

**16<sup>th</sup> Belgian Symposium on the Integration of Molecular Biology  
Advances into Oncology Clinical Practice**



# **Selective estrogen receptor degraders (SERDs) and new SERMS in breast cancer**

Caroline DUHEM, MD

Centre Hospitalier de Luxembourg -Kribszentrum



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and new SERMS in breast cancer**

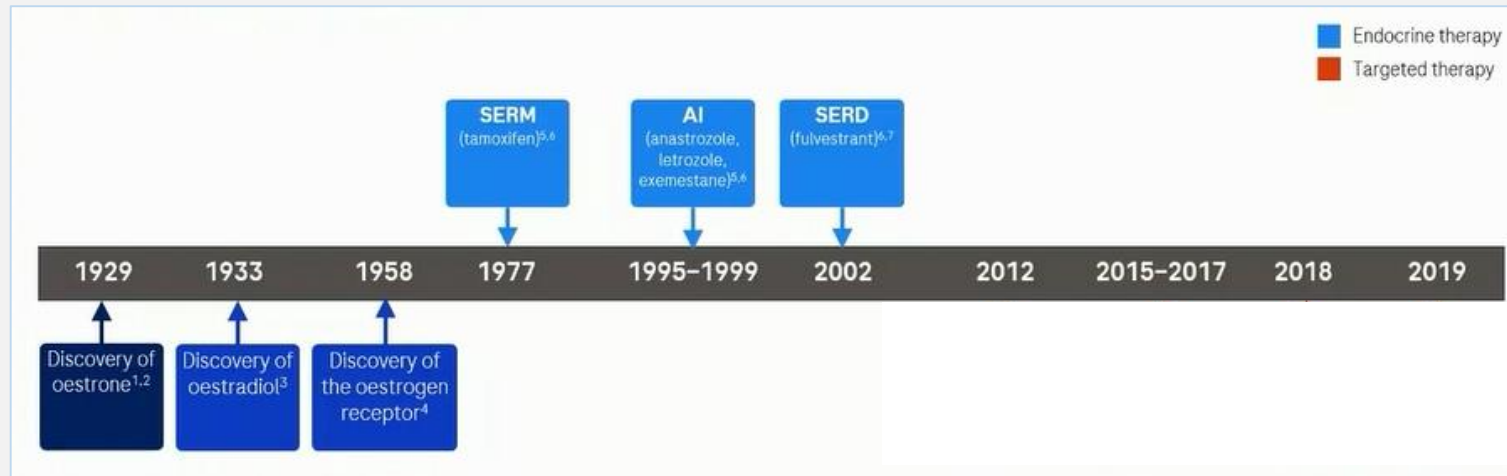
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**I Have no disclosure related to this  
presentation**

# Treatment landscape for HR+ BC over the past century

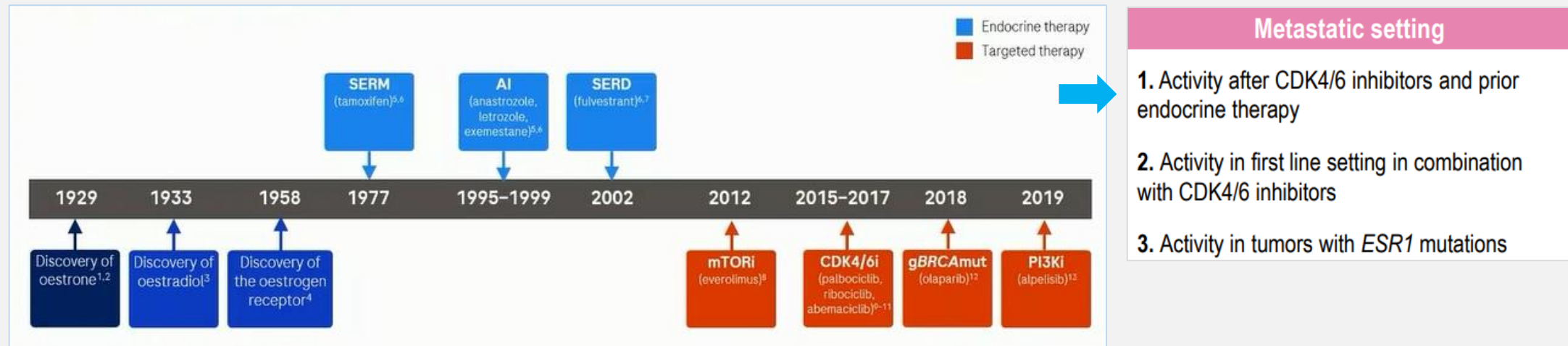
## The endocrine pathway remains a critical target



**Lack of substantial efficacy improvements with current ET: highlights the Challenge of achieving large efficacy gain with novel agents**

# Treatment landscape for HR+ BC over the past century

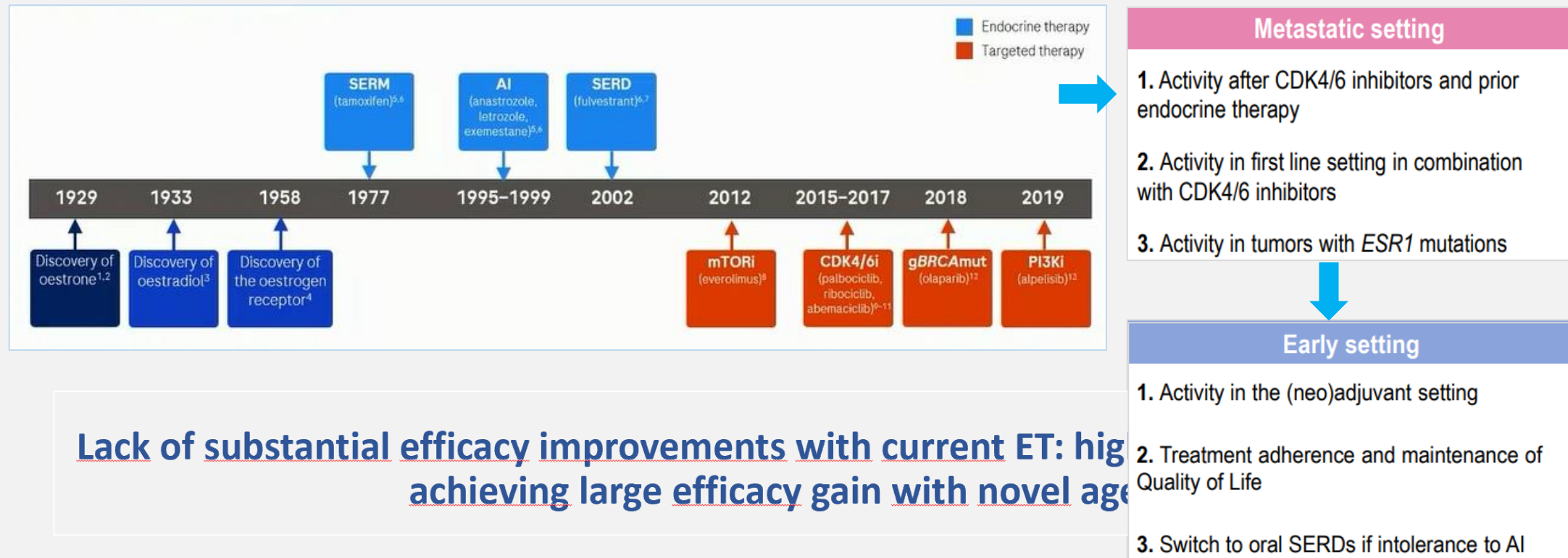
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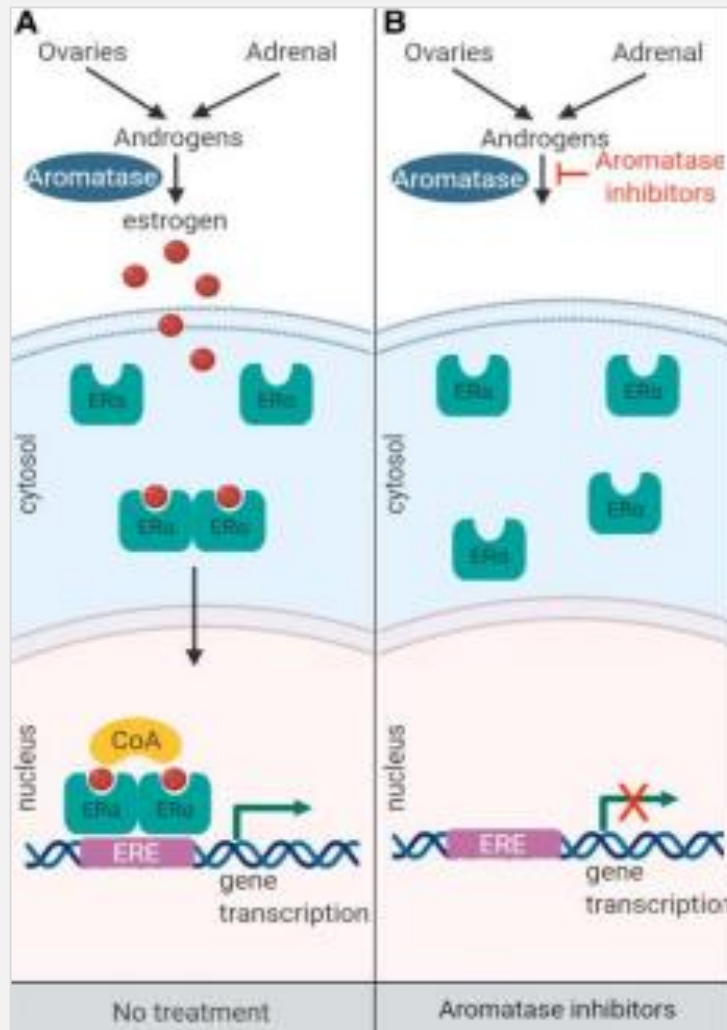
## The endocrine pathway remains a critical target



**Lack of substantial efficacy improvements with current ET: high achieving large efficacy gain with novel agents**

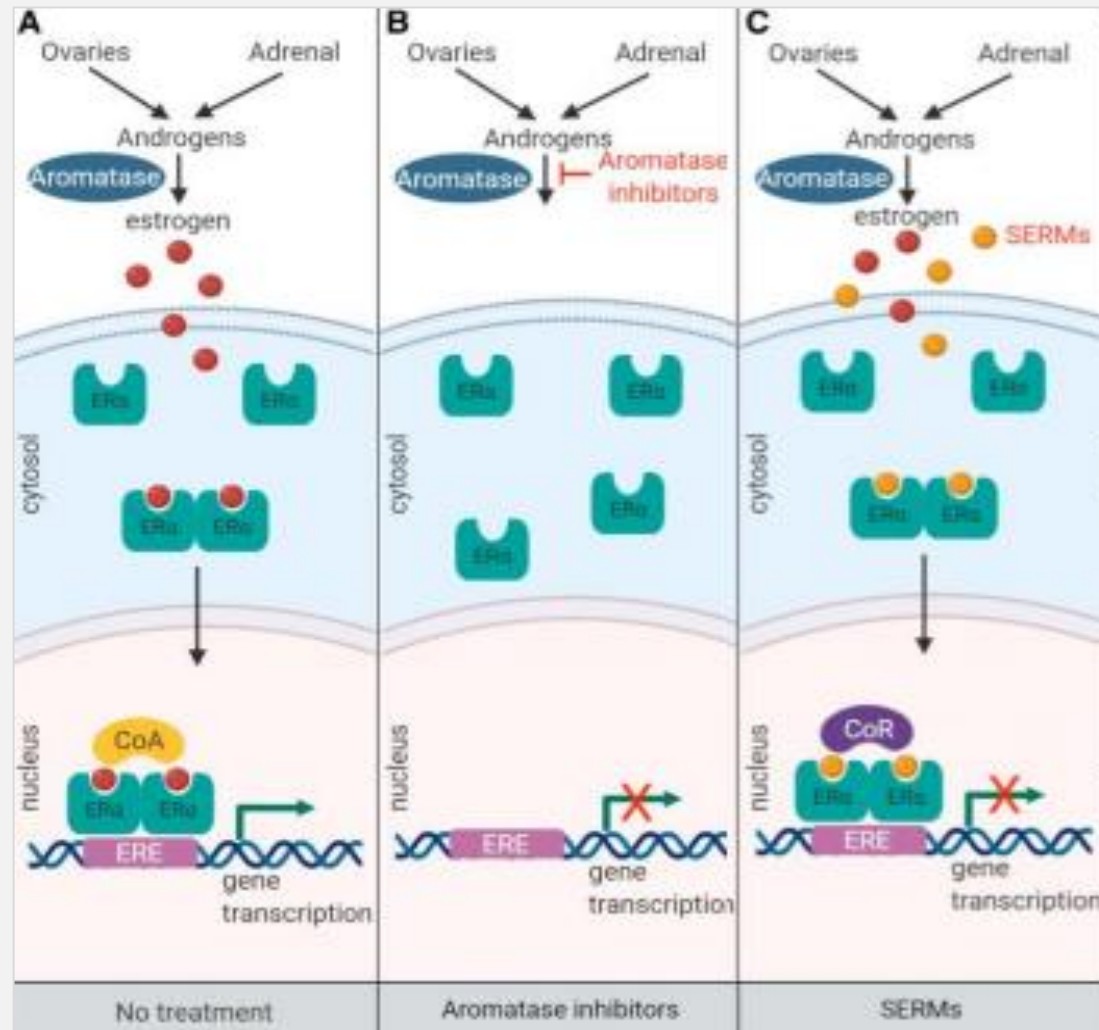
# Mechanisms of action of Endocrine Therapies

Hanker AB et al. Cancer Cell 2020;37:496-513 | McDonnell D et al. J Clin Oncol 2021;39(12):1383-1388



