University of Colorado Cancer Center
University of Colorado Hospital
University of Colorado Health Sciences Center

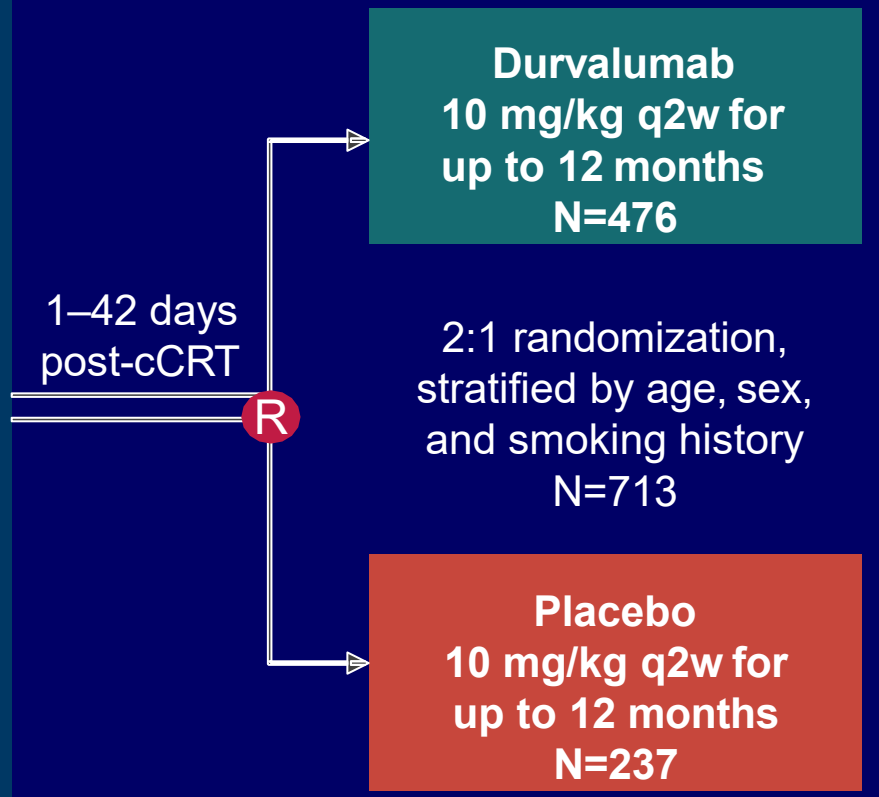
Innovation in Unresectable stage III NSCLC

Paul A. Bunn, Jr, MD, Distinguished Professor and Dudley Endowed Chair, Univ. of Colorado Cancer Center, Aurora, CO, USA

PACIFIC: Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study in unresectable stage III NSCLC

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population



Co-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

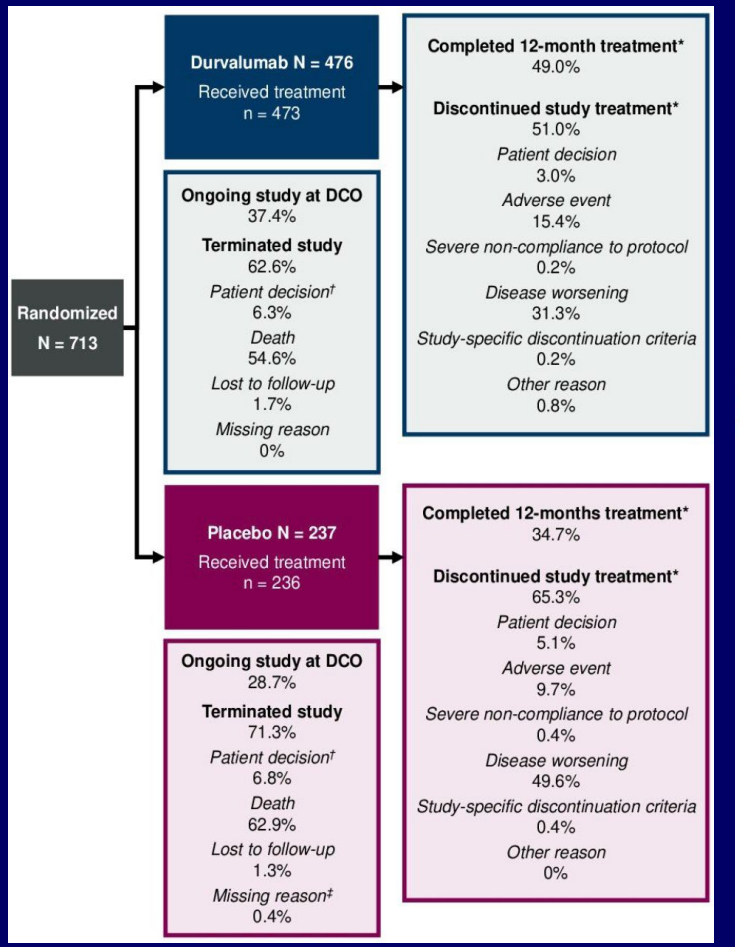
Key secondary endpoints

- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

*Defined as the time from randomization (which occurred up to 6 weeks post-cCRT) to the first documented event of tumor progression or death in the absence of progression.
ClinicalTrials.gov number: NCT02125461 BICR, blinded independent central review; cCRT, concurrent chemoradiation therapy; DoR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization

5-year Survival Outcomes with Durvalumab after Chemoradiotherapy in Unresectable Stage III NSCLC – an Update from the PACIFIC Trial

David R. Spigel,[1] Corinne Faivre-Finn,[2] Jhanelle E. Gray,[3] David Vicente,[4] David Planchard,[5] Luis Paz-Ares,[6]



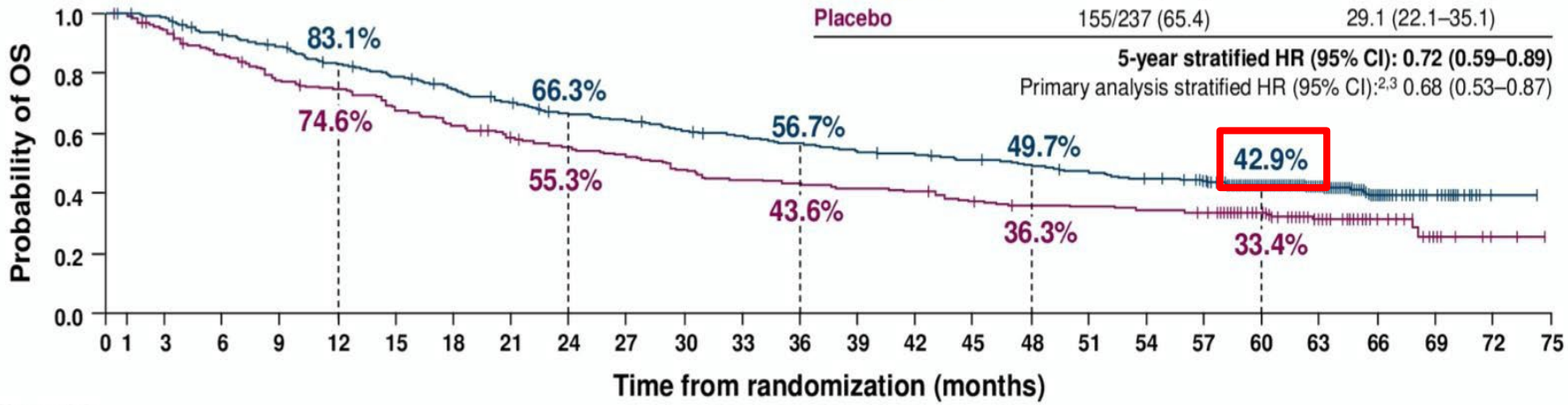
5 yr PFS=33%
5 yr OS=43%

Spigel ASCO 21

Figure 3. 5-year OS and PFS (BICR) (ITT)

	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	264/476 (55.5)	47.5 (38.1–52.9)
Placebo	155/237 (65.4)	29.1 (22.1–35.1)

5-year stratified HR (95% CI): 0.72 (0.59–0.89)
Primary analysis stratified HR (95% CI):[2,3] 0.68 (0.53–0.87)

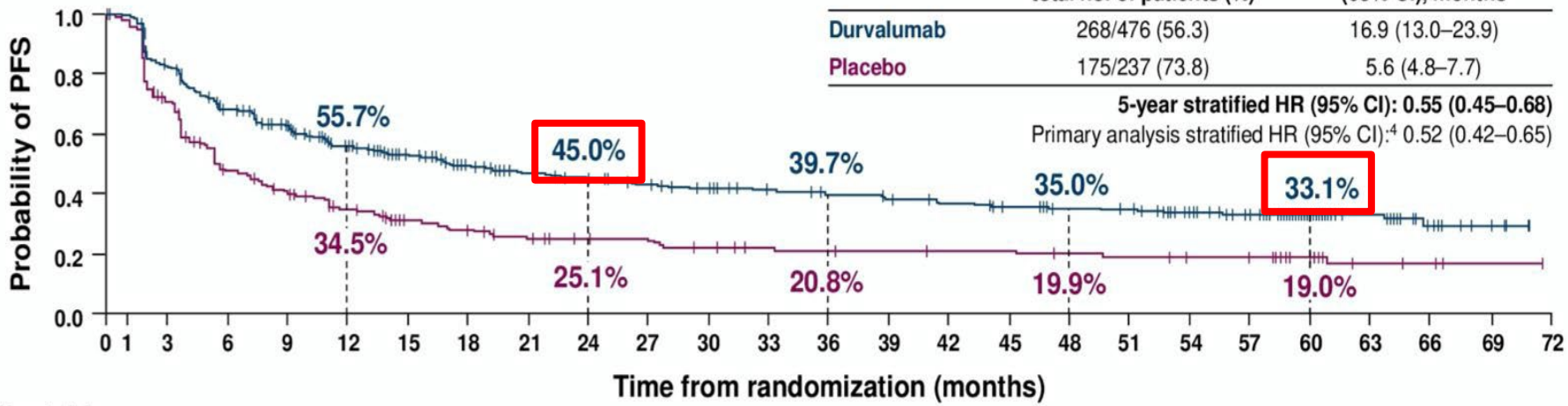


No. at risk

Durva.	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

	No. of events/ total no. of patients (%)	Median PFS (95% CI), months
Durvalumab	268/476 (56.3)	16.9 (13.0–23.9)
Placebo	175/237 (73.8)	5.6 (4.8–7.7)

5-year stratified HR (95% CI): 0.55 (0.45–0.68)
Primary analysis stratified HR (95% CI):[4] 0.52 (0.42–0.65)



No. at risk

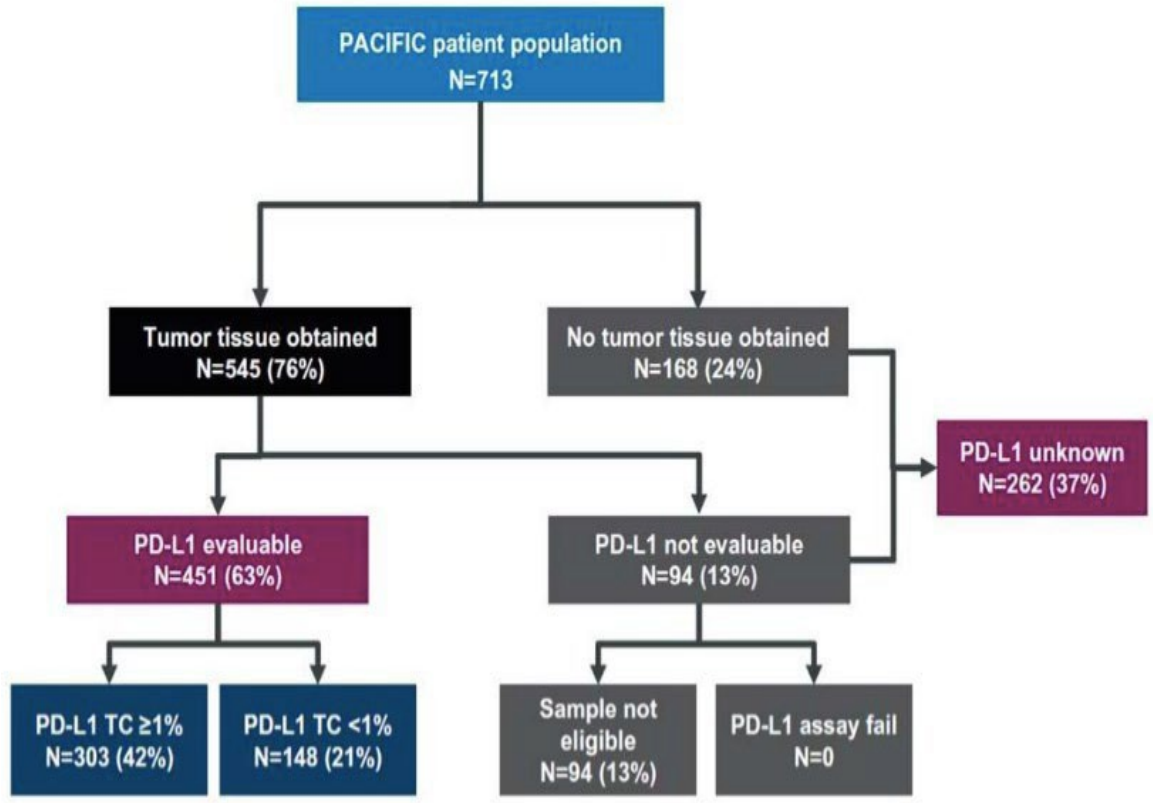
Durva.	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

