#ESMOUPDATES

Iniciativa científica de:

GECP lung cancer research

# LUNG CANCER UPDATES

## ESMO HIGHLIGHTS

**27 SEPTIEMBRE - 1 OCTUBRE 2019**


Con la colaboración de:

Bristol-Myers Squibb

illumina

Lilly

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BARCELONA

# Novedades en cáncer de pulmón no microcítico localizado y localmente avanzado (II)

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Con la colaboración de:
Bristol-Myers Squibb
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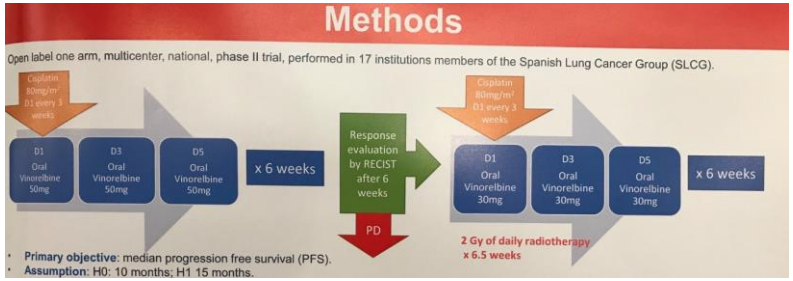
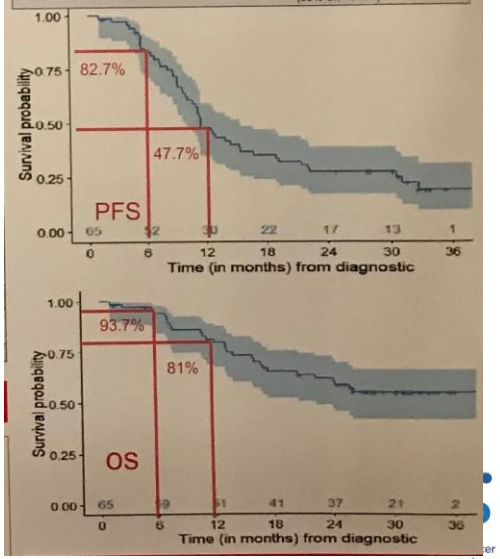
# NORA trial (GECP 15/02): Updated results of the Spanish Lung Cancer Group (SLCG) phase II trial of concurrent chemo-radiotherapy (CT-RT) with cisplatin (P) plus metronomic oral vinorelbine (mOV) for unresectable locally advanced non-small cell lung cancer (LA-NSCLC). Guirado M et al.




Objetivo primario: PFS.
Objetivos secundarios: ORR, tasa de control de la enfermedad, duración de la respuesta y OS.

| Adverse events per patients excluding all grade 1-2 less than 1 case (1.8%) (N=65) | Grade 1-2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|
| Alopecia | 3 (4.6) | - | - |
| Anemia | 30 (46.1) | 3 (4.6) | 0 |
| Anorexia | 11 (16.9) | 0 | 0 |
| Arthralgia | 3 (4.6) | 0 | 0 |
| Constipation | 10 (15.4) | 0 | 0 |
| Creatinine increase | 3 (4.6) | 0 | 0 |
| Diarrhea | 21 (32.3) | 1 (1.5) | 0 |
| Dizziness | 2 (3.1) | 0 | 0 |
| Dysgeusia | 3 (4.6) | 0 | 0 |
| Dyspepsia | 2 (3.1) | 0 | 0 |
| Dysphagia | 16 (24.6) | 0 | 0 |
| Dyspnea | 3 (4.6) | 0 | 0 |
| Esophagitis | 22 (33.8) | 2 (3.1) | 0 |
| Fatigue | 25 (38.5) | 1 (1.5) | 0 |
| Febrile neutropenia | - | 3 (4.6) | 1 (1.5) |
| Fever | 2 (3.1) | 0 | 0 |
| Gastroesophageal reflux disease | 2 (3.1) | 0 | 0 |
| Gastrointestinal pain | 4 (6.2) | 0 | 0 |
| Other gastrointestinal disorders | 8 (12.3) | 2 (3.1) | 0 |
| Headache | 2 (3.1) | 0 | 0 |
| Hiccups | 2 (3.1) | 0 | 0 |
| Hypocalcemia | 0 | 1 (1.5) | 0 |
| Hypomagnesemia | 3 (4.6) | 1 (1.5) | 0 |
| Oral mucositis | 7 (10.8) | 0 | 0 |
| Nausea | 29 (44.6) | 1 (1.5) | 0 |
| Neutropenia | 17 (26.1) | 6 (9.2) | 7 (10.8) |
| Renal and urinary disorders | 4 (6.2) | 0 | 0 |
| Skin and subcutaneous disorders | 11 (16.9) | 1 (1.5) | 0 |
| Pneumonitis | 0 | 1 (1.5) | 0 |
| Paresthesia | 2 (3.1) | 0 | 0 |
| Thrombocytopenia | 11 (16.9) | 1 (1.5) | 0 |
| Tinnitus | 3 (4.6) | 0 | 0 |
| Vomiting | 20 (30.8) | 1 (1.5) | 0 |

