Combining Immunotherapy with Radiation for LA-NSCLC

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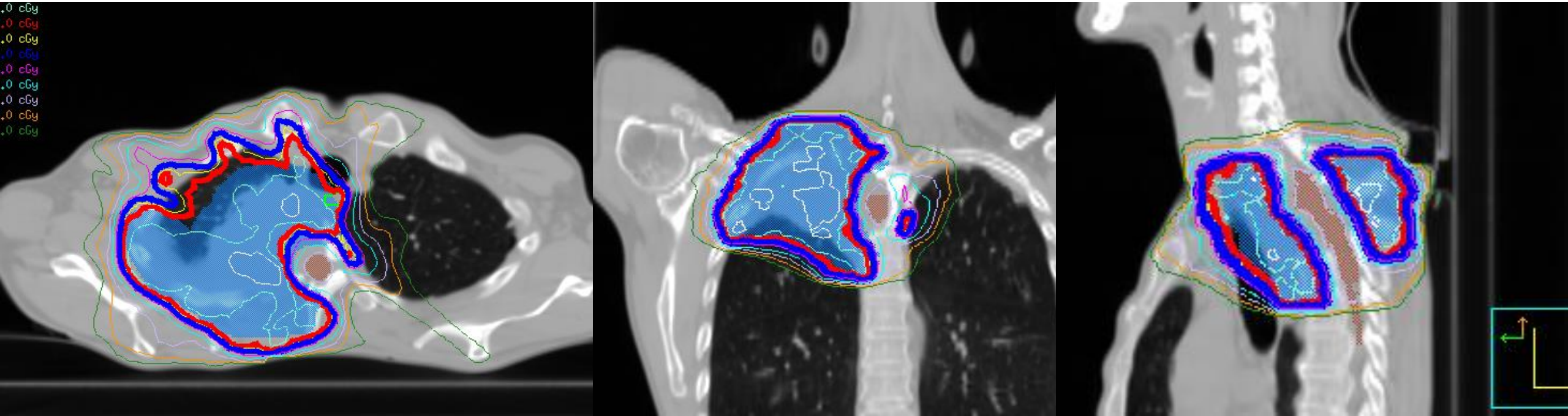
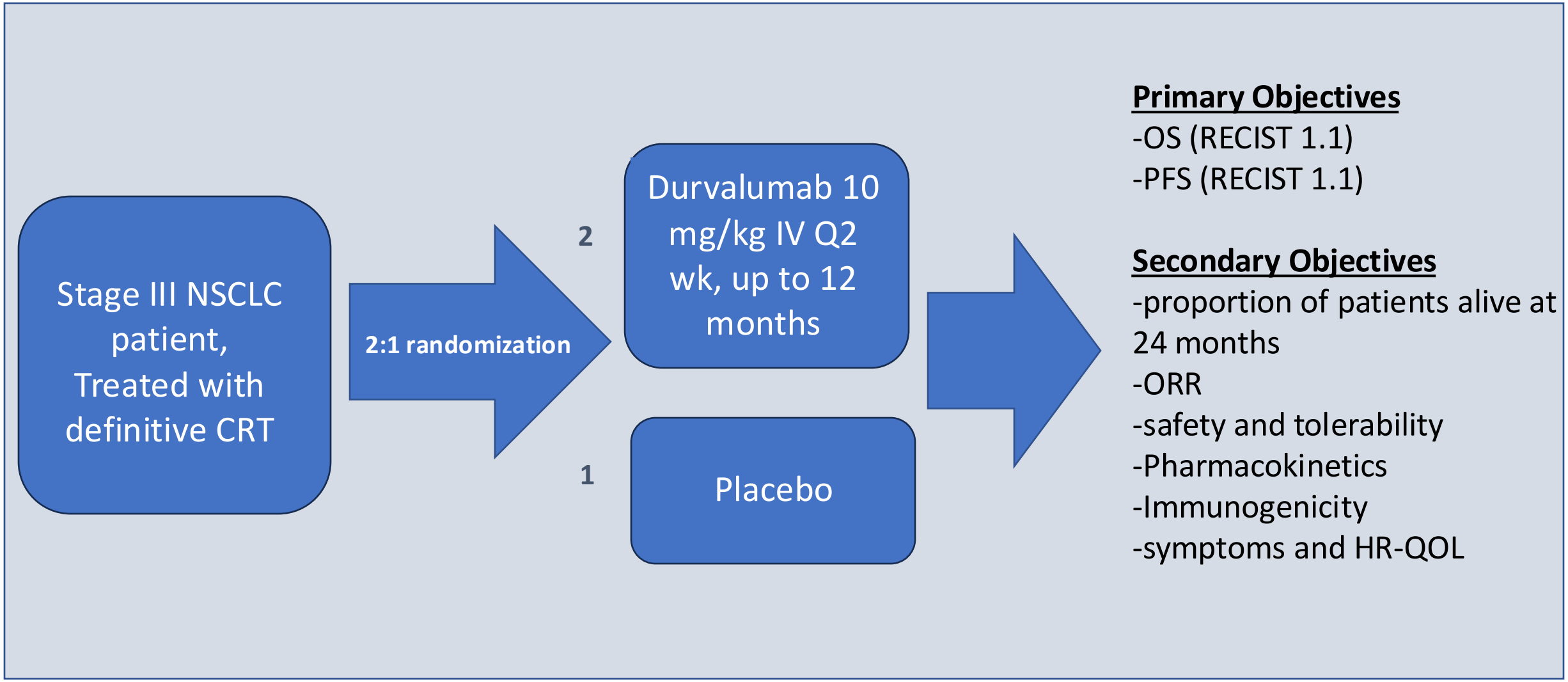
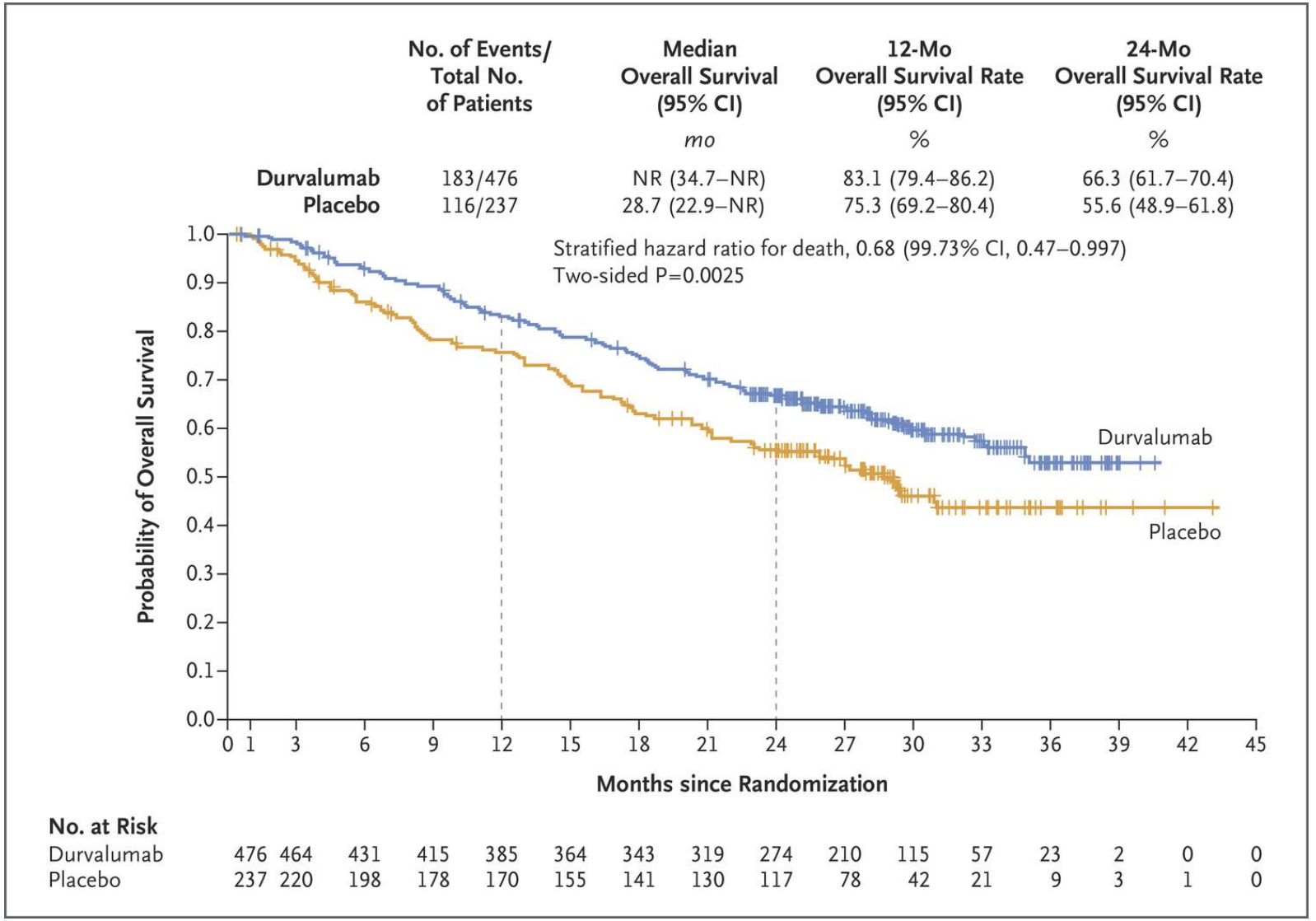


