Basics in clinical trials design

Monica Arnedos MD

Breast Unit

Gustave Roussy

France

monica.arnedos@gustaveroussy.fr

The History of interventional clinical trials

1st clinical trial: 1747 Clinical trial on scurvy

A CLINICAL TRIAL OF SANOCRYSIN IN PULMONARY TUBERCULOSIS[1]

J. BURNS AMBERSON, JR., B. T. McMAHON AND MAX PINNER

Obviously, the matching could not be precise, but it was as close as possible, each patient having previously been studied independently by two of us. Then, by a flip of the coin, one group became identified as group I (sanocrysin-treated) and the other as group II (control). The members of the separate groups were known only to the nurse in charge of the ward and to two of us. The patients themselves were not aware of any distinction in the treatment administered.

Traditional approach

	Phase 1	Phase 2	Phase 3	Phase 4
Number of participants	15-30 people	Less than 100 people	Generally, from 100 to thousands of people	Several hundred to several thousand people
Purpose	• To find a safe dosage • To decide how the agent should be given • To observe how the agent affects the human body	• To determine if the agent or intervention has an effect on a particular cancer • To see how the agent or intervention affects the human body	• To compare the new agent or intervention (or new use of a treatment) with the current standard	• To further evaluate the long-term safety and effectiveness of a new treatment

Cancer Clinical Trials, The Basic Workbook; September 2002

Traditional approach

The Drug Development and Approval Process

	Preclinical Testing		Clinical Trials			Post-Clinical Trials		Total Years for Drug Approval
	Step 1 Laboratory/ Preclinical Testing	*Step 2* File IND[1] application with FDA[2]	*Step 3* Phase 1	*Step 4* Phase 2	*Step 5* Phase 3	*Step 6* File NDA[3] or BLA[4] with FDA	*Step 7* FDA Approval	
Purpose	Assess safety and biological activity in the laboratory and in animal models	Obtain FDA approval to begin clinical testing in humans after promising results in laboratory	Determine what dosage is safe, how treatment should be given	Evaluate effective-ness, looks for side effects	Determine whether the new treatment (or new use of a treatment) is a better alternative to current standard	Inform the FDA of Phase 3 data which supports drug safety and better performance over standard treatment	Review process/ approval	
All anticancer drugs (average number of years)	4.4 years		8.6 years				1.4 years	14.4 years
All drugs* (average number of years)	3.8 years		10.4 years				1.5 years	15.7 years

[1]IND = Investigational New Drug
[2]FDA = Food and Drug Administration
[3]NDA = New Drug Application
[4]BLA= Biologics License Application

Cancer Clinical Trials, The Basic Workbook; September 2002

Traditional approach: Dogmas

- "People who participates in Phase 1 trials are those who have no known effective treatment options, or they have already tried other treatment options"

- "…when a phase 2 trial begins, it is not yet known if the agent tested works against the specific cancer being studied"

- "In phase 3 trials, participants have an equal chance to be assigned to one of two or more groups (…) Placebos are almost never used in cancer clinical trials"

The National Cancer Institute Clinical Trials Education Series

Traditional approach

- **Issues**
  - Lengthy
  - Costly: estimated cost of bringing new drug to the market $800 million to $2 billion[1]
  - In 2000, a new medical compound entering Phase 1 had 5 to 8% chance of eventually reaching the market and around 45% of the Phase 3 programs do not have the optimum dose[2]

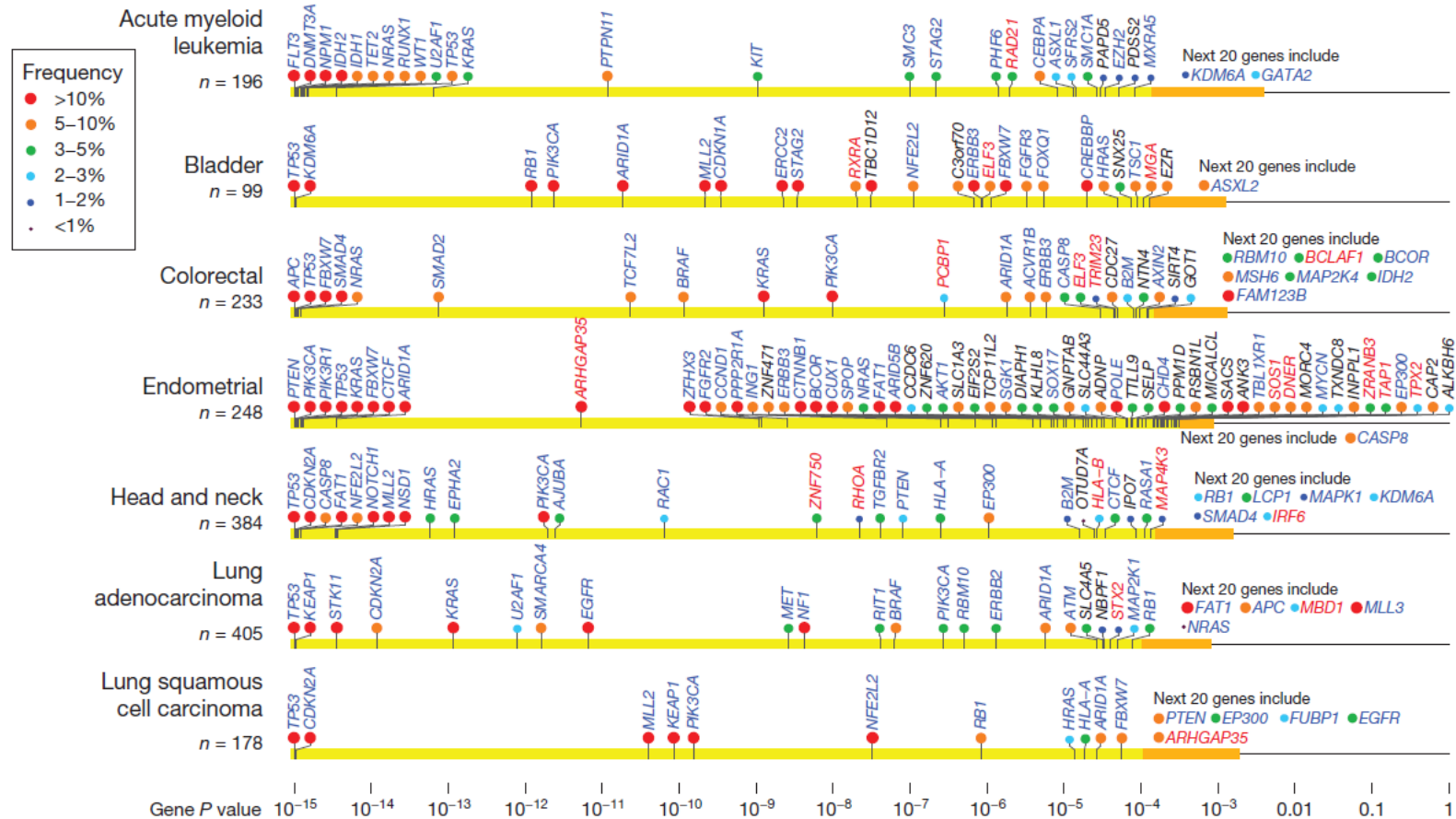- **Need to evolve to adapt to molecular pre-screening**

1. DiMasi et al, J Health Econ 2003;22:151-185
2. Kola et al, Nat Rev Drug Discov 2004; 3:711

Molecular landscape of breast cancer
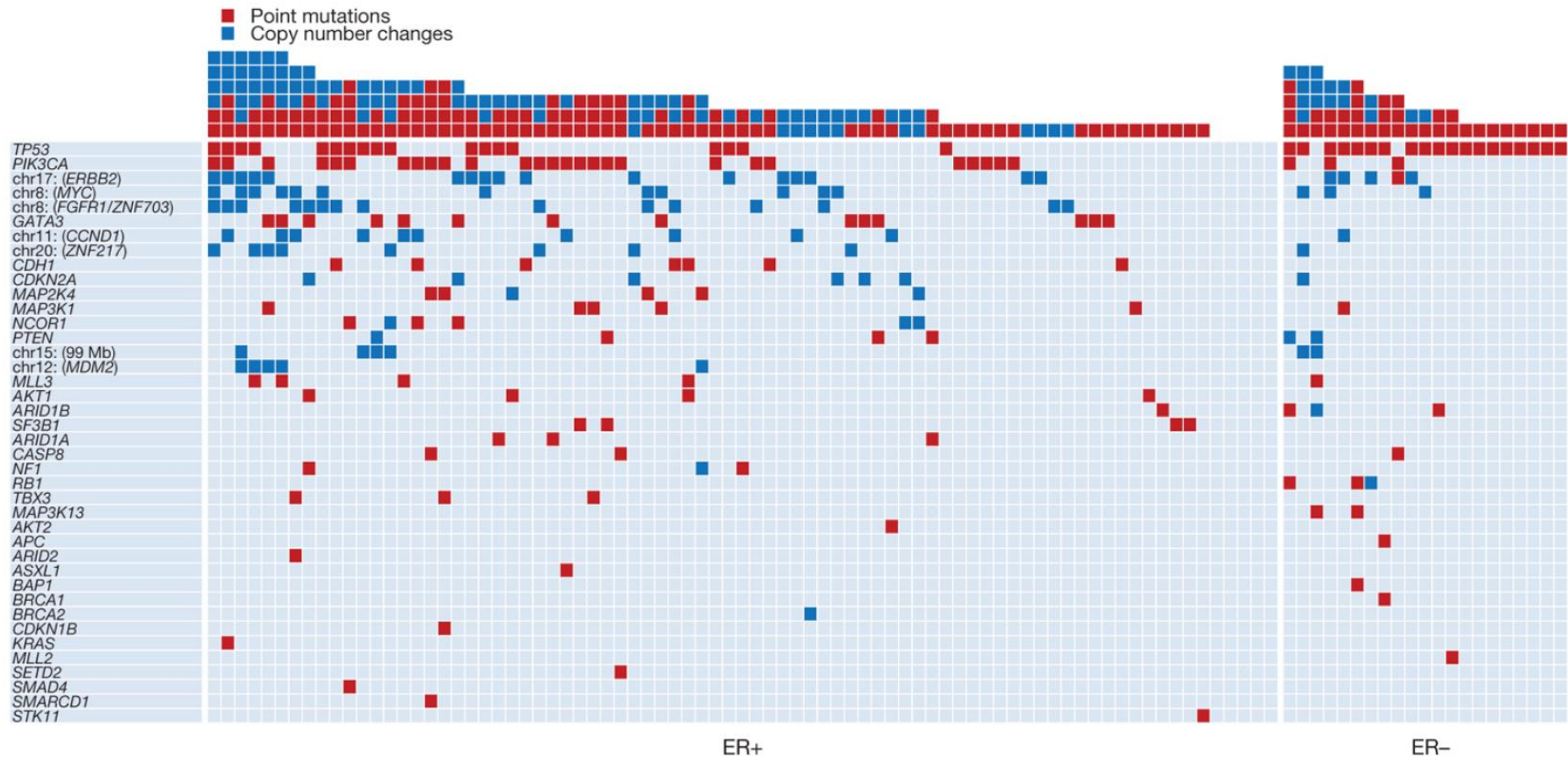
Stephens et al, Nature 2012

Integration of biomarkers in clinical trial designs


Lawrence et al, Nature 2014; 505: 495

How clinical research is evolving to become more efficient and to adapt to this new era of targeted therapy?

