Locally Advanced NSCLC: New Concepts in Combined Modality Therapy

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Stage III NSCLC: Overview

- Stage III NSCLC represents a heterogeneous group of patients with many distinct subsets
- Goals are local control (RT +/- chemotherapy) and eradication of distant micrometastases (chemotherapy)
- Chemotherapy + Radiotherapy has now emerged as the standard of care for patients with bulky stage IIIA N2 or stage IIIB

NSCLC: Stage Distribution

Lung Cancer

172,000 new cases
15% SE

Less than stage IV
Stage IV

Stages IA / IB
Stage IIA / IIB
Stage IIIA
Stage IIIB
Stage IIIC
Stage IV

NSCLC 28%
SCLC 20%

Gandara: Clinical Cancer Res, 2005

Chemoradiotherapy Paradigms in Stage III NSCLC

Sequential Chemotherapy → Radiotherapy
Induction Chemotherapy X X
RT

Concurrent Chemoradiotherapy
Chemotherapy (x) (x) (x)
RT

Induction Chemotherapy → Concurrent Chemoradiotherapy
Induction Chemotherapy X X
Concurrent Chemotherapy (x) (x) (x)
RT

Concurrent Chemoradiotherapy → Consolidation Chemotherapy
Concurrent Chemotherapy (x) (x) (x)
RT
Consolidation Chemotherapy X X X

Gandara: Clinical Cancer Res, 2005
**Stage III NSCLC: Overview**

- Despite these advances, the great majority continue to relapse and die of recurrent NSCLC (distant metastases).
- Integration of novel targeted therapies into Chemoradiation may improve these results & is under study.

**Integration of Molecular Targeted Therapies in Locally Advanced NSCLC**

**Targeting the EGFR Pathway**

**Epidermal Growth Factor Receptor (EGFR) Inhibitors in NSCLC**

- Gefitinib
- Erlotinib

  - Active single agents
  - EGFR mutation increases activity
  - TKIs + Chemo are negative (INTACT VII TRIBUTE, TALANT)

**SWOG 0023: Gefitinib vs Placebo After Chemoradiation Followed by Docetaxel**

**Schema**

- **ChemoRT**
  - CDDP 50 mg/m² d 1,8,29,36
  - VP-16 50 mg/m² d 1-5, 29-33
  - XRT 1.8-2 Gy/d 61 Gy

- **Consolidation**
  - Docetaxel 70 mg/m² x 3 cycles

- **Maintenance**
  - Gefitinib 500 mg/day 250 mg/day (5-1-03)

**Endpoints**

1° Endpoint: overall survival; 2° Endpoint: PFS, toxicity and correlative science.

Stratification factors: IIIA vs IIIB; measurable vs non-measurable disease; squamous vs nonsquamous.

Kelly et al. ASCO 2007, Abs 7512
SWOG 0023: Overall Survival from Initial Registration

- CDDP+VP-16+RT
- N: 571
- Events: 366
- Median in Months: 19

Kelly et al, IASLC Chicago, 2006

SWOG 0023: Progression-free Survival from Randomization

- Gefitinib
  - N: 118
  - Events: 84
  - Median in Months: 8
- Placebo
  - N: 125
  - Events: 82
  - Median in Months: 12
- P = 0.17

Kelly et al, JCO 2008

SWOG 0023: Toxicity

- Decreased survival in gefitinib arm did not appear to be a result of toxicity
  - 2% toxicity death rate noted
- Most common cause of death was disease progression
Epidermal Growth Factor Receptor (EGFR) Inhibitors in NSCLC

**Cetuximab: Mechanism of Action**
- IgG1 monoclonal antibody
- Binds to EGFR
- Competitively inhibits ligand binding (e.g., EGF)
- Mechanisms different from TKI:
  - Receptor Internalization
  - Antibody-Dependent Cellular Cytotoxicity (ADCC)
- Combinations with Radiation or Chemotherapy effective in other tumor types
  - Radiation: H & N Cancer
  - Chemotherapy: Colon Cancer

