STATE OF THE ART FOR STAGE III UNRESECTABLE NSCLC

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Unresectable Stage III NSCLC

IASLC 2023 World Conference on Lung Cancer

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

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

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

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

Consolidation Immunotherapy following prior concurrent or sequential chemoradiotherapy

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

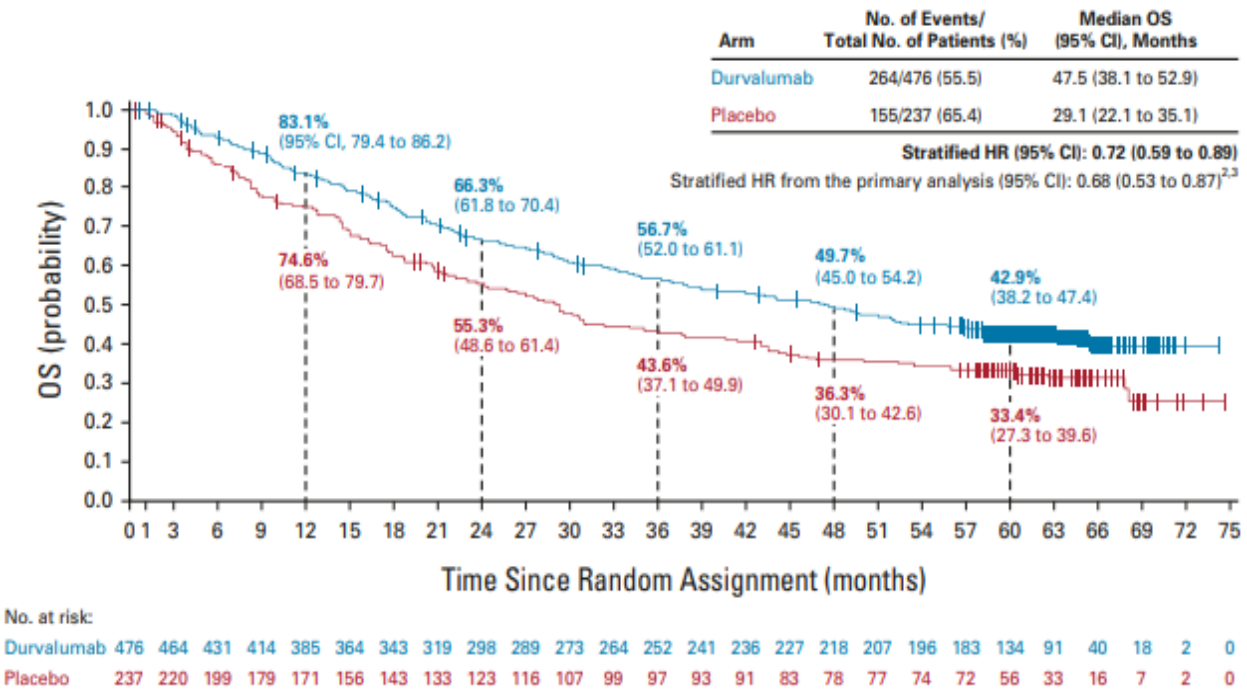
- PFS by BICR using RECIST v1.1*
- OS

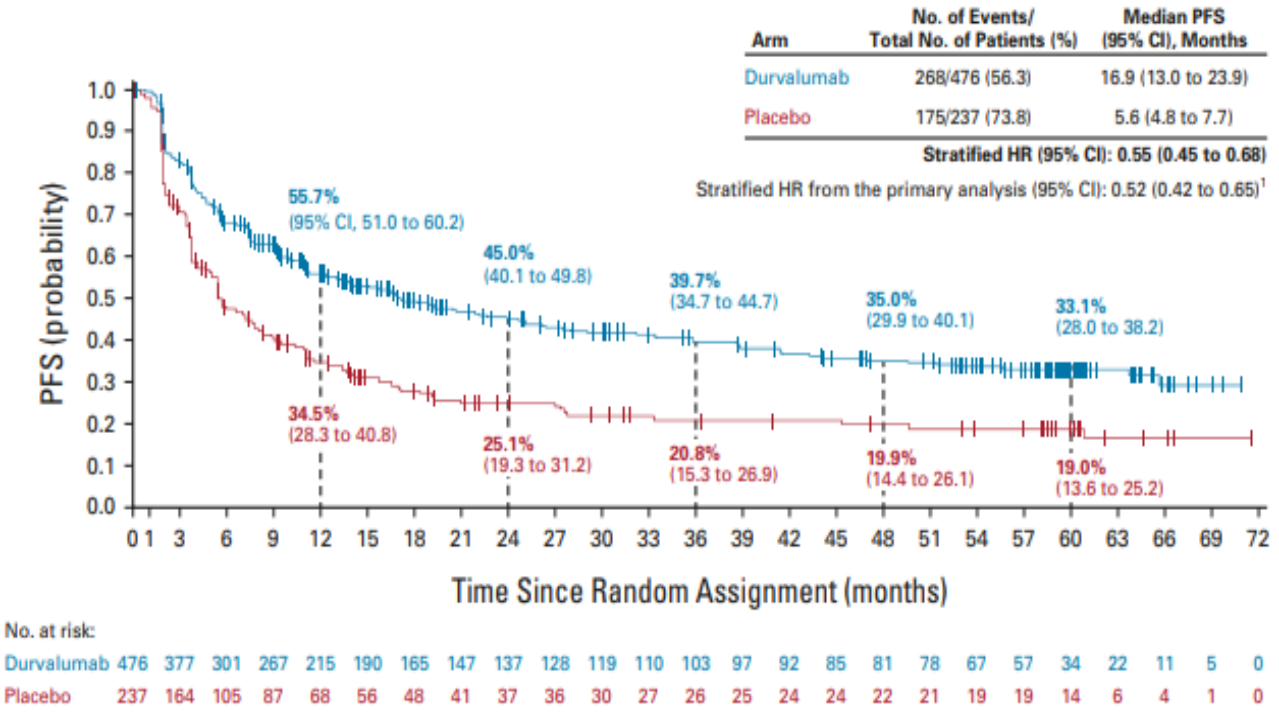
Key secondary endpoints

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

Antonia SJ et al. NEJM 2017.

PACIFIC: Durvalumab Improves 3 and 5-Year Progression-free Survival and Overall Survival



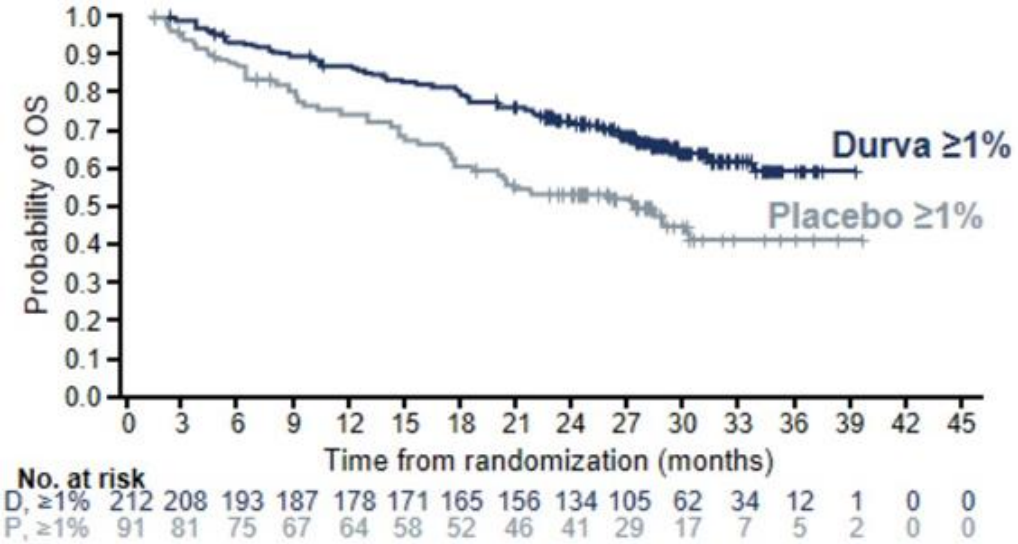


Gray et al. JTO. 2020. Spigel et al. JCO 2022.

PACIFIC: OS improved for PD-L1 ≥ 1% compared to PD-L1 < 1%

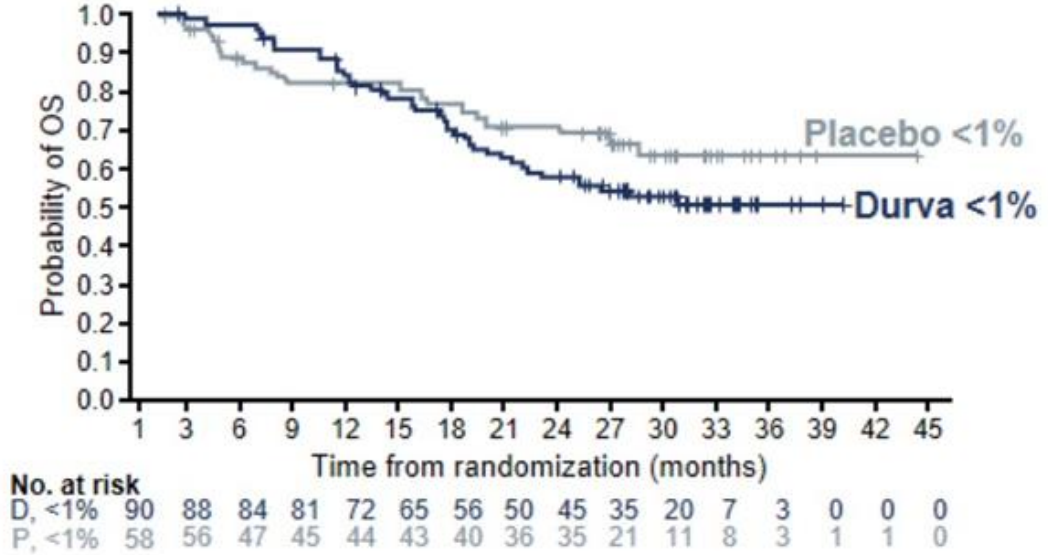
OS (BICR) by PD-L1 TC ≥1%

	No. events / no. patients (%)	Median OS (95% CI), mo
Durvalumab, ≥1%	70/212 (33.0)	NR (NR, NR)
Placebo, ≥1%	45/91 (49.5)	29.1 (17.7, NR)
	≥1% OS HR 0.53 (95% CI 0.36, 0.77)	



OS (BICR) by PD-L1 TC <1%

	No. events / no. patients (%)	Median OS (95% CI), mo
Durvalumab, <1%	41/90 (45.6)	NR (20.8, NR)
Placebo, <1%	19/58 (32.8)	NR (27.3, NR)
	≥1% OS HR 1.36 (95% CI 0.79, 2.34)	



Antonia SA…, Gray JE. et al. NEJM 2018.

PACIFIC: Updated Safety Summary

DCO: March 22, 2018

	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	145 (30.5)	61 (26.1)
Outcome of death	21 (4.4)	15 (6.4)
Leading to discontinuation	73 (15.4)	23 (9.8)
Serious AEs, n (%)	138 (29.1)	54 (23.1)
Any-grade pneumonitis/radiation pneumonitis, n (%)	161 (33.9)	58 (24.8)
Grade 3/4	17 (3.6)	7 (3.0)
Outcome of death	5 (1.1)	5 (2.1)
Leading to discontinuation	30 (6.3)	10 (4.3)

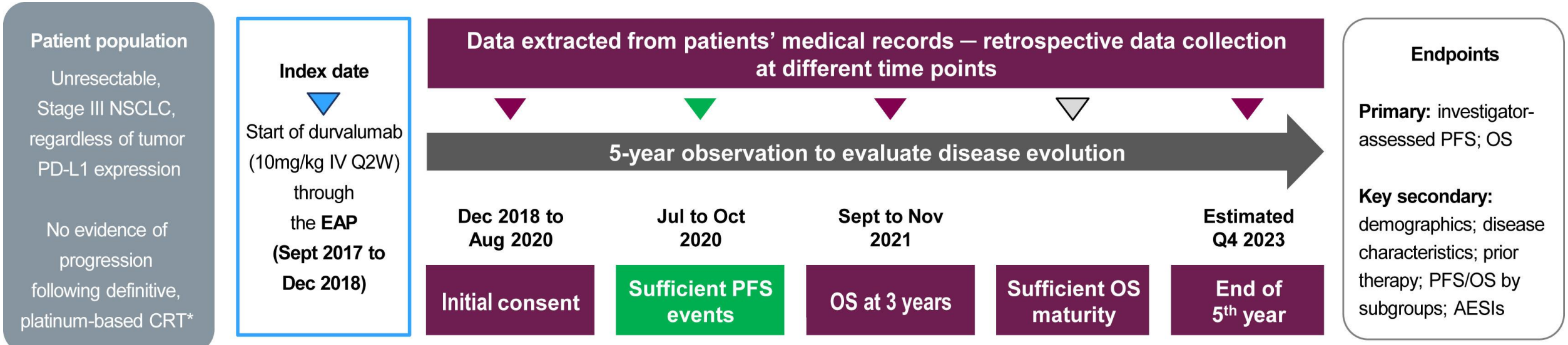
Exploratory Subgroup Analysis in Pneumonitis: Time to Onset (WCLC 2018)

	Durvalumab	Placebo
Time to onset from 1st dose, median days (range) [N]	55.0 (1–406) [161]	55.0 (1–255) [58]
Time to onset from radiotherapy, median days (range) [N]	73.0 (20–433) [161]	76.5 (24–280) [58]
Duration, median days (range) [N]*	64.0 (3–568) [79]	57.0 (5–187) [23]

Antonia SA…, Gray JE et al. NEJM. 2018.; Vansteenkiste JF, et al. WCLC. 2018.

PACIFIC Real-World Study (PACIFIC-R)

NCT03798535



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

Figure 1. PACIFIC-R study design. The current analysis is based on the second data extraction of PACIFIC-R (highlighted in green), which was timed to allow sufficient PFS maturity. *Patients had completed platinum-based chemotherapy concurrent or sequential to radiotherapy within the previous 12 weeks without evidence of disease progression. AESIs, adverse events of special interest; CRT, chemoradiotherapy; EAP, early access program; IV, intravenously; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q, quarter; Q2W, every 2 weeks.

Girard N. et al. JTO 2023.

PACIFIC-R: Patient Characteristics & Median PFS compared to PACIFIC

Patient Characteristics & Durvalumab Treatment

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

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

Cut-off date for data extraction: 8 April 2021

*Percentages based on patients for whom the data were available; †PD-L1 expression tested but not clearly reported.

[A]Disease stage was missing for n=7 and n=74 had were diagnosed at a stage <III; [B]Histology was missing for n=2; [C]CRT type was missing for n=2; [D]PD-L1 was not tested for n=432

CRT, chemoradiotherapy; EAP, expanded access programme; ECOG/WHO PS, Eastern Cooperative Oncology Group/World Health Organization performance status; FAS, full analysis set; PD-L1, programmed cell death-ligand 1; RT, radiotherapy

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

Girard N, et al ESMO congress 2021. 1171 MO.

