



**ASCO** HIGHLIGHTS

**31 MAYO - 4 JUNIO 2019**



Con la colaboración de:



**Bristol-Myers Squibb**

**illumina**

*Lilly*



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## Adyuvancia en estadíos iniciales CPNM

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Día 1

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# Factores de riesgo para recaída en estadio I

- Análisis retrospectivo de factores pronósticos en 1.278 p con CPNM en estadio I tratados con lobectomía/neumonectomía.
- Factores pronósticos para RFS, OS, CSS

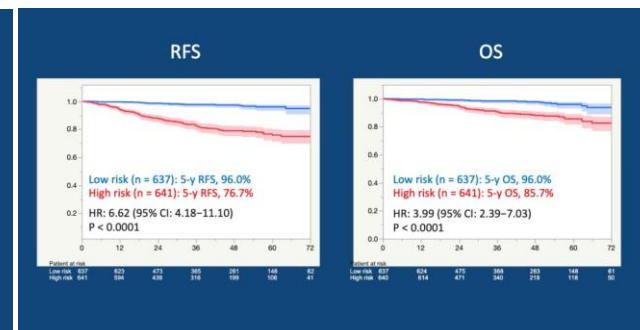
| Patients characteristics          |                         | n = 1,278      |
|-----------------------------------|-------------------------|----------------|
| Age, y (IQR)                      |                         | 69 (63-75)     |
| Gender                            | Male                    | 661 (51.7%)    |
| Histology                         | Adenocarcinoma          | 1069 (83.6%)   |
|                                   | Squamous cell carcinoma | 141 (11.0%)    |
|                                   | Others                  | 68 (5.3%)      |
| Invasive component size, cm (IQR) |                         | 1.6 (0.9-2.45) |
| Lymphatic permeation              |                         | 220 (17.2%)    |
| Vascular invasion                 |                         | 329 (25.7%)    |
| Visceral pleural invasion         |                         | 216 (16.9%)    |
| Stage                             | IA                      | 973 (76.1%)    |
|                                   | IB                      | 305 (23.9%)    |
| Adjuvant chemotherapy             |                         | 305 (23.9%)    |

| Multivariable Cox analysis for RFS |      |           |         |
|------------------------------------|------|-----------|---------|
| Variables                          | HR   | 95% CI    | P value |
| Age (> 70 y)                       | 2.14 | 1.50-3.09 | <0.0001 |
| Gender (Female)                    | 0.71 | 0.48-1.05 | 0.089   |
| Invasive component size (> 2 cm)   | 1.60 | 1.09-2.36 | 0.016   |
| Histology (Adenocarcinoma)         | 0.92 | 0.62-1.40 | 0.698   |
| Lymphatic permeation               | 1.67 | 1.13-2.43 | 0.008   |
| Vascular invasion                  | 2.78 | 1.84-4.22 | <0.0001 |
| Visceral pleural invasion          | 1.81 | 1.22-2.68 | 0.003   |



**High-risk group (n = 641)**  
Invasive component size > 2 cm  
or  
Lymphatic permeation  
or  
Vascular invasion  
or  
Visceral pleural invasion

**Low-risk group (n = 637)**  
Invasive component size ≤ 2 cm  
and  
No lymphatic permeation  
and  
No vascular invasion  
and  
No visceral pleural invasion



- Edad > 70 a (HR 2.14), afectación pleura visceral (HR 1.81), componente invasivo > 2 cm (HR 1.6) invasión linfática (HR 1.67) o vascular (HR 2.78)
- Factores de riesgo en 461 p. RFS 81.4% si CIR+QT (n=222) vs RFS 73.8% si CIR (p=0.023). Sup 5-a y Supervivencia específica: 92.7 % - 95% vs 81.7%-89.5% (p<0.0001; p=0.012)
- Para grupo sin factores de riesgo (637 p) (83 p con QT postop), no difs. en RFS (98.1% vs 95.6%), OS (98% vs 95.6%) CSS (100% vs 99.4%)

# Impacto de la QT adyuvante en estadio I

## Patients characteristics (Low-risk group)

| Variables                         | Observation<br>(n = 554) | Adjuvant chemotherapy<br>(n = 83) | P value |
|-----------------------------------|--------------------------|-----------------------------------|---------|
| Age, y (IQR)                      | 68 (62-75)               | 66 (60-72)                        | 0.35    |
| Gender (Female)                   | 324 (58.5%)              | 43 (51.8%)                        | 0.25    |
| Invasive component size, cm (IQR) | 0.9 (0.5-1.5)            | 1.3 (0.8-1.7)                     | 0.002   |
| Histology (Adenocarcinoma)        | 523 (94.4%)              | 81 (97.6%)                        | 0.22    |

