Decennale di
HIGHLIGHTS in
RADIOTERAPIA

Update degli Studi
Practice Changing 2024

Undicesima Edizione

In memoria di Renzo Corvò

New evidence and practice changing treatments in thoracic tumors.

Marco Trovò

ROMA
30-31 gennaio 2025
Starhotels Metropole

No conflicts of interest to disclose

Treatment De-intensification in NSCLC

Radiotherapy Volumes
Chemotherapy
PORT
Technology

Original Reports | Radiation Oncology

Selective Personalized RadioImmunotherapy for Locally Advanced Non–Small-Cell Lung Cancer Trial (SPRINT)

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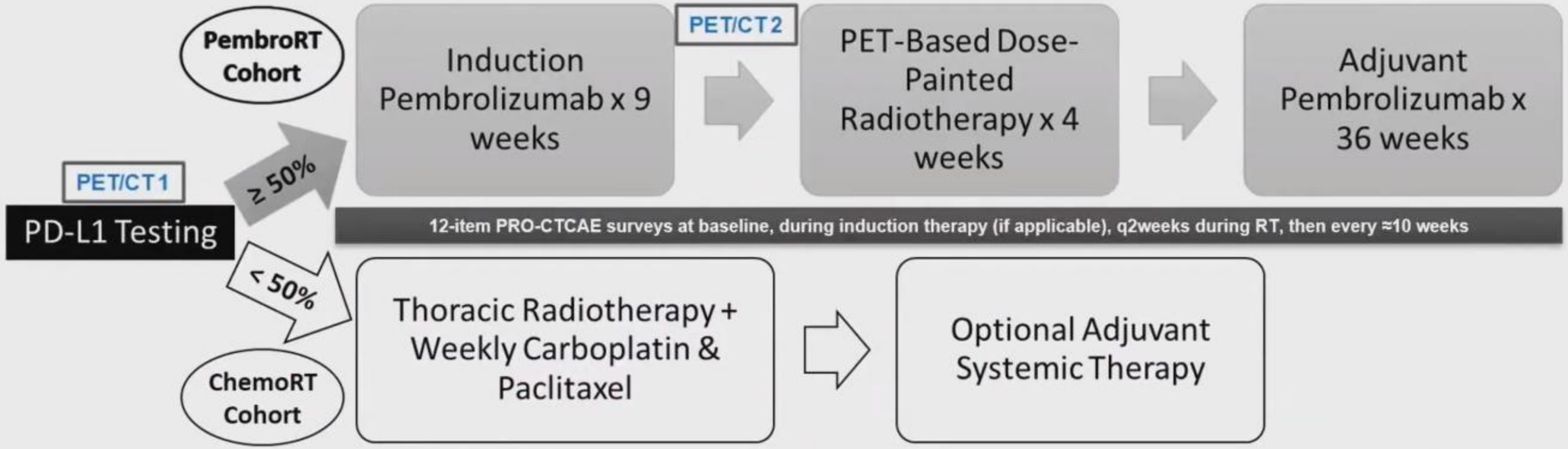
HYPOTHESIS: COMBINATION OF PEMBROLIZUMAB AND RISK-ADAPTIVE RADIOTHERAPY, WITHOUT CHEMOTHERAPY, COULD IMPROVE OUTCOMES AND TOXICITY

SPRINT Study Design



Key Eligibility Criteria:

- AJCC v8 unresectable stage II or stage III NSCLC
- ECOG performance status 0-1
- Known PD-L1 TPS for treatment assignment (not randomized)
- No contraindication to protocol-specified therapy

Play

Risk-Adapted Radiotherapy

PembroRT Cohort

PET/CT 1

PD-L1 Testing

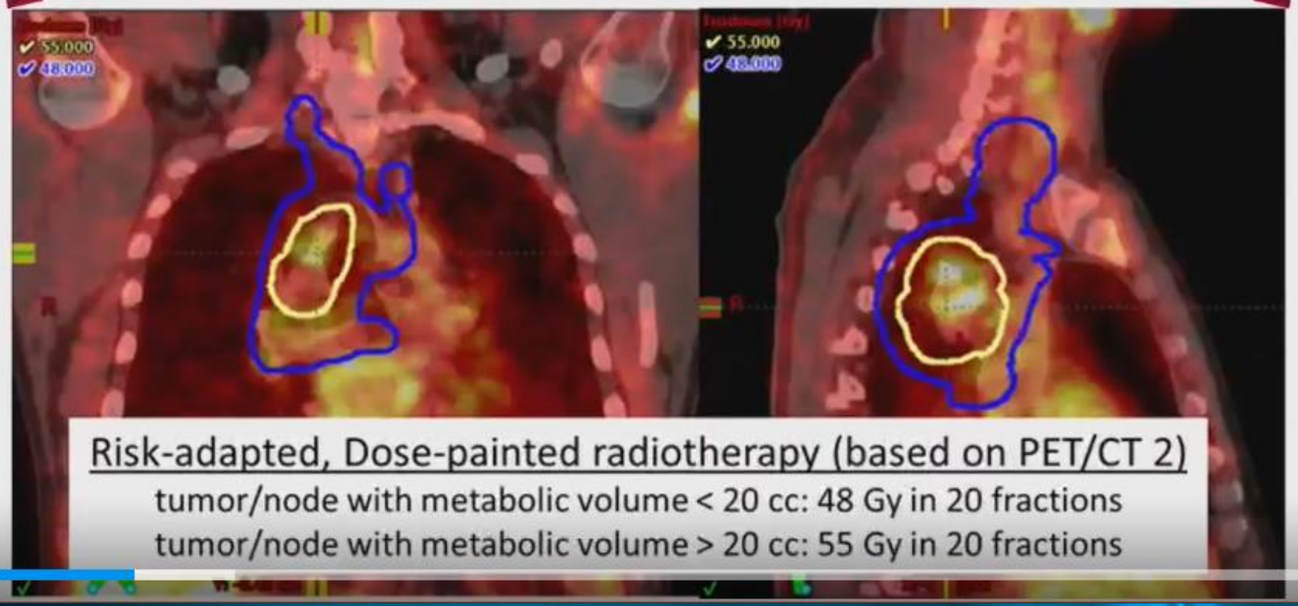
≥ 50%

Induction Pembrolizumab x 9 weeks

PET/CT 2

(DE-INTENSIFIED) PET-Based Dose-Painted Radiotherapy x 4 weeks

Adjuvant Pembrolizumab x 36 weeks



Risk-adapted, Dose-painted radiotherapy (based on PET/CT 2)

