State-of-the-art: standard of care for resectable NSCLC

Adjuvant Chemotherapy

JY DOUILLARD MD PhD
Professor of Medical Oncology
Integrated Centers of Oncology R Gauducheau
University of Nantes
France
Adjuvant chemotherapy is a concept of proven efficacy in several frequent cancers including breast, colon, ovarian...

Its role in NSCLC was still unclear until recent studies provided evidence of benefit.

But, recent studies results however are still controversial in term of patients to whom adjuvant chemotherapy should be offered.

Targeted therapies have been evaluated as well in the adjuvant setting
The MRC 1995 meta-analysis: a landmark in adjuvant CT

- 14 randomized trials on 4357 patients

- 3 groups analyzed according to chemotherapy regimen:
  - Alkylating agents-containing regimen:
    - ↑ risk of death (+15%), ↓ survival (-4% at 2y, –5% at 5 y.)
  - UFT-based CT (Japanese trials):
    - Non conclusive results, ns. ↓ of risk of death
  - Cisplatin-based CT (7 trials)
    - ↓ risk of death 13%
    - ↑ survival (3% at 2y., 5% at 5y.)
    - Non significant (p=0.08) however

Non-small cell lung cancer collaborative group - BMJ 1995; 311: 899-909
Major Adjuvant Studies in NSCLC

7 additional adjuvant trials were performed (2003-2008) with conflicting results*:

- **ALPI-EORTC** (Scagliotti et al) JNCI October 2003 **negative**
- **IALT** (Lechevalier et al.) NEJM January 2004 **positive transient**
- **Big Lung Trial** (Waller D. et al) Eur J Cardi Thoac Surg 2004 **negative**
- **KATO et al** NEJM April 2004 (UFT stage I) **positive in IB only**
- **BR 10** (Winton et al) NEJM June 2005 **positive in II only**
- **CALGB 9633** (Stauss et al) JCO 2008 **positive transient**
- **ANITA 01** (Douillard et al.) ASCO 2005 **positive in II and IIIA**

* TNM V and VI classification
Major Adjuvant Studies in NSCLC

• Additional meta-analysis have brought new information:

  • Hotta meta-analysis 2004\(^{(1)}\)
    - 11 trials (6 UFT based) on 5716 patients since the 1995 meta-analysis
      - Significant reduction of risk of death in both UFT single agent (\(p=0.015\)) or cisplatin-based CT (\(p=0.012\))

  • Hamada meta-analysis 2005\(^{(2)}\)
    - UFT single agent-based adjuvant CT in Japan
    - 6 studies, 2003 pts, mostly early stage (65% pT1, 96% pN0, 84% adenocarcinomas)
      - Risk of death 26%,
      - Survival (4.3% at 5y, 7% at 7y, \(p=0.011\) and 0.001)

(1) Hotta at al. JCO 22; 19, october 2004   (2) Hamada et al JCO 23; 22 august 2005
Major Adjuvant Studies in NSCLC: IALT

• Randomized phase III, 1st end point: SURVIVAL

Chemotherapy

1867 resected pts

Optional adjuvant RT 50Gy med. dose

Observation

Population:
- Stage I: 36%, II 24%, IIIA 40%,
- pneumonectomy 35%
- squamous 46%

Radiation: 31% of patients

The International Adjuvant Lung Cancer Trial Collaborative Group NEJM January 22, 2004, 351-360
Major Adjuvant Studies in NSCLC: IALT

CHEMOTHERAPY REGIMEN ADMINISTERED

<table>
<thead>
<tr>
<th>Dose of Cisplatin</th>
<th>Drug Combined with Cisplatin</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vindesine</td>
<td>Vinblastine</td>
<td>Vinorelbine</td>
<td>Etoposide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mg/m² for 4 cycles</td>
<td>4</td>
<td>105</td>
<td>124</td>
<td>94</td>
<td>327</td>
<td></td>
</tr>
<tr>
<td>100 mg/m² for 3 cycles</td>
<td>103</td>
<td>43</td>
<td>185</td>
<td>484</td>
<td>815</td>
<td></td>
</tr>
<tr>
<td>100 mg/m² for 4 cycles</td>
<td>0</td>
<td>57</td>
<td>48</td>
<td>436</td>
<td>541</td>
<td></td>
</tr>
<tr>
<td>120 mg/m² for 3 cycles</td>
<td>1</td>
<td>0</td>
<td>143</td>
<td>40</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>108</td>
<td>205</td>
<td>500</td>
<td>1054</td>
<td>1867</td>
<td></td>
</tr>
</tbody>
</table>
The International Adjuvant Lung Cancer Trial Collaborative Group NEJM January 22, 2004, 351-360

- Significant benefit of cisplatin-based CT:
  - HR 0.86, p=0.03
  - +4.1% at 5 years,

- 74% received at least 240 mg/m2 of CDDP

- Toxic death: 0.8%

- This study is probably underpowered since initial statistics were based on an accrual of 3000pts
According to the author, all test for interaction are negative, not allowing p values among groups.

