The place of targeted agents in multimodality treatment of stage III NSCLC

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Disclosures

I have provided consultation, attended advisory boards and/or provided lectures for:

F. Hoffmann–La Roche, Ltd; Eli Lilly and Company Oncology, AstraZeneca, Pfizer, Boehringer-Ingelheim, BMS, Daiichi-Sankyo, Morphotek, Merrimack, Merck Serono, Amgen, Clovis and Tesaro, for which I received honoraria.

I declare no conflict of interest.
Most stage III patients are treated with induction or concurrent CT-RT
Optimal chemotherapy regimen remains to be defined in this context.
Targeted agents in stage III: Rational

Agents that are known to enhance RT-induced tumour cell killing while having moderate effect on normal tissues should be considered in combination with thoracic RT.
EGFR inhibition and RT in A549 NSCLC cells

Wang, Cancer Res 2011
We will discuss...

- Cetuximab with definitive (CT) RT
- Erlotinib (crizotinib) with definitive (CT) RT
- Bevacizumab with definitive (CT) RT
- Cetuximab in surgical stage III induction
- Erlotinib in surgical stage III induction
- Bevacizumab in surgical NSCLC induction
Cetuximab and radiotherapy

- Cetuximab alone + RT
- Induction CT -> Cetuximab + RT
- CT-RT + cetuximab; RTOG 0617
# Cetuximab + RT

## 3 phase II trials

<table>
<thead>
<tr>
<th>Not candidates for chemoradiation</th>
<th>30 patients 66 Gy in 33 fx</th>
<th>400 mg/m2 then 250 mg/m2 wkly +consolidation</th>
<th><strong>OS</strong> 19.6 mo <strong>PFS</strong> 8.5 mo</th>
<th>NEAR Jensen et al Cancer 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 &gt; 1.5 or 40% Weight loss &lt; 5%</td>
<td>127 patients 64.8-69.6 Gy BID</td>
<td>OS 12 mo Jeremic IJROBP 2012</td>
<td><strong>OS</strong> 15.1 mo <strong>PFS</strong> 7.2 mo</td>
<td>NCCTG Jatoi et al Ann Oncol 2010</td>
</tr>
<tr>
<td>IIIA, dry IIIB</td>
<td>77 patients 60 Gy in 30 fx</td>
<td>OS 9.6 mo CALGB 8433 Dillman JNCI 1996</td>
<td><strong>OS</strong> 14 mo <strong>PFS</strong> 8 mo</td>
<td>S0429 Chen et al Front Oncol 2013</td>
</tr>
<tr>
<td>Phase III, Arm 1</td>
<td></td>
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</tr>
</tbody>
</table>
## Induction CT -> Cetuximab + RT
**3 phase II trials**

<table>
<thead>
<tr>
<th>IIIA, dry IIIB</th>
<th>71 patients</th>
<th>Cisplatin/docetaxel x 2 Cetuximab 400 mg/m2 IV prior, 250 mg/m2 weeks 1-3</th>
<th>OS 17 mo</th>
<th>Satellite Hallqvist Lung Cancer 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV &gt; 1 or 40%p</td>
<td>68 Gy in 34 fx</td>
<td>[SI]</td>
<td>16% PR 7% CR</td>
<td></td>
</tr>
<tr>
<td>12 patients</td>
<td>Platinum doublet x 3</td>
<td>OS 10 mo</td>
<td>RTOG 9410 Curran JNCI 2011</td>
<td></td>
</tr>
<tr>
<td>IIIA/B</td>
<td>63 Gy in 34 fx Cetuximab 400 mg/m2 IV prior, 250 mg/m2 weeks 1-3 Weekly cetuximab, Carboplatin/placlitaxel</td>
<td>OS 19.4 mo 1 G5 pneumonitis</td>
<td>Ramalingam Lung Cancer 2013</td>
<td></td>
</tr>
<tr>
<td>195 patients Phase III Arm A</td>
<td>63 Gy in 34 fx Cisplatin/Vinbl x2</td>
<td>OS 14.6 mo 30% CR</td>
<td>SCRATCH Hughes JTO 2008</td>
<td></td>
</tr>
<tr>
<td>40 patients</td>
<td>63 Gy in 34 fx Cetuximab 400 mg/m2 IV prior, 250 mg/m2 weeks 1-3 Weekly cetuximab, Carboplatin/placlitaxel</td>
<td>OS 19.4 mo 1 G5 pneumonitis</td>
<td>Ramalingam Lung Cancer 2013</td>
<td></td>
</tr>
</tbody>
</table>
## Concurrent CT-RT + Cetuximab

