# MasterClass

## Radioterapia en cáncer de pulmón 2025

ORGANIZADO POR:

GRUPO ONCOLÓGICO ESPAÑOL DE CÁNCER DE PULMÓN (GOECP)

13 FEB 2025

## 1ª Sesión:

## Radioterapia en cáncer de pulmón de célula no pequeña estadio III irresecable

# Ensayos clínicos con inmunoterapia


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SEOR
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# Introducción

- Cáncer no microcítico de pulmón estadio III irresecable:
  - ¿Qué es estadio III?

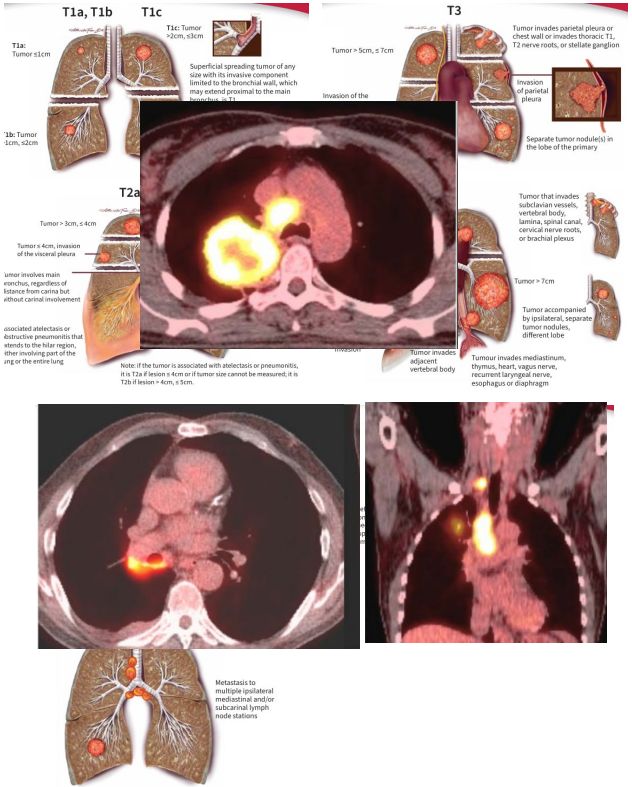
The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groups in the Forthcoming (Ninth) Edition of the TNM Classification for Lung Cancer

IASLC

Staging Cards in Thoracic Oncology, 9th Edition | IASLC

**9th Edition TNM Descriptors and Stages**

| T/M | Categories and Descriptors | N0 | N1 | N2 | | N3 |
|---|---|---|---|---|---|---|
| | | | | N2a | N2b | |
| T1 | T1a ≤1 cm | IA1 | IIA | IIB | IIIA | IIIB |
| | T1b >1 to ≤2 cm | IA2 | IIA | IIB | IIIA | IIIB |
| | T1c >2 to ≤3 cm | IA3 | IIA | IIB | IIIA | IIIB |
| T2 | T2a Visceral pleura / central invasion | IB | IIB | IIIA | IIIB | IIIB |
| | T2a >3 to ≤4 cm | IB | IIB | IIIA | IIIB | IIIB |
| | T2b >4 to ≤5 cm | IIA | IIB | IIIA | IIIB | IIIB |
| T3 | T3 >5 to ≤7 cm | IIB | IIIA | IIIA | IIIB | IIIC |
| | T3 Invasion | IIB | IIIA | IIIA | IIIB | IIIC |
| | T3 Same lobe separate tumor nodules | IIB | IIIA | IIIA | IIIB | IIIC |
| T4 | T4 >7 cm | IIIA | IIIA | IIIB | IIIB | IIIC |
| | T4 Invasion | IIIA | IIIA | IIIB | IIIB | IIIC |
| | T4 Ipsilateral separate tumor nodules | IIIA | IIIA | IIIB | IIIB | IIIC |
| M1 | M1a Contralateral tumor nodules | IVA | IVA | IVA | IVA | IVA |
| | M1a Pleural / pericardial effusion, nodules | IVA | IVA | IVA | IVA | IVA |
| | M1b Single extrathoracic metastasis | IVA | IVA | IVA | IVA | IVA |
| | M1c1 Multiple metastases in 1 organ system | IVB | IVB | IVB | IVB | IVB |
| | M1c2 Multiple metastases in >1 organ systems | IVB | IVB | IVB | IVB | IVB |

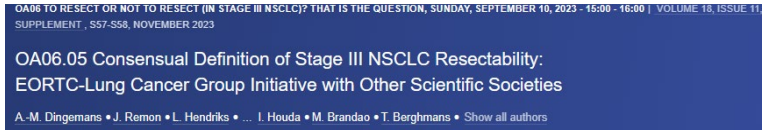


# Introducción

- Cáncer no microcítico de pulmón estadio III irresecable:
  - ¿Qué es irresecable?


| | N0 | N1 | N2 SINGLE (non-bulky, non-invasive) | N2 MULTI (non-bulky, non-invasive) | N2 BULKY¶ | N2 INVASIVE | N3 |
|---|---|---|---|---|---|---|---|
| T1-2 | NOT STAGE III DISEASE | NOT STAGE III DISEASE | RESECTABLE | POTENTIALLY RESECTABLE* | UNCLEAR | UNRESECTABLE | UNRESECTABLE |
| T3 size / satellite / invasion | NOT STAGE III DISEASE | RESECTABLE | RESECTABLE | POTENTIALLY RESECTABLE* | UNRESECTABLE | UNRESECTABLE | UNRESECTABLE |
| T4 size / satellite | RESECTABLE | RESECTABLE | RESECTABLE | POTENTIALLY RESECTABLE* | UNRESECTABLE | UNRESECTABLE | UNRESECTABLE |
| T4 invasion | POTENTIALLY RESECTABLE§ | POTENTIALLY RESECTABLE§ | POTENTIALLY RESECTABLE§ | POTENTIALLY RESECTABLE*§ | UNRESECTABLE | UNRESECTABLE | UNRESECTABLE |

*Multiple station N2: case-by-case discussion; the exact number of nodes/stations cannot be defined
¶Bulky N2: lymph nodes with a short-axis diameter >2.5-3 cm; in specific situations of *highly selected patients*, including those patients in multidisciplinary trials with surgery as local therapy can be discussed
§Some T4 tumours by infiltration of major structures are potentially resectable – see Table 1


OA06 TO RESECT OR NOT TO RESECT (IN STAGE III NSCLC)? THAT IS THE QUESTION, SUNDAY, SEPTEMBER 10, 2023 - 15:00 - 16:00 | VOLUME 18, ISSUE 11, SUPPLEMENT , S57-S58, NOVEMBER 2023

OA06.05 Consensual Definition of Stage III NSCLC Resectability: EORTC-Lung Cancer Group Initiative with Other Scientific Societies

A.-M. Dingemans • J. Remon • L. Hendriks • ... I. Houda • M. Brandao • T. Berghmans • Show all authors

- N3
- N2 bulky, invasive:
  - Multiple (N2b): No hay consenso. Case by case.
- T4 invasivo:
  - Por infiltración de estructuras: valoración individual y considerar derivar a centros de referencia

