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Integrating Biomarkers in Clinical Trials: an overview

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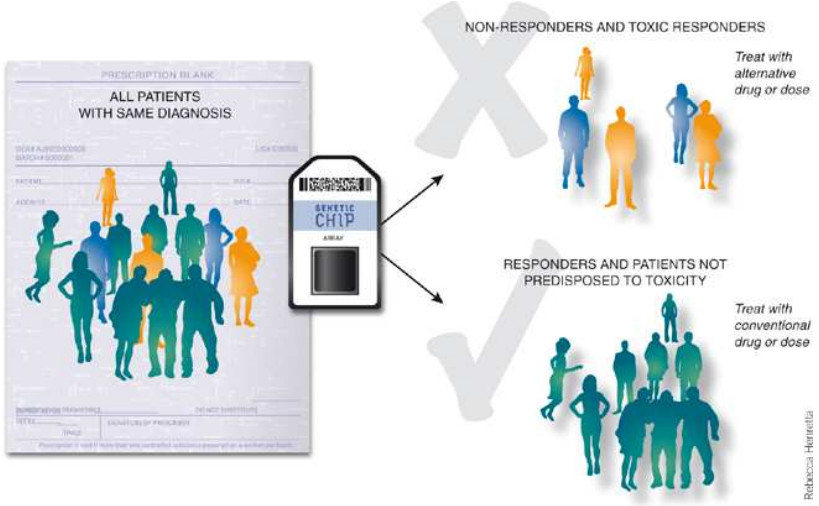


Ref: Piquette-Miller & Grant, Clin Pharmacol Ther 2007

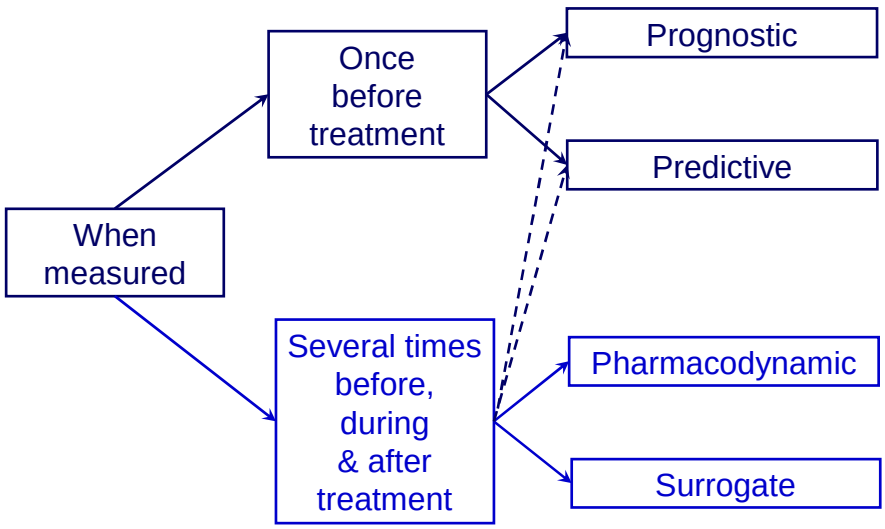
TYPES OF BIOMARKERS (1)

"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

- Prognostic biomarkers, which affect the outcome of patients in terms of a clinical endpoint
- Predictive biomarkers, which affect the effect of a specific treatment on a clinical endpoint
- Surrogate biomarkers, which may replace a clinical endpoint in clinical trials carried out to evaluate the effect of a specific treatment

Ref: Buyse & Michiels, in Kelly & Halabi, Eds: Oncology Clinical Trials 2010

TYPES OF BIOMARKERS (2)



BIOMARKER-BASED TRIAL DESIGNS

Trial phase	Effect of treatment	Type of biomarker	Effect of biomarker
II	*Known*	*Prognostic*	*Known*
III	*Unknown*	*Predictive*	*Unknown*

➥ Trial design

➥ Examples

Ref for this presentation: Buyse, Michiels et al, Expert Rev Mol Diag (to appear).

BIOMARKER-BASED TRIAL DESIGNS

Trial phase	Effect of treatment	Type of biomarker	Effect of biomarker
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➥ Trial designs
Retrospective series

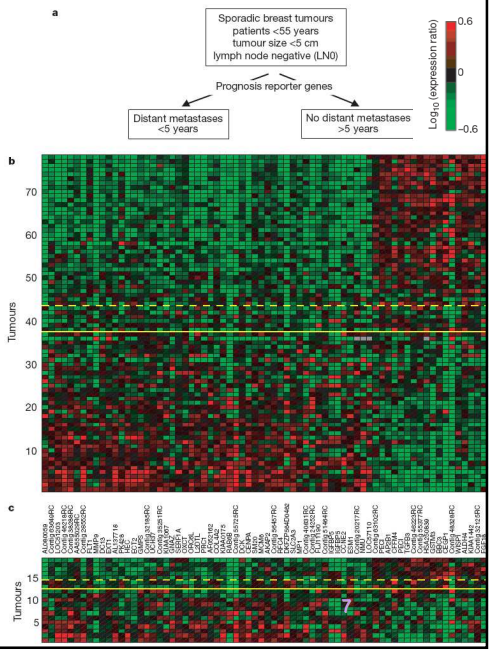
➥ Examples
Gene signatures (Mammaprint™, OncotypeDX®)

MAMMAPRINT® DEVELOPMENT

- Training set: 78 pts, 34 with distant metastasis at 5 years
- Gene expression levels ranked by correlation coefficient with metastatic status at 5 years
- 70 genes with highest correlations

  = « molecular signature »

Ref: van't Veer, Nature 2002



EXTERNAL VALIDATION OF MAMMAPRINT®

Validation study 1

- N=295 breast cancers from one single center
- Potential bias: inclusion of 61 pts of the training set
- Accuracy of MammaPrint for distant relapse at 5-years:

  Se (correctly classifying pts who relapsed) = 93% (CI95% 81% to 99%)

