

Il trattamento della malattia localmente avanzata inoperabile

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ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO



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Congresso Nazionale sul carcinoma del polmone

CARCINOMA DEL POLMONE: QUALI NOVITÀ NEL 2023?

9 OTTOBRE 2023

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CON IL PATROCINIO



PATROCINI RICHIESTI

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Disclosures

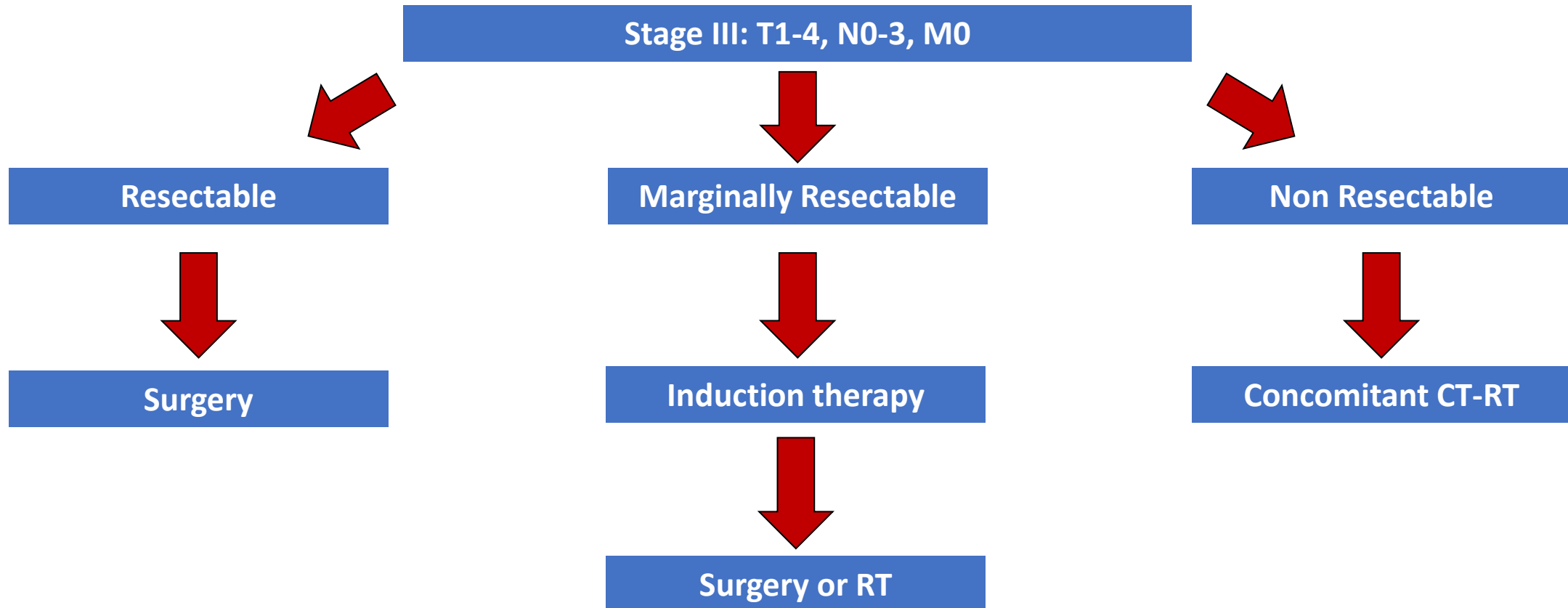
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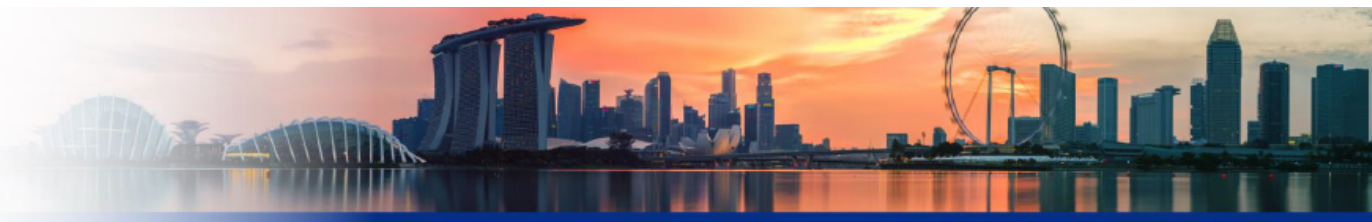
Stage III NSCLC: one stage for many diseases





2023 World Conference
on Lung Cancer

SEPTEMBER 9-12, 2023 | SINGAPORE



Consensual definition of stage III NSCLC Resectability: EORTC-Lung Cancer Group initiative with other scientific societies

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	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY [†]	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	UNCLEAR	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 size / satellite	RESECTABLE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 invasion	POTENTIALLY RESECTABLE [§]	POTENTIALLY RESECTABLE [§]	POTENTIALLY RESECTABLE [§]	POTENTIALLY RESECTABLE* [§]	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE

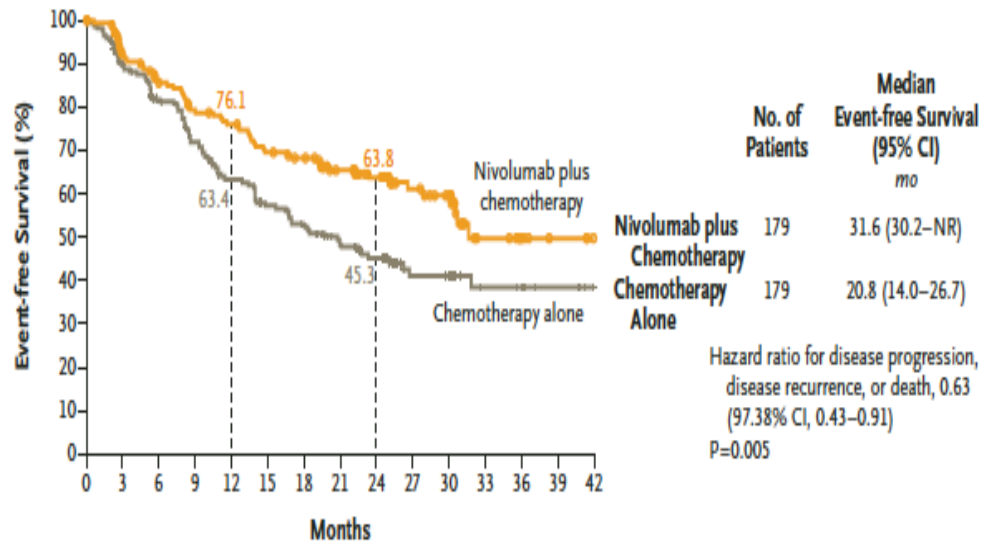
*Multiple station N2: case-by-case discussion; the exact number of nodes/stations cannot be defined

[†]Bulky N2: lymph nodes with a short-axis diameter >2.5-3 cm; in specific situations of *highly selected patients*, including those patients in multidisciplinary trials with surgery as local therapy can be discussed

[§]Some T4 tumours by infiltration of major structures are potentially resectable – see Table 1

Two main crucial points in stage III

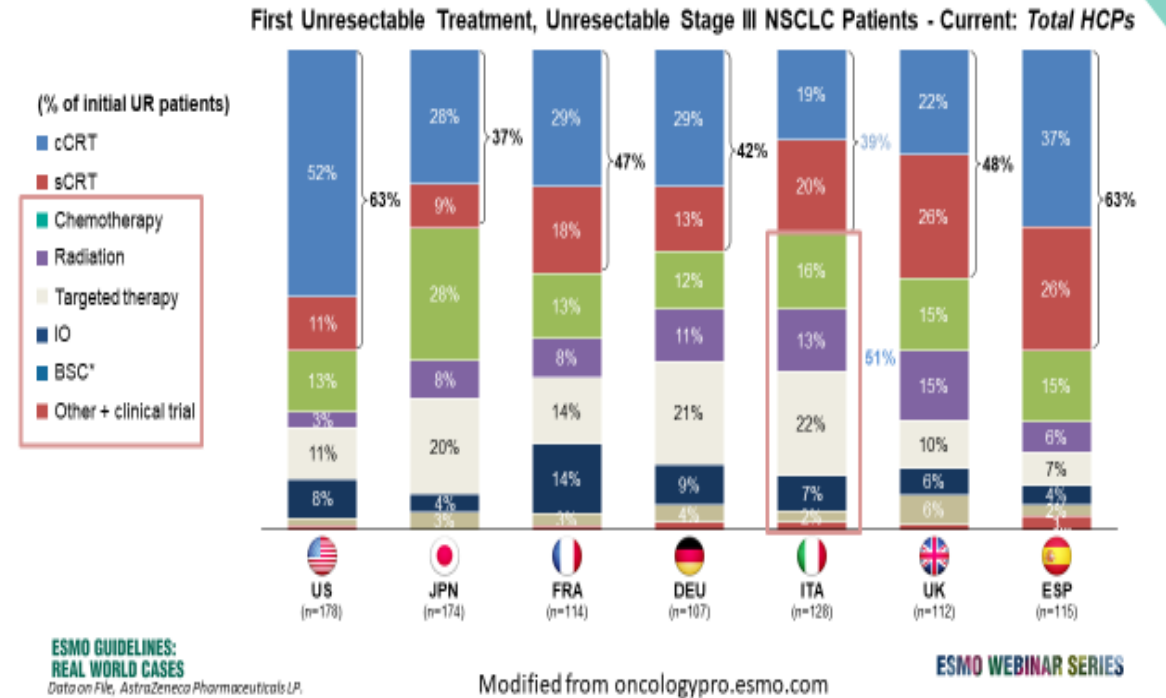
1. Chemo-IO in resectable Stage III disease



