Design di clinical trials innovativi nella gestione del tumore mammario

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Changing nature of early development trials

- Enrichment strategies: by subtype of by genomic alterations

- Novel dose escalation methods applied

- Research biopsies

- Driving go-no-go decisions based on their ability to provide proof of concept

- Trends in increase in the sample size of phase I trials

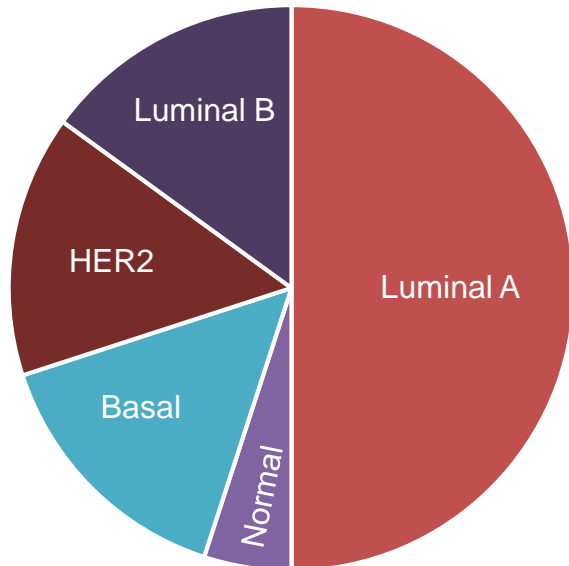- Expanding cohorts being conducted for multiple purposes

"Cancer moonshot initiative"

"What if matching a cancer cure to our genetic code was just as easy, just as standard?" - President Obama, January 30, 2015
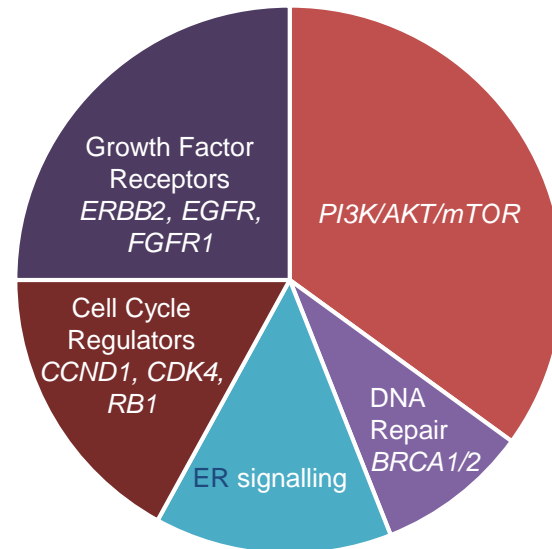
Cancer as an orphan disease

2000: Breast cancer subtypes

Pie chart segments:
- Luminal A
- Luminal B
- HER2
- Basal
- Normal

Clinical decisions based on **affected tissue, histology** and **disease stage**

2017: Genomic drivers

Pie chart segments:
- PI3K/AKT/mTOR
- Growth Factor Receptors *ERBB2, EGFR, FGFR1*
- Cell Cycle Regulators *CCND1, CDK4, RB1*
- ER signalling
- DNA Repair *BRCA1/2*

Clinical decisions based on the **results of comprehensive genomic profiling**

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Historical perspective

1940   1960   1980   2000   2020

Chemotherapy ⟶ **Targeted therapy**
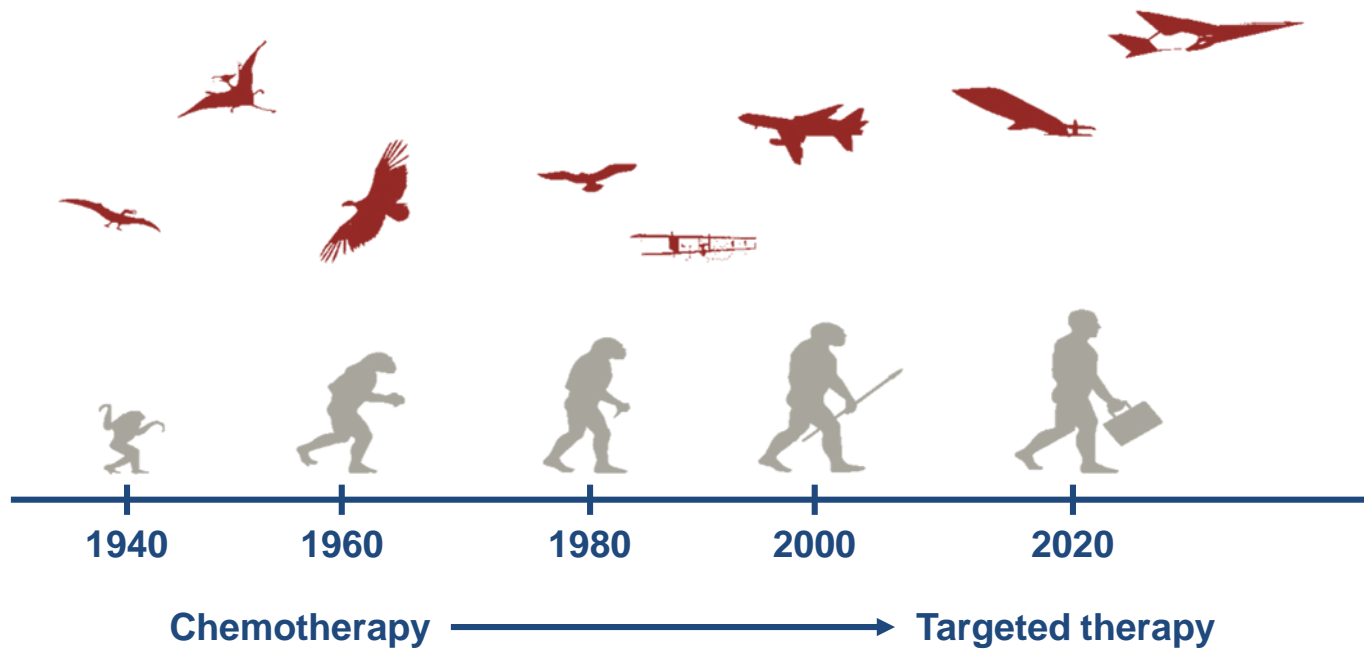
The evolution of molecular testing
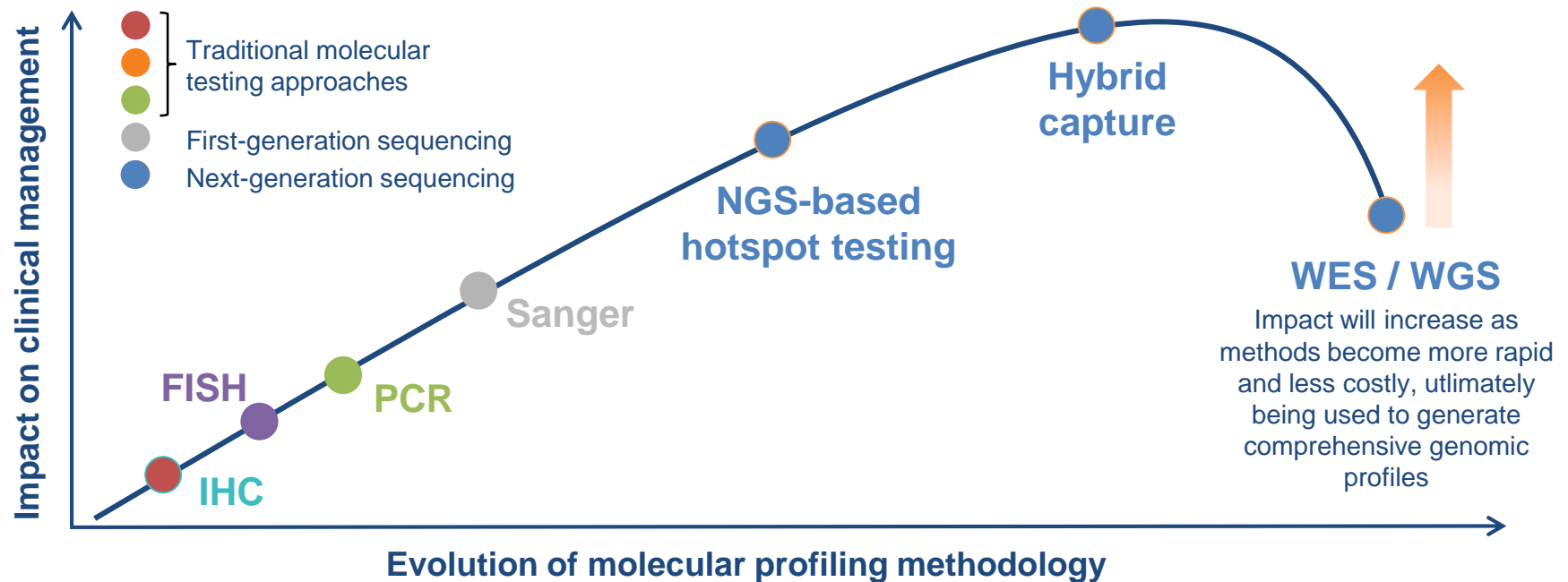
FISH: fluorescence in situ hybridisation; IHC: immunohistochemistry; NGS: next-generation sequencing; PCR: polymerase chain reaction; WES: whole exome sequencing; WGS: whole genome sequencing.
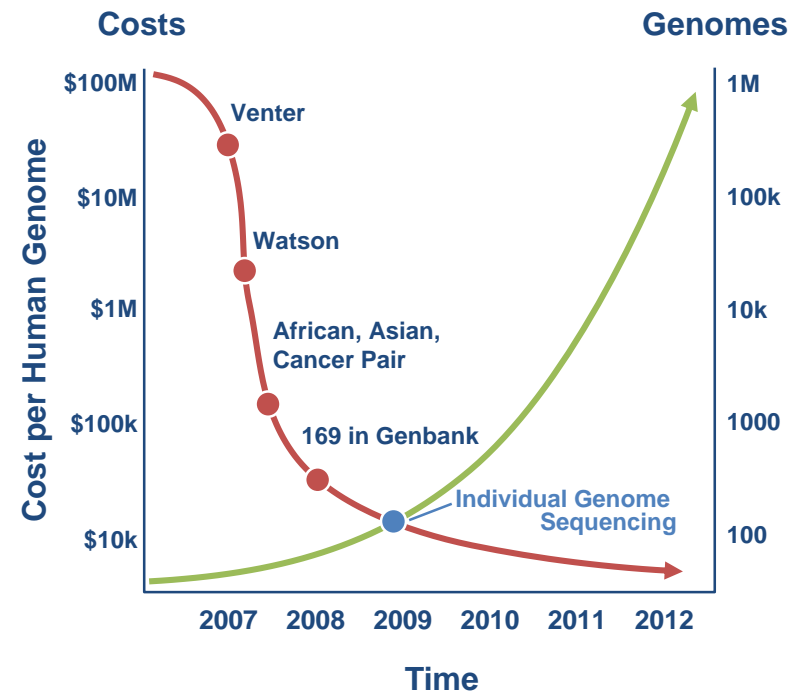
Netto, G.J., et al. (2003) *Proc Bayl Univ Med Cent.* 16:379-83.
de Matos, L.L., et al. (2010) *Biomark Insights.* 5:9-20.
Dong, L., et al. (2015) *Curr Genomics.* 16:253-63.