# Mechanisms of action of Endocrine Therapies

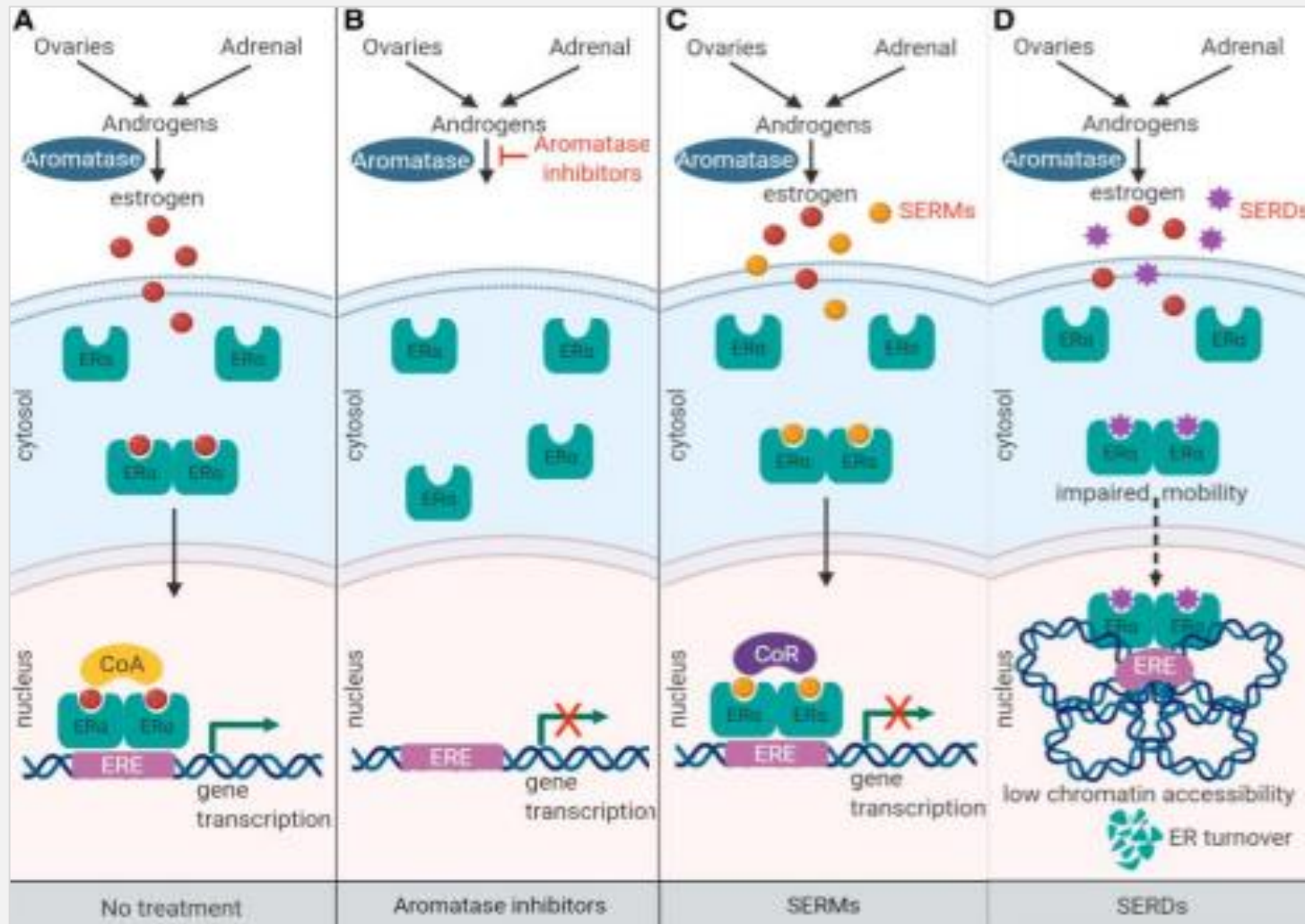
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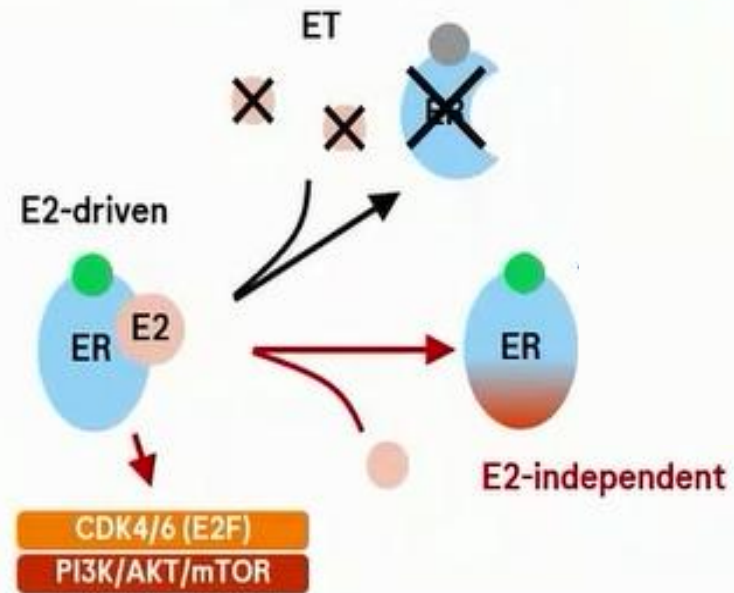
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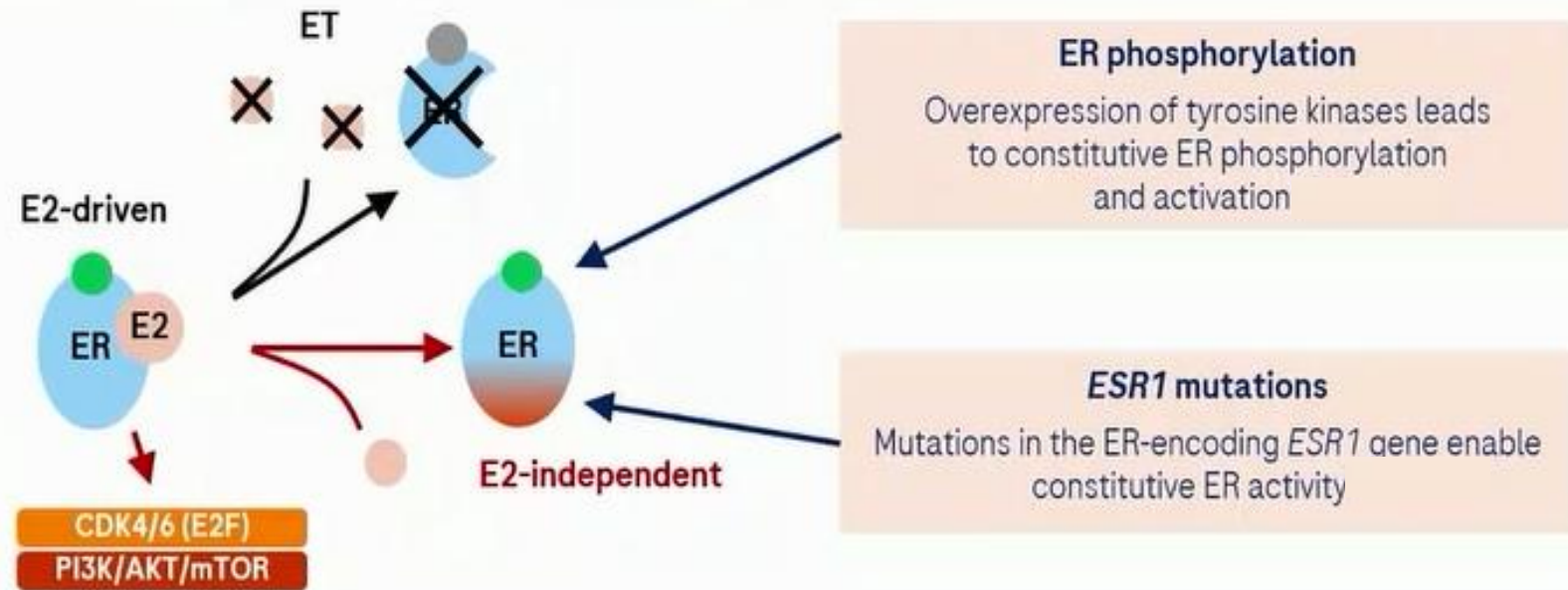




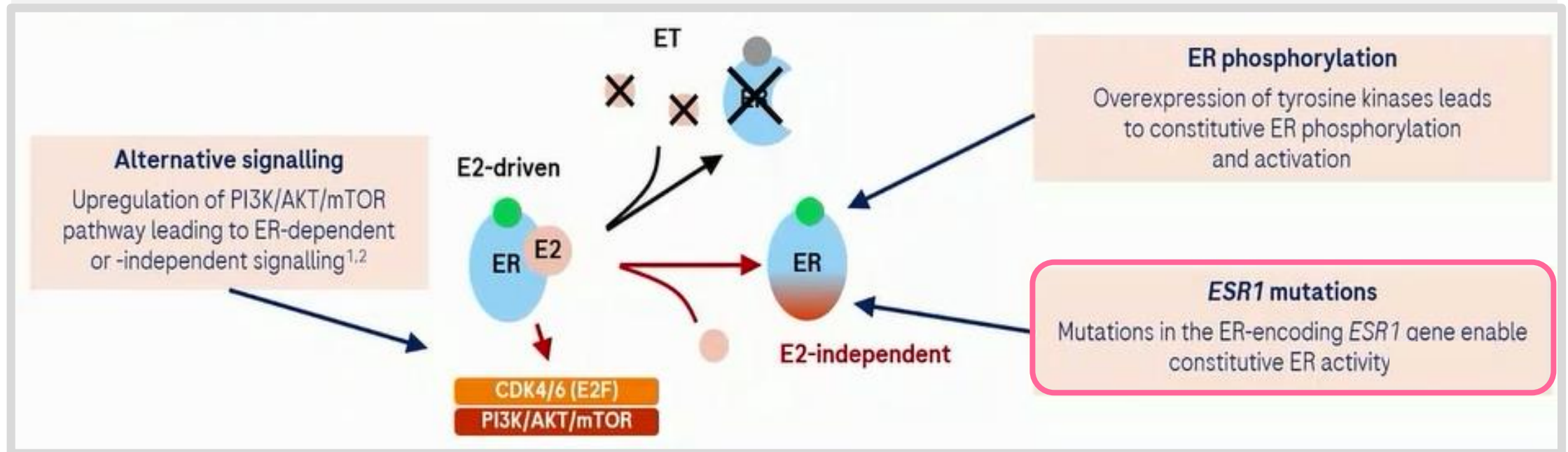
# Mechanisms of Resistance to Endocrine Therapies



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## ESR 1mut as Biomarker of ER-depdt resistance ?

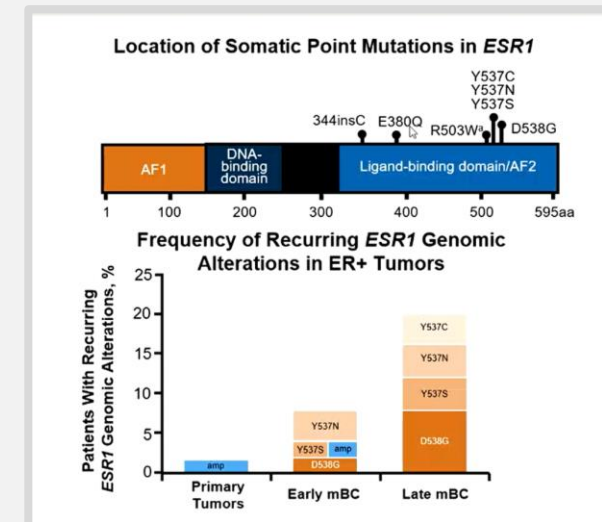
### ❖ ESR 1 frequency

- ↗ with line(s) of treatment(s)
- Exposure to AIs + duration of exposure

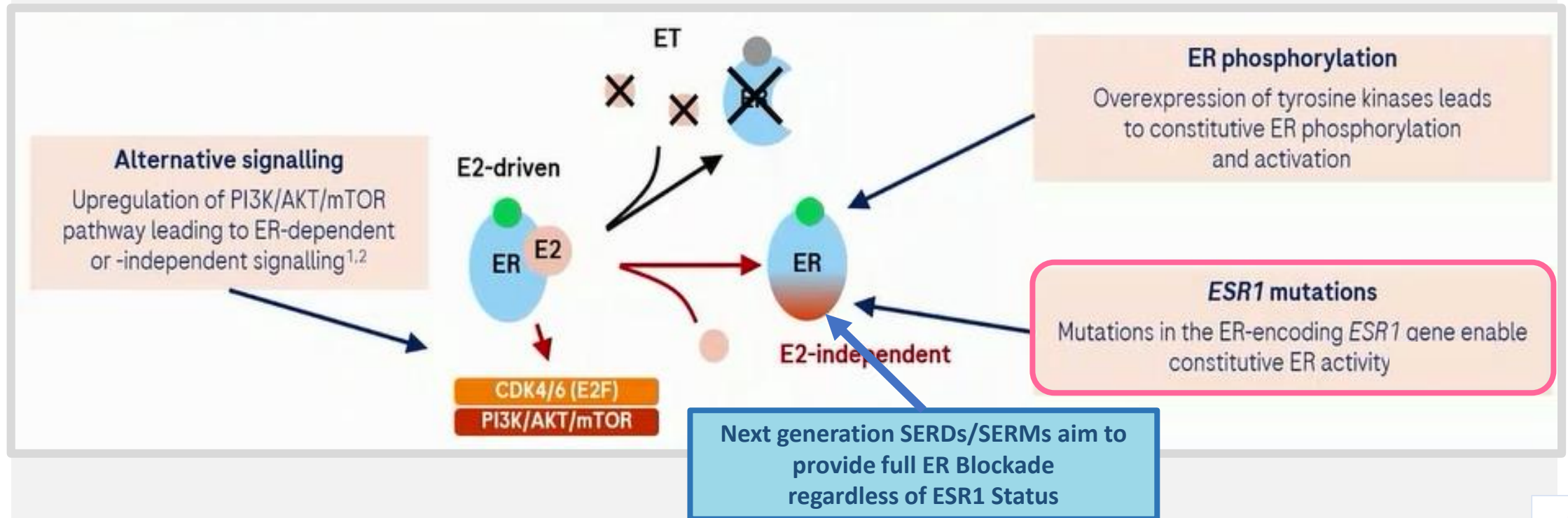
### ❖ Detection in plasma(ct DNA) > metastatic Tissue

Pascual J., Ann Oncol 2022

- ctDNA NGS (genotyping )/ddPCR
- not (yet) of« clinical utility «
- Important factor for decision making

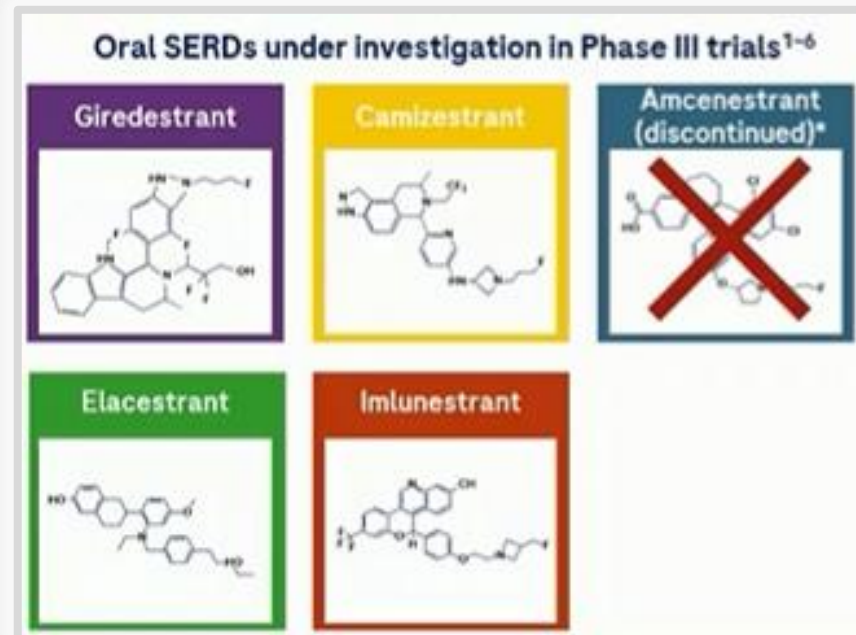


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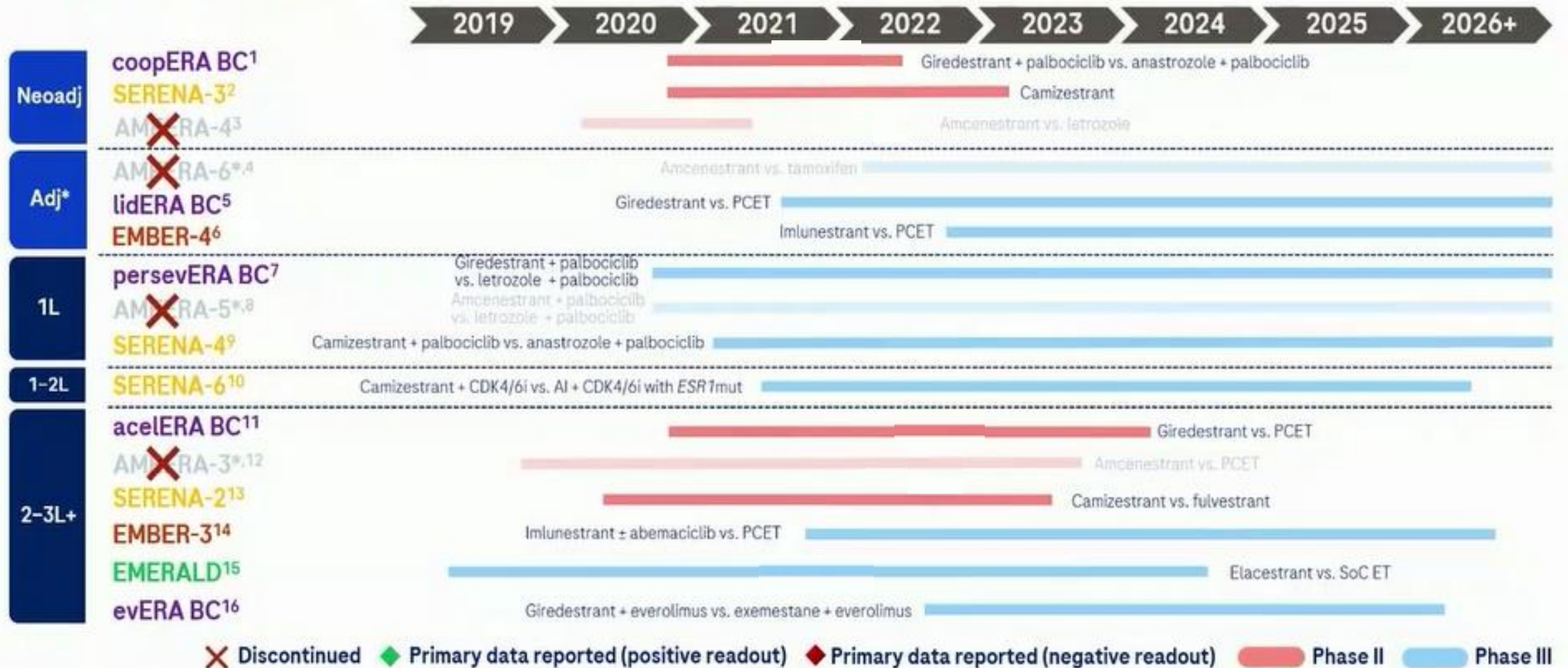
## « Next generation » SERDs

