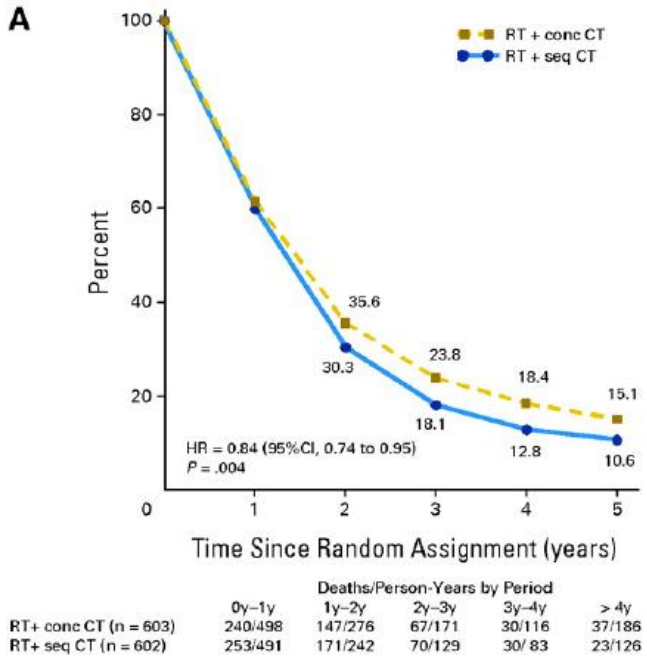
Il trattamento della malattia localmente avanzata inoperabile

Dott. Gabriele Minuti
Istituto Nazionale Tumori Regina Elena
Roma

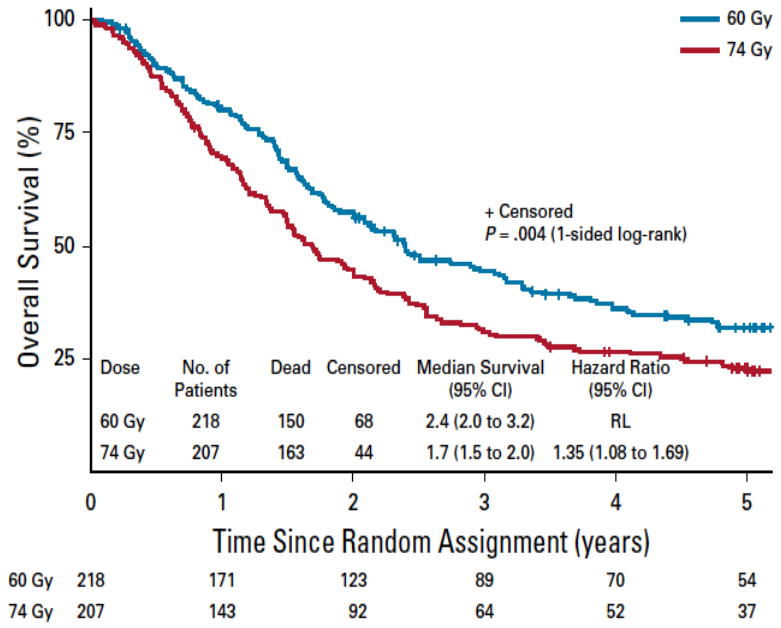
Changes in the treatment paradigm for unresectable stage III NSCLC

Older CRT studies (< 2005)

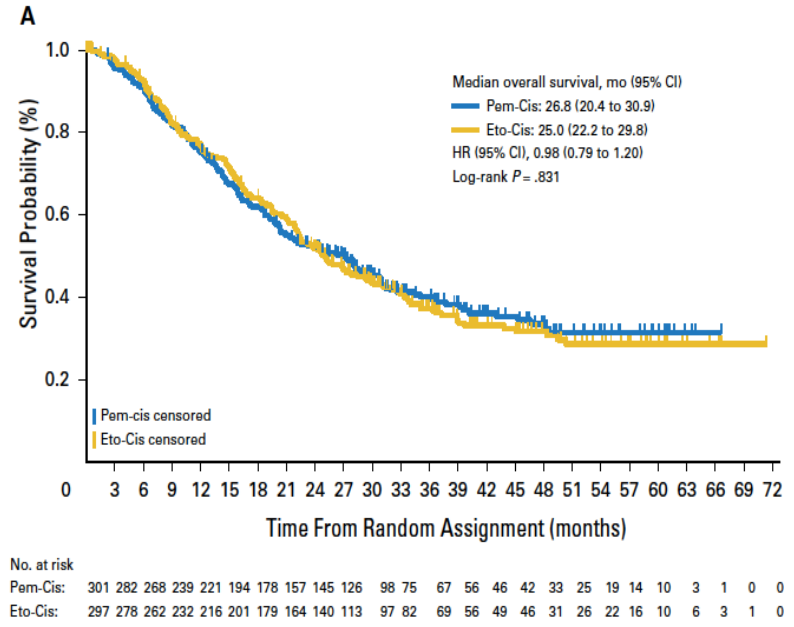


cCRT vs sCRT meta-analysis

Modern cCRt (2005-2018)



RTOG 0617: 60 vs. 74 Gy



PROCLAIM: cis-pem vs. cis-eto for non-squamous

Auperin et al, JCO 2010; Senan et al, JCO 2016; Bradley et al, JCO 2021.

PACIFIC phase 3 study design

- 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

1–42 days post-cCRT

R

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

2:1 randomization, stratified by age, sex, and smoking history

Placebo
10 mg/kg q2w for up to 12 months
N=237

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

Key secondary endpoints

- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; DoR, duration of response; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PFS2, time to second objective disease progression; PRO, patient-reported outcome; q2w, once every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis; WHO PS, World Health Organization performance status

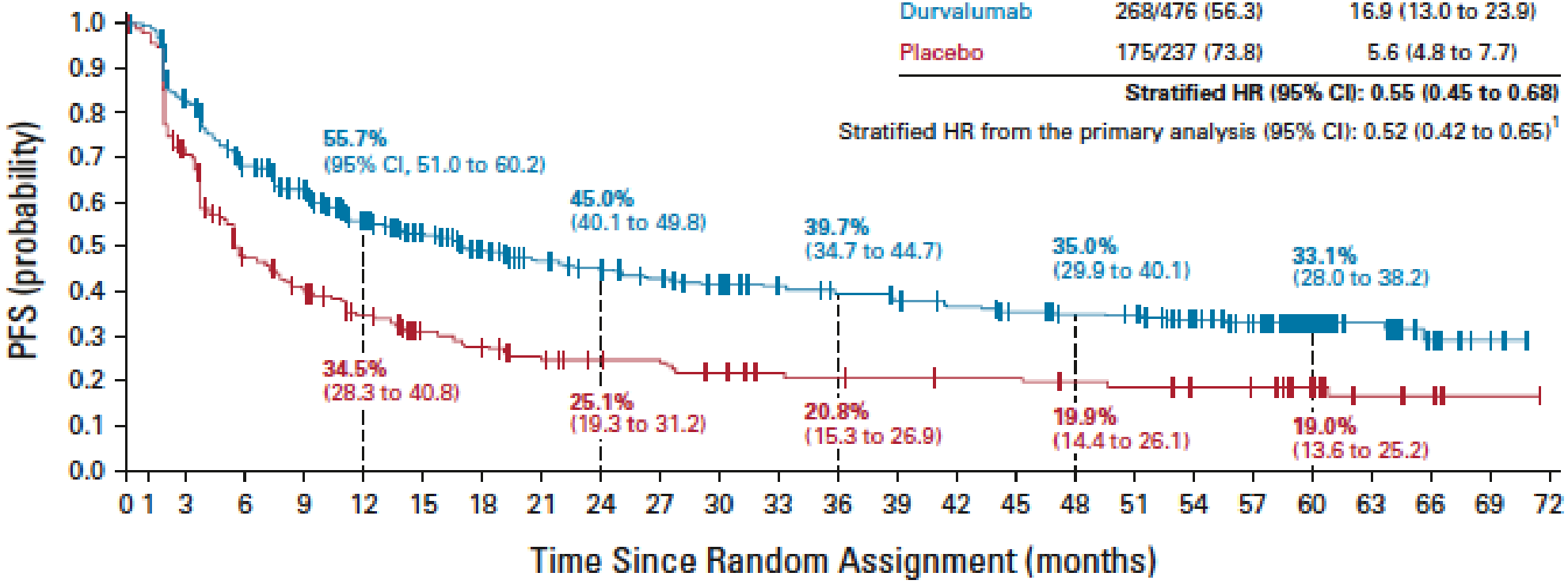
Antonia SJ et al. NEJM 2017

PACIFIC: 5-years PFS

Arm	No. of Events/ Total No. of Patients (%)	Median PFS (95% CI), Months
Durvalumab	268/476 (56.3)	16.9 (13.0 to 23.9)
Placebo	175/237 (73.8)	5.6 (4.8 to 7.7)

