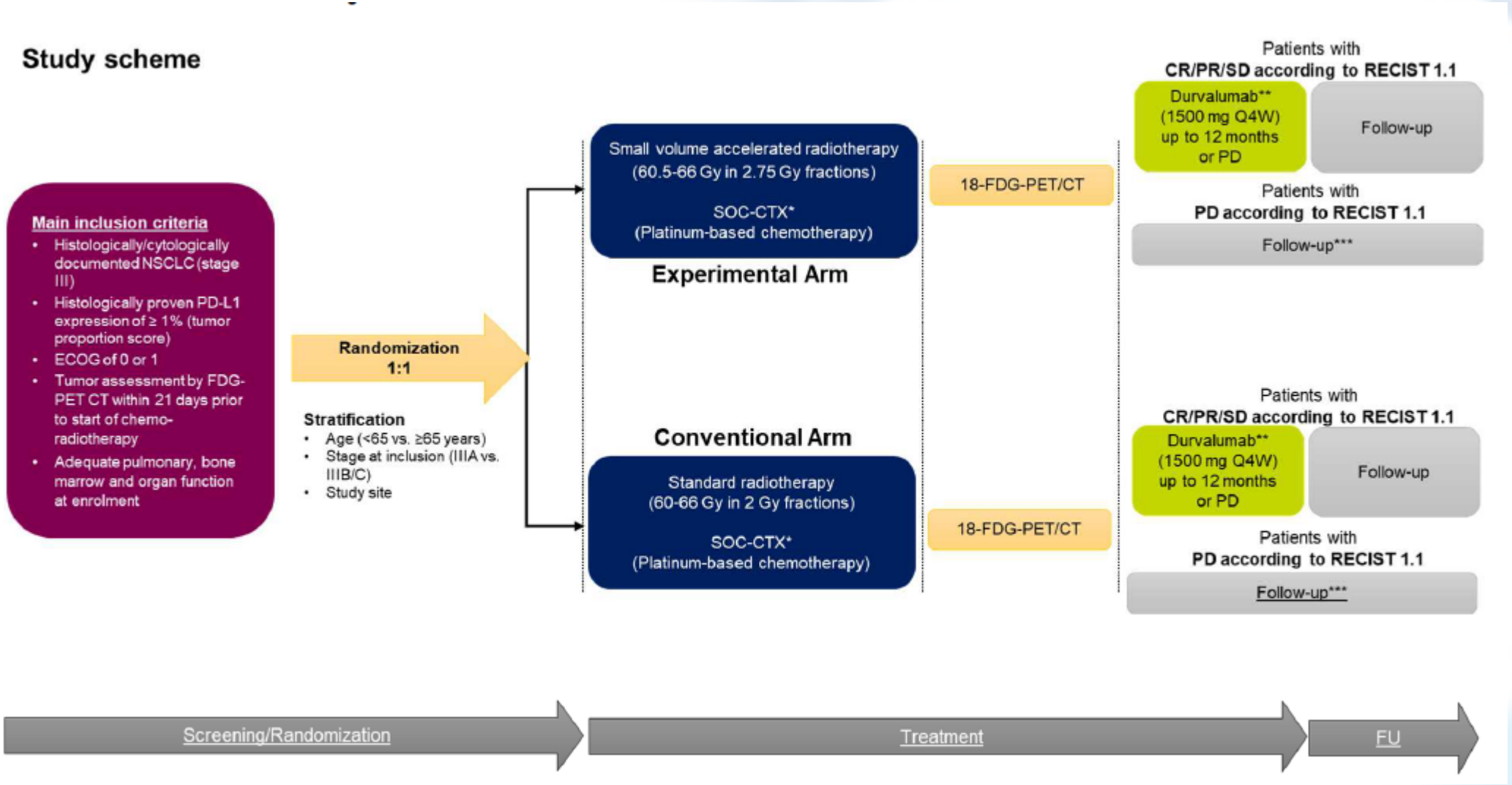
	mo
Osimertinib	39.1 (31.5–NC)
Placebo	5.6 (3.7–7.4)

