CRT in the era of neo-adjuvant chemo/IO

A radiation oncologist's perspective

M Lambrecht

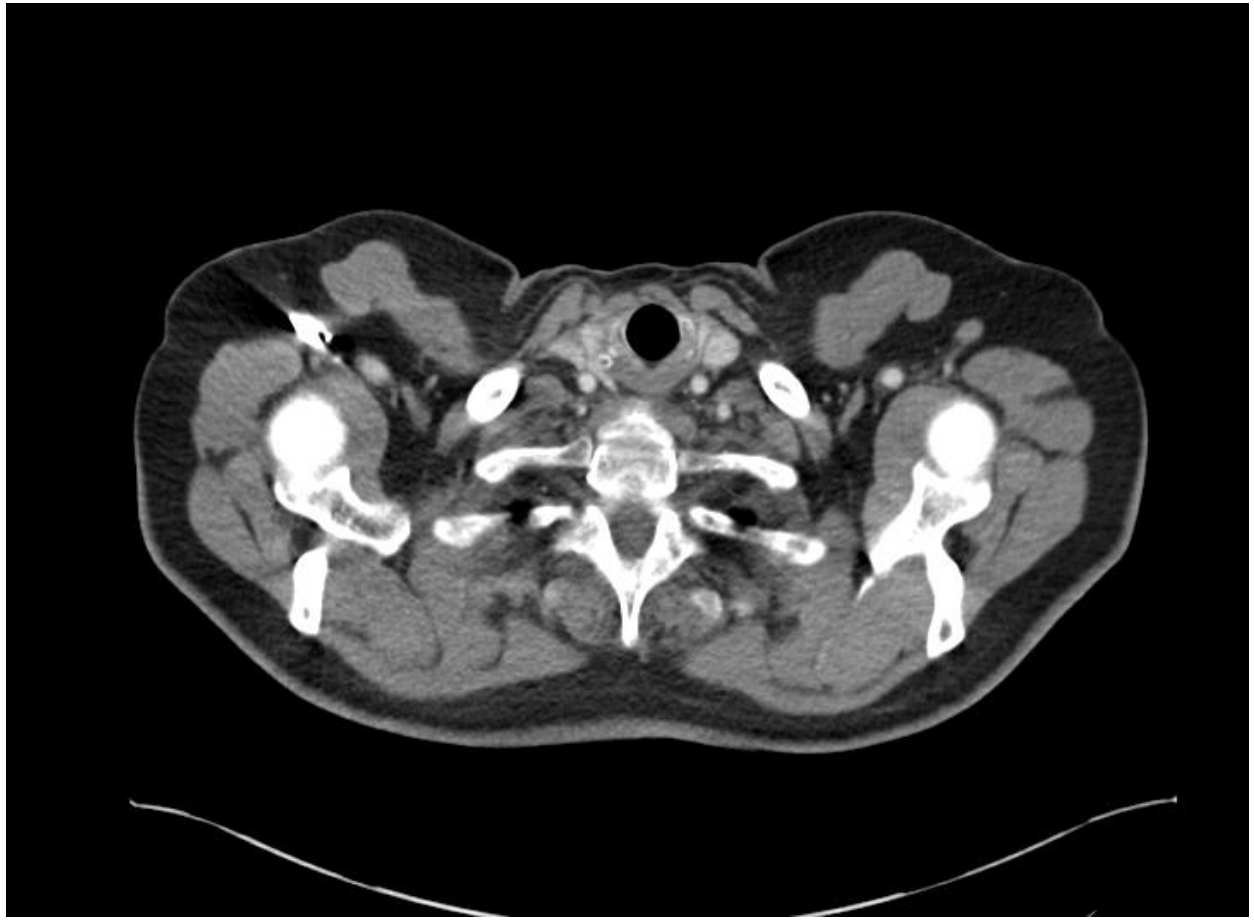
COI

- Radiation Oncologist

Case 1

- ♂, 79 years
- 35 PY
- WHO 1
- History: rectal adenocarcinoma
- Increase CEA

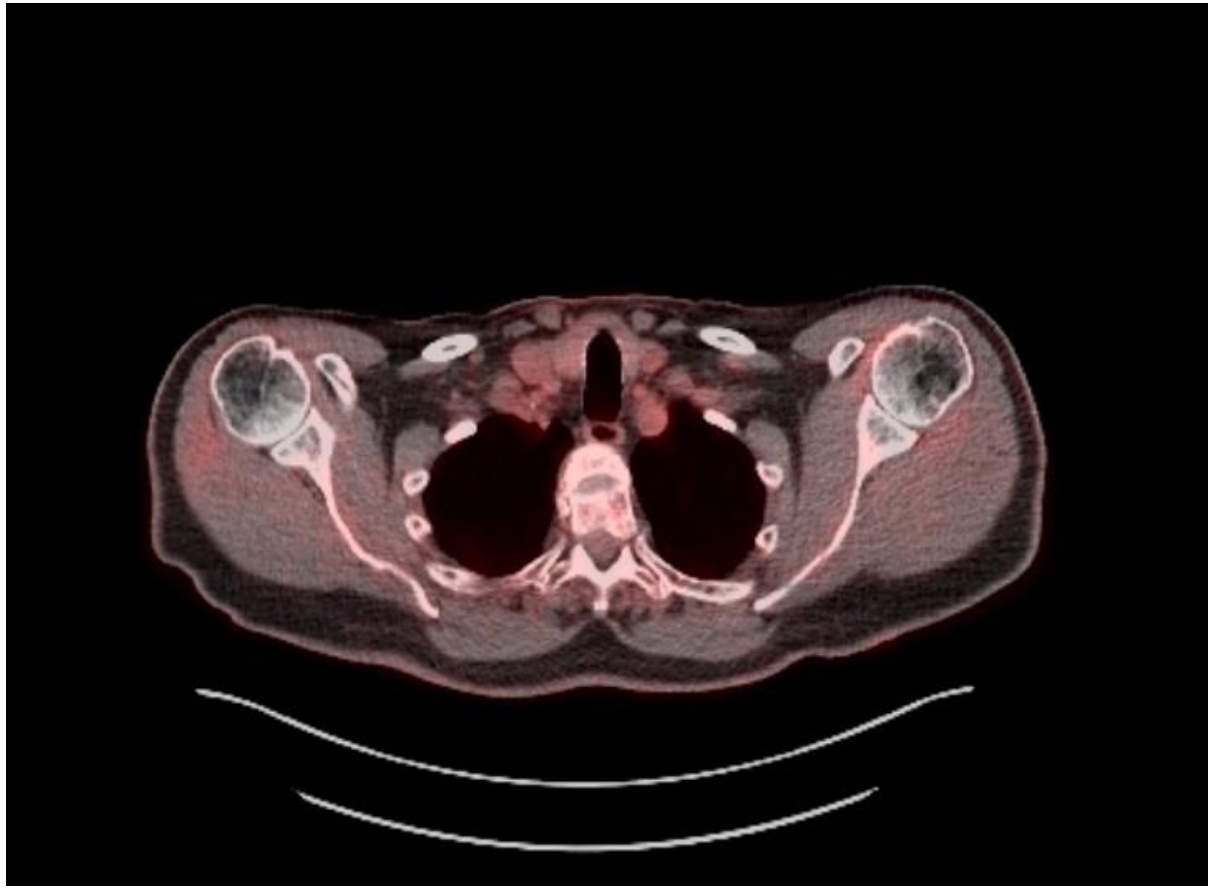
⇒CT thorax-abdomen



Pathology and imaging

- ♂, 79 years
- WHO 1
- FEV1: 71%, DLCO 49%
- Pathology EBUS-TBNA
  - Adenocarcinoma
  - PD-L1: 40%
  - KRAS G12S

cT4N2M0: bulky N2 disease



What's your treatment of choice

1. Upfront surgery followed by chemo-immunotherapy
2. Induction chemo-immunotherapy followed by surgery
3. Induction chemo-immunotherapy followed by re-evaluation and local modality depending on response
4. Primary CRT followed by Durvalumab

Setting the stage (III)

- 25-30% of all NSCLC patients present with Stage III disease
- Large spectrum
  - Patient
    - Age
    - Co-morbidities
    - Performance status
  - Disease
    - Extension
    - Subtype
    - Molecular profile

9th Edition TNM Descriptors and Stages

T/M	Categories and Descriptors	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a Visceral pleura / central invasion	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe separate tumor nodules	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 >7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral separate tumor nodules	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Contralateral tumor nodules	IVA	IVA	IVA	IVA	IVA
	M1a Pleural / pericardial effusion, nodules	IVA	IVA	IVA	IVA	IVA
	M1b Single extrathoracic metastasis	IVA	IVA	IVA	IVA	IVA
	M1c1 Multiple metastases in 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Multiple metastases in >1 organ systems	IVB	IVB	IVB	IVB	IVB

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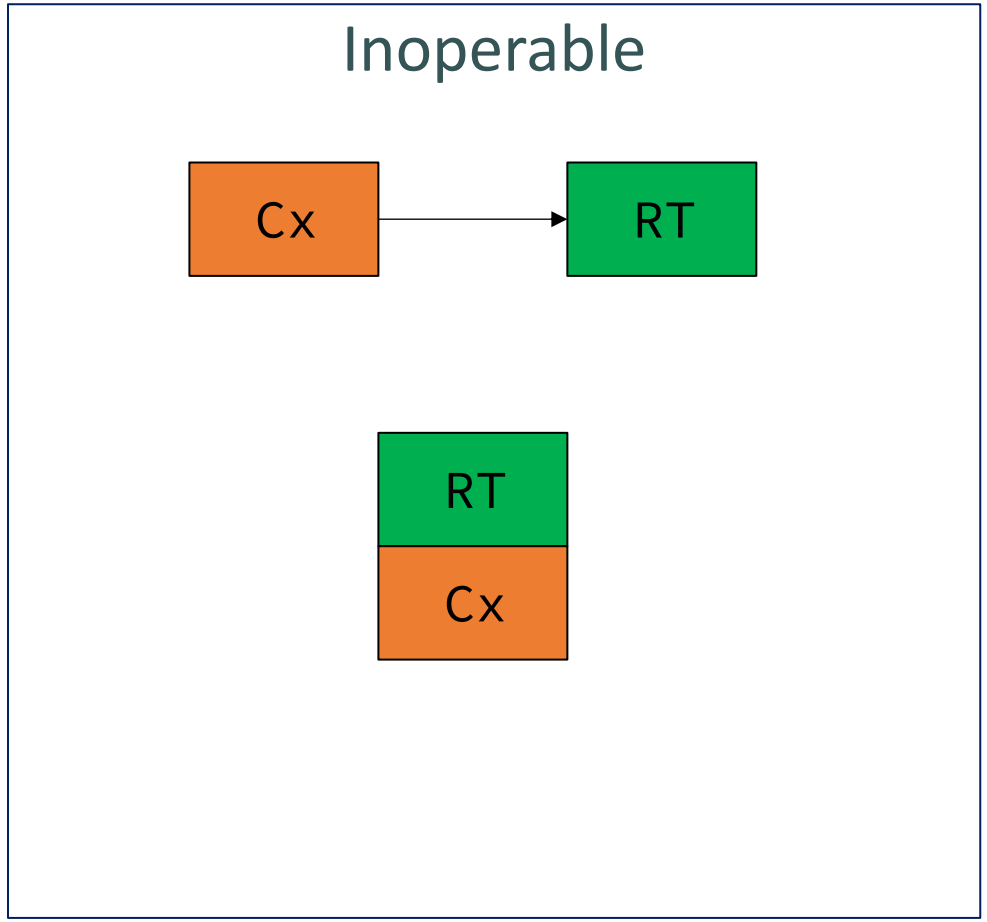
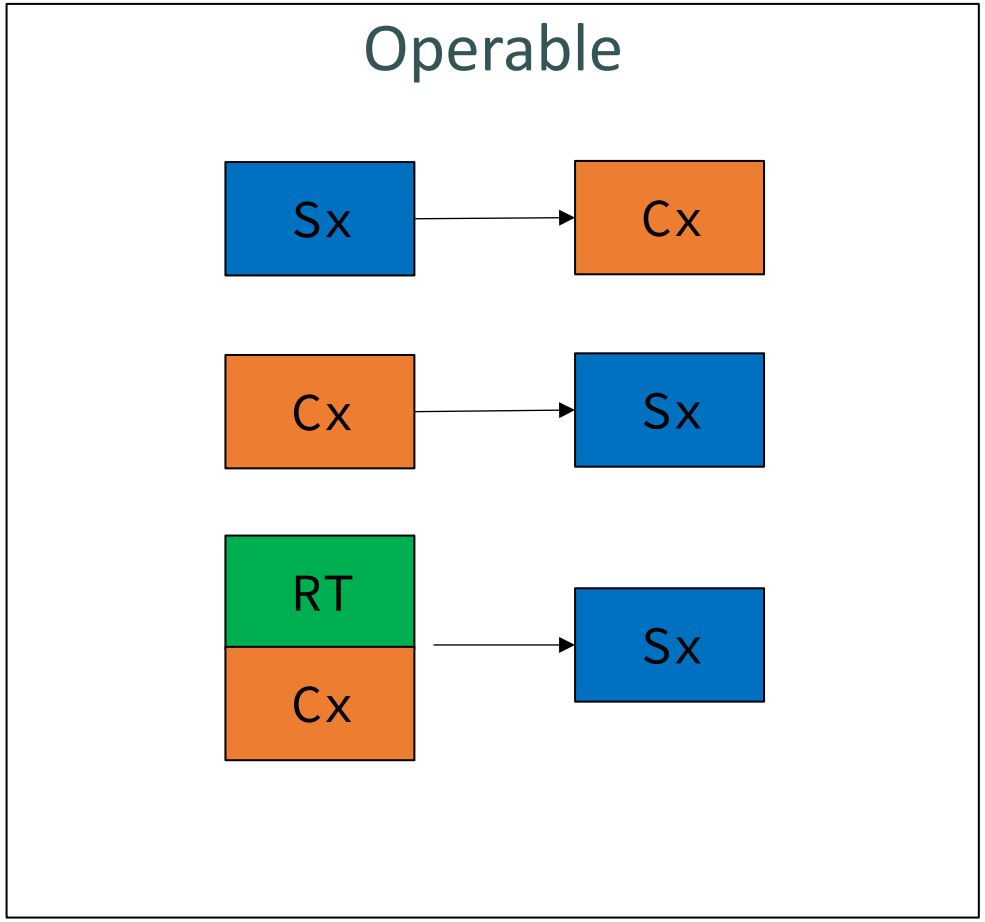
Modalities in stage III?





