Nuovi SERD nel carcinoma mammario

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Conflict of interest

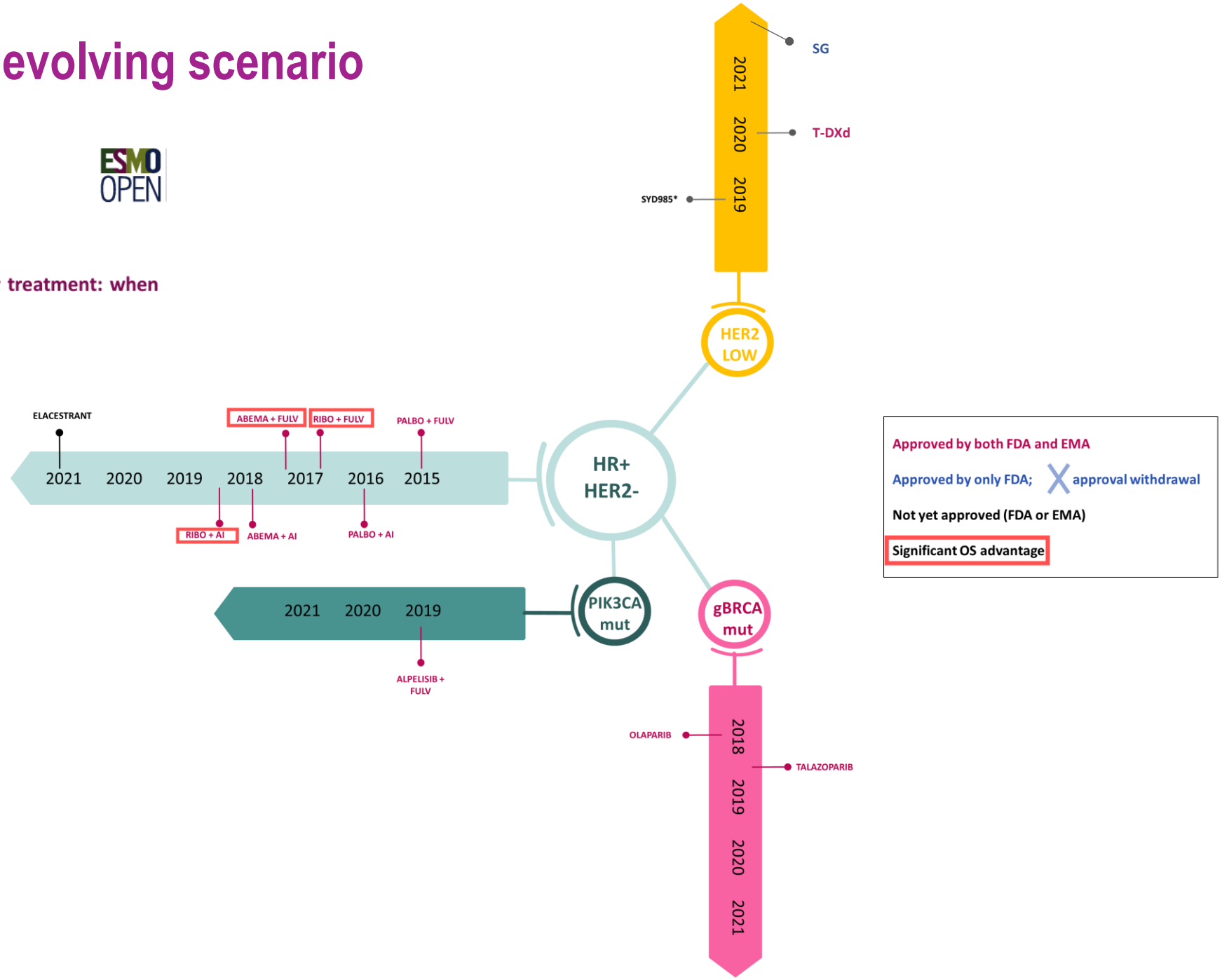
- PF Roche
- PF Gilead
- PF Novartis
- PF Pfizer

HR+/HER2- MBC: an evolving scenario

REVIEW

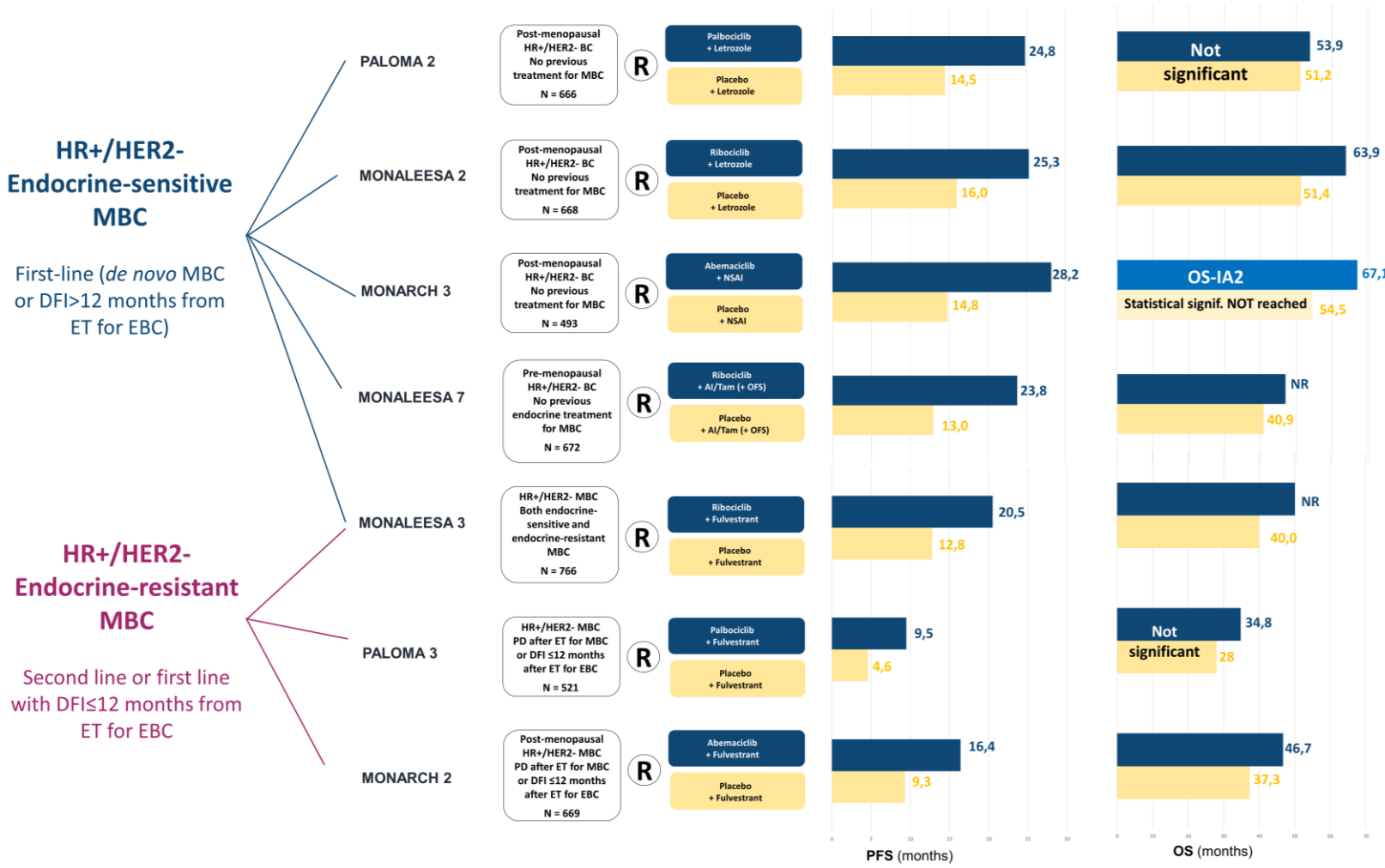
Major advancements in metastatic breast cancer treatment: when expanding options means prolonging survival

