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

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CALGB-30801: Primary Therapeutic Objective

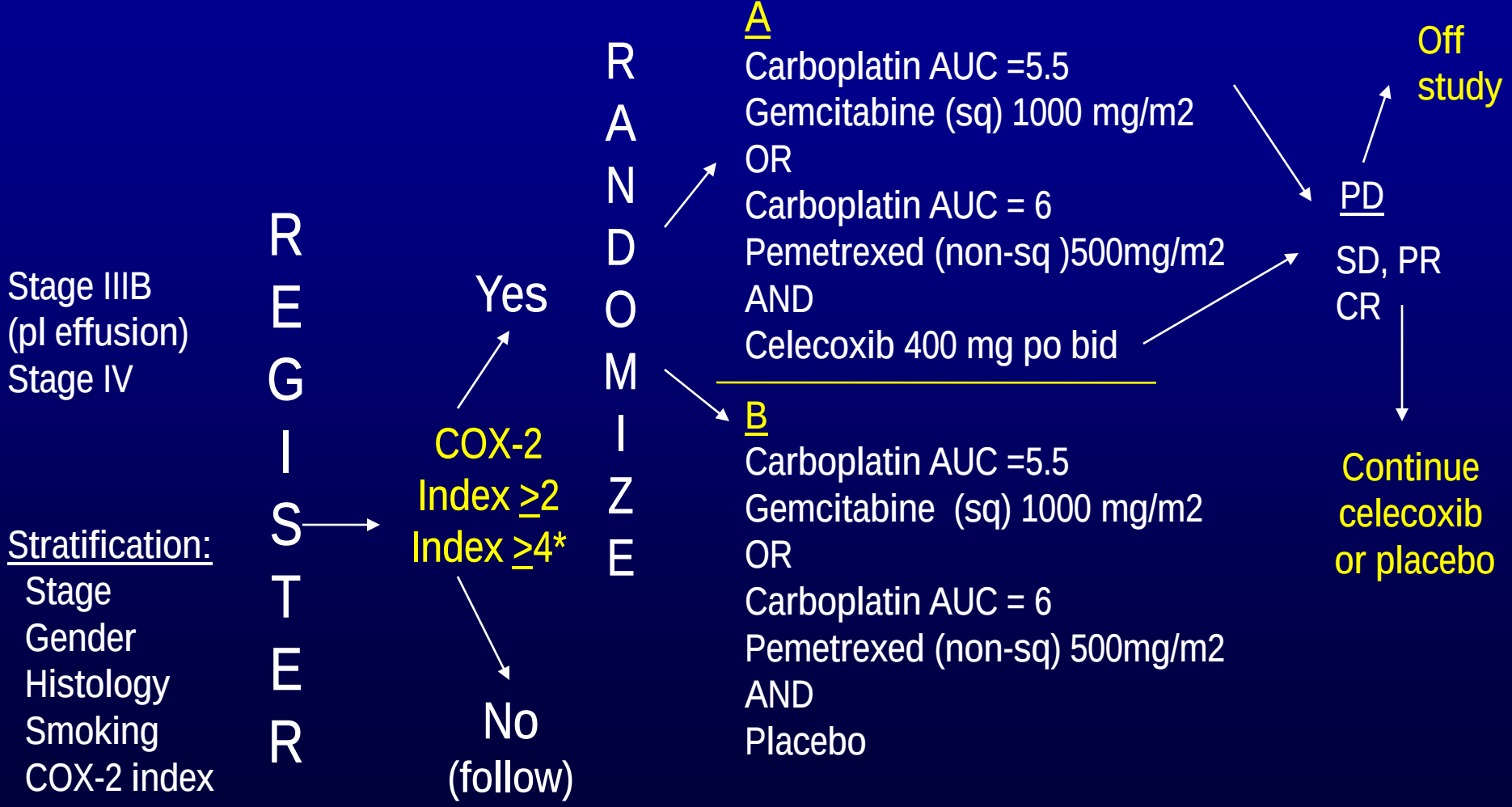
- Primary therapeutic objective of CALGB-30801 is to determine if pre-selected patients with NSCLC with moderate to high overexpression of COX-2 (unfavorable population) will benefit from standard chemotherapy plus celecoxib

