Updates in Locally Advanced *Unresectable* Stage III NSCLC

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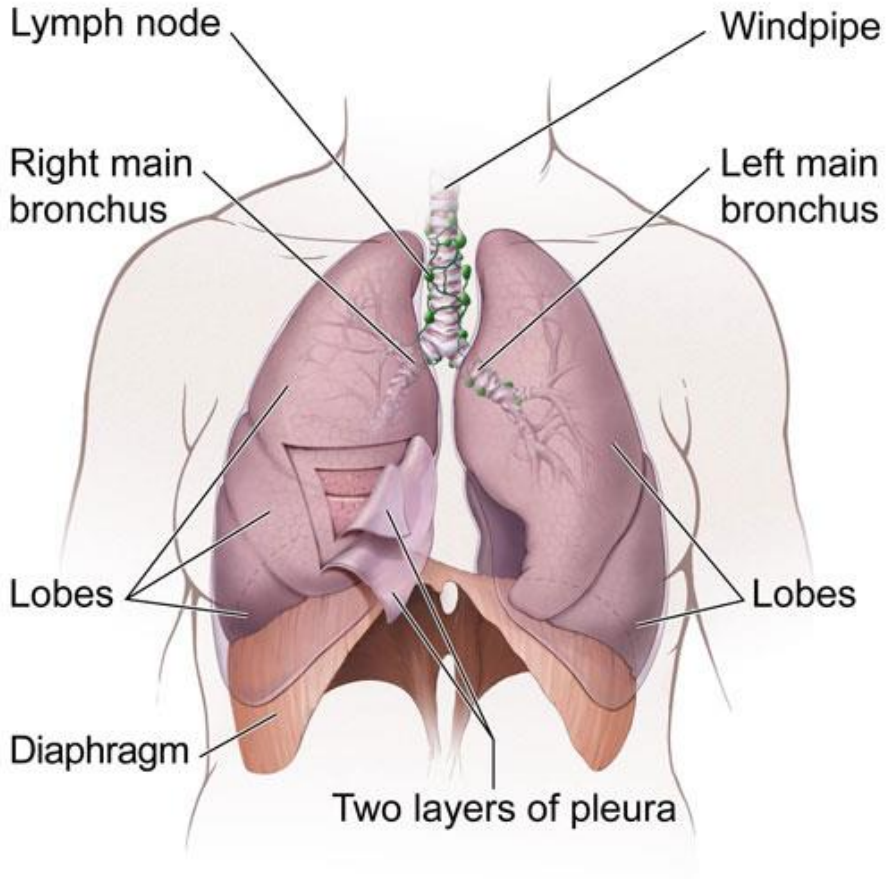
What is *unresectable?*

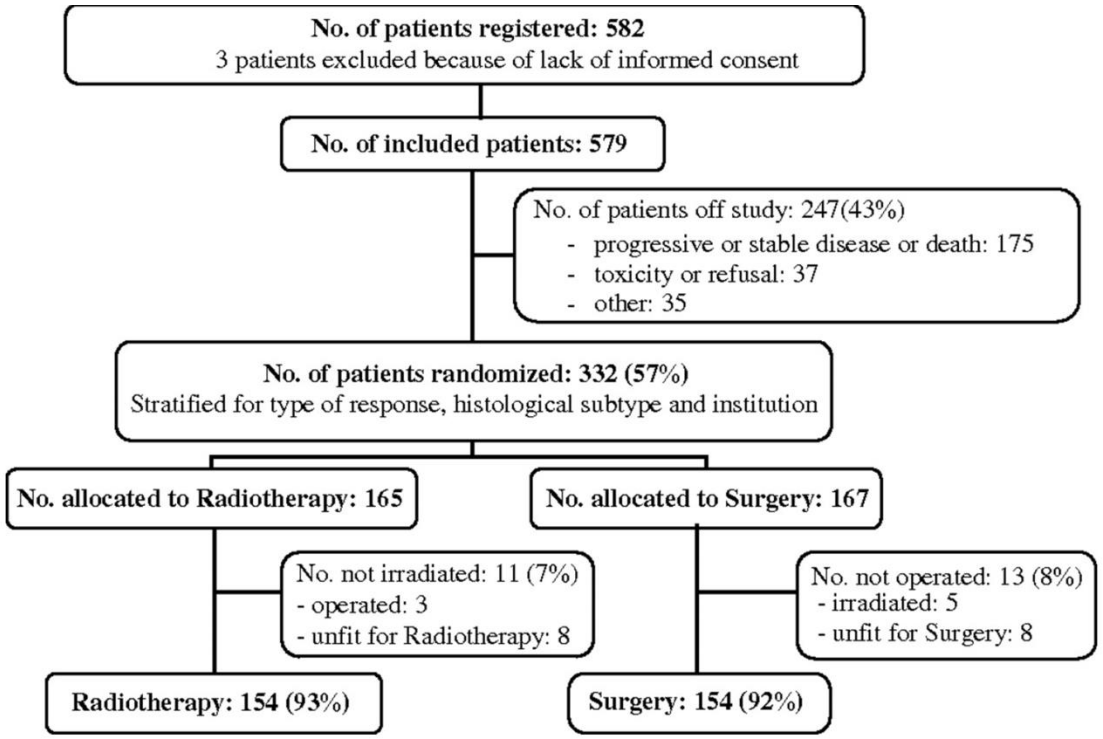
- All NCCN Member Institutions treat select N2 patients with multimodality therapy that includes surgery.
- All NCCN Member Institutions consider surgery for single-station non-bulky N2 disease.
- Approximately half of the institutions consider surgery for single-station bulky disease, 39% for multi-station non-bulky disease, and 21% for multi-station bulky disease.
- Two-thirds of NCCN Member Institutions prefer induction chemotherapy; one-third prefer chemoradiation.

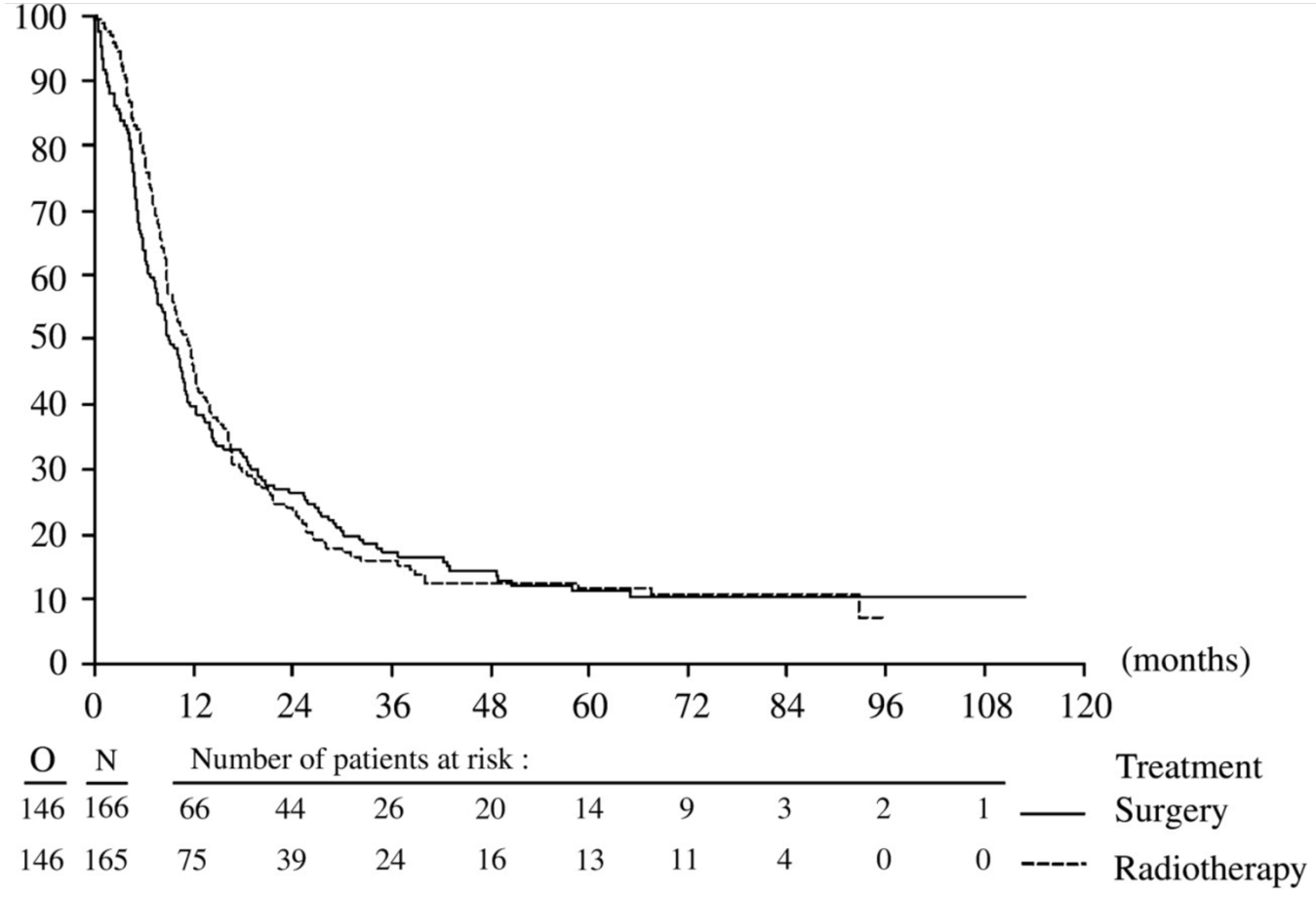


NCCN Guidelines Version 7.2024

Is surgery essential for N2 disease?

