



Associazione Italiana di Oncologia Medica  
SEZIONE REGIONE LAZIO



**POST ESMO**

*from*  
**BARCELONA**

*to*  
**REAL WORLD**

— ROMA —

NH Collection Vittorio Veneto - C.so d'Italia, 1

2 - 3 Dicembre 2019

— ***Biopsia Liquida*** —

***Patrizio Giacomini***

***nel mondo reale***

[patrizio.giacomini@ifo.gov.it](mailto:patrizio.giacomini@ifo.gov.it)



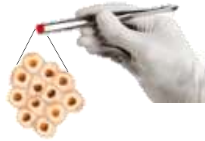
# Modulo dichiarazione conflitto di interessi

Tutti i rapporti finanziari intercorsi negli ultimi due anni devono essere dichiarati.

- Non ho rapporti (finanziari o di altro tipo) con le Aziende del farmaco
- Ho / ho avuto rapporti (finanziari o di altro tipo) con le Aziende del farmaco

<b>Relationship</b>	<b>Company/Organization</b>
Grant supporting LiqHERcept/GIM21	Roche Pharmaceuticals
Grant supporting anti HER2 antibody development	Ibi Lorenzini

# - *Tissue Biopsy & Liquid Biopsy: complementary*



Invasive

- Bias in tissue sampling  
Single time point



Analyte virtually unlimited  
Many aberrations at once (large panels)  
high sensitivity

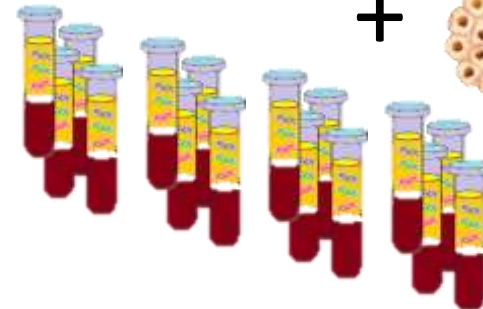
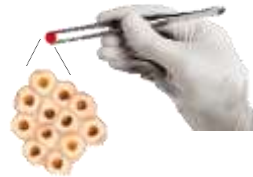


Minimally invasive  
No bias  
Longitudinal

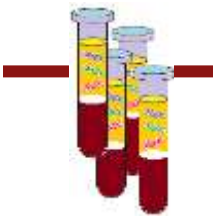


ctDNA degraded and scarce  
Limits in panel complexity  
low sensitivity

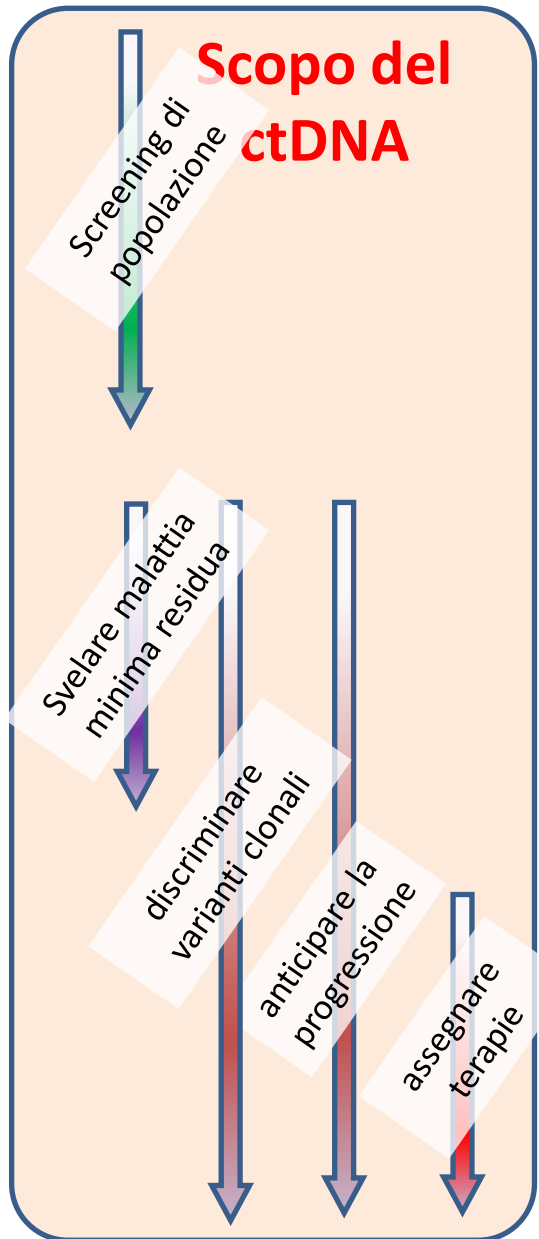
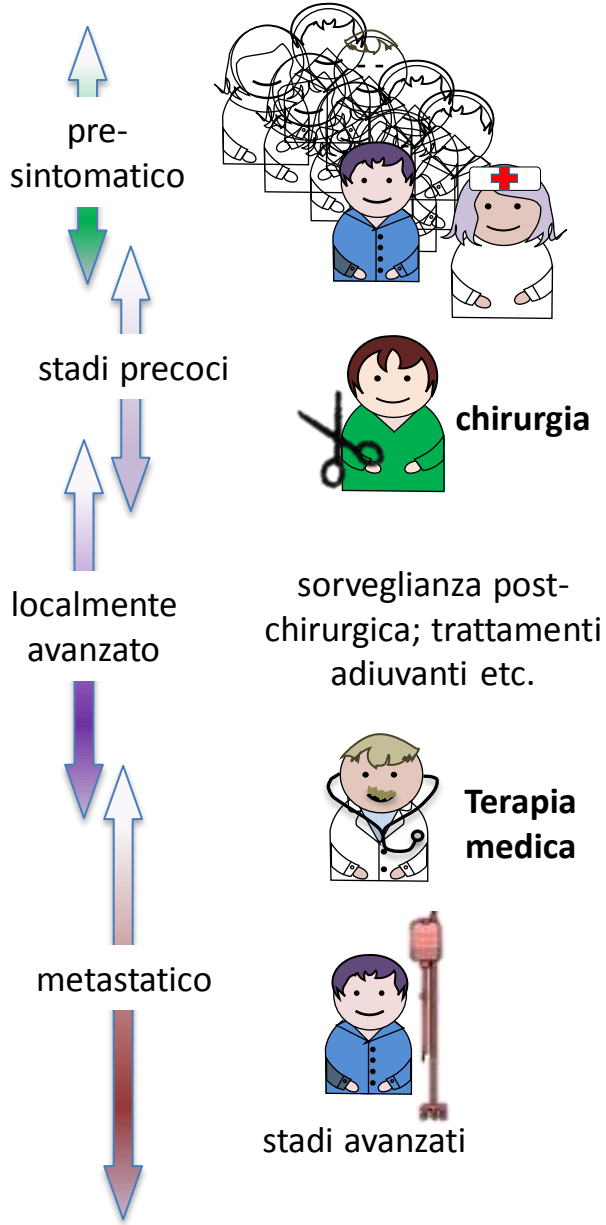
*combining  
tissue biopsy,  
liquid biopsy  
and re-biopsy*