T4 by infiltration of major structures

| Table | Unresectable | Potentially resectable |
|---|---|---|
| Pulmonary artery in the pericardium | | ✓ |
| Superior vena cava | | ✓ |
| Diaphragm | | ✓ |
| Heart | ✓* | |
| Carina | | ✓ |
| Trachea | ✓* | |
| Oesophagus | ✓* | |
| Spinal cord | ✓ | |
| Vertebral body | | ✓ |
| Recurrent laryngeal nerve | | ✓ |
| Mediastinal fat | | ✓ |
| Great vessels: aorta, inferior vena cava, pulmonary vein | | ✓ |

*Some locations as heart, trachea and oesophagus are generally considered unresectable

# Introducción

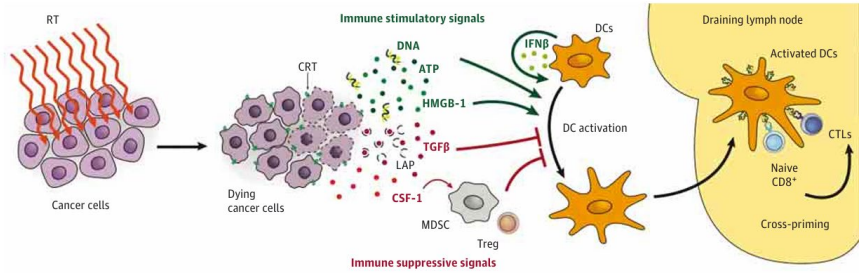
- Enfermedad heterogénea; 25-30% de los pacientes CPNCP
- El objetivo del tratamiento es la curación, pero históricamente el pronóstico ha sido pobre

| Estudio/año | Nº | Brazo I | Brazo II | Brazo III | Mediana Spv |
|---|---|---|---|---|---|
| RTOG 7301<br>1973-1978 | 365 | RT 40Gy | RT 50Gy | RT 60Gy | RT 60Gy: 11,8m |
| CALGB 8433<br>1984-1987 | 155 | RT (60Gy)→QT (VNB, CDDP) | RT 60Gy | - | RTQTsec: 13,7m |
| RTOG 9410<br>1994-1998 | 610 | QT (CDDP, VNB)→RT (60Gy) | QT (CDDP, VNB) + RT(60Gy) | QT+RT hiperfx | RTQTcc: 17m |
| RTOG 0617<br>2007-2011 | 544 | 60Gy RT + Carbo-Paclitaxel +/- Cetuximab | 74Gy RT + Carbo-Paclitaxel +/- Cetuximab | - | RTQT (60Gy): 28,7m |
| **PACIFIC**<br>**2014-2016** | 713 | RTQT | RTQT → Durvalumab | - | RTQT: 29,1m<br>RTQT → Durva: **47,5m** |

# Introducción

La RT juega un papel inmunomodulador:

1. Aumenta la presentación antigénica
2. Señales proinflamatorias
3. Incremento de actividad de linfocitos T CD8
4. Modulación microambiente celular
5. Up-regulation de la expresión de PDL-1

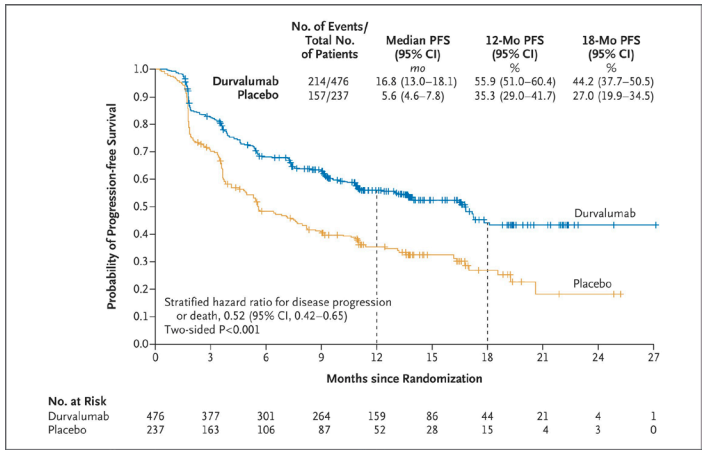



JAMAOncol.2015;1(9):1325-1332.doi:10.1001/jamaoncol.2015.2756

The NEW ENGLAND JOURNAL of MEDICINE

Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

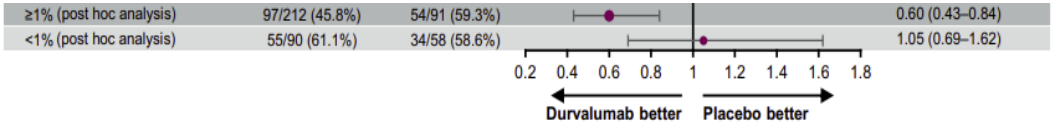
- PACIFIC trial. Año 2017; Scott J. Antonia
- Addition of the anti–PD-L1 antibody durvalumab for 12 months.
- **PFS**: 16,8m vs 5,6m
  - PS 0-1
  - Edad: 64a
- Toxicidad:
  - Grade 3 or 4: 29.9% vs 26.1%
  - Pneumonia G3-4: 4.4% and 3.8%

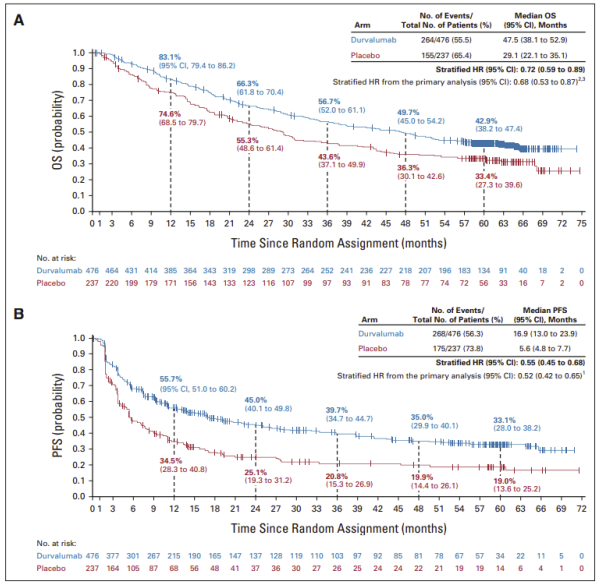


# Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

- Año 2022
- Seguimiento de 34,2 meses
- **OS: 47,5m** vs 29,1m
- **OS_5 años: 42,9%** vs 33,4%
- **PFS: 16,9m** vs 5,6m

- Mejor en: EGFR no mutado; No escamoso; Cisplatino; inicio de Durvalumab <14 días tras RT
- PDL1 > 1%



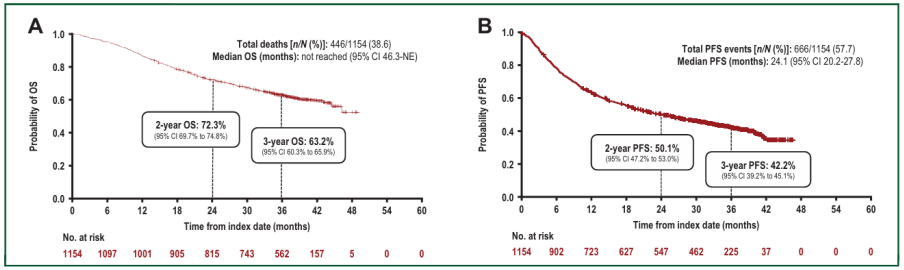
# MasterClass en Radioterapia de Pulmón 2025

