COMBINED MODALITY TREATMENT FOR UNRESECTABLE NSCLC

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The Christie NHS Foundation Trust

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DECLARATION OF INTERESTS

Honoraria for lectures – Astra Zeneca

OVERVIEW

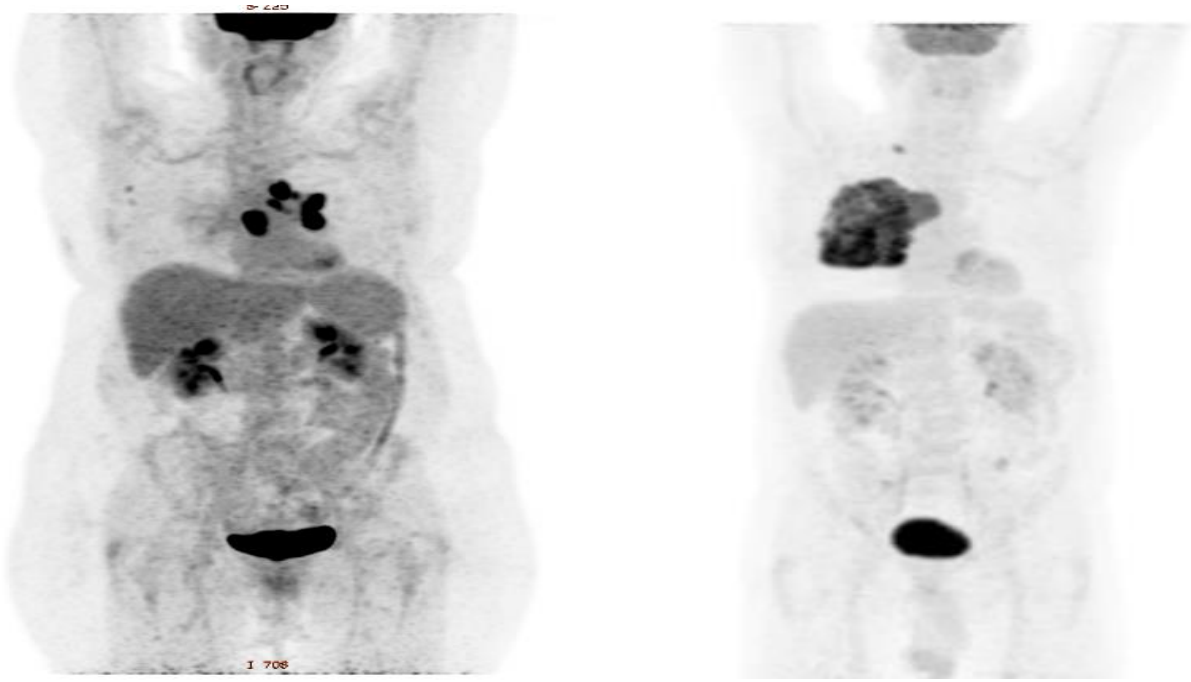
- Background – stage III NSCLC
- The evidence base
  - Systemic treatment
  - Radiotherapy
- Future directions

BACKGROUND

- 25-30% of NSCLC pts have stage III disease
- Few locally advanced NSCLC patients are candidates for surgery
- Survival is poor
  - Traditionally stage IIIA -10-25% 5 year survival
- Scope for improving local and distant control

CHALLENGES OF TREATING STAGE III DISEASE

- Patient factors
  - Age
  - PS
  - Co-morbidities
- Tumour factors
  - Disease location and extent
  - Tumour subtype, molecular profile
  - Intrinsic tumour heterogeneity



RADICAL OPTIONS FOR STAGE III DISEASE

- Surgery
- Radiotherapy alone
- Sequential chemo-radiotherapy
- Concurrent chemo-radiotherapy

- Trimodality treatment

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SEQUENTIAL AND CONCURRENT CHEMORADIOTHERAPY

SEQUENTIAL CHEMORADIOTHERAPY

- BMJ metanalysis 1995:
  - hazard ratio of 0.87 in favour of combined treatment
  - 13% reduction in the risk of death
  - absolute benefit of 4% at two years

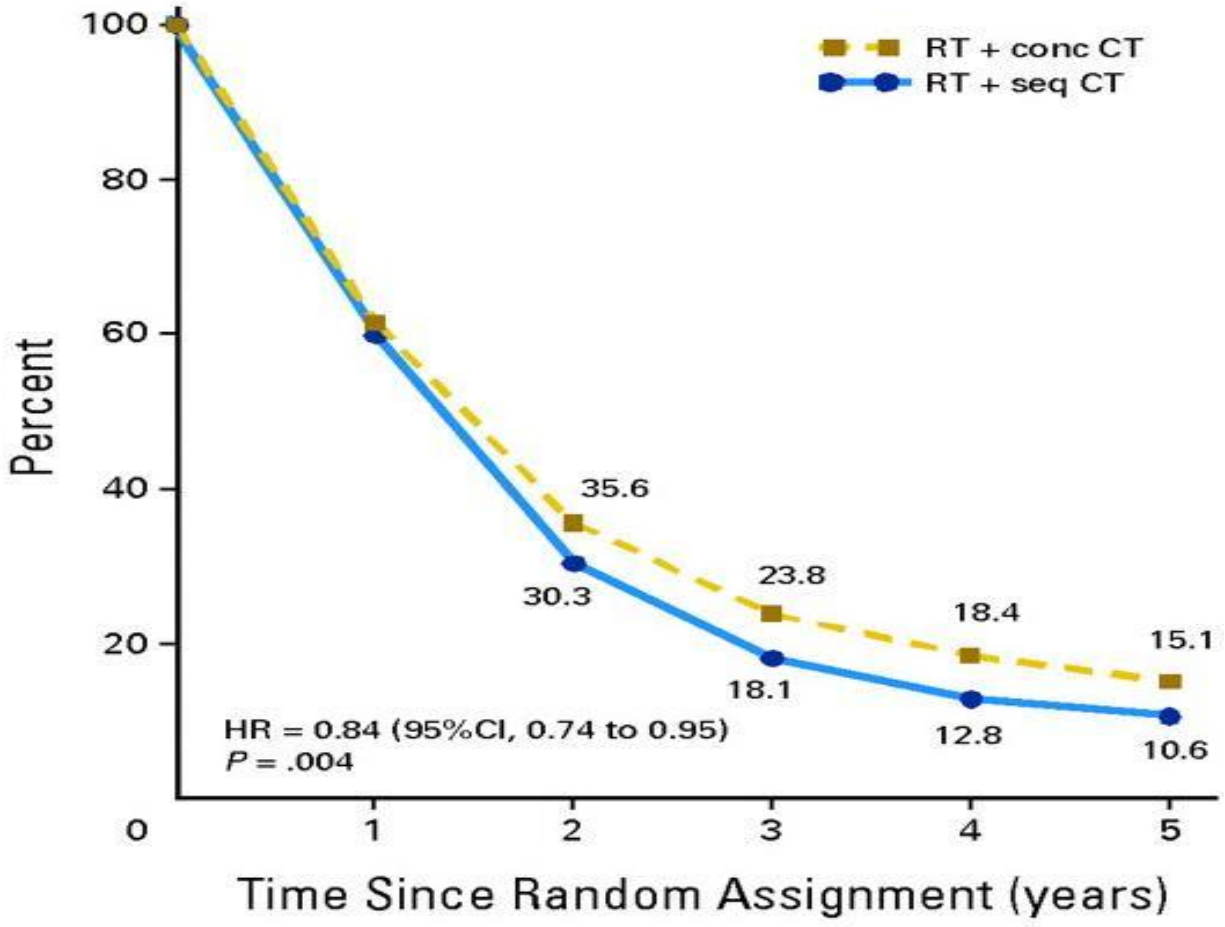
- Heterogeneity in chemotherapy regimens and radiotherapy schedules used

CONCURRENT CHEMORADIOTHERAPY

Auperin metanalysis 2010:

- Concurrent CTRT superior to sequential
- HR 0.83 overall survival in favour of concurrent
- 4.5% survival benefit at 5 years

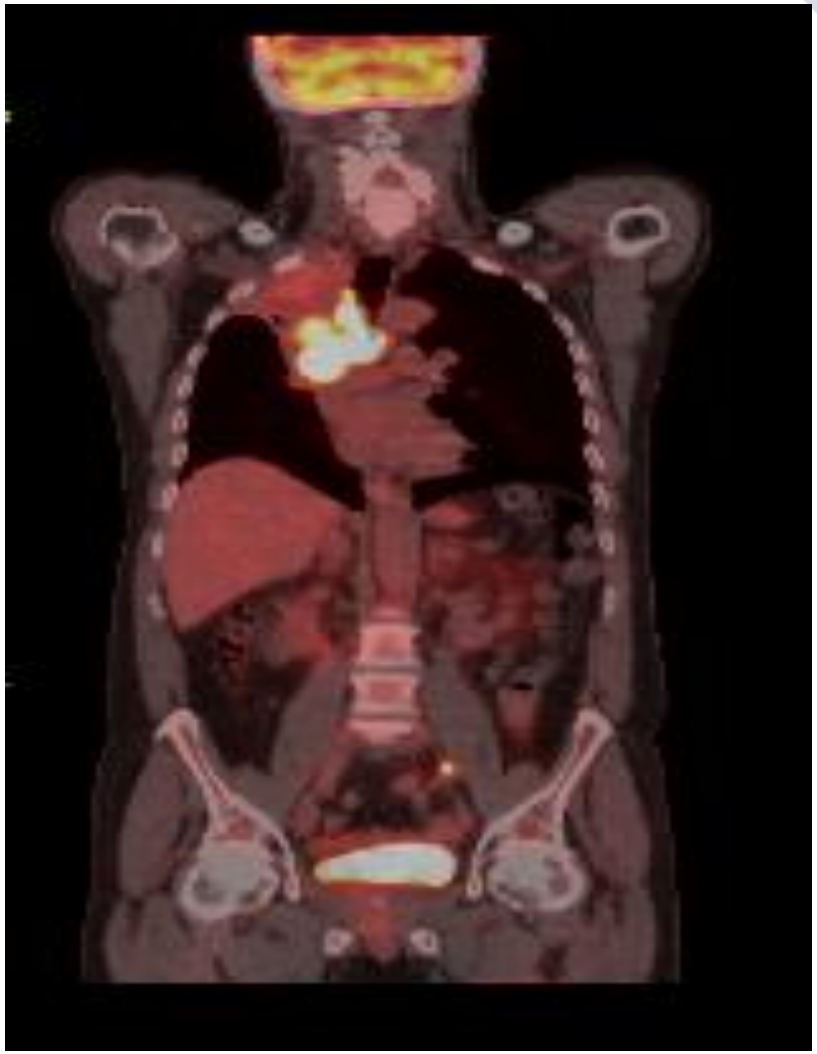
- Significantly higher oesophagitis rate (HR 4.9)
- Similar pneumonitis rate



Anne Aupérin et al. JCO 2010;28:2181-2190

PATIENT SELECTION

- Performance status
  - PS 0-1
- Co morbidities incl renal function
- PET
- Mediastinal staging (EBUS)
- Brain imaging
- Pulmonary function testing
  - FEV_1 > 40%
  - KCO >40%
- ? PDL1 status



WHICH CHEMOTHERAPY?