PACIFIC-R: Toxicity

Durvalumab Treatment Discontinuation

FAS (N=1,399)	Discontinuation reason, n (%)*	Median time from durva. start to discontinuation
Patient decision	20 (1.4)	6.1 months
AE	233 (16.7)	2.8 months
Completed treatment†	659 (47.1)	12.0 months
Disease progression	377 (26.9)	5.1 months
Death	21 (1.5)	1.9 months

- **Pneumonitis/interstitial lung disease (ILD)** was the most common AE leading to (% of FAS):
  - **Permanent** discontinuation: 133 (**9.5%**)‡
  - **Temporary** interruption: 73 (**5.2%**)‡

Pneumonitis/ILD

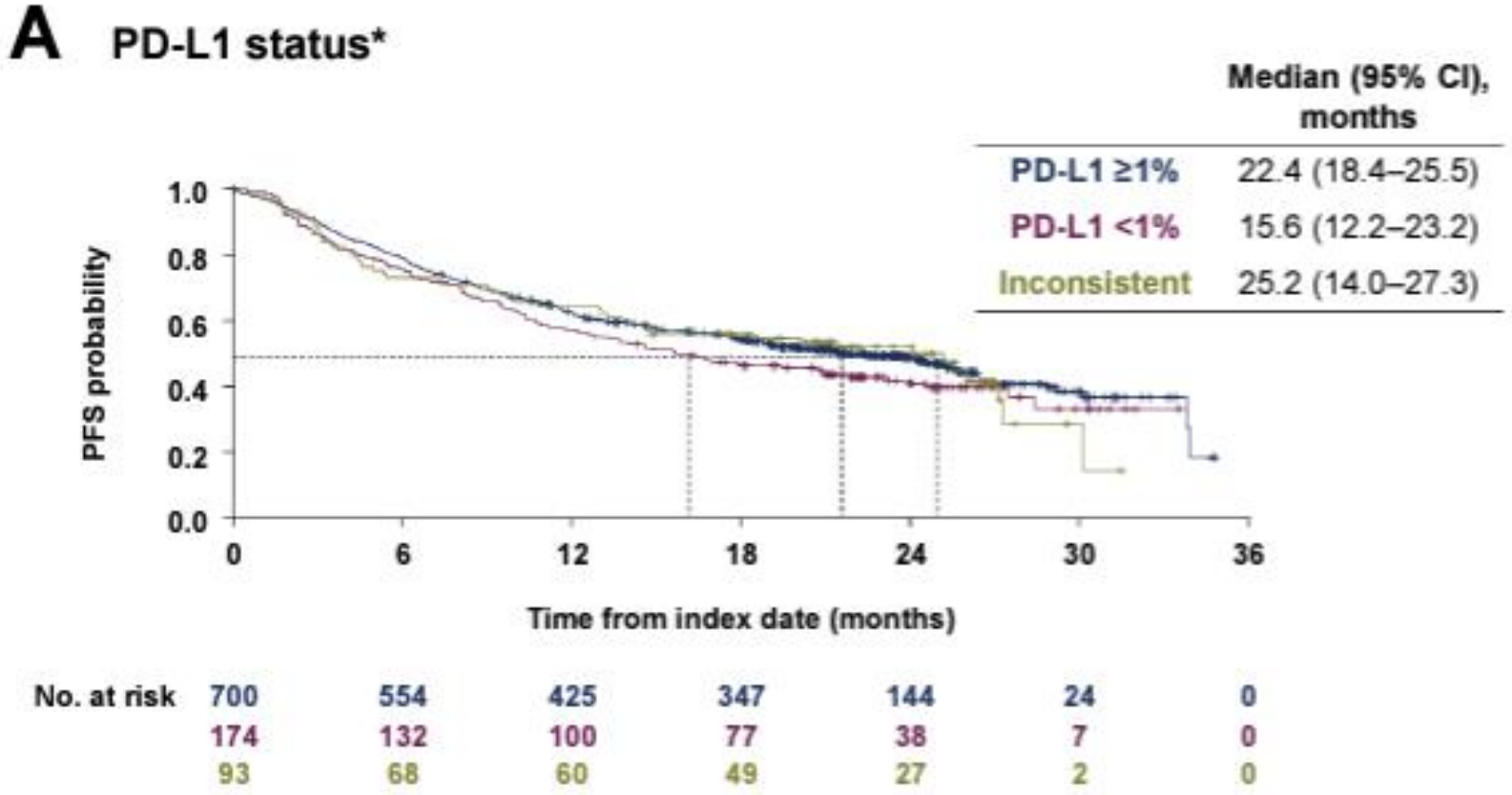
	FAS (N=1,399)
Patients with any pneumonitis/ILD, n (%)§	250 (17.9)
Mild event¶	56 (4.0)
Moderate event¶	118 (8.4)
Severe event¶	41 (2.9)
Life-threatening or fatal event¶	5 (0.4)

- Median **time to onset** of pneumonitis/ILD from durvalumab initiation: **2.5 months**
- **Corticosteroid** administration was required in **71.3%** of events#

*Other discontinuation reason: missing (n=2), 'other' reasons (n=68), lost to follow-up (n=3), and ongoing durvalumab at time of data extraction (n=16); †Investigator's decision per country protocol and, where applicable, was after >12 months' treatment; ‡Categories are not mutually exclusive (i.e. a single patient could both interrupt and permanently discontinue durvalumab due to pneumonitis/ILD); §37/1,399 patients (2.6%) had pneumonitis/ILD events of unknown severity; ¶Categories are not mutually exclusive – patients experiencing ≥2 events of different severity can be counted under both categories. #A total of 279 pneumonitis/ILD events were reported among the 250 patients who experienced pneumonitis/ILD
AE, adverse event; FAS, full analysis set; ILD, interstitial lung disease

Girard N, et al ESMO congress 2021. 1171 MO.

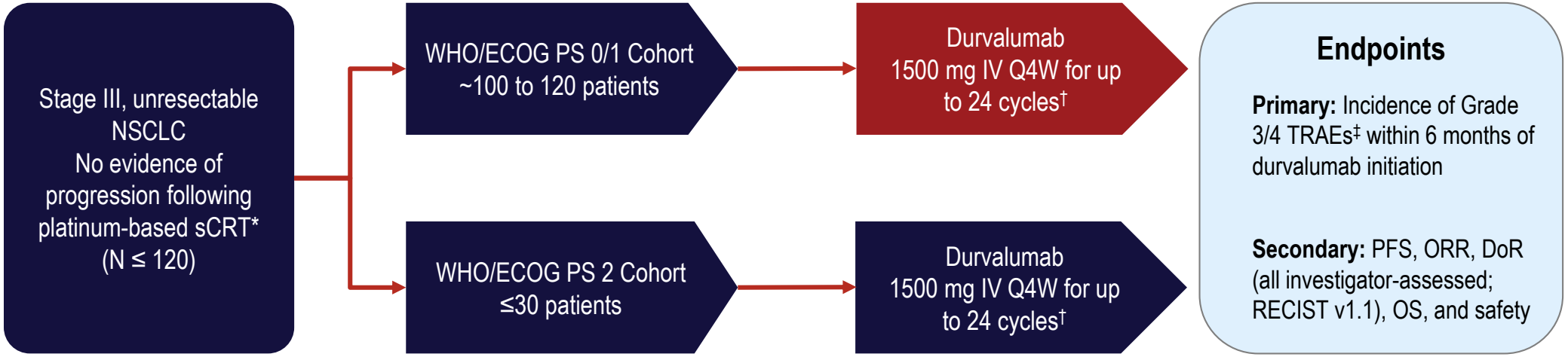
PACIFIC-R: Improved PFS observed for PD-L1 ≥ 1% vs. PD-L1 < 1%



Girard N. et al. JTO 2023.

PACIFIC-6: Phase 2, Open-label, Multicenter, International Trial

NCT03693300



Incidence of AEs (CTCAE v4.03), and the ORR, were summarised with descriptive statistics

PFS and OS were analysed by Kaplan–Meier method (to estimate medians, 12-month rates and associated 95% CIs)

- US/UK/France
- N: 150

- Dosing Interval
- ECOG 2
- 2 year >1 year?

*Defined as ≥2 cycles of platinum-based CT before RT with ≤6 weeks interval between the last dose of CT and the start of RT. Patients who received no more than 1 cycle of overlapping platinum-based CT and RT were also eligible.
†Or until disease progression, alternative anticancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.
‡As reported by the investigator and alternatively referred to as PRAEs in the case report form.

Garassino, ELCC 2022. 108MO

PACIFIC-6: Patient and Disease Characteristics

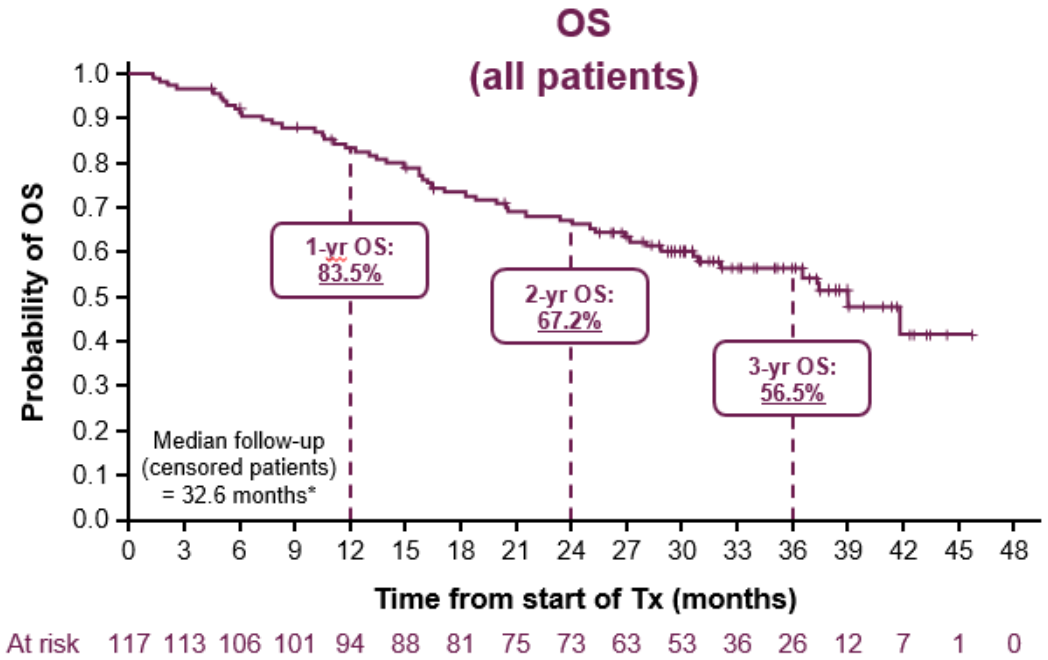
- **Majority are men**
- **Low % ECOG PS 2**
- **Majority Stage IIIB**
- **Unknown PD-L1 status**

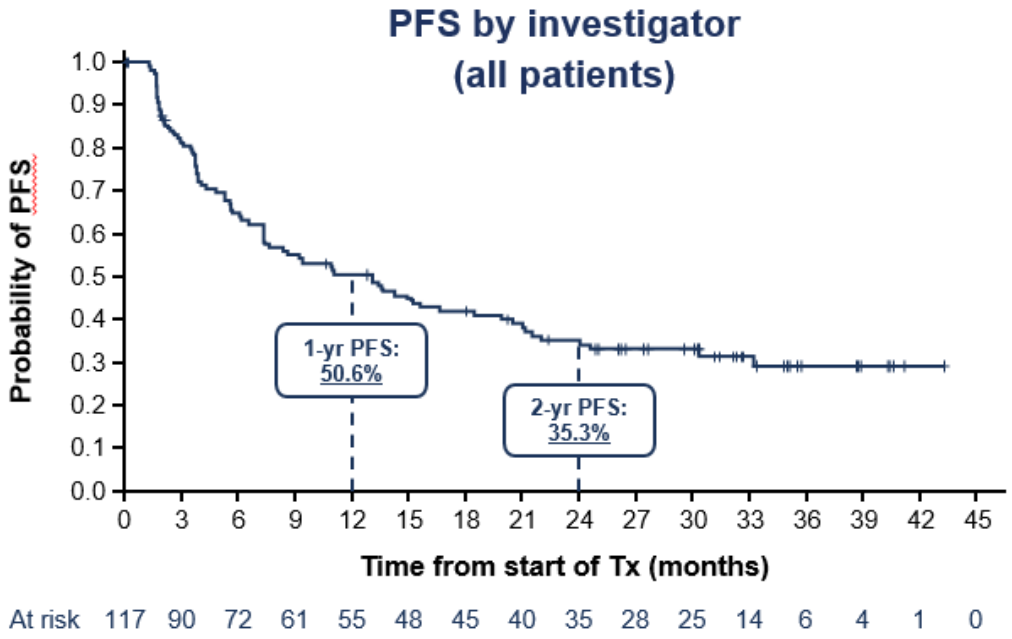
Table 1. Baseline Patient and Disease Characteristics

Characteristic	ECOG PS 0 or 1 (n = 114)	ECOG PS 2 (n = 3)	All Patients (N = 117)
Median age (range), y	68.0 (39-85)	65.0 (53-77)	68.0 (39-85)
Age group, n (%)			
<65 y	39 (34.2)	1 (33.3)	40 (34.2)
≥65 y	75 (65.8)	2 (66.7)	77 (65.8)
≥75 y	20 (17.5)	1 (33.3)	21 (17.9)
Sex, n (%)			
Men	71 (62.3)	2 (66.7)	73 (62.4)
Women	43 (37.7)	1 (33.3)	44 (37.6)
Race, n (%)			
White	101 (88.6)	3 (100.0)	104 (88.9)
Unknown	13 (11.4)	0	13 (11.1)
Smoking history, n (%)			
Never smoker	9 (7.9)	0	9 (7.7)
Former smoker	73 (64.0)	2 (66.7)	75 (64.1)
Current smoker	32 (28.1)	1 (33.3)	33 (28.2)
ECOG PS, n (%)			
0	47 (41.2)	0	47 (40.2)
1	67 (58.8)	0	67 (57.3)
2	0	3 (100.0)	3 (2.6)
Histologic type, n (%)			
Adenocarcinoma	63 (55.3)	0	63 (53.8)
Squamous cell	42 (36.8)	3 (100.0)	45 (38.5)
Other	9 (7.9)	0	9 (7.7)
Disease stage at baseline, n (%)			
IA	1 (0.9)	0	1 (0.9)
IIIA	44 (38.6)	0	44 (37.6)
IIIB	58 (50.9)	1 (33.3)	59 (50.4)
IIIC	11 (9.6)	2 (66.7)	13 (11.1)
PD-L1 expression on TCs, n (%)			
<1%	34 (29.8)	0	34 (29.1)
≥1%	33 (28.9)	3 (100.0)	36 (30.8)
Missing	47 (41.2)	0	47 (40.2)

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1; PS, performance status; TC, tumor cell.

