Possible solutions to overcome current limitations of precision medicine in the breast cancer field

Fabrice ANDRE

Gustave Roussy

Villejuif, France

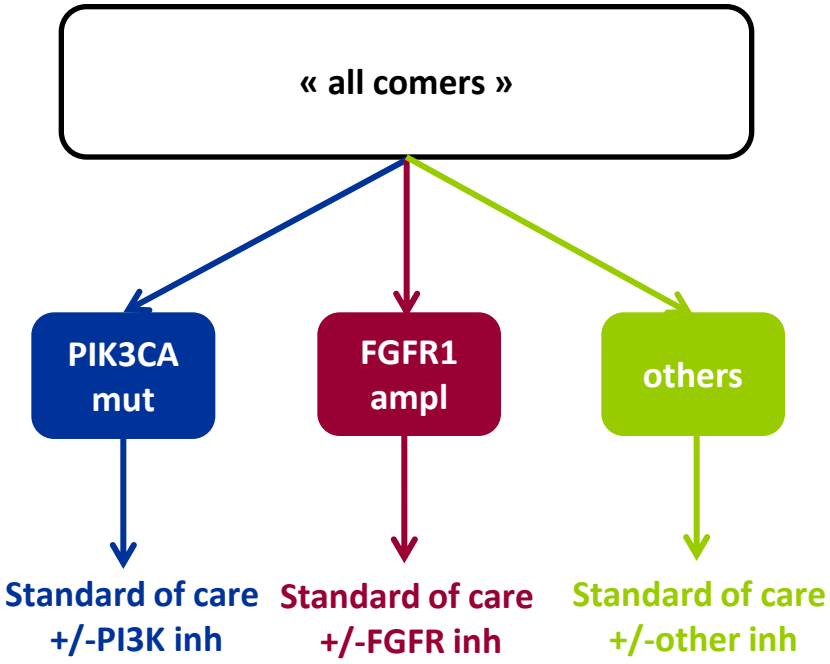
Outline

- **Current limitations of precision Medicine: illustration based on two trials**

- Solutions to speed-up development of precision medicine

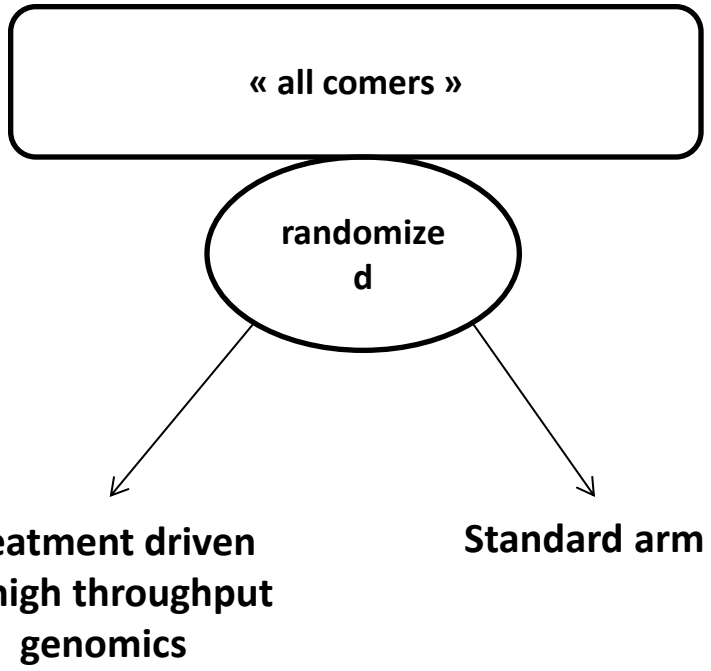
Stratified versus personalised medicine

Drugs are evaluated in genomic segments: Stratified Medicine



Each genomic alteration defines a new rare entity

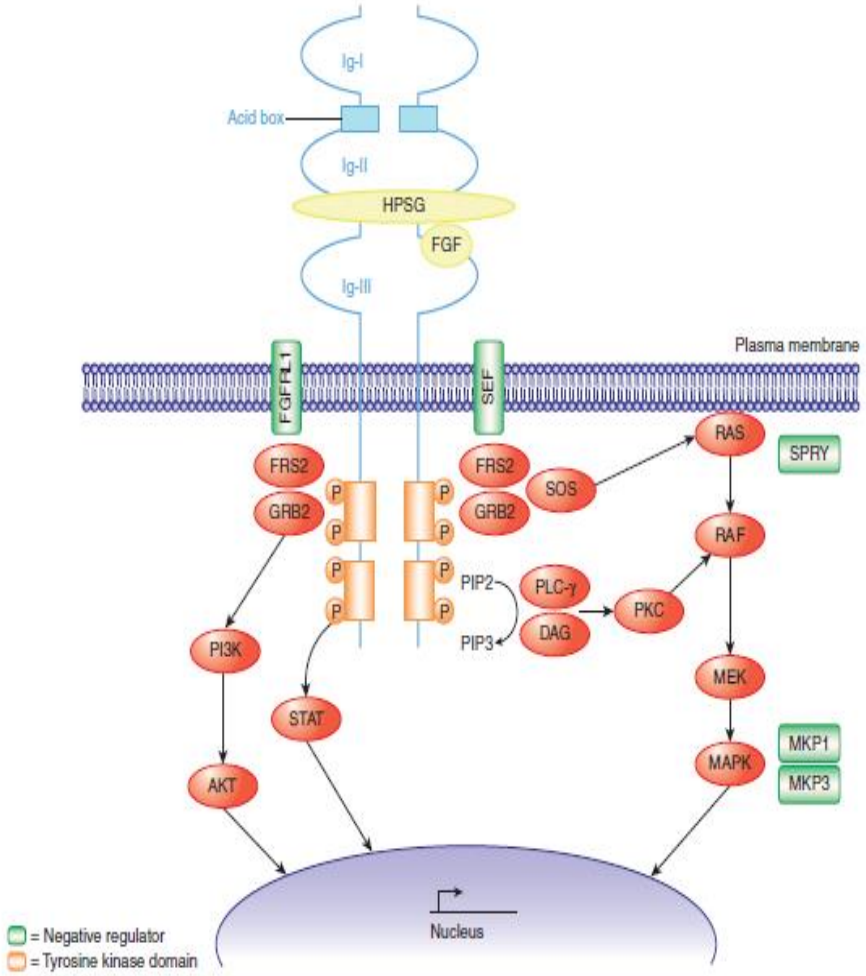
The method for treatment allocation is evaluated in the overall population



