TREATMENT OF LOCALLY ADVANCED NSCLC WITH CHEMO-RADIOThERAPY

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About 30% of non-small cell lung cancers are locally advanced, mainly unresectable.

This group of patients is very heterogeneous according to mediastinal lymph node burden.

The objectives of treatment are:

- Local control of thoracic tumour and lymph nodes extension
- Micro-metastatic disease control

Despite progress in therapeutic strategies, prognosis remains poor with overall survival rate around 15%.
A VERY HETEROGENEOUS POPULATION OF PATIENTS

Mediastinal infiltration
Discrete node enlargement
Clinically occult N2

Schematic of types of patients included in studies using different treatment approaches

↑ Tumour burden
Stage III patient characteristics
↑ Performance status

HISTORY

- In the 1960s, radiotherapy became standard therapy of patients with unresectable stage III NSCLC
- RTOG showed that local control was improved by increasing total dose to 60 grays delivered in 30 fractions over 6 weeks
- This radiotherapy schedule has been used until now in many countries
- In recent years, the aim of several studies has been to optimise radiotherapy administration in terms of total dose and to use new technologies
A number of randomised phase III trials showed that chemo-radiotherapy association was better in terms of survival that radiotherapy alone. These results were confirmed by a meta-analysis published in 1995.

The reduction of death-risk was 13% with the association: 
RR 0.87 (p = 0.005)

Survival in trials of radical radiotherapy vs radical radiotherapy plus chemotherapy (only trials using regimens based on cisplatin)
HOW TO ASSOCIATE CHEMOTHERAPY AND RADIOTHERAPY?

Sequential chemo-radiotherapy:

CT  CT  (CT)  \(\text{RT}\)

Exclusive concomitant chemo-radiotherapy:

CT  CT  (CT)  \(\text{RT}\)

Induction chemotherapy before concomitant chemo-radiotherapy:

CT  CT  (CT)  CT  CT  (CT)  \(\text{RT}\)

Consolidation chemotherapy after concomitant chemo-radiotherapy:

CT  CT  (CT)  CT  CT  (CT)  \(\text{RT}\)
CONCOMITANT CHEMO-RADIOThERAPY IS THE STANDARD OF CARE
CONCOMITANT VS. SEQUENTIAL CT-RT: A META-ANALYSIS

- Meta-analysis using up-dated data on individual patients:
  - 6 randomised available trials
  - 1205 patients, NSCLC, PS = 0-1: 97%; stage IIIb: 61%

Toxicities:
- Concomitant CT-RT increased acute oesophageal toxicity (grade 3-4): from 4% to 18%; RR = 4.9 (95% CI: 3.1 - 7.8); p < 0.0001
- Non significant difference regarding acute pulmonary toxicity: RR = 0.69 (95% CI: 0.42 - 1.12); p = 0.13

## CONCOMITANT VS. SEQUENTIAL CT-RT: A META-ANALYSIS

### Overall survival: Absolute benefit

<table>
<thead>
<tr>
<th></th>
<th>2 years</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 8831</td>
<td>5.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WJLCG</td>
<td></td>
<td>5.7%</td>
<td></td>
</tr>
<tr>
<td>RTOG 9410</td>
<td></td>
<td></td>
<td>4.5%</td>
</tr>
<tr>
<td>GMMA Ankara 95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLOT-GFPC NPC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 0972</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5.3%</td>
<td>5.7%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

Aupérin A, et al., J Clin Oncol 28(13), 2010:2181–90. Reprinted with permission © 2010 American Society of Clinical Oncology. All rights reserved.
PROGNOSTIC FACTORS

- Less than 50% of patients are eligible to a concomitant chemo-radiotherapy\(^1\):
  - 66% for patients \(\leq 59\) years vs. 0% for patients > 75 years
- Several factors are predictive of a poor outcome\(^1\)–\(^4\):
  - Age > 75 years
  - GTV \(\geq 100\) cc (GTV = Gross Tumour Volume)
  - Alteration of pulmonary function tests:
    - \(\text{FEV}_1\) \(\leq 80\%
    - Diffusion capacity (DLCO) \(\leq 80\%
  - Weight loss > 5% between start and third week of CT-RT5
    - Overall survival median = 23 months vs. 13 months

WHICH CHEMOTHERAPY TO ASSOCIATE WITH RADIOTHERAPY?
CHEMO-RADIOThERAPY OR CHEMO-RADIOSENSITIZATION?