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## Multivariable Cox analysis (Low-risk group)

| Variables                    | RFS         |                  |             | OS          |                  |             | CSS                  |            |            |
|------------------------------|-------------|------------------|-------------|-------------|------------------|-------------|----------------------|------------|------------|
|                              | HR          | 95% CI           | P value     | HR          | 95% CI           | P value     | HR                   | 95% CI     | P value    |
| Age (>70 y)                  | 4.31        | 1.64–13.42       | 0.003       | 3.57        | 1.32–11.26       | 0.012       | 9.61x10 <sup>7</sup> | 0.007–1.14 | 1.0        |
| Gender (Female)              | 0.36        | 0.13–0.93        | 0.034       | 0.36        | 0.12–0.97        | 0.044       | 0.00                 | 0.22–1.03  | 1.0        |
| Histology (Adenocarcinoma)   | 1.35        | 0.27–24.57       | 0.76        | 1.14        | 0.22–20.86       | 0.90        | 4.52x10 <sup>8</sup> | N/A        | 1.0        |
| <b>Adjuvant chemotherapy</b> | <b>0.37</b> | <b>0.06–1.35</b> | <b>0.14</b> | <b>0.42</b> | <b>0.06–1.54</b> | <b>0.21</b> | <b>0.00</b>          | <b>N/A</b> | <b>1.0</b> |

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## Patients characteristics (High-risk group)

| Variables                         | Observation<br>(n = 419) | Adjuvant chemotherapy<br>(n = 222) | P value |
|-----------------------------------|--------------------------|------------------------------------|---------|
| Age, y (IQR)                      | 71 (65-77)               | 67 (62-71.3)                       | < 0.001 |
| Gender (Female)                   | 156 (37.2%)              | 94 (42.3%)                         | 0.21    |
| Invasive component size, cm (IQR) | 2.4 (1.8-3.0)            | 2.5 (2.0-3.1)                      | 0.21    |
| Histology (Adenocarcinoma)        | 287 (68.5%)              | 178 (80.2%)                        | 0.002   |
| Lymphatic permeation              | 139 (33.2%)              | 81 (36.5%)                         | 0.40    |
| Vascular invasion                 | 218 (52.0%)              | 111 (50.0%)                        | 0.63    |
| Visceral pleural invasion         | 120 (28.6%)              | 96 (43.2%)                         | 0.0002  |

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## Multivariable Cox analysis (High-risk group)

| Variables                       | RFS         |                  |              | OS          |                  |               | CSS         |                  |              |
|---------------------------------|-------------|------------------|--------------|-------------|------------------|---------------|-------------|------------------|--------------|
|                                 | HR          | 95% CI           | P value      | HR          | 95% CI           | P value       | HR          | 95% CI           | P value      |
| Age (>70 y)                     | 1.70        | 1.15–2.55        | 0.008        | 2.72        | 1.53–5.11        | 0.0005        | 1.16        | 0.56–2.48        | 0.7          |
| Gender (Female)                 | 0.82        | 0.53–1.24        | 0.34         | 0.63        | 0.33–1.14        | 0.13          | 0.99        | 0.43–2.14        | 0.97         |
| Invasive component size (>2 cm) | 1.33        | 0.89–2.05        | 0.17         | 1.41        | 0.80–2.60        | 0.24          | 1.72        | 0.79–4.17        | 0.18         |
| Histology (Adenocarcinoma)      | 0.93        | 0.61–1.42        | 0.74         | 0.63        | 0.37–1.08        | 0.09          | 0.56        | 0.26–1.19        | 0.13         |
| Lymphatic permeation            | 1.54        | 1.06–2.25        | 0.025        | 1.20        | 0.70–2.00        | 0.50          | 1.66        | 0.82–3.36        | 0.16         |
| Vascular invasion               | 2.27        | 1.51–3.49        | < 0.001      | 2.11        | 1.23–3.71        | 0.006         | 3.46        | 1.52–8.95        | 0.003        |
| Visceral pleural invasion       | 1.89        | 1.28–2.79        | 0.001        | 1.54        | 0.90–2.60        | 0.11          | 2.75        | 1.31–5.96        | 0.008        |
| <b>Adjuvant chemotherapy</b>    | <b>0.57</b> | <b>0.36–0.87</b> | <b>0.008</b> | <b>0.31</b> | <b>0.15–0.59</b> | <b>0.0002</b> | <b>0.27</b> | <b>0.10–0.63</b> | <b>0.002</b> |

