MaTOS™
Masters in Thoracic Oncology Summit
Albuquerque, New Mexico | November 16 - 19, 2023

What's After PACIFIC? Can We Raise the Bar?

Jhanelle E. Gray, MD

Department Chair, Program Leader & Senior Member, Thoracic Oncology
Co-Leader, CCSG Molecular Medicine Program
Moffitt Cancer Center, Tampa, FL
SWOG Lung Committee Chair

November 2023

PACIFIC

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 After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer

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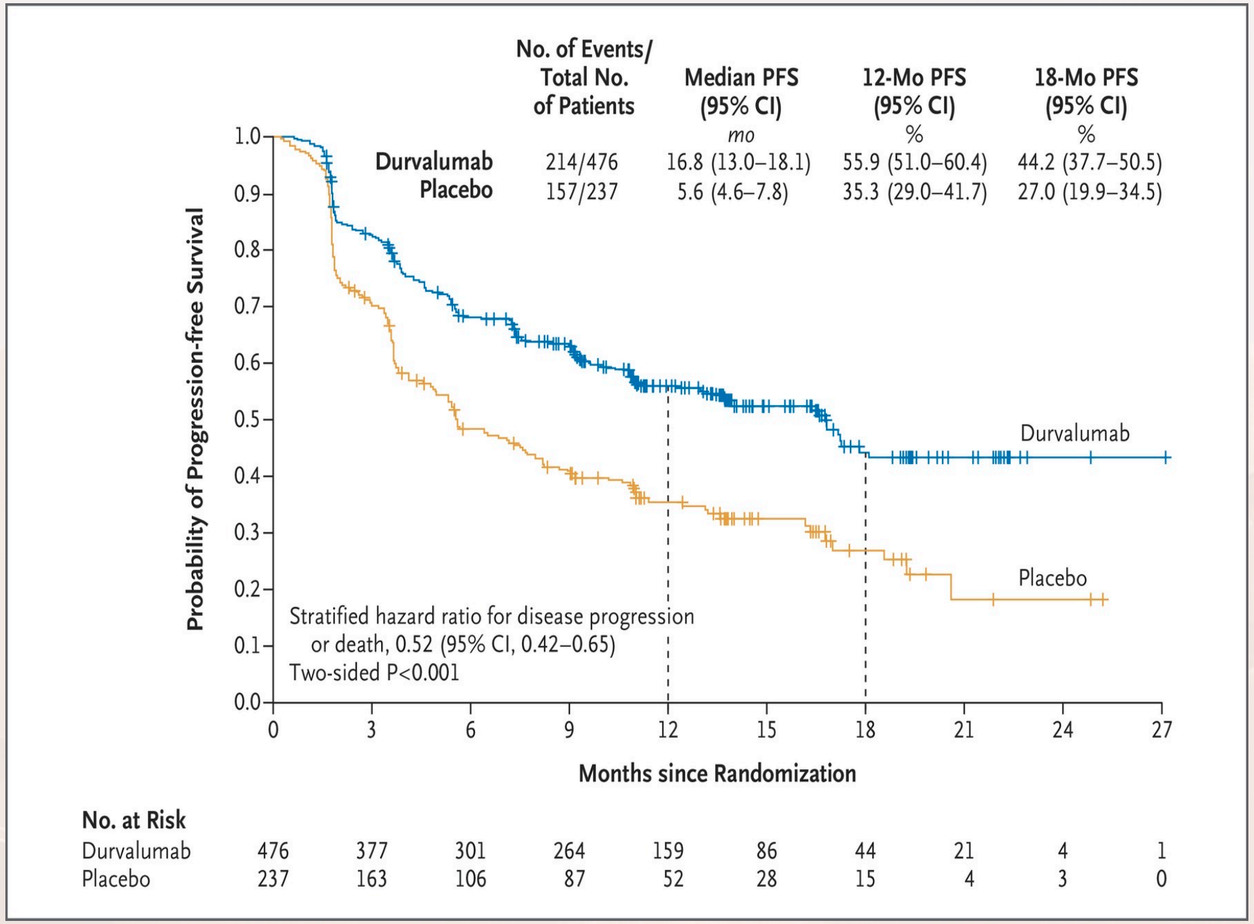
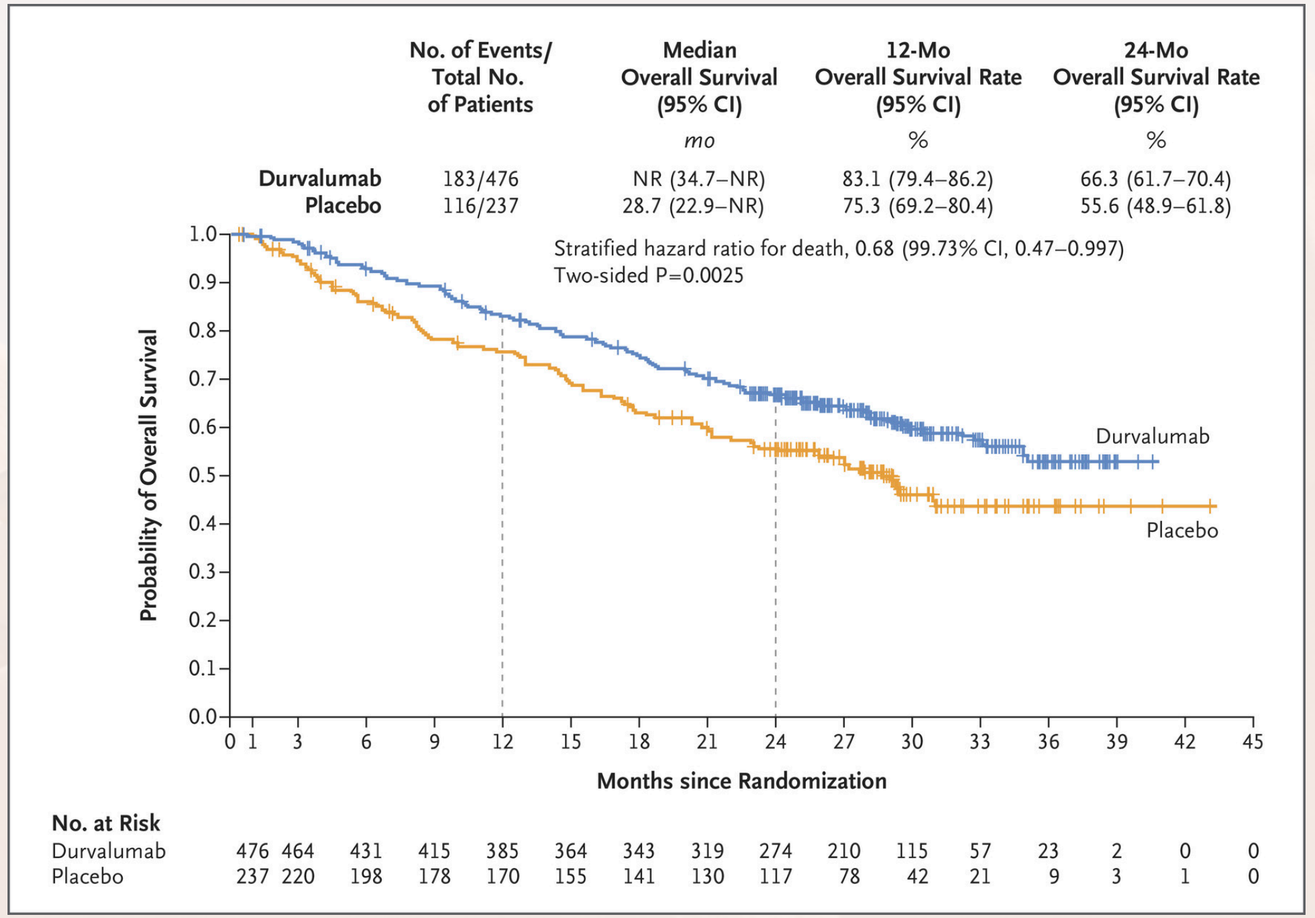




Antonia SA…, Gray JE et al. NEJM. 2017 & 2018.

