ARRAY CGH AND DNA SEQUENCING TO PERSONALIZE THERAPY FOR METASTATIC BREAST CANCER: A PROSPECTIVE NATIONAL TRIAL (UNICANCER SAFIR-01)

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Breast cancer disease includes a large number of RARE genomic segments. Treatment should include specific agent for each segment.

Personalized Medicine: To identify and target the right molecular pathway for each patient

Targeted therapy according to the genomic profile

Biopsy metastases

Whole genome profiling

Identification of the Genomic Alteration
Pathway to Personalized Medicine

Does the approach improve outcome?

Targeted therapy according to the genomic profile

Biopsy metastases

Whole genome profiling

Which technology?

Which algorithm for target identification?

Identification of the Genomic Alteration

Does the approach improve outcome?

Targeted therapy according to the genomic profile

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Which technology?

Which algorithm for target identification?

Identification of the Genomic Alteration
Aim of clinical research testing high throughput genomic tests

- **Health Care Delivery:** To substitute multiple tests by a SINGLE multiplex genome analysis (all-in-one assay)

- **Drug development / stratified medicine:** To speed-up drug development by enriching phase I/II trials with biomarker-defined patients

- **Personalized medicine:** To evaluate whether personalized medicine through whole genome analyses improves patients outcome
SAFIR program and SAFIR01 Trial Design

Pilot study
Pre-SAFIR (n=108)

SAFIR01
Metastatic breast cancer*
Biopsy of metastatic sites
Frozen sample
No PD under treatment
N=400

SAFIR02:
Randomized trial comparing treatment based to whole genome approach to same treatment no driven by biology

Target identification

PD

targeted therapy according to the alteration

Whole genome array CGH (copy number) hot spot mutations (PIK3CA/AKT)

*after 1st amendment less than 3 lines chemotherapy and bone lesions alone excluded

Metastatic breast cancer*
Biopsy of metastatic sites
Frozen sample
No PD under treatment
N=400
SAFIR01 study goals

Primary goal: To speed-up drug development through enrichment of trials in biomarker-defined patients (stratified medicine)

Primary endpoint: 30% of the patients treated according to a genomic alteration (n=120)

Secondary goals:
- To show feasibility of whole genome approach in a large population
- To suggest that whole genome approach improves outcome (personalized medicine)

Target accrual: 400 patients
SAFIR01: Clinical Operations

- Biopsy
- DNA extraction + quality control
- CGH array + Mutations PI3KCA/AKT
- Molecular MDT
- Identification of a potential Clinical Trial

18 Investigational centers
SAFIR01: Clinical Operations

- biopsy
- DNA/RNA extraction + quality control
- CGH array + Mutations $PI3KCA/AKT1$
- Molecular MDT
- Identification of a potential Clinical Trial

- 3 Agilent 4*180K
- 2 Affymetrix SNP6.0

- aCGH + Mutation $PIK3CA$ (exon 9 et 20) et $AKT1$
biopsy

DNA/RNA extraction + quality control

CGH array + Mutations PI3KCA/AKT

Molecular MDT

Identification of a potential Clinical Trial

Reference centers

Bioinformatician
biopsy

DNA/RNA extraction + quality control

CGH array + Mutations PI3KCA/AKT

Molecular MDT

Identification of a potential Clinical Trial

Is the genomic alteration targetable?

mutation/high level amplification located on gene encoding a protein targeted by a drug under development
SAFIR01 Accrual

High level of expectation

Accrual
scheduled
planned targeted therapies

423

120
Results and Interpretation

4 non BC
18 not-biopsied
105 tumor material not eligible
19 whole genome analysis non-interpretable

393 patients

251 whole genome analysis (64%)

423 patients signed

26 ongoing molecular screening

What are the main sources of failure?
Reasons for failure to provide genomic analysis

- 18 not biopsied
- 105 tumor material not eligible
- 19 whole genome analysis non-interpretable

96 patients

Low cellularity (<50%)

% of failure per organ

* excluded after the first amendment
Results and Interpretation

- 4 non BC
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393 patients

- 423 patients signed
- 26 ongoing molecular screening

251 whole genome analysis

- 69%

172 genomic alterations

- 76 patients low-frequency alteration
Targetable alterations that led to treatment proposition (excluding mutations)

- Mutations
- Copy number alterations
# Discrepancies ER / Her2

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Results and Interpretation

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172 genomic alterations

26 matched treatments

69%

76 patients low-frequency Genomic alteration

Ongoing: Most patients still not need investigational agent
Expected 80-100 in 3 years
Access to targeted therapy in line with Initial expectations and number of available slots
Matched treatments: Preliminary data

- Most of the patients did not present a PD after the genomic analysis and/or are still not eligible for targeted treatment
- 9% died

26 matched treatments

- 13 different targeted therapy regimen (single agent or combination)
- Evidence of antitumor activity in 8 patients (>30% shrinkage or metabolic response PETscan or SD≥4 months)
- Target: 80-100 according to current inclusion rates
- 4 additional patients treated with the matched targeted agent before the genomic analyses
- 4 under screening phase I
Matched treatments: tyrosine kinases
Matched treatments: intracellular kinases

+ Anti Androgen, MDM2 activator
First large prospective study to evaluate whole genome technologies for cancer care

- High enthusiasm for running genomic analyses in difficult-to-treat breast cancer = OPPORTUNITY
- Whole genome analyses can be equally delivered across hospitals
- They produce robust results and could allow proposing a « all genes-in-one » assay as a substitute for multiple tests
- They identify a high number of rare « targetable » genomic alterations
- Early signs of anti-tumor activity

This study suggests that it is time to bring personalized medicine to the field of cancer research
GAPS

- Decrease biopsy failure:
  - Bone biopsies: molecular tests difficult to perform
  - Low percentage of tumor cells in biopsies (Solution: NGS ??)

- Improve access to targeted agents outside trials

Next Steps

- Ongoing: NGS on SAFIR01 samples (n=300), implementation for clinical decision in the network

- SAFIR02: randomised study based on molecular alterations (to start within 1 year)
Personalized medicine: limiting factors for moving forward

- Number of patients treated during the first year is in line with initial expectations, but there is a gap between a dramatic accrual in SAFIR01 trial and the number of patients treated.

- Number of slots available in early trial clinical Units will allow speeding-up drug development, but will NOT allow fast large trials testing personalized medicine.

- This finding suggests that drug access will be THE limiting factor to move forward and evaluate the concept of personalized medicine.

- There is a need to develop process for free drug access for academic research on personalized medicine.
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