- In concurrent chemo-radiotherapy, chemotherapy is administered at full cytotoxic dose during radiotherapy. The objective is to have a synergistic effect on thoracic tumour and to control potential micrometastatic disease. The risk is to increase toxicities.

- In chemo-radiosensitization, chemotherapy drugs are administered at low dose. The objective is to improve radiosensitivity of tumour cells. Several drugs are good radiosensitizers: cisplatin, carboplatin, taxane, gemcitabine, pemetrexed, etc…
CALGB trial is the first randomised phase II study which evaluates the contribution of a third generation drug with cisplatin in concomitant CT-RT

<table>
<thead>
<tr>
<th>IIIAN2/B NSCLC</th>
<th>Gemcitabine (n = 62)</th>
<th>Paclitaxel (n=58)</th>
<th>Vinorebine (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin 80 mg/m²</td>
<td>1250 mg/m²</td>
<td>225 mg/m²</td>
<td>25 mg/m²</td>
</tr>
<tr>
<td>D1 &amp; 22</td>
<td>D1, 8, 22 &amp; 29</td>
<td>D1 &amp; 22</td>
<td>D1, 8, 22 &amp; 29</td>
</tr>
<tr>
<td><strong>Concomitant RT-CT:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT = 66 Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin 80 mg/m²</td>
<td>600 mg/m²</td>
<td>135 mg/m²</td>
<td>15 mg/m²</td>
</tr>
<tr>
<td>D43 &amp; 64</td>
<td>D43, 50, 64 &amp; 71</td>
<td>D43 &amp; 64</td>
<td>D43, 50, 64 &amp; 71</td>
</tr>
<tr>
<td>Grade 3 oesophagitis</td>
<td>35%</td>
<td>35%</td>
<td>13%</td>
</tr>
<tr>
<td>Grade 4 oesophagitis</td>
<td>17%</td>
<td>4%</td>
<td>12%</td>
</tr>
<tr>
<td>Grade 3 pulmonary toxicity</td>
<td>12%</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Grade 4 pulmonary toxicity</td>
<td>2%</td>
<td>8%</td>
<td>10%*</td>
</tr>
<tr>
<td>Objective response rate at the end of treatment</td>
<td>74%</td>
<td>67%</td>
<td>73%</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>18.3</td>
<td>14.8</td>
<td>17.7</td>
</tr>
<tr>
<td>3-years survival</td>
<td>28%</td>
<td>19%</td>
<td>33%</td>
</tr>
</tbody>
</table>

*One patient died of acute pulmonary toxicity

The best efficacy/tolerance ratio is obtained with cisplatin + vinorebine

MAIN CHEMOTHERAPIES USED IN CONCOMITANT CHEMO-RADIOThERAPY

- Cisplatin-etoposide (SWOG):
  - Cisplatin 50 mg/m² D1, D8 + etoposide 50 mg/m² D1-D5
    - This old schedule is still very used in US
- Cisplatin-vinorelbine:
  - Cisplatin 80 mg/m² D1 + vinorelbine 15 mg/m² D1, D8
    - This schedule is mainly used in France and in other European countries
  - Cisplatin 80 mg/m² D1 + vinorelbine orally 20 mg D1, 3 and 5 or 40 mg/m² D1 et D8
    - This regimen is an option to avoid intravenous vinorelbine
- Carboplatin-paclitaxel:
  - Carboplatin AUC=2/week + paclitaxel 40 à 50 mg/m²/week
    - This schedule is commonly used in US and around the world
    - It is safe and easy to deliver in an outpatient setting
- Platinum-docetaxel:
  - Cisplatin 40 mg/m² + docetaxel 40 mg/m² D1, D8, D29, D36
  - Carboplatin AUC = 2/week + docetaxel 20 mg/m²/week
    - This protocol was mainly developed in Japan
The aim of this Veteran Health Administration retrospective study is to compare the outcome of patients treated with either etoposide-cisplatin (EP) or carboplatin-paclitaxel (CP)