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

CheckMate 816

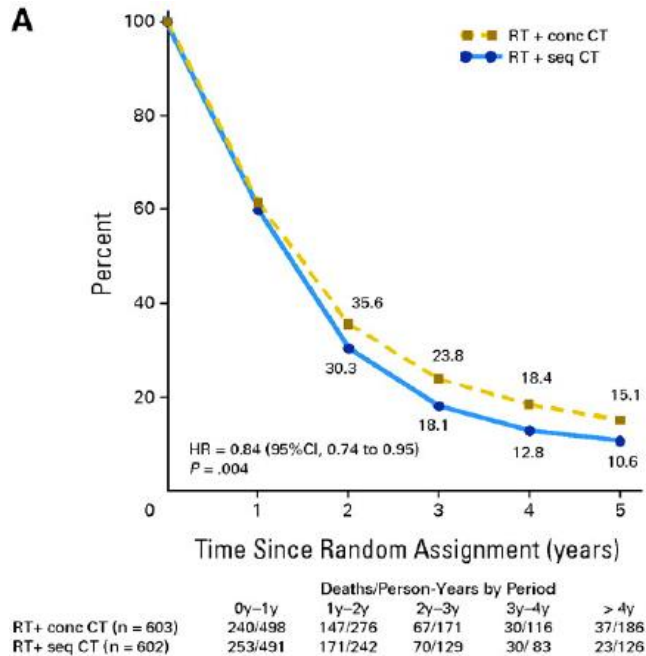
2. Underpowered CRT regimen in unresectable Stage III are still used



Italy < 30% cCRT

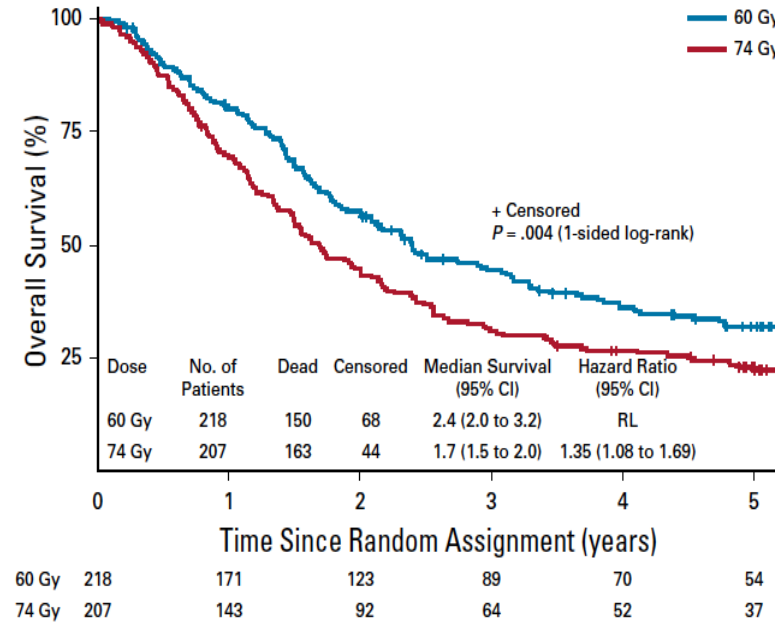
Changes in the treatment paradigm for unresectable stage III NSCLC

Older CRT studies (< 2005)

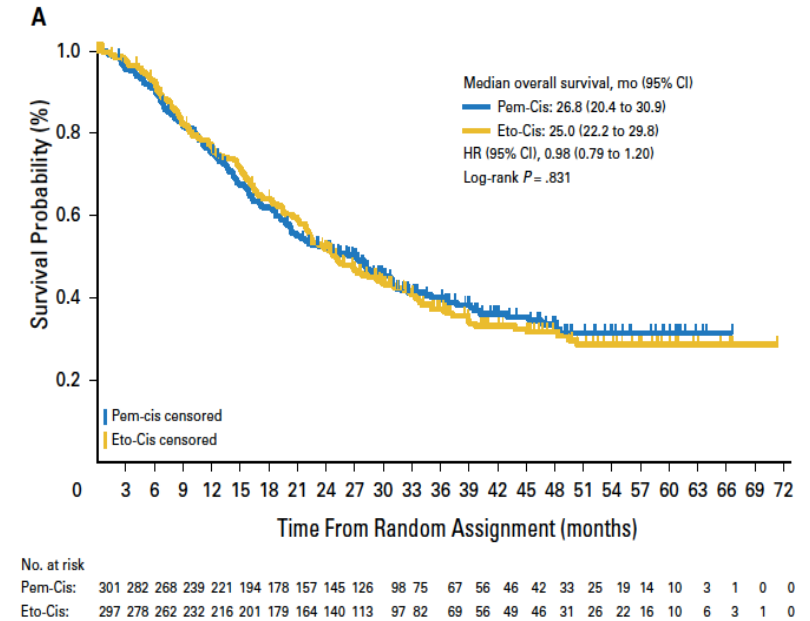


**cCRT vs sCRT
meta-analysis**

Modern cCRt (2005-2018)



**RTOG 0617:
60 vs. 74 Gy**



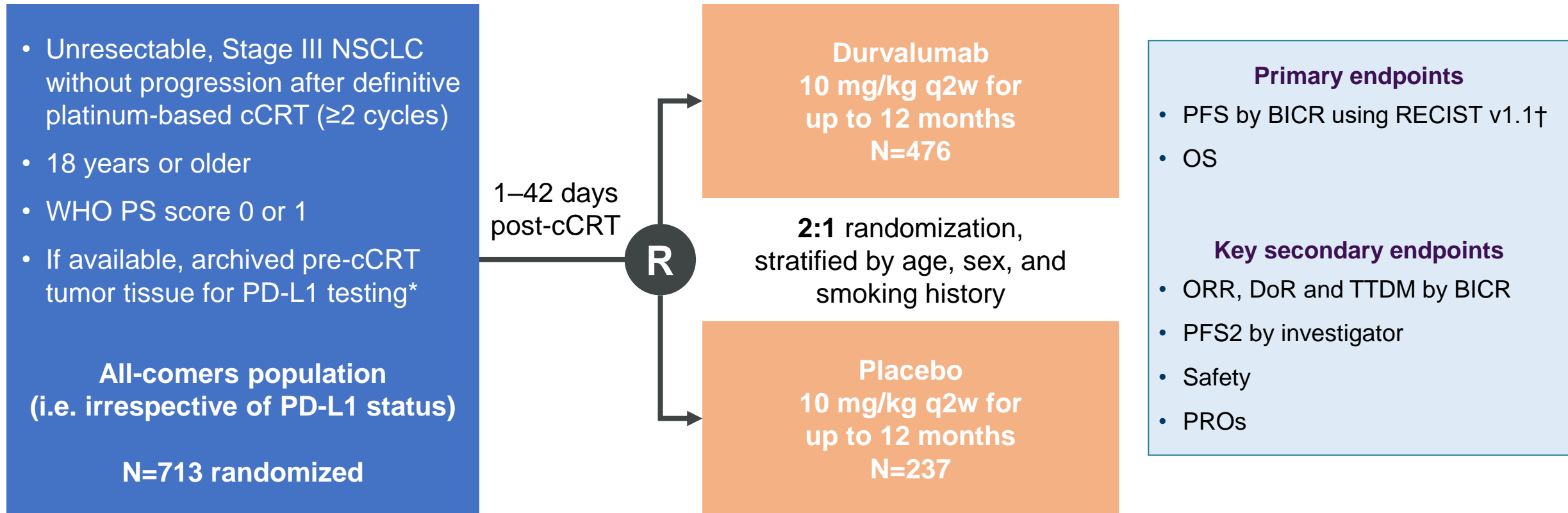
**PROCLAIM:
cis-pem vs. cis-eto for non-squamous**

Auperin et al, JCO 2010

Senan et al, JCO 2016

Bradley et al, JCO 2021

PACIFIC phase 3 study design



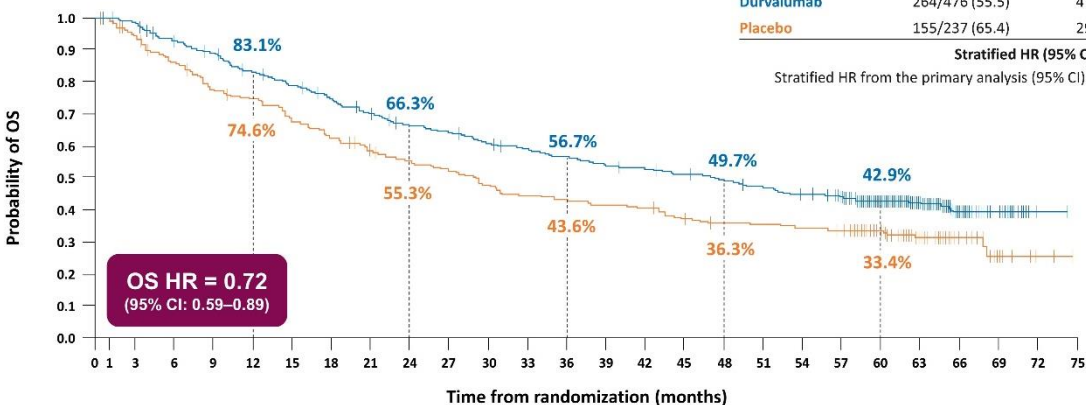
BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; DoR, duration of response; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PFS2, time to second objective disease progression; 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