PACIFIC-6: Overall and Progression-free Survival





Endpoint		All patients (N=117)	PS 0/1 cohort (n=114)†
OS	Median, months (95% CI)	39.0 (30.6–NC)	39.0 (30.6–NC)
	3-yr rate, % (95% CI)	56.5 (46.4–65.5)	57.2 (46.9–66.2)
PFS by investigator	Median, months (95% CI)	13.1 (7.4–19.9)	13.1 (7.4–19.9)
	2-yr rate, % (95% CI)	35.3 (26.5–44.3)	35.4 (26.4–44.5)
Confirmed ORR by investigator	n (%)	24 (20.5)‡	24 (21.1)‡
	[95% CI]§	[13.6–29.0]	[14.0–29.7]

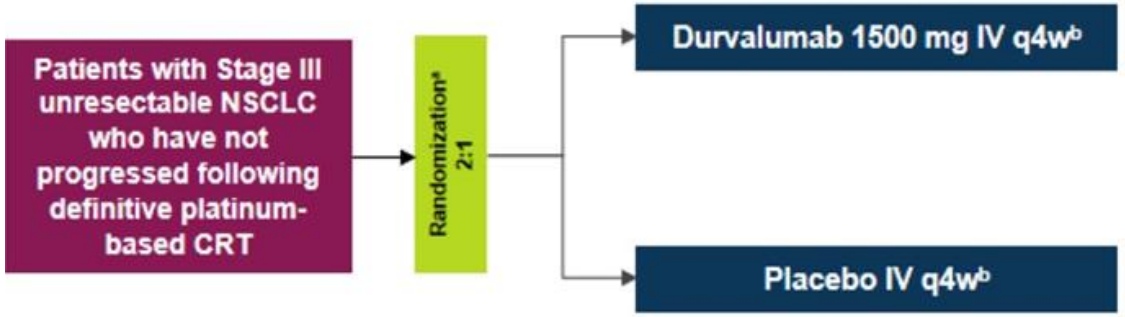
Garassino et al. ESMO Congress 2023.

Flat-dosing Durvalumab - either sCRT or cCRT.

NCT03706690

PACIFIC 5: Study Design

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



Primary Endpoints

- PFS[c]

Secondary Endpoints

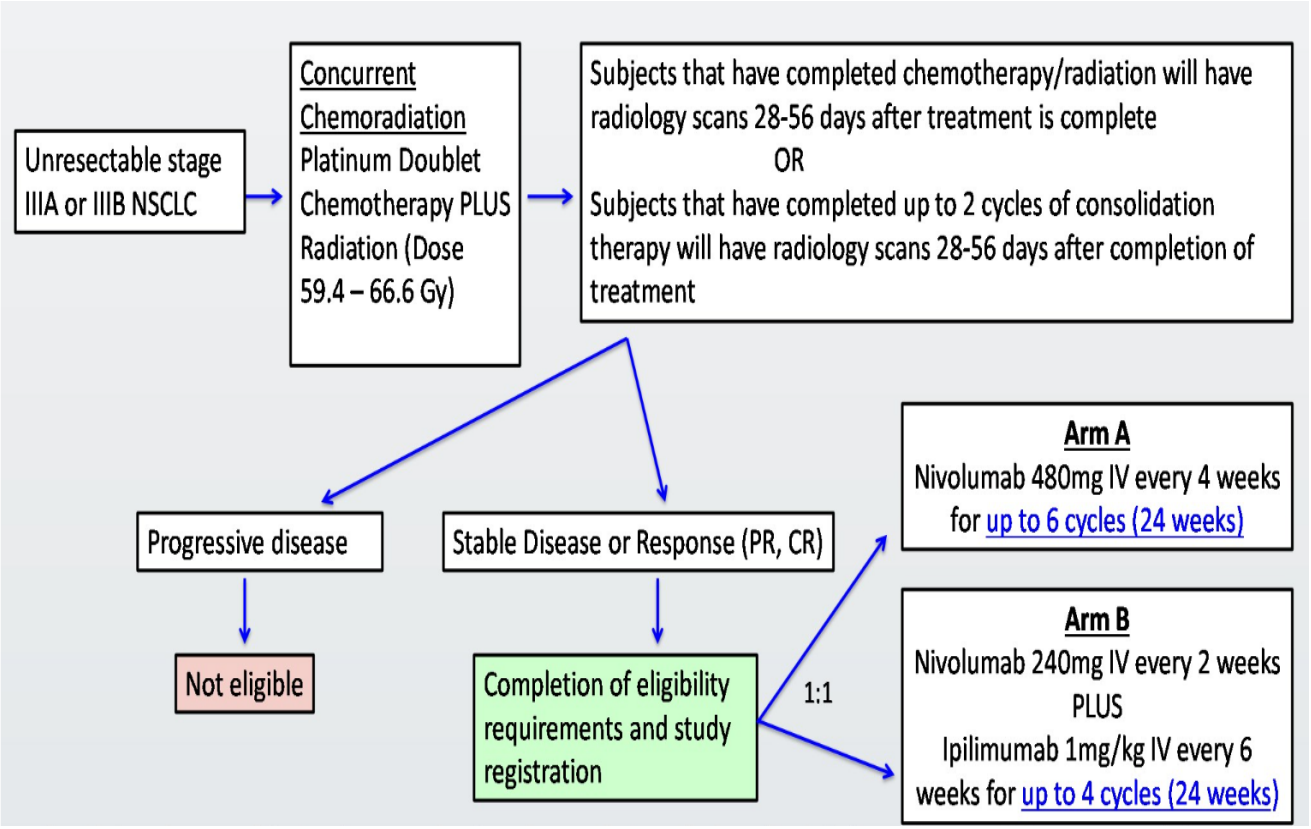
- OS
- OS24
- ORR[c]
- DoR[c]
- PFS2[d]
- PFS12[c] and PFS18[c]
- TTDM[c]
- Safety and tolerability (assessed by CTCAE version 5.0)
- PK and immunogenicity
- IHC analysis of tumoral PD-L1 expression and spatial distribution within the tumor microenvironment relative to efficacy outcomes (OS, PFS, ORR)

- Ex-US
- Activated: 11/18
- N: 360
- Treat until PD

- Dosing Interval/Length
- PD-L1 Status

NCT03285321

Consolidation nivolumab/ipilimumab vs. nivolumab post concurrent chemoradiotherapy: Big Ten Cancer Research Consortium/LUN16-081



	Arm A: Nivolumab (N: 54)	Arm B: Nivo & Ipi (N: 51)
18 mos PFS	62.3%	67%
Median PFS	25.8 mos	25.4 mos
24 mos OS	76.6%	82.8%
Toxicity		
TRAEs	72.2%	80.4%
G ≥3 TRAEs	38.9%	52.9%
G ≥2 Pneumonitis	12 (22.2%)	15 (29.4%)
G ≥3 Pneumonitis	5 (9.3%)	8 (15.7%)

Yan M et al ASCO 2020. Abstr: 9010. Durm GA et al. JCO 2022 at ASCO 2022.

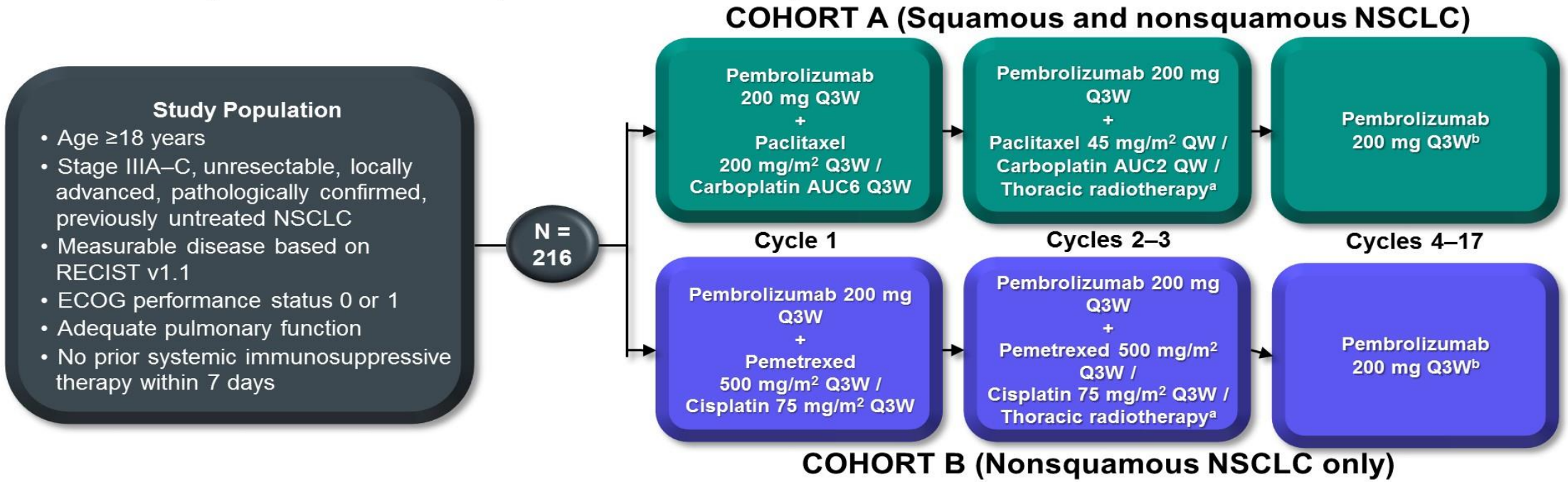
Concurrent Chemoradiotherapy with Immunotherapy followed by Consolidation

KEYNOTE-799 (NCT03631784)

Study Design
- Nonrandomized, open-label study
- Choice of chemotherapy per investigator
- Nonsquamous NSCLC patients eligible for cohort A or B
- Squamous NSCLC patients eligible for cohort A only
- Cohort A fully accrued at data cutoff; cohort B is still accruing

Primary Objectives
- ORR per RECIST version 1.1 by BICR
- Percentage of patients who develop grade ≥3 pneumonitis

Secondary Objectives
- PFS, OS, safety



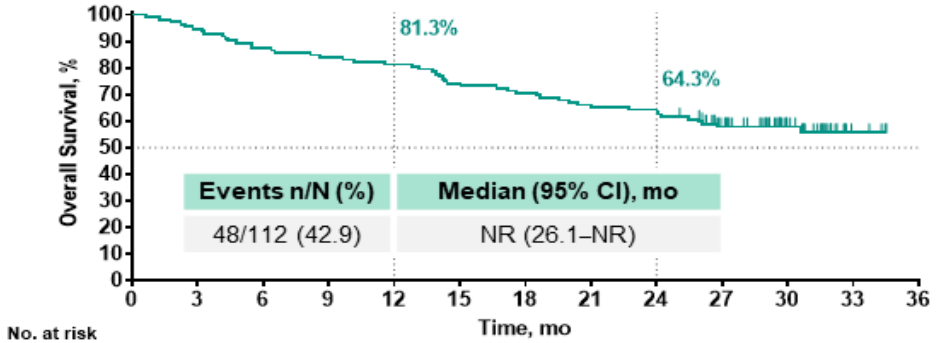
[a]60 Gy in 30 daily 2-Gy fractions.
[b]Treatment will continue until cycle 17 is completed or until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, or study withdrawal. Pembrolizumab therapy will be discontinued permanently in patients who develop grade ≥3 or recurrent grade 2 pneumonitis.

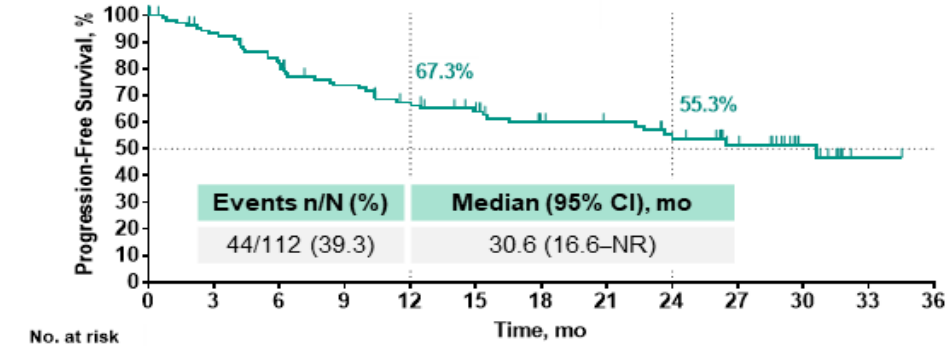
Jabbour S, et al. ASCO 2020.

2-year Update KN 799

Progression-Free Survival and Overall Survival

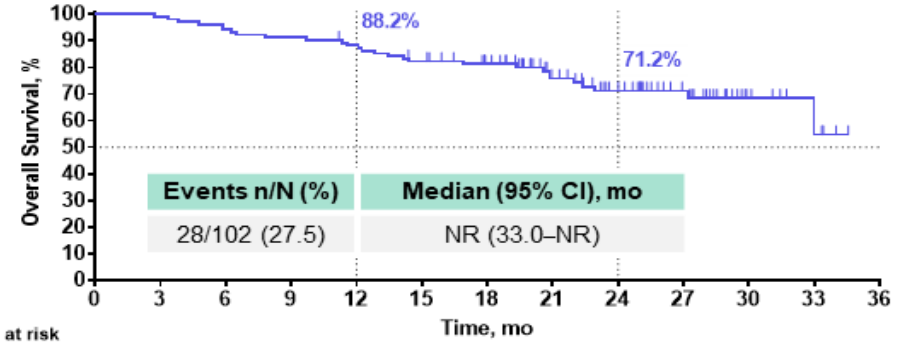
Cohort A (squamous and nonsquamous histology)

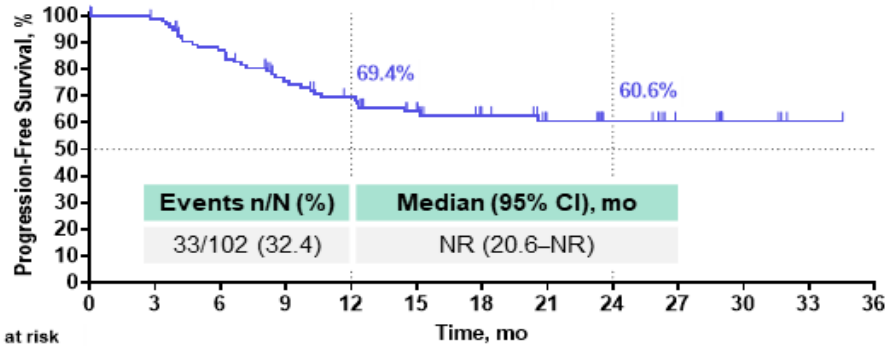




Data cutoff date: Oct 18, 2021.

