Terapia nella malattia localmente avanzata inoperabile:

stato dell'arte e prospettive future

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Disclosures

Speakers’s fee and Adivosory boards:

AstraZeneca

BMS

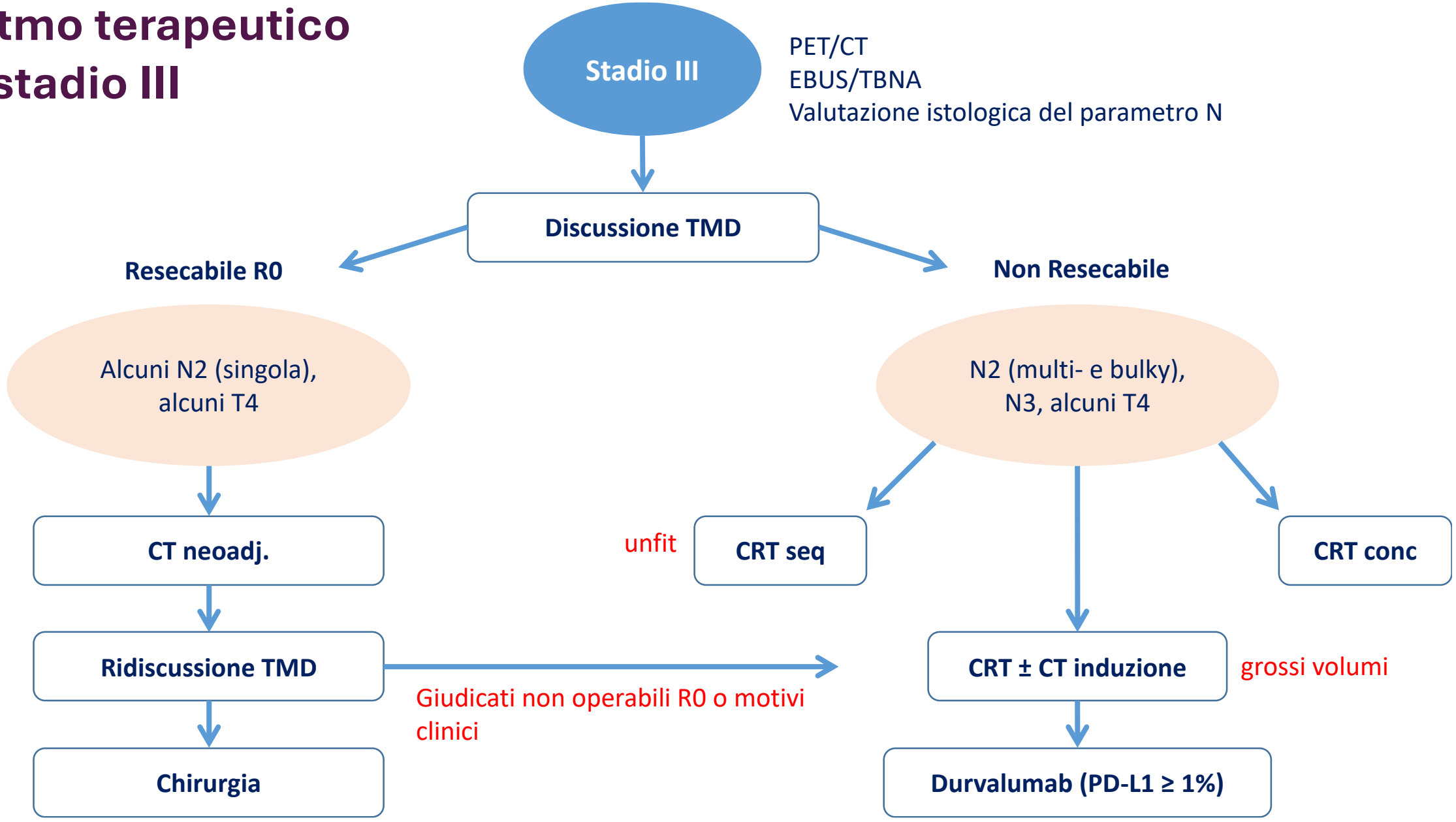
MSD

Roche

Novartis

Janssen

Algoritmo terapeutico dello stadio III



PACIFIC: The practice-changing approach in unresectable LA-NSCLC

- 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†

Patients enrolled irrespective of PD-L1 status

N = 713 randomized

1–42 days post-cCRT

R

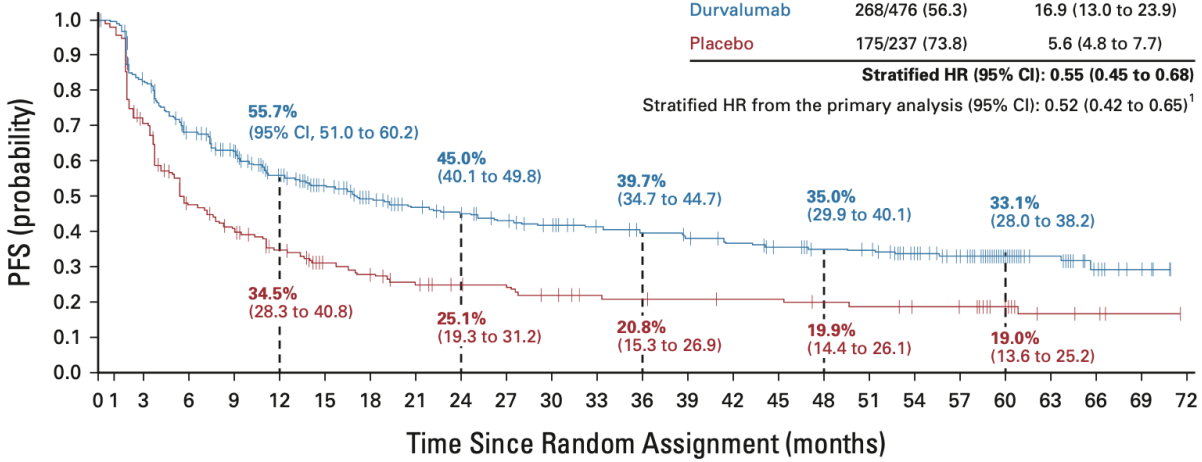
2:1 randomization, stratified by age, sex, and smoking history

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

Placebo
q2w for up to 12 months
N = 237

Primary endpoints
- PFS (BICR) using RECIST v1.1‡
- OS

Key secondary endpoints
- ORR, DoR, and TTDM (BICR) using RECIST v1.1
- Safety
- Patient-reported outcomes



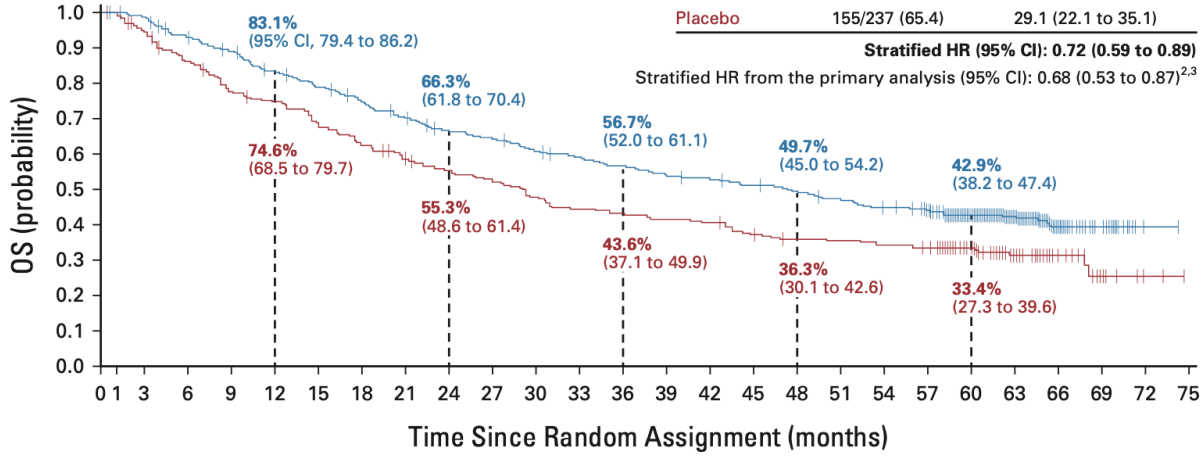
Arm	No. of Events/ Total No. of Patients (%)	Median PFS (95% CI), Months
Durvalumab	268/476 (56.3)	16.9 (13.0 to 23.9)
Placebo	175/237 (73.8)	5.6 (4.8 to 7.7)

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



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)

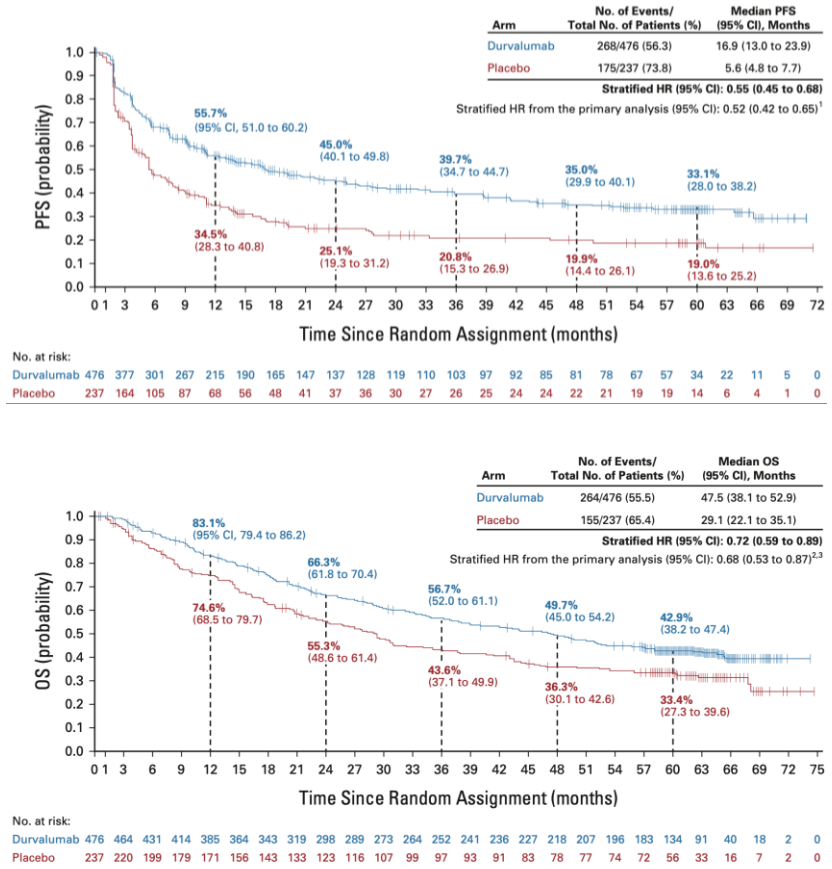
Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]

No. at risk:

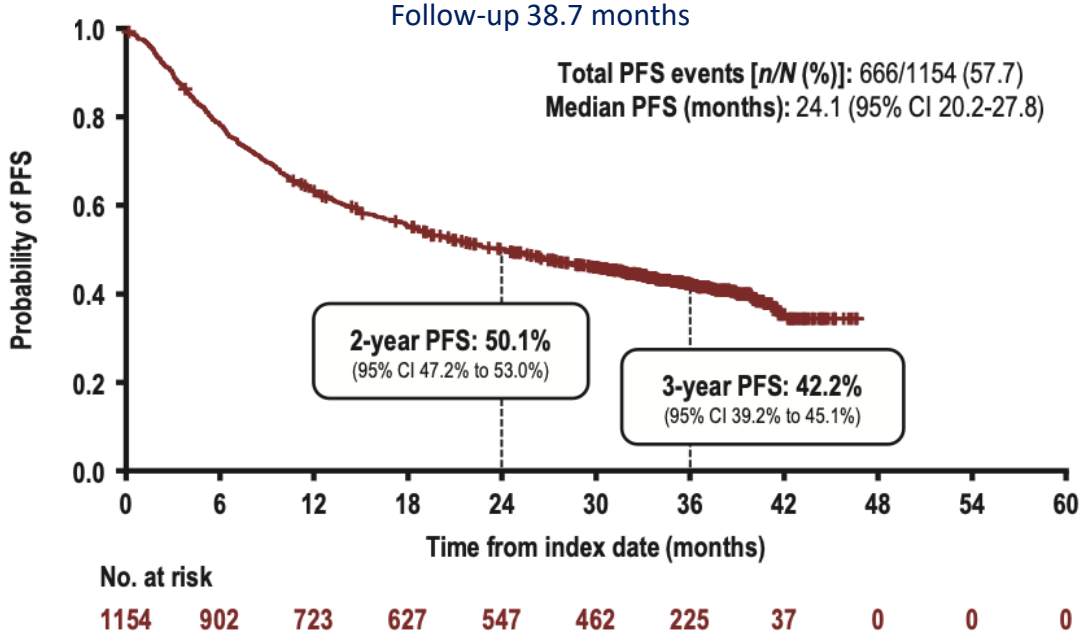
Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

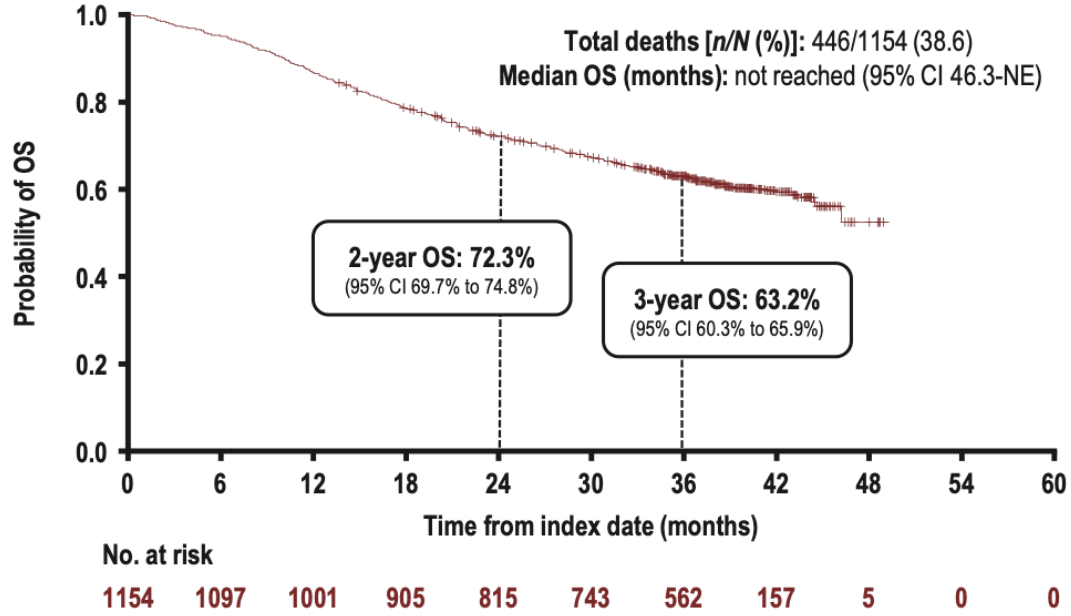
Spigel DR et al. J Clin Oncol, 2022.

PACIFIC: the standard in unresectable LA-NSCLC, also in RW (PACIFIC-R)



Follow-up 38.7 months

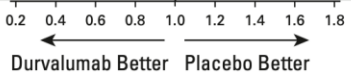


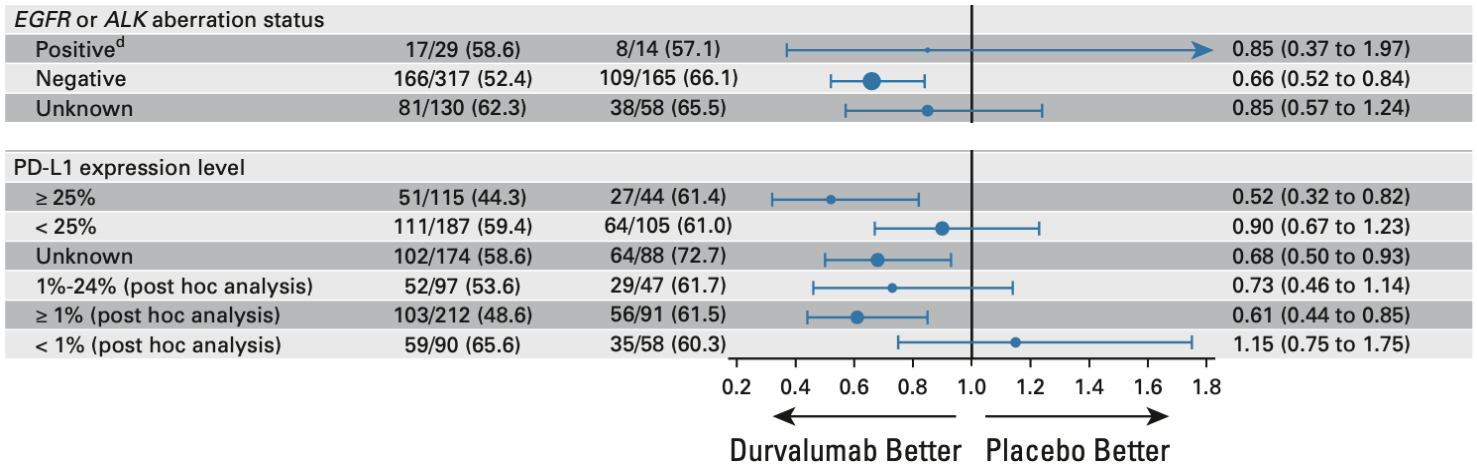


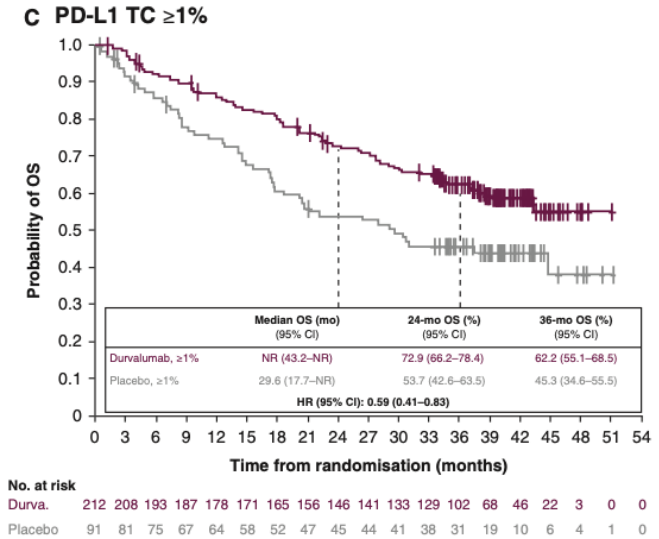
Spigel DR et al. J Clin Oncol, 2022.
Girard N et al. J Thor Oncol, 2023. Filippi AR et al. ESMO Open, 2024.

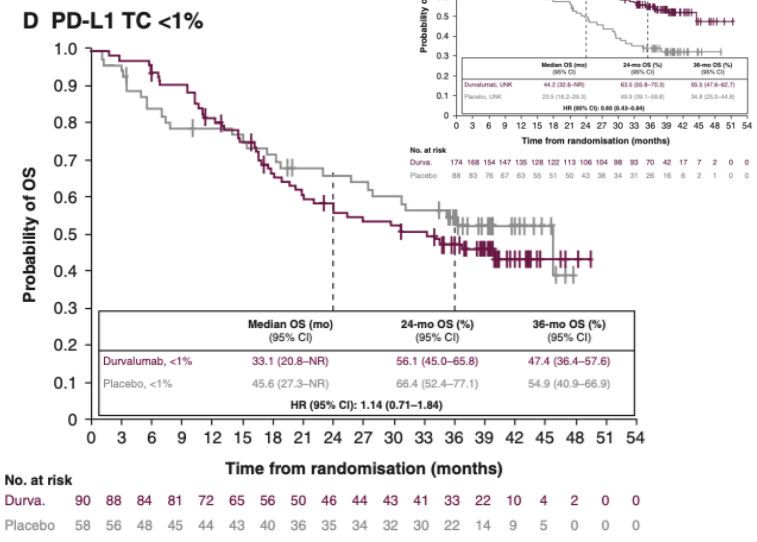
Durvalumab consolidation after CRT: OS benefit across almost all subgroups

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)





