Biomarker Studies in Multi-Center Cancer Clinical Trials: the role of cooperative groups

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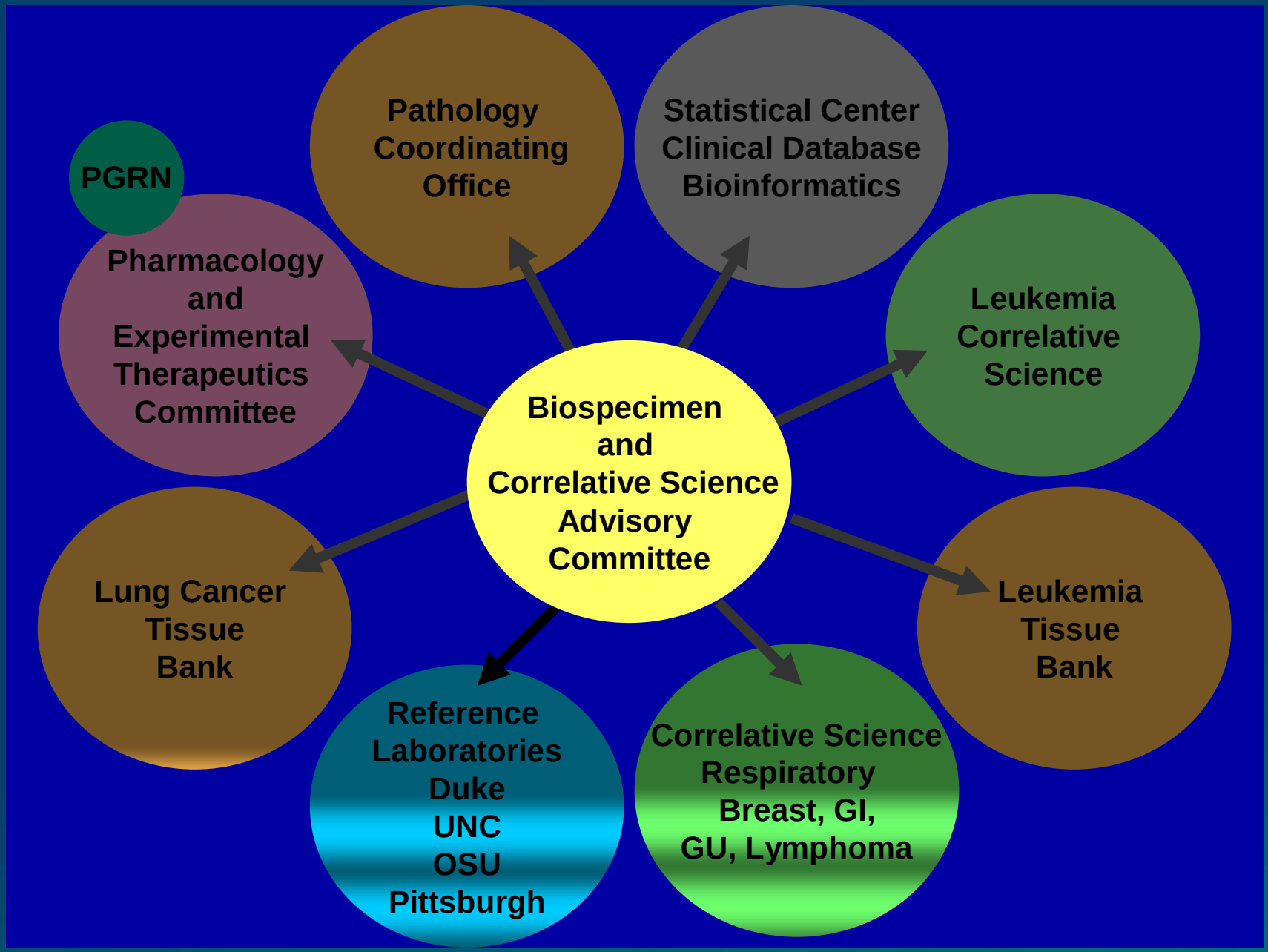
Types of Biomarker Studies Done by Cooperative Groups

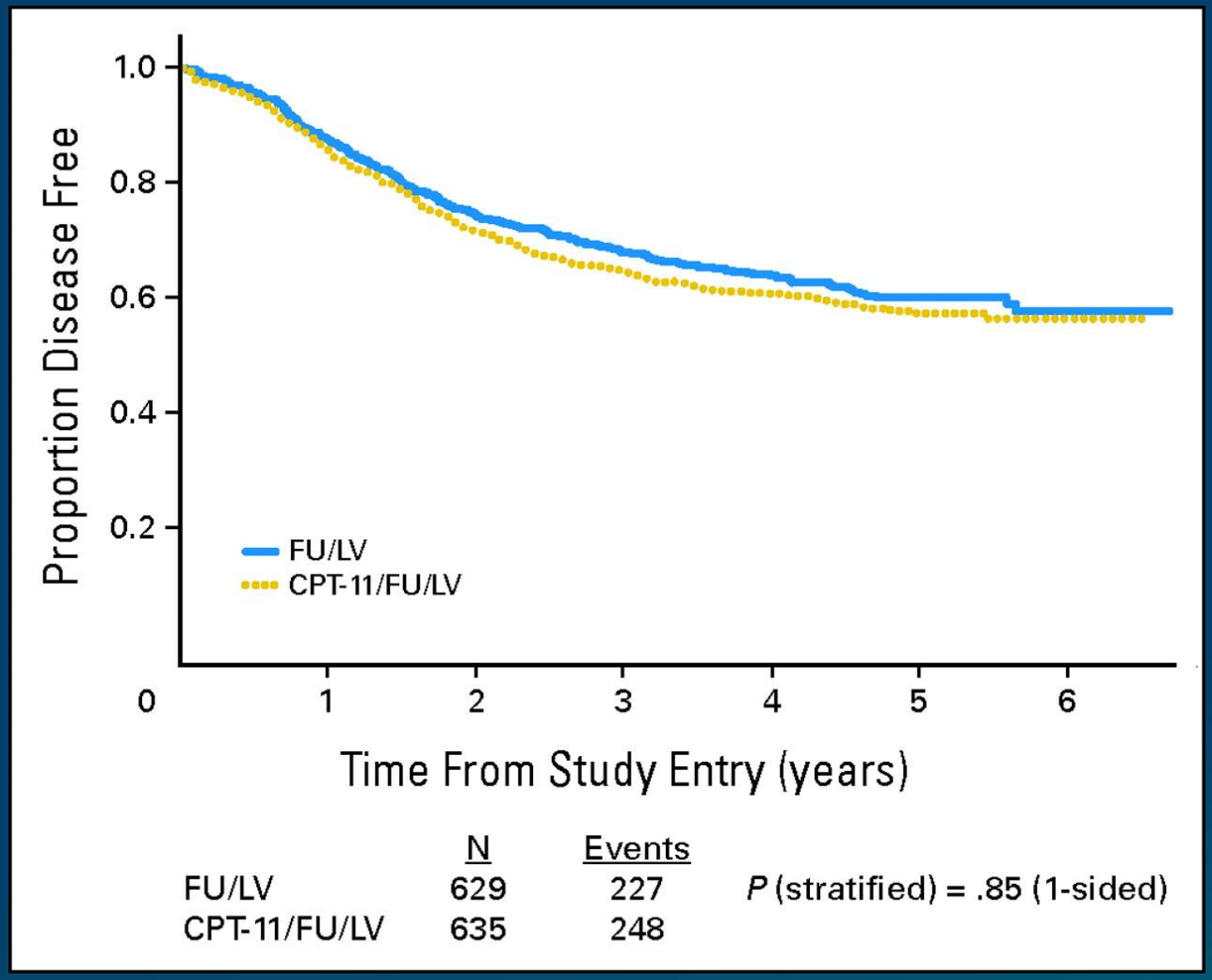
- Exploratory (correlative) studies using clinically annotated biospecimens and research assays
- “Retrospective-prospective” studies using clinically annotated specimens, known clinical outcomes and research or analytically validated assays
- Prospective biomarker-drug co-development studies
- Prospective biomarker development studies
- Prospective biomarker validation studies