| Evaluation response | N = 65 (%) |
|---|---|
| Complete response | 4 (6.2) |
| Partial response | 40 (61.5) |
| Stable disease | 11 (16.9) |
| Progression disease | 7 (10.8) |
| Non evaluable | 3 (4.6) |
| Overall Response Rate (%) | 44 (67.7) |
| Disease Control Rate (%) | 55 (84.6) |
| Median Progression Free Survival (m) | 11.5 (95% CI; 9.9-15.4) |
| Median Overall Survival (m) | NA (95% CI; 16-NR) |




**Conclusiones:** La combinación de mOV + CDDP es factible con o sin CRT, la tolerabilidad fue excelente con un buen perfil de eficacia, ORR de 67,7% y mPFS 11.5 meses, OS inmadura.

# Efficacy of Durvalumab in Patients with Stage III NSCLC who Experience Pneumonitis (PACIFIC). Vansteenkiste JF et al.

En este trabajo se presentan los datos del análisis exploratorio del PACIFIC, en el que se evalúa el impacto de la neumonitis sobre los resultados de eficacia y seguridad, y el manejo clínico la neumonitis en la población del estudio.

**Table 4. OS, PFS and TTDM adjusted for the (time-dependent) occurrence of on-study pneumonitis and for the ITT population**

| | No. of events/no. of patients (%) | | HR (95% CI) for durvalumab vs placebo | |
|---|---|---|---|---|
| | Durvalumab | Placebo | Adjusted for the time-dependent occurrence of pneumonitis | ITT population[3,4] |
| **OS** | 183/476 (38.4) | 116/237 (48.9) | | |
| Model 1 (base model) | | | 0.70 (0.55–0.88) | 0.68 (0.53–0.87) |
| Model 2 | | | 0.65 (0.51–0.83) | – |
| **PFS** | 243/476 (51.1) | 173/237 (73.0) | | |
| Model 1 (base model) | | | 0.54 (0.45–0.66) | 0.51 (0.41–0.63) |
| Model 2 | | | 0.52 (0.42–0.64) | – |
| **TTDM** | 182/476 (38.2) | 126/237 (53.2) | | |
| Model 1 (base model) | | | 0.57 (0.45–0.71) | 0.53 (0.41–0.68) |
| Model 2 | | | 0.53 (0.41–0.67) | – |

