Integration of Targeted Agents into Combined Modality Therapy for NSCLC

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Disclosures

- Lilly Oncology – Advisory Board
- Genentech – Advisory Board
Chemoradiotherapy

• Concurrent chemoradiotherapy is the standard of care for good performance status patients with Stage III NSCLC producing median survival times of 18-23 mos

• No single chemoradiotherapy regimen is utilized.

• Popular chemotherapy regimens include:
  1) Cyclic PE
  2) Weekly Paclitaxel & Carboplatin

• No definitive role for additional chemotherapy, either induction or consolidation, but it is routinely administered.
# Patterns of Failure

|                     | Wkly Pac/Carbo  
|---------------------|-----------------|  
|                     | CALGB 39801  
|                     | N = 182         |
| Local Relapse       | 9.8%            |
| Local + Distant     | 26%             |
| Distant             | 47%             |
| Brain Only          | 9%              |

Treatment Strategies for Unresectable Stage III NSCLC

CHEMORADIOTHERAPY RTOG 9410

Median survival 17 mos
1 Year Survival Rate  63%
2 Year Survival Rate  37%
3 Year Survival Rate  28%
4 Year Survival Rate  21%

Induction
Consolidation
Targeted Agents with Radiation or Chemoradiation
Maintenance Therapy
Molecular Response to Radiation

XRT causes cytotoxicity by:
1) DNA strand break

XRT can also increase cell survival by:
1) Inducing EGFR autophosphorylation
2) Activating AKT and MAPK pathways
3) Induce DNA repair processes
4) Upregulating PDGFR signaling in endothelial cells

Radiation and Drug Interaction

• Supra-additive, synergistic, or radiosensitizing
  Effect of combined therapy GREATER than
  radiation and drug alone

• No universal mechanism of interaction that defines
  radiosensitization

• Multiple mechanisms in play:
  Modification of DNA damage
  Interference with DNA repair processes
  Inhibition of proliferation
  Enhancement of apoptosis
  Inhibition of angiogenesis
  Modification of hypoxia
  Interference with signal transduction pathways
EGFR Inhibitors + Radiation

Cetuximab

Erlotinib

Targeted Agents + Radiation

Angiogenesis Inhibitor

PI3K/mTor Inhibitor

Gorski DH et al Cancer Res 59:3374-3378, 1999
# Radiosensitization & Targeted Agents

<table>
<thead>
<tr>
<th>Agents</th>
<th>Preclinical Evidence of Radiosensitization</th>
<th>Clinical Evidence of Radiosensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>EGFR-TKIs</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Angiogenesis Agents</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HDAC Inhibitors</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HSP90 Inhibitors</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>IGF-1R Inhibitors</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PI3K Pathway Inhibitors</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MEK Inhibitors</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hedgehog Inhibitors</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cox-2 Inhibitors</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Farneslytransferase Inhibitors</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*Chinnaiyan P et al. Semin Radiat Oncol 16:59-64, 2006*
Radiotherapy +/- Cetuximab

5-year survival
36.4 vs 45.6%
HR 0.73, 95% CI 0.56-0.98
A Randomized Phase II Trial

Carboplatin AUC 5 q3week x 4 cycles
Pemetrexed 500/mg² q3week x 4 cycles
XRT – 70 Gy over 7 weeks

Carboplatin AUC 5 q3week x 4 cycles
Pemetrexed 500/mg² q3week x 4 cycles
XRT - 70 Gy over 7 weeks
+ Cetuximab 400mg/m² loading
and 250mg/m² weekly

Pemetrexed 500 mg/m²
q 3 weekly x 4

CALGB 30407
Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>Chemo</th>
<th>Chemo/Cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med FFS</td>
<td>12.6 mo</td>
<td>12.3 mo</td>
</tr>
<tr>
<td>18 Mo FFS</td>
<td>29%</td>
<td>33%</td>
</tr>
<tr>
<td>Med OS</td>
<td>21.2 mo</td>
<td>25.2 mo</td>
</tr>
<tr>
<td>18 Mo OS</td>
<td>58%</td>
<td>54%</td>
</tr>
</tbody>
</table>
RTOG 0324 - Treatment Schema

**Week 1**
- **Cetuximab**: 400 mg/m² day 1

**Weeks 2-8**
- **Paclitaxel (45 mg/m²/wk)**
- **Carboplatin**: (AUC = 2/ wk)
- **Cetuximab (250 mg/m²/wk)**

**RT (63 Gy/7 weeks/35 daily fx)**

**Weeks 9-11**
- **Cetuximab**: 250 mg/m²/wk x 3

**Weeks 12-17**
- **Paclitaxel (200 mg/m² Q 3 wk x 2)**
- **Carboplatin (AUC = 6 Q 3 wk x 2)**
- **Cetuximab (250 mg/m²/wk)**

