Developments in Adjuvant Therapy of NSCLC

Stefan Zimmermann
SAMO Workshop Chest Tumours 2014
There have been no developments in adjuvant therapy !!!!
In 2014...

• Should we give adjuvant therapy?
• If yes:
  – what?
  – to whom?

• Can we customize it to the patient’s characteristics?
• What about targeted therapy in the adjuvant setting?
23 randomized trials
<table>
<thead>
<tr>
<th>Trial</th>
<th>Surgery plus chemotherapy</th>
<th>Surgery</th>
<th>Observed - expected deaths</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC LUCO2</td>
<td>415/428</td>
<td>209/215</td>
<td>18.22</td>
<td>143.32</td>
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<tr>
<td>VASAG</td>
<td>251/291</td>
<td>128/152</td>
<td>4.50</td>
<td>86.00</td>
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<tr>
<td>EORTC 08741</td>
<td>38/71</td>
<td>36/75</td>
<td>5.82</td>
<td>18.06</td>
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<tr>
<td>VASOG 5</td>
<td>292/424</td>
<td>261/417</td>
<td>20.63</td>
<td>137.53</td>
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<tr>
<td>WPL 7351</td>
<td>25/36</td>
<td>15/36</td>
<td>6.36</td>
<td>9.83</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td><strong>1021/1250</strong></td>
<td><strong>649/895</strong></td>
<td><strong>55.53</strong></td>
<td><strong>394.74</strong></td>
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<tr>
<td>Other drugs:</td>
<td></td>
<td></td>
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<tr>
<td>OLCSD 1a</td>
<td>30/163</td>
<td>28/158</td>
<td>-0.09</td>
<td>14.47</td>
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<tr>
<td>OLCSD 1b</td>
<td>27/41</td>
<td>21/42</td>
<td>6.59</td>
<td>11.36</td>
</tr>
<tr>
<td>SGACL C ACLC 1</td>
<td>70/154</td>
<td>75/152</td>
<td>-6.10</td>
<td>36.12</td>
</tr>
<tr>
<td>WJSG 2 (2 and 3)</td>
<td>38/108</td>
<td>49/100</td>
<td>-9.79</td>
<td>21.49</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>165/466</strong></td>
<td><strong>173/452</strong></td>
<td><strong>-9.39</strong></td>
<td><strong>83.44</strong></td>
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<tr>
<td>Cisplatin based:</td>
<td></td>
<td></td>
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<tr>
<td>LCSG 801</td>
<td>66/140</td>
<td>71/143</td>
<td>-1.81</td>
<td>34.21</td>
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<tr>
<td>OLCSD 1c</td>
<td>5/12</td>
<td>7/16</td>
<td>-0.19</td>
<td>2.93</td>
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<tr>
<td>FLCSD 1</td>
<td>20/54</td>
<td>30/56</td>
<td>-7.79</td>
<td>12.21</td>
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<tr>
<td>SGACL C ACLC 2</td>
<td>64/165</td>
<td>68/167</td>
<td>-4.80</td>
<td>32.68</td>
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<td>IPCR Chiba</td>
<td>11/15</td>
<td>7/14</td>
<td>1.33</td>
<td>4.07</td>
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<td>WJSG 2 (1 and 3)</td>
<td>44/115</td>
<td>49/100</td>
<td>-7.66</td>
<td>22.94</td>
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<tr>
<td>LCSG 853</td>
<td>29/94</td>
<td>32/94</td>
<td>-1.65</td>
<td>15.22</td>
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<td>JLCSG 5</td>
<td>59/111</td>
<td>52/98</td>
<td>0.98</td>
<td>27.38</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td><strong>298/706</strong></td>
<td><strong>316/688</strong></td>
<td><strong>-21.58</strong></td>
<td><strong>151.83</strong></td>
</tr>
</tbody>
</table>

Stewart LA. NSCLCCG. BMJ 1995
IALT: OS, median FU 56 months

Overall Survival (%)