Translational Science Infrastructure



Exploratory (Correlative) Biomarker Studies

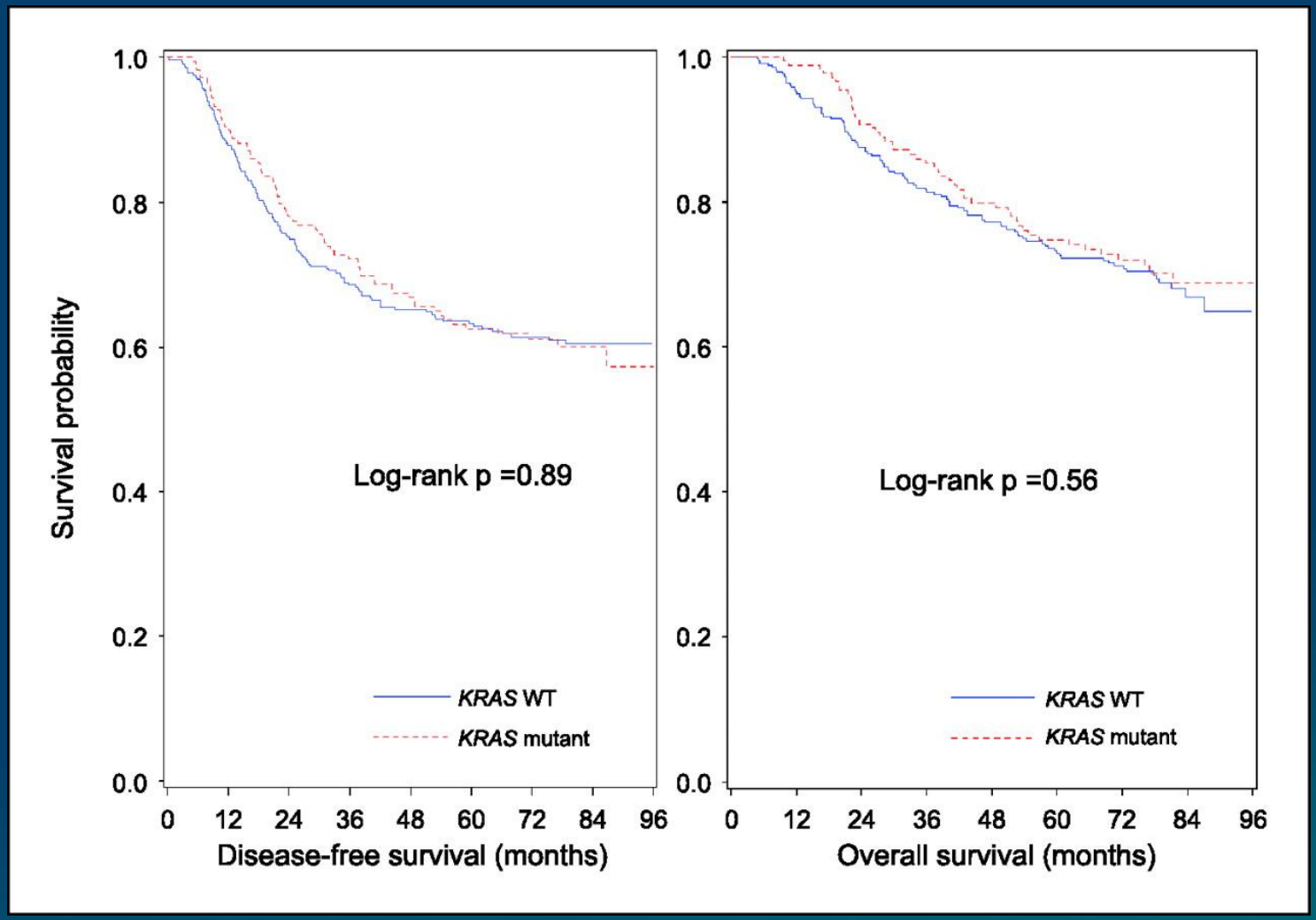
CALGB 89803: Disease-Free Survival



	N	Events	
FU/LV	629	227	*P* (stratified) = .85 (1-sided)
CPT-11/FU/LV	635	248	

Saltz, L. B. et al. J Clin Oncol; 25:3456-3461 2007

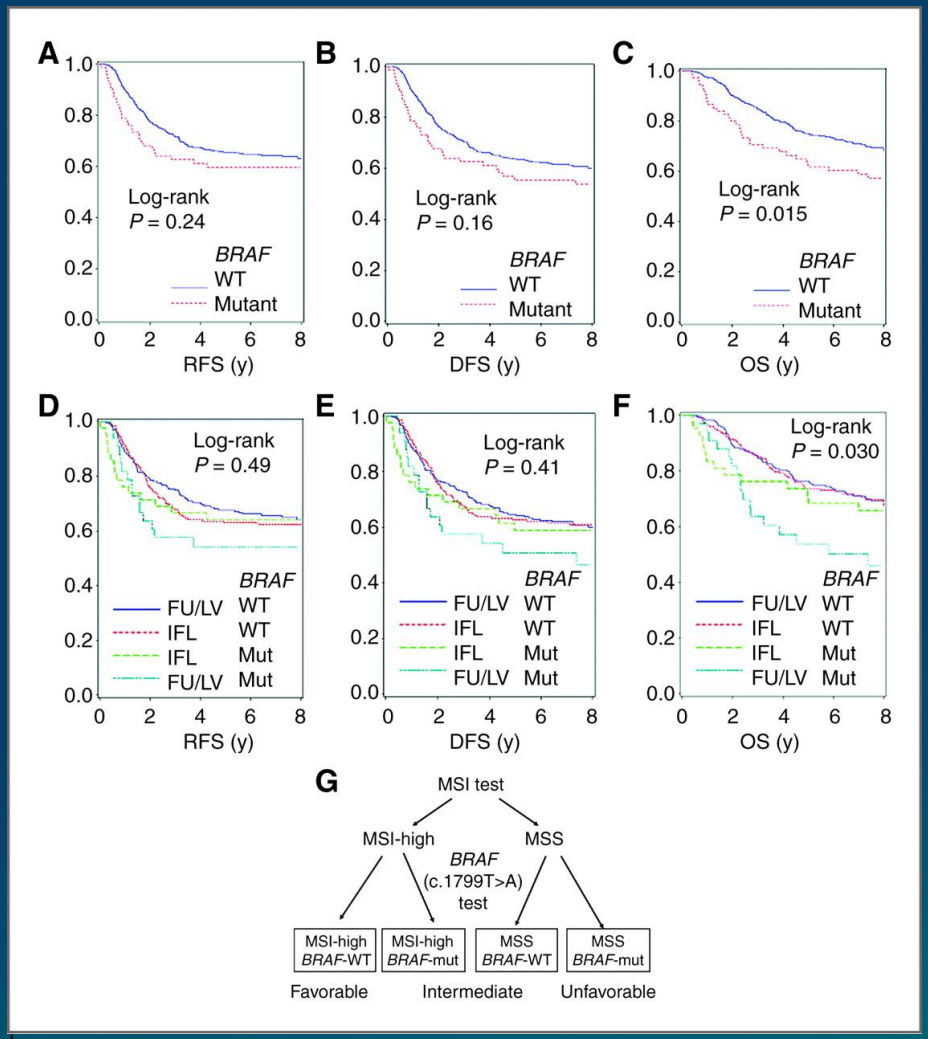
KRAS Mutation is Not Prognostic in Stage III Colon Cancer: CALGB 89803



