Design Elements of Clinical Trials Involving Biomarkers

A Biostatistician's Perspective

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Presenter's Conflict of Interest

- Gary Clark is a full-time employee of Array BioPharma Inc. and a former employee of OSI Pharmaceuticals, Inc., the company that developed erlotinib (Tarceva®), an EGFR TK inhibitor, in partnership with Genentech, Inc. and F. Hoffman-La Roche, Ltd.
- Gary Clark owns stock and has stock options in Array BioPharma Inc.
- However, the presentation today reflects the personal opinions of Gary Clark and not necessarily those of Array BioPharma Inc., OSI Pharmaceuticals, Inc. or its partners

Suppose we have a new drug and have been asked to design the first clinical trials.

What types of clinical trials should we design?

What questions should we ask before designing studies?

Questions

- What is the drug supposed to do?
  - eg, Inhibit a single molecular pathway? Inhibit multiple pathways? Interfere with an important process required by a cancer cell to survive or metastasize?
- How is it supposed to work?
  - eg, Small molecule? Antibody? Vaccine? Cytotoxic? Cytostatic? Single agent? In combination?
- Is there a target product profile?
- What preclinical data are available?
  - eg, Pharmacokinetics? Pharmacodynamics? Toxicity profile?
- What do we know about this class of agents?

Study Designs for a Targeted Therapy

- Suppose we have a new targeted therapy designed to be effective in patients with Marker X
- Suppose dose finding studies will be conducted and we will have a recommended Phase II dose and schedule

What types of clinical trials should we design?

Targeted Therapy

- Assumes we know the target
- Assumes we know how to measure the target
- Assumes we have an agent that blocks or interferes with the target
- Assumes the agent is selective and specific for the target

Patient Selection

- Should we include unselected patients in initial studies?
- Should we focus on specific tumor types in which the prevalence of the target is high?
- Should we select specific patients based on biomarker results?
  - Is a companion diagnostic test available?
  - What is required to “validate” the test?
  - When do we need a “validated” test?

Prognostic vs. Predictive Factors

Prognostic Factor: Any measurement that is associated with clinical outcome in the absence of therapy, or with the application of a standard therapy that all patients are likely to receive (a predictor of the natural history of the tumor).

Predictive Factor: Any measurement associated with response or lack of response to a particular therapy, where response can be defined using any of the clinical endpoints commonly used in clinical trials (eg, ER or HER2 for patients with breast cancer).

Clark GM. Breast Cancer Res Treat 1994; 30:117-26 & Mol Oncol 2008; 1:406-12

Clinical Trial Study Designs

If we are confident that the therapy will not work in Marker-negative patients

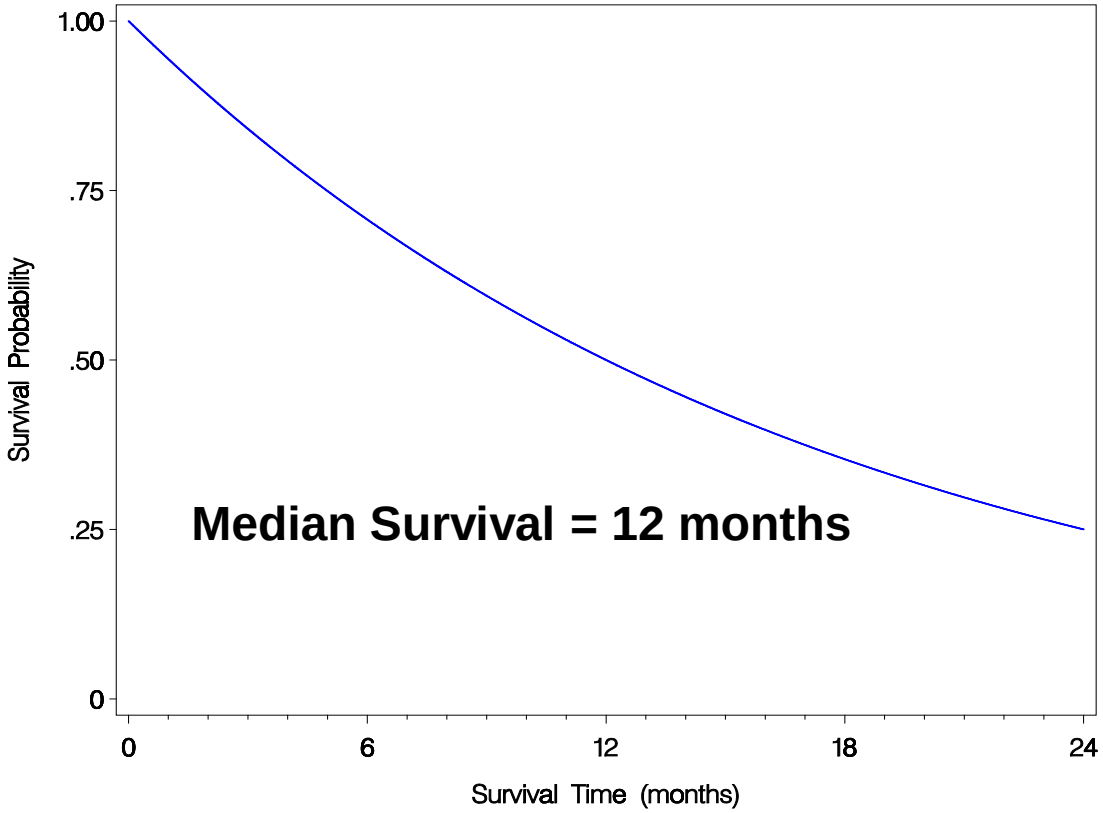
AND

We have a validated assay that can reliably assess the status of the Marker

THEN

A single-arm study in Marker + patients might make sense

Marker + Patients Treated with Targeted Therapy



- **Survival curve is influenced by prognostic effects of Marker X**
- **Cannot determine if Targeted Therapy confers meaningful benefit over Standard Therapy in this Marker + subgroup**
- **Cannot assess prognostic value of Marker X**
- **Cannot assess predictive value of Marker X**

Clinical Trial Study Designs

What if the therapy works a little bit in Marker-negative patients?

OR

What if the marker is prognostic?

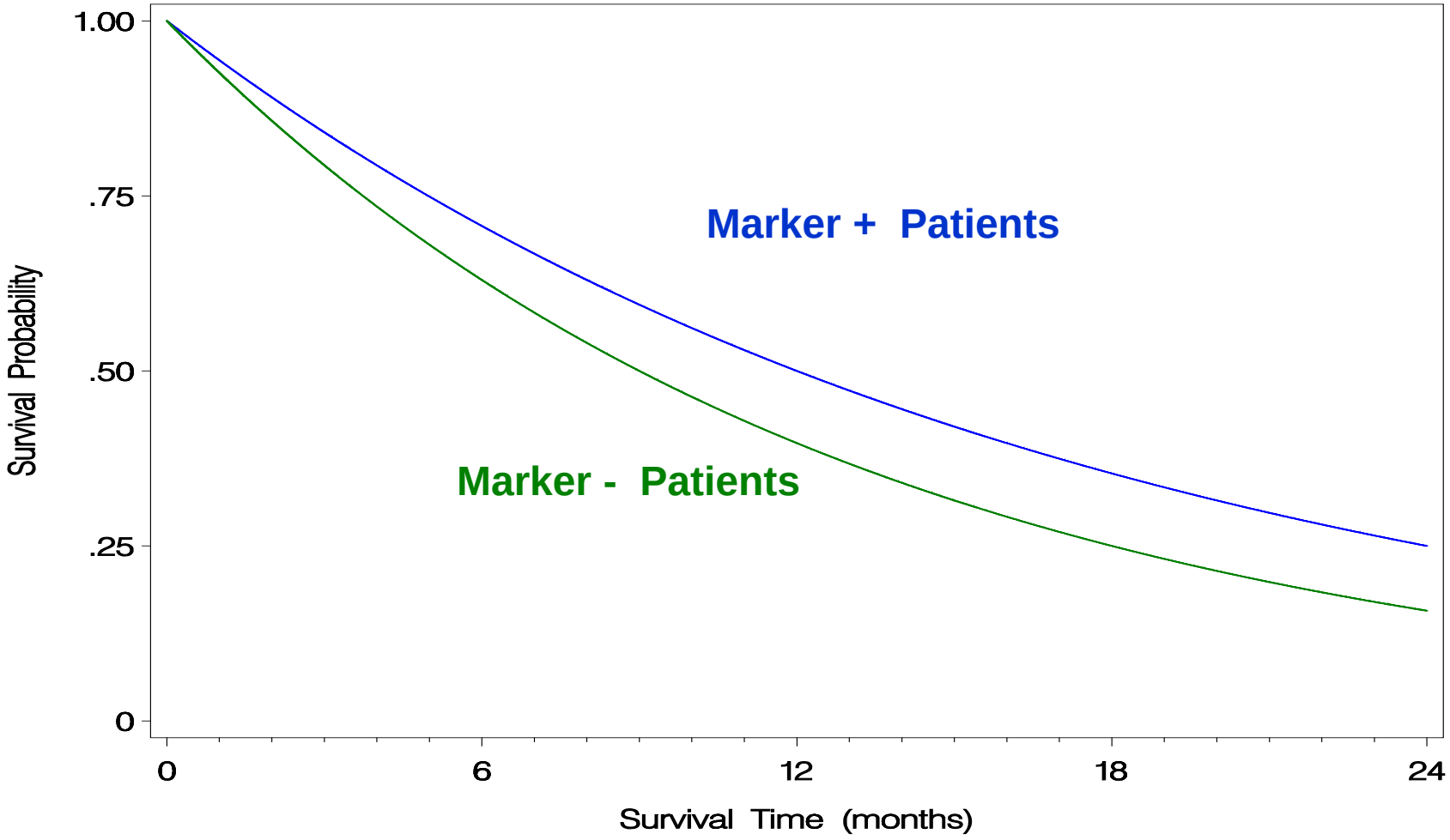
Perhaps a two-arm study would be better

Two-arm Study Designs

- Can we study unselected patients treated only with the targeted therapy?
  - *compare Marker + vs. Marker – patients?*