Stratified HR (95% CI): 0.55 (0.45 to 0.68)

Stratified HR from the primary analysis (95% CI): 0.52 (0.42 to 0.65)[1]



No. at risk:

Durvalumab	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

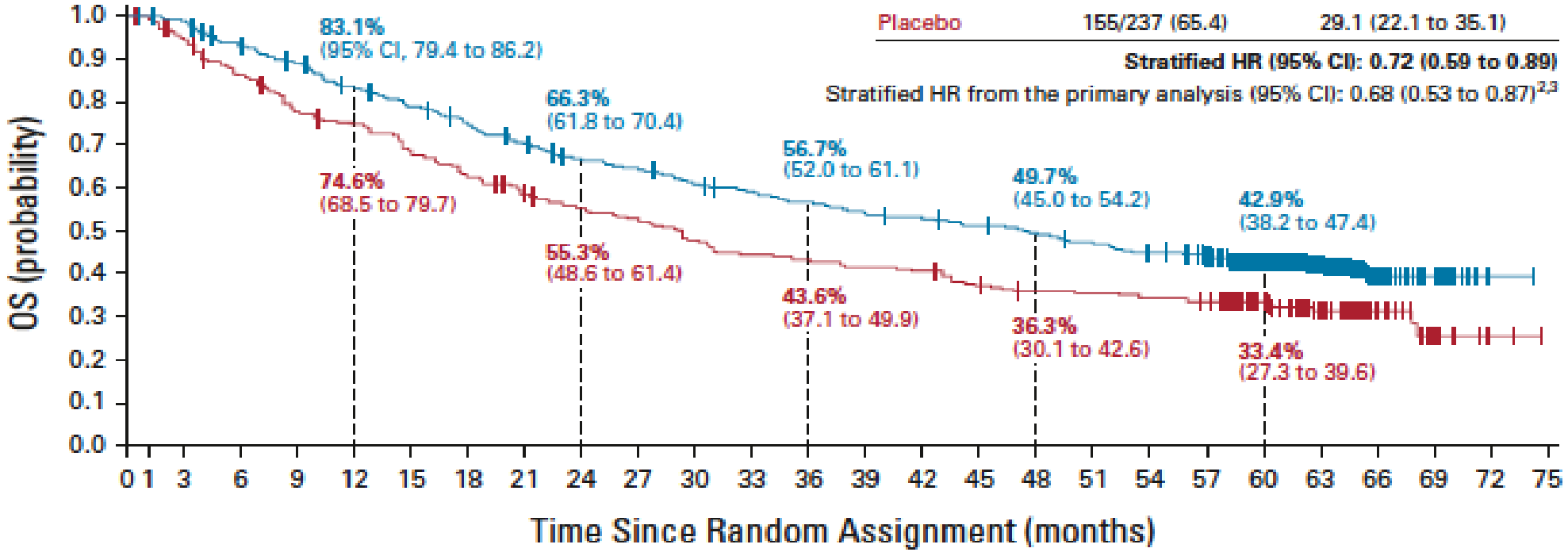
Spigel et al, JCO 2022

PACIFIC: 5-years OS

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]



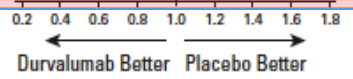
No. at risk:

Durvalumab	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

Spigel et al, JCO 2022

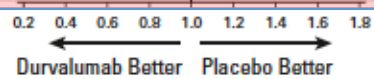
Forest Plot PACIFIC: OS and PFS

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]	2/6 (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)



OS

Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
All patients	268/476 (56.3)	175/237 (73.8)	0.58 (0.48 to 0.70)
Sex			
Male	192/334 (57.5)	122/166 (73.5)	0.61 (0.48 to 0.76)
Female	76/142 (53.5)	53/71 (74.6)	0.52 (0.36 to 0.74)
Age at random assignment			
< 65 years	140/261 (53.6)	100/130 (76.9)	0.46 (0.36 to 0.60)
≥ 65 years	128/215 (59.5)	75/107 (70.1)	0.76 (0.57 to 1.01)
Smoking status			
Smoker	246/433 (56.8)	158/216 (73.1)	0.61 (0.50 to 0.75)
Nonsmoker	22/43 (51.2)	17/21 (81.0)	0.33 (0.17 to 0.63)
NSCLC disease stage			
IIIA	132/252 (52.4)	95/125 (76.0)	0.53 (0.40 to 0.69)
IIIB	130/212 (61.3)	77/107 (72.0)	0.64 (0.48 to 0.85)
Tumor histologic type			
Squamous	138/224 (61.6)	74/102 (72.5)	0.71 (0.54 to 0.94)
All other	130/252 (51.6)	101/135 (74.8)	0.48 (0.37 to 0.63)
Best response to prior treatment			
Complete response	5/9 (55.6)	4/7 (57.1)	Not calculated[a]
Partial response	126/237 (53.2)	85/112 (75.9)	0.56 (0.43 to 0.74)
Stable disease	133/223 (59.6)	84/115 (73.0)	0.57 (0.44 to 0.76)
Prior chemotherapy type			
Gemcitabine-based	4/9 (44.4)	3/5 (60.0)	Not calculated[a]
Non-gemcitabine-based	264/467 (56.5)	172/232 (74.1)	0.58 (0.48 to 0.70)
Cisplatin	(54.9) 94/129	94/129 (72.9)	0.55 (0.42 to 0.71)
Carboplatin	114/199 (57.3)	76/102 (74.5)	0.62 (0.47 to 0.83)
Cisplatin and carboplatin	5/8 (62.5)	4/5 (80.0)	Not calculated[a]
Last radiation to random assignment			
< 14 days	62/120 (51.7)	49/62 (79.0)	0.45 (0.31 to 0.66)
≥ 14 days	206/356 (57.9)	126/175 (72.0)	0.64 (0.51 to 0.80)
WHO PS			
0 – Normal	127/234 (54.3)	82/114 (71.9)	0.62 (0.47 to 0.82)
1 – Restricted[b]	141/242 (58.3)	93/123 (75.6)	0.54 (0.41 to 0.70)
Region			
Asia	58/109 (53.2)	48/68 (70.6)	0.60 (0.41 to 0.88)
Europe	131/217 (60.4)	76/102 (74.5)	0.61 (0.46 to 0.82)
North and South America	79/150 (52.7)	51/67 (76.1)	0.47 (0.33 to 0.67)
Race			
White	195/337 (57.9)	117/157 (74.5)	0.58 (0.46 to 0.73)
Black or African American	7/12 (58.3)	2/2 (100.0)	Not calculated[a]
Asian	62/120 (51.7)	51/72 (70.8)	0.57 (0.39 to 0.83)
Other[c]	3/6 (50.0)	5/6 (83.3)	Not calculated[a]
EGFR or *ALK* aberration status			
Positive[d]	21/29 (72.4)	11/14 (78.6)	0.82 (0.39 to 1.71)
Negative	169/317 (53.3)	124/165 (75.2)	0.52 (0.41 to 0.65)
Unknown	79/130 (60.0)	40/58 (69.0)	0.74 (0.51 to 1.09)
PD-L1 expression level			
≥ 25%	61/115 (53.0)	33/44 (75.0)	0.44 (0.29 to 0.67)
< 25%	105/187 (56.1)	77/105 (73.3)	0.64 (0.48 to 0.86)
Unknown	102/174 (58.6)	65/88 (73.9)	0.60 (0.44 to 0.82)
1%-24% (post hoc analysis)	50/97 (51.5)	36/47 (76.6)	0.51 (0.33 to 0.78)
≥ 1% (post hoc analysis)	111/212 (52.4)	69/91 (75.8)	0.47 (0.35 to 0.64)
< 1% (post hoc analysis)	55/90 (61.1)	41/58 (70.7)	0.80 (0.53 to 1.20)

