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

Analisi dei Paper

Carmine De Angelis, MD, PhD

UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

carmine.deangelis1@unina.it

@CarmineDeA1

Disclosures

- **Consulting/Advisor**: Roche, AstraZeneca, Lilly, GSK, Novartis, Pfizer, Clovis
- **Honoraria**: Novartis, Pfizer, Lilly, Daiichi Sankyo, Roche, AstraZeneca, Clovis, GSK
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ER+/HER2- mBC is heterogeneous according to endocrine resistance

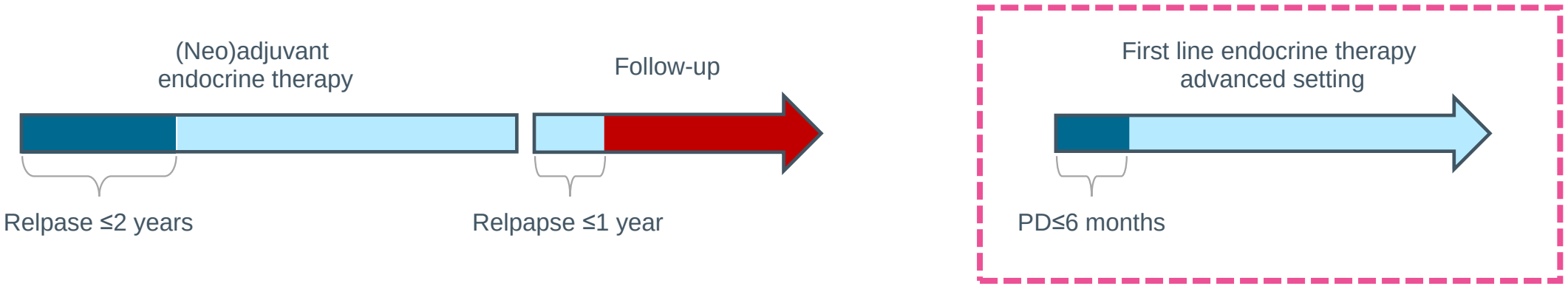
ENDOCRINE RESISTANCE

PRIMARY

SECONDARY (ACQUIRED)

ENDOCRINE SENSITIVE

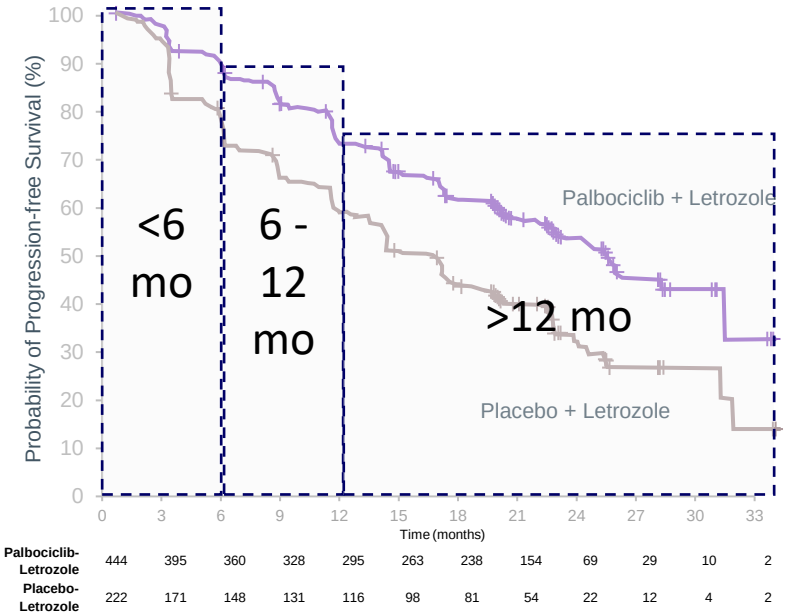
+ De Novo disease



Cardoso F Ann Oncol 2014; Cardoso F Breast 2014; Cardoso F et al. Ann Oncol 2017; Cardoso F Ann Oncol 2018

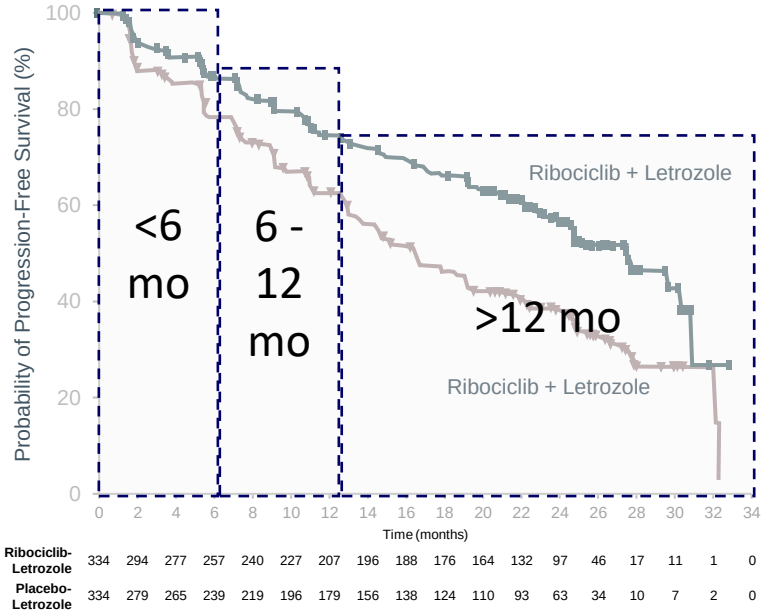
First-line ET + CDK4/6 inhibitors

PALOMA 2



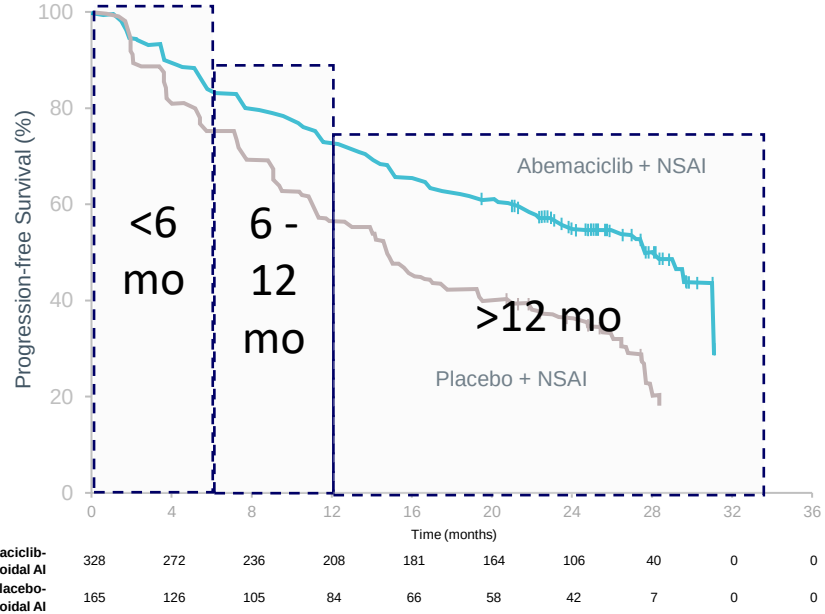
Palbociclib-Letrozole	444	395	360	328	295	263	238	154	69	29	10	2
Placebo-Letrozole	222	171	148	131	116	98	81	54	22	12	4	2

MONALEESA 2



Ribociclib-Letrozole	334	294	277	257	240	227	207	196	188	176	164	132	97	46	17	11	1	0
Placebo-Letrozole	334	279	265	239	219	196	179	156	138	124	110	93	63	34	10	7	2	0

MONARCH 3



Abemaciclib-nonsteroidal AI	328	272	236	208	181	164	106	40	0	0
Placebo-nonsteroidal AI	165	126	105	84	66	58	42	7	0	0

Finn R, et al. NEJM. 2016; 2Hortobagyi GN, et al. Ann Oncol. 2018; Johnston S, et al. NPJ Breast Cancer 2019

Novel agents to overcome endocrine resistance

Drugs targeting genomic alterations

- PI3K-pathway inhibitors
- PARP inhibitors
- *HER2 inhibitors*
- *FGFR1/2 inhibitors*
- …

CDK4/6i beyond progression

- Abemaciclib
- Ribociclib
- Palbociclib

Novel endocrine therapies

- Oral SERD
- PROTAC
- SERCA
- New SERM
- CERAN

ADCs

- T-DXd
- Sacituzumab Govitecan
- Dato-DXd

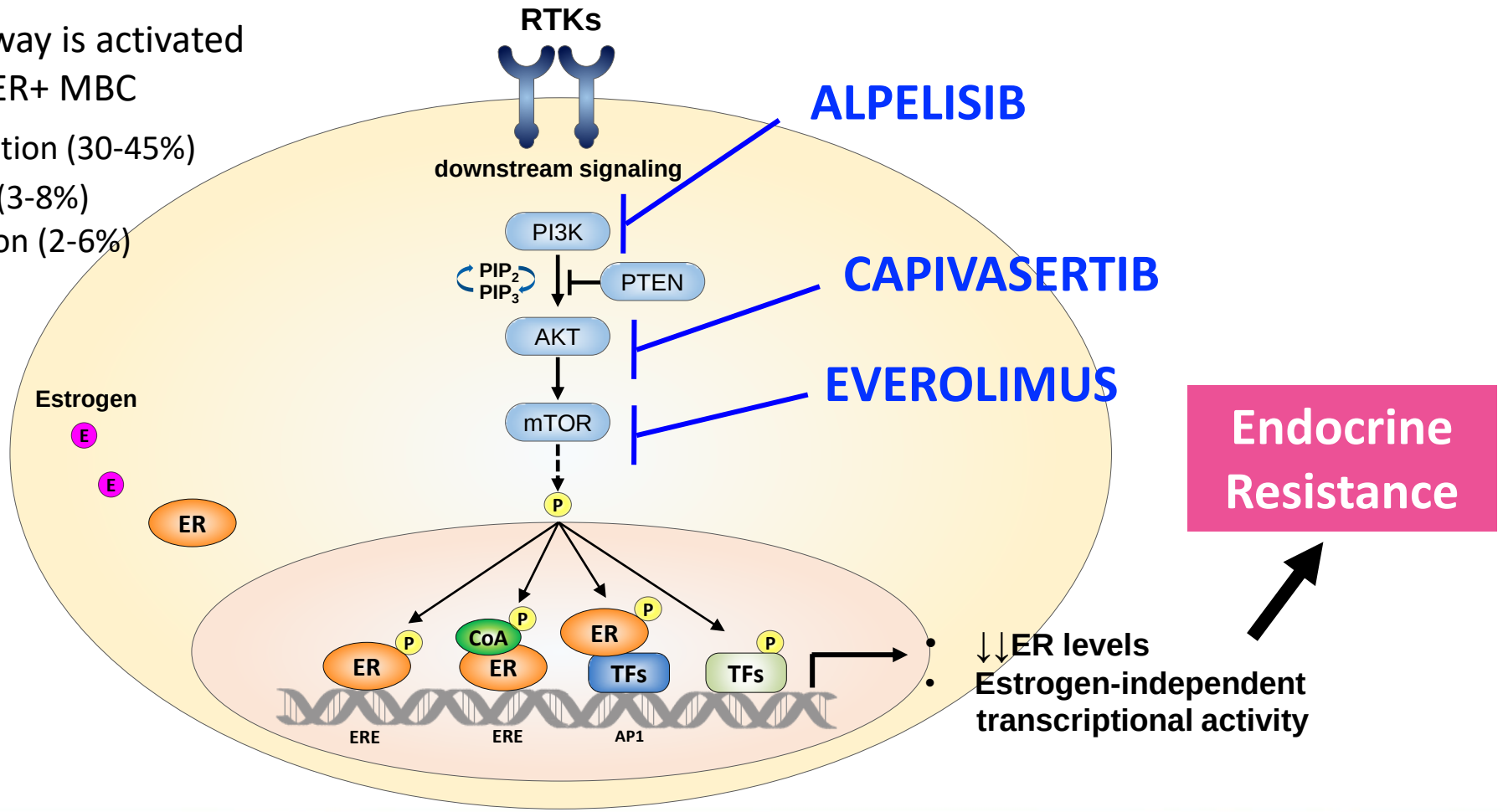
IO

- ?

