Endpoints and Novel Designs in the Era of Targeted Therapies

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Endpoint Hierarchy

- True clinical efficacy measure
- Validated surrogate endpoint (*Rare*)
- Surrogate endpoint "reasonably likely to predict clinical benefit"
- None of the above: A correlate that is solely a measure of biological activity

Endpoints: Fit to purpose

- Phase II goal: Go/No-go phase III decision
  - Historically: Endpoint with good correlation with clinical benefit outcomes ok
  - Reconsidered: If goal is successful phase III trial, more rigor in phase II endpoint is appropriate
- Phase III goal: Agent approval
  - Clinical benefit or validated surrogate endpoint needed

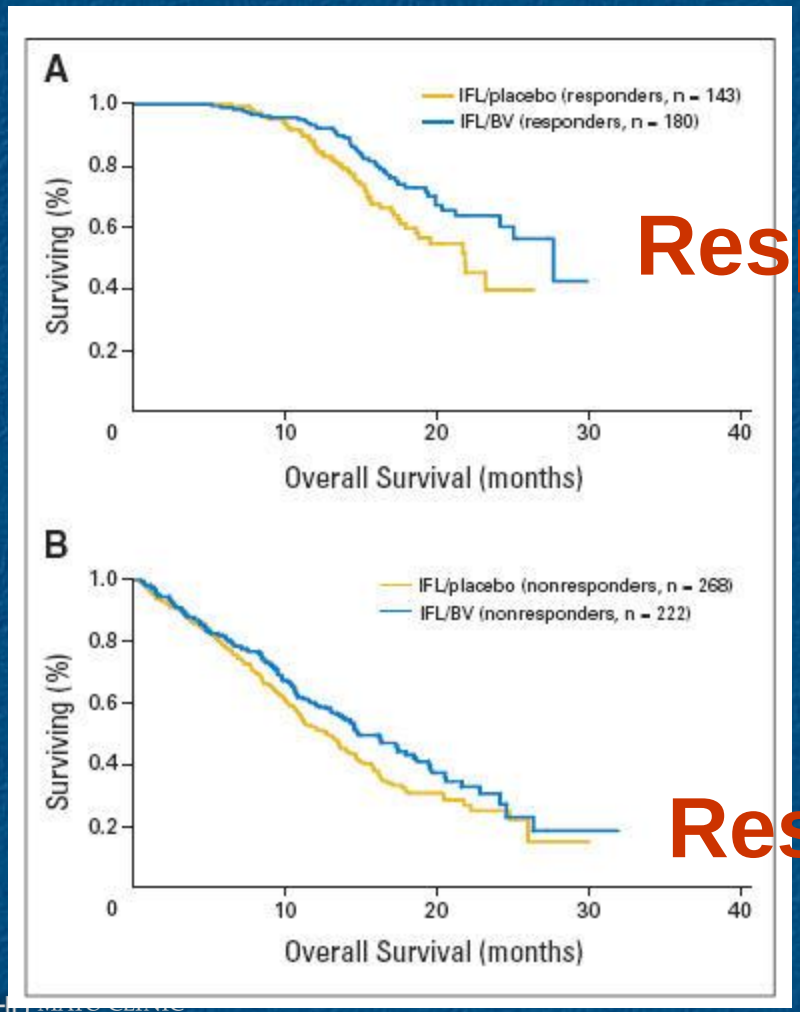
Phase II endpoints

- Tumor response (RECIST)
  - Patients live longer even without response[1]
- Novel imaging
  - Cannot validate a new endpoint and a new therapy in the same trial
- PFS at an early time point
  - Captures disease stabilization