### 3 phase II/1 phase III trials

<table>
<thead>
<tr>
<th>IIIA or IIIB</th>
<th>87 patients</th>
<th>Carboplatin/paclitaxel weekly during, x 2 consolidation</th>
<th>OS 23 months</th>
<th>68% G3+</th>
<th>RTOG 0324</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 &gt; 1.2</td>
<td>63 Gy in 35 fx</td>
<td></td>
<td>29% CR</td>
<td>6 Grade 5</td>
<td>Blumenschein JCO 2010</td>
</tr>
<tr>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>195 patient Phase III Arm 2</th>
<th>63 Gy in 34 fx</th>
<th>Cisplatin/vinblastine</th>
<th>OS 17 months</th>
<th>52% G3+</th>
<th>RTOG 9410 Curran et al JNCI 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA or dry IIIB</td>
<td></td>
<td></td>
<td>42% CR</td>
<td>4 Grade 5</td>
<td></td>
</tr>
<tr>
<td>102 patient Phase II</td>
<td>63 Gy in 34 fx</td>
<td>Cisplatin/etoposide docetaxel</td>
<td>OS 26 mo 7% CR</td>
<td>54% G3+ 2 Grade 5 12% stopped</td>
<td>SWOG S9504 Gandara Cancer 2005</td>
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<tr>
<td></td>
<td></td>
<td>Daily cisplatin 6 mg/m2</td>
<td>2 yr OS 58% vs 62% w/ CTX (NS)</td>
<td>Higher Grade 3+ with combination 65% v 45%</td>
<td>Van Den Heuvel et al, R&amp;O 2013</td>
</tr>
</tbody>
</table>
RTOG 0617

<table>
<thead>
<tr>
<th>Stratify</th>
<th>Concurrent Treatment</th>
<th>Consolidation Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Arm A</strong></td>
<td><strong>Arm A</strong></td>
</tr>
<tr>
<td><strong>RT Technique</strong></td>
<td>Concurrent chemotherapy*</td>
<td>Consolidation chemotherapy*</td>
</tr>
<tr>
<td>1. 3D-CRT</td>
<td>RT to 60 Gy, 5 x per wk for 6 wks</td>
<td></td>
</tr>
<tr>
<td>2. IMRT</td>
<td></td>
<td></td>
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<tr>
<td><strong>Zubrod</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PET Staging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Squamous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Non-Squamous</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Randomize</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Arm B</strong></td>
<td>Concurrent chemotherapy*</td>
<td><strong>Arm B</strong></td>
</tr>
<tr>
<td></td>
<td>RT to 74 Gy, 5 x per wk for 7.5 wks</td>
<td>Consolidation chemotherapy*</td>
</tr>
<tr>
<td><strong>Arm C</strong></td>
<td>Concurrent chemotherapy* and Cetuximab</td>
<td><strong>Arm C</strong></td>
</tr>
<tr>
<td></td>
<td>RT to 60 Gy, 5 x per wk for 6 wks</td>
<td>Consolidation chemotherapy*</td>
</tr>
<tr>
<td><strong>Arm D</strong></td>
<td>Concurrent chemotherapy* and Cetuximab</td>
<td><strong>Arm D</strong></td>
</tr>
<tr>
<td></td>
<td>RT to 74 Gy, 5 x per wk for 7.5 wks</td>
<td>Consolidation chemotherapy*</td>
</tr>
</tbody>
</table>

