bjclub breast Journal Club
20 - 21 APRILE 2023 ROMA
THE HIVE HOTEL

I nuovi farmaci sono un punto di svolta nella creazione di un nuovo algoritmo che vada oltre l'endocrinoresistenza – CONTRO

April 21st, 2023

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Disclosures

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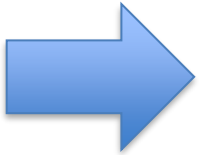
Vi do 5 ragioni che supportano la posizione "CONTRO"

Paradigm shift

We need <u>new</u> drugs

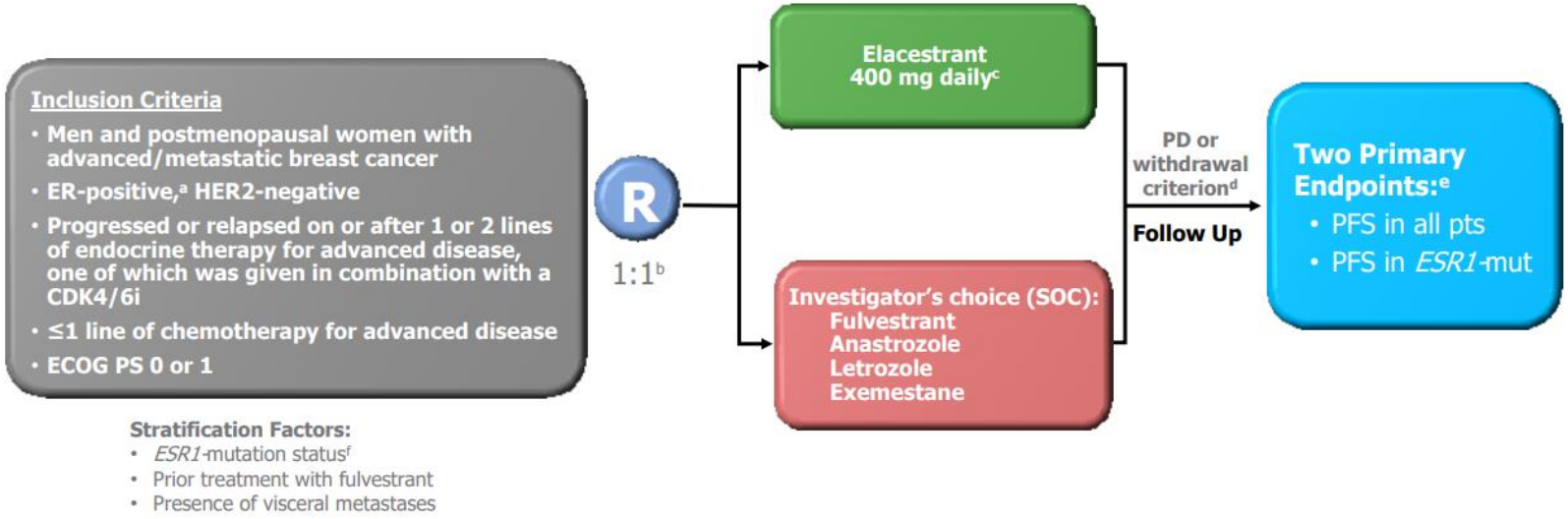


We need <u>good</u> drugs and greater efficiency in the search for biomarkers, which is vital to the process of precision medicine

Pharma has led great randomized clinical trials to test new drugs, but we need to better understand the disease!

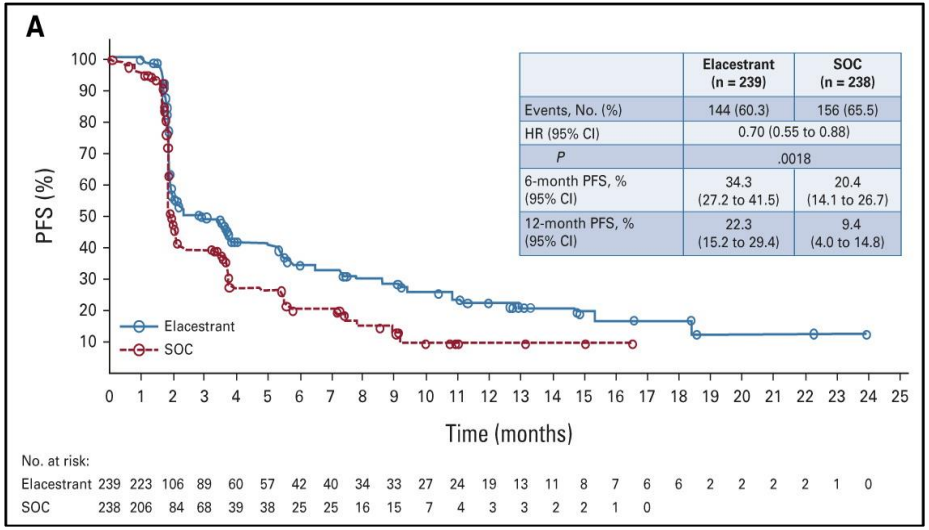
Finding biomarkers of response to better select patients who will benefit from a treatment should come from academic efforts

EMERALD: Phase III, randomized trial



EMERALD: Progression-Free Survival

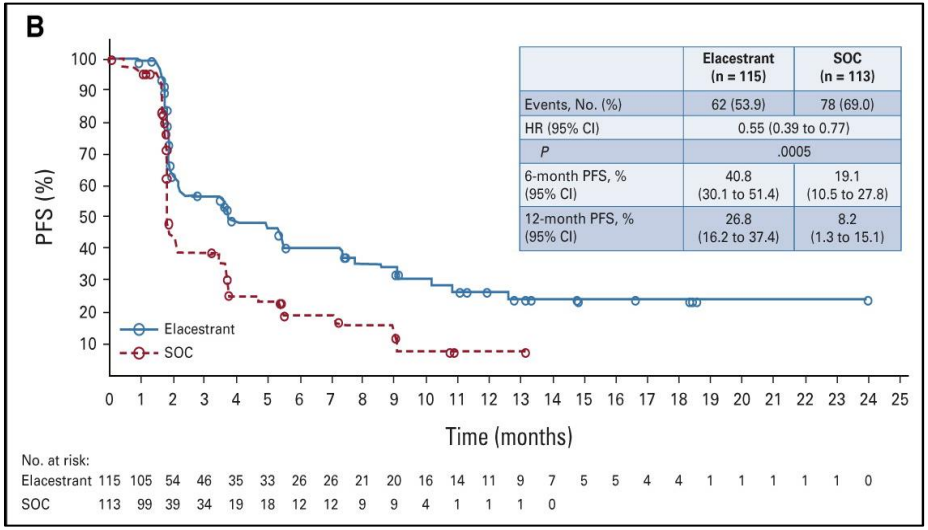
All patients



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

12-mos PFS **22.3% vs. 9.4%**
HR 0.70 (0.55-0.88)

