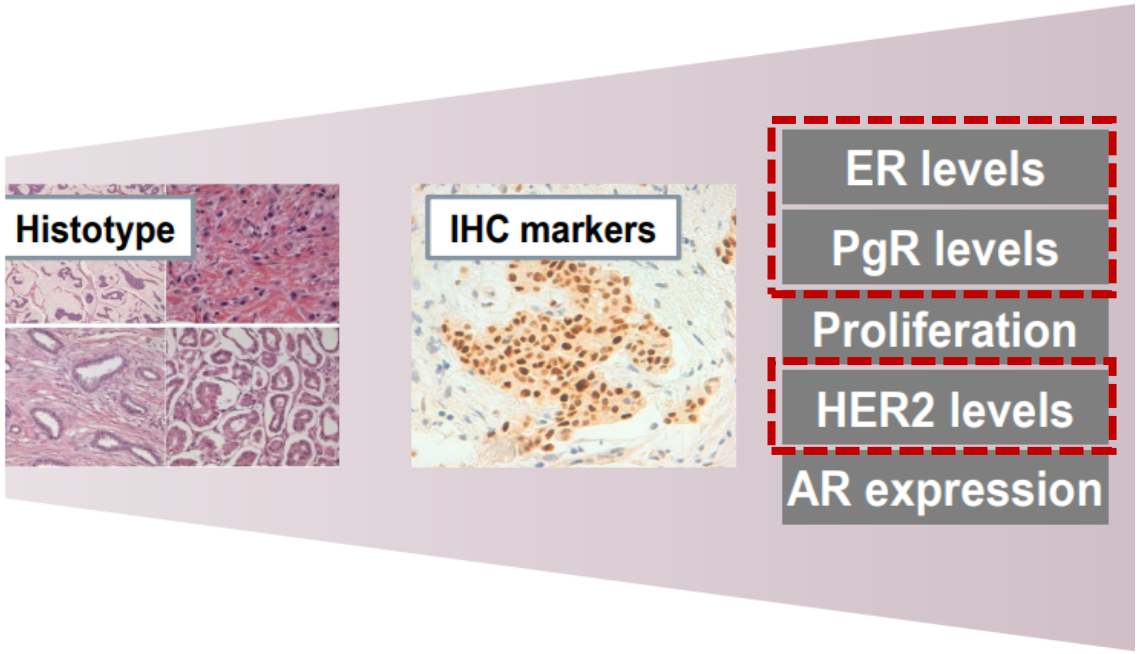
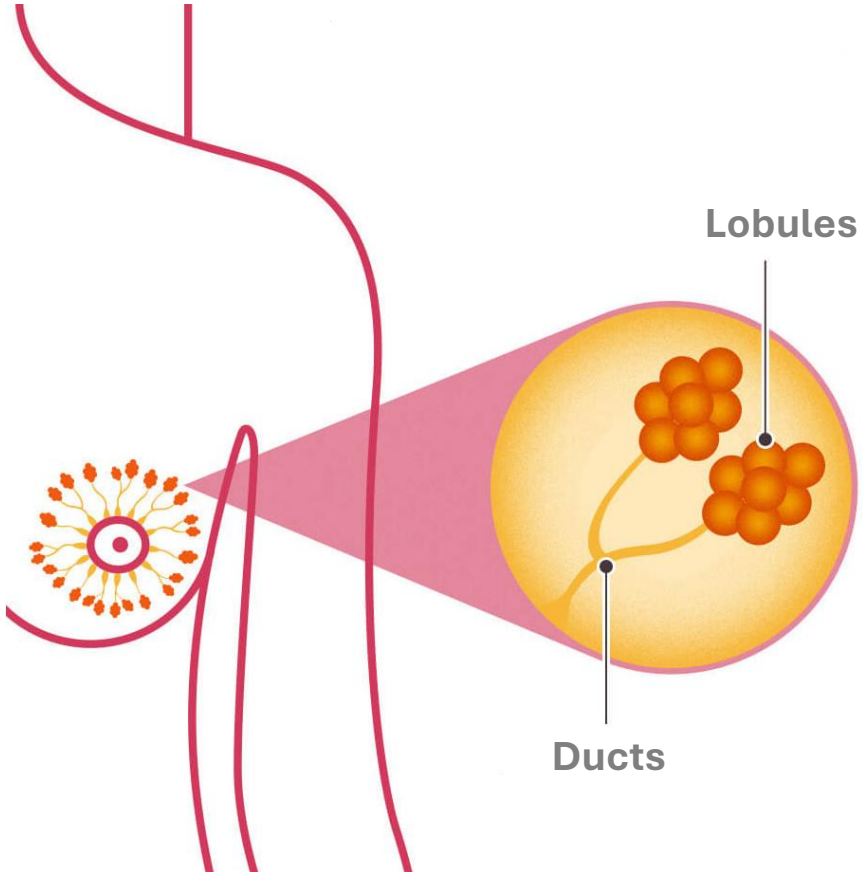
Il carcinoma metastatico HR+HER2negativo: dagli inibitori di cdk4/6 agli inibitori di pi3k

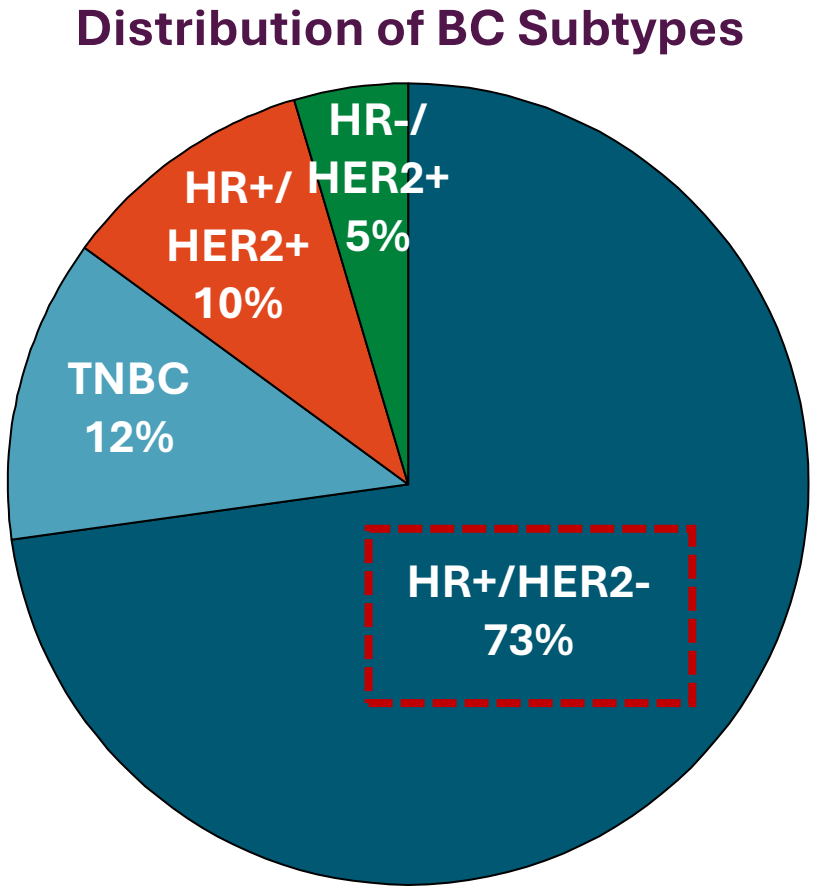
Grazia Arpino, MD, PhD

Breast Cancer is an heterogenous disease



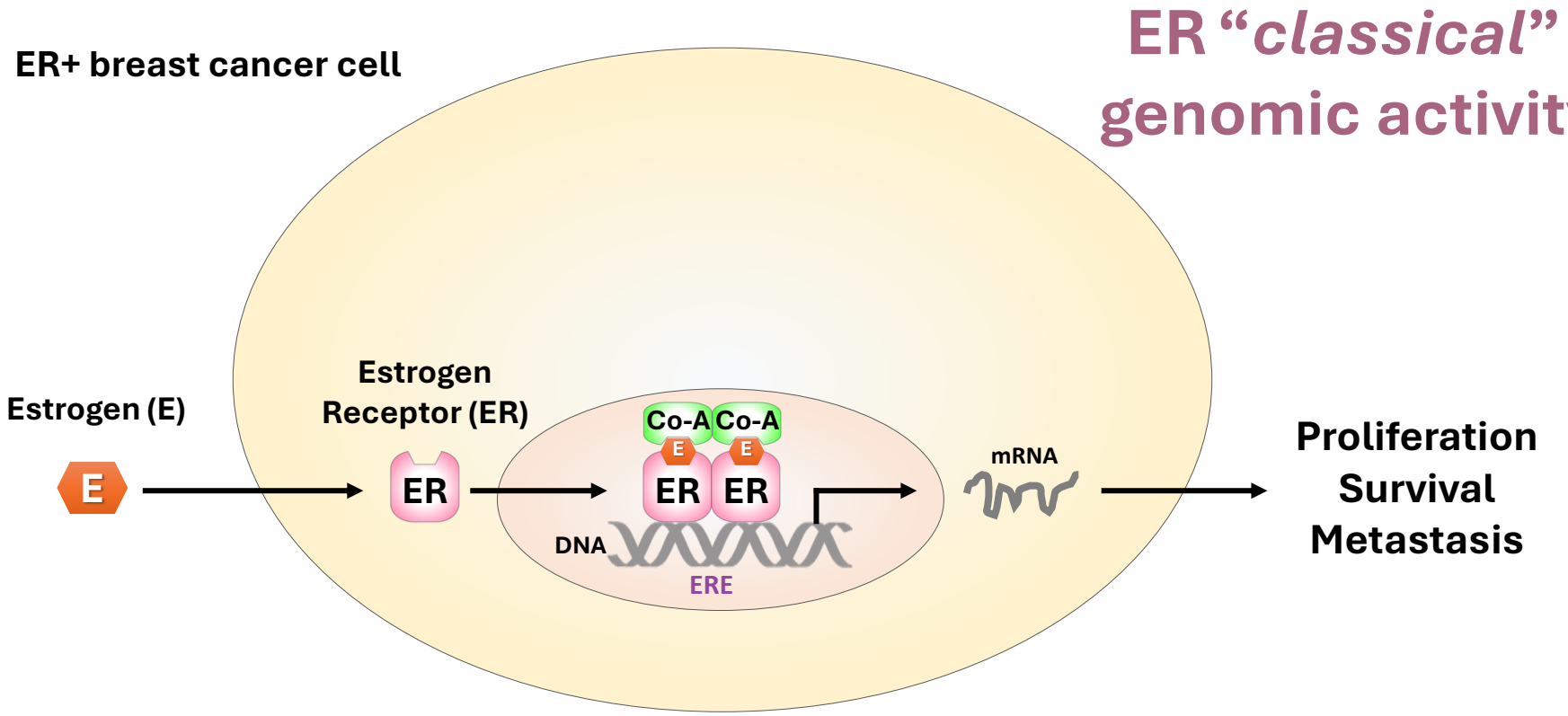
Luminal breast cancer is the most represented breast cancer subtype





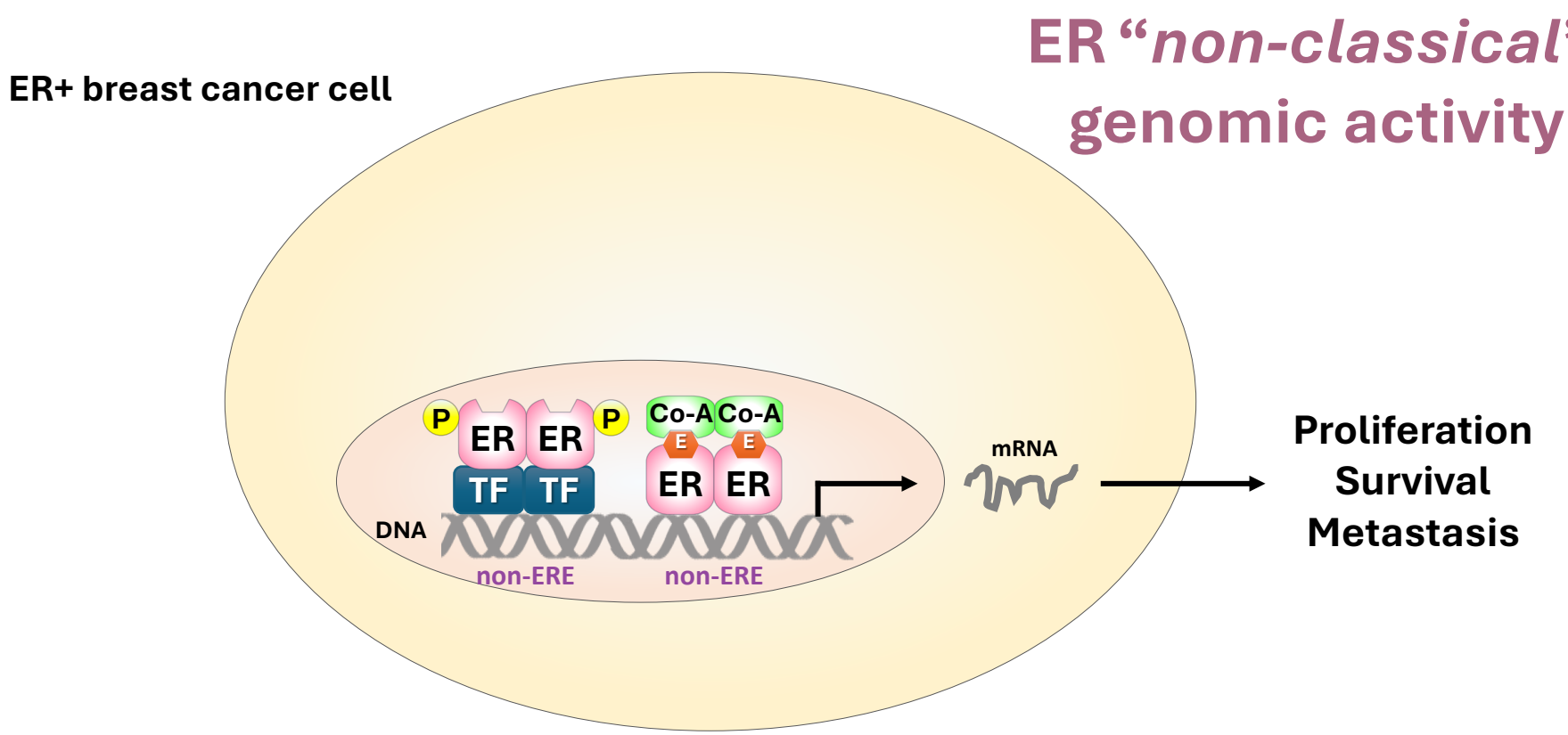
NIH SEER. Cancer stat facts: female breast cancer.; Howlader N, et al. J Natl Cancer Inst. 2014;106. Brufsky AM. Cancer Treat Rev. 2017;59:22-32.

The Estrogen Receptor signaling pathways in breast cancer



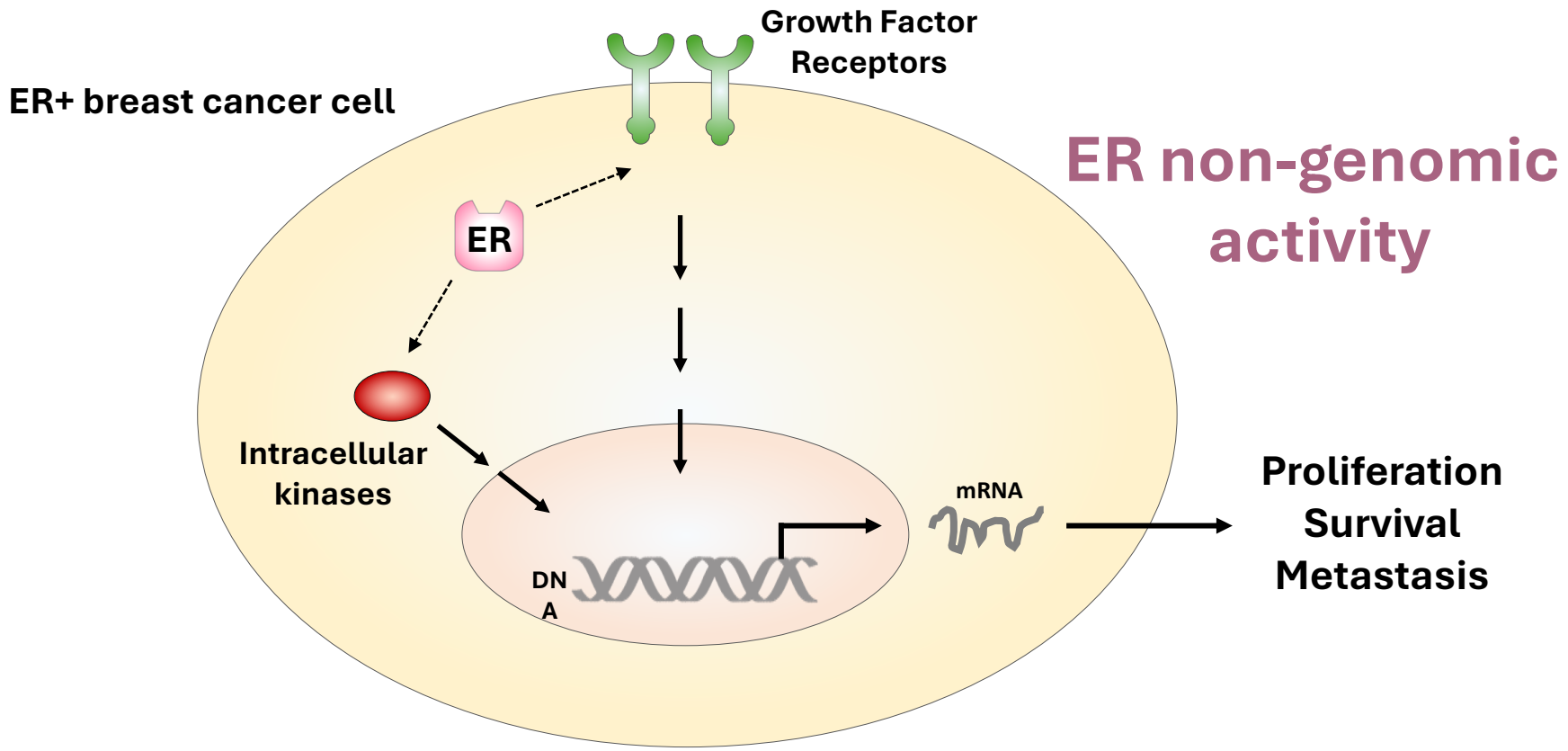
CoA, co-activator; ERE, Estrogen Responsive Elements; mRNA, messenger RNA

The Estrogen Receptor signaling pathways in breast cancer

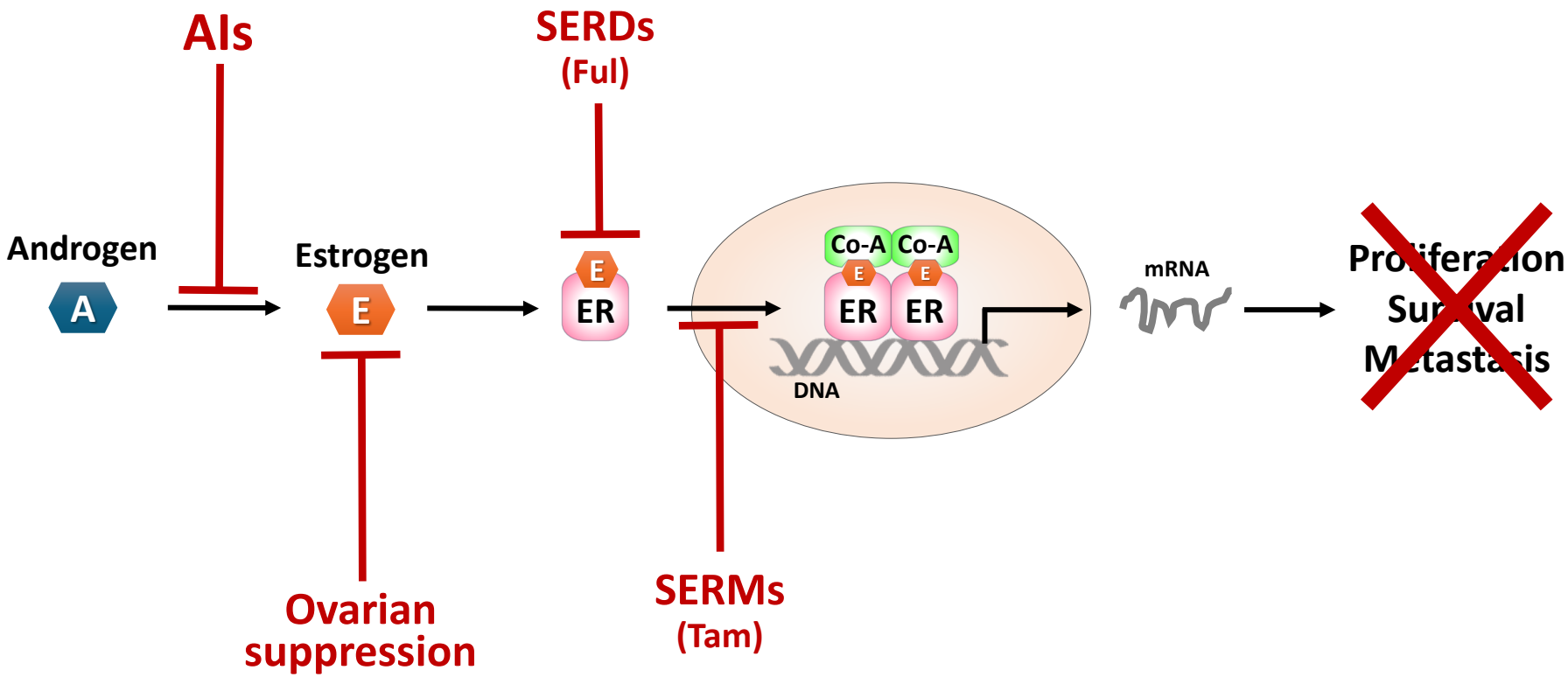


CoA, Co-Activator; TF, transcription factor

The Estrogen Receptor signaling pathways in breast cancer

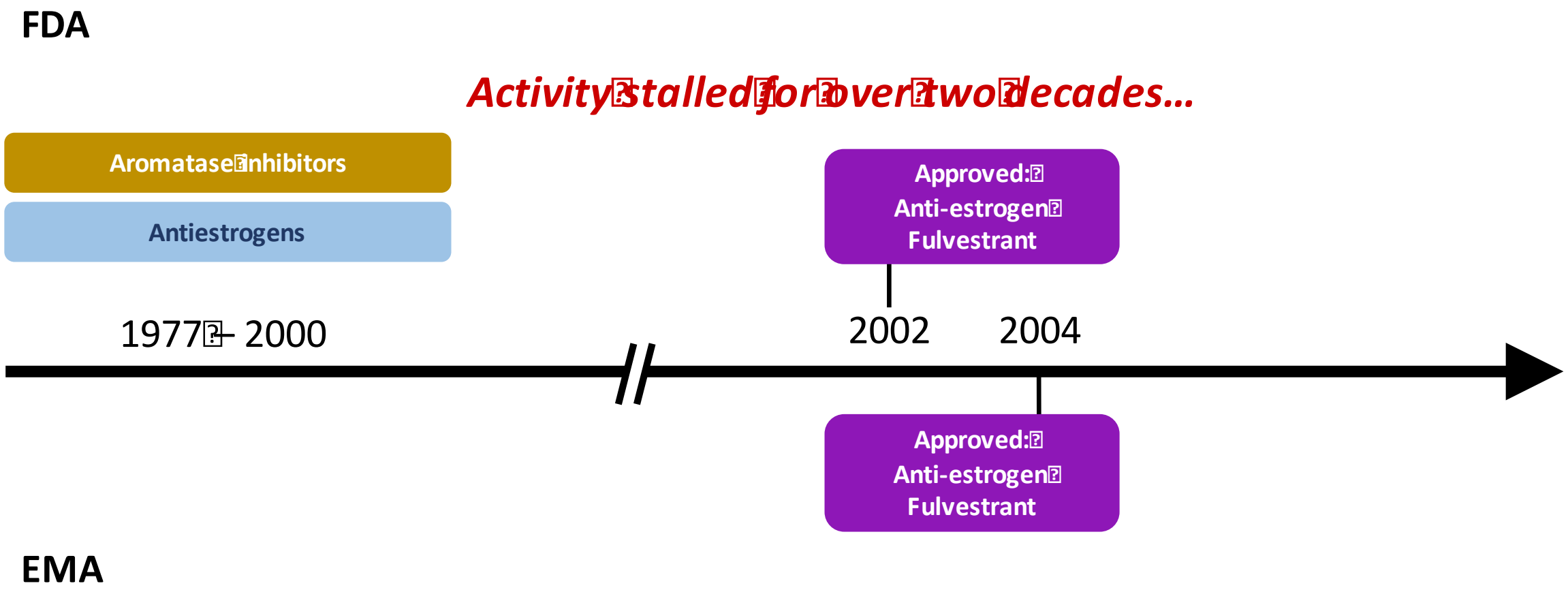


Endocrine therapy is the backbone of treatment in early and advanced hormone receptor-positive breast cancers

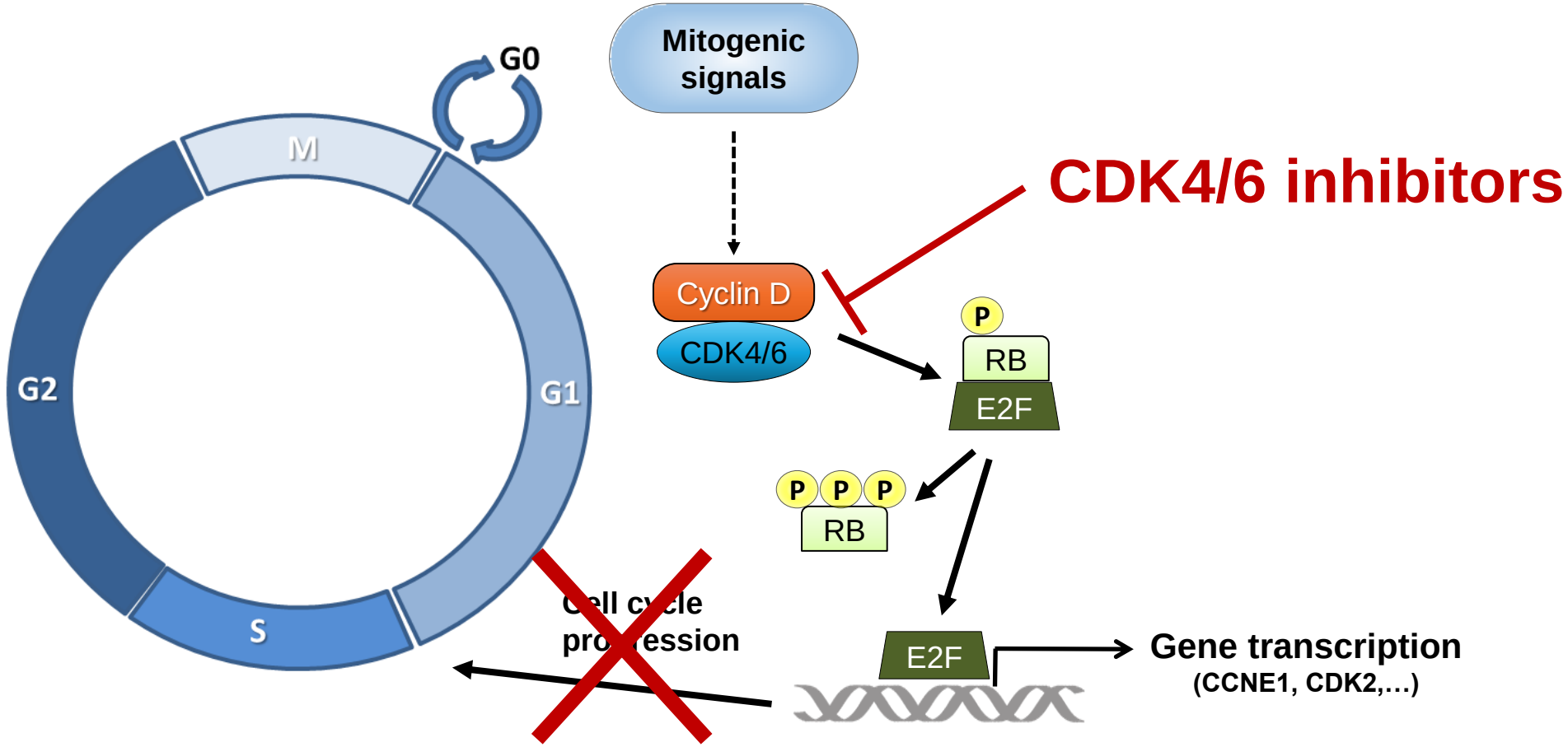


AIs, aromatase inhibitors; SERDs, selective estrogen down-regulators; SERMs, selective estrogen modulators

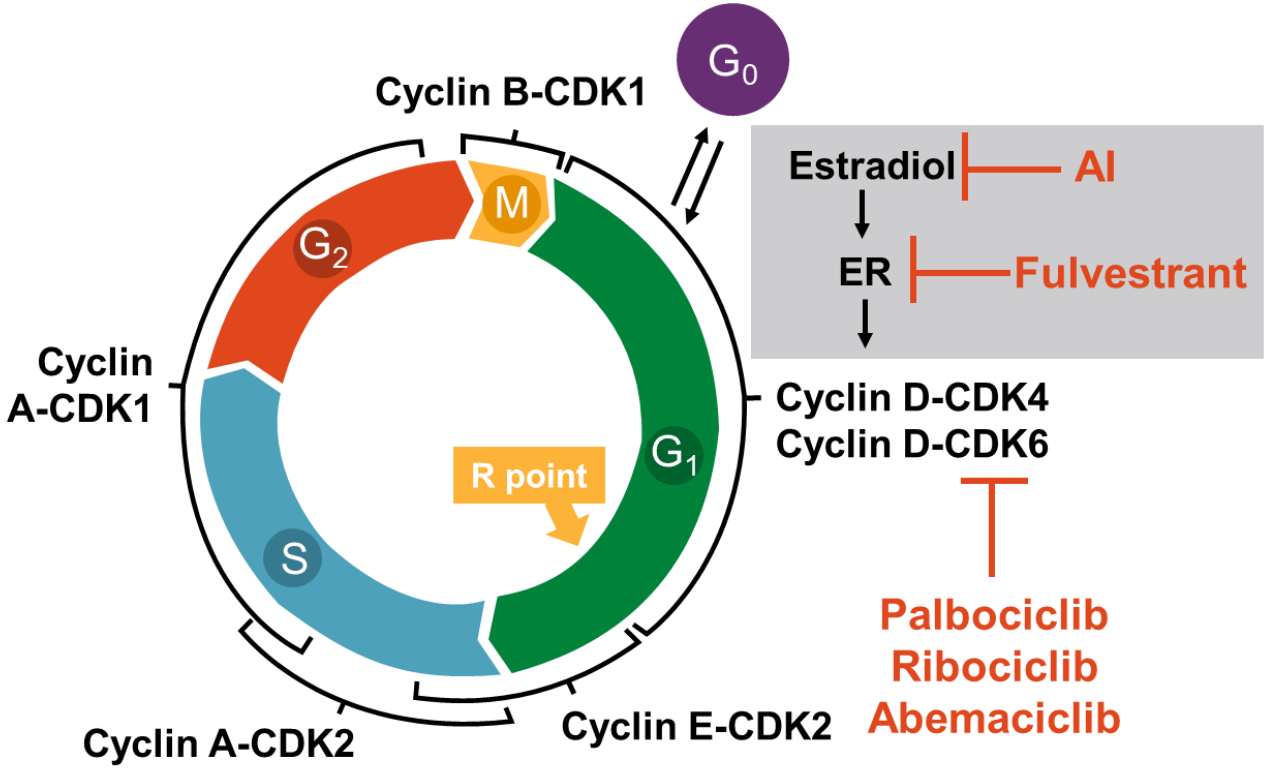
Drugs approved for the management of HR+/HER2– MBC



CDK4/6 inhibitors



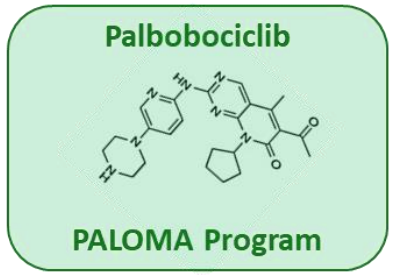
Targeting CDK4/6 in HR+/HER2- BC: Rationale

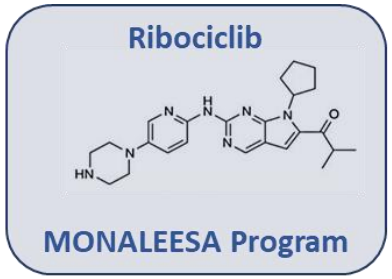


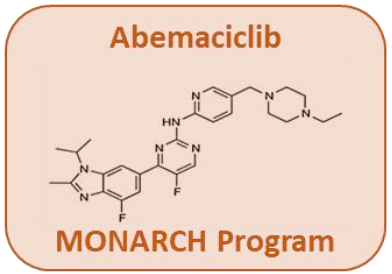
1. Mitogenic pathways, including estrogen signaling, stimulate cyclin D production
2. Binding of cyclin D activates CDK4/6, an important player in driving cell cycle progression in ER+ BC
3. Selectively inhibiting CDK4/6 causes cell cycle arrest in G1 phase, resulting in reduced cell viability and tumor shrinking

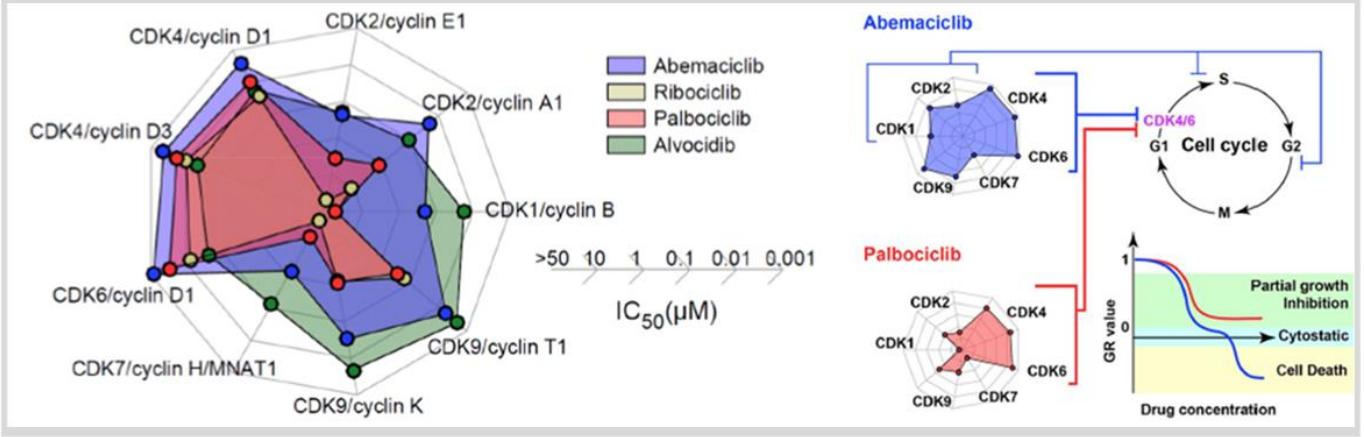
Because cyclin D–CDK4/6 activation occurs downstream of estrogen signaling,
ET + CDK4/6 inhibitor combination therapy has synergistic antitumor activity against HR+ BC

CDK4/6 Inhibitors: Comparison of Key Characteristics



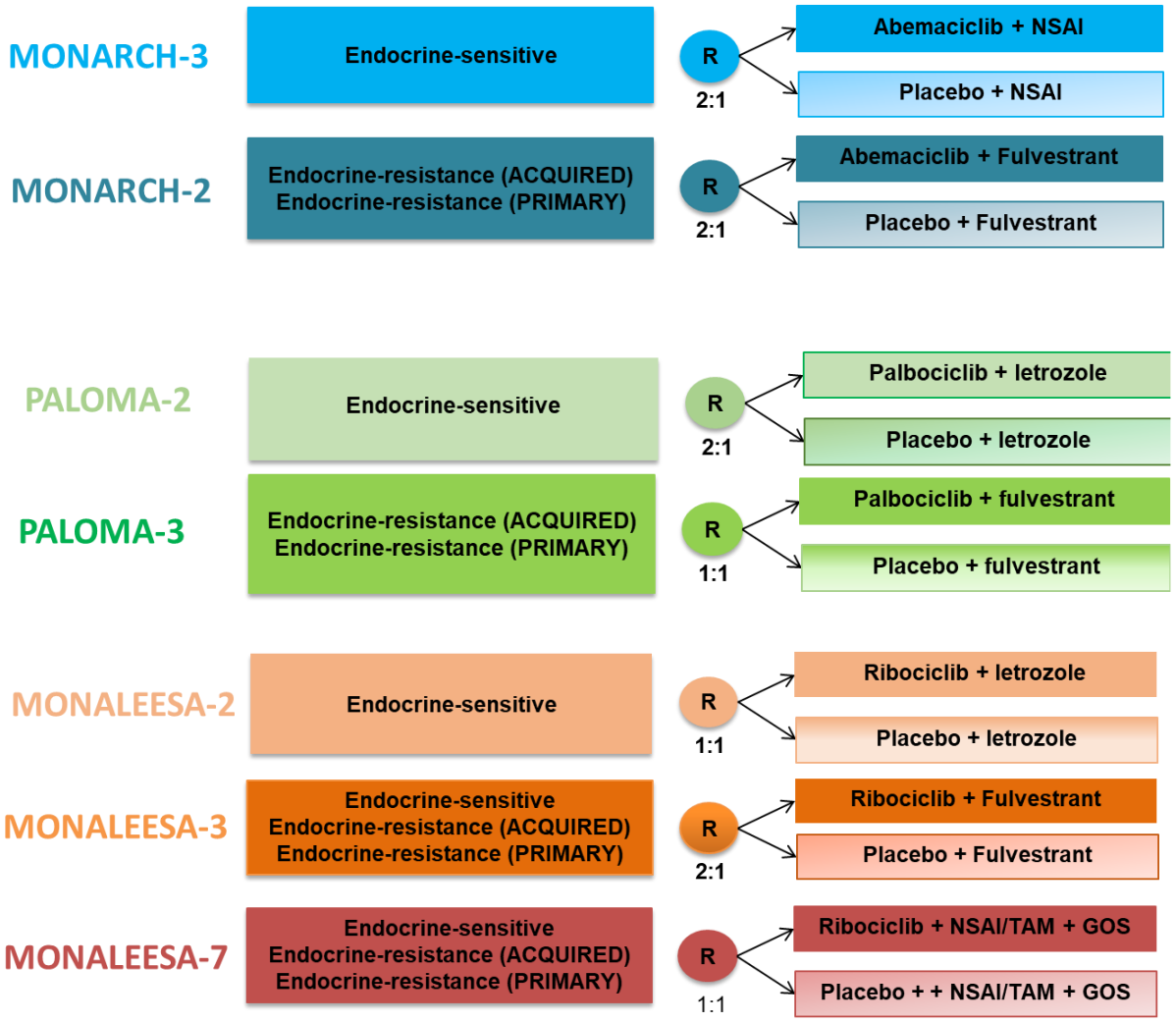




Characteristic	Palbociclib[1-3]	Ribociclib[4,5]	Abemaciclib[5,6]
Dose, mg	125 QD	600 QD	150 BID (+ET), 200 BID (mono)
Schedule	3 wks on/1 wk off	3 wks on/1 wk off	Continuous
Half-life, hr	27	32.6	17-38
Targets			

1. DeMichele A, et al. Clin Cancer Res. 2015;21:995-1001. 2. Hamilton E, et al. Cancer Treatment Rev. 2016;45:129-138. 3. Costa R, et al. Ann Oncol. 2017;28:44-56.
4. Infante JR, et al. Clin Cancer Res. 2016;22:5696-5705. 5. Barroso-Sousa R, et al. Breast Care. 2016;11:167-173. 6. Dickler MN, et al. ASCO 2016. Abstract 510.