Targeting genomic alterations and vulnerabilities

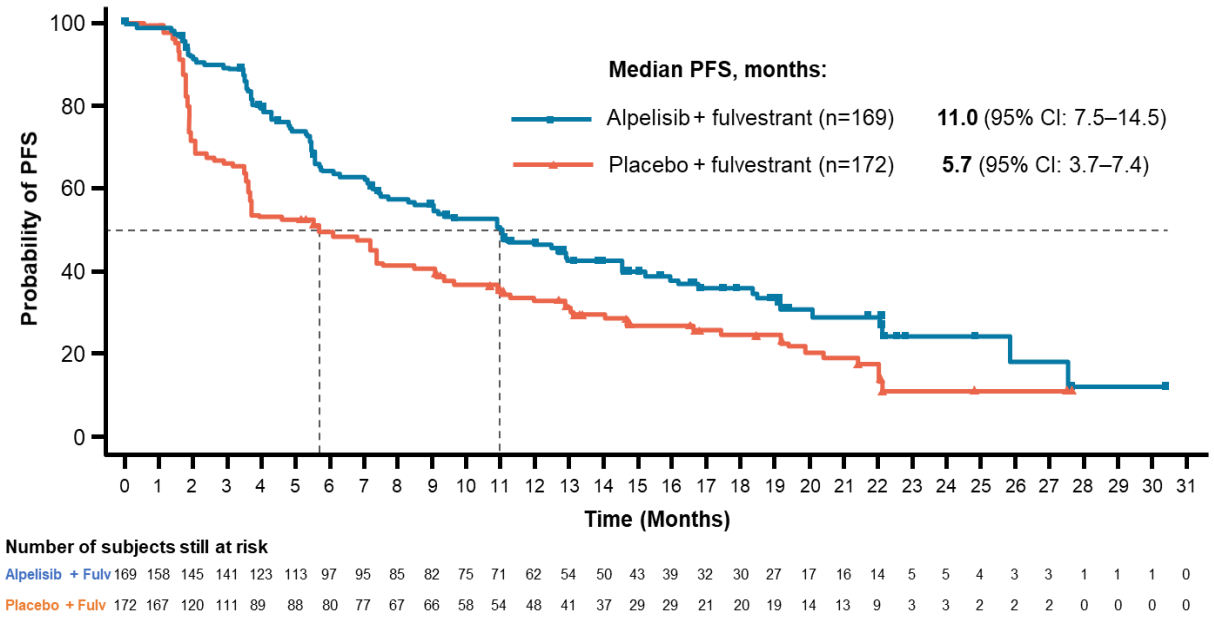
PI3K/Akt/mTOR pathway activation as a mechanism of endocrine resistance

- The PI3K/AKT/PTEN pathway is activated in approximately 50% of ER+ MBC
  - *PIK3CA* activating mutation (30-45%)
  - PTEN loss/inactivation (3-8%)
  - AKT1 activating mutation (2-6%)



SOLAR-1: Alpelisib + fulvestrant for HR+/HER2– ABC

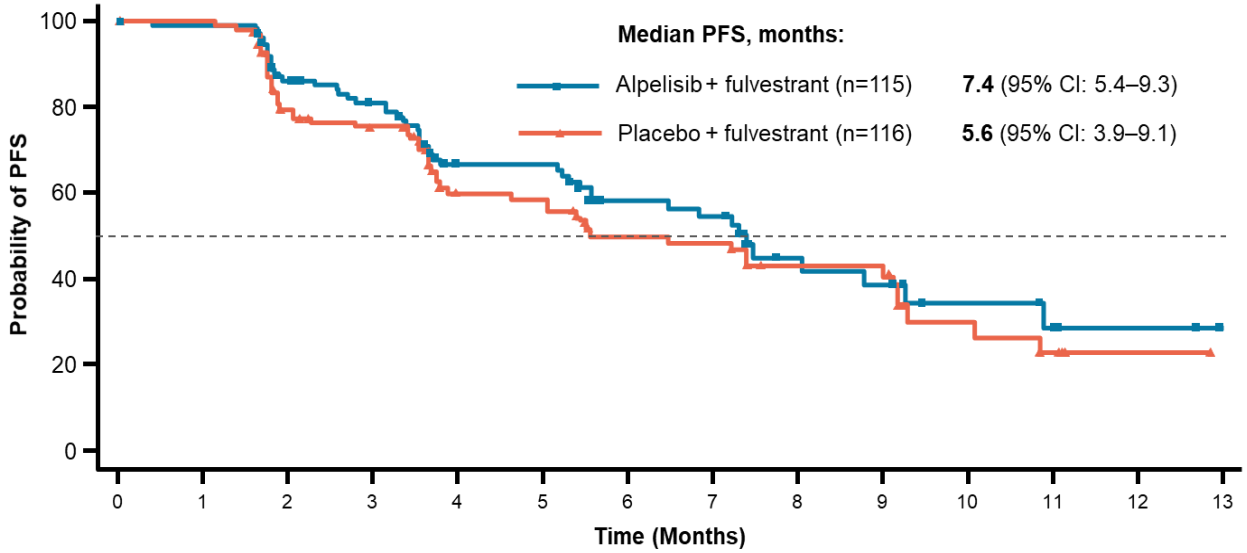
PIK3CA-mutant cohort



Number of subjects still at risk

Alpelisib + Fulv	169	158	145	141	123	113	97	95	85	82	75	71	62	54	50	43	39	32	30	27	17	16	14	5	5	4	3	3	1	1	1	0
Placebo + Fulv	172	167	120	111	89	88	80	77	67	66	58	54	48	41	37	29	29	21	20	19	14	13	9	3	3	2	2	2	0	0	0	0

PIK3CA-non-mutant cohort



Number of subjects still at risk

Alpelisib + Fulv	115	110	86	76	48	48	31	29	14	12	7	5	3	0
Placebo + Fulv	116	110	79	72	43	42	31	30	20	20	8	5	1	0

- Proof of concept criteria: estimated hazard ratio ≤0.60 and posterior probability ≥90% that the hazard ratio was <1
- Patients with *PIK3CA*-non-mutant disease were followed up for safety alongside the *PIK3CA*-mutant cohort

André F, et al NEJM 2018

André F, et al. N Engl J Med 2019

Alpelisib + fulvestrant for HR+/HER2– ABC

SOLAR-1

median PFS = 11.0 months

Characteristic	Pts	PFS HR (95% CI)
First Line	52%	0.71 (0.49–1.03)
Second Line	48%	0.61 (0.42–0.89)

André F, et al NEJM 2018

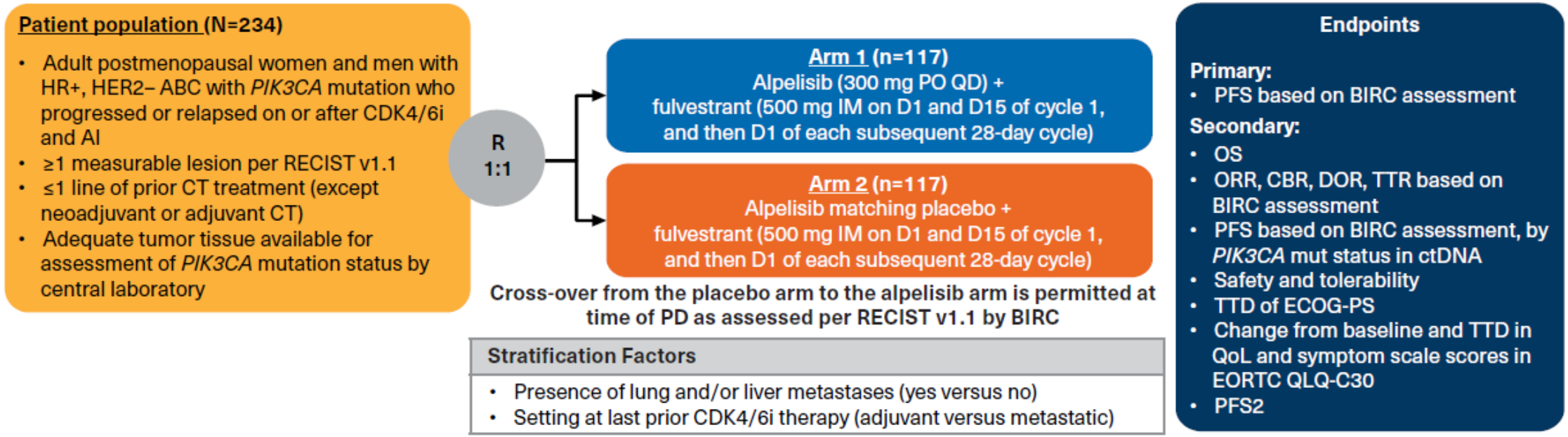
BYLieve (Cohort A)

median PFS = 7.3 months

Characteristic	Pts	PFS (95% CI) months
First Line	1.6%	
Second Line	79.5%	
Prior CDK4/6 inhibitor	100%	

Rugo HS, et al. Lancet Oncol 2021
Chia S., et al. ASCO 2021

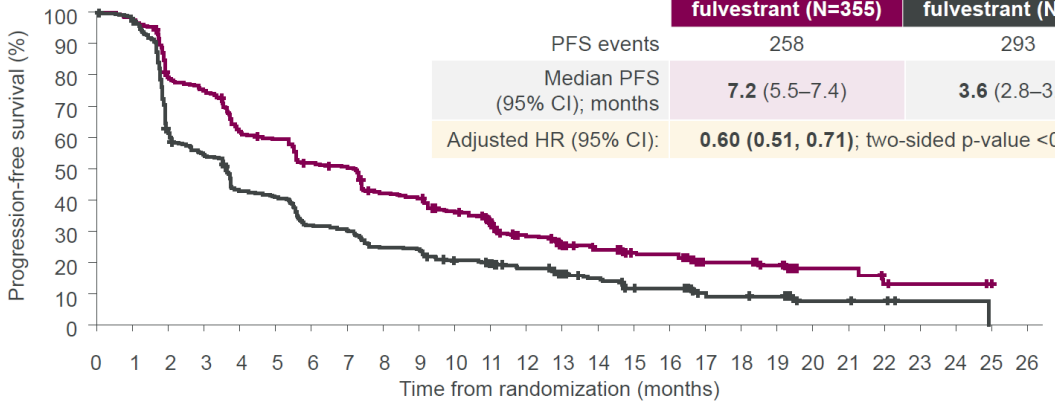
EPIK-B5: A Phase III, Randomized Study of Alpelisib + Fulvestrant in Patients With HR+/HER2, PIK3CA+ ABC Progressing On/After an AI With a CDK4/6 inhibitor



De Laurentiis M, et al. ASCO 2021

CAPITELLO-291: Dual primary endpoint

PFS in the overall population

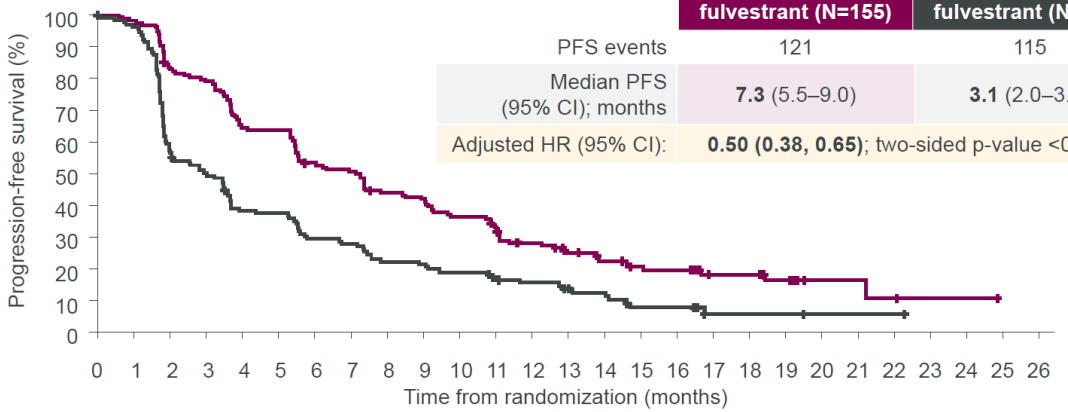


	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	

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

PFS in the AKT pathway altered* population



	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	

Number of patients at risk

Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

*≥1 PIK3CA, AKT, or PTEN alteration

Turner NC et al. SABCS 2022

CAPITELLO-291: PFS by subgroups

Overall Population

median PFS = 7.2 months

Characteristic	Pts	PFS HR (95% CI)
First Line	11.3%	
Second Line	80.6%	

AKT pathway altered population (43%)