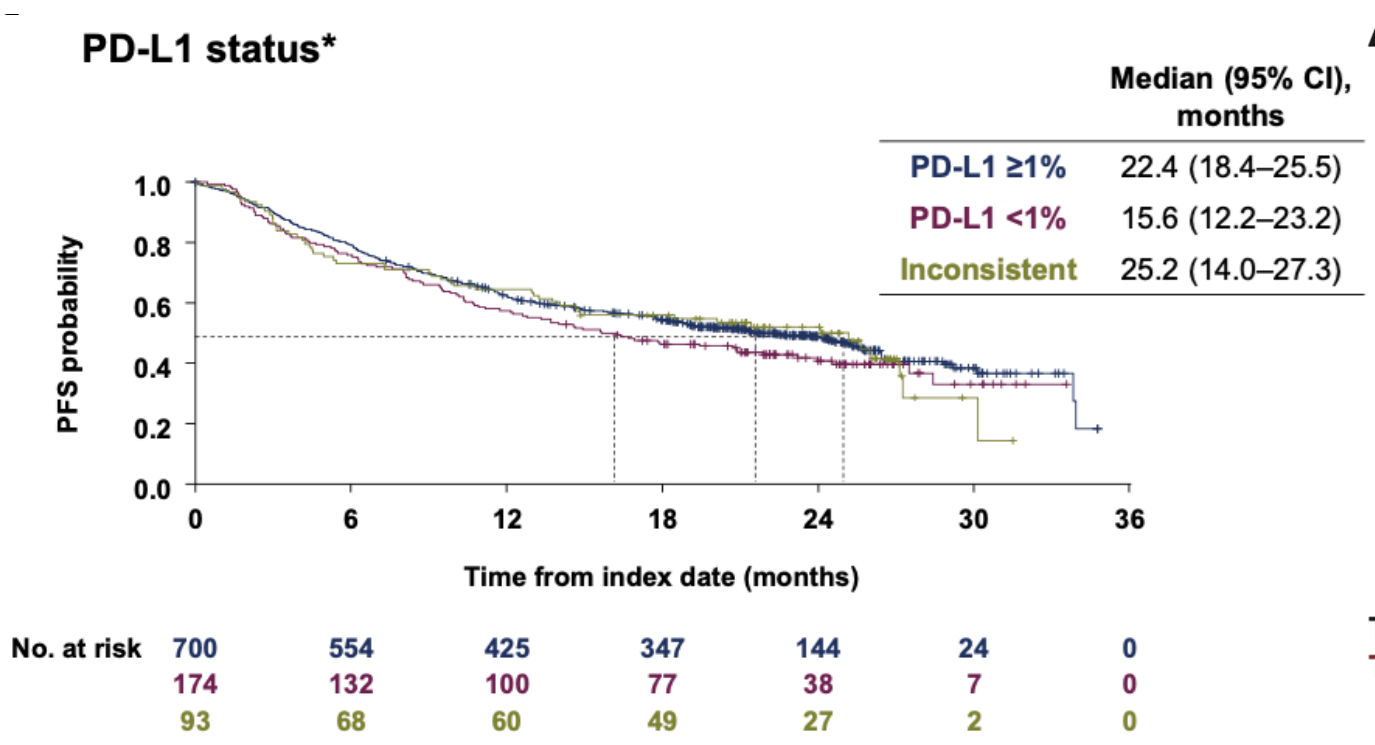


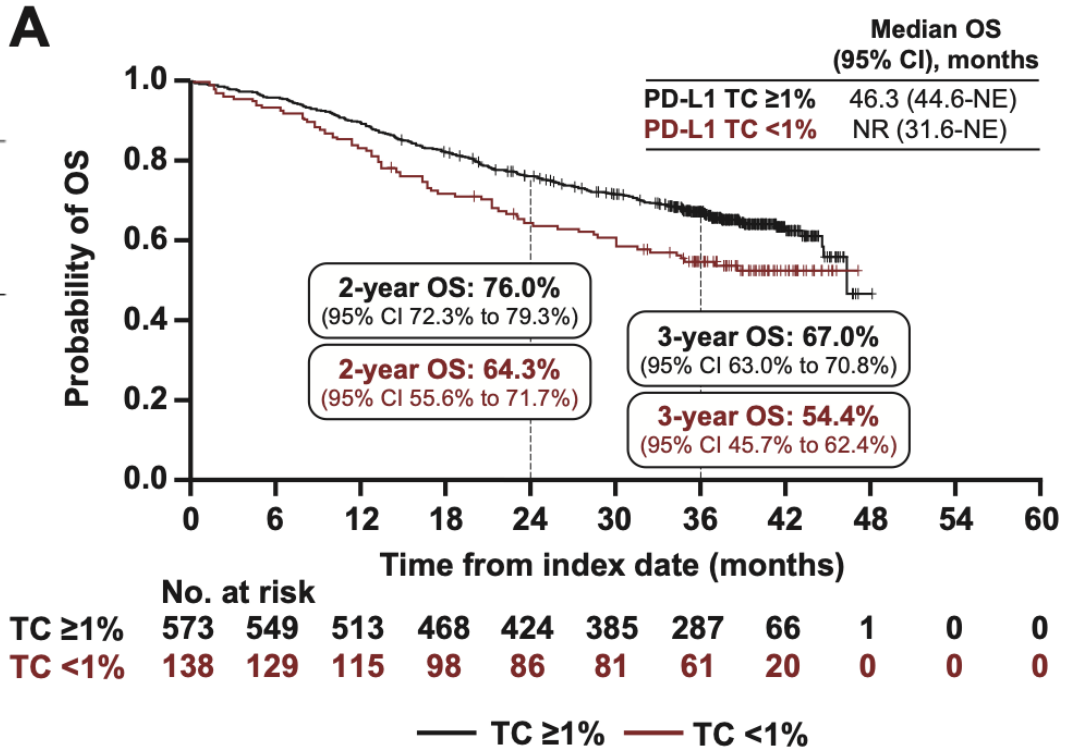


Spigel DR et al. J Clin Oncol, 2022.

Paz-Ares L et al. Ann Oncol, 2020.

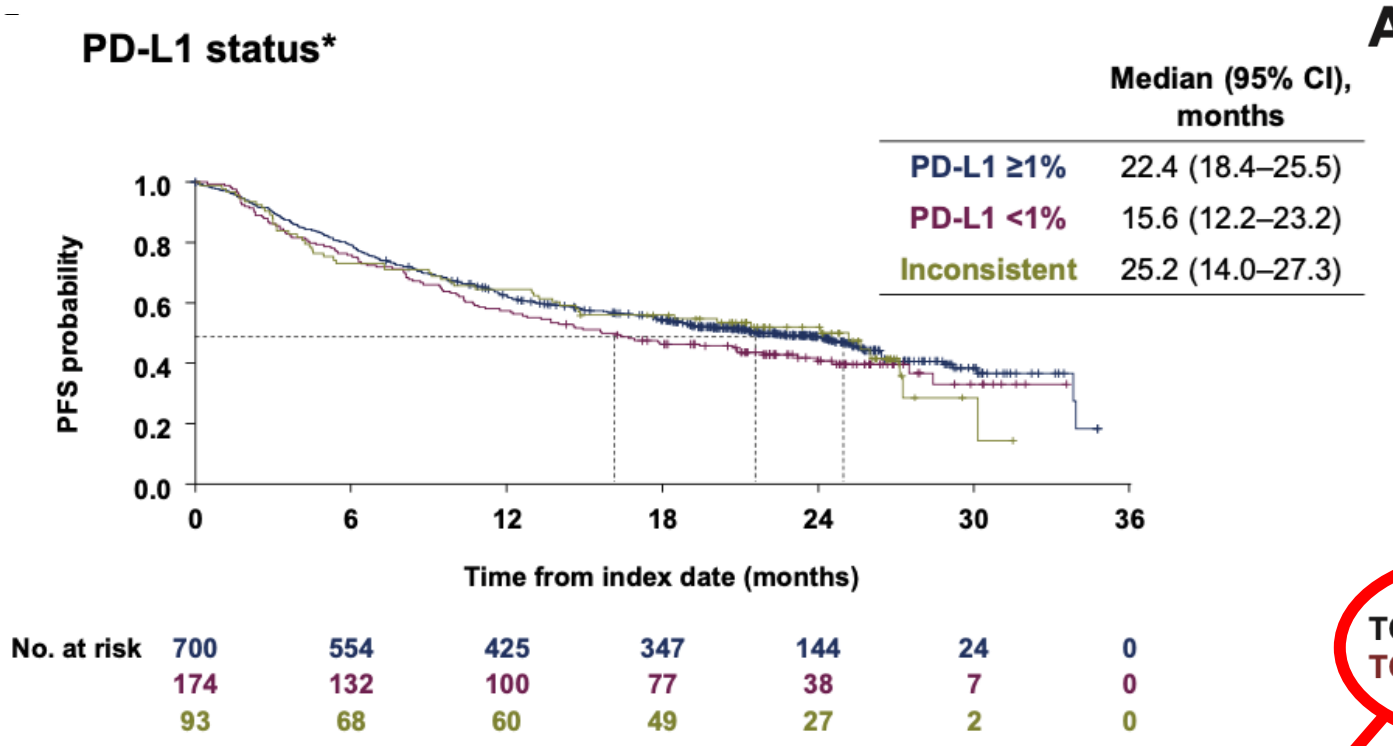
PD-L1 TPS matters also in RW

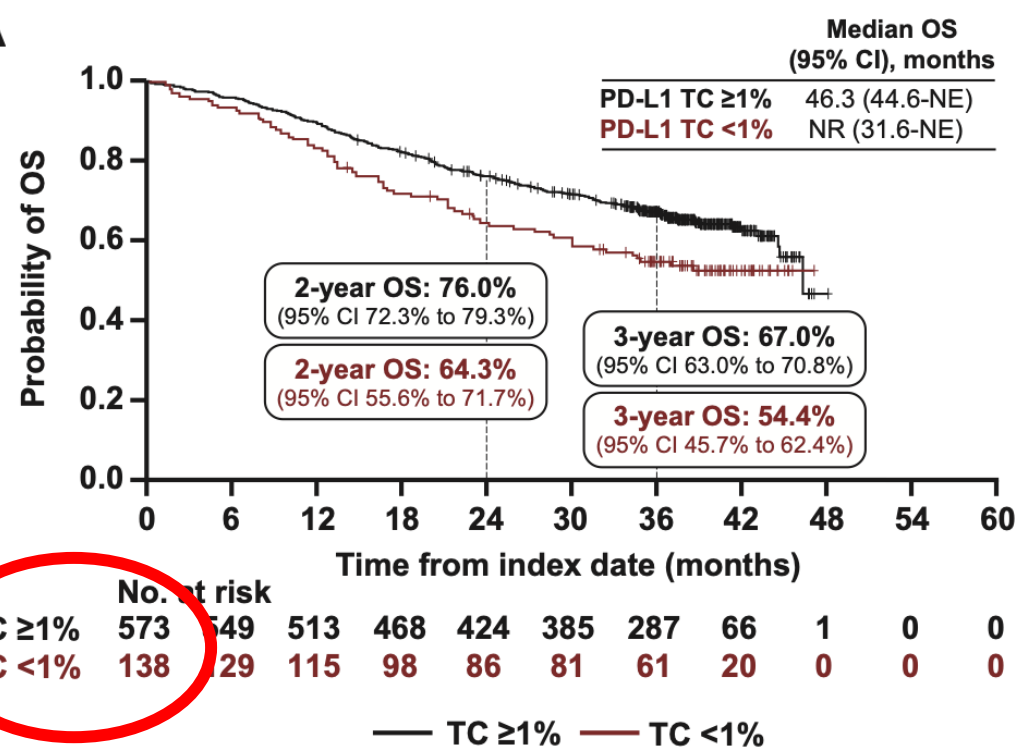




Girard N et al. J Thor Oncol, 2023.
Filippi A et al. ESMO Open, 2024.

Does PD-L1 TPS matter also in RW ?



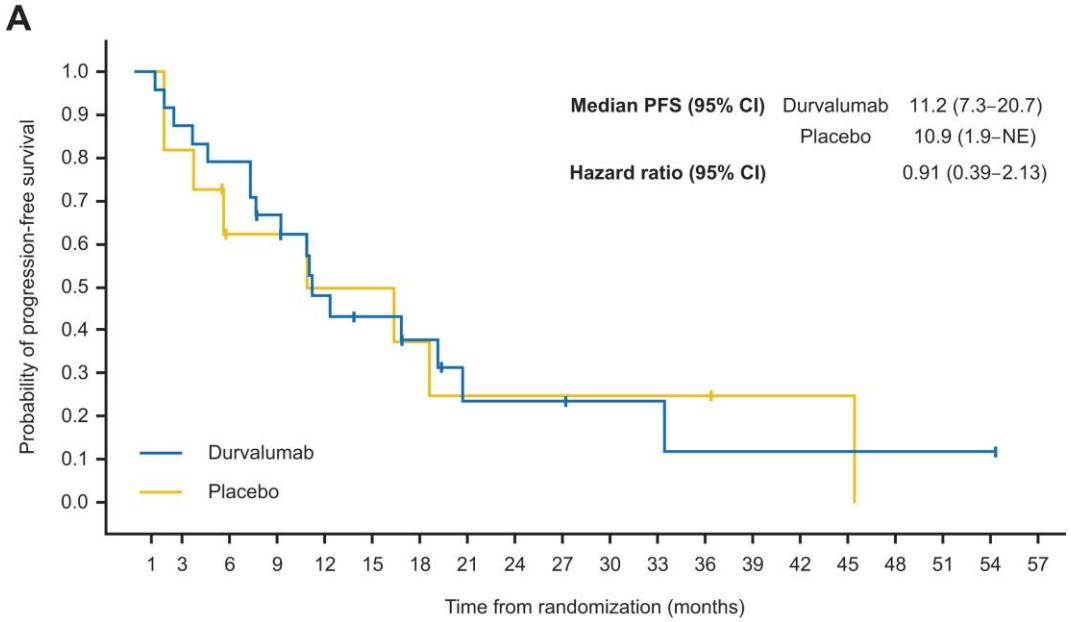


…and the remaining 39%?

PACIFIC: placebo arm 2 yrs OS 55%

Girard N et al. J Thor Oncol, 2023.
Filippi A et al. ESMO Open, 2024.

EGFRm patients should not receive Durvalumab



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
Durvalumab	24	21	19	15	10	8	6	3	3	3	2	2	1	1	1	1	1	1	1	0
Placebo	11	9	5	5	4	4	3	2	2	2	2	2	2	1	1	1	0	0	0	0

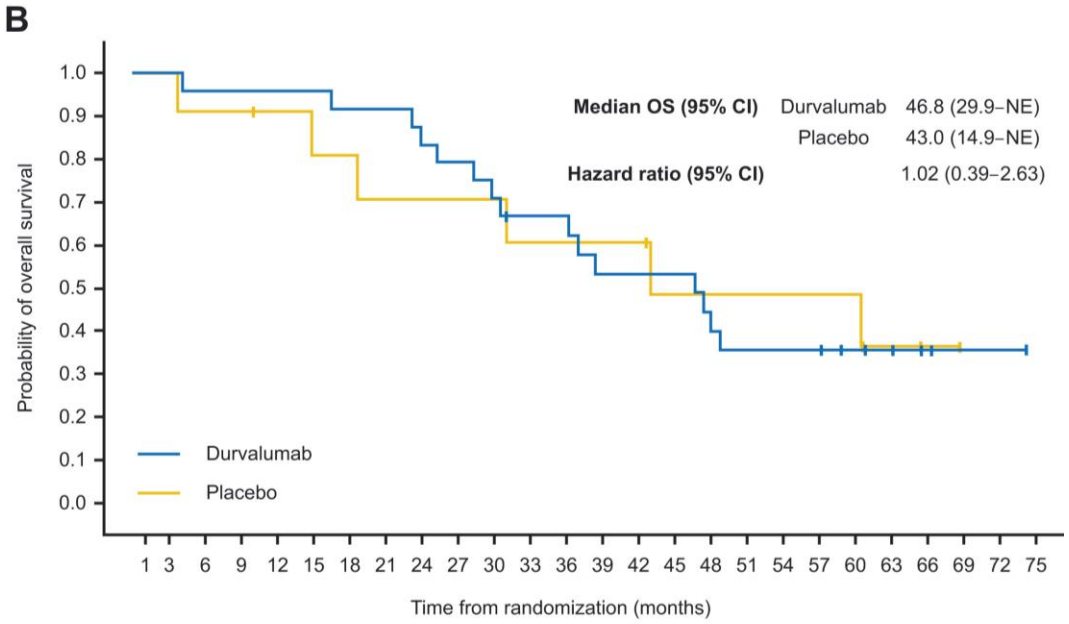
Naidoo J et al. J Thor Oncol, 2023.

ESMO consensus

9: In patients with *EGFR*-mutant inoperable stage III NSCLC, undergoing curative-intent chemoradiotherapy, what is the role of consolidation ICI therapy?

STATEMENT: In *EGFR*-positive disease, the use of consolidation ICI therapy after curative-intent chemoradiotherapy (CT-RT), is not recommended [I,C].

Passaro A et al. Ann Oncol, 2022.



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

Osimertinib: the new standard in unresectable LA-NSCLC EGFRm LAURA phase 3 trial

Patients with locally advanced, unresectable stage III* EGFRm NSCLC with no progression during / following definitive CRT† treatment

Key inclusion criteria:
- ≥18 years (Japan: ≥20)
- WHO PS 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Maximum interval between last dose of CRT and randomization: 6 weeks

Osimertinib 80 mg, once daily

Randomization 2:1 (N=216)

Stratification by:
Concurrent vs sequential CRT
Stage IIIA vs stage IIIB/IIIC
China vs non-China

Placebo, once daily

Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria

Open-label osimertinib after BICR-confirmed progression offered to both treatment arms§

Tumor assessments:
- Chest CT / MRI and brain MRI
- At baseline, every 8 weeks to Week 48, then every 12 weeks until BICR-assessed progression

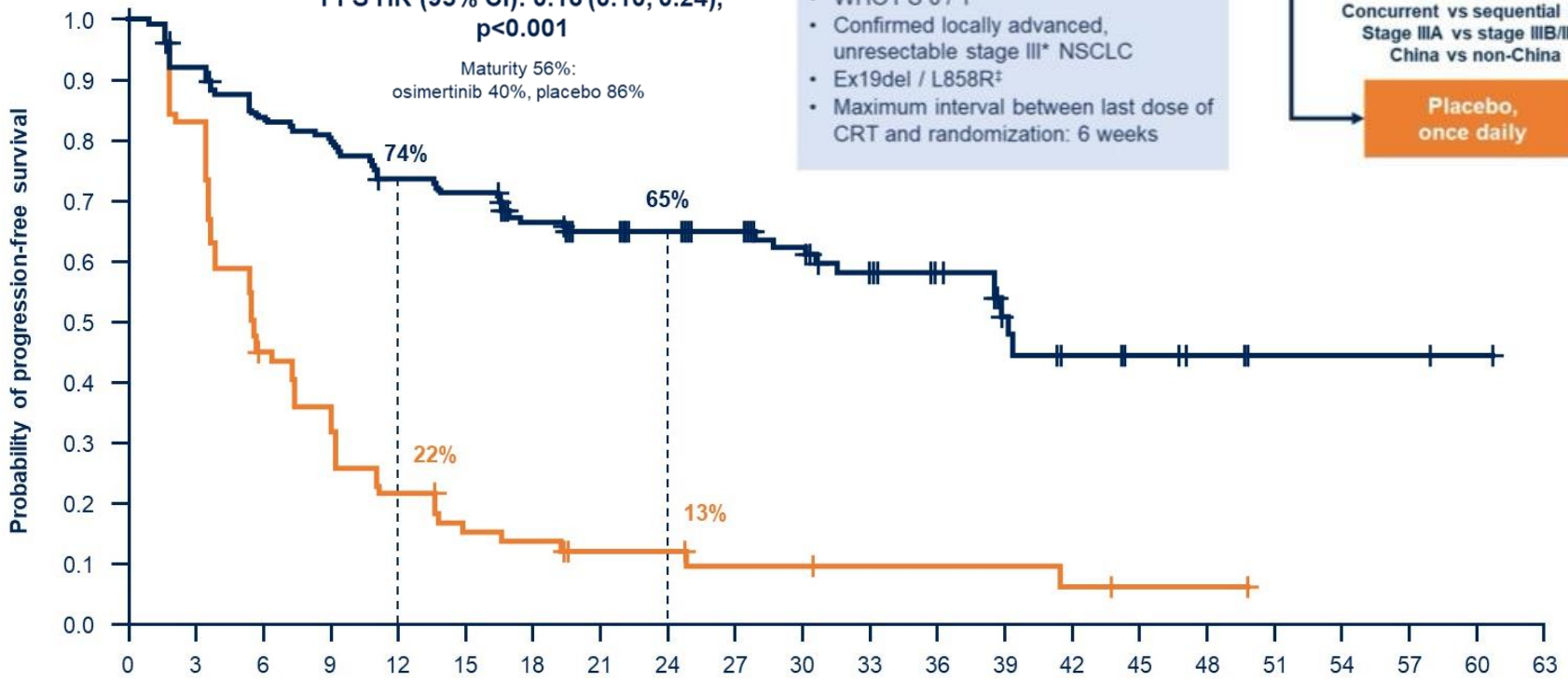
BIRC

Median PFS, months (95% CI)

Osimertinib	39.1 (31.5, NC)
Placebo	5.6 (3.7, 7.4)

PFS HR (95% CI): 0.16 (0.10, 0.24), p<0.001

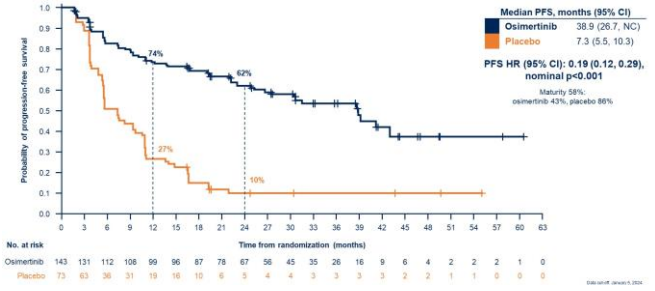
Maturity 56%:
osimertinib 40%, placebo 86%



No. at risk

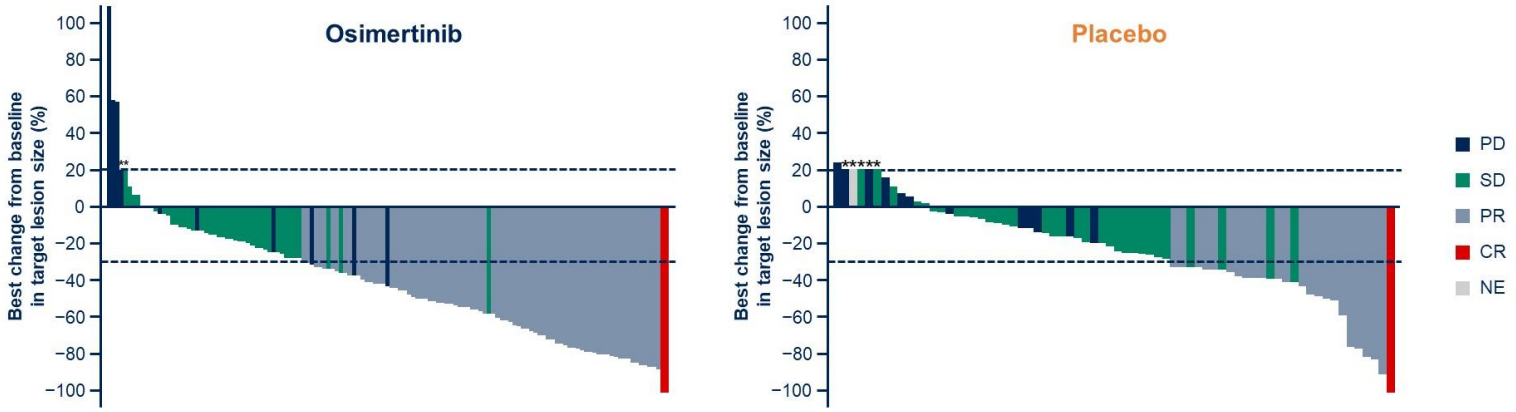
Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Investigators

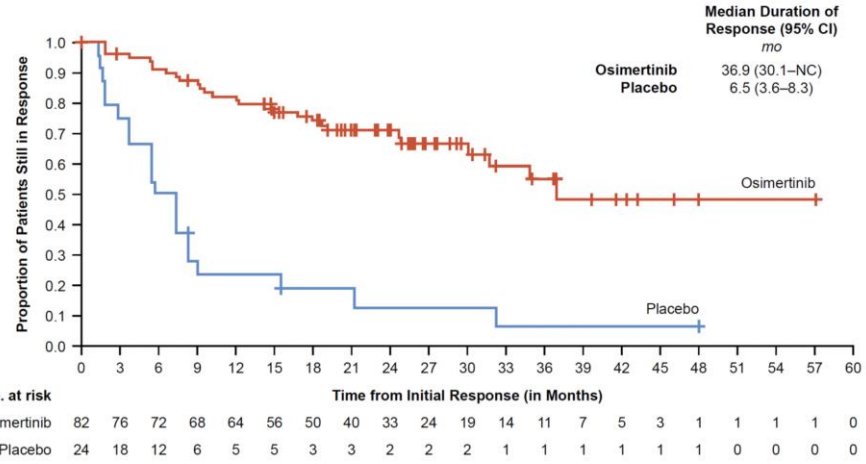


Ramalingam SS. ASCO, 2024.
Lu S et al. N Eng J Med, 2024.

