16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

GECP lung cancer research

Feasibility concomitant immunotherapy and radiotherapy

REYES BERNABÉ CARO

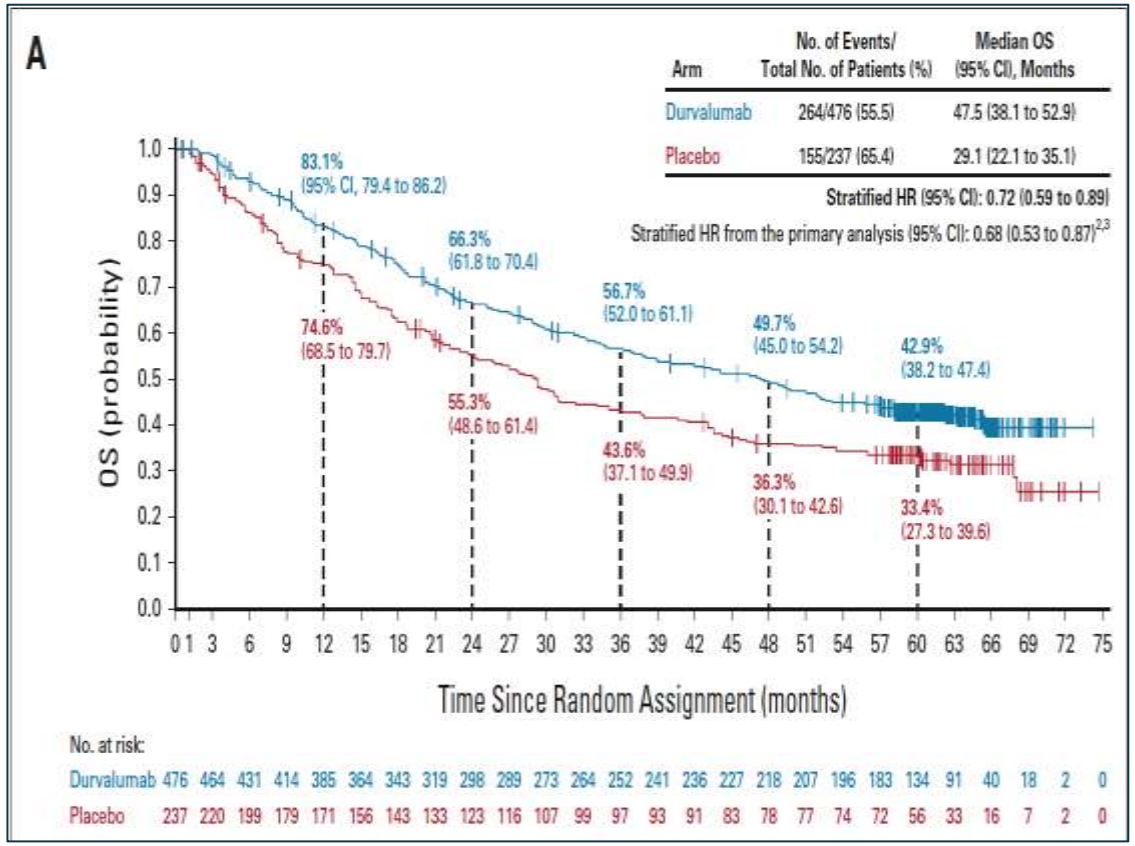
HOSPITAL VIRGEN DEL ROCIO . SEVILLA

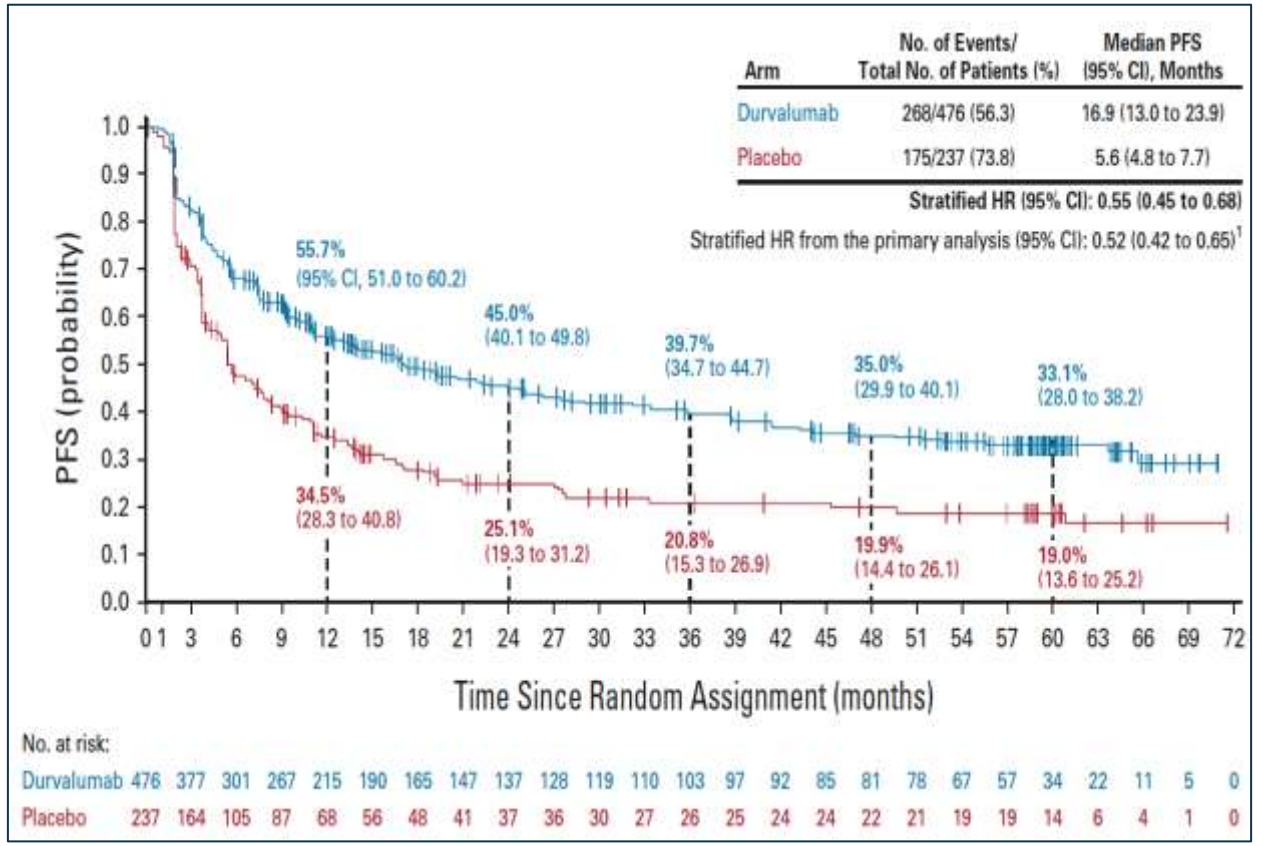
CONFLICTO DE INTERESES

- Consultant or Advisory Role: Astra Zeneca, Roche, BMS, Lilly, MSD, Takeda, Janssen, Amgen,BeOne, PharmaMar

- Research Funding: Roche
- Speaking: Astra Zeneca, Roche, BMS, Lilly, MSD, Takeda, Janssen, Amgen, Pfizer.

Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer



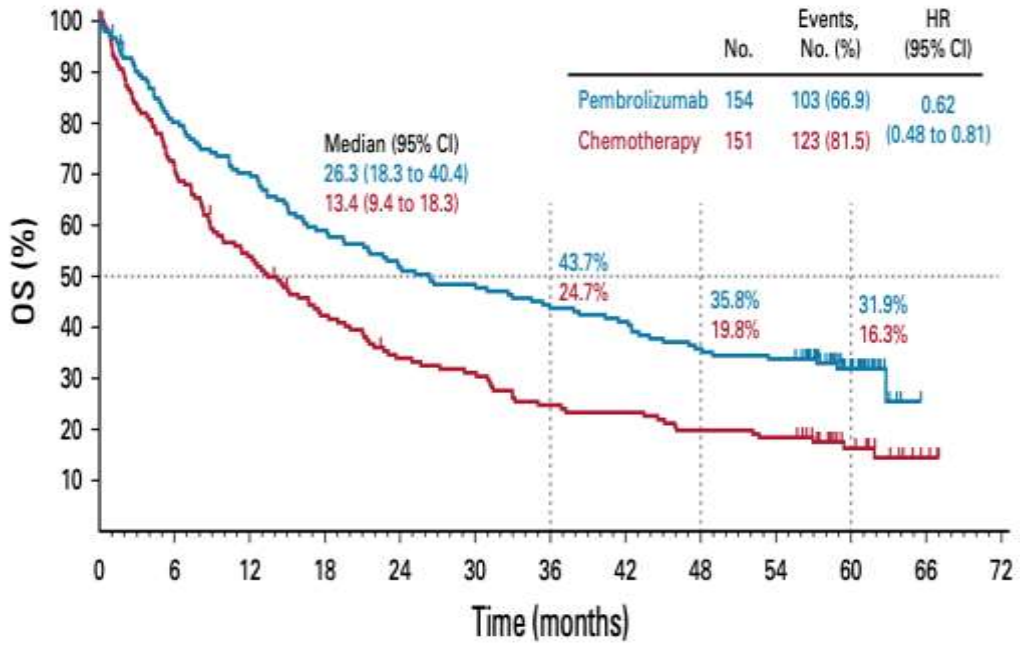


Entre 30-50% estadio III no llega a recibir la consolidación con Durvalumab

Spigel, JCO 2022, 40:12; Front. Oncol. 2020, 10, 586449; Respir. Investig. 2019, 57, 466–471.

