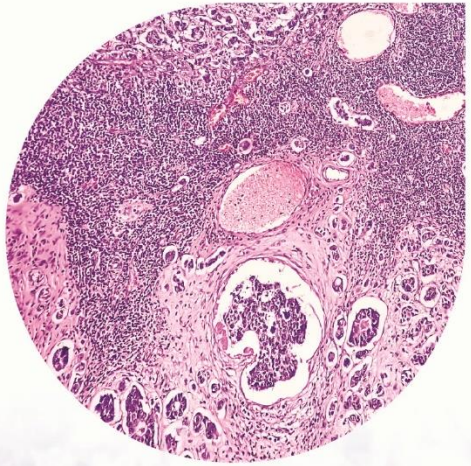
Global Breast Cancer Academy



Global Breast Cancer Academy Europe

26 November 2024

Silver sponsor: Menarini Stemline
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APTITUDE HEALTH

Global Breast Cancer Academy

Welcome and meeting overview

Nadia Harbeck

APTITUDE HEALTH

Meet the Faculty

CHAIR

Nadia Harbeck, MD, PhD
Ludwig-Maximilian University of Munich, Germany

FACULTY

Joseph Gligorov, MD, PhD
Sorbonne University and Tenon Hospital (AP-HP), Paris, France

Antonio Llombart, MD, PhD
University Hospital Arnau de Vilanova, Valencia, Spain

Virtual Plenary Sessions (1/2)

26 November 2024; 16.30 – 19.30 CET (Central European Time)

Time	Title	Speaker
16.30 – 16.40	Welcome and meeting overview; introduction to the voting system	Nadia Harbeck
Advancing Treatment Strategies in HR+ mBC: From Endocrine Therapy Foundations to Novel Targeted Options		
16.40 – 17.00	Endocrine therapy of HR+ mBC – where to start and where to go (15-min presentation + 5-min Q&A) • Discuss the selection of patients who are most suitable for ET vs ET + CDK4/6 inhibitor as a first-line treatment • Explore the importance of *ESR1* mutations and the role of oral SERDS (eg, elacestrant) in the treatment landscape	Nadia Harbeck
17.00 – 17.20	Beyond endocrine therapy in HR+ mBC (15-min presentation + 5-min Q&A) • Discuss the role of biomarkers, molecular profiling, and resistance mechanisms in guiding treatment decisions • Explore the role of targeted therapies such as PI3K inhibitors (eg, alpelisib), mTOR inhibitors (eg, everolimus), AKT inhibitors (eg, capivasertib), and PARP inhibitors (eg, olaparib) after failure of ET	Joseph Gligorov
17.20 – 17.40	Treatment options for high-risk and endocrine-resistant HR+ mBC (15-min presentation + 5-min Q&A) • Define the criteria and characteristics of high risk in HR+ mBC • Discuss the role of chemotherapy for patients with high-risk or endocrine-resistant disease • Discuss treatment options for HR+, HER2+ mBC • Review the emerging role of ADCs as a treatment option for patients who have exhausted ET options	Antonio Llombart
17.40 – 17.50	Break	

Virtual Plenary Sessions (2/2)

26 November 2024; 16.30 – 19.30 CET (Central European Time)

Time	Title	Speaker
How Does HR+ mBC Treatment Look Today and Tomorrow?		
17.50 – 18.20	Panel discussion: What is the optimal sequencing strategy for HR+, HER2– mBC?	Nadia Harbeck and all faculty
18.20 – 18.35	How bright is the future of HR+, HER2– mBC? Ongoing and planned clinical trials (10-min presentation + 5-min Q&A) • Highlight ongoing clinical trials and novel therapeutic strategies for HR+ mBC	Joseph Gligorov
18.35 – 19.20	BC case-based panel discussion • Case 1: HR+, HER2– mBC – what should be the 1L therapy after progression on adjuvant therapy with AI + CDK4/6 inhibitor? ▪ (10-min presentation + 5-min discussion) – Alexander König (Germany) • Case 2: HR+, HER2– mBC – 2L therapy after early progression in metastatic disease ▪ (10-min presentation + 5-min discussion) – Lauren Seknazi (France) • Case 3: HR+, HER2– mBC – 2L therapy after long exposure to ET ± CDK4/6 inhibitor ▪ (10-min presentation + 5-min discussion) – Paula Llor (Spain)	Nadia Harbeck and all faculty
19.20 – 19.30	Session close	Nadia Harbeck

Global Breast Cancer Academy

Introduction to the voting system

Nadia Harbeck

APTITUDE HEALTH

Question 1

Which languages do you speak? *(Select all that apply.)*

A. Arabic
B. English
C. French
D. German
E. Italian
F. Polish
G. Spanish
H. Other

Question 2

In the last 12 months, how many patients with HR+ mBC have you treated?

A. ≤5
B. 6–15
C. 16–25
D. 26–35
E. ≥36

Question 3

According to the current ESMO guidelines, which of the following biomarkers should be tested after progression on ET + CDK4/6 inhibitor? *(Select all that apply.)*

A. Germline *BRCA1/2*
B. Germline *PALB2*
C. *PIK3CA* mutation
D. *ESR1* mutation
E. *PTEN* mutation
F. *AKT1* mutation

Question 4

How does an *ESR1* mutation affect endocrine therapy in HR+ mBC?

A. Enhances CDK4/6 inhibitor activity
B. Causes endocrine sensitivity
C. Promotes HER2 overexpression
D. Leads to endocrine resistance

Objectives

Understand clinical and pathologic factors that influence first-line choice of therapy for patients with HR+ mBC

Discuss the role of biomarkers, molecular profiling, and resistance mechanisms in guiding treatment choices

Examine the role of targeted therapies following endocrine therapy failure

Gain insights into the care of patients with high-risk and endocrine-resistant HR+ mBC

Explore current and future sequencing strategies for HR+, HER2– mBC

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

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LMU KLINIKUM
Gemeinsam. Fürsorglich. Wegweisend.

Endocrine therapy in HR+, HER2– MBC:

Where to start and where to go

LMU Breast Center | 12/9/2024 | Prof. Nadia Harbeck, MD

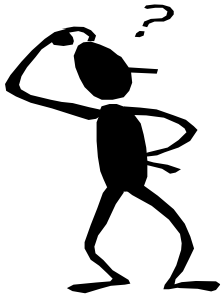
Brustzentrum im Klinikum der Universität München

CCC MÜNCHEN COMPREHENSIVE CANCER CENTER LMU KLINIKUM

TUMORZENTRUM MÜNCHEN | TZM

HR+ HER2- *metastatic* breast cancer
CDK4/6i and beyond

- Guideline recommendations
- CDK4/6 inhibitors in 1st line therapy
- Oral SERDs
  - Role of *ESR1* mutation
  - Efficacy and safety
- Open clinical questions



Endocrine Resistance in Metastatic Breast Cancer

Guidelines Breast
Version 2024.1E

Primary endocrine resistance:

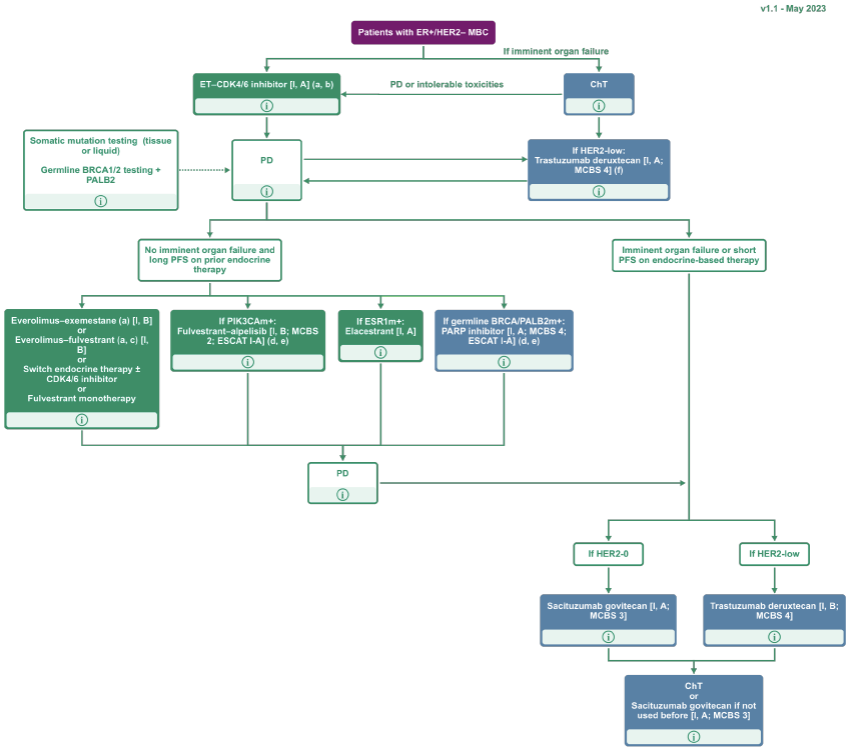
- **Relapse within 2 years of adjuvant endocrine treatment (ET)**
- **Progressive disease within first 6 months of first-line ETx for MBC**

Secondary (required) endocrine resistance:

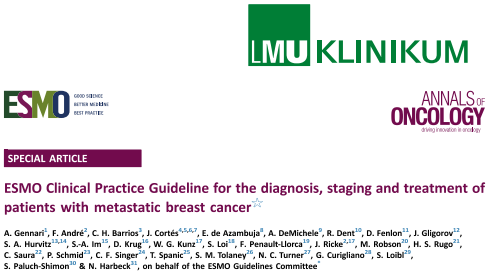
- **Relapse while on adjuvant ET but after the first 2 years or a relapse within 12 months after completing adjuvant ET**
- **PD ≥6 months after initiation of ET for MBC**

ESMO *metastatic* breast cancer guidelines

HR+ HER2- 1st and 2nd line[1]



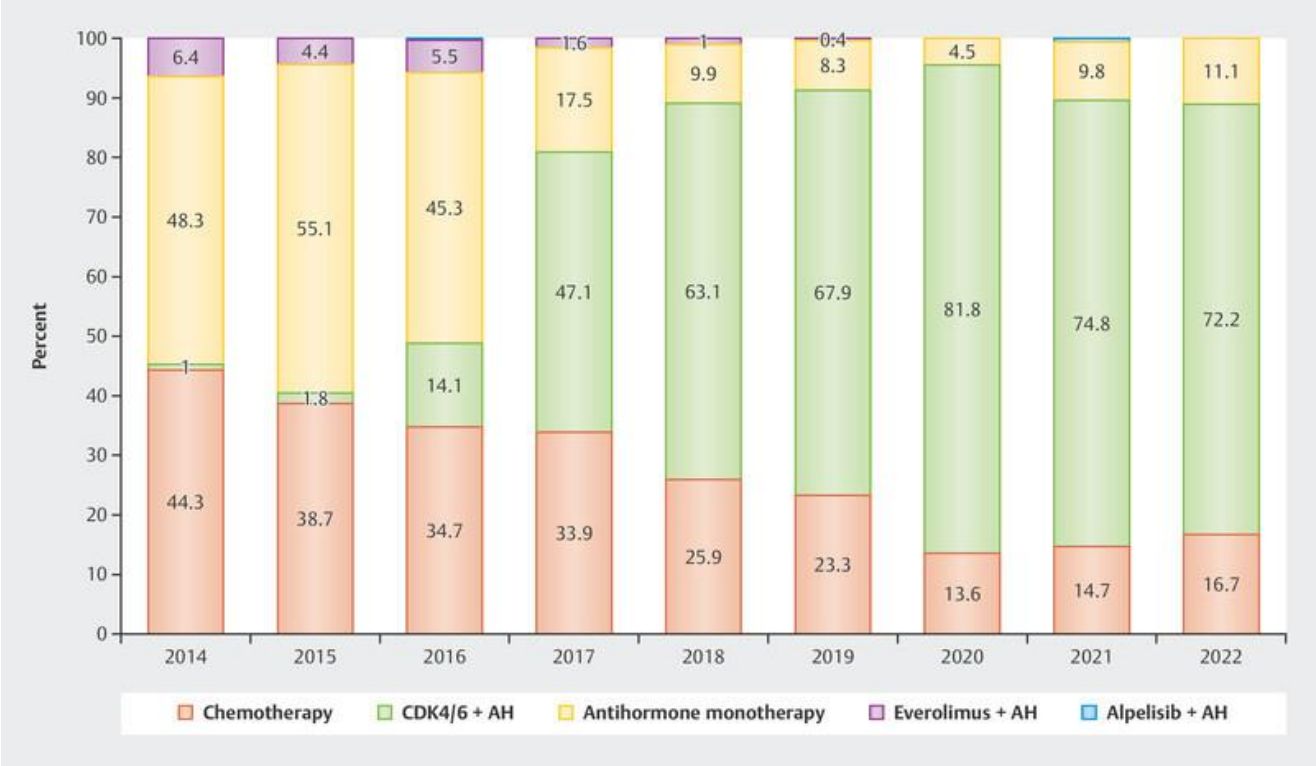
CDK4/6i are
1st line standard



[1] Gennari et al, Annals Oncol 2021; esmo.org

HR+ HER2- *metastatic* breast cancer

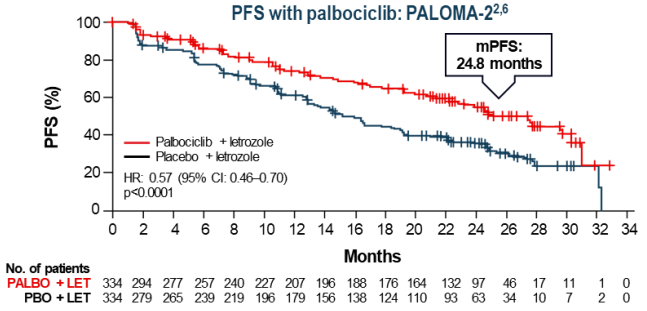
CDK4/6i use over time in Germany (PRAEGNANT Network)

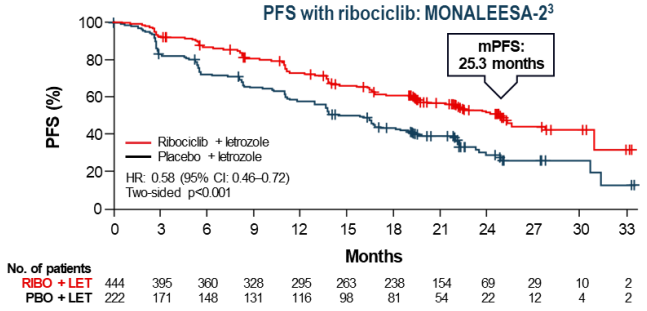


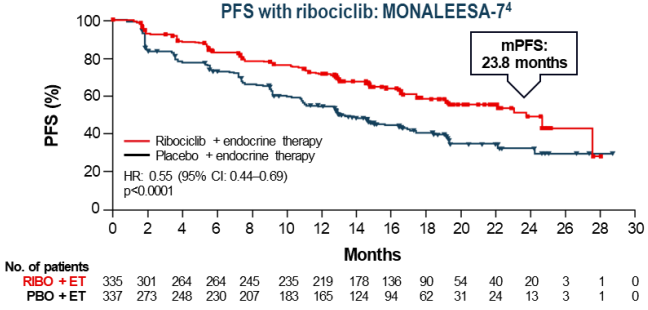
Engler et al, GEBFRA 2022

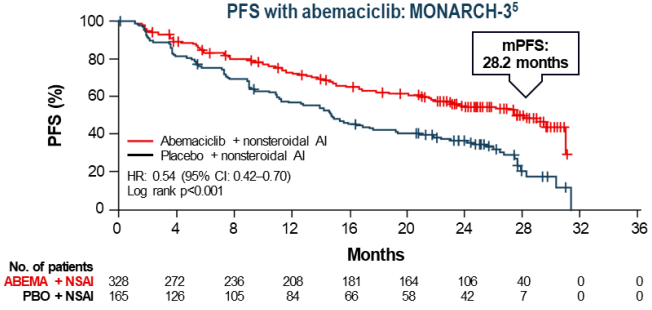
HR+ HER2- *metastatic* breast cancer

CDK4/6i in 1st line substantially improve PFS







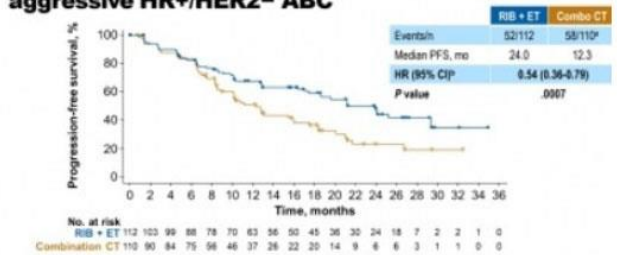


1. Han et al. Curr Probl Cancer 2020;44:100606; 2. Palbociclib Summary of Product Characteristics. 2023; 3. Hortobagyi GN et al. Ann Oncol 2018;29:1541–1547;
4. Tripathy D et al. Lancet Oncol 2018;19:904–915; 5. Goetz P et al. J Clin Oncol 2017,35:3638–3646.; 6. Finn RS et al. N Engl J Med 2016:357:1925–1936.

HR+ HER2- *metastatic* breast cancer

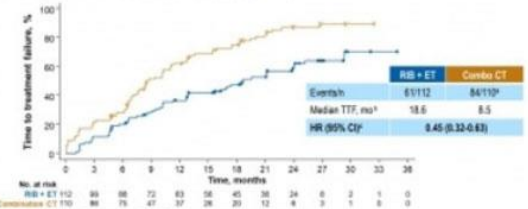
RIGHT CHOICE trial: Ribociclib in aggressive disease[1]

First-line RIB + ET achieved a statistically significant PFS benefit of ≈ 1 year over combination CT in aggressive HR+/HER2− ABC



	RIB + ET	Combo CT
Events/n	52/112	58/110[a]
Median PFS, mo	24.0	12.3
HR (95% CI)[b]	0.54 (0.36-0.79)	
P value	.0007	

Median time to treatment failure (TTF) was longer with RIB + ET vs combination CT



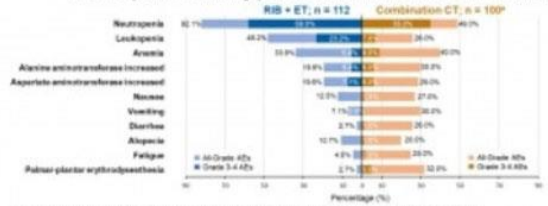
	RIB + ET	Combo CT
Events/n	61/112	84/110[a]
Median TTF, mo[b]	18.6	8.5
HR (95% CI)[c]	0.45 (0.32-0.63)	

- A sensitivity analysis[d] confirmed the TTF findings in the safety set
- The 3-month treatment failure rate[e] in the RIB arm was approximately half (n = 13; 11.6%; 95% CI, 6.3%-19.0%) that in the combination CT arm (n = 24; 21.8%; 95% CI, 14.5%-30.7%)

Fewer TRAEs with RIB + ET vs combination CT

n (%)	RIB + ET; n = 112		Combination CT; n = 100[a]	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Total AEs	112 (100.0)	84 (75.0)	100 (100.0)	71 (71.0)
Treatment-related serious AEs	2 (1.8)	1 (0.9)	8 (8.0)	7 (7.0)
Treatment-related AEs leading to discontinuation[b]	8 (7.1)	7 (6.3)	23 (23.0)	7 (7.0)

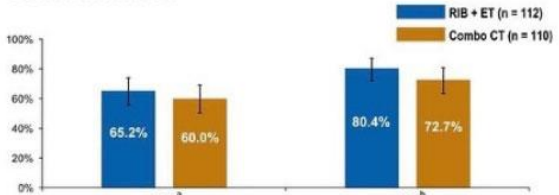
AEs irrespective of causality (≥20% incidence in either RIB or combination CT arms)



- Two patients (1.8%) in RIB arm[a] and none in CT arm showed grade ≥3 QT prolongation