*Carboplatin and paclitaxel
Overall Survival

- 18-Month Survival Rate
  - Standard: 66.9%
  - High dose: 53.9%

Local Failure

- Local Progression Rate
  - Standard (60 Gy): 34.3%
  - High dose (74 Gy): 25.1%

- HR = 1.37 (0.99, 1.89)
  - p = 0.0319

Patients at Risk
- Standard: 213, 207
- High dose: 206, 197
RTOG 0617: results

No significant difference in OS (HR 0.99, 95% CI 0.78, 1.27, p=0.4838) or PFS (HR 0.96, 95% CI 0.77, 1.19, 0.3471) between treatment groups.
RTOG 0617: results

EGFR expression and Cetuximab interaction for OS

Incidence of grade 3–5 toxicities was significantly greater with cetuximab (non-haematologic 70.5% vs. 50.7% and overall 85.2% vs. 69.2%; both p<0.0001)
EGFR TKI and radiotherapy

- As a consolidation after CT-RT in unselected NSCLC
- Concomitant to RT in unselected NSCLC
- As induction or concomitant to CT-RT in EGFR mutated NSCLC
Gefitinib after local CT-RT (+/- docetaxel consolidation)

Deaths are due to progressive disease!
Gefitinib and radiotherapy in unselected NSCLC

Chemoradiotherapy and Gefitinib in Stage III Non-small Cell Lung Cancer with Epidermal Growth Factor Receptor and KRAS Mutation Analysis
Cancer and Leukemia Group B (CALGB) 30106, a CALGB-Stratified Phase II Trial

Survival of poor-risk patients with wild type or mutated EGFR receiving sequential CRT with gefitinib was promising. Survival for good-risk patients receiving concurrent CRT plus gefitinib was disappointing even for tumors with activating EGFR mutations.

Riely, JTO 2010
Erlotinib and radiotherapy in unselecedt NSCLC

Stage I-IIIA NSCLC not suitable to receive chemotherapy, randomized to:

- 66 Gy in 33 fractions
- Same with concomitant erlotinib 150 mg/day, maintained for 6 months.

Conclusions (30pts)

- Response rate in erlotinib arm was 83.3% vs 55.5%
- The addition of erlotinib does not appear to increase in-field toxicities, being a feasible and well tolerated option

Martinez, ASCO 2008, abst 7563
Erlotinib and radiotherapy in unselected NSCLC: A prospective phase II study

Single-institution Phase II study

Key patient inclusion criteria
• Previously untreated, locally advanced, inoperable, stage III NSCLC
• Karnofsky’s performance status >70
  (n=48)

Primary endpoint
• Time to progression

Secondary endpoints
• Toxicity, response, OS
• Disease control rates

Paclitaxel 45 mg/m² + carboplatin AUC2 + erlotinib 150 mg/day for 7 weeks, followed by two paclitaxel-carboplatin cycles

Radiotherapy (63 Gy/35 fractions) +

PD

Komaki et al. J Thorac Oncol 8, 2013; (Suppl 2; O02.03)
Among 46 patients who were evaluable for a response

- Median OS and PFS were 34.1 and 13.7 months

- No grade 4 or 5; six grade 3 adverse events (acne, esophagitis and pneumonitis)

- Erlotinib when given in combination with chemoradiation might confer a radiosensitisation effect

<table>
<thead>
<tr>
<th>n (%)</th>
<th>CR</th>
<th>PR</th>
<th>SD or PD</th>
<th>Not available*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases (n=46)</td>
<td>14 (30)</td>
<td>23 (50)</td>
<td>8 (18)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>EGFR mutation (EGFR-M) (n=4)</td>
<td>3 (75)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>EGFR wild-type (n=36)</td>
<td>11 (30)</td>
<td>19 (53)</td>
<td>6 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No EGFR data (n=5)</td>
<td>0 (0)</td>
<td>4 (80)</td>
<td>1 (20)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Komaki et al. J Thorac Oncol 8, 2013; (Suppl 2; O02.03)
### Biomarker-driven treatment: EGFR TKI in stage IV