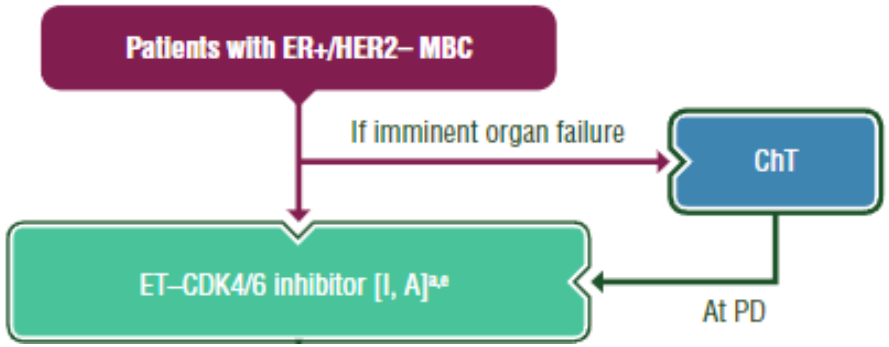
F. Miglietta[1], M. Bottosso[1], G. Griguolo[1,2], M. V. Dieci[1,2] & V. Guarneri[1,2*]



Modified from Miglietta F et al, ESMO Open 2022

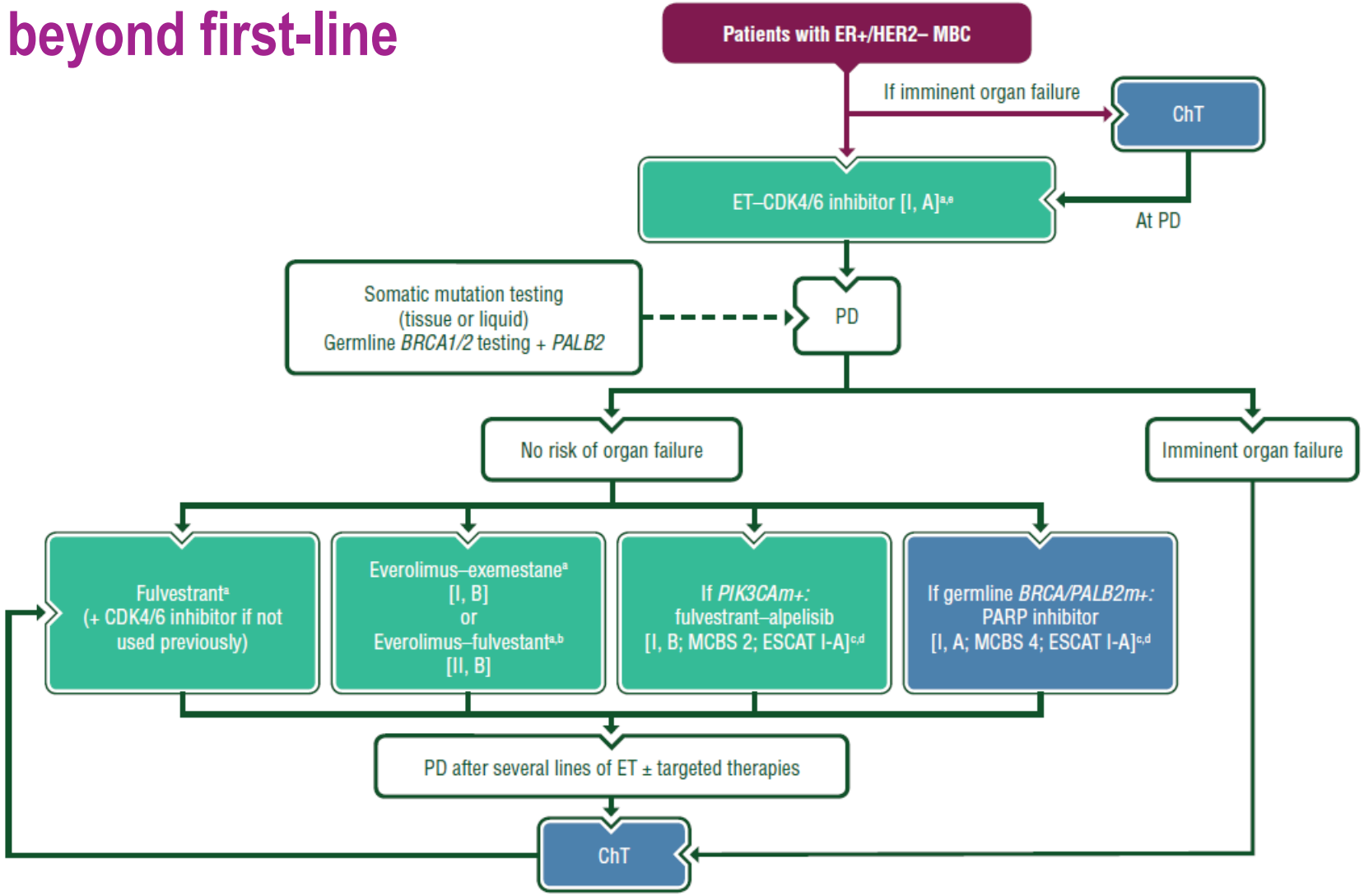
First-line SOC: CDK 4/6inh-based treatment