Cohort B (nonsquamous histology only)

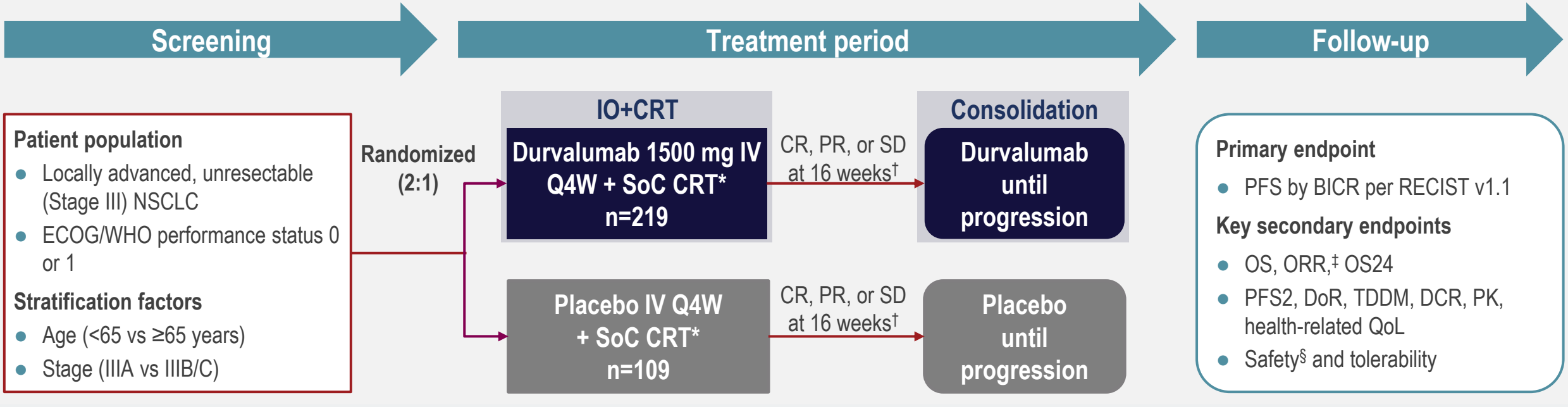




Jabbour S, et al. ASTRO 2022.

Upfront Durvalumab with Concurrent Chemoradiotherapy

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



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

*Platinum-based chemotherapy regimens include: cisplatin/etoposide, carboplatin/paclitaxel, pemetrexed/cisplatin (non-squamous only), or pemetrexed/carboplatin (non-squamous only), alongside radiation therapy (5 fractions/week for ~6 weeks [±3 days; total 60 Gy]). †Investigator assessed per RECIST v1.1.
‡Following a protocol amendment, ORR was moved from a primary endpoint to a key secondary endpoint.
§Will be reviewed by an independent data monitoring committee in an unblinded manner.

Bradley JD et al. European Lung Cancer Congress 2024

Key baseline patient characteristics (ITT population)

	Durvalumab + CRT (n=219)	Placebo + CRT (n=109)
Age group (years), n (%)		
<50	18 (8.2)	12 (11.0)
≥50 to <65	107 (48.9)	50 (45.9)
≥65 to <75	75 (34.2)	40 (36.7)
≥75	19 (8.7)	7 (6.4)
Median age (range), years	63.0 (36–84)	63.0 (38–84)
Sex, n (%)		
Male	166 (75.8)	80 (73.4)
Female	53 (24.2)	29 (26.6)
Race, n (%)		
White	141 (64.4)	62 (56.9)
Black or African American	2 (0.9)	0
Asian	65 (29.7)	39 (35.8)
American Indian or Alaska Native	7 (3.2)	7 (6.4)
Other	4 (1.8)	1 (0.9)
ECOG/WHO PS, n (%)		
0 – Normal activity	98 (44.7)	53 (48.6)
1 – Restricted activity	121 (55.3)	56 (51.4)
Histology type, n (%)		
Squamous	121 (55.3)	52 (47.7)
Non-squamous	98 (44.7)	57 (52.3)
PD-L1 status, n (%)*		
<1% (negative)	86 (39.3)	36 (33.0)
≥1% (positive)	113 (51.6)	60 (55.0)
Unknown	20 (9.1)	13 (11.9)

	Durvalumab + CRT (n=219)	Placebo + CRT (n=109)
***EGFR* mutation, n (%)**		
Positive	7 (3.2)	6 (5.5)
Negative	112 (51.1)	60 (55.0)
Unknown	100 (45.7)	43 (39.4)
AJCC stage, n (%)†		
IIIA	76 (34.7)	37 (33.9)
IIIB	109 (49.8)	51 (46.8)
IIIC	33 (15.1)	20 (18.3)
IV	1 (0.5)	1 (0.9)
TNM class at screening, n (%)		
Primary tumour		
TX	2 (0.9)	1 (0.9)
T1	15 (6.8)	10 (9.2)
T2	37 (16.9)	13 (11.9)
T3	39 (17.8)	32 (29.4)
T4	126 (57.5)	53 (48.6)
Regional lymph nodes		
N0	25 (11.4)	7 (6.4)
N1	16 (7.3)	14 (12.8)
N2	124 (56.6)	60 (55.0)
N3	54 (24.7)	28 (25.7)
Distant metastases		
M0	218 (99.5)	108 (99.1)
M1b	1 (0.5)	1 (0.9)

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ITT, intention-to-treat; PD-L1, programmed cell death ligand-1; PS, performance status; TNM, tumor, node, metastasis; WHO, World Health Organization.

*PD-L1 testing was retrospective and performed centrally.
†Per the 8th edition of the AJCC Cancer Staging Manual.

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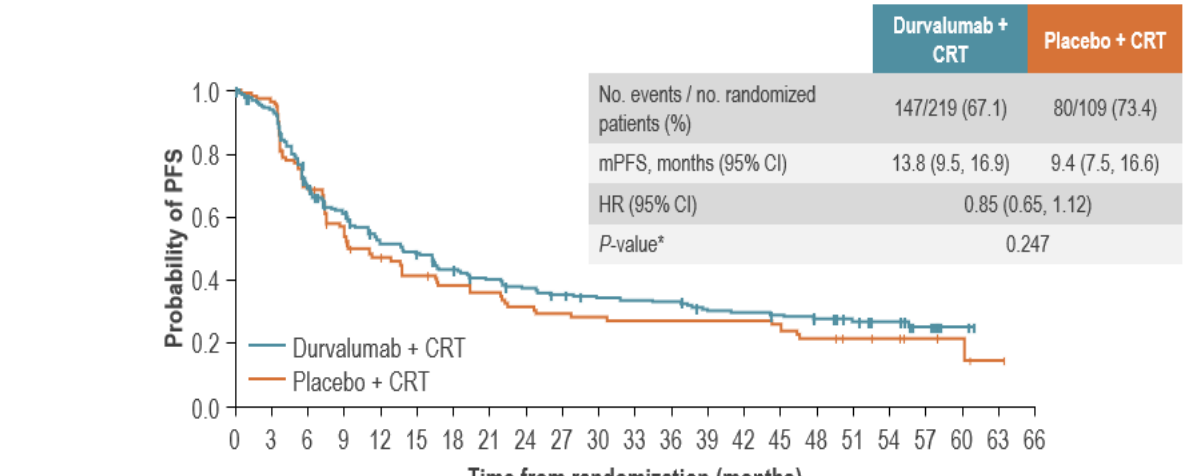
PFS by BICR and OS in the ITT

PFS



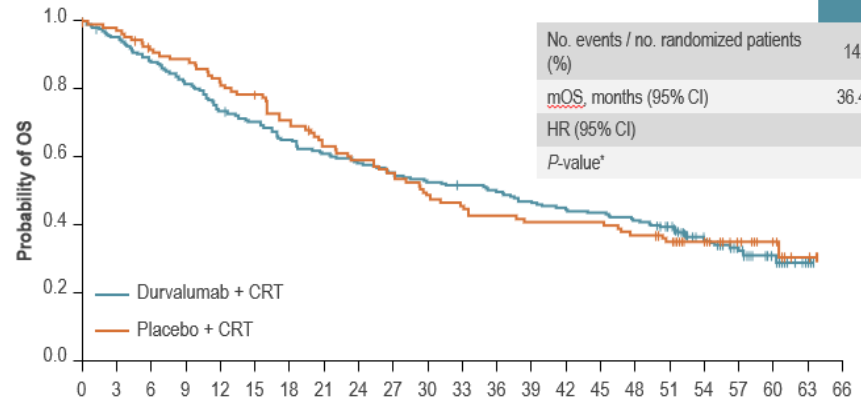
	Durvalumab + CRT	Placebo + CRT
No. events / no. randomized patients (%)	147/219 (67.1)	80/109 (73.4)
mPFS, months (95% CI)	13.8 (9.5, 16.9)	9.4 (7.5, 16.6)
HR (95% CI)	0.85 (0.65, 1.12)	
P-value*	0.247	

No. at risk:																							
Durvalumab + CRT	219	199	145	124	102	94	83	75	69	64	60	59	58	50	49	47	43	28	24	10	2	0	0
Placebo + CRT	109	104	72	58	44	38	34	32	28	26	25	24	24	24	24	23	19	15	12	7	3	1	0

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mPFS, median PFS; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Per RECIST v1.1. Tick marks on the curves indicate censored observations. *Based on the Lan and DeMets approach that approximates the O'Brien Fleming spending functions; the 2-sided p-value boundary for declaring statistical significance is 0.0416 for an overall 5% alpha.

OS



	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	

No. at risk:																							
Durvalumab + CRT	219	207	191	177	160	152	141	132	126	120	114	111	107	100	95	94	89	75	49	31	15	1	0
Placebo + CRT	109	106	98	95	87	83	75	66	62	57	51	47	45	43	43	43	39	35	27	17	9	2	0

There was no difference in ORR between the durvalumab (60.7%; 95% CI: 53.9, 67.2) and placebo (60.6%; 95% CI: 50.7, 69.8) arms (p=0.976).

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mOS, median OS; OS, overall survival; ORR, objective response rate.

Tick marks on the curves indicate censored observations. *The 2-sided p value boundary for declaring statistical significance is 4.5% or 5% depending on the previous levels of the multiple testing procedure.

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PFS by BICR (ITT population), subgroup analysis

Subgroup	n	HR (95% CI)*
All patients	328	1.03 (0.78, 1.39)
Planned chemotherapy		
Carboplatin	279	1.01 (0.75, 1.38)
Cisplatin	48	1.00 (0.45, 2.38)
Planned radiation therapy		
Intensity-modulated	262	1.00 (0.73, 1.39)
3-dimensional conformal	60	1.11 (0.58, 2.24)
Race		
White	203	0.81 (0.57, 1.17)
Black or African American	2	NC
Asian	104	1.32 (0.80, 2.24)
Other	19	NC
Sex		
Female	82	0.66 (0.36, 1.23)
Male	246	1.16 (0.84, 1.62)
Age at randomization		
<65 years	187	0.83 (0.57, 1.23)
≥65 years	141	1.36 (0.88, 2.17)
Smoking status		
Smoker	276	1.05 (0.77, 1.45)
Non-smoker	52	0.89 (0.45, 1.84)

Subgroup	n	HR (95% CI)*
All patients	328	1.03 (0.78, 1.39)
Disease stage (AJCC 8th ed.)		
IIIA	123	0.87 (0.55, 1.43)
IIIB/C	205	1.13 (0.80, 1.64)
Histology		
Squamous	174	1.02 (0.71, 1.50)
Non-squamous	154	1.01 (0.65, 1.60)
WHO performance status		
0 – Normal activity	151	0.78 (0.51, 1.21)
1 – Restricted activity	177	1.27 (0.87, 1.90)
PD-L1 status		
≥1%	173	1.05 (0.70, 1.60)
<1%	122	0.95 (0.61, 1.53)
Unknown	33	1.24 (0.54, 2.98)
EGFR mutation		
Positive	13	NC
Negative	172	1.12 (0.75, 1.70)
Unknown	143	0.93 (0.61, 1.45)
Region		
Asia	104	1.32 (0.80, 2.24)
Europe	154	0.69 (0.46, 1.05)
South America	70	1.69 (0.90, 3.41)
Planning target volume		
≥450 cm³	162	1.14 (0.77, 1.73)
<450 cm³	160	0.89 (0.59, 1.36)

A HR of <1 favors durvalumab and is associated with a longer event-free survival than placebo.
The size of circle is proportional to the number of events. The gray band represents the 95% CI for the main OS HR.
For all patients, the analysis is based on the main stratified analysis while, for the subgroups, the HR and CI were calculated using an unstratified Cox proportional hazards model, with treatment as the only covariate and ties handled by Efron approach.
*HRs and 95% CIs were not calculated if a subgroup had fewer than 5 events in each treatment arm.