PACIFIC Randomized Phase III Trial: Stage III NSCLC



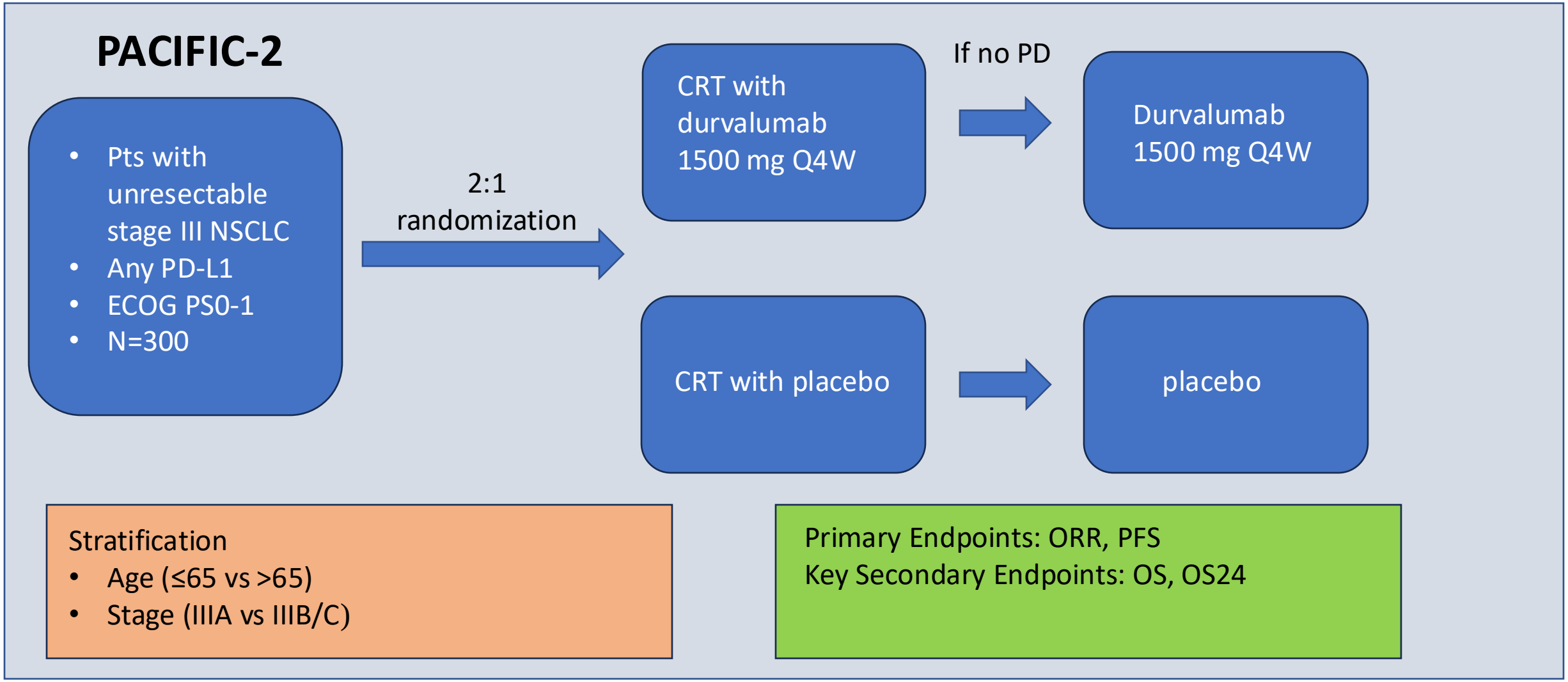
PACIFIC: OS in the Intention-to-Treat Population