Modified from Miglietta et al, ESMO Open 2022; Gennari et al, Ann Oncol 2021

Treatment beyond first-line



FIRST LINE ET

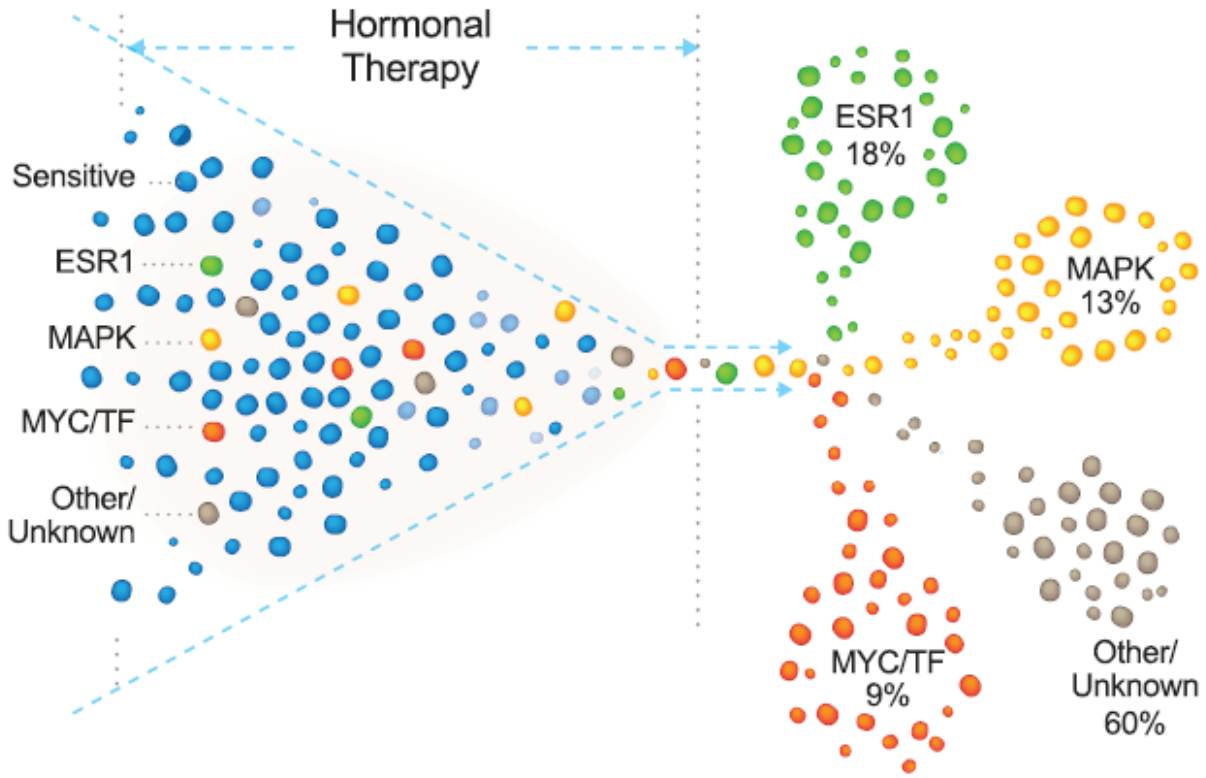
GREY ZONE BEYWEEN FIRST LINE ET AND THE FIRST CT-BASED THERAPY

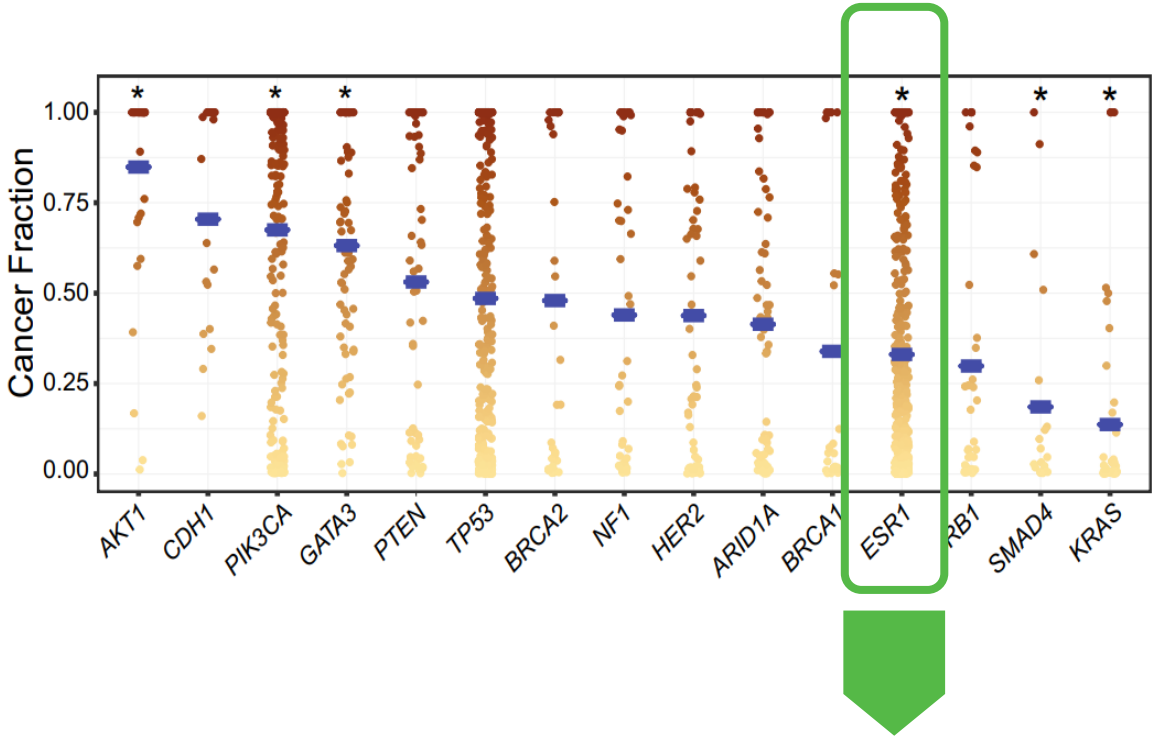
CT

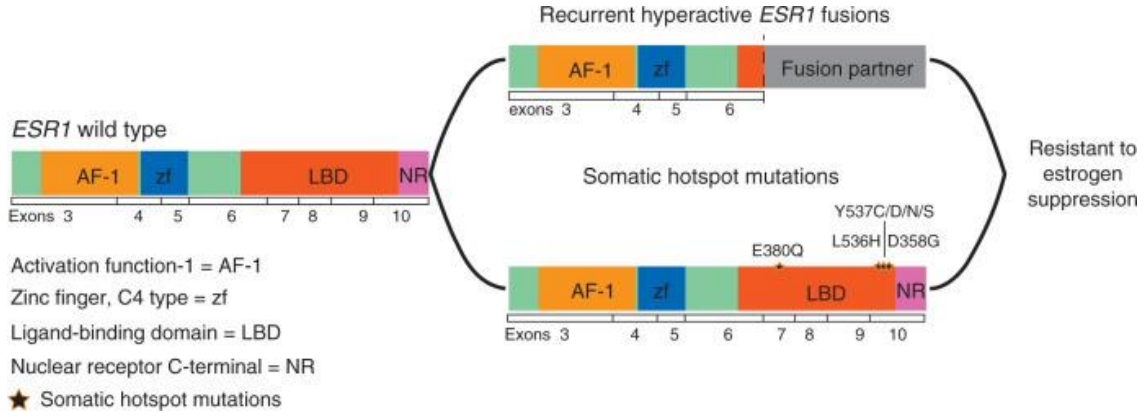
CHALLENGE to establish durable PFS in the 2nd line setting and beyond with CT-free strategies

