GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

université
PARIS-SACLAY

Precision medicine for patients with breast cancer

Fabrice ANDRE

COI

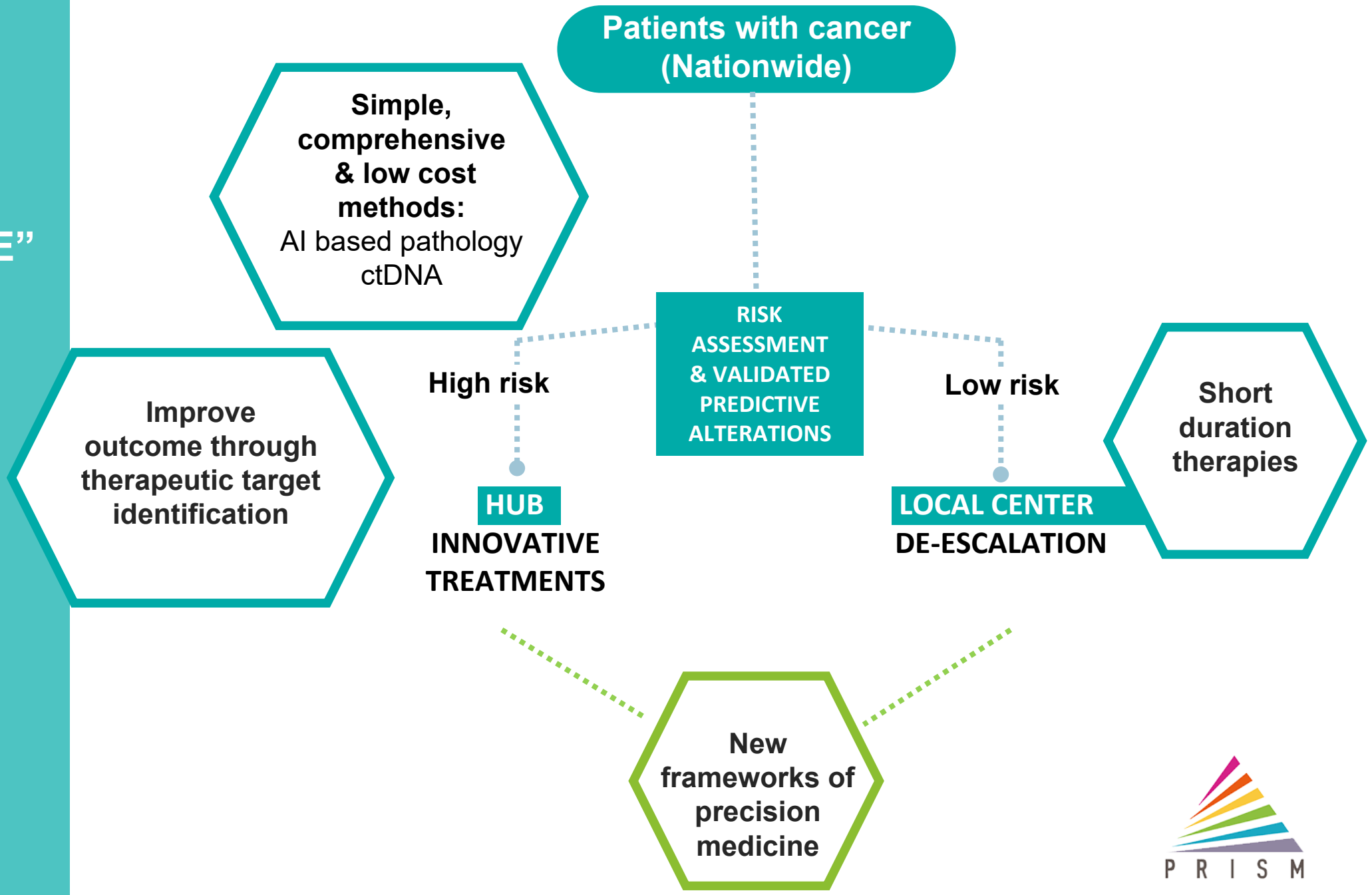
- Pr Fabrice ANDRE:
  - Research funding to the institution and advisory boards / speaker (compensated to the hospital) from AstraZeneca, Lilly, Novartis, Pfizer, Daiichi-Sankyo, Relay Tx and Roche.
  - Advisory board compensate to FA: Lilly, Galapagos

  - !!!! : FA is inventor of the patent on pathology assisted by AI mentioned in one slide, FR is founder of Resilience, FRESH is a public private partnership that includes GR

How could precision medicine reduce HC disparities ?

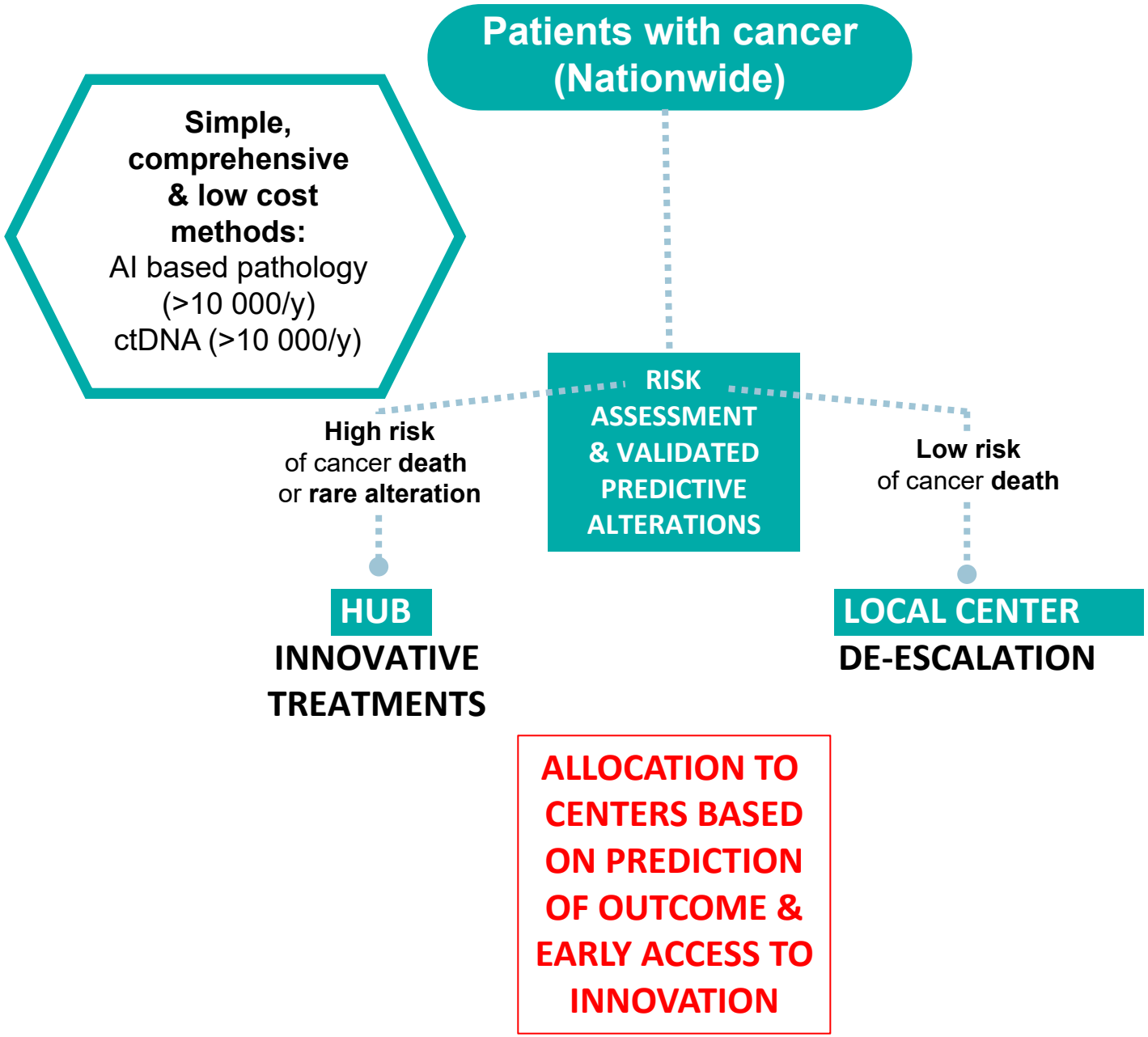
- Broad implementation of devices: simple, low cost, comprehensive (ctDNA and AI)
- Reduce requirement of complex infrastructures or expertise (ctDNA and AI)
- Allocate patients in the optimal center based on DATA (« screen for risk »
- Adress shortage of workforce by re-allocating resources to patients who need them (short treatment durations)
- Reduce impact of low education on outcome (adherence, perception)
- Substitute the MD where it does not exist anyway… (digital monitoring)
- Reduce disparities between cancer types

CLINICAL RESEARCH: "SCREEN AND CHARACTERIZE" APPROACH



PRISM

CLINICAL RESEARCH: "SCREEN AND CHARACTERIZE" APPROACH



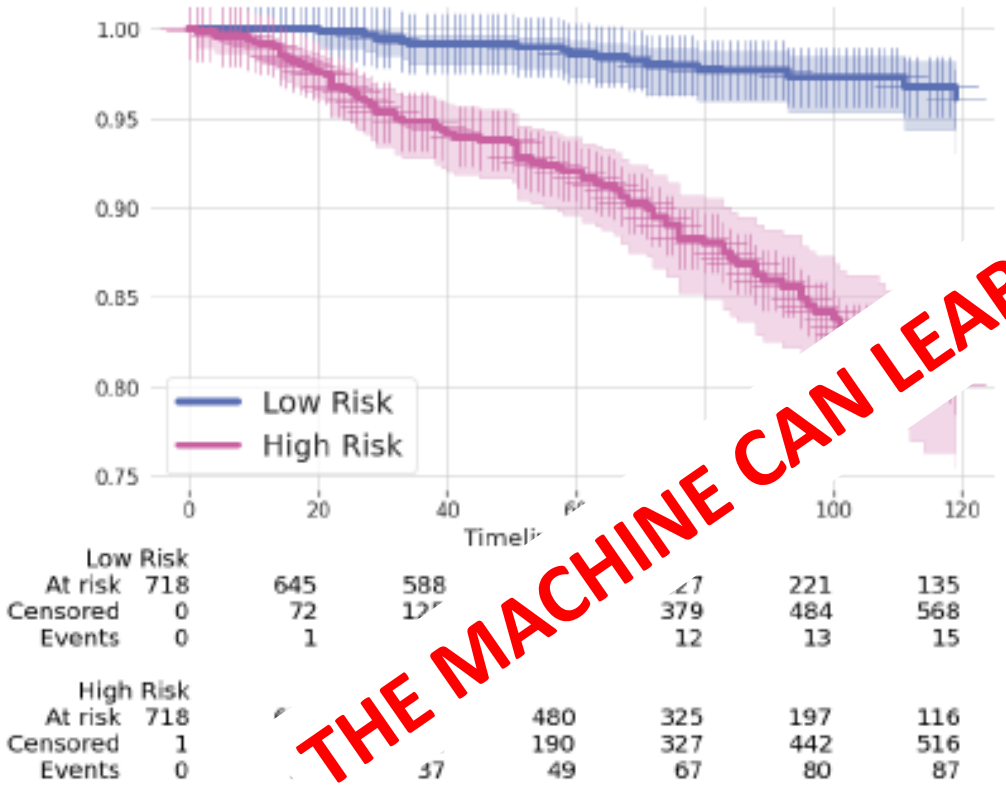
PRISM

Can pathology assisted by AI reduce healthcare disparities ?

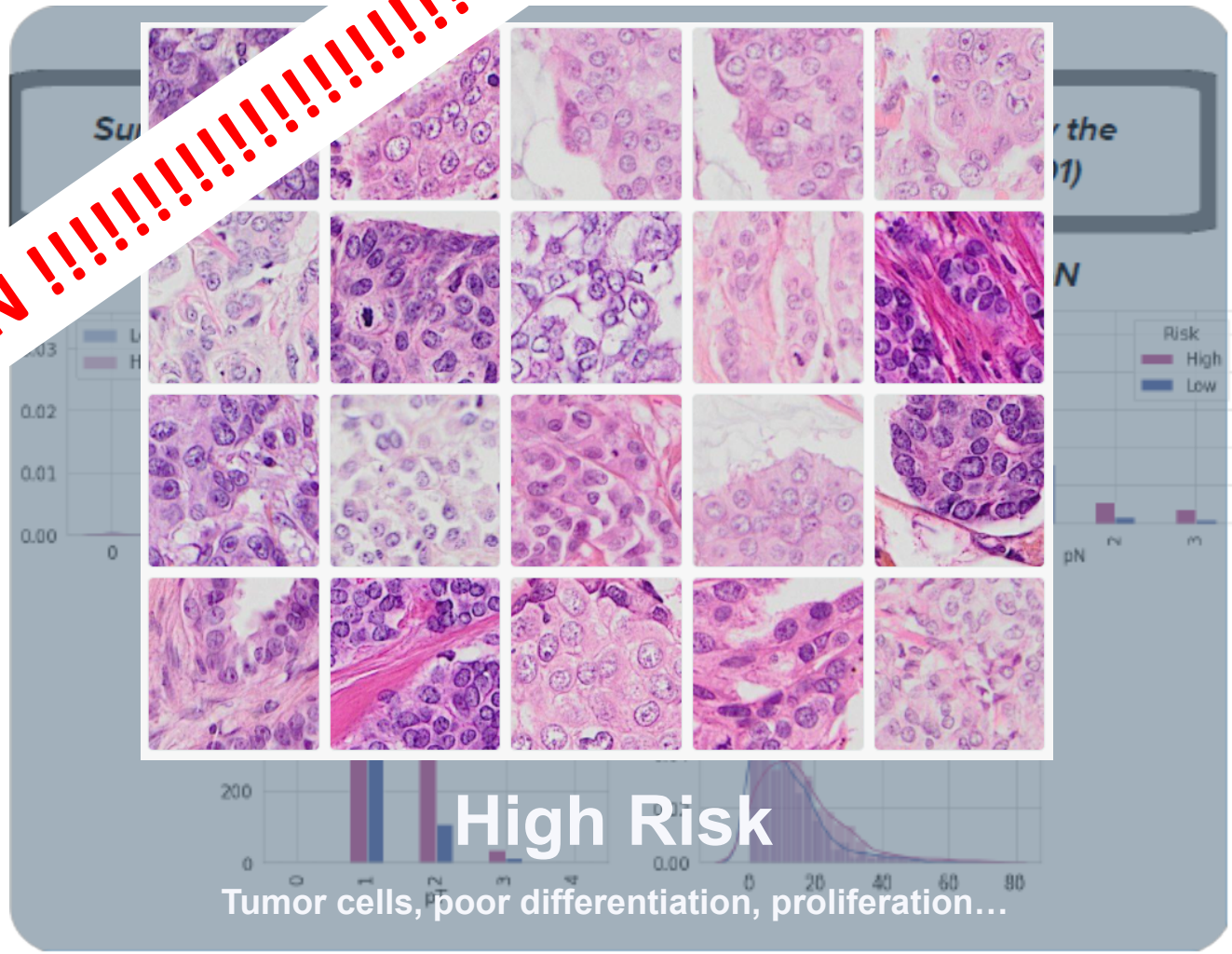
Applications:

New low-cost predictors (RlapsRisk BC)
Detect molecular targets (MSI, BRCA, ERBB2…)
Automatize difficult to read markers (Ki67)

AI model to predict relapse in patients with HR+/Her2- early stage Breast
Machine was asked to learn which features from HES slides are asso **n relapse**



THE MACHINE CAN LEARN !!!!!!!!!!!!!!!!!!!!!!