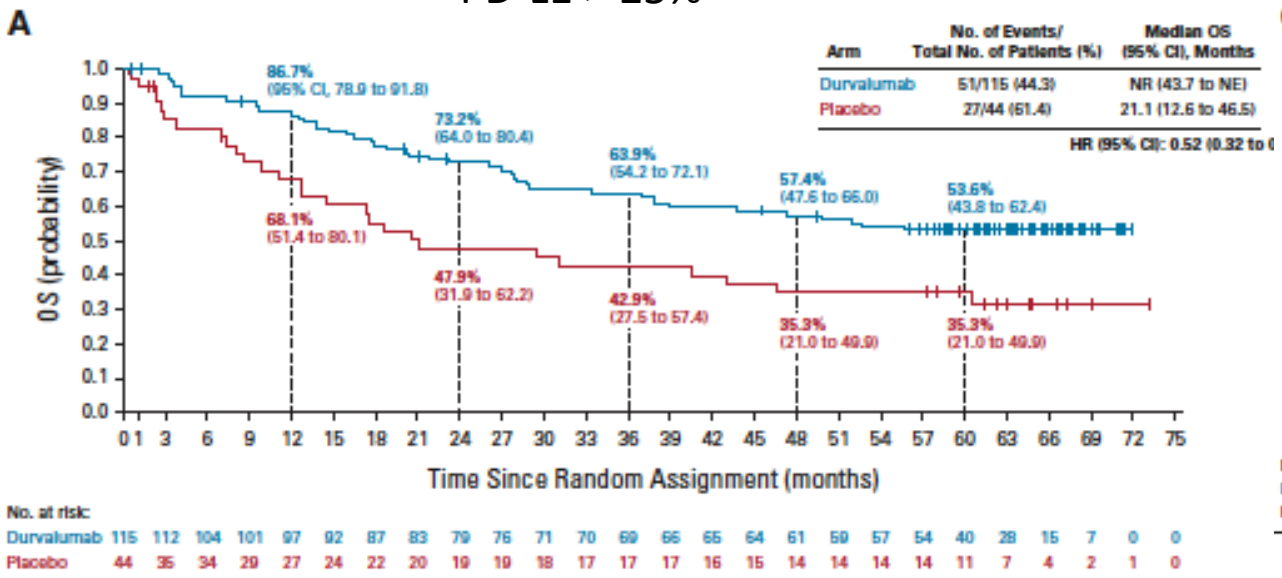


PFS

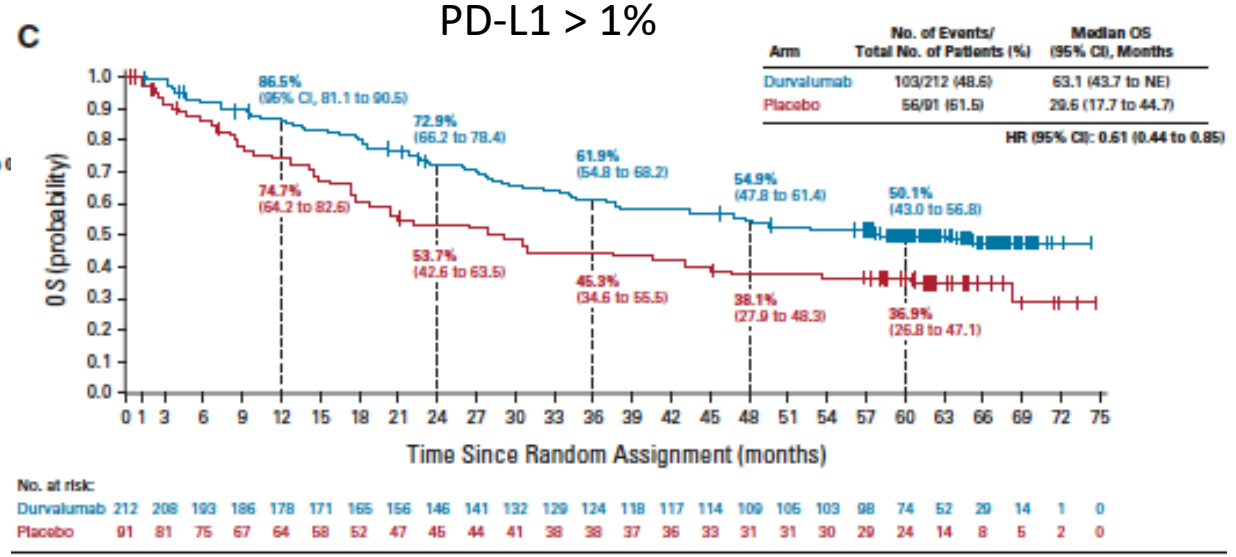
Spigel et al, JCO 2022

PACIFIC: Specific subgroups (1)