Chemoradiotherapy followed by consolidation durvalumab is the standard of care in unresectable stage III NSCLC

5-year OS

	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)

Stratified HR (95% CI): **0.72 (0.59–0.89)**
 Stratified HR from the primary analysis (95% CI):^{1,2} 0.68 (0.53–0.87)



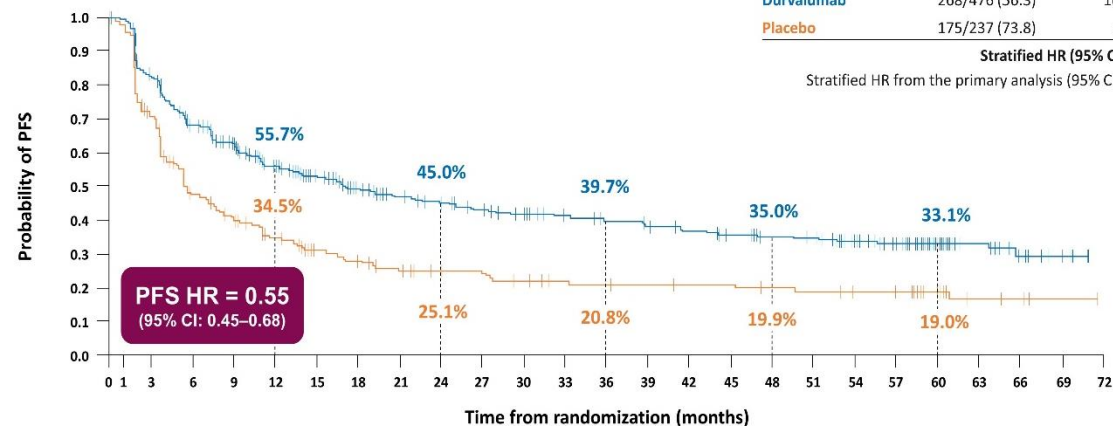
No. at risk	0	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0	
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0	

- **28% Reduction in the risk of death**
- **Median OS 47.5 months**
- **5-yr OS rate 42.9%**

5-year PFS

	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)



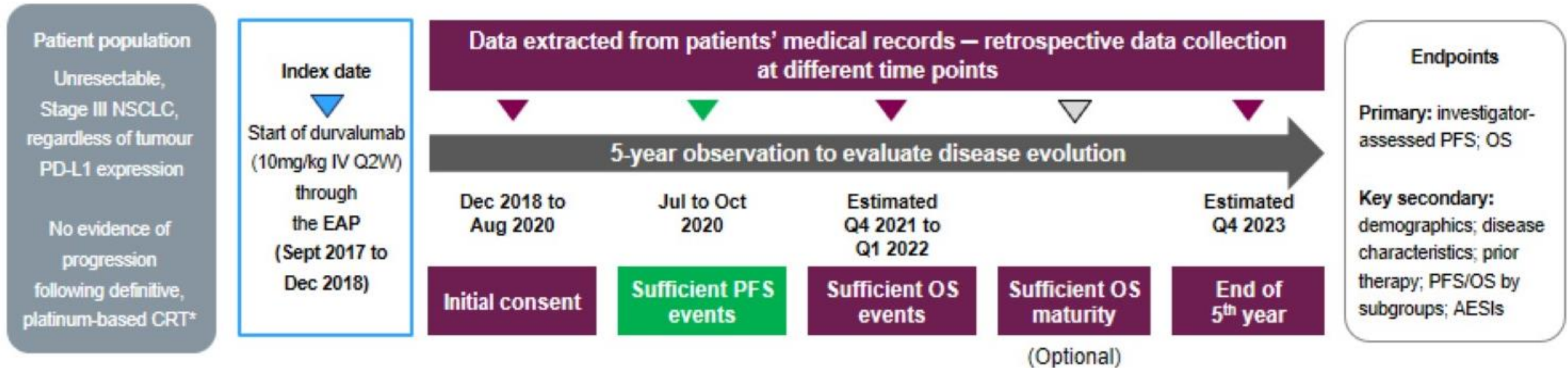
No. at risk	0	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72
Durvalumab	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0	
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0	

- **45% Reduction in the risk of progression**
- **Median PFS 16.9 months**
- **5-yr PFS rate 33.1%**

RR 28.4% (+ RR 50% to prior CRT)

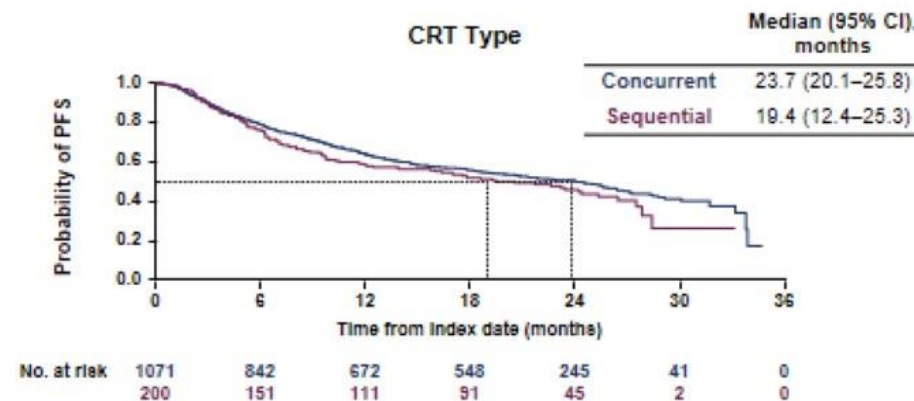
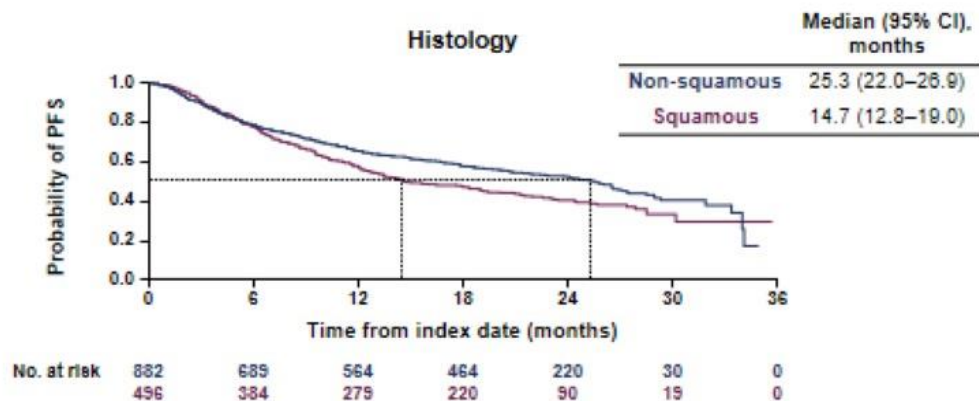
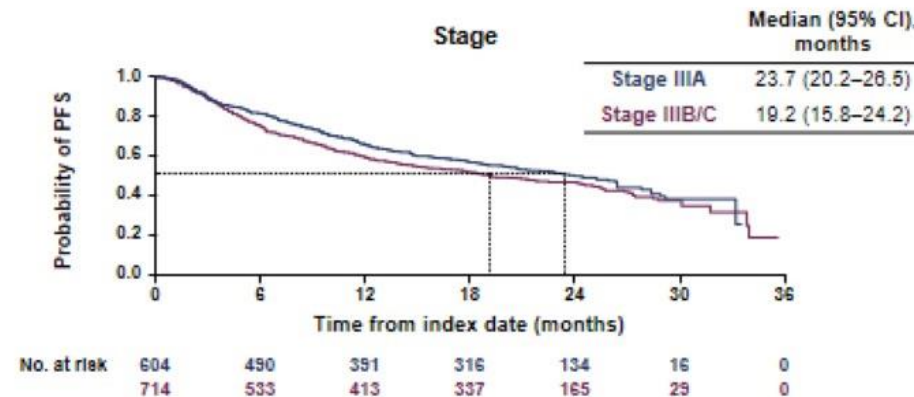
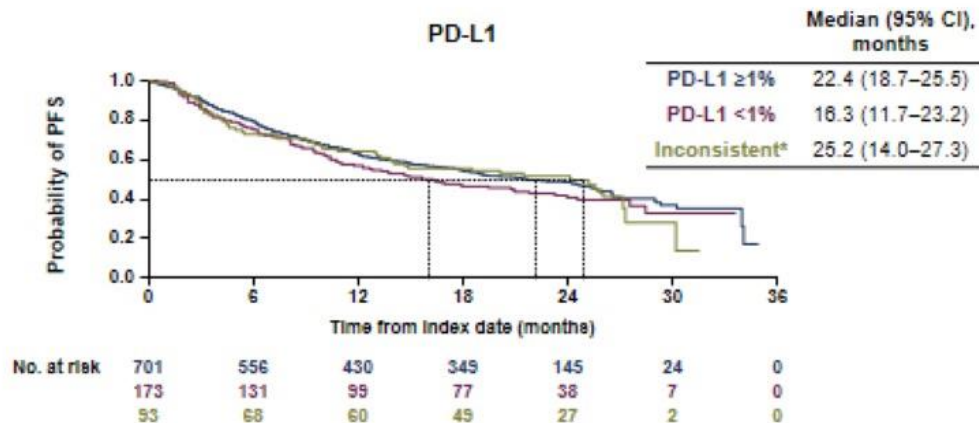
Does PACIFIC fit Real World ?

