De veranderende rol voor radiotherapie bij stadium III NSCLC.

Maastro

DTG congres 18-10-2024
Stéphanie Peeters, MD, PhD

Disclosure

Geen

Overzicht

Wat weten we al langer over de behandeling van stadium III

Plaats van postoperatieve radiotherapie in stadium III

Radiotherapie voor stadium III & immunotherapie

- concurrent
- sequentieel
- zonder chemo
- voordeel van protonen?

Wat met driver mutaties?

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Wat weten we al langer? **(in het pre-ICI tijdperk)**

NSCLC Stadium III = heterogene groep

TNM9th cN2a, cN2b

Bimodale behandeling: systeemtherapie + 1 lokale therapie

↳ radiotherapie OF chirurgie

Resectable vs. unresectable: definitie? → R0-resectie

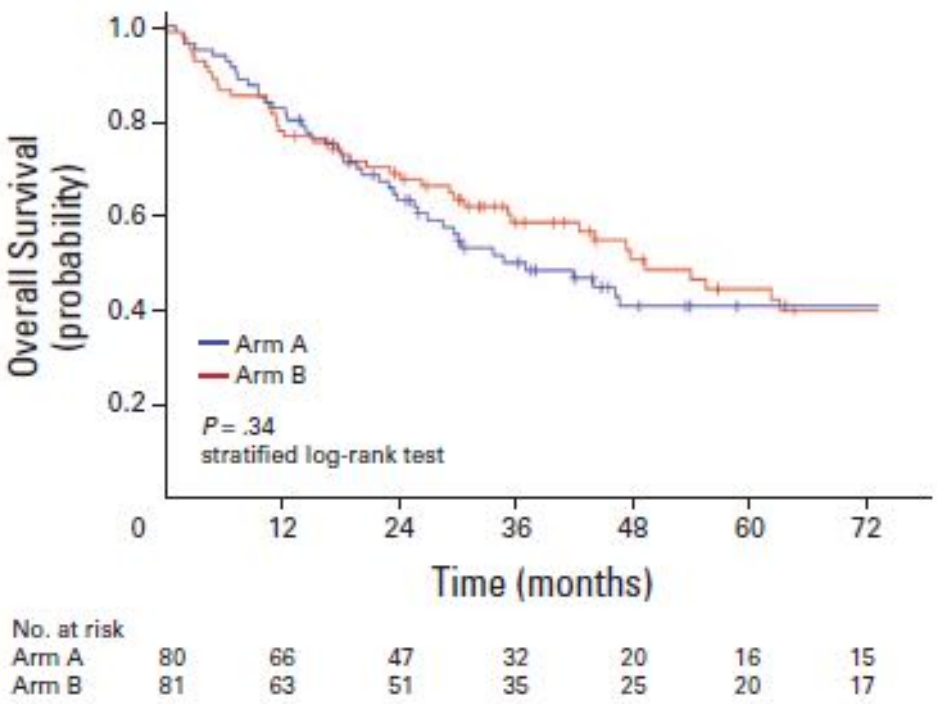
Dingemans et al. JTO 2023

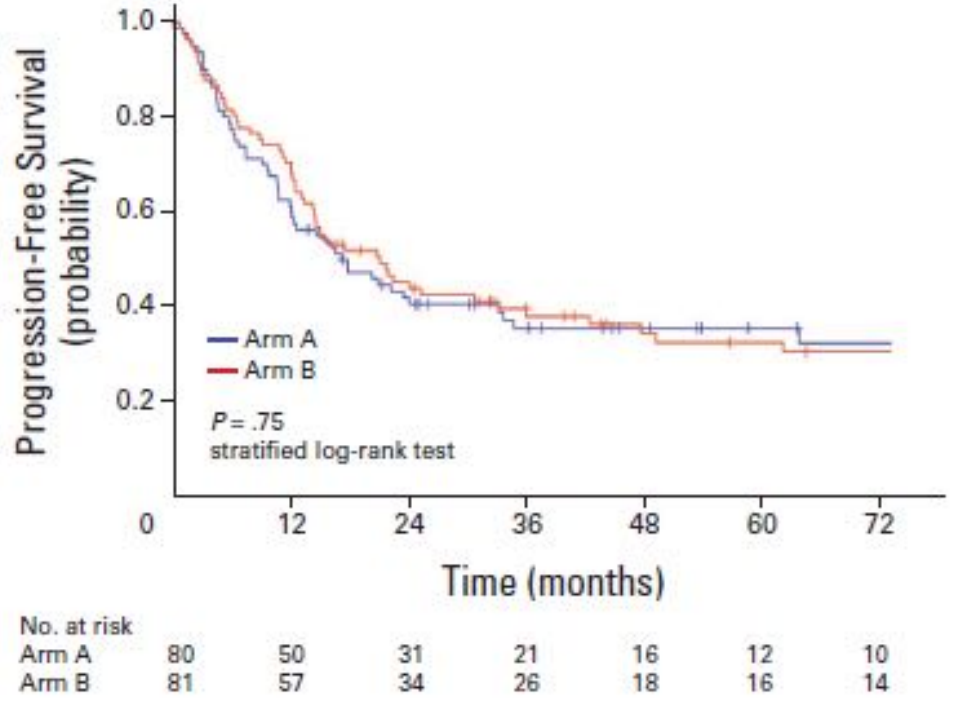
Chemotherapie + radiotherapie

ESPATUE: Resectable stage III NSCLC

Arm A: Chemoradiotherapie (65-71 Gy)

Arm B: Chemoradiotherapie (45 Gy bid) → chirurgie





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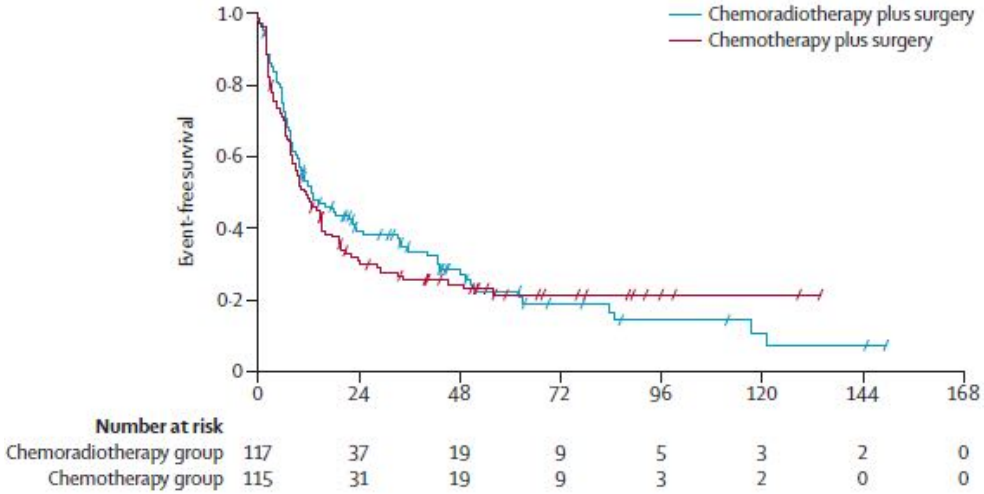
Eberhardt et al. J Clin Oncol 2015

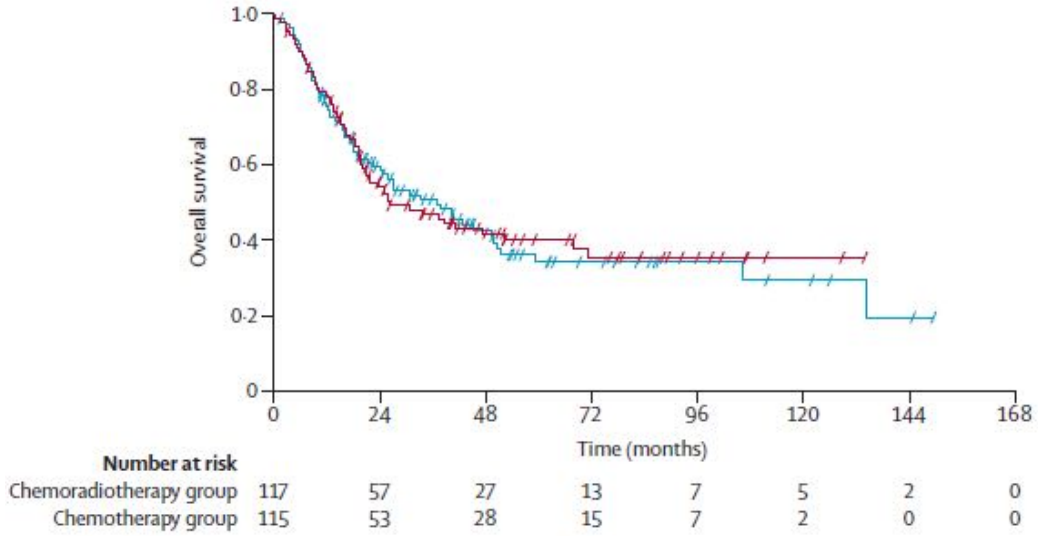
Chemotherapie + chirurgie

SAKK: Resectable stage III NSCLC

Sequentiële chemoradiotherapie (45 Gy BID) → chirurgie

Chemotherapie → chirurgie





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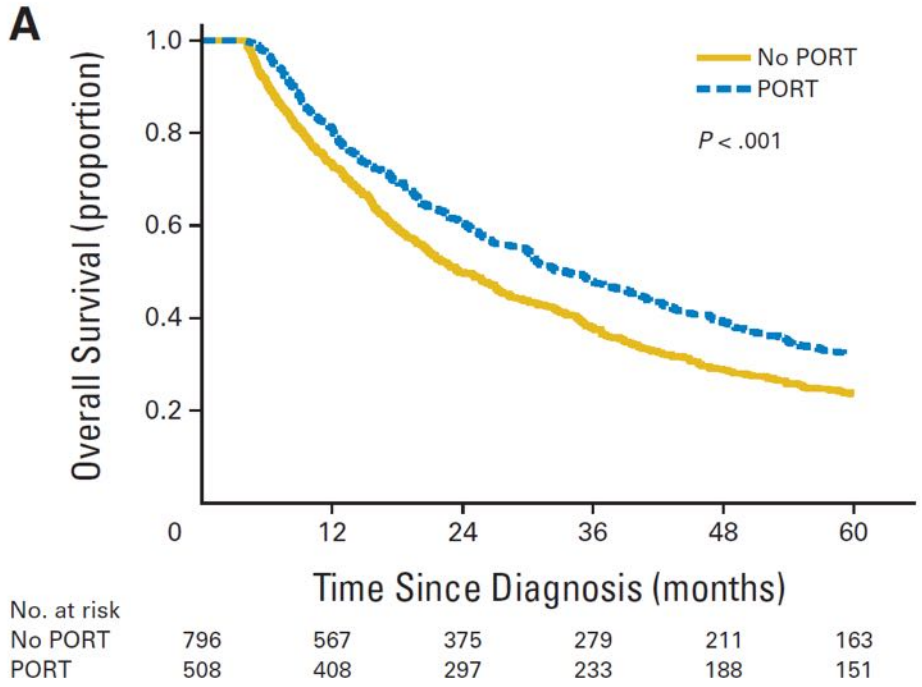
Pless et al. Lancet Oncol 2015