The transformative effect of CDK4/6i



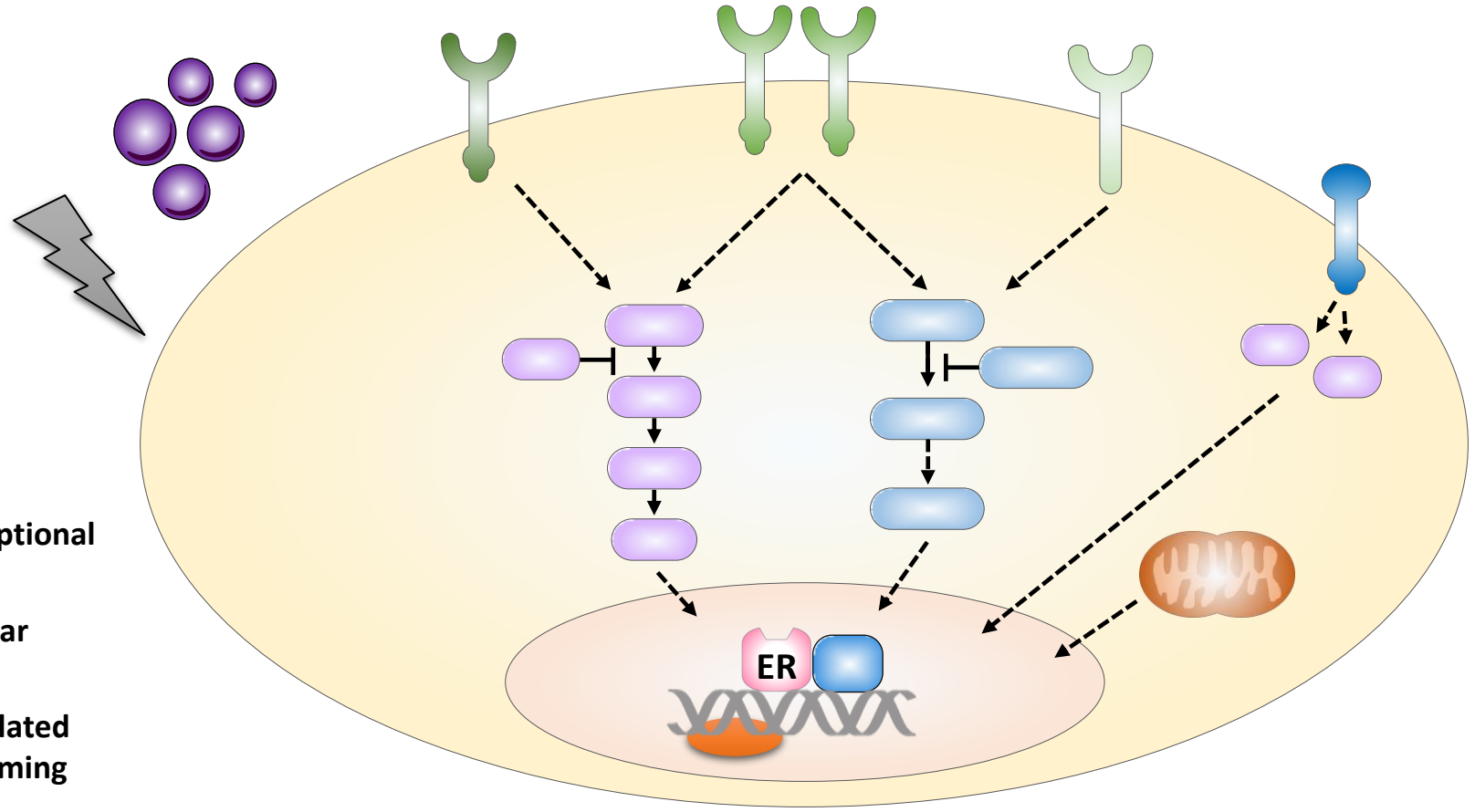
Finn et al. *Lancet Oncol.* 2015; Finn et al. NEJM 2016; Hortobagyi et al, NEJM 2016; Goetz et al. JCO 2017; Slamon et al, JCO 2018; Tripathy et al. Lancet Oncol. 2018, Goetz MP et al, ESMO 2022

Mechanisms of endocrine resistance

Resistance

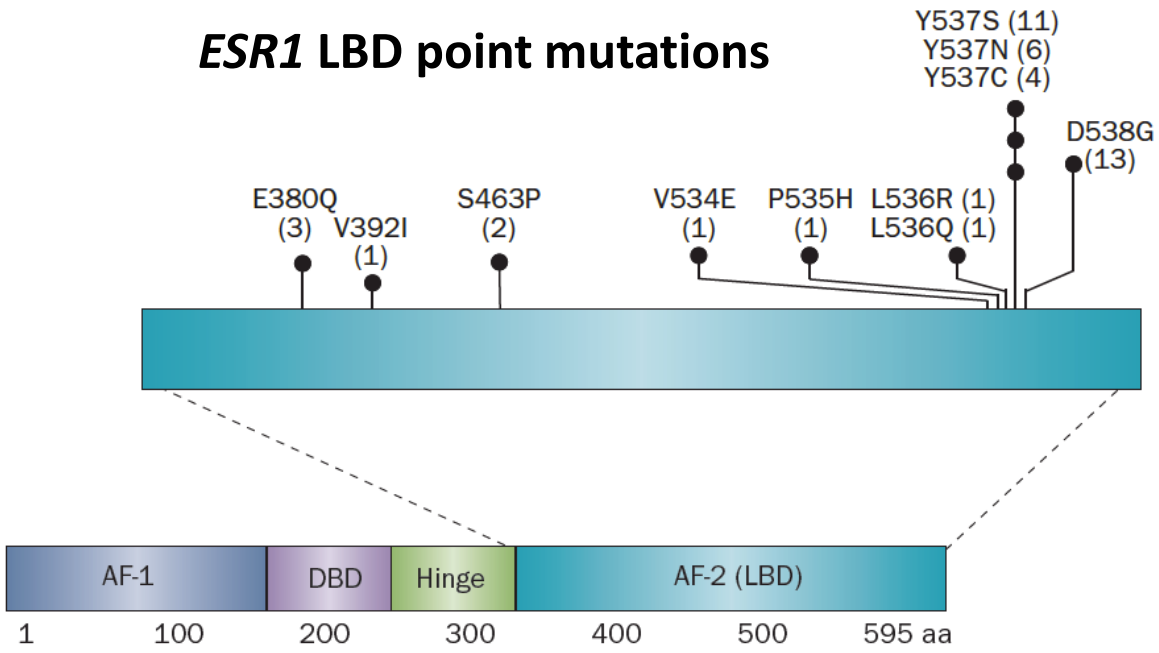
Primary **(intrinsic)**

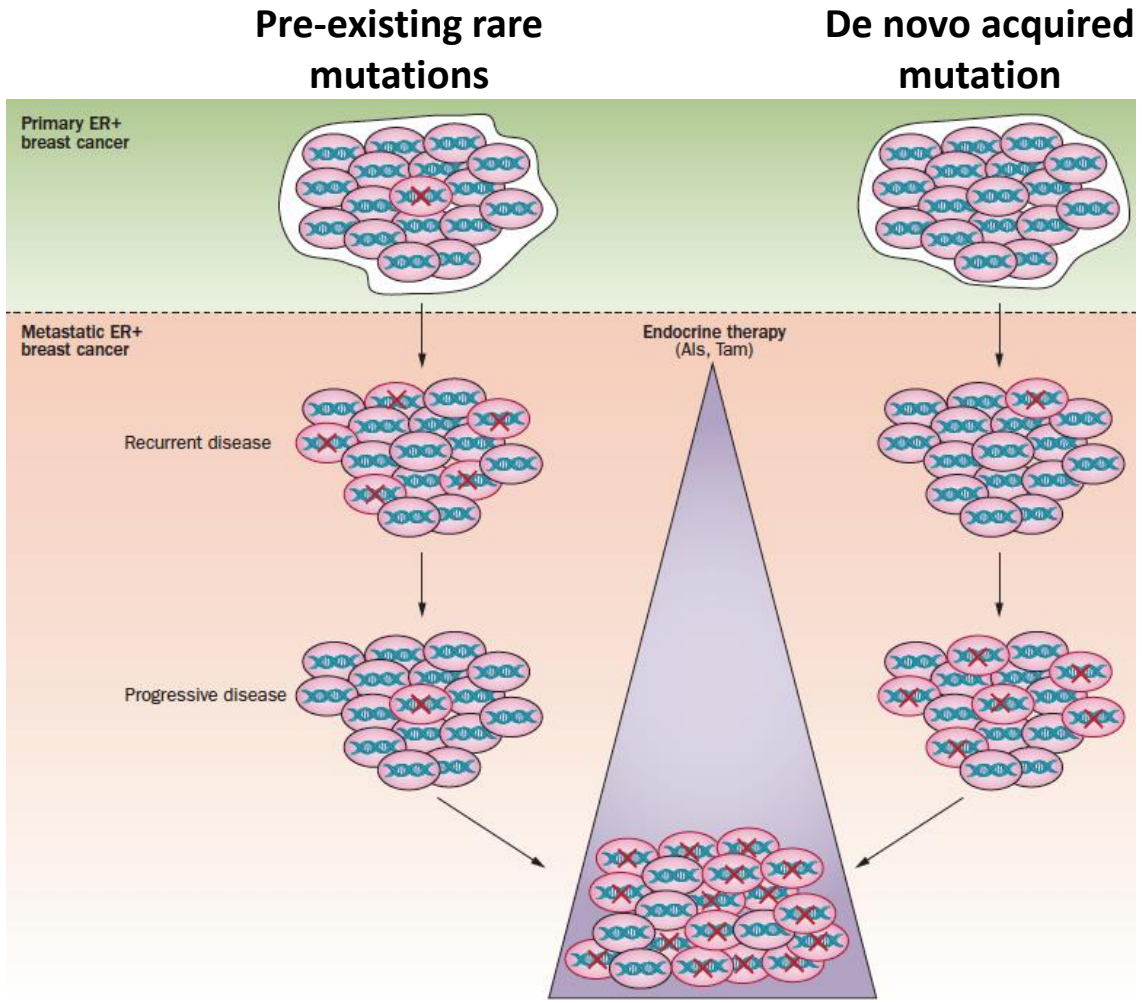
Secondary ***(acquired)***



- **ER itself: levels, mutations, post-transcriptional or translational regulation**
- **Crosstalk between the ER and GFR/cellular kinase pathways**
- **ER co-regulators and ER/co-regulators related cistromes and transcriptional reprogramming**
- **Stress related pathway and tumor microenvironment**

ESR1 mutations: a mechanism for acquired endocrine resistance in breast cancer

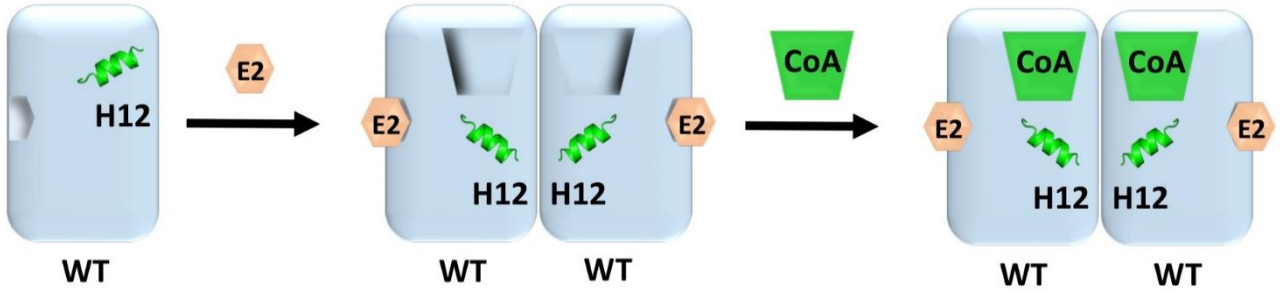




Jeselsohn et al., Nature Review Clin Onc 2015

ESR1 mutations: direct consequences of the conformational changes in the ER LBD

Wild-type ERα

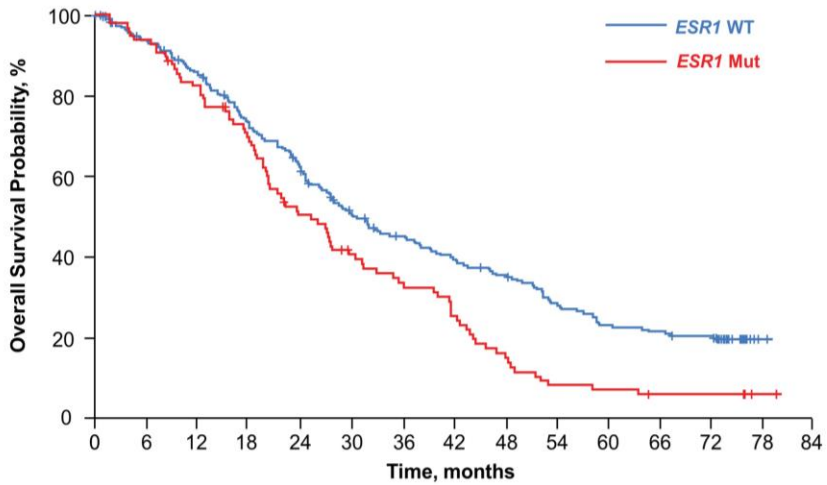


Jeselsohn et al., Curr Oncol Rep 2017

ESR1 Mutations in Advanced Luminal BC: Prognostic and Predictive Biomarker?

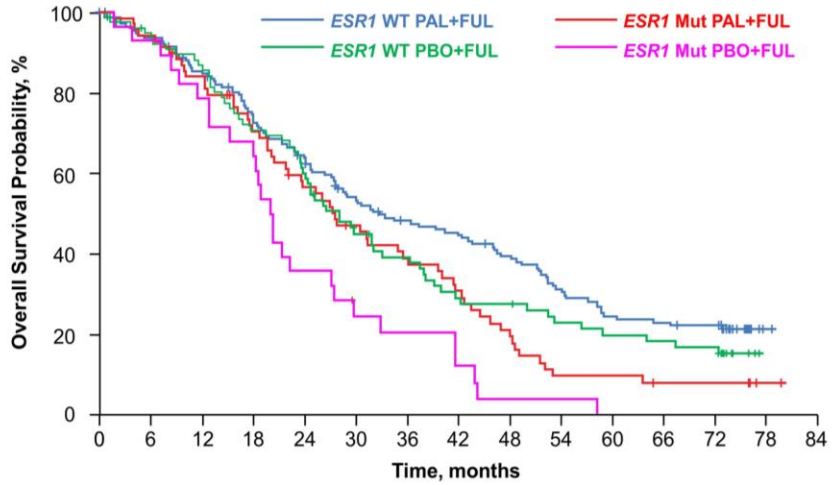
- *ESR1* mutations do not hold predictive value as biomarkers for CDK4/6 inhibitor therapy

Regardless of Treatment



	No *ESR1* Mutation	*ESR1* Mutation
Patients, n (%)	234 (70.7)	97 (29.3)
Median OS (95% CI), mo	30.7 (26.6–37.5)	25.4 (20.2–30.6)
Hazard ratio (95% CI)	1.58 (1.22–2.06)	

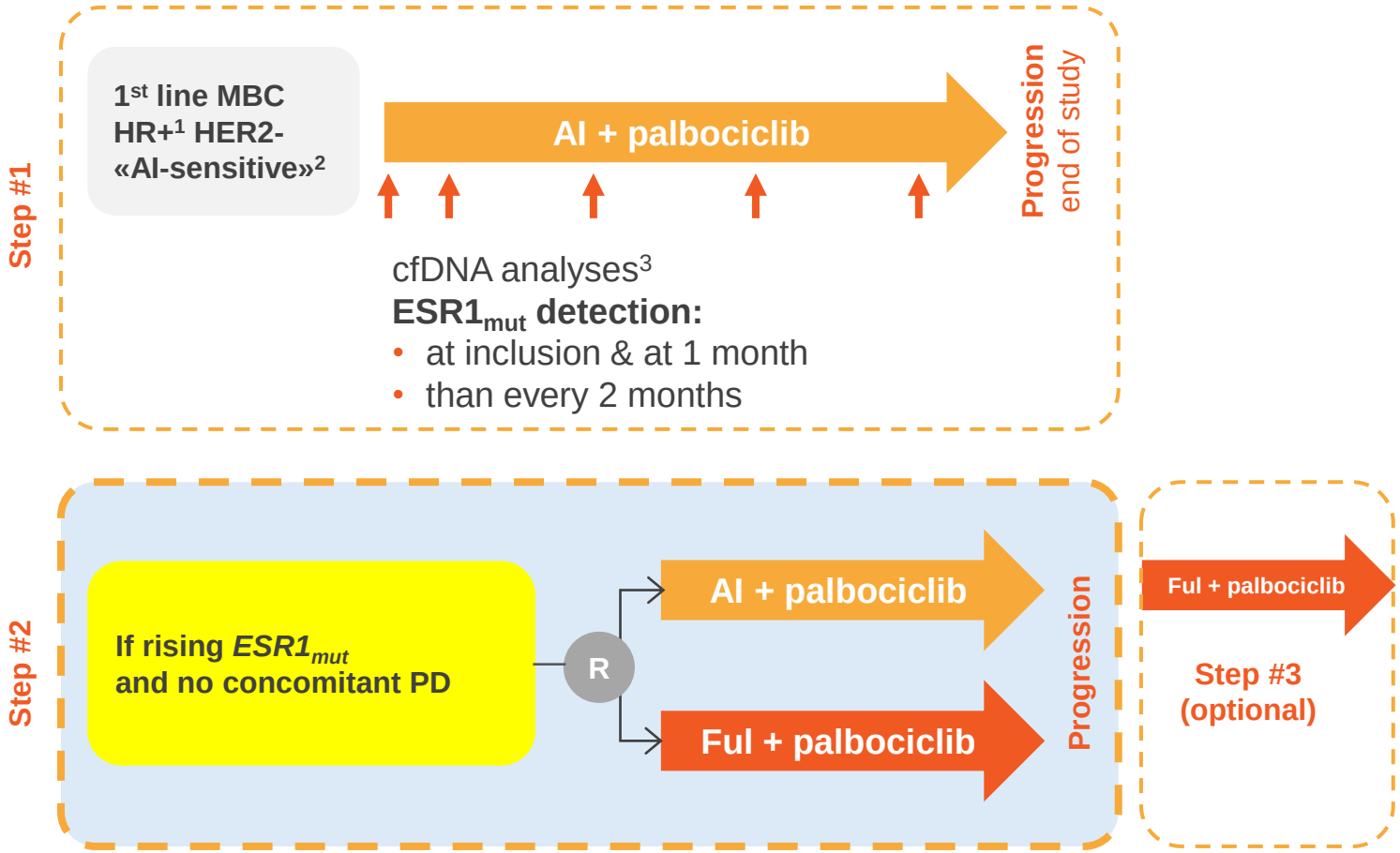
By Treatment



	Palbociclib + Fulvestrant	Placebo + Fulvestrant	Palbociclib + Fulvestrant	Placebo + Fulvestrant
	No *ESR1* Mutation		*ESR1* Mutation	
Patients, n (%)	154 (69.1)	80 (74.1)	69 (30.9)	28 (25.9)
Median OS (95% CI), mo	32.8 (27.4–46.1)	28.0 (23.6–36.3)	27.7 (20.4–36.1)	20.2 (15.3–27.1)
Hazard ratio (95% CI)	0.81 (0.59–1.11)		0.59 (0.37–0.94)	

Cristofanilli M et al., ASCO 2021

PADA-1: Palbociclib & ctDNA for *ESR1*mut detection



Co-primary endpoints: PFS (RECIST) from randomization (step#2) & safety (all steps)

Phase 3

From 04/2017 to 01/2019

1,017 patients included in step #1

PADA-1 is still ongoing

- As of April 1st, 2020
- Median FU = 21.2 months (0–34.5)
- **N = 452 pts** still in step #1
- **N = 565 pts** went out of step #1
  - **N = 135 randomizations (24%)** in step #2
    Rising *ESR1*$_{mut}$ detected before progression: Target N = 200
  - **N = 354 progressions**
    Both *ESR1*$_{wild\text{-}type}$ & *ESR1*$_{mut}$ concomitant to RECIST progression
  - **N = 76 pts out of study**
    Patient/investigator decision

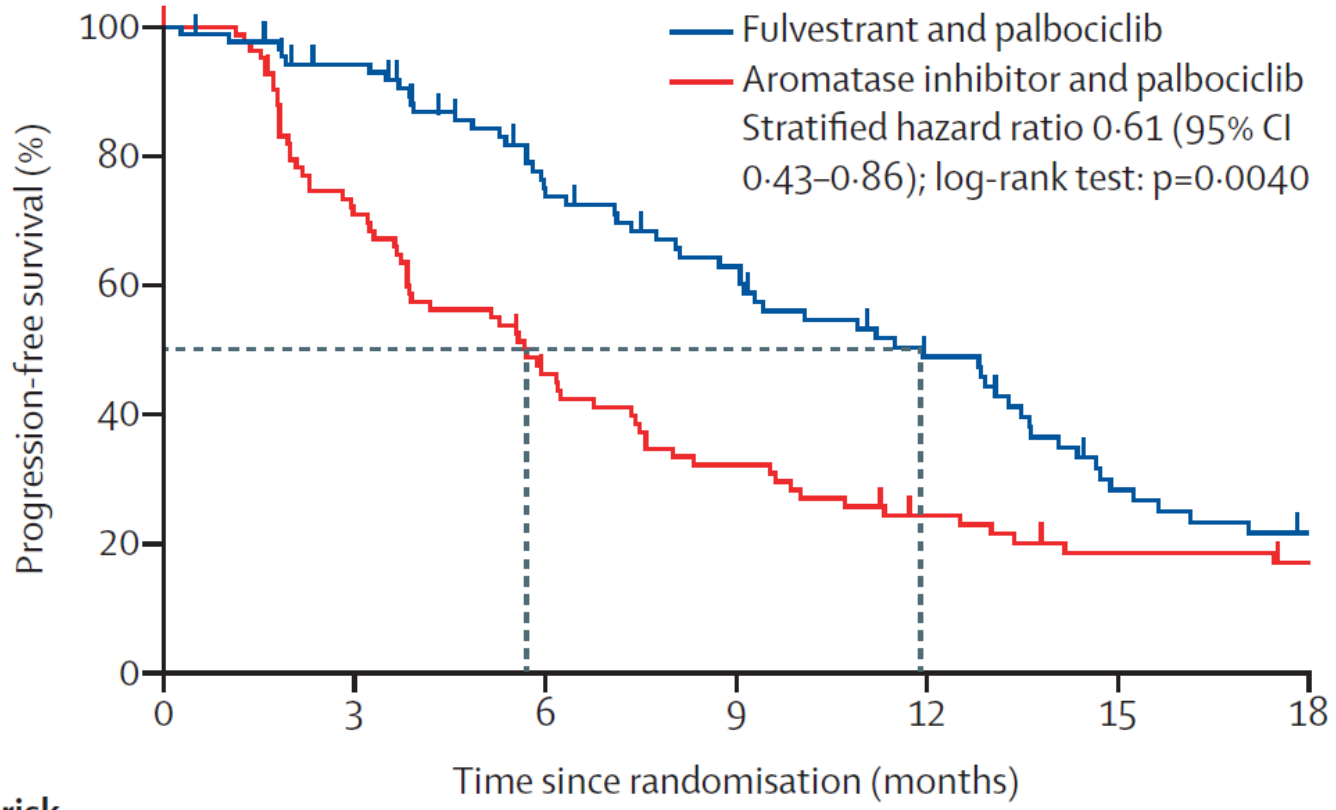
[1] ER and/or PS ≥10%
[2] «AI-sensitive»: no prior AI or DFI >12 months from adjuvant AI completion
[3] Centralized ddPCR assay cfcDNA from 4 mL of plasma (Jeannot, Oncogene 2020)

AI: Aromatase inhibitor; PD: Progression disease

Mod. da Bidard FC, et al. J Clin Oncol 38, no. 15_suppl (May 20, 2020) 1010–1010.

PADA-1: Progression-Free Survival

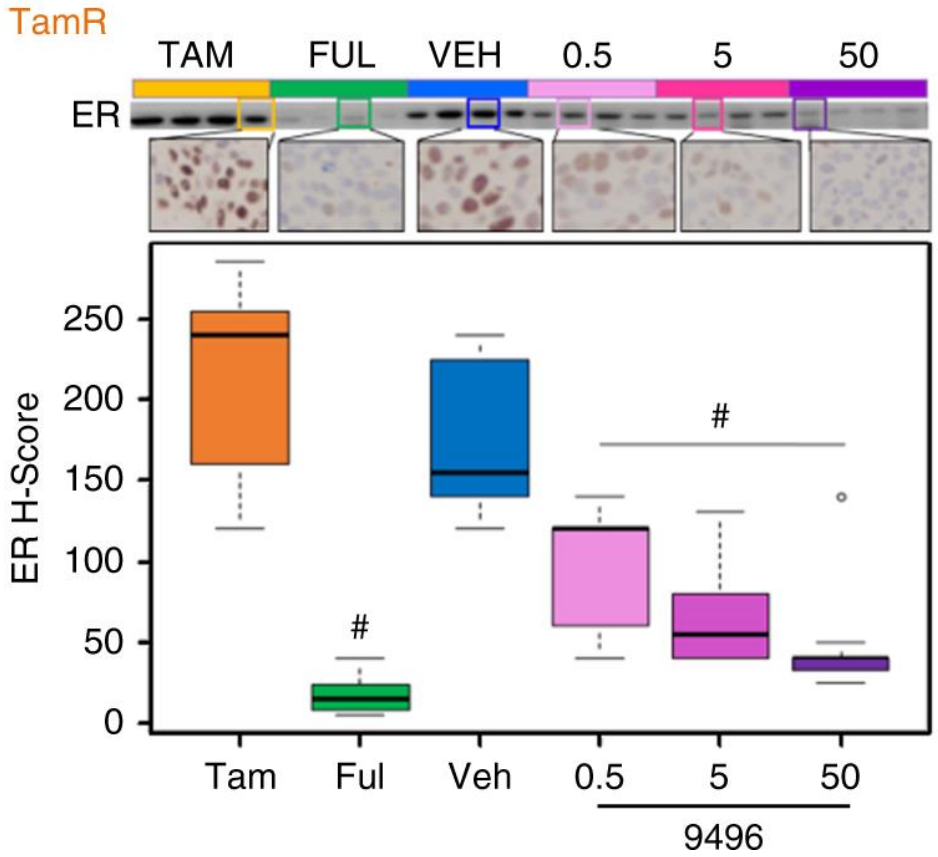
- **Early therapeutic targeting of *ESR1* mutation in blood results in significant clinical benefit**



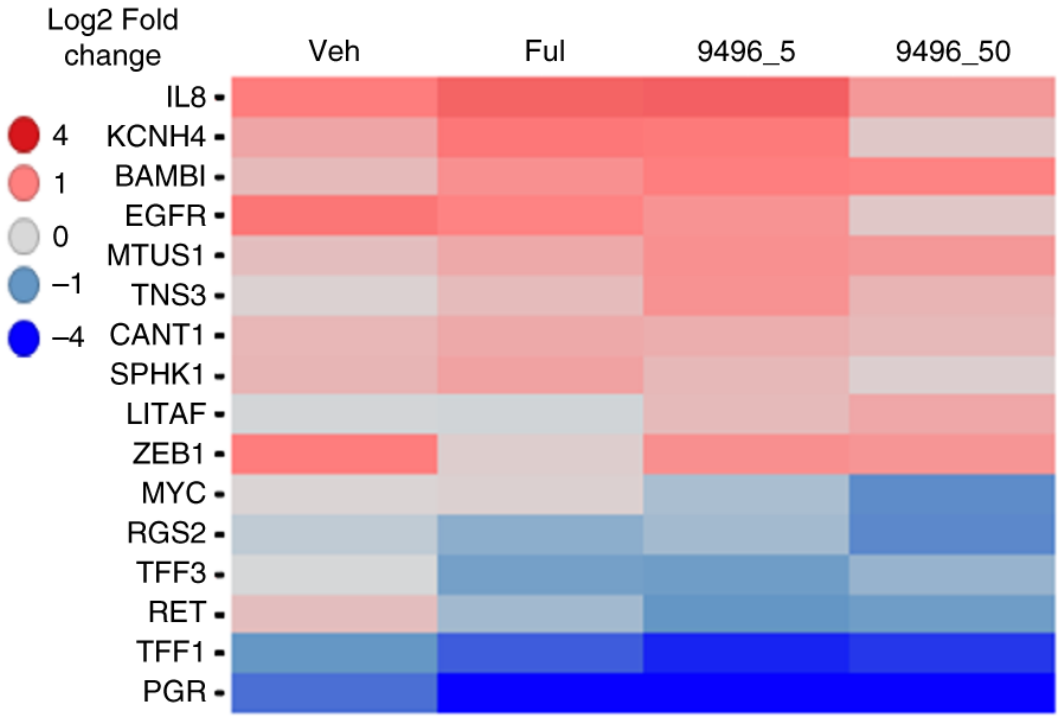
Number at risk (number censored)							
Fulvestrant and palbociclib	88 (0)	78 (5)	57 (11)	46 (13)	32 (17)	17 (19)	12 (20)
Aromatase inhibitor and palbociclib	84 (1)	58 (2)	36 (4)	25 (4)	17 (6)	12 (7)	10 (8)

Oral SERD (AZD9496) is comparable to fulvestrant in reducing ER level and activity in endocrine-resistant tumours in vivo

ER protein levels

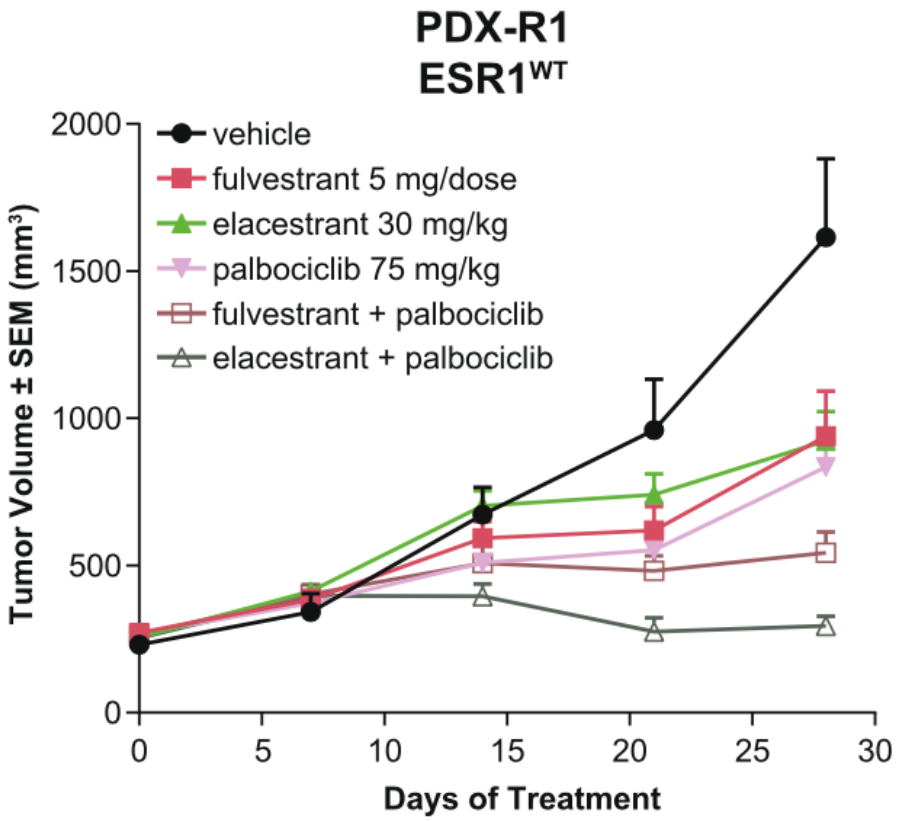


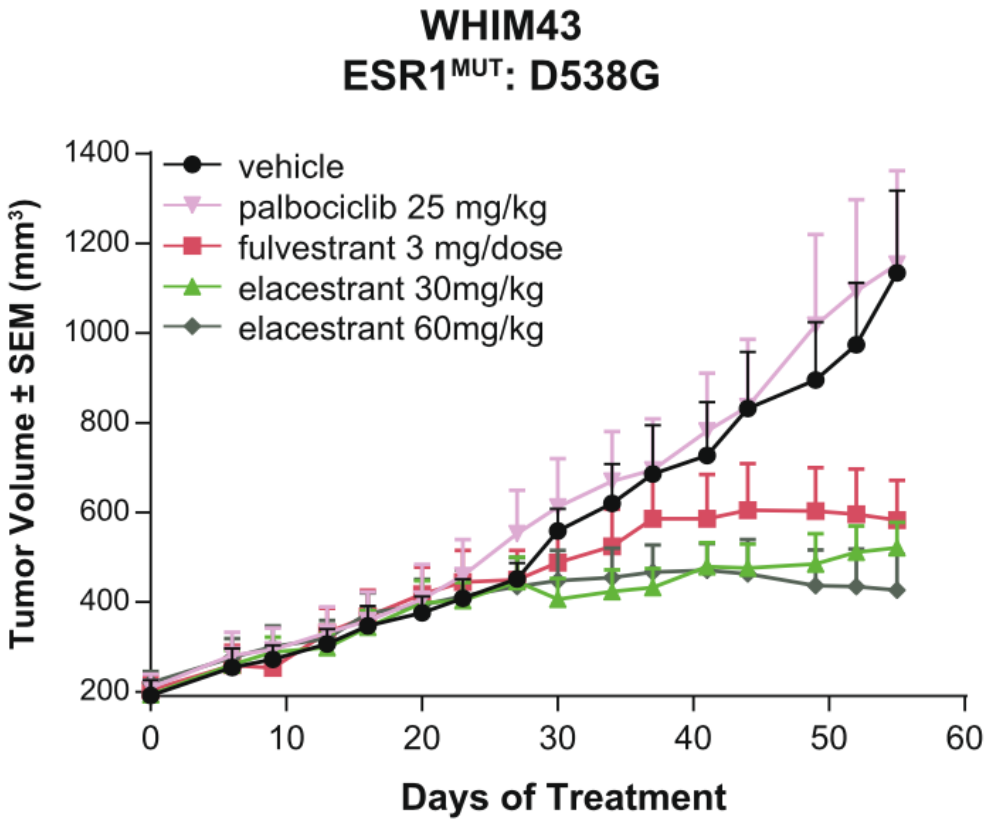
ER trascriptonal activity



Nardone A, et al. BJC 2018

Elacestrant is effective in delaying tumor growth of ESR1 WT and ESR1 mutant breast cancer PDXs

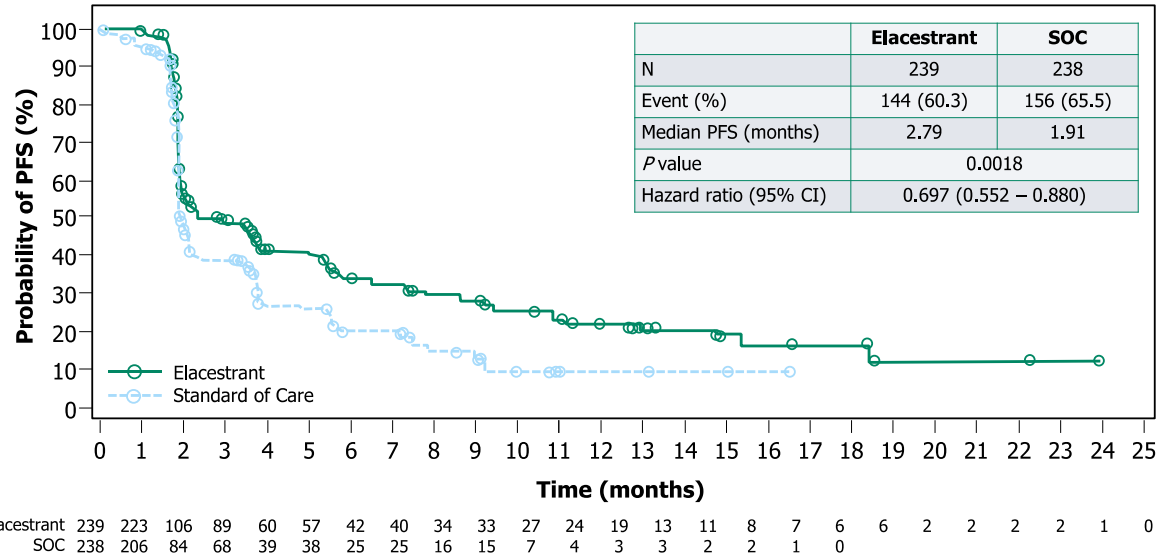




Patel H.K. et al., BCR 2019

EMERALD: Progression Free Survival

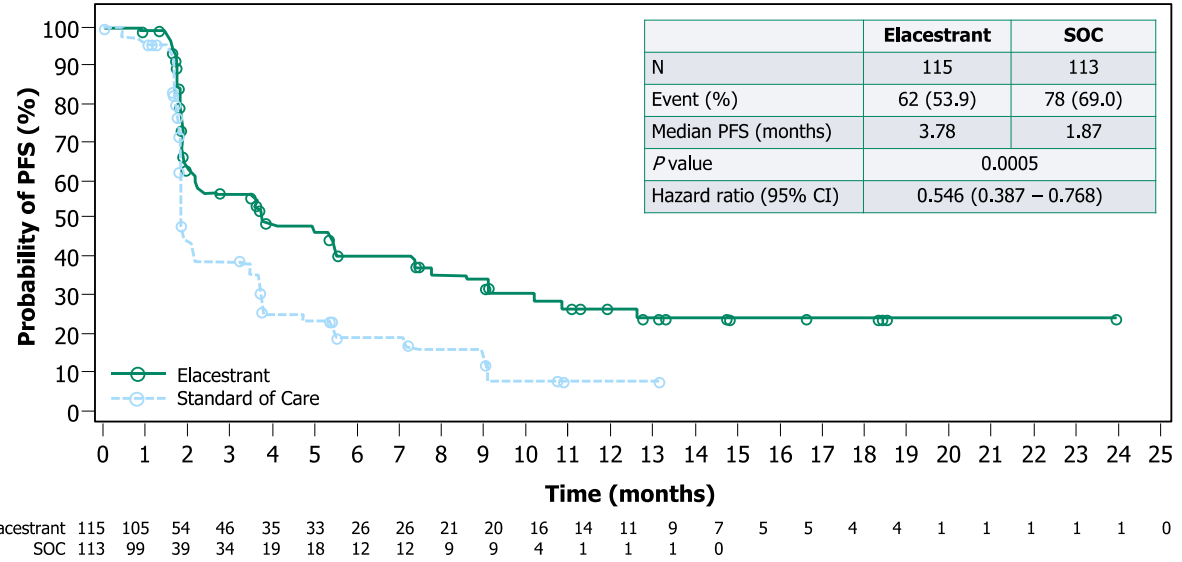
All Patients (ITT)



	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P value	0.0018	
Hazard ratio (95% CI)	0.697 (0.552 – 0.880)	

Elacestrant is associated with a 30% reduction in risk of progression or death in all patients with ER+/HER2- mBC

Patients with *mESR1*



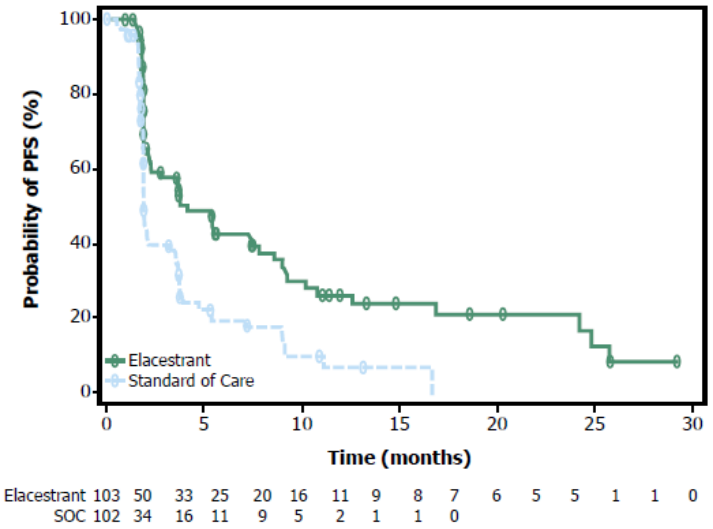
	Elacestrant	SOC
N	115	113
Event (%)	62 (53.9)	78 (69.0)
Median PFS (months)	3.78	1.87
P value	0.0005	
Hazard ratio (95% CI)	0.546 (0.387 – 0.768)	

Elacestrant is associated with a 45% reduction in risk of progression or death in patients harboring mESR1

Bardia A, et al., SABCS 2021

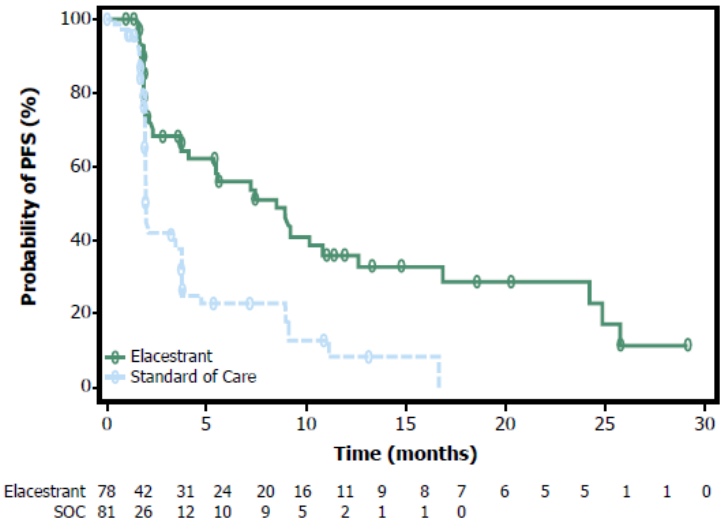
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



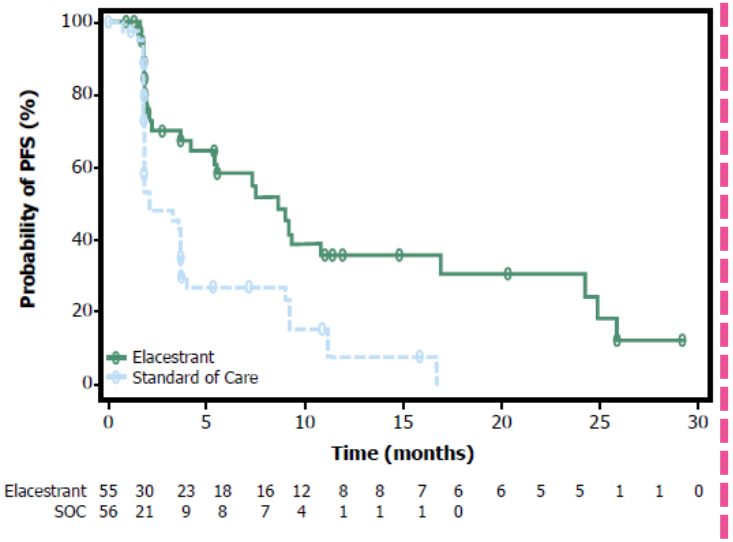
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