The benefit of using high throughput genomics is evaluated in all comers

Limitations in the field of stratified medicine: illustration with a trial

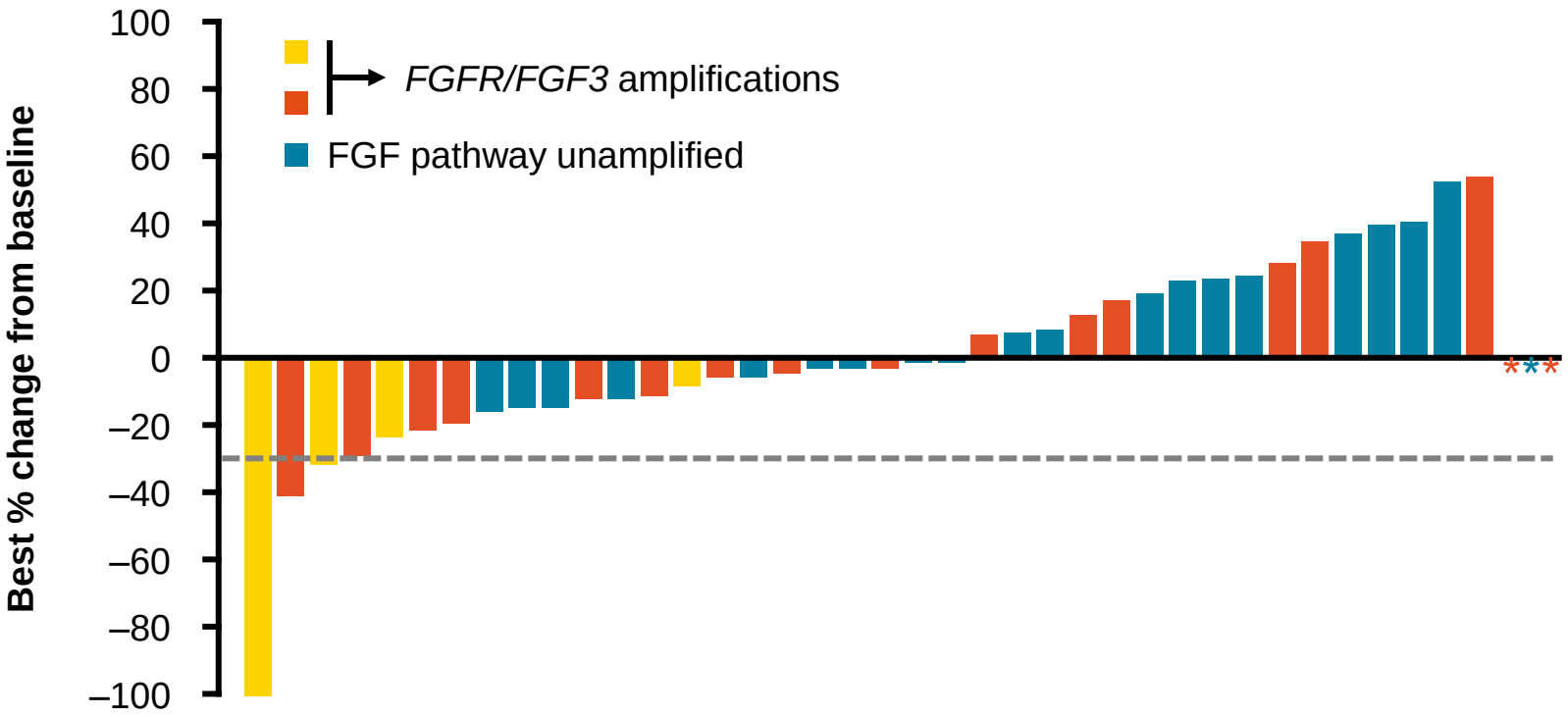
FGFR1 amplification and breast cancer



- Transmembrane tyrosine kinases
- MAPK activation
- *FGFR1* gene amplification: 10% breast cancer
- Resistance to endocrine therapy
- Less sensitivity to everolimus
- FGFR inhibition leads to antitumour effect in preclinical models
- Target is relevant and defines an unmet need