Ogino S et al. Clin Cancer Res 2009;15:7322-7329

Clinical Cancer Research

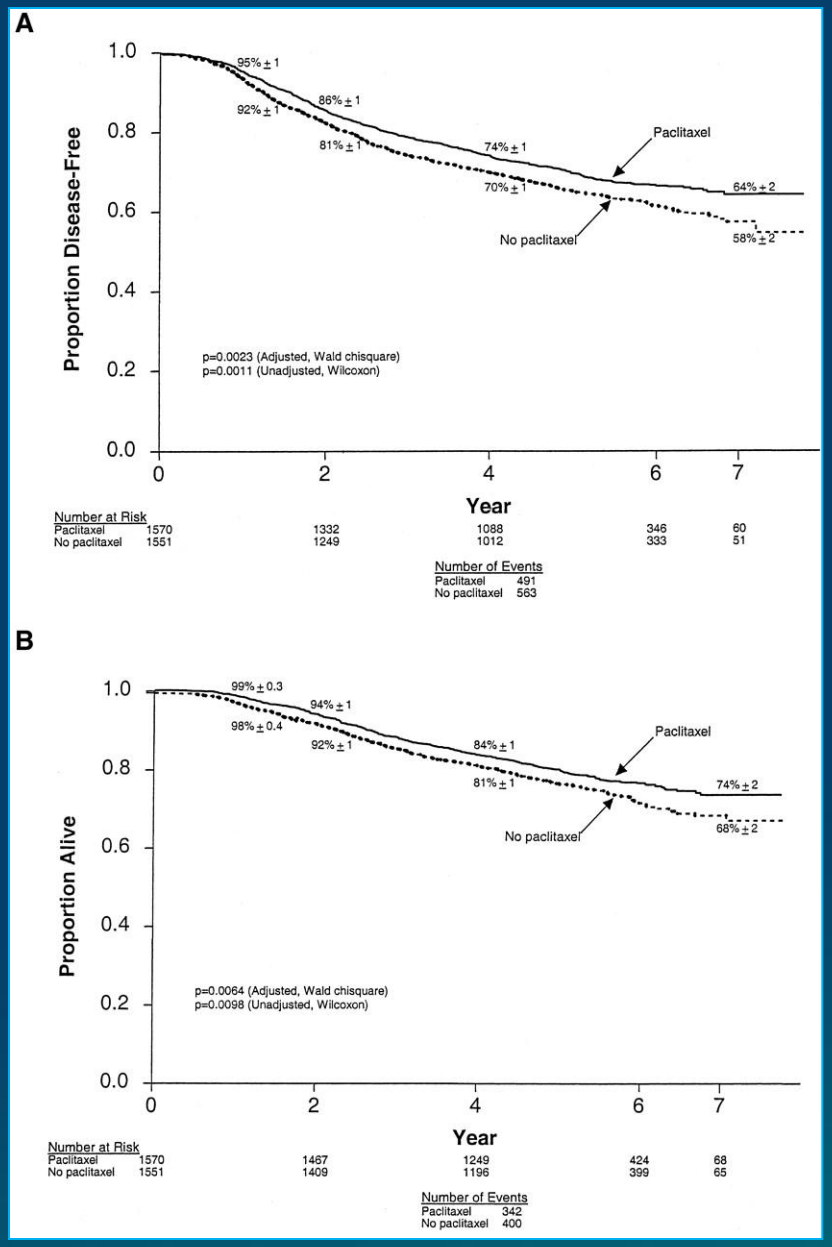
BRAF Mutation is Prognostic in Stage III Colon Cancer: CALGB 89803