ESR1-mut cohort



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
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6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

12-mos PFS **26.8% vs. 8.2%**
HR 0.55 (0.39-0.77)

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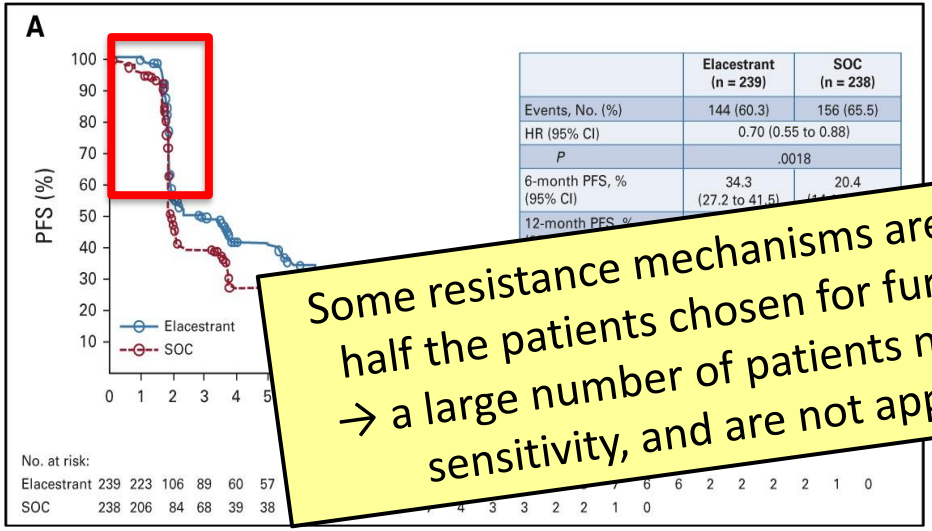
Bidard et al, *JCO* 2022

ULB iris

EMERALD: Progression-Free Survival

All patients



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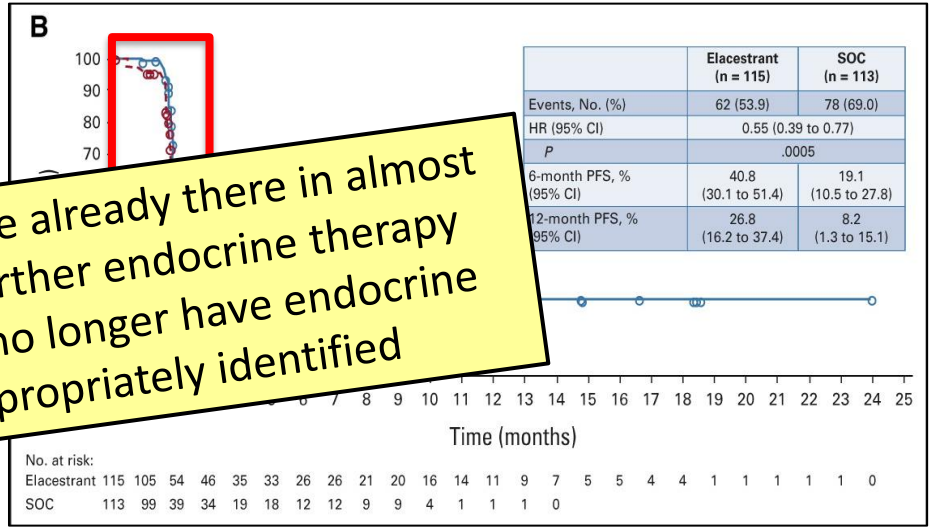

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12-mos PFS **26.8% vs. 8.2%**
HR 0.55 (0.39-0.77)

Some resistance mechanisms are already there in almost half the patients chosen for further endocrine therapy
→ a large number of patients no longer have endocrine sensitivity, and are not appropriately identified

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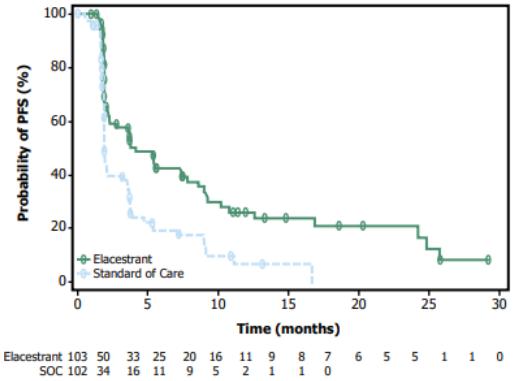
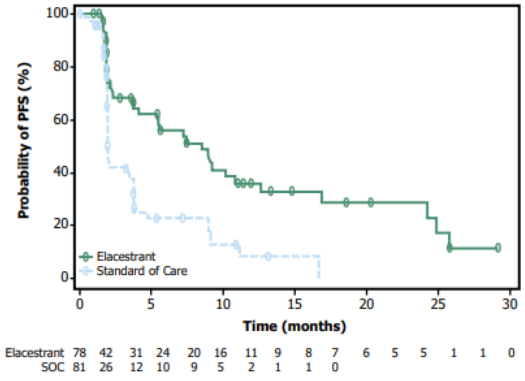
EMERALD: PFS by duration of CDK4/6i in ESR1-mut cohort

At least 6 mo CDK4/6i



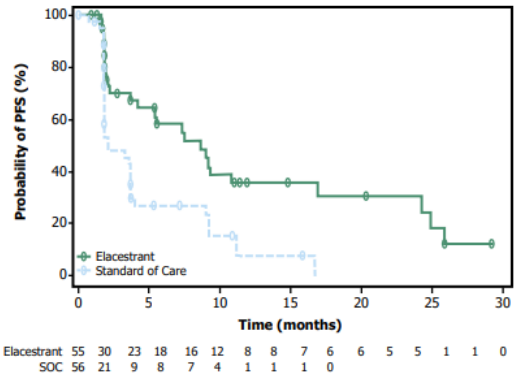
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