- <u>Primary Endpoint</u>:

  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



*Index ≥ 4 for primary endpoint

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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**

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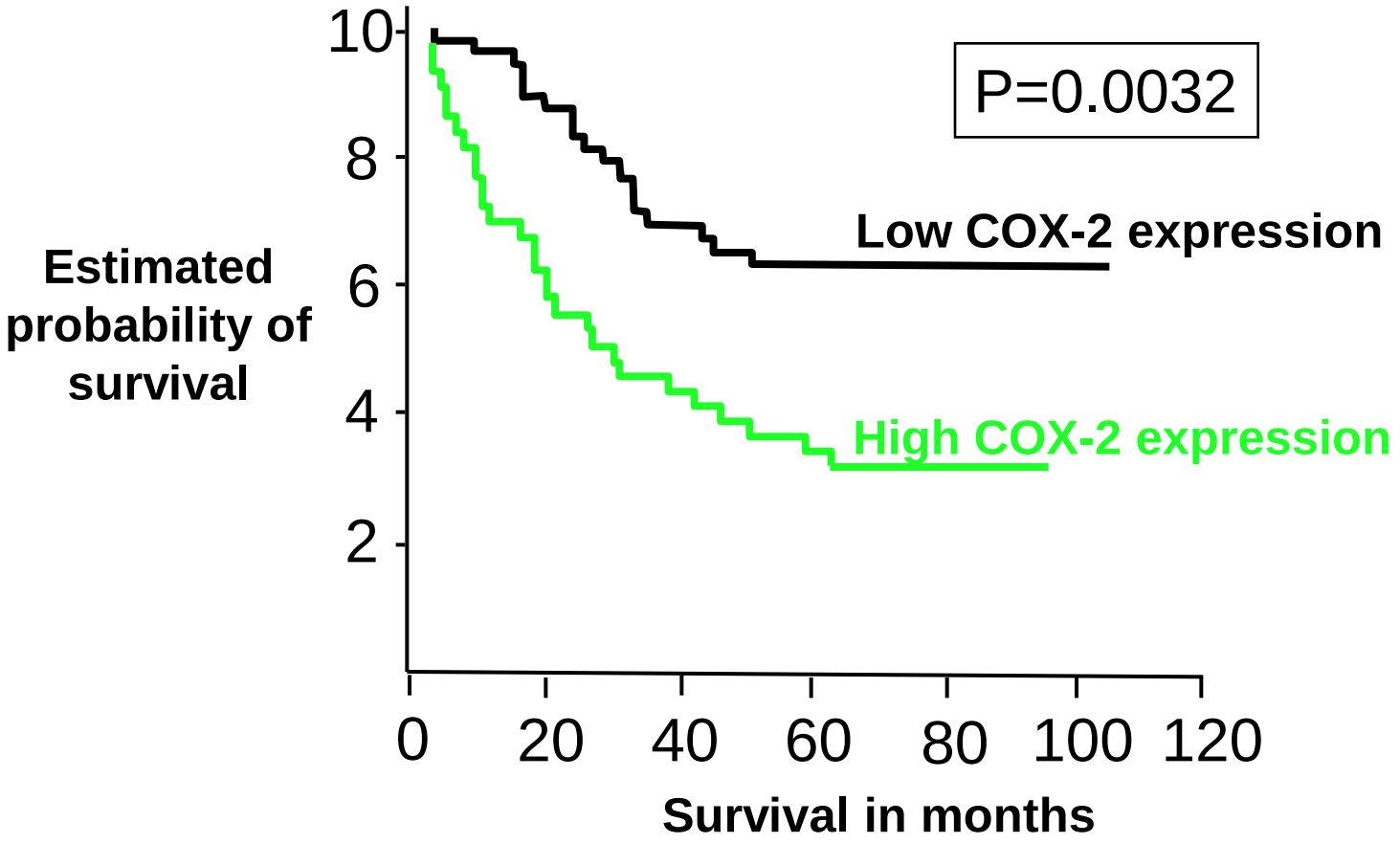
Survival of Patients with NSCLC by Cox-2 Expression