Hazard ratio for disease progression or death, 0.16 (95% CI, 0.10–0.24)
P<0.001

No. at Risk

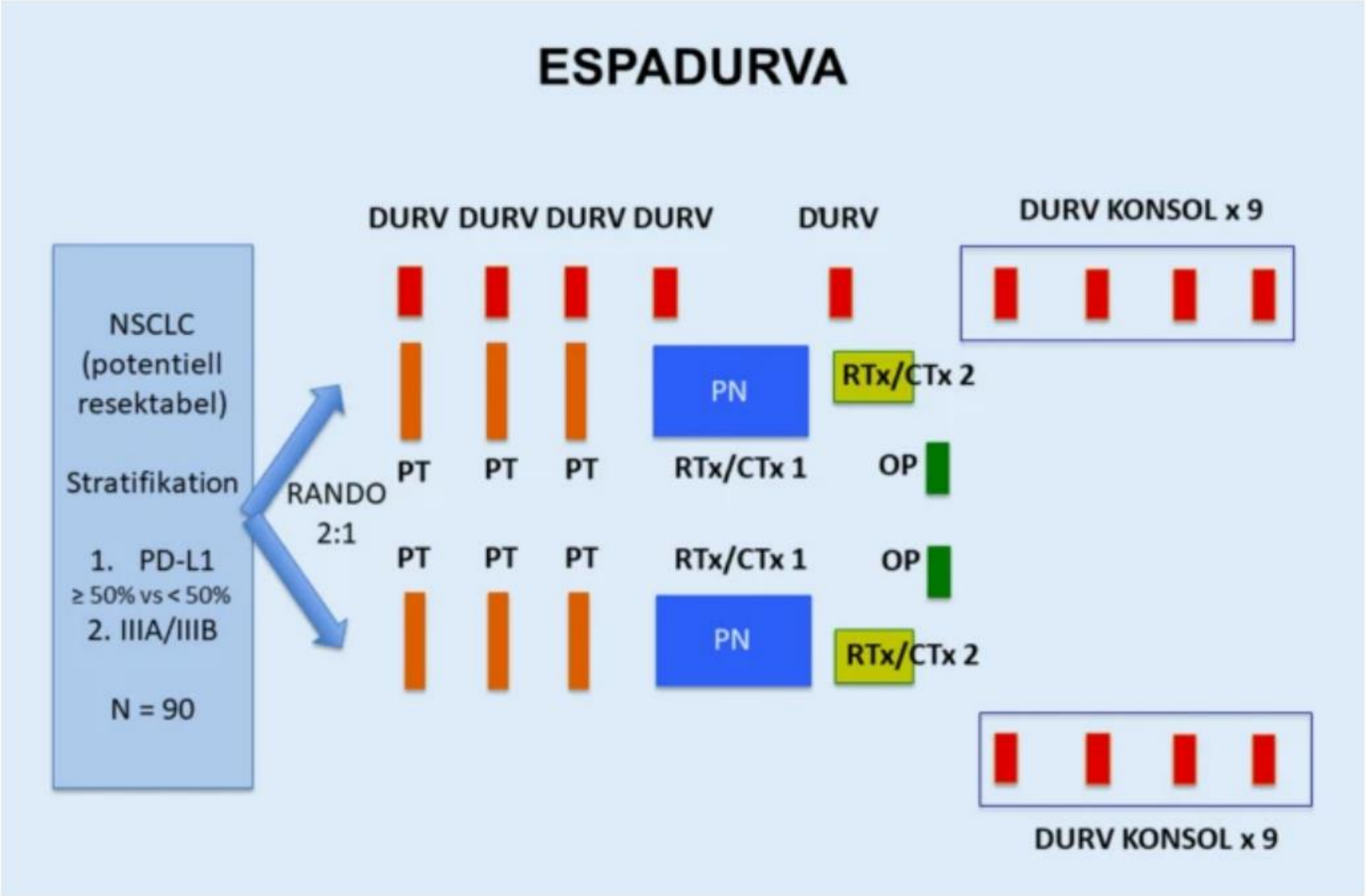
Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Intensivierung des Strahlentherapie beim inoperablen Stadium III