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



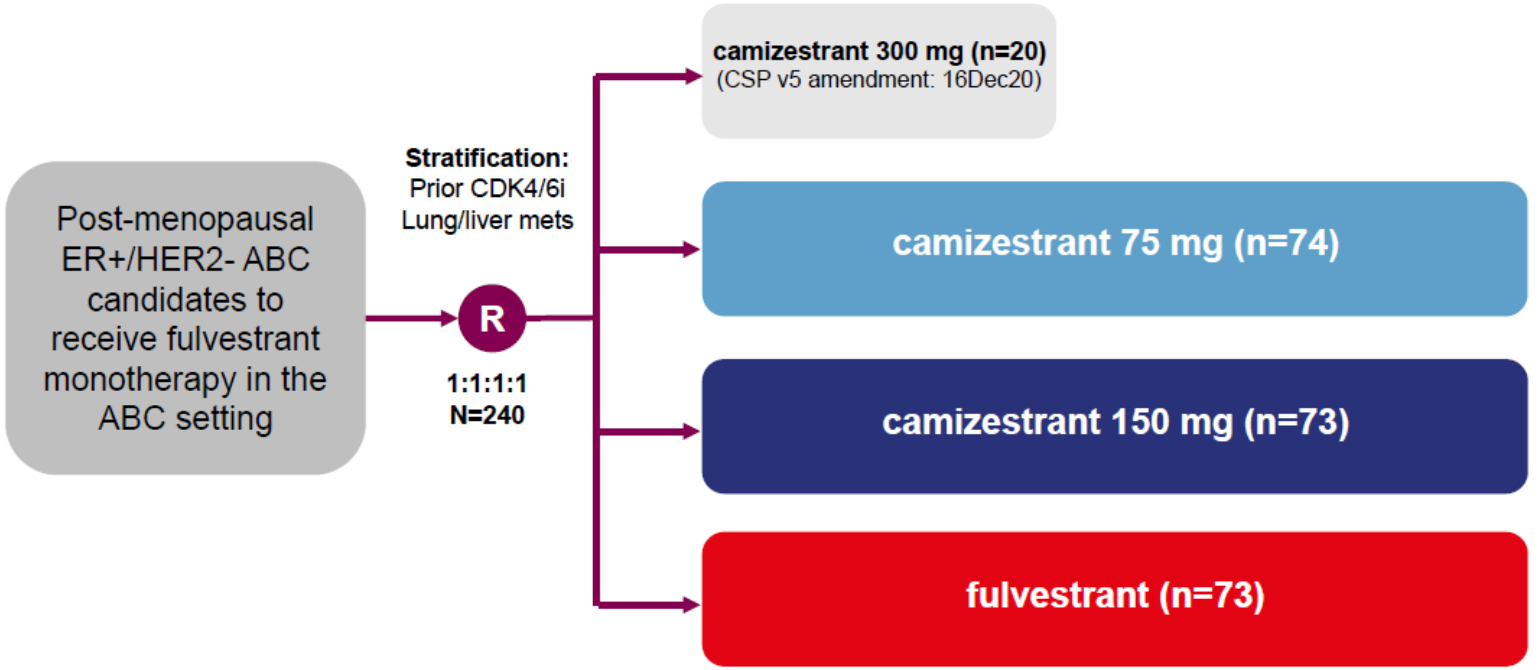
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Bardia A, et al., SABCS 2022

SERENA-2: A randomized, multi-dose phase 2 trial of Camizestrant vs fulvestrant in post-menopausal women with advanced ER+/HER2- breast cancer

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



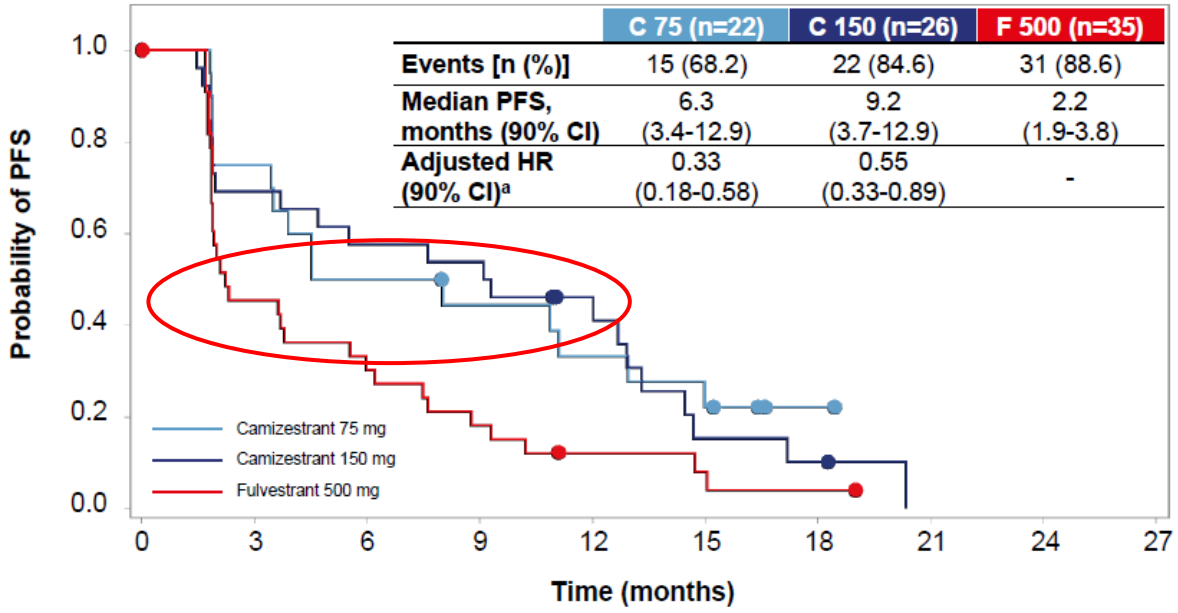
- **Primary endpoint:** PFS (investigator assessment*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

Olivera M, et al. SABCS 2022

Olivera M, et al. SABCS 2022

PFS in patients by detectable *ESR1m*

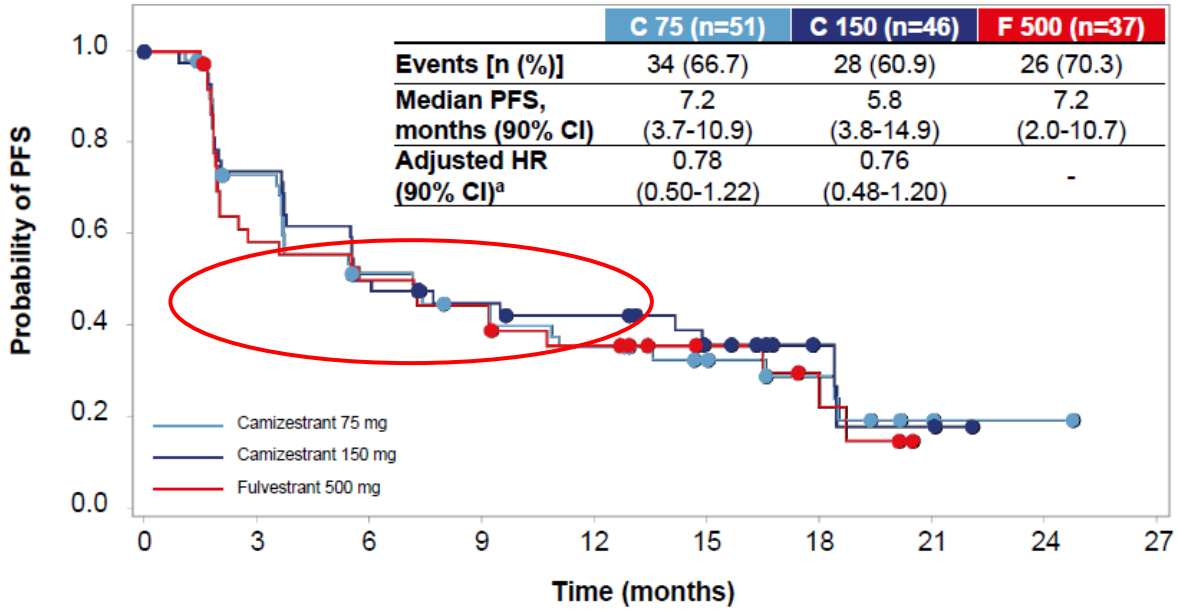
*ESR1*m detectable at baseline



	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

Oral SERD Trial Landscape in Pretreated mBC

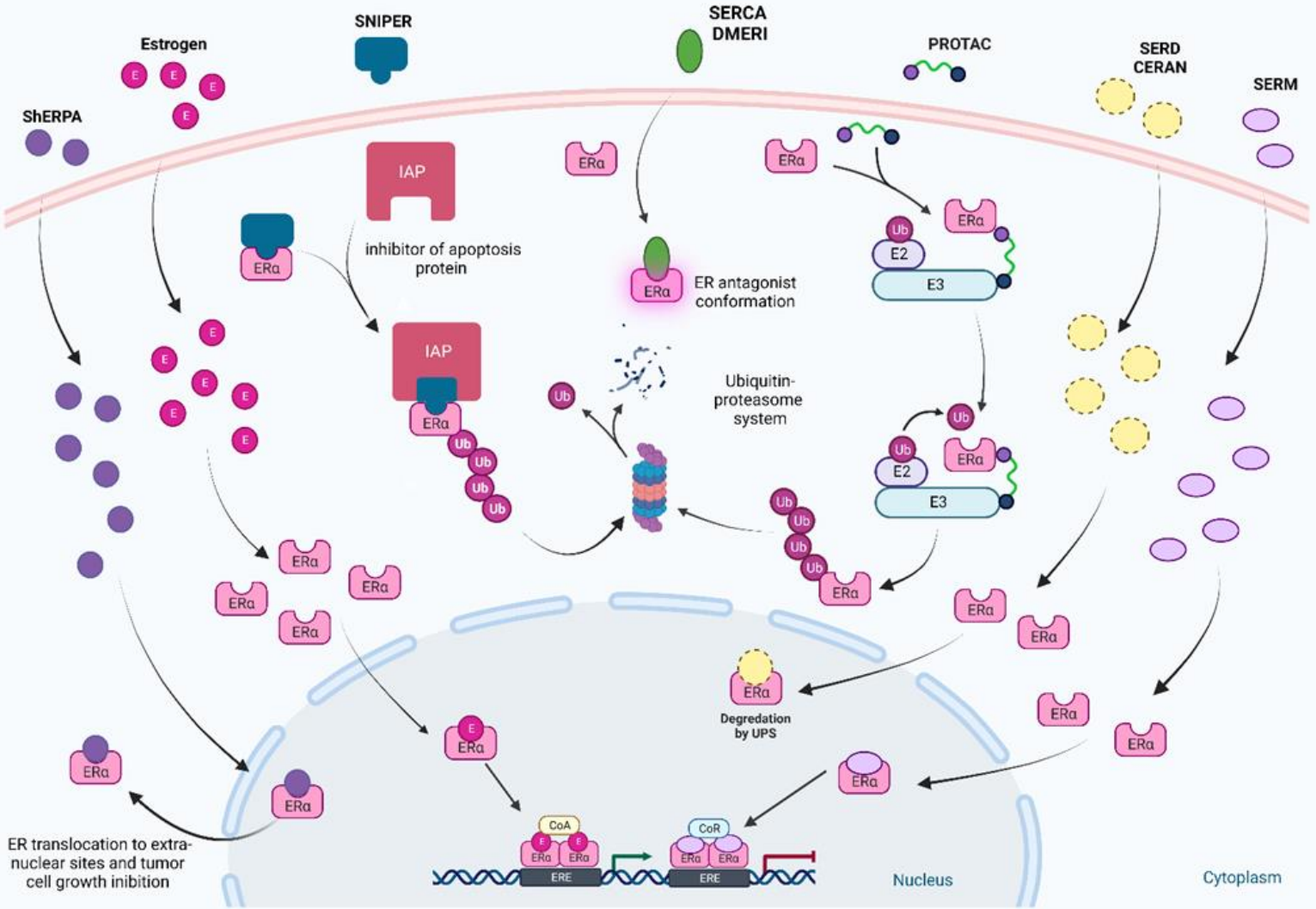
	EMERALD[1]	SERENA-2[2]	EMBER-3[3]	AMEERA-3[4-6]	acelERA[6-9]
Treatment	**Elacestrant**	**Camizestrant**	**Imlunestrant** +/- abemaciclib	**Amcenestrant**	**Giredestrant**
Control Arm	fulvestrant / AIs	fulvestrant	fulvestrant / exemestane	fulvestrant / AIs / tamoxifen	fulvestrant / AIs
Phase (n)	Phase 3 (478)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	**Required (100%)**	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed Prior Fulvestrant	**YES**	NO	NO	YES	YES
Allowed Prior Chemotherapy in mBC	**YES**	YES	NO	YES	YES
Data readout	**Positive (Registrational)**	Positive (Non-Registrational)	Ongoing	Negative	Negative

1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 2. SERENA2. ClinicalTrials.gov identifier: NCT04214288. Accessed November 18, 2022, https://clinicaltrials.gov/ct2/show/NCT04214288; 3. EMBER-3. Clinical Trials.gov identifier: NCT04975308. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04975308; 4. AMEERA3. ClinicalTrials.gov identifier: NCT04059484. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04059484; 5. Tolaney SM, et al. *Ann Oncol.* 2022; 33(7):S88-S121 (Abstr 212MO); 6. Evaluate Vantage. https://www.evaluate.com/vantage/articles/news/trial-results/roche-has-rare-breast-cancer-setback. Accessed July 20, 2022; 7. acelERA ClinicalTrials.gov identifier: NCT04576455. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04576455; 8. Martin M, et al. *J Clin Oncol.* 2021;39(15):abstr TPS1100; 9. Martin Jimenez M, et al. *Ann Oncol.* 2022;33(7):S88-S121 (abstr 211MO).

Ongoing trials with next generation SERDs in combination with other therapies

	Giredestrant (Roche)	Camizestrant (AstraZeneca)		Imlunestrant (Eli Lilly)
1L	**persevERA Breast Cancer** *1L*- Ph3 giredestrant + palbo vs. letrozole + palbo	**SERENA-4** *1L* - Ph3 camizestrant + palbo vs. anastrozole + palbo	**SERENA-6** *1L stable switch* - Ph3 camizestrant + CDK4/6i vs. AI + CDK4/6i in *ESR1*m	**EMBER** 2L+ - Ph1 LY3484356 ± abemaciclib/alpelisib/ everolimus/ Herceptin19
2L	**MORPHEUS** *2-3L* - Ph1b/2 Giredest. ± targeted therapies	**SERENA-1** *1-2L+* Ph1 camizestrant ± palbo/ eveverolimus/abema/ capivasertib		
3L				

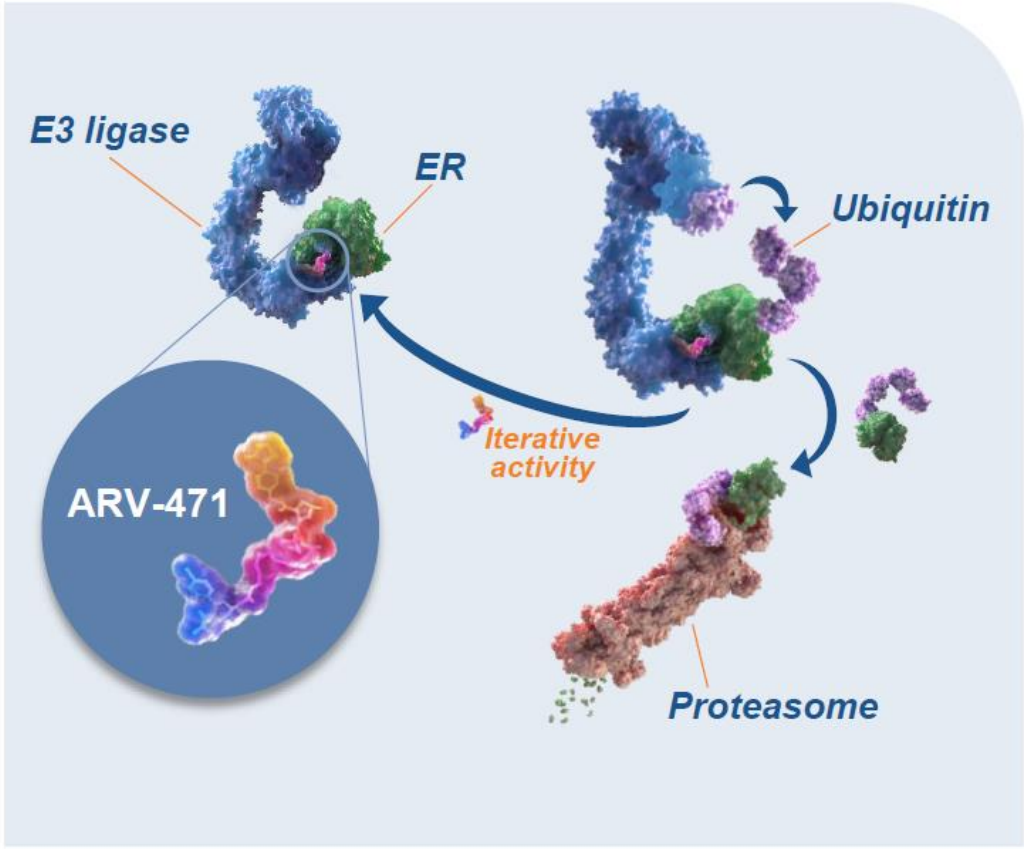
Novel Endocrine Therapies



Pagliuca M, et al. CROH 2022

ARV-471, a PROTAC® ER degrader in advanced ER+/HER2- breast cancer: phase 2 expansion (VERITAC) of a phase 1/2 study

- ARV-471 is a selective, orally administered PROTAC® protein degrader that targets wild-type and mutant ER[1]
- ARV-471 directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation
  - In contrast, SERDs indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER[2]
- Limitations of the SERD fulvestrant include its intramuscular route of administration[3] and only 40%–50% ER protein degradation at its optimal dose[4,5]
- ARV-471 treatment yielded substantially greater ER degradation and tumor growth inhibition than fulvestrant in breast cancer xenograft models[1]



Hurvitz S, et al. SABCS 2022

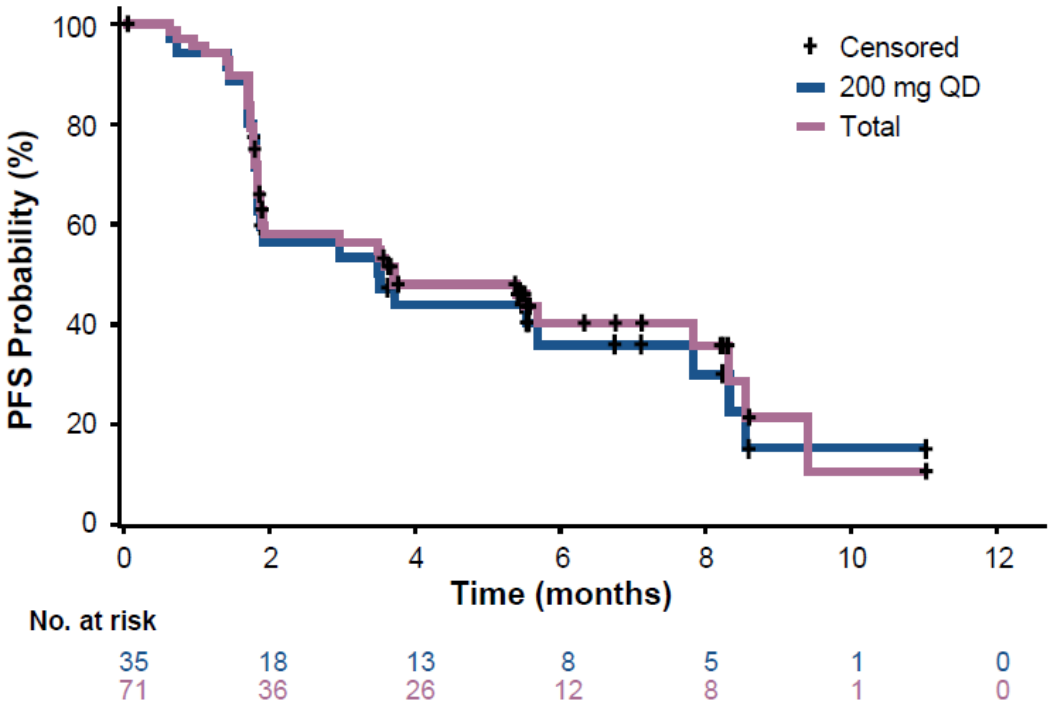
Primary Endpoint: Clinical Benefit Rate[a] (VERITAC)

	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)
Patients with mutant *ESR1*	(n=19)	(n=22)	(n=41)
CBR, % (95% CI)	47.4 (24.4–71.1)	54.5 (32.2–75.6)	51.2 (35.1–67.1)

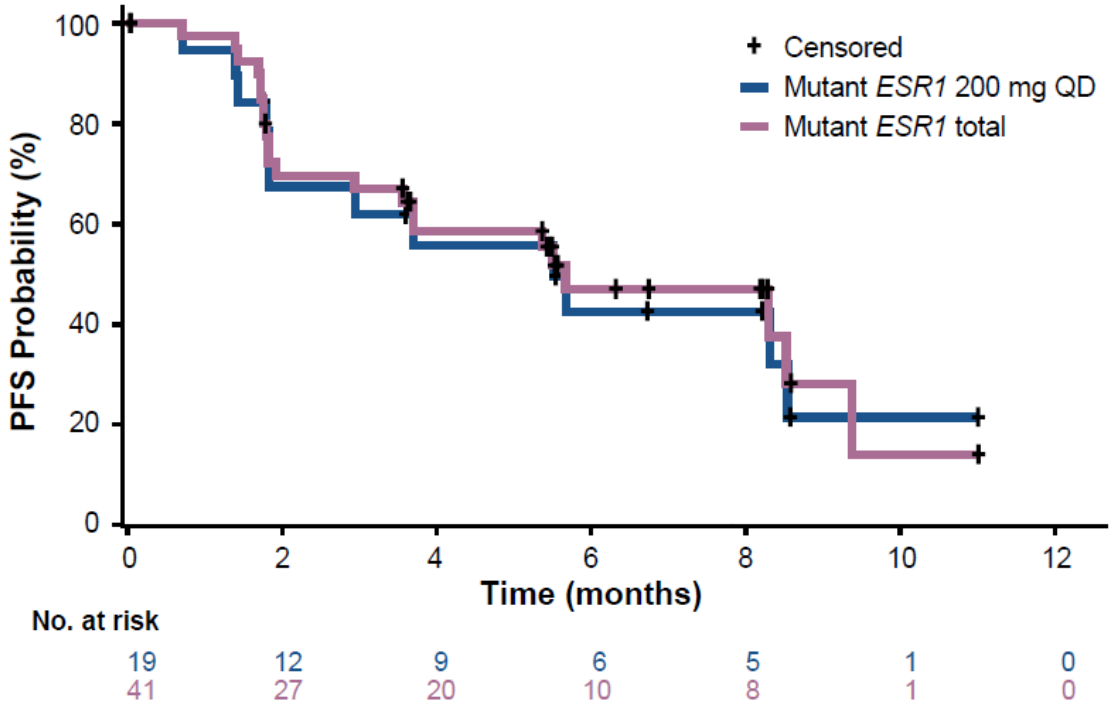
Hurvitz S, et al. SABCS 2022

Progression-Free Survival[a] (VERITAC)

	All Patients	
	200 mg QD (n=35)	Total (N=71)
Events, n (%)	24 (68.6)	41 (57.7)
mPFS, mo (95% CI)	3.5 (1.8–7.8)	3.7 (1.9–8.3)



	Mutant *ESR1*	
	200 mg QD (n=19)	Total (n=41)
Events, n (%)	12 (63.2)	22 (53.7)
mPFS, mo (95% CI)	5.5 (1.8–8.5)	5.7 (3.6–9.4)



Hurvitz S, et al. SABCS 2022

Phase 3 VERITAC-2 Trial

Key eligibility criteria

- Women or men aged ≥18 years
- Confirmed ER+/HER2- advanced breast cancer
- 1 line of CDK4/6 inhibitor therapy in combination with endocrine therapy
- ≤1 additional endocrine therapy
- Most recent endocrine treatment given for ≥6 months prior to disease progression
- No prior fulvestrant
- No prior chemotherapy for locally advanced/metastatic disease
- Radiological progression during or after the last line of therapy

RANDOMIZE 1:1

Treatment (N=560)

ARV-471
200 mg orally once daily

Fulvestrant
500 mg intramuscularly days 1 and 15 of cycle 1 and day 1 of subsequent cycles

Stratification factors

- *ESR1* mutant (yes vs no)
- Visceral disease (yes vs no)

Primary endpoint

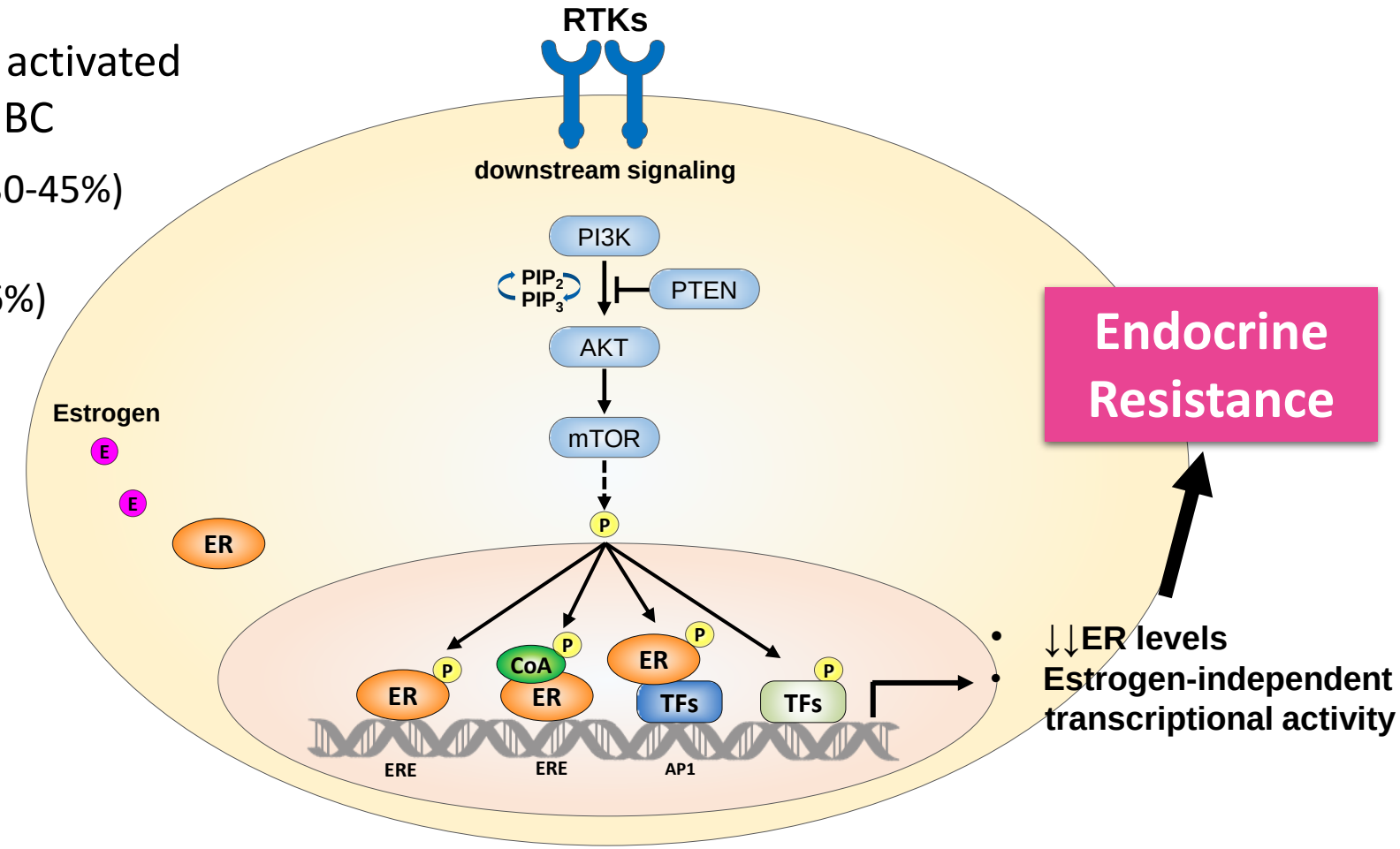
- PFS by BICR in
  - ITT population
  - *ESR1* mutant population

Secondary endpoints include:

- OS, ORR, DOR, and CBR[a]
- AEs
- QoL measurements

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

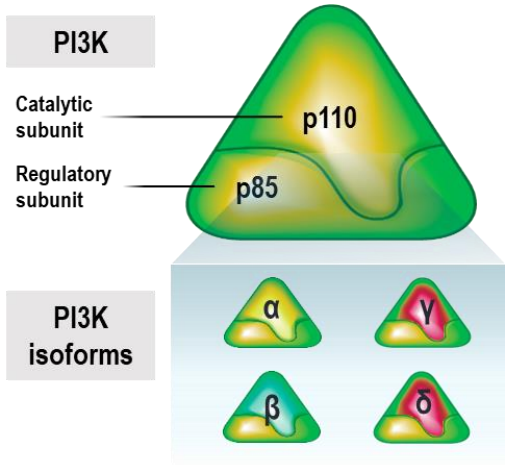
- The PI3K/AKT/PTEN pathway is activated in approximately 50% of ER+ MBC
  - *PIK3CA* activating mutation (30-45%)
  - PTEN loss/inactivation (3-8%)
  - AKT1 activating mutation (2-6%)

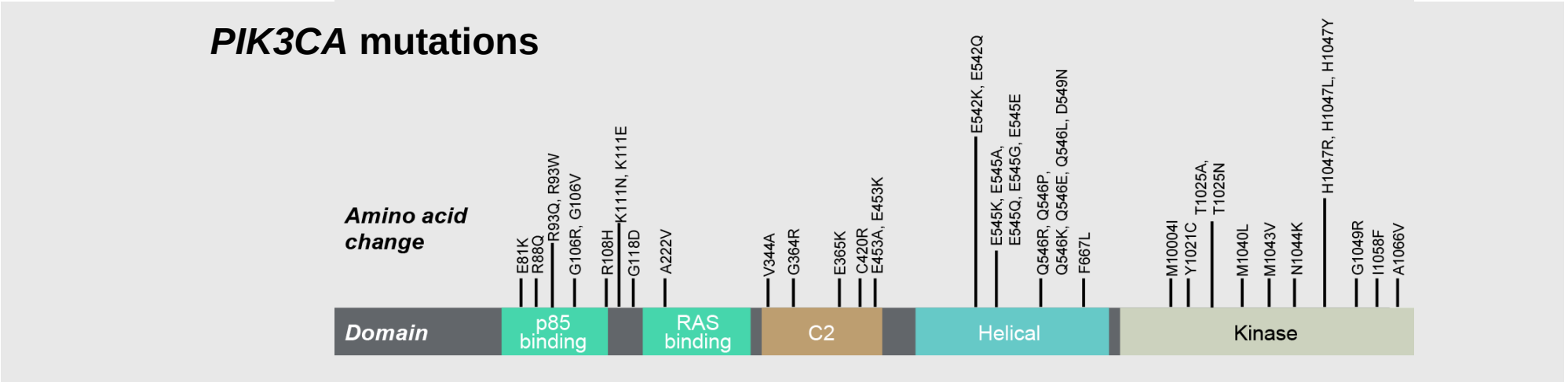


CoA, co-activator, E, Estrogen; ERE, estrogen-response-elements, TF, transcription factor

PIK3CA genetic alterations lead to PI3K pathway activation

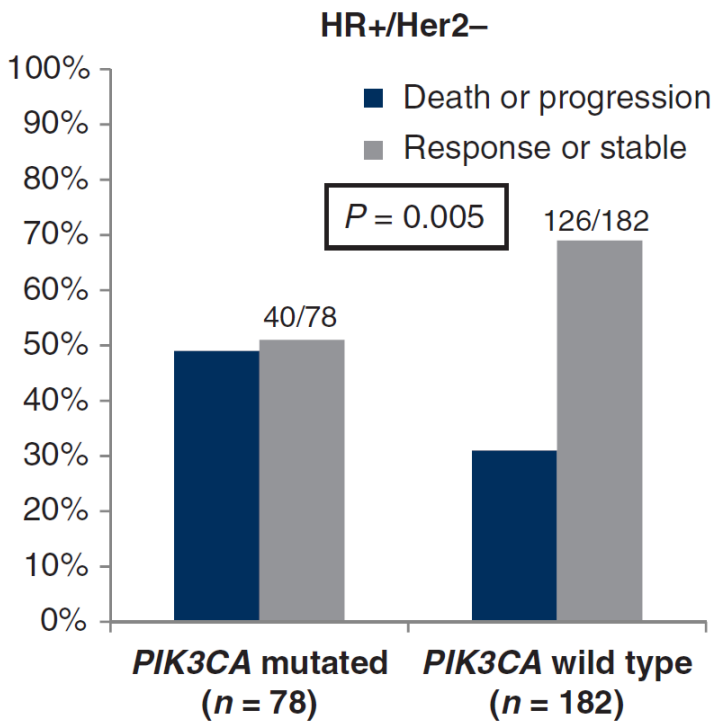
- PI3K includes catalytic and regulatory subunits[1,2]
- There are 4 isoforms of the PI3K catalytic subunit;
- *PIK3CA* encodes the α-isoform[1]
- The alpha isoform is the dominant PI3K in breast cancer[3]



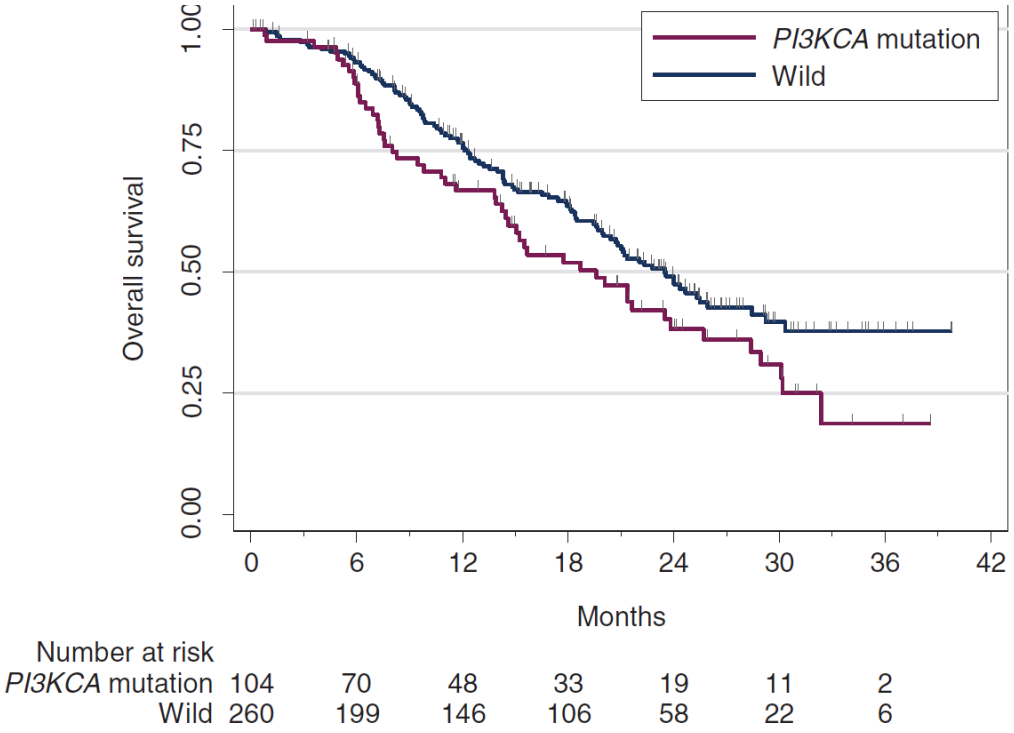


1. Engelman JA. Nat Rev Cancer 2009; 2. Janku F. Cancer Treat Rev 2017; 3. Kaklamani VG, Oncologist 2019

Response Rate and Overall Survival in HR+/Her2- MBC according to *PIK3CA* mutational status

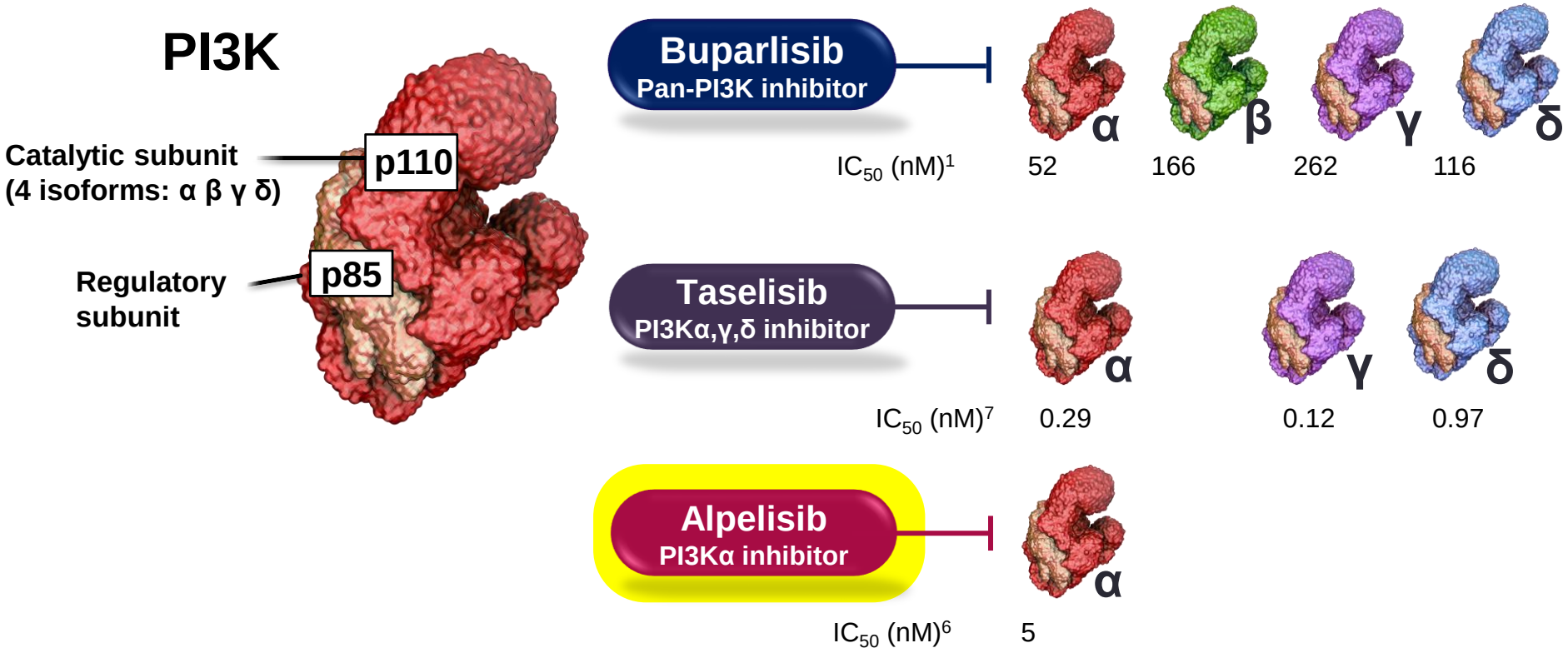


adj OR: 0.40; 95% CI (0.22-0.71)
P = 0.002



adj HR: 1.44; 95% CI (1.02-2.03)
P = 0.04

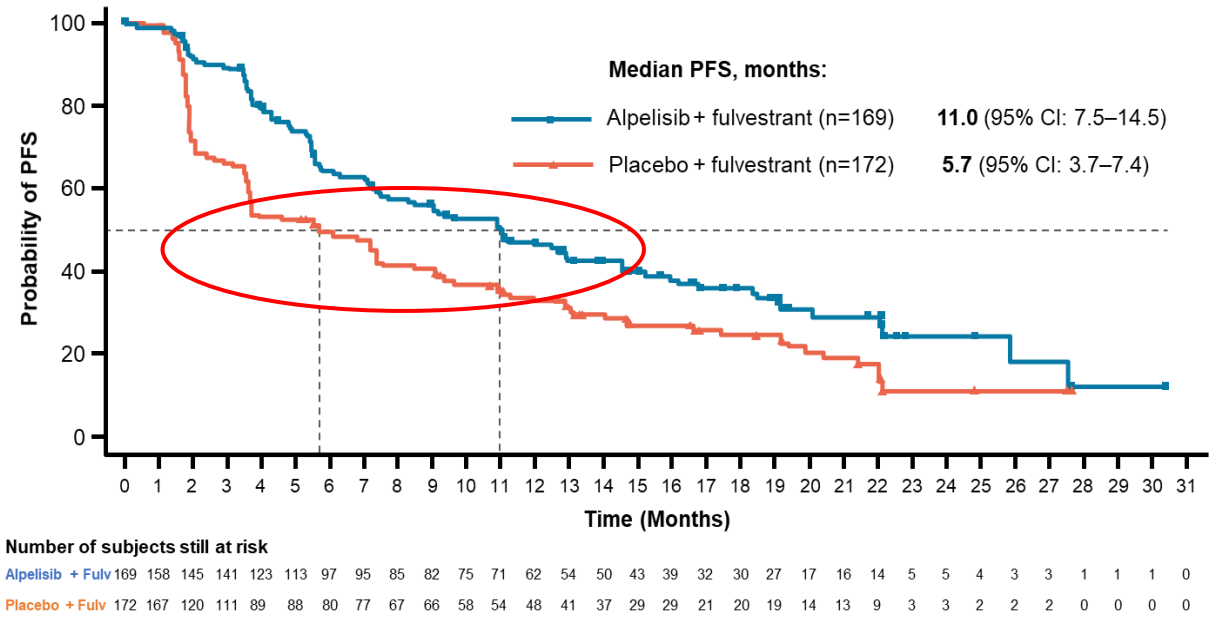
PI3K Inhibitors



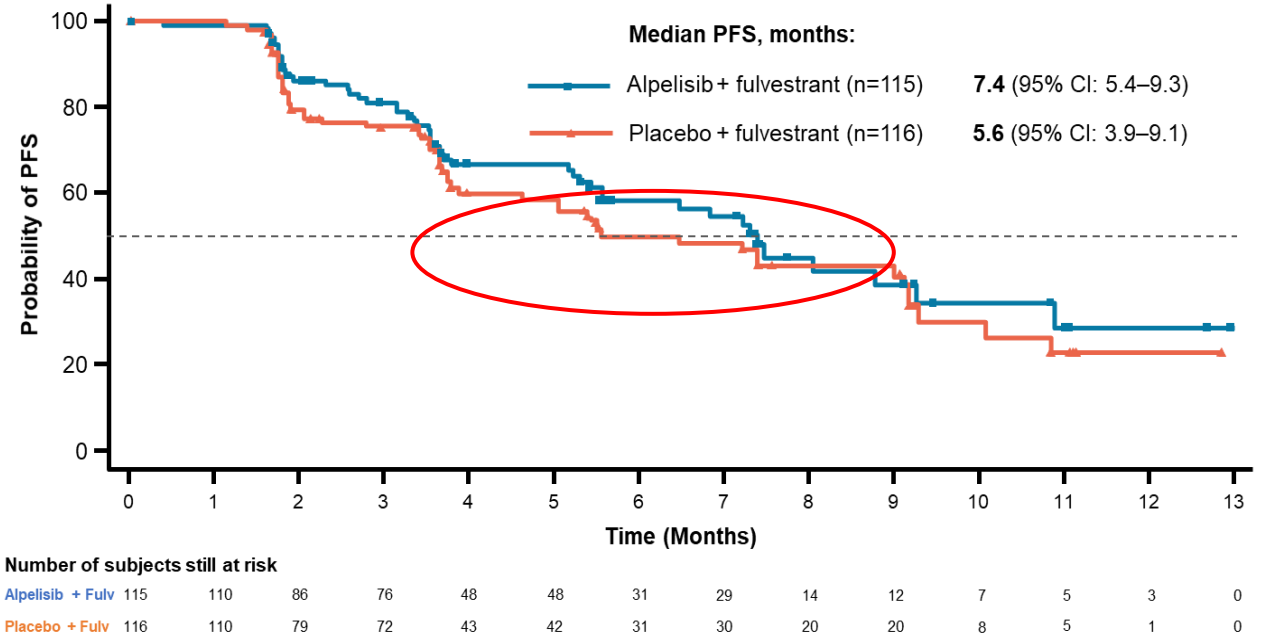
Targeting all class I isoforms may ensure broad activity in tumors with a range of molecular drivers[2–5]
Isoform-specific inhibitors may reduce off-target toxicity[5,6]