Years

Chemotherapy (469 deaths)
Control (504 deaths)

P<0.03

No. at Risk
Chemotherapy | 932 | 775 | 624 | 450 | 308 | 181
Control | 935 | 774 | 602 | 432 | 286 | 164

IALT Collaborative. NEJM 2004
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Stage</td>
<td>0.41</td>
<td>0.21</td>
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<tr>
<td>I</td>
<td>115/333</td>
<td>122/348</td>
</tr>
<tr>
<td>II</td>
<td>123/230</td>
<td>126/222</td>
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<tr>
<td>III</td>
<td>231/369</td>
<td>256/365</td>
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<tr>
<td>Histologic type</td>
<td>0.77</td>
<td>—</td>
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<tr>
<td>Squamous cell</td>
<td>205/428</td>
<td>223/444</td>
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<tr>
<td>Adenocarcinoma</td>
<td>199/386</td>
<td>208/368</td>
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<tr>
<td>Other</td>
<td>65/118</td>
<td>73/123</td>
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<tr>
<td>Dose of cisplatin per cycle</td>
<td>0.45</td>
<td>0.63</td>
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<tr>
<td>80 mg/m²</td>
<td>85/163</td>
<td>93/164</td>
</tr>
<tr>
<td>100 mg/m²</td>
<td>334/679</td>
<td>360/677</td>
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<tr>
<td>120 mg/m²</td>
<td>50/90</td>
<td>51/94</td>
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<tr>
<td>Drug combined with cisplatin</td>
<td>0.77</td>
<td>—</td>
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<tr>
<td>Vindesine</td>
<td>26/52</td>
<td>26/56</td>
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<tr>
<td>Vinblastine</td>
<td>62/103</td>
<td>70/102</td>
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<tr>
<td>Vinorelbine</td>
<td>113/248</td>
<td>128/252</td>
</tr>
<tr>
<td>Etoposide</td>
<td>268/529</td>
<td>280/525</td>
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</tbody>
</table>
JBR10 update
CALGB9633 update
LACE Meta-analysis
Big Lung Trial
CALGB9633
IALT
Customization
Clinical trials
Uncertainty
JBR10
ALPI
ANITA 1
1995 Meta-analysis
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
2010 Meta-analysis
IALT update
JBR10 update
CALGB9633 update
1995 Meta-analysis
1990
ANITA

Douillard, Lancet Oncology 2006
JBR10 update
CALGB9633 update
LACE Meta-analysis
Clinical trials
Big Lung Trial
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Customization
Clinical trials
JBR10 update
ANITA 1
ALPI
1995 Meta-analysis
1990
Uncertainty
### Overall Survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Events / No. of Patients</th>
<th>Hazard Ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>569 / 1,088</td>
<td>0.95</td>
<td>0.81 to 1.12</td>
</tr>
<tr>
<td>ANITA</td>
<td>458 / 840</td>
<td>0.82</td>
<td>0.68 to 0.98</td>
</tr>
<tr>
<td>BLT</td>
<td>186 / 307</td>
<td>0.95</td>
<td>0.71 to 1.27</td>
</tr>
<tr>
<td>IALT</td>
<td>980 / 1,867</td>
<td>0.91</td>
<td>0.81 to 1.04</td>
</tr>
<tr>
<td>JBR10</td>
<td>197 / 482</td>
<td>0.71</td>
<td>0.54 to 0.94</td>
</tr>
<tr>
<td>Total</td>
<td>2,390 / 4,584</td>
<td>0.89</td>
<td>0.82 to 0.96</td>
</tr>
</tbody>
</table>