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)

Real-world PFS by Subgroup



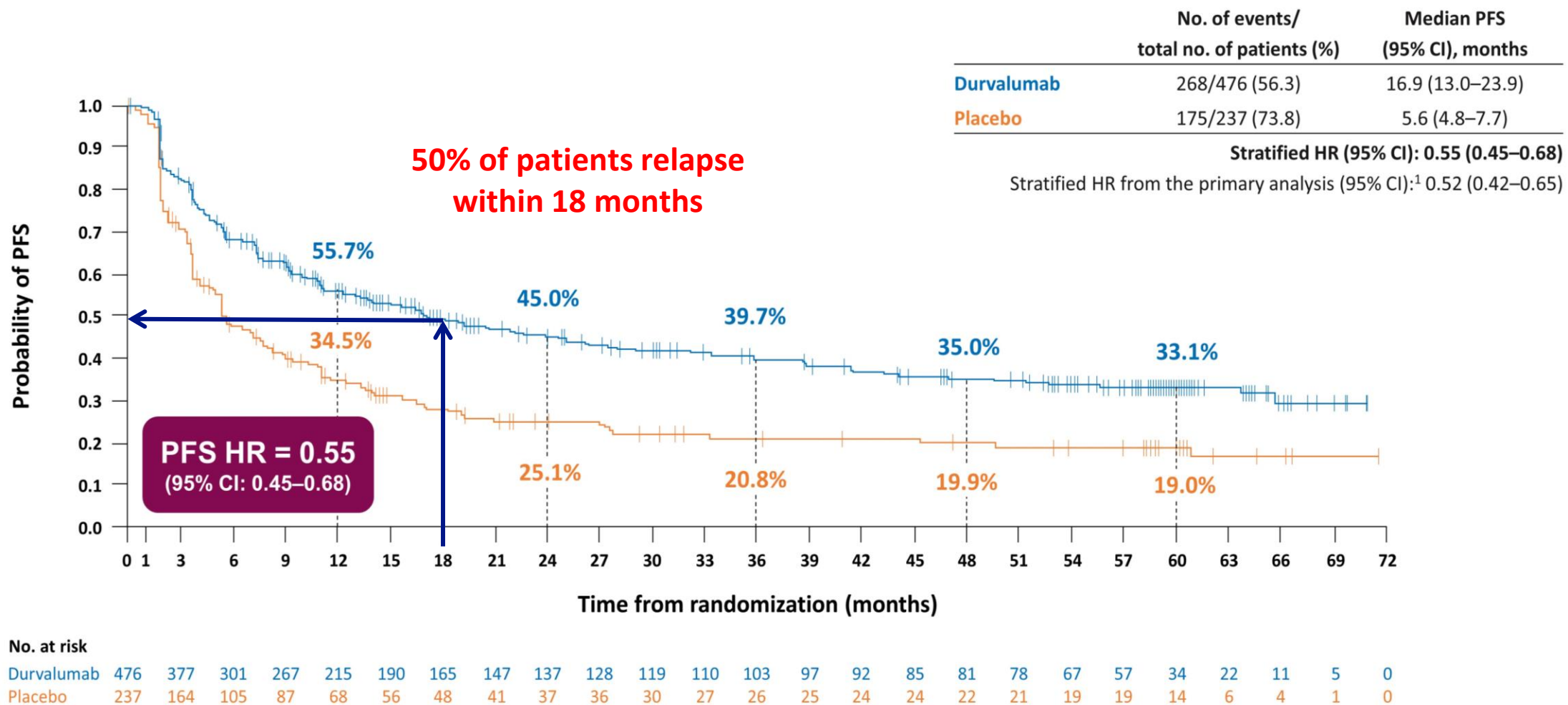
R-PACIFIC

PACIFIC

Median PFS, months	21.7	16.9
95% CI	19.2–24.5	13.0–23.9

median follow-up 23 months

Durvalumab consolidation: can we improve the results?



Future strategies in unresectable stage III

Consolidation after cCRT / sCRT

CT → RT → ICI

- PACIFIC (NCT02125560)
- GEMSTONE 301 (NCT03728556)*
- PACIFIC-5 (NCT03706690)*

STANDARD

CT → ICI

- KEYNOTE 301 (NCT03728556)*
- PACIFIC-5 (NCT03706690)*
- PACIFIC 6 (NCT03693300), cohort 1

Concurrent ICI + cCRT

ICI
CT → RT → ICI

- KEYNOTE-799 (NCT036311784)
- DETERRED (NCT02525757)
- NICOLAS (NCT02434081)
- PACIFIC 2 (NCT03519971)*
- EA5181 (NCT04092283)*
- CheckMate 73L (NCT04026412)*
- KEYLYNK-012 (NCT04380636)**
- KEYVIBE-006 (NCT05298423)*
- NCT05386888

Patients with PS ≥ 2

CT → RT → ICI

- PACIFIC 6 (NCT03693300)

RT → ICI

- SWOG 1933 (NCT04310020)
- DUART trial (NCT04249362)

ICI RT

- TRADE-Hypo (NCT04351256)
- DART (NCT03999710)
- AIRING (NCT04577638)

ICI-consolidation intensification

CT → RT → ICI → ICI

- COAST (NCT03822351)
- PACIFIC-9 (NCT05221840)*
- PACIFIC-8 (NCT05211895)*
- SKYSCRAPER-03 (NCT04513925)*
- BTCRC-LUN 16-081 (NCT03285321)
- CheckMate 73L (NCT04026412)*

Induction (CT)- ICI

CT ICI → RT → ICI

- APOLO trial (NCT04776447)
- (NCT04085250)
- DEDALUS (NCT05128630)
- BRIDGE (NCT04765709)
- PACIFIC-BRAZIL (NCT04230408)

ICI → CT RT → ICI ± CT

- AFT-16 (NCT03102242)

Chemotherapy-free

ICI → RT → ICI

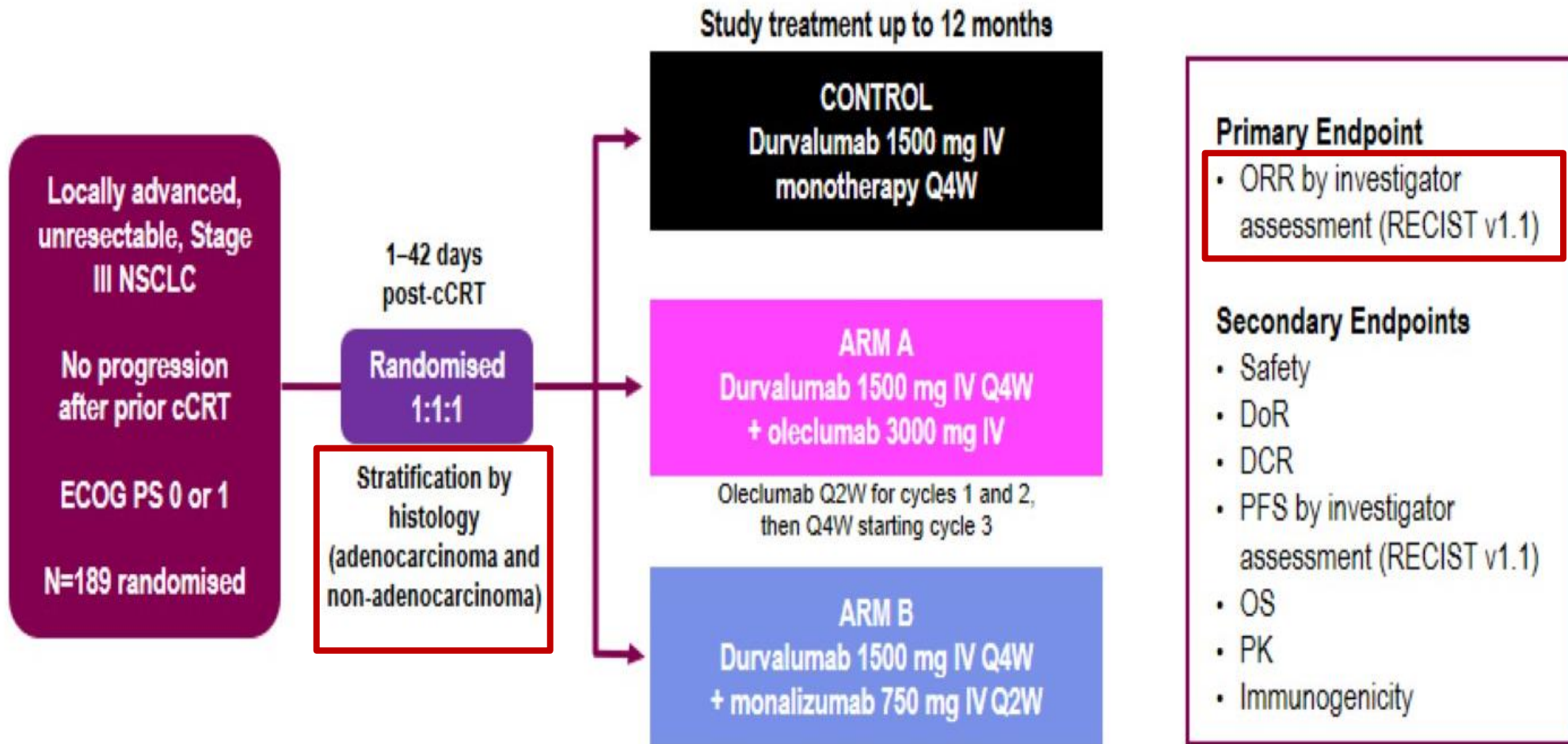
- SPRINT (NCT03523702)
- NRG-LU004 (NCT03801902)