# DNA circolante tumorale (ctDNA): 'azionabile' a tutti gli stadi di malattia



**esempi**



## ricaduta clinica

Prevenzione primaria e secondaria, sorveglianza intensificata

**CancerSEEK**

avviamento al trattamento chirurgico

anticipazione del rischio di recidiva

evoluzione e complessità della malattia

**TRACERx**

sospensione di terapia inefficace

Assegnazione terapia bersaglio anche non-standard

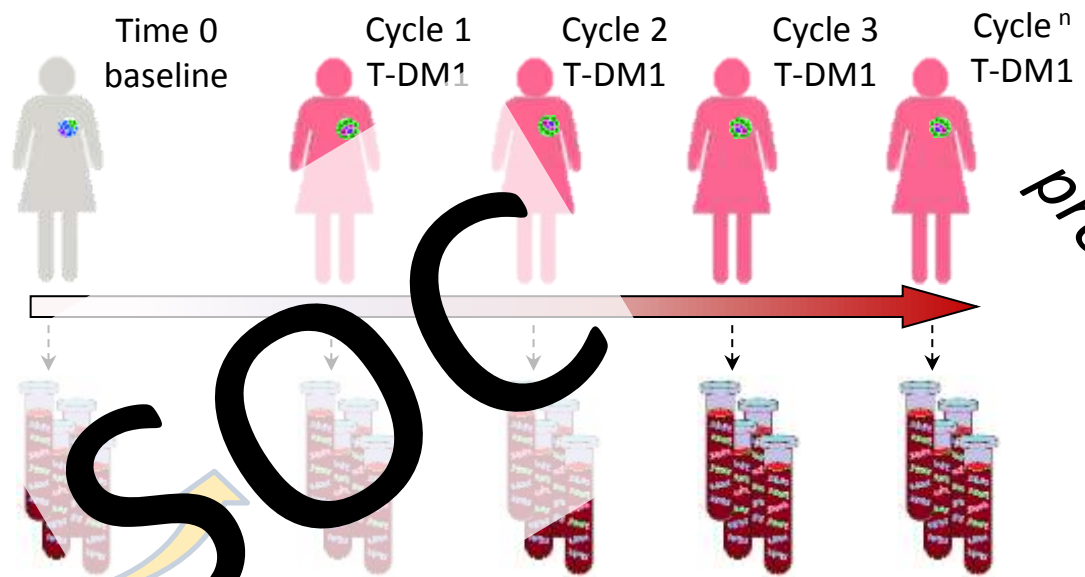
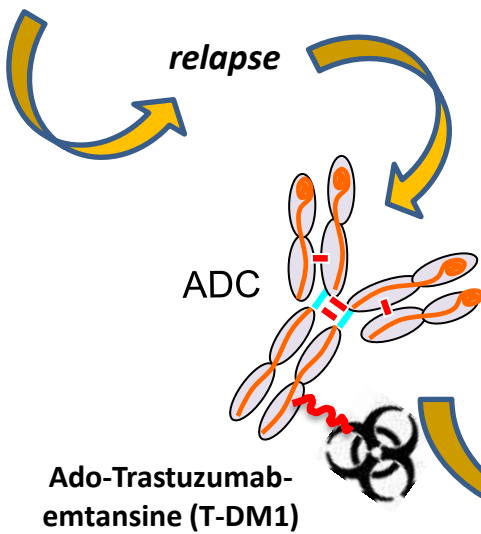
**F-One Liquid**

