Estado actual del tratamiento neoadyuvante y adyuvante a la cirugía en estadios iniciales de cáncer de pulmón no microcítico

Enriqueta Felip
Vall d’Hebron University Hospital Barcelona, Spain
Stage I-II

- ~ 25% of NSCLC cases
- Recurrence, in up to 50% p
  - High incidence of distant relapse

NEO CT in early-stage NSCLC

ADJ CT in early-stage NSCLC
Results with NEO CT: randomized trials

• French Thoracic Cooperative Group: no OS differences, DFS longer with NEO and maintained with long-term follow-up (Depierre JCO 02, Westeel ASCO 10)

• MRC22/NVALT 2/EORTC 08012: no improvement in OS (Gilligan Lancet 07)

• NEO CT vs SUR trials that closed prematurely: survival benefit trend for NEO CT (Sorensen ASCO 05, Pisters JCO 10, Scagliotti JCO 11)

• NATCH trial: NEO CT a NS trend towards improved DFS, absolute 6.5% improvement in 3-yr DFS, 4.2% in 5-yr DFS (Felip JCO 10)
NATCH trial: study design

Stratify by:
- Tumor size: (<3, 3-5 or > 5 cm)
- Age: (≤ 60 or >60 y)

Clinical stage

- IA(>2cm), IB, II, T3N1

Stratify by:
- Tumor size: (<3, 3-5 or > 5 cm)
- Age: (≤ 60 or >60 y)

Surgery

- Paclitaxel / Carboplatin

Post-op thoracic RT allowed for p-N2 disease
CT compliance

• **Preop CT, 193 pts (97%)**
  – 13 pts, < 3 cycles
  – Dose reductions 9% of pts / delays 11% of pts

• **Adj CT, 139 pts (66%)**
  – 10 pts, < 3 cycles
  – Dose reductions 11% of pts / delays 16% of pts
NATCH: disease-free survival by arm

**PREOP CT Arm vs Surgery Arm**

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>At risk:</th>
<th>PREOP CT</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>140</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>105</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

**Events**

- Surgery (N=210): 132
- PREOP CT (N=199): 117

**Median DFS (mo)**

- Surgery: 25.1
- PREOP CT: 31.5

**Probability**

- Surgery: 41.9%
- PREOP CT: 48.4%

- 5-year DFS: 34.1%
- PREOP CT: 38.3%

HR = 0.92; 95% CI (0.81 to 1.04); P = 0.176

**ADJ CT Arm vs Surgery Arm**

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>At risk:</th>
<th>ADJ CT</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>131</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>95</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

**Events**

- Surgery (N=210): 132
- ADJ CT (N=210): 125

**Median DFS (mo)**

- Surgery: 25.1
- ADJ CT: 26.0

**Probability**

- Surgery: 41.9%
- ADJ CT: 44.9%

- 5-year DFS: 34.1%
- ADJ CT: 36.6%

HR = 0.96; 95% CI (0.75 to 1.22); P = 0.73
Pre-operative CT improves survival and reduces recurrence in operable NSCLC: results of a systematic review and meta-analysis of individual pt data from 15 randomised trials

Overall effect

HR=0.87 (95% CI 0.78-0.96), p=0.007

Heterogeneity: chi-square=18.75, df=14, p=0.175, I²=25.35

Burdett Lancet 14
Overall survival, 15 trials, 2385 patients, 1427 deaths

HR=0.87, p=0.007
Absolute improvement of 5% at 5 years
<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Treatment</th>
<th>Pt No</th>
<th>5-yr</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>I-III</td>
<td>Surg MVP</td>
<td>603</td>
<td>45%</td>
<td>0.96</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>606</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IALT</td>
<td>I-III</td>
<td>Surg Cis-based</td>
<td>935</td>
<td>40%</td>
<td>0.86</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>932</td>
<td>44.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANITA</td>
<td>IB-IIIA</td>
<td>Surg Cis-vin</td>
<td>433</td>
<td>43%</td>
<td>0.80</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>407</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLT</td>
<td>I-IIIA</td>
<td>Surg Cis-based</td>
<td>189</td>
<td>58%</td>
<td>1.02</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>192</td>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCI-C</td>
<td>IB-II</td>
<td>Surg Cis-vin</td>
<td>240</td>
<td>54%</td>
<td>0.69</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>242</td>
<td>69%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB</td>
<td>IB</td>
<td>Surg Carb-pac</td>
<td>171</td>
<td>57%</td>
<td>0.80</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>173</td>
<td>59%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
LACE (Lung Adjuvant Cisplatin Evaluation)