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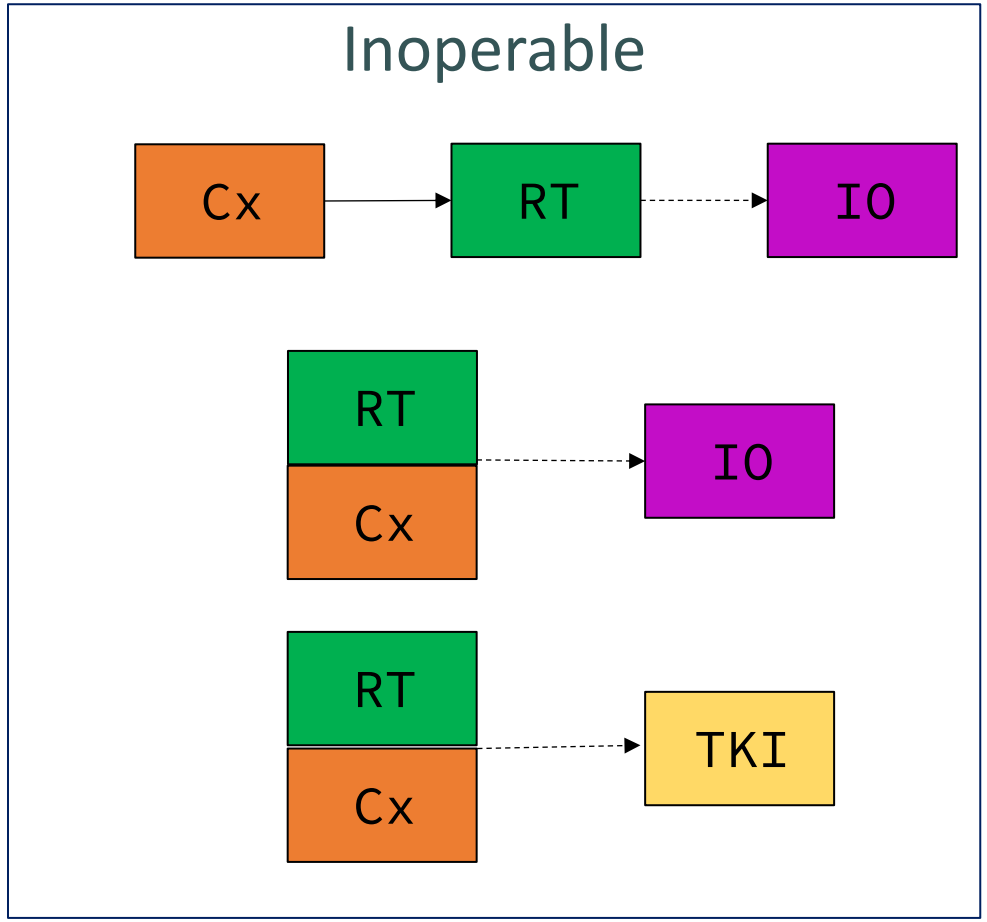
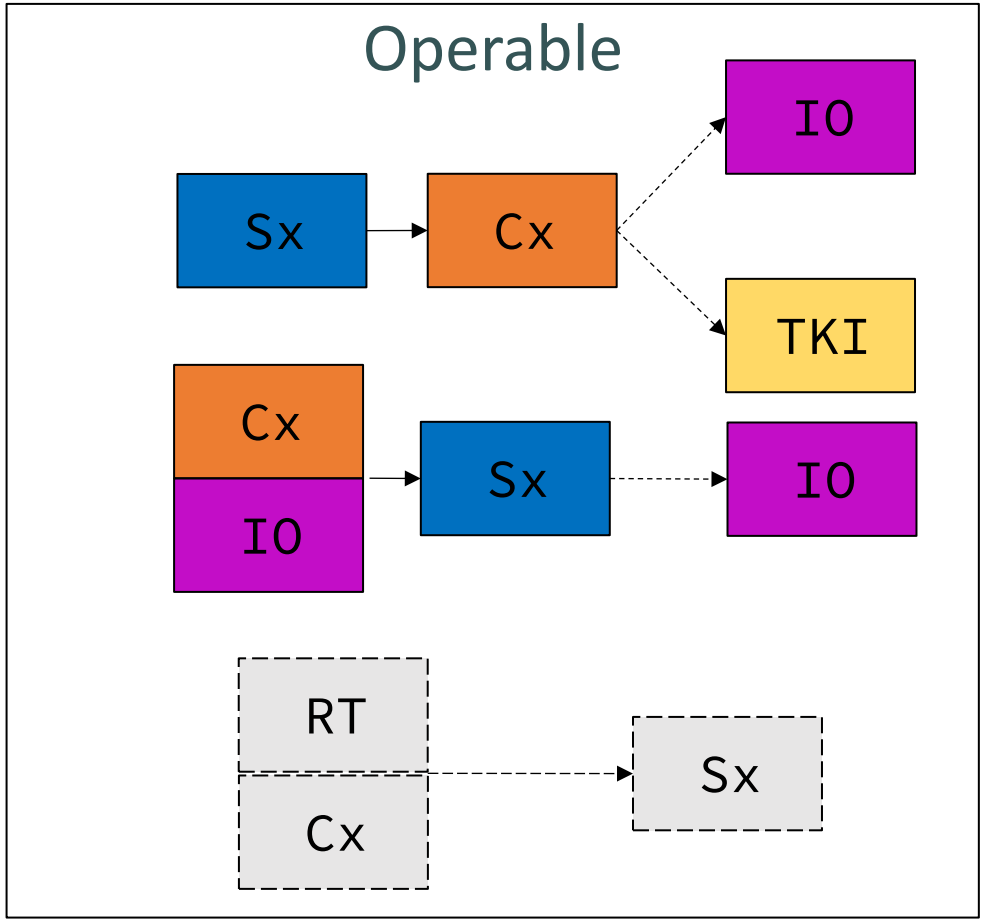
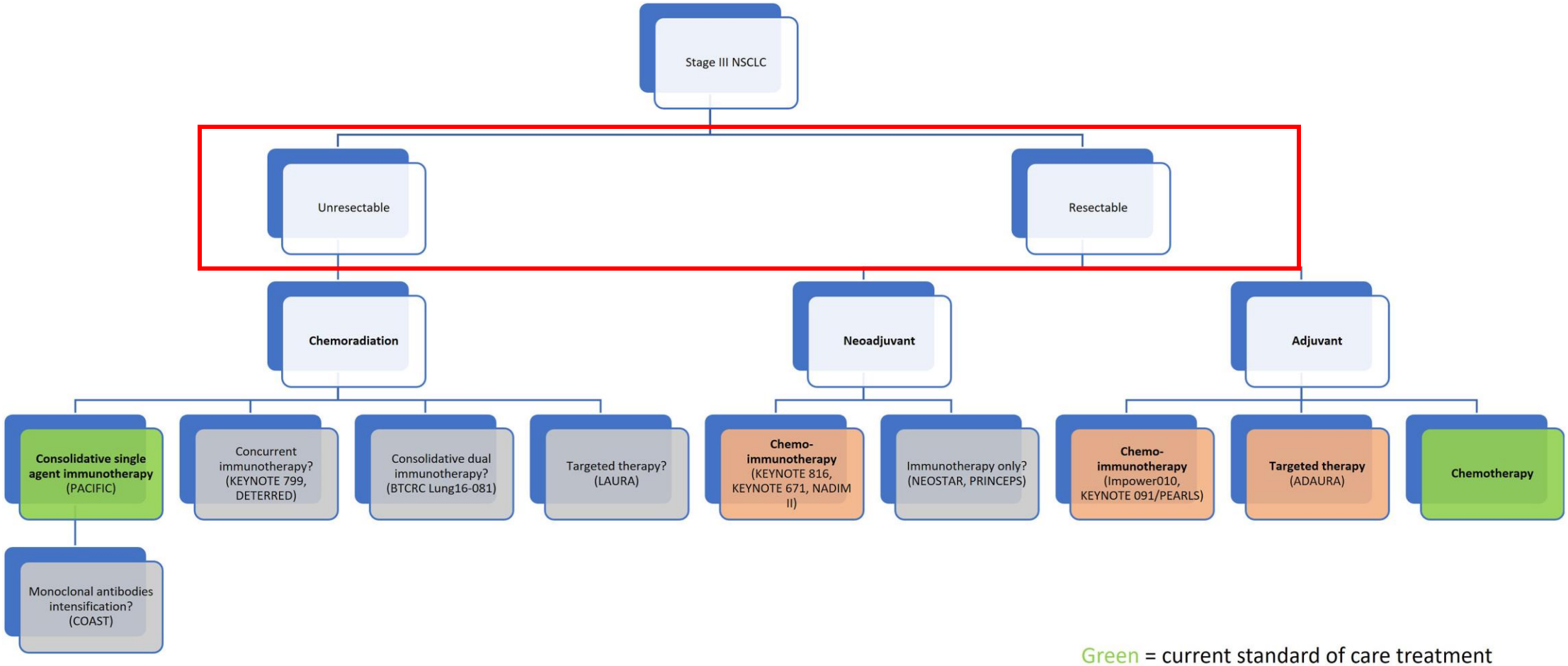




Treatment options



Green = current standard of care treatment
Orange = emerging treatments
Grey = trials in progress

Li et al JTO 2023

Resectability

	N0	N1	N2 SINGLE	N2 MULTI	N2 BULKY	N2 INVASIVE
T1-2	N/A	N/A	POTENTIALLY RESECTABLE (95%)	NO AGREEMENT (50%)	UNRESECTABLE (75%)	UNRESECTABLE (84%)
T3 SIZE	N/A	RESECTABLE (83%)[a]	POTENTIALLY RESECTABLE (87%)	NO AGREEMENT (39%)	UNRESECTABLE (80%)	UNRESECTABLE (88%)
T3 SATELLITE	N/A	POTENTIALLY RESECTABLE (94%)	POTENTIALLY RESECTABLE (79%)	NO AGREEMENT (34%)	UNRESECTABLE (84%)	UNRESECTABLE (91%)
T3 INVASION	N/A	POTENTIALLY RESECTABLE (89%)	NO AGREEMENT (71%)[b]	NO AGREEMENT (28%)[c]	UNRESECTABLE (87%)	UNRESECTABLE (92%)
T4 SIZE	POTENTIALLY RESECTABLE (94%)	POTENTIALLY RESECTABLE (90%)	NO AGREEMENT (66%)	UNRESECTABLE (77%)	UNRESECTABLE (88%)	UNRESECTABLE (93%)
T4 SATELLITE	POTENTIALLY RESECTABLE (78%)	NO AGREEMENT (71%)[b]	NO AGREEMENT (44%)	UNRESECTABLE (85%)	UNRESECTABLE (92%)	UNRESECTABLE (94%)
T4 INVASION	NO AGREEMENT (62%)[b]	NO AGREEMENT (57%)[b]	NO AGREEMENT (34%)[c]	UNRESECTABLE (90%)	UNRESECTABLE (95%)	UNRESECTABLE (94%)

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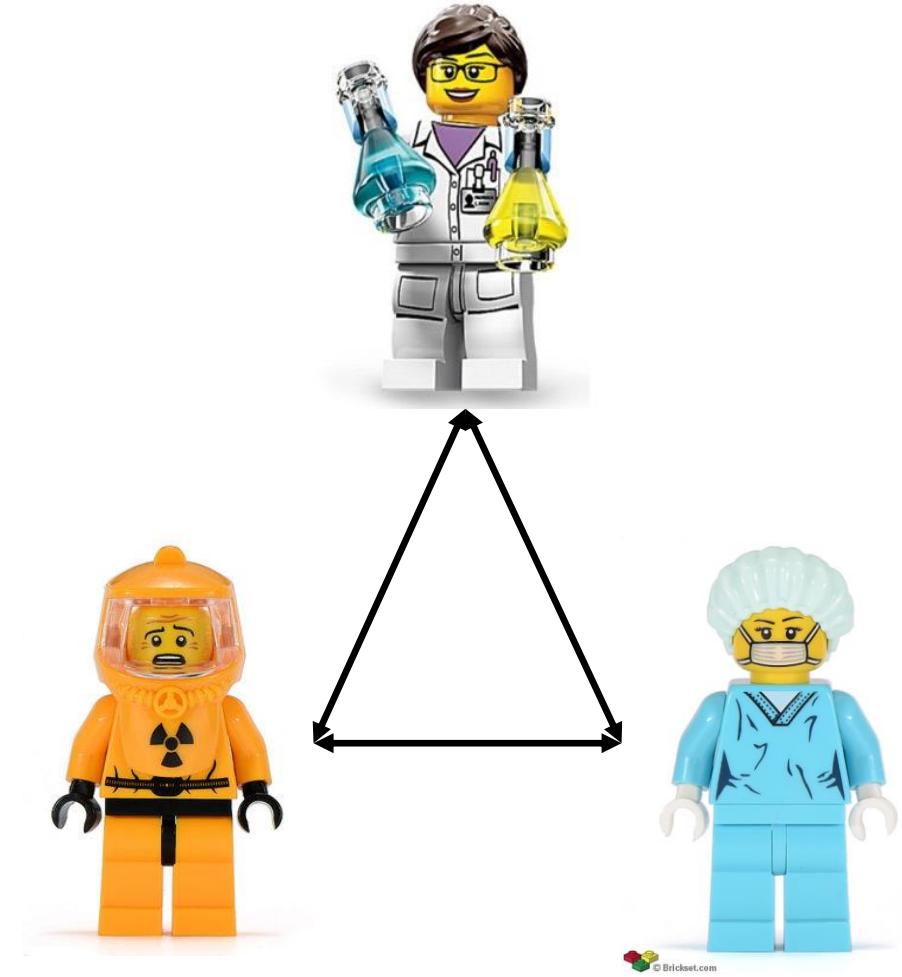
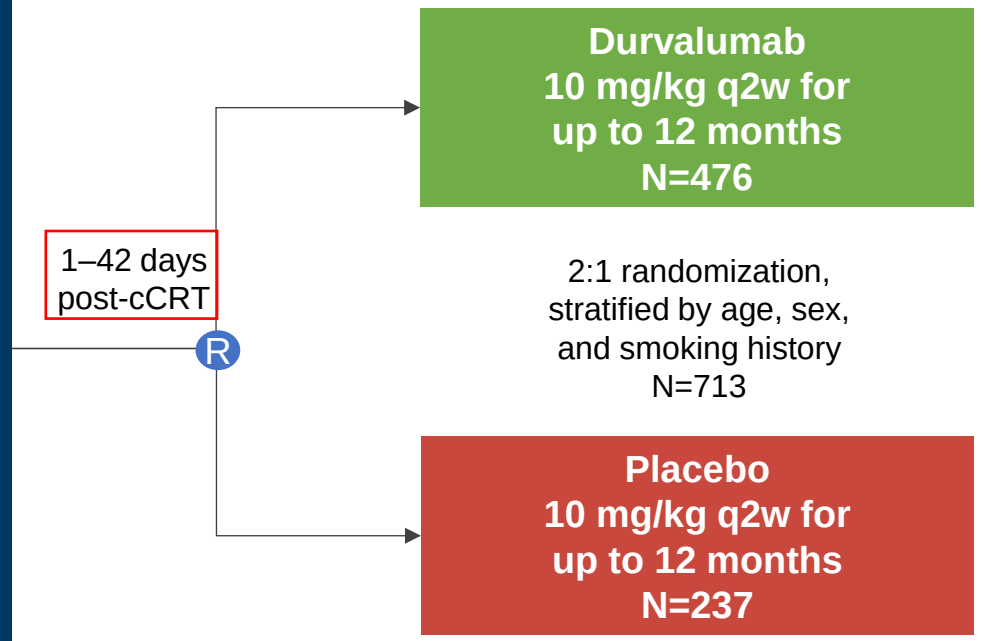
Resectability/Operability

1. Resecability
   a) Tumor extent
   b) Surgeon experience
2. Operability
   a) Patient's condition
   b) Outcome after surgery
3. Patient's perspective



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



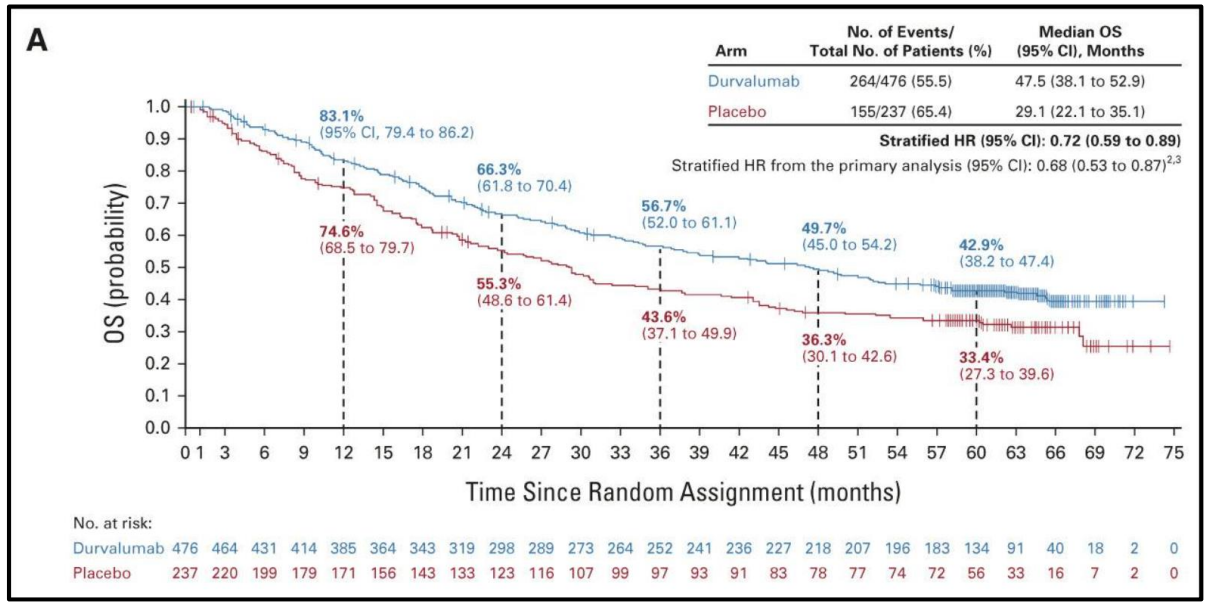
Co-primary endpoints

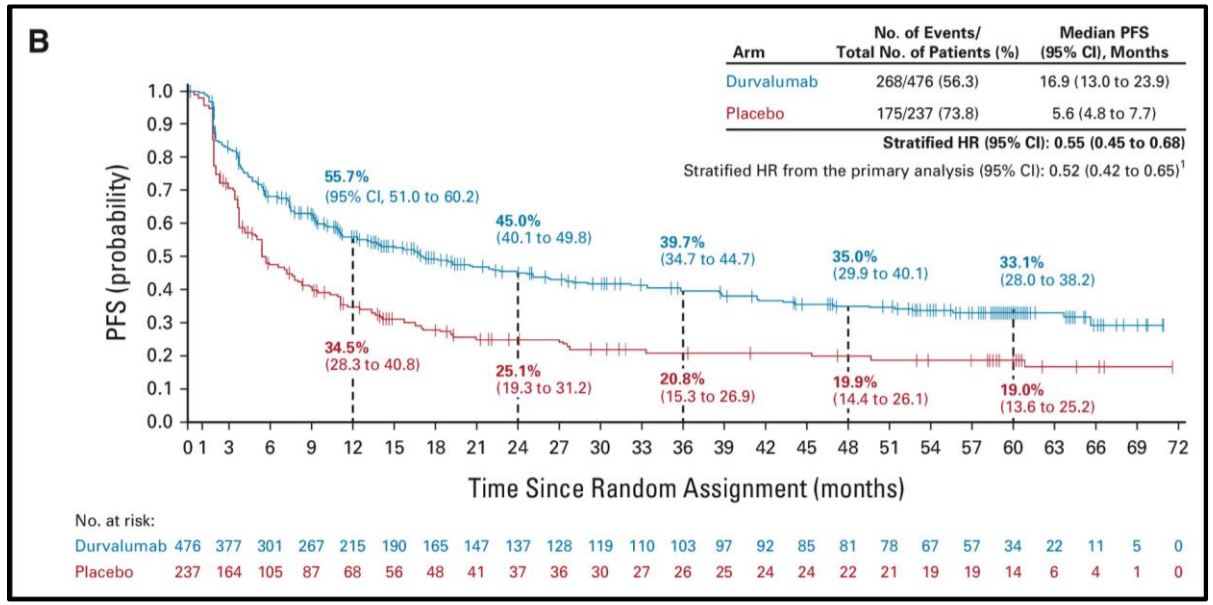
- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints

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

PACIFIC





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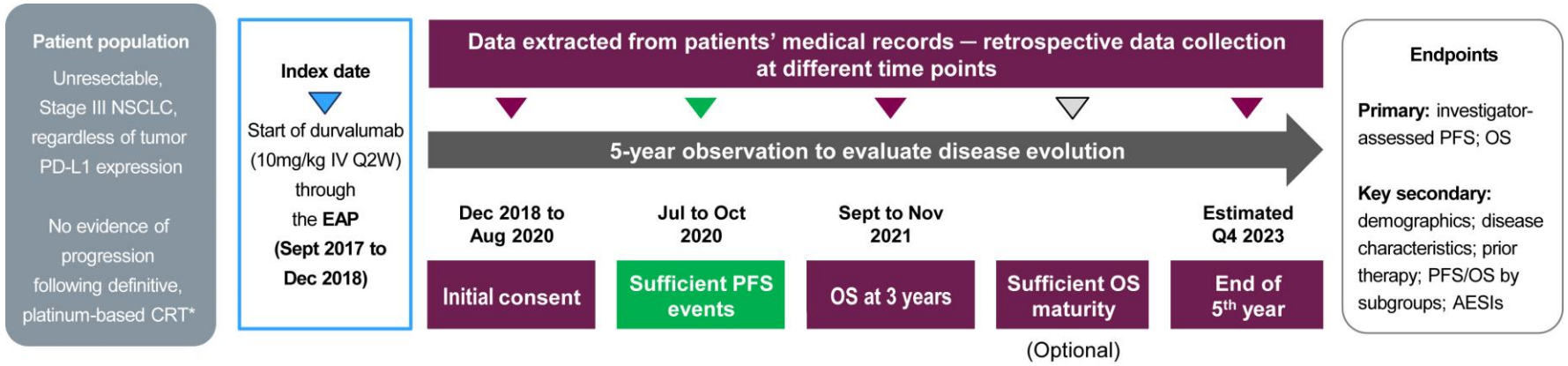
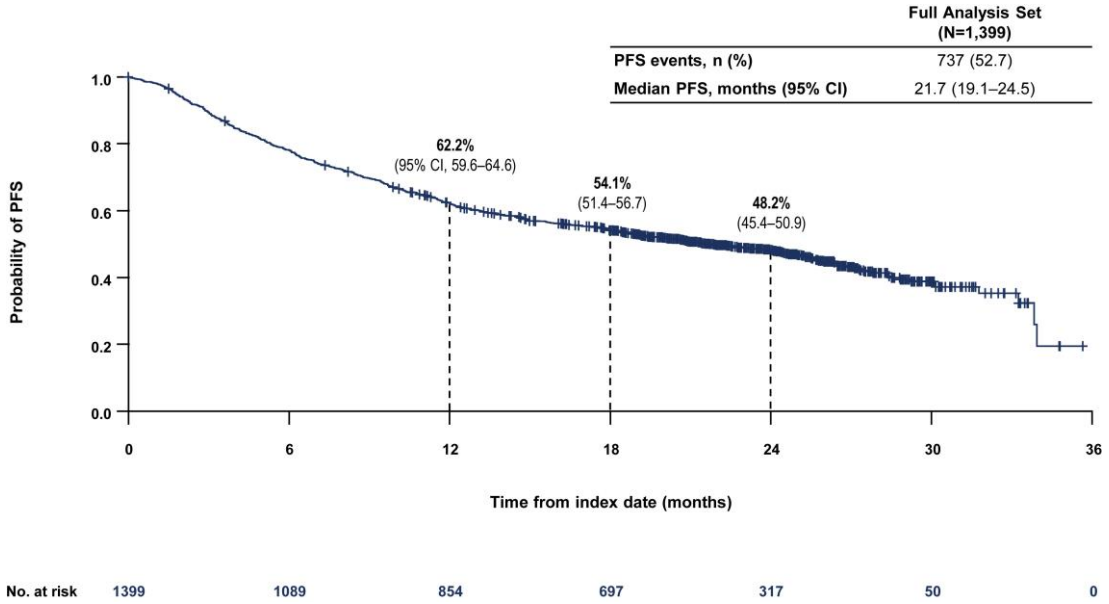
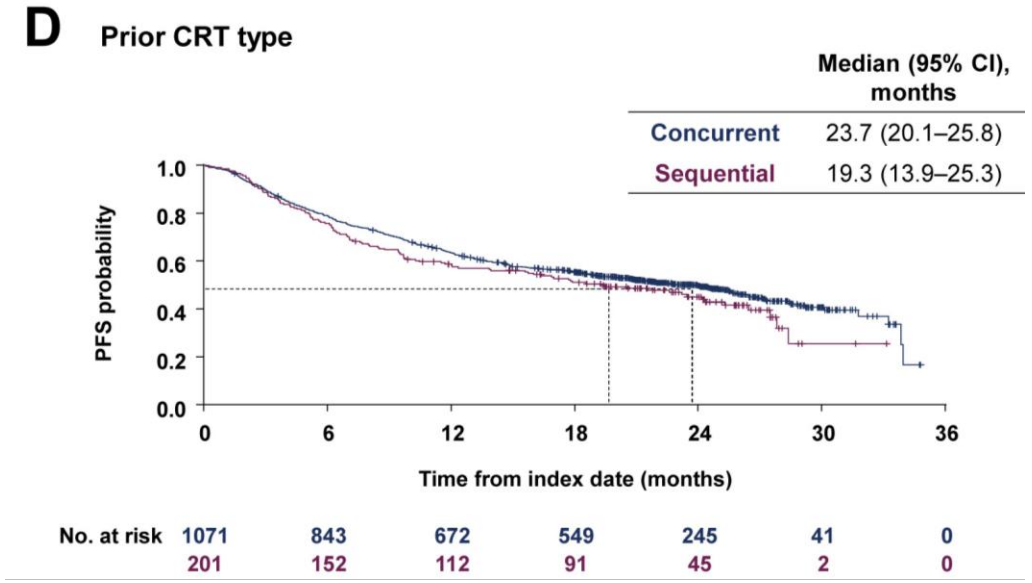
Real world data

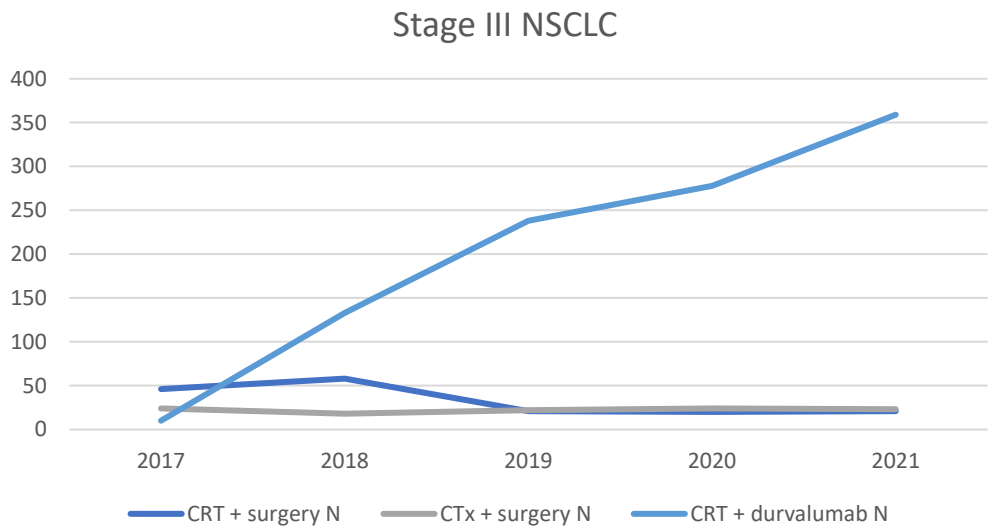


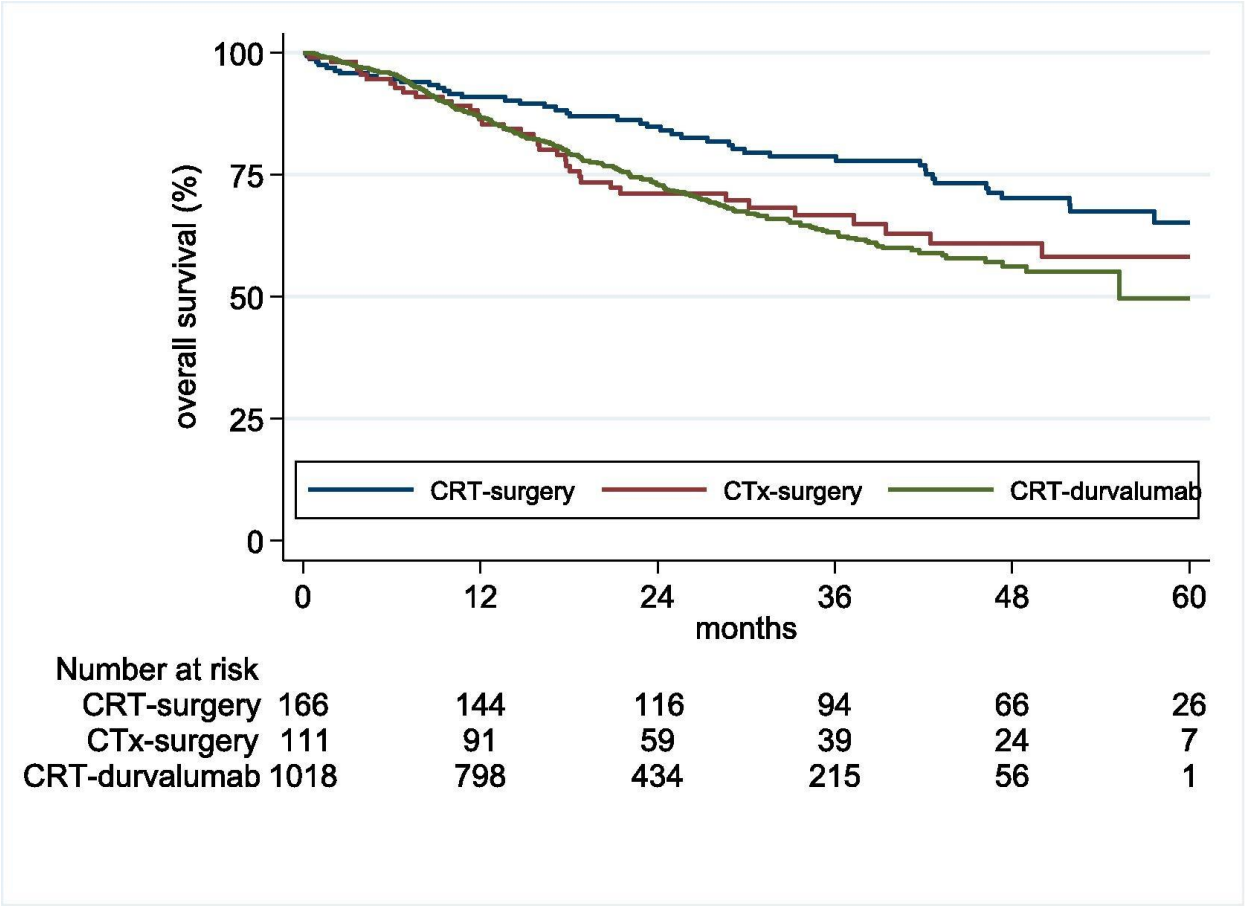




What happened?

- STAGE III from NCR
- 1016 patients
  - 3yr OS:
    - CRT-Sx: 78,7%
    - Ctx-Sx: 66,7%
    - CRT-ICI: 63,2%





Adapted from Damhuis et al. Clin Lung Cancer 2024

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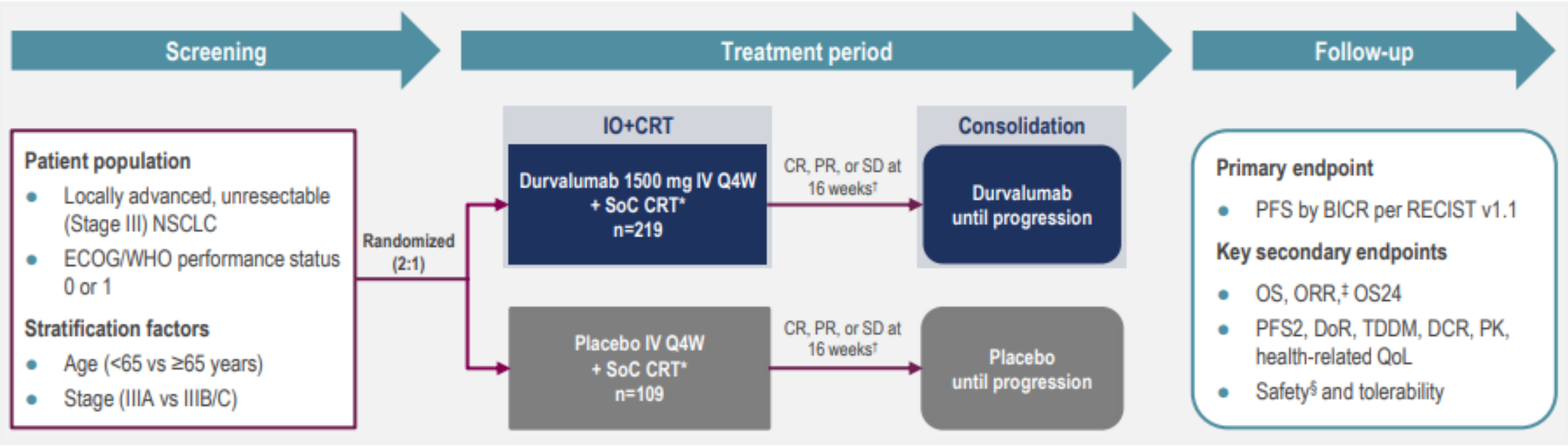
How to improve?

PACIFIC-2 (NCT03519971) is a phase 3, randomized, double-blind, placebo-controlled, multicenter, global study of durvalumab + CRT followed by durvalumab versus placebo + CRT followed by placebo



Patients were recruited from **29 March 2018** through **24 June 2019** across 106 sites in Asia, Eastern Europe, and the Americas, including: Brazil, Czech Republic, Hungary, India, Japan, Mexico, Peru, Philippines, Poland, Republic of Korea, Russia, Turkey, Thailand, and Vietnam.

Bradley et al. ELCC 2024

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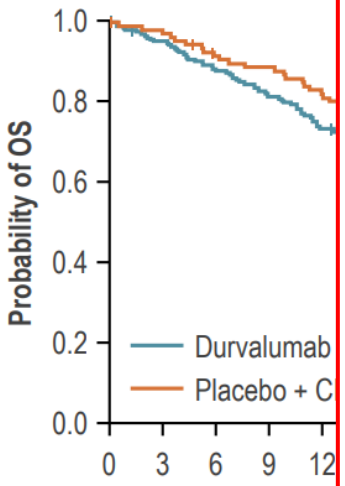
PACIFIC-2

OS and ORR (ITT population)



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

Summary of AEs (safety population)

AE category, n (%)	Durvalumab + CRT (n=219)	Placebo + CRT (n=108)
Any AE	216 (98.6)	108 (100)
Maximum grade 3 or 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 discontinuation of durvalumab/placebo†	56 (25.6)	13 (12.0)
0 to ≤4 months from start of treatment (approximates the duration of IO+CRT and ends at the first post-baseline scan)	31 (14.2)	6 (5.6)
>4 to ≤16 months from start of treatment (approximates the duration of consolidation IO in the SoC PACIFIC regimen)	12 (5.5)	6 (5.6)
>16 months from start of treatment (approximates treatment beyond the duration of consolidation IO in the SoC PACIFIC regimen)	13 (5.9)	1 (0.9)

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).