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

PIK3CA-mutant cohort



PIK3CA-non-mutant cohort



- 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. N Engl J Med. 2019

BYLieve: Primary Endpoint and PFS Results

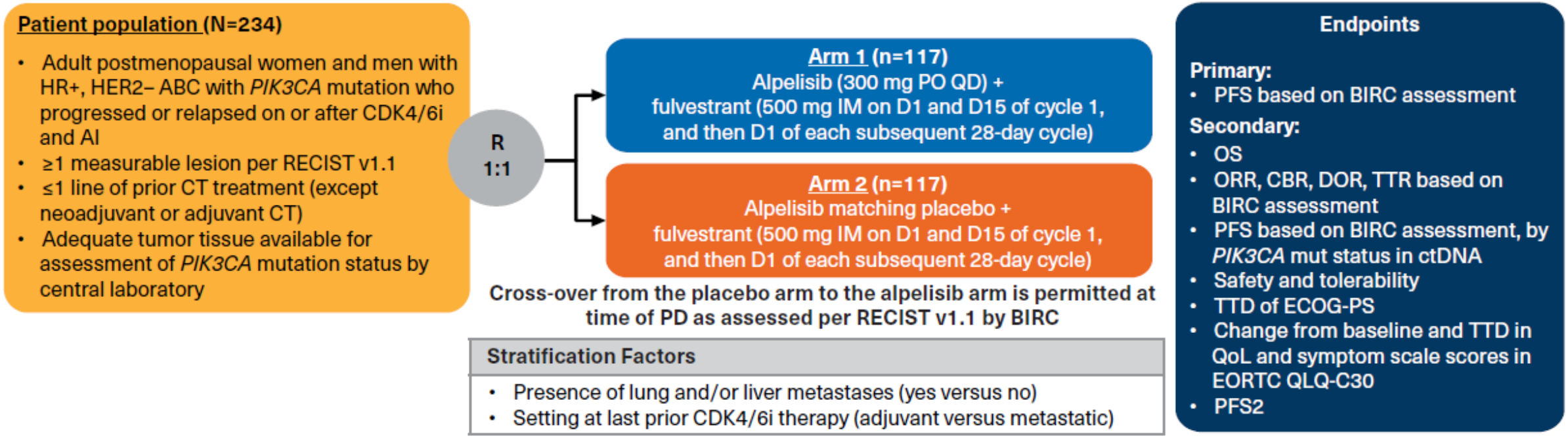
Endpoint	Prior CDKi + AI (Cohort A) (n=121)	Prior CDKi + FUL (Cohort B) (n=115)
Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)	**46.1%** (n=53; 95% CI, 36.8%-55.6%)
Median PFS	**7.3 months**	**5.7 months**
Overall response rate (ORR: CR + PR)	**17.4%** (n= 21, 95% CI (11.1-25.3)	**18%** (n=18, 95% CI (9.25-23.6)
Clinical benefit rate (CBR: CR + PR + SD+NCR/NPD ≥24 wk)	**45.5%** (n= 55, 95% CI (36.4-54.8)	**32.2%** (n= 37, 95% CI (23.8-41.5)

AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; CI, confidence interval; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

- In SOLAR-1, 44.4% of patients in the *PIK3CA*-mutant cohort with prior CDKi treated with alpelisib plus fulvestrant were alive without disease progression at 6 months

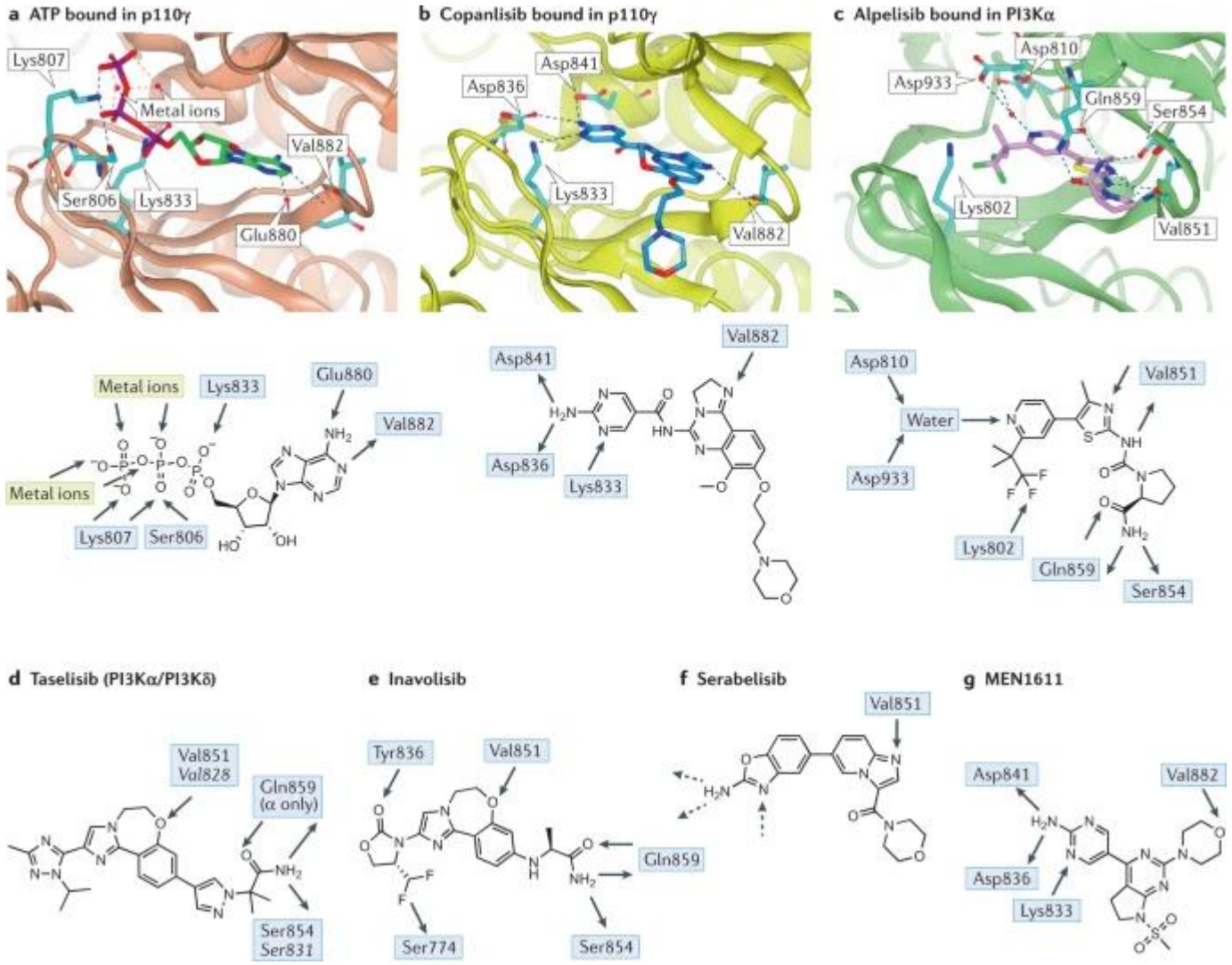
Rugo HS, et al. ASCO 2020

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



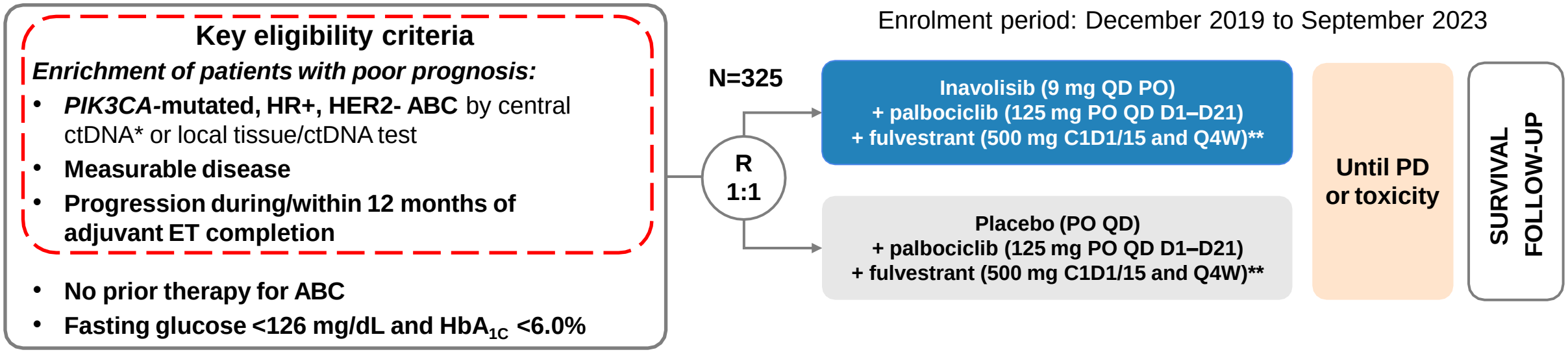
De Laurentiis M, et al. ASCO 2021

Key features of the interaction between PI3Ks and pan- and PI3Kα-selective inhibitors



Bart Vanhaesebroeck et al. Nature Reviews Drug Discovery 2021

INAVO120 study design

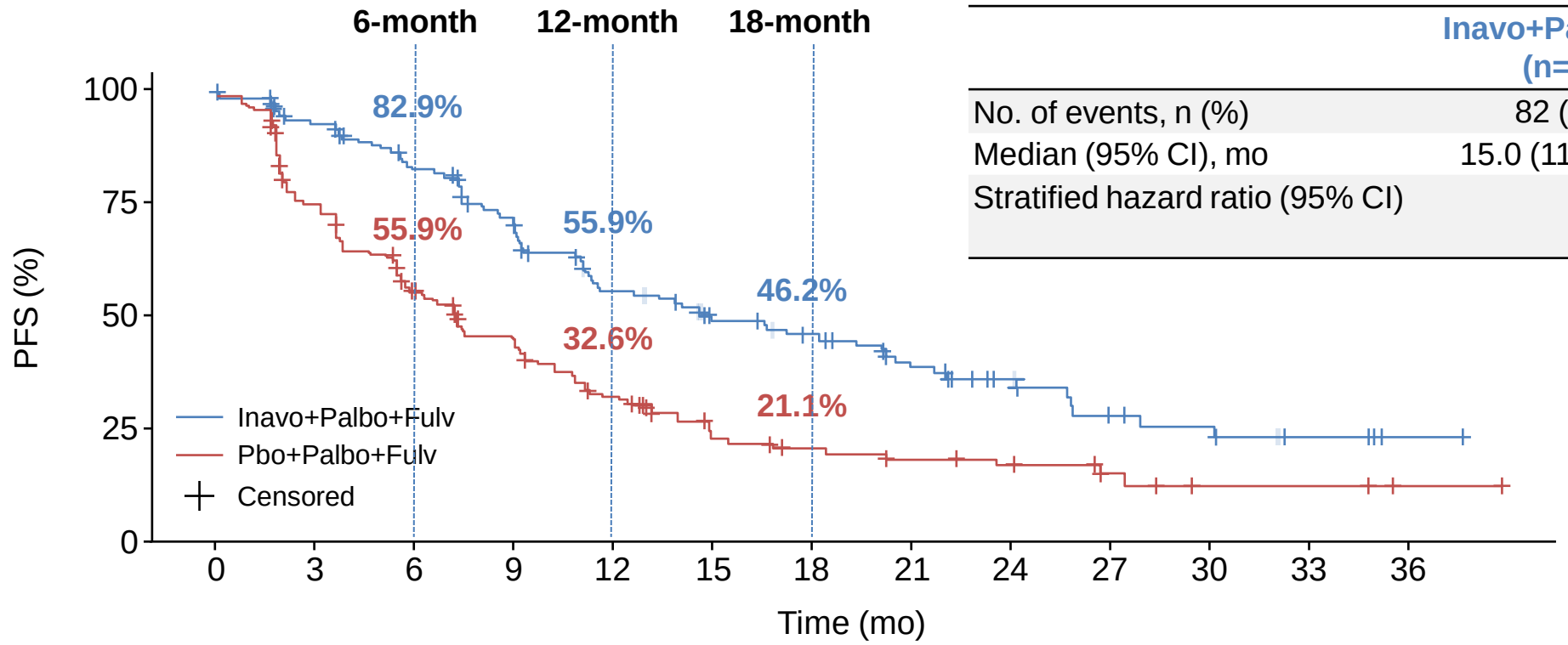


Stratification factors:
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints
- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis;
** Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29:**1634–1657.

Primary endpoint: PFS (investigator-assessed)



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59) p<0.0001**	

Patients at risk:

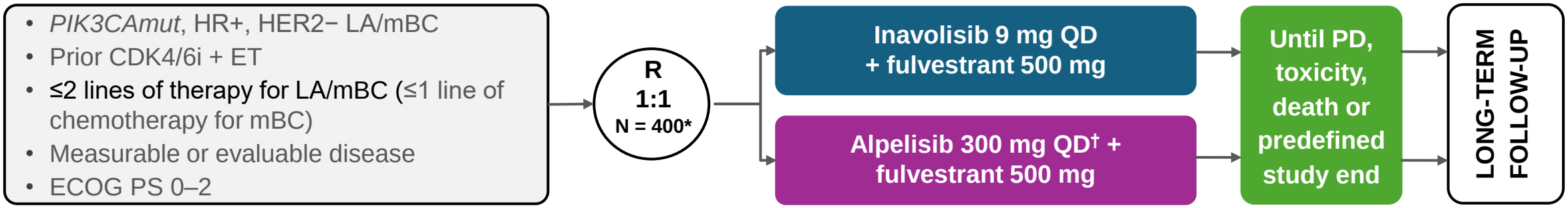
Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

CCOD: 29th September 2023

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

INAVO121: Phase III study of inavolisib + Ful vs. alpelisib + Ful in patients with PIK3CAmut, HR+/HER2- LA/mBC post-CDK4/6i + ET



Stratification factors:
- Visceral disease: yes vs. no
- Prior CDK4/6i therapy: adjuvant vs. metastatic setting

Primary endpoint:
- PFS (BICR-assessed)

Secondary endpoints:
- OS
- ORR, BoR, CBR, DoR (all BICR-assessed)
- Safety and tolerability
- TTCD in pain, physical functioning, role functioning, HRQoL
- PK

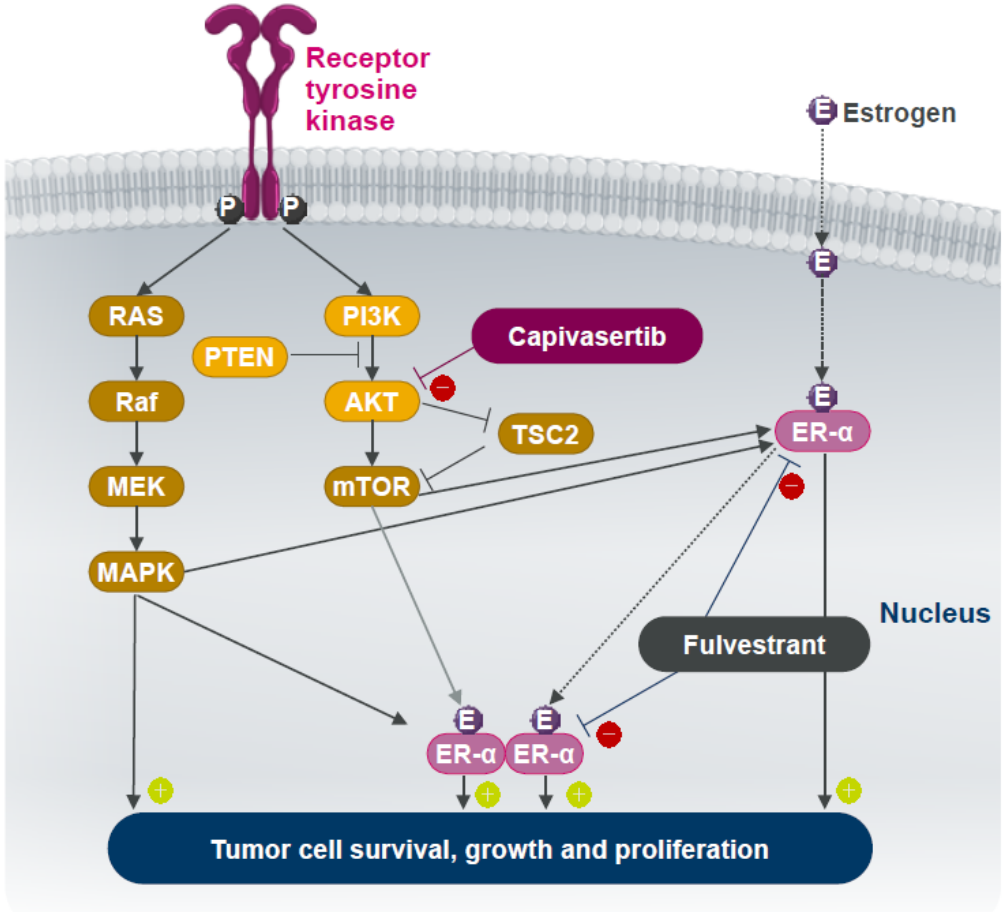
Exploratory endpoints:
- PFS2
- Biomarkers
- PK

1. https://clinicaltrials.gov/study/NCT05646862 (accessed October 2023); 2. Juric D, *et al*. ASCO 2023 (Abstract TPS1123; poster presentation); 3. Roche. Data on file.

Capivasertib and fulvestrant for pts with AI-resistant HR+/HER2- ABC: Phase III CAPItello-291 trial

Background and overview of capivasertib

- AKT pathway activation occurs in many HR+/HER2– ABC through alterations in *PIK3CA, AKT1 and PTEN*, but may also occur in cancers without those genetic alterations.[1,2] AKT signalling is also implicated in the development of resistance to endocrine therapy[2]
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)
- In the Phase II, placebo-controlled FAKTION trial[3]:
  - The addition of capivasertib to fulvestrant significantly improved PFS and OS in postmenopausal women with Airesistant HR+/HER2– ABC in the overall population, with a more pronounced benefit in pathway altered tumours
  - No patients had received prior CDK4/6 inhibitors



1. Millis et al. JAMA Oncol 2016;2:15651573;
2. Toss et al. Oncotarget. 2018;9:3160631619;
3. Howell et al. Lancet Oncol 2022;23:851–64. ABC, advanced breast cancer.

Turner NC et al., SABCS 2022

CAPItello291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

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

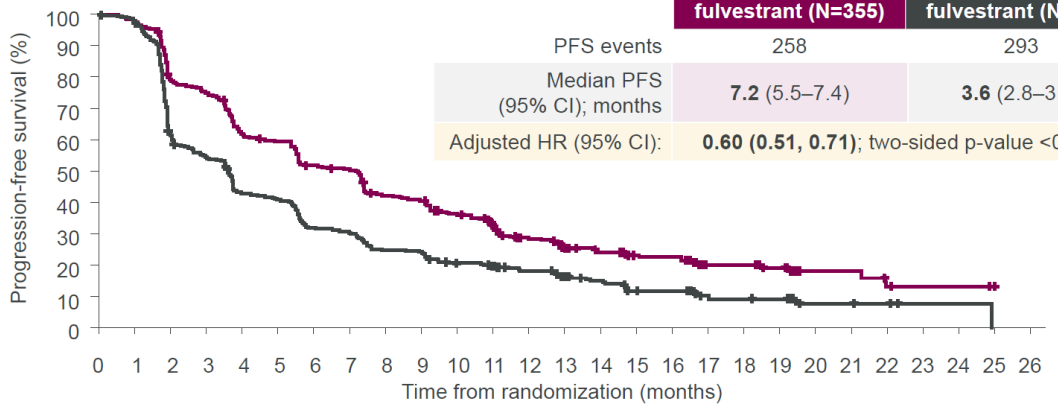
Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

Turner NC et al., SABCS 2022

CAPITELLO-291: Dual primary endpoint

PFS in the overall population



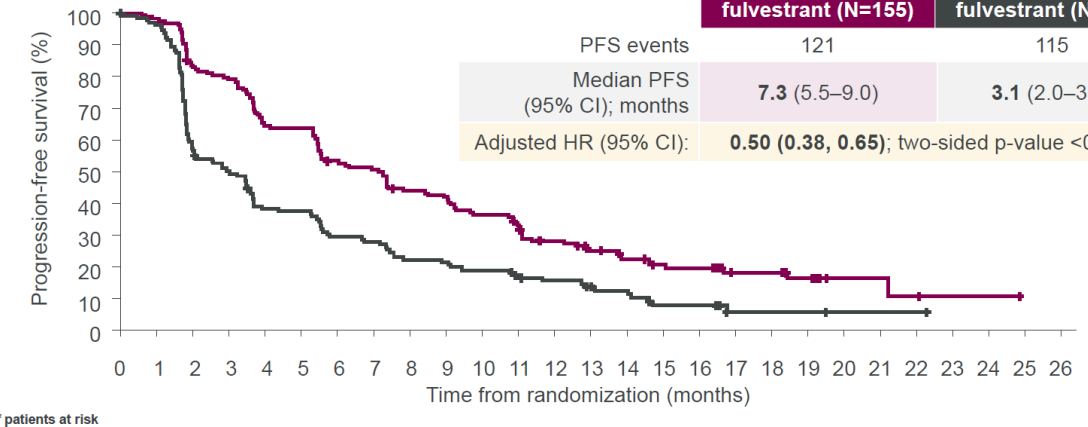
	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	

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

*≥1 PIK3CA, AKT, or PTEN alteration



	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

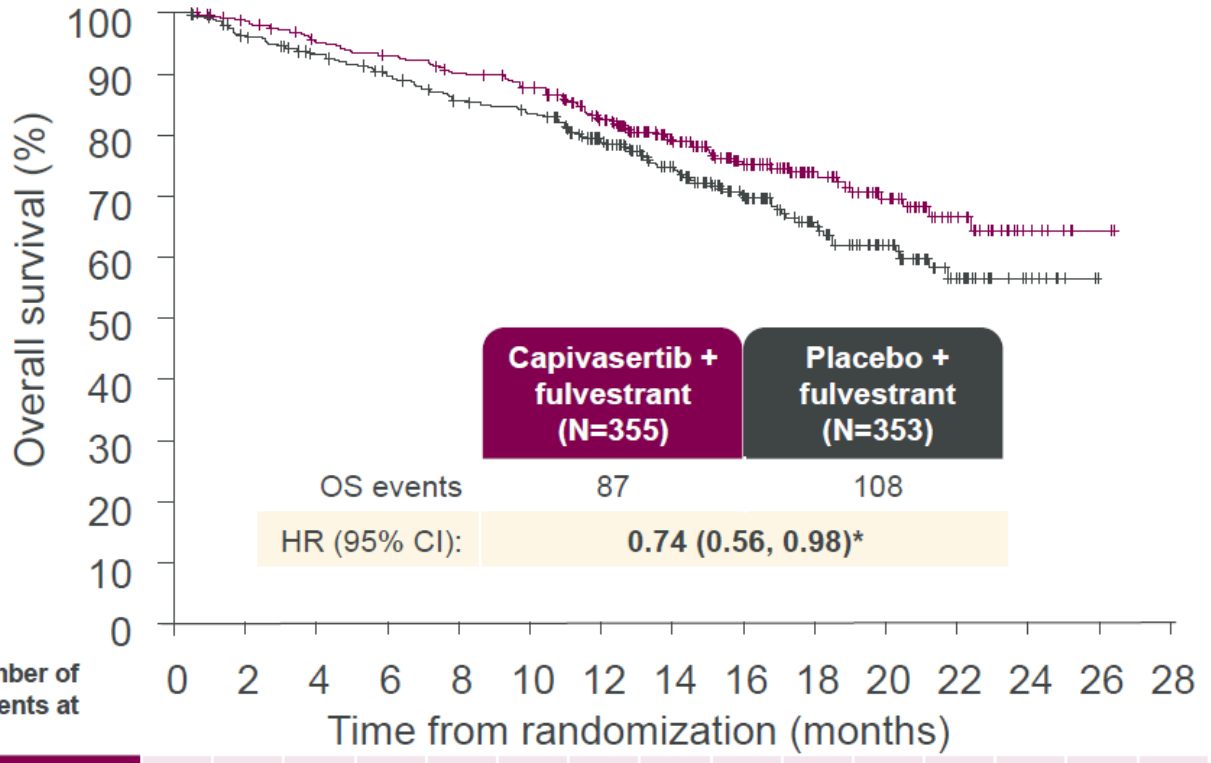
Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)

Turner NC et al. SABCS 2022

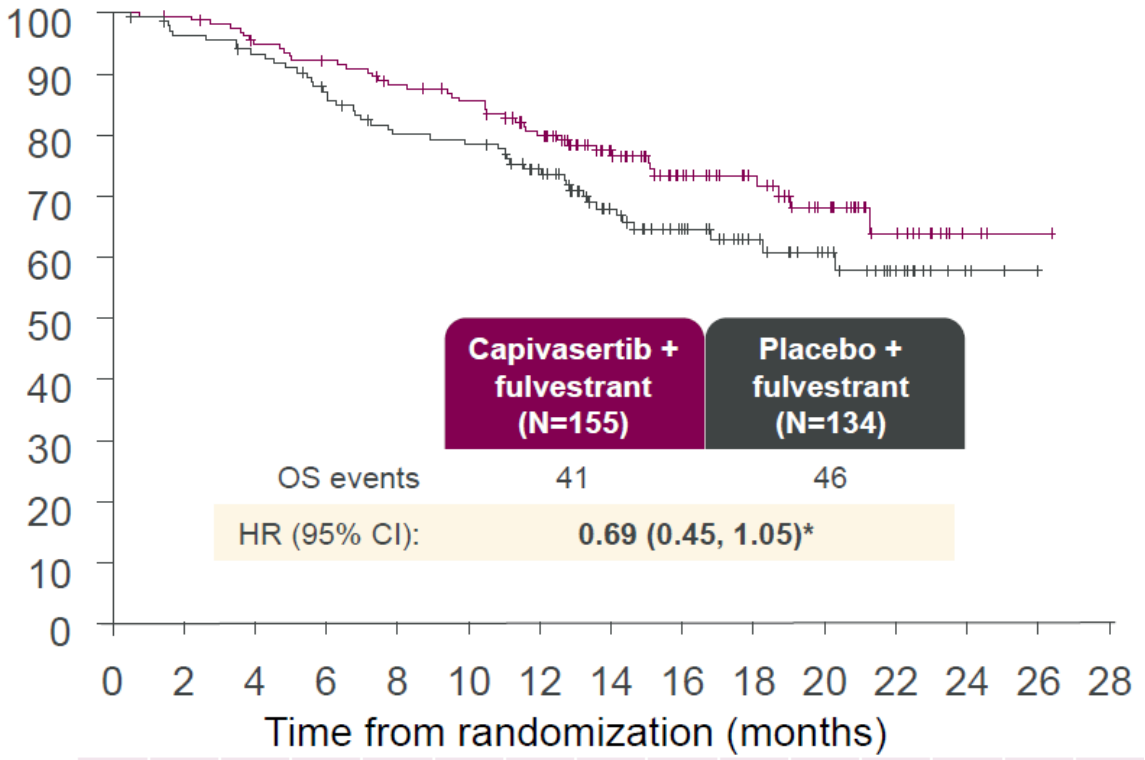
Overall survival at 28% maturity overall

Overall population



Number of patients at risk															
Capivasertib + fulvestrant	355	343	327	318	306	295	258	198	144	95	63	33	9	2	0
Placebo + fulvestrant	353	334	316	301	283	274	237	181	134	90	59	30	11	0	0

AKT pathway-altered population

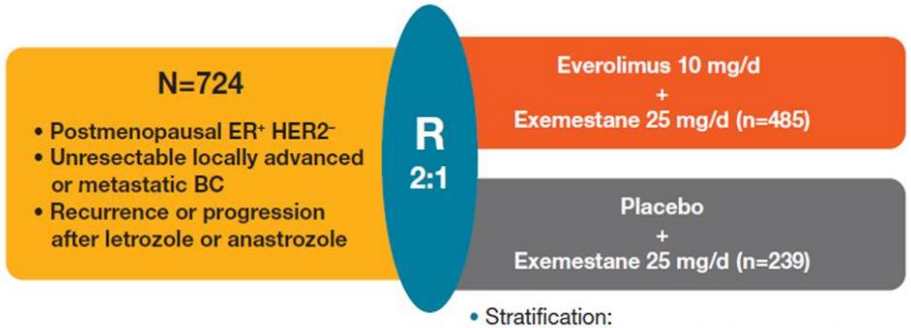


Capivasertib + fulvestrant	155	153	144	139	131	125	111	83	60	45	30	14	3	1	0
Placebo + fulvestrant	134	127	122	112	101	99	87	62	46	31	22	13	3	0	0

Turner NC et al., SABCS 2022

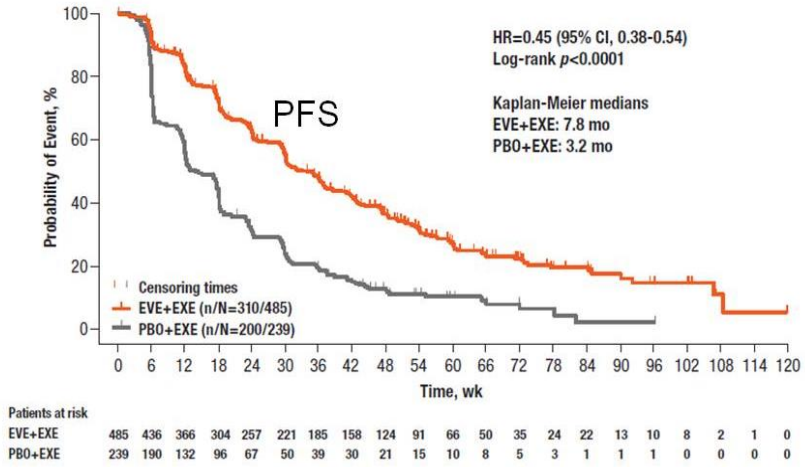
mTOR inhibition for AI resistant HER2- MBC

BOLERO-2

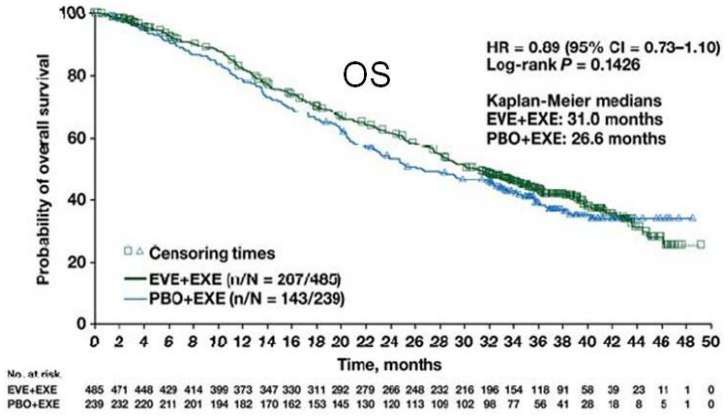


Endpoints
- **Primary:** PFS (local assessment)
- **Secondary:** OS, ORR, CBR, QOL, safety,

Endpoints



Yardley DA, et al. *Adv Ther.* 2013;30:870–884



Piccart, et al, Ann Oncol. 2014

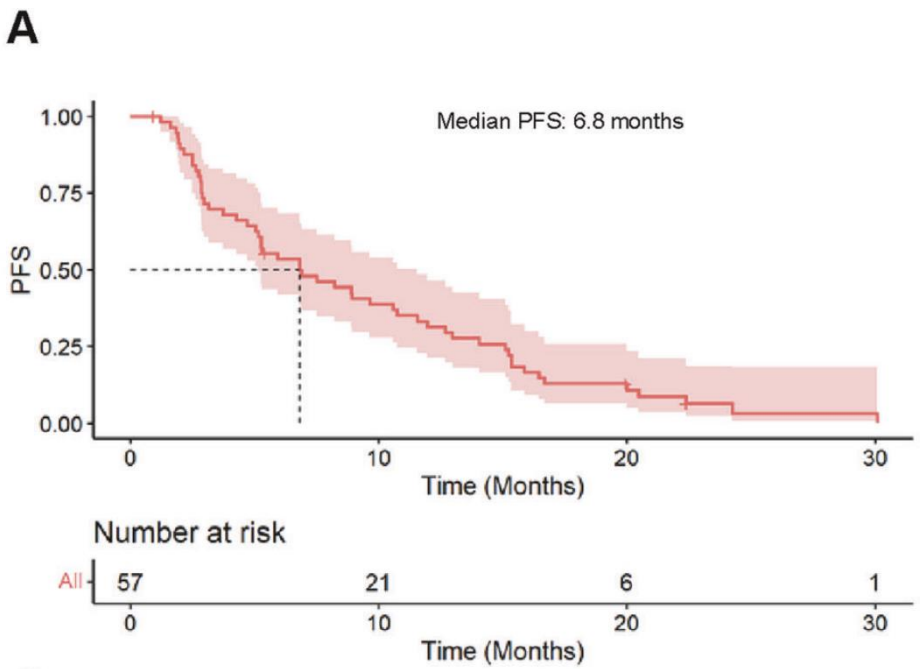
Oncogene (2024) 43:1214–1222; https://doi.org/10.1038/s41388-024-02986-6

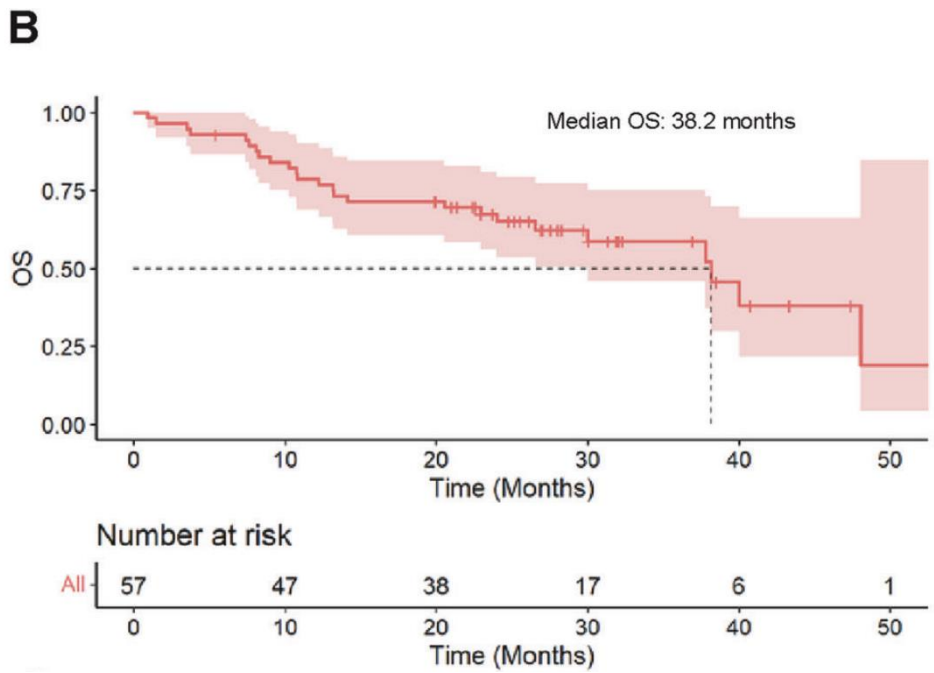
ARTICLE OPEN

Check for updates

Fulvestrant and everolimus efficacy after CDK4/6 inhibitor: a prospective study with circulating tumor DNA analysis

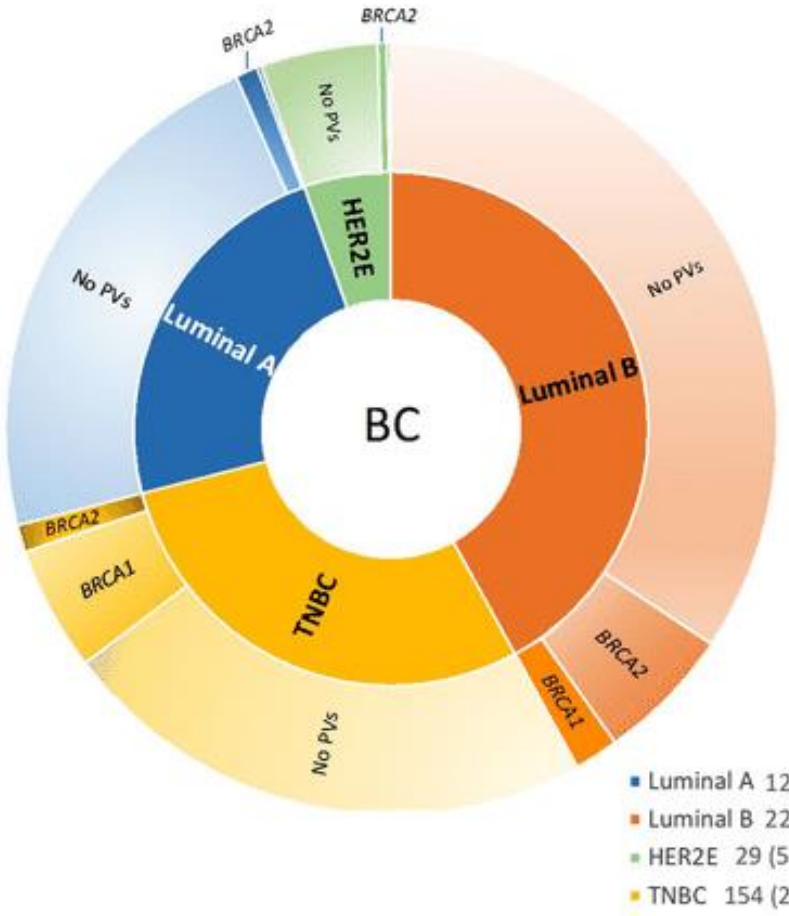
Antoine Vasseur[1,2], Luc Cabel[1], Caroline Hego[2], Wissam Takka[2], Olfa Trabelsi Grati[3], Benjamin Renouf[4], Florence Lerebours[1], Delphine Loirat[1], Etienne Brain[1], Paul Cottu[1], Marie-Paule Sablin[1], Jean-Yves Pierga[1,5], Céline Callens[3], Shufang Renault[2,7]✉ and François-Clément Bidard[1,2,6,7]✉

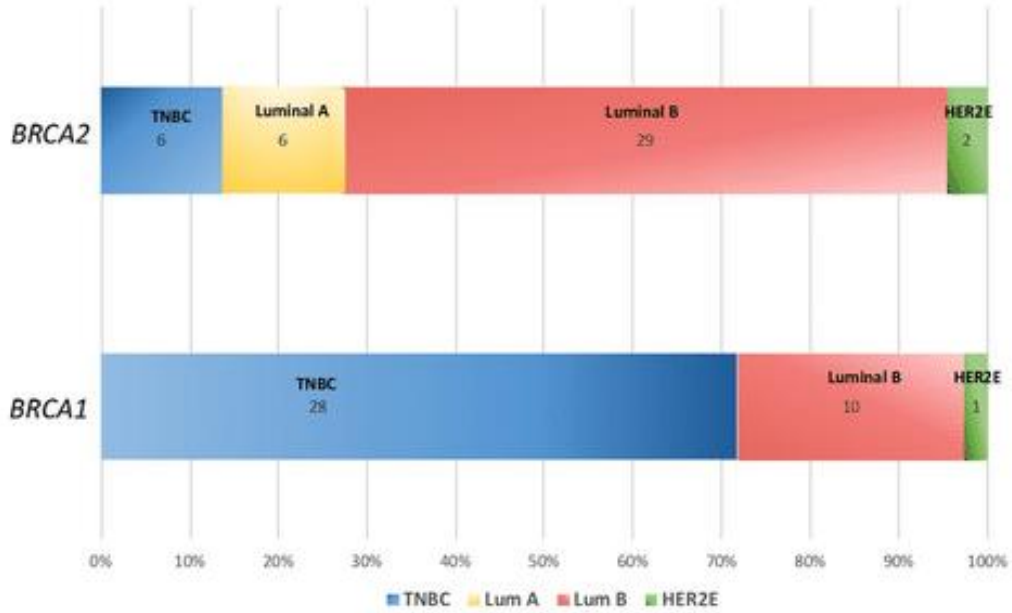




BRCA1/2 mutations in patients with Breast Cancer

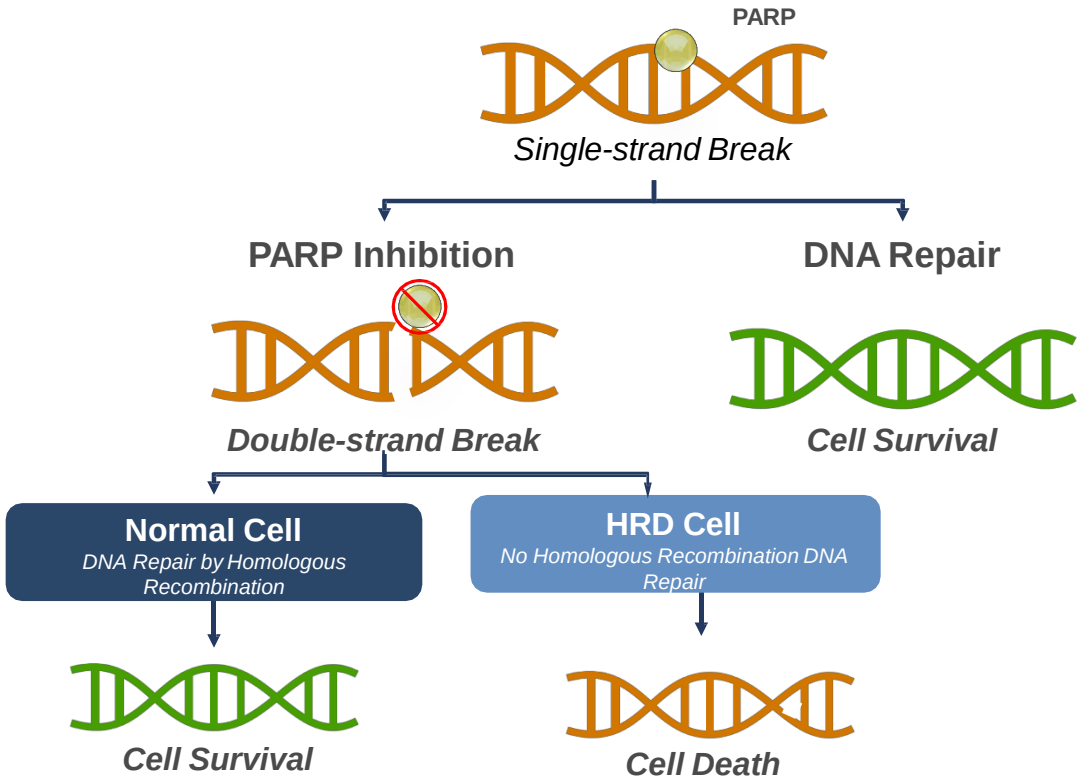
- Though most breast cancer cases are sporadic, 5–10% of cases are hereditary and mostly related to *BRCA1/2* gene mutations