I. **implementing strategies to reduce time and number of patients**

II. adapting clinical trials design to molecular pre-screening for targeted therapies

III. application of new measures by the regulatory agencies
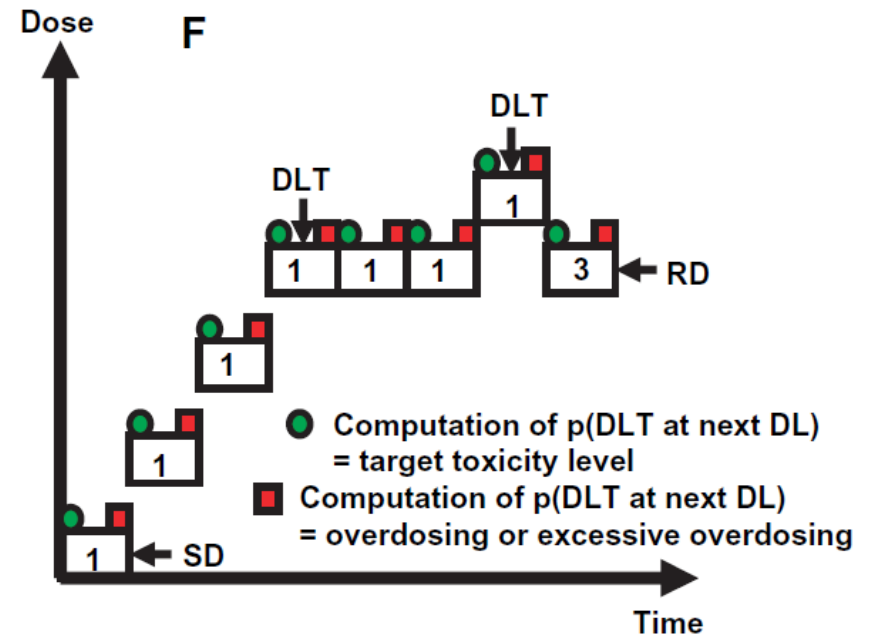
IV. exploiting new scenarios

Alternatives for Phase 1 design

3+3 design

Accelerated titration design: escalation with overdose control
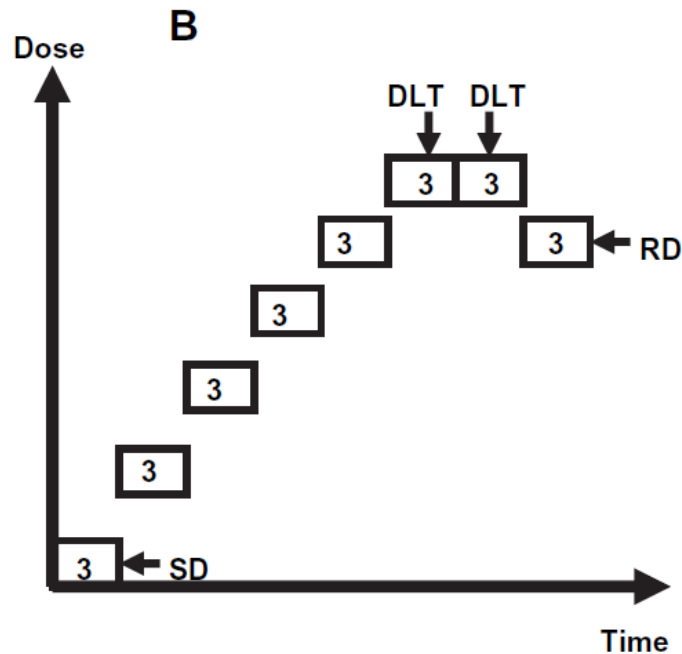
↑ Easy to implement and safe
↓ Slow with many patients
treated at subtherapeutic doses

↑ Rapid and greater proportion
of patients at higher doses
↓ Interpatient dose escalation
may mask cumulative or delayed
toxicities

Modification of Phase 1 trials

Conventional Objectives

Determination of dose and schedule for phase II trials

Safety and toxicity evaluation

Pharmacokinetic assessments

Newer Objectives

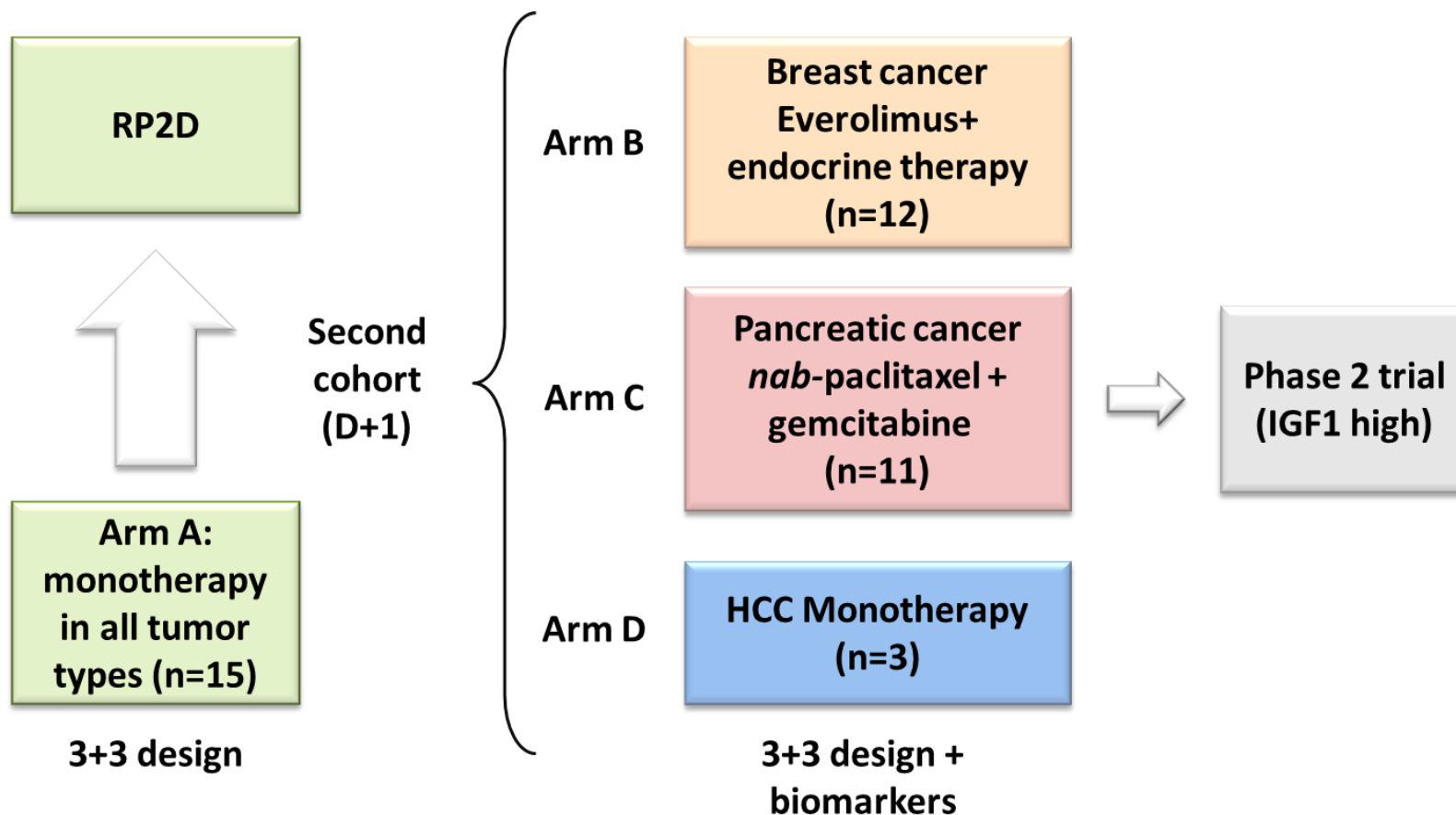Generation of preliminary evidence of target inhibition

Identification of specific target patient populations

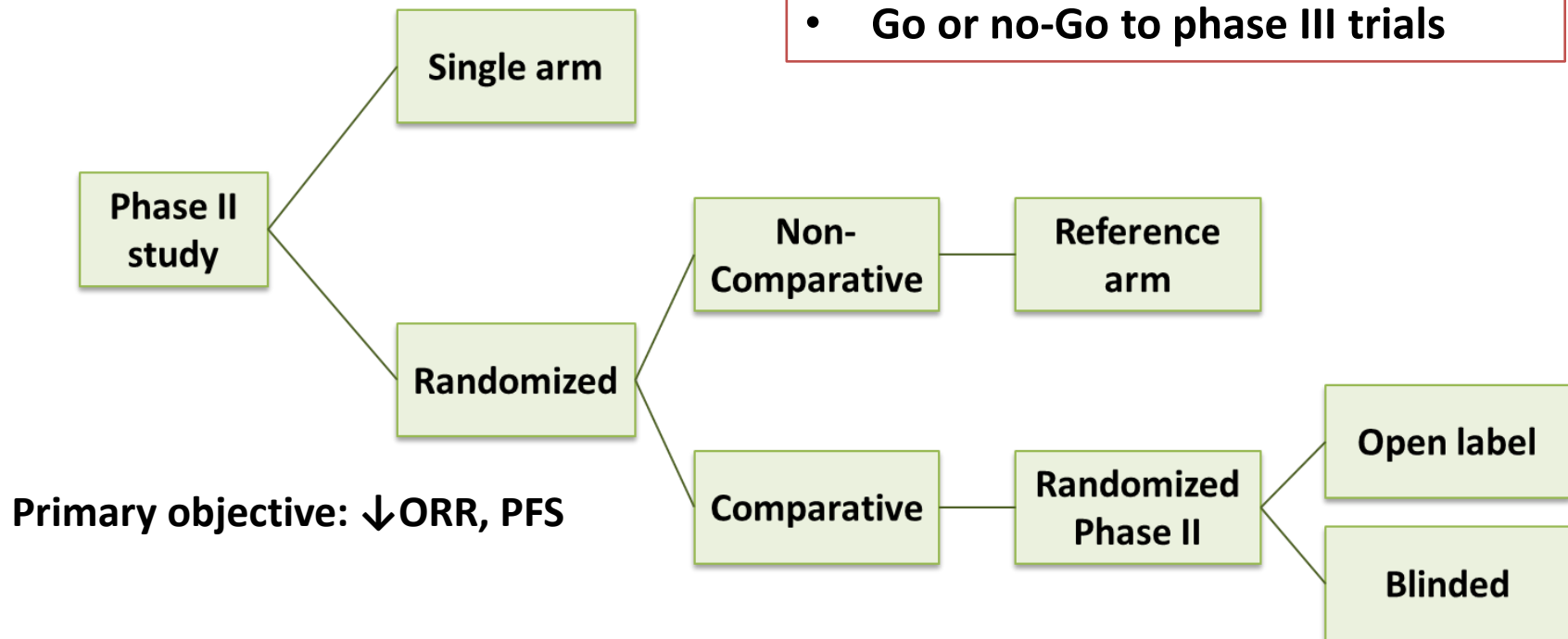Enriched Phase Ib trials (expansion cohorts)

Phase 1/1b trials

A Phase 1 Study of MM-141 (anti-IGF1R/HER3 antibody) in Patients With Advanced Solid Tumors (NCT01733004)

Phase 2 trials

Phase 3 trials

Objective: to compare the therapy with the standard-of-care, to determine if a new treatment is superior to the standard therapy
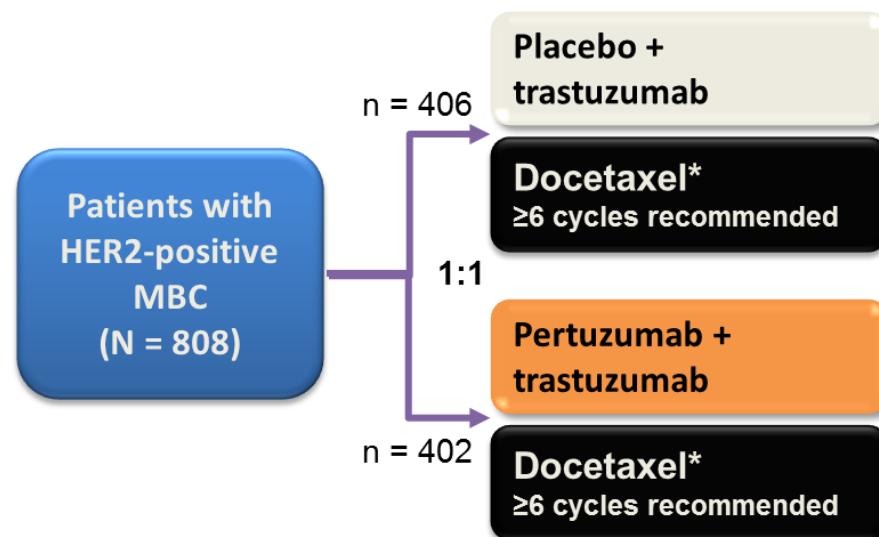
Primary objective: PFS, ↓OS