Brabender et al. *Ann of Surg* 2002;235:440

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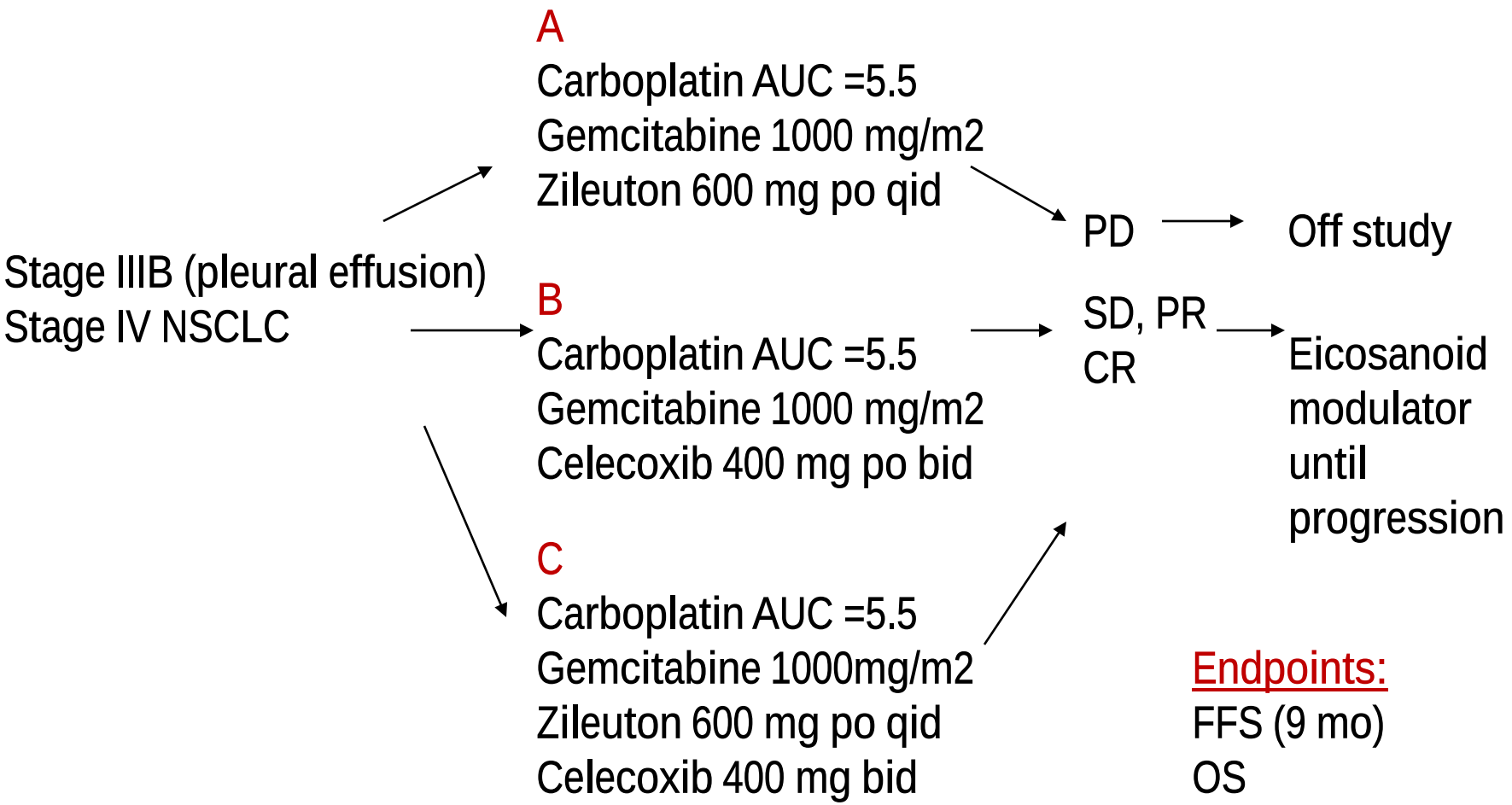
Clinical Trials in NSCLC (& other tumor types)