[1]Grothey JCO 2008

Patients without response benefit from better therapy

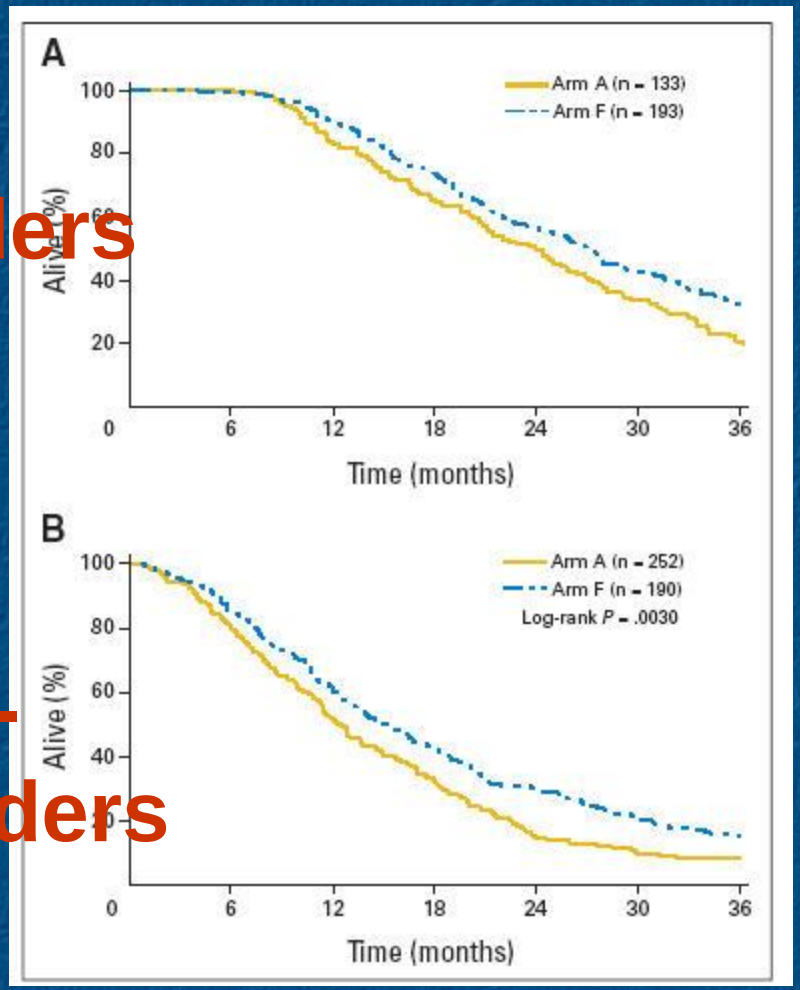
IFL +/- Bev



Responders

Non-Responders

FOLFOX vs 5FU/LV



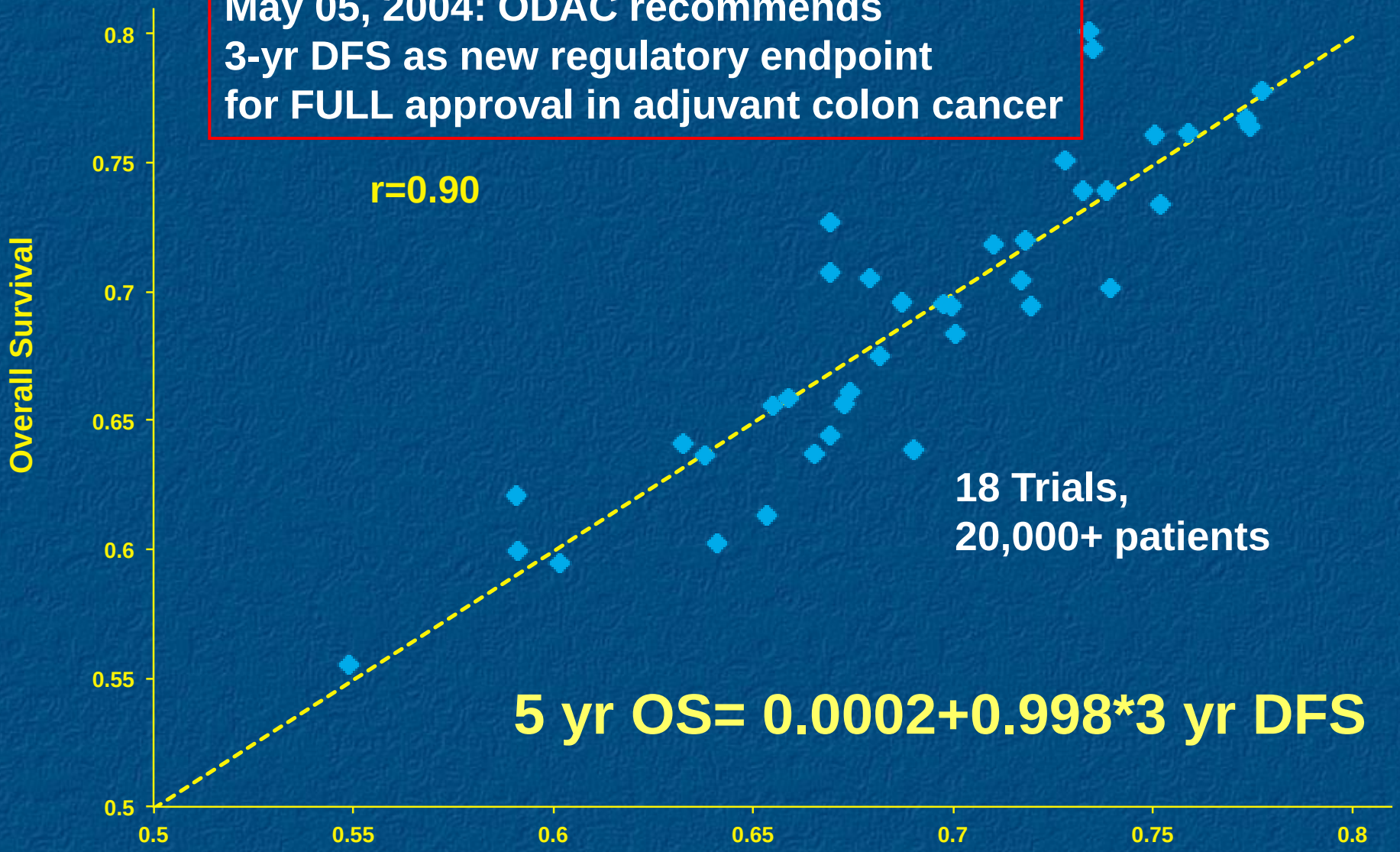
Grothey, JCO 2008

Phase III Endpoints: FDA Regulatory Standard

- Safe and Effective
- Effective (clinical benefit)
  - Live longer
  - Live better
- Live better very difficult to show in oncology

Surrogate validation: Requires meta-analysis

May 05, 2004: ODAC recommends 3-yr DFS as new regulatory endpoint for FULL approval in adjuvant colon cancer



Sargent et al., JCO 2005

Is PFS a Clinical Benefit Endpoint? Opinion: Pro

- "I have no problem accepting that, in a lethal disease such as metastatic cancer, delaying progression is a clinical benefit in itself, provided that the magnitude of the benefit is sufficient and the side-effect profile acceptable."

  R Pazdur, NCI Cancer Bulletin May 13, 2008

  http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_051308/page7

Merits of PFS as an endpoint

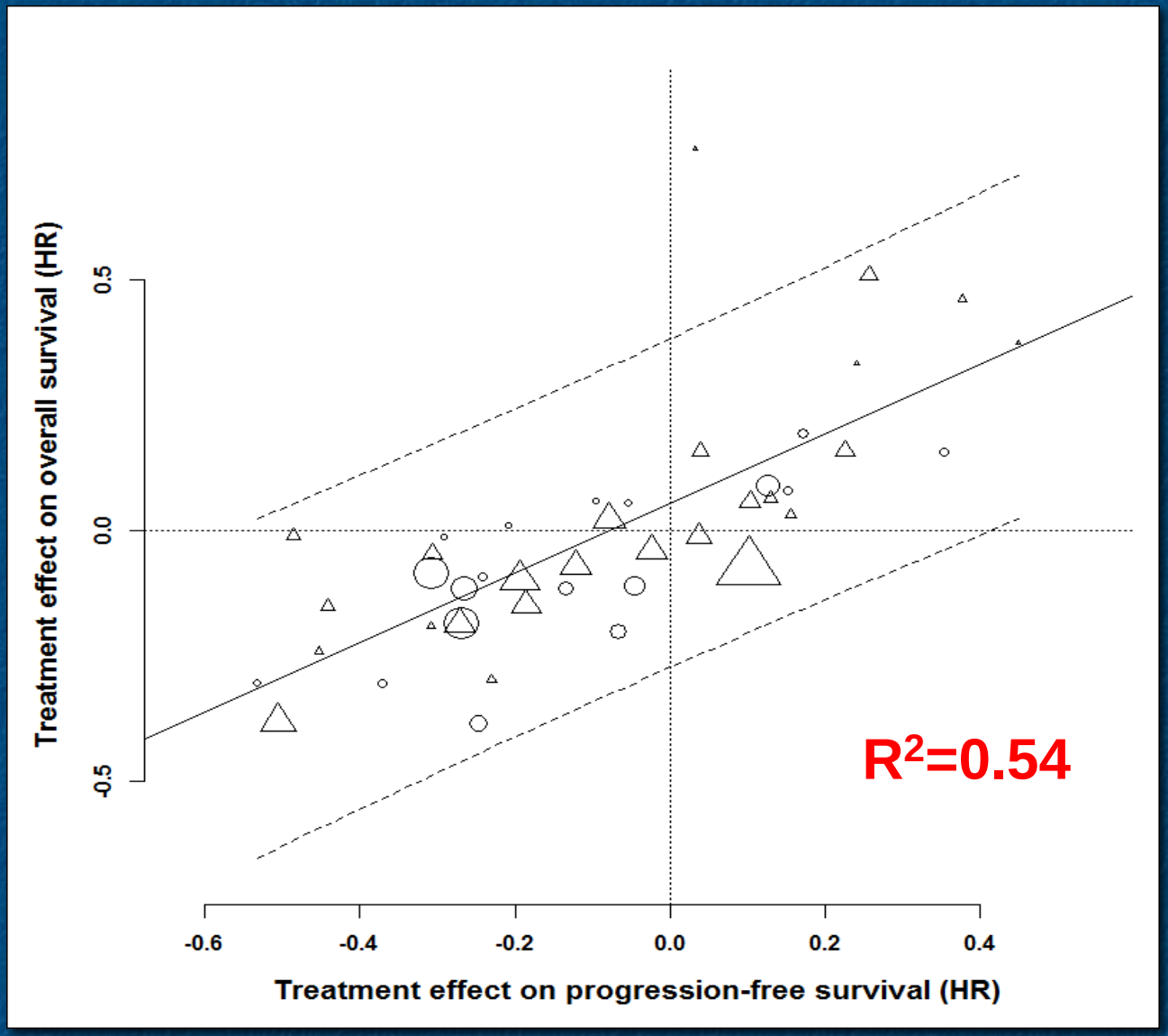
- Un-encumbered by cross-over
- Available more quickly than OS
- Variable demonstration of surrogacy for OS
  - Colon (before biologics)– Yes – Buyse JCO 2007
  - Breast – No – Burzykowski, JCO 2008
  - Lung – Unclear – Buyse ASCO 2008