- Patients with short PFS on CDK4/6i + ET do not derive benefit of further single agent SERD
  - ➢ **Should these patients be excluded from registration trials testing SERD single agent in the 2nd line setting ?**
- Since these patients do not derive benefit from 1st & 2nd line ET (PFS1+2<15 months),
  - ➢ **Should they be identified frontline & treated with modern cytotoxic agents or TT ?**

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Bardia et al, *SABCS* 2022
André F, SABCS 2022

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MAINTAIN: Phase II, randomized trial of Ribociclib after Progression on CDK4/6i

Key Entry Criteria

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed

1:1

N=120

Arm 1
Ribociclib + Switch Endocrine Therapy*

Arm 2
Placebo + Switch Endocrine Therapy*

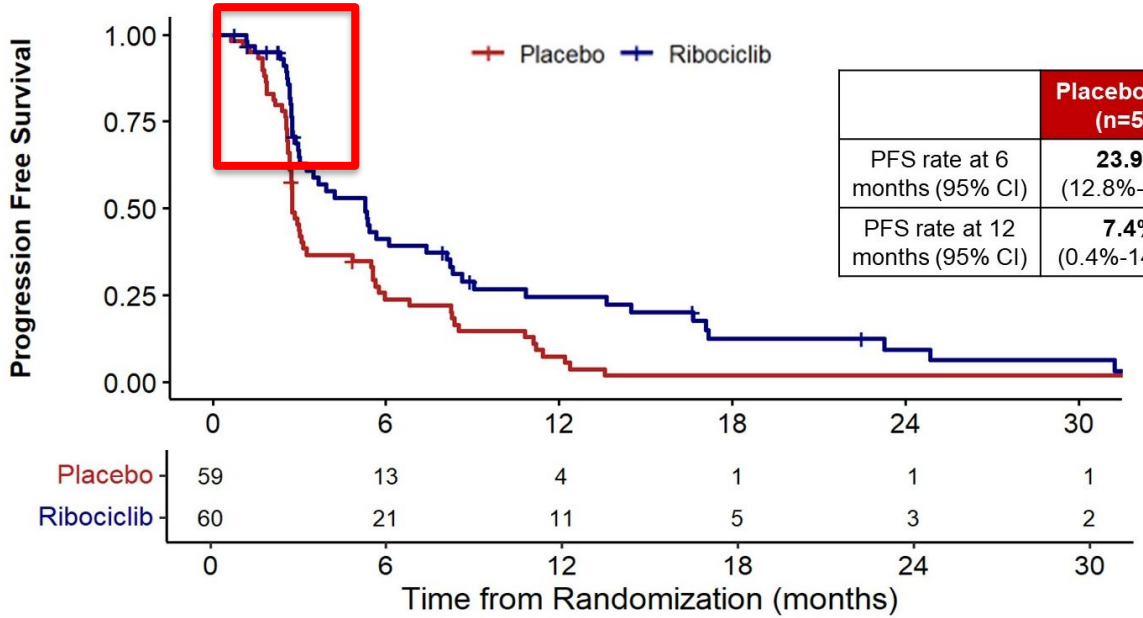
Primary Endpoint

- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints

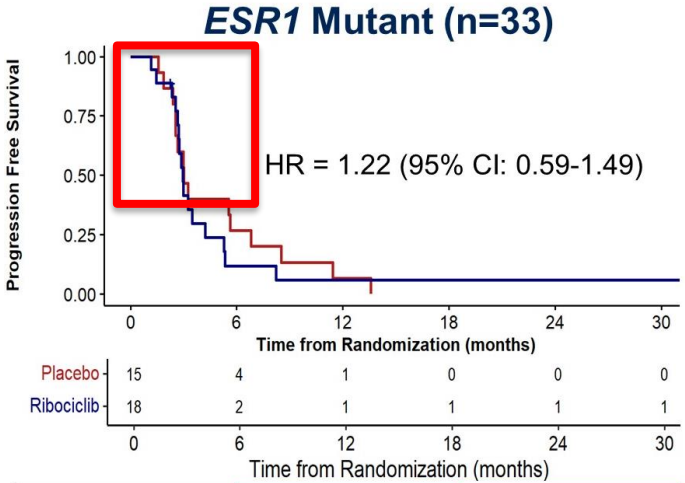
- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

MAINTAIN: Progression-Free Survival



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
PFS rate at 6 months (95% CI)	**23.9%** (12.8%-35%)	**41.2%** (27.8%-54.6%)
PFS rate at 12 months (95% CI)	**7.4%** (0.4%-14.3%)	**24.6%** (12.5%-36.7%)

MAINTAIN: PFS in Fulvestrant and *ESR1* Mutant cohort (Exploratory Analysis)

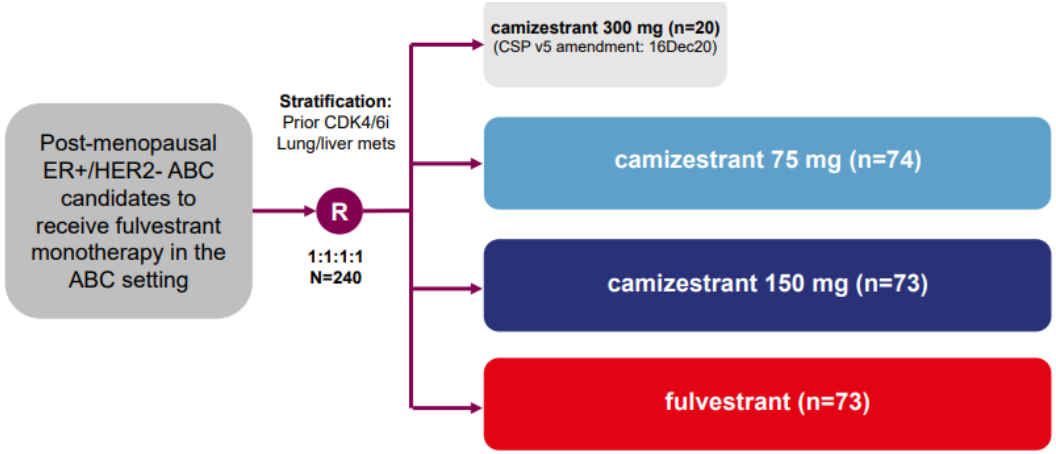


	Placebo (n=15)	Ribociclib (n=18)
Median (95% CI) (mos)	**3.02** (2.53-5.62)	**2.96** (2.66-4.21)