New combinations

Study	Intervention	Number	NCT number
A5181	CRT + durvalumab ⇒ durvalumab CRT ⇒ durvalumab	n = 660	NCT04092283
KEYLINK-012	CRT + pembrolizumab ⇒ pembrolizumab + placebo CRT + pembrolizumab ⇒ pembrolizumab + olaparib CRT ⇒ durvalumab	n = 870	NCT04380636
KEYVIBE-006	CRT + pembrolizumab + vibostolimab ⇒ pembrolizumab + vibostolimab CRT ⇒ durvalumab	n = 784	NCT05298423
CheckMate73L	CRT + nivolumab ⇒ nivolumab + ipilimumab CRT + nivolumab ⇒ nivolumab CRT ⇒ durvalumab	n = 888	NCT04026412
PACIFIC-9[a]	CRT ⇒ durvalumab + oleclumab CRT ⇒ durvalumab + monalizumab CRT ⇒ durvalumab	n = 999	NCT05221840
SKYSCRAPER-03[a]	CRT ⇒ atezolizumab + tiragolumab CRT ⇒ durvalumab	n = 800	NCT04513925

Adapted from Moghakani et al. JTO 2023

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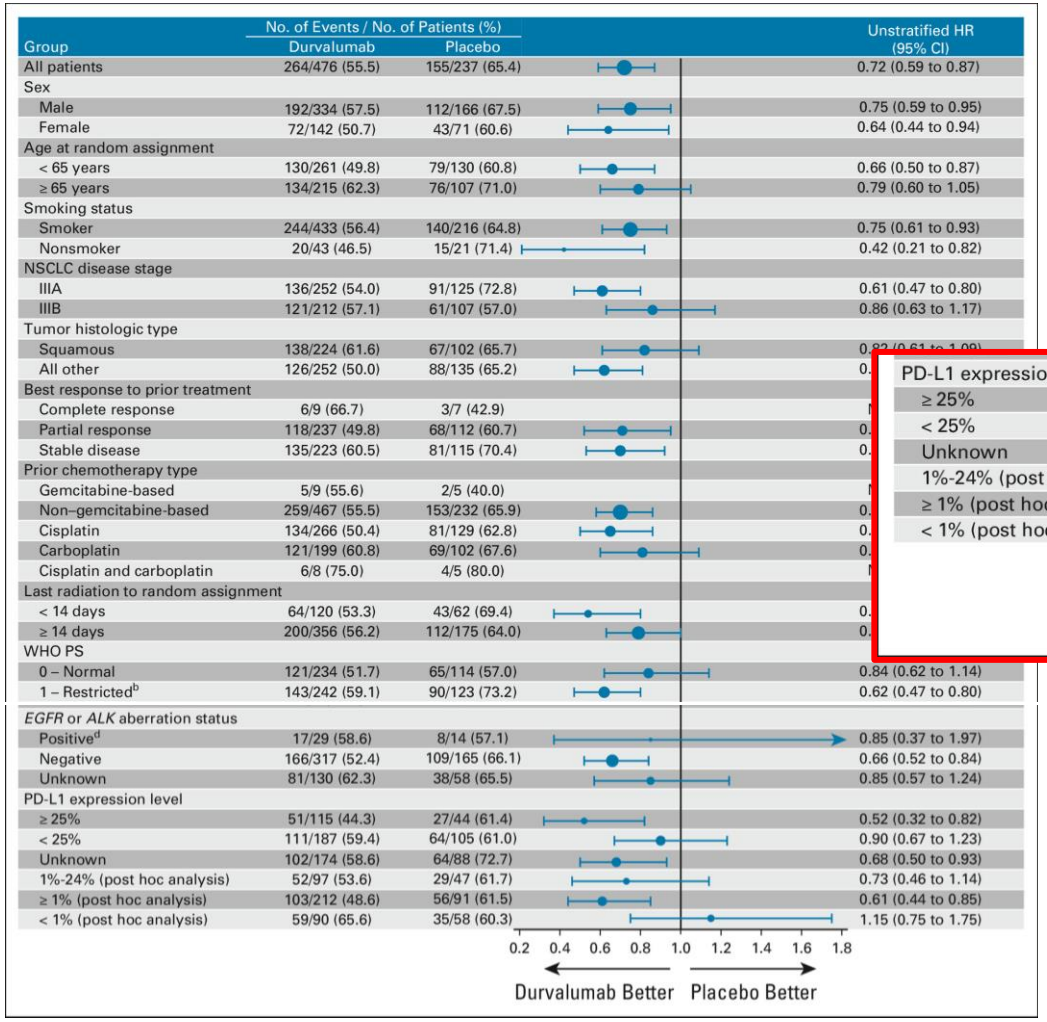
PACIFIC: for everyone?



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)	
All other	126/252 (50.0)	88/135 (65.2)	
Best response to prior treatment			
Complete response	6/9 (66.7)	3/7 (42.9)	
Partial response	118/237 (49.8)	68/112 (60.7)	
Stable disease	135/223 (60.5)	81/115 (70.4)	
Prior chemotherapy type			
Gemcitabine-based	5/9 (55.6)	2/5 (40.0)	
Non–gemcitabine-based	259/467 (55.5)	153/232 (65.9)	
Cisplatin	134/266 (50.4)	81/129 (62.8)	
Carboplatin	121/199 (60.8)	69/102 (67.6)	
Cisplatin and carboplatin	6/8 (75.0)	4/5 (80.0)	
Last radiation to random assignment			
< 14 days	64/120 (53.3)	43/62 (69.4)	
≥ 14 days	200/356 (56.2)	112/175 (64.0)	
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)
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)

0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8

Durvalumab Better Placebo Better

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Durvalumab Better Placebo Better

While consistent benefit in most subgroups
EMA approval in PD-L1≥1%

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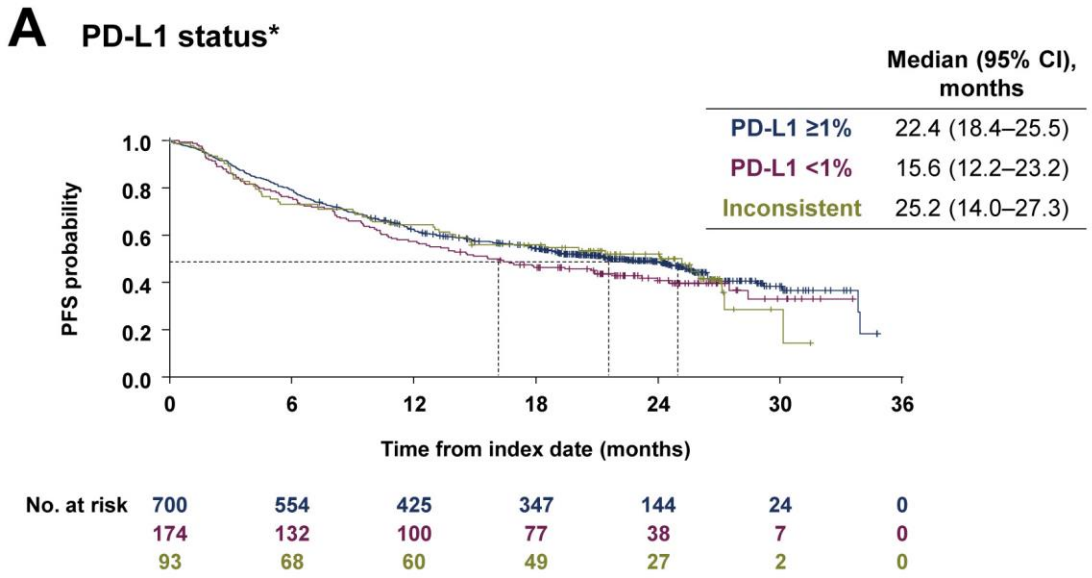
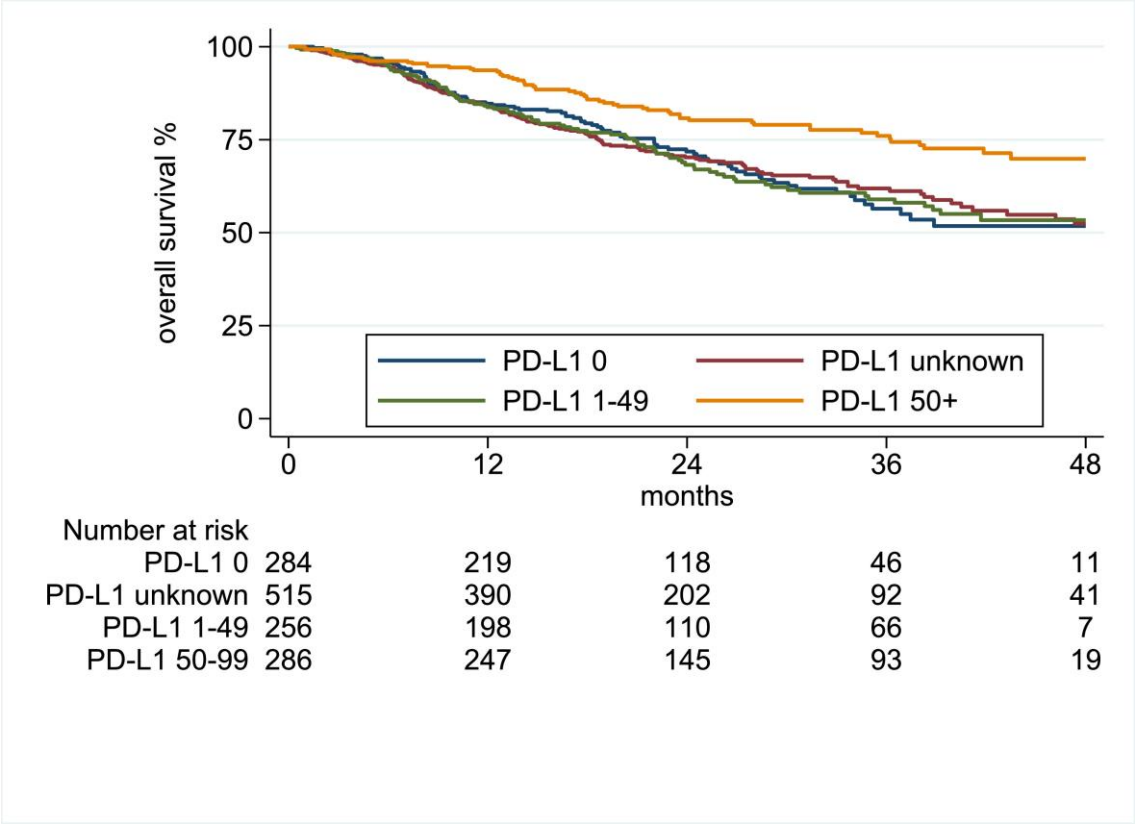
PD-L1 status in real world?

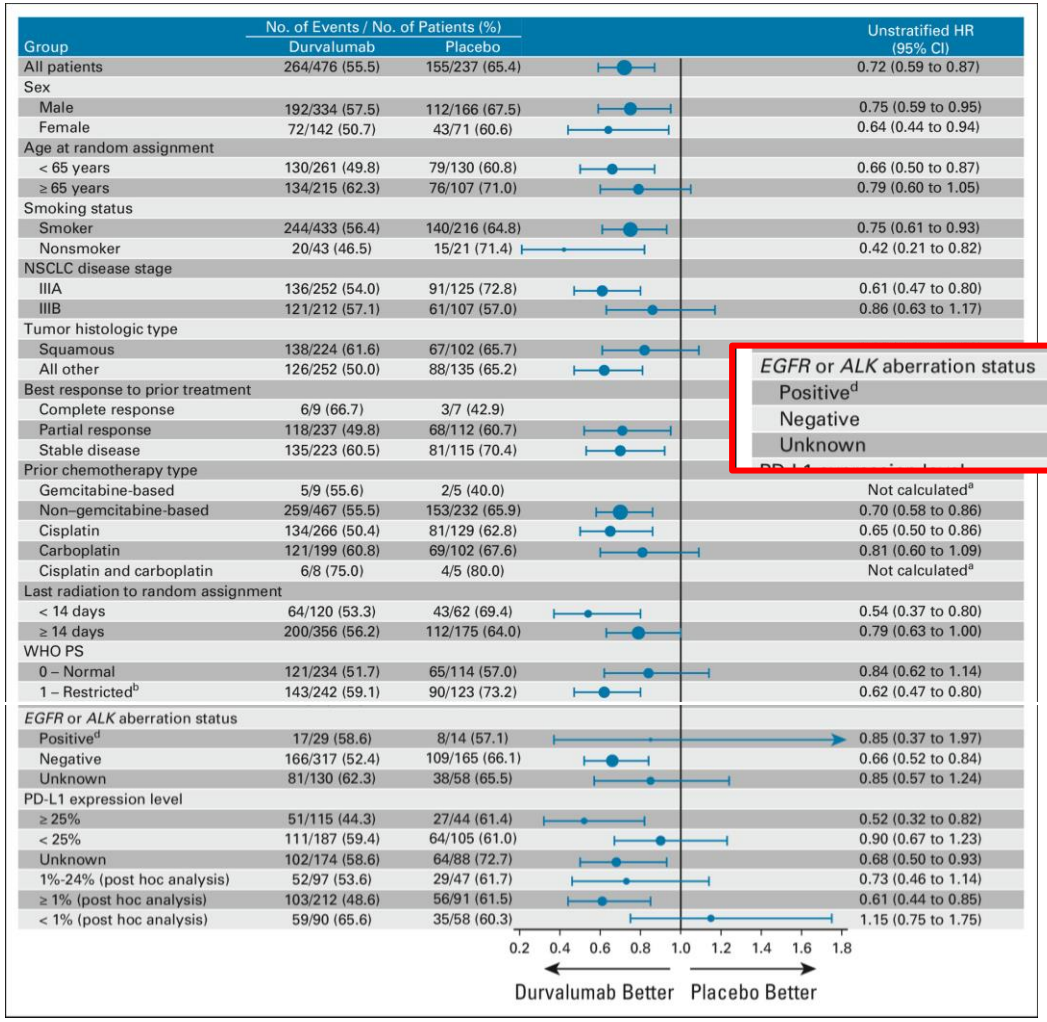
PACIFIC-R





Girard et al. JTO 2022
Damhuis et al. Clin Lung Cancer 2024

PACIFIC: for everyone?



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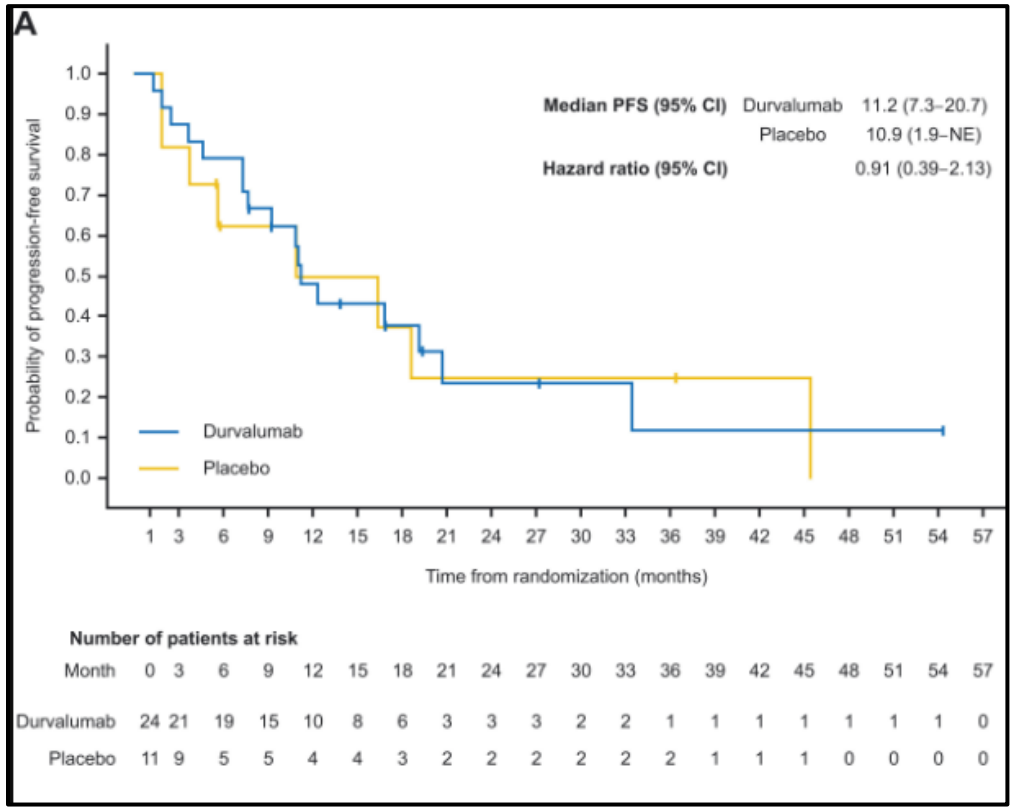
1%-24% (post hoc analysis)	52/97 (53.6)	29/47 (61.7)	0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis)	103/212 (48.6)	56/91 (61.5)	0.61 (0.44 to 0.85)
< 1% (post hoc analysis)	59/90 (65.6)	35/58 (60.3)	1.15 (0.75 to 1.75)

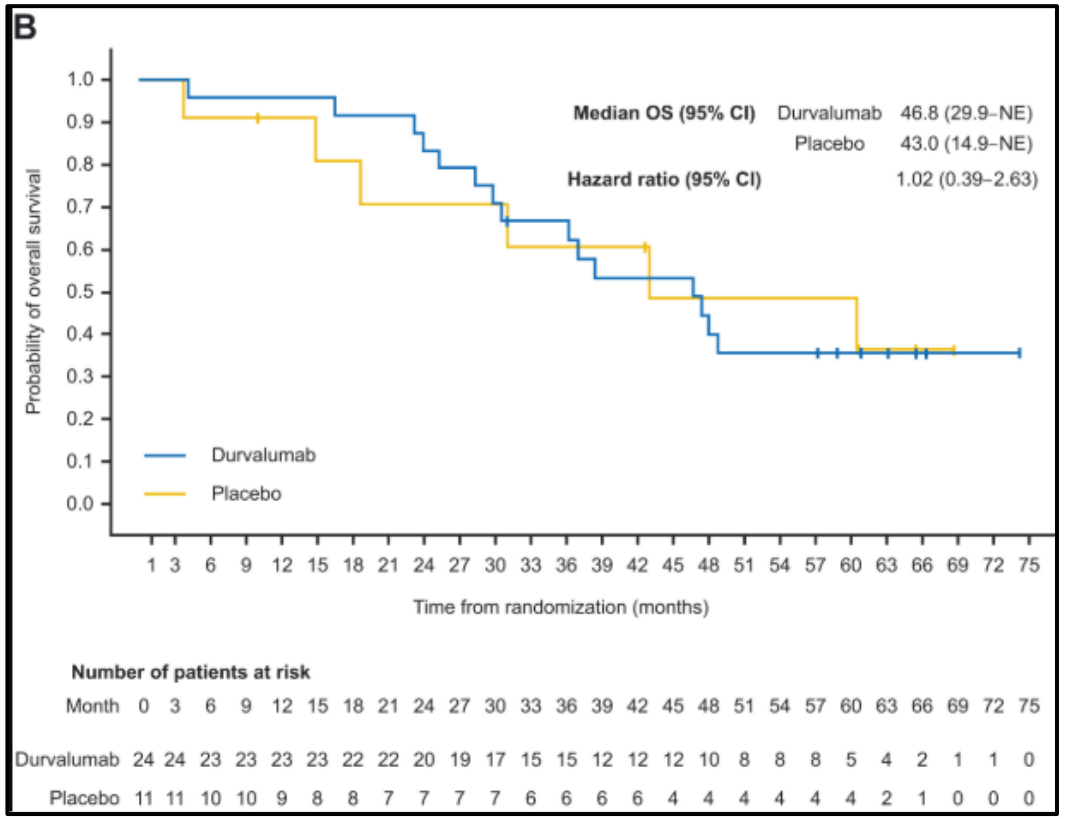
EGFR or *ALK* aberration status
Positive[d] 17/29 (58.6) 8/14 (57.1) 0.85 (0.37 to 1.97)
Negative 166/317 (52.4) 109/165 (66.1) 0.66 (0.52 to 0.84)
Unknown 81/130 (62.3) 38/58 (65.5) 0.85 (0.57 to 1.24)

Spigel JCO 2022

For everyone?