PACIFIC: updated safety summary

	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	145 (30.5)	61 (26.1)
Outcome of death	21 (4.4)	15 (6.4)
Leading to discontinuation	73 (15.4)	23 (9.8)
Serious AEs, n (%)	138 (29.1)	54 (23.1)
Any-grade pneumonitis/radiation pneumonitis, n (%)	161 (33.9)	58 (24.8)
Grade 3/4	17 (3.6)	7 (3.0)
Outcome of death	5 (1.1)	5 (2.1)
Leading to discontinuation	30 (6.3)	10 (4.3)

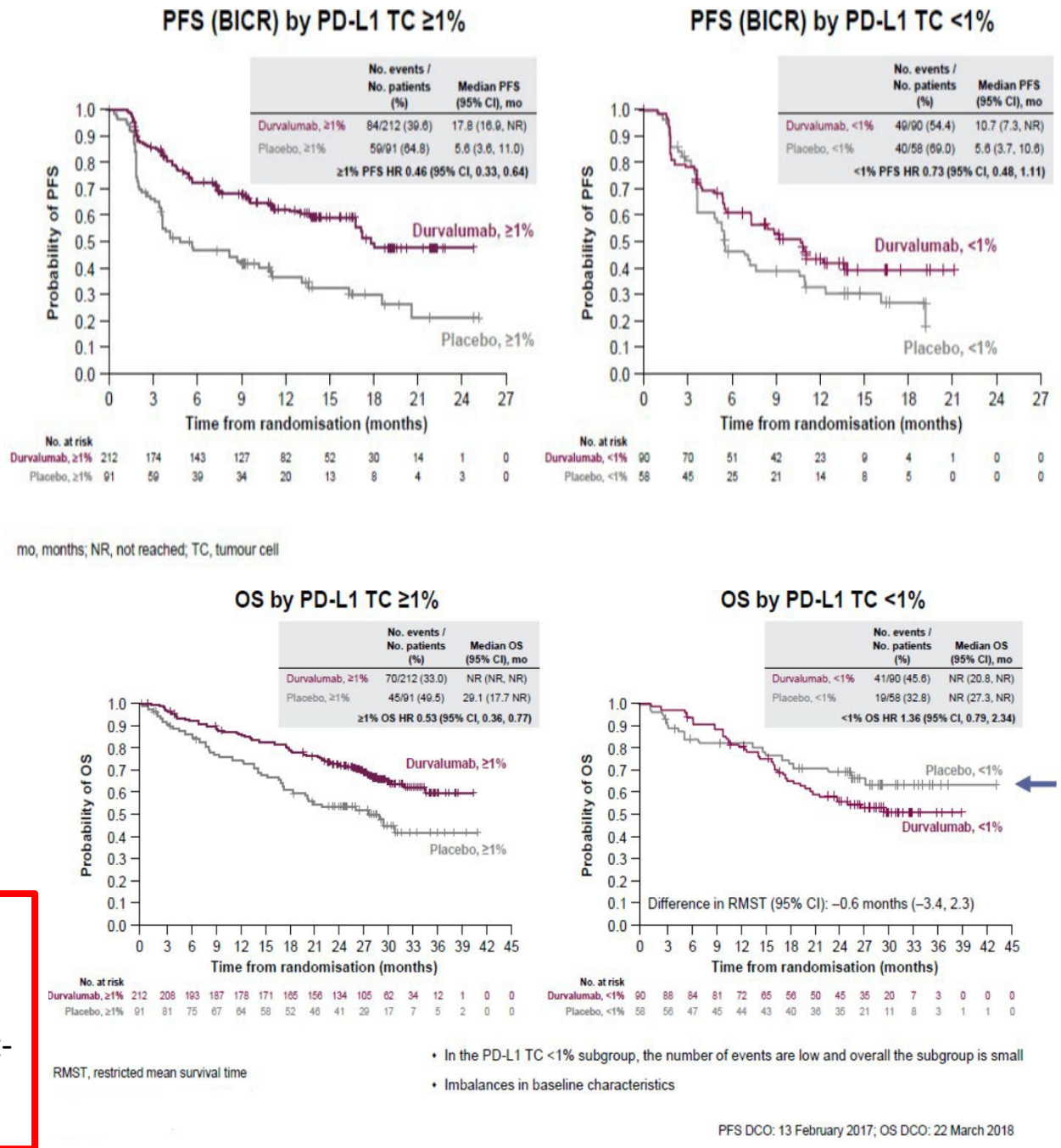
Antonia NEJM 18

Subgroup analysis by PD-L1 status



PD-L1 TC, PD-L1 expression on tumor cells.

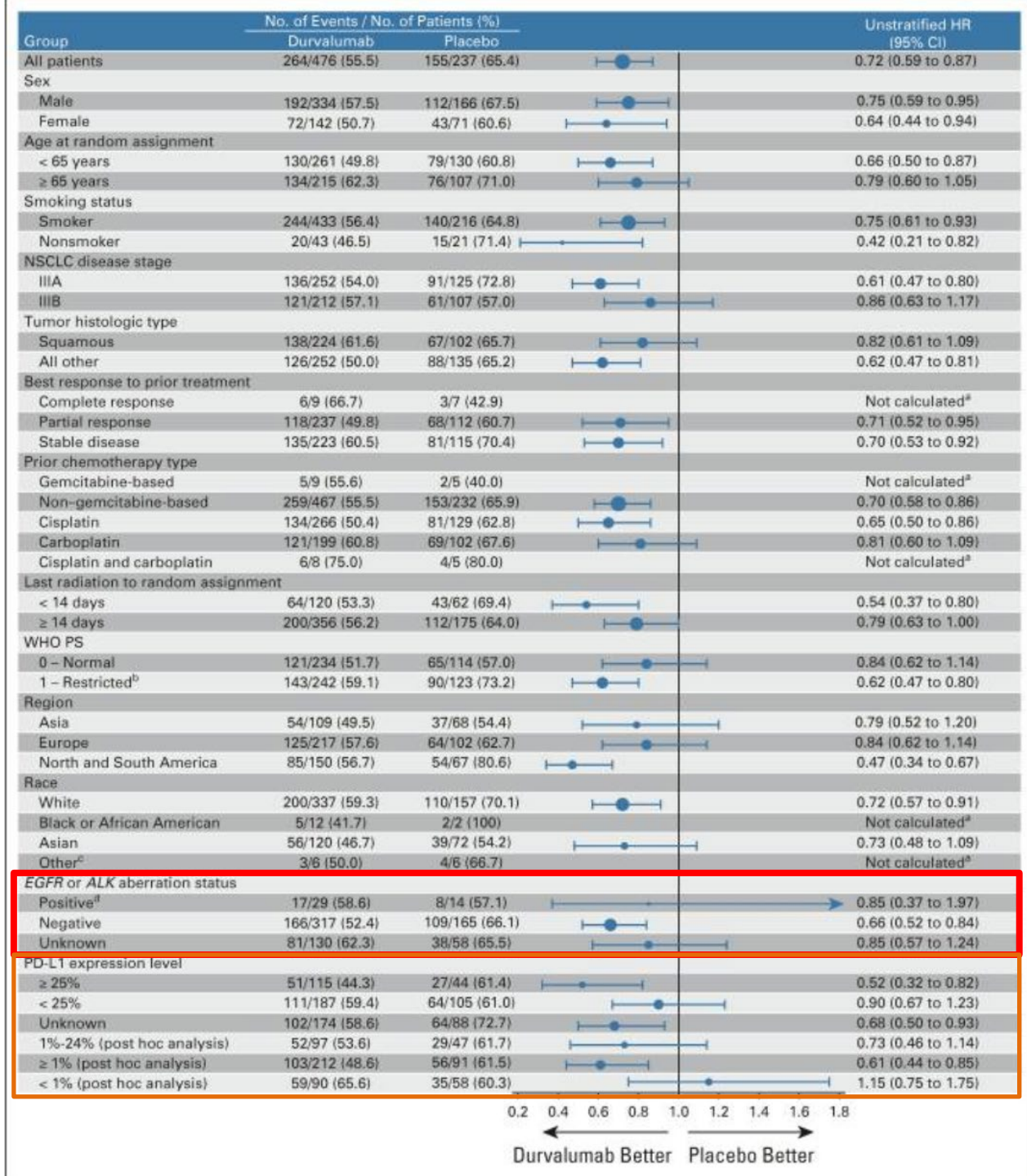
- PD-L1 testing was not required
- 37% of patients with unknown PD-L1 status
- PD-L1 expression-level cutoff of 1% was part of an unplanned post-hoc analysis requested by a health authority



Faivre-Finn ESMO 18

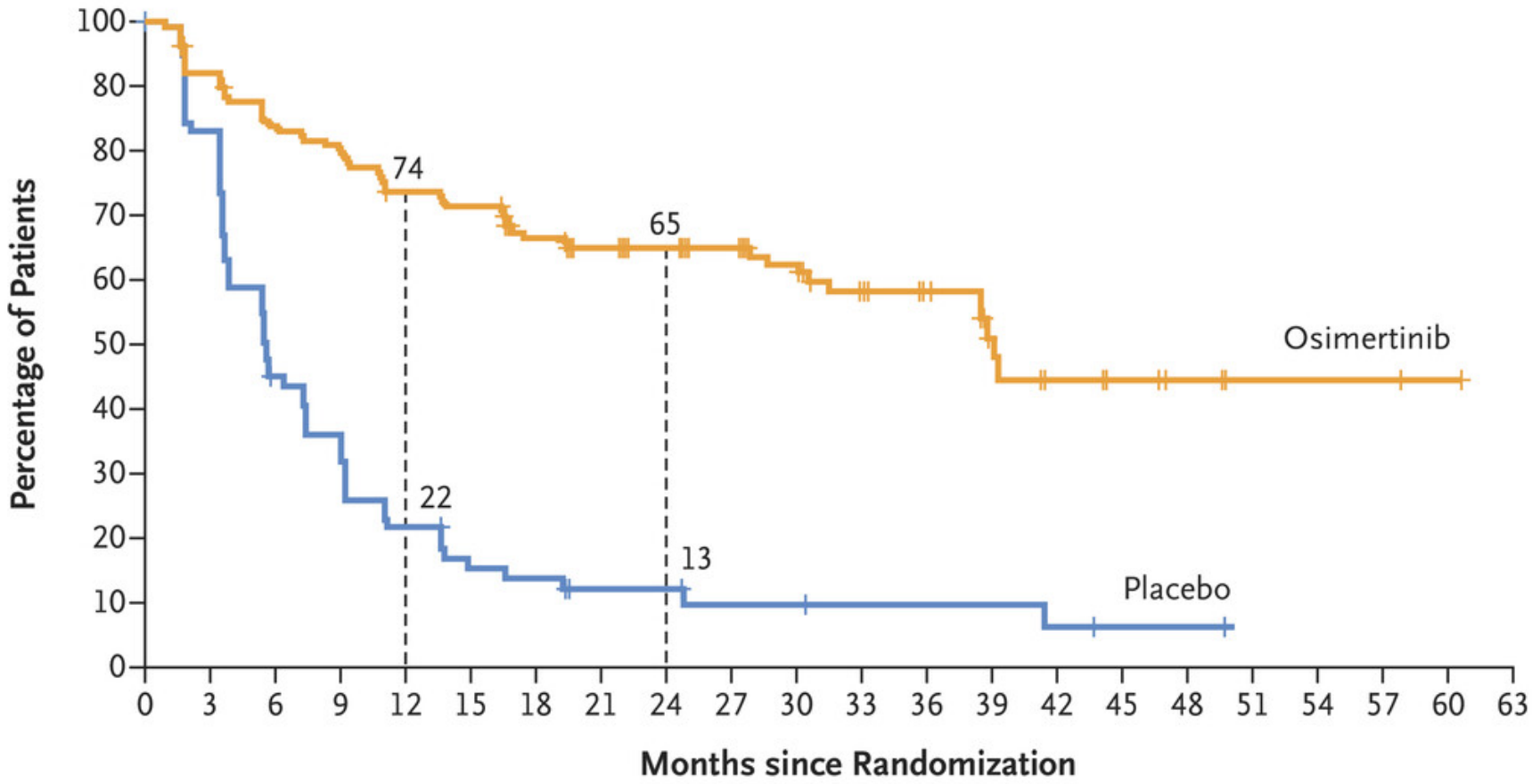
Forest Plot of OS results From Pacific Trial

Spigel DR et al
JCO 40:1271-1274,2022



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)

Laura: Osimertinib or placebo after CT/RT in stage III 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