RTOG 0324 - Efficacy

Median PFS - 12 mos

Median OS 22.7 mos
RTOG 0617/NCCTG N0628/CALGB 30609/ECOG Stage III NSCLC

Randomization

- Chemo XRT (60Gy) - Chemotherapy
- Chemo XRT (60Gy) + Cetuximab - Chemotherapy Cetuximab
- Chemo XRT (74Gy) - Chemotherapy
- Chemo XRT (74Gy) + Cetuximab - Chemotherapy Cetuximab
RTOG 0522

Initial Results of RTOG Clinical Trial Show No Survival Benefits by the Addition of Cetuximab to Chemoradiation Treatment for Patients with Locally Advanced Head and Neck Cancer

<table>
<thead>
<tr>
<th></th>
<th>CDDP  (N = 449)</th>
<th>CDDP + Cetuximab (N = 447)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS 2 YR</td>
<td>64.3%</td>
<td>63.4%</td>
<td>1.05 (p=0.66)</td>
</tr>
<tr>
<td>OS 2 YR</td>
<td>79.7%</td>
<td>82.6%</td>
<td>0.87 (p=0.17)</td>
</tr>
</tbody>
</table>

10% in field grade 3-4 mucositis and dermatitis

Ang KK et al. J Clin Oncol 29:360s, 2011
SWOG 0429
Poor risk patients

Schema

REGISTRATION

Cetuximab (400 mg) x 1 → Weekly Cetuximab (250 mg) + RT → *Weekly Cetuximab (250 mg) (maintenance)

*Maintenance Cetuximab continues until disease progression or up to 2 years

Progression-Free Survival by Treatment Arm
Eligible Patients with Follow-up
Data as of January 4, 2011

Overall Survival by Treatment Arm
Data as of January 4, 2011

Chen Y et al J Clin Oncol 29:463s #7040, 2011
## EGFR-TKIs + Radiation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Pts</th>
<th>TKI</th>
<th>Chemotherapy</th>
<th>RT</th>
<th>Efficacy</th>
<th>RR</th>
<th>Survival</th>
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</thead>
<tbody>
<tr>
<td>Okamoto et al</td>
<td>I</td>
<td>7</td>
<td>Gefitinib</td>
<td>None</td>
<td>60 Gy</td>
<td>57%</td>
<td></td>
<td>11.5 months</td>
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<tr>
<td>Center et al</td>
<td>I</td>
<td>16</td>
<td>Gefitinib</td>
<td>Docetaxel</td>
<td>70 Gy</td>
<td>46%</td>
<td></td>
<td>21 months</td>
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<tr>
<td>Rothschild et al</td>
<td>I</td>
<td>5</td>
<td>Gefitinib</td>
<td>None</td>
<td>63 Gy</td>
<td>21.4%</td>
<td></td>
<td>382 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concurrent: cisplatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stinchcombe et al</td>
<td>I</td>
<td>23</td>
<td>Gefitinib</td>
<td>Induction: carbo/irino/pac; concurrent: carboplatin/paclitaxel</td>
<td>74 Gy</td>
<td>NR</td>
<td></td>
<td>16 months</td>
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<tr>
<td>Ready et al</td>
<td>II</td>
<td>21</td>
<td>Gefitinib</td>
<td>Induction: carboplatin/paclitaxel</td>
<td>66 Gy</td>
<td>53%</td>
<td></td>
<td>19 months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Induction &amp; concurrent: carboplatin/paclitaxel</td>
<td></td>
<td>81%</td>
<td></td>
<td>13 months</td>
</tr>
<tr>
<td>Choong et al</td>
<td>I</td>
<td>17</td>
<td>Erlotinib</td>
<td>Concurrent: cisplatin/etoposide; consolidate: docetaxel</td>
<td>66 Gy</td>
<td>65%</td>
<td></td>
<td>10.2 months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Induction &amp; concurrent: carboplatin/paclitaxel</td>
<td></td>
<td>59%</td>
<td></td>
<td>13.7 months</td>
</tr>
<tr>
<td>Martinez et al</td>
<td>II</td>
<td>10</td>
<td>None</td>
<td>None</td>
<td>66 Gy</td>
<td>55.5%</td>
<td></td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>83.3%</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>Erlotinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Xu, Y et al. Lung Cancer epub July 2011
The Role of Maintenance Therapy
SWOG 0023