Consolidation with TKI

CT → RT → TKI

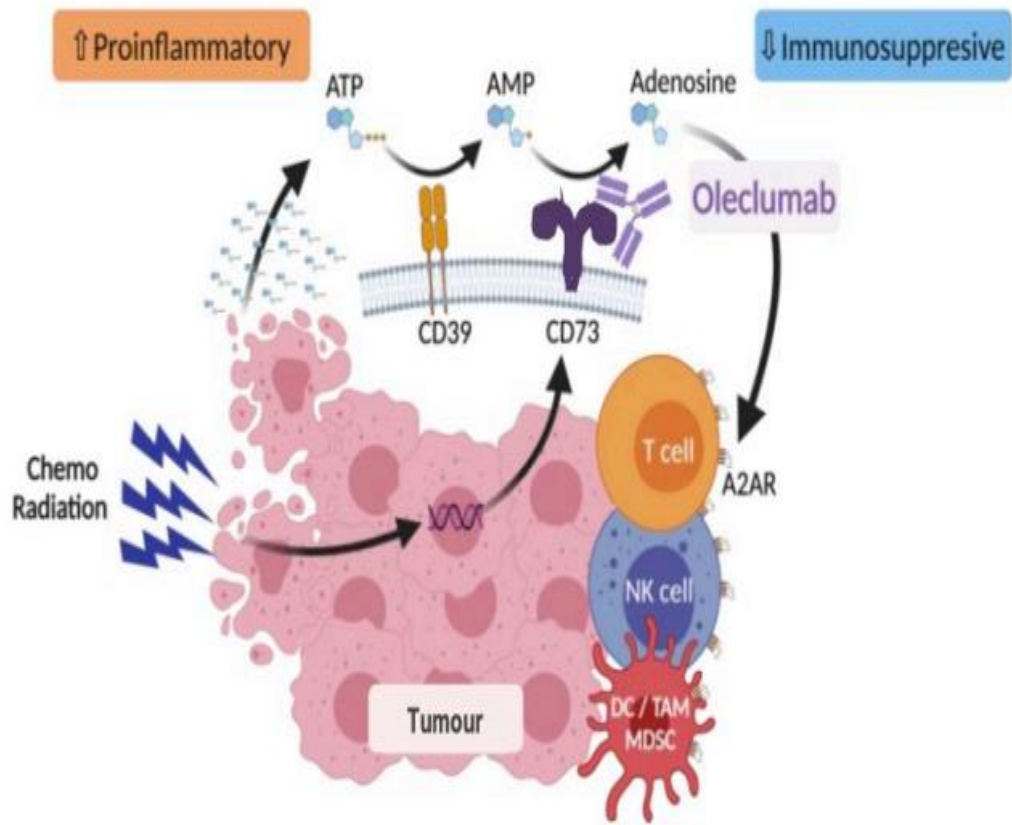
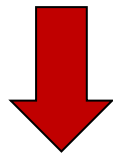
- LAURA (NCT03521154)*
- BO42777 (NCT05170204)*

COAST: Phase II, randomized open-label study



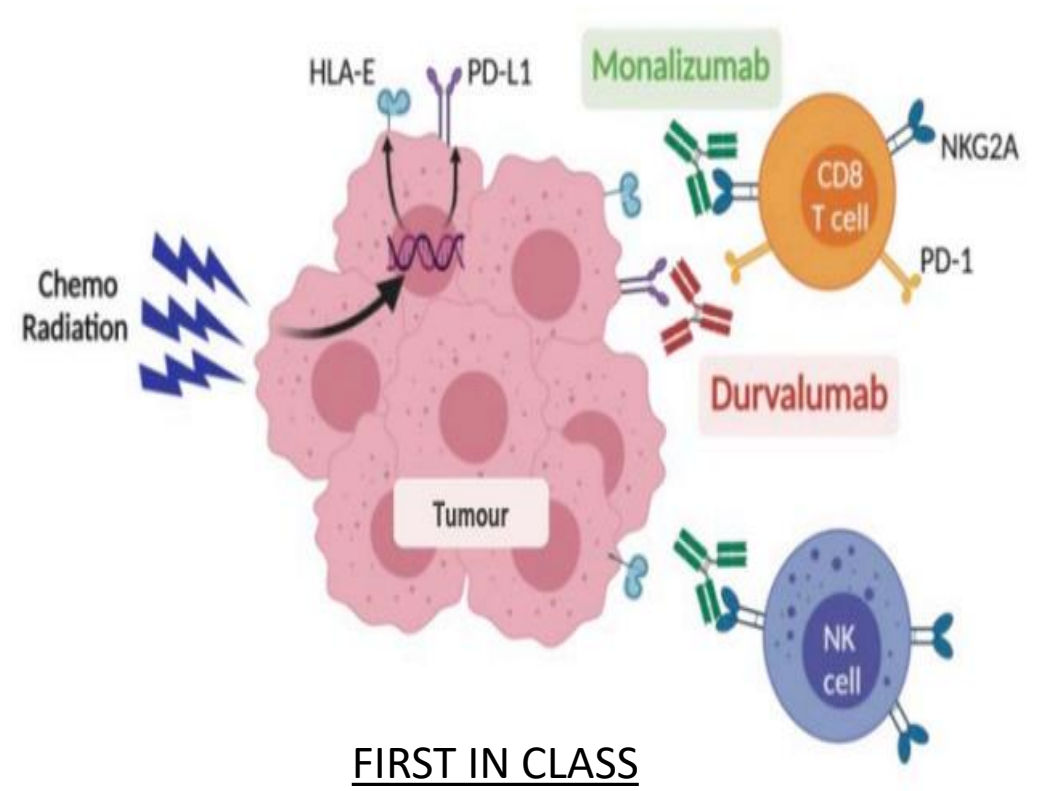
OLECLUMAB anti-CD73

Reduce extracellular adenosine production
Promotes antitumor immunity



MONALIZUMA blocks NKG2A

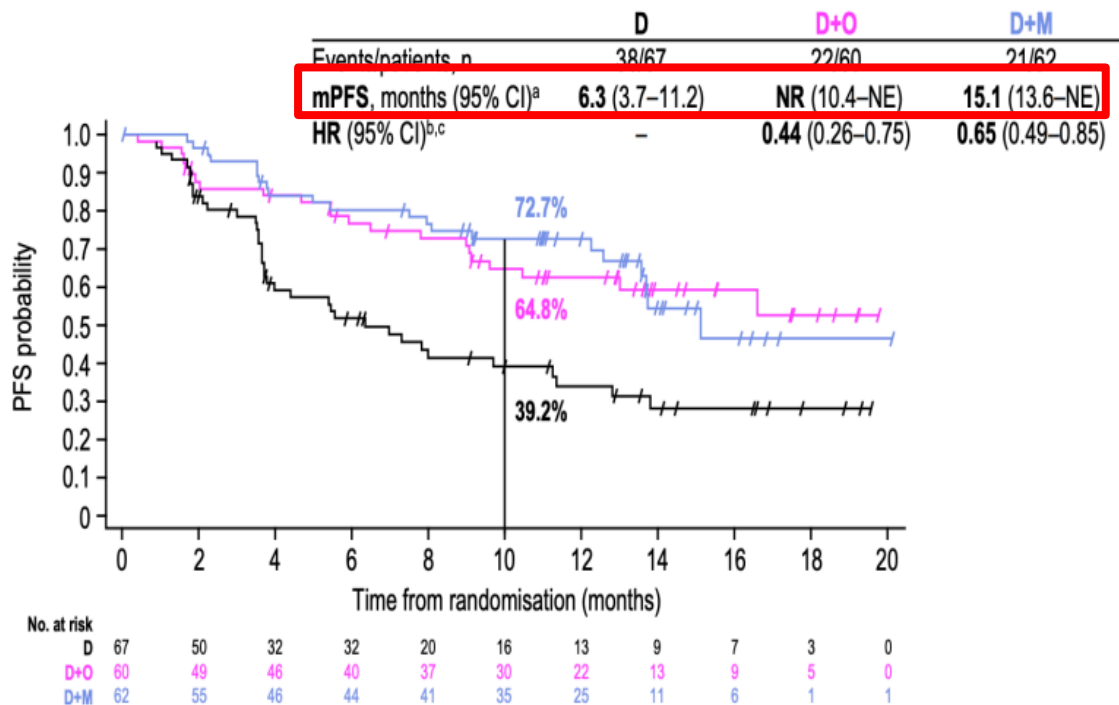
Reduce inhibition of NK and CD8+ T cells



COAST: ORR, PFS and Safety

Antitumor activity	D (n = 67)	D+O (n = 60)	D+M (n = 62)
Confirmed ORR	17.9	30	35.5
DCR 16 weeks	58.2	81.7	77.4
Median DoR (months)	NR	12.9	NR
mPFS	6.3	NR	15.1
HR	-	0.44	0.65

Incidence, n (%)	D (n = 66)	D+O (n = 59)	D+M (n = 61)
Any TEAEs	65 (98.5)	57 (96.6)	61 (100)
Grade 3 TEAEs	26 (39.4)	24 (40.7)	17 (27.9)
Study drug-related AEs	49 (74.2)	46 (78.0)	50 (82.0)
Study drug-related SAEs	6 (9.1)	7 (11.9)	5 (8.2)
AEs leading to discontinuation	11 (16.7)	9 (15.3)	9 (14.8)
Deaths*,†	7 (10.6)	4 (6.8)	3 (4.9)