  Sp (correctly classifying pts who did not) = 53% (CI95% 44% to 61%)

Validation study 2

- N=307 breast cancers from 5 European centers
- Accuracy of MammaPrint for distant relapse at 5-years:

  Se = 90% ($CI_{95\%}$ 78% to 95%)

  Sp = 42% ($CI_{95\%}$ 36% to 48%)

Ref: Van de Vijver, NEJM 2002; Buyse, JNCI 2006; Michiels, BJC 2007

BIOMARKER-BASED TRIAL DESIGNS

Trial phase	Effect of treatment	Type of biomarker	Effect of biomarker
II	*Known*	*Prognostic*	*Known*
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➥ Trial designs

Retrospective analyses of randomized phase III trials

➥ Examples

- *KRAS mutations in CRC*
- *EGFR mutations in NSCLC*

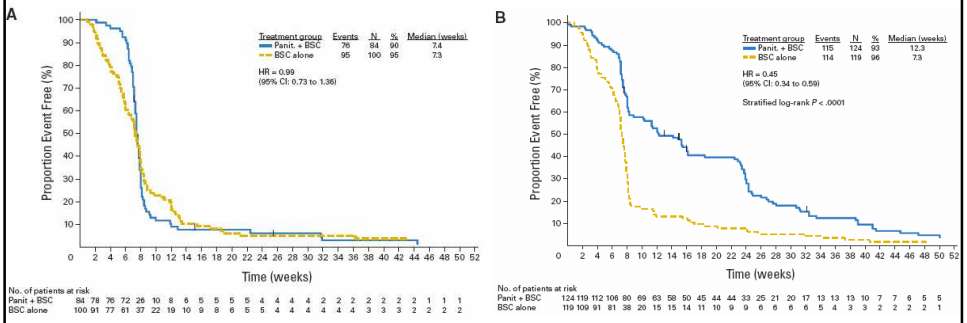
LACK OF RESPONSE OF MUTANT KRAS TUMORS: 1ST EVIDENCE IN SMALL RETROSPECTIVE SERIES

Reference	Responses among *KRAS* mutant	Responses among *KRAS* wild-type
Lièvre 2006	0/13	11/17 *(65%)*
Di Fiore 2007	0/16	12/43 *(28%)*
Khambata-Ford 2007	3/30	24/50 *(48%)*
Benvenuti 2007	1/16	10/32 *(31%)*
Frattini 2007	1/10	9/17 *(53%)*
De Roock 2008	0/42	27/66 *(41%)*
Lièvre 2008	0/36	34/78 *(44%)*
Amado 2008	0/84	21/124 *(17%)*

RETROSPECTIVE ANALYSIS OF PHASE III TRIALS

KRAS mutated

KRAS Wild type



Interaction Test p<0.0001 (progression-free survival)

Ref: Amado, JCO 2008

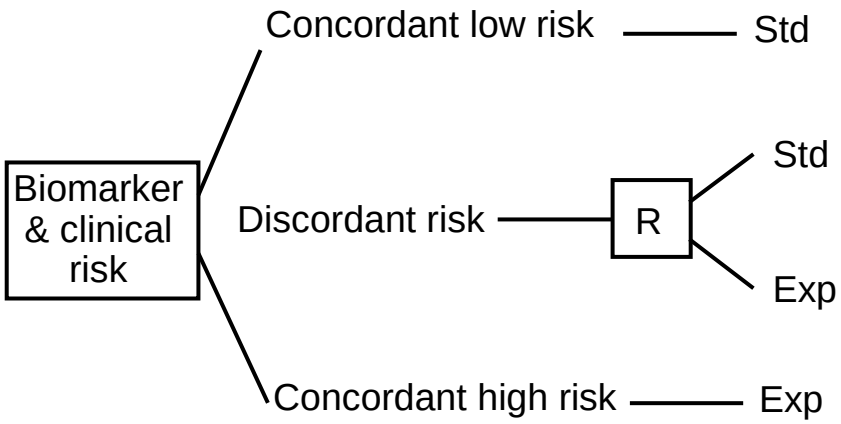
BIOMARKER-BASED TRIAL DESIGNS

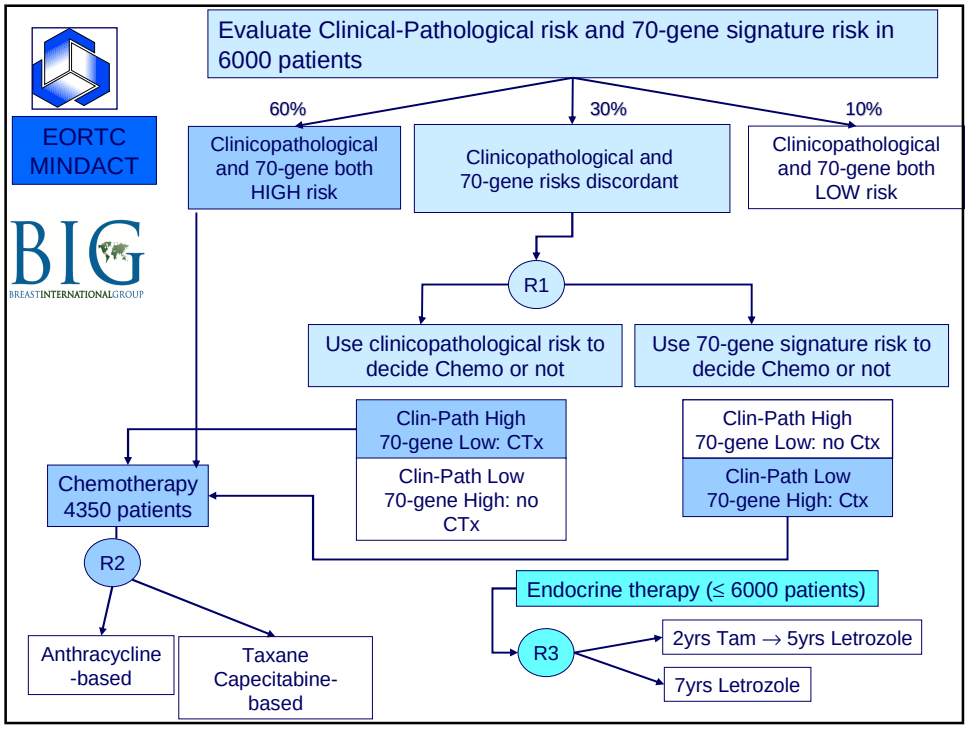
Trial phase	Effect of treatment	Type of biomarker	Effect of biomarker
II	*Known*	*Prognostic*	*Known*
III	*Unknown*	*Predictive*	*Unknown*