SERENA-2: Phase II, randomized trial of camizestrant (SERD) vs. fulvestrant

Key inclusion/exclusion criteria:

- Recurrence or progression on at least one line of ET
- No prior fulvestrant or oral SERD in ABC
- No more than one line of ET in ABC setting
- No more than one line CT in ABC setting
- Measurable and non-measurable disease



- **Primary endpoint:** PFS (investigator assessment*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

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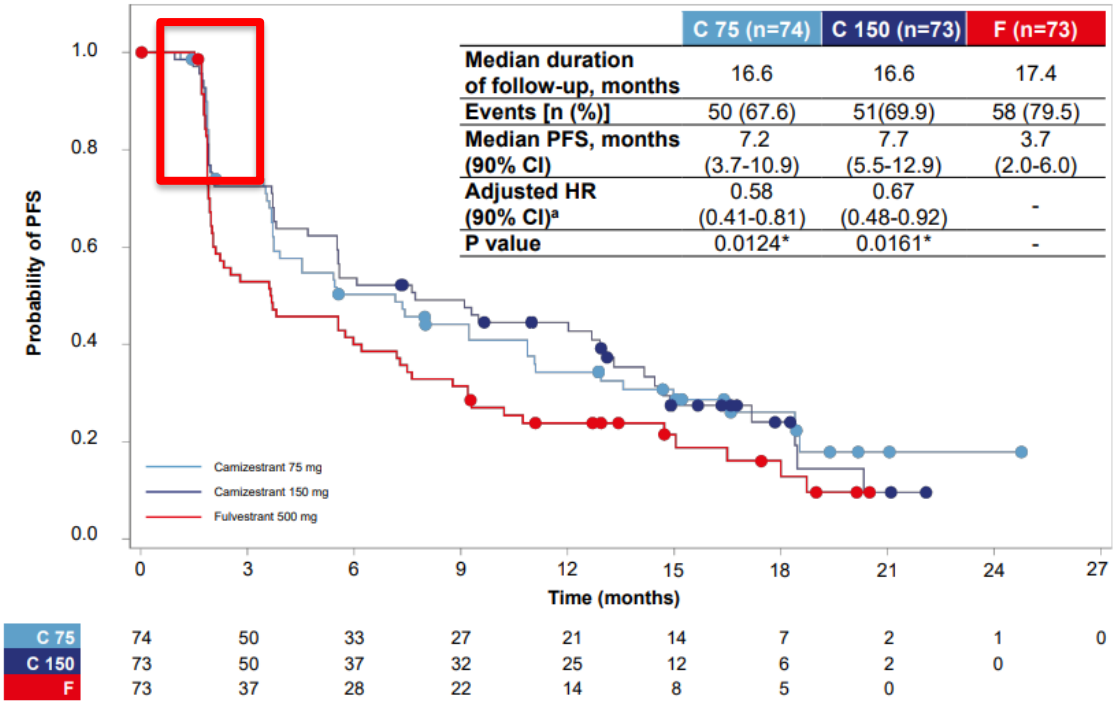
Oliveira et al., SABCS 2022

ULB iris

SERENA-2: PFS by Investigator Assessment



	C 75 (n=74)	C 150 (n=73)	F (n=73)
Median duration of follow-up, months	16.6	16.6	17.4
Events [n (%)]	50 (67.6)	51(69.9)	58 (79.5)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR (90% CI)[a]	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124*	0.0161*	-

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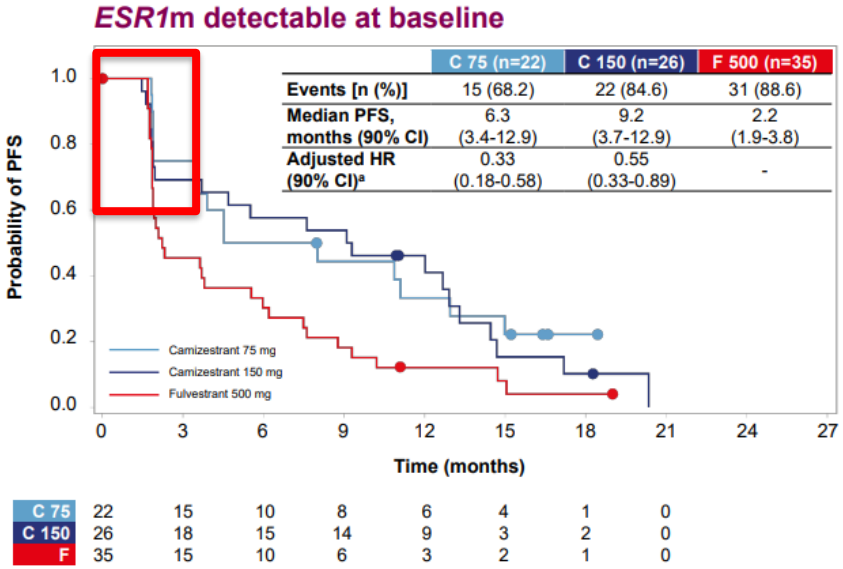
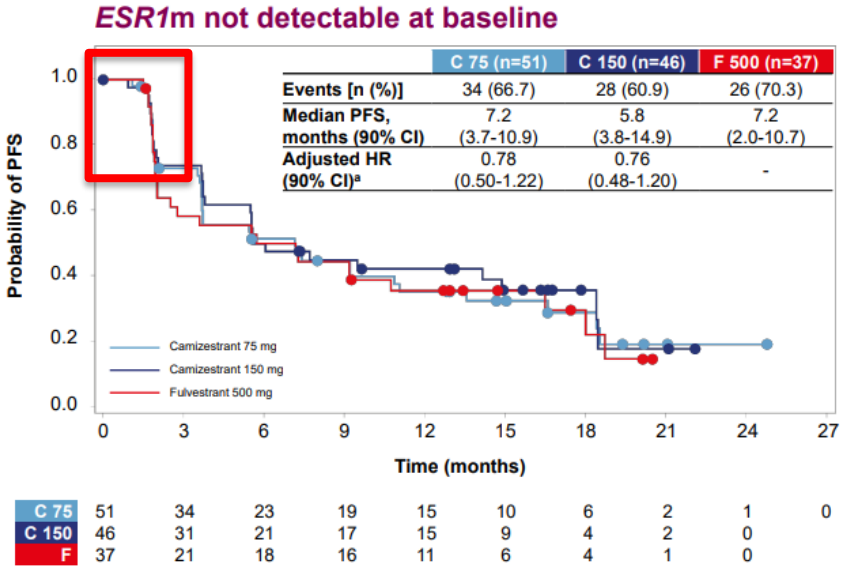
SERENA-2: PFS by *ESR1* mutational status