<table>
<thead>
<tr>
<th>Study</th>
<th>EGFR TKI</th>
<th>n</th>
<th>Median PFS in TKI arm (months)</th>
<th>P value</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib</td>
<td>154</td>
<td>13.1</td>
<td>&lt;0.0001</td>
<td>0.16</td>
</tr>
<tr>
<td>First Signal</td>
<td>Gefitinib</td>
<td>42</td>
<td>8.4</td>
<td>0.084</td>
<td>0.61</td>
</tr>
<tr>
<td>IPASS</td>
<td>Gefitinib</td>
<td>261</td>
<td>9.5</td>
<td>&lt;0.0001</td>
<td>0.48</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>Gefitinib</td>
<td>177</td>
<td>9.2</td>
<td>&lt;0.001</td>
<td>0.48</td>
</tr>
<tr>
<td>NEJSG 002</td>
<td>Gefitinib</td>
<td>200</td>
<td>10.8</td>
<td>&lt;0.001</td>
<td>0.36</td>
</tr>
<tr>
<td>Ensure</td>
<td>Erlotinib</td>
<td>217</td>
<td>11</td>
<td>&lt;0.0001</td>
<td>0.34</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib</td>
<td>174</td>
<td>9.4</td>
<td>&lt;0.0001</td>
<td>0.42</td>
</tr>
<tr>
<td>LUX-3</td>
<td>Afatinib</td>
<td>308</td>
<td>13.6</td>
<td>&lt;0.0001</td>
<td>0.47</td>
</tr>
<tr>
<td>LUX-6</td>
<td>Afatinib</td>
<td>364</td>
<td>11.0</td>
<td>&lt;0.0001</td>
<td>0.28</td>
</tr>
</tbody>
</table>
EGFR TKI and radiotherapy
In EGFR mutated NSCLC
RTOG 1210/Alliance 31101

Co-Principal Investigators’
Alliance: Ramaswamy Govindan, MD
RTOG: Hak Choy, MD

Eligibility Criteria
• Non-squamous NSCLC
• Unresectable stage IIIA or IIIB disease;
• Presence of mutations in EGFR TK or EML4-ALK translocation
• Absence of T790M mutation in the EGFR TK domain;
• PS≤1
• Determined to be a candidate for concurrent chemoradiation
Individualized Combined Modality Therapy for Stage III For EGFR / ALK driven tumours RTOG 1210/Alliance 31101

**Stratification**

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Weight Loss (in prior 6 mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. EGFR</td>
<td>1. ≤ 5%</td>
</tr>
<tr>
<td>2. ALK</td>
<td>2. &gt; 5%</td>
</tr>
</tbody>
</table>

**ALK Translocation Cohort**

**Arm 1:** Crizotinib, 250 mg/bid, 12 wks

**Arm 2:** Concurrent

Chemotherapy regimen: Cisplatin and etoposide or Paclitaxel and carboplatin

Concurrent chemotherapy and radiation, 64 Gy
Endpoints

- Primary endpoint
  - Phase II: Progression-free survival (PFS)
  - Phase III: Overall survival (OS)

- Interim analysis for futility in each arm is planned when half of the required events have been reached

If there is sufficient evidence of PFS superiority favoring the experimental therapy, the study will be expanded into its phase III portion for that specific mutation
Other ongoing EGFR TKI + radiotherapy phase II trials in EGFR M+ Stage III

• A randomized phase II to evaluate the efficacy and safety of Erlotinib versus Etoposide plus Cisplatin With concurrent RT (China, primary endpoint PFS)

• A randomized phase II study of induction CT or Erlotinib followed by concurrent CT-RT (Corea, primary endpoint RR)

• A phase II trial of RT combined with Gefitinib (China, primary endpoint RR)

NCT01714908/NCT00620269/NCT01391260
Bevacizumab and radiotherapy

- **Two** independent phase II clinical trials in NSCLC and SCLC using bevacizumab in combination with chemotherapy and radiation.