- Promising activity , regardless of
  - ESR1 status
  - Prior Tt with Fulvestrant , Cdk4/6 or ChemoT
- Oral drugs , acceptable toxicity profiles as monoTh / Combination with Cdk4/6i



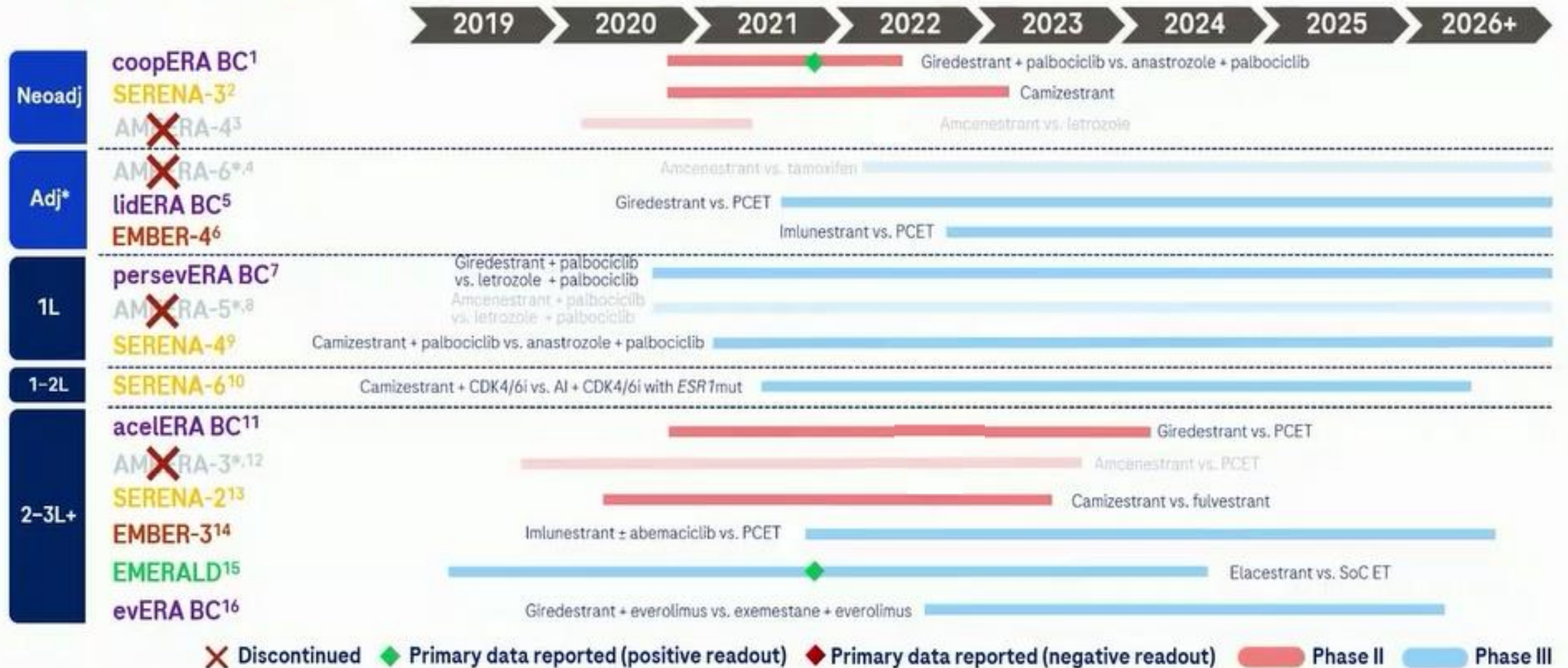


# Programme of completed and ongoing Phase II/III Trials of Oral SERDs

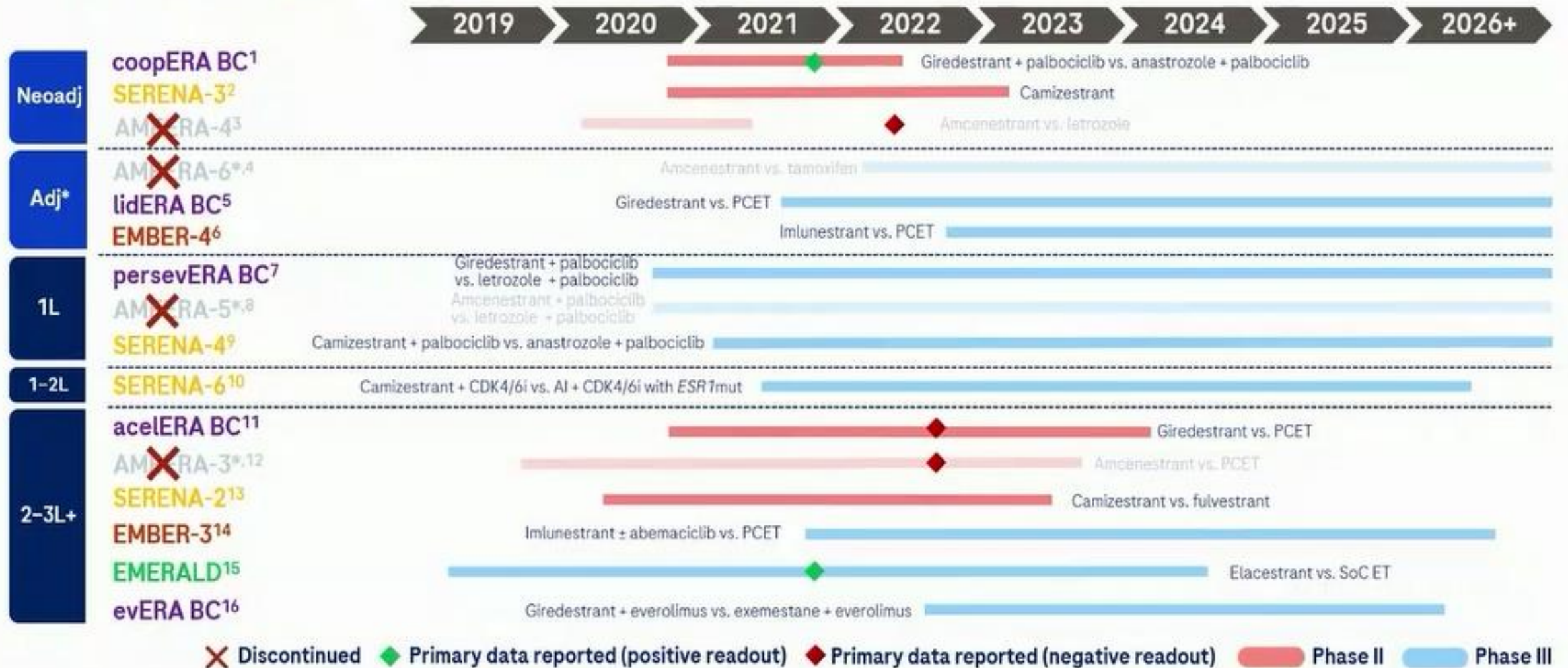




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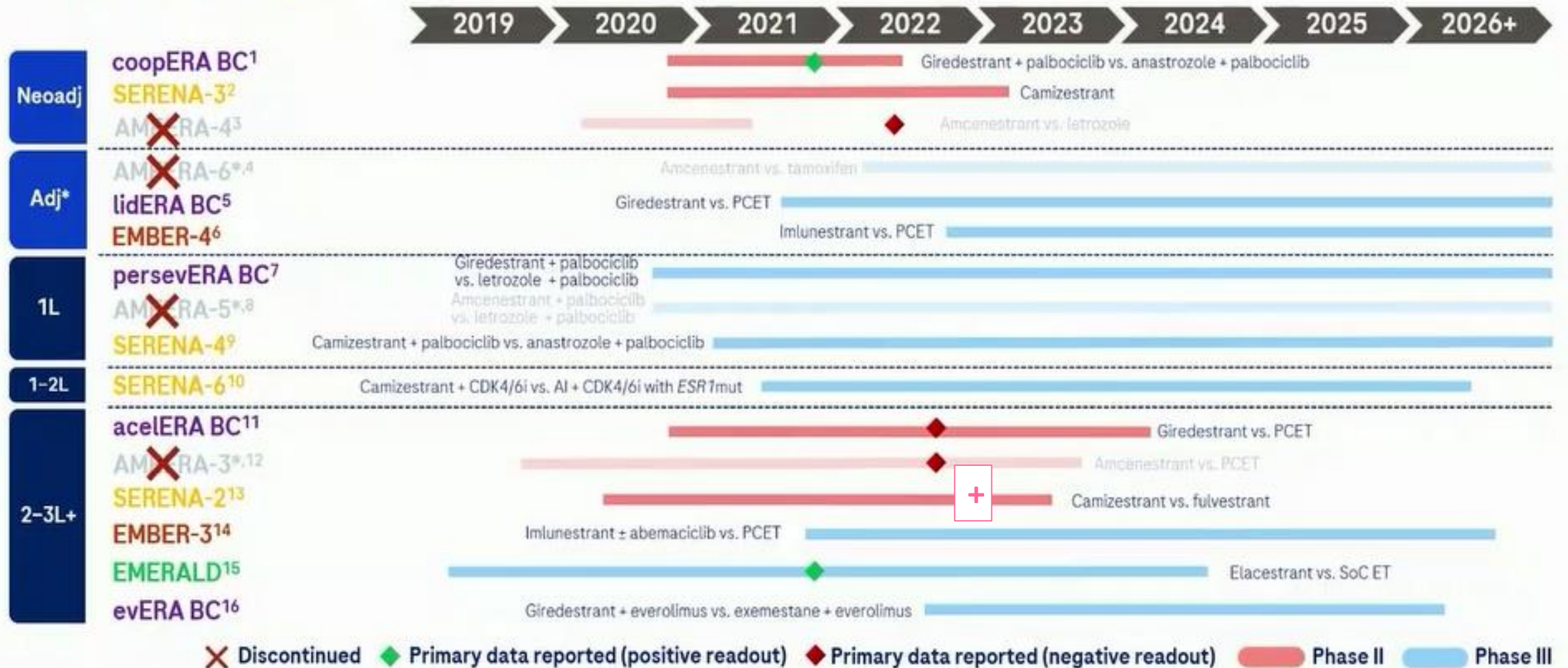


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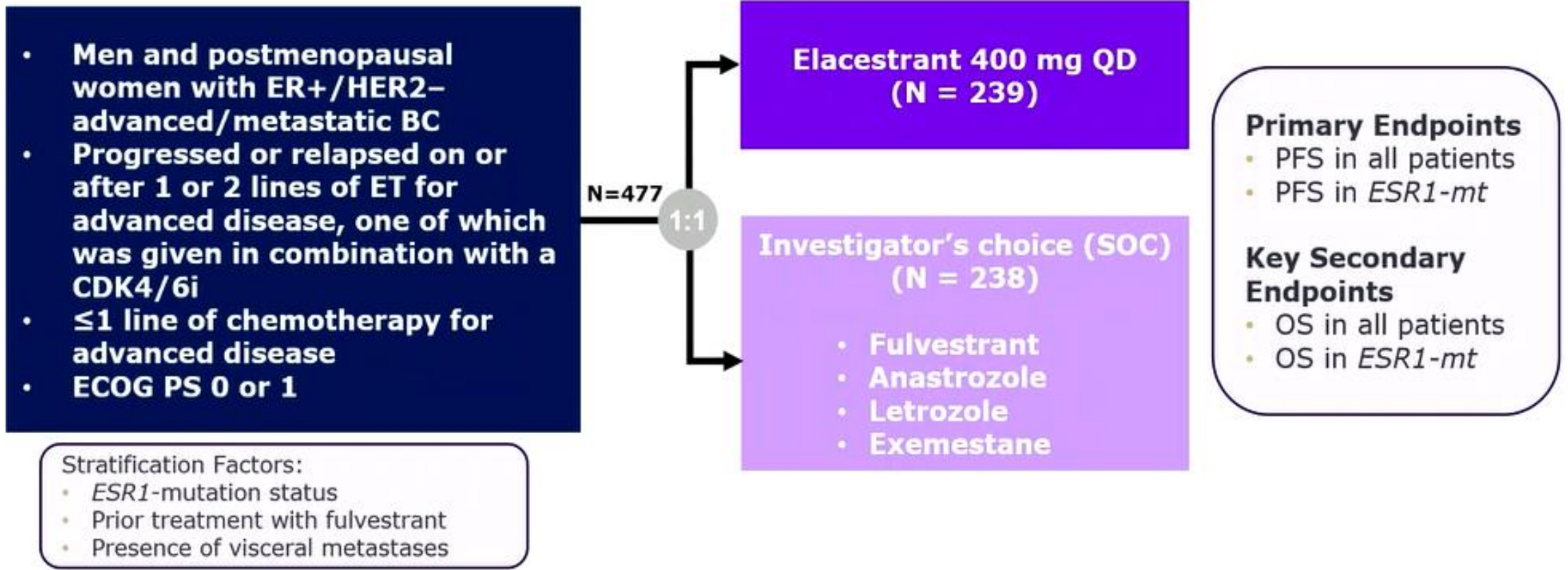