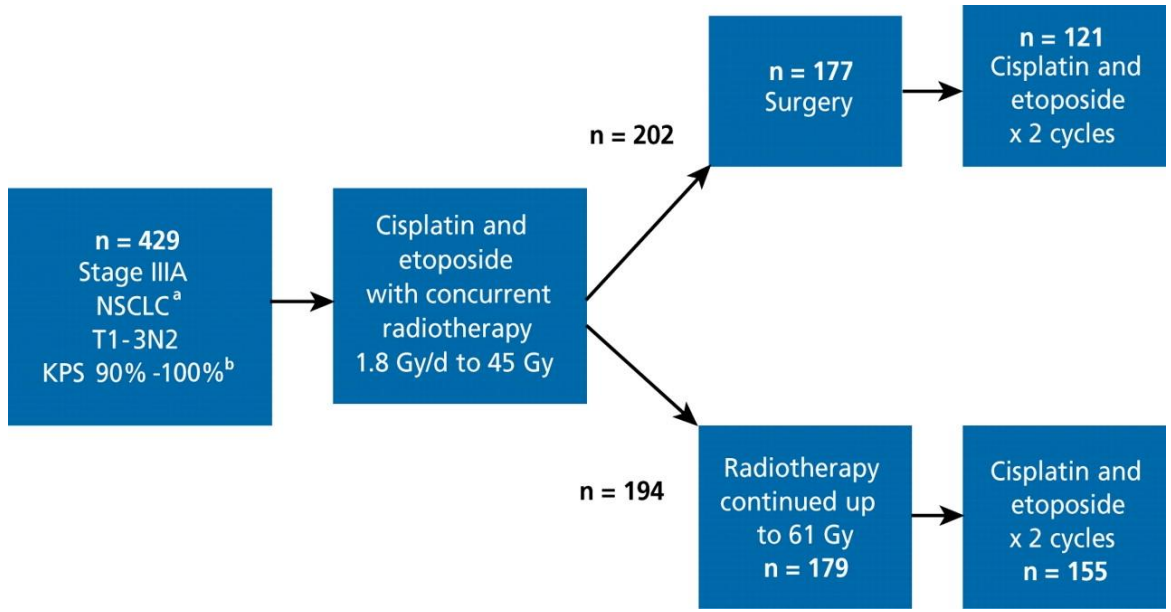
EORTC 8941





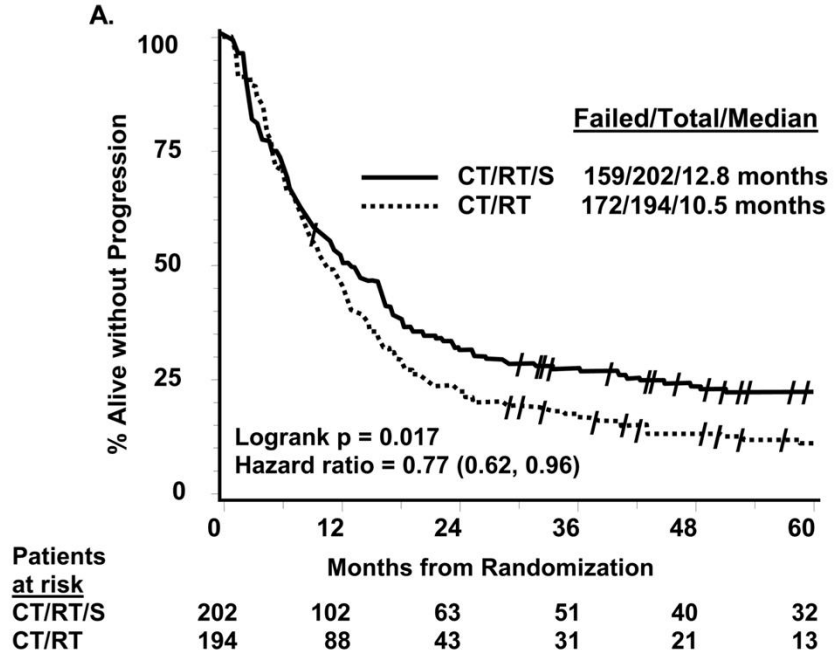
JNCI: Journal of the National Cancer Institute, Volume 99, Issue 6, 21 March 2007

Intergroup 0139



Lancet 2009 Aug 1;374(9687):379-86. 24.

PFS



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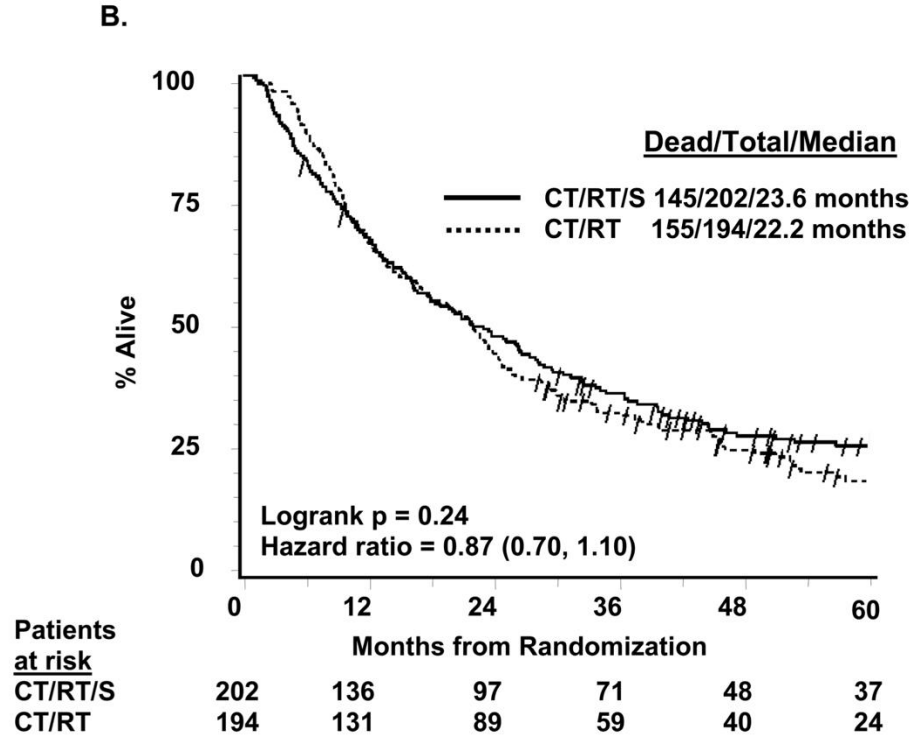
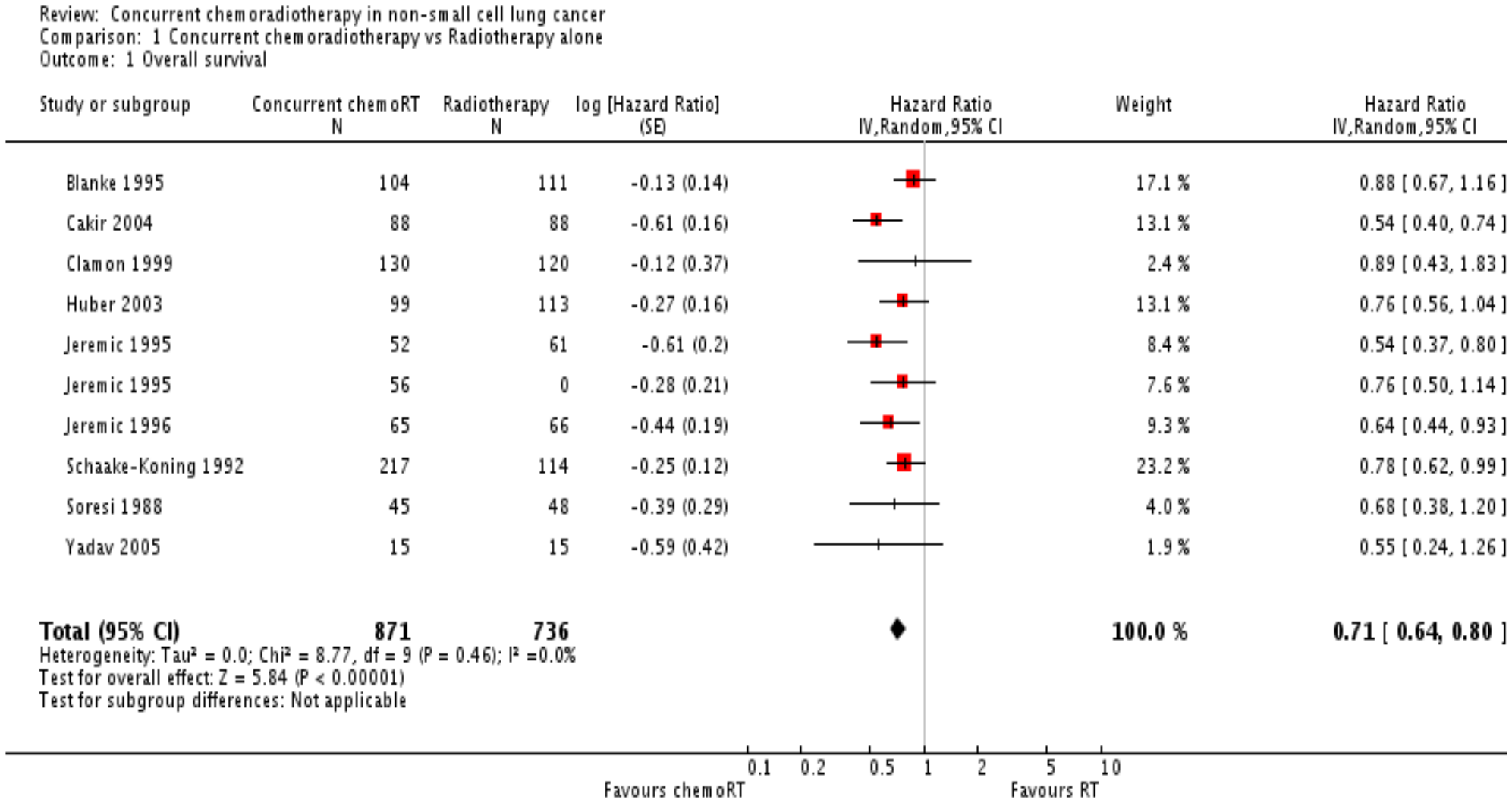


Concurrent Chemoradiation vs. Radiation alone in stage III NSCLC: Cochrane Systematic Review



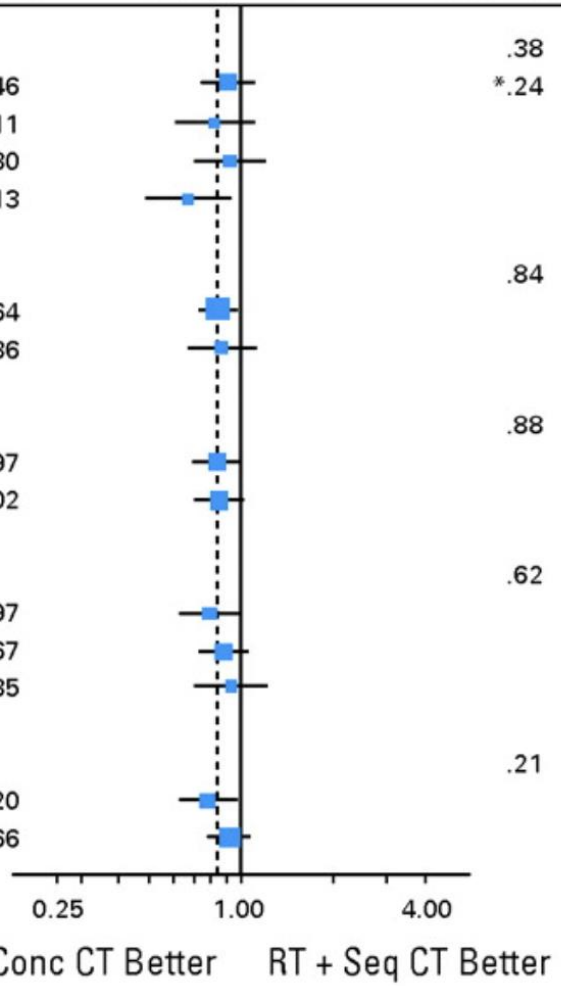
Cochrane Database of Systematic Reviews 2010

