MCM Tampa Bay Edition

Stage III Unresectable NSCLC: Any Progress Beyond PACIFIC?

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NCCN Guidelines Version 1.2025
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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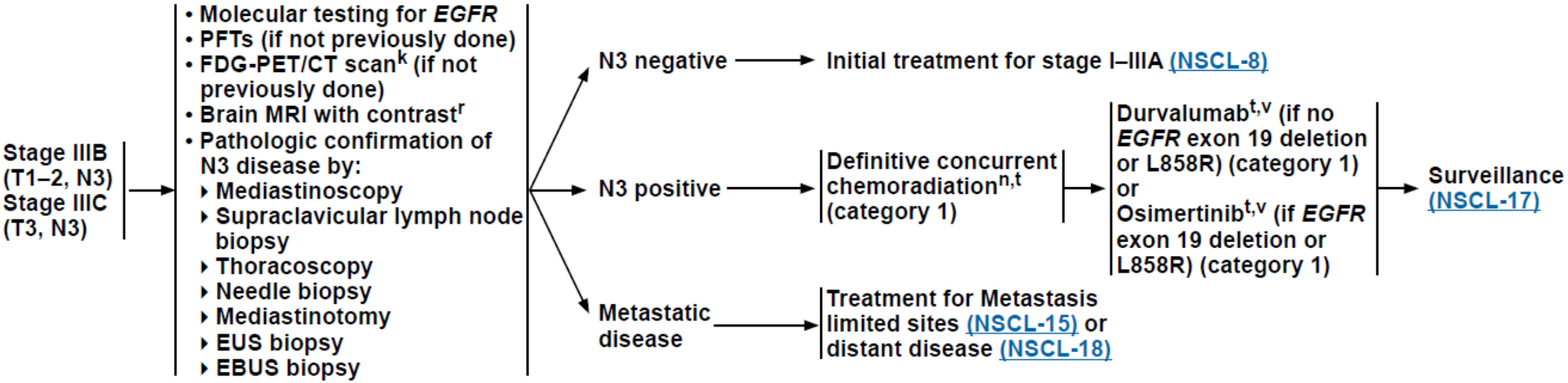
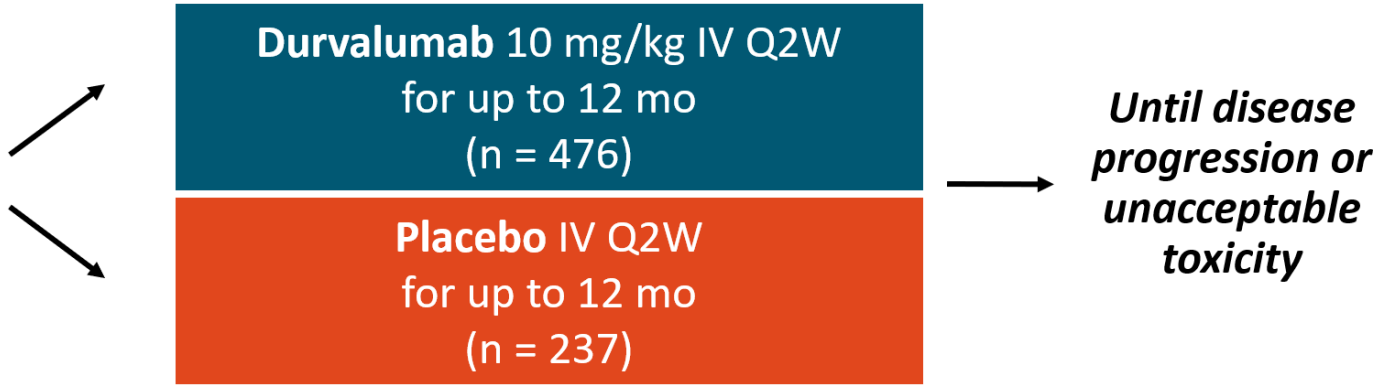


PACIFIC Study Design

Randomized, double-blind, placebo-controlled phase III trial

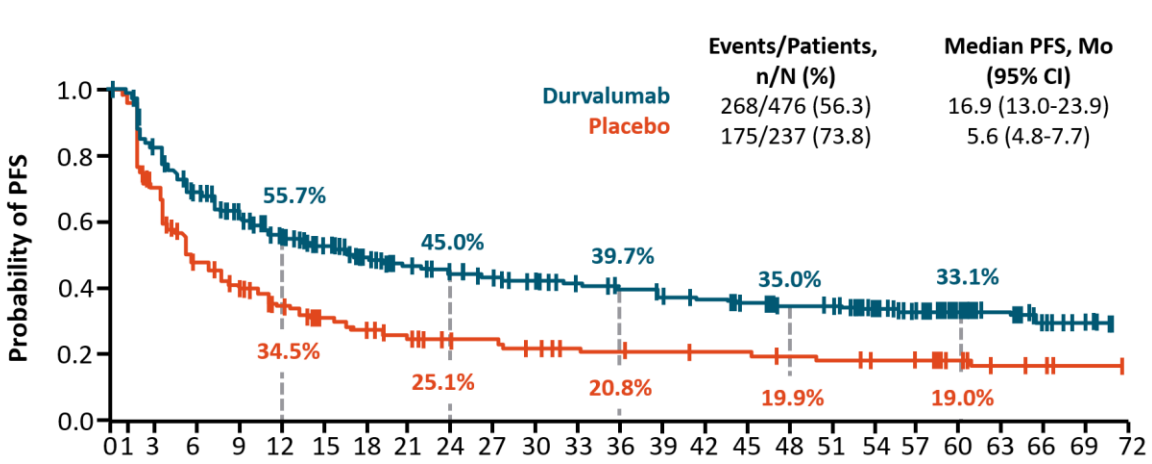
Primary endpoints: PFS by BICR, OS

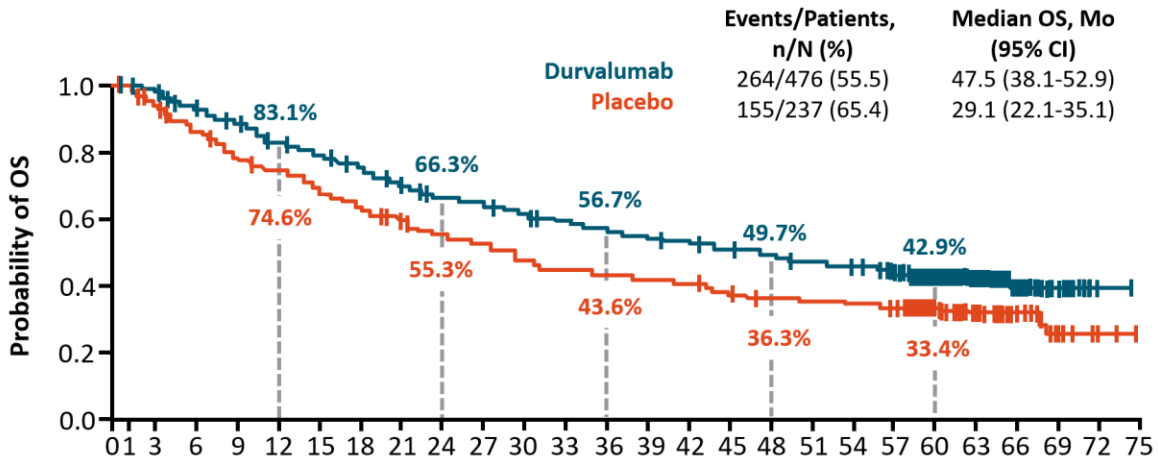
Adult patients with locally advanced, unresectable, stage III NSCLC without progression following ≥2 cycles platinum-based chemotherapy concurrent with radiation therapy; WHO PS 0/1
(N = 713)



Spigel. ASCO 2021. Abstr 8511.