Dieci et al, Cancer Discov 2013

Efficacy of dovitinib (FGFR inhibitor) according to *FGFR1* amplifications



Single agent activity is modest

Andre et al, Clin Cancer Res 2013

Dovitinib is currently in clinical development and not available for patients outside clinical trials

screening and accrual in the dovitinib trial

Phase II trial that aimed at including 20 FGFR1-amplified mBC

Pre-screened for clinical trial and *FGFR* amplification

(N=269)

Inclusion *FGFR1*-amplification

(N=20)

Theoretical number of patients to screen:
for a phase III registration trial: 3 000

Screening and accrual is a major challenge to develop stratified medicine in BC (except for PIK3CA mutations)

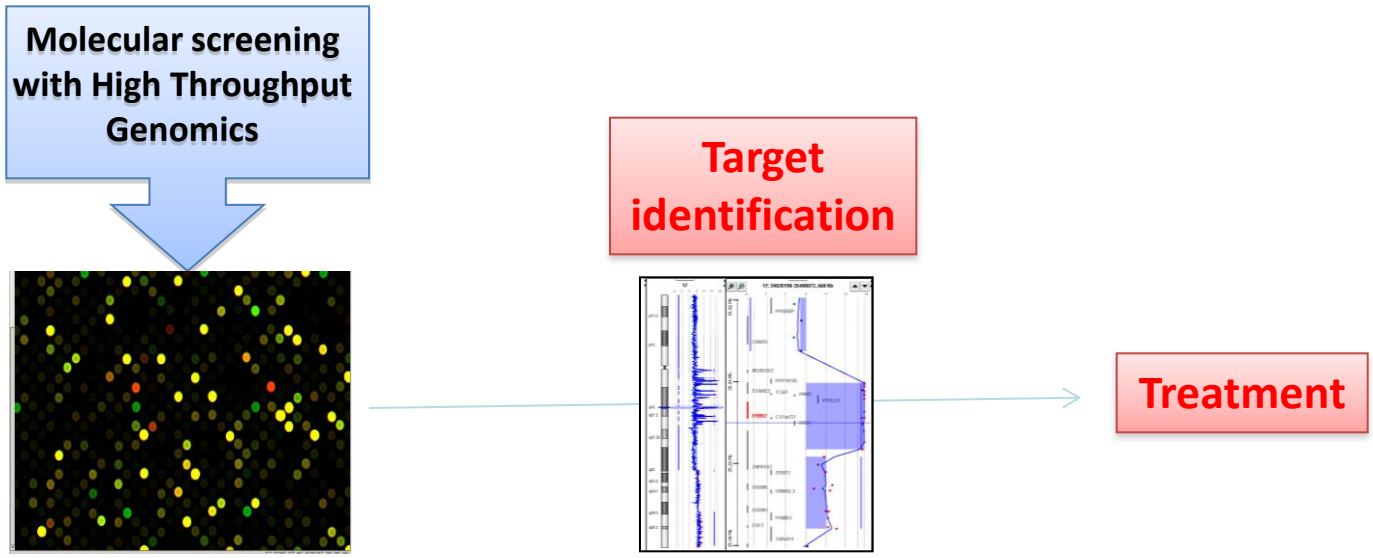
Andre F, Clin Cancer Res, 2013

Dovitinib is currently in clinical development and not available for patients outside clinical trials

Phase II dovitinib FGFR1-amplified BC: lessons

- **Each genomic segment (except PIK3CA mutations) is rare:**
  - **Need to scale-up the number of patients screened for a molecular alteration**
  - **Need to screen multiple genes to increase the likelihood of target identification for each patient**
- **Single agent presents modest activity:**
  - **Lack of tools to identify drivers at the individual level**
  - **Multiplicity of genomic alterations**

Personalized medicine programs



Andre, Delaloge, Soria, J Clin Oncol, 2011

SAFIR01 trial: results

Biopsy of breast cancer: 403 patients

Low % tumor cells (n=91)
No frozen material (n=8)
other (n=5)

DNA qualified for genomics: n=299

Decrease the Failure rate to provide genomic tests

CGH arrays only: 283 patients

Sanger sequencing alone: 297 patients

Targetable alteration in 195 patients

3% (!!)

Better access
To drugs

Treatment driven by genomics in 52 patients

+ 4 patients
ERBB2 amp
CGH array

Improve efficacy:
Detect more relevant targets
Better define target
Highly bioactive drugs combinations

Treatment efficacy (SD>16w / OR): 13 patients

Andre F, Lancet Oncol, 2014

Current limitation of precision medicine in breast cancer… and temptative explanations / solutions

limitations
completion of trials testing drugs in genomic segments is challenging
significant rate of "failure to perform" the genomic test
number of patients with an identified oncogenic driver is low
response rate and benefit are low
No evidence that personalized medicine improves outcome in breast cancer

Outline

- Current limitations of precision Medicine: illustration based on two trials

- **Solutions to speed-up development of precision medicine**

Current limitation of precision medicine in breast cancer… and temptative explanations / solutions

limitations	possible interpretation	possible solutions
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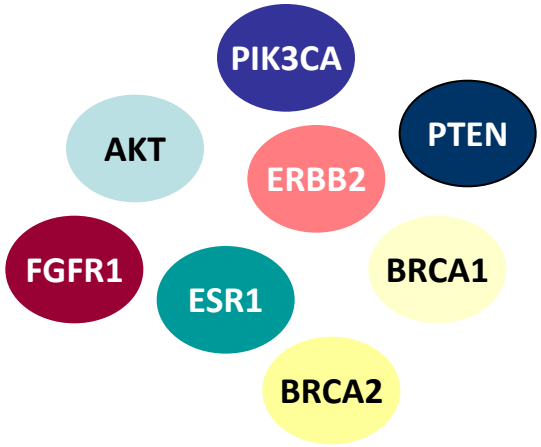
How to overcome the accrual challenges of stratified medicine ?