Three-Year Update

Overall Survival

	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
Durvalumab	210/476 (44.1)	NR (38.4–NR)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	57.0 (52.3–61.4)
Placebo	134/237 (56.5)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.5 (37.0–49.9)

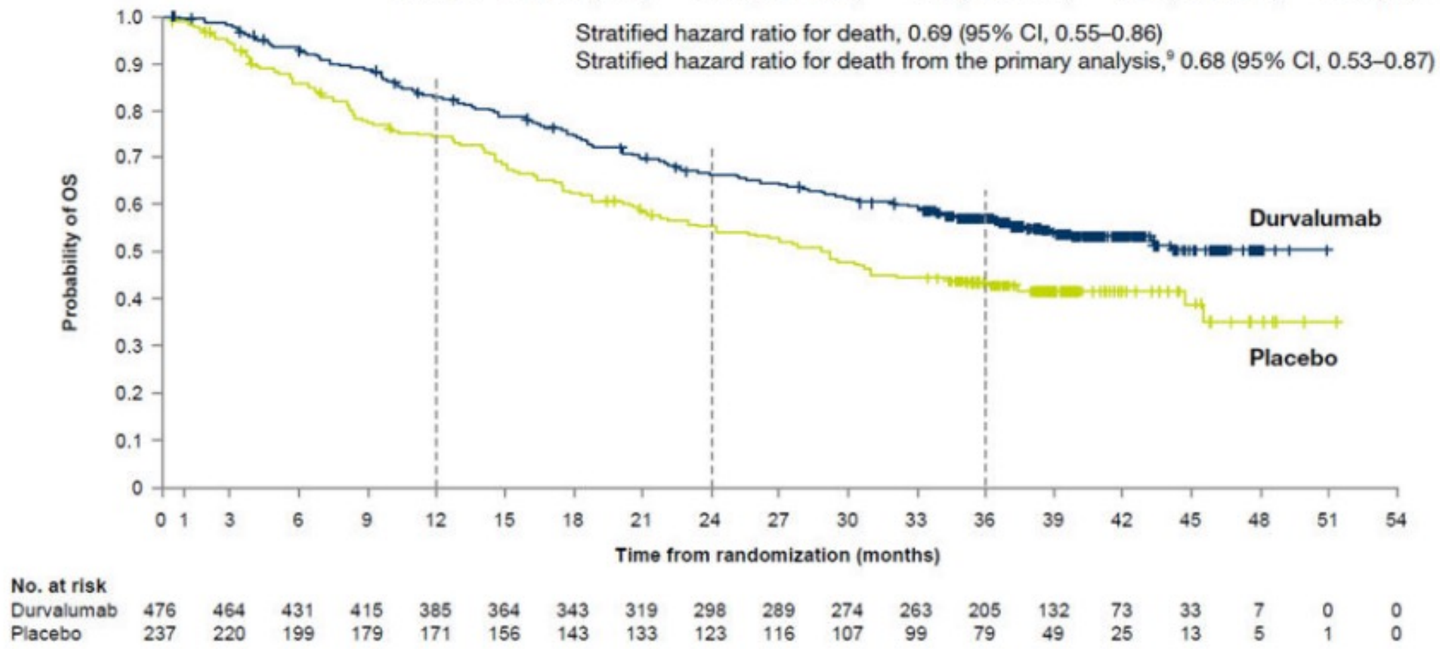
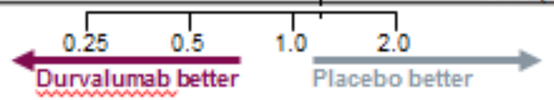


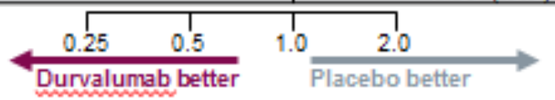
Figure 1.
Updated analysis of overall survival (OS) in the intention-to-treat population. Shown are Kaplan-Meier curves for OS. The tick marks indicate censored data, and the dashed vertical lines indicate the times of landmark analyses of OS. The intention-to-treat population included all the patients who underwent randomization. CI, confidence interval; NR, not reached.

Gray JE et al. JTO. 2020.

PFS and OS by subgroup (ITT)

		PFS (BICR)			OS		
			No. of events / No. of patients (%)			No. of events / No. of patients (%)	
		HR (95% CI)	Durvalumab	Placebo	HR (95% CI)	Durvalumab	Placebo
	All patients		214/476 (45.0)	157/237 (66.2)		183/476 (38.4)	116/237 (48.9)
Sex	Male		155/334 (46.4)	111/166 (66.9)		141/334 (42.2)	80/166 (48.2)
	Female		59/142 (41.5)	46/71 (64.8)		42/142 (29.6)	36/71 (50.7)
Age at randomisation	<65 years		108/261 (41.4)	91/130 (70.0)		89/261 (34.1)	58/130 (44.6)
	≥65 years		106/215 (49.3)	66/107 (61.7)		94/215 (43.7)	58/107 (54.2)
Smoking status	Smoker		197/433 (45.5)	140/216 (64.8)		169/433 (39.0)	103/216 (47.7)
	Non-smoker		17/43 (39.5)	17/21 (81.0)		14/43 (32.6)	13/21 (61.9)
Disease stage	Stage IIIA		108/252 (42.9)	82/125 (65.6)		101/252 (40.1)	70/125 (56.0)
	Stage IIIB		104/212 (49.1)	72/107 (67.3)		79/212 (37.3)	44/107 (41.1)
Tumour histologic type	Squamous		117/224 (52.2)	66/102 (64.7)		103/224 (46.0)	56/102 (54.9)
	Non-squamous		97/252 (38.5)	91/135 (67.4)		80/252 (31.7)	60/135 (44.4)
Prior definitive CT	Cisplatin		115/266 (43.2)	87/129 (67.4)		94/266 (35.3)	64/129 (49.6)
	Carboplatin		91/199 (45.7)	65/102 (63.7)		84/199 (42.2)	47/102 (46.1)
Best response to prior treatment	CR	NA*	2/9 (22.2)	4/7 (57.1)	NA*	2/9 (22.2)	3/7 (42.9)
	PR		99/232 (42.7)	72/111 (64.9)		83/237 (35.0)	50/112 (44.6)
	SD		108/222 (48.6)	77/114 (67.5)		93/223 (41.7)	61/115 (53.0)
EGFR status	Positive		17/29 (58.6)	11/14 (78.6)	NA*	10/29 (34.5)	6/14 (42.9)
	Negative		131/315 (41.6)	112/165 (67.9)		117/317 (36.9)	80/165 (48.5)
	Unknown		66/132 (50.0)	34/58 (58.6)		56/130 (43.1)	30/58 (51.7)
PD-L1 status (pre-specified)	≥25%		48/115 (41.7)	31/44 (70.5)		37/115 (32.2)	23/44 (52.3)
	<25%		85/187 (45.5)	68/105 (64.8)		74/187 (39.6)	41/105 (39.0)
	Unknown		81/174 (46.6)	58/88 (65.9)		72/174 (41.4)	52/88 (59.1)
PD-L1 status (post-hoc)	≥1%		84/212 (39.6)	59/91 (64.8)		70/212 (33.0)	45/91 (49.5)
	1–24%		36/97 (37.1)	28/47 (59.6)		33/97 (34.0)	22/47 (46.8)
	<1%		49/90 (54.4)	40/58 (69.0)		41/90 (45.6)	19/58 (32.8)





CR, complete response; EGFR, epidermal growth factor receptor; NA, not applicable PR, partial response; SD, stable disease

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)

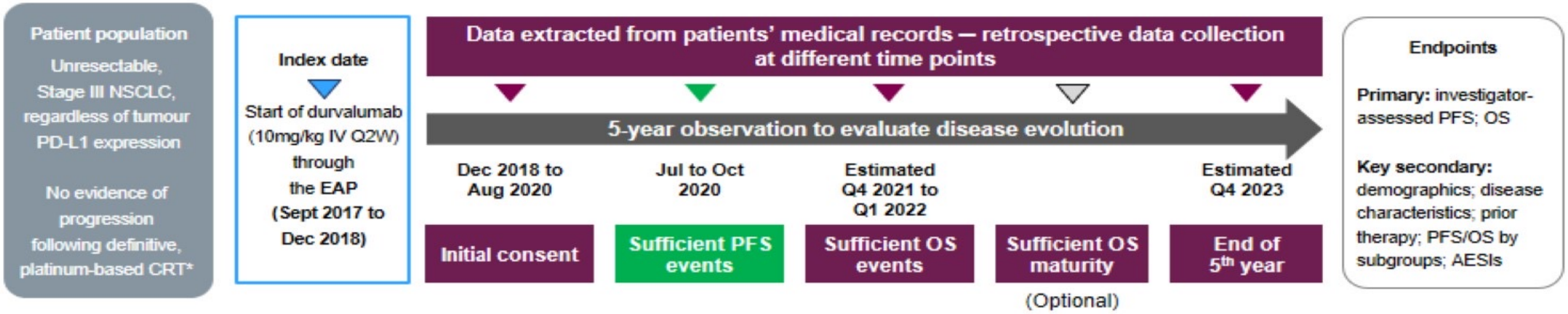
	Durvalumab	Placebo
Time to onset from 1st dose, median days (range) [N]	55.0 (1–406) [161]	55.0 (1–255) [58]
Time to onset from radiotherapy, median days (range) [N]	73.0 (20–433) [161]	76.5 (24–280) [58]
Duration, median days (range) [N]*	64.0 (3–568) [79]	57.0 (5–187) [23]

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

PACIFIC Real-World Study: ESMO 2021

Study Design & Status (NCT03798535)

PACIFIC-R: An International, Observational Study



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

*Patients had completed platinum-based chemotherapy concurrent or sequential to radiotherapy within the previous 12 weeks without evidence of disease progression; †Spanish data are from an externally sponsored study integrated in April 2021
AESI, adverse event of special interest; CRT, chemoradiotherapy; EAP, expanded access programme; IV, intravenously; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q2W, every 2 weeks