San Antonio Breast Cancer Symposium[a], December 6-10, 2022

ORR and CBR were similar between RIB + ET and combination CT

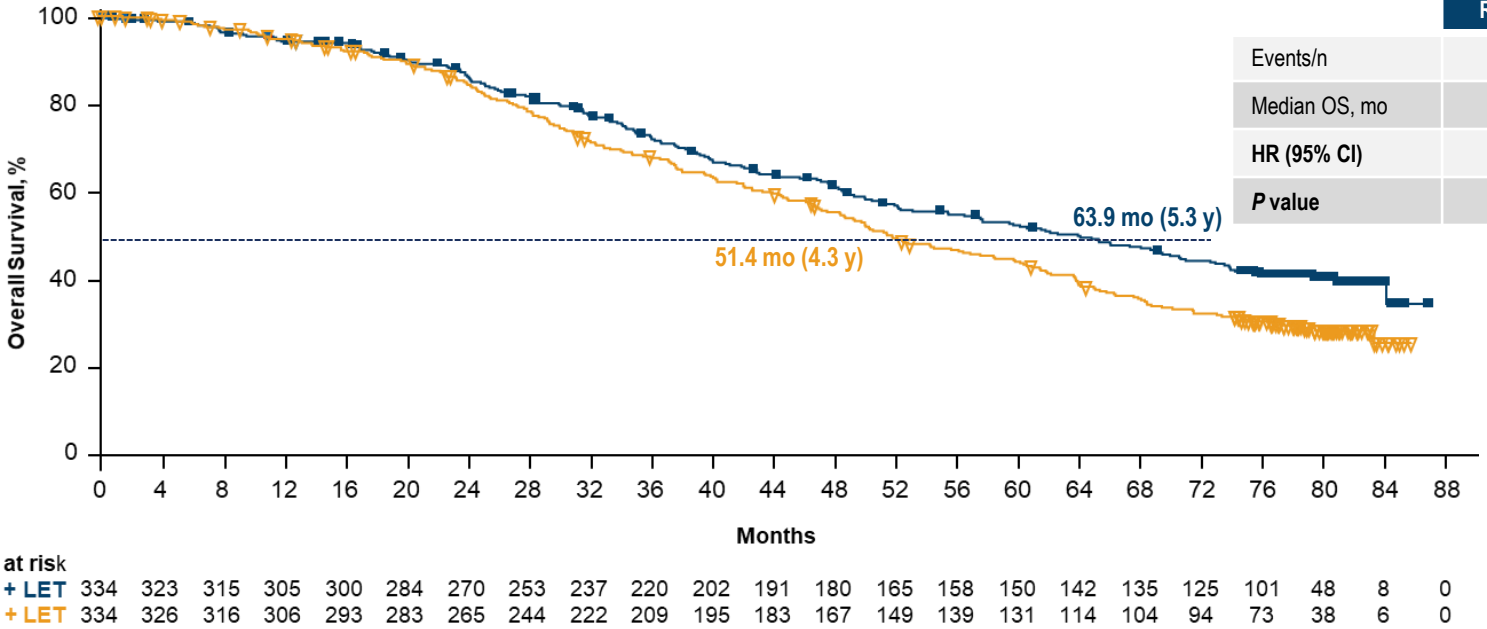


- A sensitivity analysis[c] confirmed the ORR and CBR findings in the safety set

[1] Lu et al, SABCS 2022

Ribociclib achieved statistically significant OS benefit in ML-2

Improvement in median OS was 12.5 months with ribociclib plus letrozole



	RIB + LET	PBO + LET
Events/n	181/334	219/334
Median OS, mo	63.9	51.4
HR (95% CI)	**0.76 (0.63-0.93)**	
***P* value**	**.004**	

No. at risk																						
RIB + LET	334	323	315	305	300	284	270	253	237	220	202	191	180	165	158	150	142	135	125	101	48	8	0
PBO + LET	334	326	316	306	293	283	265	244	222	209	195	183	167	149	139	131	114	104	94	73	38	6	0

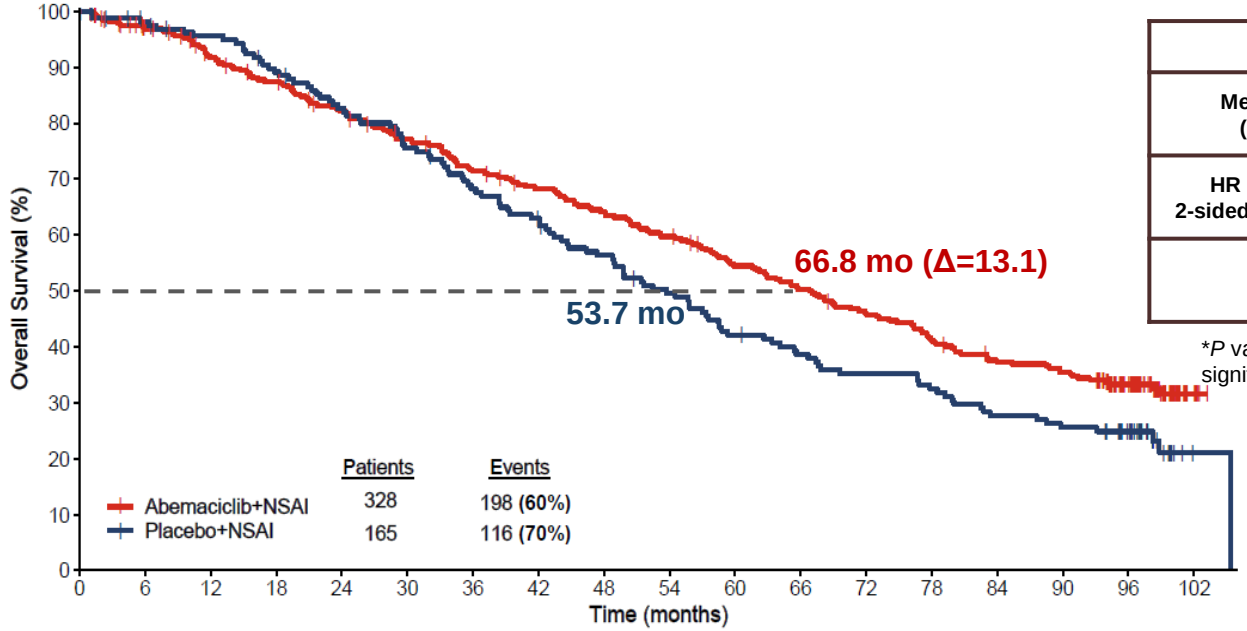
The P value of .004 crossed the prespecified boundary to claim superior efficacy

2021 ESMO congress

Gabriel N. Hortobagyi

HR, hazard ratio; ML-2, MONALEESA-2; LET, letrozole; OS, overall survival; PBO, placebo; RIB, ribociclib.

MONARCH-3: OS in the ITT Population



Number at Risk

Abemaciclib+NSAI	328	304	281	266	247	229	211	199	187	174	156	144	131	117	104	99	66	6
Placebo+NSAI	165	155	149	138	127	116	104	95	84	73	62	56	51	47	40	37	28	1

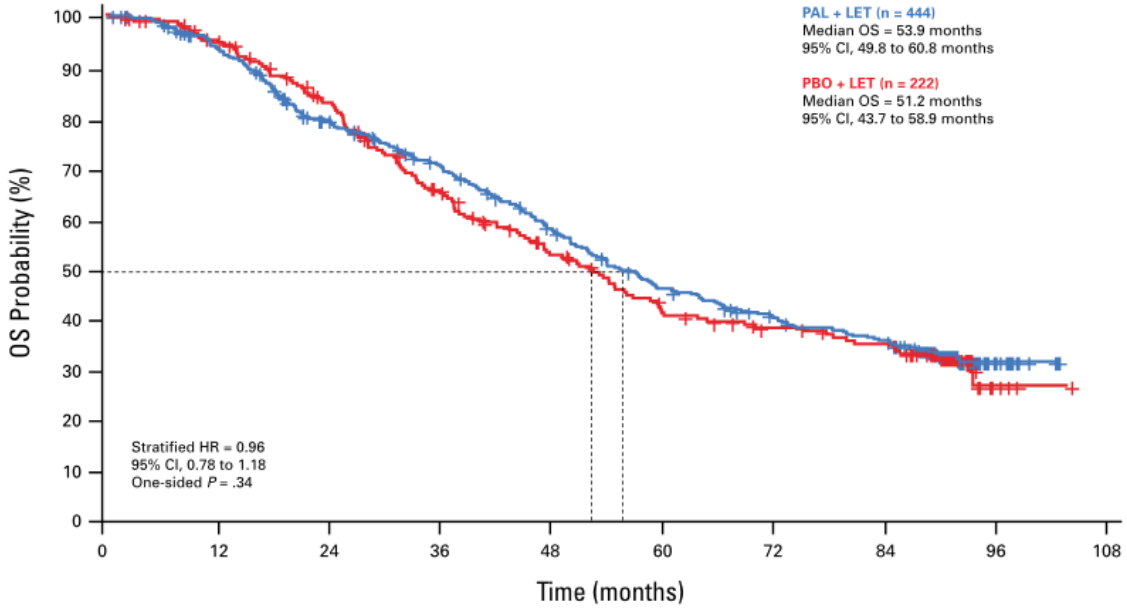
	abemaciclib + NSAI	placebo + NSAI
Median OS (months)	66.8	53.7
HR (95% CI) 2-sided *P* value	0.804 (0.637-1.015) *P* = .0664*	
Final OS Analysis Data cut: 29 Sep 2023		

**P* value did not reach threshold (0.034) for statistical significance at this final analysis.

Abemaciclib in combination with a NSAI resulted in longer OS compared to NSAI alone, however statistical significance was not reached. The observed improvement in median OS was 13.1 months.

HR+ HER2- *metastatic* breast cancer

PALOMA-2 overall survival

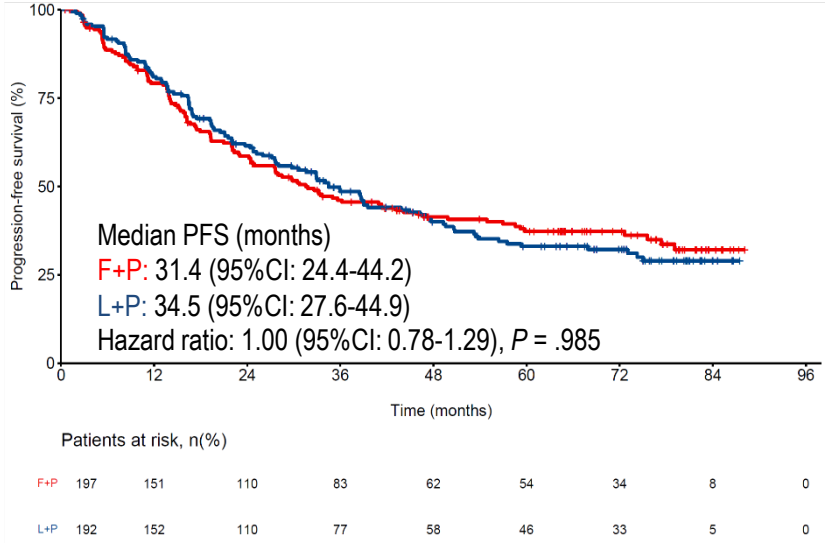


Slamon DJ et al. J Clin Oncol 2024;42:994-1000

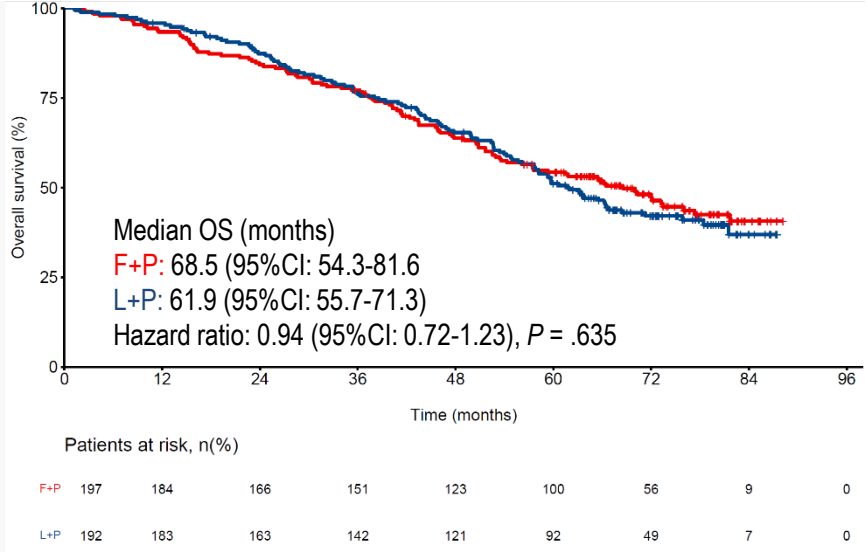
PARSIFAL-LONG:
Extended PFS and OS by treatment arm (n = 389)

Median follow-up: 59.7 months. Data cutoff: May 2023.

Progression-Free Survival (PFS)



Overall Survival (OS)



F: fulvestrant; L: letrozole; n (%), number of patients (percentage based on N); N: number of patients; OS: overall survival; P: palbociclib; PFS: progression-free survival

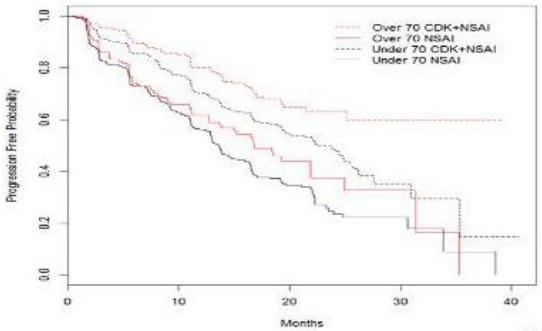
HR+ HER2- *metastatic* breast cancer

CDK4/6i in elderly

- Pooled *post hoc* analysis of elderly pts included in pivotal 1st line trials of CDK4/6i + AI
- ITT population: 1,992 pts, 555 ≥65 yr, 329 ≥70 yr

Efficacy of CDK4/6 Inhibitors in Patients ≥ 70

FDA



	Median PFS (95% CI)
Age≥70 CDK4/6 (n=280)	NR (25.1 months, NR)
Age <70 CDK4/6 (n=826)	23.75 months (21.9, 25.4)
Age ≥70 AI only	16.8 months (13.7, 21.9)
Age <70 AI only	13.8 months (12.9, 14.7)

HR 0.54 95% CI (0.47, 0.62)

No treatment difference across age subgroups.
Similar results with alternate age cut offs (>65, >75, etc)

Pooled Adverse Events: Severity

FDA

	Age < 65 years N = 625 (%)	Age ≥ 65 years N = 479(%)	Age ≥ 70 years N = 280 (%)
Grade 1-2 Adverse Events	610 (98)	470 (98)	277 (99)
Grade 3-4 Adverse Events	417 (66)	385 (80)	229 (82)
Grade 5 Adverse Events	7 (1)	11 (2)	8 (3)

Pooled Adverse Events: Tolerability

FDA

	Age < 65 years N = 625 (%)	Age ≥ 65 years N = 479 (%)	Age ≥ 70 years N = 280 (%)
AE leading to dose reduction and/or interruption	411 (66)	360 (75)	216 (77)
AE leading to discontinuation	50 (8)	76 (16)	48 (17)
Serious Adverse Events	103 (16)	147 (31)	93 (33)

Singh H et al. Abst. #GS5-06; SABCS 2017.

CDK4/6 inhibitors
Similarities and differences

	Palbociclib	Abemaciclib	Ribociclib
IC50	CDK4: 9-11 µM CDK6: 15 µM	CDK4: 2 µM CDK6: 5 µM	CDK4: 11 µM CDK6: 39 µM
Dosing	125 mg daily (3 wks on, 1 wk off)	200 mg twice daily (continuously)	600 mg daily (3 wks on, 1 wk off)
ORR in monotherapy,%	6[1]	17[2]	3[3]
CNS penetration	no	yes	no

Common AEs, %	All Grades[1]	Grade 3/4[1]	All Grades[2]	Grade 3/4[2]	All Grades[3]	Grade 3/4[3]
Neutropenia	95	54	88	27	74	59
Thrombocytopenia	76	19	42	2	9	1
Fatigue	68	0	65	13	36	2
Diarrhea	16	0	90	20	35	1
Nausea	23	0	65	5	52	2
Vomiting	5	0	35	2	29	4
Creatinine increase	NR	NR	98.5	0.8	NR	NR
QTc prolongation	NR	NR	NR	NR	3	0

CNS, central nervous system; IC50, half-maximal inhibitory concentration; HR, hormone receptor; QTc, corrected QT interval

1. DeMichele A, et al. *Clin Cancer Res.* 2015;21(5):995-1001. 2. Finn RS, et al. *J Clin Oncol.* 2016;34(suppl):Abstract 507. 3. Hortobagyi GN, et al. *N Engl J Med*. 2016;375(18):1738-1748.

Adapted from Barroso-Sousa R, et al. *Breast Care (Basel).* 2016;11(3):167-173.

HR+ HER2- *metastatic* breast cancer

Choice of CDK4/6i

ER POSITIVE / HER-2 NEGATIVE ABC: CDK4/6 INHIBITORS

The ESMO-MCBS scores for the use of a CDK4/6 inhibitor combined with endocrine therapy for ABC patients vary according to the setting and drug.
They are the following, with the current available data and FU:

- **RIBOCICLIB + ET 1st line Pre-menopausal: Efficacy score: 4 (PFS&OS); Improved QoL; ESMO-MCBS : 5**
- **RIBOCICLIB + AI 1st line Post-menopausal: Efficacy score: 4 (PFS&OS); No QoL benefit; ESMO-MCBS : 4**
- **PALBOCICLIB + AI 1st line: Efficacy score: 3 (PFS); No QoL benefit; ESMO-MCBS = 3**
- **ABEMACICLIB + AI 1st line: Efficacy score: 3 (PFS); No QoL reported; ESMO-MCBS = 3**
- **PALBOCICLIB + Fulvestrant 2nd line: Efficacy score: 3 (PFS&OS); Improved QoL; ESMO-MCBS : 4**
- **RIBOCICLIB + Fulvestrant (1st , 2nd line): Efficacy score: 4 (PFS&OS); No QoL benefit; ESMO-MCBS = 4**
- **ABEMACICLIB + Fulvestrant 2nd line: Efficacy score: 4 (PFS&OS); No QoL benefit; ESMO-MCBS = 4**

(LoE/GoR : I/A) (89%)
Of note, the three CDK4/6 inhibitors have not been compared head-to-head within a clinical trial.