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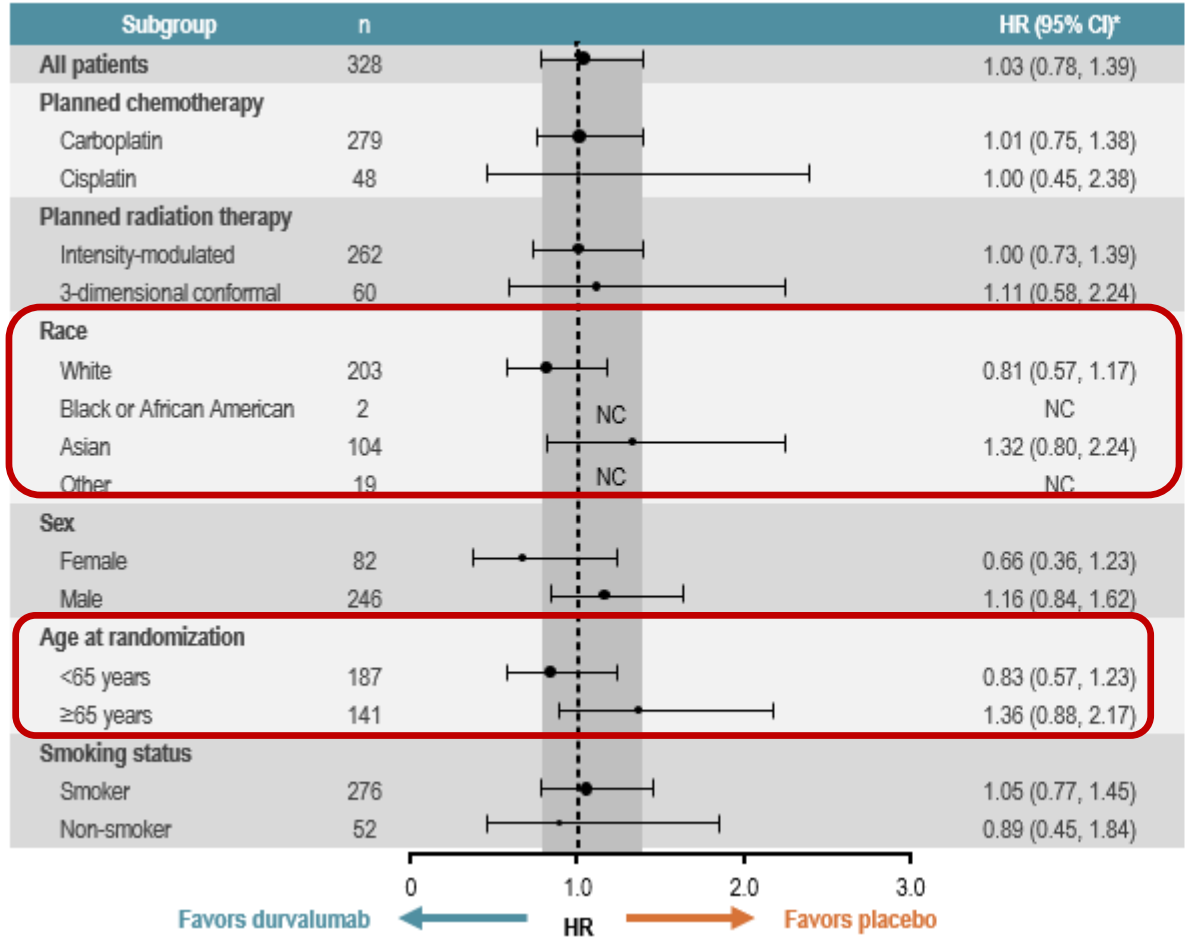
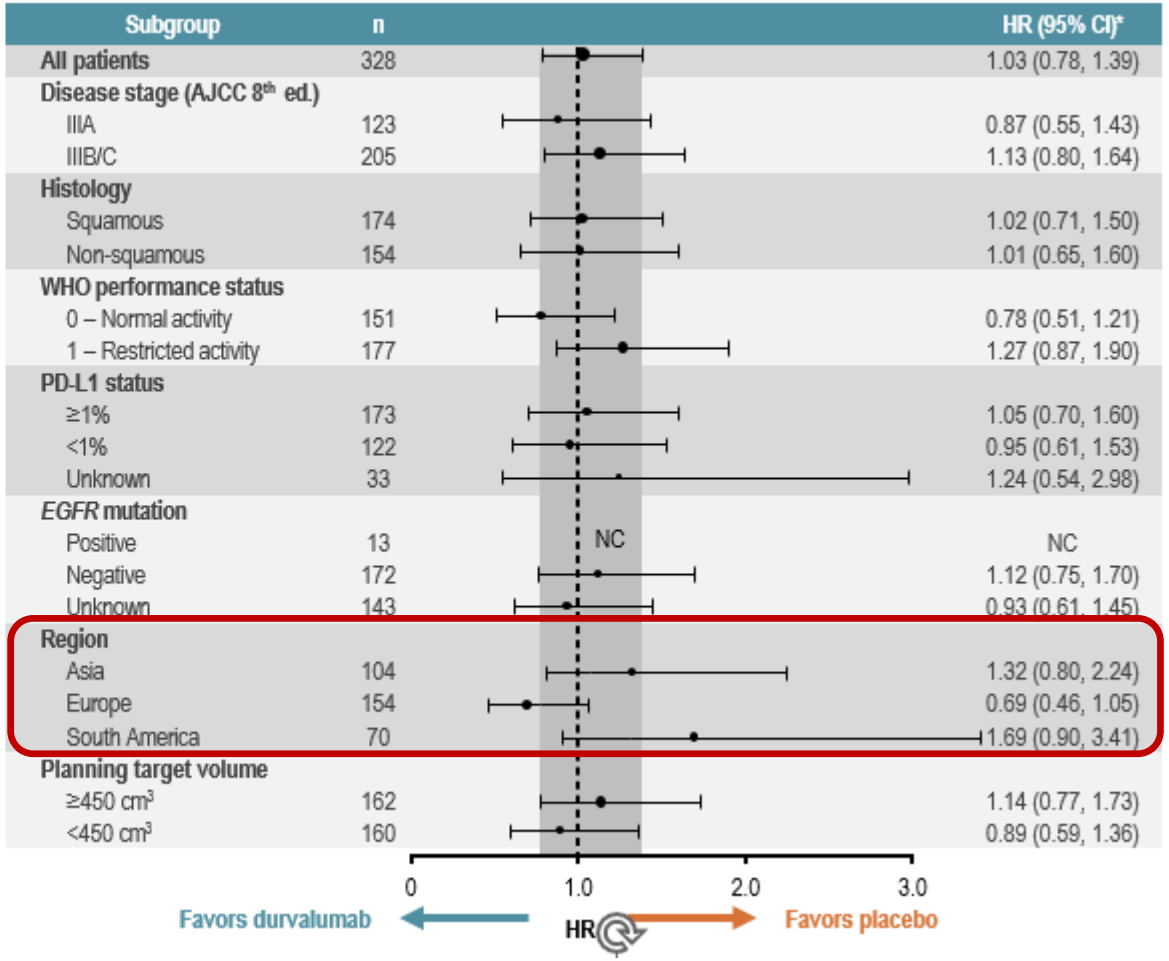
OS (ITT population), subgroup analysis





A HR of <1 favors durvalumab and is associated with a longer event-free survival than placebo.
The size of circle is proportional to the number of events. The gray band represents the 95% CI for the main OS HR.
For all patients, the analysis is based on the main stratified analysis while, for the subgroups, the HR and CI were calculated using an unstratified Cox proportional hazards model, with treatment as the only covariate and ties handled by Efron approach.
*HRs and 95% CIs were not calculated if a subgroup had fewer than 5 events in each treatment arm.

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Summary of AEs (safety population): While Pneumonitis rates were similar more Pt discontinued Durvalumab in the first 0-4 months vs. placebo.

AE category, n (%)	Durvalumab + CRT (n=219)	Placebo + CRT (n=108)
Any AE	216 (98.6)	108 (100)
Maximum grade 3 or 4*	117 (53.4)	64 (59.3)
Outcome of death	30 (13.7)	11 (10.2)
SAE	103 (47.0)	56 (51.9)
Any AE leading to discontinuation of durvalumab/placebo†	56 (25.6)	13 (12.0)
0 to ≤4 months from start of treatment **(approximates the duration of IO+CRT and ends at the first post-baseline scan)**	31 (14.2)	6 (5.6)
>4 to ≤16 months from start of treatment (approximates the duration of consolidation IO in the SoC PACIFIC regimen)	12 (5.5)	6 (5.6)
>16 months from start of treatment (approximates treatment beyond the duration of consolidation IO in the SoC PACIFIC regimen)	13 (5.9)	1 (0.9)

- **The most common treatment-emergent AEs with durvalumab + SoC CRT were:**
  - Anemia (42.0%), pneumonitis or radiation pneumonitis (28.8%), neutropenia (27.4%), and nausea (25.6%)
- **The most common treatment-emergent AEs with placebo + SoC CRT were:**
  - Anemia (38.0%), constipation (28.7%), pneumonitis or radiation pneumonitis (28.7%), and neutropenia (25.9%)
- **Combined rates of pneumonitis or radiation pneumonitis were similar in the durvalumab arm (28.8%) and placebo arm (28.7%)**
  - Grade ≥3 pneumonitis or radiation pneumonitis occurred in 10 patients (4.6%) in the **durvalumab** arm and 6 (5.6%) in the **placebo** arm

Per CTCAE v5.0.
*Excludes any patients who experienced any AE of maximum CTCAE grade 5.
†At any time, regardless of discontinuation of CRT.

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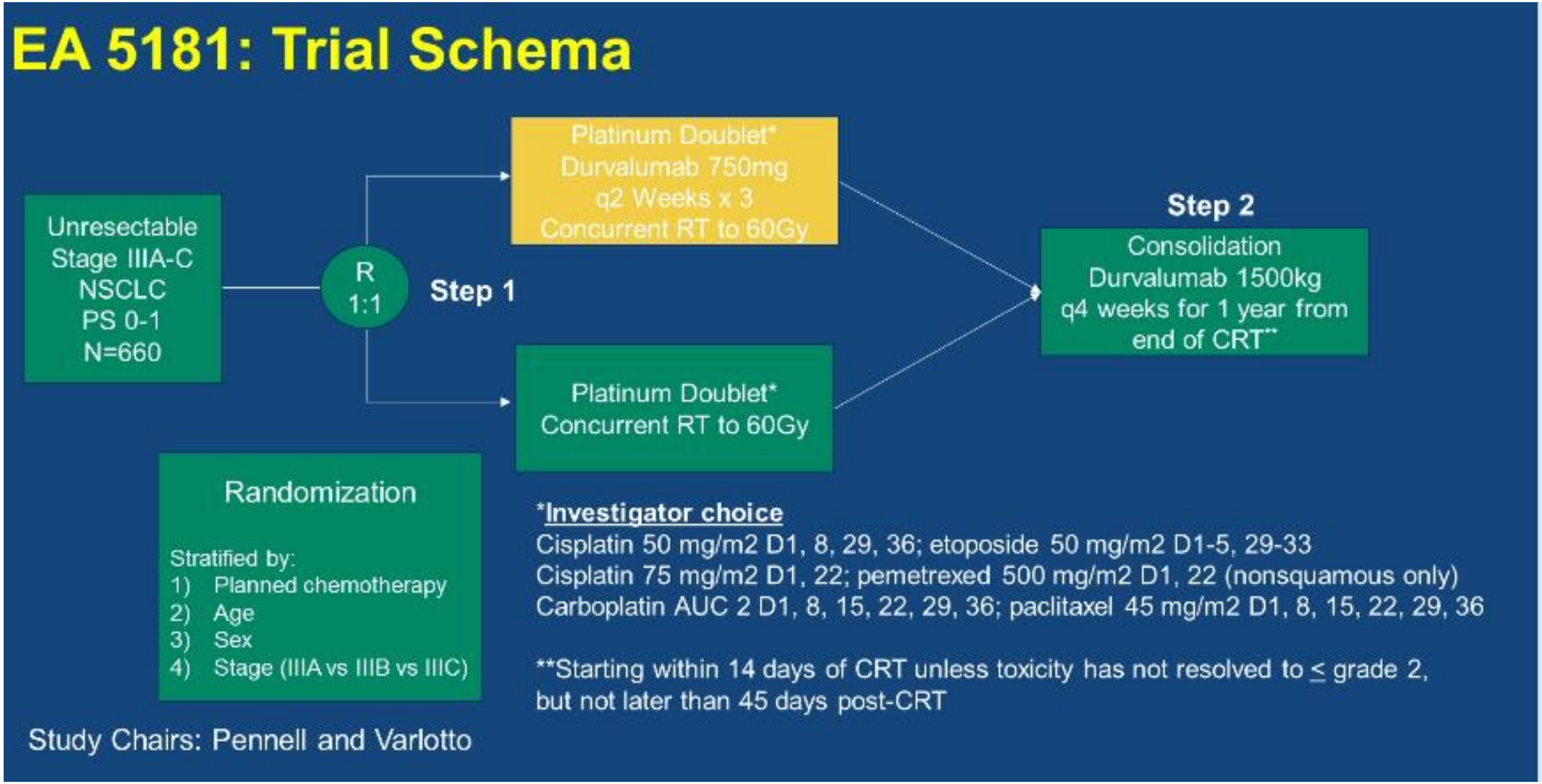
Summary of PACIFIC Trials

Trial	Phase/Study type	Study Population	N	Treatment Arms	Primary Endpoint(s)	mPFS (months)	mOS (months)
PACIFIC (NCT02125461)[1,2]	Phase 3	U.S.	713	Durvalumab (10 mg/kg) vs. placebo Q2W up to 12 months	PFS and OS	5-Year: 16.9 vs 5.6	5-Year: 47.5 vs 29.1
PAC-2 (NCT03519971)[3]	Phase 3	Global	328	Durvalumab (1500 mg) Q4W + SoC CRT vs. placebo + SoC CRT	PFS	13.8 vs 9.4	36.4 vs 29.5
PAC-5 (NCT03706690)[4]	Phase 3	China, Global	360	Durvalumab (1500 mg) Q4W vs. placebo	PFS	NA	NA
PAC-6 (NCT03693300)[5]	Phase 2	U.S., Europe	117	WHO/ECOG PS0-1 + Vs. WHO/ECOG PS2 + durvalumab (1500 mg) Q4W up to 26 doses	Incidence of grade 3-4 possibly related adverse events (PRAEs)	10.9 publication 13.3 ESMO 23 presentation	39
PAC-RW (NCT03798535)[6,7]	Observational	Global	1399	Durvalumab + cCRT vs durvalumab + sCRT	rwPFS and OS	21.7	NA

[1] Antonia SJ et al. NEJM 2017; [2] Spigel DR et al. JCO 2022; [3] Bradley J et al. ELCC 2024; [4]Wu Y et al. Annals of Oncology 2019; [5] Garassino MC et al. JTO 2022; [6]Bruni A et al. Front Oncol 2021; [7]Girard N et al. JTO 2023.

EA 5181


EA 5181: Trial Schema
Unresectable Stage IIIA-C NSCLC PS 0-1 N=660
R 1:1
Step 1
Platinum Doublet* Durvalumab 750mg q2 Weeks x 3 Concurrent RT to 60Gy
Platinum Doublet* Concurrent RT to 60Gy
Step 2
Consolidation Durvalumab 1500kg q4 weeks for 1 year from end of CRT**
Randomization
Stratified by:
1) Planned chemotherapy
2) Age
3) Sex
4) Stage (IIIA vs IIIB vs IIIC)
*Investigator choice
Cisplatin 50 mg/m2 D1, 8, 29, 36; etoposide 50 mg/m2 D1-5, 29-33
Cisplatin 75 mg/m2 D1, 22; pemetrexed 500 mg/m2 D1, 22 (nonsquamous only)
Carboplatin AUC 2 D1, 8, 15, 22, 29, 36; paclitaxel 45 mg/m2 D1, 8, 15, 22, 29, 36
**Starting within 14 days of CRT unless toxicity has not resolved to ≤ grade 2, but not later than 45 days post-CRT
Study Chairs: Pennell and Varlotto

Chemotherapy Sparing Options

DUART: DUrvalumab After RT in unresectable Stage III NSCLC ineligible for chemotherapy

Ph 2 open-label, single arm, multi-center, international study

Study Population n=150

- Stage III unresectable NSCLC
- Chemo-ineligible per physician criteria.
- Radiotherapy alone as primary treatment
- No biomarker selection
- ECOG PS 0-2

Cohort A
Standard RT
60 Gy +/- 10%
(54 Gy- 66 Gy)
or hypofractionated BED

Cohort B
Palliative RT
40 Gy-<54 Gy
(Min dose:
40 Gy) or
hypfractionated BED

SD or better

1-42 days

Durvalumab
1500 mg q4w

until 12mo or PD or unacceptable toxicity or withdrawal of consent

PRIMARY ENDPOINT
- Safety and tolerability (occurrence of Grade 3 & 4 PRAEs)

SECONDARY ENDPOINTS
- mPFS (per RECIST v1.1), PFS6 and PFS12
- ORR (per RECIST v1.1)
- DoR (per RECIST v1.1)
- mOS, OS12
- Lung cancer mortality
- Number of patients with AE, SAEs, AESIs, imAEs
- Other safety and tolerability parameters