Garberis, ESMO, 2021

PortrAIt a French consortium to accelerate precision medicine with AI-enabled digital pathology solutions, funded by BPI

Financé par l'Union européenne NextGenerationEU

2 industrial actors

OWKIN tribun HEALTH

4 Partner Centers / Networks

unicancer · GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS · cypath cabinet de pathologie · CENTRE LEON BERARD

33M € budget

5 years project

PortrAIt Lab: a collaborative **platform** to **accelerate and optimise** the development of AI diagnostics models

15 CE-marked digital pathology models in 3 indications:

- → breast cancer
- → lung cancer
- → multi-cancers

- Outcome Prediction
- Biomarker Pre-Screen
- Pathologist enhancements

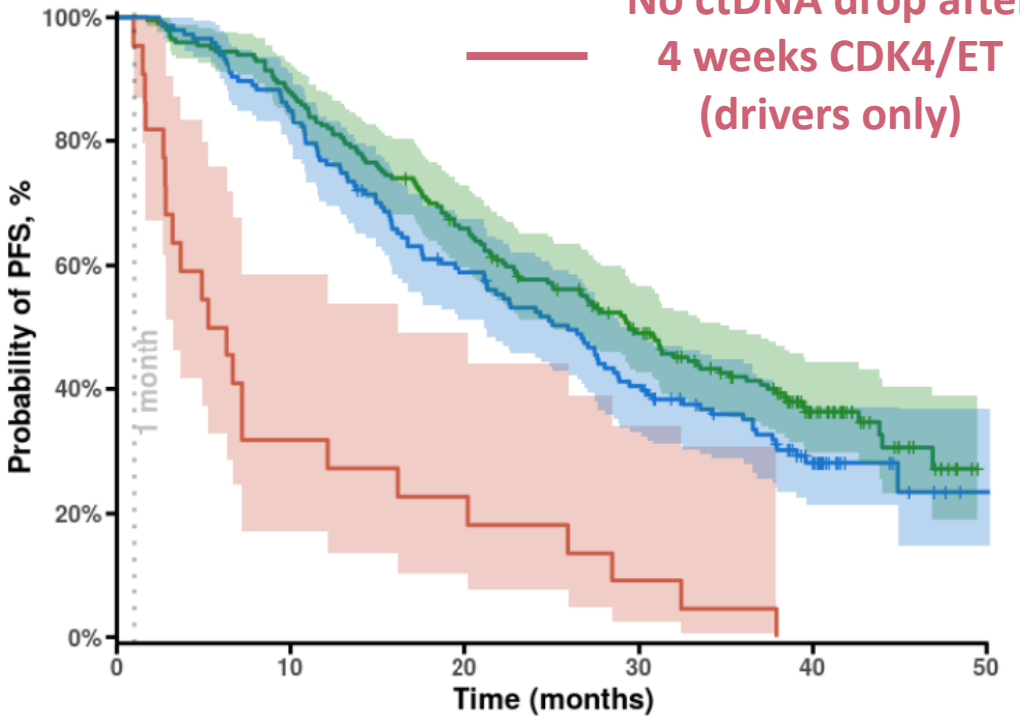
A digital pathology **marketplace**, accessible in **30+ centers (incl. the full Unicancer network)**

ctDNA to identify patients with high risk of cancer death or validated genomic alterations

Why does it decrease healthcare disparities ?

Avoid the need for interventional radiology or specialized center
Assess the outcome and therefore drive patients to innovations

Clinical utility of circulating tumor DNA sequencing with a large panel: Early detection of hard-to-treat cancers (SAFIR03)

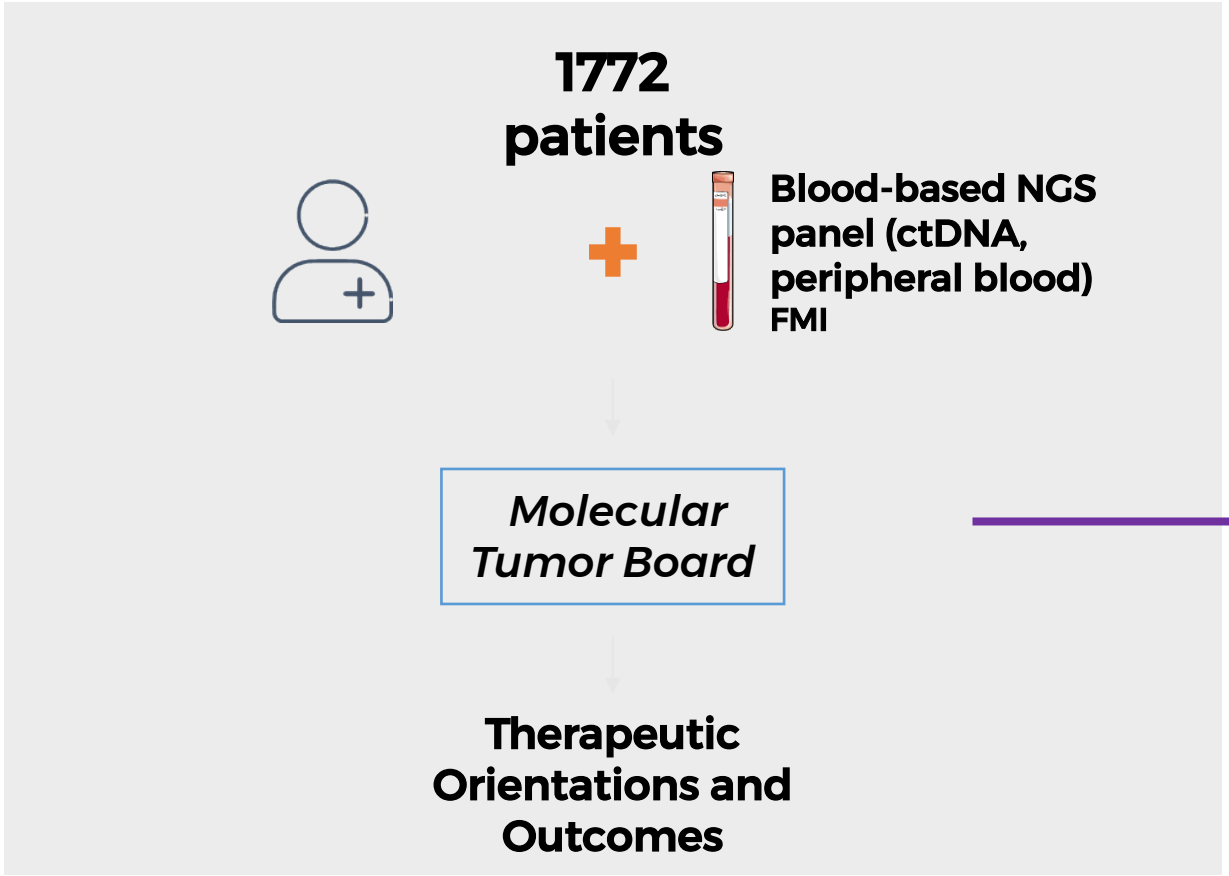


No ctDNA drop after 4 weeks CDK4/ET (drivers only)

EARLY Access to Innovatoin

PD17-02, Bailleux et al

Clinical utility of circulating tumor DNA sequencing with a large panel: Targetable genomic alterations (STING)



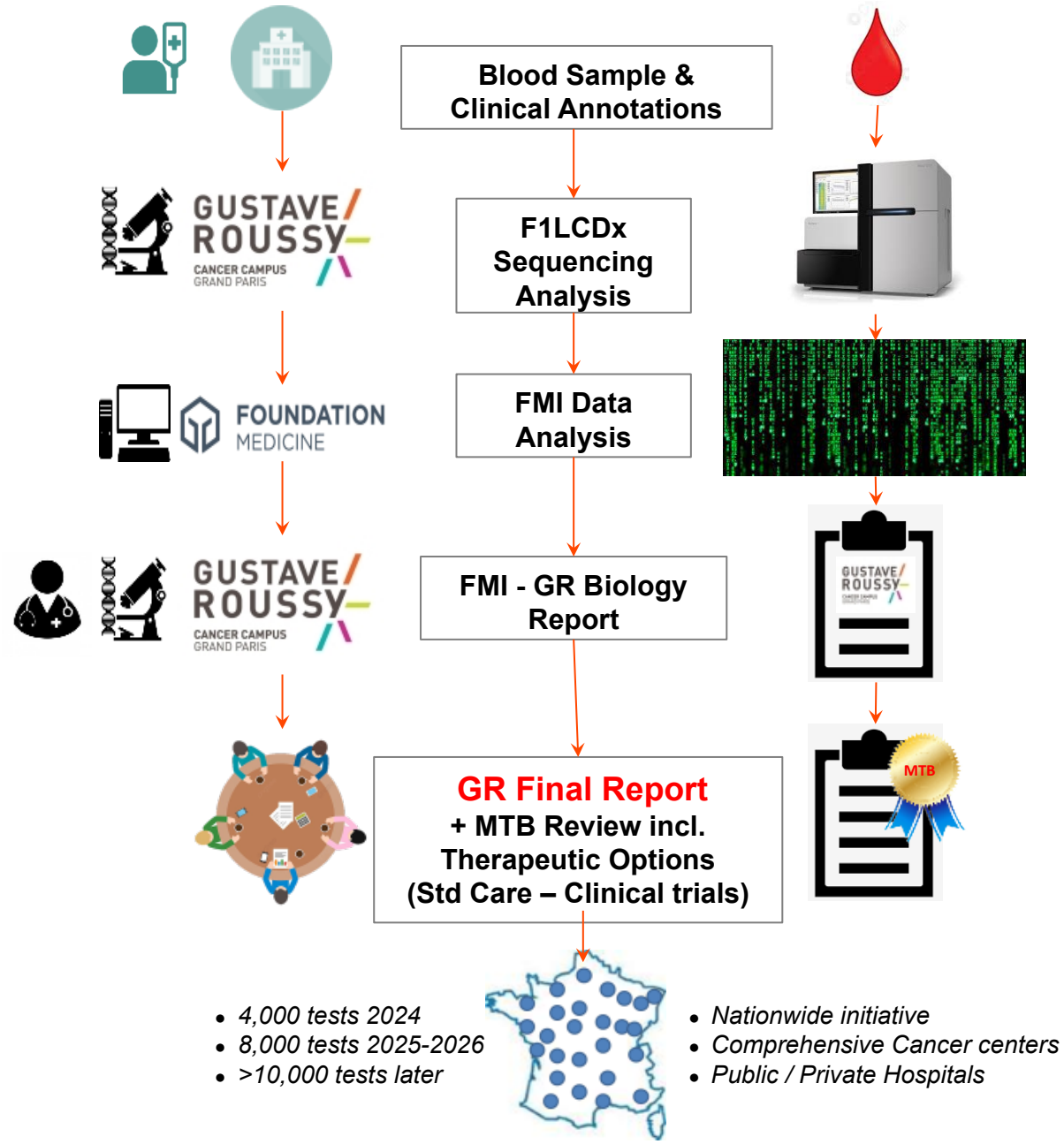
1.1% (N=19) were MSI high

Bayle et al; AACR 2022 Session PO.CL11.03

Gustave Roussy - Roche – Foundation Medicine Partnership

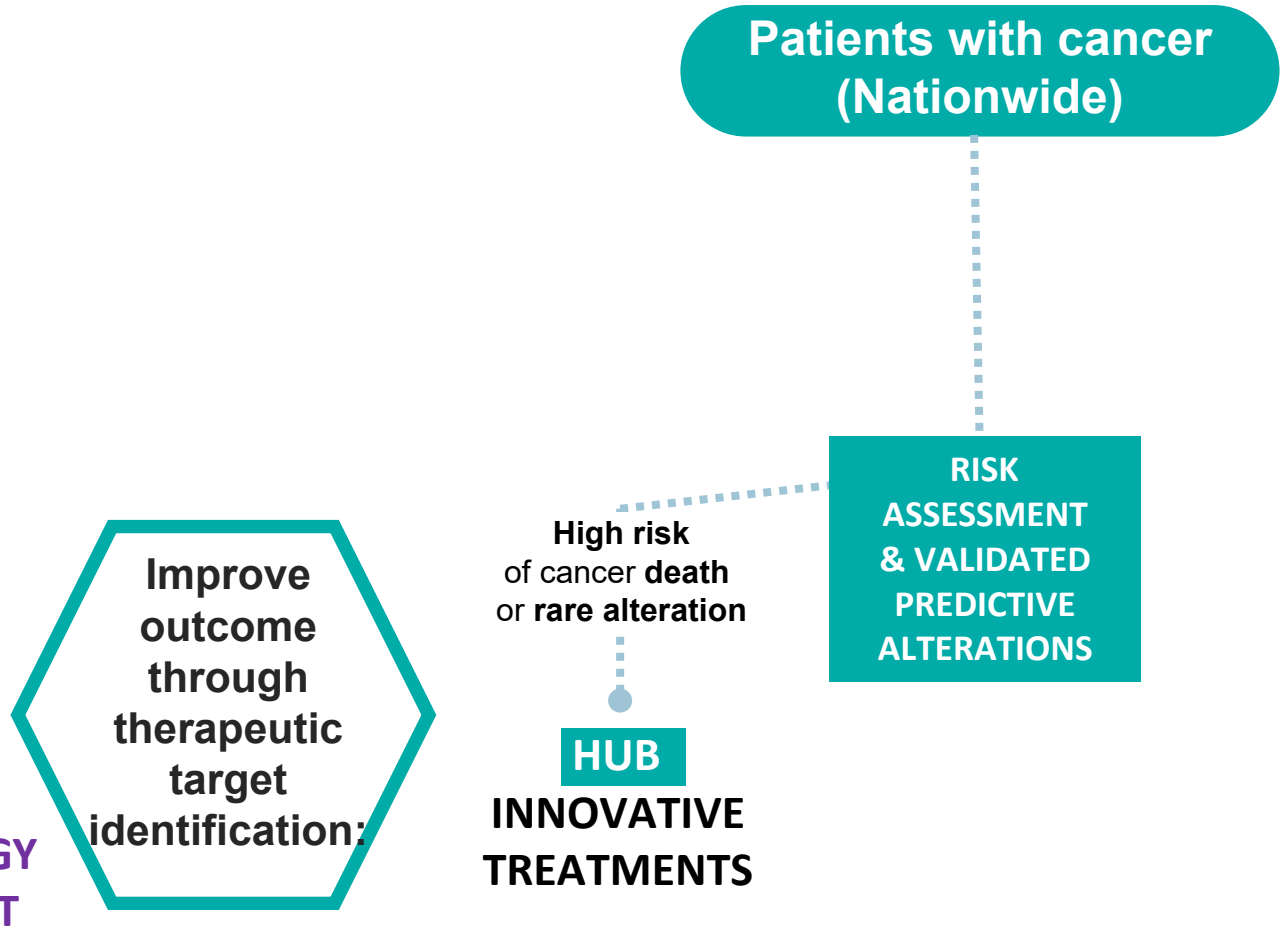
Our common ambition : extend french patients access to liquid-based comprehensive genomic profiling (CGP) beyond expert centers