- Platinum based chemo with 3rd generation drugs
  - Taxol/Gemcitabine/Vinorelbine (reduced doses)
  - Cisplatin/Etoposide (full dose)
  - Carboplatin/Paclitaxel

- No benefit of Pemetrexed in concurrent setting (PROCLAIM trial)
- No *current* evidence to support the use of concurrent TKI/RT

Vokes JCO 2002, Hanna JCO 2008, Santana-Devilla JCO 2015
Senan, JCO 2016

Induction chemotherapy

CALGB 39801 (Vokes, JCO 2007)

Consolidation [illegible]motherapy

HO[illegible] JCO 2008)
(Ahn, JCO 2015)

NO BENEFIT

More s[illegible]ic treatment

Consolidation TKI/Cetuximab

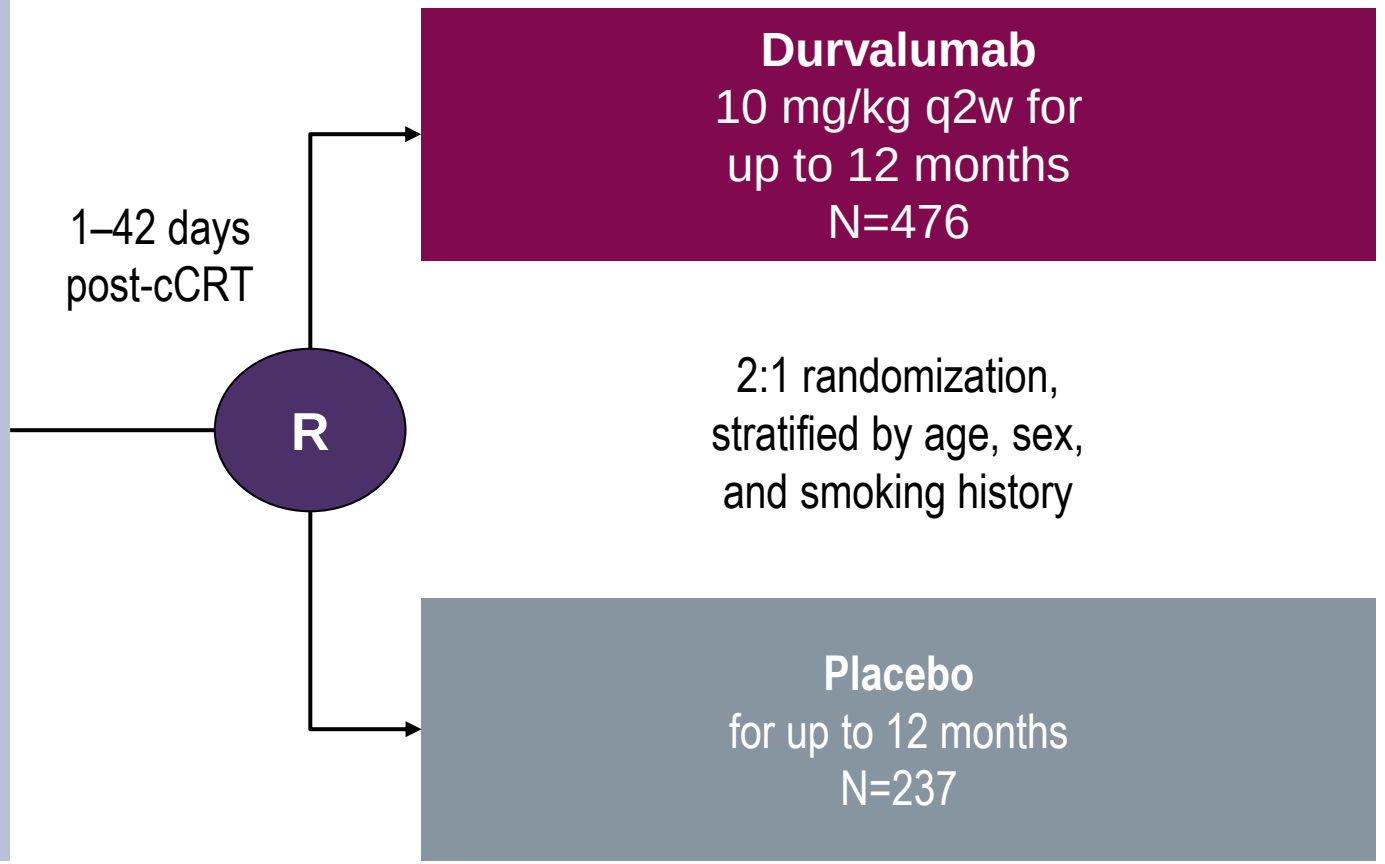
CALEB 30106 (Ready, JTO 2010)
RTOG 0617 (Bradley, Lancet 2015)

CONSOLIDATION IMMUNOTHERAPY - PACIFIC

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

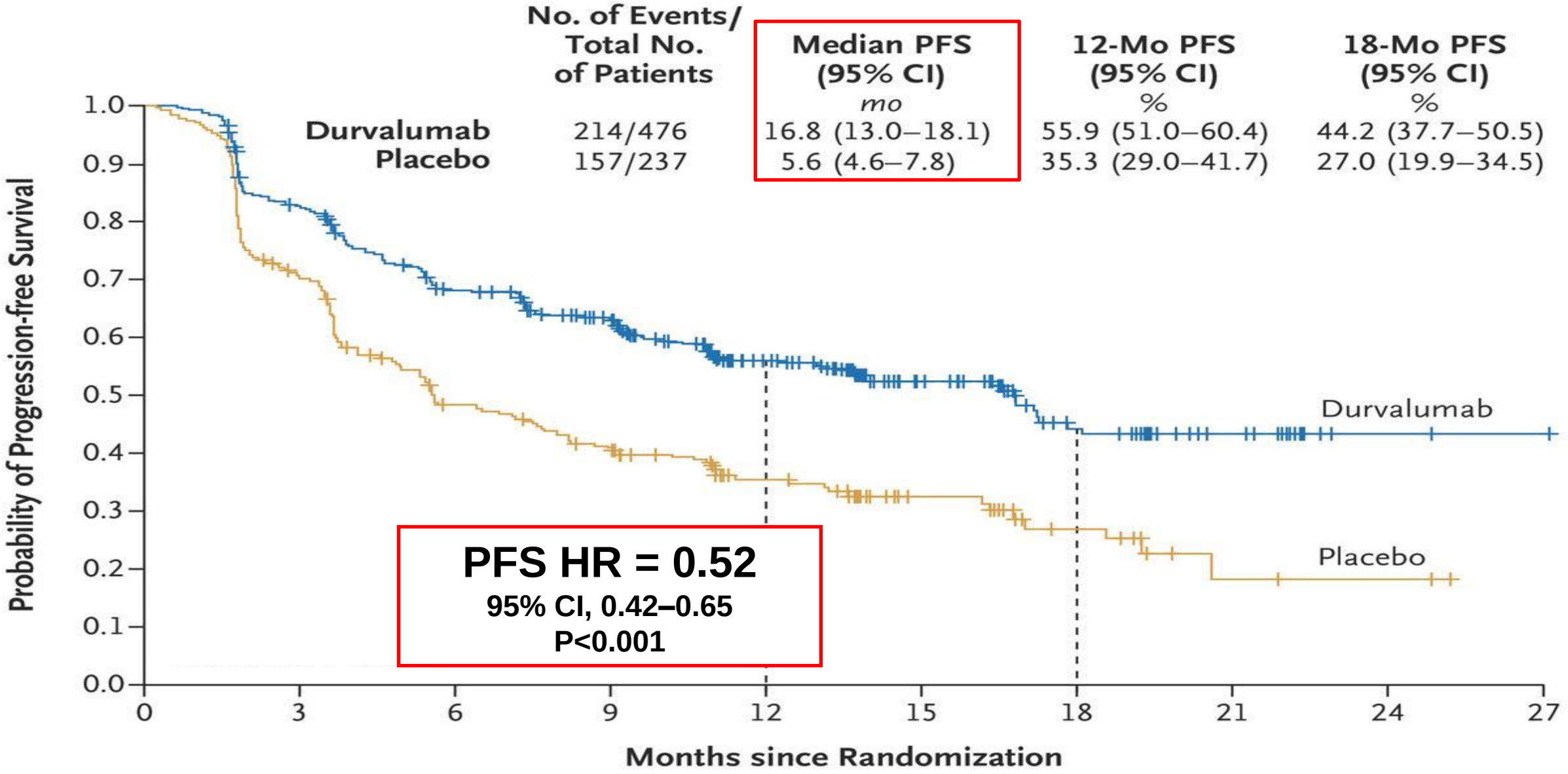
All-comers population
(i.e. irrespective of PD-L1 status)

N=713 randomized



Antonia S, et al. NEJM 2017; 377:1919–29;
Antonia S, et al. NEJM 2018; 379:2342-2350