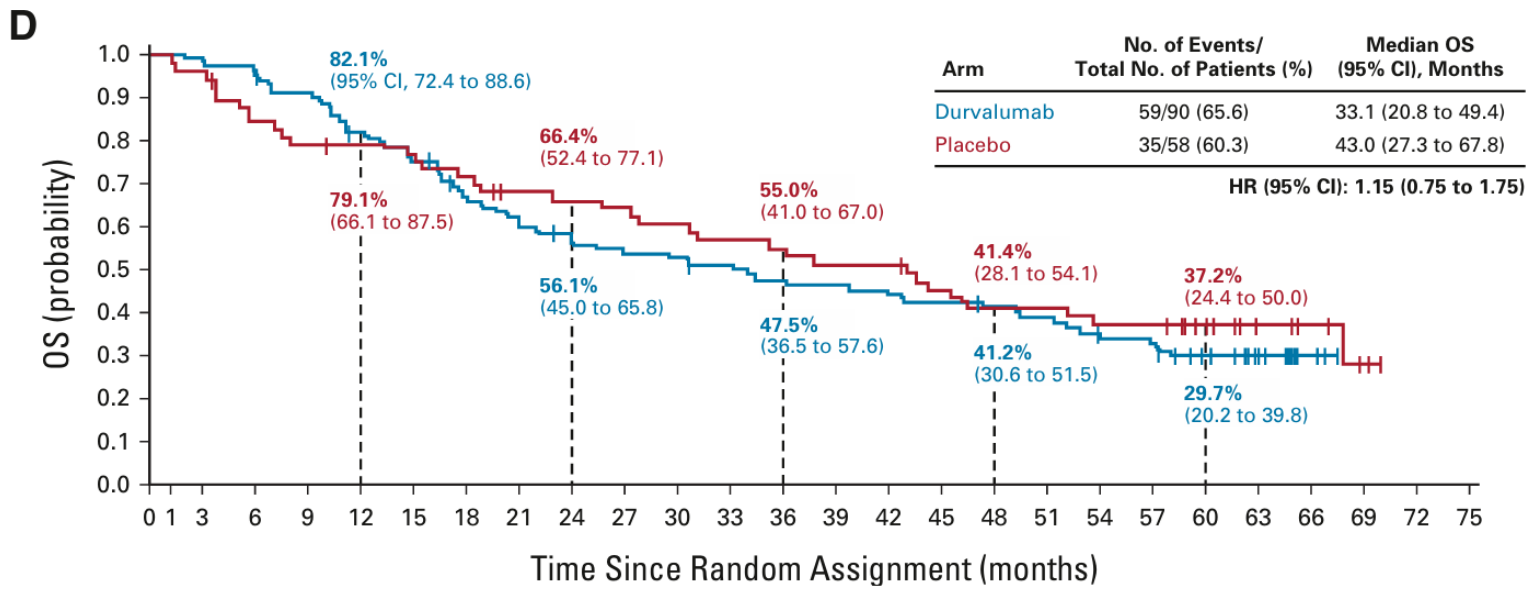
PACIFIC 5-Yr Update
OS and PFS





Spigel, JCO 2022

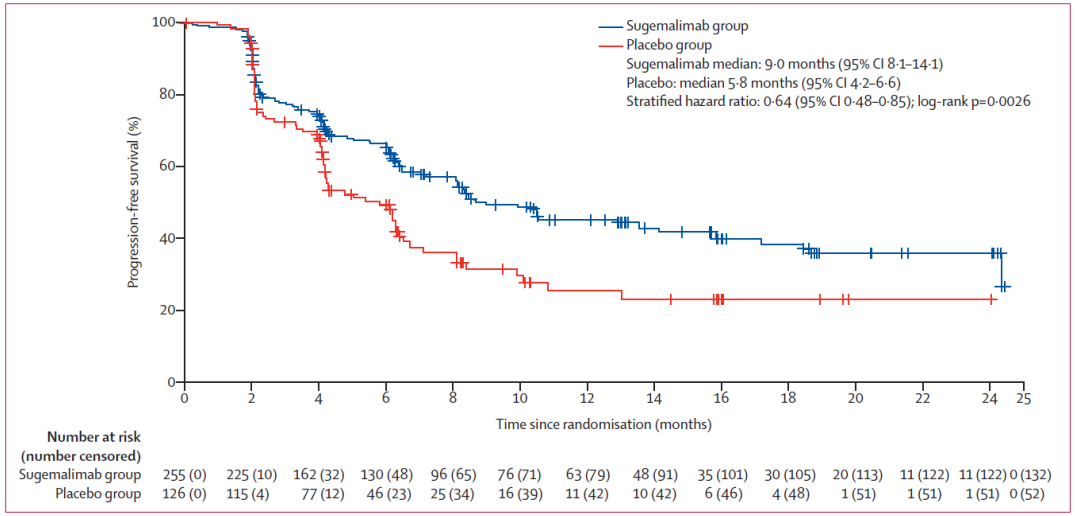
PACIFIC Overall Survival in PDL-1 Negative NSCLC