- 1842 patients were included
- 762 patients were identified by a propensity score to receive either EP or CP

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EP (n = 499)</th>
<th>CP (n = 1,343)</th>
<th>Standard Difference</th>
<th>P</th>
<th>EP (n = 381)</th>
<th>CP (n = 381)</th>
<th>Standard Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>61.3</td>
<td>65.5</td>
<td>0.50</td>
<td>&lt; .001</td>
<td>62.0</td>
<td>62.4</td>
<td>0.06</td>
<td>.3999</td>
</tr>
<tr>
<td>SD</td>
<td>7.6</td>
<td>9</td>
<td></td>
<td></td>
<td>7.4</td>
<td>7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Era of diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001-2004</td>
<td>129</td>
<td>477</td>
<td>0.24</td>
<td>&lt; .001</td>
<td>94</td>
<td>94</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2005-2007</td>
<td>194</td>
<td>393</td>
<td>0.32</td>
<td>&lt; .001</td>
<td>152</td>
<td>152</td>
<td>0.06</td>
<td>.3999</td>
</tr>
<tr>
<td>2008-2010</td>
<td>176</td>
<td>473</td>
<td>0.32</td>
<td>&lt; .001</td>
<td>135</td>
<td>135</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>281</td>
<td>759</td>
<td>0.99</td>
<td>.01</td>
<td>189</td>
<td>204</td>
<td>0.8</td>
<td>.2769</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>110</td>
<td>252</td>
<td>0.11</td>
<td>.2112</td>
<td>82</td>
<td>85</td>
<td>0.07</td>
<td>.8158</td>
</tr>
<tr>
<td>NOS</td>
<td>146</td>
<td>378</td>
<td>0.23</td>
<td>&lt; .01</td>
<td>107</td>
<td>112</td>
<td>0.26</td>
<td>.1163</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>15</td>
<td>0.11</td>
<td>.2112</td>
<td>3</td>
<td>5</td>
<td>0.1</td>
<td>.7587</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>240</td>
<td>698</td>
<td>0.11</td>
<td>.2112</td>
<td>189</td>
<td>179</td>
<td>0.1</td>
<td>.7587</td>
</tr>
</tbody>
</table>
After accounting for prognostic variables, patients treated with EP versus CP had similar overall survival.
CISPLATIN-ETOPOSIDE VS. CARBOPLATIN-PACLITAXEL?

- Systematic review of published trials to compare outcomes and toxic effects between cisplatin-etoposide and carboplatin-paclitaxel
- 79 screened trials from 1985 to 2015 (PubMed, Cochrane, EMBASE, abstracts from ASCO annual meetings and WCLC

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>Cisplatin-etoposide (EP) 31 trials (n = 3090)</th>
<th>Carboplatin-paclitaxel (CP) 48 trials (n = 3728)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>61</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>65</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Median radiation dose (Gy)</td>
<td>63</td>
<td>64.6</td>
<td></td>
</tr>
<tr>
<td>Induction therapy (%)</td>
<td>3</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Consolidation therapy (%)</td>
<td>46</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>3-year survival (%)</td>
<td>30 (CI_{95} : 27–34)</td>
<td>25 (CI_{95} : 22–28)</td>
<td>0.5</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>19.6</td>
<td>18.4</td>
<td>0.40</td>
</tr>
<tr>
<td>Locoregional relapse (%)</td>
<td>38</td>
<td>37</td>
<td>0.63</td>
</tr>
<tr>
<td>Distant metastasis (%)</td>
<td>44</td>
<td>46</td>
<td>0.5</td>
</tr>
</tbody>
</table>

- Cisplatin-etoposide and carboplatin-paclitaxel regimens were associated with comparable efficacy when used with concurrent radiotherapy

Recently, a Chinese study compared head to head EP and CP in CT-RT for unresectable stage III NSCLC was published.