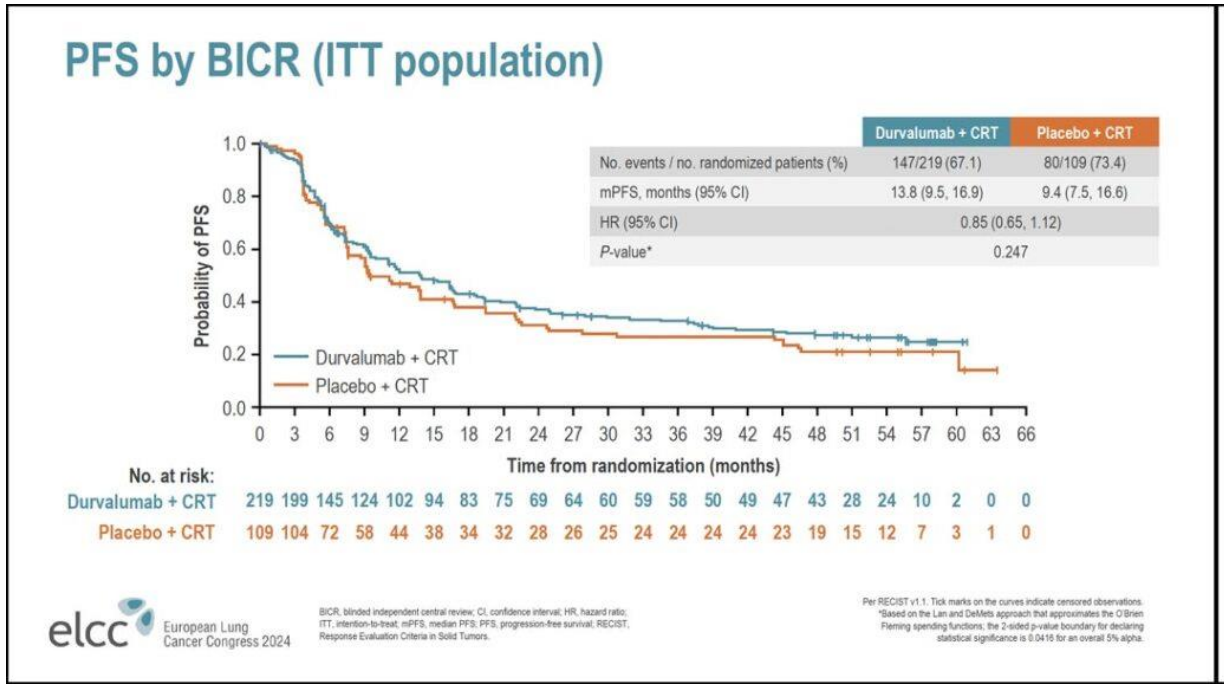
Antonia SJ et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer. N Engl J Med 2018; 379:2342-2350.

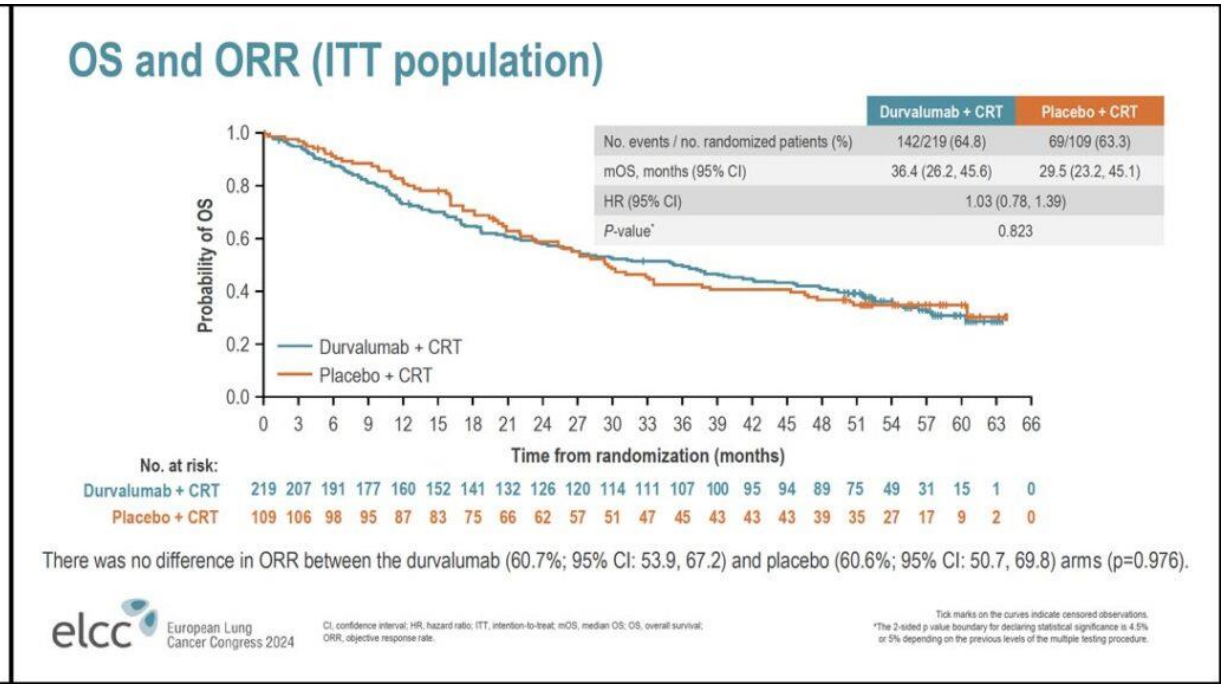
The NEW ENGLAND JOURNAL of MEDICINE

If consolidation IO is good, is concurrent better?



PACIFIC-2 Results





Bradley JD et al. Durvalumab in combination with chemoradiotherapy for patients with unresectable stage III NSCLC: Final results from PACIFIC-2. European Lung Cancer Congress 2024

ECOG/ACRIN EA5181

***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

Varlotto JM et al. EA5181 - Testing the Addition of an Antibody to Standard Chemoradiation Followed by the Antibody for One Year to Standard Chemoradiation Followed by One Year of the Antibody in Patients With Unresectable Stage III Non-Small Cell Lung Cancer. ASCO 2021

What comes next?

