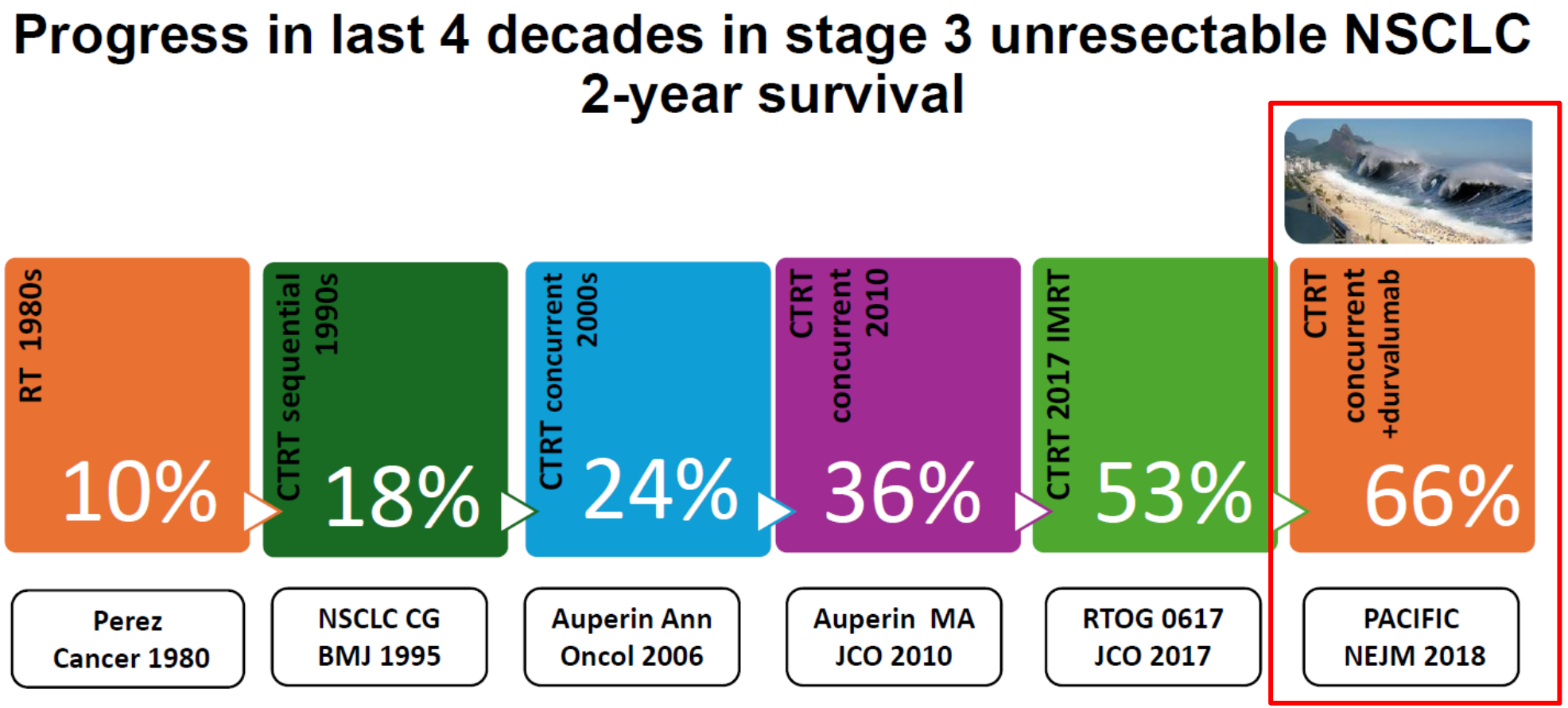
Optimal treatment options in unresectable stage III NSCLC

PACIFIC data 의 후속 연구와 RWE/표적치료제의 사용
(LAURA/platinum study)

건국대병원 호흡기내과 김인애

Introduction



Standard treatment

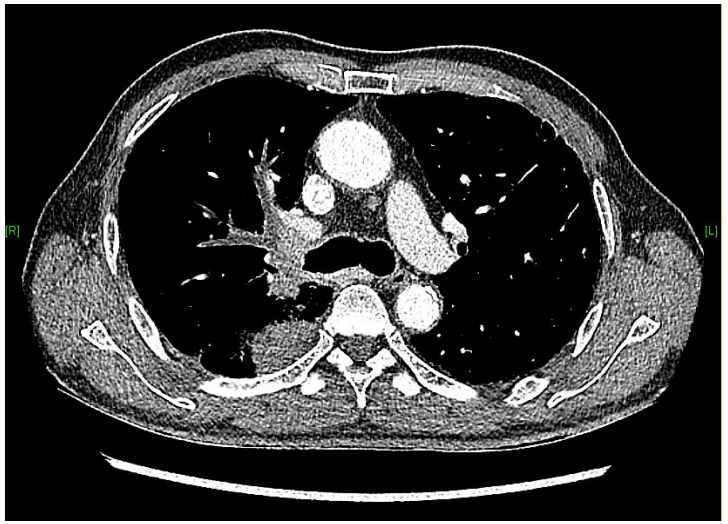
- In early 2018, the **PACIFIC trial regimen** was approved by the US FDA → changed the disease's paradigm
- **Past :** Cisplatin/etoposide and weekly Cis/Carboplatin-paclitaxel+ RT in unresectable stage III NSCLC.
  - cCRT is preferred to sequential treatment (OS benefit of 4.5% at 5 years)
  - Sequential CRT or radiotherapy (RT) alone is recommended for frail patients
  - Most patients will relapse after CCRT.
  - mPFS was short at 8-12 months, and 5-year OS rates are still low at **15**-25%.
- **Present**
  - Concurrent chemoradiotherapy ➔ **consolidation Immunotherapy for 1 year (Durvalumab)**
    - cCRT : Platinum-based doublet chemotherapy + radiotherapy (60–66 Gy in 30 faction)

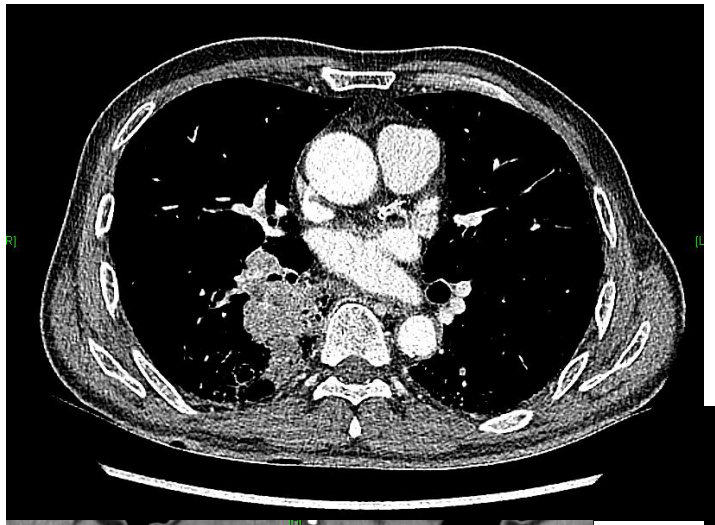
Unresectable stage III NSCLC

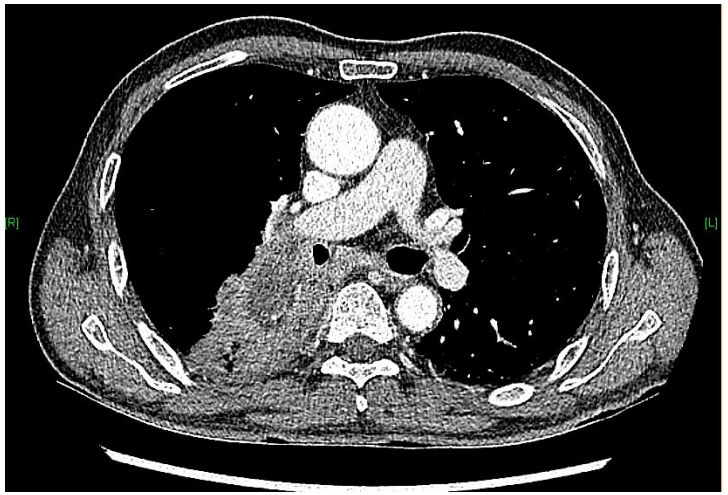
- **Definition of Unresectable Stage III NSCLC -**tumors that have spread to nearby structures or lymph nodes but have not metastasized
  - Tumor is too large (≥5 cm) or invasive viral organs(large vessel, heart, spine, diaphragm)
  - Bulky lymph node(≥3 cm), multi-station N2 or N3, supraclavicular lymph node
  - **T4 disease:** Size>7cm
    - tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus
  - Patient factor : inadequate cardiopulmonary reserve, comorbidities
  - Technical feasibility : achieving an R0 resection.

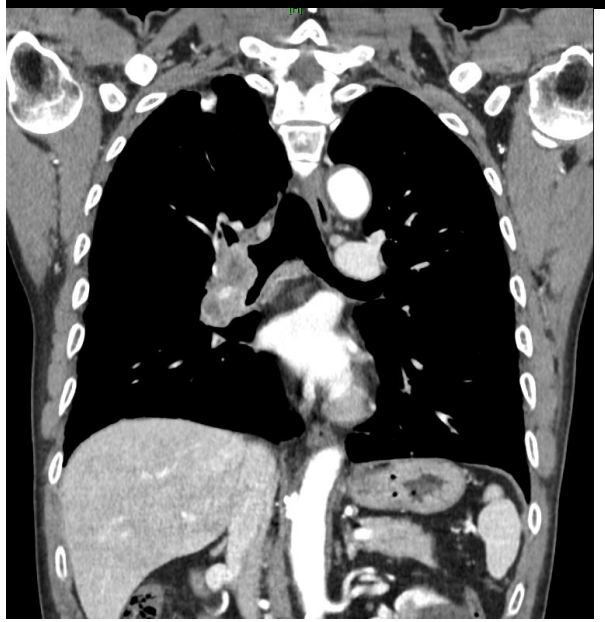
- Case-by-case basis by an experienced thoracic surgeon in a multidisciplinary team environment.

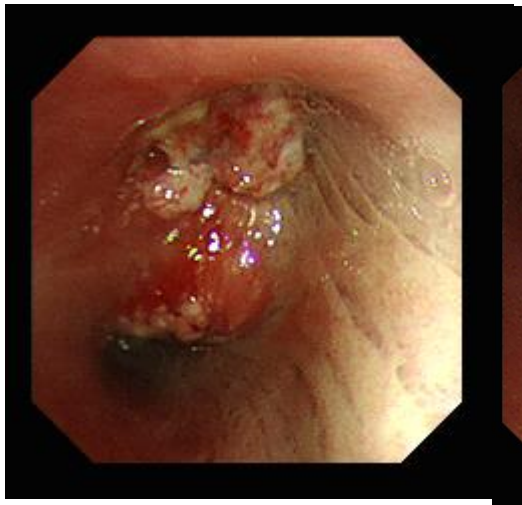
Unresectable case #1(69/M)

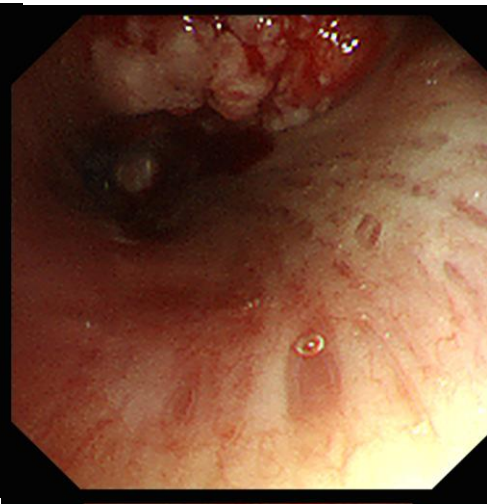


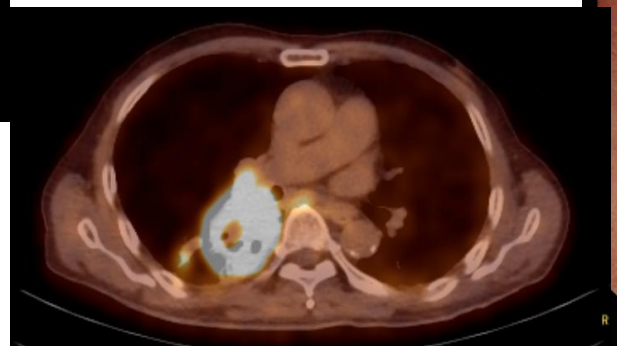


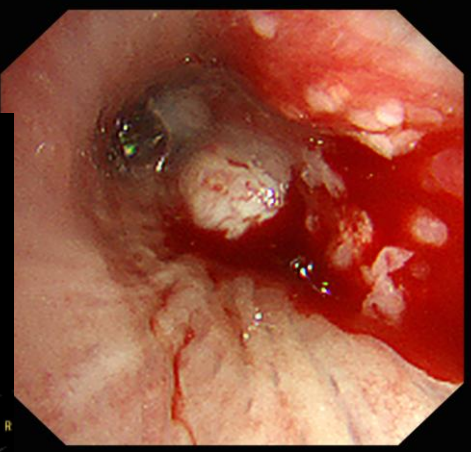










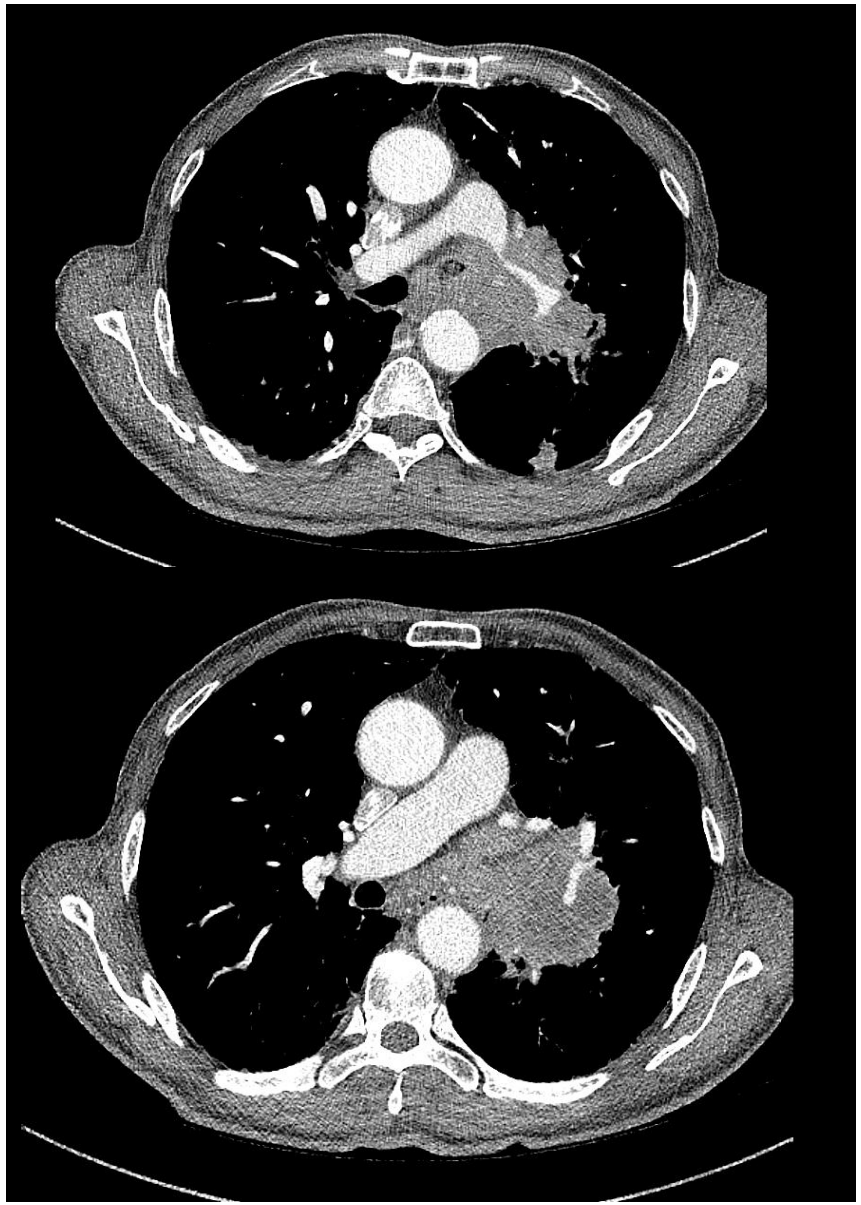


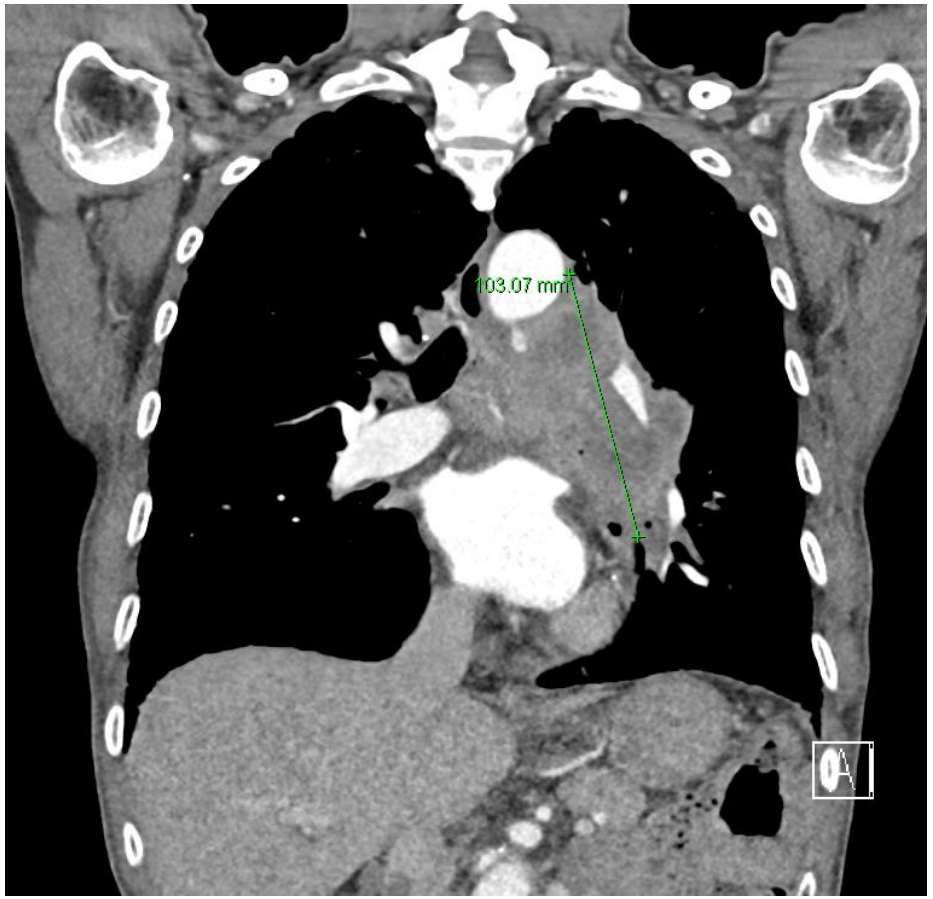
NSCLC, SqCC, cT4N2M0 IIIB
ex-smoker 50YS
PD-L1 sp263 1%
COPD (FEV1 46% DLCO 30%)

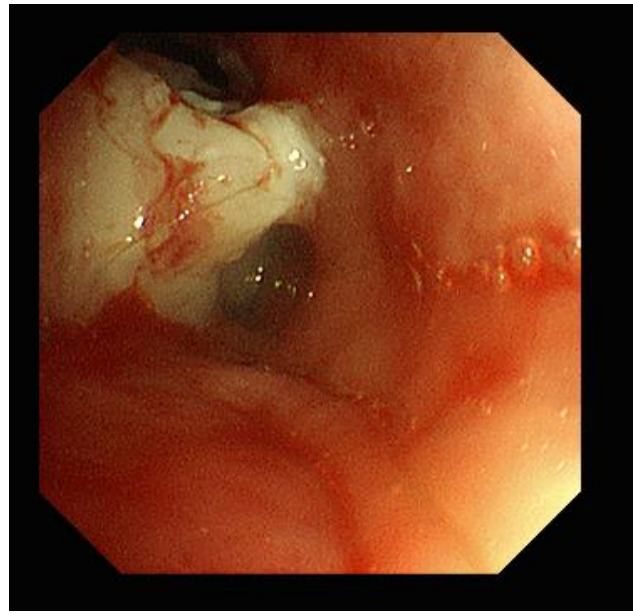
PET-CT 판독

- 6.9 cm sized hypermetabolic mass lesion, central and posterior portion of lung RUL/RML/RLL
- Hypermetabolic nodular lesions, lung RLL-R/O Lung to lung metastases.
- Hypermetabolism, 2R, prevascular, 4R, subcarinal lymph nodes

Case #2 (71/M)



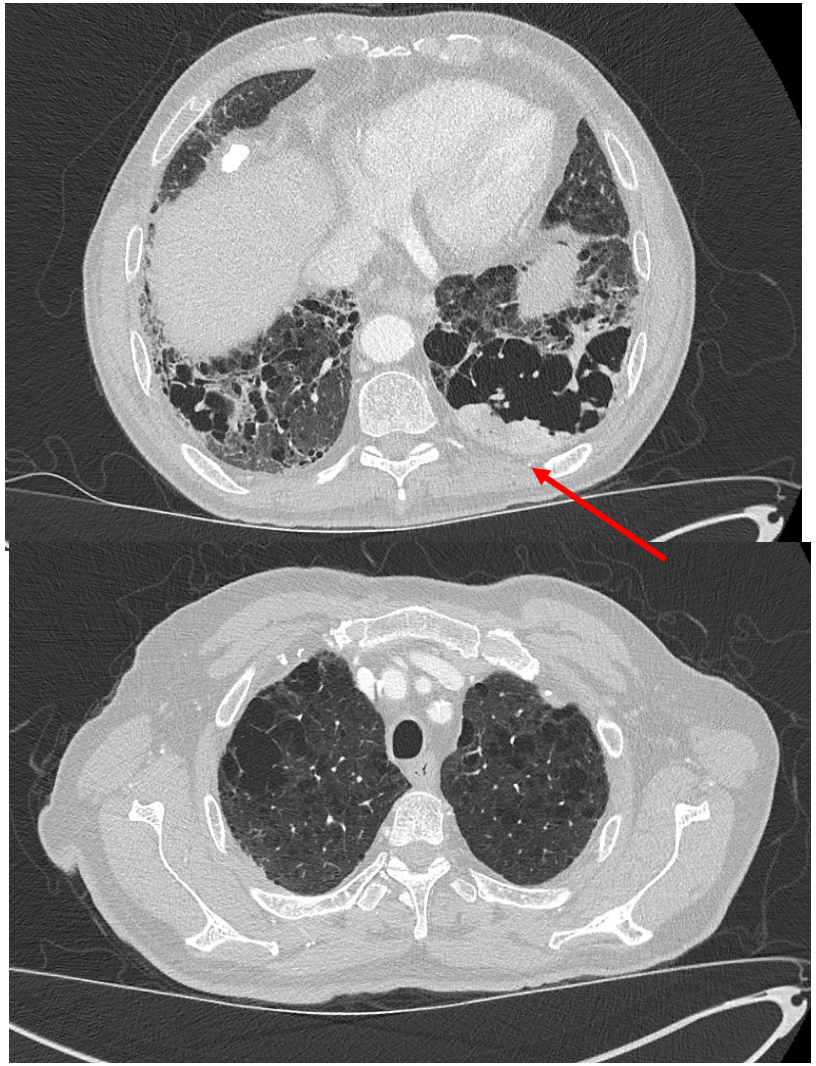


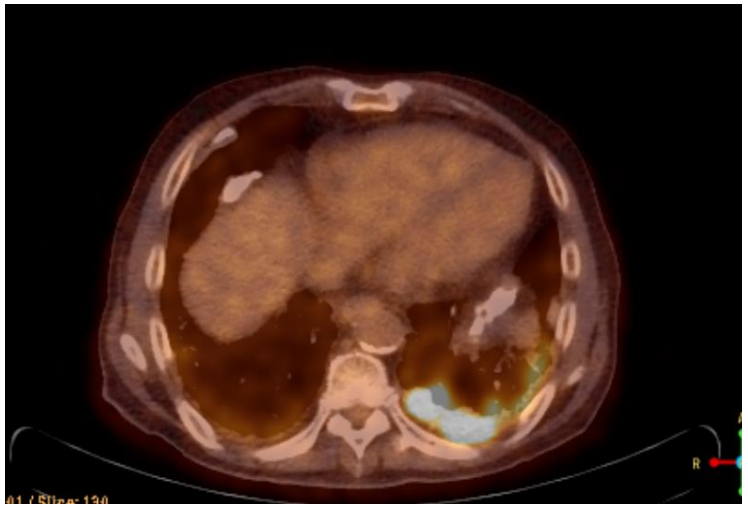


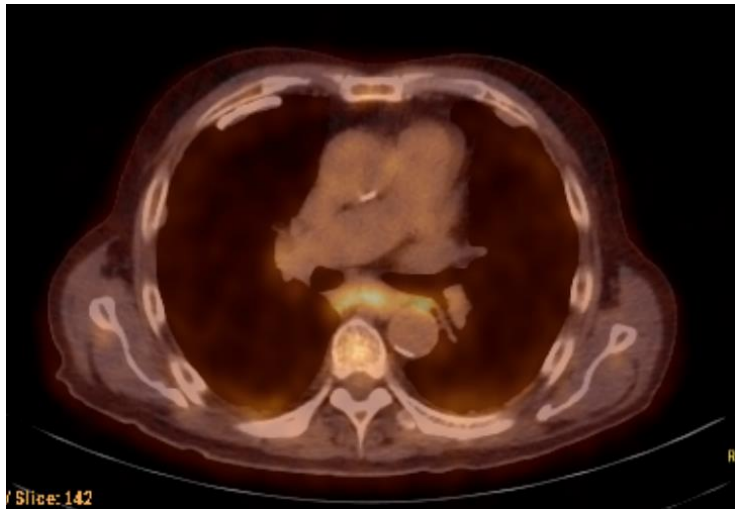
9.3 cm sized hypermetabolic mass lesion, left pulmonary hilar area.
Hypermetabolic nodular lesion at lung LLL posterior periphery

NSCLC, cT4N0M0 stage IIIIA
PDL1 sp263 = 90%
life-long smoker

Case #3 (82/M)





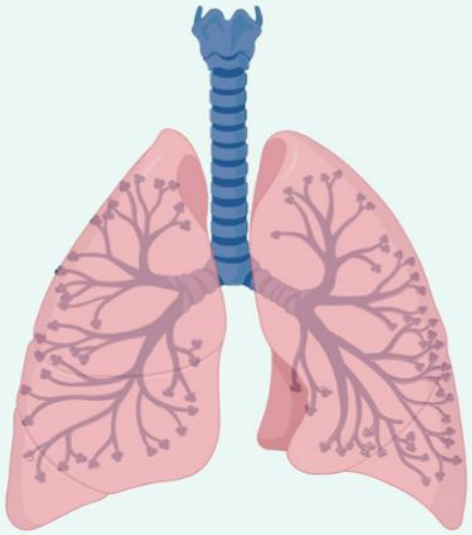


PET-CT 판독
Lung LLL 에 9.5 cm hypermetabolic multiloculated cystic mass 가 관찰됨(SUVmax=14.0)
Lt pulmonary hilar, subcarinal, celiac area 에 hypermetabolic LNs가 관찰됨 (SUVmax=5.6)
LN metastases 가능성을 배제할 수 없음.