➥ Trial designs
« Clinical utility » trials

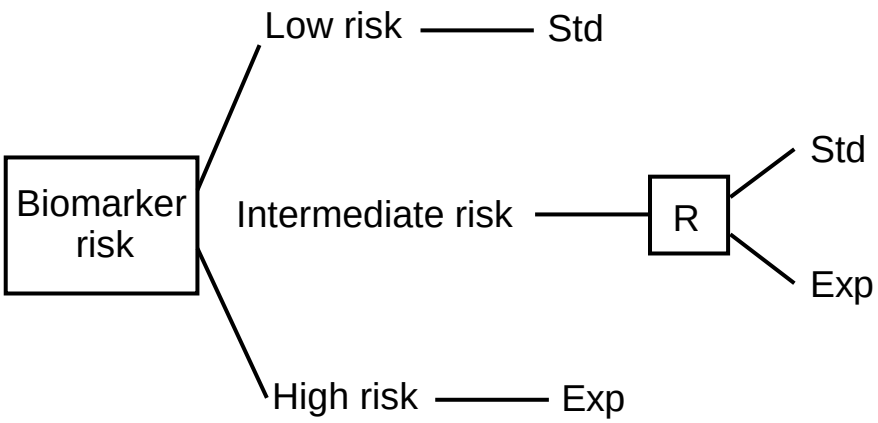
➥ Examples
MINDACT and TAILORx in early breast cancer

DISCORDANT RISK RANDOMIZED DESIGN

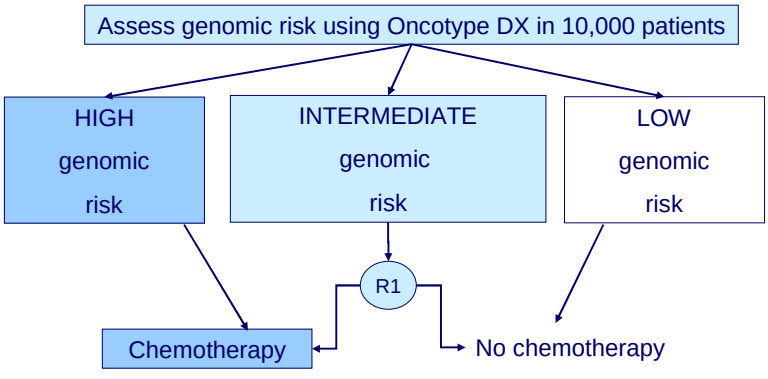




INTERMEDIATE RISK RANDOMIZED DESIGN



THE TAILOR-X TRIAL



ISSUES WITH CLINICAL UTILITY TRIALS

- Very large sample sizes are required (pragmatic trials)
- Unclear what hypothesis is being tested (treatment effect known)
- Prognostic biomarkers less useful to choose treatment than predictive biomarkers (hence emphasis from now on will be on predictive biomarkers)

Ref: Bogaerts, Nature Clin Pract 2006

BIOMARKER-BASED TRIAL DESIGNS

Trial phase	Effect of treatment	Type of biomarker	Effect of biomarker
II	*Known*	*Prognostic*	*Known*
III	*Unknown*	*Predictive*	*Unknown*

➥ Trial designs
- *Cross-over designs*
- *Bayesian*

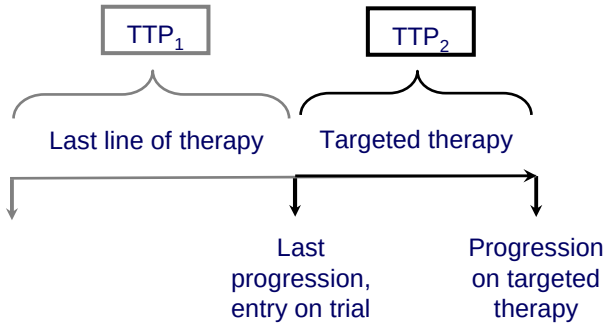
➥ Examples
- *Molecular profiling*
- *BATTLE in NSCLC*

TRIAL OF MOLECULAR PROFILING

At least two prior lines of therapy for advanced disease, no further therapy available

Molecular profiling of tumor biopsy by IHC, FISH or micro-array to identify target

Targeted agents were all approved agents (cytotoxics or biologicals)



Ref: Von Hoff, AACR 100th Annual Meeting, Denver, CO, April 18-22, 2009

TRIAL OF MOLECULAR PROFILING

Define the "Time To Progression Ratio" as
$TTPR = TTP_2 / TTP_1$

The natural history of most advanced tumors suggests that TTPR < 1 (patients tend to progress faster on successive lines of treatment)

Trial designed to test the hypothesis that at least 15% of the patients have TTPR > 1.3

Ref: Mick, Contr ClinTrials 2000

TRIAL OF MOLECULAR PROFILING

Proportion of patients with TTPR > 1.3:

18 / 66 (27%, 95% C.I. 17% - 38%, *P* = 0.007)

Breast	8 / 18 (44%)
Colorectal	4 / 11 (36%)
Ovarian	1 / 5 (20%)
Others	5 / 32 (16%)

Among the 18 patients with TTPR > 1.3, none would have received same drug through physician's choice

