CALGB 30801:
Randomized Phase 3 Double-Blind Trial Evaluating Selective COX-2 Inhibition in COX-2 Expressing Advanced Non-Small Cell Lung Cancer (NSCLC)

Biomarker, Imaging and Quality of Life Supplemental Funding Program
Primary therapeutic objective of CALGB-30801 is to determine if pre-selected patients with NSCLC with moderate to high overexpression of COX-2 (unfavorable population) will benefit from standard chemotherapy plus celecoxib.

**Primary Endpoint:**
Improvement in Progression-free Survival (PFS) for patients with COX-2 index ≥ 4 with estimated HR 0.6
CALGB 30801:
Phase 3 Placebo-Controlled Trial Evaluating COX-2 Inhibition in COX-2 Expressing Advanced NSCLC

Stratification:
Stage
Gender
Histology
Smoking
COX-2 index

Stage IIIB
(pl effusion)
Stage IV

REGISTER

COX-2 Index >2
Index >4*

RANDOMIZE

A
Carboplatin AUC =5.5
Gemcitabine (sq) 1000 mg/m2
OR
Carboplatin AUC = 6
Pemetrexed (non-sq )500mg/m2
AND
Celecoxib 400 mg po bid

Off study
PD
SD, PR
CR

REGISTER

No (follow)

B
Carboplatin AUC =5.5
Gemcitabine (sq) 1000 mg/m2
OR
Carboplatin AUC = 6
Pemetrexed (non-sq) 500mg/m2
AND
Placebo

Continue celecoxib or placebo

*Index > 4 for primary endpoint
Rationale for COX-2 Inhibition in Lung Cancer

- Overexpressed in NSCLC (~80%)
- Induced by tobacco carcinogens & preclinical studies suggest antitumor & chemopreventive efficacy
  - induces apoptosis, enhances cytotoxic effects chemotx
  - induces anti-angiogenic effects in lung cancer models
  - restores anti-tumor immunity
  - decreases tumor invasiveness
- Epidemiologic data suggest subjects who routinely use NSAIDs have ↓ lung cancer risk
- A marker of poor prognosis in stage I NSCLC
Survival of Patients with NSCLC by Cox-2 Expression

Estimated probability of survival

Low COX-2 expression

High COX-2 expression

Survival in months

P = 0.0032

Clinical Trials in NSCLC (& other tumor types)

- Mostly performed in an unselected patient population
- Results of combining COX-2 inhibitors and chemotherapy have been conflictive
- Preclinical rationale has not translated in clear clinical benefit in the therapeutic setting
CALGB 30203: Gemcitabine/ Carboplatin + Eicosanoid Modulators

Stage IIIB (pleural effusion)
Stage IV NSCLC

A

Carboplatin AUC =5.5
Gemcitabine 1000 mg/m2
Zileuton 600 mg po qid

PD → Off study

B

Carboplatin AUC =5.5
Gemcitabine 1000 mg/m2
Celecoxib 400 mg po bid

SD, PR -> Eicosanoid modulator until progression

C

Carboplatin AUC =5.5
Gemcitabine 1000 mg/m2
Zileuton 600 mg po qid
Celecoxib 400 mg bid

Endpoints:
FFS (9 mo)
OS

Required tissue submission for COX2 by IHC
CALGB 30203: OVERALL SURVIVAL

The Kaplan-Meier survival curve shows the overall survival probability for three arms (A, B, C) over different months. The graph demonstrates the survival rates for each arm, with Arm A generally having the highest survival probability, followed by Arm B, and then Arm C.
Prognostic and Predictive Value of COX-2 Index $\geq 4$

COX-2 expression

- **negative** prognostic marker for pts who *did not* receive celecoxib
- **positive** predictive marker for pts who *did* receive celecoxib
Conclusions from CALGB-30203

- COX-2 overexpression is a negative prognostic factor
- Patients with overexpressed COX-2 receiving celecoxib had better survival compared with patients with overexpression who did not receive the drug (10.6 vs. 3.8 months for index \( \geq 4 \))
- The higher the COX-2 overexpression (\( >4, >9 \)), the greater the degree of benefit from celecoxib
- Patients not overexpressing COX-2 who received celecoxib had an apparent inferior outcome
- Confirmed independent predictive value of COX-2 expression and response to celecoxib
Urinary PGEM as a Potential Biomarker

- PGE-M is a stable urinary metabolite of PGE-2
- Levels decrease with COX-2 inhibition
- Patients who had suppressed PGE-M had superior outcome
- A possible biomarker for COX-2 dependent disease

Reckamp et al Proc ASCO, 2007
A PTGS2 polymorphism is associated with high COX-2 expression

In atheromatous plaques

Cipollone et al. JAMA 2004

In FAP associated carcinoma

Brosens et al. Clin Cancer Res 2005
Is this same polymorphism (rs20417) associated with COX-2 expression in NSCLC?
Rationale for New CALGB-30801 Trial

• Significant pre-clinical & clinical data support importance of COX-2 in development & progression of NSCLC

• Despite this, clinical trials of COX-2 inhibition in NSCLC have been disappointing

• Reason for this (based on CALGB-30203) is that COX-2 inhibition may ONLY be of value in COX-2 overexpressing tumors

• Future trials must select patients based upon tumor COX-2 expression
Cox-2: Integral Marker for Pt Selection
Urinary PGEM: Integrated Marker

Tissue COX-2 by IHC
- Uses same method as precursor trial CALGB-30203
- Assay results within 72 hours
- Performed at CALGB Molecular Pathology Reference Lab (at Ohio State) - CLIA approved & CAP accredited

Cox-2 IHC Parameters
- IHC scored by intensity & percentage of cells
- Patients will be classified as
  - “over-expressed” (COX-2 index ≥ 4)
  - “moderately expressed” (COX-2 index ≥ 2 and <4)
  - “negative” (COX-2 index <2)
- Only patients with COX-2 index of ≥ 2 will be eligible

Urinary PGEM as INTEGRATED biomarker for evaluation
<table>
<thead>
<tr>
<th>PROPOSED PROJECT PERIOD 7/1/09 – 6/30/13</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
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<td>COX-2 (Integral)</td>
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• 1st therapeutic phase 3 trial to test role of selective COX-2 inhibition in pre-selected population based on COX-2 expression level

• Integral marker: Cox-2 overexpression (IHC)

• Integrated marker: Urinary PGEM