Goodbye to chemotherapy?

KEYNOTE-024

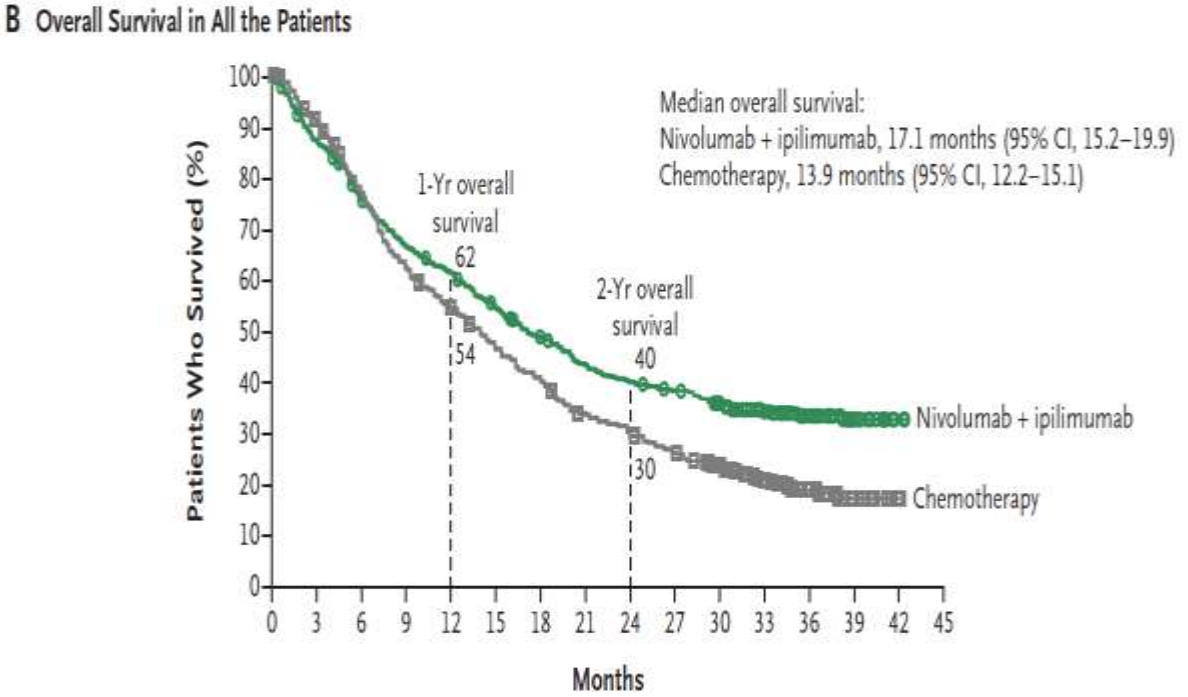


No. at risk:

Pembrolizumab	154	121	106	89	78	73	66	62	54	51	20	0	0
Chemotherapy	151	108	80	61	48	44	35	33	28	26	13	3	0

J Clin Oncol 2021 Apr 19;39(21):2339–2349

Checkmate 227

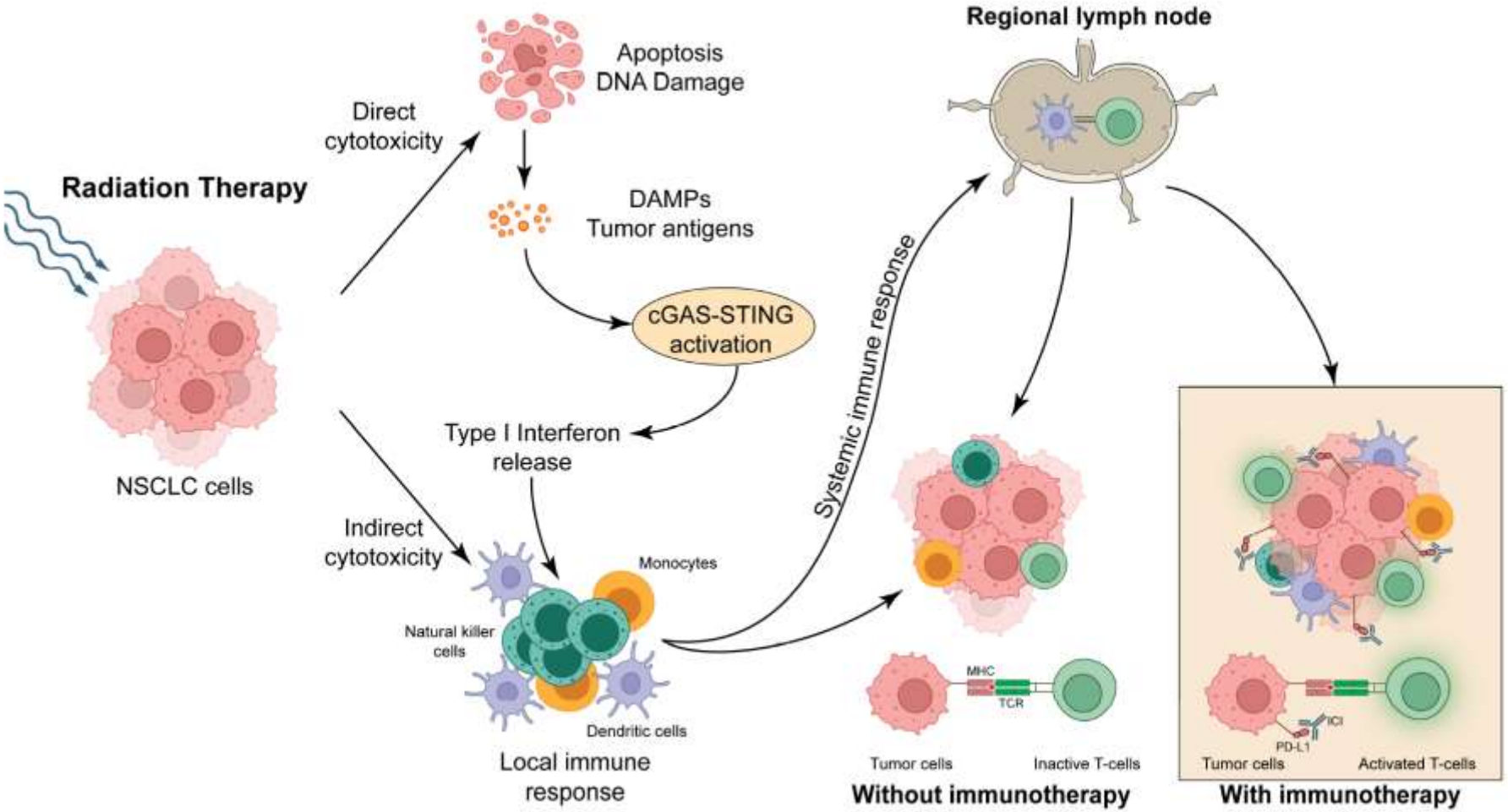


No. at Risk

Nivolumab + ipilimumab	583	506	437	384	354	312	277	245	226	214	188	125	60	17	3	0
Chemotherapy	583	522	441	357	310	264	228	190	167	147	122	76	34	11	1	0

N Engl J Med 2019;381:2020-31.