### Disease-Free Survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Events / No. of Patients</th>
<th>Hazard Ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>634 / 1,088</td>
<td>0.89</td>
<td>0.76 to 1.04</td>
</tr>
<tr>
<td>ANITA</td>
<td>526 / 840</td>
<td>0.78</td>
<td>0.66 to 0.93</td>
</tr>
<tr>
<td>BLT</td>
<td>193 / 307</td>
<td>0.93</td>
<td>0.70 to 1.23</td>
</tr>
<tr>
<td>IALT</td>
<td>1,098 / 1,867</td>
<td>0.86</td>
<td>0.77 to 0.97</td>
</tr>
<tr>
<td>JBR10</td>
<td>234 / 482</td>
<td>0.66</td>
<td>0.51 to 0.85</td>
</tr>
<tr>
<td>Total</td>
<td>2,685 / 4,584</td>
<td>0.84</td>
<td>0.78 to 0.91</td>
</tr>
</tbody>
</table>

**Chemotherapy effect**: Logrank statistic = 8.5, \( P = .005 \)

**Test for heterogeneity**: \( \chi^2 = 4.25, \ P = .37, \ p = 6\% \)

**Chemotherapy effect**: Logrank statistic = 21.1, \( P < .001 \)

**Test for heterogeneity**: \( \chi^2 = 5.18, \ P = .27, \ p = 23\% \)
IALT: OS, median FU 7.5 years

Chemotherapy: 578 deaths
- 495 deaths before 5 years
- 83 deaths after 5 years

Control: 590 deaths
- 534 deaths before 5 years
- 56 deaths after 5 years

No. at risk
Chemo 932 780 650 550 487 399 300 208 133
Control 935 775 619 520 447 372 282 208 125

Arriagada. JCO 2010
IALT: OS, median FU 7.5 years

Non-cancer mortality

Cancer mortality

Arriagada. JCO 2010
CALGB 9633: OS, median FU 34 months

HR 0.62 [0.41-0.95]

71% 59%

4 yr

Strauss GM, JCO 2004
CALGB 9633: OS, median FU 74 months

Survival Probability

HR = 0.83
90% CI: 0.64 to 1.08
P = .125

Strauss, JCO 2008
CALGB 9633: OS, median FU 74 months

Survival Probability

HR = 0.83
90% CI: 0.64 to 1.08
P = .125

Time (Months)

Chemotherapy (N = 173)
Control (N = 171)

Strauss, JCO 2008
CALGB9633: OS tumours ≥4cm

- Chemotherapy (N = 99)
- Control (N = 97)

HR = 0.69
90% CI: 0.48 to 0.99
P = .043
JBR.10: OS tumors ≥4cm
<table>
<thead>
<tr>
<th>T/M</th>
<th>Subgroup</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
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<tr>
<td>T1</td>
<td>T1a</td>
<td>Ia</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIb</td>
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<tr>
<td></td>
<td>T1b</td>
<td>Ia</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIb</td>
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<tr>
<td>T2</td>
<td>T2a</td>
<td>Ib</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIb</td>
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<td></td>
<td>T2b</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td>T3</td>
<td>T3 &gt;7</td>
<td>IIb</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
<tr>
<td></td>
<td>T3_{Inv}</td>
<td>IIb</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
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<tr>
<td></td>
<td>T3_{Satell}</td>
<td>IIb</td>
<td>IIIa</td>
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<td>IIIb</td>
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<tr>
<td>T4</td>
<td>T4_{Inv}</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
<td>IIIb</td>
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<td>T4_{Ipsi Nod}</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
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<tr>
<td>M1</td>
<td>M1a_{Contra Nod}</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
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<tr>
<td></td>
<td>M1a_{Pl Disem}</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>
Randomized Controlled Trials

- **JBR.10**
  - *JCO* 2010
  - Cisplatin/vinorelbine chemotherapy
    - HR 0.78, p=0.04

- **IALT**
  - *JNCI* 2003
  - Cisplatin-based chemotherapy
    - HR 0.91, ns

- **ANITA**
  - *Lancet Oncol* 2006
  - Cisplatin/vinorelbine chemotherapy
    - HR 0.79, p=0.013
Meta-analyses

Hotta
JCO 2004

Cisplatin-based chemotherapy
- HR 0.87, p=0.001

LACE
JCO 2008

Cisplatin-based chemotherapy
- HR stage IB 0.92, II 0.83, III 0.83

NSCLC Meta-analysis
Collaborative Group
Lancet 2010

Cisplatin-based chemotherapy
- HR 0.86, p<0.0001
In 2014...