Postoperatieve radiotherapie in stage III (in het pre-ICI tijdperk)

National Cancer Data Base, 3395 stage II-III ptn met onvolledige resectie (R1-R2), 1207 (35.6%) kregen PORT; 1304 geïncludeerd in survival analyse



Wang et al. J Clin Oncol 2015

Postoperatieve radiotherapie in stage III? (in het pre-ICI tijdperk)

Lung ART

PORT na volledige resectie (“R0”) resulteert in:

- Halvering mediastinale recidieven (28% → 14%)
- Meer overlijdens
- Meer toxiciteit

Echter GEEN betere DFS of OS

Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): an open-label, randomised, phase 3 trial

Cecile Le Pechoux, Nicolas Pourel, Fabrice Barlesi, Delphine Lerouge, Delphine Antoni, Bruno Lamezec, Ursula Nestle, Pierre Boisselier, Eric Dansin, Amaury Paumier, Karine Peignaux, François Thillays, Gerard Zalcman, Jeannick Madelaine, Eric Pichon, Anne Larrouy, Armelle Lavole, Delphine Argo-Leignel, Marc Derollez, Corinne Faivre-Finn, Matthew Q Hatton, Oliver Riesterer, Emilie Bouvier-Morel, Ariane Dunant, John G Edwards, Pascal Alexandre Thomas, Olaf Mercier, Aurelie Bardet

Summary

Background In patients with non-small-cell lung cancer (NSCLC), the use of postoperative radiotherapy (PORT) has

Lancet Oncol 2021

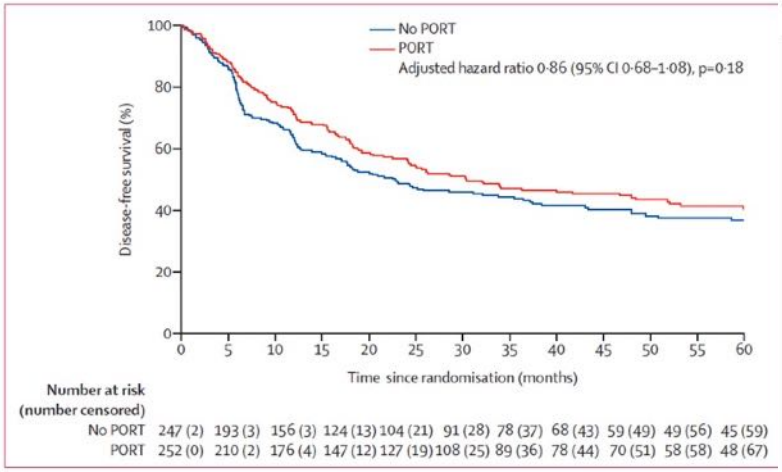
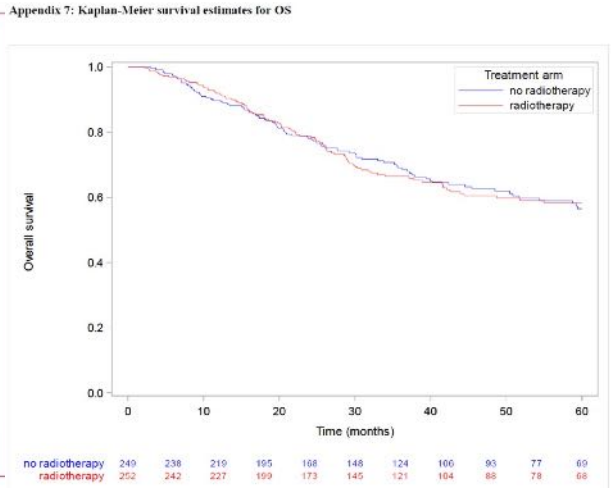


Figure 2: Kaplan-Meier survival estimates for disease-free survival
PORT=postoperative radiotherapy.



Le Pechoux et al. Lancet Oncol 2021

Postoperatieve radiotherapie in stage III? (in het pre-ICI tijdperk)

Lung ART

N2 status before any treatment		
N0 nodal involvement (N2 unforeseen)	59/240 (25%)	70/239 (29%)
N1 (N2 unforeseen)	43/240 (18%)	29/239 (12%)
Single station N2	83/240 (35%)	80/239 (34%)
Multiple station N2	55/240 (23%)	60/239 (25%)
Missing information	12	10

Quality of resection according to surgical committee review*		
R (uncertain)	101/250 (40%)	102/243 (42%)
R0	74/250 (30%)	65/243 (27%)
R1 (nodal extracapsular extension)	74/250 (30%)	75/243 (31%)
R2	1/250	1/243
Missing information	2	6

PORT-C

Chinese RCT

Zelfde besluit

PORT is enkel geïndiceerd bij onvolledige resectie/positief snijvlak

PORT cannot rescue an incomplete resection

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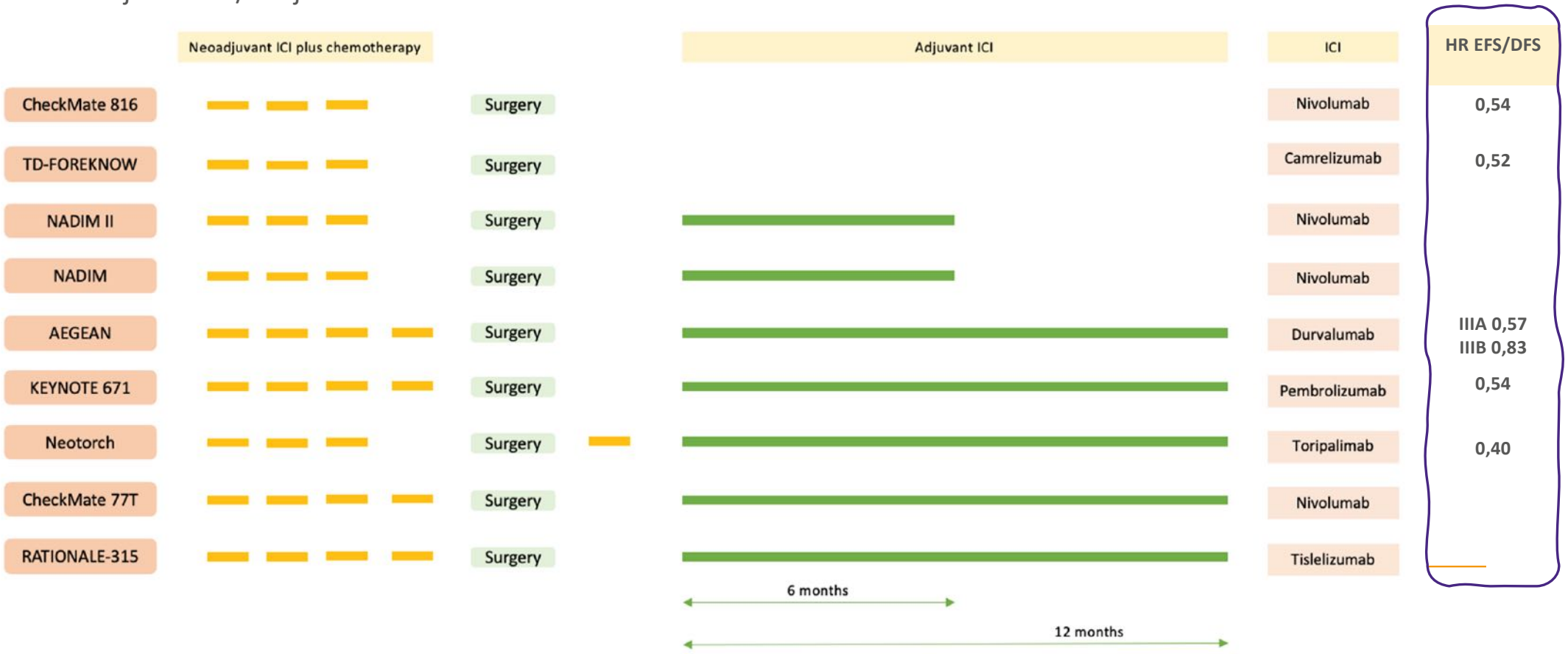
Le Pechoux et al. Lancet Oncol 2021

Hui et al. JAMA Oncol. 2021

ICI en *chirurgie* bij stadium III NSCLC

Veel studies…

Neoadjuvante +/- adjuvante ICI



ICI en *chirurgie* bij stadium III NSCLC

Enkel adjuvant ICI

	ICI	HR EFS/DFS	p
IMPOWER 010	Atezolizumab	0,81	P=0,04
Keynote 91	Pembrolizumab	0,76	P=0,0014
CCTG BR.31	Pembrolizumab	0,89	NS

