

**BEXXAR<sup>®</sup> Therapeutic Regimen  
(Tositumomab and Iodine I 131  
Tositumomab)  
BLA 125,011**

**Post-marketing Commitments**

**Oncology Drugs Advisory Committee  
08 February 2011**

# Participants

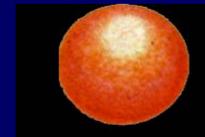
Perry Nisen, M.D. , Ph.D.	Senior Vice President, GSK Oncology
Rafael Amado, M.D.	Senior Vice President, GSK Oncology
Steven Stein, M.D.	Vice President, GSK Oncology
Thomas Lin, M.D., Ph.D.	Director Clinical Development, GSK Oncology
Christina Vleisides, D.C.	Director Clinical Development, GSK Oncology
Philip Witman, M.P.H, M.Phil.	Associate Director, Global Regulatory Affairs, GSK Biopharm and Oncology
Vanessa Williams, M.S.	Manager Statistics, GSK Oncology Biometrics and Epidemiology
Andrew Zelenetz, M.D., Ph.D.	Memorial Sloan Kettering Cancer Center Chair, NCCN Lymphoma Committee
Oliver Press, M.D., Ph.D.	Fred Hutchinson Cancer Research Center Principal Investigator, SWOG S0016
Michael LeBlanc, Ph.D.	Fred Hutchinson Cancer Research Center Statistician, SWOG S0016

# Presentation Overview

- The BEXXAR Therapeutic Regimen
- U.S. Approvals for BEXXAR
- Post-marketing Commitments
- Confirmatory study reportable under Subpart E

# BEXXAR Therapeutic Regimen

- Tositumomab
  - Murine IgG anti-CD20 mAb
  - Binds to normal and malignant B cells
- Iodine-131 radioisotope
  - Dosimetric measurement of gamma emission allows calculation of patient's clearance of BEXXAR
  - Patient-specific I-131 activity (mCi) to deliver fixed radiation dose (cGy)



# BEXXAR Therapeutic Regimen Treatment Schedule

Thyroprotection: Day -1 through 14 days post-therapeutic dose

**Day 0**

## Dosimetric step

450 mg Tositumomab

5 mCi Iodine I 131  
Tositumomab (35 mg)

Whole  
body scans  
x 3\*

- Day 0
- Day 2, 3, or 4
- Day 6 or 7

**Day 7-14**

## Therapeutic step

450 mg Tositumomab

mCi dose of Iodine I 131  
Tositumomab (35 mg)

Deliver 65-75 cGy total body  
dose

~ 200 patients received BEXXAR outside of clinical trials last year

# U.S. Approvals for BEXXAR

16 May 1994

Orphan Drug designation granted

**Full approval**

27 June 2003

Treatment of rituximab-refractory, low-grade, and transformed non-Hodgkin's lymphoma (NHL)

- Based on pivotal trial CP-97-012 and four supportive trials
- 10 Post-marketing Commitments