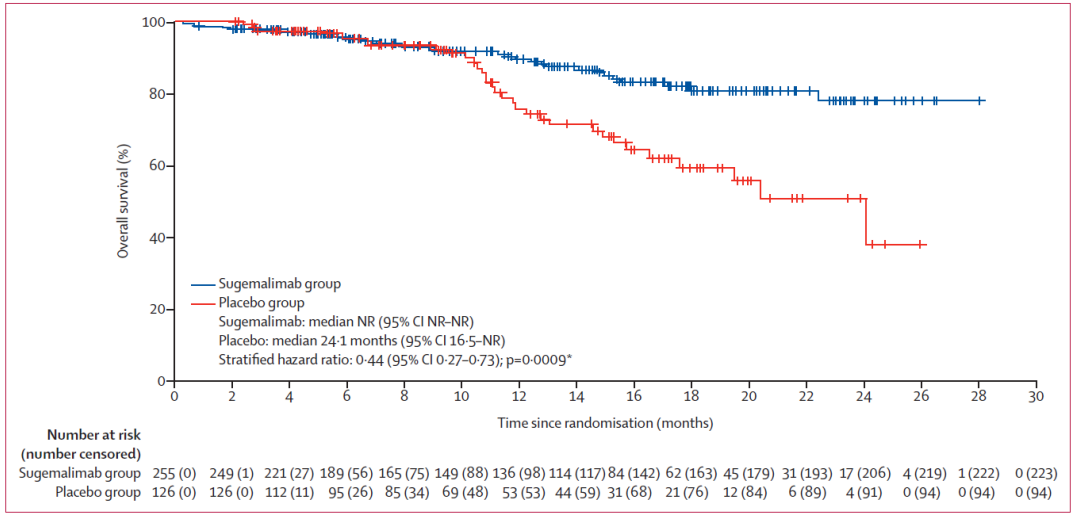


Spigel, JCO 2022

Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial

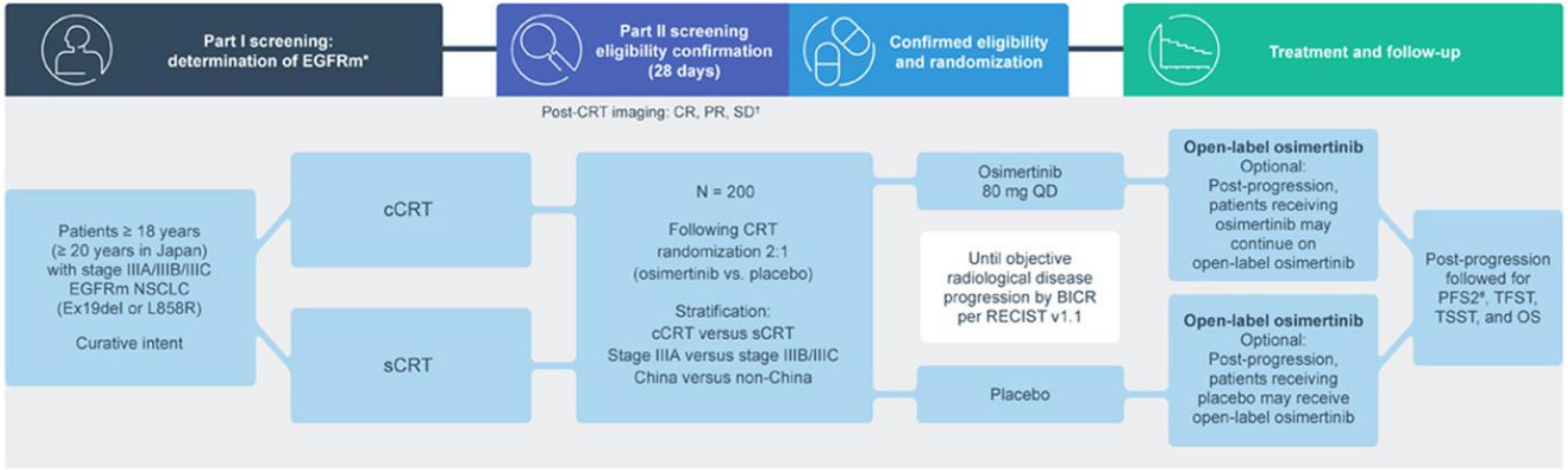
564 patients randomized to consolidation sugemalimab (anti-PDL1) or placebo

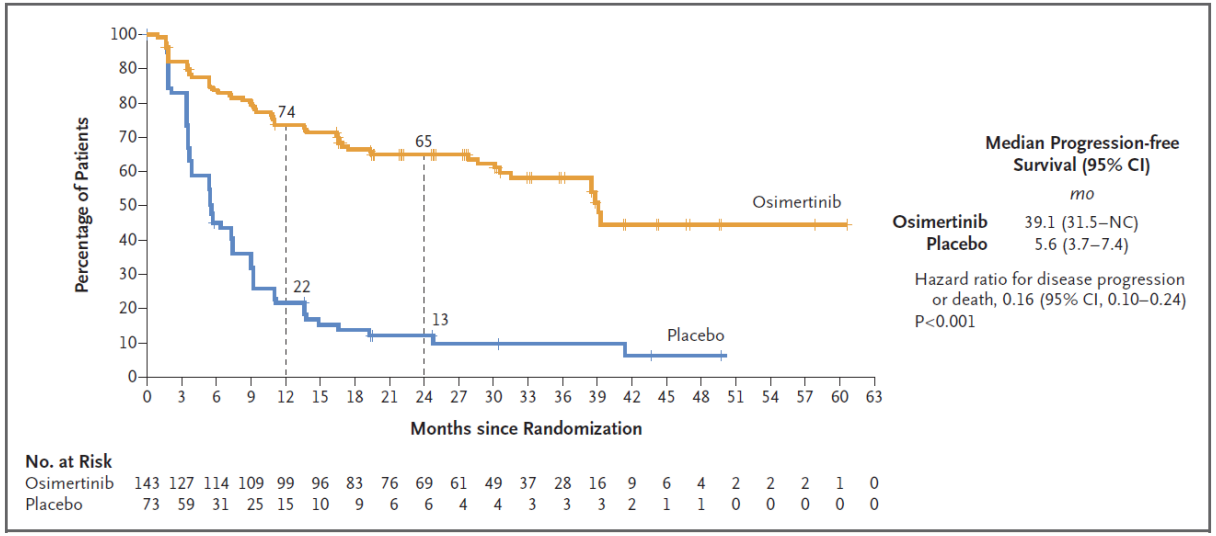




Zhou, Lancet Oncology 2022

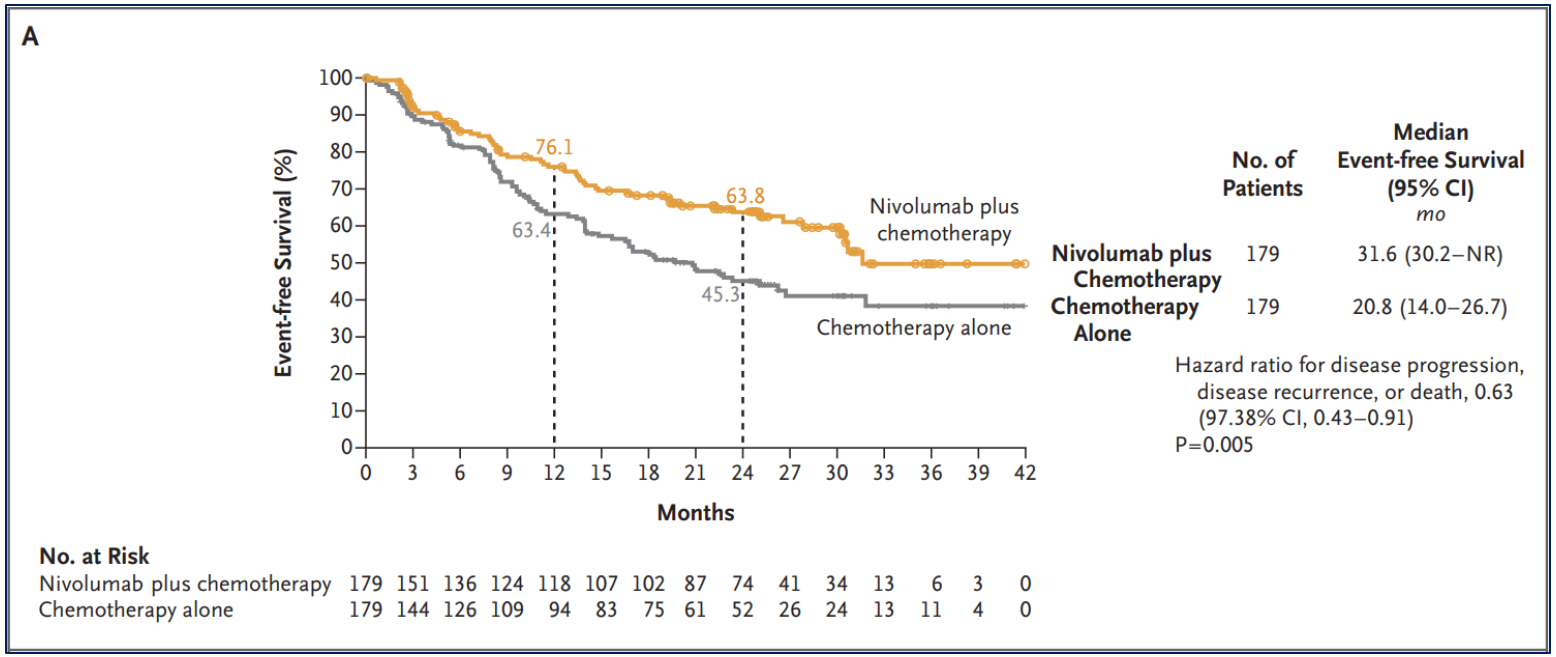
Osimertinib after Chemoradiotherapy in Stage III *EGFR*-Mutated NSCLC