LAURA: secondary efficacy endpoints



	Osimertinib (n=143)	Placebo (n=73)
Objective response rate, % (95% CI)	57 (49, 66)	33 (22, 45)
Disease control rate, % (95% CI)	89 (83, 94)	79 (68, 88)
Median duration of response, months (95% CI)	36.9 (30.1, NC)	6.5 (3.6, 8.3)

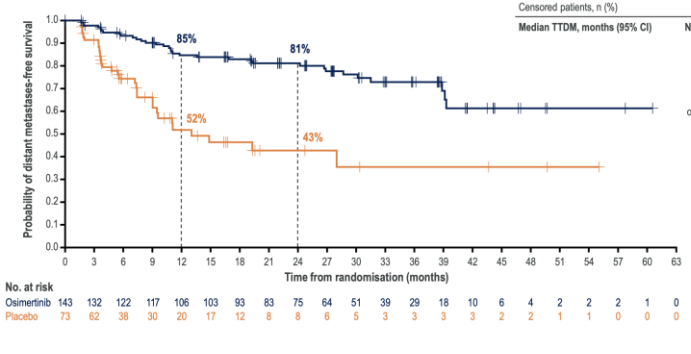


- Clinically meaningful improvement in TTDM with osimertinib vs placebo

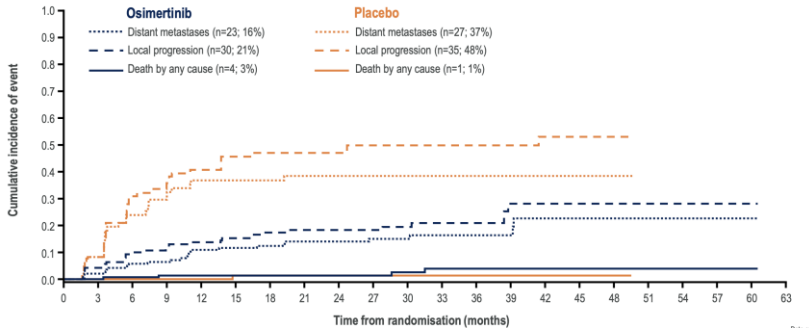
	Osimertinib (n=143)	Placebo (n=73)
Total TTDM events, n (%)	33 (23)	31 (42)
Censored patients, n (%)	110 (77)	42 (58)
Median TTDM, months (95% CI)	NR (39.3, NC)	13.0 (9.0, NC)

HR: 0.21 (0.11, 0.38), p<0.001 (nominal)

Maturity 30%: osimertinib 23%, placebo 42%

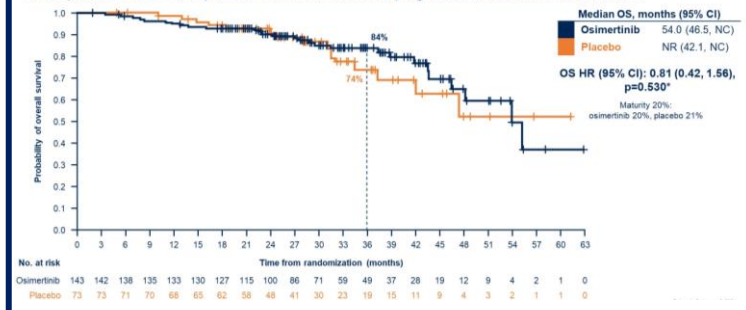


- Cumulative incidence* of distant metastases was consistently lower with osimertinib vs placebo
- The cumulative incidence* rate of distant metastases at 12 months was 11% (95% CI 6, 17) with osimertinib vs 37% (95% CI 26, 48) with placebo



OS

In the placebo arm, 81% of patients with BICR-confirmed progression crossed over to osimertinib



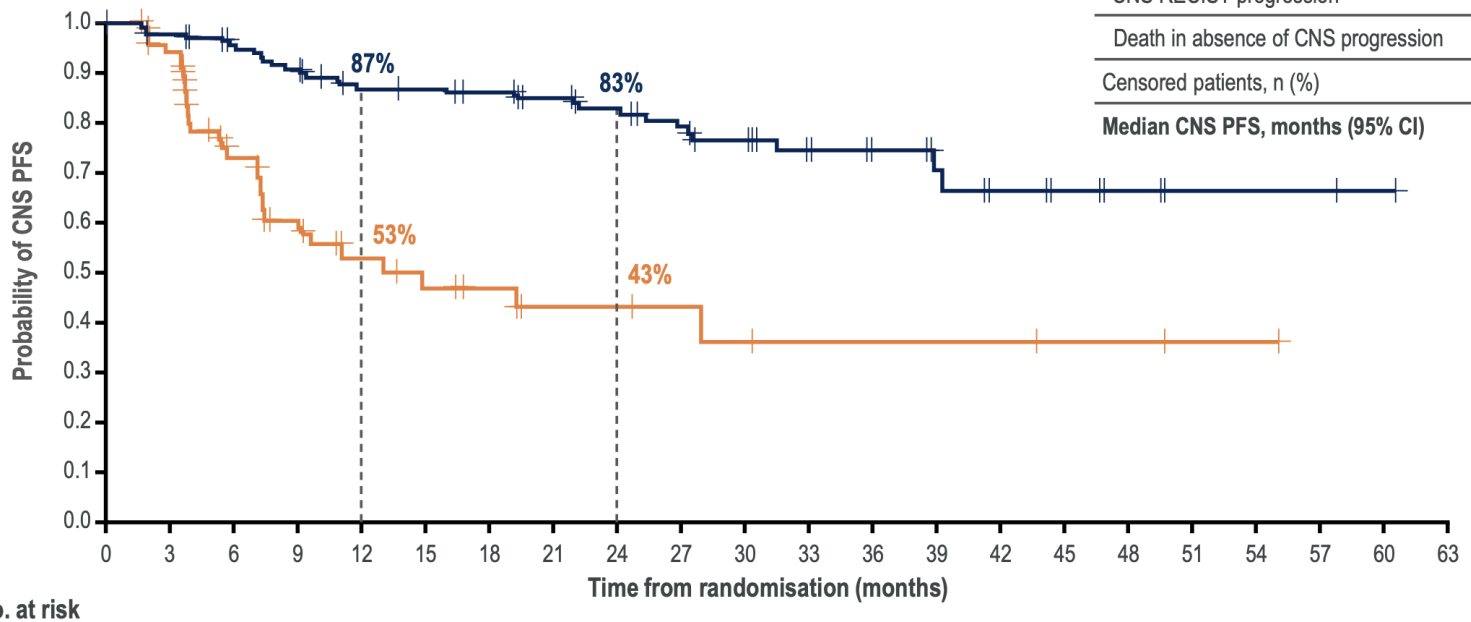
Ramalingam SS. ASCO, 2024. Lu S et al. N Eng J Med, 2024. Lu S. ESMO, 2024.

LAURA: CNS activity

- Reduced risk of CNS progression or death with osimertinib vs placebo

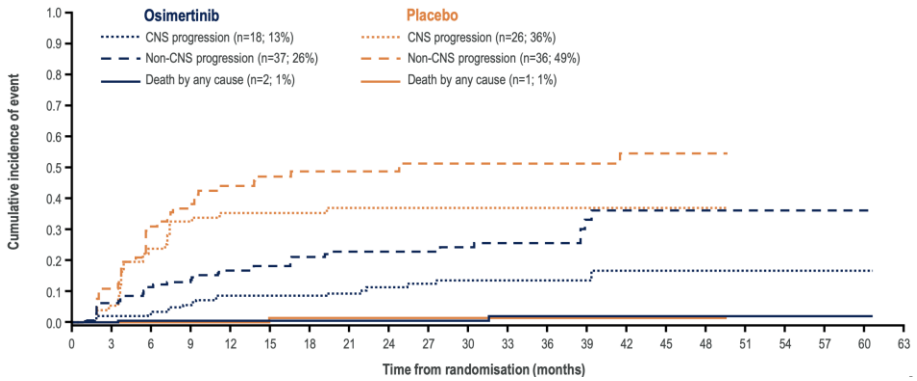
	Osimertinib (n=143)	Placebo (n=73)
Total CNS PFS events, n (%)†	29 (20)	30 (41)
CNS RECIST progression‡	18 (13)	26 (36)
Death in absence of CNS progression	11 (8)	4 (5)
Censored patients, n (%)	114 (80)	43 (59)
Median CNS PFS, months (95% CI)	**NR (NC, NC)**	**14.9 (7.4, NC)**

HR: 0.17 (0.09, 0.32), p<0.001 (nominal)



No. at risk

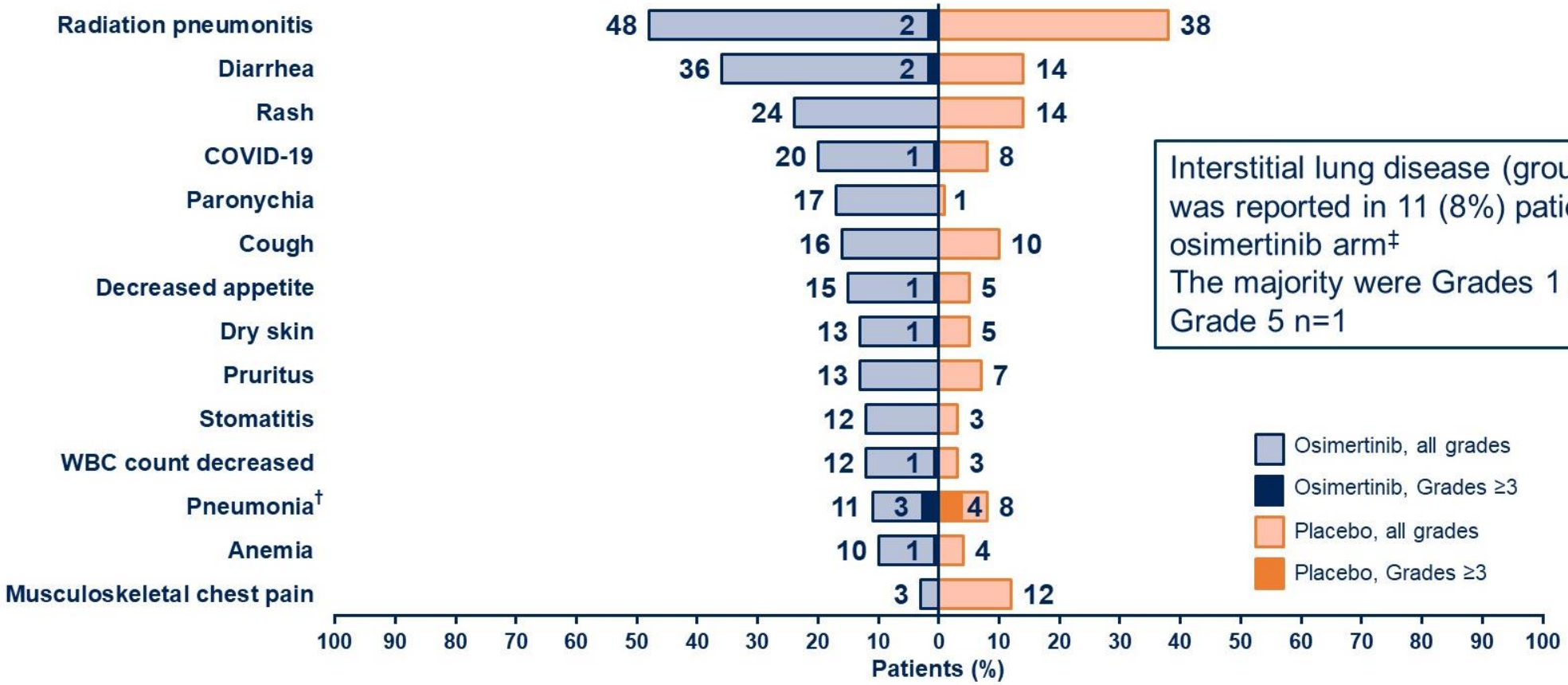
Osimertinib	143	130	121	115	105	104	94	84	74	63	49	37	28	17	9	6	4	2	2	2	1	0
Placebo	73	63	36	26	19	16	12	8	8	6	5	3	3	3	3	2	2	1	1	0	0	0



Lu S. ESMO, 2024.

All-causality adverse events (≥10%)*

- The most common AE in both arms was radiation pneumonitis; the majority were low grade (no Grade 4 / 5), non-serious and manageable



Interstitial lung disease (grouped term) was reported in 11 (8%) patients in the osimertinib arm‡
The majority were Grades 1 / 2; Grade 5 n=1

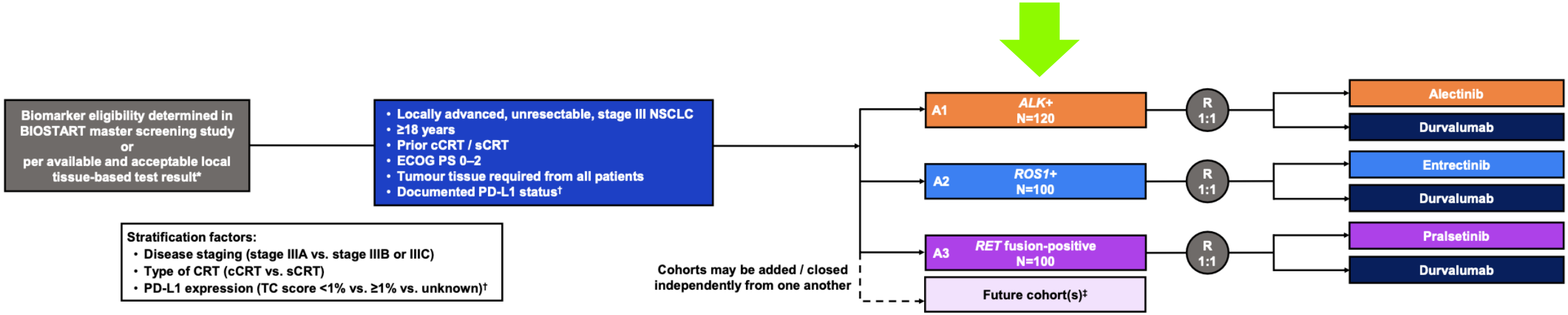
Data cut-off: January 5, 2024.

*AEs with incidence of 10% or more in either treatment arm are shown. Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy; †One grade 5 AE of pneumonia was reported in the osimertinib arm; ‡Interstitial lung disease (grouped term) was reported in 1 patient (1%) in placebo arm; AE was pneumonitis, Grade 1.

AE, adverse event; WBC, white blood cells

Ramalingam SS. ASCO, 2024. Lu S et al. N Eng J Med, 2024.

HORIZON-01: not only EGFR in unresectable LA-NSCLC



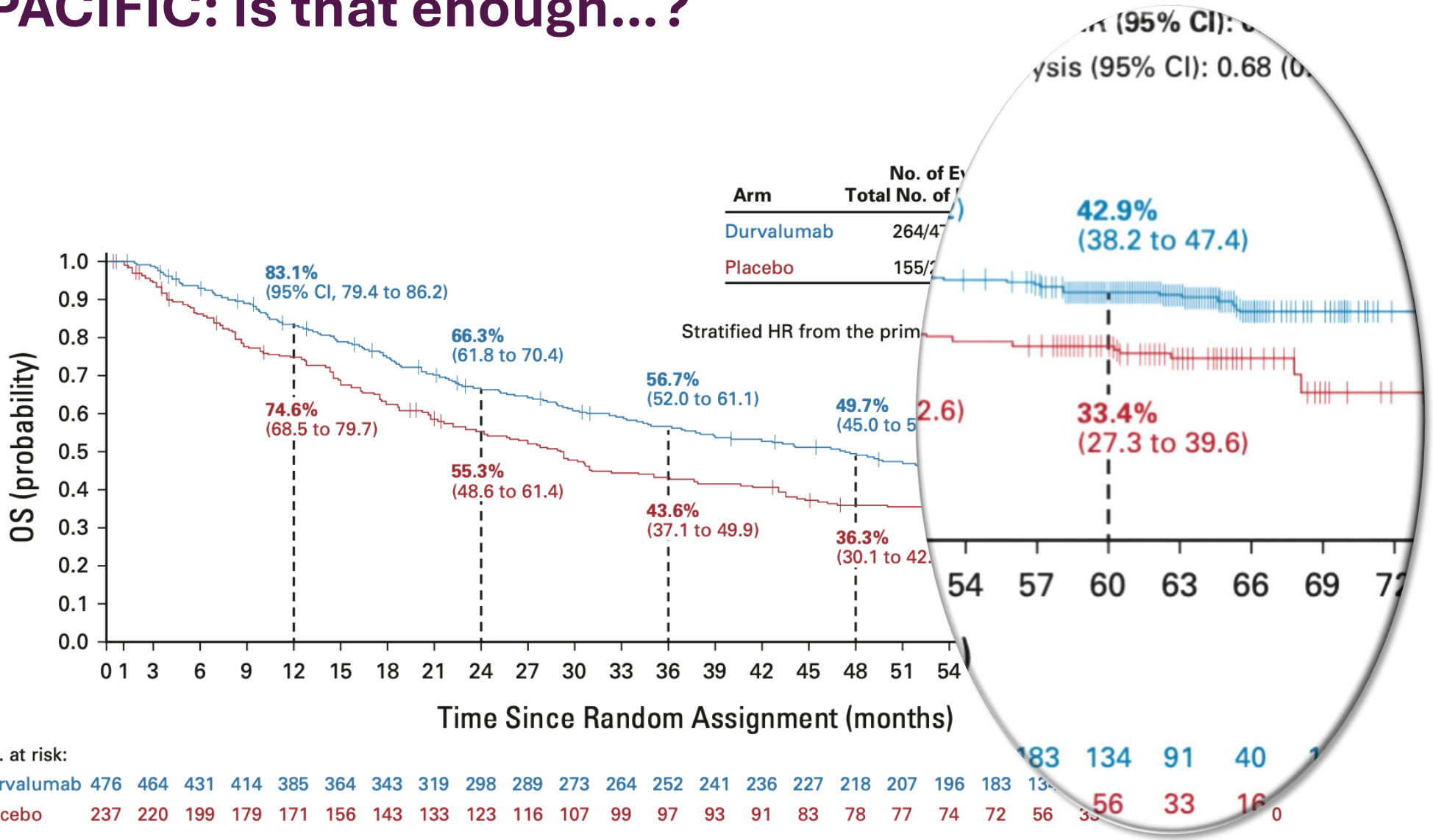
ALK

Recruiting at

IRCCS "Giovanni Paolo II"
PugliaSalute

Paz-Ares L. ELCC, 2023

PACIFIC: is that enough...?



57.1% patients dead at 5 years

Strategies to improve survival

IO concomitant cCRT

- PACIFIC-2
- CheckMate 73L
- KEYLINK-012

IO-IO strategy

- COAST
- PACIFIC-9
- SKYSCRAPER-03
- PACIFIC-8

Induction IO – IO concomitant cCRT

- AZT-16
- APOLO
- PACIFIC-Brazil
- DEDALUS

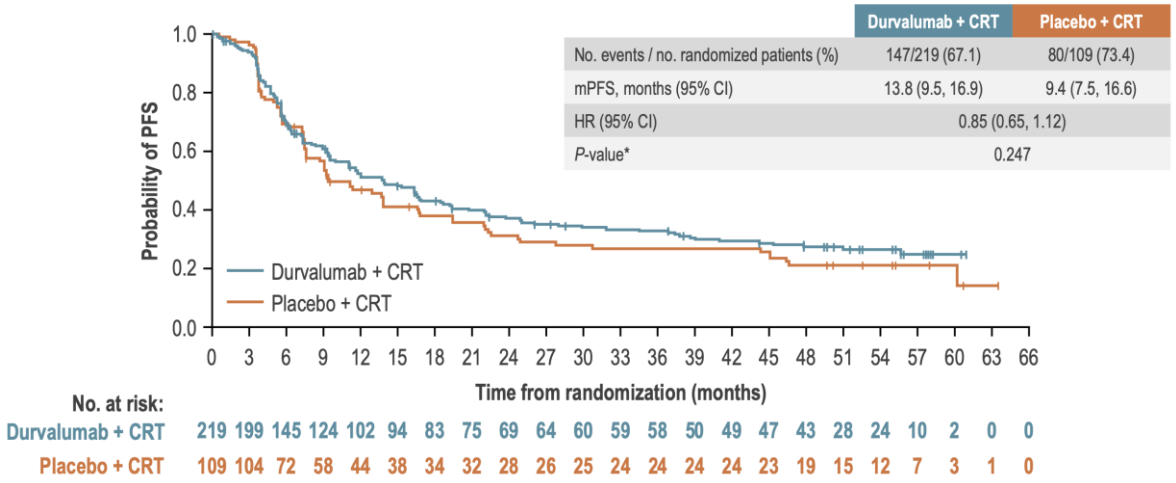
Special populations

- DUART
- DEDALUS

Move immunotherapy earlier: concomitant with cCRT

Trial	Phase	Treatment	G≥3 pneumonitis	ORR	1 yr PFS	Median PFS
PACIFIC	III	Durvalumab consolidation	3.4%	28.4%	55.3 mo	17.2 mo
Deterred	II	Atezolizumab concomitant/consolidation	6.7%	-	> 50%	13.2 mo
Nicolas	II	Nivolumab concomitant/consolidation	6.7%	73.4%	53.7%	12.7 mo
KEYNOTE-799	II	Pembrolizumab concomitant/consolidation	8 – 5.5%	67-56.6%	81.4-85.2% (6 mo)	-

PACIFIC 2



CHECKMATE 73L

Bristol Myers Squibb

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Bristol Myers Squibb Provides Update on Phase 3 CheckMate -73L Trial

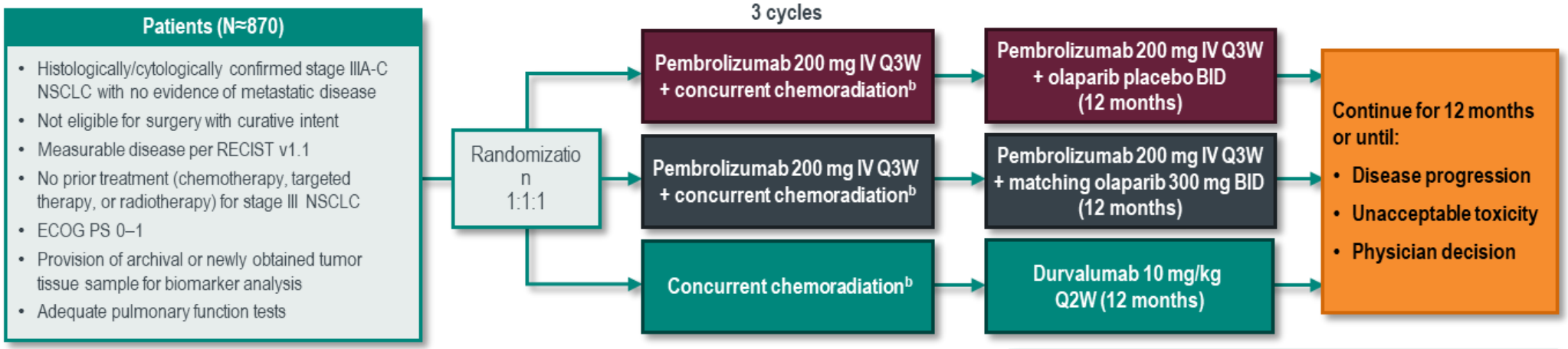
05/10/2024

CATEGORY: Corporate/Financial News

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced the Phase 3 CheckMate -73L trial did not meet its primary endpoint of progression-free survival (PFS) in unresectable, locally advanced stage III non-small cell lung cancer (NSCLC). CheckMate -73L evaluated *Opdivo*® (nivolumab) with concurrent chemoradiotherapy (CCRT) followed by *Opdivo* plus *Yervoy*® (ipilimumab) versus CCRT followed by durvalumab in patients with unresectable stage III NSCLC. The observed adverse events of *Opdivo* with CCRT followed by *Opdivo* plus *Yervoy* were generally consistent with the known profiles of each component in the regimen.