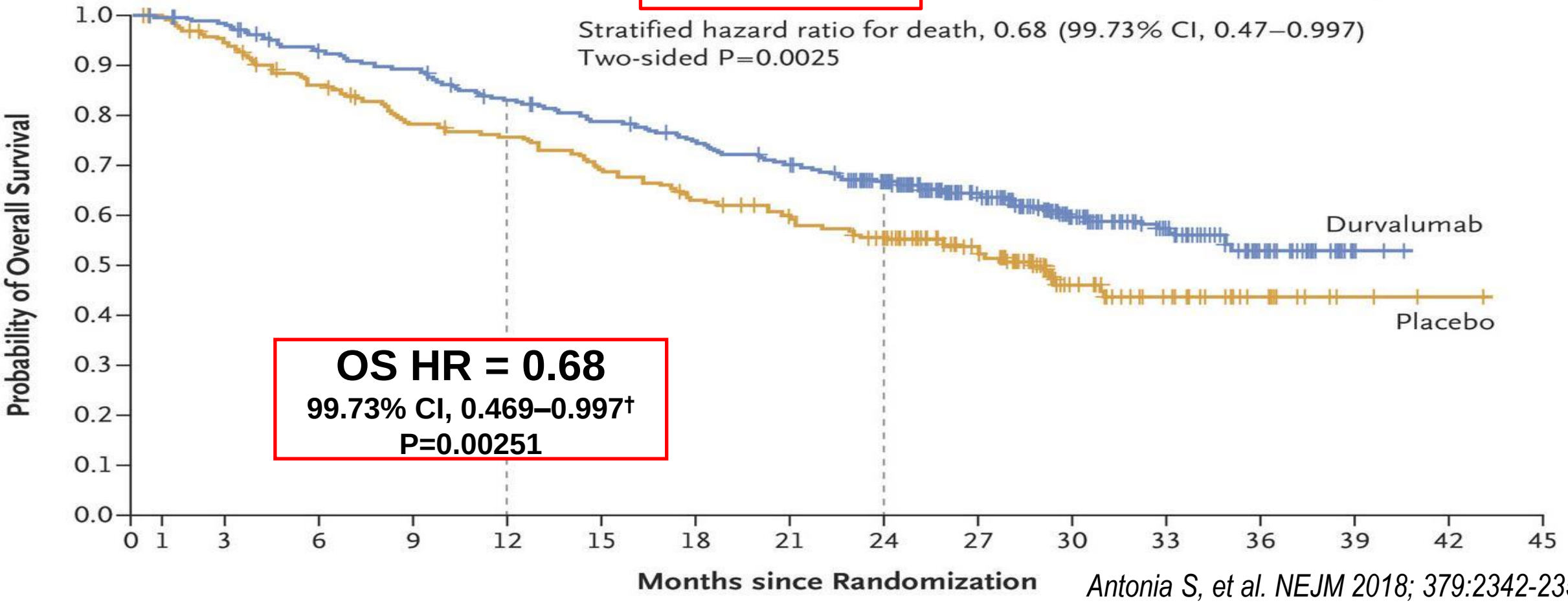
PROGRESSION FREE SURVIVAL



Antonia S, et al. NEJM 2017; 377:1919–29

OVERALL SURVIVAL

	No. of Events/ Total No. of Patients	Median Overall Survival (95% CI) *mo*	12-Mo Overall Survival Rate (95% CI) %	24-Mo Overall Survival Rate (95% CI) %
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)



OS HR = 0.68
99.73% CI, 0.469–0.997†
P=0.00251

Antonia S, et al. NEJM 2018; 379:2342-2350

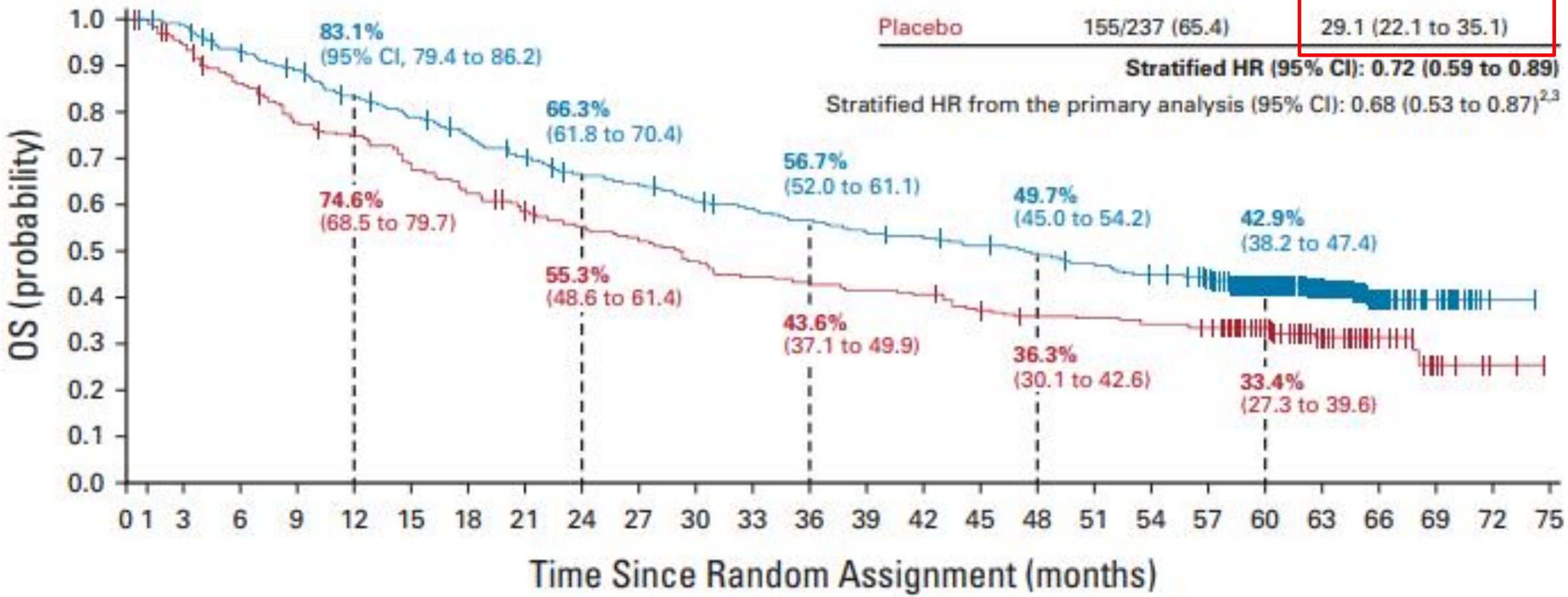
UPDATED OS

OS HR = 0.72
(95% CI, 0.59–0.89)

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



Spigel, D et al. JCO 2022; 40(12):1301-1311

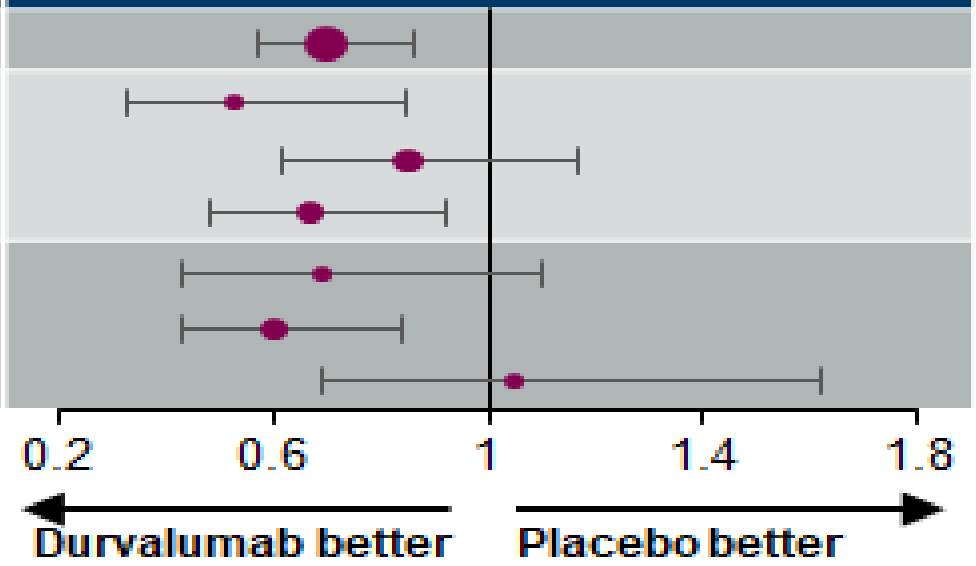
Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

TOXICITY

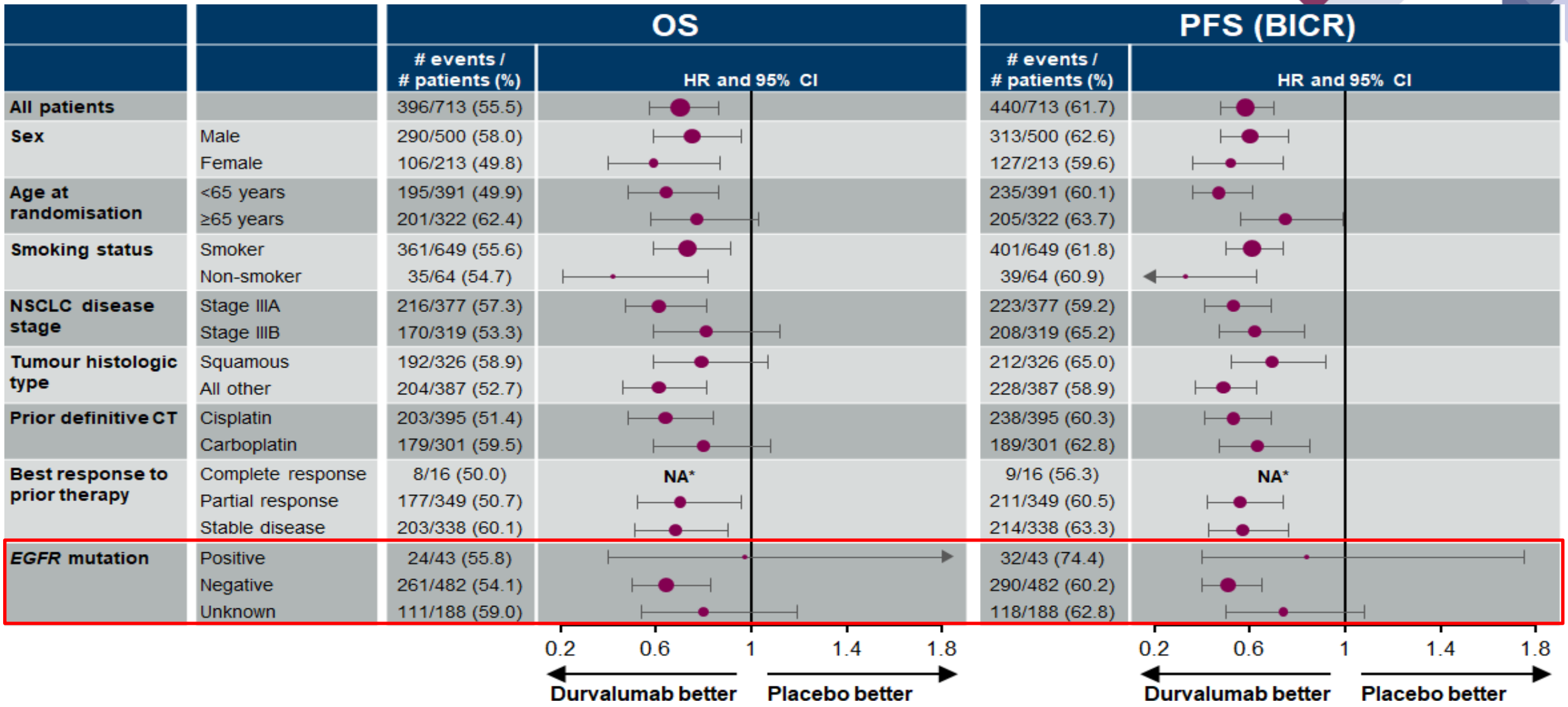
Antonia S, et al. NEJM 2017; 377:1919–29