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Patients</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
<th>No. Events / No. Patients</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>560/1088</td>
<td>0.95</td>
<td>0.81;1.12</td>
<td>634/1088</td>
<td>0.89</td>
<td>0.76;1.04</td>
</tr>
<tr>
<td>ANITA</td>
<td>458/840</td>
<td>0.82</td>
<td>0.65;0.98</td>
<td>526/840</td>
<td>0.76</td>
<td>0.66;0.93</td>
</tr>
<tr>
<td>BLT</td>
<td>186/307</td>
<td>0.95</td>
<td>0.71;1.27</td>
<td>103/307</td>
<td>0.93</td>
<td>0.79;1.23</td>
</tr>
<tr>
<td>IALT</td>
<td>950/1857</td>
<td>0.81</td>
<td>0.61;1.04</td>
<td>1059/1857</td>
<td>0.86</td>
<td>0.77;0.97</td>
</tr>
<tr>
<td>JBR10</td>
<td>107/482</td>
<td>0.71</td>
<td>0.54;0.94</td>
<td>234/482</td>
<td>0.66</td>
<td>0.51;0.85</td>
</tr>
<tr>
<td>Total</td>
<td>2390/4584</td>
<td>0.89</td>
<td>0.82;0.96</td>
<td>2688/4584</td>
<td>0.84</td>
<td>0.78;0.90</td>
</tr>
</tbody>
</table>

Chemotherapy better | Control better
Chemotherapy effect: Logrank statistic = 8.5  p = 0.004
Test for heterogeneity $X^2 = 4.25$  p = 0.37  $\hat{I}^2 = 6\%$

Chemotherapy better | Control better
Chemotherapy effect: Logrank statistic = 21.1  p < 0.001
Test for heterogeneity $X^2 = 5.16$  p = 0.27  $\hat{I}^2 = 23\%$

Deaths / person years by period
- Years 0-3
  - Control: 966 / 5155
  - Chemotherapy: 857 / 5181
- Years 4-5
  - Control: 239 / 1668
  - Chemotherapy: 203 / 1817
- Years $\geq$ 6
  - Control: 49 / 720
  - Chemotherapy: 76 / 790

Pignon JCO 08
**ADJ CT for resected early-stage NSCLC**

- 35 trials evaluating SUR plus *ADJ CT* vs SUR alone
  - 8,447 participants (3323 deaths) in 34 trial comparisons
  - Benefit of adding CT after SUR; HR 0.86, p< 0.0001; absolute increase in survival of 4% at 5 yrs

- 15 trials evaluating SUR plus RT plus CT vs SUR plus RT alone
  - 2,660 participants (1909 deaths) in 13 trial comparisons
  - Benefit of adding CT to SUR plus RT; HR 0.88, p= 0.009; absolute improvement in survival of 4% at 5 yrs

- **Results from 47 trial comparisons and 11,107 patients demonstrate clear benefit of ADJ CT**

  *Buredt et al, Cochrane Database Syst Rev. 2015*
ADJ or NEO CT in early-stage NSCLC?

