Novel Treatments for Unresectable Stage III NSCLC

Edgardo S. Santos, MD, FACP
Medical Oncology-Thoracic
Clinical Associate Professor
Charles E. Schmidt School of Medicine/Florida Atlantic University
Treasurer, FLASCO
President, FLASCO Foundation

July 15, 2023

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

OLA
Oncology Latin American Association

Clinical case.

67-year-old female presented with SOB and cough to ER. CXR revealed an opacification in the right mediastinum. CT chest w contrast revealed a RUL lesion 2.5 cm and bulky lymphadenopathy (4 cm) in the R mediastinum and 2.1cm LN in the subcarina. Patient underwent bronchoscopy and tissue confirm the presence of adenocarcinoma at the subcarinal level; PET CT scan revealed no metastatic disease (cT1cN2M0, stage IIIA). ECOG PS 0. Co-morbid conditions: HTN and hyperlipidemia. TMP revealed EGFR(-), ALK (-), and PD-L1 80%.

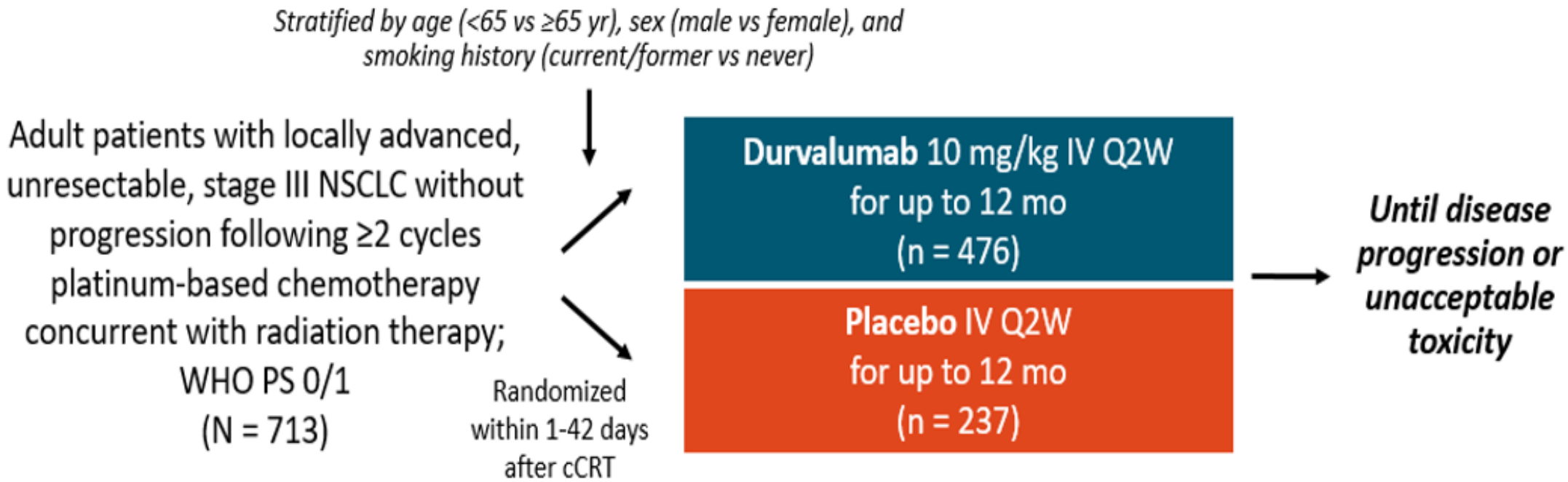
All the following therapeutic approaches may be acceptable except:

1. Neoadjuvant nivolumab plus chemotherapy followed by surgery.
2. cCRT followed by Durvalumab
3. Single agent immunotherapy
4. Sequential chemotherapy followed by cCRT followed by durvalumab.

Background.....

PACIFIC Trial

- Randomized, double-blind, placebo-controlled phase III trial

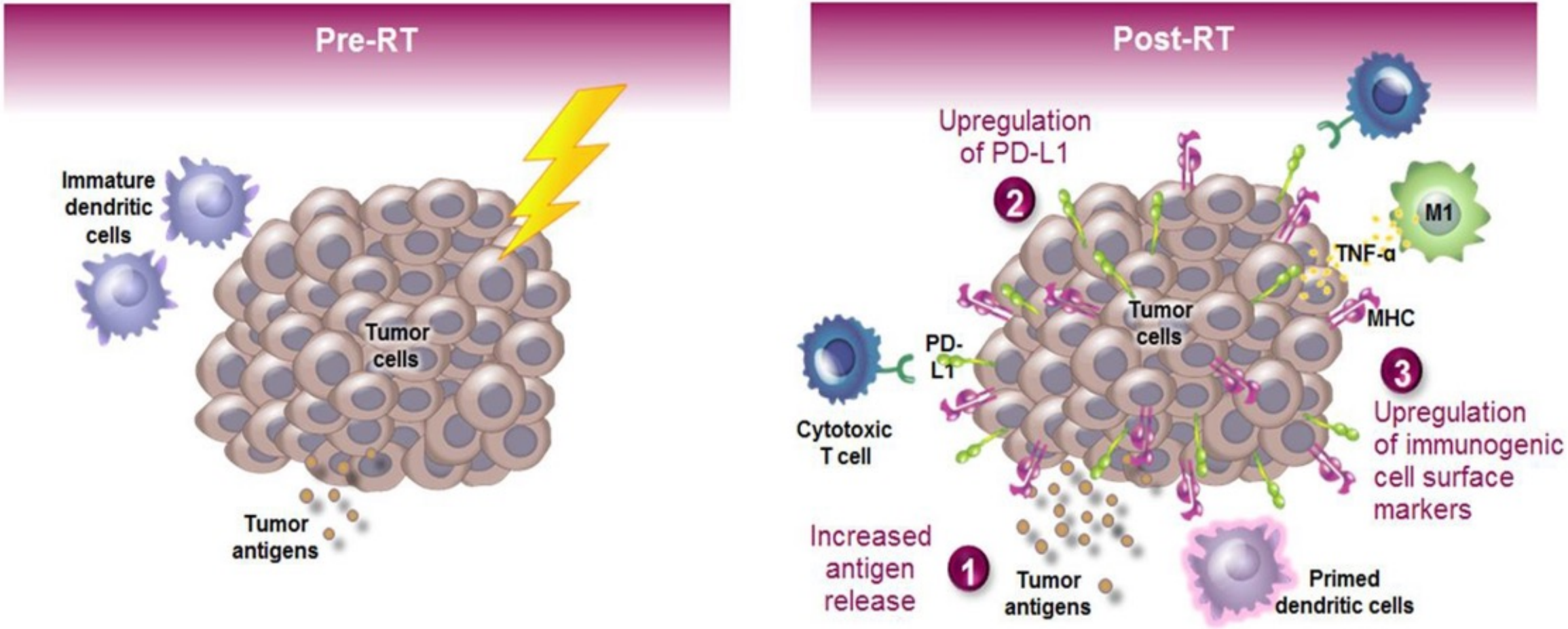


Patients enrolled regardless of PD-L1 status. If available, pre-cCRT tumor tissue archived for PD-L1 testing.

Spigel DR et al. ASCO 2021; abstr 8511

What Does RT Bring to the Table?

- Radiotherapy induces multiple immunomodulatory changes that may influence the effectiveness of immunotherapy



M1, tumor-associated macrophage; MHC I, major histocompatibility complex I; PD-L1, programmed cell death-ligand 1; TNF-α, tumor necrosis factor alpha.

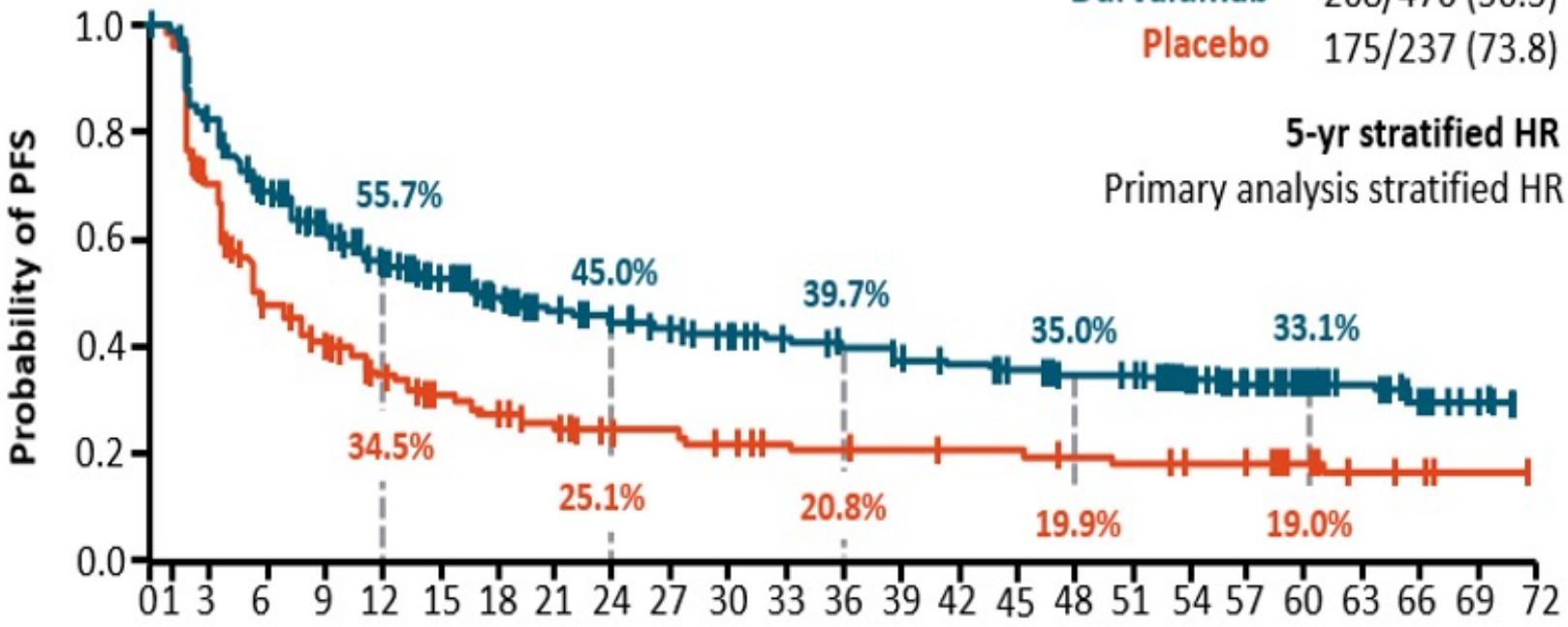
1. Daly ME, et al. *J Thorac Oncol*. 2015;10(12):1685-1693. 2. Kaur P, Asea A. *Frontiers Oncol*. 2012;2:191. 3. Deng L, et al. *J Clin Invest*. 2014;124(2):687-695.