Clin Cancer Res 2012;18:890-900
Clinical Cancer Research

CALGB 9344

Addition of Paclitaxel to AC in Stage II Breast Cancer



Henderson, I. C. et al. J Clin Oncol; 21:976-983 2003

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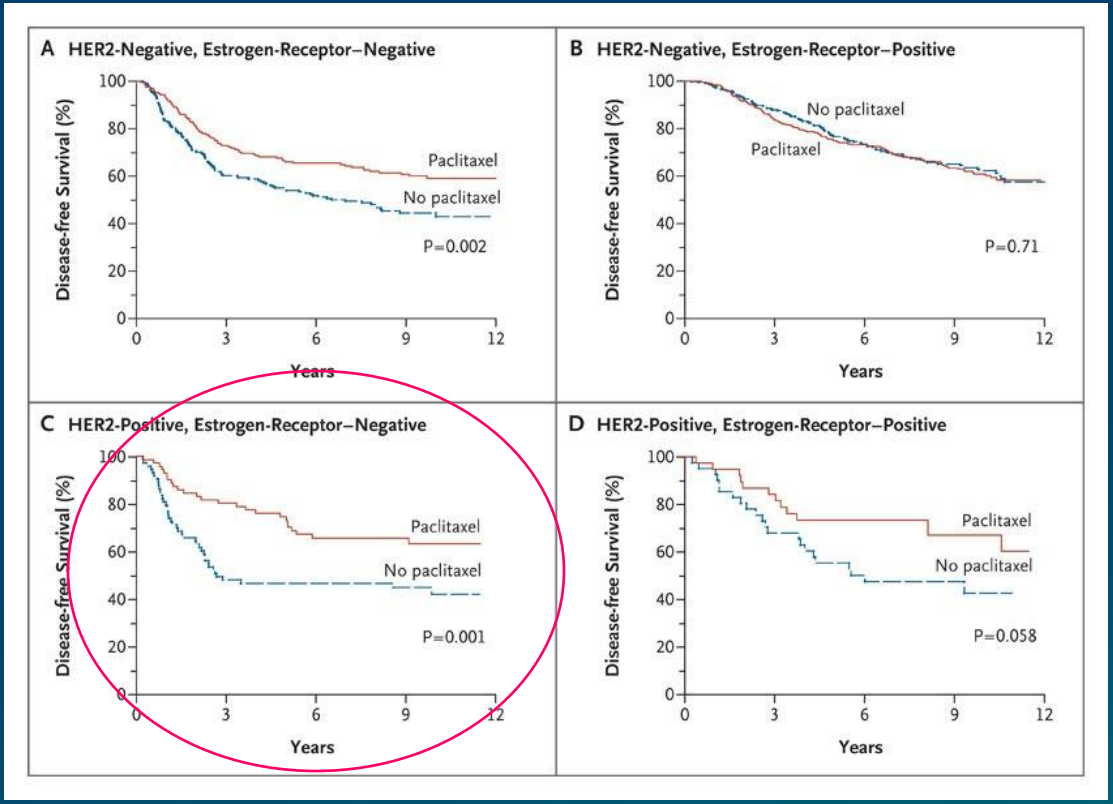
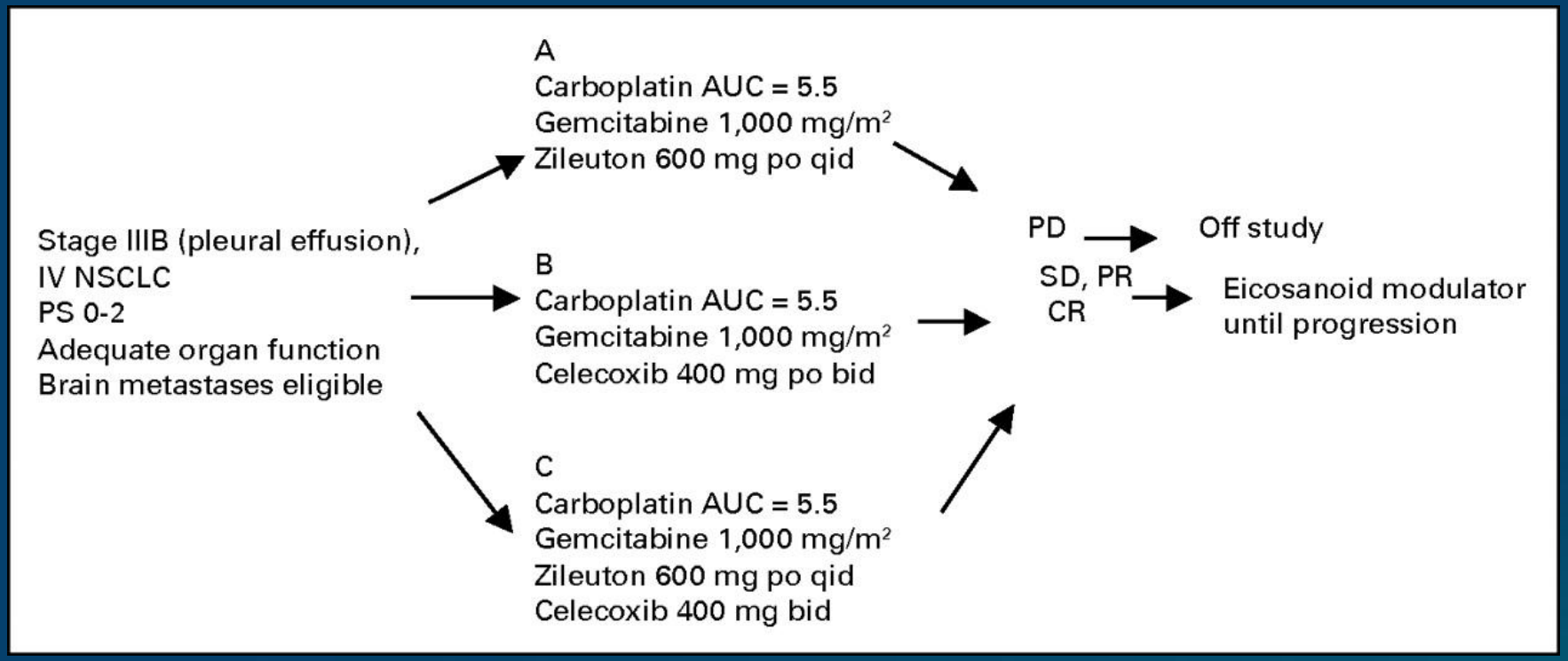
Molecular Markers and Adjuvant Paclitaxel

- Benefit of adjuvant paclitaxel is limited to women with ER negative and/or Her2 positive breast cancer