**Table 6. Pneumonitis management and outcomes (as-treated population)**

**A. Durvalumab-treated patients**

| | No. of patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | On-study pneumonitis | Management/intervention of pneumonitis | | | | | Clinical outcome of pneumonitis | | |
| Highest CTCAE grade of pneumonitis | Any AE | Treatment interrupted | Treatment discontinued | Systemic corticosteroid | High-dose corticosteroid* | Other treatment† | Resolved | Not resolved | Outcome of death |
| 1 | 67 | 11 | 2 | 17 | 3 | 0 | 20 | 47 | 0 |
| 2 | 72 | 45 | 12 | 63 | 37 | 0 | 47 | 25 | 0 |
| 3 | 17 | 4 | 11 | 16 | 11 | 0 | 12 | 5 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 5 | 0 | 5 | 5 | 5 | 2 | 0 | 0 | 5 |
| Total, n (%) | 161 (100) | 60 (37.3) | 30 (18.6) | 101 (62.7) | 56 (34.8) | 2 (1.2) | 79 (49.1) | 77 (47.8) | 5 (3.1) |

**B. Placebo-treated patients**

| | No. of patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | On-study pneumonitis | Management/intervention of pneumonitis | | | | | Clinical outcome of pneumonitis | | |
| Highest CTCAE grade of pneumonitis | Any AE | Treatment interrupted | Treatment discontinued | Systemic corticosteroid | High-dose corticosteroid* | Other treatment† | Resolved | Not resolved | Outcome of death |
| 1 | 25 | 4 | 0 | 1 | 0 | 0 | 4 | 21 | 0 |
| 2 | 22 | 15 | 3 | 19 | 14 | 0 | 15 | 7 | 0 |
| 3 | 6 | 3 | 4 | 6 | 6 | 0 | 2 | 4 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 5 | 0 | 3 | 5 | 4 | 1 | 0 | 0 | 5 |
| Total, n (%) | 58 (100) | 22 (37.9) | 10 (17.2) | 31 (53.4) | 24 (41.4) | 1 (1.7) | 21 (36.2) | 32 (55.2) | 5 (8.6) |

Data are according to electronic case report form. No statistical analyses were performed to test for between-arm differences. *A dose that equates to at least 40 mg prednisone daily. †Other immunosuppressive treatment. CTCAE, Common Terminology Criteria for Adverse Events.

**Conclusiones:** A pesar de las limitaciones, los datos sugieren que la neumonitis no altera el beneficio en PFS, OS y ORR en pacientes tratados con el régimen PACIFC. La mayor parte de los casos corresponden a G1-2 y por tanto no deberían limitar la continuación del tratamiento.

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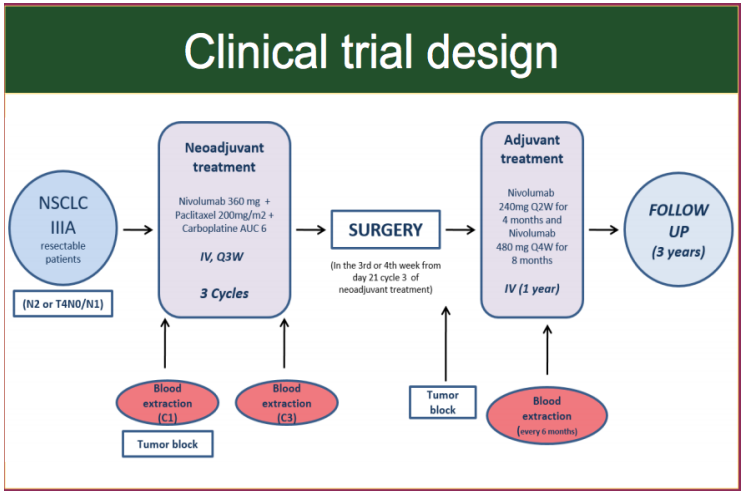
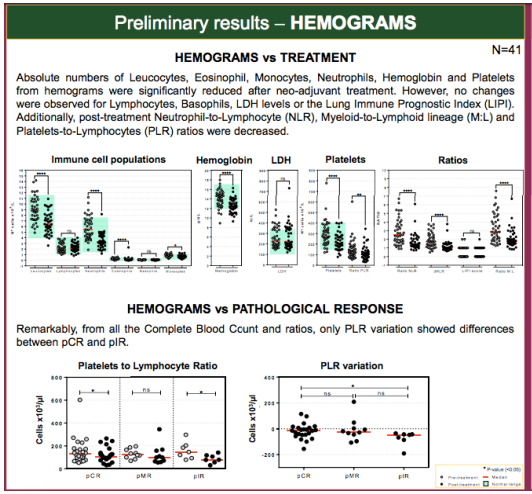
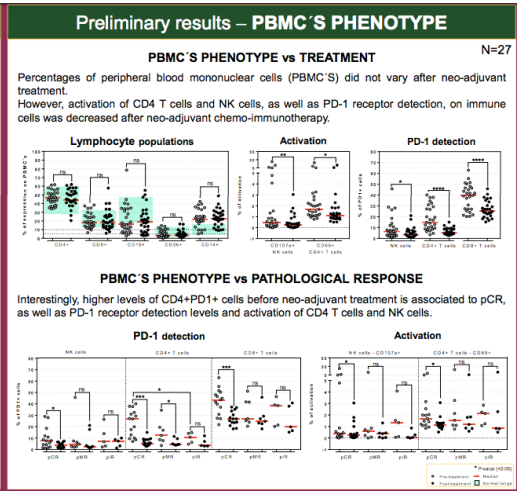
# Immune cell biomarkers on neo-adjuvant chemoimmunotherapy treatment for resectable stage IIIA NSCLC, NADIM study traslational. Laza-Briviesca R et al.