Move immunotherapy earlier: concomitant with cCRT

Phase III KEYLYNK-012 (NCT04380636)



Estimated primary completion: July 6, 2026[d]

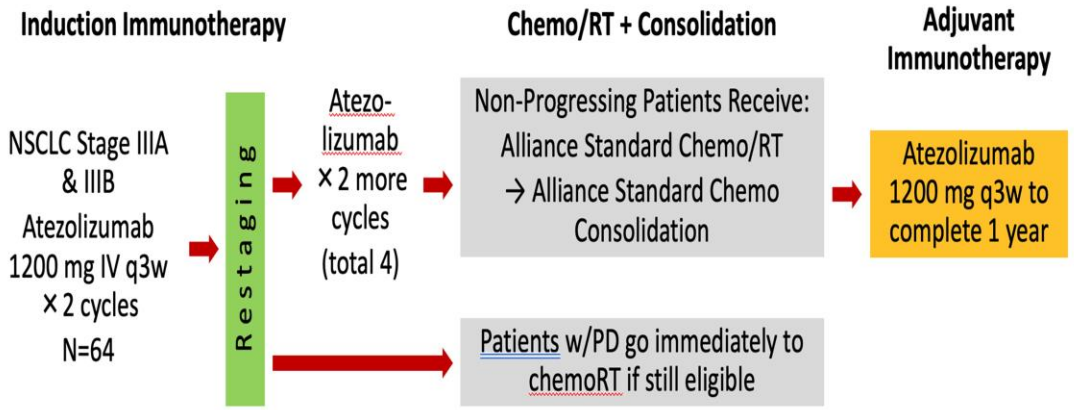
[a]Stratification occurs at randomization. [b]Platinum doublet chemotherapy and concurrent standard thoracic radiotherapy (60 Gy in 2 Gy fractions; during cycles 2 and 3). Platinum doublet options (per investigator's choice) include cisplatin + pemetrexed (NSQ histology only), cisplatin + etoposide, and carboplatin + paclitaxel. [c]Assessed per RECIST v1.1 by BICR. [d]Subject to change.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04380636. Accessed: February 24, 2021. **2.** Jabbour et al. Presented at EMSO 2020. Abstract 1256TiP.

Move immunotherapy earlier: induction

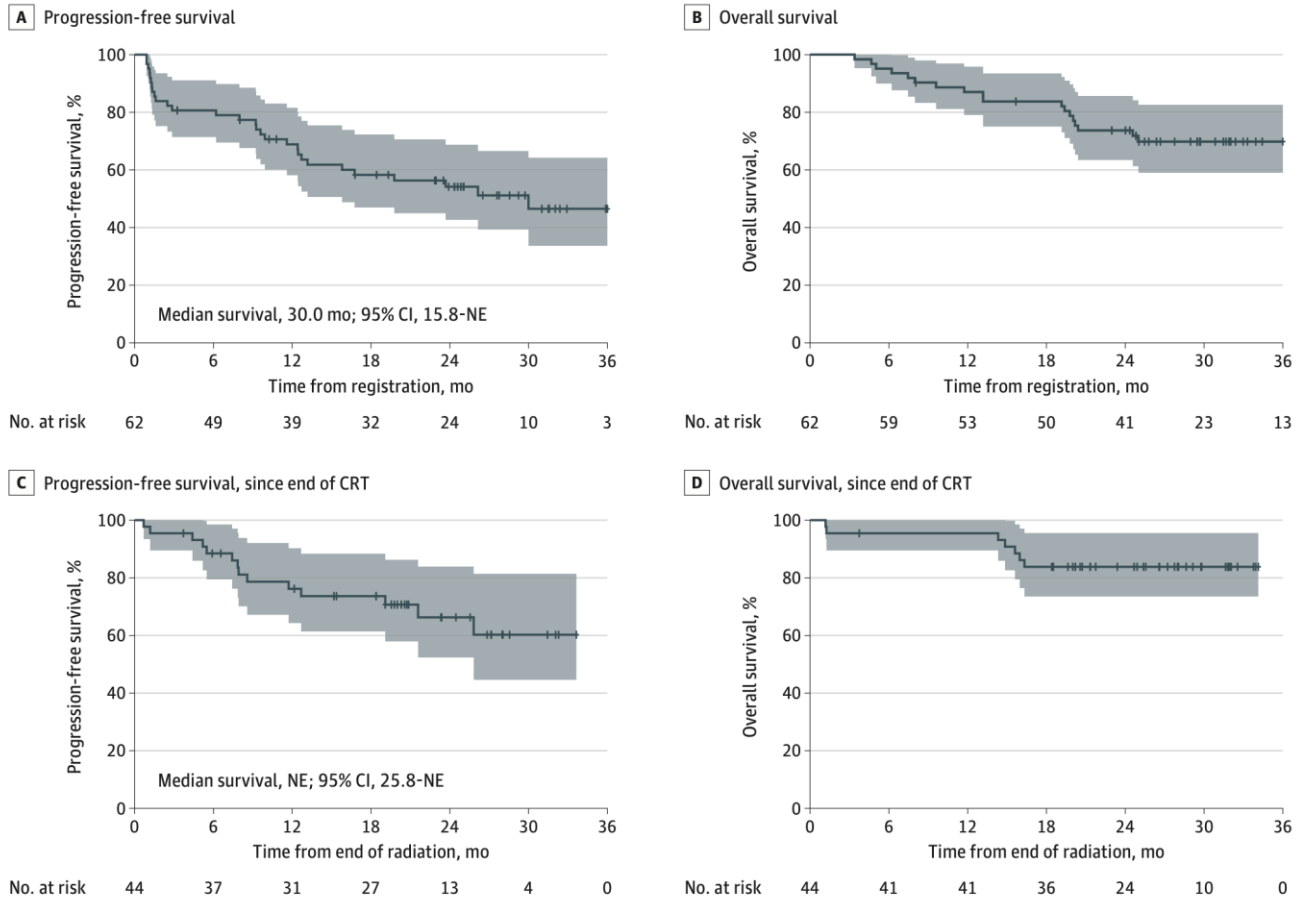
Alliance Foundation Trial (AFT)-16

Atezolizumab Before and After Chemoradiation for Unresectable Stage III Non–Small Cell Lung Cancer A Phase II Nonrandomized Controlled Trial



- 64 pts with unresectable stage III NSCLC, PS 0-1, no active autoimmune disease or significant organ dysfunction enrolled at 13 ALLIANCE sites from 11/2017 to 7/2019.
- 62 pts receiving at least 1 dose of atezolizumab are included in this analysis.

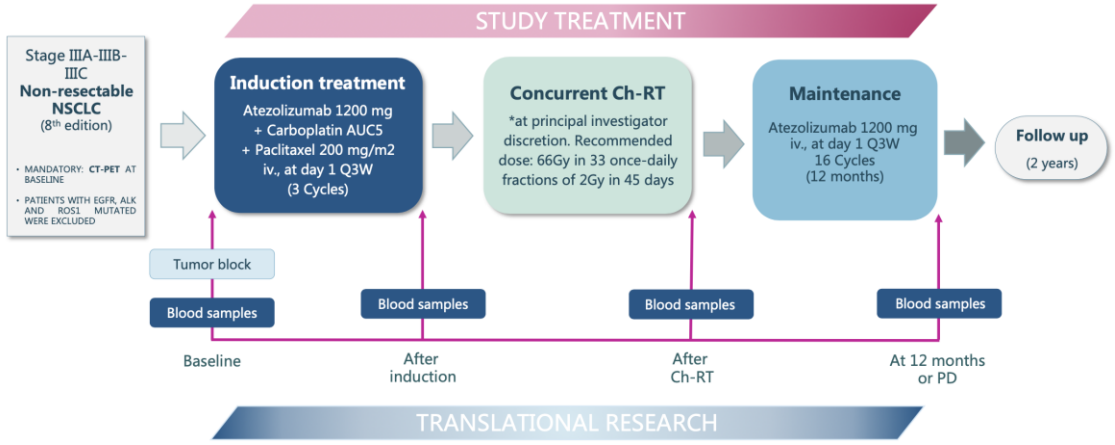
Primary EP:
DCR at 12 weeks (at least 67%): 74.2%

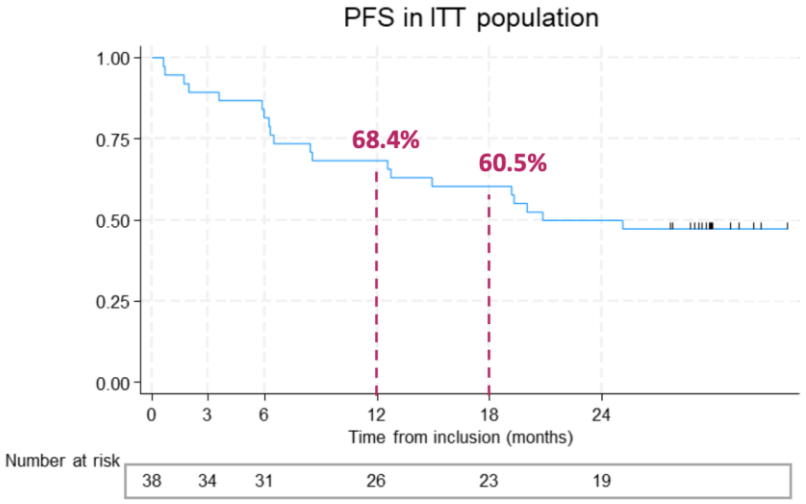


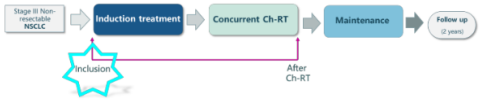
Ross HJ et al. Jama Oncol, 2024.

Move immunotherapy earlier: induction

APOLO, phase II trial: Atezolizumab + induction chemotherapy (Ch) + chemo-radiotherapy (Ch-RT) and atezolizumab maintenance in non-resectable stage IIIA-IIIB-IIIC NSCLC



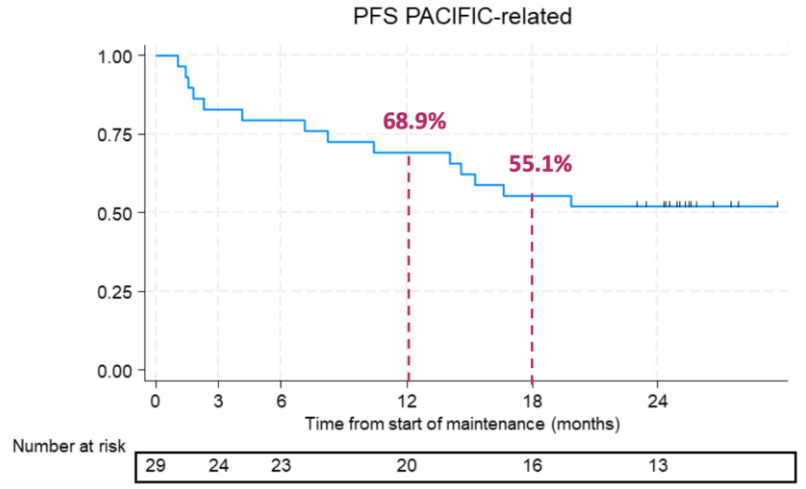




PFS 20.8 (95%CI 12.6; NR) months.

PFS in ITT population was **68.4%** (95%CI: 51.1-80.6%) **at 12 months** and **60.5%** (95%CI: 43.3-74%) **at 18 months.**

Median for follow-up: 29.6 months (95%CI: 28.8-29.8)



PFS from the start of maintenance treatment starting time in ITT population was **68.9%** (95%CI: 48.8-82.4%) **at 12 months** and **55.1%** (95%CI: 35.6-71%) **at 18 months.**

Median for follow-up: 29.6 months (95%CI: 28.8-29.8)

Provencio M. WCLC, 2024.

Move immunotherapy earlier: induction/concomitant

Intensified chemo-immuno-radiotherapy with durvalumab: a single arm phase II study PACIFIC-BRAZIL (LACOG 2218)

ELIGIBILITY CRITERIA

- ✓ Non-small cell lung cancer
- ✓ Stage III (TNM 8th ed.)†
- ✓ PS 0-1
- ✓ FEV1 ≥ 1.2 liters/second (or ≥ 50% predicted value)
- ✓ Predicted lung V20 <35%, cardiac V50 ≤25%
- ✓ No previous local or systemic therapy

INDUCTION CHEMO-IMMUNOTHERAPY

Carboplatin AUC 6 IV+
Paclitaxel 200mg/m² IV+
Durvalumab 1500mg/m² IV q3w for 2 cycles

CONCURRENT CHEMO-IMMUNO-RADIOTHERAPY

Carboplatin AUC 2 IV weekly for 6 weeks +
Paclitaxel 50 mg/m² IV weekly for 6 weeks +
Durvalumab 1500mg/m² q3w for 2 cycles +
Intensity-modulated radiation therapy to 60 Gy in 30 fractions over 6 weeks‡

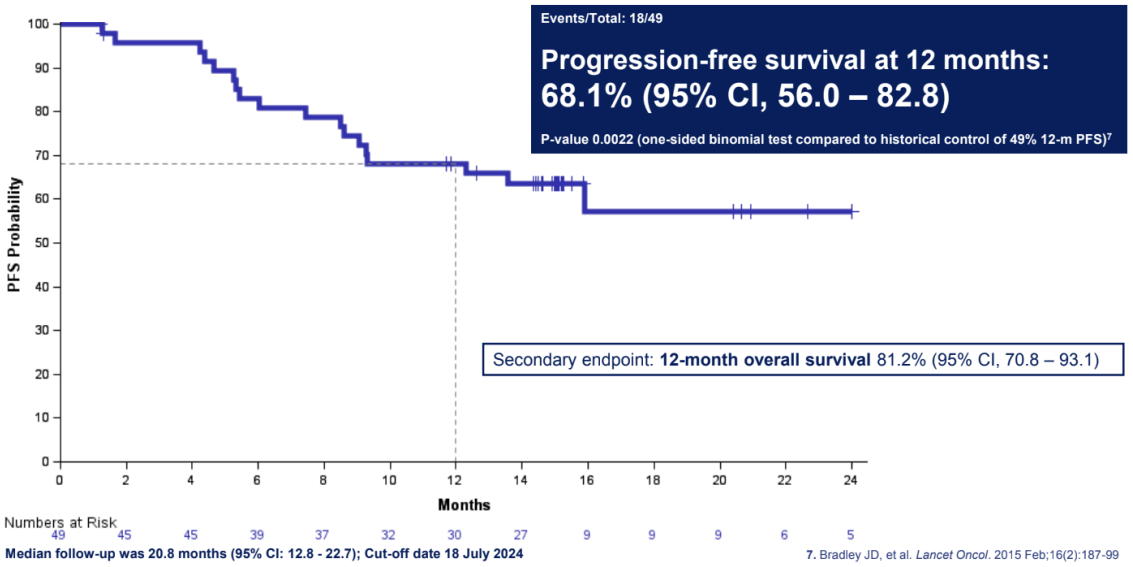
CONSOLIDATION IMMUNOTHERAPY

Durvalumab 1500mg/m² IV q4w for 12 cycles

PRIMARY ENDPOINT: 12-month progression-free survival

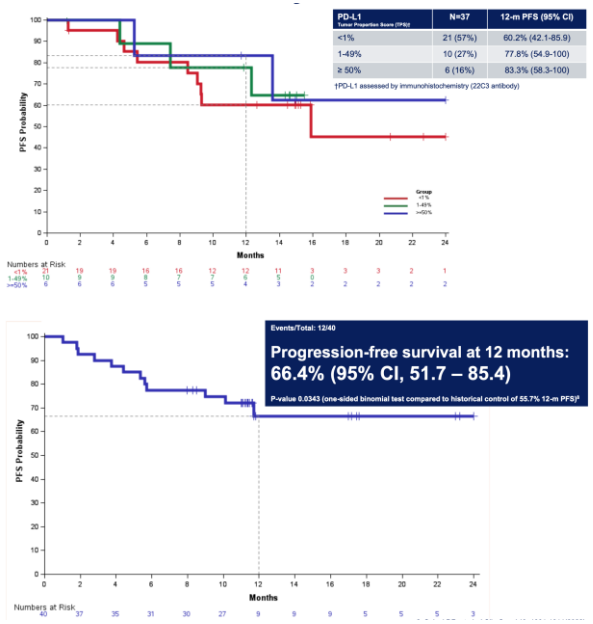
SECONDARY ENDPOINTS: Overall survival, overall response rate, duration of response, patterns of failure, efficacy (iRECIST as opposed to RECIST version 1.1), toxicity (CTCAE version 5)

EXPLORATORY ENDPOINTS: Predictive biomarkers of response/survival



Median follow-up was 20.8 months (95% CI: 12.8 - 22.7); Cut-off date 18 July 2024

7. Bradley JD, et al. *Lancet Oncol*. 2015 Feb;16(2):187-99



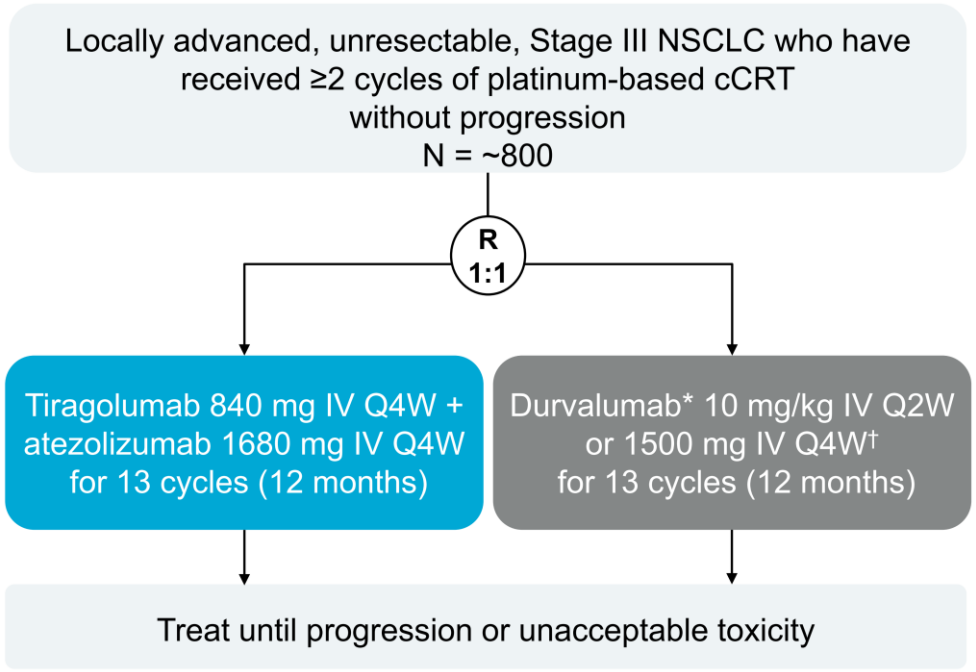
Pneumonitis: 27%

Penumonitis ≥G3: 14%

William WN. WCLC, 2024.