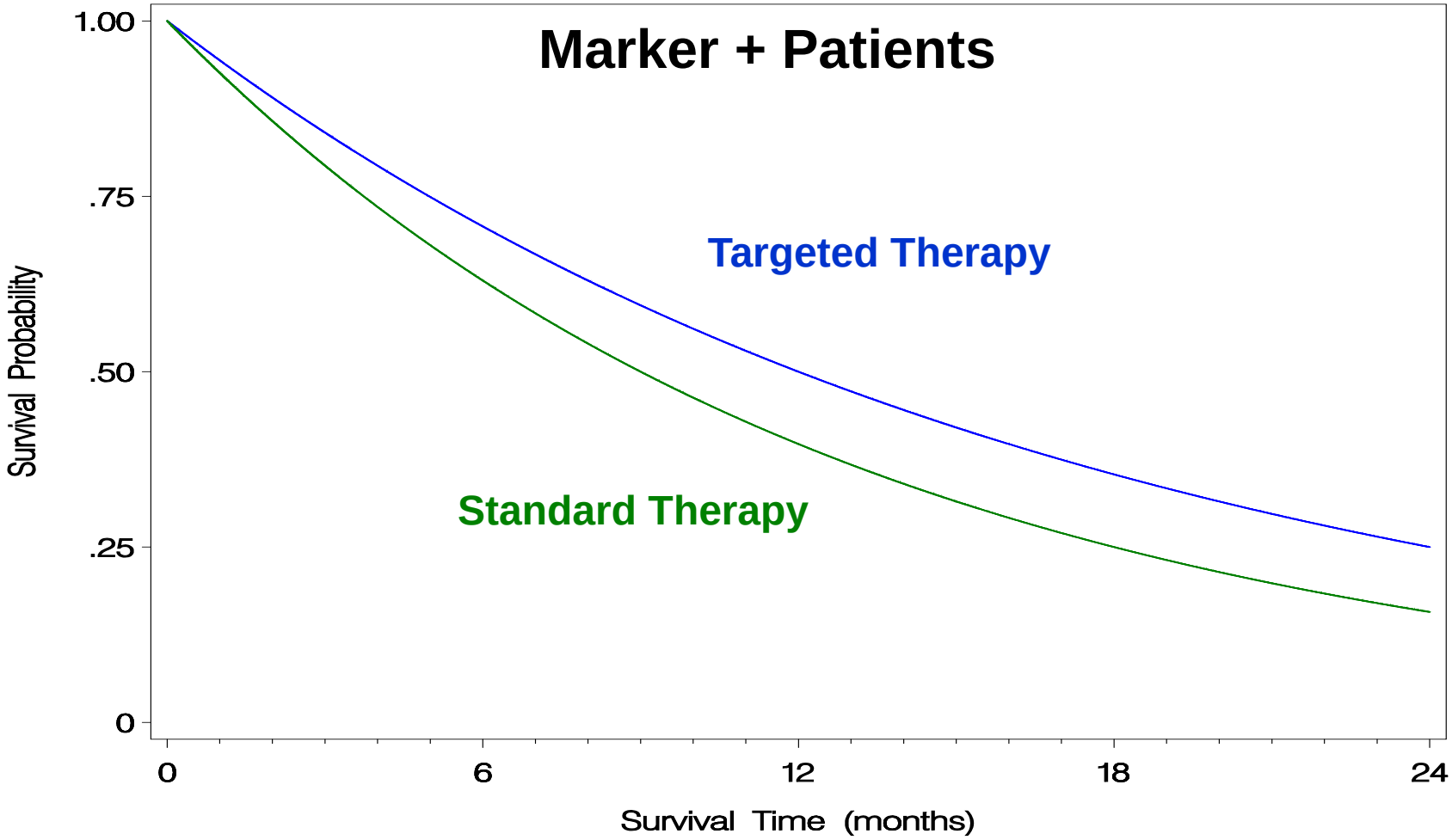
- Can we study an enriched population only?
  - *compare Targeted therapy vs. Standard therapy?*

Can we study unselected patients treated only with the targeted therapy?



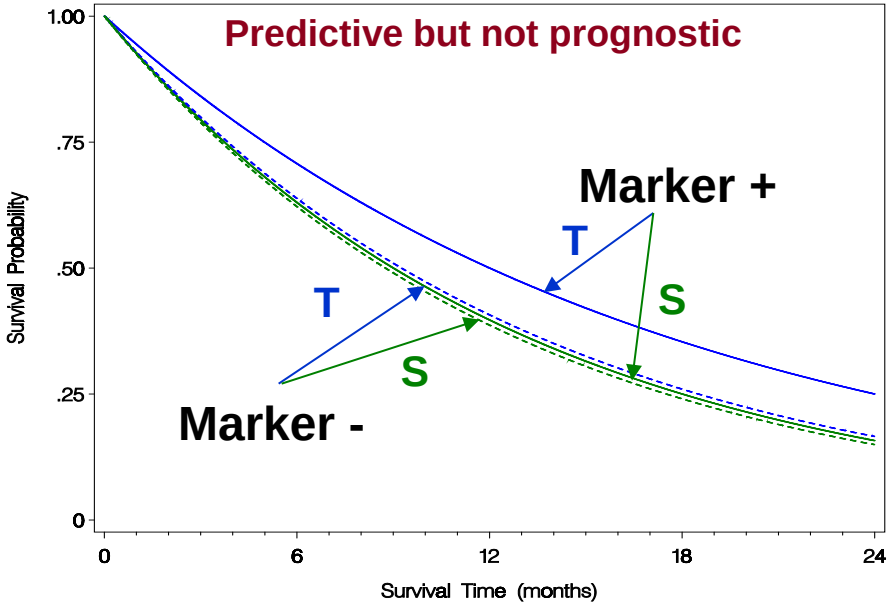
We really need a control group!

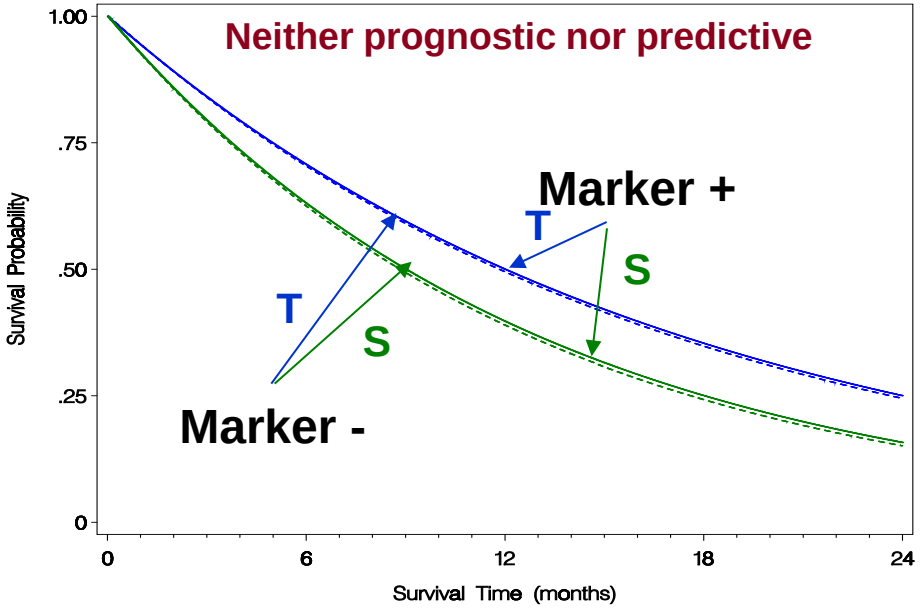
Can we study an enriched population only?

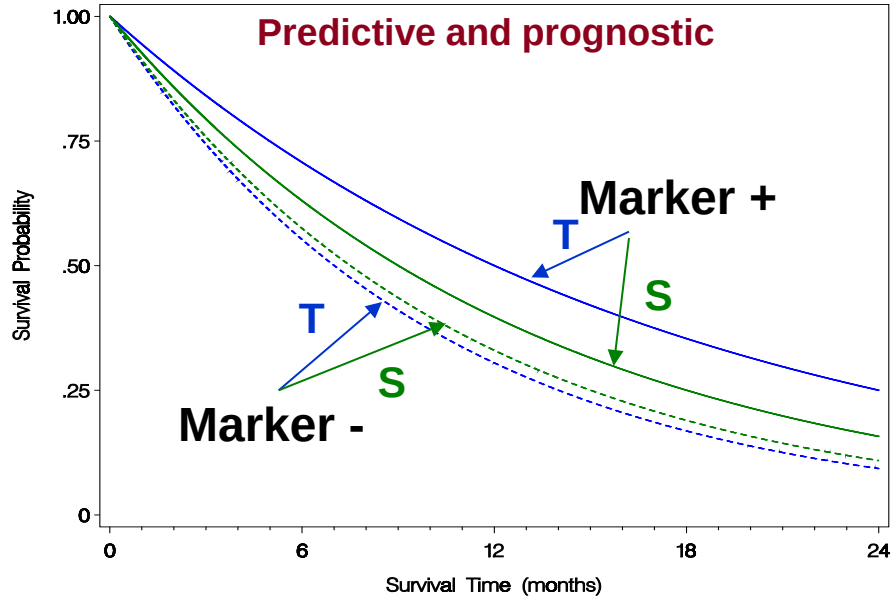


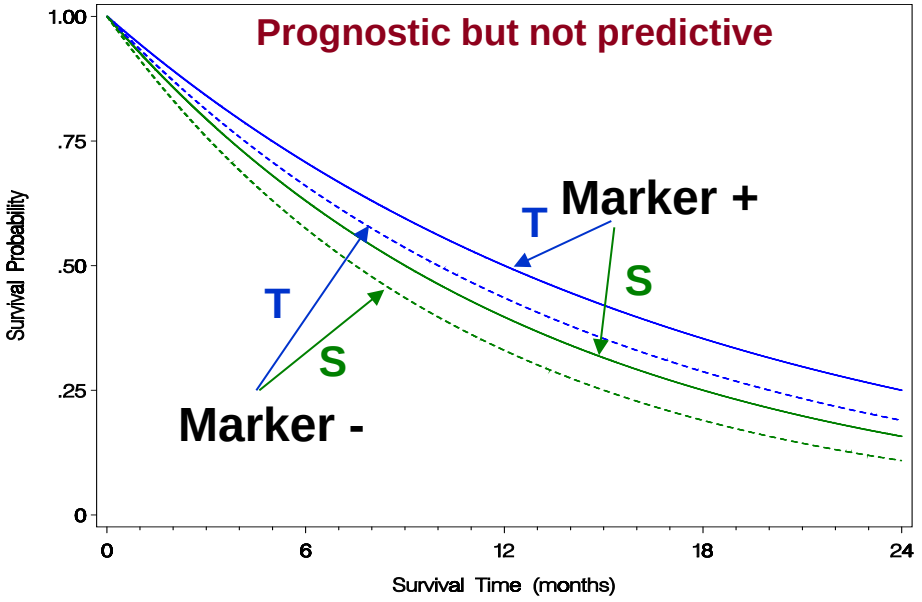
. . . only if we will be satisfied with half of an answer.