## 1ª Sesión: Radioterapia en cáncer de pulmón de célula no pequeña estadio III irresecable

Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study

**Real-world outcomes with durvalumab after chemoradiotherapy in patients with unresectable stage III NSCLC: interim analysis of overall survival from PACIFIC-R**

- Pacientes mayores
- Pacientes con PS > 1
- Incluye tratamientos secuenciales




- RESULTADOS:
  - rwPFS: 24,1m
  - rwOS: SG_3ª: 63,2%
  - 9,5% interrumpe tratamiento por neumonitis
  - Resultados consistentes. <u>Tratamiento estándar</u>
  - No retrasar el inicio del durvalumab tras fin de RT

# PACIFIC 2

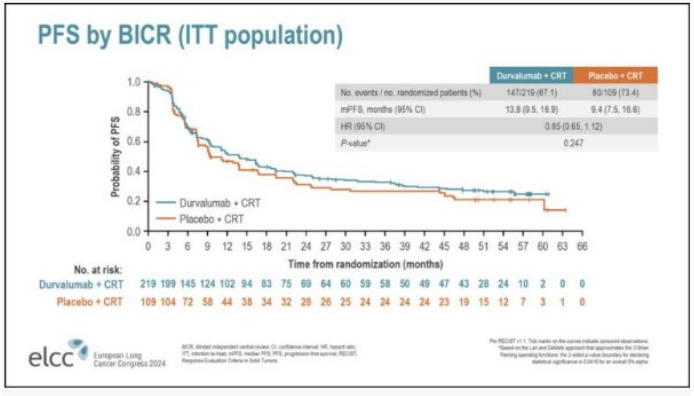
**LBA1 - Durvalumab in combination with chemoradiotherapy for patients with unresectable stage III NSCLC: Final results from PACIFIC-2**

European Lung Cancer Congress 2024

Fase III
Arm1. RTQT+Durvalumab → Durvalumab
Arm2. RTQT→ Durvalumab

PFS: 13,8m vs 9,4m (p=0,25)
OS: 36,4m vs 29,5m (p=0,82)

AE led to discontinuation: 25.6% vs 12.0%



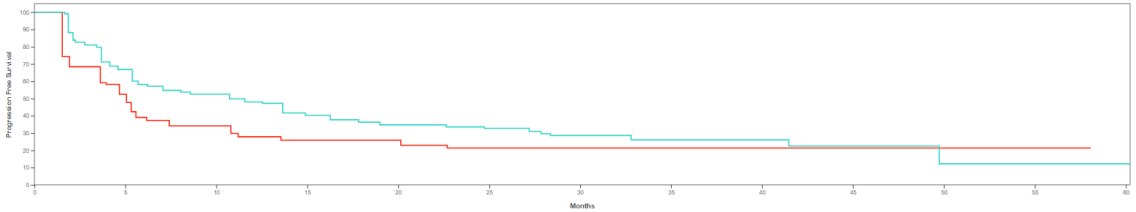

*La administración de Durvalumab concurrente con RTQT no mejora los resultados significativamente (marzo 2024)*

# PACIFIC 5

**LBA6** **PACIFIC-5: A phase III study of consolidation durvalumab (D) in patients (pts) with unresectable stage III NSCLC and no progression after concurrent or sequential chemoradiotherapy (cCRT or sCRT)**

ESMO Asia Congress 2024

Fase III; población asiática
Arm1: RTQTcc/**sec** → Durvalumab
Arm2: RTQTcc/**sec** → Placebo



PFS: 14m vs 6,5m
Subgrupos

- RTQTcc +/- Durva: 16,5m vs 9,5m
- <u>RTQTsec</u> +/- Durva <u>: 11m vs 5,4m</u>

*"PACIFIC-5 supports the use of consolidation immunotherapy after either concurrent or sequential CRT, consistent with the PACIFIC trial and real-world evidence"* *(Dic 2024 ESMO-Asia)*

# PACIFIC 6

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

Fase 2

Pacientes de más edad, peor PS y mayor carga de enfermedad que en el Pacific

Arm 1: RTQT**sec** → Durvalumab

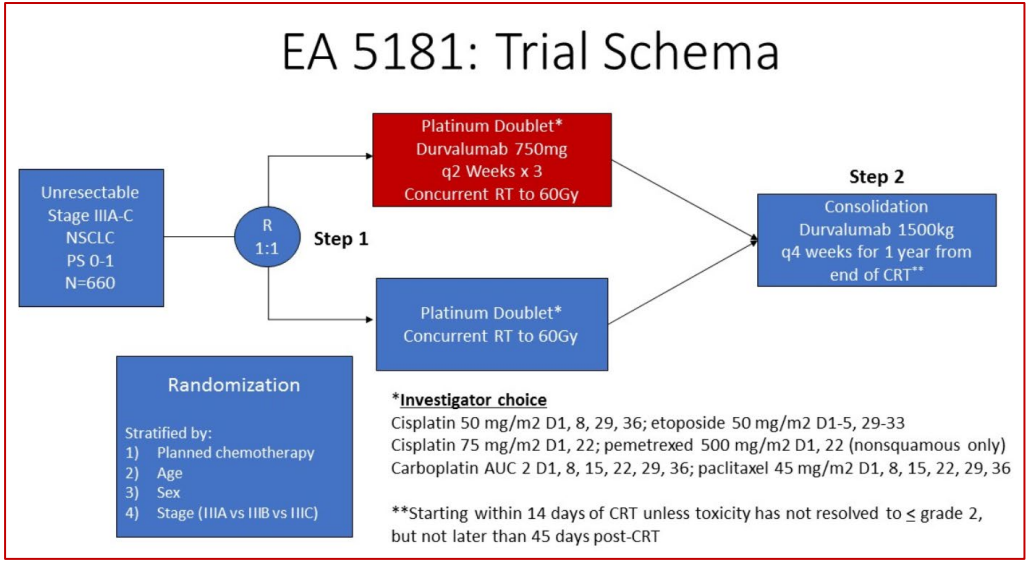
Seguridad y tolerabilidad

- Similar perfil de toxicidad que en Pacific
- PFS: 10,9m

J Thorac Oncol. 2022 Dec;17(12):1415-1427.