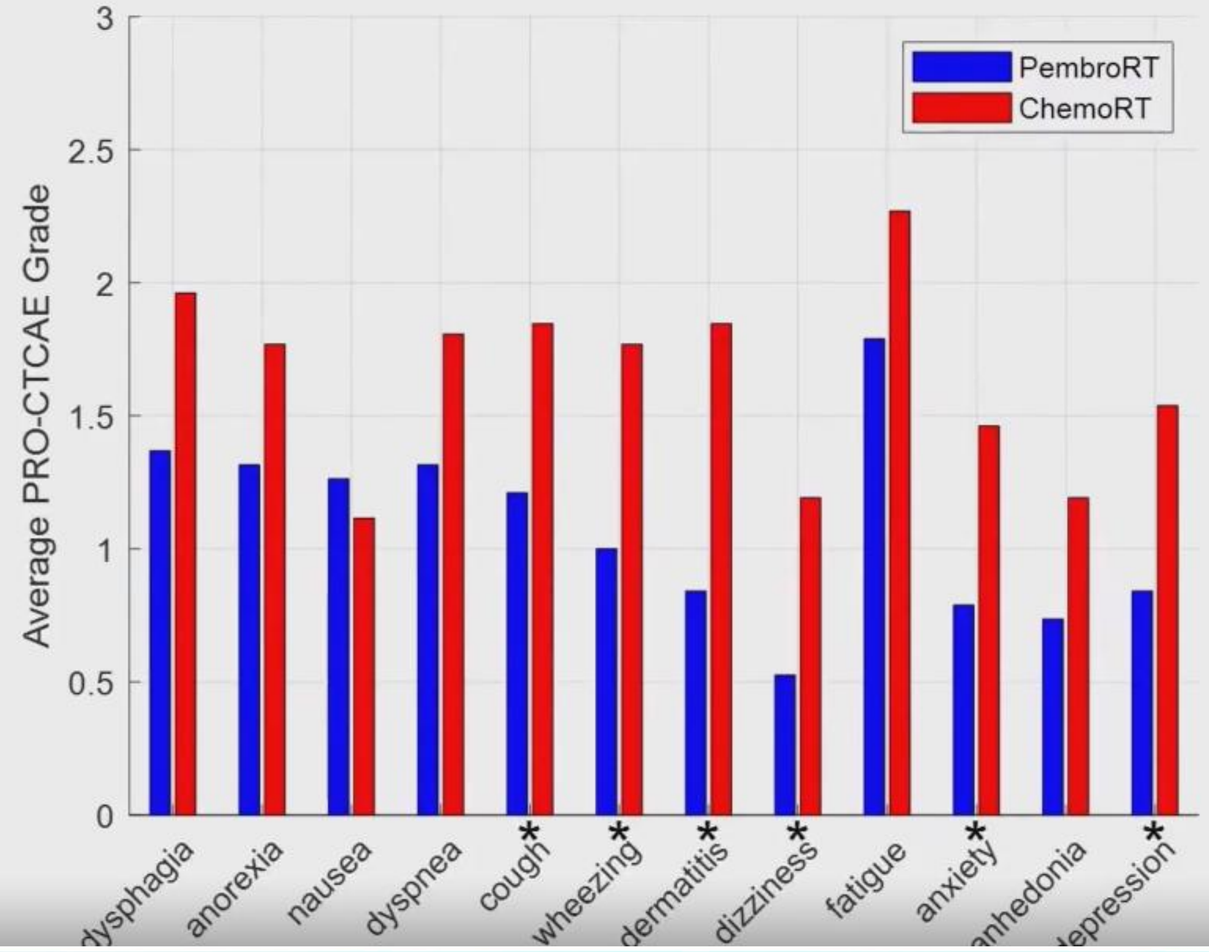
tumor/node with metabolic volume < 20 cc: 48 Gy in 20 fractions

tumor/node with metabolic volume > 20 cc: 55 Gy in 20 fractions

Patient Characteristics

	PembroRT Cohort (n=19)	ChemoRT Cohort (n=26)	p
Gender Male Female	 10 (53%) 19 (47%)	 11 (42%) 15 (58%)	0.493
Age, mean (range)	67 (53 to 86)	69 (48 to 83)	0.608
Clinical stage, n (%) II IIIA IIIB IIIC	 1 (5%) 9 (47%) 8 (42%) 1 (5%)	 1 (4%) 12 (46%) 10 (38%) 2 (8%)	1.000
ECOG Performance Status, n (%) 0 1	 7 (35%) 12 (60%)	 6 (23%) 20 (77%)	0.314
Histology, n (%) Adenocarcinoma Squamous cell carcinoma Other/not specified	 9 (47%) 8 (42%) 2 (11%)	 12 (46%) 22 (42%) 3 (12%)	1.000
PD-L1 tumor proportion score, n (%) 0 to 49% 50 to 100% Unknown	 0 (0%) 19 (100%) 0 (0%)	 16 (62%) 5 (19%) 5 (19%)	-
Metabolic tumor volume, median (range)	25 cc (3 to 614)	41 cc (2 to 191)	0.756
Mean esophagus dose, median (range)	15.2 Gy (1.5 to 29.7)	20.3 Gy (4.2 to 34.3)	0.048
Mean heart dose, median (range)	6.4 Gy (0.6 to 24.6)	9.4 Gy (0.1 to 29.2)	0.190
Mean lung dose, median (range)	8.2 Gy (4.8 to 16.7)	12.7 Gy (2.5 to 20.2)	0.003