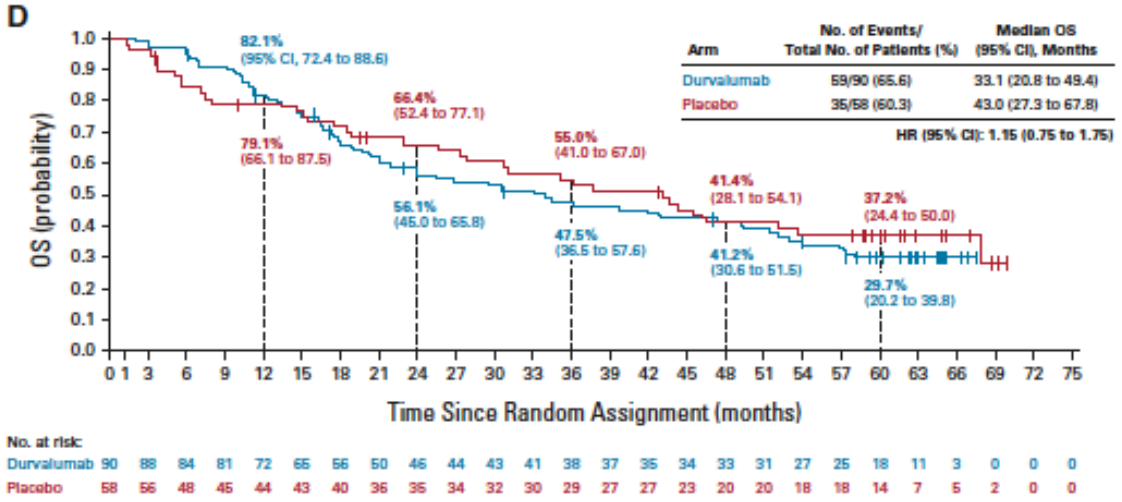
PD-L1 > 25%



PD-L1 > 1%



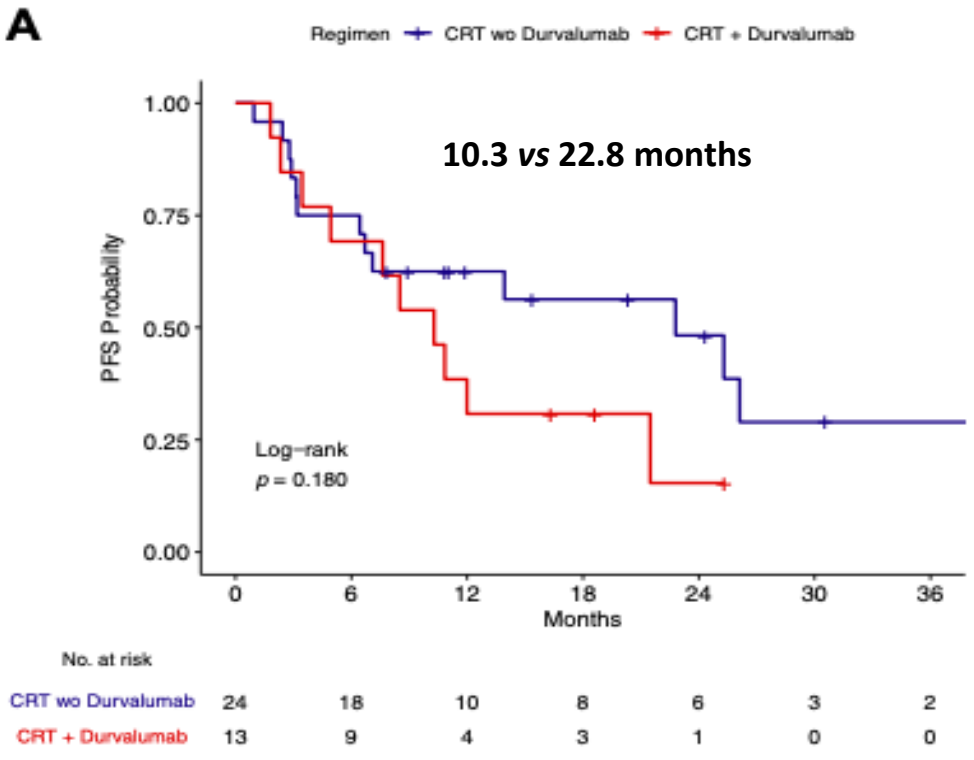
PD-L1 < 1%

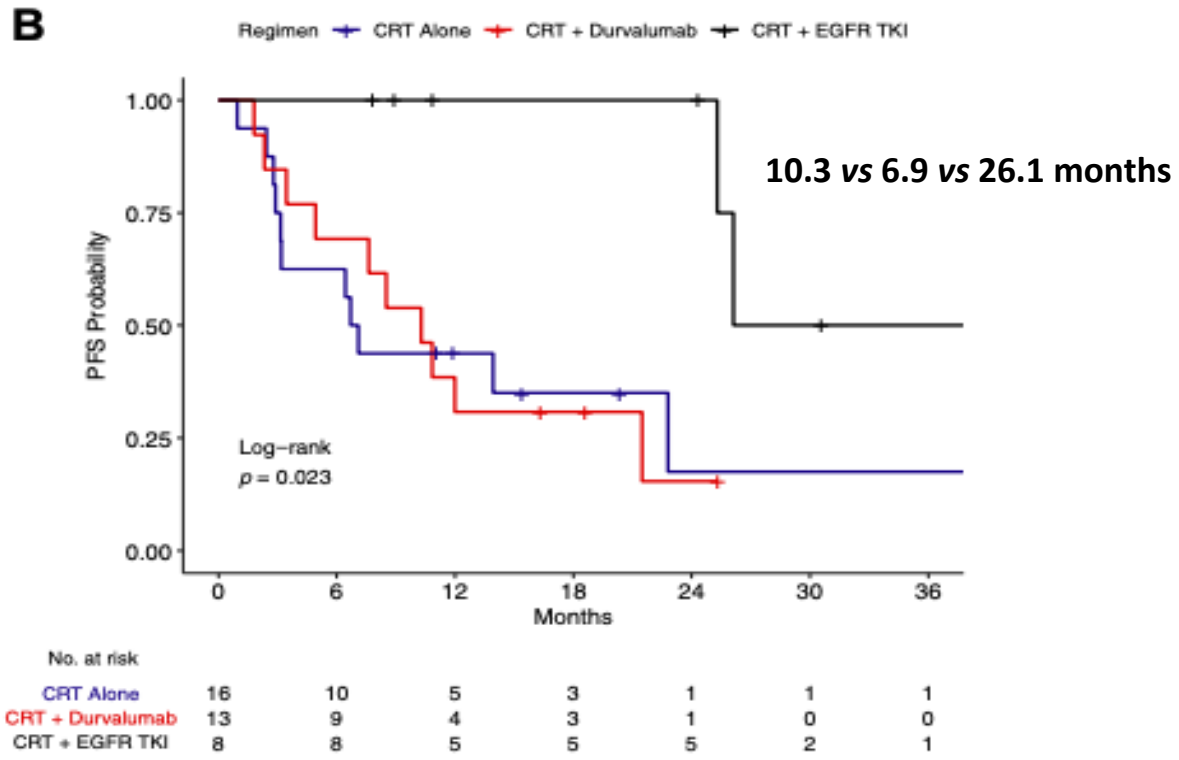


Spigel et al, JCO 2022

PACIFIC: Specific subgroups (2)