Mechanism of Synergy Between Immunotherapy and Radiation



Cancers 2025, 17, 1524

RADIATION-INDUCED LYMPHOPENIA: POTENTIALLY DELETERIOUS ROLE

Tipo de radioterapia	Fraccionamiento típico	Volumen irradiado	Incidencia de linfopenia severa	Impacto en linfocitos	Comentarios clave	Referencias
Convencional fraccionada	45-60 Gy en 15-30 fracciones	Amplio (tumor + ganglios)	Alta (hasta 64%)	Descenso marcado	Mayor riesgo si V5 pulmón/corazón elevado	[1-4]
Hipofraccionada	≥50 Gy en ≤10 fracciones	Moderado	Moderada	Menor descenso	Menos linfopenia que convencional	[1-2, 5-6]
SBRT (estereotáctica)	50-60 Gy en 3-5 fracciones	Pequeño (tumor)	Baja	Preservación	Menor linfopenia, mejor para tumores periféricos	[1-3, 7]
Radioterapia con protones	Variable, similar a SBRT	Preciso, menor dosis a órganos	Baja-moderada	Mejor preservación	Reduce dosis a órganos linfocíticos	[8-9]

La linfopenia severa (ALC <500 células/µL) se asocia con peor supervivencia y menor eficacia de la inmunoterapia.
Es fundamental minimizar el volumen irradiado y el número de fracciones

The Lancet. Oncology. 2024;25(8); doi:10.1016/j.radonc.2020.05.051; doi:10.1016/j.radonc.2021.01.034; Critical Reviews in Oncology/Hematology. 2021;159:103226;
International Journal of Radiation Oncology, Biology, Physics. 2019;105(4):812-823; Lancet (London, England). 2021;397(10278):1010-1022; Frontiers in Oncology. 2023;13:1201500;Clin Cancer Res; 30(11) June 1, 2024

Combining radiotherapy with immunotherapy in clinical practice

Caso 1:

Joven
Fumadora
Estadio IIIB no quirúrgico
Carcinoma no microcitico
No comorbilidades

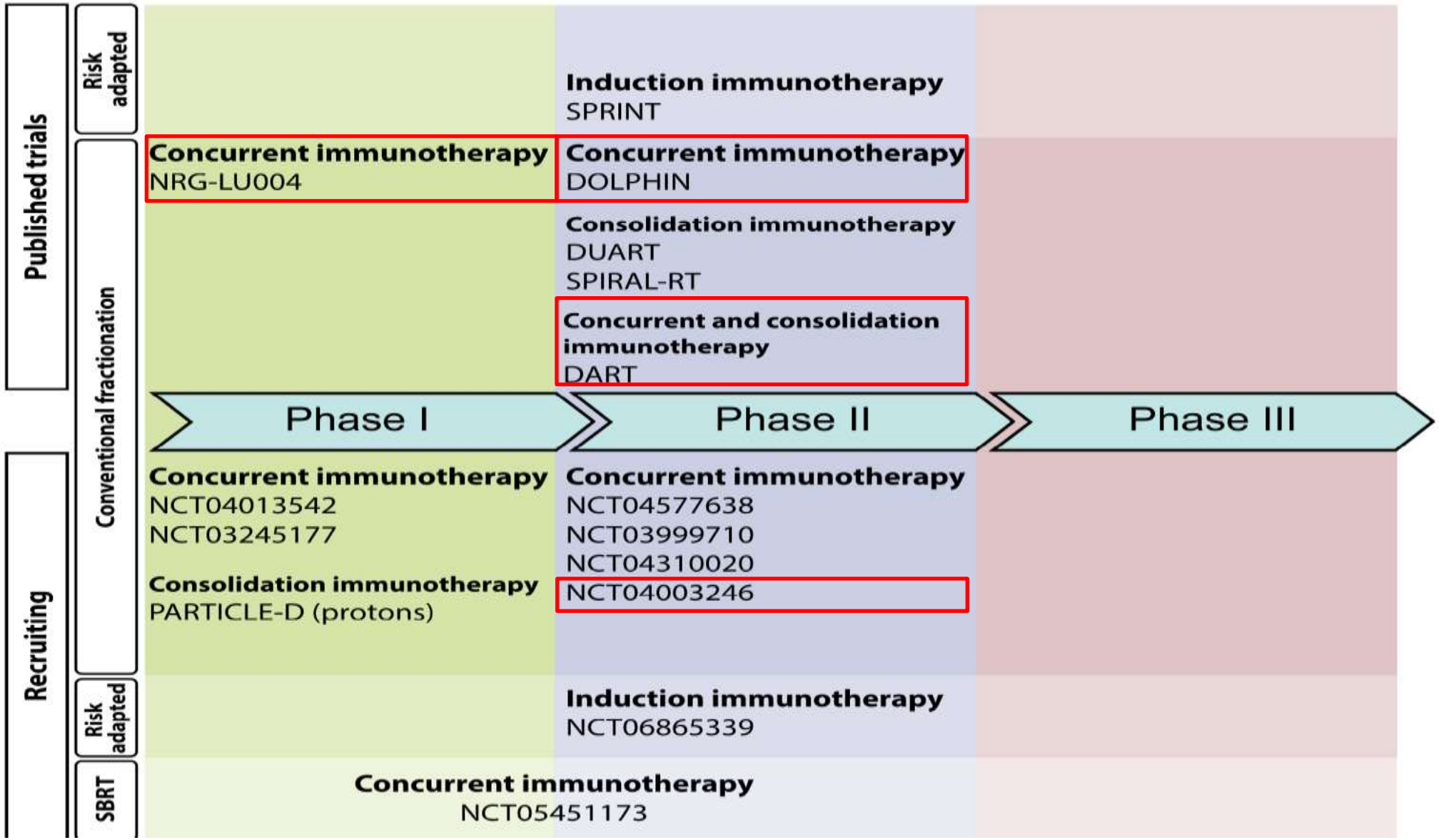
CANDIDATO A ESQUEMA PACIFIC

Caso 2:

Edad avanzada
Fumador
Estadio IIIB no quirúrgico
Carcinoma no microcitico
Con comorbilidades

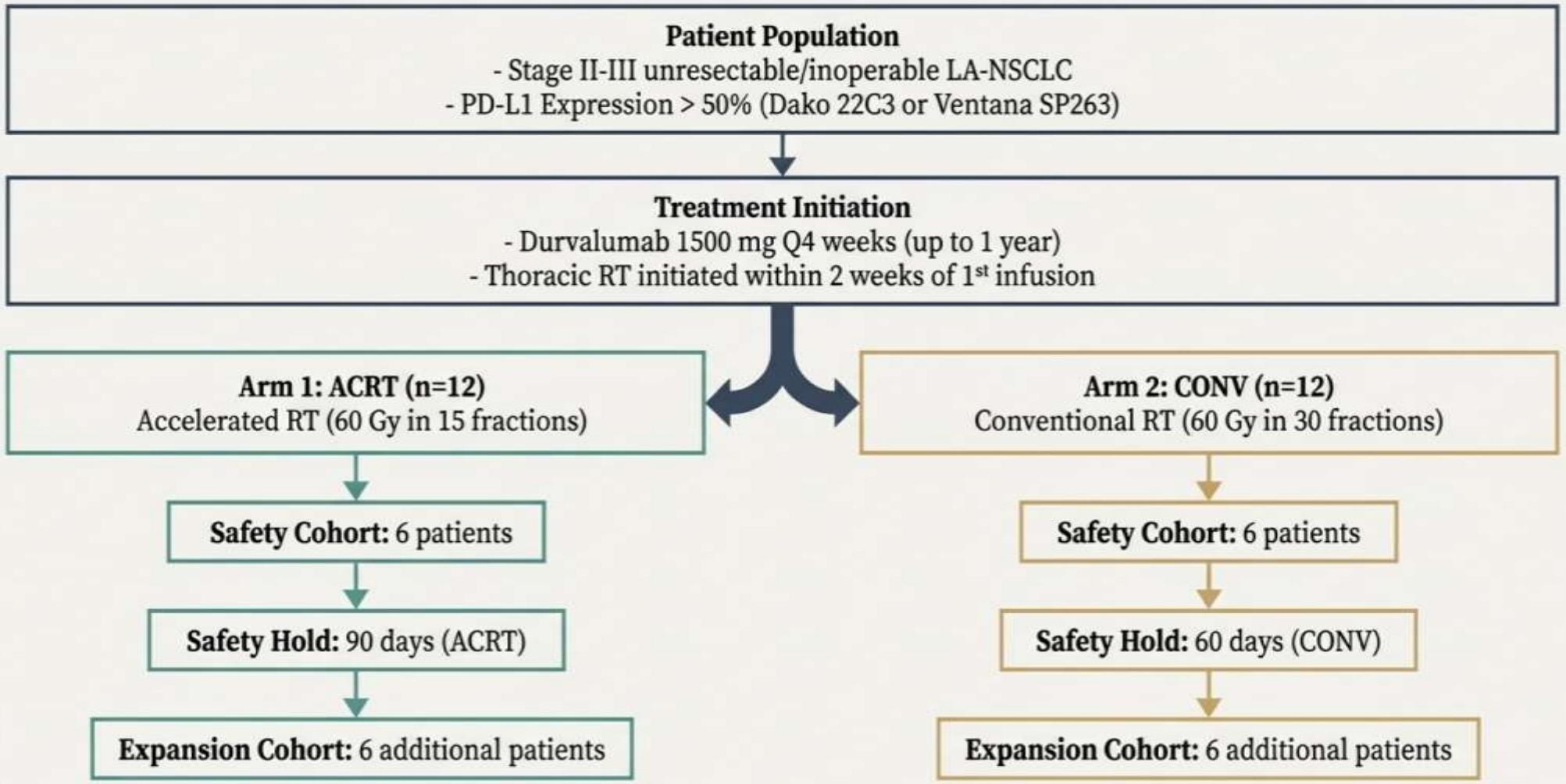
NO CANDIDATO A ESQUEMA PACIFIC

ENSAYOS DE RADIOTERAPIA +INMUNOTERAPIA



Cancers 2025, 17, 1524

NRG-LU004: A Phase I Trial to Test a Chemo-Sparing Strategy



J. Clin. Oncol. 2022, 40, 8513

NRG-LU004

Primary Endpoint: Safety

- **Metric:** Dose Limiting Toxicity (DLT)
- **Criteria for Expansion Phase:** Met if 0-1 patients in the initial 6-patient safety cohort experienced a DLT.
- **Overall Safety Definition:** Regimen deemed safe if < 4 of 12 evaluable patients per arm experienced a DLT.