Hayes D et al. N Engl J Med 2007;357:1496-1506

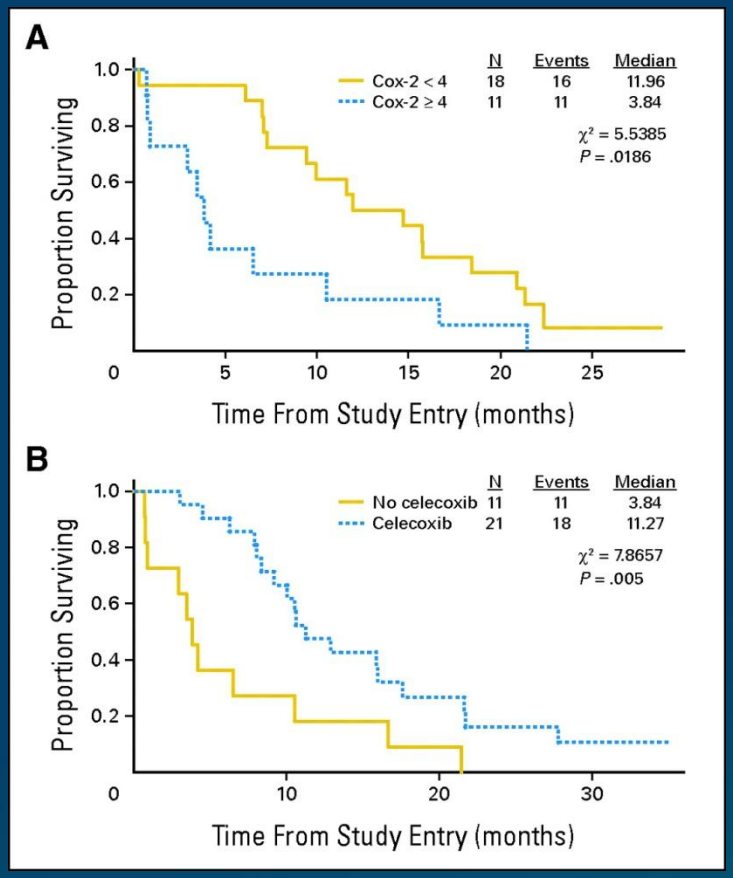
CALGB 30203



Edelman, M. J. et al. J Clin Oncol; 26:848-855 2008

COX-2 Expression and Outcome

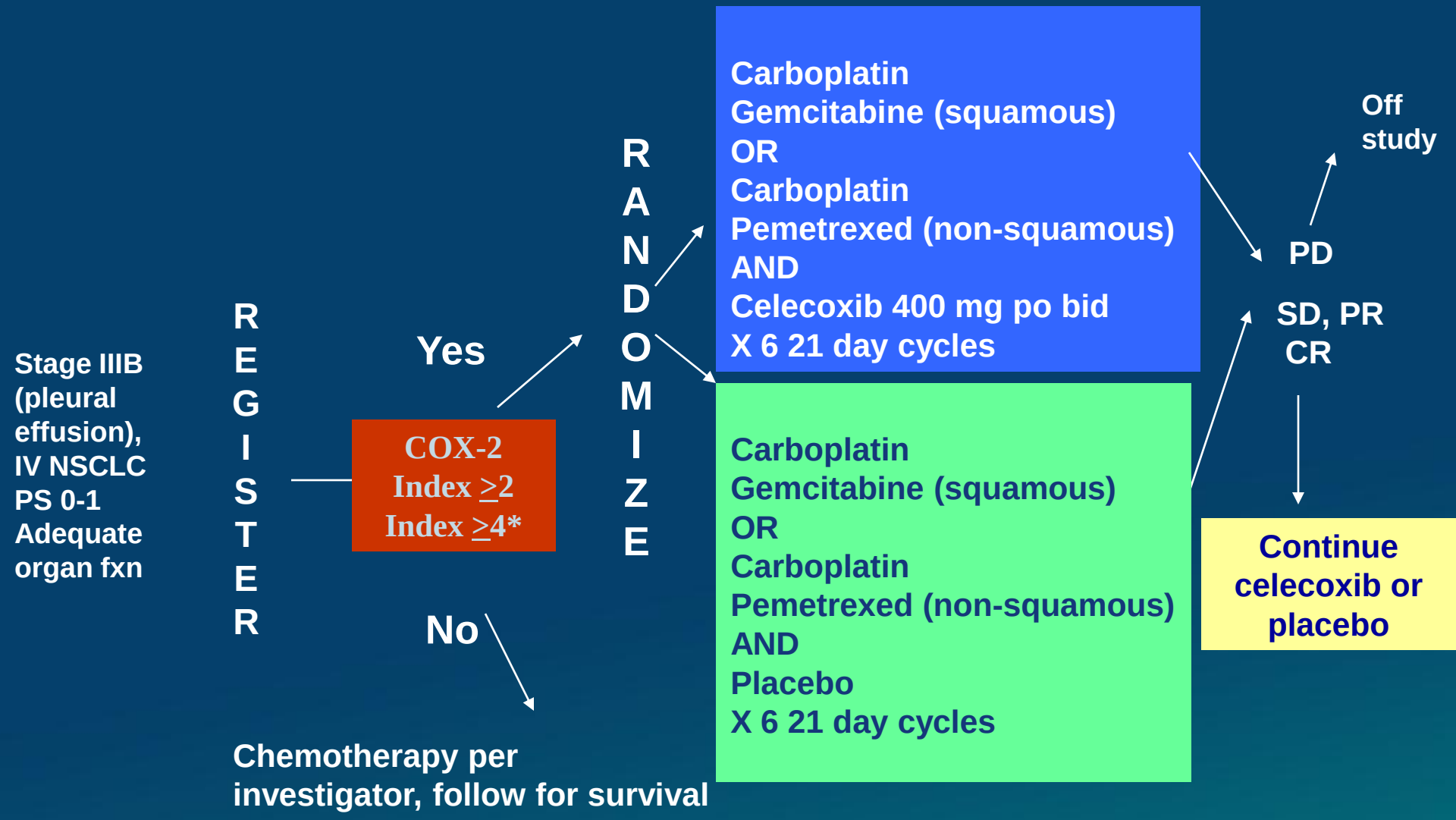
CALGB 30203



- COX-2 is an important negative prognostic marker (top) as well as a positive predictive marker of survival (bottom) for patients with advanced non small cell lung cancer who receive celecoxib in combination with chemotherapy.

Edelman, M. J. et al. J Clin Oncol; 26:848-855 2008

CALGB 30801:Randomized Phase III Trial of COX-2 Inhibition in Stage IIIb/IV COX-2 Over-expressing NSCLC



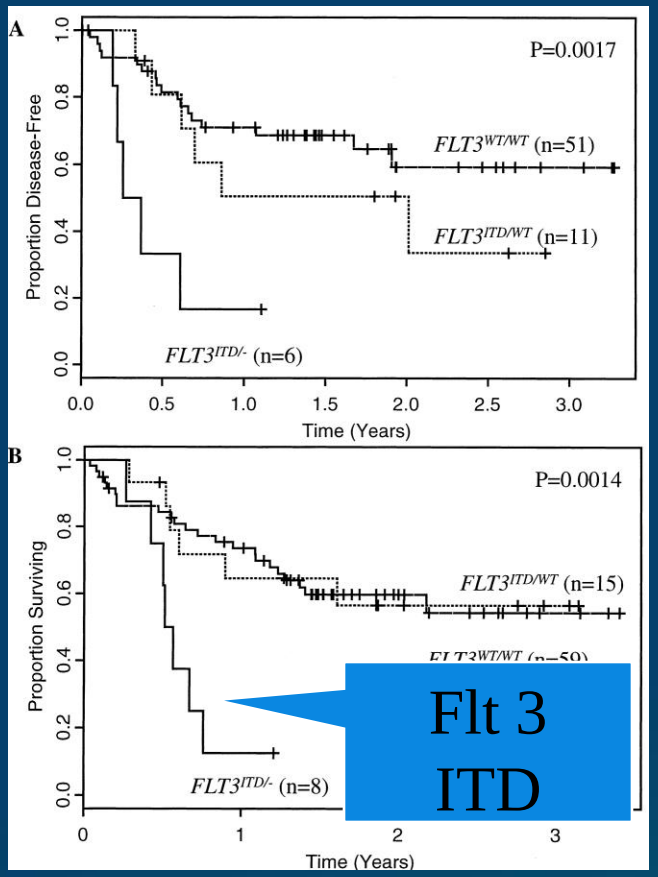
Correlates: Urinary PGEM, pk, pharmacogenetics

*Index ≥ 4 for primary endpoint

Biomarker-Drug Co-Development

PKC 412/FLT3 Mutation Analysis Co-Development

CALGB 10603



FLT Screening

Register

Randomize

Chemotherapy + Placebo → Maintenance Placebo

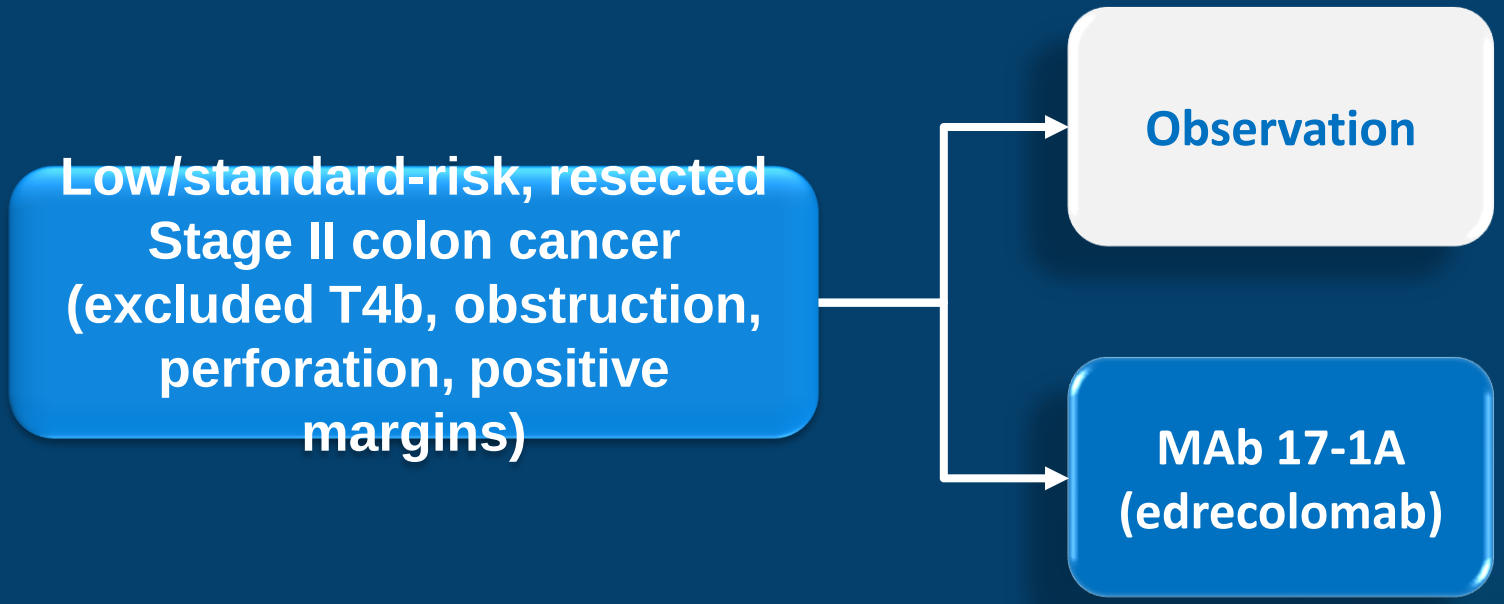
Chemotherapy + PKC 412 → Maintenance PKC 412