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

Lu et al: NEJM 391:585-597,2024

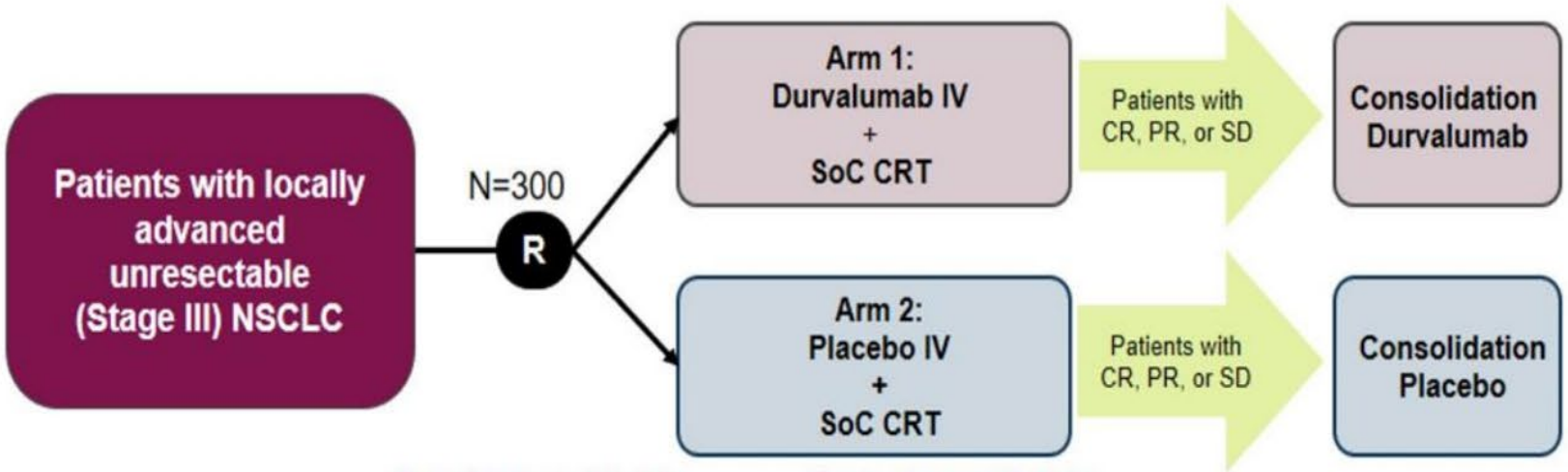
Ongoing Concurrent CT-RT + immunotherapy Trials in unresectable stage III

- PACIFIC-2 Phase III durvalumab
- EA5181 Phase III durvalumab
- CheckMate73L Phase III nivolumab
- ETOP-NICOLAS Phase II nivolumab
- KEYNOTE-799 Phase II pembrolizumab
- DETERRED Phase II atezolizumab
- NCT03840902 Phase II M7824
- PACICIC 9 Phase III durva+olecumab or monolizumab

UPFRONT DURVALUMAB WITH CONCURRENT CHEMO/XRT

PACIFIC 2: Study Design[1,2]

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study



Co-primary endpoints
- PFS
- ORR

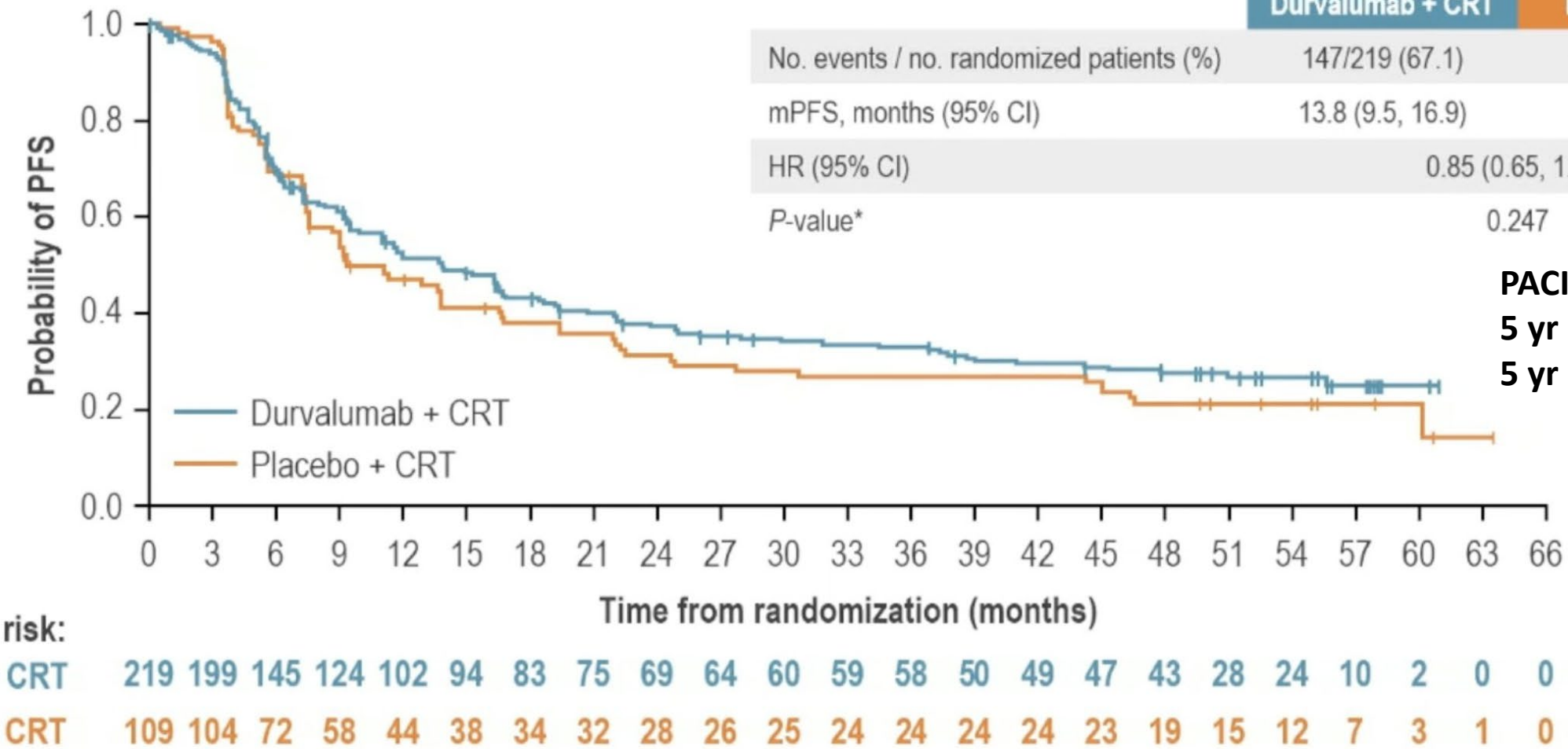
Secondary endpoints
- OS
- PK of durva in blood in combo with CRT
- Immunogenicity
- HRQoL
- DoR
- PFS2
- TTDM
- Rate of complete response

- Activated: 4/18
- N: 300
- Ex-US
- Treat until PD

- Upfront CRT & durva
- Dosing Interval/length
- PD-L1 Status

- COMPLETED ACCRUAL

PFS by BICR (ITT population)



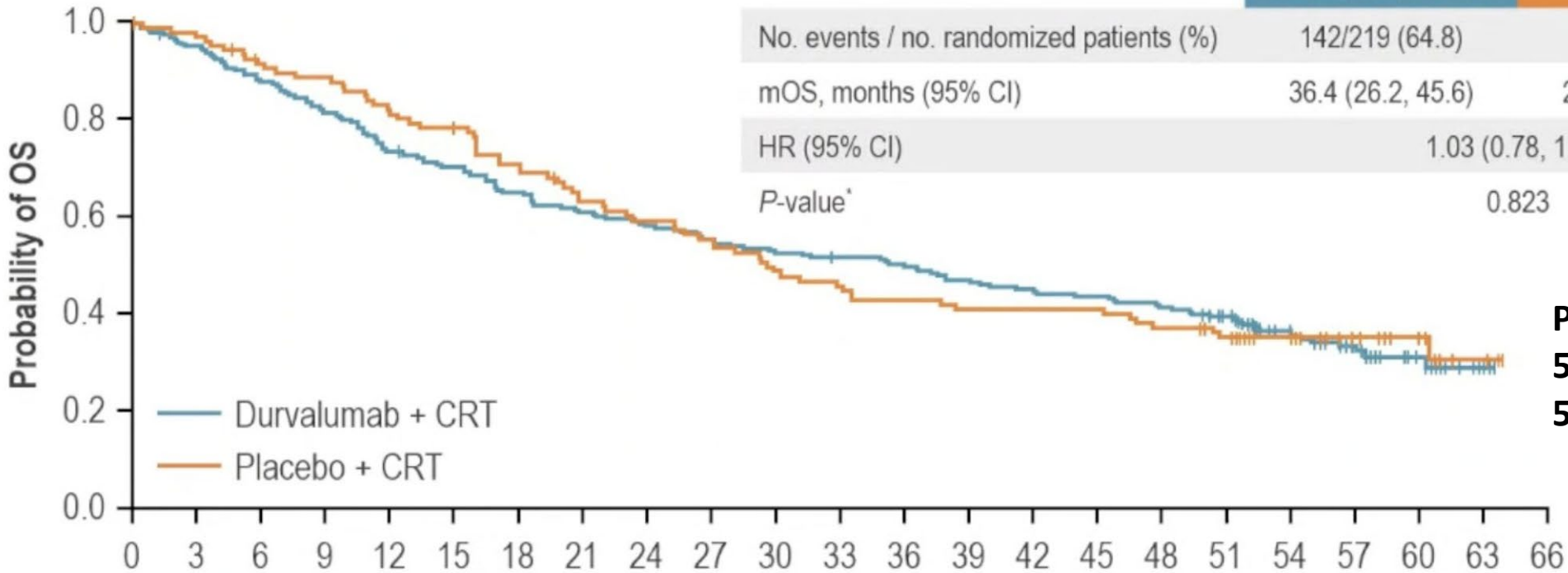
	Durvalumab + CRT	Placebo + CRT
No. events / no. randomized patients (%)	147/219 (67.1)	80/109 (73.4)
mPFS, months (95% CI)	13.8 (9.5, 16.9)	9.4 (7.5, 16.6)
HR (95% CI)	0.85 (0.65, 1.12)	
P-value*	0.247	

PACIFIC
5 yr PFS=33%
5 yr OS=43%

No. at risk:																							
Durvalumab + CRT	219	199	145	124	102	94	83	75	69	64	60	59	58	50	49	47	43	28	24	10	2	0	0
Placebo + CRT	109	104	72	58	44	38	34	32	28	26	25	24	24	24	24	23	19	15	12	7	3	1	0

OS and ORR (ITT population)

	Durvalumab + CRT	Placebo + CRT
No. events / no. randomized patients (%)	142/219 (64.8)	69/109 (63.3)
mOS, months (95% CI)	36.4 (26.2, 45.6)	29.5 (23.2, 45.1)
HR (95% CI)	1.03 (0.78, 1.39)	
P-value*	0.823	

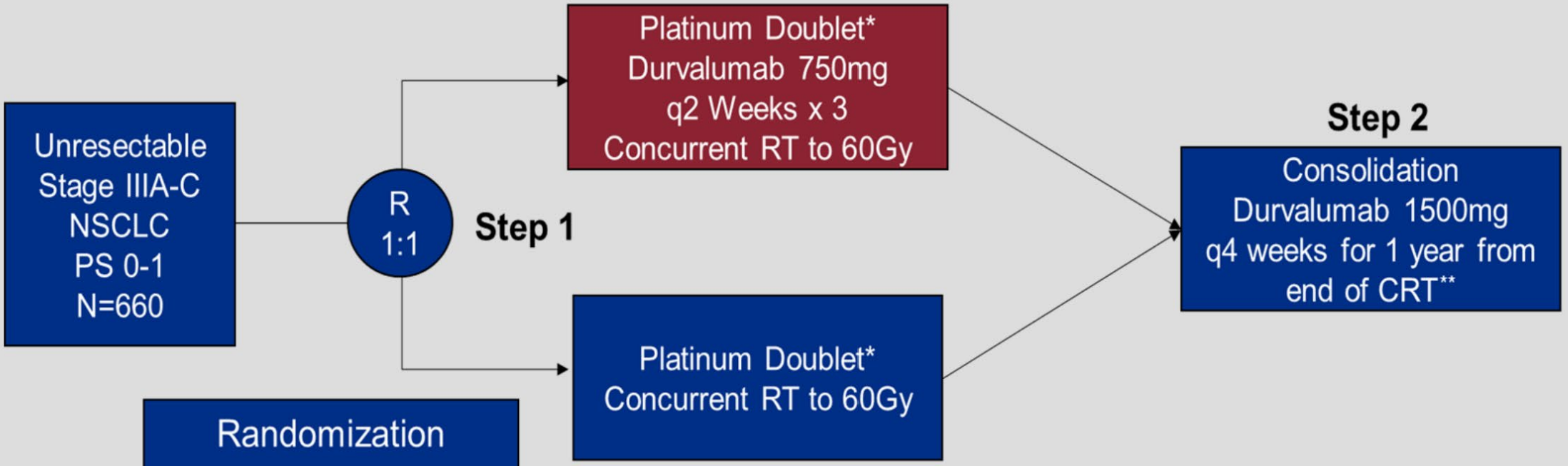


PACIFIC
5 yr PFS=33%
5 yr OS=43%

No. at risk:																							
Durvalumab + CRT	219	207	191	177	160	152	141	132	126	120	114	111	107	100	95	94	89	75	49	31	15	1	0
Placebo + CRT	109	106	98	95	87	83	75	66	62	57	51	47	45	43	43	43	39	35	27	17	9	2	0