# ECOG-ACRIN 5181
# Durvalumab concurrente y de consolidación

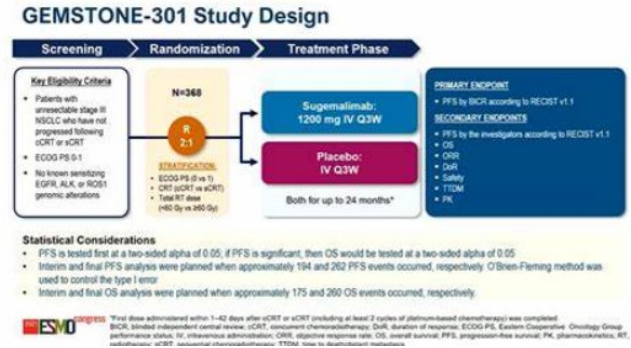
- Fase III
- Cerrado reclutamiento



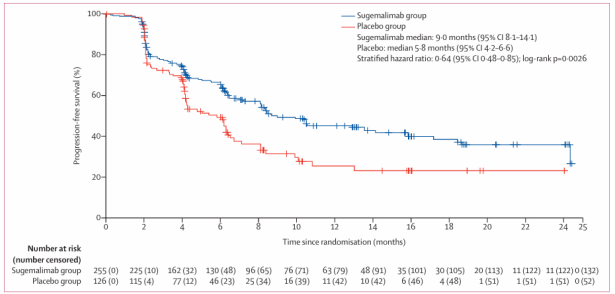
# Otros fármacos

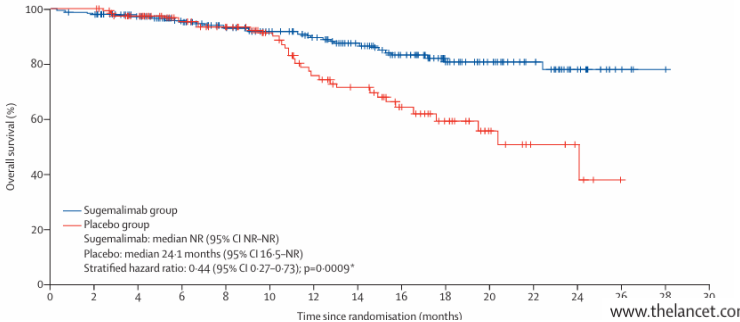
# GEMSTONE 301

**Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial**




- Fase III
- RT+QT cc/sec → Sugemalimab (AntiPDL1) vs Placebo durante 24m
- PFS: 9m vs 5,8m
- OS: NR vs 24,1m





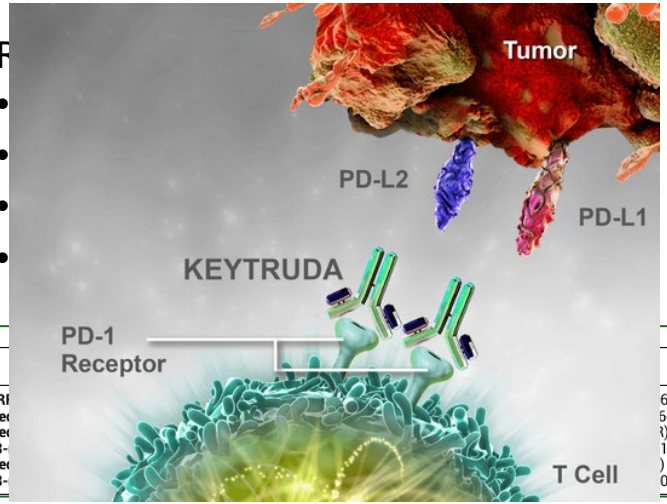
www.thelancet.com/oncology Vol 23 February 2022

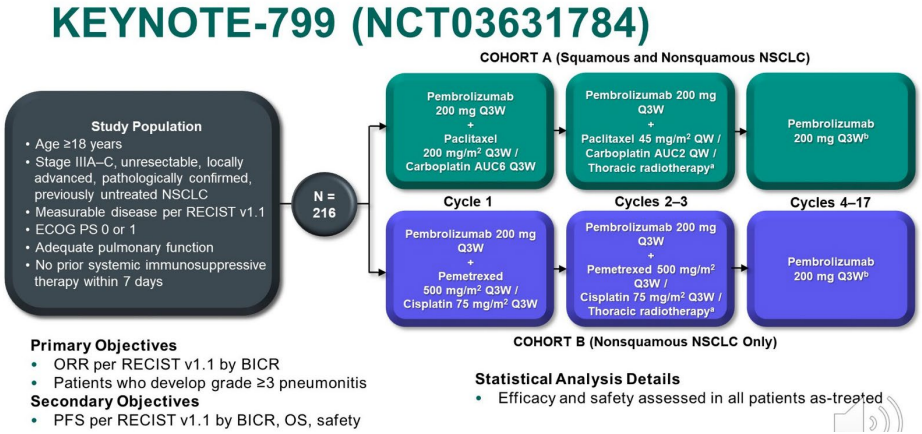
# KEYNOTE 799

## Pembrolizumab plus cCRT for unresectable, locally advanced, stage III NSCLC

Fase II

No randomizado




QT+Io → QT+Io+RT → Io

2 esquemas de QT

JAMA Oncol. 2021 Jun 4;7(9):1-9. doi: 10.1001/jamaoncol.2021.2301

# KEYNOTE 799

## Pembrolizumab plus cCRT for unresectable, locally advanced, stage III NSCLC

**Four-year outcomes and circulating tumor DNA (ctDNA) analysis of pembrolizumab (pembro) plus concurrent chemoradiation therapy (cCRT) in unresectable, locally advanced, stage III non–small-cell lung cancer (NSCLC): From KEYNOTE-799.**

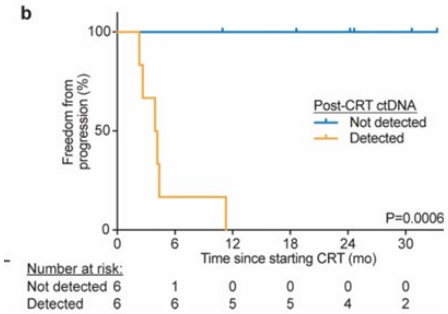
2024 ASCO Annual Meeting I

- Análisis de ctDNA
- 46 pacientes con ctDNA al inicio y analizable a los 7 ciclos
  - 70% habían negativizado
  - Estos pacientes presentaban mayor PFS y OS

**Circulating Tumor DNA Dynamics Predict Benefit from Consolidation Immunotherapy in Locally Advanced Non-Small Cell Lung Cancer**

- ctDNA tras RTQT +/- Io
- No detectable: buen px; Si sí detectable, mayor beneficio de Inmunoterapia
- Terapia personalizada según la enfermedad molecular residual

*Moding et al. 2020* *Nat Cancer.* 2020 February ; 1(2): 176–183. doi:10.1038/s43018-019-0011-0.



# Combinaciones de fármacos

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# Combinaciones de Fármacos

## CheckMate 73L

Fase III; 3 brazos

A. Nivolumab + RTQT → Nivolumab
B. Nivolumab + RTQT → Nivolumab+Ipilimumab
*C. RTQT → Durvalumab*

- PFS (A vs C): 16.7 v 15.6 mo
- No diferencias en OS ni en PFS


, December 2024

ESMO Immuno-Oncology Congress 2024

# MasterClass en Radioterapia de Pulmón 2025

## 1ª Sesión: Radioterapia en cáncer de pulmón de célula no pequeña estadio III irresecable

SKYSCRAPER-03: A Study of Atezolizumab and Tiragolumab Compared With Durvalumab in Participants With Locally Advanced, Unresectable Stage III NSCLC

A. RTQTcc → Durvalumab
B. RTQTcc → Tiragolumab + Atezolizumab

KEYLYNK-012: A Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy (CCRT) Followed by Pembrolizumab With or Without Olaparib vs. CCRT Followed by Durvalumab

A. RTQTcc → Durvalumab
B. RTQTcc +Pembrolizumab→ Pembrolizumab+/-Olaparib

PACIFIC-9: Phase III trial of durvalumab + oleclumab or monalizumab in unresectable stage III non-small-cell lung cancer

