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BEST PRACTICE

INNOVATIVE CLINICAL TRIAL DESIGNS IN THE ERA OF PRECISION ONCOLOGY

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DISCLOSURES

Ahmad Awada has reported no conflicts of interest

Hampig Raphael Kourie has reported no conflicts of interest

Stefan Sleijfer has reported no conflicts of interest

Morten Mau Sørensen has reported no conflicts of interest

Jean-Yves Blay has reported research support to and or honoraria from Novartis, Roche, MSD, BMS, PharmaMar

Nadia Harbeck has reported to be the Scientific Director of the West German Study Group. She has received honoraria for consulting or lectures from Agendia, Genomic Health, NanoString, Novartis, Pfizer and Roche

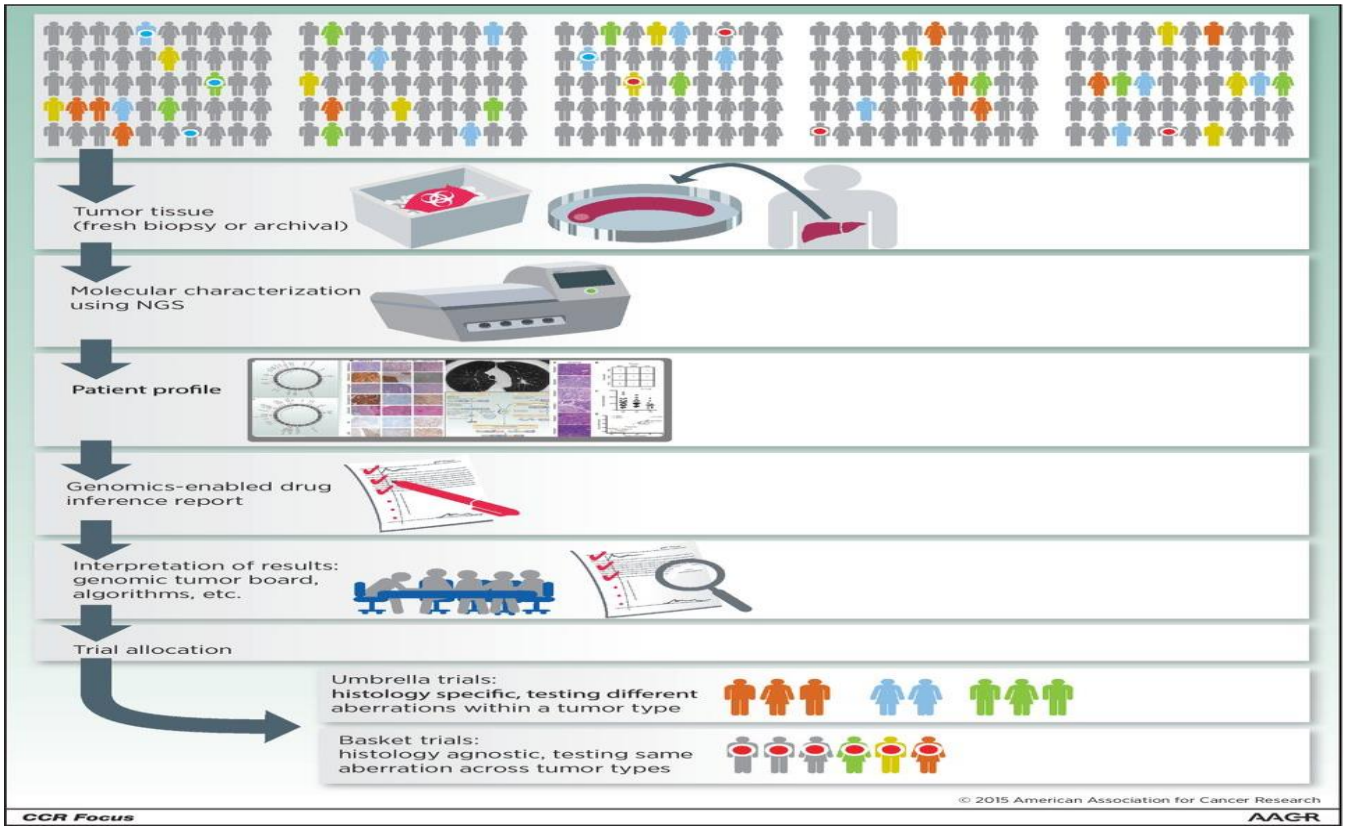
GENOTYPE-DRIVEN CLINICAL TRIALS: PRINCIPLES

Patients will be matched to the trials according to the molecular profiling of their disease as defined by the results of the tumour gene sequencing or other molecular technics

Molecular aberrations in tumour are dictating sensitivity to targeted therapies

MOLECULAR BIOLOGY TECHNICS

(e.g. NGS,…) are the basis for new clinical trial designs

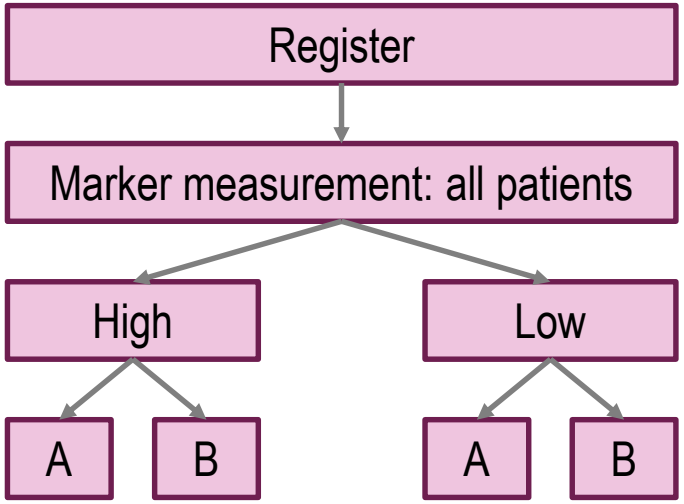


Reprinted from Clin Cancer Res, 2015, 21:4536-4544, Lilian L.Siu *et al.*, Next-Generation Sequencing to Guide Clinical Trials, with permission from AACR

EXAMPLES OF CLINICAL TRIALS DESIGNS

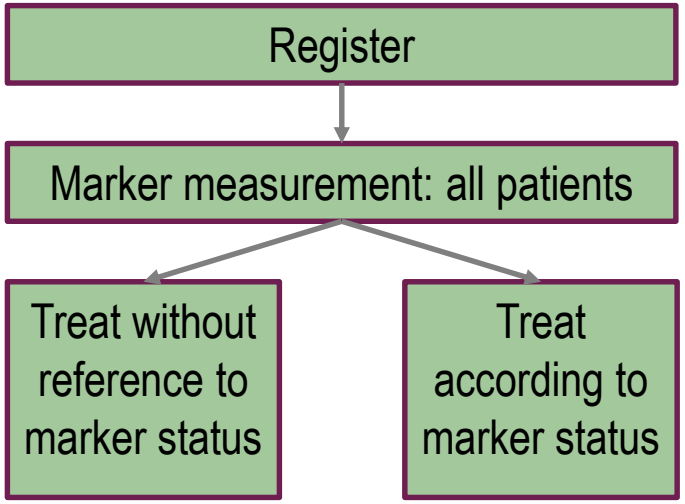
Based on molecular biomarker assessment

Marker x Treatment Interaction Design



Marker x Treatment Interaction Design for assessment of the Clinical Utility of Predictive Marker. The trial is the equivalent of 2 randomized treatment trials done in each marker status group. The design can assess whether the treatment effect depends on the marker status