HR EFS/DFS
0,54
0,52
IIIA 0,57 IIIB 0,83
0,54
0,40

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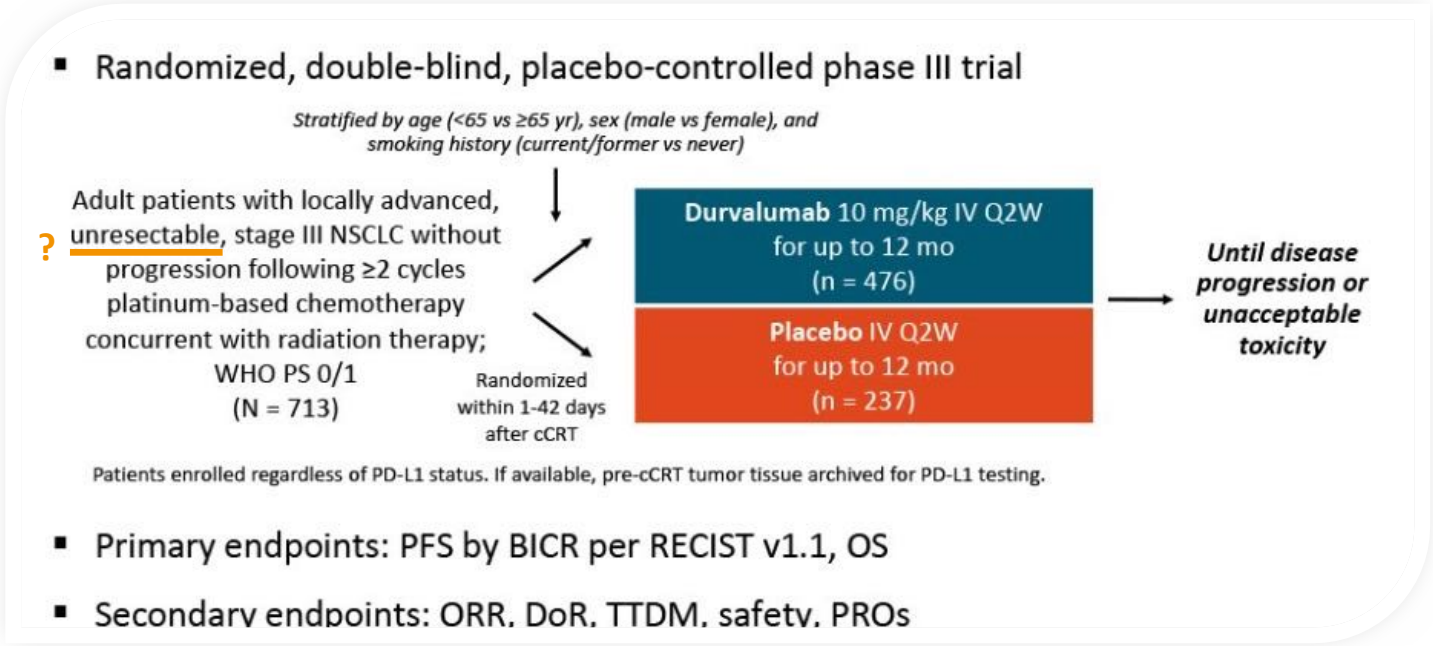
Felip et al. The Lancet 2021; O'Brien et al. Lancet Oncol 2022; Goss et al. LBA48, ESMO 2024

ICI en *radiotherapie* bij stadium III NSCLC

Concurrente CRT (cCRT) +/- adjuvant durvalumab (**PACIFIC**) – Phase III

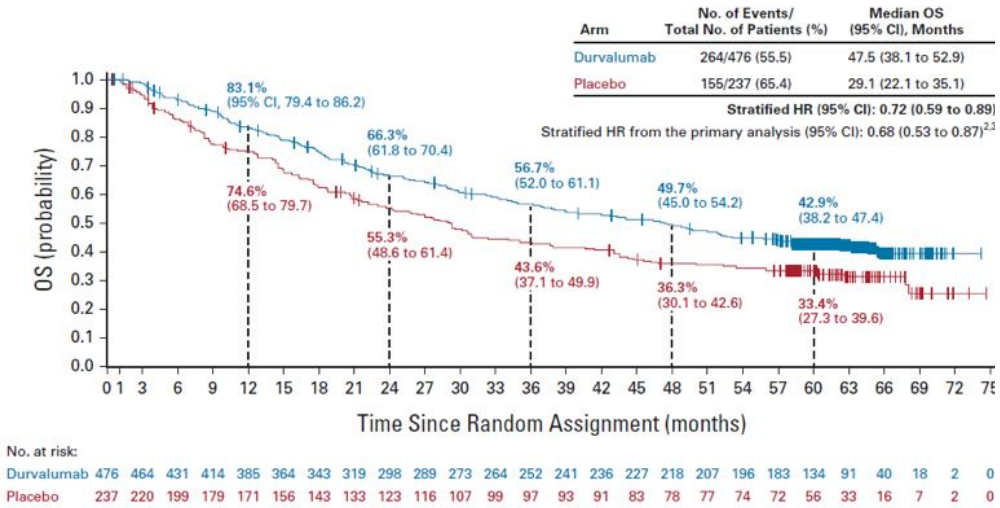


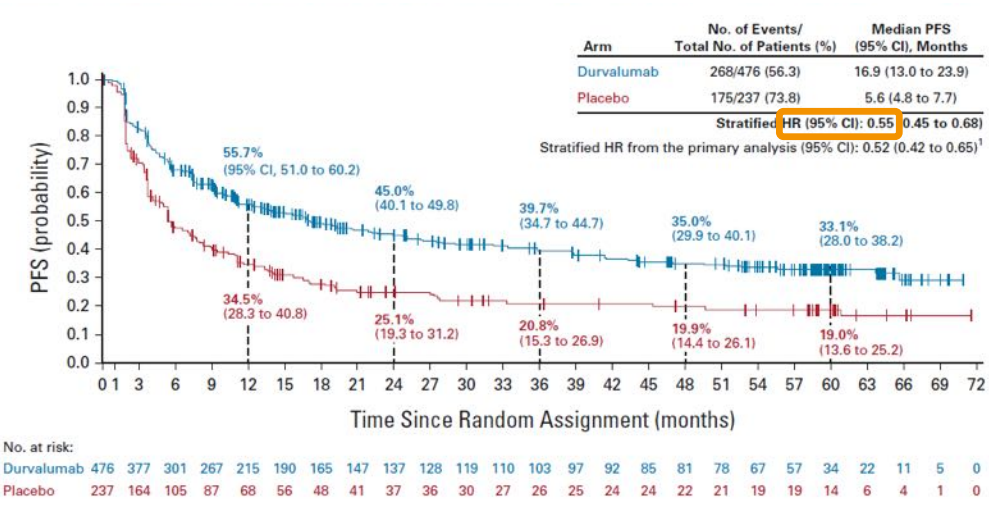
Maastro

Spigel et al. JCO 2022

ICI en cCRT bij stadium III NSCLC:

PACIFIC





	Durvalumab (N=476)	Placebo (N=237)	Total (N=713)
Disease stage			
IIIA	252 (52.9)	125 (52.7)	377 (52.9)
IIIB	212 (44.5)	107 (45.1)	319 (44.7)
Other‡	12 (2.5)	5 (2.1)	17 (2.4)

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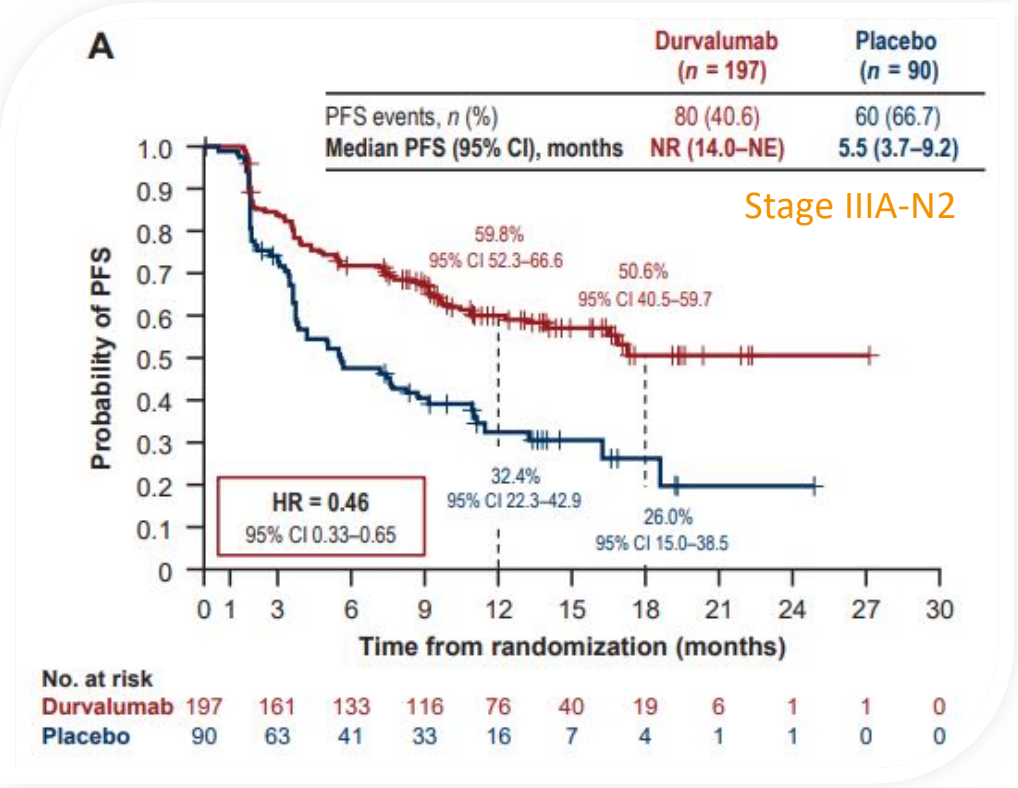
Spigel et al. JCO 2022, Antonia et al. NEJM 2018

ICI en cCRT bij stadium III NSCLC:

PACIFIC: stage IIIA-N2

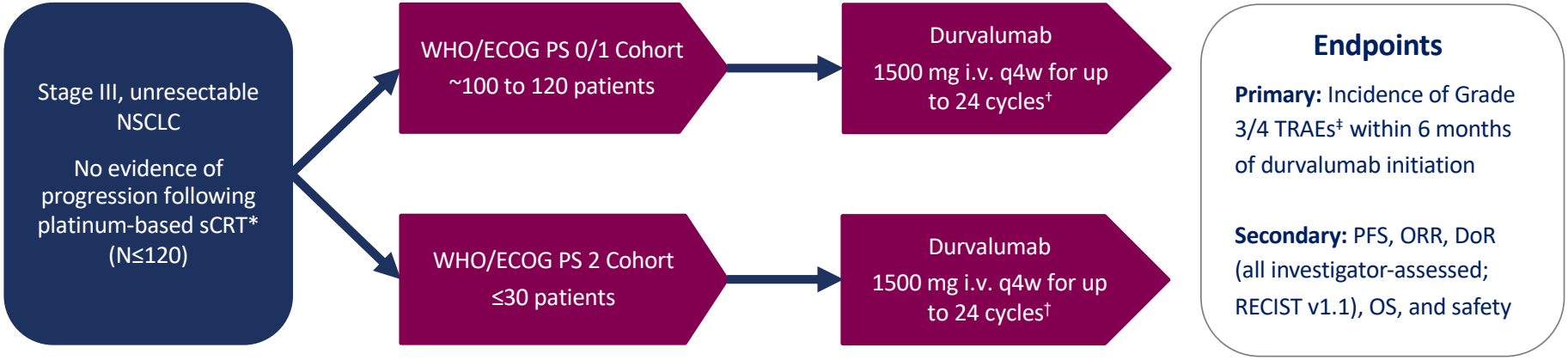


Post-hoc analysis
Senan et al. ESMO open 2022

ICI en sCRT bij stadium III NSCLC:

PACIFIC 6

Sequentiële CRT (sCRT) + adjuvant durvalumab – single arm Phase II



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Garassino et al. JTO 2022

ICI en sCRT bij stadium III NSCLC:

PACIFIC 6

Characteristic	ECOG PS 0 or 1 (n = 114)	ECOG PS 2 (n = 3)	All Patients (N = 117)
Disease stage at baseline, n (%)			
IA	1 (0.9)	0	1 (0.9)
IIIA	44 (38.6)	0	44 (37.6)
IIIB	58 (50.9)	1 (33.3)	59 (50.4)
IIIC	11 (9.6)	2 (66.7)	13 (11.1)
ECOG PS, n (%)			
0	47 (41.2)	0	47 (40.2)
1	67 (58.8)	0	67 (57.3)
2	0	3 (100.0)	3 (2.6)

	Max. CTCAE Grade (N = 117)					Action Taken With Durvalumab (N = 117)	
AE Preferred Term, n (%)	Any AE	Grade 1	Grade 2	Grade 3 or 4	Grade 5	Interrupted	Discontinued
Pneumonitis	22 (18.8)	2 (1.7)	17 (14.5)	2 (1.7)	1 (0.9)	8 (6.8)	12 (10.3)
Interstitial lung disease	3 (2.6)	1 (0.9)	2 (1.7)	0	0	0	3 (2.6)
Radiation pneumonitis	4 (3.4)	1 (0.9)	1 (0.9)	2 (1.7)	0	0	3 (2.6)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Max., maximum.