200 patients were randomised:

<table>
<thead>
<tr>
<th>Patients characteristics and results</th>
<th>Cisplatin-etoposide (EP)</th>
<th>Carboplatin-paclitaxel (CP)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>59</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>84.2</td>
<td>88.5</td>
<td></td>
</tr>
<tr>
<td>Radiation dose ≥ 60 Gy (%)</td>
<td>83.2</td>
<td>85.4</td>
<td>0.668</td>
</tr>
<tr>
<td>Chemotherapy (EP &lt; 2 or CP &lt; 5 weeks) (%)</td>
<td>13.7</td>
<td>35.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Consolidation therapy (%)</td>
<td>50.5</td>
<td>35.4</td>
<td>0.035</td>
</tr>
<tr>
<td>3-year survival (%)</td>
<td>41.1 (CI₉₅: 31.1-50.7)</td>
<td>26 (CI₉₅: 17.8-35.1)</td>
<td>0.024</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>23.3</td>
<td>20.7</td>
<td>0.095</td>
</tr>
</tbody>
</table>

In this trial, EP might be superior to CP

However, deliverance of chemotherapy was inferior in CP arm.

PHASE III PROCLAIM STUDY: CISPLATIN-PEMETREXED VS. CISPLATIN-ETOPOSIDE

- 600 patients were planned:
  - PS = 0 or 1, weight loss ≤ 5%
  - Stage IIIA/B unresectable non-squamous NSCLC
  - Primary objective: OS improvement with cisplatin-pemetrexed + RT (HR = 0.74)

Study was stopped early for futility
598 patients were included and 555 patients were treated
Cisplatin-pemetrexed combined with concurrent RT and followed by pemetrexed was not superior to standard chemo-radiotherapy

INDUCTION OR CONSOLIDATION?
# Induction Chemotherapy vs. Consolidation Chemotherapy

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction or delayed RT-CT</strong></td>
<td></td>
</tr>
<tr>
<td>♦ Tumour volume reduction before RT</td>
<td>♦ Delay to synergistic treatment administration</td>
</tr>
<tr>
<td>♦ Full dose chemotherapy</td>
<td>♦ Theoretical risk of cross resistance</td>
</tr>
<tr>
<td>♦ Time to organise RT</td>
<td>♦ Chemotherapy doses reduction during RT</td>
</tr>
<tr>
<td>♦ Patients selection according to chemotherapy efficacy</td>
<td>♦ Compromised administration of CT-RT by induction related toxicities</td>
</tr>
<tr>
<td><strong>Consolidation or early RT-CT</strong></td>
<td></td>
</tr>
<tr>
<td>♦ Early administration of synergistic association</td>
<td>♦ Too large tumour volume</td>
</tr>
<tr>
<td>♦ Theoretical decrease of cross-resistance</td>
<td>♦ Less eligible patients for concurrent CT-RT</td>
</tr>
<tr>
<td>♦ Local control improvement</td>
<td>♦ Delay to start CT-RT</td>
</tr>
</tbody>
</table>
INDUCTION CHEMOTHERAPY

CALGB 39801 trial

- Carboplatin AUC 2 + paclitaxel 50 mg/m²/week x 7 week + concurrent RT (66 Gy)

- Carboplatin AUC 6 + paclitaxel 200 mg/m² every 3 weeks x 2 cycles (induction CT) then Carboplatin AUC 2 – paclitaxel 50 mg/m²/week x 7 week + concurrent RT (66 Gy)

<table>
<thead>
<tr>
<th></th>
<th>CT/RT (n=161)</th>
<th>CT → CT/RT (n=170)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IIIA/IIIB (%)</td>
<td>50/50</td>
<td>52/48</td>
<td></td>
</tr>
<tr>
<td>WL &lt; 5% / &gt; 5% (%)</td>
<td>63/37</td>
<td>76/24</td>
<td></td>
</tr>
<tr>
<td>Oesophagitis (gr 3-4)</td>
<td>32%</td>
<td>36%</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary toxicity (gr 3-4)</td>
<td>4%</td>
<td>10%</td>
<td>NS</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>12</td>
<td>14</td>
<td>0,3</td>
</tr>
<tr>
<td>2-years survival</td>
<td>29%</td>
<td>31%</td>
<td></td>
</tr>
</tbody>
</table>