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

- **Cluster several genomic alterations into single pathway (ex: BRCA1 and 2, FGFR1 and 2…)**
- **Scale-up capacities of molecular screening (use of circulating DNA, nationwide screening, International groups…)**
- **Perform part of the drug development in the preoperative setting in early BC**
- **Approve drugs based on phase II in genomic segments associated with very poor outcome**

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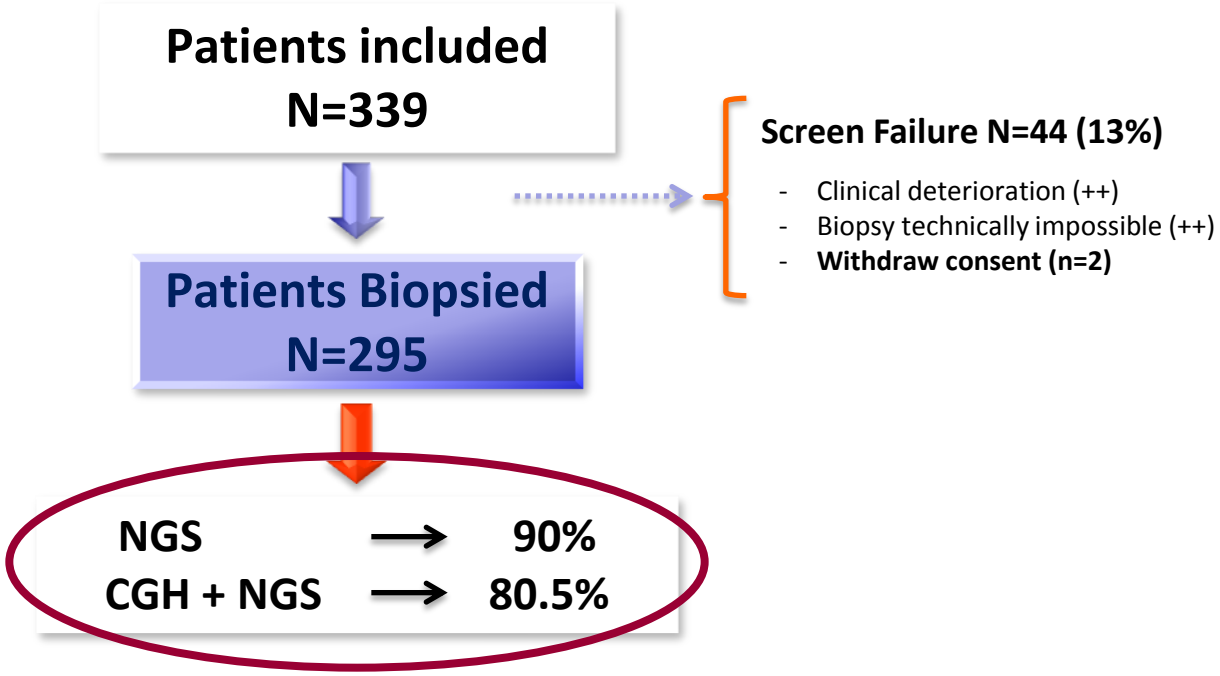
Implement NGS to decrease the failure rate and increase the number of detected targetable genomic alterations

Does NGS decrease the failure rates ?



MOSCATO trial, update sept 2013

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How to improve our capacity to identify drivers in individual with breast cancer ?