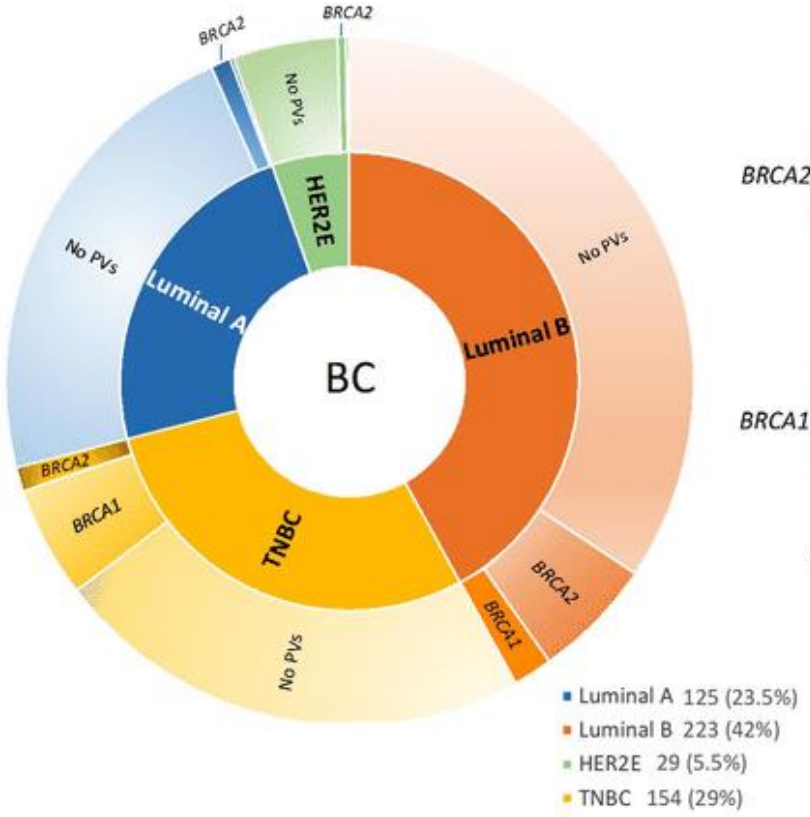
median PFS = 7.3 months

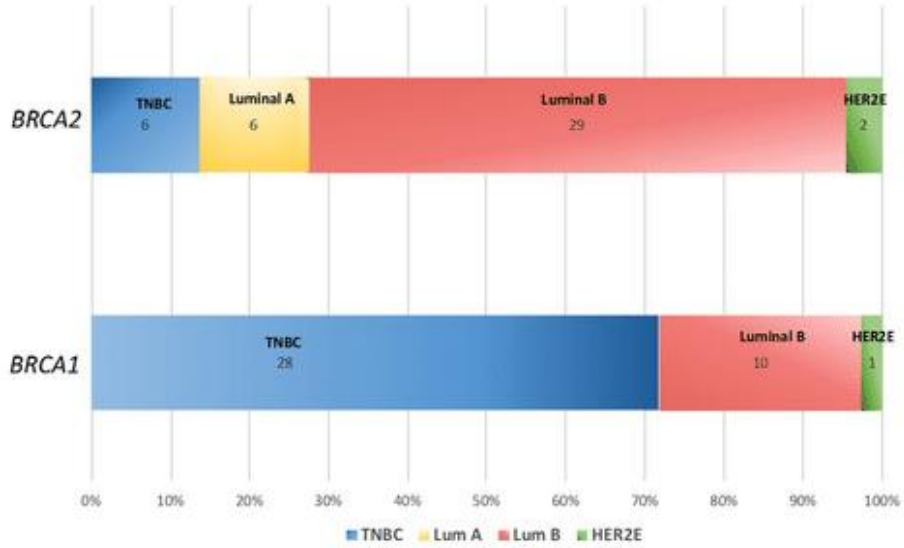
Characteristic	Pts
First Line	9%
Second Line	83.9%

Turner NC, et al. SABCS 2022

BRCA1/2 mutations in patients with Breast Cancer

- Though most breast cancer cases are sporadic, 5–10% of cases are hereditary and mostly related to *BRCA1* or *BRCA2* gene mutations.

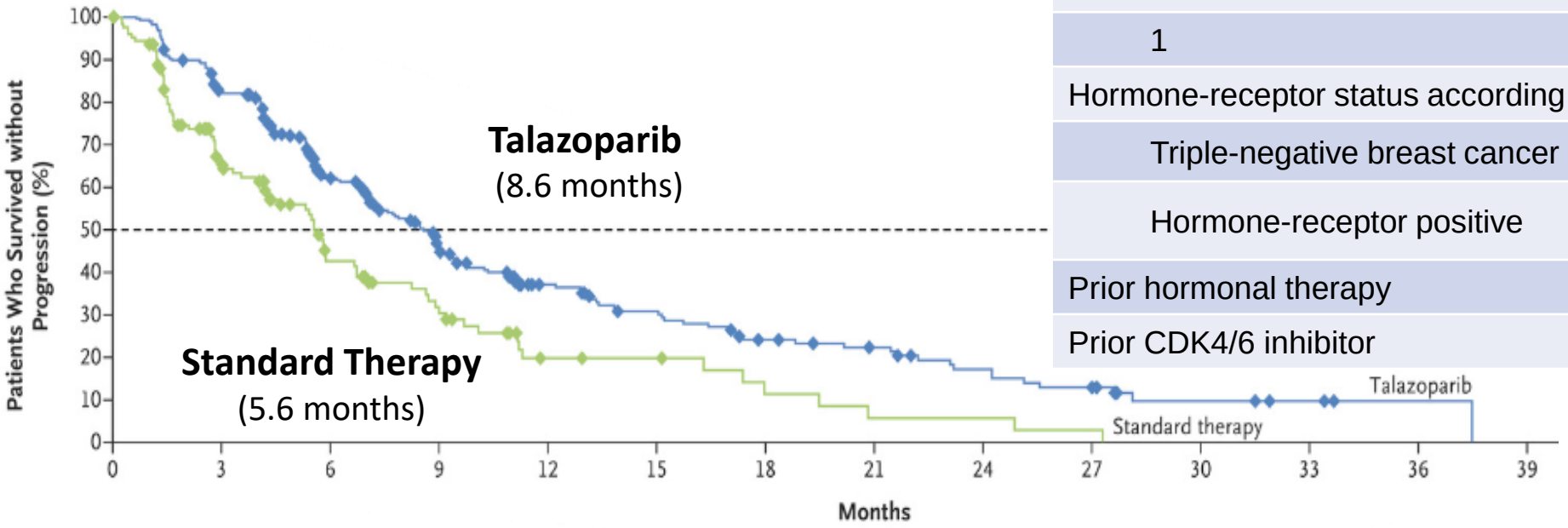




Incorvaia L, et al. Therapeutic Advances in Medical Oncology 2020

EMBRACA: talazoparib vs. chemotherapy in patients with advanced gBRCA-mutation BC

Progression Free Survival



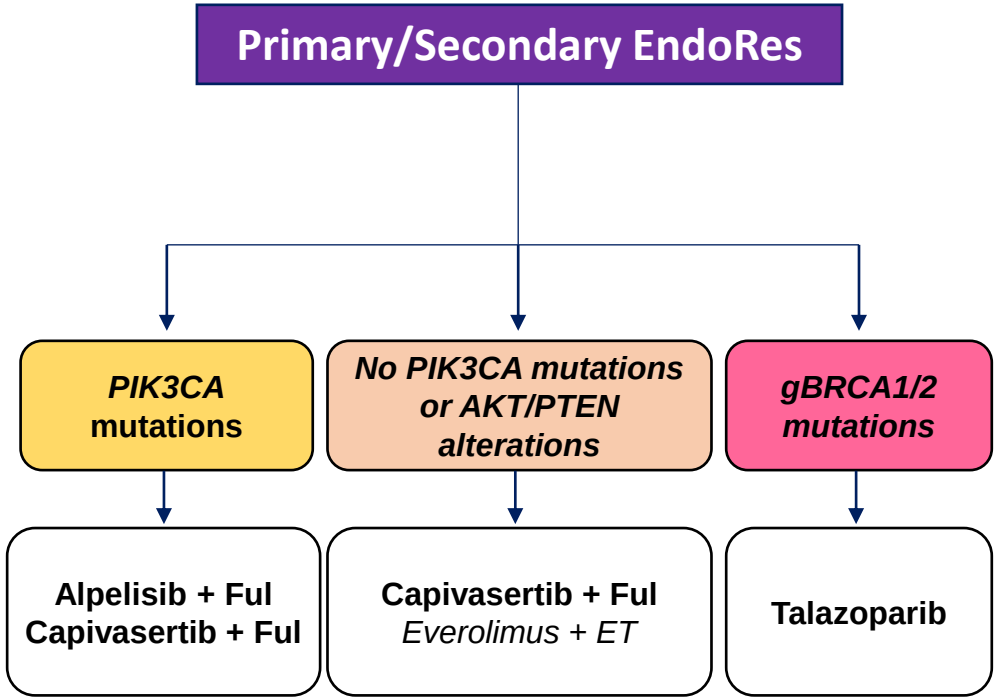
Characteristic	Pts	PFS HR (95% CI)
Previous regimes of cytotoxic chemotherapy		
0	39%	0.57 (0.34 – 0.95)
1	37%	0.51 (0.33 – 0.80)
Hormone-receptor status according to most recent biopsy		
Triple-negative breast cancer	45%	0.60 (0.41 - 0.87)
Hormone-receptor positive	55%	0.47 (0.32 - 0.71)
Prior hormonal therapy	56%	0.57 (0.34 – 0.95)
Prior CDK4/6 inhibitor	0%	-

Litton J, et al. NEJM 2018

Post-CDK4/6i: Proposed Algorithm

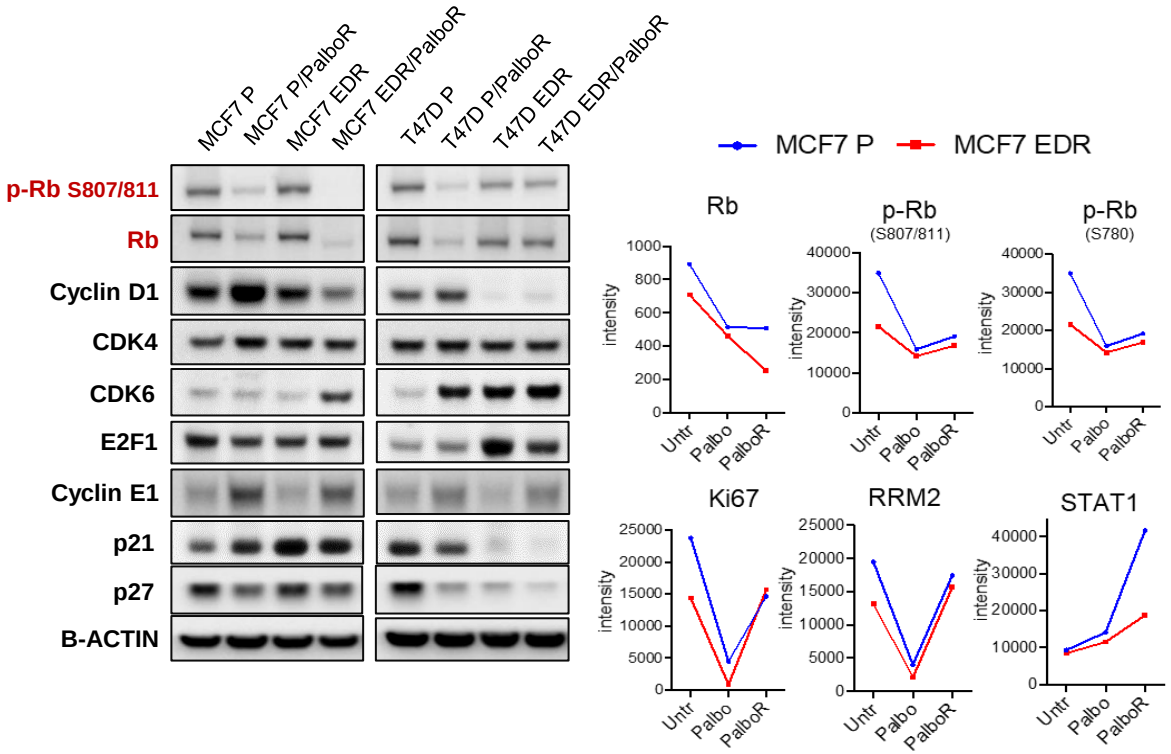
Progression on first-line endocrine therapy + CDK4/6 inhibitor