Ex-smoker 16 y, 125 py NSCLC, SqCC, cT4N2M0 stage IIIC
COPD FEV1/FVC 69 FVC 77% FEV1 90% DLCO 30% → Medically inoperable

Heterogeneous group

Stage III NSCLC



Stage IIIA

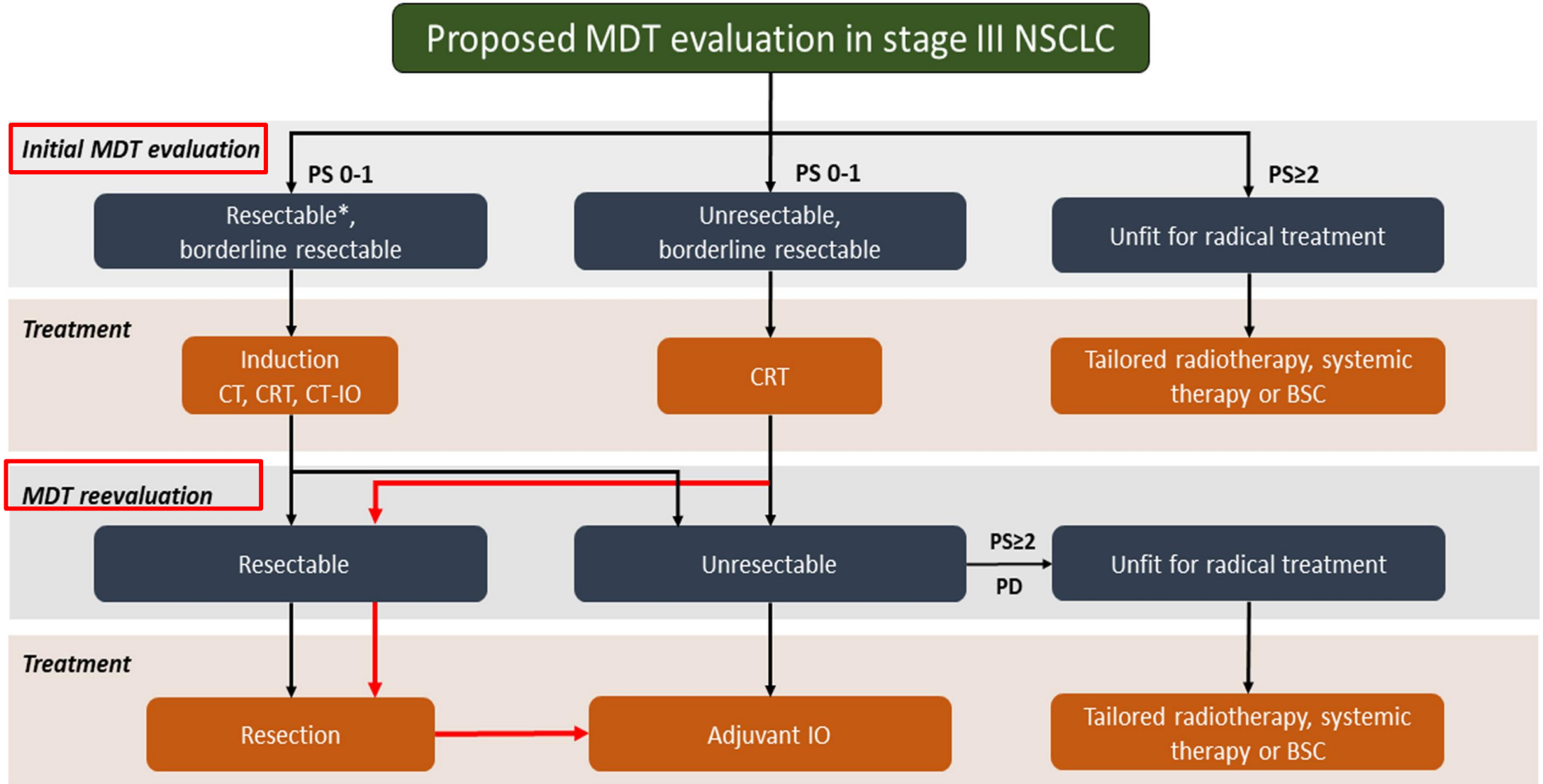
- Neoadjuvant Chemotherapy + Immunotherapy
  - CHECKMATE 816
    - Nivolumab+ cCT vs chemo
    - mEFS : 31.6 mos vs 20.8 mos, PCR: 24% vs 2.2%
  - KEYNOTE 671
    - Pembrolizumab+ cCT vs chemo
    - mEFS : NR vs 17 mos, major pathological response 30.2% vs 11%
  - → Definitive Surgery
    - +/- → Adjuvant Chemotherapy +/- Radiation
      - To be incorporated on a case-by-case basis
    - → Adjuvant Pembrolizumab
      - KEYNOTE 671
- Definitive Surgery
  - 바로 수술
  - → Adjuvant Targeted Therapy
    - ADAURA (*EGFR exon 19 deletion or Exon 21 L858R mutation*)
      - Osimertinib vs Placebo +/- adjuvant chemotherapy
      - DFS at 24 months: 98% vs 85%
    - ALINA (*ALK positive*)
      - Alectinib vs Placebo
      - DFS at 24 months: 93.6% vs 63.7%
  - → Adjuvant Chemotherapy + Immunotherapy
    - IMpower 010 in PD-L1≥ 1%
      - Atezolizumab vs best supportive care
      - PD-L1≥ 1%, 3-yr DFS 60% vs 48%
    - KEYNOTE-091
      - Pembrolizumab vs placebo, adjuvant CT optional
      - 3-yr median DFS 53.6 months vs 42 months
- Medically not fit for surgery/in-operable location of tumor
  - → Concurrent Chemotherapy + Radiation
    - → Maintenance Durvalumab
      - PACIFIC

Stage IIIB

- T3-T4, N2
  - Pathological confirmation of N2 disease after biopsy of ipsilateral and contralateral mediastinal lymph nodes
  - → Evaluate Surgical Candidacy and consider treatment as Stage IIIA disease
- T3-T4, N2
  - Clinical N2 disease, lack of pathological assessment of contralateral mediatinal lymph nodes
  - → Concurrent Chemotherapy + Radiation
    - → Maintenance Durvalumab
      - PACIFIC
- T1-T2, N3
  - Pathological confirmation of N3 disease
  - → Concurrent Chemotherapy + Radiation
    - → Maintenance Durvalumab
      - PACIFIC

Stage IIIC

- → Concurrent Chemotherapy + Radiation
  - → Maintenance Durvalumab
    - PACIFIC
    - Durvalumab vs Placebo
    - mOS 47.5 months vs 29.1 months



* = to be redefined

Abbreviations: PS = performance score, CT = chemotherapy, IO = immune oncology agents, CRT = chemoradiotherapy, BSC = best supportive care, PD = progressive disease, MDT = multidisciplinary tumor board , NSCLC = non-small cell lung cancer

Index: black arrow = conventional algorithms, red arrows = reassessing resectability after radical chemoradiotherapy but prior to adjuvant immunotherapy

The NEW ENGLAND JOURNAL of MEDICINE

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Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

713 pts with unresectable stage III NSCLC

PACIFIC: Study Design

Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Study

- 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

All-comers population

1-42 days post-CRT

R

2:1 randomization, stratified by age, sex, and smoking history N=713

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

Placebo N=237

Co-primary endpoints
- PFS by BICR using RECIST v1.1
- OS

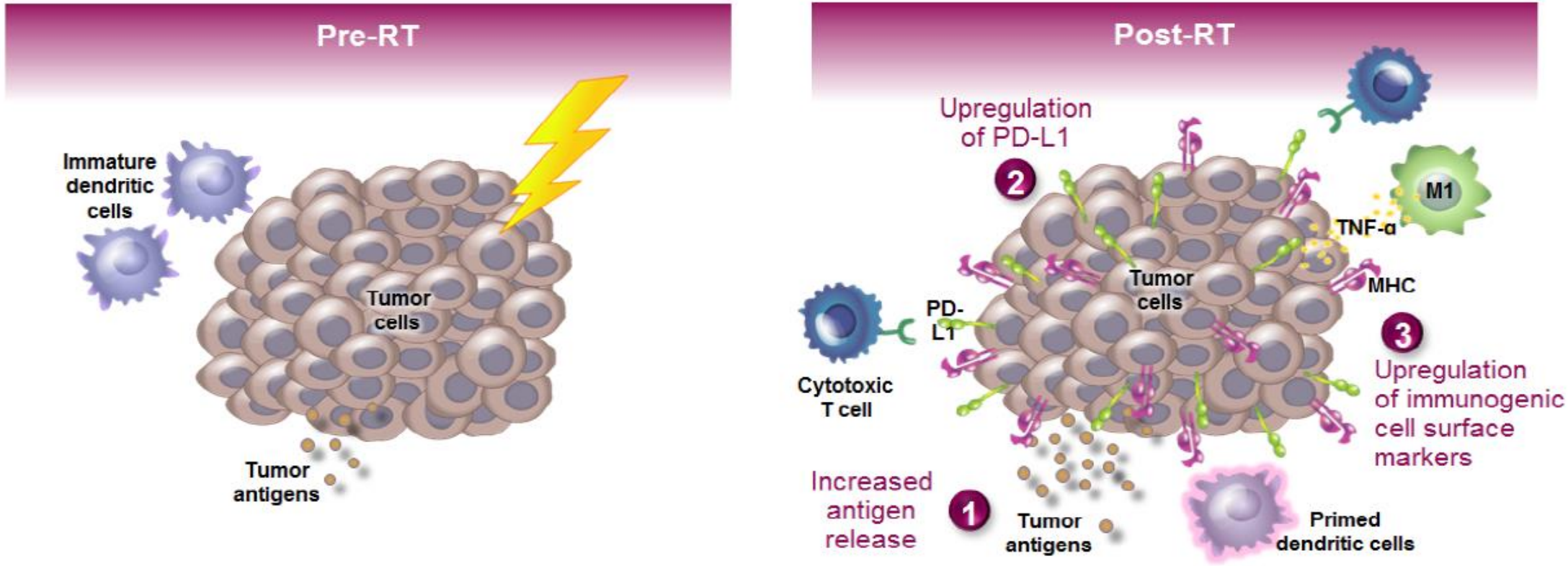
Key secondary endpoints
- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

Durvalumab PDL1 inhibitor

Table 1. Baseline Characteristics, Stratification Factors, and Prior Therapy in the Intention-to-Treat Population.*

Characteristic	Durvalumab (N=476)	Placebo (N=237)	Total (N=713)
Age — yr			
Median	64	64	64
Range	31–84	23–90	23–90
Sex — no. (%)			
Male	334 (70.2)	166 (70.0)	500 (70.1)
Female	142 (29.8)	71 (30.0)	213 (29.9)
Race — no. (%)†			
White	337 (70.8)	157 (66.2)	494 (69.3)
Black	12 (2.5)	2 (0.8)	14 (2.0)
Asian	120 (25.2)	72 (30.4)	192 (26.9)
Disease stage — no. (%)			
IIIA	252 (52.9)	125 (52.7)	377 (52.9)
IIIB	212 (44.5)	107 (45.1)	319 (44.7)
Other‡	12 (2.5)	5 (2.1)	17 (2.4)
WHO performance-status score — no. (%)§			
0	234 (49.2)	114 (48.1)	348 (48.8)
1	240 (50.4)	122 (51.5)	362 (50.8)
Tumor histologic type — no. (%)			
Squamous	224 (47.1)	102 (43.0)	326 (45.7)
Nonsquamous	252 (52.9)	135 (57.0)	387 (54.3)
Smoking status — no. (%)			
Current smoker	79 (16.6)	38 (16.0)	117 (16.4)
Former smoker	354 (74.4)	178 (75.1)	532 (74.6)
Never smoked	43 (9.0)	21 (8.9)	64 (9.0)
Previous radiotherapy — no. (%)¶			
<54 Gy	3 (0.6)	0	3 (0.4)
≥54 to ≤66 Gy	442 (92.9)	217 (91.6)	659 (92.4)
>66 to ≤74 Gy	30 (6.3)	19 (8.0)	49 (6.9)
Previous chemotherapy — no. (%)‖			
Induction	123 (25.8)	68 (28.7)	191 (26.8)
Concurrent with radiation therapy	475 (99.8)	236 (99.6)	711 (99.7)
Best response to previous chemoradiotherapy — no. (%)			
Complete response	9 (1.9)	7 (3.0)	16 (2.2)
Partial response	232 (48.7)	111 (46.8)	343 (48.1)
Stable disease	222 (46.6)	114 (48.1)	336 (47.1)

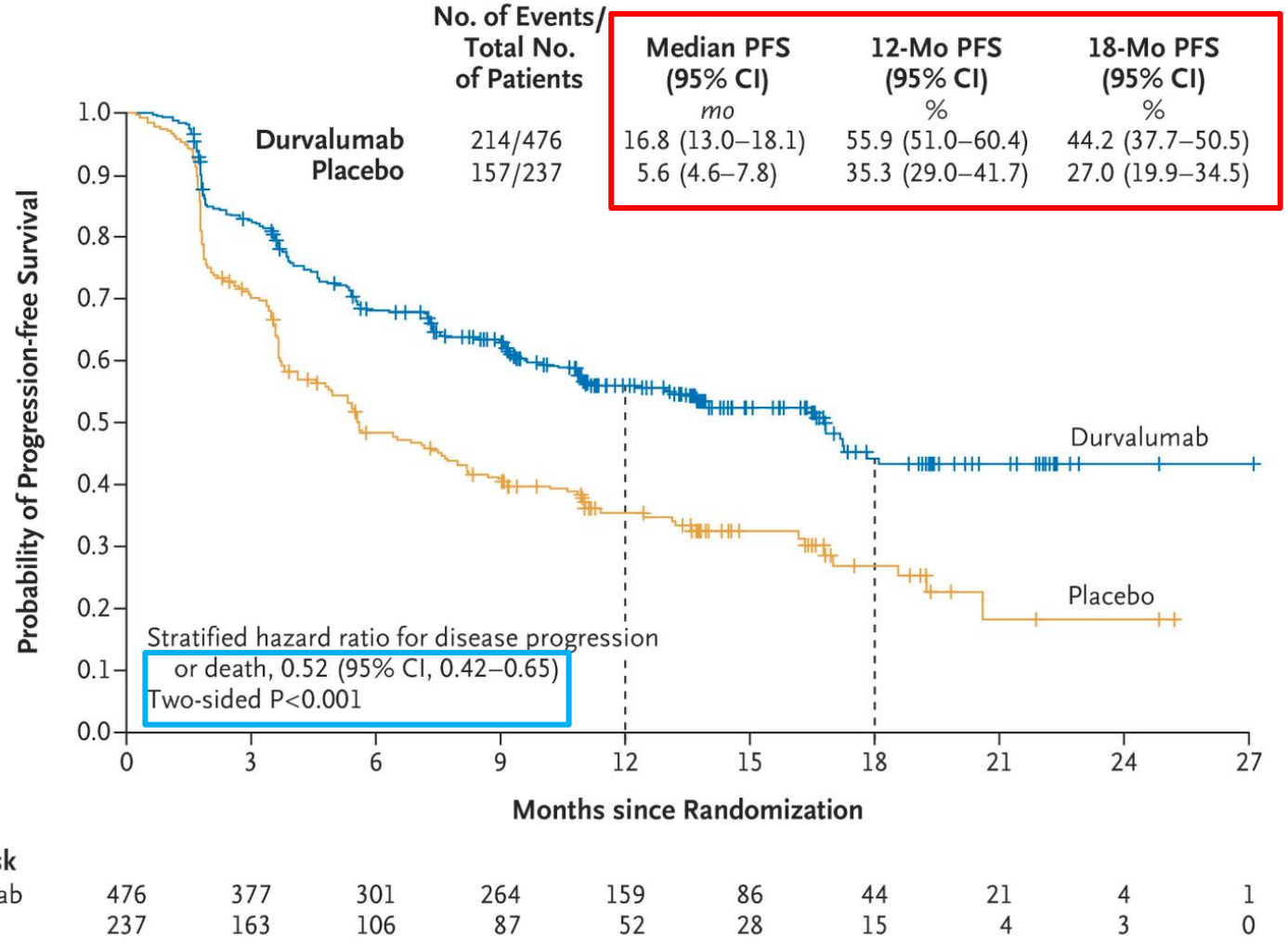
RT Induces Multiple Immunomodulatory Changes That May Influence the Effectiveness of Immunotherapy[1-3]



M1, tumor-associated macrophage; MHC I, major histocompatibility complex I; PD-L1, programmed cell death-ligand 1; TNF-α, tumor necrosis factor alpha.
1. Daly ME, et al. *J Thorac Oncol*. 2015;10(12):1685-1693. 2. Kaur P, Asea A. *Frontiers Oncol*. 2012;2:191. 3. Deng L, et al. *J Clin Invest*. 2014;124(2):687-695.

Preclinical evidence suggests that chemotherapy and RT may upregulate PD-L1 expression in tumor cells. Radiotherapy may increase the production and presentation of tumor antigens and induce interferon signaling that enhances the antitumor immune responses

Progression-free Survival in the Intention-to-Treat Population



Duvalumab vs Placebo

Median PFS: 16.8 vs 5.6 months

Response rate: 28.4 vs 16%

Grade >III AE 29.9 vs 26.1%

N Engl J Med 2017;377:1919-29.

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
Smoking status			
Smoker	433	216	0.59 (0.47–0.73)
Nonsmoker	43	21	0.29 (0.15–0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40–0.71)
IIIB	212	107	0.59 (0.44–0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50–0.92)
Nonsquamous	252	135	0.45 (0.33–0.59)
Best response			
Complete response	9	7	—
Partial response	232	111	0.55 (0.41–0.75)
Stable disease	222	114	0.55 (0.41–0.74)
PD-L1 status			
≥25%	115	44	0.41 (0.26–0.65)
<25%	187	105	0.59 (0.43–0.82)
Unknown	174	88	0.59 (0.42–0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)

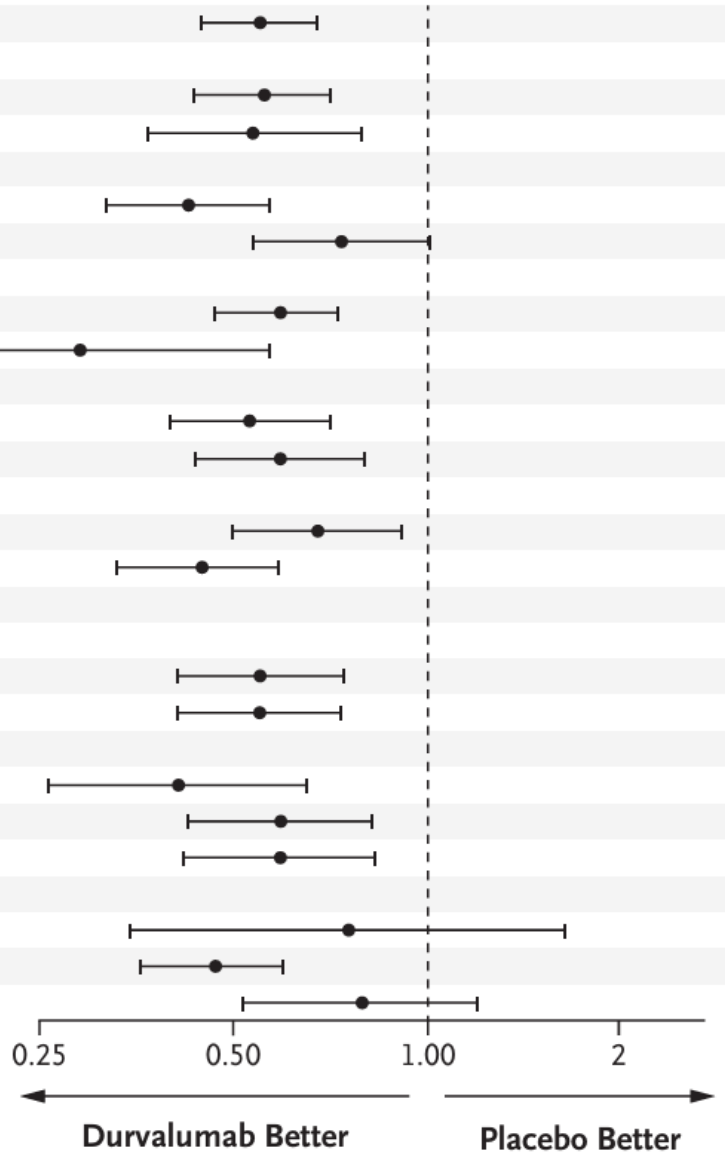


Figure 2. Subgroup Analysis of Prognostic Factors for Progression-free Survival in the Intention-to-Treat Population.

Meeting Abstract: 2019 ASCO Annual Meeting I

FREE ACCESS | Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers | May 26, 2019

Three-year overall survival update from the PACIFIC trial.

Authors: Jhanelle Elaine Gray, Augusto E. Villegas, Davey B. Daniel, David Vicente, Shuji Murakami, Rina Hui, Takayasu Kurata, ... SHOW ALL ... , and Scott Joseph Antonia | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 37, Number 15_suppl • https://doi.org/10.1200/JCO.2019.37.15_suppl.8526

BRIEF REPORT

IASLC

Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC—an Update From the PACIFIC Trial

Check for updates

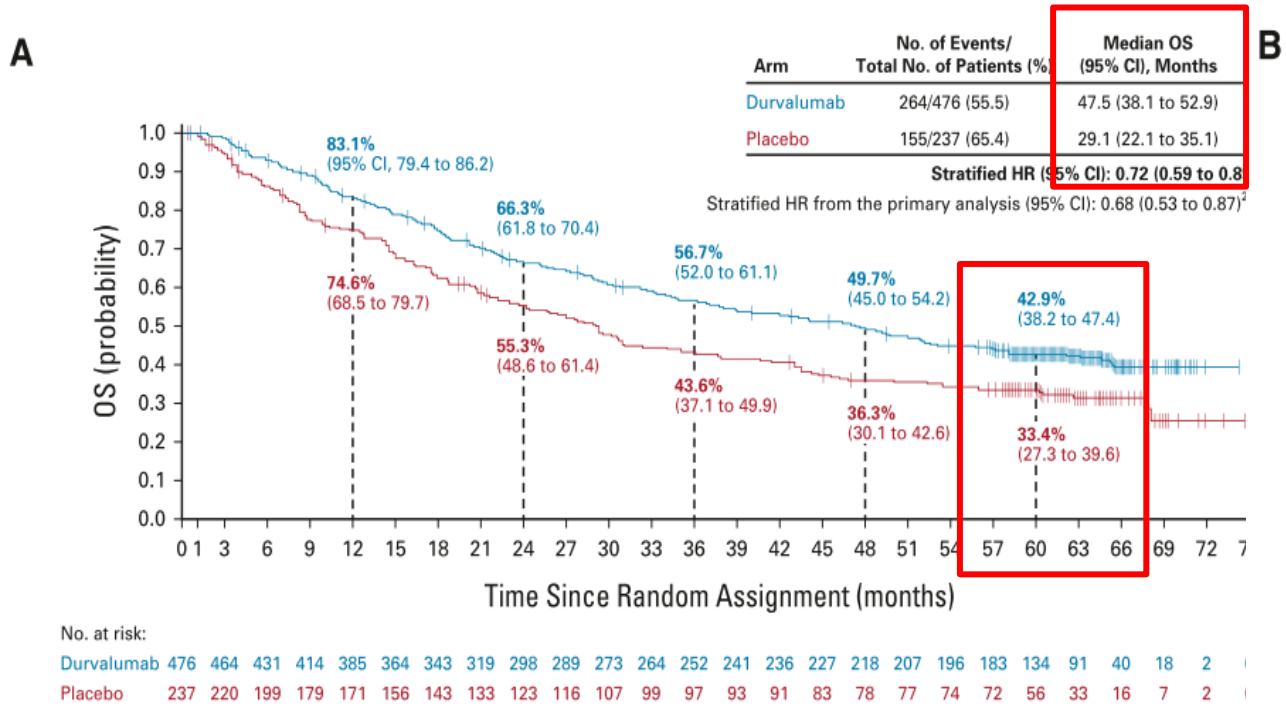
J Thorac Oncol 2021

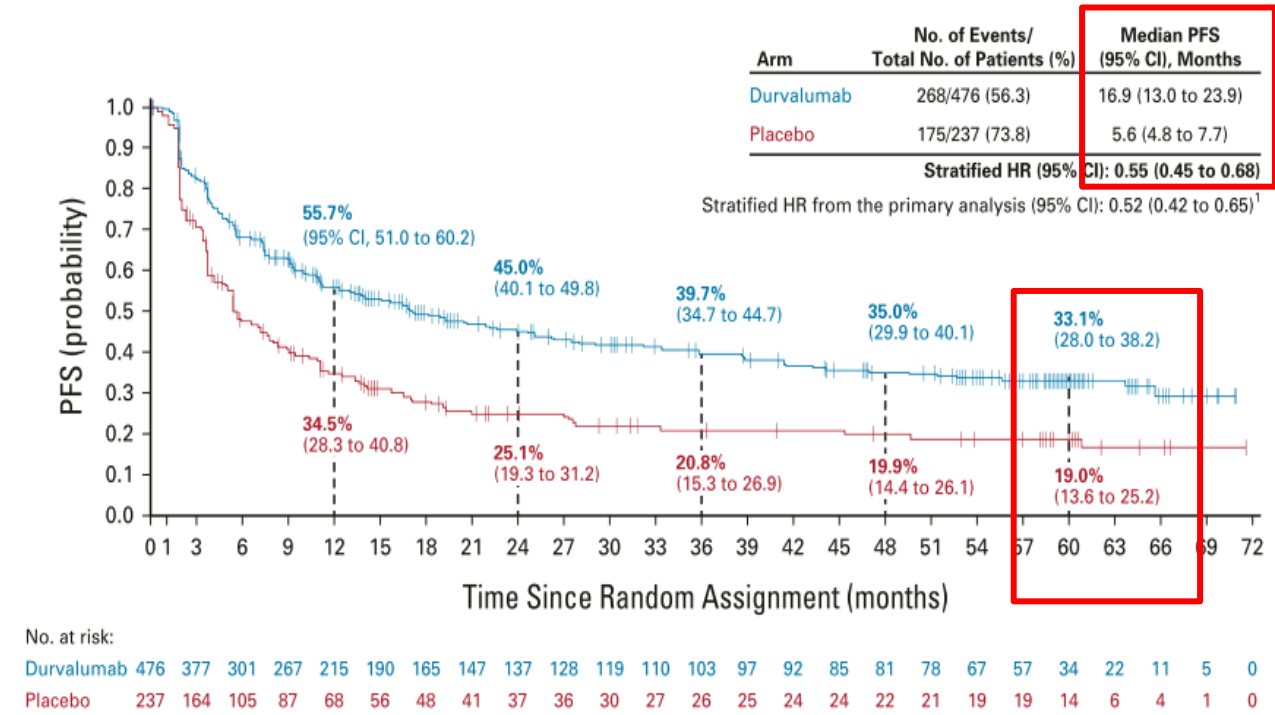
Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

J Clin Oncol 2022

Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

PACIFIC 5-Year Update





5-year OS Duvalumab **42.9%**
mOS **47.5** months(HR 0.68)
5-year PFS **33.1%** → 5년 후에도 재발 안한 사람이 30%
Distance metastasis 가 감소

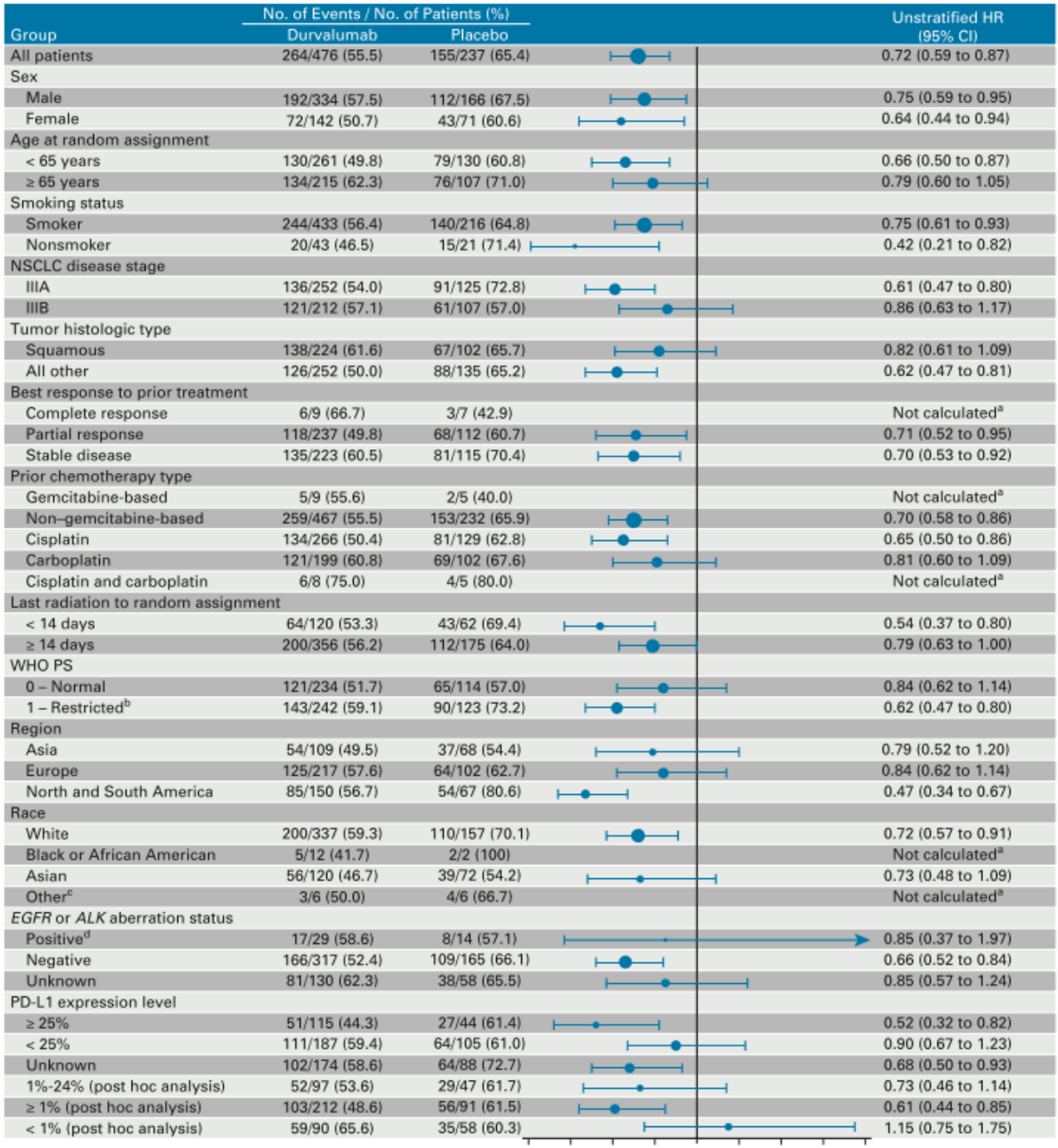
Spigel et al. **J Clin oncol 2022**

Prognostic factor

- Younger age (<65 years)
- Objective tumor response
- Nonsquamous tumor
- WHO PS 0 >1
- Cisplatin use

- Durable antitumor response
- Reduced frequency of metastases

* OS did not improve in tumors with PD-L1 ⩽1%



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)

Updated OS

TABLE 3. Multivariable Cox Regression Analysis of Prognostic Baseline Factors for Overall Survival in the Intent-to-Treat Population