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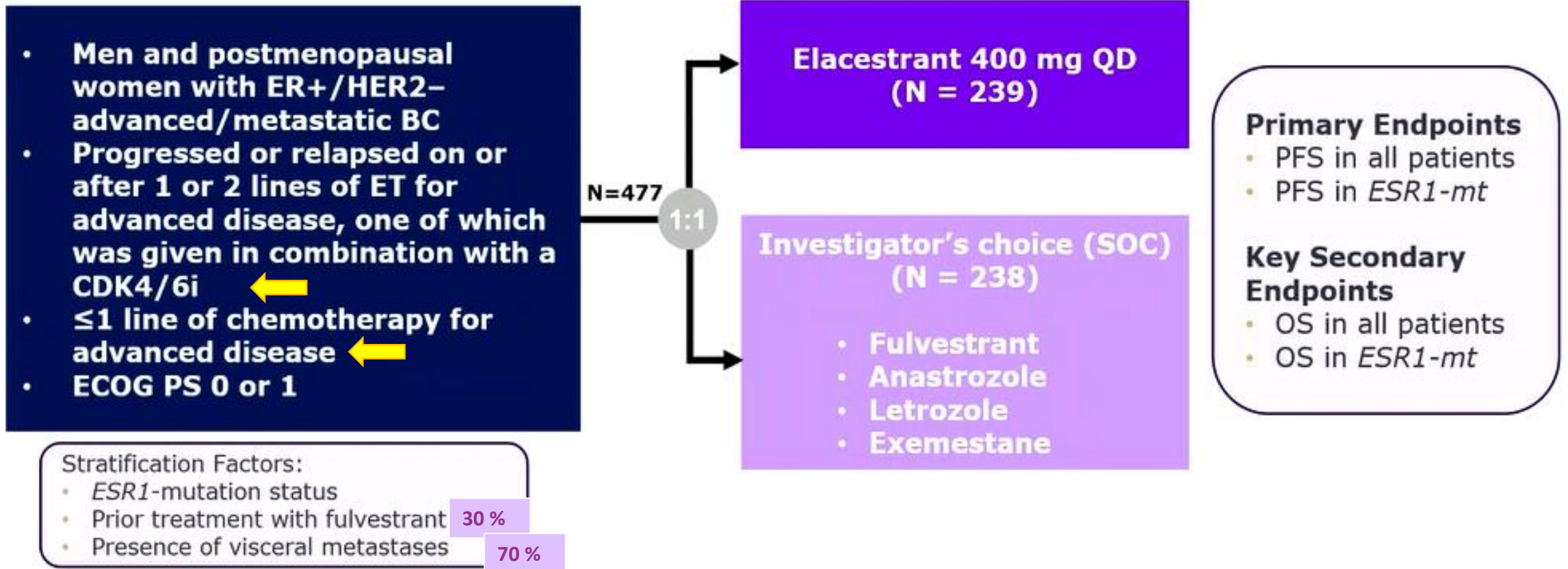
# Phase III EMERALD Trial : Elacestrant vs SOC after Cdk4/6i

Bidard FC et al , JCO 2022



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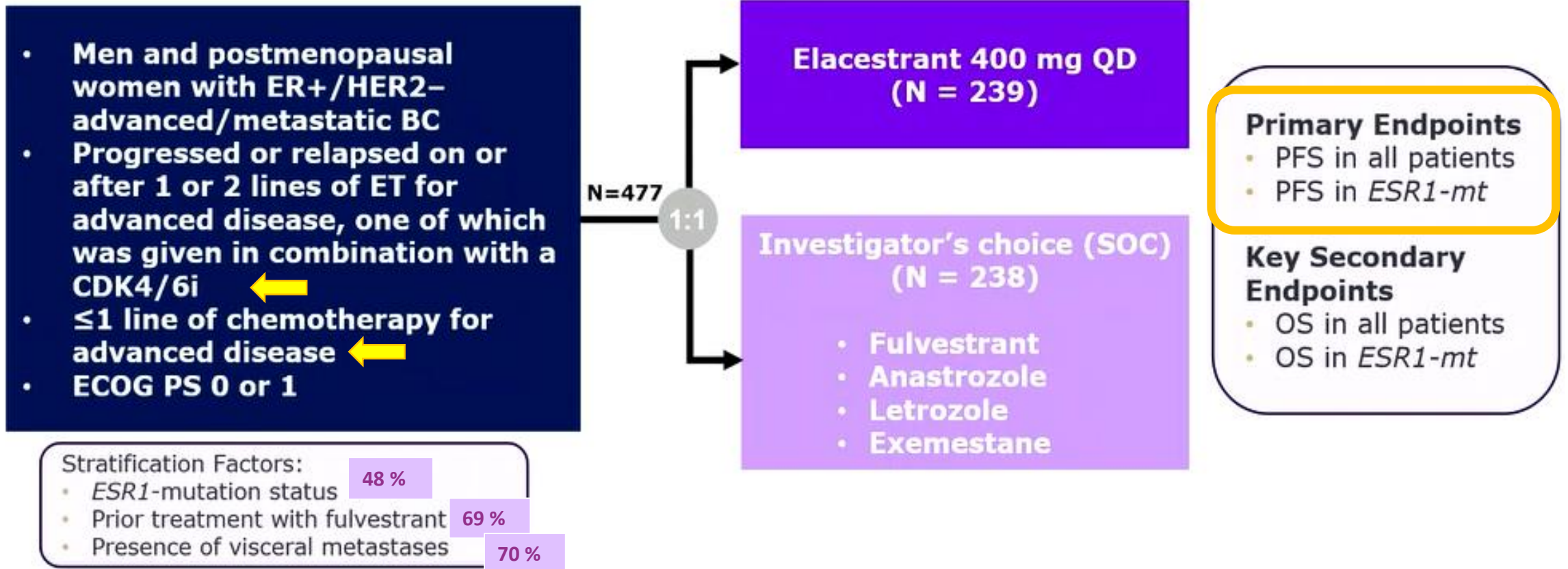
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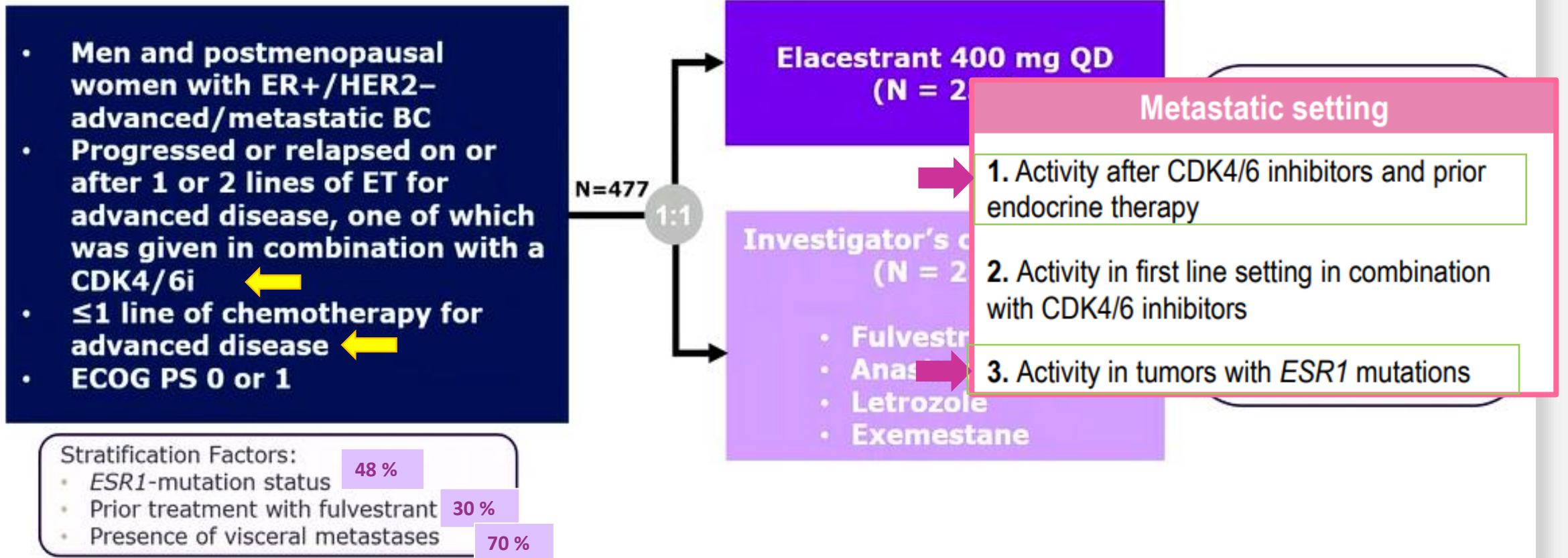
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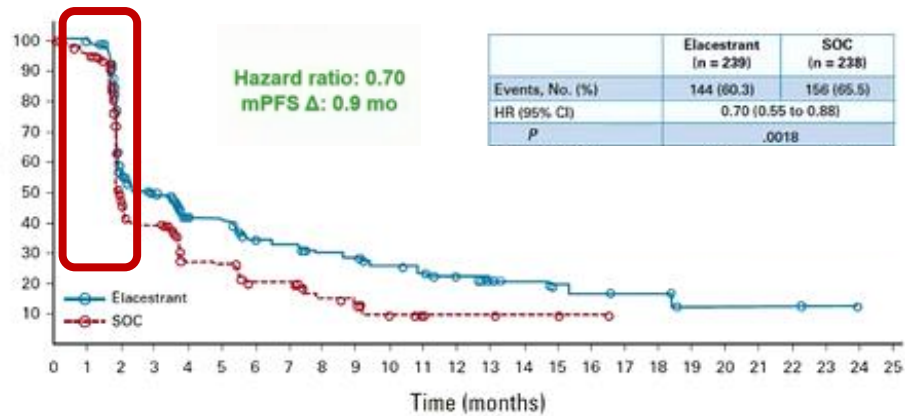




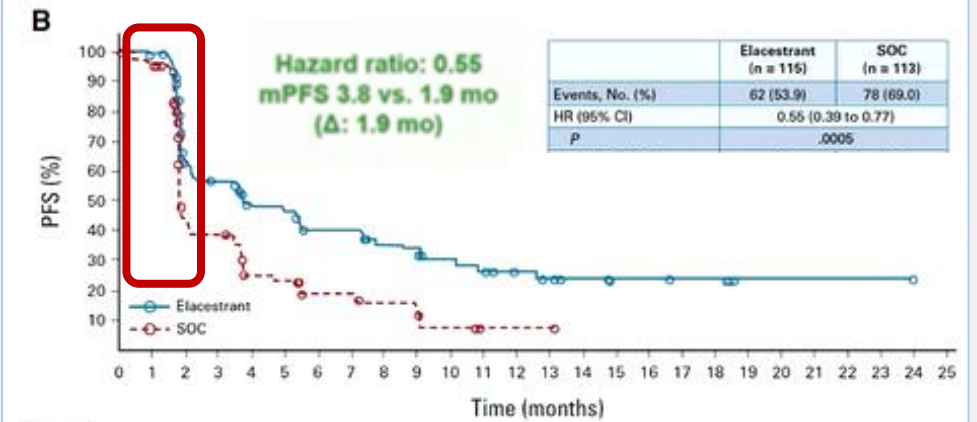
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## All Patients (ITT) by ICR



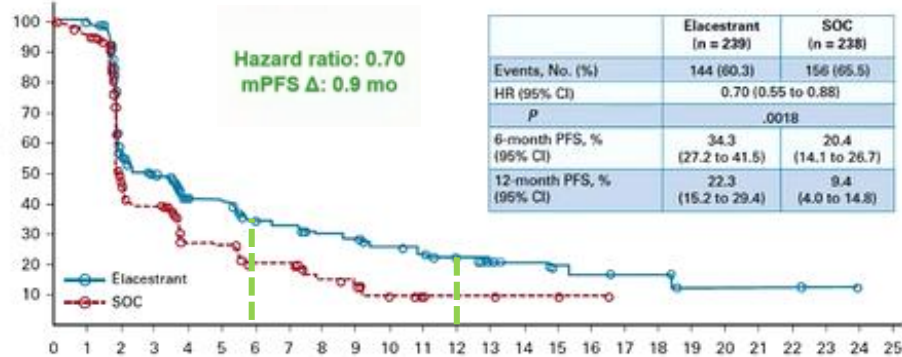
## Patients with *ESR1-mt* by ICR



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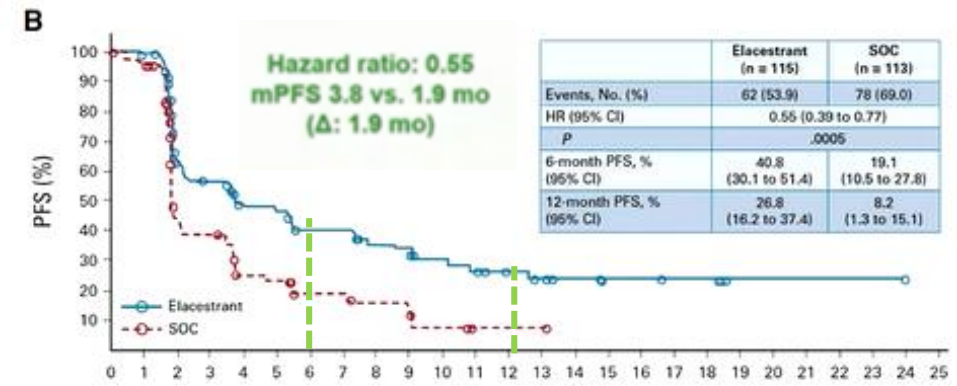
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**30% reduction** in the risk of progression or death in all patients with ER+/HER2- MBC

## Patients with *ESR1-mt* by ICR



**45% reduction** in the risk of progression or death in patients harboring *ESR1mut*

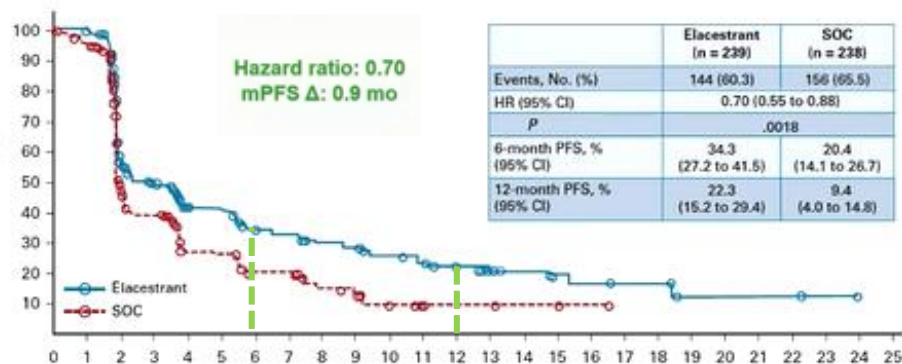
## Sub groups and Post Hoc analysis

- Control arm
  - AI vs Fulv [Aftimos Ph ,ESMO 2022](#)
- Pre Treatment
  - Chemot [Kaklamani V, ASCO 2022](#)
  - Duration of Cdk4/6i [KaklamaniV , SABCS 2022 GS3-01](#)

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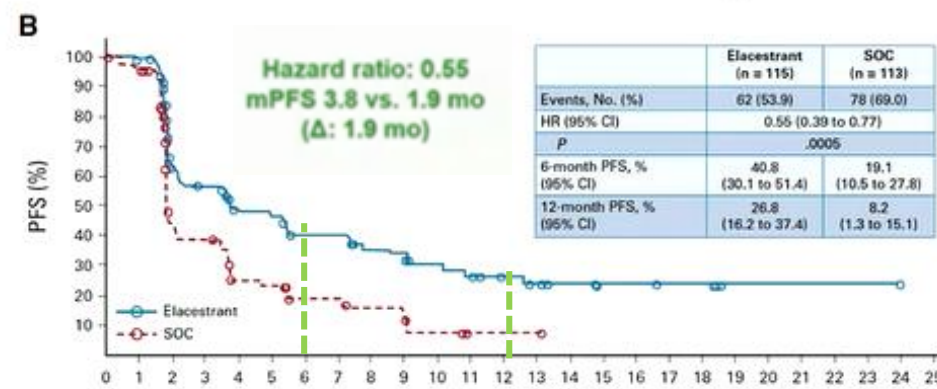
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  - Duration of Cdk4/6i KaklamaniV , SABCS 2022 GS3-01