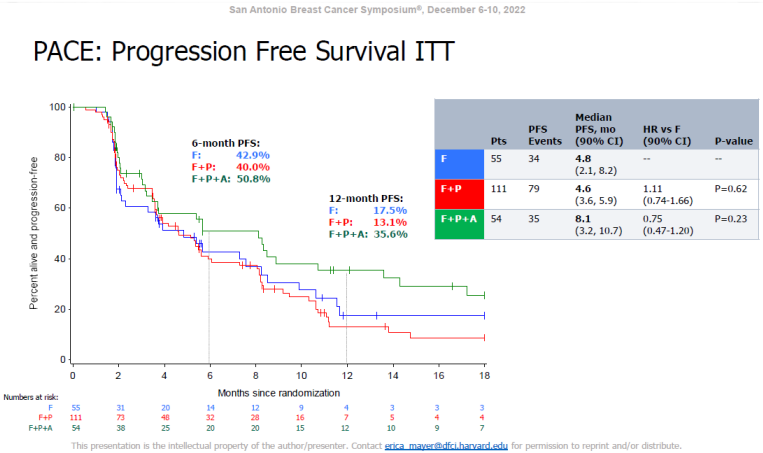
loso et al, The Breast 2024

MCBS scores are updated when new data is published

F. Cardoso et al, The Breast 2024, in preparation

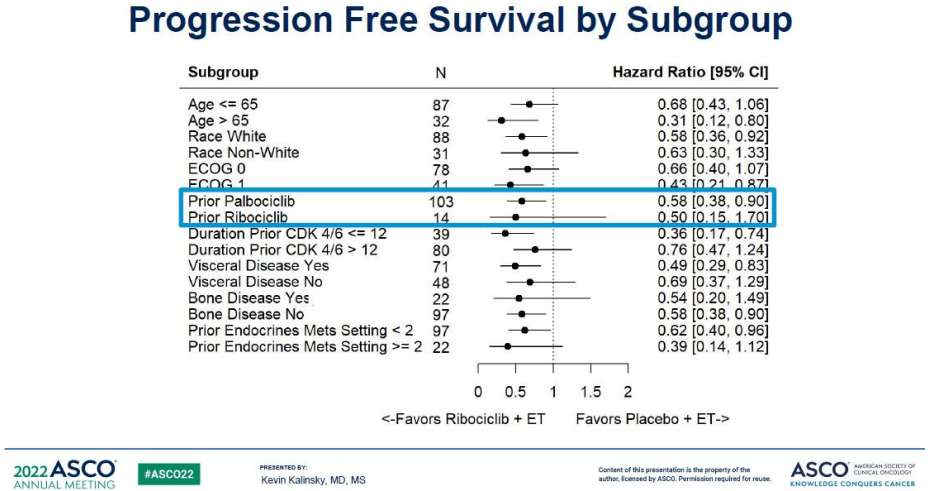
CDK4/6 inhibitors
Treatment beyond progression

PACE: Palbociclib after palbociclib



	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	4.8 (2.1, 8.2)	--	--
F+P	111	79	4.6 (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62
F+P+A	54	35	8.1 (3.2, 10.7)	0.75 (0.47-1.20)	P=0.23

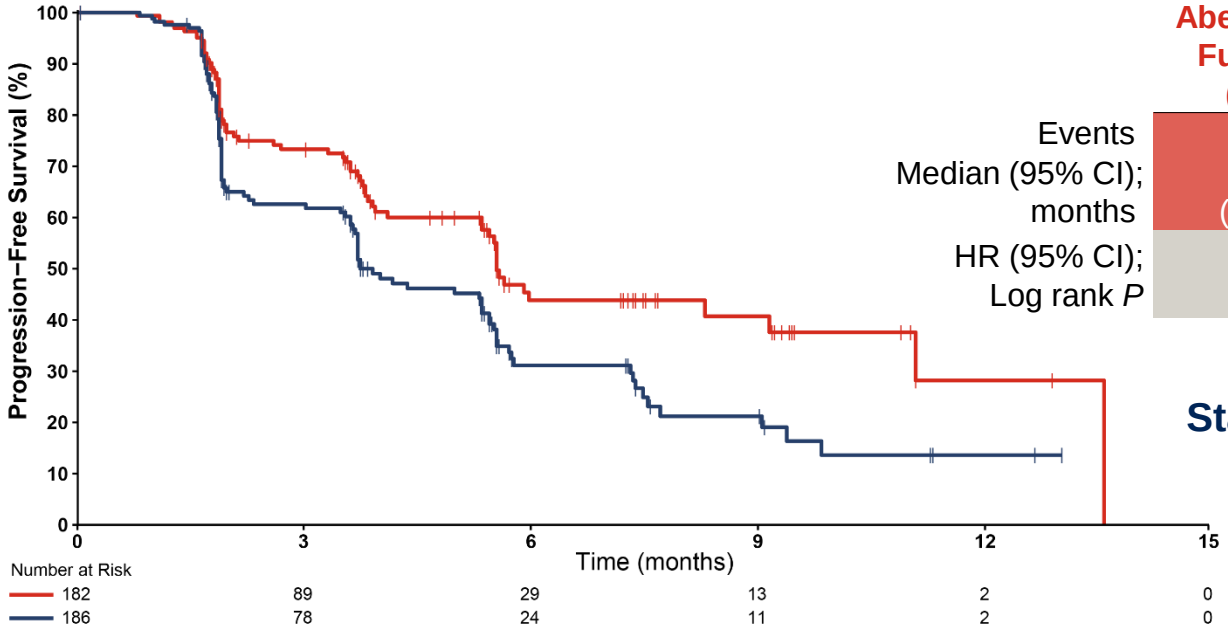
MAINTAIN: Ribociclib after palbociclib or ribociclib



Kalinsky et al, ASCO 2022; Mayer et al, SABCS 2022

CDK4/6 inhibitors
Treatment beyond progression

postMONARCH: Abemaciclib after palbociclib or ribociclib (only 8% abemaciclib)



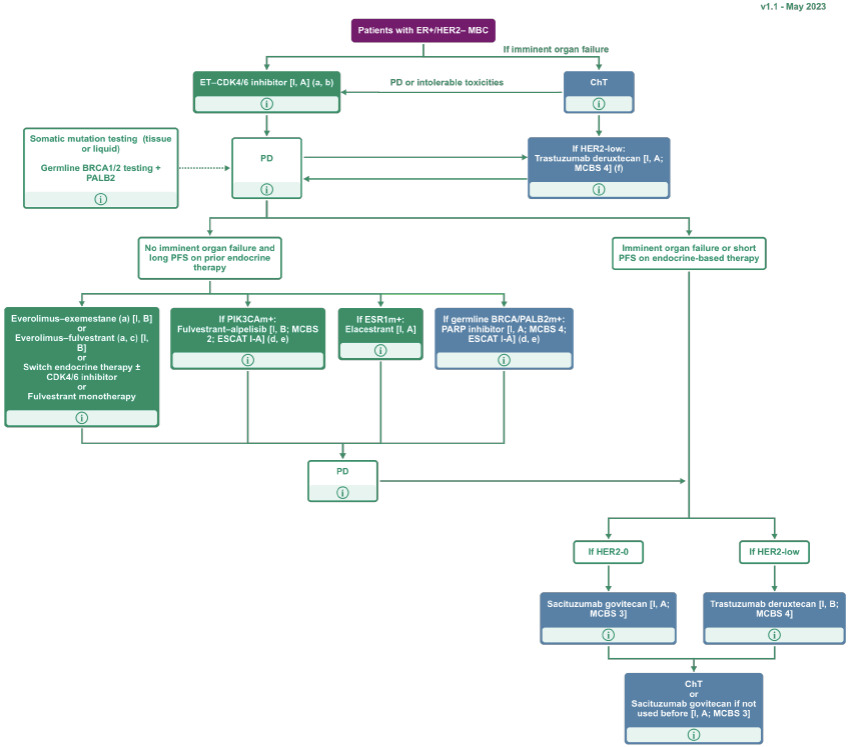
	Abemaciclib + Fulvestrant (N=182)	Placebo + Fulvestrant (N=186)
Events	70	99
Median (95% CI); months	**5.6** (5.4–9.2)	**3.9** (3.7–5.4)
HR (95% CI); Log rank *P*	**0.66 (0.48–0.91)** 0.01	

Statistical Significance Met at Interim Analysis

Kalinsky et al, ASCO 2024

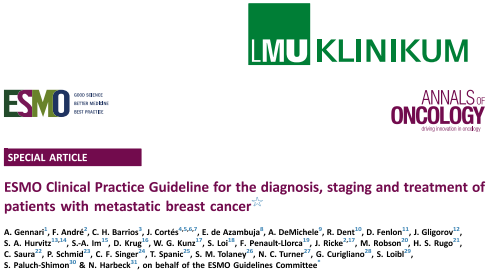
ESMO *metastatic* breast cancer guidelines

HR+ HER2- 1st and 2nd line[1]



CDK4/6i are
1st line standard

No optimal standard for 2nd line
- biomarker driven

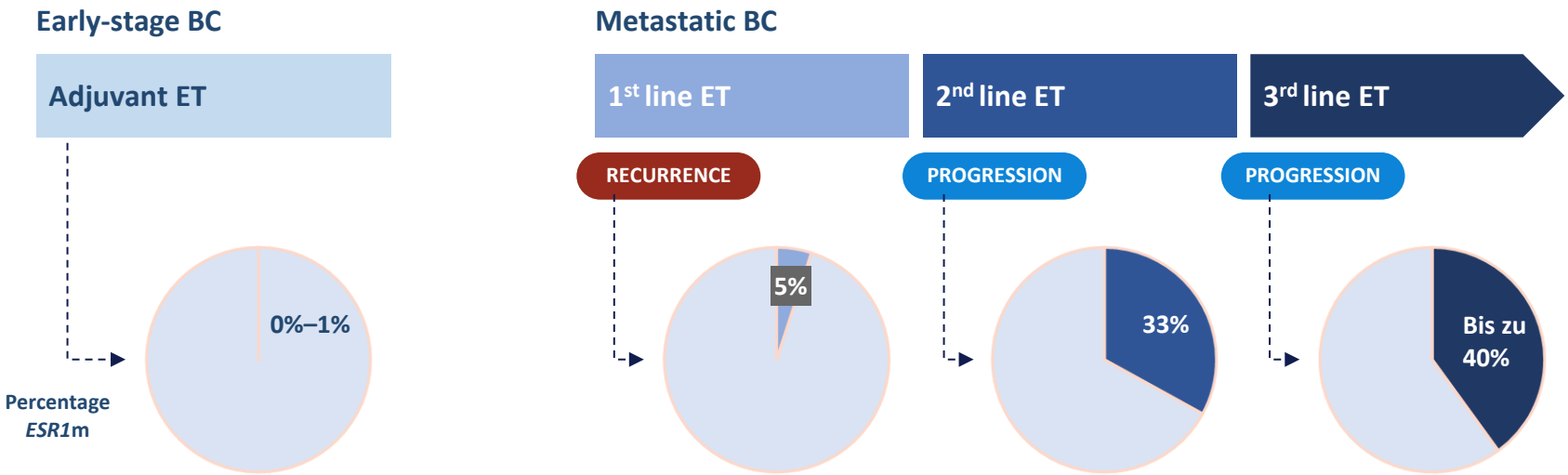


[1] Gennari et al, Annals Oncol 2021; esmo.org

HR+ HER2- *metastatic* breast cancer

Kinetics of *ESR1* mutations[1-5]

- *ESR1* mutations develop under evolutionary pressure

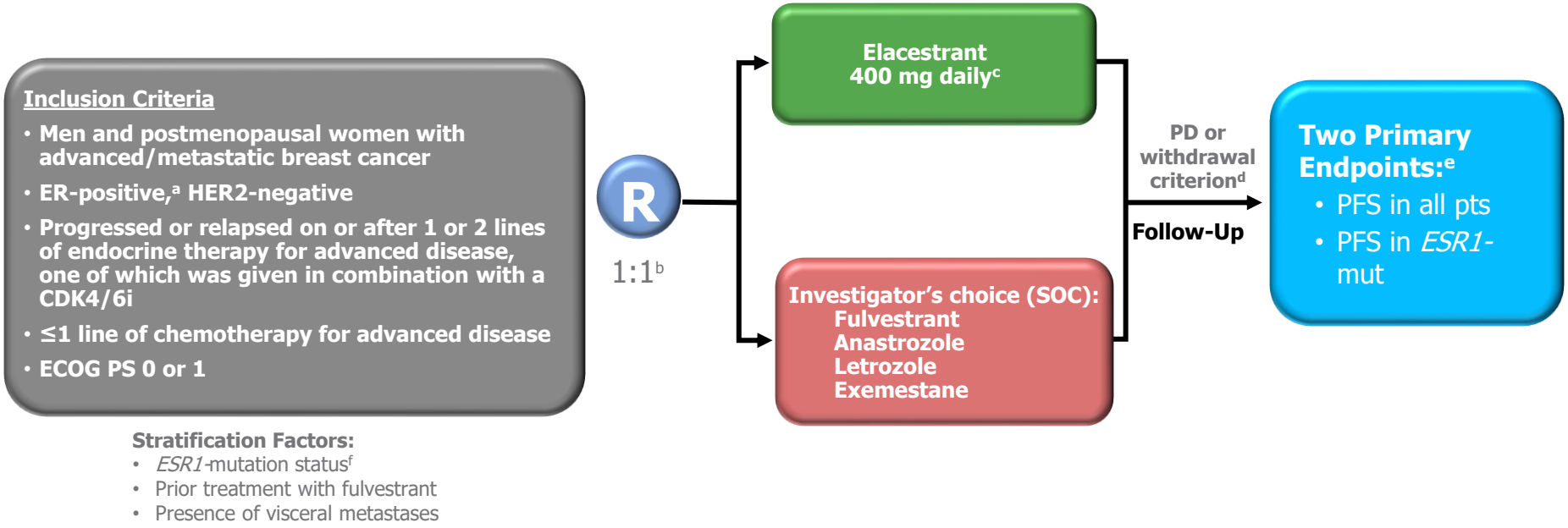


ESR1, estrogen receptor alpha; ET, endocrine therapy

Modified from: 1 Jeselsohn R et al. Clin. Cancer Res 2014;20:1757-1767.; 2 Jeselsohn R et al. Cancer Cell 2018;33:173-186.; 3 Allouchery V et al. Breast Cancer Res 2018;20:40.: 4 Schiavon G et al. Sci Transl Med 2015;7:313ra182.; 5 Brett JO, et al. Breast Cancer Res 2021;23:85.

EMERALD Phase 3 Study Design

- 477 pts; PD on CDKi
- 70% fulvestrant as SOC
- 70% visceral metastases
- 25% one prior line of chemo

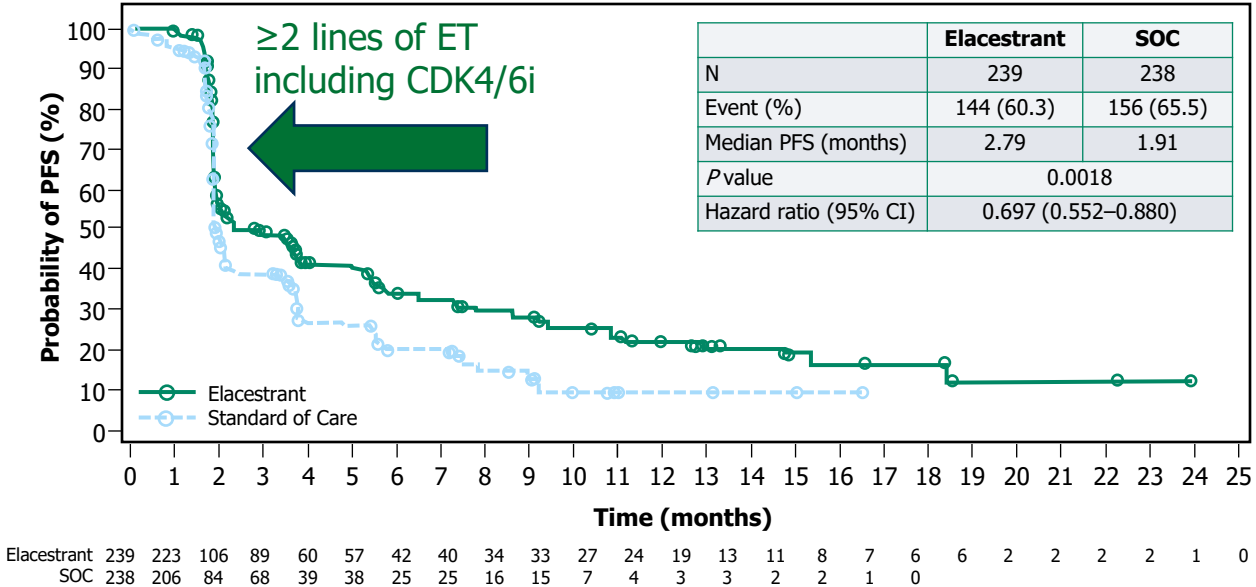


[a]Documentation of ER+ tumor with ≥1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant Health, Redwood City, CA).

PFS, progression-free survival; Pts, patients; R, randomized; SOC, standard of care.

EMERALD: Primary Endpoint (PFS by IRC)

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 the risk of progression or death in all patients with ER+/HER2- mBC

- Elacestrant showed a statistically significant and clinically meaningful PFS improvement versus SOC in all patients with ER+/HER2- advanced/metastatic breast cancer following CDK4/6i therapy

HR+ HER2- *metastatic* breast cancer

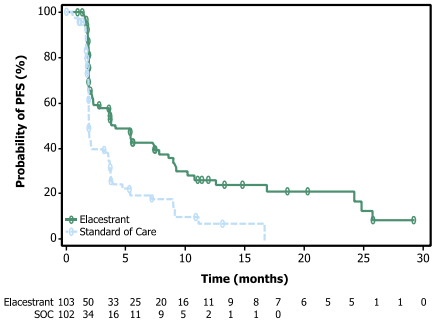
Oral SERDs: Elacestrant

San Antonio Breast Cancer Symposium®, December 6-10, 2022

2023

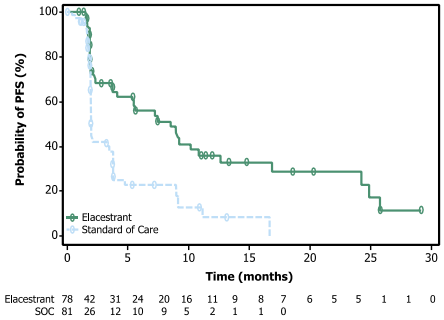
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



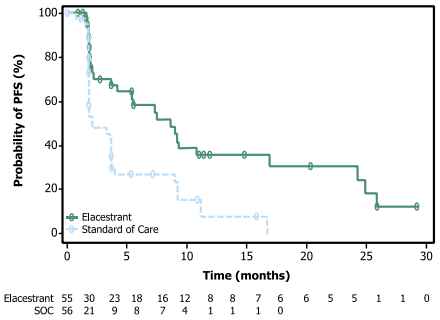
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



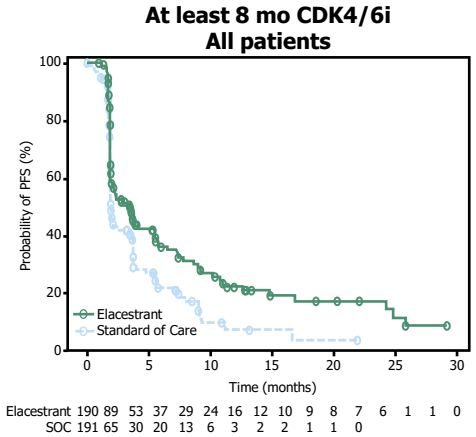
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

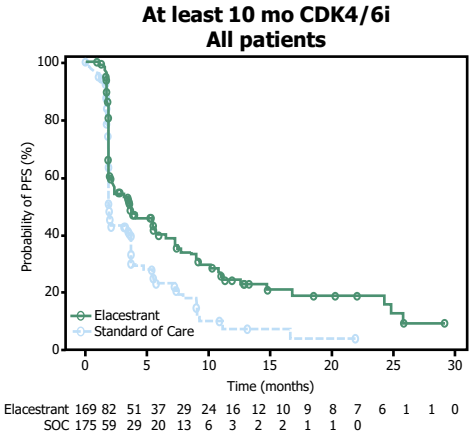
At least 18 mo CDK4/6i

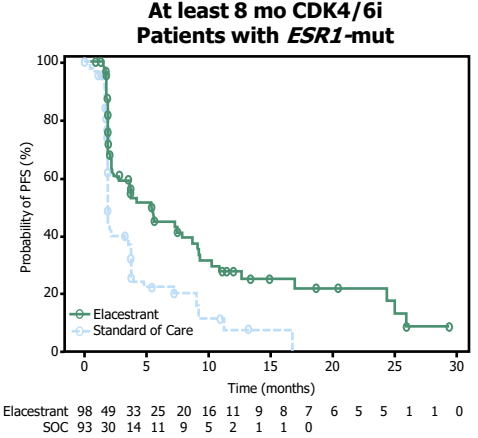


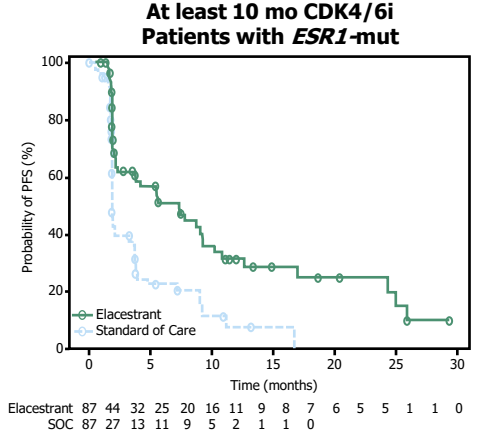
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

mPFS Benefit of Elacestrant Positively Associated with CDK4/6i Duration









Duration on CDK4/6i in the Metastatic Setting		At Least 6 Months		At Least 8 Months		At Least 10 Months		At Least 12 Months	
		Elacestrant	SOC Hormonal Therapy	Elacestrant	SOC Hormonal Therapy	Elacestrant	SOC Hormonal Therapy	Elacestrant	SOC Hormonal Therapy
All Patients	n	202	205	190	191	169	175	150	160
	Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)	**3.52** (2.10 - 5.32)	**1.91** (1.87 - 2.43)	**3.65** (2.20 - 5.72)	**1.91** (1.87 - 3.52)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)
	Hazard ratio (95% CI)	0.688 (0.535 - 0.884)		0.685 (0.527 - 0.891)		0.642 (0.485 - 0.848)		0.613 (0.453 - 0.828)	
ESR1-mut	n	103	102	98	93	87	87	78	81
	Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**5.32** (2.33 - 8.61)	**1.87** (1.87 - 3.29)	**7.26** (3.65 - 9.23)	**1.87** (1.84 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
	Hazard ratio (95% CI)	0.517 (0.361 - 0.738)		0.512 (0.351 - 0.744)		0.452 (0.301 - 0.674)		0.410 (0.262 - 0.634	

Safety Summary

Updated safety data were consistent with previously reported results:

- Most adverse events (AEs), including nausea, were grade 1 and 2, and no grade 4 treatment-related AEs (TRAEs) were reported.
- Only 3.4% of patients receiving elacestrant and 0.9% receiving SOC discontinued therapy due to any TRAE.
- No deaths assessed as treatment-related were reported in either arm.
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia.