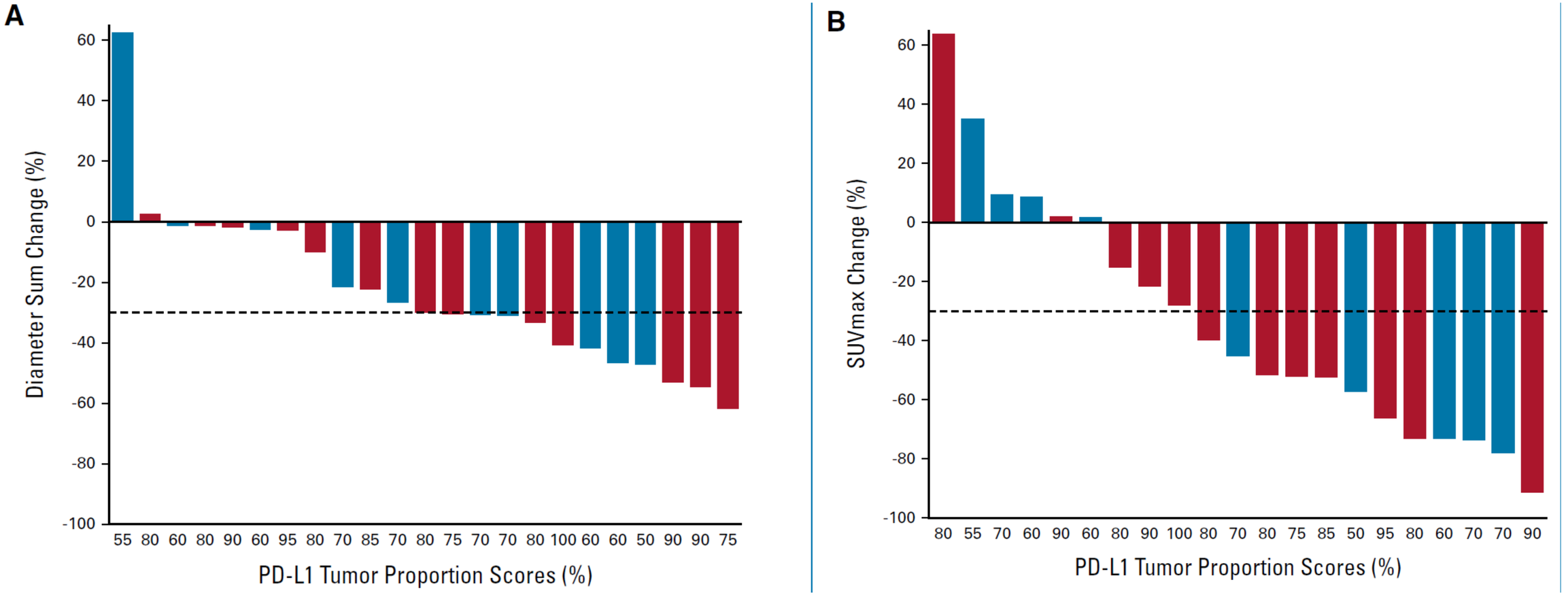
PRO-CTCAE Adverse Events



*p<0.05

Pause

RESPONSE to IMMUNOTHERAPY



RESULTS

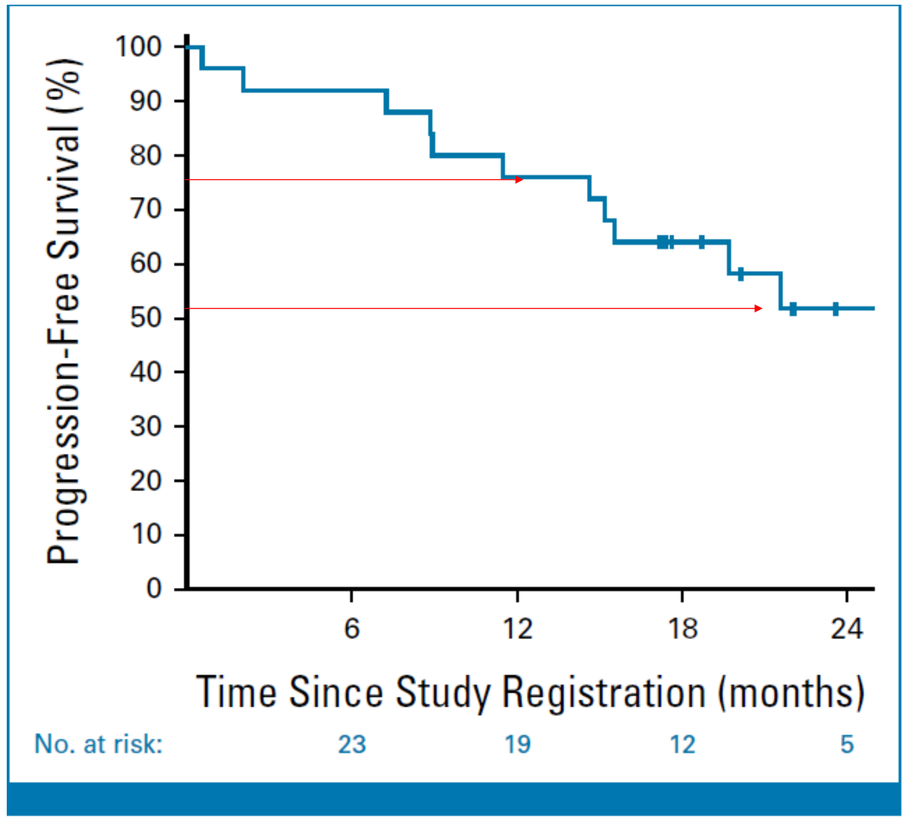


FIG 3. Kaplan-Meier curve for progression-free survival.

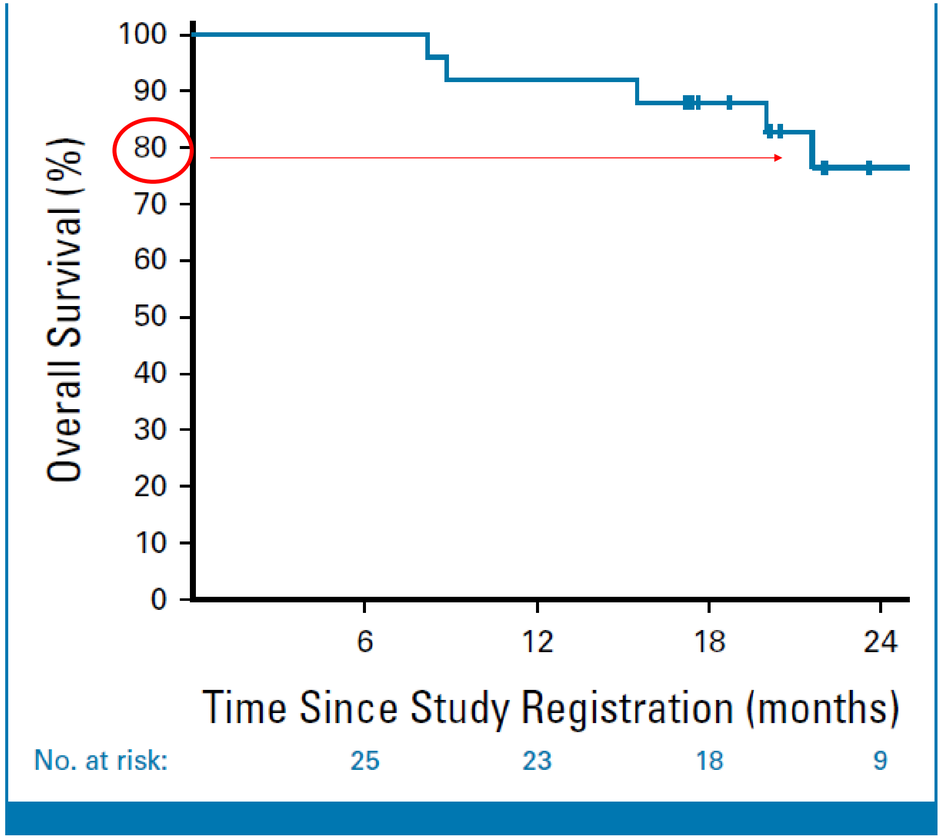
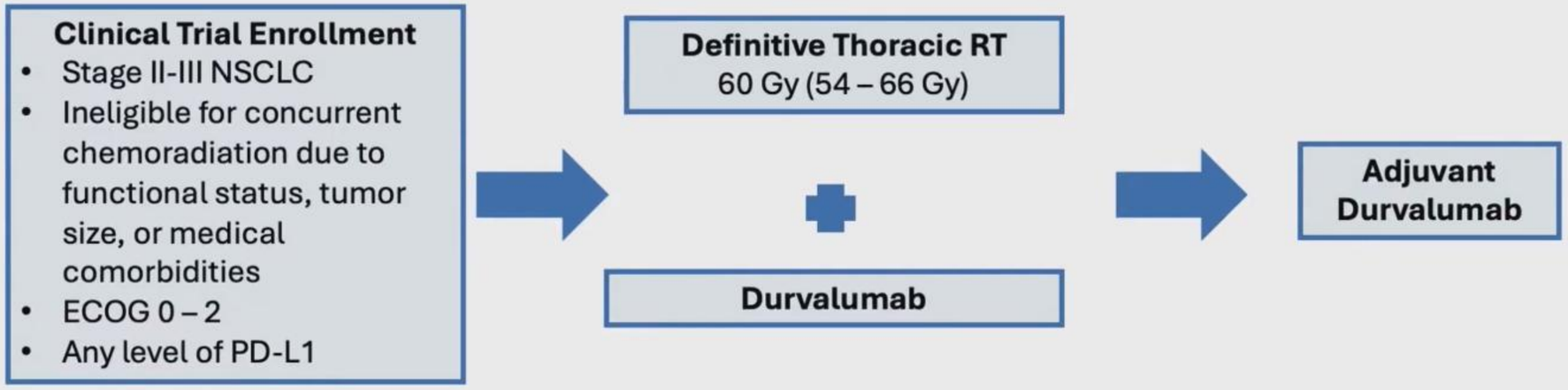


FIG 4. Kaplan-Meier curve for overall survival.