5-year update: PFS

	Events/Patients, n/N (%)	Median PFS, Mo (95% CI)
Durvalumab	268/476 (56.3)	16.9 (13.0-23.9)
Placebo	175/237 (73.8)	5.6 (4.8-7.7)

5-yr stratified HR (95% CI): 0.55 (0.45-0.68)

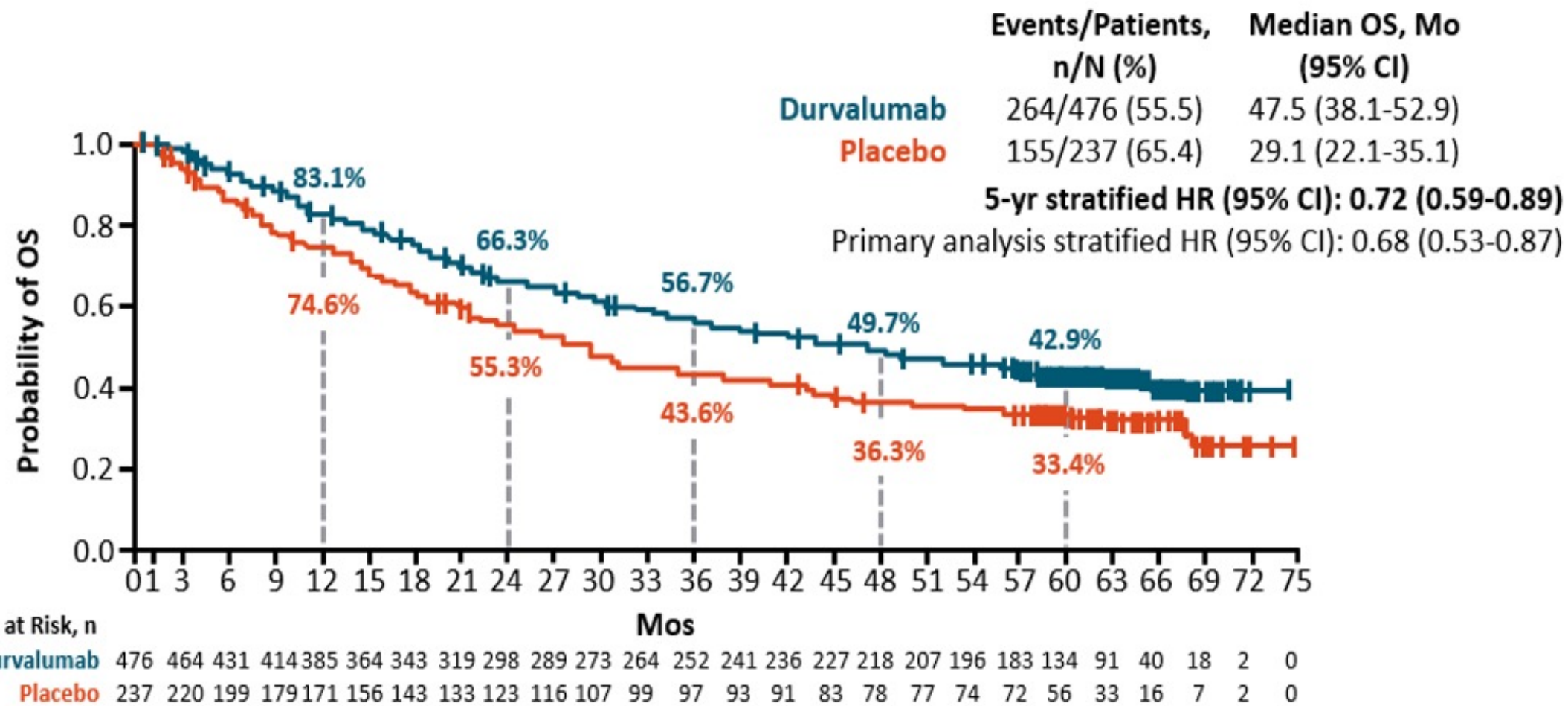
Primary analysis stratified HR (95% CI): 0.52 (0.42-0.65)



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

Spigel DR et al. ASCO 2021; abstr 8511

5-year update: Overall Survival



Spigel DR et al. ASCO 2021; abstr 8511

PACIFIC into Perspective….

	Albain	RTOG 0617	PACIFIC	PACIFIC
Arm	CCRT→Resection	CCRT (60 Gy)	CCRT	CCRT→durva
Median follow up	1.88 yrs	5.1 yrs	5.0 yrs	5.0 yrs
OS (median)	23.6 mos	28.7 mos	29.1 mos	47.5 mos
5-year OS	NR	32.1%	33.4%	42.9%
5-year PFS	22%	23%	19%	33.1%

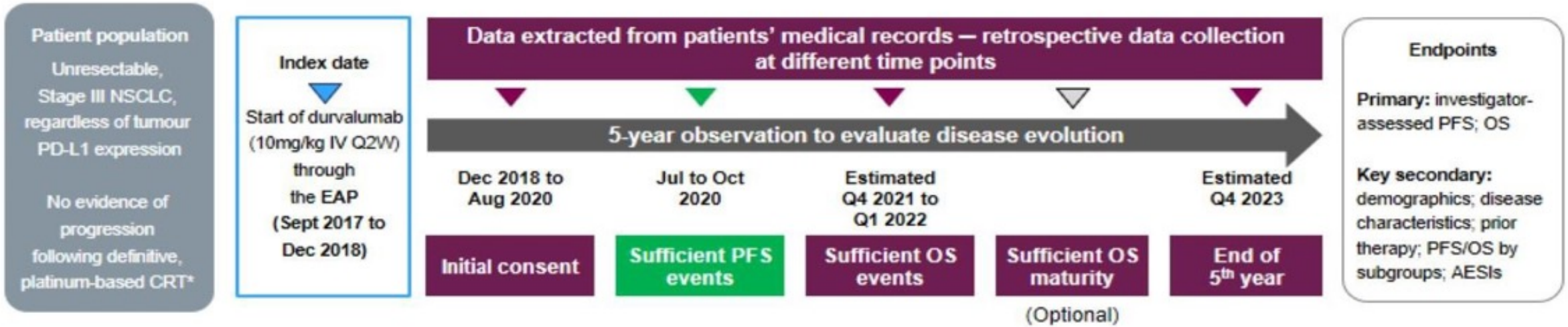
PACIFIC: Summary

- Durvalumab demonstrated improvements in PFS and OS versus placebo.
- Patients who received durvalumab had a lower incidence of new lesions including brain metastases compared with placebo.
- No new safety signals were identified.
- For patients with unresectable Stage III NSCLC who have not progressed post 2 cycles of definitive chemoradiation, durvalumab is FDA approved and category 1 on NCCN.

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

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

PACIFIC-R DATA

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 <IIIB; [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

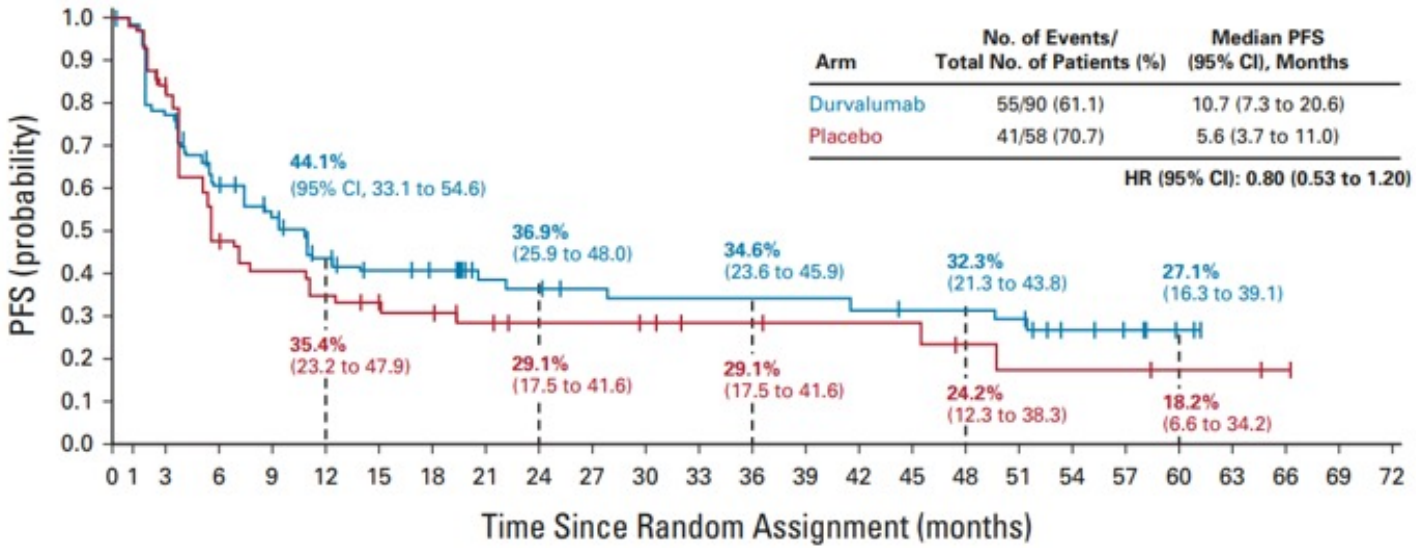
	PACIFIC-R FAS	PACIFIC trial (durva. arm)[1]
PFS	N=1,399	N=476
Total events, N (%)	737 (52.7)	268 (56.3)†
Progression per RECIST	456 (32.6)	
Progression per physician assessment	170 (12.2)	
Progression, assessment unknown	30 (2.1)	
Deaths in absence of progression	81 (5.8)	
Median PFS, months	**21.7**	**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.