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Oliveira et al., SABCS 2022

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CAPItello-291: Phase III, randomized trial of capivasertib and fulvestrant in AI-resistant patients

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

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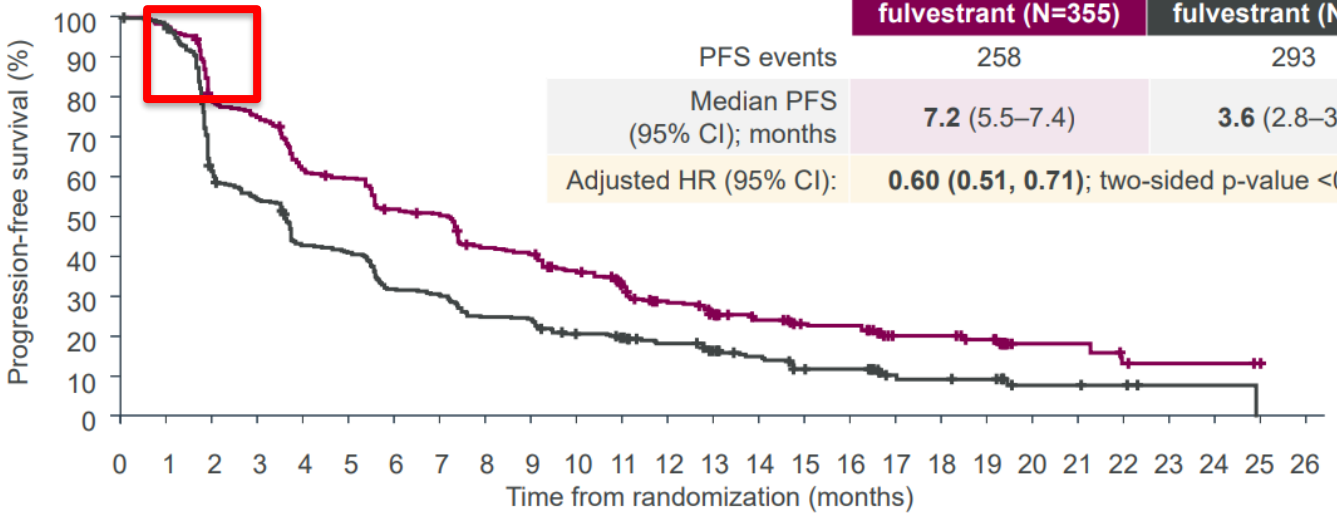
Turner et al., SABCS 2022

ULB iris

CAPItello-291: Phase III, randomized trial of caapivasertib and fulvestrant in AI-resistant patients



	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	

Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

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Turner et al., SABCS 2022

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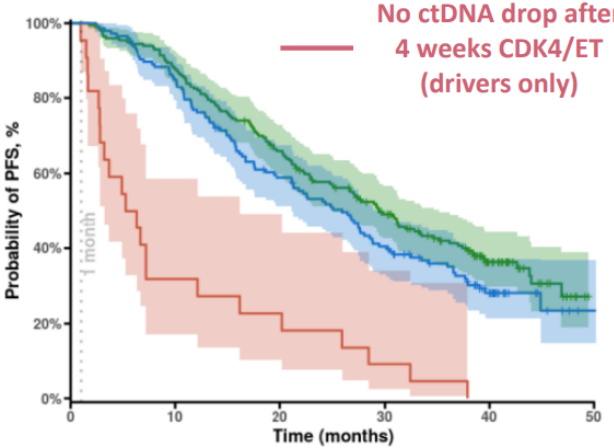
- A non-negligible proportion of patients do not benefit from CDK4/6i in first line (PFS<6-12 months)
- These patients do not derive benefit from SERD (elacestrant, exploratory analysis of EMERALD)
- All studies with ET post-CDK4/6i (MAINTAIN, EMERALD, SERENA-2, CAPItello-291) show a vertical drop at the beginning of the curves → this drop represents patients who are endocrine resistant and do not benefit from these agents
- In these patients, a PD before 3 months of treatment means that there is no benefit and that we are losing time by administrating this treatment

- **These patients should be identified upfront, and treated NOT with new fancy ET, but with good old chemotherapy (or new good chemotherapy, i.e., ADCs)**