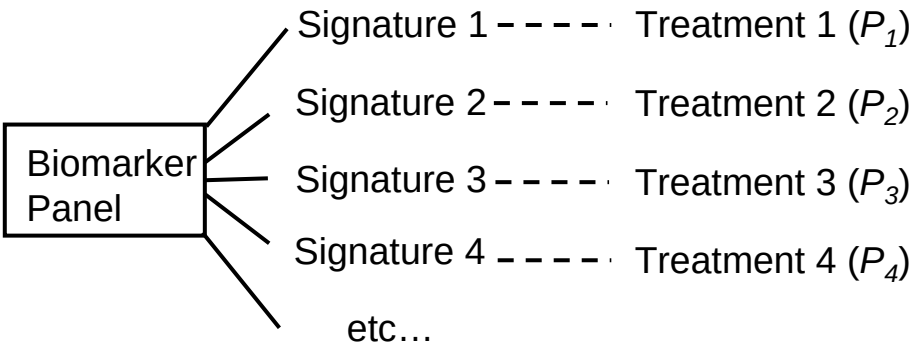
Ref: Von Hoff, AACR 100th Annual Meeting, Denver, CO, April 18-22, 2009.

ISSUES WITH TRIAL OF MOLECULAR PROFILING

- Only 66 patients of 106 could have molecular profiling
- Non-randomized trial, hence no evidence that physician's choice would have yielded inferior results
- Is TTPR > 1.3 a relevant endpoint?
- Cross-over design inefficient if low correlation between TTP_1 and TTP_2

Ref: Von Hoff, AACR 100th Annual Meeting, Denver, CO, April 18-22, 2009.

BAYESIAN ADAPTIVE PHASE II DESIGN *(PUTATIVE BIOMARKER)*



P_i : probability of allocating treatment *i*

BATTLE (Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination)

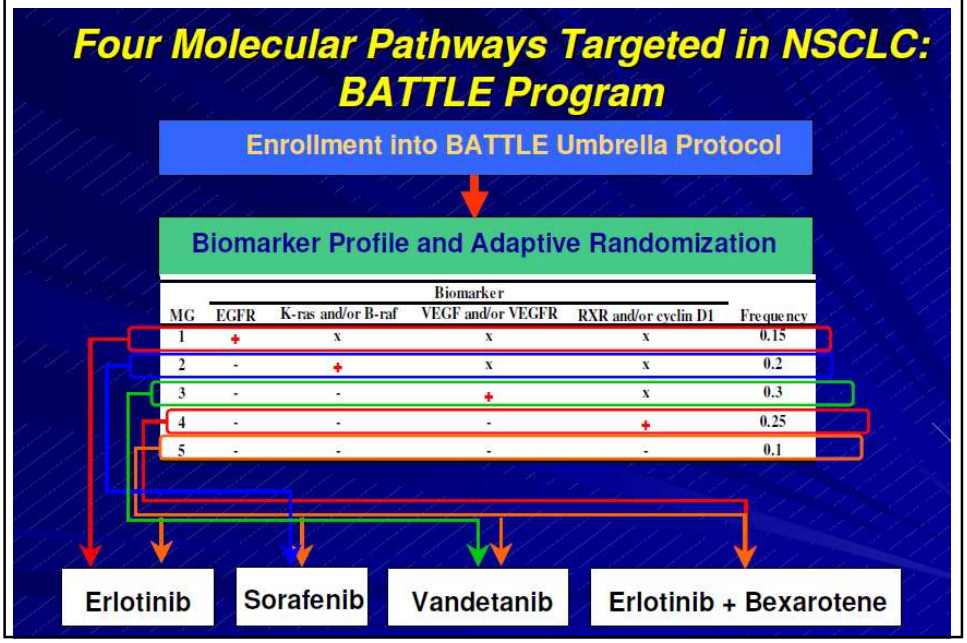
- Evaluate targeted therapy agent(s) with different biomarker profiles
- Stage IV recurrrent non-small cell lung cancer with endpoint: 8-week disease-free survival (DFS) rate

Ref: Lee, Clin Trials 2008; Kim, AACR 2010

BATTLE CHARACTERISTICS (1)

- Treat more patients in promising groups according to each pt's biomarker profile
- Start with equal randomization but switch to « adaptive » randomization after 20 pts in each treatment arm
- Early stopping for lack of efficacy in a biomarker × treatment group
- Provide an accurate estimate of true DFS in each of the biomarker × treatment groups
- Borrow strength from patients treated with same agent but different biomarker profile

BATTLE CHARACTERISTICS (2)



ISSUES WITH BATTLE DESIGN

- Needs prior information to form and rank biomarker groups
- Needs prior distribution for treatment effects
- Choice of adaptive randomization (when to start, what allocation ratio)
- Ethics of adaptive randomization
- Need fast outcome assessment
- Missing or incomplete biomarker profile (with inadequate amount of tissue)
- No power gain as compared to equal randomization

Ref: Lee, Clin Trials 2008

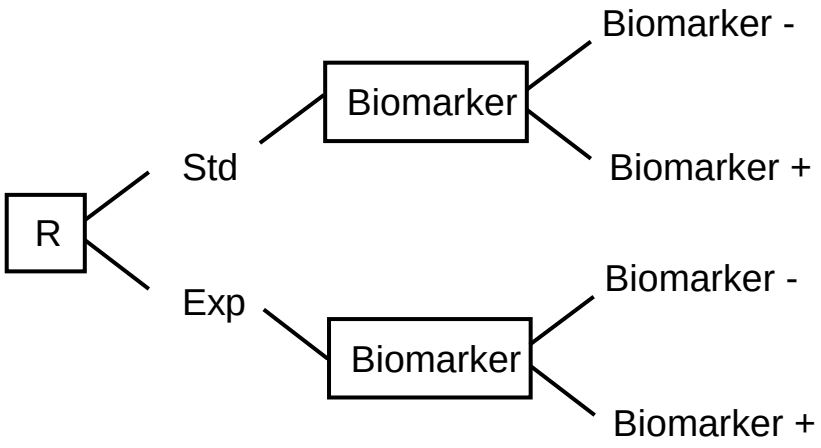
BIOMARKER-BASED TRIAL DESIGNS

Trial phase	Effect of treatment	Type of biomarker	Effect of biomarker
II	*Known*	*Prognostic*	*Known*
III	*Unknown*	*Predictive*	*Unknown*

