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

Fabrice Andre, MD PhD
Gustave Roussy
Villejuif, France
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)

- ALK-transloc
  - Standard of care +/-ALK inh

- EGFR mut
  - Standard of care +/- EGFR inh

- ERBB2 amp
  - Standard of care +/- Her2 inh

Clinical trials testing the genomic test

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

- « all comers »
  - Randomized
  - Choice of treatment according to a genomic tool
  - Standard arm
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

<table>
<thead>
<tr>
<th>context</th>
<th>design</th>
<th>Biomarker-negative cohorts</th>
<th>example</th>
</tr>
</thead>
<tbody>
<tr>
<td>The target is known, the drug has amazing activity in the genomic segment and the disease has poor outcome</td>
<td>Registration based on phase I/II trials performed in patients WITH the genomic alteration</td>
<td>Patients without genomic alterations should be included, except if preclinical studies suggest it’s not ethical</td>
<td>ALK - crizotinib</td>
</tr>
</tbody>
</table>
### Biomarker-driven trials to show that a drug works specifically in a genomic segment

<table>
<thead>
<tr>
<th>context</th>
<th>design</th>
<th>Biomarker-negative cohorts</th>
<th>example</th>
</tr>
</thead>
<tbody>
<tr>
<td>The target is known, the drug has modest activity or the disease outcome is good/difficult to predict</td>
<td>Phase III trial performed in patients with the genomic alteration</td>
<td>No signal in phase II: NO</td>
<td>Her2 – trastuzumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Little activity in phase II: YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• One cohort with two coprimary endpoints: all comers + genomic (control the n)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Two cohorts (genomic + and – pts): Interim futility analysis</td>
<td>PIK3CA mutations - Alpelisib</td>
</tr>
</tbody>
</table>
Men or postmenopausal women, with HR+, HER2− ABC
- Recurrence/progression on/after prior AI
- Identified PIK3CA status (in archival or fresh tumor tissue)
- Measurable disease or ≥1 predominantly lytic bone lesion
- ECOG performance status ≤1 (N=572)

Primary endpoint
- PFS in PIK3CA-mutant cohort (locally assessed)

Secondary endpoints include:
- OS (PIK3CA-mutant cohort)
- PFS (PIK3CA-non-mutant cohort)
- PFS (PIK3CA mutation in ctDNA)
- OS (PIK3CA-non-mutant cohort)
- ORR/CBR
- Safety

Andre, NEJM, 2019
Biomarker-driven trials to show that a drug works specifically in a genomic segment

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

- PIK3CA mut
  - Standard of care +/- PI3K inh
- AKT1 mut
  - Standard of care +/- AKT inh
- ERBB2 mut
  - Standard of care +/- HER inh
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 decision-making genomic tools
  – Illustration
  – Current limitations (standard arm, heterogeneity, combination phase I)
Genomic segments and breast cancer

% of primary tumors

PIK3CA mut
ESR1 mut
FGFR1 ampli
CCND1 ampli
ERBB2 ampli
PTEN loss or mut
MDM2 ampli
AKT1 mut
BRCA1 mut
BRCA2 mut
Rb1 mut
EGFR ampli
FGFR2 ampli
ERBB2 mut
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 patient 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?

Institution-based multiple genes screening using NGS

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

- **PIK3CA mut**
  - Standard of care +/- PI3K inh

- **AKT1 mut**
  - Standard of care +/- AKT inh

- **FGFR1 amp**
  - Standard of care +/- FGFR inh
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 decision-making genomic tools
  – Illustration
  – Current limitations (standard arm, heterogeneity, combination phase I)
Challenge in drug development for RARE genomic segments: ACCRUAL

Accrual is the challenge of stratified medicine in mBC

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

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

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

AKT  PTEN  PIK3CA
FGFR1  ERBB2  ESR1  BRCA1
BRCA2
Cluster several genomic alterations into pathways: PARP inh (rucaparib) in HR-deficient mBC

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

Screening phase: Run Throughout the US- 500+ sites

**MASTER PROTOCOL**

- **Common Broad Platform CLIA Biomarker Profiling***

  - **PI3K**
    - M: *PIK3CA* mut
  - **CDK4/6**
    - M: *CCND1*, *CCND2*, *CCND3*, *cdk4* ampl,mut
  - **FGFR**
    - M: *FGFR* ampl, mut, fusion
  - **HGF**
    - M: c-Met Expr

- **Non-match**
  - CT*
  - Anti–PD–L1: MEDI4736

- **GDC–0032**
- **PD–0332991**
- **AZD4547+CT**
- **AMG102+E**

Endpoint PFS

Therapeutic trials: do the drugs work in specific genomic segments?
Register drugs based on single arm phase II trials

Drug Development and Implementation in Orphan Molecular Entities
- Rare genomic alterations with unmet medical need
- Single-group practice-changing trial
- After regulatory approval

Larotrectinib in Cancers with NTRK Translocation
- NTRK fusions in <1% of cancers
- Oncogenic
- No treatment available
- Objective response rate, 80%
- 71% of responses ongoing at 1 yr
- After regulatory approval?