Nausea Summary	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, n (%)	6 (2.5%)	2 (0.9%)
Dose-reduction rate due to nausea, n (%)	3 (1.3%)	Not applicable
Discontinuation rate due to nausea, n (%)	3 (1.3%)	0 (0%)
Antiemetic use	8%	10.3% (AI) 1.3% (Ful)

Second- and Subsequent-Line Therapies for HR+ HER2- Metastatic Breast Cancer

(Specific mutations/alterations required)

Guidelines Breast
Version 2024.1D

	Oxford		
	LoE	GR	AGO
▪ ***ESR1*-mutated and CDK4/6i-pretreatment**			
Elacestrant*	1b	B	+
▪ ***PIK3CA*-mutated**			
Alpelisib + Fulvestrant	1b	B	+
▪ **Alterations in *PIK3CA, AKT1, or PTEN***			
Capivasertib + Fulvestrant**	1b	B	+
▪ ***gBRCA*-mutated**			
Olaparib	1b	A	++
Talazoparib	1b	A	++

*Particularly in patients who experienced prolonged PFS on the prior lines of ET and CDK4/6 inhibitors.

**No EMA approval yet (01/2024)

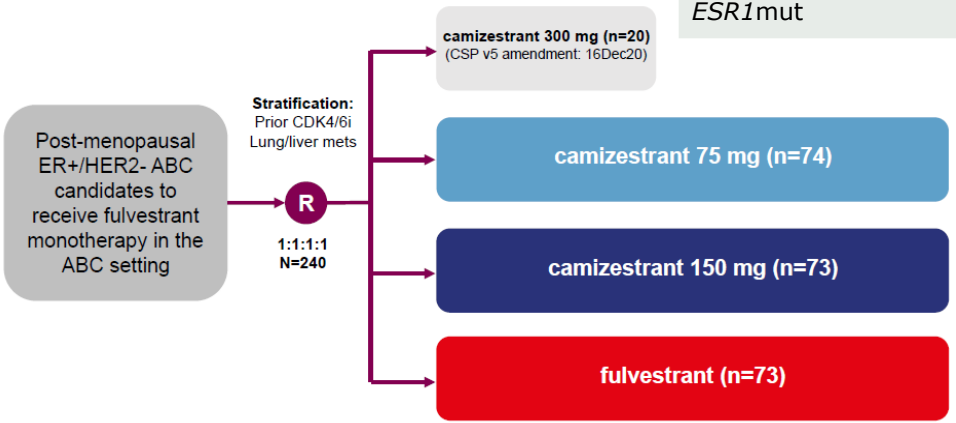
HR+ HER2- *metastatic* breast cancer

SERENA-2 (Camizestrant)

Patient Characteristics	%
2nd line	68.8%
Prior AI (mBC)	63.3%
Prior AI (eBC)	35.8%
Prior CDKi	49.6%
Visceral metastasis	58.3%
*ESR1*mut	37.7%

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

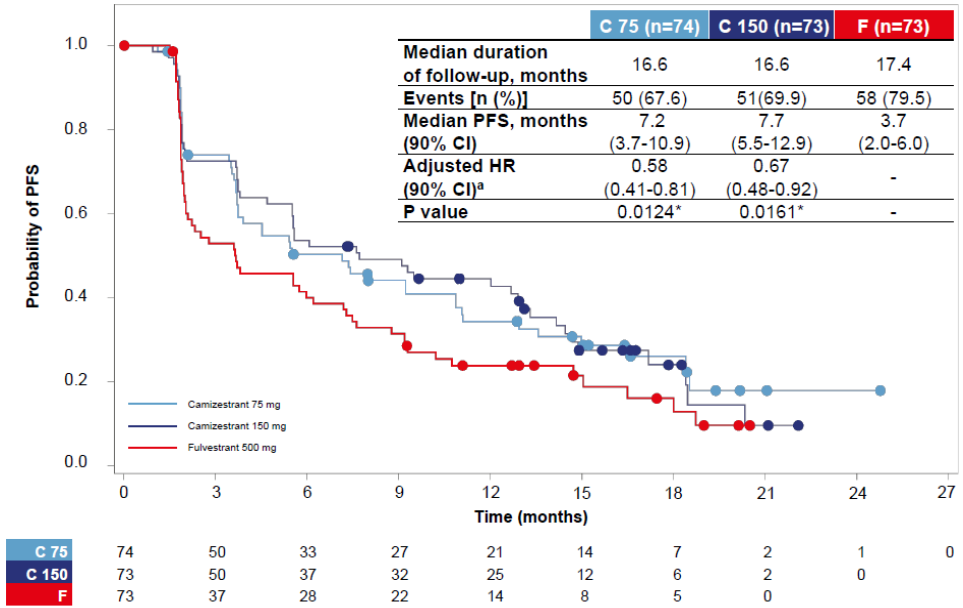
*disease progression assessed by the Investigator and defined using RECIST, version 1.1
ABC: advanced breast cancer; CBR24: clinical benefit rate at 24 weeks; CDK4/6i: CDK4/6 inhibitor; CT: chemotherapy; CTC: circulating tumor cells; ctDNA: circulating tumor DNA; ER: estrogen receptor; *ESR1*m: mutation in estrogen receptor 1 gene; ET: endocrine therapy; HER2: human epidermal growth factor; PFS: progression-free survival; R: randomization; RECIST: Response Evaluation Criteria for Solid Tumors; SERD: selective estrogen receptor degrader

1 Oliveira M et al. GS3-02; SABCS 2022.; 2 Oliveira M Lancet Oncol 2024;25:1424-1439

HR+ HER2- *metastatic* breast cancer

SERENA-2 (Camizestrant)

PFS (investigator assessed) - Primary endpoint



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

C 75	74	50	33	27	21	14	7	2	1	0
C 150	73	50	37	32	25	12	6	2	0	
F	73	37	28	22	14	8	5	0		

*Statistically significant; [a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

CDK4/6i: CDK4/6 inhibitor; CI: confidence interval; HR: hazard ratio; PFS: progression-free survival

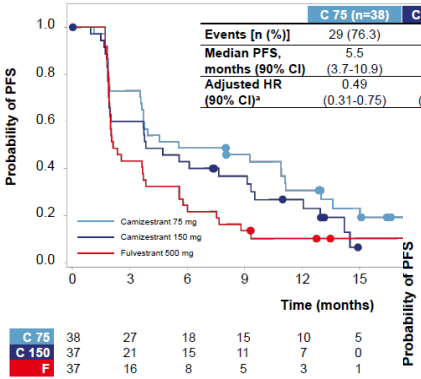
1 Oliveira M et al. GS3-02; SABCS 2022.; 2 Oliveira M Lancet Oncol 2024;25:1424-1439

HR+ HER2- *metastatic* breast cancer

SERENA-2 (Camizestrant)

Prior CDK4/6i

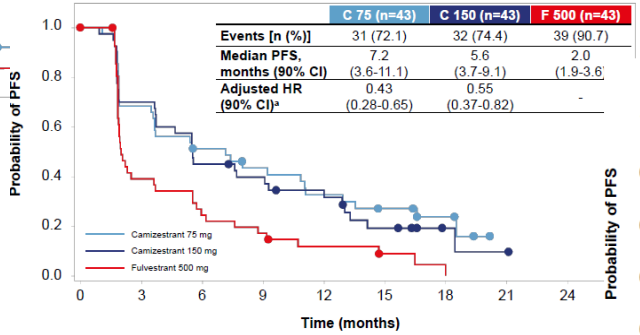
	C 75 (n=38)	C 150 (n=37)	F 500 (n=37)
Events [n (%)]	29 (76.3)	29 (78.4)	33 (89.2)
Median PFS, months (90% CI)	5.5 (3.7-10.9)	3.8 (2.0-7.6)	2.1 (1.9-3.7)
Adjusted HR (90% CI)[a]	0.49 (0.31-0.75)	0.68 (0.44-1.04)	-



C 75	38	27	18	15	10	5
C 150	37	21	15	11	7	0
F	37	16	8	5	3	1

Presence of lung and/or liver metastases

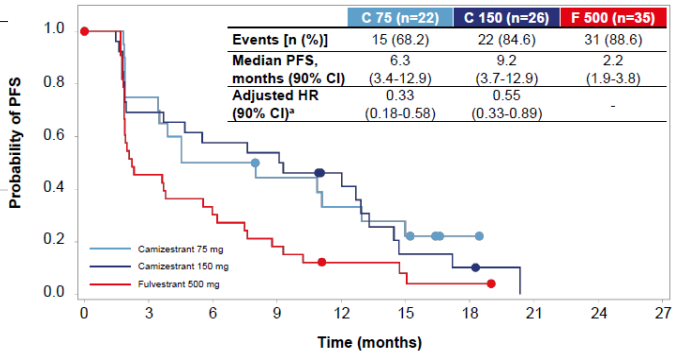
	C 75 (n=43)	C 150 (n=43)	F 500 (n=43)
Events [n (%)]	31 (72.1)	32 (74.4)	39 (90.7)
Median PFS, months (90% CI)	7.2 (3.6-11.1)	5.6 (3.7-9.1)	2.0 (1.9-3.6
Adjusted HR (90% CI)[a]	0.43 (0.28-0.65)	0.55 (0.37-0.82)	-



C 75	43	28	20	16	12	9	4	0
C 150	43	28	18	15	12	6	2	1	0
F	43	16	10	7	4	2	1	0

*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

1 Oliveira M et al. GS3-02; SABCS 2022.; 2 Oliveira M Lancet Oncol 2024;25:1424-1439

HR+ HER2- *metastatic* breast cancer

SERENA-2 (Camizestrant)

- Camizestrant grade 3/4 toxicity numerically dose-dependent
- Grade 3/4 toxicity C 75 mg comparable with fulvestrant
- 12.2% grade 1/2 photopsia
- No relevant nausea

	C 75 (n=74)		C 150 (n=73)		C 300 (n=20)		F 500 (n=73)	
AE, n (%)	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	57 (77.0)	9 (12.2)	66 (90.4)	16 (21.9)	19 (95.0)	3 (15)	50 (68.5)	10 (13.7)
Photopsia	9 (12.2)	0	18 (24.7)	0	7 (35.0)	0	0	0
(Sinus) bradycardia	4 (5.4)	0	19 (26.0)	0	8 (40.0)	0	0	0
Fatigue	4 (5.4)	0	13 (17.8)	1 (1.4)	4 (20.0)	0	3 (4.1)	0
Anemia	8 (10.8)	0	11 (15.1)	1 (1.4)	1 (5.0)	0	5 (6.8)	2 (2.7)
Asthenia	6 (8.1)	0	11 (15.1)	0	2 (10.0)	0	4 (5.5)	0
Arthralgia	3 (4.1)	0	9 (12.3)	1 (1.4)	2 (10.0)	0	2 (2.7)	0
AST increased	2 (2.7)	0	6 (8.2)	0	2 (10.0)	0	5 (6.8)	1 (1.4)
ALT increased	1 (1.4)	0	6 (8.2)	1 (1.4)	3 (15.0)	0	4 (5.5)	1 (1.4)
Covid-19	4 (5.4)	0	4 (5.5)	0	3 (15.0)	0	3 (4.1)	0
Diarrhea	4 (5.4)	0	4 (5.5)	0	3 (15.0)	1 (5.0)	2 (2.7)	1 (1.4)
Pain in extremity	1 (1.4)	0	4 (5.5)	1 (1.4)	2 (10.0)	0	3 (4.1)	0
Dyspepsia	1 (1.4)	0	3 (4.1)	0	2 (10.0)	0	1 (1.4)	0
Insomnia	1 (1.4)	0	3 (4.1)	0	2 (10.0)	0	1 (1.4)	0
Hyponatremia	0	0	3 (4.1)	1 (1.4)	2 (10.0)	0	1 (1.4)	1 (1.4)
Blood pressure increased	2 (2.7)	1 (1.4)	1 (1.4)	1 (1.4)	2 (10.0)	1 (5.0)	0	0
Cataract	2 (2.7)	0	0	0	2 (10.0)	0	0	0
Vitreous floaters	2 (2.7)	0	0	0	2 (10.0)	0	0	0

1 Oliveira M et al. GS3-02; SABCS 2022.; 2 Oliveira M Lancet Oncol 2024;25:1424-1439

HR+ HER2- *metastatic* breast cancer

Oral SERDs

San Antonio Breast Cancer Symposium®, December 6-10, 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).


So, Where are we exactly?

HR+ HER2- *metastatic* breast cancer
CDK4/6i and beyond

- CDK4/6i standard in 1st line therapy of HR+ HER2- MBC: Three available options (abemaciclib, palbociclib, ribociclib) – all substantially improve PFS (HR 0.5); ribociclib with significant OS benefit in 1st line
  - Safety profiles and monitoring requirements differ
- After CDK4/6i, no optimal standard – therapy depends on, eg, duration of response to prior CDK4/6i, biomarkers (eg, g*BRCA*, *PIK3CA*, *ESR1*), patient preferences, and access
- Guidelines recommend endocrine-based therapy for several lines in endocrine-sensitive MBC
- CDK4/6i after CDK4/6i is an evidence-based option for 2nd line therapy (postMONARCH, MAINTAIN)
- Elacestrant is the first oral SERD for clinical use – approved in *ESR1*mut tumors (EMERALD)
  - Efficacy increases with duration of prior CDK4/6i benefit
  - Manageable safety, low discontinuation rates
- Other oral SERDs in development – toxicities differ

Breast cancer

Guidelines, standards, and open questions . . .

WEBINAR DATE	ESMO DEEP DIVE WEBINAR SERIES 2024: BREAST CANCER Series Coordinators: Nadia Harbeck, Peter Schmid
7 February 2024	Loco-Regional Therapy in Times of Individualised (and Increasingly Neoadjuvant) Treatment Concepts
March 2024	Early Stage ER-positive Breast Cancer: Hot Topics and Future Trends
April 2024	Early Stage HER2-positive Breast Cancer: Hot Topics and Future Trends
May 2024	Early Stage TNBC: Hot Topics and Future Trends
June 2024	Breakthroughs in Personalised, Molecularly-informed Risk Prediction, Screening and Early Detection of Breast Cancer
July 2024	HR+ Metastatic Breast Cancer: Refining Practice and Steering Research
September 2024	HER2+ Metastatic Breast Cancer: Refining Practice and Steering Research
October 2024	TNBC Metastatic Breast Cancer: Refining Practice and Steering Research

2025 ESMO BREAST CANCER
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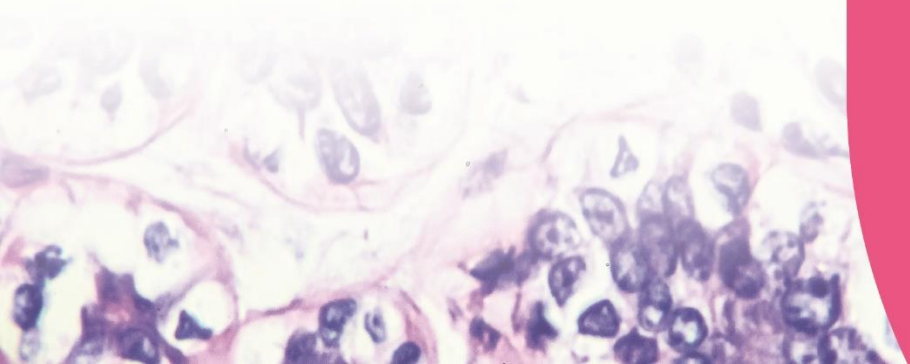
Global Breast Cancer Academy

Q&A



APTITUDE HEALTH

Objectives

Understand clinical and pathologic factors that influence first-line choice of therapy for patients with HR+ mBC

Discuss the role of biomarkers, molecular profiling, and resistance mechanisms in guiding treatment choices

Examine the role of targeted therapies following endocrine therapy failure

Gain insights into the care of patients with high-risk and endocrine-resistant HR+ mBC

Explore current and future sequencing strategies for HR+, HER2– mBC

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

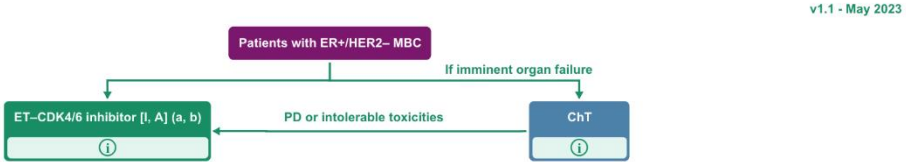
Beyond endocrine therapy in HR+ mBC

Pr Joseph Gligorov

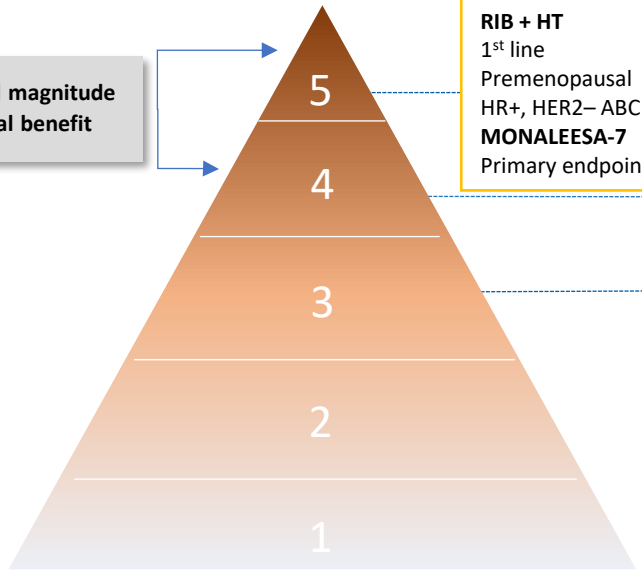
Disclosures

Affiliations/ disclosures	
Research and Care support	Eisai, Exact Science, Roche Genentech
Consultancy honoraria	Daiichi, Eisai, Exact Science, Eva Pharm, Lilly, Merck, Novartis, Onxeo, Pfizer, Roche Genentech, Seattle Genetics, Sothema
Stock options	Non
Family relationship	Non
Other (institutions & associations)	Sorbonne Université, AP-HP, Inserm (Employeurs et affiliations principales) Cours de Nice St Paul de Vence (responsabilité de programme de formation continue et de recommandations) ESMO, ESO, ABC, AROME, SoFOM, SFMPP, SPCC (membre de sociétés savants et associations médicales) Alliance Contre le Cancer, Vaincre le Cancer (associations de soutien à la recherche et aux soins)

Hypothesis


v1.1 - May 2023
Patients with ER+/HER2– MBC
If imminent organ failure
ET–CDK4/6 inhibitor [I, A] (a, b)
PD or intolerable toxicities
ChT

ESMO-MCBS Scoring: 1st line HR+ ABC



Final adjusted magnitudie of clinical benefit grade: OS, PFS, DFS, HR, RR, QoL, toxicity

Score: 5

RIB + HT
1st line
Premenopausal
HR+, HER2– ABC
MONALEESA-7
Primary endpoint: PFS

Score: 4

RIB + LET
1st line
Postmenopausal
HR+, HER2– ABC
MONALEESA-2
Primary endpoint: PFS

Score: 3

PAL + LET
1st line
Postmenopausal
ER/PR+ ABC
PALOMA-2
Primary endpoint: PFS

Score: 3

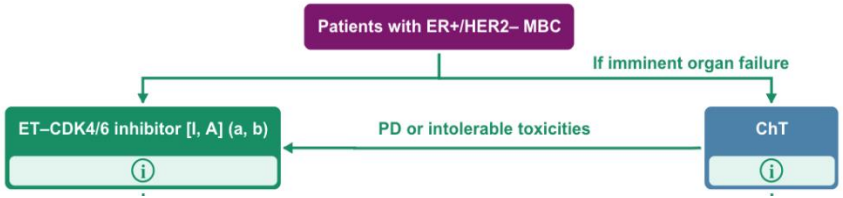
ABE + HT
1st line
Postmenopausal
ER/PR+ ABC
MONARCH-3
Primary endpoint: PFS

The ESMO-MCBS grading highlights treatments with substantially improve OS and/or the quality of life (QoL)

MCBS, Magnitude of Clinical Benefit Scale
ESMO-Magnitude of Clinical Benefit Scale (V1.1). Available at: https://www.esmo.org/guidelines/esmo-mcbs

What to do next ?

v1.1 - May 2023



Ann Oncol 2021;32(12): 1475-1495
ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023"

What do we now about expectations after 1st line CDK4/6 inh +ET ?