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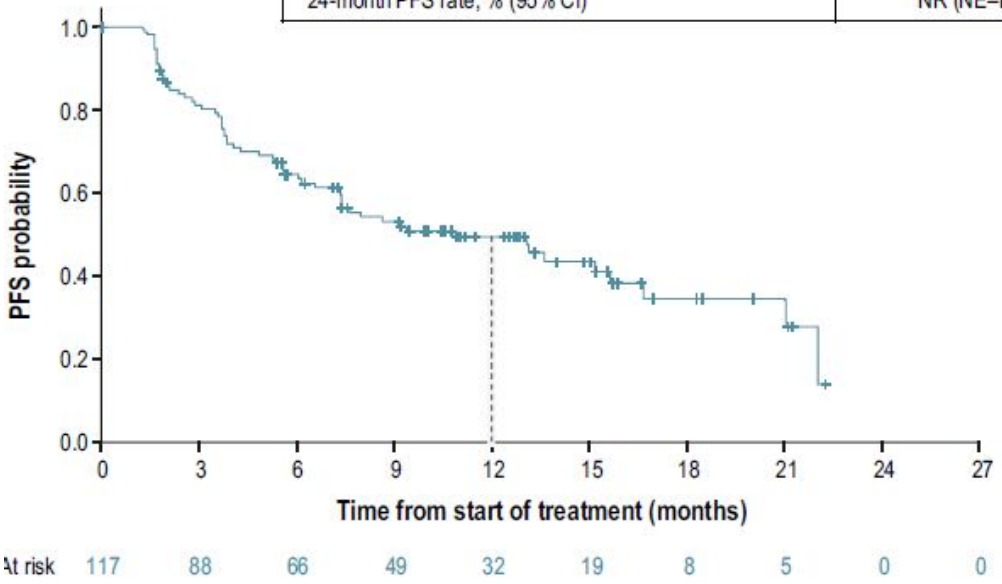
Garassino et al. JTO 2022

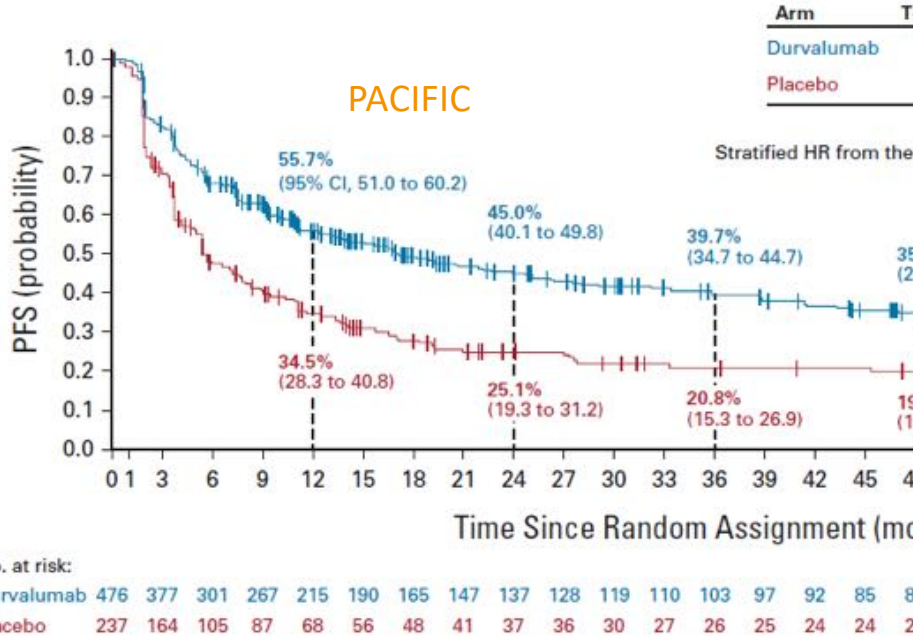
ICI en sCRT bij stadium III NSCLC:

PACIFIC 6

	All patients (N = 117)
Total progression events, n (%)	61 (52.1)
Median PFS, months (95% CI)	10.9 (7.3–15.6)
12-month PFS rate, % (95% CI)	49.6 (39.5–58.9)
24-month PFS rate, % (95% CI)	NR (NE–NE)



PACIFIC



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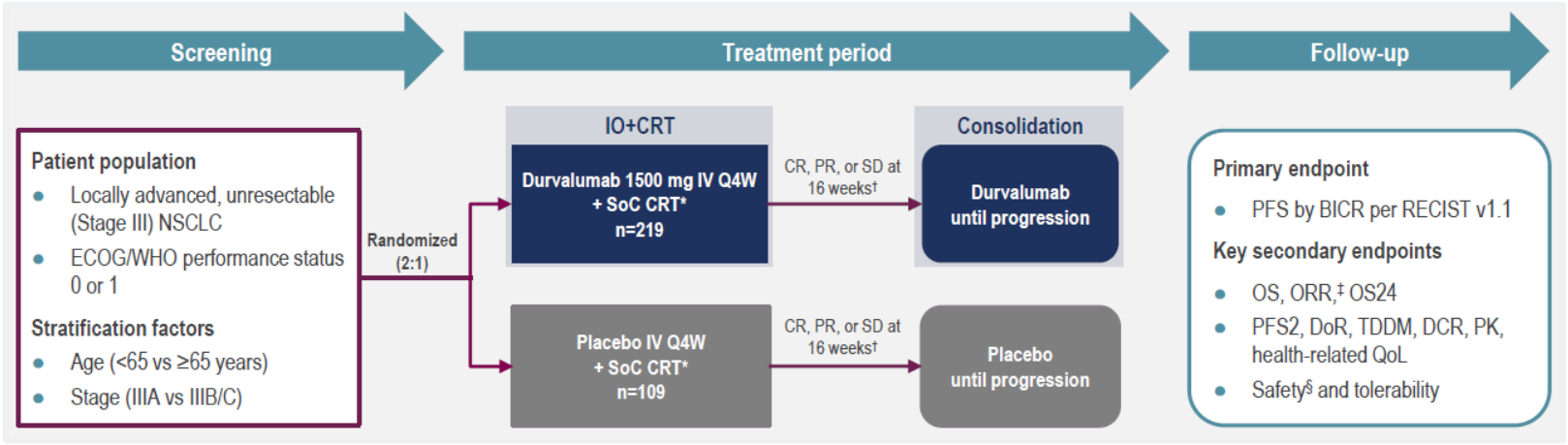
ICI en cCRT bij stadium III NSCLC:

PACIFIC 2

Concurrente CRT +/- concurrent en adjuvant durvalumab – Phase III

Study design

PACIFIC-2 (NCT03519971) is a phase 3, randomized, double-blind, placebo-controlled, multicenter, global study of durvalumab + CRT followed by durvalumab versus placebo + CRT followed by placebo



Patients were recruited from **29 March 2018** through **24 June 2019** across 106 sites in Asia, Eastern Europe, and the Americas, including: Brazil, Czech Republic, Hungary, India, Japan, Mexico, Peru, Philippines, Poland, Republic of Korea, Russia, Turkey, Thailand, and Vietnam.

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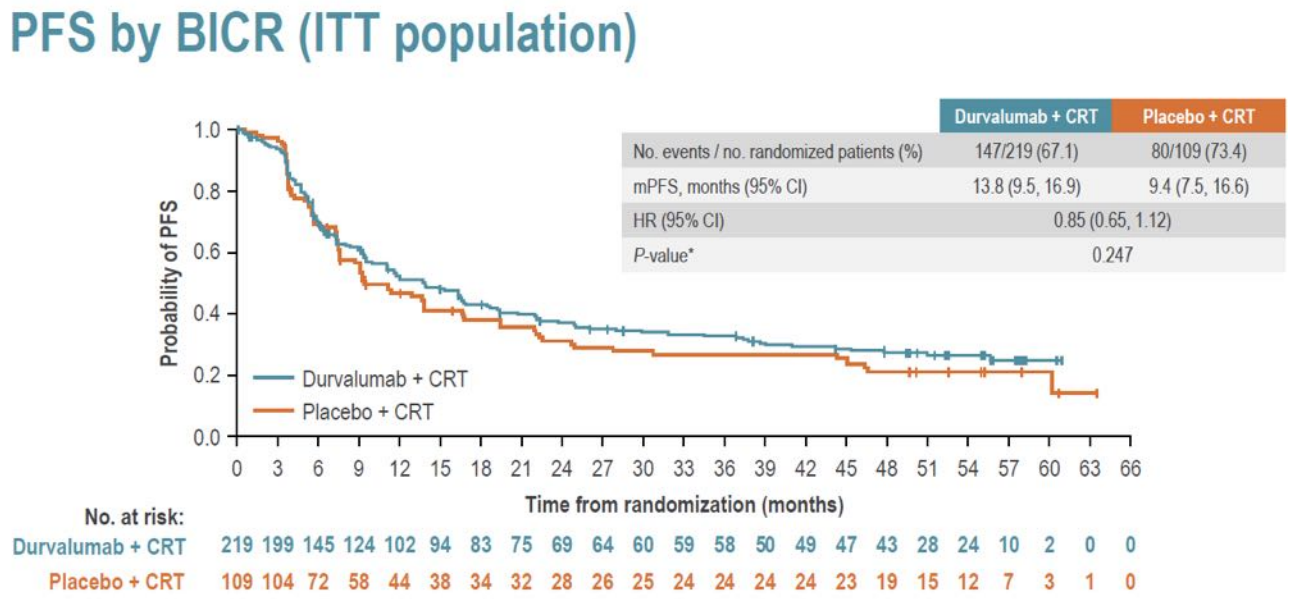
Jeffrey D. Bradley et al. LBA1. ELCC 2024

ICI en cCRT bij stadium III NSCLC:

PACIFIC 2



Concurrent administration of Durvalumab with platinum-based chemoradiotherapy, followed by consolidation Durvalumab, did not improve PFS, ORR, and OS compared to concurrent CRT in patients with unresectable Stage III NSCLC

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Jeffrey D. Bradley et al. LBA1. ELCC 2024

Radiotherapy enhances antitumour immunity, but also induces immunosuppressive responses[1]

Right dose, right fractioning, and right timing?