A different analysis on stage published by Strauss et al showed a significant p value for stage III only (p=0.035) (Hematol Oncol Clin N Am 2005 19, 263-281).

The study was initially calculated on 3000 pts and therefore lacks power for subgroup analysis.
Recent Adjuvant Studies in NSCLC: IALT

- The IALT study was initially published after 5y FU (2004)
- An updated analysis was later published at 7.5 y (2010)

<table>
<thead>
<tr>
<th>Follow-up in years</th>
<th>5</th>
<th>7.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR survival</td>
<td>0.86</td>
<td>0.91</td>
</tr>
<tr>
<td>Pvalue</td>
<td>0.03</td>
<td>0.10</td>
</tr>
</tbody>
</table>

- A excess of non-cancer related deaths was noticed in the chemotherapy arm with time
- Long FU is needed to really evaluate the benefit of adjuvant CT
Recent Adjuvant Studies in NSCLC: CALGB 9633

• Randomized phase III primary end-point: SURVIVAL

  Observation

  344 resected pts

  Closed early (384) 4 cycles TAXOL 200mg/m²

  Carboplatin AUC=6 Q 3w

Population:  - Stage IB
  - Lobectomy 89%
  - Squamous 39%

Tolerance (n=149/173): Neutropenia grade 3-4 36%, no toxic death

Strauss et al ASCO 2004 and J clin Oncol 2008; 26: 5043-5041
OVERALL SURVIVAL

THEN AND NOW

**ASCO: 2004**

- HR = 0.62; 90% CI: 0.44-0.89
- p = 0.01

**ASCO: 2006**

- HR = 0.80; 90% CI: 0.60-1.07
- p = 0.10

Strauss et al ASCO 2004 and J Clin Oncol 2008; 26: 5043-5041
CALGB 9633
Survival: Patients with Tumor ≥ 4.0 cm

HR=0.66; 90% CI: 0.45-0.97; p=0.04

N=97
N=99

Strauss et al ASCO 2004 and J clin Oncol 2008; 26: 5043-5041
CALGB 9633
FINAL CONCLUSIONS

- Significant advantages in disease-free survival and 3-year survival provide some evidence that adjuvant chemotherapy is effective
  - raise the possibility that adjuvant chemotherapy may delay recurrence, even if it does not enhance curability
  - exploratory analysis suggests that benefit of adjuvant chemotherapy may be limited to patients with larger tumors

- Results of CALGB 9633 do not mandate adjuvant chemotherapy as the standard of care in all stage IB patients
Recent Adjuvant Studies in NSCLC: BR 10

**Randomized phase III, primary end-point: SURVIVAL**

**Observation**

- 482 resected pts
- 4 cycles CDDP (50mg/m² D1 and 8) Q 4 w
- NVB weekly 25mg/m² x 16w (initially 30mg/m² in 18 pts)

**Population:**
- Stage IB: 45%, IIA 15% IIB 40%,
- lobectomy 69% bilobectomy 8% pneumonectomy 23%
- adenocarcinoma 53%

**Tolerance:**
- neutropenia 88% (73% grade 3-4), 7% Febrile Neutropenia

Recent Adjuvant Studies in NSCLC: BR 10

Overall benefit on:
- **RFS** (61 vs. 49% at 5y)
- **OS** (MS 94 vs 73m)

Demonstrated in stage II only (+20% at 5y)
Not in stage IB (+7% at 5y)

Biomolecular markers:
- Pts with mutated Ras do not benefit from adjuvant CT as opposed to wild type Ras, the interaction test between Ras status and treatment outcome however is not statistically significant.