	Comparator		Reference		
Baseline Variable	**Group**	**No. of Events/Total No. of Patients (%)**	**Group**	**No. of Events/Total No. of Patients (%)**	**HR (95% CI)**
Treatment arm	Durvalumab	264/476 (55.5)	Placebo	155/237 (65.4)	0.71 (0.58 to 0.87)[a]
Age, years	≥ 65	210/322 (65.2)	< 65	209/391 (53.5)	1.30 (1.06 to 1.59)[a]
Disease stage[b]	IIIB	182/319 (57.1)	IIIA	227/377 (60.2)	1.03 (0.84 to 1.26)
Best response to prior treatment[c]	CR/PR	195/365 (53.4)	SD	216/338 (63.9)	0.88 (0.72 to 1.08)
Tumor histologic type	Squamous	205/326 (62.9)	Nonsquamous	214/387 (55.3)	1.28 (1.04 to 1.58)[a]
WHO PS	1[d]	233/365 (63.8)	0	186/348 (53.4)	1.23 (1.01 to 1.50)[a]
Prior platinum CT agent[e]	Cisplatin	215/395 (54.4)	Carboplatin	190/301 (63.1)	0.84 (0.69 to 1.03)
Race	Asian	95/192 (49.5)	White	310/494 (62.8)	0.63 (0.49 to 0.81)[a]
	Black or African American	7/14 (50.0)			0.81 (0.38 to 1.73)
	Other[f]	7/13 (53.8)			0.91 (0.41 to 1.99)
Sex	Male	304/500 (60.8)	Female	115/213 (54.0)	1.27 (1.01 to 1.61)[a]
Smoking status	Smoker	384/649 (59.2)	Nonsmoker	35/64 (54.7)	0.83 (0.56 to 1.22)
Time from CRT to random assignment, days	≥ 14	312/531 (58.8)	< 14	107/182 (58.8)	0.97 (0.77 to 1.22)
EGFR or *ALK* aberration status	Positive[g]	25/43 (58.1)	Negative	275/482 (57.1)	1.06 (0.69 to 1.64)
	Unknown	119/188 (63.3)			0.95 (0.73 to 1.23)
PD-L1 expression level	TC ≥ 25%	78/159 (49.1)	TC < 25%	175/292 (59.9)	0.82 (0.62 to 1.07)
	Unknown	166/262 (63.4)			1.19 (0.92 to 1.54)

Standard of treatment

- **The PACIFIC trial, a phase 3 randomized trial**
- Durvalumab as monotherapy
  ① locally advanced, unresectable stage III NSCLC, tumor PDL1 on ≥1%
  ② disease has not progressed following platinum-based concurrent chemoradiotherapy

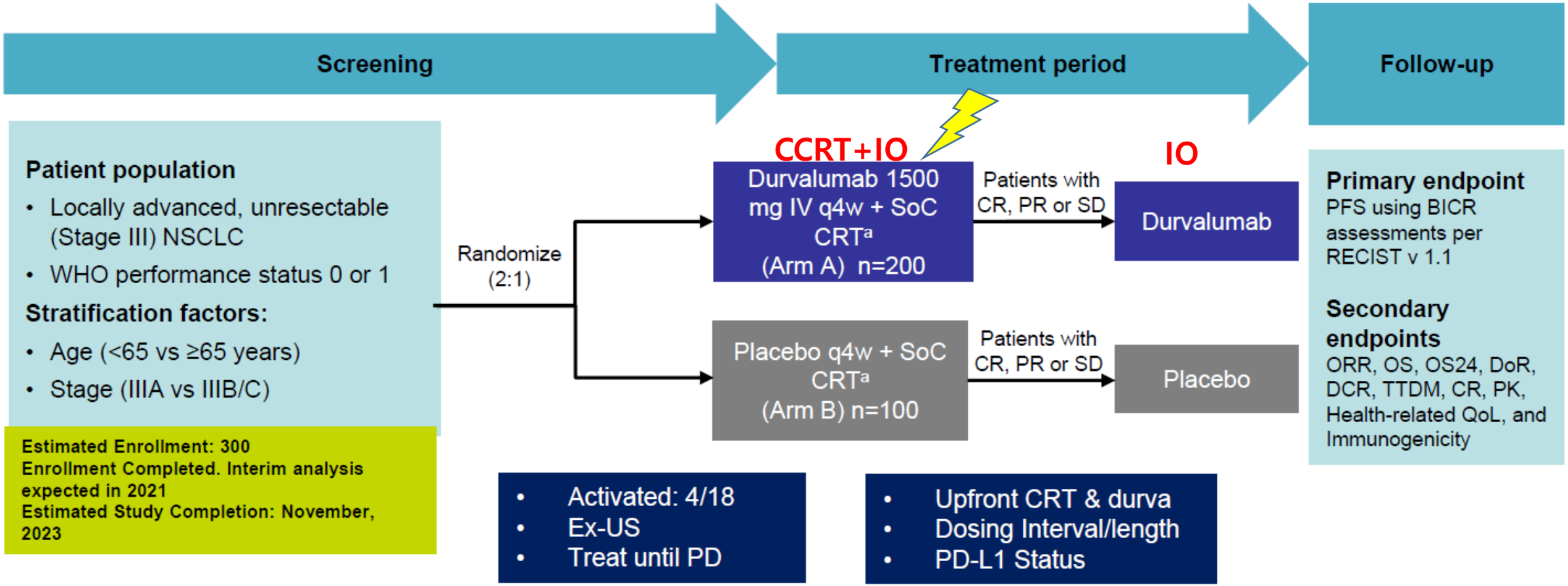
→ The PACIFIC regimen is now a global standard of care

PACIFIC 후속 연구들

PACIFIC 2 Study Design:

Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study[1,2]

Durvalumab + CRT followed by durvalumab versus placebo + CRT followed by placebo



[a]Platinum-based chemotherapy regimens include cisplatin/ etoposide, carboplatin/paclitaxel, pemetrexed/cisplatin (nonsquamous only) or pemetrexed/carboplatin (nonsquamous only), alongside radiation therapy (5 fractions/week for ~6 weeks [±3 days; total 60 Gy]).

1. Bradley JD et al. Poster presented at: ASCO Annual Meeting; May 31-June 4, 2019; Chicago, IL. Poster TPS8573; 2. Study NCT03519971. ClinicalTrials.gov website.

PACIFIC 4 Study Design: Phase 3, randomized, placebo-controlled, double-blind, multicenter study: Durvalumab first dose concurrently administered with SBRT[1]

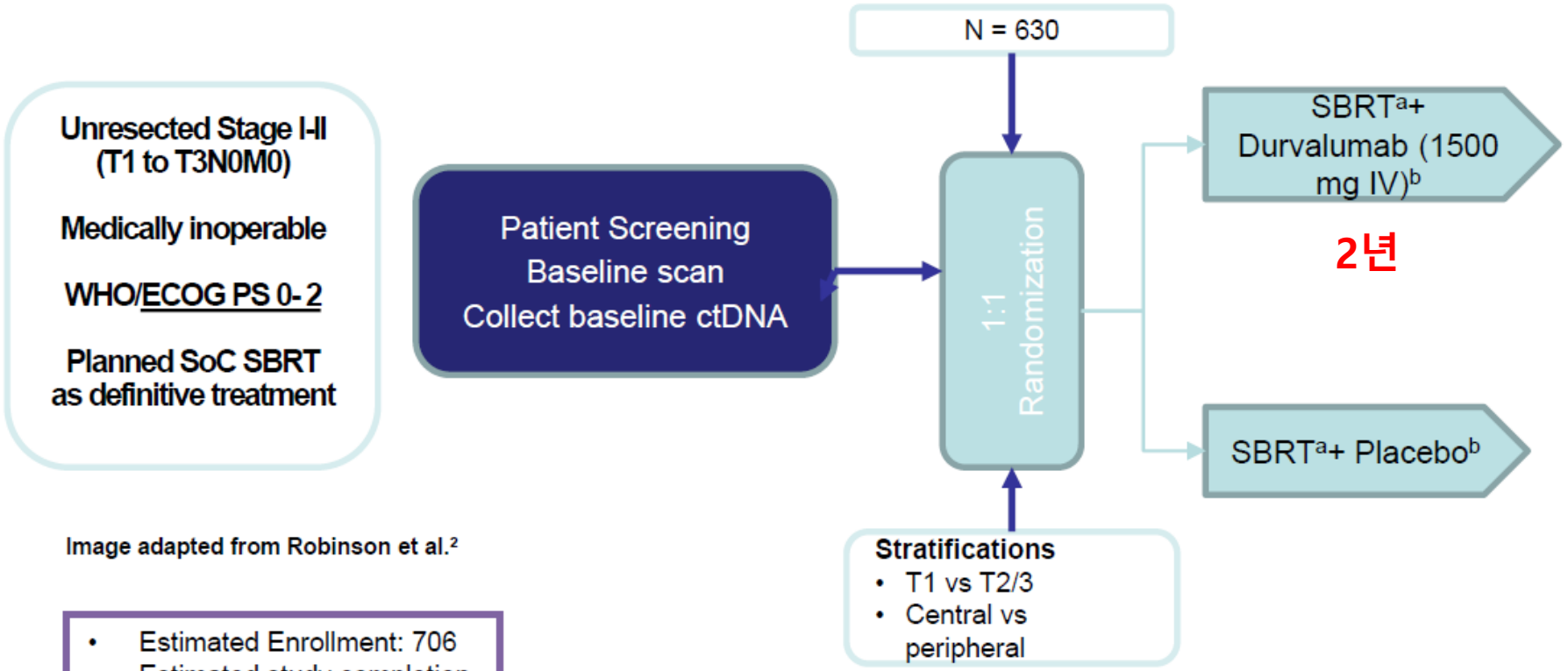


Image adapted from Robinson et al.[2]

- Estimated Enrollment: 706
- Estimated study completion date: June 2024

Primary endpoint:[1] PFS[c,d]

Key secondary endpoints:[1]
- PFS[c,d]
- OS
- Lung cancer specific mortality
- Safety and tolerability
- PFS24[e]
- PFS2[f]
- PK and immunogenicity
- TTP[e]
- TTDM[e]
- PROs

Exploratory Endpoints[2]
- Biomarkers in tumor, plasma, and/or serum; relationship between biomarker status, durvalumab PK exposure and clinical outcomes
- Additional analysis of PROs
- Health resource utilization
- Blood and tissue DNA collection for future assessment of biomarkers and gene susceptibility

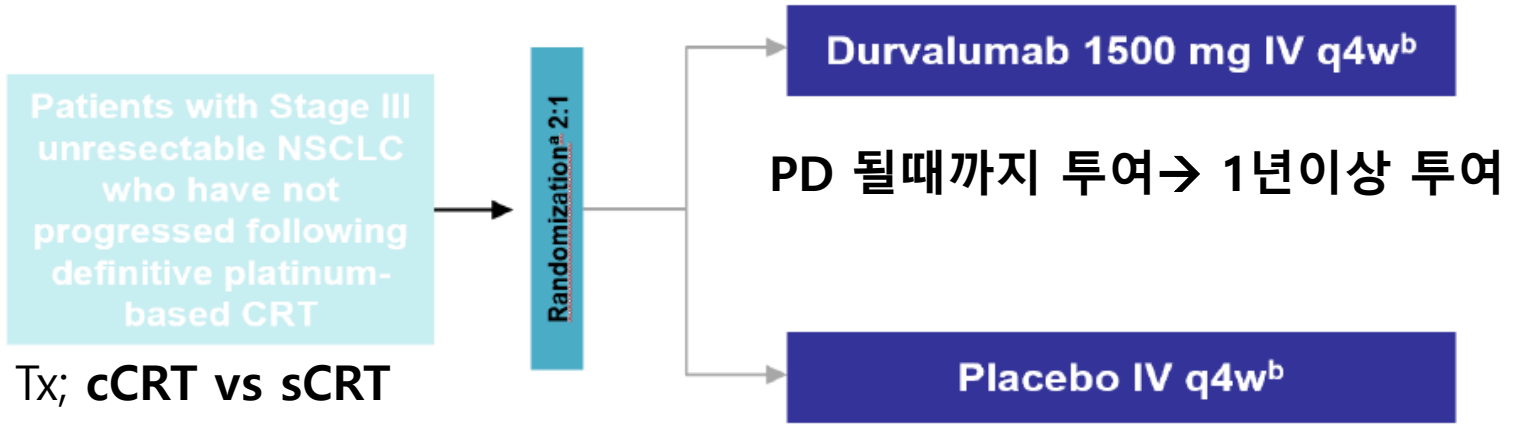
[a]Delivered in 3, 4, 5 or 8 fractions; [b]Q4W x 24 months until PD/ other discontinuation criteria are met; [c]Assessed by BICR per RECIST version 1.1; [d]In subpopulation of patients with Stage I/II NSCLC; [e]In all randomized patients with Stage I/II NSCLC; [f]Using local standard clinical practice .

1. Study NCT03833154. ClinicalTrials.gov website. 2. Robinson C, et al. Presented at: IASLC 2019 World Conference on Lung Cancer (WCLC); September 7-10, 2019, Barcelona, Spain. Poster P1.18-12.

초기 1-2 기인데 수술 못하는 경우 RT 후→ consolidation Duvalumab 4주 간격으로 2년 투여 연구 진행중. 작년 등록을 마침

PACIFIC 5 Study Design:

Phase III, randomized, double-blind, placebo-controlled, multicenter study (ex-US)



Primary Endpoints

- PFS[c]

Secondary Endpoints

- OS
- OS24
- ORR[c]
- DoR[c]
- PFS2[d]
- PFS12[c] and PFS18[c]
- TTDM[c]
- Safety and tolerability (assessed by CTCAE version 5.0)
- PK and immunogenicity
- IHC analysis of tumoral PD-L1 expression and spatial distribution within the tumor microenvironment relative to efficacy outcomes (OS, PFS, ORR)

[a]*EGFR* or *ALK* mutation randomized will be capped at approximately 15%; [b]Treatment until clinical progression/deterioration or confirmed radiological progression; [c]Assessed by BICR per RECIST version 1.1; [d]Investigator-assessed (defined according to local standard clinical practice).

Clinicaltrials.gov website. https://www.clinicaltrials.gov/ct2/show/NCT03706690. Accessed November 21, 2018.

median PFS (95% CI) was D 14.0 (10.9 vs 18.0) vs P 6.5 (5.4 vs 13.8) mo. Subgroup analyses suggested consistent PFS benefit after cCRT (HR 0.76; 95% CI: 0.55e1.06) or sCRT (HR 0.75; 95% CI: 0.49e1.18)

PACIFIC 6 Study Design: Phase 2, open-label, multicenter, international study

Sequential RT

Patients with unresectable Stage III NSCLC, who have not progressed following platinum-based sequential chemoradiation therapy[a]

Screening (max 28 days)

WHO/ECOG PS 0-1 → **Durvalumab 1500 mg IV q4w up to 24 cycles or until disease progression/ other discontinuation criterion n≈120**

WHO/ECOG PS 2 → **Durvalumab 1500 mg IV q4w up to 24 cycles or until disease progression/ other discontinuation criterion n≈30**

Stratification factors

- WHO/ECOG PS 0-2
- Histological Subtype

- US/UK/France
- N: 150
- Sequential CRT
- Dosing Interval
- 2 year > 1 year?

- Enrollment is completed October 2021;
- Prelim results submitted to ELCC

Primary Endpoints

- Safety and tolerability (occurrence of Grade 3 and Grade 4 TRAEs[c])

Secondary Endpoints[2]

- PFS[d]
- OS
- ORR[d]
- DoR[d]
- Lung cancer mortality
- Other safety and tolerability parameters

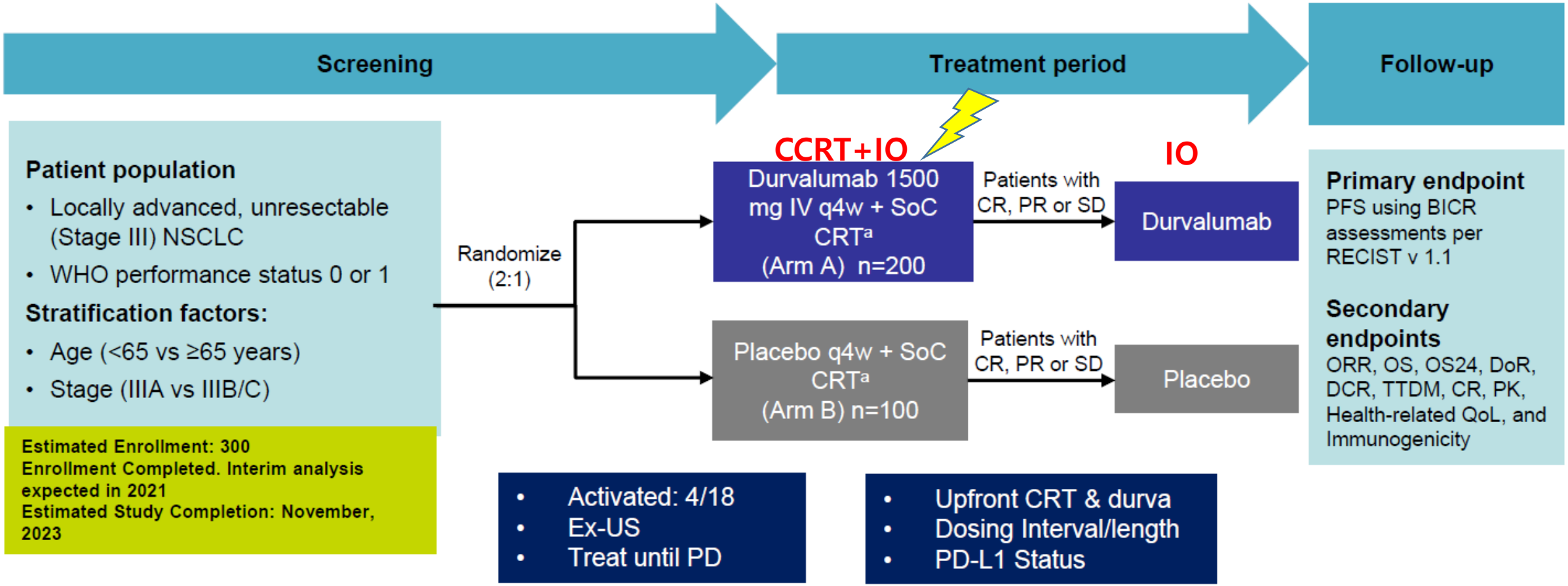
[a]Sequential CRT is defined as ≥2 cycles of platinum-based chemotherapy before radiation therapy, with ≤6 weeks interval between administration of the last dose of chemotherapy and the start of radiation therapy. If a patient received no more than 1 cycle of platinum-based chemotherapy concurrent with radiation treatment, this patient will be eligible to participate in the study; initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other discontinuation criterion; [c]within 6 months from the initiation of durvalumab treatment; [d]Per RECIST 1.1 as assessed by the investigator.

1. AstraZeneca. Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03693300. Accessed September 10, 2019. 2. Garassino et al. Poster presented at: WCLC Annual Meeting; September 7-10, 2019. P1.01-108.

PACIFIC 2 Study Design:

Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study[1,2]

Durvalumab + CRT followed by durvalumab versus placebo + CRT followed by placebo



[a]Platinum-based chemotherapy regimens include cisplatin/ etoposide, carboplatin/paclitaxel, pemetrexed/cisplatin (nonsquamous only) or pemetrexed/carboplatin (nonsquamous only), alongside radiation therapy (5 fractions/week for ~6 weeks [±3 days; total 60 Gy]).

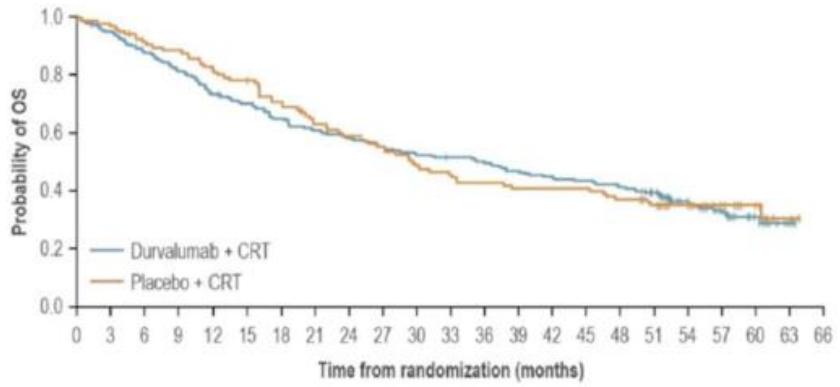
1. Bradley JD et al. Poster presented at: ASCO Annual Meeting; May 31-June 4, 2019; Chicago, IL. Poster TPS8573; 2. Study NCT03519971. ClinicalTrials.gov website.

CCRT combined with duvalumab

- The treatment of cT4N2M0 NSCLC is controversial
- Recent RCTs (NADIM-2, KN-671, AEGEAN) demonstrated promising outcomes with neoadjuvant/perioperative approaches
- PACIFIC-2 : No survival benefit to concurrent therapy
  - Large proportion of patients with cT4 tumors (57.4%)
  - Potentially significant AE's in this population
- Median PFS was 13.8 vs 9.4 months. (HR, 0.85; 95% CI: 0.65-1.12)

PACIFIC-2

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



Bradley Et al. (2024)

2024 WCLC

PACIFIC 6 Study Design: Phase 2, open-label, multicenter, international study

Patients with unresectable Stage III NSCLC, who have not progressed following platinum-based sequential chemoradiation therapy[a]

Screening (max 28 days)

- WHO/ECOG PS 0-1 → **Durvalumab 1500 mg IV q4w up to 24 cycles or until disease progression/ other discontinuation criterion n≈120**
- WHO/ECOG PS 2 → **Durvalumab 1500 mg IV q4w up to 24 cycles or until disease progression/ other discontinuation criterion n≈30**

Stratification factors

- WHO/ECOG PS 0-2
- Histological Subtype

CTx 후 6주 이내 RT 시작

- US/UK/France
- N: 150
- Sequential CRT
- Dosing Interval
- 2 year > 1 year?

- Enrollment is completed October 2021;
- Prelim results submitted to ELCC

Primary Endpoints

- Safety and tolerability (occurrence of Grade 3 and Grade 4 TRAEs[c])

Secondary Endpoints[2]

- PFS[d]
- OS
- ORR[d]
- DoR[d]
- Lung cancer mortality
- Other safety and tolerability parameters

[a]Sequential CRT is defined as ≥2 cycles of platinum-based chemotherapy before radiation therapy, with ≤6 weeks interval between administration of the last dose of chemotherapy and the start of radiation therapy. If a patient received no more than 1 cycle of platinum-based chemotherapy concurrent with radiation treatment, this patient will be eligible to participate in the study; initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other discontinuation criterion; [c]within 6 months from the initiation of durvalumab treatment; [d]Per RECIST 1.1 as assessed by the investigator.

1. AstraZeneca. Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03693300. Accessed September 10, 2019. 2. Garassino et al. Poster presented at: WCLC Annual Meeting; September 7-10, 2019. P1.01-108.

IASLC

Durvalumab After Sequential Chemoradiotherapy in Stage III, Unresectable NSCLC: The Phase 2 PACIFIC-6 Trial

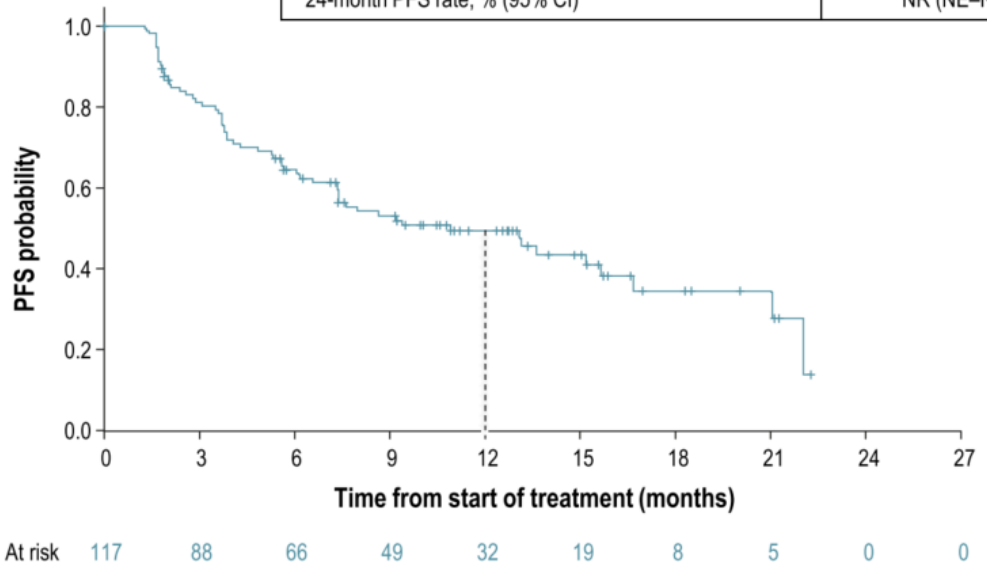
- Stage III, unresectable NSCLC and no progression after platinum-based sCRT
- least 2-4 cycles of platinum-based chemotherapy→ RT→every 4 weeks for up to 24months
- 53.8% respiratory disorders (COPD), cough (14.5%), dyspnea (9.4%),
- More than 65 years, 65.8% IIIA 38.6%< **IIIB 50.9%** (PACIFIC 52%, 44%)
- Grade 3 or 4 AEs : 21.4% Treatment discontinuation, cough (31.6%), asthenia (23.9%), dyspnea (23.1%), and fatigue (20.5%)
- Median PFS : **10.9 months** (PACIFIC **16.9 months** vs 5.6 month)
- 12-month PFS, OS : 49.6% and 84.1% (comparable of PACIFIC 55.9 %, 83.1% data)
- Advanced age, frailty, comorbidities, poorer PS, more advanced disease, a less efficacious CRT regimen (sCRT)
- **Survival outcomes for patients who receive sCRT may be improved with subsequent use of durvalumab**

Garassino et al. J Thorac Oncol. 2022

Results

A

	All patients (N = 117)
Total progression events, n (%)	61 (52.1)
Median PFS, months (95% CI)	10.9 (7.3–15.6)
12-month PFS rate, % (95% CI)	49.6 (39.5–58.9)
24-month PFS rate, % (95% CI)	NR (NE–NE)



B

	All patients (N = 117)
Deaths, n (%)	25 (21.4)
Median OS, months (95% CI)	25.0 (25.0–NE)
12-month OS rate, % (95% CI)	84.1 (75.6–89.9)
24-month OS rate, % (95% CI)	69.8 (55.8–80.2)

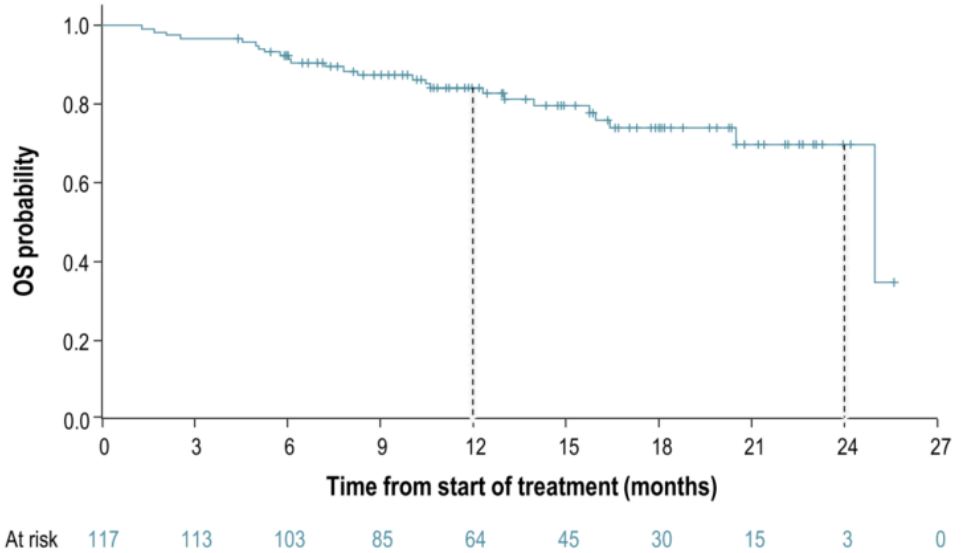
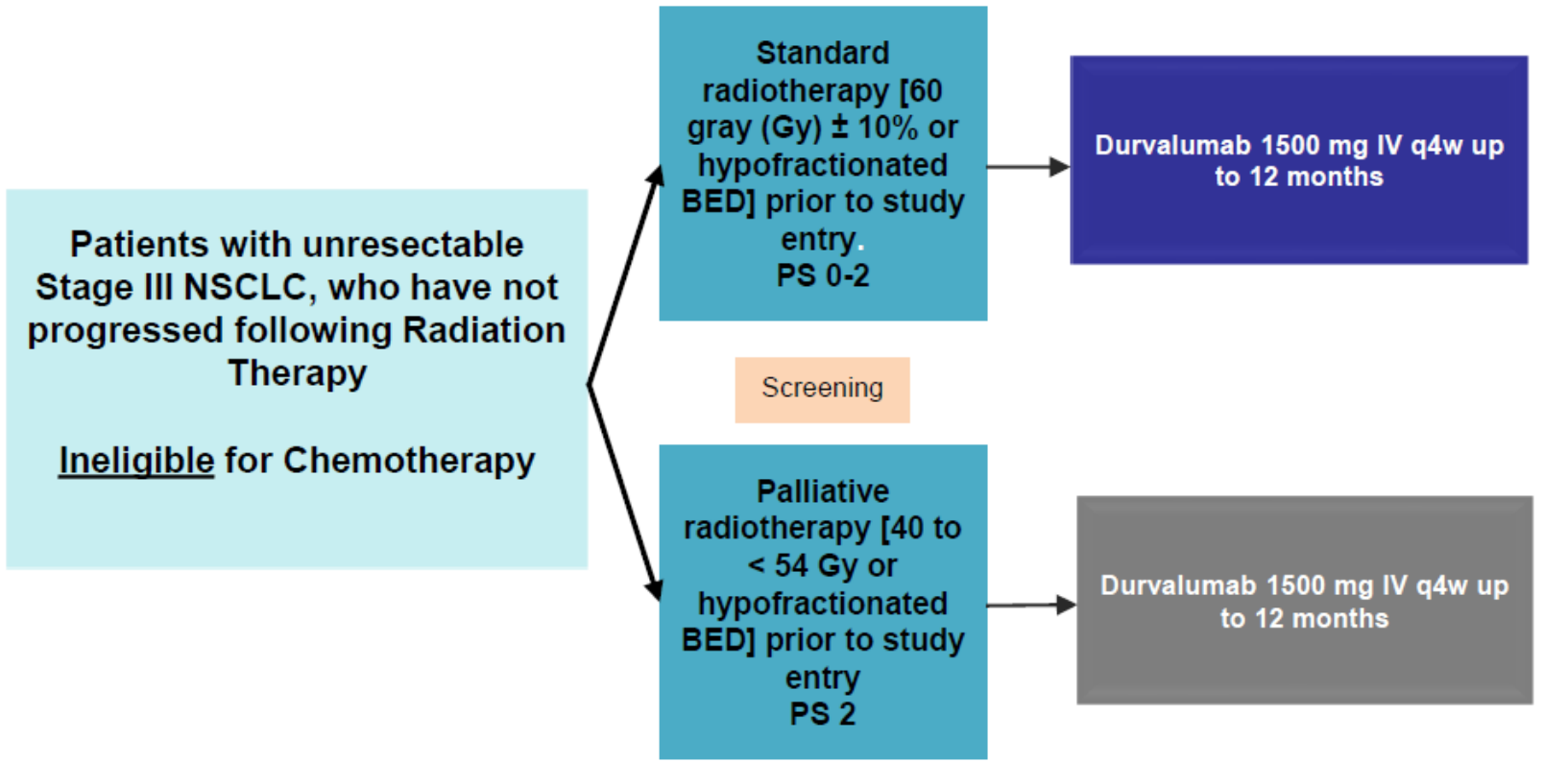