Unselected Patients

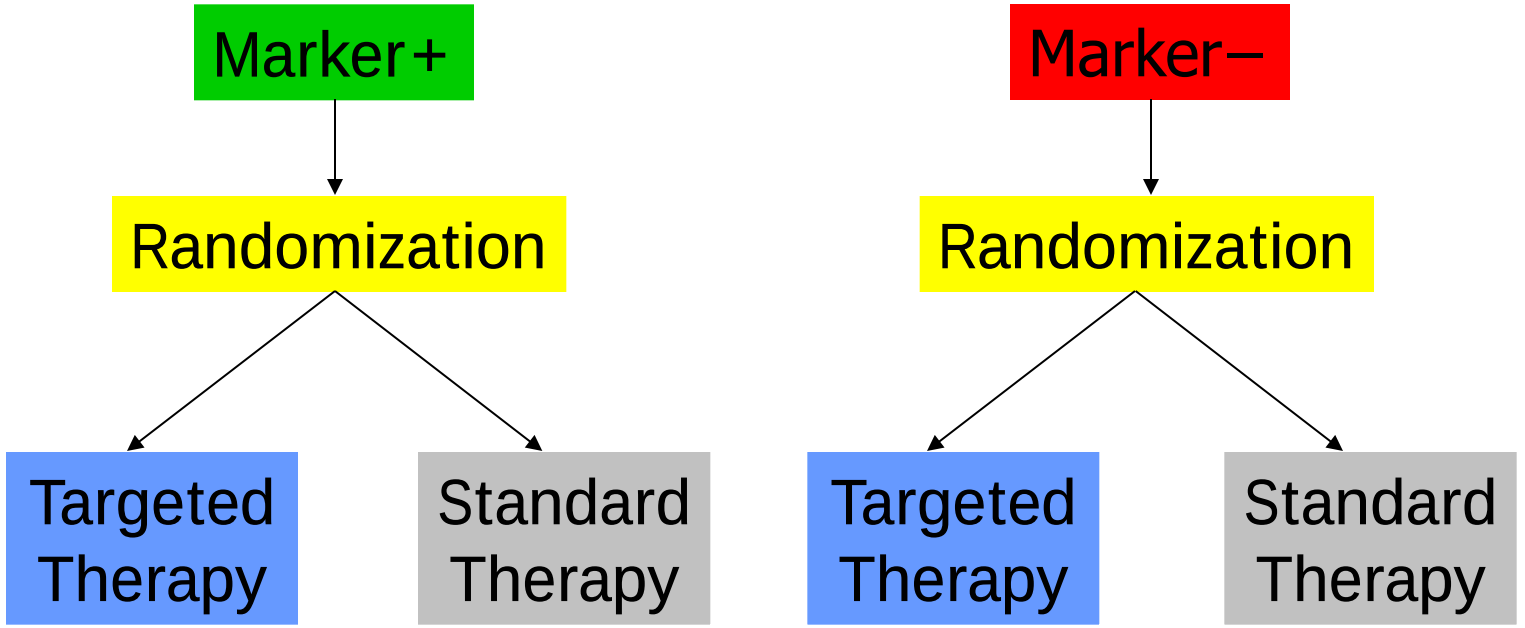








The most informative design



But, adaptive designs might be more efficient in certain scenarios

Is the issue of prognostic vs. predictive really a problem in practice?

Shah et al. *Practical management of patients with non-small-cell lung cancer treated with gefitinib*.

J Clin Oncol 2005; 23:165-74

Table 1: Pretreatment clinical factors that can or cannot predict gefitinib sensitivity

Factors predicting sensitivity to gefitinib

- Never smoking cigarettes
- Presence of bronchiolalveolar features in pathologic specimens
- Female sex
- Born in eastern Asia

Factors that do not predict sensitivity to gefitinib

- Type of prior chemotherapy
- Number of prior chemotherapy regimens
- Presence or intensity of EGFR staining in pathologic specimens determined by immunohistochemistry

Birnbaum A, Ready N. *Gefitinib therapy for non-small cell lung cancer.*
Curr Treat Options Oncol 2005; 6:75-81

"Nonsmokers, women, and patients with adenocarcinoma are more likely to have major objective responses than other patients."

"It is reasonable to move gefitinib into second-line therapy for patients who are known to have a tumor that is more likely to respond to gefitinib. Also, I would treat such patients with gefitinib as first-line therapy on an appropriate clinical trial approved by the Institutional Review Board (IRB)."

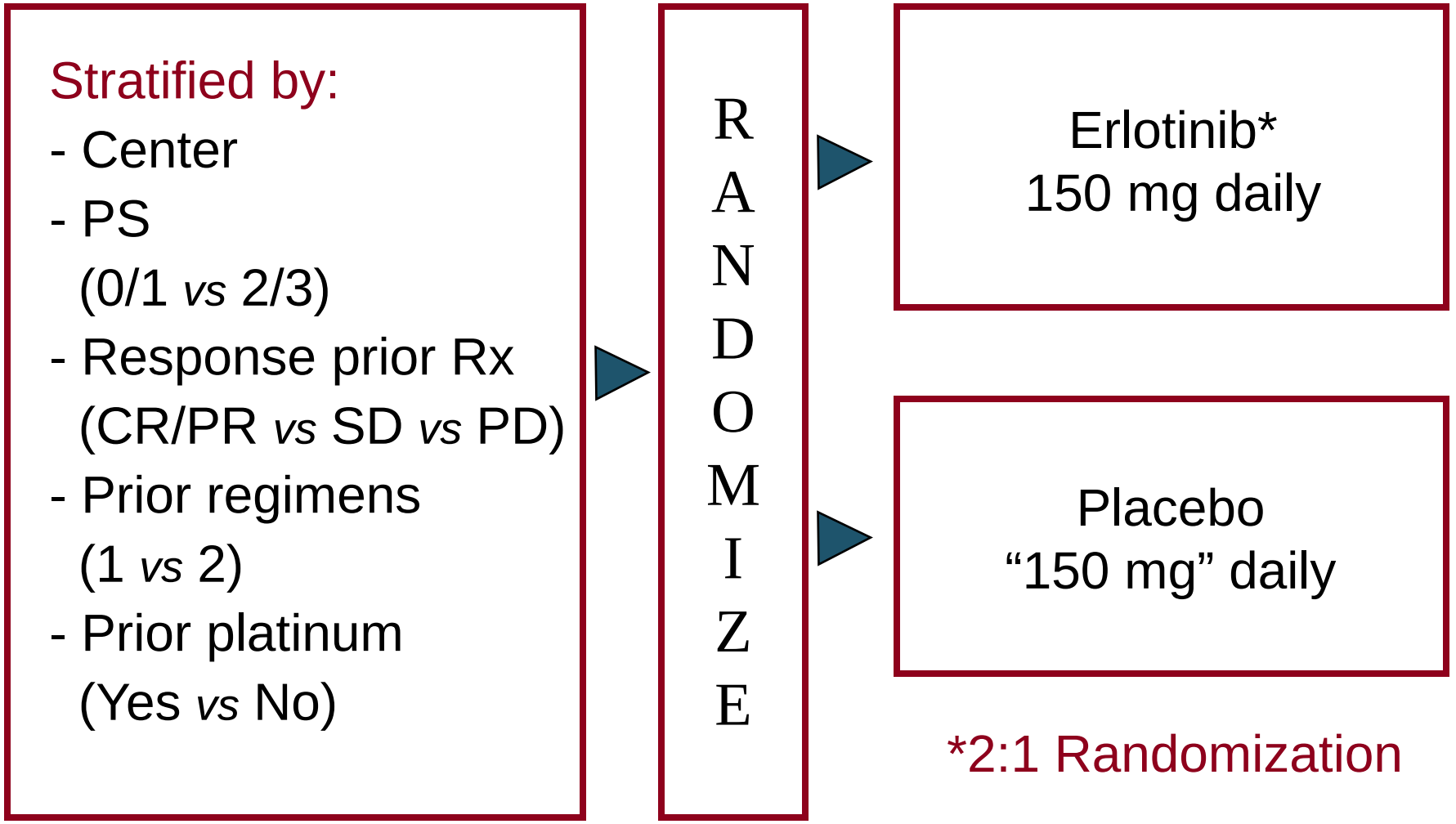
These conclusions were based on randomized Phase II trials of Gefitinib

- Designed to evaluate two doses of gefitinib
- No control group
- Primary endpoints: tumor response and symptom benefit

Would these conclusions still be true if these clinical trials had included a control group?

Would these conclusions still be true if survival had been the primary endpoint?

NCIC CTG BR.21 Schema

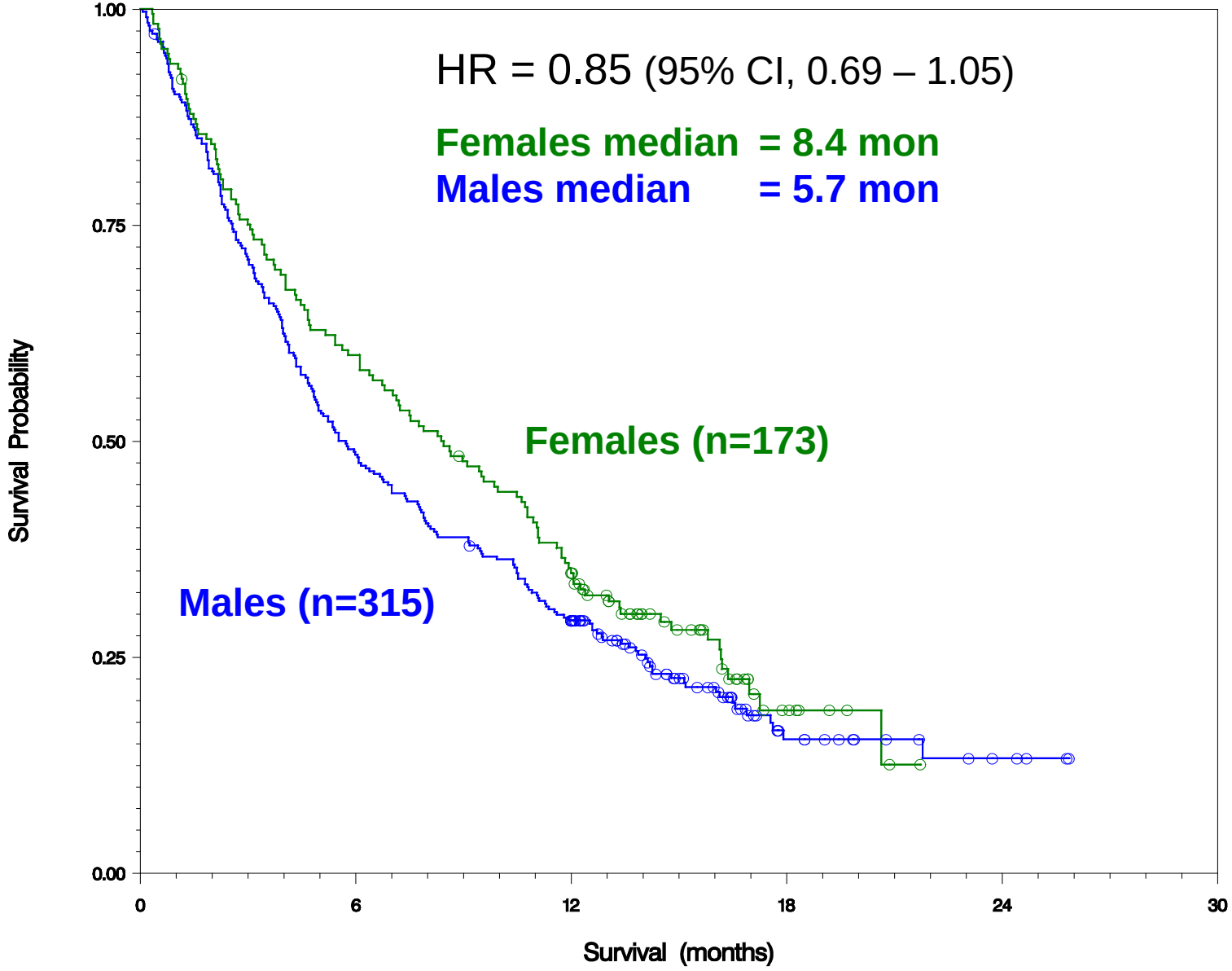


Shepherd FA et al. NEJM 2005; 353:123-32

Response Rates in Selected Subsets for gefitinib(Iressa®) and erlotinib (Tarceva®)