The evolution of molecular testing

Genome sequenced (publication year)	HGP (2003)[1]	Venter (2007)[1]	Watson (2008)[1]	Current (2015)[2]
Time taken (start to finish)	13 years	4 years	4.5 months	~1 days
Number of scientists listed as authors	> 2,800	31	27	
Cost of sequencing (start to finish)	$ 2.7 billion	$ 100 million	< $ 1.5 million	~ $ 1000
Coverage	8 - 10 x	7.5 x	7.4 x	30-50 x
Number of institutes involved	16	5	2	
Number of countries involved	6	3	1	

1. Wadman, M. (2008) *Nature*. 452(7189):788.
2. Retrieved from: https://www.genome.gov/27565109/the-cost-of-sequencing-a-human-genome/ [Accessed September 2017].

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Access to testing

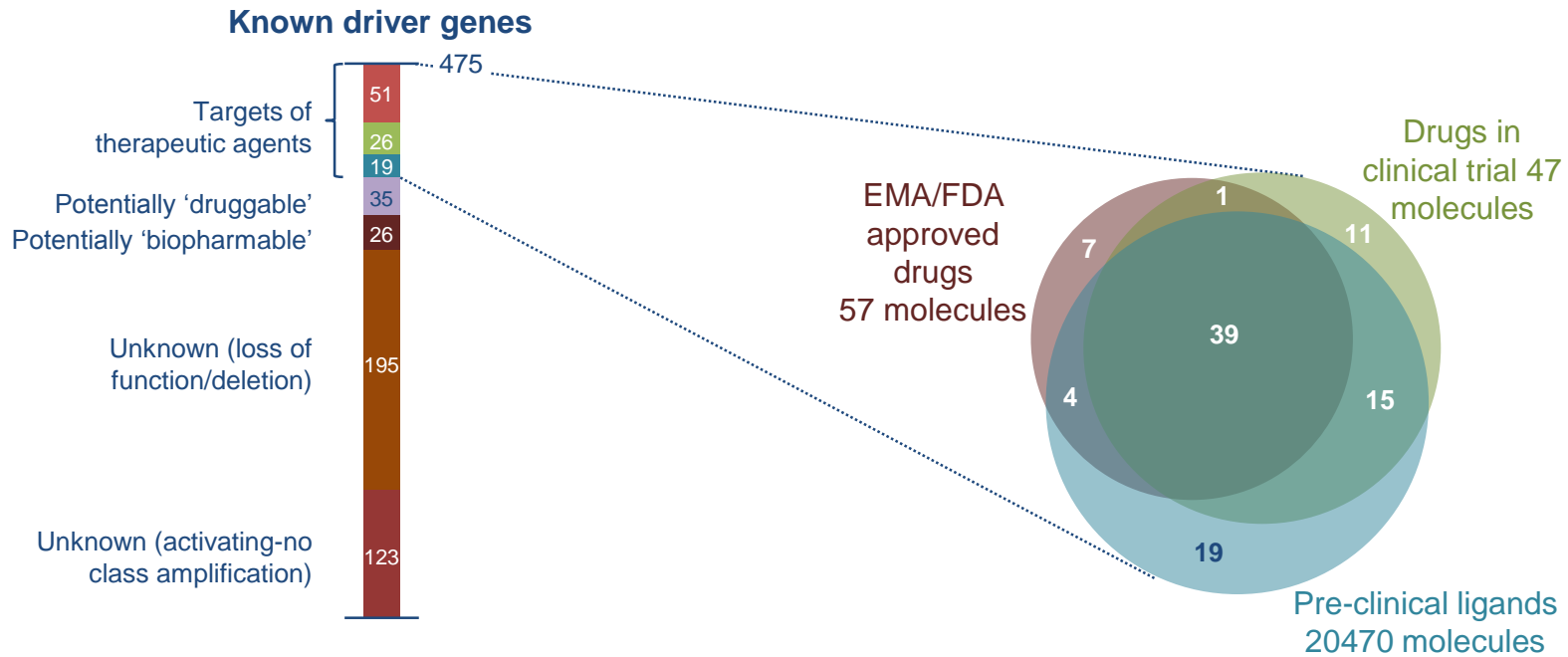| Genomics England 100k Genomes [2]	France Genomics 2025 [1]
Objectives: 1. Ethical and transparent programme 2. Provide benefits of genomic medicine to patients 3. Enable new scientific discovery and medical insights 4. Kick start the development of a UK genomics industry	Objectives: 1. Position France as one of the leading countries in personalised medicine 2. Integrate genomic medicine in clinical care 3. Foster scientific and technological innovation

1. Retrieved from:
http://www.gouvernement.fr/sites/default/files/document/document/2016/06/22.06.2016_remise_du_rapport_dyves_levy_-_france_medecine_genomique_2025.pdf [Accessed September 2017];
2. Retrieved from: https://www.genomicsengland.co.uk/the-100000-genomes-project/ [Accessed September 2017].

Treatment allocation

Known driver genes

475

Targets of therapeutic agents
- 51
- 26
- 19

Potentially 'druggable' — 35
Potentially 'biopharmable' — 26

Unknown (loss of function/deletion) — 195

Unknown (activating-no class amplification) — 123

EMA/FDA approved drugs 57 molecules

Drugs in clinical trial 47 molecules

Pre-clinical ligands 20470 molecules

1
7
11
39
4
15
19

Adapted from Rubio-Perez, C., et al. (2015) *Cancer Cell.* 27(3):382–96.

Why drug development is changing?

- Knowledge of molecular biology is accumulating and technology is rapidly evolving

- Molecularly targeted agents and immuno-oncology agents are becoming important

- Infrastructure resources are limited

- Desire to accelerate drug development process to bring active compounds to the clinic and improve cancer cures have fueled these changes