There was no difference in ORR between the durvalumab (60.7%; 95% CI: 53.9, 67.2) and placebo (60.6%; 95% CI: 50.7, 69.8) arms (p=0.976)

EA5181 Schema



Randomization

Stratified by:
1) Planned chemotherapy
2) Age
3) Sex
4) Stage (IIIA vs IIIB vs IIIC)

Investigator choice

Cisplatin 50 mg/m2 D1, 8, 29, 36; etoposide 50 mg/m2 D1-5, 29-33
Cisplatin 75 mg/m2 D1, 22; pemetrexed 500 mg/m2 D1, 22 (nonsquamous only)
Carboplatin AUC 2 D1, 8, 15, 22, 29, 36; paclitaxel 45 mg/m2 D1, 8, 15, 22, 29, 36

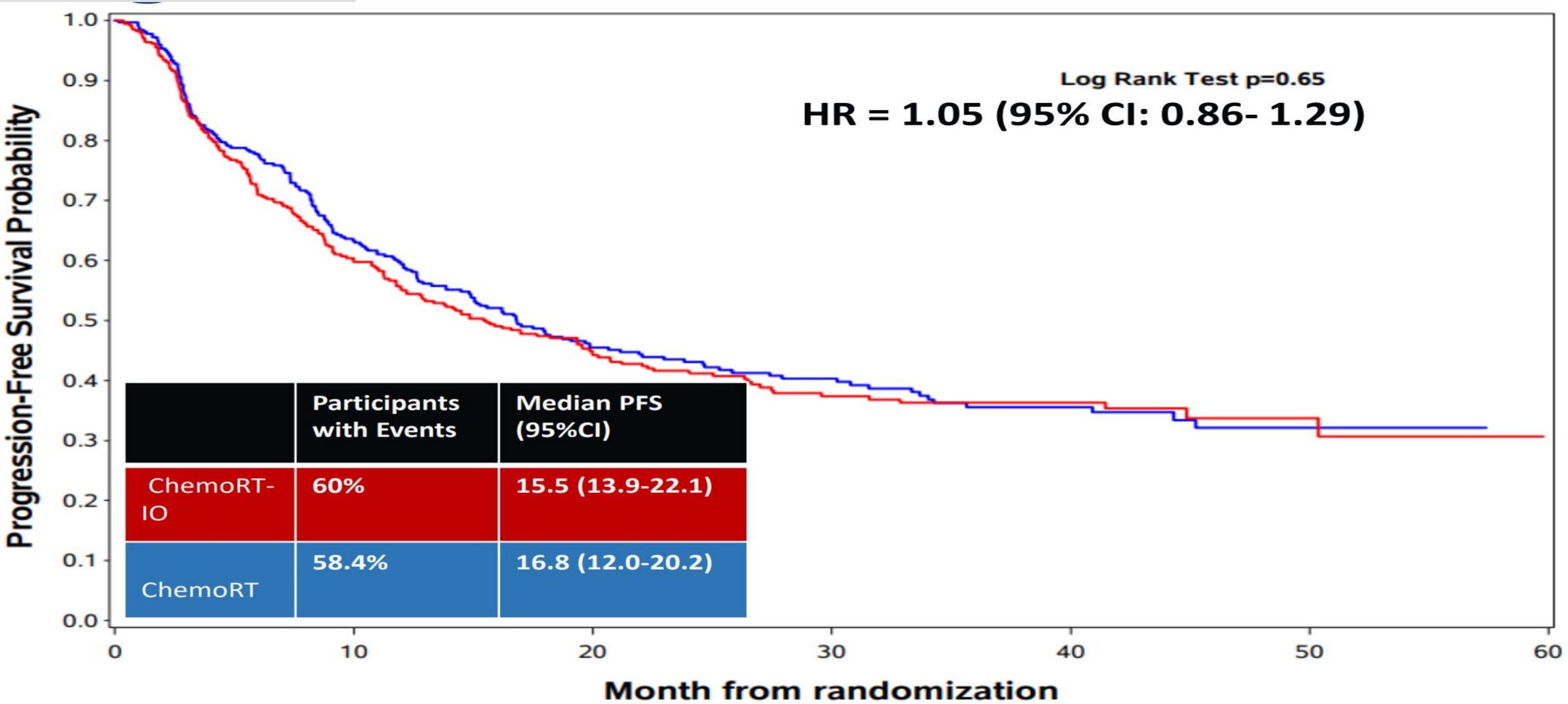
**Starting within 14 days of CRT unless toxicity has not resolved to ≤ grade 2, but not later than 45 days post-CRT

Primary endpoint – OS intention to treat population; 25% reduction in OS HR

Secondary endpoint –PFS, toxicity, ORRs, and Recurrence patterns

ECOG-ACRIN
cancer research group

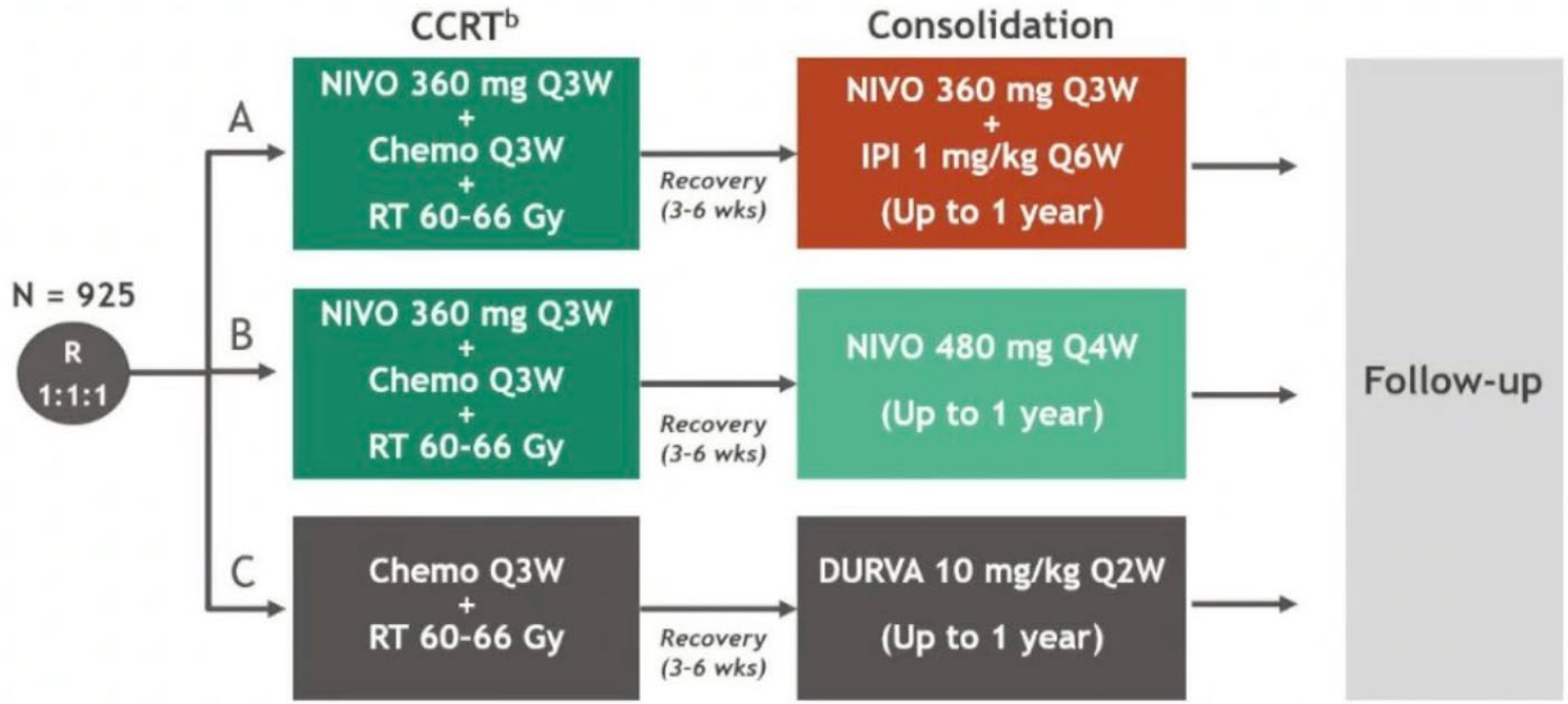
EA5181: Overall Survival



CheckMate 73L[a] study design

Key eligibility criteria:
- Stage III NSCLC amenable to CCRT
- No prior systemic therapy
- ECOG PS 0-1

Stratified by:
- Age (< 65 vs ≥ 65 years)
- Stage (IIIA vs IIIB vs IIIC)
- PD-L1 (≥ 1% vs < 1% vs not evaluable/indeterminate)



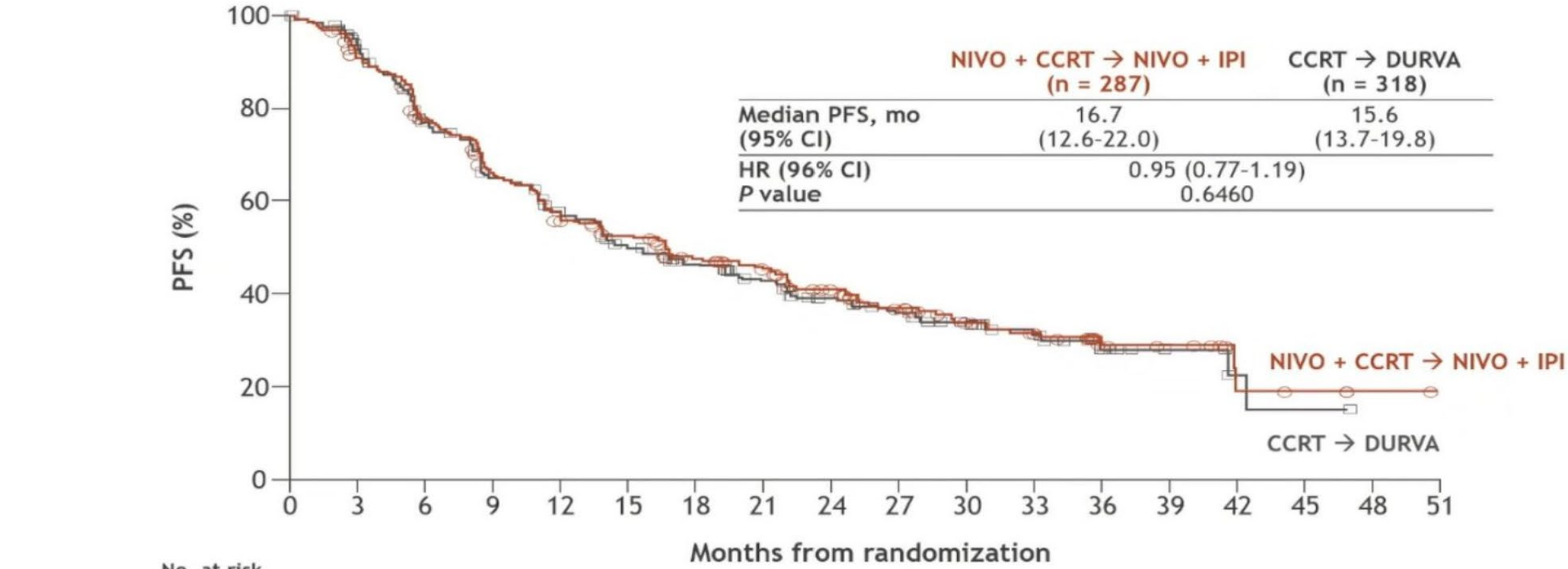
Primary endpoint:
- PFS per BICR (Arm A vs Arm C)

Key secondary endpoints:
- OS (Arm A vs Arm C; Arm B vs Arm C)
- PFS (Arm B vs Arm C)
- ORR (Arm A vs Arm C; Arm B vs Arm C)
- Safety

Checkmate 77L

CheckMate 73L: NIVO + CCRT → NIVO ± IPI in unresectable stage III NSCLC

Primary endpoint:
PFS per BICR with NIVO + CCRT → NIVO + IPI vs CCRT → DURVA



	NIVO + CCRT → NIVO + IPI (n = 287)	CCRT → DURVA (n = 318)
Median PFS, mo (95% CI)	16.7 (12.6-22.0)	15.6 (13.7-19.8)
HR (96% CI)	0.95 (0.77-1.19)	
P value	0.6460	