- Promote precision medicine toward the oncology community
- Give opportunities and patients' ethical access to innovation (biomarker-driven clinical trials)
- Facilitate translational research programs by building very large clinically-annoted molecular databases
- Demonstrate and support value recognition by HTAs and national authorities
- Ambition: >10 000 patients per year



CLINICAL RESEARCH:

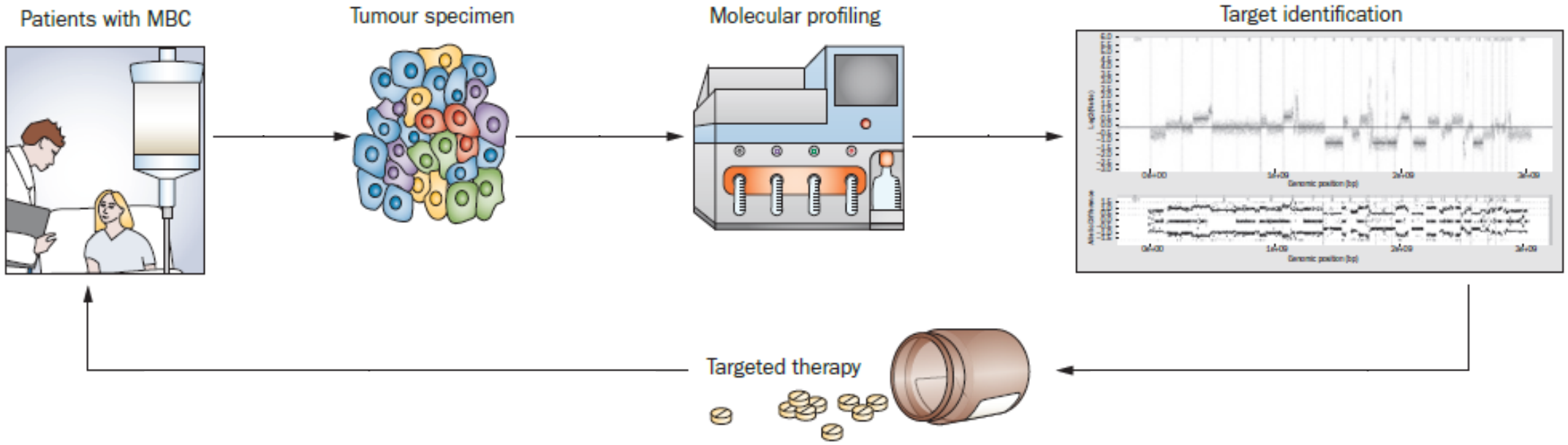
"SCREEN AND CHARACTERIZE" APPROACH



= MODEL BIOLOGY IN EACH PATIENT

PRISM

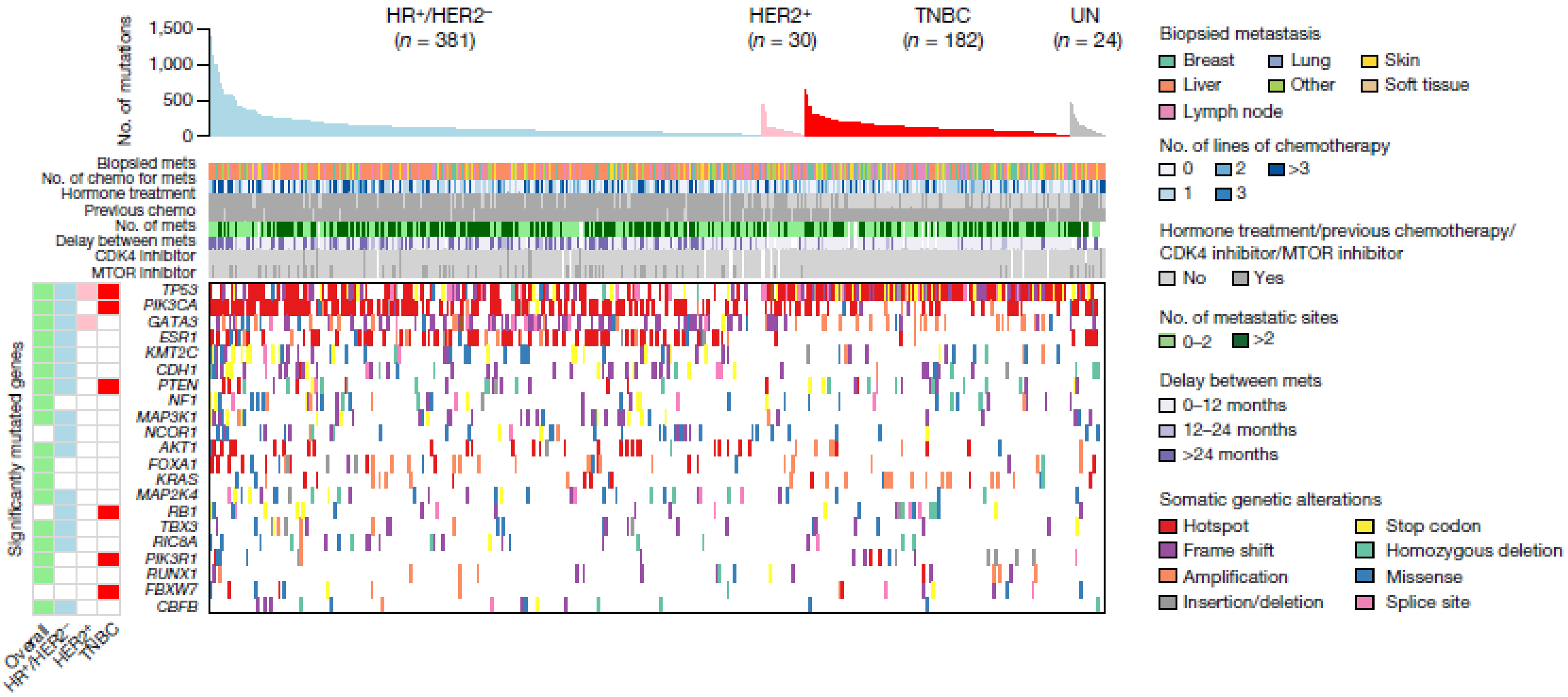
Hypothesis: if we identify the mechanisms of cancer progression or mechanism of drug sensitivity in each patient, it should improve PFS and OS



Arnedos et al, Nat Rev Clin Oncol, 2015

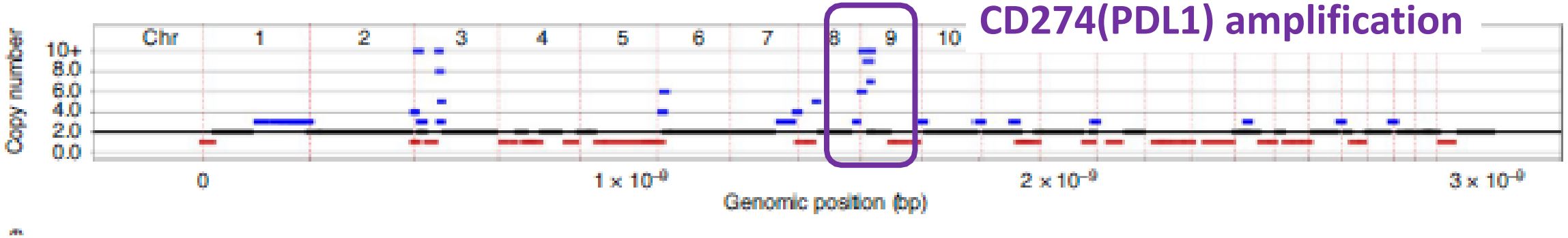
Cancer Modelling I :
Sequencing coding regions of DNA (= DNA sequencing)

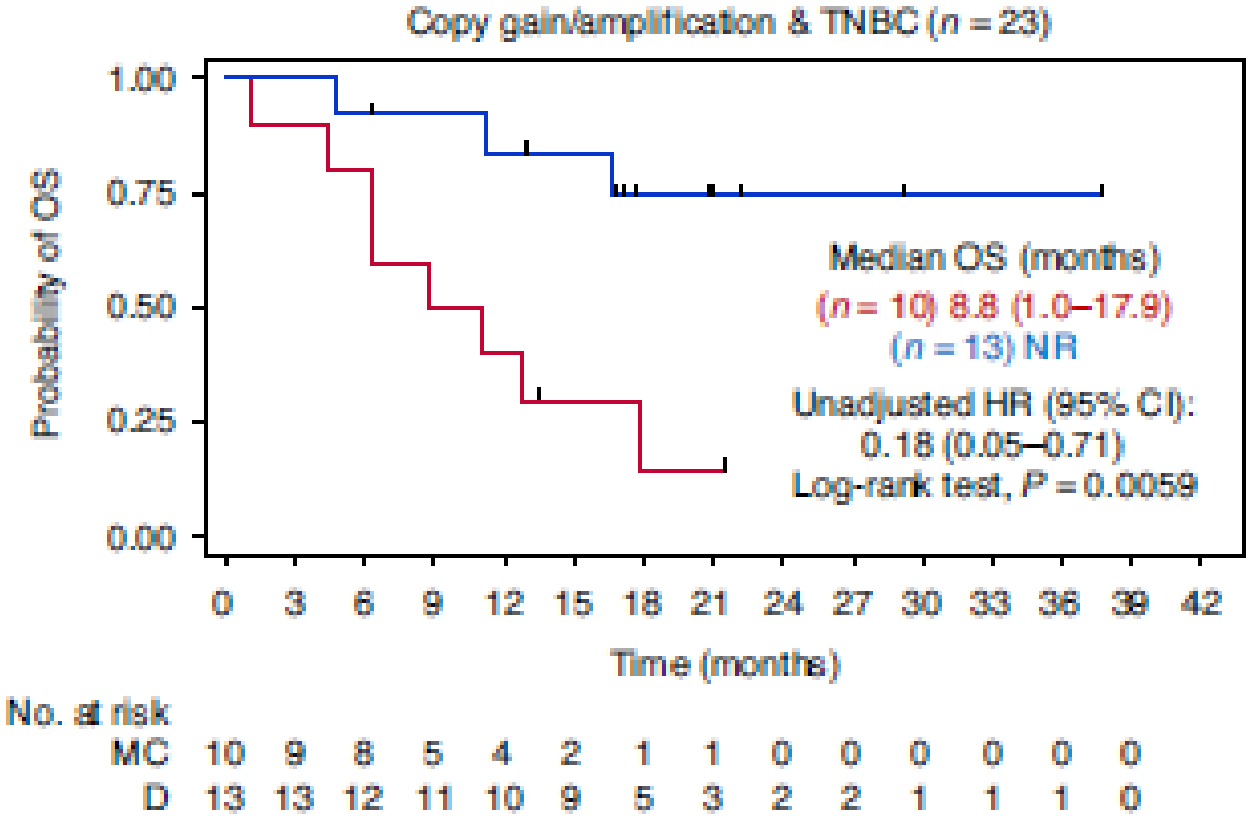
Are they recurrent genomic drivers in metastatic breast cancers ?



Bertucci, Nature, 2019

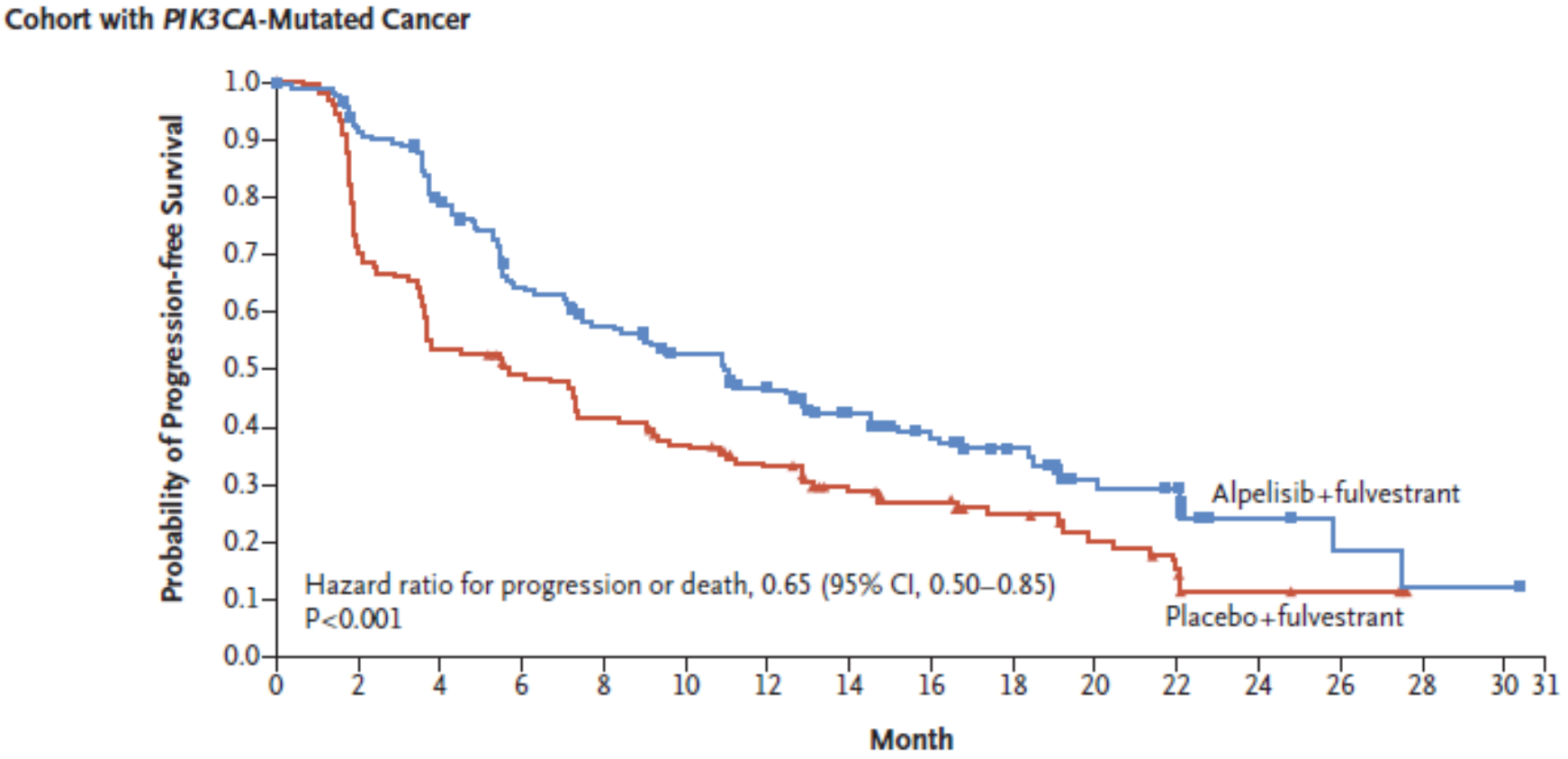
Are genomic alterations only involved in cancer cell biology ?