Status evaluation of ***PIK3CA*** (±PI3K pathway components), ***gBRCA1/2***



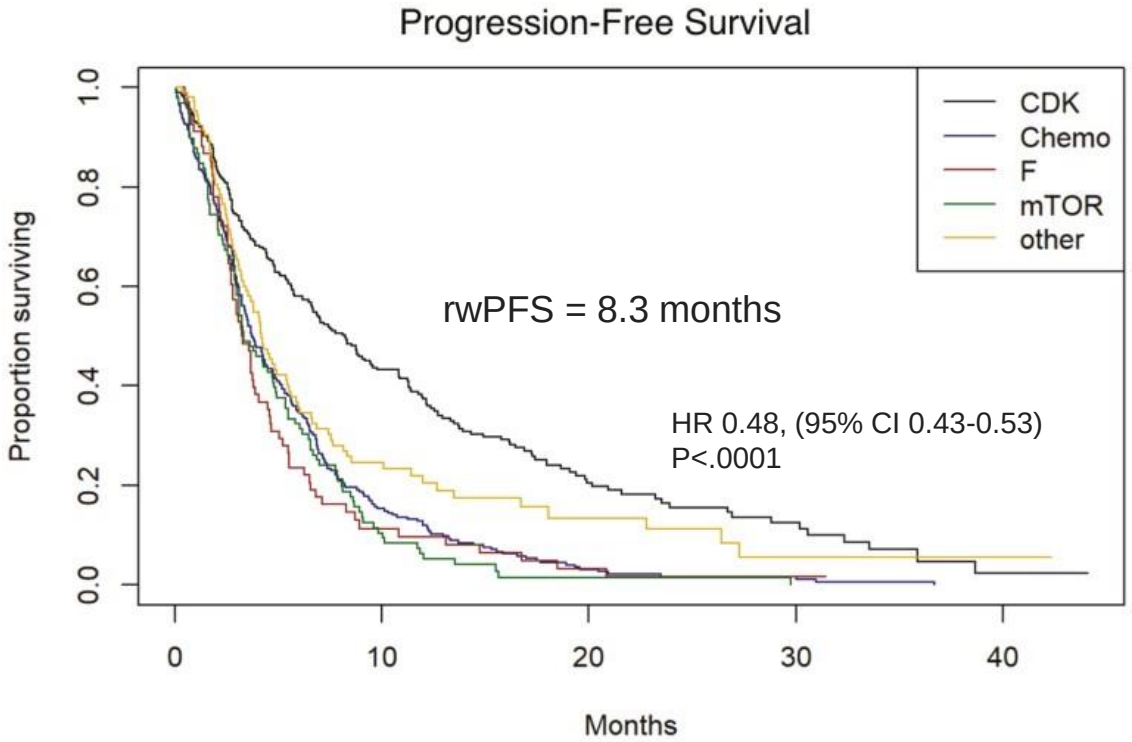
CDK4/6 inhibition beyond progression to CDK4/6i

Preclinical evidences:



De Angelis C, et al. Clin Can Res 2021

Clinical evidences:



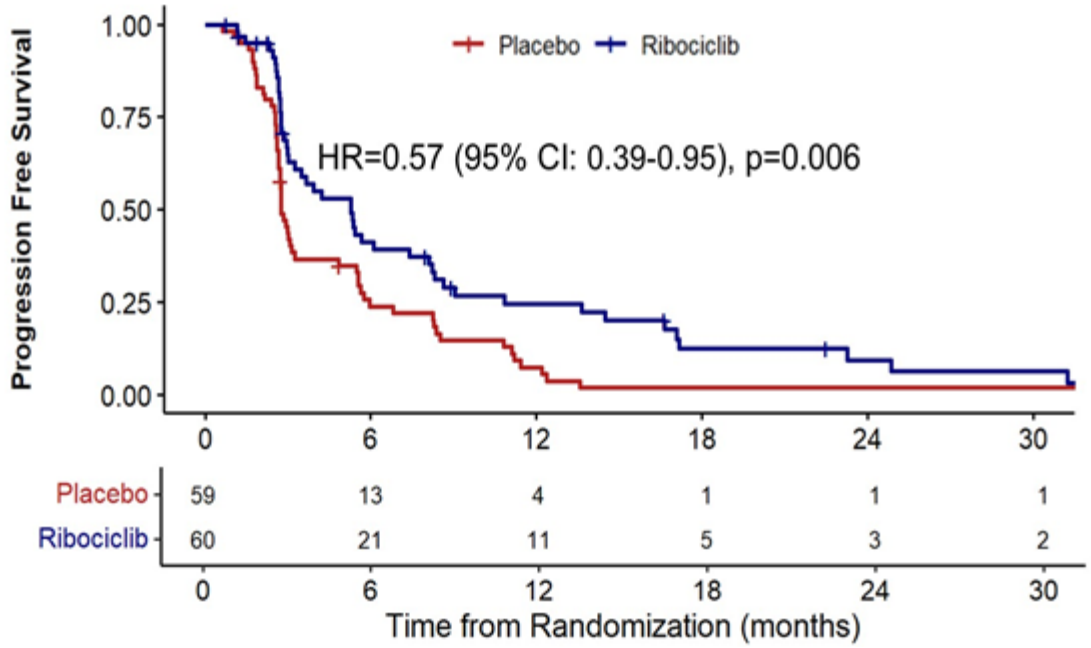
Matin JM, et al. The Oncologist 2022

Completed and Ongoing Phase II clinical trials of CDK4/6 inhibitors beyond progression

Study name (NCT)	Population	Study treatment
GIM-24-PalboBP (NCT04318223)	MBC pts treated with prior CDK4/6i+AI (est. N=168)	Palbo+Ful
PALMIRA (NCT03809988)	MBC pts treated with prior Palbo+ ET (AI or Ful) (est. N=198)	- Palbo+ ET (Ful or AI) - ET (Ful or AI)
BIOPER (NCT03184090)	MBC pts treated with prior Palbo+ET	Palbo+ ET
PACE (NCT03147287)	MBC pts treated with prior Palbo+ET	- Fulv - Fulv+Palbo - Fulv+Palbo+ Avelumab
NCT02738866	MBC pts treated with prior Palbo+AI (est. N=100)	Palbo+Ful
MAINTAIN (NCT02632045)	MBC pts treated with Palbo/Ribo+AI (est. N=132)	- Ribo+Ful - PBO+Ful

MAINTAIN
(Ribociclib)

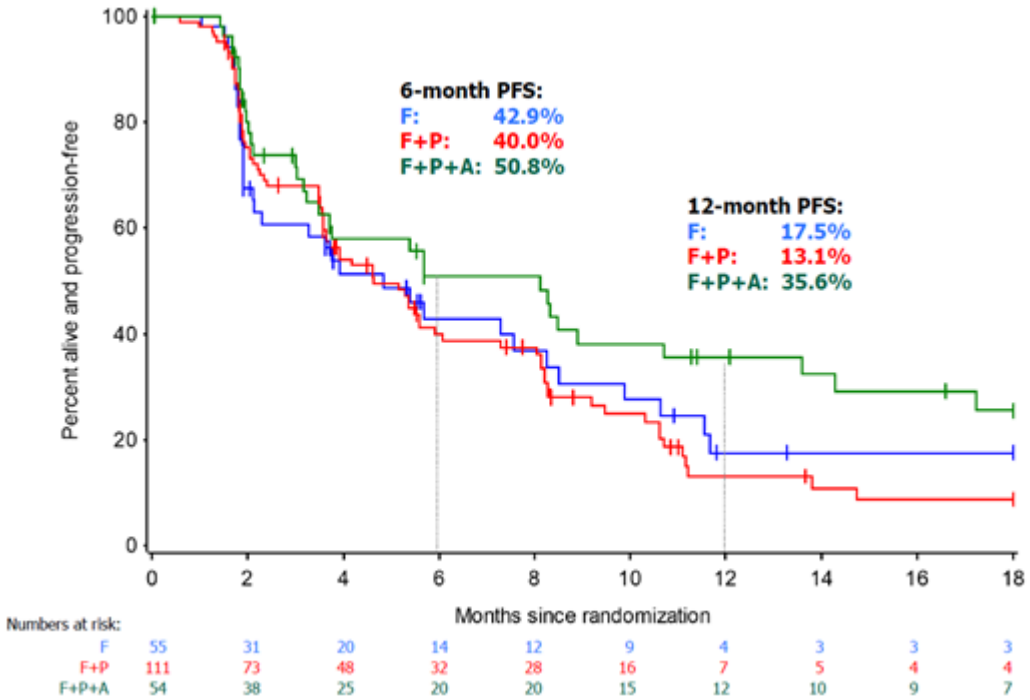
median PFS = 5.3 months



Kalinsky K, et al. ASCO 2022

PACE
(Palbociclib)

median PFS = 4.6 months (Ful+Palbo)



Meyer EL, et al. SABCS2022

MAINTAIN
(Ribociclib)

median PFS = 5.29 months (ribociclib + ET)

Characteristic	Pts	PFS HR (95% CI)
Primary endocrine resistance	-	
Secondary endocrine resistance	-	
Prior CDK4/6 inhibitor		
Palbociclib	**87%**	0.58 (0.38 – 0.90)
Ribociclib	10%	0.50 (0.15 – 1.70)
Abemaciclib	3%	-

Kalinsky K, et al. ASCO 2022

PACE
(Palbociclib)

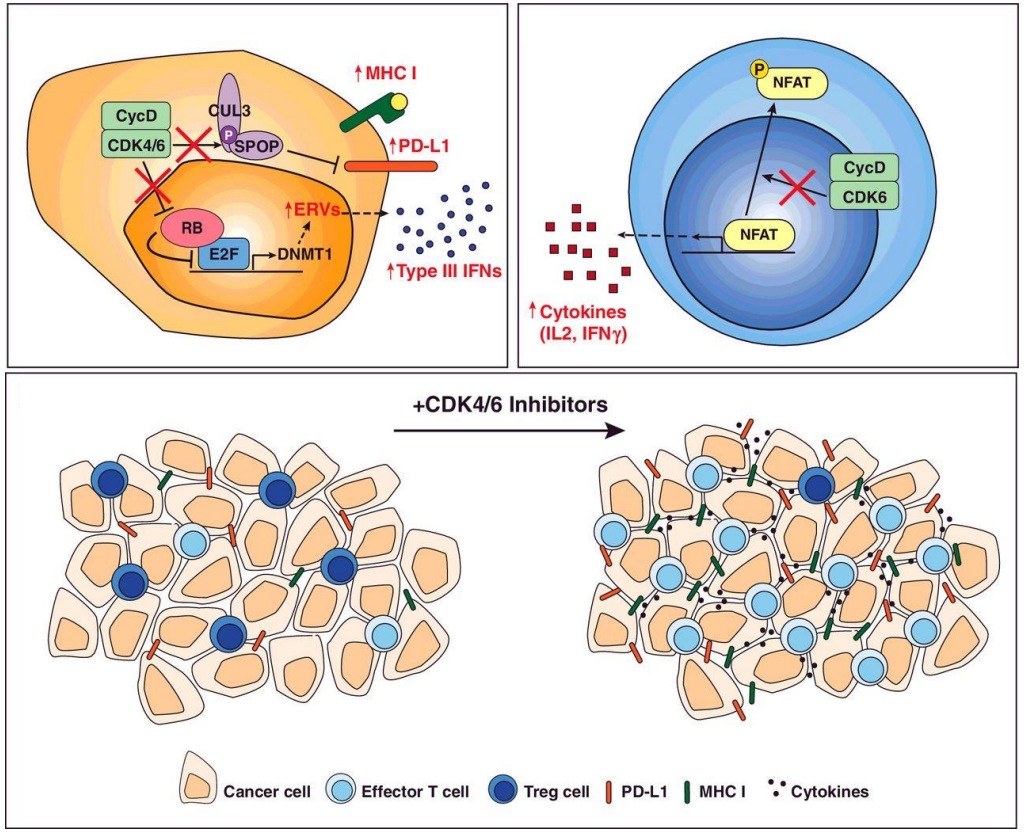
median PFS = 4.6 months (palbociclib + fulvestrant)