Figure 1. Kaplan-Meier distributions for (*A*) PFS and (*B*) OS. PFS is defined as the time from the date of the first dose of durvalumab to the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient discontinues durvalumab or receives another anticancer therapy before progression. OS is defined as the time from the date of the first dose of durvalumab to death from any cause. The median follow-up duration was 11.0 (range:

DUART Study Design: Phase 2, open-label, multicenter, international study



Primary Endpoints

- Safety and tolerability (occurrence of Grade 3 and Grade 4 (possibly) PRAEs[c])

Secondary Endpoints[2]

- PFS
- OS
- ORR
- DoR
- Lung cancer mortality
- Other safety and tolerability parameters

Palliative RT

- Open to enrollment

ORR was higher and median PFS and OS were longer in the definitive RT cohort. The efficacy and safety data from DUART suggest **that durvalumab following definitive or palliative RT may be a potential treatment option in a frailer and older population ineligible for CT.**

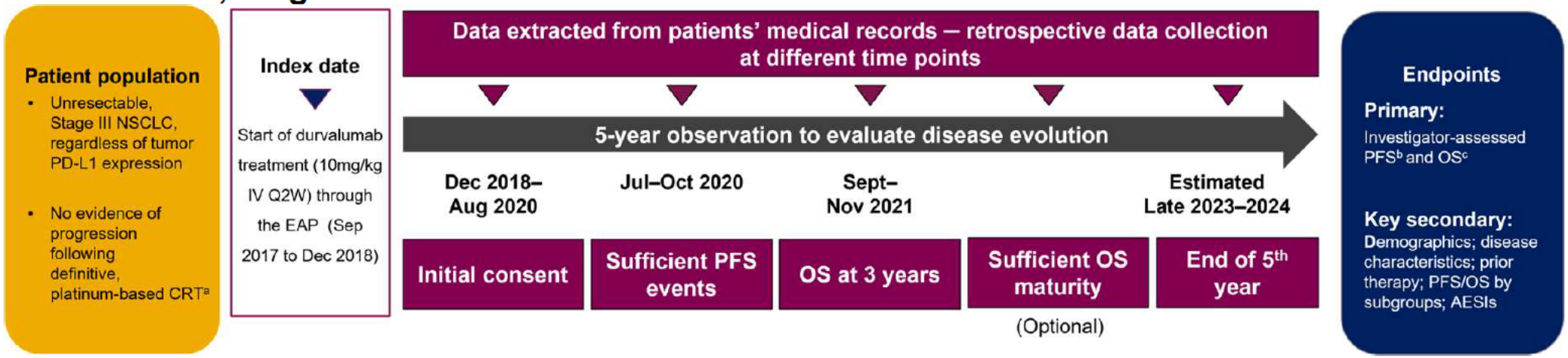
	Cohort A (definitive RT; n=53)	Cohort B (palliative RT; n=49)	Total (N=102)
PFS Events (%) Median (95% CI), mo[a] 12-mo PFS rate (95% CI), %[a]	33 (62.3) 10.3 (7.5–16.6) 46.8 (31.9–60.4)	31 (63.3) 7.6 (5.6–11.0) 31.8 (18.1–46.3)	64 (62.7) 9.2 (7.4–11.9) 39.6 (29.3–49.8)
OS Events (%) Median (95% CI), mo[a] 12-mo OS rate (95% CI), %[a]	23 (43.4) 21.1 (11.6–NC) 64.0 (49.0–75.6)	23 (46.9) 16.8 (10.6–NC) 65.5 (49.9–77.3)	46 (45.1) 21.1 (14.8–NC) 64.7 (54.2–73.3)

ORR was higher and median PFS and OS were longer in the definitive RT cohort. The efficacy and safety data from DUART suggest that durvalumab following definitive or palliative RT may be a potential treatment option in a frailer and older population ineligible for CT.

Real World Study

PACIFIC-R Trial (NCT03798535)

Figure I: Observational/non-interventional, retrospective, international study of patients with unresectable, stage III NSCLC within AstraZeneca-initiated EAP.[1-5,9]



[a]Patients had completed platinum-based chemotherapy concurrent or sequential to radiotherapy within the previous 12 weeks without evidence of disease progression; [b]PFS is time from the index date to the date of investigator-determined disease progression or death (if no progression) or the end of follow-up; [c]OS defined as time from the index date to death or end of follow-up.

Objectives

To assess the effectiveness of durvalumab in a real-world by evaluating rwPFS and OS in unresectable stage III NSCLC patients who had received durvalumab in an EAP.[1-3]

PACIFIC-R study

- Median follow-up : **23.5 months**
- Primary outcomes : real-world PFS & OS
- N =1399
- Median age 66 years, ⩾ 75 years 10% , 67% males
- FEV_1 >50%, DLCO >40%
- PACIFIC-R enrolled patients **without any restrictions on ECOG PS**
- Patients could receive **either c/sCRT**

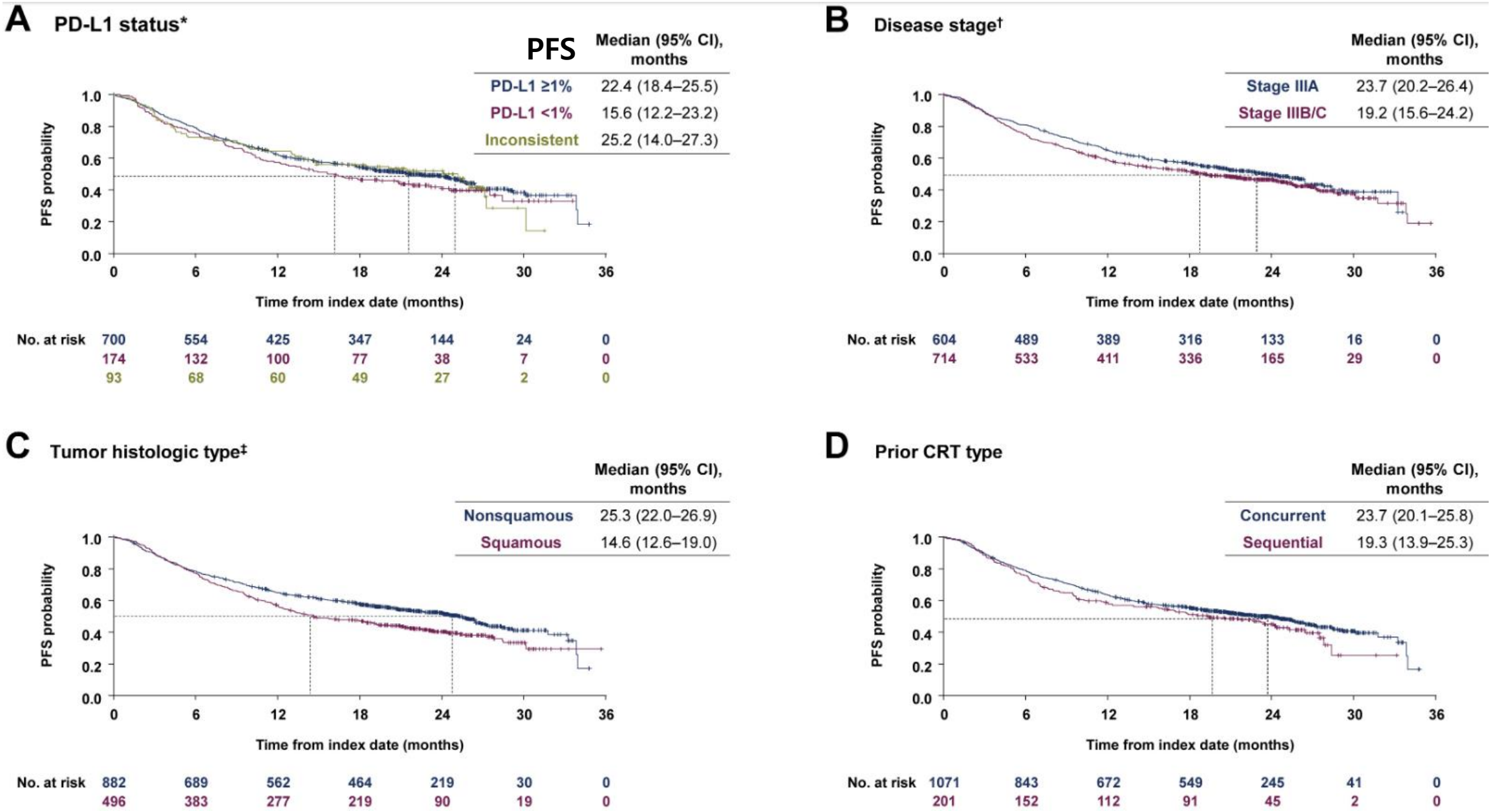
ORIGINAL ARTICLE

Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study

France (342), Spain (244), Australia (165), The Netherlands (155), Belgium (118), Italy (116), Israel (92), Germany (62), UK(54), Norway (36), Switzerland (15).

- N=1399, ECOG 2-3 : 2%, sCRT 14.4%, PDL1<1%: 18%
- **mPFS 21.7 months** : 거의 반 이상이 재발없이 2년 이상 생존 (PACIFIC mPFS **16.9 mon**)
- mPFS IIIA: 23.7 mons vs IIIB/C: 19.2 mons
- **cCRT:** 23.7 months, **sCRT: 19.4 months** (>>PACIFIC **16.9 mon**)
- Nonsquamous : squamous =**25.3** : **14.7** mons
- PD-L1 ⩾1% → 22.4mons, PD-L1 <1% →16.3 mons
- Rates of durvalumab discontinuation due to AEs (16.7%), disease progression (26.9%)

Girard et al. J of Thorac Oncol **2022**



거의 반 이상이 2년 시점에 살아 있다

Reasons for Discontinuing Durvalumab

Reason[a]	Full Analysis Set (N = 1399)	
	n (%)	Median Time to Discontinuation, mo (Range)[b]
Completed treatment[c]	659 (47.1)	11.9 (5.5-28.5)[d]
Disease progression	377 (26.9)	4.9 (0.0-30.2)[d]
Adverse event	233 (16.7)	2.8 (0.0-19.6)
Death	21 (1.5)	1.9 (0.0-13.6)
Patient decision	20 (1.4)	6.0 (0.0-19.5)
Other	68 (4.9)	5.9 (0.0-28.2)[d]

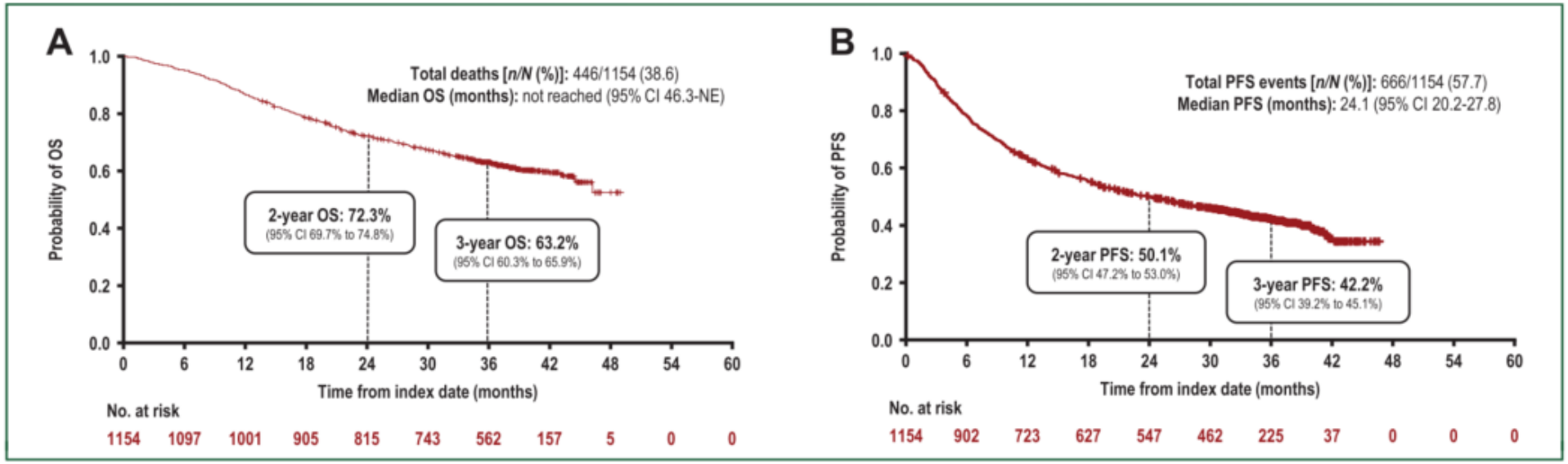
AESIs Leading to Interruption and Permanent Discontinuation of Durvalumab

AESI Category	Full Analysis Set (N = 1399)	
	Temporary Interruption, n (%)	Permanent Discontinuation, n (%)
Any	156 (11.2)	231 (16.5)
Pneumonitis or ILD	73 (5.2)	133 (9.5)
Diarrhea or colitis and intestinal perforation	16 (1.1)	15 (1.1)
Hepatitis or transaminase increases	10 (0.7)	17 (1.2)
Endocrinopathies	18 (1.3)	10 (0.7)
Other[a]	33 (2.4)	51 (3.6)

ORIGINAL RESEARCH

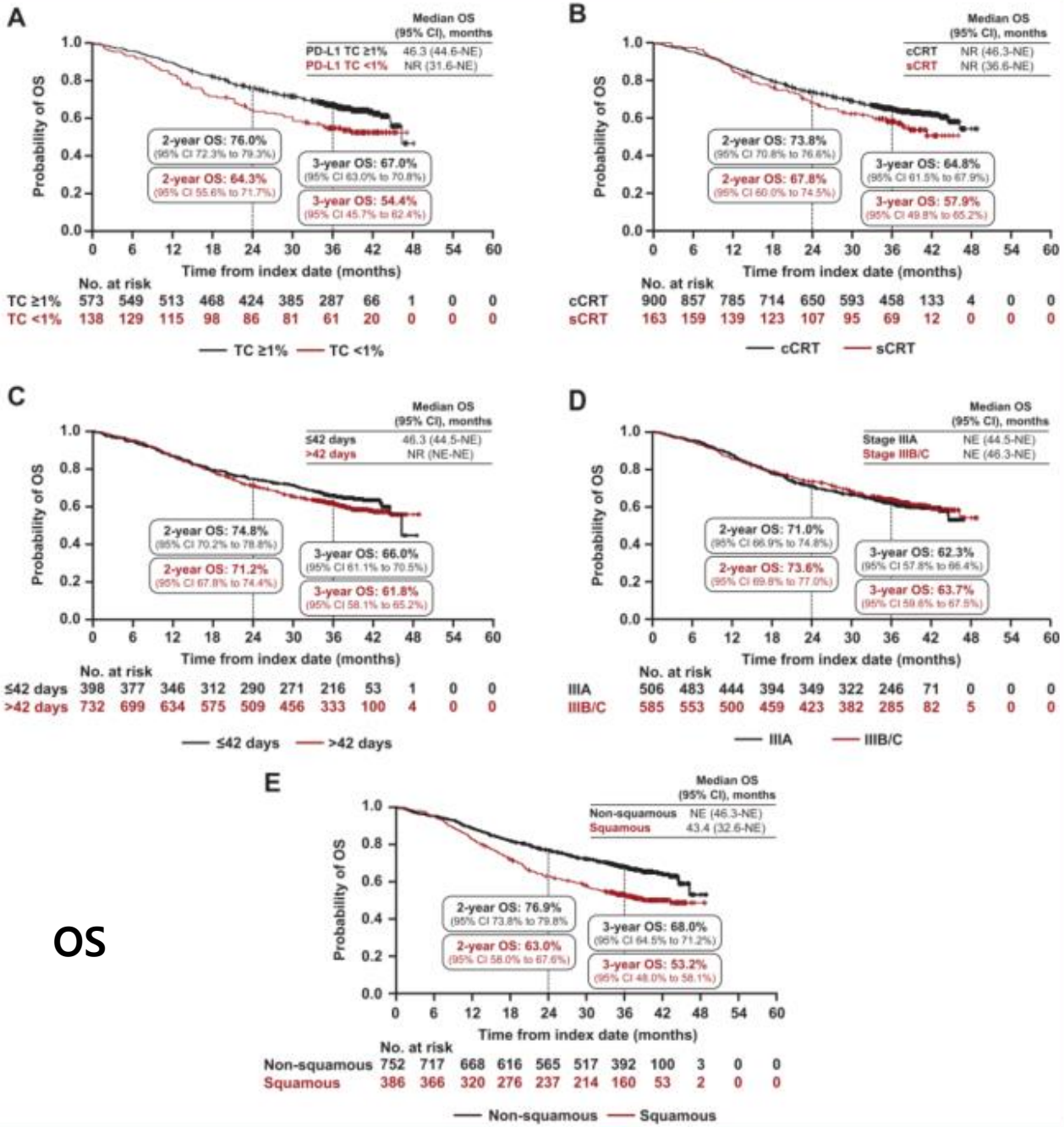
Real-world outcomes with durvalumab after chemoradiotherapy in patients with unresectable stage III NSCLC: interim analysis of overall survival from PACIFIC-R

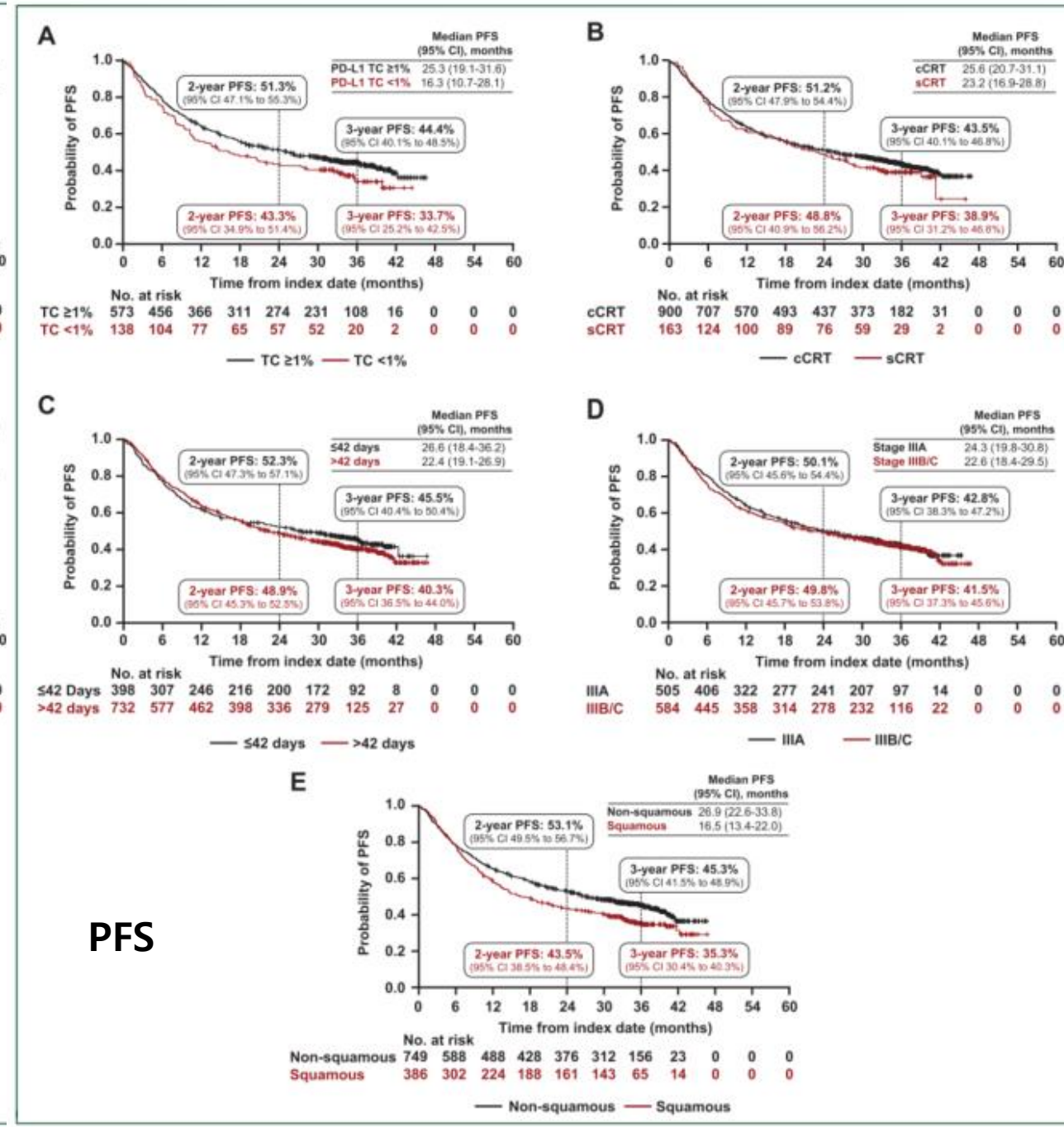
- 1154 participants from 10 countries (mF/U **38.7** months)
- 3-year OS rate 63.2% (cf. PACIFIC 56.7%), mOS : NR
- 3-year OS rate : PD-L1 ≥1% : <1%= **67.0%** : 54.4%
- cCRT : sCRT = **64.8%** : 57.9%, **non-squamous** > squamous



3년 시점에 60% 이상이 살아 있다.

Filippi et al ESMO Open **2024**


A
Median OS (95% CI), months
PD-L1 TC ≥1% 46.3 (44.6-NE)
PD-L1 TC <1% NR (31.6-NE)
2-year OS: 76.0% (95% CI 72.3% to 79.3%)
2-year OS: 64.3% (95% CI 55.6% to 71.7%)
3-year OS: 67.0% (95% CI 63.0% to 70.8%)
3-year OS: 54.4% (95% CI 45.7% to 62.4%)
Probability of OS
Time from index date (months)
No. at risk
TC ≥1% 573 549 513 468 424 385 287 66 1 0 0
TC <1% 138 129 115 98 86 81 61 20 0 0 0
TC ≥1% TC <1%
B
Median OS (95% CI), months
cCRT NR (46.3-NE)
sCRT NR (36.6-NE)
2-year OS: 73.8% (95% CI 70.8% to 76.6%)
2-year OS: 67.8% (95% CI 60.0% to 74.5%)
3-year OS: 64.8% (95% CI 61.5% to 67.9%)
3-year OS: 57.9% (95% CI 49.8% to 65.2%)
Probability of OS
Time from index date (months)
No. at risk
cCRT 900 857 785 714 650 593 458 133 4 0 0
sCRT 163 159 139 123 107 95 69 12 0 0 0
cCRT sCRT
C
Median OS (95% CI), months
≤42 days 46.3 (44.5-NE)
>42 days NR (NE-NE)
2-year OS: 74.8% (95% CI 70.2% to 78.8%)
2-year OS: 71.2% (95% CI 67.8% to 74.4%)
3-year OS: 66.0% (95% CI 61.1% to 70.5%)
3-year OS: 61.8% (95% CI 58.1% to 65.2%)
Probability of OS
Time from index date (months)
No. at risk
≤42 days 398 377 346 312 290 271 216 53 1 0 0
>42 days 732 699 634 575 509 456 333 100 4 0 0
≤42 days >42 days
D
Median OS (95% CI), months
Stage IIIA NE (44.5-NE)
Stage IIIB/C NE (46.3-NE)
2-year OS: 71.0% (95% CI 66.9% to 74.8%)
2-year OS: 73.6% (95% CI 69.8% to 77.0%)
3-year OS: 62.3% (95% CI 57.8% to 66.4%)
3-year OS: 63.7% (95% CI 59.8% to 67.5%)
Probability of OS
Time from index date (months)
No. at risk
IIIA 506 483 444 394 349 322 246 71 0 0 0
IIIB/C 585 553 500 459 423 382 285 82 5 0 0
IIIA IIIB/C
E
Median OS (95% CI), months
Non-squamous NE (46.3-NE)
Squamous 43.4 (32.6-NE)
2-year OS: 76.9% (95% CI 73.8% to 79.8%)
2-year OS: 63.0% (95% CI 58.0% to 67.6%)
3-year OS: 68.0% (95% CI 64.5% to 71.2%)
3-year OS: 53.2% (95% CI 48.0% to 58.1%)
Probability of OS
Time from index date (months)
No. at risk
Non-squamous 752 717 668 616 565 517 392 100 3 0 0
Squamous 386 366 320 276 237 214 160 53 2 0 0
Non-squamous Squamous
OS


A
Median PFS (95% CI), months
PD-L1 TC ≥1% 25.3 (19.1-31.6)
PD-L1 TC <1% 16.3 (10.7-28.1)
2-year PFS: 51.3% (95% CI 47.1% to 55.3%)
2-year PFS: 43.3% (95% CI 34.9% to 51.4%)
3-year PFS: 44.4% (95% CI 40.1% to 48.5%)
3-year PFS: 33.7% (95% CI 25.2% to 42.5%)
Probability of PFS
Time from index date (months)
No. at risk
TC ≥1% 573 456 366 311 274 231 108 16 0 0 0
TC <1% 138 104 77 65 57 52 20 2 0 0 0
TC ≥1% TC <1%
B
Median PFS (95% CI), months
cCRT 25.6 (20.7-31.1)
sCRT 23.2 (16.9-28.8)
2-year PFS: 51.2% (95% CI 47.9% to 54.4%)
2-year PFS: 48.8% (95% CI 40.9% to 56.2%)
3-year PFS: 43.5% (95% CI 40.1% to 46.8%)
3-year PFS: 38.9% (95% CI 31.2% to 46.6%)
Probability of PFS
Time from index date (months)
No. at risk
cCRT 900 707 570 493 437 373 182 31 0 0 0
sCRT 163 124 100 89 76 59 29 2 0 0 0
cCRT sCRT
C
Median PFS (95% CI), months
≤42 days 26.6 (18.4-36.2)
>42 days 22.4 (19.1-26.9)
2-year PFS: 52.3% (95% CI 47.3% to 57.1%)
2-year PFS: 48.9% (95% CI 45.3% to 52.5%)
3-year PFS: 45.5% (95% CI 40.4% to 50.4%)
3-year PFS: 40.3% (95% CI 36.5% to 44.0%)
Probability of PFS
Time from index date (months)
No. at risk
≤42 Days 398 307 246 216 200 172 92 8 0 0 0
>42 days 732 577 462 398 336 279 125 27 0 0 0
≤42 days >42 days
D
Median PFS (95% CI), months
Stage IIIA 24.3 (19.8-30.8)
Stage IIIB/C 22.6 (18.4-29.5)
2-year PFS: 50.1% (95% CI 45.6% to 54.4%)
2-year PFS: 49.8% (95% CI 45.7% to 53.8%)
3-year PFS: 42.8% (95% CI 38.3% to 47.2%)
3-year PFS: 41.5% (95% CI 37.3% to 45.6%)
Probability of PFS
Time from index date (months)
No. at risk
IIIA 505 406 322 277 241 207 97 14 0 0 0
IIIB/C 584 445 358 314 278 232 116 22 0 0 0
IIIA IIIB/C
E
Median PFS (95% CI), months
Non-squamous 26.9 (22.6-33.8)
Squamous 16.5 (13.4-22.0)
2-year PFS: 53.1% (95% CI 49.5% to 56.7%)
2-year PFS: 43.5% (95% CI 38.5% to 48.4%)
3-year PFS: 45.3% (95% CI 41.5% to 48.9%)
3-year PFS: 35.3% (95% CI 30.4% to 40.3%)
Probability of PFS
Time from index date (months)
No. at risk
Non-squamous 749 588 488 428 376 312 156 23 0 0 0
Squamous 386 302 224 188 161 143 65 14 0 0 0
Non-squamous Squamous
PFS

Korean Real-World Data on Patients With Unresectable Stage III NSCLC Treated With Durvalumab After Chemoradiotherapy: PACIFIC-KR

Cheol-Kyu Park, MD, PhD,[a] Hyung-Joo Oh, MD,[a] Young-Chul Kim, MD, PhD,[a] Yong-Hyub Kim, MD, PhD,[b] Sung-Ja Ahn, MD, PhD,[b] Won Gi Jeong, MD,[c] Jeong Yeop Lee, MD,[c] Jae Cheol Lee, MD, PhD,[d] Chang Min Choi, MD, PhD,[e] Wonjun Ji, MD, PhD,[e] Si Yeol Song, MD, PhD,[f] Juwhan Choi, MD, PhD,[g] Sung Yong Lee, MD, PhD,[g] Hakyoung Kim, MD, PhD,[h] Shin Yup Lee, MD, PhD,[i] Jongmoo Park, MD, PhD,[j] Seong Hoon Yoon, MD,[k] Ji Hyeon Joo, MD,[l] In-Jae Oh, MD, PhD[a,*]

Cf) Duvalumab
Median PFS: **16.8 vs 5.6 months**

- Efficacy and safety of durvalumab consolidation after chemoradiotherapy
- 157 patients were enrolled.
- Median F/U : 19.1 months
- Median rwPFS : 25.9 months
- 1, 2, 3-year rwPFS → 59.4%, 51.8%, and 43.5%
- 1, 2, 3-year OS rates →87.8%, 71.0%, and 69.2%
- Monocyte-to-lymphocyte ratio → The most significant risk factor for RP requiring steroid treatment

Park et al. JTO 2023 Vol 18, 1042

Result

- Age :65, Male 85.4%, ECOG 2-3: 10.8%, PD-L1 >1% : 91.1%
- COPD 31.8% Pul. fibrosis 82.8%, Cardiovascular 42% HTN 36.9%
- CCRT 97.5%, weekly platinum based CTx, 54-66 Gy, 3D-CRT, IMRT
- 81.5% : within 42 days after the last date of RT
- Radiation pneumonitis requiring steroid treatment → shorter rwPFS
- ECOG 2-3 : only risk factor for a shorter OS
- Progression was confirmed in 73 patients (46.5%)
- Locoregional progression (56.2%) was the predominant type of relapse
  - Lungs (60.3%), lymph nodes (35.6%), brain (13.7%) bones (13.7%).