Bachelot, Nat Med, 2021

What is the impact of targeting the protein encoded by a driver alteration in BC ?



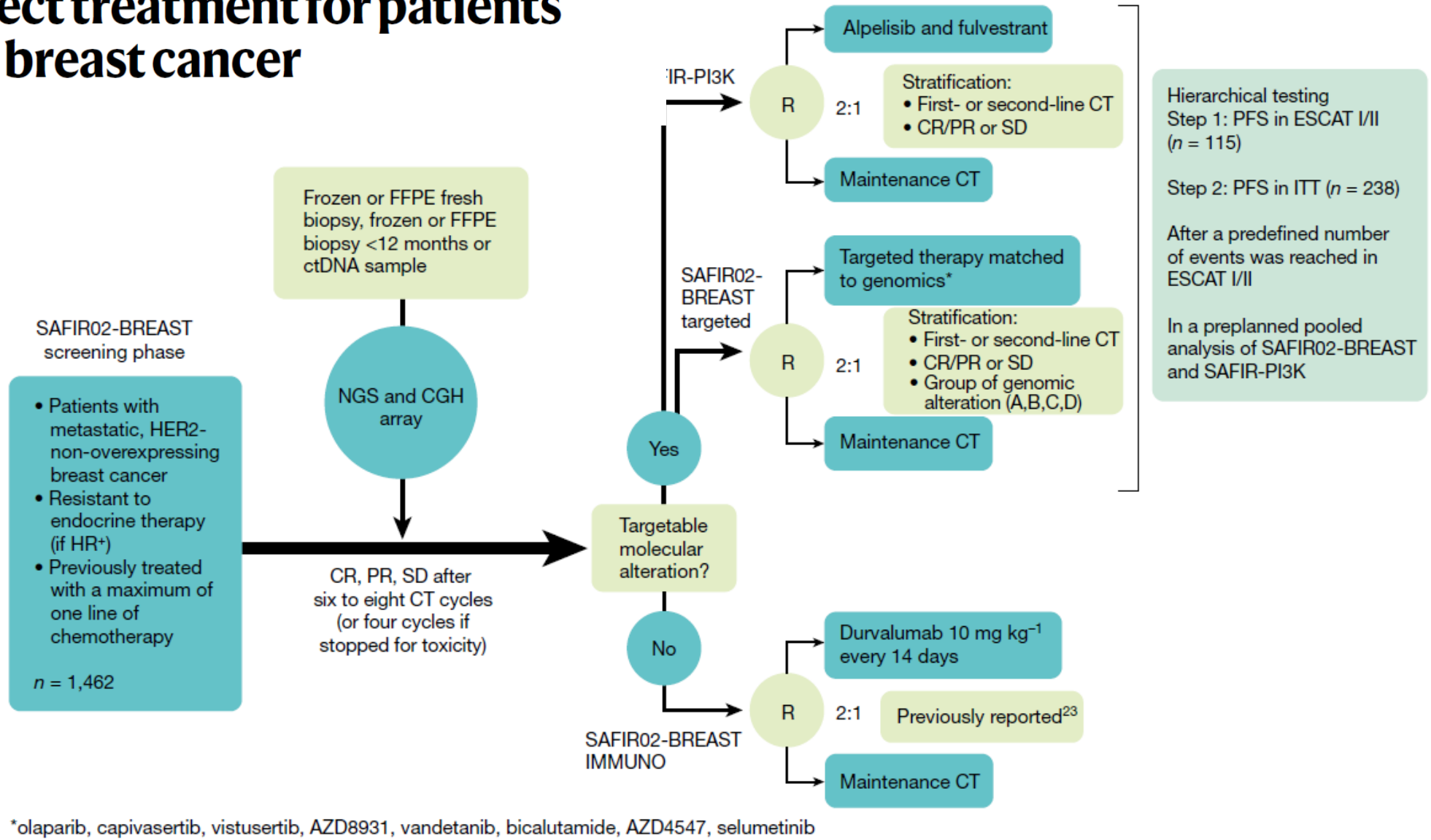
Andre F, NEJM, 2019

Targeting recurrent validated genomic drivers leads to tumor responses and improved PFS in patients presenting the alteration, but not in the population without the alteration

There is a need to perform genomic testing in patients with metastatic breast cancer

What is the benefit of multigene sequencing ?

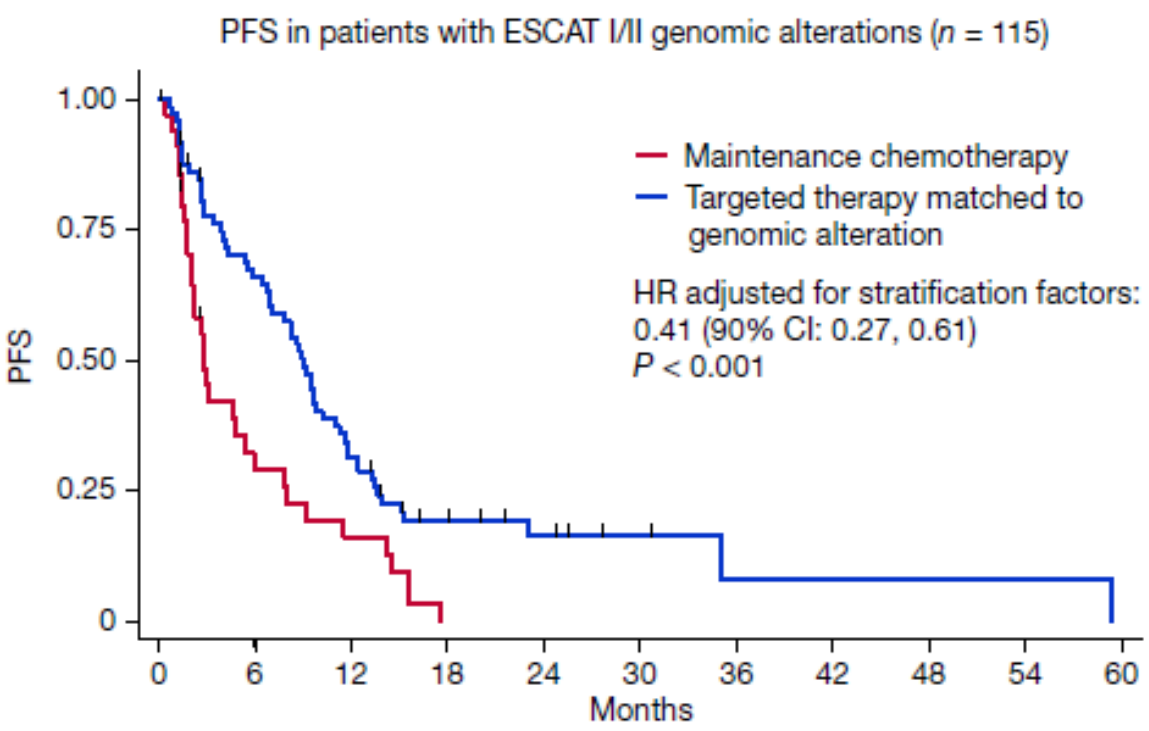
Genomics to select treatment for patients with metastatic breast cancer

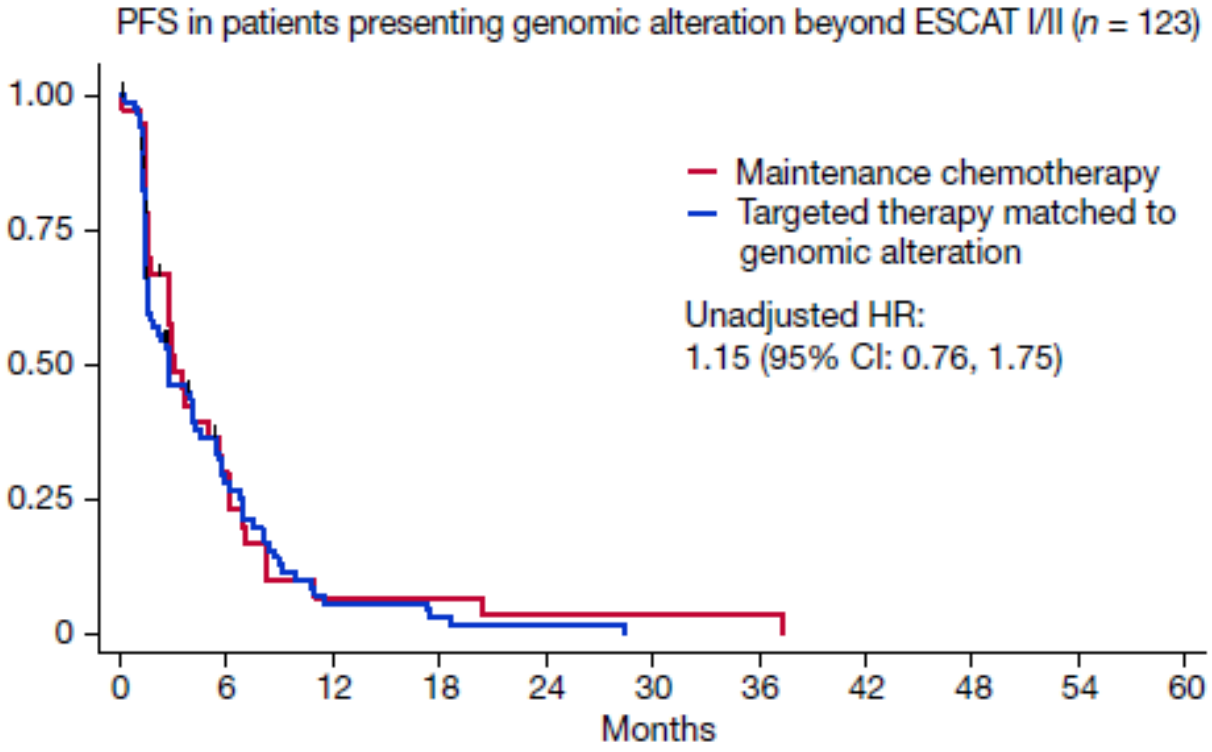


Andre, Nature, 2022

Article

Genomics to select treatment for patients with metastatic breast cancer





It is useful to perform multigene sequencing IF analysed with the right framework of target classification

Andre, Nature, 2022

Summary

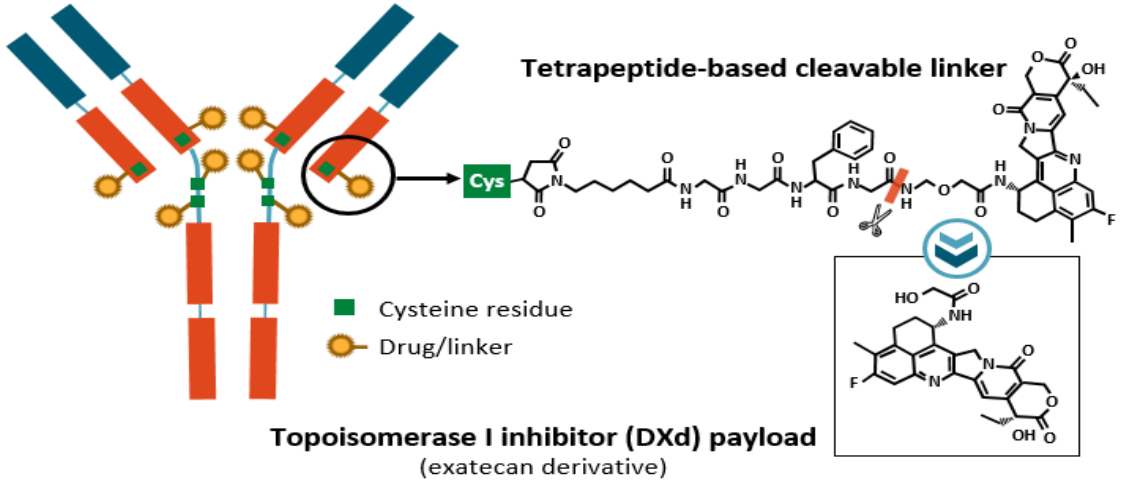
- Genomics is useful is around 10% of patients with metastatic cancer (maybe a little bit more in mBC because of PIK3CA)
- Genomics has reached a plateau
- What are the next technologies to model cancer biology and develop precision medicine ?