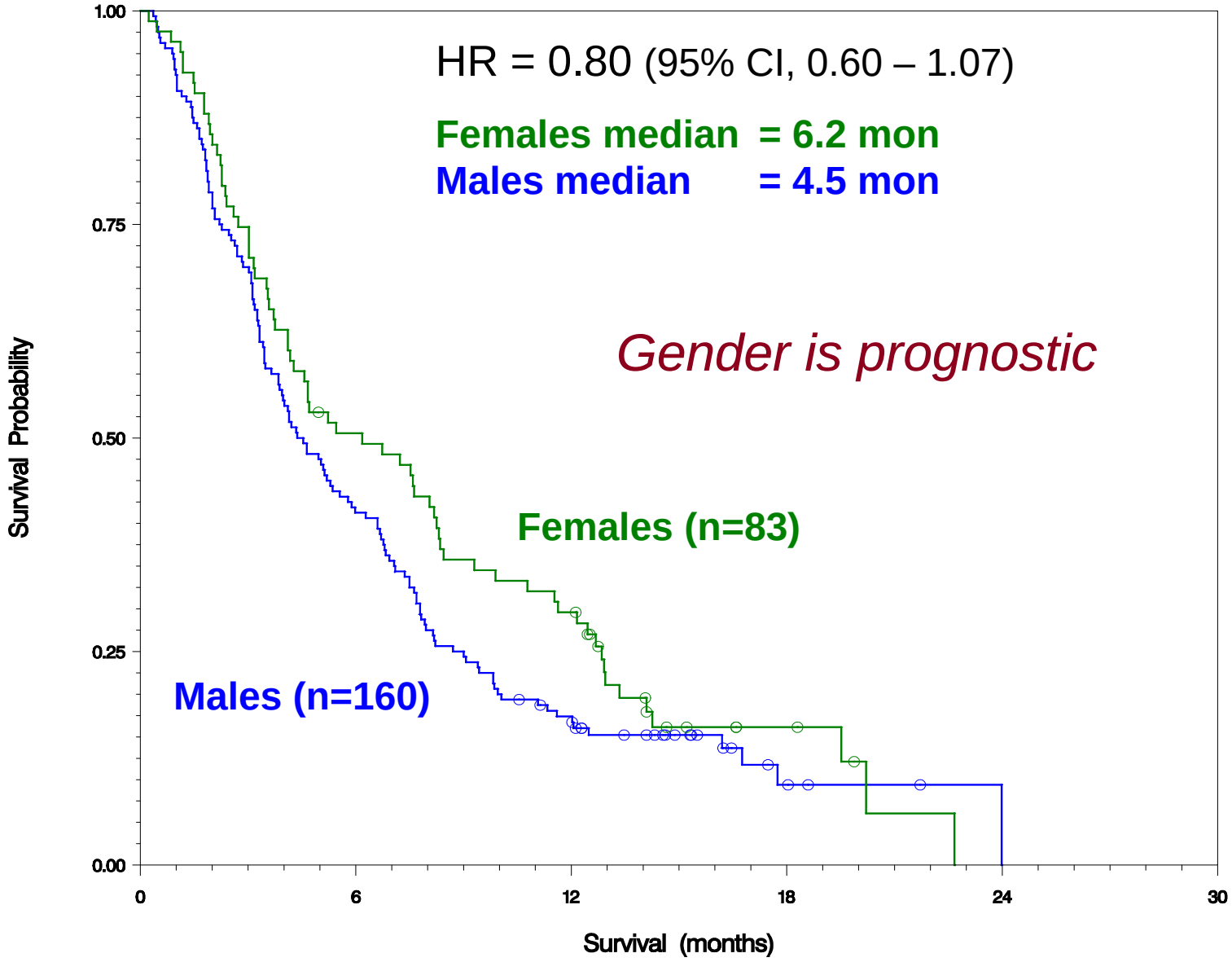
Subset	Gefitinib Iressa® Package Insert (250mg and 500mg combined)	Erlotinib NCIC Study BR.21 (150 mg)
Females	17.5%	14.4%
Males	5.1%	6.0%
Adenocarcinoma	12.4%	13.9%
Other histologies	6.7%	4.5%
Nonsmokers	29.4%	24.7%
Previous/Current Smoker	4.6%	3.9%