• *ADJ / NEO* CT administration similar impact on survival benefit

• More conclusive evidence available favoring *ADJ* strategies

• A subset of pts may benefit from a *NEO* strategy, but this is yet to be defined

• Personalized medicine: having enough tumor material essential, the use of *ADJ* favored
**ADJ CT in stage IB**

- A pooled exploratory analysis of the effect of tumor size on survival benefit from **ADJ** platinum-based CT in node-negative NSCLC (Cuffe JTO 12)
  - 461 node-negative p (CALGB 9633 and JBR.10) reclassified as T2a, T2b or T3
  - A non-significant trend for increased CT effect on OS with advancing T-size (HR T2a 0.90, T2b 0.69, T3 0.57)

_Tumor size is a relevant factor to consider to decide ADJ CT in stage I, although not prospectively validated_
## ADJ CT in the elderly

<table>
<thead>
<tr>
<th></th>
<th>Median age yr (range)</th>
<th>% ≥ 65 yrs</th>
<th>% ≥ 70 yrs</th>
<th>% ≥ 75 yrs</th>
<th>Subset analyses according age</th>
</tr>
</thead>
<tbody>
<tr>
<td>IALT</td>
<td>59 (27-77)</td>
<td>27%</td>
<td>1%</td>
<td>p older than 75 yrs excluded</td>
<td>No significant interaction between treatment effect and age (&lt;55, 55-64, &gt; 64 yr)</td>
</tr>
<tr>
<td>JBR.10</td>
<td>61</td>
<td>32%</td>
<td>15%</td>
<td>5%</td>
<td>p &gt; 65 yrs CT prolonged OS (HR 0.61)</td>
</tr>
<tr>
<td>ANITA</td>
<td>59 (32-75)</td>
<td>28%</td>
<td>8%</td>
<td>p older than 75 yrs excluded</td>
<td>No</td>
</tr>
<tr>
<td>LACE</td>
<td>60</td>
<td>29%</td>
<td>9%</td>
<td>_</td>
<td>p ≥ 70 yrs OS benefit from ADJ CT; HR 0.90</td>
</tr>
</tbody>
</table>

• No available information in p > 80 yrs
Which platin combination in the ADJ setting?

- *Cis/vin*, the most studied in randomized trials
- Feasibility phase II studies with other CT combinations
- No direct comparison in phase III among doublet platin-combinations
- Phase II randomized trial of *ADJ cis/pem vs cis/vin* (TREAT): *cis/pem*, safe and feasible and less toxic than *cis/vin* *(Kreuter Ann Oncol 12)*
PORT for pathologic N2 NSCLC treated with ADJ CT: a review of the National Cancer Database

• **Study objectives**
  – To investigate the impact on survival of modern PORT on OS in N2 NSCLC after surgery and ADJ CT

• **Study design**
  – Retrospective analysis of data from the National Cancer Database from 4483 patients who had undergone complete resection (R0) and ADJ CT between 2006 and 2010, of whom 1850 (41.3%) received PORT

*Robinson et al. J Clin Oncol 2015*
PORT for pathologic N2 NSCLC treated with ADJ CT
a review of the National Cancer Database

• Key results
  – In multivariate analysis, younger age, treatment at an academic facility, higher income, lower Charlson score, smaller tumour, ≥ lobectomy, and use of PORT (HR for PORT 0.89 [95% CI 0.80, 0.99]; p=0.029) predictive of improved OS for the entire group

• Modern PORT may confer an additional 5% survival advantage in NSCLC p after complete resection beyond that achieved with ADJ CT alone

• Ongoing clinical trial LUNGART

7501: A randomized, double-blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection with or without adjuvant chemotherapy in patients (pts) with stage IB-IIIA EGFR positive (IHC/FISH) non-small cell lung cancer (NSCLC): RADIANT results – Kelly K et al

**Study objective**
- To evaluate adjuvant erlotinib vs placebo following complete tumour resection in patients with stage IB–IIIA NSCLC and EGFR FISH+ or EGFR IHC+

**Key patient inclusion criteria**
- Complete resected NSCLC
- Stage IB–IIIA
- EGFR IHC+/FISH+
- ECOG PS 0–2 (n=973)

**Stratification**
- Histology, stage, prior adjuvant CT, EGFR FISH status, smoking status, country

**Erlotinib 150 mg/day (n=623)**

**Placebo (n=350)**

**R 2:1**

**≤4 cycles of platinum-based doublet**

**Primary endpoint**
- Disease-free survival (FAS)

**Secondary endpoints**
- OS (FAS)
- Disease-free survival and OS (EGFR M+ subset)

FAS, full analysis set

Kelly et al. J Clin Oncol 2014; 32 (suppl 5; abstr 7501)
RADIANT: DFS and OS in EGFR mut+