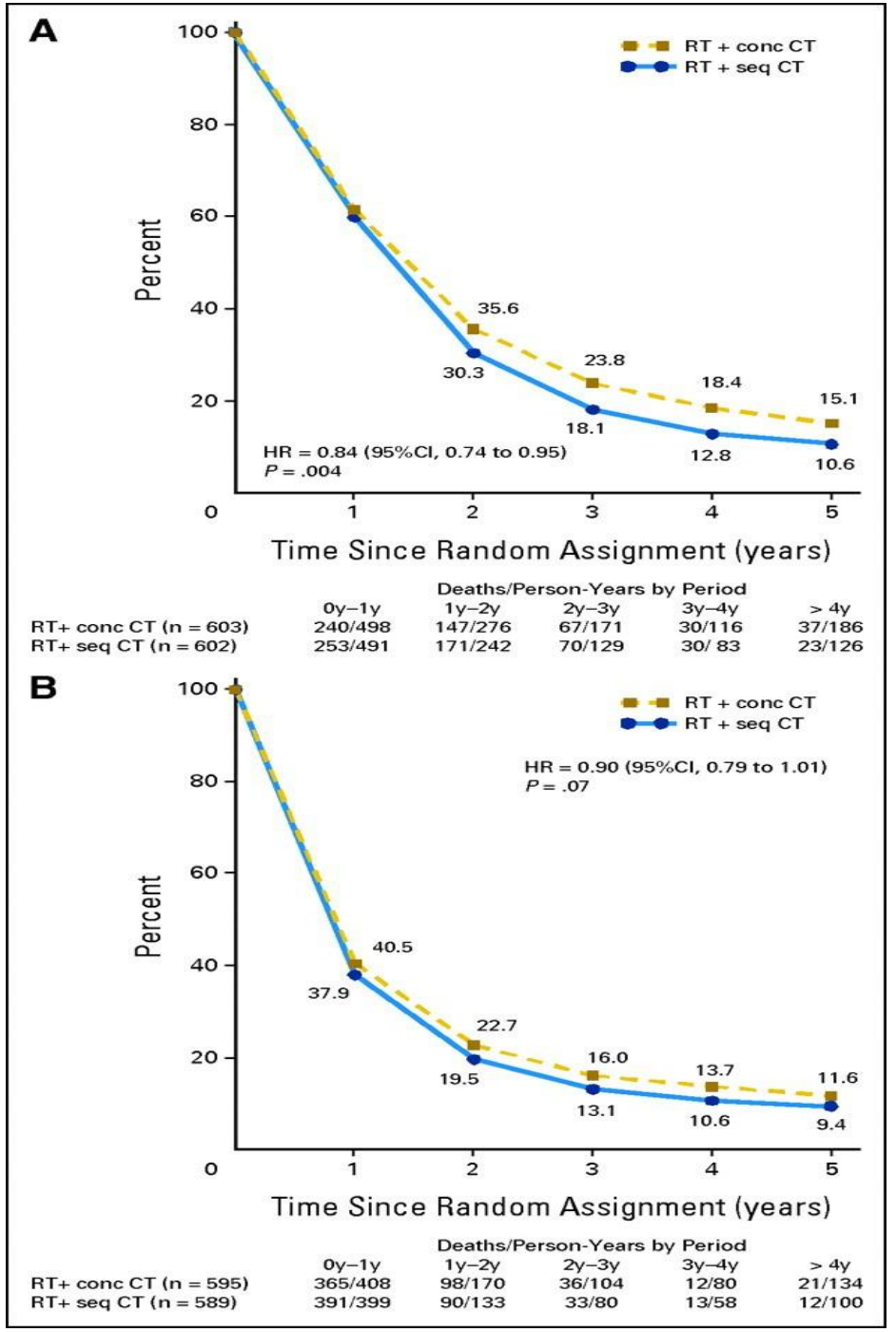
Concurrent vs. Sequential Chemoradiation: Meta-analysis

Aupérin et al. JCO 2010;28:2181-2190

C

Category	No. Deaths/ No. Entered RT + Conc CT	RT + Seq CT	Hazard Ratio	*P* of Interaction trend* test
Age				.38
Less than 60	239/273	217/246		*.24
60-64	95/114	100/111		
65-69	123/140	122/130		
70 or over	64/76	106/113		
Gender				.84
Male	396/457	423/464		
Female	124/144	124/136		
Performance Status				.88
PS = 0	265/309	268/297		
PS ≥ 1	254/291	278/302		
Histology				.62
Adenocarcinoma	164/198	181/197		
Squamous	254/282	244/267		
Other	102/121	121/135		
Stage				.21
Stage IIIA	186/221	200/220		
Stage IIIB	325/369	333/366		



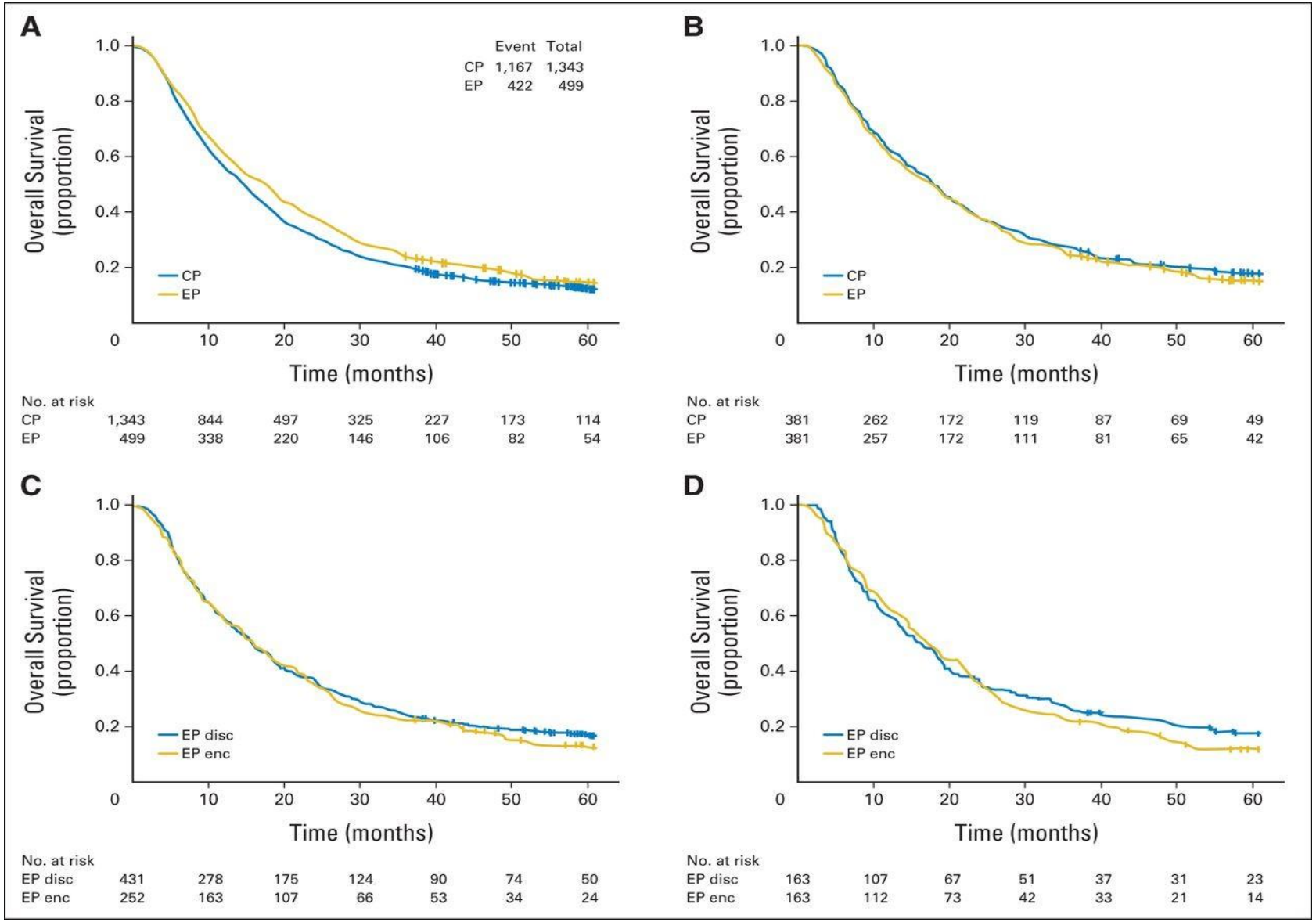


Chemoradiation +/- Consolidation Chemotherapy in stage III NSCLC

Study	Year	Strategy	No.	MST (mos)	3 or 4 yr OS
HOG/USO	2007	EP/XRT EP/XRT ? Docetaxel	203	23.2 21.2	26.1% 27.1%
GILT	2012	PV/XRT PV/XRT PV	165	20.8 18.5	25.3% 21.4%
Park	2014	P/Docetaxel/XRT P/Docetaxel/XRT>P/Docetaxel	419	20.6 21.2	NR

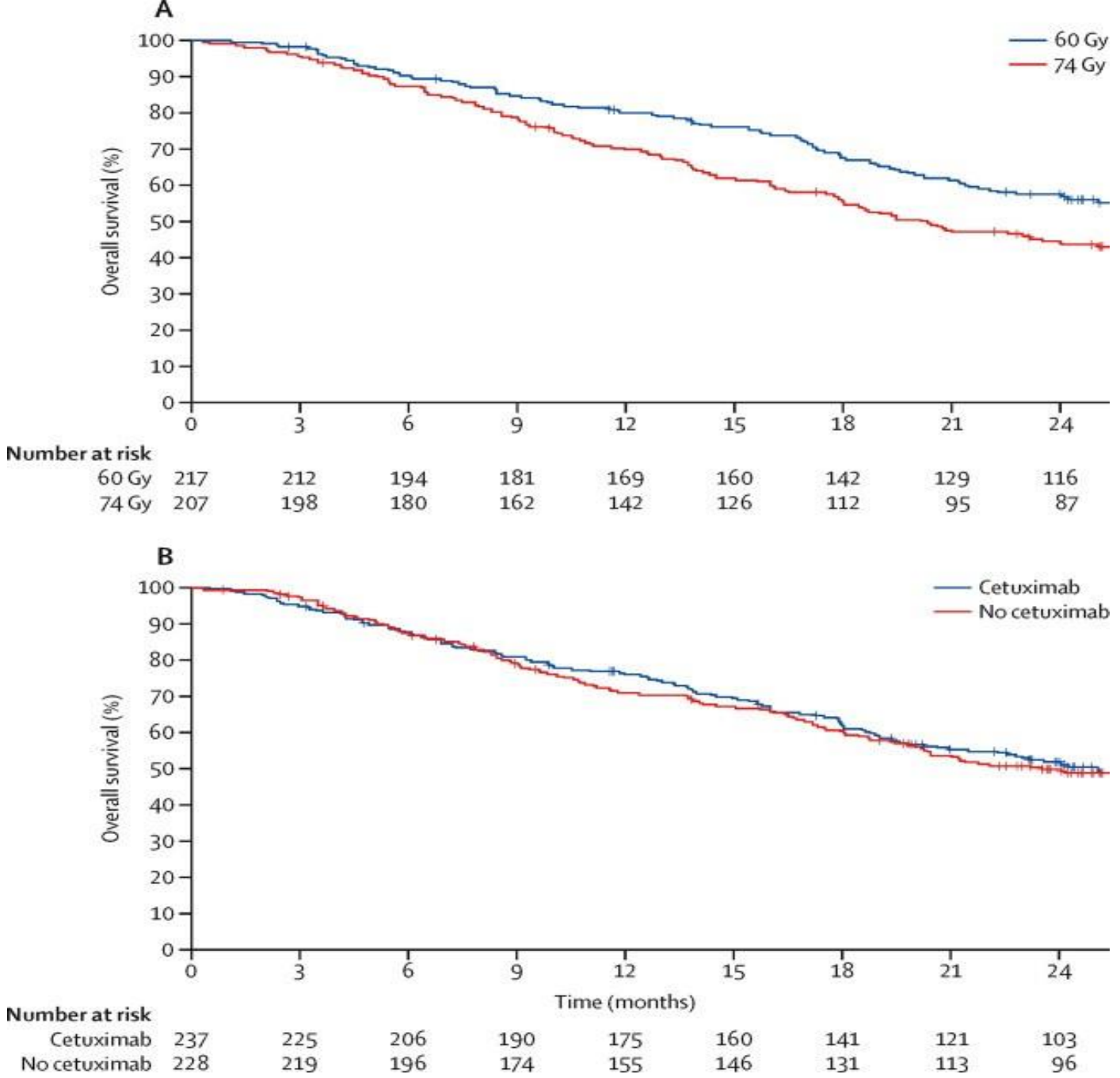
Cisplatin/Etoposide /XRT vs. Carboplatin/Paclitaxel/XRT: Retrospective Analysis of Veteran's Health Administration Data