**Conclusiones:**

Niveles más altos de expresión de PD-1 en células T CD4 pre-tratamiento, así como la disminución en la detección de PD-1 en células T CD4, CD8 y Nk post-tratamiento se asocian a pRC.

La disminución del ratio plaquetas/linfocitos tras el tratamiento se asocia a respuesta menor.

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# A Phase Ib Trial of Neoadjuvant Chemoradiotherapy and Durvalumab(MEDI4736) for Potentially Resectable stage III Non-Small Cell Lung Cancer (NSCLC)

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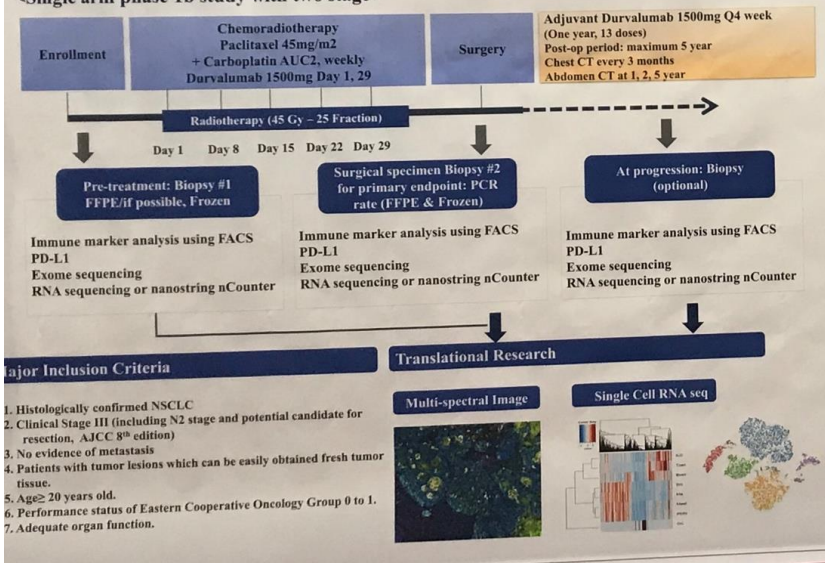
## ckground

lthough definitive concurrent chemoradiotherapy (CRT) is considered standard of care for most of stage III NSCLC patients, neoadjuvant treatment followed by rgery can be considered to some potentially resectable patients due to its tumor regression effect before surgery, early eradication of micrometastasis and better lerability of chemotherapy than post-surgical setting.

tegarding potential benefit of combining PD-L1 blockade to CRT, here we have an ongoing phase Ib trial which assesses the safety and feasibility of the ombination of neoadjuvant CRT with durvalumab in potentially resectable stage III NSCLC (NCT03694236).