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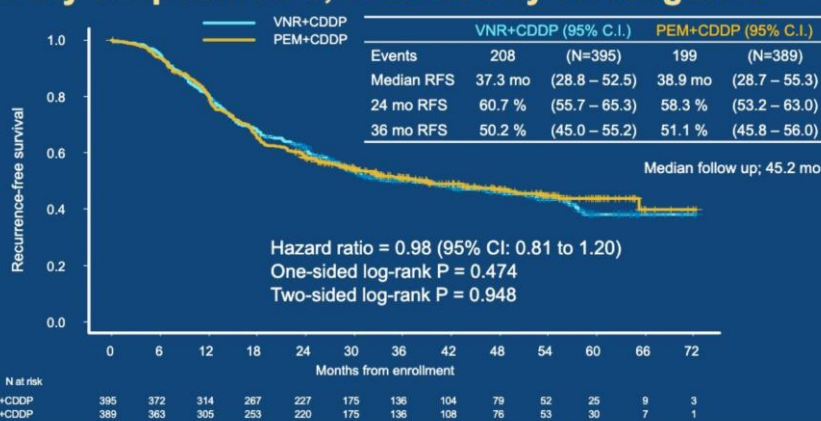
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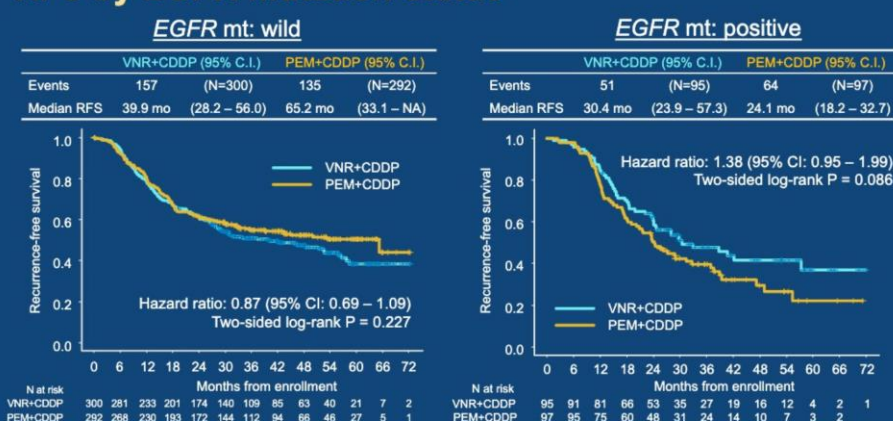
- Debilidades: Retrospectivo; Indicación QT; Esquemas QT, análisis no preplanificado

- Cisplatino-Pemetrexed vs Cisplatino-Vinorelbina adyuvante en estadios II-IIIa. JIPANG Trial (50 centros)
  - Objetivo RFS (enmienda OS). HR 0.75
  - Mar/12-Ago/16. 804 p aleatorizados. 784 p evaluables. Histología Adenocarcinoma. **24-25% EGFR mut+**
  - Mediana seguimiento 45.2 m
  - Mediana RFS 38.9 m Cis-Pem vs 37.3 m Cis-Vin (HR 0.98)
  - EGFR mut+ HR 1.38, EGFR wt HR 0.87 (**p interacción = 0.046**)
  - Cumplimiento terapéutico 87.9% vs 72.7% ( $p < 0.001$ ) con reducción significativa de neutropenia, fiebre neutropénica y anemia en Cis-Pem

## Primary endpoint: RFS, assessed by investigators

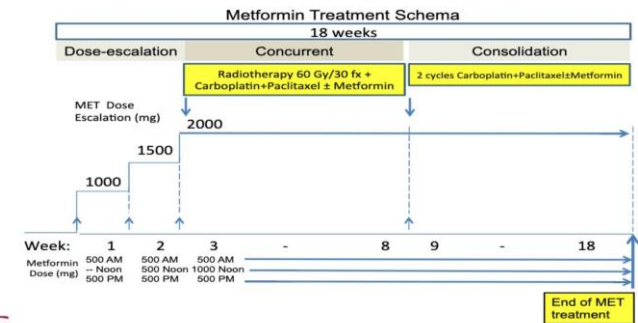


## RFS by EGFR mutation status



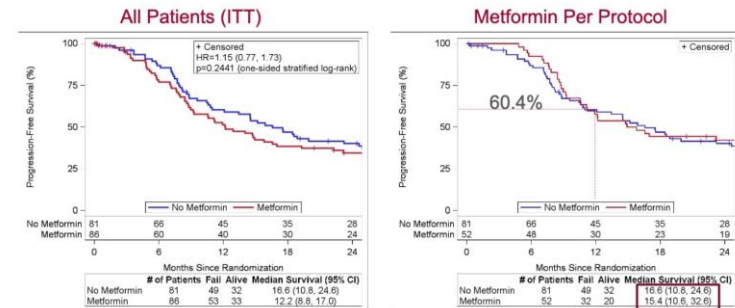
- Asociación de metformina al tratamiento QT-RT concomitante en CPNM localmente avanzado (NRG-LU001). Metformina induce stress metabólico mediante bloqueo mitocondrial
  - Objetivo primario PFS 1-a HR 0.85
  - Estadíos IIIA/B
  - Aleatorización 1:1. PFS, OS, TLRP, TTDM
  - RT + Carbo-Paclitaxel → Carbo-Paclitaxel consolidación +/- Metformina 2000 mg/24 h durante el tto QT
  - Ago-14-Dic-16. 170 p
  - No difs. EAs. Cumplimiento por protocolo 63%
  - PFS 1 a: 60.4% (control) vs 51.3% (experimental) HR 1.20 (p=0.36)
  - OS 2 a: 65.4% (control) vs 64.9% (experimental) (HR 1.03)
  - Muertes atribuibles a la neoplasia 90% vs 71%

## NRG LU001 Metformin delivery



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NRG  
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