**Accelerated approval**

22 December 2004

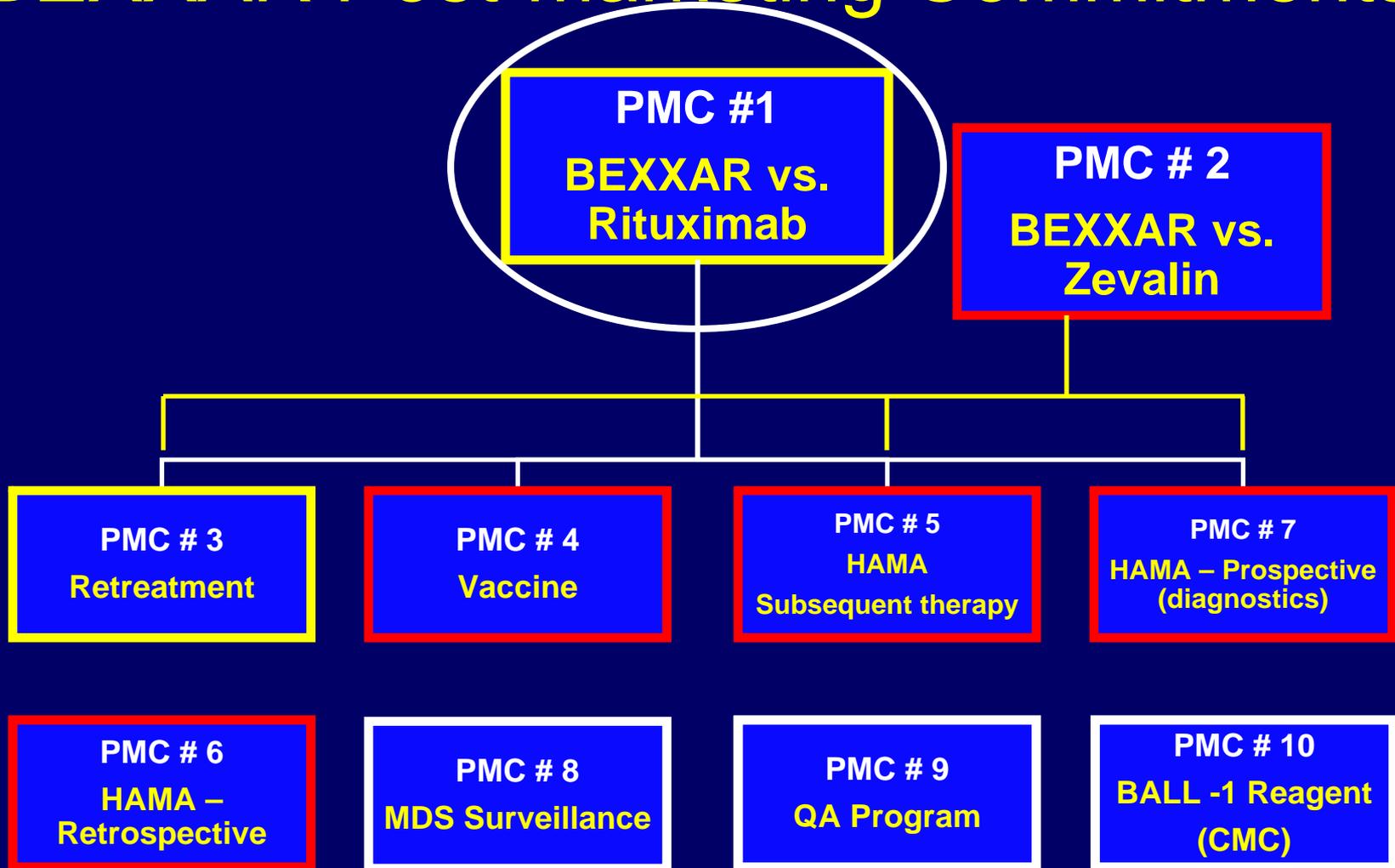
Expanded indication for the treatment of **relapsed** and refractory, low-grade, and transformed follicular lymphoma

- Based on pivotal trial RIT-II-004 and three supportive trials
- Same 10 Post-marketing Commitments
- PMC #1 now reportable under subpart E

# Pivotal Studies: Clinical Efficacy Results

	Study CP-97-012 (n = 40) (Study 1 from PI)	Study RIT-II-004 (n = 60) (Study 2 from PI)
Patient Population	Rituximab-refractory	Chemo-refractory
Overall Response Rate	68%	47%
Response Duration, Median	16 months	12 months
CR Rate	33%	20%
CR Duration, Median	Not reached	47 months
Duration of Follow-up, Median	26 months	30 months