**DFS**

Erlotinib vs Placebo

- Erlotinib (39 events)
  - Median: 46.4 m
- Placebo (32 events)
  - Median: 28.5 m

Log-rank test: p=0.0391 (not statistically significant due to hierarchical testing)

HR: 0.61 (95% CI: 0.384, 0.981)

**OS**

Erlotinib vs Placebo

- Erlotinib (22 events)
  - Median: not reached
- Placebo (13 events)
  - Median: not reached

Log-rank test: p=0.8153

HR: 1.09 (95% CI: 0.545, 2.161)

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>59</td>
<td>102</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>94</td>
<td>100</td>
</tr>
</tbody>
</table>

Kelly K, ASCO 2014
Eligibility:
NSCLC, non-squamous
Resectable
Clinical TNM Stage for Pre-Op Option
~ OR ~
Pathologic TNM Stage for Post-Op Option
Stage 1B>4 cm, Stage II A – III A
PS 0-1; Age ≥ 18
Adequate organ function
Adequate tissue for central EGFR & ALK genotyping must be available
Not known to be EGFR & ALK neg, or KRAS pos, on local testing
Willing to answer epidemiology questionnaire and donate de-identified data, tissue, & blood for research

If only slides are available in post-op option, only genotyping for EGFR & ALK will be done for possible assessment for adjuvant trials if positive, otherwise patient is off-study (no CCG research component)

PRE-OP (Intra-OP)
FFPE Block
Epi Questionnaire Blood

If patient is not resectable and/or pTNM does not fit eligibility criteria, the patient is off-study

POST-OP
FFPE Block
Epi Questionnaire Blood

Assessment for Adjuvant Tx Trials
If EGFR or ALK pos but not able to go on adjuvant tx trial
If EGFR or ALK neg

Follow to recurrence or for 5-years (whichever 1st) with abbreviated collection of treatment data & genomics

*Primary endpoints of the treatment trials are based on patients with EGFR or ALK pos by CLIA Central Lab; however, those

Blood Sent Directly:
For DNA germline analysis patients assessed for genomics
Tissue testing
RGI or
Genomics
Deep sequencing, exon sequencing

Recurrent:
Sent to RGI
Genomic comparison of specimen
At recurrence, patient should undergo confirm recurrence deemed appropriate for clinical trial

ALCHEMIST TRIAL – SCREENING COMPONENT
# Protocol Details – Trial Design

<table>
<thead>
<tr>
<th>Trial Category</th>
<th>ALCHEMIST SCREEN Component A151216</th>
<th>ALCHEMIST - ALK E4512</th>
<th>ALCHEMIST - EGFR A081105</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Registry/Intervention with biopsy at recurrence</td>
<td>ALK+</td>
<td>EGFRmut</td>
</tr>
<tr>
<td>Prevalence</td>
<td>all comers</td>
<td>~5%</td>
<td>~10%</td>
</tr>
<tr>
<td>Total Sample Size</td>
<td>6000 – 8000</td>
<td>378 (5% ineligible)</td>
<td>430 (5% ineligible)</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>N/A</td>
<td>Overall Survival</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>Power</td>
<td>N/A</td>
<td>80%</td>
<td>85%</td>
</tr>
<tr>
<td>One-sided $\alpha$</td>
<td>N/A</td>
<td>0.025</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Potential role of targeted agents in ADJ setting

- MAGRIT: phase III MAGE-A3 immunotherapy vs placebo in completely resected MAGE-A3-positive p; negative study

- ECOG1505: CT vs CT/bevacizumab: 4 cycles of cis-doublet +/- bev up to 1 yr; negative study
Prognostic / predictive markers in early-stage disease

• **ERCC1**
  - IALT-Bio, p with ERCC1-negative tumors benefit from CT; p with ERCC1-positive do not (*Olausen NEJM 06*)
  - Validation set of samples obtained from 494 p (JBR.10 and CALGB) using 8F1 antibody; unable to validate the predictive effect of immunostaining for ERCC1 protein (*Friboulet NEJM 13*)