Durvalumab after CRT in *EGFR*$^{mut+}$ NSCLC: a retrospective trial

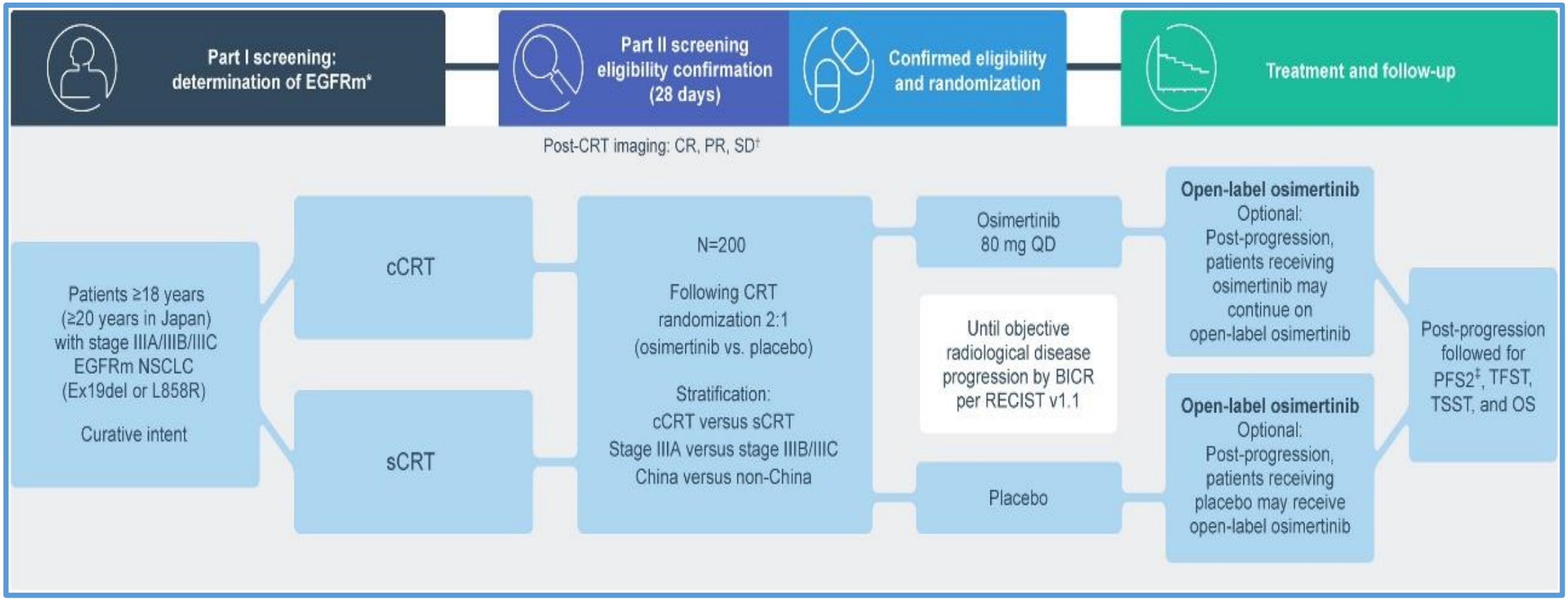




Retrospective series:
37 pts *EGFRmut+*
1 case of G4 pneumonitis

Aredo JV, et al. JTO 2021

LAURA phase 3 trial for unresectable, stage III, *EGFRmut+* NSCLC

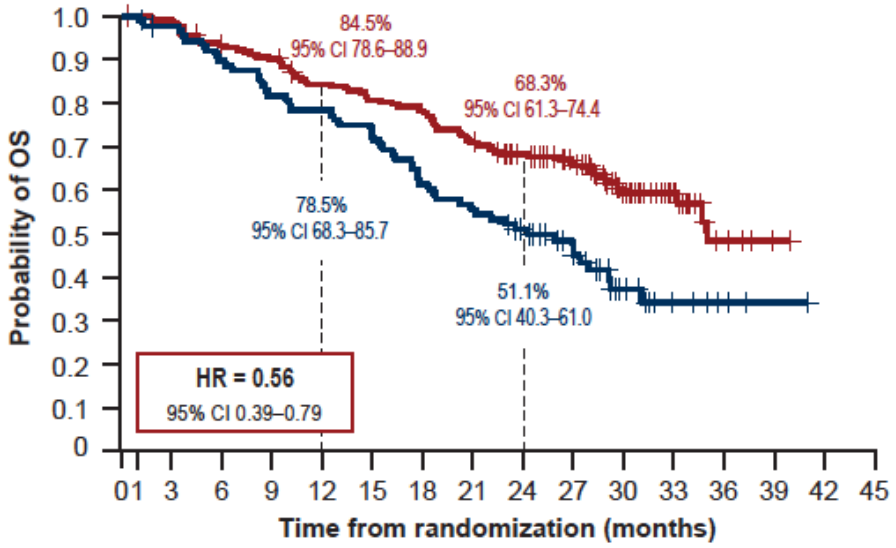


Lu et al, Lung Cancer 2021

Exploratory post-hoc analysis: IIIA-N2 and elderly (> 70 years)

N2

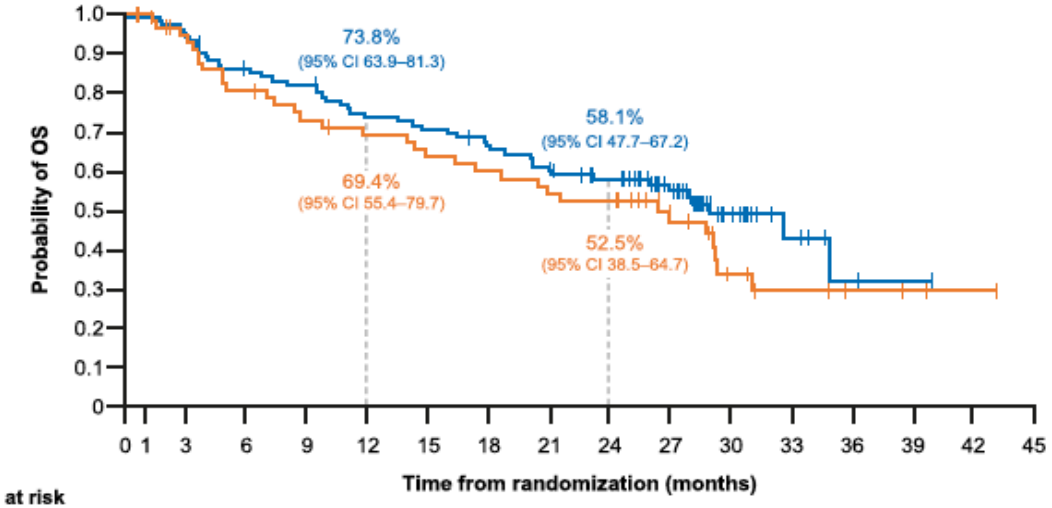
	Durvalumab (*n* = 197)	Placebo (*n* = 90)
OS events, *n* (%)	75 (38.1)	52 (57.8)
Median OS (95% CI), months	34.9 (33.2–NE)	24.2 (18.3–29.2)



No. at risk																
Durvalumab	197	194	181	175	162	155	150	136	118	93	48	24	7	1	0	0
Placebo	90	87	79	72	69	64	54	49	42	28	14	6	3	1	0	0

Elderly

Aged ≥70 years	No. events/No. patients (%)	Median OS (95% CI), months
Durvalumab	48/101 (47.5)	29.0 (21.0–NE)
Placebo	33/57 (57.9)	26.9 (14.9–29.3)
Hazard ratio (95% CI)		0.78 (0.50–1.22)

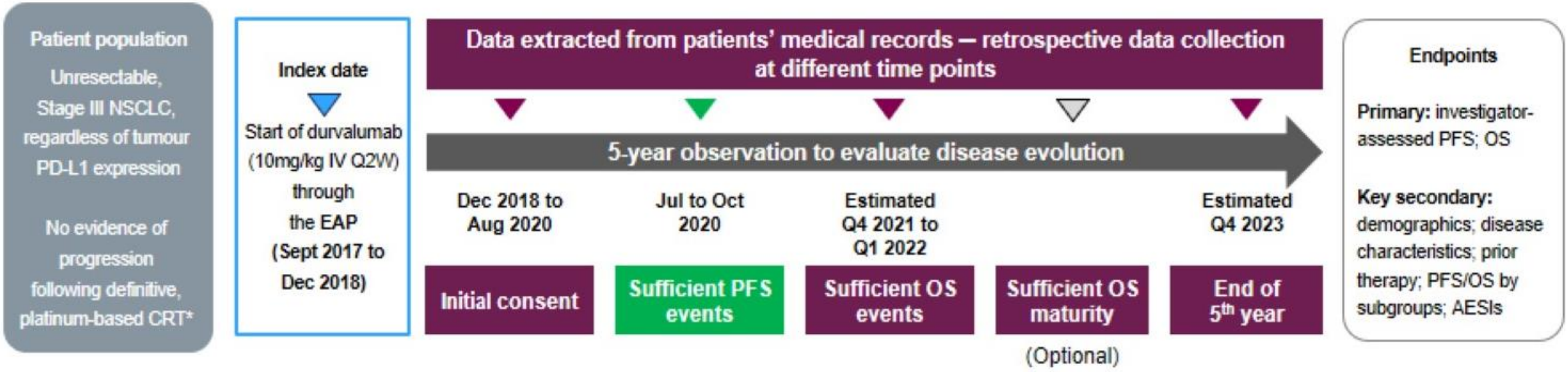


No. at risk																
Durvalumab	101	95	85	81	72	69	64	58	51	37	15	7	3	1	0	0
Placebo	57	53	45	40	37	34	32	29	28	18	9	5	3	2	1	0

Spigel et al, JCO 2022

Does PACIFIC fit Real World ?

PACIFIC-R: An International, Observational Study



- **1,399 patients** included in the **full analysis set (FAS)** from **290 active sites** in **11 participating countries**
  - France (n=342), Spain (244)†, Australia (165), Netherlands (155), Belgium (118), Italy (116), Israel (92), Germany (62), UK (54), Norway (36), and Switzerland (15)

ISG IRE

Girard N, et al. ESMO 2021

Patient Characteristics & Durvalumab Treatment

Characteristics		FAS (N=1,399)
Age at EAP inclusion (years)	Median (range)	66.0 (26–88)
Age categories, %	≤75 years / >75 years	89.6 / 10.4
Sex, %	Male / Female	67.5 / 32.5
Smoking status at EAP inclusion, %	Never / Current / Former	7.9 / 32.6 / 59.5
Stage at diagnosis, %*[A]	Stage IIIA	43.2
	Stage IIIB/C	51.0
Histological subtype, %*[B]	Squamous	35.5
	Non-squamous	63.1
	Unknown	1.4
ECOG/WHO PS at EAP inclusion, %	0 / 1 / 2 / 3	51.4 / 46.6 / 1.9 / 0.1
CRT type, %*[C]	Concurrent	76.6
	Sequential	14.3
	Other	9.1
PD-L1 expression, %*[D] (Based on n=967 tested patients)	≥1%	72.5
	<1%	17.9
	Inconsistent†	9.6

- **Median time to durvalumab initiation** from the end of RT = **56 days**
- Overall **median durvalumab treatment duration =** 335 days (**~11 months**)
  - >12 months' treatment: 20.1%
  - >14 months' treatment: 4.4%
- Patients received a **median of 22 durvalumab infusions**
  - 7.1% received >26 infusions