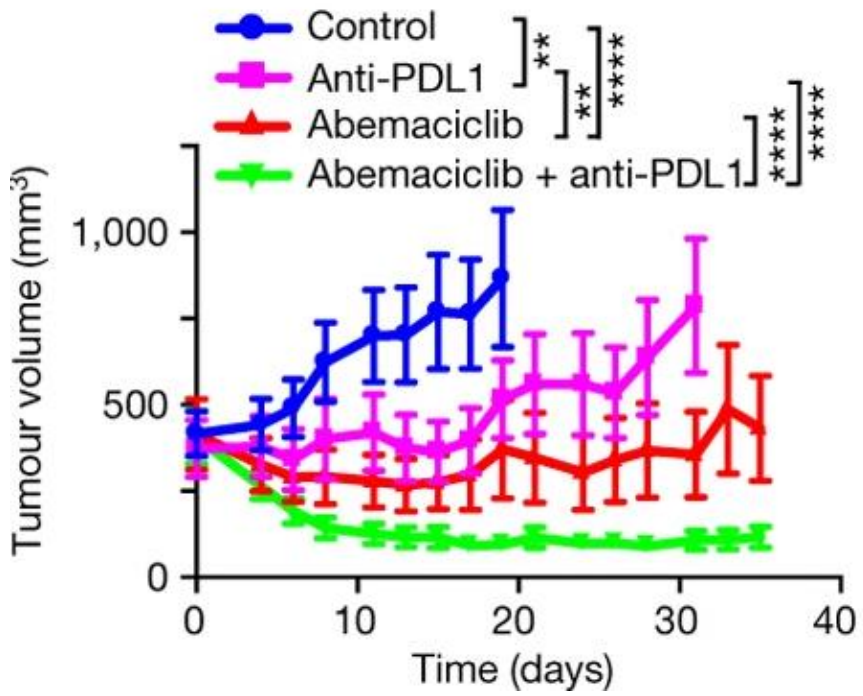
Characteristic	Pts	PFS HR (95% CI)
Primary endocrine resistance	26.4%	-
Secondary endocrine resistance	72.7%	-
Prior CDK4/6 inhibitor		
Palbociclib	**90.1%**	1.15 (0.81 – 1.63)
Ribociclib	4.5%	0.63 (0.16 – 2.50)
Abemaciclib	4.1%	

Meyer EL, et al. SABCS2022

CDK4/6 inhibition modulates the immune milieu and triggers anti-tumor immunity

Noncanonical anticancer effects of CDK4/6 inhibitors

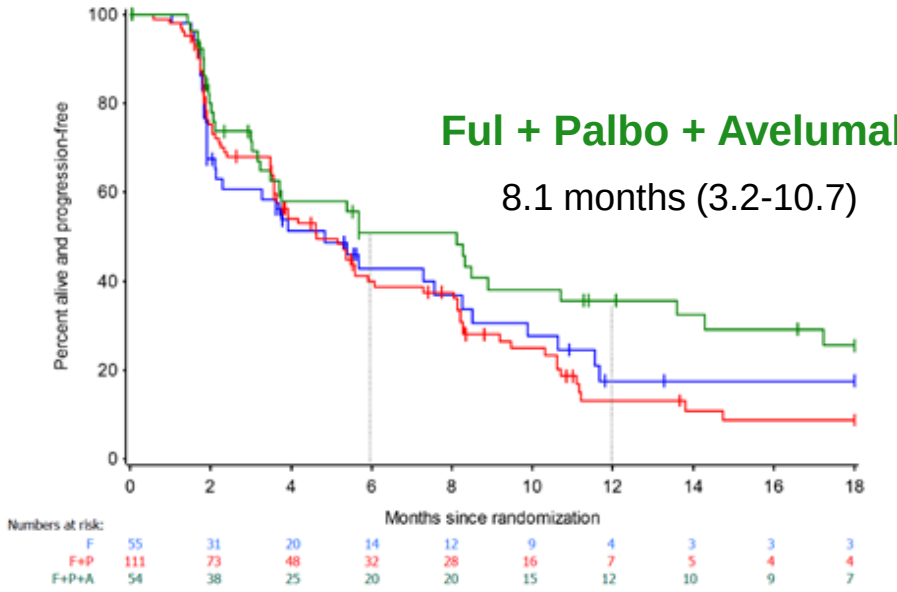




Goel, S., DeCristo, M., Watt, A. *et al.* CDK4/6 inhibition triggers anti-tumour immunity. *Nature* **548**, 471–475 (2017)

PACE trial: Fulvestrant + Palbociclib + Avelumab arm

Progression Free Survival



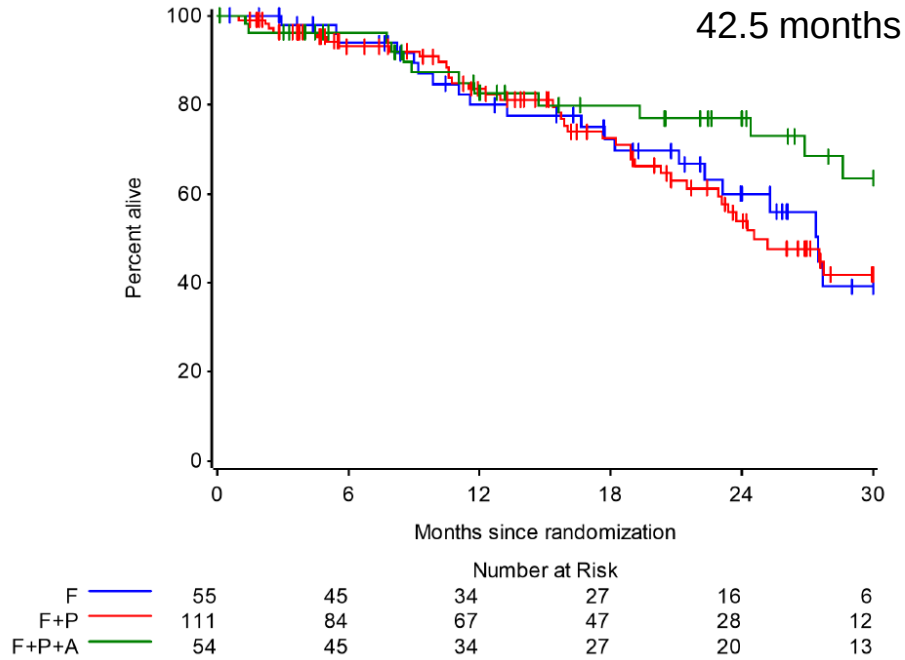
Ful + Palbo + Avelumab

8.1 months (3.2-10.7)

Overall Survival

Ful + Palbo + Avelumab

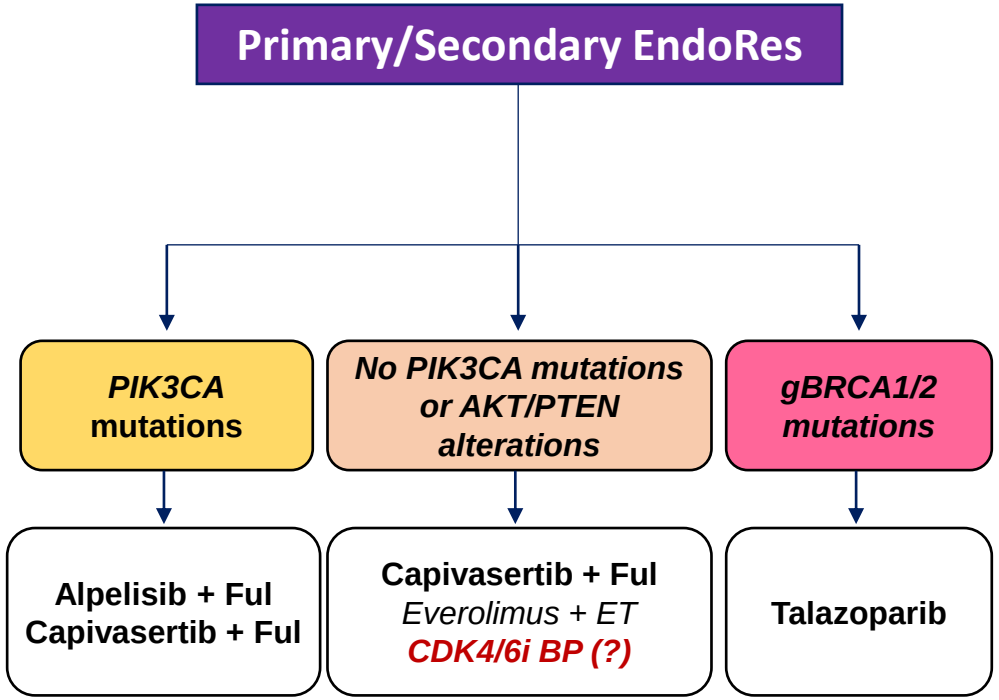
42.5 months (26.8 – 46.0)



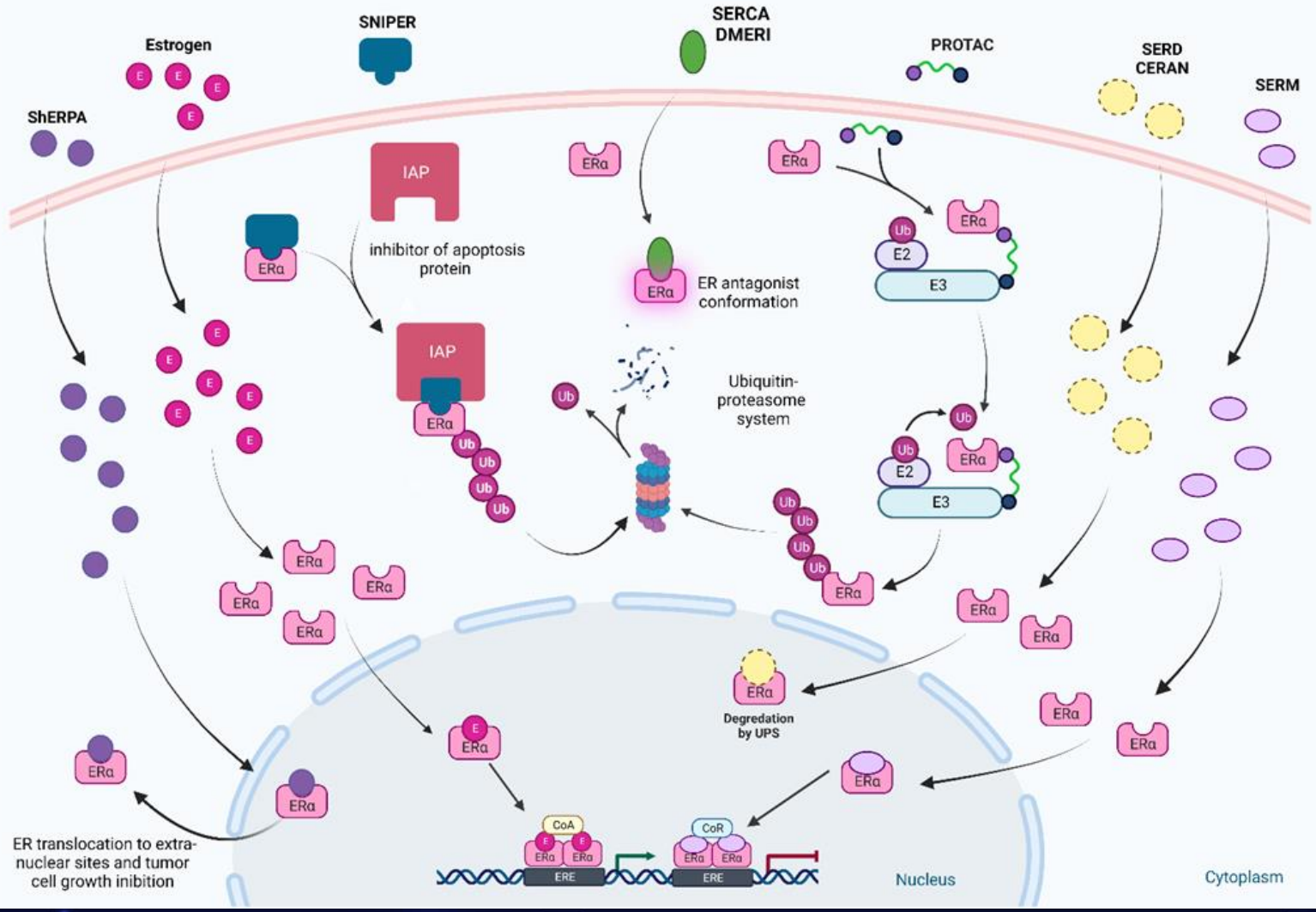
Meyer EL, et al. SABCS2022

Post-CDK4/6i: Proposed Algorithm

Progression on first-line endocrine therapy + CDK4/6 inhibitor



Novel Endocrine Therapies



Pagliuca M, et al. CROH 2022

EMERALD
(Elacestrant)

median PFS = 2.8 months (ITT); 3.8 months (ESR1mut)