Predict endocrine resistance at diagnosis in patients with ER-positive mBC

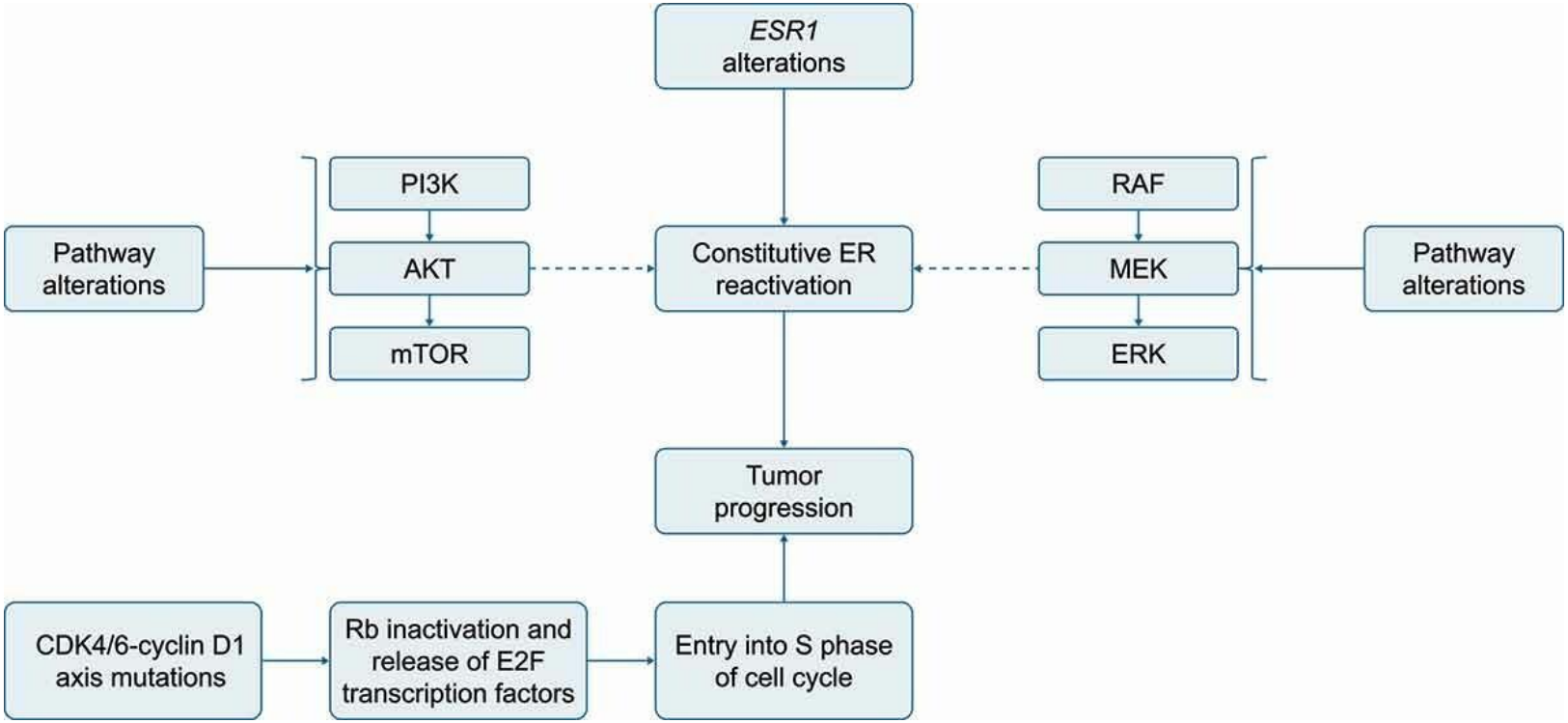


PD17-02, Bailleux et al

and treat them with modern therapies (ADC, targeted therapies, IO SAFIR03 trial, funded by BCFR)

Modern diagnostic tools and therapies allow to challenge the dogma that patients with ER+ mBC must receive ET 1st line

Mechanisms of Resistance to ER-targeting drugs



Chen et al., Exp Opinion Investig Drugs, 2022

ctDNA sequencing of patients enrolled in PlasmaMATCH

nature COMMUNICATIONS

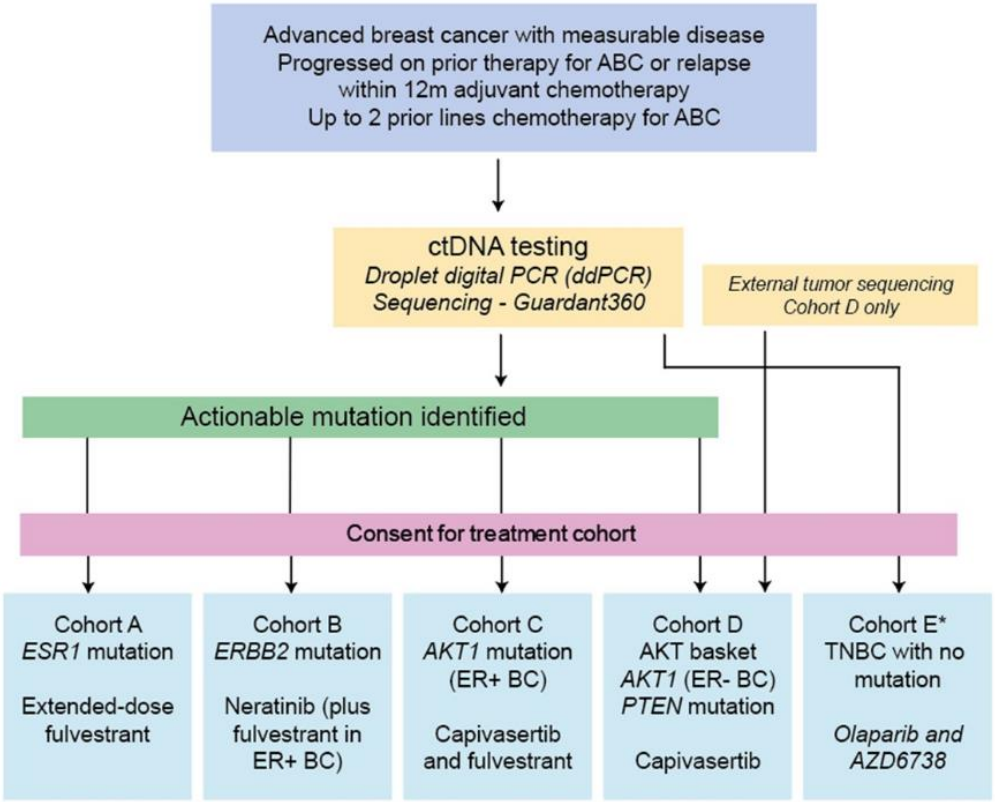
ARTICLE

https://doi.org/10.1038/s41467-021-22605-2 OPEN

Genomic profile of advanced breast cancer in circulating tumour DNA

Belinda Kingston[1], Rosalind J. Cutts[1], Hannah Bye[2], Matthew Beaney[1], Giselle Walsh-Crestani[1], Sarah Hrebien[1], Claire Swift[1], Lucy S. Kilburn[3], Sarah Kernaghan[3], Laura Moretti[3], Katie Wilkinson[3], Andrew M. Wardley[4], Iain R. Macpherson[5], Richard D. Baird[6], Rebecca Roylance[7], Jorge S. Reis-Filho[8], Michael Hubank[2], Iris Faull[9], Kimberly C. Banks[9], Richard B. Lanman[9], Isaac Garcia-Murillas[1], Judith M. Bliss[3], Alistair Ring[10]✉ & Nicholas C. Turner[1,10]✉