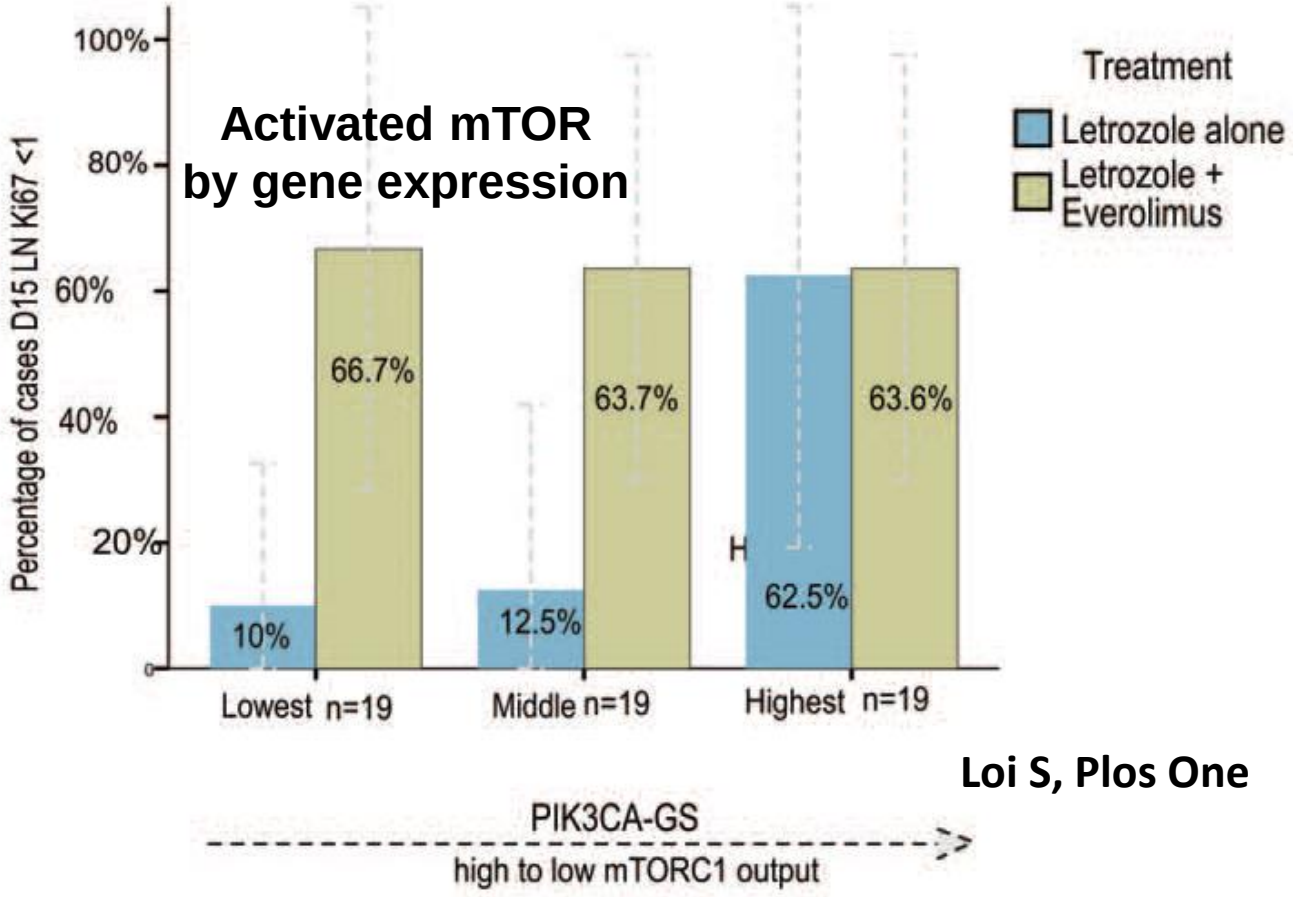
How to better identify drivers in each single patient ?

- **Develop a catalogue of cancer genes according to their likelihood of being drivers (Lawrence, Nature, 2014)**

- **Develop level of evidence for each target**

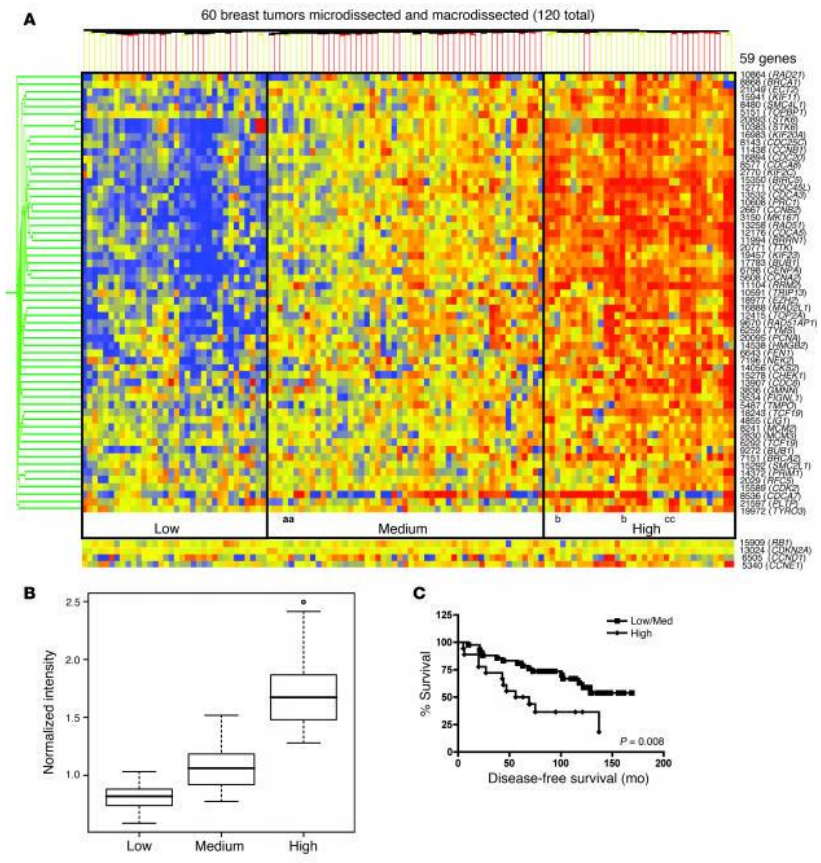
- **Understand the rules that define a driver within a tumor:**
  - **Is the alteration clonally dominant ? (high % cancer cells, all tumor sites)**
  - **Is the pathway activated ?**