***HER2 breast cancer  
T-DM1***



# **LiqBreasTrack: tracking mutational trajectories in T-DM1-treated HER2 breast carcinoma patients by Liquid Biopsy**

**TTZ/PTZ  
+ taxanes etc**



Matteo Allegretti



Alessandra Fabi



Michelangelo Russillo



Francesco Cognetti



Simonetta Buglioni



Edoardo Pescarmona

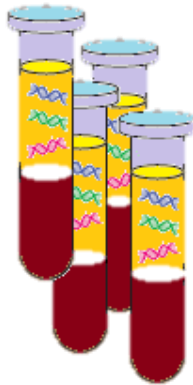
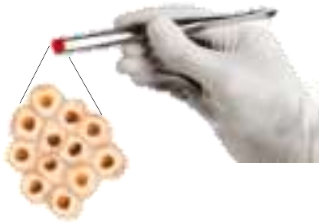


Elena Giordan  
i



Paolo Romania

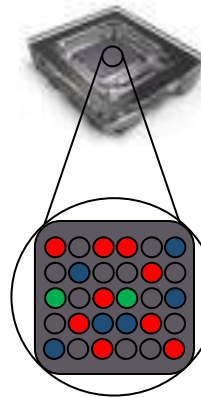
# *LiqBreasTrack: monitoring by NGS & dPCR*



Thermo Fisher Scientific Pan-cancer  
NGS targeted panel: 52 genes +  
12CNV + 92 fusions



**NGS**



**dPCR**



## ***LiqBreasTrack: primary aims***



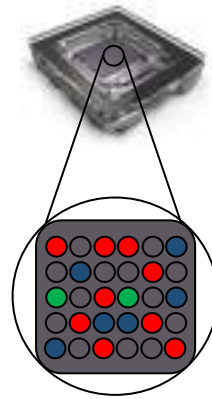
- 1. Lead time to progression (ctDNA PD vs. RECIST PD)***
- 2. Recurrent mutational patterns on progression***



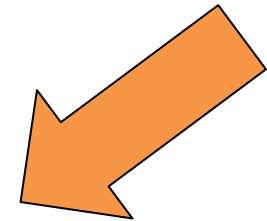
# ***LiqBreasTrack: HER2 amplification***