## udy design

<Single arm phase 1b study with two stage>




## ajor Inclusion Criteria

1. Histologically confirmed NSCLC
2. Clinical Stage III (including N2 stage and potential candidate for resection, AJCC 8th edition)
3. No evidence of metastasis
4. Patients with tumor lesions which can be easily obtained fresh tumor tissue.
5. Age≥ 20 years old.
6. Performance status of Eastern Cooperative Oncology Group 0 to 1.
7. Adequate organ function.

## Translational Research

Multi-spectral Image



Single Cell RNA seq



## Research Hypothesis & Objectives

- Adding Durvalumab to neoadjuvant chemoradiation therapy in NSCLC (non-small cell lung cancer) can increase pCR (pathologic complete response) rate an improve patients' disease and overall survival.
- The primary endpoints are safety and tolerability. The secondary endpoints are objective response rate (ORR), R0 resection rate, disease-free survival (DFS), overall survival (OS), clinical or pathological downstaging rate and, pathologic complete response (pCR) rate in the primary tumor. Immune marker analysis FACS, exome sequencing and RNA sequencing using cancer tissue of pre-treatment, after surgery, and after recurrence will be performed.

## Table.1. Outline of ACTS30 trial

| Summary of trial | | | |
|---|---|---|---|
| **Steps of trial** | **No. of patients** | | **Considerations** |
| **Neoadjuvant** (weekly paclitaxel 45 mg/m2 and carboplatin AUC 2, radiotherapy 45 Gy in 25 fractions, durvalumab day 1 and 29, 1500mg) | **Stage 1**[1] | 9 | 1) If patients of ≥5 has grade≥3 TRAE the trial holds<br>2) If patients of ≤4 has grade≥3 TRAE the trial proceeds to the 2nd stage. |
| | **Stage 2** | 21 | If patients of ≤13(43%) has grade≥3 TRAE during the neoadjuvant treatment it will be c onsidered tolerable and further analysis will be performed.[2] |
| **Surgery** | The time and modality of surgery will depend on the surgeon's discretion.<br>The maximum allowed interval between the end of neoadjuvant therapy and surgery is 9 weeks.<br>If disease progresses during or after the neoadjuvant therapy, or if the surgeon thinks that the surgery is not fea sible, concurrent chemoradiation or chemotherapy alone can be continued. | | |
| **Adjuvant** (durvalumab 1500mg for one year every 4 weeks, total of 13 times.) | The maximum allowed interval between the surgery and adjuvant therapy is 12 weeks. | | |
| **Follow up** | Response evaluation will be done until 5 years after the surgery.<br>(Chest CT every 3 months, Abdominal pelvic CT at 1, 2, 5 years after the surgery) | | |

[1] Additional enrollment will be hold until the first 9 patients proceeds surgery.
[2] Grade≥3 TRAE during neoadjuvant chemoradiotherapy is expected to be 30–50% according to the previous data.
[3] Assessed according to the Response Evaluation Criteria in Solid Tumors(RECIST), version 1.1
TRAE; treatment-related adverse event, CT; Computed tomography

## Statistical Methods and Data Analysis

- The primary endpoint of the study is safety and tolerability.
- DFS was defined as the time from treatment start until the first documented sign of disease recurrence or death from any cause
- OS was defined as the time from first treatment until death from any cause.
- Eleven patients have been enrolled and 9 patients have underwent surgery . (Stage 1 completed )

## Reference


- Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. Invest 2014;124:687-95.
- Zeng J, See AP, Phallen J, Jackson CM, Belcaid Z, Ruzevick J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracrania gliomas. Int J Radiat Oncol Biol Phys 2013;86:343-9.