Assessing new dimensions of the biology for treatment selection

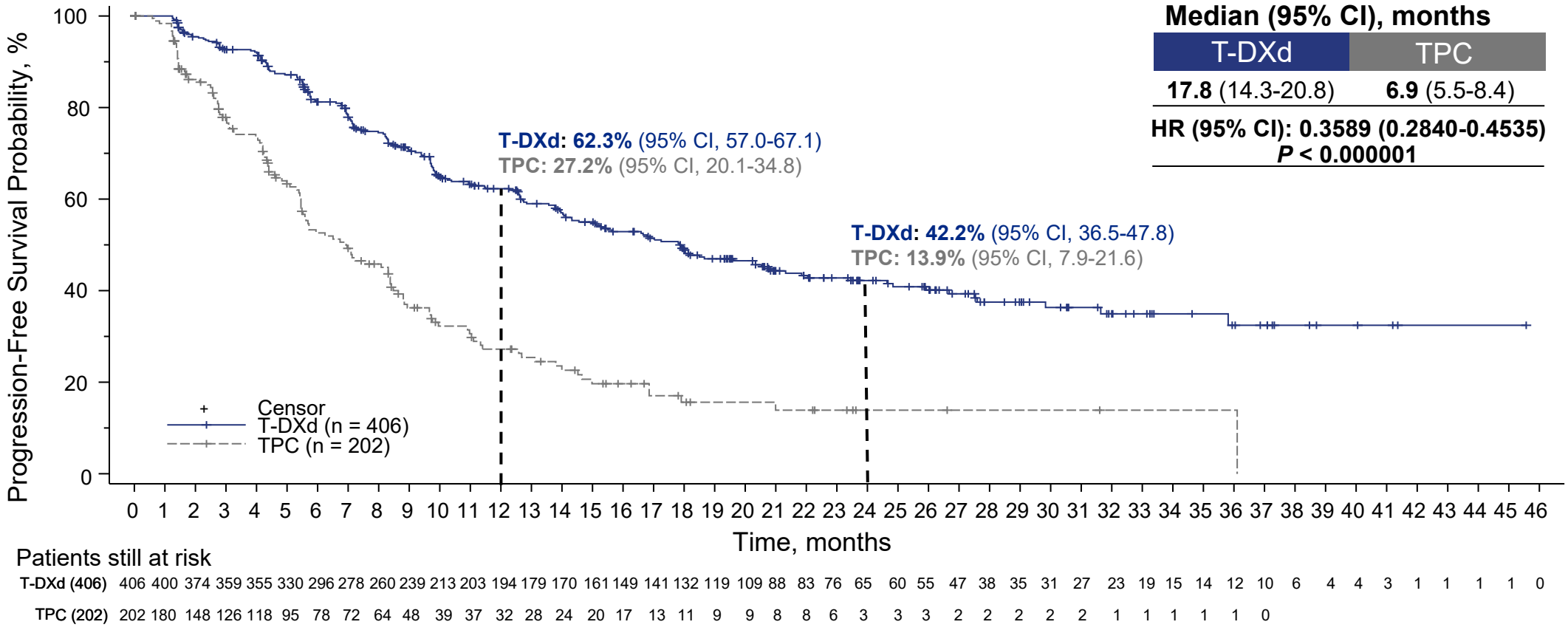
- Linking ATAC seq / CHIP seq with epigenetic reprogramming
- **Predicting sensitivity to biotechnological therapeutics by spatial biology**
- Monitoring cancer adaptation to new therapies by CTCs
- Organoids
  - Cancer cells
  - Cytotoxic T cells

Illustration I: T-DXd

- **Antibody:** Monoclonal humanized anti-Her2 IgG1
- **Linker:** Cleavable linker (Gly-Gly-Phe-Gly)
- **Payload:** Topoisomerase I inhibitor
- **DAR:** ~8:1



Trastuzumab deruxtecan in patients with Her2 3+ mBC



Andre F, Lancet, 2023

DAISY: Study Design

- Patients with mBC*
- ≥ 18 years old
- ≥ 1 chemotherapy regimen in metastatic setting

COHORT 1 HER2 overexpressing: HER2 IHC 3+ or IHC 2+/ISH+ (*n*=72)

COHORT 2 HER2-low: HER2 IHC 2+/ISH- or IHC 1+ (*n*=74)

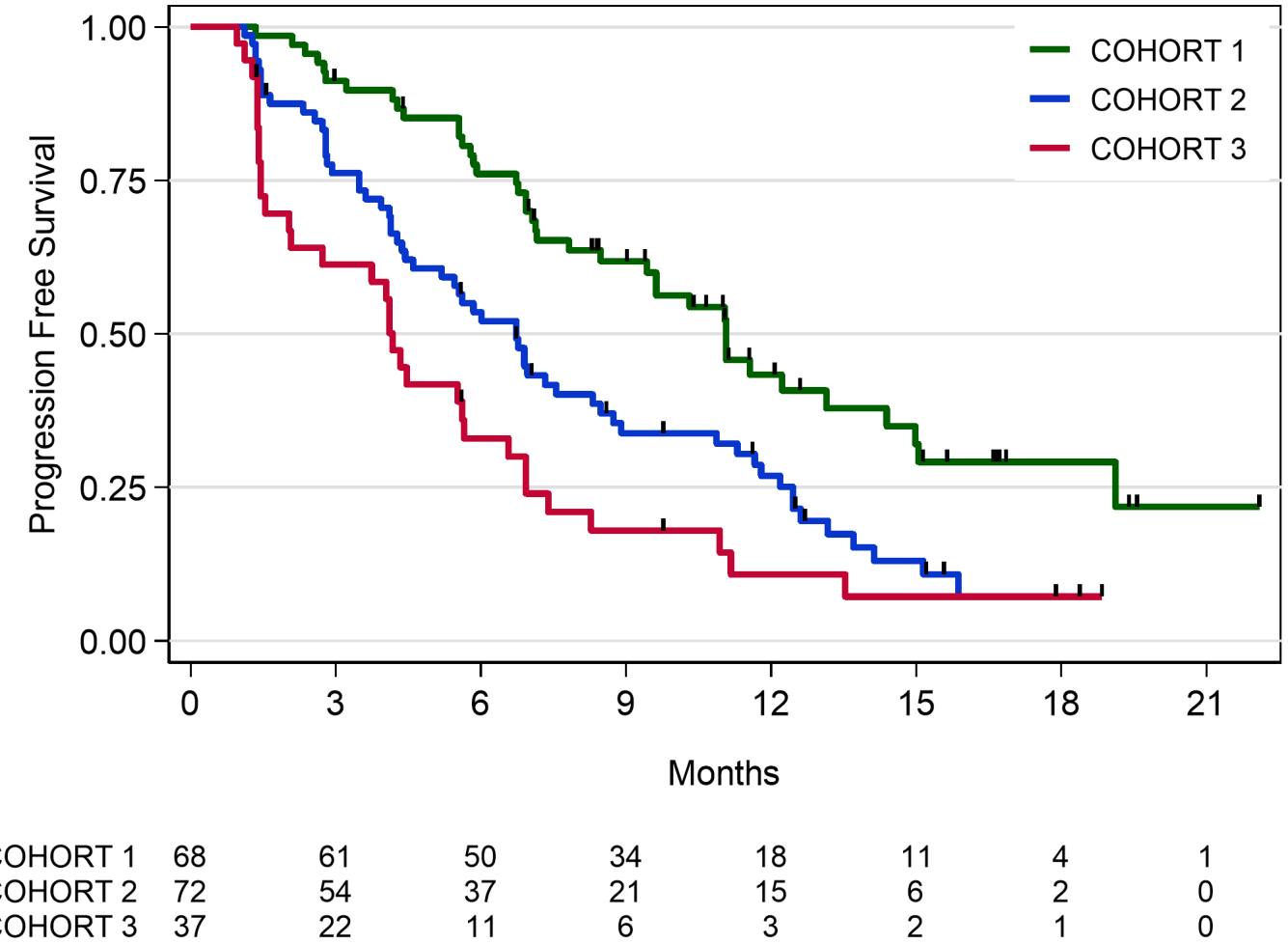
COHORT 3 HER2 non-expressing: HER2 IHC 0 (*n*=40)

T-DXd IV 5,4 mg/kg Q3W
Upon PD or unacceptable toxicity

Mosele, Nat Med, 2023

Drug efficacy is driven by Her2 expression

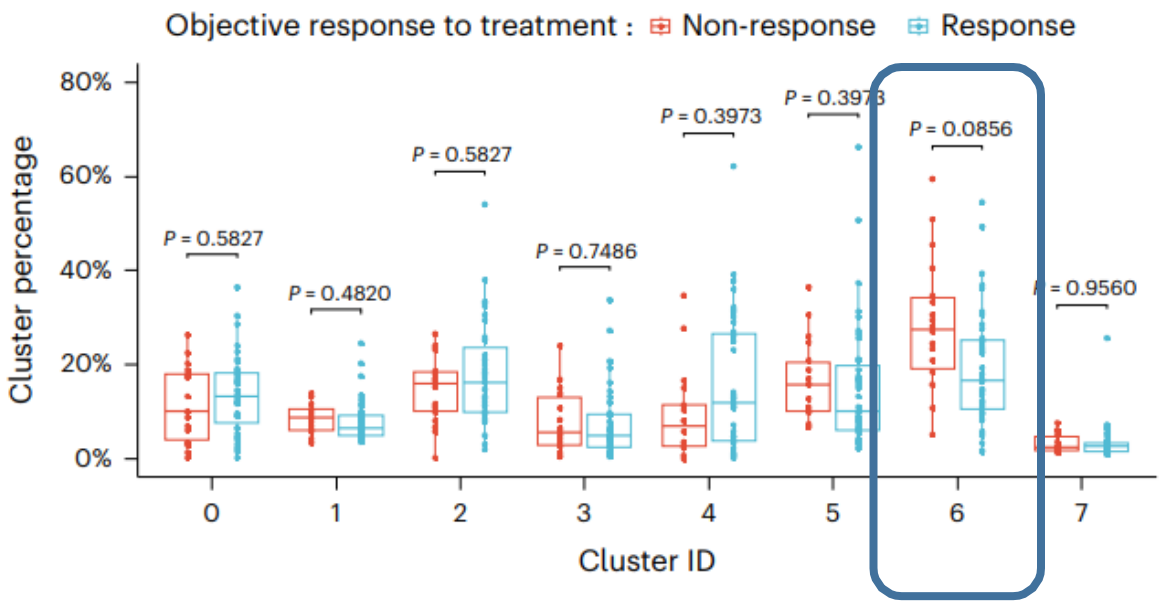
Data cut-off: Oct 19, 2021	Cohort 1 HER2 IHC 3+ or IHC 2+/ISH+ (n=68)	Cohort 2 HER2 IHC 2+/ISH- or IHC 1+ (n=72)	Cohort 3 HER2 IHC 0 (n=37)
Median PFS (mths) (95% CI)	11.1 (8.5–14.4)	6.7 (4.4-8.3)	4.2 (2-5.7)
HR (95% CI)	0.53 (0.34-0.84)	1.00	1.96 (1.21-3.15)
***p*-value**	***p* <0.0001**		

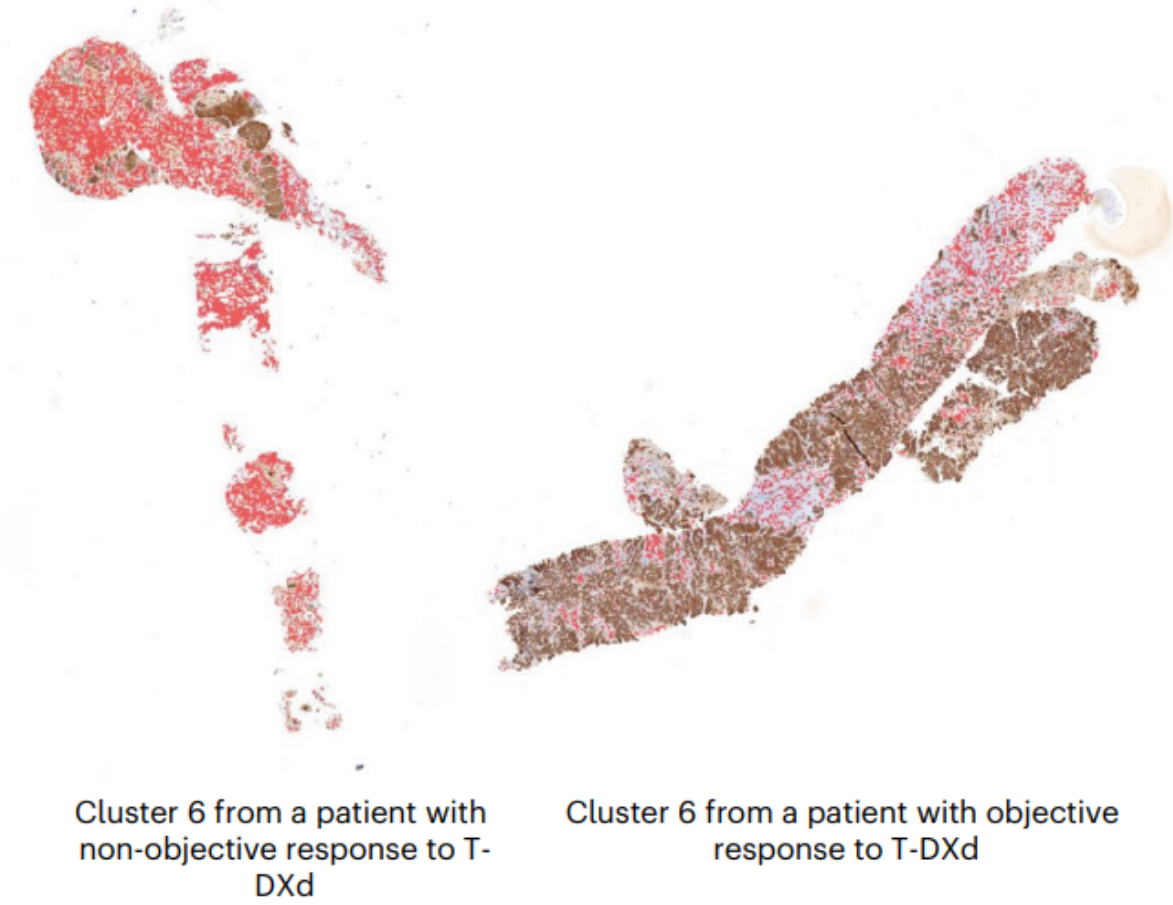


Mosele, Nat Med, 2023

NCT04132960

Large Her2-null area is associated with lower response rates in patients with Her2-overexpressing cancers





Cluster 6 from a patient with non-objective response to T-DXd

Cluster 6 from a patient with objective response to T-DXd

Mosele, Nat Med, 2023

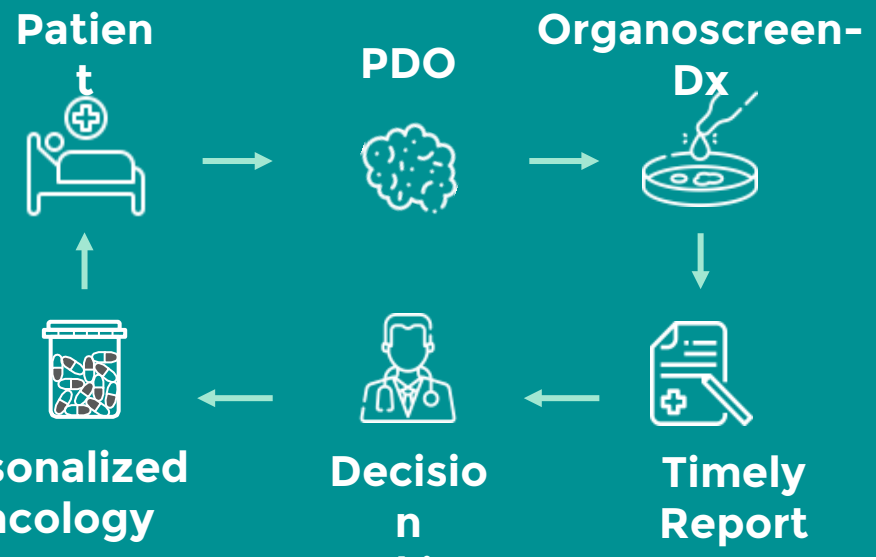
Assessing new dimensions of the biology for treatment selection

- Linking ATAC seq / CHIP seq with epigenetic reprogramming
- Predicting sensitivity to biotechnological therapeutics by spatial biology
- Monitoring cancer adaptation to new therapies by CTCs
- **Organoids**
  - **Cancer cells**
  - **Cytotoxic T cells**

ORGANOTREAT Clinical trial

	Phase :	Organ :	Patients
ORGANOTREAT-01	I/II	CRC	60 (GMI)
ORGANOTREAT-02R	III	PDAC	314
ORGANOTREAT-02R	III	CRC	582
ORGANOTREAT-02	II	Other	...