**NGS**



**dPCR**

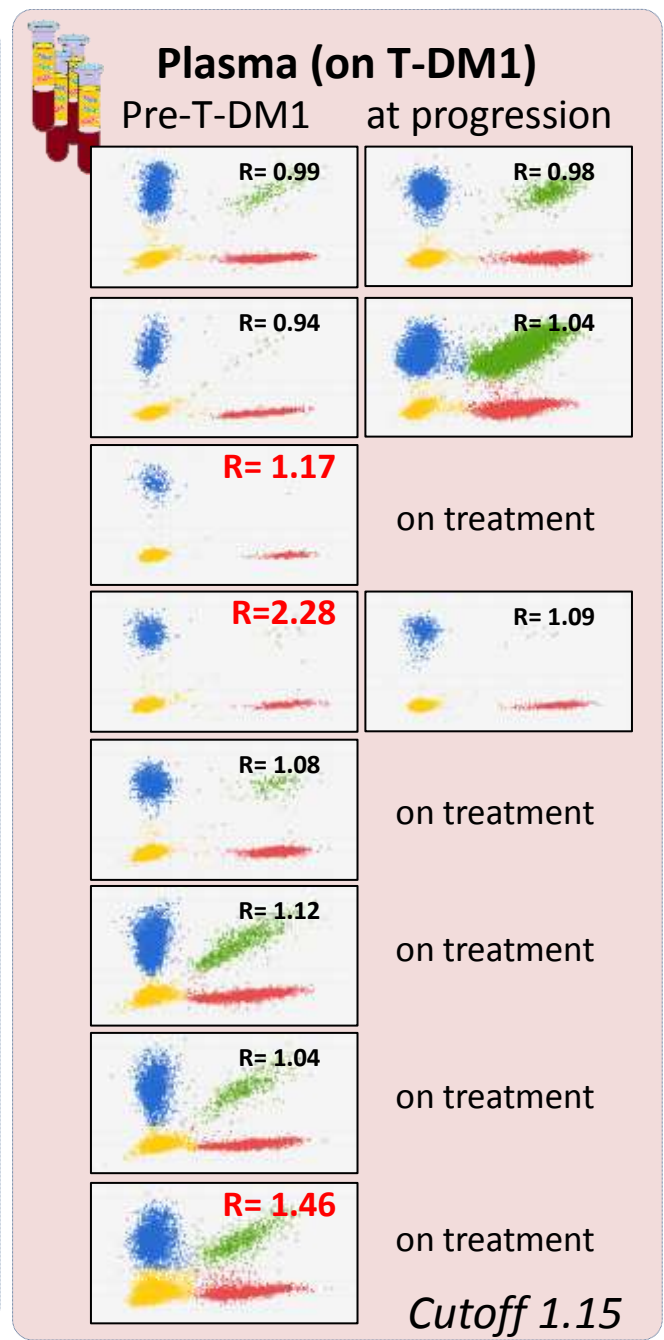
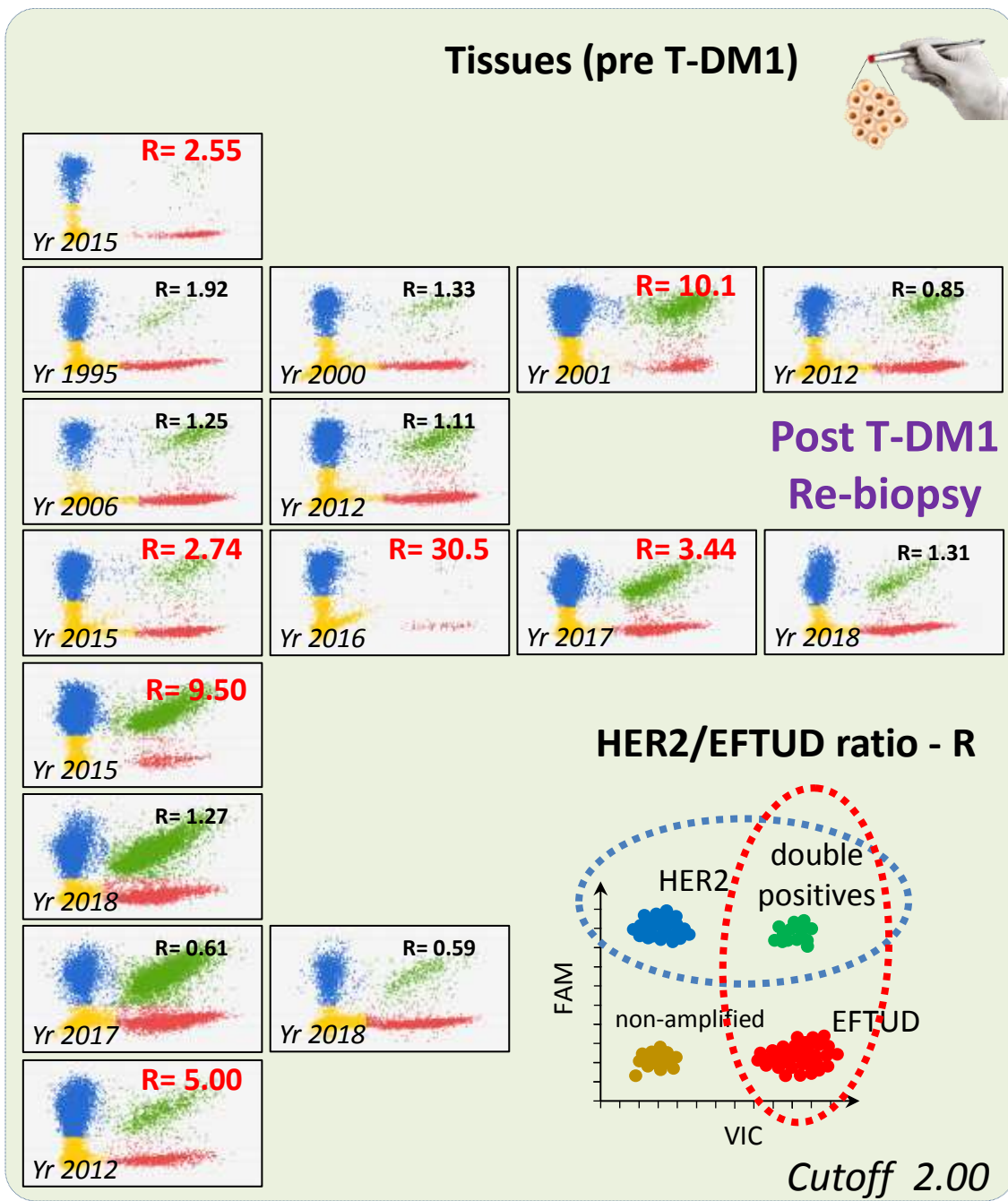




“My mom always said life was like a box of chocolates. You never know what you're gonna get.”



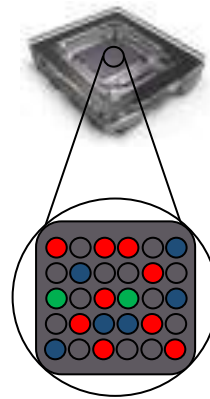
**Monitoring T-DM1 treated patients by liquid biopsy - HER2 amplification**