Stage III NSCLC

cCRT → ICI	ICI + cCRT → ICI
PACIFIC	PACIFIC-2
	CheckMate-73L

Stage I-II NSCLC

SABR → ICI	SBRT → ICI
I-SABR	Keynote-867

ICI en cCRT bij stadium III NSCLC

Table 2. Phase II and phase III trials evaluating the incorporation of immunotherapy with chemoradiation in stage III NSCLC. cCT, concurrent chemotherapy; cCRT, concurrent chemoradiotherapy.

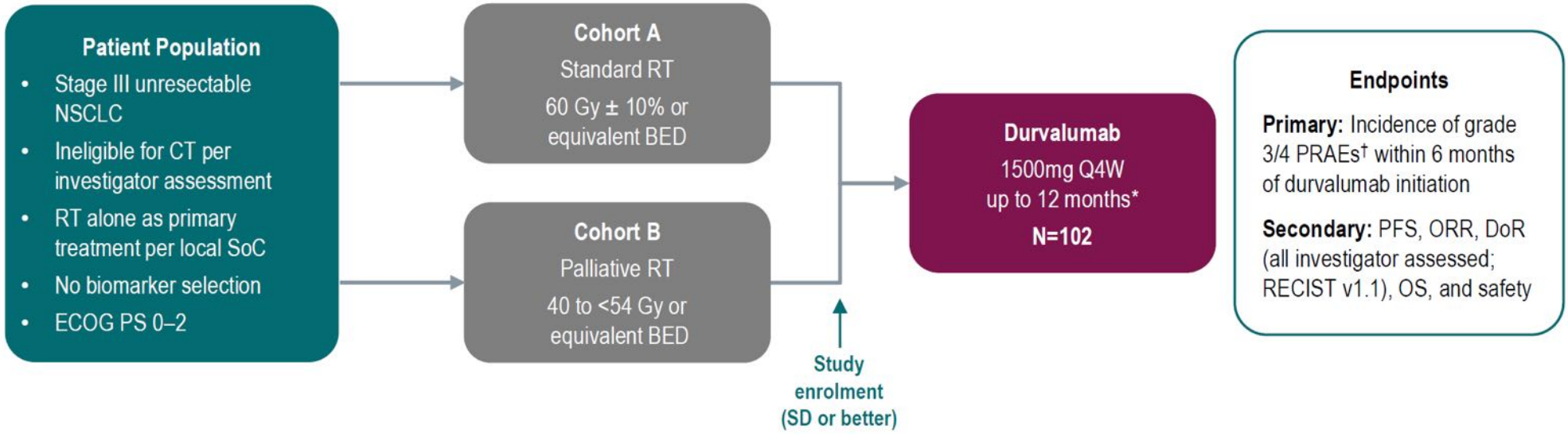
Trial Name	Study Phase	Experimental Arm	Control Arm	Clinical Trials Identifier
PACIFIC-2 [65]	Phase 3	cCRT with durvalumab	cCRT with placebo	NCT03519971
PACIFIC-5 [66]	Phase 3	cCRT followed by fixed-dose durvalumab	cCRT followed by placebo	NCT03706690
COAST [62]	Phase 2	Arm 1: cCRT followed by durvalumab Arm 2: cCRT followed by durvalumab + oleclumab Arm 3: cCRT followed by durvalumab + monalizumab	-	NCT03822351
Alliance Foundation Study [64]	Phase 2	2 or 4 cycles of induction atezolizumab → cCRT → 2 cycles of consolidation chemotherapy with carboplatin and paclitaxel → adjuvant atezolizumab for 1 year of therapy from the start of induction.	-	NCT03102242
CONSIST	Phase 3	cCRT followed by sintilimab for 1 year	cCRT alone	NCT03884192
GEMSTONE-301 [67]	Phase 3	cCRT followed by Sugenlimab for 2 year	cCRT followed by placebo	NCT03728556
KEYNOTE-799 [68]	Phase 2	One cycle of chemotherapy with pembrolizumab → cCRT with 2 cycles of pembrolizumab → pembrolizumab × 14 cycles	-	NCT03631784
CheckMate 73L [69]	Phase 3	Arm 1: cCRT with nivolumab → nivolumab + ipilimumab Arm 2: cCRT with nivolumab → nivolumab	cCRT followed by durvalumab	NCT04026412

Sridar et al. 2024

ICI en RT (zonder chemo) bij stadium III NSCLC:

DUART

A phase 2, open-label, multicentre, international study



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Filippi et al. LBA62 ESMO 2023

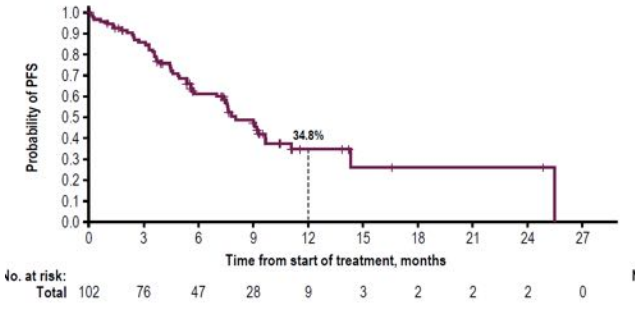
ICI en RT (zonder chemo) bij stadium III NSCLC:

DUART

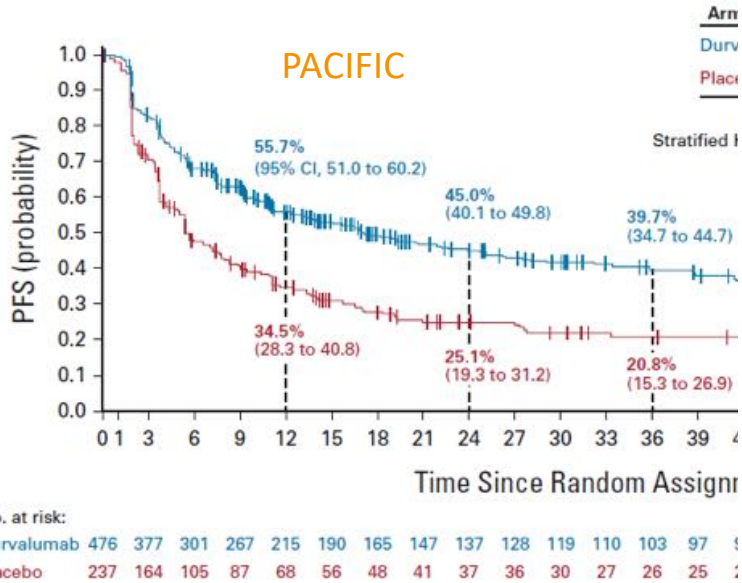
- **Grade 3/4 PRAEs* within 6 months (primary endpoint): 9.8% (95% CI: 4.8–17.3)†**
  - Cohort A: 11.9% (95% CI: 4.9–22.9)†
  - Cohort B: 7.0% (95% CI:1.5–19.1)†
- 9.8% had PRAEs leading to discontinuation, most commonly pneumonitis (3.9% of all patients)

PFS

	Cohort A (standard RT)	Cohort B (palliative RT)	Total
No. events / no. patients (%)	26/59 (44.1)	25/43 (58.1)	51/102 (50.0)
Median PFS (95% CI)*, months	9.0 (5.6–NC)	7.6 (5.3–11.0)	8.0 (7.0–9.7)
12-month PFS rate (95% CI)†, %	40.2 (23.6–56.3)	29.3 (13.8–46.7)	34.8 (23.0–46.9)



PACIFIC



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Protonen

Na cCRT met in st III NSCLC,

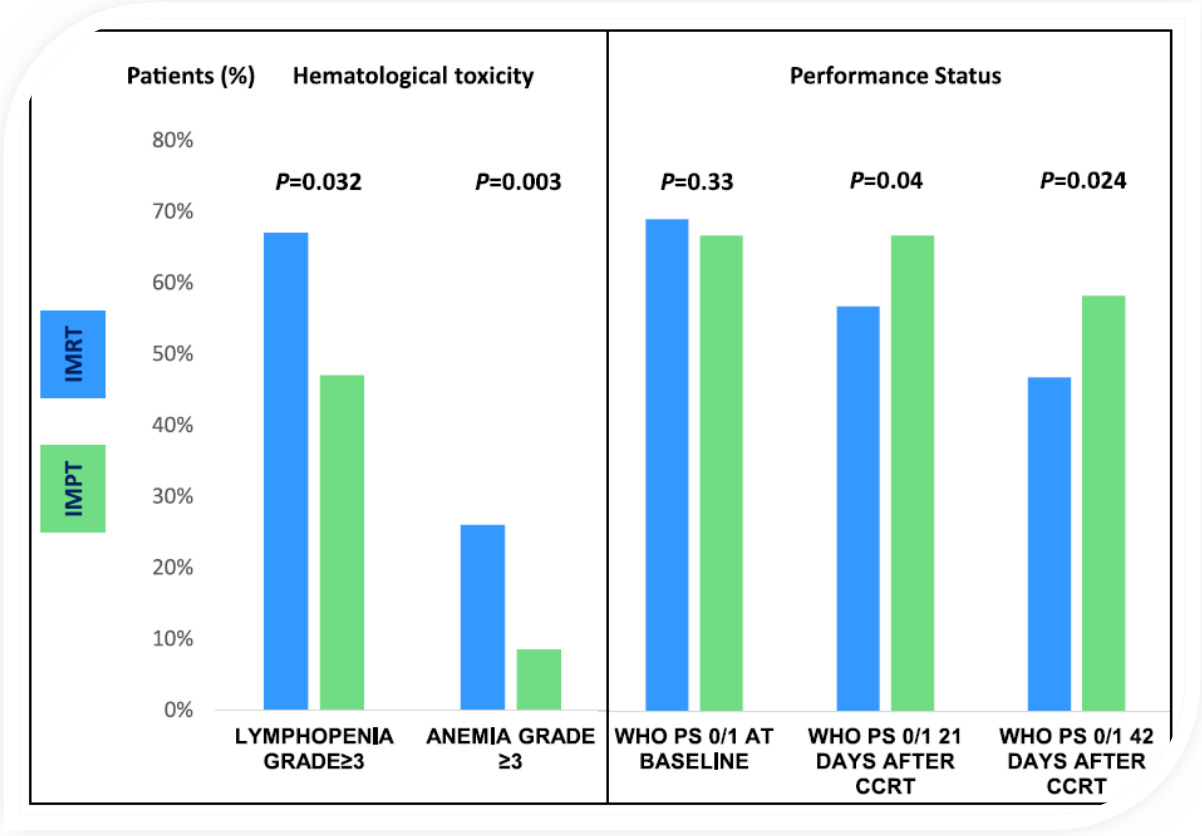
met **protonen**:

- Minder anemie en lymfopenie
- Betere conditie
- Hogere kans op adj durvalumab

(74 % protonen vs. 52 % fotonen , OR 0.35, 95 % CI: 0.16–0.79, P = 0.01)

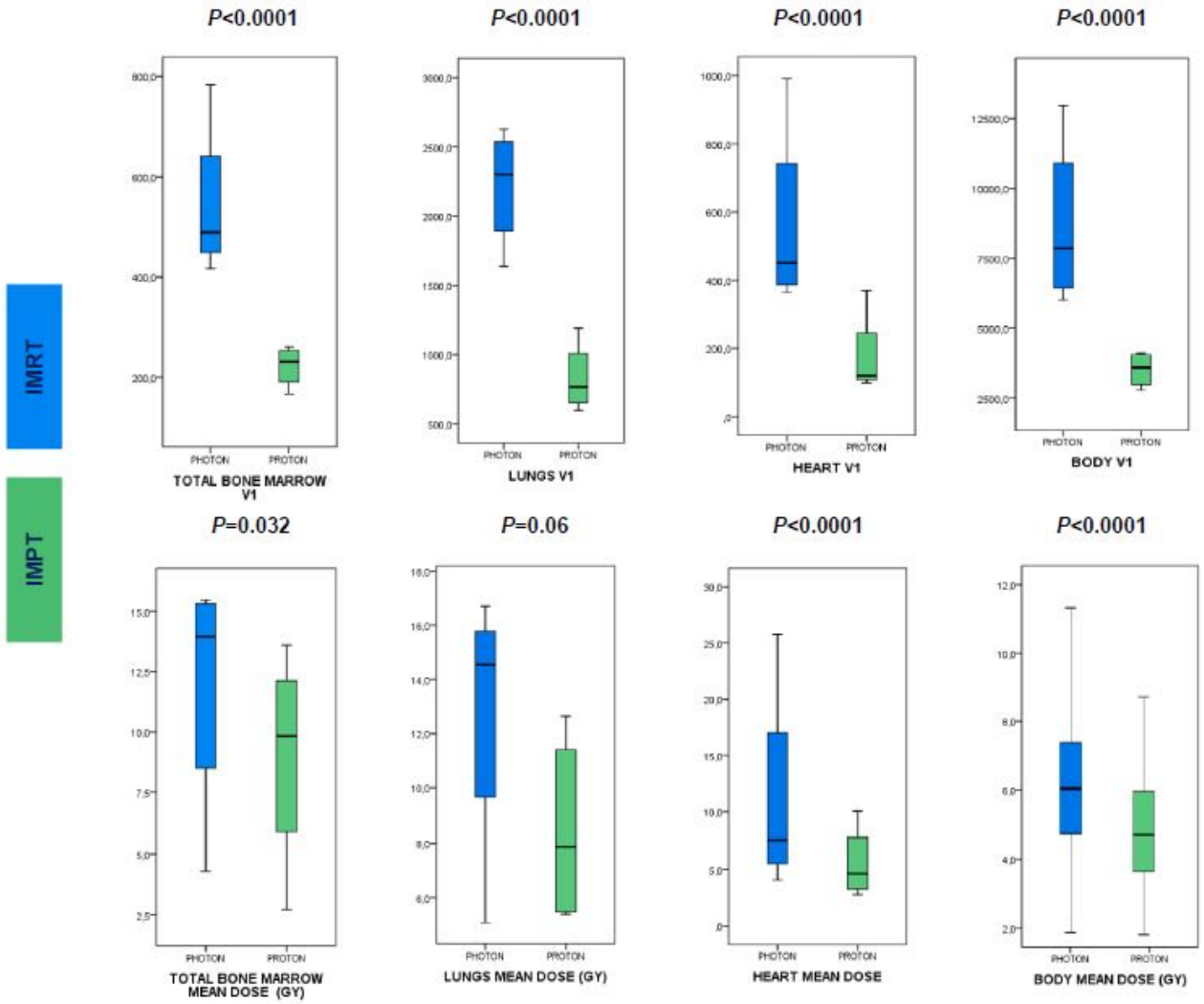
- Sneller starten met adj durvalumab

(Median time from end CCRT and durvalumab: 31 days (PT) vs. 41 days (photons). p=0.013)



IMRT = intensity modulated photon radiotherapy
IMPT = intensity modulated proton therapy