Study Design

DART



Pause

Methods

Primary endpoint:

2-year Progression-Free Survival (PFS)

Secondary endpoints:

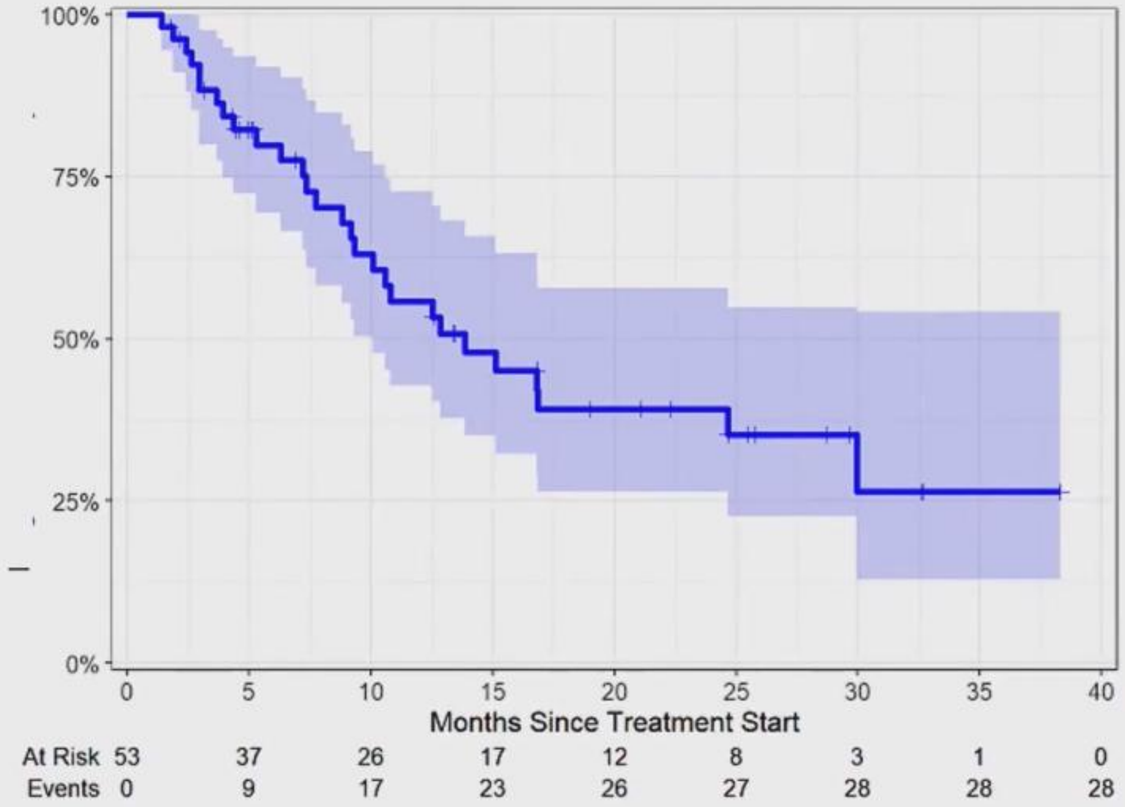
- 2-year Overall Survival (OS)
- Safety and tolerability
- Response rate per RECIST 1.1
- ctDNA biomarker analysis

Statistical Power:

One-sided log-rank test for an improvement from

- 2-year PFS of 20% (null hypothesis based on historical results of sequential CRT) to
- 2-year PFS of 36% (alternative hypothesis)

Results
Progression-Free Survival



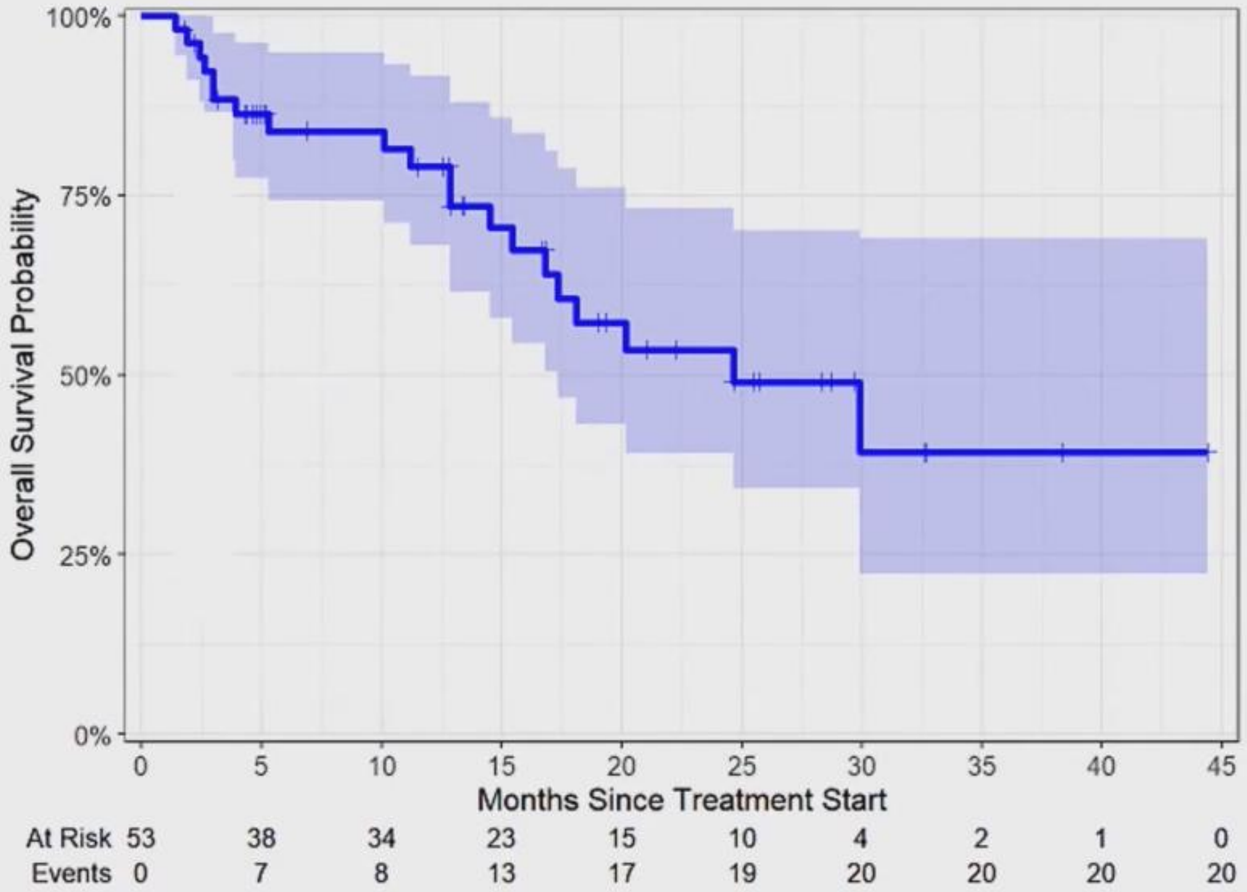
Median: 14 months

1-year PFS: 56%

2-year PFS: 39%

One-sided CI for the 2-year PFS estimate is (28%, ∞).

