Endorsed by

CELEBRATING 50 YEARS IASLC 1974–2024

ATLANTA
LUNG CANCER SYMPOSIUM

Locally Advanced NSCLC: Role of IO and Emerging Advances

Ticiana Leal, MD
Associate Professor
Director, Thoracic Oncology Program
Winship Cancer Institute of Emory University

PACE
Partners for Advancing Clinical Education

Bio Ascend™

Introduction

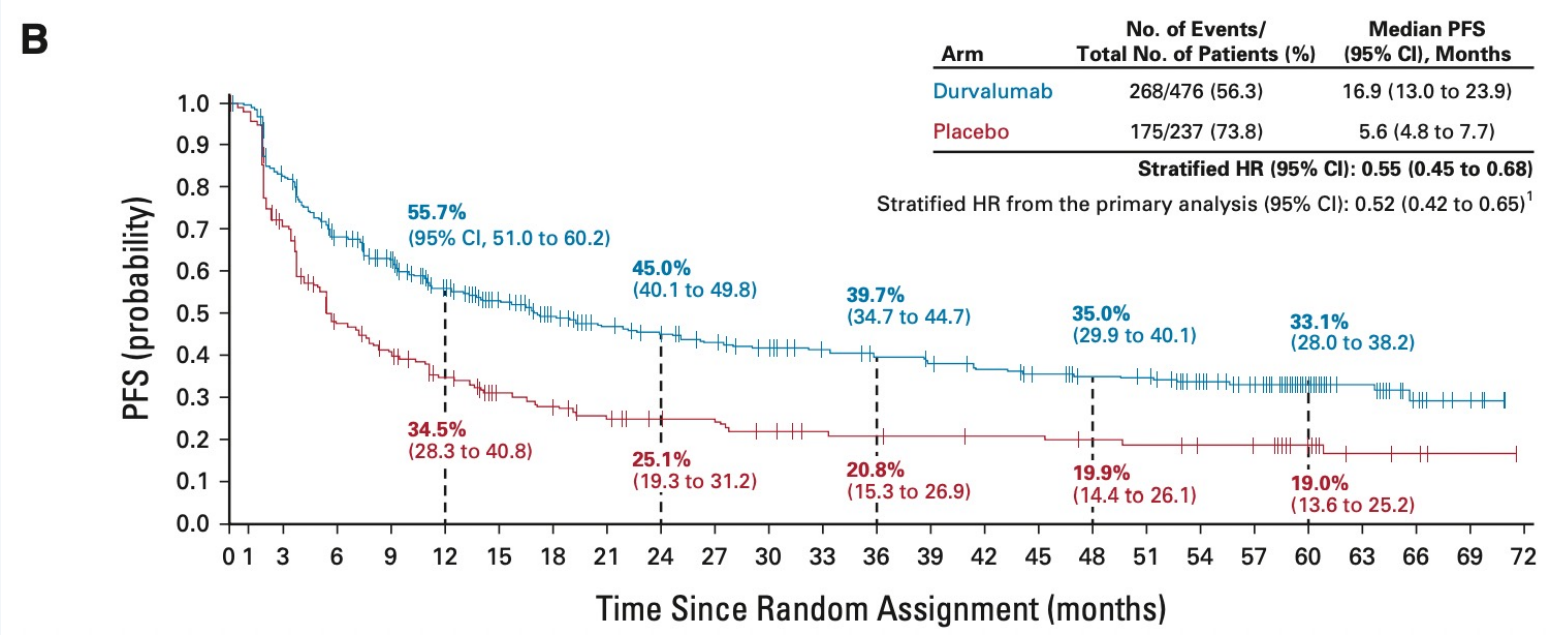
- Stage III lung cancer includes a heterogeneous group of patients with significant differences in terms of tumor volume, local invasion, and lymph node involvement.
- For this reason, multimodal evaluation and treatment, including consideration of surgery, radiotherapy, and systemic treatments are key.

	N0	N1	N2 SINGLE	N2 MULTI	N2 BULKY	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	POTENTIALLY RESECTABLE	?	UNRESECTABLE[2]	UNRESECTABLE	UNRESECTABLE
T3 size	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE	?	UNRESECTABLE	UNRESECTABLE	
T3 satellite	NOT STAGE III DISEASE	POTENTIALLY RESECTABLE	POTENTIALLY RESECTABLE	?	UNRESECTABLE	UNRESECTABLE	
T3 invasion	NOT STAGE III DISEASE	POTENTIALLY RESECTABLE	?[1]	?	UNRESECTABLE	UNRESECTABLE	
T4 size	POTENTIALLY RESECTABLE	POTENTIALLY RESECTABLE	?	UNRESECTABLE[2]	UNRESECTABLE	UNRESECTABLE	
T4 satellite	POTENTIALLY RESECTABLE	?[1]	?	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE	
T4 invasion	?[1]	?[1]	?	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE	

Brandao et al. WCLC 2023

PACIFIC 5 Year Overall Survival Data

- The PACIFIC trial demonstrated significant improvement in PFS and OS with consolidation durvalumab in stage III unresectable NSCLC.
- The estimated 5-year OS rate was 42.9% with durvalumab vs. 33.4% with placebo

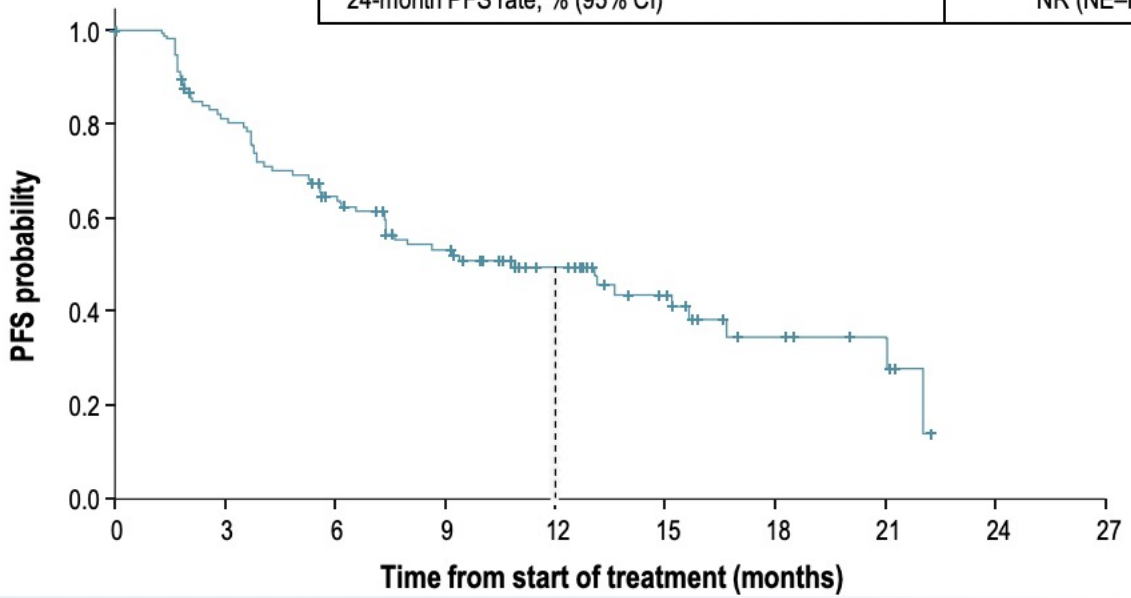


Spigel DR et al. 2021 ASCO Annual Meeting. Abstract 8511. Spigel DR et al. *J Clin Oncol*. 2022;40(12):1301-1311.

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

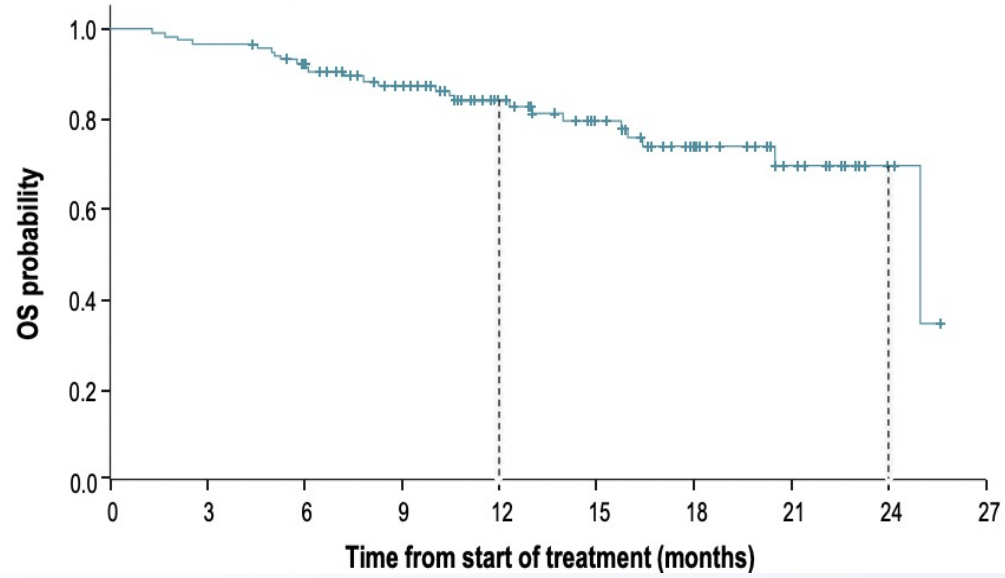
A

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



B

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



Garassino et al, JTO 2022

KEYNOTE-799 (NCT03631784) Study Design

Study Population
- Age ≥18 years
- Stage IIIA–C, unresectable, locally advanced, pathologically confirmed, previously untreated NSCLC
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1
- Adequate pulmonary function
- No prior systemic immunosuppressive therapy within 7 days