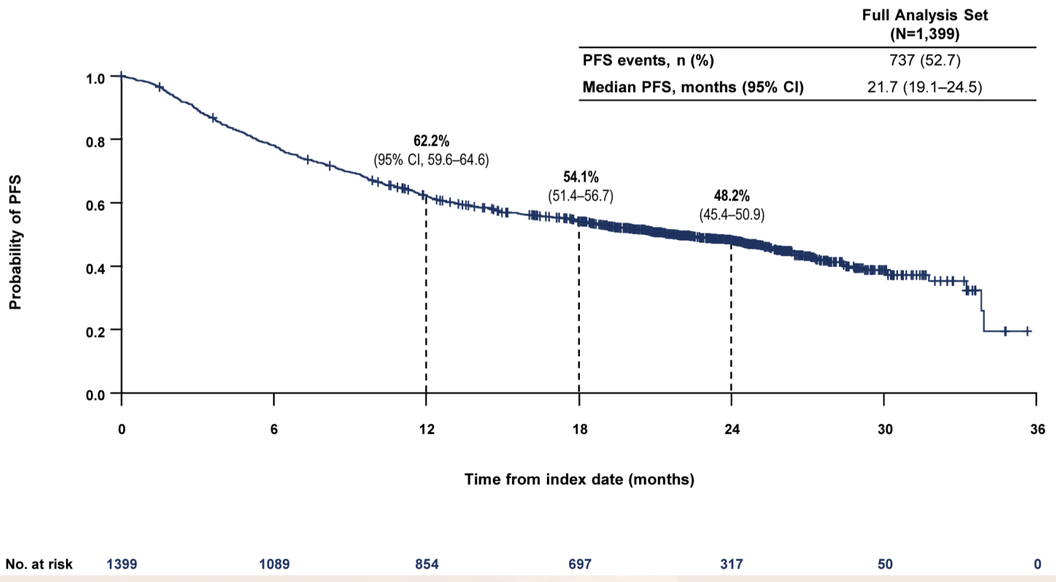
PACIFIC-R Data

Table 1. Patient Demographics and Disease Characteristics

Characteristics	Full Analysis Set (N = 1399)
Median age at EAP inclusion, y (range)	66.0 (26-88)
Age category at EAP inclusion, n (%)	
<70 y	958 (68.5)
70-75 y	296 (21.2)
>75 y	145 (10.4)
Sex, n (%)	
Male	944 (67.5)
Female	455 (32.5)
Smoking status at EAP inclusion, n (%)	
Never	111 (7.9)
Current	456 (32.6)
Former	832 (59.5)
ECOG or WHO PS at EAP inclusion, n (%)	n = 951[a]
0	489 (51.4)
1	443 (46.6)
2 or 3	19 (2.0)
Disease stage at initial NSCLC diagnosis, n (%)	n = 1392[b]
IA to IIB	74 (5.3)
IIIA	604 (43.4)
IIIB or IIIC	714 (51.3)
Histologic subtype at stage III diagnosis, n (%)	n = 1378[c]
Squamous	496 (36.0)
Nonsquamous	882 (64.0)
PD-L1 status, n (%)	n = 967[d]
≥1%	700 (72.4)
<1%	174 (18.0)
Inconsistent	93 (9.6)
EGFR status, n (%)	n = 582[e]
Mutated	46 (7.9)
Wild type	517 (88.8)
Inconclusive or unknown	19 (3.3)

- **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

	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.
Girard, N et al. JTO. 2023.

PACIFIC-R Toxicity Data

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.

BEYOND PACIFIC

SEQUENTIAL CHEMORADIATION & ECOG 2

PACIFIC 6 Study Design

Phase 2, open-label, multicenter study

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

Screening (max 28 days)

Stratification factors
- WHO/ECOG PS 0-2

WHO/ECOG PS 0-1 → **Durvalumab 1500 mg IV q4w up to 24 months or until disease progression n=120**

WHO/ECOG PS 2 → **Durvalumab 1500 mg IV q4w up to 24 months or until disease progression n=30**

Primary Endpoints
- Safety and tolerability (occurrence of Grade 3 and Grade 4 TRAEs)

Secondary Endpoints
- mPFS[a], PFS12, PFS24
- mOS, OS12, OS24, OS36
- ORR[a]
- DoR[a]
- Number of patients with AE, SAEs, AESIs, imAEs
- Other safety and tolerability parameters

- US/UK/France
- N: 150

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

PAC-6 Patient and Disease Characteristics

- **Majority are men**
- **Low % ECOG PS 2**
- **Majority Stage IIIB**
- **Unknown PD-L1 status in ~ 40%.**

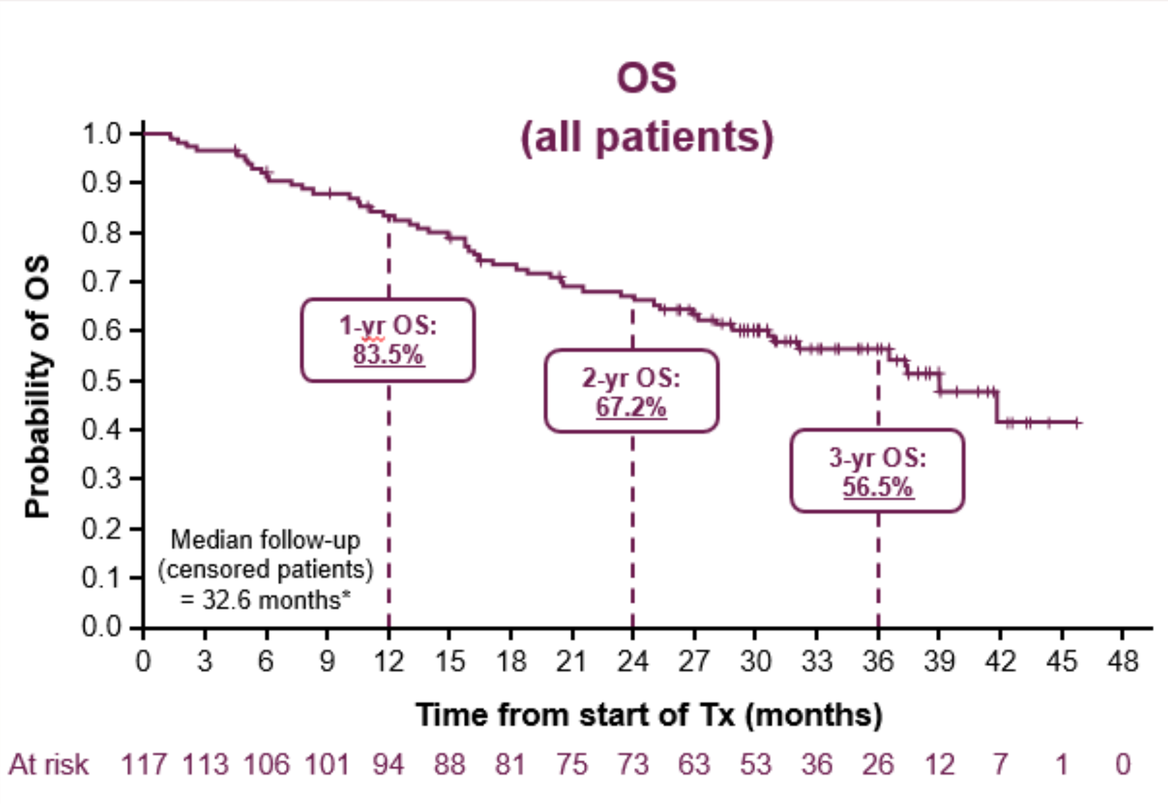
Table 1. Baseline Patient and Disease Characteristics

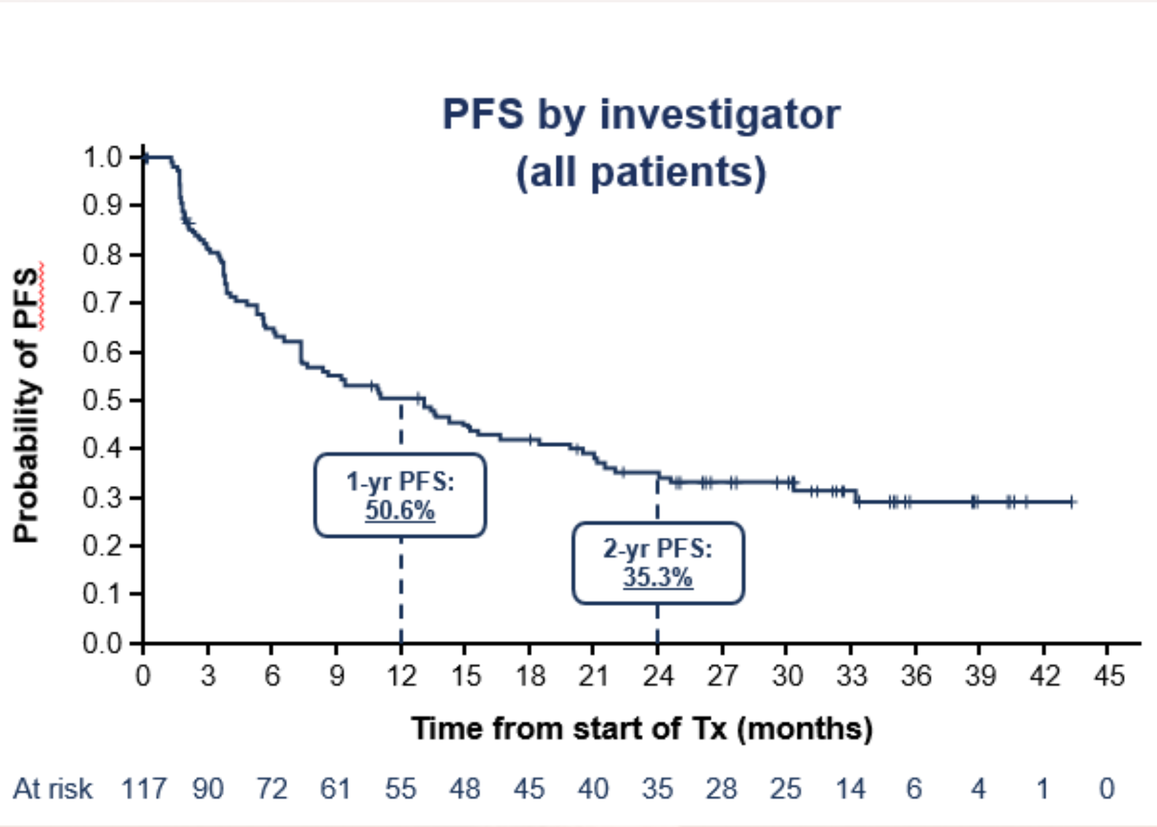
Characteristic	ECOG PS 0 or 1 (n = 114)	ECOG PS 2 (n = 3)	All Patients (N = 117)
Median age (range), y	68.0 (39-85)	65.0 (53-77)	68.0 (39-85)
Age group, n (%)			
<65 y	39 (34.2)	1 (33.3)	40 (34.2)
≥65 y	75 (65.8)	2 (66.7)	77 (65.8)
≥75 y	20 (17.5)	1 (33.3)	21 (17.9)
Sex, n (%)			
Men	71 (62.3)	2 (66.7)	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.