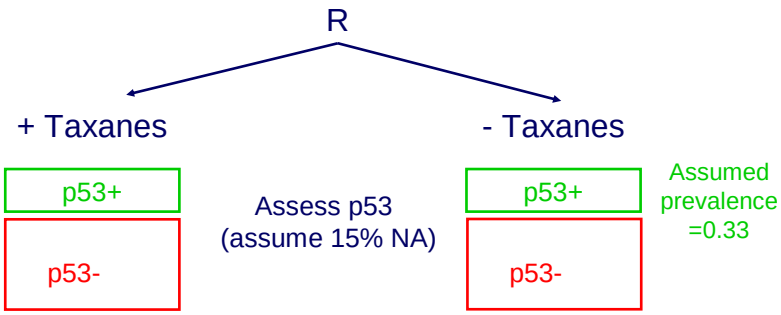
➥ Trial designs
- *Randomize-all*
- *Interaction*
- *Biomarker-strategy*

➥ Examples
- *P53 in ABC*
- *MARVEL in NCSLC*
- *ERCC1 in NSCLC*

RANDOMIZE-ALL DESIGN



EORTC 10994 ("P53") TRIAL IN ADVANCED BREAST CANCER



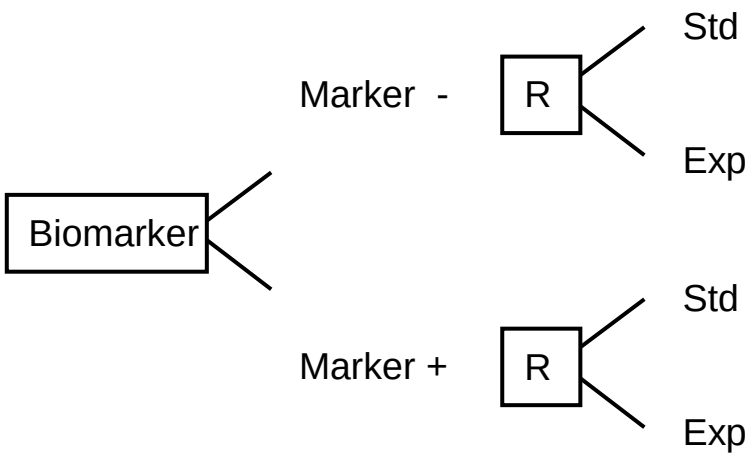
- Powered for detecting a larger effect in p53+ subgroup
- Overall: 80% power of detecting a HR=1.25 at α=0.02
- Also planned to test for interaction
- Anticipated 5.5 yr accrual, analyses 2.5 yrs after last entry

ISSUES WITH RANDOMIZE-ALL DESIGN

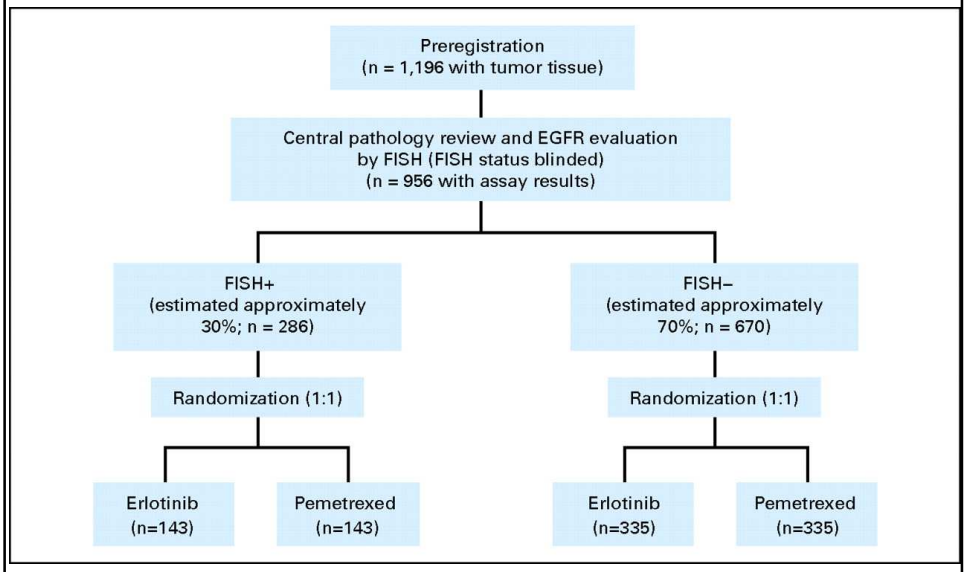
- Randomize-all design not efficient if
  - there is a strong biological rationale for no or little treatment effect in the biomarker - subgroup
  - the prevalence of biomarker + is low
  - the positive predictive value of the assay is high (> 0.90)

Ref: Maitournam, Stat Med 2005; Simon, CCR 2006; Simon, CCR 2008; George, CCR 2008; Hoering, CCR 2008