PDL1 STATUS

		OS	
		# events / # patients (%)	HR and 95% CI
All patients		396/713 (55.5)	
PD-L1 status (pre-specified)	≥25%	76/159 (47.8)	
	<25%	164/292 (56.2)	
	Unknown	156/262 (59.5)	
PD-L1 status (post-hoc)	1–<25%	75/144 (52.1)	
	≥1%	151/303 (49.8)	
	<1%	89/148 (60.1)	



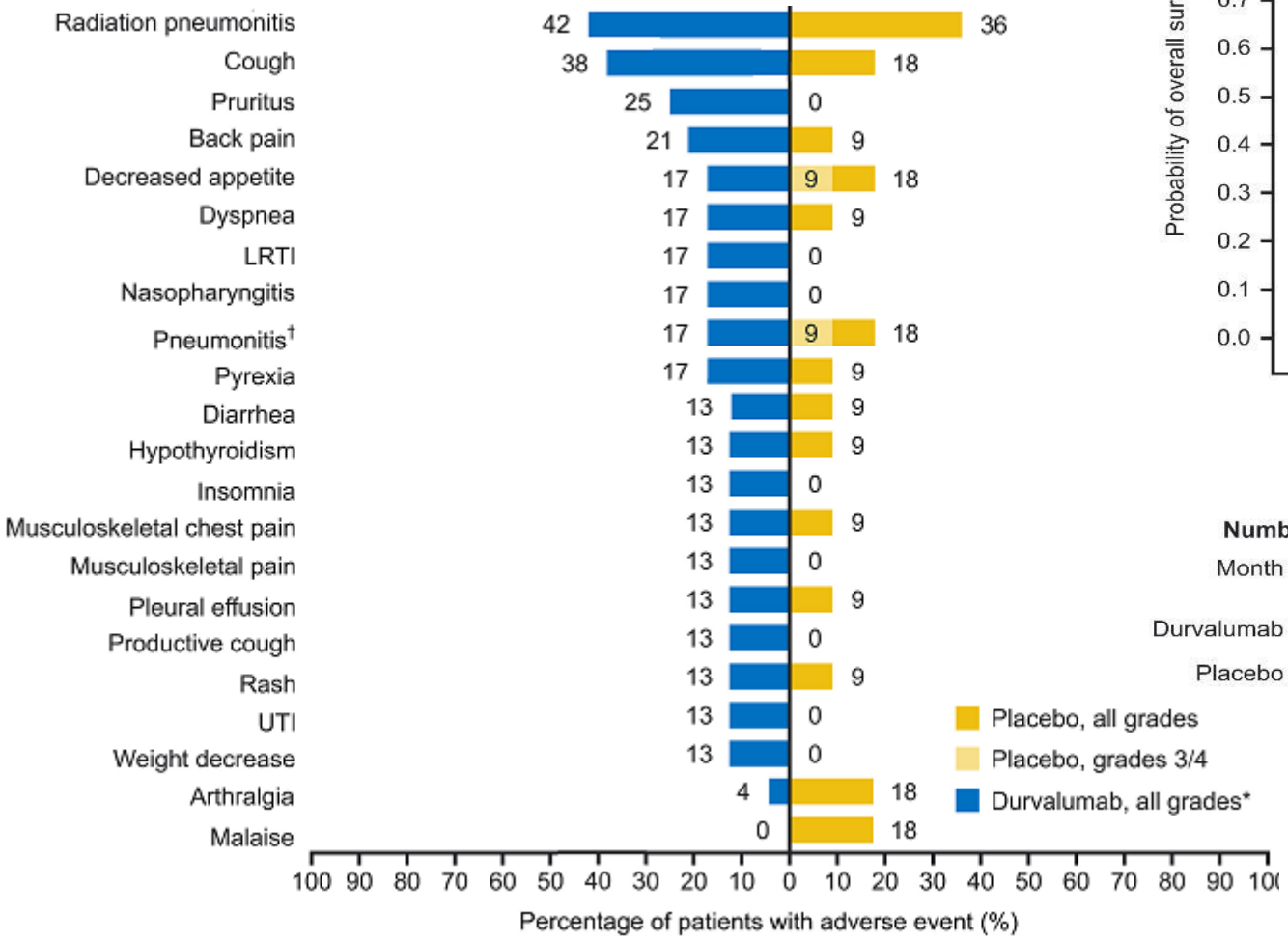
Faivre-Finn, C et al. J Thorac Oncol 2021;16(5):860-867

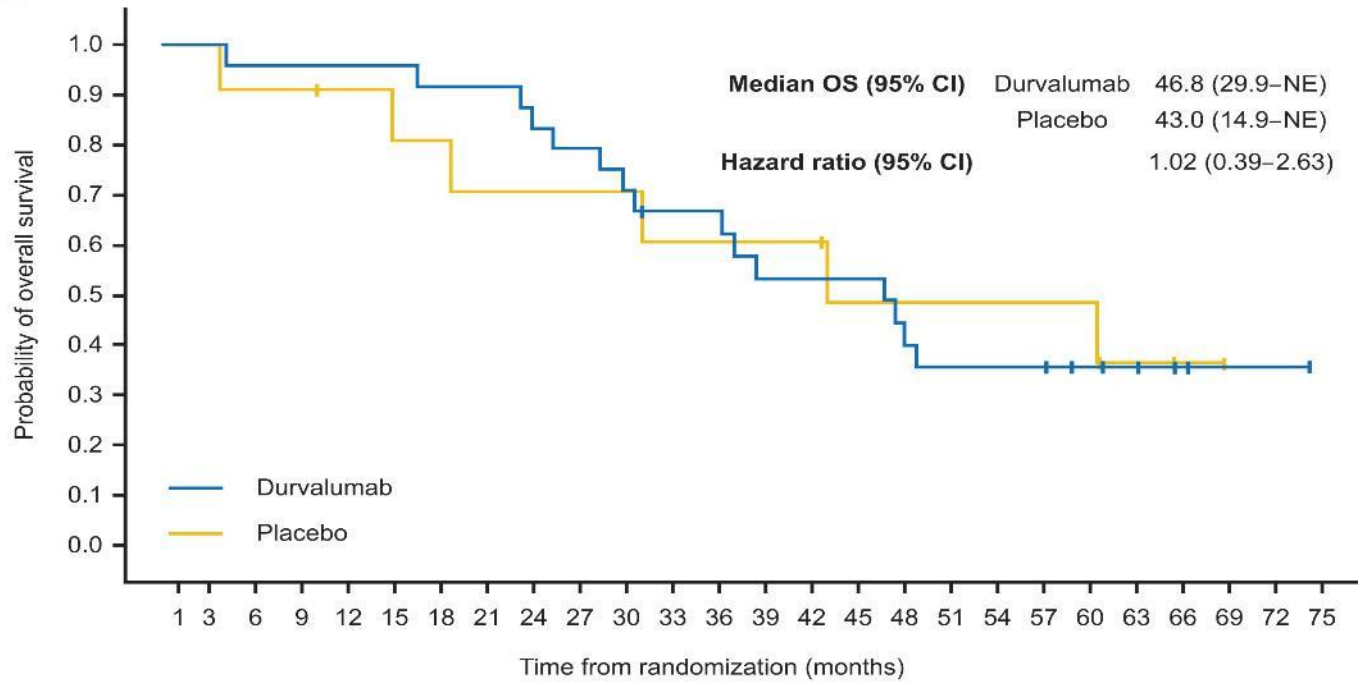


Faivre-Finn, C et al. J Thorac Oncol 2021;16(5):860-867

Brief Report: Durvalumab After Chemoradiotherapy in Unresectable Stage III *EGFR*-Mutant NSCLC: A Post Hoc Subgroup Analysis From PACIFIC

Jarushka Naidoo, MbChB., MHS,[a,*] Scott Antonia, MD, PhD,[b] Yi-Long Wu, MD,[c] Byoung Chul Cho, MD, PhD,[d] Piruntha Thiyagarajah, MD,[e] Helen Mann, MSc,[e] Michael Newton, PharmD,[f] Corinne Faivre-Finn, PhD[g]