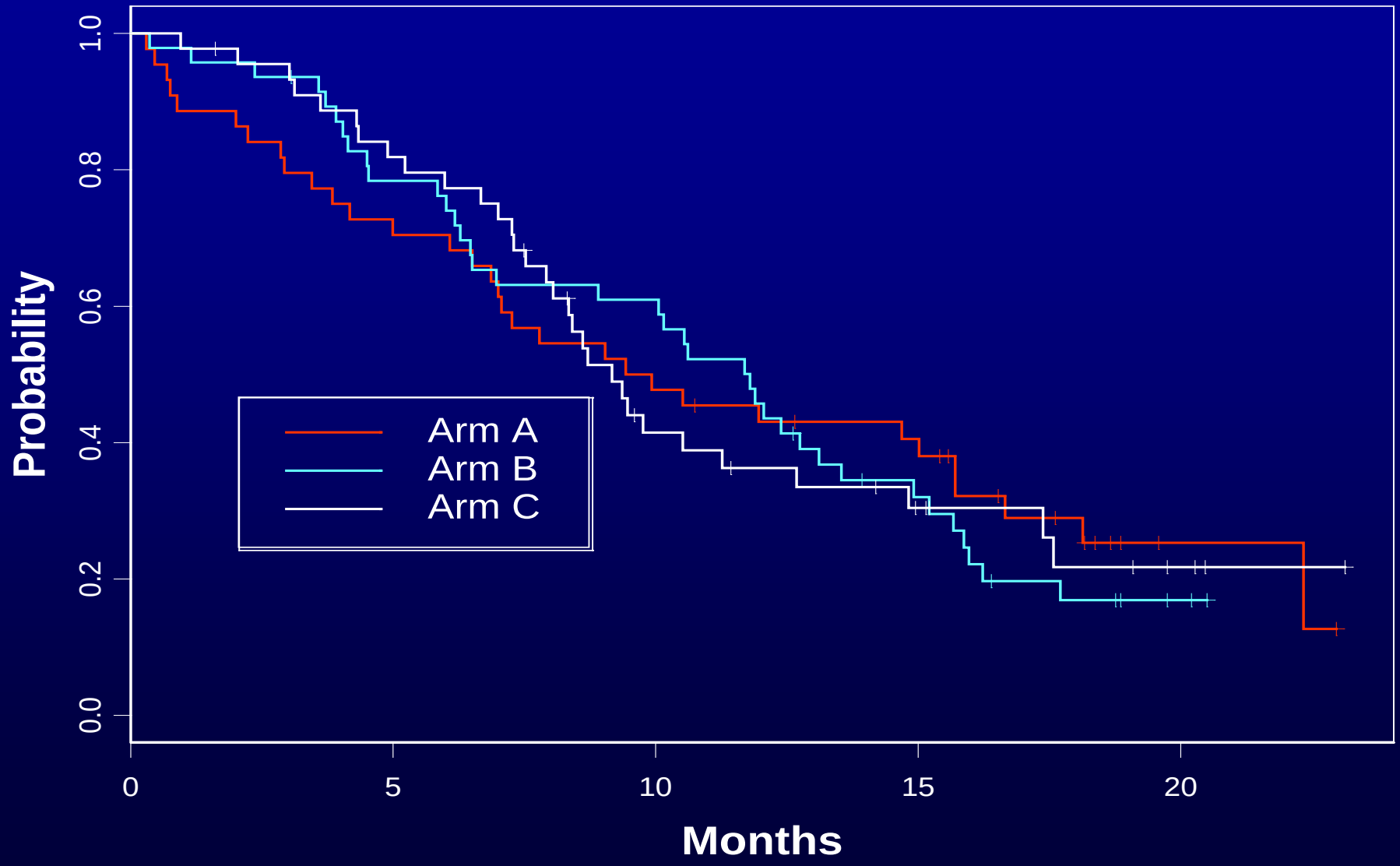
- **Mostly performed in an unselected patient population**
- **Results of combining COX-2 inhibitors and chemotherapy have been conflictive**
- **Preclinical rationale has not translated in clear clinical benefit in the therapeutic setting**