Santana-Davila et al, JCO 2014



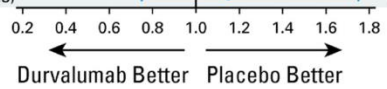
60 vs. 74 Gy XRT + concurrent and consolidation chemo +/- cetuximab in stage III NSCLC

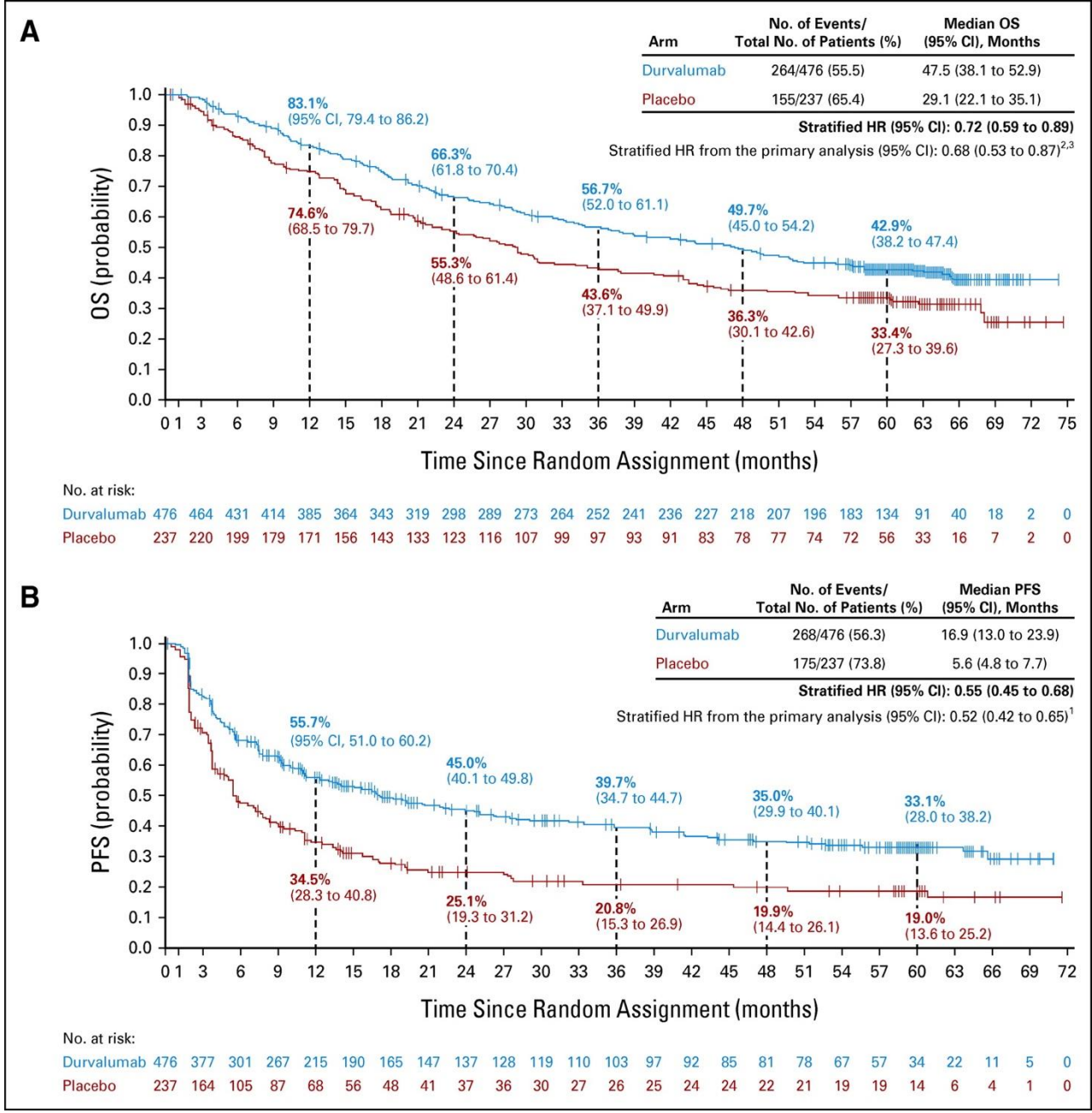
Bradley et al, Lancet Oncology 2015;16:187-199



Pacific 5-year follow-up

Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
All patients	264/476 (55.5)	155/237 (65.4)	0.72 (0.59 to 0.87)
Sex			
Male	192/334 (57.5)	112/166 (67.5)	0.75 (0.59 to 0.95)
Female	72/142 (50.7)	43/71 (60.6)	0.64 (0.44 to 0.94)
Age at random assignment			
< 65 years	130/261 (49.8)	79/130 (60.8)	0.66 (0.50 to 0.87)
≥ 65 years	134/215 (62.3)	76/107 (71.0)	0.79 (0.60 to 1.05)
Smoking status			
Smoker	244/433 (56.4)	140/216 (64.8)	0.75 (0.61 to 0.93)
Nonsmoker	20/43 (46.5)	15/21 (71.4)	0.42 (0.21 to 0.82)
NSCLC disease stage			
IIIA	136/252 (54.0)	91/125 (72.8)	0.61 (0.47 to 0.80)
IIIB	121/212 (57.1)	61/107 (57.0)	0.86 (0.63 to 1.17)
Tumor histologic type			
Squamous	138/224 (61.6)	67/102 (65.7)	0.82 (0.61 to 1.09)
All other	126/252 (50.0)	88/135 (65.2)	0.62 (0.47 to 0.81)
Best response to prior treatment			
Complete response	6/9 (66.7)	3/7 (42.9)	Not calculated[a]
Partial response	118/237 (49.8)	68/112 (60.7)	0.71 (0.52 to 0.95)
Stable disease	135/223 (60.5)	81/115 (70.4)	0.70 (0.53 to 0.92)
Prior chemotherapy type			
Gemcitabine-based	5/9 (55.6)	2/5 (40.0)	Not calculated[a]
Non–gemcitabine-based	259/467 (55.5)	153/232 (65.9)	0.70 (0.58 to 0.86)
Cisplatin	134/266 (50.4)	81/129 (62.8)	0.65 (0.50 to 0.86)
Carboplatin	121/199 (60.8)	69/102 (67.6)	0.81 (0.60 to 1.09)
Cisplatin and carboplatin	6/8 (75.0)	4/5 (80.0)	Not calculated[a]
Last radiation to random assignment			
< 14 days	64/120 (53.3)	43/62 (69.4)	0.54 (0.37 to 0.80)
≥ 14 days	200/356 (56.2)	112/175 (64.0)	0.79 (0.63 to 1.00)
WHO PS			
0 – Normal	121/234 (51.7)	65/114 (57.0)	0.84 (0.62 to 1.14)
1 – Restricted[b]	143/242 (59.1)	90/123 (73.2)	0.62 (0.47 to 0.80)
Region			
Asia	54/109 (49.5)	37/68 (54.4)	0.79 (0.52 to 1.20)
Europe	125/217 (57.6)	64/102 (62.7)	0.84 (0.62 to 1.14)
North and South America	85/150 (56.7)	54/67 (80.6)	0.47 (0.34 to 0.67)
Race			
White	200/337 (59.3)	110/157 (70.1)	0.72 (0.57 to 0.91)
Black or African American	5/12 (41.7)	2/2 (100)	Not calculated[a]
Asian	56/120 (46.7)	39/72 (54.2)	0.73 (0.48 to 1.09)
Other[c]	3/6 (50.0)	4/6 (66.7)	Not calculated[a]
EGFR or *ALK* aberration status			
Positive[d]	17/29 (58.6)	8/14 (57.1)	0.85 (0.37 to 1.97)
Negative	166/317 (52.4)	109/165 (66.1)	0.66 (0.52 to 0.84)
Unknown	81/130 (62.3)	38/58 (65.5)	0.85 (0.57 to 1.24)
PD-L1 expression level			
≥ 25%	51/115 (44.3)	27/44 (61.4)	0.52 (0.32 to 0.82)
< 25%	111/187 (59.4)	64/105 (61.0)	0.90 (0.67 to 1.23)
Unknown	102/174 (58.6)	64/88 (72.7)	0.68 (0.50 to 0.93)
1%-24% (post hoc analysis)	52/97 (53.6)	29/47 (61.7)	0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis)	103/212 (48.6)	56/91 (61.5)	0.61 (0.44 to 0.85)
< 1% (post hoc analysis)	59/90 (65.6)	35/58 (60.3)	1.15 (0.75 to 1.75)





Spigeel DR. J Clin Oncol. 2022 Apr 20;40(12):1301-1311.

PD-L1

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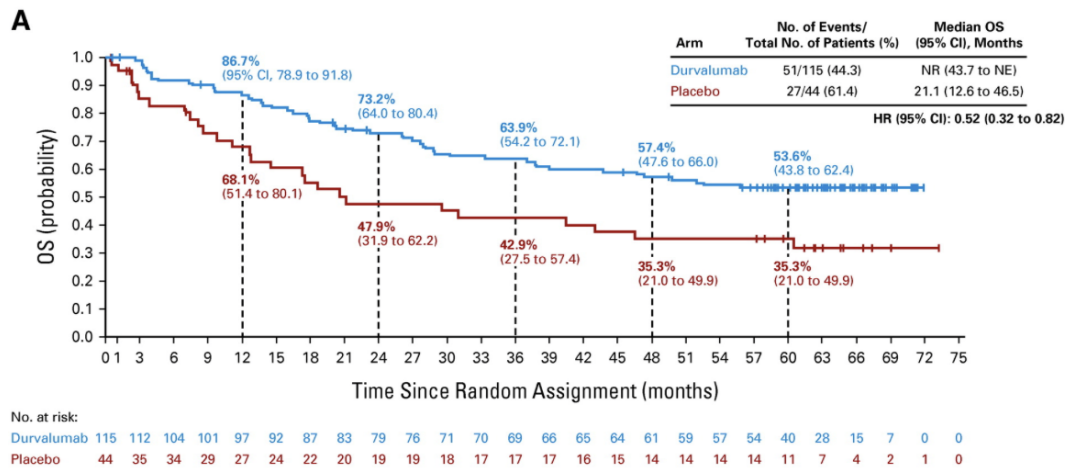

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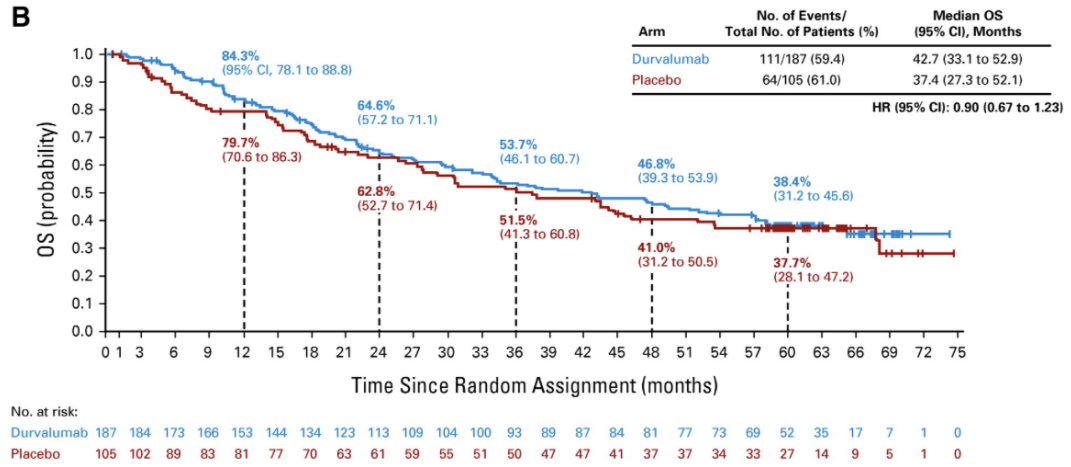