Whitman, S. P. et al. Cancer Res 2001;61:7233-7239

3 continents, 8 reference labs

Retrospective-Prospective Biomarker Validation

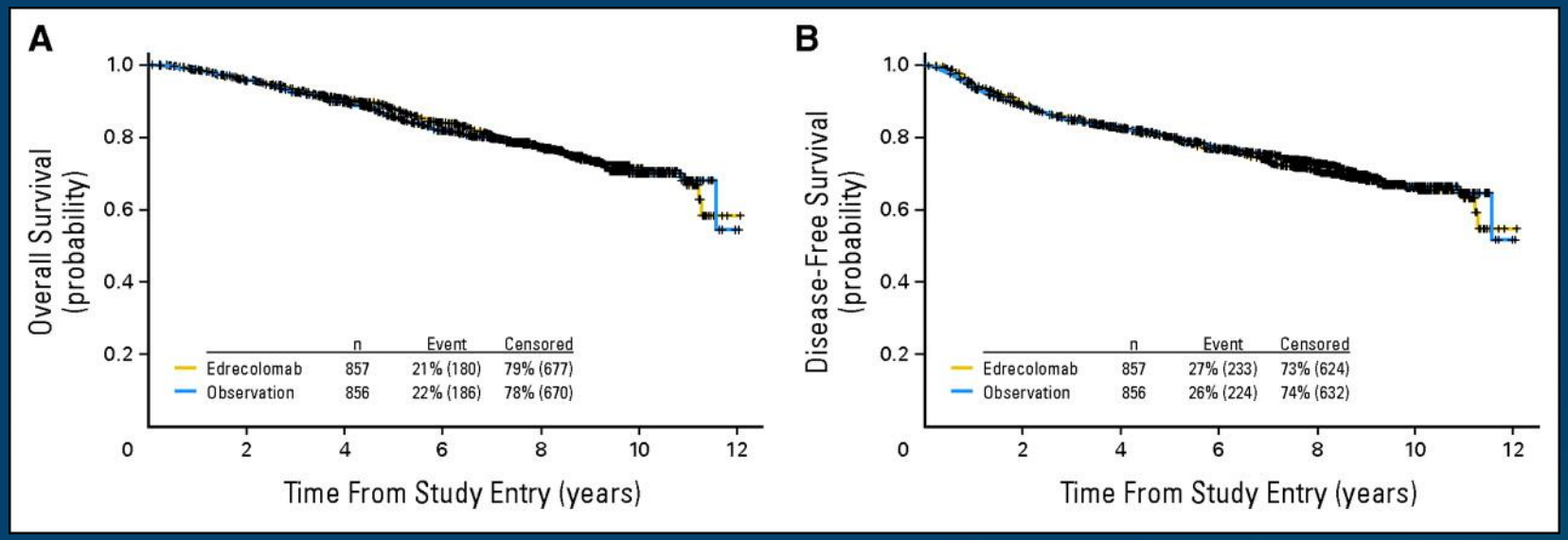
CALGB 9581
Randomized Phase III Clinical Trial in Stage II Colon Cancer



- 1738 patients enrolled 1997-2002
- Negative results for MAb 17-1A
- Targeted and enrolled primarily low-risk stage II patients (excluded pT4b, obstruction/perforation, positive margins)

Niedzwiecki D, et al. *J Clin Oncol*. 2011;29. Oncol. 2011; 29:3146.

Natural History of Stage II Colon Cancer: CALGB 9581



Niedzwiecki D et al. JCO 2011;29:3146-3152

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The 12-Gene Oncotype DX® Colon Cancer Recurrence Score®

Recurrence Score

STROMAL
FAP
INHBA
BGN

CELL CYCLE
Ki-67
C-MYC
MYBL2

GADD45B

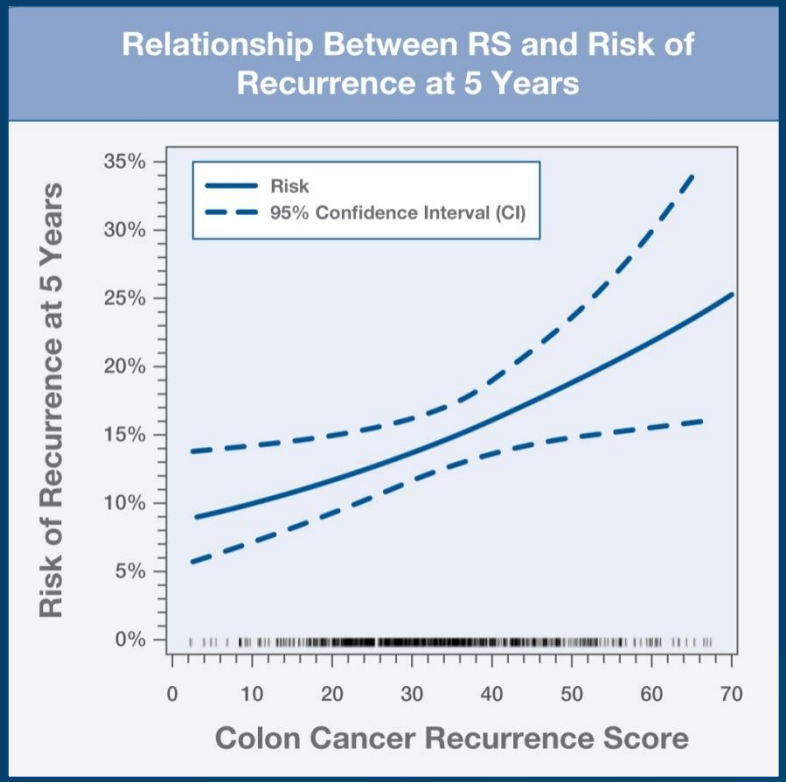
Reference Genes

ATP5E
GPX1
PGK1
UBB
VDAC2

Recurrence Score =
0.15 × Stromal Group
– 0.30 × Cell Cycle Group
+ 0.15 × GADD45B

O'Connell MJ, et al. *J Clin Oncol*. 2010;28:3937-3944.
Kerr D, et al. *J Clin Oncol*. 2009;27: abstract 4000.