No. at risk

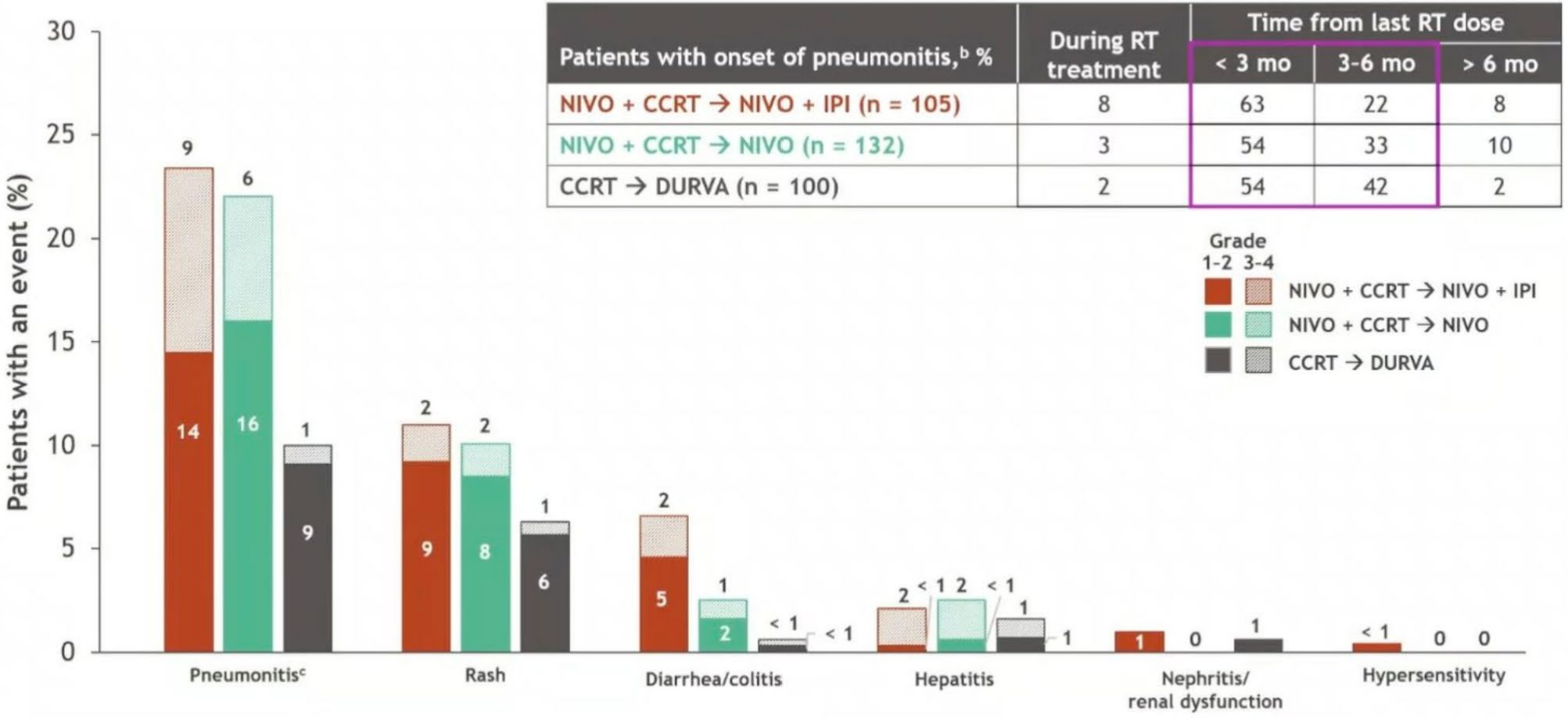
NIVO + CCRT → NIVO + IPI	287	254	213	177	150	135	116	102	79	61	46	37	18	12	4	3	1	0
CCRT → DURVA	318	284	225	189	163	137	118	96	77	65	46	28	15	8	3	2	0	0

Median follow-up (range): 30.5 months (16.0-52.5).

Checkmate 77L

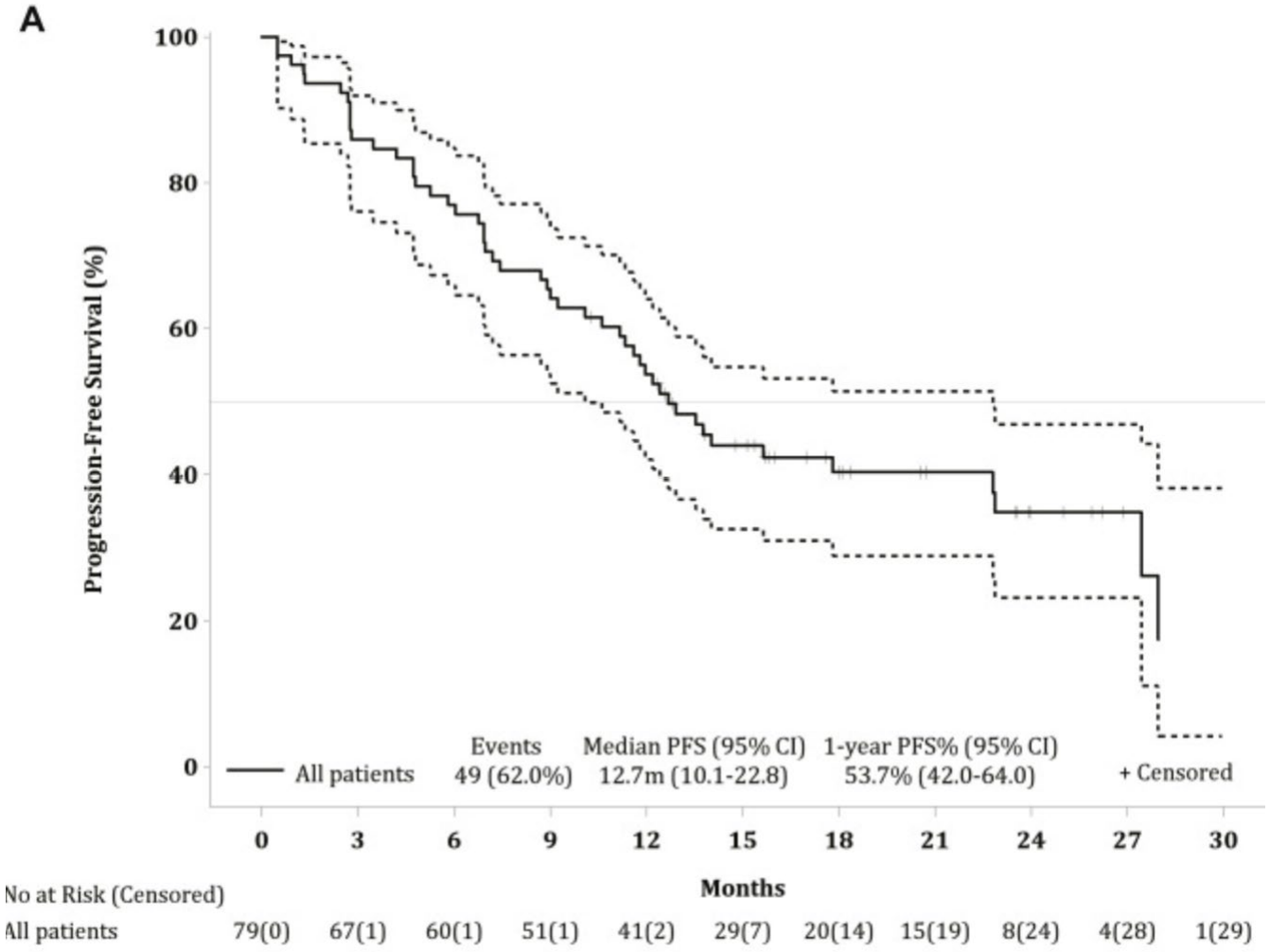
Immune-mediated AEs[a] and onset of pneumonitis

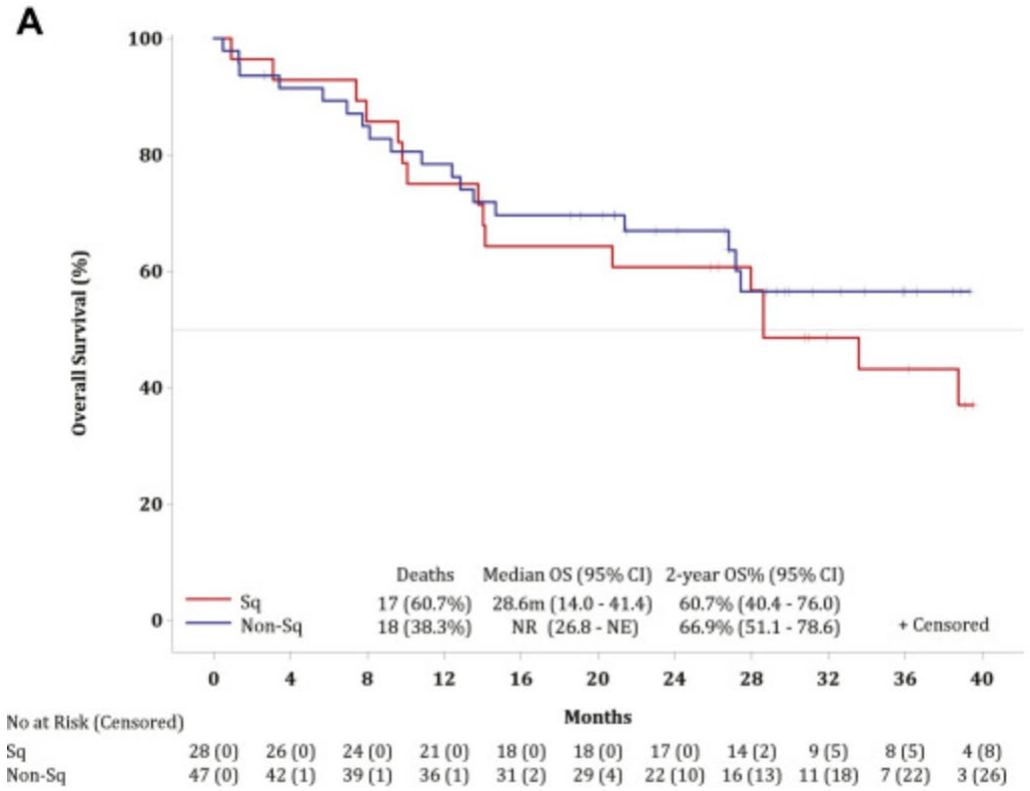
Patients with onset of pneumonitis,[b] %	During RT treatment	Time from last RT dose		
		< 3 mo	3-6 mo	> 6 mo
NIVO + CCRT → NIVO + IPI (n = 105)	8	63	22	8
NIVO + CCRT → NIVO (n = 132)	3	54	33	10
CCRT → DURVA (n = 100)	2	54	42	2



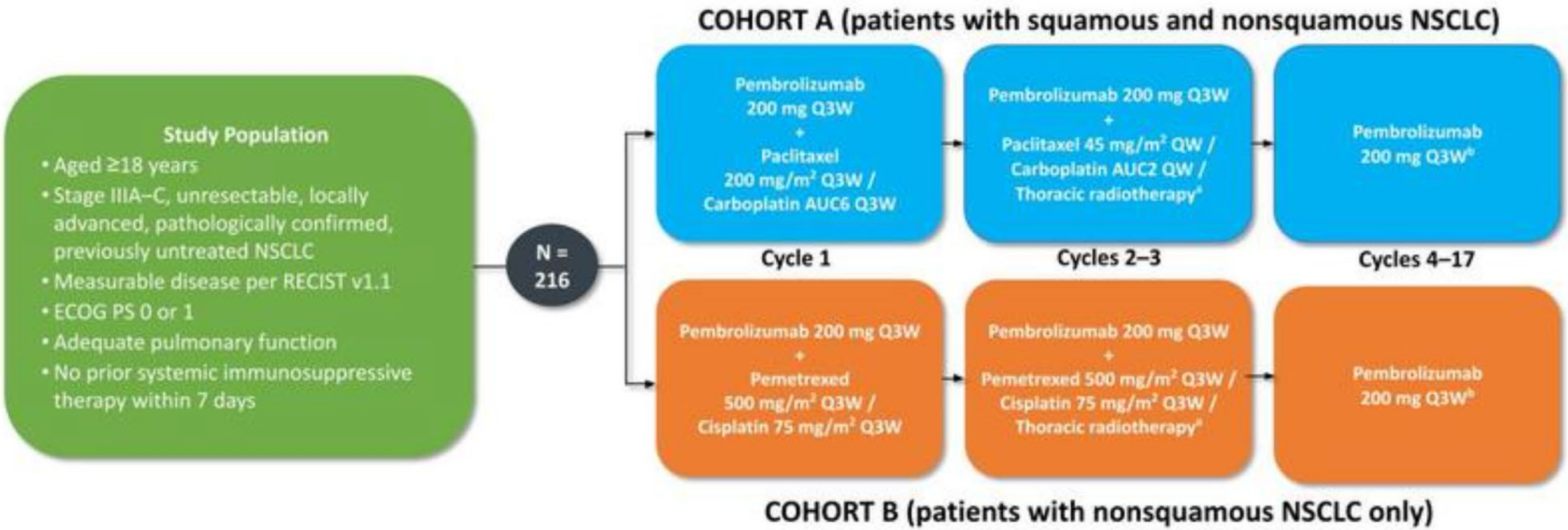
[a]Immune-mediated AEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) have been ruled out. [b]In patients treated with RT. Pneumonitis included pneumonitis, radiation pneumonitis, and interstitial lung disease. [c]All-cause pneumonitis included pneumonitis, immune-mediated lung diseases, and interstitial lung disease.