EMBRACE Trial

762 advanced BC patients

2:1

Eribulin n=508

TPC n=254

CLEOPATRA Trial

Patients with HER2-positive MBC (N = 808)

n = 406

1:1

n = 402

Placebo + trastuzumab

Docetaxel* ≥6 cycles recommended

Pertuzumab + trastuzumab

Docetaxel* ≥6 cycles recommended
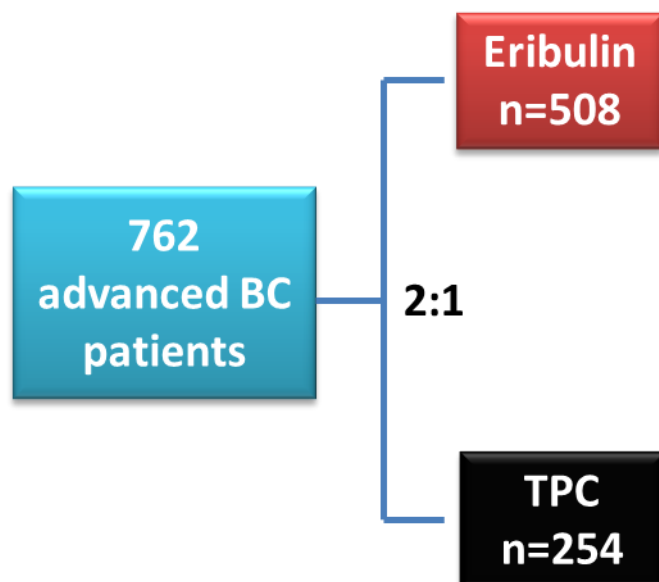
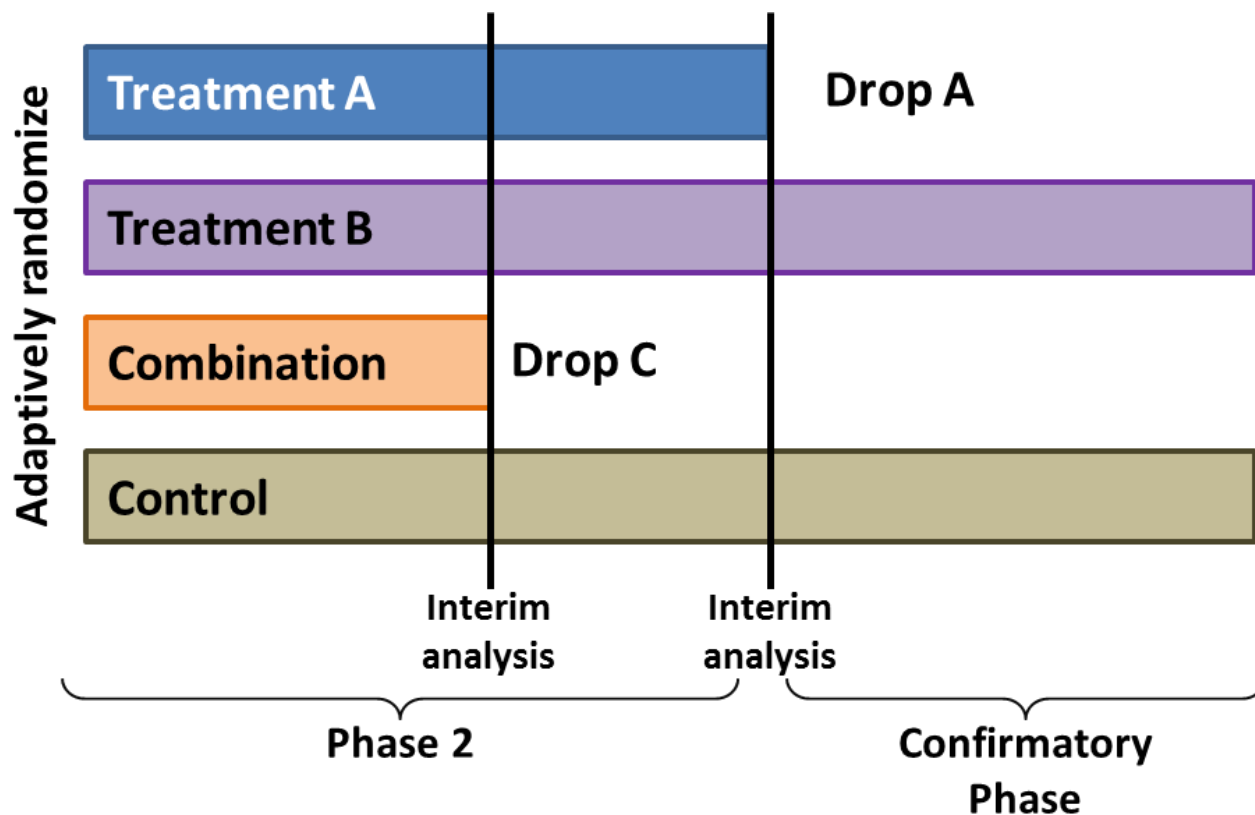**Cortes et al, Lancet 2011; 377: 914–23**

Baselga J, et al. N Engl J Med 2012; 366:109–119.

Standard clinical research
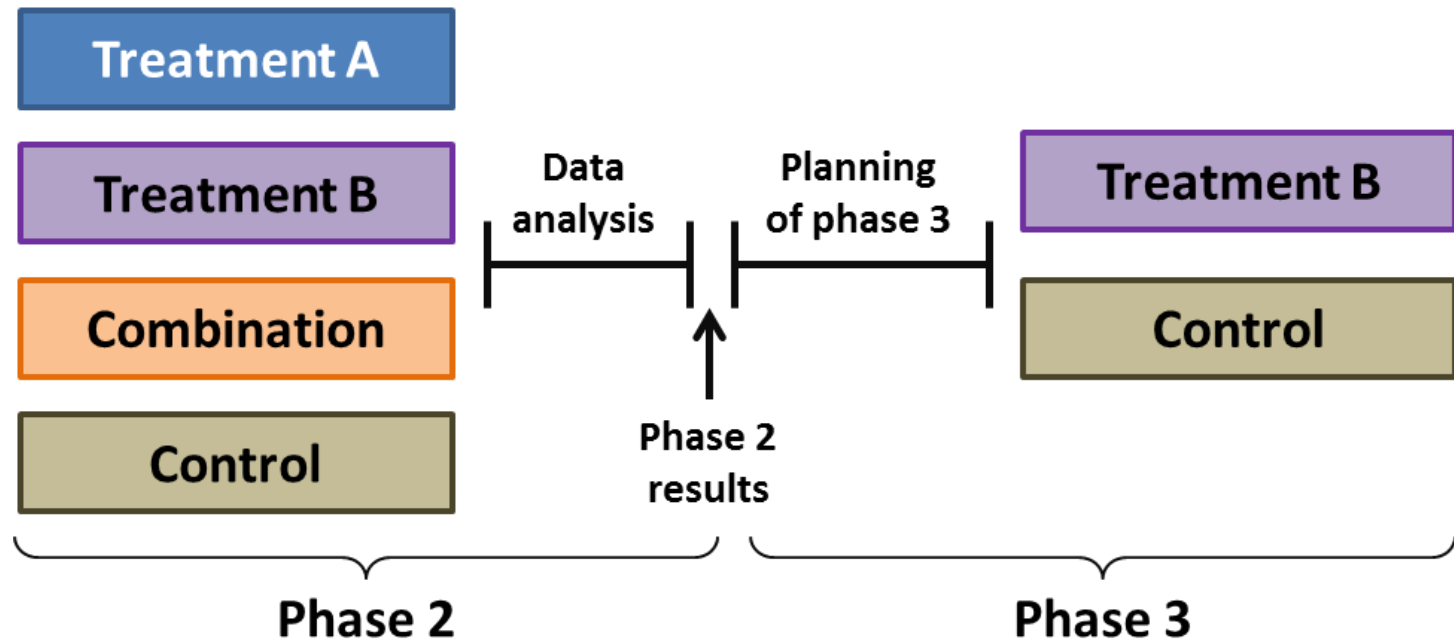
Improvement: Adaptive designs

Seamless adaptive designs

Advantages: shorter duration time, flexible, allows many simultaneous treatment arms and modifications

Requirements: use complicated bayesian approach, frequent interim analysis with a proactive role of the IDMC

I.   implementing strategies to reduce time and number of patients

II.   adapting clinical trials design to molecular pre-screening for targeted therapies

III. application of new measures by the regulatory agencies

IV. exploiting new scenarios

Background and Assumptions

- **Targeted therapy**: treatment designed to affect a particular biologic pathway, mutation, receptor, etc

- A **bioassay** (M) is used to judge presence or absence of the target A prognostic or predictive biomarker

- M can be measured on the eligible patients: Two groups based on the biomarker (M- and M+)

- Targeted therapy is assumed a priori to work primarily in patients with the target (M+)

Things to consider

- How certain is the assumption that the treatment effect will be limited to M+ patients?

- How appropriate is the binary classification into M+ and M-? Is the classification based on a continuous measurement?

- What is the prevalence of M+ patients?
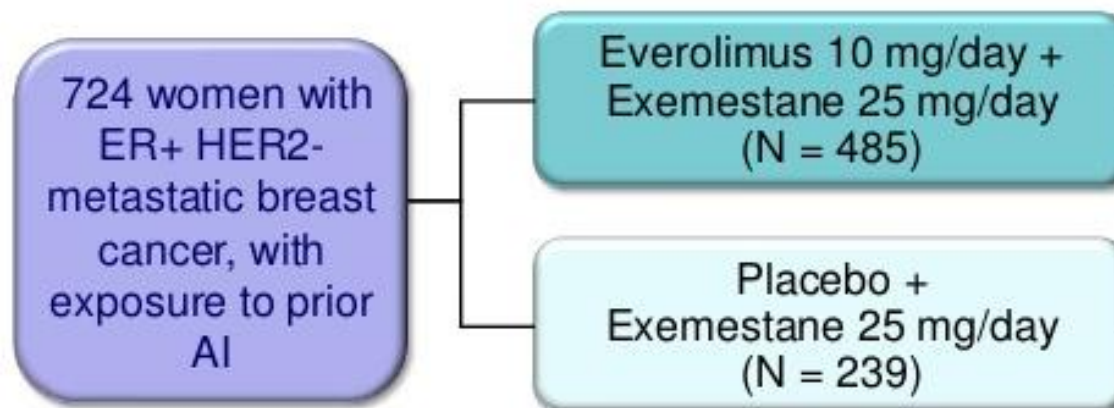
- How accurate is the assay?