Key Secondary Endpoint: Feasibility

- **Metric:** Completion of initial immunotherapy course.
- **Definition:** At least 80% of patients in each arm receiving at least 80% of the planned dose of durvalumab during the first 8 weeks (i.e., receiving the 2nd infusion).

Primary Safety Endpoint Met: The Chemo-Free Regimen is Safe

24 evaluable patients enrolled between January 2019 and June 2021.

0
DLTs in ACRT Arm
(n=12)

1
DLT in CONV Arm
(n=12)
(unrelated bronchopulmonary hemorrhage)

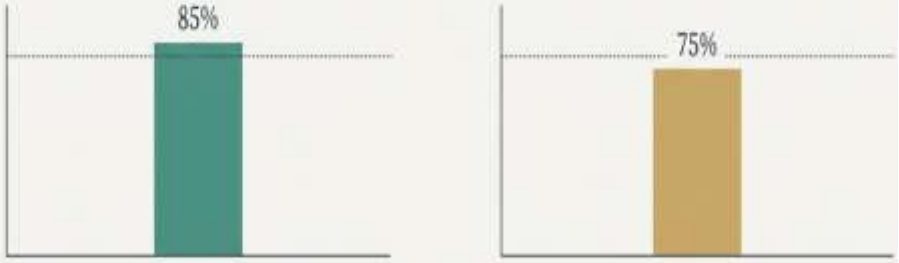
The safety criteria were met in the initial cohorts.
Both arms successfully advanced to the expansion phase.

Adverse Event Grade	ACRT Arm (n=12)	CONV Arm (n=12)
Grade 3 AEs	4	8
Grade 4 AEs	1 (Lymphopenia)	0
Grade 5 AEs	1*	1**

*Grade 5 event (lung infection) was assessed as unrelated to therapy.
**Grade 5 event (respiratory failure) was assessed as unrelated to therapy.

Assessing Treatment Feasibility: Delivery of Initial Immunotherapy

Feasibility Goal: ≥80% of patients receive the second durvalumab dose (at week 4).



ACRT Arm

10 of 12 patients (85%) received the second dose.

Outcome: Feasibility endpoint met.

ACRT Arm (2 patients)
- Shingles
- Unrelated death

CONV Arm

9 of 12 patients (75%) received the second dose.

Outcome: Below pre-specified 80% threshold.

CONV Arm (3 patients)
- Viral hepatitis
- Bronchopulmonary hemorrhage (the DLT)
- Respiratory failure (the Grade 5 AE)

All events leading to the missed second dose were assessed as unrelated to the study therapy.

J. Clin. Oncol. 2022, 40, 8513

PHASE 1: RECRUITING

Ipilimumab and Nivolumab in Combination With Radiation Therapy in Treating Patients With Stage 2-3 Non-small Lung Cancer

ClinicalTrials.gov ID NCT04013542

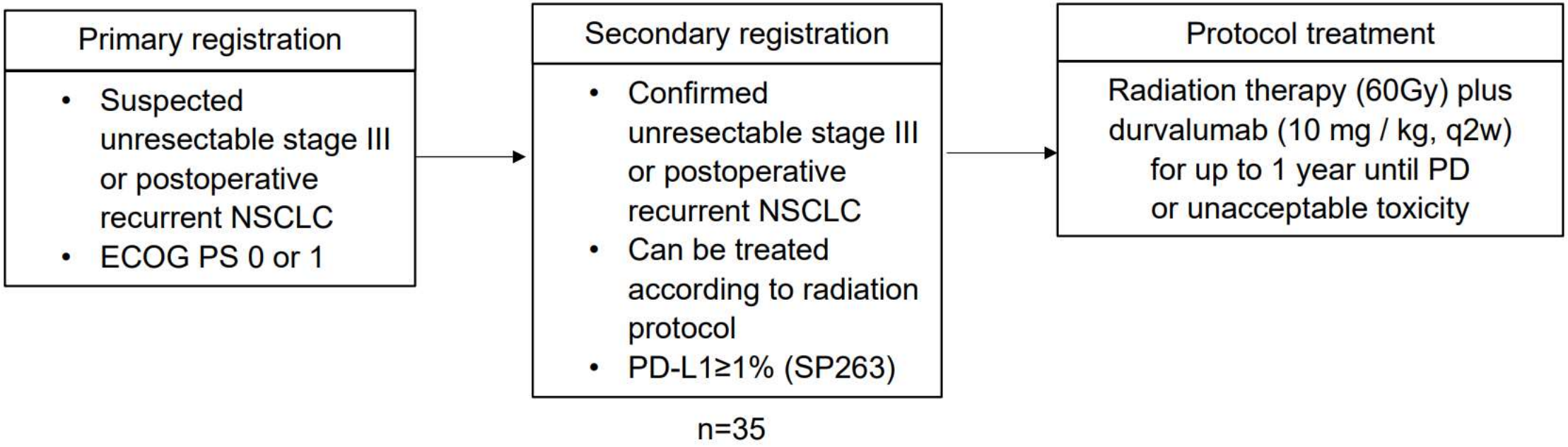
Pembrolizumab in Combination With Radiotherapy in Locally Advanced Non-Small Cell Lung Cancer (NSCLC) (PARIS)

ClinicalTrials.gov ID NCT03245177

Proton Based Cardiac Sparing Accelerated Fractionated RadioTherapy in Unresectable NSCLC

ClinicalTrials.gov ID NCT03818776

The DOLPHIN Phase 2 Nonrandomized Controlled Trial



Primary endpoint: 12-month PFS rate from 2nd registration (assessed by independent central review)

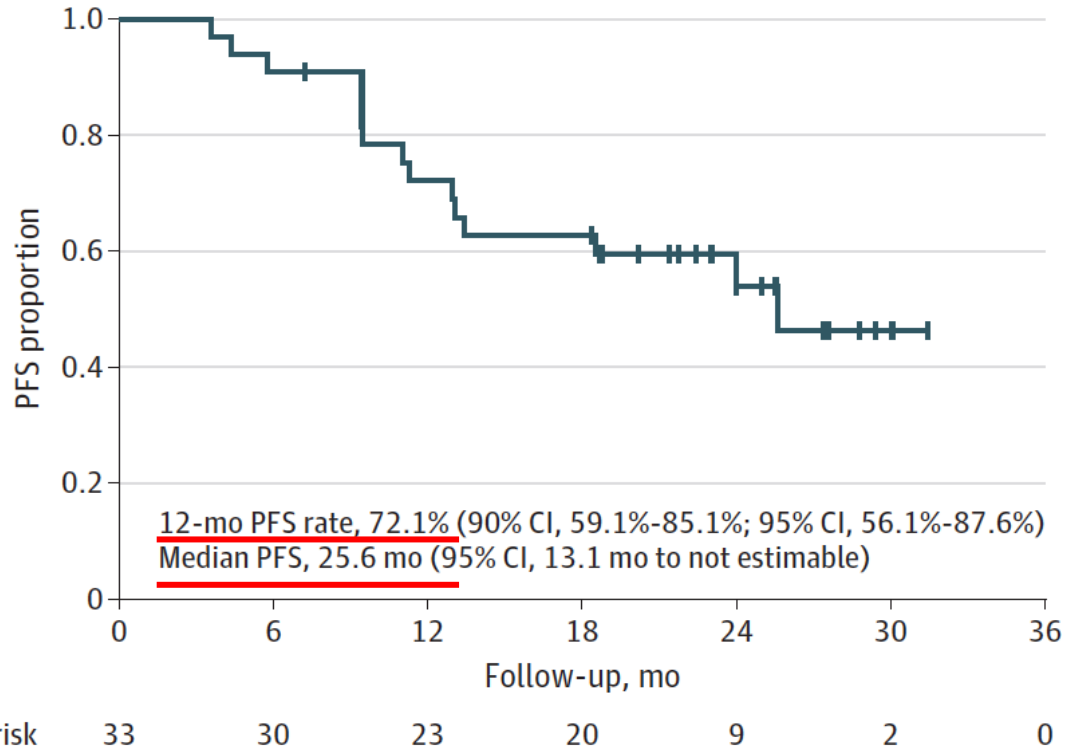
Secondary endpoints: PFS, OS, objective response rate, disease control rate, time to death or distant metastasis, treatment completion rate, and safety

JAMA Oncol. 2023;9(11):1505-1513.