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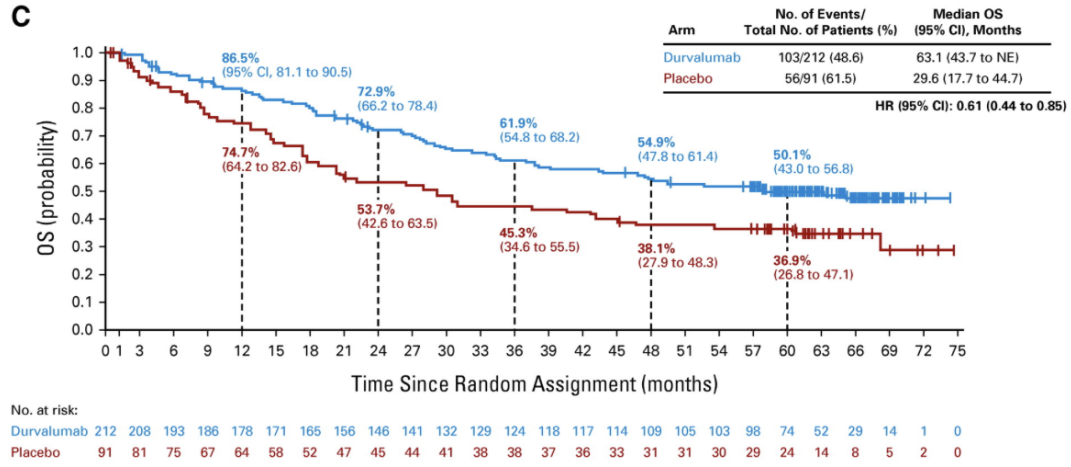

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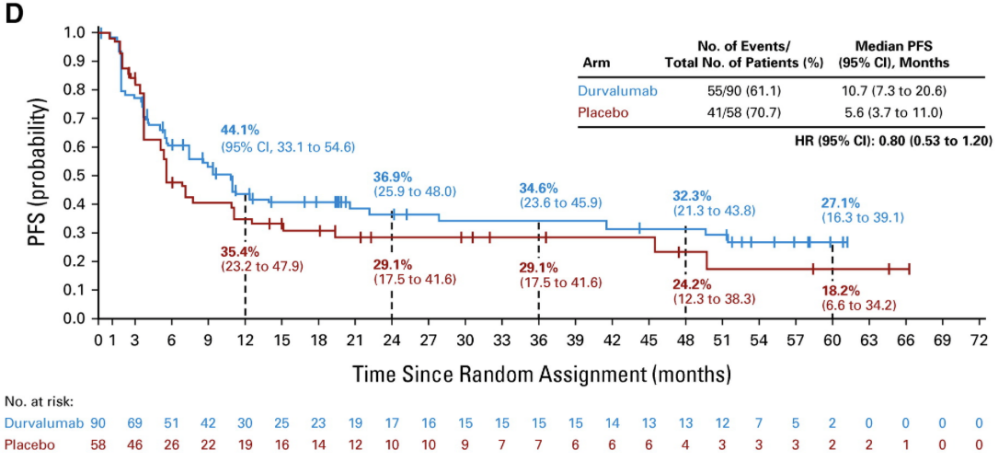

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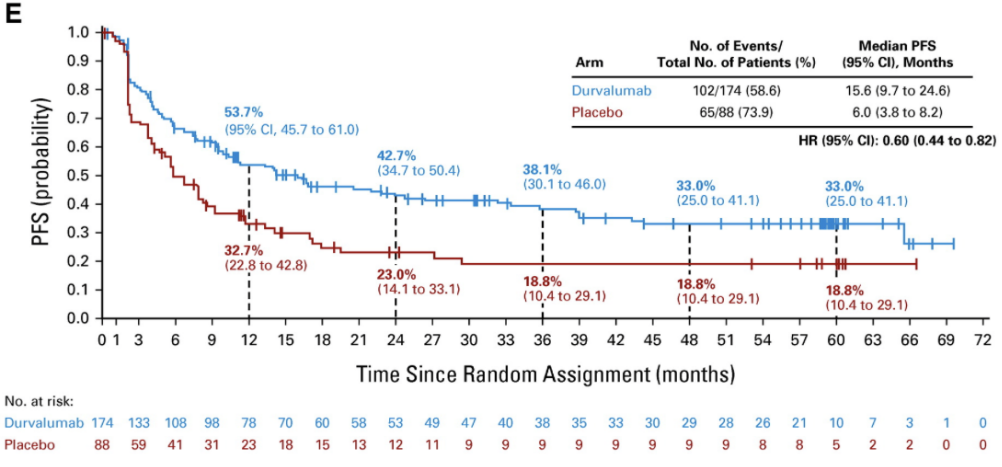

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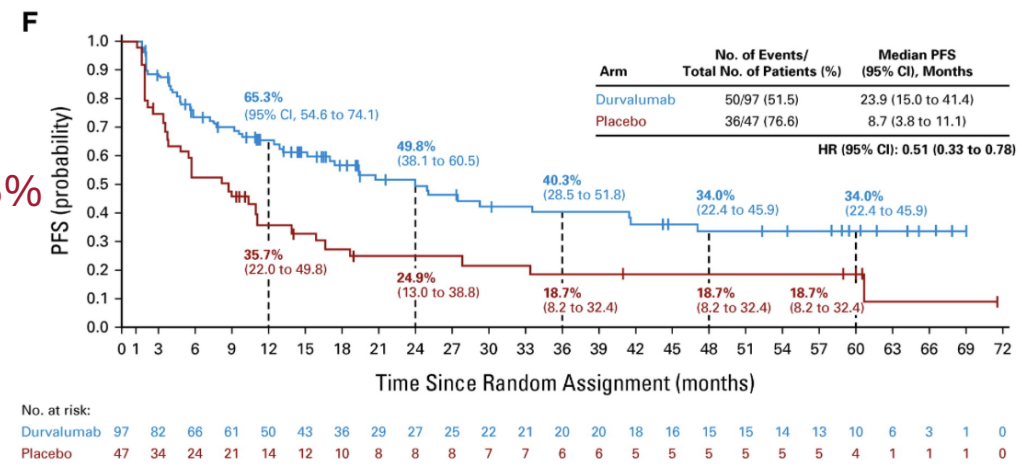
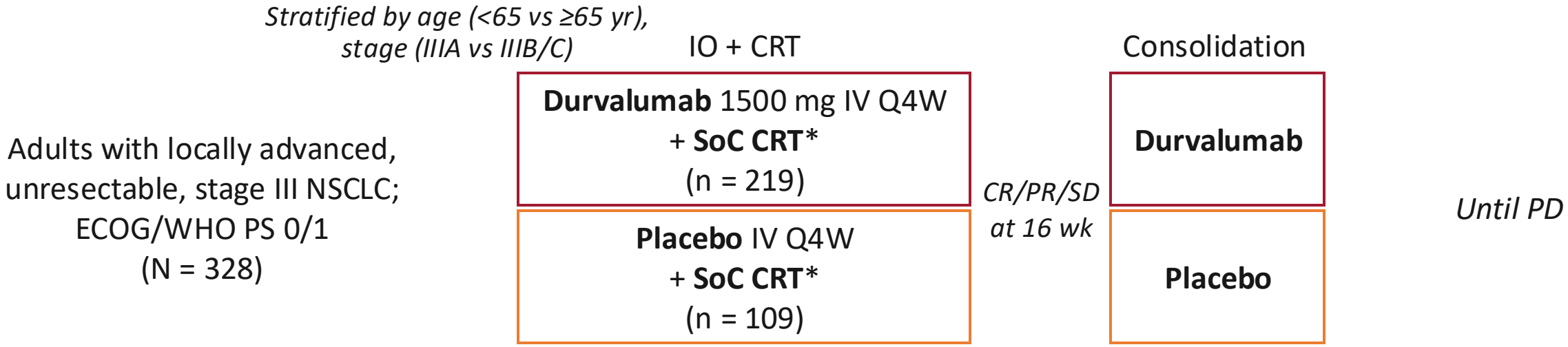


PACIFIC-2: Study Design

- Randomized, international, double-blind phase III trial (data cutoff: Sept 7, 2023; median follow-up: 30.5 mo)



*Platinum-based CT regimens included cis/etoposide, carbo/pac, pem/cis (nonsquamous), pem/carbo (nonsquamous). RT comprised 5 fractions/wk x ~6 wk ± 3 d (total 60 Gy).

Primary endpoint: PFS by BICR per RECIST v1.1

Key secondary endpoints: OS, ORR, OS24, PFS2, DoR, time to death/distant metastasis, DCR, PK, HRQoL, safety

Bradley. ELCC 2024. Abstr LBA1.

PACIFIC-2: Baseline Characteristics

Characteristics, n (%)		Durva + CRT (n = 219)	Pbo + CRT (n = 109)
Age group	▪ <50 yr	18 (8.2)	12 (11.0)
	▪ ≥50 to <65 yr	107 (48.9)	50 (45.9)
	▪ ≥65 to <75 yr	75 (34.2)	40 (36.7)
	▪ ≥75 yr	19 (8.7)	7 (6.4)
Median age, yr (range)		63.0 (36-84)	63.0 (38-84)
Male		166 (75.8)	80 (73.4)
Race			
▪ White		141 (64.4)	62 (56.9)
▪ Black		2 (0.9)	0
▪ Asian		65 (29.7)	39 (35.8)
▪ American Indian or Alaska Native		7 (3.2)	7 (6.4)
▪ Other		4 (1.8)	1 (0.9)
ECOG/WHO PS 1		121 (55.3)	56 (51.4)
Squamous histology		121 (55.3)	52 (47.7)
PD-L1 status*	▪ <1%	86 (39.3)	36 (33.0)
	▪ ≥1%	113 (51.6)	60 (55.0)
	▪ Unknown	20 (9.1)	13 (11.9)

Characteristics, n (%)		Durva + CRT (n = 219)	Pbo + CRT (n = 109)
EGFR mutation	▪ Positive	7 (3.2)	6 (5.5)
	▪ Negative	112 (51.1)	60 (55.0)
	▪ Unknown	100 (45.7)	43 (39.4)
AJCC stage (8th ed)	▪ IIIA	76 (34.7)	37 (33.9)
	▪ IIIB	109 (49.8)	51 (46.8)
	▪ IIIC	33 (15.1)	20 (18.3)
	▪ IV	1 (0.5)	1 (0.9)
Primary tumor	▪ TX	2 (0.9)	1 (0.9)
	▪ T1	15 (6.8)	10 (9.2)
	▪ T2	37 (16.9)	13 (11.9)
	▪ T3	39 (17.8)	32 (29.4)
	▪ T4	126 (57.5)	53 (48.6)
Regional LNs	▪ N0	25 (11.4)	7 (6.4)
	▪ N1	16 (7.3)	14 (12.8)
	▪ N2	124 (56.6)	60 (55.0)
	▪ N3	54 (24.7)	28 (25.7)
M1b		1 (0.5)	1 (0.9)

