Integration of Targeted Agents into Combined Modality Therapy for NSCLC

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UC Davis Cancer Center

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

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Failure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Relapse</td>
<td>9.8%</td>
</tr>
<tr>
<td>Local + Distant</td>
<td>26%</td>
</tr>
<tr>
<td>Distant</td>
<td>47%</td>
</tr>
<tr>
<td>Brain Only</td>
<td>9%</td>
</tr>
</tbody>
</table>


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
Maintenance Therapy
Targeted Agents with Radiation or Chemoradiation

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) Inducing DNA repair processes
4) Upregulating PDGFR signaling in endothelial cells

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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

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EGFR Inhibitors + Radiation
- H226: Cetuximab, Erlotinib

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Targeted Agents + Radiation
- Control: IR (40 Gy)
- Anti-VEGF: Angiogenesis Inhibitor, PI3K/mTor Inhibitor
- IR + Anti-VEGF: LLC Angiogenesis Inhibitor, PI3K/mTor Inhibitor
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**Radiosensitization & Targeted Agents**

<table>
<thead>
<tr>
<th>Agent</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>HSP90 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>IGF1R 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>HDAC Inhibitors</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Farnesyltransferase</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

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**Radiotherapy +/- Cetuximab**

Bonner JA The Lancet Oncology 2010
5-year survival 36.4 vs 45.6%
HR 0.73, 95% CI 0.56-0.98

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**CALGB 30407 Schema**


Integration of Targeted Agents Into Combined Modality Therapy for NSCLC
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**CALGB 30407**

**Efficacy Results**

<table>
<thead>
<tr>
<th></th>
<th>Chemo</th>
<th>Chemo/Cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFS</td>
<td>12.6 mo</td>
<td>12.3 mo</td>
</tr>
<tr>
<td>18 Mo</td>
<td>29%</td>
<td>33%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Chemo</th>
<th>Chemo/Cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>21.2 mo</td>
<td>25.2 mo</td>
</tr>
<tr>
<td>18 Mo</td>
<td>58%</td>
<td>54%</td>
</tr>
</tbody>
</table>

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**RTOG 0324 - Treatment Schema**

- **Week 1**
  - Cetuximab 250 mg/m²/wk
  - Paclitaxel (45 mg/m²/wk)
  - Carboplatin (AUC = 2/ wk)

- **Weeks 2-8**
  - Paclitaxel (200 mg/m² Q 3 wk x 2)
  - Carboplatin (AUC = 6 Q 3 wk x 2)
  - Cetuximab (250 mg/m²/wk)

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

- **Weeks 12-17**
  - Cetuximab


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**RTOG 0324 - Efficacy**

- **Median PFS** - 12 mos
- **Median OS** - 12 mos
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**RTOG 0617/NCCTG N0628/CALGB 30609/ECOG Stage III NSCLC**

**Randomization**
- Chemotherapy
- Cetuximab

- **Chemo XRT (60Gy)** + Cetuximab

- **Chemo XRT (74Gy)** + Cetuximab

**Chemotherapy**

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**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

Ang KK et al. J Clin Oncol 29:360s, 2011

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

10% in field grade 3-4 mucositis and dermatitis

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**SWOG 0429**

Poor risk patients

Y et al J Clin Oncol 29:463s #7040, 2011

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**EGFR-TKIs + Radiation**

**Trial** | **Phase** | **Pts** | **TKI** | **Chemotherapy** | **RT** | **Efficacy** | **Survival**
--- | --- | --- | --- | --- | --- | --- | ---
Okamoto et al | I | 7 | Gefitinib | None | 60 Gy | 57% | 11.5 months
Center et al | I | 16 | Gefitinib | Docetaxel | 70 Gy | 46% | 21 months
Rothschild et al | I | 5 | Gefitinib | None | 63 Gy | 21.4% | 382 days
Stinchcombe et al | I | 23 | Gefitinib | Induction: carbo/irino/pac; concurrent: carboplatin/paclitaxel | 74 Gy | NR | 16 months
Ready et al | II | 21 | Gefitinib | Induction: carboplatin/paclitaxel | 66 Gy | 53% | 19 months
Choong et al | I | 17 | Erlotinib | Concurrent: cisplatin/etoposide; consolidate: docetaxel | 66 Gy | 65% | 10.2 months
Martinez et al | II | 10 | None | None | 66 Gy | 55.5% | NR