Garassino et al. JTO 2022

PAC-6 Progression-free and Overall 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

INTERIM ANALYSIS CONSOLIDATION
NIVO/IPI VS NIVO POST CONCURRENT CHEMORADIOTHERAPY: Big Ten Cancer Research Consortium/LUN16-081

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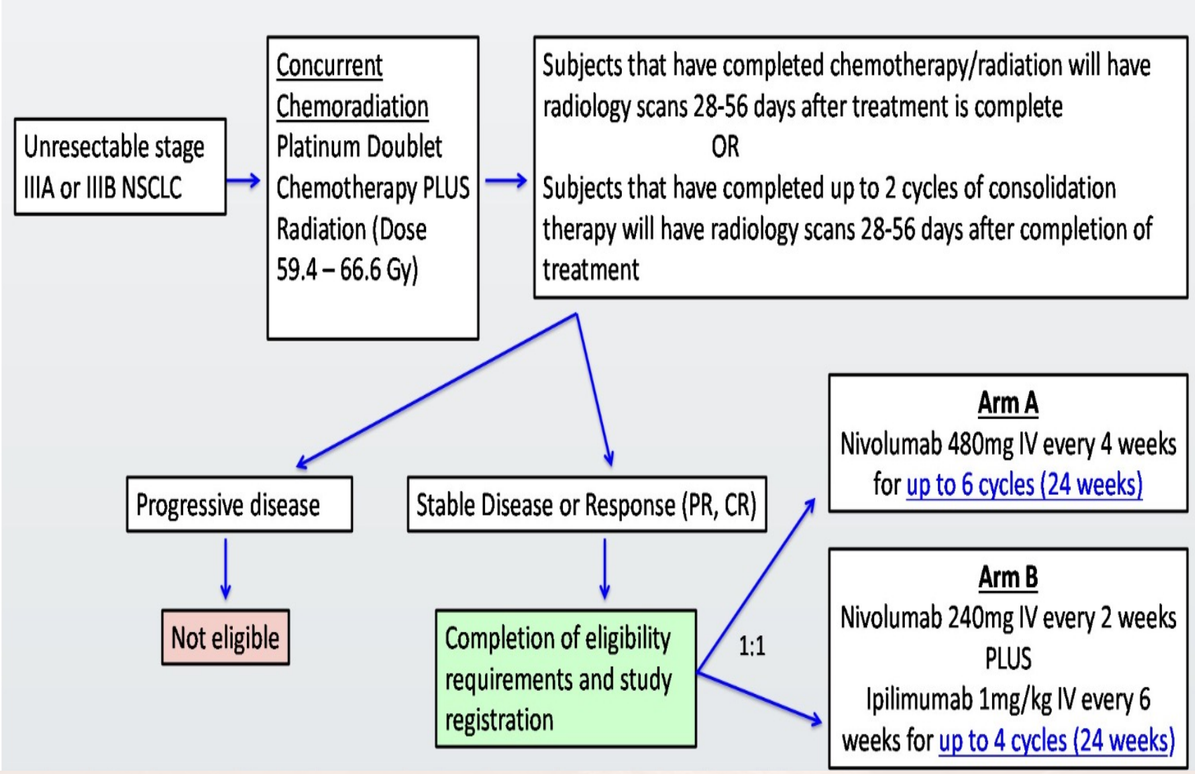


Adverse Event	Arm A (N=25)		Arm B (N=25)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
	number of patients (%)			
Any event	25 (100)	8 (32)	25 (100)	11 (44)
Treatment-related AE leading to discontinuation	4 (16)¶	2 (8)	10 (40)¶	7 (28)
Treatment-related AE leading to death	0	0	0	0
Occurred in ≥ 10% of patients in either group				
Fatigue	6 (24)	0	9 (36)	1 (4)
Cough	3 (12)	0	4 (16)	0
Dyspnea	3 (12)	0	9 (36)	0
Musculoskeletal pain	3 (12)	0	3 (12)	0
Diarrhea	1 (4)	0	5 (20)	1 (4)
Immune-mediated				
Any	11 (44)	4 (16)	15 (60)	8 (32)
Pneumonitis	4 (16)	1 (4)	5 (20)	4 (16)
Rash	5 (20)	3 (12)	3 (12)	1 (4)
Colitis	0	0	0	1 (4)^
Pancreatitis	0	0	0	1 (4)*
Amylase/lipase elevation	0	0	4 (16)	2 (12)*

Yan et al ASCO 2020. Abstr: 9010

CONSOLIDATION NIVO/IPI VS NIVO POST CONCURRENT CHEMORADIOTHERAPY: Big Ten Cancer Research Consortium/LUN16-081- UPDATE

	Arm A: Nivolumab (N: 54)	Arm B: Nivolumab & Ipilimumab (N: 51)
18 mos PFS	62.3%	67%
Median PFS	25.8 mos	25.4 mos
18 mos OS	82.1 %	85.5 %
24 mos OS	76.6%	82.8%

	Arm A: Nivolumab (N: 54)	Arm B: Nivolumab & Ipilimumab (N: 51)
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%)

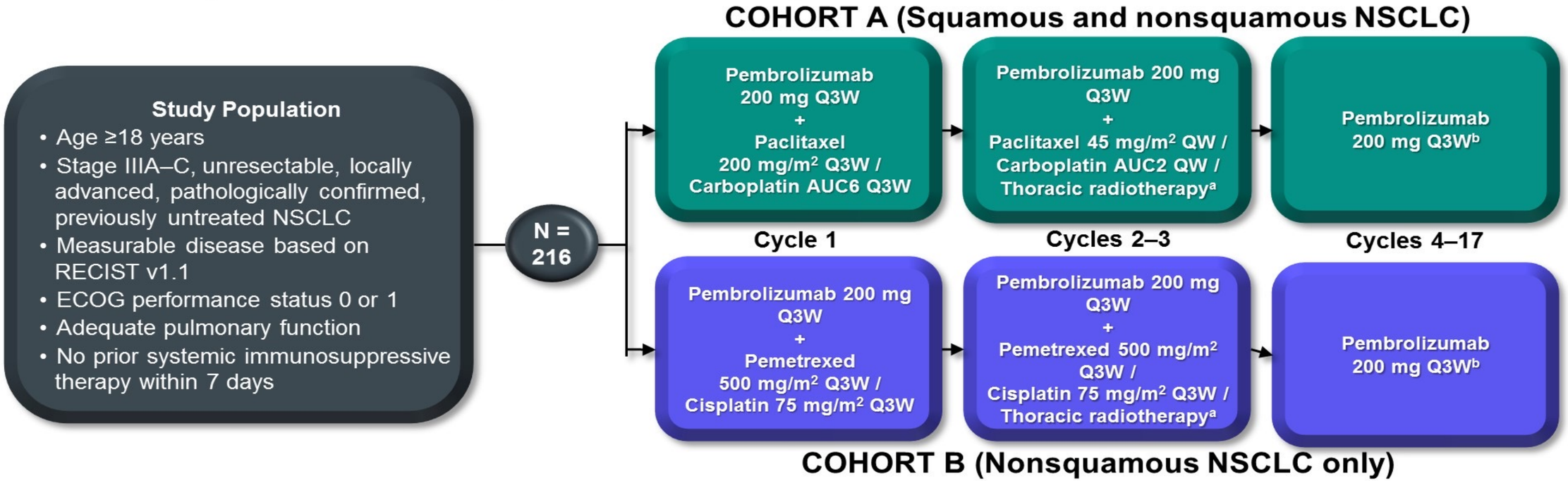
Durm GA et al. JCO 2022 at ASCO 2022.

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

Demographics and Baseline Characteristics

	Cohort A[a] (n = 112)	Cohort B[b] (n = 102)
Age, median (range), y	66.0 (46–90)	64.0 (35–81)
Men	76 (67.9)	62 (60.8)
ECOG PS 1	61 (54.5)	45 (44.1)
Former/current smoker	106 (94.6)	97 (95.1)
Squamous histology	75 (67.0)	N/A
Nonsquamous histology	37 (33.0)	102 (100)
PD-L1 TPS		
<1%	21 (18.8)	28 (27.5)
≥1%	66 (58.9)	40 (39.2)
Unknown	25 (22.3)	34 (33.3)

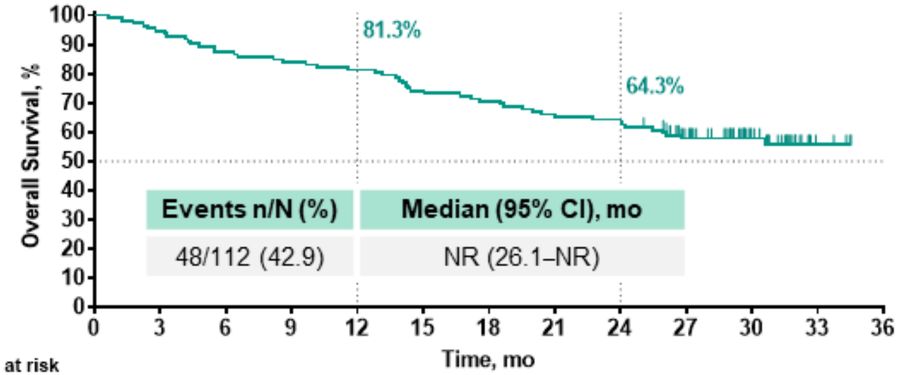
Data are n (%) unless specified otherwise.
[a]Squamous and nonsquamous histology. [b]Nonsquamous histology only.
Data cutoff date: Oct 18, 2021.

Two Year Update

S Jabbour. ASTRO 2022

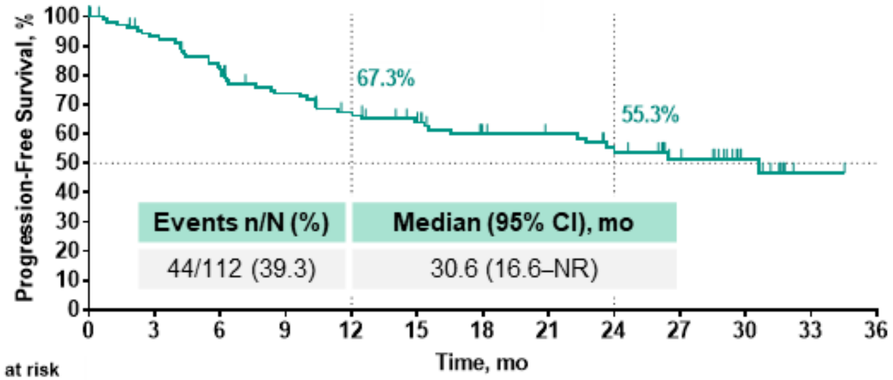
Progression-Free Survival and Overall Survival

Cohort A (squamous and nonsquamous histology)



No. at risk

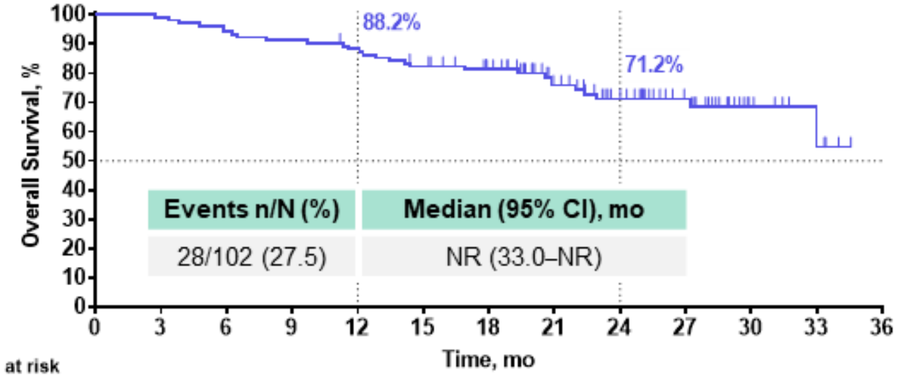
Cohort A	112	106	98	94	91	83	79	74	72	54	28	4	0



No. at risk

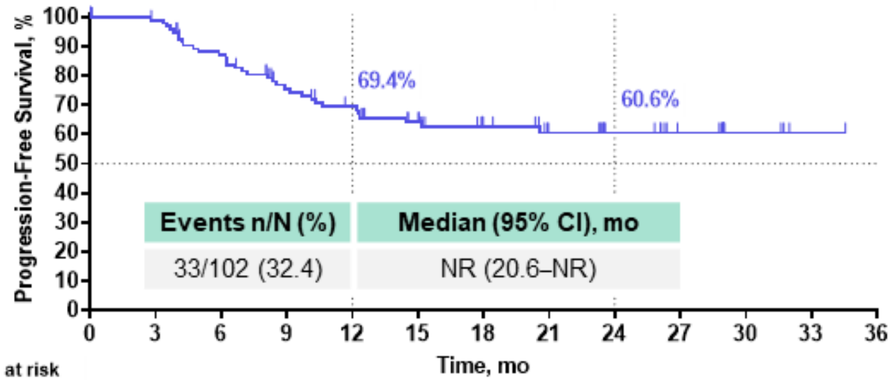
Cohort A	112	93	82	70	60	53	42	40	34	22	11	1	0

Cohort B (nonsquamous histology only)



No. at risk

Cohort B	102	101	96	93	89	82	73	53	40	26	9	4	0



No. at risk

Cohort B	102	93	79	62	54	44	33	26	19	13	4	1	0

Data cutoff date: Oct 18, 2021.

EA 5181: Trial Schema

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

Summary of Progression-Free Survival Estimates

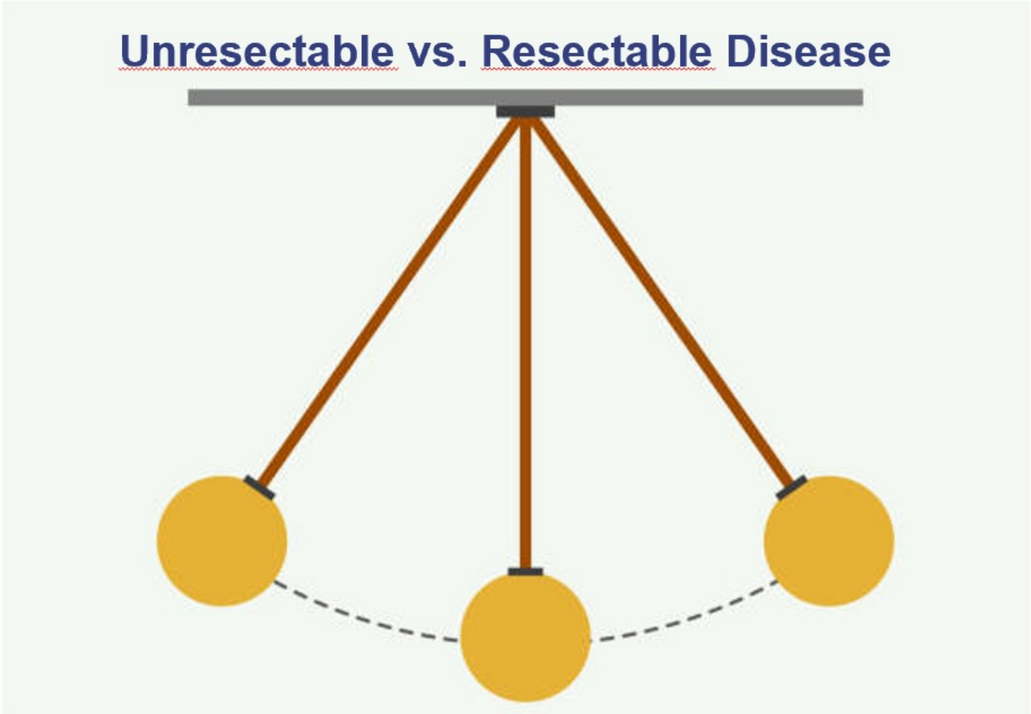
Trial	N	Median PFS (months)	1-year PFS (%)	2-year PFS (%)
PACIFIC	476	16.9	55.7	45.0
KN 799* Cohort A	112 (squamous & nonsquamous)	30.6	67.3	55.3
KN 799* Cohort B	102 (nonsquamous)	NR	69.4	60.6
PAC-6	117	13.3	49.6	35.3
PAC-RW	1399	21.7	62.4	48.2
Nivo	54	25.8	NR [62.3%, 18 mos]	NR
Ipi/Nivo	51	25.4	NR [67%, 18 mos]	NR

*T0 started pre CCRT

PERIOPERATIVE AND ADJUVANT CHEMOIMMUNOTHERAPY

Shifting Paradigms in Stage III NSCLC?

CRT + consolidative Immunotherapy



Neoadj Chemo IO + Surgery

2017- First PACIFIC publication

2022 - Checkmate-816
2023 - KEYNOTE-671

Courtesy of/Adapted from slide by Dr. Kristin Higgins

MAIN STUDIES IN THE PERIOPERATIVE AND ADJUVANT SETTING

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Trial	Setting	Drug	Accrual	Primary Endpoint	HR	Median EFS/DFS (ICI vs placebo)	OS
Impower-010 ★	Adjuvant	Atezolizumab	1,280 in 35 months	DFS	0.66 (0.50,0.88)	NR vs 35.3 months	76.8% vs 67.5% (5 years)
PEARLS (KN-091)	Adjuvant	Pembrolizumab	1,177 in 52 months	DFS	0.73 (0.60,0.89)	58.7 vs 34.9 months	82% (3 year)
CheckMate-816	Neoadjuvant	Nivolumab	773 in 30 months	EFS & pCR	0.63 (0.45,0.87)	31.6 vs 20.8 months	82.7% (2 year)
KEYNOTE-671	Perioperative	Pembrolizumab	797 in 44 months	Dual EFS & OS	0.58 (0.46,0.72)	NR vs 17.0 months	67.1% vs 51.5% (4 years)
AEGEAN	Perioperative	Durvalumab	802 in 39 months	EFS & pCR	0.68 (0.53,0.88)	NR vs 25.9 months	Not reported
CheckMate -77T	Perioperative	Nivolumab	461 Pts	EFS	0.58	NR vs 18.4 months	Not reported

References: **Impower-010:** Felip E, Lancet 2021; 398: 1344-1357 and Felip E WCLC 2022. **PEARLS:** OK'Brien M, Lancet Oncol 2022; 23: 1274-1286. **CheckMate-816:** Forde PM, N Engl J Med 2022; 386: 1973-1985 and Girard N, European Lung Cancer Congress 2023 abst 340. **KEYNOTE-671:** Wakelee H, N Engl J Med 2023; 389:491-503. **AEGEAN: Heymach JV,** N Engl J Med Oct 2023. **CheckMate-77T:** Cascone T, ESMO 2023.

★ **Data for OS from Impower-010 are underpowered and immature**

Adapted from/Courtesy of Dr. Raid Aljumaily

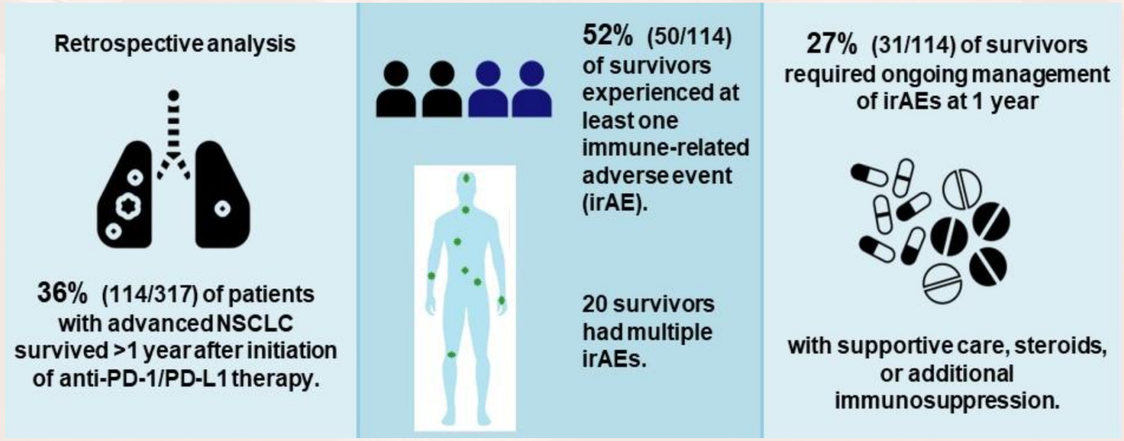
KN671: TOXICITY MATTERS

TRAEs

	Pembro Arm (n = 396)	Placebo Arm (n = 399)
Treatment-related AEs[a]	383 (96.7%)	381 (95.5%)
Led to discontinuation of all study treatment	54 (13.6%)	21 (5.3%)
Immune-mediated AEs and infusion reactions	103 (26.0%)	36 (9.0%)
Grade 3-5	26 (6.6%)	6 (1.5%)
Serious	24 (6.1%)	6 (1.5%)

When does it occur?

	Neoadjuvant	Adjuvant
Pembro-Chemo		
G3-5 TRAEs	40.7%	11.7%
G3-5 irAEs	4%	3.4%
Chemotherapy Arm		
G3-5 TRAEs	36.8%	6%
G3-5 irAEs	0.3%	1.9%



26% pts on KN671 pembro arm had irAEs
37% ongoing at time of data cut-off
No toxicity data beyond 90 days collected

Burden of toxicity will factor into decisions

Spicer et al, ESMO 2023, Hsu, Naidoo et al, Oncologist 2020. Jarushka Naidoo, et al. ESMO 2023. KN 671 Discussion.

CHEMOTHERAPY FREE OPTIONS

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

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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

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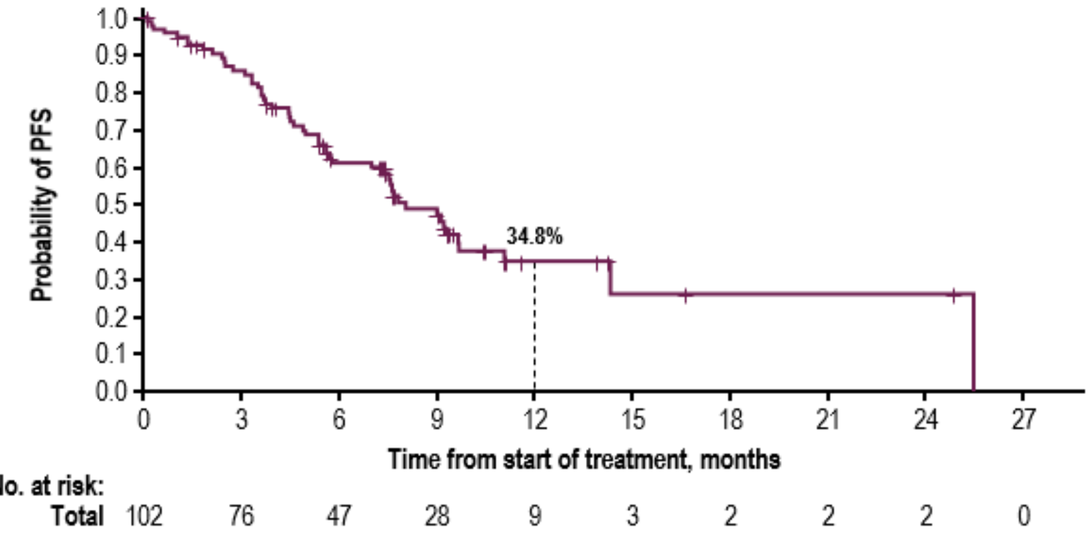
PFS

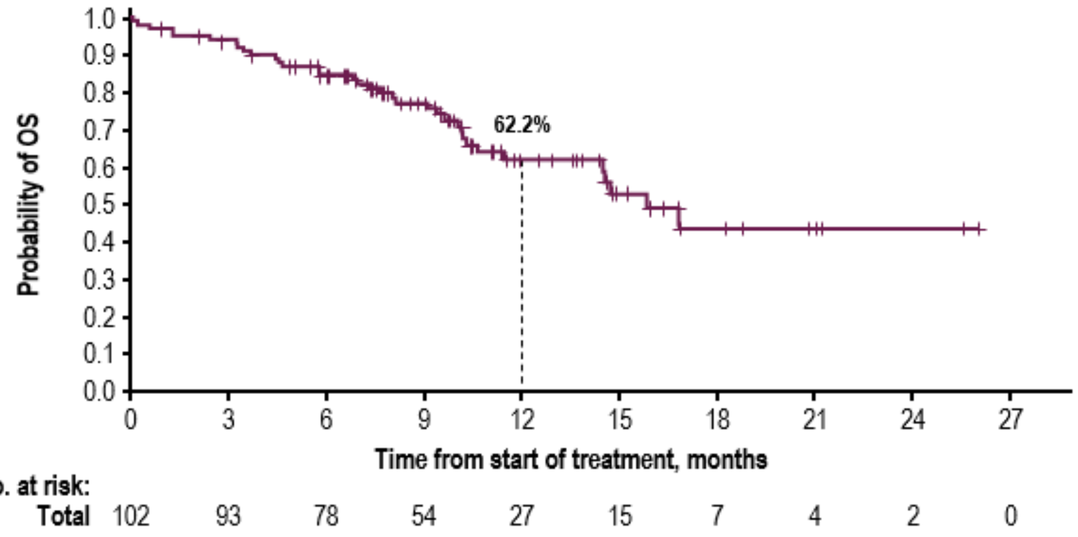
	Cohort A (standard RT)	Cohort B (palliative RT)	Total
No. events / no. patients (%)	26/59 (44.1)	25/43 (58.1)	51/102 (50.0)
Median PFS (95% CI)*, months	9.0 (5.6–NC)	7.6 (5.3–11.0)	8.0 (7.0–9.7)
12-month PFS rate (95% CI)†, %	40.2 (23.6–56.3)	29.3 (13.8–46.7)	34.8 (23.0–46.9)



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

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Key Inclusion

Step 1: Before RT

- Stage III NSCLC with PS 2

  OR

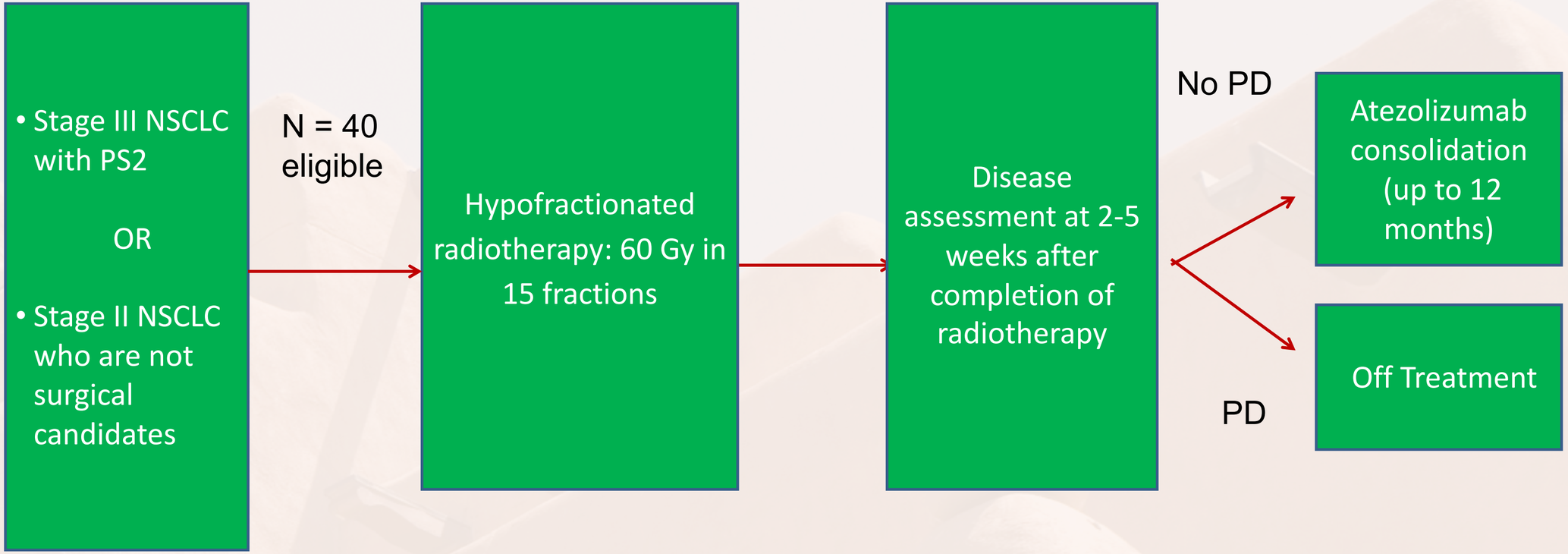
- Stage II NSCLC with PS0-2 and are not surgical candidates

Step 2: Post-RT & before Atezo.

- Received ≥ 45 Gy radiation and no PD

Exclusion Criteria

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



Total: 55
Hypofractionated RT: 31
Atezolizumab: 24

PI: Raid Aljumaily, MD
SWOG

KEYNOTE-867 Recruiting

Phase 3 study of SBRT ± pembrolizumab for patients with unresected stage I or II NSCLC (NCT03924869)

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Patients (N≈530)

- Previously untreated histologically/cytologically confirmed stage I or II NSCLC
- Does not undergo thoracic surgery due to medical illness[a] or unwillingness/refusal[b]
- No previous thoracic RT
  - Patients who received contralateral breast RT ≥5 years prior to randomization may still be eligible
- ECOG PS 0–2
- Candidate for SBRT and does not have an ultra-centrally located tumor
- No pneumonitis requiring steroids

R
1:1

17 cycles

SBRT to primary tumors (over ~2 weeks)[c]
+
pembrolizumab 200 mg IV Q3W

SBRT to primary tumors (over ~2 weeks)[c]
+
placebo IV Q3W

Stratification Factors

- Stage (I vs II)
- ECOG PS (0/1 vs 2)
- Geographic region (East Asia vs non–East Asia)
- Reason for not receiving surgery (medically inoperable vs refused surgery)

Primary End Points

- EFS[d]
- OS[e]

Secondary End Points

- Time to death or distant metastases
- Safety/tolerability
- HRQoL[f]

Exploratory End Points

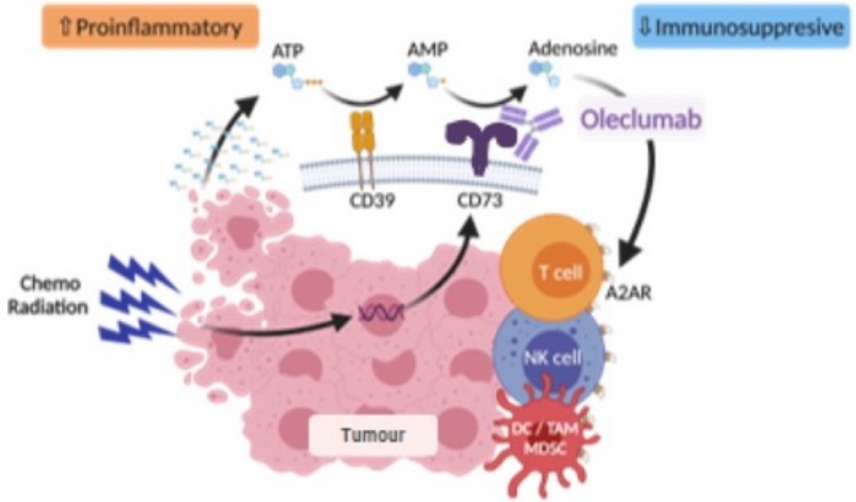
- Time to subsequent treatment
- Disease-specific survival
- Time to recurrence/progression on subsequent line of therapy

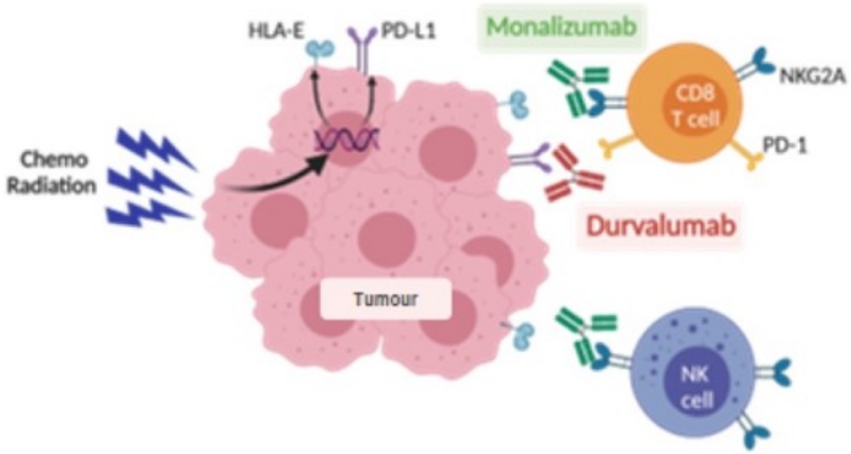
Estimated primary completion: April 11, 2025[g]

- [a]As determined by the site's multi-disciplinary tumor board [b]Medically operable patients who decide to treat with stereotactic body radiotherapy (SBRT) as definitive therapy rather than surgery are also eligible, if patient's unwillingness to undergo surgical resection is clearly documented [c]Peripheral tumors: 45–60 Gy in 3 fractions (preferred regimen), 48–50 Gy in 4 fractions or 50–55 Gy in 5 fractions (acceptable regimen); tumors abutting the chest wall: 48–50 Gy in 4 fractions or 50–55 Gy in 5 fractions; central tumors: 50–55 Gy in 5 fractions or 60–70 Gy in 8 fractions. [d]Up to approximately 58 months; defined as any of the following: radiographic recurrence by BICR, positive pathology by local assessment, physical examination by local assessment confirmed by positive pathology and/or radiographic recurrence by BICR. [e]Up to approximately 68 months [f]Using EORTC QLQ-C30 and QLQ-LC13. [g]Subject to change.
- ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03924869. Accessed June 7, 2022. Jabbour SK, et al. Presented at ASCO 2022. Abstract TPS8597.

NOVEL COMBINATIONS

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





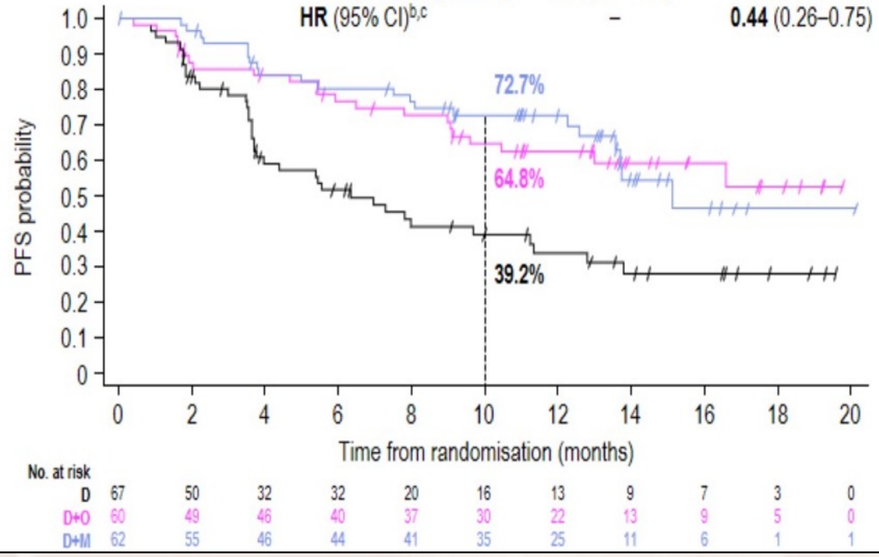
- RT induces expression of CD73 and HLA-E (NKG2A ligand), which inhibit antitumour immune response[1-4]
- Oleclumab inhibits CD73 to reduce extracellular adenosine production, thereby promoting antitumour immunity.[5] Oleclumab combined with durvalumab produced durable responses with manageable safety 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]

ATP, adenosine triphosphate; AMP, adenosine monophosphate; DC, dendritic cell; *EGFR*m, epidermal growth factor receptor mutant; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-(L)1, programmed cell death (ligand) 1; R/M HNSCC, recurrent/metastatic head and neck squamous cell carcinoma; RT, radiotherapy; TAM, tumour-associated macrophages

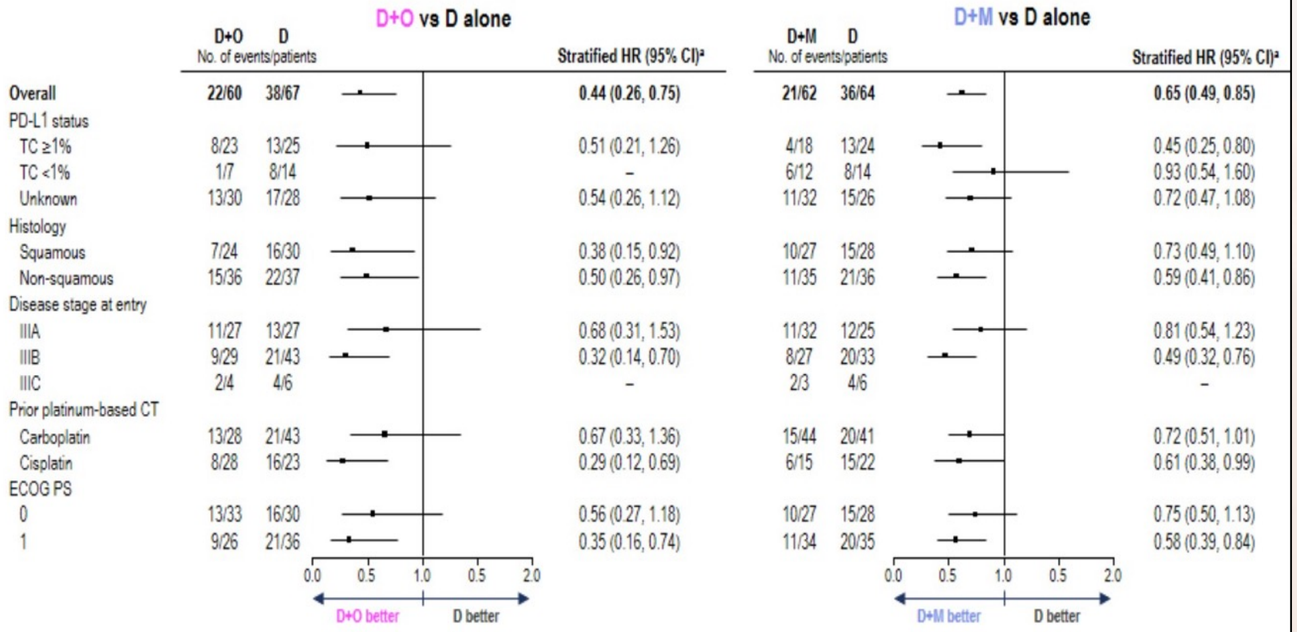
1. Wennerberg E, et al. Cancer Immunology Res 2020;8:465-478; 2. Tsukui H, et al. BMC Cancer 2020;20:411; 3. Nguyen AM, et al. Mol Cell Proteomics, 2020;19:375-389; 4. Battaglia NG, et al. J Immunol 2020;204:241.24; 5. Geoghegan JC, et al. MAbs 2016;8:454-467; 6. Bendell J, et al. J Clin Oncol 2021;39.no. 15_suppl:9047; 7. André P, et al. Cell 2018;175:1731–1743.e13; 8. Cohen RB et al. J Clin Oncol 38: 2020 (suppl; abstr 6516). Figures created with BioRender.com.

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)

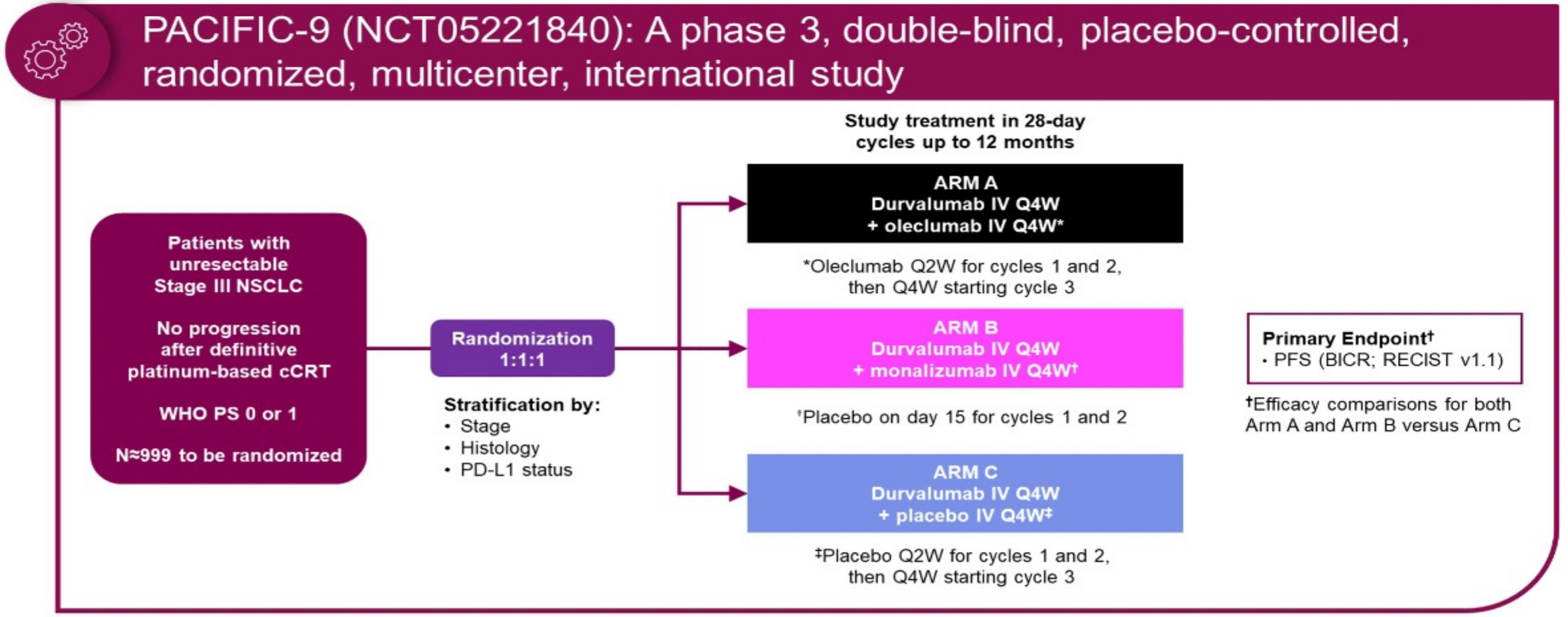


AESIs for durvalumab
(as-treated population)

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)

Martinez-Marti, et al. ESMO 2021.

PACIFIC-9



- 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.

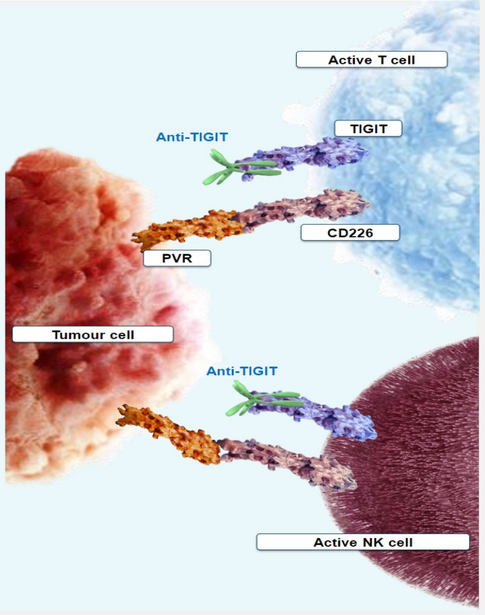
Barlesi et al. ASCO 2023

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

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

NCT05298423

KEYVIBE-006

Recruiting

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

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
	Pembrolizumab 200 mg IV Q3W + CCRT[b]	Pembrolizumab 200 mg IV Q3W + matching olaparib placebo PO BID[c]
	Pembrolizumab 200 mg IV Q3W + CCRT[b]	Pembrolizumab 200 mg IV Q3W + olaparib 300 mg PO BID[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.

Take Home Messages

- Durvalumab post concurrent CRT is the SOC for patients with Unresectable NSCLC

- Ongoing trials are evaluating whether:
  - PDL1 status predicts response in this population
  - The addition of immunotherapy to concurrent CRT improves outcomes

- 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 accruing large trials (eg EA5181) as well as those with novel targets

THANK YOU!

QUESTIONS?