CALGB 30203: Gemcitabine/ Carboplatin + Eicosanoid Modulators

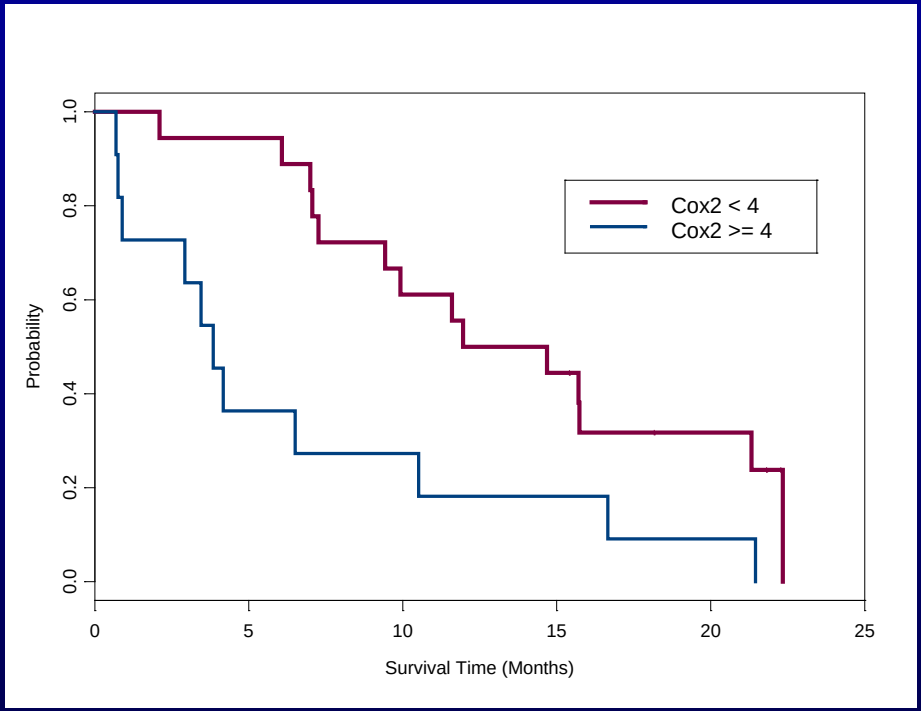


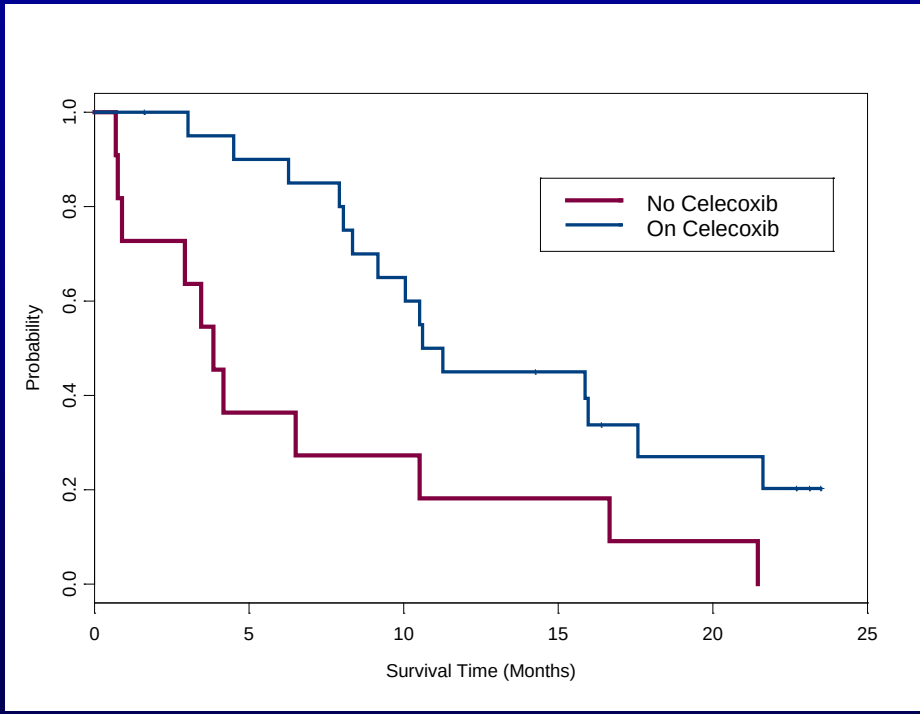
Required tissue submission for COX2 by IHC