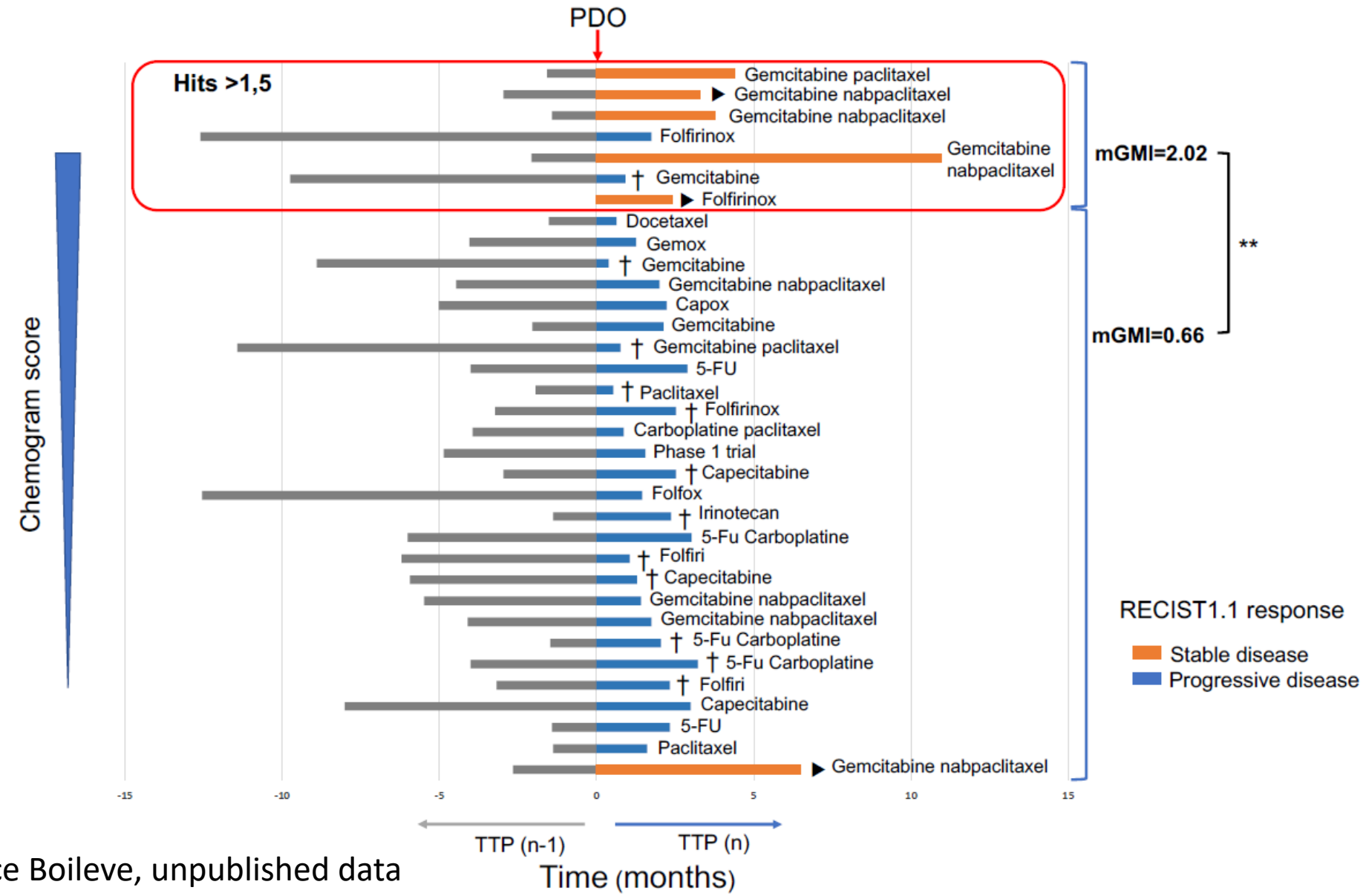
PI/Clinic: Pr Michel Ducreux
PI/Scientific: F. Jaulin



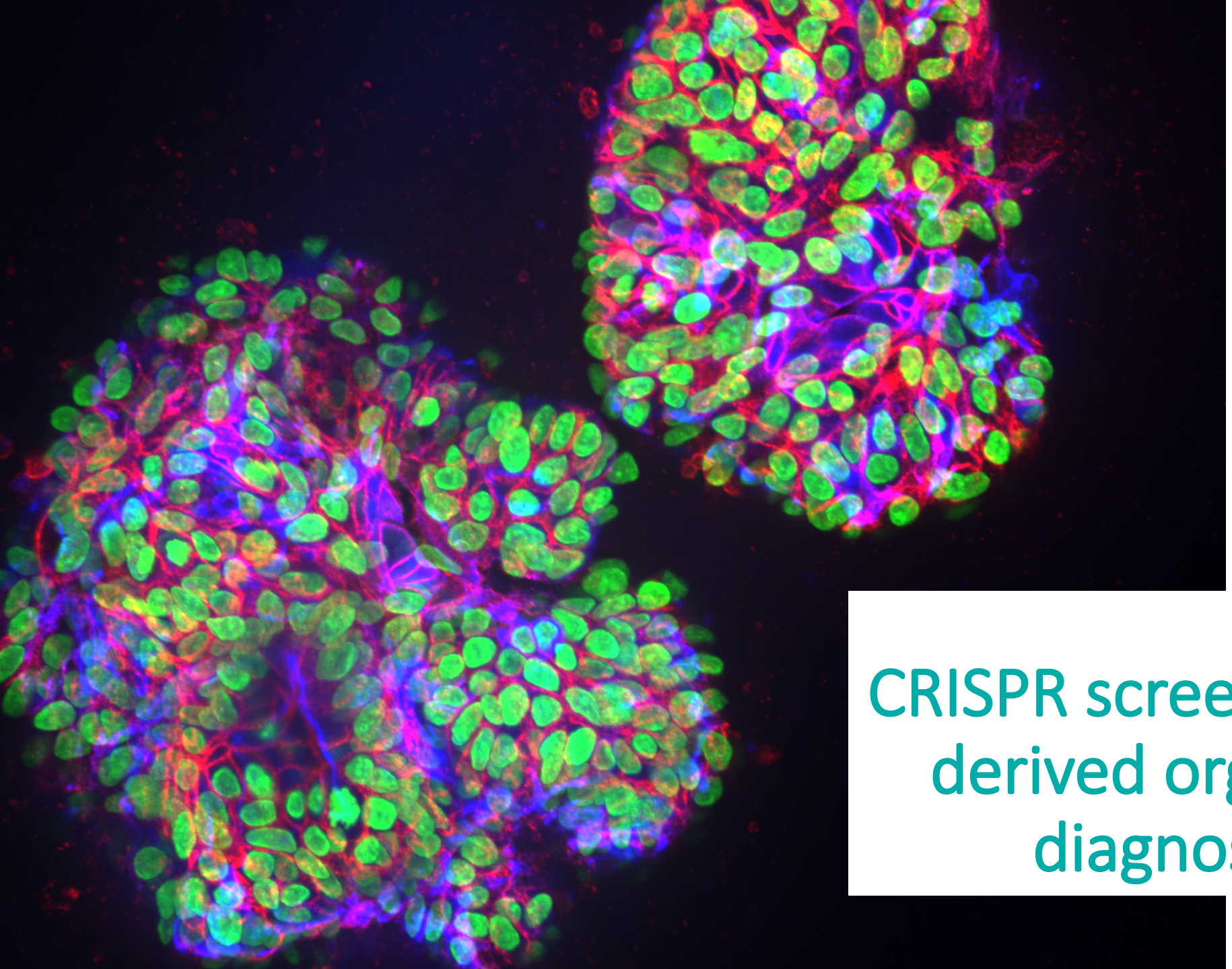
Interventional trial

ALL solid tumors, >1000 patients

Treatment guided by organoids is associated with stable diseases in patient with pancreatic cancer and high chemogram score

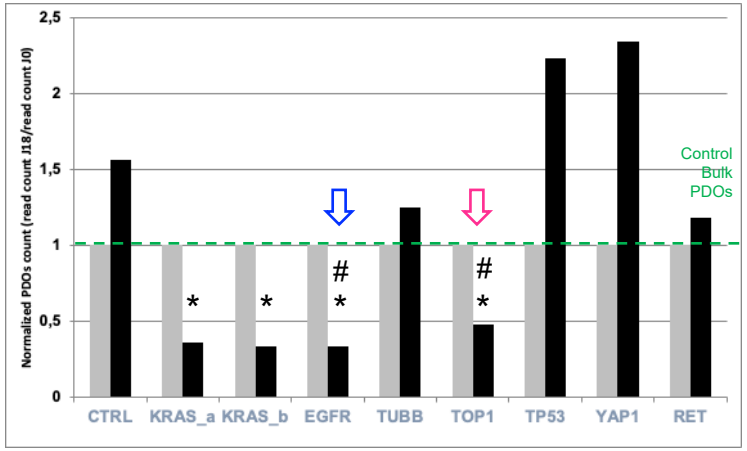


Fanny Jaulin & Alice Boileve, unpublished data



CRISPR screen on patient-derived organoids for diagnostic use

CRISPR-based screen in patient-derived organoids



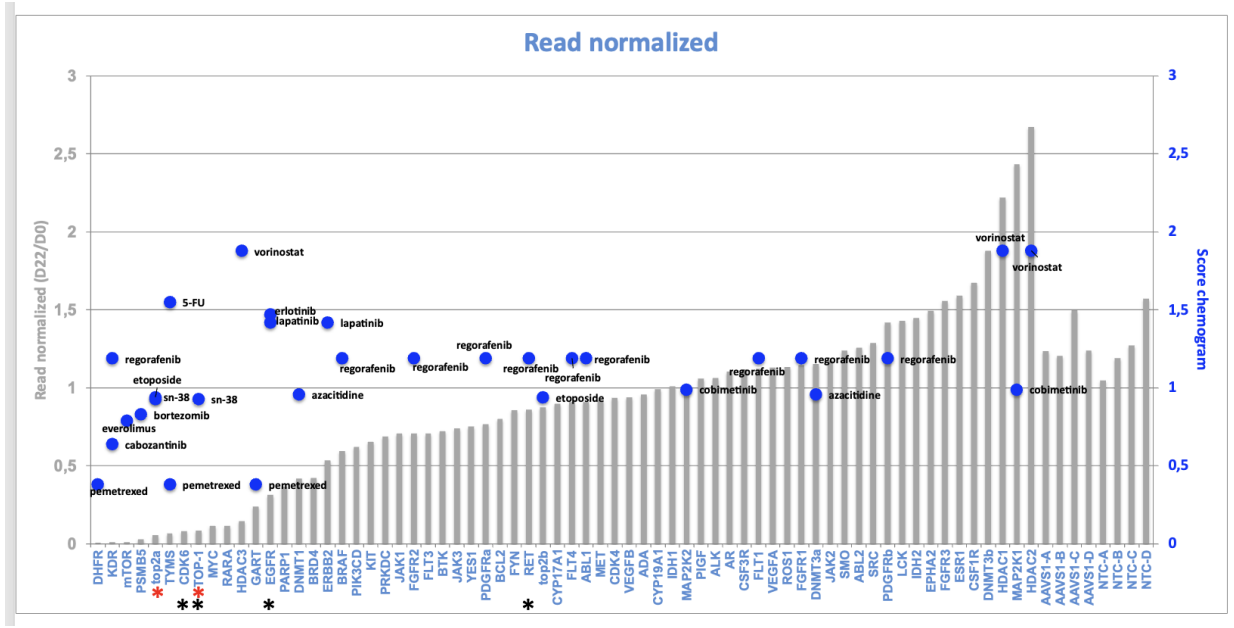
Targeted CRISPR screen on PDO from PDAC patient PGR-20

* hits => PDO growth is inhibited

\# could not be predicted based-on genomics

Sensitivity to EGFR confirmed by Erlotinib & Lapatinib

Sensitivity to TOP1 confirmed by Irinotecan



Here: PDAC PDO + “Druggable oncogenome” library (**66 genes**, Hu et al Biomaterials. 2022) Addgene#182133)