Marker Strategy Design



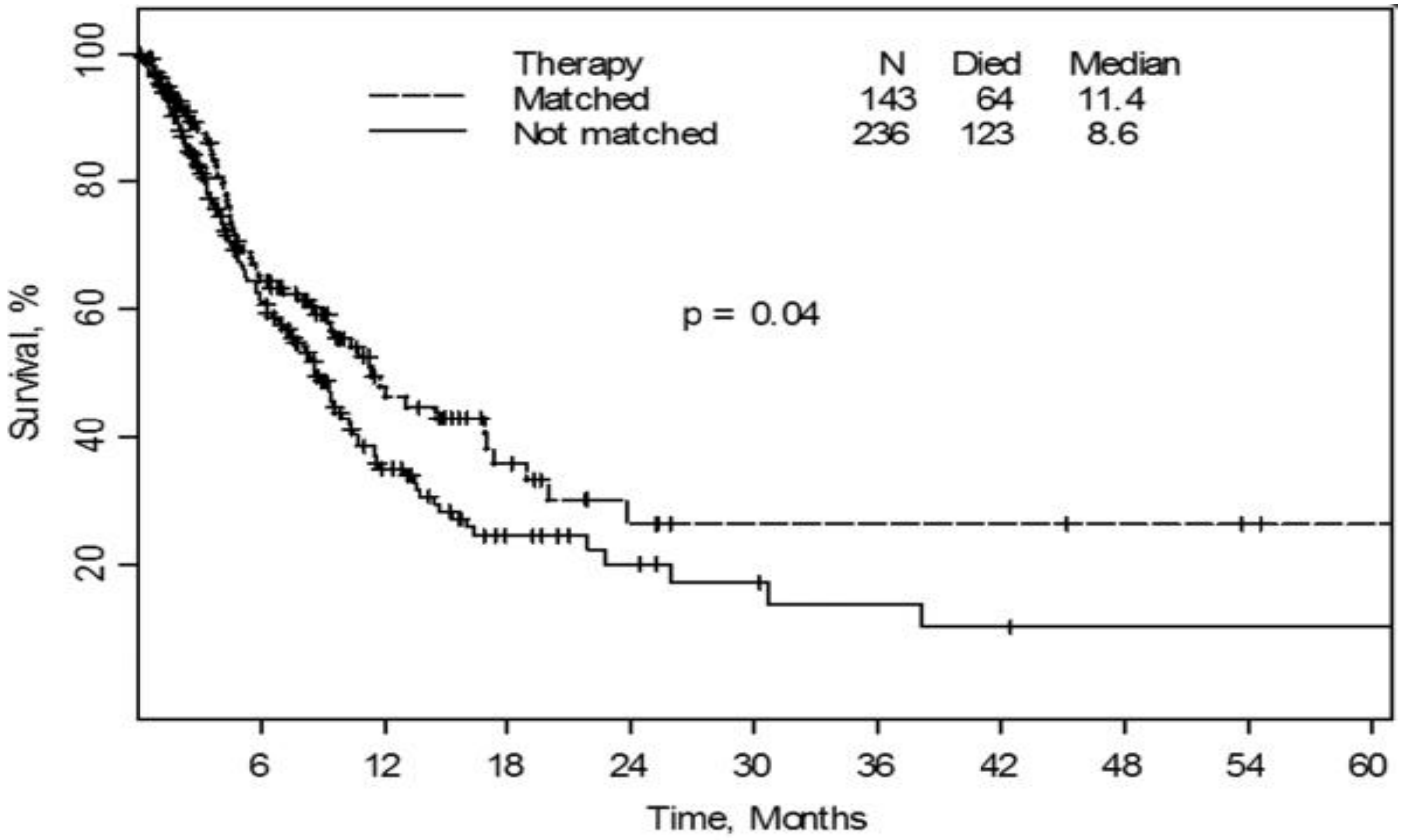
Marker Strategy Design: This design assesses whether there is benefit to using a marker when choosing a treatment for a patient, compared to not using the marker (treating as is commonly done now, without considering predictive marker)

Sargant DJ, *et al.,* J Clin Oncol 2005;23:2020–7

Hayes DF, *et al*., Trans Am Clin Climatol Assoc, 2015

PHASE I TRIALS

Advanced cancer patients treated with targeted agents matched with tumour molecular alteration have improved outcome in phase I trials



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Reprinted from Clin Cancer Res, 2014; 20(18):4827-4836, Tsimberidou AM, *et al.*, Personalized Medicine for Patients with Advanced Cancer in the Phase I Program at MD Anderson: Validation and Landmark Analyses. With permission from AACR

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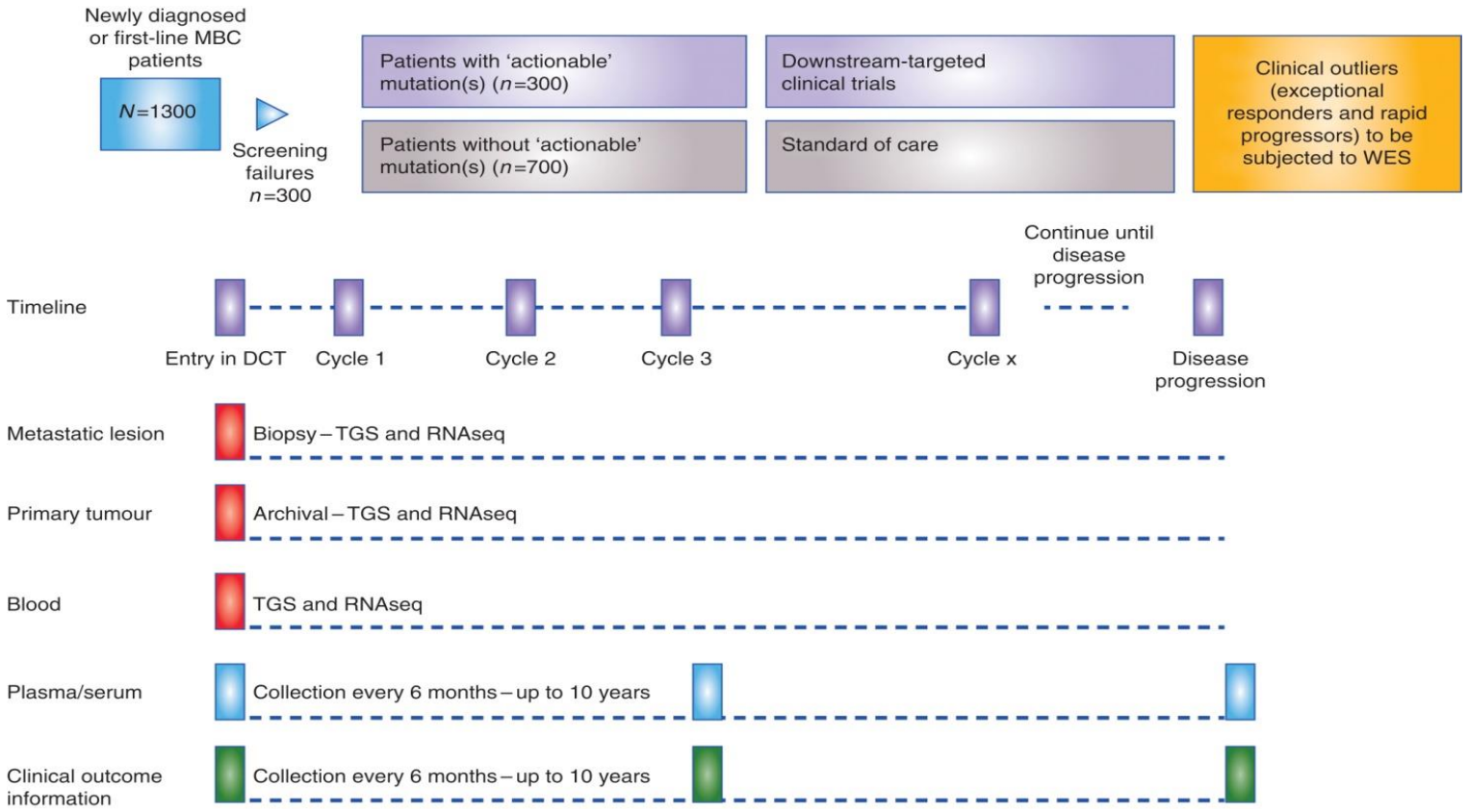
EARLY METASTATIC BREAST CANCER SETTING

AURORA study design



Zardavas D , British Journal of Cancer (2014) 111, 1881-1887

MOLECULAR-DRIVEN CLINICAL TRIALS: PROS AND CONS

Pros

- New and selective therapeutic options for patients
- Better outcome

Cons

- Absence of agents in some detected driver targets
- No direct clinical implication or benefit in a large proportion of screened patients
- Difficulties to discriminate drivers from passengers targets

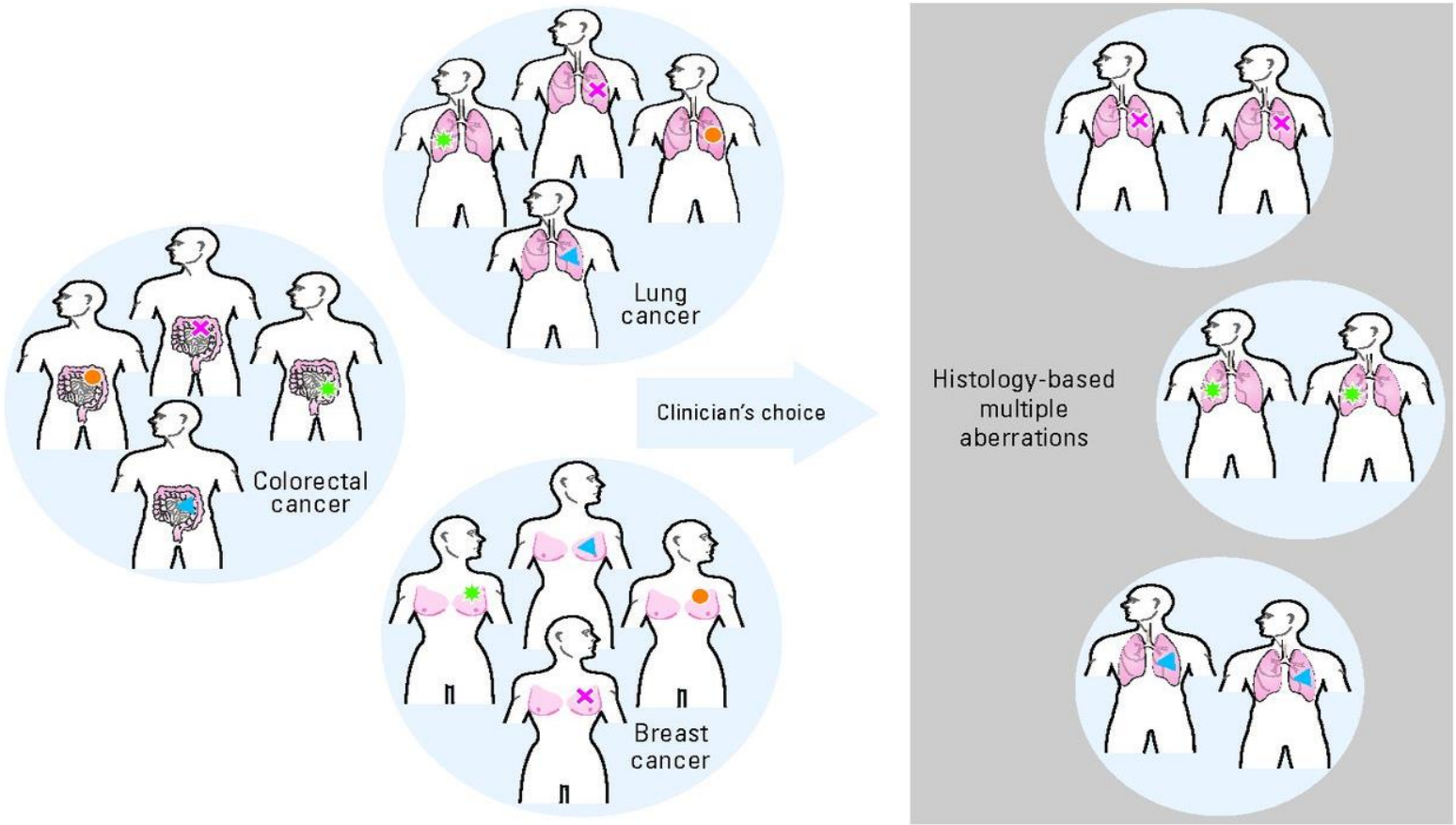
UMBRELLA TRIAL

- Different targeted agents investigated in parallel in the same tumour type and within independent cohorts of patients

- **Defined by specific molecular aberrations** that could predict sensitivity to the investigational agent under assessment

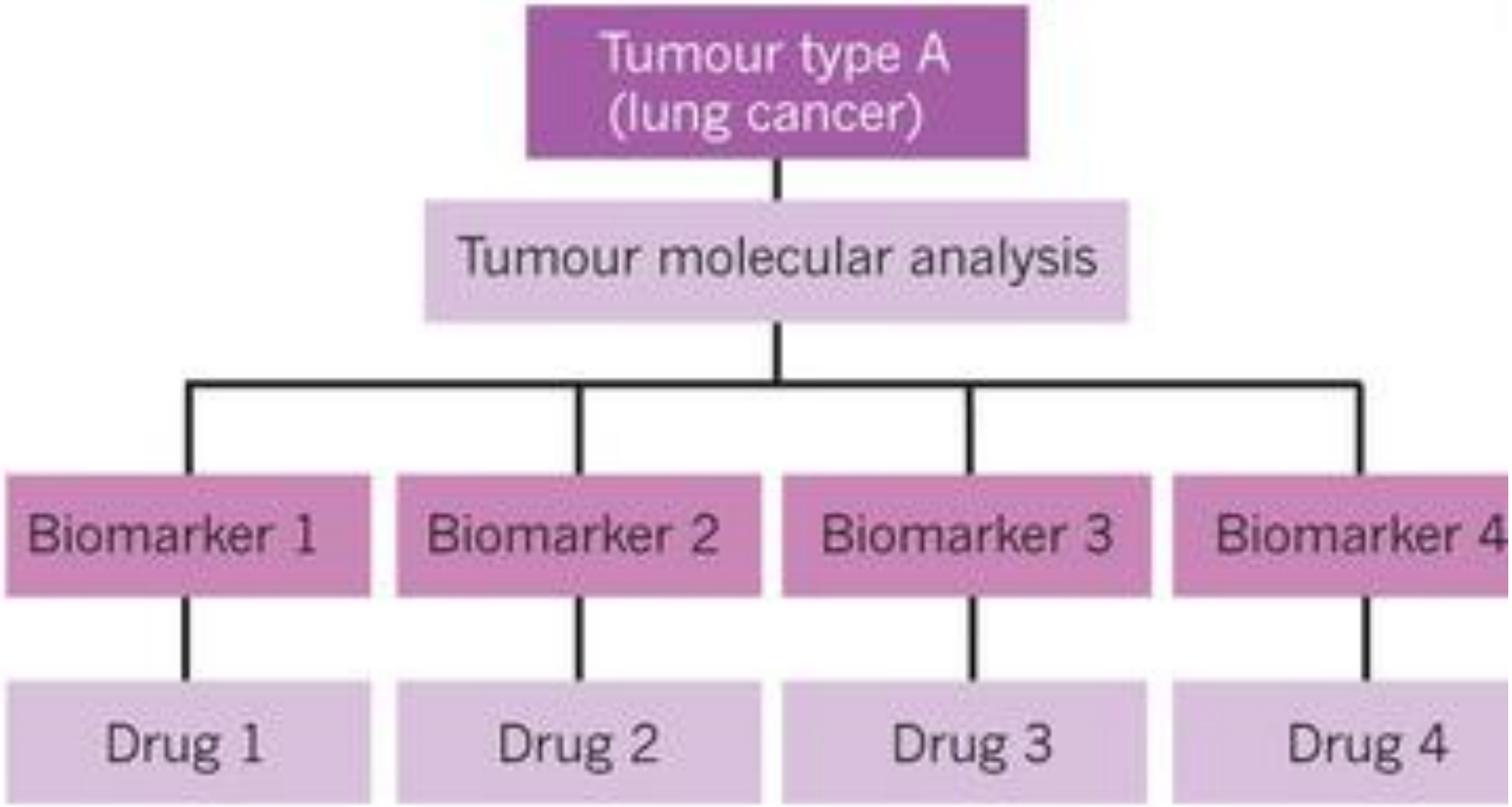
HISTOLOGY-BASED CLINICAL TRIAL DESIGN

To evaluate multiple molecular aberrations



Sleijfer S, *et al.,* J Clin Oncol, 31(15); 2013:1834-1841.

UMBRELLA TRIAL



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Biankin AV, *et al.* , Nature 14 October 2015; 526, 361-370. Reprinted by permission from Macmillan Publishers Ltd: Nature copyright 2015

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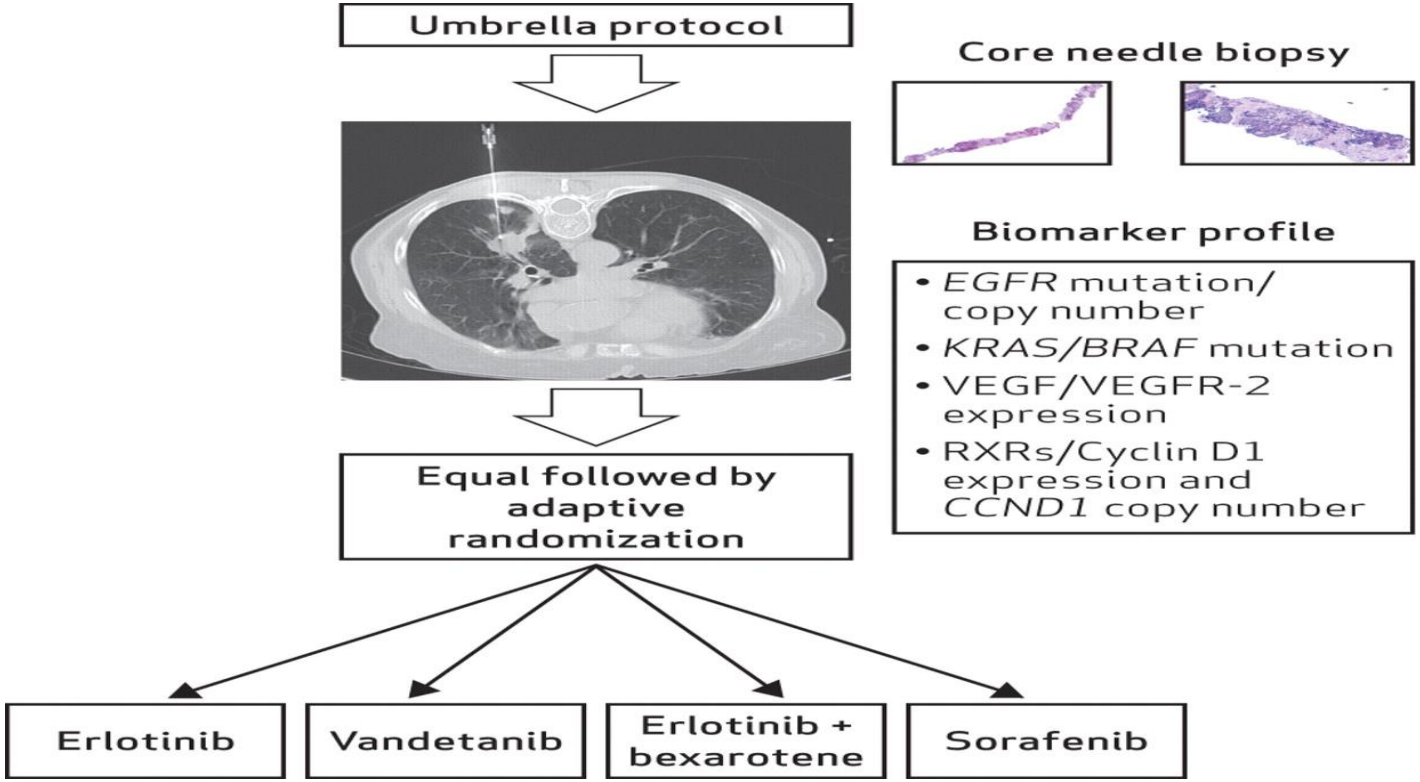
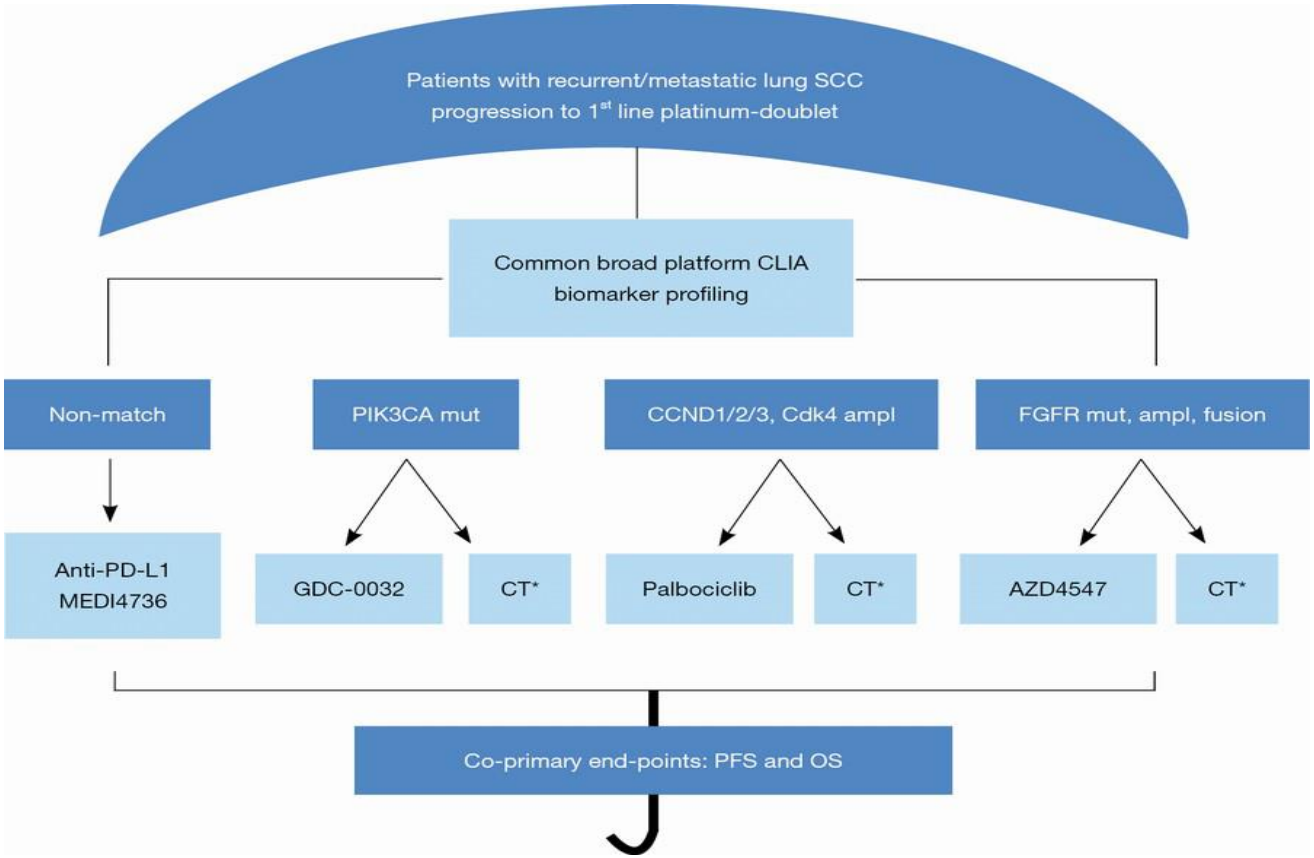
EXAMPLE OF UMBRELLA TRIAL (1): BATTLE TRIAL FOR NSCLC



Reprinted from Cancer Discovery, Copyright 2011, 1(1): 44.53, Kim ES, *et al*.The BATTLE Trial: Personalizing Therapy for Lung Cancer, with permission from AACR

EXAMPLE OF UMBRELLA TRIAL (2): LUNG-MAP PROTOCOLE



Herbst RS, *et al*., Clin Cancer Res, 2015, Apr1; 21(7): 1514-1524

UMBRELLA TRIAL: PROS AND CONS

Pros

- Less screening failure to enter clinical trial
- Possibly more patients will beneficiate from a targeted treatment

Cons

- Multiple arms
- More patients to be included
- Active and dynamic follow-up of the study is needed

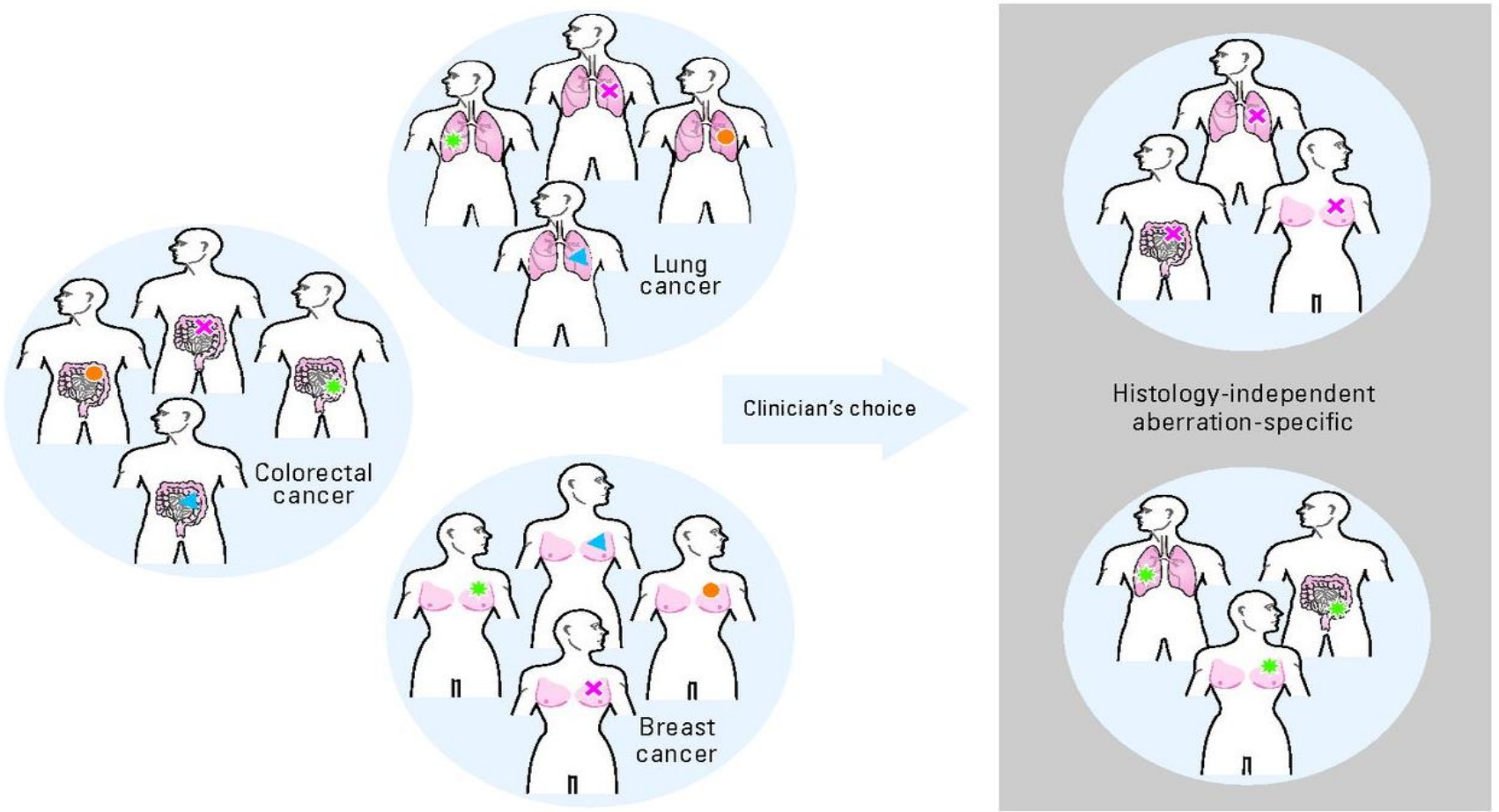
BASKET TRIAL

Histology-independent trial design

Patients with cancers of different histologies enrolled in the clinical trial based on the presence of a **specific molecular aberration**

TRIAL DESIGN

Histology-independent, aberration-specific clinical trial design



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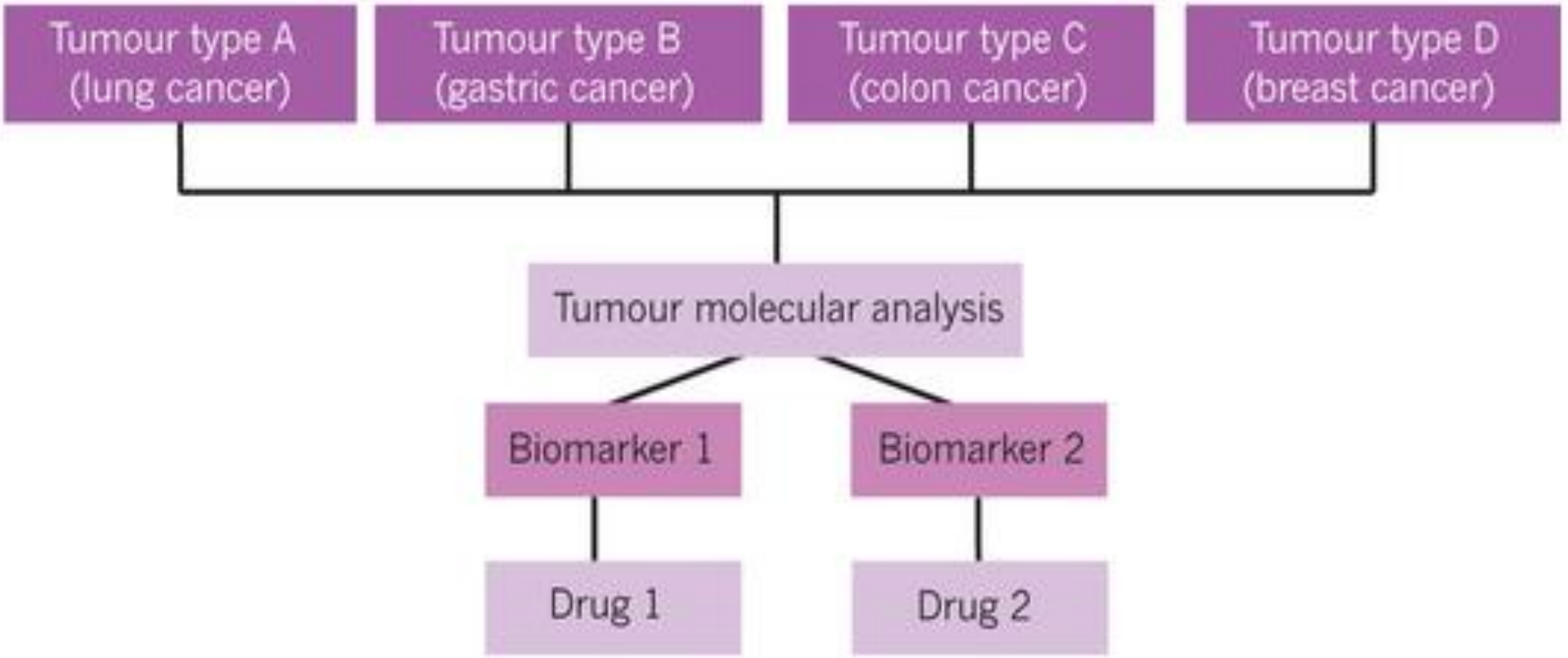
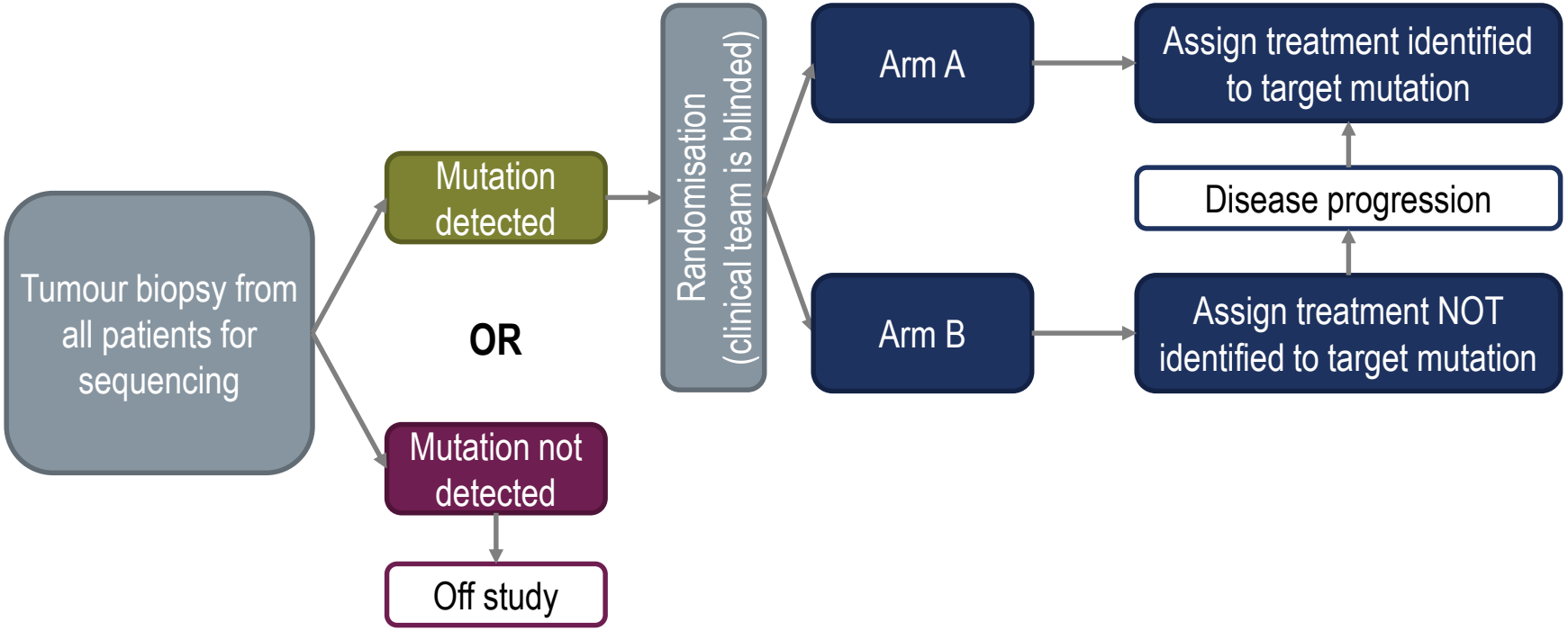
BASKET TRIAL



Biankin AV, *et al.*, Nature 14 October 2015; 526, 361-370. Reprinted by permission from Macmillan Publishers Ltd: Nature, copyright 2015

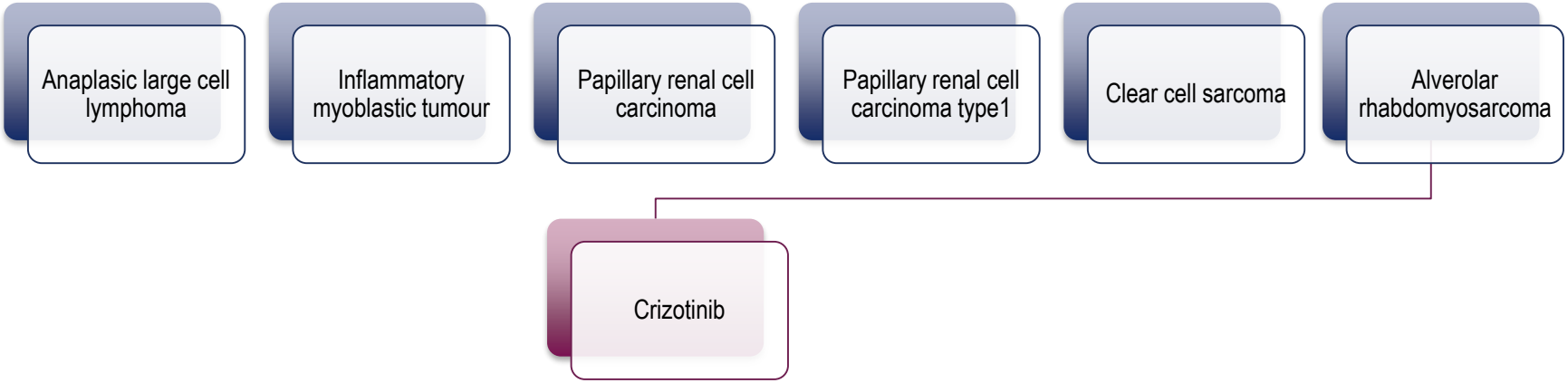
EXAMPLE: NCI MPACT BASKET TRIAL



Kummar S, *et al.*, ASCO Annual Meeting 2014 poster
Courtesy of Shivaani Kummar NCI MPACT: National Cancer Institute Molecular Profiling-based Assignment of Cancer Therapy.

CREATE EORTC TRIAL

- Six Cohorts of rare solid tumours and anaplasic large cell lymphoma
- ALK and/or MET alterations are considered to play a role of the carcinogenesis process of these tumours



PHASE II TRIAL 90101 "CREATE"

Activity of crizotinib in patients with clear cell sarcoma (CCSA) in EORTC

"CREATE" phase II trial assesses the safety and activity of ALK/MET inhibitor crizotinib in 6 different ALK- or MET-driven tumour types including CCSA

Full results of this trial are pending

Schöffski P, *et al.,* ASCO Annual Meeting 2015

BASKET TRIAL: PROS AND CONS

Pros

- Determining potential tumour efficacy of a single targeted agent in different cancer types with the same gene abnormality

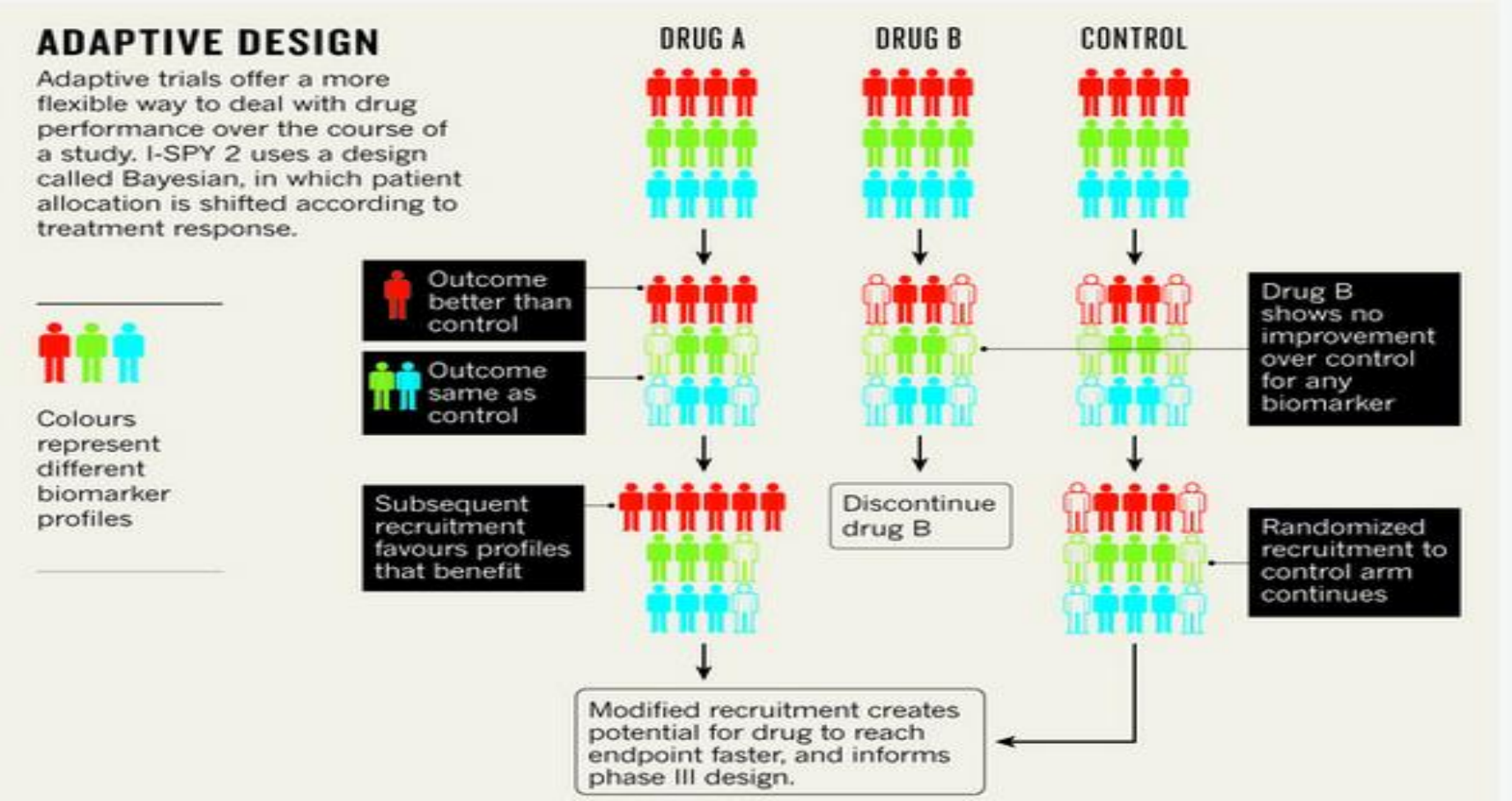
Cons

- Risk of overlooking the impact of tumour histology type. In fact, different tumour responses by targeting the same mutation in several cancer types could be observed. (e.g. BRAF in melanoma versus BRAF in colorectal cancer: RR 50%-60% versus <5%)

ADAPTIVE TRIALS

The principle of this trial is based on **modifying parameters (dose, sample size, drug, schedule …)** of a clinical trial evaluating a treatment in accord with observed outcomes in participants

ADAPTIVE TRIAL DESIGN



Eisenstein M,*et al.,* Nature, 2014; 509:S55-57 Reprinted by permission from Macmillan Publishers Ltd, copyright 2014

A COMPARISON

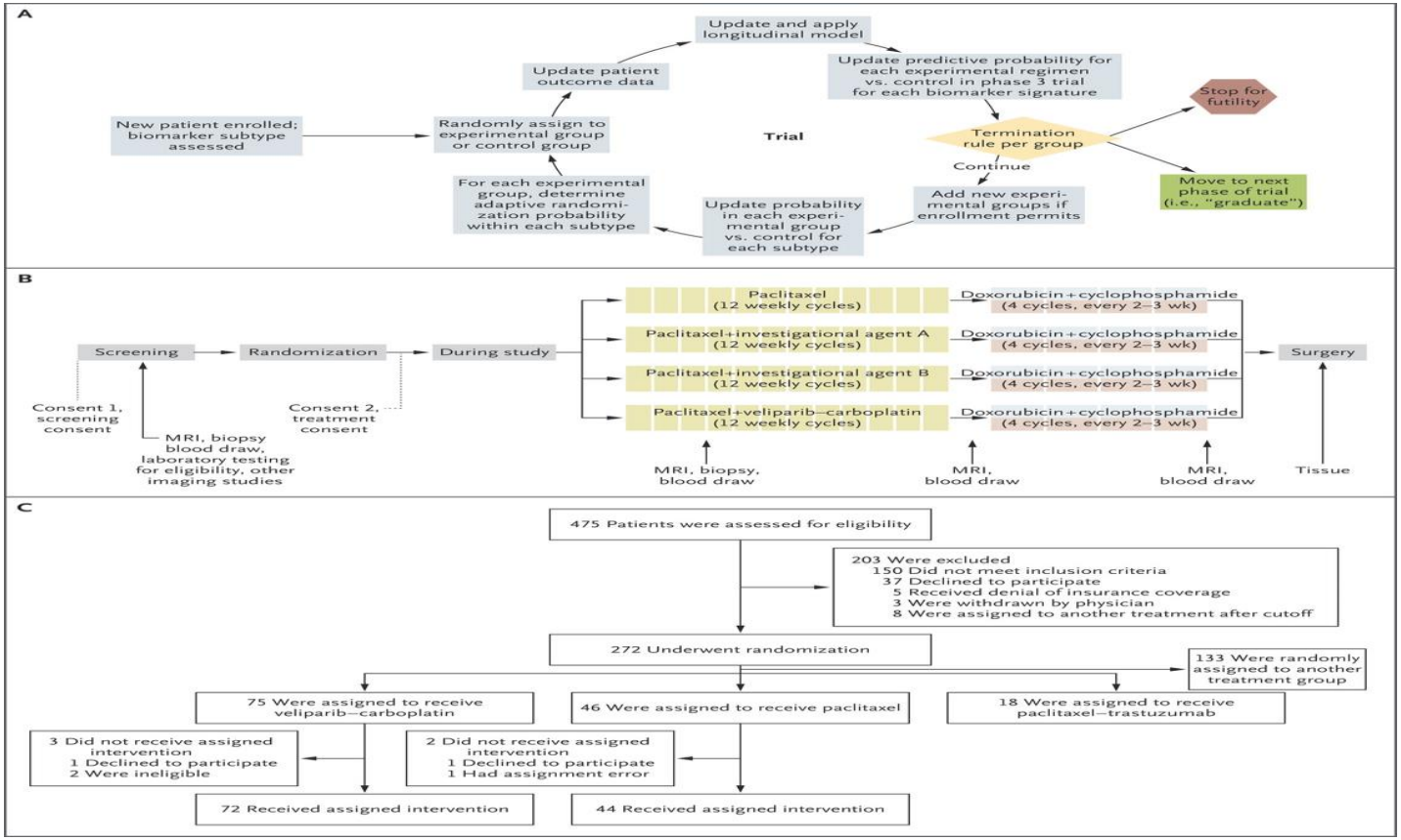
Between the "Bayesian" and "Frequentist" approaches

Variable	Bayes	Frequentist
Differences		
Main goal of inference	Predict outcomes of future trials and absolute risk for future patients	Estimate population average effects
Assumptions	Requires explicit specification of prior distributions of unknown population parameters. Incorporates a prior knowledge and clinical judgment formally. May be sensitive to specification of prior distributions	Does not require explicit specification of prior distributions of unknown population parameters. Incorporates a prior knowledge and clinical judgment informally
Interim monitoring	Only the data actually obtained are relevant for final conclusions (e.g., a credible interval or predictive probability). Whether or not a clinician examines accumulating evidence with the possibility of stopping the trial does not affect inference	Both the data actually obtained and the probabilities of data not obtained are relevant for final conclusions (e.g., a P value). Whether or not a clinician examines accumulating evidence with the possibility of stopping the trial does affect inference
Ease of use	Often computationally complex; careful modelling often requires simulation-based calculations	Often computationally simple, though careful modelling may require simulation-based calculations
Similarities		
Adaptation	Can incorporate adaptive designs, multistage trials, early stopping, and adaptive randomisation	
Role of statistical judgment	Options for data-driven analyses are available. Skill and substance-area knowledge of the data analyst are important in drawing correct conclusions	
Compatibility	It is feasible to combine a Bayesian design with a frequentist analysis or a frequentist design with a Bayesian analysis	
Prior knowledge	Both approaches rely on prior knowledge and clinical judgment (though they incorporate them in different fashions)	

Harrington D, *et al.,* N Engl J Med 2016;375:7–9

I-SPY2

Adaptive Randomisation of Veliparib–Carboplatin Treatment in Breast Cancer



ADAPTIVE TRIAL DESIGN: PROS AND CONS

Pros

- Faster evaluation of the drug
- Modification of drug, dosage and sample size during the trial according to the observed results

Cons

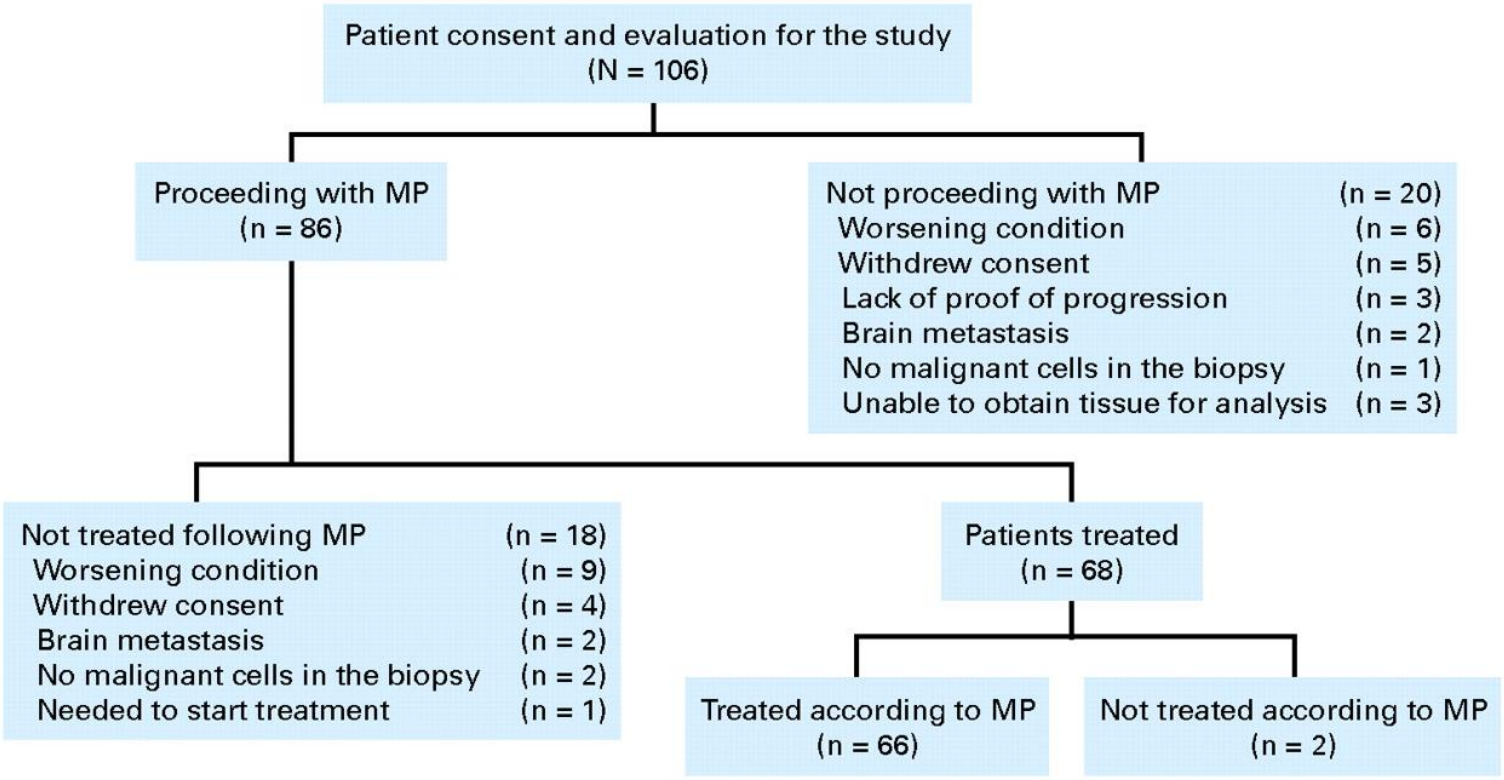
- Practical difficulties during the performance of the trial
- The clinicians are not familiar with the essential statistical part of this approach
- Active and dynamic follow-up of the trial is needed

N-OF-1 TRIALS

Recruitment of patients exposed to different experimental agents or placebo in different sequencing, with washout periods in between