BR.21 Erlotinib Arm: Survival by Gender



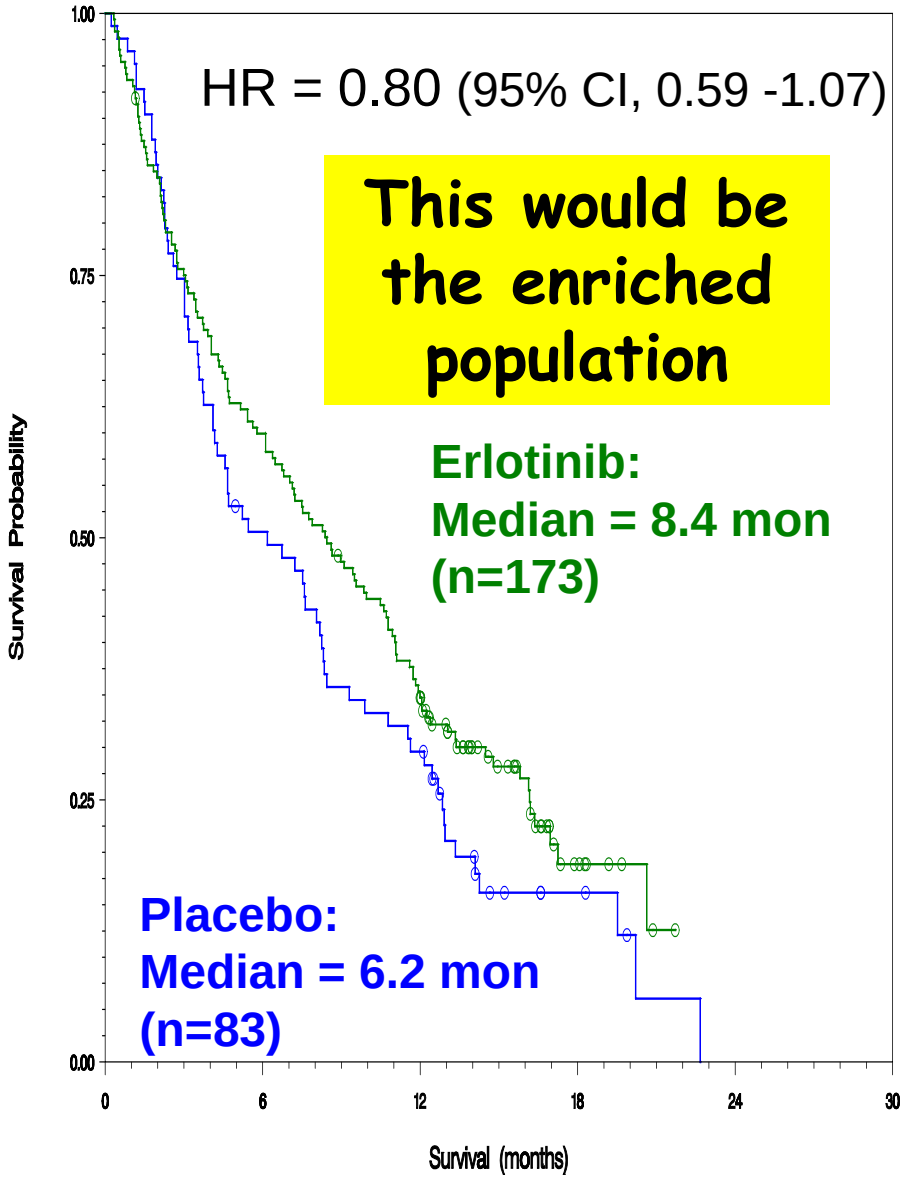
Clark GM. Mol Oncol 2008; 1:406-12

BR.21 Placebo Arm: Survival by Gender

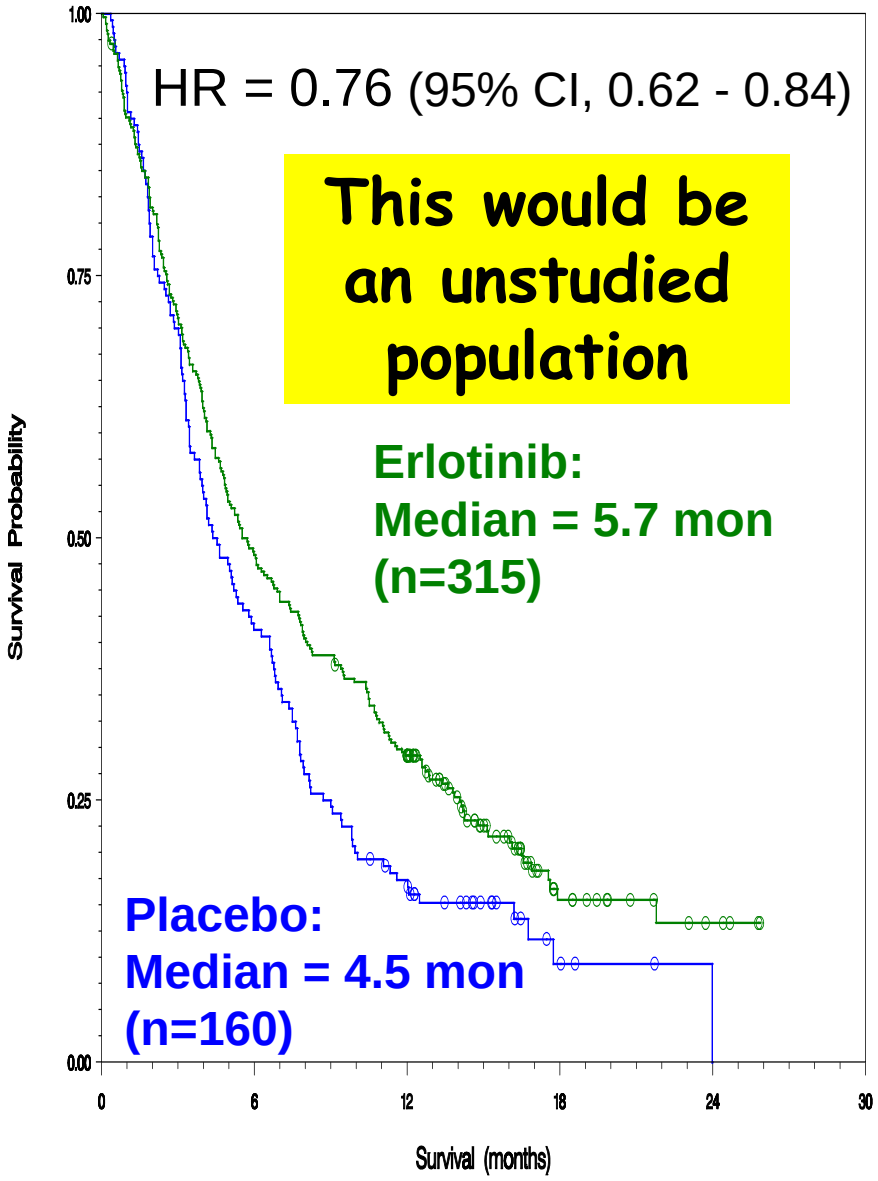


Clark GM. Mol Oncol 2008; 1:406-12

Females

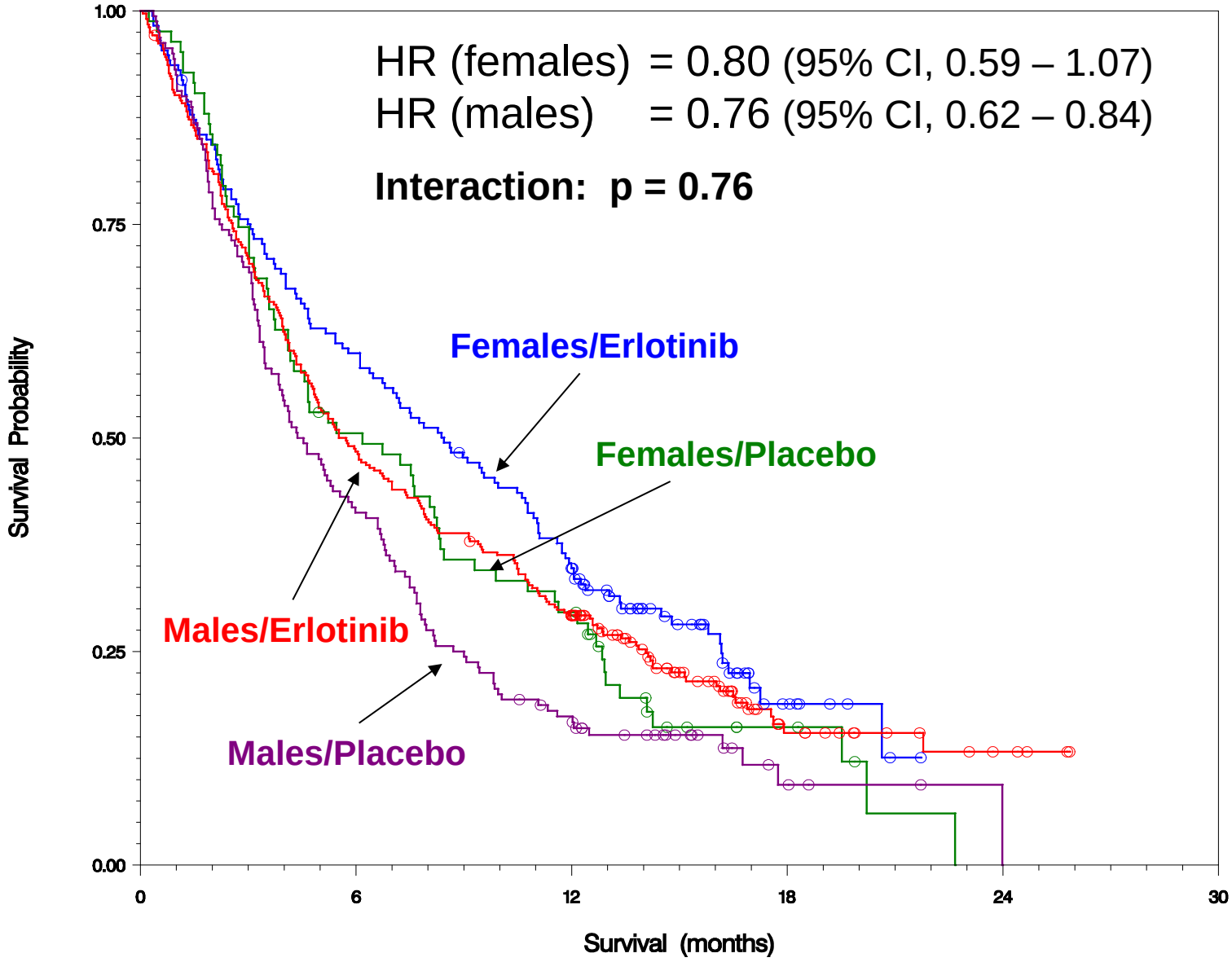


Males



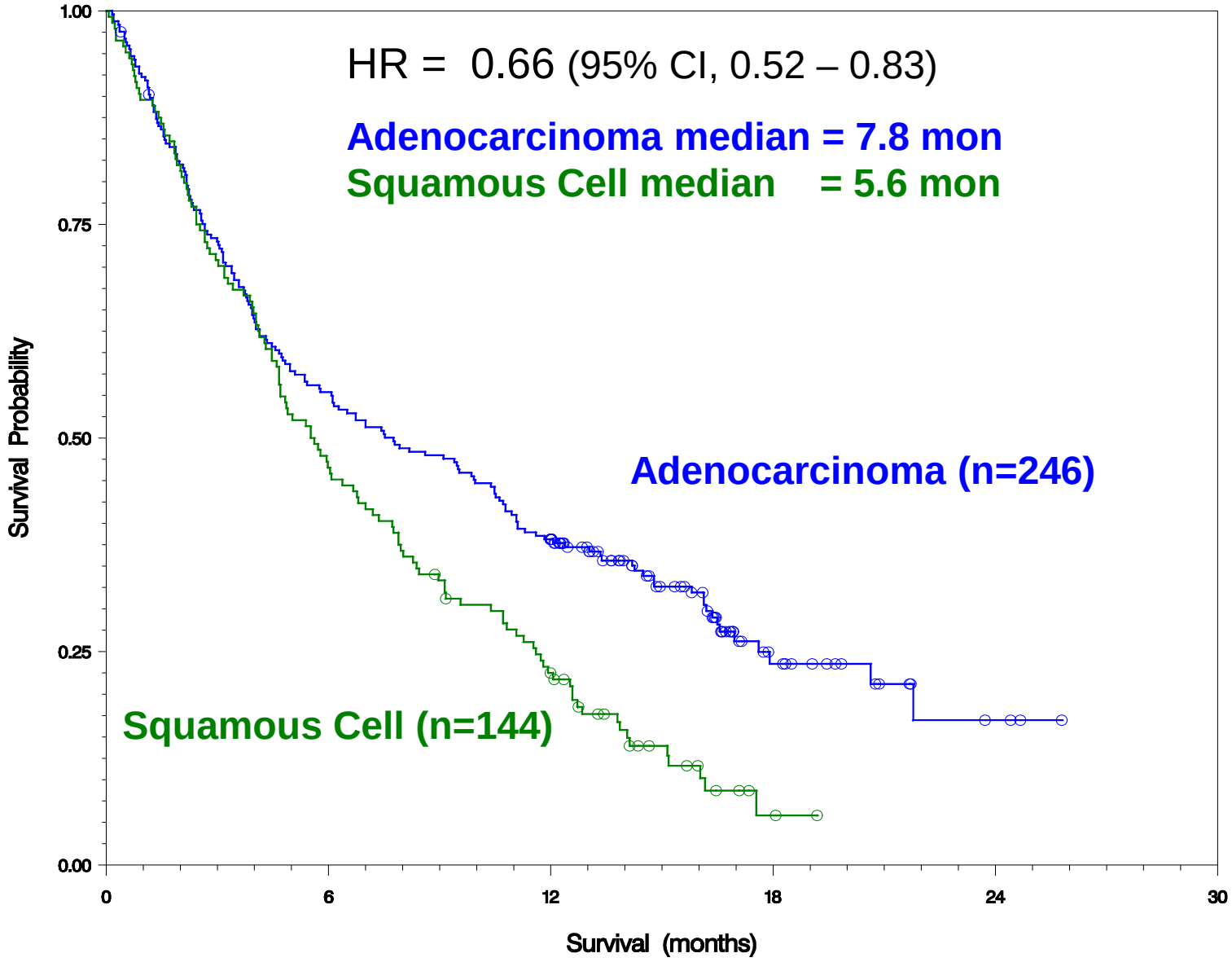
Clark GM. Mol Oncol 2008; 1:406-12

BR.21: Gender is Prognostic but not Predictive



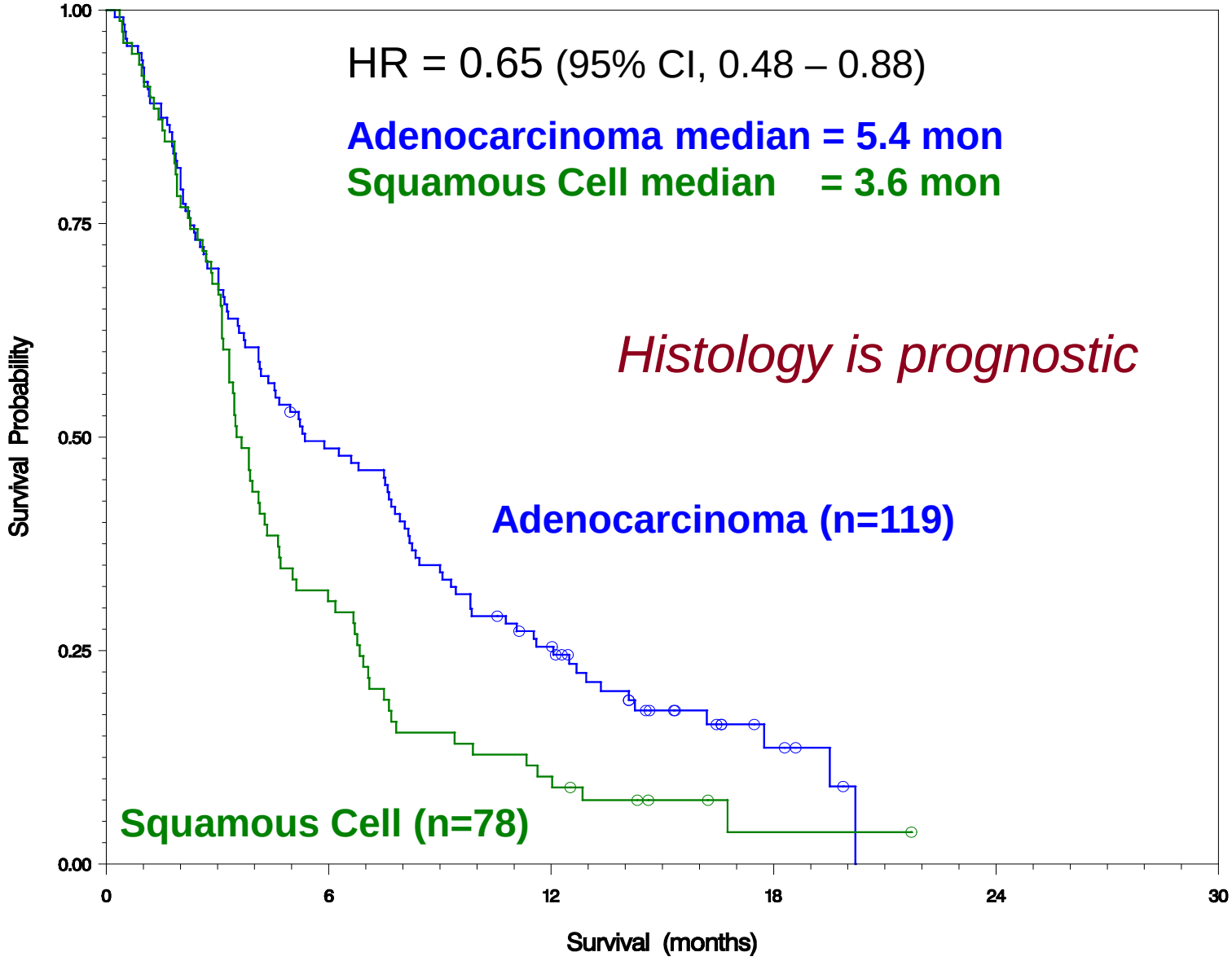
Clark GM. Mol Oncol 2008; 1:406-12

BR.21 Erlotinib Arm: Survival by Histology



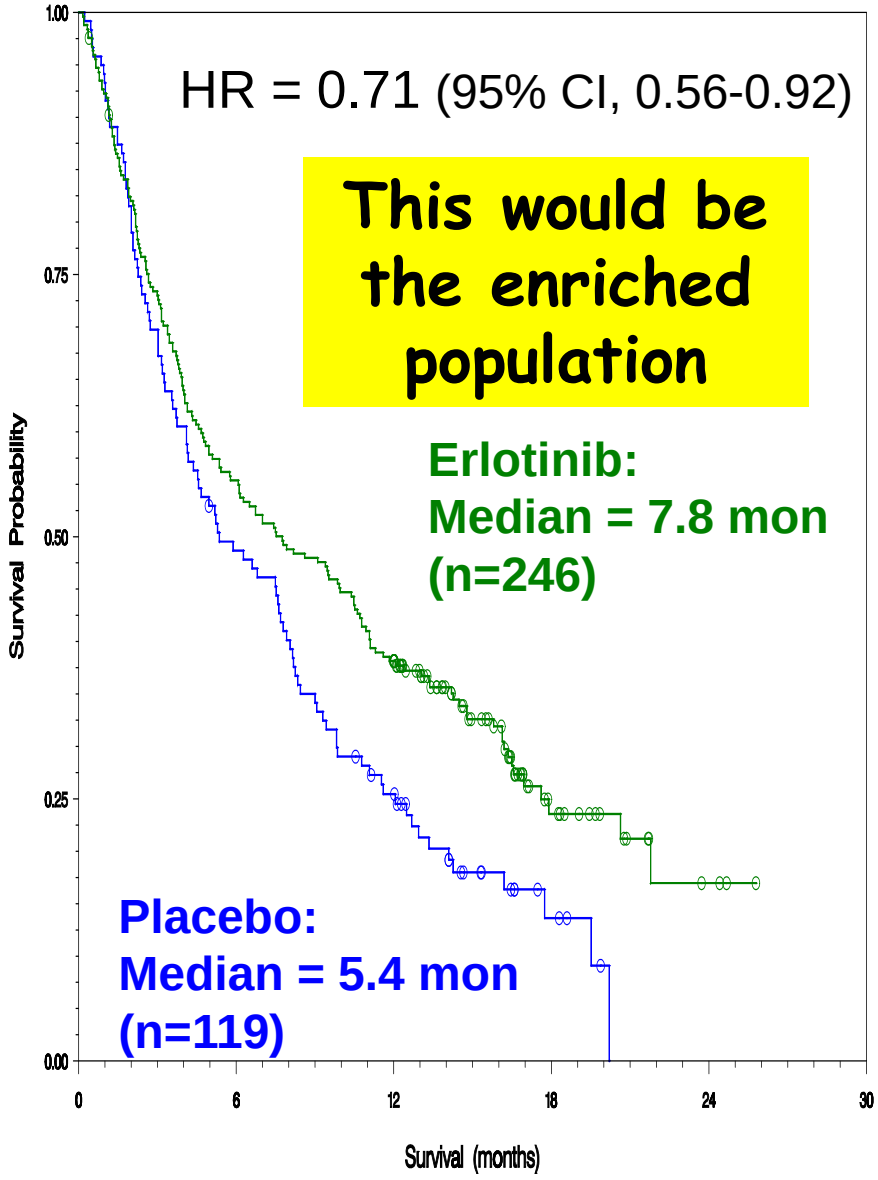
Clark GM. Mol Oncol 2008; 1:406-12

BR.21 Placebo Arm: Survival by Histology

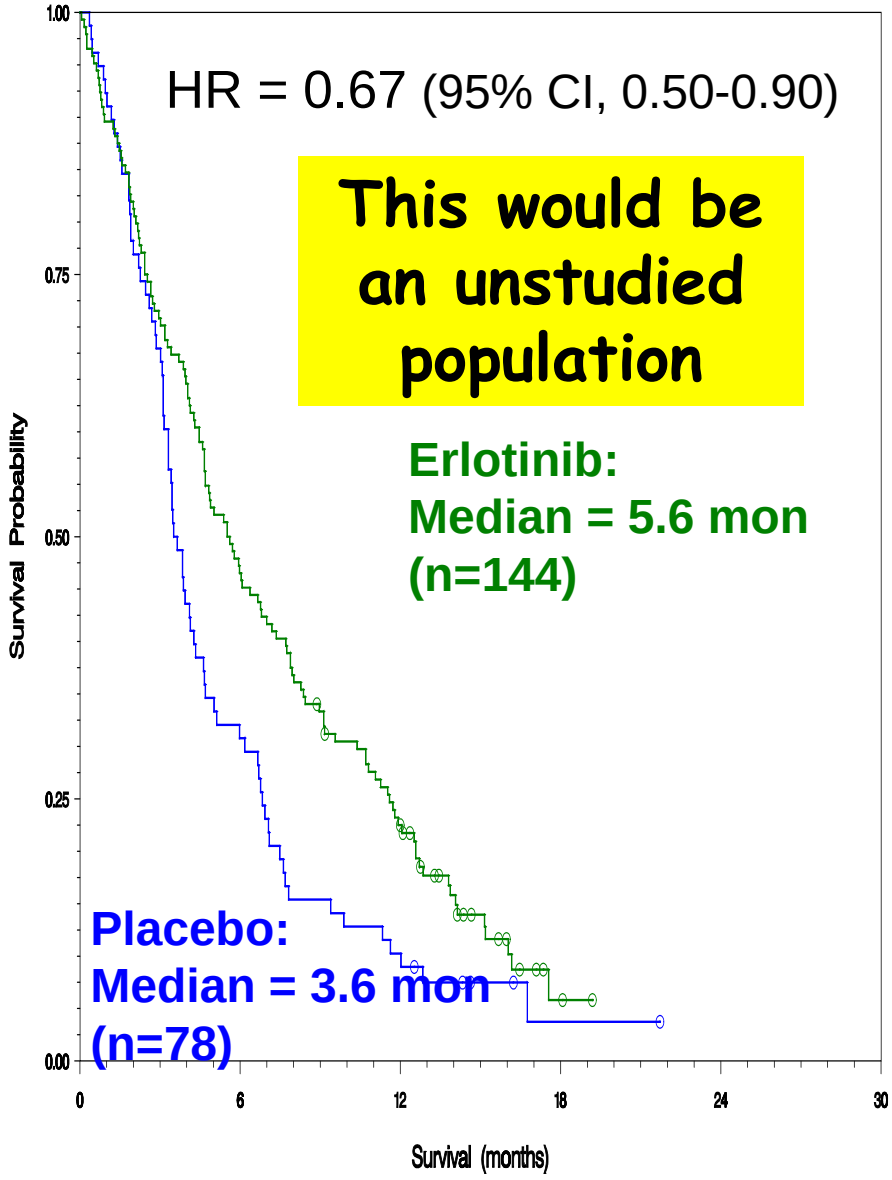


Clark GM. Mol Oncol 2008; 1:406-12

Adenocarcinoma

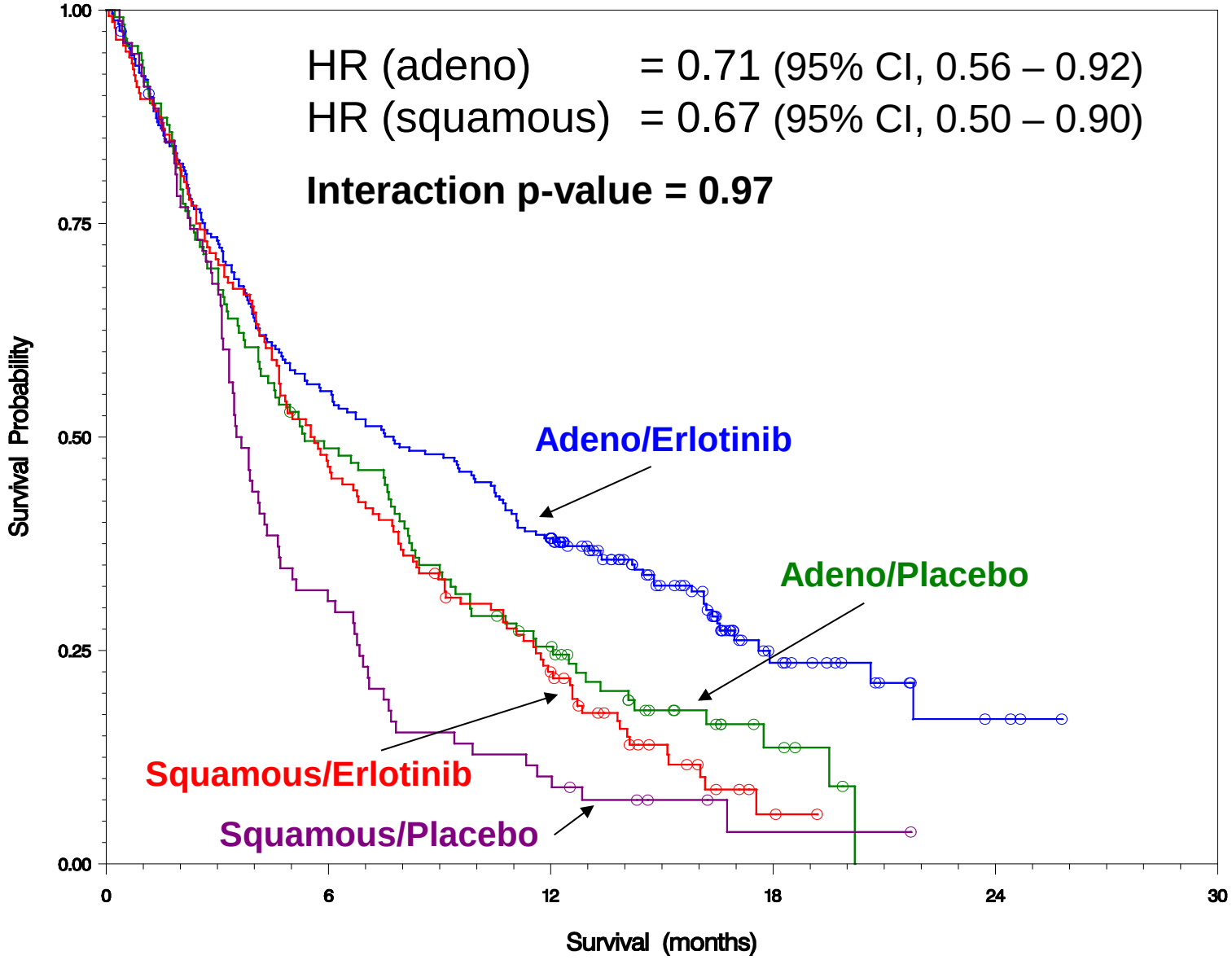


Squamous Cell



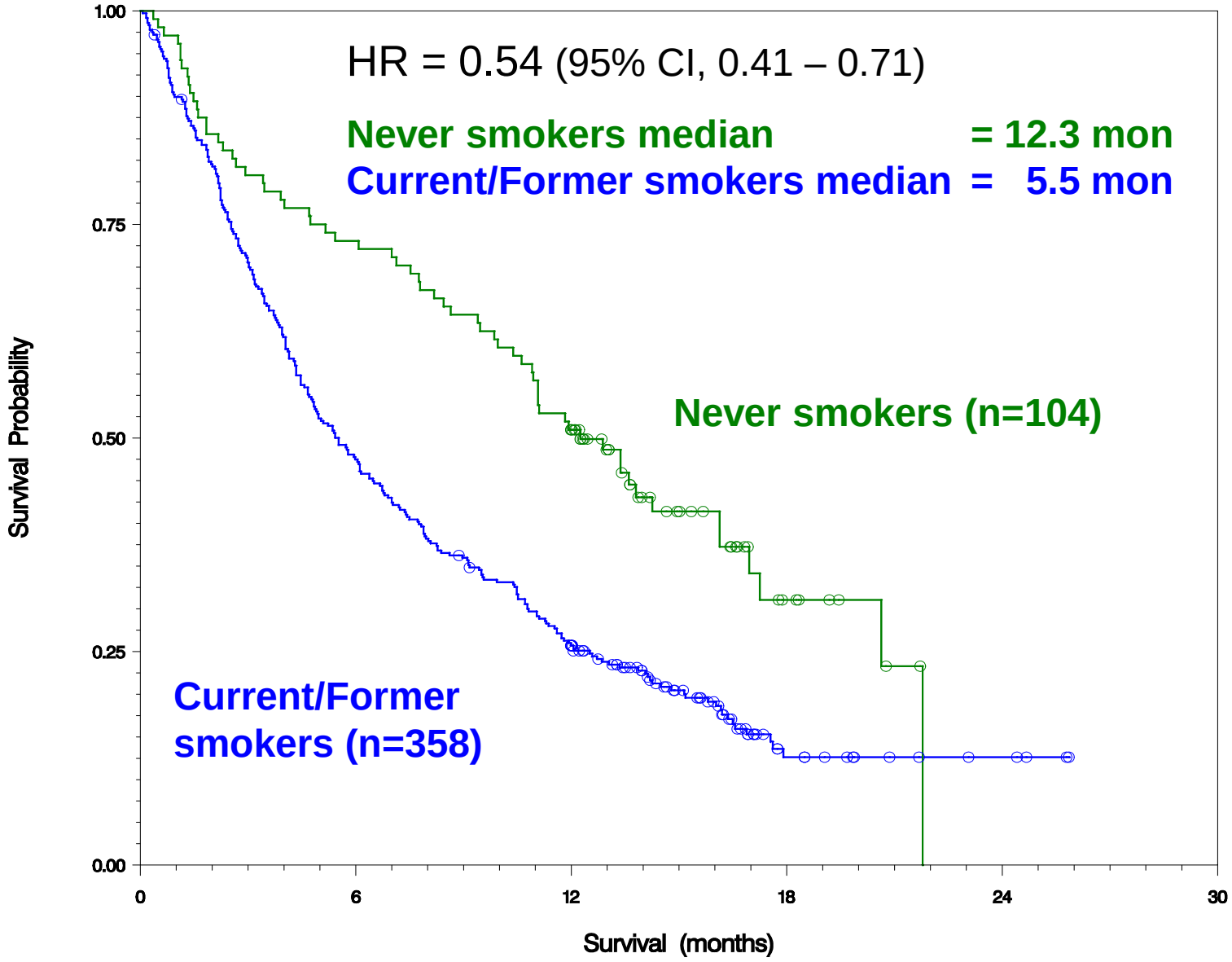
Clark GM. Mol Oncol 2008; 1:406-12

BR.21: Histology is Prognostic but not Predictive



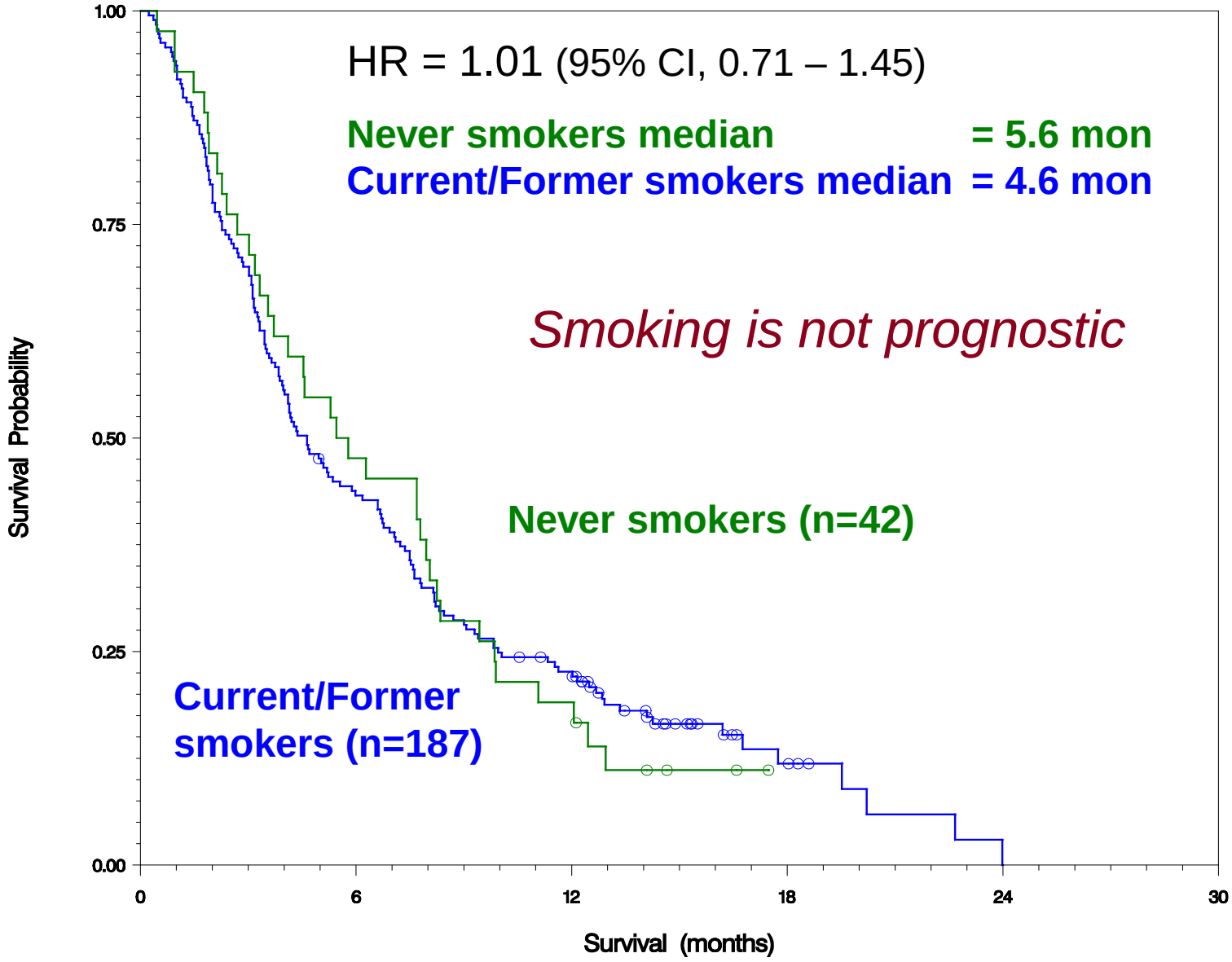
Clark GM. Mol Oncol 2008; 1:406-12

BR.21 Erlotinib Arm: Survival by Smoking



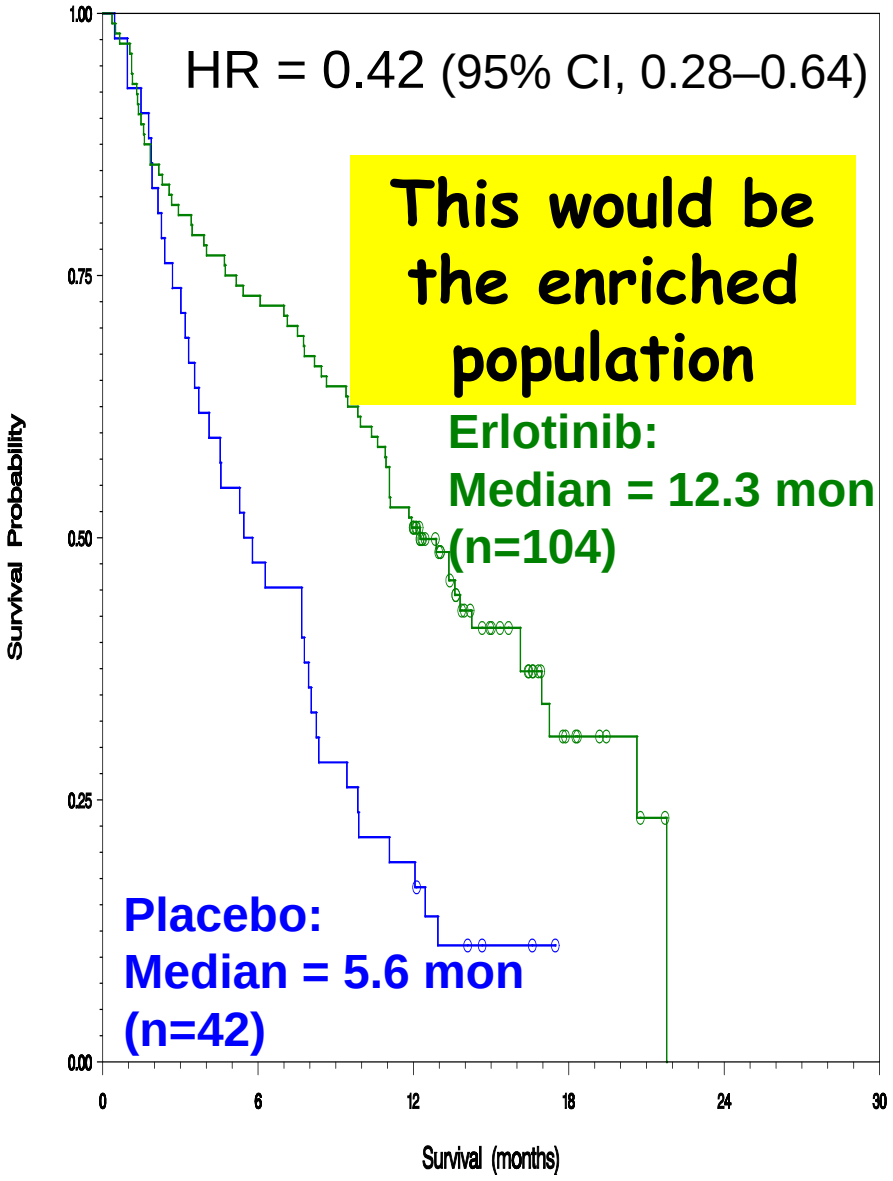
Clark GM. Mol Oncol 2008; 1:406-12

BR.21 Placebo Arm: Survival by Smoking

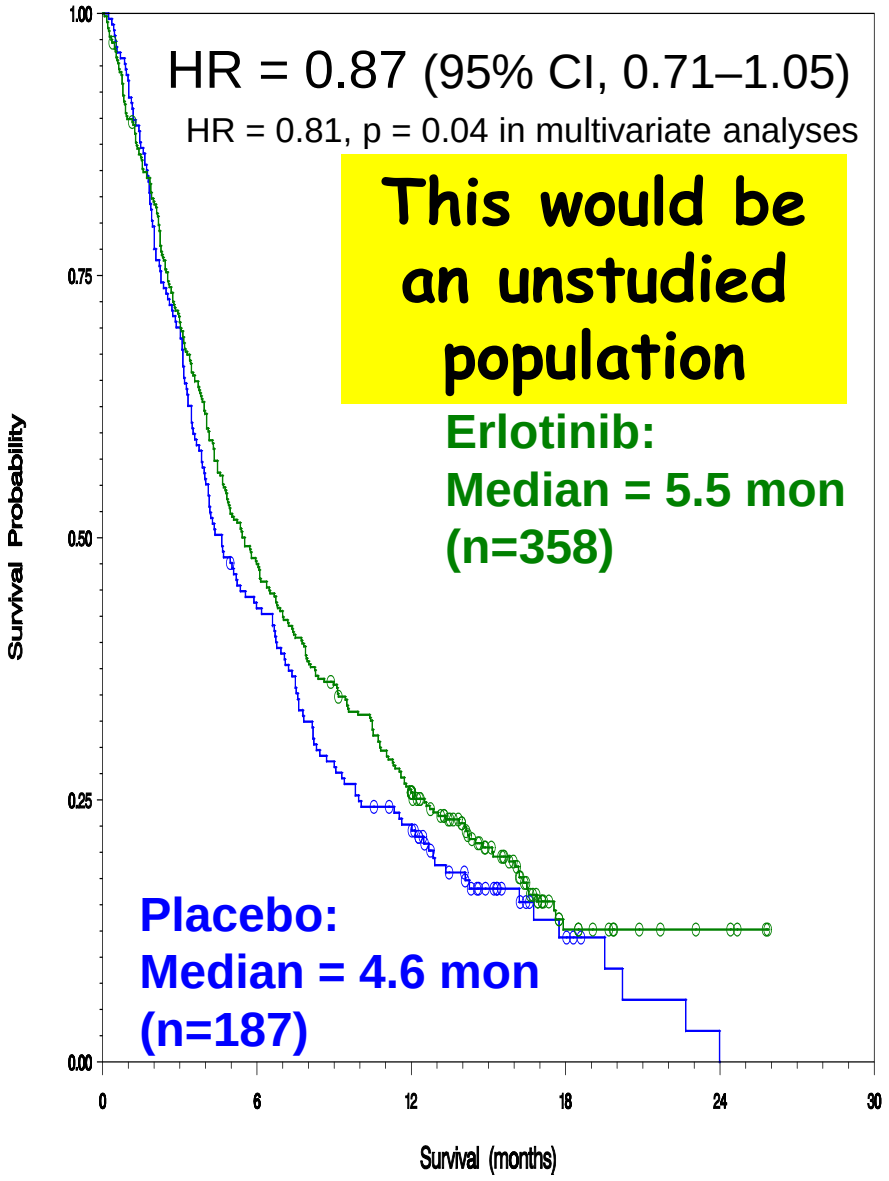


Clark GM. Mol Oncol 2008; 1:406-12

Never Smokers