INTERACTION (BIOMARKER-STRATIFIED) RANDOMIZED DESIGN



MARVEL TRIAL IN NSCLC

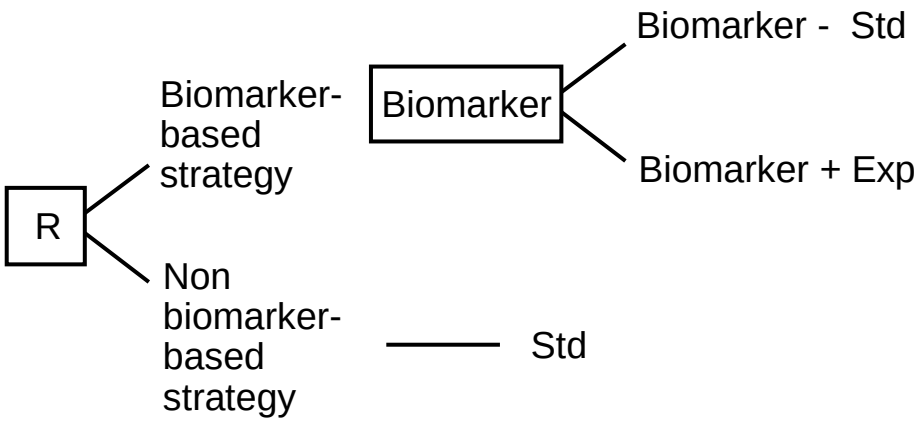


ISSUES WITH INTERACTION DESIGNS

- Biomarker often unknown or poorly defined (e.g. EGFR mutations in NSCLC, *KRAS* mutations in colorectal cancer) for prospective stratification
- The power of the “interaction test” is very low, hence huge sample sizes are required and/or a very sensitive endpoint (e.g. PSA, tumor measurements or functional imaging)

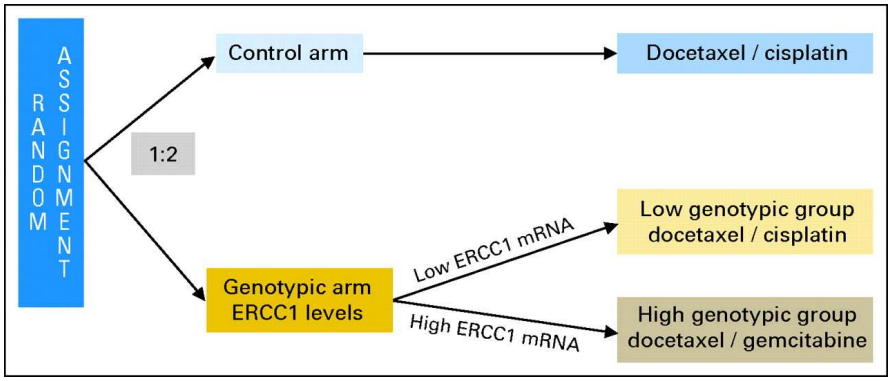
Ref: Buyse, Nature Rev Clin Oncol 2010

BIOMARKER-BASED STRATEGY DESIGN WITH STANDARD CONTROL



Ref: Sargent, JCO 2005

SPANISH ERCC1 TRIAL



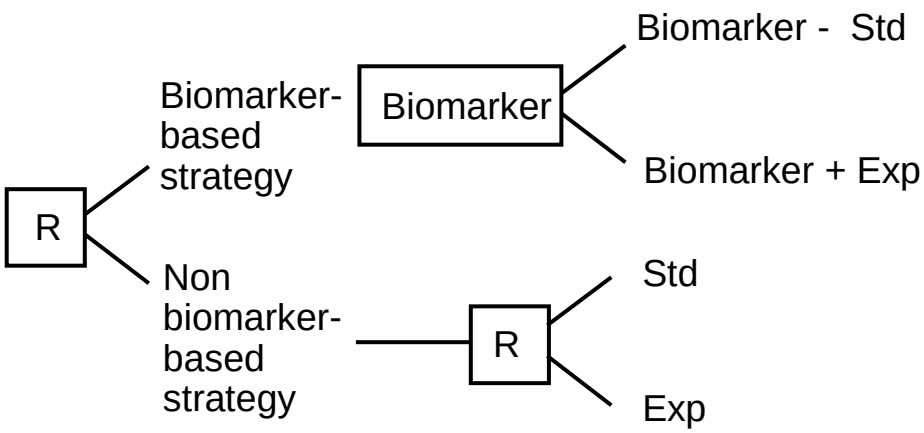
Ref: Cobo, JCO 2007

ISSUES WITH BIOMARKER-BASED STRATEGY WITH STANDARD CONTROL

- Low statistical power, especially if prevalence of biomarker is low, since in that case few patients benefit from the marker-based treatment optimization
- Confounding between predictive effect of biomarker and effect of experimental therapy

Ref: Mandrekar, JCO 2009; Freidlin, JNCI 2010; Hoering, CCR 2008; Young, Clin Trials 2010; Lee, Clin Trials 2010; Michiels, Stat Med (in

BIOMARKER-BASED STRATEGY DESIGN WITH RANDOMIZED CONTROL



ISSUES WITH BIOMARKER-BASED STRATEGY WITH RANDOMIZED CONTROL

- Very low statistical power, since random strategy will lead to correct treatment for many patients
- Randomization ratio must reflect biomarker prevalence, often unknown in advance

Ref: Mandrekar, JCO 2009; Freidlin, JNCI 2010; Hoering, CCR 2008; Young, Clin Trials 2010; Lee, Clin Trials 2010

BIOMARKER-BASED TRIAL DESIGNS

Trial phase	Effect of treatment	Type of biomarker	Effect of biomarker
II	*Known*	*Prognostic*	*Known*
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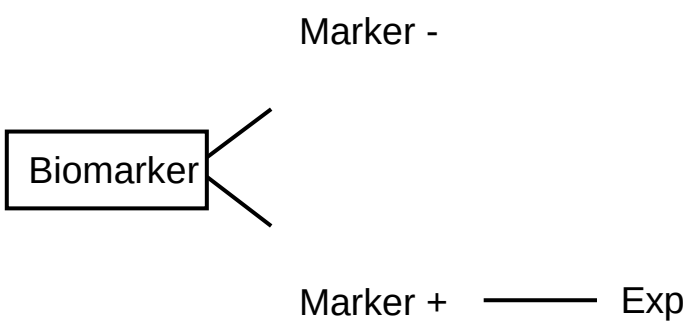
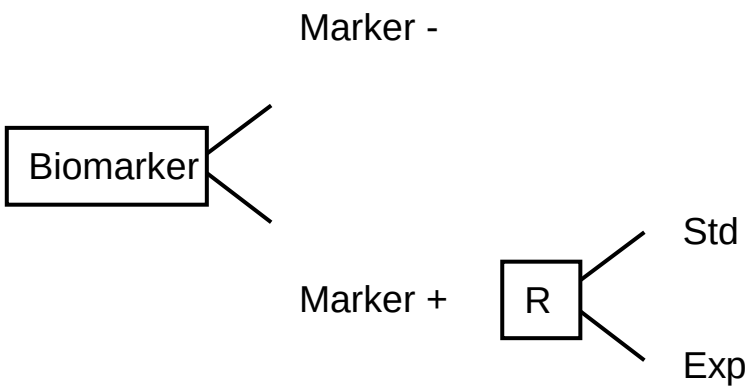
➥ Trial designs
- *Targeted (selection)*