• Should we give adjuvant therapy? **Yes**
• If yes:
  – what? *Cisplatin*-based only. Companion drug: *vinorelbine* only has demonstrated durable long-term efficacy in phase III randomized trials
• to whom? **Stages II and III benefit. Stage IB > 4cm (TNM 6th) might benefit**
• **But** shrinking benefit over time:
  – reduction in cancer mortality is offset by increase in non-cancer mortality
Prognostic versus predictive

- **Prognostic marker**
  - Indicates survival benefit/detriment regardless of therapy
  - Stage, tumour size, sex, number of lymph nodes

- **Predictive marker**
  - Predicts for differential benefit from a particular therapy
<table>
<thead>
<tr>
<th>DNA lesion</th>
<th>Repair pathway</th>
<th>Bulky lesions</th>
<th>O^6^MeG</th>
<th>Mismatch</th>
<th>Double-strand break</th>
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</thead>
<tbody>
<tr>
<td>Single-strand break</td>
<td>BER</td>
<td>NER</td>
<td>DR</td>
<td>MMR</td>
<td>HR NHEJ</td>
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<td>Single-base damage</td>
<td></td>
<td>GG-NER</td>
<td>AGT</td>
<td></td>
<td></td>
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<tr>
<td>Bulky lesions</td>
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<td>TC-NER</td>
<td></td>
<td></td>
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<tr>
<td>Crosslinks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Proteins involved/biomarkers**

- OGG1
- PARP1
- PARP2
- XPC
- ERCC1
- ERCC1/XPF
- Pol β
- PCNA
- Pol δ
- Pol ε
- FEN 1
- Ligase I
- Ligase III
- RNA pol β
- CSA, CSB
- MSH2
- MSH6
- MLH1/PMS2
- EXO1/PCNA/RCF
- Pol δ
- Pol ε
- Pol μ
- ATM
- MRN complex
- RPA
- BRCA2/FANCD
- RAD51, FANCF
- DNA PKs
- Artemis
- XRCC4-XLF
- KU70, KU80
- Ligase I
- Ligase IV
Predictive markers in advanced NSCLC

• In general, low levels = sensitivity
  – ERCC1 – platinum
  – Thymidilate synthase – pemetrexed
  – RRM1 – gemcitabine
  – BRCA1 – low platinum, high taxanes
  – EGFR mutation – EGFR TKIs
IALT Bio study

ERCC1 negative

ERCC1 positive

Clinical trial graphs showing overall survival for chemotherapy and control groups in ERCC1 negative and positive patients.

Olaussen, NEJM 2006
TAilored Post-Surgical Therapy in Early Stage NSCLC (TASTE)

Key inclusion criteria
• Completely resected

Standard

Cisplatin + Pemetrexed

Randomisation 1:1
n=150

Secondary endpoints
• DFS

Primary endpoint
• Feasability

Key inclusion criteria
• Completely resected
• Non-squamous
• IIA, IIB, IIIA (N2 excluded)
• ECOG PS 0-1

ERCC1 low
Cisplatin + Pemetrexed

ERCC1 high
No treatment

Phase III canceled
LACE Bio analysis

ERCC1 negative

ERCC1 positive

Soria, NEJM 2013
International Tailored Chemotherapy Adjuvant Trial (ITACA)

Tumors tested for ERCC1 and TS

ERCC1
(Planned N = 700)