Characteristic	Elacestrant (Pts)	SoC (pts)
Prior CDK4/6 inhibitor	100%	100%

Bardia A, et al. SABCS 2021
Bardia A, et al. SABCS 2022

SERENA-2
(Camizestrant)

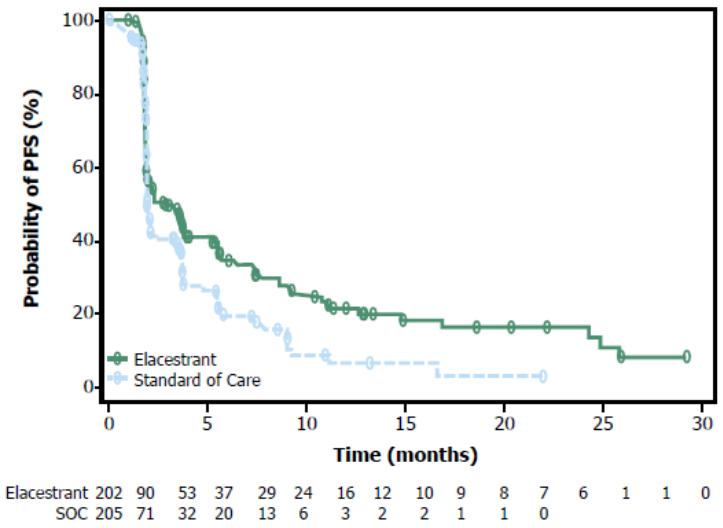
median PFS = 7.2 months (C75); 7.7 months (C150)

Characteristic	C 75 (Pts)	C 150 (pts)	F (Pts)
Prior CDK4/6 inhibitor	51.4%	50.7%	50.7%

Olivera M, et al. SABCS 2022

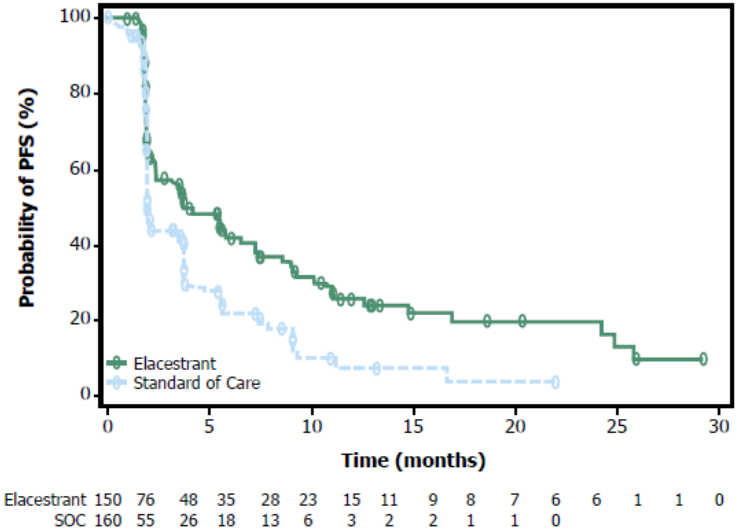
All Patients: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



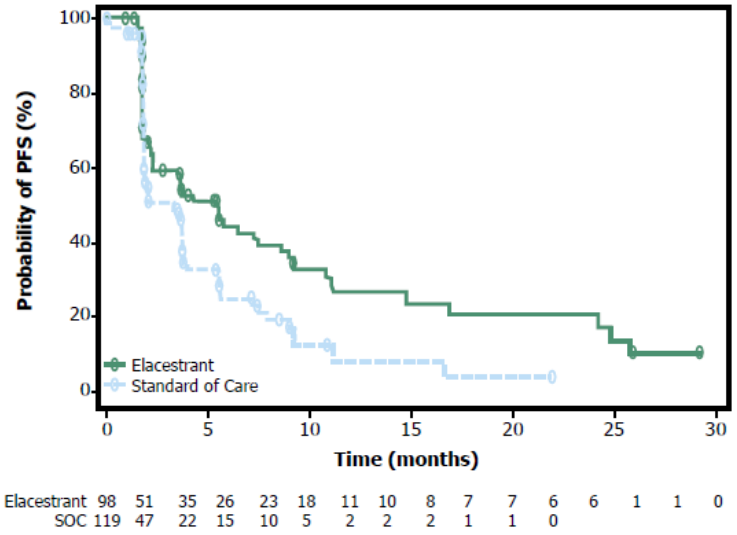
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)	

At least 12 mo 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 mo CDK4/6i

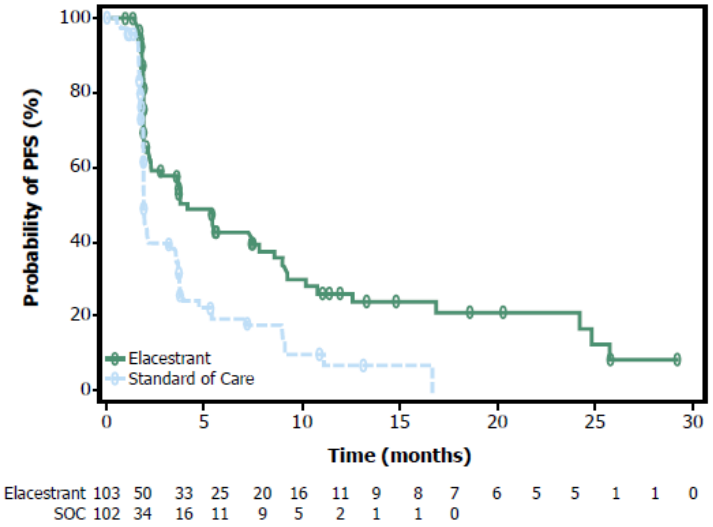


	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 12 months, % (95% CI)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
Hazard ratio (95% CI)	**0.703** (0.482 - 1.019)	

Bardia A, et al., SABCS 2022

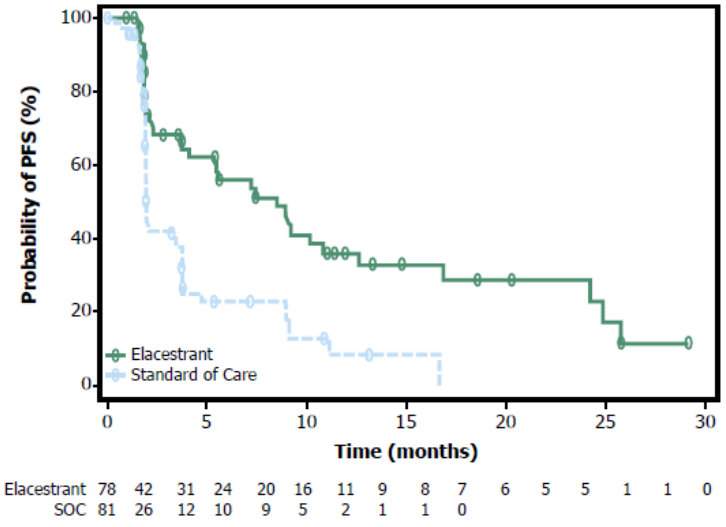
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



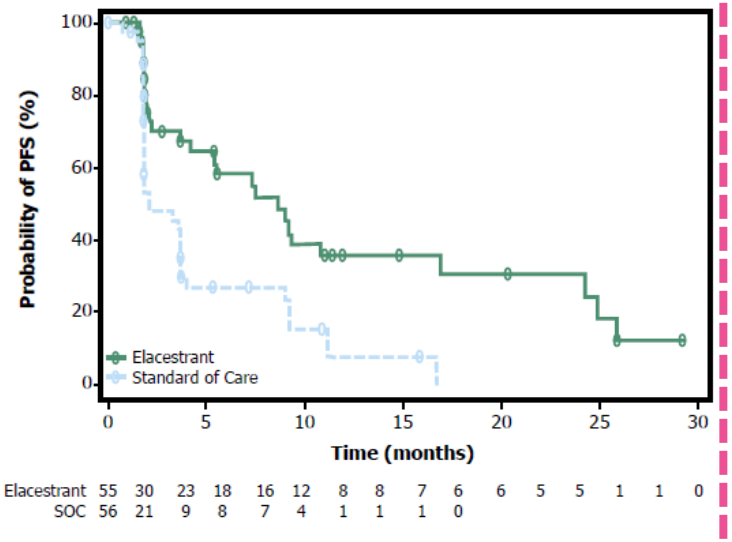
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

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

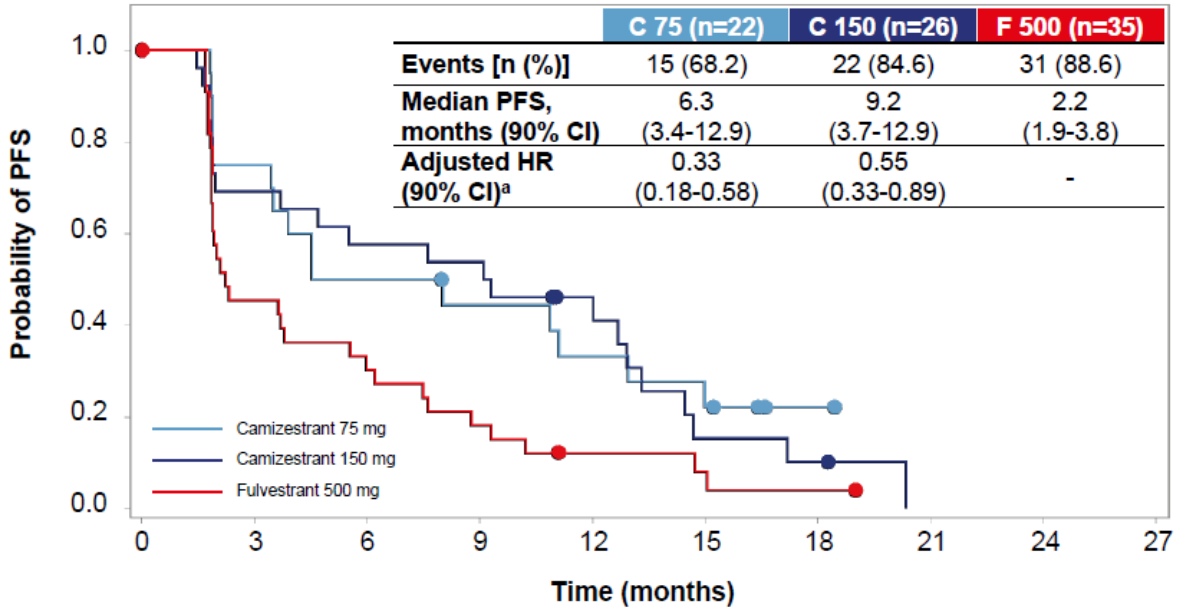


	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Bardia A, et al., SABCS 2022