Gennari et al, Ann Oncol 2021

Endocrine-resistance is virtually an inevitable phenomenon





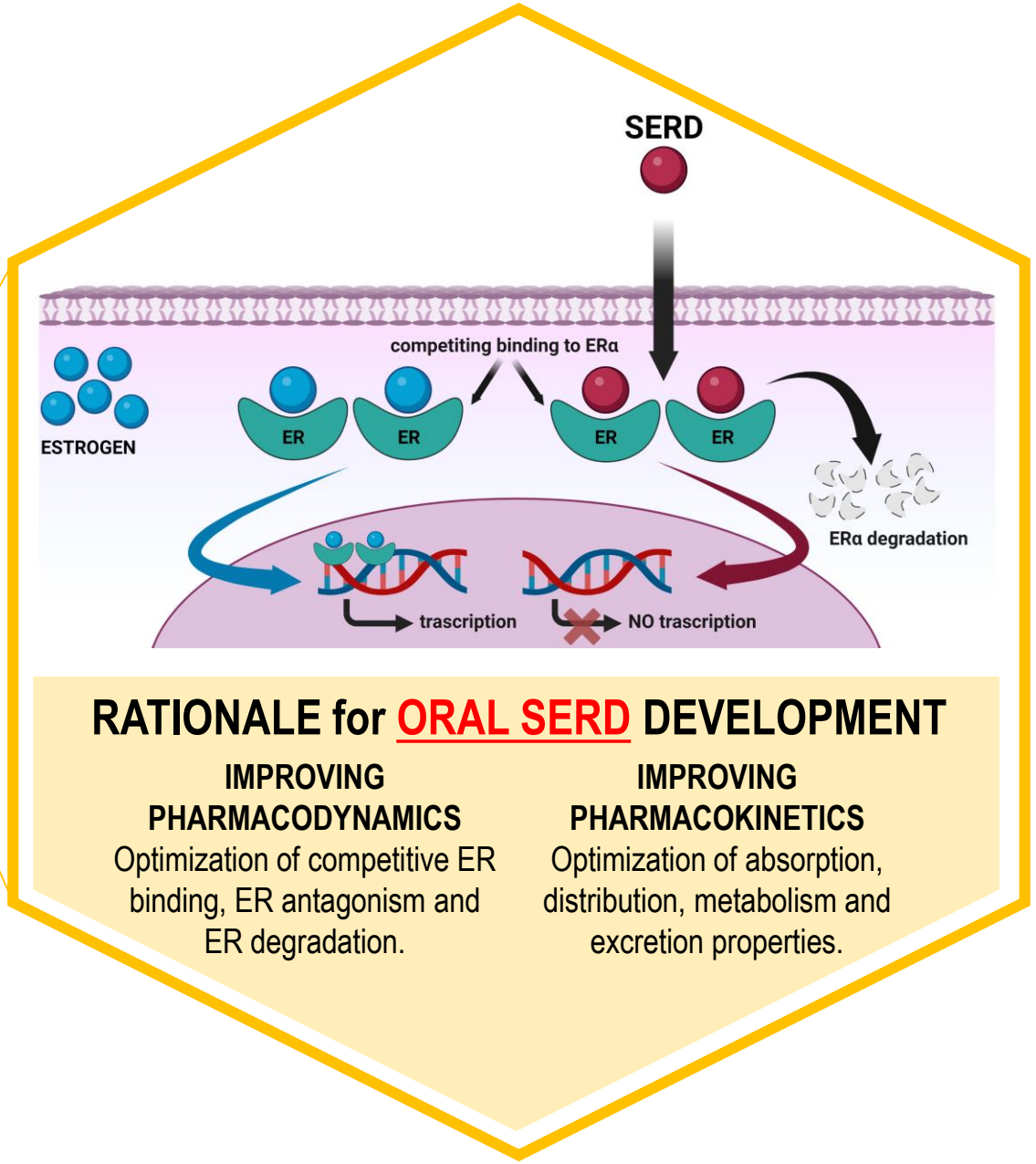


ESR1 mutation

ESR1 mutant BC could define a subset of patients with ER-driven resistance

Razavi et al, Cancer Cell 2018; Toi et al, Nat Genet 2013; Kingston et al, Nat Comm, 2021

Pharmacological interventions that could tackle ER-driven resistance



Oral SERDs: an old answer to novel questions?

EMERALD	SERENA-2	AMEERA-3	acelERA
ELACESTRANT*	CAMIZESTRANT*	AMCENESTRANT	GIREDESTRANT

Are oral SERDs effective as monotherapy after PD to ET?

Are oral SERDs effective as monotherapy
in a contemporary endocrine-resistant setting?

Are oral SERDs superior to Fulvestrant?

Which is the role of ESR1 mutation in driving oral SERD benefit?

Oral SERDs: an old answer to novel questions?

Are oral SERDs effective as monotherapy after PD to ET?

EMERALD	SERENA-2	AMEERA-3	acelERA
ELACESTRANT*	**CAMIZESTRANT***	**AMCENESTRANT**	**GIREDESTRANT**
vs Fulvestrant/AI	*vs* Fulvestrant	*vs* Fulvestrant/AI/tam	*vs* Fulvestrant/AI
Phase III (478)	Phase II (240)	Phase II (367)	Phase II (303)
I^{ary}: PFS in ITT/ESR1+	I^{ary}: PFS in ITT	I^{ary}: PFS in ITT	I^{ary}: PFS in ITT
Prior CDK4/6i 100%	**Prior CDK4/6i 46.6%**	**Prior CDK4/6i 78.9%**	**Prior CDK4/6i 42%**
Prior Fulvestrant 30.3%	Prior Fulvestrant 0%	Prior Fulvestrant 9.6%	Prior Fulvestrant 19%
Prior CT (≤1) 22.3%	Prior CT (≤1) 19.2%	Prior CT (≤1) 11.4%	Prior CT (≤1) 32%
Visceral 69.7%	Visceral 58.3%**	Visceral 63.8%	Visceral 68%
ESR1mut: 47.7%**	**ESR1mut***: 36.7%**	**ESR1mut*: 41.4%**	**ESR1mut: 39%**
POSITIVE	**POSITIVE**	**NEGATIVE**	**NEGATIVE**
(median PFS: 2.8 vs 1.9 mos)	**(median PFS: 7.2-7.7 vs 3.7 mos)**	**(median PFS: 3.6 vs 3.7 mos)**	**(median PFS: 5.6 vs 5.4 mos)**
*Elacestrant is both a ER degrader and inhibithor of estradiol-dependent ER-directed gene trascription	*The dose of 75 mg will go forward	*digital PCR	*FoundationOne liquid CDx
**Gaurdant 360	**lung and/or liver disease	***AMCENESTRANT DEVELOPMENT: STOPPED***	
	***GuardantOMNI™		

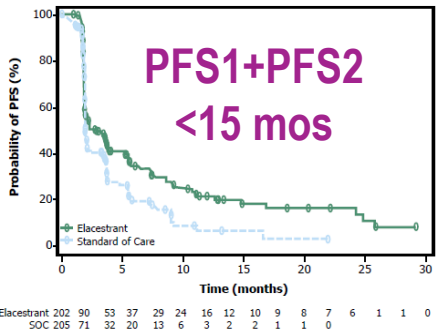
Bidard et al, JCO 2022; Bardia et al, SABCS2022; Oliveira et al, SABCS2022; Tolaney et al, ESMO 2022; Martin et al, ESMO 2022

Oral SERDs: an old answer to novel questions?

