Designing clinical trials to evaluate the clinical utility of cancer genomic data… *in patients with metastatic cancers*

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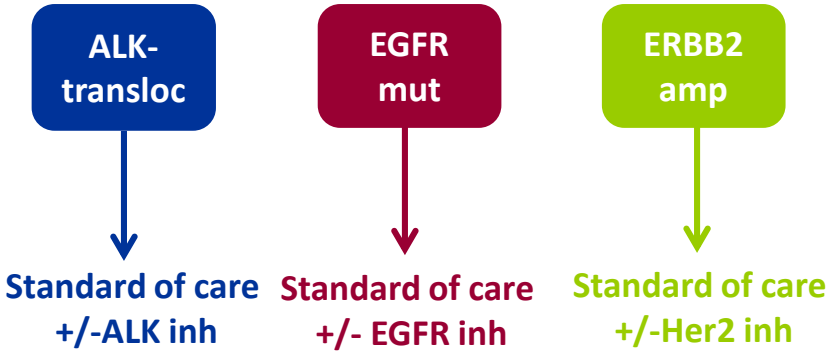
How to generate evidence that a genomic tool improves outcome ? Two different models

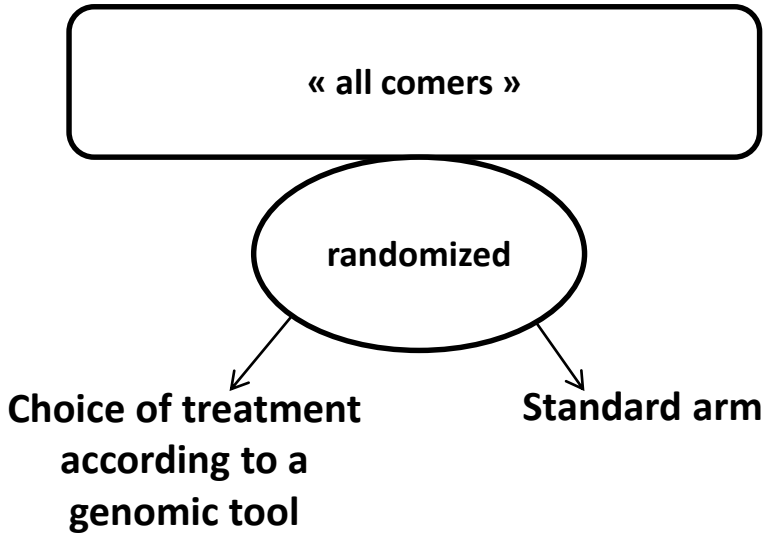
Clinical trials testing the drugs

Hypothesis:
ONE drug (or combination) improves outcome SPECIFICALLY in ONE genomic segment (and not in patients without genomic alteration)



Clinical trials testing the genomic test

Hypothesis:
ONE decision-making tool that includes (multiple) genes to predict (multiple) drugs improves the outcome



Outline

- Testing ONE drug in a population defined by ONE genomic alteration
  - **Possible designs**
  - Rationale for multigene screening
  - How to overcome accrual challenges
  - The cherry on the cake: target discovery using molecular screening approaches
  - Ethical issues

- Testing multigene,multidrug decision-making tools
  - Illustrations
  - Current limitations (standard arm, heterogeneity, combination phase I)

Clinical utility of a genomic test for drug registration

Register ONE drug (or combination)

in a population defined by ONE genomic alteration

=

1. The drug works in patients with the genomic alteration
2. The drug does not work when the genomic alteration is not present

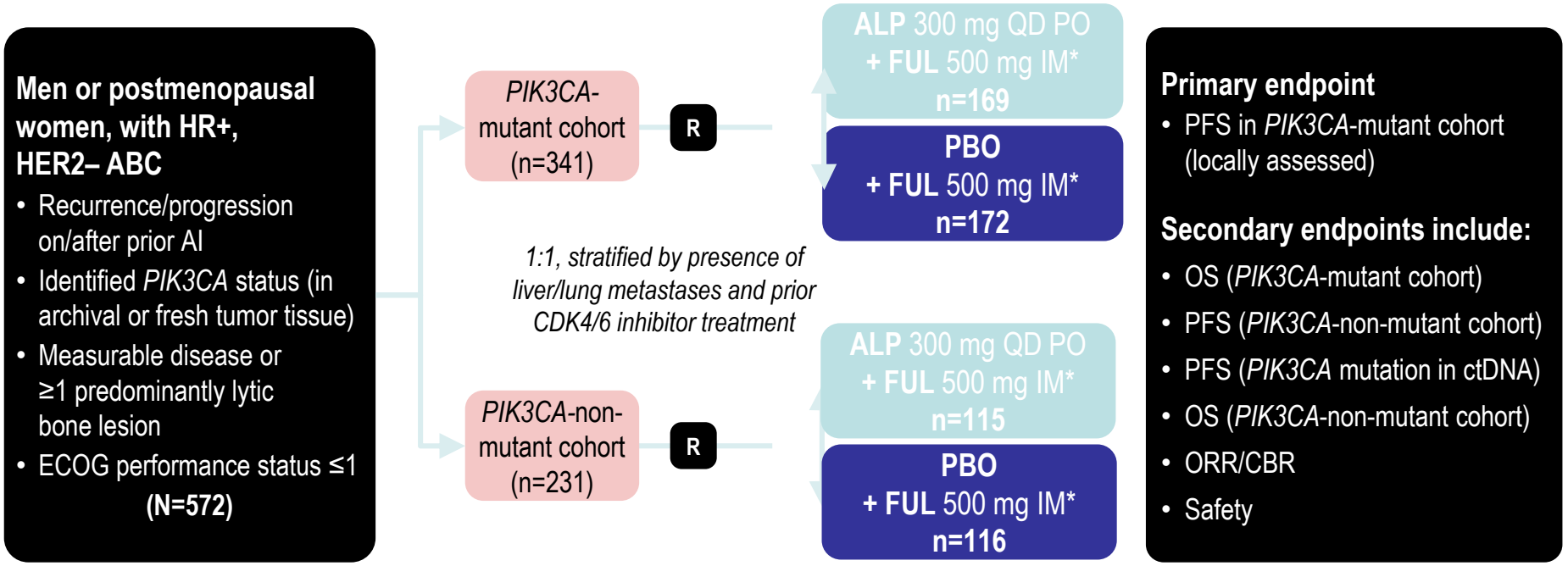
Biomarker-driven trials to show that a drug works specifically in a genomic segment

context	design	Biomarker-negative cohorts	example
The target is known, the drug has amazing activity in the genomic segment and the disease has poor outcome	Registration based on phase I/II trials performed in patients WITH the genomic alteration	Patients without genomic alterations should be included, except if preclinical studies suggest it's not ethical	ALK - crizotinib

Biomarker-driven trials to show that a drug works specifically in a genomic segment

context	design	Biomarker-negative cohorts	example
The target is known, the drug has modest activity or the disease outcome is good/difficult to predict	Phase III trial performed in patients with the genomic alteration	No signal in phase II: NO	Her2 – trastuzumab
		Little activity in phase II: YES • One cohort with two coprimary endpoints: all comers + genomic (control the n) • Two cohorts (genomic + and – pts): Interim futility analysis	PIK3CA mutations - Alpelisib

SOLAR-1: A Phase III randomized, controlled trial (NCT02437318)



Andre , NEJM, 2019

Biomarker-driven trials to show that a drug works specifically in a genomic segment

context	design	Biomarker-negative cohorts	example
The target was unknown at the time of study completion and the drug is already approved in all comers	Consistent retrospective analyses of randomized trials (Simon, JNCI)	Interaction tests	K-Ras - panitumumab

Take home message: drug development in a genomic segment

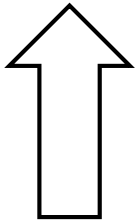
Patients should be selected based on genomic alterations as soon as possible during the drug development

Next questions:

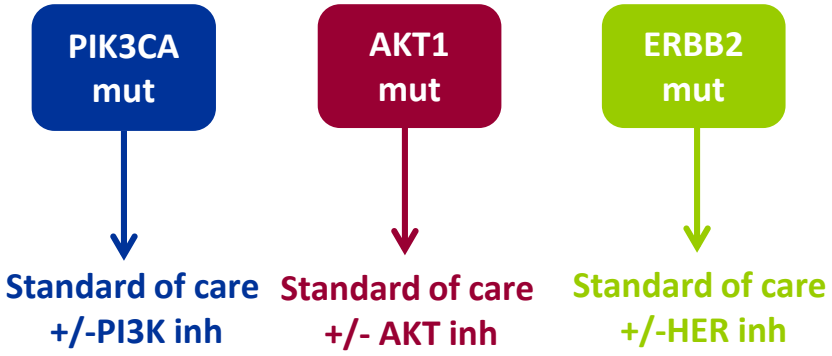
a. What are the optimal models for molecular screening ?
b. What are the challenges of genomic-driven drug development ?

Designing clinical research program to register drugs in genomic segments

How to screen for genomic alterations ?



Phase I-III trials testing drugs in population defined by a genomic alteration



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  - Possible designs
  - **Rationale for multigene screening**
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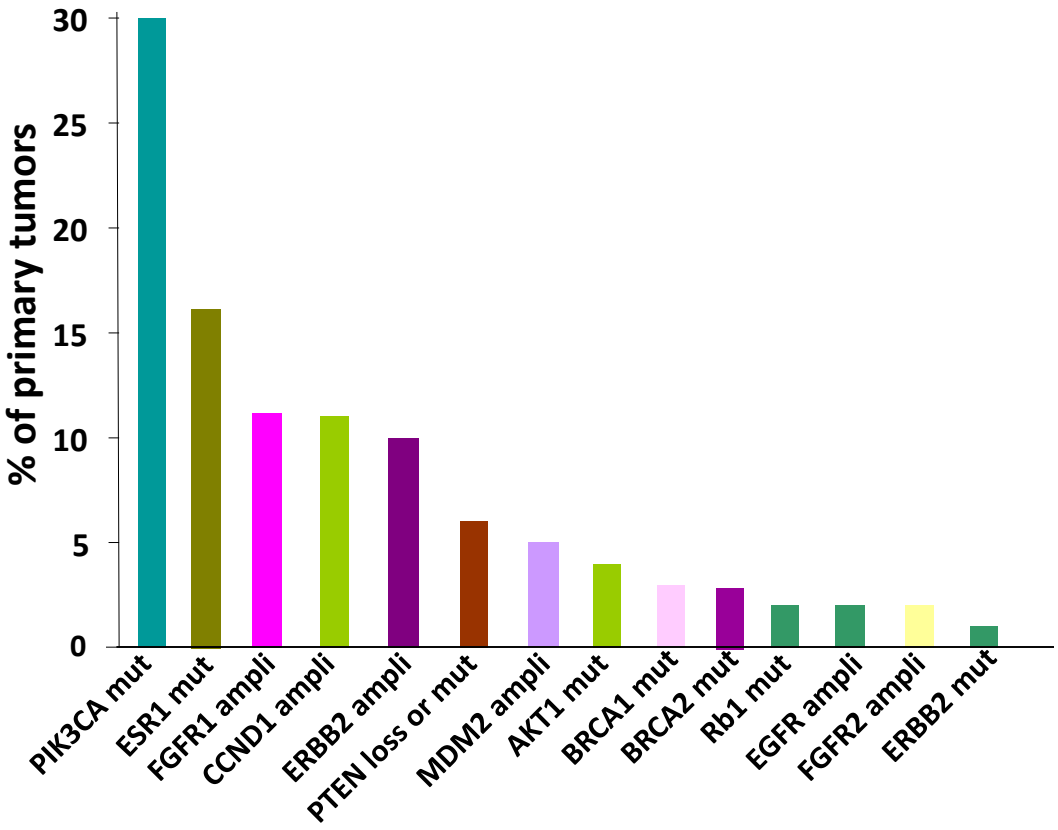
- Testing decision-making genomic tools
  - Illustration
  - Current limitations (standard arm, heterogeneity, combination phase I)

Genomic segments and breast cancer



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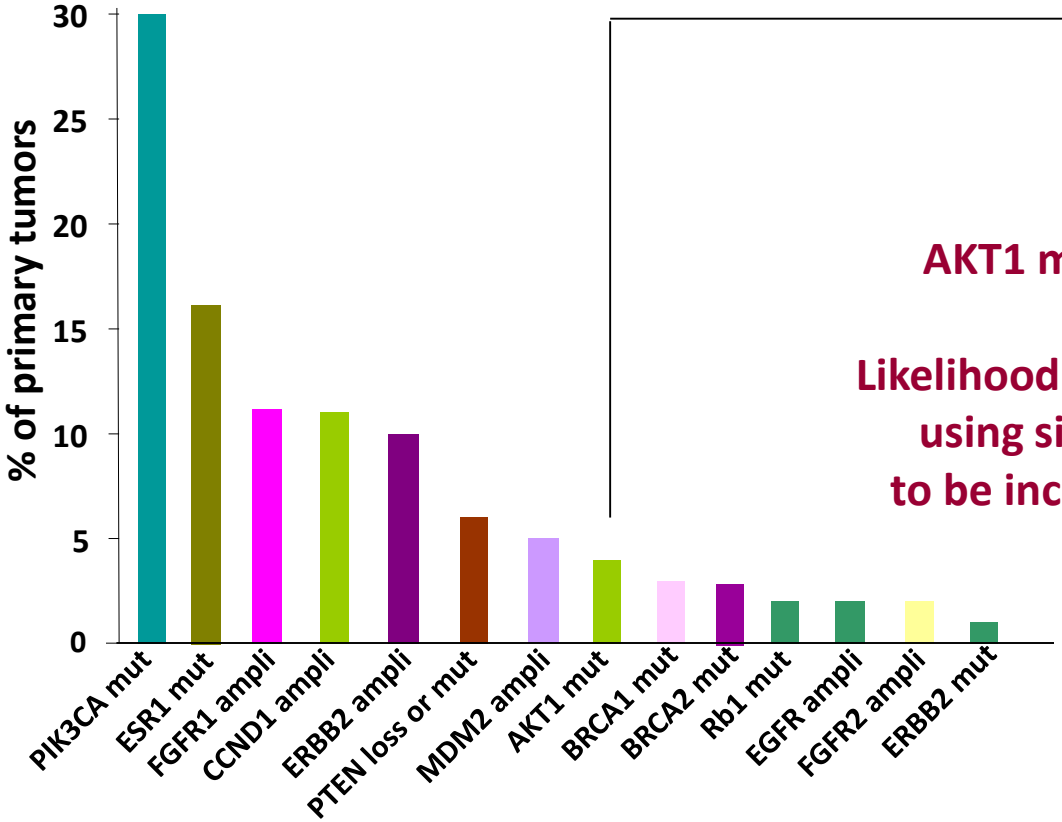


AKT1 mutations : 4% of BC

Likelihood for a patient screened using single gene approach to be included in a trial: <4% !

There is a need to test multiple genes in each patients in order to increase the likelihood of being included in a therapeutic trial

Molecular screening programs: Concept

Goal: To develop drugs in population defined by a biomarker

Each downstream therapeutic trial has its own hypothesis

Ideal genomic alterations: strong candidate, incidence 1-10% population

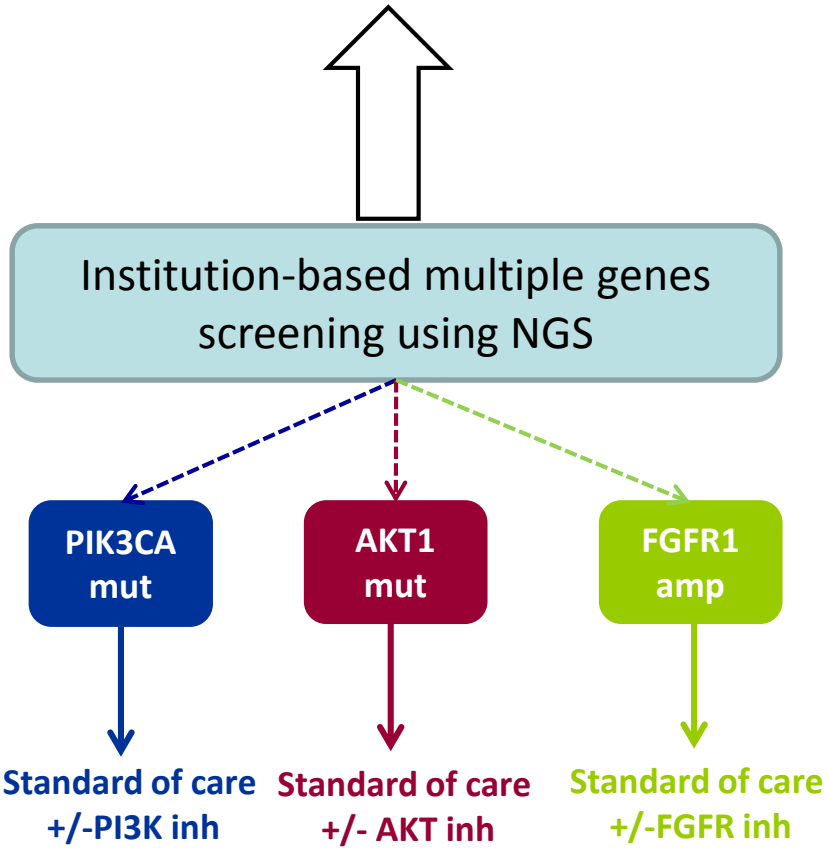
Andre, Delaloge, Soria, J Clin Oncol, 2011

Take home message

- Effective (and ethical) molecular screening must include multiple genes / patient
- Institution-based molecular screenings are currently sized to enrich phase I/II trials in patients with the candidate genomic alteration
- Which molecular screening to perform large genomic-driven phase II or phase III trials ?

Designing clinical research program to register drugs in genomic segments

How to screen genomic alterations to perform registration genomic-driven trials ?



Phase I-II trials testing drugs in population defined by a genomic alteration

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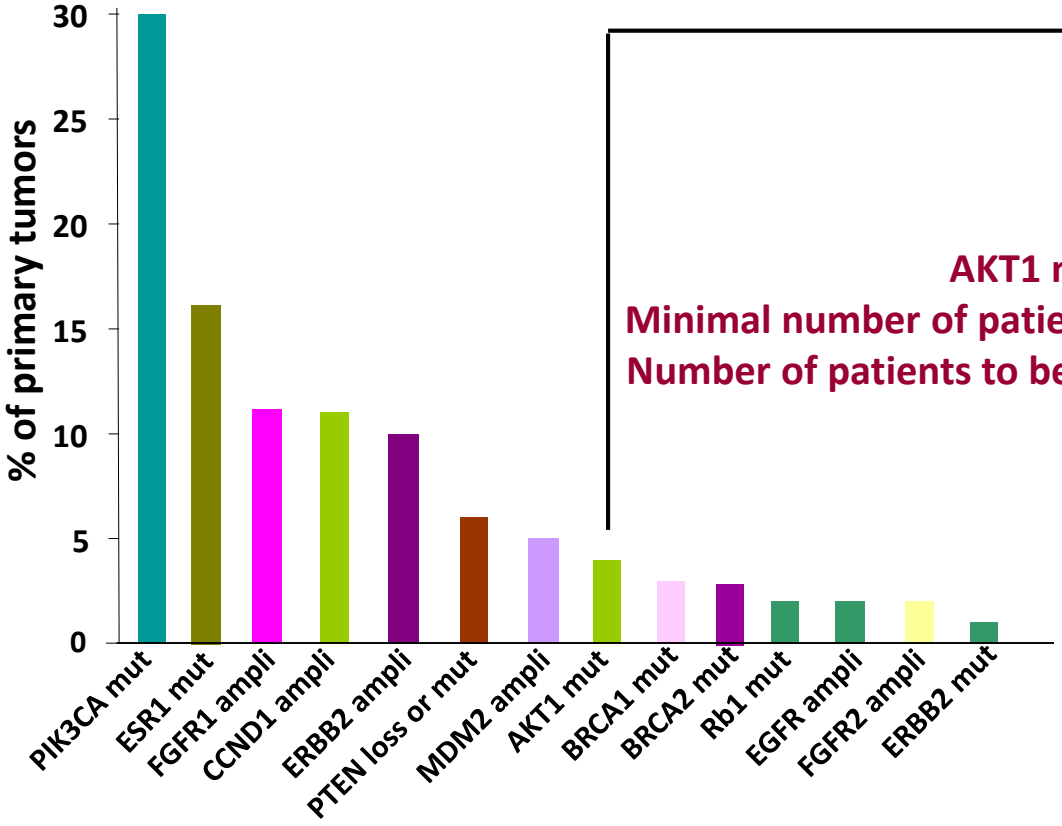
Challenge in drug development for RARE genomic segments: ACCRUAL



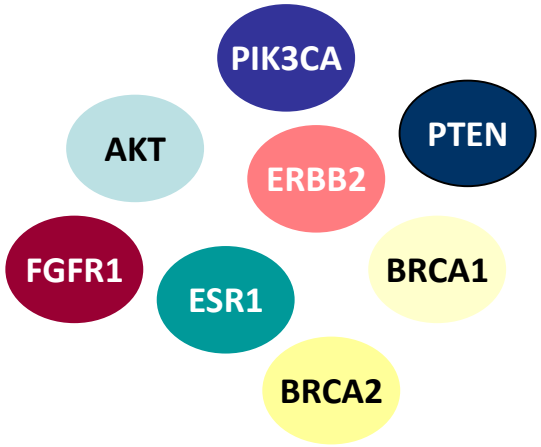
AKT1 mutations : 4% of BC

Minimal number of patients needed for a randomized trial: 200

Number of patients to be screened for the mutation: 5 000 !!!!!

Accrual is the challenge of stratified medicine in mBC

How to overcome the accrual challenges of drug development in rare genomic segments ?

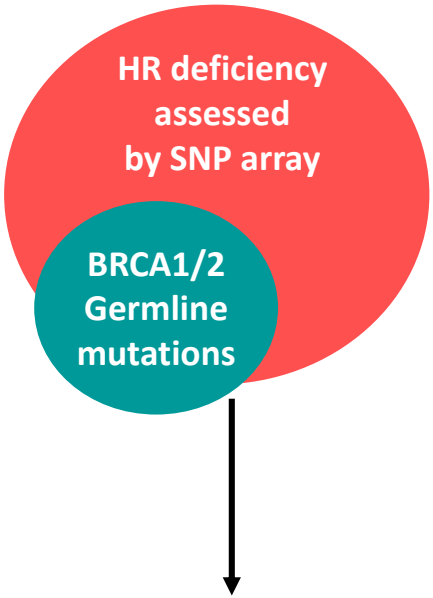


rare genomic segments: need to screen large number of patients with mBC to perform therapeutic trials

- **Cluster several genomic alterations into single pathway**
- **Scale-up capacities of molecular screening (use of circulating DNA, nationwide screening, International groups…)**
- **Approve drugs based on phase II in genomic segments associated with very poor outcome**
- **Perform part of the development in the preoperative setting in early BC**

Cluster several genomic alterations into pathways: PARP inh (rucaparib) in HR-deficient mBC

RUBY study; breast cancer



Phase II single agent rucaparib in HR-deficient mBC diagnosed by SNP6.0 arrays (PI: Patsouris/Vicier)

A test that incorporates BRCA1/2 mutations and HRD deficiency ay increase the number of patients eligible and sensitive to PARP inhibito

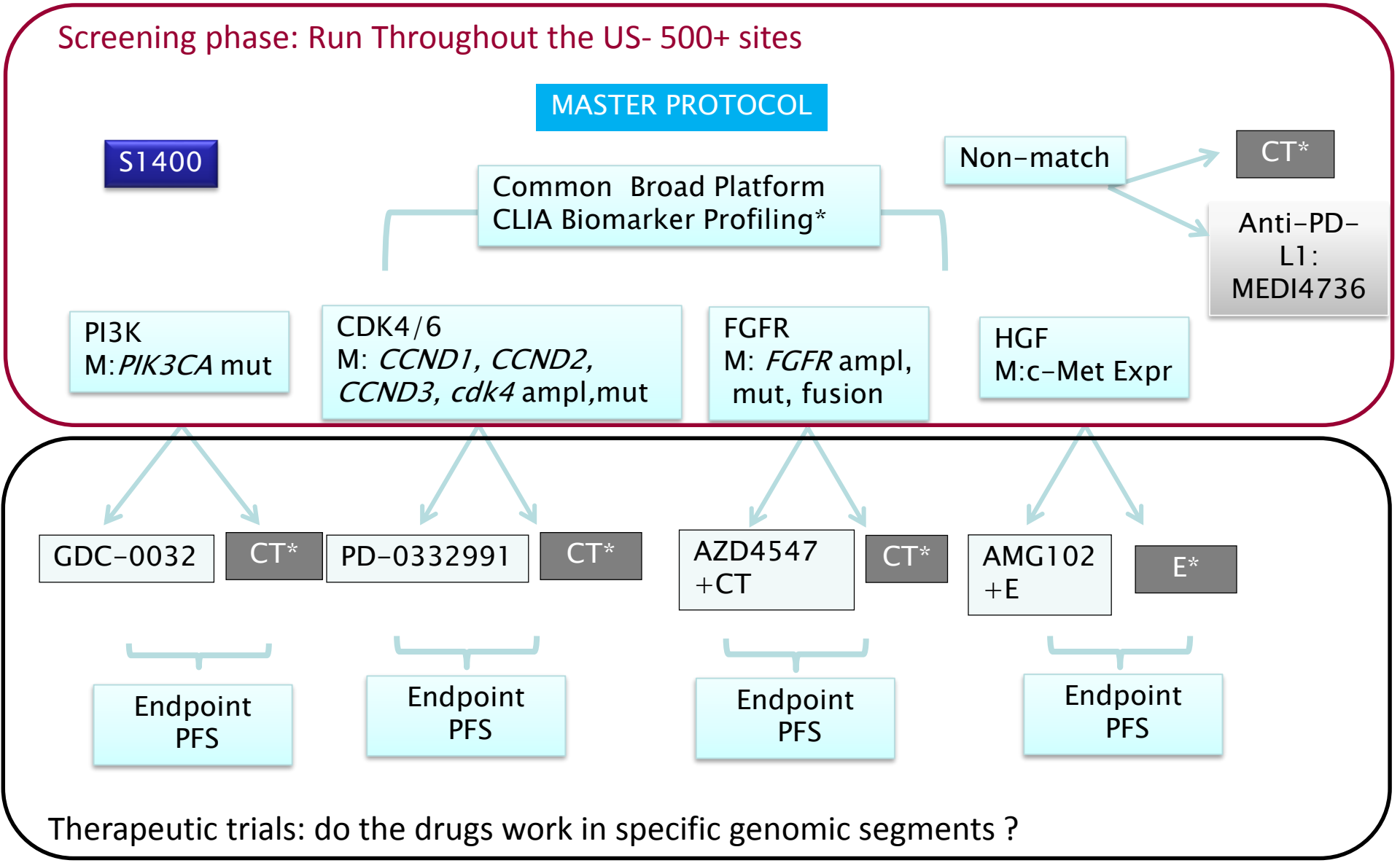
Scale-up capacities of screening: nationwide screening

AcSè program

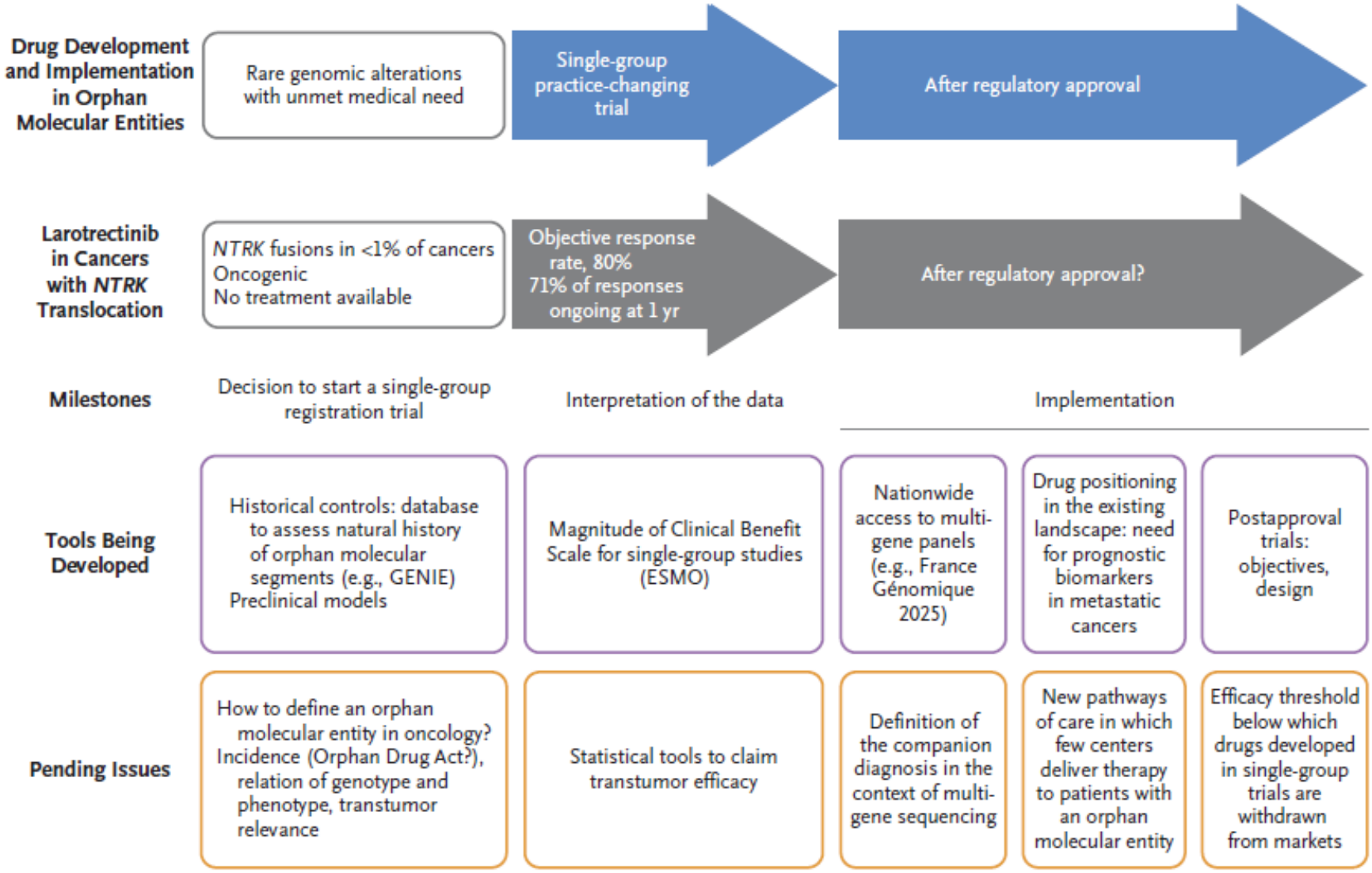
150 sites opened
Covers comprehensive cancer centers
University Hospitals
Community hospitals
Private clinics

Nationwide programs allows screening patients who are usually not proposed for genotype-driven trials

Scale-up capacities of screening: nationwide screening



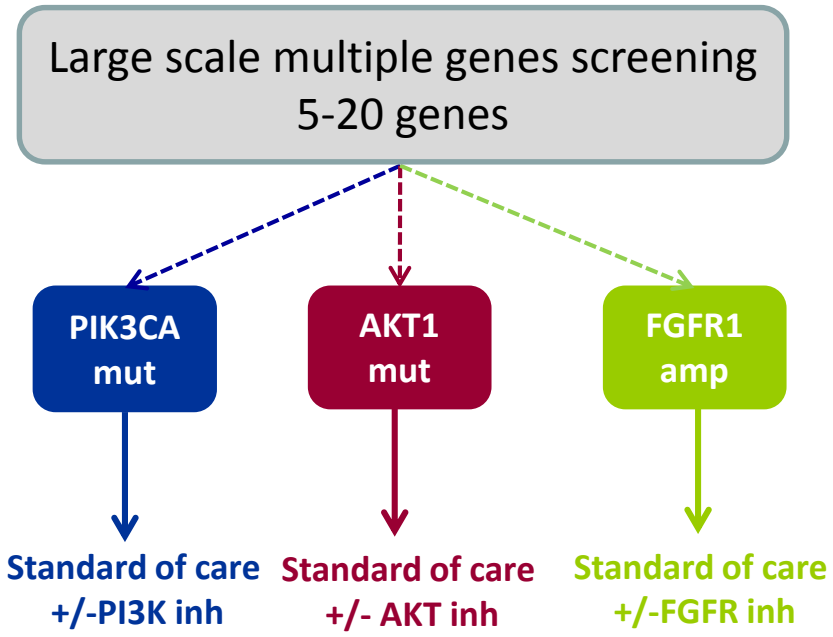
Register drugs based on single arm phase II trials



Andre F, NEJM, 2018

Designing clinical research program to register drugs in genomic segments

Phase I-III trials testing drugs in population defined by a genomic alteration



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  - Rationale for multigene screening
  - How to overcome accrual challenges ?
  - **The cherry on the cake: target discovery using molecular screening approaches**
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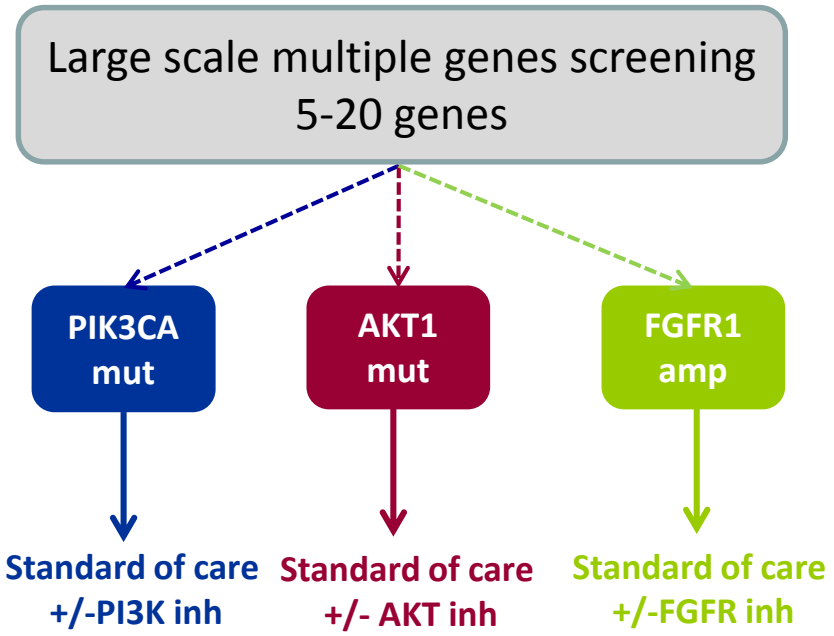

Designing clinical research program to register drugs in genomic segments

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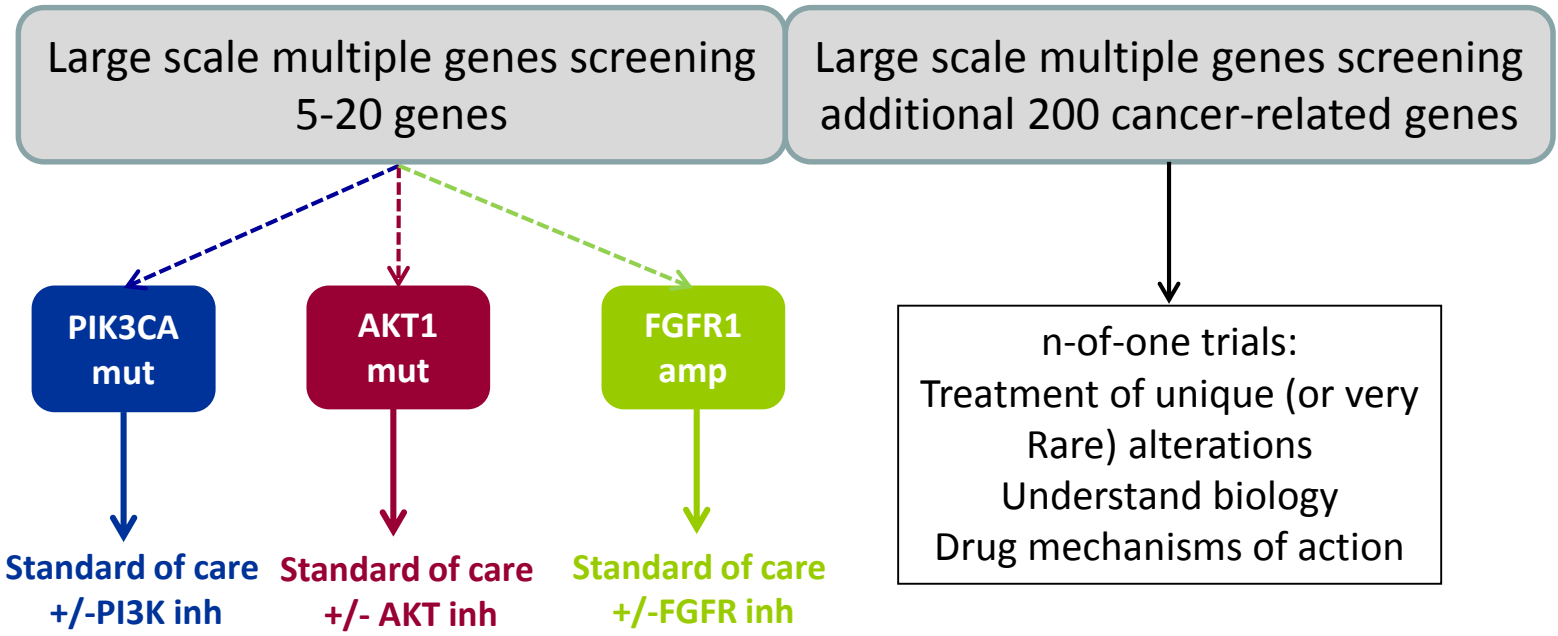
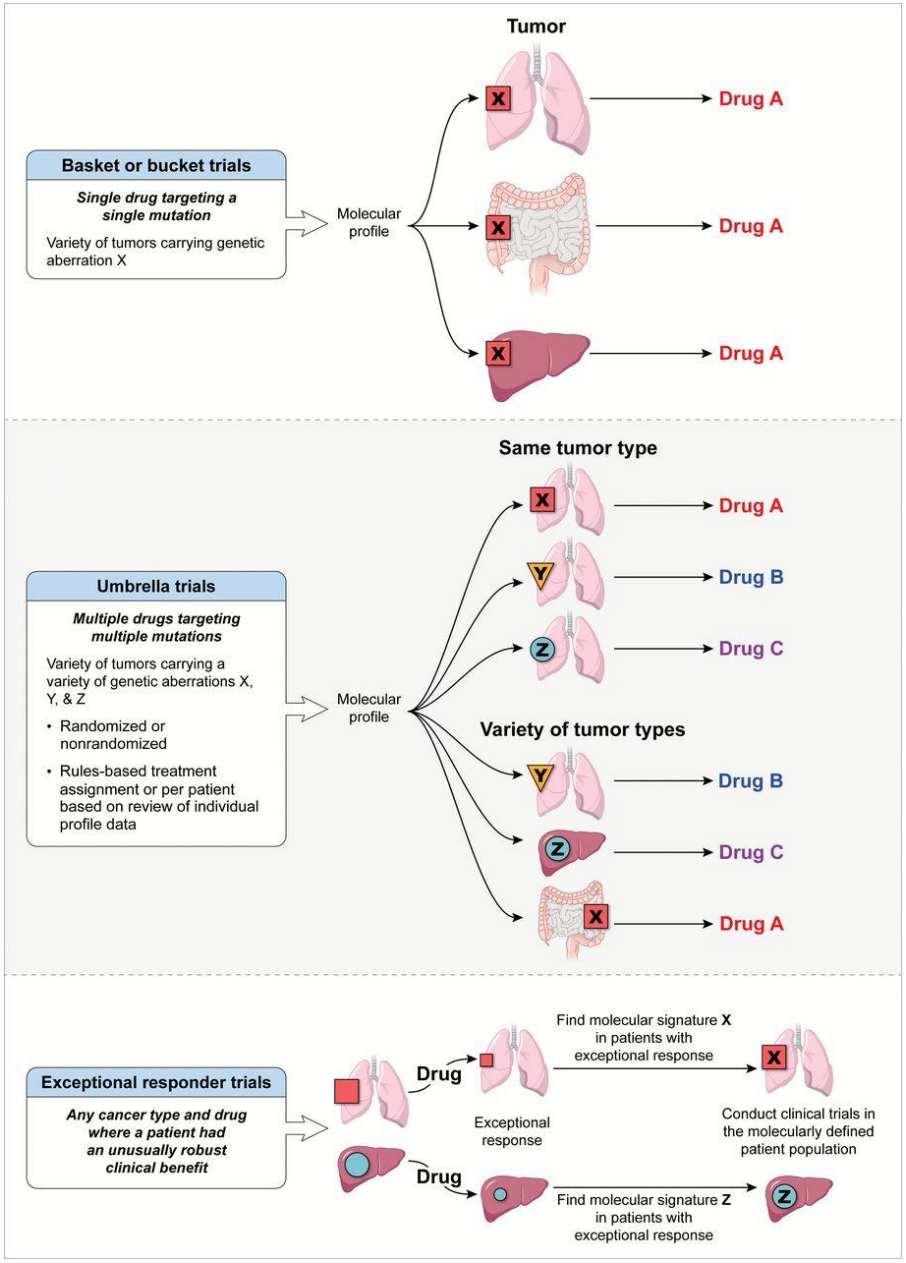


Clinical trial designs utilizing molecular profiling.



Shivaani Kummar et al. JNCI J Natl Cancer Inst 2015;107:djv003

How to use genomic test to optimally develop drugs

- Developing drug in specific genomic segment requires molecular screening
- Need to enrich trials in patients with the candidate genomic alteration
- Screening Multiple genes / patients is more relevant
- Scale-up number of patients for registration trials (AcSe, MASTER)
- Define genomic segments with poor outcome
- Increase number of genes to develop a target discovery cohort
- No drug – no gene : don’t provide genomic results when drugs are obviously not available

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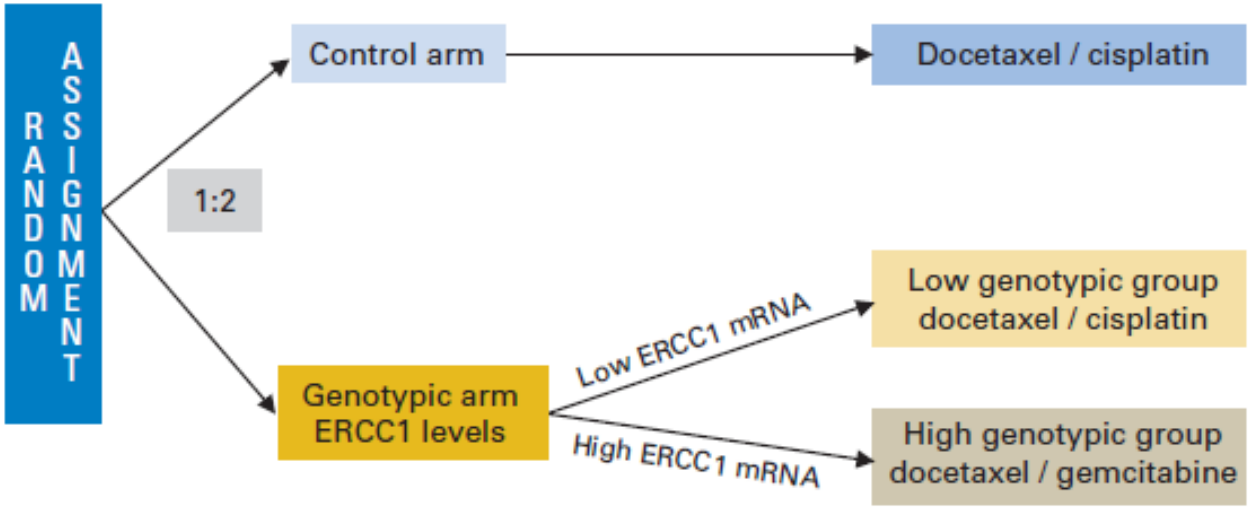
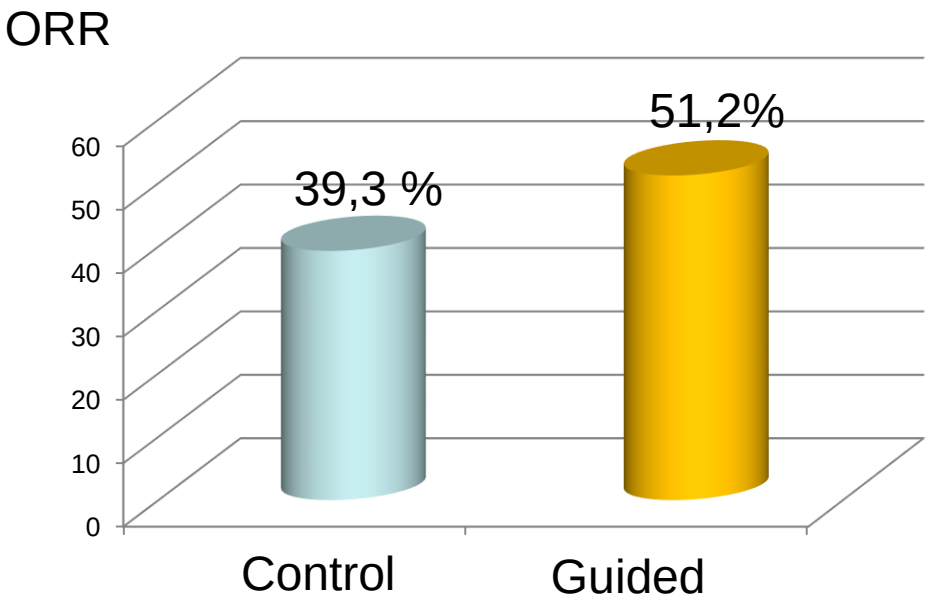
  - **Illustration**
  - Current limitations (standard arm, heterogeneity, combination phase I)

Trials evaluating the medical utility of the genomic test (or decision-making tool)

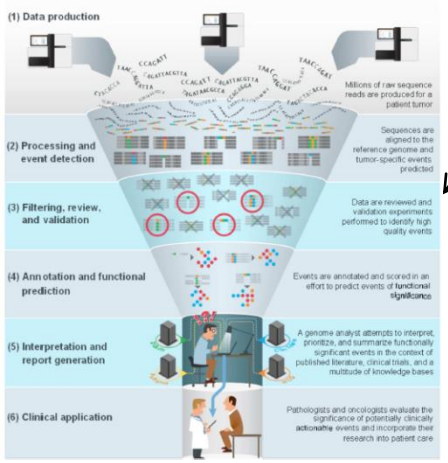




Current application of this trial design: Testing the medical utility of bioinformatic tools to analyse high throughput genomic analyses

« all comers »

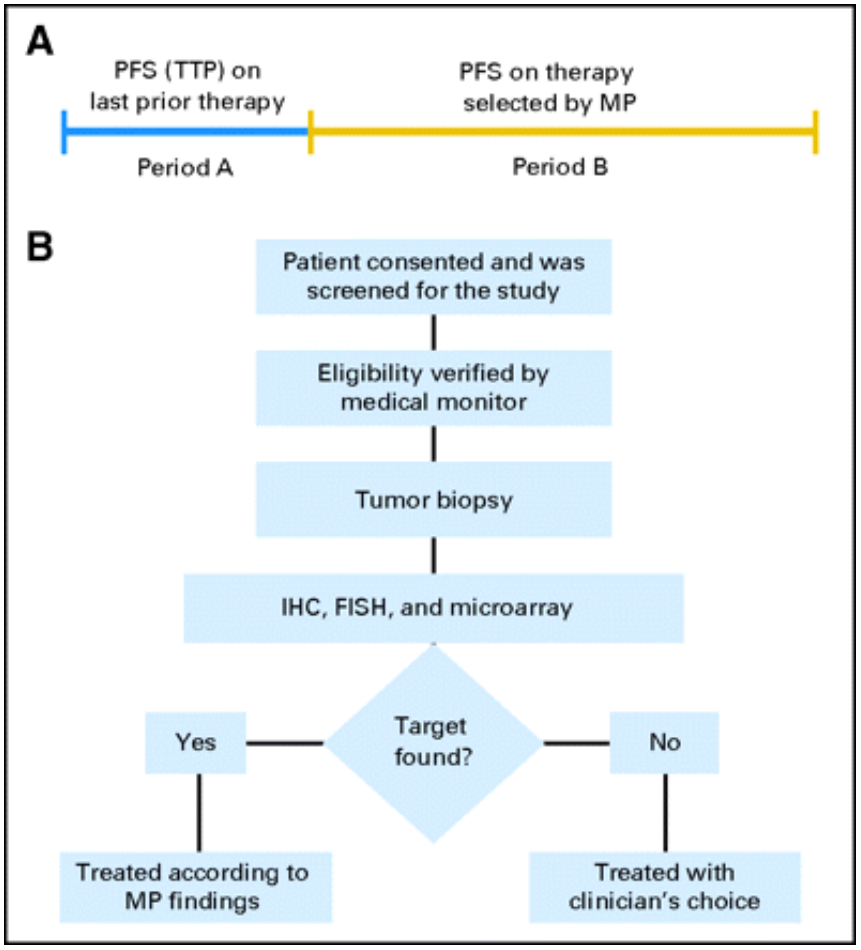
randomized



Standard arm

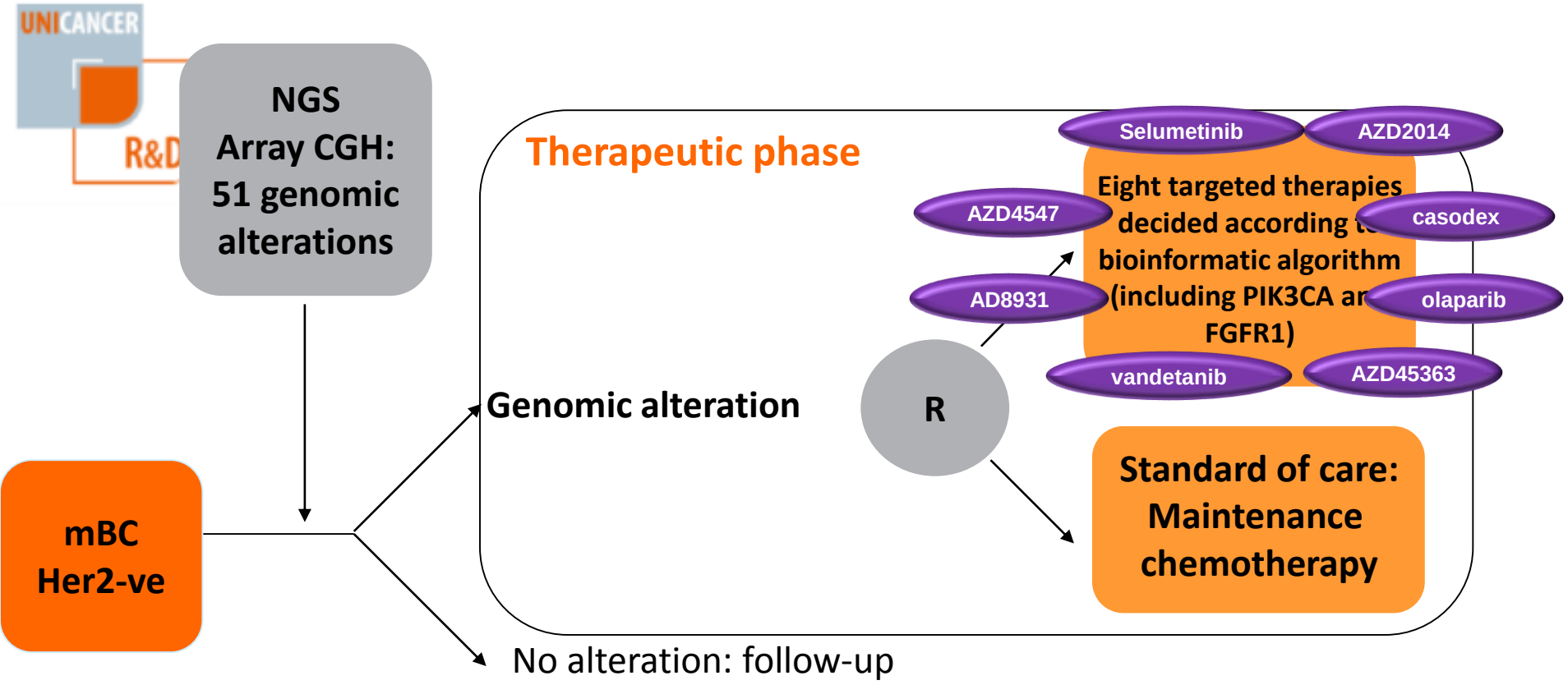
Hypothesis: the use of high throughput genomic analyses and their interpretation improves outcome, independantly to each targeted therapy

Non-randomized trial:



Von Hoff, J Clin Oncol, 2010

Randomized trial testing high throughput genomics: SAFIR02



Primary objective: genomic arm improves PFS as compared to standard of care
Sample size: n=240 (PFS: 3 > 5.5 months)

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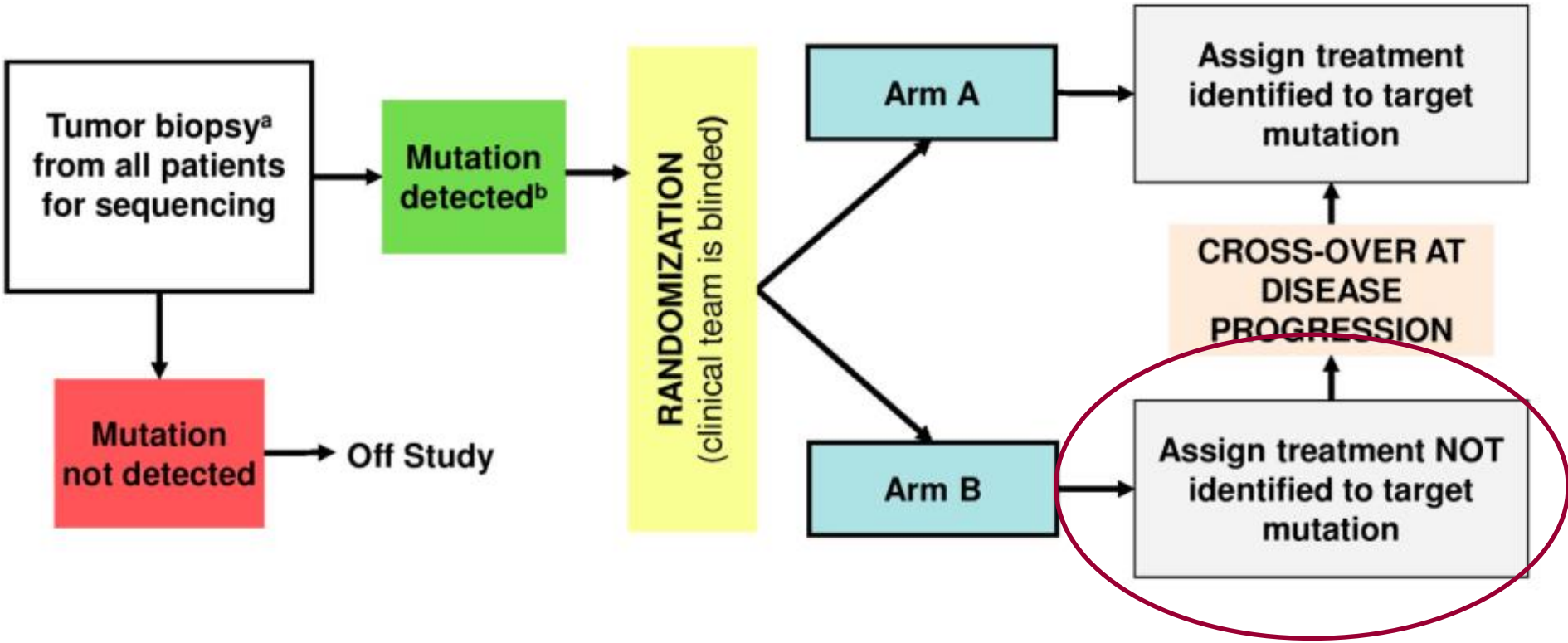
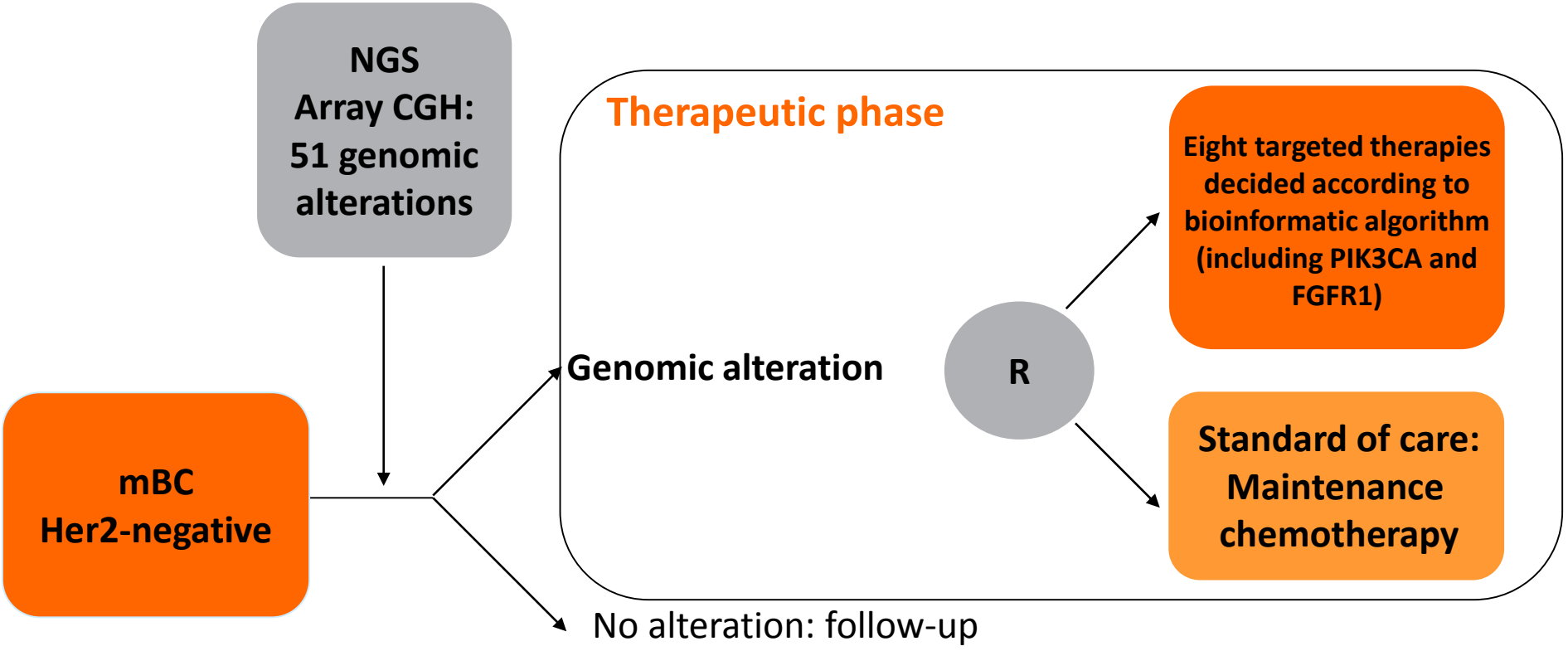
Pitfall I: standard of care should include same drugs given randomly

Molecular Profiling-based Assignment of Cancer Therapy (M-PACT)



S. Kummar

Pitfall II: The trial must avoid (or control) outlier drugs (one or two drugs highly effective who will make the trial positive while the other ones don't work)

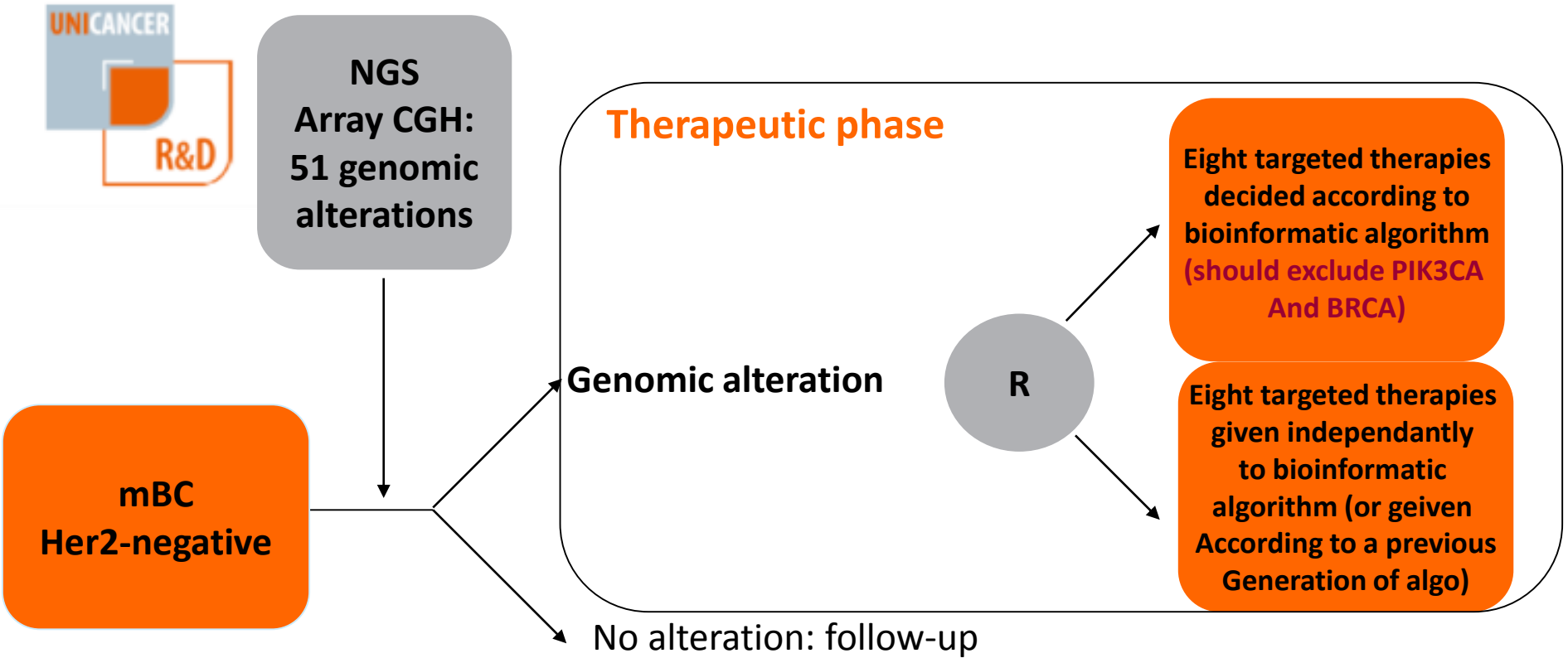


Primary objective: genomic arm improves PFS as compared to standard of care

Secondary objective should control that the overall effect is not related to a few drugs, test for lack of heterogeneity in drug effects across the molecular groups

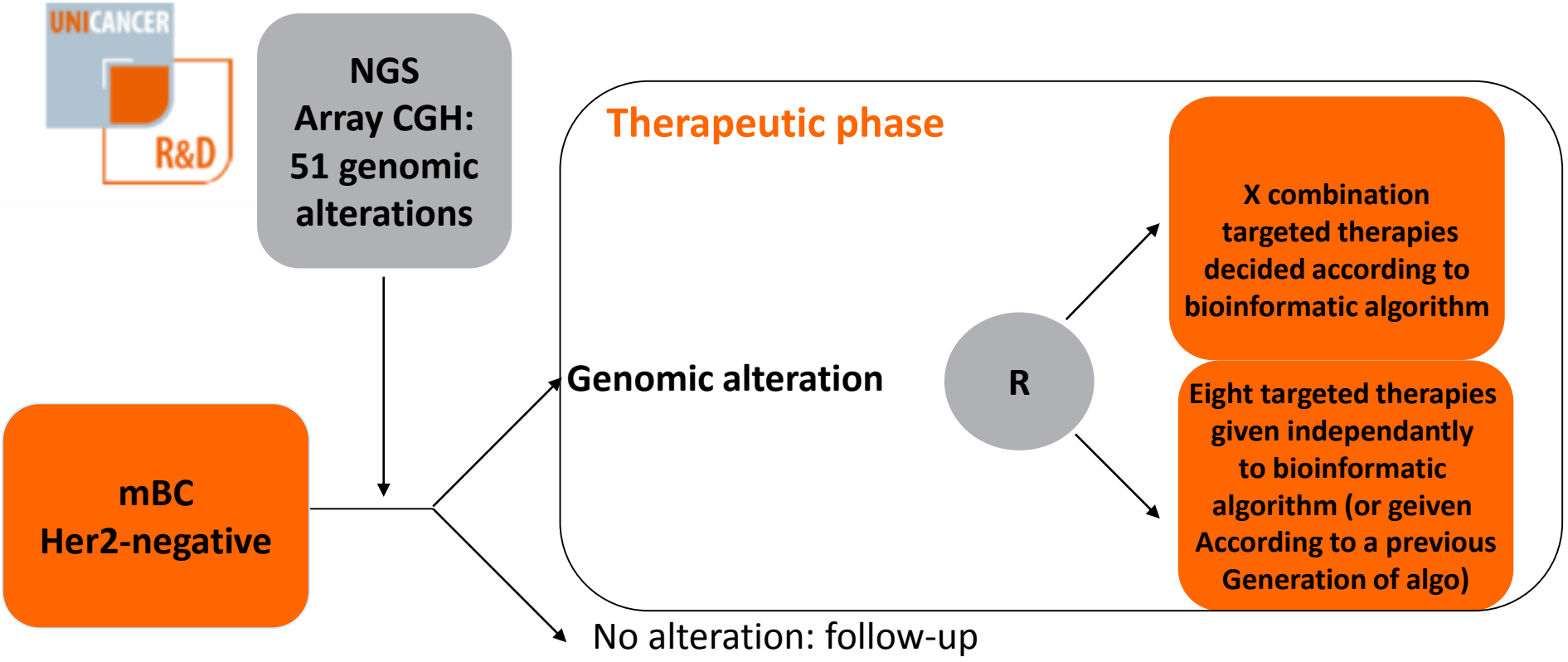
Sample size: calculated to control lack of heterogeneity in HR across all drugs

Pitfall III: The trial should not contain recurrent alterations for which drugs are under phase III trial



Primary objective: genomic arm improves PFS as compared to standard of care
Secondary objective: control that the overall effect is not related to a few drugs, test for lack Of heterogeneity in drug effects across the molecular groups
Sample size: calculated to control lack of heterogeneity in HR across all drugs

Limitation IV: The trial should propose large number of OPTIMAL drugs or combinations



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FAQ related to trials

- Metas vs primary ?
- How to prioritize when multiple ?
- How to take into account heterogeneity ?