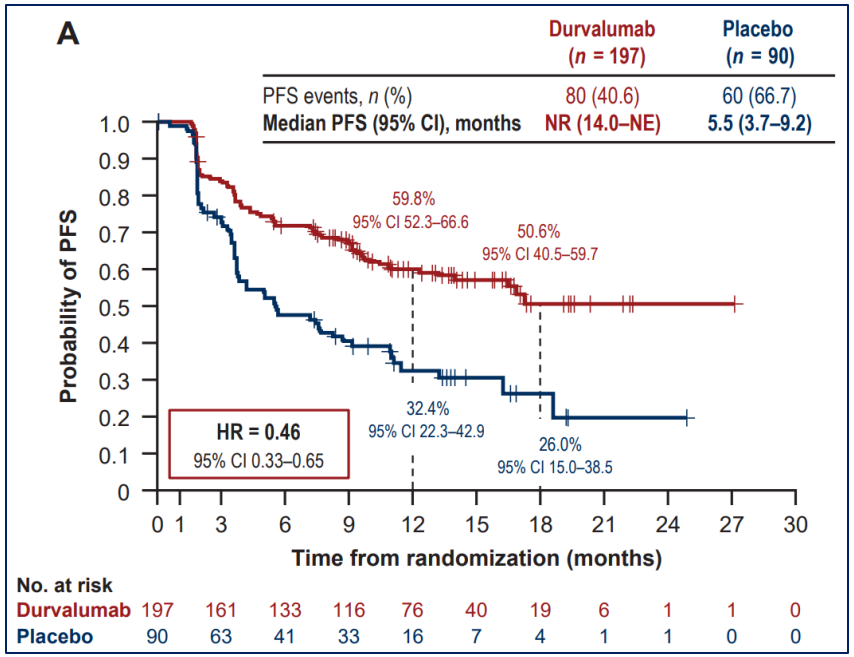




Lu, NEJM 2024

Checkmate 816 vs Pacific EFS/PFS for Stage IIIA

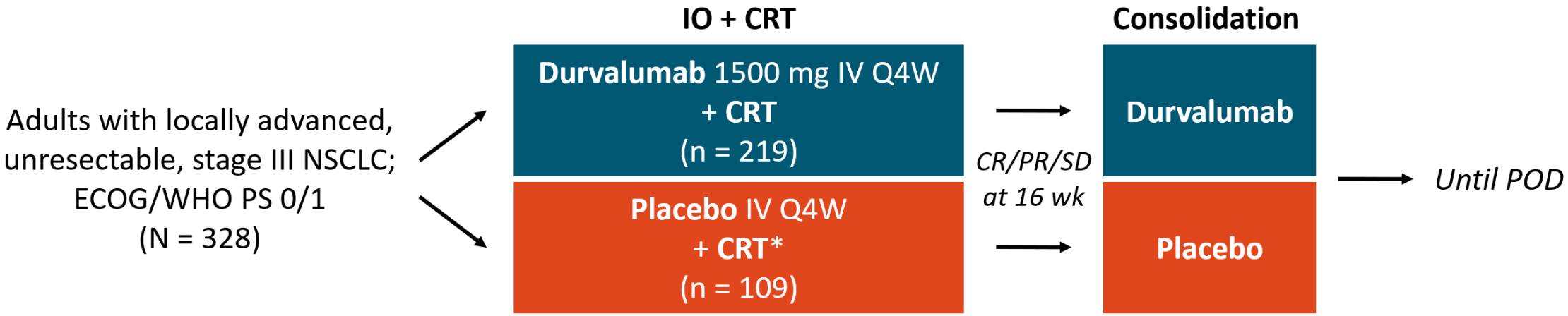




Forde, NEJM 2022 Senan, ESMO OPEN 2022

What has not worked?

PACIFIC-2 Study Design



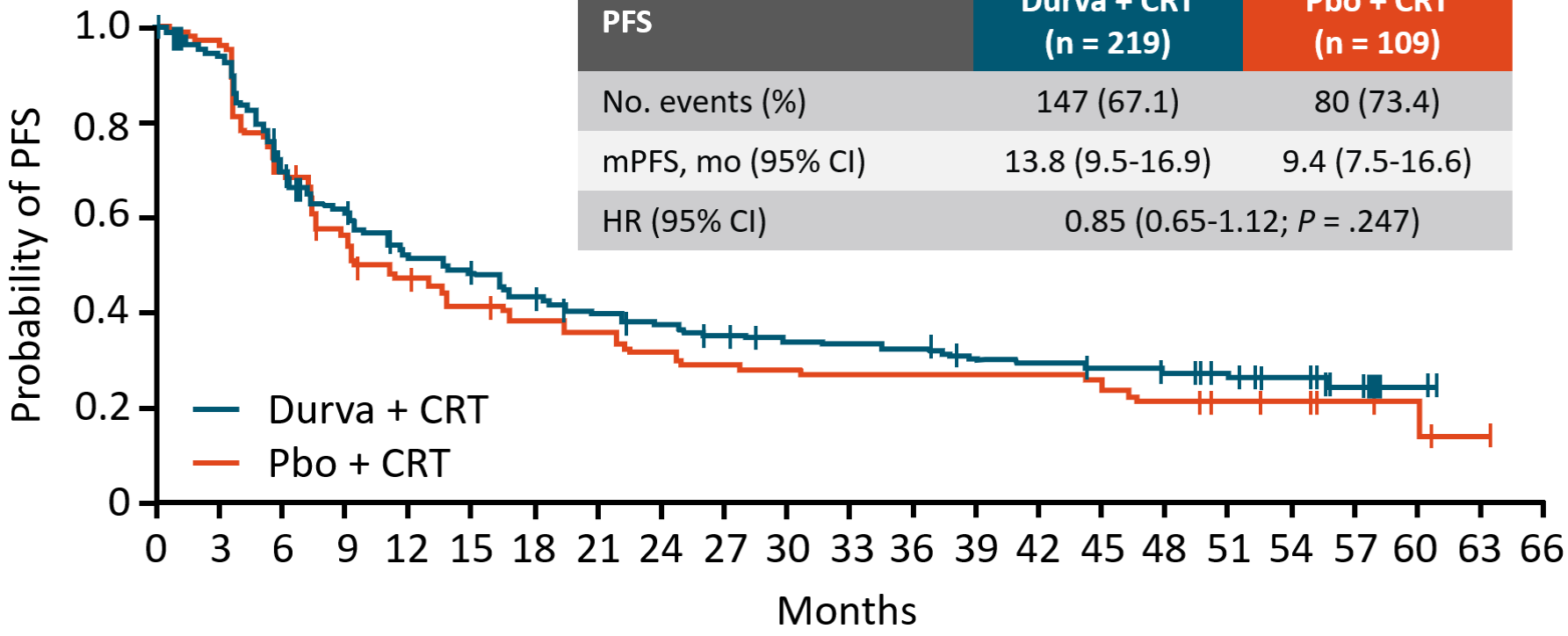
PACIFIC-2 Baseline Characteristics

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)

Bradley. ELCC 2024

PACIFIC-2 PFS



PFS	Durva + CRT (n = 219)	Pbo + CRT (n = 109)
No. events (%)	147 (67.1)	80 (73.4)
mPFS, mo (95% CI)	13.8 (9.5-16.9)	9.4 (7.5-16.6)
HR (95% CI)	0.85 (0.65-1.12; *P* = .247)	

Bradley. ELCC 2024

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%)

Bradley. ELCC 2024. Abstr LBA1.