***LiqBreasTrack: other genomic alterations (SNVs) in blood (and tissues)***

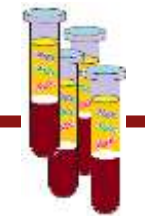


**NGS**



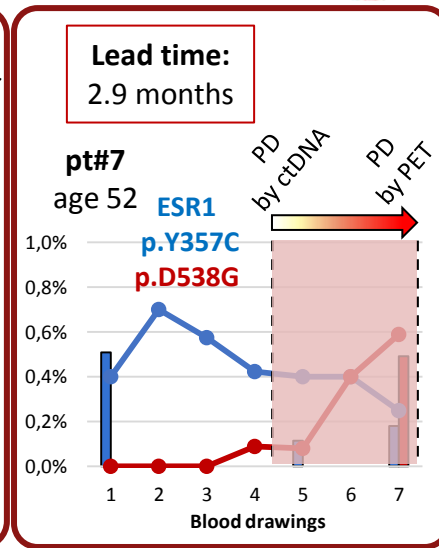
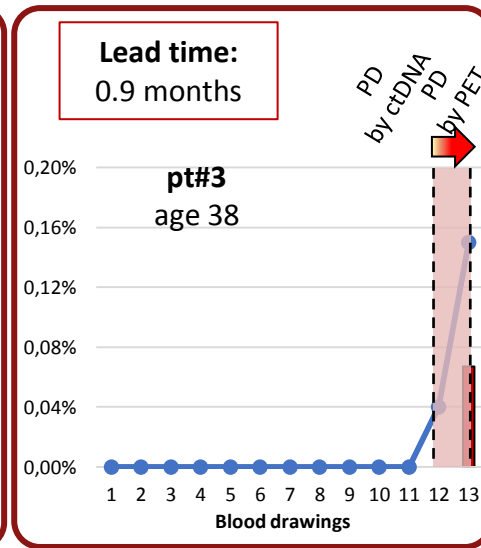
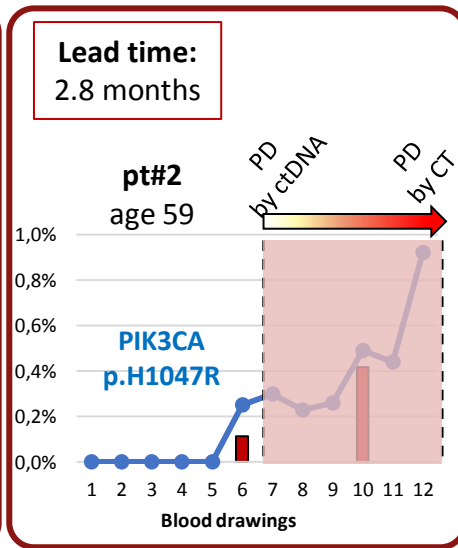
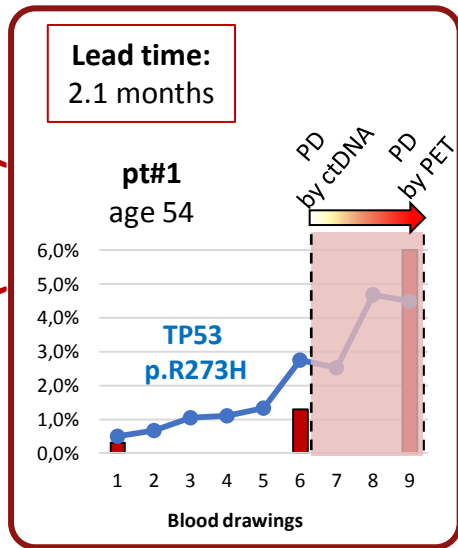
**dPCR**





# - *LiqBreastTrack: recurrent ctDNA patterns*

VAF (blood)



ctDNA present at time 0,  
and slowly going up

*resistance (primary)*

ctDNA **NOT** present at time 0,  
but de novo appearing some  
time after the beginning of  
treatment

*resistance  
(acquired/adaptive)*

delayed ctDNA  
appearance

*sensitivity  
(best responders)*

intersecting ctDNA  
trajectories

*sensitivity &  
resistance  
(bi-clonal ear-  
marking)*

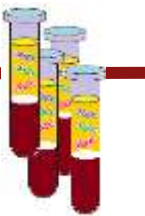


NGS



dPCR

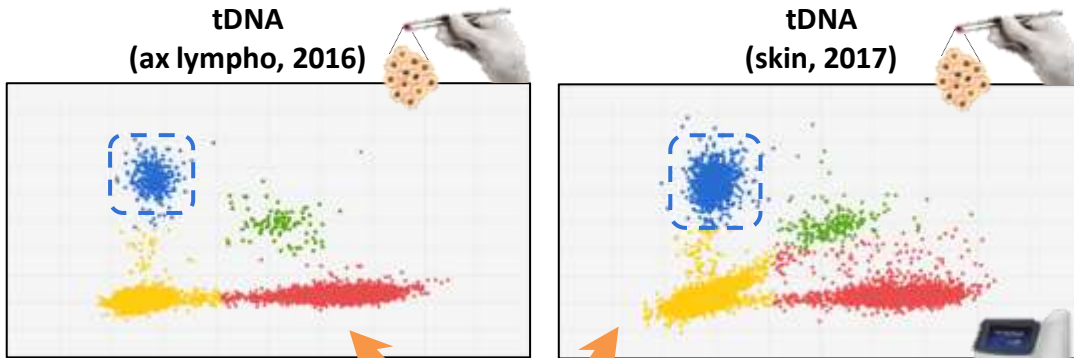
# LiqBreasTrack: ultra-fast ctDNA clearance



PIK3CA E545K  
(NGS IRE Anat Patol)