Results
Overall survival



Median OS: 25 months

1-year OS: 79% (95% CI 68% - 92%)

2-year OS: 53% (95% CI 39% - 73%)

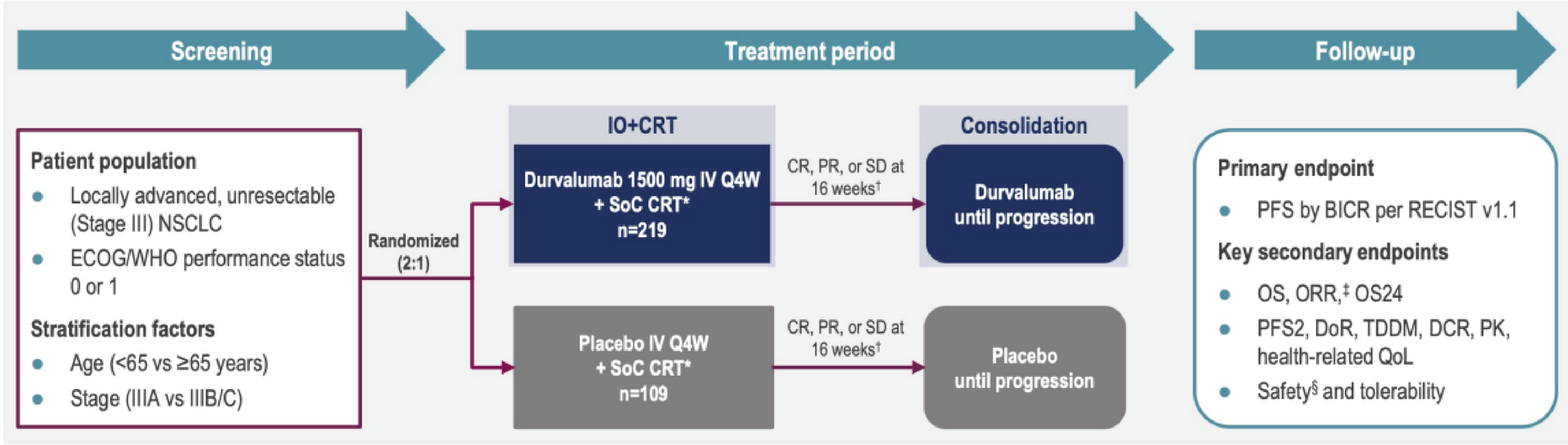
Single-Arm Phase II Studies on RT + durvalumab

Trial	cCRT eligibility	PD-L1	Intervention	12-month PFS
DART	Ineligible	Any	RT with concurrent and adjuvant durvalumab	56%
UTSW[1]	Ineligible	Any		20%
DOLPHIN[2]	Eligible	≥ 1%		72%
DUART[3]	Ineligible	Any	RT with adjuvant durvalumab	40%
PACIFIC[4]	Eligible	Any	Adjuvant durvalumab following cCRT	56%
PACIFIC-6[5]	Ineligible	Any	Durvalumab after sequential CRT	49%

[1]Zhang et al. *International Journal of Radiation Oncology*Biology*Physics*. 2024
[2]Tachihara et al. *JAMA Oncol*. 2023.
[3]Filippi et al. *Future Oncol*. 2021, ESMO 2023
[4]Antonia et al. *NEJM*. 2017.
[5]Garassino et al. *JTO*. 2022.

PACIFIC-2

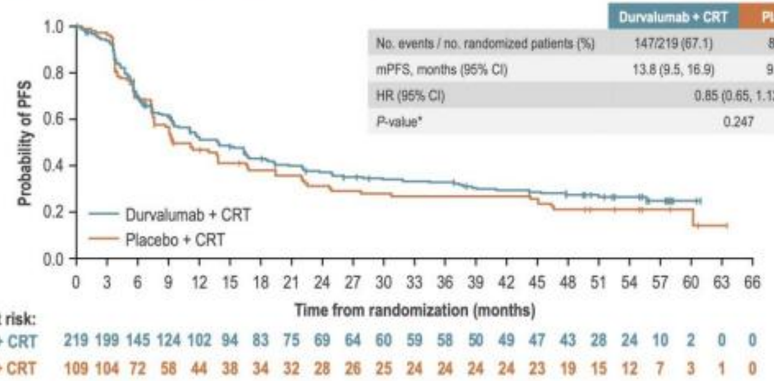
PACIFIC-2 (NCT03519971) is a phase 3, randomized, double-blind, placebo-controlled, multicenter, global study of durvalumab + CRT followed by durvalumab versus placebo + CRT followed by placebo



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

Courtesy of J. D. Bradley from ELCC2024

PFS by BICR (ITT population)



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

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

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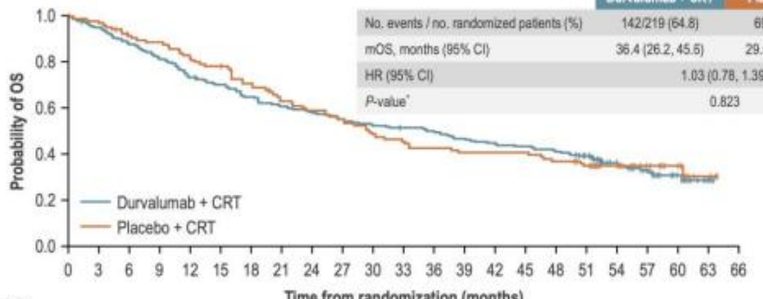
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mPFS, median PFS; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

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

OS and ORR (ITT population)



	Durvalumab + CRT	Placebo + CRT
No. events / no. randomized patients (%)	142/219 (64.8)	69/109 (63.3)
mOS, months (95% CI)	36.4 (26.2, 45.6)	29.5 (23.2, 45.1)
HR (95% CI)	1.03 (0.78, 1.39)	
P-value*	0.823	

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

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

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

Tick marks on the curves indicate censored observations.
*The 2-sided p value boundary for declaring statistical significance is 4.8% or 5% depending on the previous levels of the multiple testing procedure.