PACIFIC-2: Time to Onset of AEs and Type of Fatal AEs

Time to Onset of AE, n (%)	Any		Maximum Grade 3/4		Leading to Death	
	Durva + CRT (n = 219)	Pbo + CRT (n = 108)	Durva + CRT (n = 219)	Pbo + CRT (n = 108)	Durva + CRT (n = 219)	Pbo + CRT (n = 108)
Any time	216 (98.6)	108 (100)	117 (53.4)	64 (59.3)	30 (13.7)	11 (10.2)
0 to ≤4 mo	216 (98.6)	107 (99.1)	125 (57.1)	57 (52.8)	15 (6.8)	5 (4.6)
>4 to ≤16 mo	142 (64.8)	74 (68.5)	34 (15.5)	16 (14.8)	5 (2.3)	5 (4.6)
>16 mo	67 (30.6)	32 (29.6)	16 (7.3)	13 (12.0)	10 (4.6)	1 (0.9)

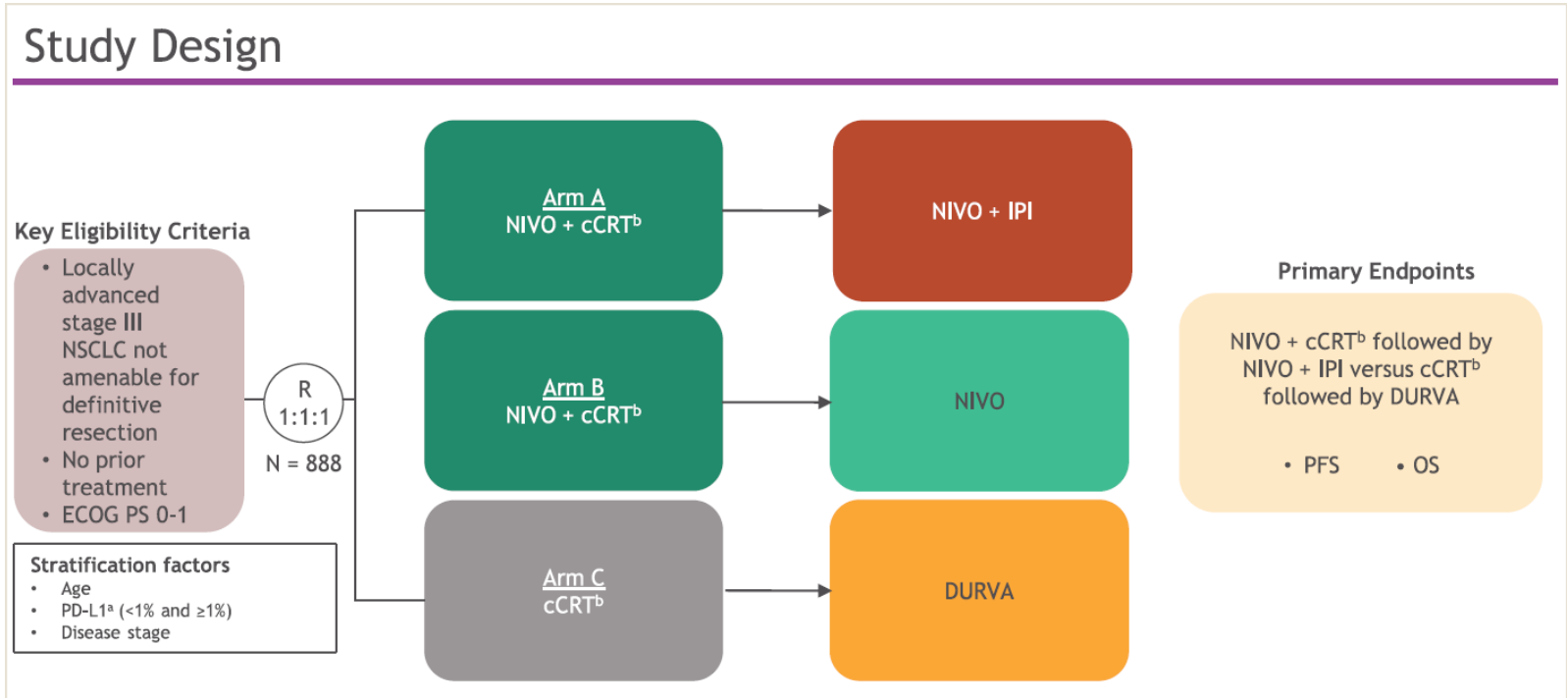
- More grade 3/4 AEs and AEs leading to death occurred from 0 to ≤4 mo with durva + CRT
  - Infection was main type of fatal AE driving difference between arms
  - Fatal hemoptysis/pulmonary hemorrhage also more common (in 2.3% vs 0% with placebo)

Type of Fatal AEs With Onset of 0 to ≤4 Mo, n (%)	Durva + CRT (n = 219)	Pbo + CRT (n = 108)
Infections/infestations	6 (2.7)	0
Cardiac disorders	1 (0.5)	1 (0.9)
Respiratory, thoracic, and mediastinal disorders	7 (3.2)	3 (2.8)
Injury, poisoning, and procedural complications	1 (0.5)	1 (0.9)

Bradley. ELCC 2024. Abstr LBA1.

CheckMate 73L: A Phase 3 Study Comparing Nivolumab Plus Concurrent Chemoradiotherapy Followed by Nivolumab With or Without Ipilimumab Versus Concurrent Chemoradiotherapy Followed by Durvalumab for Previously Untreated, Locally Advanced Stage III Non-Small-Cell Lung Cancer

- **925 patients randomized**
- **No benefit in OS or PFS**



Peters, ESMO 2024

Where are we going?

COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non-Small-Cell Lung Cancer

186 patients randomized after chemoradiation

ARM A
Durvalumab IV Q4W
+ oleclumab IV Q4W*

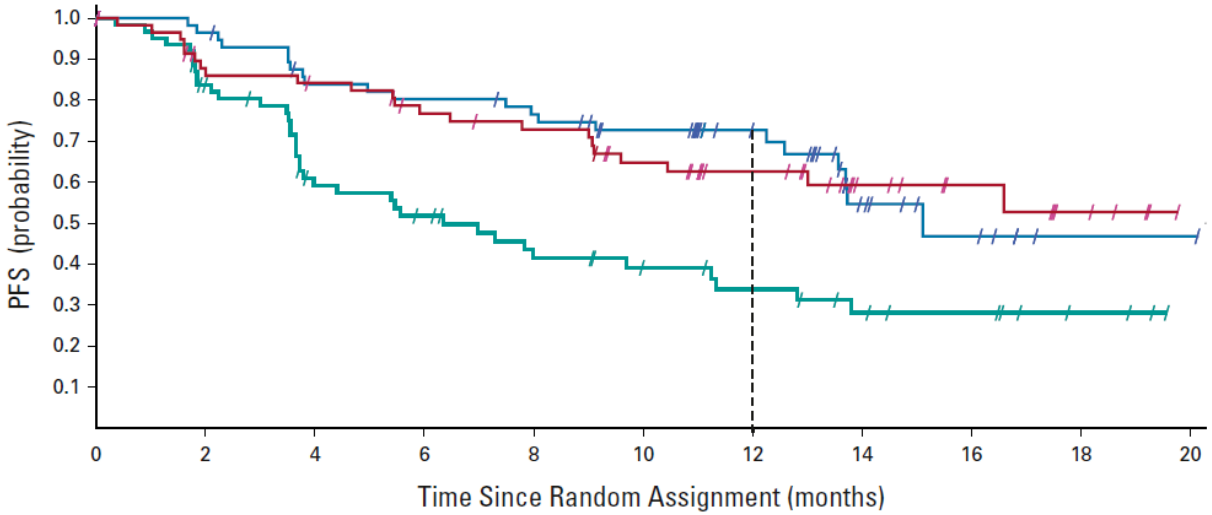
*Oleclumab Q2W for cycles 1 and 2, then Q4W starting cycle 3

ARM B
Durvalumab IV Q4W
+ monalizumab IV Q4W†

†Placebo on day 15 for cycles 1 and 2

ARM C
Durvalumab IV Q4W
+ placebo IV Q4W†

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)	–

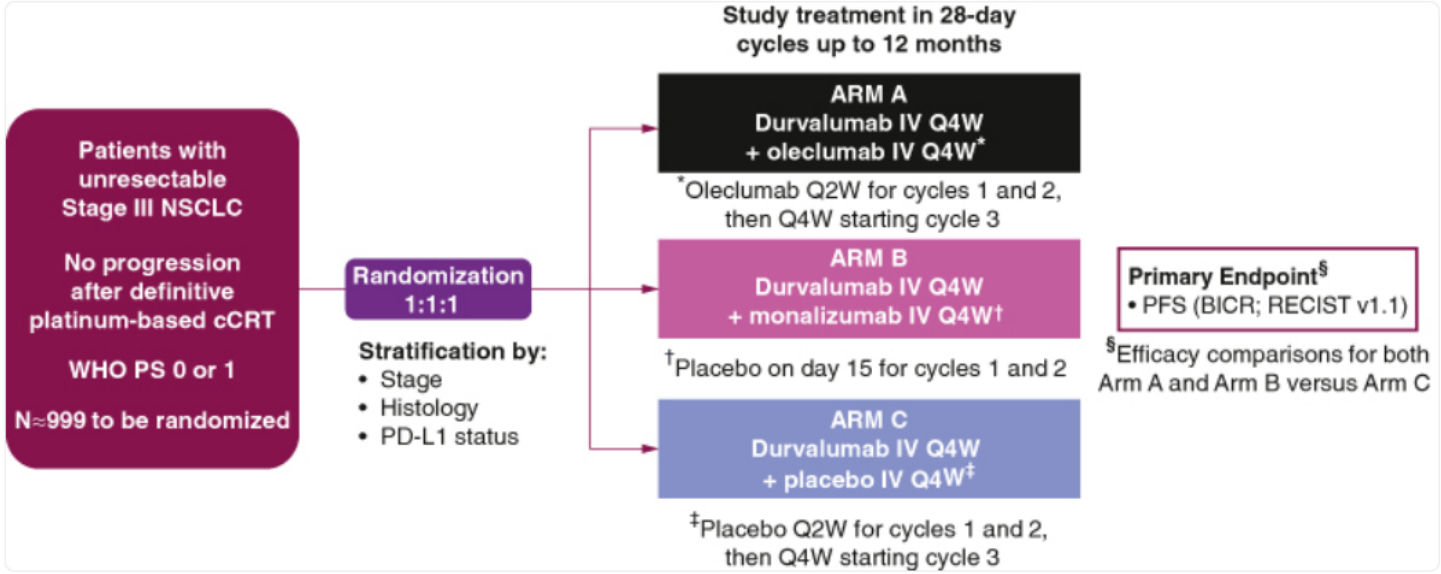


No. at risk:											
Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab	67	50	32	27	20	16	13	9	7	3	0

Herbst, JCO 2022

Phase 3 study of durvalumab combined with oleclumab or monalizumab in patients with unresectable stage III NSCLC (PACIFIC-9)

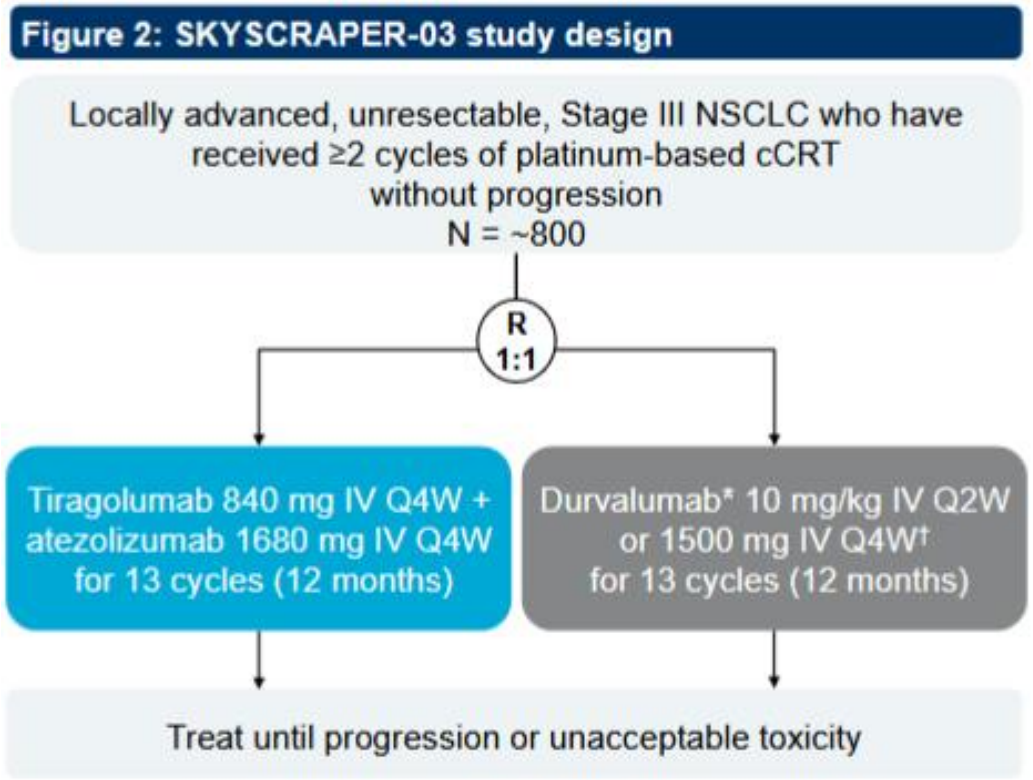
Recruitment goal of 999 patients



Phase III, open-label randomised study of atezolizumab + tiragolumab vs durvalumab in patients with locally advanced, unresectable, stage III NSCLC who have not progressed after platinum-based concurrent chemoradiation (SKYSCRAPER-03)