Fanny Jaulin & Alice Boileve, unpublished data

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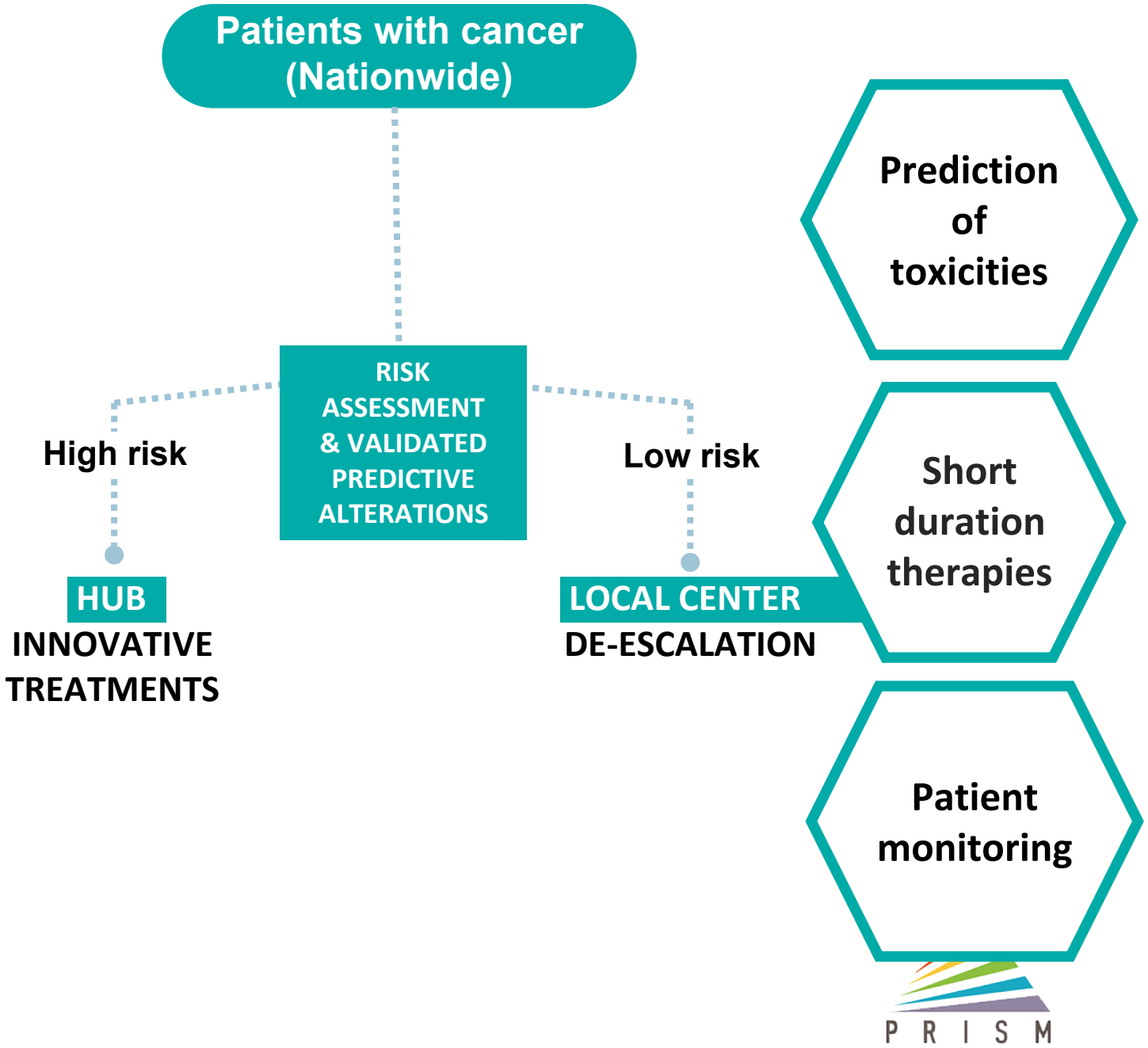
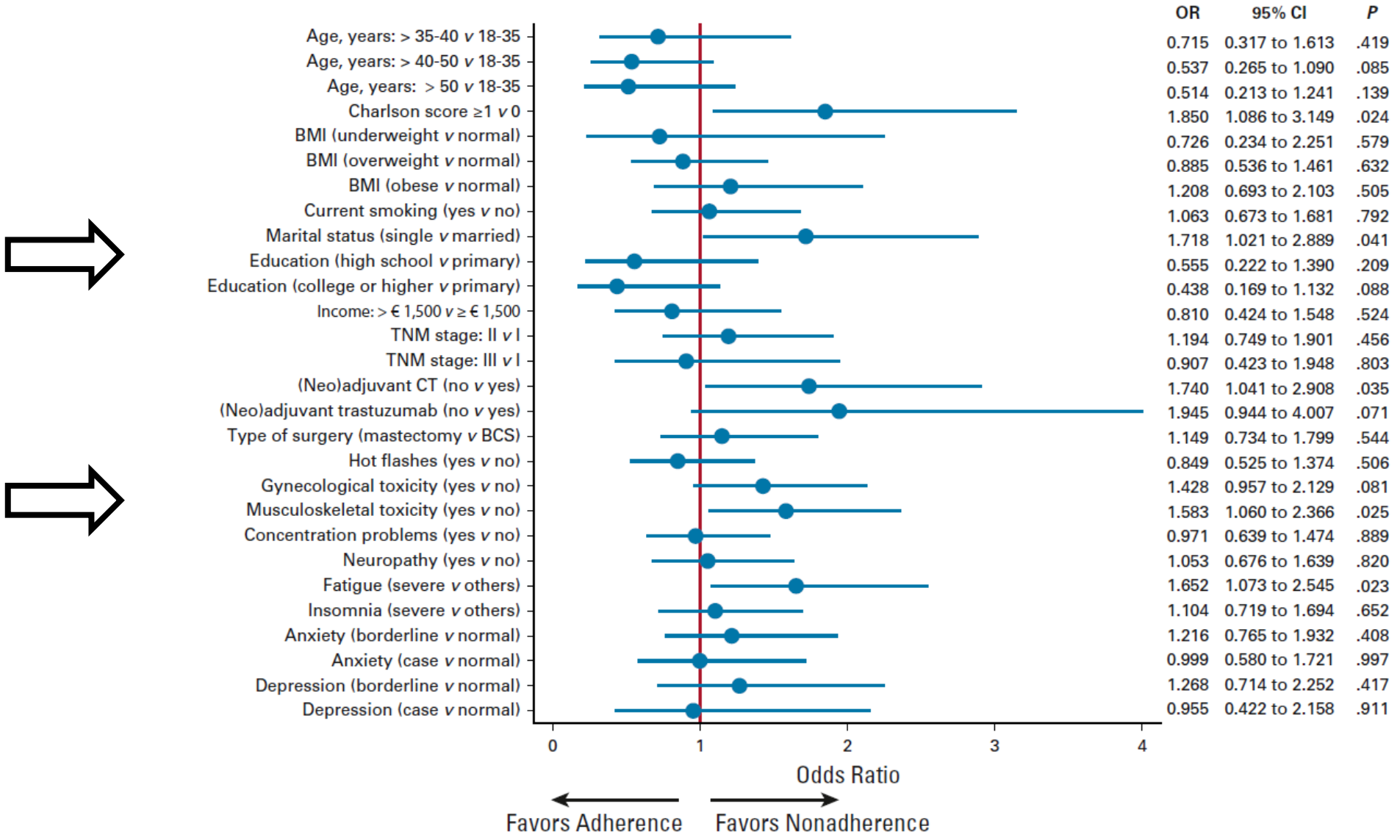


Social determinants of health and toxicities are associated with lower adherence to therapy



Pistilli, J Clin Oncol, 2020

Can shorter therapies cure patients ?

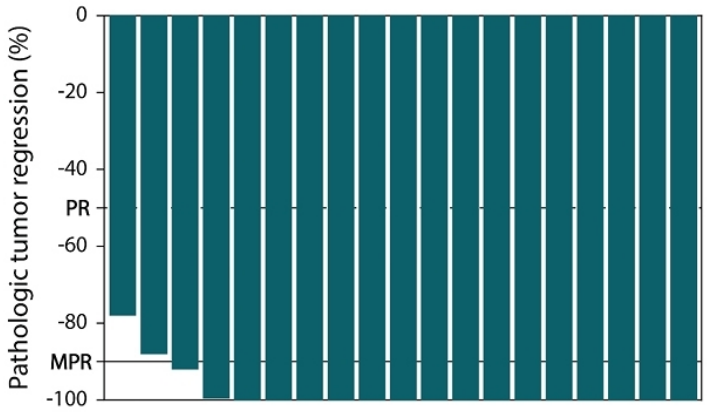
- Short duration therapies in patients with excellent outcome (LESS, UNICANCER, PI: E Deluche)
- Short duration therapies in patients with outlier reponse to new drug (POP-DURVA, PRISM, PI: J Ribeiro)
- Impacts:
  - Reduce compliance issues
  - Reallocate resources to patients with high unmet medical need

Can short duration IO cure some patients selected by biological markers ?

MMR-deficient colon cancers

Pathologic response in 100% of patients; 79% pCR

The primary endpoint was met in stage I with a pathologic response rate of 100%

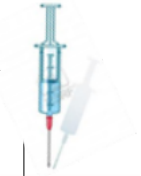


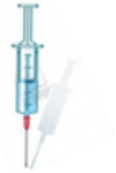
Pathologic response (RVT)	Patients *n* = 19
Yes (≤50%)	19 (100%)
Major (≤50%)	17 (89%)
Complete (0%)	15 (79%)
Partial (10-50%)	2 (11%)
No (>50%)	0

Adjuvant chemotherapy
All patients had ypN0 disease at resection and no patients received adjuvant chemotherapy

POP-Durva

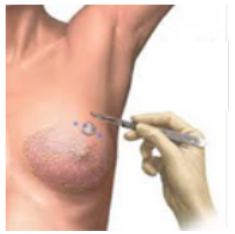
Eligibility criteria
- TNBC
- TILs ≥ 5%





Durvalumab Q2w x **2 cycles**
10 mg/Kg

4 weeks



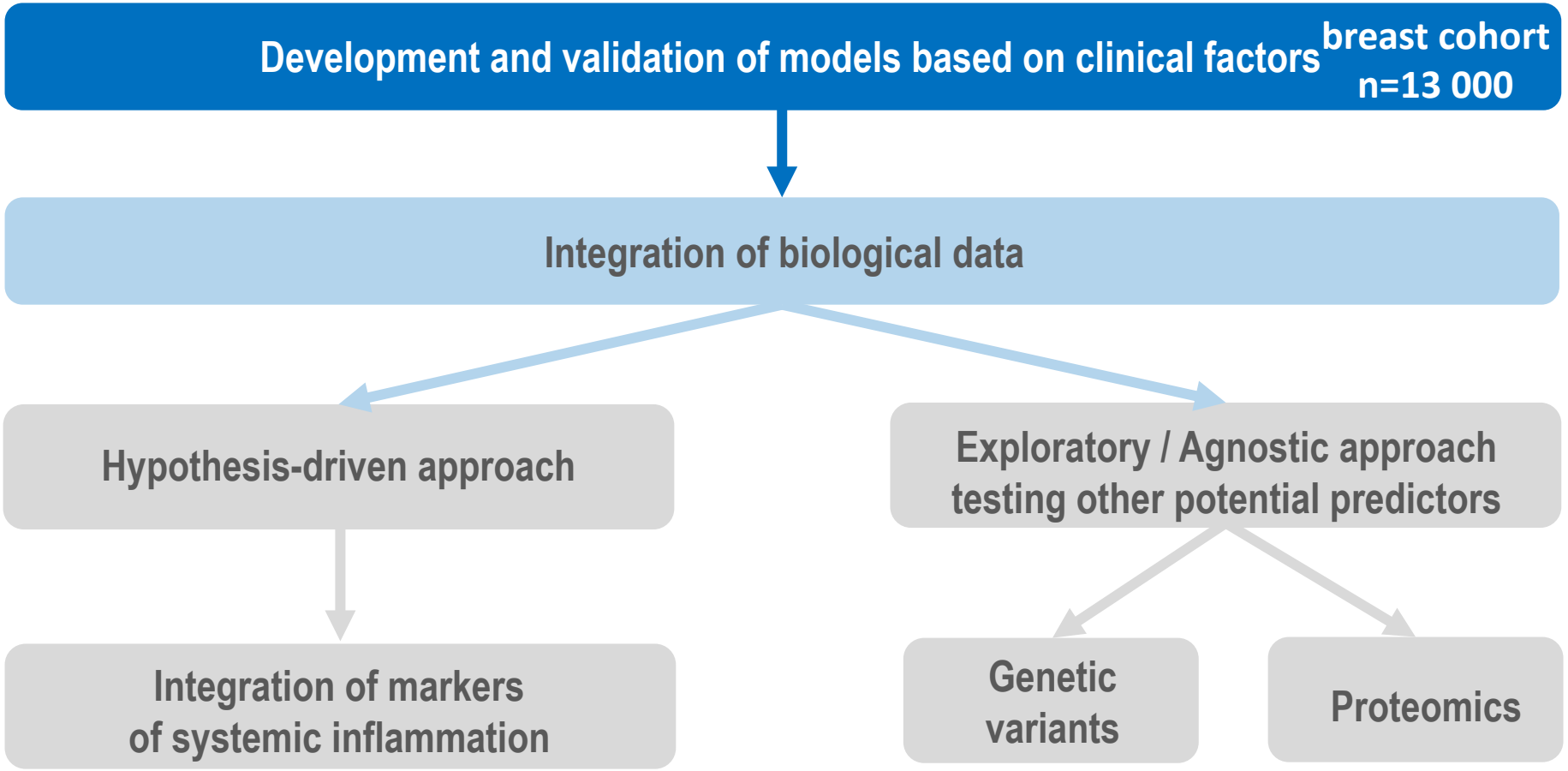
-30 D1 D15 D22 Surgery

Can biology predict risk of toxicities ?

WHY ????

To provide supportive care or to substitute with a less toxic drug in order to improve QOL and improve adherence

Building a bio-behavioral predictor of long-term cancer & treatment related fatigue among survivors



cantoj
CANcer TOxicities

Di Meglio & Vaz Luis, personal communication

Building a bio-behavioral predictor of long-term cancer & treatment related fatigue among survivors: The triade Inflammation-biological aging-frailty

Systemic inflammation (n=1373, 16 markers + metabolic sd array)

Variable	Odds Ratio	95% CI		p
Severe fatigue at diagnosis, Yes vs. No	3.99	2.81	5.66	<.0001
Age, continuous	0.98	0.97	0.99	0.0021
Tobacco use behavior, Former vs. Never	0.96	0.68	1.35	0.7991
Tobacco use behavior, Current vs. Never	1.81	1.26	2.58	0.0012
Pain, continuous	1.01	1	1.02	0.0023
Insomnia, continuous	1.01	1	1.01	0.0002
IL-6, middle low vs. low	1.27	0.87	1.86	0.2234
IL-6, middle high vs. low	1.15	0.78	1.69	0.4957
IL-6, high vs. low	**2.06**	**1.4**	**3.03**	**0.0002**
Intercept	0.49	0.22	1.05	0.0672

Clonal Haematopoiesis (n=1000 , 17 genes)

Predictive model of CRF at Y-4	Odds Ratio	95% CL		Pr > |t|
Menopausal status, Post- vs. Pre-	0.600	0.438	0.821	0.0014
Hormonotherapy, Yes vs. No	1.382	0.913	2.092	0.1258
Severe fatigue at diagnosis, Yes vs. No	3.025	2.071	4.418	<.0001
Anxiety, Doubtful case vs. Non-case	1.340	0.900	1.993	0.1490
Anxiety, Case vs. Non-case	1.717	1.175	2.509	0.0052
Insomnia, continuous	1.006	1.001	1.011	0.0184
Pain, continuous	1.017	1.009	1.024	<.0001
CH, VAF >= 2% vs <2%	**1.643**	**1.077**	**2.509**	**0.0213**