PFS vs. OS in modern First line colon cancer trials

- ARCAD database: Individual patient data from 22 First line trials, 1997-2006
- 16,762 patients
- 12/22 tested targeted therapies

Shi et al, JCO 2014 to appear

Trial level treatment effects: PFS vs. OS

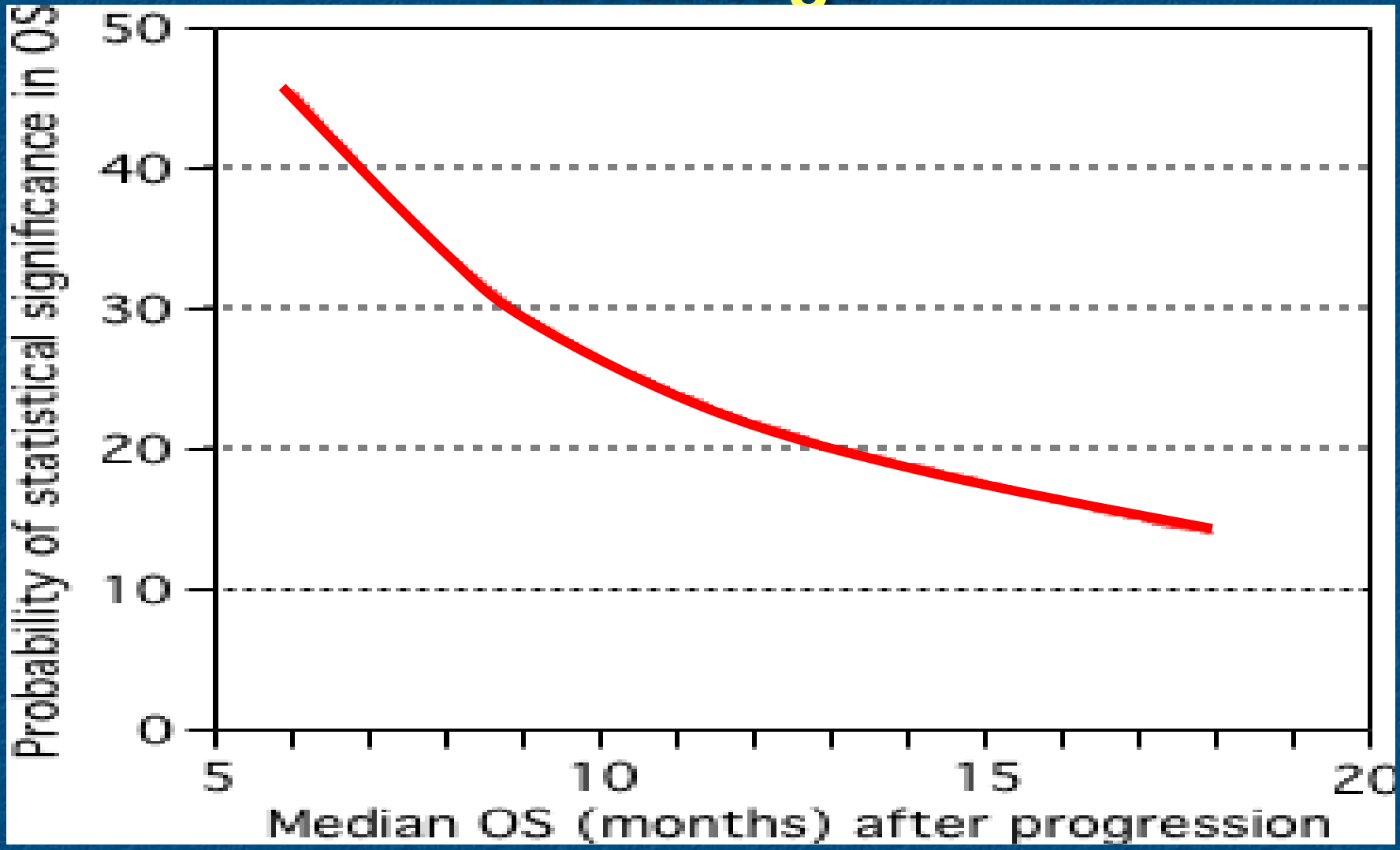


Shi et al, JCO 2014 To appear

Post-progression challenges

- Out of protocol's control
  - Perhaps unbalanced
  - Some crossovers without prog
- Same benefit in ΔPFS, even if directly translates to ΔOS, results in smaller HR
  - PFS: 6 mo v 9 mo: HR=0.66
  - OS: 12 mo vs 15 mo: HR=0.80
    15 mo vs 18 mo: HR=0.83
    21 mo vs 24 mo: HR=0.875
- Implication: PFS trials inherently underpowered for OS