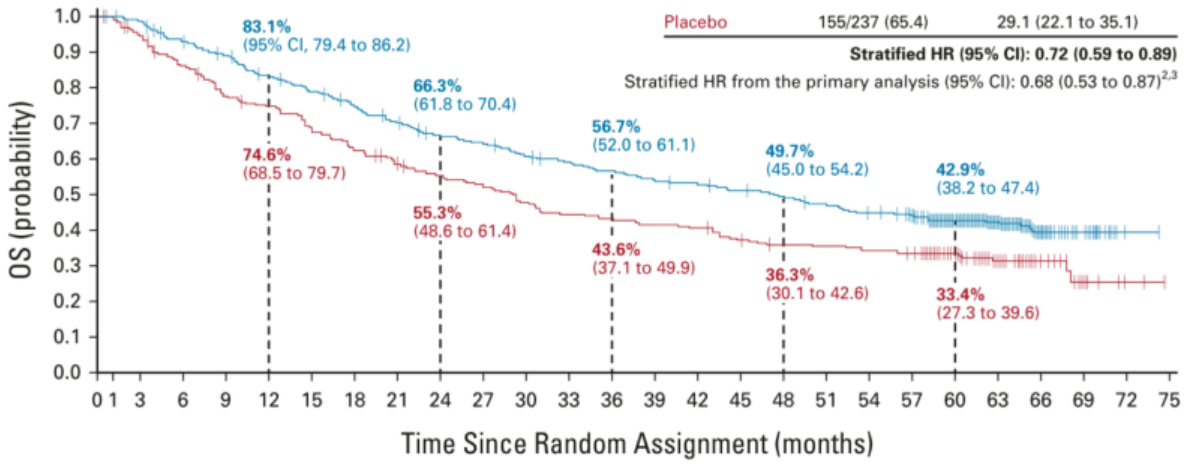
A

PACIFIC-OS

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

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



No. at risk:

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

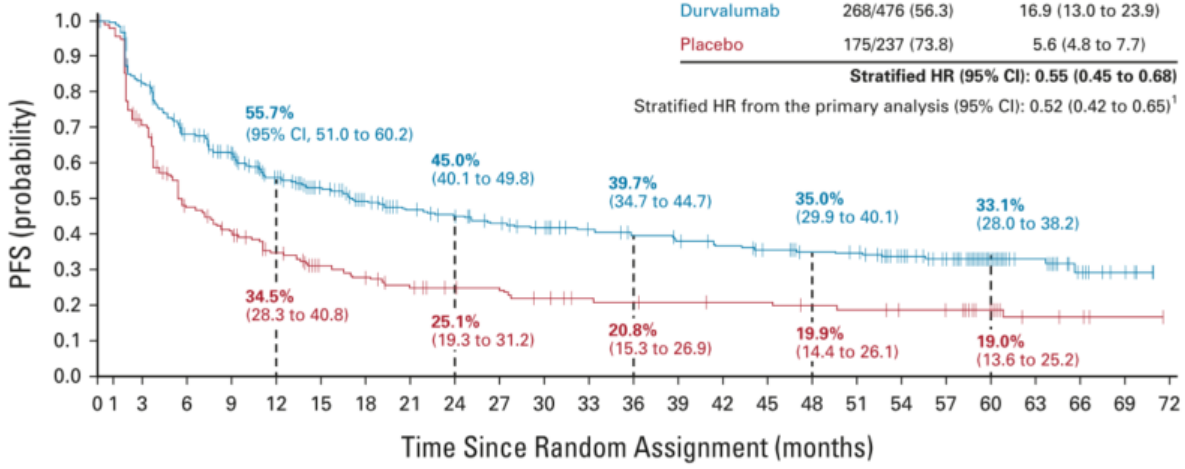
B

PACIFIC-PFS

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

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

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

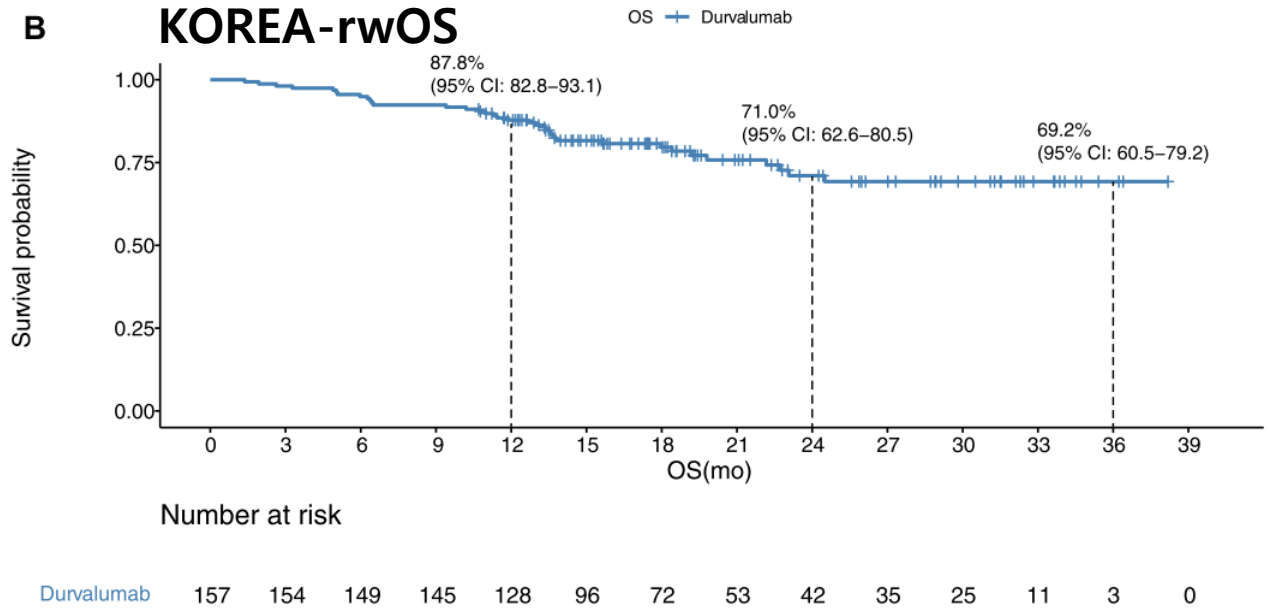


No. at risk:

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

B

KOREA-rwOS

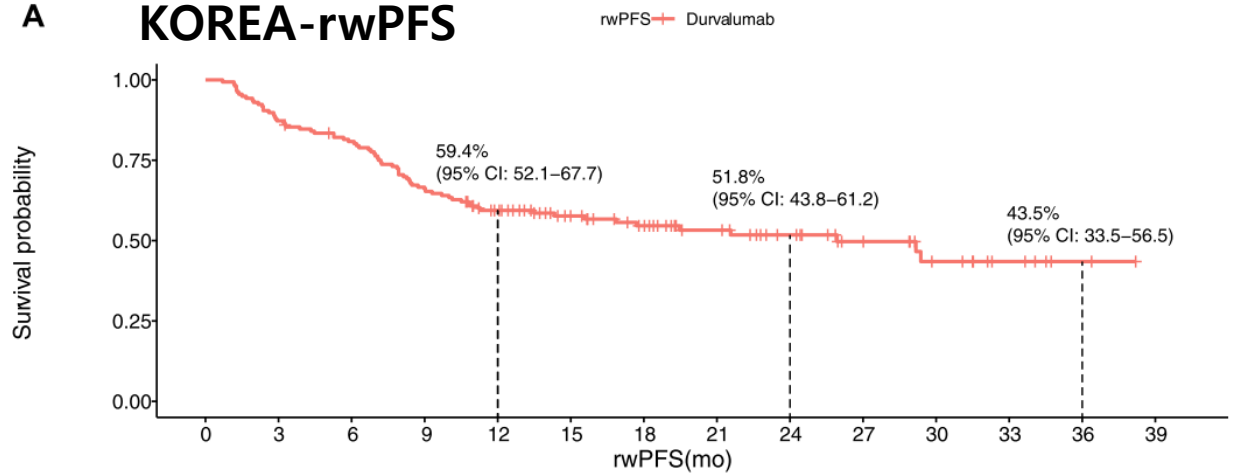


Number at risk

Durvalumab	157	154	149	145	128	96	72	53	42	35	25	11	3	0

A

KOREA-rwPFS



Number at risk

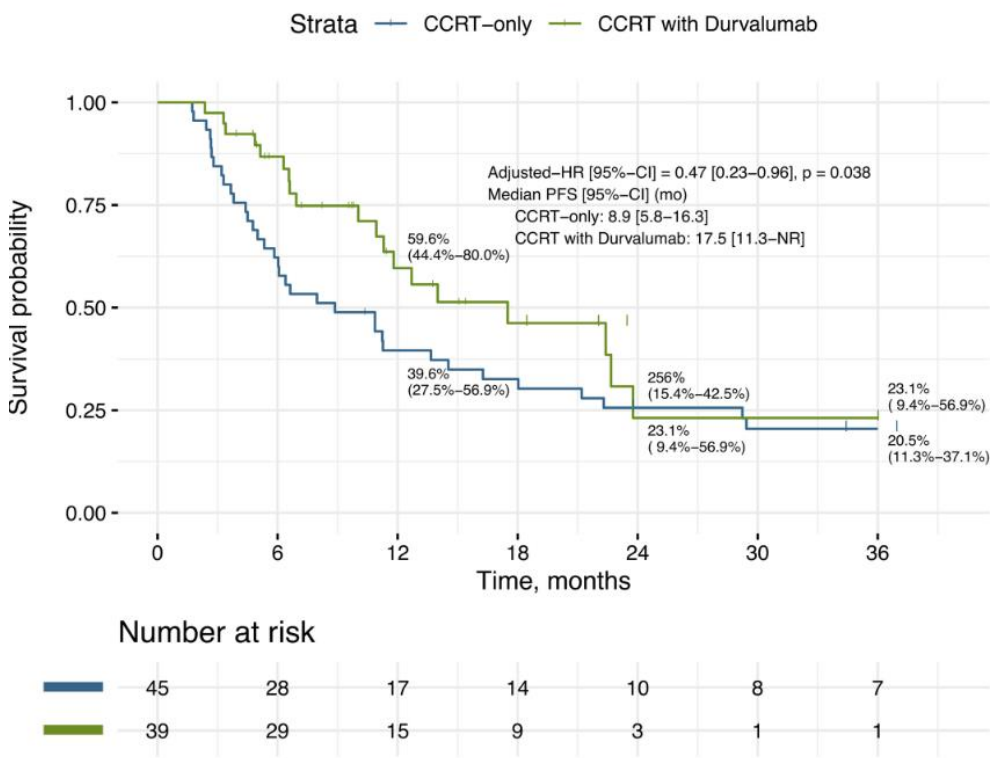
Durvalumab	157	137	125	103	82	62	50	38	30	22	13	6	2	0

Figure 1. rwPFS and OS in patients treated with durvalumab. (*A*) Kaplan-Meier curve for the rwPFS and 1-, 2-, and 3-year rwPFS rates. (*B*) Kaplan-Meier curve for OS and the 1-, 2-, and 3-year OS rates. CI, confidence interval; OS, overall survival; rwPFS, real-world progression-free survival.

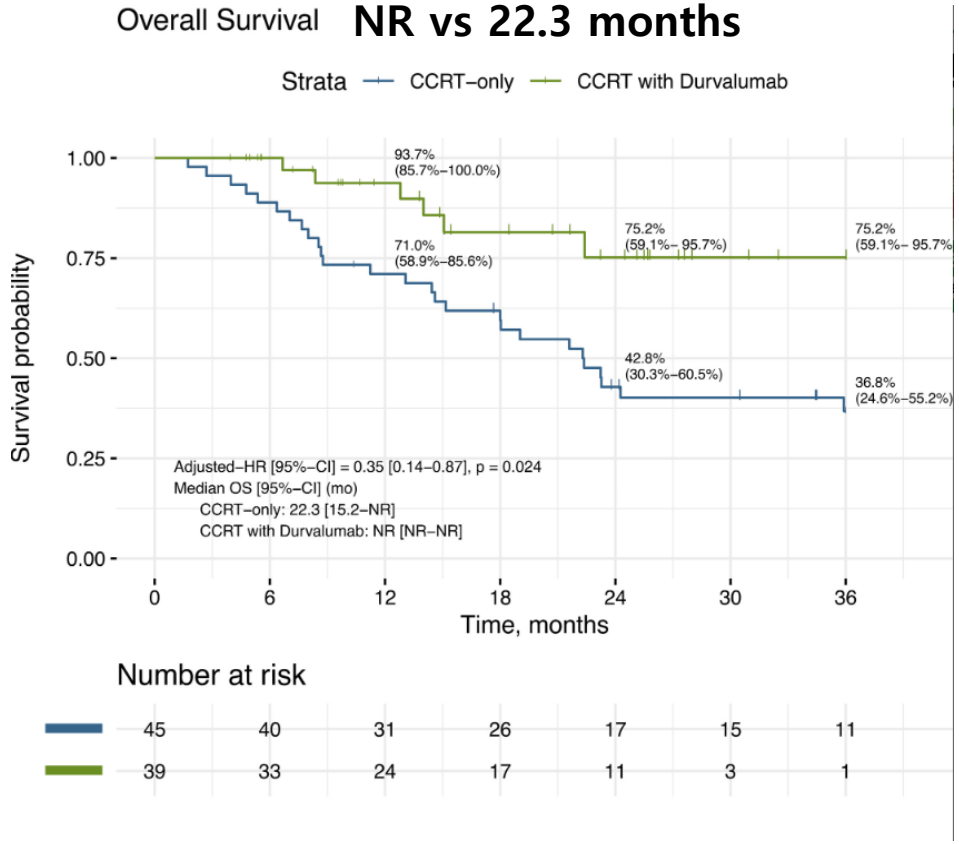
Real-world experience of consolidation durvalumab after concurrent chemoradiotherapy in stage III non-small cell lung cancer

Duvalumab **mPFS**: **16.8 vs 5.6 개월**
mOS : 47.5 vs 29.1 개월

Progression Free Survival **17.5 vs 8.9 months**



Overall Survival **NR vs 22.3 months**



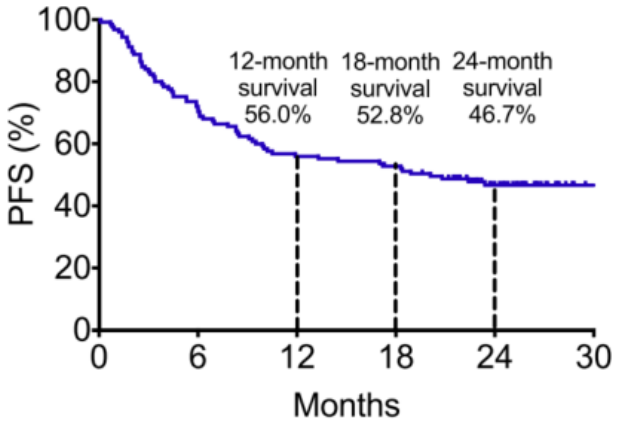
Efficacy and safety of durvalumab in the real-world setting(싱가폴)

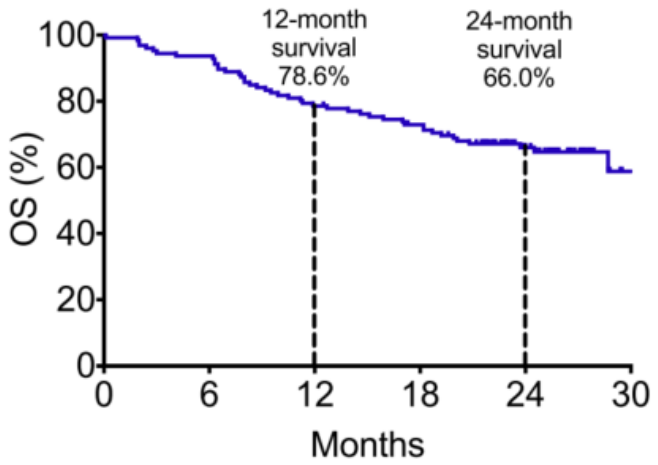
Thorac Cancer. 2022;13:3152–3161.

독일

Durvalumab after definitive chemoradiotherapy in locally advanced unresectable non-small cell lung cancer (NSCLC): Real-world data on survival and safety from the German expanded-access program (EAP)

- Following the PACIFIC trial, durvalumab has been approved by EMA for consolidation of locally advanced PD-L1+ NSCLC after CRT.
- 2017.11 ~2018.10 efficacy and safety of consolidation Durvalumab
- 126 patients, oligometastatic stage IV +autoimmune disease
- 42.9 % completed 12 months of durvalumab
- Stage IV patients (n = 7) had encouraging OS
- Autoimmune disease did not affect survival.
- PFS and OS were similar in PD-L1 (-) pts (n = 32) and PD-L1 (+) pts (n = 79).
- **Survival in the EAP was comparable to the PACIFIC trial.**
- Selected stage IV pts and pts with autoimmune disease may benefit from durvalumab consolidation





Faehling at al Lung Cancer 150 (2020) 114–122

Durvalumab Consolidation After Chemoradiotherapy in Elderly Patients With Unresectable Stage III NSCLC: A Real-World Multicenter Study

Ji Eun Park,[1,#] Kyung Soo Hong,[2,#] Sun Ha Choi,[1] Shin Yup Lee,[1] Kyeong-Cheol Shin,[2] Jong Geol Jang,[2] Yong Shik Kwon,[3] Sun Hyo Park,[3] Keum-Ju Choi,[4] Chi Young Jung,[4] Jung Seop Eom,[5] Saerom Kim,[5] Hee Yun Seol,[5] Jehun Kim,[6] Insu Kim,[7] Jin Han Park,[8] Tae Hoon Kim,[9] June Hong Ahn[2]

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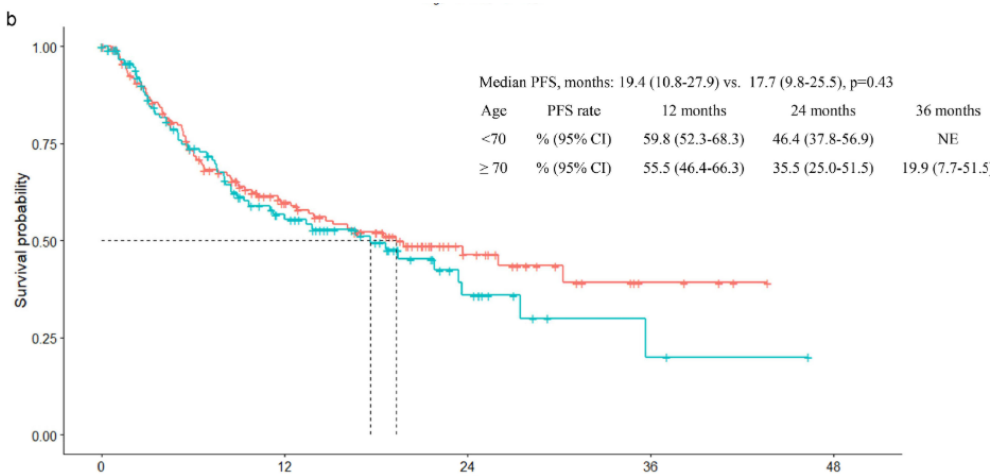
Volume 25, Issue 4, June 2024, Pages 354-364



- 2017.09 ~2022.09. N=286
- Durvalumab consolidation showed comparable outcome in elderly patients
- ≥ 70 years 42.0%
- mPFS (17.7 vs. 19.4 months; *P* = .43)
- mOS (35.7 mon vs. NR *P* = .13)
- Discontinuation, Durvalumab AE were more common in elderly pts.
- ECOG PS 0 or 1, PDL1>50% : favorable factor for PFS.
- Cisplatin-based regimen : worse factor for OS.

Clinical Lung Cancer June 2024

Real-world data supports PACIFIC trial outcomes in broader populations

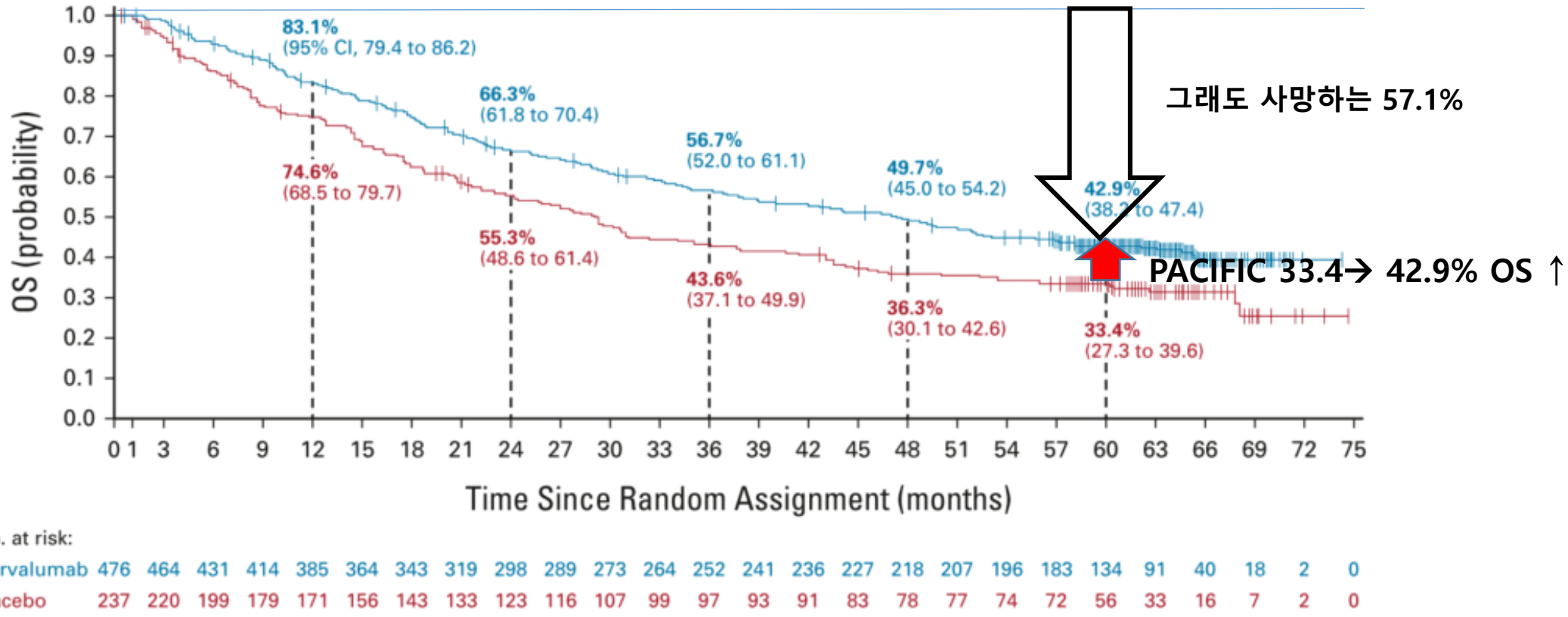
- Similar survival benefit observed in real world study.
- But slightly higher discontinuation rates due to toxicity or comorbidities.
- **The favorable real-world outcomes found in the sCRT subset, irrespective** PD-L1 status
- **Challenges in real-world settings** -not all patients complete CCRT due to performance status.
- Neutrophil-to-lymphocyte were associated with shorter PFS with durvalumab
- Pneumonitis : most common AE, radiation pneumonitis : 36.3% within 3–6 months after CCRT
- Treatment interruption : 15.9%
- Older, with a higher proportion of comorbidities [COPD, cardiovascular diseases]
- PFS was longer in the real-world than in the trial, while OS was similar.

Radiation pneumonitis

- Pneumonitis grade ≥ 2, 36.05%, grade ≥ 3 6.75%
- Durvalumab consolidation therapy interrupted due to pneumonitis 26.35%

  → the interruption of durvalumab because of an AE was associated with decreased of both OS and PFS, suggesting caution when considering discontinuation of adjuvant durvalumab.
- History of smoking, COPD, interstitial lung disease increased risk of RILI.
- Older age (patients >65 years old) and Asian ethnicity → risk factors for pneumonitis.