The first study to show a clear benefit of modern chemotherapy overall but mainly in stage II
Adjuvant Studies in NSCLC: J-BR 10

Updated survival analysis

- J-BR10: 5 year survival benefit: + 15%
- J-BR10 updated analysis at 9.3 years: benefit preserved

<table>
<thead>
<tr>
<th>Follow-up in years</th>
<th>5</th>
<th>9.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR survival</td>
<td>0.69</td>
<td>0.78</td>
</tr>
<tr>
<td>Pvalue</td>
<td>0.009</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- Benefit maintained with time with adjuvant Vinorelbine-Cisplatin
- Still restricted to stage II
- HR of 0.66 (P 0.13) in stage 1 > 4cm
Recent Adjuvant Studies in NSCLC: ANITA 1

• Randomized phase III primary end-point: SURVIVAL

Observation

840 resected pts

4 cycles CDDP (100mg/m²) Q 4 w

NVB weekly 30mg/m² x 16w

Population:
- Stage IB: 35%, II 30% IIIA 35%
- Lobectomy 58% pneumonectomy 37%
- Squamous 59%

Tolerance:
- Neutropenia 85% grade 3-4, 9.3% Febrile Neutropenia
- Nausea, vomiting grade 3-4 27%
- Toxic death 1.7%

Compliance:
Median % planned dose: CDDP 76%, NVB 56%
Douillard JY et al. The Lancet Oncol. 2006; 7: 719-727
ANITA: DFS and OS

+ 8.6% at 5 years

Douillard JY et al. The Lancet Oncol. 2006; 7: 719-727
### OS according to pTNM stage

#### Stage I
- OBS. n=155
- CT n=146
- % 5 y. OS: 63.5 vs. 61.9
- Median months: 99.7 vs. Not reached

#### Stage II
- OBS. n=114
- CT n=89
- % 5 y. OS: 39.1 vs. 51.7
- Median m: 36.5 vs. 65.8

#### Stage III A
- OBS. n=159
- CT n=166
- % 5 y OS: 25.7 vs. 42.1
- Median m: 24.14 vs. 38.6

**Observation**
- No difference at 5 y.
- NVB + P + 12.6% at 5 y.
- NVB + P + 16.4% at 5 y.
ANITA: outcome according to N stage

<table>
<thead>
<tr>
<th>N0</th>
<th>OBS. n= 188</th>
<th>NVB + CDDP n= 179</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>Median</td>
<td>99.6</td>
<td>95.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N1</th>
<th>OBS. n= 136</th>
<th>NVB + CDDP n= 107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>87</td>
<td>54</td>
</tr>
<tr>
<td>Median</td>
<td>31.2</td>
<td>65.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N2</th>
<th>OBS. n= 106</th>
<th>NVB + CDDP n= 118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>84</td>
<td>74</td>
</tr>
<tr>
<td>Median</td>
<td>20.0</td>
<td>32.6</td>
</tr>
</tbody>
</table>
## Survival: Univariate analysis

<table>
<thead>
<tr>
<th>Covariates</th>
<th>P value</th>
<th>Hazard ratio [95% CI]</th>
</tr>
</thead>
</table>
| **Age:**
  > 55 years                | 0.04    | 1                     |
  < 55 years                | 0.81 [0.67 - 0.99] |
| **WHO Performance Status:**
  0                           | 0.012   | 1                     |
  1-2                        | 1.27 [1.05 - 1.52] |
| **Type of surgery:**
  Pneumonectomy              | 0.001   | 1                     |
  Other type                 | 0.73 [0.60 - 0.88] |
| **PORT:**
  No                         | 0.003   | 1.34 [1.10 - 1.63]    |
  Yes                        |          | 1                     |
| **Stage:**
  IIIA                      | < 0.001 | 1                     |
  IB-II                     | 0.54 [0.45 - 0.65] |
| **Lymph Nodes N:**
  N+                         | < 0.001 | 1                     |
  N0                         | 0.53 [0.44 - 0.65] |
| **Histological type:**
  Adenocarcinoma             | 0.733   | 1                     |
  Other type                 | 0.97 [0.80 - 1.17] |
Conclusions

- Significant improvement in survival with adjuvant navelbine/cisplatin
- The effect of navelbine/cisplatin is demonstrated in stage II and IIIA but not in IB
- The effect of post-operative radiotherapy should be investigated in randomized studies for N2 patients in combination with chemotherapy

Douillard JY et al. The Lancet Oncol. 2006; 7: 719-727
Lung Adjuvant Cisplatin Evaluation (LACE)
A Pooled Analysis of 5 Randomized Trials Including 4,584 Patients
(A) Overall survival (OS): hazard ratio (HR) of death with chemotherapy versus control (no chemotherapy).