Summary of AEs (safety population)

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

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

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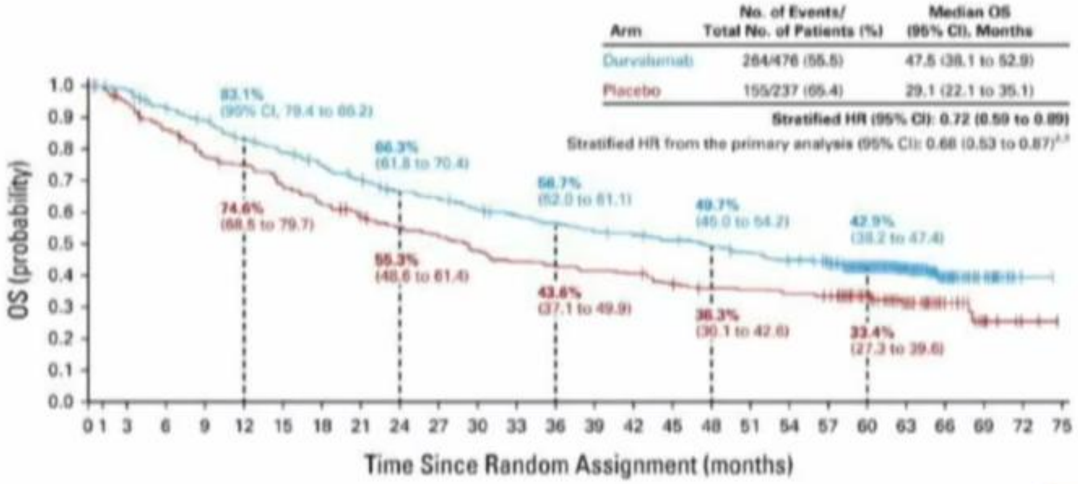
AE, adverse event; CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; IO, immunotherapy; SAE, serious adverse event; SoC, standard of care.

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

Courtesy of J.D. Bradley from ELCC2024

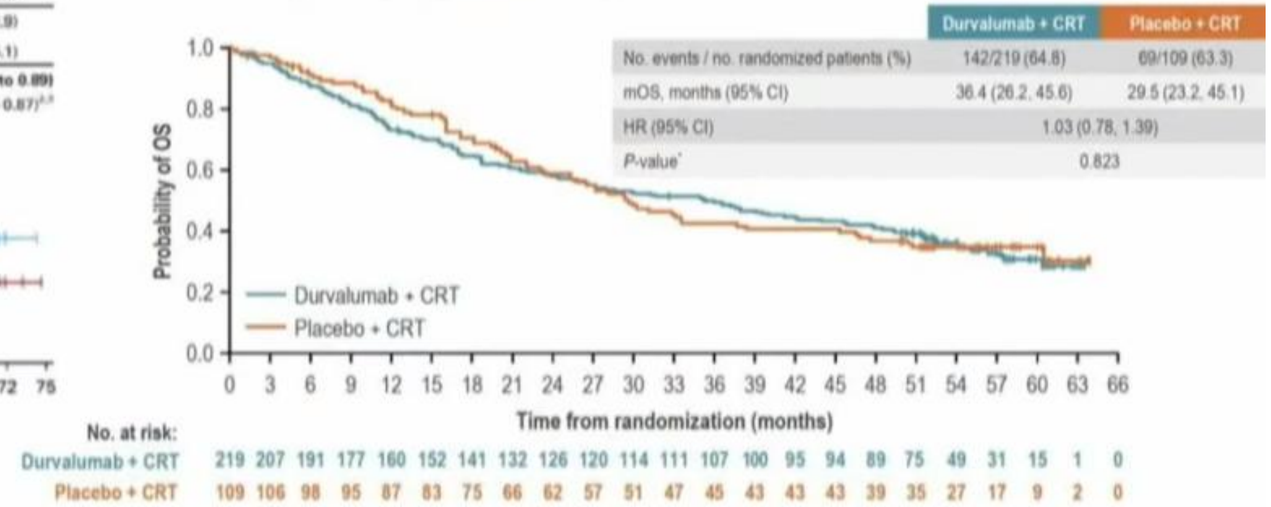
Consolidation vs. Concurrent Immunotherapy

PACIFIC: Consolidative durvalumab



Spigel et al, JCO 2022

PACIFIC-2: Concurrent durvalumab



Bradley et al, ELCC 2024

Lesson 2: Concurrent radiation may limit immunotherapy benefit

Checkmate 73L, CALLA, Head and Neck (JAVELIN)

ASTRO 2024

Targeting Provider Wellness

FOR EXCEPTIONAL PATIENT CARE

ASTRO 66TH ANNUAL MEETING

September 29 – October 2, 2024 • Walter E. Washington Convention Center, Washington, DC

Long-term Outcomes of Postoperative Radiotherapy for Patients with pN2 Non–Small Cell Lung Cancer After Complete Resection and Adjuvant Chemotherapy ——The Phase 3 PORT-C Randomized Clinical Trial

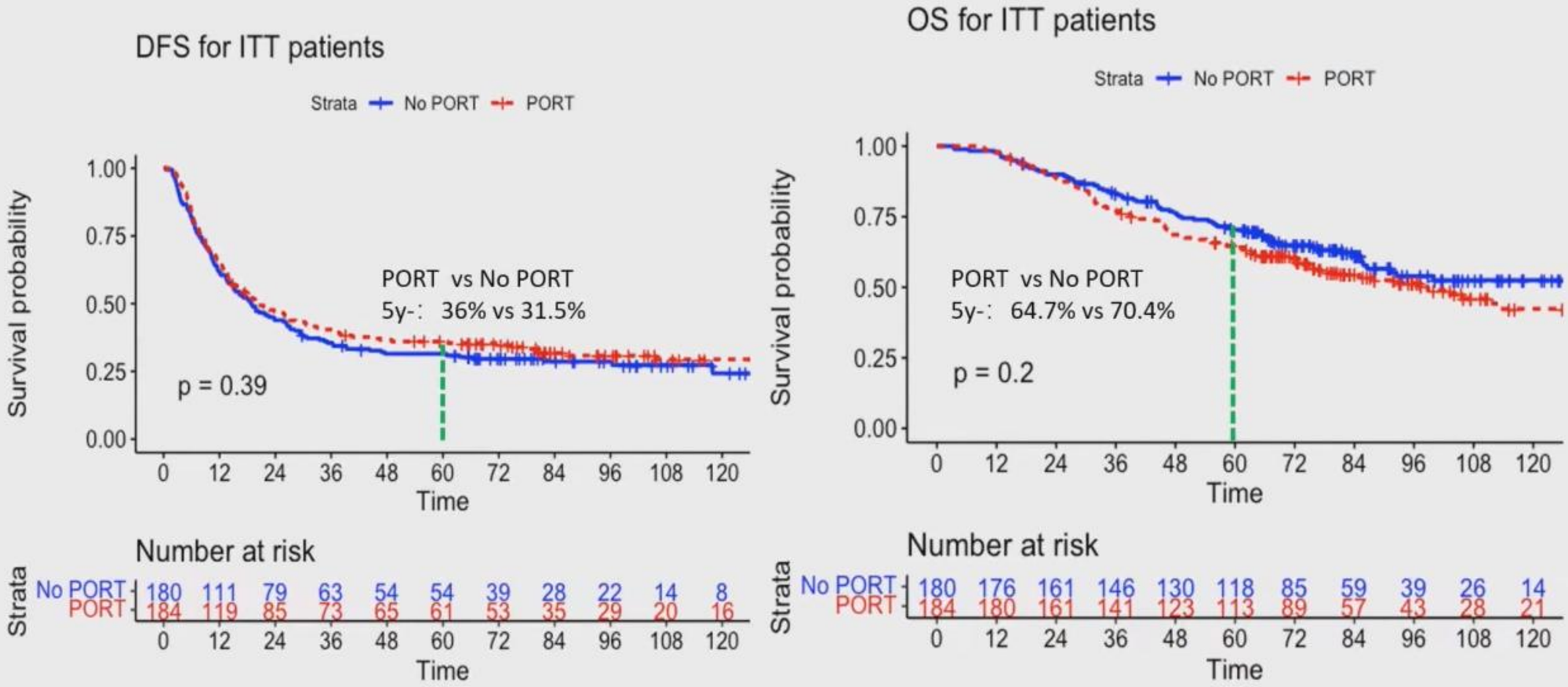
*Yu Men; **Zeliang Ma**; Yongxing Bao; Nan Bi; Zongmei Zhou; Jun Liang; Jima Lv; Qinfu Feng; Zefen Xiao; Yan Wang; Junling Li; Jie Wang; Shugeng Gao; Zhouguang Hui; Luhua Wang; Jie He*