➥ Examples
- *Herceptin trials in ABC*

TARGETED (SELECTION) SINGLE-ARM DESIGN



TARGETED (SELECTION) RANDOMIZED DESIGN



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Trial phase	Effect of treatment	Type of biomarker	Effect of biomarker
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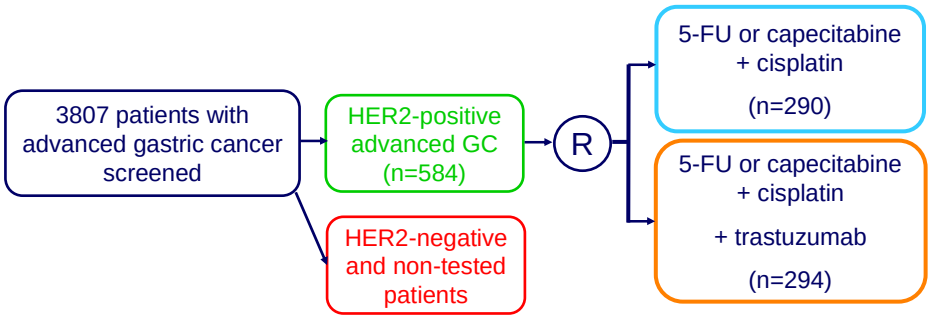
➥ Trial designs
- *Targeted*

➥ Examples
- *TOGA in AGC*

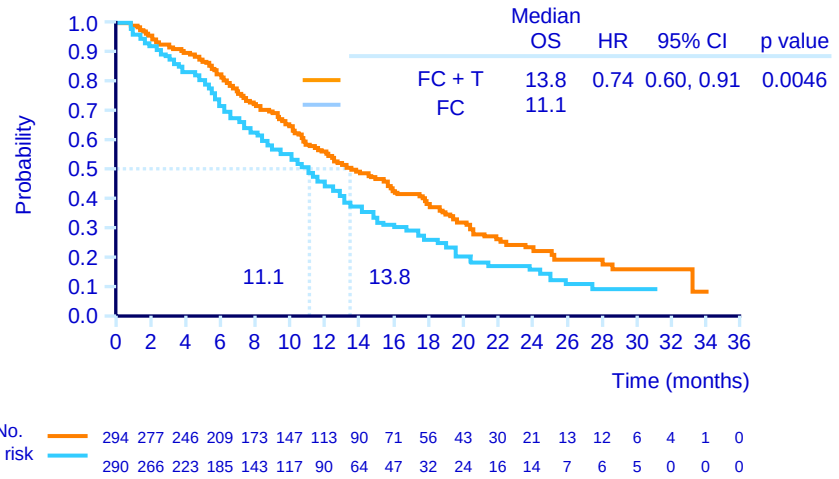
TOGA TRIAL DESIGN

Phase III, open-label international study



Ref: Bang, ASCO 2009; Abstract 4556

TOGA PRIMARY ENDPOINT: OS



CI, confidence interval; T, trastuzumab

ISSUES WITH TARGETED DESIGN

- Targeted design may be less efficient than randomize-all design if drug has at least some activity in biomarker - patients
- Effect in biomarker - patients may never be known (e.g. effect of adjuvant trastuzumab in patients with early breast cancer)
- Loss of opportunity for biomarker - patients
- In a randomize-all design, multiple candidate biomarkers can be tested

Ref: Maitournam, Stat Med 2005; Simon, CCR 2006; Simon, CCR 2008; George, CCR 2008; Hoering, CCR 2008; Michiels, Stat Med (in press)

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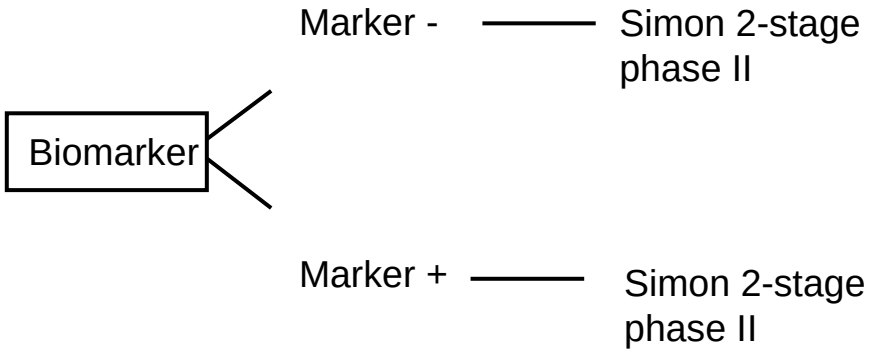
➥ Trial designs
- *Adaptive parallel*
- *Tandem two-stage*

➥ Examples
- *FGFR1 inhibitor in BC*
- *saracatinib in PC*

ADAPTIVE PARALLEL

PUTATIVE BIOMARKER



Example : phase II trial of dovitinib in FGFR1-amplified and nonamplified HER2-negative metastatic breast cancer

Ref: Jones 2007; McShane 2009; André et al ASCO 2010

TANDEM TWO-STAGE
(BIOMARKER NOT KNOWN AT ALL)

- Simon 2-stage design in overall population
- End of stage 1:
  - if enough responses ⇨ continue in overall population
  - else ⇨ develop molecular predictor & only recruit patients predicted to be « responders »
- Example : phase II clinical trial of saracatinib as monotherapy in previously treated patients with metastatic pancreatic cancer