Power for OS with 2-month PFS & OS Advantage

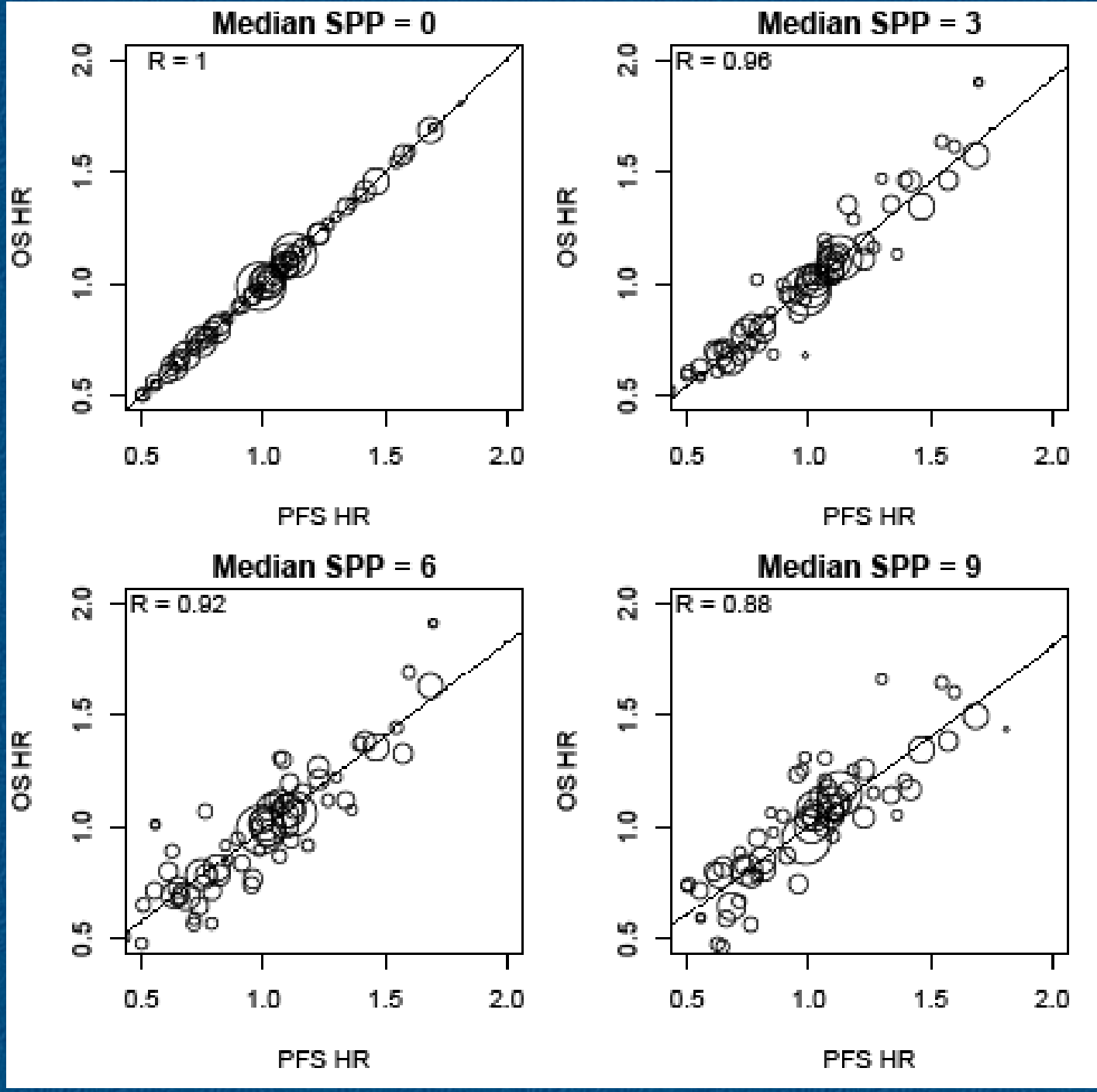


Broglio, JNCI 2009

Impact of Post-Progression survival on surrogacy

SPP=Survival Post-Progression

Broglio, JNCI 2009



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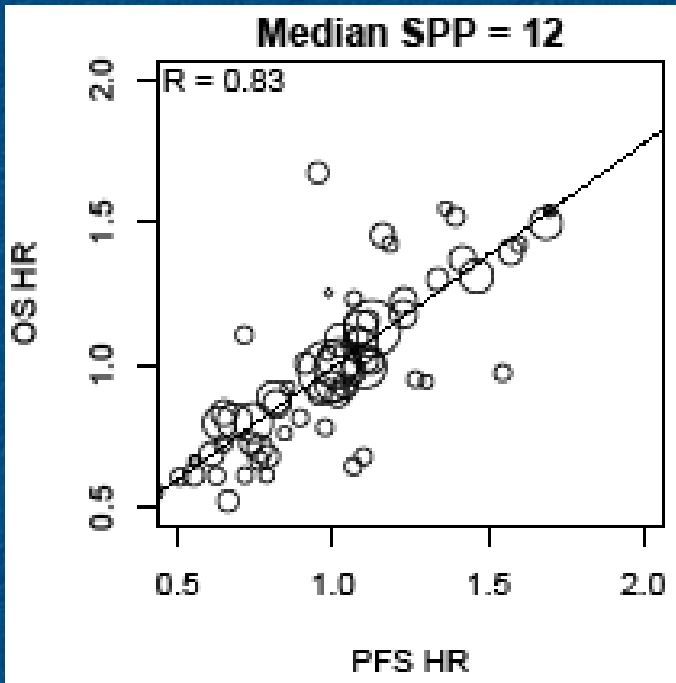
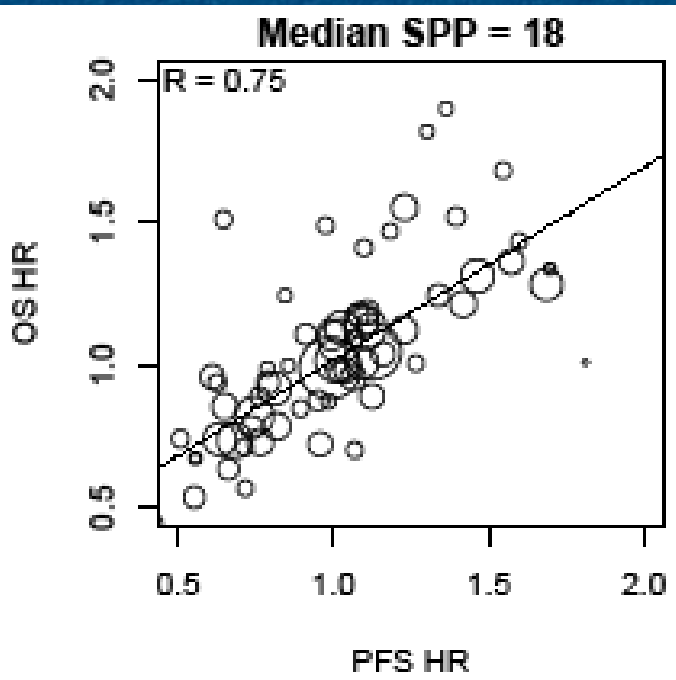
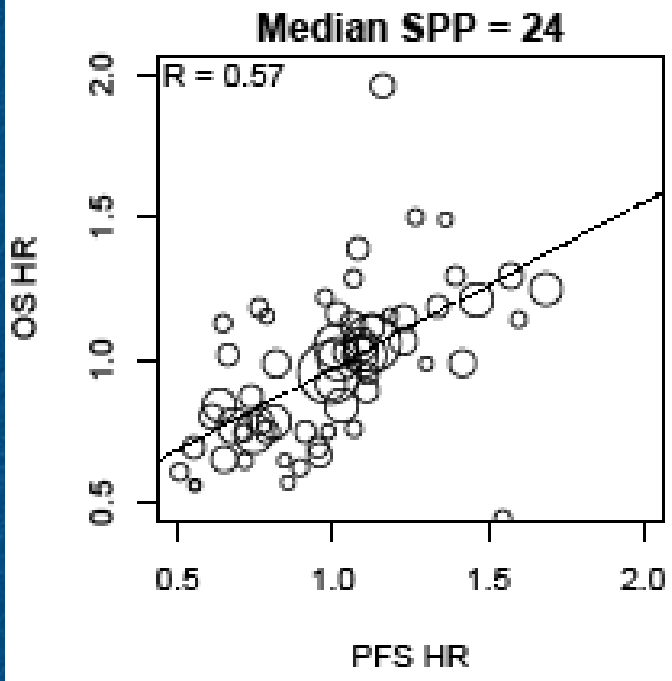