ISG IRE

Girard N, et al. ESMO 2021

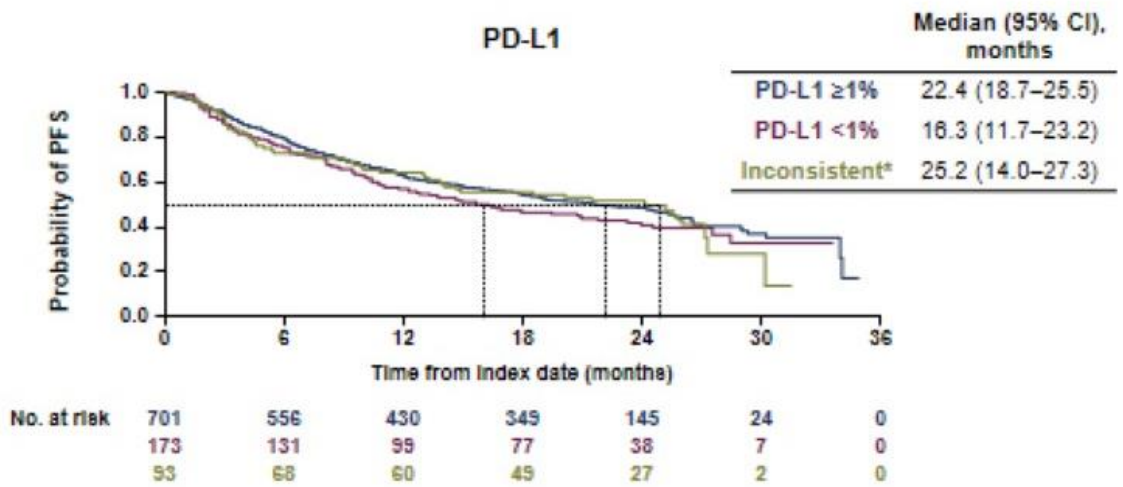
Real-world PFS (FAS) – Median Follow-up Duration = 23.0 Months*

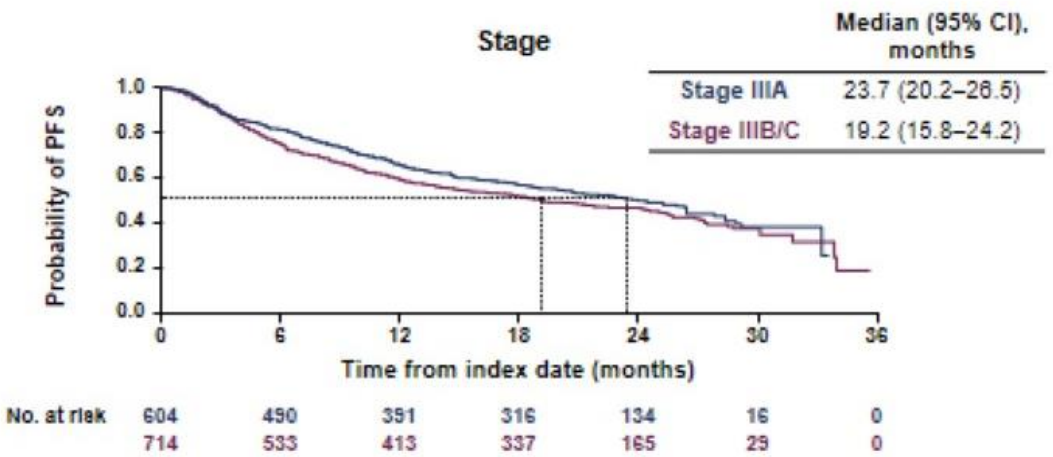
- Median rwPFS in PACIFIC-R was higher than the median PFS reported for the durva. arm of the PACIFIC trial[1†]
- Challenges with collecting rwPFS data limit comparisons between PACIFIC-R and PACIFIC
- RwPFS is likely overestimated as:
  - Germany and UK sites did not collect deaths that occurred prior to study enrolment[‡] (50 early deaths not counted)
  - RECIST criteria for tumour assessments is used heterogeneously across countries
  - Assessments for progression in the real world may not occur as frequently or consistently as in clinical trials; the COVID-19 pandemic may also have resulted in fewer hospital visits

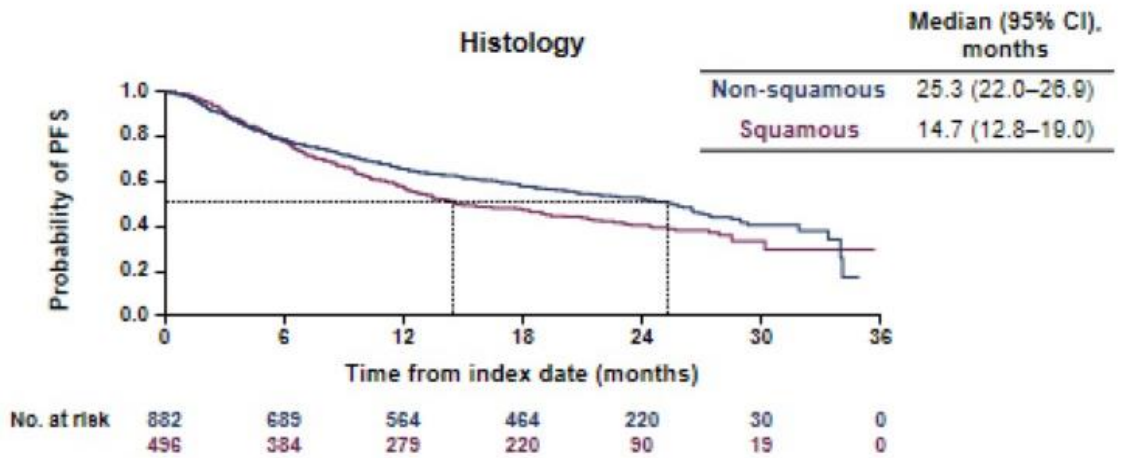
	PACIFIC-R FAS	PACIFIC trial (durva. arm)[1]
PFS	N=1,399	N=476
Total events, N (%)	737 (52.7)	268 (56.3)[†]
Progression per RECIST	456 (32.6)	
Progression per physician assessment	170 (12.2)	
Progression, assessment unknown	30 (2.1)	
Deaths in absence of progression	81 (5.8)	
Median PFS, months	**21.7**	**16.9**
95% CI	19.2–24.5	13.0–23.9
PFS rate, %		
12 months	62.4	55.7
24 months	48.2	45.0