The DOLPHIN Phase 2 Nonrandomized Controlled Trial

Characteristic	Participants, No. (%)
Age, median (range), y	72 (44-83)
Sex, No. (%)	
Female	4 (11.4)
Male	31 (88.6)
Smoking history, No. (%)	
Never	1 (2.9)
Former	16 (45.7)
Current	18 (51.4)
Pathology, No. (%)	
Adenocarcinoma	19 (54.3)
Squamous cell carcinoma	15 (42.9)
NOS	1 (2.9)
Stage, No. (%)	
Postoperative recurrence	9 (25.7)
IIIA	16 (45.7)
IIIB	7 (20.0)
IIIC	3 (8.6)
ECOG performance status score, No. (%)[a]	
0	19 (54.3)
1	16 (45.7)
PD-L1 TPS, median (range)[b]	60 (1-100)
Radiotherapy, No. (%)	
3D-CRT	24 (70.6)
IMRT	11(29.4)

Progression-Free Survival (PFS) Since Second Registration by Independent Central Review

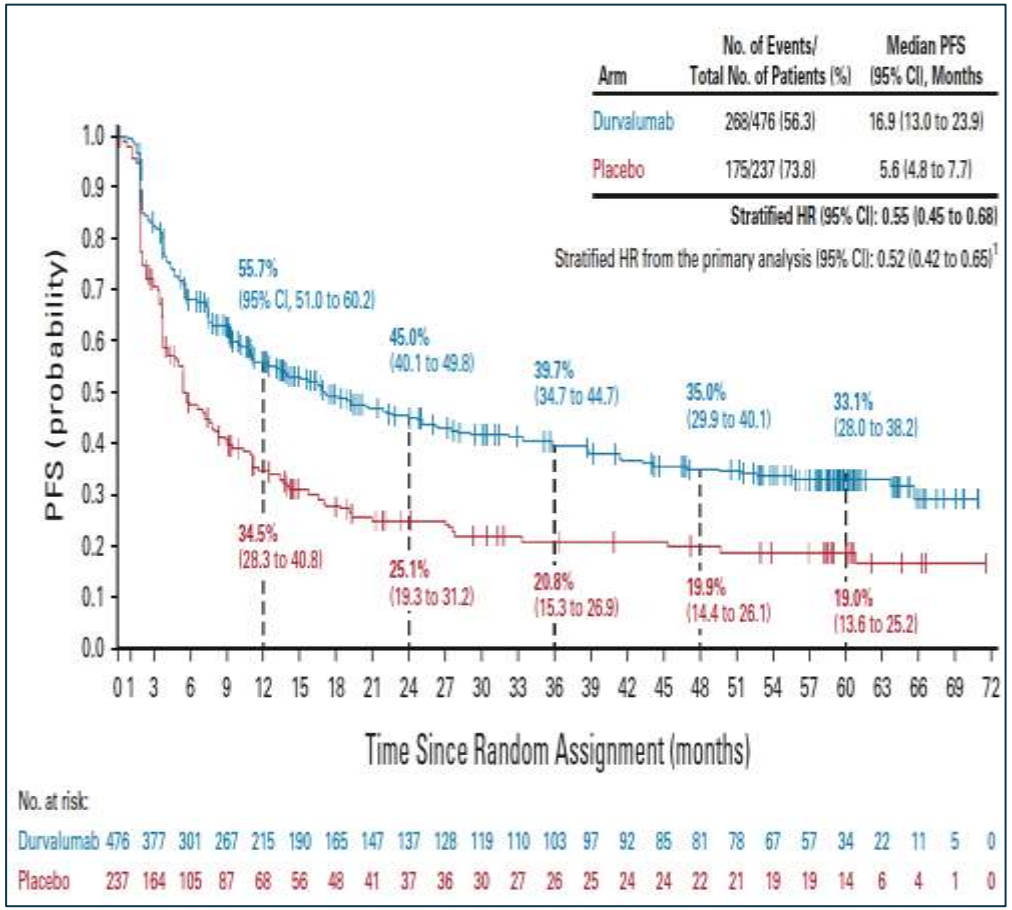


Median follow-up was 22.8 months; range, 4.3-31.8 months.

JAMA Oncol. 2023;9(11):1505-1513.

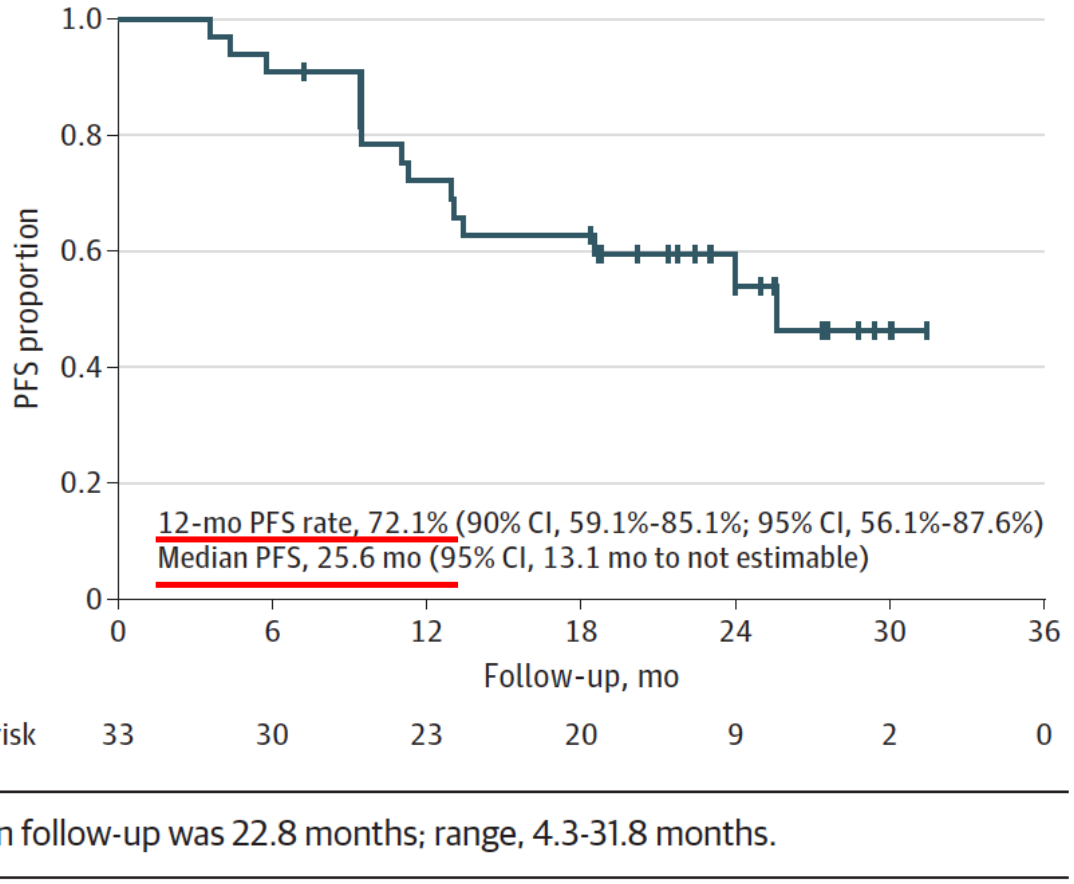
The DOLPHIN Phase 2 Nonrandomized Controlled Trial

PACIFIC



Spigel, JCO 2022, 40:12

Progression-Free Survival (PFS) Since Second Registration by Independent Central Review

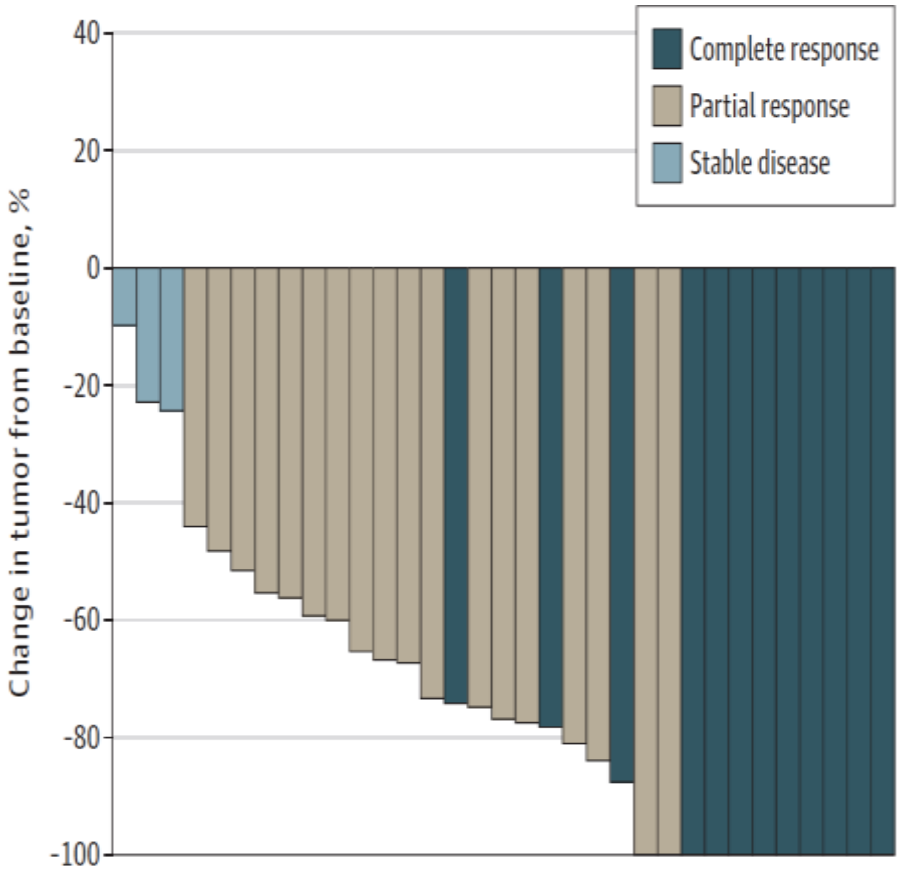


Median follow-up was 22.8 months; range, 4.3-31.8 months.