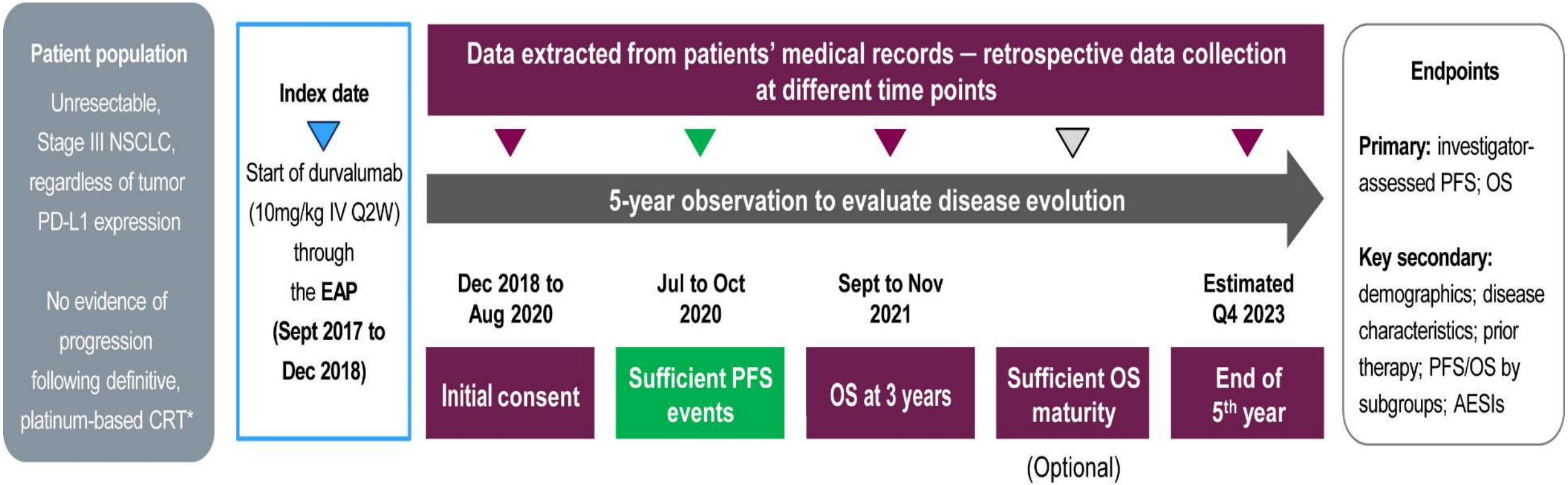


Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
Durvalumab	24	24	23	23	23	23	22	22	20	19	17	15	15	12	12	12	10	8	8	8	5	4	2	1	1	0
Placebo	11	11	10	10	9	8	8	7	7	7	7	6	6	6	6	4	4	4	4	4	4	2	1	0	0	0

Naidoo, J et al. JTO; 2023;18(5):657-663

PACIFIC-R (REAL WORLD DATA)

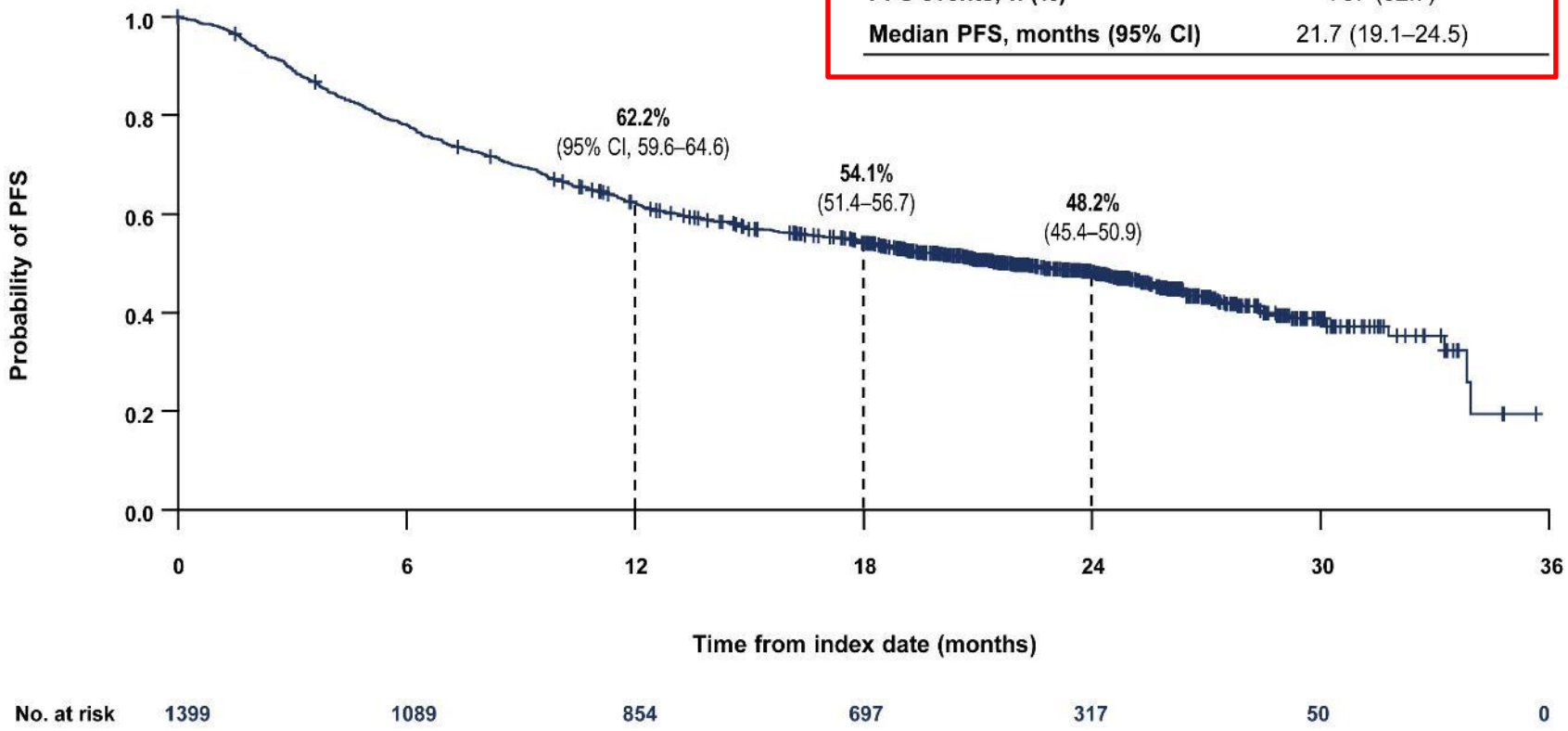


Girard N, et al. JTO; 2023;18(2):181-193

PACIFIC-R: PFS

Characteristic	Full set (n=1399)
Median age at EAP inclusion, yrs (range)	66.0 (26–88)
Age category at EAP inclusion, n (%)	
<70	958 (68.5)
70-75	296 (21.2)
>75	145 (10.4)
ECOG PS at EAP inclusion, n (%)	
0	489 (51.4)
1	443 (46.6)
2-3	19 (2.0)
Histology, n (%)	
Squamous	496 (36.0)
Non-squamous	882 (64.0)
PD-L1 status, n (%)	
≥ 1	700 (72.4)
< 1	174 (18.0)
EGFR status, n (%)	
Mutated	46 (7.9)
Wild type	517 (88.8)
Inconclusive/unknown	19 (3.3)

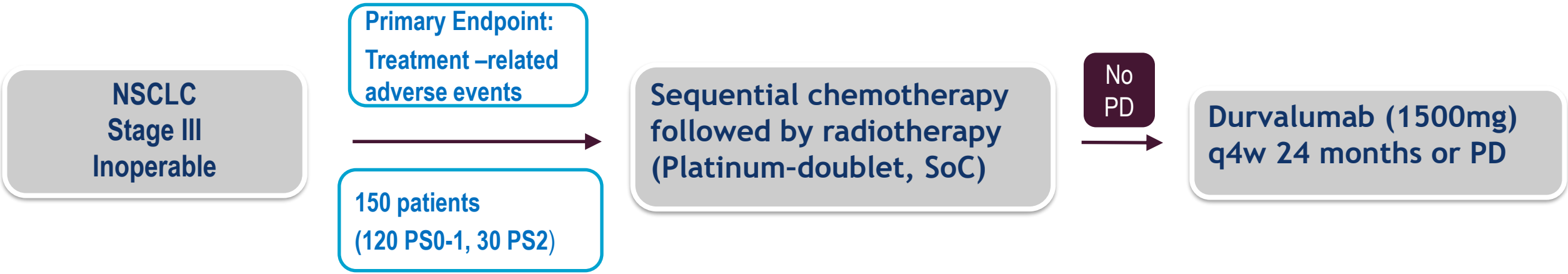
	Full Analysis Set (N=1,399)
PFS events, n (%)	737 (52.7)
Median PFS, months (95% CI)	21.7 (19.1–24.5)



Girard N, et al. JTO; 2023;18(2):181-193

PACIFIC-6

Ph II trial of Durvalumab following **SEQUENTIAL** chemotherapy and radiotherapy for stage III unresectable NSCLC



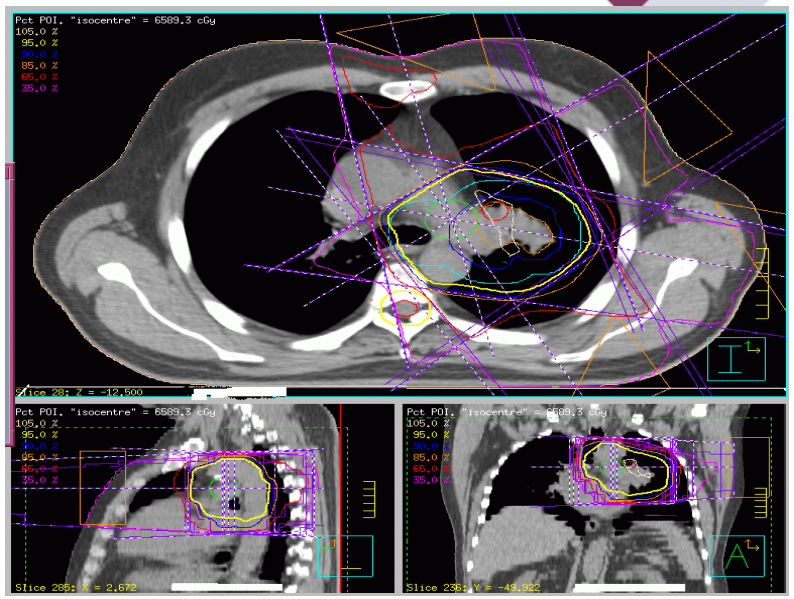
- Patients were older, more comorbid, with poorer PS than PACIFIC
- Safety profile similar to that seen in the concurrent setting
- 12 month PFS 49.6%, OS 84.1% (comparable to 12 month PFS/OS of 55.7% and 83.1% in PACIFIC study)