CONSOLIDATION CHEMOTHERAPY
PHASE III RANDOMISED STUDY
HOG LUN 01-24/USO-023

- Stage IIIAN2/B
- 203 pts
- Cisplatin 50 mg/m² D1, 8, 29, 36
- Etoposide 50 mg/m² D1–5 and D29–33
- RT = 59.4 Gy

Docetaxel 75 mg/m²/3 weeks x 3 cycles

Observation

<table>
<thead>
<tr>
<th>Grade 3-5 toxicities after RT-CT</th>
<th>Docetaxel (n=73)</th>
<th>Observation (n=74)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>11%</td>
<td>0%</td>
<td>0.003</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>8.2%</td>
<td>1.4%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RT –related deaths</td>
<td>5.5%</td>
<td>0%</td>
<td>0.058</td>
</tr>
<tr>
<td>Hospitalisations</td>
<td>28.8%</td>
<td>8.1%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

CONSOLIDATION CHEMOTHERAPY
PHASE III RANDOMISED STUDY
HOG LUN 01-24/USO-023

Overall survival: randomised patients (n = 147)

Consolidation docetaxel did not improve overall survival

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>3-years survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel (months)</td>
<td>21.5</td>
<td>27.2%</td>
</tr>
<tr>
<td>Observation (months)</td>
<td>24</td>
<td>27.6%</td>
</tr>
</tbody>
</table>
CT-RT in first:
- 420 patients
- RT 66 Gy 33 fractions, 6 weeks
- Concurrent chemotherapy: cisplatin 20 mg/m²/week + docetaxel 20 mg/m²/week

Consolidation chemotherapy:
- Cisplatin 35 mg/m² + docetaxel 35 mg/m² D1 and D8
- 62% of patients received 3 cycles

Progression-free survival and overall survival were not improved by consolidation chemotherapy
The meta-analysis of 5 Phase 2 randomised trials shows similar results in terms of overall survival for induction or consolidation chemotherapy.

- **Induction vs. Consolidation: A Meta-Analysis**

- Overall survival

Heterogeneity test, $p = 0.41$, $I^2 = 0\%$

HR $= 0.96$; CI$_{95}$ $: 0.79$-$1.17$

WHICH RADIOTHERAPY IN 2017?
Conformational radiotherapy with 3D dosimetry should be systematically used in routine practice\(^1\)

Altered fractionation\(^2\):
- Conventional daily 1.8 to 2.0-Gy fractionation is the standard in combination with radiotherapy
- There is a little survival benefit in favour of accelerated or hyper fractionated radiotherapy but this modality is not easy to use in routine practice

Intensity-modulated radiation therapy (IMRT)\(^3\):
- Can reduce pulmonary and cardiac toxicities
- Can optimise treatment of tumours close to organs at risk as spinal cord
- Should be used to allow greater tailoring of the radiation dose distribution to patient anatomy

---

WHICH RADIOTHERAPY IN 2017?

- 4D techniques\(^1\):
  - 4D techniques and respiratory control (gating or tracking) during radiotherapy permit to exploit the full potential of IMRT
- Target definition\(^1,2\):
  - The impact of positron emission tomography scan (PET-SCAN) is essential to define target volume

<table>
<thead>
<tr>
<th>N=200 pts</th>
<th>2-years survival</th>
<th>5-years local control</th>
<th>Pneumonitis risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENI (60 – 64 Gy)</td>
<td>25,6%</td>
<td>36%</td>
<td>29%</td>
</tr>
<tr>
<td>IFRT (68 – 74 Gy)</td>
<td>39,4(^\text{p=0.048})</td>
<td>51%</td>
<td>17% (^\text{p=ns})</td>
</tr>
</tbody>
</table>

WHICH RADIOTHERAPY IN 2017?