PFS in patients by detectable ESR1m

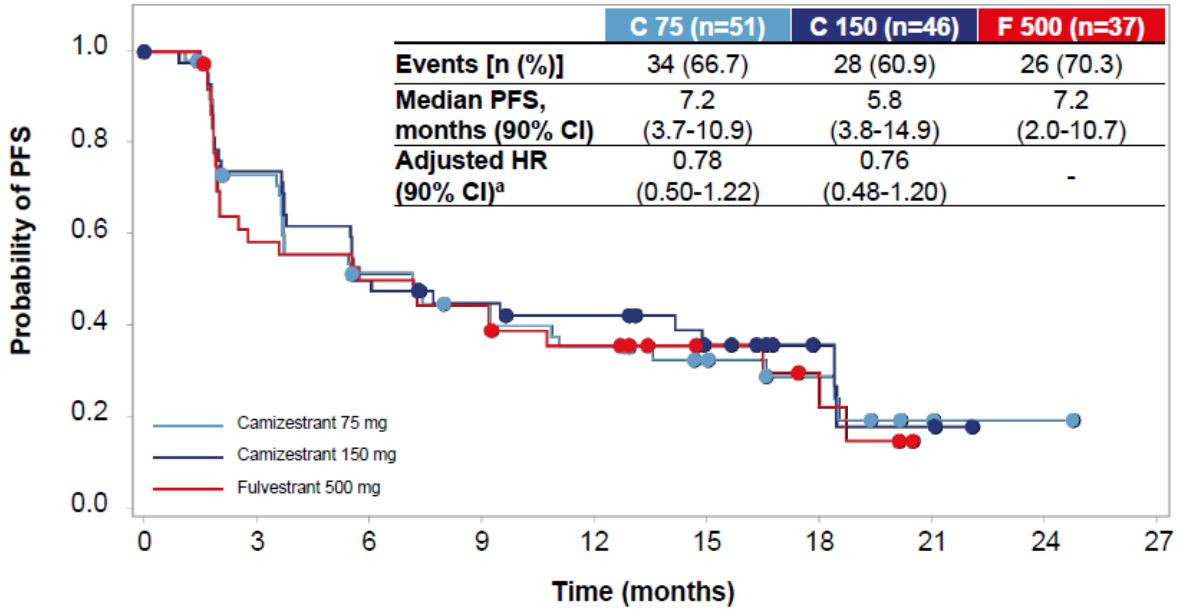
*ESR1*m detectable at baseline



	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)	-

C 75	22	15	10	8	6	4	1	0
C 150	26	18	15	14	9	3	2	0
F	35	15	10	6	3	2	1	0

*ESR1*m not detectable at baseline

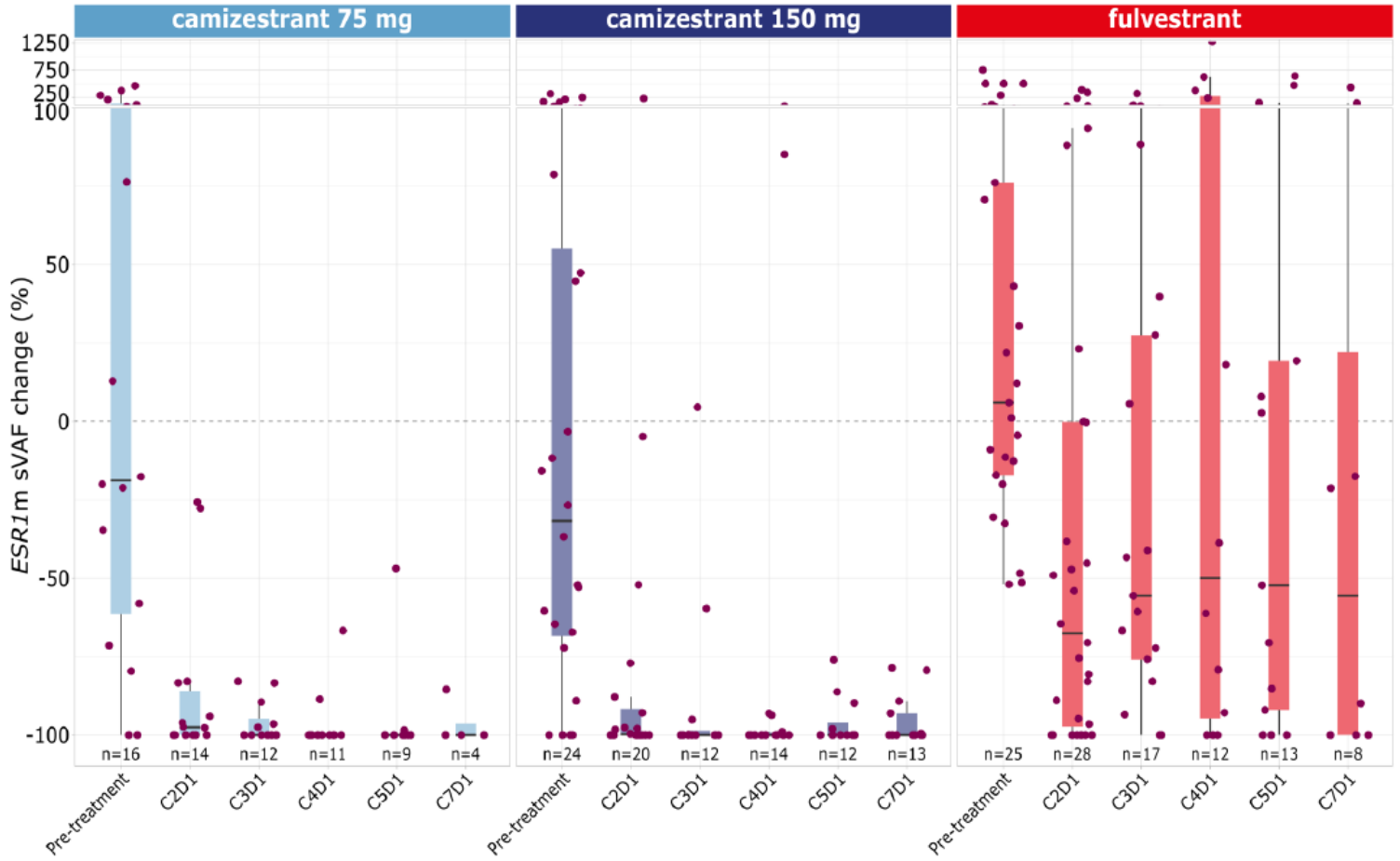


	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-

C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

Olivera M, et al. SABCS 2022

Changes in *ESR1m* ctDNA variant allele frequency



- Treatment with camizestrant 75 and 150 mg reduced the level of *ESR1*m ctDNA to undetectable or near undetectable levels by Cycle 2 Day 1 and maintained this to Cycle 7 Day 1
- Fulvestrant also reduced levels of *ESR1*m ctDNA, but not to the same extent as camizestrant

*ESR1*m classed as E380Q, V422del, S463P, L536H/P/R, Y537C/D/N/S, D538G. Pre-treatment = % change in *ESR1*m sVAF from screening to Cycle 1 Day 1, CXD1 = % change from Cycle 1 Day 1 to Cycle X Day 1

ctDNA: circulating tumor DNA; *ESR1*m: mutation in estrogen receptor 1 gene; *ESR1*m sVAF: Summed variant allele frequency of qualifying *ESR1*m

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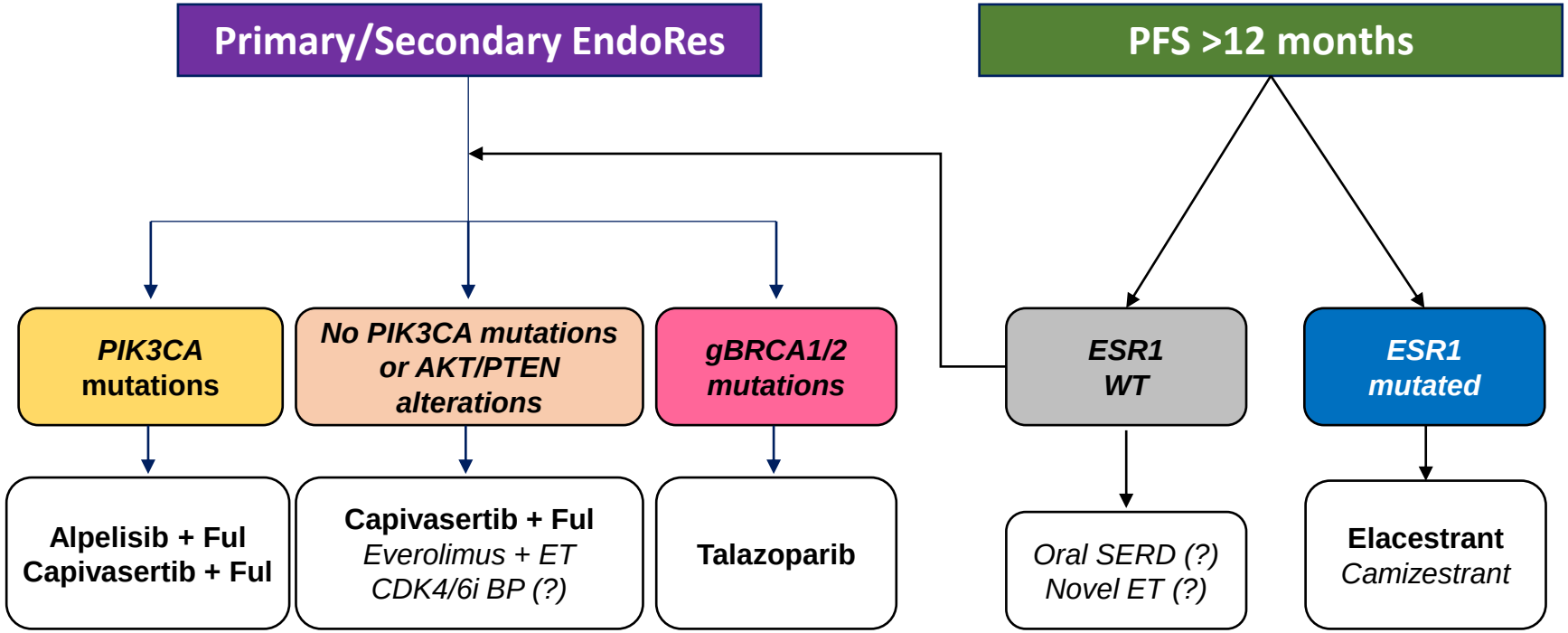
Post-CDK4/6i: Proposed Algorithm

Progression on first-line endocrine therapy + CDK4/6 inhibitor

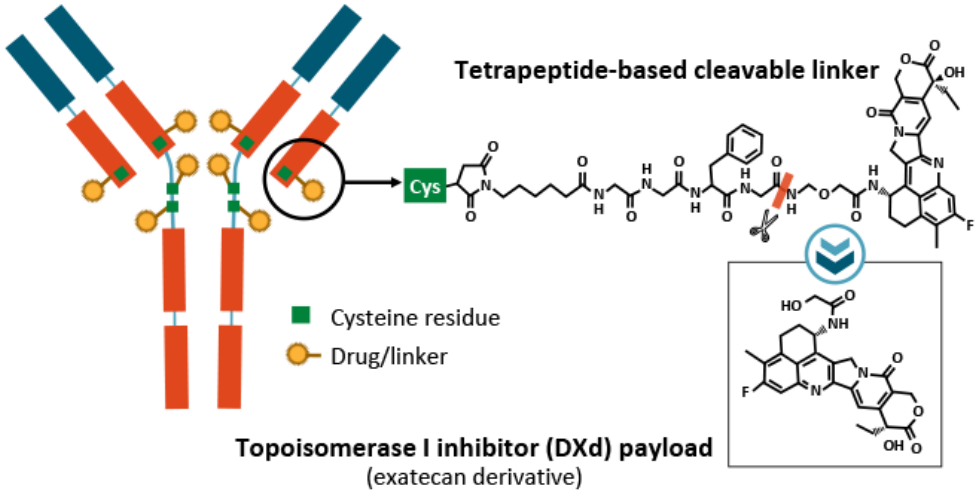
Status evaluation of ***PIK3CA*** (±PI3K pathway components), ***gBRCA1/2***, ***ESR1***



Antibody-Drug Conjugates in Breast Cancer

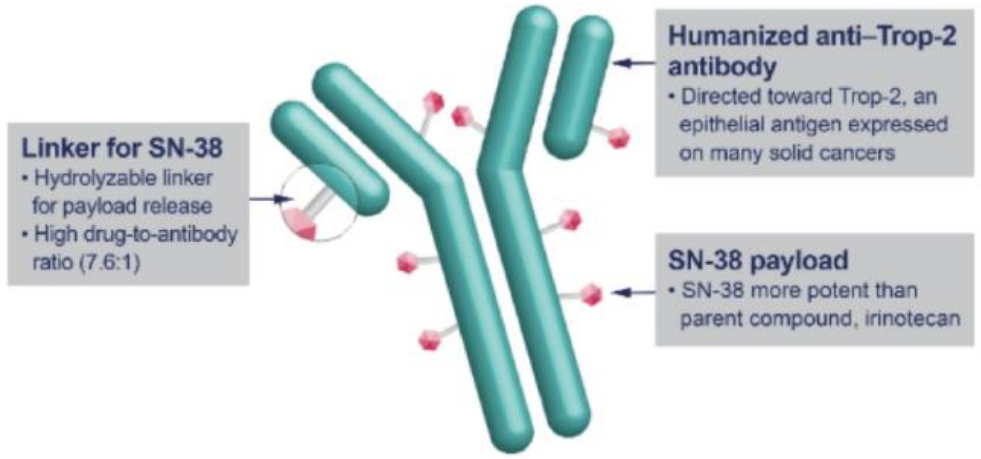
- **<u>Trastuzumab deruxtecan</u>**

  ✓ HER2-directed antibody-drug conjugate
  ✓ Active in **HER2 Low**-Expressing Breast Cancer