Assess pathway activation and dependancy using Protein- or RNA-based assays



Gene expression could be useful to identify drivers of cancer progression and pathway dependancy

CDK4 / Rb pathway activation assessed by gene expression array



Bosco, J Clin Invest, 2007

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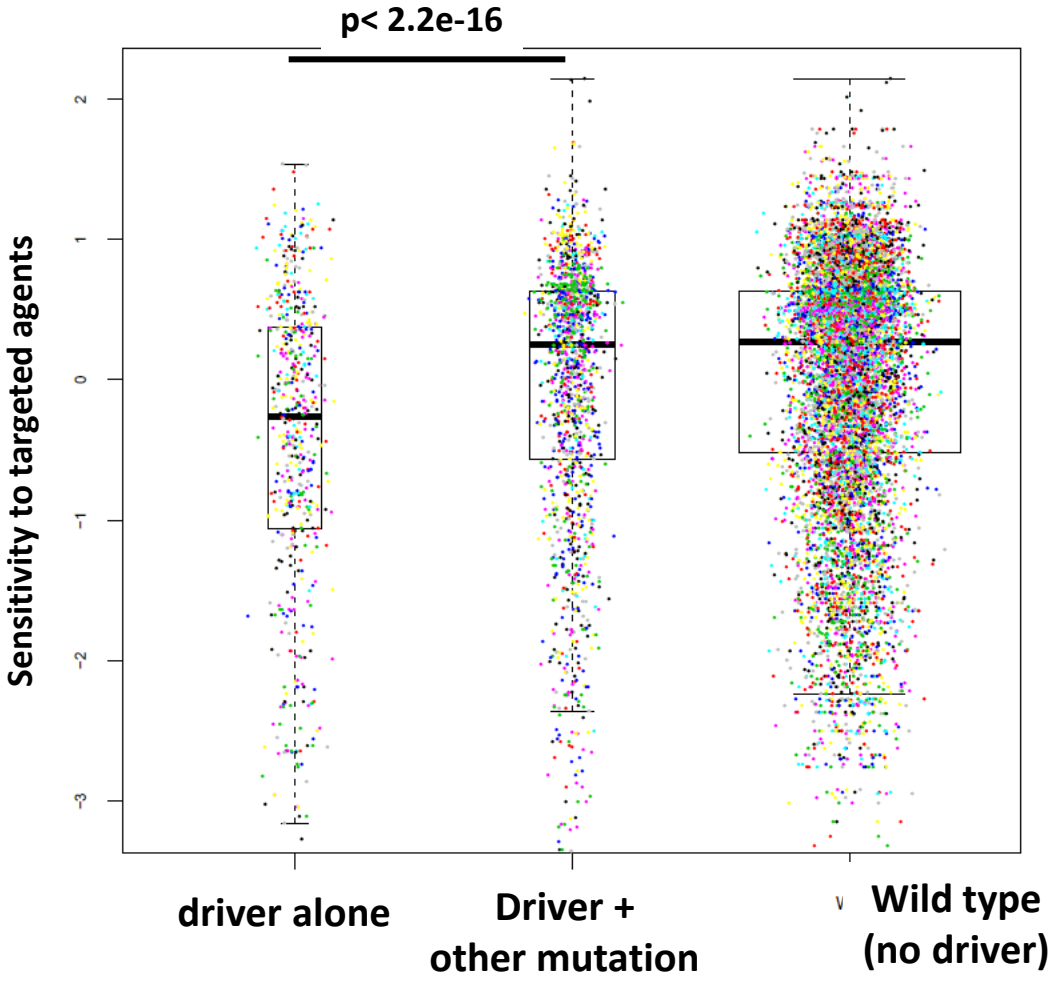
What are the implications of co-existing mutations ?