Traditional design

No pre-selection
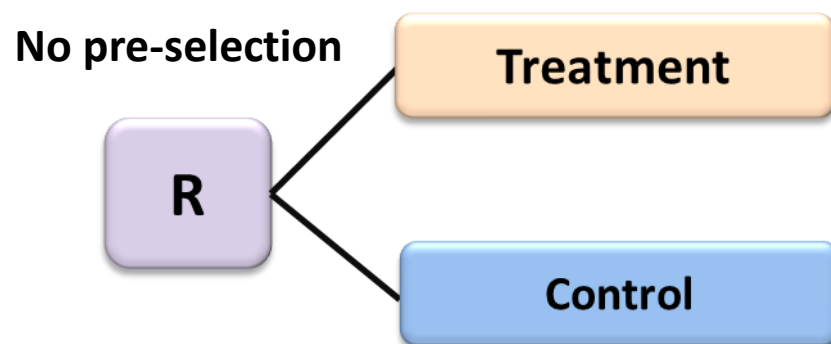
Advantages
- Simple
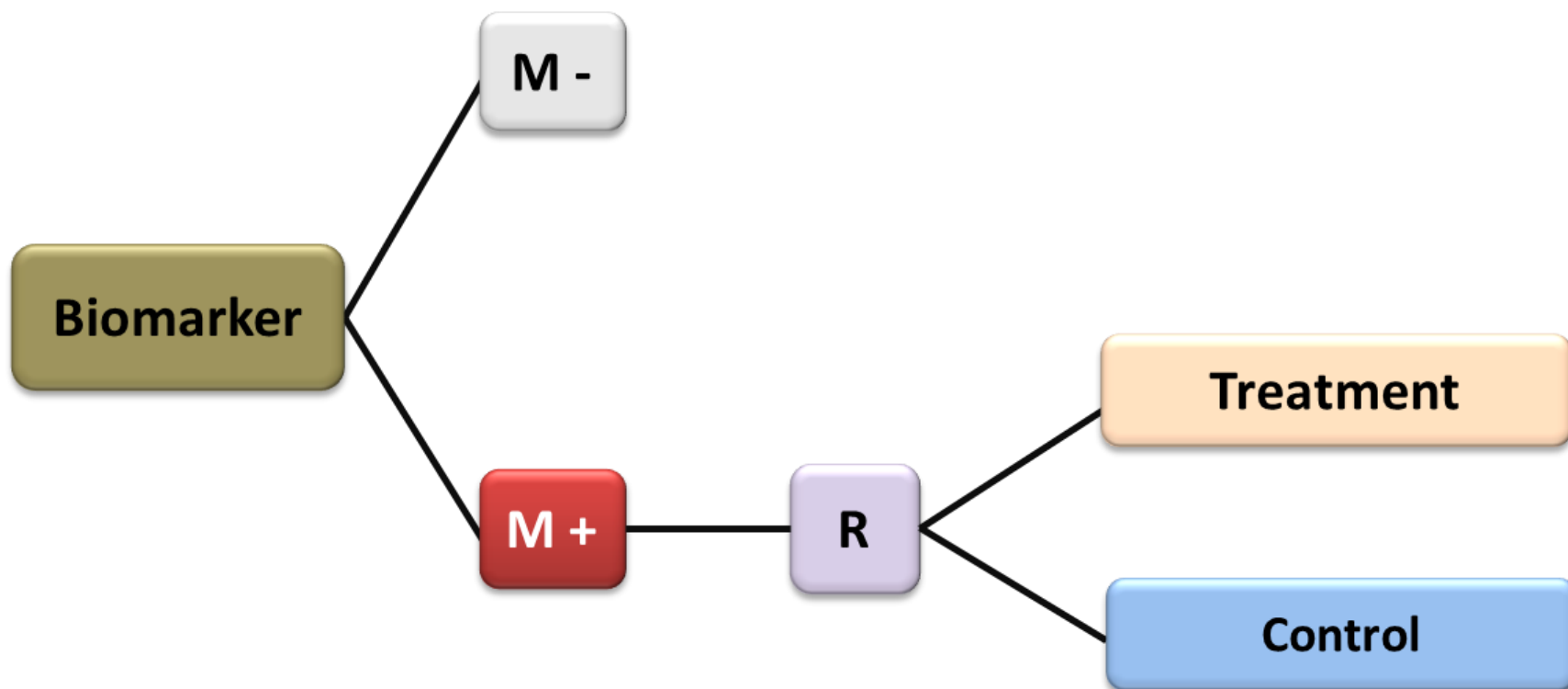- Addresses a broad population question

Disadvantages
- Large sample size
- Potentially unnecessary treatment for M- patients
- Cannot assess prospectively effect in M+ or M- patients
- Risk of being negative if effect only limited in M+
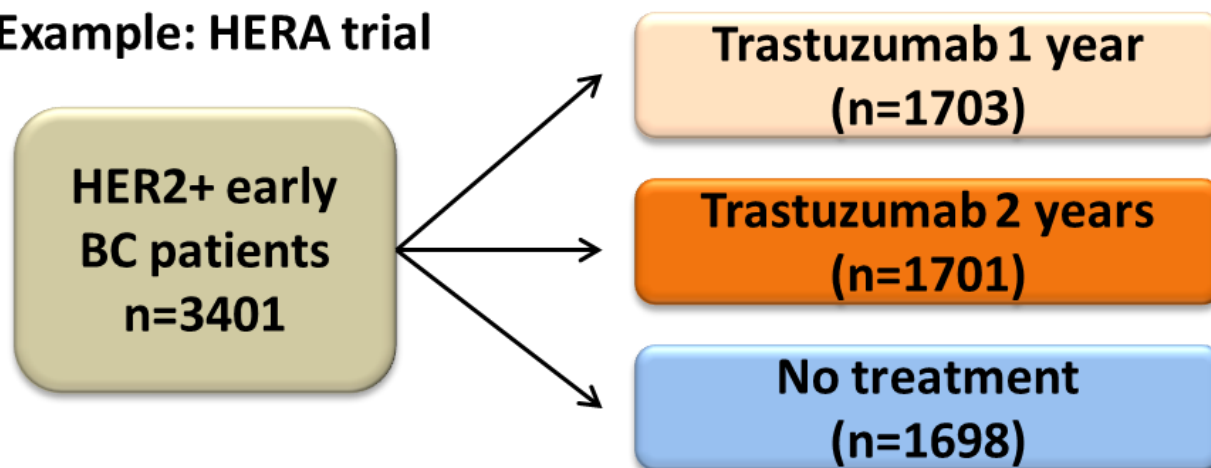
Example: BOLERO-2 trial

Targeted design

Prescreening population for clinical trial

Buyse, Michiels et al, Expert Rev Mol Diag 2011

Targeted design

Prescreening population for clinical trial

Example: HERA trial

HER2+ early
BC patients
n=3401

→ Trastuzumab 1 year
(n=1703)

→ Trastuzumab 2 years
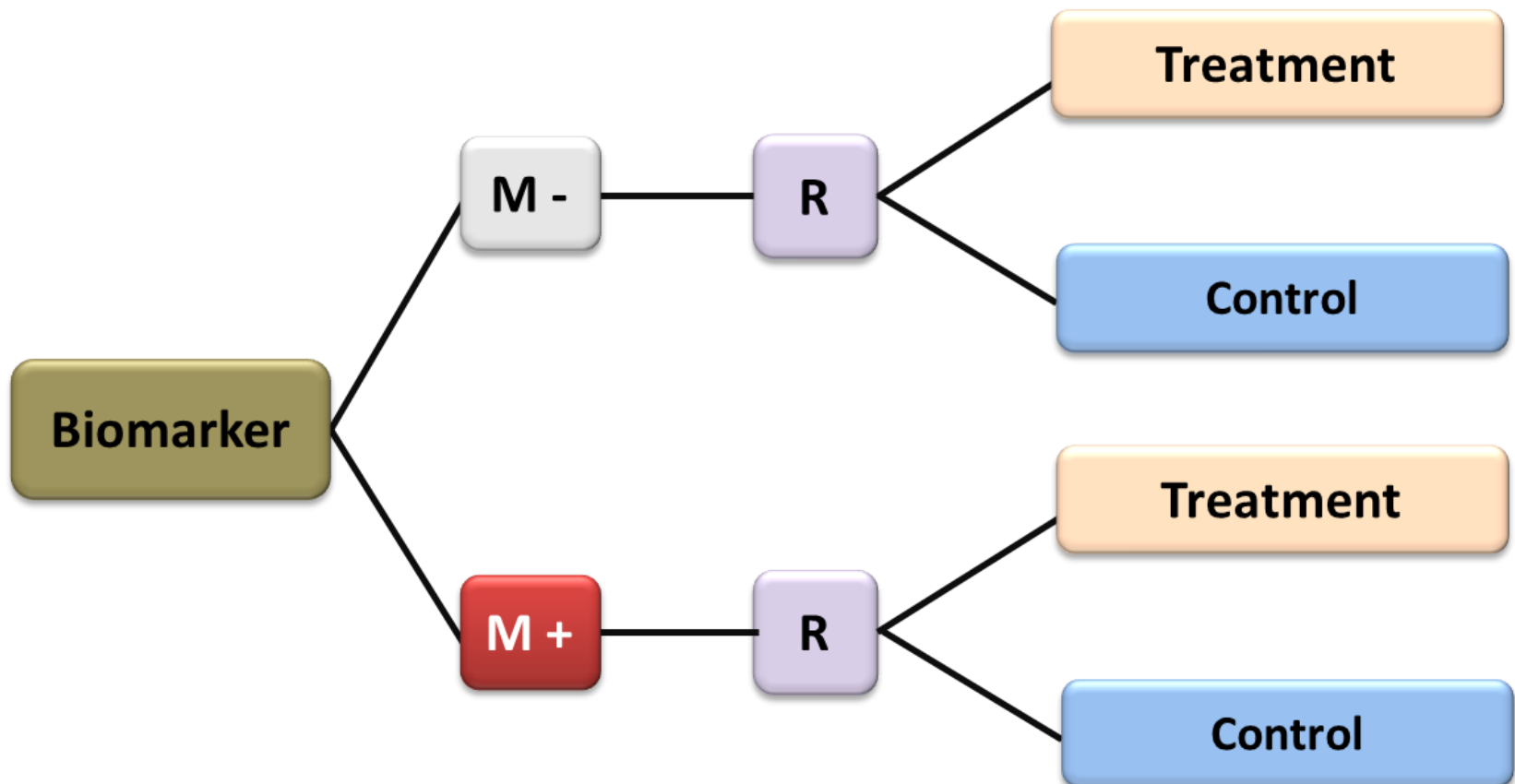(n=1701)

→ No treatment
(n=1698)

Advantages
- Requires many fewer patients
- Avoids potentially unnecessary treatment for M-

Disadvantages
- Cannot assess effect in M- patients
- Slow accrual
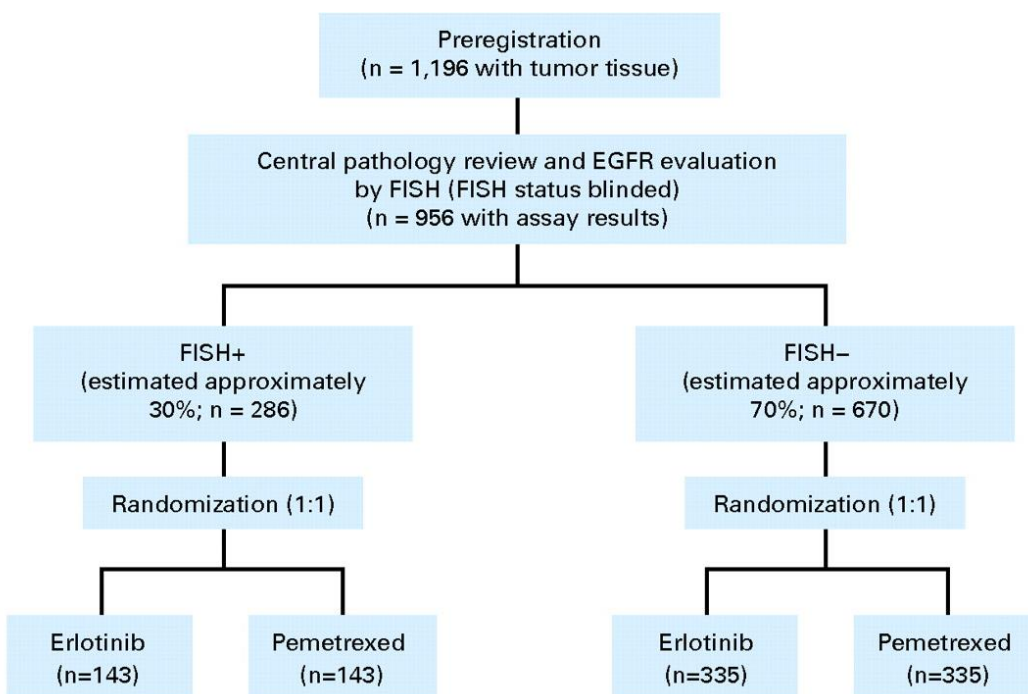- Less efficient that randomize-all design if drug has some activity in M- patients