If Expo to cdk4:/6 i ≥ 12 mo

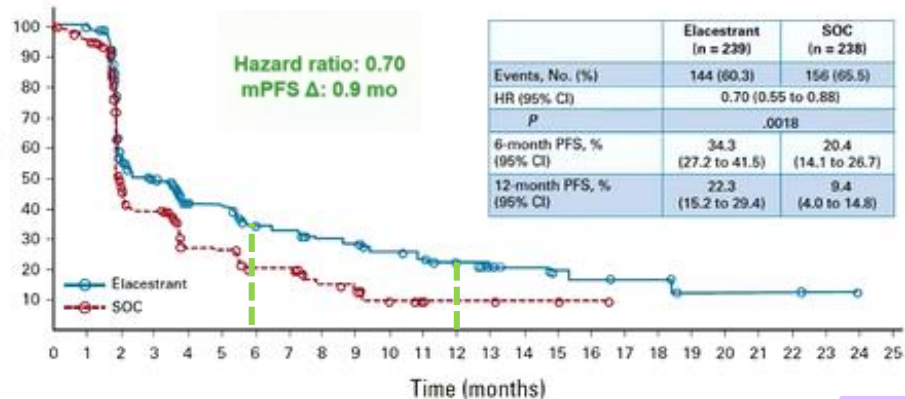
→ PFS

- All Pts, 1,9 vs 3,9 mo (HR 0,61)
- *ESR1-mt* 1,9 vs 8,6 mo (HR 0,41)

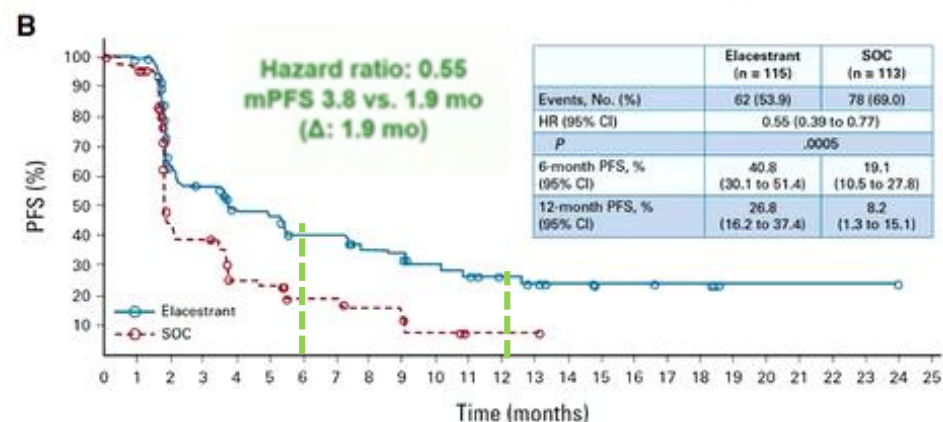
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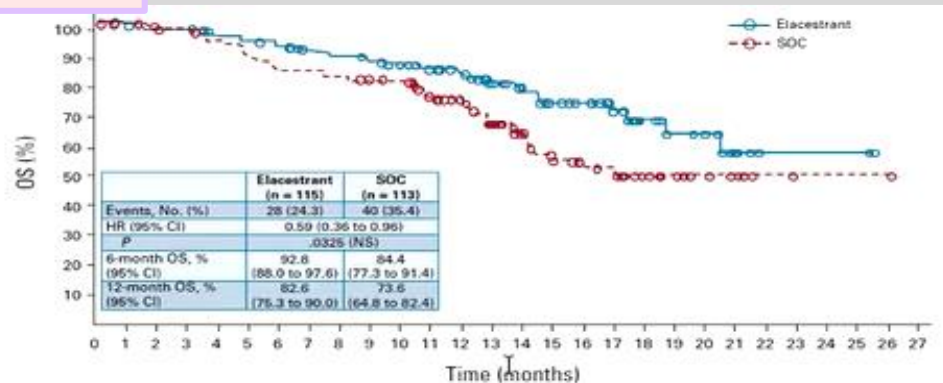
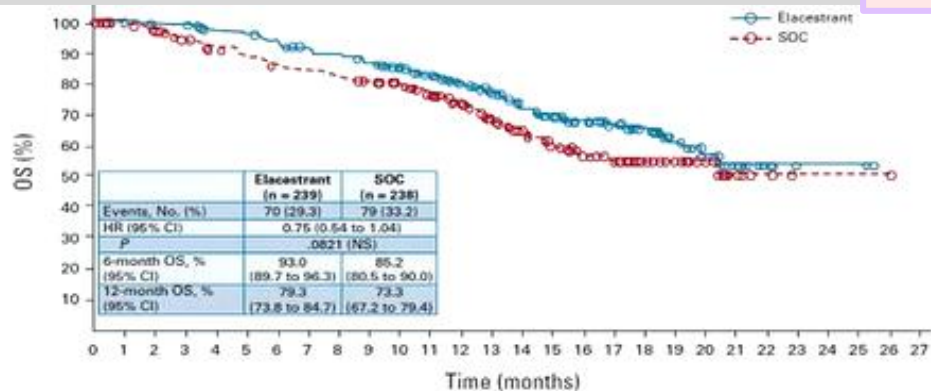


## Patients with *ESR1-mt* by ICR



Interim OS

« OS data : SABCS 2022 »





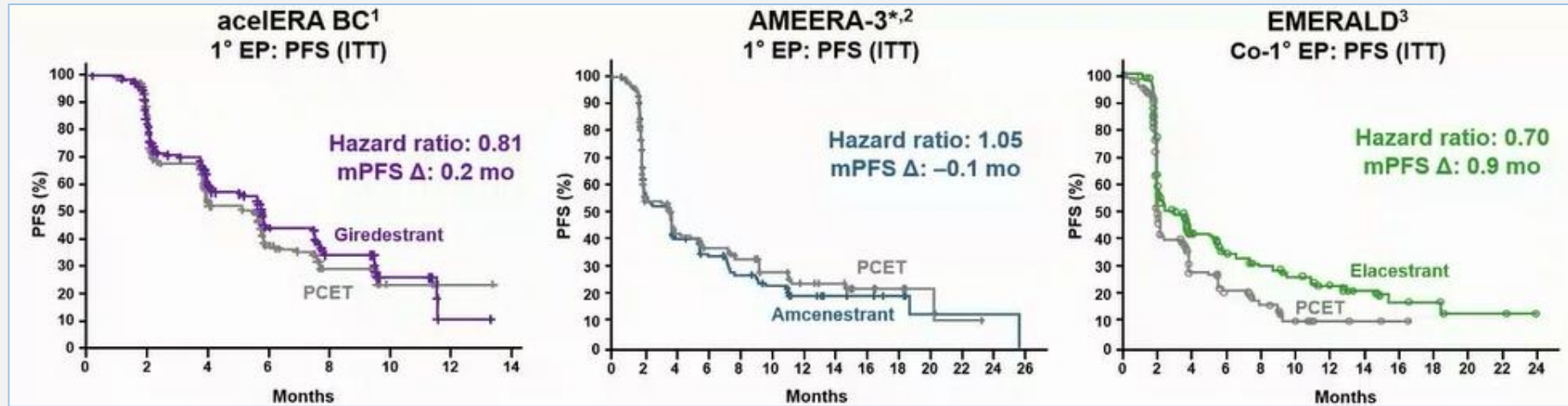
# Oral SERDs in Phase II/III 2-3L mBC trials

	aceIERA BC <sup>1,2</sup> (Phase II; N = 303)	AMEERA-3 <sup>*,3,4</sup> (Phase II; N = 290)	EMERALD <sup>5,6</sup> (Phase III; N = 477)
Oral SERD	Giredestrant 30 mg PO qd	Amcenestrant 400 mg PO qd	Elacestrant 400 mg PO qd
Comparator arm	Fulvestrant or AI	Fulvestrant, AI or tamoxifen	Fulvestrant or AI
Prior treatment for mBC	1–2 lines of systemic therapy (1 line of ET; ≤1 targeted therapy/CT)	0–2 lines of ET; ≥80% with prior CDK4/6i; ≤1 targeted therapy/CT	1–2 lines of ET (one of which in combination with a CDK4/6i)
Patients	Males and pre-/peri-/postmenopausal females	Males and pre-/peri-/postmenopausal females	Males and postmenopausal females
	39% with <i>ESR1</i> mutations <sup>†</sup>	43% with <i>ESR1</i> mutations <sup>‡</sup>	48% with <i>ESR1</i> mutations (47% planned per protocol <sup>§</sup> )
Primary endpoint(s)	PFS (all patients)		PFS (all patients; <i>ESR1</i> mut population)

- ✓ PreTT
- ✓ Prior exposure to CDK4/6i ( 42- 80 -100 %)
- ✓ % of mut*ESR1* tumors

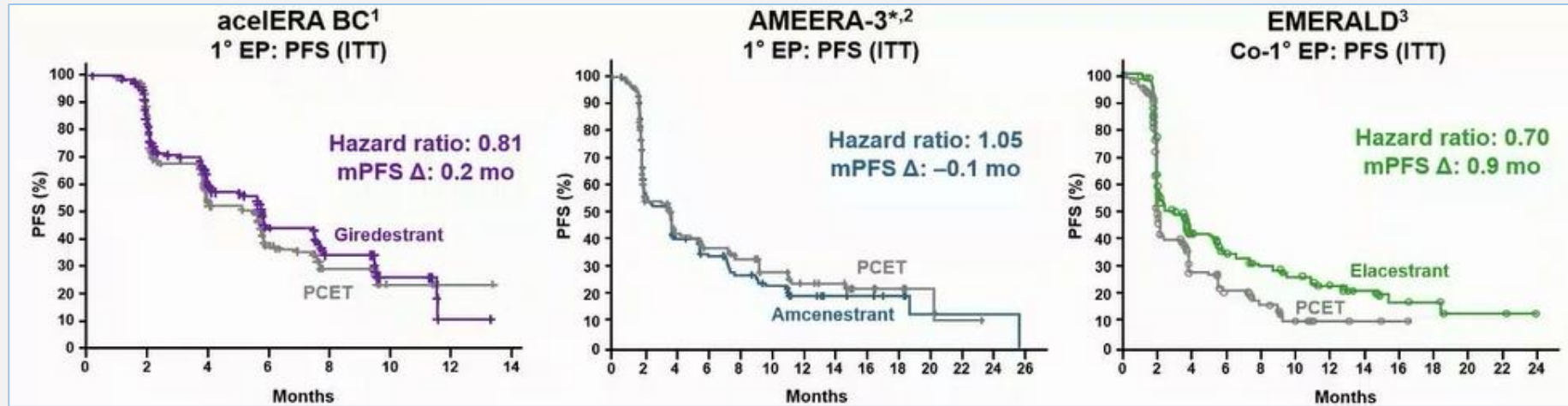
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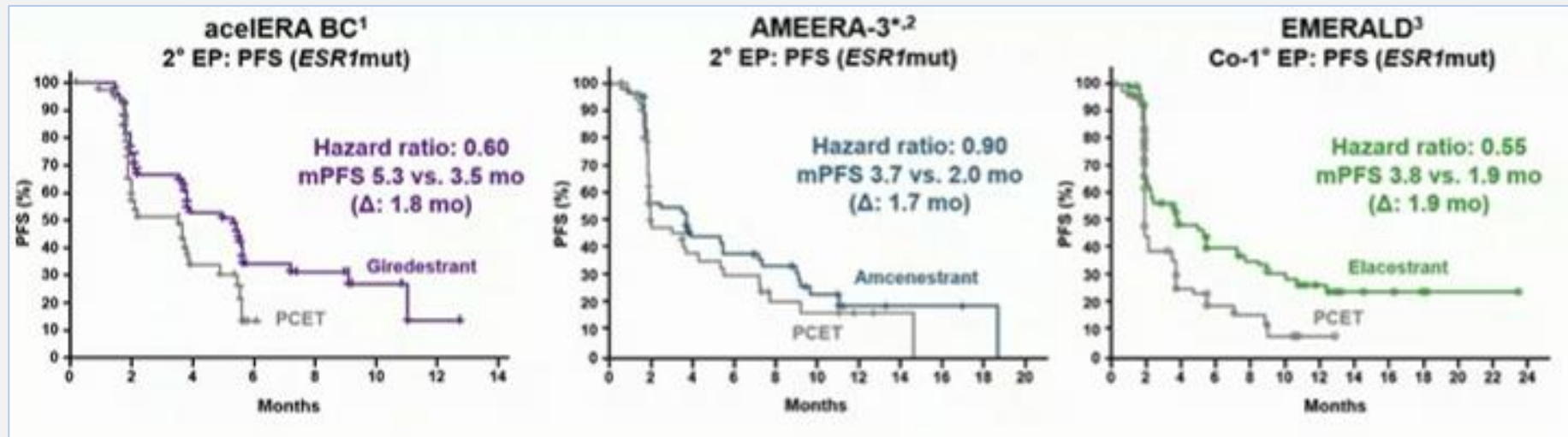


# Oral SERDs in Phase II/III 2-3L mBC trials

ITT Pop.



ERS1 Mut Pop.