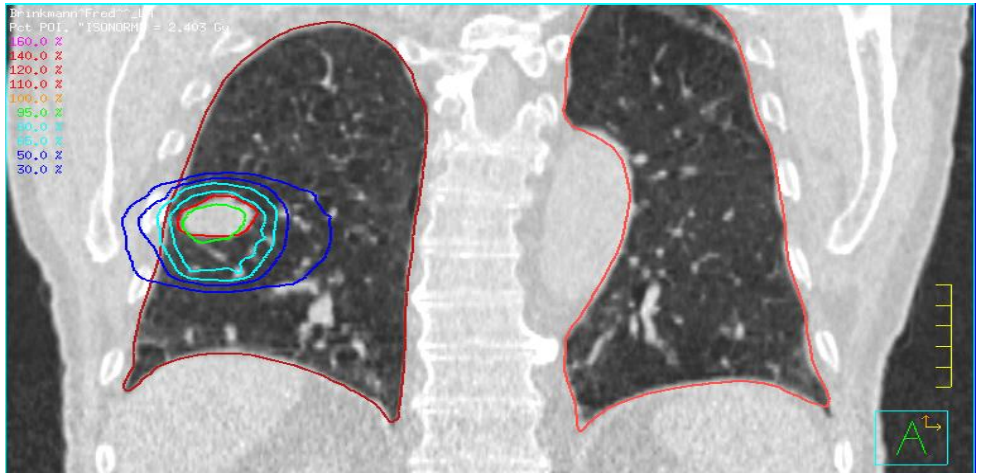
Garassino, M et al. JTO; 2022;17(12):1415-1427

RADIOTHERAPY CONSIDERATIONS

RADIOTHERAPY PLANNING

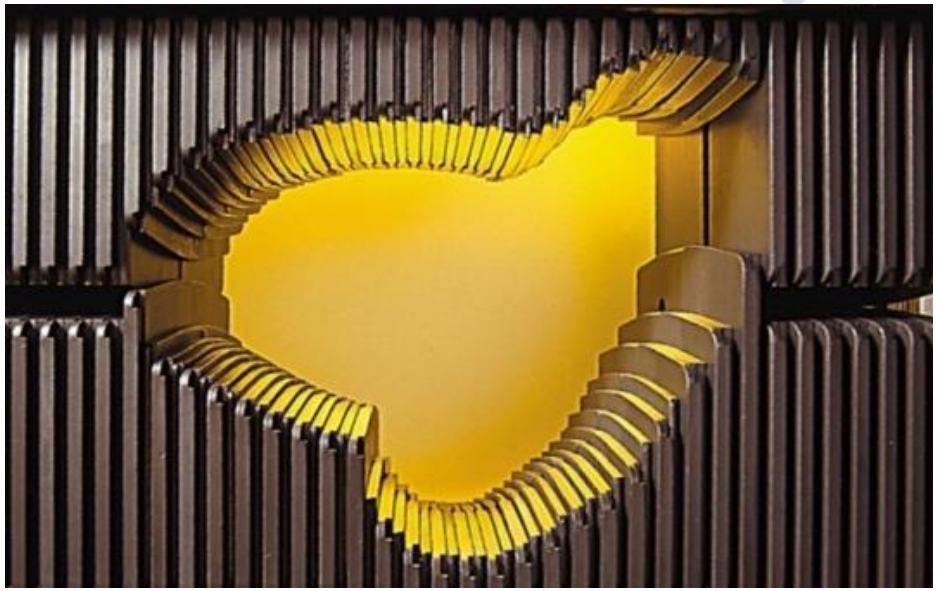
- RT commences D1 chemotherapy
  - RT planning scan done asap
- Motion management
  - 4D CT
  - Respiratory gating/Breath hold
- Advanced RT techniques
  - IMRT
  - IGRT

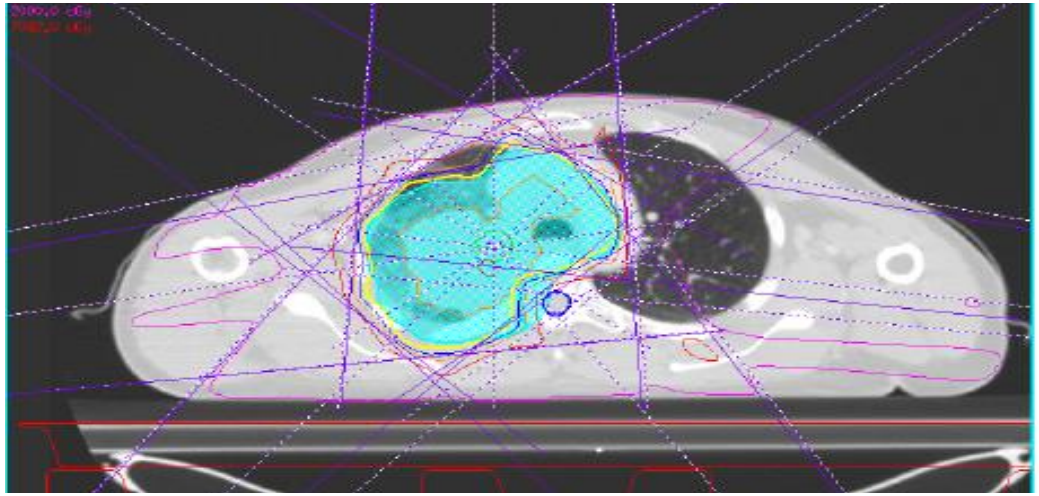


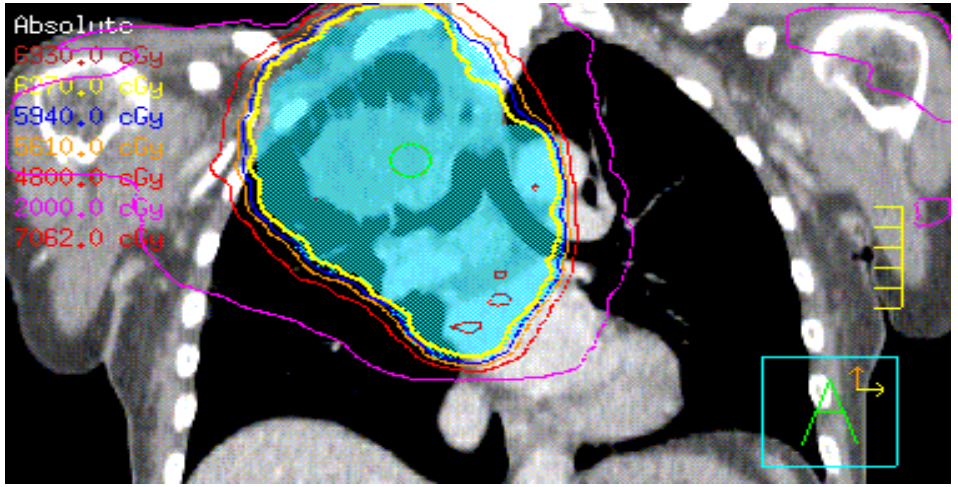


INTENSITY MODULATED RADIOTHERAPY - IMRT

- Improved conformity
- Avoidance of radiosensitive structures
  - e.g. spinal cord
- Retreatments
- Large volumes







WHAT RADIOTHERAPY DOSE?

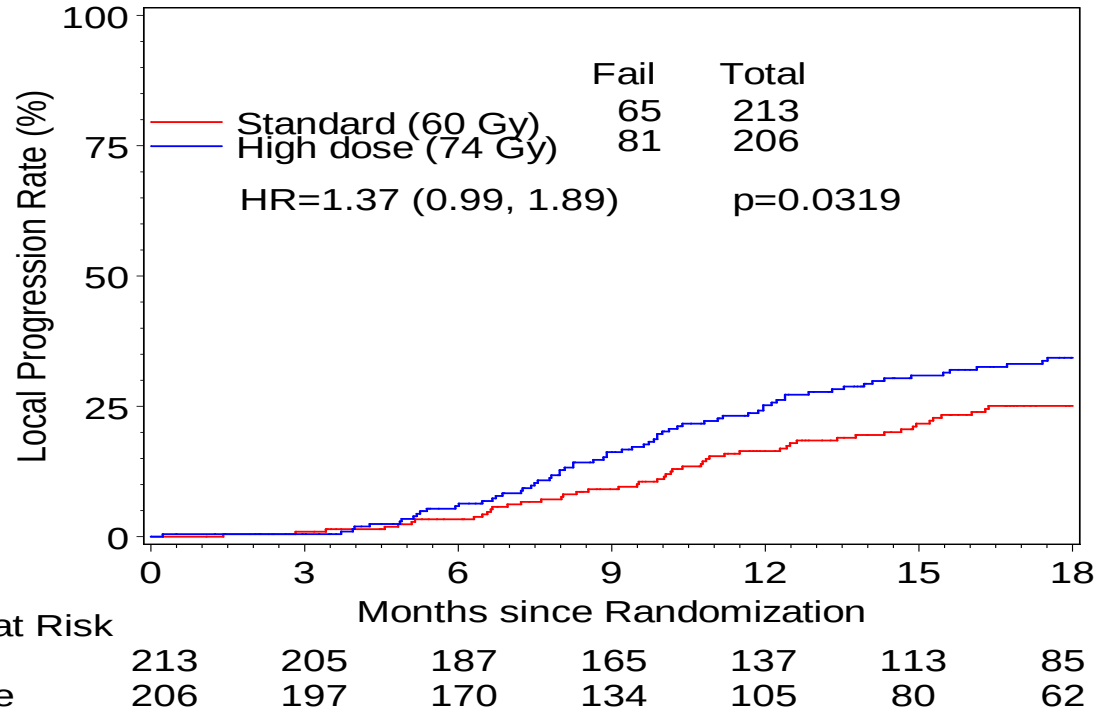
- Sequential CTRT
  - 60-66Gy/30-33# OD
  - 55Gy/20# OD
  - 54Gy/36# TDS (CHART)