Dual Consolidation Trials

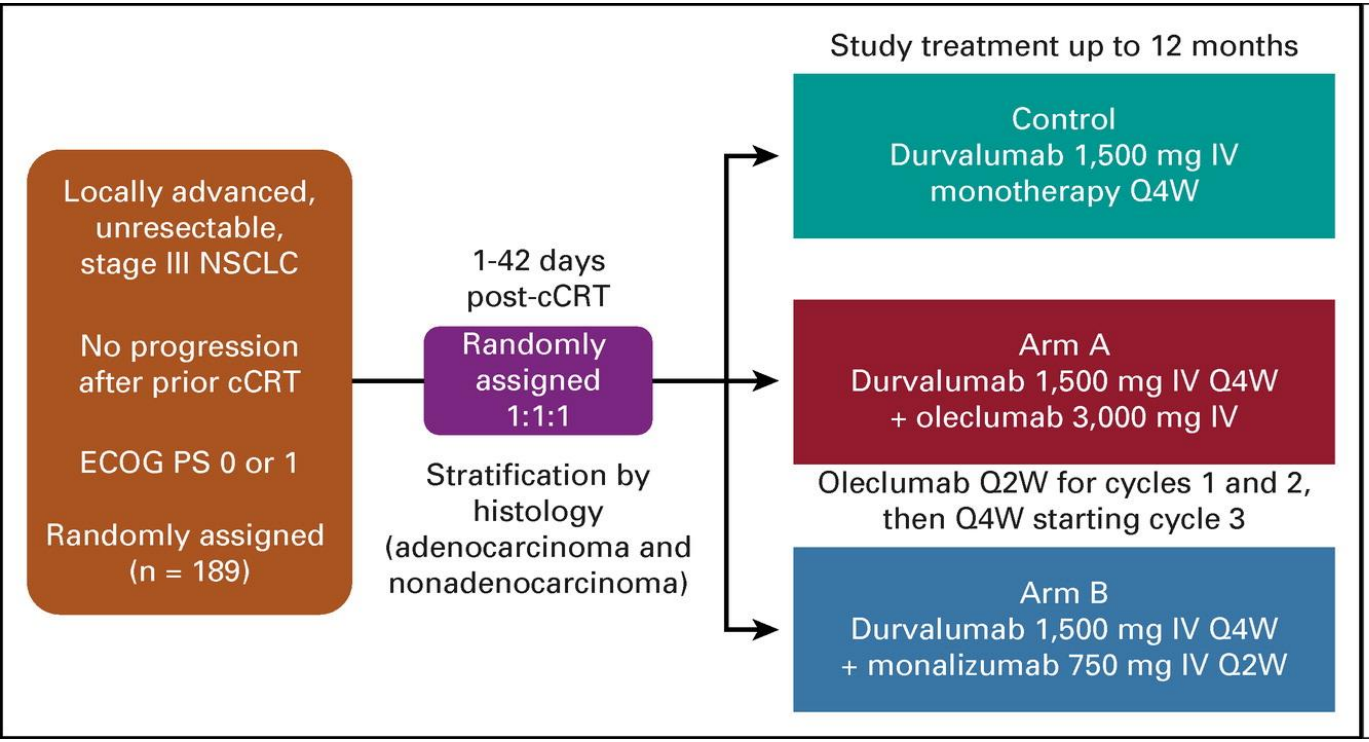
Induction Chemoimmunotherapy Trials

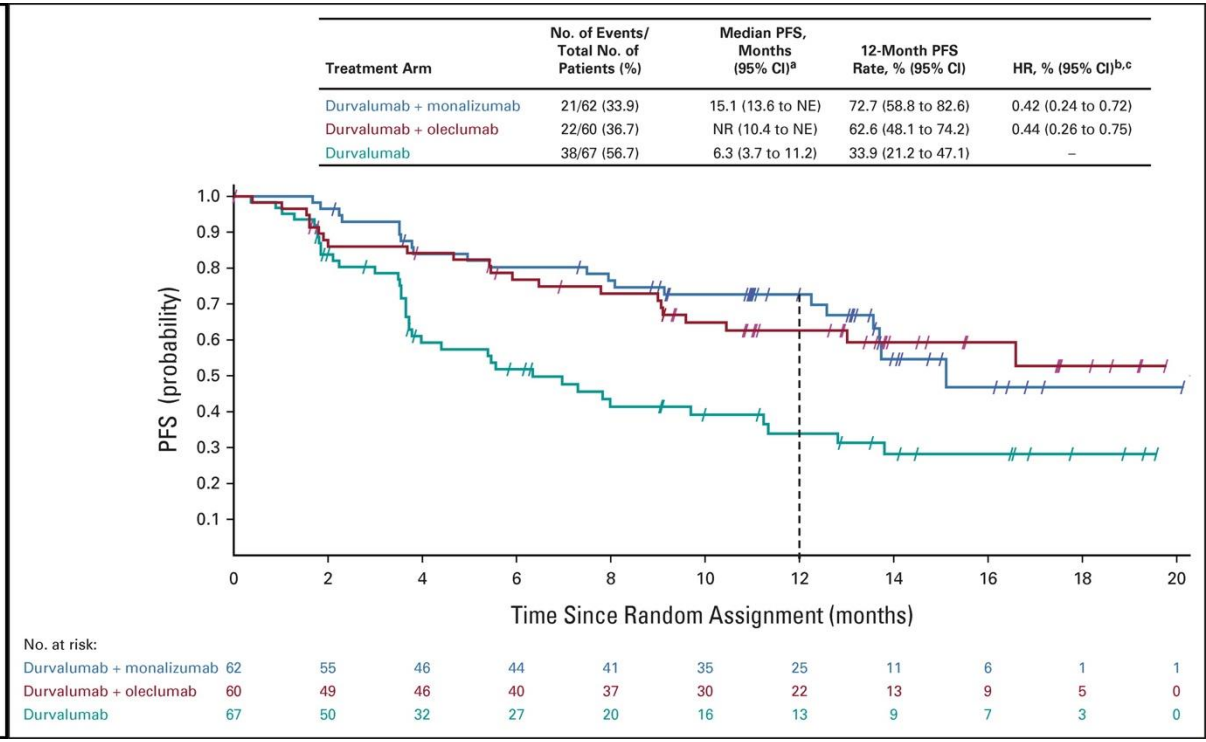
Chemotherapy-Free Immunotherapy/Radiation Trials

Select Dual Consolidation Trials

Trial	Drugs	Design	Endpoint	N
COAST	Durvalumab, Oleclumab, and Monalizumab	Phase 2: CRT followed by randomization to durvalumab, durva/oleclumab, or durva/monalizumab	ORR	189
SKYSCRAPER-03	Atezolizumab and Tiragolumab	Phase III: Adjuvant anti-PD-L1+anti-TIGIT versus adjuvant anti-PD-L1	PFS	800
PACIFIC-8	Durvalumab and Domvanalimab	Phase III: Adjuvant anti-PD-L1+anti-TIGIT versus adjuvant anti-PD-L1	PFS	860
PACIFIC-9	Durvalumab, Oleclumab, and Monalizumab	Phase III: Adjuvant anti-PD-L1+anti-CD-73 vs anti PDL1+anti-NKG2A vs anti-PD-L1	PFS	999
KEYVIBE-006	Pembrolizumab and Vibostolimab	Concurrent and adjuvant anti-PD-L1+anti-TIGIT vs adjuvant anti-PD-L1	OS/PFS	784
KEYLYNK-012	Pembrolizumab and Olaparib	Concurrent and adjuvant PD-L1 with or without adjuvant PARP inhibitor	OS/PFS	870