CALGB 9581 Primary Analysis: Association of Continuous RS with Recurrence Risk



Variable	HR	95% CI	P value
RS per 25 units	1.52	(1.09, 2.12)	0.013

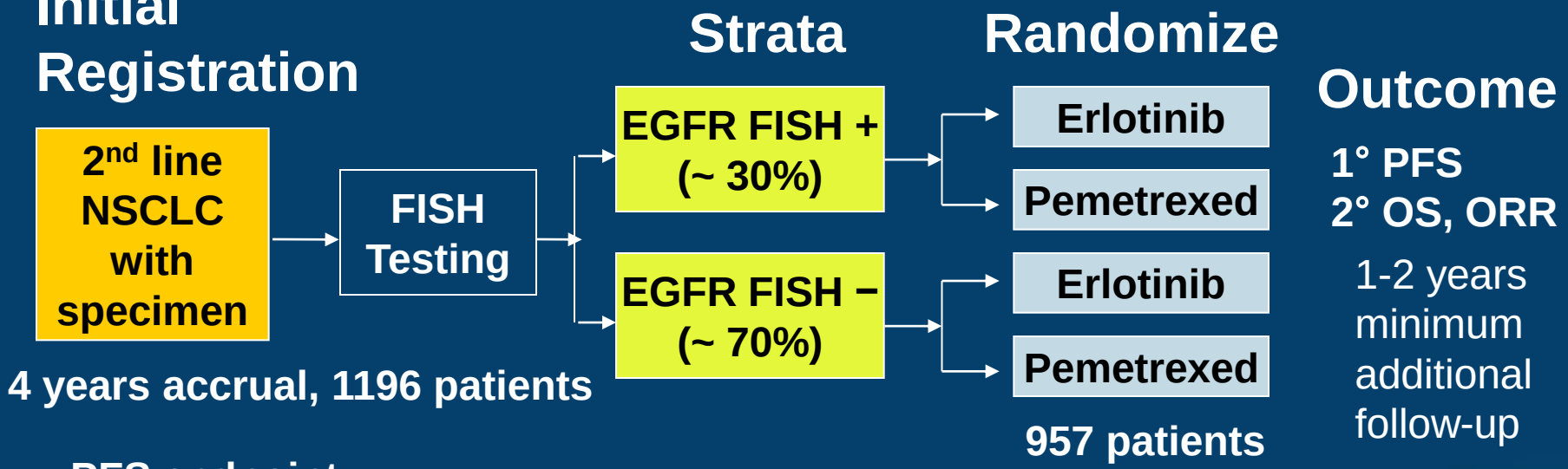
- The continuous RS was significantly associated with the risk of recurrence
- Strength of association consistent with QUASAR

Venook AP, et al. *J Clin Oncol*. 2011;29: abstract 3518.

Prospective Marker Validation Studies

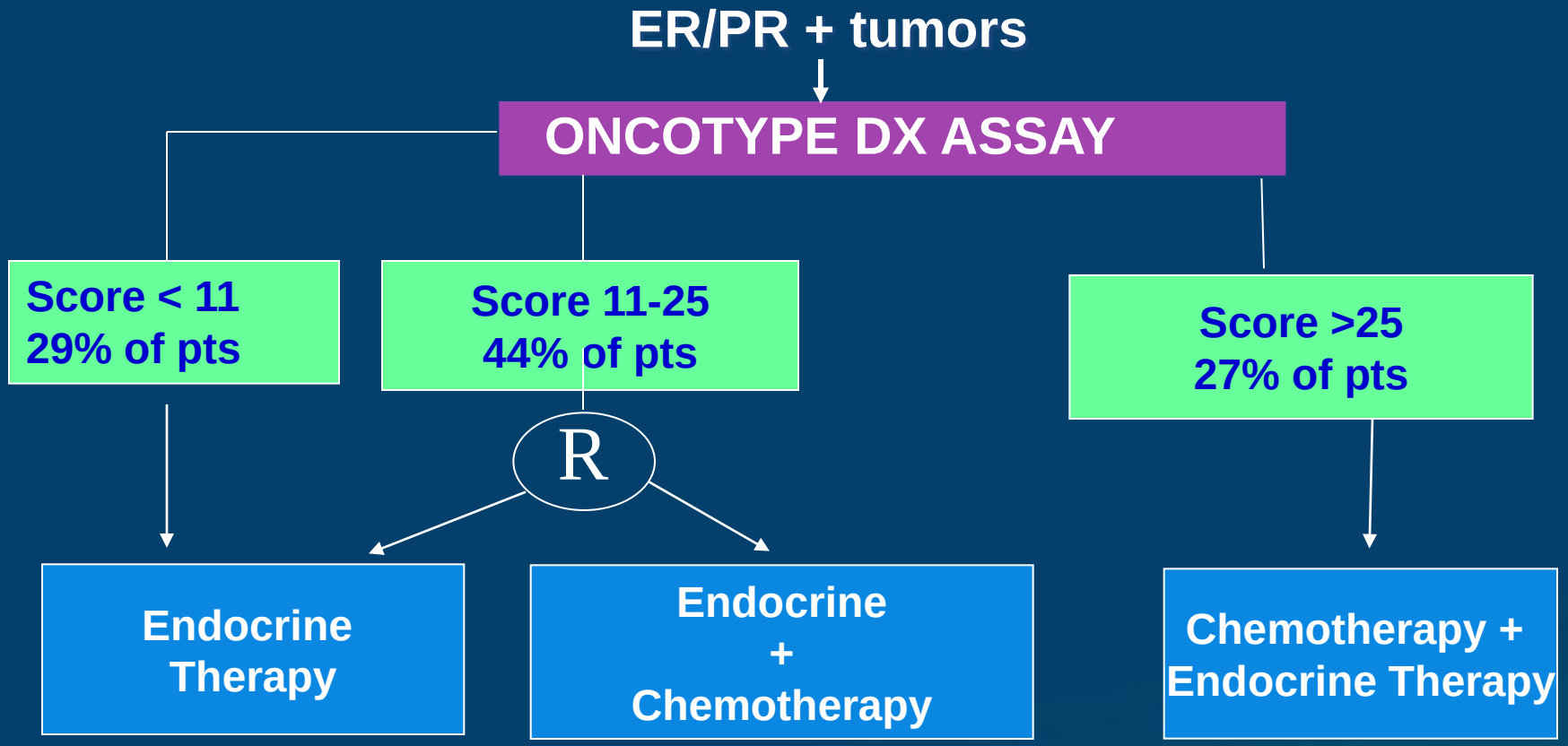
N0723: Predictive Marker Study Design

NCCTG (Study Chair: Alex Adjei) + CALGB, ECOG, SWOG, NCIC
Others: C-Path & industry partners, Pharma



- PFS endpoint
  - Less influenced by treatment crossover
  - Will require synchronized treatment schedules, independent blinded imaging review
- Power
  - 90% to detect 50% PFS improvement favoring erlotinib in FISH+, 2.5---3.75m
  - 90% to detect 30% PFS improvement favoring pemetrexed in FISH−, 1.92--2.5m
  - > 90% to detect interaction