A. RTQTcc → Durvalumab
B. RTQTcc → Durvalumab + Oleclumab or Monalizumab

PACIFIC-8: Phase 3 trial of durvalumab combined with domvanalimab following concurrent chemoradiotherapy (cCRT) in patients with unresectable stage III NSCLC

A. RTQTcc → Durvalumab
B. RTQTcc → Durvalumab + Domvanalimab

# Pacientes frágiles

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# DUART

**Durvalumab after radiotherapy in patients with unresectable Stage III NSCLC ineligible for chemotherapy: final analysis of the phase 2 DUART study**


Fase II; pacientes no candidatos a QT; 100 pacientes
2 cohortes:

A: RT radical → Durvalumab: PFS: 10,3m; OS: 21,1m
B: RT paliativa → Durvalumab: PFS: 7,6m; OS: 16,8m

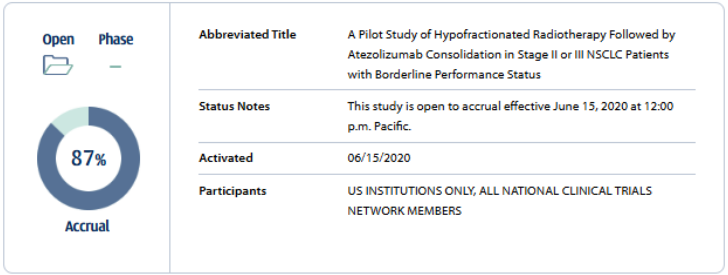
*Mejor respuesta con RT radical*
*Mejor respuesta en PDL1>1%*
*Mejores resultados que en series de RT exclusiva*

# SWOG S1933

## A Pilot Study of Hypofractionated Radiotherapy Followed by Atezolizumab Consolidation in Stage II or III NSCLC Patients with Borderline Performance Status

Fase II; No candidatos a QT

RT hipofraccionada (60Gy en 15 fracciones) → Atezolizumab



# Tablas de estudios

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**Table 1.** Consolidative Immunotherapy Trials in Locally Advanced NSCLC after Radiation Therapy.

| Study | Phase | n | Staging | Stage Distribution | Treatment | Primary Endpoints | Results | Factors Affecting Treatment Outcomes | | | Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Histology | PDL-1 | Other Factors | |
| PACIFIC, NEJM 2017; JCO 2022 | III | 713 | Stage IIIA-IIIB (IASLC Staging Manual in Thoracic Oncology) | IIIA: 52.9% IIIB: 44.7% Other: 2.4% | cCRT [54–66 Gy + platinum-based chemo ≥2 cycles] f/b durvalumab (10 mg/kg IV q 2w) vs. placebo ×1 yr. | PFS, OS | 5 yr PFS: 42.9% vs. 33.1% 5 yr OS: 33.4% vs. 19.0% | Sq (HR 0.68, 95% CI: 0.50–0.92) Non-sq (HR 0.45, 95% CI: 0.33–0.59) | 25% (HR 0.41, 95% CI: 0.26–0.65) <25% (HR 0.59, 95% CI: 0.43–0.82) Unknown (HR 0.59, 95% CI: 0.42–0.83) | EGFRPositive HR 0.76 (95% CI: 0.35–1.64)Negative HR 0.47 (95% CI: 0.36–0.60)Unknown HR 0.79 (95% CI: 0.52–1.20) | 15.4% discontinuation (RP and related toxicities). |
| PACIFIC-R, JTO 2022 | Retrospective | 1399 | Stage IIIA-IIIB/IIIC (AJCC 7th or 8th) | IA-IIB: 5.3% IIIA: 43.4% IIIB or IIIC: 51.3% | Platinum-based CRT (median RT dose 66 Gy) + consolidative durvalumab (10 mg/kg IV every 2 weeks) for up to 1 year. 52.4%: >60 to ≤66 Gy 41.4%: ≤60 Gy | rwPFS, OS | Median rwPFS: 21.7 mo (95% CI: 19.1–24.5) 2 yr OS: 71.2% (95% CI: 68.8–73.6) | Sq: 14.6 months Non-sq: 25.3 months | ≥ 1% (22.4 months) < 1% (15.6 months) | Stage: IIIA (23.7 months) vs. IIIB/IIIC (19.2 months)CRT Type: cCRT (23.7 months) vs. sCRT (19.3 months)Durvalumab Timing: ≤42 days (25.7 months) vs. >42 days (20.8 months)Age: <70 years (22.8 months) vs. 70–75 years (22.4 months) vs. >75 years (19.2 months). | 16.5% led to permanent discontinuation. (9.5%-RP/ILD) |
| PACIFIC-6, JTO 2022 | II | 117 | Stage IIIA-IIIB/IIIC (IASLC staging manual 8th Edition) | IIIA: 37.6% IIIB: 50.4% IIIC: 11.1% | (sCRT): 2+ cycles of platinum-based chemo (cisplatin or carboplatin with vinorelbine, taxane, or pemetrexed) followed by 60 Gy ± 10%) + consolidative durvalumab (1500 mg IV q4weeks). 66.7%: ≥54 to ≤60 Gy and 31.6%: ≥ 60 Gy to ≤ 66 Gy. | G 3-4 PRAE within 6 months | Median PFS: 10.9 mo (95% CI: 7.3–15.6) 1 yr PFS: 49.6% (95% CI: 39.5–58.9) 2 yr OS: 69.8% (95% CI: 5.8–80.2) | NR | 1 yr PFS ≥1%: 54.8% <1%: 49.4% 2 yr OS ≥1%:60.2% <1%:70.3% | NR | G 3-4 PRAE within 6 months in 4.3%; 12.8% led to discontinuation due to pneumonitis, 3% discontinuation due to ILD and radiation pneumonitis. |
| GEMSTONE-301, The Lancet Oncol 2022 | III | 381 | Stage IIIA-IIIB/IIIC(IASLC staging manual 8th edition) | IIIA: 27.8% IIIB: 55.4% IIIC: 16.0% Other: 0.8% | (cCRT or sCRT): 2+ cycles of platinum-based chemo (etoposide, vinorelbine, vinblastine, pemetrexed, taxanes, or gemcitabine; exception, gemcitabine is not allowed in cCRT) with 54–66 Gy RT, followed by sugemalimab 1200 mg IV q3 weeks up to 2 years vs. placebo. | PFS | Median PFS: 9.0 mo (sugemalimab) vs. 5.8 mo (placebo) (HR 0.64, $p = 0.0026$) 1 yr PFS: 45.4% (sugemalimab) vs. 25.6% (placebo). | Sq: 8.31 mo vs. 4.21 mo, HR 0.57 (95% CI 0.41–0.80); Non-Sq: 24.35 mo vs. 9.92 mo, HR 0.77 (95% CI 0.42–1.140). | NR | ChemoRTsCRT 8.08 mo vs. 4.07 mo, HR 0.59 (95% CI 0.39–0.91) cCRT 10.51 mo vs. 6.37 mo, HR 0.66 (95% CI 0.44–0.99)RT Dose:≤60 Gy 10.51 mo vs. 6.21 mo, HR 0.55 (95% CI 0.27–1.12)>60 Gy 8.44 mo vs. 5.39 mo, HR 0.66 (95% CI 0.48–0.90) | Grade 3–4 TRAEs: 9% (sugemalimab) vs. 6% (placebo).Pneumonitis/ immune-mediated pneumonitis was most common grade 3–4 AE (3% sugemalimab vs. <1% placebo). |