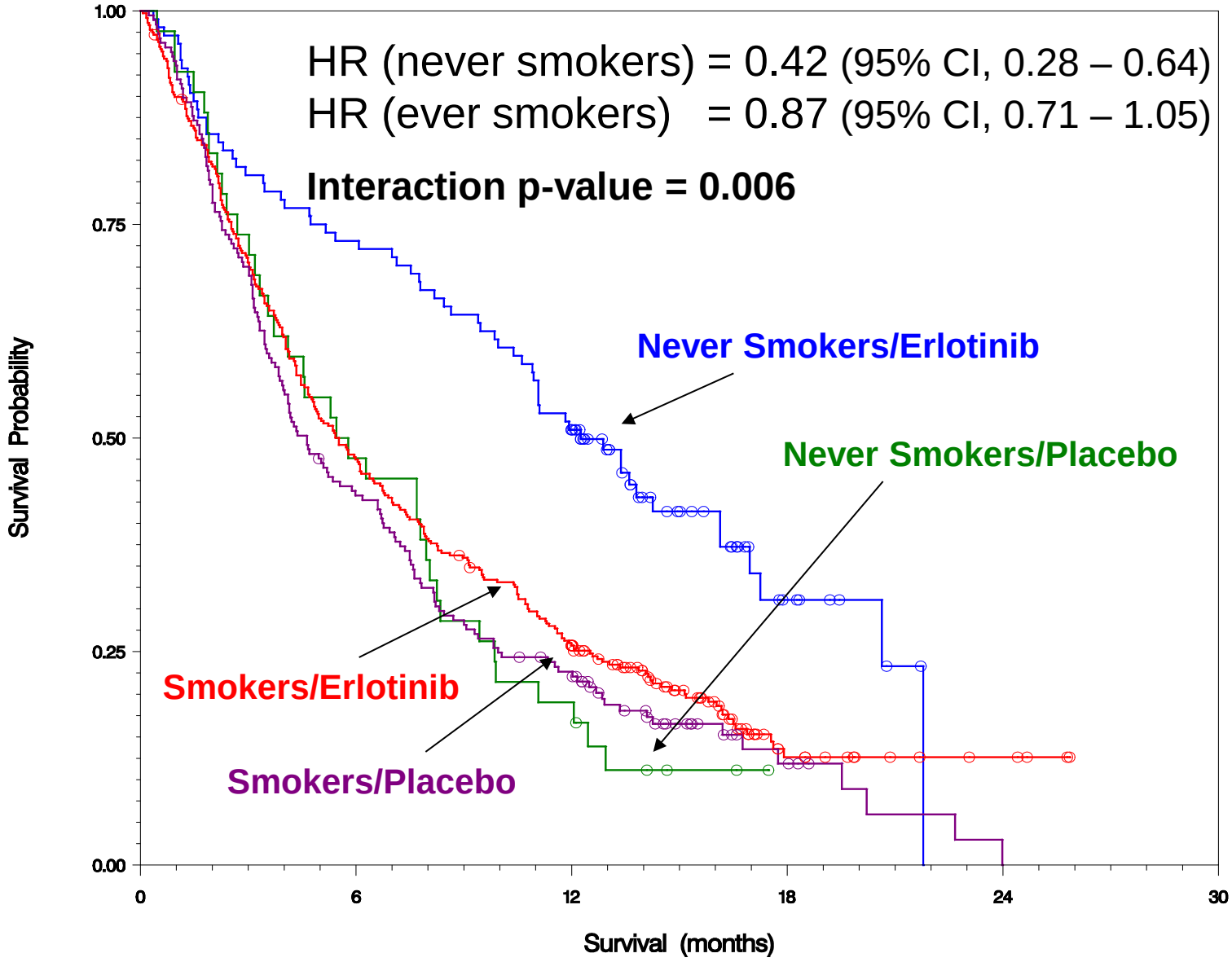


Current/Former Smokers



Clark GM. Mol Oncol 2008; 1:406-12

BR.21: Smoking is Predictive but not Prognostic



Clark GM. Mol Oncol 2008; 1:406-12

Patient selection early in drug development runs the risk of selecting the wrong biomarker and/or the wrong assay

Initial Cetuximab Package Insert

ERBITUX® (cetuximab) was approved for the treatment of certain patients who have colorectal cancer that has spread to other parts of the body. **Only patients whose tumors have a protein called Epidermal Growth Factor Receptor (EGFR) should receive ERBITUX.** FDA-approved tests should be used to determine if tumors have this protein.

VOLUME 23 · NUMBER 9 · MARCH 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cetuximab Shows Activity in Colorectal Cancer Patients With Tumors That Do Not Express the Epidermal Growth Factor Receptor by Immunohistochemistry

Ki Young Chung, Jinru Shia, Nancy E. Kemeny, Manish Shah, Gary K. Schwartz, Archie Tse, Audrey Hamilton, Dorothy Pan, Deborah Schrag, Lawrence Schwartz, David S. Klimstra, Daniel Fridman, David P. Kelsen, and Leonard B. Saltz

Current Cetuximab Package Insert
(FDA version)

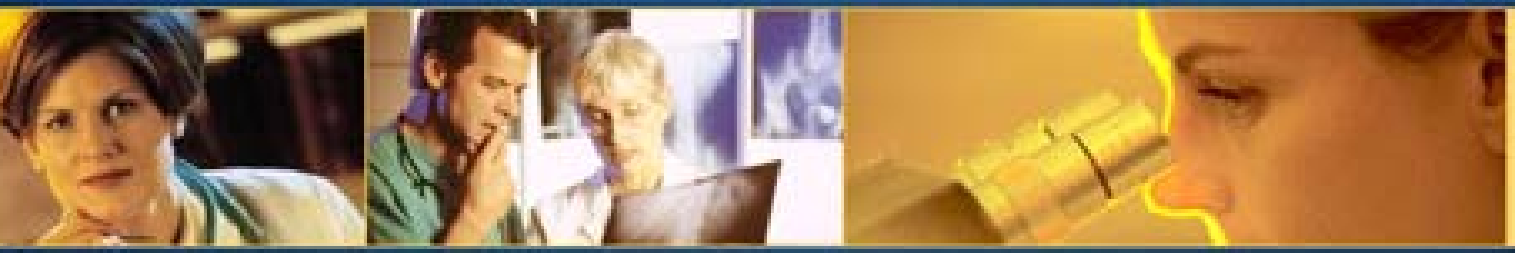
ERBITUX® … is indicated for treatment of:

Colorectal Cancer