Efficacy of digital remote monitoring of patients under anticancer oral drugs

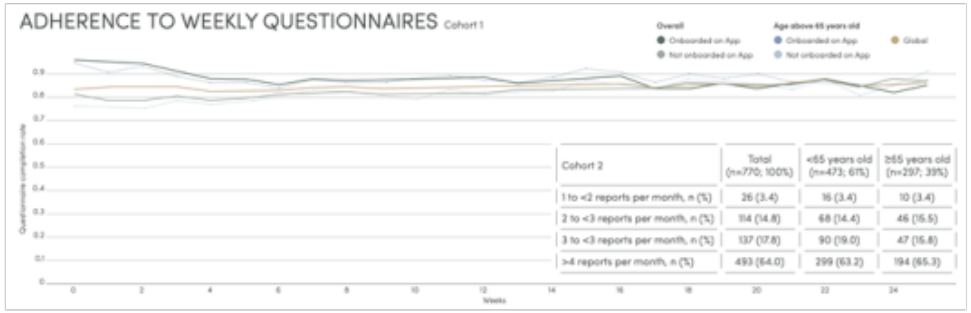
Relative Dose Intensity	Remote Digital monitoring	Control		
RDI (until study discontinuation)				
No. of patients	272	287	559	$t = 4.38$
Mean (s.d.)	0.9344 (0.2590)	0.8943 (0.1914)	0.9138 (0.2275)	$P = 0.0426$
95% CI	0.9035-0.9653	0.8720-0.9165	0.8949-0.9327	
Min-Max	0.20-2.00	0.00-1.51	0.00-2.00	
Median	1.00	1.00	1.00	
Q1-Q3	0.80-1.00	0.80-1.00	0.80-1.00	
RDI (until study discontinuation) adjusted for global adherence				
No. of patients	255	265	520	$t = 4.07$
Mean (s.d.)	0.8417 (0.2632)	0.7998 (0.2090)	0.8204 (0.2378)	$P = 0.0451$
95% CI	0.8093-0.8742	0.7745-0.8251	0.7999-0.8408	
Min-Max	0.0-2.0	0.0-1.3	0.0-2.0	
Median	0.9	0.8	0.9	
Q1-Q3	0.7-1.0	0.7-1.0	0.7-1.0	

Mir, Nat Med, 2022

Digital health as an opportunity: participatory care and behavioural interventions: routine care

Diagnosis → Active treatment → After treatment-survivorship phase

Remote patient monitoring with ePROs + therapeutic education during active treatment phase



2055 patients across 26 highly diverse centers:

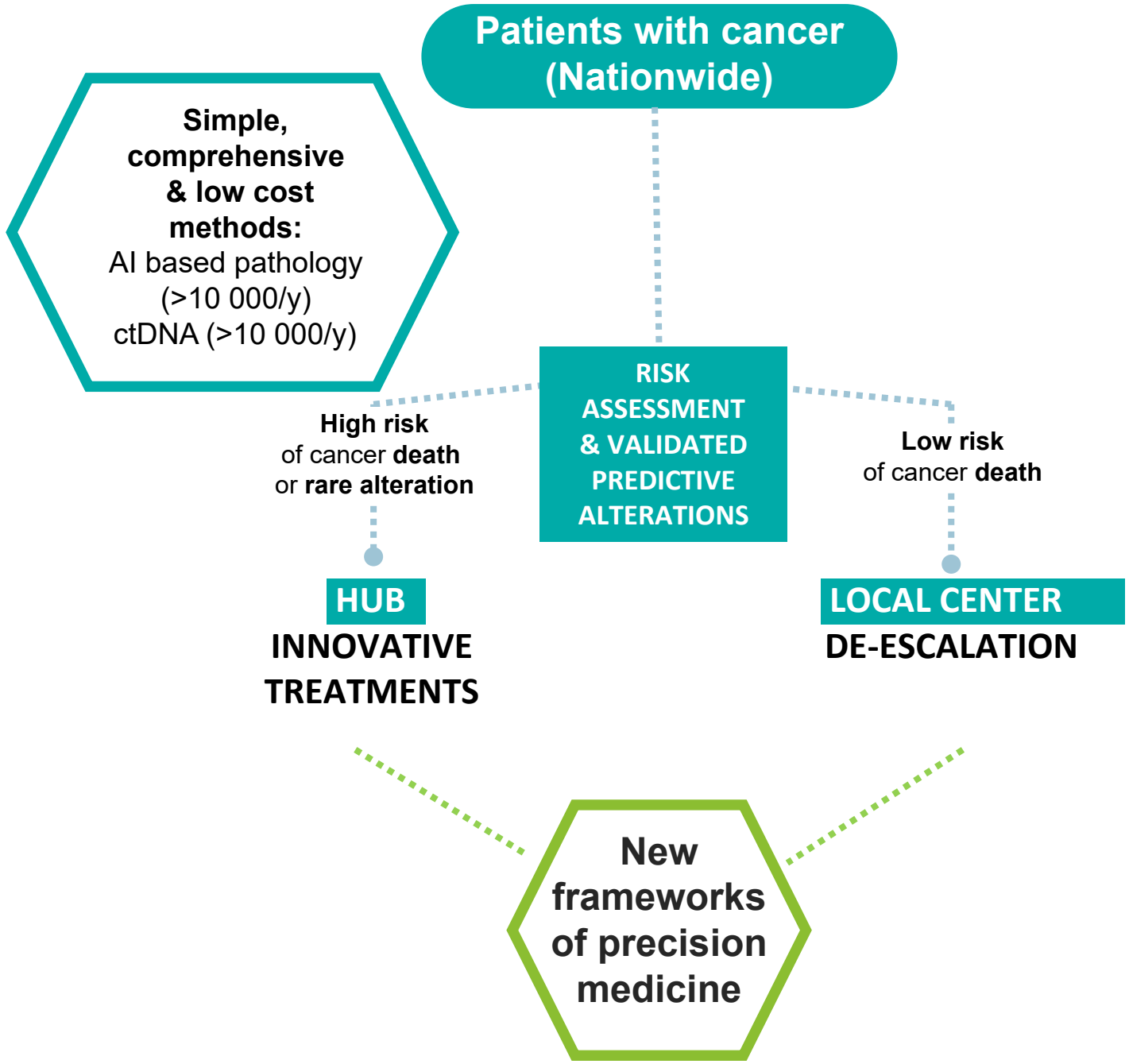
- 70% patients reporting via mobile app
- **Adherence to weekly ePRO reporting: 85% (overall); 81.1% (>65y)**

Digital therapeutics

Qualitative studies during the co-design phase (n=35): elevated satisfaction and interest

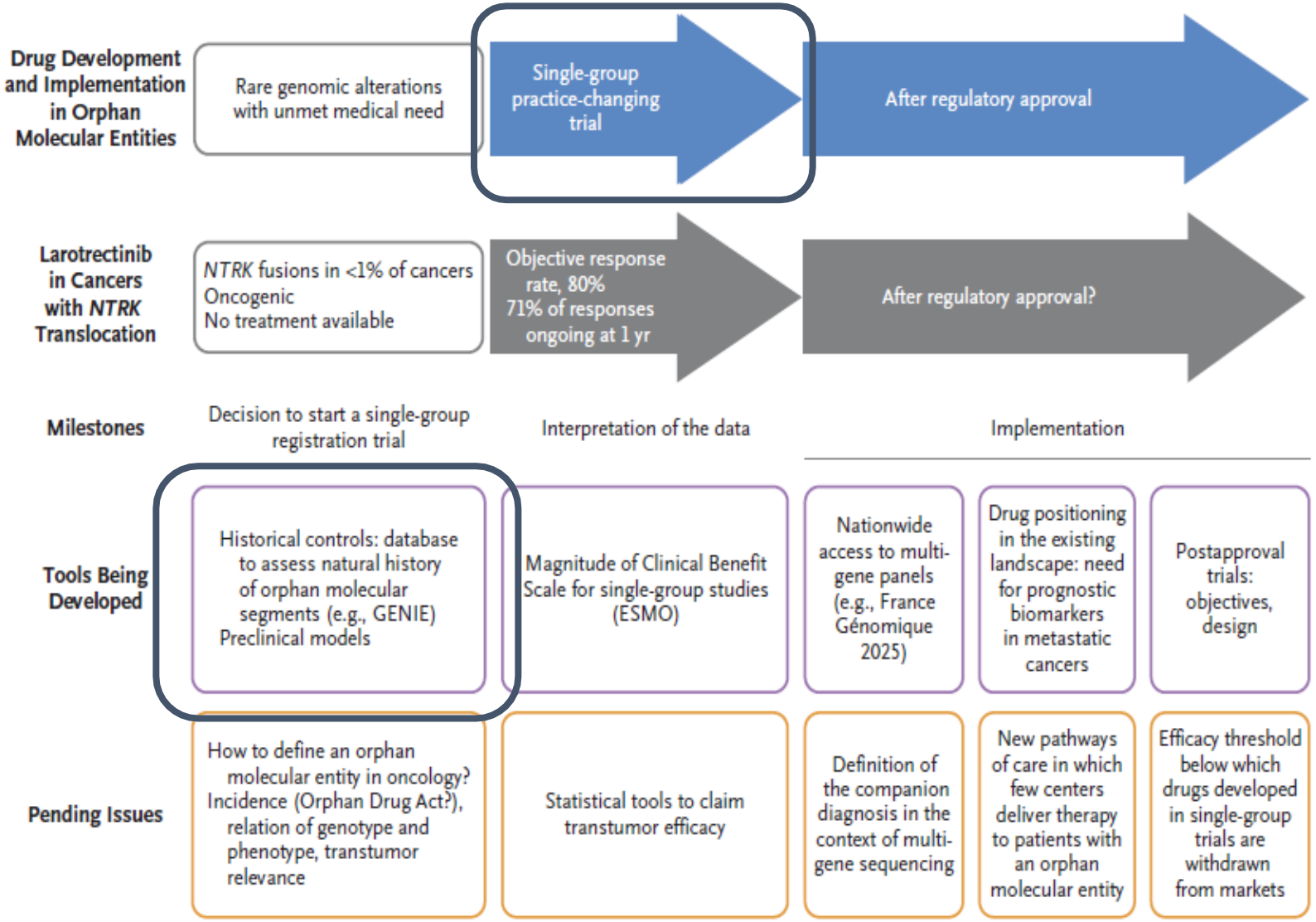
Ferreira A & Franzoi MA, ASCO 2023. Franzoi MA AFSOS 2023.

CLINICAL RESEARCH: "SCREEN AND CHARACTERIZE" APPROACH



PRISM

Drug development in rare genomic entities: Single arm trials for drug registration



Andre F, NEJM, 2018

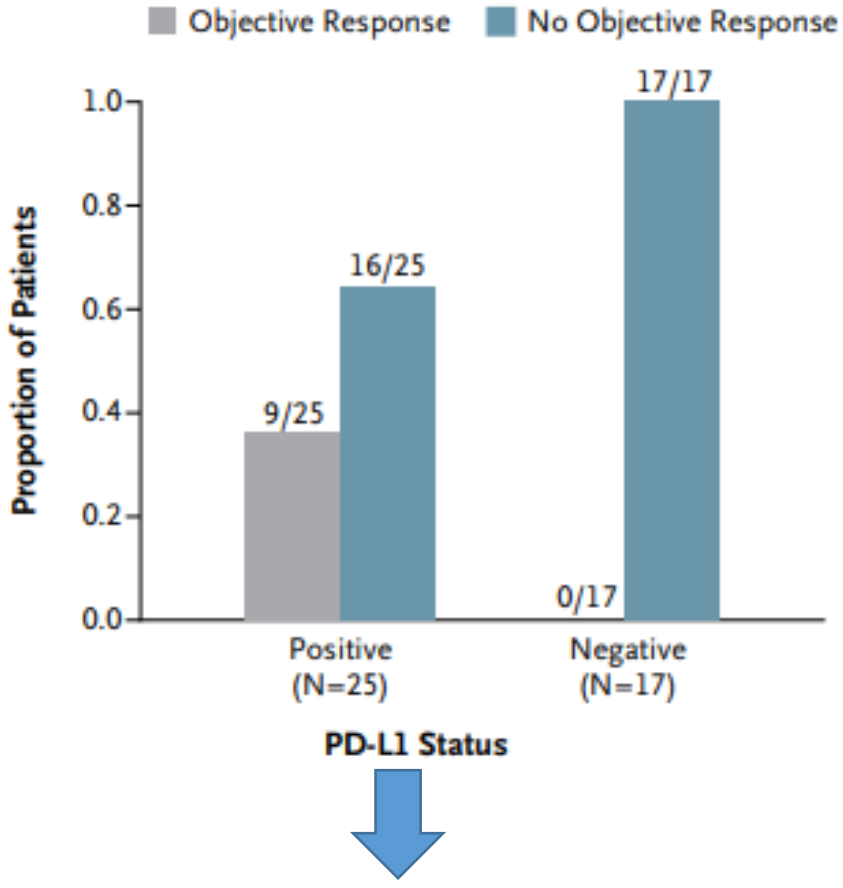
Should we move organ-agnostic developments ?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.



TARGET

= key element of classification !

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Trial Investigators*

This article was published on October 20, 2018, and updated on November 15, 2018, at NEJM.org.

N Engl J Med 2018;379:2108-21.
DOI: 10.1056/NEJMoa1809615

30%* 30% * 600 k * 6 years =
>300 000 more patients with TNBC
would have got access
to anti-PD1 if we classified cancers
by their targets
(under the hypothesis that drugs
are available everywhere…)

Pancancer estimate : around 3 M patients
missed access to anti-PD1 because cancer
Classifications are not based on biology

Change disease representation

Patient perception of cancer driven by its complexity and including biology

- "I have a *HER2*-positive cancer located in the breast"
- "My tumor is hormone-receptor positive and has a specific mutation called *PIK3CA* and is primary located in the breast" "Both of our cancers are located in the breast but are different tumors!"
- "My cancer responds well to oral therapy; this is why I need to take them everyday and discuss side effects with the care team and seek for available strategies close to home to manage them"
- "I should not compare my history to other because each cancer is unique, and the complexity of each case is different"

- "My tumor has a specific mutation that does not respond well to usual care. The best treatment for me is a novel clinical trial in a complex cancer center"
- "Oh, I see… Mine although located in the same organ as you has all the characteristics that respond well to standard treatment, this is why I can be treated close to home
- "I discussed with my doctor the pros and cons of the treatment options and which side effects would be acceptable for me in my daily life"

- "We knew that this could happen and allowed us to plan ahead"
- "Yes, and knowing all this allowed us to participate in advocacy and research initiatives, that can also help others facing a similar situation"

Consequences:

- Trust in the healthcare system and research
- Improved research participation and representation
- Rationale use of healthcare resources
- Better adherence to treatment plans
- Increased participation in their care (self-management, shared decision making, advocacy)

Changing cancer representations toward comprehensive portraits to empower patients in their care journey, Franzoi, Ann Oncol, 2023

Conclusion

- There is a need to develop large scale screening of patients presenting a high risk of cancer death or toxicities in order to provide them early access to innovation
- Sequencing coding region of DNA as a screening tool has allowed acceleration of drug development but has now reached a plateau
- There is a need to develop new modalities of target screening for patients eligible to therapeutic trials
- Short treatment duration driven by molecular analyses could allow rationale use of resources and avoid compliance issues
- Digital monitoring could increase treatment compliance and patient follow-up
- Implementation of molecular oncology requires development of new frameworks for drug development, oncology practice and disease representation