Pignon J et al. JCO 2008;26:3552-3559
Survival curves

Chemotherapy
No chemotherapy

Absolute difference

at 3 years: 3.9% ± 1.5%
at 5 years: 5.3% ± 1.6%

+5.3 %
The effect of cisplatin+vinorelbine was marginally better than the effect of other drug combinations, this is significant when the other combinations are pooled (p=0.04, post-hoc analysis)
CT may be detrimental for stage IA, but stage IA patients were generally not given the potentially best combination cisplatin + vinorelbine (13% of stage IA patients versus ~43% for other stages).
Conclusions

- Cisplatin-based adjuvant CT improves overall and disease-free survivals of patients with NSCLC

- Vinorelbine associated with 320 to 400 mg/m² of cisplatin appears as the most promising drug combination

- Despite the large number of patients, multivariate analyses were not able to study the respective role of the associated drug and cisplatin dose
Original Article

Adjuvant Cisplatin and Vinorelbine for Completely Resected Non-small Cell Lung Cancer

Subgroup Analysis of the Lung Adjuvant Cisplatin Evaluation

Jean-Yves Douillard, MD, PhD,* Hélène Tribodet, MSc,† Delphine Aubert, MSc,‡
Frances A. Shepherd, MD,§ Rafael Rosell, MD, PhD,‖ Keyue Ding, PhD,¶ Anne-Sophie Veillard, MSc,†
Lesley Seymour, PhD,¶ Thierry Le Chevalier, MD,# Stephen Spiro, MD,** Richard Stephens,††
Jean Pierre Pignon, MD, PhD,† and on behalf of the LACE Collaborative Group

JY Douillard J Thorac Oncology 2010 5 220-228
## OS by trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Entered</th>
<th>(Chemo / Control)</th>
<th>HR</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANITA</td>
<td>458 / 840</td>
<td></td>
<td>0.82</td>
<td>[0.68;0.98]</td>
</tr>
<tr>
<td>BLT</td>
<td>30 / 66</td>
<td></td>
<td>0.57</td>
<td>[0.27;1.20]</td>
</tr>
<tr>
<td>IALT</td>
<td>244 / 500</td>
<td></td>
<td>0.88</td>
<td>[0.68;1.13]</td>
</tr>
<tr>
<td>JBR10</td>
<td>197 / 482</td>
<td></td>
<td>0.71</td>
<td>[0.54;0.94]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>929 / 1888</strong></td>
<td></td>
<td><strong>0.80</strong></td>
<td>[0.70;0.91]</td>
</tr>
</tbody>
</table>

Heterogeneity test: \( p = 0.57 \)

CT effect: \( p = 0.0007 \)

JY Douillard J Thorac Oncology 2010 5 220-228
Survival curves

At 3-year: 6.6% ± 2.3% for chemotherapy, 64.1% for control.
At 5-year: 8.9% ± 2.5% for chemotherapy, 55.0% for control.

CT effect: *p* = 0.0007

JY Douillard et al J Thorac Oncology 2010 5 220-228
Contribution of vinorelbine in adjuvant treatment of resected lung cancer

**Graph 1:**
- **Chemotherapy** vs. **No chemotherapy**
- Survival (%) over time from randomization (Years)
- Absolute difference:
  - At 3 years: 3.9% ± 1.5%
  - At 5 years: 5.3% ± 1.6%
- **Control**
  - Survival: 46%
- **Vinorelbine-CDDP**
  - Survival: 55%
  - Increase: +9%
- **P = 0.0007**

**Graph 2:**
- Survival (%) over time from randomization (Years)
- **P = 0.004**
CT effect on survival and Stage

<table>
<thead>
<tr>
<th>No. Deaths / No. Entered</th>
<th>Hazard ratio (Chemotherapy / Control)</th>
<th>HR</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I 236 / 679</td>
<td>[0.78;1.31]</td>
<td>1.01</td>
<td>[0.78;1.31]</td>
</tr>
<tr>
<td>Stage II 369 / 721</td>
<td>[0.60;0.90]</td>
<td>0.73</td>
<td>[0.60;0.90]</td>
</tr>
<tr>
<td>Stage III 324 / 488</td>
<td>[0.54;0.84]</td>
<td>0.67</td>
<td>[0.54;0.84]</td>
</tr>
</tbody>
</table>

Test for trends: $p = 0.02$

JY Douillard et al J Thorac Oncology 2010 5 220-228
Adjuvant chemotherapy for Non-small Cell Lung Cancer

Special populations:

• Elderly
# Adjuvant chemotherapy for Non-small Cell Lung Cancer in the Elderly

<table>
<thead>
<tr>
<th>Trial</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></td>
<td>p older than 75 yrs excluded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p older than 75 yrs excluded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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>

Courtesy of Enriqueta Felip
LACE ELDERLY
(A,B,C) Overall survival and (D,E,F) event-free survival by treatment arm and by age group.