JAMA Oncol. 2023;9(11):1505-1513.

The DOLPHIN Phase 2 Non-randomized Controlled Trial

Objetive Response Rate



The confirmed objective response rate by ICR was 90.9%
Among 33 patients, 11 (33.3%) had a complete response, and 19 (57.6%) had a partial response as assessed by ICR

Safety Summary

AE	No. (%)
Any grade AEs	34 (100)
Grade 3 or 4	18 (52.9)
Grade 5	2 (5.9)
Leading to discontinuation of protocol treatment	6 (17.6)
Leading to discontinuation of durvalumab	7 (20.6)
Leading to discontinuation of radiotherapy	1 (2.9)
Any grade study drug-related AE	31 (91.2)
Grade 3 or 4	10 (29.4)
Grade 5	1 (2.9)
AEs of special interest	25 (73.5)
Grade 3 or 4	6 (17.6)
Grade 5	0
Corticosteroid required	7 (20.6)
Pneumonitis or radiation pneumonitis	23 (67.6)
Grade 3 or 4	4 (11.8)
Grade 5	0
Leading to discontinuation of durvalumab	3 (8.8)
Leading to discontinuation of radiotherapy	1 (2.9)

eTable 3. Adverse Events of Any Cause in ≥10% of Patients

Event	Any grade	Grade 3 or 4	Grade 5
	No. (%)		
Any events	34 (100)	18 (52.9)	2 (5.9)
Radiation dermatitis	15 (44.1)	0	0
Pneumonitis	14 (41.2)	4 (11.8)	0
Constipation	11 (32.4)	0	0
Radiation pneumonitis	9 (26.5)	0	0
Esophagitis	9 (26.5)	0	0
Lung infection	8 (23.5)	3 (8.8)	1 (2.9)
Dermatitis	8 (23.5)	0	0
Diarrhea	7 (20.6)	0	0
Hypothyroidism	7 (20.6)	0	0
Hyperthyroidism	6 (17.6)	0	0
Pyrexia	6 (17.6)	0	0
Pruritus	6 (17.6)	0	0
Rash	8 (17.6)	0	0
Anemia	6 (17.6)	0	0
Thrombocytopenia	6 (17.6)	1 (2.9)	0
Cough	5 (14.7)	0	0
Fatigue	5 (14.7)	0	0
Amylase increased	5 (14.7)	1 (2.9)	0
Lipase increased	5 (14.7)	1 (2.9)	0
Lymphocyte count decreased	5 (14.7)	5 (14.7)	0
Nausea	4 (11.8)	0	0
Decreased appetite	4 (11.8)	0	0
Musculoskeletal pain	4 (11.8)	0	0
Hyperglycemia	4 (11.8)	3 (8.8)	0
AST increased	4 (11.8)	2 (5.9)	0
Leukopenia	4 (11.8)	0	0

The treatment completion rate of the protocol was 57.6%.

JAMA Oncol. 2023;9(11):1505-1513.

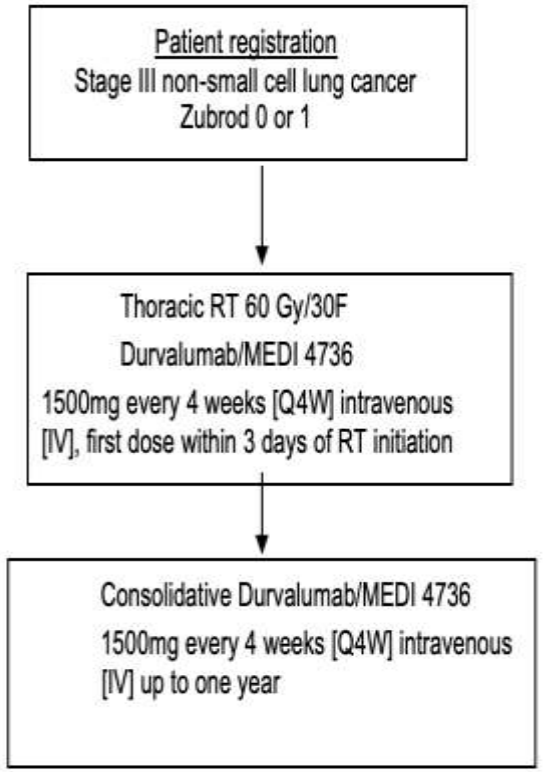
N:35

	PACIFIC	GEMSTONE-301	KEYNOTE-799		DOLPHIN	SPRINT
			Cohort A	Cohort B		
Phase	III	III	II	II	II	II
PD-L1 (TPS)	Any level	Any level	Any level	Any level	≥ 1%	> 50%
Drug	Durvalumab	Sugemalimab	Pembrolizumab	Pembrolizumab	Durvalumab	Pembrolizumab
Radiotherapy	54–66 Gy	54–66 Gy	60 Gy	60 Gy	60 Gy	48 Gy/20f or 55 Gy/20f[a]
Intervention/ treatment	Durvalumab for up to 12 months after cCRT	Sugemalimab for up to 24 months after cCRT or sCRT	Pembrolizumab plus cCRT	Pembrolizumab plus cCRT	Concurrent RT plus durvalumab for up to 12 months	3 cycles of pembrolizumab followed by RT up to 12 cycles
Primary endpoints	PFS, OS	PFS	ORR, AE	ORR, AE	1-year PFS rate	PFS
ORR	NA	NA	69.6%	70.5%	90%	NA
1-year PFS rate	55.6%	45.4%	67.2%	65.2%	72.1%	73%
1-year OS rate	83.1%	86%	81.2%	88%	NA	91%
Safety	29.9% (> grade 3)	9% (grade 3/4 AEs)	64.3% (> grade 3)	46.5% (> grade 3)	47.1% (grade 3/4 AEs)	0% (grade 4/5 AEs)

Cancer Biol Med 2023. doi: 10.20892

Safety and Efficacy of Concurrent and Consolidative Durvalumab With Thoracic Radiation Therapy in PDL1-Unselected StageIII Non-Small Cell Lung Cancer: phase 2 clinical trial (NCT04003246)

STUDY SCHEMA



Registration #, Trial Name	Sample Size	Phase	Primary Endpoint	Immunotherapy Schedule and Timing	RT Schedule	Patient/Biomarker Selection	Key Findings
NCT04003246 [27]	10	II	PFS rate	Durvalumab, every four weeks for one year, starting concurrently with RT.	54–66 Gy in 27–33 fractions	Medically inoperable disease or unwilling to undergo surgery PD-L1 TPS (any)	1-year PFS = 20%

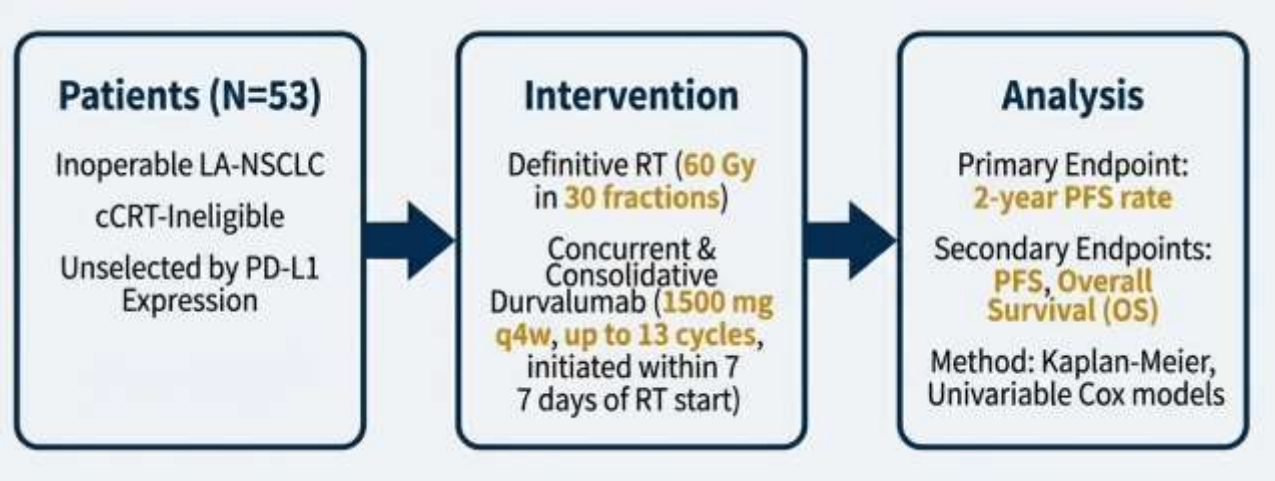
* Six patients experienced a total of 15 treatment-related grade ≥3 Aes (11attributed to radiation, 12 to durvalumab, and 8 to both).
* One grade 4 acute kidney injury during consolidation phase
* Two grade 5 pulmonary AEs.