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

Mechanism of PARP Inhibition



Inhibition of **PARP prevents DNA repair**, leading to accumulation of DNA breaks

Cells with homologous repair deficiency or **HRD** (e.g., a mutation in the **BRCA** gene) are **unable to repair the DNA breaks**

By this mechanism, PARP inhibition is believed to **contribute to death in cells harboring DNA repair deficiencies**

H. Farmer et al., Nature 2005

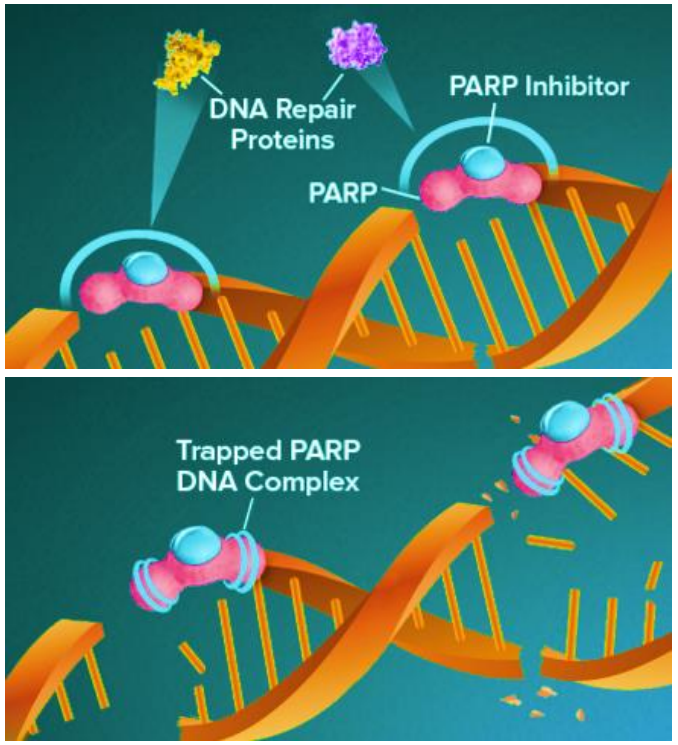
PARP inhibitors in development for Breast Cancer

Potency for catalytic inhibition

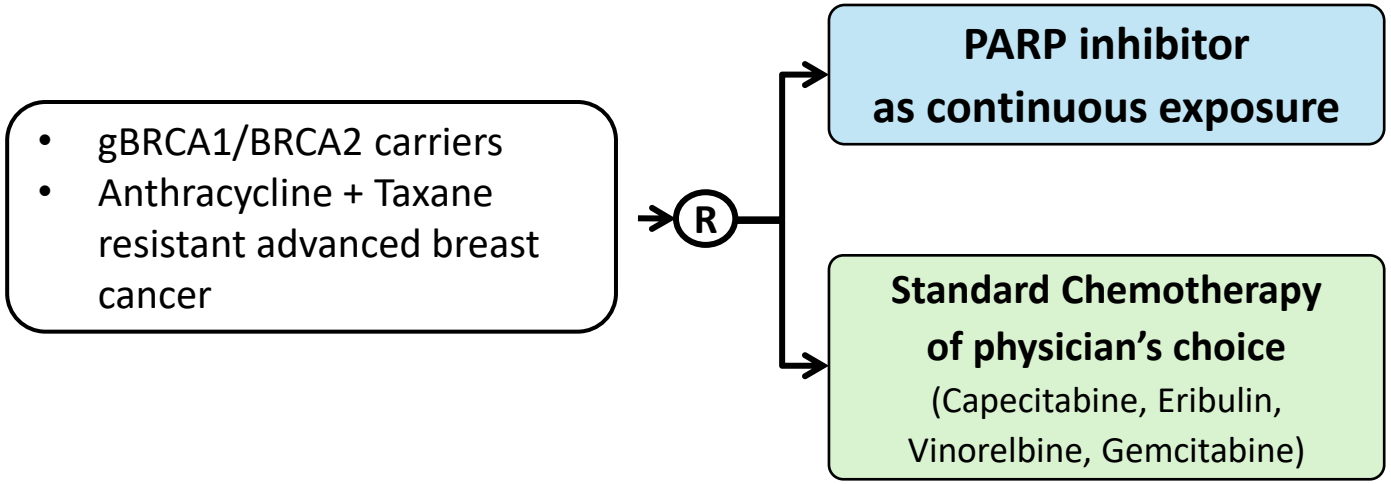
Highest

Lowest

Drug Name	PARP Inhibition			Trapping PARP-DNA complex
	PARP 1	PARP 2	PARP 3	
Talazoparib (BMN-673)	■	■		Yes
Niraparib (MK-4827)	■	■		Yes
Rucaparib (AG-14699)	■	■	■	Yes
Olaparib (AZD2281)	■	■	■	Yes
Veliparib (ABT-888)	■	■		No/weak



Single agent PARPi: FDA Registration studies for BRCA1/2 mutated Advanced Breast Cancer Patients



Primary endpoint:
Progression-free survival

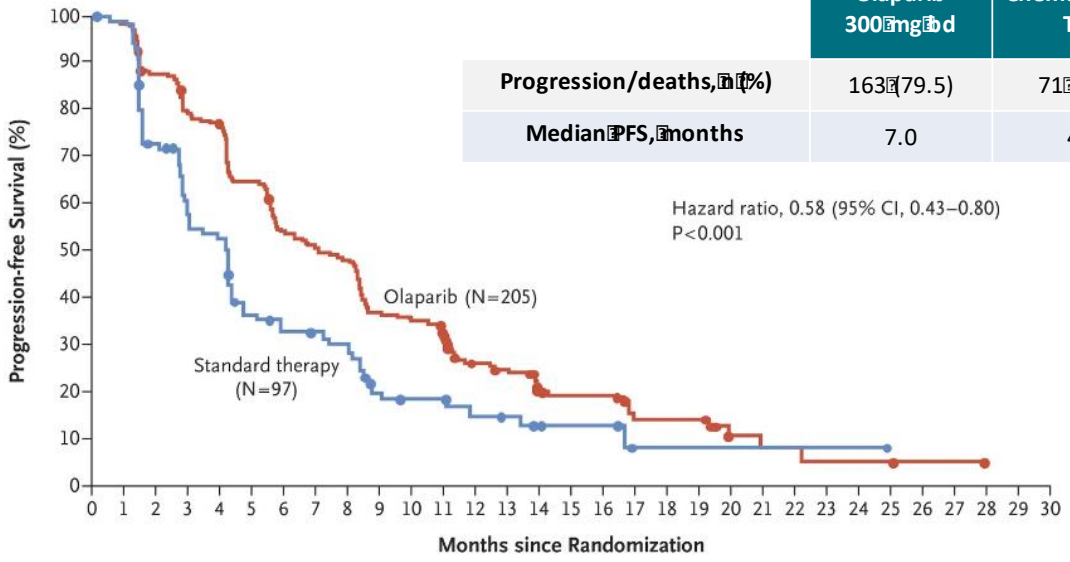
Note: Platinum is not included in comparator arm

PARP inhibitor	Study	NCT number	Status	
Olaparib	**OLYMPIAD**	NCT02000622	completed	Approved by FDA and EMA
Talazoparib	**EMBRACA**	NCT 01945775	completed	Approved by FDA and EMA
Niraparib	**BRAVO**	NCT01905592	halted	

Progression-Free Survival

OlympiAD

	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2

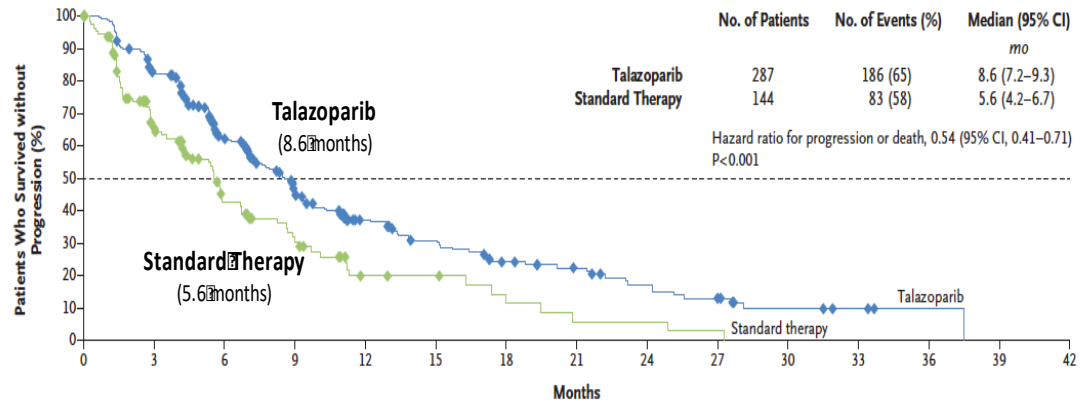


No. at Risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	0	0	0	0	

Robson M et al. NEJM 2017

EMBRACA



	No. of Patients	No. of Events (%)	Median (95% CI) mo
Talazoparib	287	186 (65)	8.6 (7.2–9.3)
Standard Therapy	144	83 (58)	5.6 (4.2–6.7)

Hazard ratio for progression or death, 0.54 (95% CI, 0.41–0.71)
P<0.001

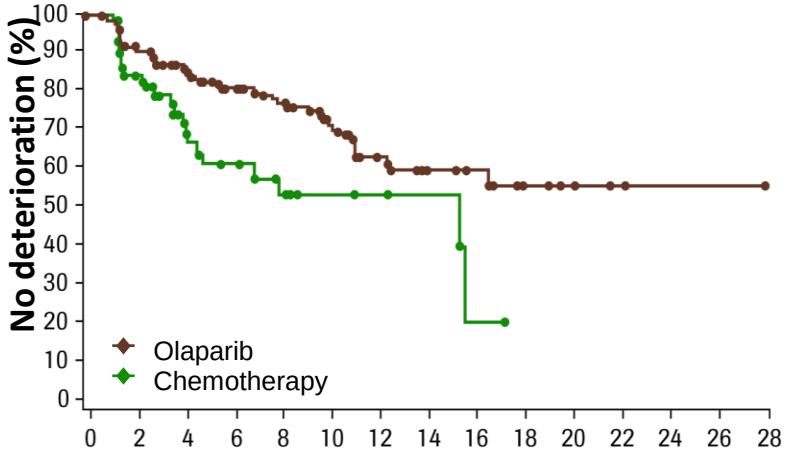
No. at Risk (events/cumulative events)

Talazoparib	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)										
Standard therapy	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)										

Litton J et al. NEJM 2018

Time to deterioration of global HRQoL

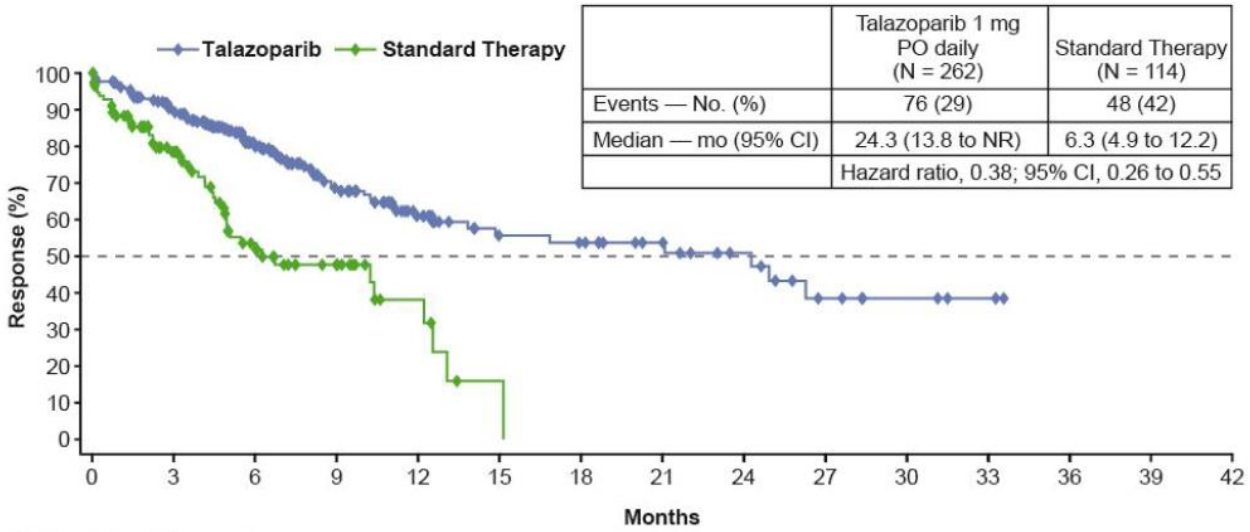
OlympiAD



At risk, n															
Olaparib 300 mg bd	201	164	134	93	77	56	40	20	15	7	4	2	1	1	0
Chemotherapy TPC	93	54	30	19	13	8	7	4	1	0	0	0	0	0	0

Robson M et al. NEJM 2017

EMBRACA

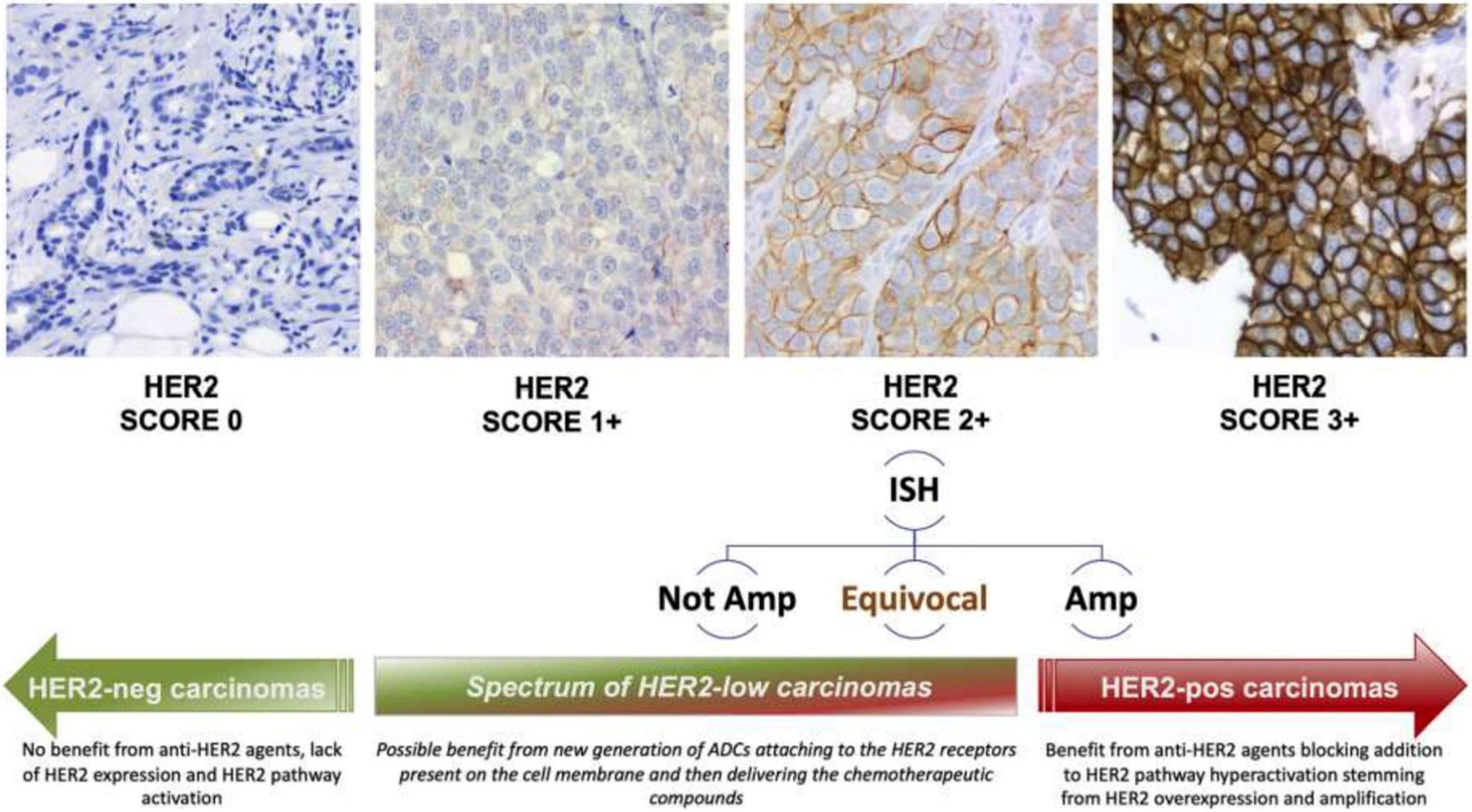


	Talazoparib 1 mg PO daily (N = 262)	Standard Therapy (N = 114)
Events — No. (%)	76 (29)	48 (42)
Median — mo (95% CI)	24.3 (13.8 to NR)	6.3 (4.9 to 12.2)
	Hazard ratio, 0.38; 95% CI, 0.26 to 0.55	

No. at Risk (events/cumulative events)															
Talazoparib	262 (0/0)	212 (26/26)	139 (18/44)	78 (17/61)	44 (7/68)	28 (3/71)	26 (1/72)	20 (0/72)	14 (1/73)	7 (3/76)	4 (0/76)	2 (0/76)	0 (0/76)	0 (0/76)	0 (0/76)
Standard Therapy	114 (0/0)	64 (22/22)	30 (17/39)	17 (3/42)	6 (2/44)	1 (3/47)	0 (1/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)	0 (0/48)

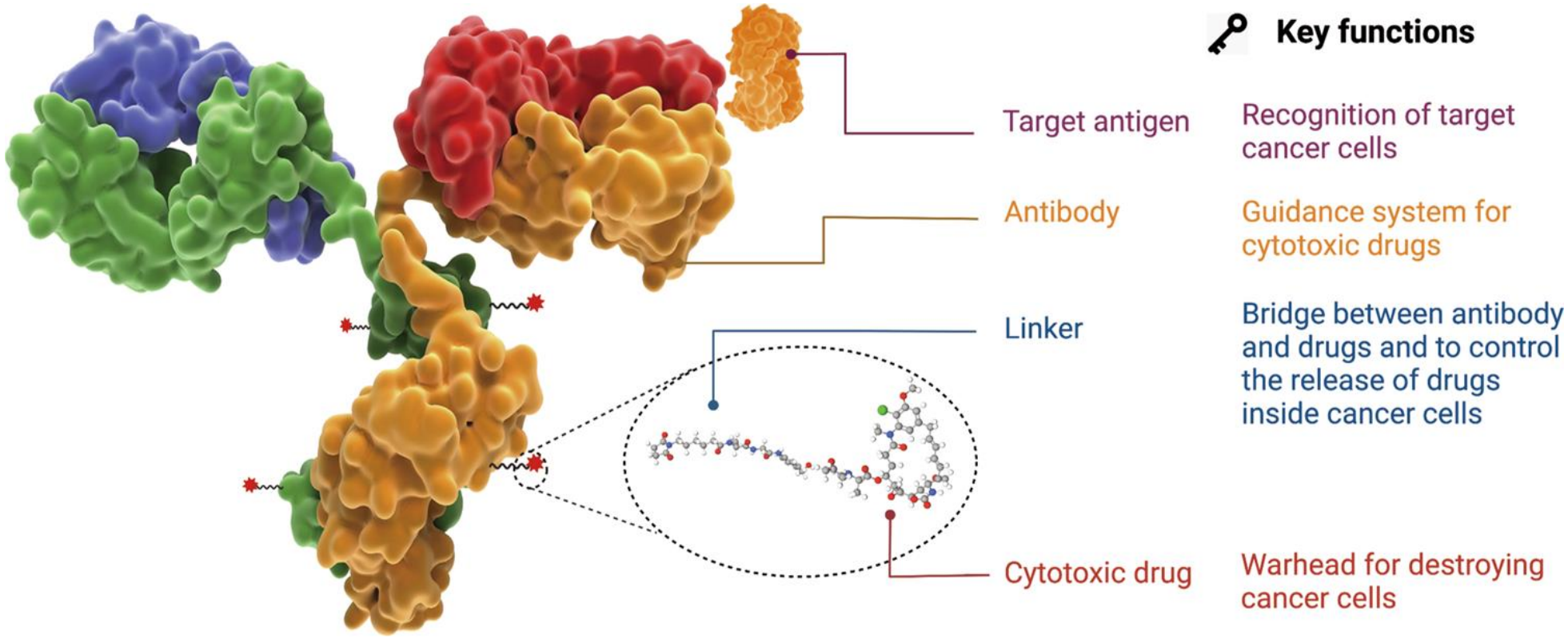
Litton J et al. NEJM 2018

HER2 Testing:



Marcio C et al, Seminars in Cancer Biology, 2020

Antibody Drug Conjugates (ADC)

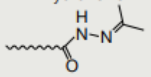
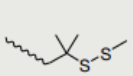
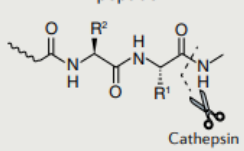
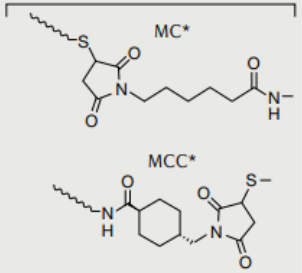


Adapted from Fu Z, et al. Signal Transduction and Targeted Therapy 2022

Antibody drug conjugates

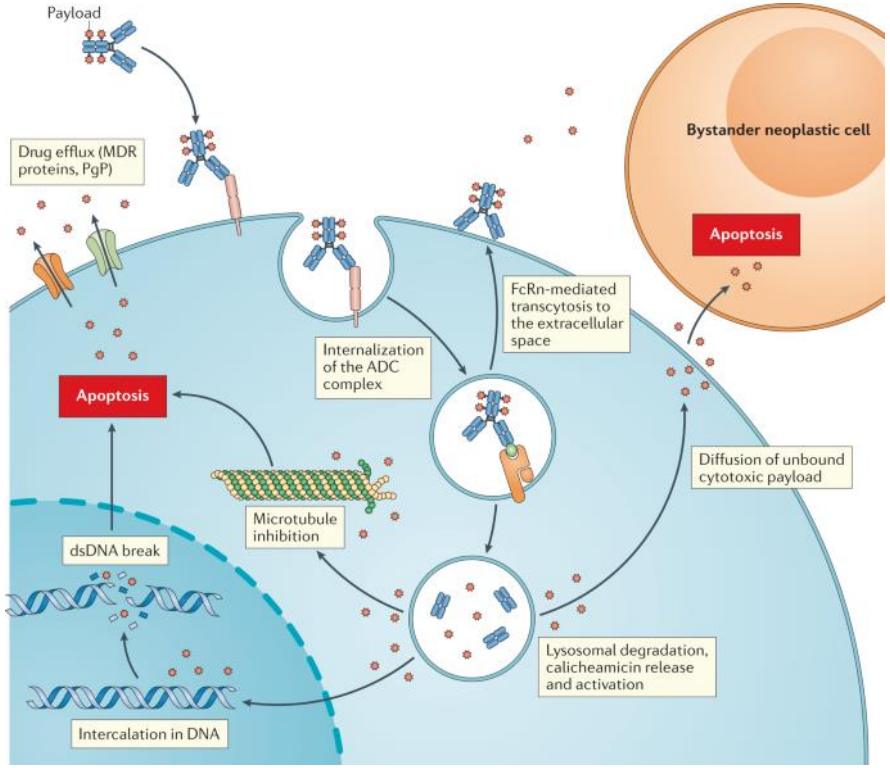
Modular components

	IgG1	IgG2	IgG3	IgG4
Antibodies				
Serum half-life	21 days	21 days	7–21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate

	Cleavable			Non-cleavable
Linkers	Hydrazone	Disulfide	Dipeptide	MC* / MCC*
			 Cathepsin	
	Acid cleavable	Reducible	Protease cleavable	

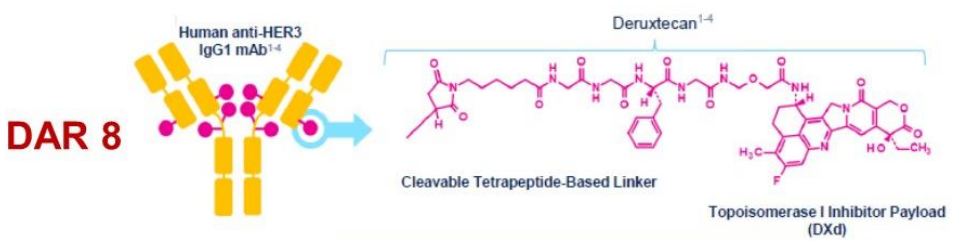
Payloads	 Auristatins	 Maytansinoids	 Calicheamicins	 Camptothecins
	Anti-microtubule	Anti-microtubule	DNA cleavage	Topoisomerase 1 inhibition

Mechanism of action

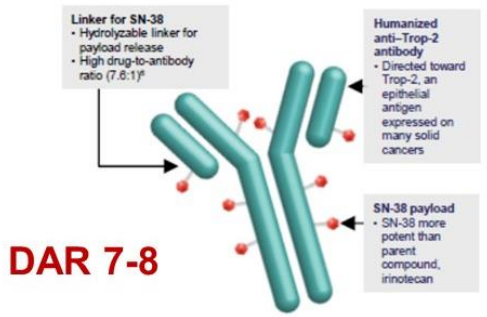


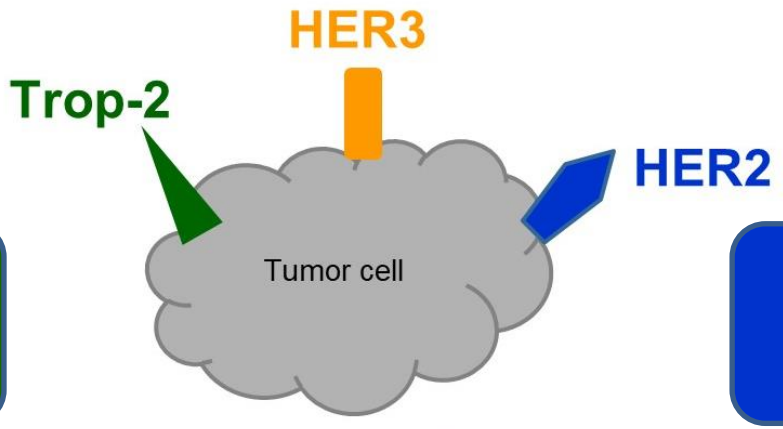
Drago JZ et al, NRCO 2021

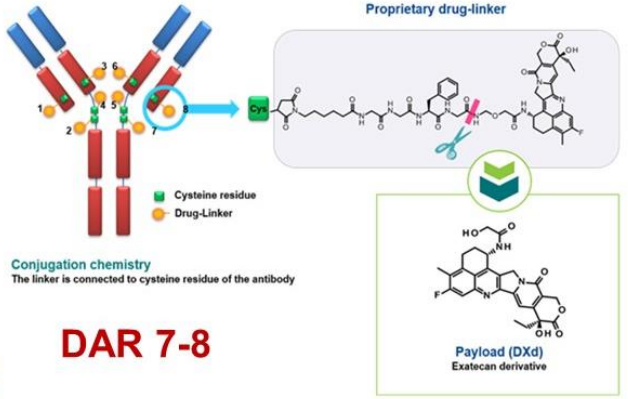
New generations of ADCs in Breast Cancer



Patritumab Deruxtecan





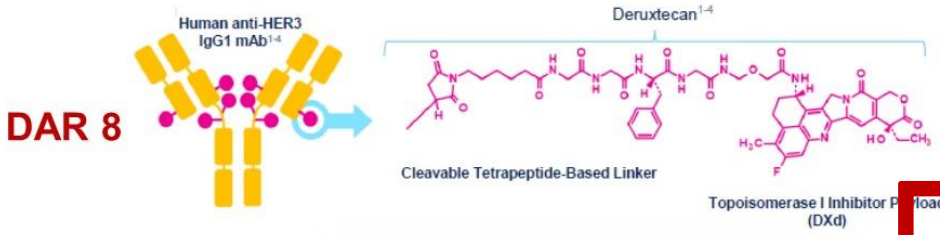


Sacituzumab Govitecan
Datopotamab-DXd

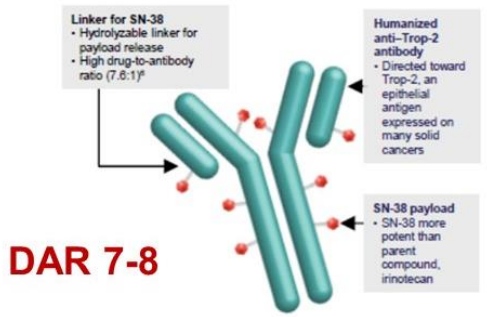
Trastuzumab Deruxtecan

PAYLOAD: Topo-I inhibitor
SN38 and DXd exatecan

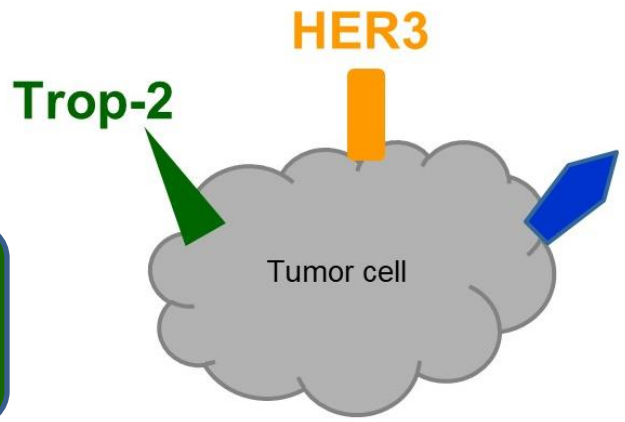
New generations of ADCs in Breast Cancer

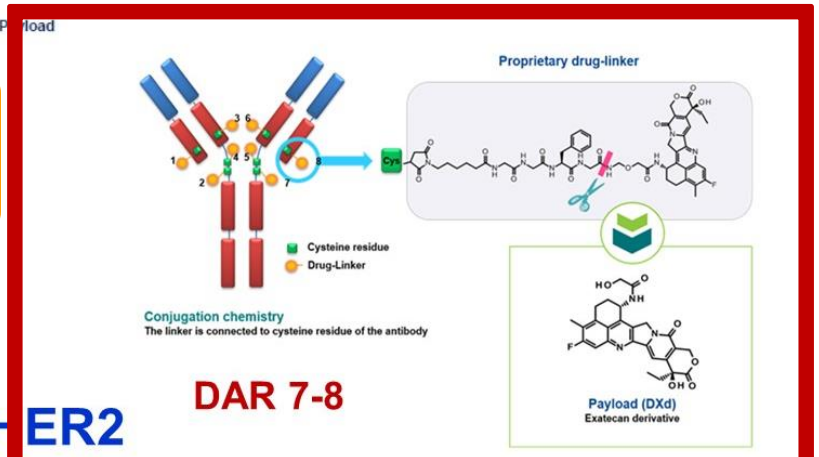


Patritumab Deruxtecan



Sacituzumab Govitecan Datopotamab-DXd





Trastuzumab Deruxtecan

PAYLOAD: Topo-I inhibitor SN38 and DXd exatecan

DESTINY-Brest04: Study Design

An open-label, multicenter study (NCT03734029)[1-3]

Patients[a]
- HER2-low (IHC 1+ or IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

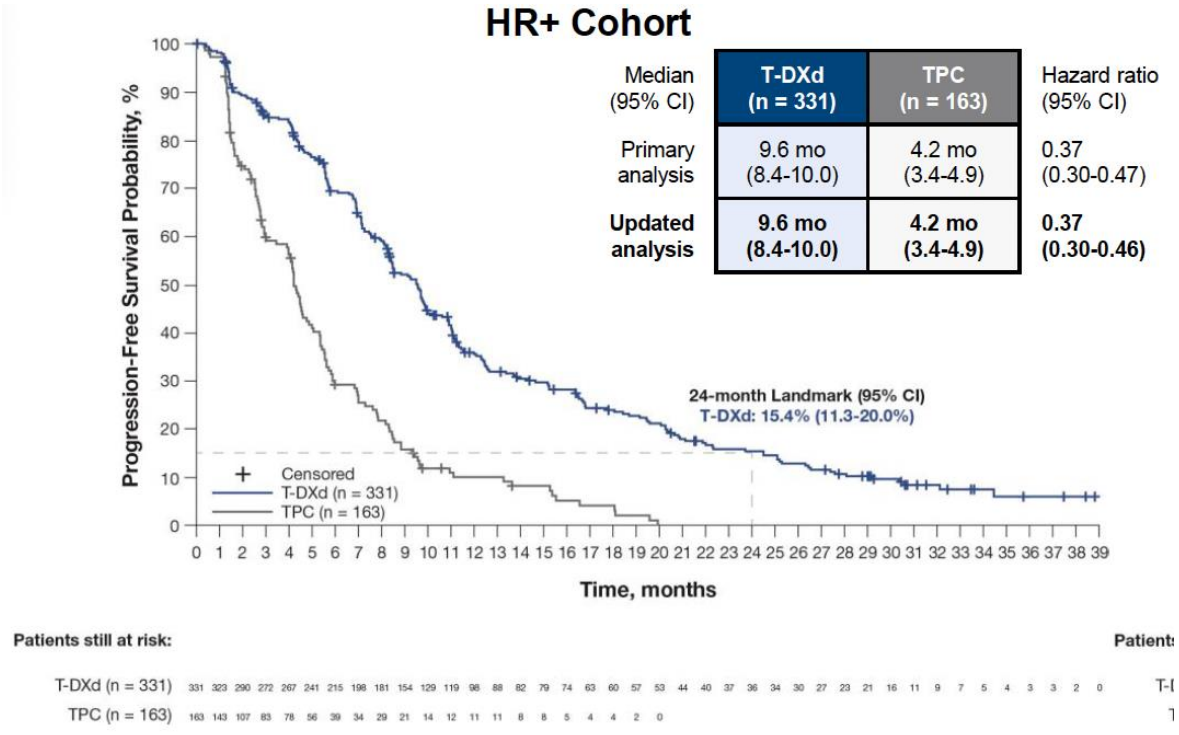
Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

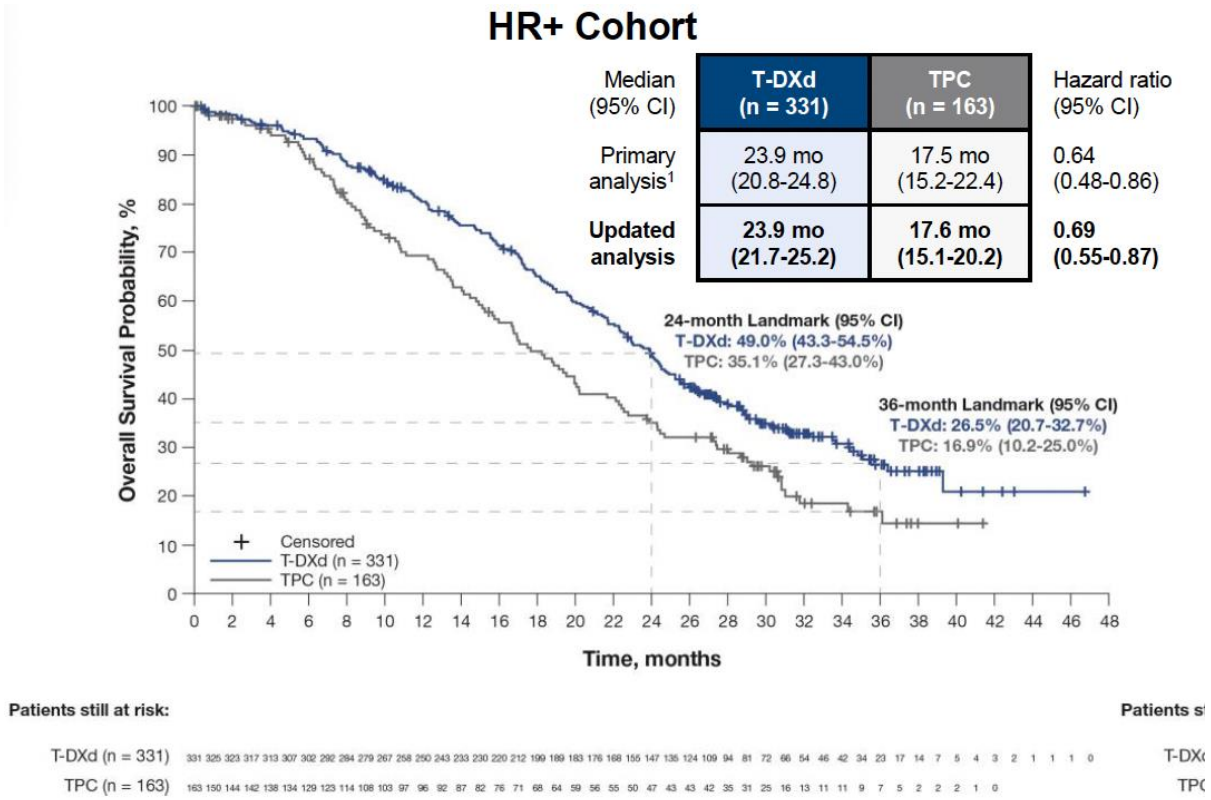
Stratification factors
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

Modi S et al, ASCO 2022; Modi S et al, ESMO 2023

DESTINY-Breast04: PFS and OS in HR+/HER2-low





Modi S et al, ESMO 2023

T-DXd vs physician's choice of chemotherapy in pts with HR+/HER2–low or HER2-ultralow MBC with prior endocrine therapy: primary results from DESTINY-Breast06

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=436)

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options: capecitabine, nab-paclitaxel, paclitaxel

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

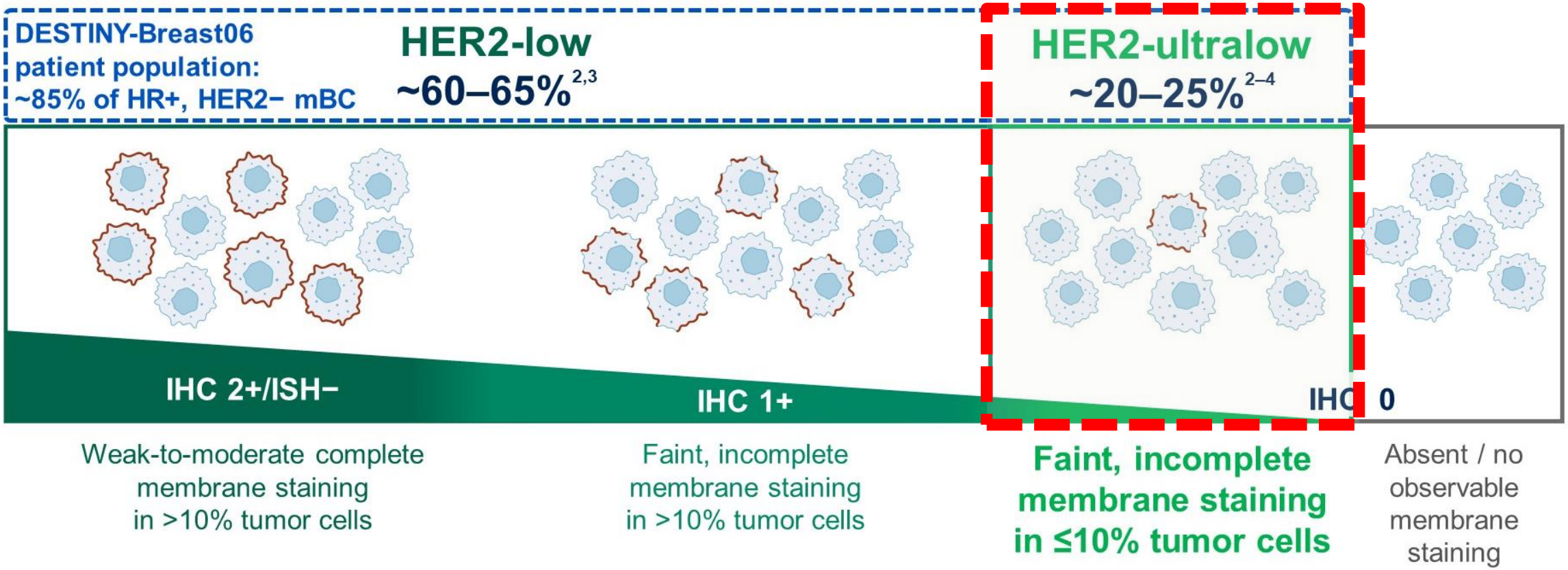
Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

Curigliano G, et al. ASCO 2024

Targeting ‘low’ and ‘ultralow’ HER2-expressing tumors in mBC

HER2 IHC categories within HR+, HER2-negative (HER2−) mBC (per ASCO/CAP[1])



ASCO/CAP, American Society of Clinical Oncology / College of American Pathologists; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

Images adapted from Venetis K, et al. *Front Mol Biosci.* 2022;9:834651. CC BY 4.0 license available from: https://creativecommons.org/licenses/by/4.0/

1. Wolff AC, et al. *J Clin Oncol.* 2023;41:3867–3872; 2. Denkert C, et al. *Lancet Oncol.* 2021;22:1151–1161; 3. Chen Z, et al. *Breast Cancer Res Treat.* 2023;202:313–323; 4. Mehta S, et al. *J Clin Oncol.* 2024;42(Suppl. 16):Abstract e13156

