For CALGB Participants Only

Correlative Science Directed
CALGB Lung Cancer Studies
(Part 1 of 3)

Robert Kratzke, MD
University of Minnesota
CALGB CRA Continuing Education Workshop, June 2007

CALGB studies using molecular predictors for prognosis and response to therapy

- Stage 4 NSCLC pharmacogenomic study
  - CALGB 307XX
- Stage 1a adjuvant therapy study
  - CALGB 30506
- Stage 4 NSCLC molecular array directed study
  - In development

For CALGB Participants Only Slide 3

Special Thanks

- Anil Potti
- Marty Edelmann

For CALGB Participants Only Slide 4

COX-2 Expression is a Positive Predictive Factor for Celecoxib + Chemotherapy in Advanced Non-Small Cell Lung Cancer: CALGB 30203

MJ Edelman, DM Watson, X Wang, RA Kratzke, AM Mauer, S Jewell, SL Graziano, GA Masters, MM Bedor, M R Green, EE Vokes for the CALGB
**Introduction**

- Abnormalities of the eicosanoid/prostaglandin signal pathway occur frequently in lung cancer.
- Increased levels of end products of these pathways can increase tumor proliferation, angiogenesis and inhibit apoptosis.
- COX-2 overexpression has been associated with inferior outcome in NSCLC.
- Inhibition of COX-2 and/or 5-LOX in cell and animal models prevents the development and can inhibit the growth of lung and other aerodigestive cancers.
- Inhibition of COX-2 and/or 5-LOX in cell lines and animal models is additive or synergistic with chemotherapy.

**Hypothesis**

- Inhibition of COX-2 or 5-LOX will enhance the effect of platinum based chemotherapy in advanced NSCLC.
- “Dual pathway” inhibition (i.e. both COX-2 and 5-LOX) will be superior to either alone.
- This enhancement would result in increased time to progression.

---

**Arachidonic Acid Metabolism**

Cell membrane phospholipids $\rightarrow$ Arachidonic Acid $\rightarrow$ Prostaglandins

- Sphingomyelinases
- Neutral sphingomyelinase
- Ceramide
- COX 1,2
- 5HETE, 12HETE, 15HETE

**CALGB 30203: Gemcitabine/ Carboplatin + Eicosanoid Modulators**

- Stage IIIB (pleural effusion), IV NSCLC
- PS 0-2
- Adequate organ function
- Brain metastases ineligible
- Carboplatin AUC = 5.5
- Gemcitabine 1000 mg/m²

A: Carboplatin 600 mg/m² po qd
B: Gemcitabine 1000 mg/m²
C: Zoleuton 600 mg po qid

PD $\rightarrow$ Off study
SD, PR, CR $\rightarrow$ Eicosanoid modulator until progression

Correlates: COX2, 5LOX, VEGF, CYFRA

Endpoints:
- FFS (9 mo)
- OS
Correlative Studies
- Pre-planned analysis for IHC of COX-2 and 5-LOX as potential predictive and prognostic markers.
- Blocks/unstained slides required
- Adequate specimens available for 83 (of 136 pts, submission from 107)

Immunohistochemistry Studies
- Performed at CALGB PCO.
  - IHC scored by intensity (0-3) and percentage of cells: 0 (0), 1-9% (1), 10-49% (2), 50-100% (3).
  - Index (0-9) = intensity (0-3) x percentage (0-3).
- Data analyzed by CALGB statistical center
- Exploratory analyses conducted to determine if COX2 and/or 5-LOX were predictive or prognostic
  - "cut points" based upon IHC index were correlated with FFS and survival.
  - Numbers small
  - Multiple determinations
- Hypothesis generating, NOT conclusive
OS and Cox-2 expression (<4 vs >=4) for Pts Who Did Not Receive Celecoxib

Survival Time (Months) vs Probability

Cox2 < 4
Cox2 >= 4

COX-2: Predictive Factor

Comparison of patients who did not (N=29) or did (N=54) receive celecoxib (ARM A vs B/C)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Cut point of COX-2 index (n for A vs B/C)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>Did not receive celecoxib</th>
<th>Did receive celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>&lt;4 (11,24)</td>
<td>1.601 (0.895,3.054)</td>
<td>.154</td>
<td>13.3 (4.9,21.3)</td>
<td>6.6 (4.9,11.8)</td>
</tr>
<tr>
<td>Survival</td>
<td>&gt;=4 (11,15)</td>
<td>3.43 (0.154, 764)</td>
<td>.009</td>
<td>3.8 (0.9,10.5)</td>
<td>10.9 (8.1,17.4)</td>
</tr>
<tr>
<td>FFS</td>
<td>&lt;4 (18,29)</td>
<td>1.088 (0.408,1.947)</td>
<td>.777</td>
<td>4.7 (2.9,6.7)</td>
<td>4.1 (2.9,6.1)</td>
</tr>
<tr>
<td>FFS</td>
<td>&gt;=4 (11,17)</td>
<td>3.12 (0.135, 718)</td>
<td>.006</td>
<td>3.40 (8.6, 47)</td>
<td>6.5 (4.8,8.4)</td>
</tr>
</tbody>
</table>

Conclusions

- CALGB 30203 failed to achieve its predefined goal of a 9 month FFS >50%.
- IHC studies suggest that COX-2 is a negative prognostic factor for survival but a positive predictive factor for survival if patients received celecoxib. *The numbers are small and this analysis is hypothesis generating.*
- Multivariate analysis confirms the interaction of COX-2 expression and response to celecoxib.
- This study demonstrates the importance of obtaining tissue specimens for correlative studies.
- A phase III randomized trial testing the hypothesis that COX-2 inhibition in COX-2 overexpressing patients is under discussion.