PACIFIC 5-year Overall Survival



그래도 사망하는 57.1%

PACIFIC 33.4→ 42.9% OS ↑

Keywords

- **Agents**
  - **Duvalumab** -PDL1 Inhibitor
  - Atezolizumab-PDL1 Inhibitor
  - Pembrolizumab- PD1 Inhibitor
  - Nivolumab - PD1 Inhibitor

- **Treatment**
  - IO-CRT-IO vs IO+CRT-IO
  - CRT→ IO+IO combination

Consolidation after cCTRT / sCTRT

CT RT → ICI

- PACIFIC (NCT02125461)*
- GEMSTONE 301 (NCT03728556)*
- PACIFIC-5 (NCT03706690)*

CT → RT → ICI

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

Concurrent ICI + cCTRT

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 → CT 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)

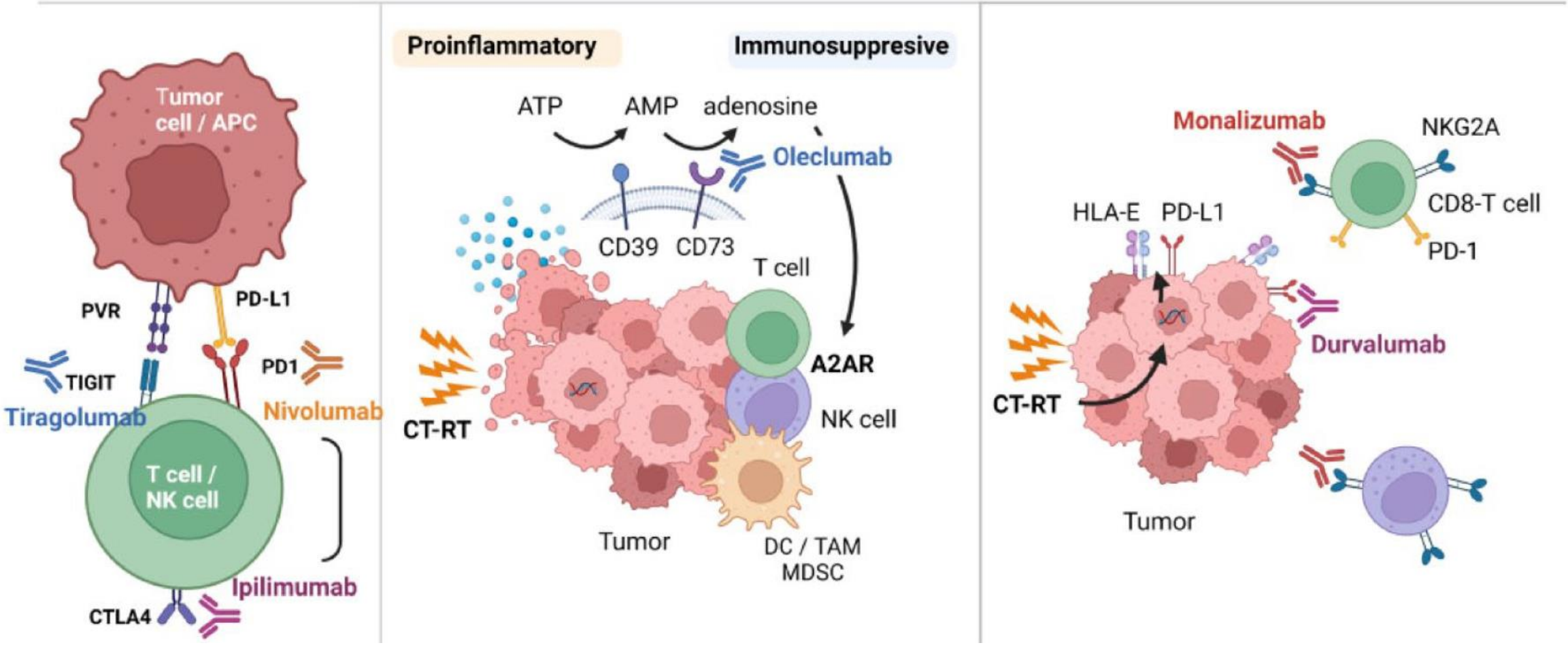
Consolidation with TKI

CT RT → TKI

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

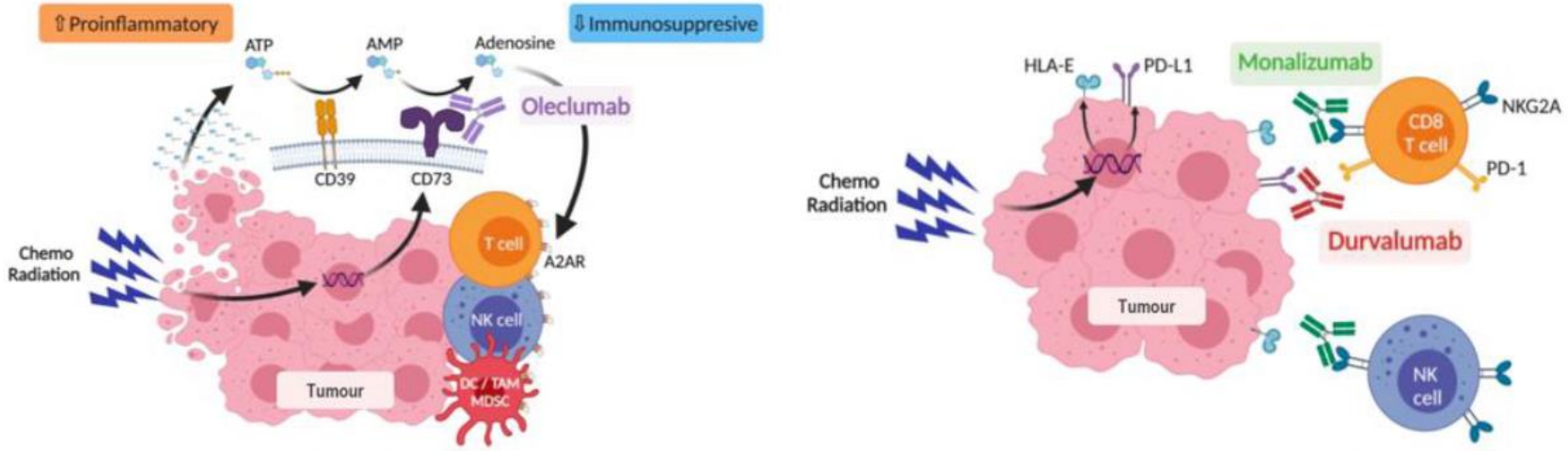
ICI consolidation intensification

To cure


Tumor cell / APC
PVR
PD-L1
TIGIT
PD1
Tiragolumab
Nivolumab
T cell / NK cell
Ipilimumab
CTLA4
Proinflammatory
Immunosuppresive
ATP
AMP
adenosine
Oleclumab
CD39
CD73
T cell
A2AR
NK cell
CT-RT
Tumor
DC / TAM MDSC
Monalizumab
NKG2A
CD8-T cell
HLA-E
PD-L1
PD-1
Durvalumab
CT-RT
Tumor

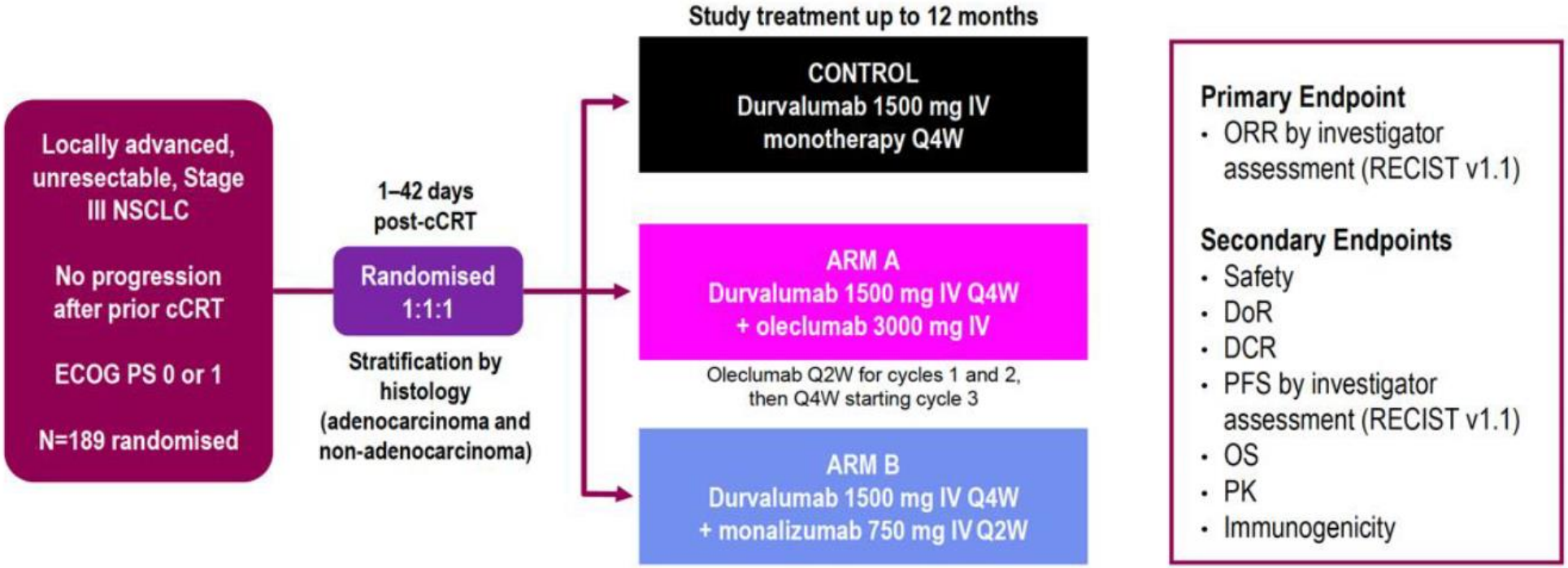
COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III NSCLC

Rationale for combining durvalumab with oleclumab (anti-CD73) or monalizumab (anti-NKG2A)



- RT induces expression of CD73 and HLA-E (NKG2A ligand), which inhibit antitumour immune response[1-4]
- Oleclumab inhibits CD73 to reduce extracellular adenosine production, thereby promoting antitumour immunity.[5] Oleclumab combined with durvalumab produced durable responses with manageable safety in a Ph I study of advanced *EGFR*m NSCLC[6]
- Monalizumab blocks NKG2A to reduce inhibition of NK and CD8+ T cells.[7] Monalizumab combined with cetuximab had promising activity with manageable safety in a Ph I/II trial of patients with R/M HNSCC[8]
- Combinations of RT and anti-CD73/NKG2A ± anti-PD-(X) show increased antitumour activity in preclinical models[1,2,4]

COAST: Phase 2, randomised open-label study



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

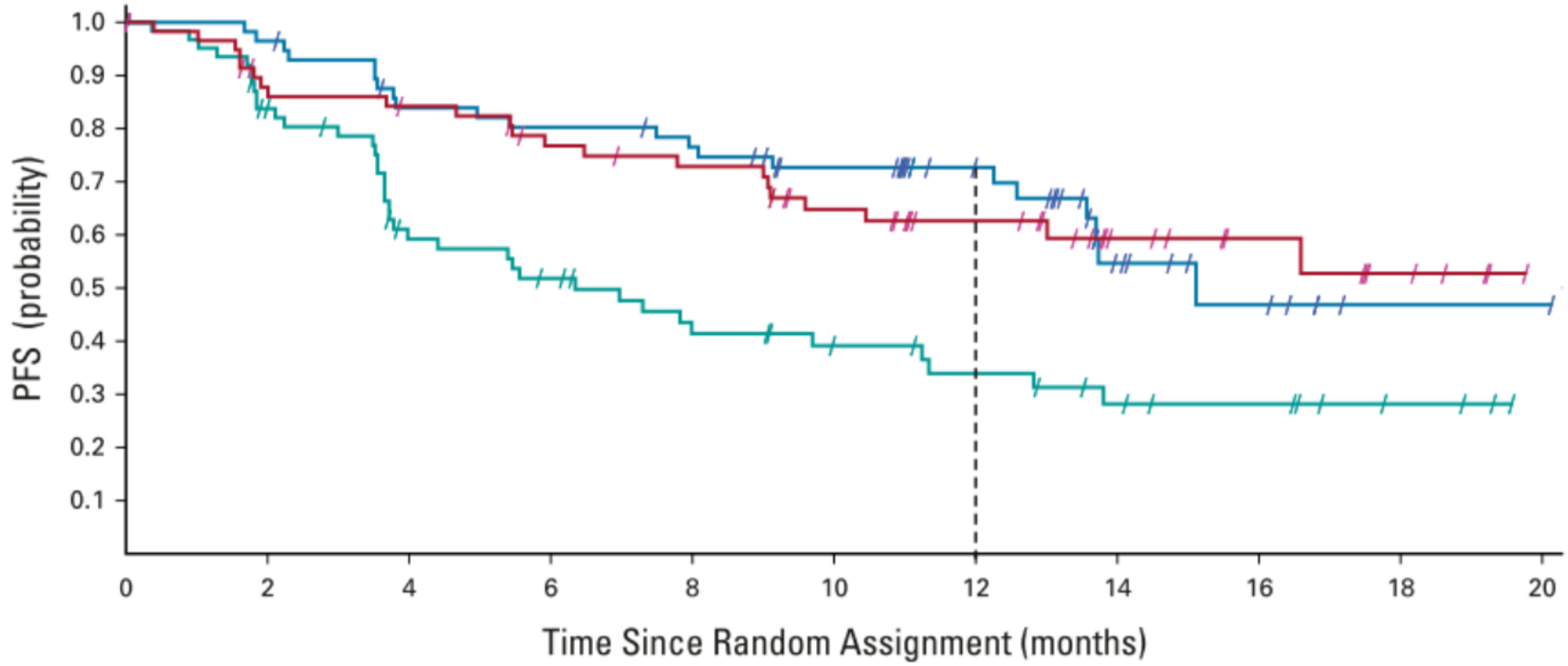
TABLE 1. Baseline Characteristics and Prior CRT

Characteristic[a]	Durvalumab (n = 67)	Durvalumab + Oleclumab (n = 60)	Durvalumab + Monalizumab (n = 62)
Median age, years (range)	66.0 (46-81)	65.0 (37-83)	65.0 (44-87)
Male, %	67.2	70.0	67.7
Race, No. (%)[b]			
American Indian or Alaska Native	0	1 (1.7)	0
Asian	5 (7.7)	4 (6.8)	5 (8.1)
Black or African American	1 (1.5)	5 (8.5)	2 (3.2)
Native Hawaiian or Other Pacific Islander	1 (1.5)	0	0
White	57 (87.7)	47 (79.7)	55 (88.7)
Other	1 (1.5)	2 (3.4)	0
ECOG PS, No. (%)[b]			
0	30 (45.5)	33 (55.9)	27 (44.3)
1	36 (54.5)	26 (44.1)	34 (55.7)
Ever smoked, No. (%)	63 (94.0)	54 (90.0)	59 (95.2)
Histology, No. (%)			
Squamous	30 (44.8)	24 (40.0)	27 (43.5)
Nonsquamous	37 (55.2)	36 (60.0)	35 (56.5)
Disease stage at study entry, No. (%)			
IIIA	27 (40.3)	27 (45.0)	32 (51.6)
IIIB	34 (50.7)	29 (48.3)	27 (43.5)
IIIC	6 (9.0)	4 (6.7)	3 (4.8)
PD-L1 status, No. (%)[c]			
TC $\geq$ 1%	30 (44.8)	23 (38.3)	20 (32.3)
TC $<$ 1%	16 (23.9)	7 (11.7)	12 (19.4)
Unknown	21 (31.3)	30 (50.0)	30 (48.4)
Prior RT dose, Gy, No. (%)			
54-66	62 (92.5)	54 (90.0)	57 (91.9)
$>$ 66	5 (7.5)	6 (10.0)	5 (8.1)
Time from last RT to random assignment, days, No. (%)			
$<$ 14	9 (13.4)	4 (6.7)	6 (9.7)
14-28	27 (40.3)	27 (45.0)	30 (48.4)
29-42	31 (46.3)	29 (48.3)	26 (41.9)
Prior platinum-based CT, No. (%)[d]			
Cisplatin	23 (34.3)	28 (46.7)	15 (24.2)
Carboplatin	43 (64.2)	28 (46.7)	44 (71.0)

Antitumour activity by investigator assessment
(interim analysis; ITT population)

Antitumour activity	D (N=67)	D+O (N=60)	D+M (N=62)
Confirmed ORR (95% CI),[b] %	**17.9 (9.6, 29.2)**	**30.0 (18.8, 43.2)**	**35.5 (23.7, 48.7)**
[n]	[12]	[18]	[22]
Confirmed + unconfirmed ORR (95% CI),[b] %	**25.4 (15.5, 37.5)**	**38.3 (26.1, 51.8)**	**37.1 (25.2, 50.3)**
[n]	[17]	[23]	[23]
ORR odds ratio (95% CI)[a,b]	–	**1.83 (0.80, 4.20)**	**1.77 (0.77, 4.11)**
Objective responses by RECIST,[a] n (%)			
CR	2 (3.0)	1 (1.7)	3 (4.8)
PR	15 (22.4)	22 (36.7)	20 (32.3)
SD	27 (40.3)	25 (41.7)	27 (43.5)
PD	15 (22.4)	7 (11.7)	7 (11.3)
NE	8 (11.9)	5 (8.3)	4 (6.5)
DCR at 16 weeks (95% CI),[a,c] %	**58.2 (45.5, 70.2)**	**81.7 (69.6, 90.5)**	**77.4 (65.0, 87.1)**
[n]	[39]	[49]	[48]
Median DoR (95% CI),[a] months	**NR (2.3, NA)**	**12.9 (6.7, NA)**	**NR (9.0, NA)**
Range	0.0+, 17.5+	0.0+, 16.9+	1.9+, 18.4+

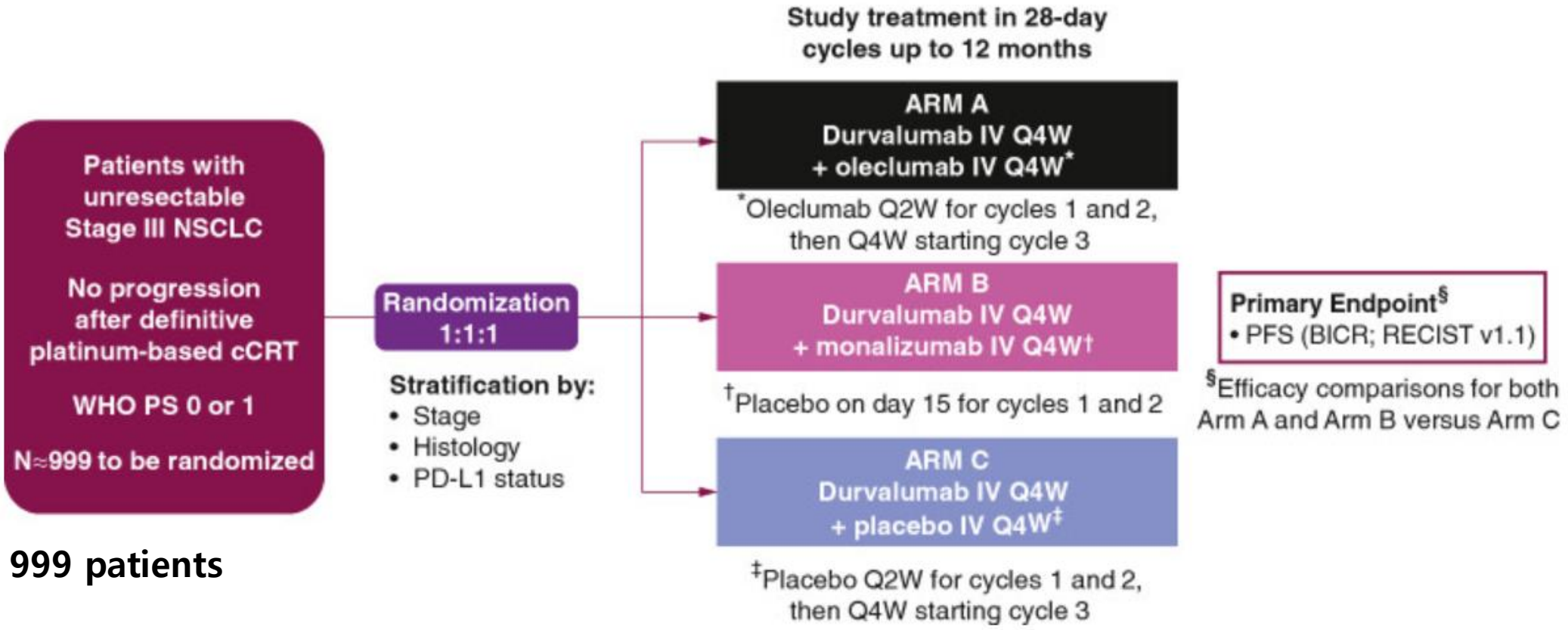
Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)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

FIG 2. Progression-free survival (ITT population). Data cutoff: May 17, 2021 (median follow-up of 11.5 months; range, 0.4-23.4 months). [a]Interim analysis was performed when all patients had a 10-month minimum potential follow-up; Kaplan-Meier estimates for PFS, PFS rate, and 95% CIs. [b]PFS

PACIFIC-9: Phase III trial of durvalumab + oleclumab or monalizumab in unresectable stage III non-small-cell lung cancer



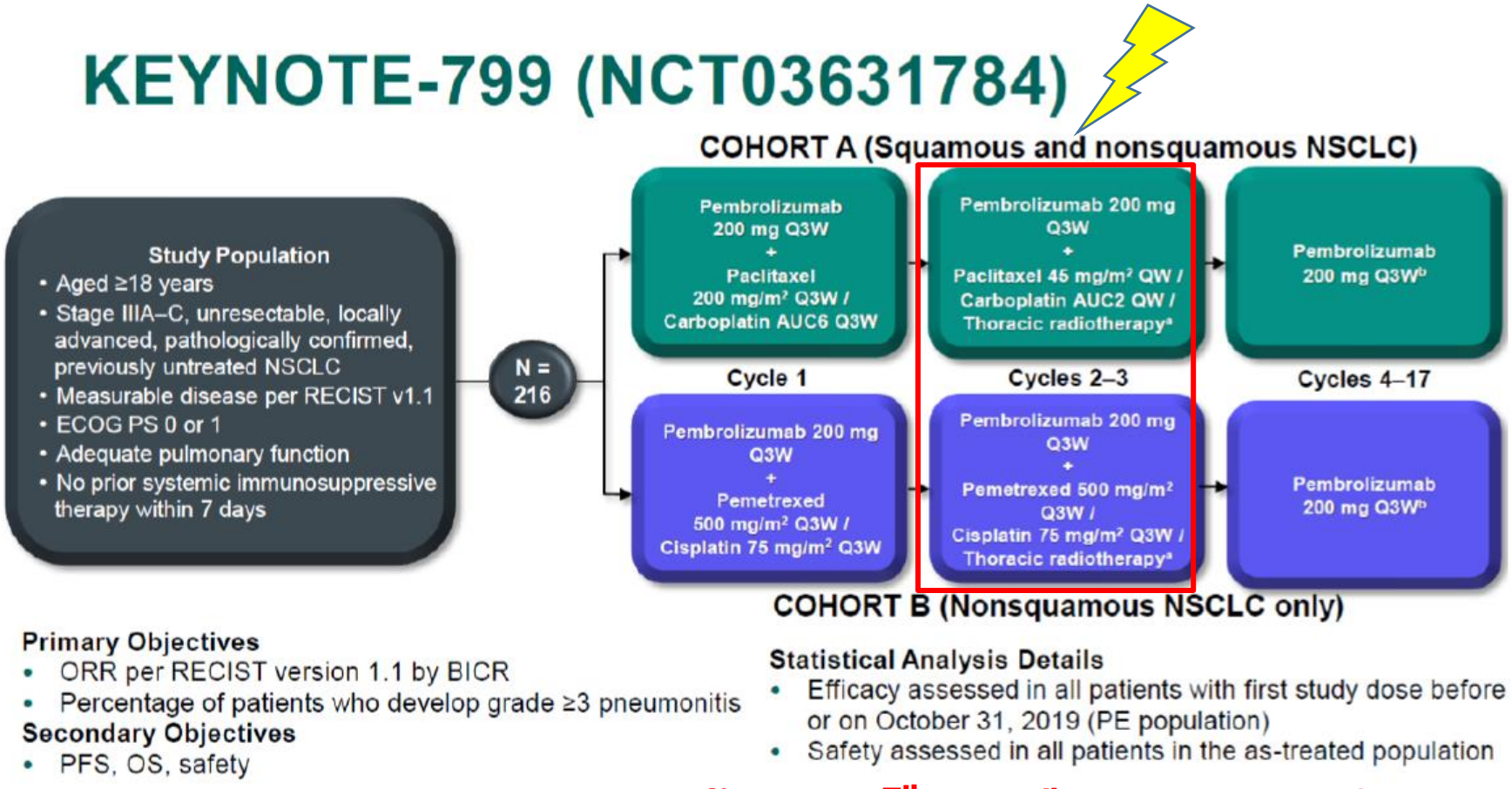
999 patients

Pembrolizumab (Keytruda®)

JAMA Oncology | Original Investigation

Pembrolizumab Plus Concurrent Chemoradiation Therapy in Patients With Unresectable, Locally Advanced, Stage III Non-Small Cell Lung Cancer
The Phase 2 KEYNOTE-799 Nonrandomized Trial

Salma K. Jabbour, MD; Ki Hyeong Lee, MD, PhD; Nikolaj Frost, MD; Valeriy Breder, MD, PhD; Dariusz M. Kowalski, MD, PhD; Theodore Pollock, DO; Evgeny Levchenko, MD, PhD; Noemi Reguart, MD, PhD; Alex Martinez-Marti, MD; Baerin Houghton, MBBS, BSc, MM; Jean-Baptiste Paoli, MD; Sufia Safina, MD; Keunchil Park, MD; Takefumi Komiya, MD; Amy Sanford, MD; Vishal Boolell, BSc, MBBS; Hong Liu, MD; Ayman Samkari, MD; Steven M. Keller, MD; Martin Reck, MD



Neoadjuvant 3제 3제+RT IO

Jabbour et al. JAMA Oncol. 2021

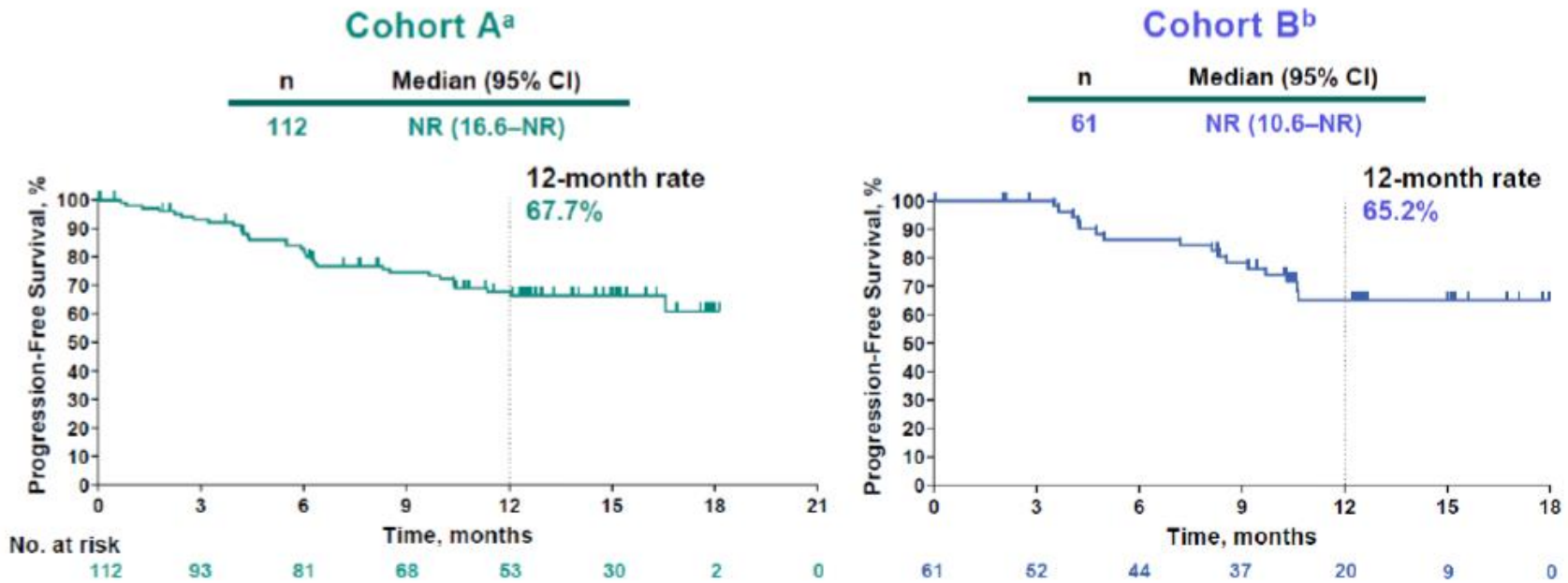
Inclusion criteria

- previously untreated, unresectable, pathologically or radiologically confirmed stage IIIA, IIIB, or IIIC NSCLC.
- ECOG 0-1
- FEV1> 50%, DLCO > 40%

Treatment

- SqCC : Paclitaxel +carboplatin+Pembrolizumab → weekly TC 6wks+ 2 cycle Pembrolizumab+ RT→ 1yr Pembrolizumab
- Non-squamous : 3 cycle Pemetrexate + cisplatin + Pembrolizumab +RT → 1yr Pembrolizumab
- ORR >70% irrespective of disease stage, tumor histologic type, and PD-L1
- High ORR and prolonged DOR
- **AE** : Pneumonitis and radiation pneumonitis are common. Grade III< 10%
- higher-than-expected rate of pneumonitis.