- Subgroup analysis of PACIFIC





Naidoo et al. JTO 2023

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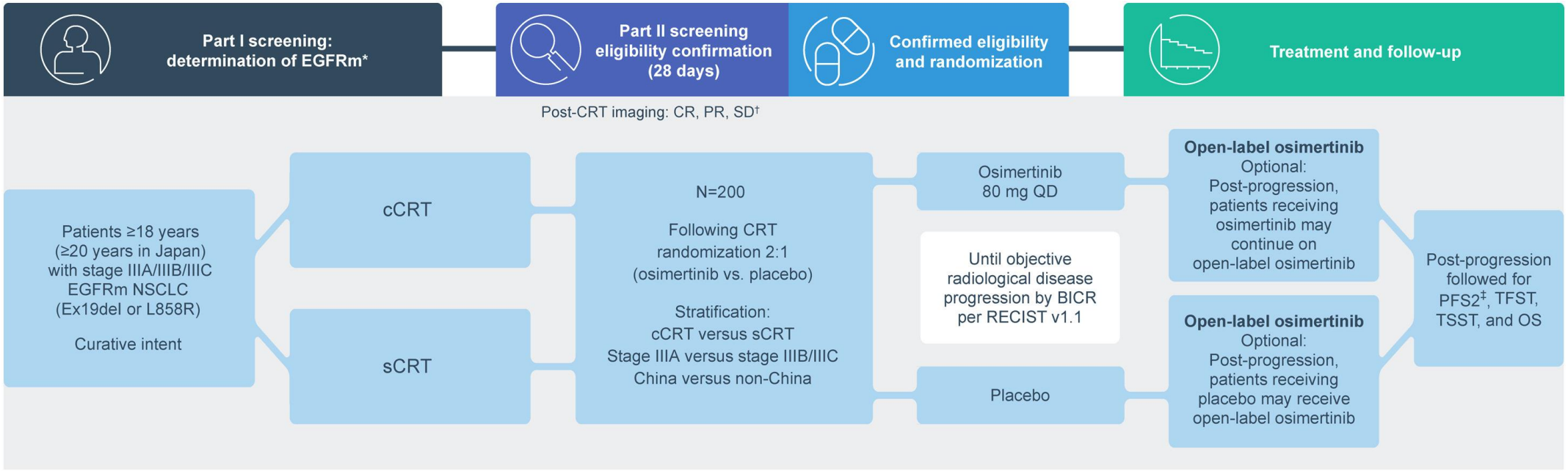
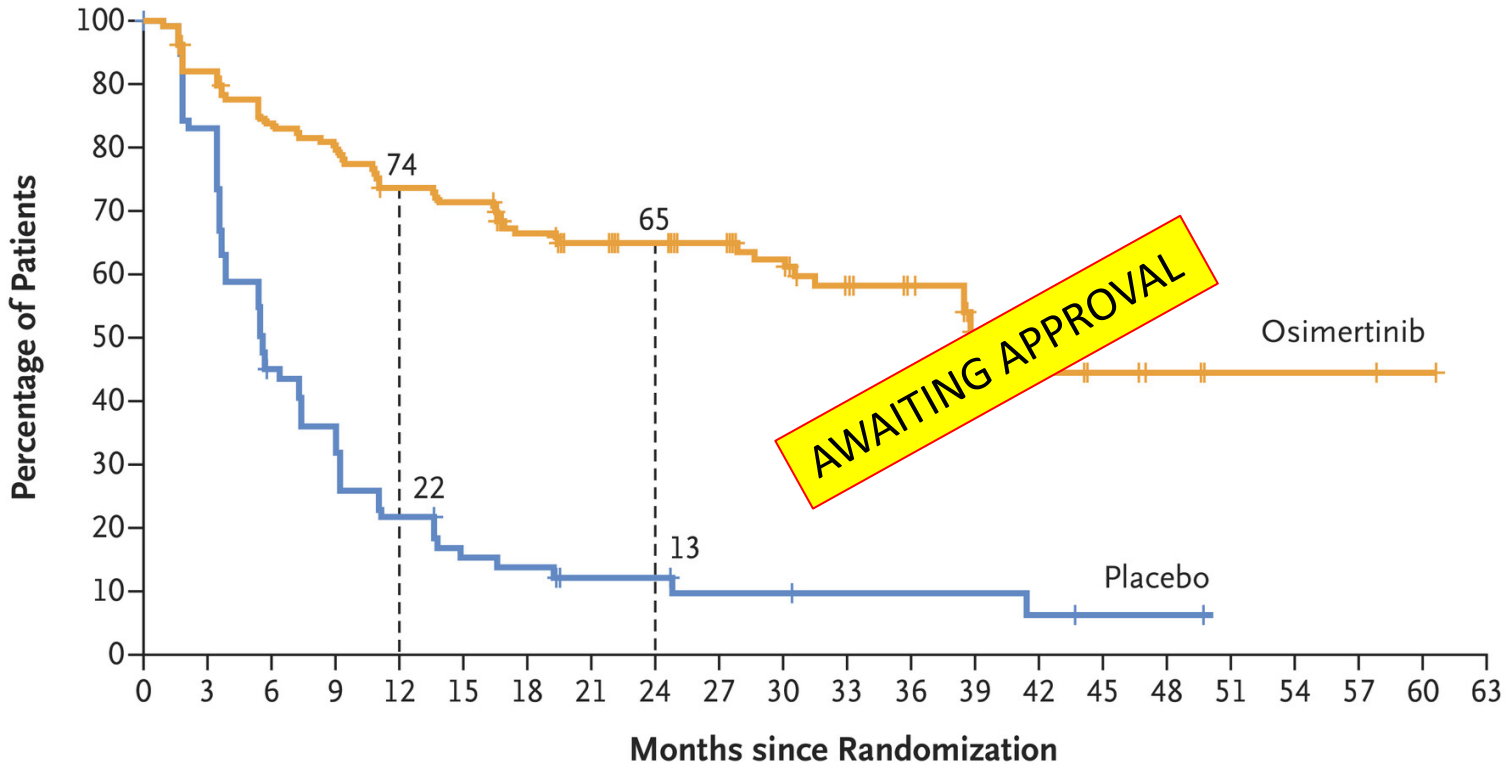
LAURA



Lu et al. CLC 2021

LAURA



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

Median Progression-free Survival (95% CI)

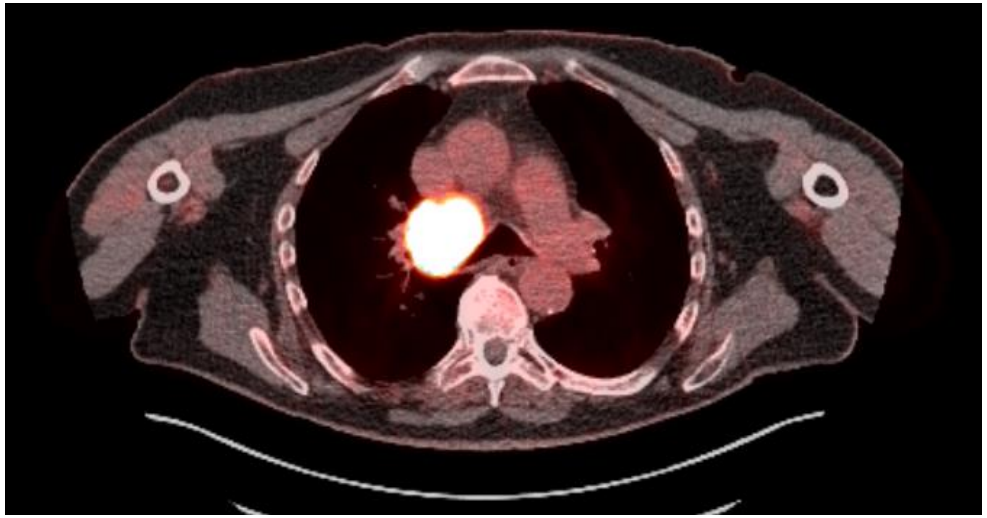
	mo
Osimertinib	39.1 (31.5–NC)
Placebo	5.6 (3.7–7.4)

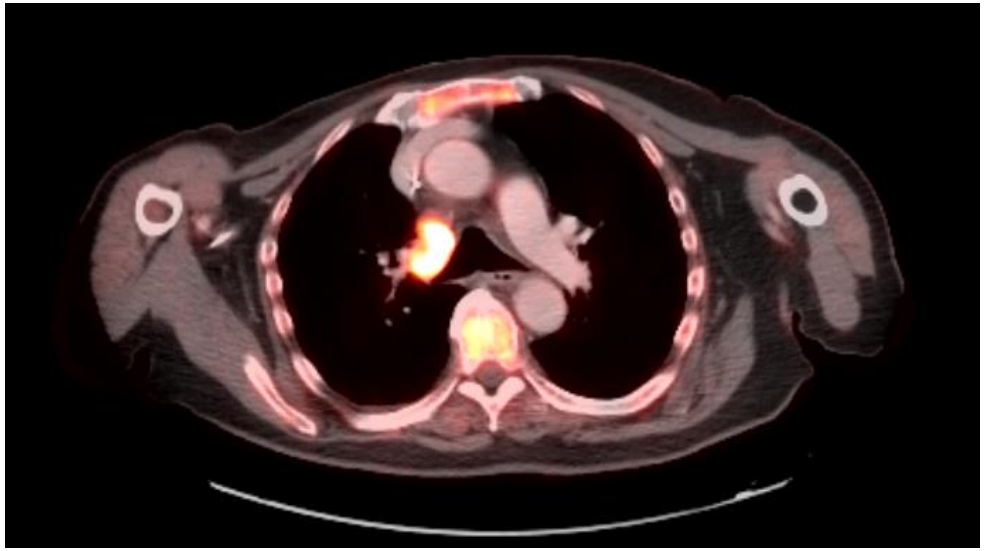
Hazard ratio for disease progression or death, 0.16 (95% CI, 0.10–0.24)
P<0.001

Lu et al. NEJM 2024

Back to the case

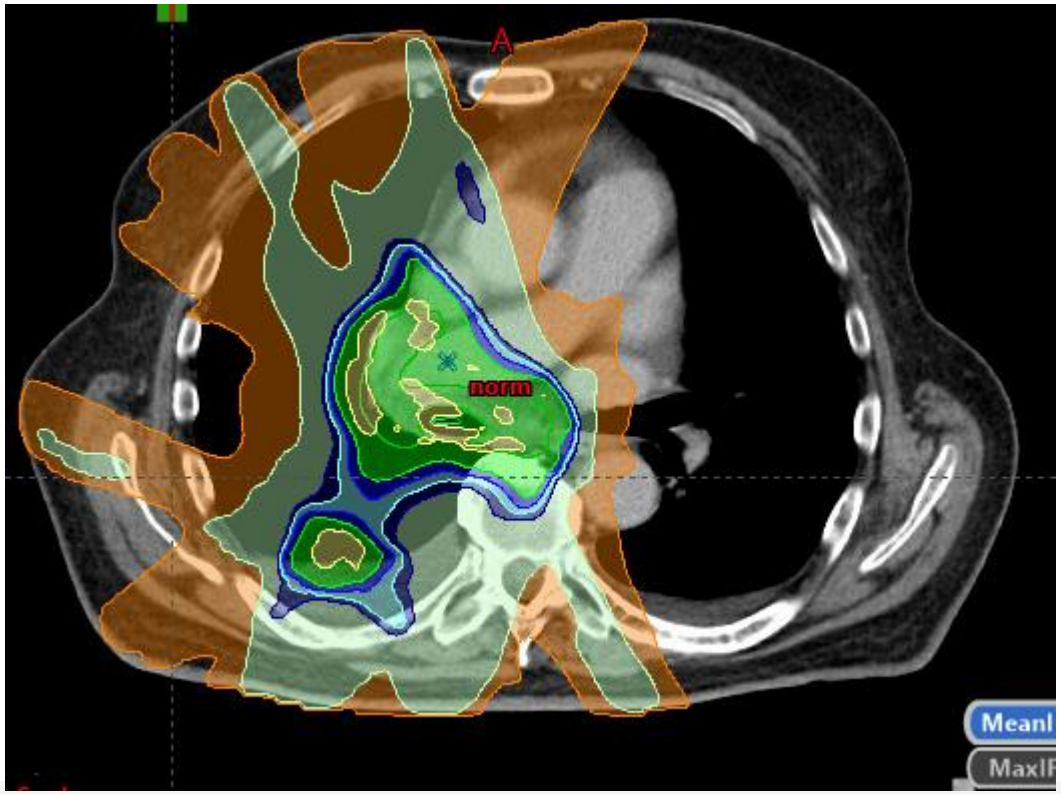
- ♂, 79 years
- Because of age and general condition: sequential CRT
- 3 courses of carboplatin-pemetrexed

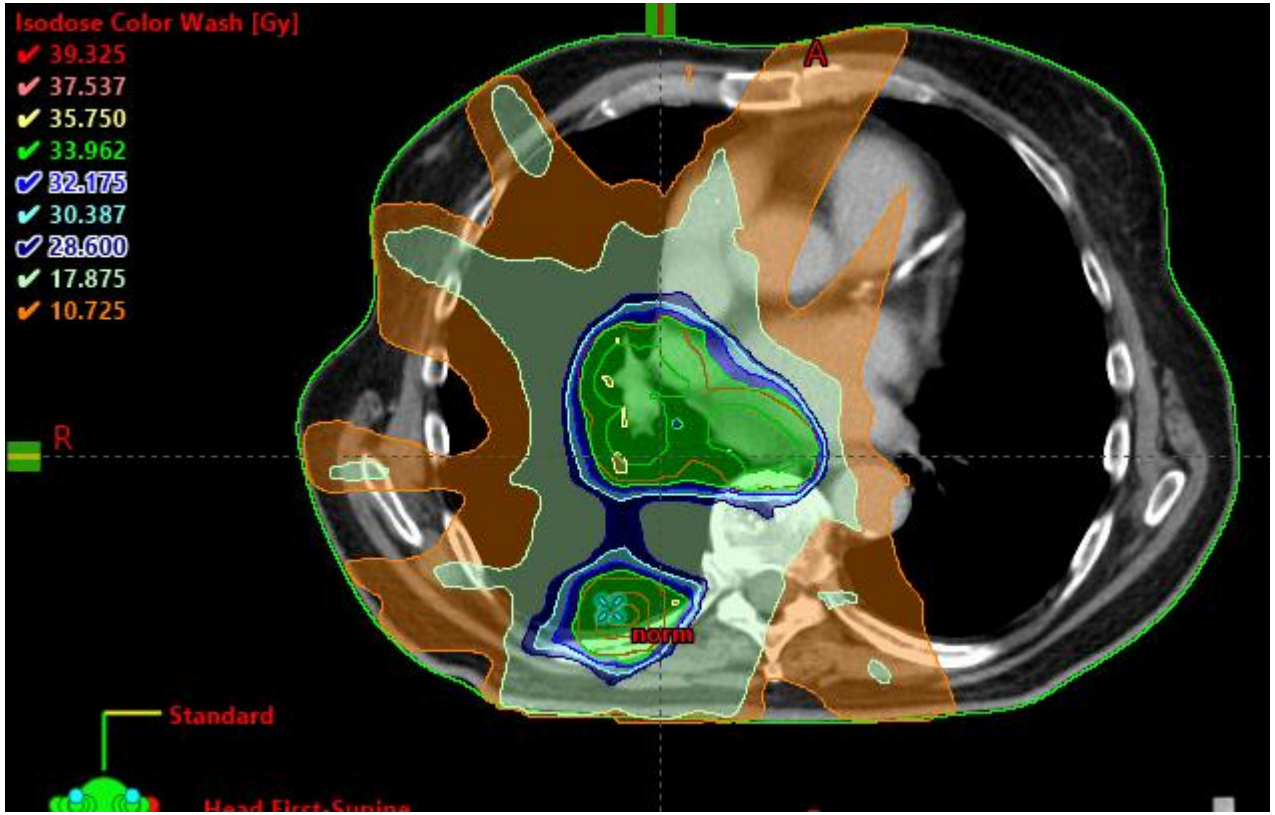




Radiotherapy

- 22 fractions of 2.75 Gy
- Adaptive approach





Concurrent vs Sequential?