COAST: A Multi-Drug Platform Study

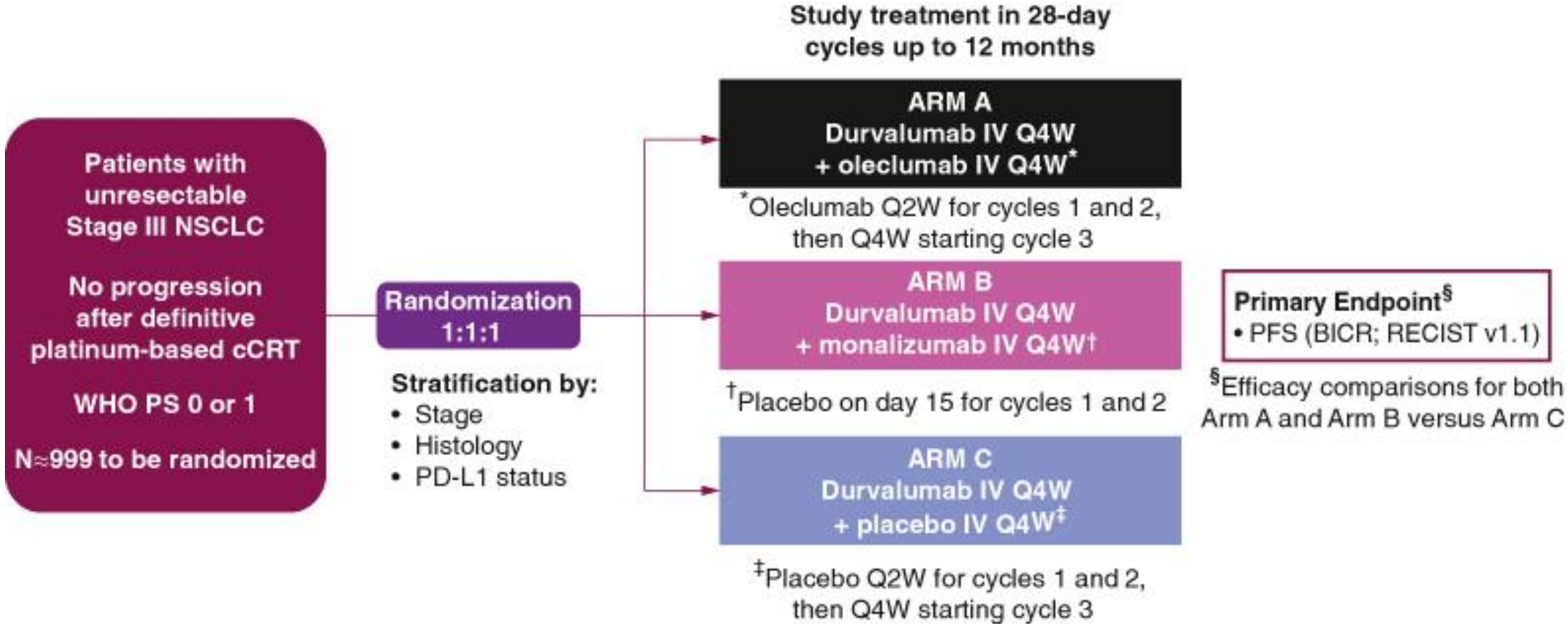




Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–

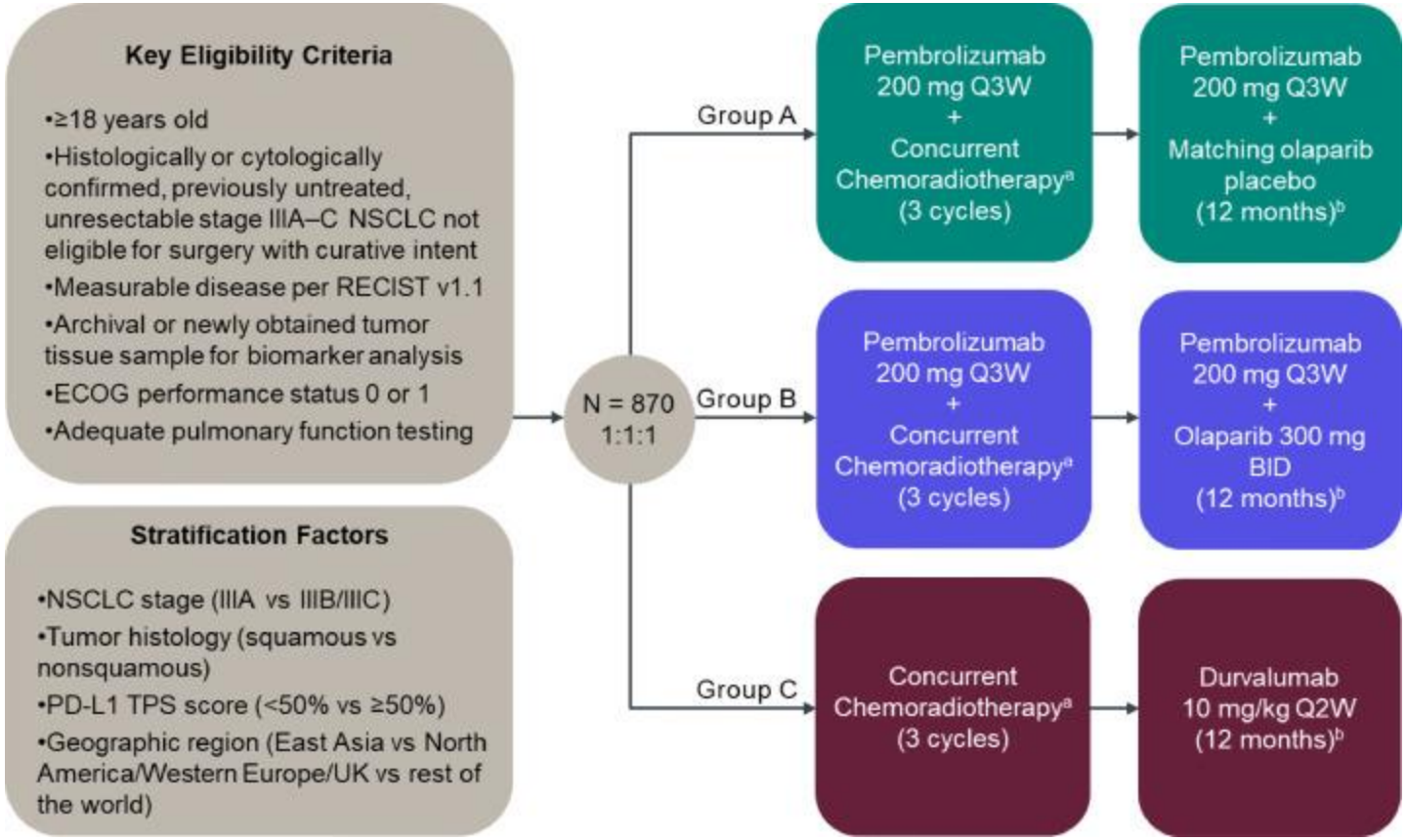
Herbst RS et al. COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 2022.