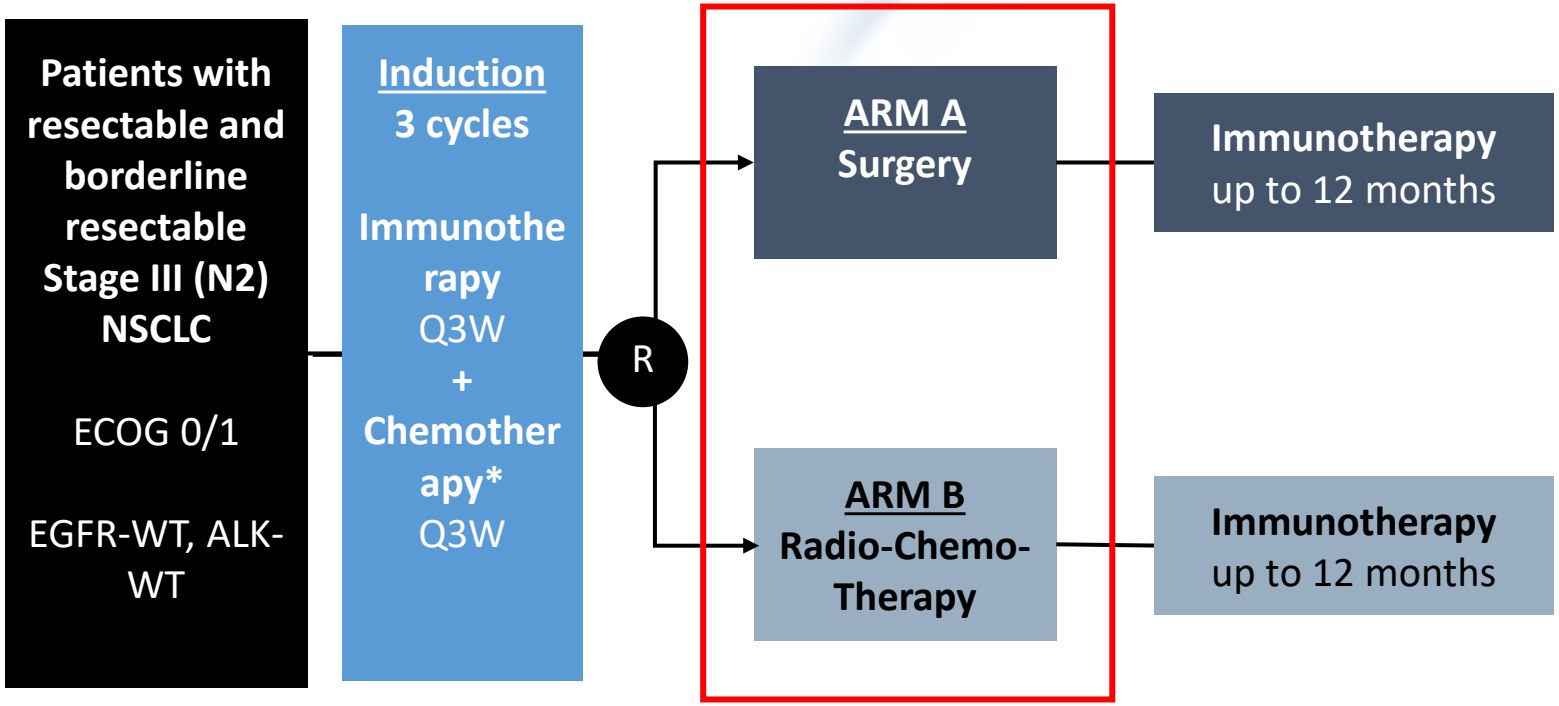
PI: U. Nestle

Neoadjuvante Radiochemoimmuntherapie



PI: W. Eberhardt

InDuRanS – Study Design
OP vs RCTx nach Chemoimmutherapie



*platinum-based doublet

ukb Klinik für Strahlentherapie und Radioonkologie

PI: E. Gkika
Co-PIs:S. Schmidt, C. Waller

UNIVERSITÄT BONN

Welche ist die bessere Therapiestrategie beim Stadium III?

- Welche ist die Rolle der Strahlentherapie neoadjuvant?

Bei der Radio-Chemo-Immuntherapie neoadjuvant könnnen deutlich höhere pCR Raten erreicht werden (50-60%) vergleichen mit der Chemoimmuntherapie (25%).

- Wie können wir die Radiotherapie optimieren? Kleinere Felder? Höhere Dosen?

Lokalkontrollraten von 80-90% ohne Immuntherapie.

- Ist die Op besser für die lokale Kontrolle als die Strahlentherapie?

Ohne Immuntherapie kein Überlebensunterschied zwischen Op und RT im operablen Stadium III.