Are oral SERDs effective as monotherapy in a contemporary endocrine-resistant setting?

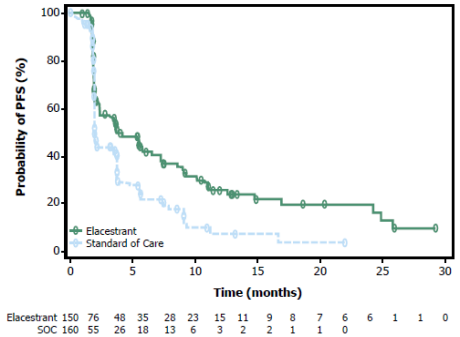
EMERALD Elacestrant

At least 6 mos CDK4/6i



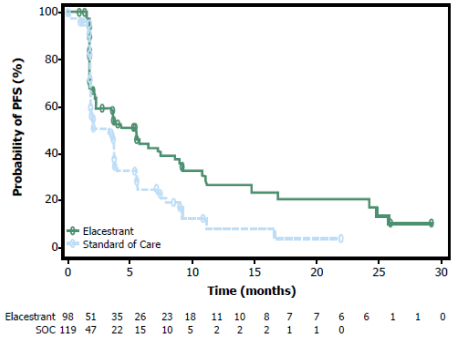
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)	

At least 12 mos CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)
PFS rate at 12 months, % (95% CI)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)
Hazard ratio (95% CI)	**0.613** (0.453 - 0.828)	

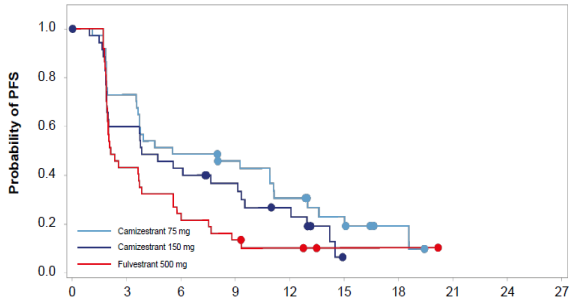
At least 18 mos CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 12 months, % (95% CI)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
Hazard ratio (95% CI)	**0.703** (0.482 - 1.019)	

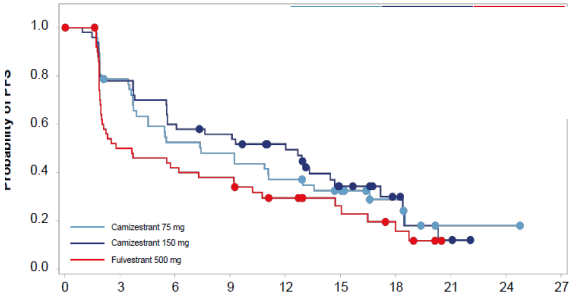
SERENA-2 Camizestrant

Prior CDK4/6i



	C 75 (n=38)	C 150 (n=37)	F 500 (n=37)
Events [n (%)]	29 (76.3)	29 (78.4)	33 (89.2)
Median PFS, months (90% CI)	5.5 (3.7-10.9)	3.8 (2.0-7.6)	2.1 (1.9-3.7)
Adjusted HR (90% CI)[a]	0.49 (0.31-0.75)	0.68 (0.44-1.04)	-

At least 12 mos CDK4/6i



	C 75 (n=50)	C 150 (n=53)	F 500 (n=53)
Events [n (%)]	34 (68.0)	35 (66.0)	40 (75.5)
Median PFS, months (90% CI)	7.4 (4.5-11.1)	12.0 (5.6-14.5)	3.2 (2.0-7.3)
Adjusted HR (90% CI)[a]	0.53 (0.35-0.79)	0.58 (0.39-0.86)	-

CHALLENGE

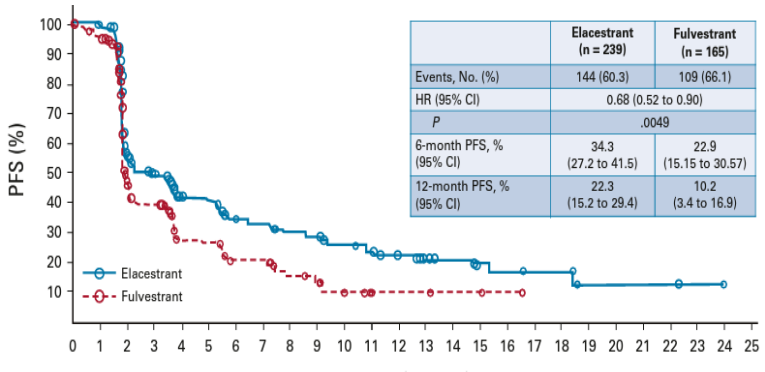
Challenge: to identify patients with limited benefit to ET (HR+ BC NOT driven by ER) → should they be treated with modern cytotoxic agents or TT?

Oral SERDs: an old answer to novel questions?

Are oral SERDs superior to Fulvestrant?

EMERALD
Elacestrant

Elacestrant vs Fulvestrant



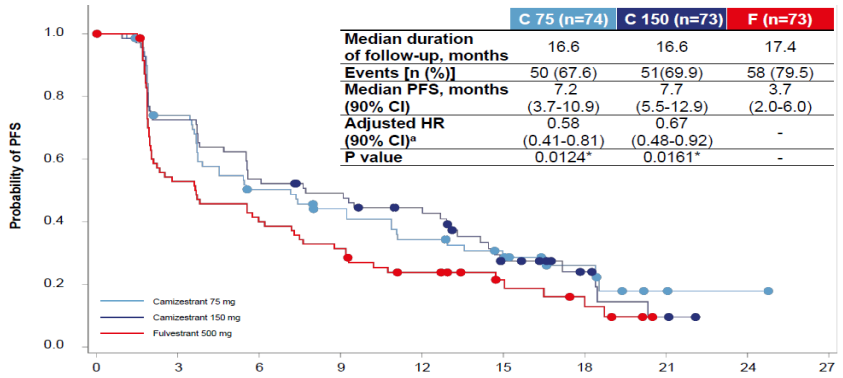
	Elacestrant (n = 239)	Fulvestrant (n = 165)
Events, No. (%)	144 (60.3)	109 (66.1)
HR (95% CI)	0.68 (0.52 to 0.90)	
P	.0049	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	22.9 (15.15 to 30.57)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	10.2 (3.4 to 16.9)