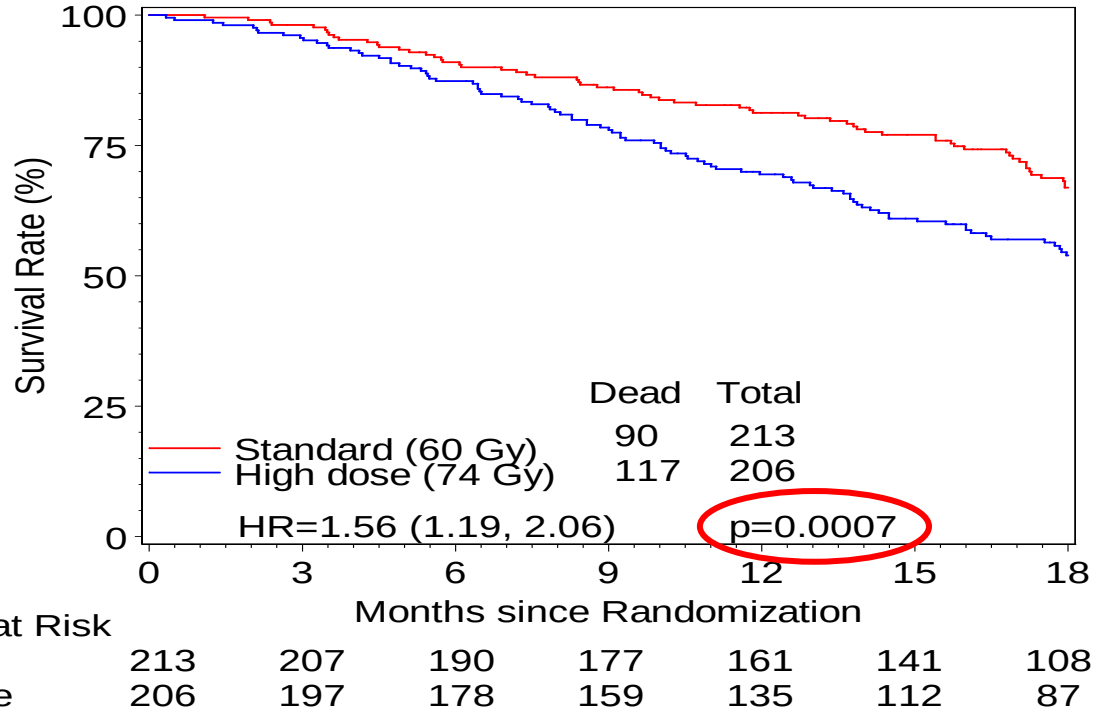
- Concurrent CTRT
  - 60-66 Gy in 30-33 fractions OD
  - 55Gy/20# (SOCCAR)

- Is there a role for more radiotherapy?
  - Greater local control correlates with improved survival
  - Modern RT techniques allow dose escalation

RTOG 0617

- Higher dose arm:
  - Greater risk of locoregional failure
  - Poorer survival



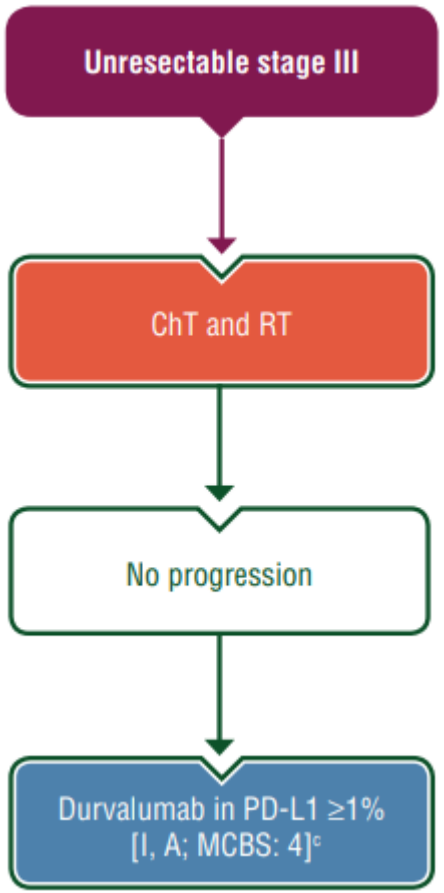


Bradley et al, Lancet Oncol 2015; 16: 187–99

CLINICAL PRACTICE GUIDELINES

Treatment

Locally advanced NSCLC (stage III) – Unresectable



2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer

Summary of recommendations	LoE, GoR
Concurrent CRT is the treatment of choice for unresectable stage IIIA and IIIB • If not possible, ChT followed by definitive RT is a valid alternative • Cisplatin-based ChT is optimal for combination with RT in stage III • For CRT in stage III, 2–4 cycles of concomitant ChT should be delivered	I, A
For concurrent CRT, 60–66 Gy in 30–33 daily fractions is recommended	I, A
• The maximum treatment time should not exceed 7 weeks	III, B
'Biological intensification' is not standard practice in concurrent CRT schedules	III, B
In sequential approaches, RT over a short treatment time is recommended	I, A
There is no role for prophylactic cranial RT in stage III	II, A
There is no role for targeted agents in stage III outside clinical trials	I, A

Eberhardt, W et al. Annals of Oncology 2015; 26: 1573–1588
Remon, J et al. Annals of Oncology. 2021;32 (12):1637-1642

FUTURE DIRECTIONS

- Individualised treatment
  - Molecular drivers
  - Personalised RT dose
- Determining best use of immunotherapy
- Combination with novel agents in sequential setting

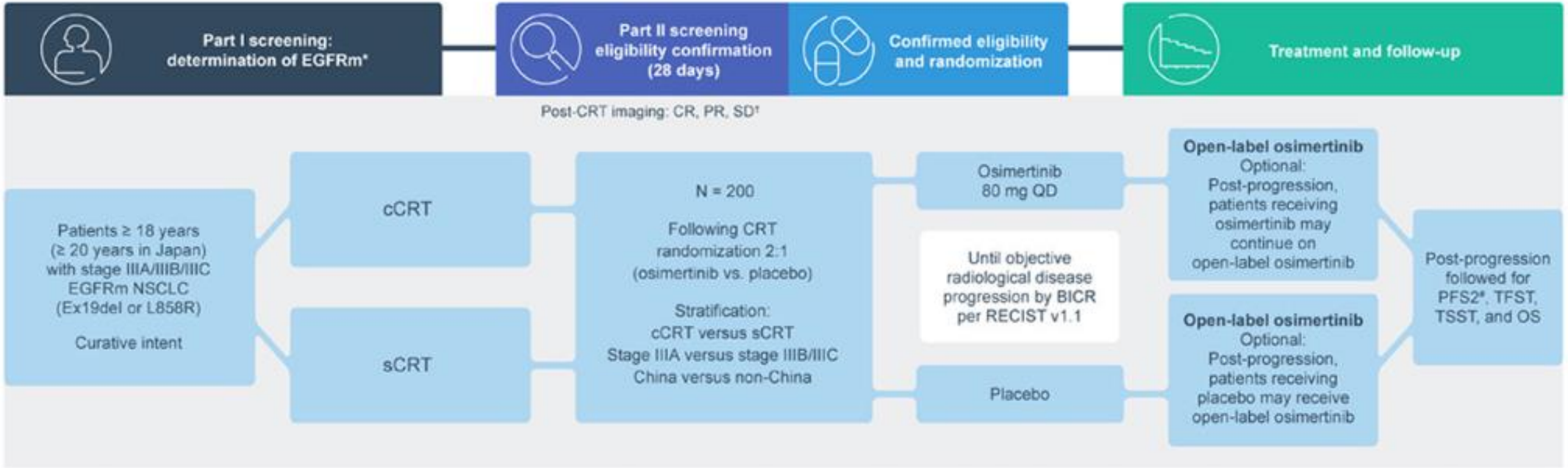
LAURA STUDY – OSIMERTINIB POST CTRT

TRIAL OVERVIEW

Study design:
Phase III
Double-blind
Randomized
Placebo-controlled

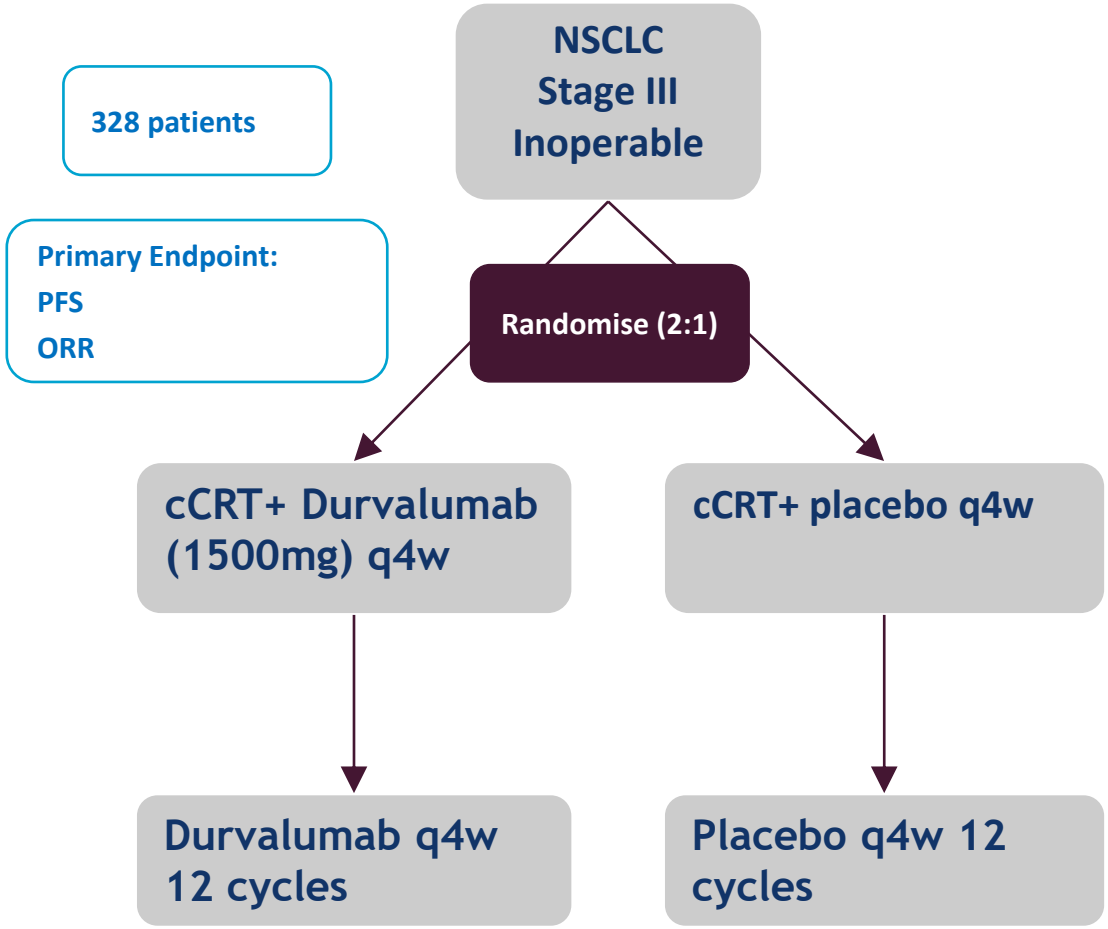
Objective:
To evaluate the efficacy and safety of osimertinib as maintenance therapy in patients with locally advanced, unresectable, EGFRm, stage III NSCLC without disease progression during/ following definitive platinum-based CRT