K-Ras wild-type, **EGFR-expressing**, metastatic colorectal cancer as determined FDA-approved tests…

ASCO®

AMERICAN SOCIETY OF CLINICAL ONCOLOGY



2007
Annual Meeting
Abstract #511

Benefit from adjuvant trastuzumab may not be confined to patients with IHC 3+ and/or FISH-positive tumors: Central testing results from NSABP B-31.

S. Paik, C. Kim, J. Jeong, C. E. Geyer, E. H. Romond, O. Bohn, E. P. Mamounas, D. L.Wickerham, J. P. Costantino, N. Wolmark
NSABP Operations and Biostatistics Center, Pittsburgh, PA

Advice Regarding Patient Selection

- Do not use selection/enrichment strategies too early unless:
  - You are absolutely certain of target functionality
  - You have a validated assay that can reliably assess the status of the biomarker
- Collect tissue samples to obtain preliminary information about biomarkers in early development studies to generate hypotheses for future definitive studies
- Conduct randomized clinical trials with appropriate control arms in early development

Take-Home Messages (1)

- Drug development is a team sport and that requires active participation of different disciplines
  - Requires strong foundation in statistics, augmented by knowledge of molecular biology, translational research, clinical research, regulatory requirements, etc., and familiarity with terminology from all disciplines
- Early drug development of targeted therapies requires an understanding of biological pathways, biomarkers, preclinical experimental designs, PK, PD, etc. in order to design efficient clinical trials
- These concepts are independent of the setting (eg, academia, big pharma, small biotech)

Take-Home Messages (2)

- At each step in the development process, carefully assess the preliminary information that is available
  - Is the right question being asked?
  - Is the preliminary information sufficient for addressing the question being asked?
  - Should additional preliminary study(s) be conducted before launching a definitive study to answer the question?

Take-Home Messages (3)

- Consider patient selection strategies very carefully, taking into account requirements for validated biomarker assays, and prognostic and predictive effects of the biomarker
- Discuss single-agent and combination strategies early in development, taking into account potential indications for the agent
- Always think ahead and make sure that results from the study you are currently designing will be helpful for designing the next set of clinical trials
- The ultimate objective is to find the right dose and the right schedule for the right patient