Definitive TX

CDDP 50 mg/2
  d1, 8, 29, 36
VP-16 50 mg/m2
  d1-5, 29-33
XRT 1.8-2 Gy/d
  61 Gy

Consolidation

DOCETAXEL
  75 mg/m2
  x 3 cycles

Maintenance

PLACEBO

GEFITINIB
  500 mg/day
  250 mg/day
  (5-1-03)

1° Endpoint: Overall Survival; 2° Endpoint: PFS, toxicity and correlative science
Maintenance therapy could continue for a maximum of 5 years
Stratification factors: IIIA vs. IIIB; Measurable vs. Non-measurable disease; squamous vs. nonsquamous

Overall Survival From Randomization

- Gefitinib: N = 118, Events = 71, Median in Months = 23, 1 YR OS = 73%, 2 YR OS = 46%
- Placebo: N = 125, Events = 54, Median in Months = 35, 1 YR OS = 81%, 2 YR OS = 59%

P = .01

Median FU time: 27 months
Progression Free Survival from Randomization

Erlotinib Maintenance Schema

Primary endpoint: PFS
190 pts/arm planned

Stage III NSCLC
- Stratification - IIIA vs. IIIB
Wt loss (10%)
PS 0-1 vs. 2

Screening

Randomization

Weeks of Study

Arm A
Erlotinib 150 mg

Arm B
Matched placebo

• Docetaxel
  20 mg/m2 iv qwk x 6
• Carboplatin
  AUC = 2 iv qwk x 6
• Thoracic Radiation
  61 Gy

Stage III NSCLC - Stratification - IIIA vs. IIIB
Wt loss (10%)
PS 0-1 vs. 2

Progression Free Survival
Erlotinib vs. Placebo


<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>121</td>
<td>122</td>
</tr>
<tr>
<td>Events</td>
<td>75</td>
<td>78</td>
</tr>
<tr>
<td>PFS (mos)</td>
<td>10.4</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Logrank p=0.3629
Survival
Erlotinib vs. Placebo

Survival Probability

Surival in Months

Placebo
Erlotinib

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>121</td>
<td>122</td>
</tr>
<tr>
<td>Events</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>OS (mos)</td>
<td>26.9</td>
<td>23.6</td>
</tr>
</tbody>
</table>

Logrank $p=0.7522$

**EGFR Mutations & Chemoradiotherapy**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Pts (n=123)</th>
<th>EGFR mutant (n=29)</th>
<th>Wild-type EGFR (n=94)</th>
<th>p-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (95% CI), mos</td>
<td>40.4 (30.5-52.6)</td>
<td>61.2 (30.4-102.5)</td>
<td>34.7 (29.4-45.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>2-Yr OS</td>
<td>74.8%</td>
<td>92.6%</td>
<td>69.0%</td>
<td>0.04</td>
</tr>
<tr>
<td>2-Yr RFS</td>
<td>36.7%</td>
<td>41.4%</td>
<td>35.8%</td>
<td>0.33</td>
</tr>
<tr>
<td>2-Yr LRR</td>
<td>35.3%</td>
<td>17.8%</td>
<td>41.7%</td>
<td>0.005</td>
</tr>
<tr>
<td>2-Yr DR</td>
<td>62.6%</td>
<td>63.7%</td>
<td>61.7%</td>
<td>0.39</td>
</tr>
</tbody>
</table>

\(^a\) p-values reflect log-rank test comparing Kaplan-Meier curves between mutant and wild type groups.
Angiogenesis Inhibitors
Bevacizumab

**Limited Stage SCLC**
- ICB - irinotecan, carboplatin, bevacizumab 10 mg/kg, D1, 15
- N=29
- Study closed early for safety
- 2 patients developed TE fistulae during maintenance (1 death)
- 1 additional death from an aerodigestive hemorrhage

**Unresectable Stage III NSCLC**
- PCB - Pemetrexed, carboplatin, bevacizumab 15 mg/kg, D1 q 3 weeks
- N=5
- Study closed early for safety
- 2 patients developed TE fistulae with chemorads

Maintenance

ECOG 6508 - Phase II

Unresectable
Nonsquamous
Stage III NSCLC
Nonprogressing
after chemoradiotherapy*

Bevacizumab
+ L-BLP25

*Weekly paclitaxel and carboplatin
2 cycles of consolidation paclitaxel and carboplatin
INDUCTION?
Conclusion

• Significant advances in our understanding of the molecular biology of radiosensitization and radioresistance have been made.

• Successful integration of molecular therapies with radiotherapy remains challenging.