N = 216

COHORT A (Squamous and Nonsquamous NSCLC)

Cycle 1	Cycles 2–3	Cycles 4–17
Pembrolizumab 200 mg Q3W + Paclitaxel 200 mg/m² Q3W / Carboplatin AUC6 Q3W	Pembrolizumab 200 mg Q3W + Paclitaxel 45 mg/m² QW / Carboplatin AUC2 QW / Thoracic radiotherapy[a]	Pembrolizumab 200 mg Q3W[b]

COHORT B (Nonsquamous NSCLC Only)

Cycle 1	Cycles 2–3	Cycles 4–17
Pembrolizumab 200 mg Q3W + Pemetrexed 500 mg/m² Q3W / Cisplatin 75 mg/m² Q3W	Pembrolizumab 200 mg Q3W + Pemetrexed 500 mg/m² Q3W / Cisplatin 75 mg/m² Q3W / Thoracic radiotherapy[a]	Pembrolizumab 200 mg Q3W[b]

Primary Objectives
- ORR per RECIST v1.1 by BICR
- Proportion of patients with grade ≥3 pneumonitis[c]

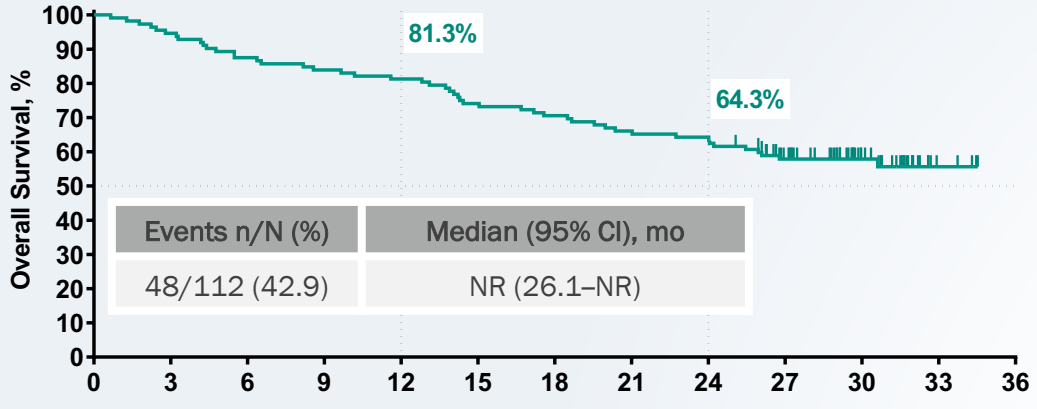
Secondary Objectives
- PFS per RECIST v1.1 by BICR, OS, and safety

Statistical Analysis Details
- Efficacy and safety assessed in all patients as-treated

Jabour et al, JAMA Oncol 2021

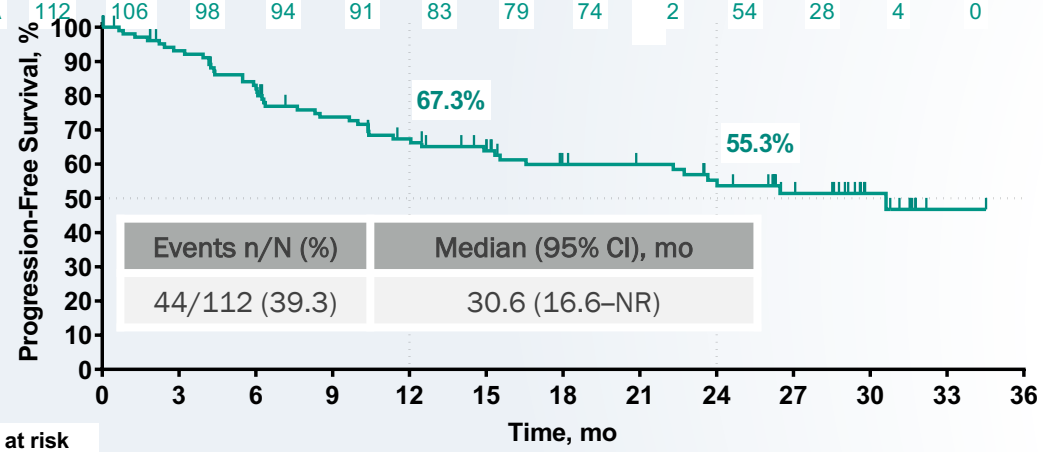
Progression-Free Survival and Overall Survival

Cohort A
(squamous and nonsquamous histology)



No. at risk

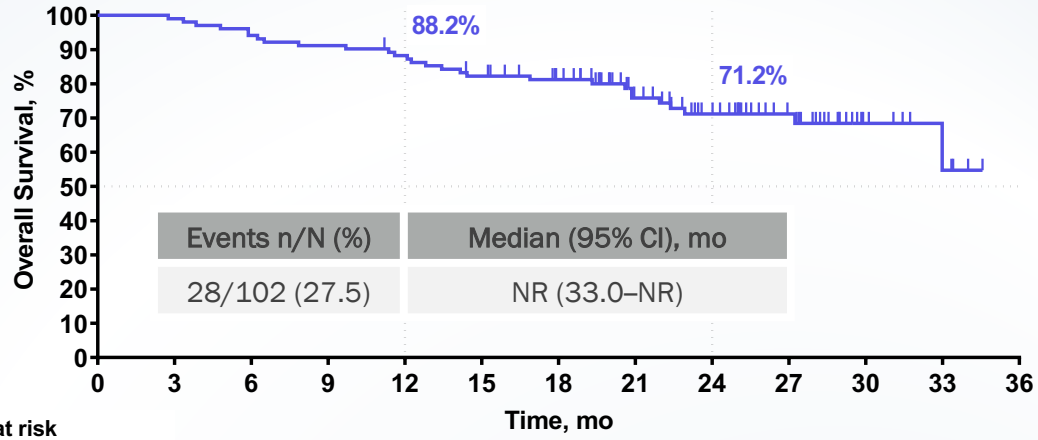
Cohort A	112	106	98	94	91	83	79	74	2	54	28	4	0



No. at risk

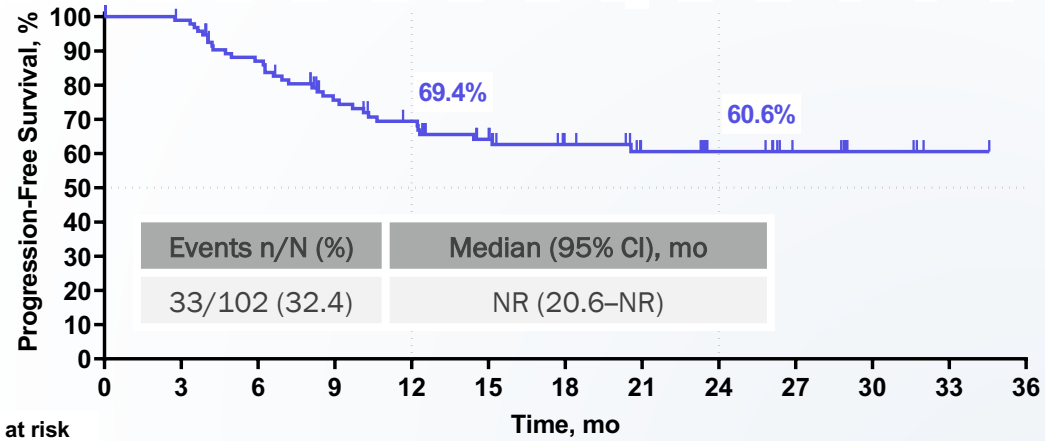
Cohort A	112	93	82	70	60	53	42	40	34	22	11	1	0

Cohort B
(nonsquamous histology only)