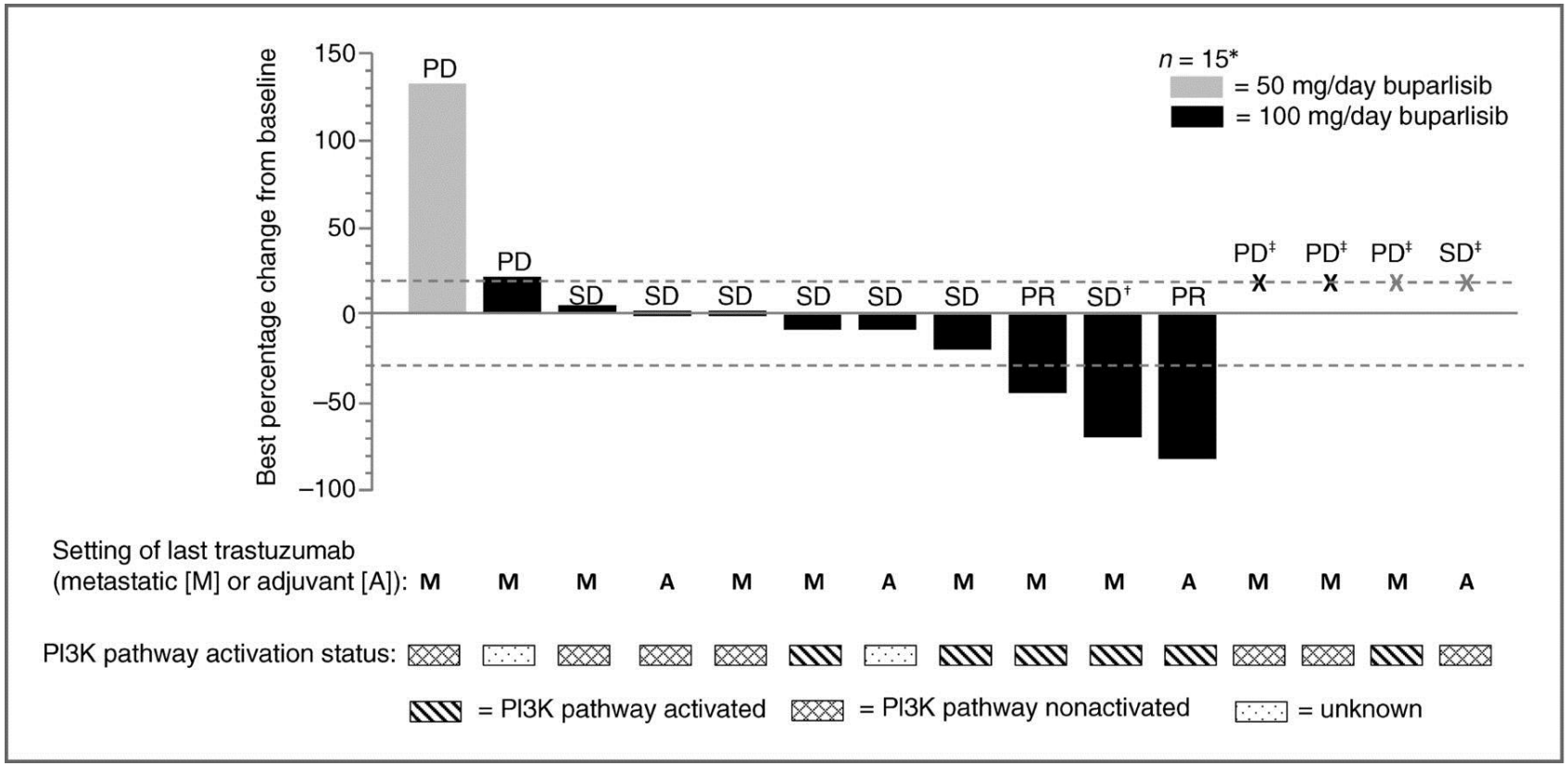
Each color represent one drug/target couple

Co-existing mutations could be associated with resistance

Lefebvre & Yu, Personal data

Drug combination to optimally target multiple drivers

Combining Her2-inh and PI3K inh to treat patients with Her2+++ / PIK3CA mutated cancers



Saura C et al. Clin Cancer Res 2014;20:1935-1945

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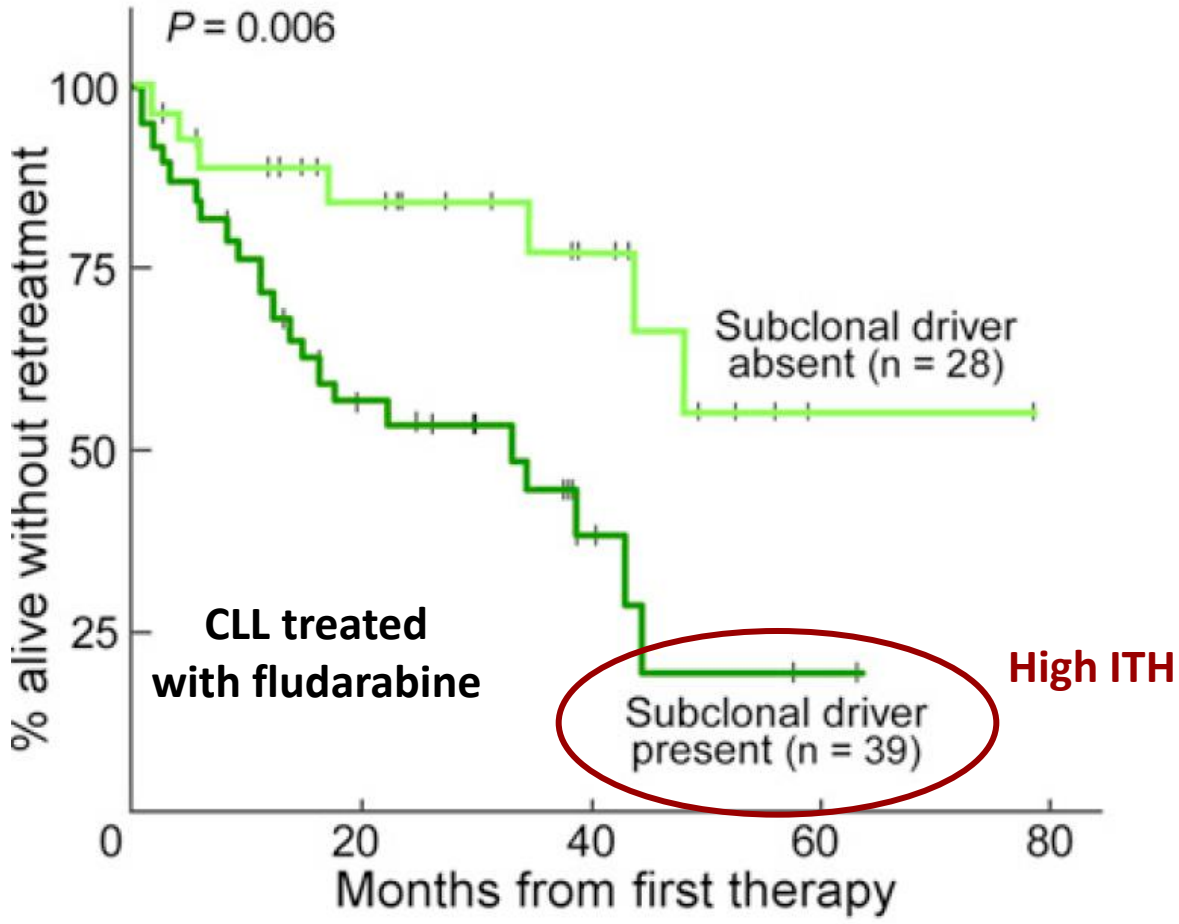
Does intratumor heterogeneity predict resistance to therapy ?