Biomarker-stratified design

Prescreening population for clinical trial

Biomarker-stratified design
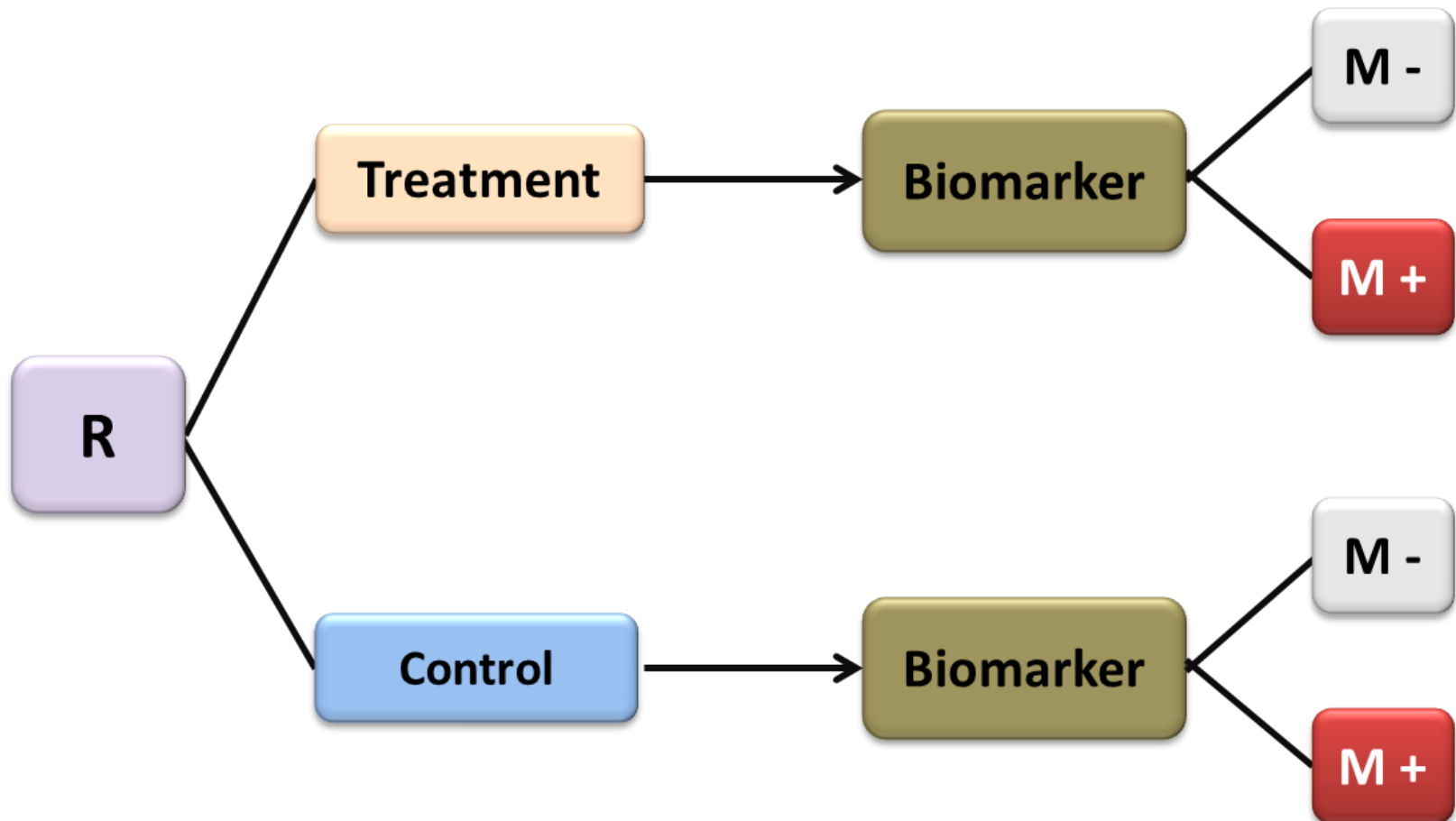
Example: Marvel trial

Advantages
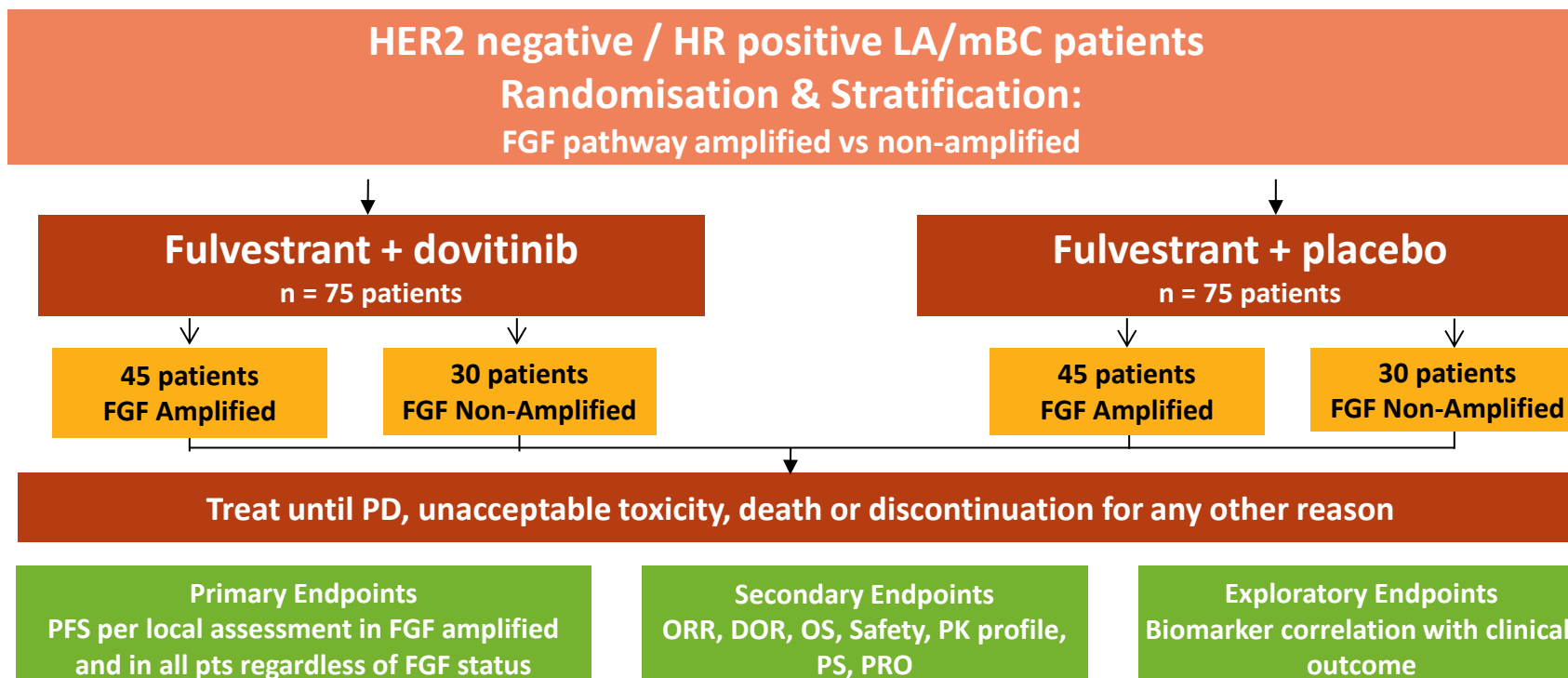- Test of predictive ability of biomarker (interaction)

Disadvantages
- power of "interaction test" is very low, huge sample sizes are required
- Potential for overtreatment of M- patients
- Biomarker often unknown or poorly defined for prospective stratification
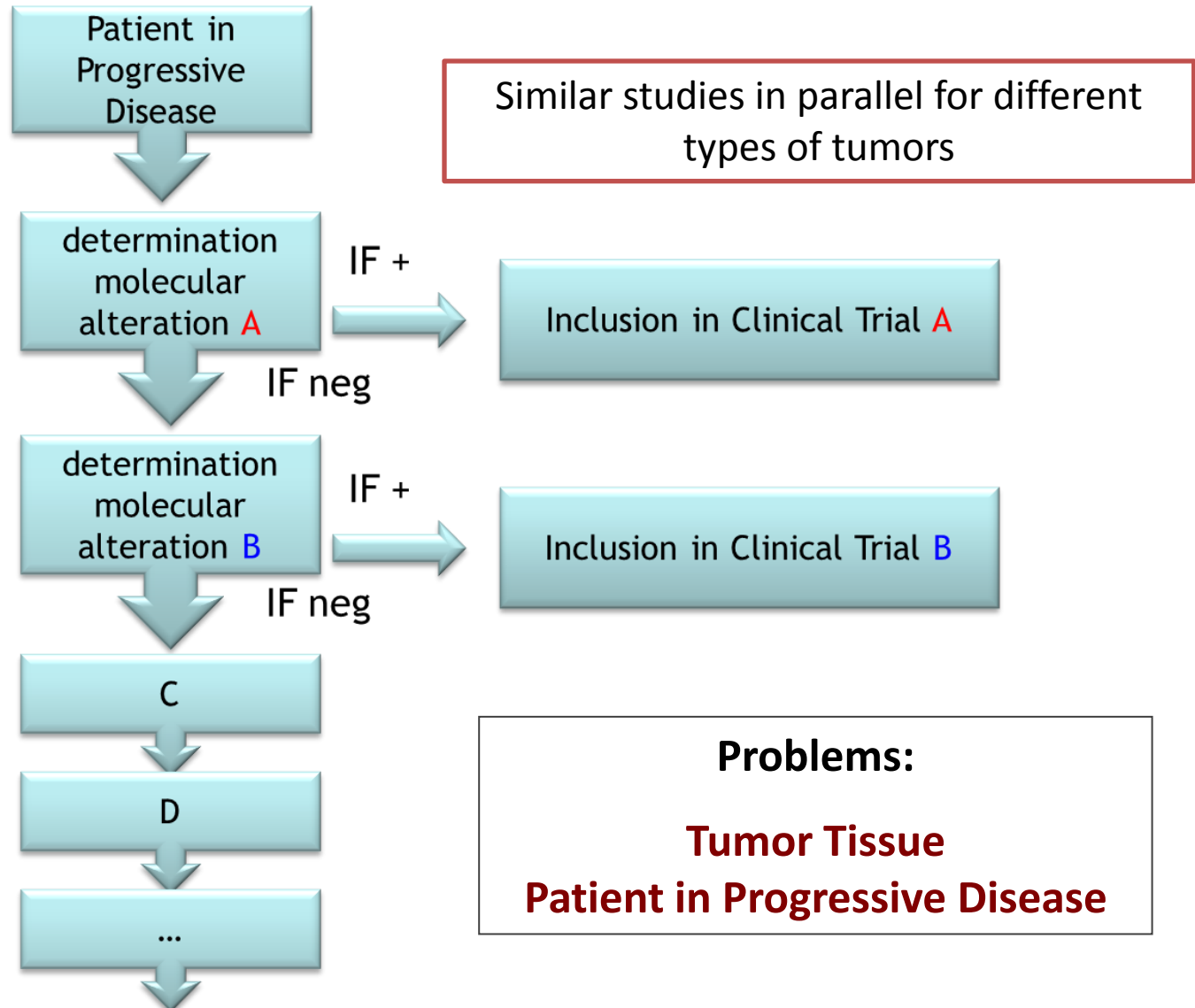
Adaptive parallel
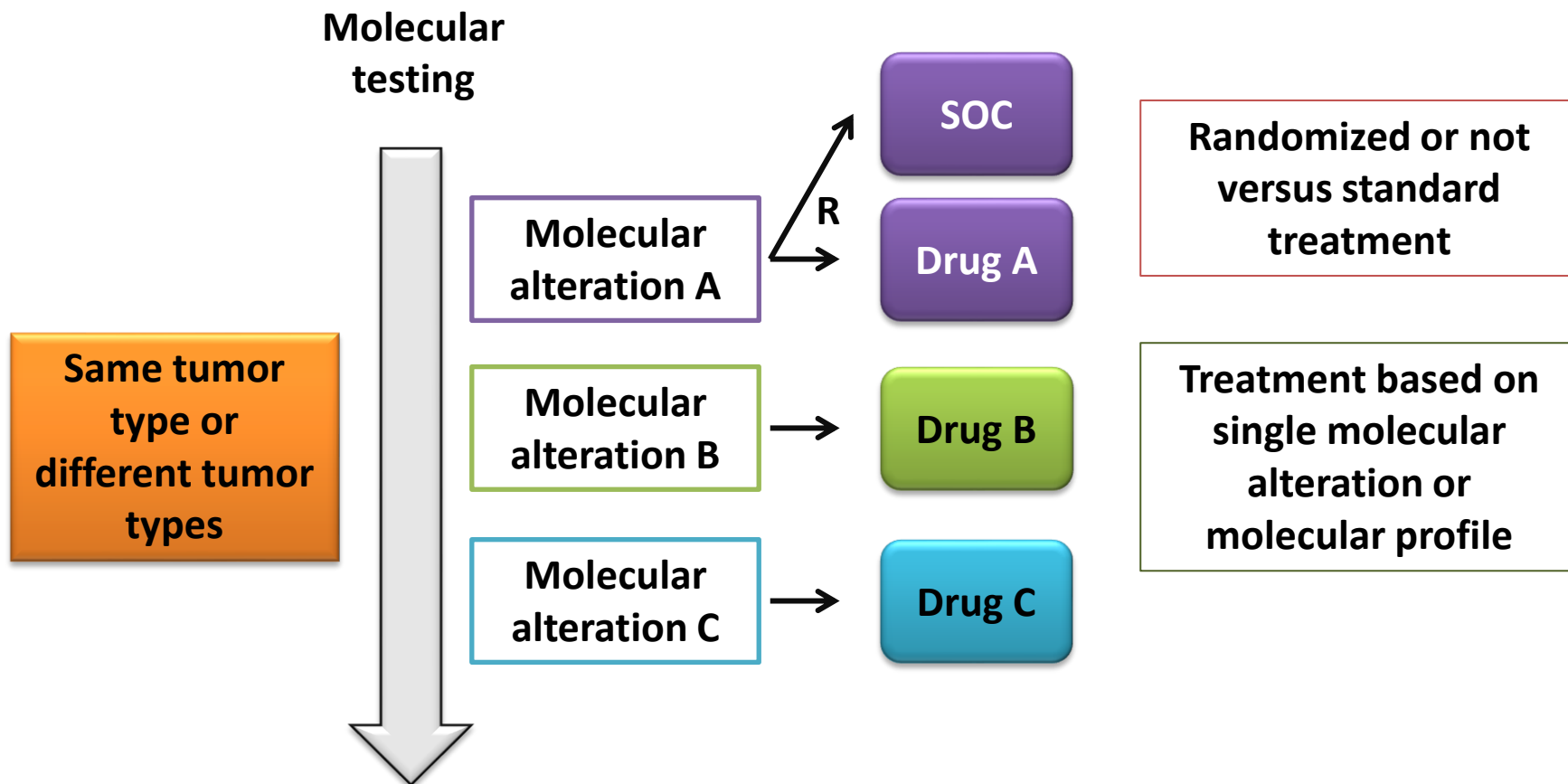
Biomarker-stratified design