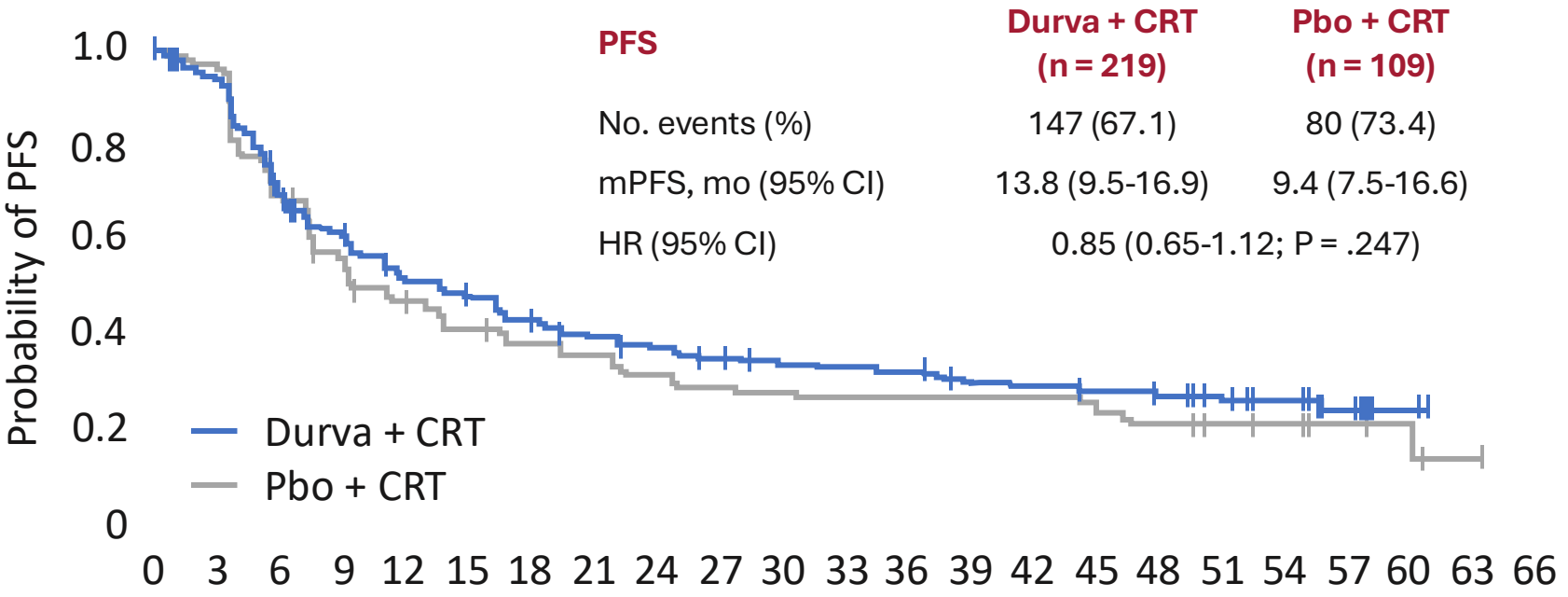
PACIFIC-2: Patient Disposition

CRT Disposition, n (%)	Durva + CRT (n = 219)	Pbo + CRT (n = 109)
Received CRT	218 (99.5)	109 (100)
▪ Cis/etoposide	11 (5.0)	11 (10.1)
▪ Carbo/pac	166 (75.8)	81 (74.3)
▪ Pem/cis	18 (8.2)	8 (7.3)
▪ Pem/carbo	23 (10.5)	9 (8.3)
▪ RT	215 (98.2)	107 (98.2)
Completed CRT	192 (88.1)	99 (90.8)
Discontinued CRT	26 (11.9)	10 (9.2)
▪ AE	20 (9.2)	5 (4.6)
▪ PD	4 (1.8)	2 (1.8)
▪ Patient decision	2 (0.9)	1 (0.9)
▪ Other	0	2 (1.8)

Durva/Pbo Disposition, n (%)	Durva + CRT (n = 219)	Pbo + CRT (n = 109)
Received durva/pbo	218 (99.5)	109 (100)
Discontinued durva/pbo at any time	183 (83.9)	92 (84.4)
▪ AE	58 (26.6)	15 (13.8)
▪ PD	117 (53.7)	67 (61.5)
▪ Patient decision	5 (2.3)	7 (6.4)
▪ Met study-specific d/c criteria	0	1 (0.9)
▪ Other	3 (1.4)	2 (1.8)

- Most common CT regimen was carbo/pac
- Durva arm had higher rates of AEs leading to discontinuation of CRT and durva consolidation

PACIFIC-2: PFS by BICR (Primary Endpoint)



- No significant difference in PFS with durva + CRT vs pbo + CRT (*P* = .247)
- Subgroup analyses suggested potential benefit with durva + CRT in some patients: women, aged <65 yr, in Europe, with smaller tumors (<450 cm^3)

Bradley. ELCC 2024. Abstr LBA1..

PACIFIC-2: OS and ORR

Outcome	Durva + CRT (n = 219)	Pbo + CRT (n = 109)
OS		
▪ No. events (%)	142 (64.8)	69 (63.3)
▪ Median OS, mo (95% CI)	36.4 (26.2-45.6)	29.5 (23.2-45.1)
▪ HR (95% CI)	1.03 (0.78-1.39; P = .823)	
ORR, %	60.7	60.6

- No significant difference in OS between arms (*P* = .823)
  - Subgroup analyses suggested potential OS benefit with durva + CRT in same patients who had PFS benefit: women, aged <65 yr, in Europe, with smaller tumors (<450 cm^3)
- No significant difference in ORR between arms (*P* = .976)

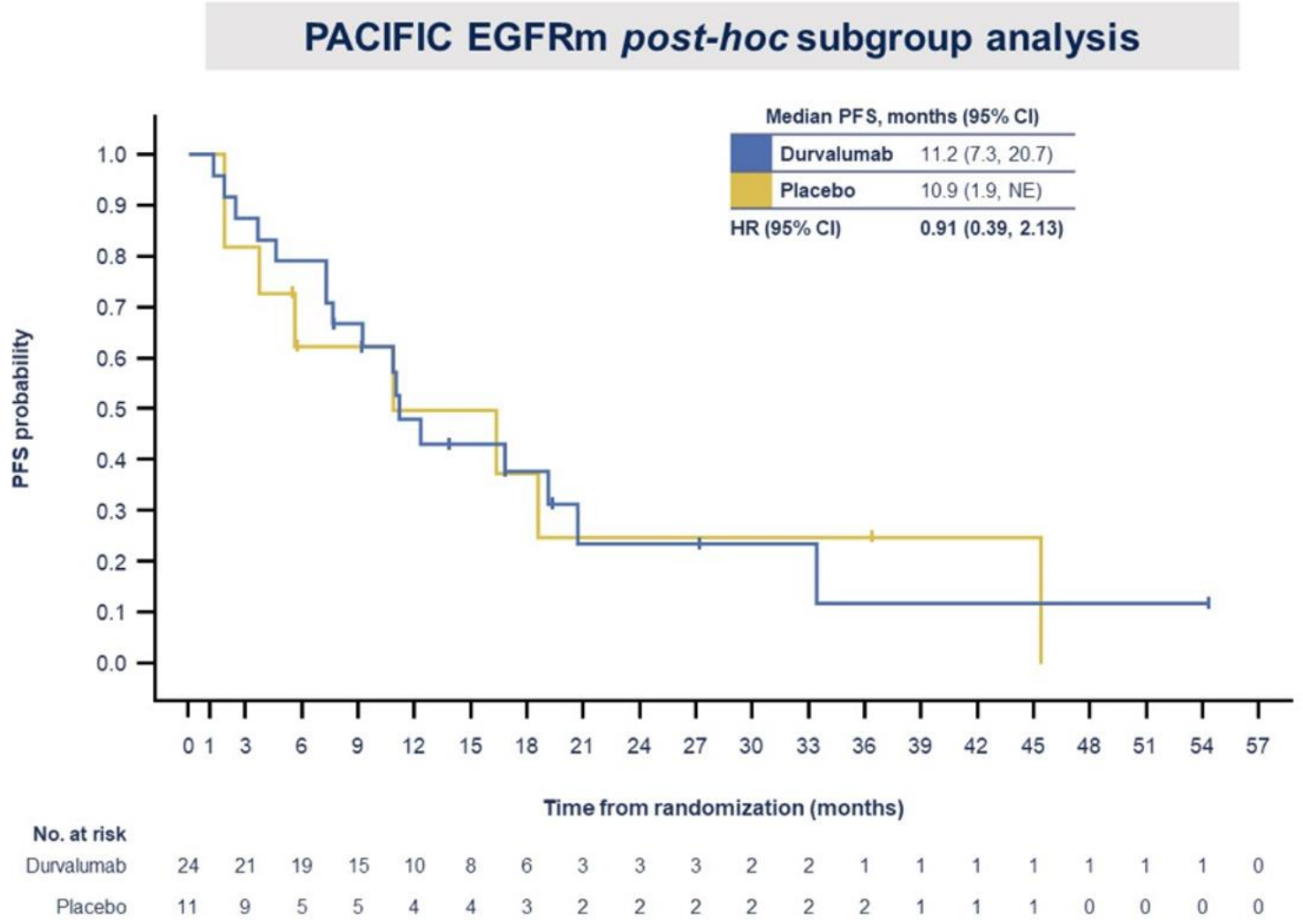
Bradley. ELCC 2024. Abstr LBA1.

PACIFIC-2: Safety

AE, n (%)	Durva + CRT (n = 219)	Pbo + CRT (n = 108)
Any AE	216 (98.6)	108 (100)
▪ Maximum grade 3/4	117 (53.4)	64 (59.3)
▪ Outcome of death	30 (13.7)	11 (10.2)
▪ SAE	103 (47.0)	56 (51.9)
Any AE leading to d/c of durva/pbo from start of treatment (approximate treatment period)	56 (25.6)	13 (12.0)
▪ 0 to 4 mo (durva + CRT → first postbaseline scan)	31 (14.2)	6 (5.6)
▪ >4 to ≤16 mo (consolidation durva in SoC PACIFIC regimen)	12 (5.5)	6 (5.6)
▪ >16 mo (after consolidation durva in SoC PACIFIC regimen)	13 (5.9)	1 (0.9)

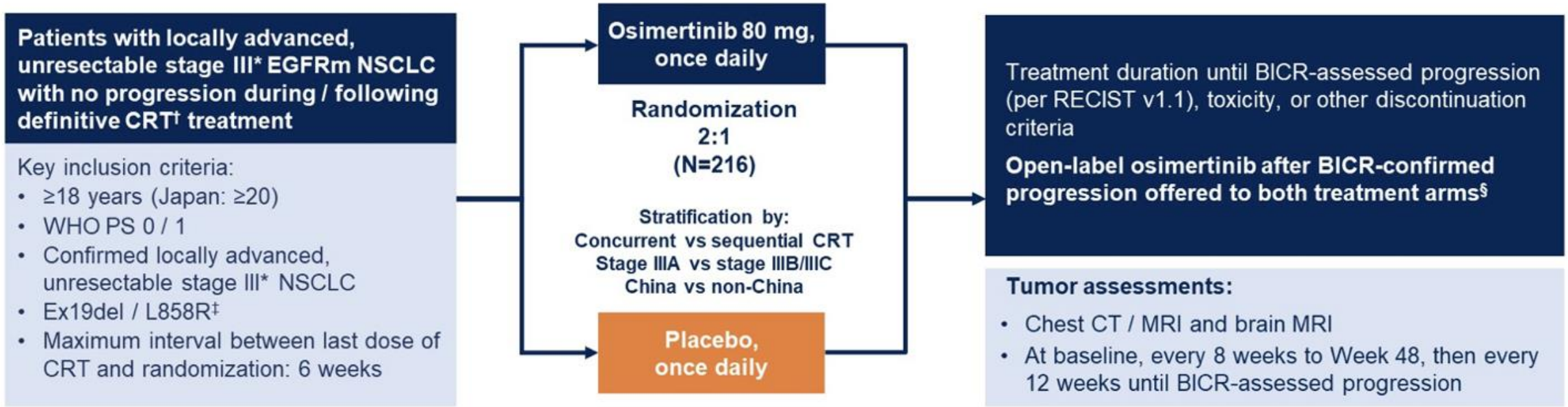
- Most common TEAEs:
  - Durva + CT: anemia (42.0%), pneumonitis/radiation pneumonitis (28.8%, grade ≥3: 4.6%), neutropenia (27.4%), nausea (25.6%)
  - Pbo + CT: anemia (38.0%), constipation (28.7%), pneumonitis/radiation pneumonitis (28.7%, grade ≥3: 5.6%), neutropenia (25.9%)