- PACIFIC: no sCRT
- Reimbursement allows sequential approach

		Durvalumab (n=252)	Placebo (n=129)
Prior therapy, n (%)	cCRT	168 (66.7)	90 (69.8)
	sCRT	84 (33.3)	39 (30.2)

PACIFIC-5 study design

- A phase 3, randomized, double-blind, placebo-controlled, multicenter study of durvalumab as consolidation therapy in patients with locally advanced, unresectable, NSCLC (Stage III) who have not progressed following definitive, platinum-based chemoradiotherapy

Study population

(ITT N=407; mITT N=381)

- Unresectable, Stage III NSCLC
- No progression following either cCRT or sCRT
- ECOG PS 0-1
- PD-L1, *EGFR*, and *ALK* status available

Randomized 2:1

Stratified by:
CRT type (cCRT vs sCRT)
PD-L1 TC (≥1% vs <1%)

Durvalumab 1500 mg Q4W until PD

Placebo Q4W until PD

Endpoints

Primary (mITT)
PFS by BICR per RECIST v1.1

Key secondary (mITT)
OS

Modified intent-to-treat (mITT): all randomized patients in the ITT who are without sensitizing *EGFR* mutations or *ALK* rearrangement

Wu et al. ESMO ASIA 2024

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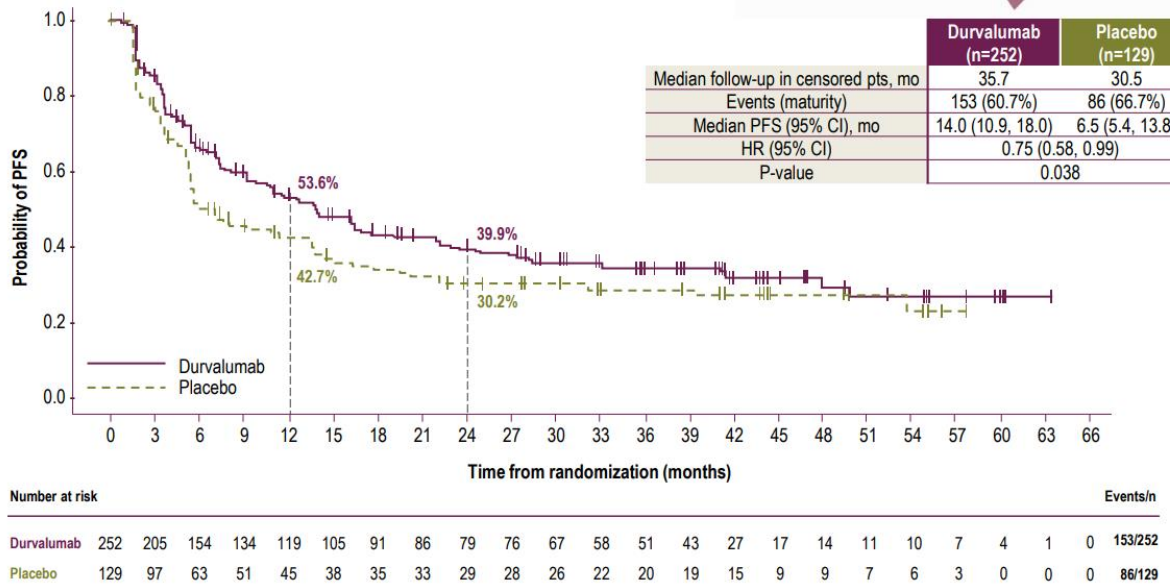
PACIFIC-5

PFS by BICR (mITT)

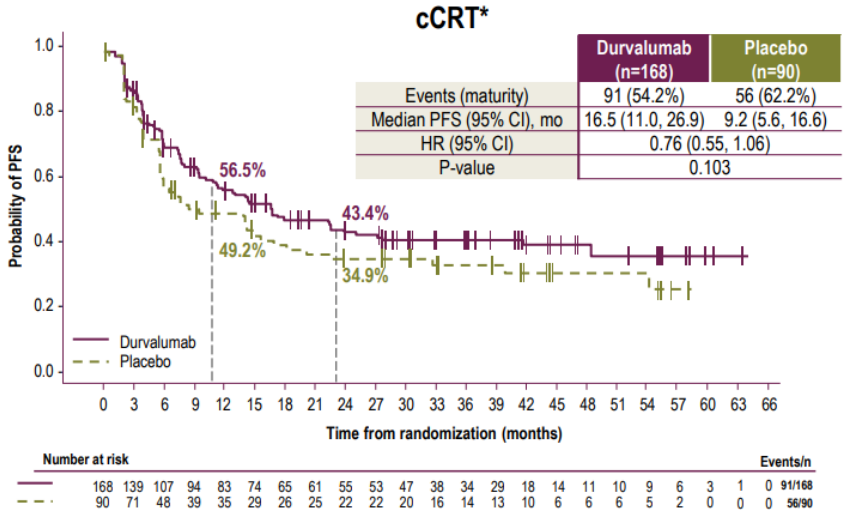
- Durvalumab demonstrated a statistically significant and clinically meaningful benefit in PFS compared to placebo

	Durvalumab (n=252)	Placebo (n=129)
Median follow-up in censored pts, mo	35.7	30.5
Events (maturity)	153 (60.7%)	86 (66.7%)
Median PFS (95% CI), mo	14.0 (10.9, 18.0)	6.5 (5.4, 13.8)
HR (95% CI)	0.75 (0.58, 0.99)	
P-value	0.038	



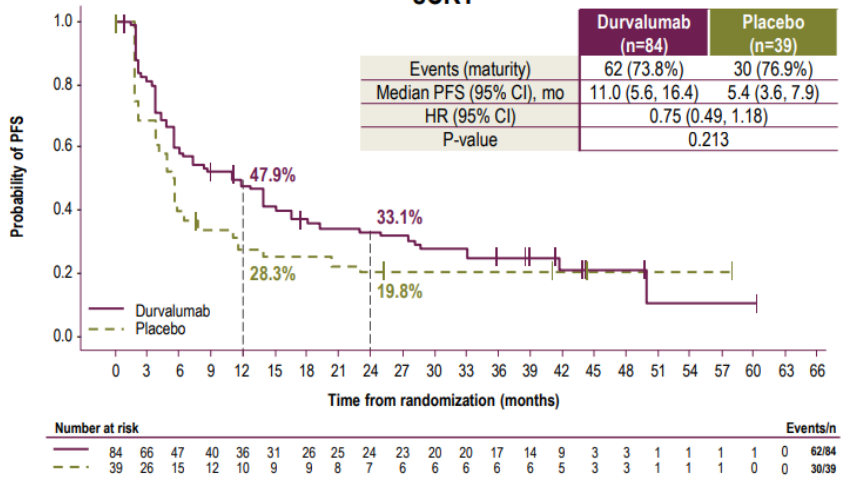
cCRT*

	Durvalumab (n=168)	Placebo (n=90)
Events (maturity)	91 (54.2%)	56 (62.2%)
Median PFS (95% CI), mo	16.5 (11.0, 26.9)	9.2 (5.6, 16.6)
HR (95% CI)	0.76 (0.55, 1.06)	
P-value	0.103	



sCRT*

	Durvalumab (n=84)	Placebo (n=39)
Events (maturity)	62 (73.8%)	30 (76.9%)
Median PFS (95% CI), mo	11.0 (5.6, 16.4)	5.4 (3.6, 7.9)
HR (95% CI)	0.75 (0.49, 1.18)	
P-value	0.213	



Wu et al. ESMO ASIA 2024

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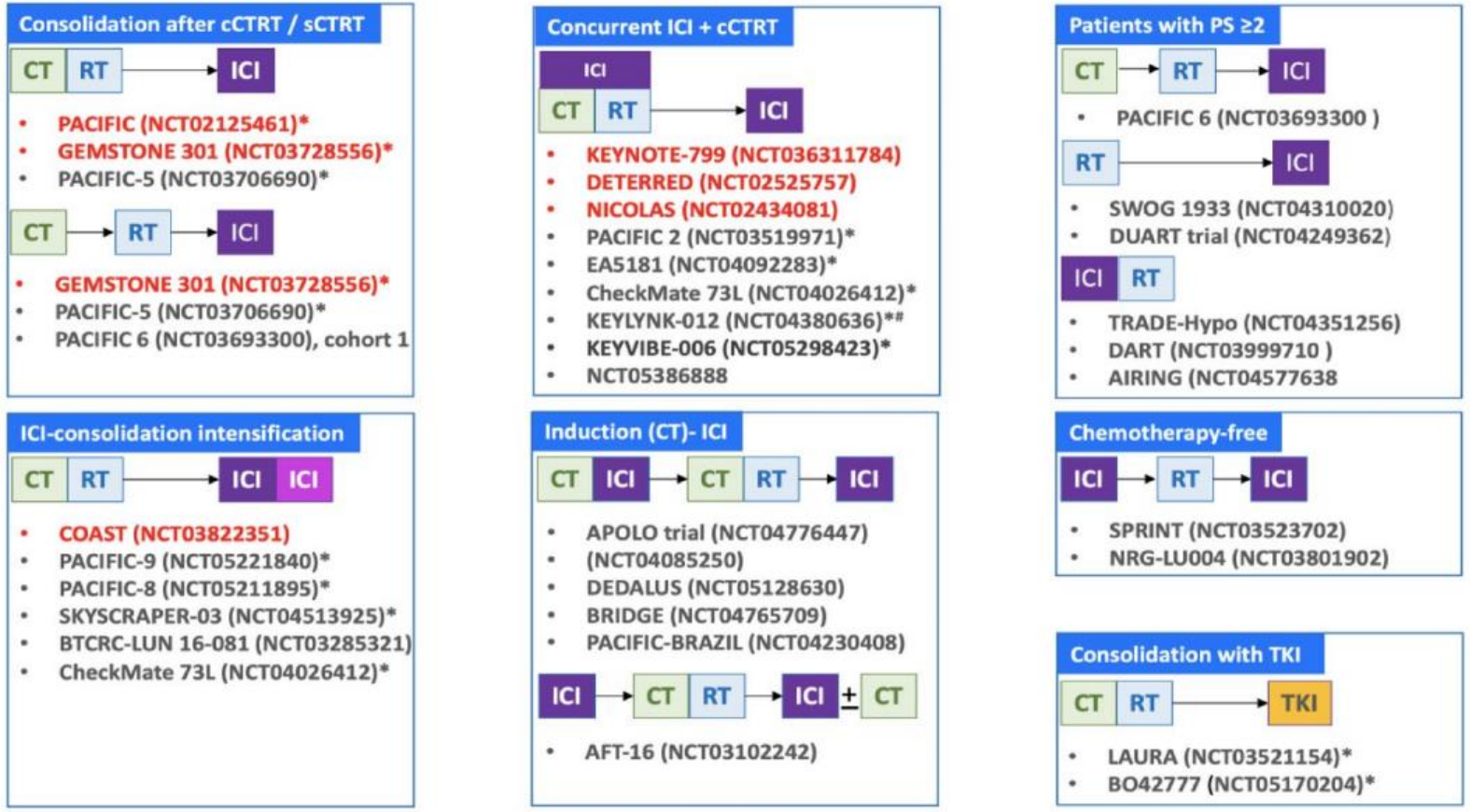
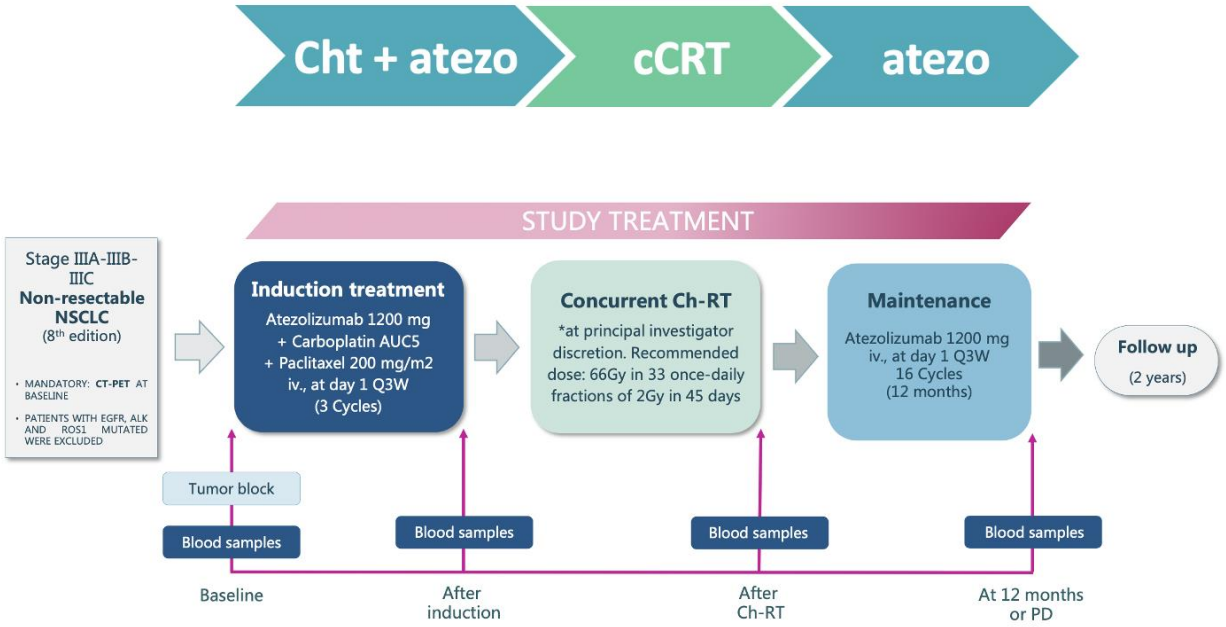
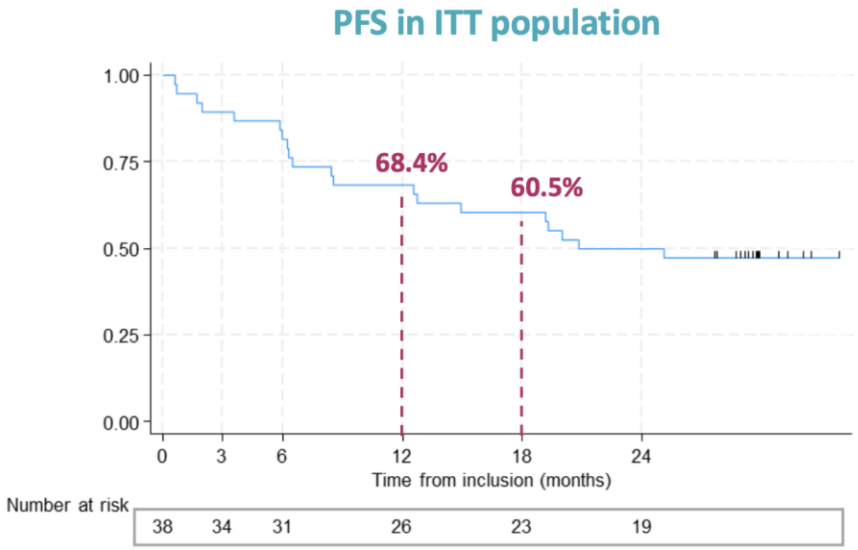
Future strategies