PlasmaMatch trial



plasmaMATCH: A study utilizing **ctDNA testing to identify actionable mutations** and select patients for matched targeted therapies. Primary Objective: response rate of therapies matched to ctDNA mutations

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Kingston B et al, ASCO 2022

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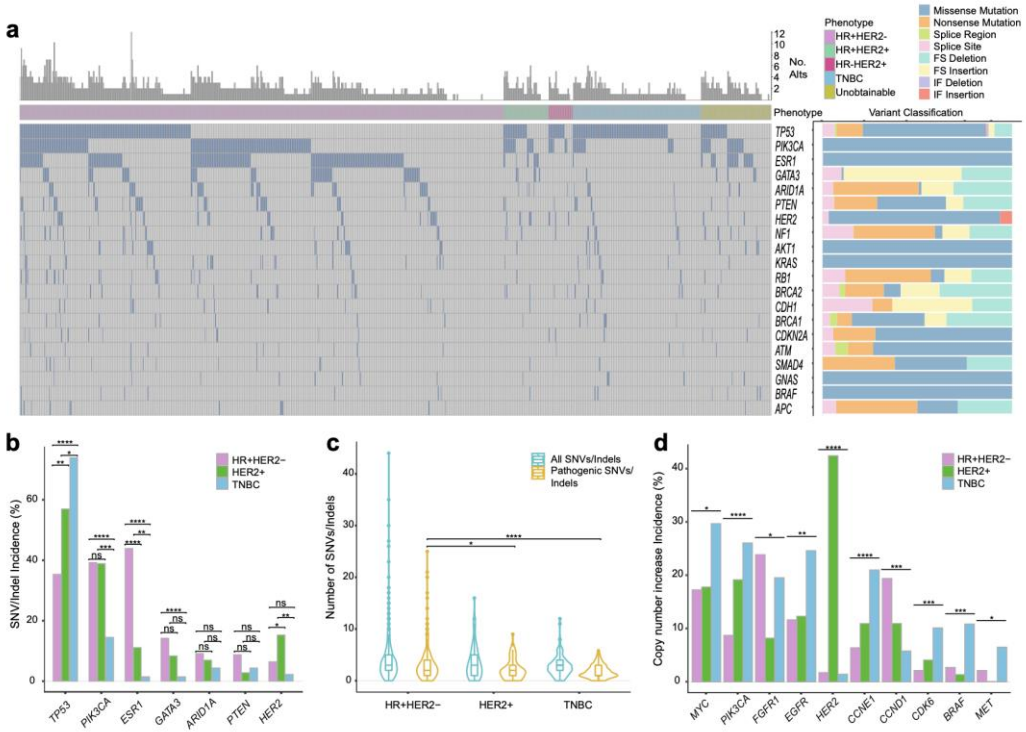
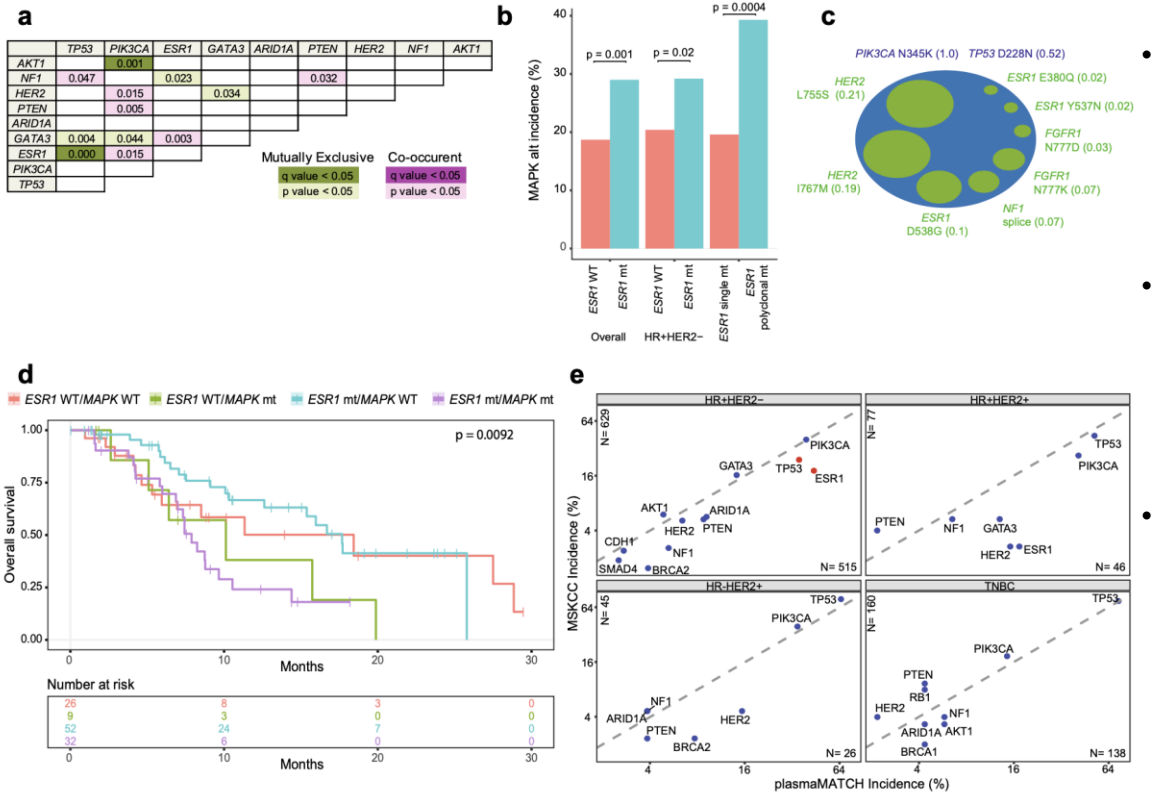
Mutational profile of advanced breast cancer by ctDNA sequencing