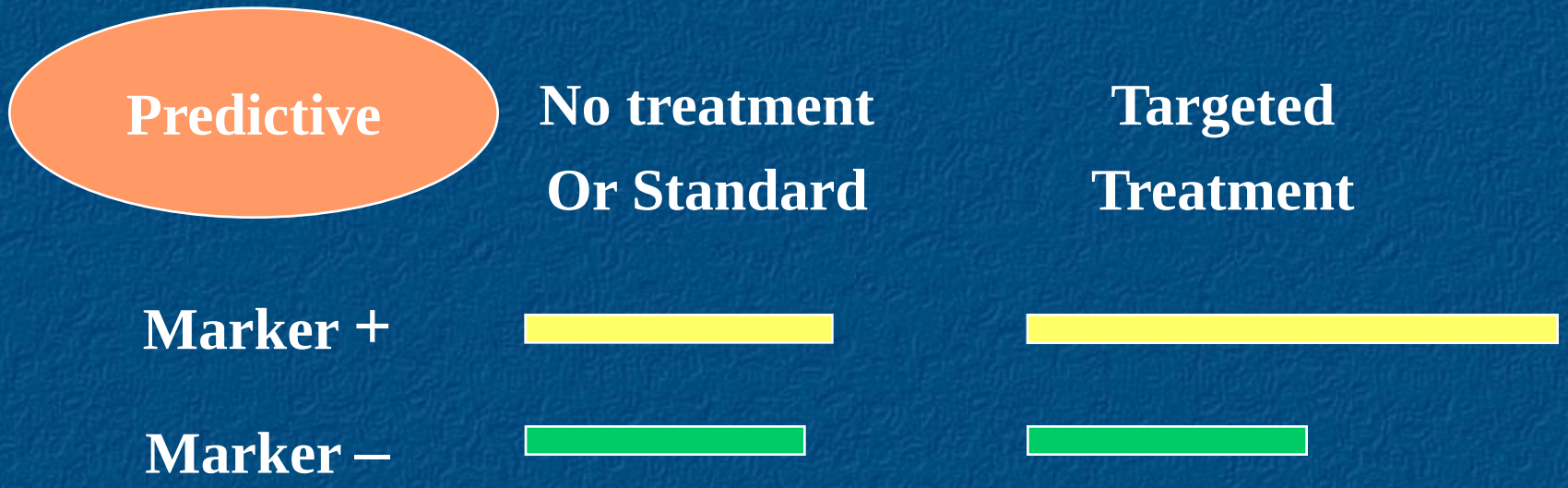


PFS as a surrogate endpoint

- Is PFS a surrogate for OS in cancer?
  - When no effective 2nd line rx: Yes
  - When effective 2nd and later lines rx: likely no
- As survival beyond progression lengthens, surrogacy becomes difficult
  - Attenuated HR
  - Additional noise
- Only currently realistic endpoint for phase III trials in diseases with multiple lines of therapy

Biomarkers: Predictive Marker

Single trait or signature of traits that separates different populations with respect to the outcome of interest in response to a particular (targeted) treatment



Enrichment Design

- Screens patients for the presence or absence of a marker or a panel of markers, AND
- Only includes patients in the clinical trial who either have or do not have a certain marker characteristic or profile

- **Paradigm:** Not all patients will benefit from the study treatment under consideration
  - Understand the safety, tolerability and clinical benefit of a treatment in the subgroup of the patient population defined by a specific marker status

Enrichment Designs

Appropriate when:

- Mechanism of drug action is known
- Assay is reliable
- Compelling preliminary evidence suggesting that patients with or without that marker profile do not benefit from the treatments in question
- Needs fewer overall randomized patients compared to an “untargeted” design

Trials in targeted populations

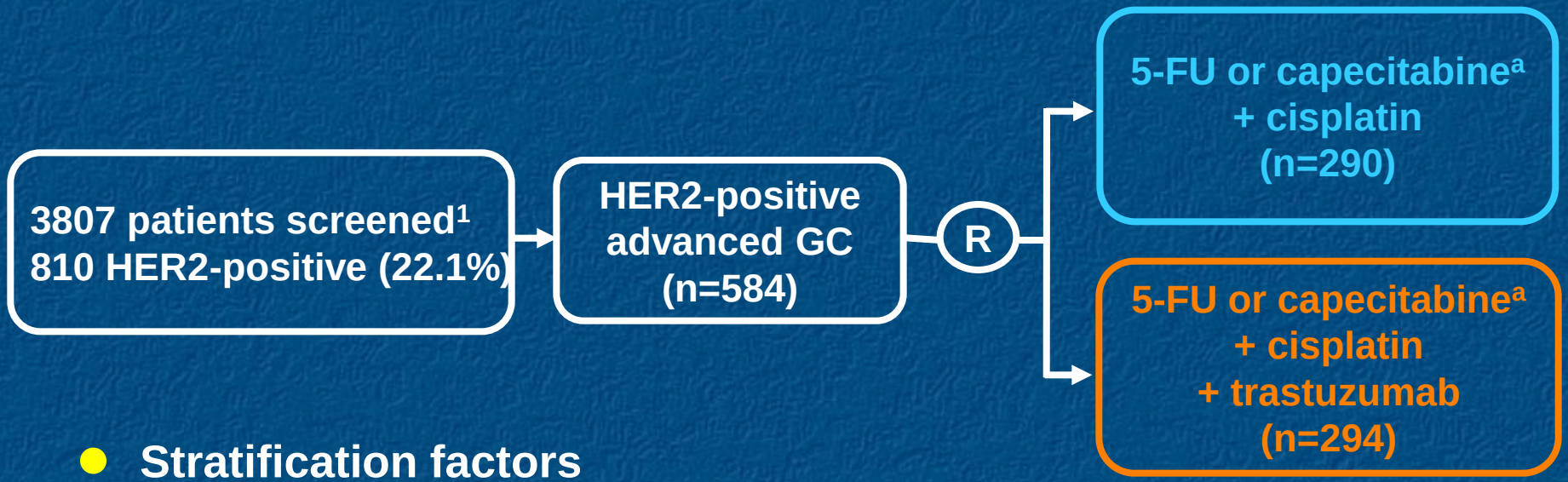
- **Gains in efficiency depend on marker prevalence and relative efficacy in marker + and marker - patients**

(Simon & Maitournam, CCR 2004)

Prevalence	Relative Efficacy	Efficiency Gain
25%	0%	16x
25%	50%	2.5x
50%	0%	4x
50%	50%	1.8x
75%	0%	1.8x
75%	50%	1.3x