Ref: Pusztai, CCR 2007; Nallaparedy, ASCO GI 2010

BIOMARKER-BASED TRIAL DESIGNS

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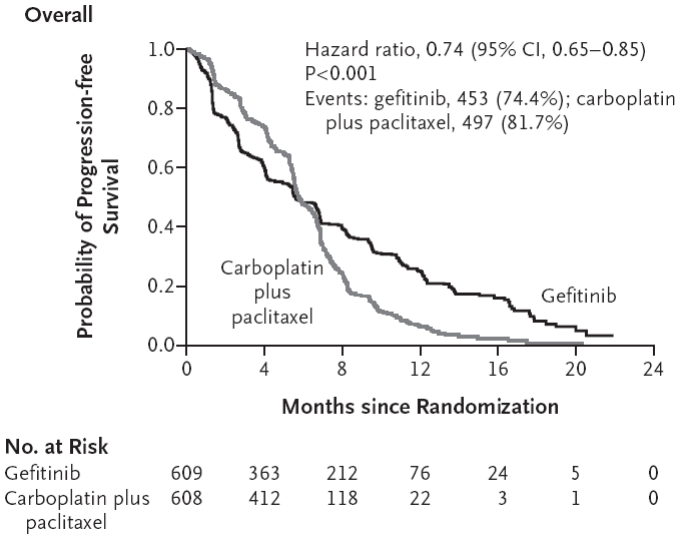
➥ Trial designs
- *Enrichment*
- *Prospective subset*

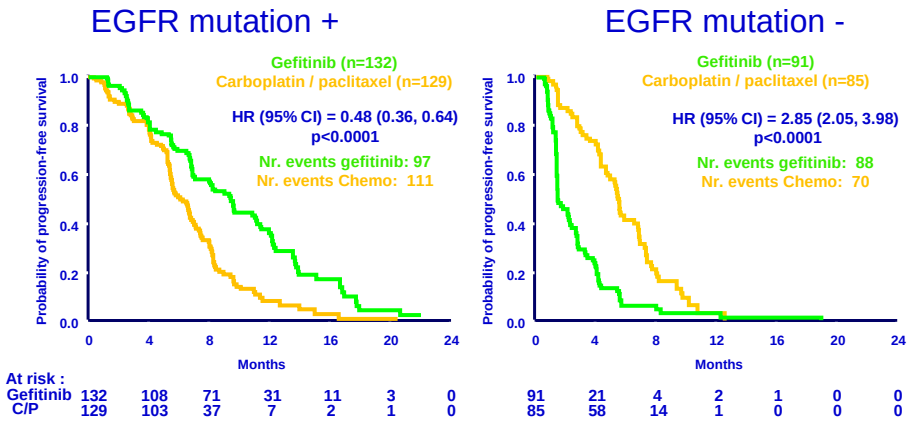
➥ Examples
- *IPASS in NSCLC*
- *SATURN in NSCLC*

IPASS TRIAL ENRICHED FOR MUTATION + PATIENTS (ASIAN POPULATION)



Ref: Mok, NEJM 2009

IPASS TRIAL ENRICHED FOR MUTATION + PATIENTS (ASIAN POPULATION)



Ref: Mok, NEJM 2009

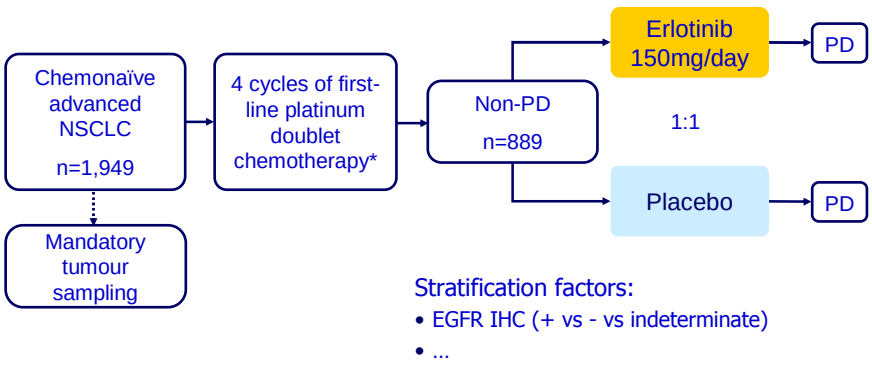
PROSPECTIVE SUBSET

- Simplest approach: split significance level:
  $\alpha = \alpha_{all} + \alpha_{biomarker+}$
  - the new treatment is compared with the control in the overall population, ignoring the biomarker
  - if $p_{all} \leq \alpha_{all}$ claim effectiveness for all patients
  - if not, the new treatment is compared with the control in biomarker + patients only, and if $p_{biomarker+} \leq \alpha_{biomarker+}$, claim effectiveness for biomarker + patients only

- There are less conservative, yet properly controlled, ways of adjusting α for both (correlated) tests

Ref: Wang, Pharm Stat 2007; Jiang, JNCI 2007; Alosh, Stat Med 2009; Wang, Biom J 2009; Spiessens, Contr Clin Trials 2010

SATURN DESIGN



Co-primary endpoints:

- PFS in all patients
- PFS in patients with EGFR IHC+ tumours

SATURN OVERALL RESULTS

	Erlotinib (n = 438)	Placebo (n = 451)	HR	*P*
PFS	(n = 437)	(n = 447)		
PFS at 12 weeks	53%	40%	0.71	< .0001
PFS at 24 weeks	31%	17%		
Median PFS	12.3 weeks	11.1 weeks		
Median OS	12 months (n = 436)	11 months (n = 445)	0.81	.0088

KEY QUESTIONS FOR DESIGN CHOICE

- What do we know reliably before the trial starts (in terms of treatment and biomarker effects)?
- What do we want to know reliably after the trial is done (i.e. is the trial for discovery or confirmation ?)
- What are the consequences of type I and type II errors in terms of biomarker usefulness?
- Will there be repeat trials?