Kingston B et al, Nat Comm 2021

Co-enrichment of MAPK pathway and ESR1 polyclonal mutations



- In HR + HER2-neg breast cancer ctDNA analysis demonstrates **divergent routes to endocrine resistance** in individual patients, suggesting that different metastases may develop divergent mechanisms of resistance.
- Tissue sequencing studies demonstrated mutual exclusivity of ESR1 mutations and MAPK pathway alterations; in contrast, in liquid biopsy ESR1 mutations may co-exist with MAPK pathway alterations;
- This occurs particularly in patients with polyclonal ESR1 mutations, with **polyclonal resistance** associated with **poor overall survival**

Kingston B et al, Nat Comm 2021

Two Key Messages from Kingston et al., Nature Communications 2021

- The **poly-clonal nature of endocrine resistance** likely **substantially challenges attempts to treat** endocrine resistant disease

- Taken together, these findings emphasize the importance of **investigating upfront** combination approaches **to prevent endocrine resistance**

5 reasons why the new drugs are not the turning point to overcome endocrine resistance

1. A not negligible proportion of patients do not benefit from 1st line CDK4/6i and do not benefit from new 2nd line agents (SERD, AKTi, PI3Ki..)

   → in these patients there is no way to revert their endocrine resistance using ET; giving ET is a waste of time; we should learn to identify these patients upfront, and treat them accordingly (e.g., CT, ADCs)

2. **Endocrine resistance is not based on one mechanism**
   - There are several mechanisms of resistance to ER-targeting drugs
   - The one-size fits all approach cannot work here

5 reasons why the new drugs are not the turning point to overcome endocrine resistance

3. The **poly-clonal nature of endocrine resistance** likely **substantially challenges attempts to treat** endocrine resistant disease

- It's important to **investigate upfront** combination approaches **to prevent endocrine resistance**

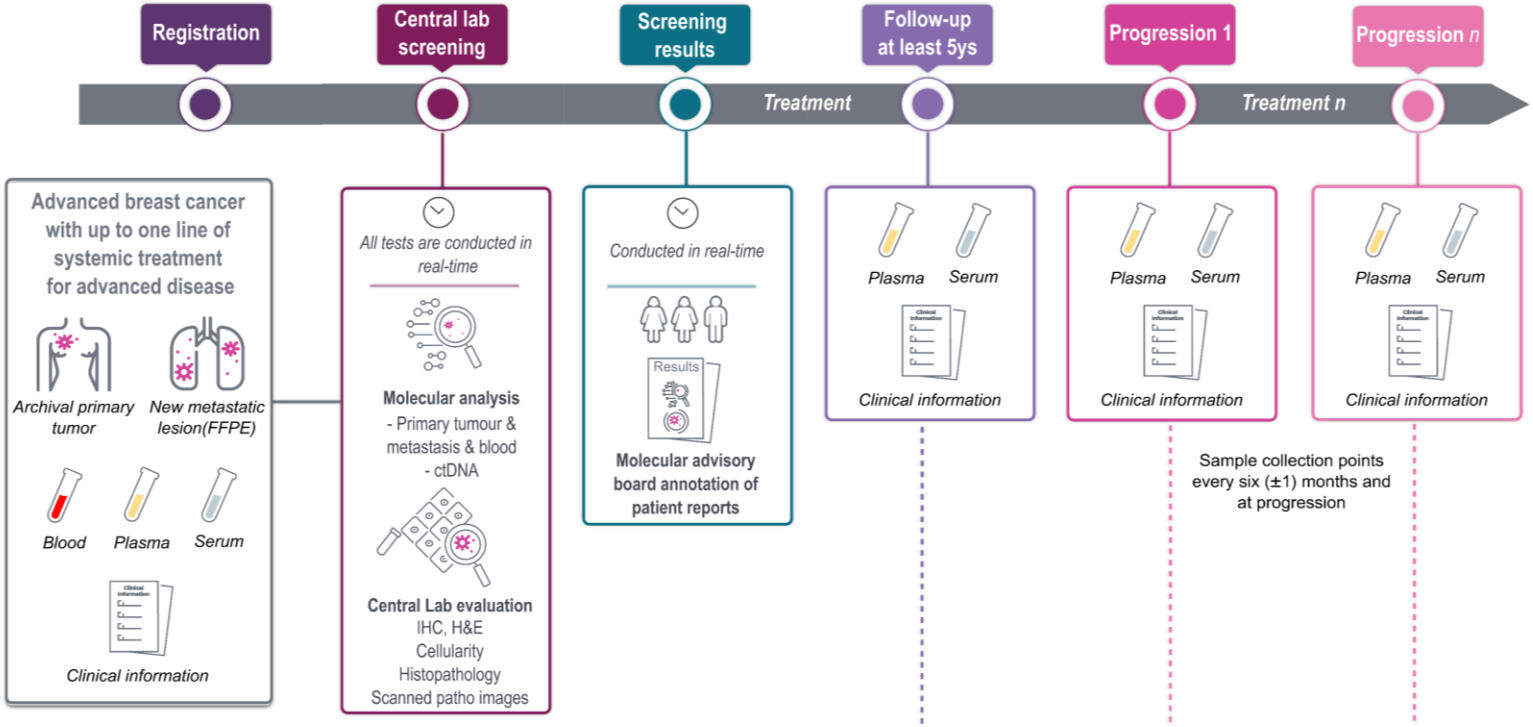
4. Modern diagnostic tools will allow to **predict endocrine resistance at diagnosis,** and **will challenge the dogma** that patients with **ER+ mBC must receive ET in 1st and 2nd line**

5 reasons why the new drugs are not the turning point to overcome endocrine resistance

5. Pharma has led great randomized clinical trials to test new drugs, but we need to better understand the disease!

- Finding biomarkers of response to better select patients who will benefit from a treatment should come from academic efforts

AURORA: a Breast International Group (BIG) Molecular Screening Initiative



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https://clinicaltrials.gov/ct2/show/NCT03028740

ULB iris

Thank you for your attention!

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L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

20 - 21 APRILE 2023 ROMA

THE HIVE HOTEL

Via Torino, 6

THE OXFORD DEBATE EDITION


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