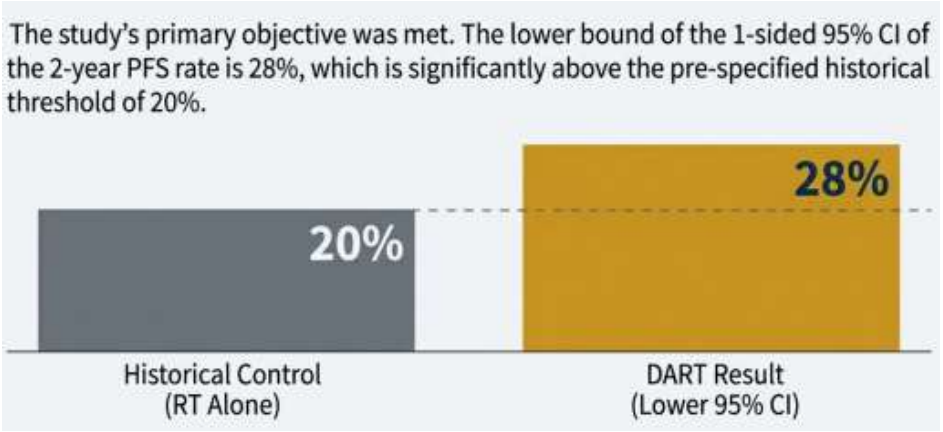
Cierre Precoz por toxicidad

Int. J. Radiat. Oncol. Biol. Phys. 2025, 121, 68–74.

DART TRIAL

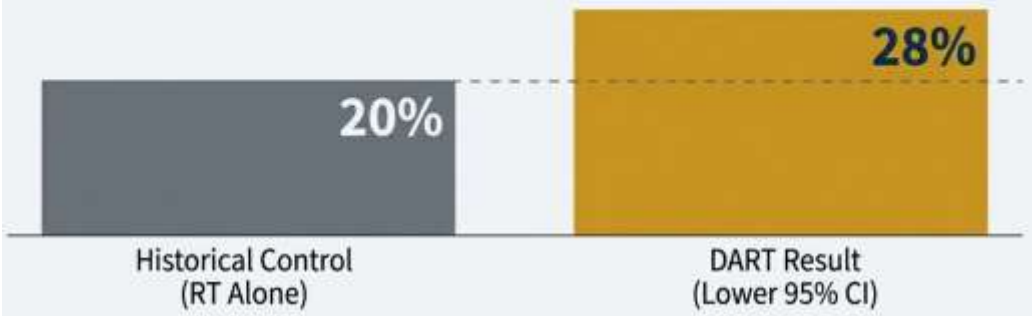
PRIMARY OBJETIVE: Evaluate a novel regimen of definitive radiation therapy wiht concurrent and consolidative durvalumab, without chemotherapy, among patients who were not candidates for cCRT

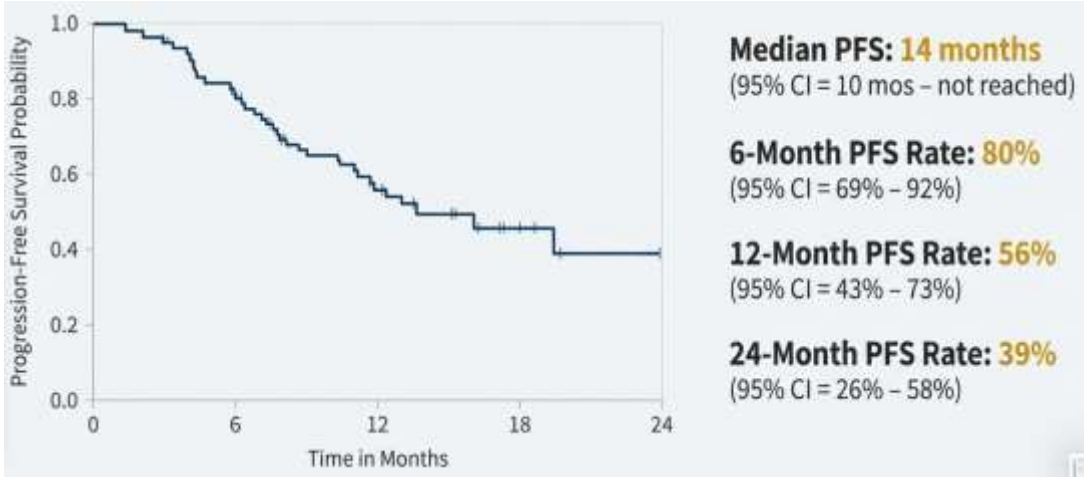




DART TRIAL

The study's primary objective was met. The lower bound of the 1-sided 95% CI of the 2-year PFS rate is 28%, which is significantly above the pre-specified historical threshold of 20%.



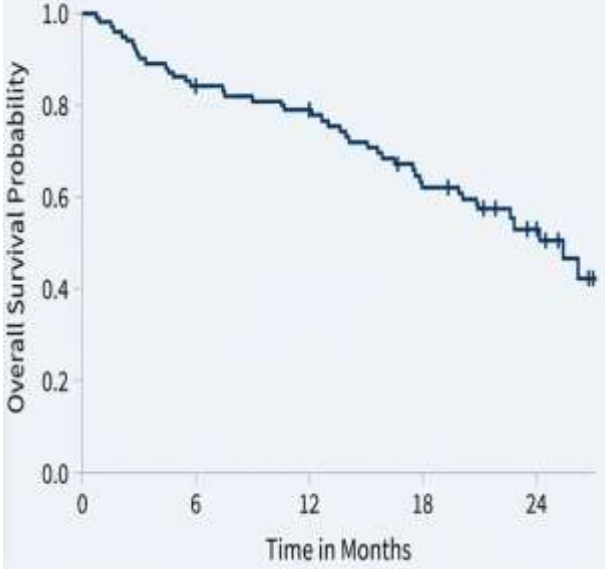


Median PFS: 14 months
(95% CI = 10 mos – not reached)

6-Month PFS Rate: 80%
(95% CI = 69% – 92%)

12-Month PFS Rate: 56%
(95% CI = 43% – 73%)

24-Month PFS Rate: 39%
(95% CI = 26% – 58%)



Median OS: 25 months
(95% CI = 17 mos – not reached)

6-Month OS Rate: 84%
(95% CI = 74% – 95%)

12-Month OS Rate: 79%
(95% CI = 68% – 92%)

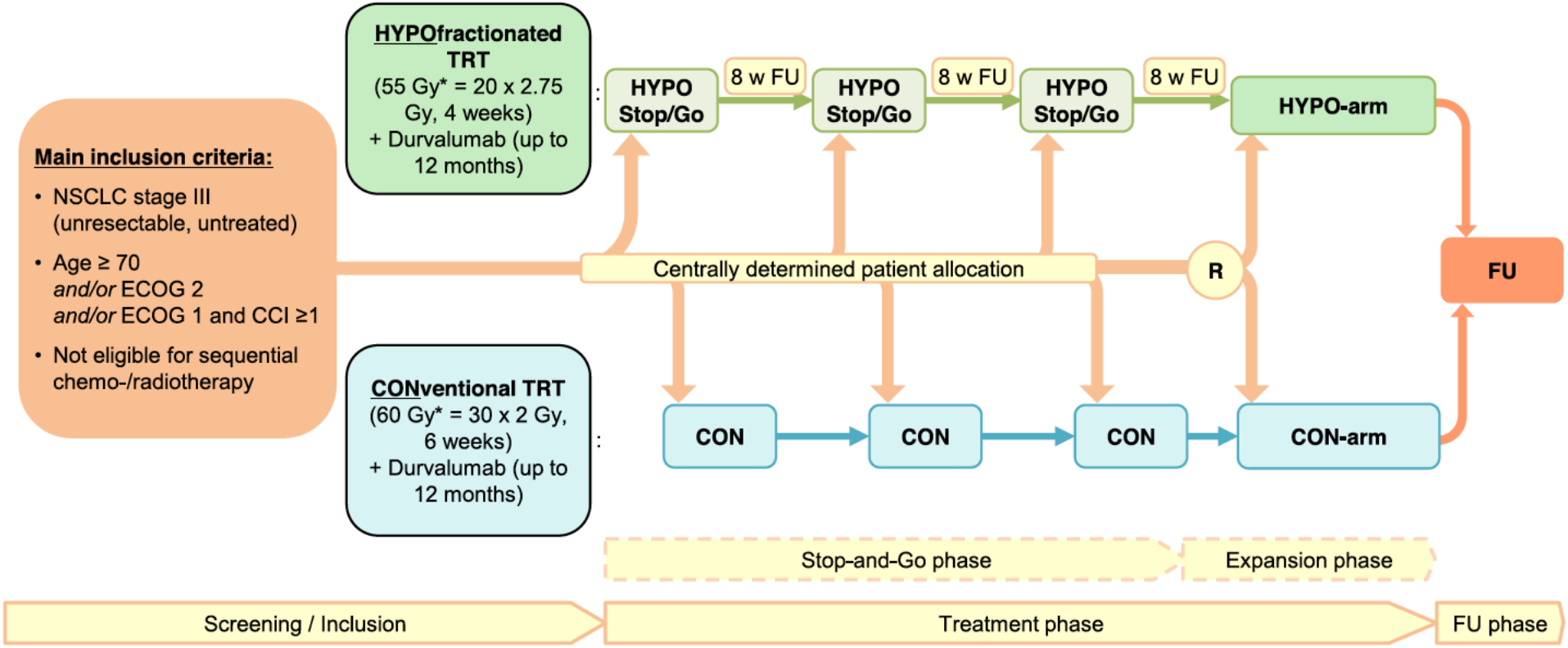
24-Month OS Rate: 53%
(95% CI = 39% – 73%)