No. at risk

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

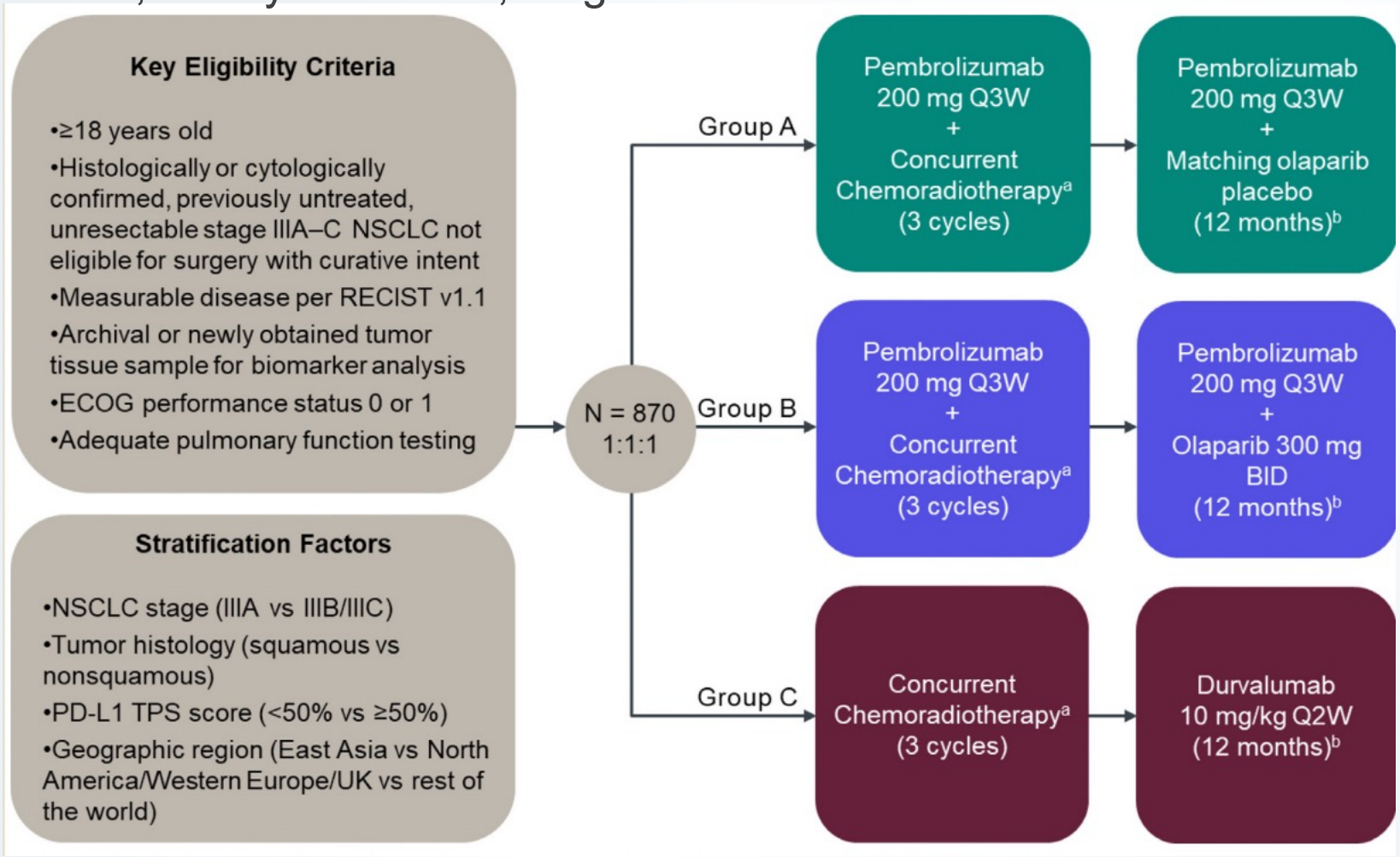


No. at risk

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

KEYLINK-012: Study design

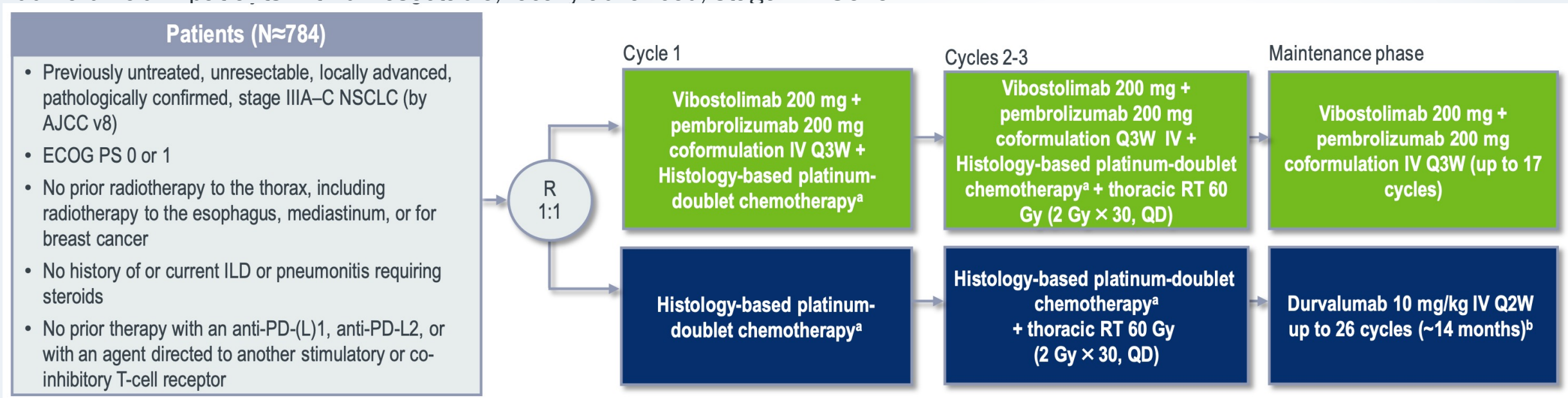
Phase 3, randomized, double-blind, placebo-controlled study of pembrolizumab in combination with concurrent CRT followed by pembrolizumab ± olaparib vs CCRT followed by durvalumab in patients with unresectable, locally advanced, stage III NSCLC



Jabbour et al, Clin Lung Cancer 2022

KEYVIBE-006

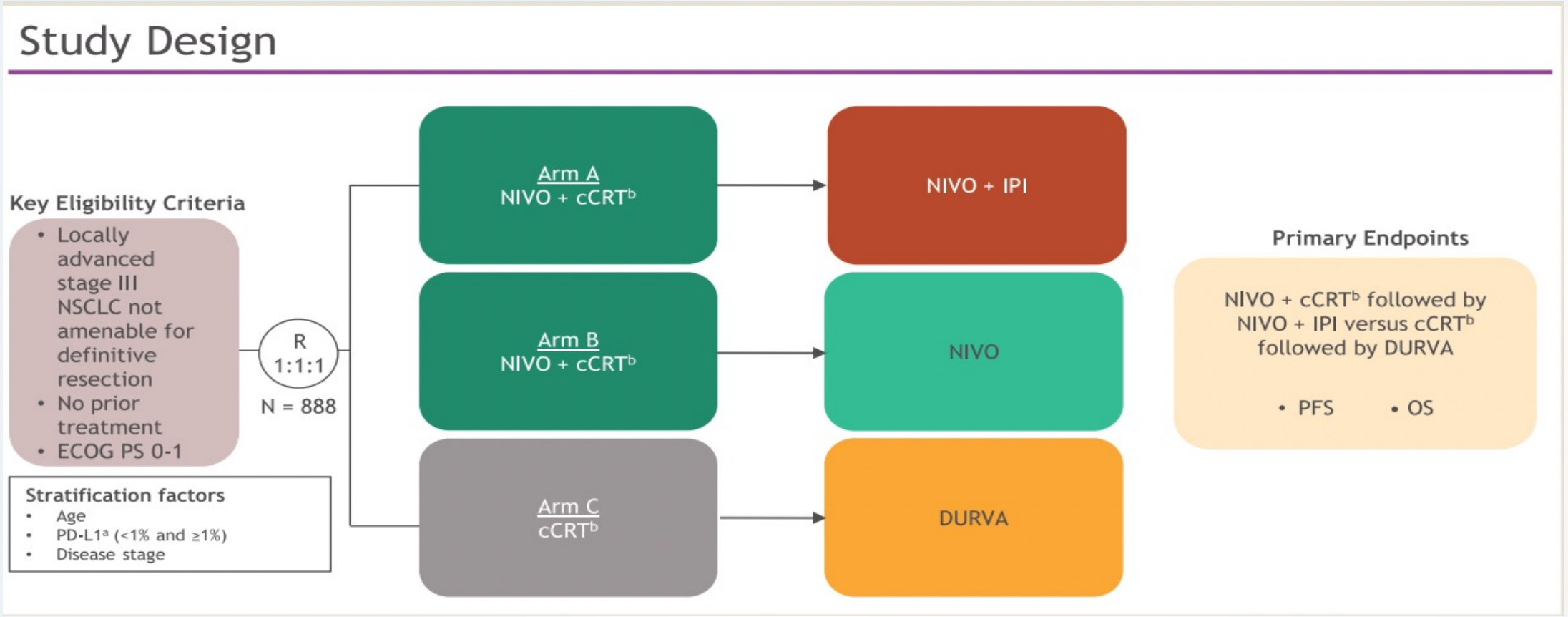
Phase 3, randomized, open-label study evaluating vibostolimab + pembrolizumab coformulation + CCRT vs CCRT followed by durvalumab in patients with unresectable, locally advanced, stage III NSCLC