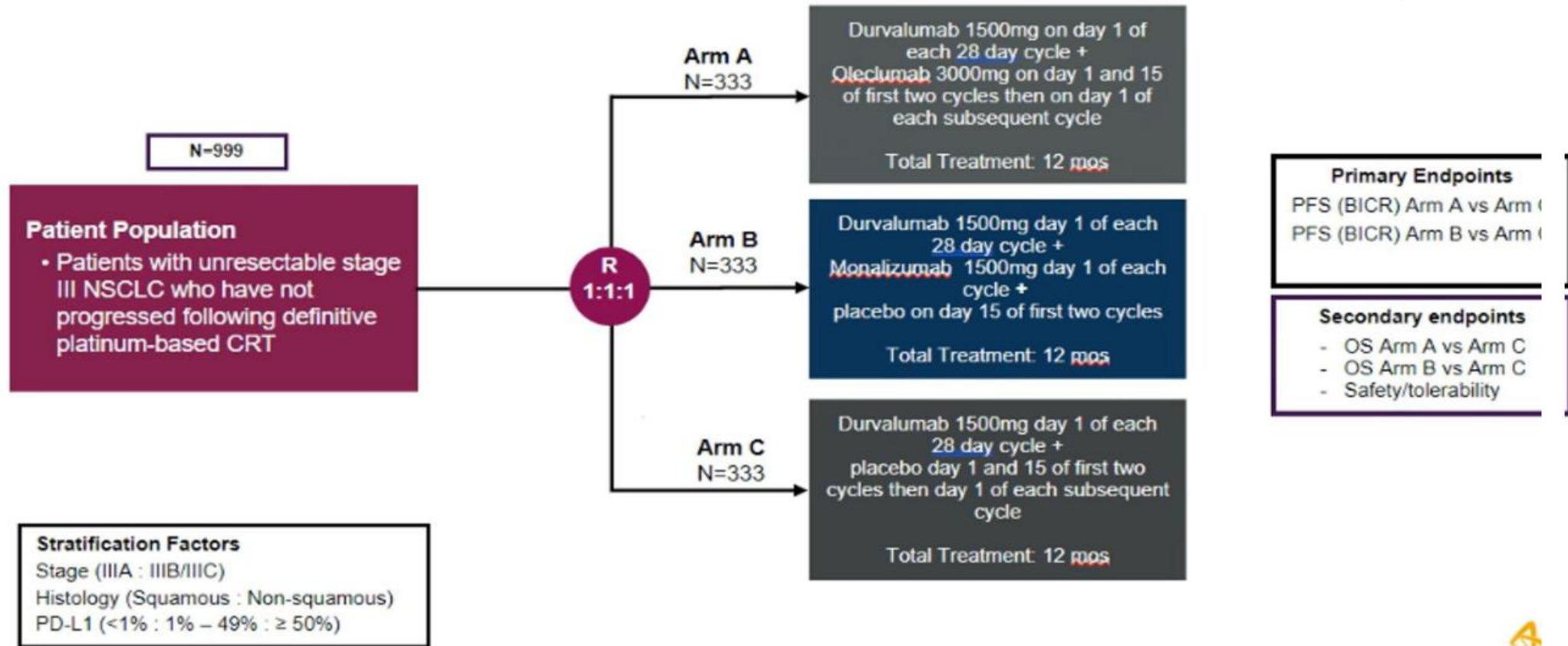
Median follow-up 11.5 months

Interim Analysis performed a 10-month minimum potential follow-up

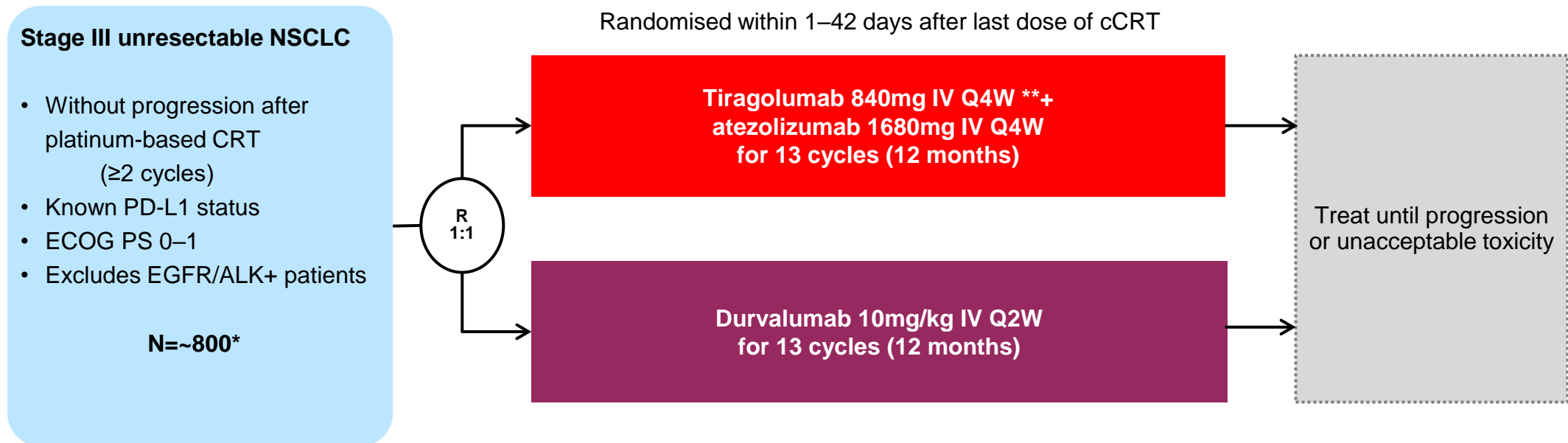
PACIFIC-08, study design

Durvalumab + Oleclumab/Placebo or Monalizumab/Placebo in Stage III unresectable NSCLC

Phase III, double-blind, multicenter international study of durvalumab + oleclumab and durvalumab + monalizumab for the treatment of patients who have not progressed following concurrent chemoradiation treatment for locally-advanced, stage III, unresectable NSCLC.



SKYSCRAPER-03 (GO41854), study design: durvalumab versus tiragolumab + atezolizumab in Stage III unresectable NSCLC



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

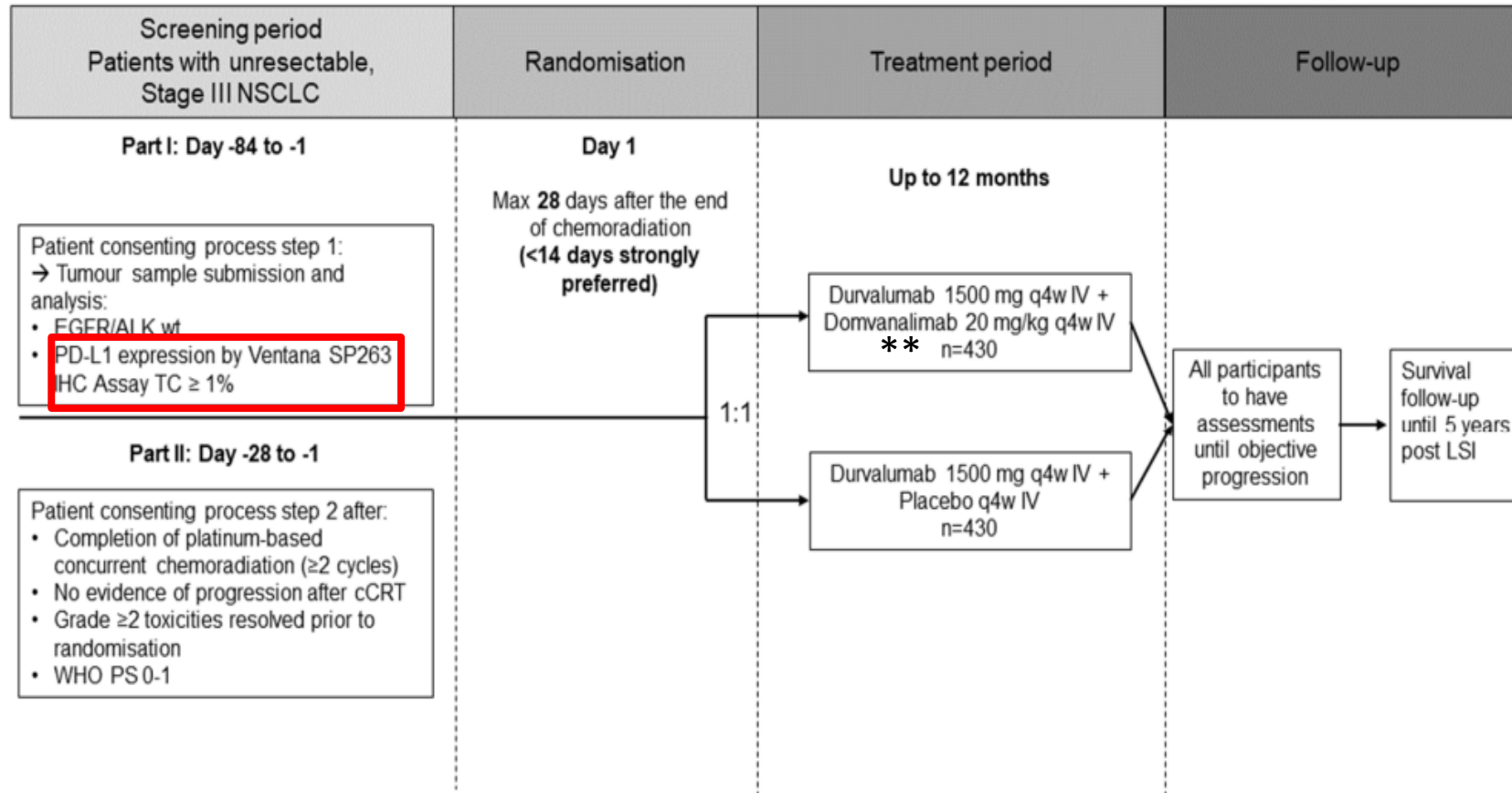
- Time to death or distant metastasis
- Time to confirmed deterioration
- Safety