EXPLORATORY ENDPOINTS
- QoL/ PROs
- Tumor PD-L1

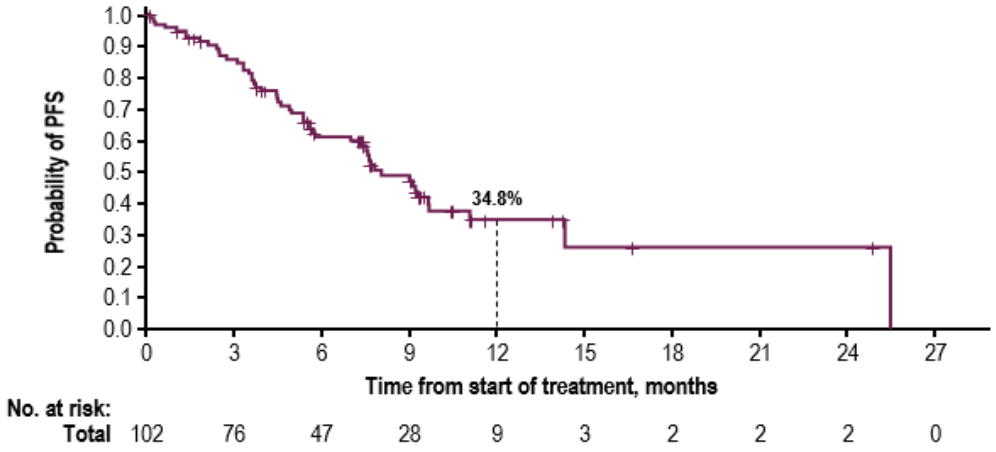
BED: bioequivalent dose; DoR: Duration of response; Durva: durvalumab; ECOG: Eastern Cooperative Oncology Group; Gy: gray; m: Month; mOS: median overall survival; mPFS: median progression-free survival; NSCLC: Non small-cell lung cancer; ORR: Overall response rate; OS12: Overall survival at 12 months; PD: Progressive disease; PFS6, PFS12: Progression-free survival at 6, 12 months, respectively; PRAE: Possibly related adverse event; PS: Performance status; q4w: Every 4 weeks; RT: radiation therapy

ClinicalTrials.gov NCT04249362

DUART: DUrvalumab After RT in unresectable Stage III NSCLC ineligible for chemotherapy

PFS

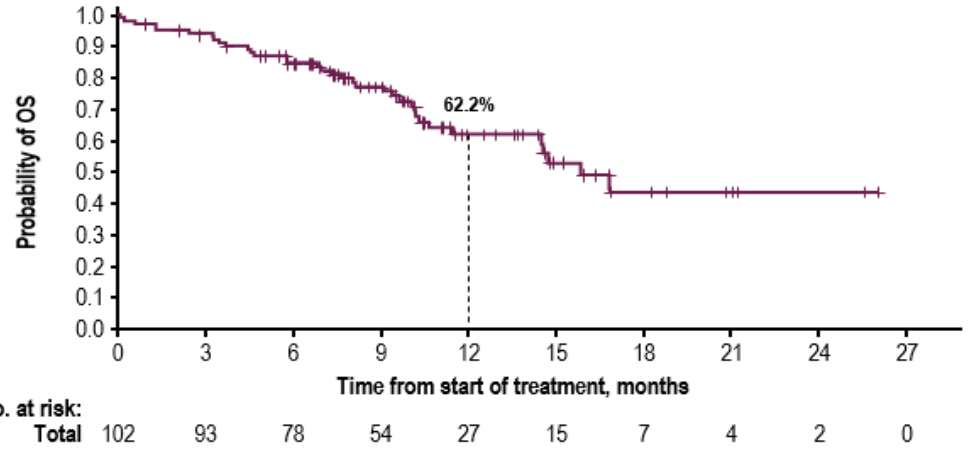
	Cohort A (standard RT)	Cohort B (palliative RT)	Total
No. events / no. patients (%)	26/59 (44.1)	25/43 (58.1)	51/102 (50.0)
Median PFS (95% CI)*, months	9.0 (5.6–NC)	7.6 (5.3–11.0)	8.0 (7.0–9.7)
12-month PFS rate (95% CI)†, %	40.2 (23.6–56.3)	29.3 (13.8–46.7)	34.8 (23.0–46.9)



Median follow-up (range) for patients censored for PFS: 7.4 months (0.0–24.9).

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)



Median follow-up (range) for patients censored for OS: 9.9 months (0.9–26.0).

Filippi AR et al. ESMO Congress 2023

S1933 A Phase II Feasibility Trial of Hypofractionated RT followed by Atezolizumab Consolidation in Stage II or III NSCLC Patients with Borderline Performance Status

Key Inclusion

Step 1: Before RT

- Stage III NSCLC with PS 2

OR

- Stage II NSCLC with PS0-2 and are not surgical candidates

Step 2: Post-RT & before Atezo.

- Received ≥ 45 Gy radiation and no PD

Exclusion Criteria

- Active autoimmune disease
- Hx of ILD or ≥ G3 pneumonitis

- Stage III NSCLC with PS2

OR

- Stage II NSCLC who are not surgical candidates

N = 40 eligible

Hypofractionated radiotherapy: 60 Gy in 15 fractions

Disease assessment at 2-5 weeks after completion of radiotherapy

No PD → Atezolizumab consolidation (up to 12 months)

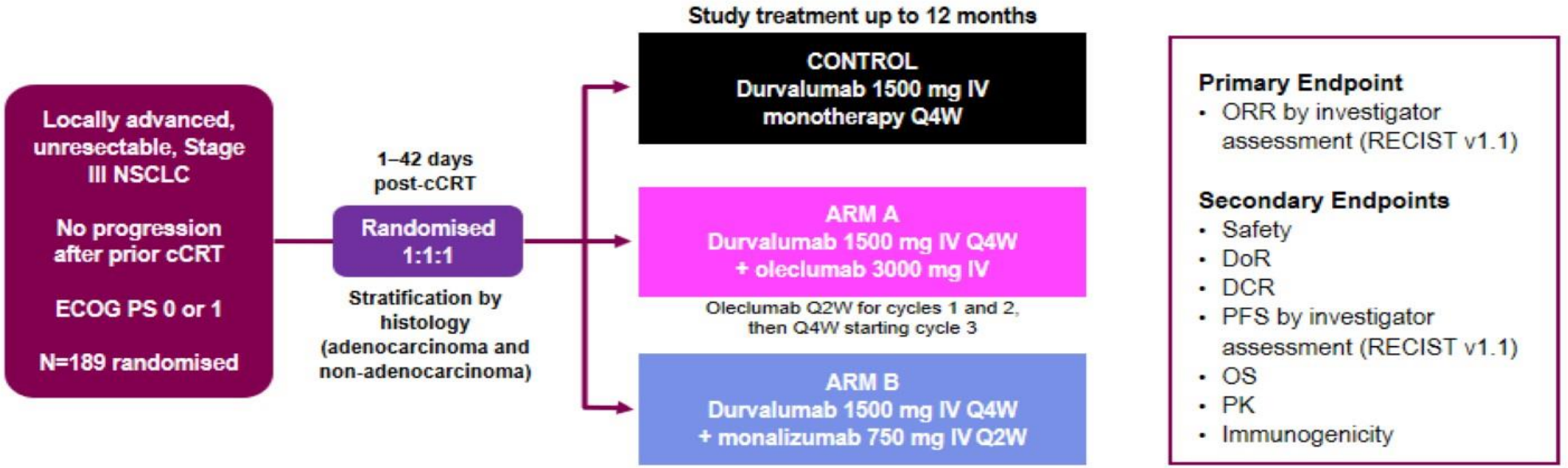
PD → Off Treatment

Total: 55
Hypofractionated RT: 31
Atezolizumab: 24

PI: Raid Aljumaily, MD
SWOG

Novel Combination Approaches

COAST: Phase 2, randomised open-label study



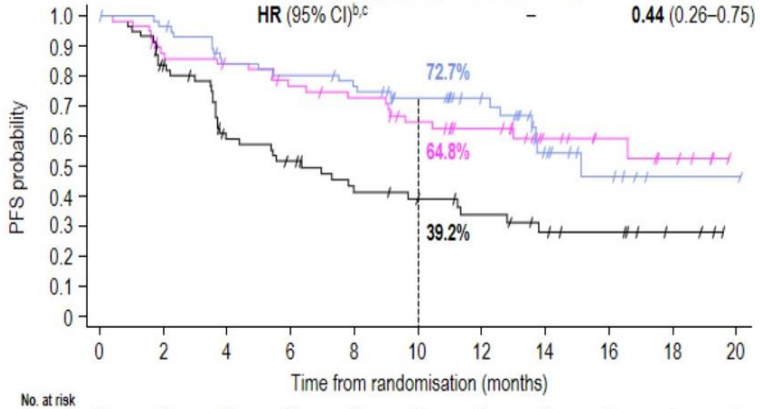
- A planned sample size of 60 patients per arm was designed to provide acceptable precision in estimating antitumour activities in an early phase setting
- Between Jan 2019 and Jul 2020, 189 patients were randomised of whom 186 received D (n=66), D+O (n=59) or D+M (n=61)
- As of 17 May 2021, all patients 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)

2021 ESMO congress

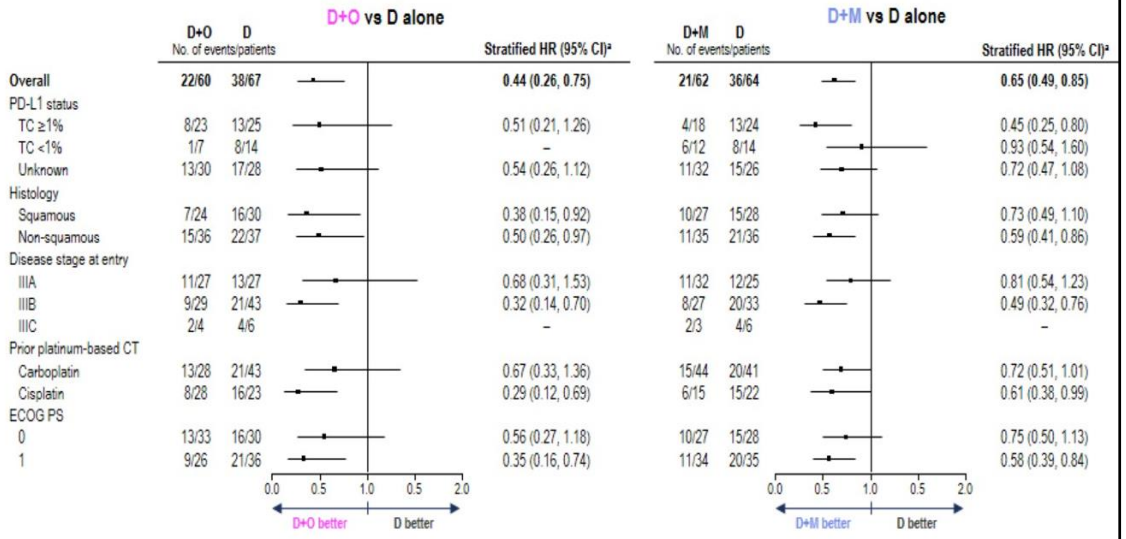
D, durvalumab; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; M, monalizumab; O, oleclumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours

PFS by investigator assessment
(interim analysis; ITT population)

	D	D+O	D+M
Events/patients, n	38/67	22/60	21/62
mPFS, months (95% CI)[a]	**6.3** (3.7–11.2)	**NR** (10.4–NE)	**15.1** (13.6–NE)
HR (95% CI)[b,c]	–	**0.44** (0.26–0.75)	**0.65** (0.49–0.85)



PFS subgroup analysis by investigator assessment
(interim analysis; ITT population)



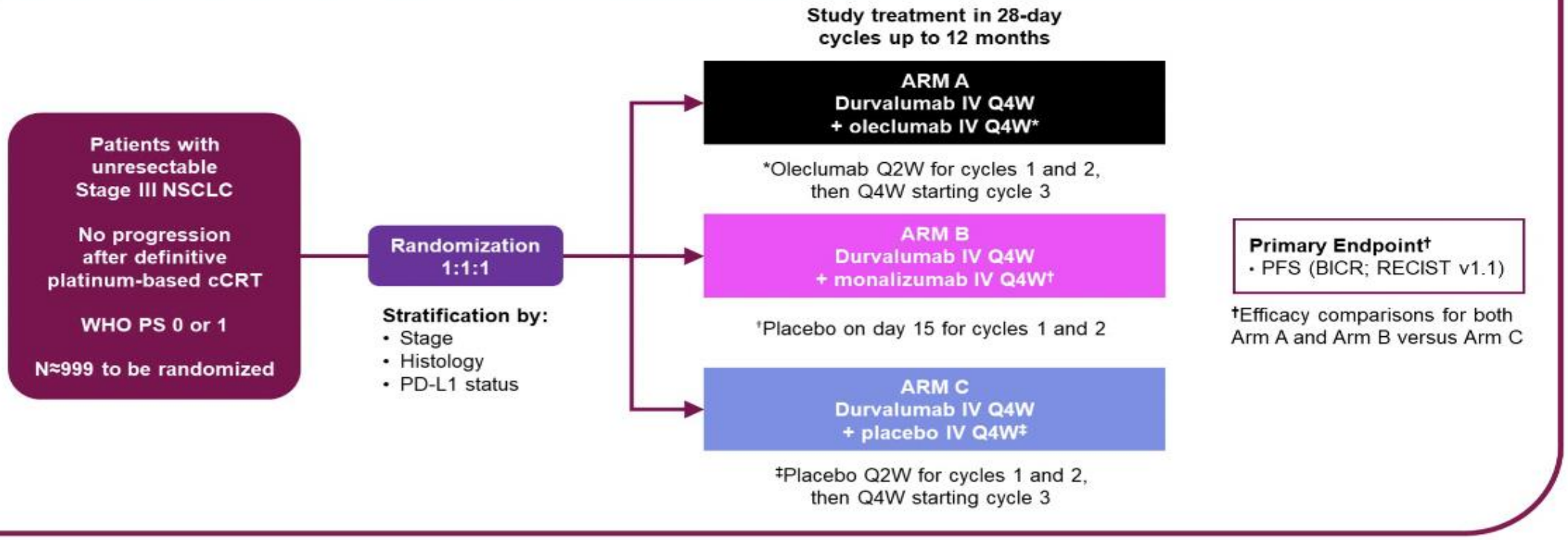
AESIs for durvalumab
(as-treated population)

Grouped term, n (%)	D (N=66)	D+O (N=59)	D+M (N=61)
	All Grades	All Grades	All Grades
Any AESI	37 (56.1)	36 (61.0)	41 (67.2)
Pneumonitis	12 (18.2)	12 (20.3)	11 (18.0)

PACIFIC-9

Consolidation Oleclumab: Anti-CD73
Consolidation Monalizumab: Anti-NKG2A

PACIFIC-9 (NCT05221840): A phase 3, double-blind, placebo-controlled, randomized, multicenter, international study



- Study enrollment 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:
  - Sites open: Australia, Brazil, Canada, China, Colombia, France, Germany, Italy, Japan, Poland, Republic of Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom, United States of America, and Vietnam
  - Sites planned but not yet active: Portugal and Peru.

Barlesi et al. ASCO 2023.