Gaps after PACIFIC and How to Improve

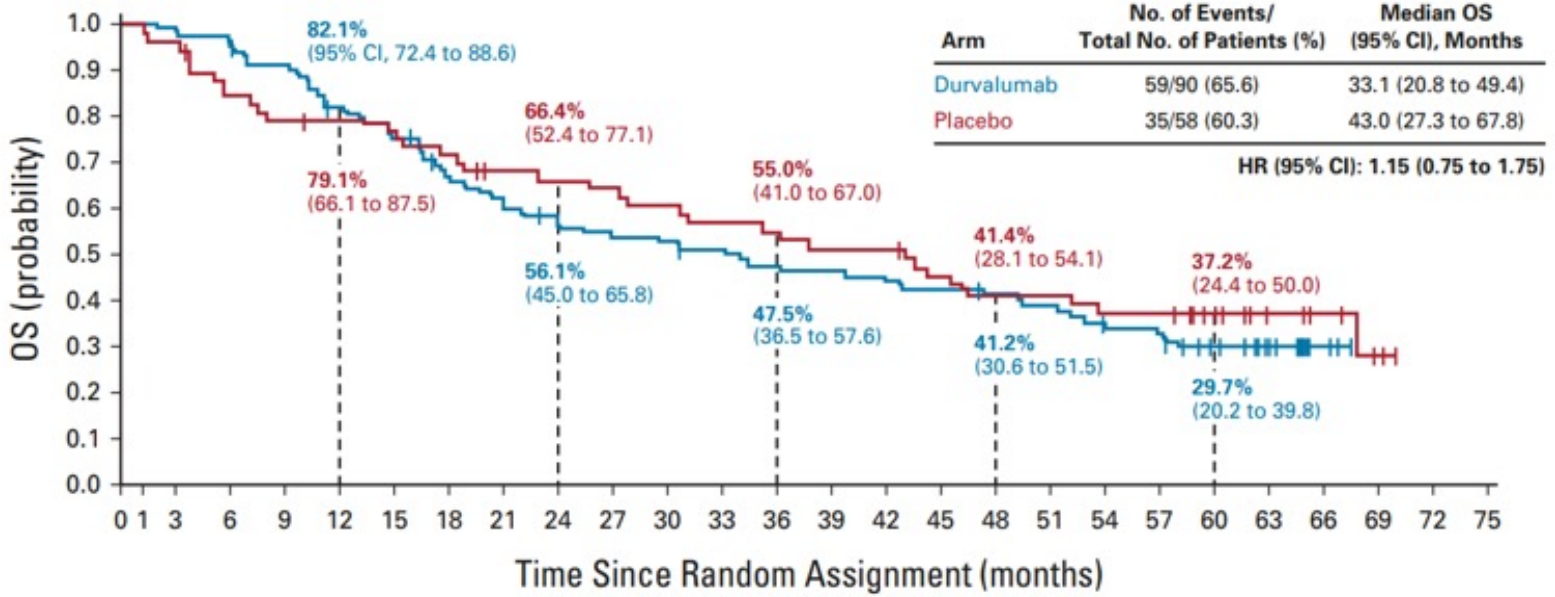
- Patients with limited KPS
- Concurrent immunotherapy with chemoRT
- Neoadjuvant chemoimmunotherapy prior to chemoRT
- Novel adjuvant therapies

PACIFIC: 5-Year PFS and OS in PD-L1 <1



Arm	No. of Events/ Total No. of Patients (%)	Median PFS (95% CI), Months
Durvalumab	55/90 (61.1)	10.7 (7.3 to 20.6)
Placebo	41/58 (70.7)	5.6 (3.7 to 11.0)

HR (95% CI): 0.80 (0.53 to 1.20)



Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	59/90 (65.6)	33.1 (20.8 to 49.4)
Placebo	35/58 (60.3)	43.0 (27.3 to 67.8)

HR (95% CI): 1.15 (0.75 to 1.75)

Spigel, JCO 2022

PACIFIC: PD-L1 Limitations

- These include the use of tumor samples collected before CRT to determine PD-L1 expression.
- PD-L1–assessable samples were not available for 37% of randomly assigned patients.
- Relatively small number of patients with PD-L1 TC expression < 1% (n = 148).
- The placebo arm appeared to overperform with respect to OS among patients with PD-L1 TC expression < 1% compared with the full PACIFIC ITT population which may have been driven by imbalances in potentially prognostic baseline factors.

Patients with limited Karnofsky's PS

Standard of Care: ~~CCRT~~→durvalumab

Sequential therapy: chemo→ RT→durvalumab[1]

RT alone: RT→durvalumab[2]

Study	Type	Cohort 1	Cohort 2	Study Size	Start	Estimated completion
[1]PACIFIC-6	Phase II	chemo→RT→ Durva (PS 0-1)	chemo→RT→ Durva (PS 2)	117	April 2019	April 2023
[2]DUART	Phase II	RT (60 Gy^) →Durva	RT (40-54 Gy^) →Durva	150	Jan 2020	Nov 2022

^hypofractionation allowed

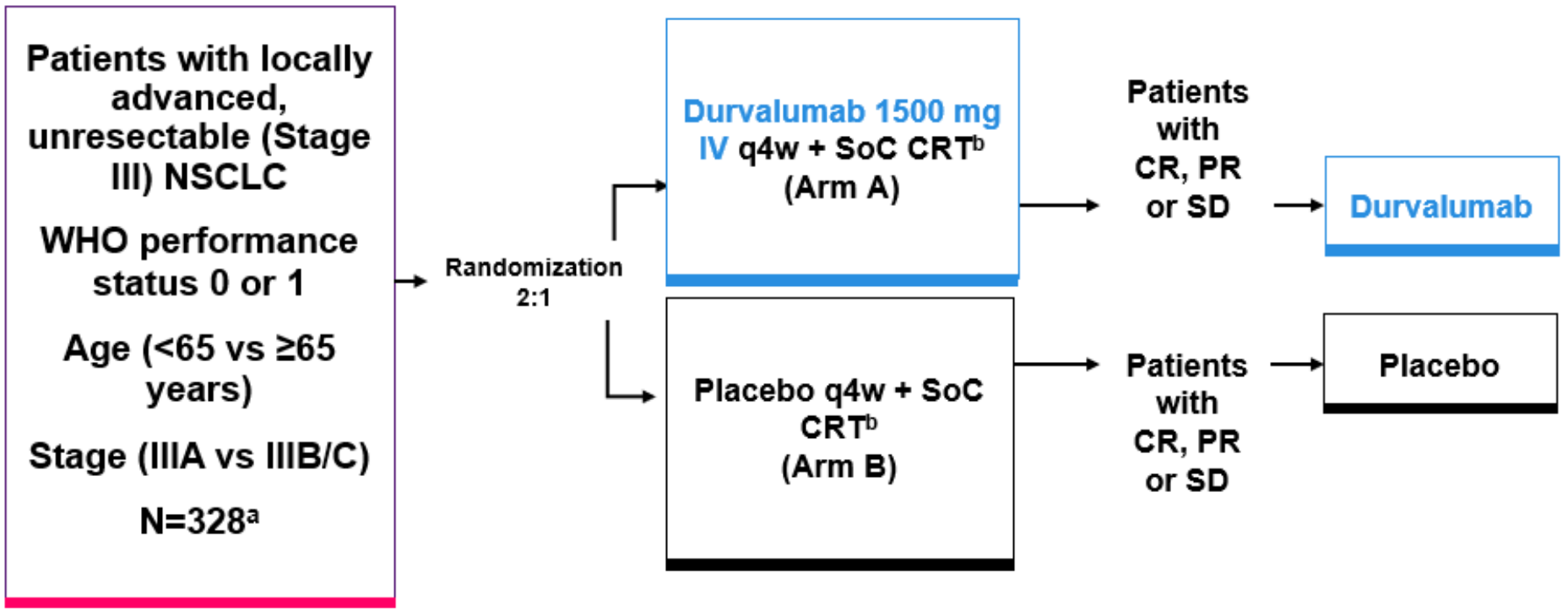
Concurrent immunotherapy with chemoRT

PACIFIC → Standard of Care: CCRT→ Durvalumab

[1,2]Durvalumab + CCRT → Durvalumab ← (PACIFIC 2)

PACIFIC-2 (ex-US)

Phase III, randomized, double-blind, multicenter, global study[1,2]



Primary endpoint

- PFS using BICR assessments per RECIST v 1.1

Secondary endpoints

- ORR
- OS
- OS24
- DoR
- DCR
- PFS2
- TTDM
- CR
- PK
- Health-related QoL
- Immunogenicity

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

BICR = blinded independent central review; CRT = chemoradiotherapy; CR = complete response; DCR = disease control rate; DoR = duration of response; Gy = gyron; IV = intravenous; NSCLC = non-small-cell lung cancer; ORR = overall response rate; OS = overall survival; OS24 = overall survival at 24 months; PD = progressive disease; PFS = progression-free survival; PFS2= time from randomization to second progression; PK = pharmacokinetics; PR = partial response; Q4W = every 4 weeks; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SoC = standard of care; TTDM = time to death or distant metastasis; WHO = World Health Organization.