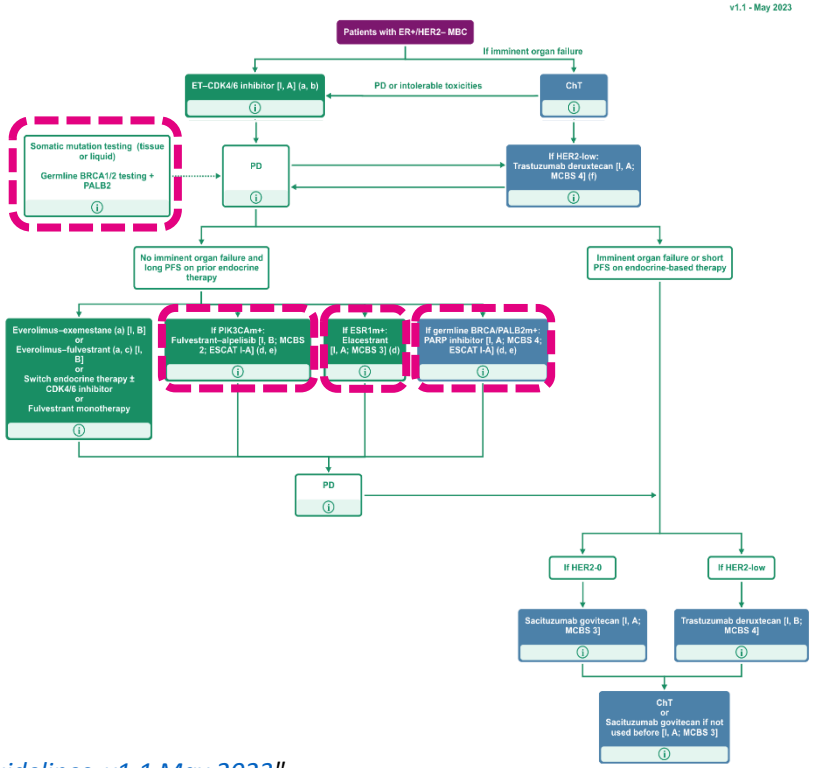
Table 1. Main characteristics and results of the studies included

	1st line										≥2nd line				1st and 2nd line	
	MONALEESA-2		MONALEESA-7		MONARCH-3		PALOMA-1		PALOMA-2		MONARCH-2		PALOMA-3		MONALEESA-3	
	Rib + L	Pbo + L	Rib + T/NSAI	Pbo + T/NSAI	Abe + NSAI	Pbo + NSAI	Pal + L	L	Pal + L	Pbo + L	Abe + F	Pbo + F	Pal + F	Pbo + F	Rib + F	Pbo + F
N	334	334	335	337	328	165	84	81	444	222	446	223	347	174	484	242
PFS2 median, months	NR	NR	NE	32.3	NR	NR	NR	NR	NR	NR	23.1	20.6	18.8	14.1	37.4	28.1
PFS2 HR (95% CI)	NR		0.69 (0.55-0.87)		0.64 (0.50-0.82)		NR		NR		0.68 (0.56-0.82)		0.68 (0.56-0.84)		0.69 (0.57-0.84)	
TTC median, months	50.6	38.9	NE	36.9	NR	NR	26.7	17.7	40.4	29.9	50.2	22.1	17.6	8.8	48.1	28.8
TTC HR (95% CI)	0.74 (0.61-0.91)		0.60 (0.46-0.77)		0.51 (0.38-0.69)		0.66 (0.45-0.99)		0.74 (0.59-0.92)		0.63 (0.50-0.78)		0.58 (0.47-0.73)		0.70 (0.57-0.88)	
PFS median, months	25.3	16.0	23.8	13.0	28.2	14.8	20.2	10.2	27.6	14.5	16.9	9.3	11.2	4.6	20.6	12.8
PFS HR (95% CI)	0.57 (0.46-0.70)		0.55 (0.44-0.69)		0.53 (0.42-0.67)		0.49 (0.32-0.75)		0.56 (0.46-0.69)		0.54 (0.45-0.65)		0.50 (0.40-0.62)		0.59 (0.49-0.71)	
OS median, months	63.9	51.4	NE	40.9	NR	NR	37.5	34.5	NR	NR	46.7	37.3	34.9	28.0	53.7	41.5
OS HR (95% CI)	0.76 (0.63-0.93)		0.71 (0.54-0.95)		NR		0.90 (0.62-1.29)		NR		0.76 (0.61-0.95)		0.81 (0.64-1.03)		0.73 (0.59-0.90)	

Abe, abemaciclib; CI, confidence interval; F, fulvestrant; HR, hazard ratio; L, letrozole; NE, not estimable; NR, not reported; NSAI, nonsteroidal aromatase inhibitor (letrozole or anastrozole); OS, overall survival; Pal, palbociclib; Pbo, placebo; PFS, progression-free survival; PFS2, second progression-free survival; Rib, ribociclib; T, tamoxifen; TTC, time to chemotherapy.

Munzone et al. Esmo open 2021

Do we need specific biomarkers, tests to improve treatment decision strategy?



Ann Oncol 2021;32(12): 1475-1495

ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023"

The key questions ?

- Is the tumour still endocrine sensitive, according to the resence of the target ?
- Do we have any mechanism of resistance we might target ?
- Do we have any other target of interest out of those involved in the ER pathway ?

Arguments to consider advanced ER positive breast cancer still endocrine sensitive after CDK4/6i + first line ET exposure

- Needs to have been considered ET at the previous line (including CDK4/6 inh exposure).
- Needs to still have the presence of the target (ER).
- Needs to verify the absence of mutations of the target.

ENDOCRINE SENSIVITY/RESISTANCE

NEW/MODIFIED

ET NAÏVE: unknown if there is sensitivity or resistance to endocrine therapy (ET) since has never received ET

PRIMARY ENDOCRINE RESISTANCE is defined as:

Relapse while on the first 2 years of adjuvant ET, or
PD within first 6 months of 1st line ET-based therapy for ABC
(note: this definition is the same regardless of whether therapy included a CDK4/6i or not)

SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE is defined as:

All other clinical situations of endocrine-resistance
(examples include: 1) Relapse while receiving adjuvant ET but after at least 2 years; 2) PD after at least 6 months of 1st line ET-based therapy for ABC; 3) PD after any duration of 2nd+ line ET-based therapy for ABC; 4) Known ESR1 mutation)
(note: definition unaffected by therapy with CDK4/6i, mTOR/PI3Ki, or other adjunctive drugs)

ENDOCRINE INSENSITIVITY is defined as:

PD within 2 months of later-line ET-based therapy for ABC and no additional ET-based approaches likely to result in clinically meaningful benefit

(LoE: Expert opinion/NA) (95%)

Note: resistance is a continuum, and these definitions help clinical trials but do not necessarily dictate clinical practice

F. Cardoso et al, The Breast 2024,

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Mays Cancer Center UT Health San Antonio MD Anderson Cancer Center
AACR American Association for Cancer Research

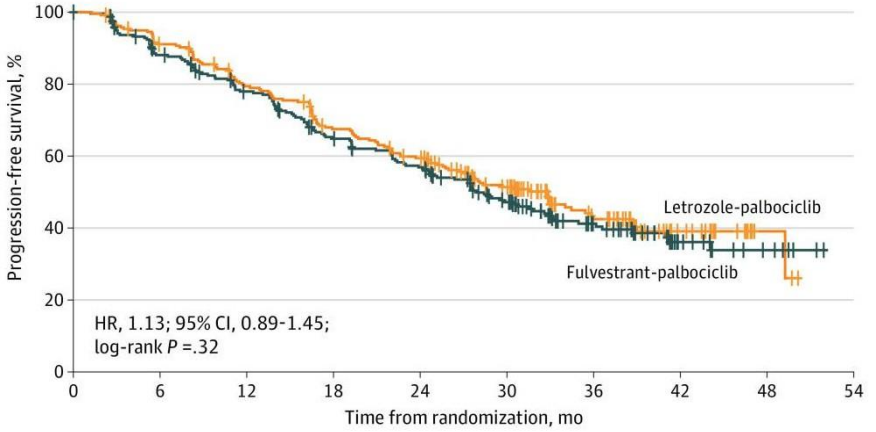
PARSIFAL-LONG: Extended follow-up of hormone receptor- positive/HER2-negative advanced breast cancer patients treated with fulvestrant and palbociclib vs letrozole and palbociclib in the PARSIFAL study

Antonio Llombart Cussac[1,2], José Manuel Pérez-García[1,3], Meritxell Bellet[4], Florence Dalenc[5], Miguel Gil-Gil[6], Manuel Ruiz-Borrego[7], Joaquín Gavila[8], Peter Schmid[9], Pilar Zamora[10], Duncan Wheatley[11], Eduardo Martínez-de Dueñas[12], Kepa Amillano[13], Antonio Anton[14], Paul Cottu[15], Gemma Viñas[16], Thierry Petit[17], Petra Tesarová[18], Juan Cueva[19], Marco Colleoni[20], Maria Purificación Martínez del Prado[21], Raquel Andres[22], Elena Aguirre[23], Marta Díaz[1], Susana Vitorino[1], Miguel Sampayo-Cordero[1], Javier Cortés[1,3,25]

1) Medica Scientia Innovation Research, Barcelona, Spain and Ridgewood, New Jersey, USA; 2) Hospital Arnau de Vilanova, Universidad Católica, Valencia, Spain; 3) International Breast Cancer Center, Pangaea Oncology, Quiron Group, Barcelona, Spain; 4) Vall d'Hebrón University Hospital, and Vall d'Hebrón Institute of Oncology (VHIO), Ba rcelona, Spain; 5) Oncopole Claudius Regaud, IU CT-, C RC T, Inserm, Depa rtment of Medical Oncology, Toulouse, France; 6) Medical Oncology Depa rtment, Institut Català d' Oncología, Insitut d'Investigació Biomèdica Bellvitge, Barcelona, Spain; 7) Hospital Universitario Virgen del Rocío, Sevilla, Spain 8) Medical Oncology Department, Fundación Instituto Valenciano de Oncología, Valencia, Spain; 9) Barts Experimental Cancer Medicine Centre, Barts Cancer Institute, Queen Ma ry University of London, and Barts Hospital, N HS Trust, London, United Kingdom; 10) Cent ro de Investigación Biomédica en Red de Oncología, Mad rid, Spain; 11) Royal Co rnwall Hospitals NHS Trust, Tru ro, United Kingdom; 12) Medical Oncology Department, Consorcio Hospitalario Provincial de Castellón, Castellón, Spain; 13) Medical Oncology Department, Hospital Universitari Sant Joan de Reus, Reus, Spain; 14) Depa rtment of Medical Oncology, Hospital Universitario Miguel Servet, IIS Aragón, Universidad de Zaragoza, Spain; 15) Oncologie Médicale, Institut Curie, PSL Research University, Paris, France; 16) Medical Oncology, Catalan Institute of Oncology, Hospital Universitari Dr. Josep Trueta, Girona, Spain; Precision Oncology Group (OncoGI R-Pro), Institut d'Investigació Biomèdica de Girona (IDIB GI), Salt, Spain; 17) Department of Medical Oncology, Cent re Paul Stauss, Strasbourg, France; 18) Depa rtment of Oncology, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; 19) Complexo Hospital Universitario de Santiago de Compostela, Santiago de Compostela, Spain; 20) Division of Medical Senology, Istituto Europeo di Oncologia (IEO), IR CCS, Milano, Italy; 21) Medical Oncology Department, Hospital Universitario Basurto, Bilbao, Spain; 22) Oncology Department, Hospital Lozano Blesa, Zaragoza, Spain; 23) Instituto Oncológico, Quriónsalud Zaragoza, Zaragoza, Spain; 24) Department of Medical Oncology, Hospital Universitario Miguel Servet, IIS Aragón, Universidad de Zaragoza, Spain; 25) Universidad Europea de Madrid, Madrid, Spain

Background: Parsifal Study

PARSIFAL (NCT02491983): An international, multicenter, phase II clinical trial assessing whether fulvestrant or letrozole was the optimal endocrine partner for palbociclib in patients with untreated, endocrine sensitive, HR[+]/HER2[-] advanced breast cancer



No. at risk

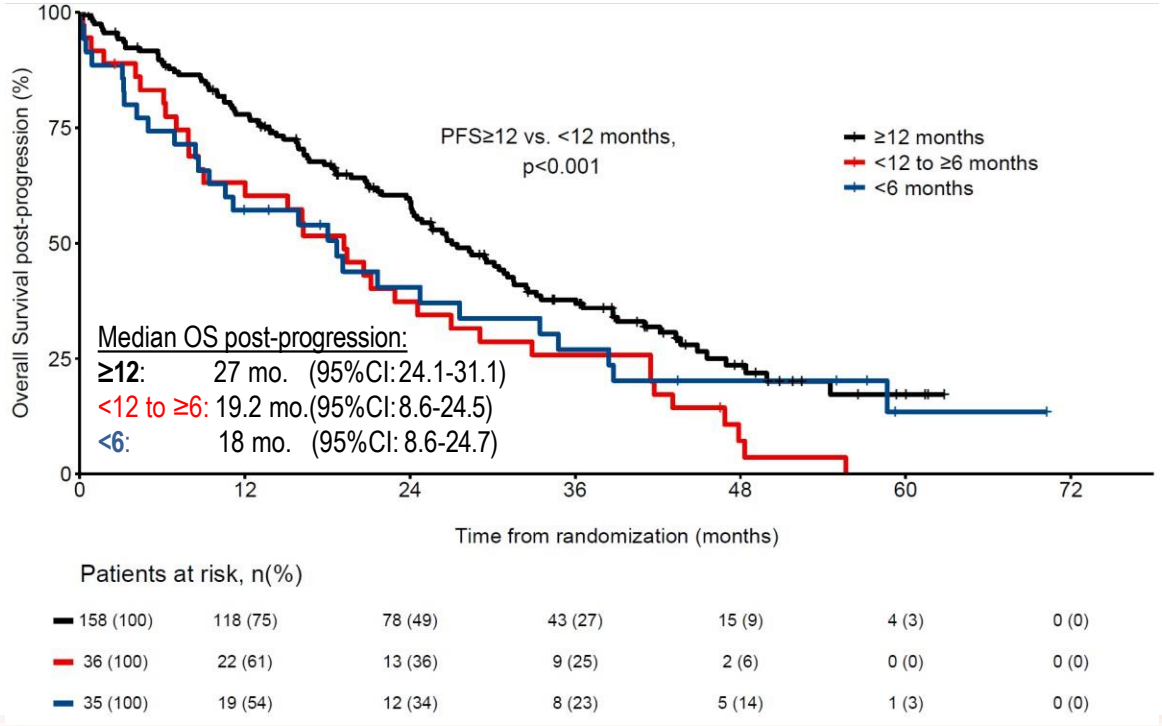
Fulvestrant-palbociclib	243 (100)	204 (84)	174 (72)	141 (58)	121 (50)	86 (35)	51 (21)	20 (8)	7 (3)	0 (0)
Letrozole-palbociclib	243 (100)	212 (87)	182 (75)	151 (62)	131 (54)	92 (38)	51 (21)	23 (9)	3 (1)	0 (0)

The trial failed to demonstrate an improvement in PFS of palbociclib + fulvestrant over palbociclib + letrozole, with a median follow-up of 32 months (IQR, 24.2-39.7).

Llombart-Cussac A, et al. *JAMA Oncol*. 2021 Dec 1;7(12):1791-1799.