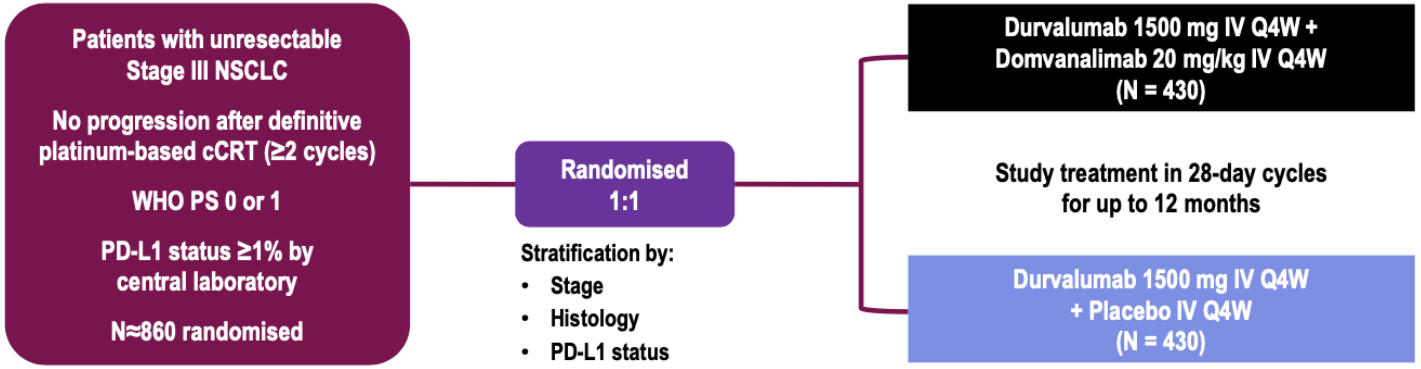
Adding IO: IO-IO strategy (TIGIT + PD1/PD-L1)

SKYSCRAPER-03



Dziadziuszko R, ESMO 2021.

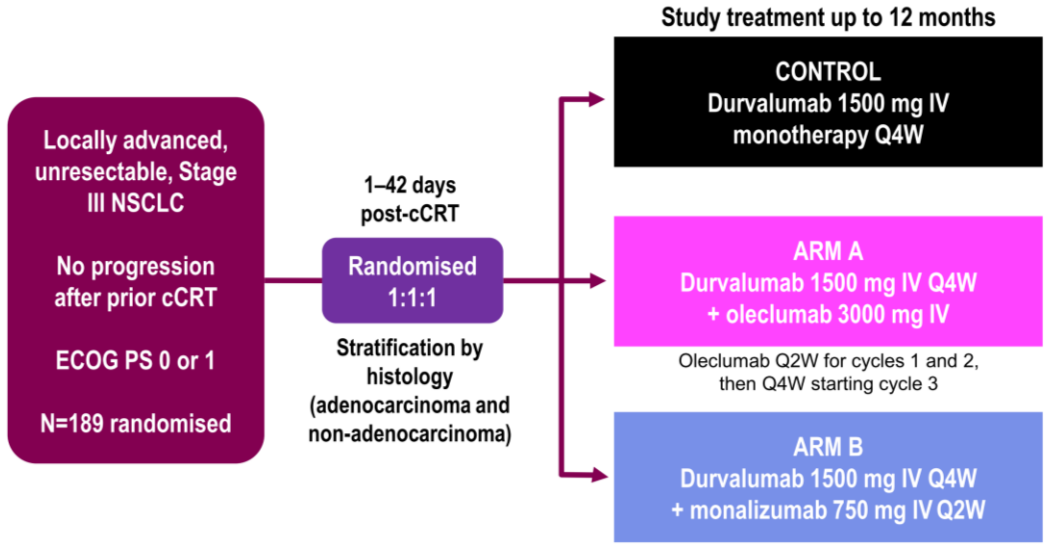
PACIFIC-8



Ozguroglu M. ESMO, 2022.

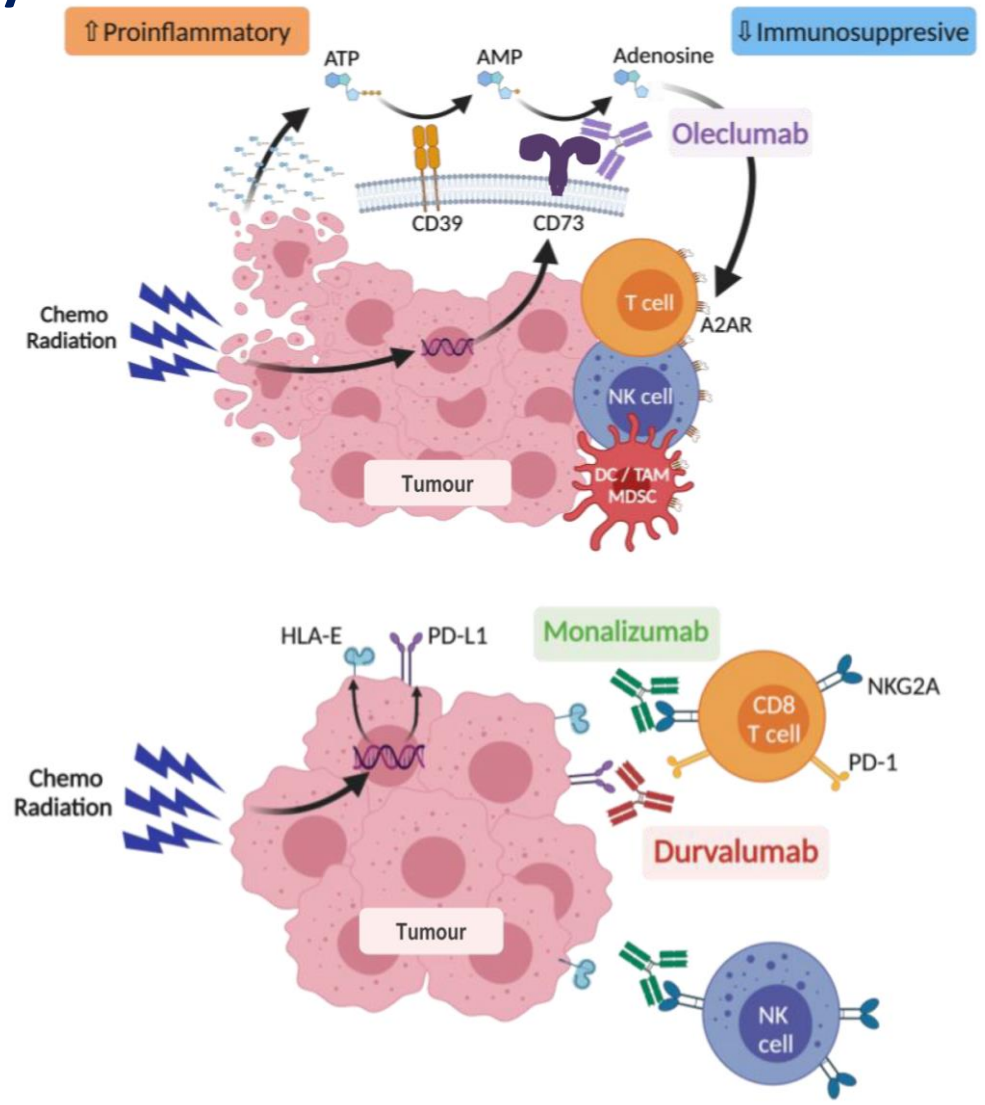
Adding IO: IO-IO strategy

COAST: An Open-Label, Phase II, Multidrug Platform Study Of Durvalumab Alone or in Combination With Oleclumab Or Monalizumab in Patients With Unresectable, Stage III NSCLC



Primary Endpoint
- ORR by investigator assessment (RECIST v1.1)

Secondary Endpoints
- Safety
- DoR
- DCR
- PFS by investigator assessment (RECIST v1.1)
- OS
- PK
- Immunogenicity

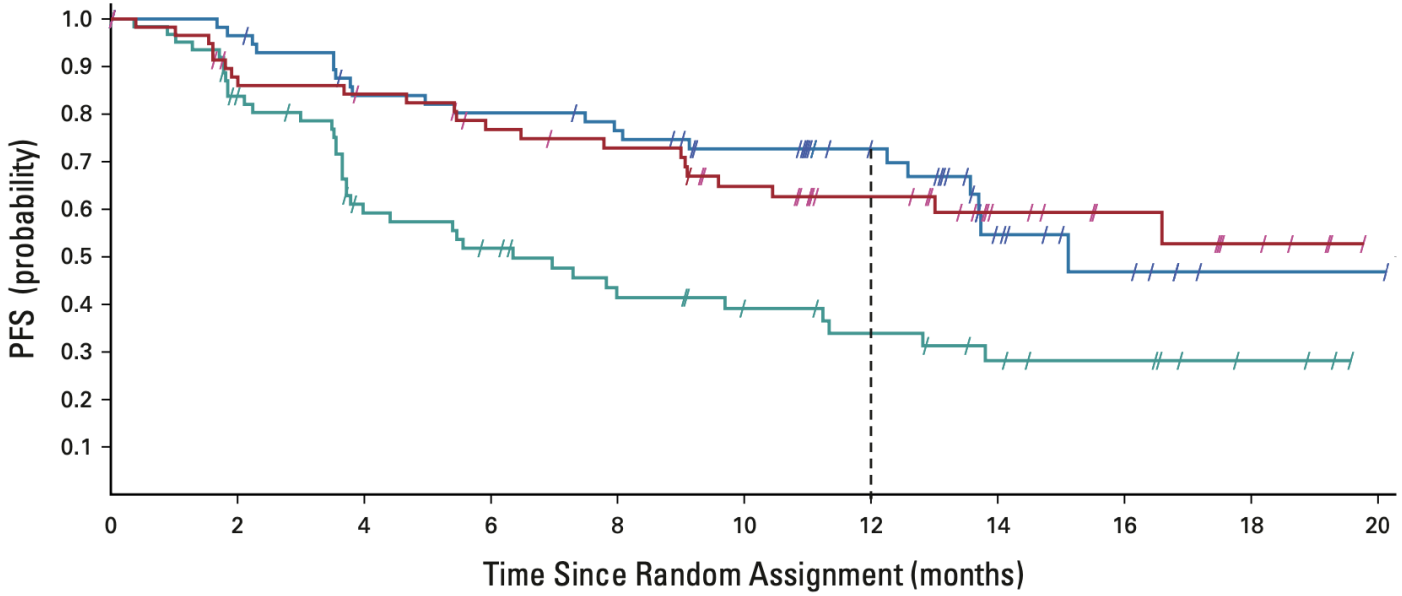


Martinez-Marti A. ESMO, 2021.

Adding IO: IO-IO strategy

COAST: Durvalumab Alone or in Combination With Oleclumab or Monalizumab

Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–



No. at risk:

Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab	67	50	32	27	20	16	13	9	7	3	0

Antitumor Activity	Durvalumab (n = 67)	Durvalumab + Oleclumab (n = 60)	Durvalumab + Monalizumab (n = 62)
Confirmed ORR, % (95% CI)[a] (No.)	17.9 (9.6 to 29.2) (12)	30.0 (18.8 to 43.2) (18)	35.5 (23.7 to 48.7) (22)
Difference in confirmed ORR, % (95% CI)[b]	—	12.1 (–2.7 to 26.9)	16.7 (1.5 to 32.0)
Best overall response by RECIST,[c,d] No. (%)			
CR	2 (3.0)	1 (1.7)	3 (4.8)
PR	10 (14.9)	17 (28.3)	19 (30.6)
SD	37 (55.2)	32 (53.3)	31 (50.0)
PD	11 (16.4)	6 (10.0)	4 (6.5)
NE	7 (10.4)	4 (6.7)	4 (6.5)
DCR at 16 weeks, % (95% CI)[c,e] (No.)	55.2 (42.6 to 67.4) (37)	80.0 (67.7 to 89.2) (48)	77.4 (65.0 to 87.1) (48)
Median DoR, months (95% CI)[c] Range	NR (7.4 to NA) 1.9+ to 17.5+	NR (12.9 to NA) 1.8+ to 16.9+	NR (9.0 to NA) 1.9+ to 18.4+

Safety summary (as-treated population)

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[a,b]	7 (10.6)	4 (6.8)	3 (4.9)

[a]All reported deaths within 90 days post-last dose, regardless of relationship to study drug
[b]In total, 4 deaths were related to study drug, 2 (pneumonitis and radiation pneumonitis) in the D arm, 1 (pneumonitis) in the D+O arm, and 1 (myocardial infarction) in the D+M arm

Martinez-Marti A. ESMO, 2021.
Herbst RS et al. J Clin Oncol, 2022.

Phase 3 study of durvalumab combined with oleclumab or monalizumab in patients with unresectable Stage III NSCLC (PACIFIC-9)

Fabrice Barlesi[1], Sarah B. Goldberg[2], Helen Mann[3], Aarthi Gopinathan[3], Michael Newton[4], Charu Aggarwal[5]

[1]Gustave Roussy, Villejuif, France; Aix Marseille University, CNRS, INSERM, CRCM, Marseille, France; [2]Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA; [3]AstraZeneca, Cambridge, UK; [4]AstraZeneca, Gaithersburg, MD, USA; [5]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

Poster P1.10-01

Plain language summary

Why are we performing this research?

Durvalumab is an immunotherapy that helps the body's immune system to identify and attack cancer cells by binding to and blocking a protein called PD-L1.

The Phase 3 PACIFIC study established treatment with durvalumab as the standard of care for patients with Stage III non-small-cell lung cancer for whom surgery is not an option, if they have previously completed treatment with both chemotherapy and radiotherapy ('chemoradiotherapy') without their disease getting worse. In PACIFIC, patients who received durvalumab lived longer and had a lower chance of their disease growing or spreading compared with placebo.

Oleclumab and monalizumab are two novel immunotherapies that help the immune system to identify and attack cancer cells. Oleclumab blocks the activity of a protein called CD73, preventing cancer cells from obstructing the immune system's attack on them. Monalizumab blocks the activity of a protein called NKG2A, making cancer cells more susceptible to being seen and killed by the immune system.

There is a strong scientific rationale for combining either of these immunotherapies with durvalumab following chemoradiotherapy in this patient population in order to further improve survival outcomes. In addition, promising clinical data from a Phase 2 study (COAST; NCT03822351) provided support for their further evaluation in the Phase 3 PACIFIC-9 study.

How are we performing this research?

We are aiming to recruit approximately 999 patients with Stage III non-small-cell lung cancer for whom surgery is not an option and who have completed chemoradiotherapy without their disease getting worse.

These patients will then be randomly assigned to a treatment group in equal numbers, neither the patients nor researchers will know which of 3 possible treatments is being administered:

- durvalumab + oleclumab
- durvalumab + monalizumab
- durvalumab + placebo.

Each patient will continue to receive their designated treatments for up to 12 months.

The primary efficacy measure is the length of time that the patients remain alive without their disease growing or spreading, and each combination treatment will be compared with durvalumab alone.

[1]Herbst RS, *et al. J Clin Oncol* 2022; JCO.22.00227. ePub ahead of print.

Background

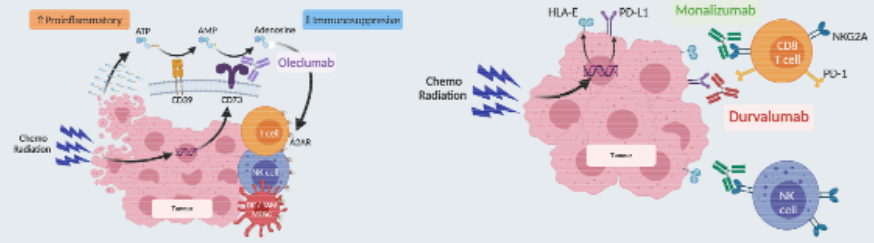
- Based on results from the PACIFIC study (NCT02125461), consolidation treatment with durvalumab is the standard of care for patients with unresectable Stage III NSCLC and no disease progression following CRT (the 'PACIFIC regimen').[1–4]
- To further improve the outcomes for this patient population, immunotherapy combinations that build upon the backbone of PD-L1 inhibition with durvalumab are being explored, including combinations with anti-TIGIT, anti-CD73, and anti-NKG2A mAbs.
- Oleclumab and monalizumab are two such candidates that have demonstrated encouraging clinical activity in the Phase 2 COAST study (NCT03822351), when combined with durvalumab in this patient population.[5]

Durvalumab in locally advanced NSCLC

- Durvalumab is a selective, high-affinity human IgG1 mAb that binds to PD-L1 and blocks it from binding to PD-1 and CD80, thereby overcoming PD-L1 mediated inhibition of T-cell activation.[6]
- In the placebo-controlled Phase 3 PACIFIC study, durvalumab significantly improved OS and PFS in patients with unresectable Stage III NSCLC whose disease had not progressed after platinum-based cCRT, with a manageable safety profile and no detrimental effect on PROs.[1,2,7]
  - Recently, 5-year data from PACIFIC demonstrated robust and sustained OS benefit plus durable PFS benefit with durvalumab (vs placebo), with 42.9% of patients alive and 33.1% alive and progression free at 5 years (35.4% and 19.0% with placebo, respectively).[8]

Rationale for combining durvalumab with oleclumab or monalizumab

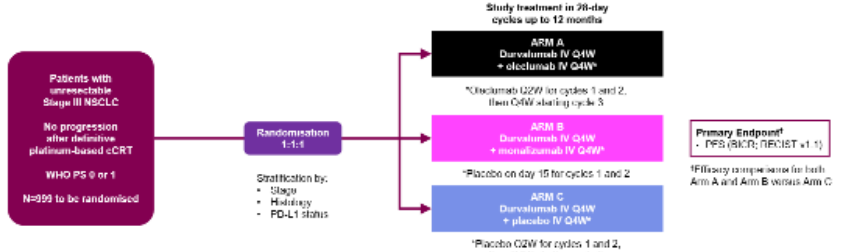
- Oleclumab (MEDI9447) is a human IgG1A mAb that inhibits CD73 to reduce extracellular adenosine production, thereby promoting antitumour immunity.[9]
- Monalizumab is a first-in-class, humanised IgG1 mAb that selectively binds to NKG2A, blocking the binding of HLA-E (NKG2A ligand), thereby reducing inhibition of NK and CD8+ T cells.[10]
- RT increases tumour expression of CD73, HLA-E (NKG2A ligand), and PD-L1; therefore, combined blockade of these immune checkpoints may improve outcomes in patients with unresectable Stage III NSCLC who have undergone cCRT.[11–14]
  - In preclinical models, the combination of RT and CD73 or NKG2A inhibitors (with or without PD-[L]1 inhibitors) have shown increased antitumour activity.[11,13,14]
- In the randomised Phase 2 COAST study (N=189), the combination of oleclumab or monalizumab with durvalumab increased ORR (30.0% and 35.5%, respectively, vs 17.9% with durvalumab alone) and prolonged PFS (HR 0.44 and HR 0.42, respectively, vs durvalumab alone), with no new or significant safety signals identified, in patients with unresectable Stage III NSCLC and no progression after cCRT.[5]
- These findings support further evaluation of these novel immunotherapy combinations in the Phase 3 PACIFIC-9 study (NCT05221840), which is being conducted to assess the efficacy and safety of durvalumab in combination with either oleclumab or monalizumab relative to durvalumab plus placebo (i.e., durvalumab monotherapy) in patients with unresectable Stage III NSCLC.



[1] (guise adapted from Martinez Marti et al. LBMO 2021 oral presentation [LBA42] [as originally created with BioRender.com])

PACIFIC-9 (NCT05221840): study design

Phase 3, double-blind, placebo-controlled, randomised, multicentre, international study



Study endpoints

1°
- PFS (BICR per RECIST v1.1).

2°
- OS and 24-month OS rate.
- 6-, 12-, 18-, and 24-month PFS rates (BICR per RECIST v1.1).
- PFS (investigator assessment).
- ORR and DoR (BICR per RECIST v1.1).
- PFS2.
- TTDM (RECIST v1.1) and TFST.
- IHC analysis of PD-L1 TC expression relative to efficacy outcomes (OS, PFS, and ORR).
- Time to first confirmed deterioration of cough, dyspnoea, and chest pain.
- Pharmacokinetics and immunogenicity of durvalumab, oleclumab, and monalizumab.
- Safety and tolerability.

Key inclusion criteria

- Patients must be aged ≥18 years at the time of screening.
- Patients must have histologically- or cytologically-documented NSCLC (per the IASLC Staging Manual in Thoracic Oncology 8th ed.) and have been treated with definitive, platinum-based cCRT for unresectable Stage III NSCLC.
  - At least 2 cycles of chemotherapy (cisplatin- or carboplatin-based) concurrent with radiotherapy (total dose, 60 Gy ±10%).
- Patients must not have progressed following cCRT.
- Tumour sample requirements:
  - Documented tumour PD-L1 status by a central laboratory.
  - Documented EGFR and ALK wild-type status.
- WHO performance status of 0 or 1.
- Patients must have adequate organ and marrow function.

Key exclusion criteria

- History of another primary malignancy, with the exceptions of:
  - malignancies treated with curative intent with no known active disease >5 years before the first dose of study intervention and of low potential risk for recurrence
  - basal or squamous cell carcinoma of the skin or lentigo maligna that has undergone potentially curative therapy
  - adequately treated carcinoma in situ or Ta tumours treated with curative intent and without evidence of disease.
- Mixed small-cell and non-small-cell lung cancer histology.
- Patients who receive sequential CRT for unresectable Stage III NSCLC or who have progressed during platinum-based cCRT.
- Patients with unresolved CTCAE grade >2 toxicity or grade ≥2 pneumonitis from prior cCRT.
- History of idiopathic pulmonary fibrosis, organising pneumonia, drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis, ILD, pleural effusion, or pulmonary fibrosis, diagnosed in the past 6 months prior to randomisation.
- Patients with a history of MI, TIA, stroke, or PE diagnosed in the past 6 months or venous thrombosis diagnosed in the past 3 months prior to the scheduled first dose of study treatment.
- Active or prior documented autoimmune or inflammatory disorders (with exceptions).
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab.

Study status

- Study enrolment began in February 2022 and primary completion is anticipated in May 2026.
- PACIFIC-9 is currently active and plans to recruit at 199 sites across 20 countries, including Australia, Brazil, Canada, China, Colombia, France, Germany, Italy, Japan, Peru, Poland, Portugal, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom, United States of America, and Vietnam.

References

1. Antonia SJ, *et al. New Engl J Med* 2017;377:1919–29.
2. Antonia SJ, *et al. New Engl J Med* 2018;379:2342–50.
3. Daly ME, *et al. J Clin Oncol* 2022;40:1595–94.
4. Remon J, *et al. Ann Oncol* 2021;32:1637–42.
5. Herbst RS, *et al. J Clin Oncol* 2022; JCO.22.00227. ePub ahead of print.
6. Stewart R, *et al. Cancer Immunol Res* 2015;3:1052–62.
7. Hui R, *et al. Lancet Oncol* 2019;20:1670–80.
8. Spigel DR, *et al. J Clin Oncol* 2022;40:1301–11.
9. Geoghegan JC, *et al. MAbs* 2016;8:454–67.
10. André P, *et al. Cell* 2018;175:1731–43.
11. Battaglia NG, *et al. J Immunol Res* 2021;2021:1234–41.
12. Wang X, *et al. J Thorac Oncol* 2017;12:1669–87.
13. Takai H, *et al. BMC Cancer* 2017;17:1–11.
14. Wennerberg E, *et al. Cancer Immunol Res* 2020;8:465–78.