# BEXXAR Post-marketing Commitments



## Legend

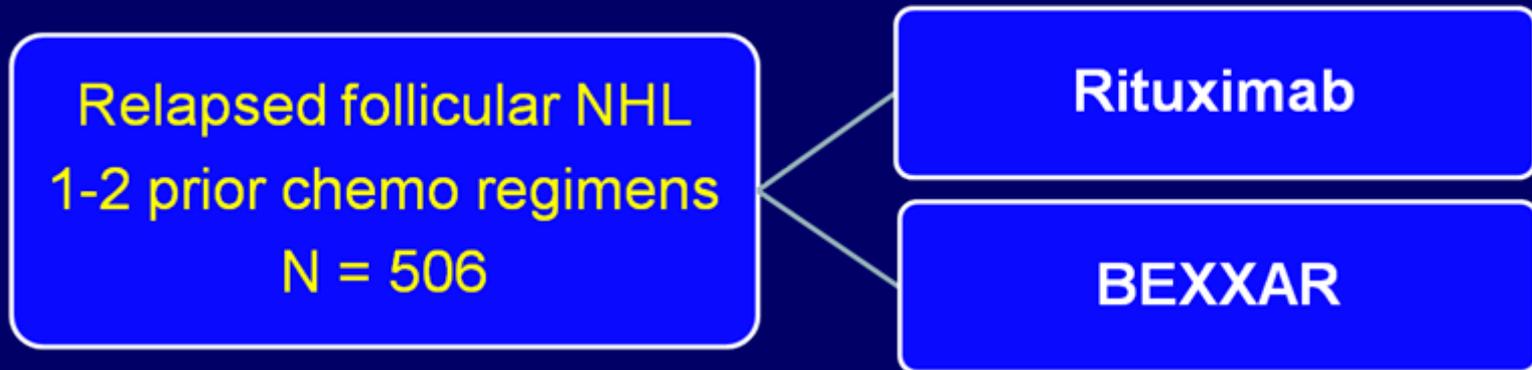
Fulfilled / Ongoing

Released

Delayed

# Post-marketing Commitment 1

## Initially proposed study: SB-393229/028



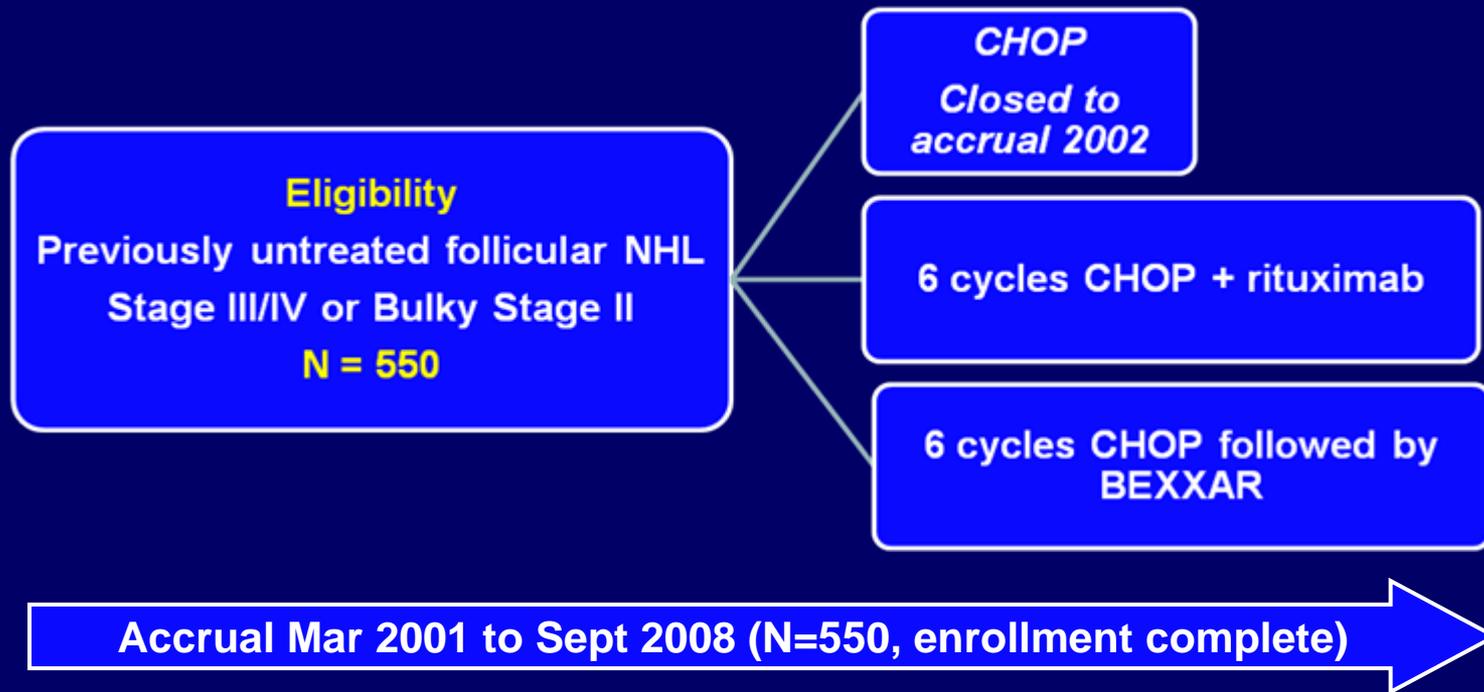
- Only 15 patients were enrolled over 30 months
- October 2005 – FDA concurred with GSK that the study was not feasible to conduct, GSK to propose alternative
  - *FDA acknowledged that GSK “employed appropriate due diligence in working to accomplish the post-marketing commitments”*