Fulvestrant PRE-TREATED pts

Subgroup	HR (95%CI)	p for interaction
Prior fulvestrant	**0.67** (0.43-1.029)	**0,970**
No prior fulvestrant	**0.66** (0.50-0.87)	

SERENA-2
Camizestrant

Camizestrant vs Fulvestrant



	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*	-

Oral SERDs are superior to Fulvestrant and are effective beyond PD to fulvestrant

→ Oral SERDS seem to be more potent than IM SERD

→ Oral dosing may allow increased bioavailability

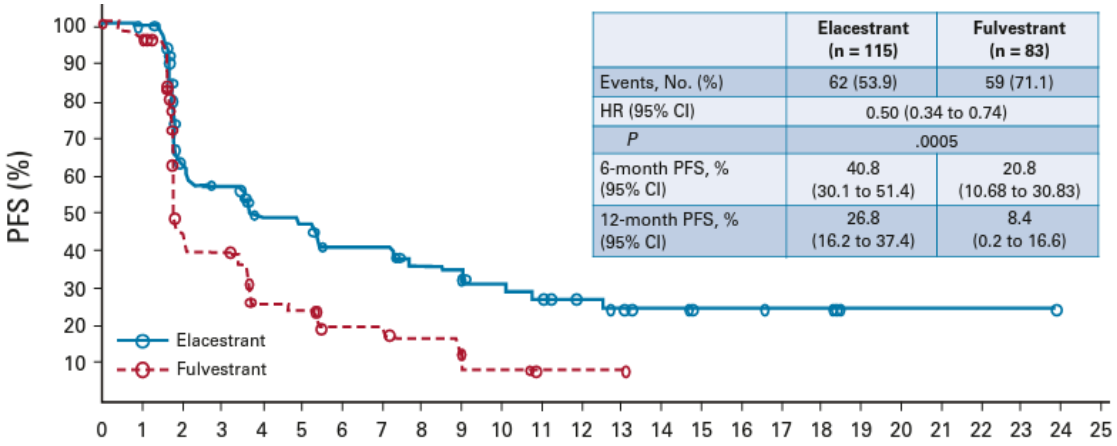
Bardia et al, SABCS2022; Oliveira et al, SABCS2022

Oral SERDs: an old answer to novel questions?

Which is the role of ESR1 mutation in driving oral SERD benefit?

EMERALD
Elacestrant

ESR1m

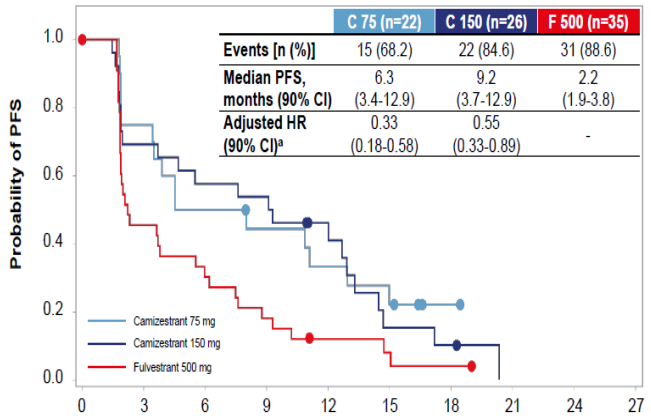


	Elacestrant (n = 115)	Fulvestrant (n = 83)
Events, No. (%)	62 (53.9)	59 (71.1)
HR (95% CI)	0.50 (0.34 to 0.74)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	20.8 (10.68 to 30.83)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.4 (0.2 to 16.6)

Median PFS 8,61 mos with Elacestrant in ESR1m with at least 12 mos of PFS with CDK 4/6i

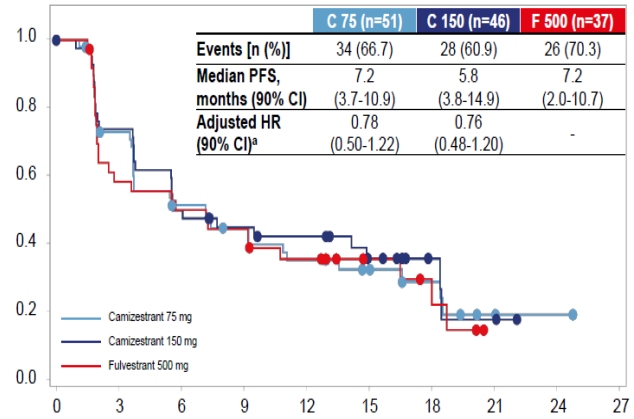
SERENA-2
Camizestrant

ESR1m



	C 75 (n=22)	C 150 (n=26)	F 500 (n=35)
Events [n (%)]	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-

ESR1wt



	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-

Camizestrant appears superior to Fulv in ESR1m and at least as effective as Fulv in pts without ESR1m

The subgroup of patients derving the greatest benefit from oral SERDs are ESR1 mutant BC with SECONDARY resistance to CDK4/6i

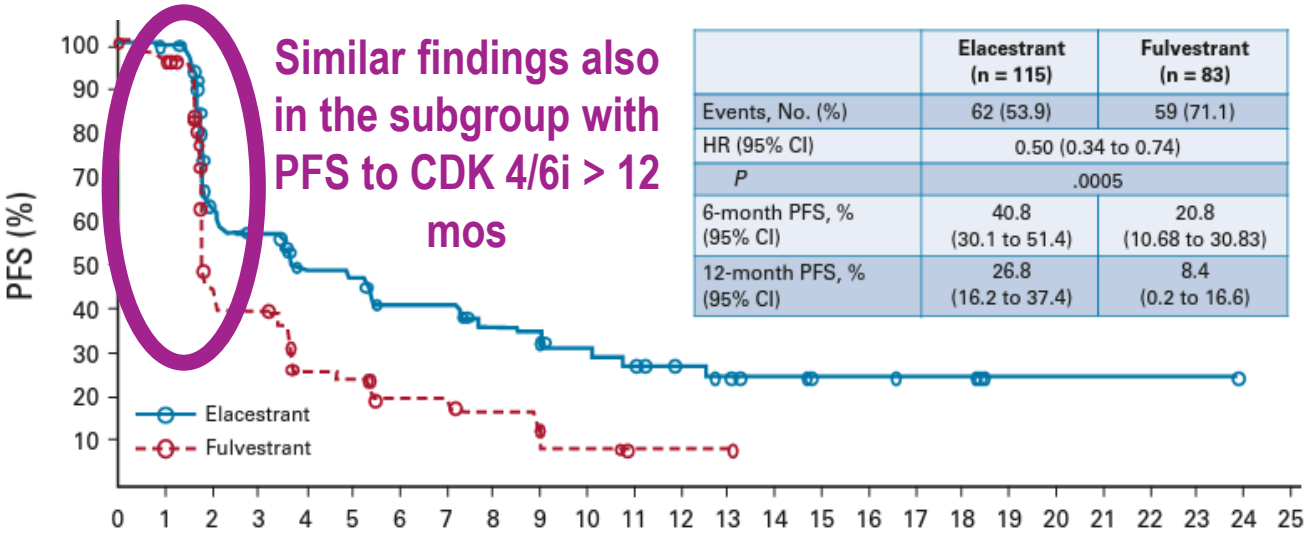
Bidard et al, JCO 2022; Bardia et al, SABCS2022; Oliveira et al, SABCS2022

Oral SERDs: an old answer to novel questions?