Estimated accrual 800 patients

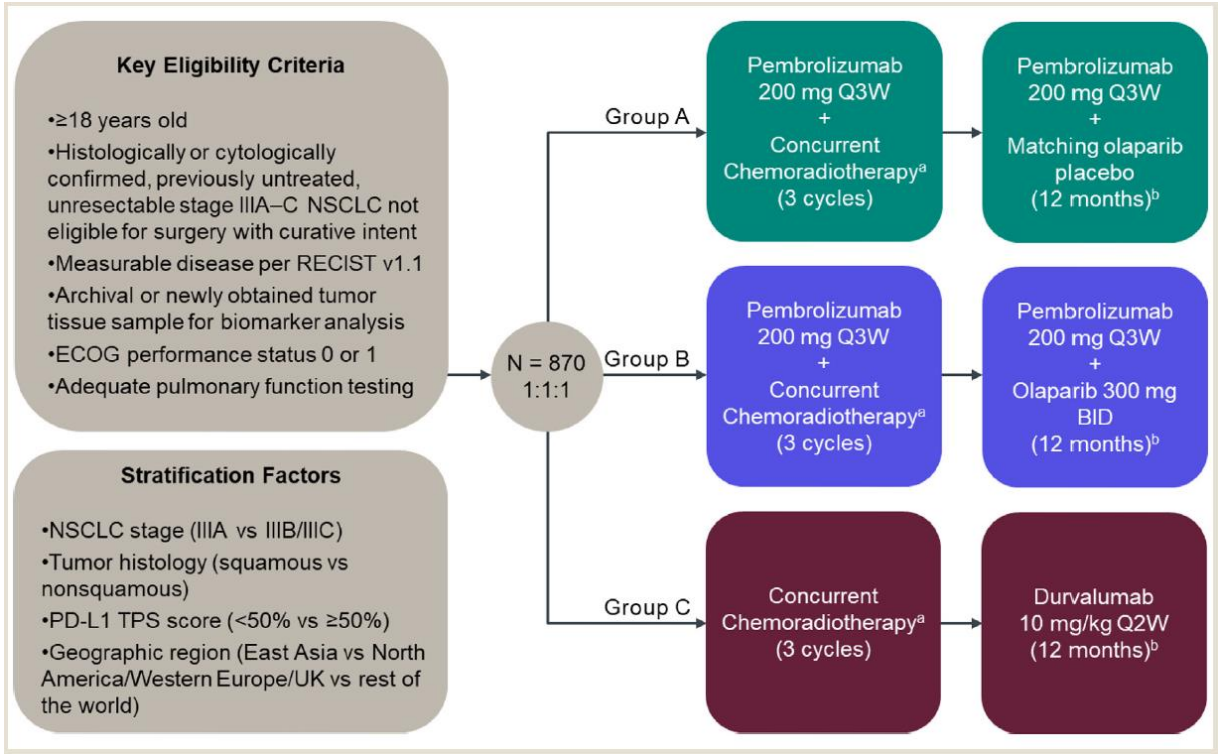
Figure 2: SKYSCRAPER-03 study design



Dziadziuszko, Annals of Oncology 2021

KEYLYNK-012: Study of Pembrolizumab and Concurrent Chemoradiotherapy Followed by Pembrolizumab With or Without Olaparib for Stage III Non-Small-Cell Lung Cancer

Estimated enrollment of 870 patients



Jabbour, Clinical Lung Cancer 2022

Different approaches

Atezolizumab Before and After Chemoradiation for Unresectable Stage III Non-Small Cell Lung Cancer: A Phase II Nonrandomized Controlled Trial (AFT-16)

- 64 patients enrolled
- 4 cycles of atezolizumab
- chemoradiation with paclitaxel and carboplatin
- 2 cycles of consolidation paclitaxel and carboplatin
- Atezolizumab for 12 months