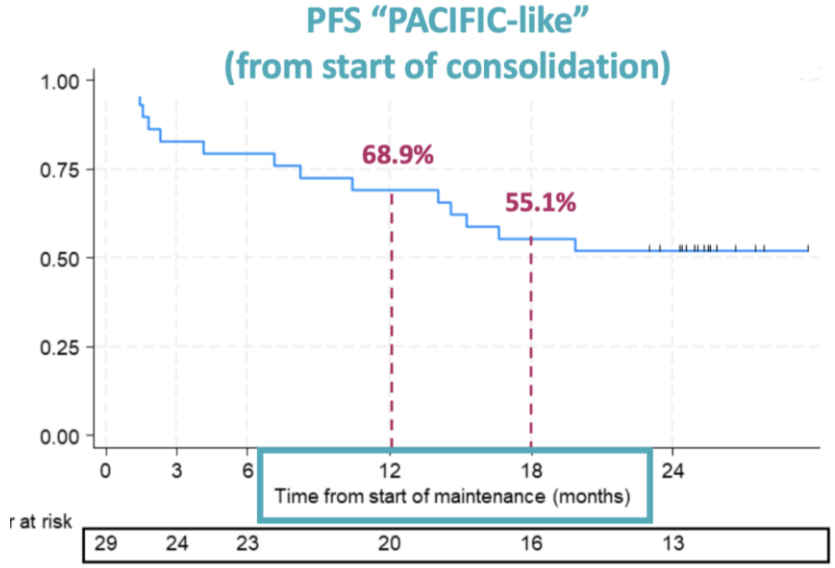


Remon et al. Ther Adv Med Oncol 2022

Rethink strategies







Provincio et al. WCLC 2024

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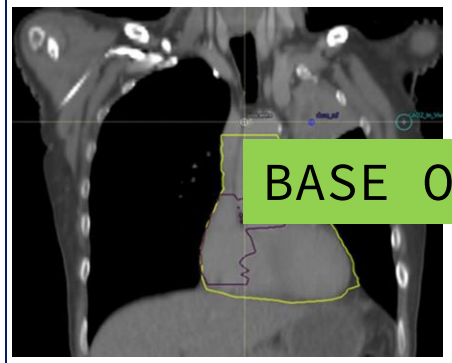
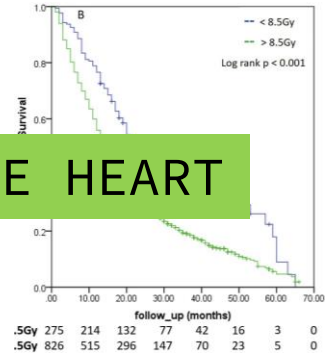
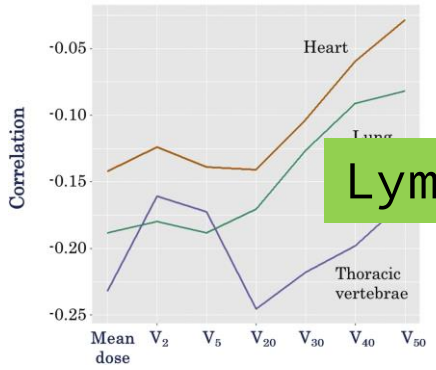
Radiotherapy is evolving

New OAR

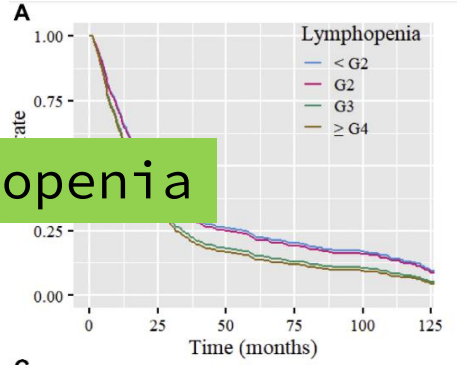


BASE OF THE HEART

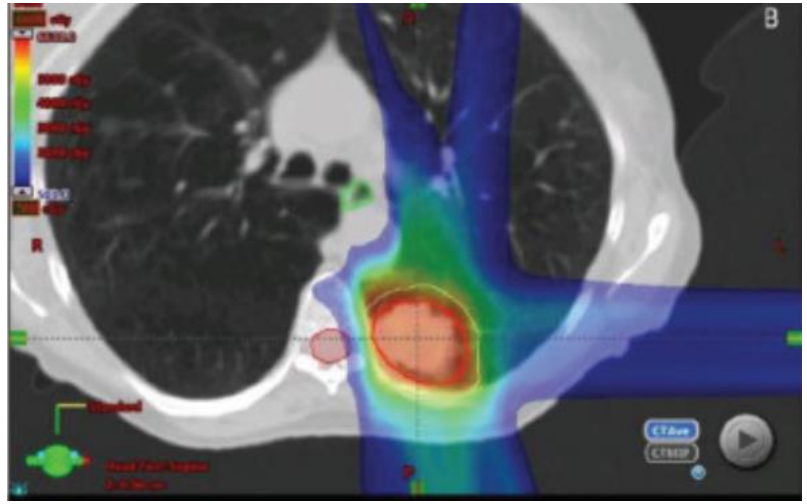




Lymphopenia



New techniques

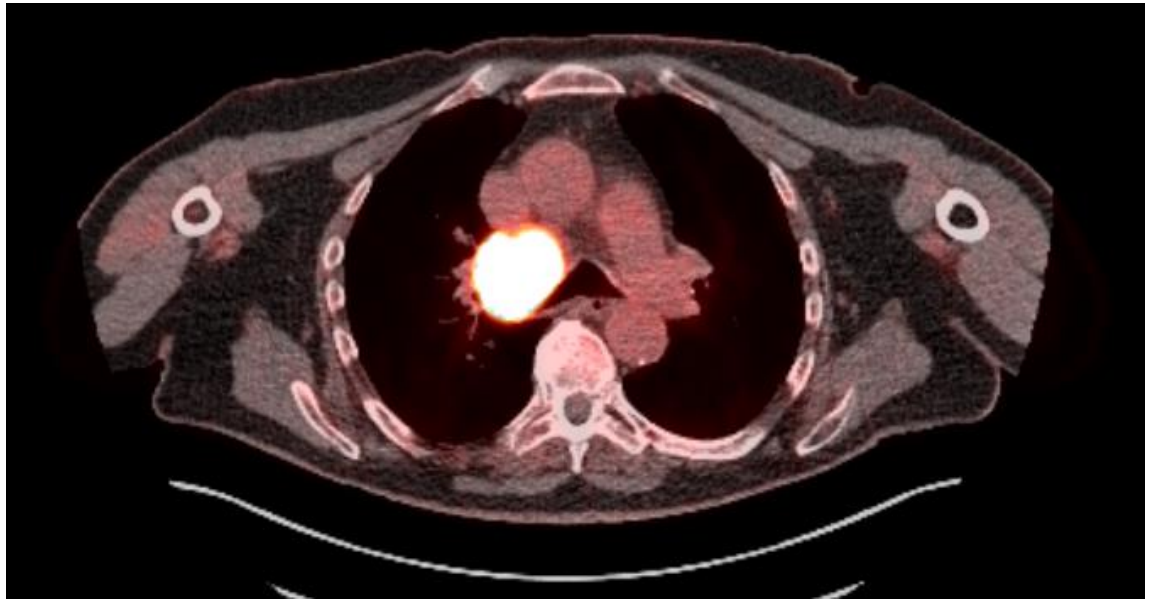


McWilliam et al. EJC 2017
Abravan et al. JTO 2020

What if??

- ♂, 45 years
- WHO 1
- FEV1: 95%, DLCO 50%
- Pathology EBUS-TBNA
  - Adenocarcinoma
  - PD-L1: 100%

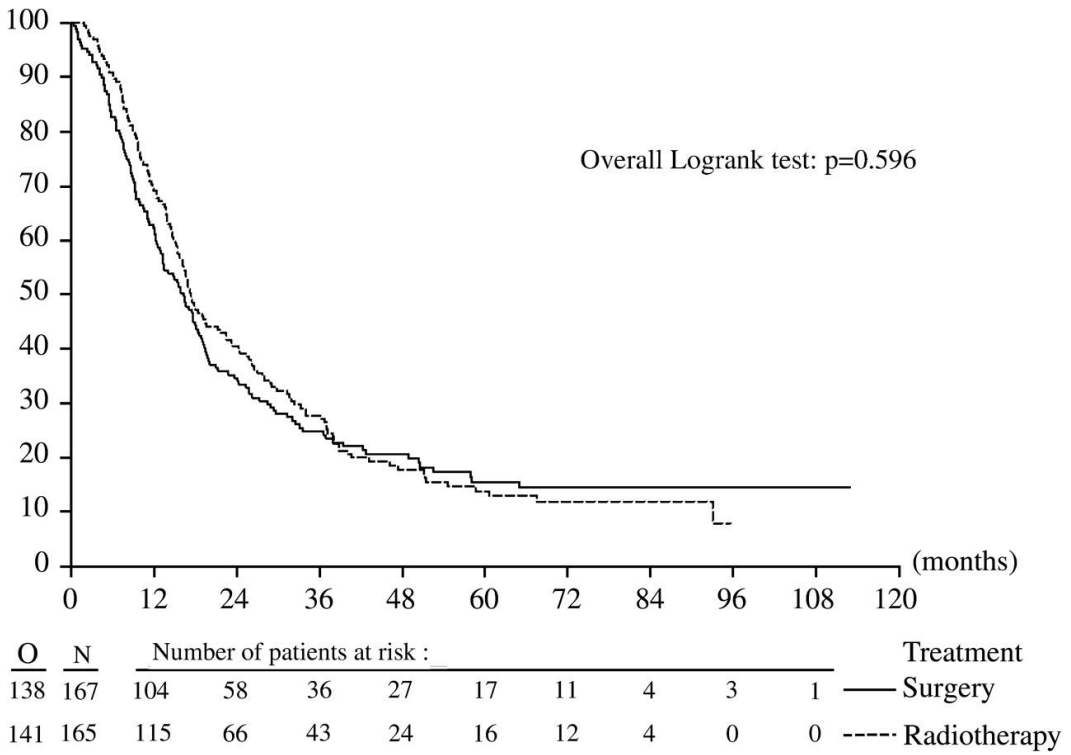
cT4N2M0: bulky N2 disease



Resectable after chemo?

- EORTC 08941
  - Unresectable stage IIIA-N2 NSCLC
  - Induction chemotherapy
  - Followed by Sx vs RT
  - No OS benefit
    - pCR rate: 5%
    - R0: 50%
  - However:
    - Definition unresectable?
    - No cCRT, no min invasive surgery

⇔ pCR rates 17-25% with chemo-IO



Van Meerbeeck et al. JNCI 2007
Van Schil et al. Eur Respir J 2005

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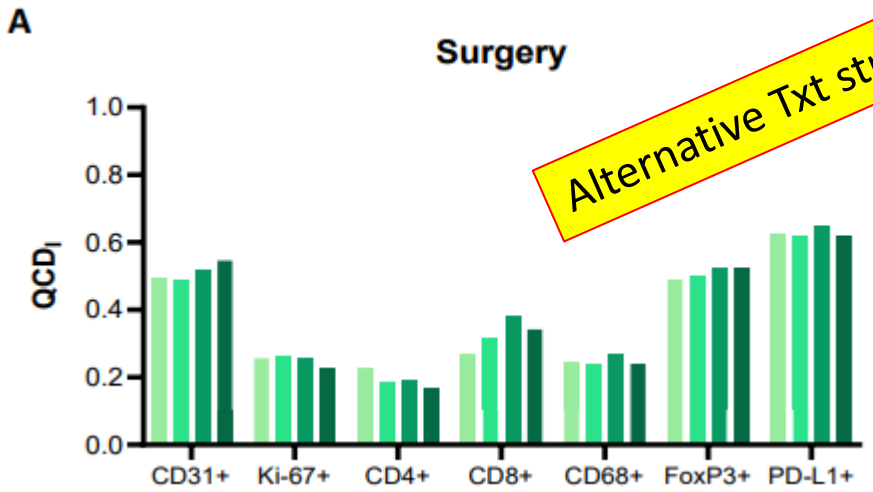
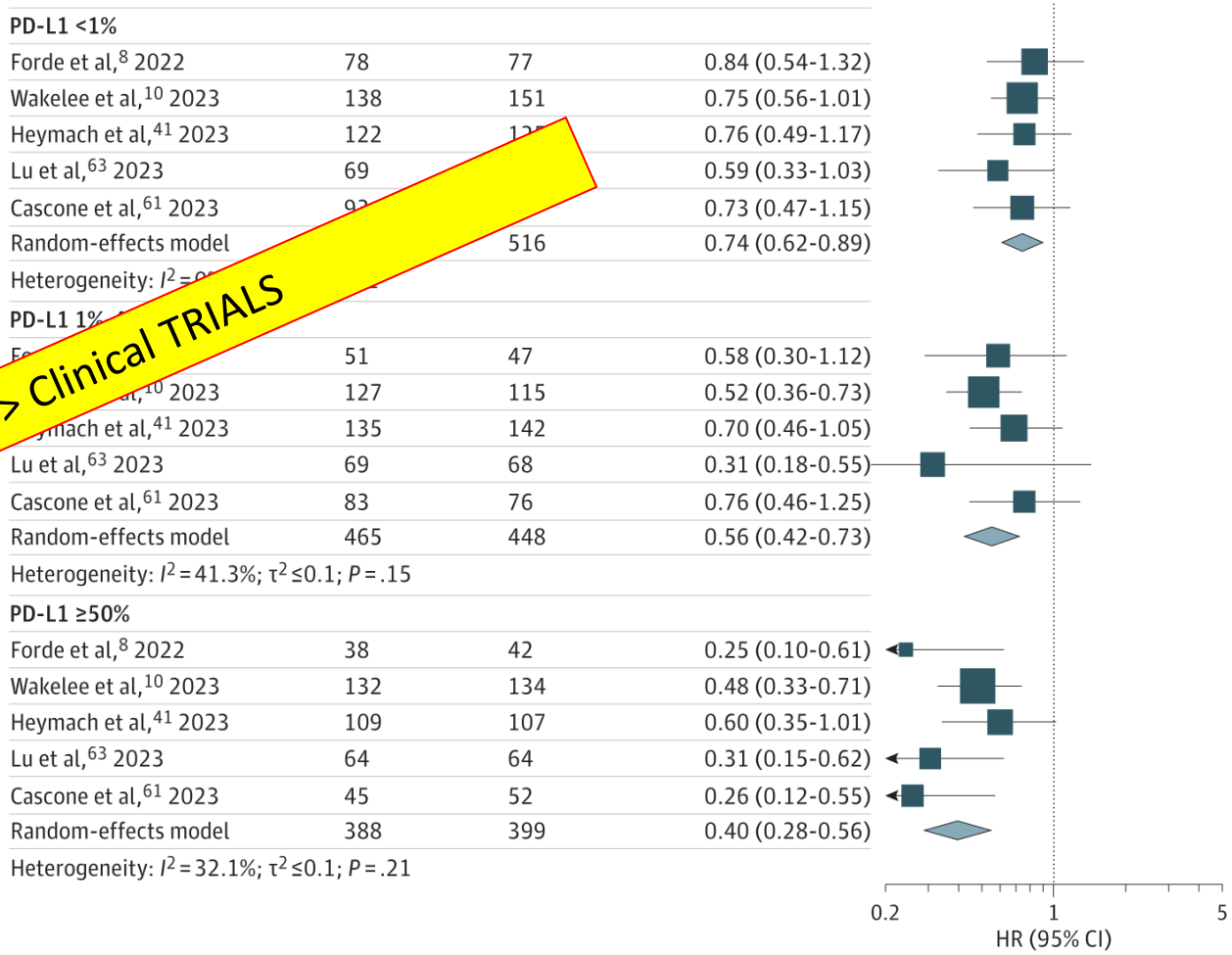
Biomarkers

- PD-L1 not an optimal biomarker
  - Sensitivity
  - Heterogeneity



Alternative Txt strategies => Clinical TRIALS



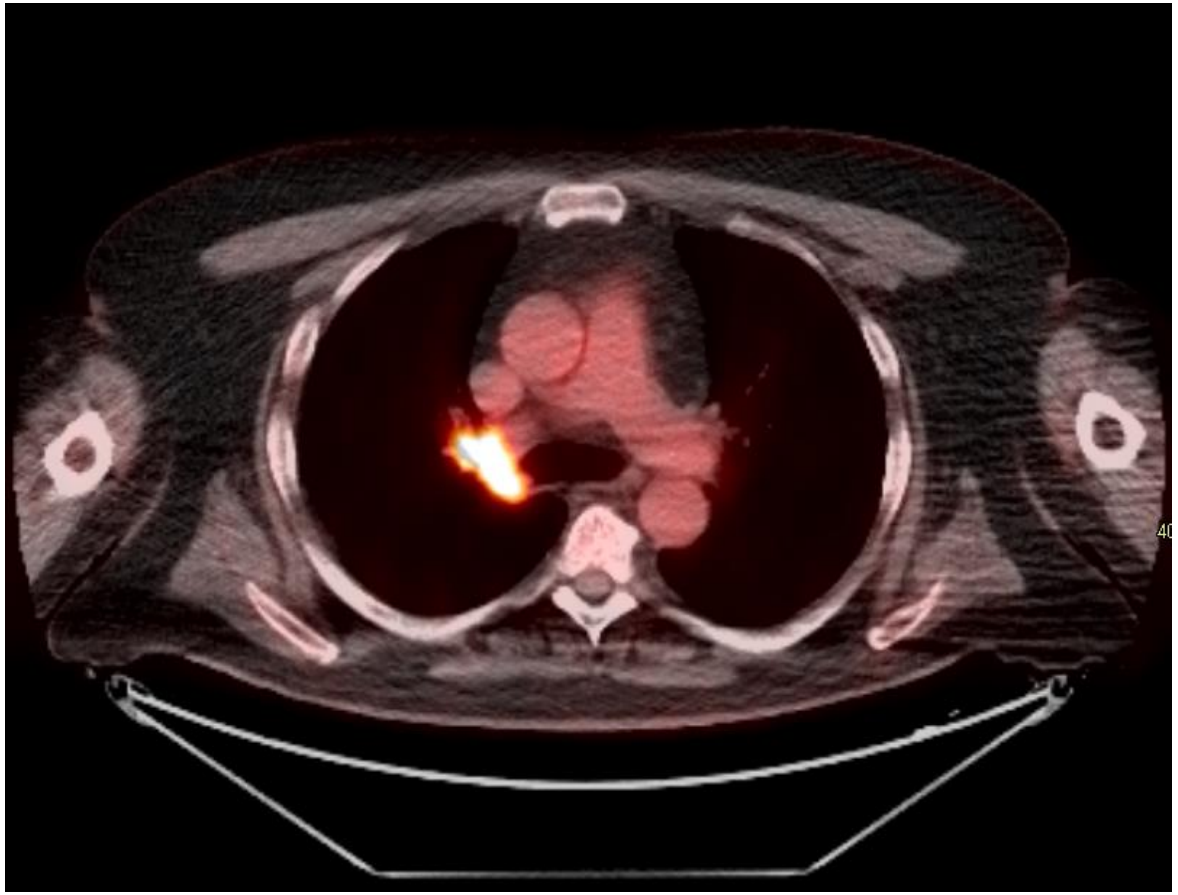
Sorin et al. JAMA 2024
Reynders et al. Unpublished data