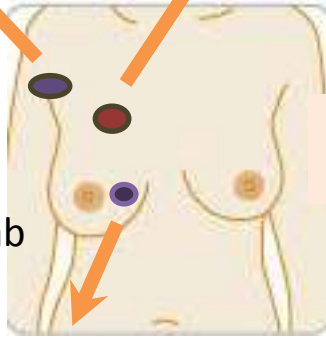
pt#6, age 47



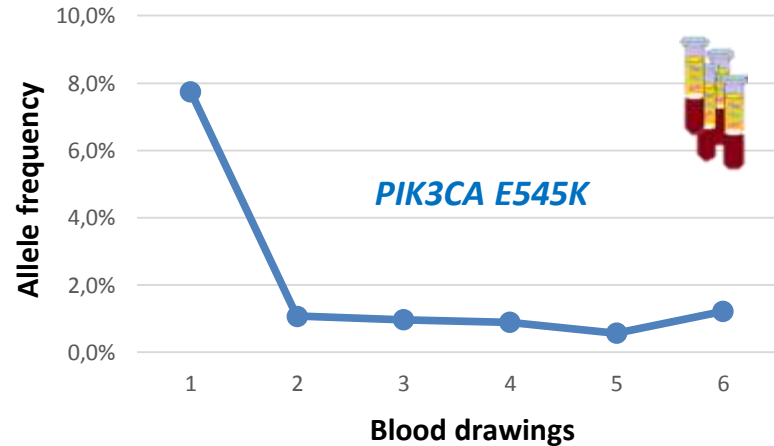
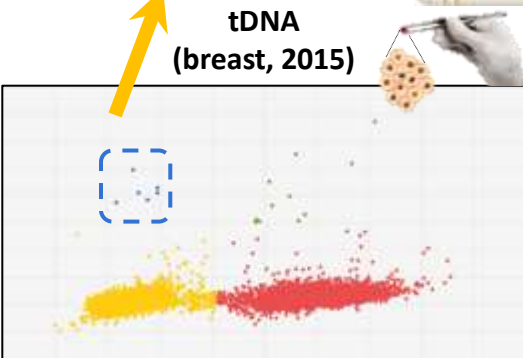
PATIENT RESULTS		TUMOR TYPE: BREAST INVASIVE DUCTAL CARCINOMA (IDC)	
3 genomic findings	7 therapies associated with potential clinical benefit	Genomic Alterations Identified <sup>†</sup> ERBB2 amplification PIK3CA E545K TP53 G302fs*41	
0 therapies associated with lack of response	13 clinical trials		
THERAPEUTIC IMPLICATIONS			
Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials

<sup>†</sup> For a complete list of the genes assayed and performance specifications, please refer to the Appendix.