# Obstacles to Accrual to 028 Study

Objections raised by potential study sites:

- Change in standard of care
  - Reluctance to randomize patients to rituximab-only arm
- Requirement for a gamma camera equipped with a high-energy collimator ( $\geq 364$  KeV)
  - Per US Prescribing Information
- Other
  - Logistical issues including specialized training
  - Competing studies in the relapsed FL population

# Proposed Study to Fulfill PMC #1: SWOG S0016



## Objectives

- Primary endpoint: to compare PFS of R-CHOP vs. CHOP/ BEXXAR
- To compare overall survival
- To evaluate response rates
- To evaluate toxicities
- To compare molecular remission rates
- To determine incidence and time to HAMA positivity

# Rationale to Fulfill PMC #1 with S0016

- More clinically relevant than originally proposed study
- Phase III study vs. R-CHOP, the most commonly used frontline treatment for follicular lymphoma
- Ongoing study which has now completed accrual
  - Results to report within next year
- Not possible to conduct another study of BEXXAR vs. rituximab after S0016 was initiated

# Interactions with FDA to Resolve PMC #1

- GSK proposed S0016 to fulfill PMC #1
- Discussed S0016 in three FDA meetings
- FDA agreed in principle to S0016 study design
- A few outstanding issues remain

# Proposed Solutions to Outstanding Issues

- Collecting CT scans
  - Requested by FDA for independent review
  - CRO engaged, scan collection not feasible
  - Investigator assessment of primary endpoint using local radiology measurements
- Collecting quantitative laboratory data
  - Requested by FDA for safety assessment
  - SWOG to collect data and transfer to GSK
- Data validation / monitoring
  - Critical variables identified for quality check of database vs. CRFs

# Conclusions

- GSK pursued originally agreed study for PMC #1 (BEXXAR vs. rituximab) with due diligence
  - Study closed due to poor accrual and lack of feasibility
- GSK proposed SWOG S0016 to fulfill PMC #1
  - SWOG S0016 is relevant to current standard of care
  - Study has finished accrual, results anticipated within 1 year
- Division has agreed in principle to S0016 study design but resolution of outstanding issues is required