# Economics and logistics of personalized medicine trials
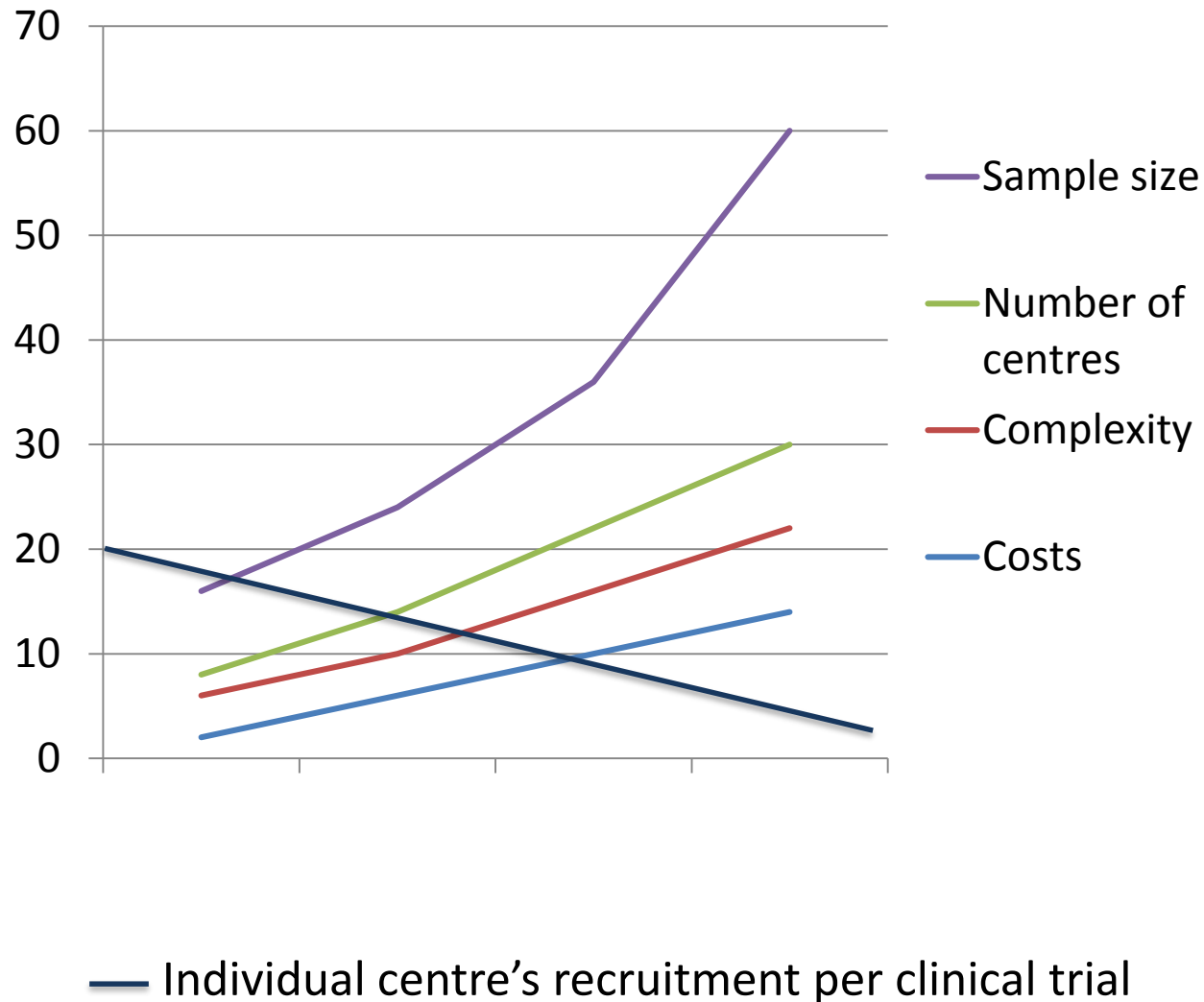
The traditional drug development paradigm

Phase I	Phase II	Phase III
Safety	Efficacy in selected tumors	Meaningful benefit in a randomized setting against existing standard
Tolerability	ORR	OS
Pharmacokinetics	TTP	
Pharmacodynamics	PFS	
Preliminary antitumor activity		

The current drug development paradigm

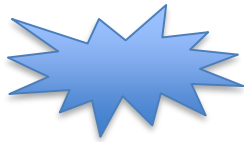| Proof of mechanism	Proof of concept Early	Late
Safety, tolerability, on target and off target effects	Predictive biomarkers explored	Predictive biomarkers confirmed
Preliminary antitumor activity	Antitumor activity seen using surrogate endpoints	Proof of concept using a validated clinical endpoint
Evidence of target engagement in valid pharmacodynamic biomarkers	ORR TTP PFS	OS

New trend in Oncology Drug development
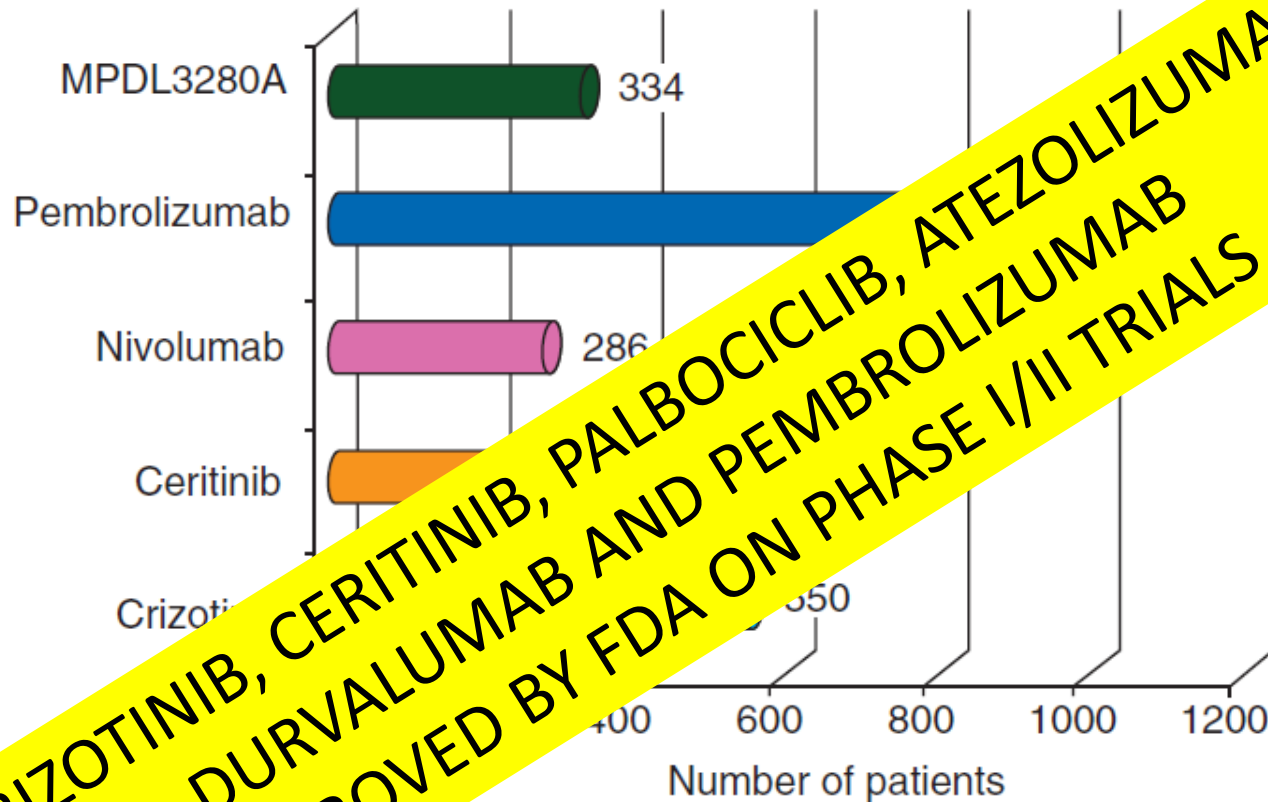
of patients enrolled in recent phase 1 trials having led to approval or breakthrough designations (based on www.

CRIZOTINIB, CERITINIB, PALBOCICLIB, ATEZOLIZUMAB, DURVALUMAB AND PEMBROLIZUMAB APPROVED BY FDA ON PHASE I/II TRIALS

Postel-Vinay S Annals of Oncology 2014

Neoadjuvant Trials

Newly diagnosed pt Tumor in place	DRUG RX →	Post-treatment clinical and correlative data
	Therapeutic intent and duration	

- Good ☺:
  - Small, fast
  - Pick-a-winner
  - pCR is a good surrogate endpoint (FDA registrational option)
  - DFS/OS can be collected in same cohort

- Bad ☹:
  - pCR only validated endpoint. Irrelevant in many (ER+)
  - Quantitative relationship pCR to DFS/OS not established
    - Trials underpowered for these endpoints
  - Macromet = micromet?
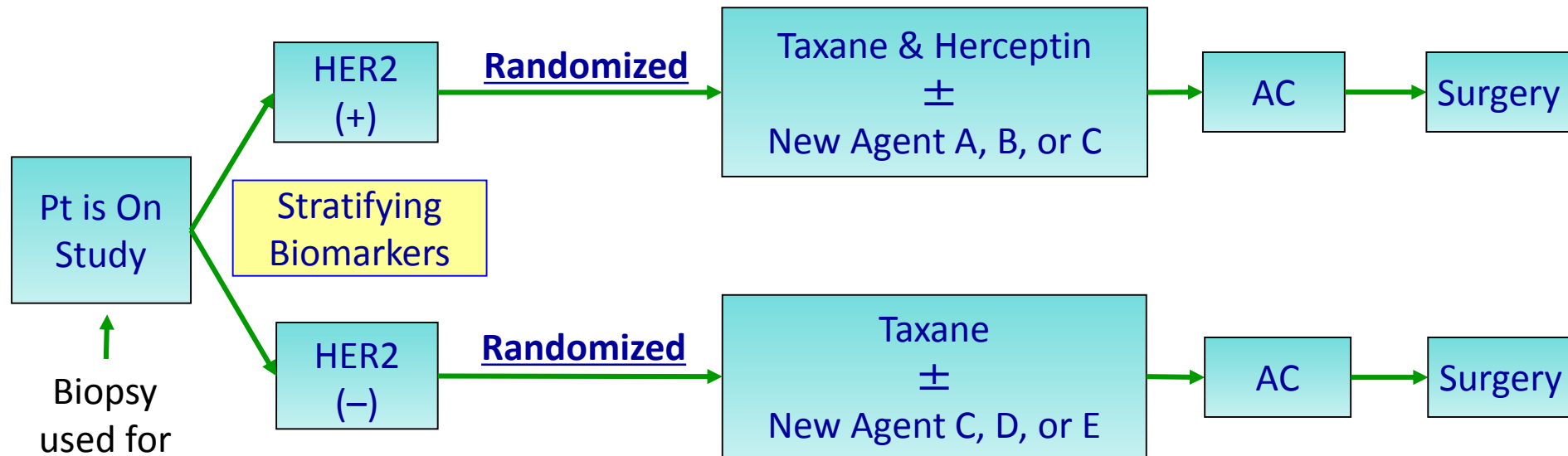 - Drugs must be well known

Adaptive Trials

Adaptive algorithm

↓

Early/iterative analysis

(drug or biomarker working?)