PACIFIC-9



Barlesi F et al. PACIFIC-9: Phase III trial of durvalumab + oleclumab or monalizumab in unresectable stage III non-small-cell lung cancer. Future Oncology 2024.

KEYLYNK-012



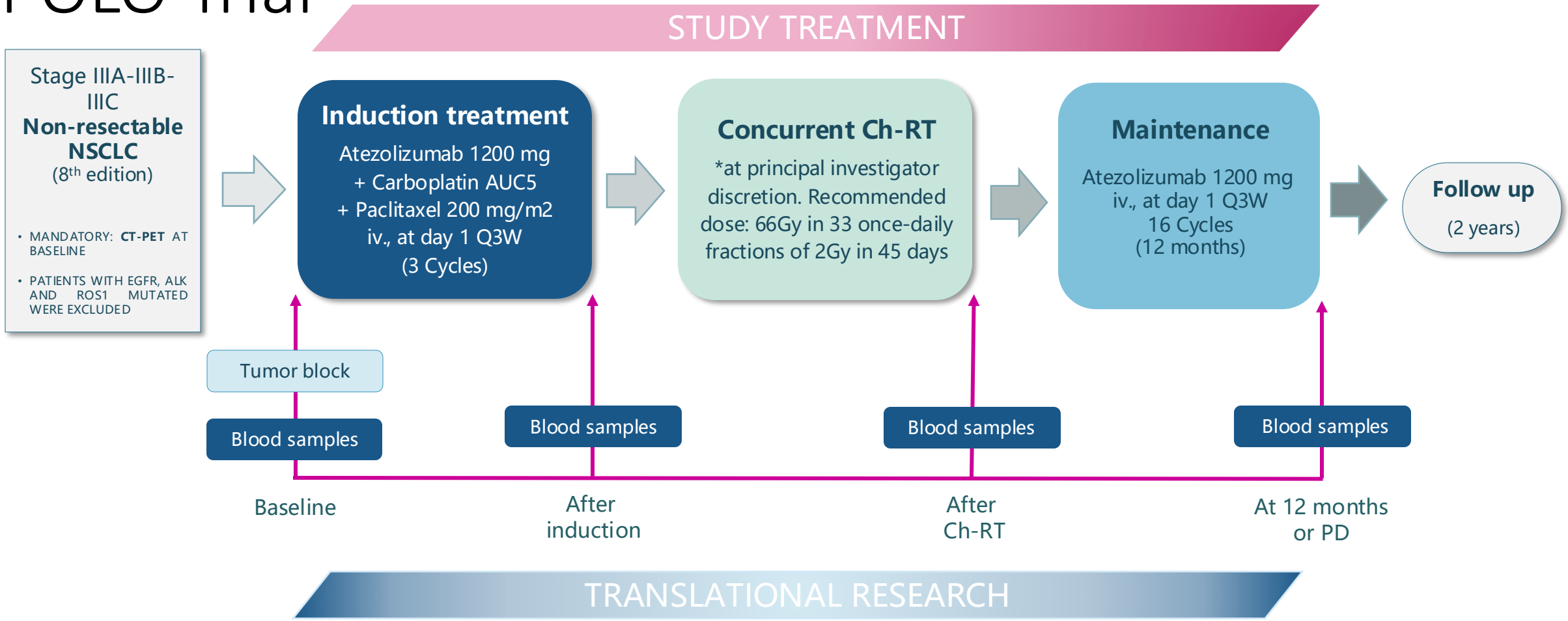
Primary Endpoints: PFS and OS
N=870

Jabbour SK et al. Rationale and Design of the Phase III KEYLYNK-012 Study of Pembrolizumab and Concurrent Chemoradiotherapy Followed by Pembrolizumab With or Without Olaparib for Stage III Non-Small-Cell Lung Cancer. Clinical Lung Cancer 2022.

Select Induction Chemoimmunotherapy Trials

Trial	Drugs	Design	Endpoint	N
APOLO	Atezolizumab	Single arm phase II: Induction chemo-IO with atezolizumab followed by concurrent CRT then maintenance atezolizumab 12 mos	12-month PFS	38
PACIFIC Brazil	Durvalumab	Single arm phase II: Induction chemo-io with durvalumab then concurrent CRT with durvalumab then consolidation durvalumab	12-month PFS	49
DEDALUS	Durvalumab	Single arm Phase II: Induction chemo-IO with durvalumab, then RT-durvalumab (no chemo) then maintenance durvalumab	Adverse events	45

APOLO Trial



Median PFS 20.8 months (95% CI 12.6, NR)
12-month PFS in ITT population 68.4%
18-month PFS in ITT population 60.5%

Provencio M et al. Atezolizumab + induction chemotherapy (Ch) + chemo-radiotherapy (Ch-RT) and atezolizumab maintenance in non-resectable stage IIIA-IIIB-IIIC non-small cell lung cancer (NSCLC): APOLO trial. WCLC 2024

PACIFIC-BRAZIL

ELIGIBILITY CRITERIA

- ✓ Non-small cell lung cancer
- ✓ Stage III (TNM 8th ed.)†
- ✓ PS 0-1
- ✓ FEV1 ≥ 1.2 liters/second (or ≥ 50% predicted value)
- ✓ Predicted lung V20 <35%, cardiac V50 ≤25%
- ✓ No previous local or systemic therapy

INDUCTION CHEMO-IMMUNOTHERAPY

Carboplatin AUC 6 IV+
Paclitaxel 200mg/m² IV+
Durvalumab 1500mg/m² IV q3w for 2 cycles

CONCURRENT CHEMO-IMMUNO-RADIOTHERAPY

Carboplatin AUC 2 IV weekly for 6 weeks +
Paclitaxel 50 mg/m² IV weekly for 6 weeks +
Durvalumab 1500mg/m² q3w for 2 cycles +
Intensity-modulated radiation therapy to 60 Gy in 30 fractions over 6 weeks‡

CONSOLIDATION IMMUNOTHERAPY

Durvalumab 1500mg/m² IV q4w for 12 cycles

PRIMARY ENDPOINT:	**12-month progression-free survival**
SECONDARY ENDPOINTS:	Overall survival, overall response rate, duration of response, patterns of failure, efficacy (iRECIST as opposed to RECIST version 1.1), toxicity (CTCAE version 5)
EXPLORATORY ENDPOINTS:	Predictive biomarkers of response/survival

N=49
12-month PFS: 68.1%
12-Month OS 81.2%

William WN et al. Intensified chemo-immuno-radiotherapy with durvalumab for stage III NSCLC: A single arm phase II study – PACIFIC –BRAZIL (LACOG 2218) WCLC 2024