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

CheckMate 73L

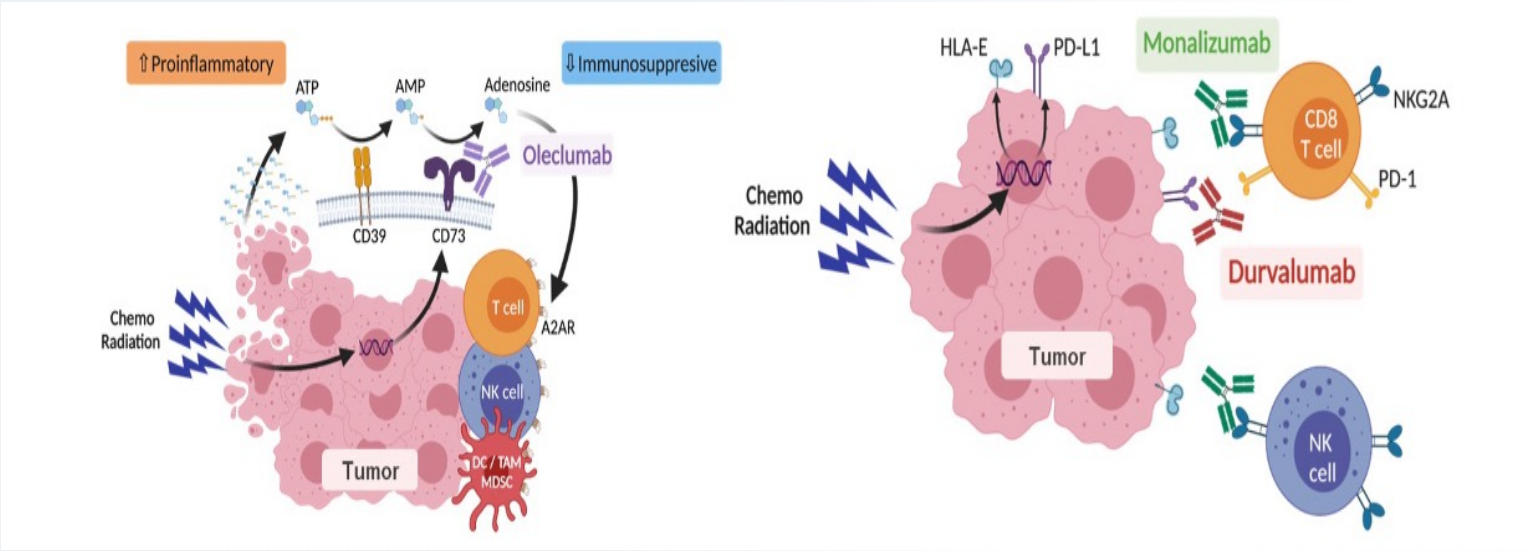


- Press release:

Nivolumab Combo Does Not Meet PFS End Point in Unresectable NSCLC

De Ruysscher et al. Clin Lung Cancer 2021

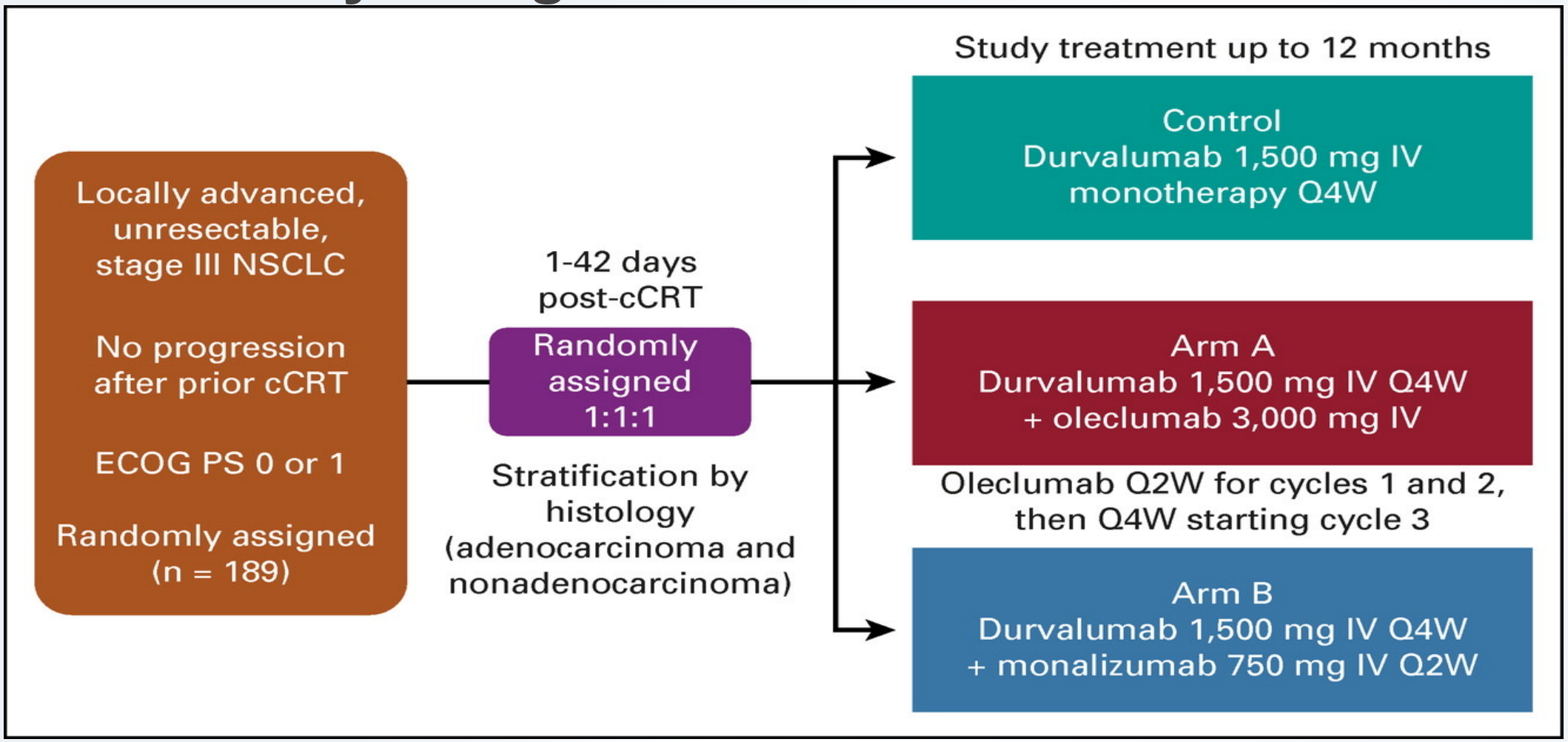
Rationale for COAST study: Phase II study of durvalumab alone or combined with oleclumab or monalizumab



- RT increases tumor expression of CD73, HLA-E (NKG2A ligand) and PD-L1
- In pre-clinical models, the combination of RT and CD73 or NKG2A inhibitors (+/- PD-L1 inhibitors) showed increased anti-tumor activity.

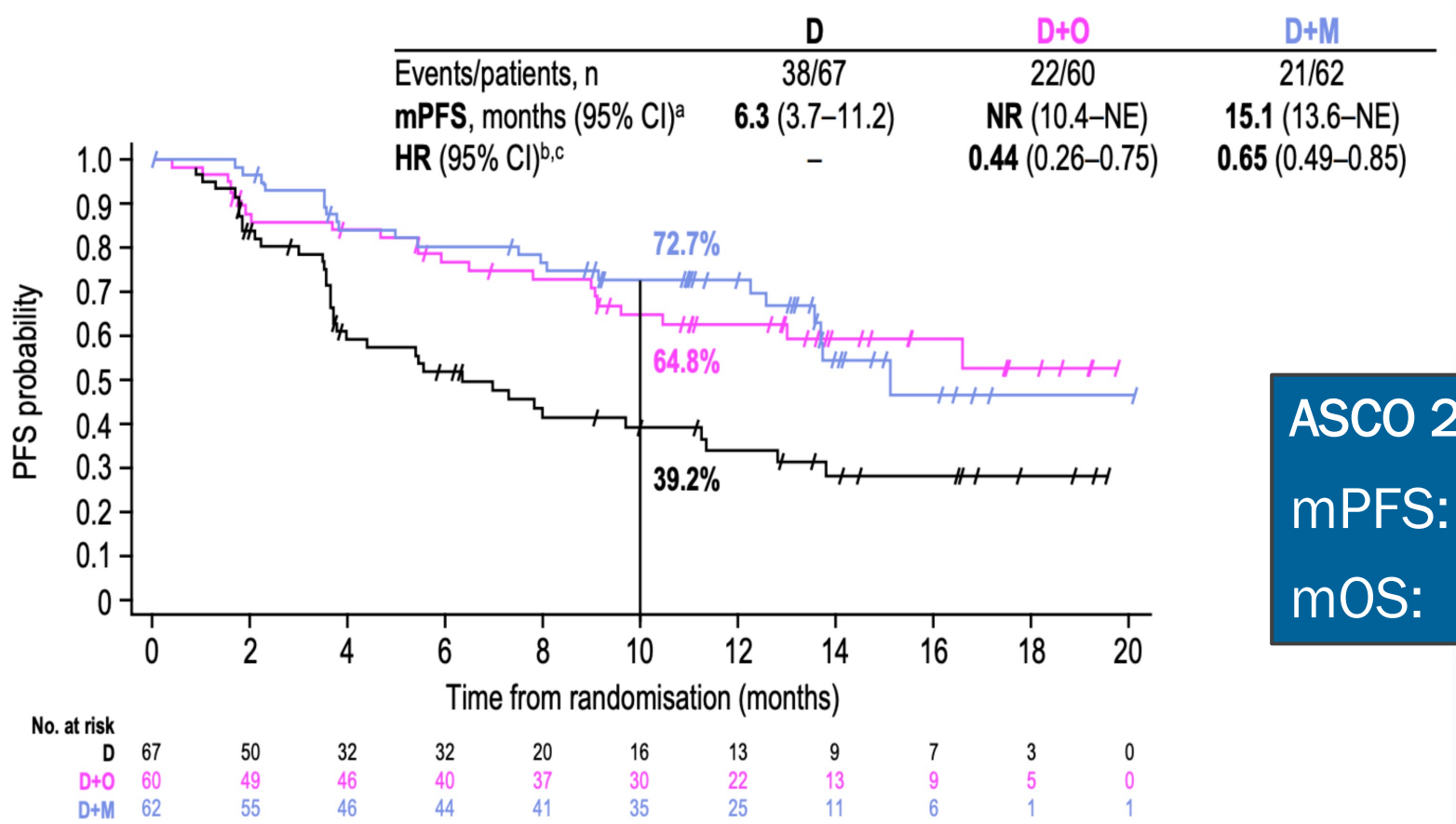
Battaglia et al. J Immunol 2020; Gong et al. JTO 2017; Tsukui et al. BMC Cancer 2020; Wennerberg et al. Cancer Immunol Res 2020.