| Study | Phase | n | Staging | Stage Distribution | Treatment | Primary Endpoints | Results | Factors Affecting Treatment Outcomes | | | Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SPIRAL-RT, EJC 2023 | II | 33 | Stage IIIA-IIIB/IIIC | IIIA: 51.5% IIIB: 45.5% IIIC: 3.0% | RT monotherapy (54–66 Gy) in chemotherapy in-eligible patients followed by sequential durvalumab (10 mg/kg IV q2 weeks up to 1 year). | 1 yr PFS | Median PFS: 8.9 mo (95% CI: 7.4–19.4 mo) 1 yr PFS: 39.1% (90% CI: 24.7–54.6%, meeting the primary endpoint threshold of 16%). | Sq: 7.4 m Non-Sq: 19.4 m | Median PFS PDL1 < 25%: 7.4 m PDL1 ≥ 25%: 10.2 m Unknown: 19.4 m | EGFR pos: 10.4 mEGFR neg/unknown: 7.7 m | 51.5% had radiation pneumonitis, with no cases ≥ Grade 3 |
| LUN14-179, Cancer 2020 | II | 93 | Stage IIIA-IIIB | IIIA: 60% IIIB: 40% | cCRT (cisplatin/etoposide, cisplatin/pemetrexed, or carboplatin/paclitaxel) with 59.4–66.6 Gy followed by consolidative pembrolizumab (200 mg IV Q3W for up to 12 months). | TMDD | Median TMDD: 30.7 mo (95% CI: 18.7 mo to NR); Median PFS: 18.7 mo (95% CI: 12.4–33.8 mo) | NA | NA | NA | Grade ≥ 2 pneumonitis: 10.8%; Grade 3 pneumonitis: 4.3%. |
| BTCRC LUN 16-081, JCO 2022 | II | 105 | Stage III unre-sectable | | After cCRT: randomized to Arm A: nivolumab (480 mg IV Q4W) for up to 24 weeks or Arm B: nivolumab (3 mg/kg IV Q2W) + ipilimumab (1 mg/kg IV Q6W) for up to 24 weeks. | 18-month PFS | Median PFS: 25.8 mo (Arm A), 25.4 mo (Arm B). 18-month PFS: 62.3% (Arm A), 67% (Arm B) (both $p < 0.1$ vs. historical con-trols) | NA | NA | NA | ≥Grade 3 events: 39% (Arm A), 53% (Arm B) |
| COAST, JCO 2022 | II | 189 | Stage IIIA-IIIB/IIIC unre-sectable | | After cCRT (≥2 cycles platinum chemo [cisplatin or carboplatin] + 54–66 Gy RT) with no progression and randomly assigned 1:1:1. Control Arm: Durvalumab 1500 mg Q4W. Arm A: Durvalumab 1500 mg Q4W + oleclumab 3000 mg Q2W (cycles 1–2), then oleclumab Q4W (cycle 3 onwards). Arm B: Durvalumab 1500 mg Q4W + monalizumab 750 mg q2 wks | ORR | Confirmed ORR: 30.0% (Arm A) vs. 35.5% (Arm B) vs. 17.9% (durvalumab) 1 yr PFS: 62.6% (Arm A) vs. 72.7% (Arm B) vs. 33.9% (durvalumab). | NA | NA | NA | Grade 3–4 TRAEs: 40.7% (Arm A); 27.9% (Arm B); 39.4% (durvalumab); Most common grade 3–4 AEs:Pneumonia (6.8% Arm A, 1.6% Arm B, 9.1% durvalumab); Lymphopenia (6.8% Arm A, 0% Arm B 3% durvalumab). |

| Study | Phase | n | Staging | Stage Distribution | Treatment | Primary Endpoints | Results | Factors Affecting Treatment Outcomes | | | Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Histology | PDL-1 | Other Factors | |
| Jabbour et al. JAMA Oncology, 2020 | I | 21 | Stage III un-resectable | IIIA: 38%<br>IIIB: 62% | cCRT (paclitaxel + carboplatin + pembrolizumab + RT 60 Gy/30 fractions) followed by consolidative pembrolizumab | Safety, Toxicity | Median PFS: 18.7 mo<br>1 yr PFS: 69.7% | NA | No difference in PFS with PDL1 status | | Grade ≥3 IRAE–18%<br>Grade 5 pneumonitis–1 patient |
| NICOLAS, JTO 2020 | II | 79 | Stage IIIA-B unre-sectable | IIIA: 35.4%<br>IIIB: 63.3%<br>Missing: 1.3% | cCRT (2–3 cycles cisplatin/carboplatin +etoposide/pemetrexed/vinorelbine + RT 66 Gy/33 fractions), followed by nivolumab 360 mg Q3W × 4 (2 cycles with cCRT) followed by nivolumab alone 480 mg Q4W, up to 1 year. | 1-yr PFS | Median PFS: 12.7 mo<br>Median OS: 38.8 mo<br>1-yr PFS: 53.7% | No OS difference between Sq and Non-sq | NA | Stage 2 yr OS: 63.7% (higher for IIIA 81.0% vs. IIIB 55.6%, $p = 0.037$) | Grade ≥3 pneumonitis: 11.7% |
| DETERRED, Lung Cancer 2022 | II | 40 | Stage III un-resectable | | Part 1 (Sequential): chemoRT (60–66 Gy with weekly carboplatin and paclitaxel 50 mg/m$^2$) followed by consolidation (carboplatin, paclitaxel 200 mg/m$^2$, and atezolizumab 1200 mg q3w for 2 cycles) then atezolizumab 1200 mg q3w for up to 1 year if no progression.<br>Part 2<br>(Concurrent): Atezolizumab 1200 mg q3w concurrent with chemoRT (60–66 Gy with weekly carboplatin and paclitaxel 50 mg/m$^2$), followed by the same consolidation as for Part 1. | PFS, OS | Median PFS: 18.9 months (Part 1) vs. 15.1 months (Part 2) HR 1.30 (95% CI: 0.56–3.04, $p = 0.54$)<br>Median OS: 26.5 months (Part 1) vs. NR (Part 2) HR 0.71 (95% CI: 0.25–1.99, $p = 0.51$) | NA | <1%: 11.0 mo<br>>1%: 27.4 mo | Targetable driver oncogene mutation: shorter PFS (9.4 vs. 16.6 months, HR 3.49 (95% CI: 1.19–10.29) | NA |
| KEYNOTE-799, JAMA Oncol 2022 | II | 216 | Stage III un-resectable | IIIA: 37.4%<br>IIIB: 49.1%<br>IIIC: 13.6% | Cohort A (n = 112, sq/non-sq):1 cycle carboplatin/paclitaxel/pembrolizumab, then weekly carboplatin/paclitaxel × 6 cycles + pembrolizumab q3w × 2 cycles concurrent with RT (60 Gy), followed by pembrolizumab 200 mg q3w for up to 1 year.<br>Cohort B (n = 102, non-sq): 3 cycles of cisplatin/pemetrexed + pembrolizumab Q3 wks concurrent with RT (60 Gy) in last 2 cycles, followed by pembrolizumab 200 mg Q3 wks for up to 1 year. | ORR, Grade 3–5 pneumonitis | ORR: 70.5% (cohort A), 70.6% (cohort B)<br>12-month DOR: 79.7% vs. 75.6%<br>1-year PFS: 67.1% vs. 71.6%<br>1-year OS: 81.3% vs. 87% | Cohort A (ORR)<br>Sq: 71.2%<br>Non-sq: 69.2%<br>Cohort B (ORR)<br>Non-sq: 70.6% | Cohort A (ORR)<br>PDL 1 < 1%: 66.7%<br>PDL 1 ≥ 1%: 75.8%<br>Cohort B (ORR)<br>PDL 1 < 1%: 71.4%<br>PDL 1 ≥ 1%: 72.5% | NA | Grade 3–5 pneumonitis: 8% vs. 6.9%<br>Any grade 3–5 TRAE: 64.3% vs. 50% |