No Benefit to Durvalumab in EGFR subgroup



J Thorac Oncol, Vol 18, Naidoo et al.,

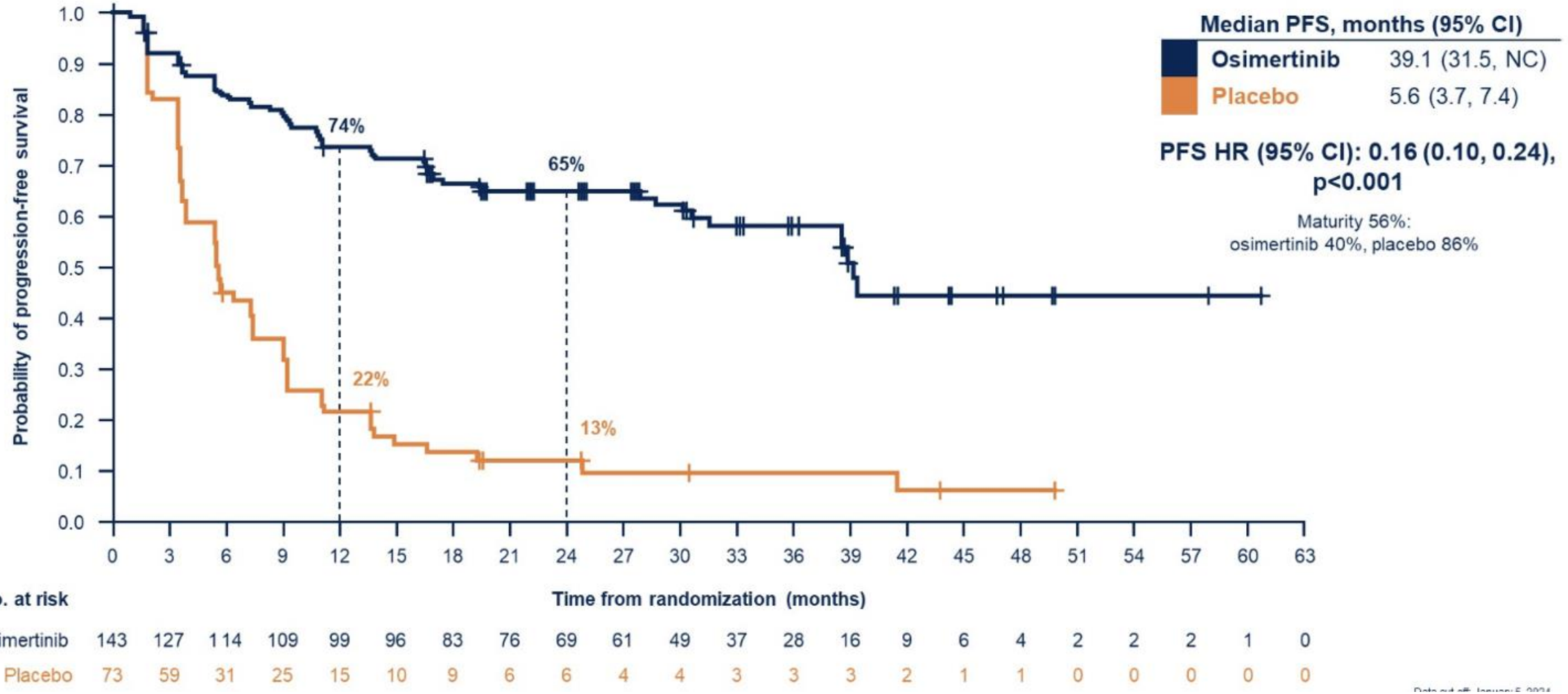
LAURA STUDY DESIGN



PRIMARY ENDPOINT: PFS
SCONDARY ENDPOINTS: OS, CNS PFS, SAFETY

RAMALINGAM ET AL, ASCO 2024

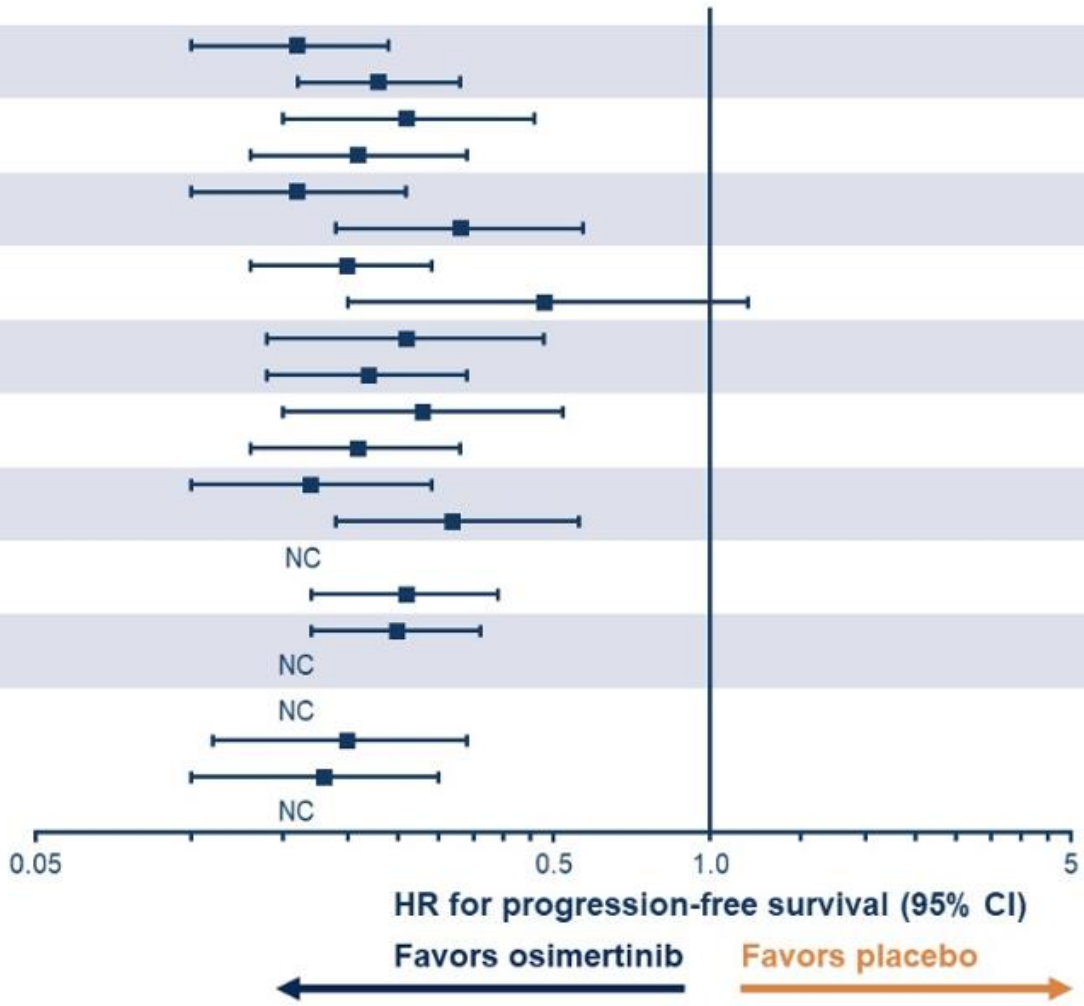
PRIMARY ENDPOINT: PFS BY BICR



RAMALINGAM ET AL, ASCO 2024

LAURA: Subgroup Analysis

Subgroup		No. of events / patients	HR	95% CI
Overall (N=216)	Stratified log-rank	120 / 216	0.16	0.10, 0.24
	Unadjusted Cox PH	120 / 216	0.23	0.16, 0.33
Sex	Male	50 / 84	0.26	0.15, 0.46
	Female	70 / 132	0.21	0.13, 0.34
Age	<65 years	67 / 120	0.16	0.10, 0.26
	≥65 years	53 / 96	0.33	0.19, 0.57
Race	Asian	98 / 178	0.20	0.13, 0.29
	Non-Asian	22 / 38	0.48	0.20, 1.19
Smoking history	Current / former (yes)	42 / 65	0.26	0.14, 0.48
	Never (no)	78 / 151	0.22	0.14, 0.34
Stage*	IIIA	42 / 76	0.28	0.15, 0.52
	IIIB / IIIC	78 / 140	0.21	0.13, 0.33
EGFR mutation†	Ex19del	65 / 117	0.17	0.10, 0.29
	L858R	55 / 98	0.32	0.19, 0.56
China cohort	Chinese	18 / 40	NC	NC, NC
	Non-Chinese	102 / 176	0.26	0.17, 0.39
Chemoradiotherapy	Concurrent	107 / 193	0.25	0.17, 0.36
	Sequential	13 / 23	NC	NC, NC
Response to prior CRT	Complete response	3 / 7	NC	NC, NC
	Partial response	53 / 94	0.20	0.11, 0.34
	Stable disease	58 / 98	0.18	0.10, 0.30
	Non-evaluable	6 / 17	NC	NC, NC



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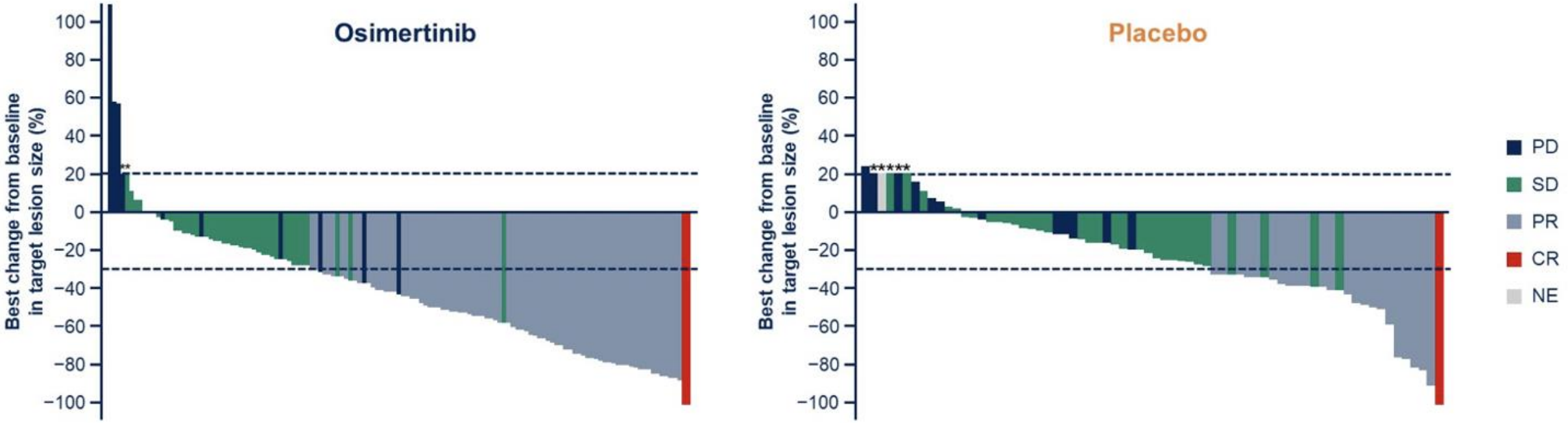
LAURA: Response Rate