Continue data collection

Stopping rule met?

Yes

No

Revise allocation per algorithm e.g. randomize more to Drug A arm

Stop trial or begin next phase
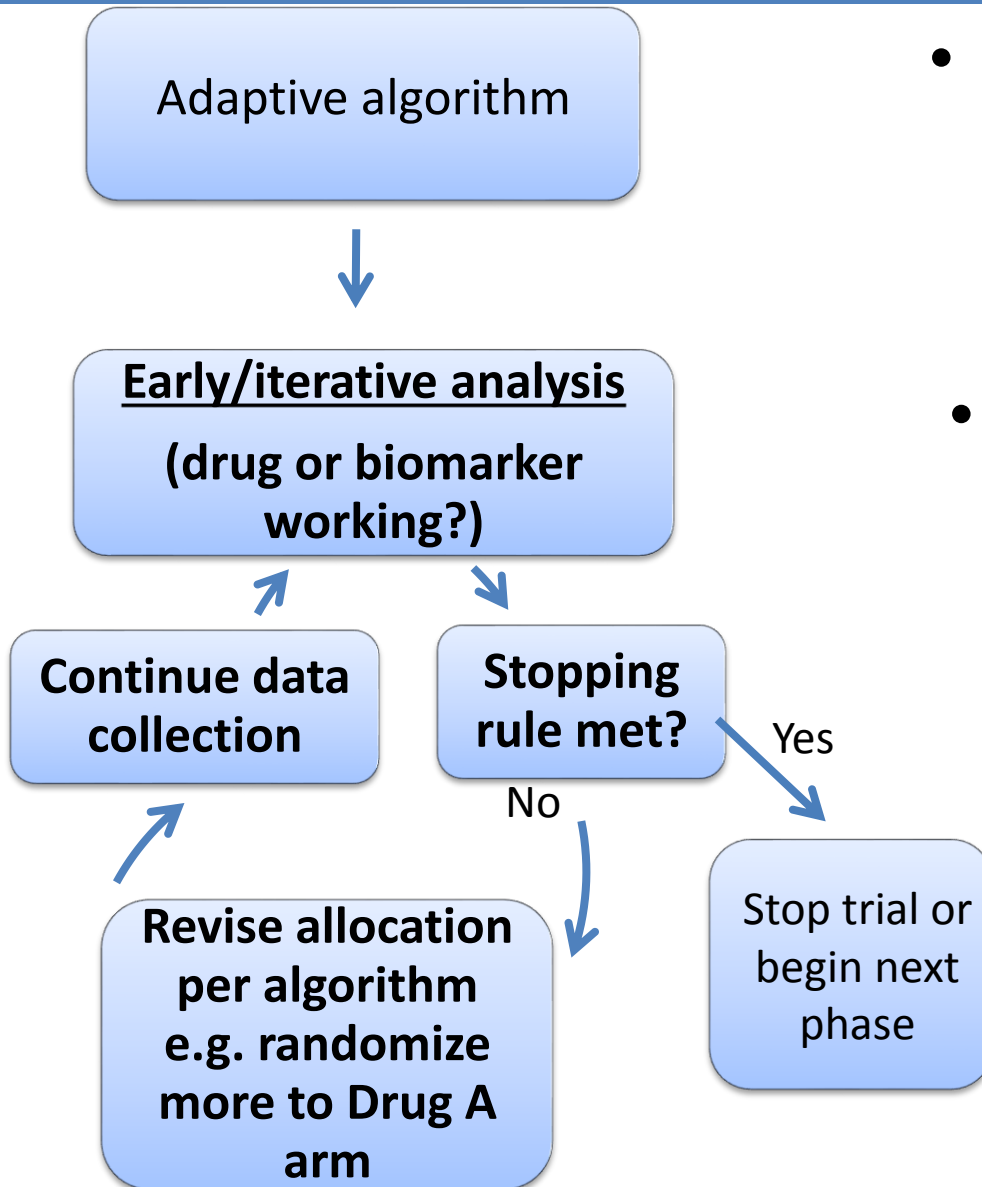
- Good ☺:
  - Pick-a-winner
  - Can adapt on drug or biomarker
  - Smaller, conserve resources
- Bad ☹:
  - Interim estimates= ↑error risk
  - Complicated! Continuously collecting response data
  - If biomarker-based
    - Must be validated.
    - Need real-time results
    - Cannot do discovery

Example: ISPY2 - novel biologics in combination with chemotherapy

I-SPY 2 TRIAL

```
                                        Randomized      ┌──────────────────────┐
                        ┌─────────┐     ─────────────>  │  Taxane & Herceptin  │     ┌──────┐      ┌─────────┐
                        │  HER2   │                     │          ±           │ ──> │  AC  │ ───> │ Surgery │
                        │   (+)   │                     │  New Agent A, B, or C │     └──────┘      └─────────┘
                        └─────────┘                     └──────────────────────┘
  ┌──────────┐      ↗
  │ Pt is On │        ┌─────────────┐
  │  Study   │        │ Stratifying │
  └──────────┘        │ Biomarkers  │
       ↑            ↘ └─────────────┘
                        ┌─────────┐     Randomized      ┌──────────────────────┐
  Biopsy                │  HER2   │     ─────────────>  │       Taxane         │     ┌──────┐      ┌─────────┐
  used for              │   (−)   │                     │          ±           │ ──> │  AC  │ ───> │ Surgery │
  Biomarkers            └─────────┘                     │  New Agent C, D, or E │     └──────┘      └─────────┘
                                                        └──────────────────────┘
```

Stratifying Biomarkers (Established/Approved/IDE)
ER, PR
HER2 (IHC, FISH, RPMA, 44K-microarray)
MammaPrint 44K microarray

"Window of Opportunity" Trials

Newly diagnosed pt Tumor in place

Drug Rx →

Short duration
Not intended for therapy

Reprogramming?
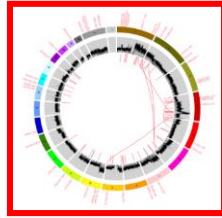**Resistance?**

- Good for:
  – Discovery
  – Proof of principle (e.g. Johnson presentation)

- Bad for:
  – Unknown agents
  – ? Testing combinatorial strategies
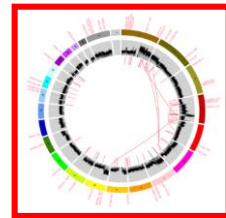   - Doses?
    - Toxicity issues

These contribute to scientific knowledge and therapeutic hypotheses, not clinical care
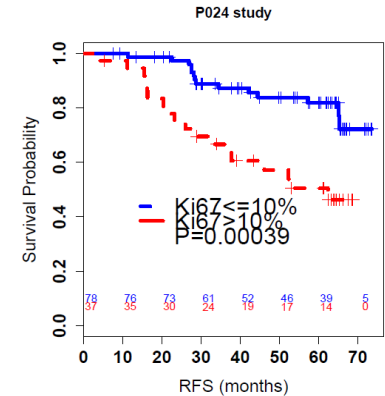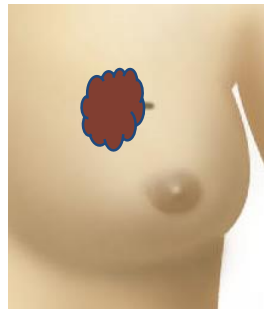
"Genome-Forward" Trials

