



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

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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

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Slide 2

Special Thanks

- Anil Potti
- Marty Edelmann

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Slide 3

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

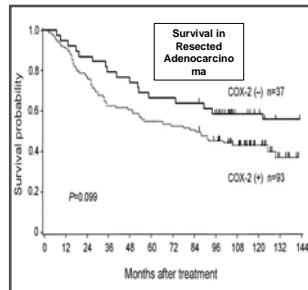
MJ Edelman, DM Watson, X Wang, RA
Kratzke, AM Mauer, S Jewell, SL
Graziano, GA Masters, MM Bedor, M R
Green, EE Vokes for the CALGB

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Slide 4

Introduction

- Abnormalities of the eicosanoid/prostaglandin signal pathway occur frequently in lung cancer.¹
- Increased levels of end products of these pathways can increase tumor proliferation, angiogenesis and inhibit apoptosis.²
- COX-2 overexpression has been associated with inferior outcome in NSCLC.³
- 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.^{4,5}
- Inhibition of COX-2 and /or 5-LOX in cell lines and animal models is additive or synergistic with chemotherapy.⁶



1. Clin Lung Ca 4:271-277, 2002 2. JCI 97:806-13, 1996 3. Clin Ca Res 5:1001, 1999 4. Pancreatology 2:54-60, 2002 5. Lung Cancer 40:33-44, 2003 6. Hida, Clin Ca Res 2000

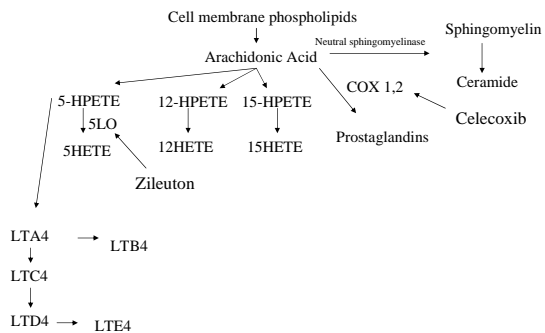
Hypothesis

- 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.

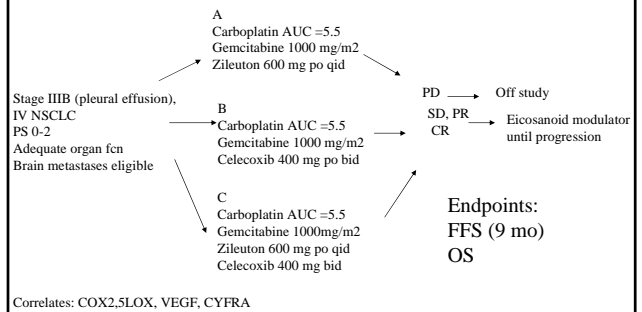
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Slide 6

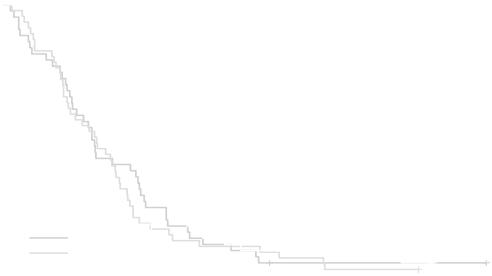
Arachidonic Acid Metabolism



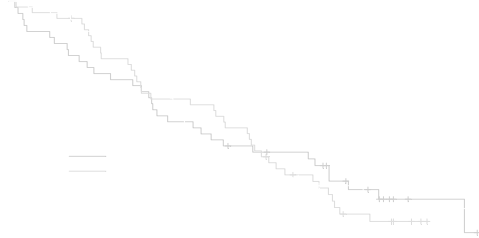
CALGB 30203: Gemcitabine/ Carboplatin + Eicosanoid Modulators



CALGB 30203: FAILURE-FREE SURVIVAL



CALGB 30203: OVERALL SURVIVAL



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)

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Slide 11

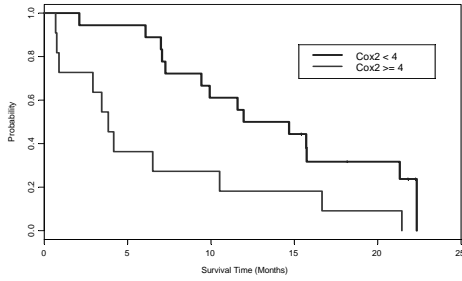
Immunohistochemistry Studies

- 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

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Slide 12

OS and Cox-2 expression (<4 vs >=4) for Pts Who Did Not Receive Celecoxib



COX-2: Predictive Factor

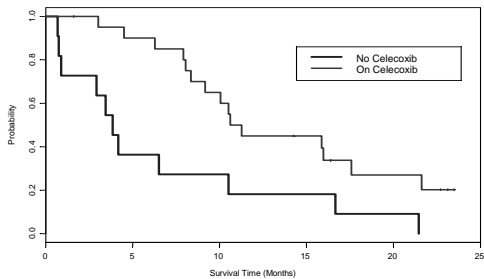
Comparison of patients who **did not** (N=29) or **did** (N=54) receive celecoxib (ARM A vs B/C)

Endpoint	Cut point of COX-2 index (n for A vs B/C)	HR (95% CI)	P-value	Did not receive celecoxib	Did receive celecoxib
Survival	<4 (11,24)	1.601 (.839,3.054)	.154	13.3 (9.4,21.3)	8.6 (4.9,11.8)
Survival	≥4 (11,15)	.343 (0.154,.764)	.009	3.8 (0.9,10.5)	10.9 (8.3,17.6)
FFS	<4 (18,29)	1.088 (0.608,1.947)	.777	4.7 (2.9,6.7)	4.1 (2.9,6.1)
FFS	≥4 (11,17)	.312 (0.135,.718)	.006	3.4(0.8,6.4)	6.5 (4.8,8.4)

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Slide 14

OS and Celecoxib for COX-2 ≥ 4



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.

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Slide 16