# Back-up Slides

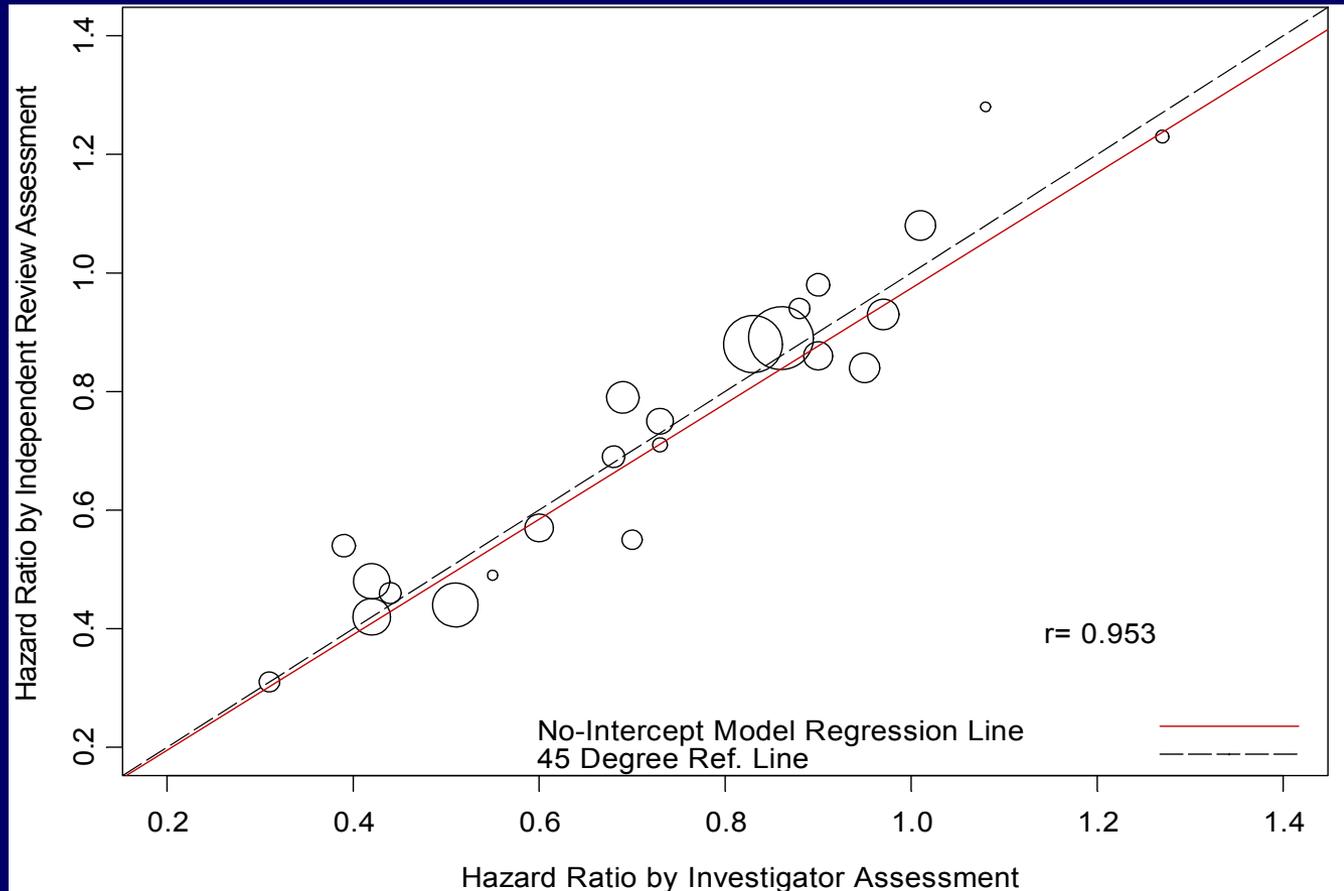
# PMC #1 to Confirm Clinical Benefit: SB-393229-028

## Commitment timelines

Milestone	Assigned Date	Actual Date
Full (Initial) Approval	27 June 2003	
Submit Special Protocol Assessment	15 August 2003	15 August 2003
SPA accepted by FDA	30 September 2003	
First patient enrolled	02 January 2004	05 October 2004
Final patient enrolled	03 March 2006	06 April 2006
Study completion (LSLV)	03 September 2007	23 February 2009
Submit final study report	09 May 2008	CTRS posted