**RTOG 0324: A Phase II Trial of Cetuximab with Chemoradiation**

**Eligibility**
- unresectable Stage III NSCLC, PS≤1, weight loss < 5% over 3 months, FEV<1 >1.2 L

**Primary Endpoint:** Safety and feasibility

**RTOG 0324: Updated Results**
- 93 patients enrolled (87 evaluable)
  - 57% male, median 64 years, 47% PS 0, 46% Stage IIIA
- RR 62%, median OS 22.7 mo, 2-yr OS 49%
- Adverse Events
  - 20% grade 4 hematologic toxicities
  - 8% grade 3 esophagitis
  - 7% grade 3/4 pneumonitis
- 5 treatment-related deaths
RTOG 0324: EGFR FISH Analysis

- 45 (of 87 evaluable) patients with tissue available for EGFR FISH analysis (method as per Hirsch et al, JCO 2008)

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<thead>
<tr>
<th></th>
<th>FISH +</th>
<th>FISH -</th>
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<tbody>
<tr>
<td>2-yr OS</td>
<td>61.9%</td>
<td>53.8%</td>
</tr>
<tr>
<td>TTP</td>
<td>57.1%</td>
<td>45.8%</td>
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<tr>
<td>CR/PR</td>
<td>24%</td>
<td>8%</td>
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Summary:
- Tissue testing for EGFR FISH is feasible
- FISH +ve patients trended for more responses

Olsen et al, ASCO 2008, Abs 7607

CALGB 30407: Concurrent Chemoradiation ± Cetuximab in Unresectable Stage III NSCLC

- A Randomized Phase II Trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Carboplatin AUC 5 x 3week x 4 cycles</th>
<th>Pemetrexed 500 mg/m² x 3week x 4 cycles</th>
<th>XRT – 70 Gy over 7 weeks</th>
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Consolidation
- Pemetrexed 500 mg/m² x 4 cycles
- Cetuximab 400mg/m² loading & 250mg/m² weekly

Eligibility: unresectable Stage III NSCLC; PS ≤1, no significant wt loss
Primary Endpoint: Overall survival
Govindan et al, ASCO 2008, Abs 7518

CALGB 30407: Early Evaluation of Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Cetuximab</th>
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<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>39%</td>
<td>38%</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>36%</td>
<td>37%</td>
</tr>
<tr>
<td>Esophagitis*</td>
<td>35%</td>
<td>22%</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td>Rash*</td>
<td>3%</td>
<td>22%</td>
</tr>
</tbody>
</table>

* Grade 3/4

Summary:
- Feasible and well tolerated

Govindan et al, ASCO 2008, Abs 7518

PROCLAIM: A Phase III Randomized Superiority Trial in Locally Advanced NSCLC

N=600
- 3 cycles of pemetrexed + cisplatin + radiation therapy (66 Gy in 33) sequenced to 4 cycles of pemetrexed

Primary objective: OS survival
Superiority design
80% Powered to detect Hazard Ratio=0.74

2 cycles of etoposide + cisplatin + radiation therapy (66 Gy in 33) sequenced to 2 cycles of platinum doublet consolidation

Govindan et al, ASCO 2008, Abs 7518
Integration of Molecular Targeted Therapies in Locally Advanced NSCLC

Targeting the Angiogenesis Pathway

Anti-Angiogenesis Therapeutic Strategies

- Antisense Antisense (VEGF AS)
- Ribozymes
- Anti-VEGF Antibodies (Bevacizumab)
- Anti-VEGF Antibodies (IMC-1121B)
- Soluble VEGF Receptors (VEGF-Trap)
- Small Molecule TKIs

Rationale for Bevacizumab in Combined Modality Therapy

- E4599: Survival benefit for bevacizumab combined with platinum-doublet chemotherapy in advanced NSCLC
- Higher doses of radiation required to kill tumor cells in hypoxic environments
  - Inhibition of VEGF leads to "normalization" of tumor blood vessels and improvements in tumor oxygenation
- Pre-clinical studies demonstrate increased activity of RT when combined with bevacizumab