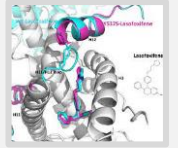




# 3d Generation Oral SERMs : LASOFOXIFENE

## ➤ Pure oral SERM (5 mg /d)

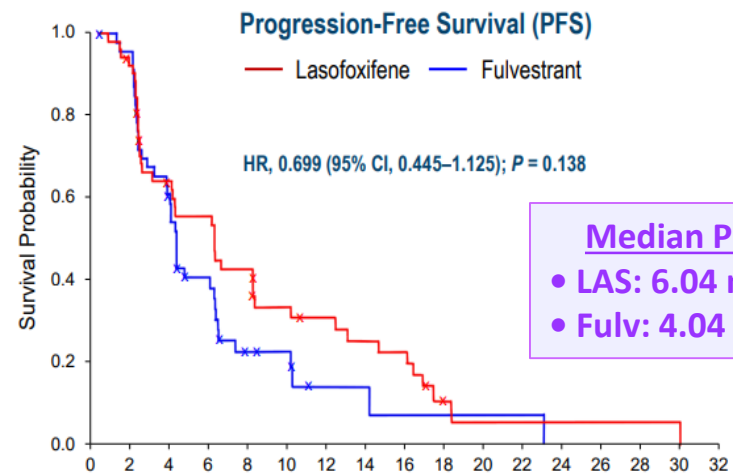
- Tt of Osteoporosis (PEARL Trial ; NEJM 2010) → ↓ Incidence of BC
- In vitro activity in ESR-1-Mut cell lines



**ELAINE-1: Open label randomized study of Lasofoxifene vs Fulvestrant in ER+/HER2-ve MBC and ERS1 mutation post progression on AI and CDK4/6i**

Goetz MP, ESMO 2022, LBA 20

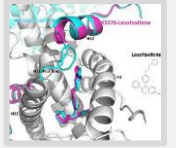
## Results (N=103)



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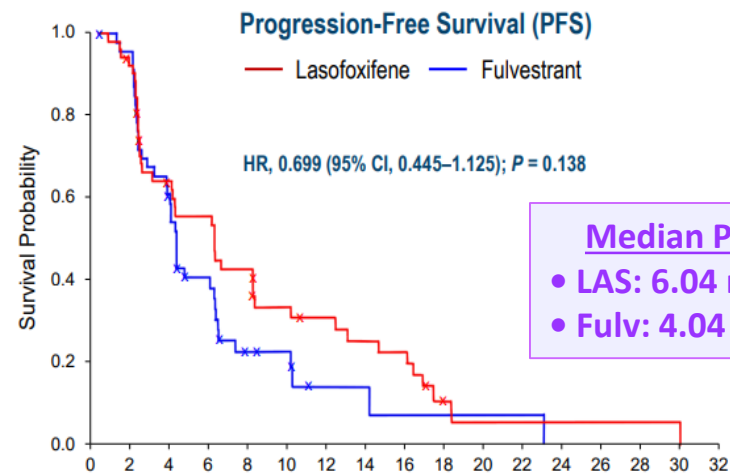
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Goetz MP, ESMO 2022, LBA 20

## Results (N=103)



### Median PFS

- LAS: 6.04 mos
- Fulv: 4.04 mos

## Exploratory ctDNA Analyses

( Sysmex-Inostics SafeSeq Assay )

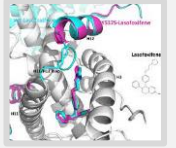
8-weeks ctDNA samples, ESR1-mutant allele fraction assessed

- LAS ↓ 87.1%
- Fulv ↓ 14.7%

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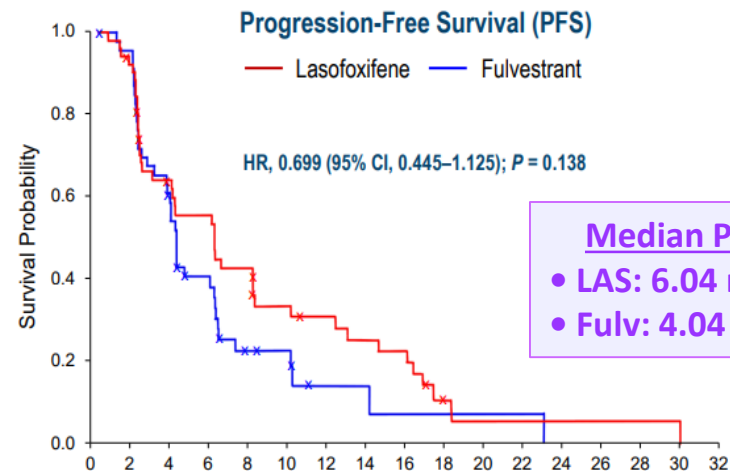
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Goetz MP, ESMO 2022, LBA 20

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8-weeks ctDNA samples, ESR1-mutant allele fraction assessed

- LAS ↓ 87.1%
- Fulv ↓ 14.7%



MutESR1 clearance is associated with ↑ PFS and CB in LAS ,  
but Not in Ful Goetz M , SABCS 2022

# 3d Generation Oral SERMs : LASOFOXIFENE

- In ELAINE-2 Ph II : 29 Heavily prett Pts (97% cdk4/6i, 79 % Fulv, 48% ChemoT)

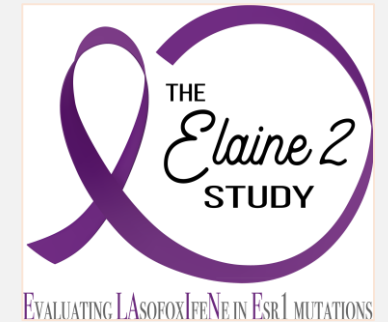
AND + ctDNA for mutESR1

Damodaran S , ASCO 2022



LAS + Abemaciclib resulted in

- an ORR of 50 %
- a **mPFS of 13,9 m**



- **Exploratory ct DNA analyses** : same correlation between ct DNA clearance

(↘in 81% of pts at W 4 ) and clinical benefit

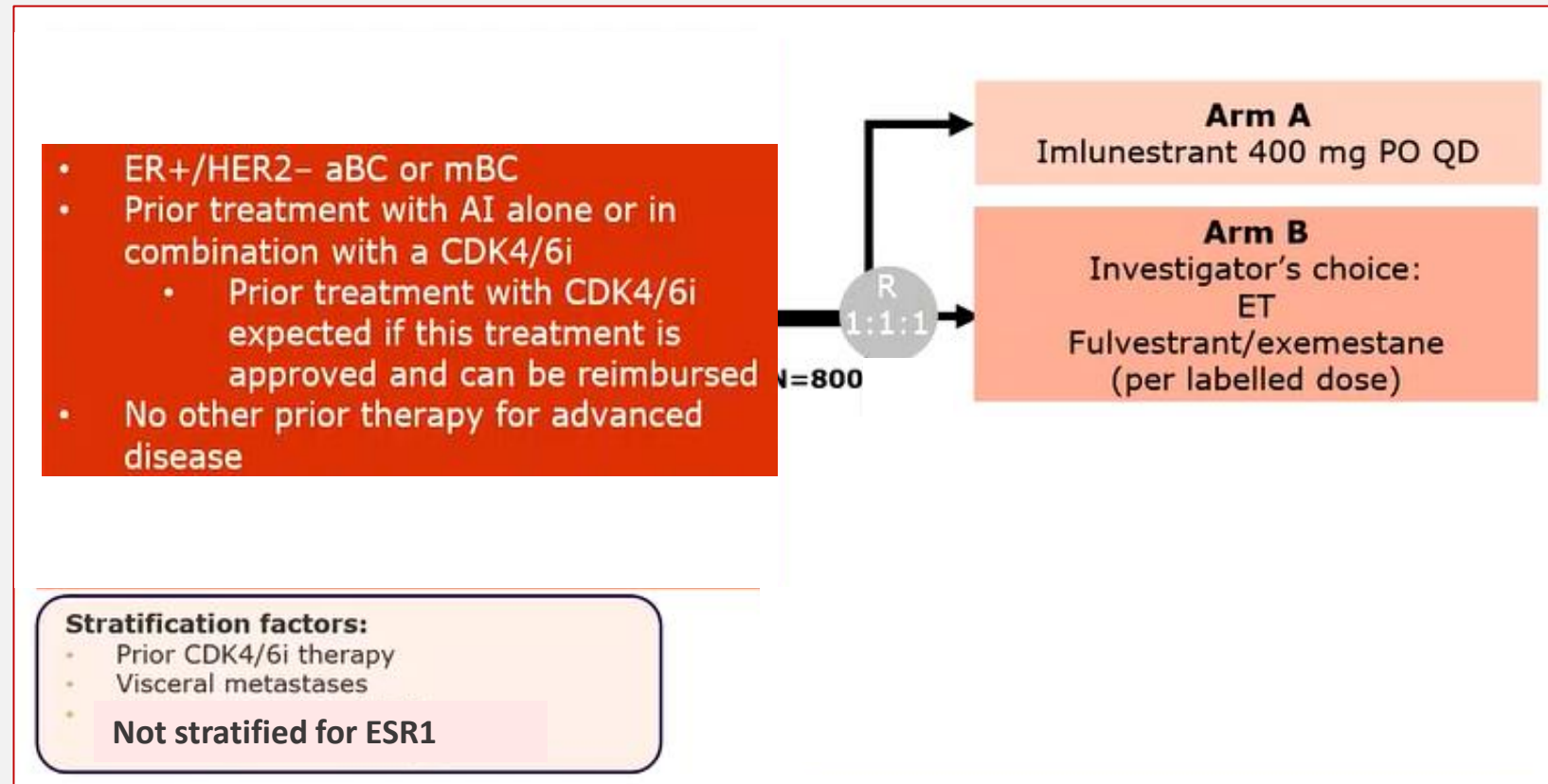
Damodaran S , SABCS 2022

= Non-invasive surrogate marker for efficacy?



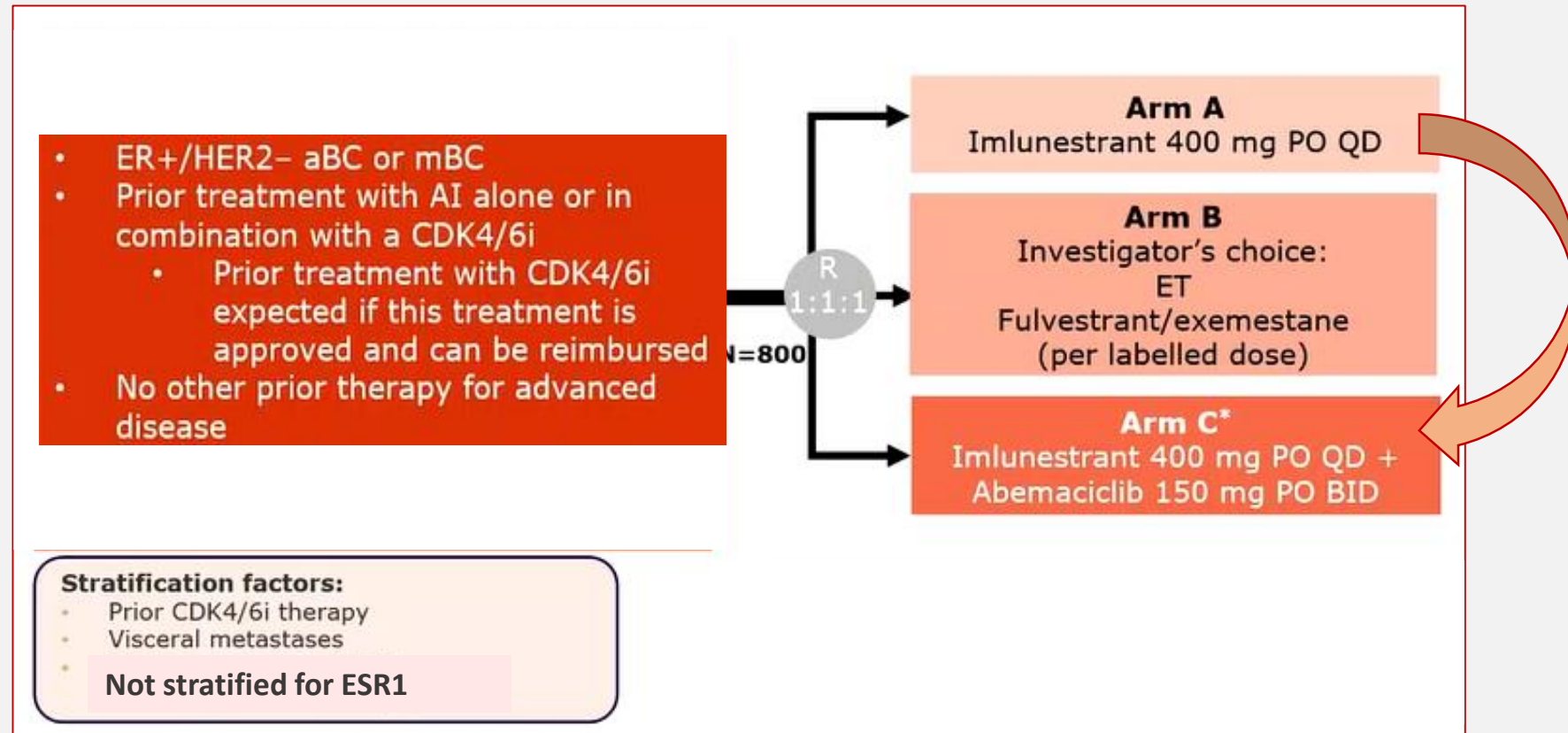
# ET vs Oral SERD +/- ABEMA as 2d line therapy

## EMBER-3 : a Phase III randomized , open-label study



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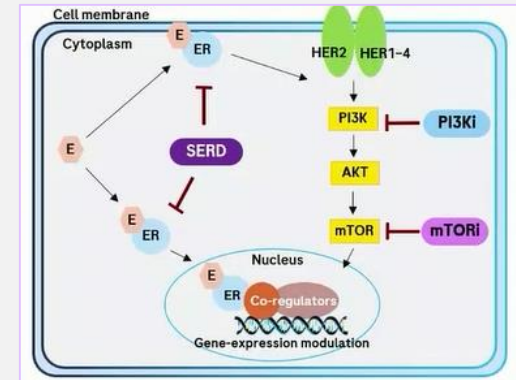


# Association of SERDs with targeted therapies in 2-3d line ?

## ❖ Addition of PI3Ki and mTORi (AKTi?) to SERDS

→ personalization of the Tt (40 % of PIK3CA mutant)

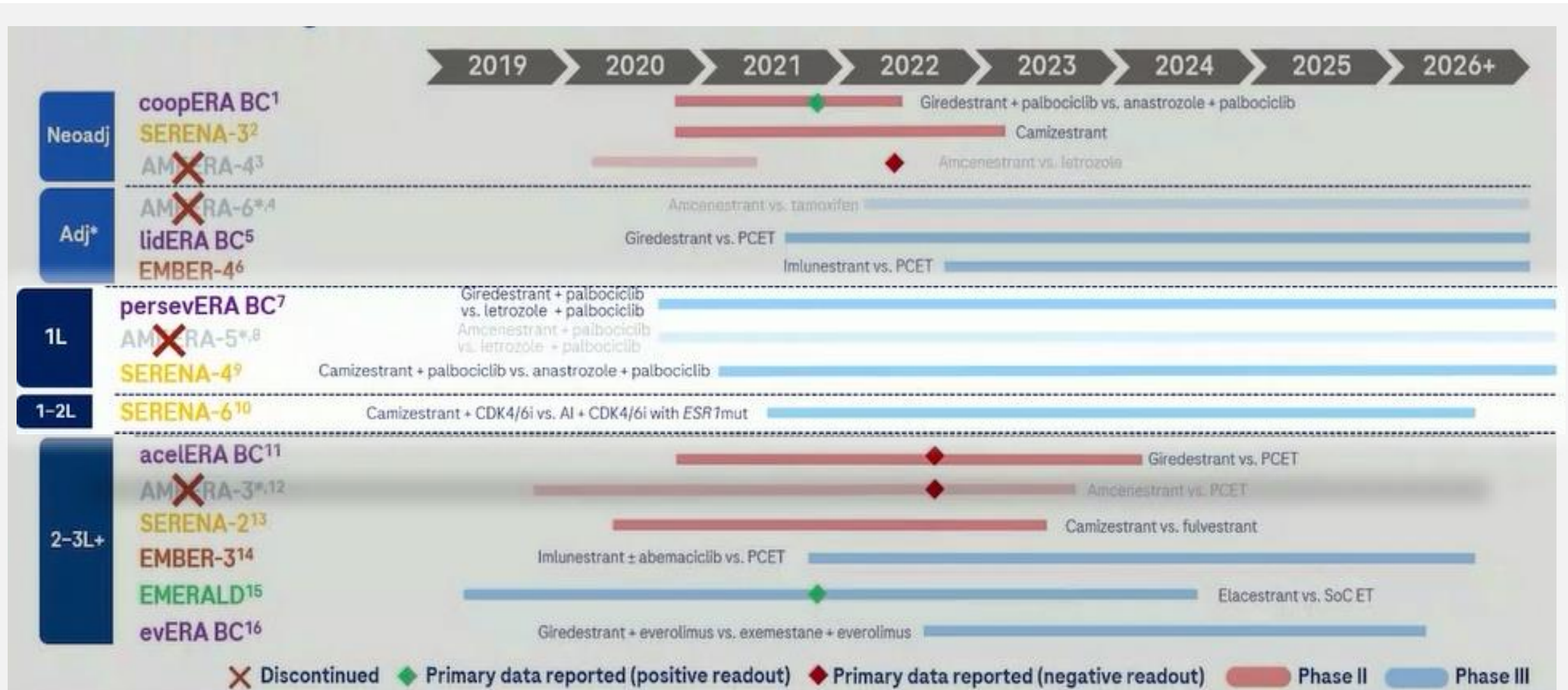
Optimal sequence ?