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital
Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Study Design

- ✓Primary endpoint: DFS
- ✓Secondary endpoints: OS, LRFS, DMFS
- ✓Planned sample size: 360 patients to detect a HR of 0.69 with a power of 80% at 1-sided type 1 error of 0.025
- ✓PORT: 3D-CRT/IMRT; 50Gy/25f.
  Ipsilateral hilum, subcarinal region and ipsilateral mediastinum.
  The stump of the central lesions.

Results-survivals(mITT)



MD Anderson

Study Design

Screening

NSCLC Selection Criteria:

- Concurrent chemoradiation with 60-74Gy
- Stage IIB to IIIB;
- Stage IV with a single brain metastasis
- Recurrent lung or mediastinal disease after surgery
- KPS more than 70

Treatment period (2009 to 2014 year)

IMRT & PSPT plans acceptable

Bayesian adaptive randomization

- IMRT
- PSPT

Follow-up (10 year)

Primary endpoints:

- Grade ≥3 radiation pneumonitis (RP)
- Local failure (LF)

Secondary endpoints:

- Overall survival (OS)
- Progression-free survival (PFS)
- Esophageal toxicity
- Major Adverse Cardiac Events (MACE)

- Historical data indicated a 15% RP rate at 1 year for the IMRT group, while the PSPT group had a 5% RP rate at 1 year. Both groups were expected to have a 25% LF rate due to identical tumor dosing.
- The study had 81% power with 150 evaluable patients. The Bayesian adaptive design ensured robust frequentist properties.
- Patients with paired plans meeting dose constraints for both PSPT and IMRT were randomly assigned to one of the two treatment arms

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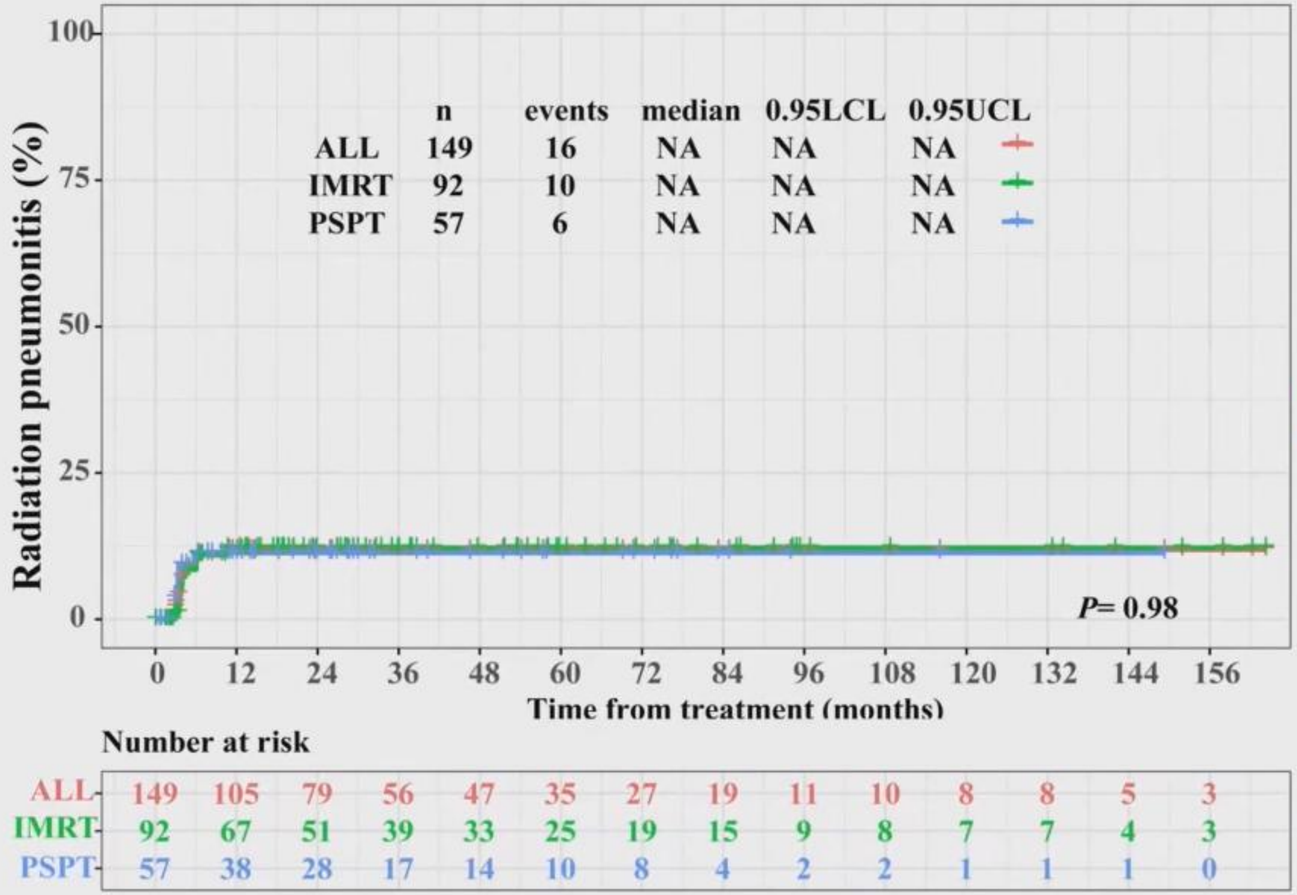
Grade ≥3 Pneumonitis: No difference between 2 arms



Grade ≥3 radiation pneumonitis (RP)
- IMRT group: 10 (10.5%)
- PSPT group: 6 (10.9%)