ToGA trial design

Phase III, randomized, open-label, international, multicenter study

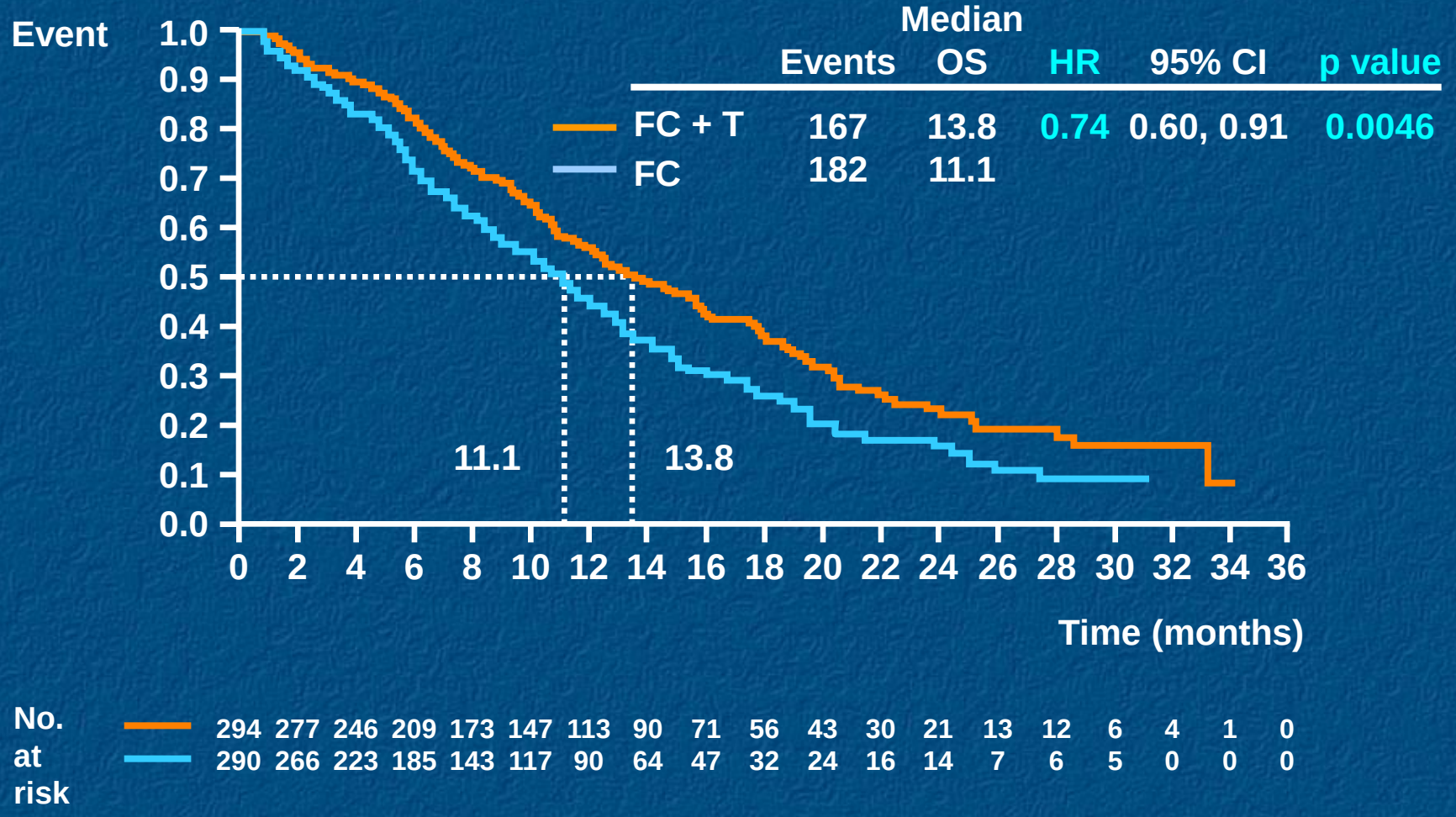


- **Stratification factors**
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

[a]Chosen at investigator's discretion
GEJ, gastroesophageal junction

Bang et al; Lancet 2010

TOGA Primary end point: OS



MAYO CLINIC

T, trastuzumab

Bang et al; Lancet 2010

Unselected Designs

- Sequential Testing Strategy Designs

- Marker based strategy design
  - Randomize subjects to treatment either based on or independent of the marker status

- Marker by treatment interaction design
  - Use the marker status as a stratification factor when randomizing subjects to treatment

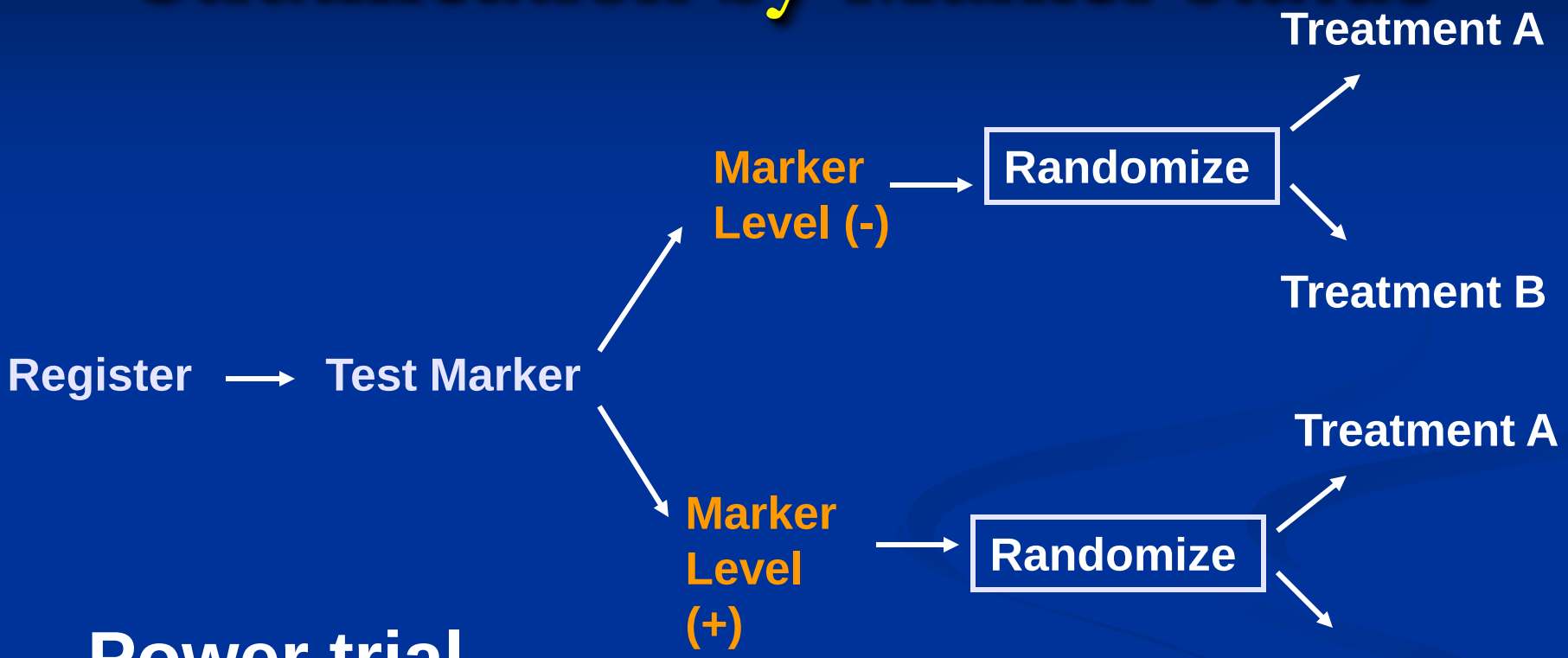
All patients of a specific disease type and stage are eligible for the clinical trial, regardless of their actual marker status

Sequential testing: MaST Design

- Test marker positive first at α_1 (< 0.025)
- If positive, test marker negative at full α (0.025)
- If not positive, test overall treatment effect at level $\alpha - \alpha_1$