High
Low

High
Low

TS

High
Low

Profile 4
Profile 3
Profile 2
Profile 1

Taxane
Control*
Pemetrexed
Control*
Cis/Gem
Control*
Cis/Pem
Control*

High/Low ERCC1 and TS selected according to median level of mRNA expression in historical series
Randomized Customized Adjuvant Chemotherapy (GECP-SCAT)

Key inclusion criteria
- Completely resected
- IIA, IIB, IIIA
- ECOG PS 0-2

n=150

Primary Endpoint
- Feasability
Secondary endpoints
- DFS

Standard
- Cisplatin + Docetaxel
  - 4 cycles
  - Randomisation 1 : 1

Custom
- High BRCA1
  - Docetaxel
- Intermediate BRCA1
  - Cisplatin + Docetaxel
- Low BRCA1
  - Cisplatin + Gemcitabine
SWOG 0720

Key inclusion criteria
- Completely resected
- IA, IB
- ECOG PS 0-2

High RRM1
AND
High ERCC1
Active surveillance

Low RRM1
and/or
Low ERCC1
Cisplatin + Gemcitabine

Primary Endpoint
- Feasability
Secondary endpoints
- 2-y DFS
In 2014...

• Should we give adjuvant therapy? **Yes**
  
• If yes:
  – what? *cisplatin + vinorelbine*
  – to whom? *Stages II, III A, and larger stages IB*

• Can we customize it to the patient’s characteristics? **not yet (if ever!)**

• What about targeted therapy in the adjuvant setting?
JBR.19 Adjuvant Gefitinib in Completely Resected NSCLC

Key inclusion criteria
- Completely resected
- IB - IIIA

Gefitinib 2 years

Randomisation 1:1 *

Placebo

Primary Endpoint
- OS

n=503

*Stratification by stage, histology, sex, adjuvant chemotherapy
Protocol amended in 2003 to permit adjuvant chemotherapy
### JBR.19 Adjuvant Gefitinib in Completely Resected NSCLC

<table>
<thead>
<tr>
<th>Outcome (years)</th>
<th>Gefitinib (n=251)</th>
<th>Placebo (n=252)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>5.1</td>
<td>NR</td>
<td>1.23 (0.94-1.64)</td>
<td>0.136</td>
</tr>
<tr>
<td>Median PFS</td>
<td>4.2</td>
<td>NR</td>
<td>1.22 (0.93-1.61)</td>
<td>0.152</td>
</tr>
</tbody>
</table>

Goss, ASCO 2010, LBA7005
JBR.19 Adjuvant Gefitinib in Completely Resected NSCLC

• Prognostic of OS benefit?
  – KRAS mutation/wild type HR: 1.13 (0.78-1.65) \( P = 0.512 \)
  – EGFR mutation/wild type HR: 1.06

• Predictive of OS benefit?

<table>
<thead>
<tr>
<th>Median OS (years)</th>
<th>Gefitinib (n=251)</th>
<th>Placebo (n=252)</th>
<th>HR (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS mutation</strong></td>
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<td></td>
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</tr>
<tr>
<td>• Wild type</td>
<td>5.4</td>
<td>NR</td>
<td>1.13 (0.78-1.65)</td>
<td>0.512</td>
</tr>
<tr>
<td>• Mutated</td>
<td>3.3</td>
<td>NR</td>
<td>1.51 (0.84-2.70)</td>
<td>0.163</td>
</tr>
<tr>
<td><strong>EGFR mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Wild type</td>
<td>5.0</td>
<td>NR</td>
<td>1.21 (0.84-1.73)</td>
<td>0.301</td>
</tr>
<tr>
<td>• Mutated</td>
<td>3.7</td>
<td>5.1</td>
<td>1.58 (0.83-3.00)</td>
<td>0.160</td>
</tr>
</tbody>
</table>
RADIANT Adjuvant Chemotherapy +/- Erlotinib in EGFR positive NSCLC