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

Concurrent immunotherapy with chemoRT

PACIFIC → Standard of Care: CCRT→ Durvalumab

[1,2]Durvalumab + CCRT → Durvalumab ← (PACIFIC 2)

[3]Nivo +CCRT → Nivo ← (NICOLAS)

[4]Nivo/Ipi +CCRT → Nivo ← (Checkmate 73L)

Study	Type	Arm 1	Arm 2	Study Size	Start	Est. completion
[1]PACIFIC-2	Randomized	Durva+CCRT →Durva	Placebo+CCRT →Placebo	328	March 2018	June 2022
[2]NCT04092283	Randomized	Durva+CCRT →Durva	Placebo+CCRT →Durva	660	April 2020	October 2028
[3]NICOLAS	Phase II, Safety/Efficacy	n = 79	mF-U: 21.0 mos	mPFS: 12.7 mos	mOS: 38.8 mos	2-yr OS: 63.7%
CheckMate 73L	Randomized	Nivo + CCRT+ Ipi (Arm A)	Nivo+CCRT (Arm B) Durva + CCRT (Arm C)	888	July 2019	June 2025

Neoadjuvant Chemoimmunotherapy prior to ChemoRT

PACIFIC → Standard of Care: CCRT→durvalumab

Chemo[1]Nivo→ CCRT[2] → Nivolumab
CCRT[2] → Observation

Study	Type	Arm A	Arm B	Study Size	Start	Est. completion
NCT04085250	Phase II, Randomized	ChemoNivo→ CRT→Nivo	ChemoNivo→ CRT→Observe	264	Nov 2019	Nov 2023

[1]chemo: docetaxel+cisplatin

[2]RT: Hypofractionated

Neoadjuvant Chemoimmunotherapy prior to ChemoRT

PACIFIC → Standard of Care: CCRT→durvalumab

Pembro/Chemo[1]→ CCRT + Pembro →Pembro

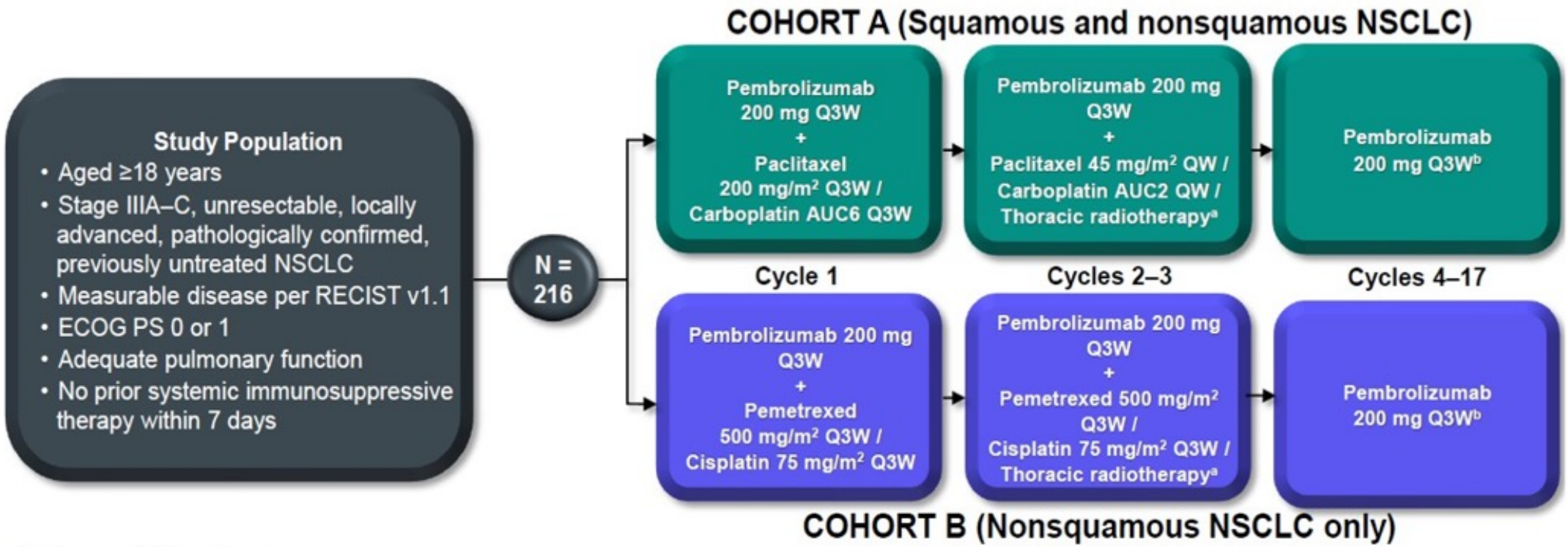
Study	Type	Cohort A	Cohort B	Study Size	Start	Est. completion
[1]Keynote-799	Phase II, nonrandomized	Pembro/Chemo[A] →PembroCRT→ Pembro	Pembro/chemo[B] →PembroCRT→ Pembro	217	Oct 2018	May 2023

[A]chemo: carboplatin+paclitaxel

[B]chemo: cisplatin+pemetrexed

Jabbour SK et al. JAMA Oncol. 2021; 7(9):1-9.

KEYNOTE-799 (NCT03631784)



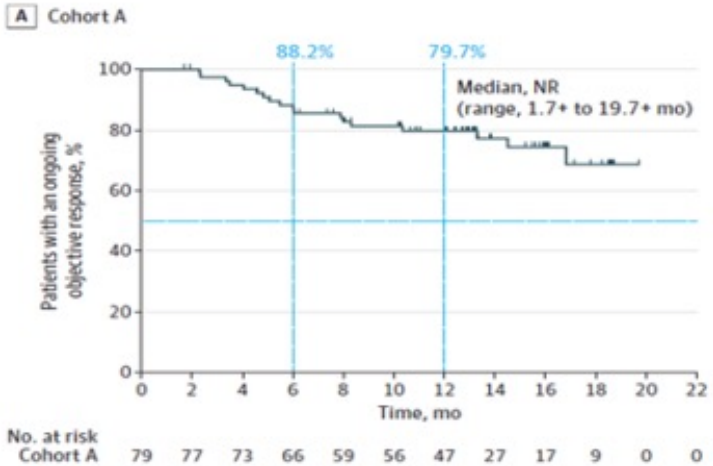
Primary Objectives
- ORR per RECIST version 1.1 by BICR
- Percentage of patients who develop grade ≥3 pneumonitis

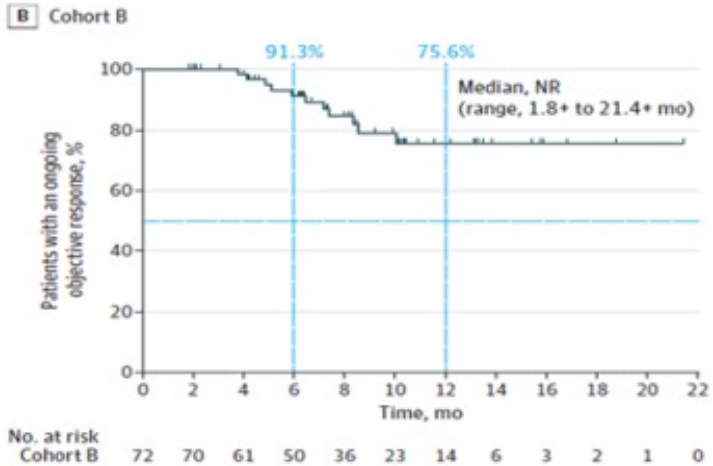
Secondary Objectives
- PFS, OS, safety

Statistical Analysis Details
- Efficacy assessed in all patients with first study dose before or on October 31, 2019 (PE population)
- Safety assessed in all patients in the as-treated population

KEYNOTE-799

- Primary endpoint:
  - Objective response rate
  - Grade 3-5 pneumonitis incidence





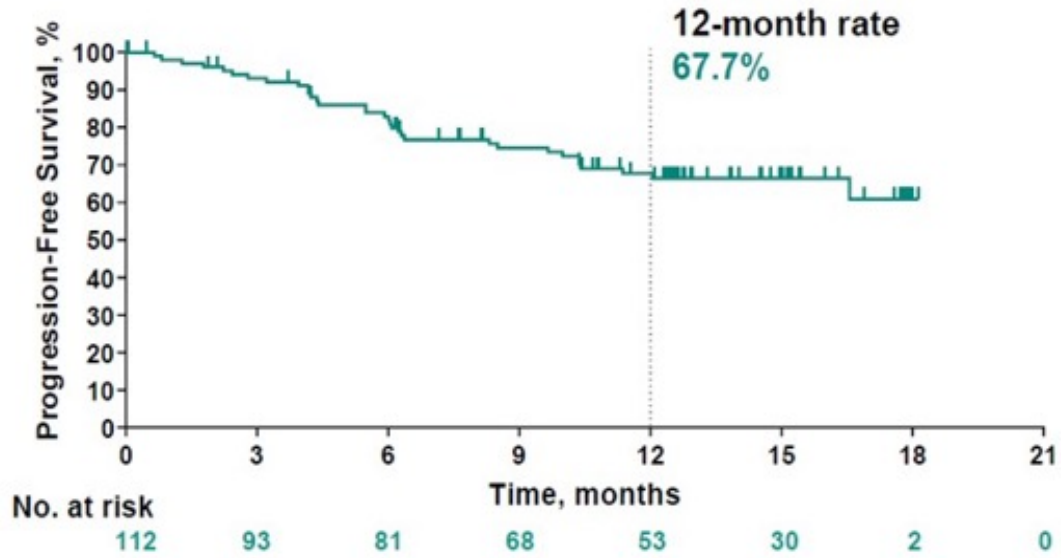
	No. (%)			
Adverse event	Cohort A (n = 112)		Cohort B (n = 102)	
Treatment-related adverse event[a]	105 (93.8)		99 (97.1)	
Grade 3-5	72 (64.3)		51 (50.0)	
Led to discontinuation of any treatment	38 (33.9)		19 (18.6)	
Led to death	4 (3.6)[b]		1 (1.0)[c]	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Pneumonitis	22 (19.6)	7 (6.3)	19 (18.6)	5 (4.9)
Radiation pneumonitis	20 (17.9)	2 (1.8)	8 (7.8)	1 (1.0)

Jabbour SK et al. JAMA Oncol. 2021; 7(9):1-9.