- The total dose 60 to 66 Gy in 30 to 33 fractions should be used routinely\(^1\)
- Dose escalation to 74 Gy is possible and safe in several phase II studies\(^1\)
- Nevertheless, RTOG 06-17 trial showed that dose escalation to 74 Gy given in 2-Gy fractions with concurrent chemotherapy was deleterious compared with 60 Gy\(^2\)

<table>
<thead>
<tr>
<th>Median OS</th>
<th>HR: p</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 Gy (months)</td>
<td>20.3</td>
</tr>
<tr>
<td>60 Gy (months)</td>
<td>28.7</td>
</tr>
</tbody>
</table>

1. Stinchcombe TE, Bogart JA. The Oncologist 2012;17(5):682–93;
2. Reprinted from The Lancet Oncol 16(2), Bradley JD, et al., Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study, 187–99, Copyright 2015, with permission from Elsevier.
TARGETED THERAPIES AND CHEMO-RADIOTherapy
TARGETED THERAPIES AND CHEMO-RADIOTHERAPY

- Anti-angiogenic agents with chemo-radiotherapy\(^1,4\):
  - Do not improve results\(^2,3\)
  - Are dangerous and must be prohibited\(^2,3\)
- There is a rational to associate EGFR inhibitors with radiotherapy or chemo-radiotherapy in stage III NSCLC\(^4\):
  - EGFR is overexpressed in 80% of NSCLC
  - Preclinical models showed synergistic action between radiation and EGFR inhibitors (cetuximab or tyrosine-kinase inhibitors)
  - In locally advanced head and neck squamous-cell carcinoma, cetuximab plus radiotherapy improves local control and survival comparing to radiotherapy alone\(^5\)

On the basis of encouraging phase II trials, the second aim of this phase III study was to show if addition cetuximab to concurrent standard chemo-therapy improved survival.

- **NSCLC**
- **Stage IIIA/B**
- **PS 0–1**

**Stratification**
- PS 0 versus 1
- 3D-RT versus IMRT
- PET versus no PET
- Squamous versus non-squamous

**CT-RT**
Carboplatin AUC=2 + paclitaxel 45 mg/m²/week. (6 à 7 weeks)
Cetuximab 400 mg/m² initial dose then 250 mg/m²/week.

**Consolidation CT**
Carboplatin AUC=6 + paclitaxel 200 mg/m² (2 cycles)
Cetuximab 250 mg/m²/week

Addition of cetuximab to concurrent CT-RT and consolidation treatment provided no benefit survival in stage III unresectable NSCLC.

Reprinted from The Lancet Oncol 16(2), Bradley JD, et al., Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. 187-99, Copyright 2015, with permission from Elsevier.
Several trials showed efficacy of tyrosine-kinase inhibitors in first line in stage IV NSCLC with oncogenic drivers (EGFR mutations, ALK or ROS1 fusions).

In stage III NSCLC with oncogenic drivers, there are 2 modalities using specific inhibitor:

- Induction treatment with tyrosine-kinase inhibitor (TKI) to reduce tumour volume
- Concurrent administration of TKI with radiotherapy or chemo-radiotherapy

Several trials are ongoing in Asia.
One small phase II study presented at 2017 ASCO meeting compared erlotinib plus concurrent radiotherapy (60 Gy) with standard concurrent chemo-radiotherapy (etoposide-cisplatin 2 cycles during radiotherapy) for stage III EGFR mutants NSCLC.

<table>
<thead>
<tr>
<th></th>
<th>Erlo + RT (n=20)</th>
<th>CT-RT (n=21)</th>
<th>HR; p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td>27.86</td>
<td>6.41</td>
<td>HR=0.0053; p&lt;0.0001</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>60</td>
<td>38.1</td>
<td>p=0.217</td>
</tr>
</tbody>
</table>

In unresectable stage III EGFR mutant NSCLC patients, erlotinib/RT provides a statistically significant PFS improvement.
IMMUNOTHERAPY AND CHEMO-RADIOThERAPY
DIFFERENT WAYS TO COMBINE IMMUNOTHERAPY AND RADIOTHERAPY

- Immunotherapy as adjuvant treatment after CT-RT:
  - Check-points inhibitors (anti PD-1 and anti PDL-1):
    - PACIFIC trial with durvalumab
  - Lung tumour vaccines:
    - Negative START study
    - START2 and INSPIRE trials
- Immunotherapy as induction treatment before surgery
- Immunotherapy during RT or CT-RT:
  - Locally advanced stage III NSCLC:
    - One trial with pembrolizumab during CT-RT
  - Stage IV disease:
    - SABR on one site + immunotherapy
    - Abscopal effect?
    - Case reports
START STUDY  
(TECEMOTIDE OR L-BLP25)