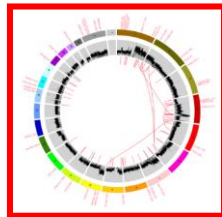2 baseline frozen cores
70%+ tumor cellularity
DNA extracted
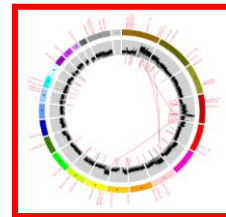
Ki67 in surgical sample
Greater that 10% = Unfavorable
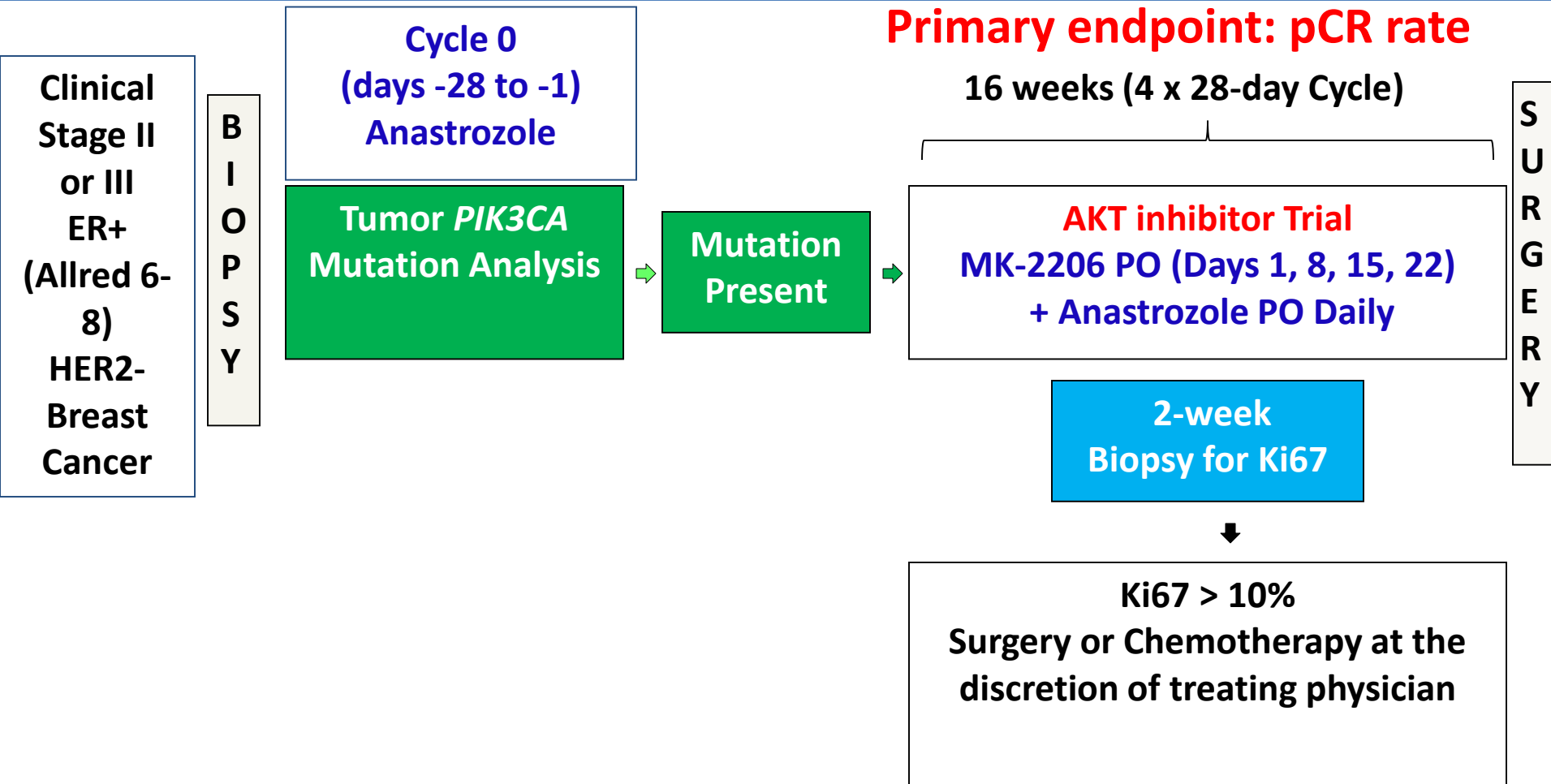
16 to 18 weeks of aromatase inhibition

2 baseline frozen cores
70%+ tumor cellularity
DNA extracted
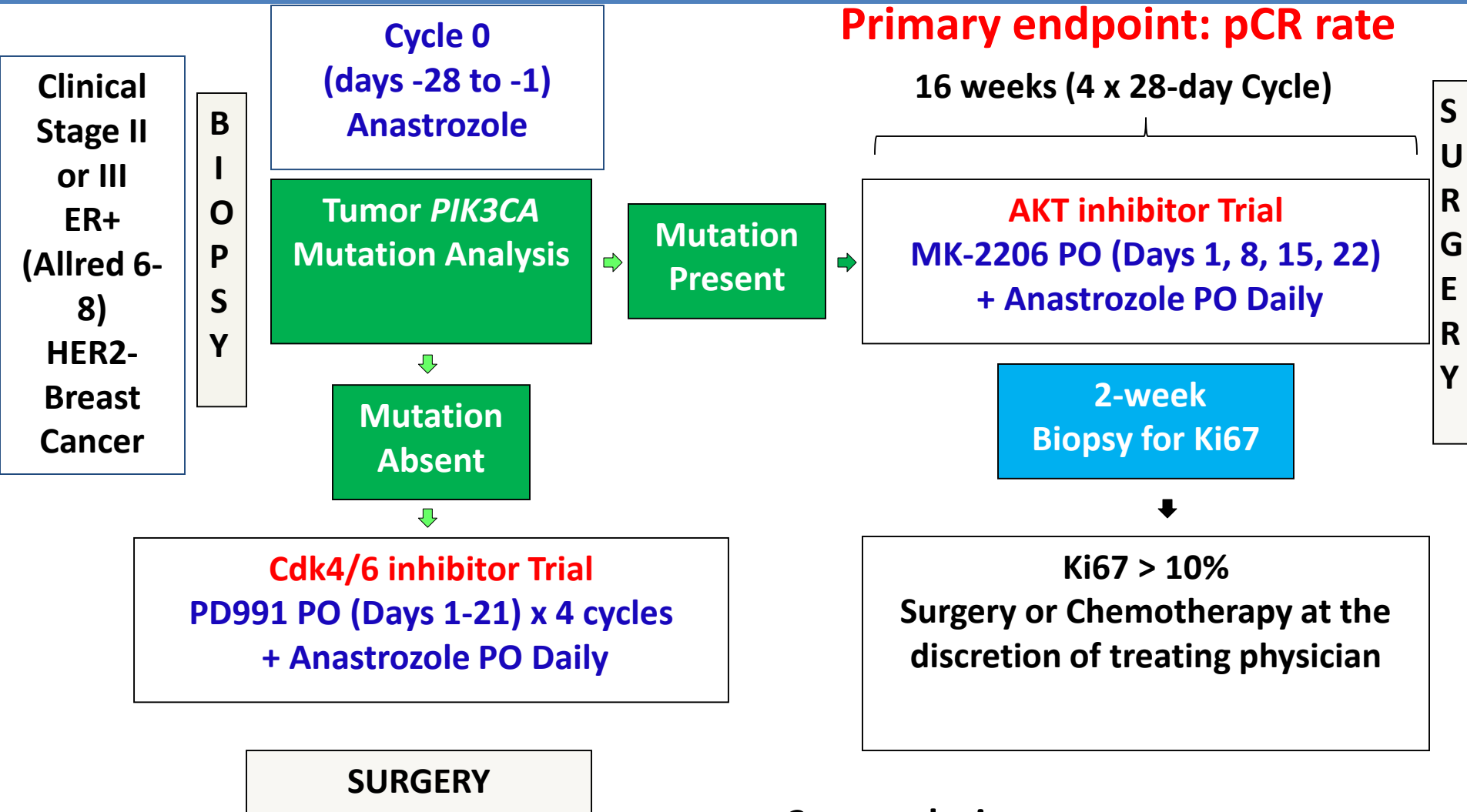
Ki67 in surgical sample
Less than10% = Favorable

P024 study

Survival Probability

Ki67<=10%
Ki67>10%
P=0.00039

RFS (months)

BCRF, NHGRI, NCI

"Genome-Forward" Trials

Clinical Stage II or III ER+ (Allred 6-8) HER2- Breast Cancer

BIOPSY

Cycle 0 (days -28 to -1) Anastrozole

Tumor *PIK3CA* Mutation Analysis

Mutation Present

Primary endpoint: pCR rate

16 weeks (4 x 28-day Cycle)

AKT inhibitor Trial MK-2206 PO (Days 1, 8, 15, 22) + Anastrozole PO Daily

2-week Biopsy for Ki67

Ki67 > 10% Surgery or Chemotherapy at the discretion of treating physician

SURGERY

2 stage design:
1st stage: n=13
2nd stage: n=16

"Genome-Forward" Trials

Clinical Stage II or III ER+ (Allred 6-8) HER2- Breast Cancer

B I O P S Y

Cycle 0 (days -28 to -1) Anastrozole

Primary endpoint: pCR rate

16 weeks (4 x 28-day Cycle)

S U R G E R Y

Tumor *PIK3CA* Mutation Analysis

Mutation Present

AKT inhibitor Trial MK-2206 PO (Days 1, 8, 15, 22) + Anastrozole PO Daily

Mutation Absent

2-week Biopsy for Ki67

Cdk4/6 inhibitor Trial PD991 PO (Days 1-21) x 4 cycles + Anastrozole PO Daily

Ki67 > 10% Surgery or Chemotherapy at the discretion of treating physician

SURGERY

2 stage design:
1st stage: n=13
2nd stage: n=16

Later Stage Trials
Biomarkers: Enrich or Stratify?

- Enrich = "integral"
  - Certainty about biomarker
  - Certainty that you do not wish to test others
  - Assay clinically valid (FDA is watching you!)