Conclusions Unresectable

- PACIFIC regimen remains SOC in unresectable, EGFR-, NSCLC PD-L1 ≥ 1%
- Resectability should be determined upfront
- Toxicity is major issue in treatment intensification
- Novel RT techniques/approaches
  - Adaptive RT
  - Heart sparing
  - Importance of lymphopenia
- In EGFR mutated patients: consolidation osimertinib is coming

Case 2

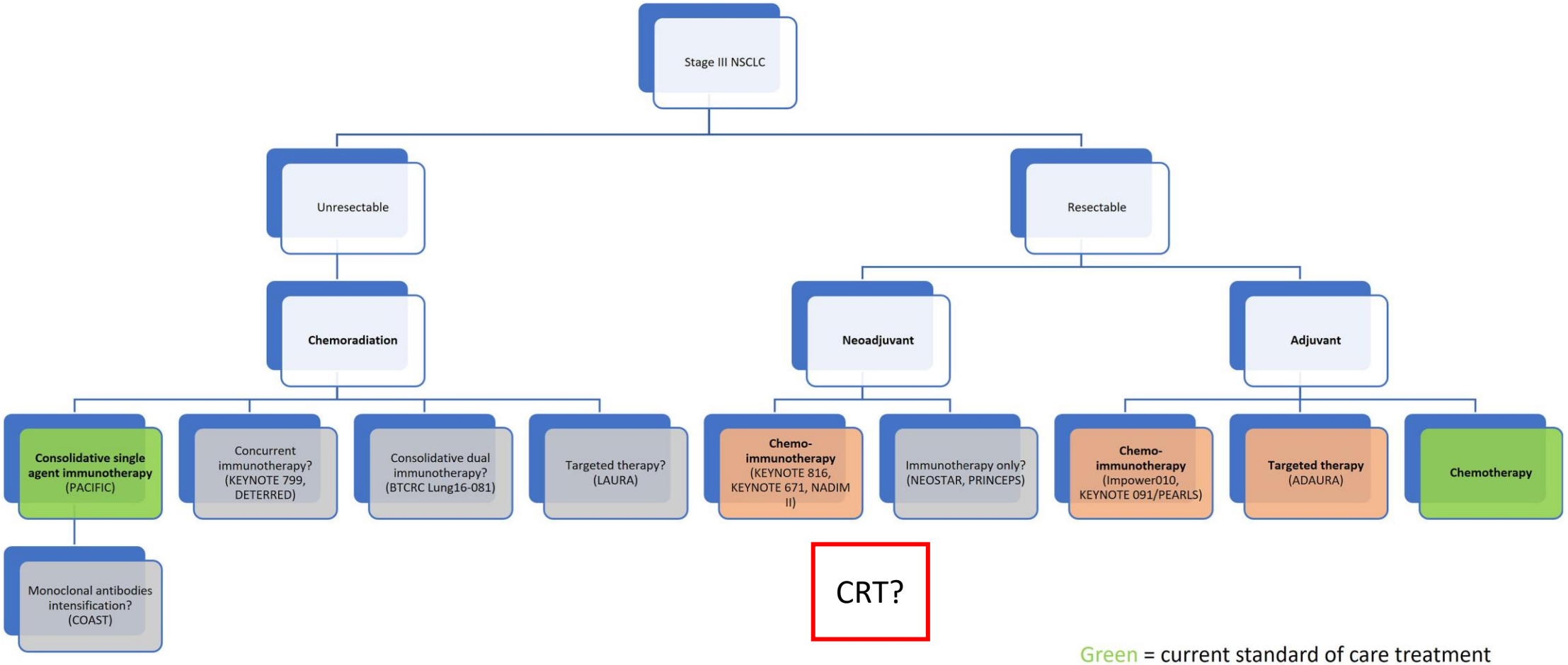
- ♂, 59 years
- 20 PY
- Adenocarcinoma
- PD-L1: 80%
- FEV1: 69%, DLCO: 103%
- cT4N0



What's your treatment of choice

1. Upfront surgery followed by chemo-immunotherapy
2. Induction chemo-immunotherapy followed by surgery
3. Induction chemoradiotherapy followed by surgery
4. Primary CRT followed by Durvalumab

Treatment options



Green = current standard of care treatment
Orange = emerging treatments
Grey = trials in progress

Li et al JTO 2023

What happened to induction CRT?

	SWOG9416/ INT0160	JCOG9806	ESPATUE	INT0139	SAKK trials
Dose	45Gy	45Gy	45Gy	45Gy	s44Gy
pCR	34%	21%	33%	18%	19%
MPR	61%	46%	/	/	/
PD	9%	5%	1.6%	/	/
Progressed to surgery	80%	76%	/	81%	79%
R0 resection	94%	89%	/	87%	80%

Rusch et al JCO 2007
Kunitoh et al. JCO 2008

Albain et al Lancet 2009
Eberhardt et al. JCO 2015
Konig ESMO Open 2022

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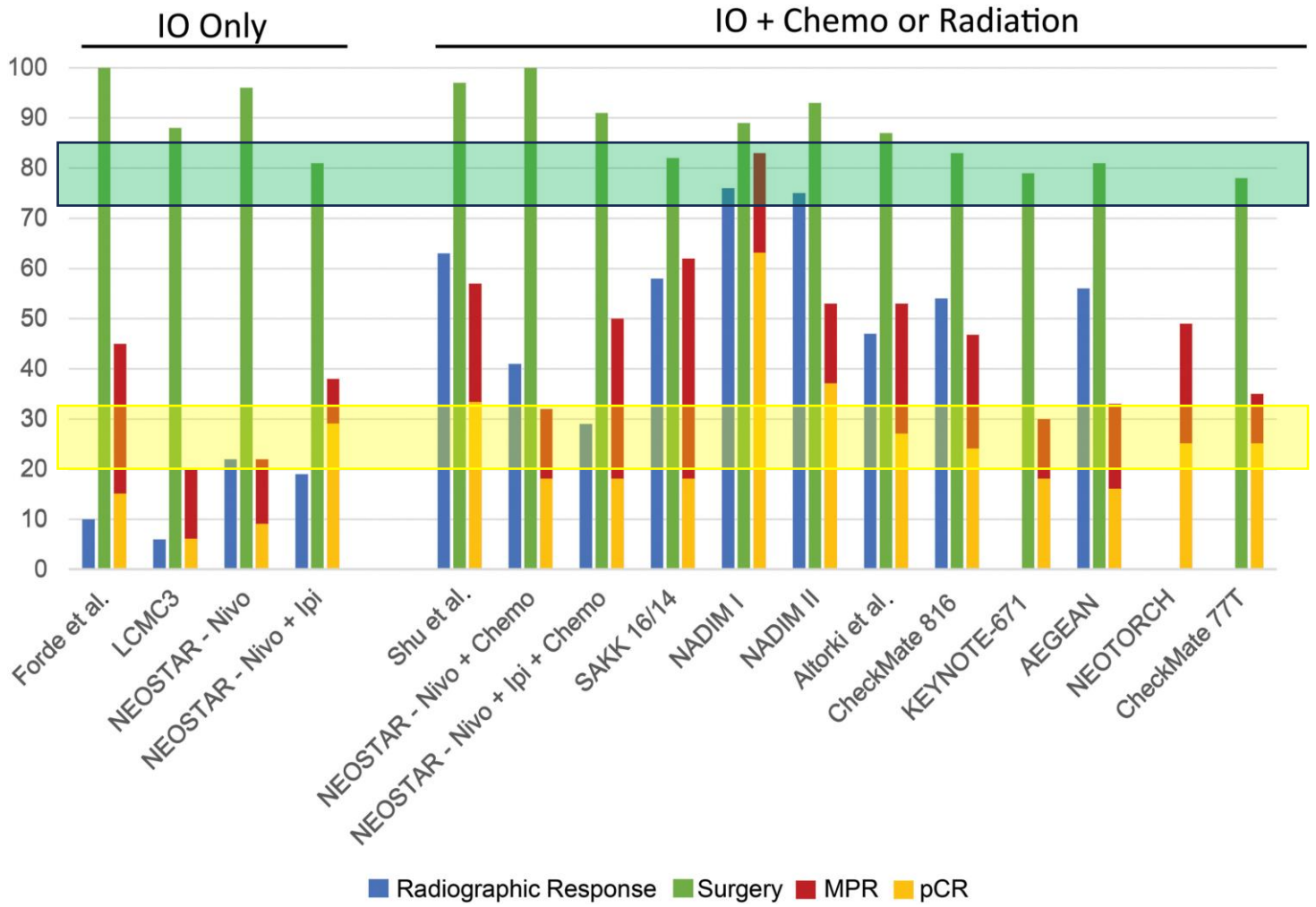
Comparable to Chemo-IO



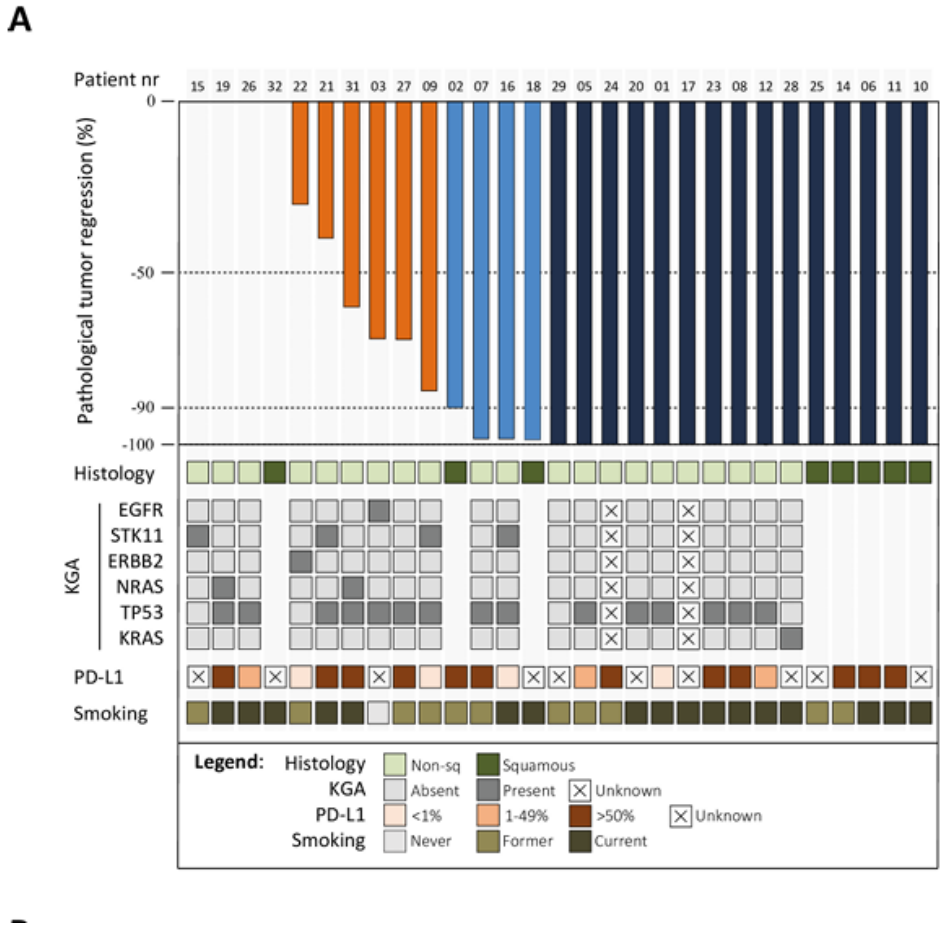
Dunne et al. Ann Thorac Surg 2024

Induction C-RT

IO-CRT induction

Phase II INCREASE trial

- 30 pts
- cT3-4N0-2M0 NSCLC
- Ipi-Nivo-CRT
  - pCR: 50%
  - MPR: 63%
  - R0 rate: 100%
  - Grade 3-4 TRAE: 70%



Bahce et al. J ImmunoTher of Cancer 2024

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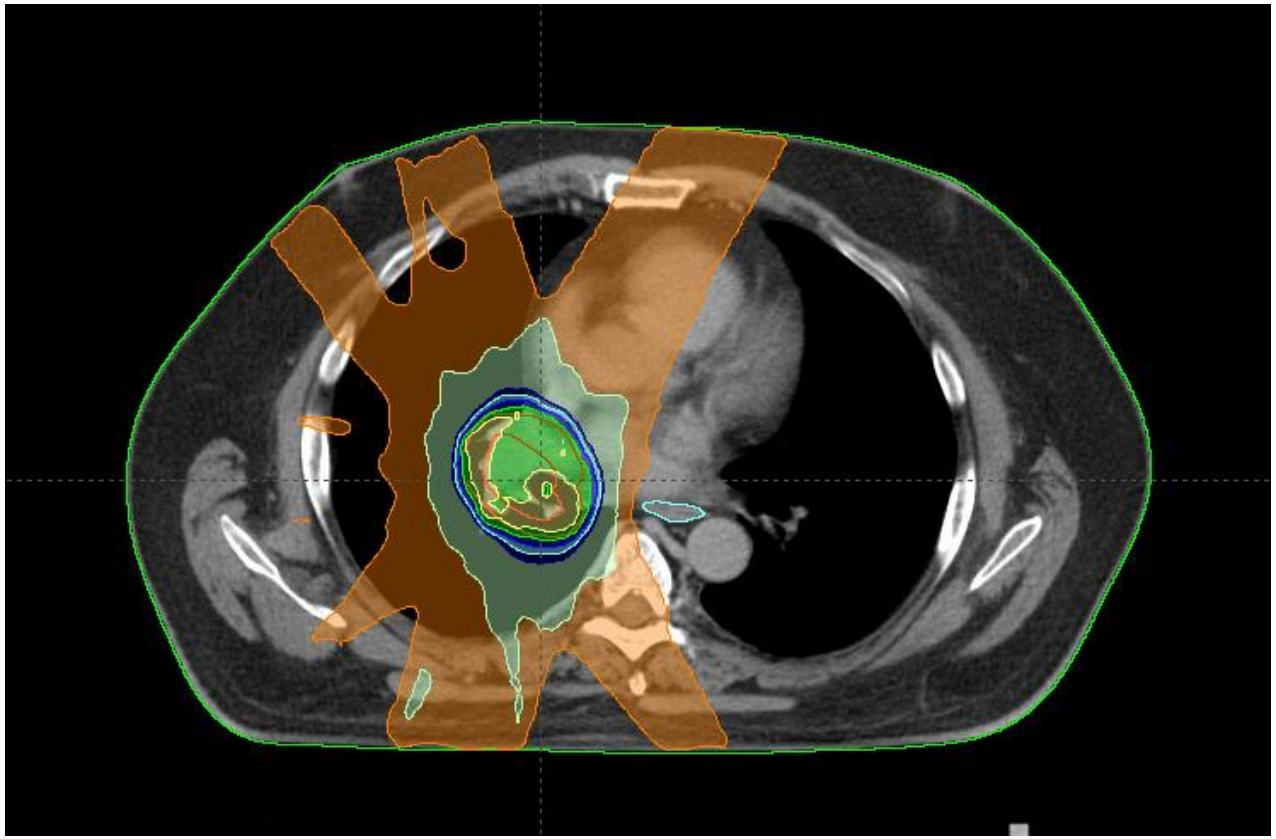
Back to the case

- Upfront resectable
- Advanced T-stage
- cN0
- No reliable biomarker

=> cCRT 45Gy



Conclusions

- Evolution in systemic treatment is rapidly changing the landscape in NSCLC and stage III disease
- Complexity increases
- Rethink dogmas on how local Txt fits into new treatment paradigms
  - True multidisciplinary cooperation
  - Need for well-run academic trials

Thank you for you attention

www.llcg.be

- E. Wauters
- C. Dooms
- P. De Leyn
- Y. Jansen
- P. Berkovic

QUESTIONS?