S0533: A Pilot Trial of Chemoradiation + Bevacizumab for Inoperable Stage III NSCLC

HYPOTHESIS: Radiation to the primary tumor will eliminate or minimize hemorrhage

- Incorporate bevacizumab into an active chemoradiation regimen (S9504)
- Define timing for bevacizumab + chemoradiation
- Define safety in both low risk & high risk patient subsets
**S0533: Stratification by High Risk vs. Low Risk**

**STRATUM 1 (LOW RISK)**
- Unresectable Stage III nonsquamous NSCLC
- No cavitation and no tumor close to a major vessel
- No hemoptysis (≥ ½ tsp within 28 days of registration)

**STRATUM 2 (HIGH RISK)**
- Unresectable Stage III squamous cell CA
  - OR
- Tumor of any histology with cavitation or adjacent to a major vessel
  - OR
- History of hemoptysis

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**TE Fistula: Bevacizumab with Radiotherapy**

- **TE fistula** development in patients with LS-SCLC treated with chemoradiation plus concurrent and sequential bevacizumab
  
- Safety assessment of 5 patients enrolled into a trial for Stage III, unresectable, nonsquamous NSCLC
  - **Induction**
    - Carboplatin + pemetrexed + BV 15 mg/kg wks 1 & 4
    - Concurrent with RT (61.2 Gy)
  - **Consolidation**
    - Carboplatin + pemetrexed + BV 15 mg/kg wks 16,19,22
  - **Maintenance**
    - BV q3 wks x 9 cycles
  
- 2 of 5 with TE fistula
  - 34 wks into therapy (4th cycle of maintenance BV)
  - 40 wks into therapy (6th cycle of maintenance BV)
  - Both patients with severe esophagitis

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**S0533: Integration of Bevacizumab (B) into CRT in Low Risk & High Risk Patient Subsets**

<table>
<thead>
<tr>
<th>Cohort 1 (B introduced after Chemoradiotherapy)</th>
<th>Cohort 2 (B introduced on day 8 during Chemoradiotherapy)</th>
<th>Cohort 3 (B introduced on day 1 of Chemoradiotherapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent Chemoradiotherapy → Consolidation Chemotherapy</td>
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<tr>
<td>D B D B</td>
<td>D B D B</td>
<td>D B D B</td>
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<tr>
<td>X X Cisplatin-Etoposide, D: Docetaxel, B: Bevacizumab</td>
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**Integration of Molecular Targeted Therapies in Locally Advanced NSCLC**

Dual Inhibition of the EGFR and Angiogenesis Pathway

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1. Spigel et al, ASCO 2008, #7554
2. Spigel et al, Lung Cancer Congress, 2008, Abs 15
LCCC 0511: Incorporation of Bevacizumab and Erlotinib with Chemoradiation in Stage III NSCLC

**Eligibility**
- Stage IIIA/B NSCLC, PS 0-1, FEV1 ≥ 1 L, SCC allowed

**Treatment**
- **Induction**
  - Carbo AUC 6 + Paclitaxel 225 mg/m² + Bev 15 mg/kg x 2 cycles
- **Concurrent ChemoRT**
  - TCRT 74 Gy
  - Carbo AUC 2 + Paclitaxel 45 mg/m² weekly x 7
  - Cohort I: Bev 10 mg/m² q2wks Erlotinib 0 mg
  - Cohort II: Bev 10 mg/m² q2wks Erlotinib 100 mg (T→F)
  - Cohort III: Bev 10 mg/m² q2wks Erlotinib 150 mg (T→F)
- **Consolidation**
  - Bev 15 mg/kg q3wks x 6 cycles + Erlotinib 150 mg/day for the 6 cycles

Socinski et al, ASCO 2008, Ab 7517

LCCC 0511: Results

**Primary Endpoint**
- PFS at 1 yr (results not yet available)

**Induction**
- RR: 40% (8/20)

**Concurrent**
- Cohorts 1 and 2 well tolerated
- Cohort 3: 3/5 gr 3 DLTs: pulmonary hemorrhage (SCC patient), interstitial lung disease, RT pneumonitis
- MTD for phase II portion of study deemed to be cohort II dose levels
- 25% grade 3 esophagitis