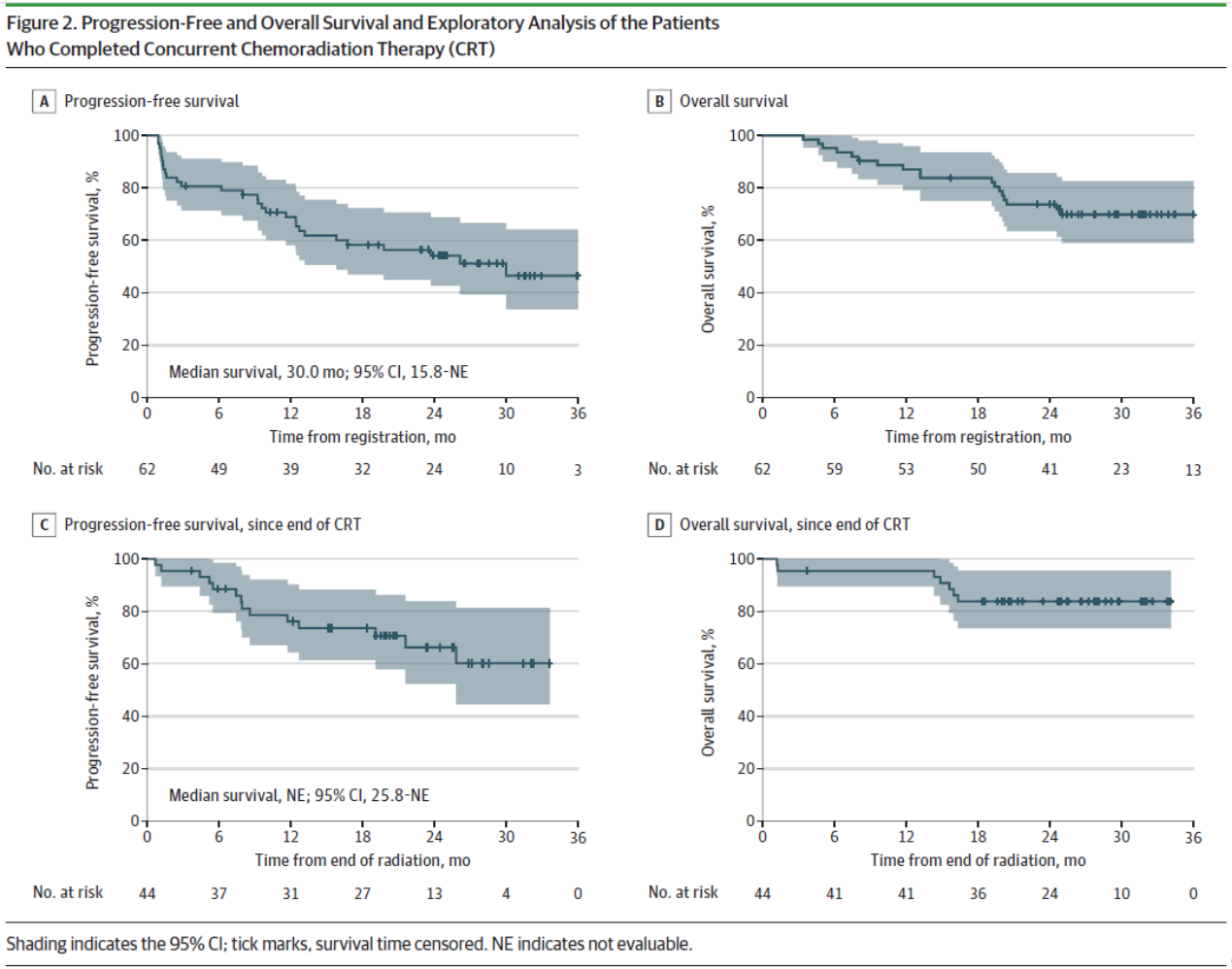


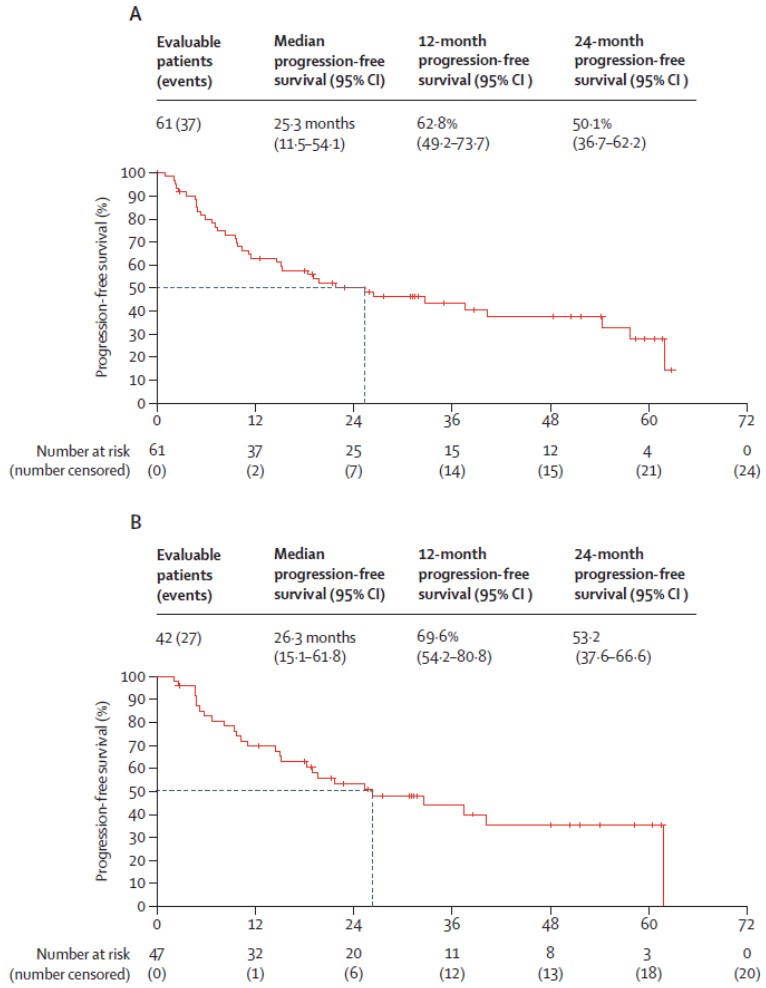
Figure 2. Progression-Free and Overall Survival and Exploratory Analysis of the Patients Who Completed Concurrent Chemoradiation Therapy (CRT)

Shading indicates the 95% CI; tick marks, survival time censored. NE indicates not evaluable.

Ross, JAMA Oncology 2024

Primary lung tumour stereotactic body radiotherapy followed by concurrent mediastinal chemoradiotherapy and adjuvant immunotherapy for locally advanced nonsmall-cell lung cancer: a multicentre, single-arm, phase 2 trial

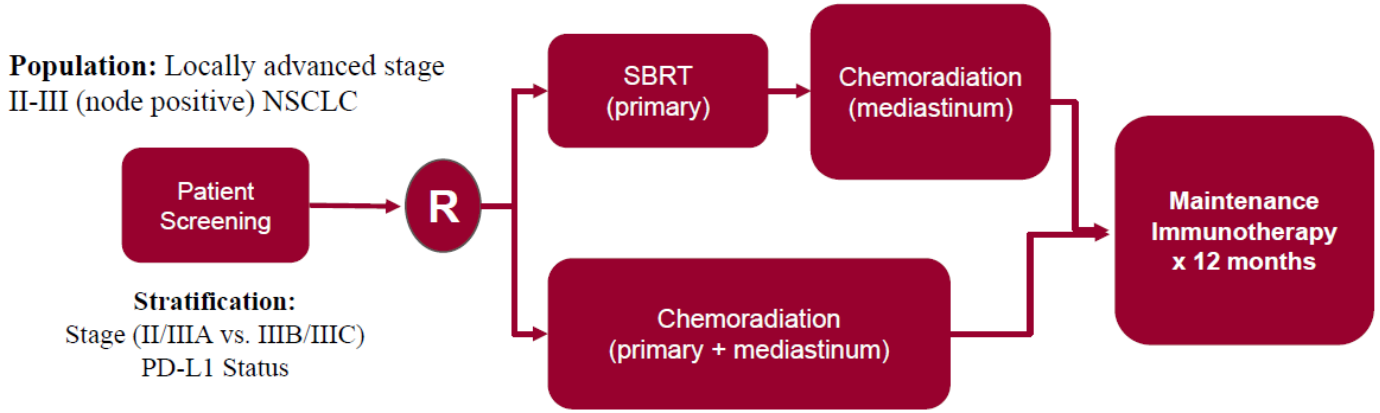
- 61 patients with stage II or 3 unresectable NSCLC.
- SBRT to the primary tumor (50-54 Gy in 3-5 fractions)
- Followed by standard chemoradiation (involved lymph nodes)
- Followed by consolidation durvalumab after approval
- Primary endpoint: 1 year PFS



Heinzerling, Lancet 2024,

Adding high-dose, targeted radiation to the usual treatment for locally-advanced, inoperable non-small cell lung cancer

LU008 Schema: Phase III



- Control arm: chemoradiation to the primary and mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
- Experimental arm: SBRT to the primary (standard BED ≥100 Gy dose regimen) → chemoradiation to mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
  - SBRT to primary tumor:
    - 3 fractions to 54 Gy (BED10 of 151.2 Gy) [peripheral]
    - 4 fractions to 50 Gy (BED10 of 112.5 Gy) [peripheral]
    - 5 fractions to 50 Gy (BED10 of 100 Gy) [peripheral or central]
  - Radiation to involved hilar/mediastinal lymph nodes: 2 Gy x 30 fx to 60 Gy, IMRT or proton therapy
  - Concurrent chemotherapy: carboplatin + paclitaxel, cisplatin + etoposide, cisplatin + pemetrexed, or carboplatin + pemetrexed
  - Maintenance immunotherapy: durvalumab x 12 months [if durvalumab is NOT given, carbo/paclitaxel pts receive 2 cycles of consolidation]

NRG ONCOLOGY™

APOLO: Phase II Trial of Induction Chemo-Immunotherapy Plus Chemoradiotherapy and Maintenance Immunotherapy in Stage III NSCLC

- **38 patients enrolled**
- **Induction**
  - Paclitaxel/carboplatin/atezolizumab
- **Chemoradiation**
- **Consolidation atezolizumab 12 mo**

PFS at 12 months: 78.1%

OS at 12 months: 90.6%

Provencio, JTO 2024