Curigliano G, et al. ASCO 2024

T-DXd vs physician's choice of chemotherapy in pts with HR+/HER2–low or HER2-ultralow MBC with prior endocrine therapy: primary results from DESTINY-Breast06

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=436)

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options: capecitabine, nab-paclitaxel, paclitaxel

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

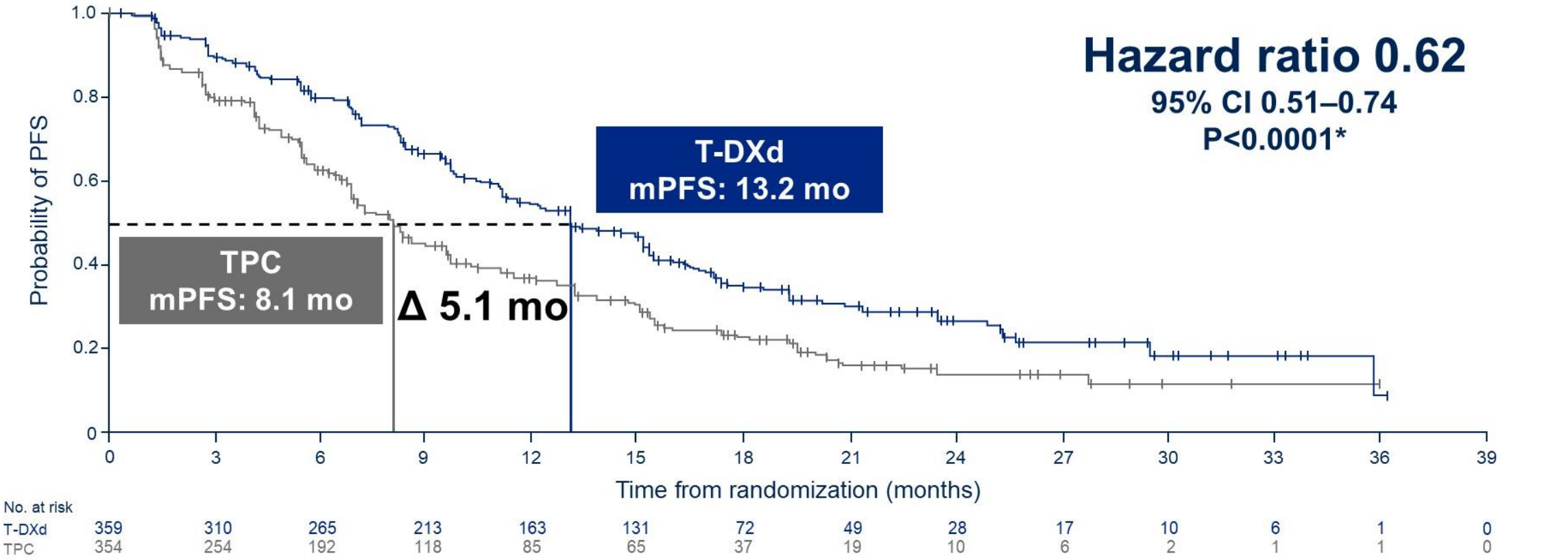
- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

Curigliano G, et al. ASCO 2024

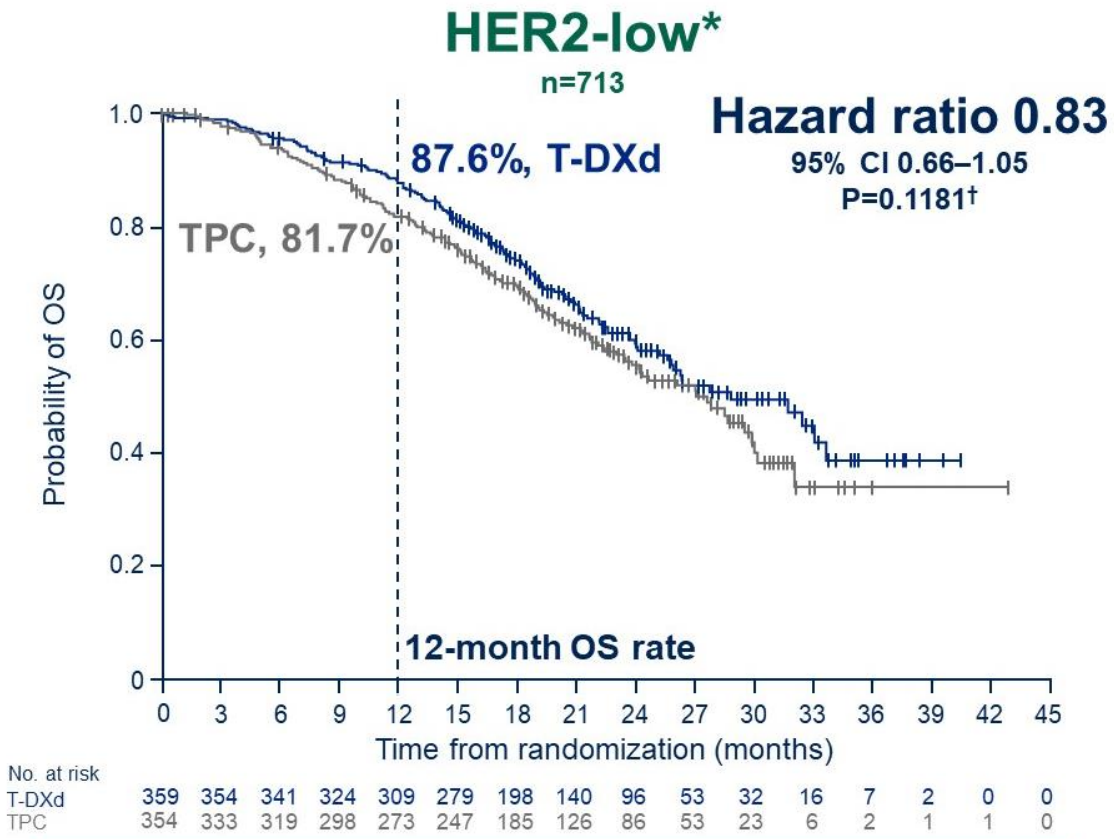
PFS (BICR) in HER2-low: primary endpoint



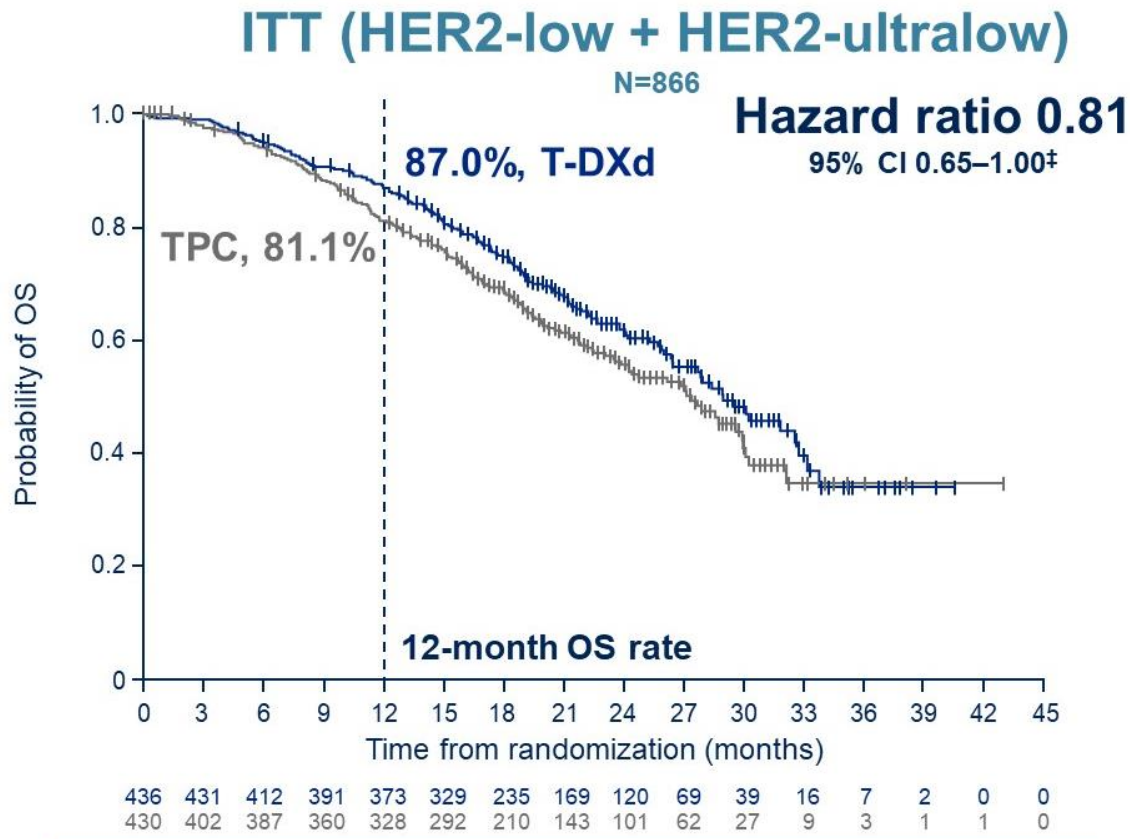
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

Curigliano G, et al. ASCO 2024

OS in HER2-low and ITT: key secondary endpoints (~40% maturity)



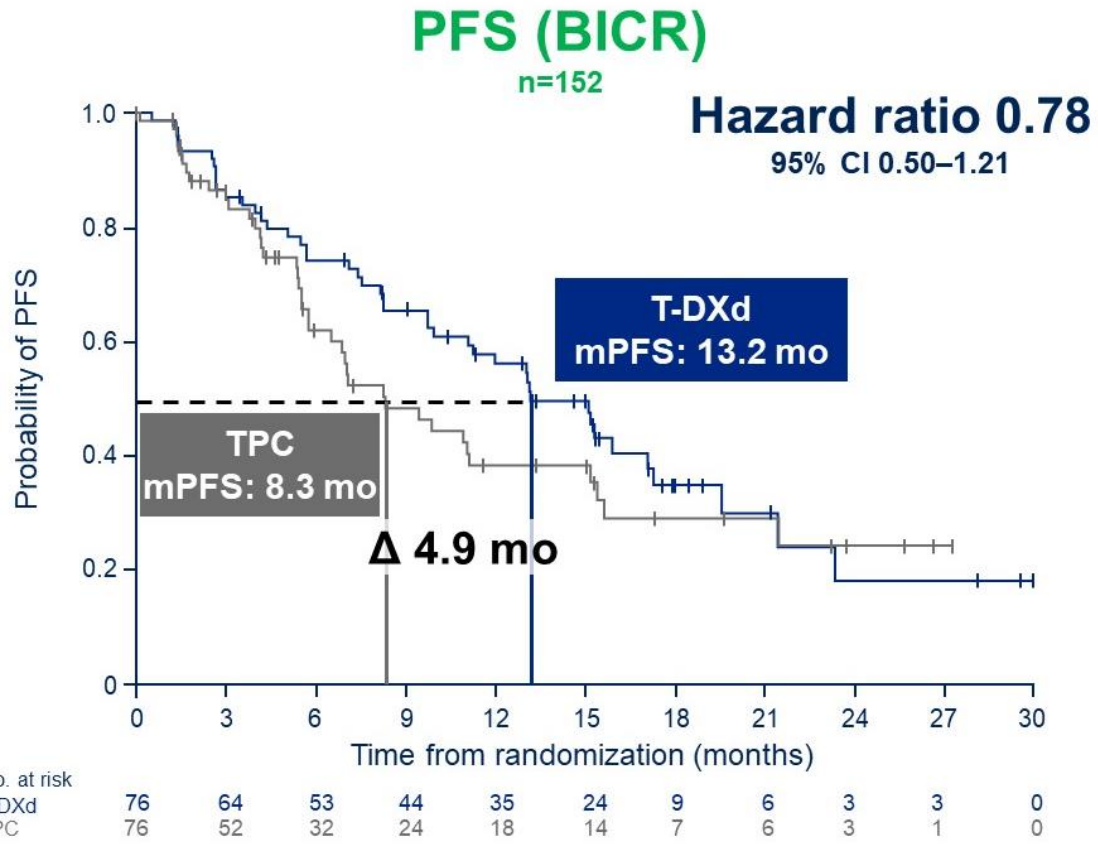
20.1% of patients in the TPC group received T-DXd post treatment discontinuation (HER2-low)

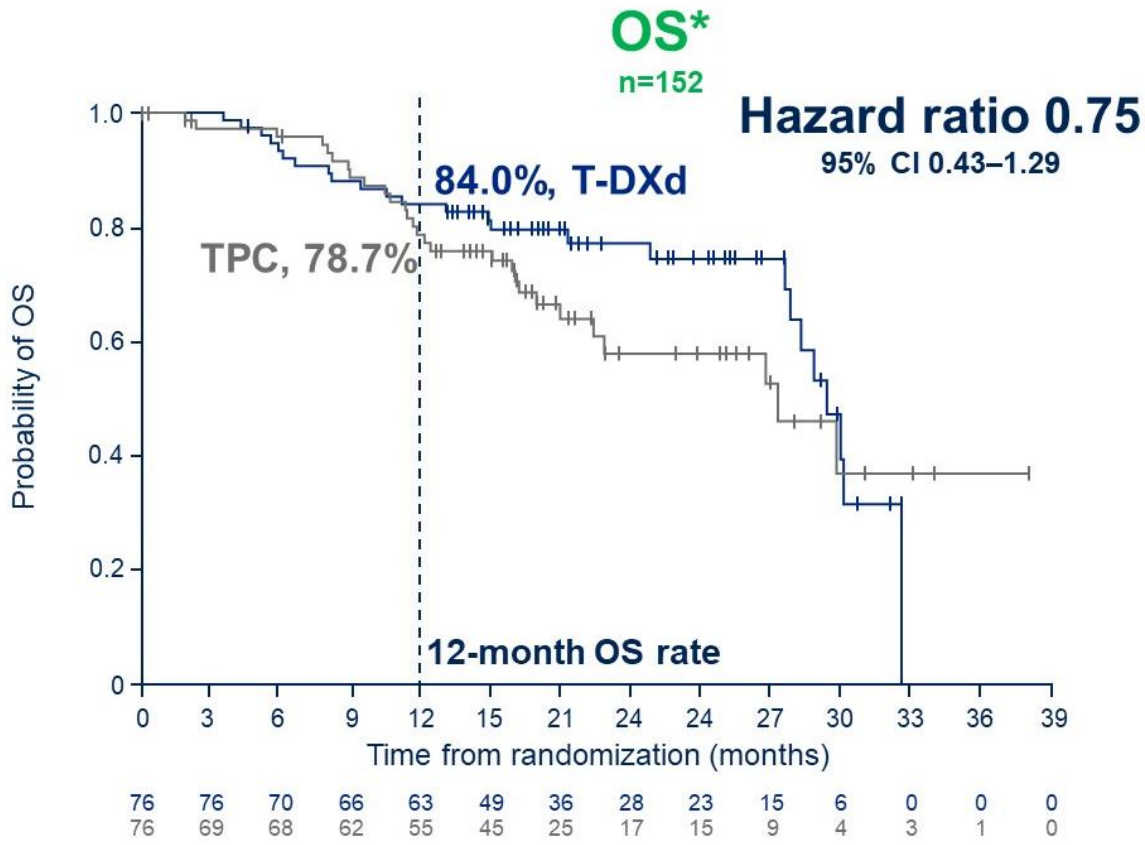


17.9% of patients in the TPC group received T-DXd post treatment discontinuation (ITT)

Curigliano G, et al. ASCO 2024

PFS and OS in HER2-ultralow: prespecified exploratory analyses

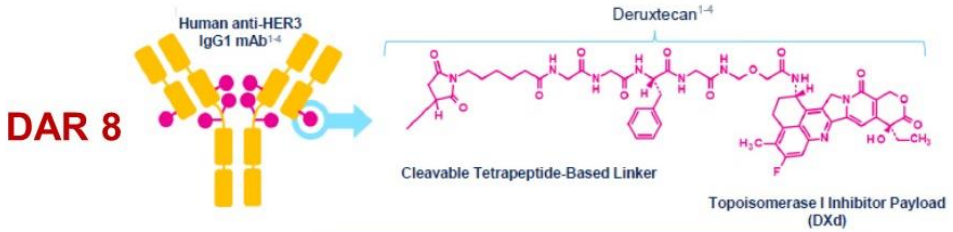


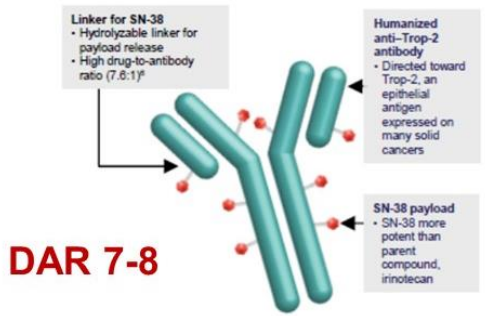


PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

Curigliano G, et al. ASCO 2024

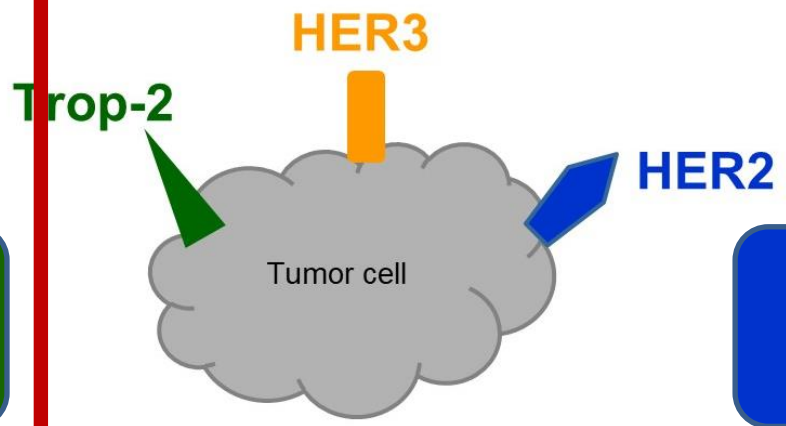
New generations of ADCs in Breast Cancer

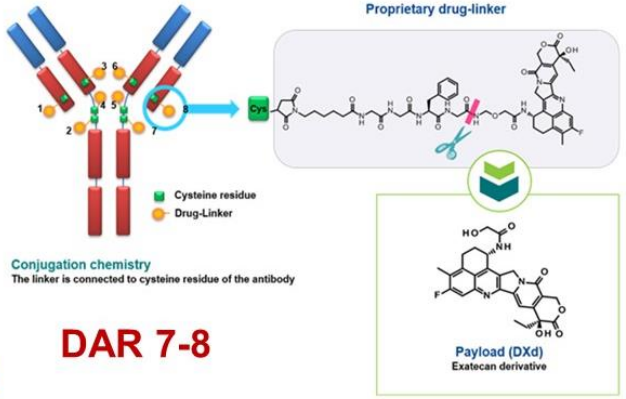




Sacituzumab Govitecan
Datopotamab-DXd

Patritumab Deruxtecan



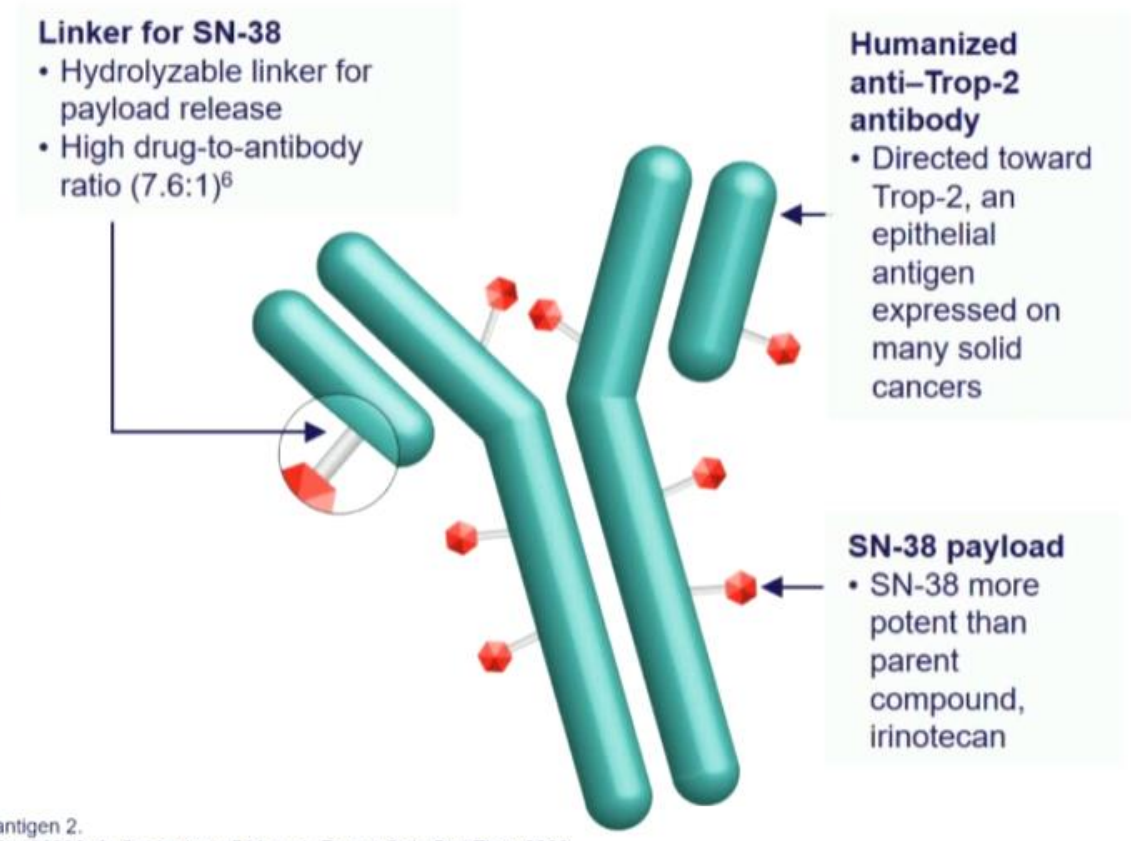


Trastuzumab Deruxtecan

PAYLOAD: Topo-I inhibitor
SN38 and DXd exatecan

Sacituzumab Govitecan is a first-in-class anti-Trop-2 ADC

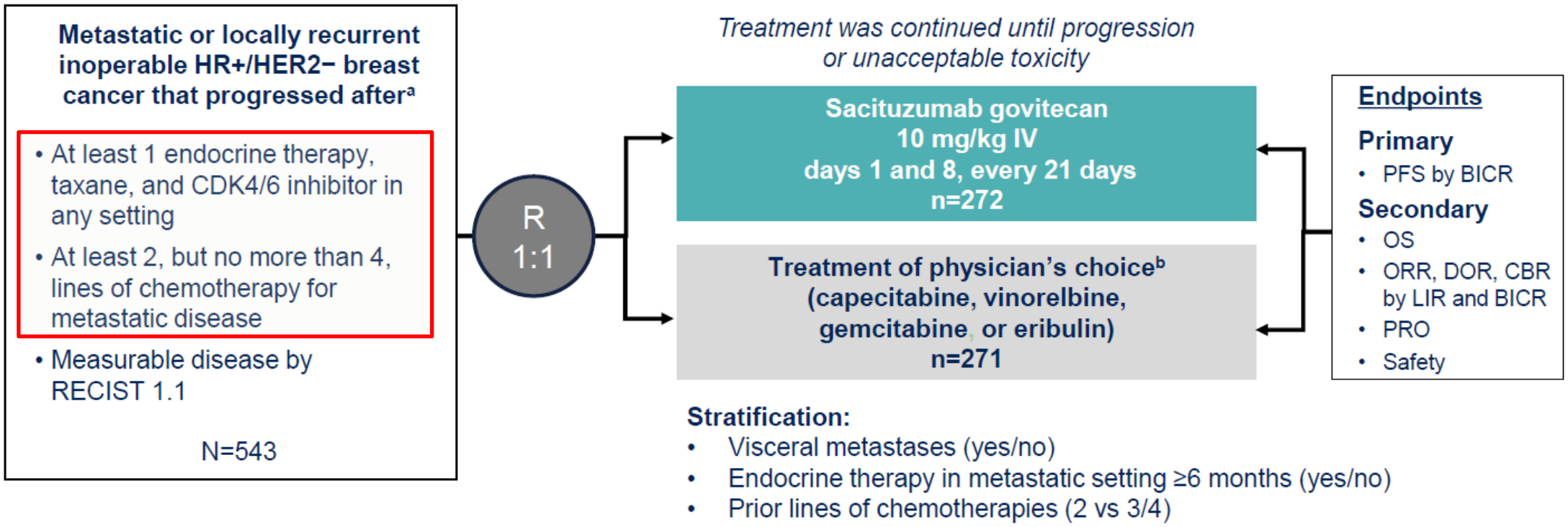
- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and fast-track designation in metastatic urothelial cancer[7]



ADC, antibody–drug conjugate; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Vidula N et al. *J Clin Oncol*. 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One*. 2014;9(5):e96993. 3. Goldenberg DM et al. *Expert Opin Biol Ther*. 2020 Aug;20(8):871-885. 4. Nagayama A et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 5. Cardillo TM et al. *Bioconjugate Chem*. 2015;26:919-931. 6. Goldenberg DM et al. *Oncotarget*. 2015;6:22496-224512. 7. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020.

TROPICS-02: Phase 3 study of SG in HR+/HER2- locally recurrent inoperable or metastatic breast cancer



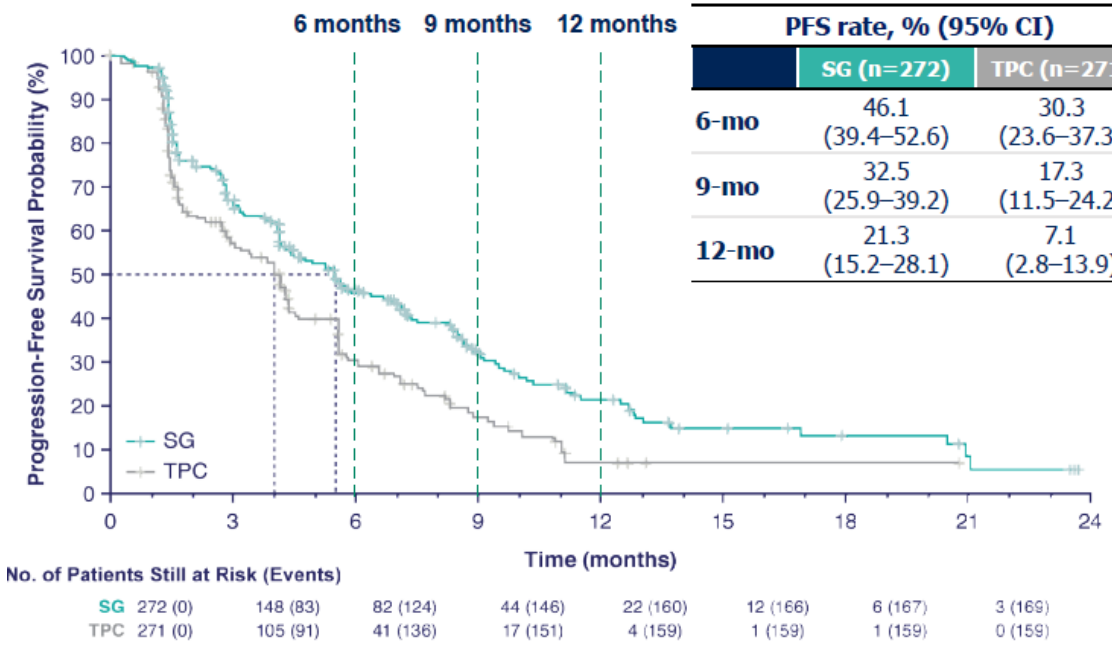
[a]Disease histology based on the ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DOR, duration of response; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IV, intravenously; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

Dieras V, et al. ASCO 2022

TROPICS-02: PFS & OS in the ITT Population

PFS[1]

BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



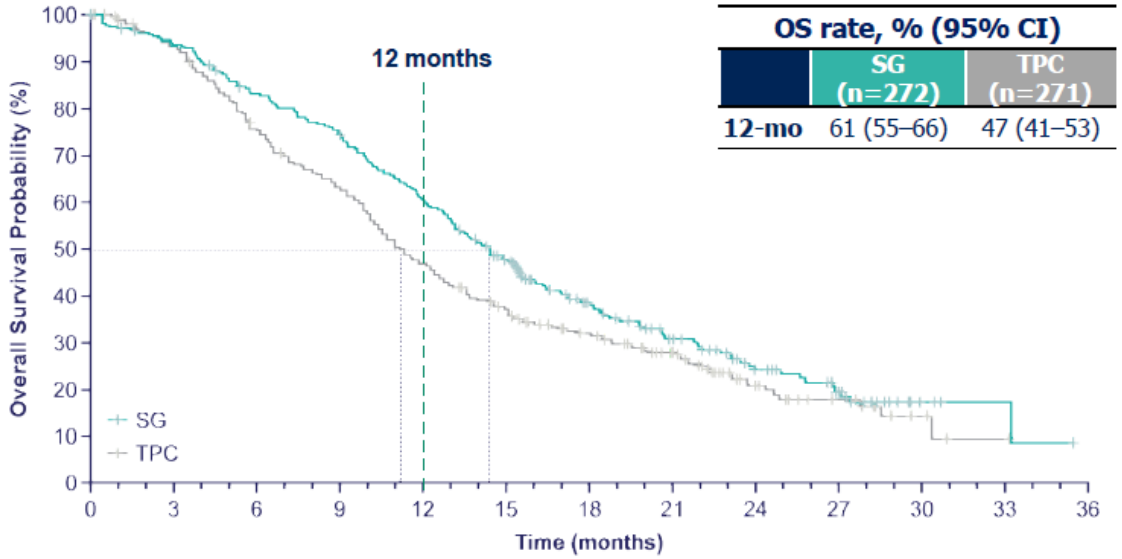
PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

No. of Patients Still at Risk (Events)

SG	272 (0)	148 (83)	82 (124)	44 (146)	22 (160)	12 (166)	6 (167)	3 (169)	0 (170)
TPC	271 (0)	105 (91)	41 (136)	17 (151)	4 (159)	1 (159)	1 (159)	0 (159)	

OS[2]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

No. of Patients Still at Risk (Events)

SG	272 (0)	252 (16)	221 (44)	197 (67)	160 (104)	120 (137)	80 (158)	53 (173)	31 (183)	20 (188)	4 (190)	2 (190)	0 (191)	
TPC	271 (0)	246 (16)	196 (64)	164 (95)	122 (137)	92 (163)	70 (174)	49 (183)	23 (193)	13 (196)	5 (198)	1 (199)	0 (199)	

SG demonstrated a statistically significant improvement in PFS and OS vs TPC

Median follow-up was 10.2 months.

BICR, blinded independent central review; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol. 2022.* doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology. 2. Rugo H, et al. ESMO 2022. Oral LBA76.

TROPION-Breast01: Study Design

Randomised, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

ICC
Q3W as per protocol directions† (eribulin mesylate, vinorelbine, capecitabine, or gemcitabine)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

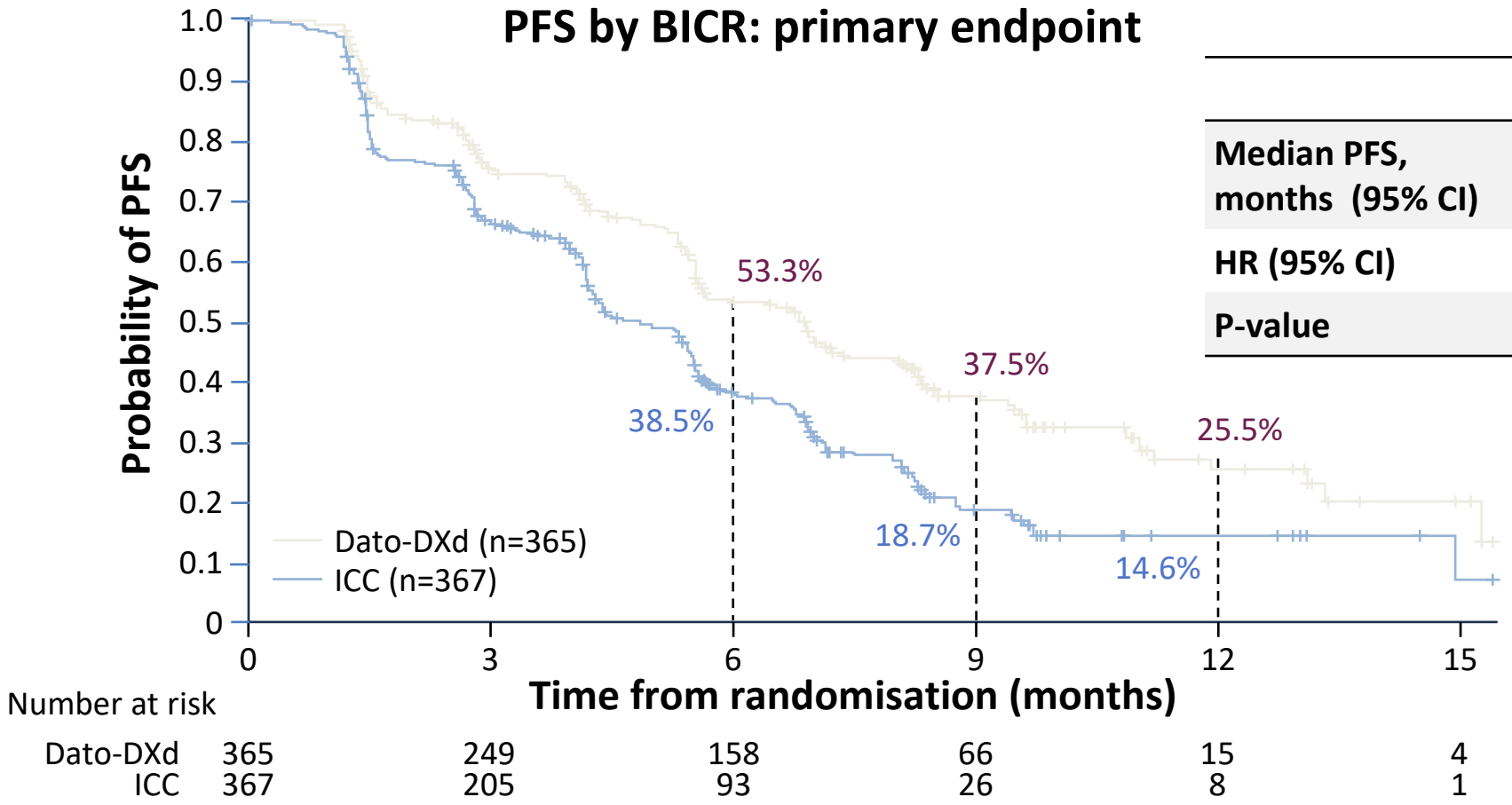
Randomisation stratified by:

- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until investigator-assessed PD (RECIST v1.1), unacceptable tolerability, or other discontinuation criteria
- At this data cut-off, the criteria for performing the primary PFS analysis were met (~419 events)

Bardia A, et al. *Future Oncol* 2023;
doi: 10.2217/fon-2023-0188.

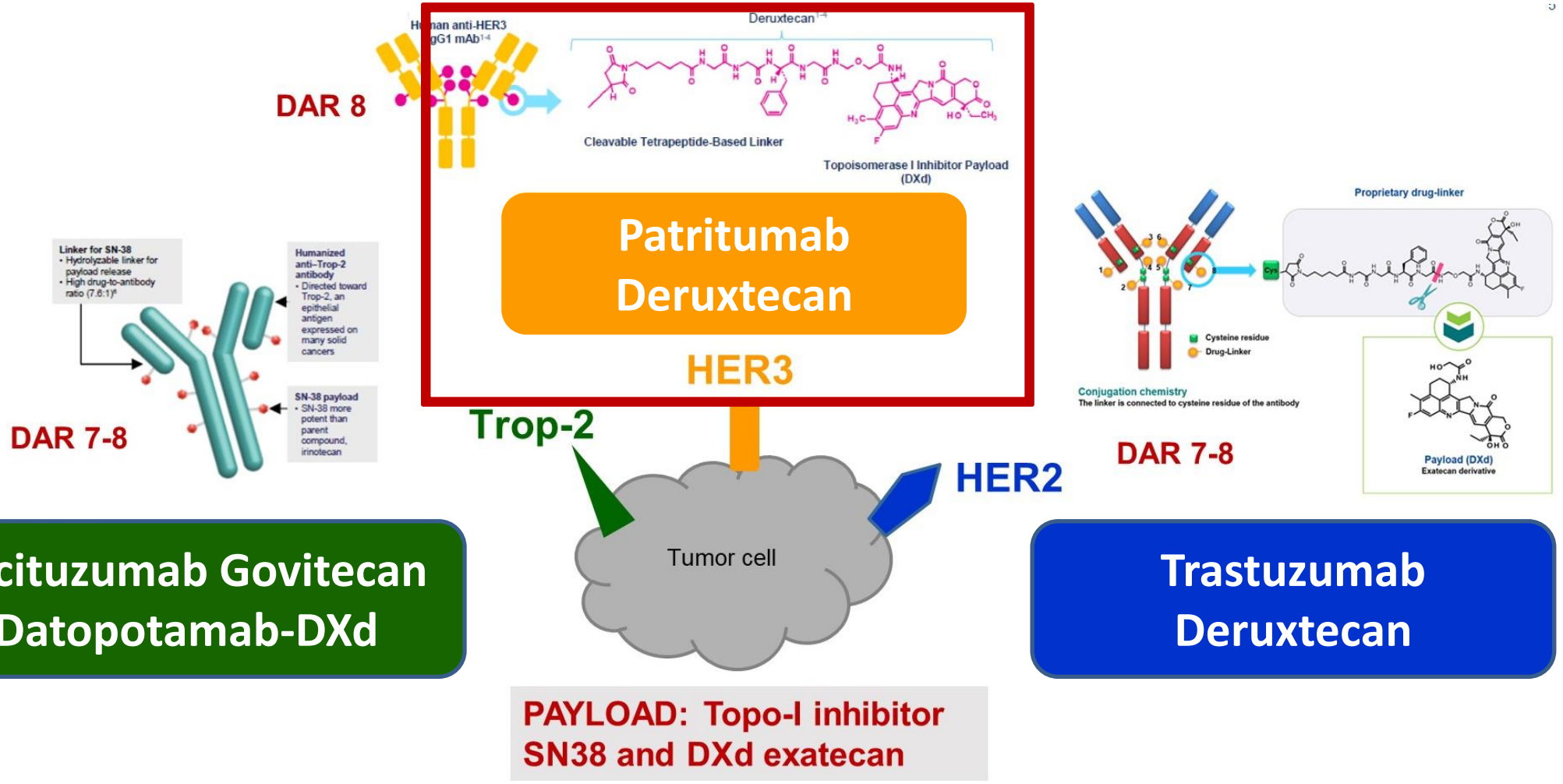
TROPION-Breast01: Progression-Free Survival



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	

CI, confidence interval; HR, hazard ratio

New generations of ADCs in Breast Cancer



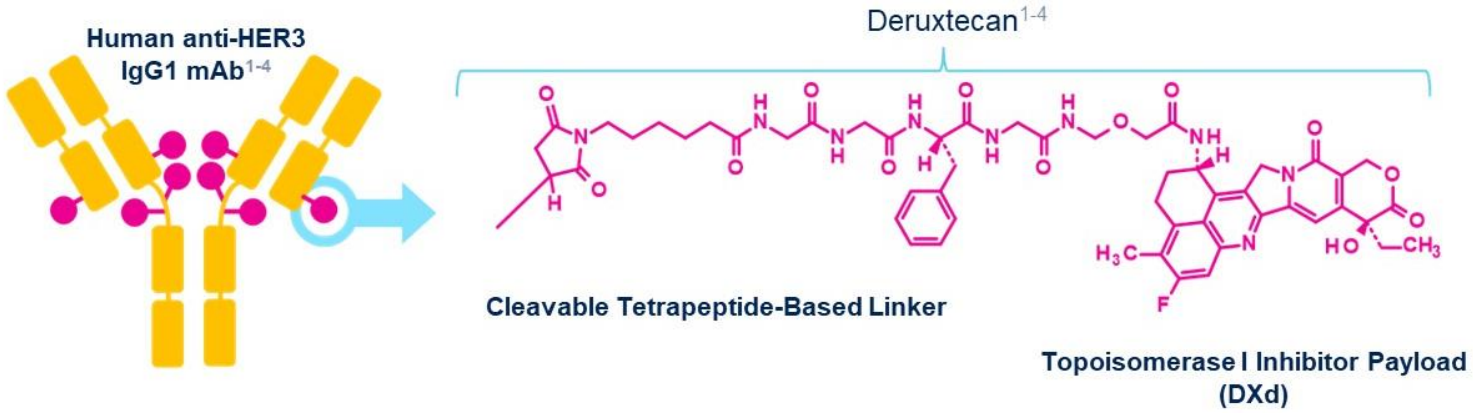
Sacituzumab Govitecan
Datopotamab-DXd

Trastuzumab Deruxtecan

PAYLOAD: Topo-I inhibitor
SN38 and DXd exatecan

Patritumab Deruxtecan (HER3-DXd)

- HER3-DXd is an ADC with 3 components[1-6]:
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker

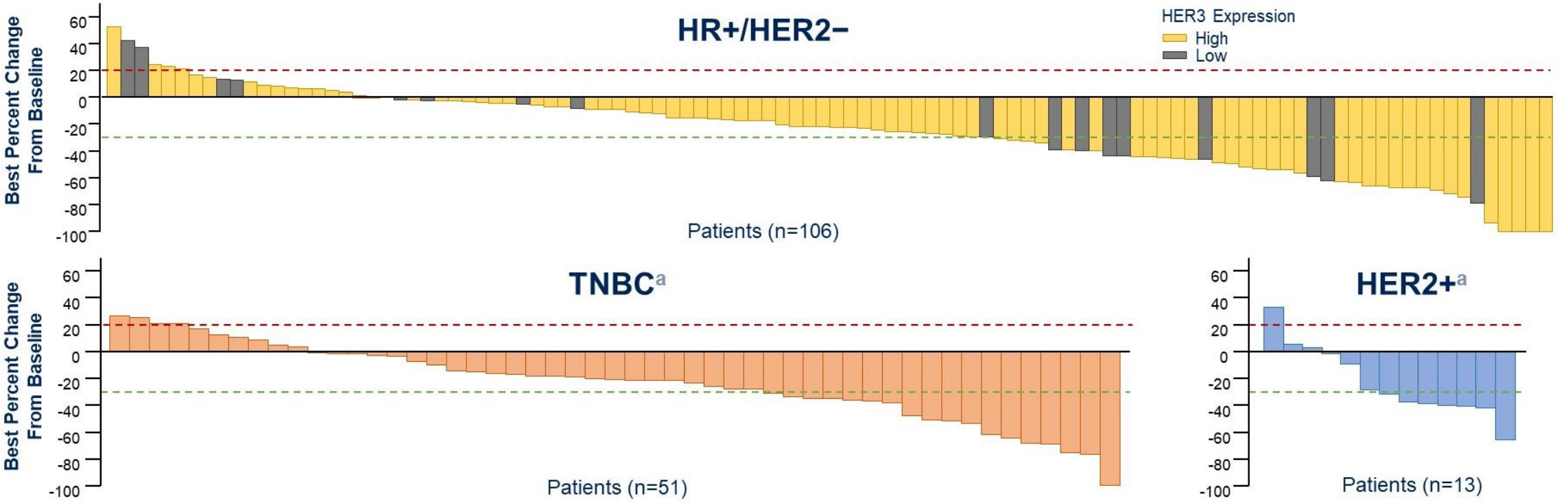


7 Key Attributes of HER3-DXd

Payload mechanism of action: topoisomerase I inhibitor[a,1-4]
High potency of payload[a,1-4]
High drug to antibody ratio ≈ 8[a,1,2]
Payload with short systemic half-life[a,b,2,3]
Stable linker-payload[a,2-4]
Tumor-selective cleavable linker[a,1-5]
Bystander antitumor effect[a,2,6]

Krop IA, et al. ASCO 2022

Change in tumor size from baseline



HER3-DXd induced a clinically meaningful decrease in tumor size by BICR in most patients across BC subtypes.[b]

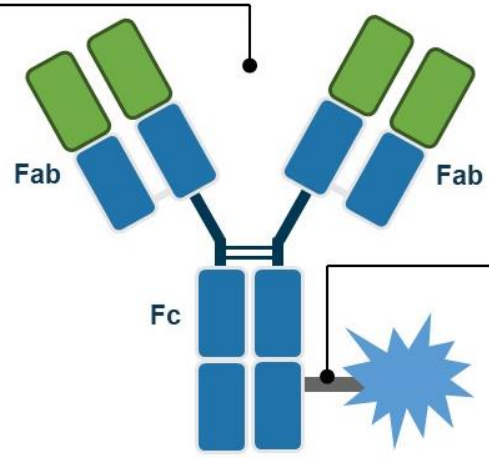
Krop IA, et al. ASCO 2022

What's next for ADCs

Antigen
- High homogeneous expression on tumor
- Low or no expression on healthy tissues
- High affinity and avidity for antibody recognition

Antibody
- High affinity and avidity for tumor antigen
- Chimeric or humanized to decrease immunogenicity
- Long half-life and high molecular weight

Cytotoxic Payload
- Highly potent agents:
  - Calicheamicin
  - Maytansine derivative (DM1 or DM4)
  - Auristatin (MMAE or MMAF)
  - SN-38
  - DXd topoisomerase I inhibitor
- Optimal DAR (range: 2 to 8)

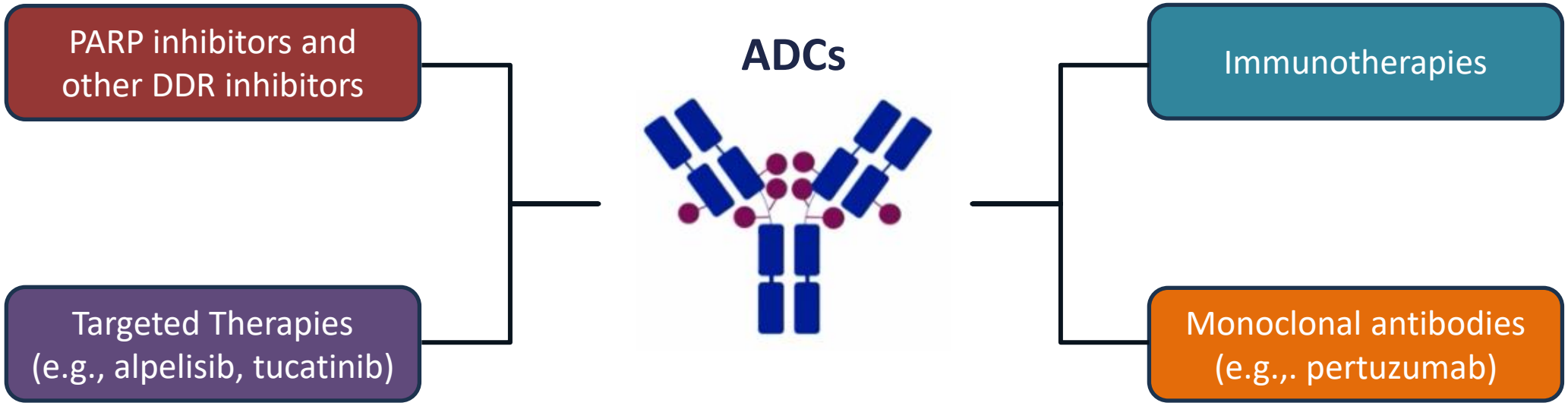


Linker
- Stable in circulation
- Efficient release of payload at target site
- Prevents premature release of payload at nontarget tissue
- Efficient linker technology **(cleavable vs noncleavable)**
- Site of conjugation
- DAR affects drug distribution and pharmacokinetics

Cleavable Linkers
Depend on physiological conditions: pH, proteolysis, or high intracellular glutathione

Noncleavable Linkers
Depend on lysosomal degradation

ADC combinations to prevent/overcome resistance



- Can lead to additive or synergistic antitumor effect
- Can help overcome primary or acquired drug resistance

ADC + other targeted therapy combinations

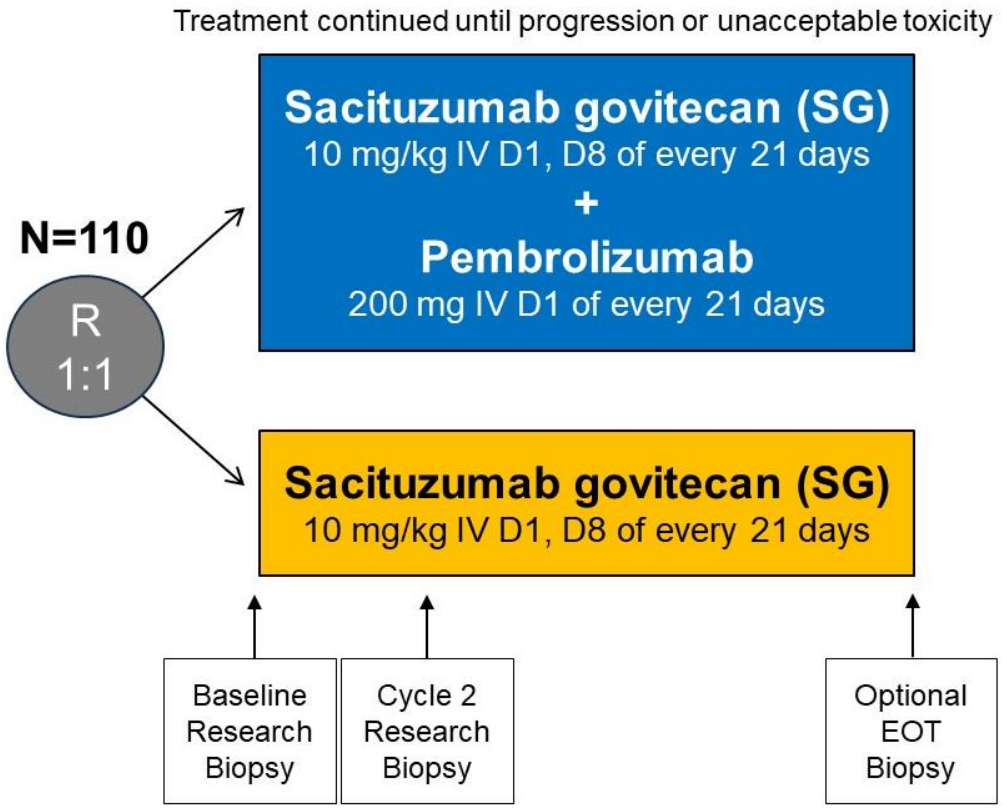
Ongoing trials

ADC	ADC Target	Trial ID (name)	Phase	Combination therapy	Patient population
Trastuzumab deruxtecan (T-DXd)	HER2	NCT04556773 (DESTINY Breast-08)	Ib/II	Capivasertib (Akt inhibitor)	1-2L metastatic HER2-low MBC
				Anastrozole (NSAI)	1-2L metastatic HER2-low MBC
				Fulvestrant (SERD)	1-2L metastatic HER2-low MBC
		NCT04553770 (TALENT)	II	Anastrozole (NSAI)	HR+/HER2-low (neoadjuvant setting)
		NCT04704661 (DASH)	I	AZD6738 (ATR inhibitor)	Advanced solid tumors with HER2 expression
Sacituzumab govitecan (SG)	Trop-2	NCT05143229 (ASSET)	I	Alpelisib (a specific Pi3K inhibitor)	≥2L HER2- MBC
		NCT05006794	I	GS9716 (Mcl-1 antagonist)	Advanced solid tumors including TNBC
Patritumab deruxtecan	HER3	NCT05569811 (VALENTINE)	II	Endocrine therapy	High risk HR+/HER2- BC Neoadjuvant
Enfortumab vedotin (EV)	Nectin 4	NCT04963153	I	Erdafitinib (FGFR inhibitor)	Metastatic urothelial cancer with FGFR2/3 genetic alterations

SACI-IO HR+: A randomized phase II trial of sacituzumab govitecan with or without pembrolizumab in patients with metastatic HR+/ HER2- breast cancer

Metastatic or locally advanced unresectable breast cancer

- HR-positive (ER ≥ 1% or PR ≥ 1%), HER2-negative (IHC 0, 1+, or 2+/ ISH-)
- No restriction on PD-L1 status[a]
- ≥1 endocrine therapy for mBC or progression on or within 12 months of adjuvant endocrine therapy
- 0-1 prior chemotherapy for mBC
- No prior topoisomerase I-inhibitor ADC, irinotecan, or PD-1/-L1 inhibitor
- No known active brain metastases or leptomeningeal disease



Endpoints

Primary:
- PFS (ITT)

Secondary:
- PFS (PD-L1+)[b]
- OS (ITT, PD-L1+)
- ORR, DOR, TTOR, CBR (ITT, PD-L1+)
- Safety

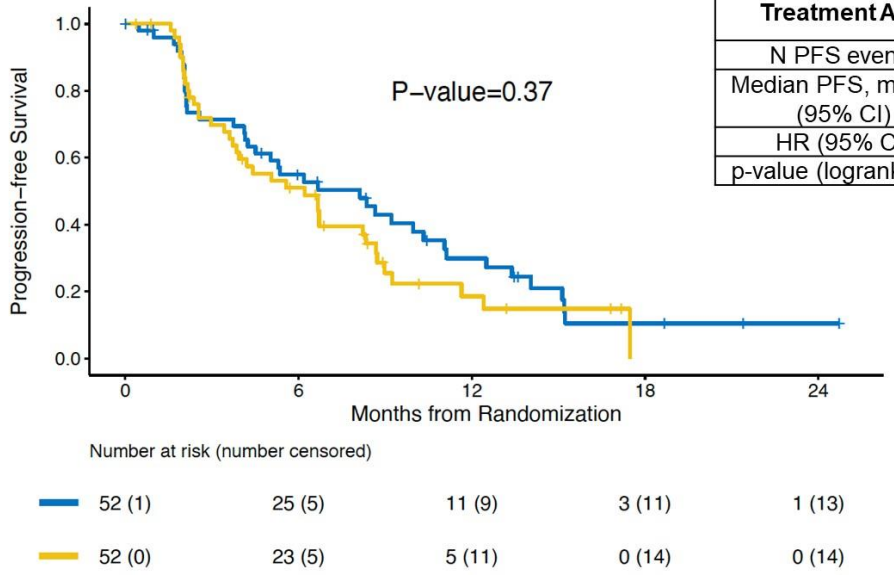
Exploratory:
- Correlative
- HRQoL

NCT04448886

Garrido-Castro AC, et al, ASCO 2024

SACI-IO HR+: Survival Outcomes

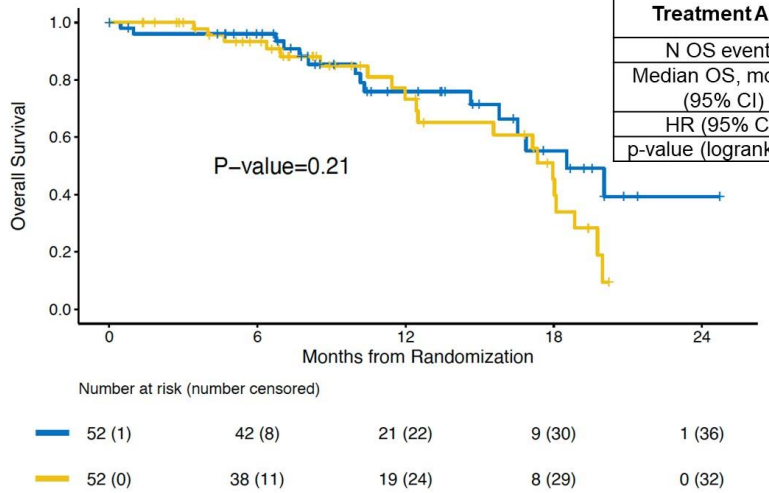
Progression-Free Survival



Treatment Arm	SG + Pembrolizumab (N=52)	SG (N=52)
N PFS events	38	38
Median PFS, months (95% CI)	**8.12** (4.51-11.12)	**6.22** (3.85-8.68)
HR (95% CI)	**0.81** (0.51-1.28)	
p-value (logrank test)	0.37	

The addition of pembrolizumab to SG showed a numerical improvement in r
compared to SG alone that did not reach statistical sign

Overall Survival

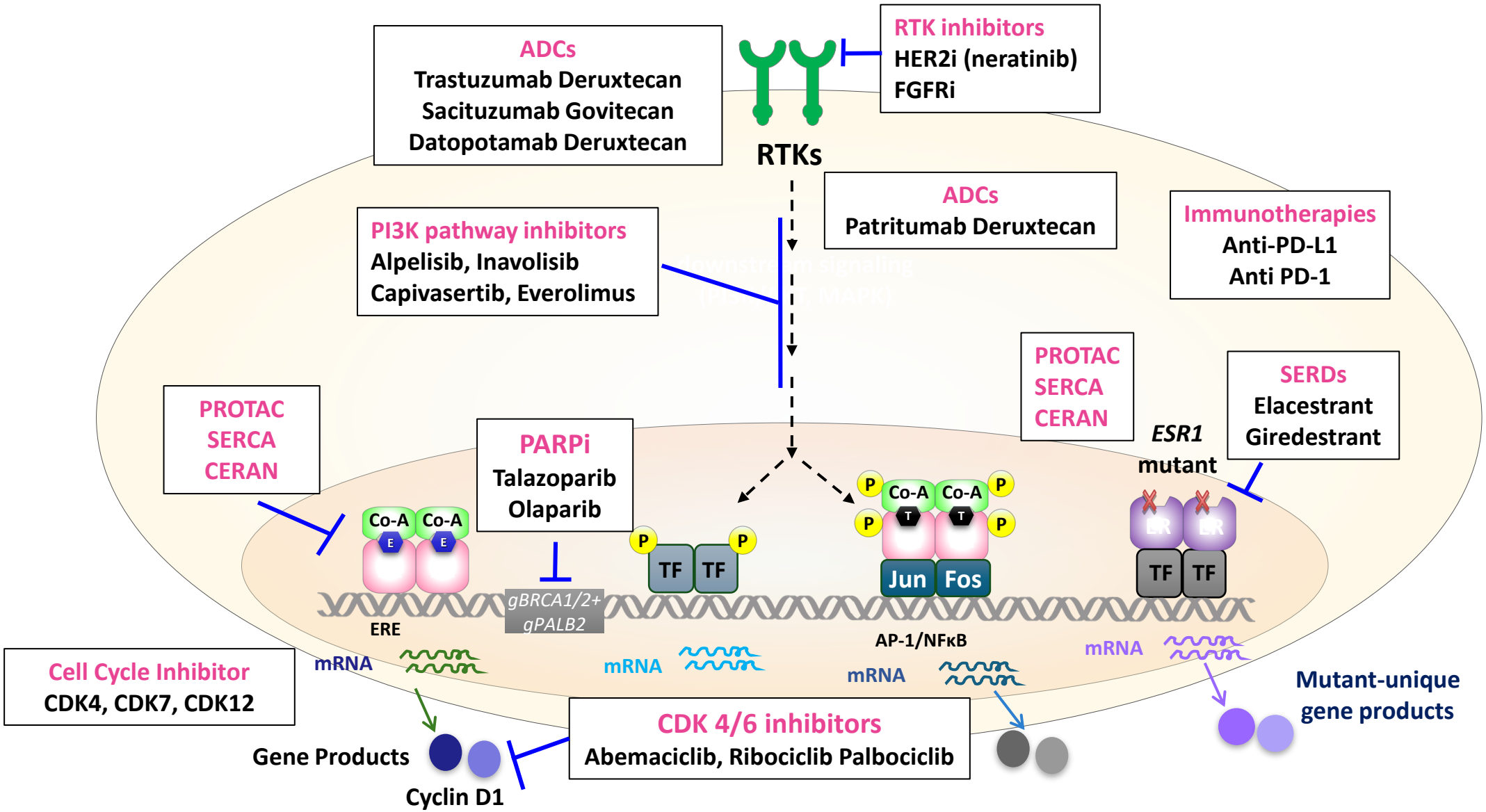


Treatment Arm	SG + Pembrolizumab (N=52)	SG (N=52)
N OS events	15	20
Median OS, months (95% CI)	**18.52** (16.55-NA)	**17.96** (12.50-NA)
HR (95% CI)	**0.65** (0.33-1.28)	
p-value (logrank test)	0.21	

At a median follow-up of 12.5 months, no significant difference in OS was observed with SG plus pembrolizumab compared to SG alone

Garrido-Castro AC, et al, ASCO 2024

The evolving therapeutic landscape for ER+/HER2- BC



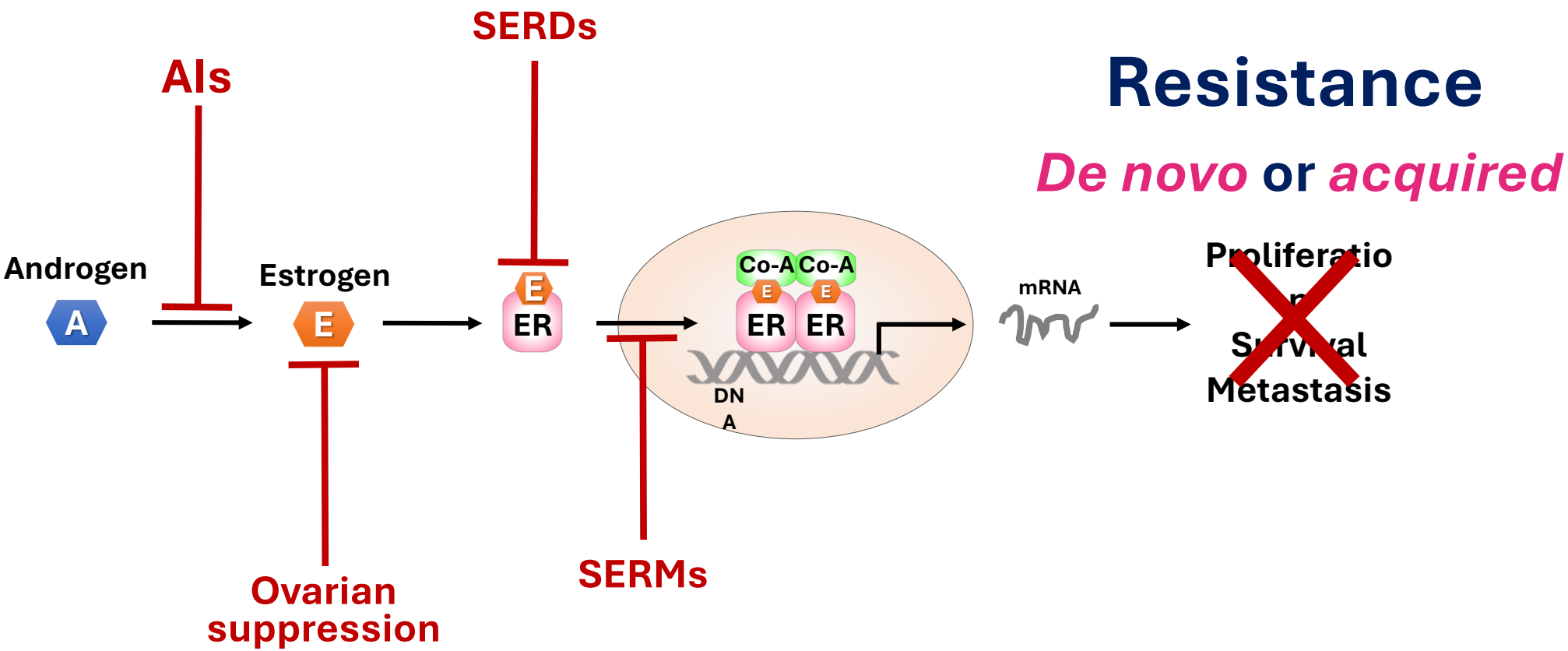
thank you

Grazia Arpino, MD, PhD

UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

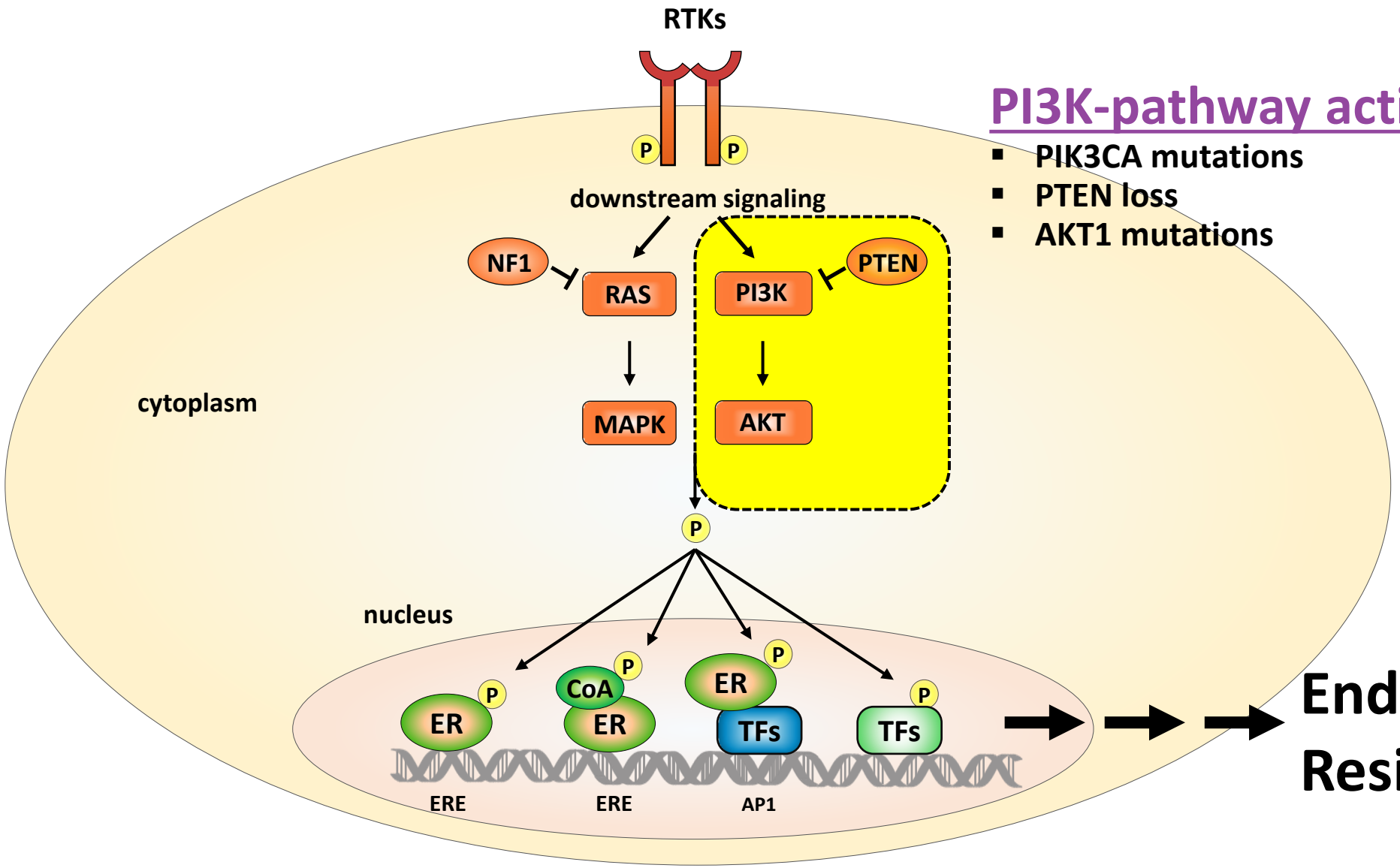
grazia.arpino@unina.it

Endocrine Therapies: Mechanisms of Action



AIs, aromatase inhibitors; SERDs, selective estrogen down-regulators; SERMs, selective estrogen modulators

Intracellular signaling cascade



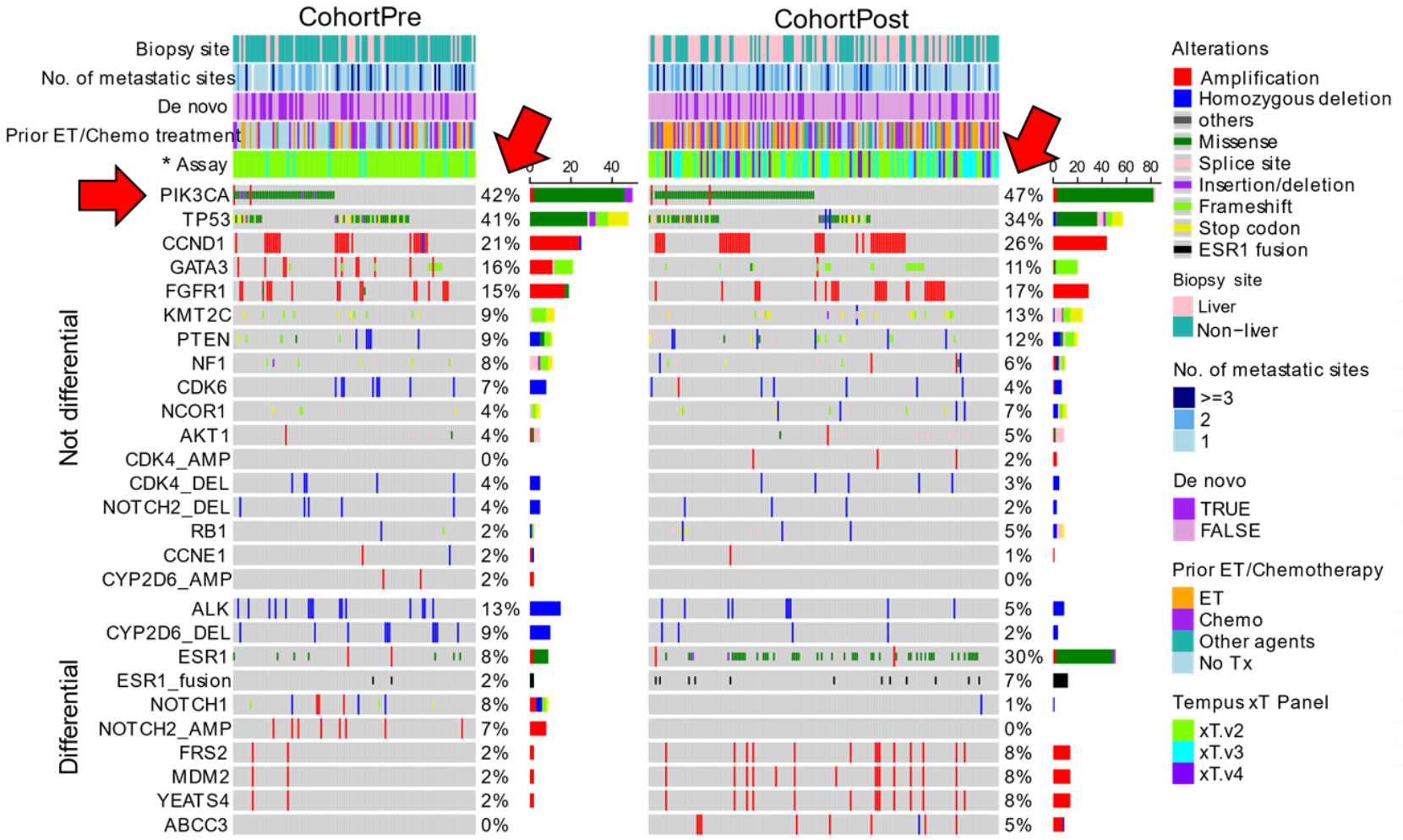
PI3K-pathway activation

- PIK3CA mutations
- PTEN loss
- AKT1 mutations

Endocrine Resistance

OncoPrint of Genomic Alterations pre- and post-CDK4/6 inhibitors

- Overall, there were 10 significant (FDR < 0.2) genomic alteration frequency differences between CohortPre vs. CohortPost (Fig 4):
  - ALK; 13% vs 5%
  - NOTCH2 AMP;7% vs 0%
  - CYP2D6 DEL; 9% vs 2%
  - ESR1; 8% vs 30%
  - ESR1 Fusion; 2% vs 7%
  - NOTCH1; 8% vs 1%
  - FRS2; 2% vs 8%
  - MDM2; 2% vs 8%
  - YEATS4; 2% vs 8%
  - ABCC3; 0% vs 5%

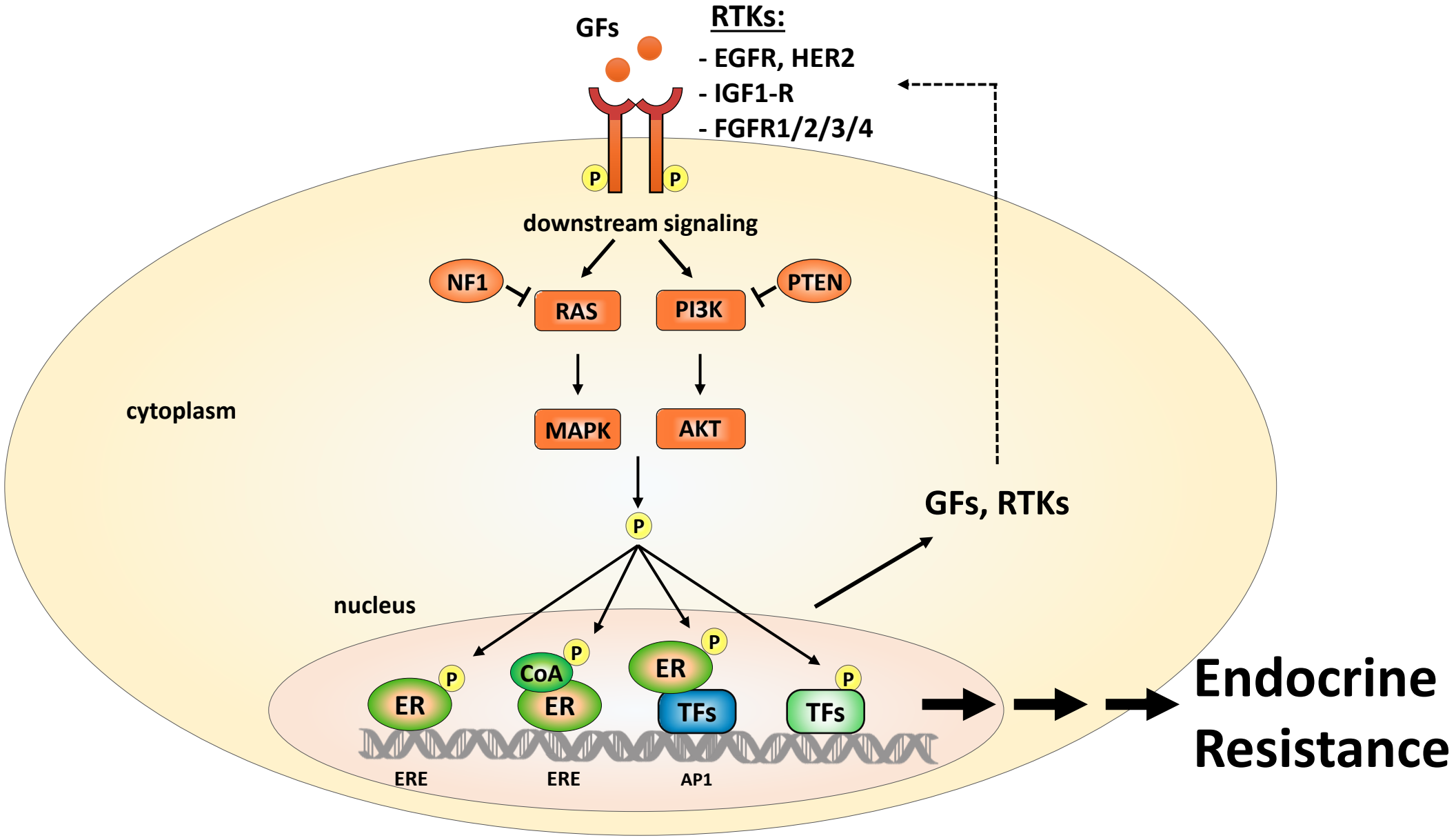


Genes: ALK, Anaplastic Lymphoma Kinase; NOTCH, Notch Receptor; CYP2D6, Cytochrome P450 2D6; ESR1, Estrogen Receptor 1; FRS2, Fibroblast Growth Factor Receptor Substrate 2; MDM2, Mouse Double Minute 2; YEATS4,YEATS domain containing 4; ABCC3, ATP-binding cassette, subfamily C member 3.

*variable for de novo status yields 1 less patient vs stage IV variable as outlined in patient characteristics

André F et al, ASCO 2021

ER Signaling and GFR Crosstalk

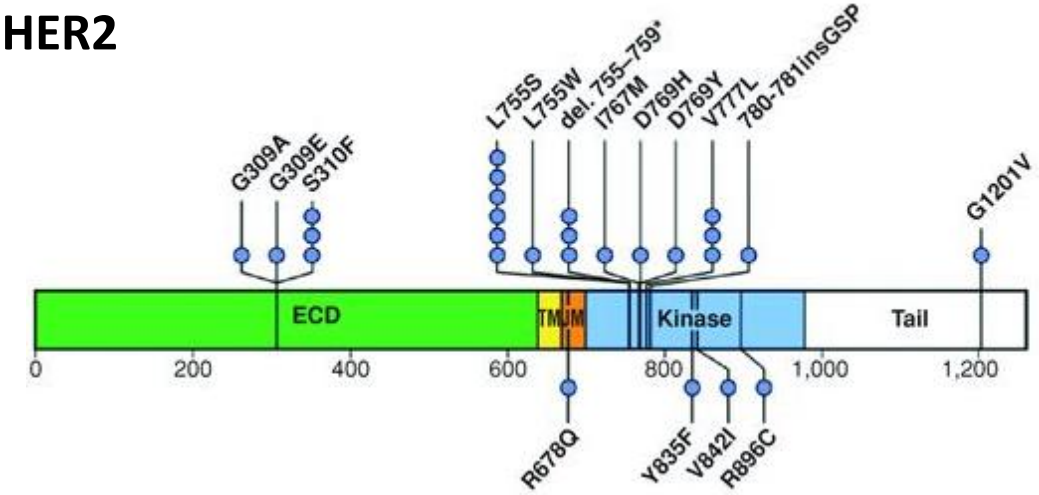


HER2 mutations

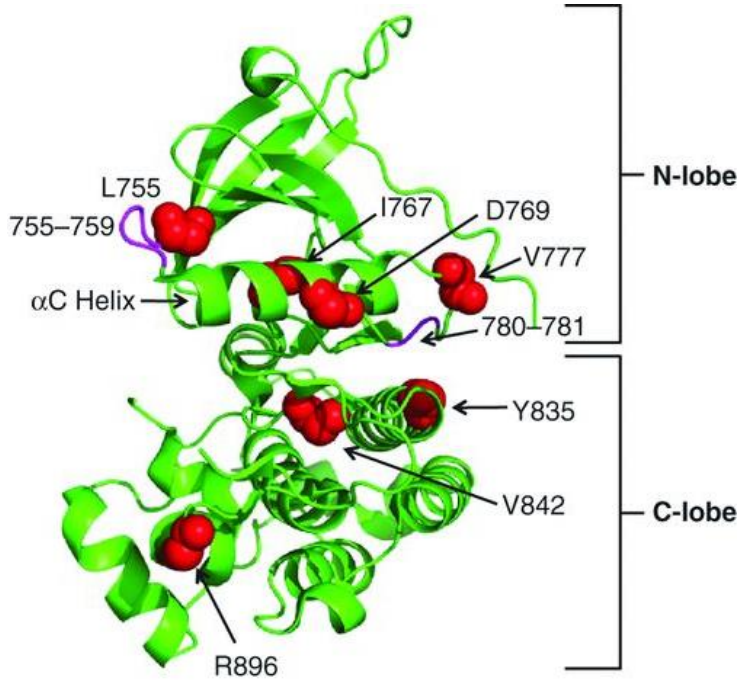
MSKCC, Nat Med 2017

Metastatic BC	ERBB2 non-Amplified (n=640)
putative driver	24 (4%)
putative passenger	7 (1%)
Primary BC	**ERBB2 non-Amplified (n=382)**
putative driver	9 (2%)
putative passenger	0 (0%)

HER2

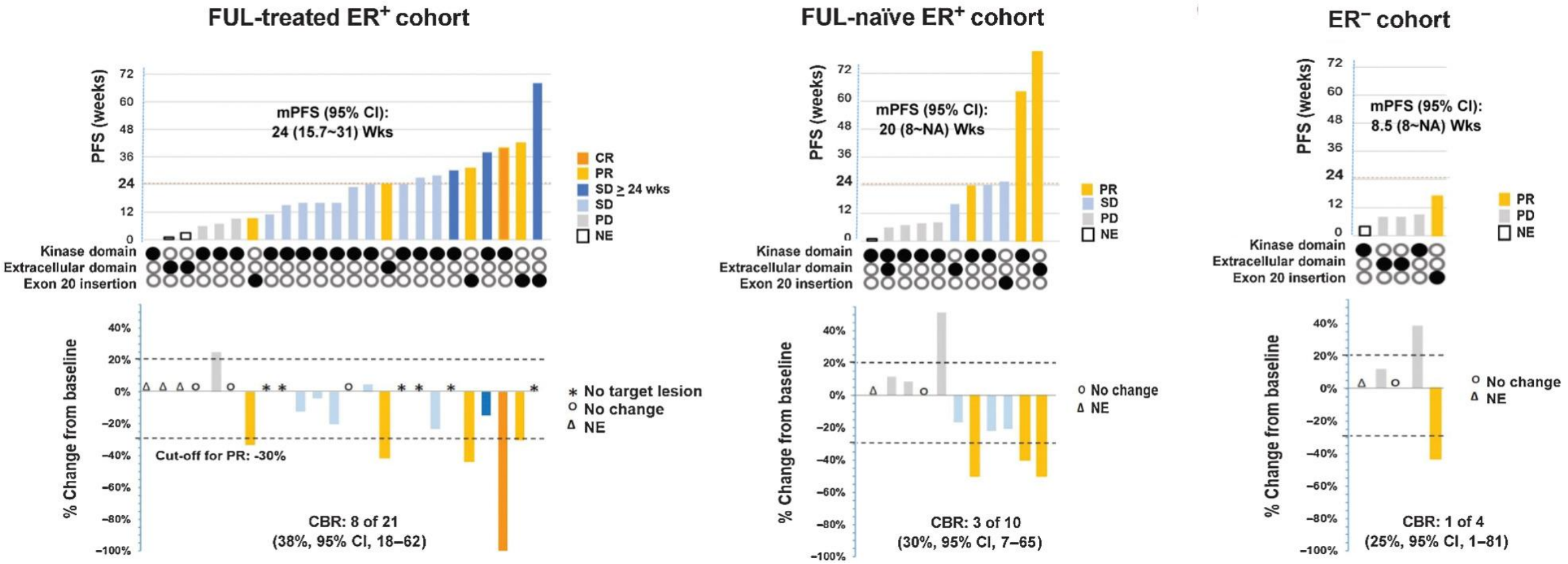


Protein structure visualization of the HER2 somatic mutations



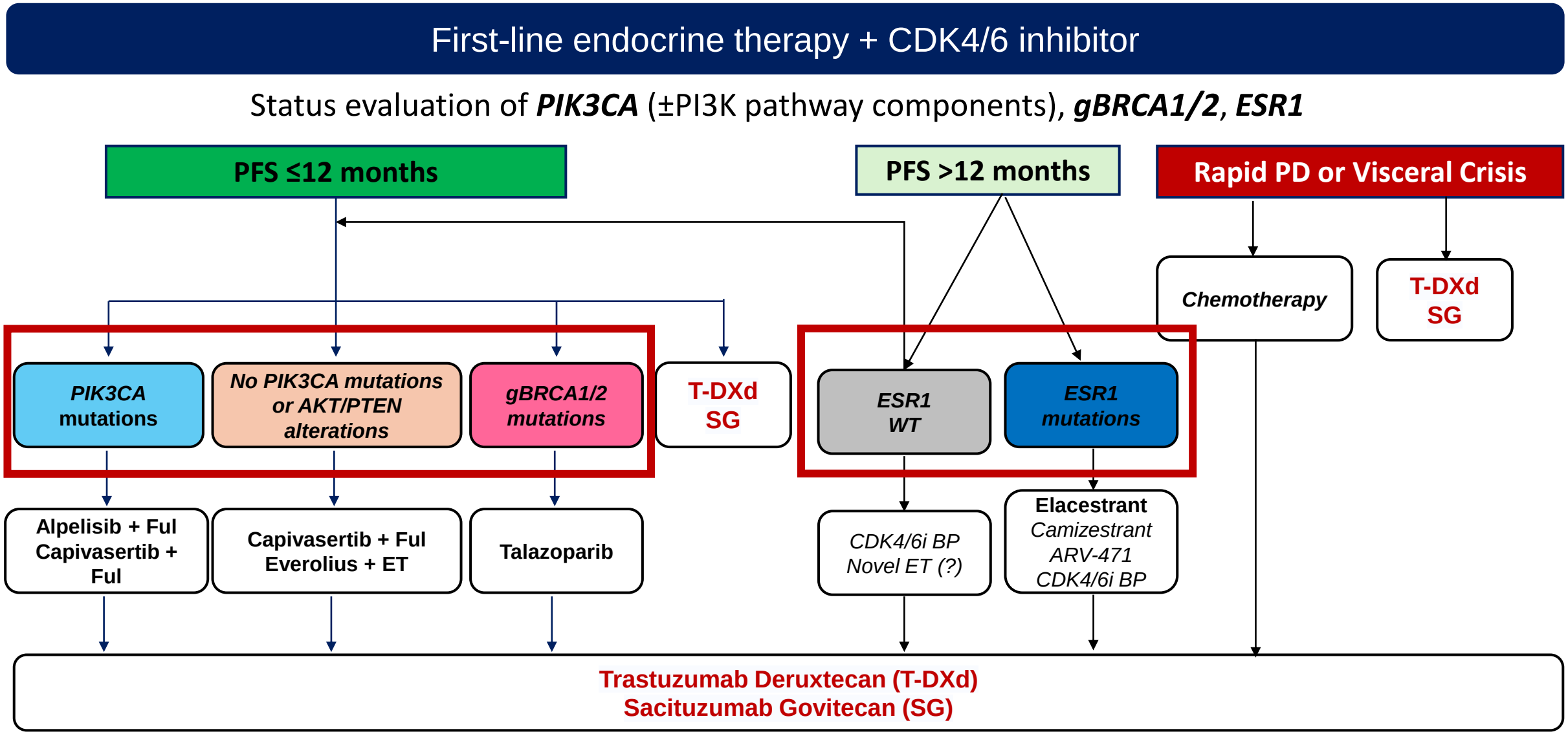
Constitutively HER2 activation

The Phase II MutHER Study of Neratinib ± Fulvestrant in HER2-Mutated, Non-amplified Metastatic Breast Cancer

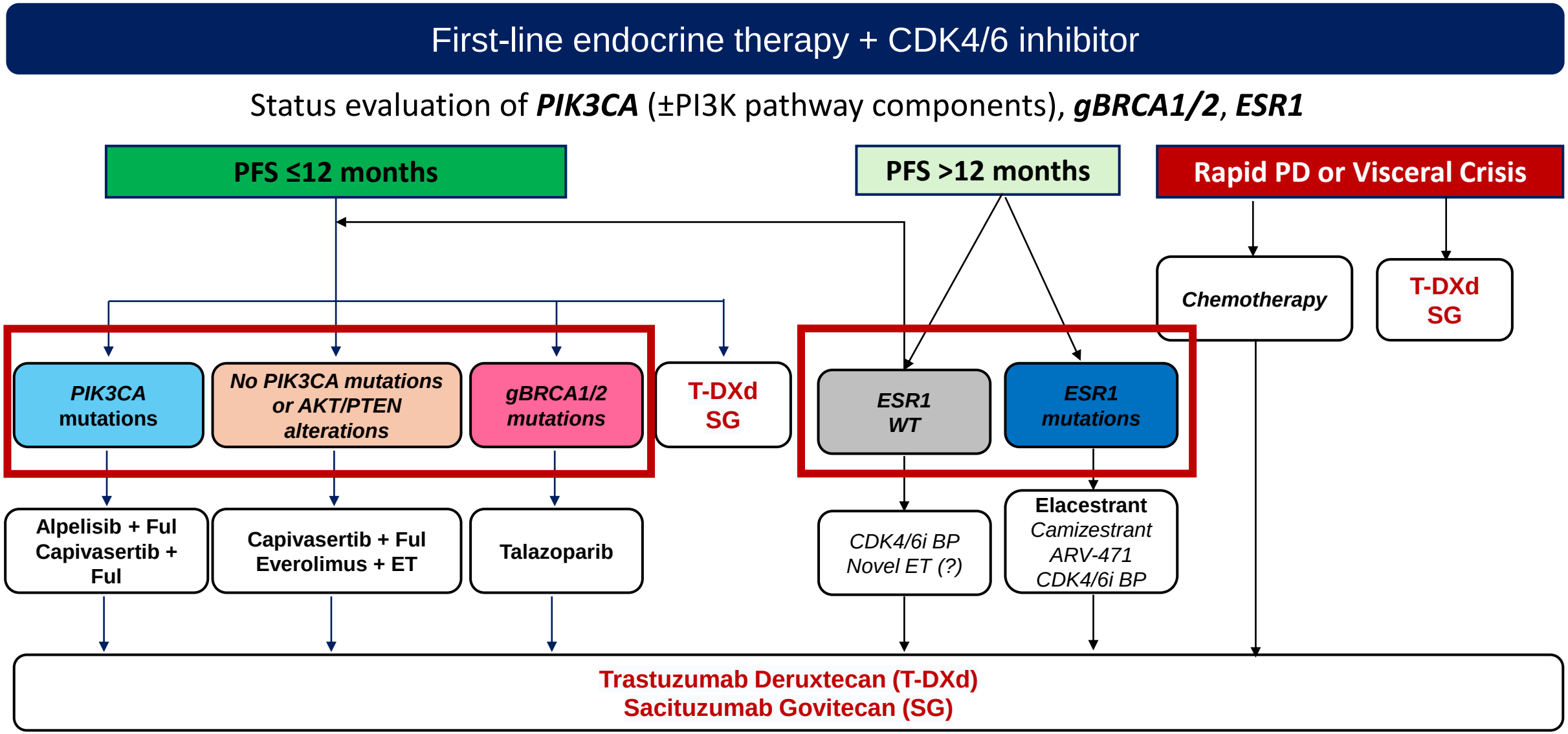


Ma CX et al., Clin Cancer Res, 2022

HR+/HER2- Proposed Algorithm

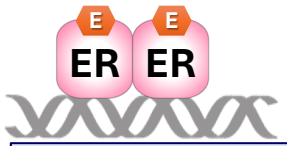


HR+/HER2- Proposed Algorithm



Navigating the post-CDK4/6i treatment landscape
How?