Each involved patient serves as his or her own comparator, through the comparison of the efficacy seen for the different experimental agents that the patient receives

EXAMPLE OF N-OF-1 TRIALS : STUDY FLOW DIAGRAM

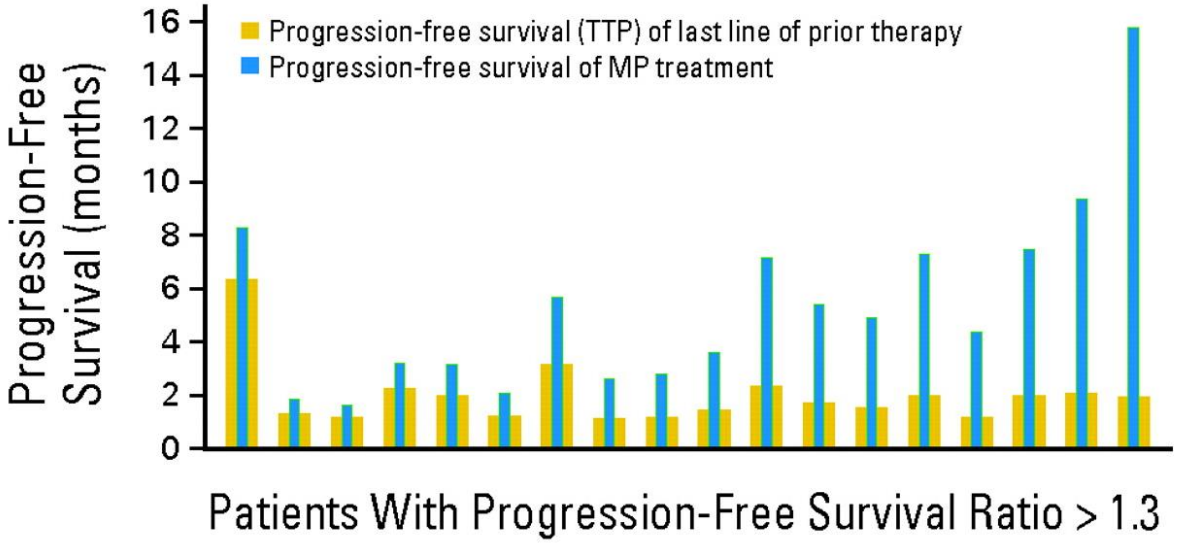


MP: molecular profiling

Von Hoff D, *et al.*, J Clin Oncol, Vol 28, (33) 2010, 4877-4883. Reprinted with permission © 2010 American Society of Clinical Oncology. All rights reserved

EXAMPLE OF N-OF-1 TRIALS

In 27% of patients, the molecular profiling approach resulted in a longer PFS on an MP-suggested regimen than on the regimen not based on molecular profiling on which the patient had just experienced progression.



MP: molecular profiling

Von Hoff D, *et al*., J Clin Oncol, Vol 28, (33) 2010, 4877-4883, Reprinted with permission © 2010 American Society of Clinical Oncology. All rights reserved

N-OF-1 TRIALS : PROS AND CONS

Pros

- *In vivo* testing of agents in the same patient
- Eliminating the inter-individual genetic differences affecting drug metabolism

Cons

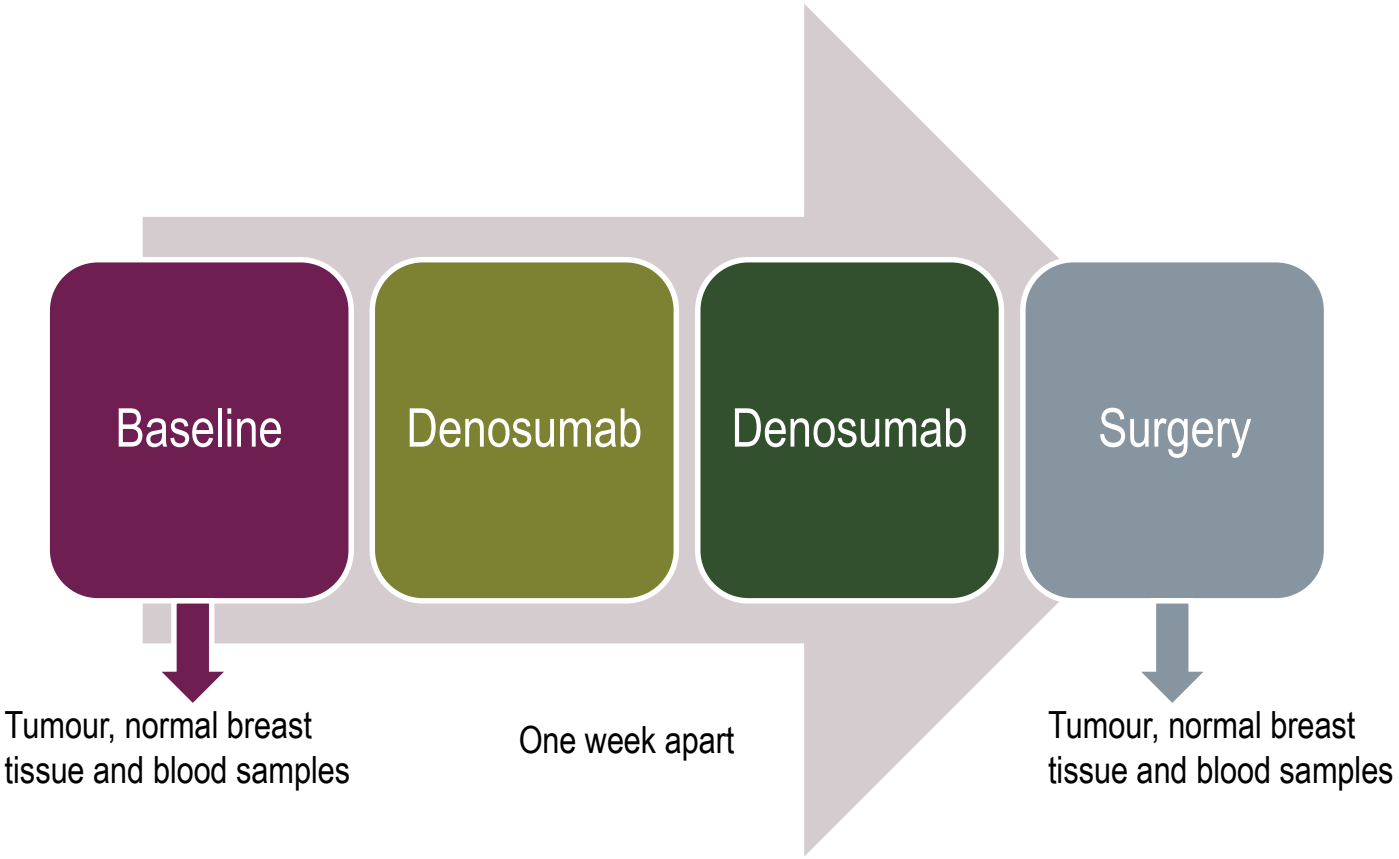
- The difference in outcome might be of multifactorial origin. As example, it could be due to difference in consecutive treatment sequence and change in the biology (sensitivity/resistance) of the disease
- Translation of the finding of these studies to future patients is difficult and unclear

WINDOW-OF-OPPORTUNITY TRIALS

- Assessing the administration of an investigational agent over a short period of time
- Most often in the pre-surgical setting, sometimes in metastatic
- No major efficacy endpoint
- *In vivo* biological effect(s) (pharmacodynamics) of an experimental agent

WINDOW-OF-OPPORTUNITY TRIALS

D-BEYOND trial design in early breast cancer



NCT01864798

WINDOW-OF-OPPORTUNITY TRIALS: PROS AND CONS

Pros

- *In vivo* evaluation of the mechanism of action of a drug or if the target is affected

Cons

- No direct clinical implication
- Short period treatment

CHALLENGES OF THE NEW CLINICAL TRIAL DESIGNS

- To show significant benefit in overall survival
- Rapidly evolving and not validated technics in use for tumour sequencing (NGS, circulating tumour cells, circulating tumour DNA…)
- High number of screened patients is needed

MORE EFFORTS ARE NEEDED ON :

- Networking between institutions to render molecular tumour board accessible to the majority of centres and consequently to clinical trials and new drugs
- More collaboration between pharmaceutical companies due to the need of drugs (including off label drugs) with the different mechanisms of action to be used in precision medicine at the right time for the patient
- Role of liquid biopsy in determining the biological heterogeneity and evolution of the tumour
- Role of biomarkers and/or molecular imaging in determining mainly the negative predictive value of an evaluated drug

Thank you!