CALGB 30203: OVERALL SURVIVAL



Prognostic and Predictive Value of COX-2 Index ≥ 4





COX-2 expression

- *negative* prognostic marker for pts who *did not* receive celecoxib
- *positive* predictive marker for pts who *did* receive celecoxib

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Conclusions from CALGB-30203

- COX-2 overexpression is negative prognostic factor
- Pts with overexpressed COX-2 receiving celecoxib had better SV compared with pts with overexpression who did not receive drug (10.6 vs. 3.8 months for index ≥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 apparent inferior outcome
- Confirmed independent predictive value of COX-2 expression and response to celecoxib

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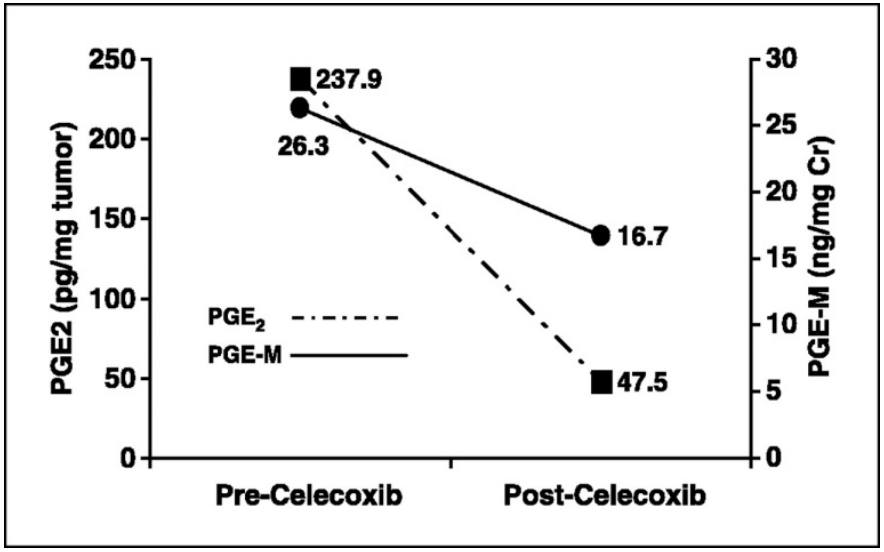
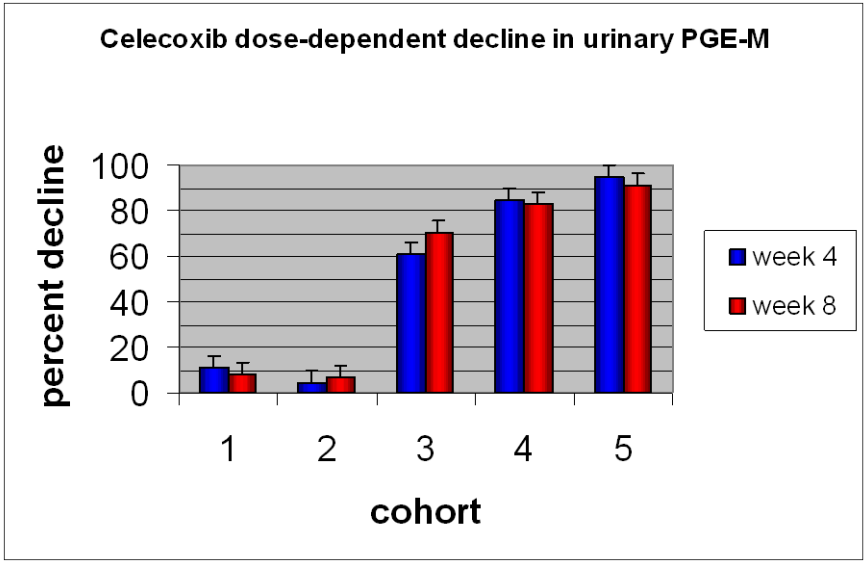
Urinary PGEM as a Potential Biomarker