** Anti TIGIT Mab

CLOSED TO ENROLLMENT

PACIFIC-08 study design

Durvalumab+Domvalimab/Placebo in Stage III unresectable NSCLC

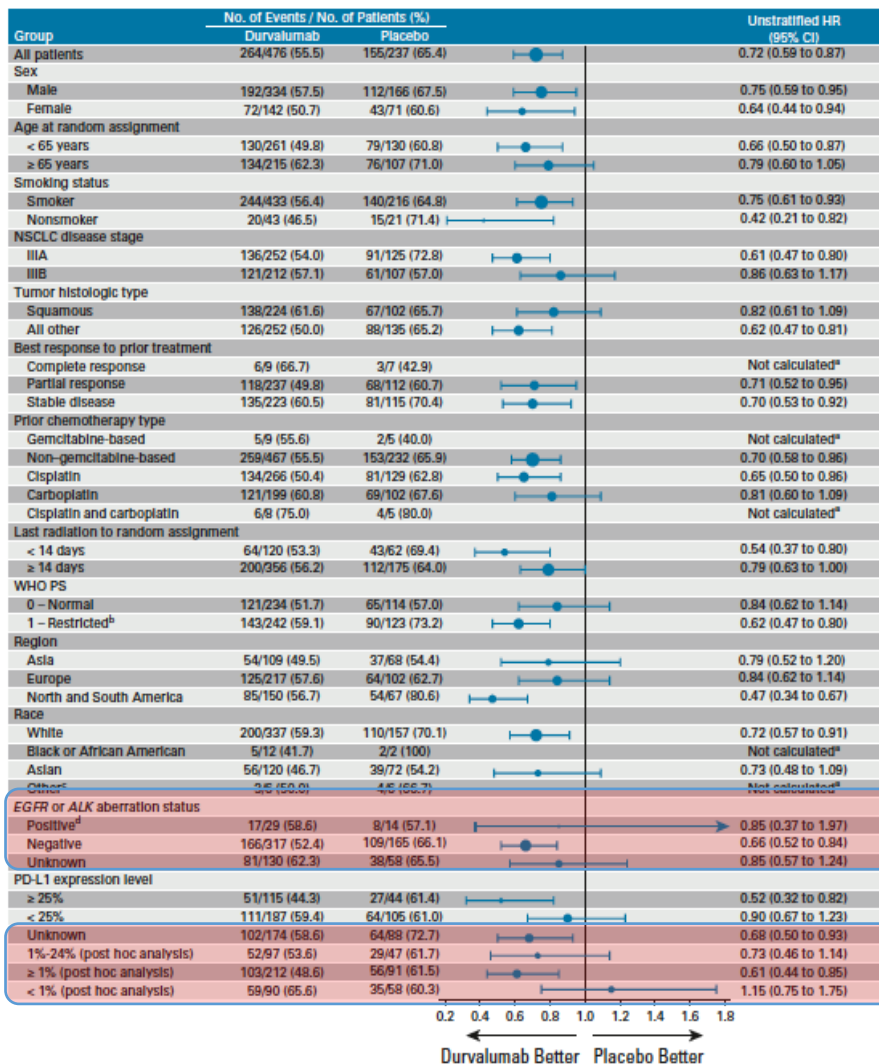


** Anti TIGIT Mab

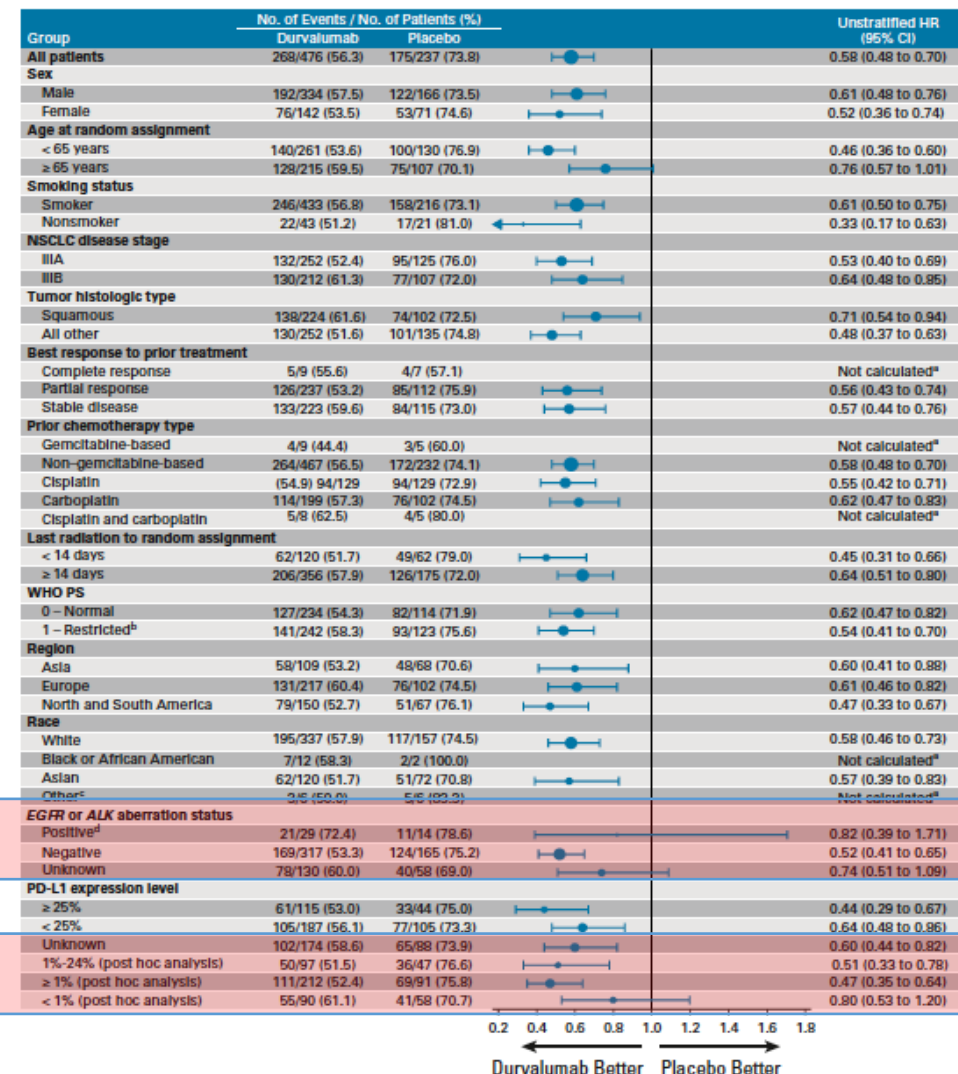
ENROLLMENT ACTIVE

Forest Plot of PACIFIC trial: OS and PFS

OS



PFS



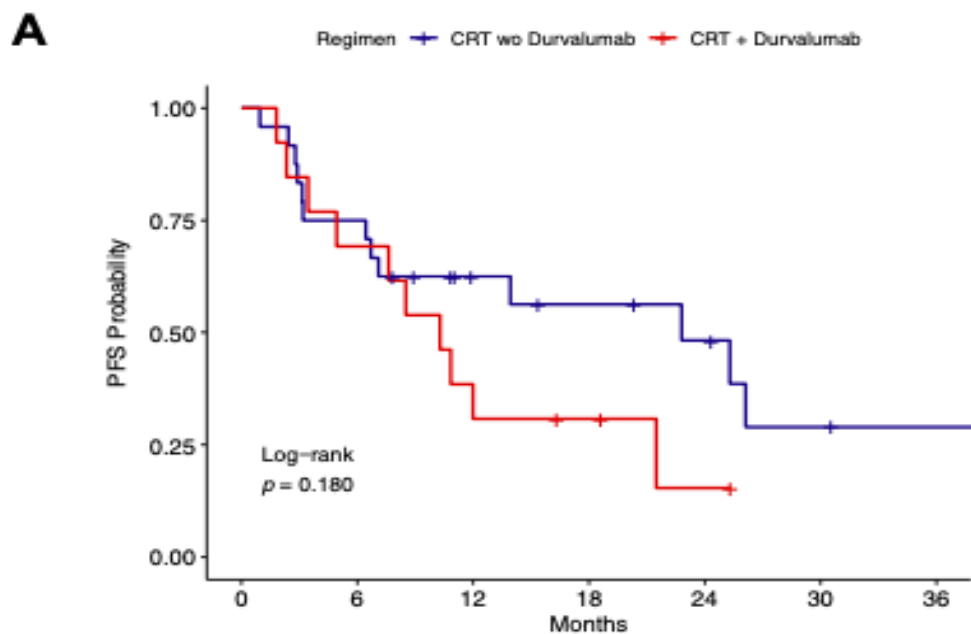
AIFA restriction of DURVA in PD-L1 negative