Lymph node resection  
Trastuzumab/Pertuzumab neoadjuvant

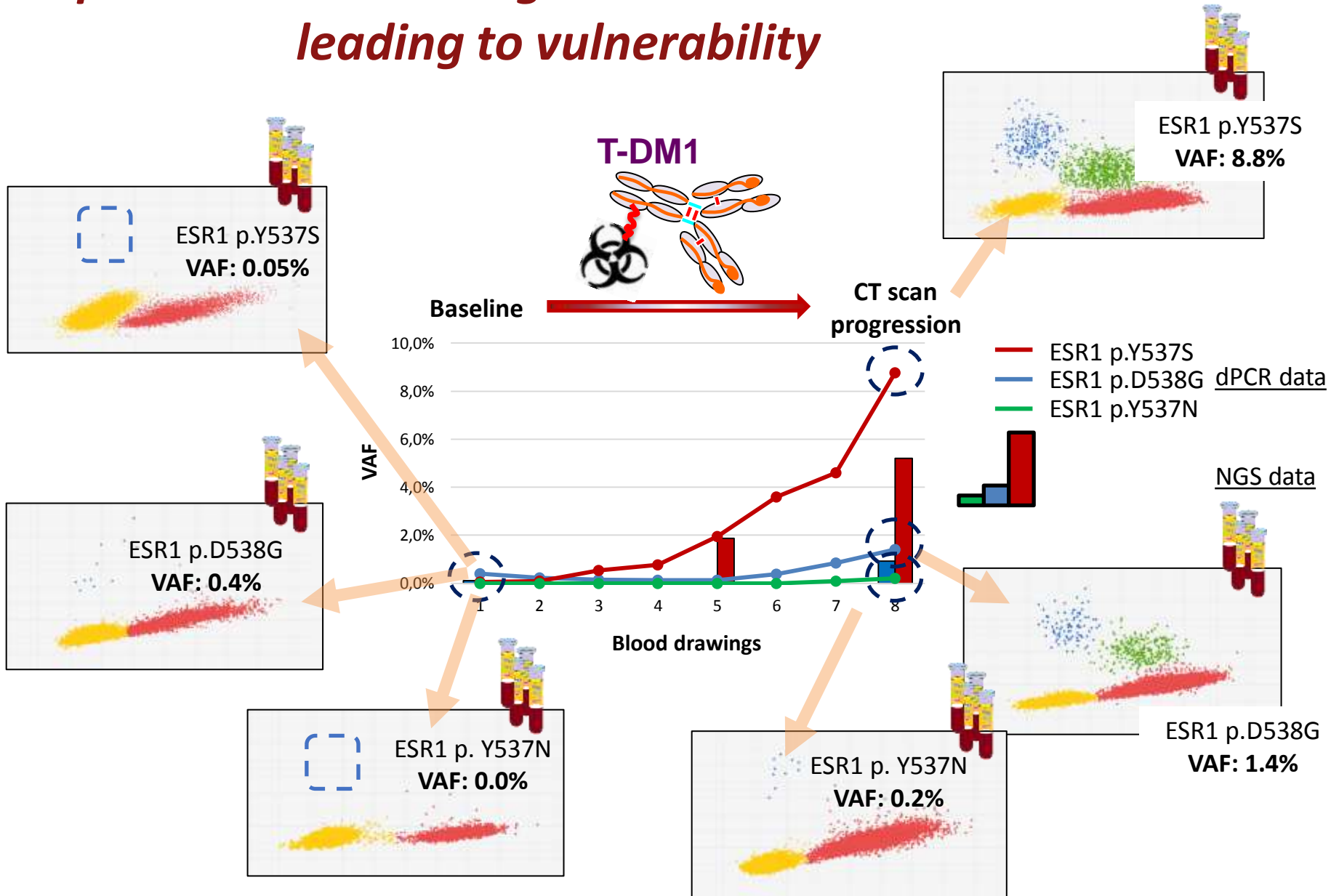


Foundat

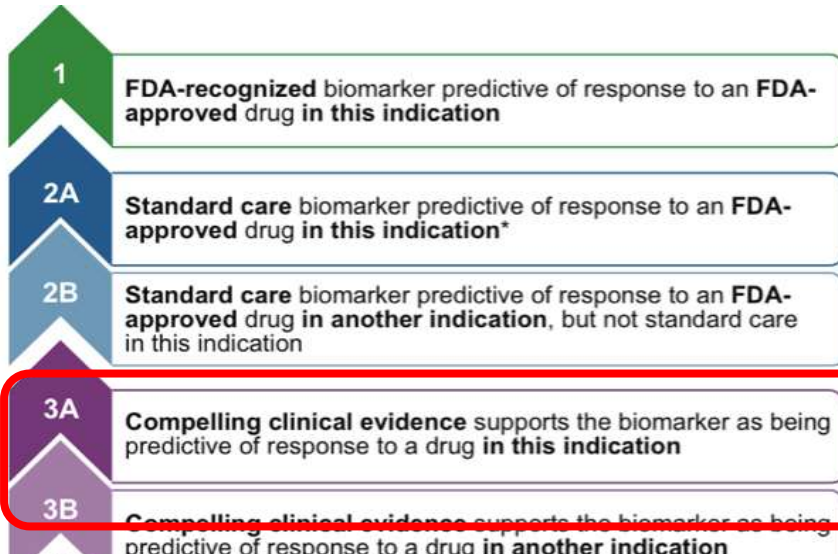


Therapy	Implication
Trastuzumab/Pertuzumab	Yes, see clinical trials section
erolimus	Yes, see clinical trials section
None	None

# LiqBreasTrack: convergent Darwinian evolution leading to vulnerability



# — LiqBreastTrack: assigning NON-SOC therapy by ctDNA



**Standard Therapeutic Implications**  
 \*Includes biomarkers that are recommended as standard care by the NCCN or other expert panels but not necessarily FDA-recognized for a particular indication

**Investigative Therapeutic Implications**  
 possibly directed to clinical trial

frequency 8.3% advanced BrCa



Alteration	Cancer Type	Drug(s)
Oncogenic Mutations	Breast Cancer	AZD9496 Fulvestra

### IRE Molecular Tumor Board

- hematologist
- surgeon
- nurse
- bioinformatician
- medical oncologist
- pathologist
- biostatistician
- Pharmacologist – Hospital Pharmacist
- Molecular Biologist

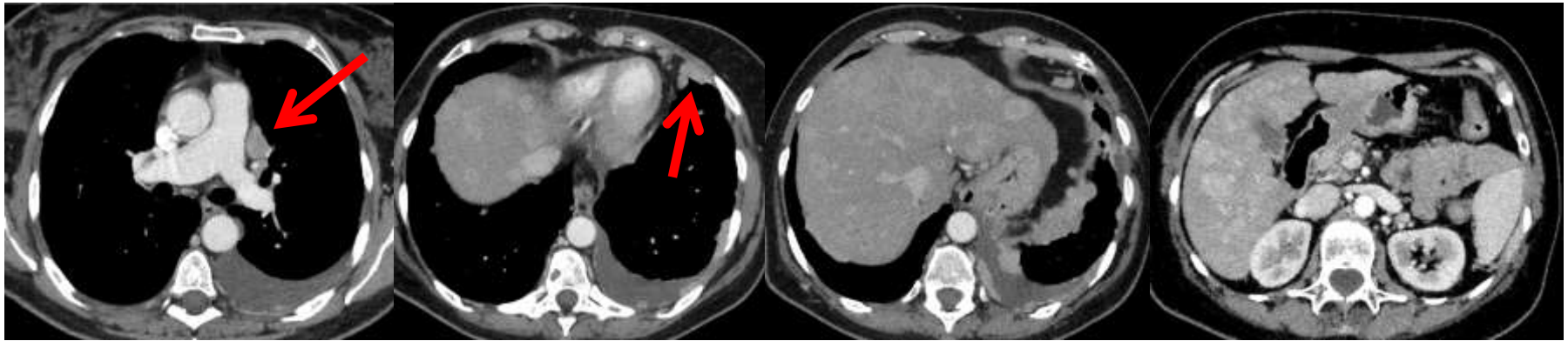
result in a constitutively active receptor, which is shown to confer acquired resistance to estrogen deprivation therapies.