Key inclusion criteria
- Completely resected
- IB – IIIA
- EGFR positive by IHC or FISH
- Adjuvant chemotherapy allowed

Primary Endpoint
- PFS

Secondary Endpoint
- OS
- Safety

Randomisation 2 : 1 *

n=1252

*Stratification by histology, sex, age, adjuvant chemotherapy, smoking status

Wait for subgroup analysis (EGFR mutation)
SELECT: Adjuvant Erlotinib following Surgery and Standard Adjuvant Therapy

**Key inclusion criteria**
- Completely resected
- IA – IIIA
- EGFR mutation positive
- Adjuvant chemotherapy allowed

**Erlotinib**
- 2 years

**Primary Endpoint**
- DFS

**Secondary Endpoint**
- OS
- Safety

n= 36

Neal, ASCO 2012, Abst 7010
SELECT: DFS

Median follow-up time: 2.7 years

94% 2-Year DFS

Censored observation

Time from initiating adjuvant erlotinib (Years)

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

Survival Probability

Patients at Risk 36 35 34 34 33 19 7 5 1 0
SELECT: treatment duration and intensity

69% of patients completed >90% of therapy
Adjuvant EGFR TKI: conclusions

• No prospective randomized data yet

• But:
  – Feasible but toxic (39% dose reductions, 31% discontinuation)
  – At least a cytostatic effect on micrometastatic disease

• Very few patients recur during treatment
• All remain sensitive to erlotinib when treated for recurrent disease

Wait for further trials (NCT01405079, NCT01410214, NCT01683175)
Selected ongoing trials with targeted therapy

- Erlotinib in EGFR mutated patients:
  - EURECA: chemo +/- erlotinib 2 years
  - CTONG1104: chemo versus gefitinib

- Bevacizumab:
  - E1505: cisplatin-based chemo +/- bevacizumab (accrual completed)
Hey, how am I supposed to hear his request for new drug approval with all your screaming?
MAGRIT MAGE-A3 as Adjuvant Non-Small Cell Lung Cancer Immunotherapy

Resected MAGE-A3 (+) NSCLC

Pathological stage IB, II, IIIA

No chemo

Randomization

MAGE-A3 ASCI

Placebo

Powered for efficacy

Chemo

Randomization

Up to 4 cycles of platinum-based chemo

MAGE-A3 ASCI

Placebo

Powered for efficacy

n= screened 13’824
2270 randomized
Randomized controlled phase III trial of adjuvant chemotherapeutic and immunotherapy with activated killer T cells and dendritic cells in patients with resected primary lung cancer

Hideki Kimura, Yukiko Matsui, Aki Ishikawa, Takahiro Nakajima, Mitsuru Yoshino, Yuichi Sakairi
Chiba Cancer Center  Japan

Conflict of Interest statement: The authors indicate no potential conflicts of interest.
Procedure for chemo-immunotherapy

Tumor draining lymph nodes (TDLN)
(IL2, 2-4W)

Activated killer T cells + Dendritic cells

Co-culture

AKT-DC

Chemo 4 courses

2 years

10-14 courses

PBL

surgery

2-4W

1W

1W

8 W

8W

surgery

TDLN culture

Chemo

AKT-DC

Chemo

AKT-DC

AKT-DC

AKT-DC
Kaplan-Meier estimates of overall survival for group A and B.

HR = 0.229
95% CI: 0.093 to 0.564
P = 0.0013

Log-rank p = 0.0005

<table>
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<tr>
<th>Group</th>
<th>n</th>
<th>Event</th>
<th>Censored</th>
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In 2014...

• Should we give adjuvant therapy? **Yes**
• If yes:
  – what? *cisplatin + vinorelbine*
  – to whom? **Stages II, III A, and larger stages IB**

• Can we customize it to the patient’s characteristics? **not yet (if ever!)**
• What about targeted therapy in the adjuvant setting? **not yet outside of a clinical trial**
“So, does anyone else feel that their needs aren’t being met?”