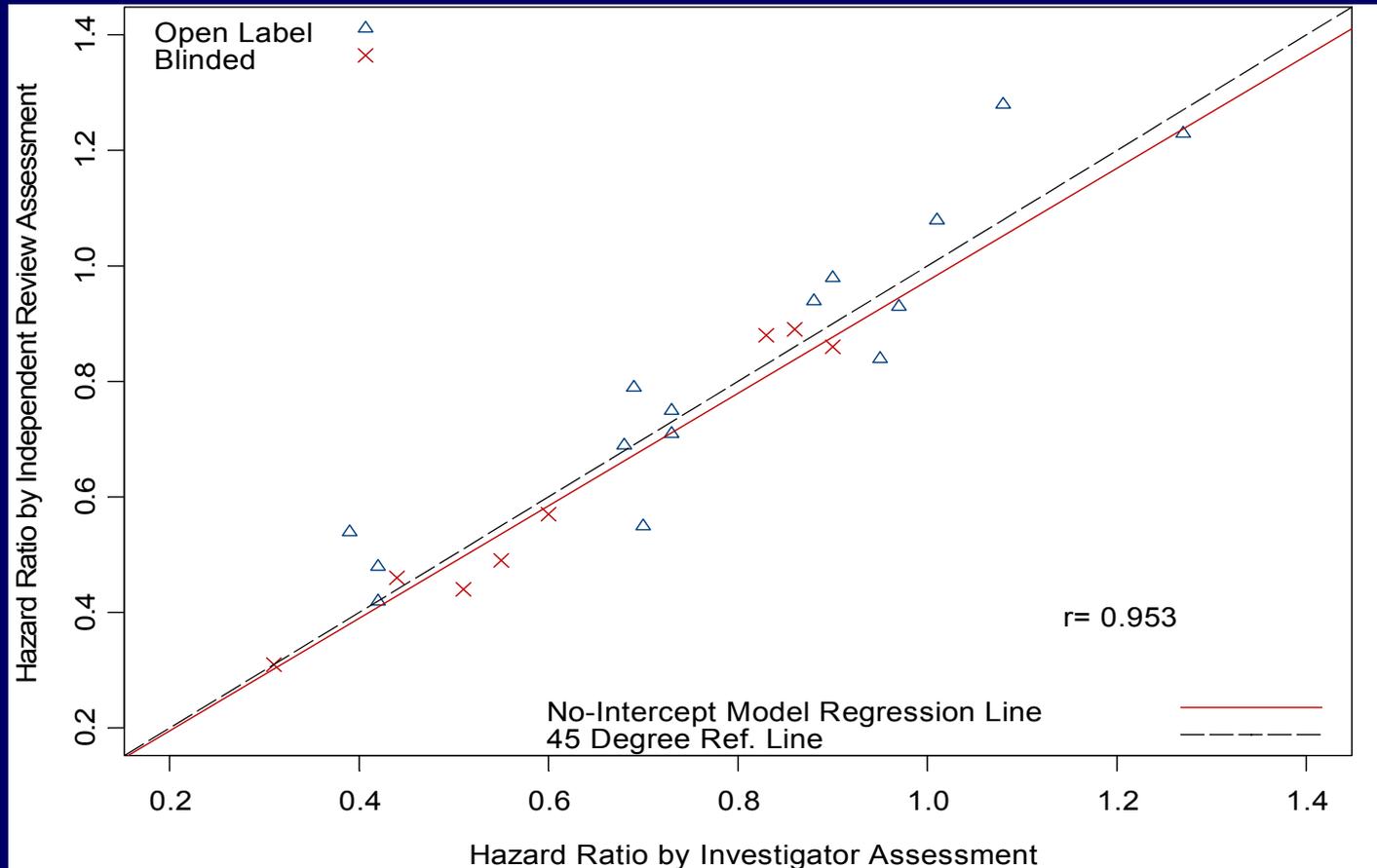
- Primary endpoint = event free survival
- Enrollment:
  - **Expected duration:** 26 months to enroll 506 subjects
  - **Actual duration:** 30 months to enroll 15 subjects

# Estimates of Tx effect are Strongly Correlated



HR ratio (95% CI): 1.02 (0.96,1.07)

# Effect of Blinding



\*Brookings Institute Conference on Clinical Cancer Research, September 14, 2009