• **KRAS**
  - Pooled analysis of prognostic /predictive effects of KRAS in early-stage (IALT, JBR10, CALGB9633, ANITA) (*Shepherd JCO 13*)
    - KRAS mutation is not significantly prognostic
    - KRAS status cannot be recommended to select p for ADJ CT
    - In p with mut in codon 13, outcome with ADJ CT, particularly poor; small sample size
Prognostic / predictive markers in early-stage disease

- Increased BRCA1 mRNA: independent prognostic variable in completely resected chemo-naive NSCLC p (Rosell PLoS 07)

- A 15-gene signature predictive of ADJ-CT benefit in JBR10 (Tsao JCO 10)

- A 14-gene expression assay, prognostic tool in completely resected stage I non-SCC p (Kratz Lancet 12)

- A DNA methylation signature prognostic in stage I (Sandoval JCO 13)

- Three miRNAs encoded at 14q32 (miR-411, miR-370, and miR-376a) associated with poor survival after lung ADC resection (Nadal Clin Can Res 14)
Results of adjuvant phase II trial (IFCT-0801, TASTE trial) from the French Collaborative Intergroup

- Randomised, phase II study of control CT (4 cycles of cisp-pem [CP]) vs. customised CT (EGFR mut p received erlotinib for 1 yr, ERCC1- p received 4 cycles of CP, ERCC1+ p closely monitored)
- 150 p randomised (74 in control arm, 76 in customised arm; 51% ≥60 yrs; 61% male; 91% smokers; 69, 48 and 32 p with stage IIA, IIB and IIIA p-stage)
- ERCC1+ in 38 p (19 in each arm), EGFR mut identified in 10 p (3 in control arm, 7 in customised arm)
- Feasibility demonstrated with all p starting therapy within 2 mo of surgery
- Phase III study cancelled due to the unexpected unreliability of the ERCC1 IHC read-out

*Soria et al JCO 14*
Randomized phase III trial of customized adjuvant CT according BRCA-1 expression levels in pts with node positive resected NSCLC SCAT: A SLCG

Study objective
• To investigate the role of BRCA1 as a differential regulator in the response of patients with NSCLC to cisplatin and antimicrotubule agents

Key patient inclusion criteria
• Stage II and III post-surgery NSCLC
• R0
• pN1/pN2 (n=500)

Primary endpoint
• OS

Secondary endpoints
• DFS, toxicity, recurrence pattern

Experimental groups
- **Low BRCA1**: Gemcitabine 1250 mg/m² D1, 8 + cisplatin 75 mg/m² D1 (n=110)
- **Intermediate BRCA1**: Docetaxel 75 mg/m² + cisplatin 75 mg/m² D1 (n=127)
- **High BRCA1**: Docetaxel 75 mg/m² D1 (n=110)

Control group
- Docetaxel 75 mg/m² + cisplatin 75 mg/m² D1 (n=108)

Stratification
• N1 vs. N2
• Age ≤65 vs. >65 years
• Non-squamous vs. squamous
• Lobectomy vs. pneumonectomy

Randomized phase III trial of customized adjuvant CT according BRCA-1 expression levels in pts with node positive resected NSCLS SCAT: A SLCG

- **Key results**
  - No significant difference was seen in OS (HR=0.86) between the experimental and control groups
  - Treatment according to BRCA1 levels did not improve OS
Preliminary Results of the International Tailored Chemotherapy Adjuvant Trial: The ITACA Trial

Study objective

- To compare ADJ pharmacogenomics-driven (personalised) CT, based on TS and ERCC1 gene expression vs standard ADJ CT

Primary endpoint

- OS (5-year rate)

Secondary endpoints

- Disease-free interval (DFI), toxicity

Key patient inclusion criteria

- Completely resected NSCLC
- Stage II–IIIA
- ECOG PS 0–1
(n=761)