- Stage III NSCLC
- Unresectable
- Non-progressive after CT-RT
- Platin-based CT
- RT > 50 Gy
- Sequential or concurrent CT-RT

CTRT followed by L-BLP25  
Until disease progression

n = 1513

CTRT followed by placebo  
Until disease progression

- No difference in terms of OS,
- Significant benefit in terms of OS for patients treated by concurrent CT-RT:
  - 29.4 months vs. 20.8 months
  - HR = 0.81 (CI95%: 0.68-0.98); p=0.026
- Development has been discontinued

**PACIFIC TRIAL: DURVALUMAB AFTER CTRT**

- Stage III NSCLC
- Unresectable
- Non-progressive after at least 2 cycles of chemotherapy and radiotherapy
- Platin-based CT

- Primary objective:
  - PFS
- Secondary objectives:
  - Overall survival
  - Response rate
  - Safety

- Progression-free survival was significantly longer with durvalumab than with placebo. The secondary end points also favoured durvalumab, and safety was similar between the groups

- There was a small increase in the frequency of radiation pneumonitis and immune-related adverse events as expected in the durvalumab arm

Concurrent chemo-radiotherapy is the standard treatment for patients with unresectable stage III NSCLC:

- Fit patients with PS = 0 or 1, age <70 or 75 years, weight loss <5%, without important co-morbidities
- Conformational 3D-RT, 60 to 66 Gy, 1.8 to 2 Gy daily, to begin early,
- PET-SCAN to define target volume to treat
- Platinum-based chemotherapy at cytotoxic dose, 3 to 4 cycles or carboplatin-paclitaxel weekly
- No consolidation, no maintenance chemotherapy
- Induction chemotherapy 1 to 2 cycles if delay needed to begin radiotherapy or to reduce tumour volume

Only 40% of patients with unresectable stage III NSCLC are eligible for concurrent chemo-radiotherapy

For the other patients, sequential chemo-radiotherapy or chemotherapy or radiotherapy alone are preferable

2nd ESMO Consensus Conference on Lung Cancer
FOR CLINICAL PRACTICE IN 2017

CT  
CT  
CT  
CT  
RT 60 – 66 Gy

or

CT  
CT  
CT  
CT  
RT 60 – 66 Gy

or

CT  
CT  
CT  
CT  
RT 60 – 66 Gy

Median Survival

<table>
<thead>
<tr>
<th>Decade</th>
<th>Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s</td>
<td>9.8</td>
</tr>
<tr>
<td>1990s</td>
<td>13.8</td>
</tr>
<tr>
<td>2000s</td>
<td>17.7</td>
</tr>
<tr>
<td>2010s</td>
<td>20 – 24</td>
</tr>
</tbody>
</table>

FOR CLINICAL PRACTICE IN 2017
IS PROGRESS DUE TO BETTER TREATMENT OR BETTER PATIENTS SELECTION?

- In these 3 trials, chemotherapy is the same, only radiotherapy changes.
- In 10 years, the overall survival improvement can be due to:
  - A better selection of patients with stage migration:
    - PET-SCAN, brain CT or MRI systematically at initial diagnosis
  - The impact of new technologies in radiotherapy: conformational 3D-RT, IMRT, better definition of target volume, related-RT toxicities decrease
  - A better management of chemo-radiotherapy and treatment-related toxicities

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>RT</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K. Furuse (1999)</td>
<td>MVP</td>
<td>56 Gy (split)</td>
<td>16</td>
</tr>
<tr>
<td>Y. Segawa (2010)</td>
<td>MVP</td>
<td>60 Gy</td>
<td>23.7</td>
</tr>
<tr>
<td>N. Yamamoto (2010)</td>
<td>MVP</td>
<td>60 Gy</td>
<td>20.5</td>
</tr>
</tbody>
</table>

THANK YOU!