HER2 negative / HR positive LA/mBC patients
Randomisation & Stratification:
FGF pathway amplified vs non-amplified

Fulvestrant + dovitinib	**Fulvestrant + placebo**
n = 75 patients	n = 75 patients

45 patients FGF Amplified	30 patients FGF Non-Amplified	45 patients FGF Amplified	30 patients FGF Non-Amplified

Treat until PD, unacceptable toxicity, death or discontinuation for any other reason

Primary Endpoints PFS per local assessment in FGF amplified and in all pts regardless of FGF status	Secondary Endpoints ORR, DOR, OS, Safety, PK profile, PS, PRO	Exploratory Endpoints Biomarker correlation with clinical outcome

Clinical Trial terminated earlier due to low recruitment FGF-Amplified patients

Classical screening

Patient in Progressive Disease

→ determination molecular alteration A — IF + → Inclusion in Clinical Trial A

IF neg ↓

determination molecular alteration B — IF + → Inclusion in Clinical Trial B

IF neg ↓

C

D

...

Similar studies in parallel for different types of tumors

Problems:

Tumor Tissue
Patient in Progressive Disease

The umbrella trials

The BATTLE Program

End-point: PFS at 8 weeks - DCR

Kim et al, Cancer Discov. 2011;1(1):44-53
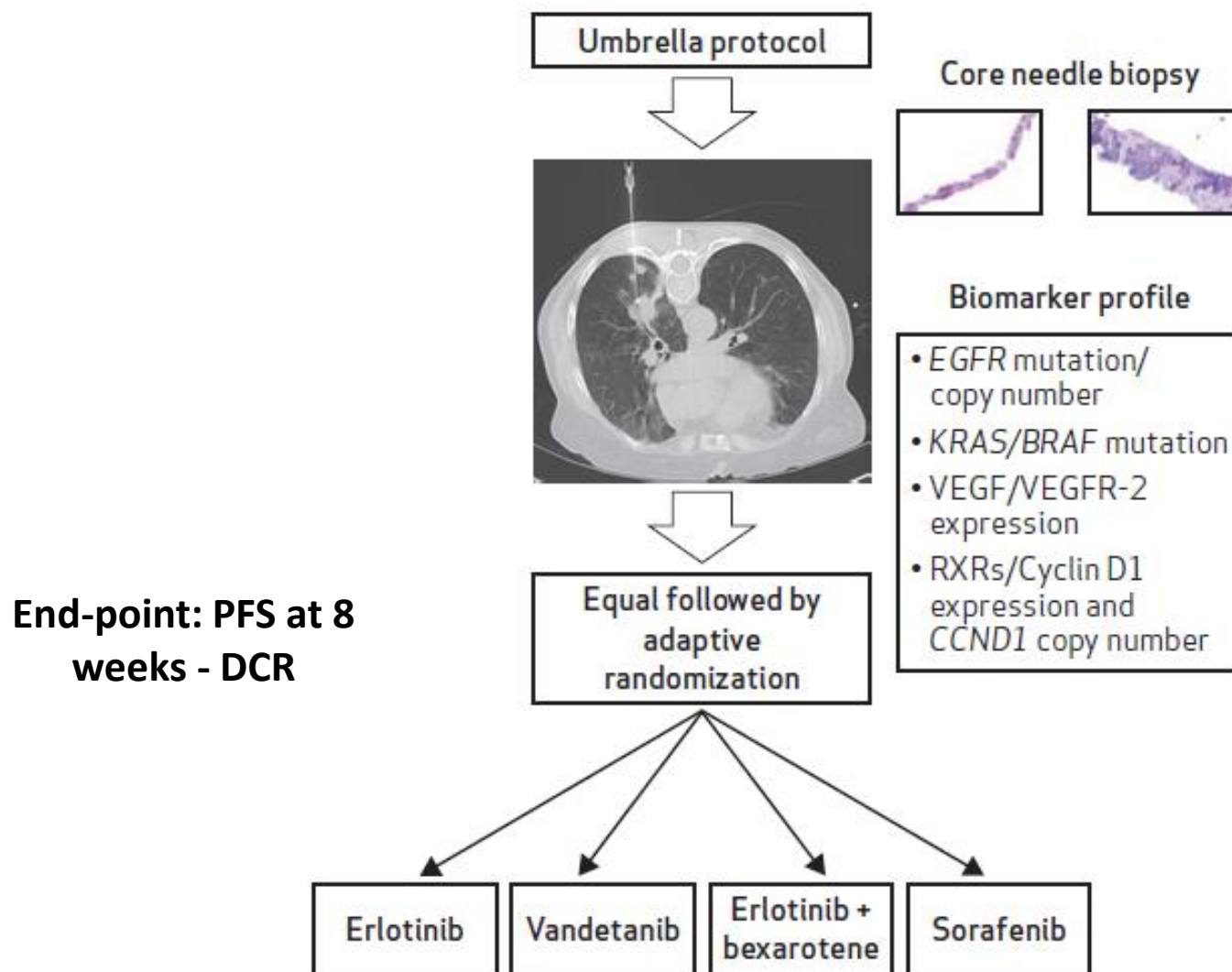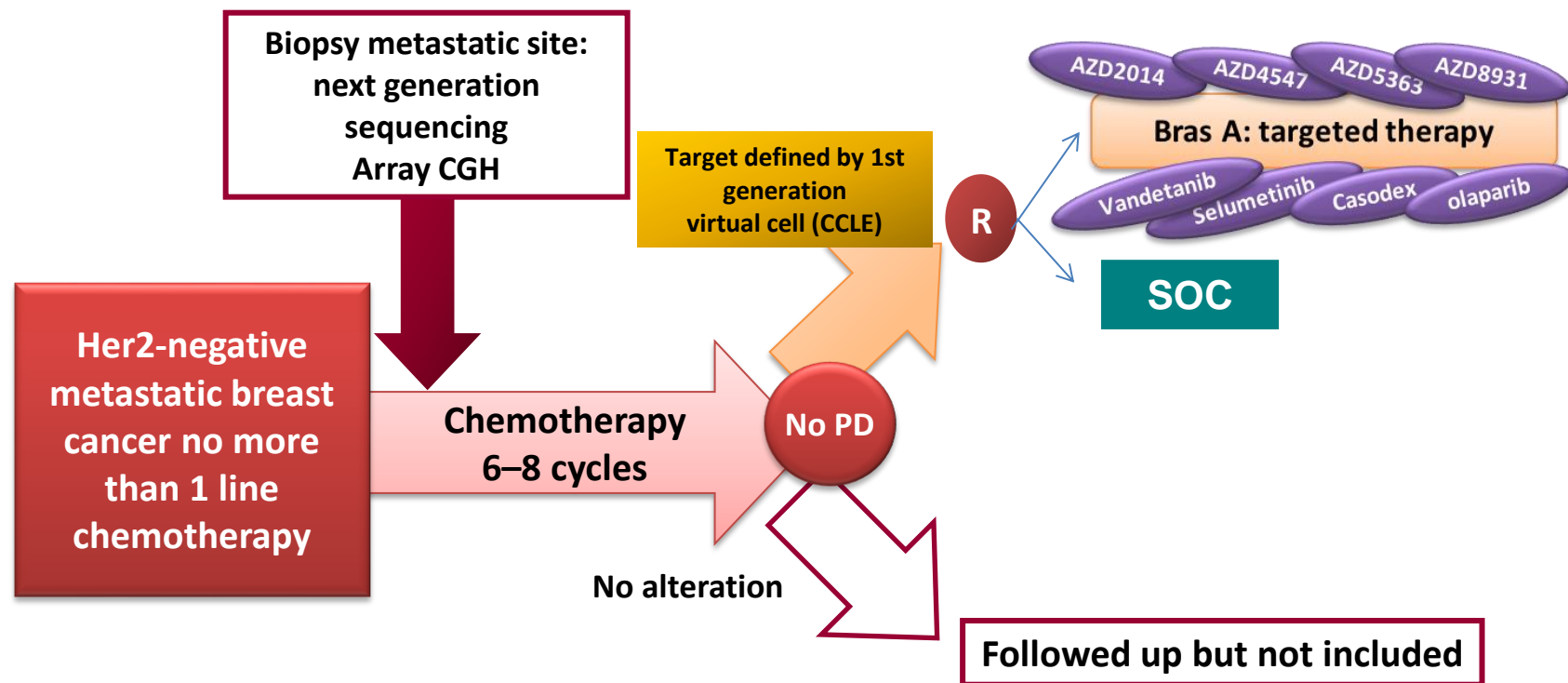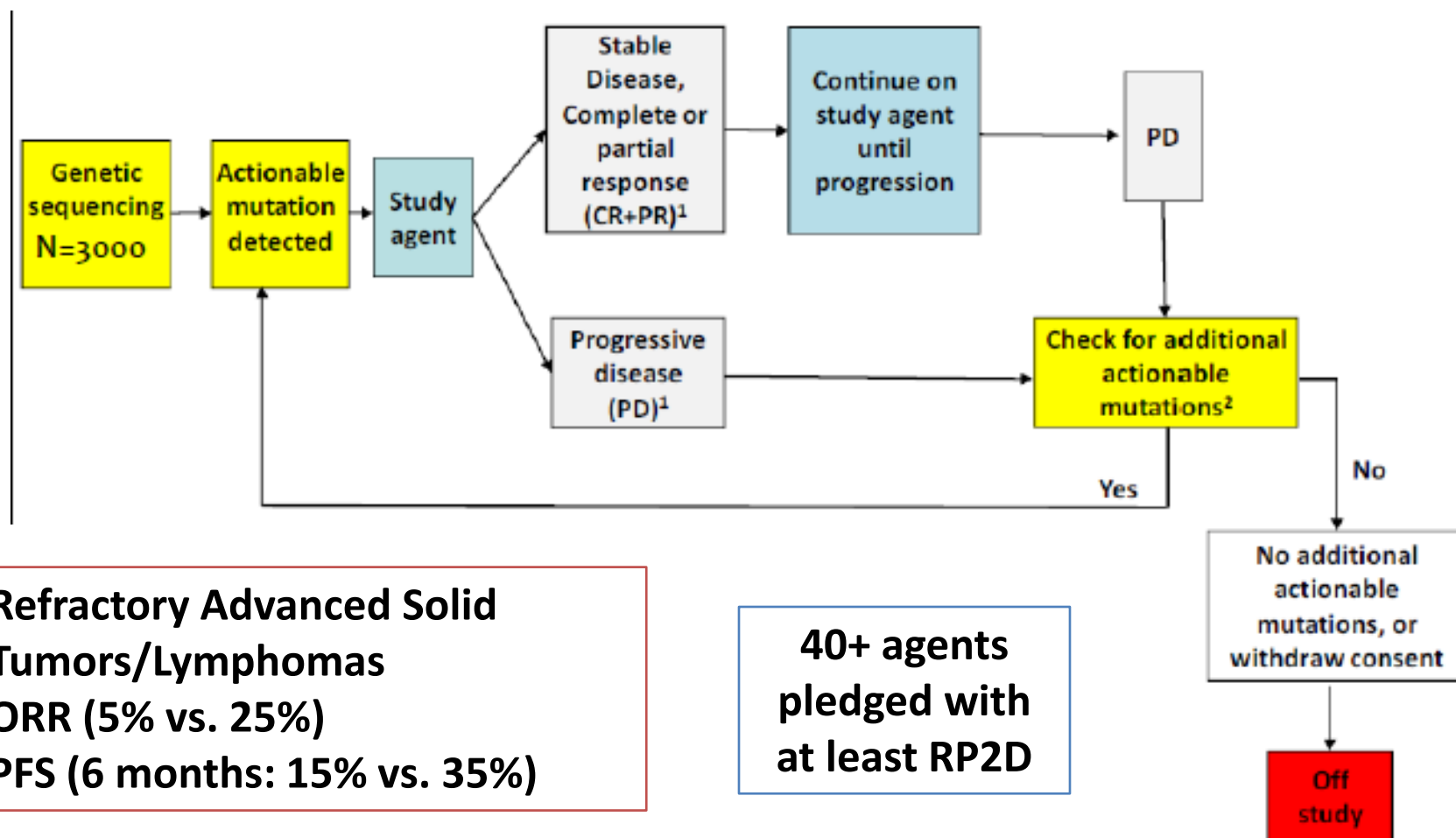
SAFIR02 trial