- **<u>Sacituzumab Govitecan</u>**:

  ✓ Trop-2–directed antibody–drug conjugate
  ✓ Active in HR+/HER2- MBC



DESTINY-B04
(Trastuzumab Deruxtecan)

- HR+ BC considered endocrine refractory

	Hormone receptor–positive	
	T-DXd (n = 331)	TPC (n = 163)
Lines of systemic therapy (metastatic setting)		
Number of lines, median (range)	3 (1-9)	3 (1-8)
Number of lines, n (%)		
1	23 (7)	14 (9)
2	85 (26)	41 (25)
≥3	223 (67)	108 (66)
Lines of chemotherapy (metastatic setting)		
Number of lines, median (range)	1 (0-3)	1 (0-2)
Number of lines, n (%)		
0	1 (0.3)	1 (0.6)
1	203 (61.3)	93 (57.1)
2	124 (37.5)	69 (42.3)
≥3	3 (0.9)	0
Lines of endocrine therapy (metastatic setting)		
Number of lines, median (range)	2 (0-7)	2 (0-6)
Number of lines, n (%)		
0	28 (8)	17 (10)
1	105 (32)	49 (30)
2	110 (33)	53 (33)
≥3	88 (27)	44 (27)
Prior targeted cancer therapy, n (%)		
Targeted therapy	259 (78)	132 (81)
CDK4/6 inhibitor	233 (70)	115 (71)

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TROPICS-02
(Sacituzumab Govitecan)

	SG (n=272)	TPC (n=271)
Median time from initial metastatic diagnosis to randomization, mo (range)	48.5 (1.2- 243.8)	46.6 (3.0- 248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)	173 (64)	184 (68)
Prior endocrine therapy use in the metastatic setting ≥6 mo, n (%)	235 (86)	234 (86)
Prior CDK4/6 inhibitor use, n (%)		
≤12 months	161 (59)	166 (61)
>12 months	106 (39)	102 (38)
Unknown	5 (2)	3 (1)
Median prior chemotherapy regimens in the metastatic setting, n (range)[d]	3 (0-8)	3 (1-5)

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DESTINY-B04
(Trastuzumab Deruxtecan)

- median PFS in HR+/HER2-low = 10.1 months ☑
  HR 0.51 (0.40 - 0.64), p<0.0001
- median OS in HR+/HER2-low = 23.9 months ☑
  HR 0.64 (0.48 - 0.86), p<0.0028

Modi S, et al. ASCO 2022

TROPICS-02
(Sacituzumab Govitecan)

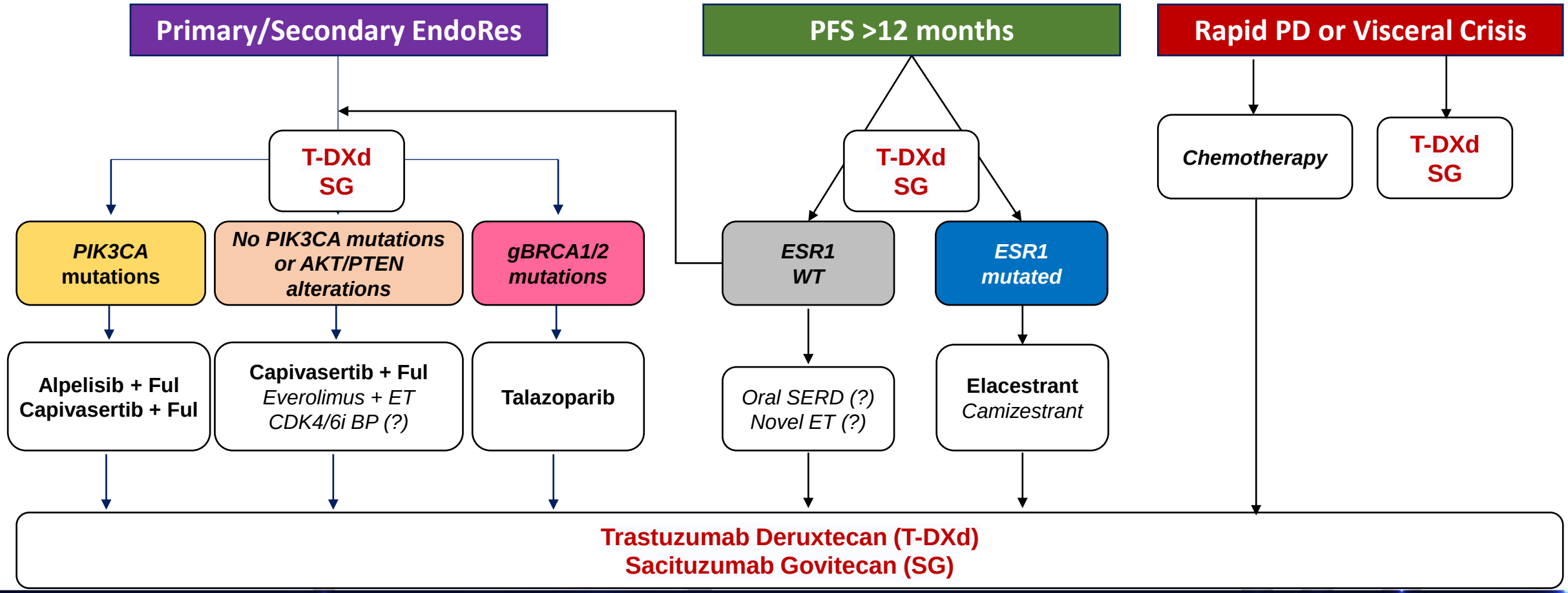
- median PFS = 5.5 months ☑
  HR 0.51 (0.40 - 0.64), p<0.0003
- median OS = 14.4 months ☑
  HR 0.79 (0.65 -0.96), p<0.020

Rugo HS, et al. ASCO 2022

Post-CDK4/6i: Proposed Algorithm

Progression on first-line endocrine therapy + CDK4/6 inhibitor

Status evaluation of ***PIK3CA*** (±PI3K pathway components), ***gBRCA1/2***, ***ESR1***



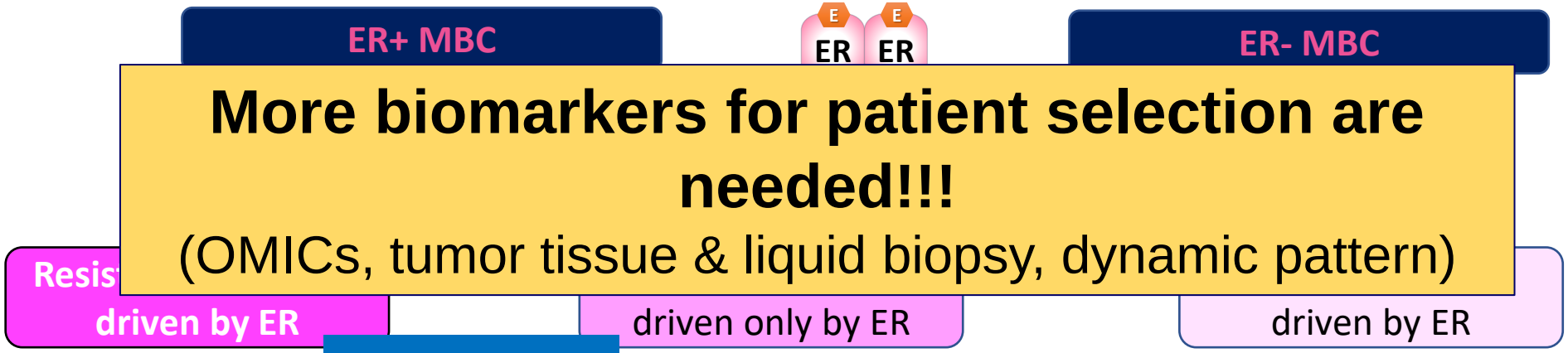
Carmine De Angelis, MD, PhD

UNIVERSITÀ DEGLI STUDI DI NAPOLI
FEDERICO II

carmine.deangelis1@unina.it

@CarmineDeA1

Different scenarios of Endocrine Resistence



- **ER is a target**

(SERD, SERCA, SERMs, PROTAC)

- **ER is a targ**

(SERD, SERCA, SERMs, PROTAC)

+

- **GFR/DS inhibitors**

(PI3K, AKT, mTOR, HER2, FGFR1)

- **DDR, IO, …**

- **ER is NOT a target**

- **ADCs**
- **DDR**
- **IO**

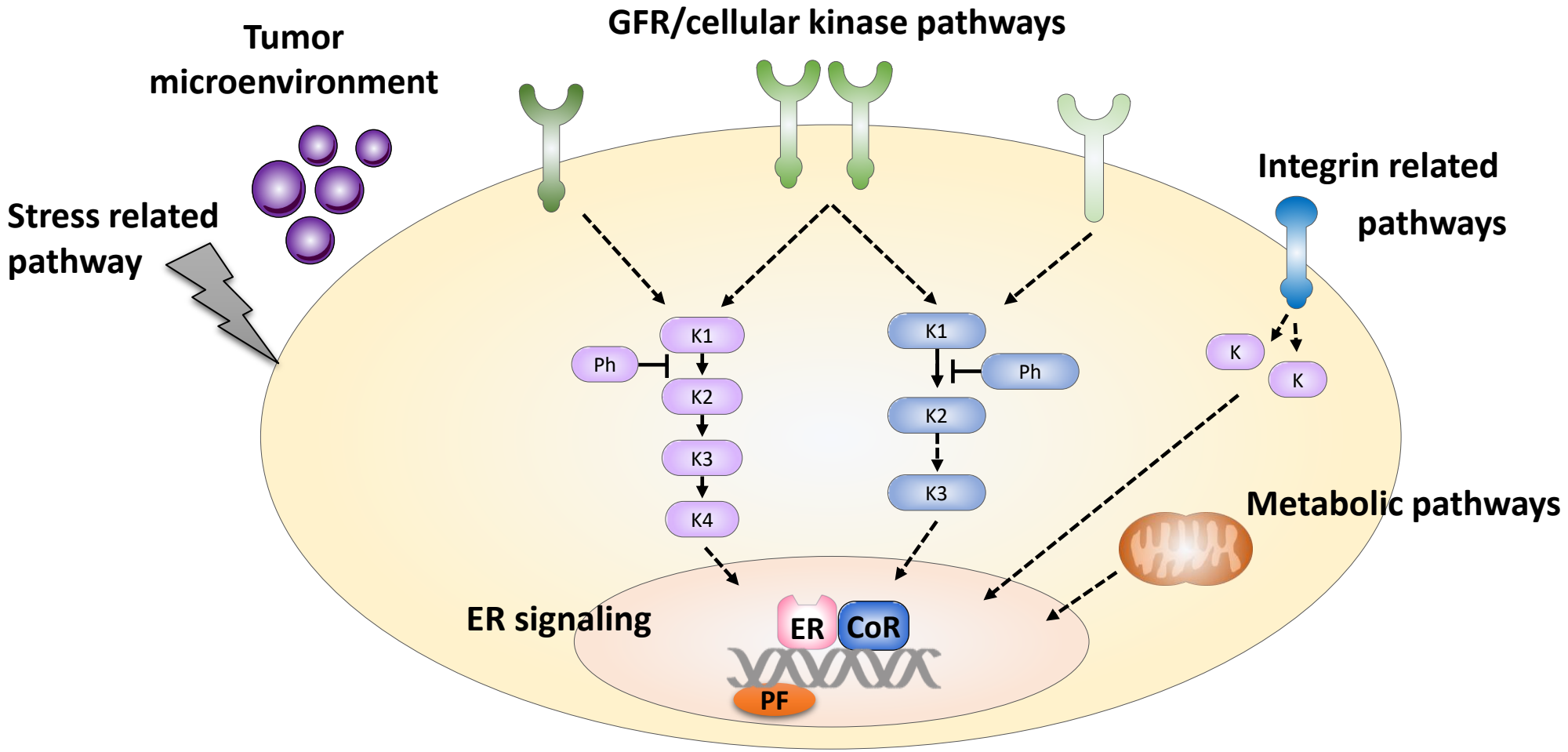
Carmine De Angelis, MD, PhD

UNIVERSITÀ DEGLI STUDI DI NAPOLI
FEDERICO II

carmine.deangelis1@unina.it

@CarmineDeA1

Mechanisms of endocrine resistance



ER, estrogen receptor; CoR, co-regulators; PF, pioneer factor, K, kinase; Ph, phosphate