- PGE-M is 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

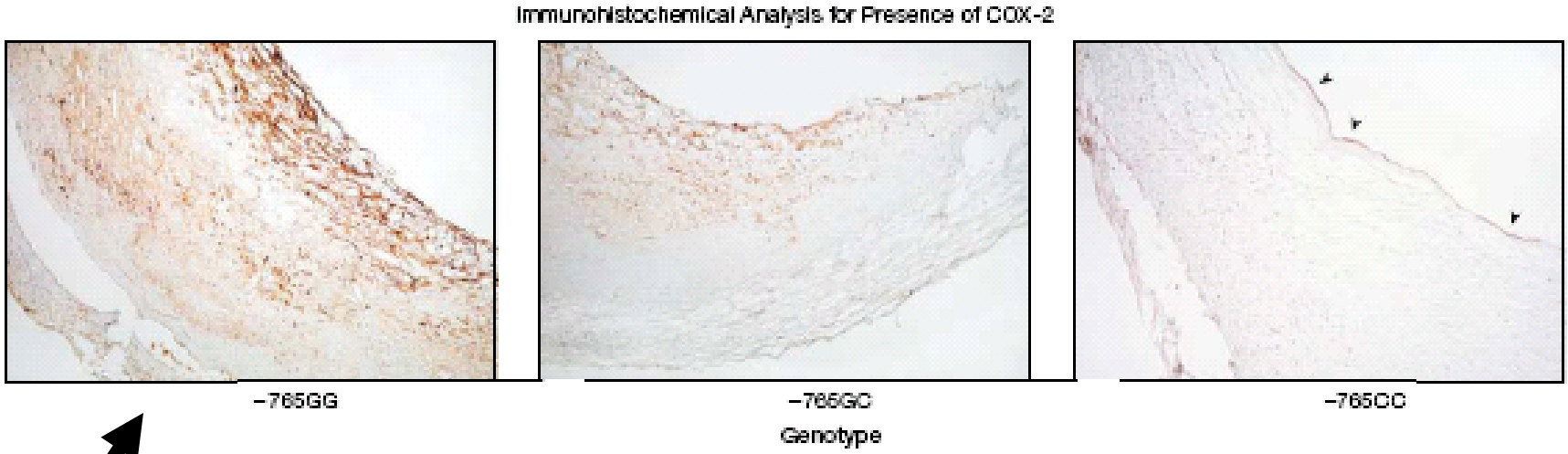




Csiki et al. Clin Cancer Res 2005;11:6634-40
Reckamp et al Proc ASCO, 2007

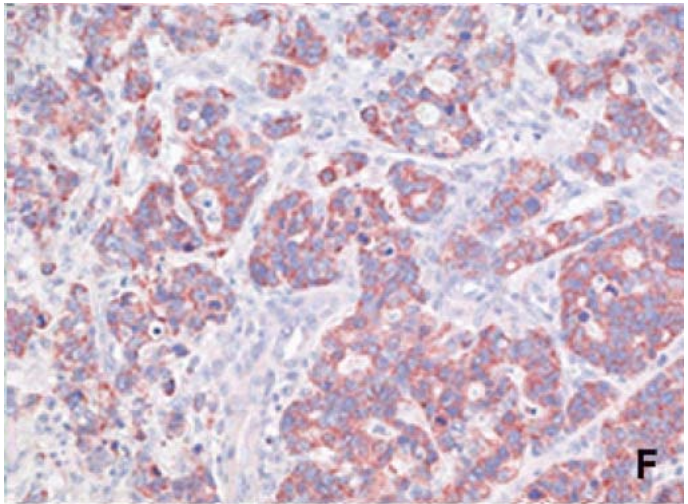
A *PTGS2* polymorphism is associated with high COX-2 expression

Figure 1. Immunohistochemical Analysis for Presence of COX-2 and MMP-9 in Atherosclerotic Carotid Plaques