Stratification

- Stage II vs. III and smoking status

Profile 1: ERCC1 low, TS low

- Cis/pem
- Control

Profile 2: ERCC1 low, TS high

- Cis/gem
- Control

Profile 3: ERCC1 high, TS low

- Pemetrexed
- Control

Profile 4: ERCC1 high, TS, high

- Taxanes
- Control

Novello et al. J Thorac Oncol 2015; 10 (suppl 2): ORAL04.03
In total, 386 pts received standard ADJ therapy and 375 pts received personalised ADJ therapy

- Proportion in each arm: Profile 1, 37.5%; Profile 2, 11.6%; Profile 3, 26.8%; and Profile 4 24.2%

- AEs observed similar to those observed in other ADJ trials

- For profile 1 (ERCC1 low and TS low), the proportion of discontinuations due to SAEs was significantly higher in the standard vs personalised ADJ treatment arms

Novello et al. J Thorac Oncol 2015; 10 (suppl 2): ORAL04.03
Anti-PD1 & anti-PDL1 strategies

• A reality in the management of stage IV disease

• Ongoing trials in the ADJ setting and in stage III after radical CT/RT treatment

• NEO strategies
In view of the equivalence of NEO and ADJ CT for overall survival, the consistent results and broad evidence base support ADJ CT as the timing of choice [I, A]
ADJ CT should be offered to patients (p) with resected stage II or III NSCLC [I, A] and can be considered in patients with resected stage IB disease and a primary tumour >4 cm [II, B]. However, pre-existing co-morbidity and postoperative recovery need to be taken into account in this decision.

For ADJ CT, a two-drug combination with cis is preferable [I, A]. In randomised studies, the attempted cumulative cis dose was up to 300 mg/m², delivered in three to four cycles. The most frequently studied regimen is cis–vin.

Currently, ADJ CT is not recommended in stage IA, with reports of potential harm, although the number of patients in this subgroup was small [II, B].

Age per se is not a contra-indication for ADJ CT.
Should factors, other than stage, guide the choice of ADJ therapy?

- P with severe comorbidity were excluded from clinical trials

- Evidence of benefit from ADJ CT established in p PS 0, 1 rarely PS 2 [I, A]

- Precise interval limits to start ADJ CT not properly addressed in clinical trials

- In case of R1 resection postoperative RT should be considered [III, B]. Even if such p were not included in the RCTs, ADJ CT is advised for R1 resection regardless of nodal status [V, A]. In case CT and RT are both administered, RT should be administered after CT [V, C]
• Given the current state of knowledge, the choice of ADJ therapy should not be guided by molecular analyses such as ERCC1 or mutation testing [IV, B]

• Given the current state of knowledge, targeted agents should not be used in the ADJ setting [II, A]
SEOM clinical guidelines for the treatment of non-small cell lung cancer (NSCLC) 2015

R. García-Campelo¹ · R. Bernabé² · M. Cobo³ · J. Corral⁴ · J. Coves⁵ · M. Dómine⁶ · E. Nadal⁷ · D. Rodríguez-Abreu⁸ · N. Viñolas⁹ · B. Massuti¹⁰

Adjuvant therapy

The beneficial effect in terms of survival of adjuvant cisplatin based chemotherapy in completely resected fit stage II–III NSCLC patients is now well established [9].

- For patients with completely resected stage II NSCLC, four cycles of postoperative platinum-based chemotherapy are recommended (IA).
- Postoperative chemotherapy is not recommended for patients with completely resected stage IA NSCLC (IB) and its use remains controversial in patients with large IB tumors (≥4 cm) (IC).
- In elderly fit patients (≤80 years), postoperative platinum-based chemotherapy should be considered as well.

Targeted agents are not recommended in the postoperative setting. Adjuvant erlotinib did not improve disease-free survival in patients with EGFR-expressing NSCLC or in the EGFR mutant subgroup [11]. Several trials are currently testing the use of targeted therapies in patients with resected EGFR/ALK positive NSCLC.
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Adjuvant chemotherapy (four cycles of adjuvant cisplatin-based chemotherapy

Not indicated in stage IA
May be considered in selected patients with stage IB
Recommended in stage II
Not recommended

Targeted agents
Gracias!!

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