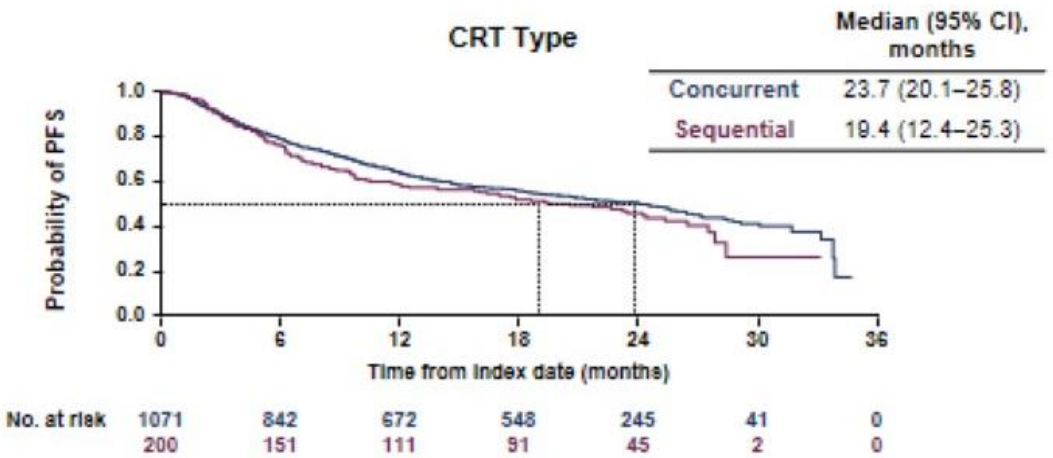
Girard N, et al. ESMO 2021

Real-world PFS by Subgroup









ISG IRE

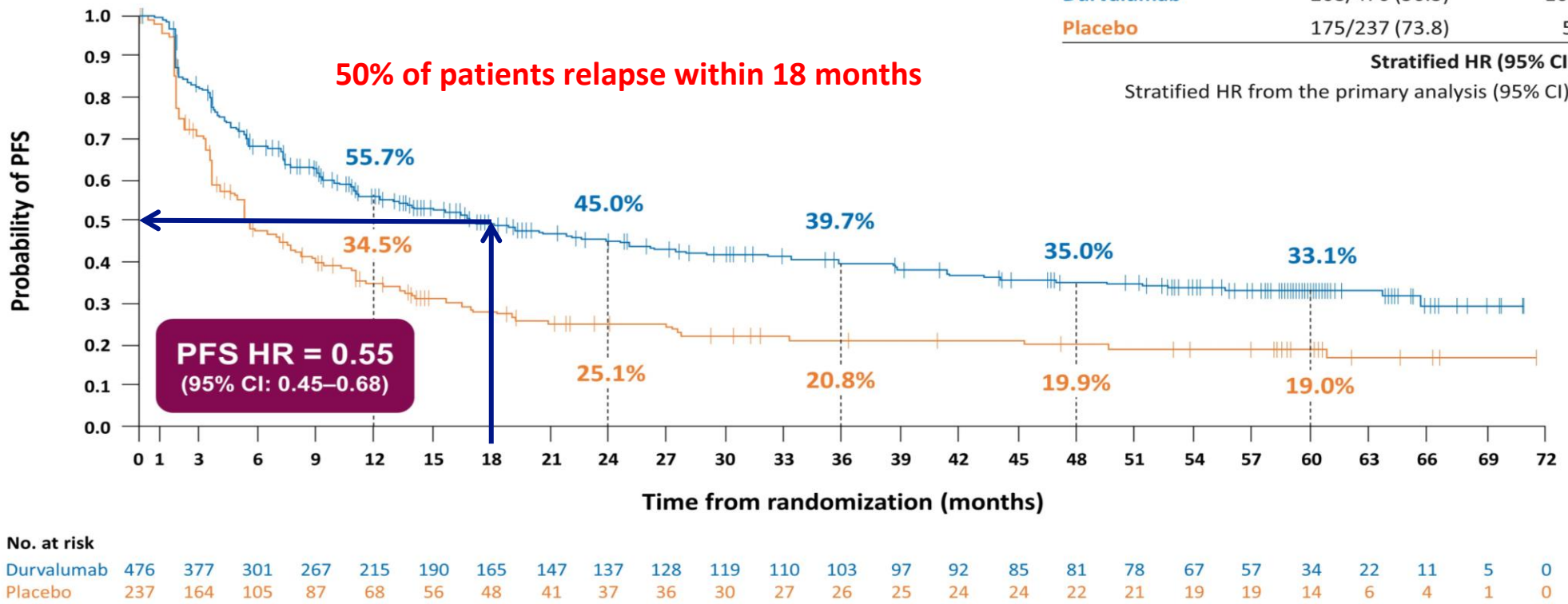
Girard N, et al. ESMO 2021

Durvalumab maintenance: can we improve the results?

	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)

Stratified HR (95% CI): 0.55 (0.45–0.68)

Stratified HR from the primary analysis (95% CI):[1] 0.52 (0.42–0.65)