Progression-Free Survival
By BICR per RECIST v1.1 (Primary Efficacy Population)



Response	Cohort A (n = 112)		Cohort B (n = 102)	
ORR, No. (%) [95% CI][a]	79 (70.5) [61.2 to 78.8]		72 (70.6) [60.7 to 79.2]	
Occurring in ≥15% of patients in either cohort	Any grade	Grade 3-5	Any grade	Grade 3-5
Radiation pneumonitis	20 (17.9)	2 (1.8)	8 (7.8)	1 (1.0)

- grade 3 to 5 pneumonitis in 9 of 112 patients (8.0%)

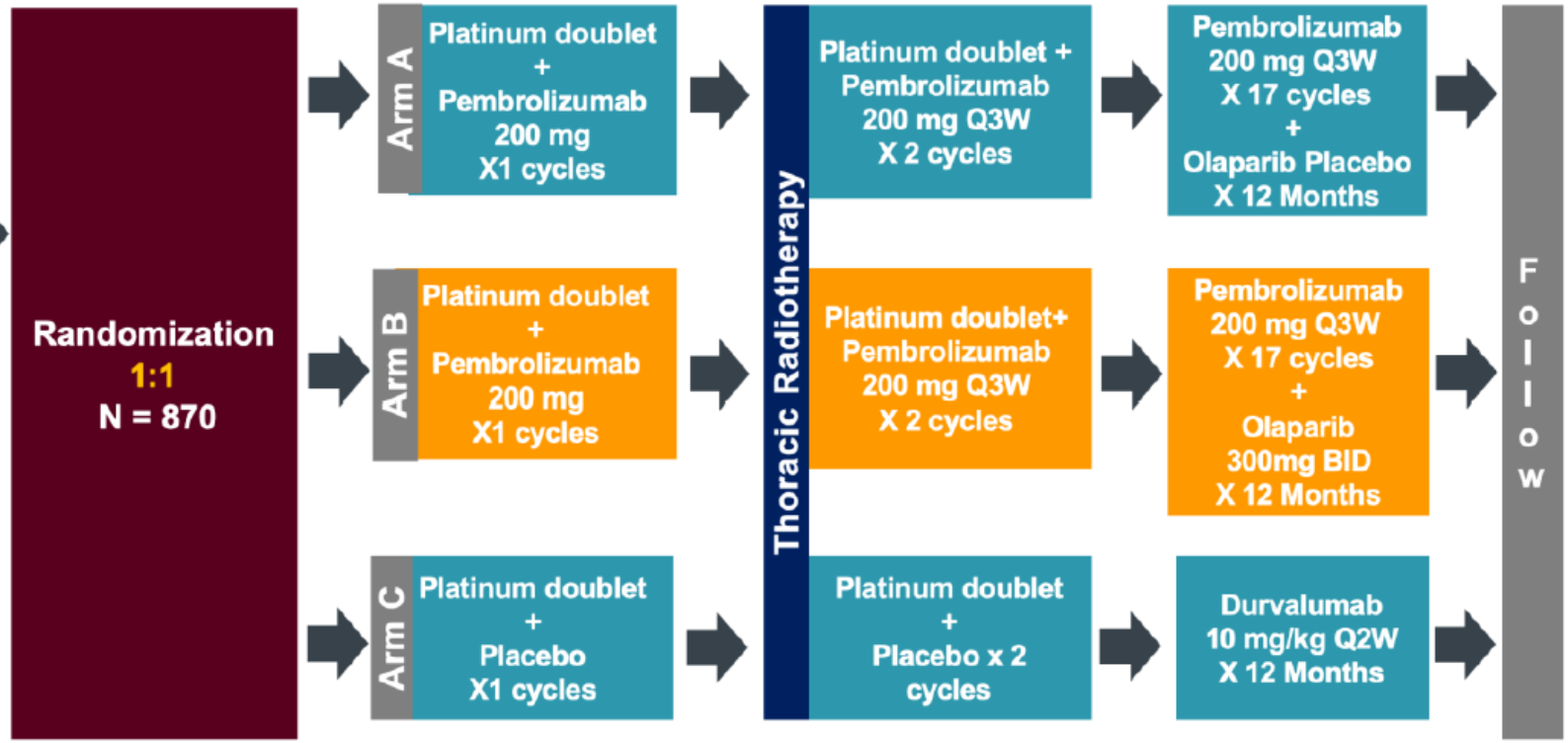
	Cohort A (N = 112)	Cohort B (N = 53)
ORR, n (%) [90% CI]	75 (67.0) [58.9–74.3]	30 (56.6) [44.4–68.2]
CR	3 (2.7)	2 (3.8)
PR	72 (64.3)	28 (52.8)
SD, n (%)	23 (20.5)	18 (34.0)
PD, n (%)	1 (0.9)	0
Not evaluable, n (%)	3 (2.7)	0
No assessment, n (%)	10 (8.9)	5 (9.4)
Duration of response, median (range),[a] mo	NR (1.6+ to 10.5+)	NR (1.7+ to 10.5+)
Response duration ≥6 mo,[a] n (%)	30 (91.1)	9 (100)
6-mo PFS rate,[a] %	81.4	85.2
6-mo OS rate,[a] %	87.2	94.8

KEYTRUDA THORACIC: Ph3 Chemo RT Combo in Locally Unresectable NSCLC

Study Design KEYLYNK 012

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

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



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

Atezolizumab (Tecentriq®)

JAMA Oncology | Original Investigation

Atezolizumab Before and After Chemoradiation for Unresectable Stage III Non–Small Cell Lung Cancer

A Phase II Nonrandomized Controlled Trial **AFT-16 trial** **Induction immunotherapy**

Duvalumab **mPFS**: **16.8 vs 5.6 개월**
mOS : 47.5 vs 29.1 개월

- **Hypothesis** : Starting atezolizumab prior to CRT may allow more patients to benefit from immunotherapy .
- **Aim**: To evaluate clinical outcomes of patients treated with atezolizumab **before and after CRT** for unresectable stage III NSCLC.
- Single-cohort, phase II, nonrandomized controlled trial, **unresectable stage III NSCLC**
- Enrollment : Jan 2018 - July 2019
- **Four 3wks cycles of atezolizumab** →(60Gy RT with weekly TC)→**1200mg 3 weeks for 1 years**
- Primary endpoint : **DCR** at 12 weeks, Secondary endpoint **: PFS, OS, ORR**, safety
- **DCR : 74.2%** **mPFS** : **30** months, 2ys-OS rate 73.7% (cf. Duvalumab 2ys OS 63.3%)

JAMA Oncol. 2024;10(9):1212-1219

Figure 1. Patient Flow Diagram

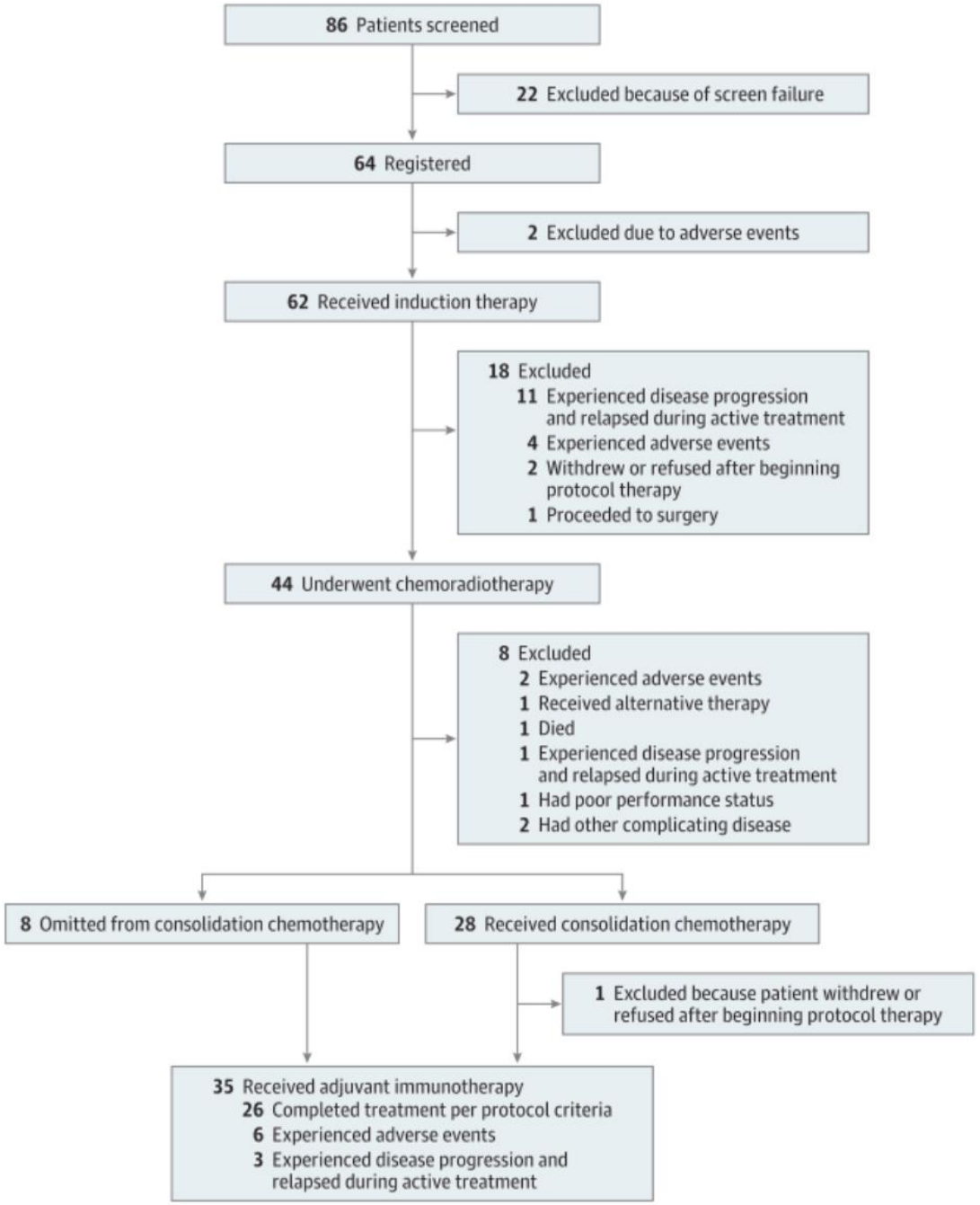
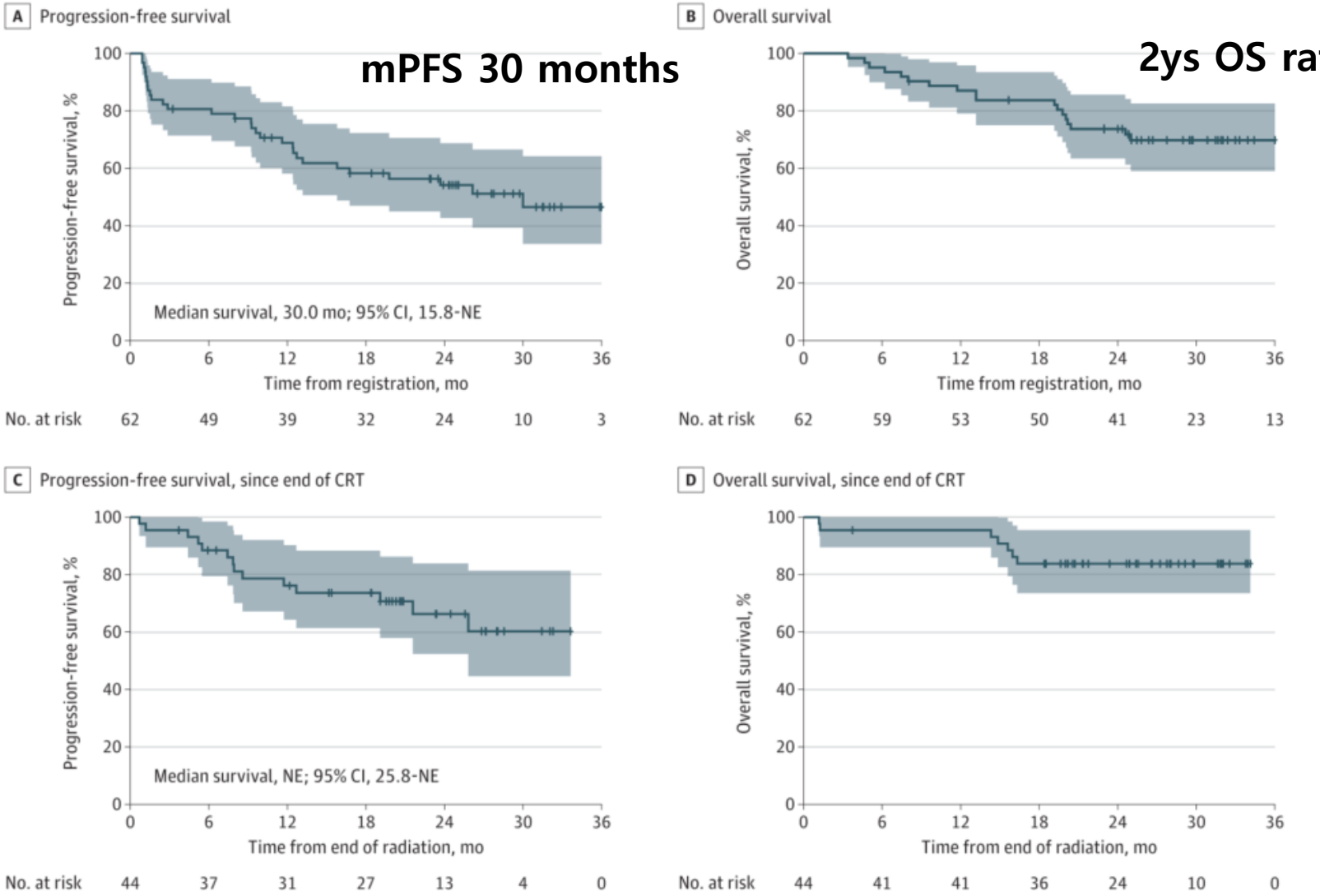


Table 1. Patient Characteristics

Characteristic	No. (%)
No. of patients	62
Age, y	
Median (IQR)	63.9 (57.7-71.1)
Range	38.1-86.5
Race	
Asian	4 (6.5)
Black, African American, or African heritage	9 (14.5)
White	48 (77.4)
Other (not further specified)	1 (1.6)
Sex	
Female	32 (51.6)
Male	30 (48.4)
Smoking history	
Current	17 (27.4)
Never	7 (11.3)
Former	38 (61.3)
Stage	
IIIA	33 (53.2)
IIIB	29 (46.8)
ECOG performance status	
0	35 (56.5)
1	27 (43.5)
Recurrent disease after resection	
No	60 (96.8)
Yes	2 (3.2)
Tumor PD-L1 status	
Positive (≥1%)	13 (26.5)
Negative (<1%)	36 (73.5)
Missing	13

PDL1
Histology

Figure 2. Progression-Free and Overall Survival and Exploratory Analysis of the Patients Who Completed Concurrent Chemoradiation Therapy (CRT)



mPFS 30 months

2ys OS rate 73.7%

Duvalumab
mPFS 16.9 mon
2ys OS 66.3%
2ys PFS 45%

- PFS rates at 1 & 2 years →76.2% & 64.3% (cf. Duval 55.7&45%, Key799 trial 67.1 & 71.6%)
- OS rates at 1 & 2 years → 87% and 73.7% (cf. Duval 83.1 and 66.3%, Key 799 trial 81.3%)
- The DCR for neoadjuvant atezolizumab did not appear to differ by (+) or (-) PD-L1 expression

Limitations

- While AFT-16 outcomes are encouraging.
- Single-arm, phase II trial, no control group
- E nrolled treatment-naive patients
- While PACIFIC enrolled only patients who had completed CRT
- Hypothesis generating
- The AFT-16 PFS and OS rates with neoadjuvant atezolizumab alone compare favorably with those reported in KEYNOTE-799 with chemoimmunotherapy.
- Biomarker :Less diverse TCR repertoire to have durable responses
- Atezolizumab administration before and after standard CRT for patients with unresectable stage III NSCLC was safe and appeared to be effective.

Progression-Free and Overall Survival for Concurrent Nivolumab With Standard Concurrent Chemoradiotherapy in Locally Advanced Stage IIIA-B NSCLC: Results From the European Thoracic Oncology Platform NICOLAS Phase II Trial (European Thoracic Oncology Platform 6-14)

Solange Peters, MD, PhD,[a] Enriqueta Felip, MD, PhD,[b] Urania Dafni, ScD,[c,d] Amanda Tufman, MD,[e,f] Matthias Guckenberger, MD,[g] Ruth Álvarez, MD,[h] Ernest Nadal, MD, PhD,[i] Annemarie Becker, MD, PhD,[j] Hansjörg Vees, MD,[k] Miklos Pless, MD,[l] Alex Martinez-Marti, MD,[b] Maarten Lambrecht, MD, PhD,[m] Nicolaus Andratschke, MD,[g] Zoi Tsourti, PhD,[c] Anne-Christine Piguet, PhD,[n] Heidi Roschitzki-Voser, PhD,[n] Adrian Gasca-Ruchti, MD,[n] Johan Vansteenkiste, MD, PhD,[o] Rolf A. Stahel, MD,[n,*] Dirk De Ruysscher, MD, PhD[p]

Original Investigation

FREE

September 7, 2023

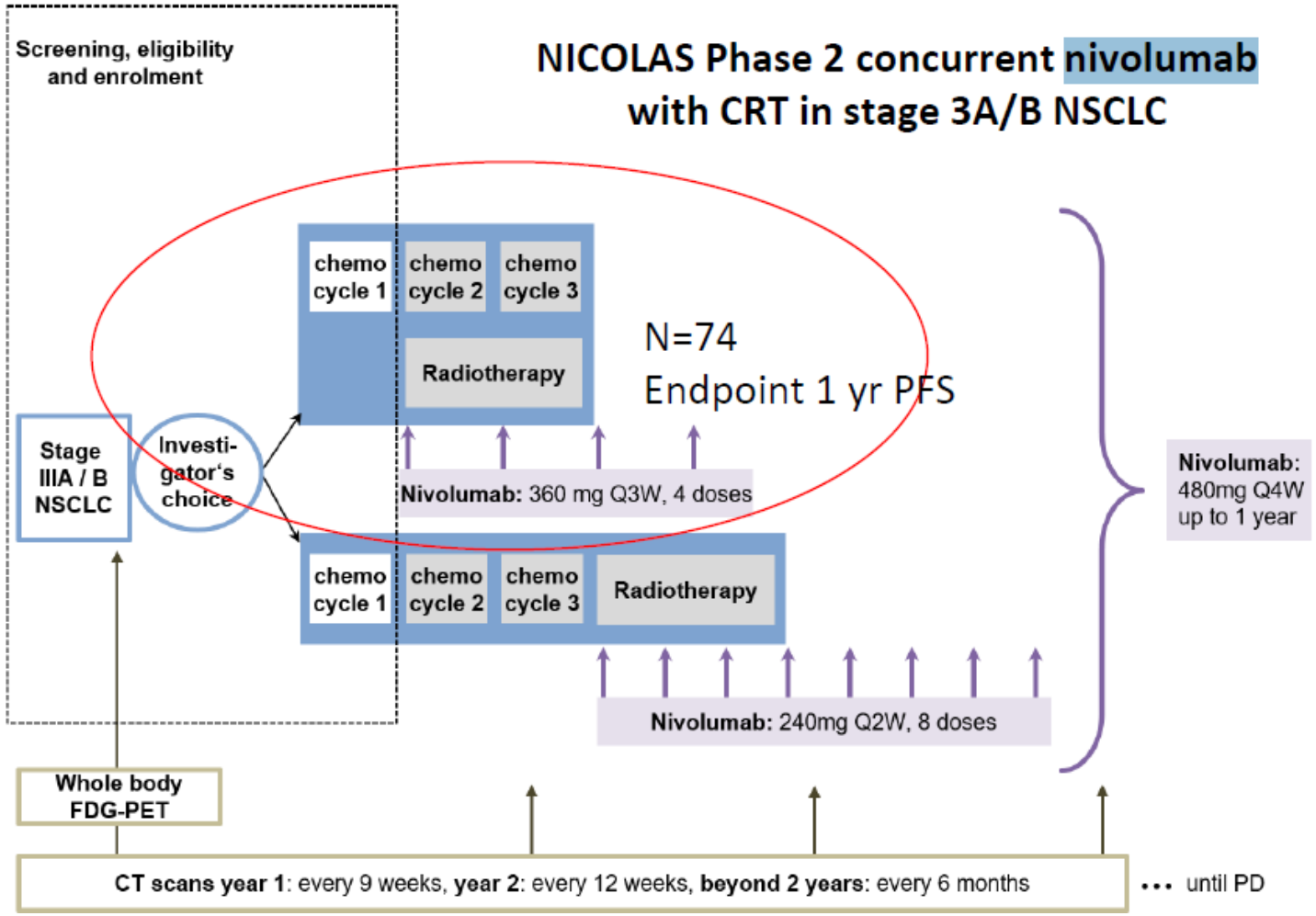
Durvalumab Plus Concurrent Radiotherapy for Treatment of Locally Advanced Non–Small Cell Lung Cancer

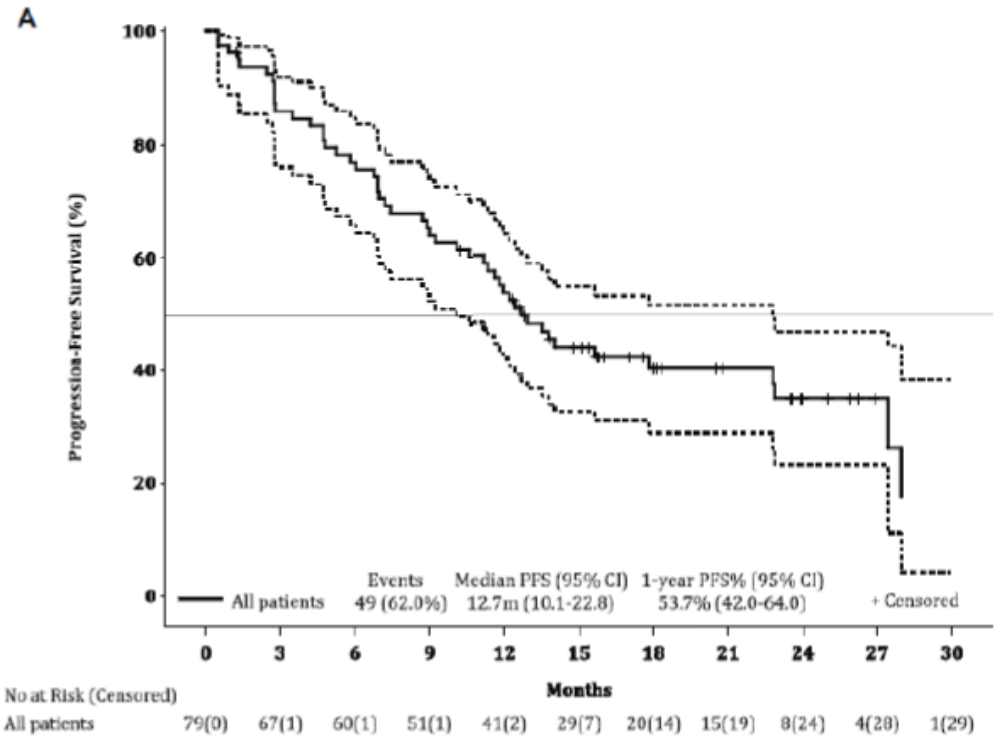
The DOLPHIN Phase 2 Nonrandomized Controlled Trial

Motoko Tachihara, MD, PhD[1]; Kayoko Tsujino, MD, PhD[2]; Takeaki Ishihara, MD, PhD[3]; et al

» Author Affiliations | Article Information

JAMA Oncol. 2023;9(11):1505-1513. doi:10.1001/jamaoncol.2023.3309



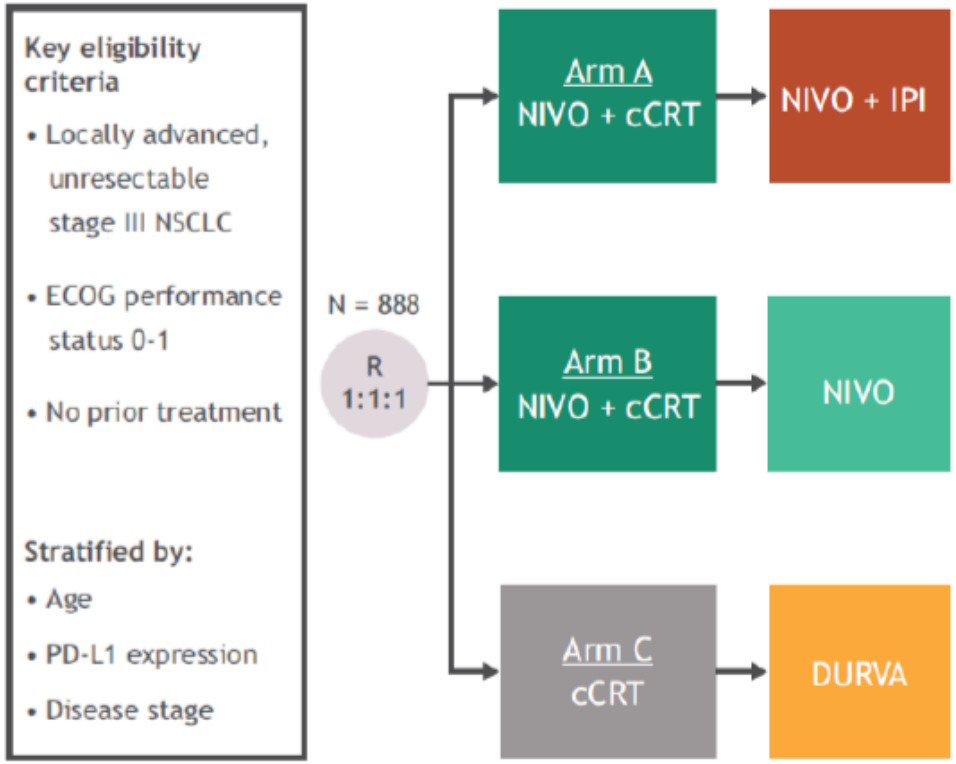


Grade 3-5 treatment related SAEs: 18% (G5 6%)
9 patients (11.7%) had G3-5 pneumonitis (1 G5)

Peters et al., JTO 2021

CheckMate 73L

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



PACIFIC arm

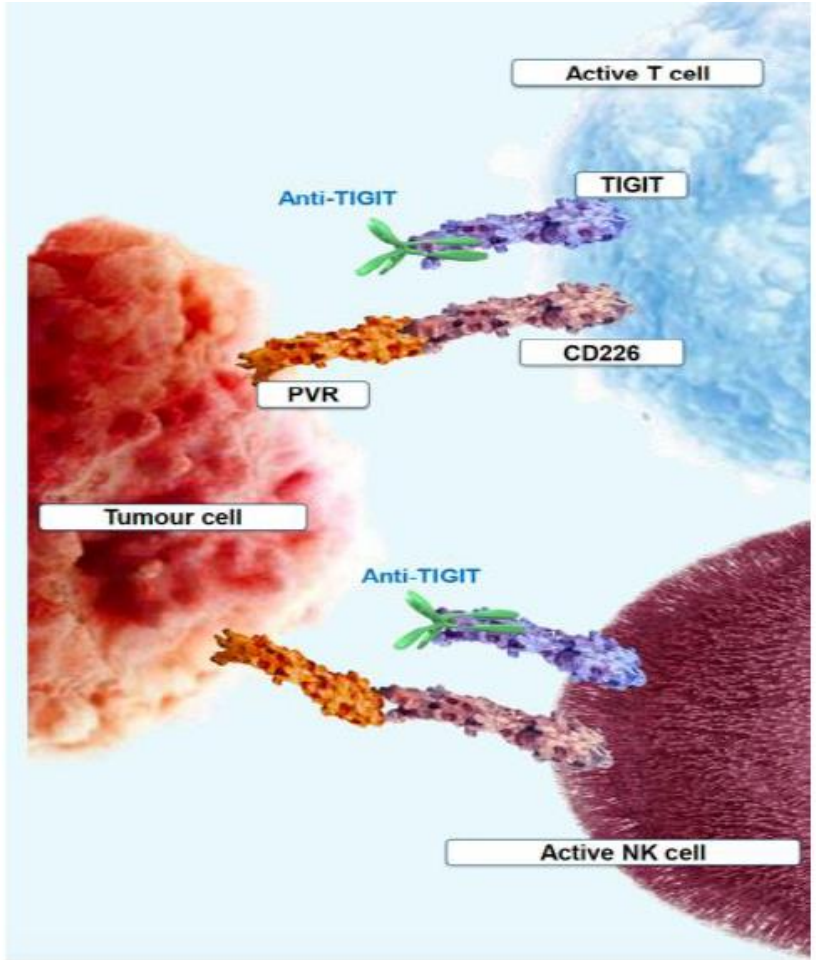
Primary endpoints:
NIVO + cCRT followed by NIVO + IPI (Arm A) vs
cCRT followed by DURVA (Arm C)

- PFS
- OS

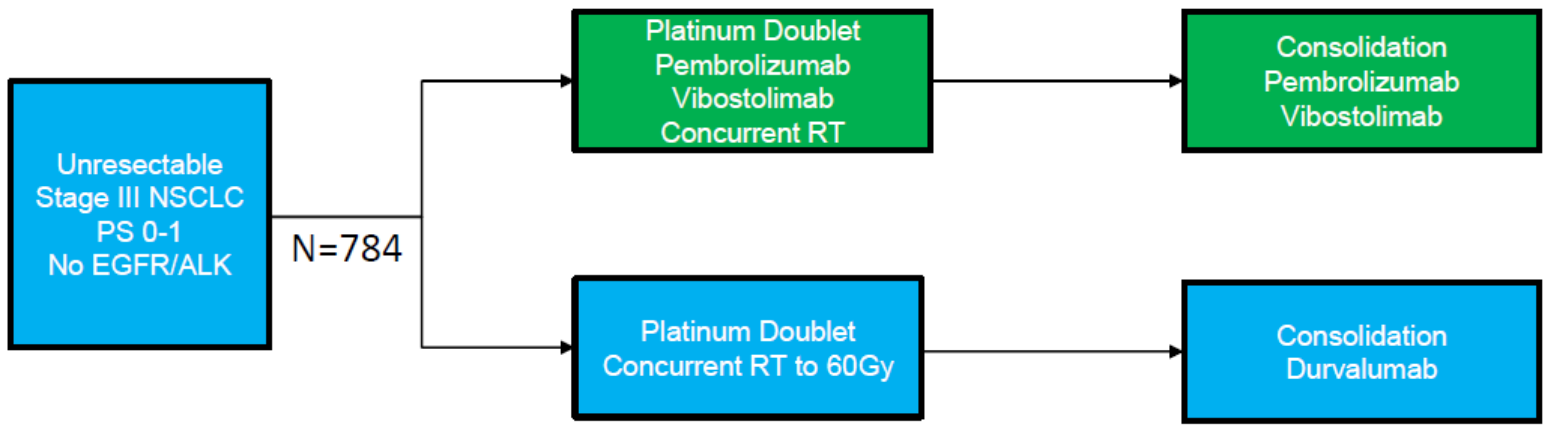
De Ruysscher et al., ESMO 2020

Anti-TIGIT Antibodies:

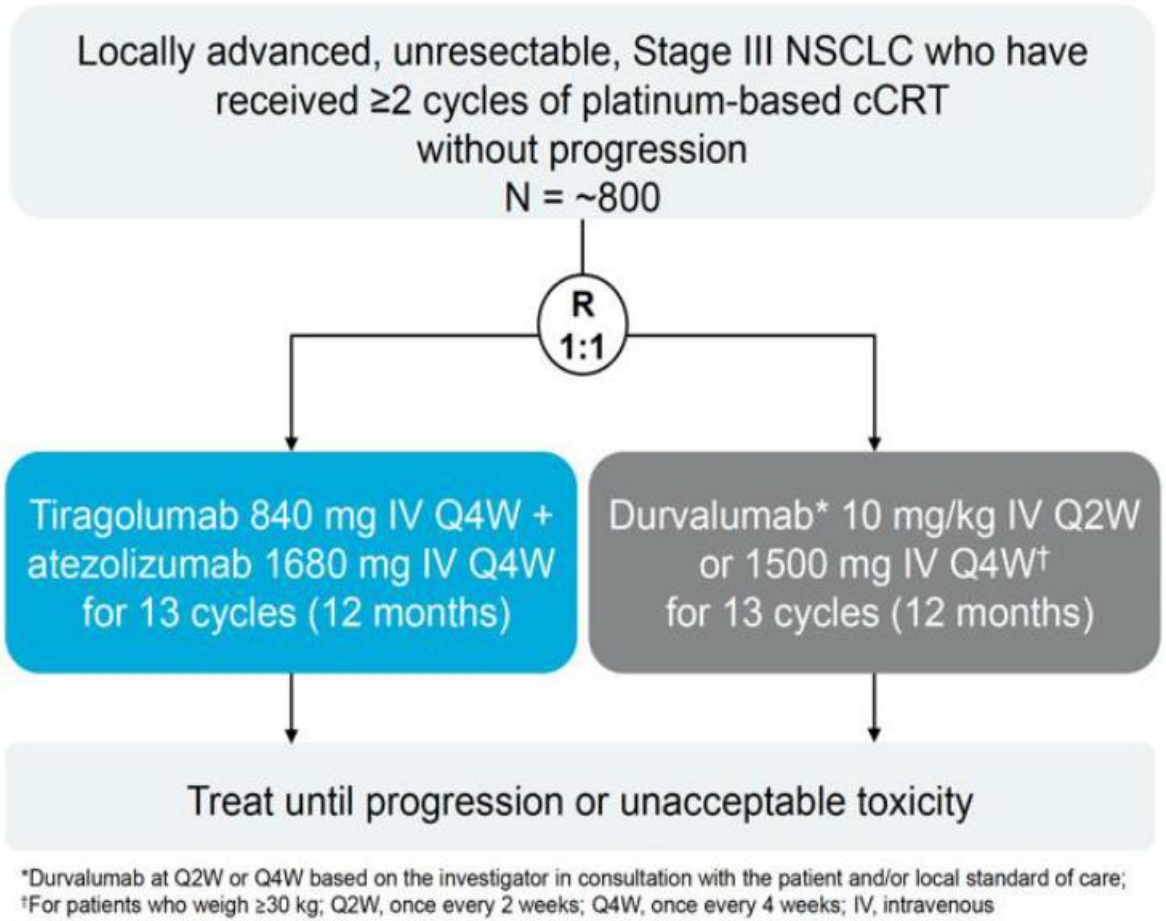
- TIGIT is a novel inhibitory checkpoint on activated T cells and NK cells
- Tiragolumab and Domvanalimab are anti-TIGIT monoclonal antibodies which block binding to its receptor PVR
- Inhibition of TIGIT/PVR may amplify the durability / duration of anti-tumor response of anti-PD-L1/PD-1 antibodies



KEYVIBE-006: Ph3 Trial Pembro/Vibostolimab (anti-TIGIT) plus Concurrent CRT Followed by Pembro/Vibostolimab Versus Concurrent CRT Followed by Durvalumab in Stage III NSCLC



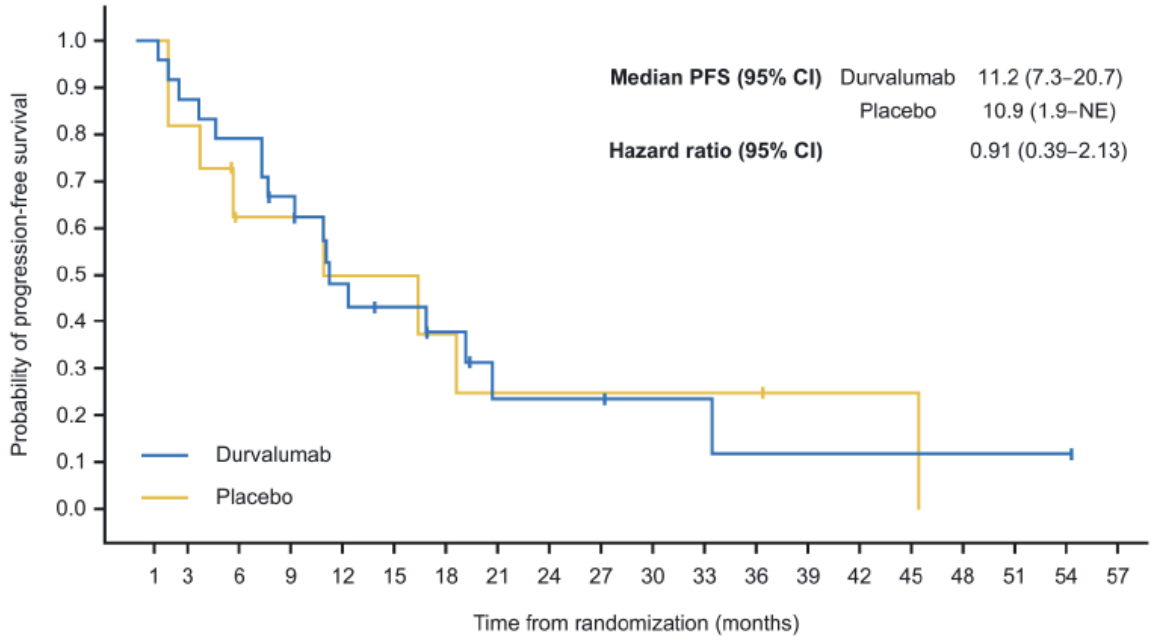
Primary Endpoints:
PFS overall and in PDL1>=1%
OS overall and in PDL1>=1%



- SKYSCRAPER-03
- Durvalumab vs. Atezo/Tiragolumab (anti-TIGIT)
- Planned 800 participants
- Start Date- 8/2020
- Primary Endpoint- PFS
- 12 months of consolidation

- A Global Study to Assess the Effects of Durvalumab + Domvanalimab (anti-TIGIT) Following Concurrent Chemoradiation in Unresectable Stage III NSCLC
- Planned 860 participants
- Start Date- 2/2022
- Primary Endpoint- PFS
- 12 months of consolidation

PACIFIC EGFRm *post-hoc* subgroup analysis



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

No clear benefit of durvalumab after CRT in unresectable stage III NSCLC with EGFR mutation

Naidoo J, et al. J Thorac Oncol 2023;18:657-663

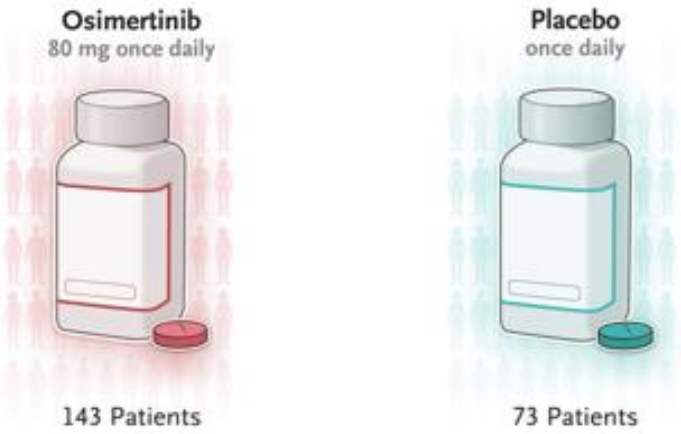
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 15, 2024 VOL. 391 NO. 7

Osimertinib after Chemoradiotherapy in Stage III *EGFR*-Mutated NSCLC

HOW WAS THE TRIAL CONDUCTED?

216 adults with stage III, unresectable, *EGFR*-mutated NSCLC who had not had disease progression during or after chemoradiotherapy were randomly assigned in a 2:1 ratio to receive oral osimertinib or placebo until disease progression or a serious toxic effect had occurred or until the patient wished to stop treatment. The primary end point was progression-free survival.



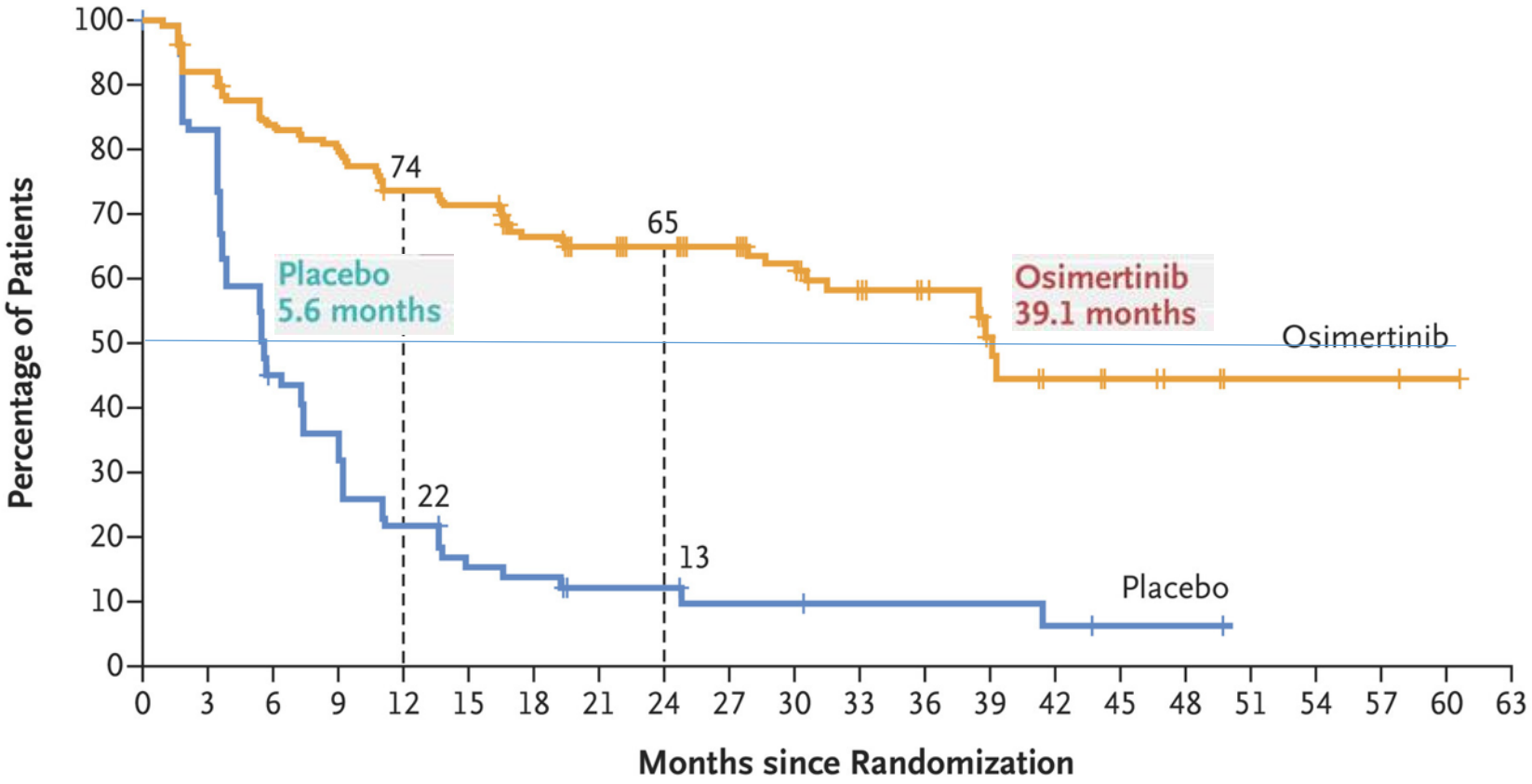
Tumors harboring EGFR mutation tend to be immune cold

The LAURA trial : **Phase 3, double-blind, randomized placebo-controlled trial**

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Osimertinib (N=143)	Placebo (N=73)
Sex — no. (%)		
Male	53 (37)	31 (42)
Female	90 (63)	42 (58)
Age — yr		
Median	62	64
Range	36 to 84	37 to 83
Smoking status — no. (%)		
Current	4 (3)	1 (1)
Former	37 (26)	23 (32)
Never	102 (71)	49 (67)
Race — no. (%)†		
Asian	116 (81)	62 (85)
Non-Asian	27 (19)	11 (15)
WHO performance-status score — no. (%)‡		
0	80 (56)	31 (42)
1	63 (44)	42 (58)
AJCC–UICC disease stage — no. (%)§		
IIIA	52 (36)	24 (33)
IIIB	67 (47)	38 (52)
IIIC	24 (17)	11 (15)
Histologic type — no. (%)		
Adenocarcinoma	139 (97)	69 (95)
Squamous-cell carcinoma	3 (2)	2 (3)
Other¶	1 (1)	2 (3)
EGFR mutation type at screening — no. (%)‖		
Exon 19 deletion	74 (52)	43 (59)
L858R mutation	68 (48)	30 (41)
Type of chemoradiotherapy — no. (%)**		
Concurrent	131 (92)	62 (85)
Sequential	12 (8)	11 (15)
Best overall response to chemoradiotherapy — no. (%)††		
Complete response	4 (3)	3 (4)
Partial response	67 (47)	27 (37)
Stable disease	61 (43)	37 (51)
Not evaluable‡‡	11 (8)	6 (8)
Target-lesion size — mm§§	33±18	36±17

Progression-free Survival



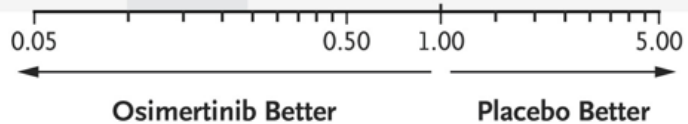
Median Progression-free Survival (95% CI)	*mo*
Osimertinib	39.1 (31.5–NC)
Placebo	5.6 (3.7–7.4)

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

No. at Risk

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

Subgroup	Osimertinib	Placebo	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/no. of patients		
Overall			
Stratified log-rank analysis	57/143	63/73	0.16 (0.10–0.24)
Unadjusted Cox proportional-hazards analysis	57/143	63/73	0.23 (0.16–0.33)
Sex			
Male	23/53	27/31	0.26 (0.15–0.46)
Female	34/90	36/42	0.21 (0.13–0.34)
Age			
<65 yr	31/81	36/39	0.16 (0.10–0.26)
≥65 yr	26/62	27/34	0.33 (0.19–0.57)
Smoking history			
Current or former	20/41	22/24	0.26 (0.14–0.48)
Never	37/102	41/49	0.22 (0.14–0.34)
Race or national group			
Chinese	7/27	11/13	NC (NC–NC)
Non-Chinese	50/116	52/60	0.26 (0.17–0.39)
Asian	43/116	55/62	0.20 (0.13–0.29)
Non-Asian	14/27	8/11	0.48 (0.20–1.19)
Stage			
IIIA	22/52	20/24	0.28 (0.15–0.52)
IIIB or IIIC	35/91	43/49	0.21 (0.13–0.33)
EGFR mutation			
Exon 19 deletion	26/74	39/43	0.17 (0.10–0.29)
L858R mutation	31/68	24/30	0.32 (0.19–0.56)
Chemoradiotherapy			
Concurrent	53/131	54/62	0.25 (0.17–0.36)
Sequential	4/12	9/11	NC (NC–NC)
Response to previous CRT			
Complete response	1/4	2/3	NC (NC–NC)
Partial response	28/67	25/27	0.20 (0.11–0.34)
Stable disease	24/61	34/37	0.18 (0.10–0.30)
Not evaluable	4/11	2/6	NC (NC–NC)



KATRD INTERNATIONAL CONFERENCE 2024

Preliminary Analysis of Lazertinib Consolidation Therapy in patients with locally Advanced, Unresectable, EGFR Mutated NSCLC following chemoradiation Therapy (PLATINUM Trial)

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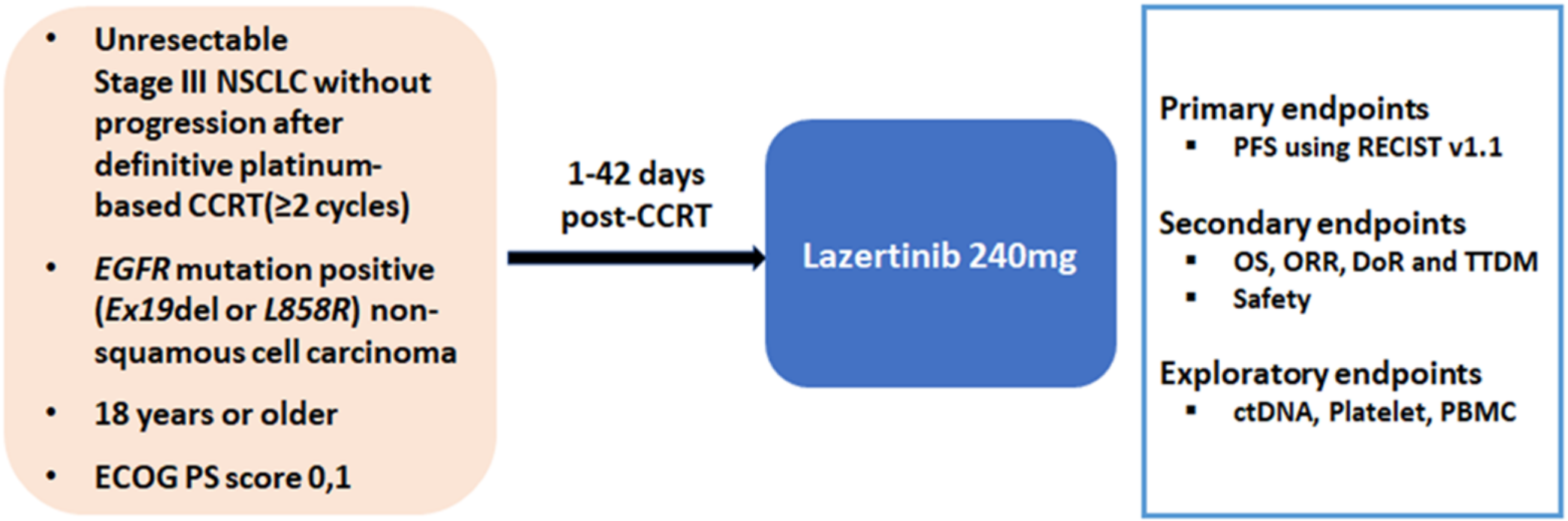
- A prospective, open, single-arm, multicenter, phase II clinical trial
- A total of 13 university hospitals in South Korea are participating in competitive patient enrollment.
- Target patient /No. : N = 49



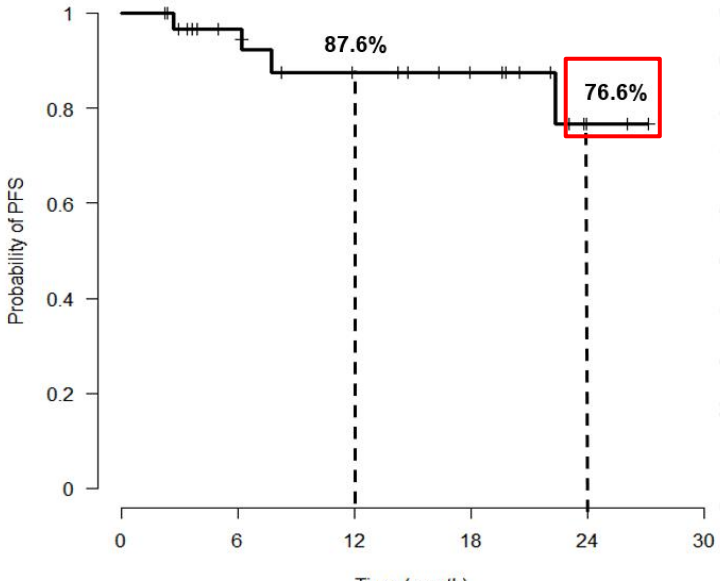
PLATINUM trial

LAURA trial

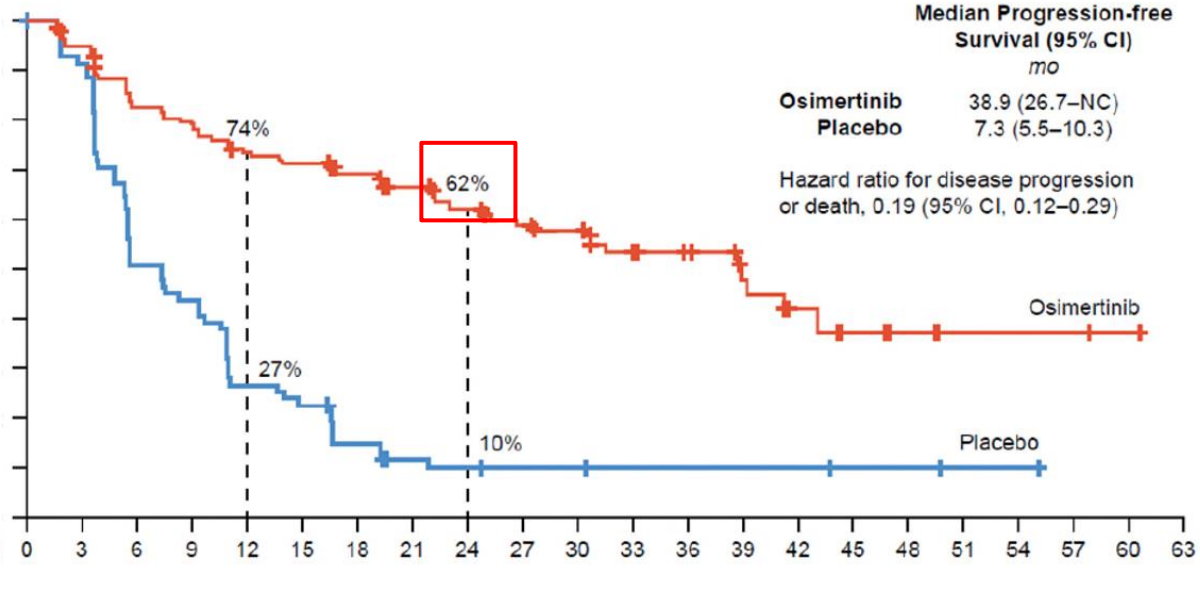
Characteristics	PLATINUM (n = 31, %)	Osimertinib (n = 143, %)	Placebo (n = 73, %)
Median F/U period			
Median (range)	16.3 (2.2 – 27.1)	22.0 (<0.1 to 60.6)	5.6 (<0.1 to 49.7)
DoR			
Median (range)	13.0 (0.8 – 25.3)	36.9	6.5
Median PFS			
Median (95% CI)	Not Reached	39.1	5.6
ORR	51.6	57	33
CR	3 (9.7%)	3 (2%)	1 (1%)
PR	13 (41.9%)	79 (55%)	23 (32%)
SD	15 (48.4%)	45 (31%)	34 (47%)

DCO : 2024-09-30

PLATINUM trial



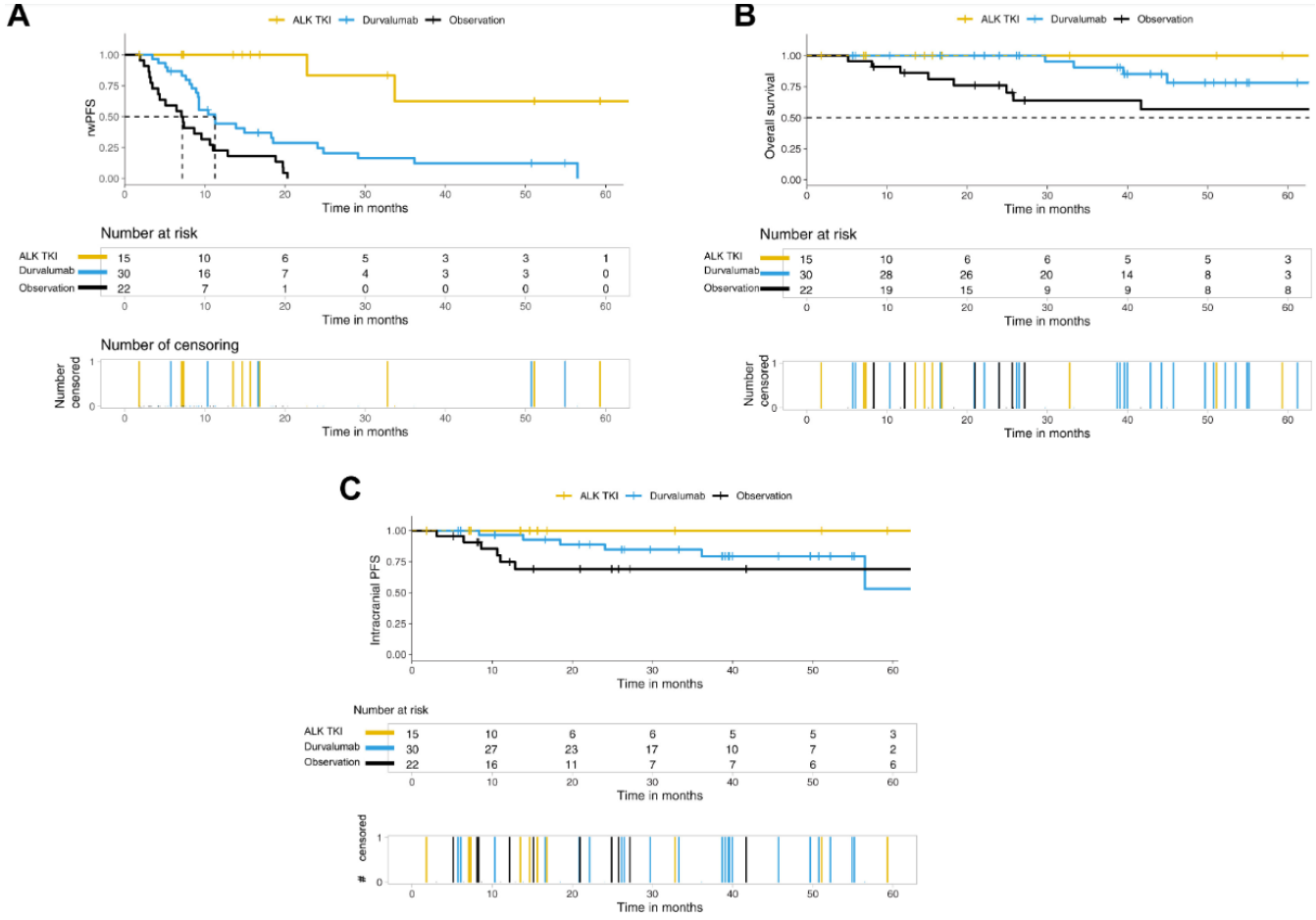
LAURA trial



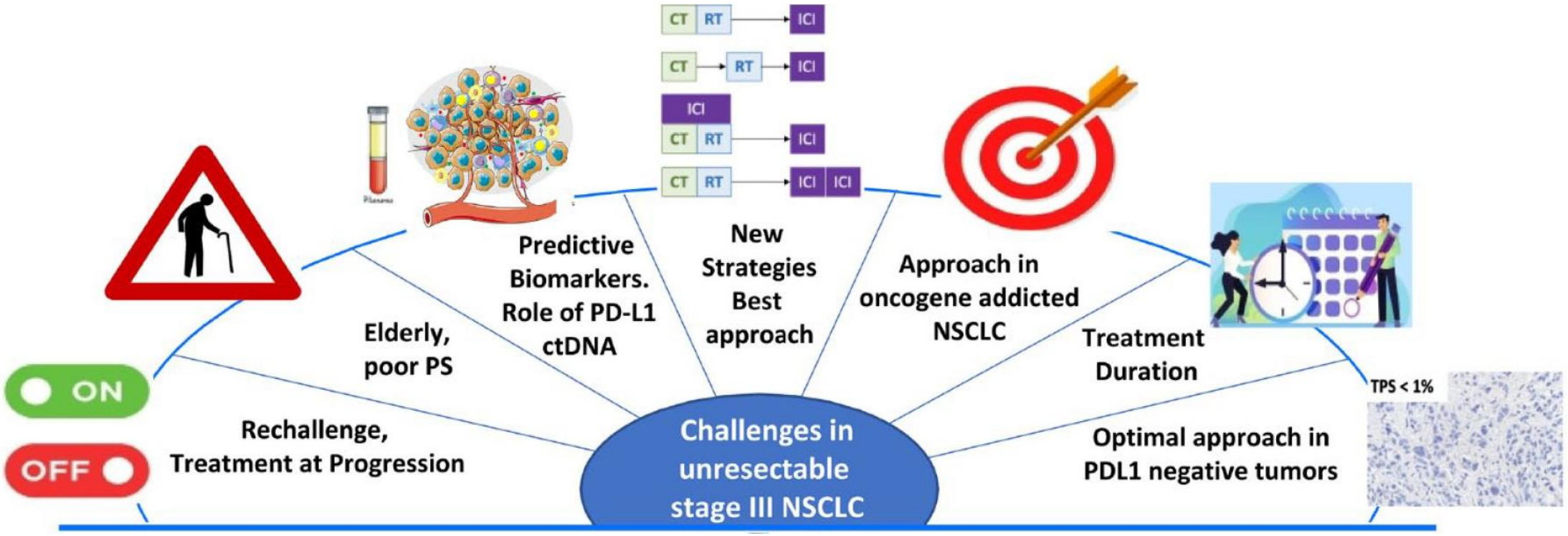
Consolidation ALK Tyrosine Kinase Inhibitors Versus Durvalumab or Observation After Chemoradiation in Unresectable Stage III ALK-Positive NSCLC

Check for updates

- Retrospective study
- unresectable stage III ALK-positive NSCLC treated
- between 2015 and 2022
- multicenter study of 17 institutions globally



Challenges in unresectable NSCLC



Take Home Message

- In locally advanced unresectable stage III NSCLC, 1 year-duvalumab consolidation therapy following platinum-based concurrent chemoradiotherapy is now a global standard of care.
- In real world studies, PACIFIC regimen has shown favorable outcomes.
- To further improve outcomes of unresectable stage III NSCLC, many clinical trials have been conducted combining other immune checkpoint inhibitors (ICIs) or different treatment platforms.
- In locally advanced unresectable stage III NSCLC with active targetable mutation, such as EGFR or ALK mutations, consolidative targeted therapies have shown favorable outcomes.

- 경청해 주셔서 감사합니다