Different scenarios of Endocrine Resistance



ER+ MBC

ER- MBC

More biomarkers for patient selection are needed!!!

(OMICs, tumor tissue & liquid biopsy, dynamic pattern)

- **ER is a target**

(SERD, SERCA, SERMs, CERAN, PROTAC)

- **ER is still a target**

(SERD, SERCA, SERMs, CERAN, PROTAC)

+

- **GFR/DS inhibitors**

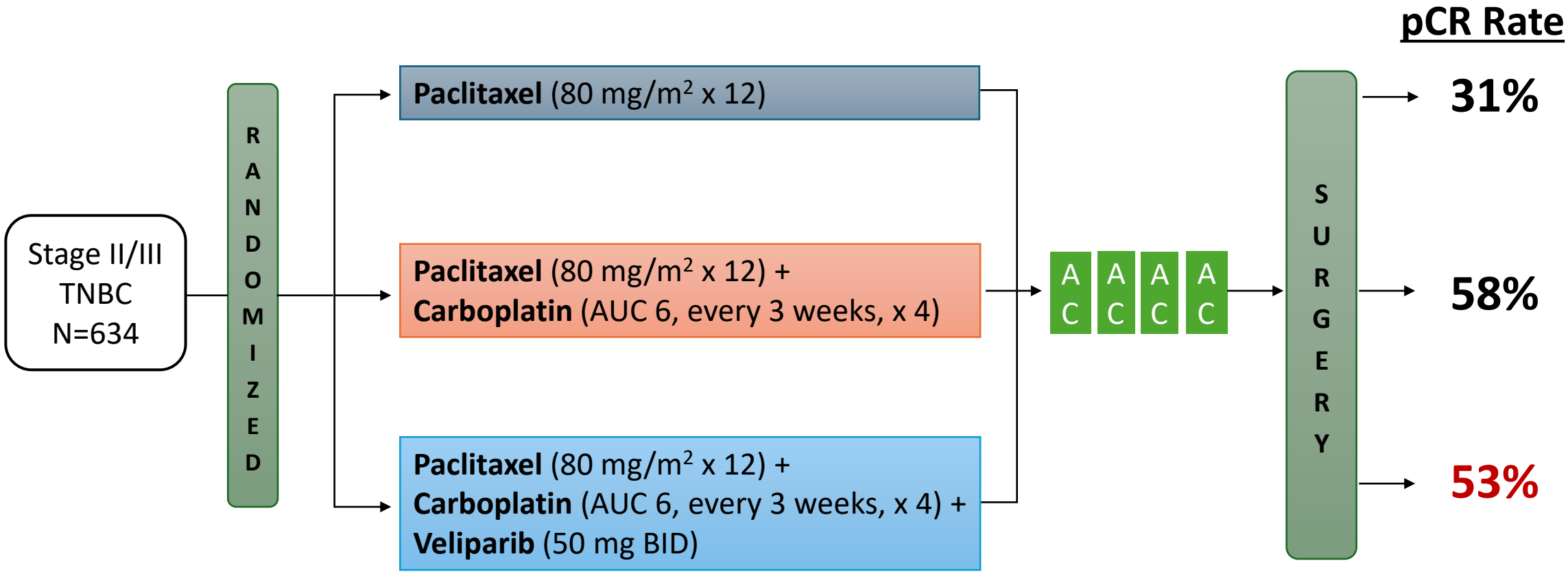
(PI3K, AKT, mTOR, HER2, FGFR1)

- **DDR, IO, …**

- **ER is NOT a target**

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

BrighTNess: Addition of carboplatin ± veliparib to standard neoadjuvant chemotherapy in TNBC

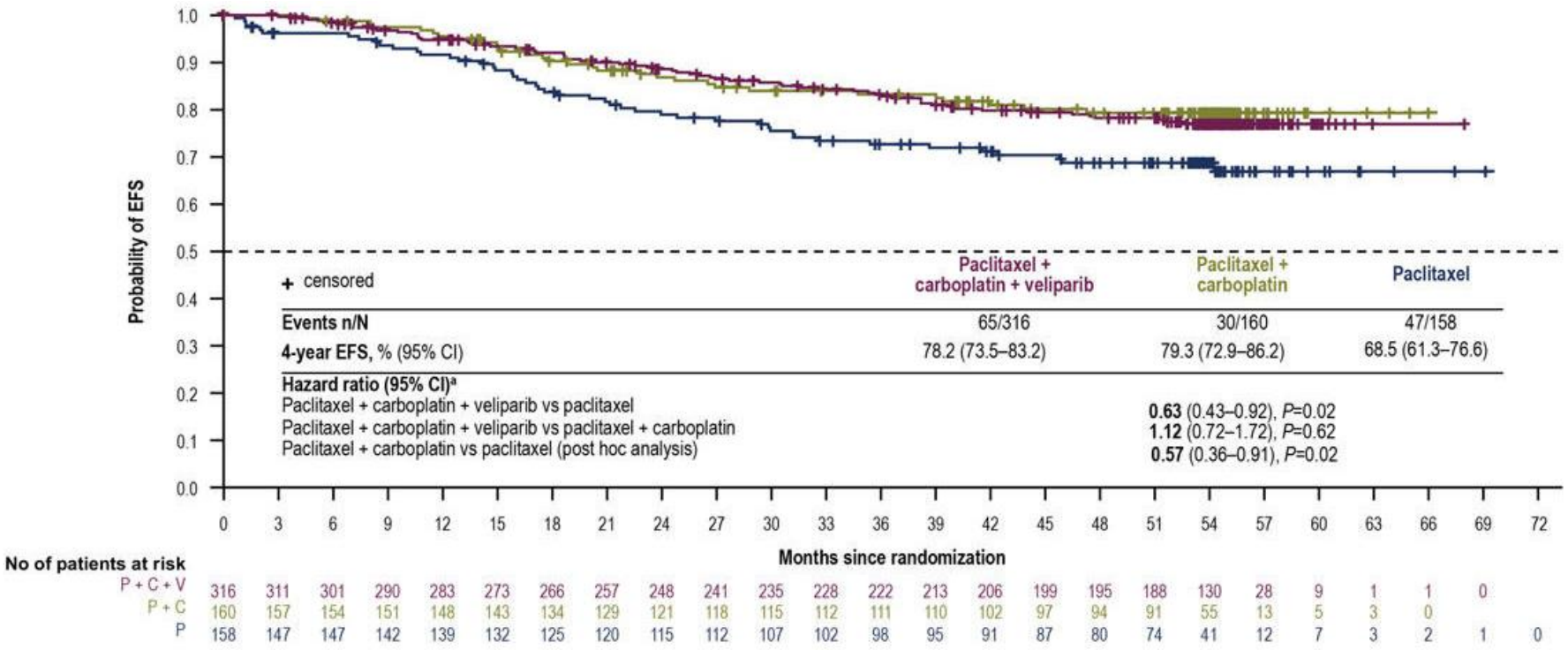


- 93 patients (15%) gBRCA+; no difference due to BRCA status

Loibl S et al., Lancet Oncol 2018

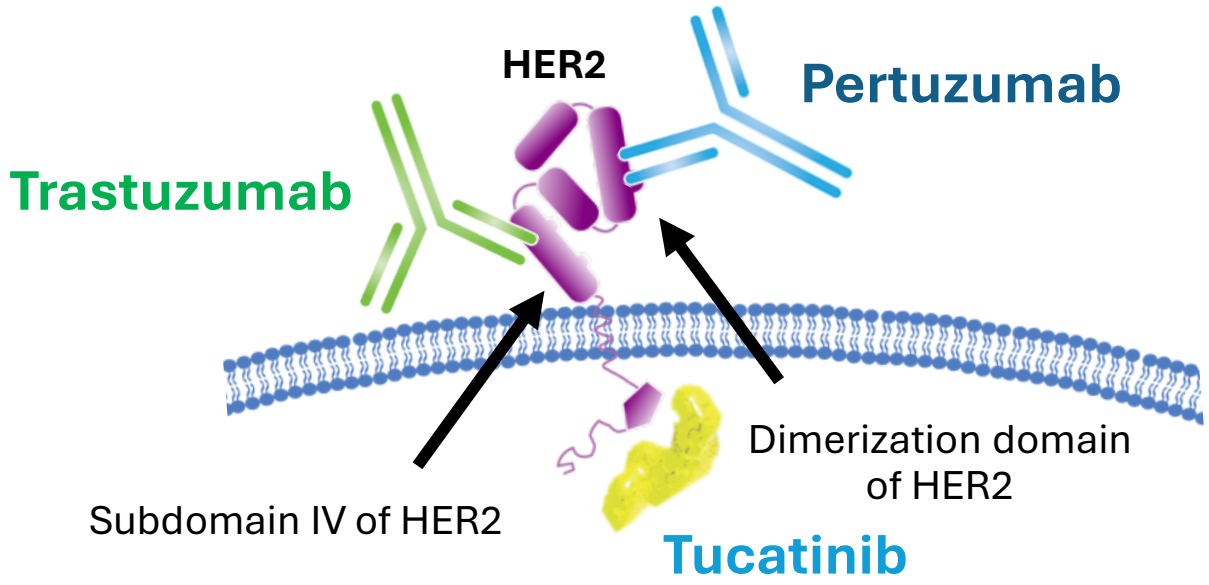
BrighTNess: The addition of carboplatin to standard neoadjuvant chemotherapy improves EFS in TNBC

Median *follow-up* of 4.5 years



Loibl S et al., Lancet Oncol 2018, ESMO 2021

Adding Tucatinib to Trastuzumab and Pertuzumab enhance HER2 blockade and antitumor activity



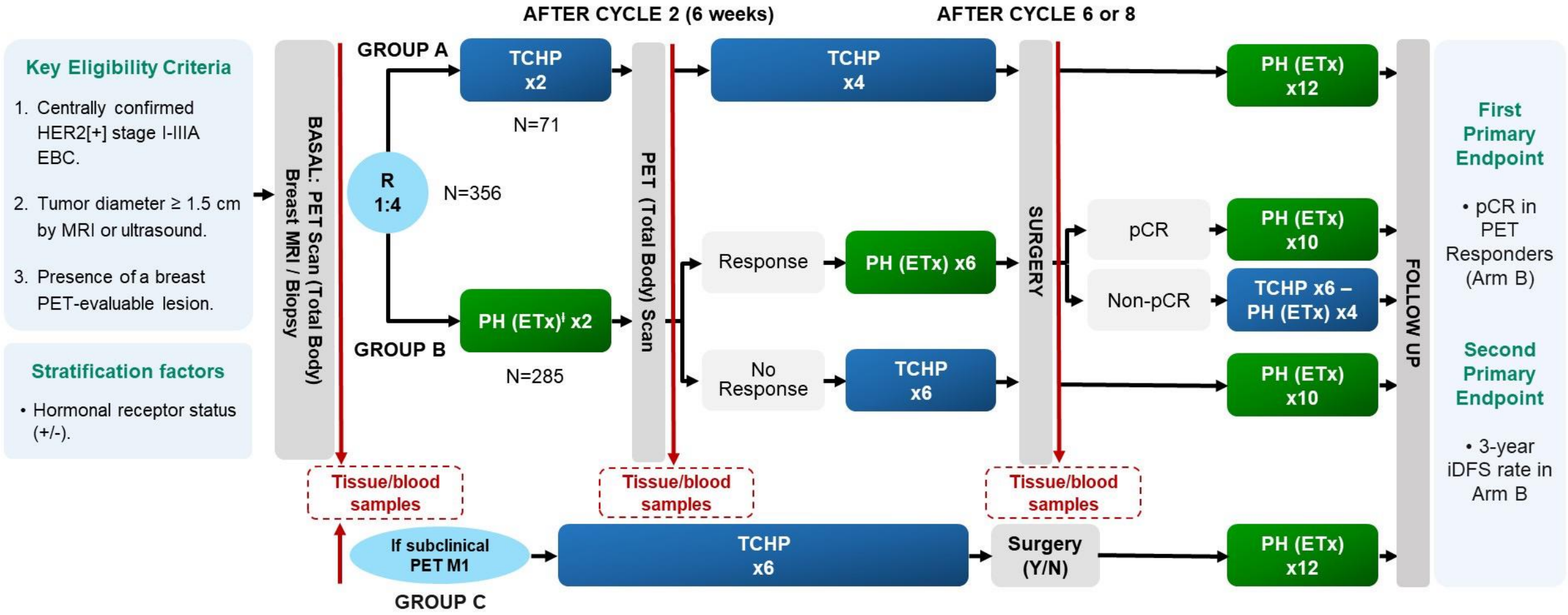
- High selectivity for HER2 TKI domain
- Potent inhibitor of HER2 signalling
- Synergistic activity in combination with trastuzumab

- Preferentially inhibits ligand-independent HER2 signalling
- Prevents shedding of HER2 ECD
- Flags cells for destruction by the immune system

- Inhibits HER2 forming dimer pairs
- Suppresses multiple HER signalling pathways, leading to a more comprehensive blockade of HER signalling
- Flags cells for destruction by the immune system

Baselga et al. Nat Rev Cancer 2009

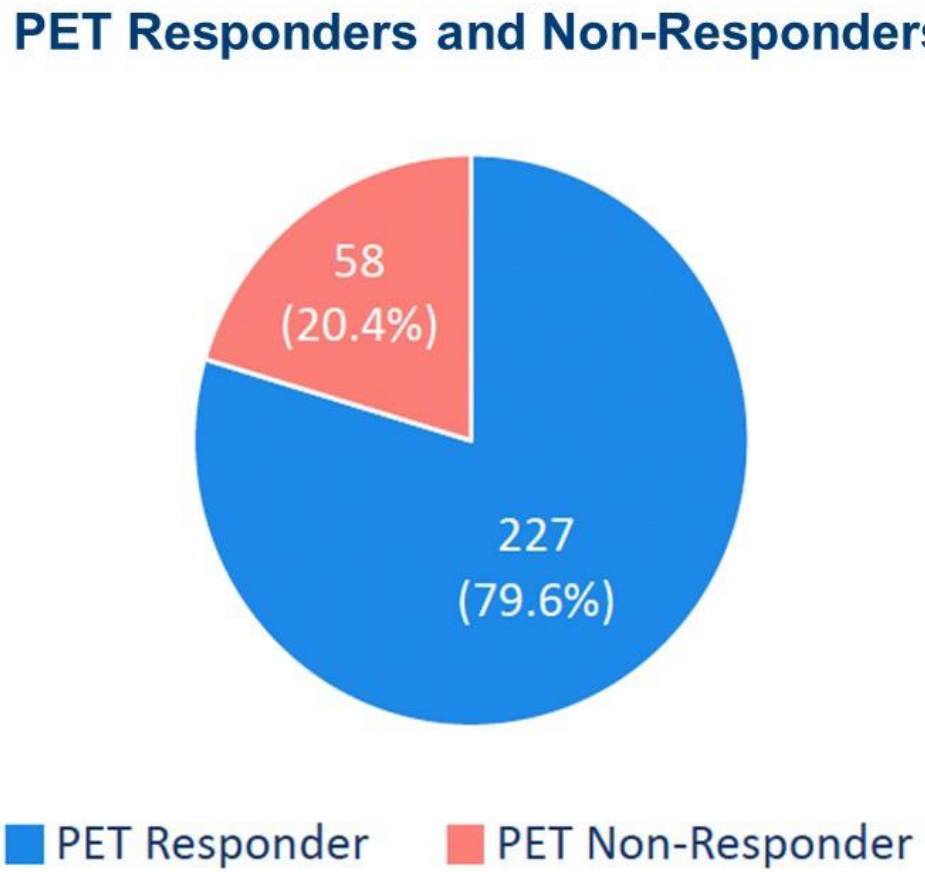
PHERGain: Chemotherapy de-escalation in HER2+ EBC

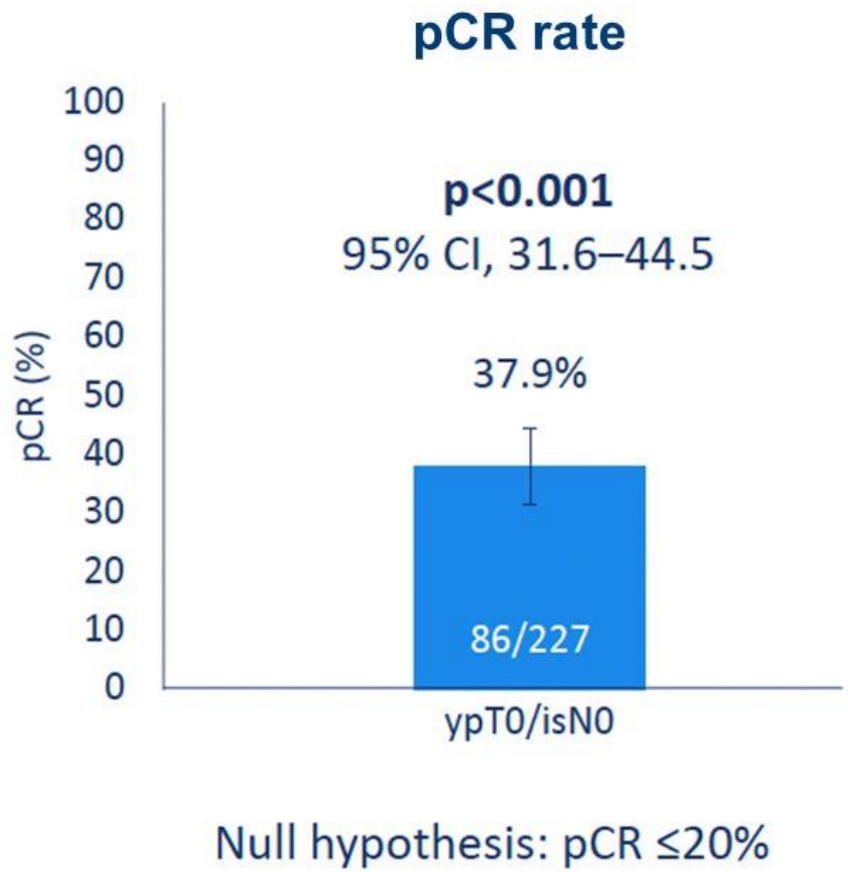


51-52% premenopausal - Node positive 45-49% - HR-negative 33-38%

Cortes J et al, ASCO 2023

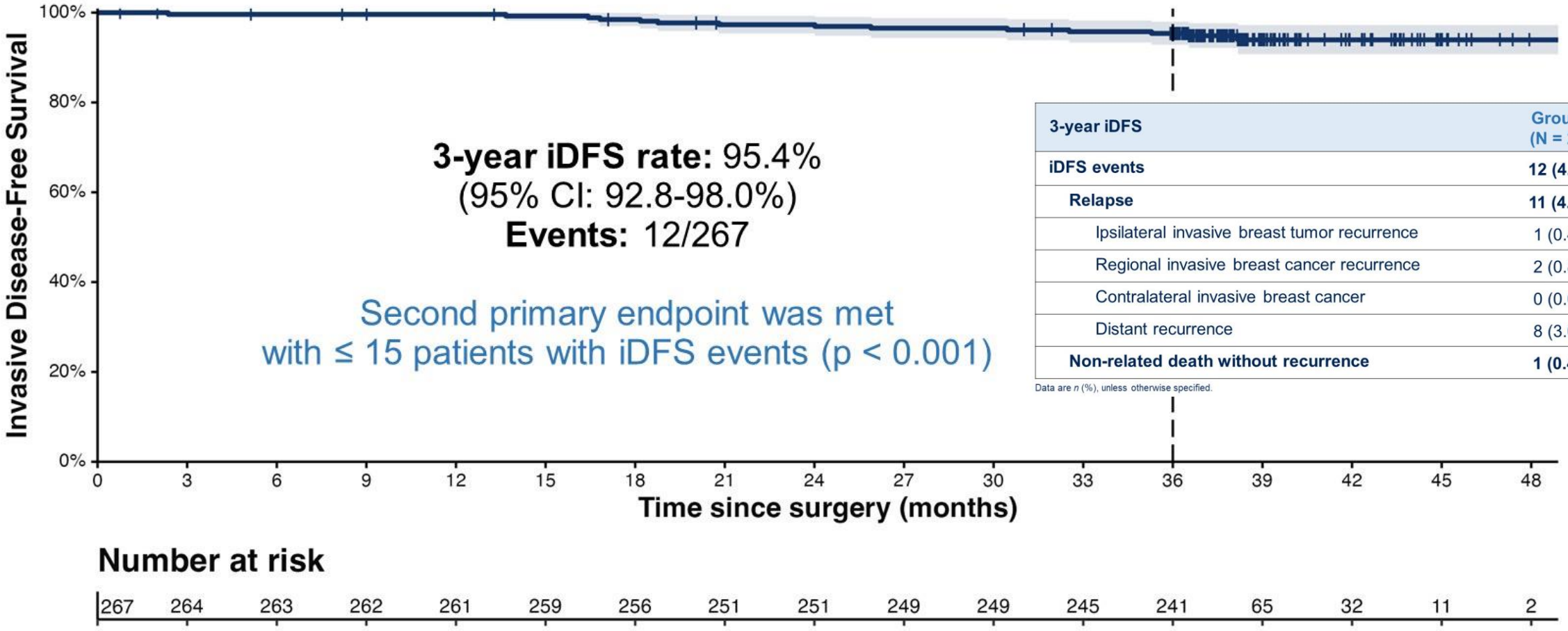
Primary endpoint: pCR in PET responders in group B





Perez-Garcia JM et al, Lancet Oncol 2021;22(6):858-871

Secondary endpoint: 3-year IDFS rate in group B (ITT population)

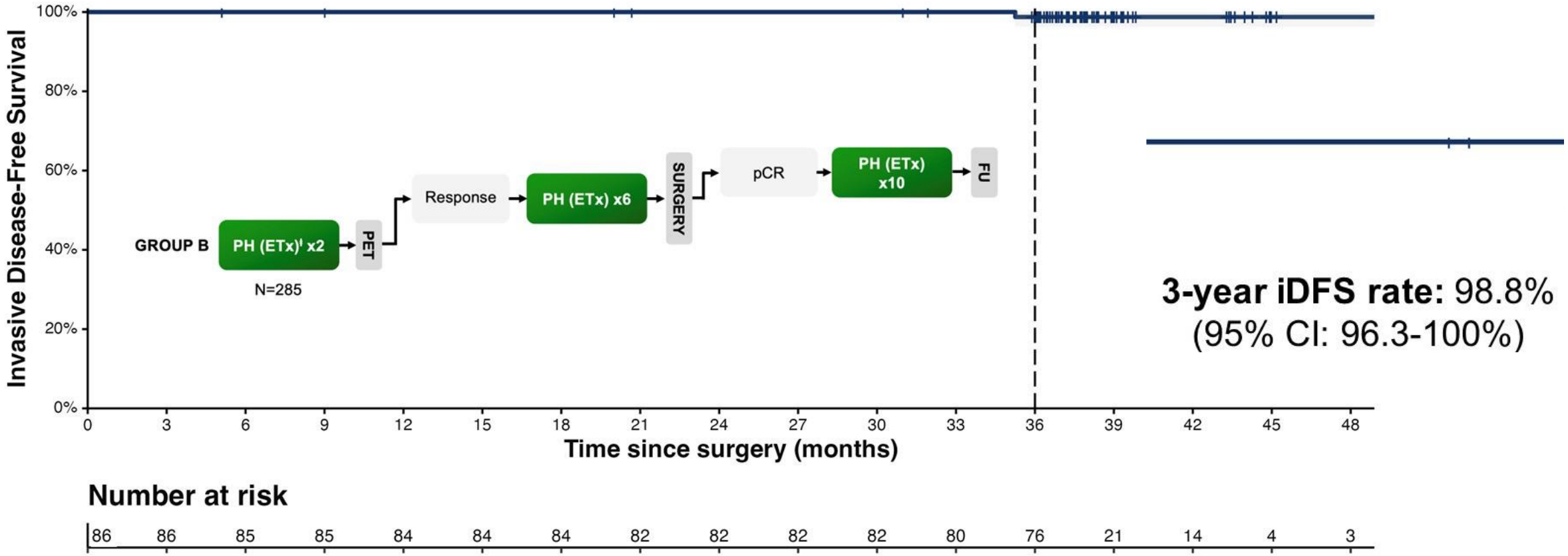


3-year iDFS	Group B (N = 267)
iDFS events	**12 (4.5%)**
Relapse	**11 (4.1%)**
Ipsilateral invasive breast tumor recurrence	1 (0.4%)
Regional invasive breast cancer recurrence	2 (0.8%)
Contralateral invasive breast cancer	0 (0.0%)
Distant recurrence	8 (3.0%)
Non-related death without recurrence	**1 (0.4%)**

Data are *n* (%), unless otherwise specified.

Cortes J, et al. *J Clin Oncol* 2023;41(suppl 16):Abstract LBA506.

Subgroup analysis:
3-year IDFS rate without CT in PET responders with pCR (N=86)



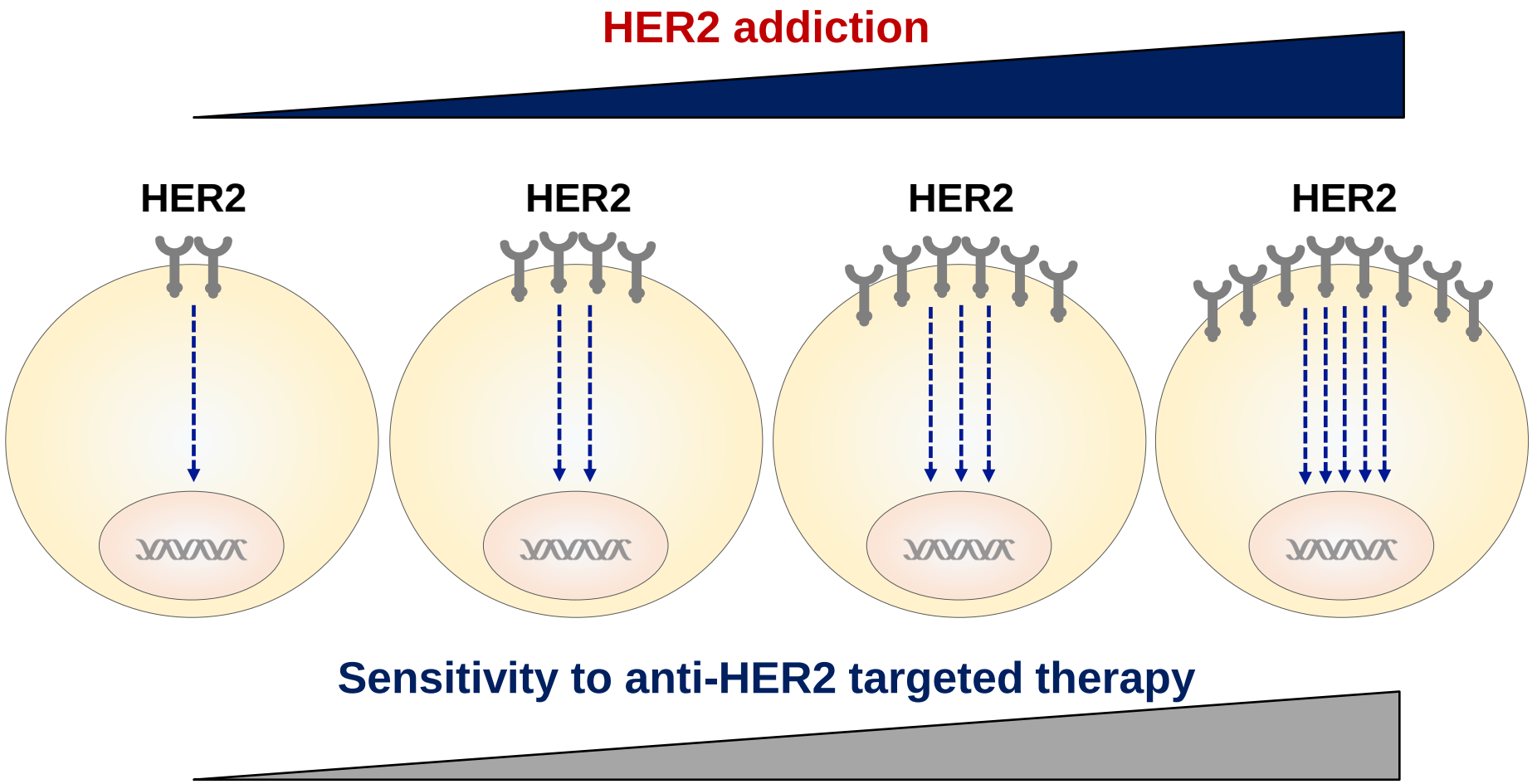
Cortes J, et al. *J Clin Oncol* 2023;41(suppl 16):Abstract LBA506.

Neoadjuvant Trials Testing chemo-free Dual HER2-Targeted Therapy

Study	Phase	PTS	HER2-Targeted therapy	Additional therapy	Duration (weeks)	pCR
TBCRC 006	II	64	**T+L**	ET (if HR+)	12	**27%**
TBCRC 023	II	33	**T+L**	ET (if HR+)	12	**9%**
		61	**T+L**	ET (if HR+)	24	**25%**
PAMELA	II	150	**T+L**	ET (if HR+)	18	**31%**
PERELISA	II	44	**T+P**	ET	15	**20.5%**
NA-PHER2	II	35	**T+P**	Fulvestrant + Palbociclib	24	**27%**

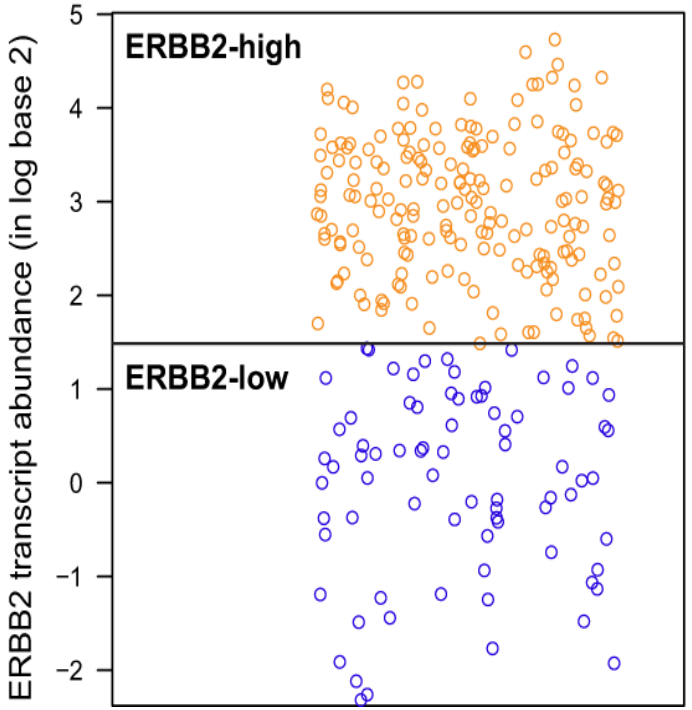
ET, Endocrine therapy; L, lapatinib; P, pertuzumab; pCR, pathological complete response; T, trastuzumab

Optimizing anti-HER2 therapy according to HER2-addiction

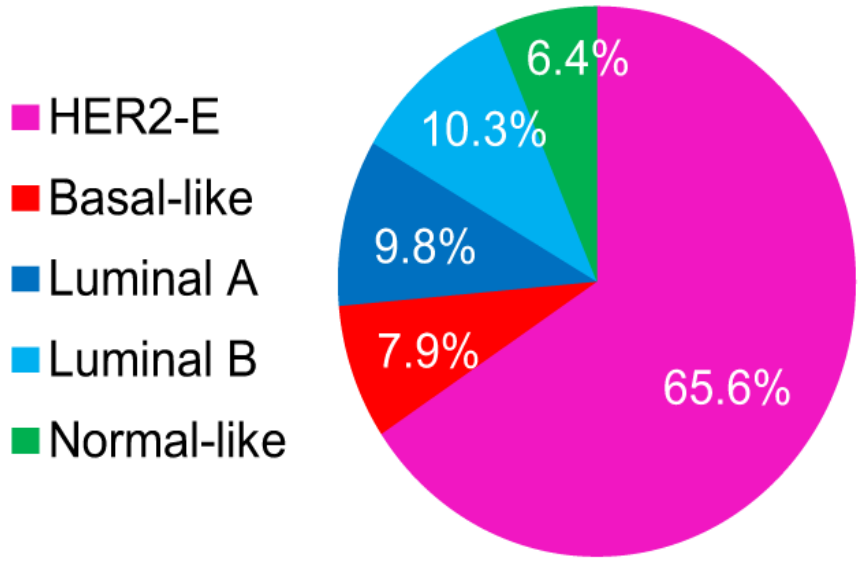


HER2+ BCs display different levels of *ERBB2* mRNA and NOT all of them are HER2-enriched

***ERBB2* mRNA levels**



Intrinsic subtype by PAM50



Prat A et al, JNCI 2020

The HER2-E/ERBB2-high group showed a higher pCR rate

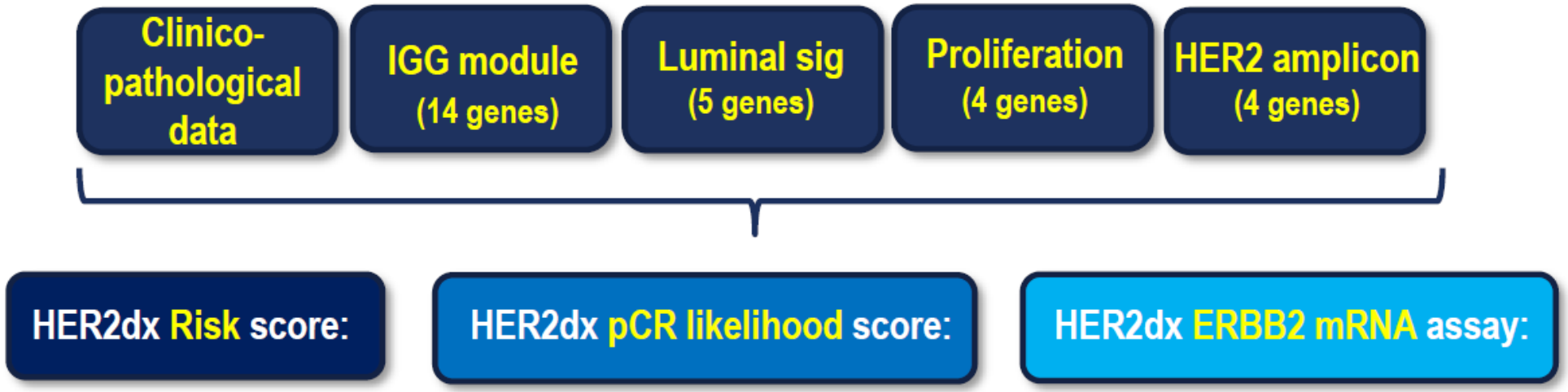
Variable	No.	pCR, %	Univariate		Multivariable	
			OR (95% CI)	*P**	OR (95% CI)	*P**
Trial						
TBCRC 006	29	24.1	1.00	—	1.00	—
TBCRC 023	85	20.0	0.78 (0.29 to 2.14)	.263	0.61 (0.19 to 2.03)	.385
PAMELA	151	30.5	1.37 (0.55 to 3.45)	.157	0.78 (0.24 to 2.51)	.973
PAM50+ERBB2						
Others	146	**11.6**	1.00	—	1.00	—
HER2-E/ERBB2-high	119	**44.5**	6.09 (3.27 to 11.35)	<.001	6.05 (3.10 to 11.80)	<.001

Odds ratios (ORs) and 95% confidence interval (CIs) were calculated for each variable. The statistical significance level was set to a two-sided α of 0.05. HER2-E = HER2-enriched.

Prat A et al, JNCI 2020

The 27-gene HER2dx test

- Multiparameter score composed of a refined list of 27-genes + clinical data (T and N):



HER2DX provides 3 types of information:

- ✓ **Risk of relapse score** (high vs. low) → prognostic
- ✓ **pCR likelihood score** (high vs. medium vs. low) → predictive
- ✓ **ERBB2 mRNA score** (high vs. medium vs. low) → diagnostic

Prat A. et al. eBiomedicine2022

HER2CLIMB-05: phase III trial incorporating tucatinib/placebo with CLEOPATRA regimen in 1L advanced HER2+ BC