- Stratify = "integrated"
  - Bigger than no-biomarker trial
  - Assay clinically valid (less scrutiny)

Phase I committed personnel

Biopsy

Histological analysis

Molecular screening
Gene-panel sequencing

phase I candidates

14 calendar days
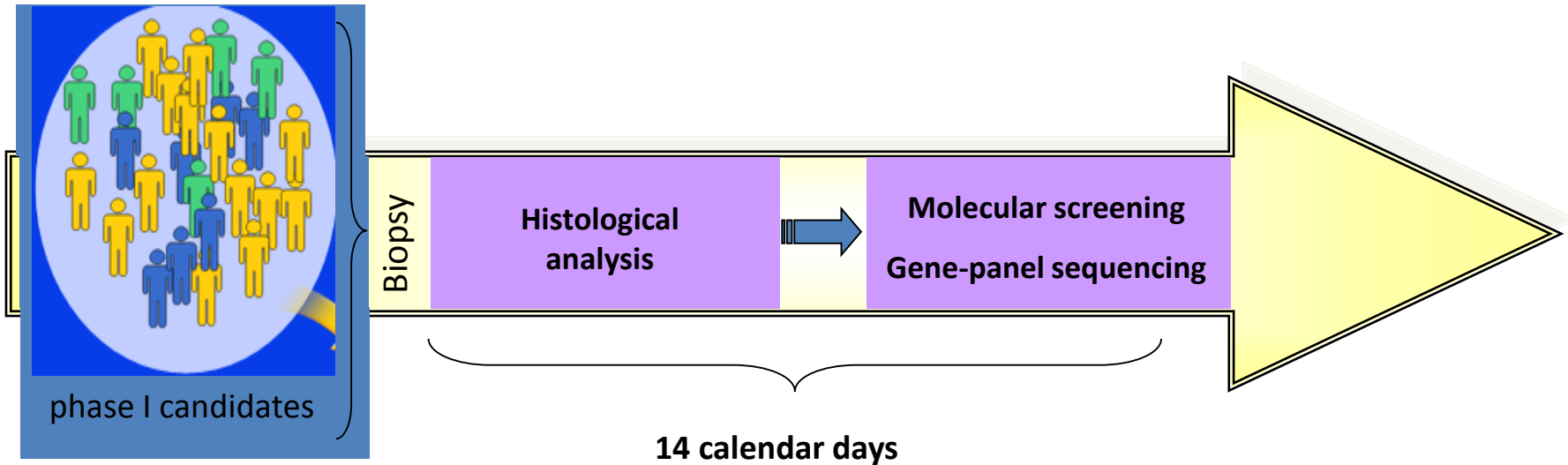
- Complex PK and PD, cardiokinetics
- Dedicated staff (research nurses, data managers, pathologists, interventional radiologists, MDs)
- Time to reaction

Biomarker-Driven Clinical Research

NNS = Number needed to screen

$$\frac{1}{(\text{fraction with biomarker X assay specificity X fraction trial-eligible X fraction giving informed consent})}$$

Example: HER2+ in BC= 1/(0.25 X 0.9 X 0.5 X 0.5) = 17.8 patients screened/1 patient entered into trial

Example: ALKtx in NSCLC = 1/(0.05 X 0.9 X 0.5 X 0.5) = 88 patients screened/1 patient entered into trial

Example: PIK3CA mut in BC = 1/(**0.03** X 0.9 X 0.5 X 0.5) = 148 patients screened/ 1 patient entered into trial

Example: FGFR in BC = 1/(**0.08** X 0.9 X 0.5 X 0.5) = 55 patients screened/ 1 patient entered into trial

Economics and logistics of personalized medicine trials

- Each center needs to open multiple studies to be economically viable

- Greater regulatory burden (protocols emendments, SUSARs)

- Cost per case increased

- Limited experience accumulated per centre

- Collection of trial data by sponsor with sharing of toxicity data by grade and frequency on a regular basis throught protocol conduct

Master Protocol

Biomarker Profiling

Unkn-Neg biomarker → CT*

Unkn-Neg biomarker → Anti PD1

Biomarker A	Biomarker B	Biomarker C	Biomarker D

Biomarker A → TT A | CT*

Biomarker B → TT B | CT*

Biomarker C → TT C+CT | CT*

Biomarker D → TT D+E | BA*

Endpoint (Interim PFS) OS	Endpoint (Interim PFS) OS	Endpoint (Interim PFS) OS	Endpoint (Interim PFS) OS
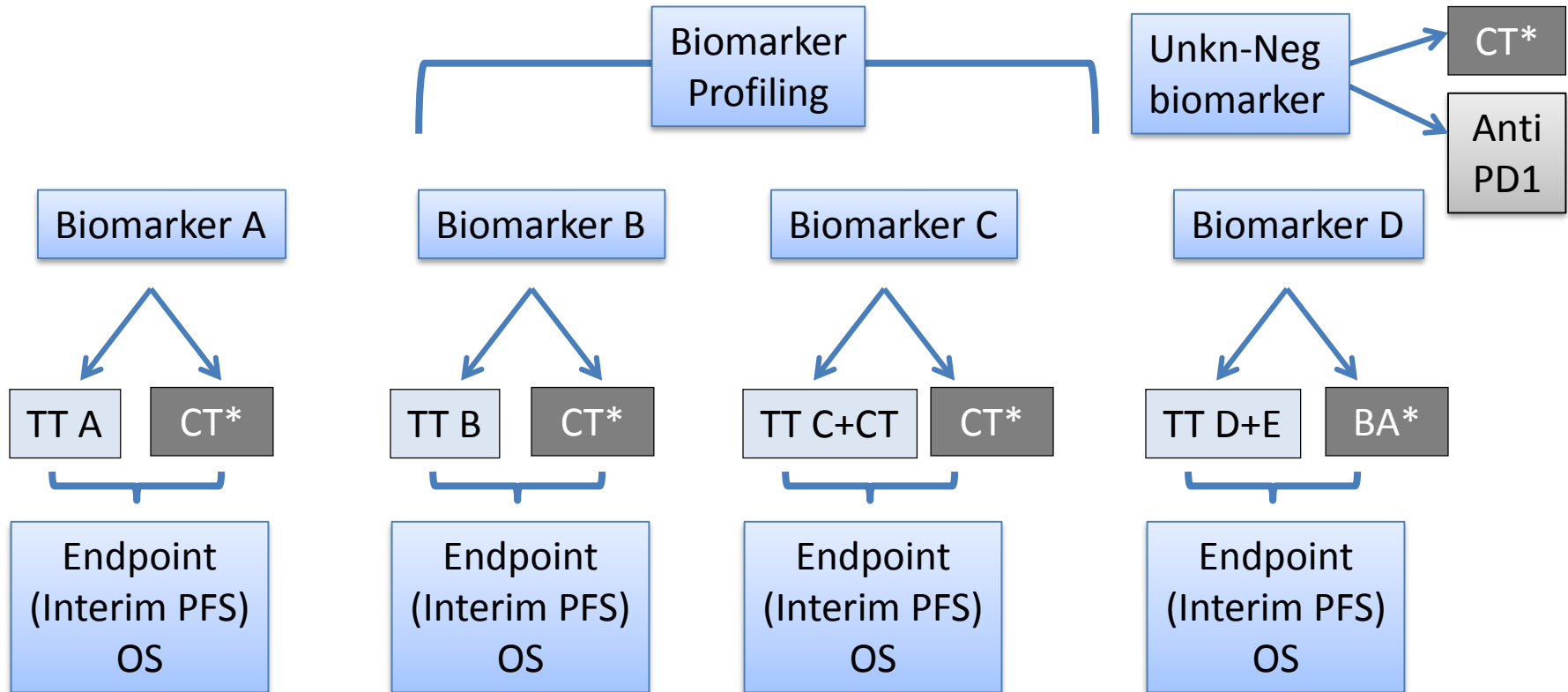
TT=Targeted therapy, CT=chemotherapy; BA=Biological Agent

Master Protocol

CAPTUR Canadian Profiling and targeted Utilization trial

DRUP The Drug Rediscovery Protocol

TAPUR Targeted Agent and Profiling Utilization Registry Study

And more...

Initiatives to decipher which patients respond to which therapies, irrespective of in which tumor type the therapies are approved in

From autoimmunity to cancer immune rejection

Hendrickx W et al. 2017, Oncoimmunology, In press
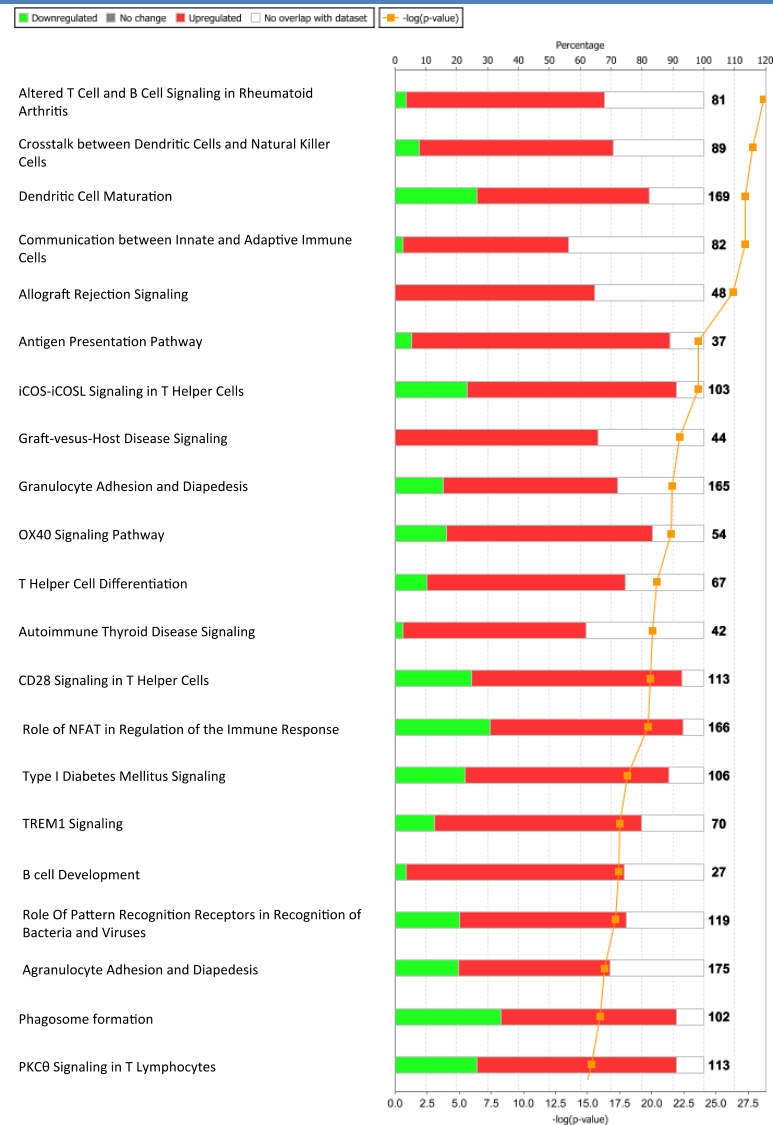
Identification of genetic determinants of breast cancer immune phenotypes

We mined copy number variation, exome, and RNA-seq data from the The Cancer Genome Atlas (TCGA) breast cancer dataset.