SKYSCRAPER-03: Phase III, Open-Label Randomised Study of Atezolizumab + Tiragolumab vs Durvalumab in Patients with Locally Advanced, Unresectable, Stage III NSCLC Who Have Not Progressed After Platinum-based Concurrent Chemoradiation

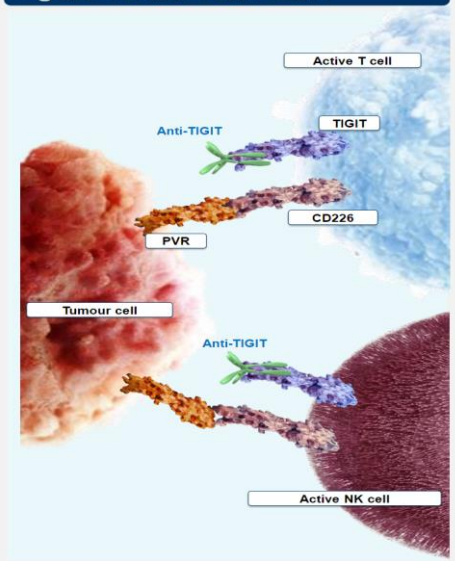
Consolidation Anti-TIGIT + Atezo

NCT04513925

Rafal Dziadziuszko[1], Myung Ju Ahn[2], Karen Kelly[3], Sanjay Popat[4], Heather Wakelee[5], Anne-Marie Baird[6], Isabelle Rooney[7], Maryam Afshari[7], Shelley Coleman[7], Zoe Zhang[7], Hiroshi Kiruki[7], Namrata Patil[7], Xiaohui Wen[7], Jeffrey Bradley[8]

[1]Medical University of Gdańsk, Gdańsk, Poland; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]UC Davis Medical Center, Sacramento, CA, USA; [4]The Royal Marsden, London, UK; [5]Stanford University Medical Center, Stanford, CA, USA; [6]Trinity College Dublin, Dublin, Ireland; [7]Genentech, Inc., South San Francisco, CA, USA; [8]Emory University School of Medicine, ATL, USA

Figure 1: Anti-TIGIT MoA



PVR, poliovirus receptor; TIGIT, T-cell immunoglobulin and ITIM domain; NK, natural killer

- TIGIT is a novel inhibitory immune checkpoint present on activated T cells and NK cells in multiple cancers; TIGIT expression correlates with PD-1, especially in tumour-infiltrating T cells[8]
- Tiragolumab is a fully human IgG1/kappa anti-TIGIT monoclonal antibody with an intact Fc region that blocks the binding of TIGIT to its receptor PVR (**Figure 1**)
- Targeted inhibition of TIGIT/PVR, by the anti-TIGIT antibody tiragolumab, may amplify the durability and duration of the anti-tumour response of anti-PD-L1/PD-1 antibodies such as atezolizumab, and broaden the patient population who may benefit

Figure 2: SKYSCRAPER-03 study design

Locally advanced, unresectable, Stage III NSCLC who have received ≥2 cycles of platinum-based cCRT without progression
N = ~800

R 1:1

Tiragolumab 840 mg IV Q4W + atezolizumab 1680 mg IV Q4W for 13 cycles (12 months)	Durvalumab* 10 mg/kg IV Q2W or 1500 mg IV Q4W† for 13 cycles (12 months)

Treat until progression or unacceptable toxicity

*Durvalumab at Q2W or Q4W based on the investigator in consultation with the patient and/or local standard of care; †For patients who weigh ≥30 kg; Q2W, once every 2 weeks; Q4W, once every 4 weeks; IV, intravenous

Primary endpoint: PFS by independent review facility assessment per RECIST v1.1

Key secondary endpoints: OS, investigator-assessed PFS, ORR, DOR, PFS and OS rates at 12, 18 and 24 months

Safety, pharmacokinetics, immunogenicity and biomarkers will also be evaluated

PACIFIC 8 ALSO with TIGIT

NCT05298423

KEYVIBE-006
Recruiting

Induction, Concurrent & Consolidation Anti-TIGIT plus Pembrolizumab

Phase 3, randomized, open-label study evaluating vibostolimab + pembrolizumab coformulation + CCRT vs CCRT followed by durvalumab in patients with unresectable, locally advanced, stage III NSCLC

Patients (N≈784)

- Previously untreated, unresectable, locally advanced, pathologically confirmed, stage IIIA–C NSCLC (by AJCC v8)
- ECOG PS 0 or 1
- No prior radiotherapy to the thorax, including radiotherapy to the esophagus, mediastinum, or for breast cancer
- No history of or current ILD or pneumonitis requiring steroids
- No prior therapy with an anti-PD-(L)1, anti-PD-L2, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor

R 1:1

	Cycle 1	Cycles 2-3	Maintenance phase
Arm 1	Vibostolimab 200 mg + pembrolizumab 200 mg coformulation IV Q3W + Histology-based platinum-doublet chemotherapy[a]	Vibostolimab 200 mg + pembrolizumab 200 mg coformulation Q3W IV + Histology-based platinum-doublet chemotherapy[a] + thoracic RT 60 Gy (2 Gy × 30, QD)	Vibostolimab 200 mg + pembrolizumab 200 mg coformulation IV Q3W (up to 17 cycles)
Arm 2	Histology-based platinum-doublet chemotherapy[a]	Histology-based platinum-doublet chemotherapy[a] + thoracic RT 60 Gy (2 Gy × 30, QD)	Durvalumab 10 mg/kg IV Q2W up to 26 cycles (~14 months)[b]

Stratification Factors

- Tumor histology (SQ vs NSQ)
- Stage (IIIA vs IIIB/IIIC)
- PD-L1 expression (TPS <1% vs ≥1%)
- Geographic region (East Asia vs North America/ Western Europe/Australia vs rest of world)

Dual Primary End Points

- PFS[c,d,e,f]
- OS[c,d,g]

Secondary End Points

- ORR[c,d,f,g]
- DOR[c,d,f,g]
- Safety[g]
- HRQoL[g]

Estimated primary completion: September 1, 2028[h]

[a]Nonsquamous histology only: cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 (D1 of Cycles 1-3); cisplatin 50 mg/m^2 (D1, D8 of Cycles 1-2 and D8, D15 of Cycle 3) and etoposide 50 mg/m^2 (D1-5 of Cycles 1-2 and D8-12 of Cycle 3); carboplatin AUC 6 mg/mL/min (D1 of Cycle 1) and AUC 2 mg/mL/min (D1, D8, D15 of Cycles 2-3) and paclitaxel 200 mg/m^2 (D1 of Cycle 1) and 45 mg/m^2 (D1, D8, D15 of Cycles 2-3). [b]1 cycle is 14 days and all other cycles are 21-day cycles. [c]In all patients. [d]In patients with PD-L1≥1%. [e]Up to approximately 55 months. [f]Assessed per RECIST v1.1 by BICR. [g]Up to approximately 75 months. [h]Subject to change. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05298423. Accessed September 14, 2022. Jabbour et al. Presented at ESMO 2022. Abstract 969TiP.

NCT04380636

KEYLYNK-012

Recruiting

Concurrent Pembro → Consolidation Anti-TIGIT plus Pembro

Phase 3, randomized, double-blind, placebo-controlled study of pembrolizumab in combination with concurrent CRT followed by pembrolizumab ± olaparib vs CCRT followed by durvalumab in patients with unresectable, locally advanced, stage III NSCLC

Patients (N≈870)

- Histologically or cytologically confirmed, previously untreated, unresectable stage IIIA-C NSCLC
- Not eligible for surgery with curative intent
- ECOG PS 0–1
- No ILD or pneumonitis requiring steroids
- No prior therapy with an anti-PD-(L)1, anti-PD-L2, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor
- No prior olaparib or other PARP inhibitors

R 1:1:1

	3 cycles	12 months
A	Pembrolizumab 200 mg IV Q3W + CCRT[b]	Pembrolizumab 200 mg IV Q3W + matching olaparib placebo PO BID[c]
B	Pembrolizumab 200 mg IV Q3W + CCRT[b]	Pembrolizumab 200 mg IV Q3W + olaparib 300 mg PO BID[c]
C	CCRT[b]	Durvalumab 10 mg/kg Q2W[c]

Stratification Factors[a]

- Stage (IIIA vs IIIB/IIIC)
- Tumor histology (SQ vs NSQ)
- PD-L1 expression (TPS <50% vs ≥50%)
- Geographic region (East Asia vs North America/ Western Europe/UK vs other)

Primary End Points

- PFS[d]
- OS

Secondary End Points

- Safety
- ORR[d]
- DOR[d]
- HRQoL

Exploratory End Points

- Assess ctDNA and its correlation with efficacy end points
- Identifiy molecular biomarkers of response, safety, and activity
- Efficacy outcomes by PD-L1 levels
- Efficacy by iRECIST (investigator assessement)
- PFS2 (per RECIST v1.1 by investigator assessement), time to first subsequent therapy (TFST), and time to second subsequent therapy (TSST)
- Characterize health utility for use in economic models

Estimated primary completion: July 6, 2026[e]

[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). [b]Platinum doublet options (per investigator's choice) include cisplatin + pemetrexed (NSQ histology only), cisplatin + etoposide, and carboplatin + paclitaxel. [c]Patients in Groups A and B may receive a maximum of 20 cycles of pembrolizumab (Q3W) and patients in Group C may receive a maximum of 26 cycles of durvalumab (Q2W). [d]Assessed per RECIST v1.1 by BICR. [e]Subject to change.

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04380636. Accessed June 22, 2022. Jabbour et al. Presented at ASCO 2021. Abstract TPS8580. Jabbour et al. *Clin Lung Cancer*. 2022;23(6):e342-e346.

Durvalumab 1-5 days after completion of ChemoXRT

CLINICAL CANCER RESEARCH | RESEARCH BRIEFS: CLINICAL TRIAL BRIEF REPORTS

Phase II Study of Durvalumab Immediately after Completion of Chemoradiotherapy in Unresectable Stage III Non–small Cell Lung Cancer: TORG1937 (DATE Study)

Shinji Nakamichi[1], Kaoru Kubota[1], Toshihiro Misumi[2], Tetsuro Kondo[3], Shuji Murakami[3], Yoshimasa Shiraishi[4], Hisao Imai[5,6], Daijiro Harada[7], Kazutoshi Isobe[8], Hidetoshi Itani[9], Saori Takata[10], Hiroshi Wakui[11], Yuki Misumi[12], Satoshi Ikeda[13], Tetsuhiko Asao[14], Naoki Furuya[15], Shinobu Hosokawa[16], Yumiko Kobayashi[17], Yuichi Takiguchi[18], and Hiroaki Okamoto[12]

Table 2. Survival and tumor response outcomes.

Survival outcomes	***n* = 47 ([a]*n* = 40, [b]*n* = 42)**	
1-year PFS rate		
From registration by IRC, % [60% CI], [95% CI]	75.0	[69.0–80.0], [59.4–85.3]
From registration by INV, % [60% CI], [95% CI]	77.8	[72.0–82.5], [62.6–87.4]
From start of durvalumab by INV, % [95% CI][a]	71.5	[54.2–83.2]
mPFS		
From registration by IRC, months [95% CI]	14.2	[13.4–NR]
From registration by INV, months [95% CI]	14.2	[13.4–17.5]
From start of durvalumab by IRC, months [95% CI][a]	12.7	[12.7–NR]
From start of durvalumab by INV, months [95% CI][a]	12.6	[12.3–16.1]
1-year OS rate		
From registration by INV, % [95% CI]	97.7	[84.6–99.7]
From start of durvalumab by INV, % [95% CI][b]	97.4	[82.8–99.6]
Tumor response outcomes		***n* = 47**
Best overall response, *n* (%)		
CR	2	(4.3)
PR	35	(74.5)
SD	9	(19.1)
PD	0	(0)
NE	1	(2.1)
ORR		
n (%) [95% CI]	37	(78.7) [64.3–89.3]
DCR		
n (%) [95% CI]	46	(97.9) [88.7–99.9]

Abbreviations: CI, confidence interval by Greenwood formula; CR, complete response; DCR, disease control rate; INV, investigator; IRC, Independent Review Committee; mPFS, median progression-free survival; NE, not evaluated; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Forty of 42 patients receiving durvalumab consolidation were available for efficacy analysis. Two patients could not be evaluated for 1-year PFS and PFS from the start of durvalumab due to withdrawal of consent and self-interruption prior to CT evaluation.
[b]Forty-two patients receiving durvalumab consolidation were available for efficacy analysis.

Table 1. Patients' characteristics.

	***n* = 47**	**(%)**
Sex		
Male	41	(87.2)
Female	6	(12.8)
Age (years)		
Median (range)	65	(42–74)
cStage		
IIIA	19	(40.4)
IIIB	21	(44.7)
IIIC	7	(14.9)
Smoking		
Current	24	(51.1)
Past	17	(36.2)
Never	6	(12.8)
PS		
0	28	(59.6)
1	19	(40.4)
Histology		
Adenocarcinoma	27	(57.4)
Squamous cell carcinoma	15	(31.9)
Adenosquamous carcinoma	1	(2.1)
Others	4	(8.5)
PD-L1 (22C3) expression		
≥50%	19	(40.4)
1%–49%	11	(23.4)
<1%	10	(21.3)
Unknown	7	(14.9)
EGFR mutation		
Negative	29	(61.7)
Positive	3	(6.4)
Unknown	15	(31.9)
ALK fusion		
Negative	25	(53.2)
Positive	5	(10.6)
Unknown	17	(36.2)

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; PS, performance status.

Pneumonitis: Any Grade: 37 (78.7%) and Grade 3: 2 (4.3%)

Targeted Therapies

ADAURA: Study Design

NCT02511106

Phase 3, Randomized, Double-blind, Placebo-controlled

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key Inclusion Criteria

- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC
- Ex19del / L858R‡
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins§
- Max. interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

STRATFICATION BY:

Stage (IB vs II vs IIIA)

EGFRm (Ex19del vs L858R)

race (Asian vs non-Asian)

R
1:1
N=682

OSIMERTINIB
80 mg, once daily

PLACEBO
once daily

Planned treatment duration: 3 years

TREATMENT CONTINUES UNTIL:

- Disease recurrence
- Treatment completed
- Discontinuation criterion met

FOLLOW UP:

- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Primary Endpoint

DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70

Secondary Endpoint

DFS in the overall population

DFS at 2, 3, 4, and 5 years,

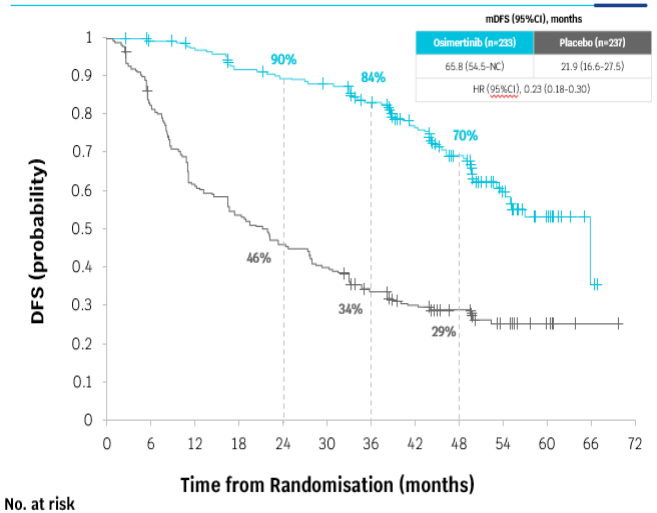
OS, safety, health-related quality of life

Following IDMC recommendation, study unblinded early due to efficacy – study had completed enrollment and all patients were followed at least 1 year.