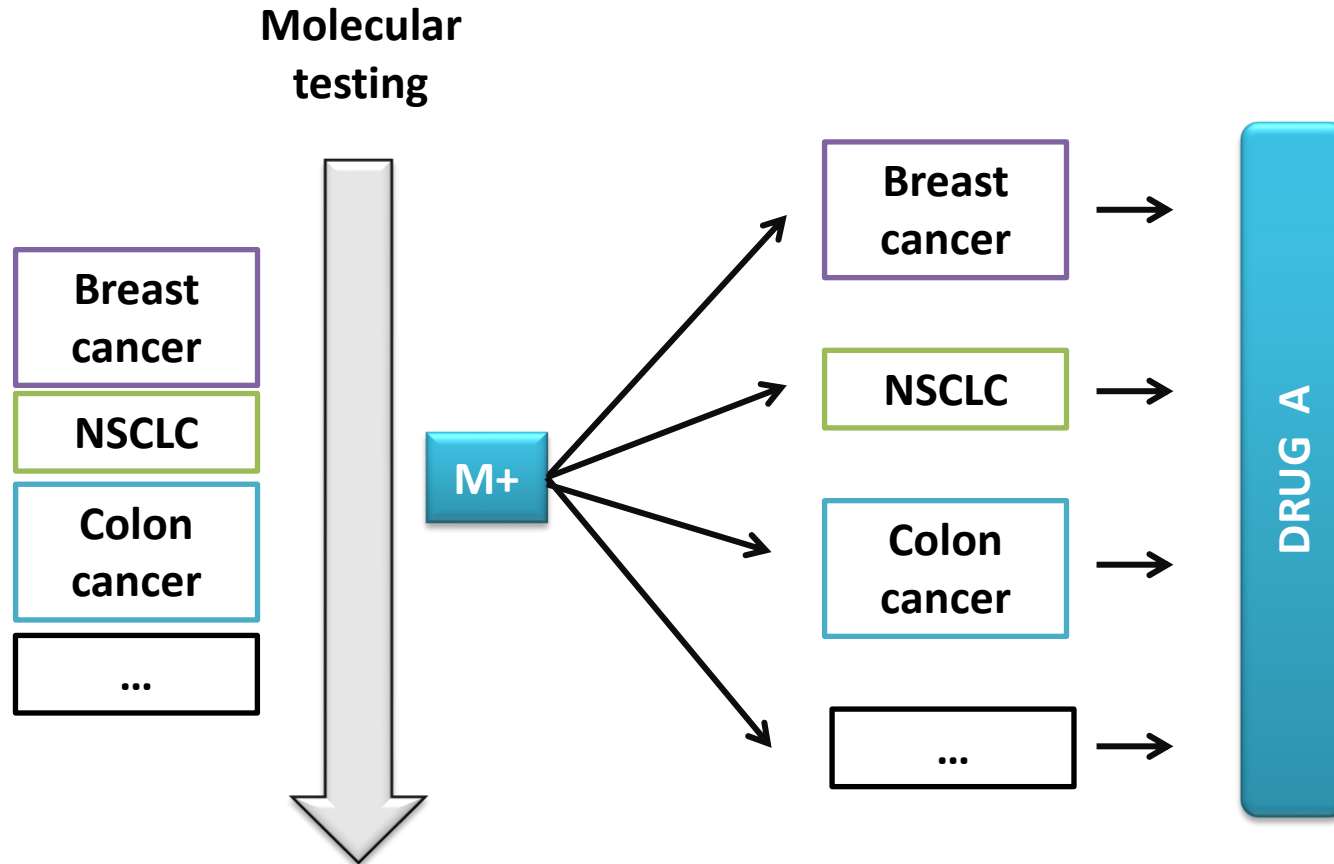- 210 randomised, around 400 screened
- **Hypothesis: median PFS 3 to 6 months**

- **Sponsor: UNICANCER**
- **Funding: French charity**
- **Pharma partner: AZ**

NCI-MATCH
(Molecular Analysis for Therapy Choice)

Refractory Advanced Solid Tumors/Lymphomas
ORR (5% vs. 25%)
PFS (6 months: 15% vs. 35%)

40+ agents pledged with at least RP2D

http://deainfo.nci.nih.gov/advisory/ncab/164_1213/Conley.pdf

The basket trials

Examples:
VE_BASKET (NCT01524978): vemurafenib in *BRAF*-mutated solid tumors and multiple mieloma
AcSé Crizotinib (NCT02034981): crizotinib in alterations *MET, ROS1, ALK*

I. implementing strategies to reduce time and number of patients

II. adapting clinical trials design to molecular pre-screening for targeted therapies

III. **application of new measures by the regulatory agencies**

IV. exploiting new scenarios

Drug approval based on Phase 1/2 data

FDA Accelerated approval to some new drugs for serious and life-threatening illnesses that lack satisfactory treatments before measures of effectiveness required for approval are available
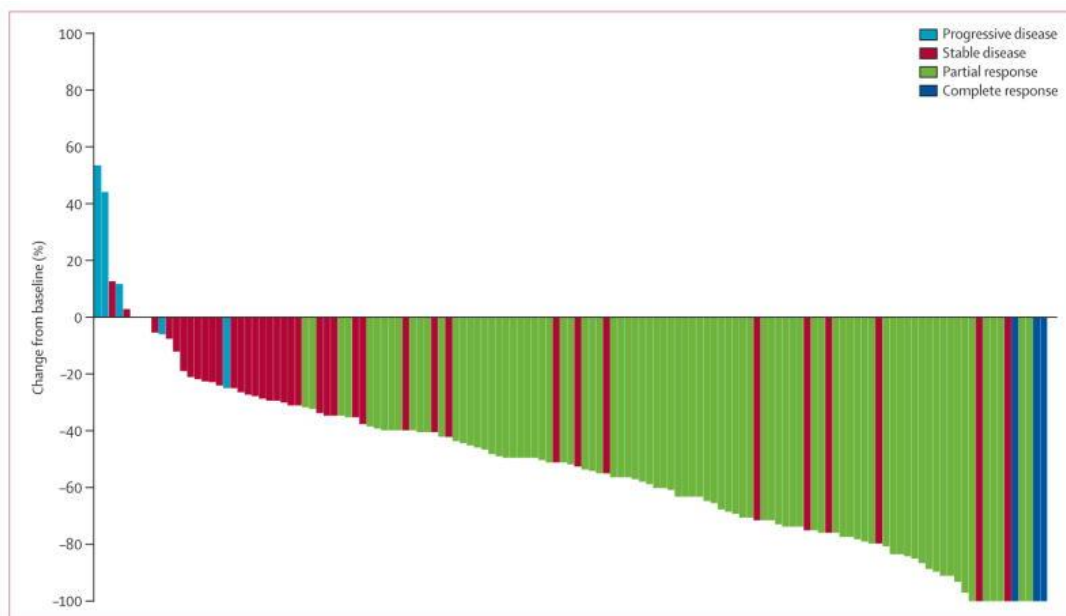
Crizotinib received accelerated approval for treatment of ALK-positive locally-advanced or metastatic NSCLC based on two Phase 1 trials
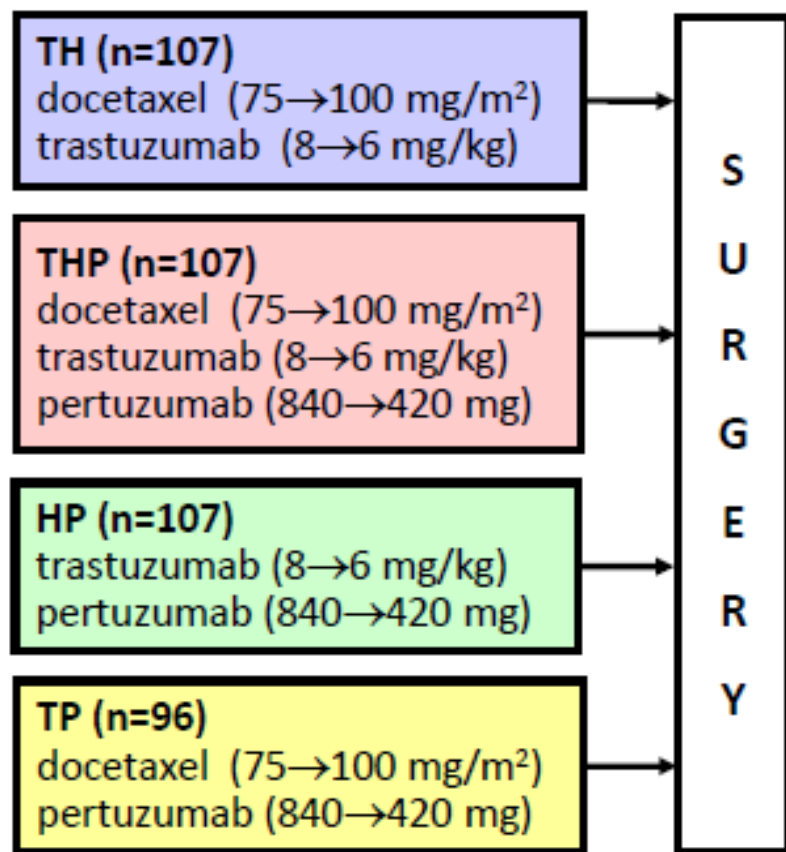
Camidge et al, Lancet Oncol. 2012; 13(10): 1011–1019