Primary endpoint: PFS by BICR per RECIST v1.1
Key secondary endpoints:
CNS PFS, OS, PFS by mutation status, and safety (adverse events by CTCAE v5)

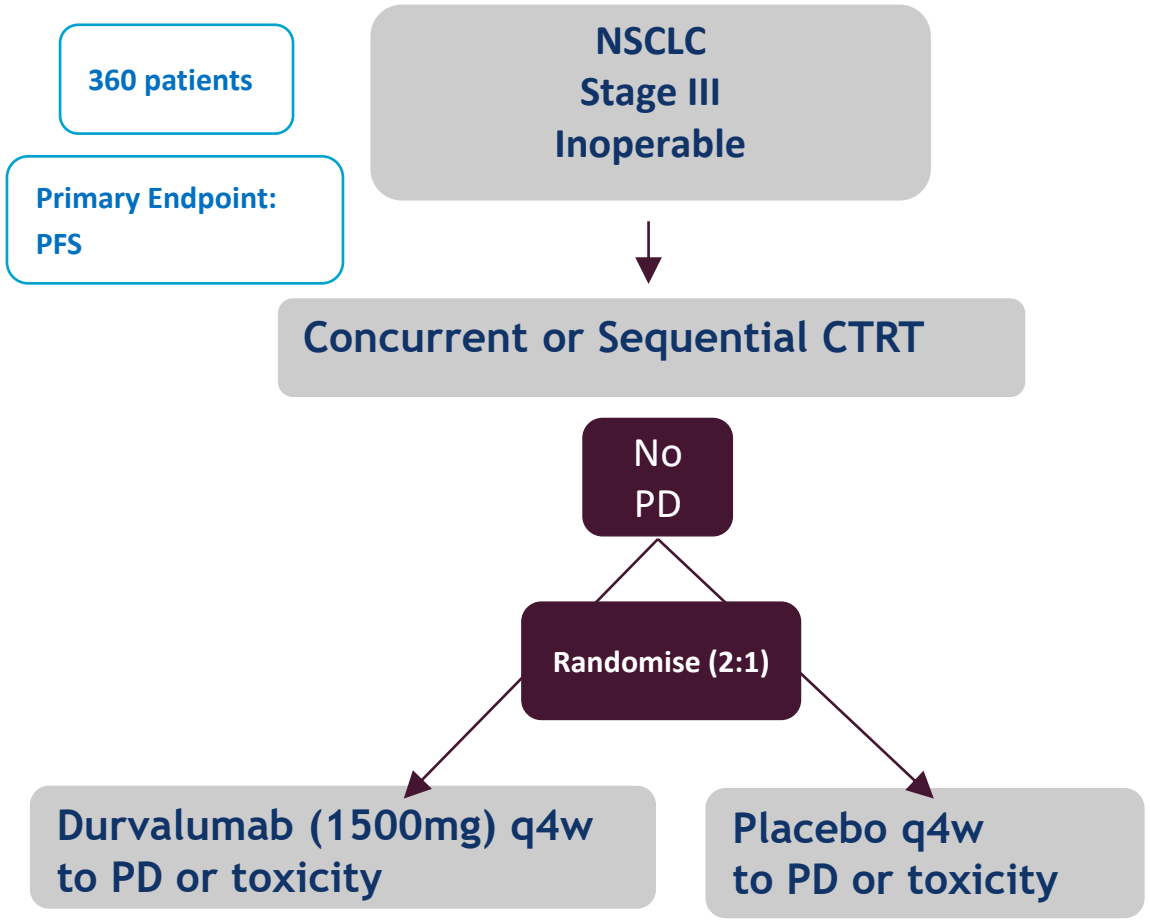


*Patients with a local cobas® EGFR Mutation Test v2 tissue positive result from a CLIA-certified or accredited laboratory do not require part I screening. †Post-CRT imaging performed to assess CR, PR and SD up to 28 days before randomization. ‡Assessment of PFS2 will not be collected after the primary PFS analysis.

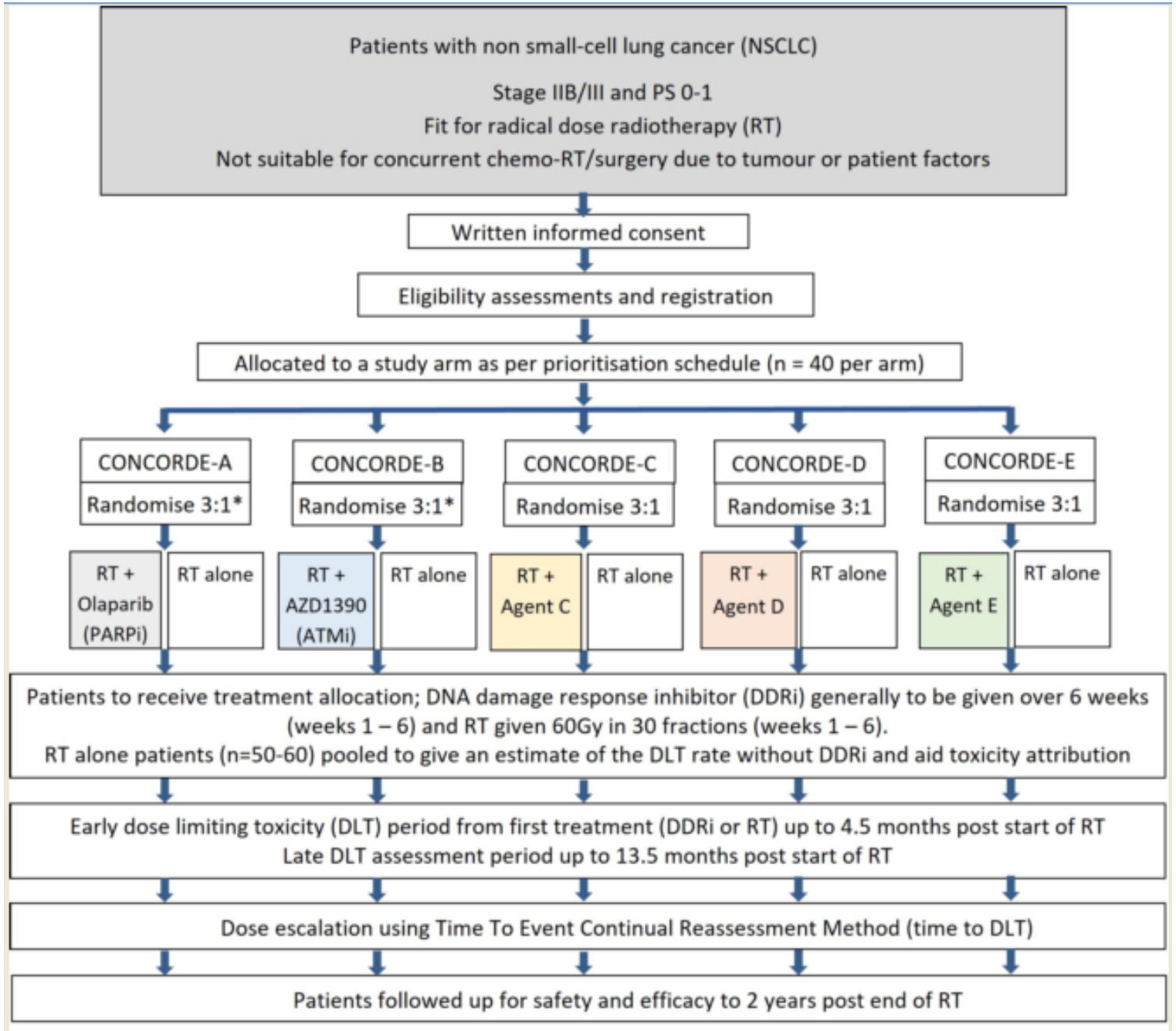
PACIFIC 2: Ph III trial of CONCURRENT CTRT +/- Durvalumab for stage III unresectable NSCLC



PACIFIC 5: Ph III trial of Durvalumab following CONCURRENT or SEQUENTIAL CTRT for stage III unresectable NSCLC



CONCORDE



TAKE HOME MESSAGES

- Concurrent platinum based chemoradiotherapy remains gold standard for inoperable stage III disease

- Overall survival benefit to consolidation Durvalumab if PDL1 > 1%
  - less evidence to support Durvalumab in patients with driver mutations
  - Increasingly important to know molecular status at diagnosis

- For patients unsuitable for concurrent treatment, sequential CTRT or RT alone
- No benefit to radiotherapy dose escalation with conventional fractionation
- Improved RT techniques may allow greater individualisation of treatment in the future