Grade 5 RP:
- IMRT group: 2 (2.2%)
- PSPT group: 0

All cases occurred within the first 12 months post-treatment

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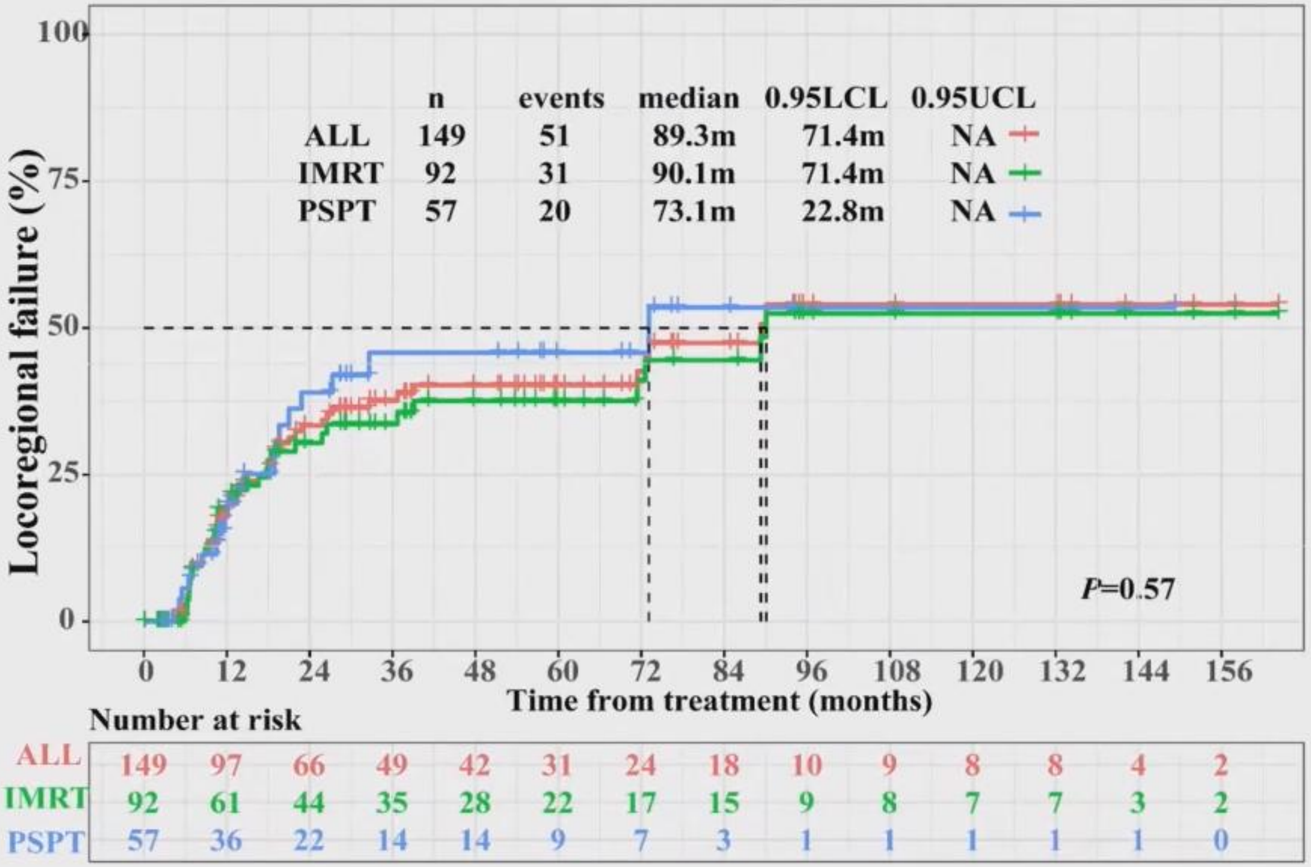
LRF and pattern: No difference between 2 arms



Total locoregional failure
- IMRT group: 31 (33.7%)
- PSPT group: 20 (35.1%)

Local failure
- IMRT group: 23 (25.0%)
- PSPT group: 16 (28.1%)

Regional failure
- IMRT group: 8 (8.7%)
- PSPT group: 3 (5.3%)

Local-regional failure
- IMRT group: 0
- PSPT group: 1 (1.8%)

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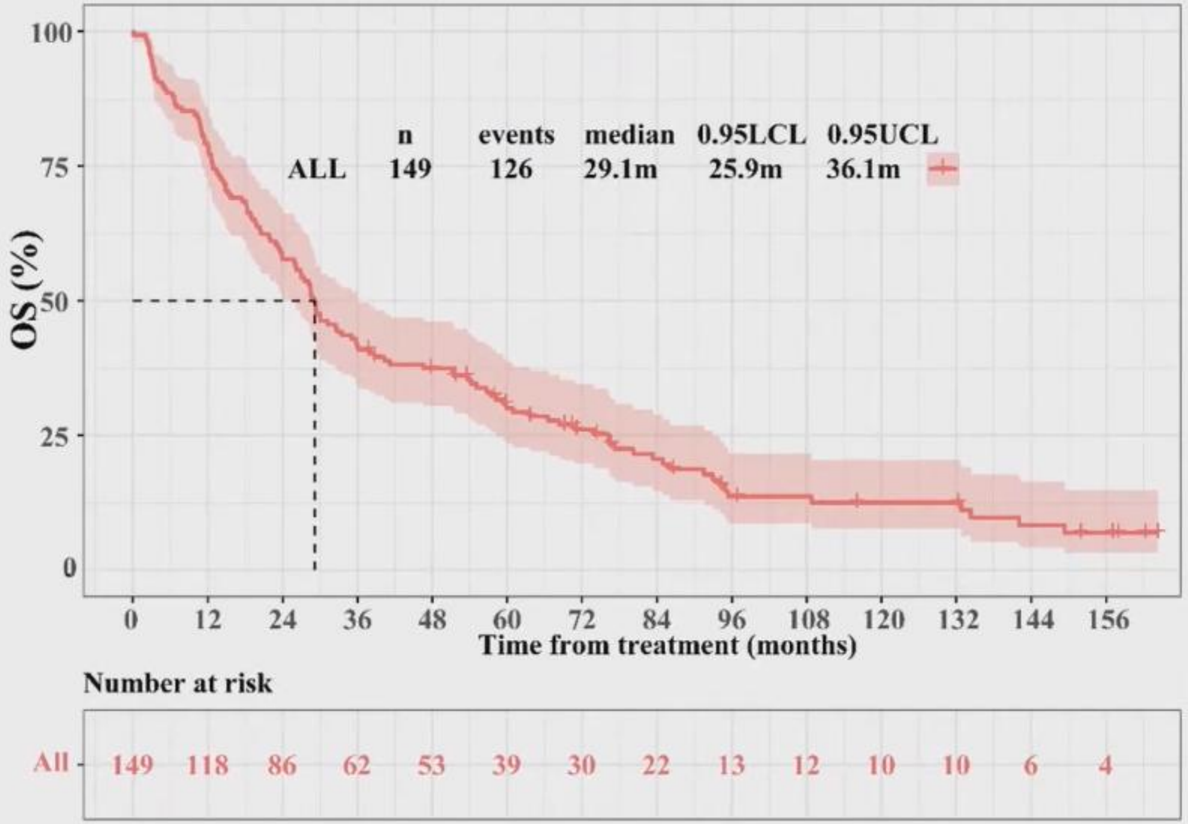
Modality (PSPT vs. IMRT) has no significant impact on OS



Factors for OS analysis

Factor	P	HR	95%CI
Age(younger)	0.056	1.021	0.999-1.043
Total dose(74Gy)	0.019	0.583	0.372-0.914
Heart V10	0.018	0.293	0.106-0.812
GTV (smaller)	0.006	1.002	1.001-1.003

Thank you for your attention!