**Consolidation**
- Of 14 eligible, 9 started but only 6 able to complete regimen
- Overall response: 73% (CR 5%)

Socinski et al, ASCO 2008, Ab 7517

LCCC 0511: Conclusions

- Integration of bevacizumab and erlotinib is feasible
- Relatively safe
  - Higher incidence of grade 3 esophagitis
  - 2/9 of SCC patients with pulmonary hemorrhage
  - Consolidation: not feasible in majority of patients
- Phase II ongoing
- ? Implications for the success of this trial in light of BeTa being negative for OS benefit

Integration of Molecular Targeted Therapies in Locally Advanced NSCLC

Vaccine Strategies Targeting MUC1
MUC1: A Mucin Glycoprotein Serving as a Tumor-associated Antigen

- Widely distributed in normal and abnormal cell
- Overexpressed and aberrantly glycosylated in many human malignancies, including NSCLC
- Involved in tumorigenicity, tumor cell migration, resistance to apoptosis and genotoxic agents, and immunosuppression

MUC1: A Potential Target for Immunotherapy

Normal MUC-1

Cancer Associated MUC1

STn carbohydrate
Exposed core peptide
Glycopeptide epitopes

L-BLP25 Composition

- Antigen: BLP25 lipopeptide
  S T A P P A H G V T S A P D T R P A P G S T A P P - Lys (PAL) G
- Adjuvant: Monophosphoryl Lipid A
- Liposomal Components:
  - Cholesterol
  - DMPG (dimyristoyl phosphatidylglycerol)
  - DPPC (dipalmityl phosphatidylcholine)

(Liposome is thought to enhance immune recognition of cancer cells)

L-BLP25: Phase IIB Trial in NSCLC

Butts et al, JCO, 2005
L-BLP25: Overall Survival

- 171 patients responding to 1st line chemotherapy
  - 65 pts with IIIB, 106 pts with wet IIIB or IV

**Phase III Trial with L-BLP25 for Inoperable Stage III NSCLC**
**START: Stimulated Targeted Antigenic Responses to NSCLC**

Conclusions

- Concurrent chemoradiotherapy has improved the survival of stage III NSCLC, providing long term survival in a subset of patients
- Research efforts to optimize chemotherapy and integrate novel molecular therapies are ongoing
Two Compartment Model of Combined Modality Therapy for Locally Advanced Lung Cancer

- Local-Regional Disease
- Brain Sanctuary
- Distant Micrometastases

Radiotherapy
Chemotherapy

Concomitant CT-RT vs Sequential CT-RT in LA NSCLC: an Individual Patient Based Meta-Analysis

- HR = 0.84 [0.74; 0.95], p = 0.004
- Absolute benefit in OS with concomitant CT:
  - At 2 years: 5.3%
  - At 3 years: 5.7%
  - At 5 years: 4.5%

**Overall Survival**

<table>
<thead>
<tr>
<th>Time from Randomization (Years)</th>
<th>Survival (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>76.2</td>
</tr>
<tr>
<td>2</td>
<td>52.6</td>
</tr>
<tr>
<td>3</td>
<td>30.3</td>
</tr>
<tr>
<td>4</td>
<td>18.1</td>
</tr>
<tr>
<td>5</td>
<td>10.6</td>
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<tr>
<td>≥5</td>
<td>5.1</td>
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RTOG 0523: Proposed Phase III Trial of CRT ± Cetuximab for Stage III NSCLC

Eligibility:
Stage IIIA/B NSCLC
Boost volume ≤ 50% ipsilateral lung
PS 0-1
Sample Size: 568

Carboplatin/paclitaxel wkly 63 Gy

Day 1
Cetuximab 400 mg/m² IV
Day 8
Cetuximab 250 mg/m² wkly
Carboplatin/paclitaxel wkly

Cetuximab 250 mg/m² wkly x 6
Carboplatin/paclitaxel