Friedlin, Clin Trial 2013

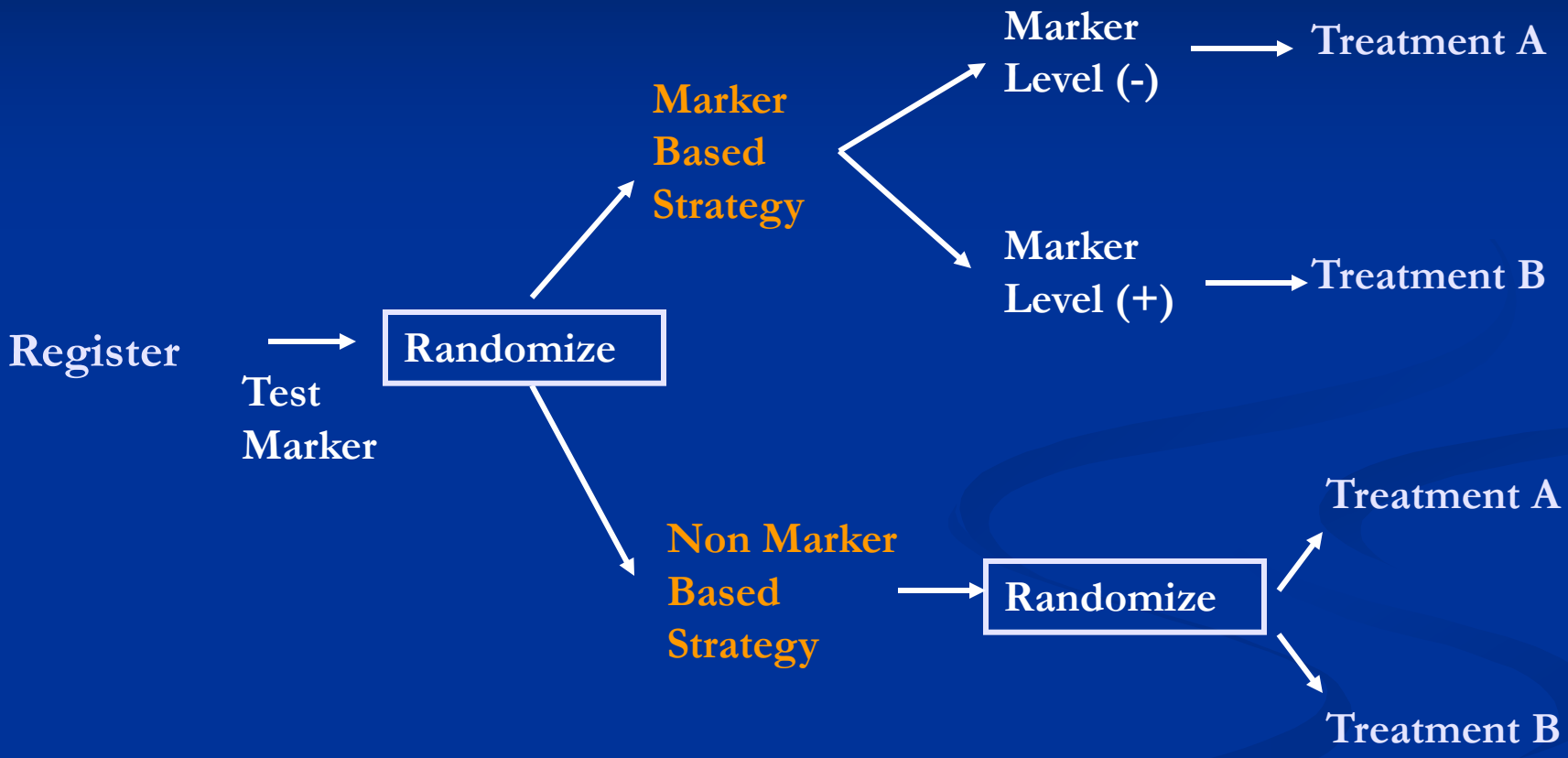
Unselected Design: Upfront Stratification by Marker status



Power trial separately within marker groups

Sargent et al., JCO 2005

Unselected Design: Marker Based Strategy



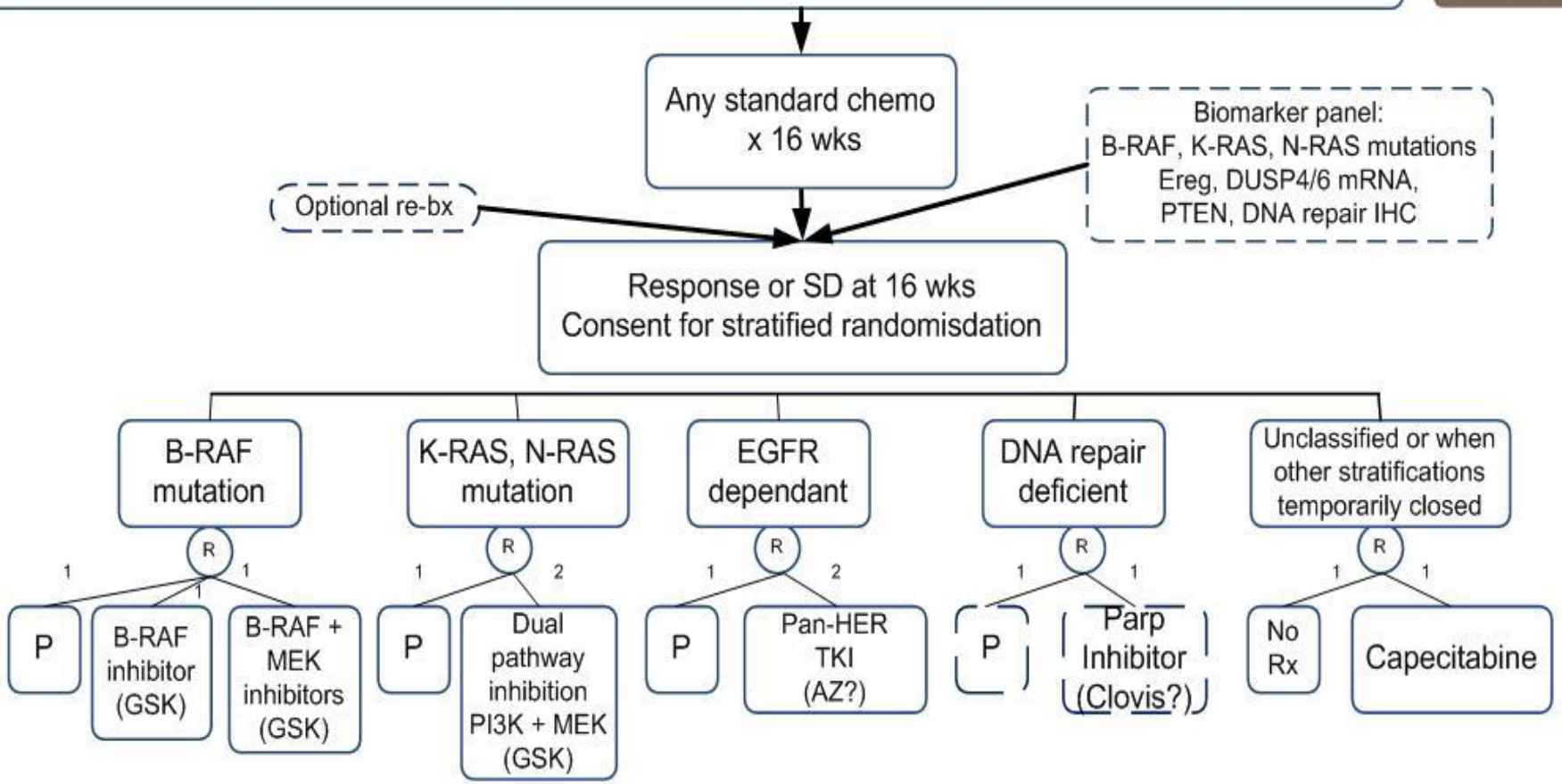
Sargent et al., JCO 2005

Beyond one mutation at a time: Umbrella Trials

- Better treatment of cancer by choosing therapies based on molecular characteristics of the tumor
- Context:
  - Advances in many tumors culminating in large-scale sequencing
  - Development of therapies directed to at least some “driver pathways”
- May be histology or mutation specific