Select Chemotherapy-Free Immunotherapy/Radiation Trials

Trial	Drugs	Design	Endpoint	N
NRG LU004/ARCHON1	Durvalumab, Oleclumab, and Monalizumab	Initial design: PD-L1>50%, Durva with RT, Amendment adds dual and triple IO cohorts and randomizes against CRT	Safety (ph 1)	48
SWOG S1933	Atezolizumab	Single arm phase II: Hypofractionated RT with atezolizumab consolidation	Adverse events	47
SPRINT	Pembrolizumab	phase II: Cohort for PD-L1>50%, induction pembrolizumab then hypofractionated RT then pembrolizumab consolidation. All others CRT	12-month PFS	25
DOLPHIN	Durvalumab	Radiation with concurrent and adjuvant durvalumab	12-month PFS	33

DOLPHIN Phase 2

Primary registration

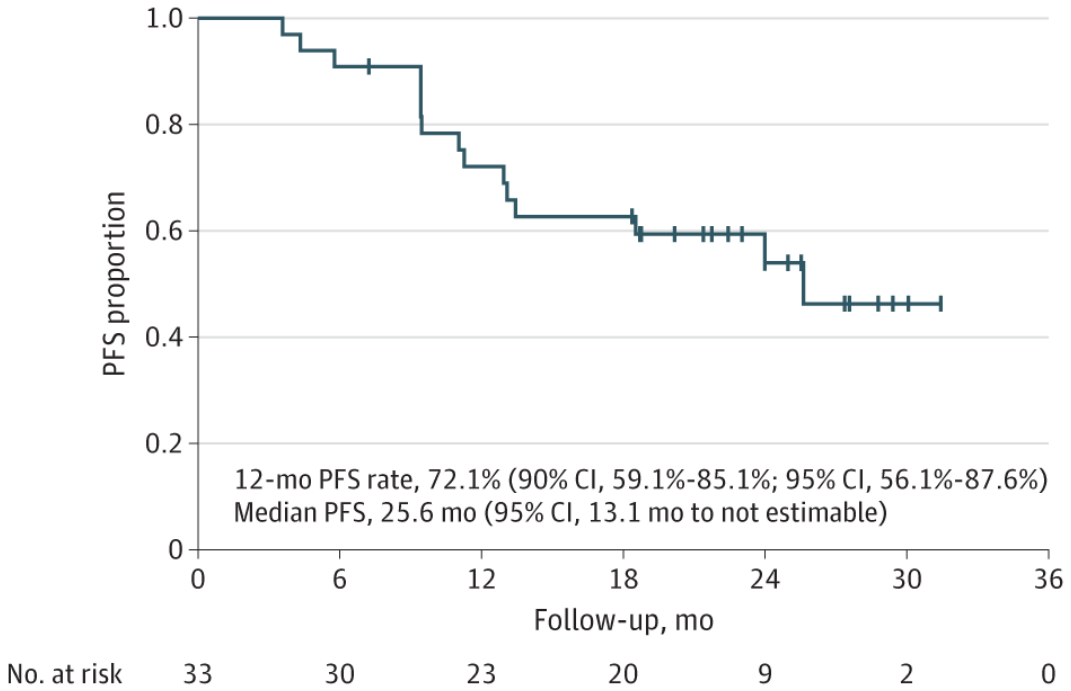
- Suspected unresectable stage III or recurrent NSCLC,
- PS0-1

Secondary registration

- Confirmed unresectable stage III or recurrent NSCLC, PS0-1
- Can be treated according to RT protocol
- PD-L1 $\geq 1\%$

Protocol Treatment

Radiation Therapy 60 Gy with durvalumab (10 mg/kg, Q2w) for up to 1 year until PD or unacceptable toxicity

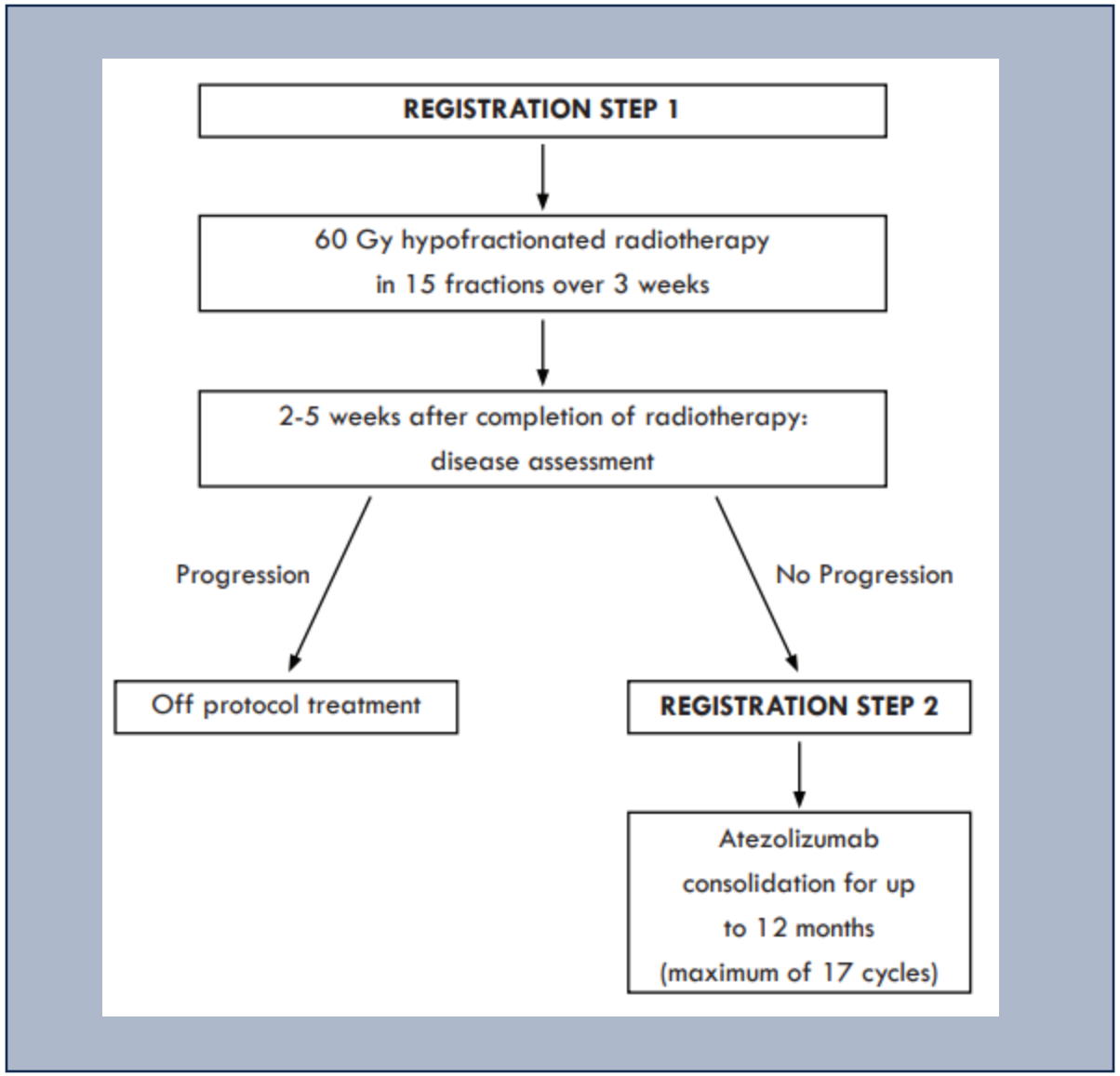


Primary Endpoint: 12-month PFS

12-month PFS: 72.1%

Tachihara M et al. Durvalumab Plus Concurrent Radiotherapy for Treatment of Locally Advanced Non–Small Cell Lung CancerThe DOLPHIN Phase 2 Nonrandomized Controlled Trial. JAMA Oncology 2023