IQR: Interquartile range (25% and 75%); HR: hazard ratio; No.: number of patients; mo: months

Results: Post-progression Survival by PFS duration (< 6, 6 - 12, and ≥12 months) for progressing patients (n=229)



Events per cohort:

≥12:	103 (65.2%)
<12 to ≥6:	34 (94.4%)
<6:	27 (77.1%)

n (%), number of patients (percentage based on N); N: number of patients; mo.: months; OS: overall survival; PFS: progression-free survival

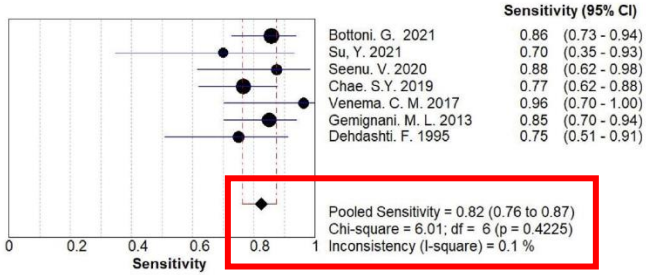
18F-fluoroestradiol positron emission tomography in patients with breast cancer: a systematic review and meta-analysis

Cristina S. Matushita[1,2,3], Francisco de Assis Romeiro Figueiroa Benicio Coelho[4,5], Camila Edith Stachera Stasiak[5,6], Denise Ferreira Rodrigues[7,8], Diego Bromfman Pianta[1,2,3], Flávia Dornelas Kurkowski[2], Marcelo Moreira da Silva[3,9], Sergio Augusto Lopes de Souza[5], Rafael Willain Lopes[1,10], Paulo Henrique Rosado de Castro[1,2,3*]

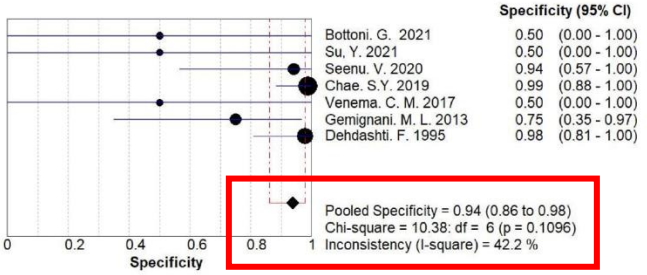
Brazilian Society of Nuclear Medicine

Rev Assoc Med Bras. 2023;69(Suppl 1):e2023S116

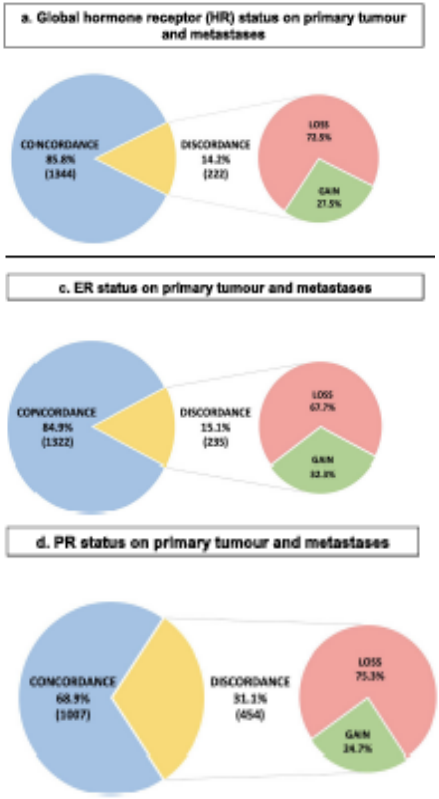
- 18F-FES PET for the detection of ER-positive lesions in breast cancer patients is
- Sensitive: a pooled sensitivity of 82%
- Highly specific: a pooled specificity of 94%
- High diagnostic accuracy: a pooled AUC of 0.8899
- Potential to be added to the breast cancer toolbox as an imaging tool for therapy guiding and predicting the endocrine therapy response

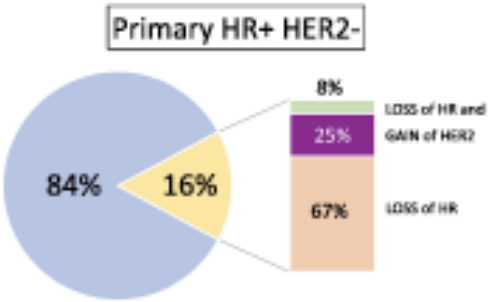


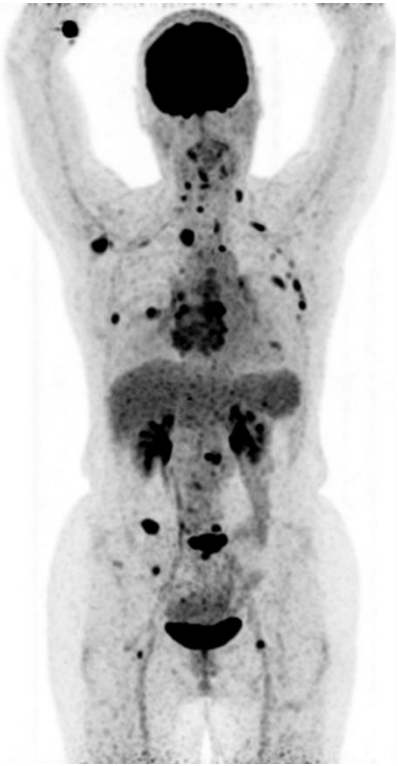
Analysis Options:
Add 1/2 to all cells of all studies
Filter OFF



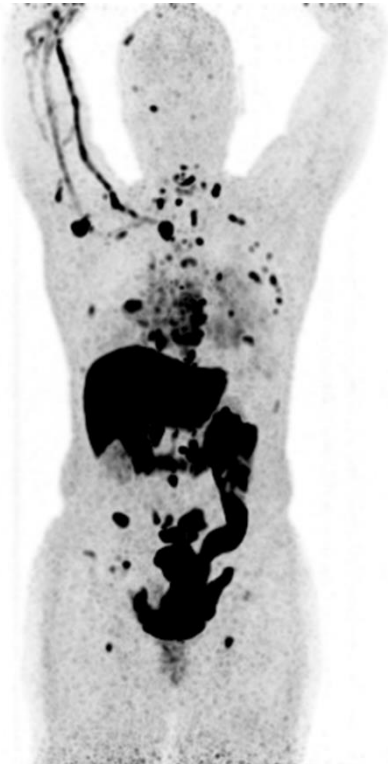
HR positivity and Cancer heterogeneity…







(^{18}F)-FDG at 60 min



(^{18}F)-FES at 60 min

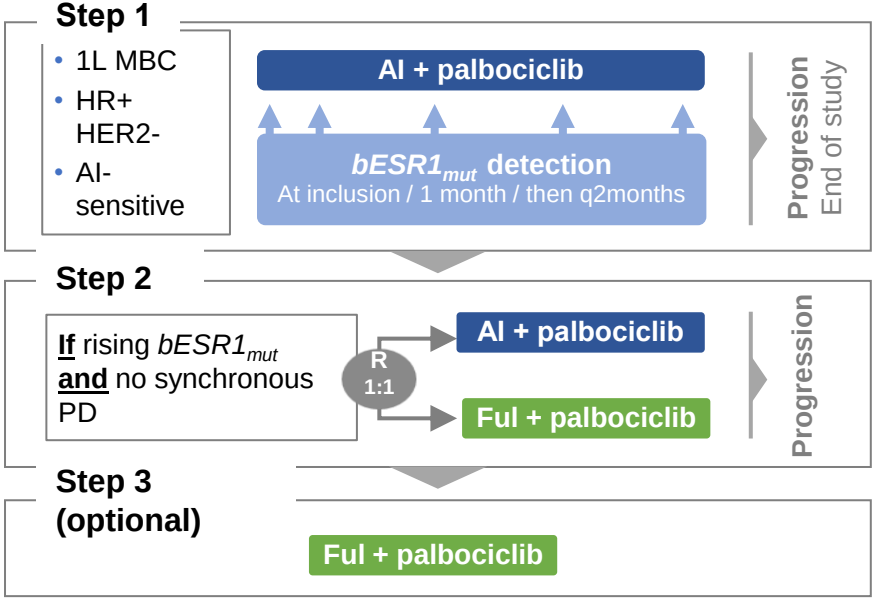
Courtesy Dr K Kerrou

Grinda T et al. NPJ J Breast Cancer 2021

Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising *ESR1* mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial

François-Clément Bidard, Anne-Claire Hardy-Bessard, Florence Dalenc, Thomas Bachelot, Jean-Yves Pierga, Thibault de la Motte Rouge, Renaud Sabatier, Caroline Dubot, Jean-Sébastien Frenel, Jean Marc Ferrero, Sylvain Ladoire, Christelle Levy, Marie-Ange Mouret-Reynier, Alain Lortholary, Julien Grenier, Camille Chakiba, Laetitia Stefani, Jérôme Edouard Plaza, Florian Clatot, Luis Teixeira, Véronique D'Hondt, Hélène Vegas, Olfa Derbel, Claire Garnier-Tixidre, Jean-Luc Canon, Barbara Pistilli, Fabrice André, Laurent Arnould, Anne Pradines, Ivan Bièche, Céline Cuillerai, Jérôme Lemonnier, Frédérique Berger, Suzette Delaloge, on behalf of the PADA-1 investigators

Lancet Oncol 2022; 23: 1367–77



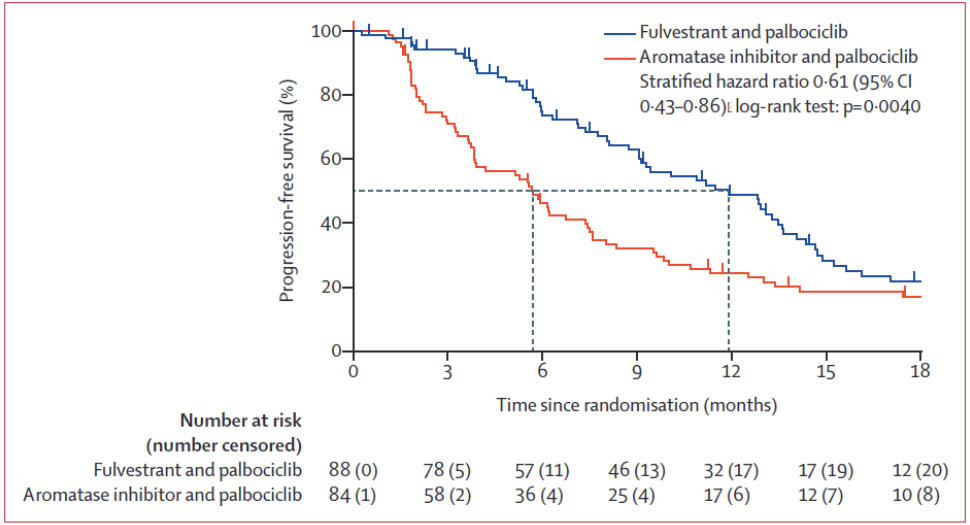


Figure 2: Progression-free survival in the second step, by treatment group (co-primary endpoint)

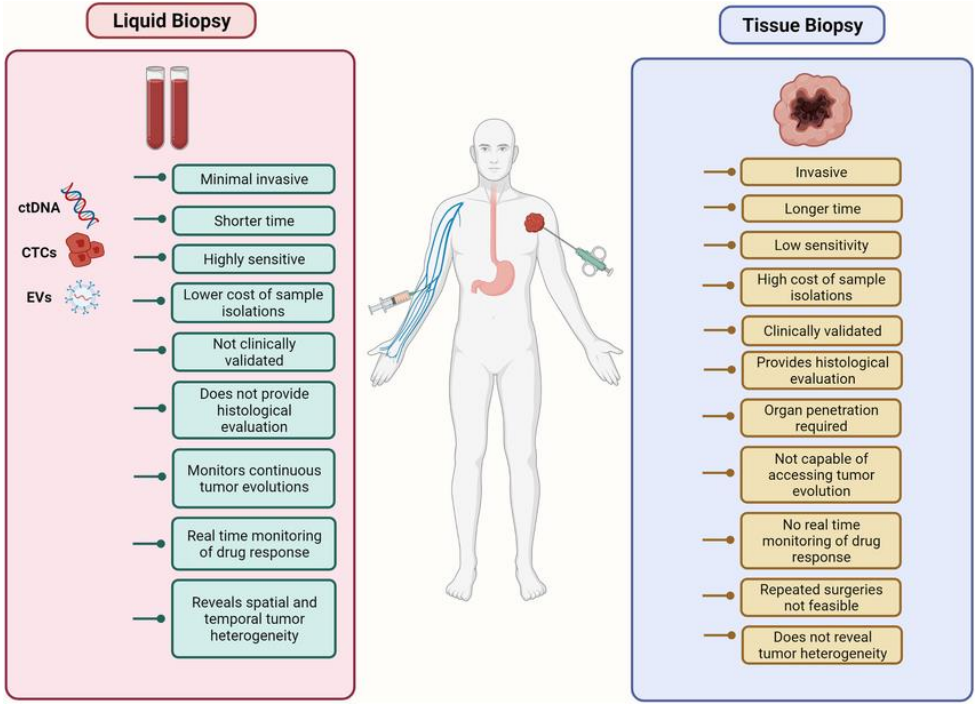
Conclusion 1

- Since CDK4/6i are part of 1st-line ET strategy, it might be important that we redefine endocrine treatment sensitivity

- We know, that lost of ER is frequent in metastatic situation, but moreover it is heterogenous, and other approaches might be helpful to better appreciate tumour heterogeneity

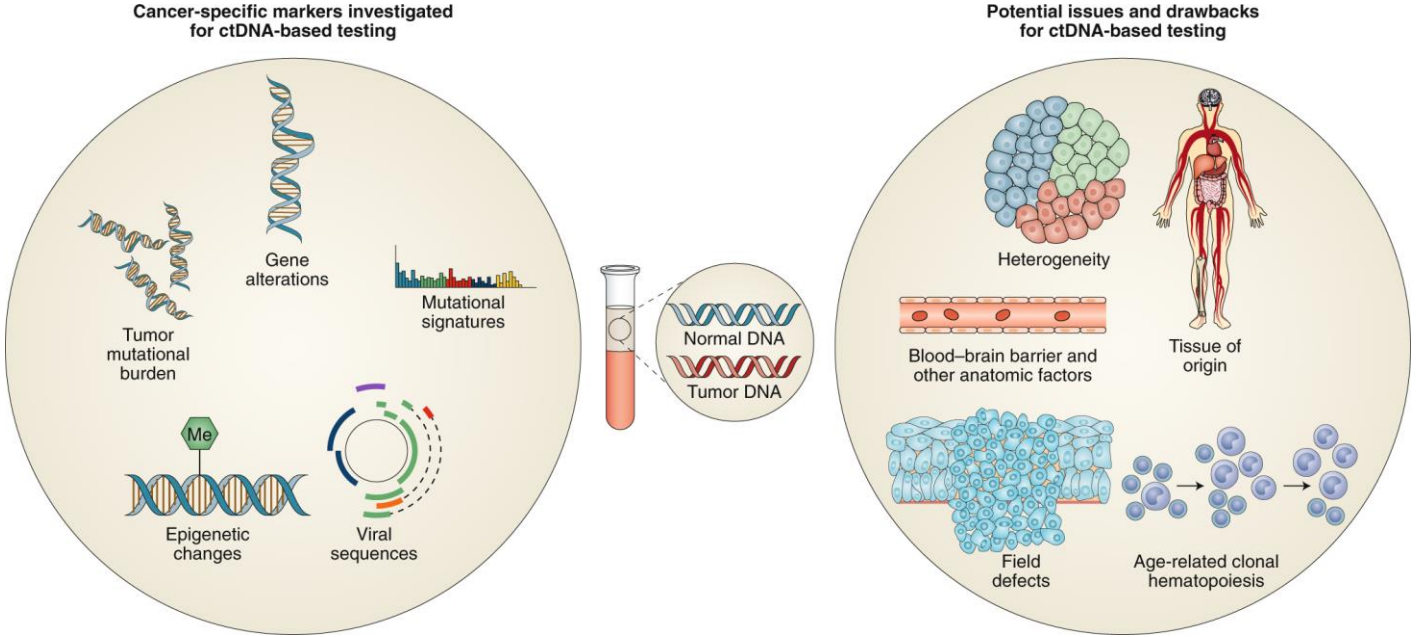
- Concerning ER, mutation rate is increasing during metastatic disease journey and might clearly influence ET sensitivity and choice…

Arguments to consider advanced ER positive breast cancer still endocrine sensitive after CDK4/6i + first line ET exposure… <u>but need to target a mechanism of resistance</u>



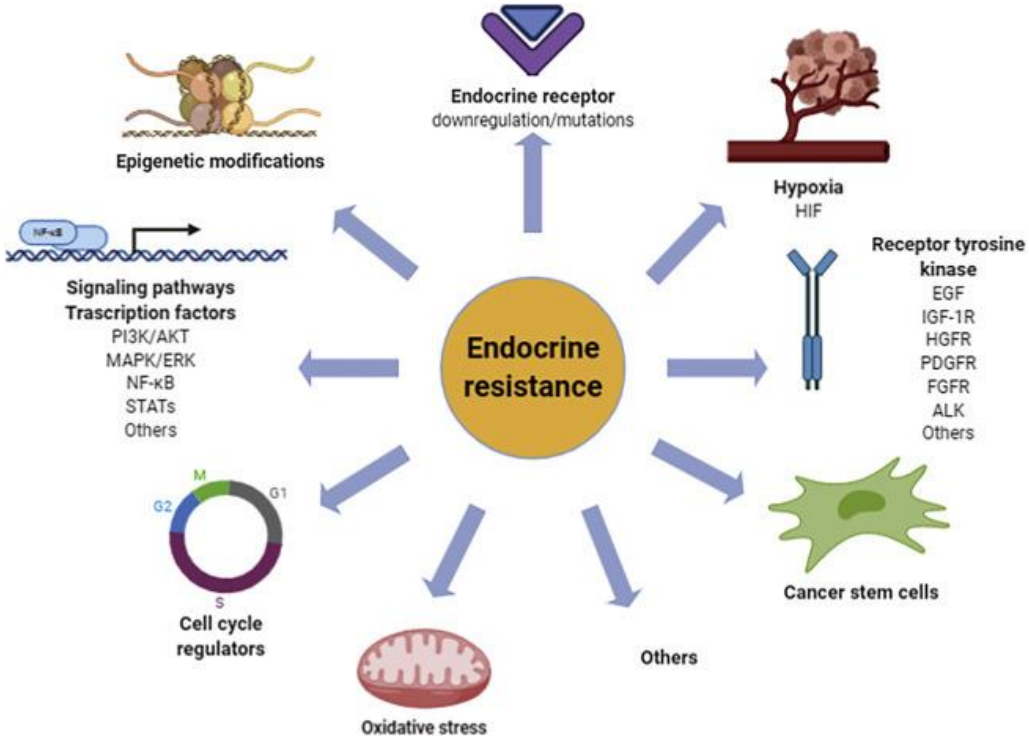
Lone et al. Molec Cancers 2022

Arguments to consider advanced ER positive breast cancer still endocrine sensitive after CDK4/6i + first line ET exposure… but need to target a mechanism of resistance



Cescon et al. Nature Cancer 2020

Arguments to consider advanced ER positive breast cancer still endocrine sensitive after CDK4/6i + first line ET exposure… <u>but need to target a mechanism of resistance</u>



Dimitrakopoulos et al. Cancer Letters 2021

Incidence of targetable alterations after CDK4/6i exposure

ORIGINAL ARTICLE

Acquired gene alterations in patients treated with ribociclib plus endocrine therapy or endocrine therapy alone using baseline and end-of-treatment circulating tumor DNA samples in the MONALEESA-2, -3, and -7 trials

F. André[1*], N. Solovieff[2], F. Su[3], A. Bardia[4], P. Neven[5], Y. S. Yap[6], D. Tripathy[7], Y.-S. Lu[8], D. Slamon[9], S. Chia[10], M. Joshi[2], A. Chakravartty[3], A. Lteif[3], T. Taran[11] & C. L. Arteaga[12*]

[1]Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; [2]Novartis Pharmaceuticals Corporation, Cambridge; [3]Novartis Pharmaceuticals Corporation, East Hanover; [4]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, USA; [5]Multidisciplinary Breast Centre, Universitair Ziekenhuis Leuven, Leuven, Belgium; [6]National Cancer Centre Singapore, Singapore, Singapore; [7]The University of Texas MD Anderson Cancer Center, Houston, USA; [8]National Taiwan University Hospital, Taipei, Taiwan; [9]David Geffen School of Medicine at UCLA, Los Angeles, USA; [10]British Columbia Cancer Agency, Vancouver, Canada; [11]Novartis Pharma AG, Basel, Switzerland; [12]UT Southwestern Simmons Comprehensive Cancer Center, Dallas, USA

Table 1. Progression-free survival in the biomarker and ITT populations

Biomarker population	Events (*n* *N*)	Median PFS (months)	Con dence interval (95)
Placebo + ET	217/274	10.9	7.4-12.8
Ribociclib + ET	167/249	14.5	11.3-16.4
ITT population	**Events (*n* *N*)**	**Median PFS (months)**	**Con dence interval (95)**
Placebo + ET	547/913	14.1	12.9-15.0
Ribociclib + ET	483/1153	23.0	22.1-24.8

ET endocrine therapy; ITT intention-to-treat; PFS progression-free survival.

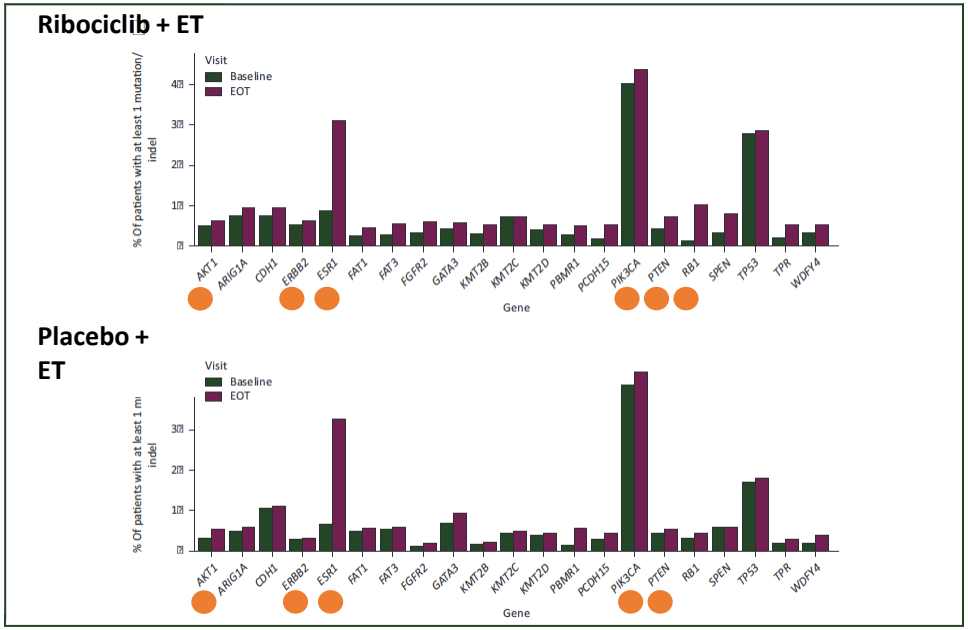


Figure 2. **Prevalence of gene alterations at baseline versus EOT with (A) ribociclib plus ET and (B) placebo plus ET[a].**
EOT, end of treatment; ET, endocrine therapy.
[a]Paired samples. Genes with an alteration prevalence of >5 at EOT were selected.