FOCUS 4: first-line mCRC, fit for chemo, excluding plts >400K, consent for biomarker analysis

MRC Clinical Trials Unit



Stage II/III Primary outcome measure: PFS from randomisation to interval therapy (recommence 1st-line chemo)

Decision points for each stratified cohort:

- 1st and 2nd and 3rd interim analyses for Lack of Activity (PFS)
- 4th analysis for PFS efficacy (target HR = 0.5 for B-RAF^{mut}, all others 0.65)

- **For biomarker-selected cohorts that pass 3rd PFS Lack of Activity stage** (alpha = 0.1): test specificity of biomarker selection in a separate cohort of patients *without* the selection biomarker
- **For larger cohorts that pass 4th Efficacy PFS stage:** Continue phase III, with final efficacy analysis on OS endpoint

Shiva Trial

PI: C. Le Tourneau

Sponsor: Institut Curie

Patients with refractory cancer (all tumor types)

Informed consent signed

Tumor biopsy + Blood sample

High Throughput Sequencing

Molecular profiling

Molecular biology board

Specific therapy available

NO

Non eligible patient

YES

Eligible patient

Informed consent signed

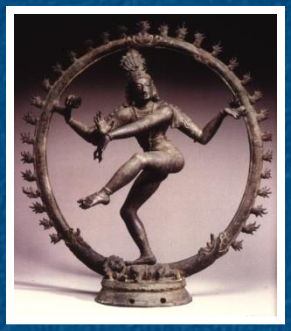
R

Therapy based on molecular profiling

- Approved molecularly targeted agent (single agent or combination if relevant)
- Chemotherapy
- Hormone therapy
- Clinical trial with drug(s) of interest

Conventional therapy based on oncologist's choice

Cross-over



NCI-MATCH

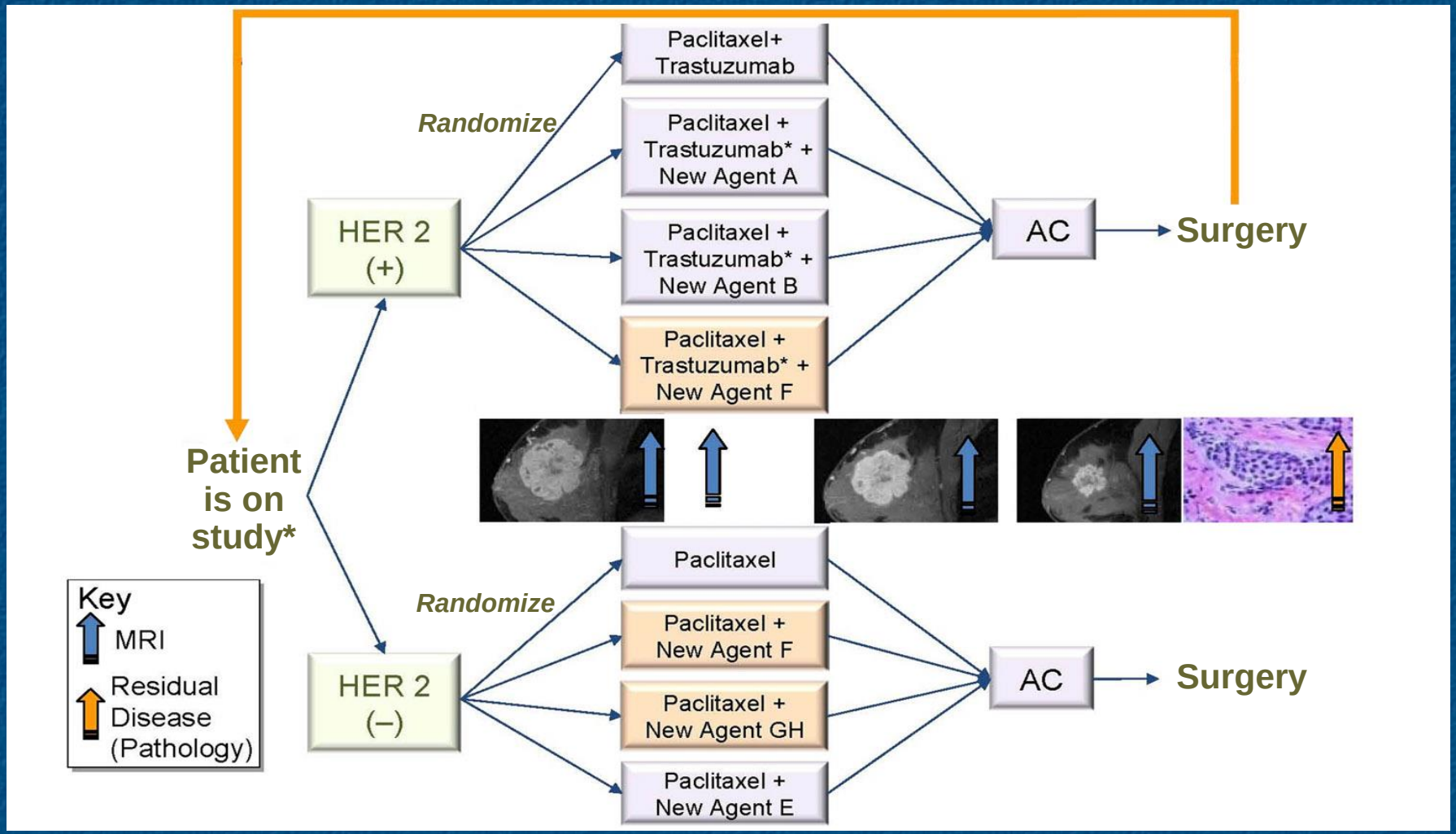
- Umbrella protocol for multiple, single-arm phase II trials
  - Each molecular subgroup matched to a targeted agent
- IND for protocol template
  - Arms could be added or deleted without affecting other arms
- Initially focused on single-agents (commercial or experimental)
  - Combinations will be considered for targets that have validated combination targeted therapy
  - Need minimum dose/safety established in phase 1 trials
- Study will be reviewed by the CIRB

Adaptive Designs

- Randomize between at least 2 arms within biomarker-defined strata
  - Different signatures, different allowed drugs
- Evaluate success in an ongoing manner
  - Alter randomization ratio?
- Drop poor performers
- 'Graduate' good performers to phase III trials
- Examples: ISPY-2 (Breast), BATTLE (NSCLC)

Zhou, Clinical Trials 2008

ISPY-2 Adaptive Design
Learn, Drop, Graduate, and Replace Agents Over Time



*Investigational agent may be used in place

Conclusions

- Targeted therapies, biomarkers require new methods for trials
  - Endpoints
  - Trial designs
- Fundamental principles still valid
  - Randomization
  - Rigorous design
- Trials will become smaller
  - By necessity (rare tumors)
  - By design (expected larger effects)
  - By strategy (?) – take more risks, bigger long-term rewards