NICOLAS (NIVO) Phase II TRIAL Results(ETOP)





Keynote-799 Trial Design



KN 799 Trial Results

Table. Summary of Efficacy in the KEYNOTE-799 Trial.

Measure	Cohort A (Patients with squamous and nonsquamous NSCLC)	Cohort B (Patients with nonsquamous NSCLC only
Number (n)	122	102
ORR: % (RECIST v1.1 by BIRC	70.5	70.6
(95% CI)	(61.2-78.8)	(60.7-79.2)
DOR ≥12 mo:%	79.7	75.6
12-mo PFS rate: %	67.1	71.6
12-mo OS rate: %	81.3	87.00
Grade 3 of higher pneumonitis: % (n)	8.0 (9)	6.9 (7)
Grade 3 to 5 treatment-related AEs: %	64.3	50.00

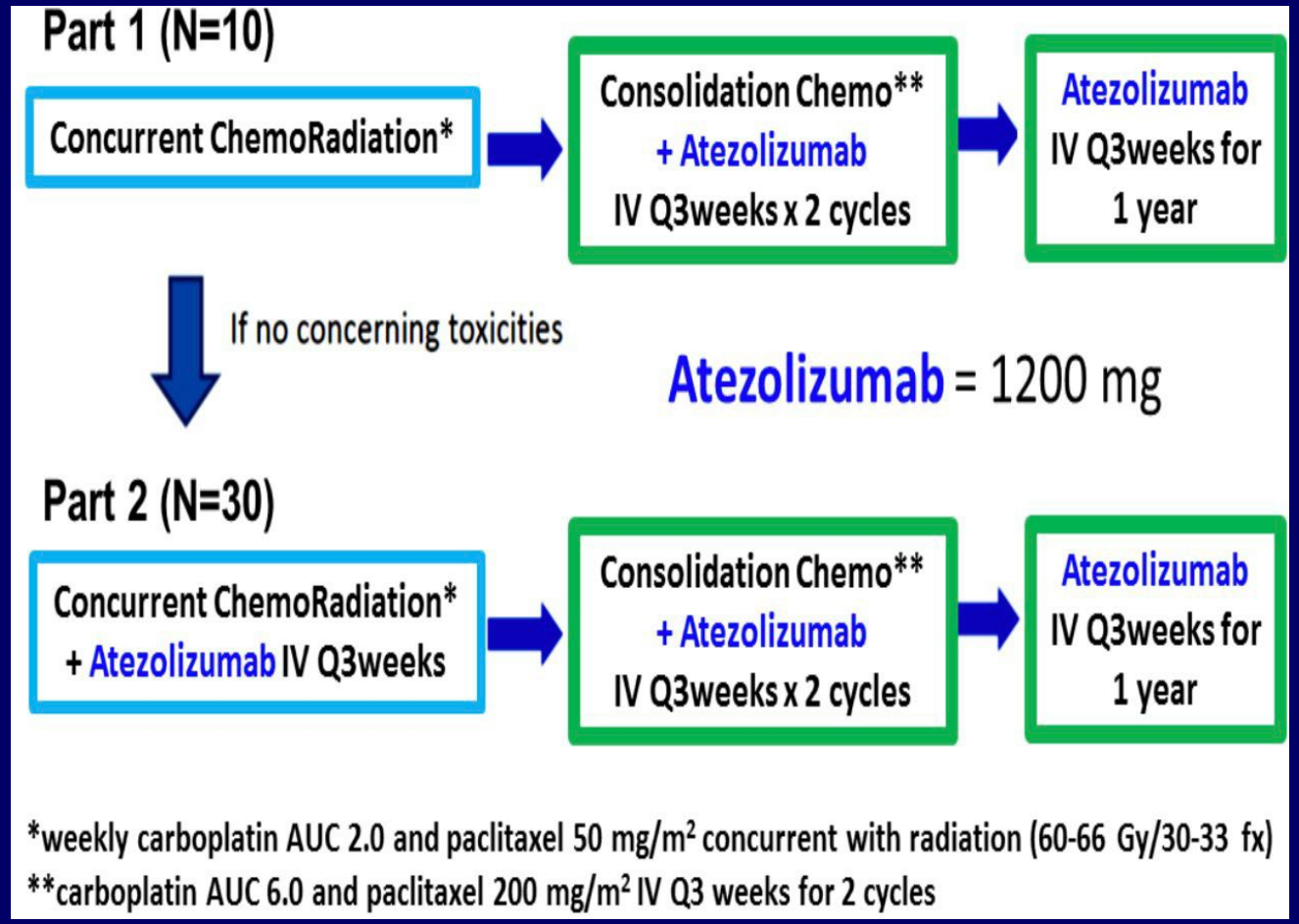
Pacific Results
1yr PFS 56%
I yr OS 83%

Abbreviations: AEs, adverse events; BIRC, blinded independent central review; DOR, duration of reponse; ORR, overall response rate; OS, overall survival; mo, months; PFS, progression free survivial.

Table courtesy of Noemi Reguart.

* Data cutoff: October 28, 2020.

Immunotherapy addition of concurrent CT/RT: DETERRED phase II

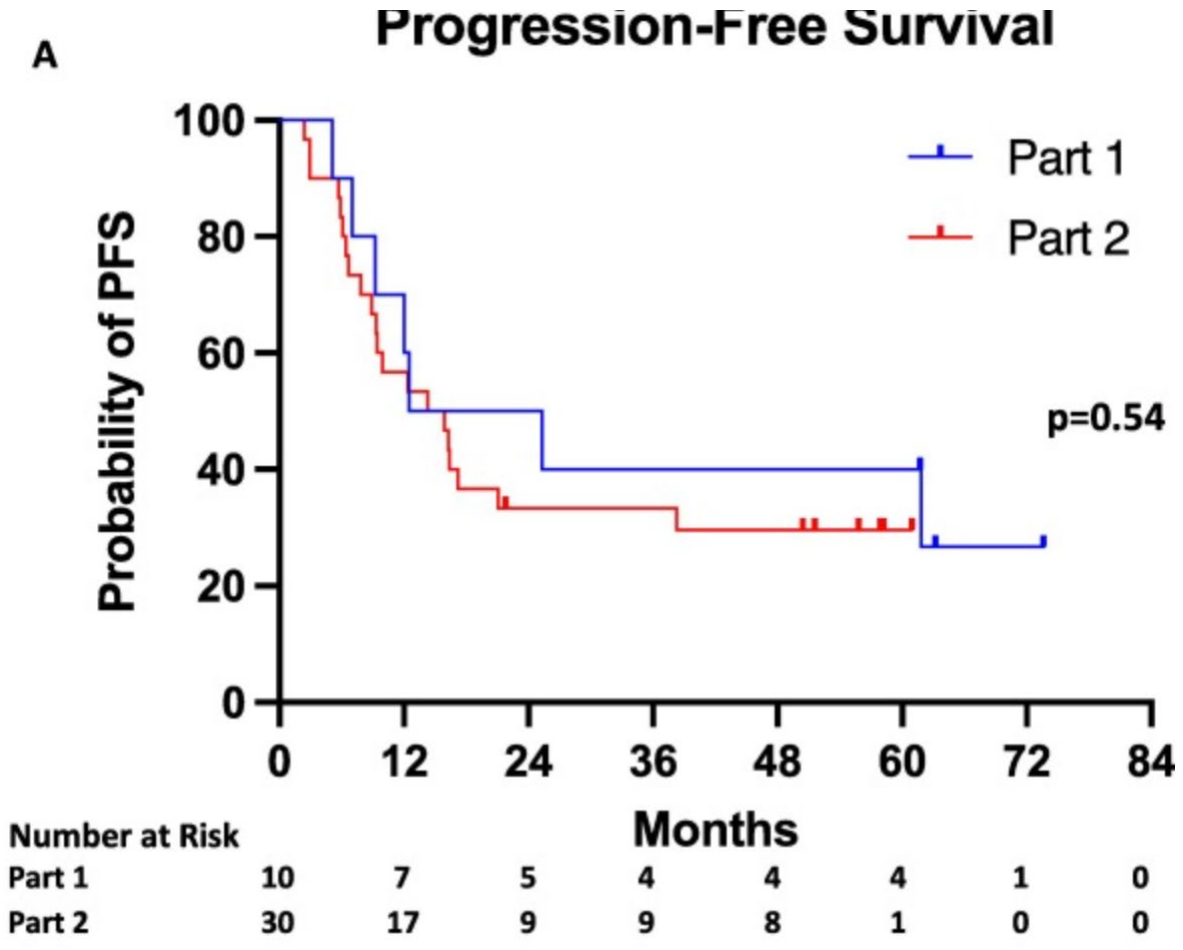


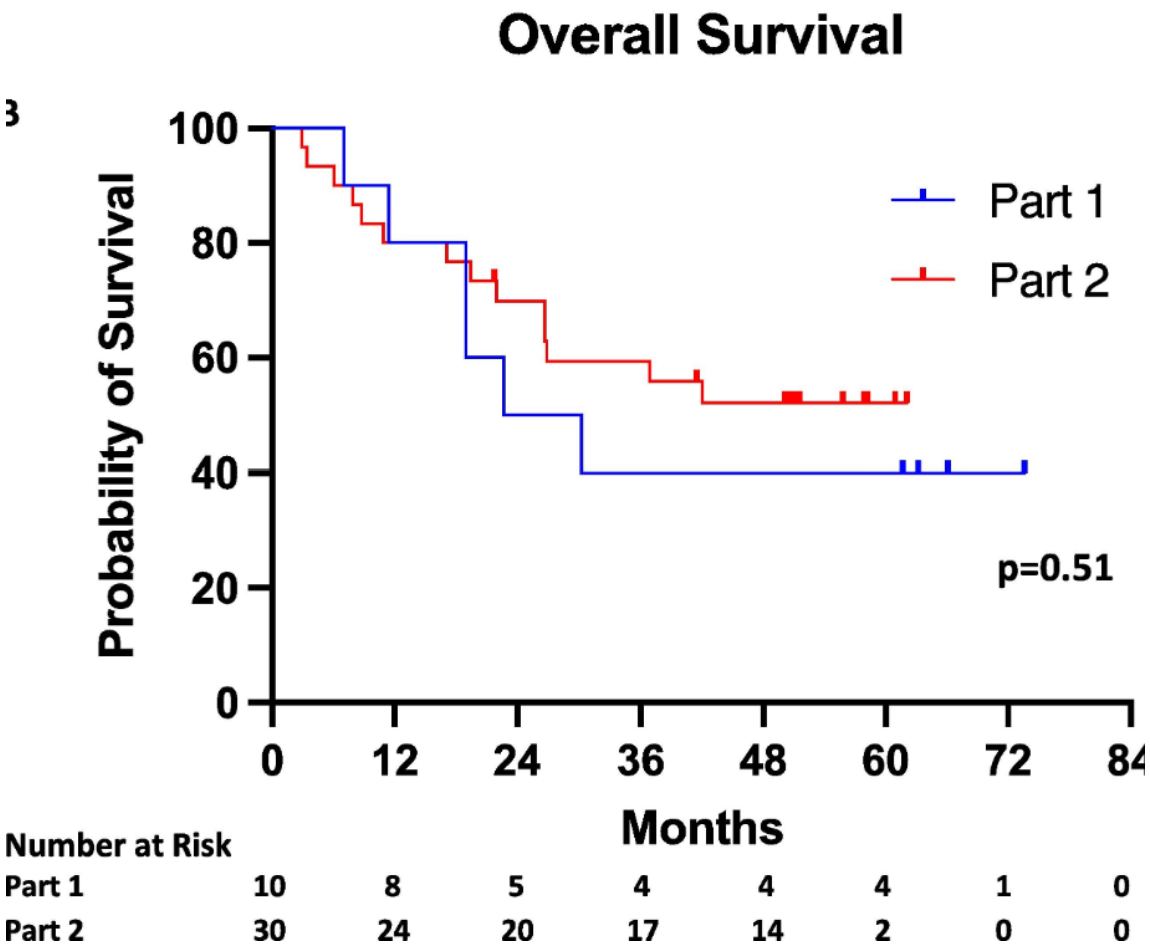
	Part 1 (N=10)	Part 2 (N=30)
mPFS, mo	12.5	13.2
mOS, mo	22.8	NR
Median follow-up, mo	22.5	15.3