In atheromatous plaques

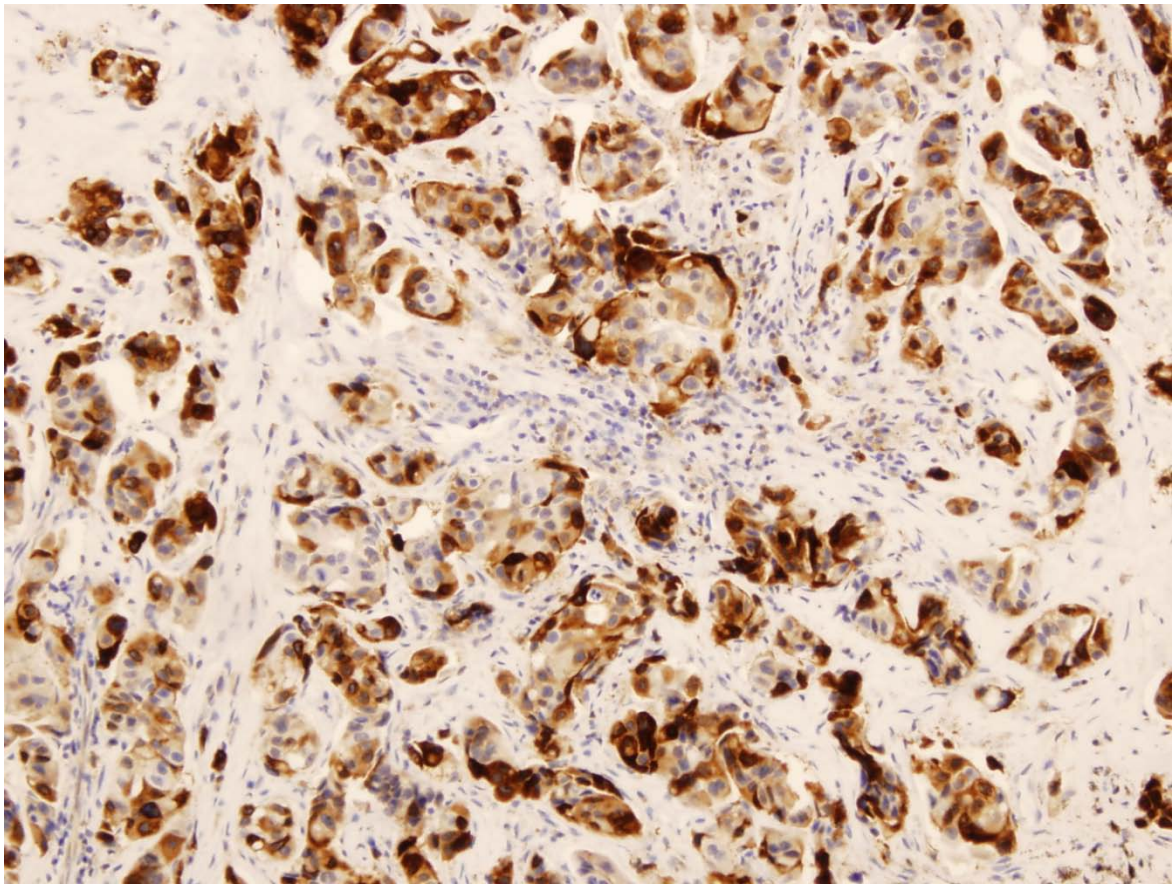
Cipollone et al
JAMA 2004



In FAP associated carcinoma

Brosens et al.
Clin Cancer Res 2005

Is this same polymorphism (rs20417) associated with COX-2 expression in NSCLC?



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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

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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

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CALGB-30801 – BIQSFP Budget

PROPOSED PROJECT PERIOD 7/1/09 – 6/30/13				
	Year 1	Year 2	Year 3	Year 4
COX-2 (Integral)	$82,795	$71,612	$72,968	$47,964
PGE-M (Integrated)			$37,800	$37,800
Total Annual Costs	$82,795	$71,612	$110,768	$85,764
TOTAL COST FOR ENTIRE 4 YEARS				$350,939

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Summary BIQSFP for CALGB-30801 Trial

- 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