## ❖ Ongoing combination studies

- Giderestrant + Everolimus vs Exemestane + Everolimus (**evERA Ph III Trial**)
- **PIK3CA mut tumors** : Giderestrant + Inavolisib , Imlunestrant + Alpelisib,..
- **ELEVATE = phase 1b/2** open-label , umbrella study Elacestrant in various combinations  
→ + Alpelisib, Everolimus, PalboC, AbemaC or RiboC

# Programme of completed and ongoing Phase II/III Trials of Oral SERDs



# Oral SERDs in Phase III mBC 1L Combination with cdk4/6 i

	persevERA BC <sup>1</sup> (N = 978)	AMEERA-5 <sup>*.2</sup> (N = 1068)	SERENA-4 <sup>3</sup> (N = 1402)	SERENA-6 <sup>4</sup> (N = 302)
Oral SERD	Giredestrant 30 mg PO qd	Amcenestrant 200 mg PO qd	Camizestrant 75 mg PO qd	
Comparator ET	Letrozole		Anastrozole	
CDK4/6i combination partner	Palbociclib			
Key patient criteria	No prior systemic treatment for mBC			
Primary endpoint	PFS			
Status	Recruiting	Discontinued on iDMC recommendation based on the outcome of a pre-specified interim analysis <sup>1</sup>	Recruiting	



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✓ Palbo + AI = Palbo + Fulv in 1L (PARSIFAL Study)  
✓ Low rate of mutESR1

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- ✓ Low rate of mutESR1
- ✓ PALBO as 1L Partner ?

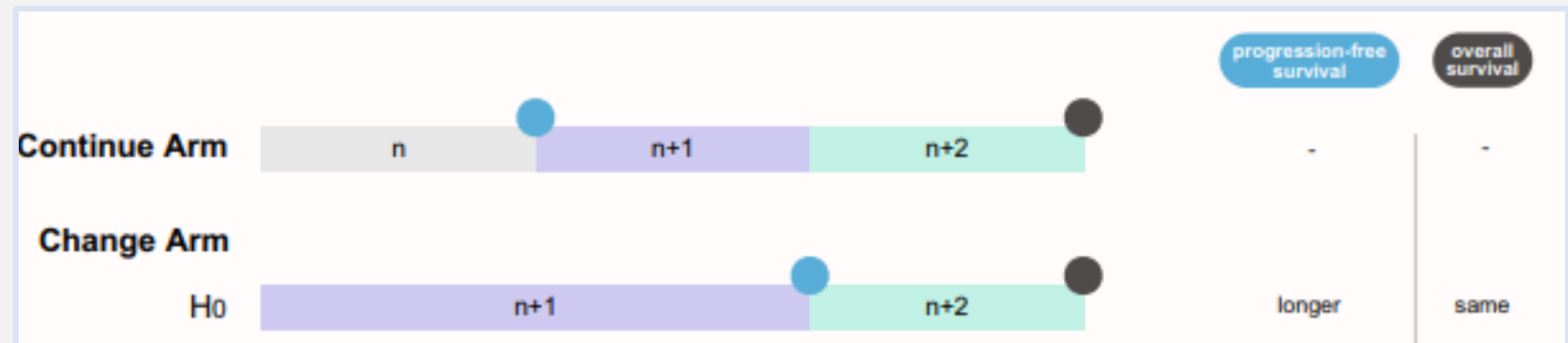
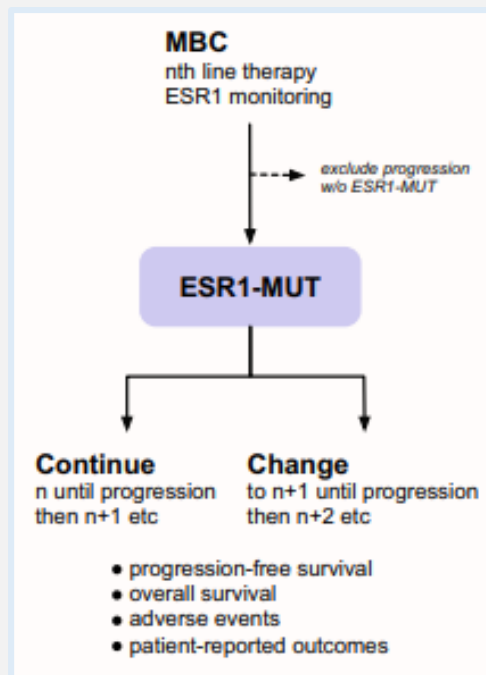
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CDK4/6i combination partner	Palbociclib			Palbociclib or abemaciclib
Key patient criteria	No prior systemic treatment for mBC			ESR1 mutation (ctDNA) Currently on AI + CDK4/6i as initial ET for mBC
Primary endpoint	PFS			
Status	Recruiting	Discontinued on iDMC recommendation based on the outcome of a pre-specified interim analysis <sup>1</sup>	Recruiting	Recruiting

# Mechanisms of Resistance to Endocrine Therapies

## Biomarker driven selection of ET backbone in 1L?

### PADA-1 Model

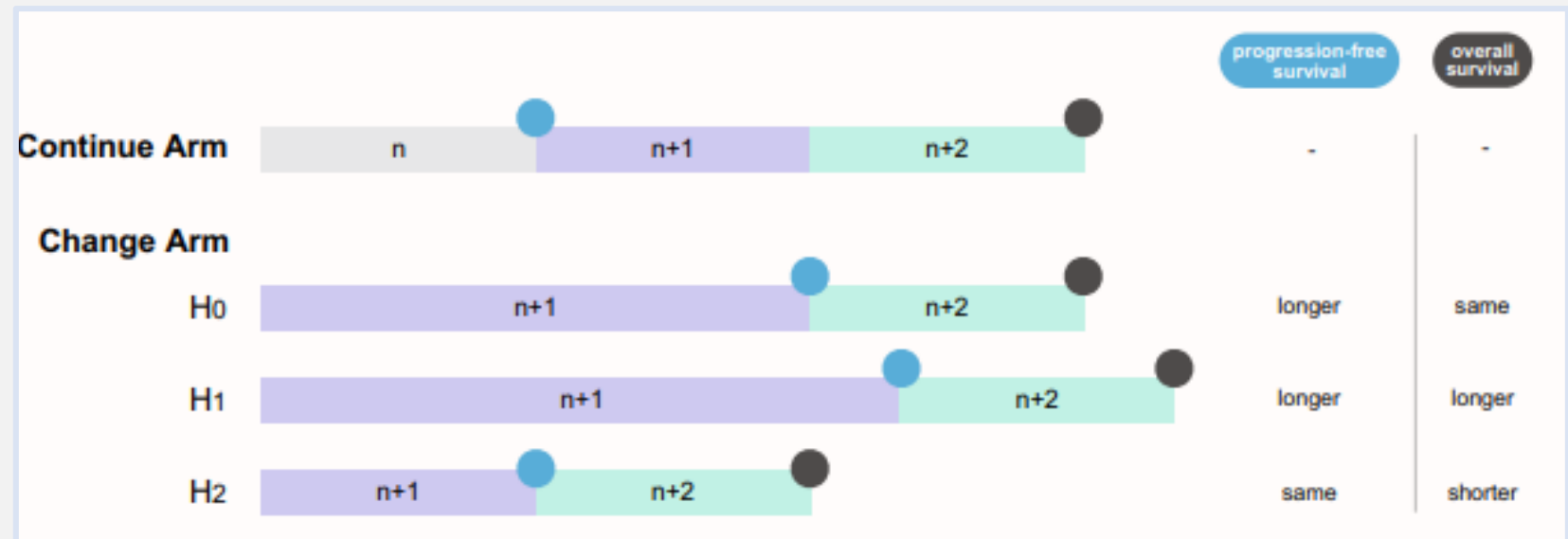
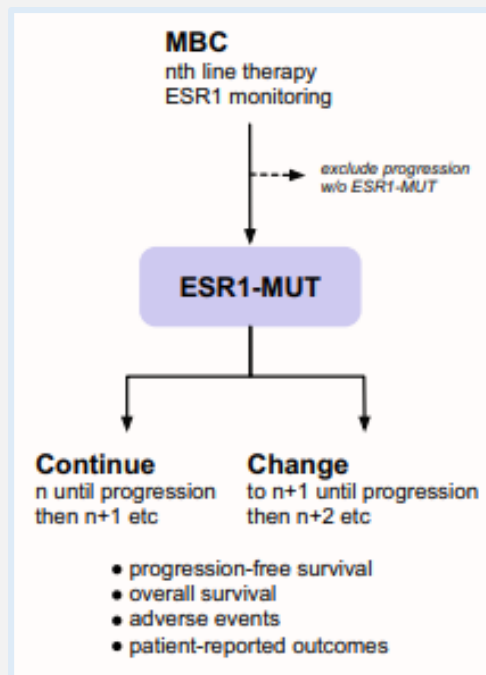


Brett J.O. et al , Breast Cancer Res 2021

# Mechanisms of Resistance to Endocrine Therapies

## Biomarker driven selection of ET backbone in 1L?

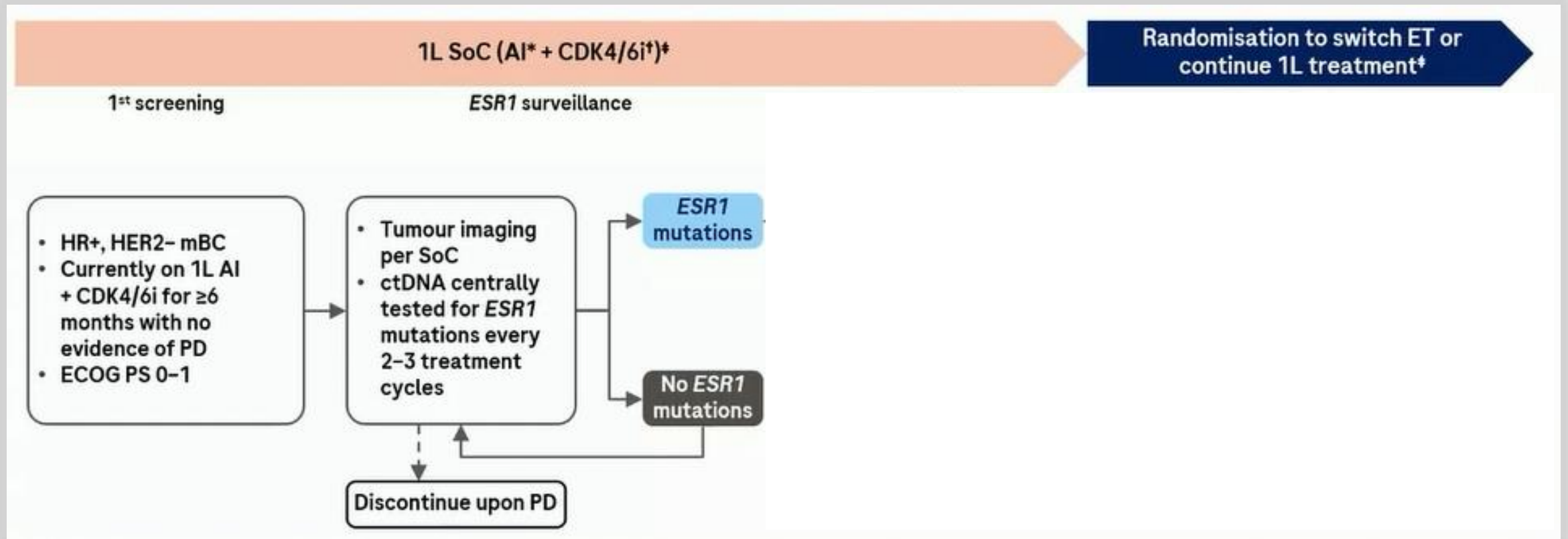
### PADA-1 Model



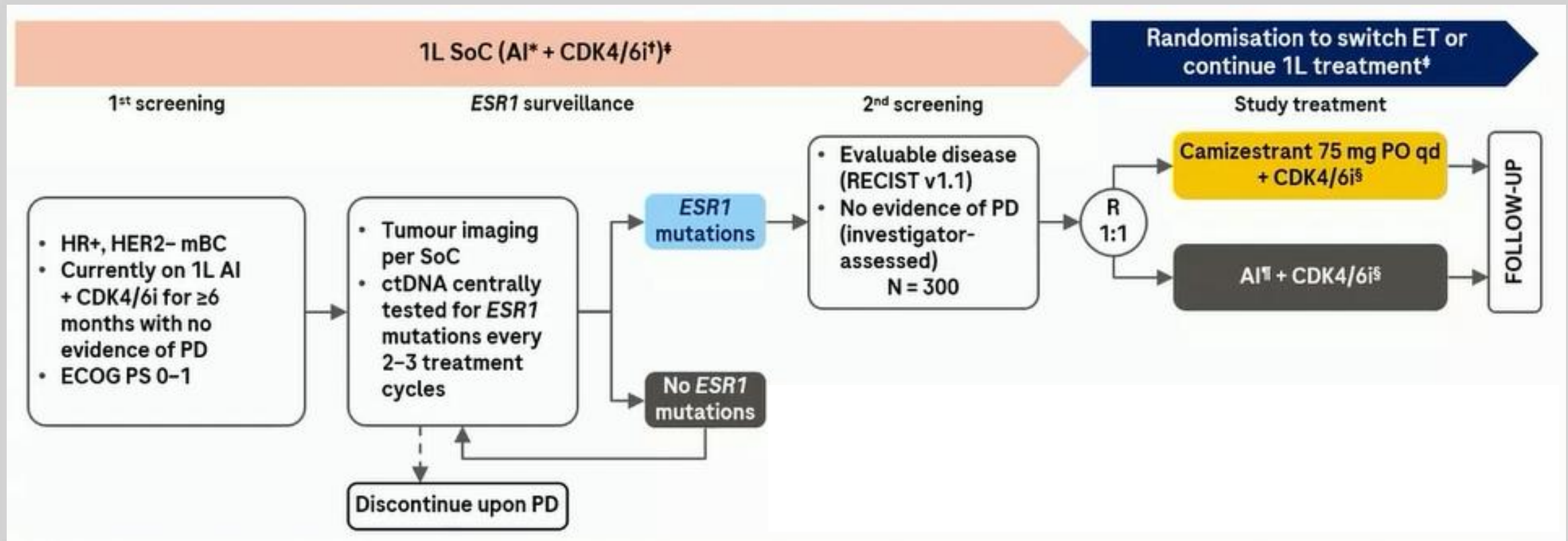
Brett J.O. et al , Breast Cancer Res 2021