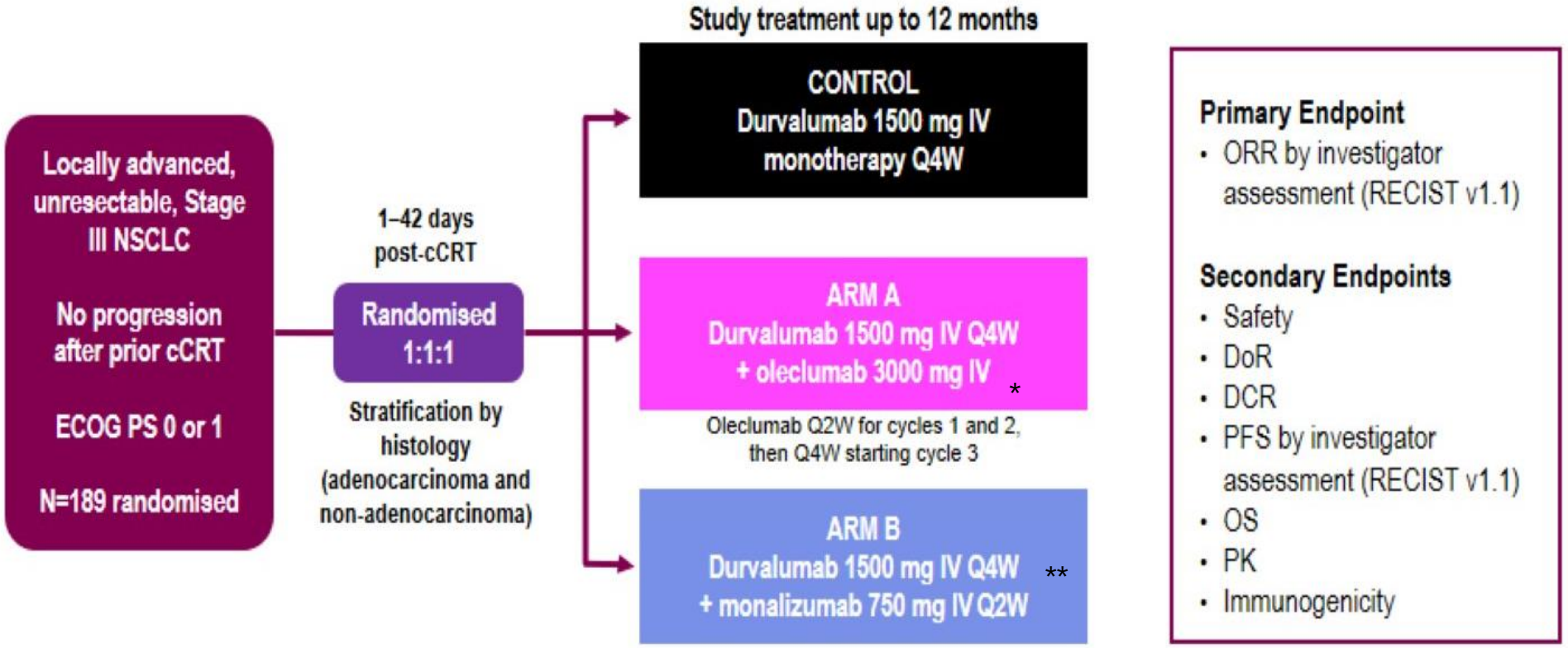


No. at risk

Durvalumab	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

Spigel et al, JCO 2022

COAST: Phase II, randomized open-label study

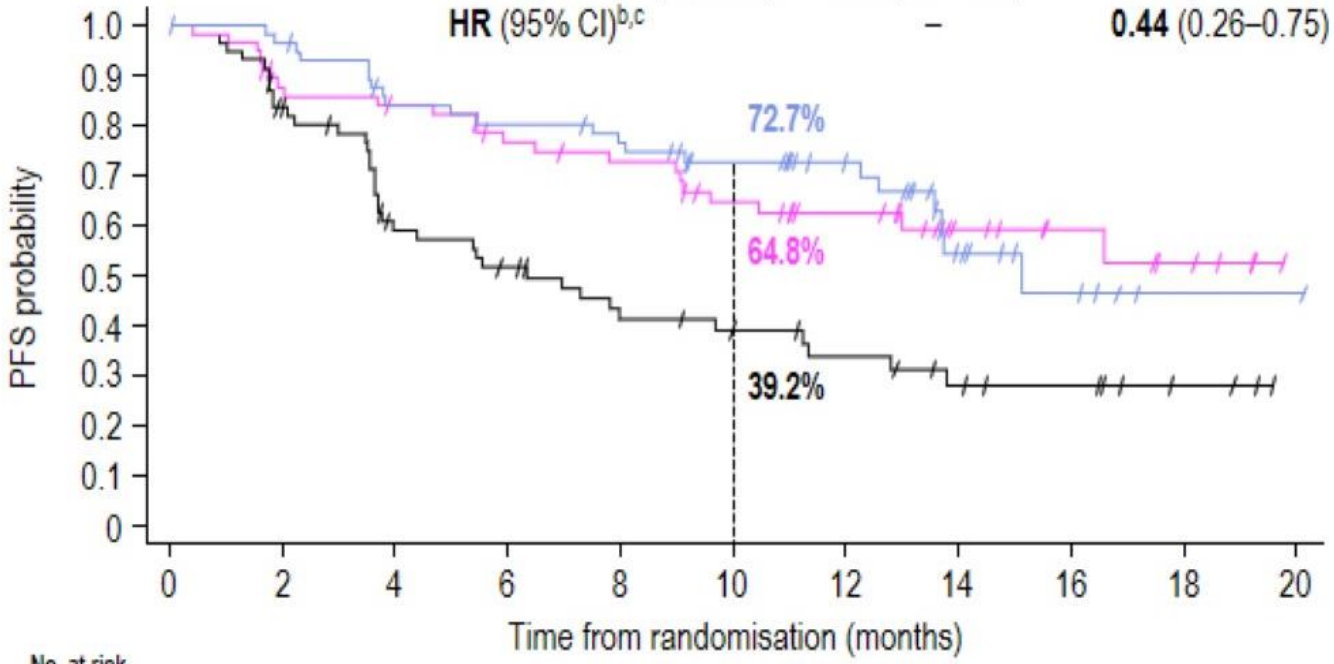


*Monoclonal antibody against the CD73
**First-in-class immune checkpoint inhibitor targeting Natural Killer Group 2A (NKG2A)

Marti AM et al ESMO 2021

COAST: PFS by investigator

	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)



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

Marti AM et al ESMO 2021

SKYSCRAPER-03 (GO41854): tiragolumab + atezolizumab in Stage III unresectable NSCLC

Stage III unresectable NSCLC

- Without progression after platinum-based CRT (≥2 cycles)
- Known PD-L1 status
- ECOG PS 0–1
- Excludes EGFR/ALK+ patients

N=~800*

Randomised within 1–42 days after last dose of cCRT

R 1:1

Tiragolumab 840mg IV Q4W + atezolizumab 1680mg IV Q4W for 13 cycles (12 months)

Durvalumab 10mg/kg IV Q2W for 13 cycles (12 months)

Treat until progression or unacceptable toxicity

Stratification factors:

- PD-L1 status (<1% vs ≥1%)
- ECOG PS (0 vs 1)
- Staging (IIIA vs IIIB or IIIC)
- Histology (NSQ vs SQ)

Primary endpoint:

- PFS (IRF-assessed)

Secondary endpoint:

- OS
- PFS (INV-assessed)
- Confirmed ORR
- DoR
- Landmark PFS/OS
- Time to death or distant metastasis
- Time to confirmed deterioration
- Safety

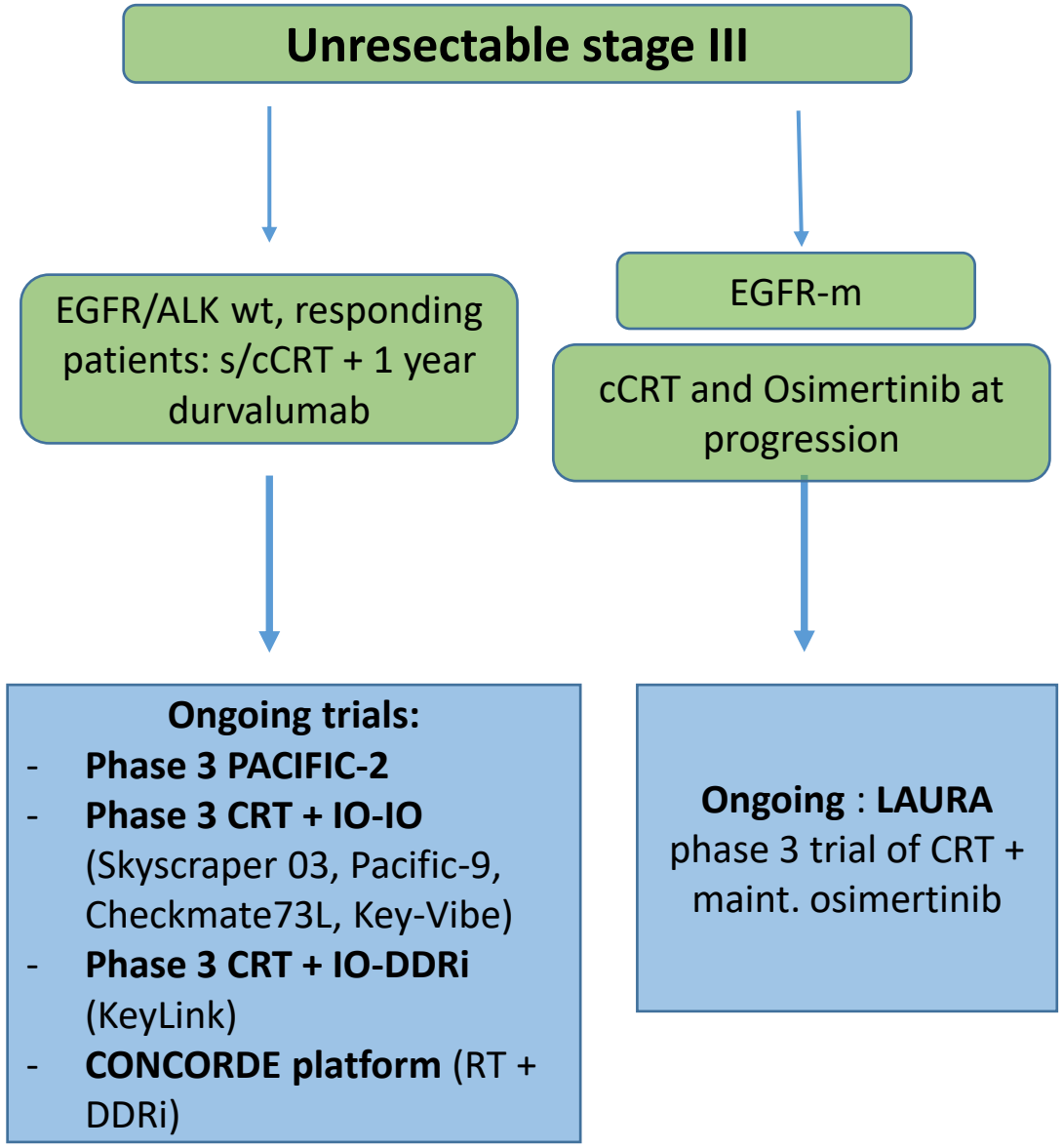
CONCLUSIONS

- Durable and sustained PFS and OS benefit (confirmed also in elderly pts)
- ORR was approximately 10% higher with durvalumab, and half of responding patients had ongoing responses at 5 year: long-term evidence for sustained improvement in local disease control (biologically and clinically relevant for future trials)
- TFST and TSST, better for durvalumab with HR 0.65 for both, suggest that the survival benefit is largely driven by PFS benefit, and differences in salvage therapies between the two arms did not affect survival benefit
- Open issues:
  - PD-L1 negative patients (confirmed lack of OS benefit? re-biopsy, other strategies?)
  - Sequential vs. concurrent CRT (PACIFIC-6 and PACIFIC-R data)?
  - Frail, chemo-ineligible patients?
  - Duration of durvalumab maintenance?
  - Therapy at progression?
  - Earlier use of IO (PACIFIC2 and other trials)

PACIFIC updated results:

PS: 0-1, responding patients after cCRT

- OS @ 5 yrs : 43%, median OS 47.5 months, HR 0.72
- PFS @ 5yrs: 33% @ 5 yrs, median 16.9 months, HR 0.55



Senan et al, ESMO Open 2022