COAST: Study Design



Herbst RS et al. *J Clin Oncol*. 2022; 40(29):3383-3393.

COAST: Efficacy



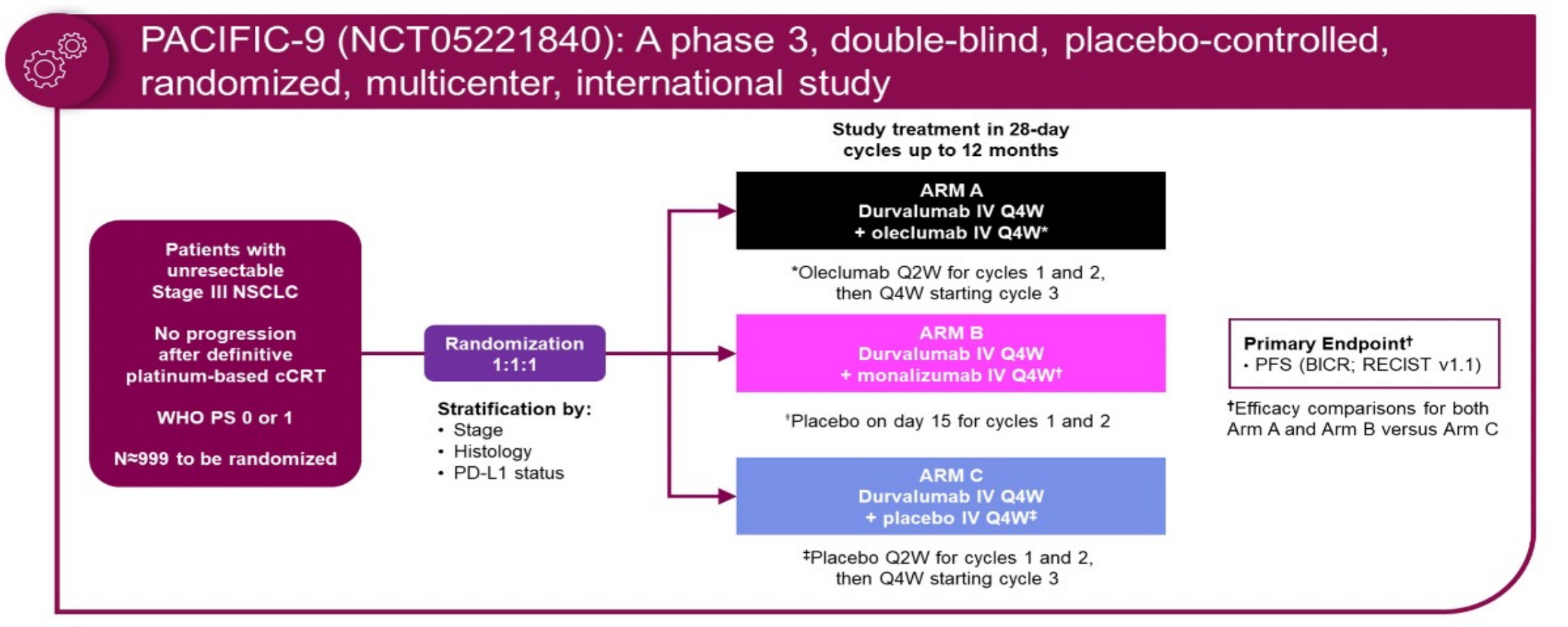
ASCO 2024 update

mPFS: D 7.3 D+O 29.9 D+M 23

mOS: D 40.9 D+O NR D+M NR

Herbst RS et al. *J Clin Oncol*. 2022; 40(29):3383-3393.

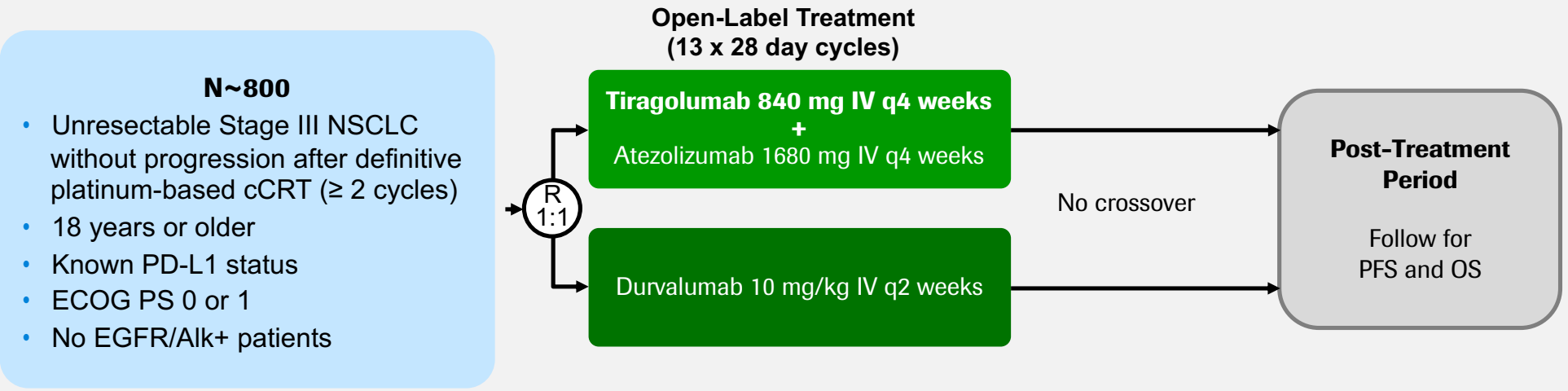
PACIFIC-9: Study design



- 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.

SKYSCRAPER-03:Tiragolumab + Atezolizumab in Stage III NSCLC

Study Schema



Stratification Factors:

- PD-L1 expression (<1% vs ≥1%)
- Staging (IIIA vs IIIB vs IIIC)
- Histology (Squamous vs Non-Squamous)
- ECOG PS (0 vs 1)

Safety Run-in:

- iDMC review after a minimum of 24 patients (approximately 12 patients per arm) have completed 2 cycles of study treatment
- Enrollment will not be paused

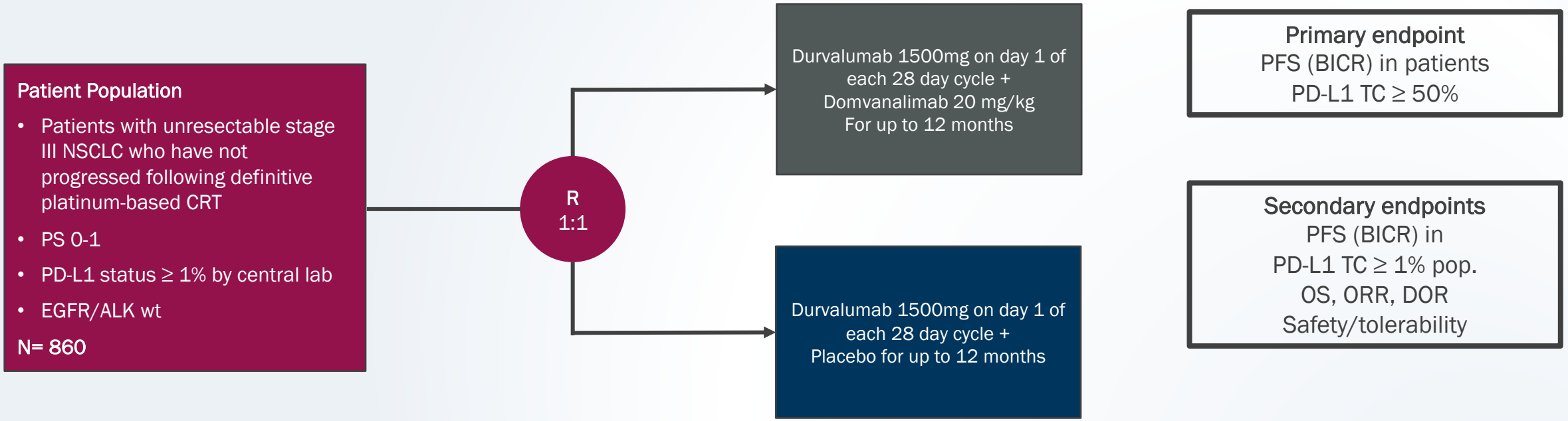
Co-Primary Endpoints:

IRF-assessed PFS in the

- PD-L1 positive population
- ITT population

PACIFIC-8

A Phase III, Randomized, Double blind, Placebo-controlled, Multicentre, International Study of Durvalumab plus Domvanalimab (AB154) in Participants with Locally Advanced (Stage III), Unresectable NSCLC



Domvanalimab (AB154) is a Fc-silent humanized IgG1 mono- clonal antibody that blocks interaction of the T cell immunoreceptor with Ig and ITIM domains (TIGIT; upregulated by immune cells) with CD112 and CD155

NCT05211895

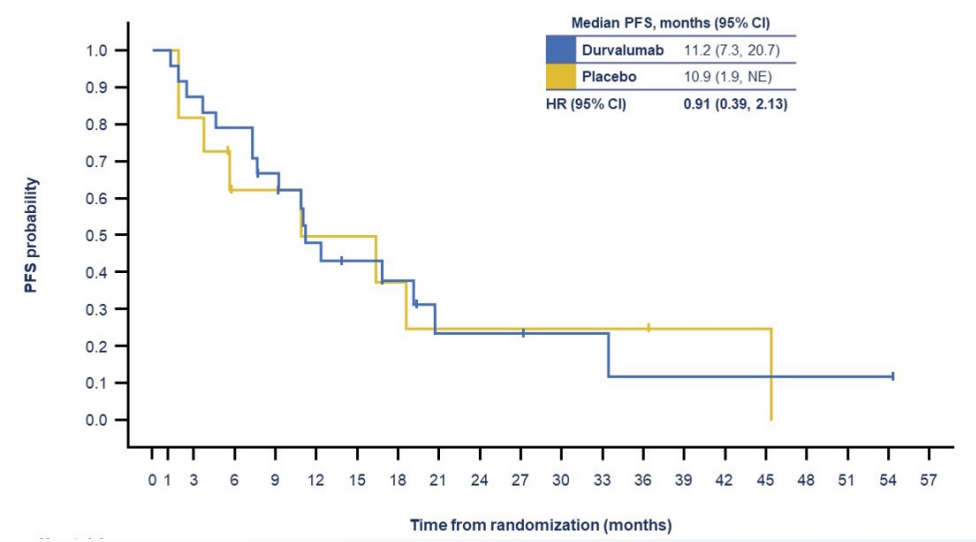
TTFields in Stage III NSCLC

- Open-label, Phase 1 clinical trial is to determine the safety of TTFields started concurrently with SOC chemoradiation and during consolidation durvalumab in locally advanced, unresectable stage III non-small cell lung cancer (NSCLC).
- Primary endpoint: safety
- Sample size: 30 participants
- Study start 4/4/2024

ClinicalTrials.gov ID NCT06124118

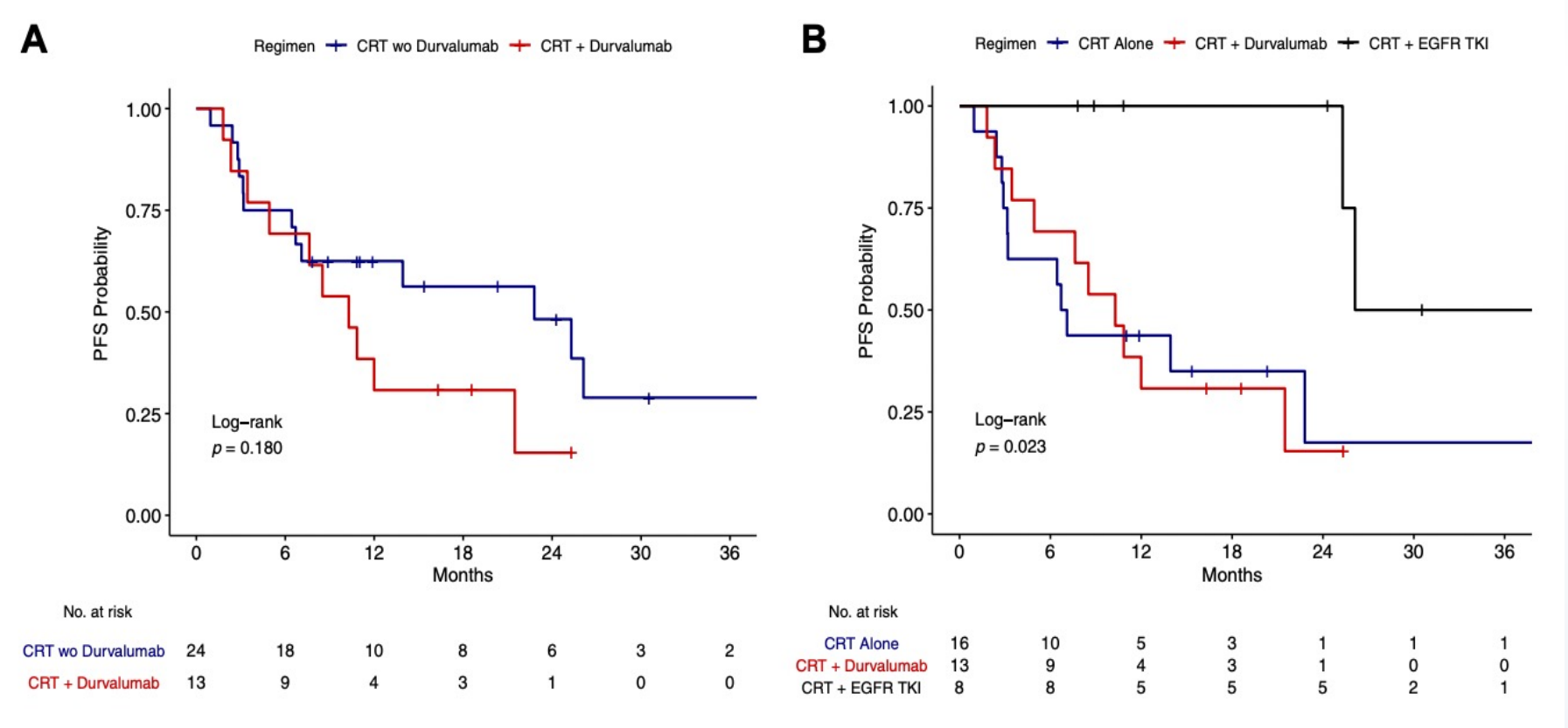
Lack of benefit with immunotherapy in EGFR NSCLC

- A post-hoc analysis of PACIFIC included 35 patients with NSCLC with EGFR mutations (69% common and 31% other EGFR alterations or combinations) revealed similar PFS between the durvalumab and placebo groups (11.2 vs. 10.9 mos.).



Naidoo et al. JTO 2023.

Durvalumab for Stage III EGFR-Mutated NSCLC After Definitive Chemoradiotherapy



Median PFS among patients who completed CRT and durvalumab versus CRT wo durvalumab was 10.3 months versus 22.8 months (log-rank p = 0.180).

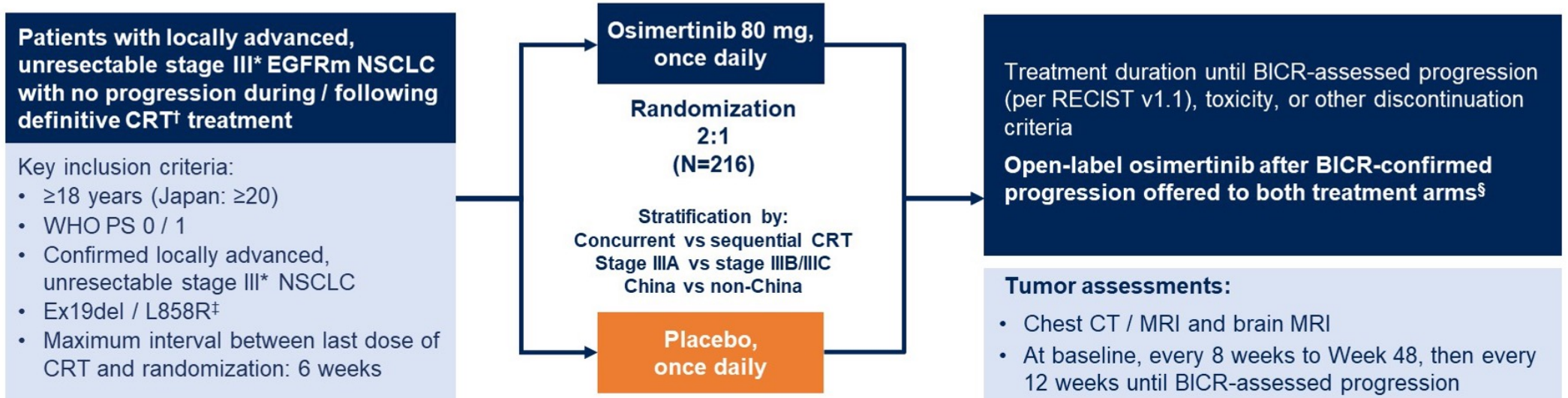
Median PFS among patients who completed CRT alone versus CRT and durvalumab versus CRT and induction or consolidation EGFR TKI was 6.9 months versus 10.3 months versus 26.1 months (log-rank p = 0.023).