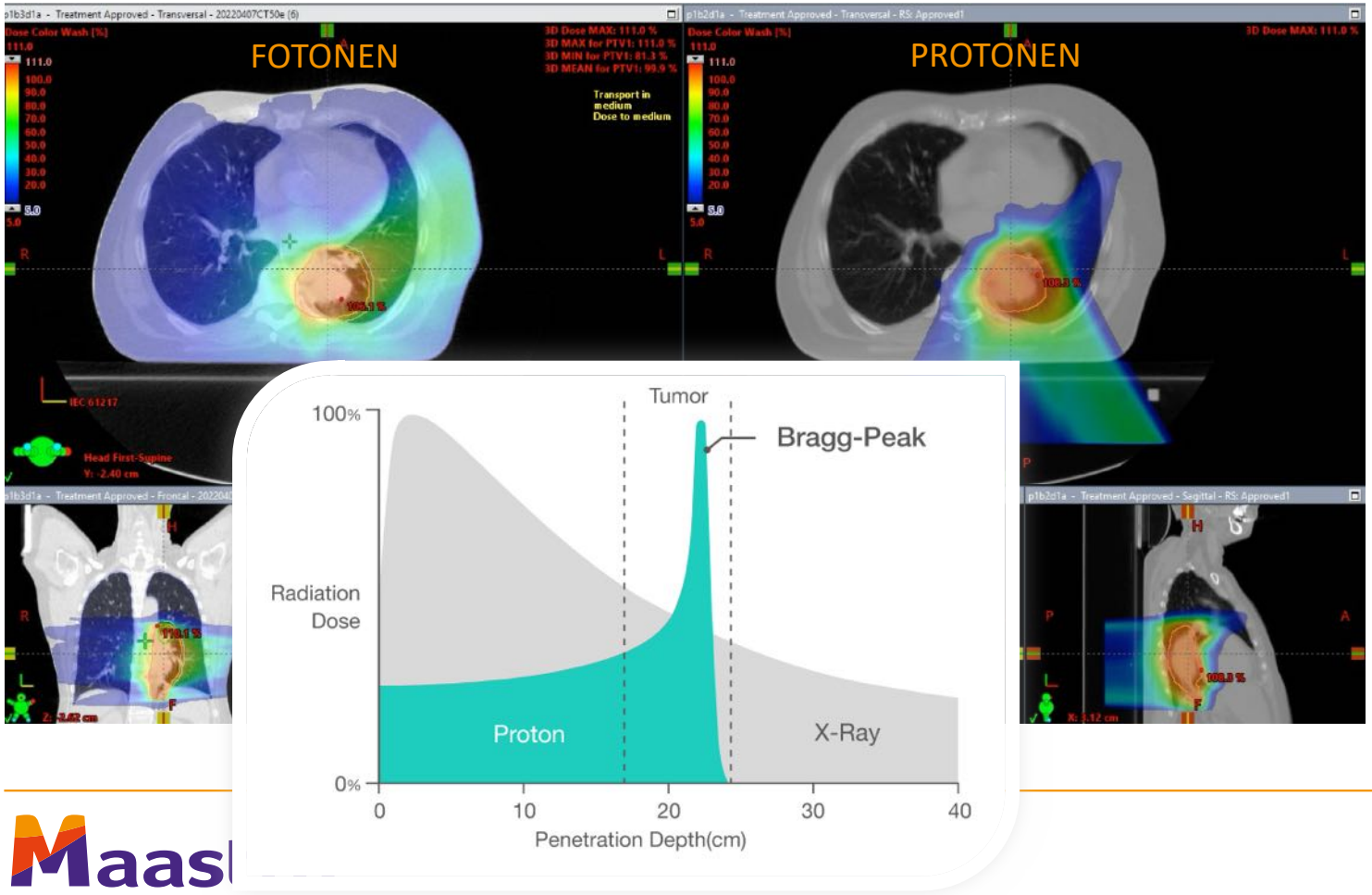
Cortiula et al. Radioth Oncol 2024



Maastro

Cortiula et al. Radioth Oncol 2024

Voorbeeld bestralingsplan: fotonen vs. protonen



Protonen

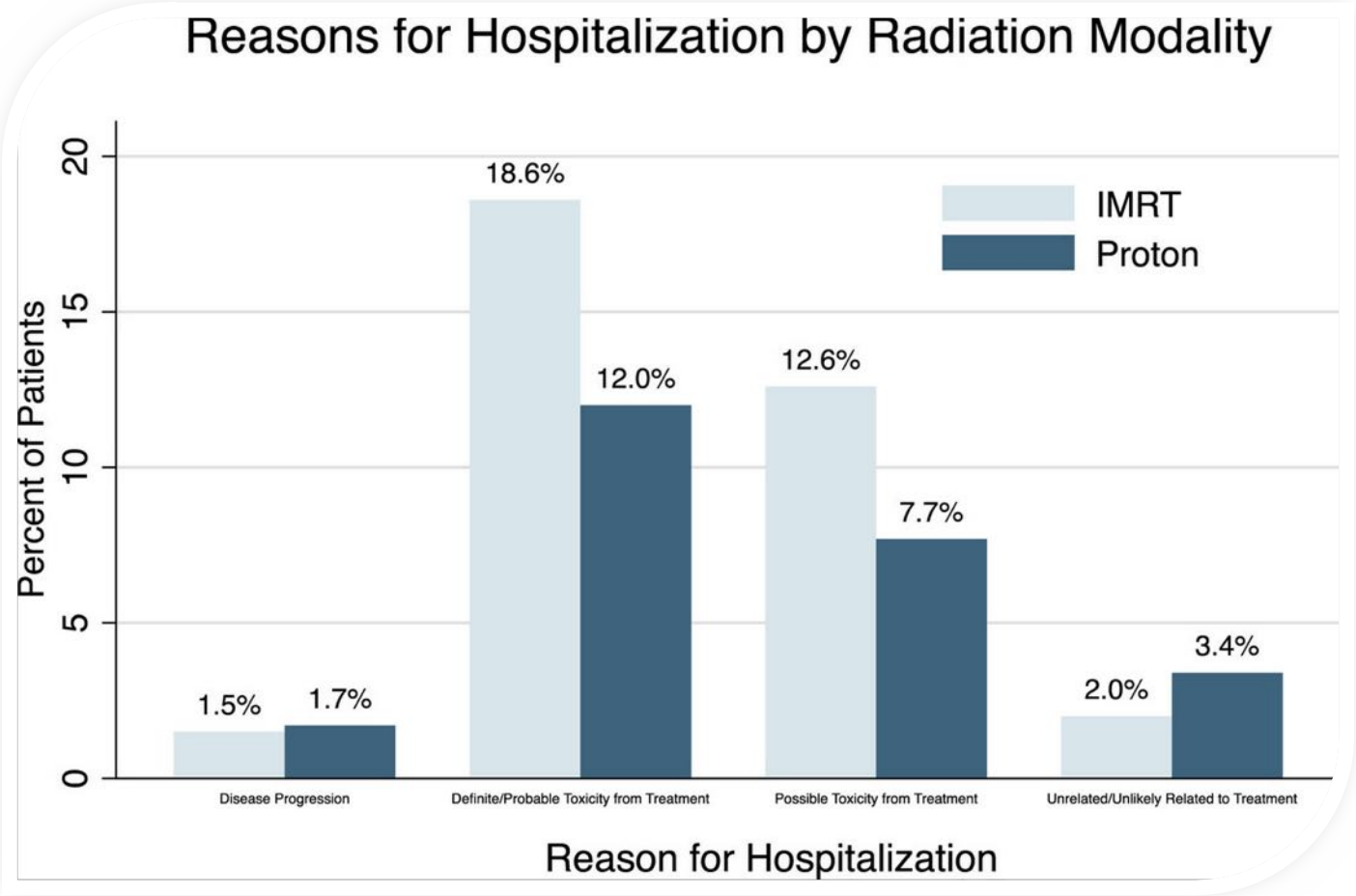
Na cCRT met in st III NSCLC,

met **protonen**:

- Minder ongeplande hospitalisaties (adjusted OR, 0.55; 95% CI, 0.38–0.81; p = .002)

- Minder G3+ lymfopenie

(adjusted OR, 0.55; 95% CI, 0.37–0.81; p = .003)



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Iocolano et al. Cancer 2024

Protonen

RTOG-1308 trial

Title: Phase III RCT comparing photon vs. proton cCRT for inoperable stage II-IIIB NSCLC

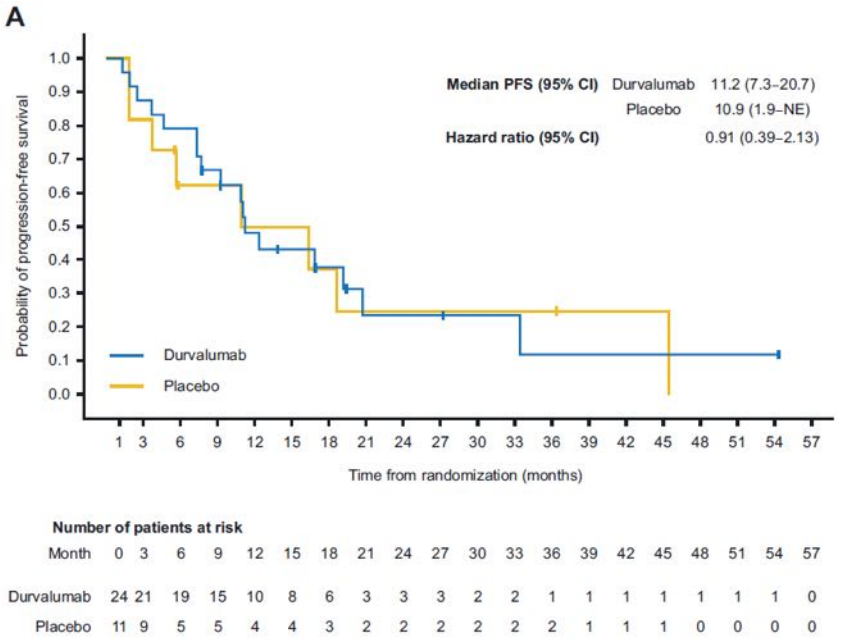
Primary objectives:

- To compare the overall survival (OS) in patients with stage II-IIIB NSCLC after image-guided, motion-managed **photon** radiotherapy (Arm 1) or after image-guided, motion-managed **proton** radiotherapy (Arm 2) both given with concurrent platinum-based chemotherapy
- To compare the cardiac toxicity and lymphopenia

Accrual completed in 2023

EGFR-gemuteerd st III NSCLC

Exploratieve subgroep analyse PACIFIC EGFRm data



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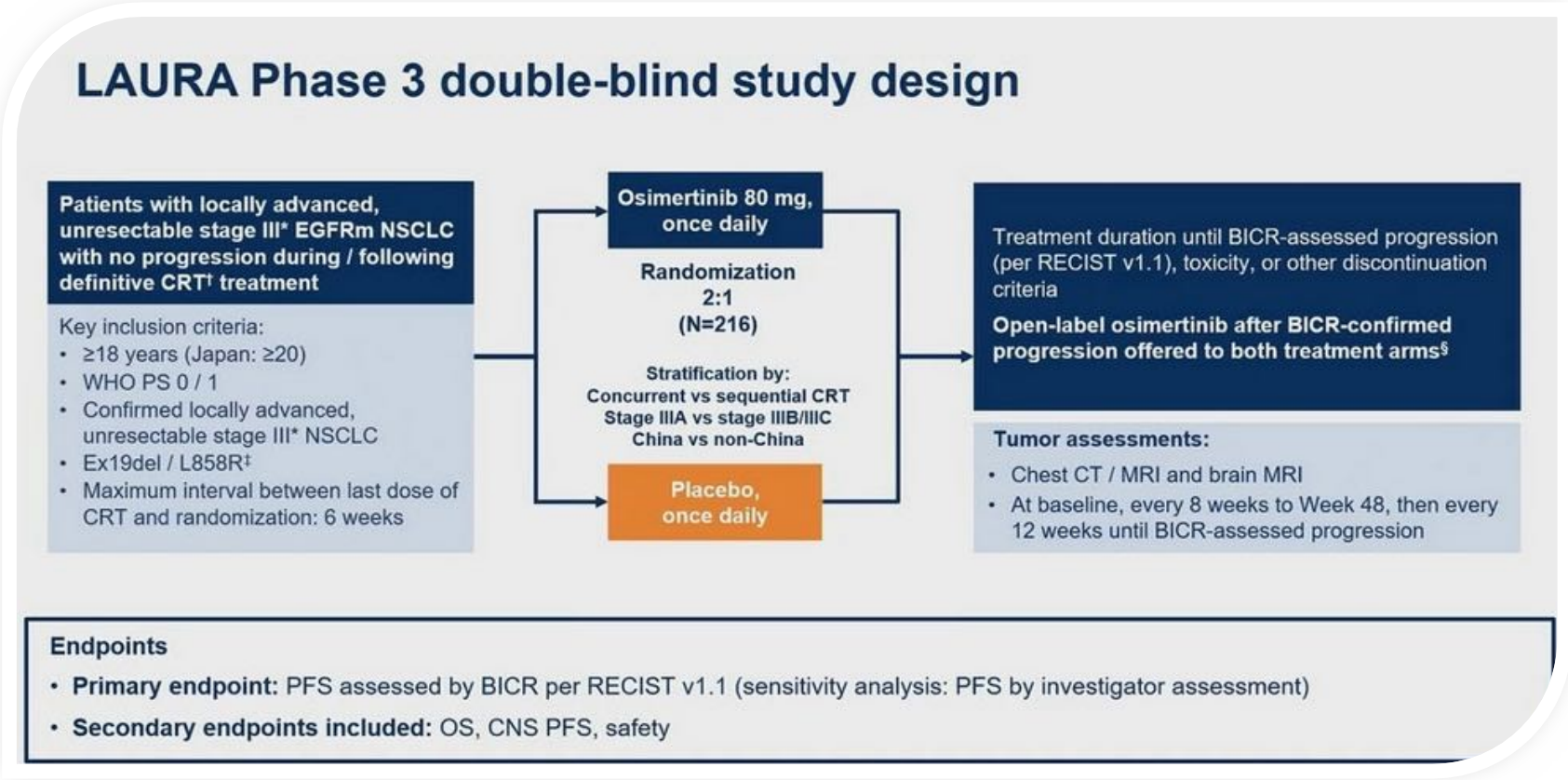
Naidoo et al. JTO 2023

EGFR-gemuteerd st III NSCLC



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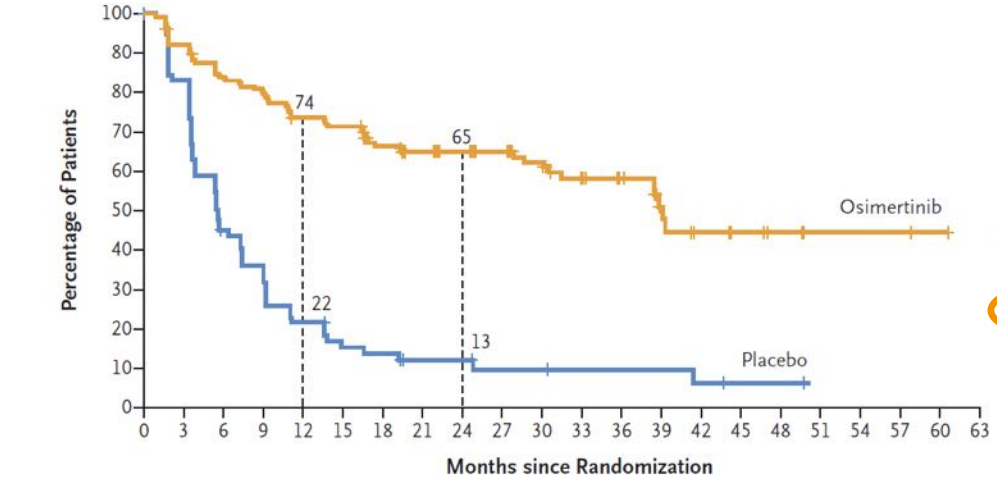
Lu et al. NEJM 2024