By using RNA-seq data from 1004 breast cancer samples, we defined 4 immune phenotypes (e.g, Immunologic Constant of Rejection (ICR) ICR1, ICR3, ICR3, and ICR4) characterized by progressive expression of immune-related genes previously associated with immune-mediated rejection.

C.

D.

G.

Hendrickx W et al. 2017, Oncoimmunology, In press
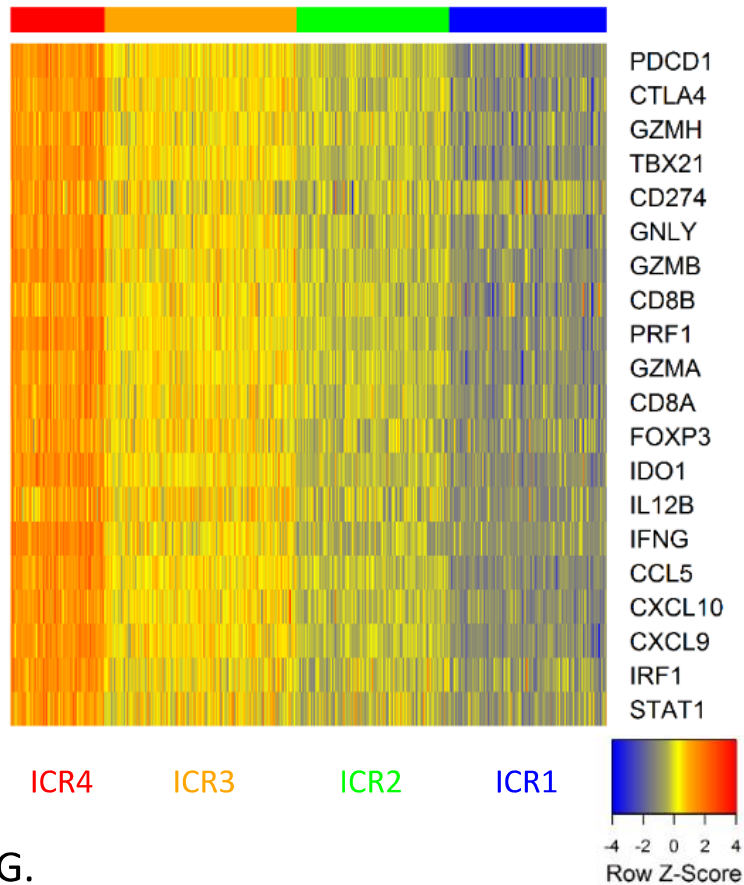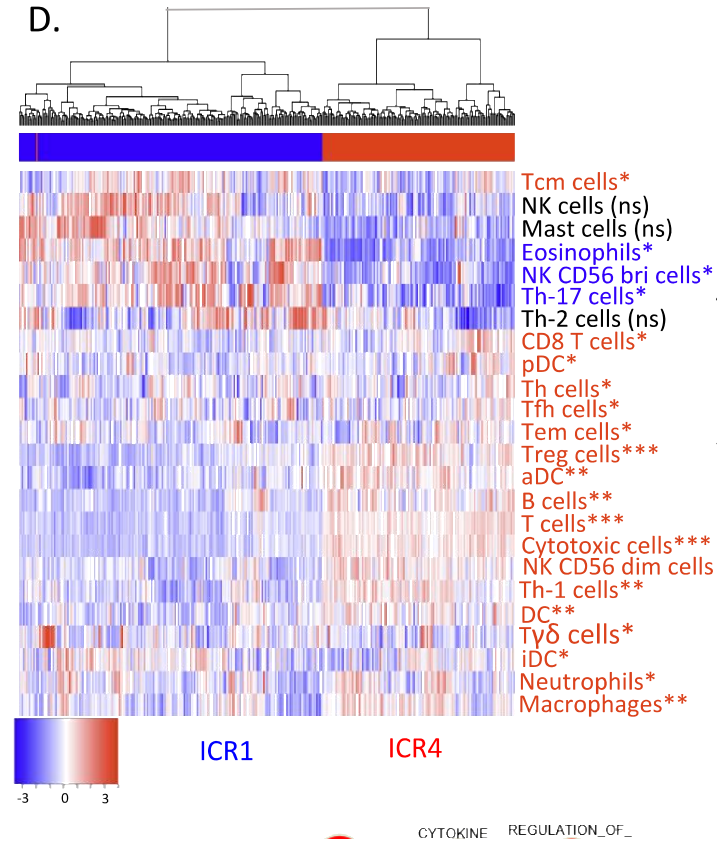
Identification of genetic determinants of breast cancer immune phenotypes

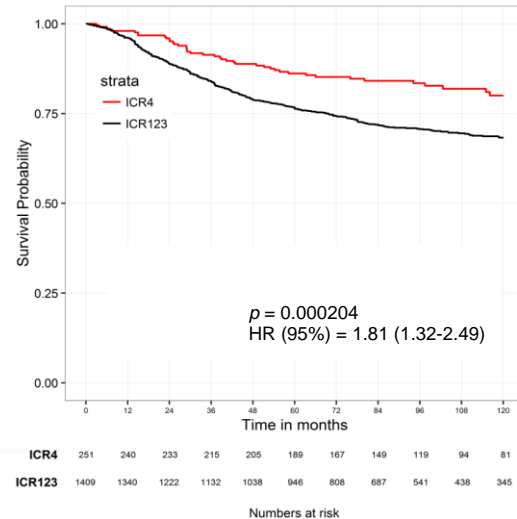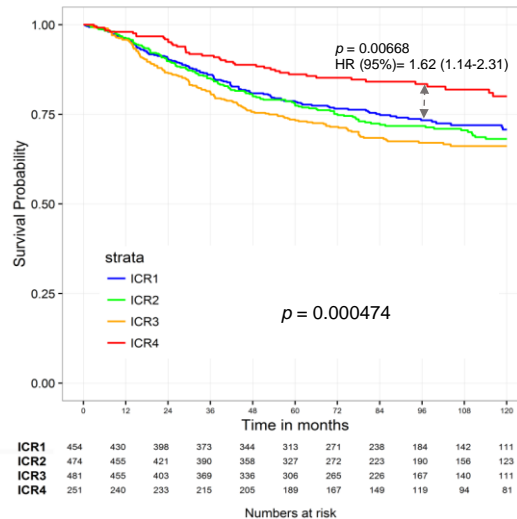We validated these findings in a large meta-cohort of 1954 cancer gene expression data.

The ICR4 phenotype, which displays the upregulation of immune-regulatory transcripts such as PDL1, PD1, FOXP3, IDO1, and CTLA4, was associated with prolonged survival.
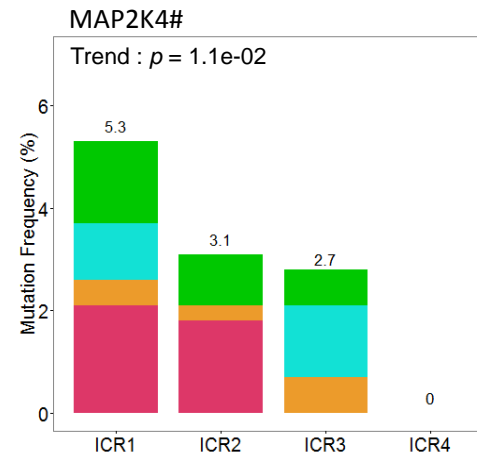
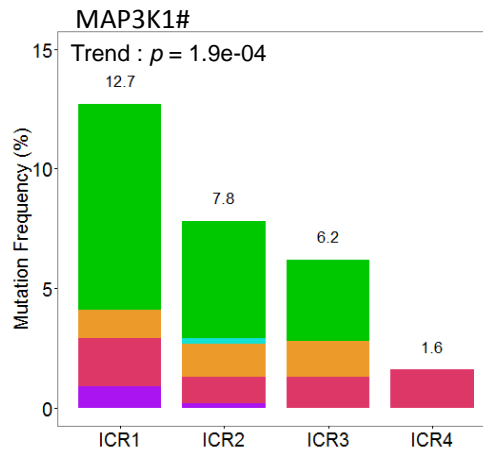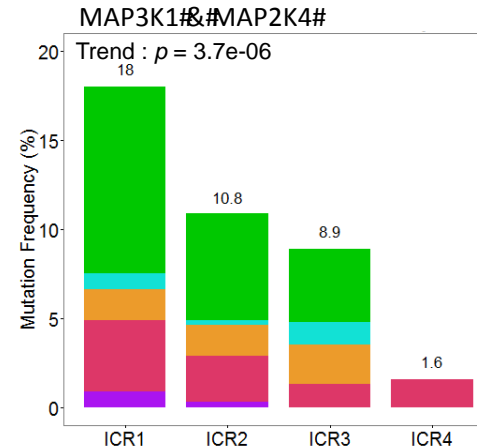# Survival and immune phenotypes