| Study | Phase | n | Staging | Stage Distribution | Treatment | Primary Endpoints | Results | Factors Affecting Treatment Outcomes | | | Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Histology | PDL-1 | Other Factors | |
| DOLPHIN, JAMA Oncol 2023 | II | 35 | Stage IIIA-IIIB/IIIC(IASLC staging manual 8th) | Post-operative recurrence: 9%<br>IIIA: 45.7%<br>IIIB: 20%<br>IIIC: 8.6% | Concurrent durvalumab (10 mg/kg IV q2weeks) with 60 Gy radiation therapy<br>3D-CRT: 70%<br>IMRT: 11% | 1 yr-PFS | Median PFS: 25.6 mo (95% CI: 13.1 mo to NE)<br>1 yr PFS: 72.1% (90% CI: 59.1–85.1%) | NA | NA | NA | Grade 3–4 AEs in 52.9%, including pneumonitis, radiation pneumonitis in 11.8%. |
| SPRINT, JCO 2023 | II | 25 | Stage IIIA-IIIB/C | II:14%<br>IIIA: 52%<br>IIIB/IIIC: 44% | PD-L1 (TPS) score<br>>50%: Induction pembrolizumab (200 mg IV q3W × 3 cycles) + risk-adapted radiotherapy (MTV < 20cc: 48 Gy and 55 Gy for larger lesions) in 4 weeks, then maintenance of pembrolizumab up to 1 yr<br><50%: Standard chemoRT followed by adjuvant durvalumab or osimertinib | 1-year PFS rate | Median PFS: 26 months<br>1 year PFS: 76%<br>2 year OS: 76% | NA | all had PDL1 ≥ 50% | Partial/complete response rate after induction pembrolizumab: 48%;<br>Median MTV Induction immunother-apy:36cc<br>Standard chemoRT: 26cc | Grade 3 AEs: colitis (8%), esophagitis (4%)<br>No grade 4–5 treatment-related AEs |

# Acerca de la RT

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Radiotherapy and Oncology 174 (2022) 133–140

Contents lists available at ScienceDirect

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Original Article

# Impact of radiation dose to the immune cells in unresectable or stage III non-small cell lung cancer in the durvalumab era

Neal S. McCall [a,*], Hamilton S. McGinnis [a], James R. Janopaul-Naylor [a], Aparna H. Kesarwala [a], Sibo Tian [a], William A. Stokes [a], Joseph W. Shelton [a], Conor E. Steuer [b], Jennifer W. Carlisle [b], Ticiana Leal [b], Suresh S. Ramalingam [b], Jeffrey D. Bradley [a], Kristin A. Higgins [a]

[a] Winship Cancer Institute of Emory University, Department of Radiation Oncology; and [b] Winship Cancer Institute of Emory University, Department of Hematology & Medical Oncology, United States

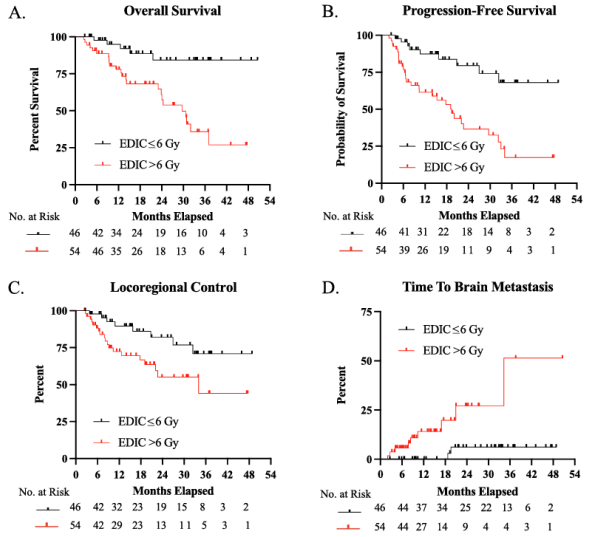



**Fig. 1.** Kaplan-Meier survival curves are shown for the following endpoints: OS (1A), PFS (1B), LRC (1C) and TTBM (1D).

## Estimated radiation doses to immune cells (EDIC)

**Higher Radiation Dose to the Immune Cells Correlates with Worse Tumor Control and Overall Survival in Patients with Stage III NSCLC: A Secondary Analysis of RTOG0617**

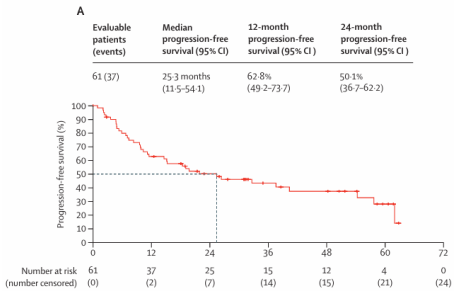
El EDIC es un predictor independiente de peor OS, PFS y LC.
La dosis incidental sobre las células inmunitarias podría contrarrestar los beneficios del durvalumab.
Es necesario validar esta hipótesis
Evaluar si nuevas técnicas de RT pueden mejorar los resultados al preservar mejor las células inmunitarias circulantes.

## Primary lung tumour stereotactic body radiotherapy followed by concurrent mediastinal chemoradiotherapy and adjuvant immunotherapy for locally advanced non-small-cell lung cancer: a multicentre, single-arm, phase 2 trial

*John H Heinzerling, Kathryn F Mileham, Myra M Robinson, James T Symanowski, Raghava R Induru, Gregory M Brouse, Christopher D Corso, Roshan S Prabhu, Daniel E Haggstrom, Benjamin J Moeller, William E Bobo, Carolina E Fasola, Vipul V Thakkar, Sridhar E Pal, Jenna M Gregory, Sarah L Norek, Xhevahire J Begic, Aparna H Kesarwala, Stuart H Burri, Charles B Simone 2nd*

- SBRT 50-54Gy en 3-5 fracciones sobre tumor primario
- RTQT sobre enfermedad ganglionar
- +/-Durvalumab

- N=61
- Buenos resultados en PFS, OS y buen perfil de toxidad




These findings serve as the basis for the ongoing randomised phase 3 study NRG Oncology LU008 (NCT05624996).