PACIFIC TRIAL RESULTS
mPFS=18 mo
mOS= 48 mo

Lin JTO 20

Deterred Phase II AtezoTrial Results

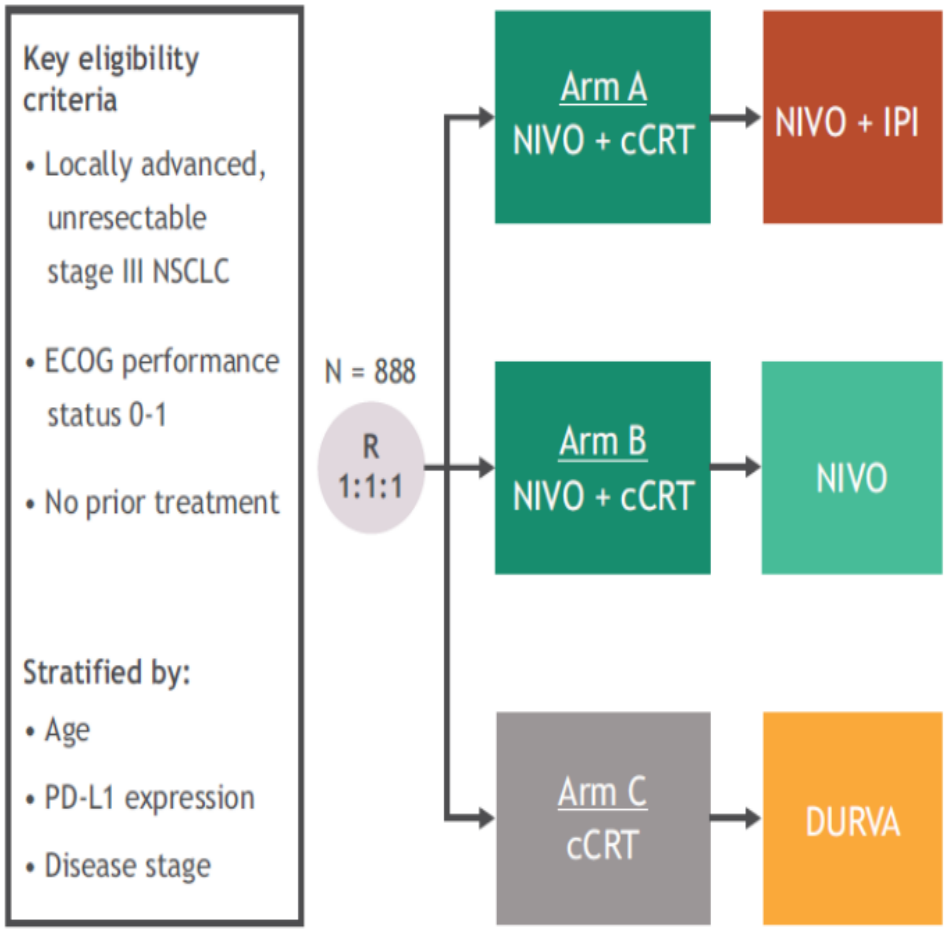




Pacific Results
1yr PFS 56%
I yr OS 83%

CheckMate 73L

A phase 3 study comparing nivolumab plus concurrent CRT followed by nivolumab ± ipilimumab versus cCRT followed by durvalumab for previously untreated, locally advanced stage III NSCLC

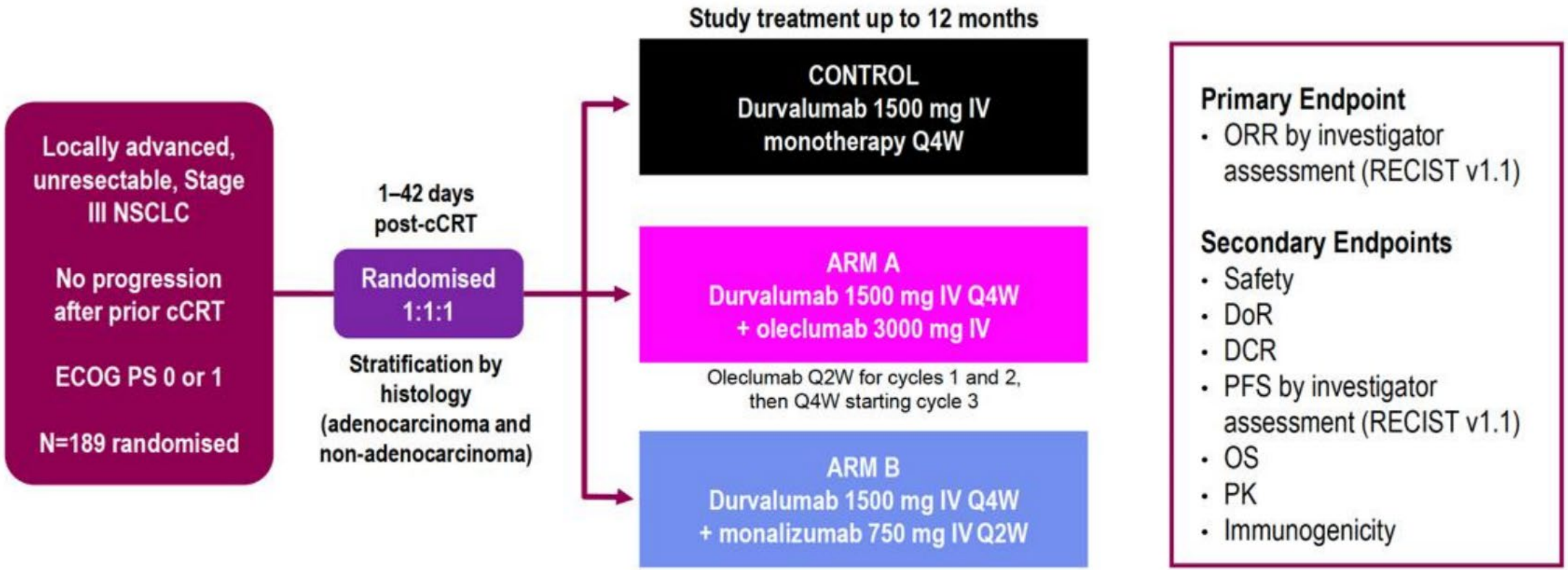


Primary endpoints:

NIVO + cCRT followed by NIVO + IPI (Arm A) vs cCRT followed by DURVA (Arm C)

- PFS
- OS

COAST: Phase 2, randomised open-label study

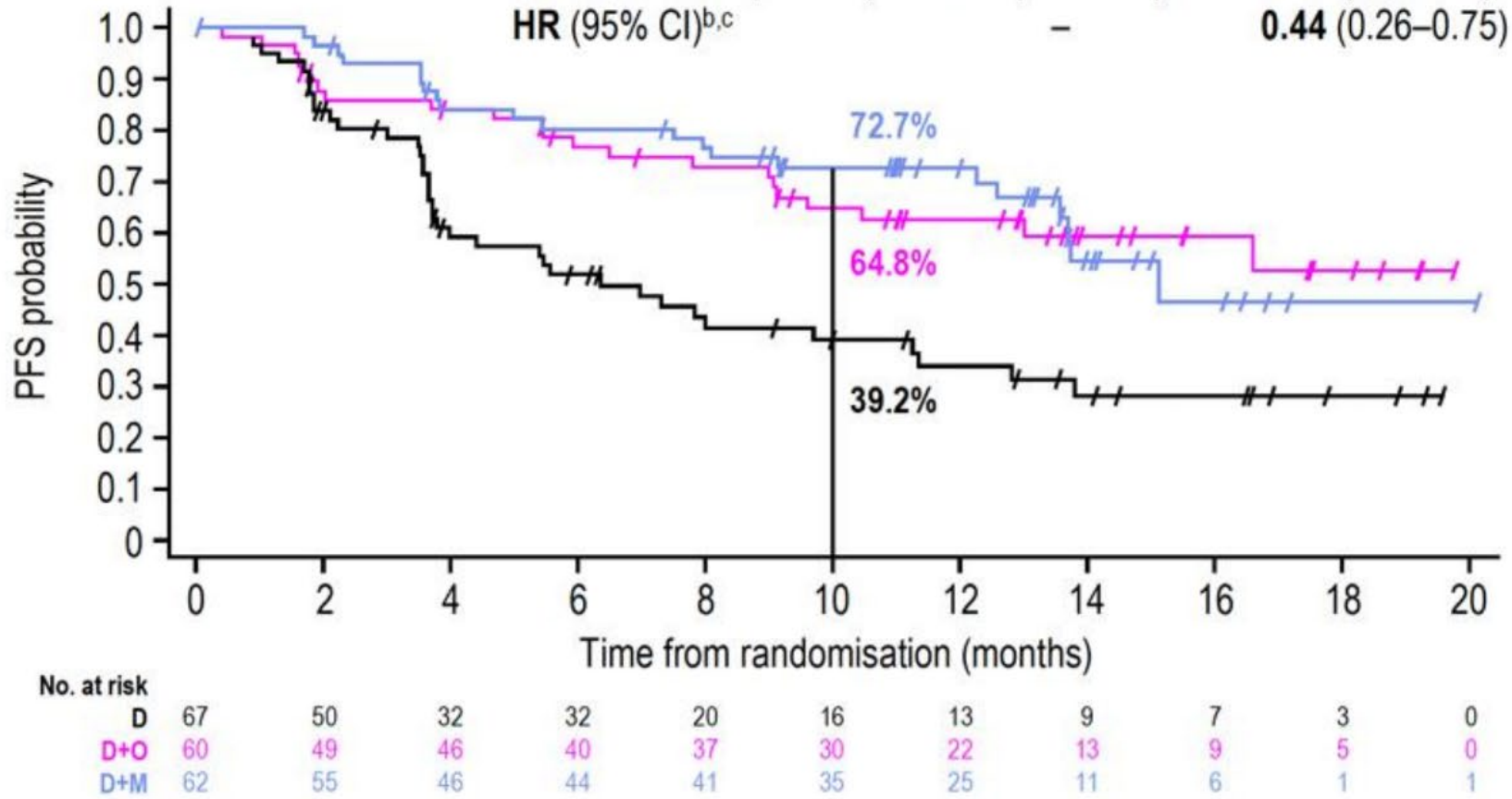


- A planned sample size of 60 patients per arm was designed to provide acceptable precision in estimating antitumour activities in an early phase setting
- Between Jan 2019 and Jul 2020, 189 patients were randomised of whom 186 received D (n=66), D+O (n=59) or D+M (n=61)
- As of 17 May 2021, all patients had a minimum of 10 months potential follow-up and the median actual follow-up was 11.5 months (range, 0.4–23.4; all patients)

D, durvalumab; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; M, monalizumab; O, oleclumab;

PFS by investigator assessment
(interim analysis; ITT population)

	D	D+O	D+M
Events/patients, n	38/67	22/60	21/62
mPFS, months (95% CI)[a]	**6.3** (3.7–11.2)	**NR** (10.4–NE)	**15.1** (13.6–NE)
HR (95% CI)[b,c]	–	**0.44** (0.26–0.75)	**0.65** (0.49–0.85)



PACIFIC TRIAL RESULTS
mPFS=18 mo
mOS= 48 mo

Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)