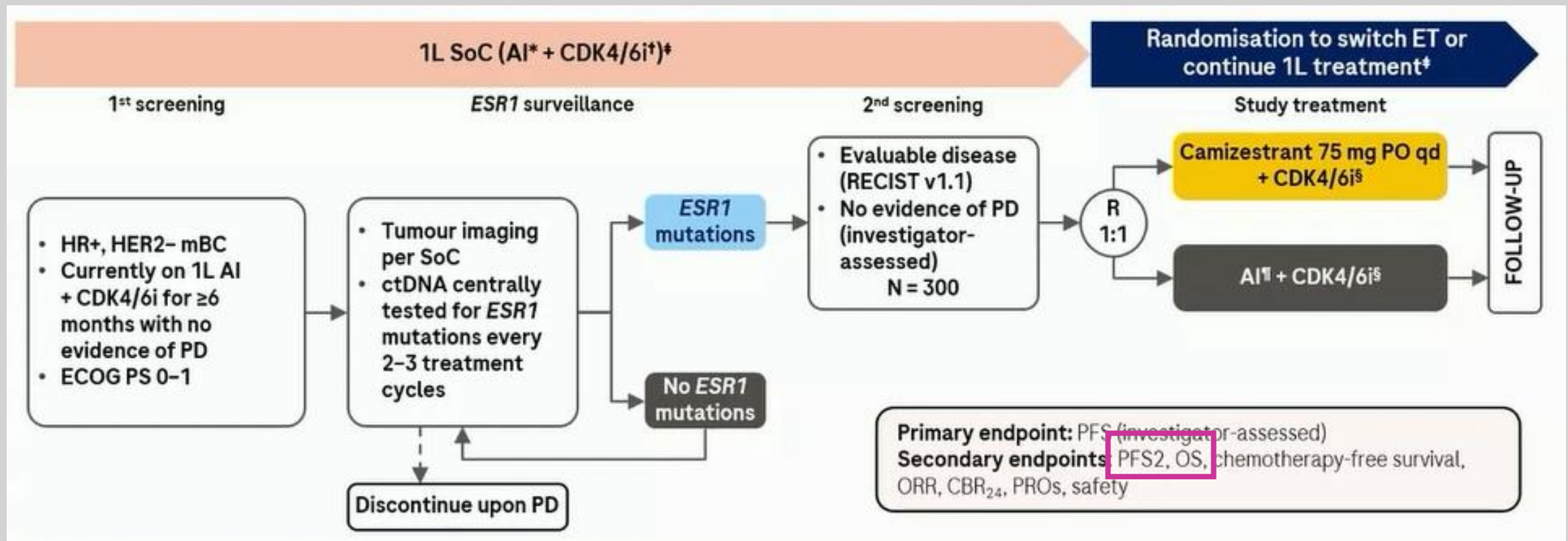
# SERENA-6: ctDNA ESR1 mutation-guided therapy



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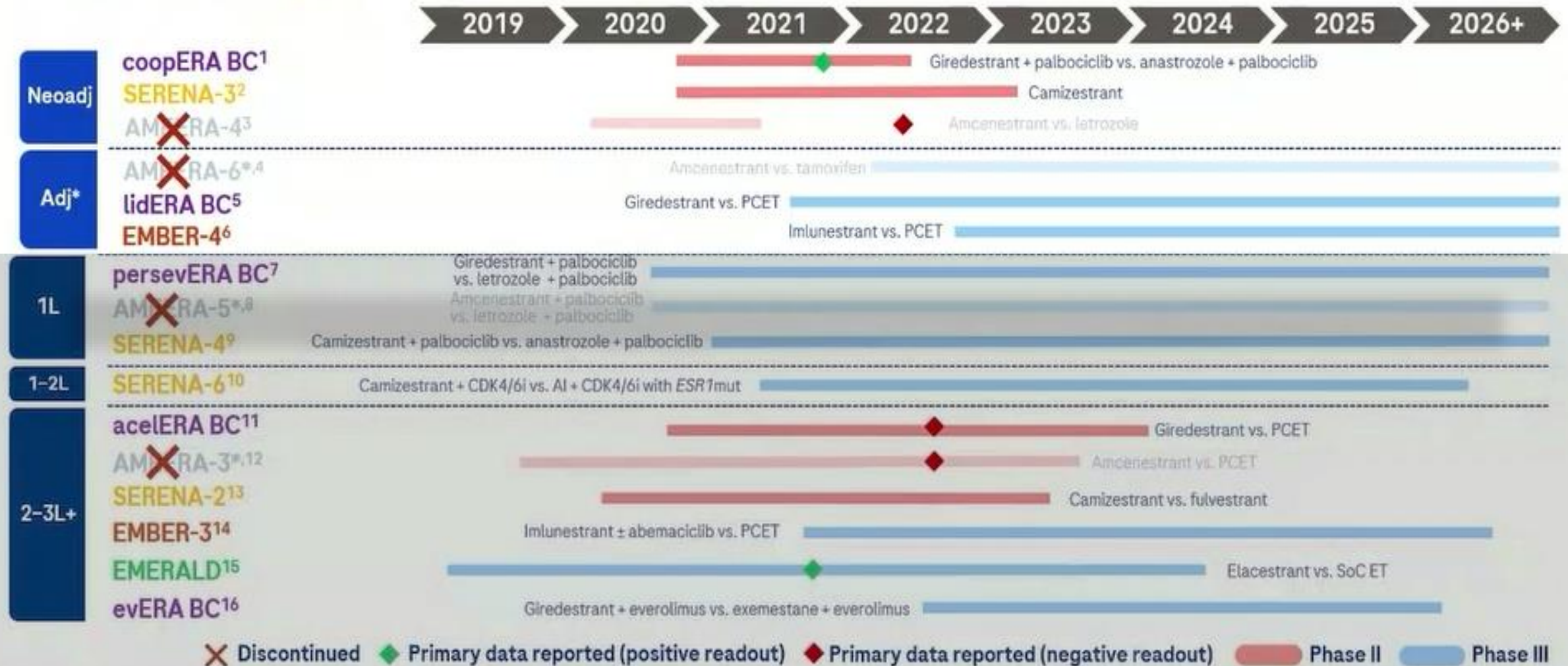
# Oral SERDs : Safety/Tolerability in mBC

## AEs in > 10 % : Single Agent and Combo with Palbociclib

Class	Drug	Single Agent	Combination with Palbociclib
<b>SERM/ SERD</b>	<b>RAD1901 (Elacestrant)</b>	Nausea, dyspepsia, vomiting, fatigue, AST increased	-
<b>Oral SERD</b>	<b>GDC-9545 (Giredestrant)</b>	Fatigue, arthralgia, back pain, nausea, vomiting	Nausea, dyspepsia, vomiting, fatigue, AST increased
	<b>SAR439859 (Amcnestrant)</b>	Hot flashes, constipation	Nausea, fatigue, arthralgia, asthenia, hot flashes*
	<b>AZD9833 (Camizestrant)</b>	Visual disturbances, bradycardia, nausea, fatigue, vomiting	Neutropenia, visual disturbances, fatigue, anemia†
	<b>LY-3484356 (Imlunestrant)</b>	Nausea, diarrhea, fatigue, arthralgia, urinary tract infection	-
	<b>G1T48 (Rintodestrant)</b>	Hot flashes, fatigue, nausea, diarrhea, vomiting	Neutropenia, leukopenia, anemia, asymptomatic bacteriuria, thrombocytopenia



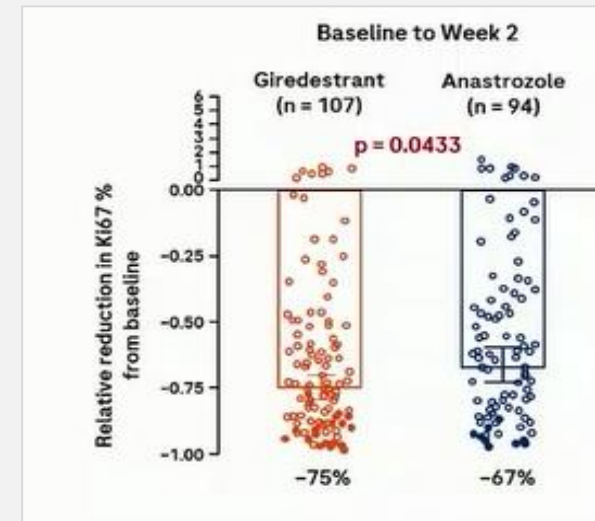
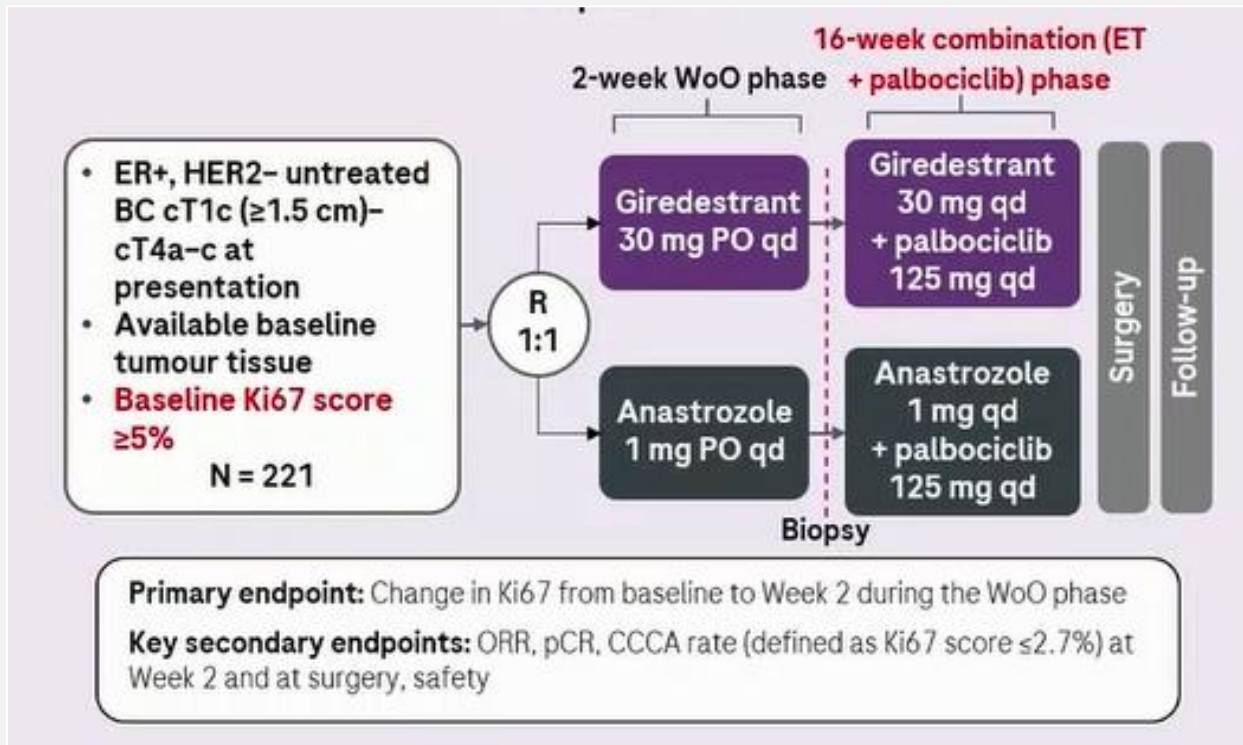
# Programme of completed and ongoing Phase II/III Trials of Oral SERDs







# Proof-of-Concept Neo Adjuvant study : coopERA Trial



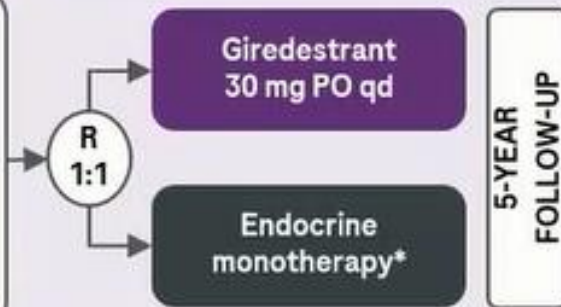
**1° EP met : superior Ki67 reduction from baseline to W 2 with GIREDESTRANT vs ANASTR.**

**Efficacy Signal supporting further investigation in the adj. setting**

# Oral SERDs in Phase III Adjuvant trials

## lidERA BC study design<sup>1,2</sup>

- ER+, HER2- medium/high-risk stage I-III eBC
  - Prior surgery with curative intent
  - Completed (neo)adjuvant chemotherapy (if administered) and/or surgery <12 mo prior to enrolment; ≤4 weeks of prior ET
- N = 4100



**Primary endpoint:** IDFS (excluding second primary non-BC)

**Key secondary endpoints:** OS, IDFS (including second primary non-BC), DFS, distant and locoregional RFI, safety, pharmacokinetics, PROs

## EMBER-4 study design<sup>3</sup>

- ER+, HER2- high-risk eBC
  - 2-5 years of prior adjuvant ET for ER+, HER2- eBC (completed or discontinued ≤6 mo prior to screening)
- N = 6000



**Primary endpoint:** IDFS (excluding second primary non-BC)

**Key secondary endpoints:** OS, DRFS, safety, pharmacokinetics, PROs

# Oral SERDs in Phase III Adjuvant trials

- ER+, HER2- medium stage I-III eBC
- Prior surgery with intent
- Completed (neo)adjuvant chemotherapy (if and/or surgery <1 year before enrolment; ≤4 weeks before randomisation) N = 410

Primary endpoint: I

**Key secondary endpoints:** OS, IDFS (including second primary non-BC), DFS, distant and locoregional RFI, safety, pharmacokinetics, PROs

- Improved outcome ?
- Optimal sequence with other ETs in the early setting ?
- Combo with AbemaC ?

**Key secondary endpoints:** OS, DRFS, safety, pharmacokinetics, PROs

Endocrine therapy

Endocrine therapy\*

FOLLOW-UP

# Oral SERDs in Phase III Adjuvant trials

- ER+, HER2- medium stage I-III eBC
- Prior surgery with intent
- Completed (neo)adjuvant chemotherapy (if and/or surgery <1 year before enrolment; ≤4 weeks before randomisation) N = 410

Primary endpoint: overall survival  
Key secondary endpoints: distant and locoregional recurrence-free survival

- Improved outcome ?
- Optimal sequence with other ETs in the early setting ?
- Combo with AbemaC ?
- Tolerability ? → Key aspect of efficacy !

Endocrine therapy

Endocrine therapy\*

FOLLOW-UP

Genetics, PROs



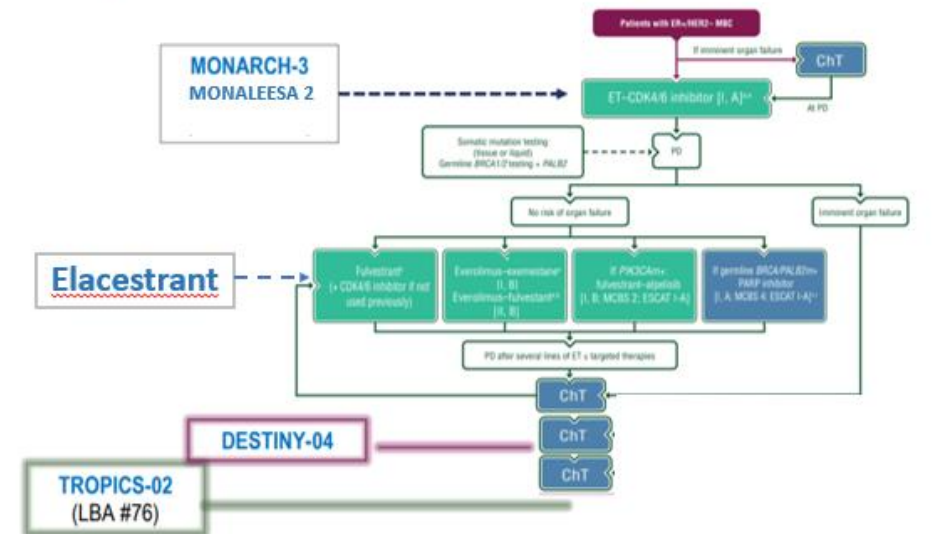
# Selective estrogen receptor degraders (SERDs) and new SERMS in breast cancer

## Conclusions

### New Endocrine Treatment ( 1st in 20 years !)

- 2d/3d line option
  - low burden MBC, long PFS 1, .. ?
  - In all comers or in mutESR1 tumors ?

#### Current management of MBC ER+HER2- Q4 - 2002





# Selective estrogen receptor degraders (SERDs) and new SERMS in breast cancer

## Conclusions



COMING SOON!

**ORSERDU**<sup>™</sup>  
elacestrant

**ORal SERD for U**

The anticipated treatment option from  
Stemline, a Menarini Group Company,  
is almost here.