Adding high-dose, targeted radiation to the usual treatment for locally-advanced, inoperable non-small cell lung cancer

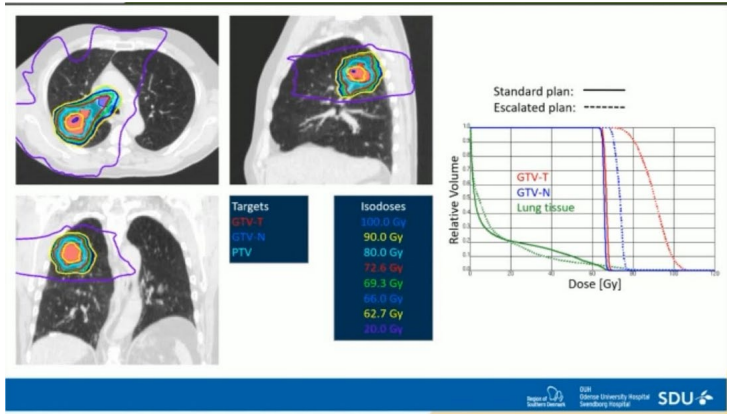
Lancet Oncol 2025; 26: 85–97

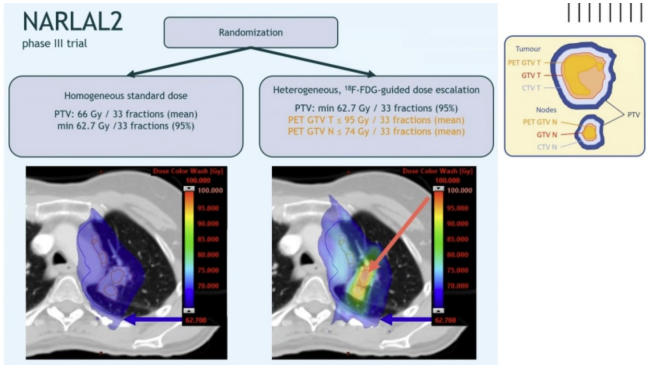
Christina M. Lutz
Aarhus University Hospital

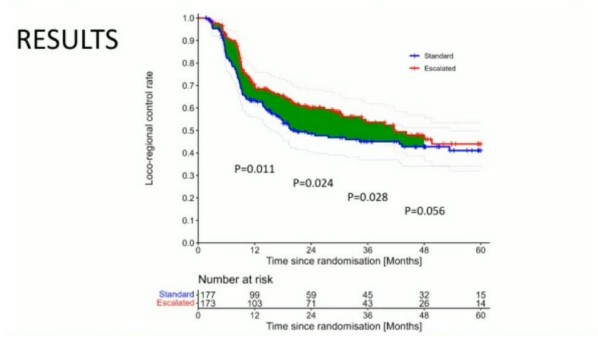
## Inhomogeneous dose escalation for NSCLC: Full dosimetric analysis of the phase III NARLAL2 trial

Christina M Lutz, Tine B Nielsen, Mikkel D Lund, Tine Schytte, Torben S Hansen,
Lone Hoffmann, Katarina W Ottosson, Cécile Peucelle, Espen Rusten, Nina Levin, Carsten Brink,
Bjørn H Grønberg, Vilde D Haakensen, Olfred Hansen, Azza A Khalil, Marianne M Knap,
Charlotte Kristiansen, Morten Nielsen, Gitte F Persson, Mette Pøhl, Rune S Thing, Ane Appelt, Ditte S Møller

OUH Odense University Hospital · Aarhus University Hospital · Herlev Hospital · Rigshospitalet · Vejle Hospital – part of Lillebaelt Hospital · Oslo University Hospital · St. Olavs Hospital Universitetssykehuset i Trondheim



Radiotherapy and Oncology 168 (2022) 234–240

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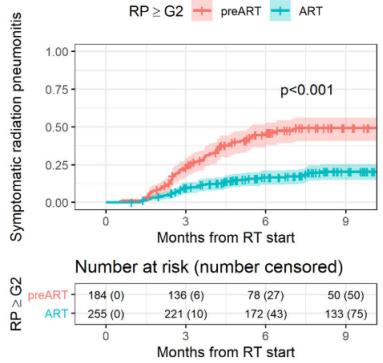
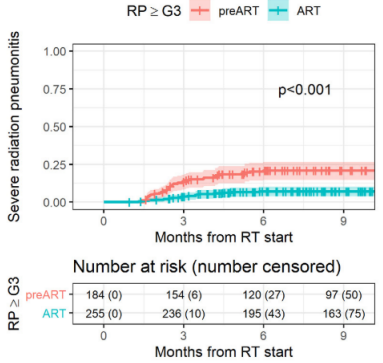
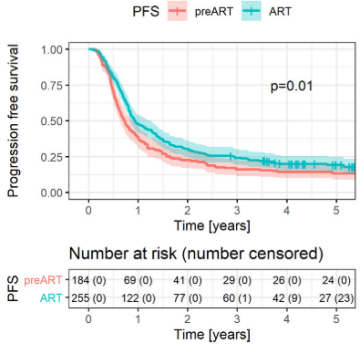
Original Article

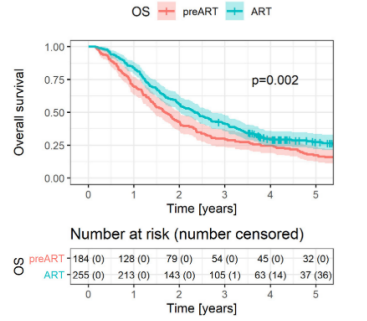
Survival benefits for non-small cell lung cancer patients treated with adaptive radiotherapy

- Escalar dosis
- Reducir dosis a tejidos sanos

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SOCIEDAD ESPAÑOLA DE ONCOLOGÍA RADIOTERÁPICA

Original Reports | Radiation Oncology

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

Nitin Ohri, MD, MS[1]; Shruti Jolly, MD[2]; Benjamin T. Cooper, MD[3]; Rafi Kabarriti, MD[1]; William R. Bodner, MD[1]; Jonathan Klein, MD[1]; Chandan Guha, MD, PhD[1]; Shankar Viswanathan, PhD[4]; Elaine Shum, MD[5]; Joshua K. Sabari, MD[5]; Haiying Cheng, MD, PhD[6]; Rasim A. Gucalp, MD[6]; Enrico Castellucci, MD[6]; Angel Qin, MD[7]; Shirish M. Gadgeel, MD[8]; and Balazs Halmos, MD[6]

Can biomarker-selected patients with locally advanced non-small cell lung cancer (LA-NSCLC) be treated safely and effectively with immunotherapy and radiotherapy and without cytotoxic chemotherapy?

Pacientes con PDL1>50%; PS 0-1;
Pembrolizumab x3 → RT* → Pembrolizumab (1 año)

*RT: 48-55Gy en 20 fracciones según volumen de enfermedad en PET

PFS: 26m
OS_2ª: 76%
*Es necesario contrastar este esquema con el SoC*

J Clin Oncol 42:562-570

# Conclusiones

1. Detección de los pacientes en los comités multidisciplinares
2. Tratamiento estándar en PDL1+: RTQT seguido de Durvalumab
3. Nuevas estrategias con la combinación de fármacos
4. Optimización de la RT en la era de la inmunoterapia
5. Búsqueda de un tratamiento más personalizado