André et al. Ann Oncol 2024

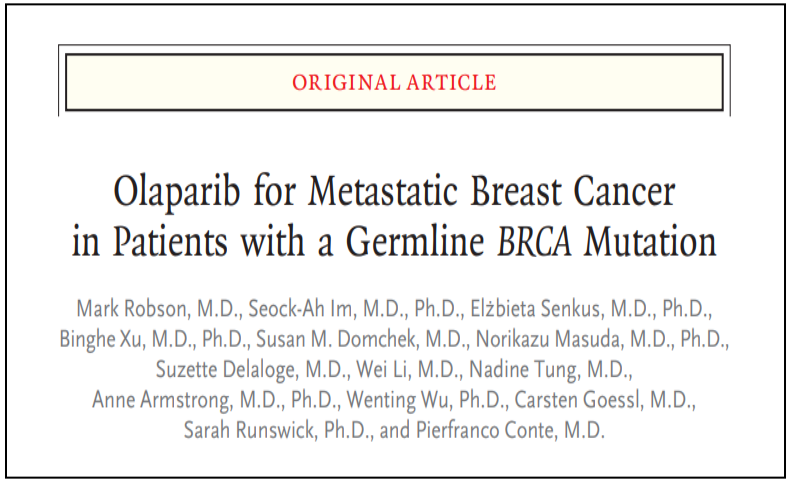
Conclusion 2

In practice, at least …and if corresponding drugs available

	When?	*How do we do it?*
BRCA 1/2	From the first line	Germinal (tumour screening possible)[3]
HER2	From the first line	IHC+/-ISH tumour
ESR1	On the second line	Priority liquid biopsy
PIK3CA	On the second line	Liquid biopsy or tumour
AKT	On the second line	Liquid biopsy or tumour
***PTEN* inactivation**	On the second line	Liquid biopsy or tumour
HER2 mutations	On the second line	Liquid biopsy or tumour

1. *Cardoso F et al. Ann Oncol 2020;31:1623-49; 2. Gennari A et al. Ann Oncol 2021;32:1475-95; 3. INCa guidelines 2019 PARP inhibitors: recommendations for a pathway in oncology genetics.*

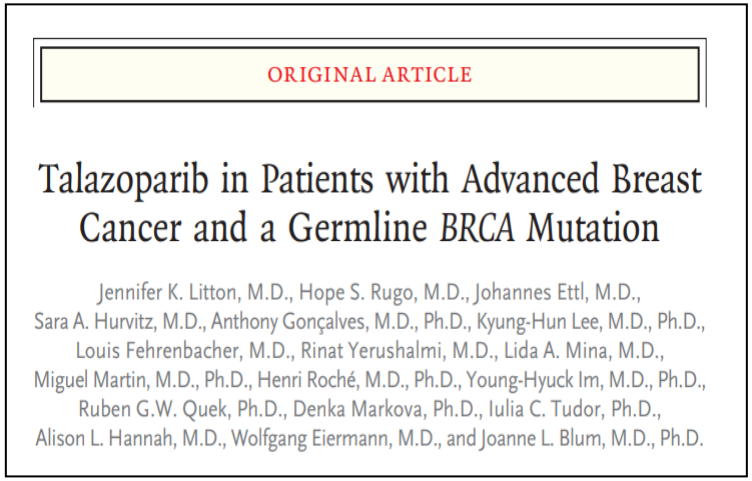
1- Targeting the BRCA germline mutation



ORIGINAL ARTICLE

Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.



ORIGINAL ARTICLE

Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation

Jennifer K. Litton, M.D., Hope S. Rugo, M.D., Johannes Ettl, M.D., Sara A. Hurvitz, M.D., Anthony Gonçalves, M.D., Ph.D., Kyung-Hun Lee, M.D., Ph.D., Louis Fehrenbacher, M.D., Rinat Yerushalmi, M.D., Lida A. Mina, M.D., Miguel Martin, M.D., Ph.D., Henri Roché, M.D., Ph.D., Young-Hyuck Im, M.D., Ph.D., Ruben G.W. Quek, Ph.D., Denka Markova, Ph.D., Iulia C. Tudor, Ph.D., Alison L. Hannah, M.D., Wolfgang Eiermann, M.D., and Joanne L. Blum, M.D., Ph.D.

Treatment of 2nd line: BRCA germline mutation (key messages)

- Cancer sein HER2 négatif métastatique
- RE pos ou RP pos ou triple négatif
- Mutation germinale BRCA

- CT (néo)adjuvante par Anthracyclines et Taxanes
- Si RH positifs,
  - au moins une ligne d'hormonothérapie adjuvante ou métastatique

- ≤2 lignes de Chimiothérapie (CT) métastatiques
- Si traitement antérieur par Sels de Platine
  - Progression > 12 mois après Sels de Platine en (neo)adjuvant
  - Pas de progression sous Sels de Platine en métastatique

Stratification
- Chimiothérapie métastatique antérieure : Oui vs Non ,
- Statut RH : RH positifs vs Triple Négatif,
- Traitement antérieur par Sels de Platine Oui vs Non

OLAPARIB 300mg x 2/ jour

R 2:1

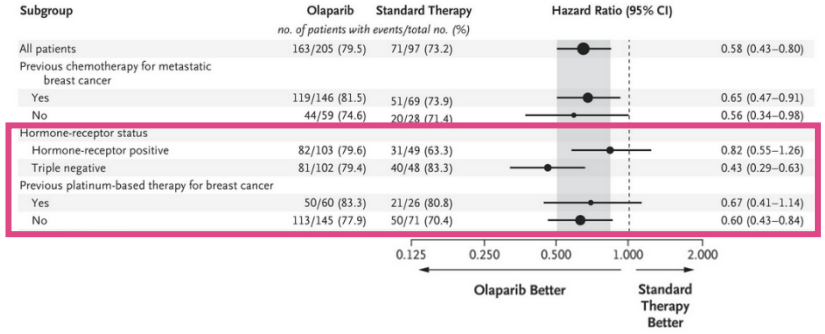
205

97

OLYMPIAD

NCT02000622

Traitement au choix de l'investigateur :
- Capecitabine 1250mg/m² x 2/ j 14j/21
- Vinorelbine IV 30 mg/m² à J1 et J8 (J1=J21)
- Eribulin 1,4 mg/m² à J1 et J8 (J1=J21)



- Cancer sein HER2 négatif métastatique
- RE pos ou RP pos ou triple négatif
- Mutation germinale BRCA

- CT (néo)adjuvante par Anthracyclines et/ou Taxanes
- Si RH positifs,
  - Pas de limite de lignes d'HT

- ≤3 lignes de Chimiothérapie (CT) métastatiques
- Si traitement antérieur par Sels de Platine
  - Progression > 6 mois après Sels de Platine en (neo)adjuvant
  - Pas de progression sous Sels de Platine en métastatique

Stratification
- Nb de Chimiothérapie métastatique antérieure : 0 vs 1-3,
- Statut RH : RH positifs vs Triple Négatif,
- Métastases du SNC Oui vs Non

TALAZOPARIB 1mg / jour

R 2:1

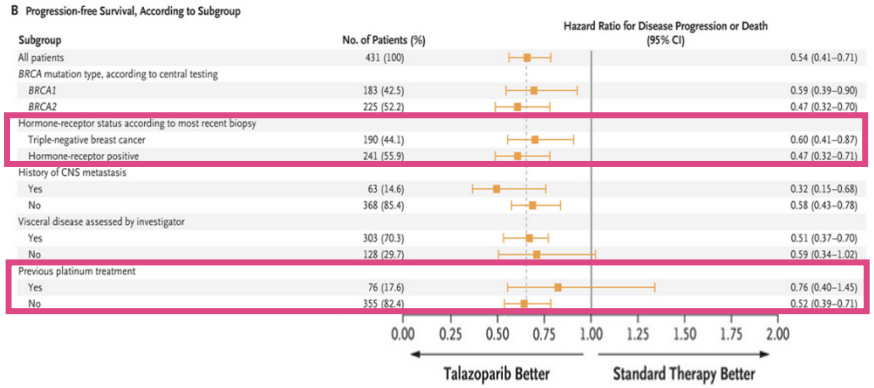
287

144

EMBRACA

NCT01945775

Traitement au choix de l'investigateur :
- Capecitabine,
- Vinorelbine
- Eribulin
- Gemcitabine



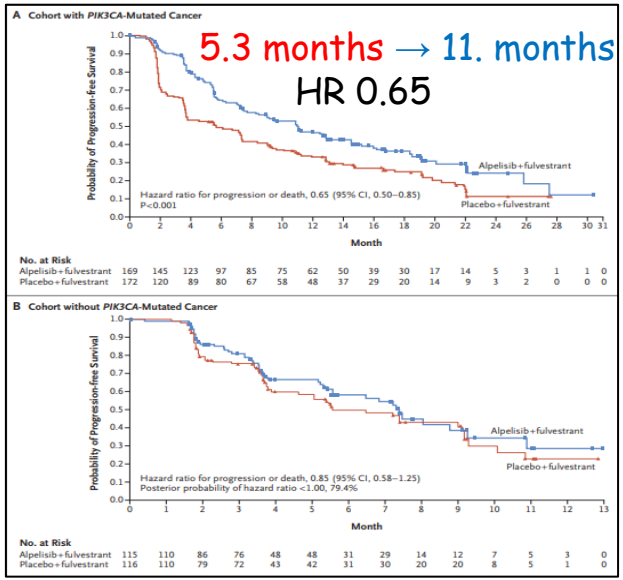
Positive studies in PFS (main objective) - but **not in OS**

2- Targeting the PI3K/AKT/m-TOR pathway

- Targeting *PIK3CA* mutations: alpelisib
- Targeting the activated pathway (*PIK3CA/AKT* mutations and/or loss of PTEN): capivasertib
- Suggest an m-TOR inhibitor: everolimus

Targeting *PIK3CA* mutations (Alpelisib, not reimbursed in France)

SOLAR-1 study: PFS



PIK3CA mutation (n=341)

No *PIK3CA* mutation (n=331)

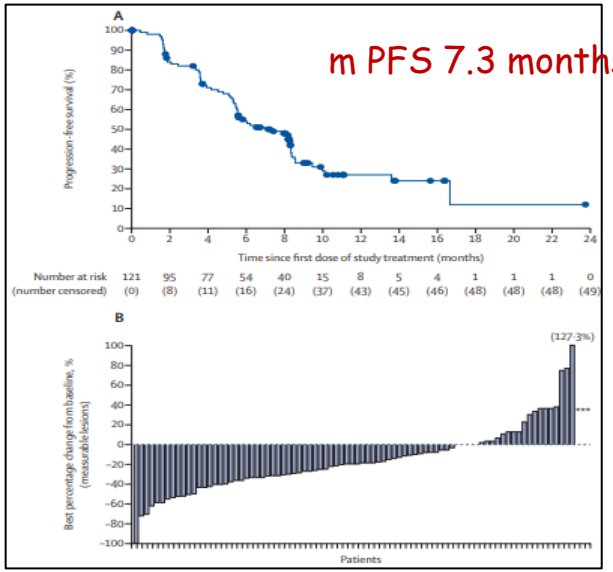
6% of patients had an i CDK4-6

Negative study in OS but + 7.9 months

André F et al, NEJM 2019 and Ann Oncol, 2021

BYLieve study (post CDK)

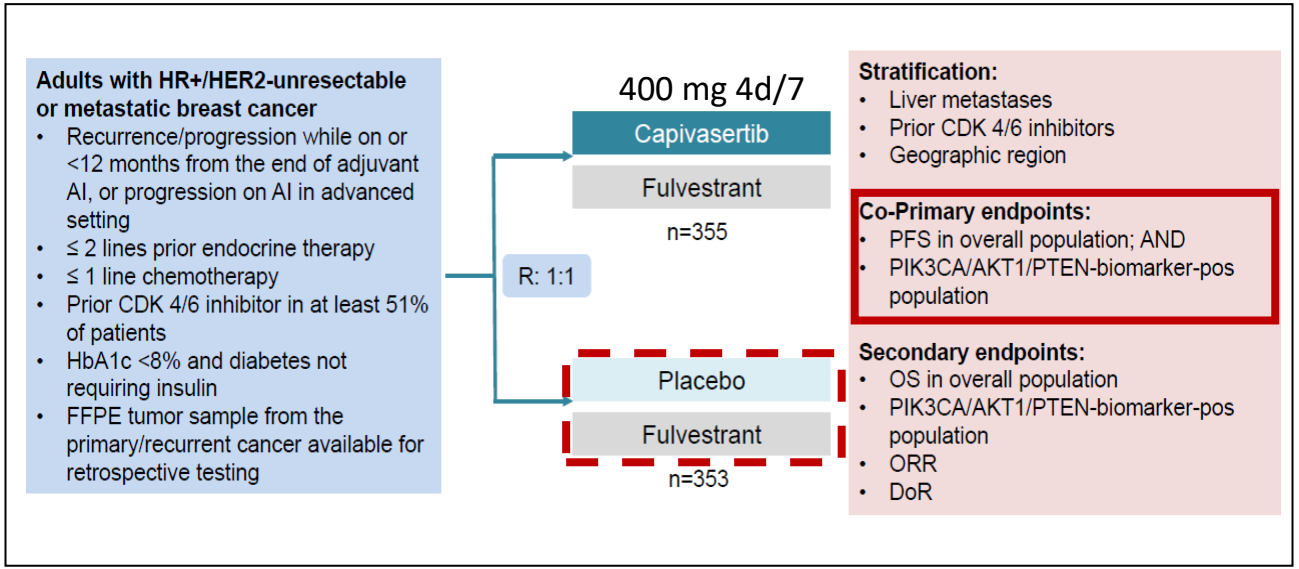
N = 127



Rugo HS et al, Lancet Oncol 2021

Capivasertib (pan-AKT inhibitor)

CAPITELLO-291 study



70% of patients had a CDK4-6i

17% no data on PIK3CA

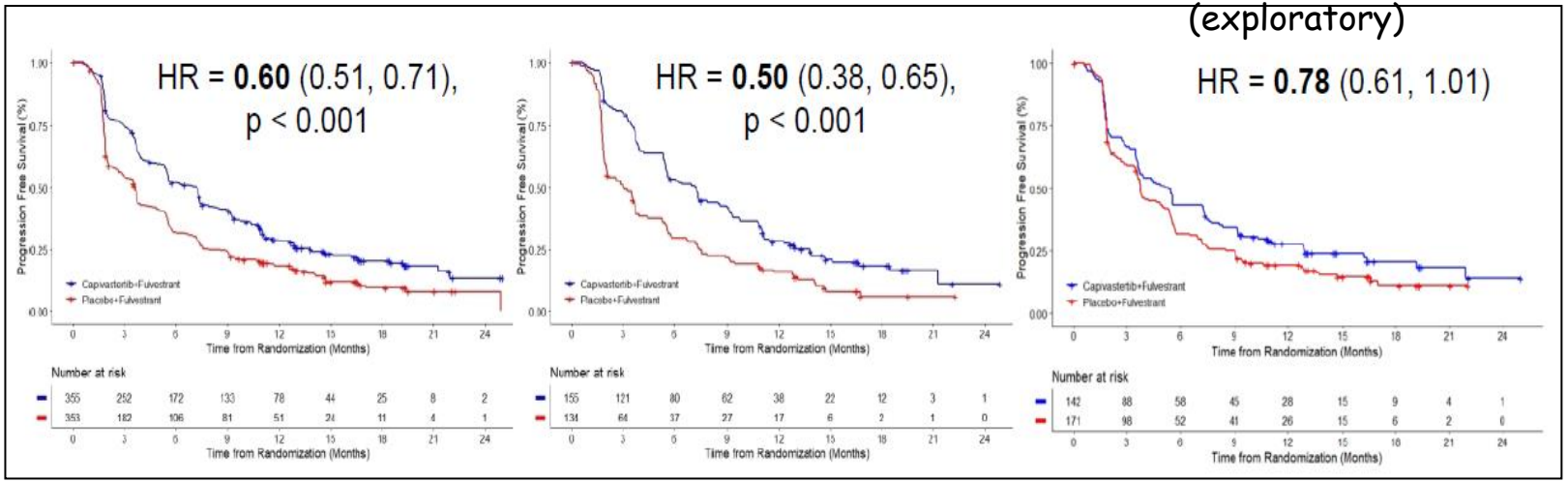
Capivasertib

CAPITELLO-291 study: results

Total population n=708

Population pathway activation n= 289

Population without activation of the track n= 313 (exploratory)



mPFS 3.6 → 7.2 months

3.1→ 7.3 months

3.7→ 5.3 months

Turner N et al, NEJM 2023

Capivasertib

CAPITELLO-291 study: Side effects

Table 2. Most Frequent Adverse Events in the Overall Population (Safety Population).*

Event	Capivasertib–Fulvestrant (N=355)					Placebo–Fulvestrant (N=350)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)									
Any adverse event	343 (96.6)	52 (14.6)	139 (39.2)	139 (39.2)	9 (2.5)	288 (82.3)	115 (32.9)	118 (33.7)	44 (12.6)	10 (2.9)
Diarrhea	257 (72.4)	164 (46.2)	60 (16.9)	33 (9.3)	0	70 (20.0)	60 (17.1)	9 (2.6)	1 (0.3)	0
Rash†	135 (38.0)	57 (16.1)	35 (9.9)	43 (12.1)	0	25 (7.1)	19 (5.4)	5 (1.4)	1 (0.3)	0
Nausea	123 (34.6)	85 (23.9)	35 (9.9)	3 (0.8)	0	54 (15.4)	42 (12.0)	10 (2.9)	2 (0.6)	0
Fatigue	74 (20.8)	49 (13.8)	23 (6.5)	2 (0.6)	0	45 (12.9)	35 (10.0)	8 (2.3)	2 (0.6)	0
Vomiting	73 (20.6)	54 (15.2)	13 (3.7)	6 (1.7)	0	17 (4.9)	10 (2.9)	5 (1.4)	2 (0.6)	0
Headache	60 (16.9)	47 (13.2)	12 (3.4)	1 (0.3)	0	43 (12.3)	33 (9.4)	8 (2.3)	2 (0.6)	0
Decreased appetite	59 (16.6)	37 (10.4)	21 (5.9)	1 (0.3)	0	22 (6.3)	11 (3.1)	9 (2.6)	2 (0.6)	0
Hyperglycemia	58 (16.3)	24 (6.8)	26 (7.3)	7 (2.0)	1 (0.3)	13 (3.7)	8 (2.3)	4 (1.1)	1 (0.3)	0
Stomatitis	52 (14.6)	24 (6.8)	21 (5.9)	7 (2.0)	0	17 (4.9)	15 (4.3)	2 (0.6)	0	0
Asthenia	47 (13.2)	29 (8.2)	14 (3.9)	4 (1.1)	0	36 (10.3)	31 (8.9)	3 (0.9)	2 (0.6)	0
Pruritus	44 (12.4)	32 (9.0)	10 (2.8)	2 (0.6)	0	23 (6.6)	19 (5.4)	4 (1.1)	0	0
Anemia	37 (10.4)	15 (4.2)	15 (4.2)	7 (2.0)	0	17 (4.9)	4 (1.1)	9 (2.6)	4 (1.1)	0
Urinary tract infection	36 (10.1)	8 (2.3)	23 (6.5)	5 (1.4)	0	23 (6.6)	2 (0.6)	21 (6.0)	0	0

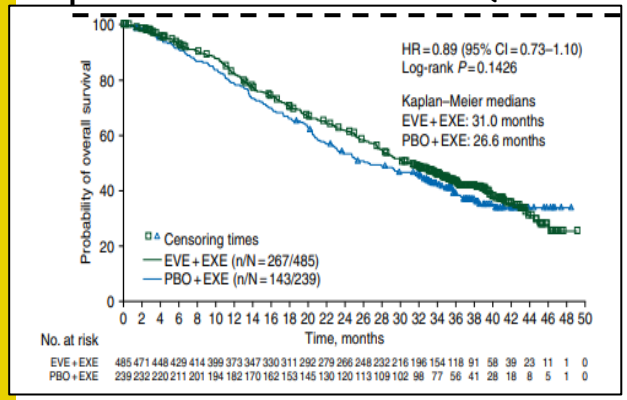
* The safety population included all the patients who received at least one dose of capivasertib, fulvestrant, or placebo. The listed events were reported as a single term (or for rash, as a group term) in at least 10% of the patients for any grade in the capivasertib–fulvestrant group. Adverse events are reported regardless of the relationship to capivasertib, fulvestrant, or placebo.