ADAURA: Osimertinib vs. placebo improved DFS and OS

Disease Free Survival

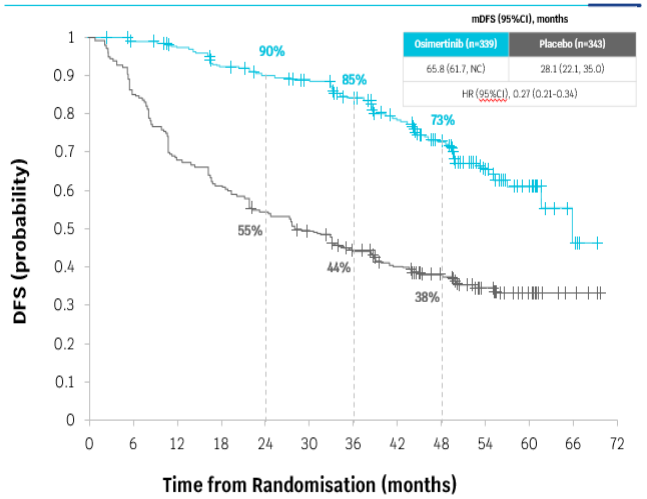
II/IIIA Disease



No. at risk													
Osimertinib	233	222	216	202	196	192	174	138	90	45	20	2	0
Placebo	237	191	141	124	106	91	74	61	41	23	11	1	0

Adapted from Herbst R, JCO Jan 2023

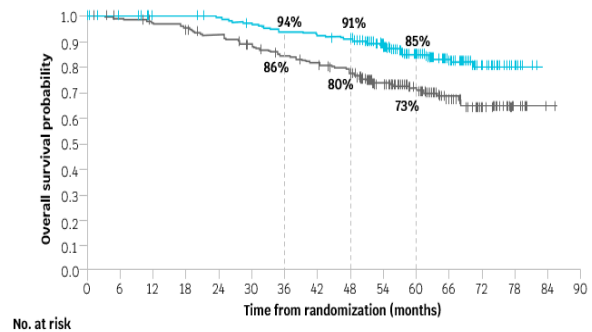
Overall Population: IB/II/IIIA Disease



No. at risk													
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

Overall Survival

II/IIIA Disease



No. at risk														
Osimertinib	233	229	224	224	221	214	208	205	200	170	115	69	33	9	0	-
Placebo	237	232	226	221	210	202	190	182	171	138	94	53	25	8	2	0

5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66,78)

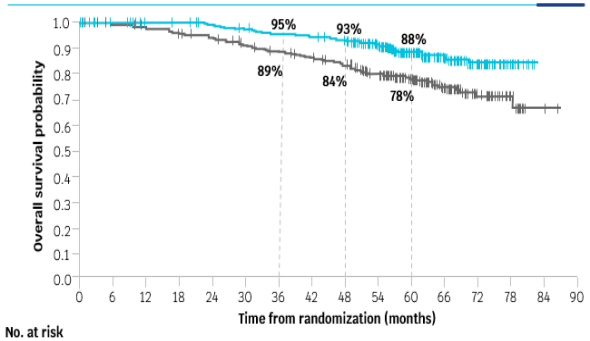
Overall OS HR (95.03% CI)	0.49 (0.33, 0.73); p=0.0004

Maturity: 21%
Osimertinib 15%, placebo 27%

Median follow-up for OS* (censored patients):
Osimertinib 61.7 months, placebo 60.4 months

Herbst, R. ASCO 2023 LBA3

Overall Population: IB/II/IIIA Disease



No. at risk														
Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	-
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)

Overall OS HR (95.03% CI)	0.49 (0.34, 0.70); p<0.0001

Maturity: 18%
Osimertinib 12%, placebo 24%

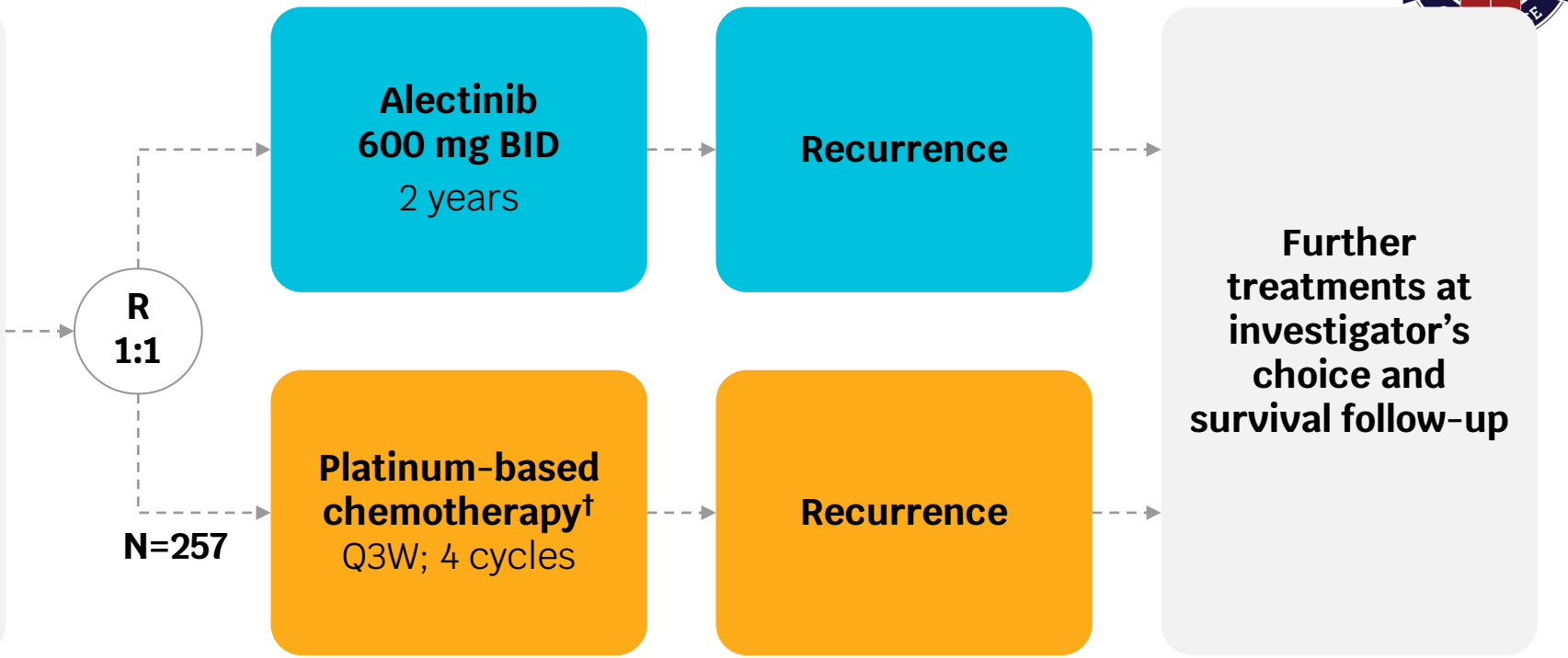
Median follow-up for OS* (censored patients):
Osimertinib 61.5 months, placebo 61.5 months

References

ALINA: ALK + Adjuvant NSCLC

Resected Stage IB (≥4cm)–IIIA
***ALK*+ NSCLC**
per UICC/AJCC 7th edition
Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian



Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

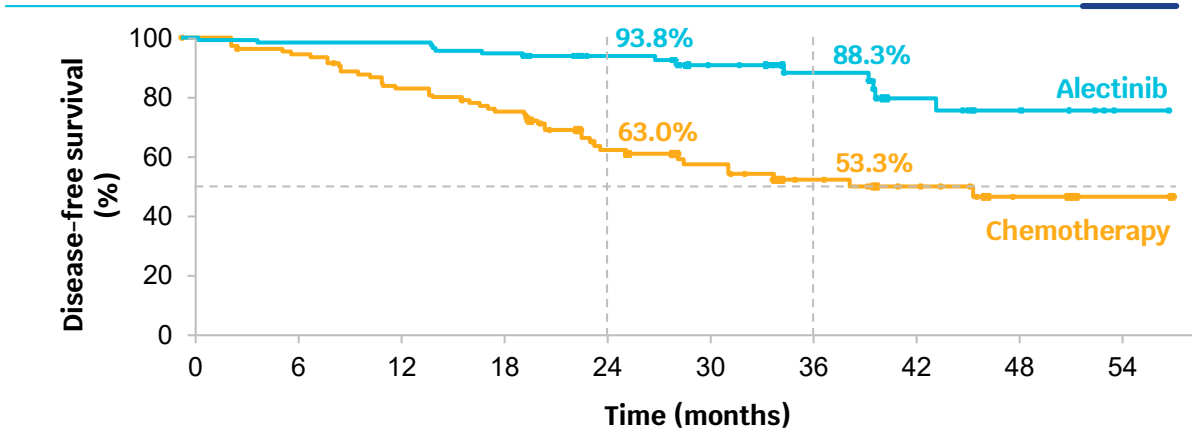
Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
†Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

Solomon B, et al. ESMO 2023

ALINA: DFS Primary Endpoint

Disease-free survival: stage II–IIIA*



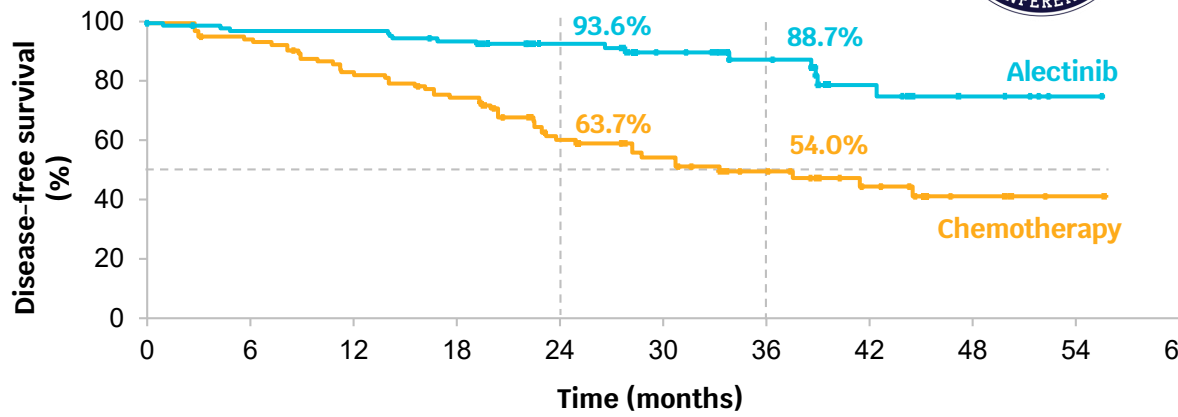
No. at risk

Alectinib	116	111	111	107	67	49	35	21	10	3
Chemo	115	102	88	79	48	35	23	17	10	2

	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event	14 (12%)	45 (39%)
Death	0	1
Recurrence	14	44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

Median survival follow up: alectinib, 27.9 months; chemotherapy, 27.8 months

Disease-free survival: ITT (stage IB–IIIA)*



No. at risk

Alectinib	130	123	123	118	74	55	39	22	10	3
Chemo	127	112	98	89	55	41	27	18	11	2

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	15 (12%)	50 (39%)
Death	0	1
Recurrence	15	49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p†<0.0001	

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported‡

Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months. *Per UICC/AJCC 7th edition; †Stratified log rank; ‡2 events in the alectinib arm, 4 events in the chemo arm; one additional patient in the chemo arm died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

Solomon B, et al. ESMO 2023

LAURA

Phase III, double-blind, randomized, placebo-controlled trial

NCT03521154

Patients with locally advanced, unresectable (Stage III) EGFRm[a] NSCLC whose disease has not progressed during or following definitive platinum-based CRT

N≈200[b]

Concurrent chemoradiation

or

sequential chemoradiation

R[c] 2:1

- **Osimertinib[d]**
- **Placebo**

Primary endpoint

- PFS

Secondary endpoints

- PFS in patients with EGFR Ex19del or L858R mutation
- PFS in patients with EGFR mutations Ex19del or L858R detectable in plasma-derived ctDNA
- Time to CNS PFS
- OS, ORR, DoR, DCR, tumor shrinkage, TTDM, TTD, PFS2, TFST, TSST
- Patients reported disease-related symptoms and HRQoL
- Incidence of adverse events
- PK

[a]Ex19del or L858R either alone or in combination with other EGFR mutations; [b]Estimated enrollment; [c]Randomized within 6 weeks of completion of chemoradiation; [d]Osimertinib dosing schedule: 80 mg PO QD.

CNS = central nervous system; CRT = chemoradiation therapy; ctDNA = circulating tumor DNA; DCR = disease control rate; DoR = duration of response; EGFR = epidermal growth factor receptor; EGFRm = epidermal growth factor receptor mutation-positive; Ex19del = exon 19 deletion; HRQoL = health-related quality of life; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS, progression-free survival; PFS2 = second progression-free survival on a subsequent treatment; PK = pharmacokinetic; PO = orally; R = randomize; TFST = time to first subsequent therapy; TSST = time to second subsequent therapy; TTD = time to treatment discontinuation; TTDM = time to death or distant metastases.

1 Study NCT03521154. ClinicalTrials.gov website.

Osimertinib demonstrated overwhelming efficacy benefit for patients with unresectable, Stage III EGFR-mutated lung cancer in LAURA Phase III trial

PUBLISHED
19 February 2024

First EGFR inhibitor and targeted treatment to demonstrate progression-free survival benefit in Stage III setting

Positive high-level results from the LAURA Phase III trial showed (osimertinib) demonstrated a statistically significant and highly clinically meaningful improvement in progression-free survival (PFS) for patients with unresectable, Stage III epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer (NSCLC) after chemoradiotherapy (CRT) compared to placebo after CRT.

Overall survival (OS) data showed a favourable trend for osimertinib although data were not mature at the time of this analysis. The trial will continue to assess OS as a secondary endpoint.

Small Cell Lung Cancer

ADRIATIC Trial: Durvalumab improved OS and PFS in patients with LS-SCLC

- **Randomized, double-blind, placebo controlled, global Phase III trial**
- **N= 730**

Table: 67TiP

Arm	Dose	Initial regimen (first 4 cycles)	Continuation regimen (up to 24 months)
D + placebo T	D = 1500 mg (intravenous [i.v.])	D + placebo T q4w	D q4w alone after the final dose of D + placebo T
D + T combination	D = 1500 mg (i.v.)T = 75 mg (i.v.)	D + T q4w	D q4w alone after the final dose of D + T
Placebo D + placebo T	i.v. saline	Placebo D + placebo T q4w	Placebo D q4w

Durvalumab significantly improved overall survival and progression-free survival for patients with limited-stage small cell lung cancer in ADRIATIC Phase III trial

Senan S. et al. Annals of Oncology 2019.

Key Take Aways

- **Durvalumab post concurrent CRT is the SOC for patients with Unresectable NSCLC**
- **PACIFIC 2 did not meet its primary endpoint. Further investigations are underway.**
- **Data also supports neoadjuvant chemotherapy plus ICB and adjuvant ICB**
  - Partnerships with our Multi-disciplinary Teams is critical
- **We eagerly await the results of the ongoing ICB trials (eg EA5181) as well as those with novel targets**