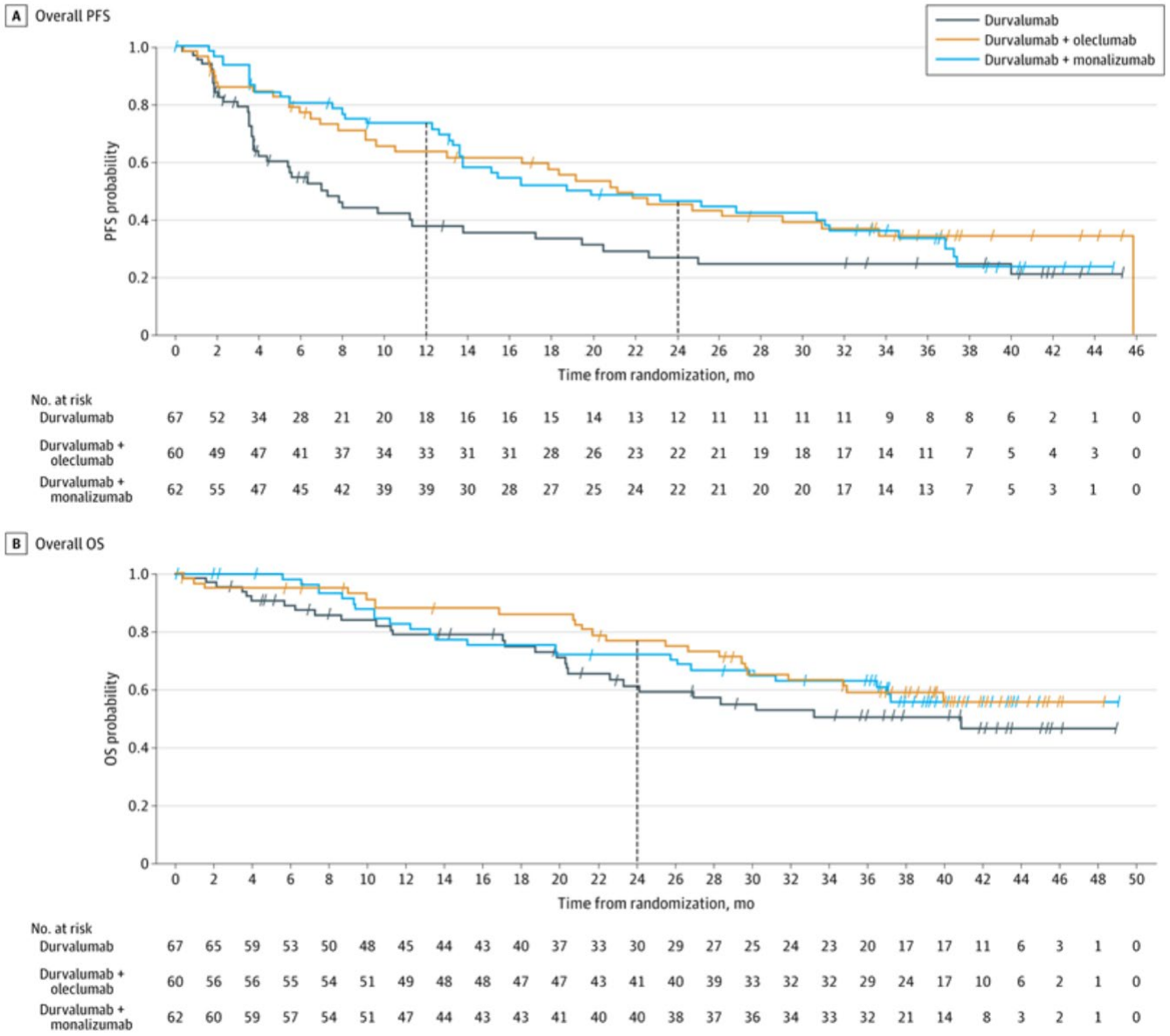
[a]Interim analysis was performed when all patients had a 10-month minimum potential follow-up; Kaplan-Meier estimates for PFS, PFS rate and 95% CIs

[b]PFS HR and 95% CI estimated by Cox regression model, stratified by histology (adenocarcinoma and non-adenocarcinoma)

[c]Compared with the 67 and 64 patients in the D arm enrolled concurrently with patients in the D+O and D+M arms, respectively

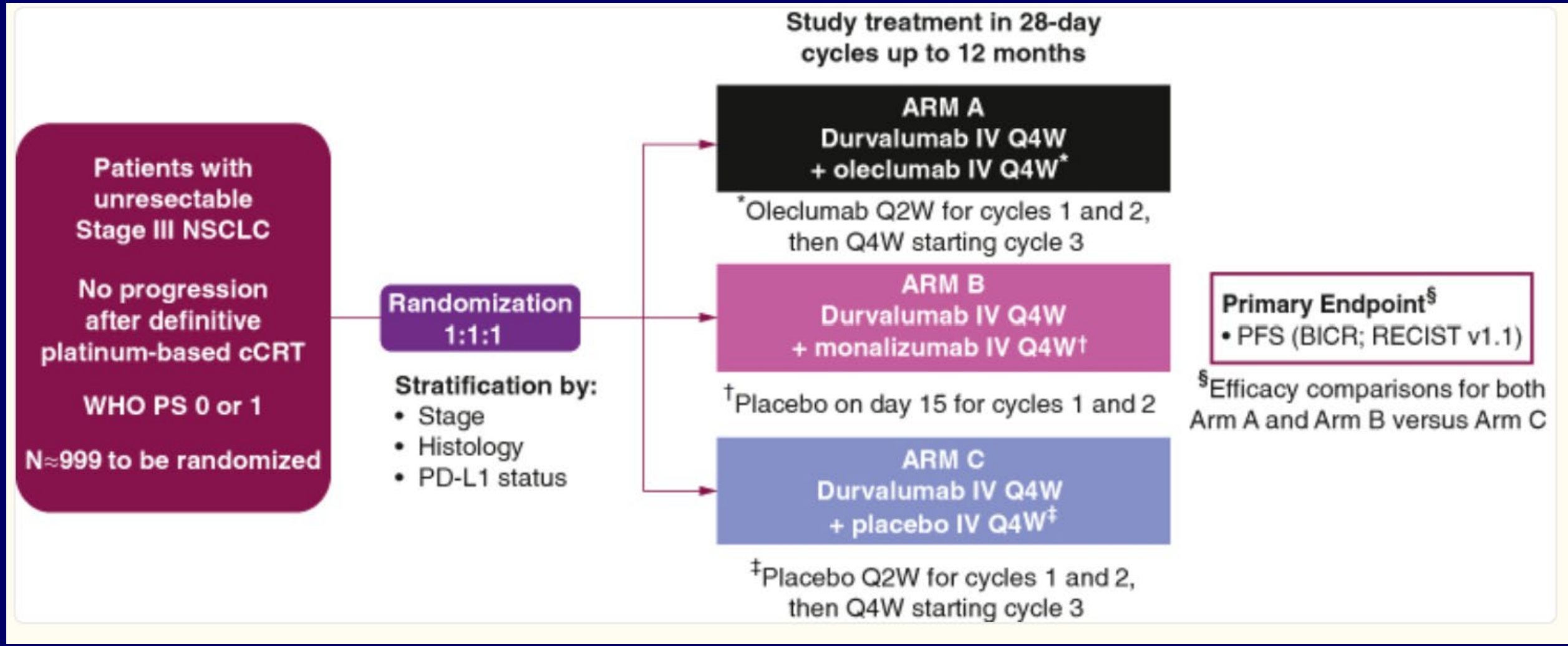
CI, confidence interval; HR, hazard ratio; ITT, intention to treat; mPFS, median PFS; NE, not estimable; NR, not reached

Figure 2. Kaplan-Meier Estimates for Progression-Free Survival (PFS) and Overall Survival (OS) for the Intention-to-Treat Population



PACIFIC TRIAL RESULTS
mPFS=18 mo
mOS= 48 mo

Pacific 9 Trial Design



Study Design KEYLYNK 012

Patients:
- Stages IIIA, IIIB, and IIIC NSCLC
- ECOG PS 0-1
- Adequate pulmonary function (PFT)

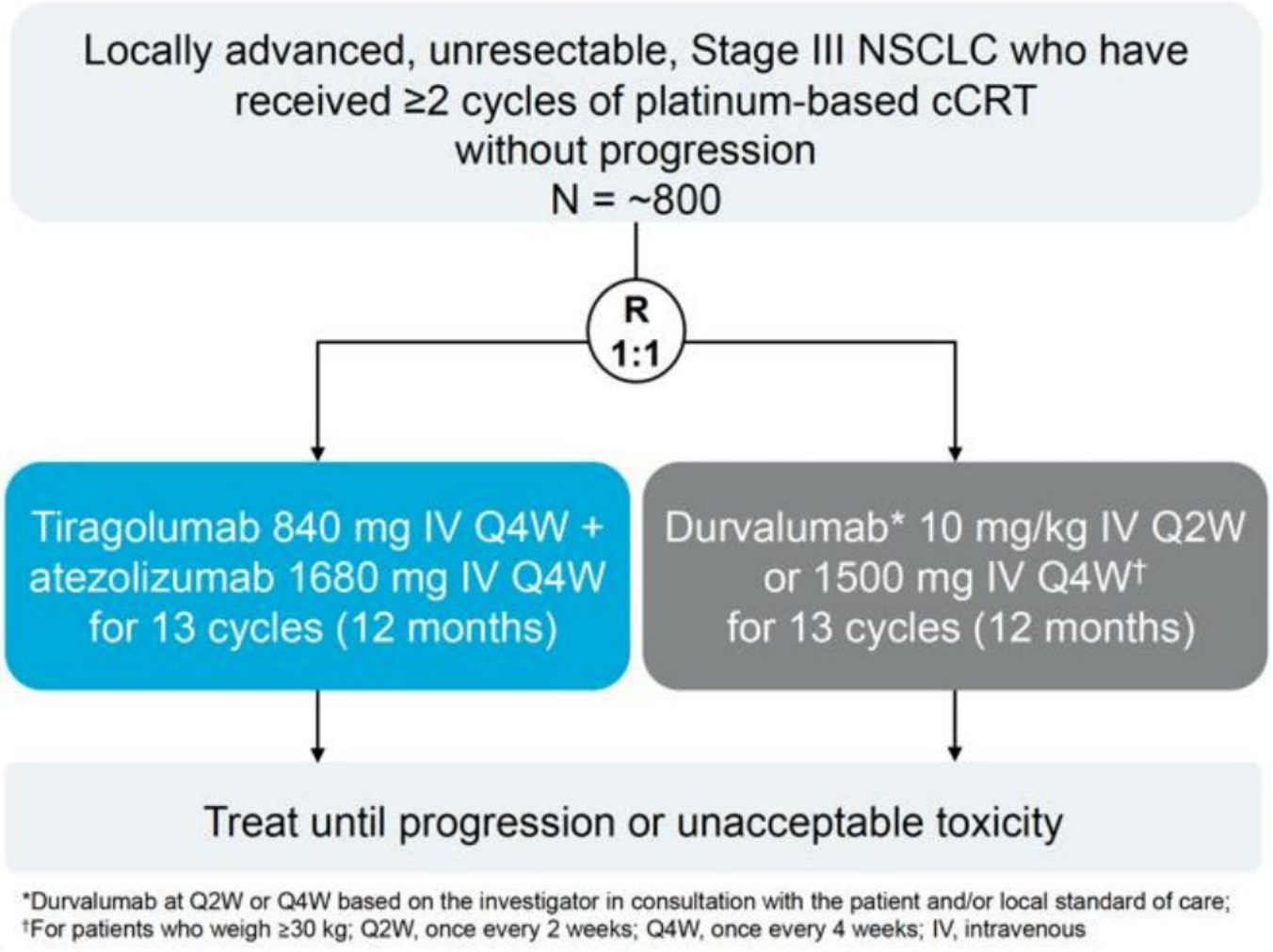
Stratification:
- Stage (IIIA vs IIIB/IIIC)
- Tumor histology (squamous vs nonsquamous)
- PD-L1 tumor proportion score (≥50% vs <50%)
- Region (East Asia vs North America/Western Europe/UK vs other)

Randomization
1:1
N = 870

	Thoracic Radiotherapy		Follow
Arm A: Platinum doublet + Pembrolizumab 200 mg X1 cycles	Platinum doublet + Pembrolizumab 200 mg Q3W X 2 cycles	Pembrolizumab 200 mg Q3W X 17 cycles + Olaparib Placebo X 12 Months	
Arm B: Platinum doublet + Pembrolizumab 200 mg X1 cycles	Platinum doublet+ Pembrolizumab 200 mg Q3W X 2 cycles	Pembrolizumab 200 mg Q3W X 17 cycles + Olaparib 300mg BID X 12 Months	
Arm C: Platinum doublet + Placebo X1 cycles	Platinum doublet + Placebo x 2 cycles	Durvalumab 10 mg/kg Q2W X 12 Months	

Primary Endpoints: PFS/OS
Secondary Endpoints: ORR, DOR, PRO
Exploratory Endpoints: Biomarker evaluation, PDL1 and outcomes, TTST and TTR

SKYSCRAPER-03:



Primary endpoint: PFS by independent review facility assessment per RECIST v1.1

Key secondary endpoints: OS, investigator-assessed PFS, ORR, DOR, PFS and OS rates at 12, 18 and 24 months

Safety, pharmacokinetics, immunogenicity and biomarkers will also be evaluated

SKYSCRAPER 03 Results

median investigator-assessed progression-free survival (PFS) in the primary analysis set was 7.0 months (95% CI, 5.6-9.8) with tiragolumab plus atezolizumab (n = 262) vs 5.6 months (95% CI, 4.4-7.0) with atezolizumab alone (n = 259), resulting in a HR of 0.78 (95% CI, 0.63-0.97; *P* = .02). Despite showing numerical improvements, this result was not deemed statistically significant, as the prespecified alpha threshold for significance was set at *P* < 0.001. The 6-, 12-, and 18-month PFS rates with the doublet were 54.6%, 37.3%, and 24.3%, respectively. Corresponding PFS rates in the control arm were 47.8%, 24.9%, and 20.5%

PACIFIC TRIAL RESULTS

mPFS=18 mo

mOS= 48 mo

Skyscraper RESULTS:

Atezo mPFS 5.6mo

Atezo +tiro mPFS 7 mo.

Conclusions:

- Pacific Trial (CT/RT followed by IO) remains the standard
  - Excludes patients with driver alterations and patients who did not respond to initial CT/RT
  - Patients with driver alterations should receive adjuvant TKI but most not studied or approved except alectinib (Laura trial)
- Multiple trials combining IO with or before CT/RT have demonstrated increased toxicities without definite improvement in DFS or OS but include all patients
- Studies combining CT/RT with new IO agents are in progress