- In each trial, tracheoesophageal fistulae development were reported.

- Related morbidity and mortality prompted early trial closures, US FDA warnings, and a change in bevacizumab labeling.

Spigel, JCO 2010
Perspectives: other targeted drugs with radiotherapy?

Dramatic Response Induced by Vemurafenib in a BRAF V600E-Mutated Lung Adenocarcinoma

Peters, J Clin Oncol, 2013
What about surgical stages III: Cetuximab?

SAKK 16/08 (recruiting)
Preoperative CT-RT plus concomittant Cetuximab in III.

- N = 69
- PFS1y (1. EP)
- Inclusion of nodule in the ipsilateral lung (new TNM-classification)
- Exclusion of supraclavicular N, malignant effusion, infiltration of aorta, esophagus, myocardium
- Cetuxi 400mg/m2 -> 250mg/m2/wk
- Interim safety analysis done after 25 pts
What about surgical stages III: Erlotinib in unselected NSCLC?

PET evaluation revealed metabolic response in 16 patients (27%) and CT response in three patients (5%). According to predefined criteria, neoadjuvant erlotinib has low toxicity and sufficient activity to deserve further testing in future studies in an “enriched” population (response 34%)

Schaake, J Clin Oncol, 2012
What about selected surgical stages III: Erlotinib in M+?

- **Erlotinib in neoadjuvant setting** in patients with stage IIIA, N2-positive NSCLC (Corea, completed)

- **Erlotinib as neoadjuvant treatment** in patients with stage IIIA N2 NSCLC with activating EGFR mutation (ML25444, China, ongoing)

- **Tarceva Before Surgery** in stage III NSCLC patients who have EGFR positive tumors (EVENT, US, ongoing)

- **Erlotinib versus Gemcitabine/Cisplatin** as neoadjuvant treatment in NSCLC, a phase II randomized trial (EMERGING, China, ongoing)

- **Erlotinib versus Docetaxel and Cisplatin** as neoadjuvant therapy in stage III NSCLC patients, a phase II randomized trial (Oncology, Taiwan, ongoing)
What about surgical stages III: Bevacizumab?

Phase II Trial of Neoadjuvant Bevacizumab Plus Chemotherapy and Adjuvant Bevacizumab in Patients with Resectable Nonsquamous Non-Small-Cell Lung Cancers

Tumor Response to Bevacizumab

Red: new cavitation

Percentage change in tumor burden 2 weeks after bevacizumab: no PR

This study failed to meet its primary endpoint (an increase from the reported 33% to a goal of 50% pathological downstaging).

Chaft, JTO, 2013
Cetuximab and radiotherapy
What have we learned?

• Cetuximab added to chemoradiotherapy does not improve OS or PFS in patients with unresectable stage III NSCLC but was associated with a significant increase in grade 3–5 toxicities

• Greater benefit with cetuximab may occur in patients with high EGFR expression, although further study including prospective validation is required
EGFR TKI and radiotherapy
What have we learned?

- Concomitant administration is feasible

- In unselected NSCLC, benefit of such a strategy will improbably be shown

- In EGFR M +, induction EGFR TKI or concomittant EGFR TKI with radiotherapy are under evaluation in several clinical trials
Radiotherapy and targeted agents
What have we learned?

• 29 mos OS can be expected for stage III NSCLC treated by CT-RT, at the era of PET-CT

• Stage III clinical trials require an enormous collaborative effort and are difficult to complete. Rigorous scientific questions only should be addressed
  ➢ Several phase I ongoing: PARPi Olaparib, nelfinavir, and Notch Hedgehog, WNT inhibitors, nelfinavir

• Place of vaccination of early disease is still under evaluation
EGFR TKI before surgery
What have we learned?

• Neoadjuvant administration is feasible

• In unselected NSCLC, benefit of such a strategy will improbably be shown

• In EGFR M +, induction EGFR TKI is under evaluation in several clinical trials
Thanks for your attention...