Abbreviations

A2AR, A2A adenosine receptor; ALK, anaplastic lymphoma kinase; AMP, adenosine monophosphate; ATP, adenosine triphosphate; BICR, Blinded Independent Central Review; CD, cluster of differentiation; CRT, chemoradiotherapy; cCRT, concurrent chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; DC, dendritic cell; DoR, duration of response; Gy, gray; HLA-E, histocompatibility complex E; IASLC, International Association for the Study of Lung Cancer; Ig, immunoglobulin; IHC, immunohistochemistry; IL12, interleukin-12; inhibitor; IV, intravenous; mAb, monoclonal antibody; MDSC, myeloid-derived suppressor cell; MI, myocardial infarction; NK, natural killer; NKG2A, Natural Killer Group 2A; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-[L]1, programmed cell death (ligand) 1; PE, pulmonary embolism; PFS, progression-free survival; PFS2, time from randomisation to second progression (or death of the progression events following initial progression, subsequent to first subsequent therapy, or death); PROs, patient-reported outcomes; Q2W, every 2 weeks; RT, radiotherapy; Tu tumour; non-invasive papillary carcinoma; TAM, tumour-associated macrophages; TC, tumour cell; TFST, time to first subsequent therapy or death; TIA, transient ischaemic attack; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TTDM, time to distant metastasis or death; WHO, World Health Organization.

Acknowledgements

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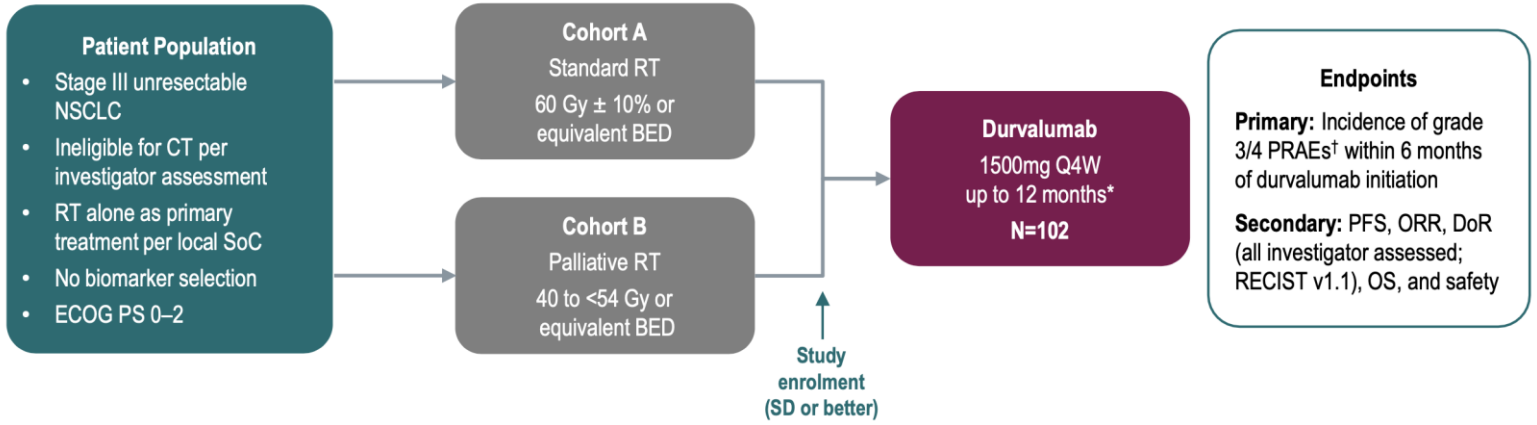
https://bit.ly/3NTbX3l

Poster presented at the IASLC 2022 World Conference on Lung Cancer (WCLC); Vienna, Austria; 6–9 August 2022

Special populations

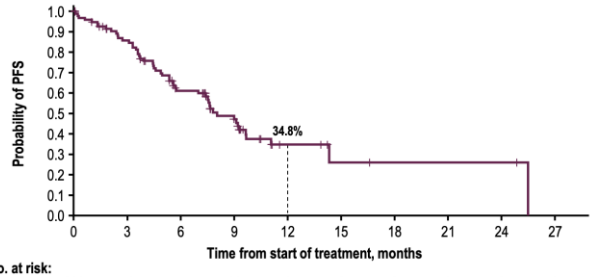
DUART: Durvalumab after radiotherapy in patients unfit for chemotherapy



	All-cause AEs			PRAEs*		
	Cohort A (standard RT; n=59)	Cohort B (palliative RT; n=43)	Total (N=102)	Cohort A (standard RT; n=59)	Cohort B (palliative RT; n=43)	Total (N=102)
Any AE, n (%)	56 (94.9)	43 (100)	99 (97.1)	40 (67.8)	21 (48.8)	61 (59.8)
Grade 3/4	25 (42.4)	15 (34.9)	40 (39.2)	9 (15.3)	3 (7.0)	12 (11.8)
Within 6 months	—	—	—	7 (11.9)	3 (7.0)	10 (9.8)
SAE	25 (42.4)	13 (30.2)	38 (37.3)	7 (11.9)	2 (4.7)	9 (8.8)
Outcome of death‡	5 (8.5)	2 (4.7)	7 (6.9)	1 (1.7)	0	1 (1.0)
Leading to Tx discontinuation	11 (18.6)	7 (16.3)	18 (17.6)	7 (11.9)	3 (7.0)	10 (9.8)
Leading to Tx interruption	31 (52.5)	17 (39.5)	48 (47.1)	8 (13.6)	5 (11.6)	13 (12.7)
AESI	26 (44.1)	15 (34.9)	41 (40.2)	21 (35.6)	9 (20.9)	30 (29.4)
imAE	23 (39.0)	13 (30.2)	36 (35.3)	22 (37.3)	12 (27.9)	34 (33.3)

PFS

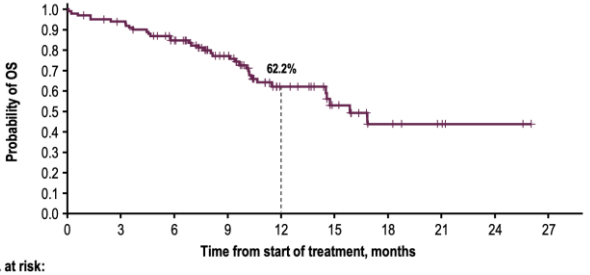
	Cohort A (standard RT)	Cohort B (palliative RT)	Total
No. events / no. patients (%)	26/59 (44.1)	25/43 (58.1)	51/102 (50.0)
Median PFS (95% CI)*, months	9.0 (5.6–NC)	7.6 (5.3–11.0)	8.0 (7.0–9.7)
12-month PFS rate (95% CI)†, %	40.2 (23.6–56.3)	29.3 (13.8–46.7)	34.8 (23.0–46.9)



No. at risk:
Total 102 76 47 28 9 3 2 2 2 0

OS

	Cohort A (standard RT)	Cohort B (palliative RT)	Total
No. events / no. patients (%)	16/59 (27.1)	19/43 (44.2)	35/102 (34.3)
Median OS (95% CI)*, months	NC (14.5–NC)	14.8 (10.1–NC)	15.9 (11.5–NC)
12-month OS rate (95% CI)†, %	67.0 (50.1–79.2)	56.3 (37.3–71.6)	62.2 (49.8–72.4)

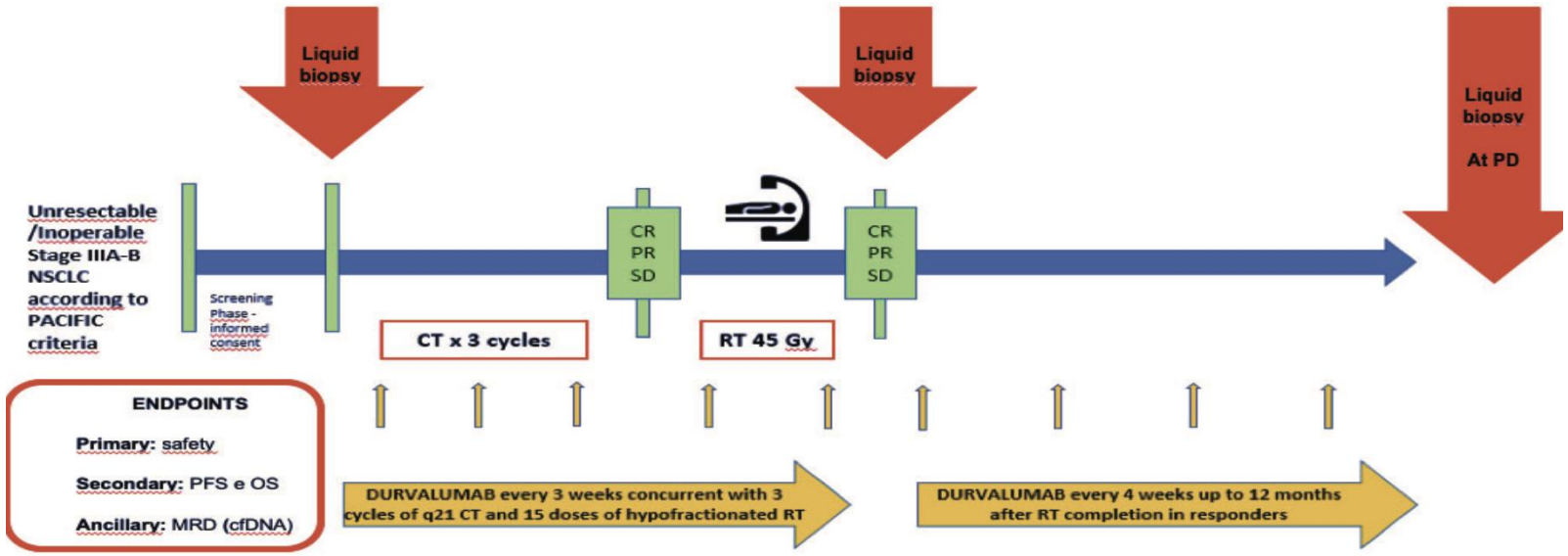


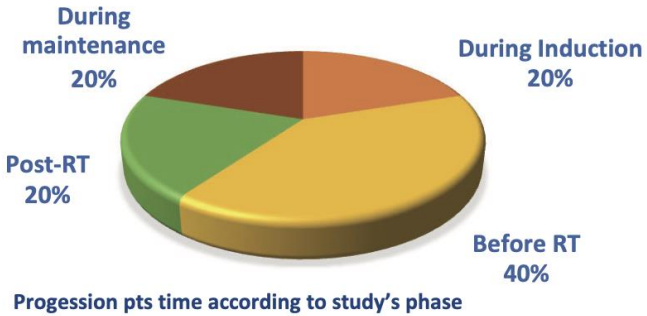
No. at risk:
Total 102 93 78 54 27 15 7 4 2 0

Filippi AR. ESMO 2023.

Special populations

DEDALUS:
Induction chemo-Durvalumab ➜ reduced dose RT + Durvalumab ➜ Durvalumab
Patients unfit for standard doses of RT





Progession pts time according to study's phase

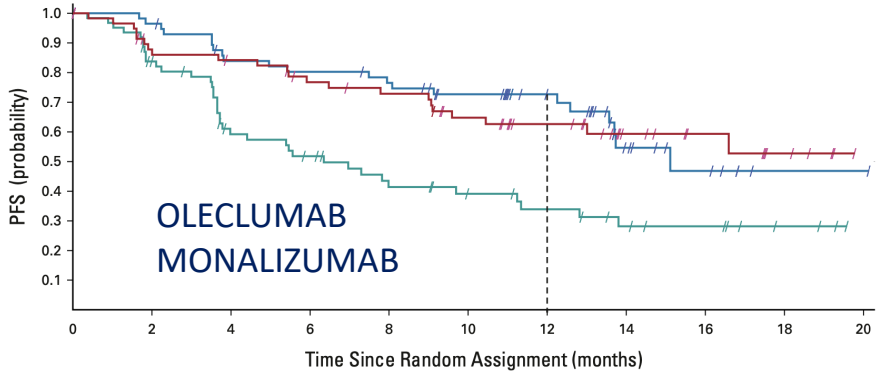
PRAEs	PTS (N)	EVENT DESCRIPTION
Any PRAEs	**5 (25%)**	
G3	4 (20%)	3 myelotoxic events –1 ipoMg^{2+}
G4	1 (5%)	1 sepsis

DISCONTINUATION	PTS (N)
PERMANENT	8 (40%)
PRAEs	**0**
SAEs	3 (15%)
Progression	5 (25%)
TEMPORARY	3 (15%)
PRAEs (G3-G4)	**1 (5%)**
SAEs (G3-G4)	2 (10%)

Filippi AR. ELCC, 2024.

Strategies to improve survival

Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–

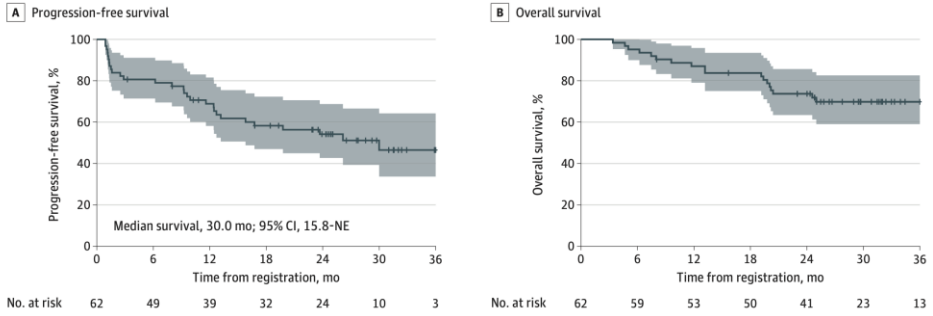


IO-IO strategy

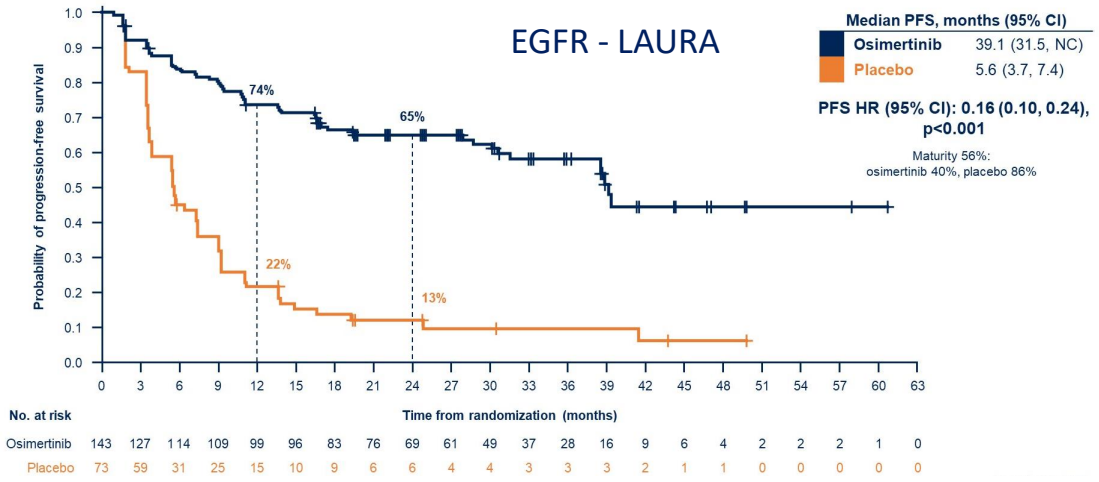
- COAST
- PACIFIC-9
- SKYSCRAPER-03
- PACIFIC-8

Induction IO – IO concomitant cCRT

AZT-16

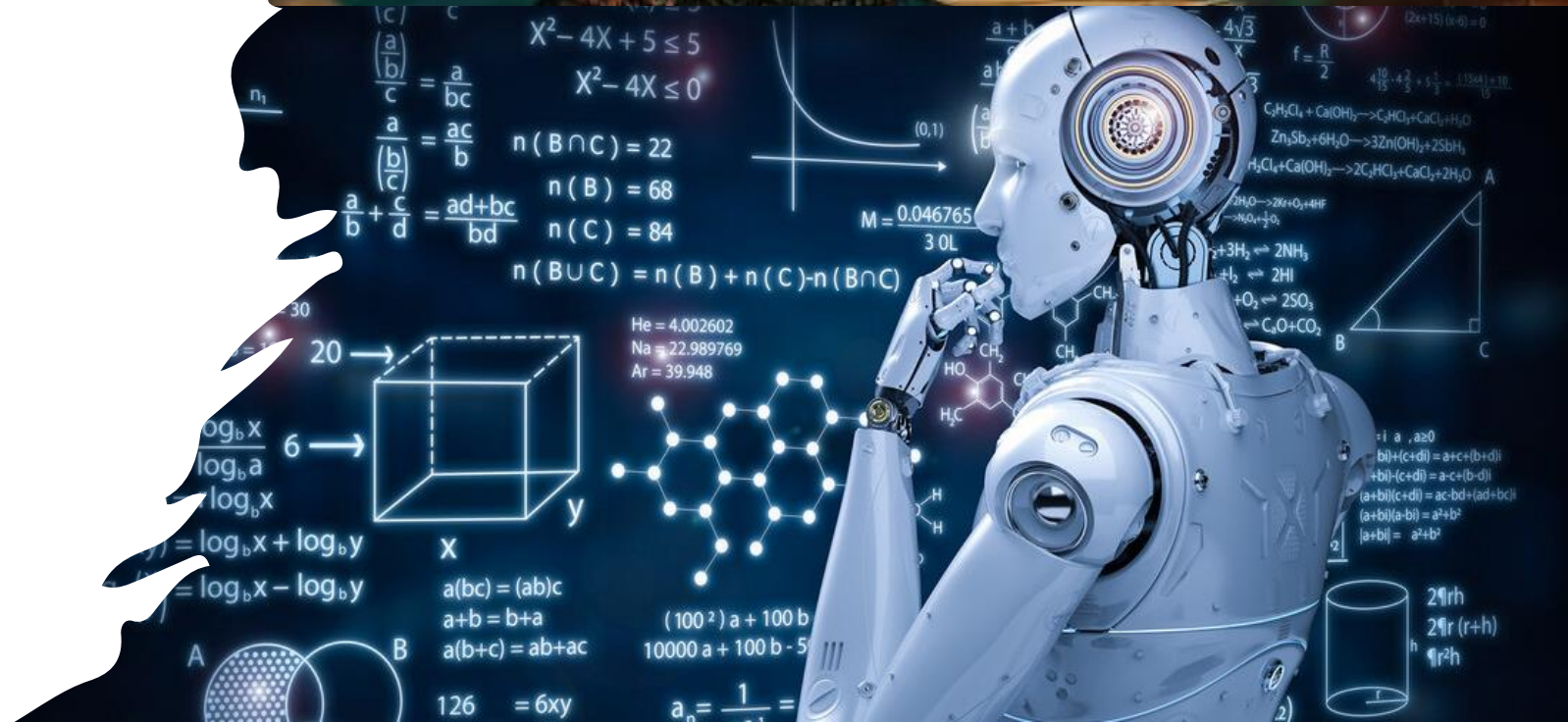


EGFR - LAURA

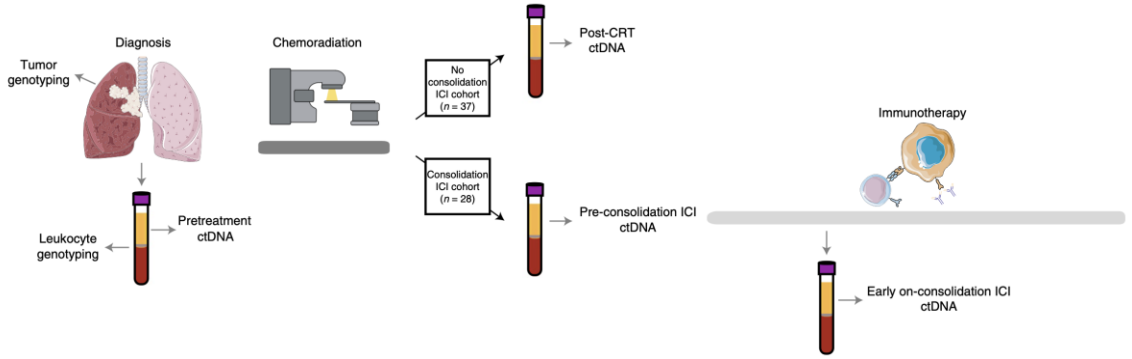


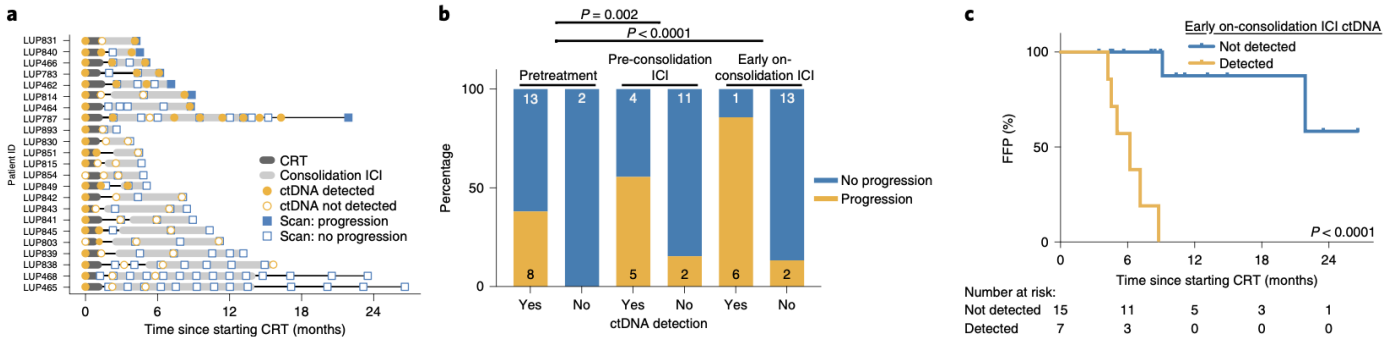
Strategies to improve survival:

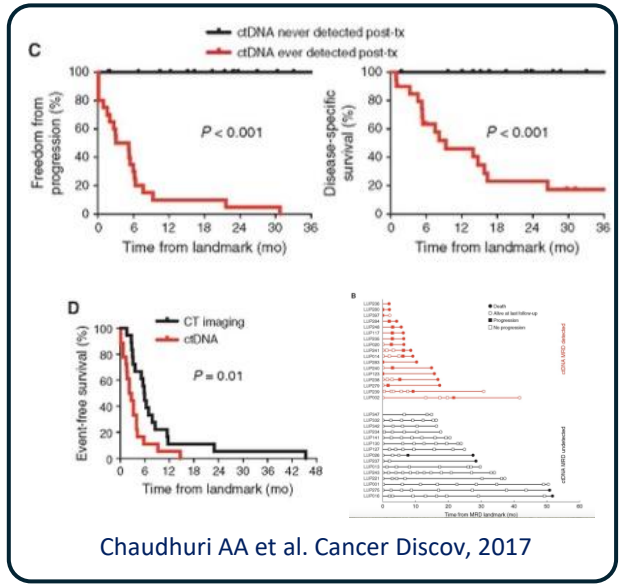
Prediction and monitoring



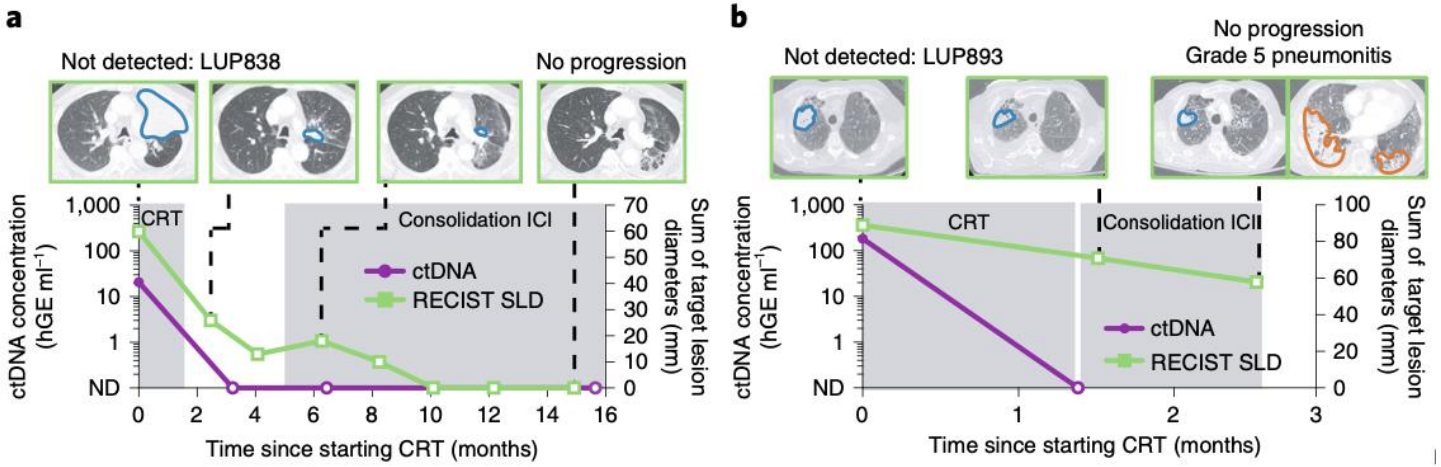
ctDNA dynamics predict benefit from consolidation immunotherapy

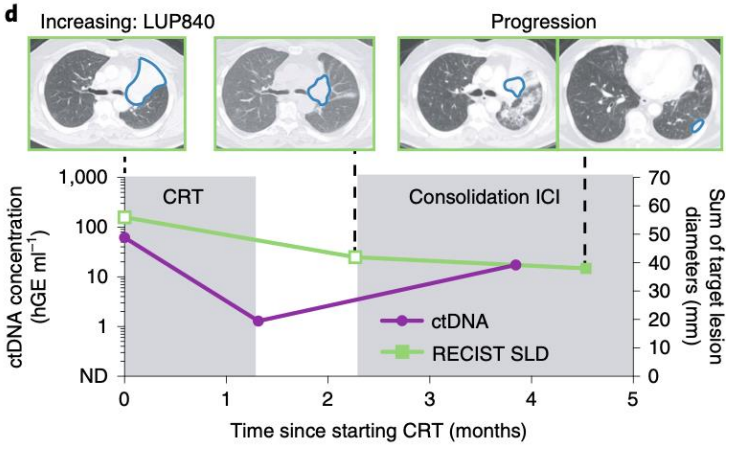






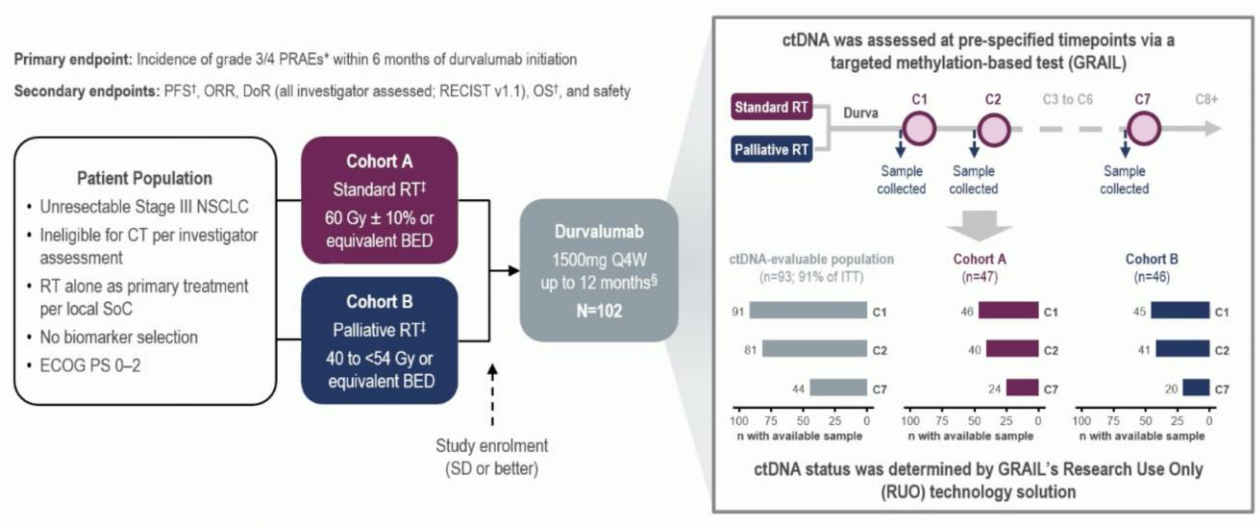
Chaudhuri AA et al. Cancer Discov, 2017

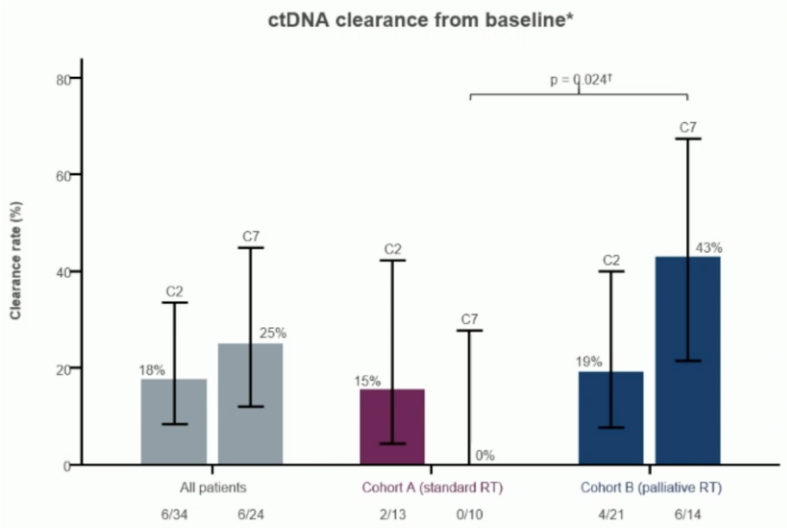


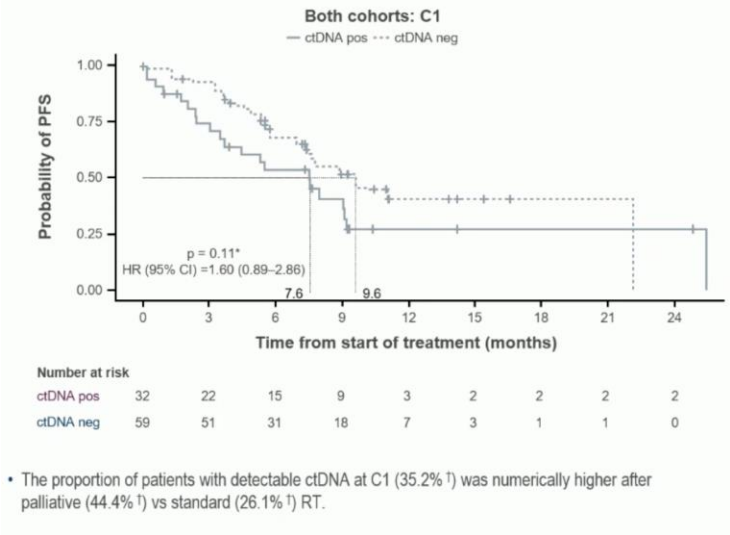


Moding EJ et al. Nature Cancer, 2020.

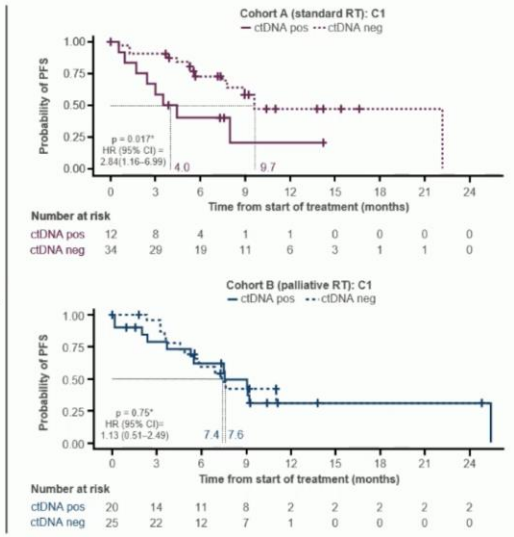
ctDNA dynamics and treatment responses in chemotherapy-ineligible patients with unresectable Stage III NSCLC from the phase 2 DUART trial

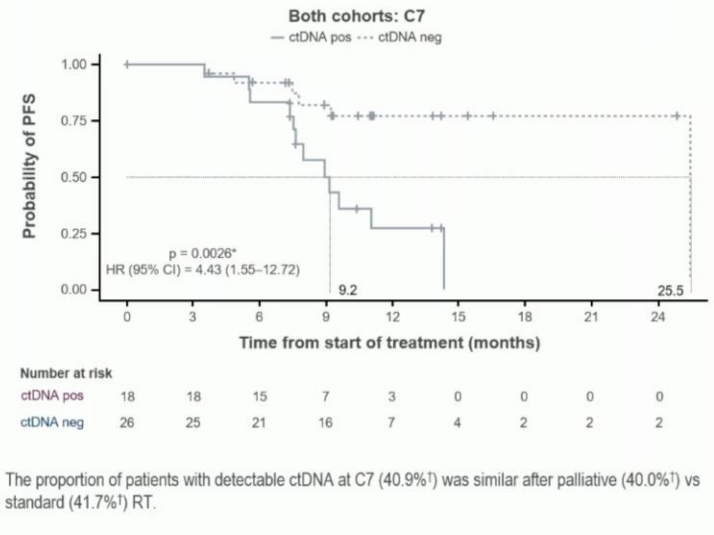




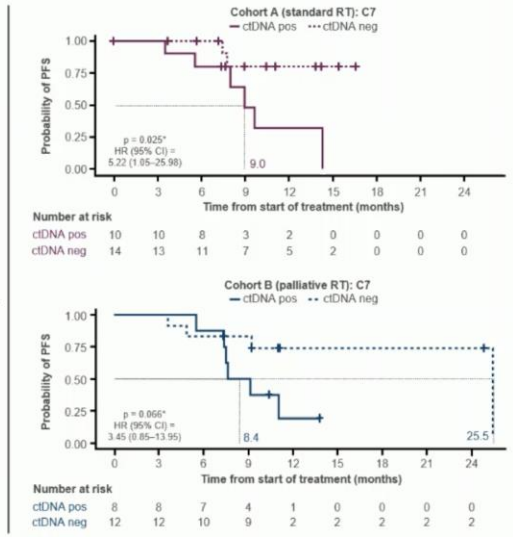


- The proportion of patients with detectable ctDNA at C1 (35.2% †) was numerically higher after palliative (44.4% †) vs standard (26.1% †) RT.



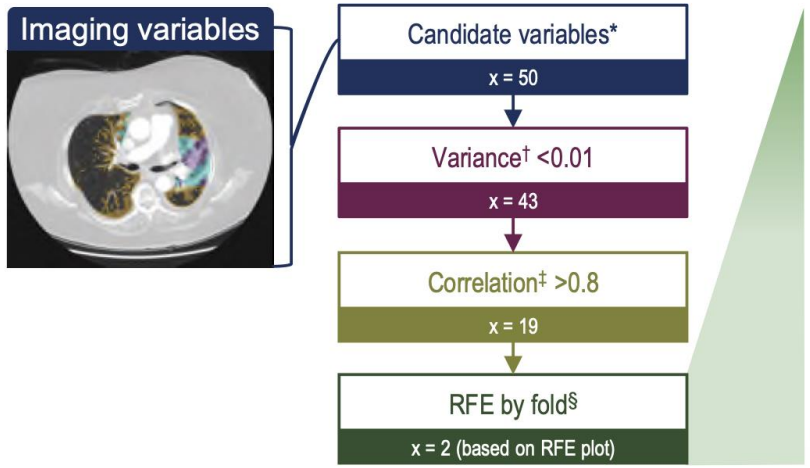


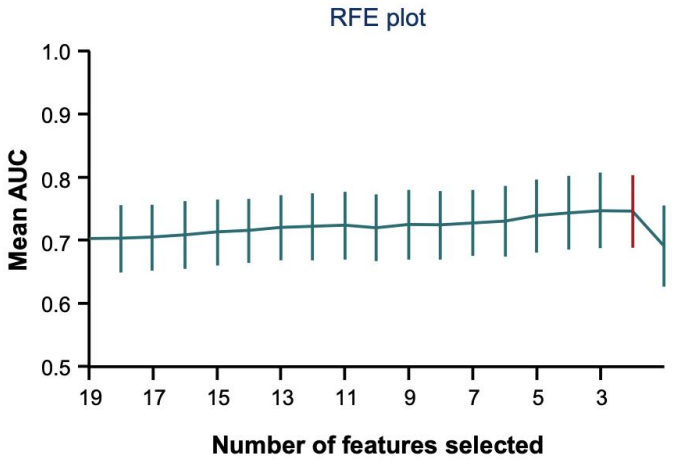
- The proportion of patients with detectable ctDNA at C7 (40.9%†) was similar after palliative (40.0%†) vs standard (41.7%†) RT.

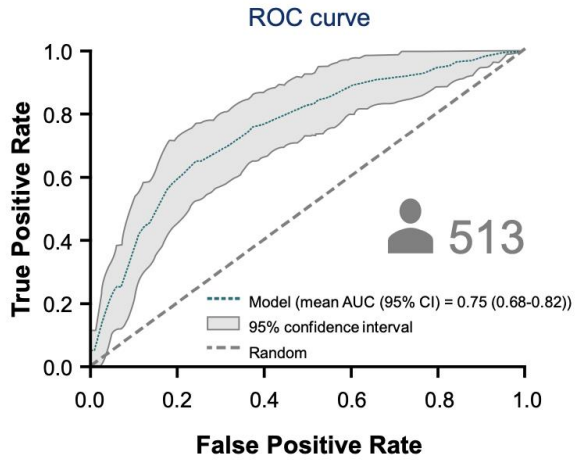


Differential diagnosis: pneumonitis vs progression

Results: AI model trained on imaging data identified symptomatic ILD/pneumonitis

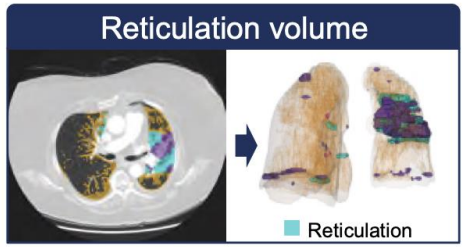


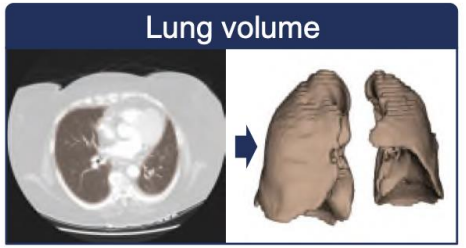




Discriminative power: AUC (95% CI) = 0.75 (0.68–0.82) **PPV¶ (95% CI) = 0.42 (0.34–0.51)** **NPV¶ (95% CI) = 0.92 (0.89–0.95)**

Variables included in the AI model after RFE		
Model feature	**OR§**	**95% CI§**
Reticulation volume/TLC	1.44	1.34–1.53
Lung volume	0.73	0.68–0.78



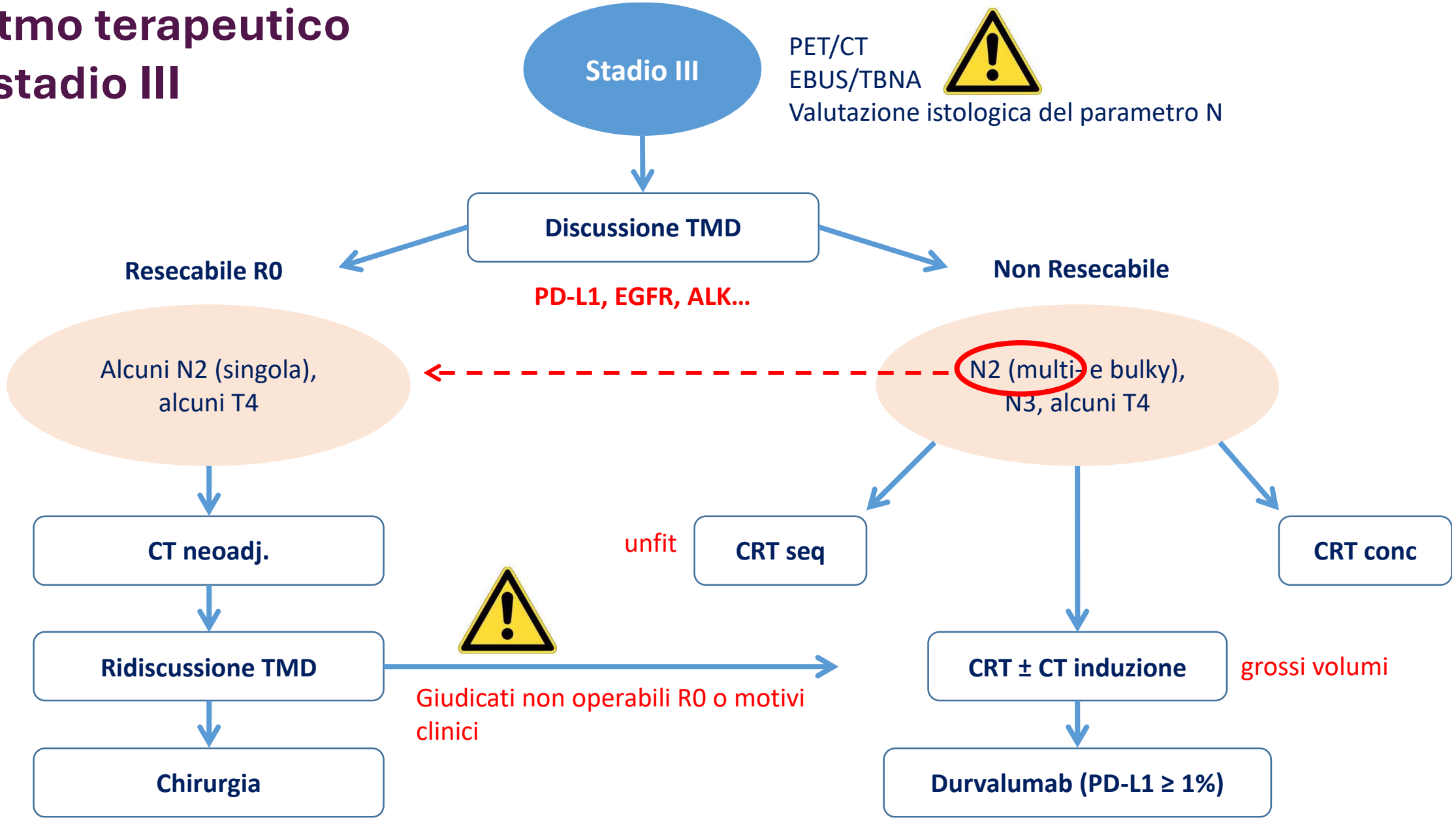


BARCELONA 2024 ESMO congress

*Full candidate variable list available in the supplemental slides.
†After min-max normalization.
‡Spearman correlation or Cramer's V association was used as appropriate.
§Regularized multivariable logistic regression model. ORs and CIs based on 10-repeat 5-fold cross validation; ORs >1 indicate positive association with symptomatic ILD/pneumonitis.
¶Using the threshold that maximized sensitivity and specificity (Youden index).
AUC, area under curve; CI, confidence interval; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RFE, recursive feature elimination; ROC, receiver operating characteristic

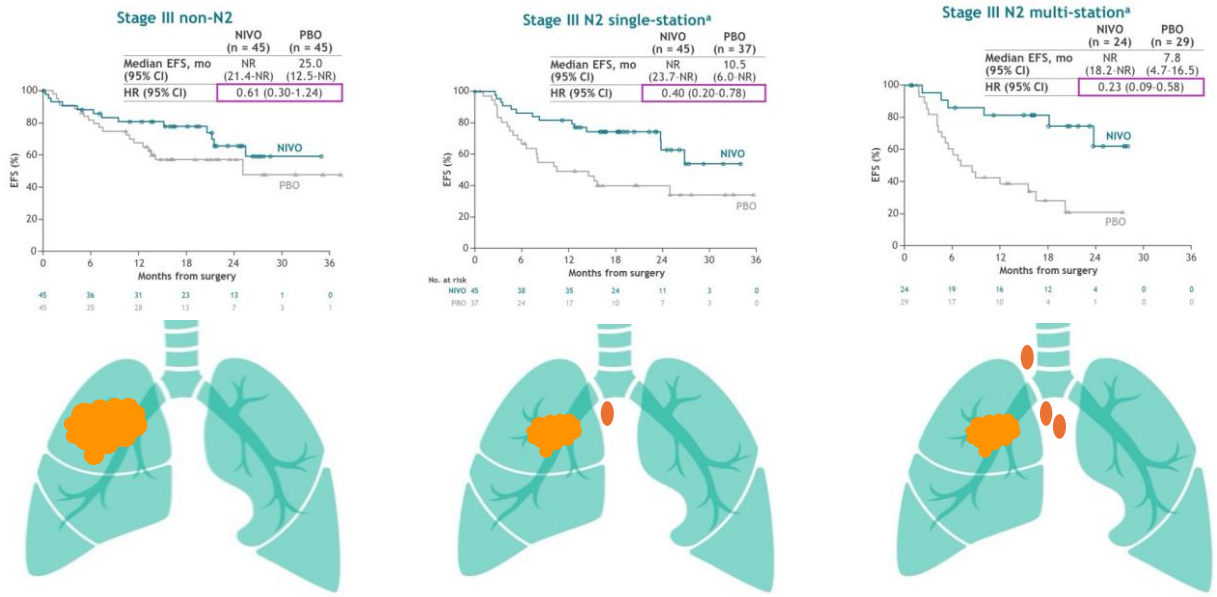
Naidoo J. ESMO, 2024.