18th Annual ATLANTA LUNG CANCER SYMPOSIUM

Aredo et al. JTO 2021

LAURA trial

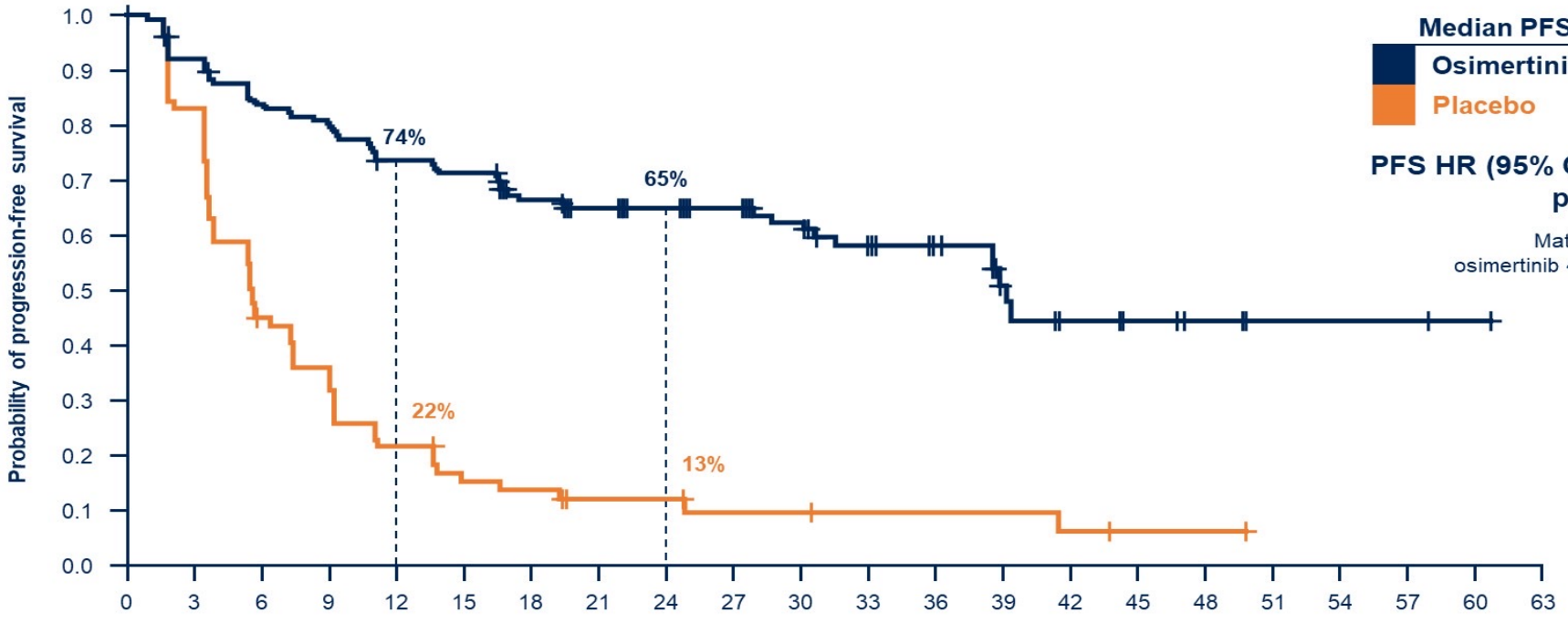
FDA approves osimertinib for locally advanced, unresectable (stage III) non-small cell lung cancer following chemoradiation therapy



Endpoints

- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Secondary endpoints included:** OS, CNS PFS, safety

Progression-free survival by BICR



Median PFS, months (95% CI)

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

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

Maturity 56%:
osimertinib 40%, placebo 86%

No. at risk

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

Data cut-off: January 5, 2024.

Tick marks indicate censored data. Median follow-up for PFS (all patients): osimertinib 22.0 months, placebo 5.6 months. Median follow-up for PFS (censored patients): osimertinib 27.7 months, placebo 19.5 months.

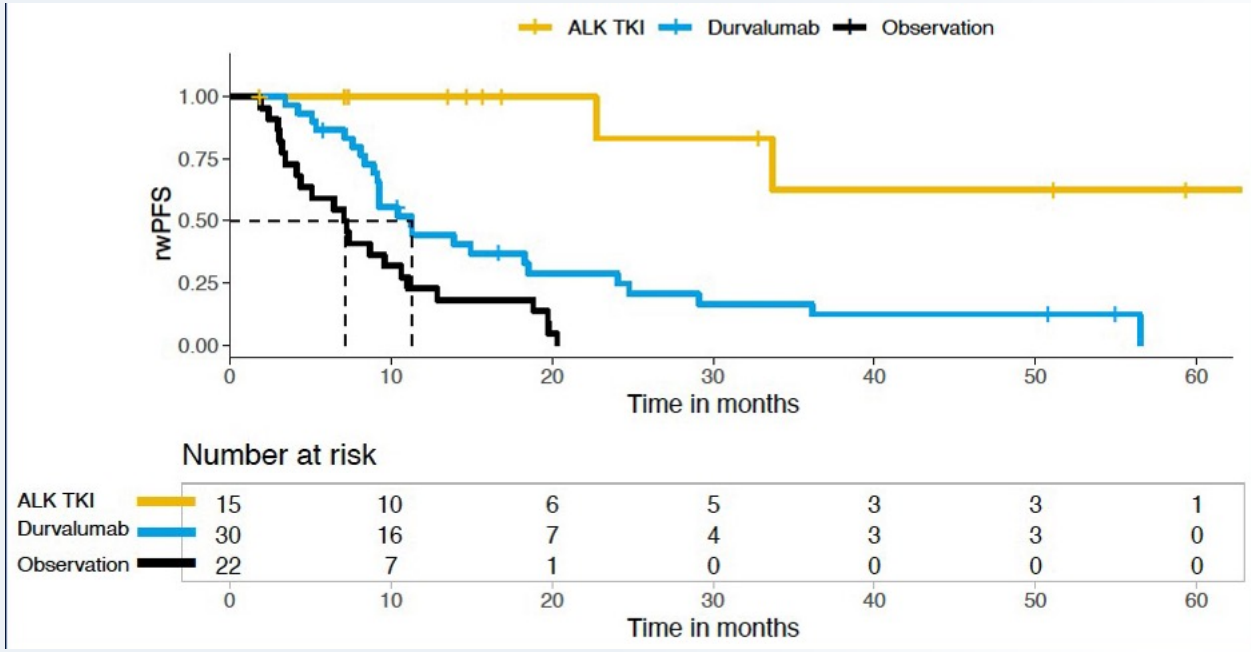
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