	Osimertinib (n=143)	Placebo (n=73)
Objective response rate, % (95% CI)	57 (49, 66)	33 (22, 45)
Disease control rate, % (95% CI)	89 (83, 94)	79 (68, 88)
Median duration of response, months (95% CI)	36.9 (30.1, NC)	6.5 (3.6, 8.3)

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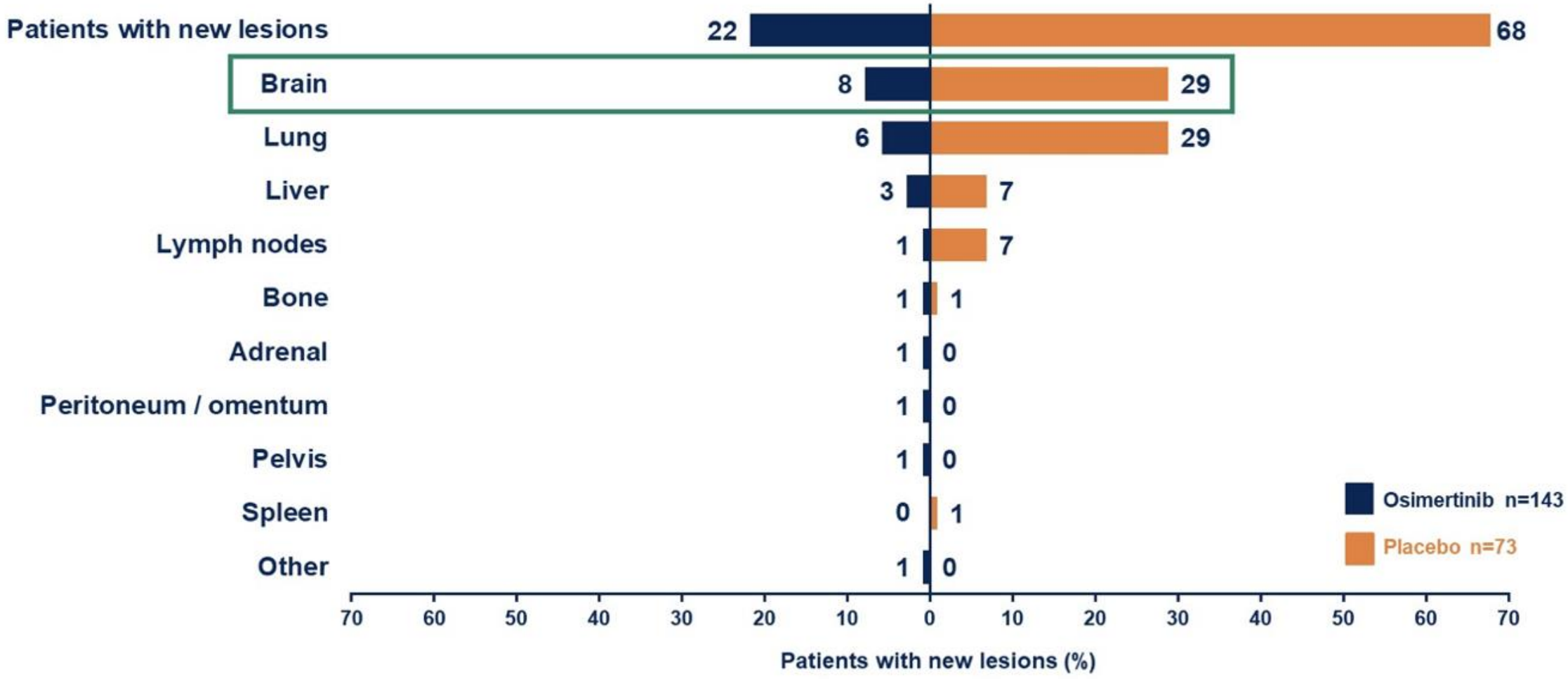
LAURA: Sites of Recurrence



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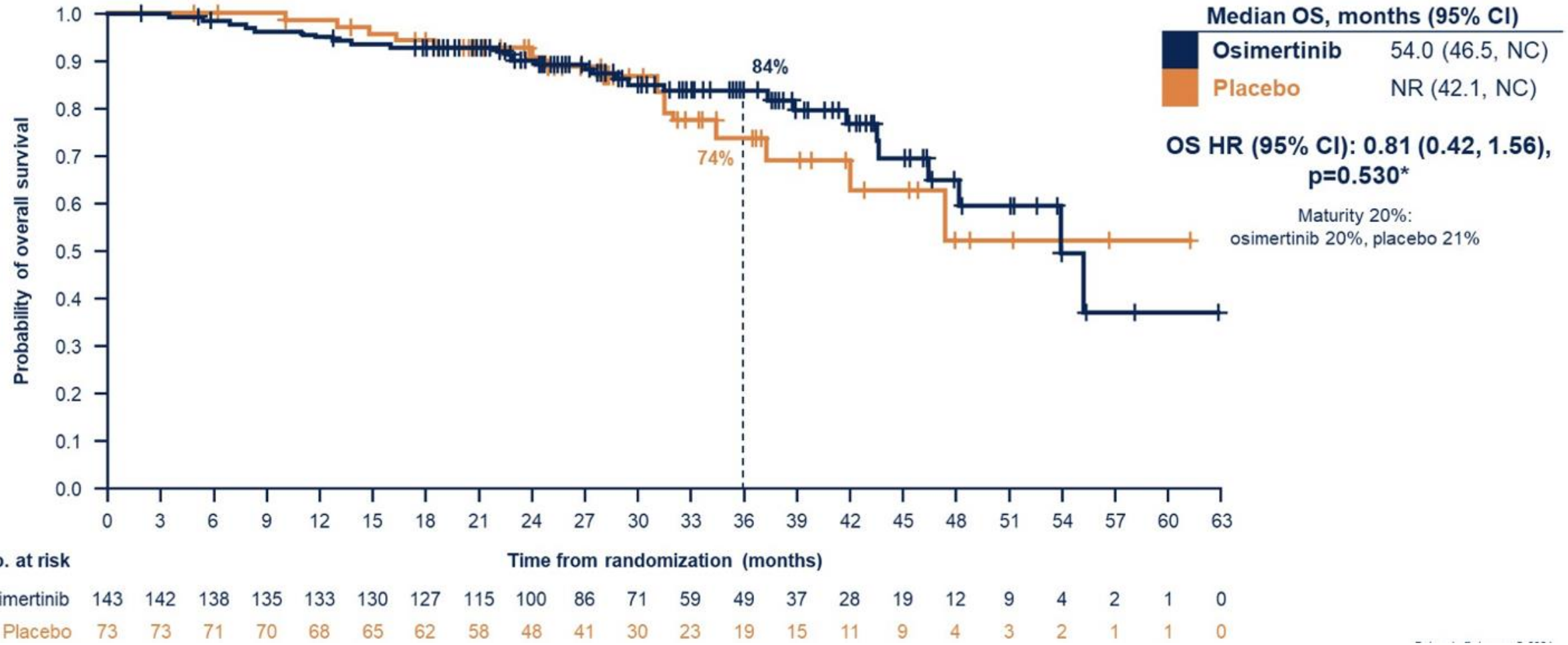
LAURA: Overall Survival – preliminary analysis

81% crossover rate



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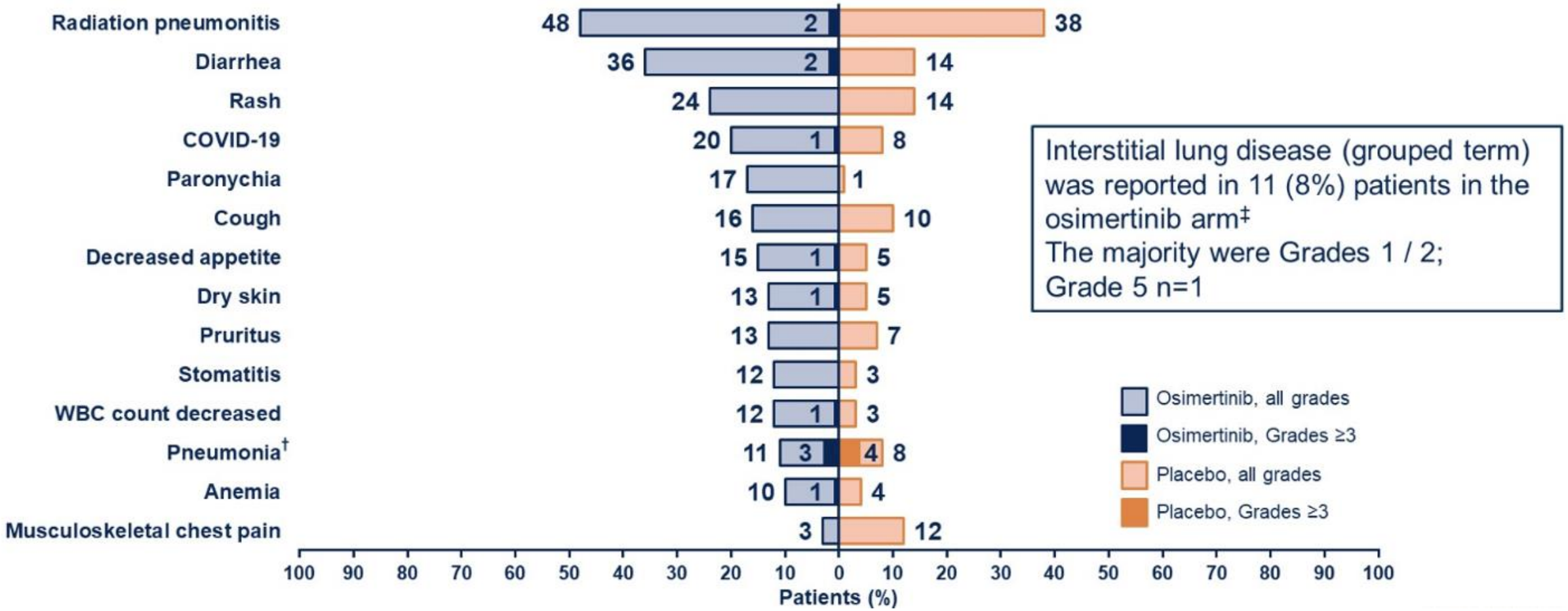
LAURA: Toxicity



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Conclusions

- Chemoradiation remains the standard of care for patients with stage III unresectable NSCLC
- Durvalumab following chemoradiation (not concurrent) remains the standard for patients with immunotherapy sensitive disease subtypes
- We lack data on best adjuvant approach for patients with ALK/ROS1/ERBB2/RET/NTRK/MET/BRAF/Uncommon EGFR mutant associated disease.
- Cure rates with EGFR mutant patients are disappointingly low with chemoradiation alone, and patients should receive Osimertinib after completion of chemoradiation (forever???)