Algoritmo terapeutico dello stadio III



The changing scenario in stage III NSCLC

	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

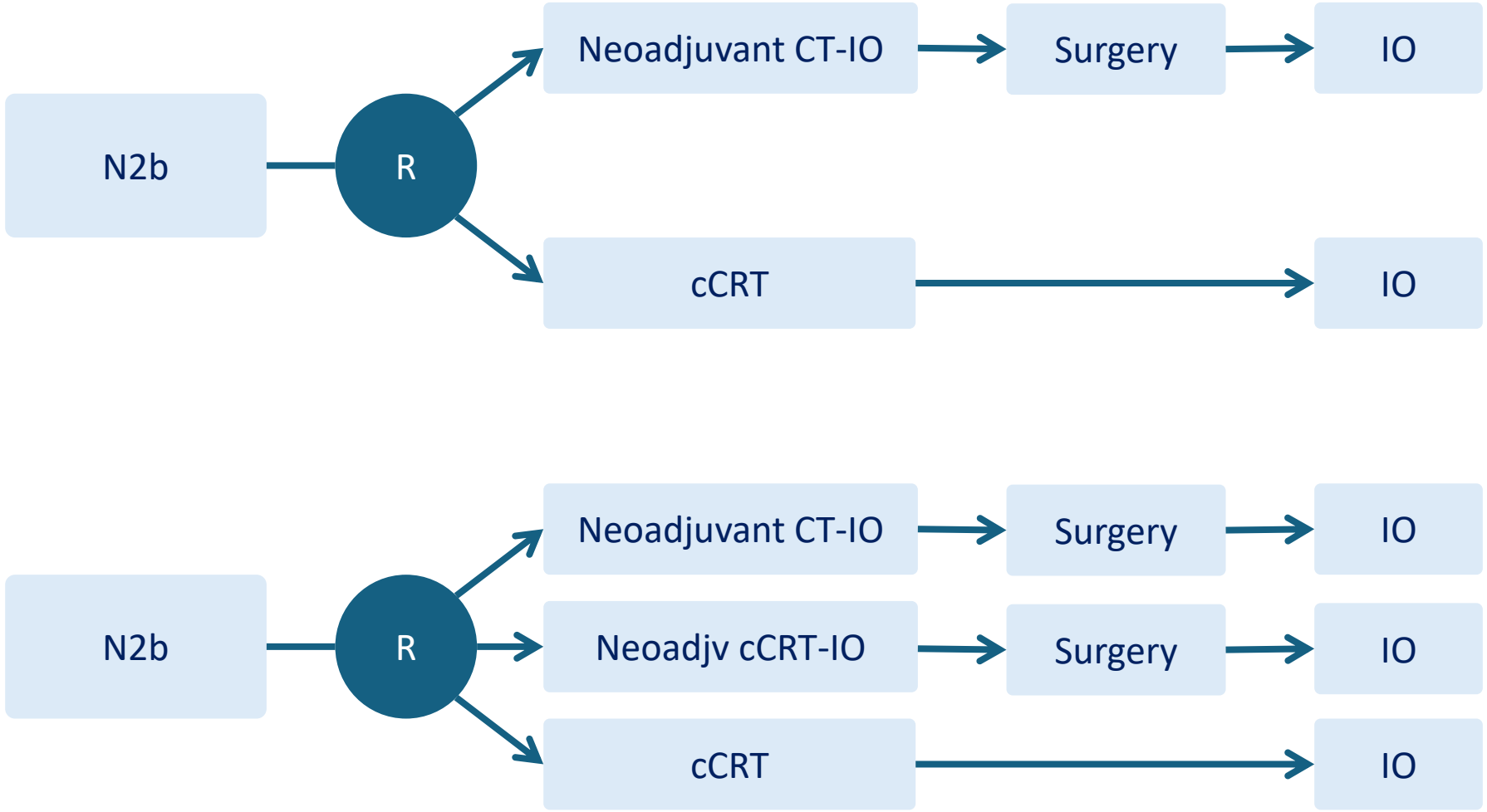


Dingemnas A, WCLC 2023.
Cascone T. ASCO, 2024

Choosing the best treatment… choosing subgroups
PFS / EFS

Study	IIIA	IIIB	N2	N2 single	N2 multi	PD-L1 neg	PD-L1 ≥ 1%	PD-L1 1-49%	PD-L1 ≥ 50%
PACIFIC	HR .53	HR .59	-	-	-	10.7 (.73)	17.8 (HR .46)	-	-
PACIFIC-R	23.7	19.2	-	-	-	15.6	22.4	-	-
CM816	31.6 (HR .54)		-	-	-	26.4 (HR .87)	NR (HR .46)	HR .58	HR .24
AEGEAN	25.8 (HR .60)	19.8 (HR .81)	-	22.8 (HR .58)	12.2 (HR .78)	20.6 (HR .69)	-	25.9 (HR .73)	NR (HR .71)
CM77T	30.2 (HR .51)		30.2 (HR .46)	30.2 (HR .49)	NR (HR .43)	29 (HR .73)	NR (HR .52)	30.2 (HR .76)	NR (HR .26)
IMpower010	32.3 (.81)		-	30.2 (HR .83)	-	-	37 (HR .97)	35.3 (HR .66)	31.4 (HR .87)	35.7 (HR .43)

Choosing the best treatment…



Definitive Chemoradiation Followed by Immunotherapy vs. Surgery for cT4N2M0 NSCLC : A Contemporary Nationwide Analysis.

Jorge Humberto Rodriguez-Quintero MD, MPH, Rajika Jindani MD, MPH, MS, Roger Zhu MD, Brian Cohen MD, Mohamed K. Kamel MD, Nandita Mahajan MD, Marc Vimolratana MD, MS, Neel Chudgar MD, Brendon Stiles MD.

Montefiore / Einstein Comprehensive Cancer Center. Albert Einstein College of Medicine. Bronx, New York.

Montefiore Einstein
Comprehensive Cancer Center

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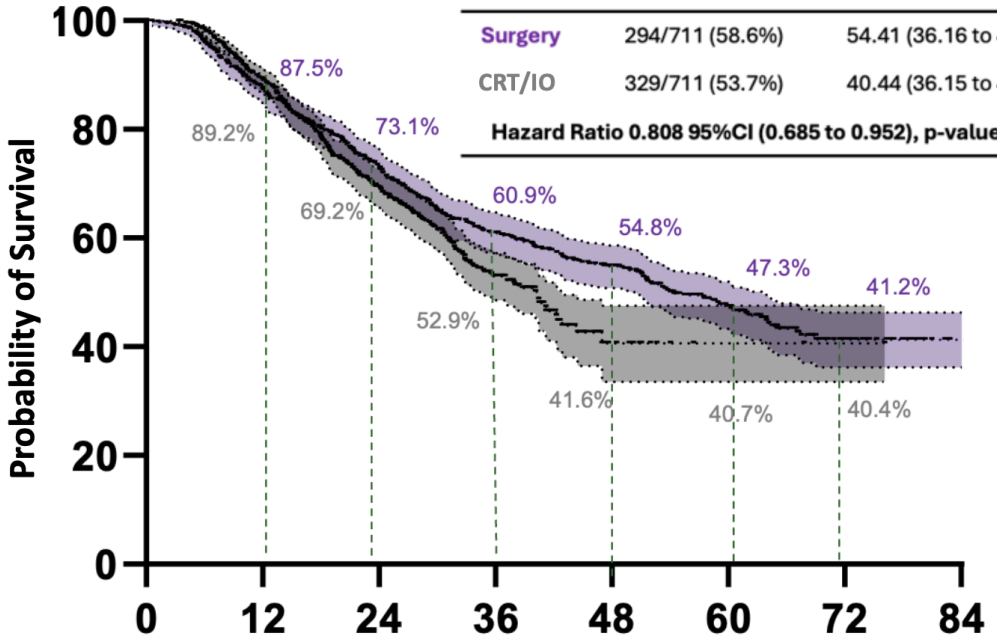
A Cancer Center Designated by the National Cancer Institute

THE SURGERY DILEMMA

Survival analysis: Surgery vs. CRT/IO in propensity-matched cohorts:

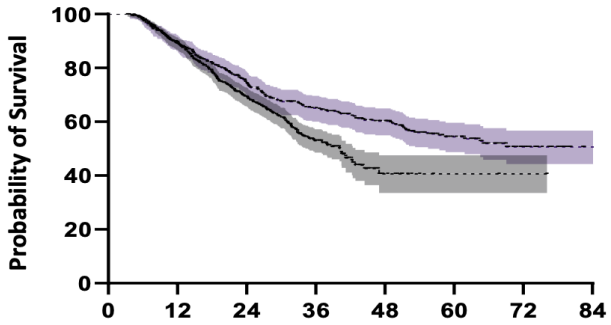
	No. of Events/Total N (%)	Median OS (95%CI), Months
Surgery	294/711 (58.6%)	54.41 (36.16 to 44.72)
CRT/IO	329/711 (53.7%)	40.44 (36.15 to 44.72)
Hazard Ratio 0.808 95%CI (0.685 to 0.952), p-value 0.011		



No at. Risk								
Surgery	711	612	471	342	243	127	40	4
CRT/IO	711	622	406	139	13	3	2	1

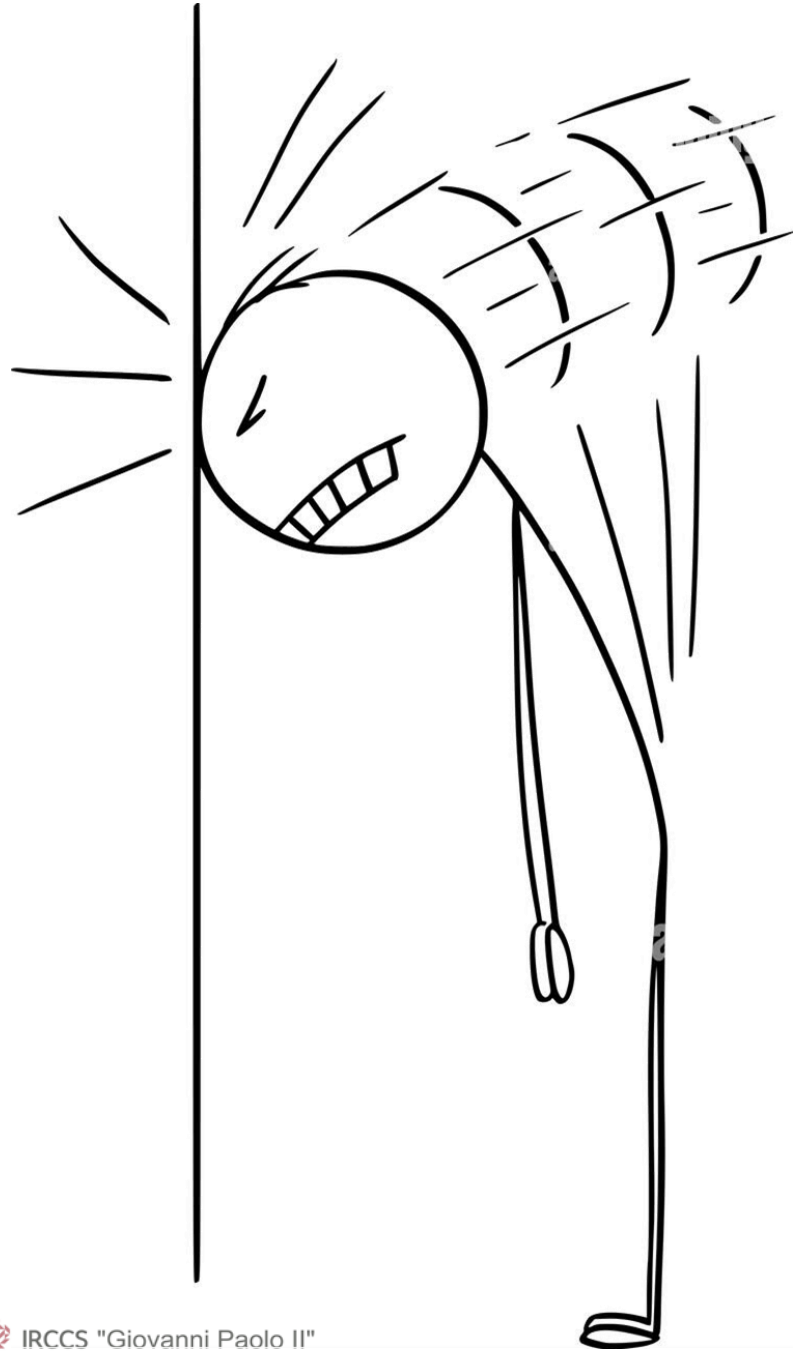
Subgroup Analysis

Neoadjuvant/Perioperative vs. CRT/IO



	No. of Events/Total N (%)	Median OS (95%CI), Months
Neoadjuvant	167/409 (40.8%)	Not-reached
Hazard Ratio 0.70 95%CI (0.58 to 0.85), p-value <0.001		

Rodriguez Quintero JH. WCLC, 2024.



What we want to know…

Demographics of the study cohort and multivariable analysis for factors associated with surgical resection.					
		Surgery (N=990, 51.9%)	CRT/IO (N=918, 48.1%)	P-value	Adjusted Odds Ratio (95%CI)
Age (Median, IQR)		65 (58 -71)	66 (60-72)	<0.001	0.98 (0.97 to 0.99)
Race, N (%)					
	White	846 (85.5%)	747 (81.4%)	0.013	Ref.
	Black	86 (8.7%)	118 (12.9%)		0.59 (0.42 to 0.82)
	Other	58 (5.9%)	53 (5.8%)		0.78 (0.51 to 1.20)
Charlson-Deyo Index, N (%)					
	0	646 (65.3%)	519 (56.5%)	<0.001	Ref.
	1	232 (23.4%)	254 (27.7%)		0.80 (0.63 to 1.00)
	2	75 (7.6%)	76 (8.3%)		0.96 (0.66 to 1.40)
	3 or >	37 (3.7%)	69 (7.5%)		0.60 (0.38 to 0.94)
Type of Facility, N (%)					
	Community	60 (6.1%)	77 (8.4%)	<0.001	Ref.
	Comprehensive Community	294 (29.7%)	365 (39.8%)		0.98 (0.66 to 1.46)
	Academic Program	434 (43.8%)	284 (30.9%)		1.59 (1.06 to 2.40)
	Integrated Network Program	202 (20.4%)	192 (20.9%)		1.29 (0.85 to 1.96)
Histology, N (%)					
	Adenocarcinoma	488 (49.3%)	351 (38.2%)	<0.001	Ref.
	Squamous	419 (42.3%)	535 (58.3%)		0.60 (0.49 to 0.74)
	Other	83 (8.4%)	32 (3.5%)		2.05 (1.27 to 3.29)
Tumor location, N (%)					
	Central	32 (3.2%)	64 (7.0%)	<0.001	Ref.
	Right	561 (56.7%)	557 (60.7%)		3.17 (1.52 to 6.60)
	Left	396 (40.0%)	293 (31.9%)		4.45 (2.10 to 9.40)

* Selected variables in the model are presented based on clinical relevance.

Characteristics of patients who underwent surgery.		
Procedure, N (%)		
	Sub-lobar resection	103 (10.4%)
	Lobectomy	875 (88.4%)
	Pneumonectomy	12 (1.2%)
Approach, N (%)		
	Robotic	46 (10.8%)
	VATS	104 (24.4%)
	Open	277 (64.9%)
Sequence of Systemic therapy, N (%)		
	Neoadjuvant	584 (59.0%)
	Adjuvant	382 (38.6%)
	Unknown	24 (2.4%)
Sequence of Radiation therapy, N (%)		
	Neoadjuvant	376 (38.0%)
	Adjuvant	281 (28.4%)
	No Radiotherapy	333 (33.6%)
Margins status, N (%)		
	Negative	823 (83.1%)
	Positive	121 (12.2%)
	Indeterminate	46 (4.6%)
Length of stay (median, IQR)		5 (3-7)
30-day mortality , N (%)		14 (1.4%)
90-day mortality , N (%)		47 (4.7%)

Rodriguez Quintero JH. WCLC, 2024.

Are these populations homogeneous?

- T4… they are not all the same…
- N2…. N2a? N2b?
- All patients in the CRT arm were unsresectable?

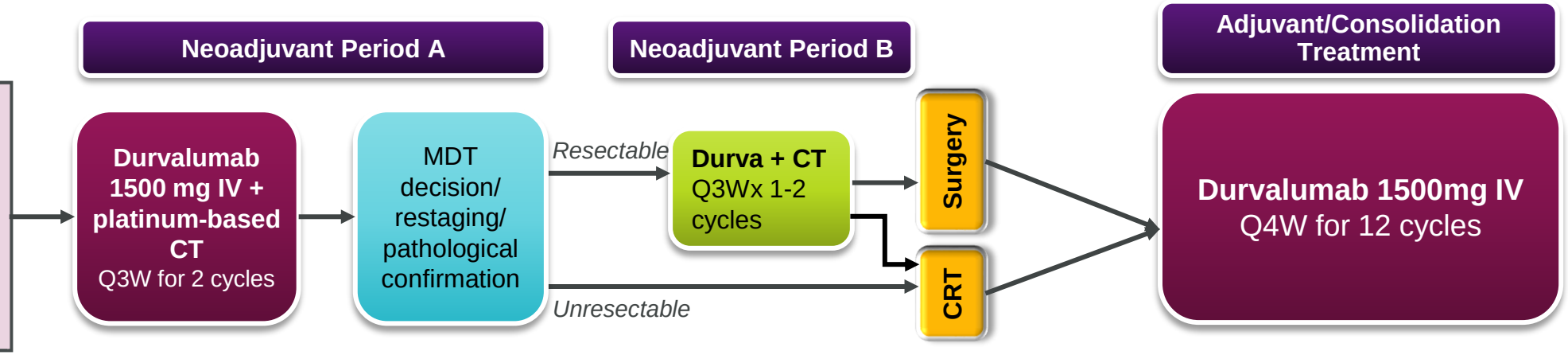
MDT-BRIDGE: Study Design

Soon recruiting at IRCCS "Giovanni Paolo II" PugliaSalute

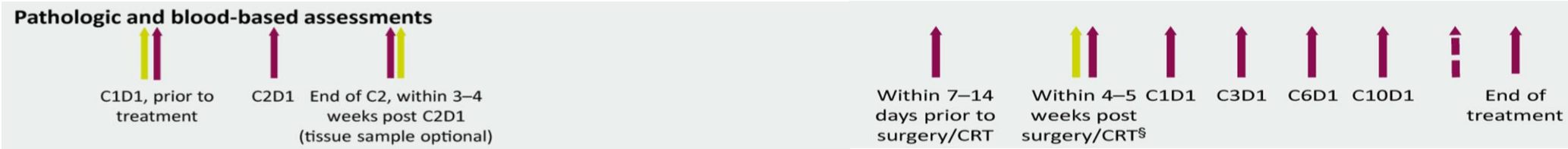
MDT Baseline Assessment

Study population

- Resectable & borderline resectable stage IIB – IIIB[a] NSCLC
- ECOG PS 0-1
- EGFRwt / ALKwt (local test)
- Pre-operation RT not allowed



Primary completion date: April 2026

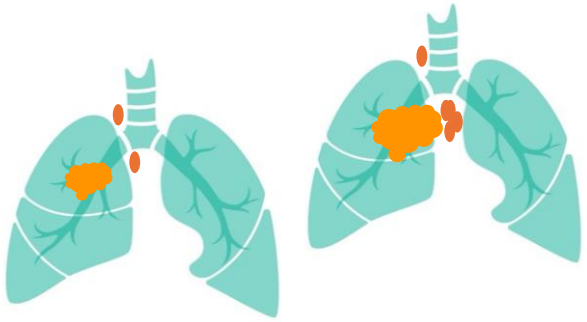


Primary	Key secondary
• Resection rate	• R0, R1, and R2 resection rates • pCR • EFS • OS • Safety • ctDNA clearance

Reck M et al. Clin Lung Cancer, 2024.

The role of multidisciplinary tumor board at modern time

R0



N
(n2b, bulky, etc.)

Molecular testing

Adj/Neo

PD-L1

Timing

Rethinking an algorithm

Unresectable

Unoperable

N2b
bulky, invasive
cCRT

PD-L1+ wt → **PACIFIC**

EGFRm → **LAURA**

ALK → **cCRT / Trial**

N2b → **T**

EGFR, ALK, PD-L1

N2b
nbni

WT

< 1% → Perioperative C-IO

1-49 → Perioperative C-IO

≥ 50% → Perioperative C-IO

Concluding remarks

- PACIFIC is still the standard of care for unresectable LA-NSCLC without genomic alterations (EGFR/ALK…)
- LAURA will be soon the standard of care for unresectable LA-NSCLC with EGFR common activating mutations
- Adding IO to IO could lead to increased cure rate and survival
- Activating mutations other than EGFR need clinical trials
- Multidisciplinary tumor board is the key step in the journey of LA-NSCLC: resectability; N-involvement; staging; molecular tests…
- Borderline-resectable is still a matter of debate: clinical trials are needed (eg. MDT-Bridge)
- ctDNA (MRD) monitoring, radiomics and AI will help clinicians in monitoring disease