EGFR-gemuteerd st III NSCLC

LAURA trial

Osimertinib na cCRT in stage III EGFR-Mutated NSCLC

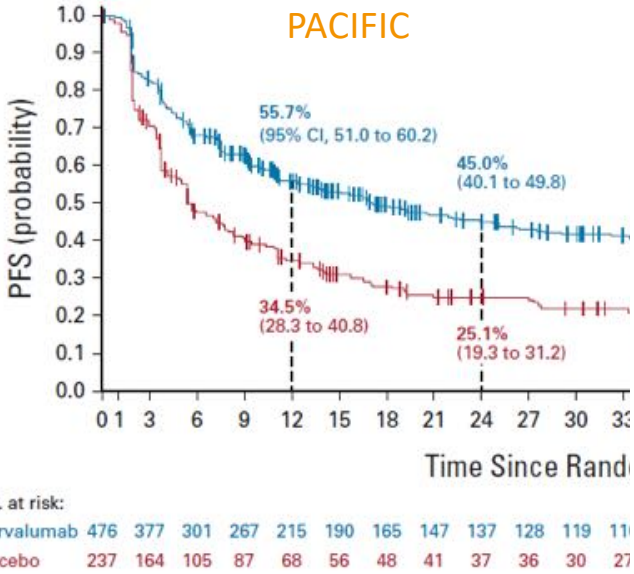


Median Progression-free Survival (95% CI)	*mo*
Osimertinib	39.1 (31.5–NC)
Placebo	5.6 (3.7–7.4)

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

P<0.001

PACIFIC



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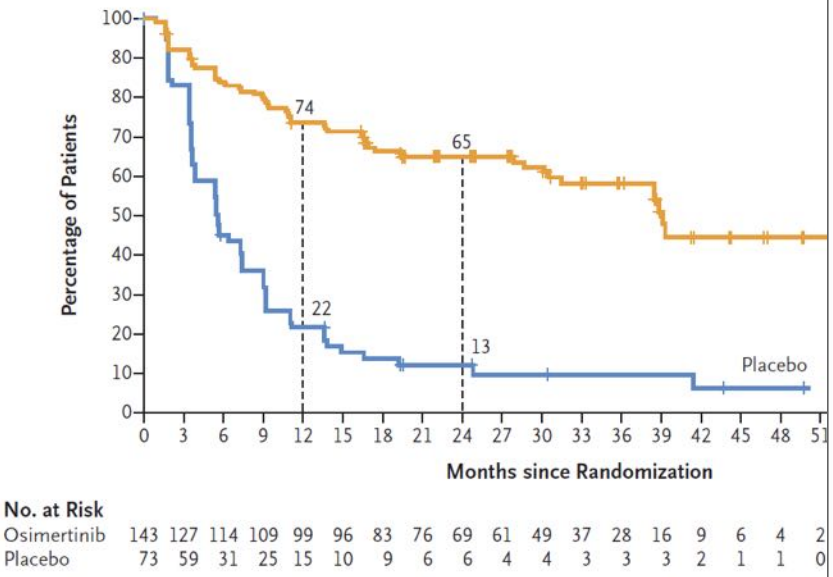
Sept 2024: FDA approval voor exon 19 deletions or exon 21 L858R

Lu et al. NEJM 2024

EGFR-gemuteerd st III NSCLC

LAURA trial

Osimertinib na cCRT in stage III EGFR-Mutated

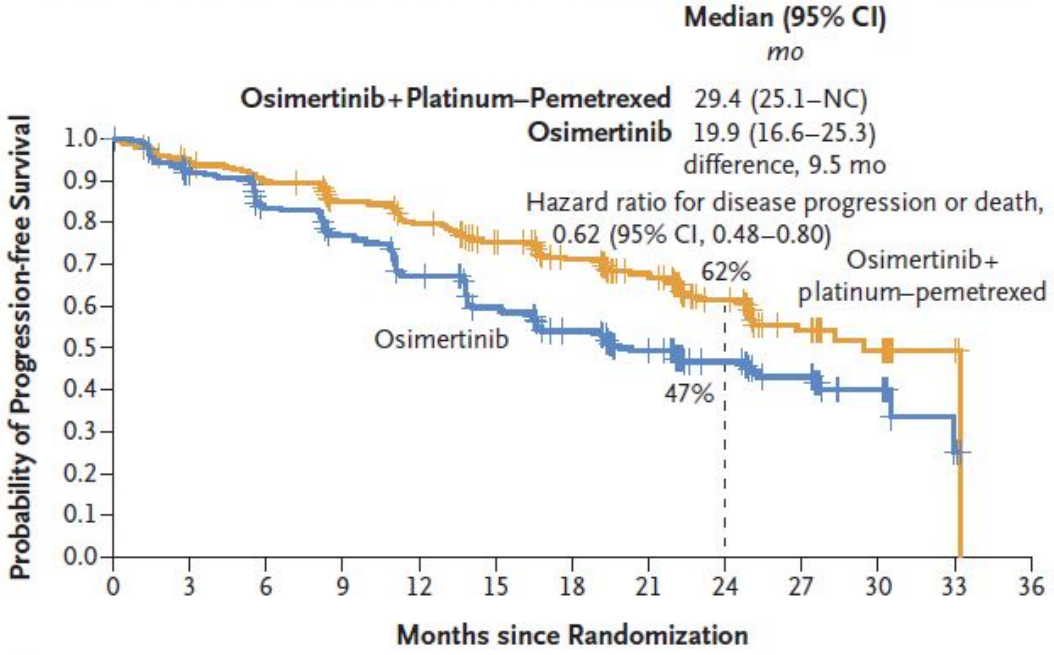


No. at Risk

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

FLAURA2 trial, st IV

B Progression-free Survival According to Blinded Independent Central Review (full analysis set)



No. at Risk

Osimertinib+ platinum–pemetrexed	279	255	242	223	207	184	158	128	81	39	20	3	0
Osimertinib	278	247	218	195	169	139	116	88	59	42	18	2	0

Maastro

Sept 2024: FDA approval voor exon 19 deletions or exon 21 L858R

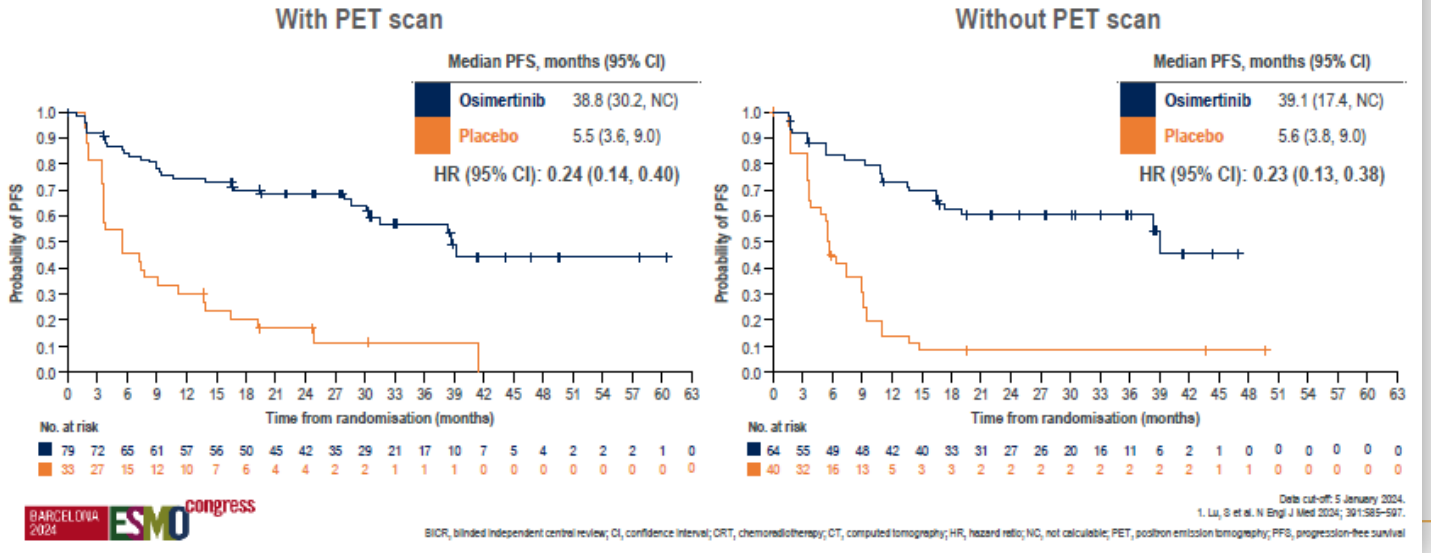
EGFR-gemuteerd st III NSCLC

LAURA trial

Osimertinib na cCRT in stage III EGFR-Mutated NSCLC

BICR-assessed PFS by pre-CRT PET scan

- Pre-CRT PET-CT staging scans were recommended but not mandatory, since diagnosis of unresectable stage III disease prior to CRT was determined by the investigator per local clinical practice
- PFS benefit with osimertinib vs placebo was consistent with or without pre-CRT staging by PET scan, and consistent with the primary PFS data[1]



BARCELONA 2024 ESMO congress

Data cut-off: 5 January 2024.

1. Lu S et al. N Engl J Med 2024; 391:585–597.

BICR, blinded independent central review; CI, confidence interval; CRT, chemoradiotherapy; CT, computed tomography; HR, hazard ratio; NC, not calculable; PET, positron emission tomography; PFS, progression-free survival

Maastro

Ahn et al. 1241MO, ESMO 2024

Conclusie

- Postoperatieve radiotherapie is enkel nog geïndiceerd bij onvolledige resectie/positief snijvlak
- Relatieve winst van immunotherapie op locoregionale recidieven lijkt gelijkaardig na concurrente chemoradio en preop chemo-immunotherapie
- Standaard adjuvant durvalumab na concurrente CRT, tenzij EGFRm → adjuvant osimertinib (*of chemo-TKI zonder RT?)*
- Standaard adjuvant durvalumab na sequentiële CRT (tenzij EGFRm), maar geen RCT
- Wat met inductie chemo-immuno gevolgd door RT?
- Radiotherapie zonder chemo: rol van immuuntherapie?
- Protonen: impact op lymfopenie, conditie, gebruik van adj durvalumab

Maastro