Patient KPS, PD-L1 Status, and Treatment Duration Were All Associated with Survival

Univariable Cox analysis identified three key factors significantly associated with both Progression-Free and Overall Survival.

Factor	Progression-Free Survival (PFS)	Overall Survival (OS)
KPS	HR = 0.95 (95% CI = 0.91-0.99), ***P* = 0.023**	HR = 0.94 (95% CI = 0.90-0.99), ***P* = 0.023**
PD-L1 Status (Positive vs. Negative)	HR = 0.45 (95% CI = 0.20-0.98), ***P* = 0.046**	HR = 0.37 (95% CI = 0.14-0.98), ***P* = 0.046**
Number of Durvalumab Cycles	HR = 0.78 (95% CI = 0.71-0.86), ***P* < 0.001**	HR = 0.81 (95% CI = 0.72-0.91), ***P* < 0.001**

Thoracic radiotherapy plus Durvalumab in elderly and/or frail NSCLC stage III patients unfit for chemotherapy - employing optimized (hypofractionated) radiotherapy to foster durvalumab efficacy: study protocol of the TRADE-hypo trial



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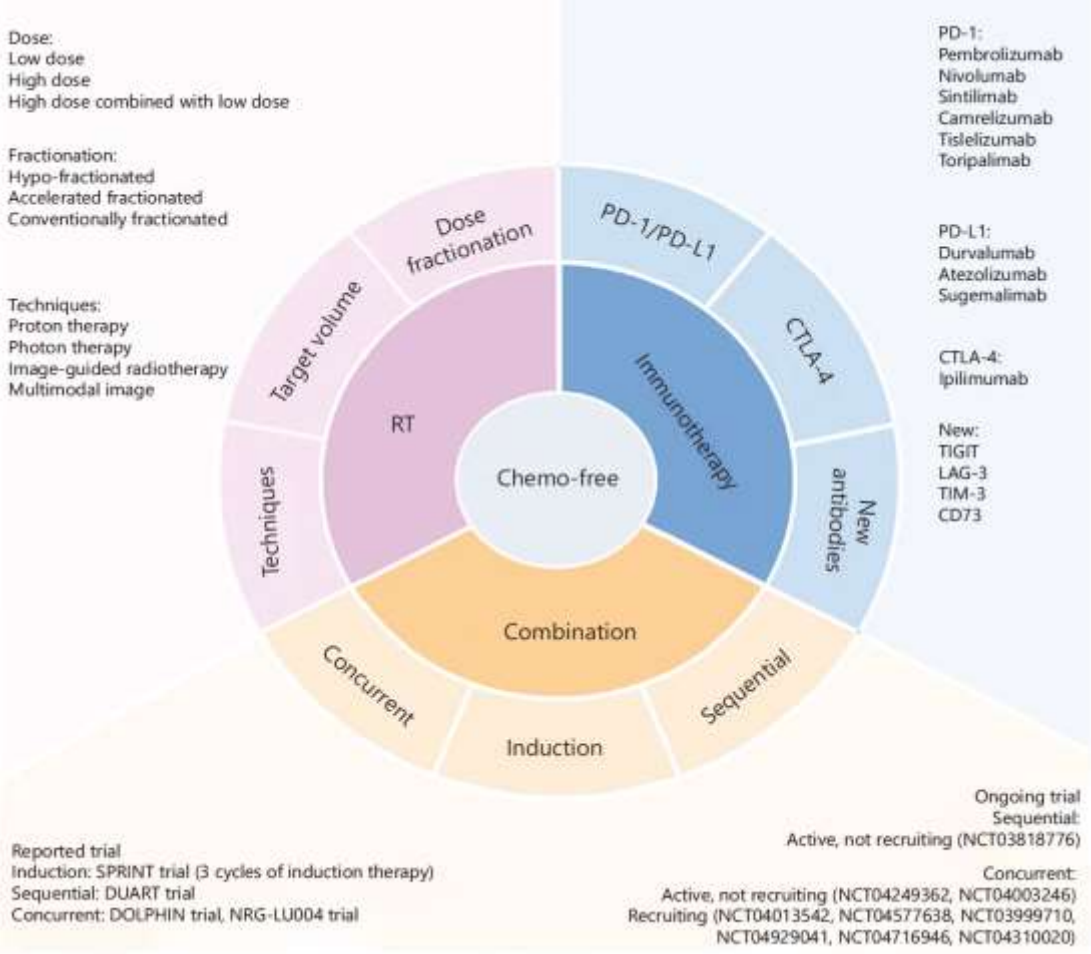
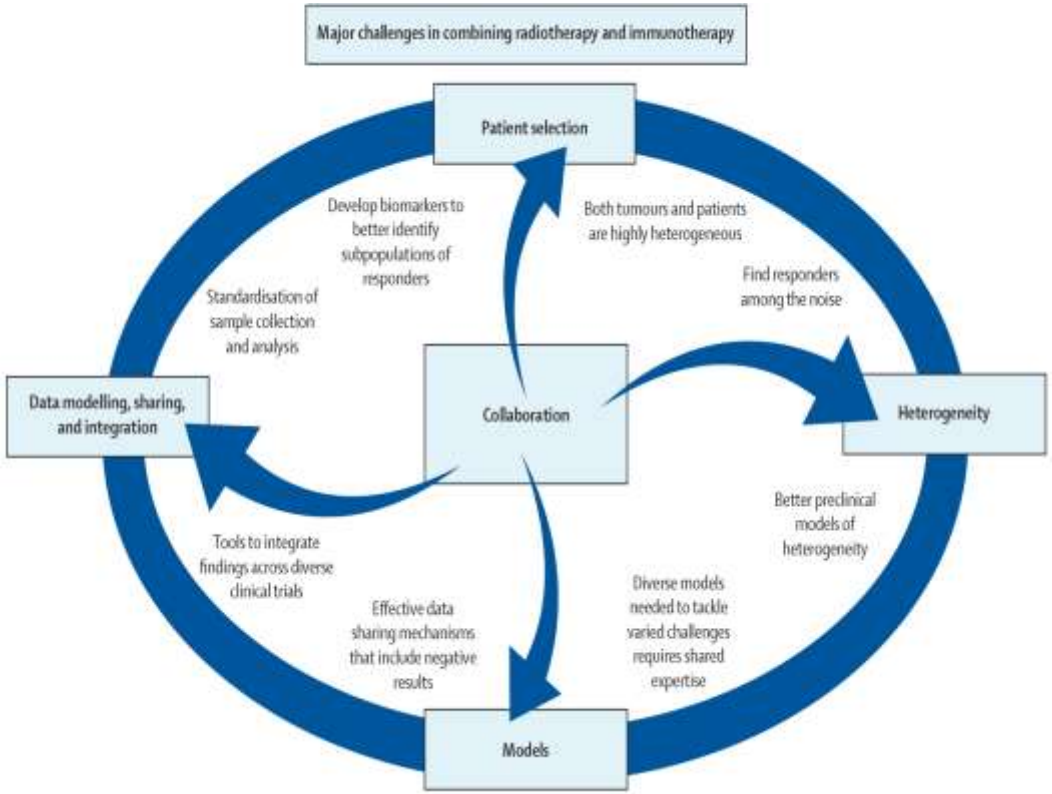
BMC Cancer. 2020 Aug 26;20(1):806

EN RESUMEN….





Cancer Biol Med 2023

16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

THANK YOU

GECP lung cancer research