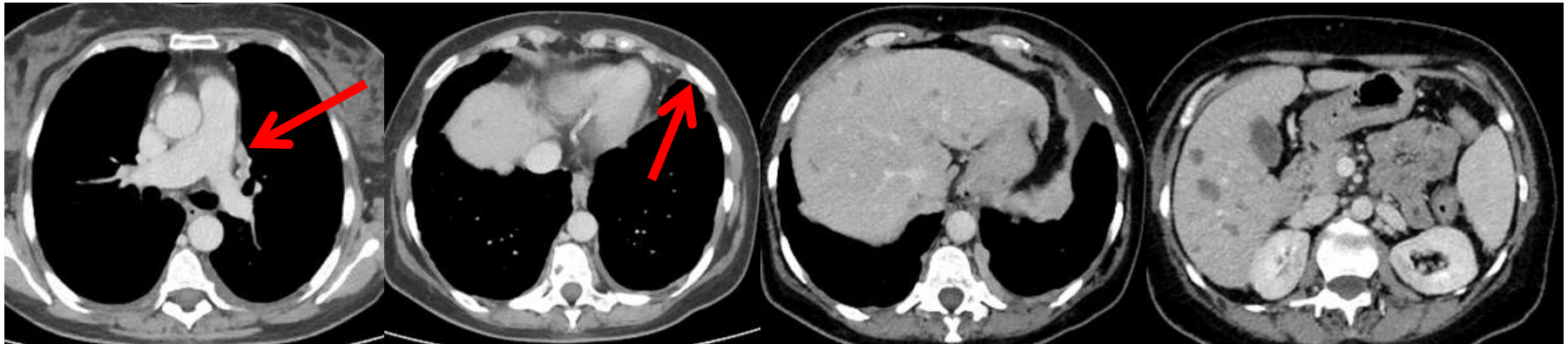
# — *LiqBreastTrack: response to NON-SOC therapy*



June 2019



October 2019



# LiqBreasTrack reveals new vulnerabilities not present in archival tumor tissues



ID	Tissue mutations (number)		Plasma mutations		Clinical behaviour (imaging)	Plasma behaviour (ctDNA)	Actionable (OncoKB level ≤3)	
	Primary	Metastasis	T=0	Prog			T=0	Prog
pt#1	-	-	✓	✓	PD	↑	✗	✗
pt#2	12	1	✗	✓	PD	→ ↑	✗	✓
pt#3	-	-	✗	✓	PD	→ ↑	✗	✓
pt#4	-	43, 11, 7	✓	✗	PD	↓ → ↑ →	✓	✗
pt#5	4	64	✗	NA	✓ SD	→ ↑ ↓ →	✗	NA
pt#6	1	1, 1, 1	✓	✓	PD	→ ↓	✓	✓
pt#7	-	-	✓	✓	PD	→ ↓ ↑	✓	✓
pt#9	2	-	✓	NA	SD	↓ →	✗	NA
pt#10	2	-	✓	✓	PD	↑	✓	✓
pt#12	-	-	✓	NA	SD	↓ →	✗	NA
pt#13	-	-	✓	✗	PD	↓	✓	✗
pt#14	-	1	✓	-	SD	not available yet	✗	-
pt#15	2	-	✗	-	SD	not available yet	✗	-
pt#16	-	-	✗	-	SD	not available yet	✗	-
pt#17	-	0	✓	-	SD	not available yet	✓	-

Pts w/actionable SNVs on progression 5/8 (62.5%)

brain metastasis

NA: Not Applicable

- Tumor vulnerabilities only seen in blood
- Tumor vulnerabilities not present at the beginning of T-DM1 treatment

# Moving forward: from LiqBreasTrack to GIM21



**XXIII**  
Azienda Ospedaliera  
Papa Giovanni XXIII  
Bergamo



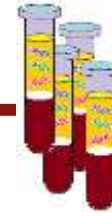
PI	Città	Centro
Chairman: F. Cognetti Study coordinator: A. Fabi	RM	IRCSS Istituto Nazionale Tumori Regina Elena
C. Tondini	BG	A.O. Papa Giovanni XXIII
L. Moscetti	MO	A.O.U. Modena
L. Del Mastro	GE	IRCSS A.O.U. San Martino IST
P. Marchetti	RM	A.O.U. Sant'Andrea
G. De Placido	NA	Università degli Studi Federico II



<https://www.oncotech.org/gim21>



## — *LiqBreasTrack: preliminary conclusions* —



Matteo Allegretti



Alessandra Fabi

1. HER2 amplification may be a marginal cancer driver at the time of T-DM1 administration

2. Yet, T-DM1 is the industry standard

3. Clinical results

4. Resistant on average

5. Target therapy blockade ...

*strikingly slow*

6. ... sometimes **treat some**

7. ... and some actionable

8. Why basket

9. Liquid biopsy

10. Liquid biopsy must go on beyond progression (additional lines of therapy)

11. Ethics, deontology, regulatory issues (and a personal perspective)



... implications upon

... trajectories

... by 2-3 months on

... **YEARS** of ERBB2

... occurs on a

... ons (**you cannot**

... treatment) of

... therapeutic decisions