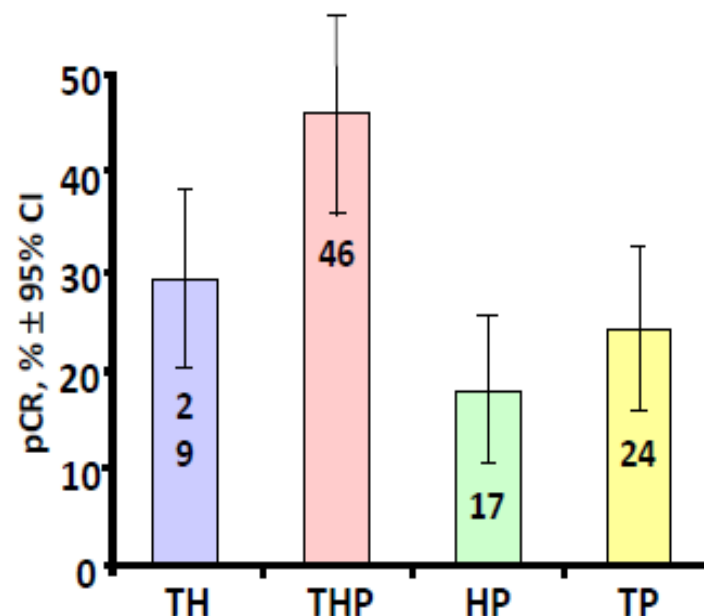# Drug approval from neoadjuvant setting in breast cancer
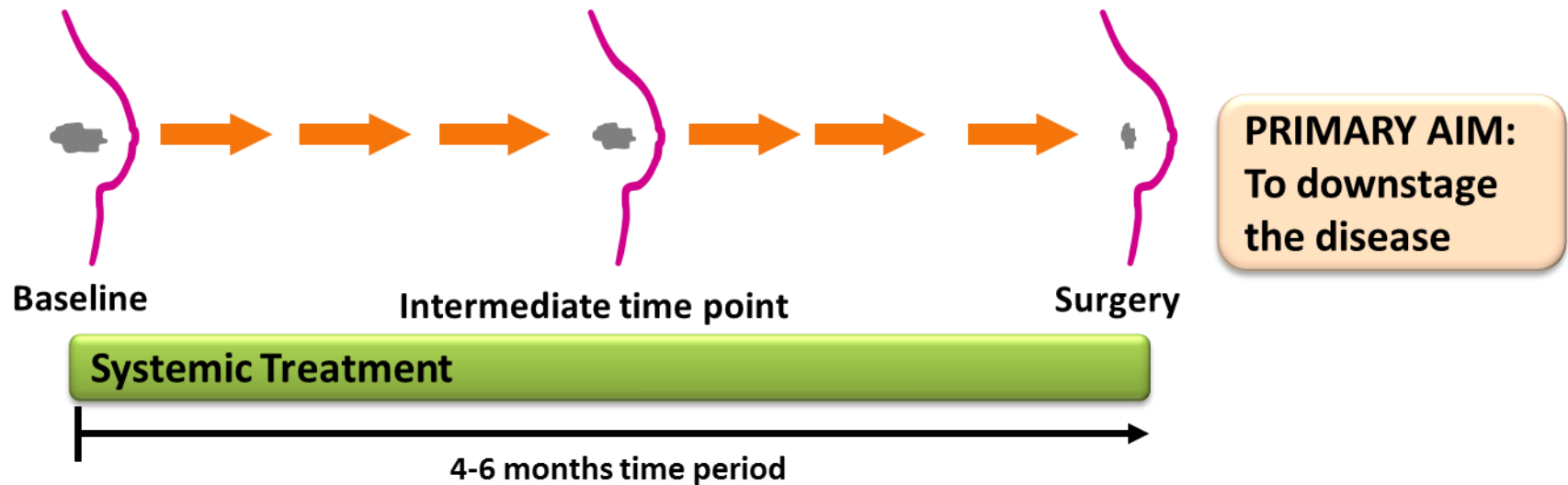
In May 2012 the **FDA** issued **draft guidance** suggesting than **pCR** could be used as an **endpoint** in neoadjuvant early-stage high risk breast cancer trials **for accelerated approval** under certain conditions

Drug approval neoadjuvant setting

TH (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)

THP (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

HP (n=107)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

TP (n=96)
docetaxel (75→100 mg/m²)
pertuzumab (840→420 mg)

S U R G E R Y

Study dosing: q3w x 4

N=417

Bar chart: pCR, % ± 95% CI — TH: 29, THP: 46, HP: 17, TP: 24

Gianni et al, Lancet Oncol 2012; 13: 25–32

Approval of docetaxel + trastuzumab + pertuzumab as neoadjuvant treatment in HER2+ BC

I.   implementing strategies to reduce time and number of patients

II. adapting clinical trials design to molecular pre-screening for targeted therapies

III. application of new measures by the regulatory agencies

IV. **exploiting new scenarios**

Pre-operative setting: Phase 0 trials

Pre-surgical treatment (Biological window trial)
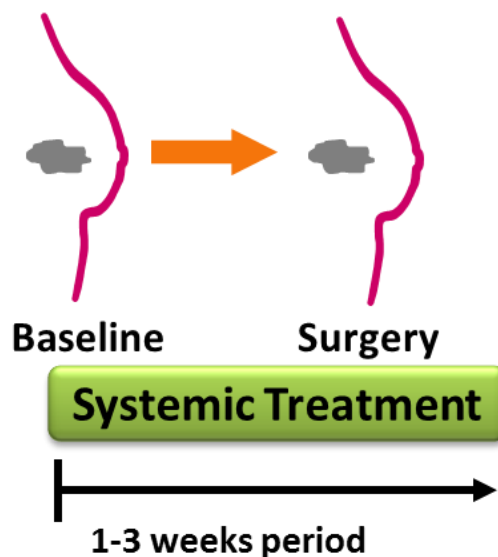
PRIMARY AIM: To evaluate the biological effect of the drug on the target

Baseline → Surgery

Systemic Treatment

1-3 weeks period

- In accordance with the FDA
- Administration of shorter periods of time
- In early disease
- Lower number of patients
- Provides pharmacodynamics and pharmacokynetics
- Validation of biomarkers

Trials in the pre-operative setting
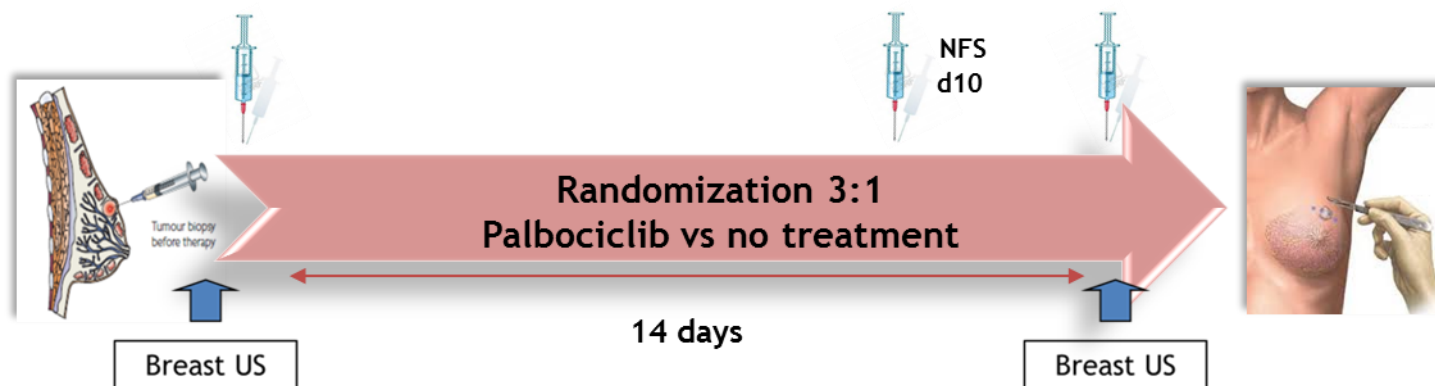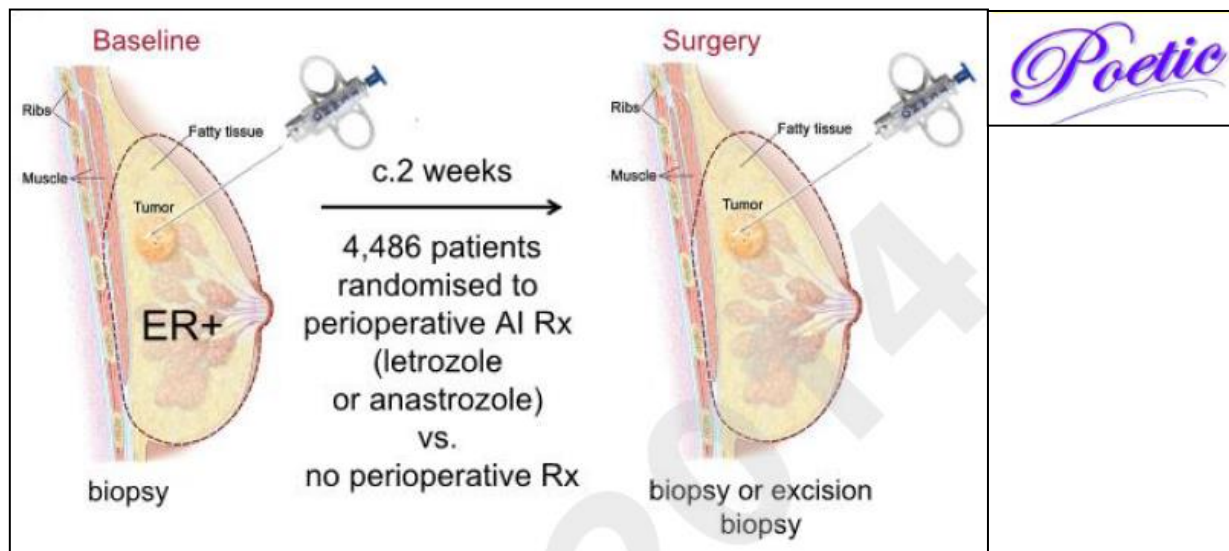
Further reading

- Le Tourneau et al, *Dose Escalation methods in Phase I clinical trials*. JNCI 2009; 101: 708
- Ivy et al, *Approaches to Phase 1 clinical trial design focused on safety, efficiency and selected patient population*. CCR 2010; 16:1726
- Seymour et al, *The design of Phase II clinical trials testing cancer therapeutics.* CCR 2010; 16: 1764
- Orloff et al, *The future of drug development: advancing clinical trial design*. Nat Rev Drug Discov 2009; 8: 949
- Rodon et al, *Molecular prescreening to select patient population in early clinical trials.* Nat Rev Clin Oncol 2012; 9:359
- Kummar et al, *Application molecular profiling in clinical trials for advanced metastatic cancers.* JNCI 2015; 107(4):djv003
- Bardia and Baselga, *Neoadjuvant Therapy as a Platform for Drug Development and Approval in Breast Cancer*. Clin Cancer Res 2013; 19; 6360
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf