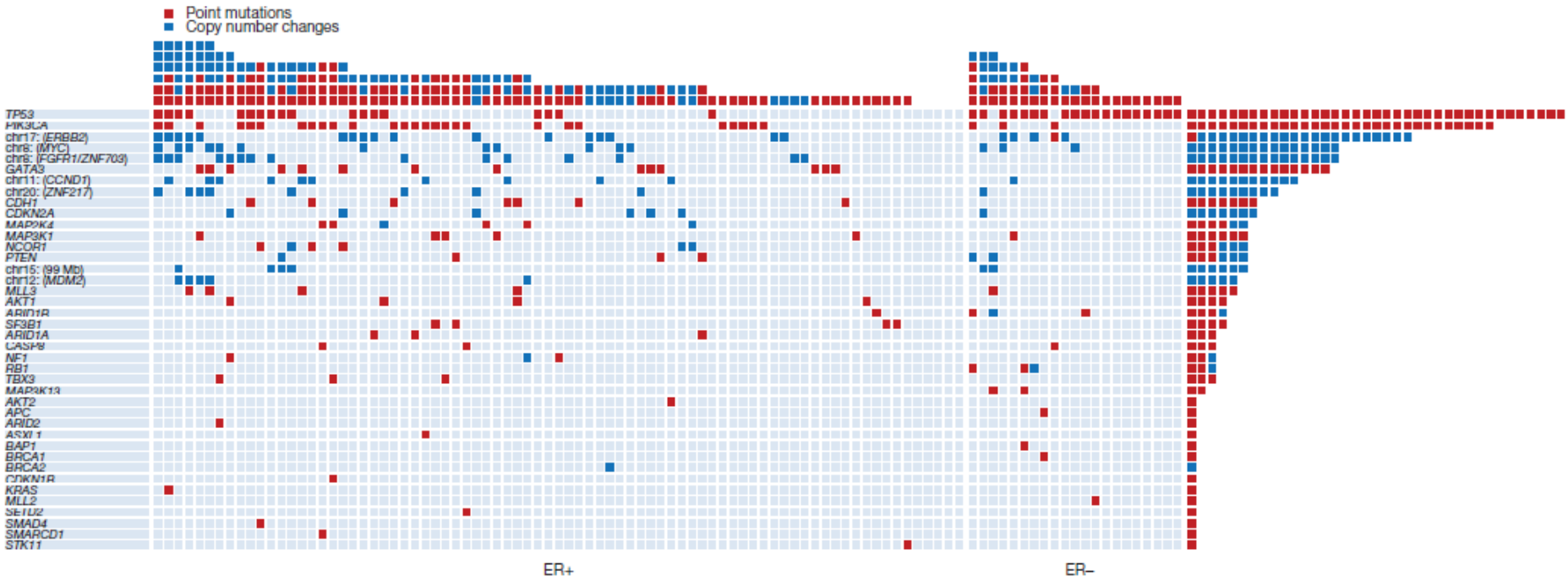
ARRAY CGH AND DNA SEQUENCING TO PERSONALIZE THERAPY FOR METASTATIC BREAST CANCER: A PROSPECTIVE NATIONAL TRIAL (UNICANCER SAFIR-01)

F. ANDRÉ[1], T. BACHELOT[2], M. CAMPONE[3], M. ARNEDOS [1], F. COMMO[1], A. GONÇALVES[4], C. LEVY[5], J.-M. FERRERO[6], L. LACROIX[1], V. DIÉRAS[7], F. DALENC[8], D. GENTIEN[7], M. LACROIX TRIKI[8], Q. WANG[2], J. ADELAIDE[4], M. JIMENEZ[7], H. BONNEFOI[10]

ESMO 2012, Vienna 1st october 2012

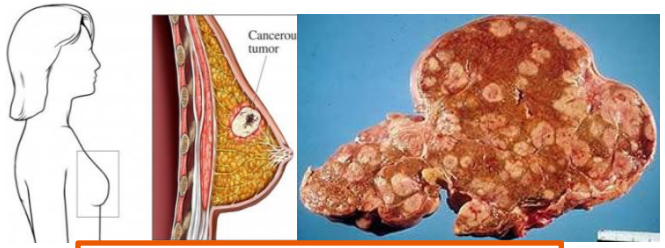
Genomic segmentation of breast cancer



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

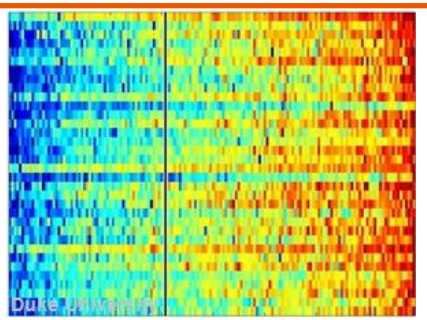
Stephens, Nature, 2012

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

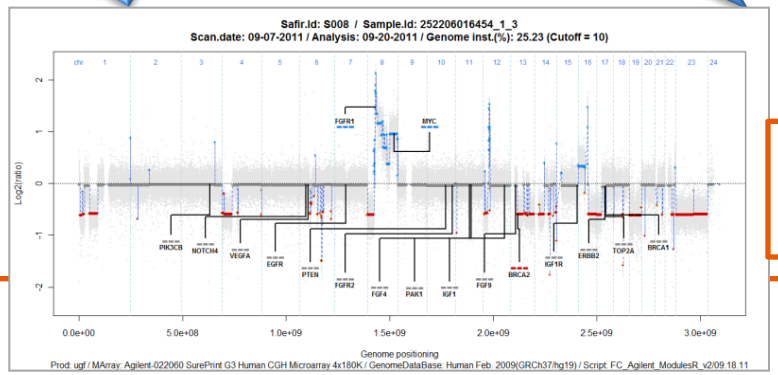


Biopsy metastases

Whole genome profiling



Identification of the Genomic Alteration

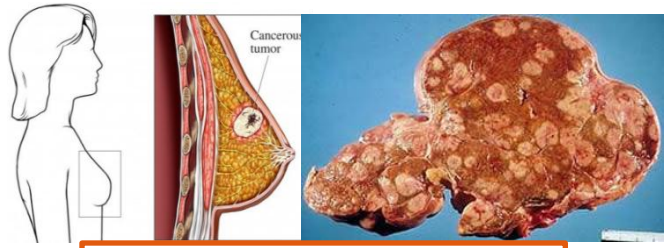


Targeted therapy according to the genomic profile

Pathway to Personalized Medicine

Does the approach improve outcome?

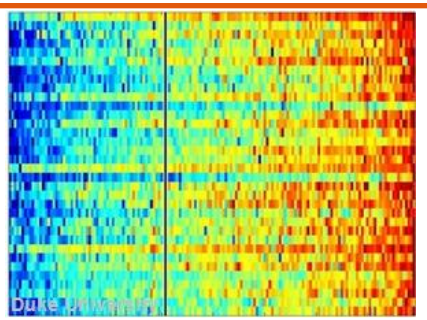
Targeted therapy according to the genomic profile



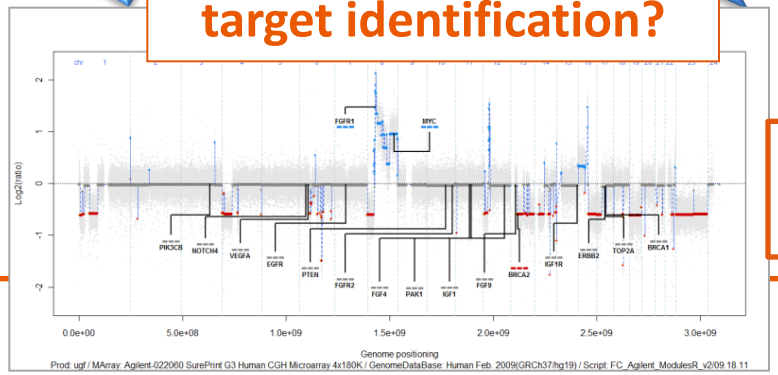
Biopsy metastases

Which technology?

Whole genome profiling



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

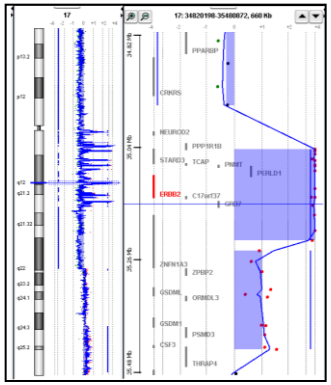
Pilot study
Pre-SAFIR (n=108)

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



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

PD

targeted therapy according to the alteration

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

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)*

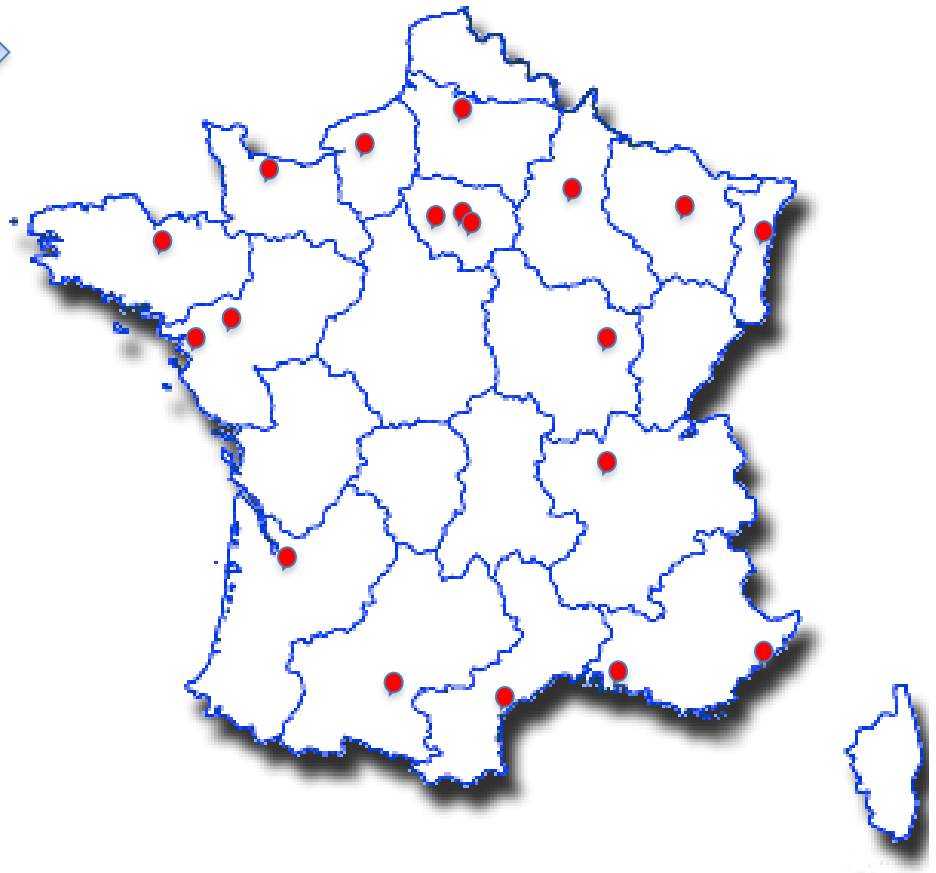
- **Target accrual: 400 patients**

SAFIR01: Clinical Operations

biopsy

DNA extraction + quality control

18 Investigational centers



CGH array + Mutations PI3KCA/AKT

Molecular MDT

Identification of a potential Clinical Trial

SAFIR01: Clinical Operations

biopsy

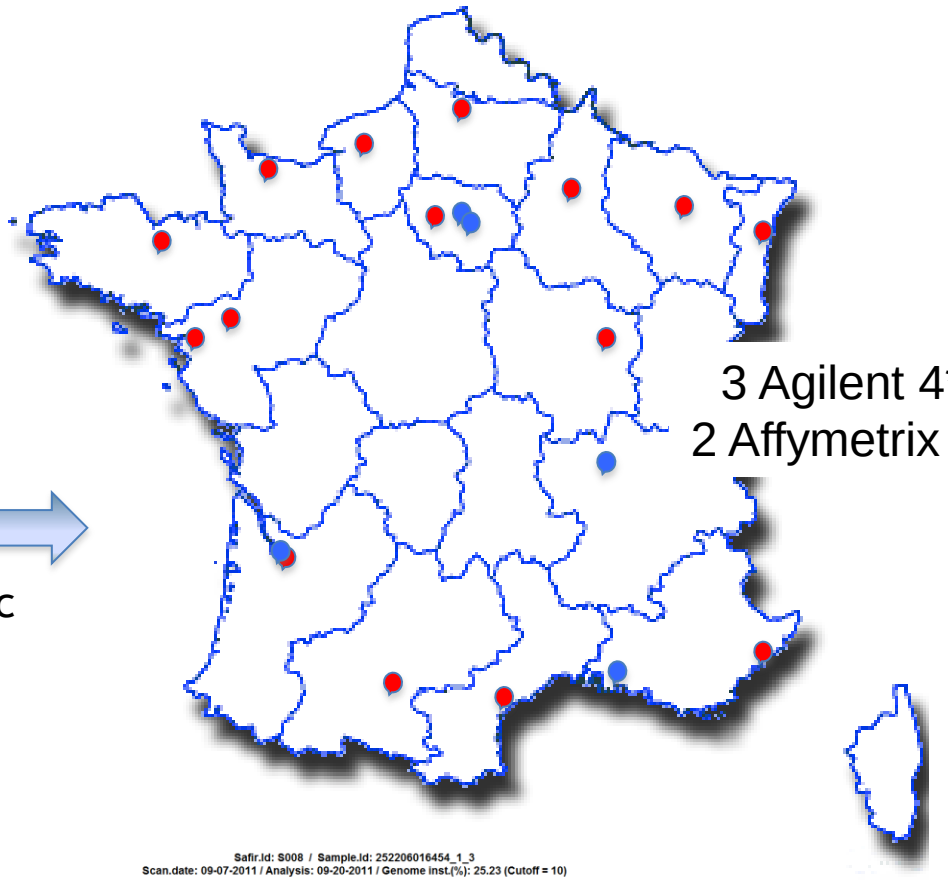
DNA/RNA extraction + quality control

CGH array + Mutations *PI3KCA/AKT1*

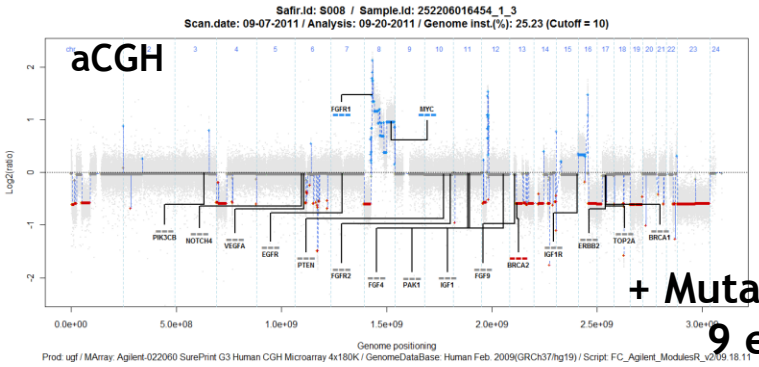
Molecular MDT

Identification of a potential Clinical Trial

5 genomic centers



3 Agilent 4*180K
2 Affymetrix SNP6.0



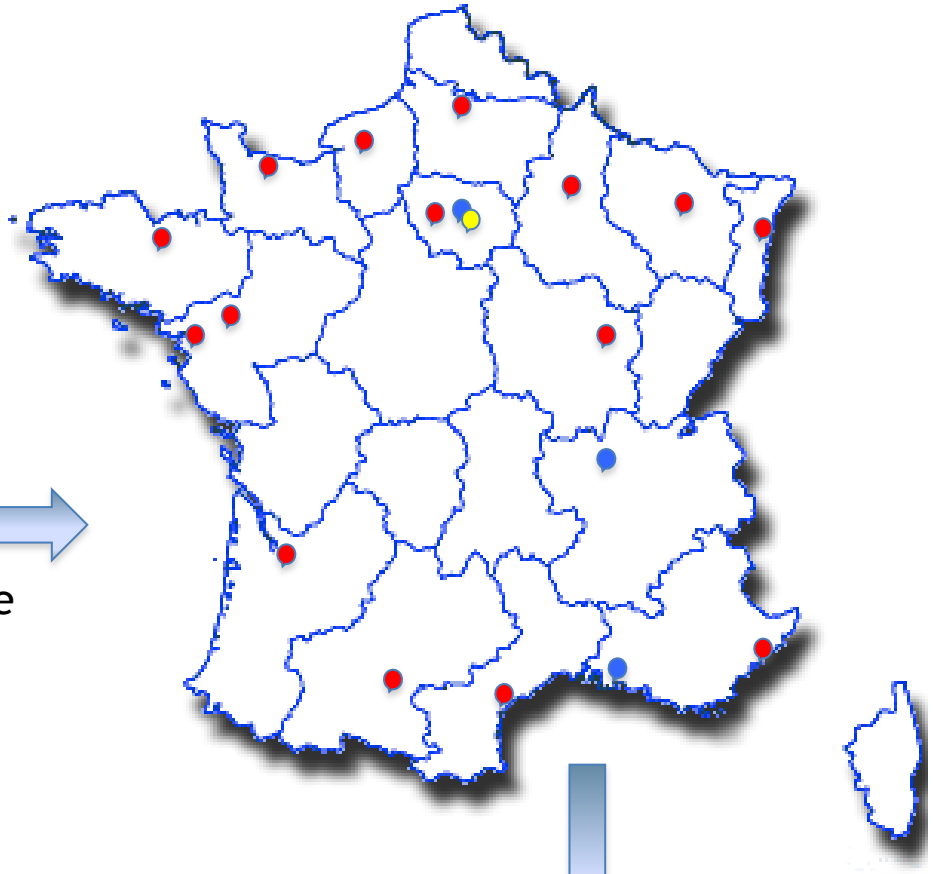
+ Mutation *PIK3CA* (exon 9 et 20) et *AKT1*

biopsy

DNA/RNA extraction + quality control

CGH array + Mutations PI3KCA/AKT

Reference centers



Bioinformatician

Molecular MDT

Identification of a potential Clinical Trial

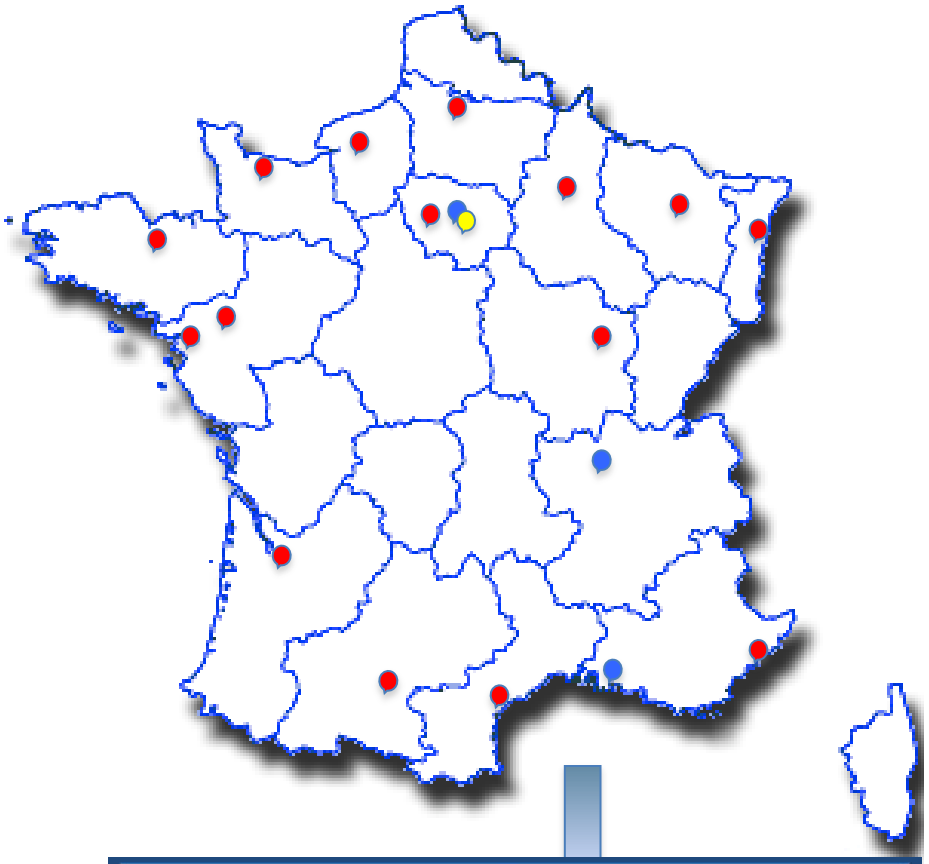
biopsy

DNA/RNA extraction + quality control

CGH array + Mutations PI3KCA/AKT

Molecular MDT

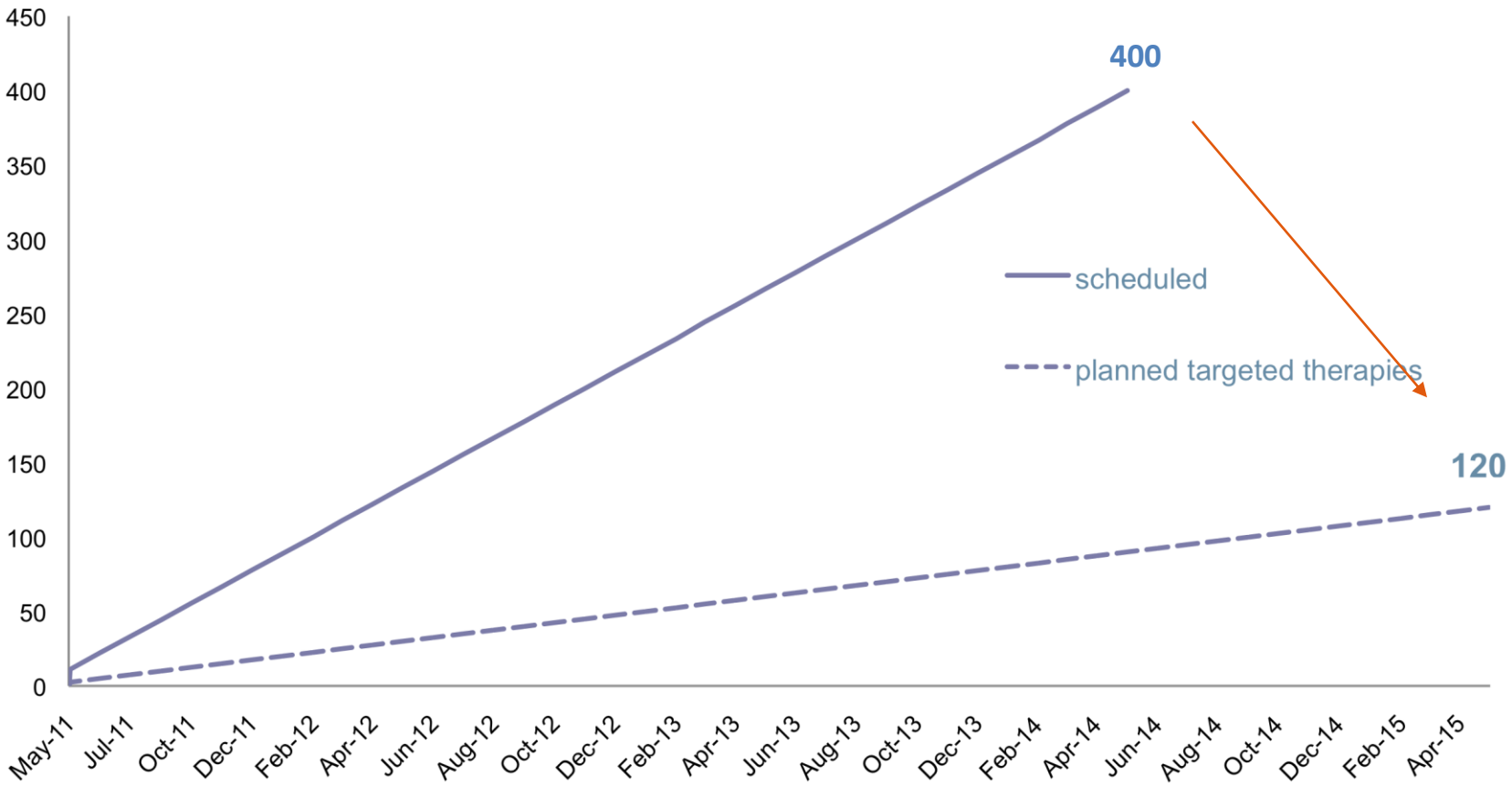
Identification of a potential Clinical Trial



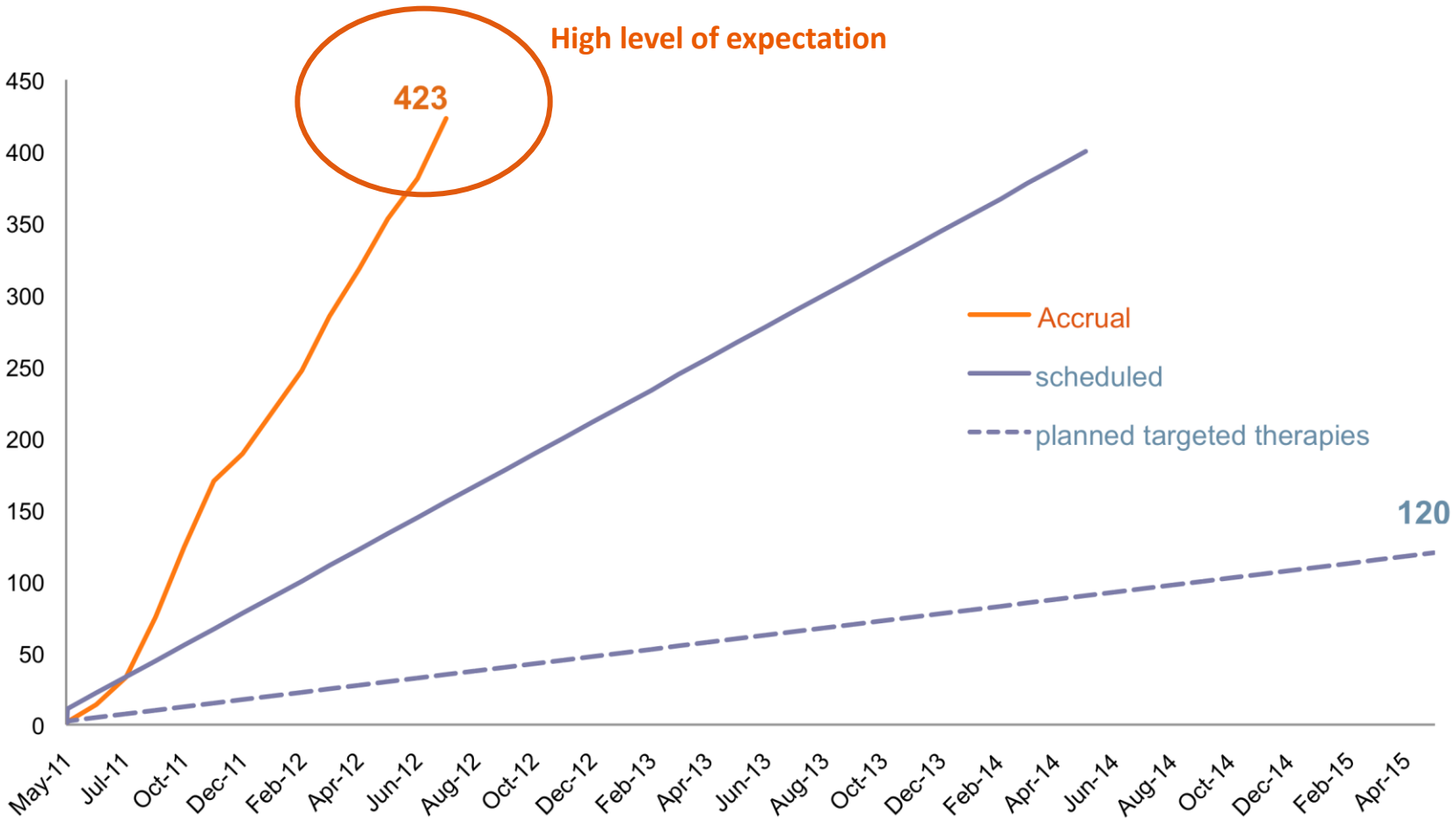
Is the genomic alteration targetable ?

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

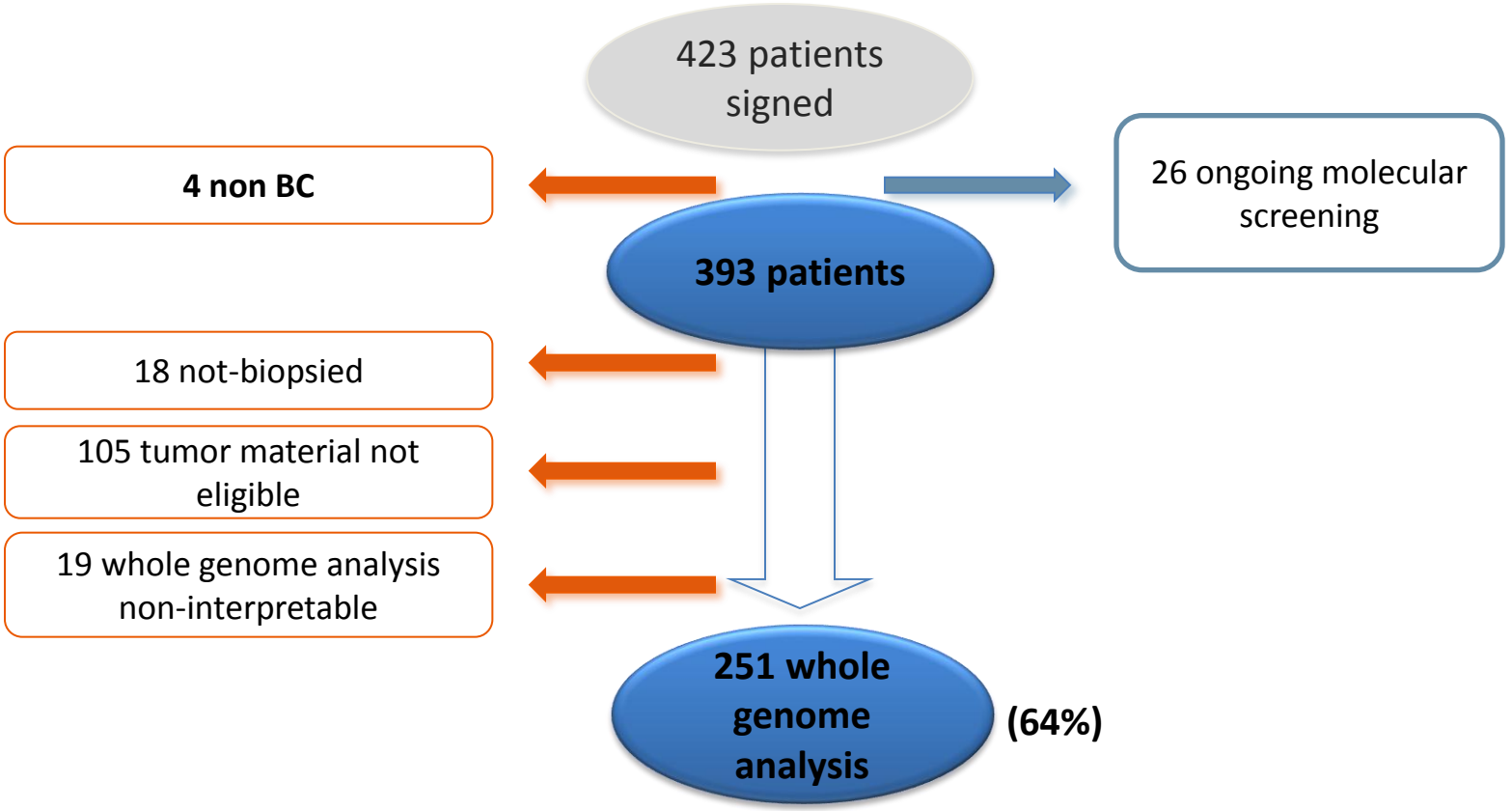
SAFIR01 Planned Accrual



SAFIR01 Accrual



Results and Interpretation



What are the main sources of failure ?

Reasons for failure to provide genomic analysis

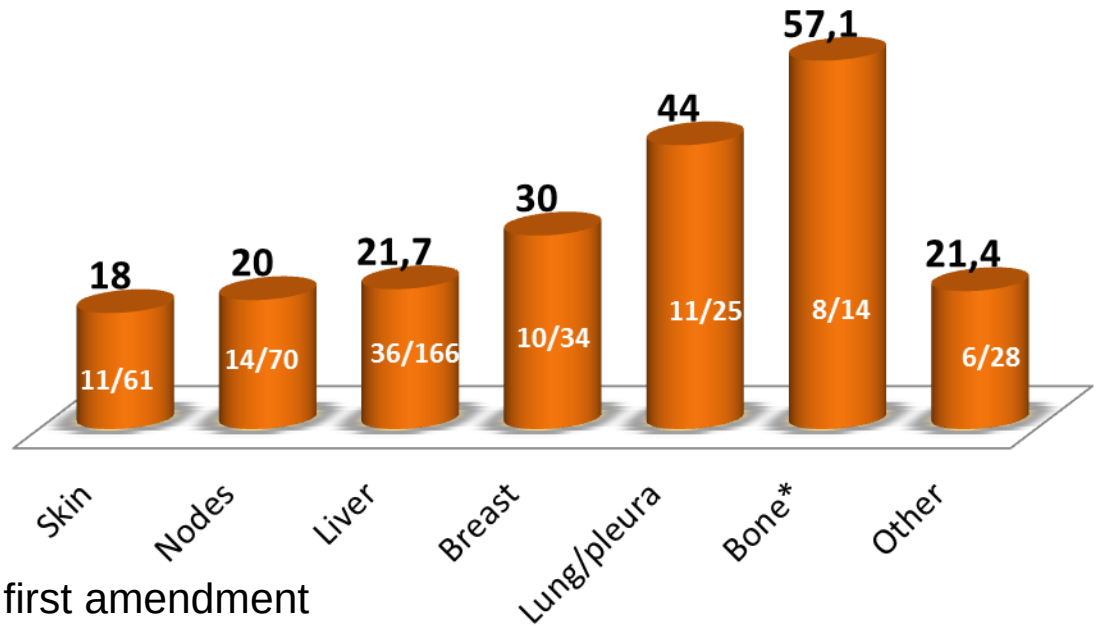
18 not-biopsied

105 tumor material not eligible

19 whole genome analysis non-interpretable

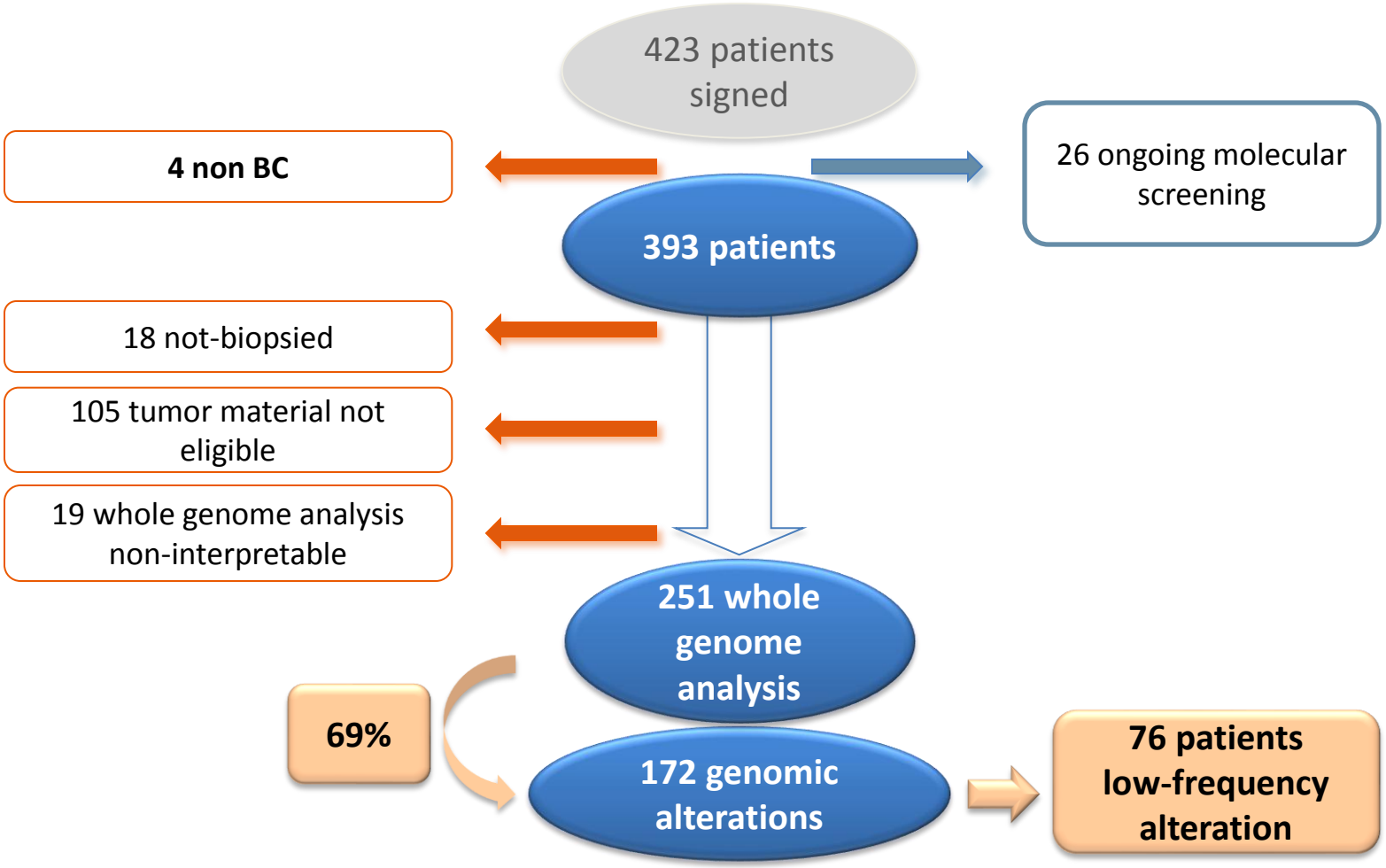
96 patients
Low cellularity (<50%)

% of failure per organ

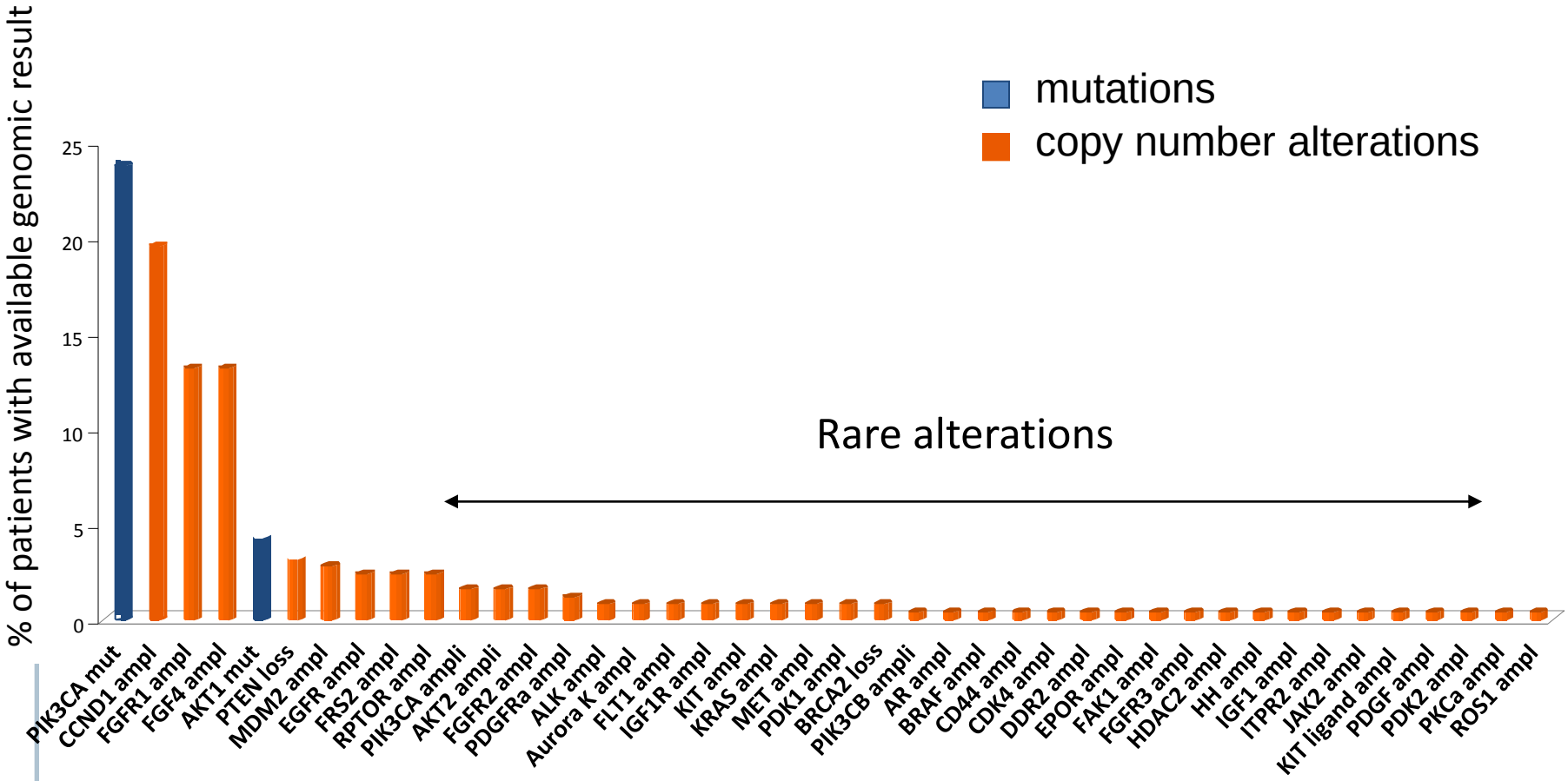


* excluded after the first amendment

Results and Interpretation



Targetable alterations that led to treatment proposition (excluding mutations)



Discrepancies ER / Her2

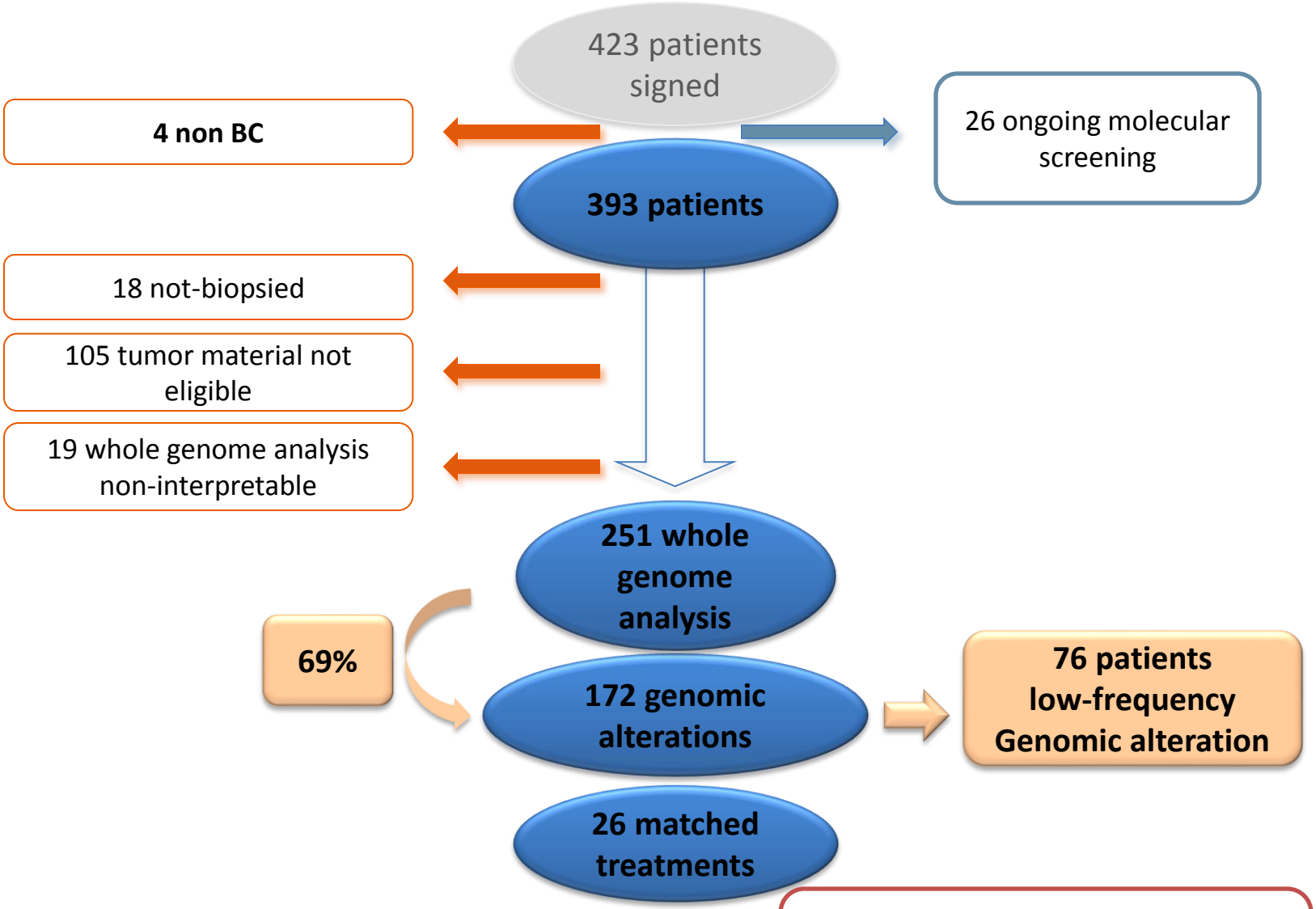
ER

		Metastasis		
		ER+	**ER-**	
Primary	**ER+**	111	**29**	140
	ER-	**11**	57	68
		122	86	**208**

HER2

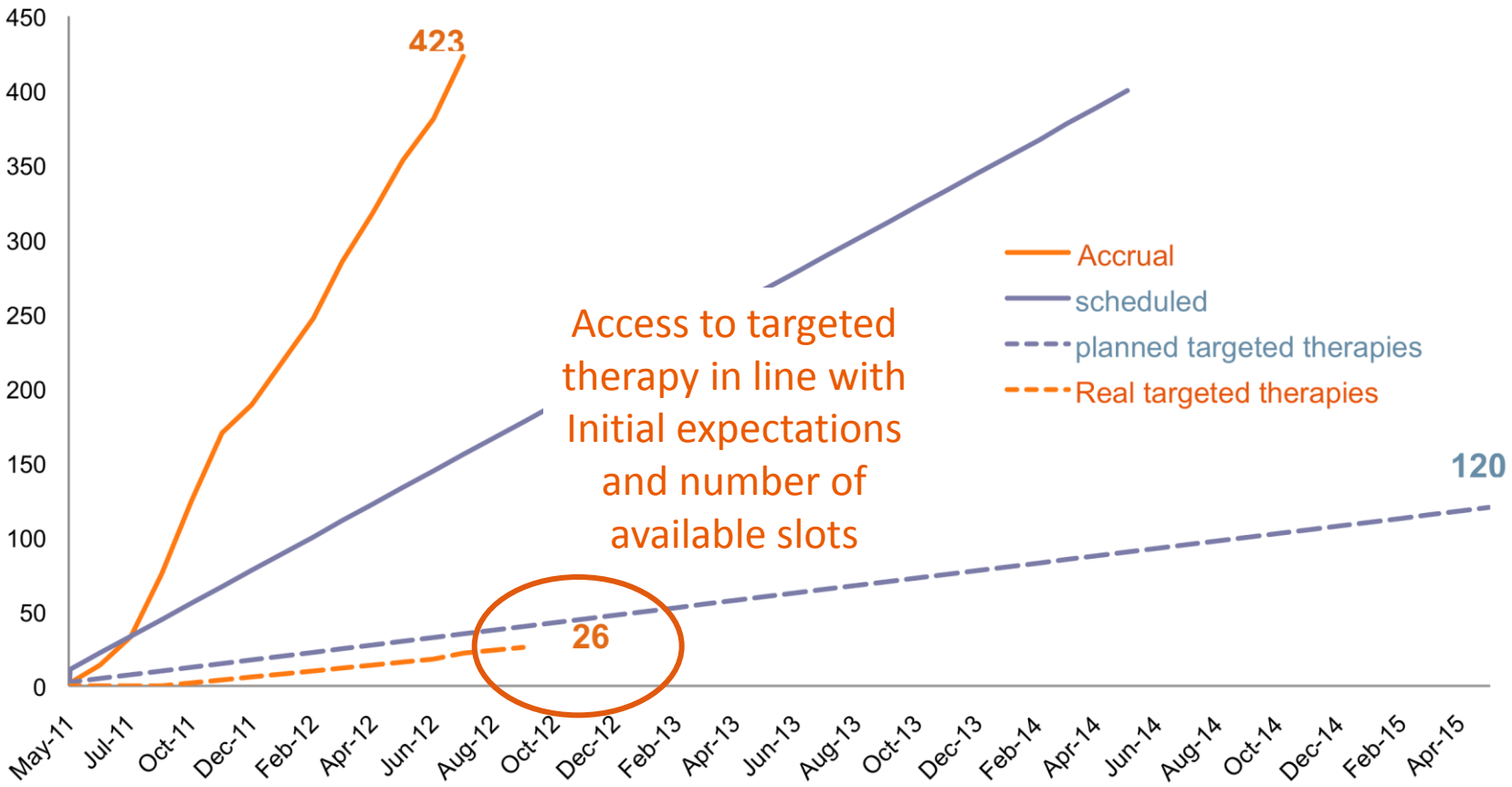
		Metastasis		
		HER2+	**HER2-**	
Primary	**HER2+**	29	**9**	38
	HER2-	**6**	128	134
		35	137	**172**

Results and Interpretation



Ongoing: Most patients **still not need investigational agent**
Expected 80-100 in 3 years

SAFIR01 Accrual



Matched treatments: Preliminary data

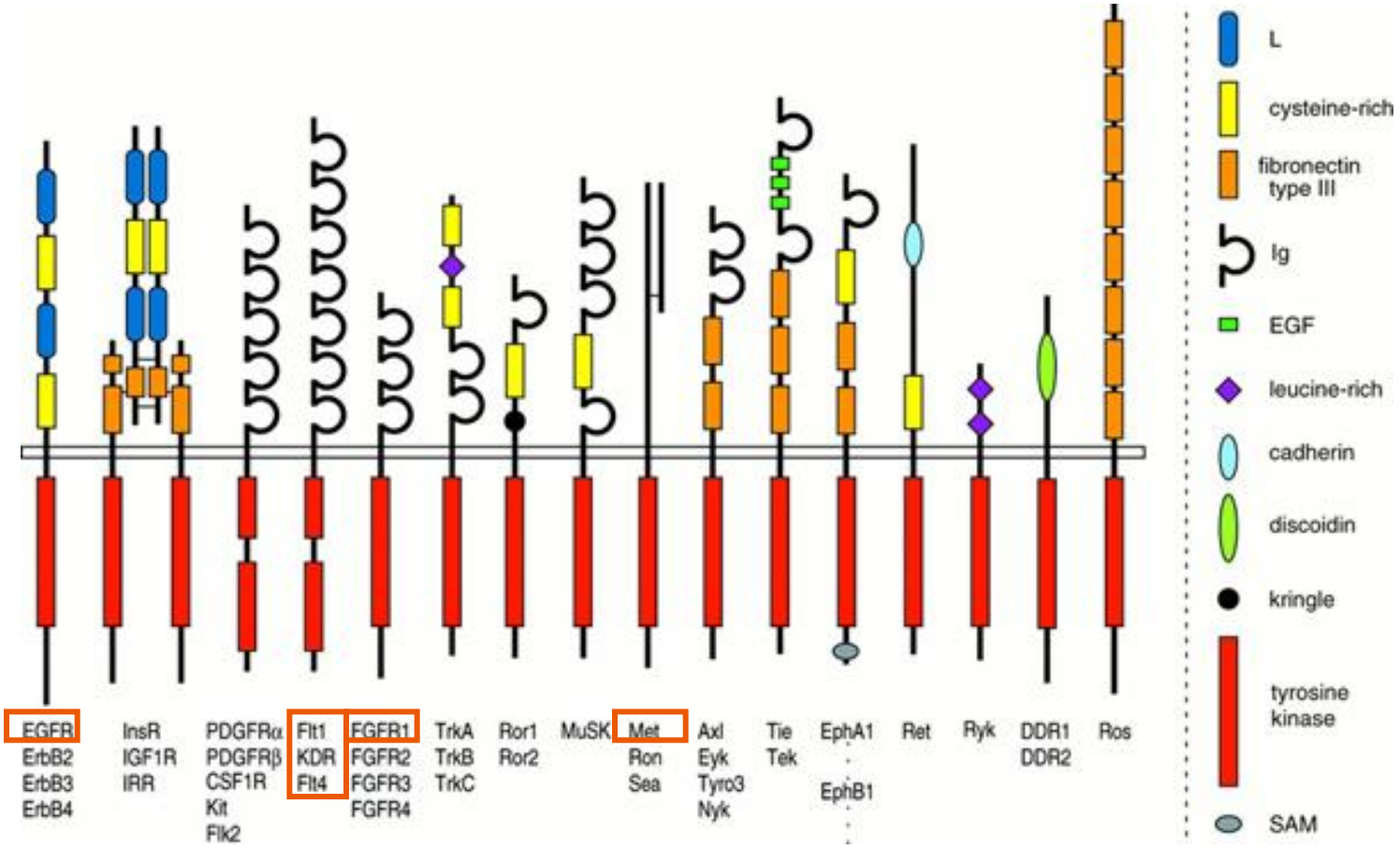
- Most of the patients did not present a PD after the genomic analysis and/or are still not eligible for targeted treatment
- 9% died

SAFIR01

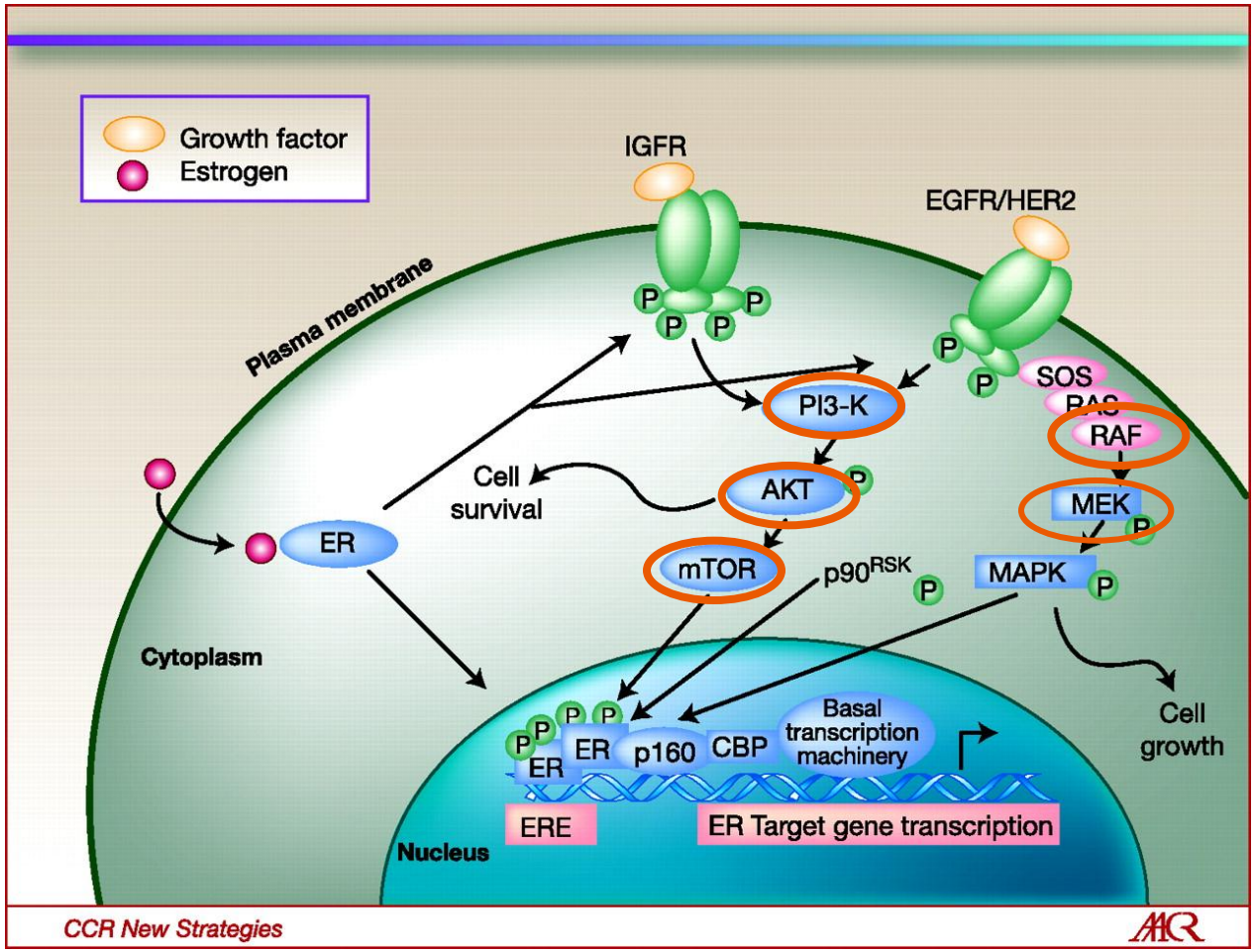
26 matched treatments

- 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 enthousiasm 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

Perspectives

GAPS

- **Decrease biopsy failure:**
  - Bone biopsies: molecular tests difficults 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**

Acknowledgements

- **Patients and families**
- **All participating teams**
  - Investigational centers : physicians, radiologists, pathologists
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  - Phase I centers
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- **Steering committee members**
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- **Breast Cancer Research Foundation**
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