SWOG S1933: Poor Performance Strategy



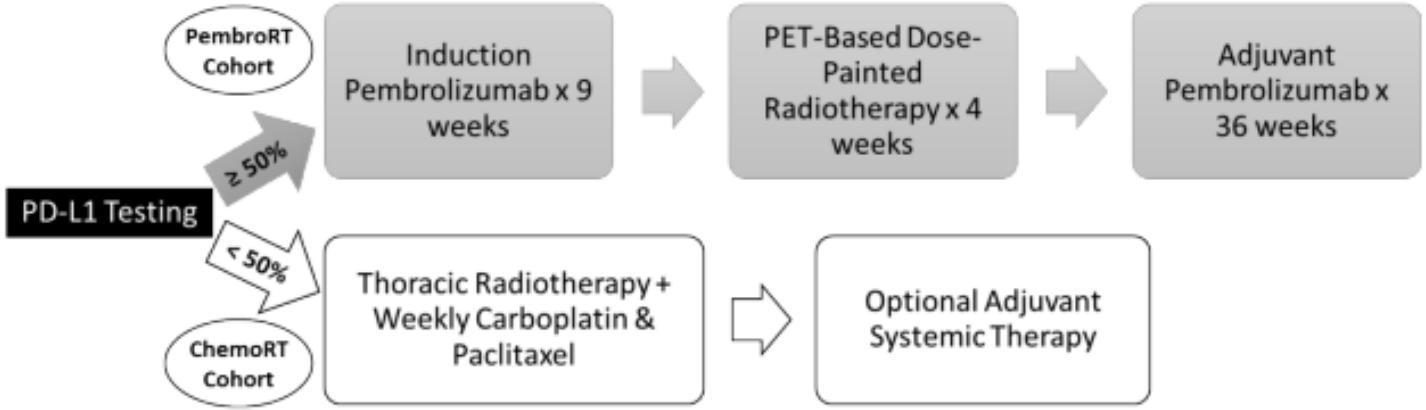
N=47

Primary Endpoint: Grade 3-5 treatment-related Aes

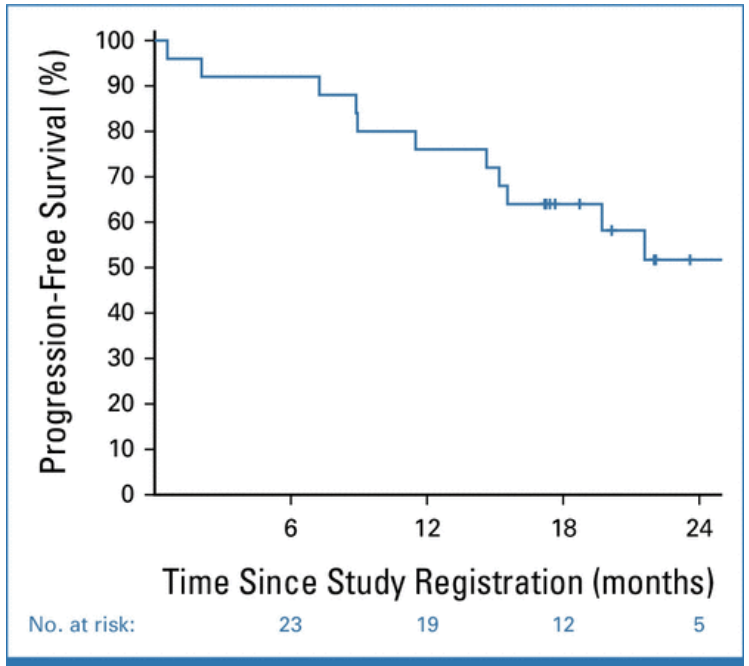
Secondary Endpoints

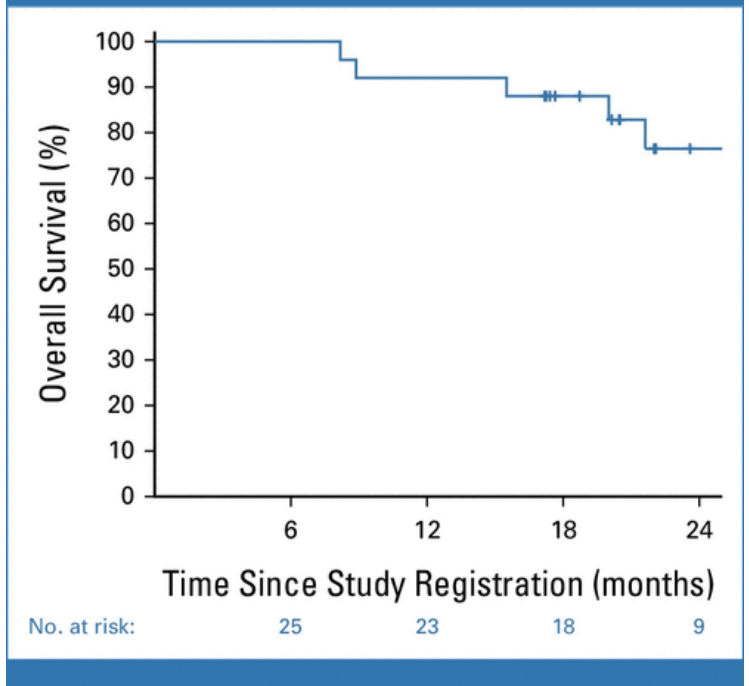
- Response rate
- PFS
- OS

SPRINT Trial



1-year PFS 76%
1-year OS 92%
2-year OS 76%





Ohri N et al. Selective Personalized RadioImmunotherapy for Locally Advanced Non–Small-Cell Lung Cancer Trial (SPRINT). JCO 2023

Summary

- Concurrent chemoradiation followed by 12 months consolidation durvalumab remains the standard of care for good performance status patients without select oncogenic drivers
- Concurrent immunotherapy with CRT has thus far been disappointing, with no benefit to PFS or OS noted
- Ongoing trials are evaluating dual consolidation strategies, induction strategies, and elimination of chemotherapy