Spigel et al, JCO 2022

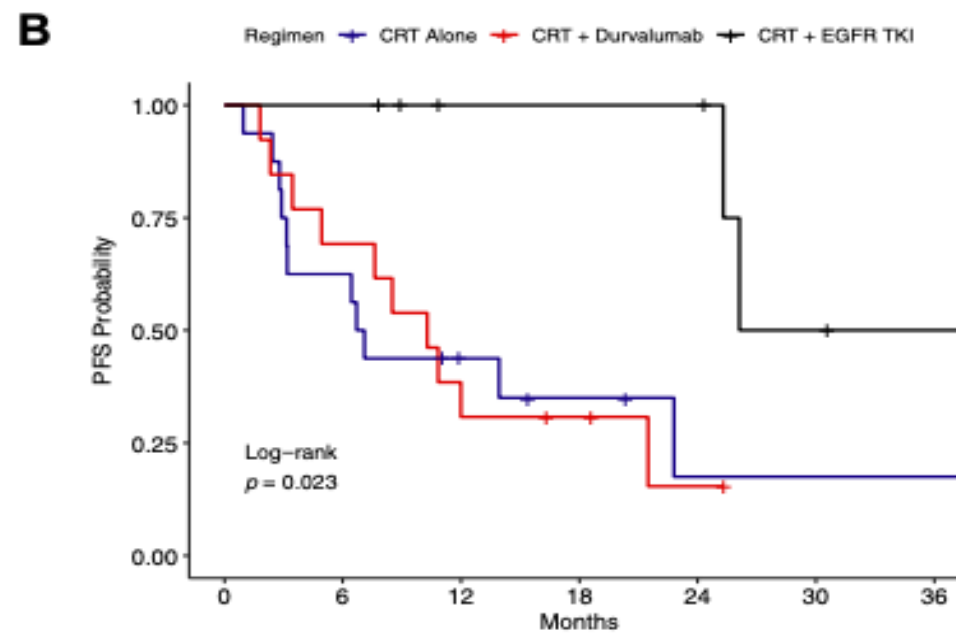


PACIFIC: Specific subgroups

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



No. at risk	0	6	12	18	24	30	36
CRT w/o Durvalumab	24	18	10	8	6	3	2
CRT + Durvalumab	13	9	4	3	1	0	0

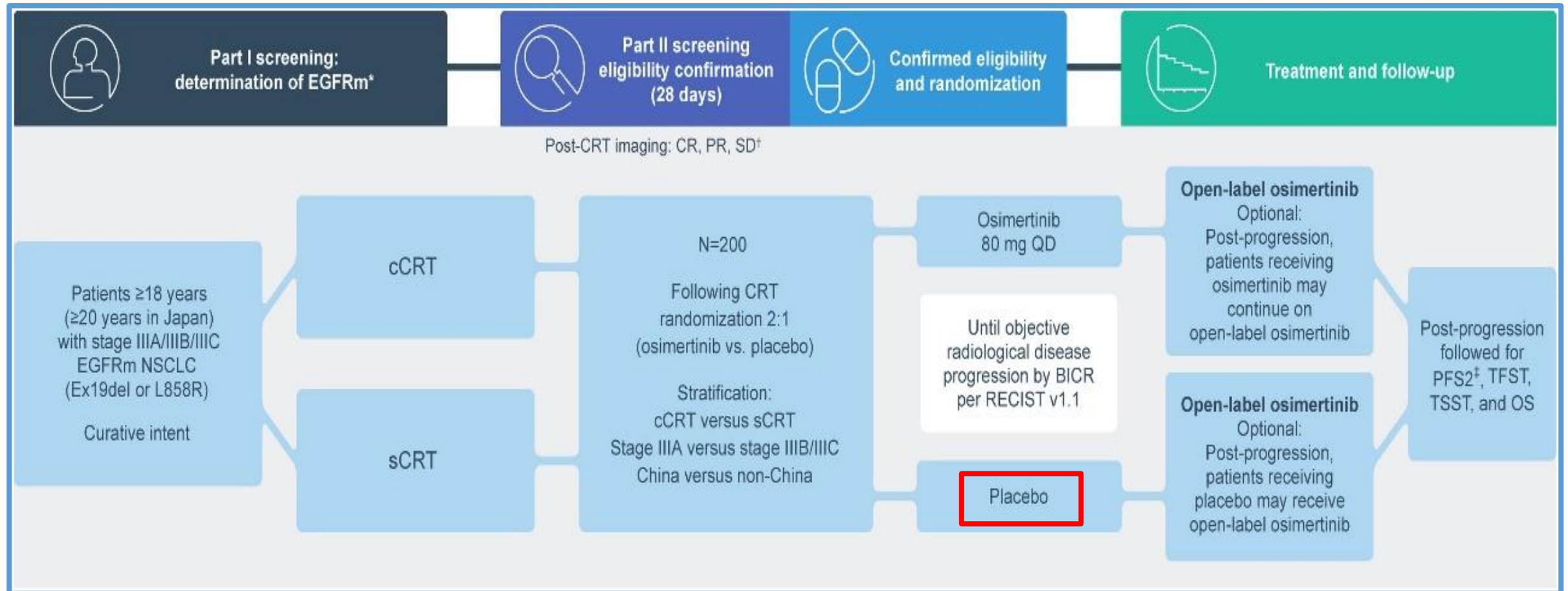


No. at risk	0	6	12	18	24	30	36
CRT Alone	16	10	5	3	1	1	1
CRT + Durvalumab	13	9	4	3	1	0	0
CRT + EGFR TKI	8	8	5	5	5	2	1

Retrospective series: 37 pts *EGFR*^{mut+}
1 case of G4 pneumonitis

LAURA trial study design

phase 3 study for unresectable, stage III *EGFRmut+* NSCLC



<https://clinicaltrials.gov/ct2/show/NCT03521154>

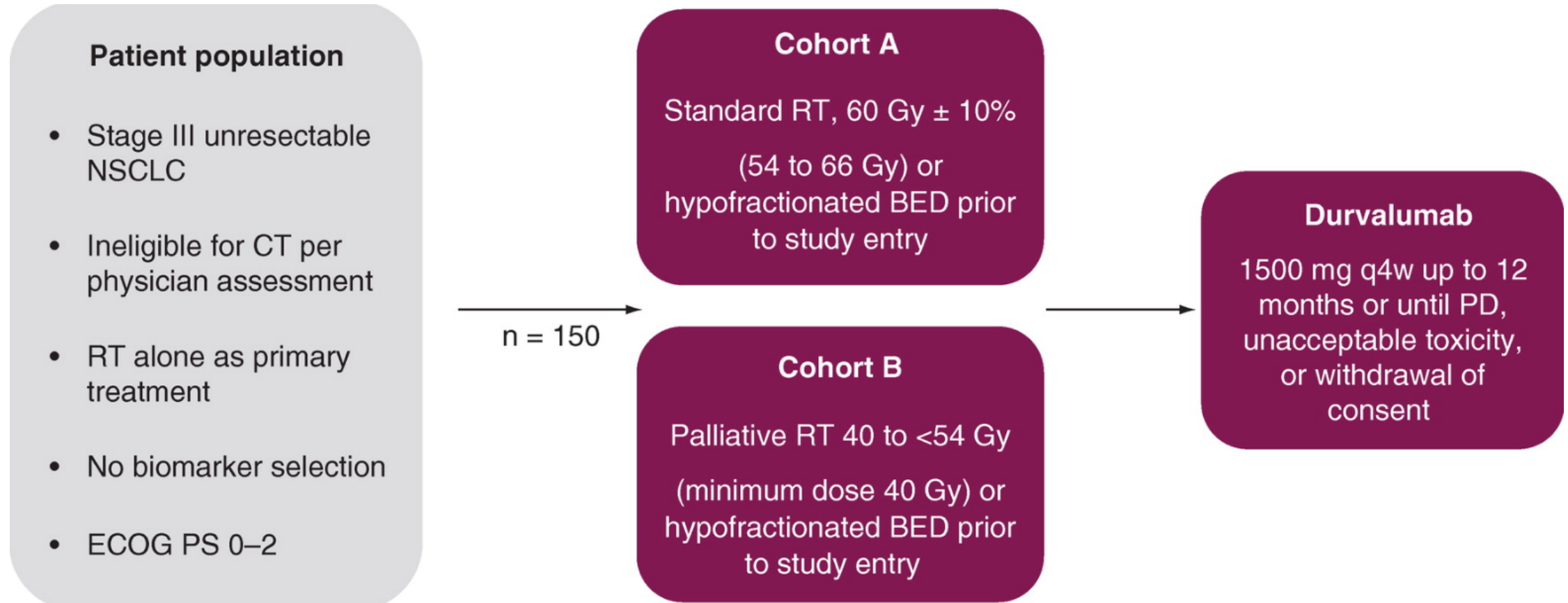
Conclusions

Define the goal of the treatment before starting any procedure!

- ✓ Management of stage III disease is challenging
- ✓ Multidisciplinary evaluation is always mandatory
- ✓ Staging and Mediastinal staging is crucial
- ✓ Evaluate clinical trials

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DUART: durvalumab after radiotherapy in patients with unresectable, stage III NSCLC ineligible for chemotherapy



CONDOR: A phase II, two cohorts, randomized trial comparing standard of care versus immune-based combination in relapsed stage III NSCLC pretreated with CT/RT and durvalumab