Intratumor heterogeneity could define a disease resistant to therapy

Landau, Cell, 2014

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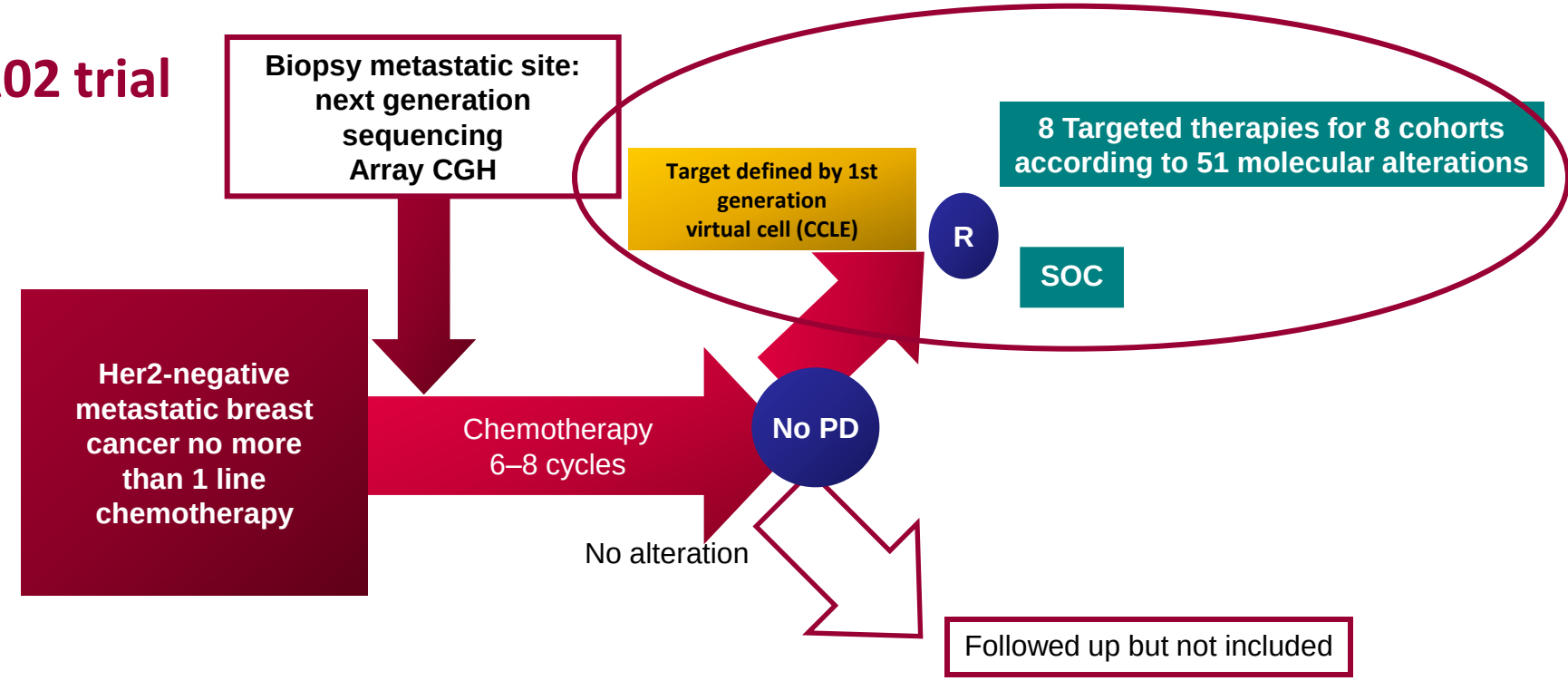
Personalized Medicine trials: testing the algorithm for target identification

SAFIR02 trial



- 210 randomised, around 400 screened
- Hypothesis: median PFS 3 to 6 months
- Sister trial in lung cancer

- Sponsor: UNICANCER
- Funding: French charity
- Pharma partner: AZ

Conclusion

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No evidence that personalized medicine improves outcome in breast cancer	Lack of trials	Run randomized trials testing the use of high throughput genomics