Früh M et al. JCO 2008;26:3573-3581
Adjuvant Chemotherapy for NSCLC

- Based on present data, chemotherapy should be recommended in stages II and IIIA.

- Its role in stage IB is still unclear, most of the western studies are negative.

- Navelbine-Cisplatin is the only « modern » chemotherapy of proven efficacy in stage II and IIIA.

- Elderly patients should not be excluded on the only basis of age.
Could other cisplatin doublets be used? From metastatic to adjuvant setting

Colon cancer

Metastatic setting 1st line
- FOLFIRI=FOLFOX

Adjuvant setting:
- FOLFOX and FLOX
  - Gercor and NSABP
    - 2 positive trials
- FOLFIRI and IFL
  - Petacc3/Accord2/CALGB
    - 3 negative trials

Breast cancer

Metastatic setting 1st line
- Adria-Cytoxan=Adria-Docetaxel
- AC=AT

Adjuvant setting:
- Randomized trial AC vs AT
  - AC < AT

Equi-efficacy in metastatic setting does not translate into equi-efficacy in adjuvant
Adjuvant chemotherapy should be offered to patients with resected stage II and III \([I,A]\) and can be considered in patients with resected stage IB disease and a primary tumor > 4cm \([II,B]\).

Pre-existing comorbidities, time from surgery and post-operative recovery need to be taken into account in this decision in a multidisciplinary tumor board \([V,A]\).

For adjuvant chemotherapy, a two-drug combination with cisplatin is preferable \([I,A]\). In randomised studies, the attempted cumulative cisplatin dose was up to 300mg/m\(^2\), delivered in 3 to 4 cycles.

The most frequently studied regimen is cisplatin-vinorelbine.

In the current stage of knowledge, the choice of adjuvant chemotherapy should not be guided by molecular analysis such as, e.g. ERCC-1 or mutation testing \([IV,B]\) »
Recent negative trials

Targeted agents: recent trials
- Bevacizumab + Cisplatin-based CT
- Radiant (Erlotinib)
- BR 19 (Gefitinib)
PLEN04.03: Randomized Phase III Trial of Adjuvant Chemotherapy with or without Bevacizumab in Resected Non-Small Cell Lung Cancer (NSCLC): Results of E1505 – Wakelee HA et al

Study objective
- To evaluate the addition of bevacizumab to adjuvant chemotherapy in early stage resected NSCLC

Key patient inclusion criteria
- Resected
- Stage IB (≥4cm)–IIIA
- 6–12 weeks post-op
- No prior chemotherapy
- ECOG PS 0–1 (n=1,501)

Chemotherapy* x 4 cycles (n=749)

Stratification
- Cisplatin doublet, stage, histology, gender

Chemotherapy* x 4 cycles + bevacizumab 15 mg/kg q3w x 1 yr (n=752)

Primary endpoint: OS
Secondary endpoints: DFS, safety

*Chemotherapy regimens q3w
Cisplatin 75 mg/m² D1 combined with any of the following:
- vinorelbine 30 mg/m² D1, 8
- docetaxel 75 mg/m² D1
- gemcitabine 1200 mg/m² D1, 8
- pemetrexed 500 mg/m² D1

Wakelee et al. J Thorac Oncol 2015; 10 (suppl 2): PLEN04.03
PLEN04.03: Randomized Phase III Trial of Adjuvant Chemotherapy with or without Bevacizumab in Resected Non-Small Cell Lung Cancer (NSCLC): Results of E1505 – Wakelee HA et al

**Key results**

**OS**

- OS FR (B:A): 0.99
- 95% CI 0.81, 1.21
- p = 0.93

**DFS**

- DFS HR (B:A) 0.98
- 95% CI 0.84, 1.14
- p = 0.75

*Wakelee et al. J Thorac Oncol 2015; 10 (suppl 2): PLEN04.03*
Disease-free survival in (A) the intent-to-treat population, and (B) the subgroup with epidermal growth factor receptor–activating mutations.
(A) Disease-free survival (B) Overall survival. Unselected population

Overall survival in placebo arm in patients with EGFR wild-type versus EGFR-mutant tumors.

Glenwood D. Goss et al. JCO 2013;31:3320-3326