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

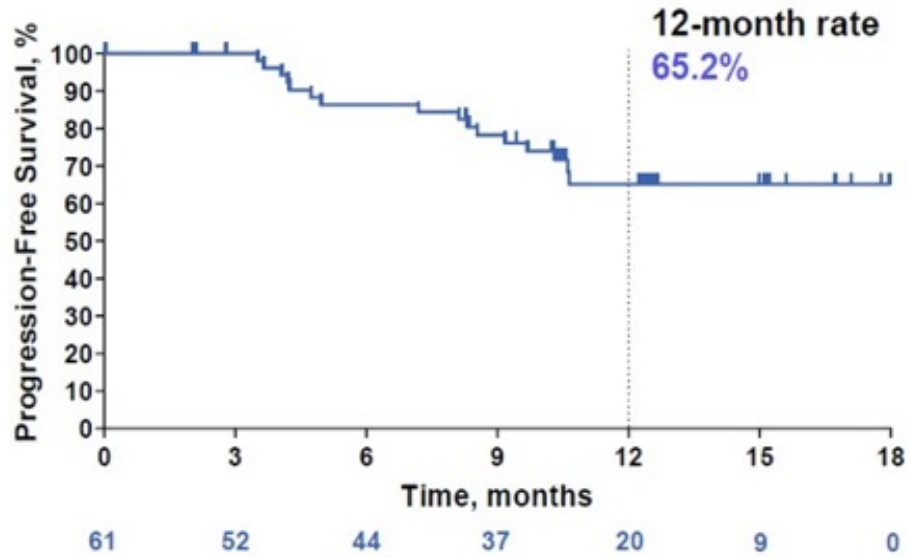
Cohort A[a]

n	Median (95% CI)
112	NR (16.6–NR)



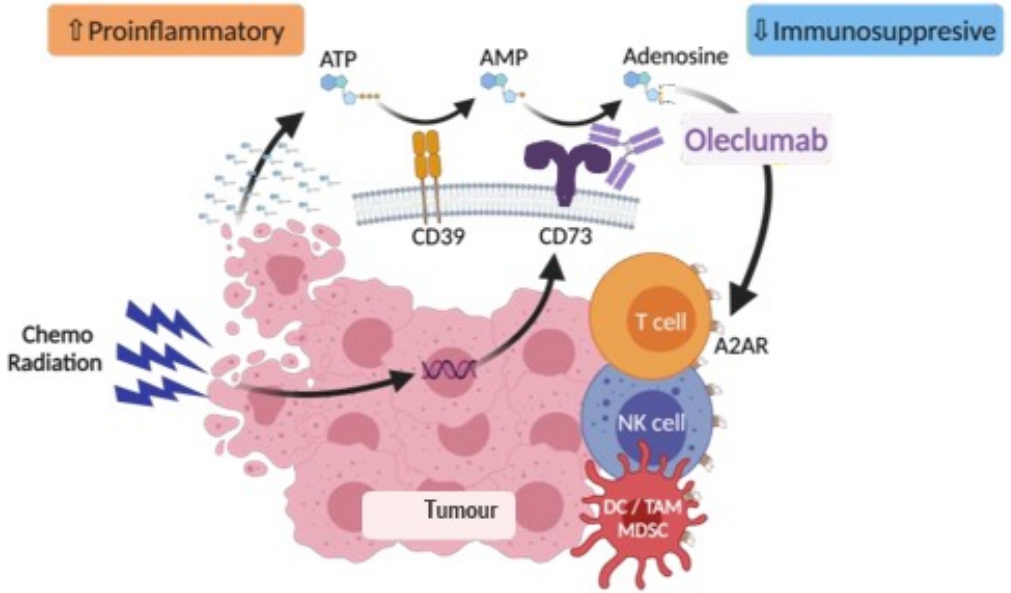
Cohort B[b]

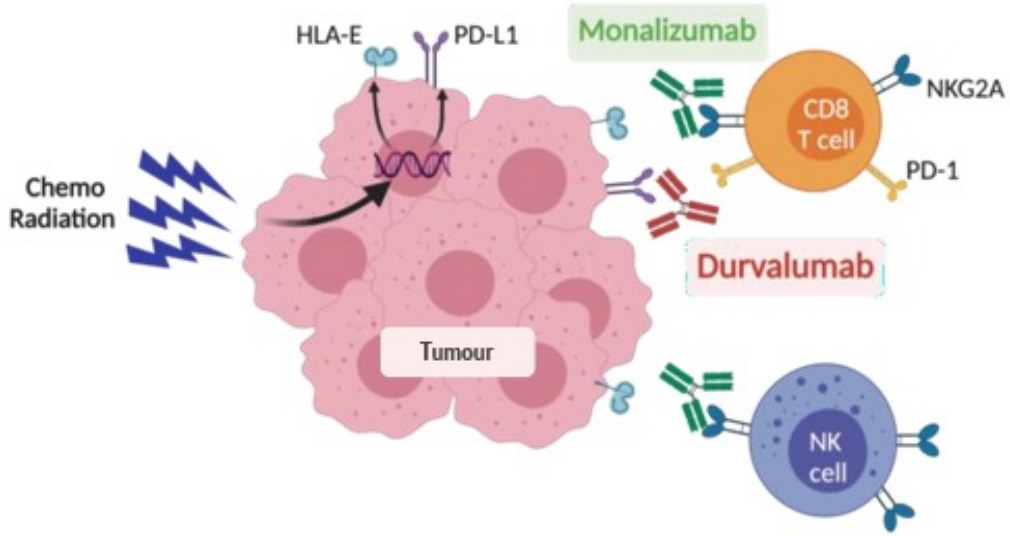
n	Median (95% CI)
61	NR (10.6–NR)



Adverse event	Cohort A (n = 112)		Cohort B (n = 102)	
Occurring in ≥15% of patients in either cohort	Any grade	Grade 3-5	Any grade	Grade 3-5
Radiation pneumonitis	20 (17.9)	2 (1.8)	8 (7.8)	1 (1.0)

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



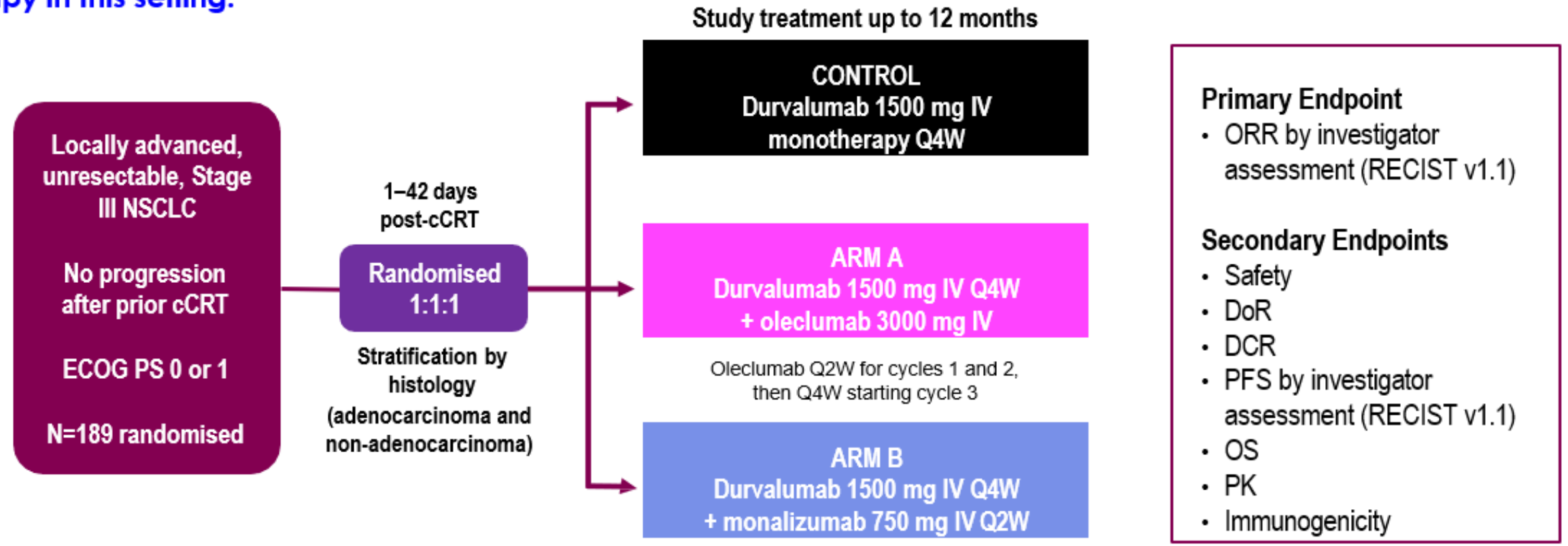


- RT induces expression of CD73 and HLA-E (NKG2A ligand), which inhibit antitumour immune response[1-4]
- Oleclumab inhibits CD73 to reduce extracellular adenosine production, thereby promoting antitumour immunity.[5] Oleclumab combined with durvalumab produced durable responses with manageable safety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

COAST: Combination Platform Study in Unresectable Stage III NSCLC. Phase 2, global, randomized open- label study of durvalumab alone or combined with the anti-CD73 mAb oleclumab or anti-NKG2A mAb monalizumab as consolidation therapy in this setting:



- 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)