A.#
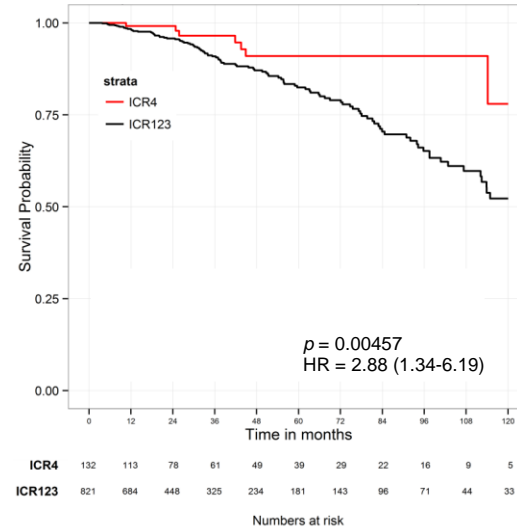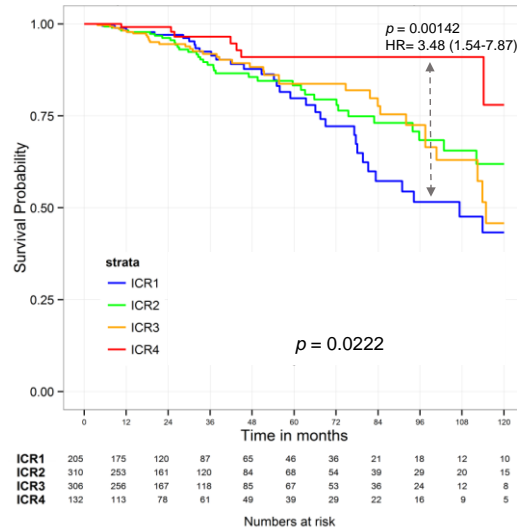
B.#

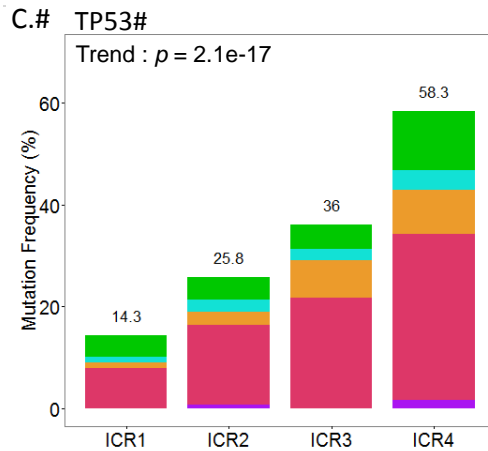# Identification of genetic determinants of breast cancer immune phenotypes
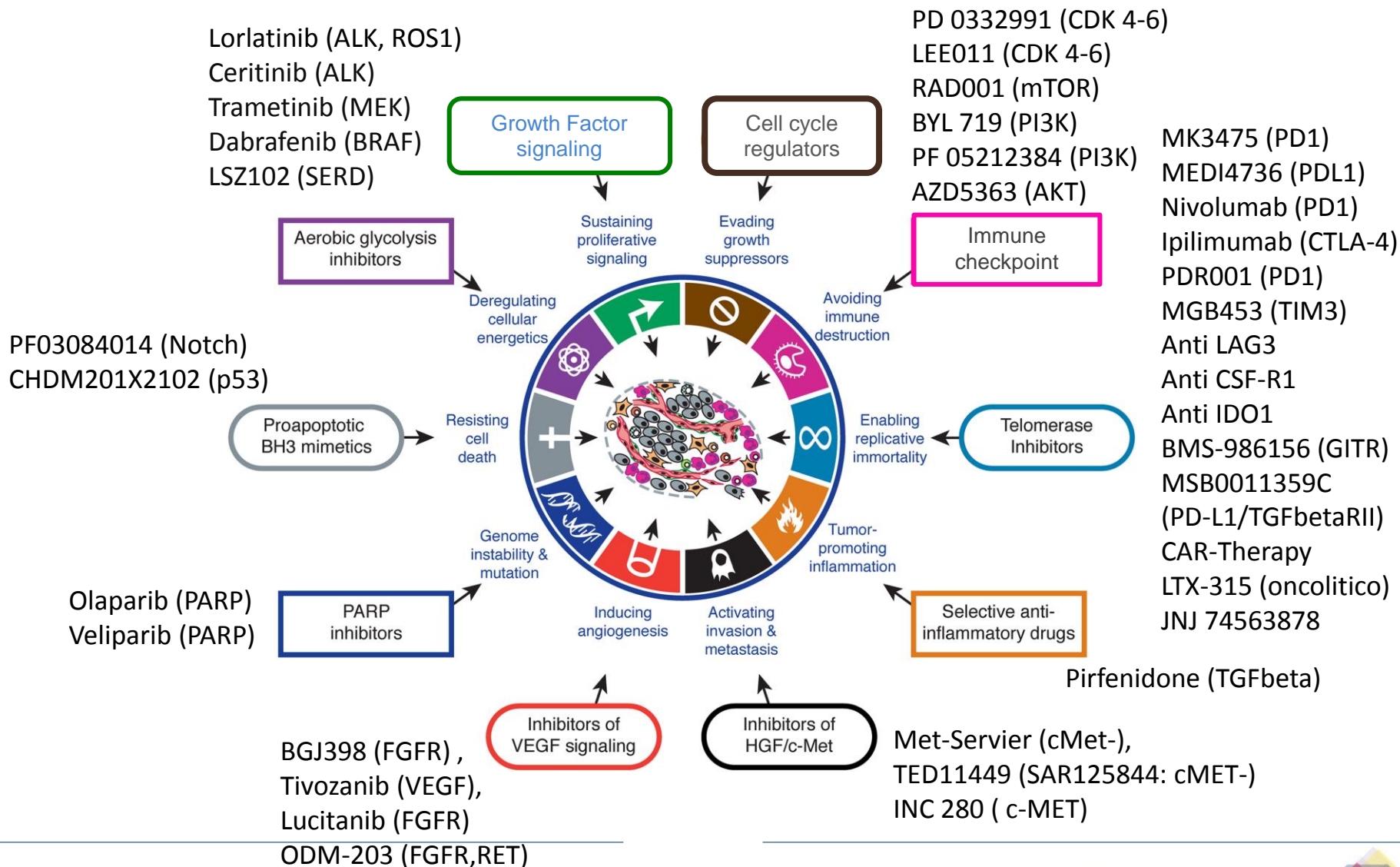
The number of non-silent or total mutations progressively decreased from ICR4 to ICR1, with a strong interaction with intrinsic molecular subtypes. No differences were observed among ICRs regarding the proportion of somatic mutations yielding predicted neoantigens.

TP53 mutations were enriched in the immune favorable phenotype (ICR4).

Specific mutations and immune phenotypes

Ongoing Phase I Clinical Trials

Lorlatinib (ALK, ROS1)
Ceritinib (ALK)
Trametinib (MEK)
Dabrafenib (BRAF)
LSZ102 (SERD)

PF03084014 (Notch)
CHDM201X2102 (p53)

Olaparib (PARP)
Veliparib (PARP)

BGJ398 (FGFR) ,
Tivozanib (VEGF),
Lucitanib (FGFR)
ODM-203 (FGFR,RET)

PD 0332991 (CDK 4-6)
LEE011 (CDK 4-6)
RAD001 (mTOR)
BYL 719 (PI3K)
PF 05212384 (PI3K)
AZD5363 (AKT)

MK3475 (PD1)
MEDI4736 (PDL1)
Nivolumab (PD1)
Ipilimumab (CTLA-4)
PDR001 (PD1)
MGB453 (TIM3)
Anti LAG3
Anti CSF-R1
Anti IDO1
BMS-986156 (GITR)
MSB0011359C
(PD-L1/TGFbetaRII)
CAR-Therapy
LTX-315 (oncolitico)
JNJ 74563878

Pirfenidone (TGFbeta)

Met-Servier (cMet-),
TED11449 (SAR125844: cMET-)
INC 280 (c-MET)

IEO
Istituto Europeo di Oncologia

Trials in the 21ˢᵗ Century

- Small
- Fast (collaboration is key)
- Rational
- Careful!

The future drug development paradigm?

Histology and molecular selection	Proof of concept
Safety and tolerability	Substancially efficacy in selected patients using innovative trial designs and endpoints
Functional target selection	Trial design accounting for interpatient and intratumor heterogeneity
Pharmacology	
Antitumor activity	

Conclusions

- Many challenges still exist from a trial design standpoint: how to identify populations, minimize heterogeneity, optimize endpoints.

- Proposal of italian network of phase I unit

- Immediate needs:
  - Consensus on how to identify the biology that we want to study
  - Validation of the assays to identify that biology
  - Determine meaningful intermediate endpoints

Thank you