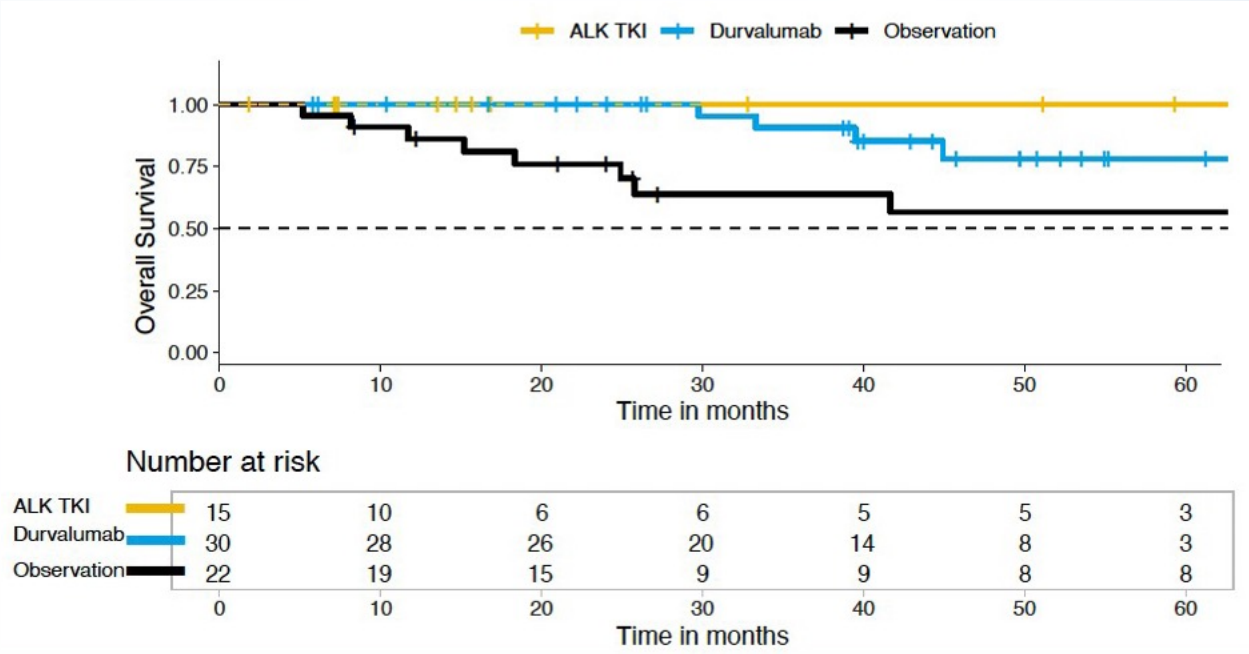
2024 ASCO ANNUAL MEETING #ASCO24

PRESENTED BY: Dr Suresh S. Ramalingam

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

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





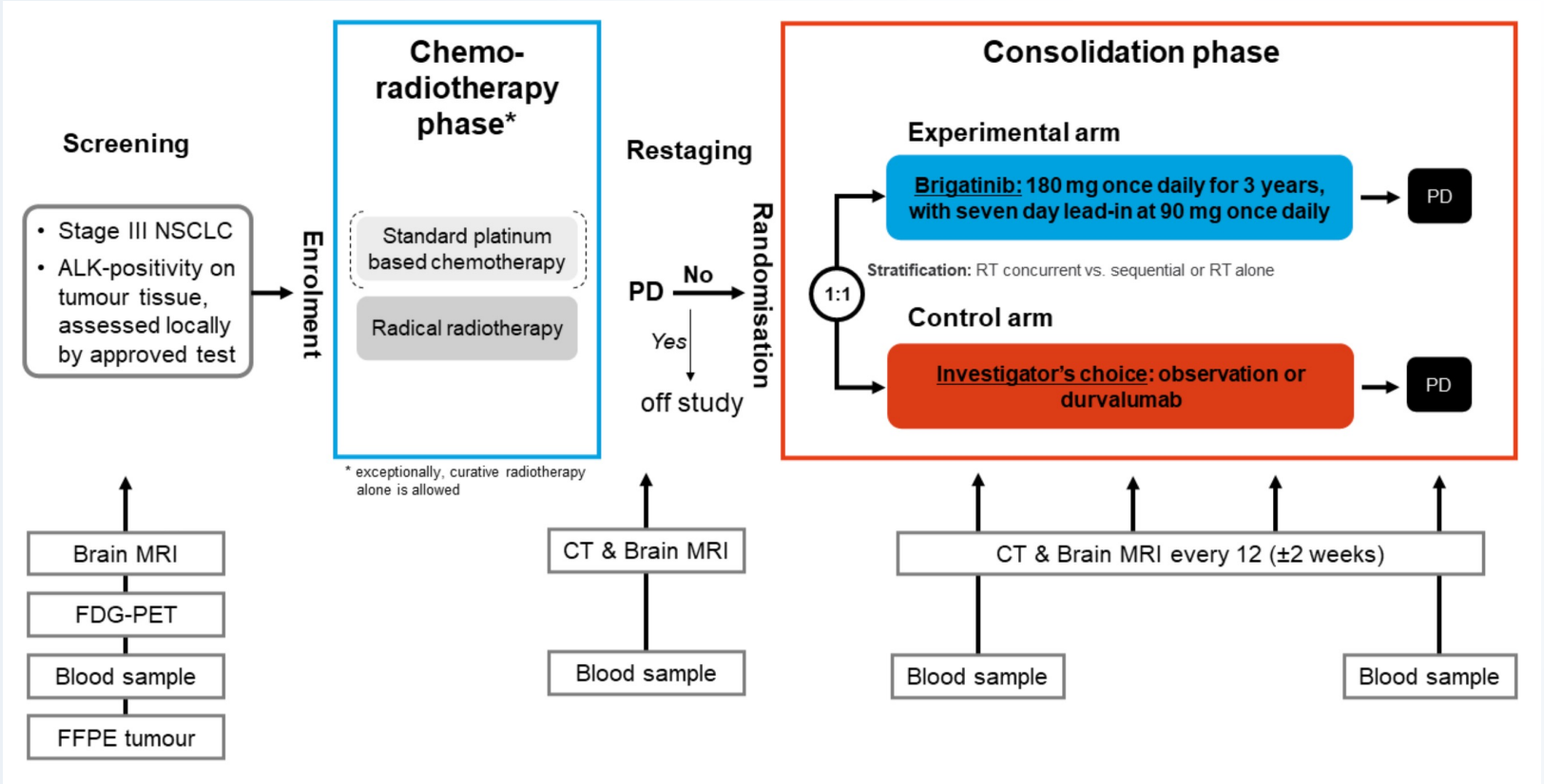
	ALK TKI	Durvalumab	Observation
Median rwPFS (95% CI)	Not reached (22.7 months-NR)	11.3 months (9.2-18.5 months)	7.2 months (3.4-10.6 months)

	ALK TKI	Durvalumab	Observation
Median OS (95% CI)	Not reached (NR-NR)	Not reached (NR-NR)	70.6 months (24.9 months-NR)

Nassar et al. J Thorac Oncol. 2024 Sep 10:S1556-0864(24)02265-2.

BOUNCE (ETOP IBCSG Partners FOUNDATION)

A multicentre, randomised, phase II trial of brigatinib consolidation versus observation or durvalumab in patients with unresectable stage III NSCLC and ALK-rearrangement, after definitive chemo-radiotherapy



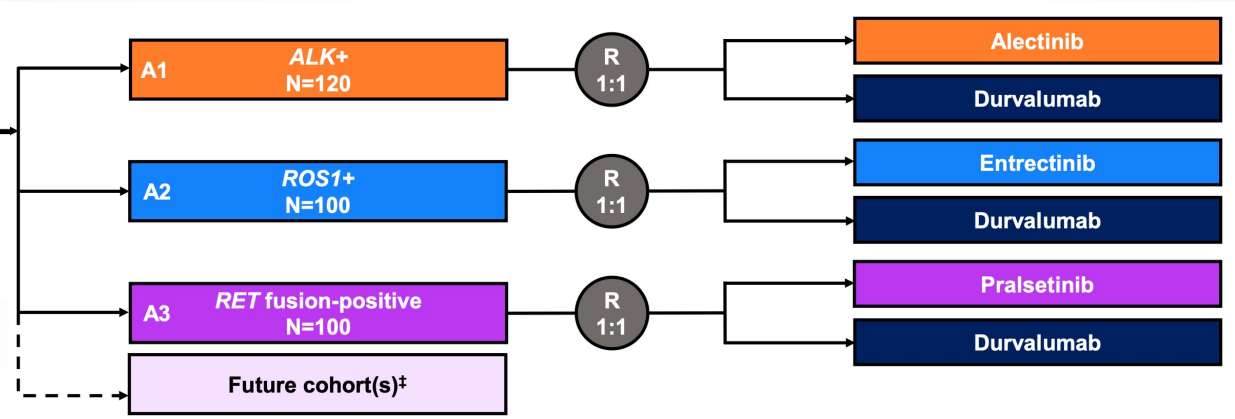
NCT05718297

HORIZON-01

A phase I–III platform study evaluating the safety and efficacy of multiple therapies in patients with biomarker-defined locally advanced, unresectable, stage III non-small cell lung cancer (NSCLC)

- **Locally advanced, unresectable, stage III NSCLC**
- **≥18 years**
- **Prior cCRT / sCRT**
- **ECOG PS 0–2**
- **Tumour tissue required from all patients**
- **Documented PD-L1 status†**

Biomarker eligibility determined in BIOSTART master screening study or per available and acceptable local tissue-based test result*



Primary endpoint – PFS
Target enrollment N=320

Stratification factors:
- **Disease staging (stage IIIA vs. stage IIIB or IIIC)**
- **Type of CRT (cCRT vs. sCRT)**
- **PD-L1 expression (TC score <1% vs. ≥1% vs. unknown)†**

Therapeutic	Administration	Dose*
Alectinib	Oral†	600 mg BID in 28-day cycles for ≤3 years
Entrectinib	Oral	600 mg QD in 28-day cycles for ≤3 years
Pralsetinib	Oral	400 mg QD in 28-day cycles for ≤3 years
Durvalumab	IV infusion	1500 mg Q4W in 28-day cycles for ≤1 year

NCT05170204

Conclusions

- The 5-year OS update from the PACIFIC trial establishes durvalumab as standard of care approach for patients with unresectable stage III NSCLC.
- Despite progress, additional work remains to further improve outcomes for this patient population.
- Immunotherapy combination strategies that build upon the durvalumab standard of care are being investigated.
- Biomarker testing should be incorporated into the management of stage III as it impact treatment decision making with approval of EGFR targeted therapy.