Milestones
- Decision to start a single-group registration trial
- Interpretation of the data
- Implementation

Tools Being Developed
- Historical controls: database to assess natural history of orphan molecular segments (e.g., GENIE)
- Preclinical models
- Magnitude of Clinical Benefit Scale for single-group studies (ESMO)
- Nationwide access to multi-gene panels (e.g., France Génomique 2025)
- Drug positioning in the existing landscape: need for prognostic biomarkers in metastatic cancers
- Postapproval trials: objectives, design

Pending Issues
- How to define an orphan molecular entity in oncology? Incidence (Orphan Drug Act?), relation of genotype and phenotype, transtumor relevance
- Statistical tools to claim transtumor efficacy
- Definition of the companion diagnosis in the context of multi-gene sequencing
- New pathways of care in which few centers deliver therapy to patients with an orphan molecular entity
- Efficacy threshold below which drugs developed in single-group trials are withdrawn from markets

Andre F, NEJM, 2018
Designing clinical research program to register drugs in genomic segments

Large scale multiple genes screening 5-20 genes

- **PIK3CA mut**
  - Standard of care +/- PI3K inh

- **AKT1 mut**
  - Standard of care +/- AKT inh

- **FGFR1 amp**
  - Standard of care +/- FGFR inh

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

• Testing drug in a population defined by a 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 decision-making genomic tools
  – Illustration
  – Current limitations (standard arm, heterogeneity, combination phase I)
Designing clinical research program to register drugs in genomic segments

Large scale multiple genes screening 5-20 genes

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

- PIK3CA mut
  - Standard of care +/-PI3K inh

- AKT1 mut
  - Standard of care +/- AKT inh

- FGFR1 amp
  - Standard of care +/- FGFR inh
Designing clinical research program to register drugs in genomic segments

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

- **PIK3CA mut**
  - Standard of care +/- PI3K inh

- **AKT1 mut**
  - Standard of care +/- AKT inh

- **FGFR1 amp**
  - Standard of care +/- FGFR inh

Large scale multiple genes screening 5-20 genes

Large scale multiple genes screening additional 200 cancer-related genes

n-of-one trials:
- Treatment of unique (or very Rare) alterations
- Understand biology
- Drug mechanisms of action
Clinical trial designs utilizing molecular profiling.

Basket or bucket trials
- Single drug targeting a single mutation
- Variety of tumors carrying genetic aberration X

Umbrella trials
- Multiple drugs targeting multiple mutations
- Variety of tumors carrying a variety of genetic aberrations X, Y, & Z
  - Randomized or nonrandomized
  - Rules-based treatment assignment or per patient based on review of individual profile data

Exceptional responder trials
- Any cancer type and drug where a patient had an unusually robust clinical benefit

Same tumor type
- Drug A
- Drug B
- Drug C

Variety of tumor types
- Drug A
- Drug B
- Drug C
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
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

• Trials testing the genomic tool
  – Illustration
  – Current limitations (standard arm, heterogeneity, combination phase I)
Trials evaluating the medical utility of the genomic test (or decision-making tool)

![Diagram showing random assignment to control or guided arms with ORR results.]

**ORR**

- Control: 39.3%
- Guided: 51.2%
**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

NGS
Array CGH: 51 genomic alterations

mBC
Her2-ve

Genomic alteration

Therapeutic phase

Eight targeted therapies decided according to bioinformatic algorithm (including PIK3CA and FGFR1)

AZD2014
AZD4547
AD8931
Selumetinib
vandetanib
AZD45363
casodex
olaparib

Standard of care: Maintenance chemotherapy

No alteration: follow-up

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

• Trials testing the genomic tool
  – Illustration
  – Current limitations
Pitfall I: standard of care should include same drugs given randomly

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

NGS
Array CGH: 51 genomic alterations

Therapeutic phase

Eight targeted therapies decided according to bioinformatic algorithm (should exclude PIK3CA and BRCA)

Eight targeted therapies given independantly to bioinformatic algorithm (or given according to a previous Generation of algo)

mBC
Her2-negative

Genomic alteration

No alteration: follow-up

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

NGS Array CGH: 51 genomic alterations

mBC Her2-negative

Genomic alteration

No alteration: follow-up

X combination targeted therapies decided according to bioinformatic algorithm

Eight targeted therapies given independantly to bioinformatic algorithm (or given According to a previous Generation of algo)

Therapeutic phase

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
FAQ related to trials

• Metas vs primary?

• How to prioritize when multiple?

• How to take into account heterogeneity?