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

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

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

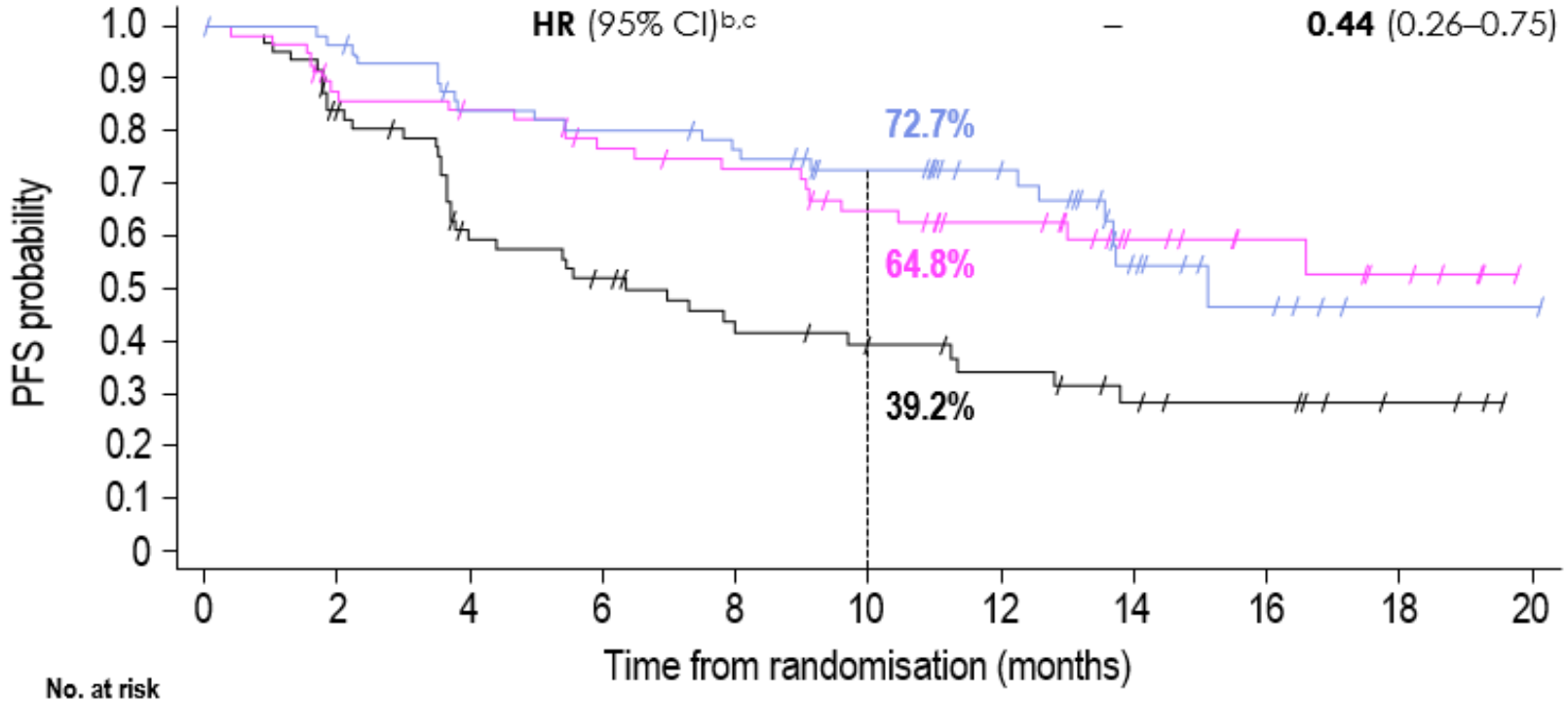
Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)

[a]Confirmed and unconfirmed responses; [b]95% CI by Clopper-Pearson exact method; [c]DCR at 16 weeks = CR + PR + SD for ≥16 weeks

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NA, not applicable; NE, not evaluable; NR, not reached; ORR, objective response rate; PR, partial response; PD, progressive disease; SD, stable disease

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)



No. at risk											
D	67	50	32	32	20	16	13	9	7	3	0
D+O	60	49	46	40	37	30	22	13	9	5	0
D+M	62	55	46	44	41	35	25	11	6	1	1

Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)

[a]Interim analysis was performed when all patients had a 10-month minimum potential follow-up; Kaplan-Meier estimates for PFS, PFS rate and 95% CIs [b]PFS HR and 95% CI estimated by Cox regression model, stratified by histology (adenocarcinoma and non-adenocarcinoma)

[c]Compared with the 67 and 64 patients in the D arm enrolled concurrently with patients in the D+O and D+M arms, respectively

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; mPFS, median PFS; NE, not estimable; NR, not reached

Conclusions

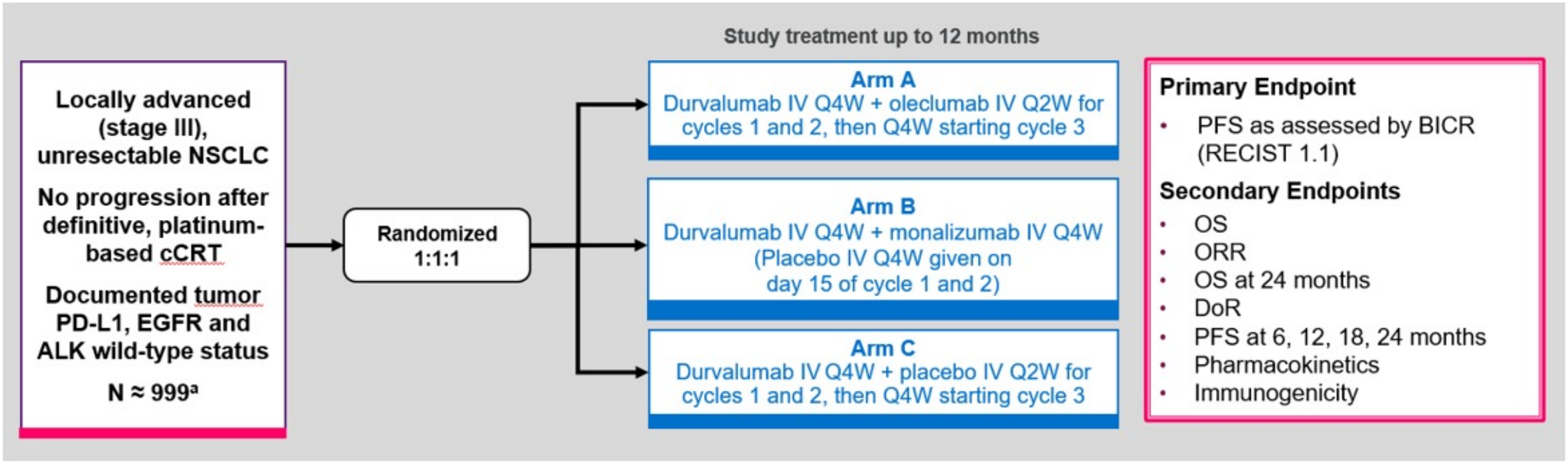
- COAST is the first randomised Phase 2 study to show evidence of improved outcomes with novel IO combinations in the PACIFIC setting
  - Interim data suggest that oleclumab or monalizumab combined with durvalumab can provide additional clinical benefit for patients with unresectable, Stage III NSCLC who have not progressed following cCRT
- Both combinations numerically increased ORR and significantly improved PFS versus durvalumab alone
  - PFS benefit with both combinations was observed across various subgroups, including those based on histology, ECOG PS, prior platinum-based CT, and PD-L1 status
- Safety profiles were consistent across arms, with no new safety signals identified in either combination arm
  - The incidence of AESIs for durvalumab, including pneumonitis, were similar across arms
- Additional translational analyses, including blood gene expression, IHC, and ctDNA, are ongoing

ctDNA, circulating tumour DNA; IHC, immunohistochemistry

These data support further evaluation of these combinations in a registration-intent study

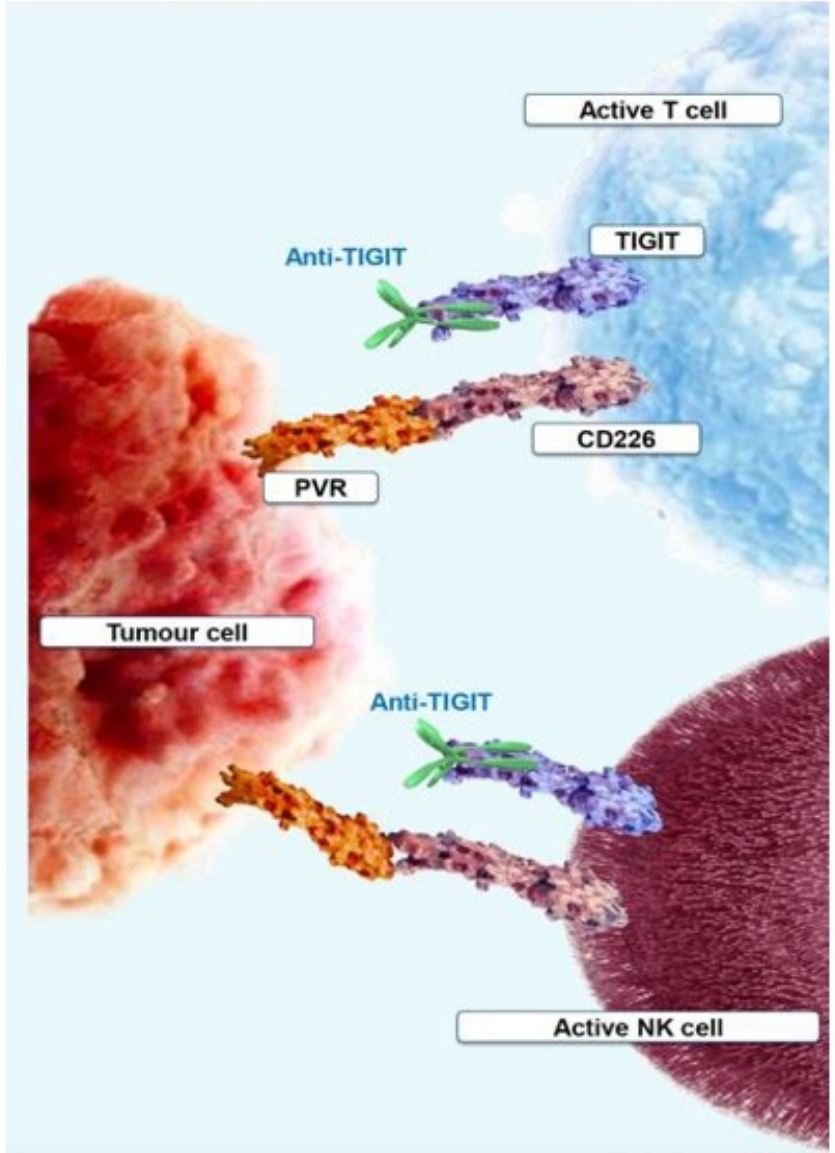
PACIFIC-9:

A Global Study to Assess the Effects of Durvalumab With Oleclumab or Durvalumab With Monalizumab Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small Cell Lung Cancer.

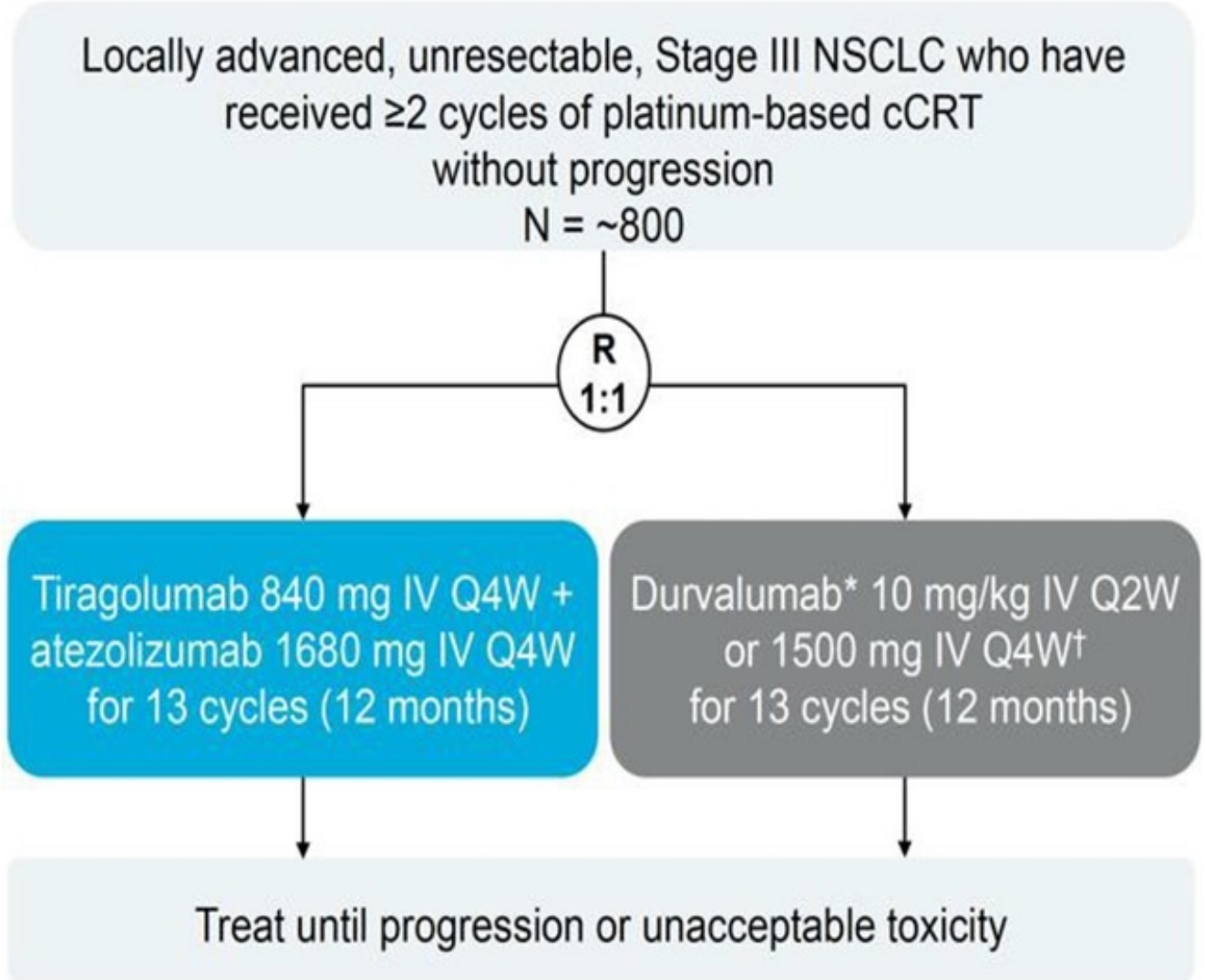


Anti-TIGIT Antibodies:

- TIGIT is a novel inhibitory checkpoint on activated T cells and NK cells.
- Tiragolumab is a fully human IgG1/kappa anti-TIGIT monoclonal antibody; blocks binding to its receptor PVR.
- Inhibition of TIGIT/PVR may amplify the durability / duration of anti-tumor response of anti-PD-L1/PD-1 antibodies



SKYSCRAPER- 03:



*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:

A Global Study to Assess the Effects of Durvalumab + Domvanalimab Following Concurrent Chemoradiation in Participants With Stage III Unresectable NSCLC.

Patients with unresectable, stage III NSCLC who have not progressed following definitive, platinum-based cCRT

Documented EGFR and ALK wild-type status

PD-L1 TC expression ≥1%

N≈860[a]

→ **Randomized 1:1**

Arm A
Durvalumab IV Q4W + domvanalimab (AB154) IV Q4W
for up to 12 months

Arm B
Durvalumab IV Q4W + placebo IV Q4W
for up to 12 months

Primary Endpoint

- PFS in PD-L1 ≥50% as assessed by BICR (RECIST 1.1)

Secondary Endpoints

- PFS in PD-L1 ≥1%
- OS
- Safety / tolerability
- ORR
- DoR
- PFS at 6, 12, 18 and 24 months
- Pharmacokinetics
- Immunogenicity

NOSCM
NEW ORLEANS SUMMER CANCER MEETING

July 14–16, 2023
The Roosevelt Hotel
New Orleans, Louisiana

18TH ANNUAL

New Orleans Summer Cancer Meeting

APPLYING PRECISION ONCOLOGY, EXPLOITING TUMOR MICROENVIRONMENT AND BREAKING DISPARITIES: ALL-IN-ONE FIGHTING AGAINST CANCER

PROGRAM DIRECTOR

Edgardo S. Santos Castillero, MD, FACP

Role of Targeted Therapies Following Chemo-RT

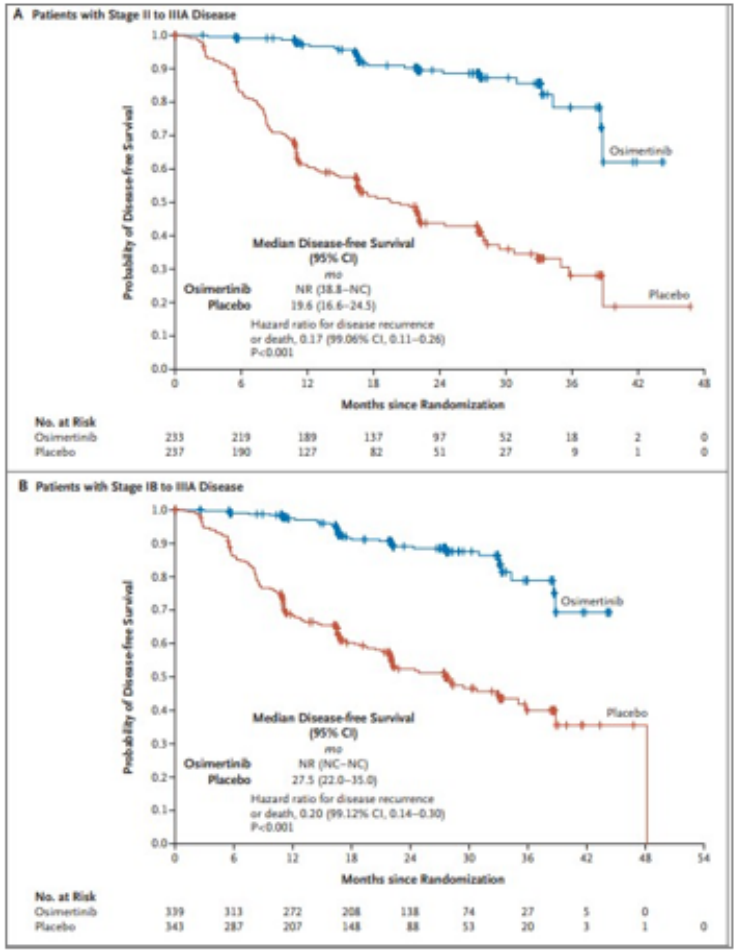
FLASCO

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

OLA

Rationale for Consolidation Targeted Therapy

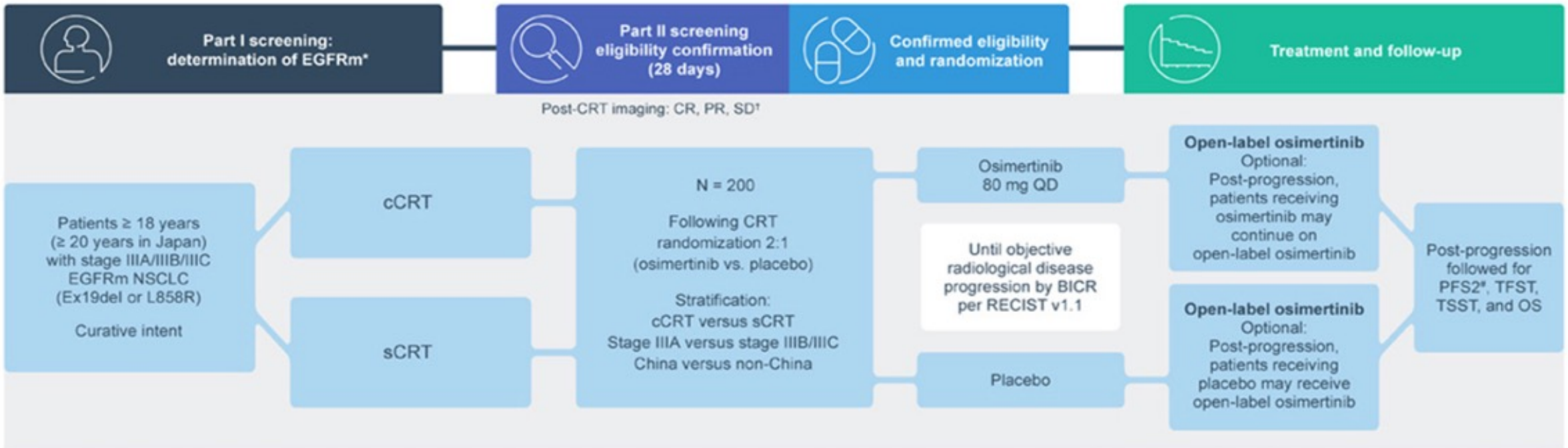
- Some patients are not candidates for consolidation immune therapy (e.g., transplant, autoimmune disease) or are at high risk for AEs.
- EGFR mutant patients may have worse outcomes after chemoradiation compared to EGFR-wt.
- Significantly improved DFS and OS in the adjuvant setting (ADAURA) and high rates of activity and also improved OS in stage IV.



Qin et al. Expert Rev Anticancer Ther 2019;19(6):533-539.
Wu et al. N Eng J Med 2020;383:1711-23.

Ongoing Trials

- **LAURA Trial (NCT03521154)**
  - Osimertinib Maintenance After Definitive Chemoradiation in unresectable EGFR Mutation+ Stage III NSCLC
  - Primary Endpoint- BICR- confirmed PFS
  - Secondary Endpoints- CNS PFS, OS, PFS by mutation status, safety
  - 1st pt- July 2018
  - Expected results- late 2022



*Patients with a local cobas® EGFR Mutation Test v2 tissue positive result from a CLIA-certified or accredited laboratory do not require part I screening. †Post-CRT imaging performed to assess CR, PR and SD up to 28 days before randomization. #Assessment of PFS2 will not be collected after the primary PFS analysis.

What About no RT for UN-NSCLC?

#8544: **Radiation therapy (RT)-free pembrolizumab plus chemotherapy (P+C) for PD-L1 TPS ≥50% locally advanced non-small cell lung cancer (LA-NSCLC): an early report analyzing depth of response from multicenter single arm phase II study (Evolution trial: WJOG11819L)**

Akito Hata[1]; Taira Ninomaru[1]; Hideaki Okada[1]; Yoshihito Kogure[2]; Masahide Oki[2]; Nobuyuki Katakami[3]; Takashi Kijima[4]; Toshihide Yokoyama[5]; Hirotaka Matsumoto[6]; Yuki Sato[7]; Terufumi Kato[8]; Shunichi Sugawara[9]; Takeshi Sawada[10]; Kenichi Yoshimura[11]; Takashi Seto[12]; Nobuyuki Yamamoto[13]; and Kazuhiko Nakagawa[14]

[1]Division of Thoracic Oncology, Kobe Minimally Invasive Cancer Center, Kobe, Japan; [2]Department of Respiratory Medicine, National Hospital Organization Nagoya Medical Center, Nagoya Japan; [3]Department of Medical Oncology, Takarazuka City Hospital, Takarazuka, Japan; [4]Department of Respiratory Medicine and Hematology, Hyogo Medical University, Nishinomiya Japan; [5]Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki Japan; [6]Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan; [7]Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan; [8]Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan; [9]Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan; [10]Department of Early Clinical Development, Graduate school of Medicine, Kyoto University, Kyoto, Japan; [11]Medical Center for Translational and Clinical Research, Hiroshima University Hospital, Hiroshima, Japan; [12]Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [13]Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan; and [14]Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan

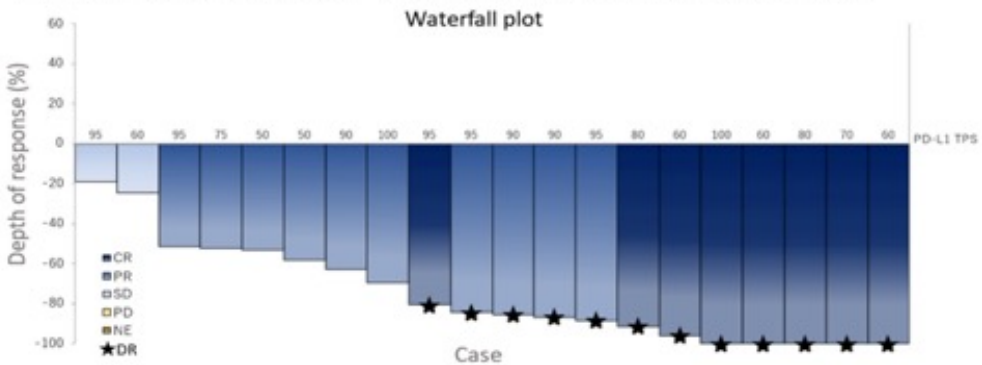
Conclusions:

- RT-free P+C exerted a notably high RR, including some CRs.
- The deeper/earlier response and higher PD-L1 TPS could be associated with the higher progression-free incidence at the data cut-off.
- To investigate our hypothesis: RT-free P+C followed by P+PEM (non-squamous) or P alone (squamous) can be a less toxic curative option in selected LA-NSCLC pts with PD-L1 TPS ≥50%, further matured data is warranted.

Correspondence: Akito Hata, akitohata@hotmail.com

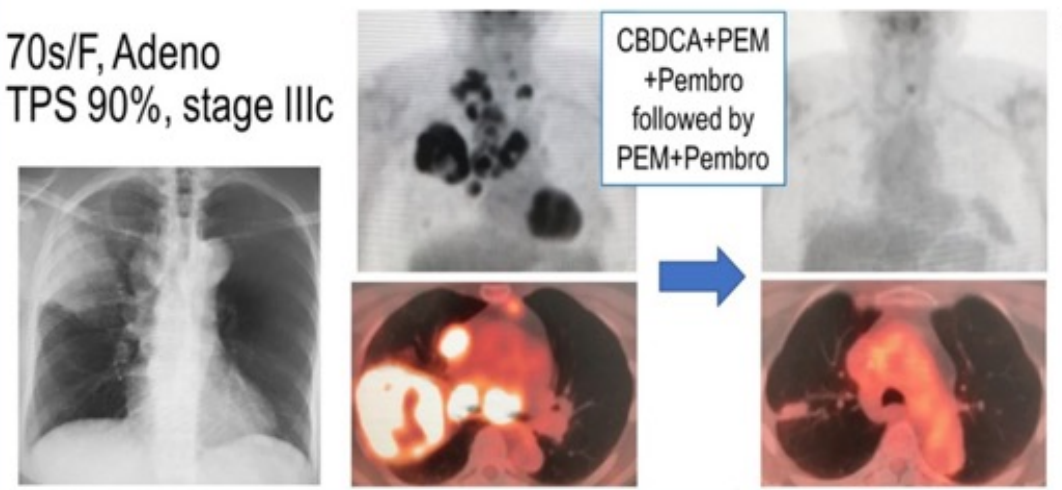
➢ Investigator-assessed best response

- 8 (38%) CR; 10 (48%) PR; 2 (10%) SD; and 1 (5%) NE: RR 86%, DCR 95%.
- RR of TPS 50-79% and 80-100% were 78% and 92%, respectively.

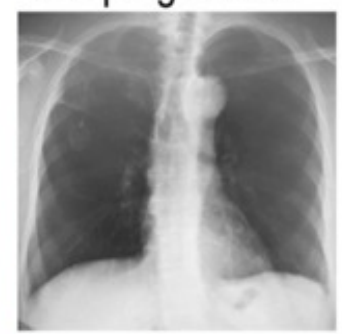


Presentation of first enrolled case

70s/F, Adeno
TPS 90%, stage IIIc



Achieved ETS+DR
over 2-yrs
w/o progression



Hata A et al. ASCO 2023, abstr 8544.

Conclusions on UR-NSCLC→

- The placebo-controlled, Phase 3 PACIFIC study established consolidation durvalumab as SOC for patients with unresectable Stage III NSCLC who have not progressed after cCRT.
  - ✓ Five-year data from PACIFIC demonstrated robust and sustained OS plus durable PFS benefit with durvalumab in this patient population
    - **42.9% remain alive** and **33.1% remain alive and progression-free** at 5 years

- COAST is the **first randomised Phase 2 study** to show evidence of improved outcomes with novel IO combinations in the PACIFIC setting ("additional immunomodulation"). PACIFIC 9 has started.

- Both combinations (D+O and D+M) numerically increased ORR and significantly improved PFS versus durvalumab alone:
  - ✓ PFS benefit with both combinations was observed across various subgroups, including those based on histology, ECOG PS, prior platinum-based CT, and PD-L1 status.

- Addition of an anti-TIGIT antibody to immunotherapy following concurrent chemoradiation is under investigation (PACIFIC 8 and others).

- Consolidation with targeted therapies following chemoradiation for stage III NSCLC is a promising strategy; a number of trials are underway in EGFR, ALK, ROS1, RET, and PARP to evaluate this approach.

- Biomarkers are needed to identify those who may benefit most from escalation of therapy.