Which is the role of ESR1 mutation in driving oral SERD benefit?

EMERALD
Elacestrant

ESR1m



Similar findings also in the subgroup with PFS to CDK 4/6i > 12 mos

	Elacestrant (n = 115)	Fulvestrant (n = 83)
Events, No. (%)	62 (53.9)	59 (71.1)
HR (95% CI)	0.50 (0.34 to 0.74)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	20.8 (10.68 to 30.83)
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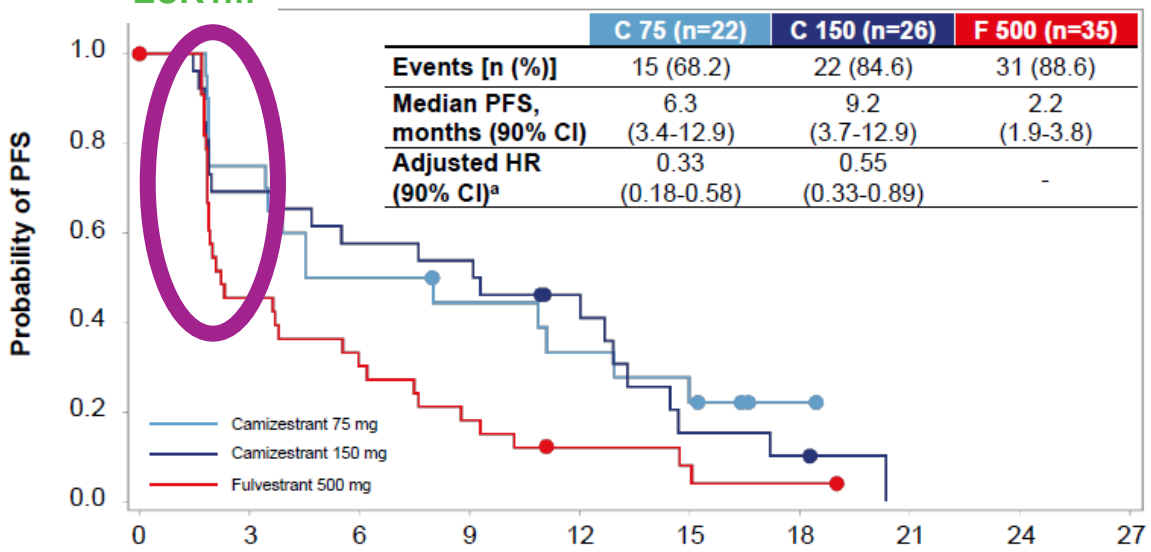
SERENA-2
Camizestrant

ESR1m



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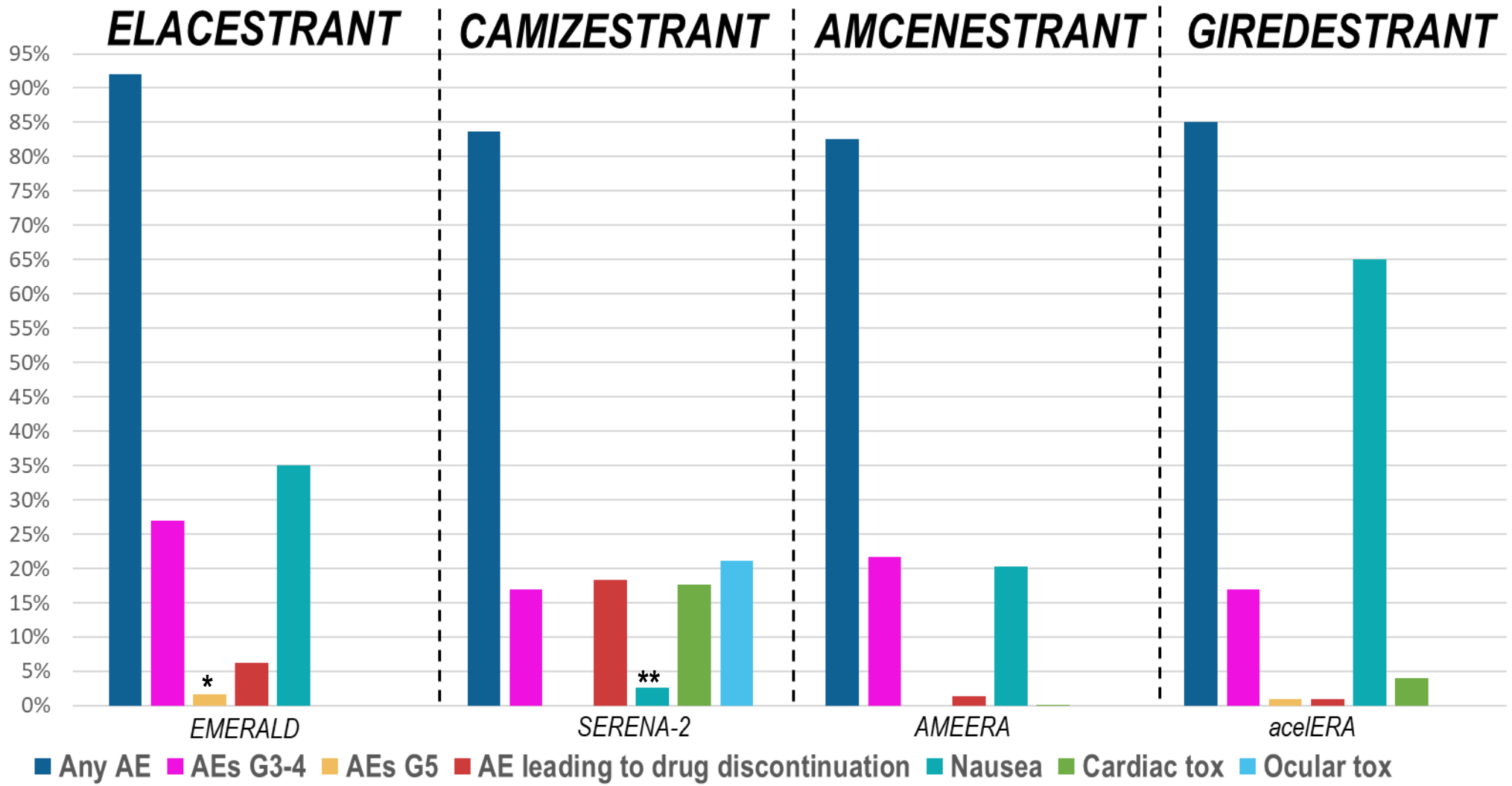
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-