EGFR-TKIs + Radiation

Xu, Y et al. Lung Cancer epub July 2011

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**The Role of Maintenance Therapy**

**SWOG 0023**

**Definitive TX** | **Consolidation** | **Maintenance**
--- | --- | ---
CDDP 50 mg/2 d 1,8,29,36 | VP-16 50 mg/m2 d1-5, 29-33 | PLACEDO
XRT 1.8-2 Gy/d 61 Gy | DOCETAXEL 75 mg/m2 x 3 cycles | GEFITINIB 250 mg/day

Endpoint: Overall Survival; 20 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


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**Overall Survival From Randomization**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>67</td>
</tr>
<tr>
<td>Placebo</td>
<td>64</td>
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</tbody>
</table>

Median FU time: 27 months

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Integration of Targeted Agents Into Combined Modality Therapy for NSCLC
Progression Free Survival from Randomization

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Median in Months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>118</td>
<td>84</td>
<td>8</td>
<td>0.28</td>
</tr>
<tr>
<td>Placebo</td>
<td>125</td>
<td>81</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>


Erlotinib Maintenance Schema

- Planned Thoracic Radiation: 61 Gy in 33 fractions over 6.5 weeks.
- The initial field was to receive 45 Gy in 25 fractions of 1.8 Gy followed by a boost field of 16 Gy in 8 fractions of 2 Gy.

Erlotinib 150 mg
- Matched placebo
- Docetaxel 20 mg/m² iv qwk x 6
- Carboplatin AUC = 2 iv qwk x 6

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

Weeks of Study - 5 - 2 - 0 - 7 - 10 - 14

Arm A
Arm B
Screening


Progression Free Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>PFS (mos)</th>
<th>Logrank p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>121</td>
<td>75</td>
<td>10.4</td>
<td>0.3629</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>122</td>
<td>78</td>
<td>7.7</td>
<td></td>
</tr>
</tbody>
</table>

Logrank test p = 0.3629

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Survival
Erlotinib vs. Placebo

Survival Probability

Survival in Months

Erlotinib vs. Placebo

Survival Probability

Placebo
Erlotinib

N                121         122
Events         49 46
OS (mos)  26.9        23.6
Logrank p=0.7522


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EGFR Mutations & Chemoradiotherapy

Outcome

All Pts
(n=123)
EGFR mutant
(n=29)
Wild-type EGFR
(n=94)
p-value

Median survival (95% CI), mos
40.4 (30.5-52.6)
61.2 (30.4-102.5)
34.7 (29.4-45.3)
0.04

2 Yr OS
74.8%
92.6%
69.0%
0.04

2 Yr RFS
36.7%
41.4%
35.8%
0.33

2 Yr LRR
35.3%
17.8%
41.7%
0.005

2 Yr DR
62.6%
63.7%
61.7%
0.39

Ap values reflect logrank test comparing Kaplan-Meier curves between mutant and wild type groups

Mak RH et al. The Oncologist 16:886-85, 2011

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Angiogenesis Inhibitors

Bevacizumab

Limited Stage SCLC
Pemetrexed, carboplatin
bevacizumab 10 mg/kg, D1 q 3 weeks

PCB

Study closed early for safety
2 patients developed TE fistulae with chemorads
1 additional death from an aerodigestive hemorrhage

Unresectable Stage III NSCLC

PCB

Study closed early for safety
2 patients developed TE fistulae during maintenance
1 death

I C B

irinotecan, carboplatin
bevacizumab 10 mg/kg, D1


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**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*