TailoRx
NODE NEGATIVE BREAST CANCER STUDY

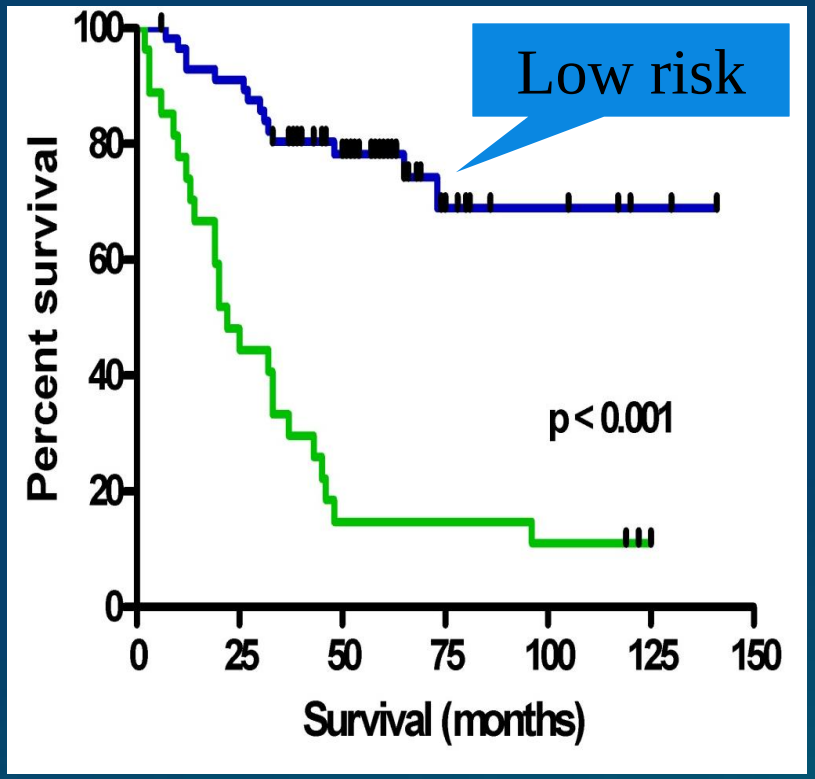


Accrual goal= 4800 randomized patients, 11000 screened

Non inferiority = decrease in 5 year DFS from 90 to 87% or less

CALGB 30506

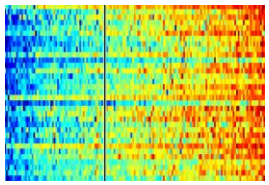
A randomized phase III trial to evaluate the potential utility of a genomic prognostic model to identify stage I non-small cell lung cancer patients as candidates for adjuvant chemotherapy



PRE-REGISTER

Surgery
Confirm:

- NSCLC
- N0
- tumor ≥ 1.7



REGISTER/RANDOMIZE

LMS<0.55, 64%

Observation

Chemotherapy
(choose 1 of the following 3):

1) Vinorelbine on d 1 & 8 and Cisplatin on d 1
2) Docetaxel on d 1 & Cisplatin on d 1
3) Gemcitabine on d 1 & 8 & Cisplatin on d 1

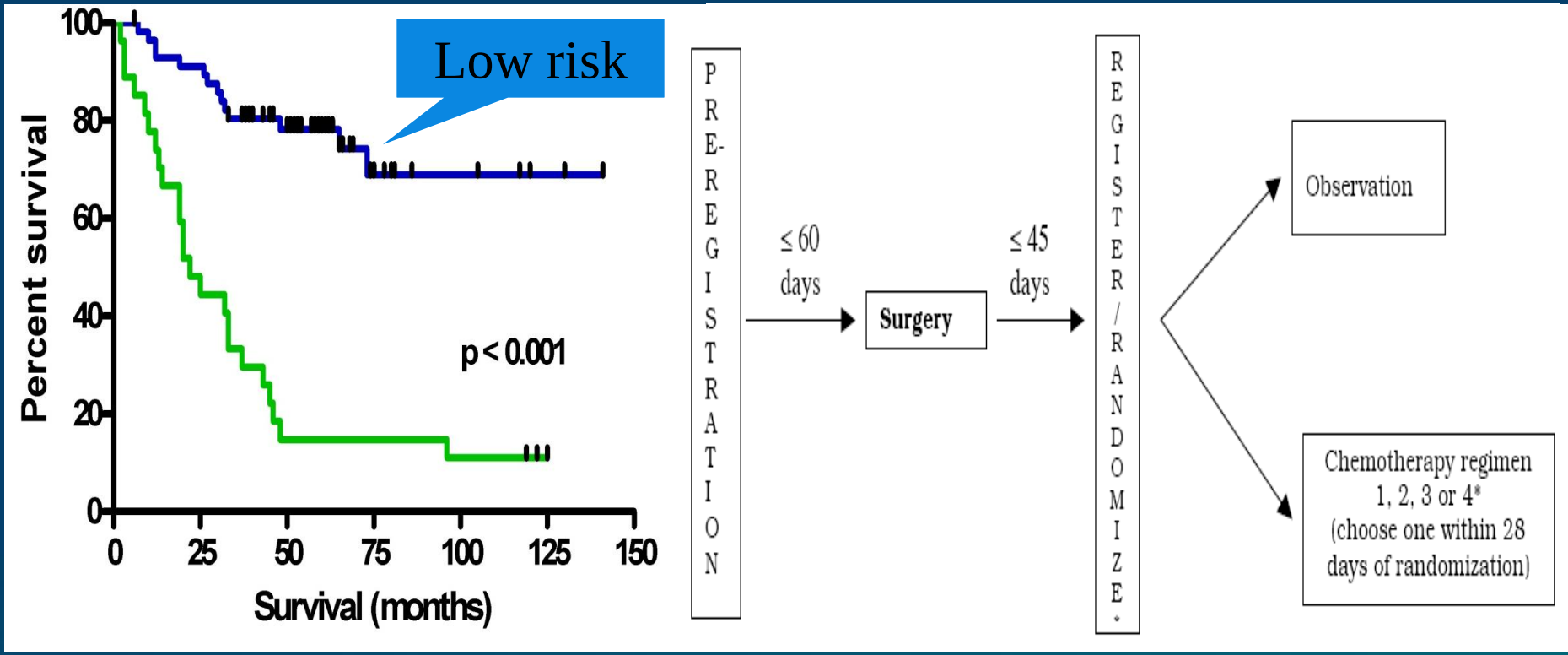
LMS≥0.55, 36%

N=1296

Potti A et al. N Engl J Med 2006;355:570-580

CALGB 30506

A randomized phase III trial to evaluate the potential utility of a genomic prognostic model to identify stage I non-small cell lung cancer patients as candidates for adjuvant chemotherapy



Potti A et al. N Engl J Med 2006;355:570-580

Obstacles to Biomarker Research in Cooperative Groups

- Adequacy of biospecimen/imaging collection
- Access to CLIA-certified labs
- Funding for biomarker studies
- Regulatory requirements
- Contractual agreements with commercial partners

Conclusions

- Cooperative groups have the capacity to conduct many types of biomarker studies, including formal validation trials
- Large numbers of patients are required for biomarker validation studies
- Commercial partners essential to meet regulatory requirements and support the costs of biospecimen analysis