A subset of patients with ESR1 mutations shows PRIMARY ENDOCRINE-RESISTANCE TO SERDS

Possible role of subclonal ESR1 mutations

Bidard et al, JCO 2022; Bardia et al, SABCS2022; Oliveira et al, SABCS2022; Kingston et al, Nat Comm 2021

Oral SERDs: safety



Bidard et al, JCO 2022; Bardia et al, SABCS2022; Oliveira et al, SABCS2022; Tolaney et al, ESMO 2022; Martin et al, ESMO 2022

*NO fatal events were attributed to study drug by the investigator
**dyspepsia (nausea not reported)

Open questions and conclusive remarks

Overall, **improvement in PFS** appears **MODEST** when used as **MONOTHERAPY** in **PRE-TREATED** pts
→ going forward, ET monotherapy will probably NOT be the SOC in endocrine-resistant pts

Results from **COMBINATION trials adopting oral SERDs as ENDOCRINE BACKBONE in FIRST-LINE** are highly awaited
SERENA-4, SERENA-6, persevERA, AMEERA-5 (announced as negative)*

Overlapping strategies in endocrine resistant patients

In pts with PIK3CA-mutated BC oncologist and patient should enter a careful discussion to weight risks and benefit of oral SERD monotherapy vs **alpelisib** + fulv.

Capivasertib is moving closer to clinical approval

Incorporation of oral SERDs within the contemporary landscape of HR+/HER2- MBC further complicated by the **availability of novel agents**

Novel ADCs (T-DXd in HER2-low and SG) are currently available for HR+/HER2- MBC pretreated with ET and CT

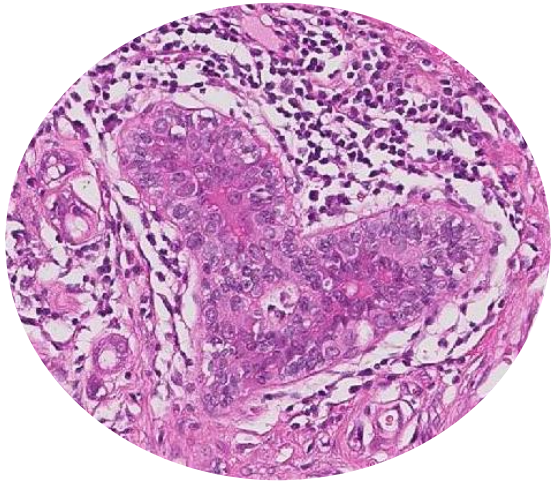
Mandatory to **IMPROVE UPFRONT PATIENT SELECTION** to predict **primary endocrine resistance**

MOLECULAR TUMOR PROFILING will likely play a crucial role
Currently, the "ESR1-resistance" match is too weak

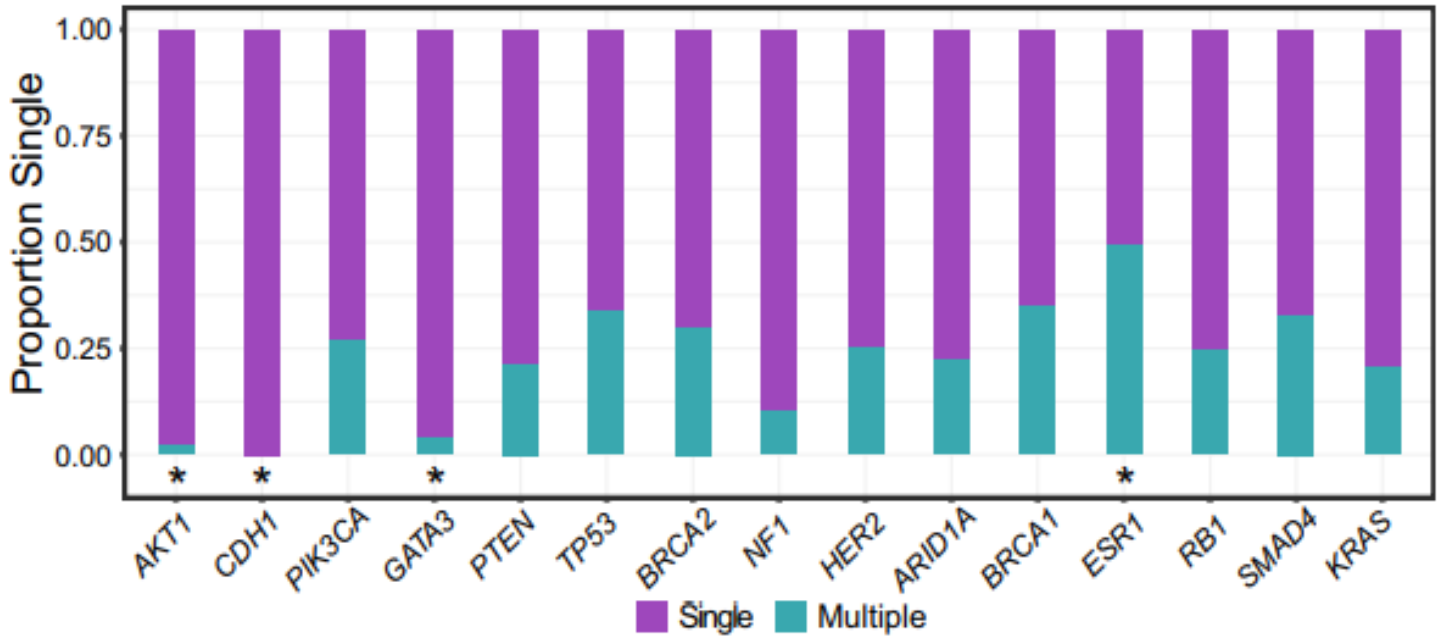
**SERENA-6: switch from AI to oral SERD while continuing CDK4/6inh in case of ESR1 mut. emergence without clinical PD*

Grazie

Federica Miglietta



Oral SERDs: an old answer to novel questions?



Kingston et al, Nat Comm 2021

- **ESR1** mutations have a strong interpatient heterogeneity in terms of allelic frequency and clonality
- Within ESR1, different mutations **vary in clonal dominance** with some mutations being highly dominant whilst others are frequently subclonal
- **It would be important to describe the clonality of ESR1 mutations within clinical trials of oral SERDs as monotherapy → may sub-clonality have a role in shaping 1ry resistance to SERD?**