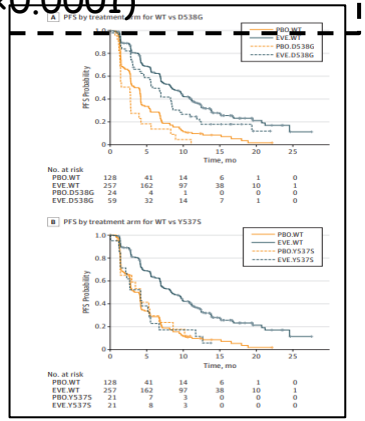
† The group term of rash includes the preferred terms of rash, rash macular, maculopapular rash, rash papular, and rash pruritic.

Fulvestrant / Exemestane + Everolimus

BOLERO 2 study, phase III

N= 724 postmenopausal patients, R 2:1 (everolimus vs placebo)
One line of stage IV CT admitted
Before the era of CDK4-6 inhibitors
PFS: 3.2 → 7.8 months (HR 0.46; p<0.0001)





MANTA study, phase II

Table. Primary and Key Secondary Efficacy End Points

End Point	Fulvestrant Plus Daily Vistusertib (n = 101)	Fulvestrant Plus Intermittent Vistusertib (n = 95)	Fulvestrant (n = 66)	Fulvestrant Plus Everolimus (n = 64)
PFS, median (95% CI), mo	7.6 (5.9-9.4)	8.0 (5.6-9.9)	5.4 (3.5-9.2)	12.3 (7.7-15.7)
HR vs fulvestrant (95% CI)	0.88 (0.63-1.24)	0.79 (0.55-1.12)	NA	NA
P value	.46	.16	NA	NA
HR vs fulvestrant plus everolimus (95% CI)	0.63 (0.45-0.90)	0.71 (0.49-1.01)	0.63 (0.42-0.92)	NA
P value	.01	.06	.01	NA
Objective response rate, % (95% CI)	31.6 (21.4-43.3)	28.6 (18.8-40.0)	26.0 (14.6-40.3)	41.2 (27.6-55.8)
Clinical benefit rate, % (95% CI)	44.7 (33.3-56.6)	39.0 (28.0-50.8)	38.0 (24.7-52.8)	56.9 (42.2-70.7)
Duration of response median (95% CI), mo	11.8 (8.4-13.7)	9.4 (5.9-14.5)	16.7 (10.8-19.3)	17.6 (9.1-19.1)
Duration of clinical benefit median (95% CI), mo	11.9 (10.9-13.7)	13.4 (11.2-18.9)	16.7 (12.8-20.2)	14.3 (12.2-18.6)
Overall survival median (95% CI), mo	27.1 (20.0-NR)	24.2 (20.6-NR)	24.4 (17.3-NR)	NR

Abbreviations: HR, hazard ratio; NA, not applicable; NR, not reached; PFS, progression-free survival.

Schmid P et al. JAMA Oncol, 2019

Baselga J et al, NEJM 2012; Piccart M et al, Ann Oncol, 2014
Chandarlapaty et al. Jama Oncol;, 2026

PrE0102 : Randomized Phase II Trial of **Fulvestrant Plus Everolimus** or Placebo in Postmenopausal Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy:

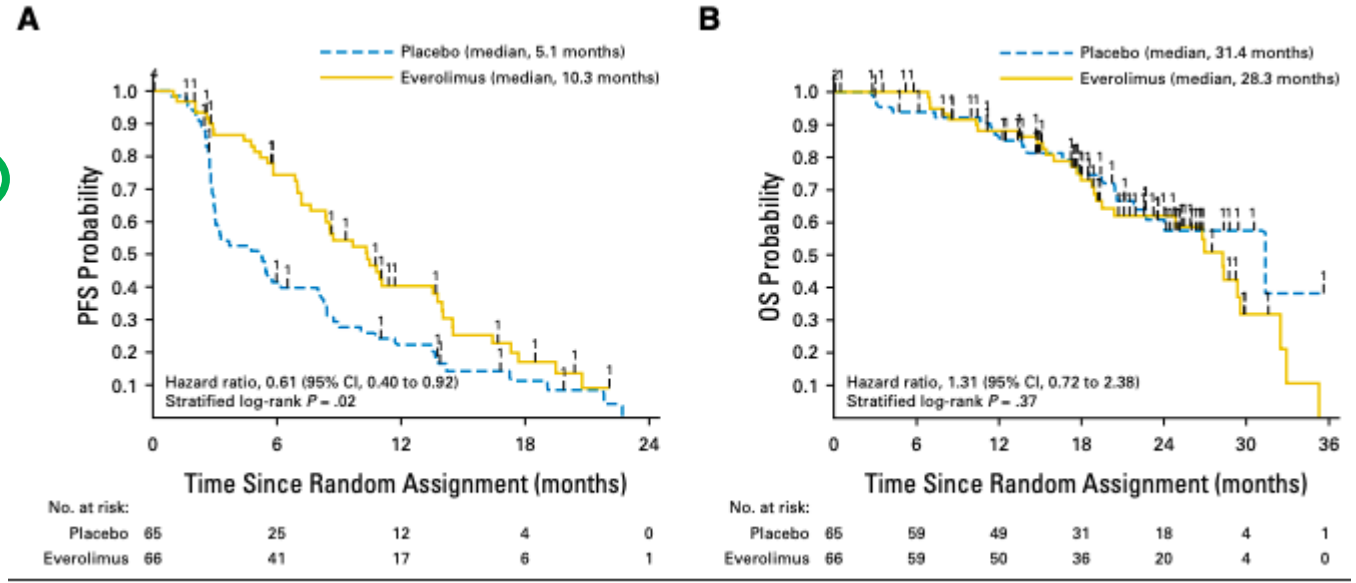


Fig 2. Kaplan-Meier estimates of investigator-assessed (A) progression-free survival (PFS) and (B) overall survival (OS) in the intent-to-treat (ITT) population.

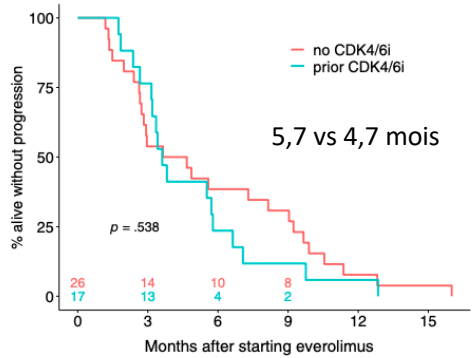
Tamoxifen or fulvestrant can also be combined with everolimus.
(LoE/GoR : II/B) (80%)

Kornblum et al. JCO 2018

The Oncologist
Breast Cancer

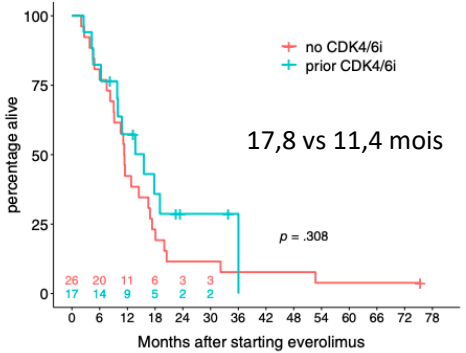
Everolimus Plus Exemestane Treatment in Patients with Metastatic Hormone Receptor-Positive Breast Cancer Previously Treated with CDK4/6 Inhibitor Therapy

Madeline M. Cook,[c] Luai Al Rabadi,[d] Andy J. Kaempf,[b] Megan M. Saraceni,[a] Michael A. Savin,[d] Zahi I. Mitri[d]
[a]Department of Pharmacy and [b]Knight Cancer Institute Biostatistics Shared Resource, [c]Oregon Health & Science University, Portland, Oregon, USA; [d]Department of Hematology Oncology, Oregon Health & Science University, Knight Cancer Institute, Portland, Oregon, USA



5,7 vs 4,7 mois

Figure 1. Progression-free survival by CDK4/6i exposure. Abbreviation: CDK4/6i, CDK4/6 inhibitor.



17,8 vs 11,4 mois

Figure 2. Overall survival by CDK4/6i exposure. Abbreviation: CDK4/6i, CDK4/6 inhibitor.

A REAL-WORLD EVIDENCE STUDY OF EVEROLIMUS PLUS ENDOCRINE THERAPY BEYOND CDK4/6 INHIBITORS FOR HR+/HER2- ADVANCED BREAST CANCER

Rodrigo Sanchez-Bayona[1], Manuel Alva[1], Alfonso López de Sa[2], Yolanda Jerez Gilarranz[2], Ana Sánchez de Torre[4], Pablo Tolosa[1], Alicia de Luna[2], Sara López-Tarruella[3], Laura Lema[1], Fernando Moreno[2], Isabel Echavarria[3], Ainhoa Madariaga[1], Javier Benítez[2], Blanca Herrero[3], Macarena Rey[1], Justo Ortega[2], Salvador Gámez[2], Andrea Modrego[1], Rocío Martín[2], Luis Figuero[1], Roberto Jiménez[2], Marta González Sevilla[1], Irene González[2], Marianela Bringas[2], María de Toro[2], Tatiana Massarrah[2], María del Monte-Millán[2], Marina Pinardo[2], Luis Manso[1], Coralia Bueno[4], Jose Ángel García Sáenz[2], Miguel Martín[3], Eva Ciruelos[1]
(1) Hospital Universitario 12 de Octubre, Madrid, Spain. (2) Hospital Clínico San Carlos, Madrid, Spain. (3) Hospital Universitario Gregorio Marañón, Madrid, Spain. (4) Hospital Infanta Cristina, Madrid, Spain.

Sanchez –Bayona et al. SABCS 2022

STUDY POPULATION: 297 patients with HR+/HER2- metastatic breast cancer treated with EVE plus ET → 152 patients previously treated with CDK4/6 inhibitors

TYPE, SITE & TIME OF STUDY: Retrospective, incident cases, 4 Spanish hospitals, September 2011 - April 2022

Main objective: to estimate the median progression-free survival (mPFS) for EVE + ET in patients pretreated with a CDK4/6 inhibitor

edian follow-up time: 19.7 months (IQR: 10-36 months)

Table 1. Baseline characteristics of patients (n=152)	
Mean age, years (SD)	52 (12)
Previous lines of treatment, median (range)	2 (1-8)
Menopausal status, n (%)	
Premenopausal	81 (54)
Postmenopausal	67 (44)
unkwown	4 (2)
Disease setting, n (%)	
De novo metastatic	36 (24)
Metastatic recurrent	115 (76)
Metastatic site, n (%)	
Visceral	52 (35)
Non-visceral	100 (65)
Endocrine-resistant, n (%)	32 (21)
Previous chemotherapy for advanced disease, n (%)	
Yes	41 (28)
	109 (72)
Previous CDK4/6 inhibitor, n (%)	
Palbociclib	95 (62)
Ribociclib	42 (28)
Abemaciclib	15 (10)

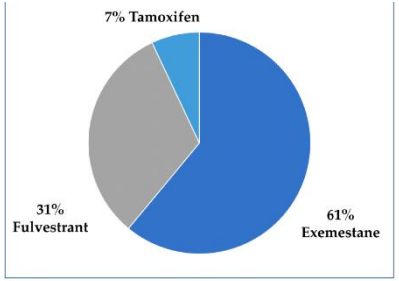
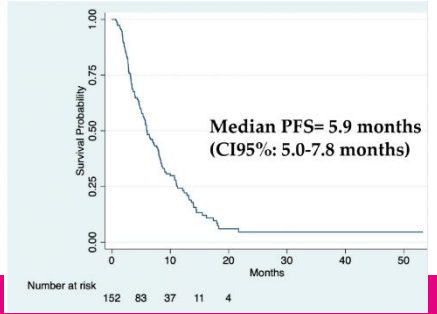


Figure 1. Proportion (%) of type of endocrine treatment in combination with everolimus.



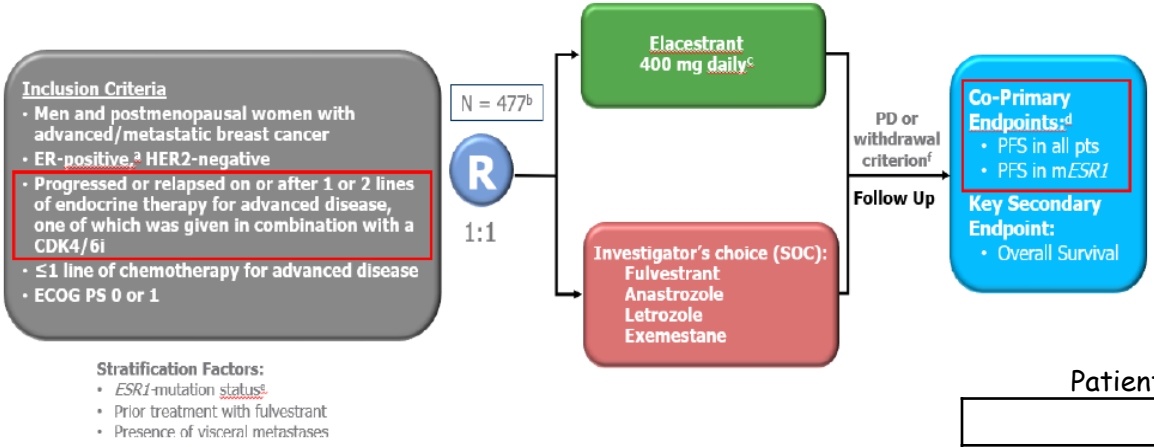
3- Targeting *ESR1* mutations

- How do we do it?
  - Oral SERDs
  - Other new classes of hormone therapy (PROTACs, etc.)

- When?
  - Clinical/radiological progression?
  - As soon as the appearance of an *ESR1* mutation is detected?

Oral SERDs: phase II/III data (1)

Diagram of the phase III EMERALD study (Elacestrant)



Patient characteristics

	Elacestrant	SOC
m *ESR1*	48%	47%
Meta visc	68%	70%
2 L AND	46%	41%
1 L CT	20%	24%

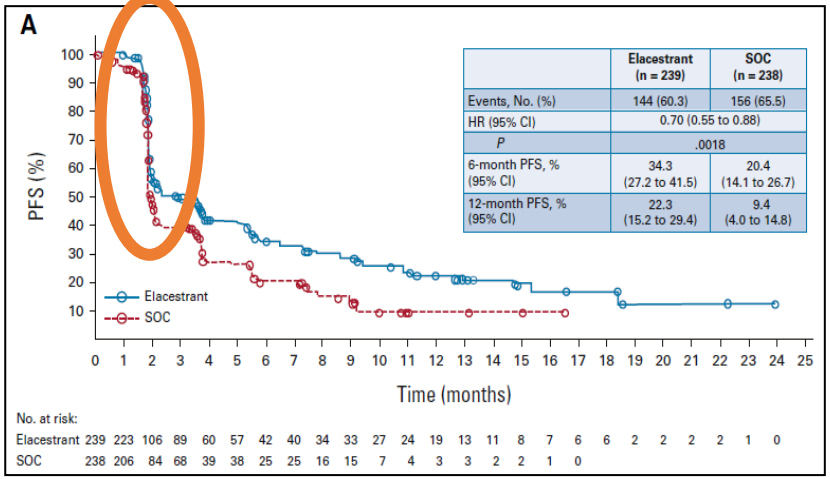
Bardia et al, JCO 2021

Oral SERDs: phase II/III data (2)

EMERALD: results (1)

Potentially non-hormone-dependent tumours and L2 has to be a TC, and tomorrow an ADC?

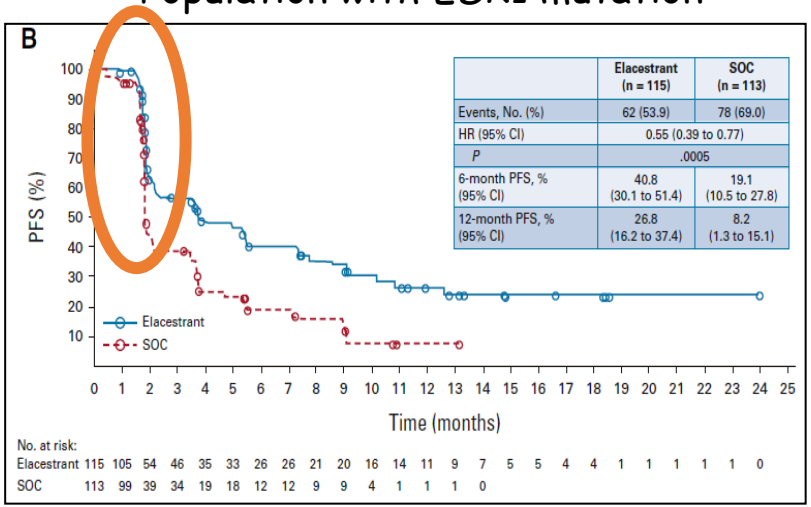
Total population



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

PFS: 1.9 vs 2.8 months elacestrant (HR 0.70)

Population with *ESR1* mutation



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

PFS: 1.9 vs 3.8 months elacestrant (HR 0.55)

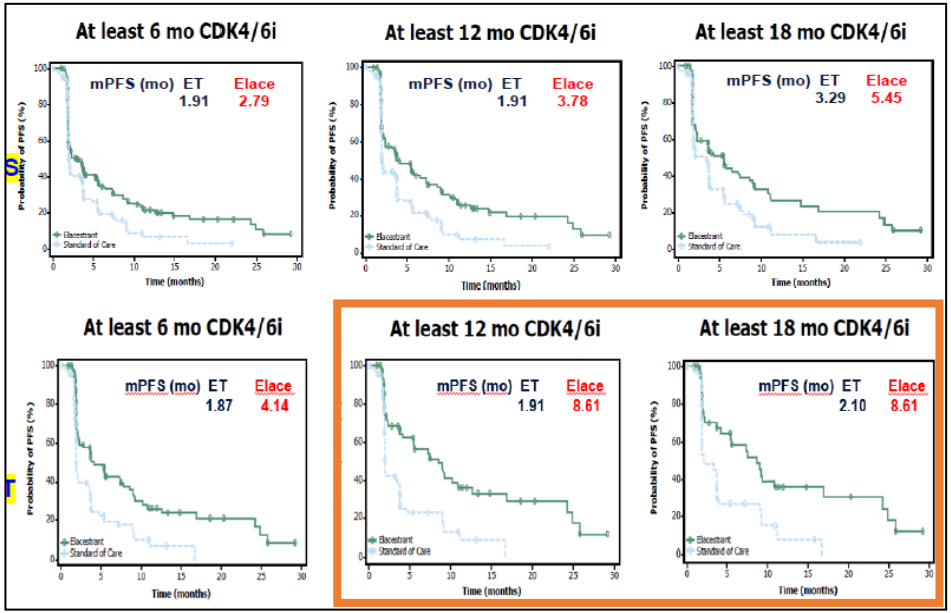
Bardia et al, JCO 2021

Oral SERDS: phase II/III data (3)

EMERALD: results (2)

Total population

Population with *mESR1*



The longer the PFS with elacestrant, the longer the PFS with CDK4-6i

Patients who received > 12 months of CDK therapy had a PFS of 8.6 vs 1.9 months with elacestrant and SOC respectively.

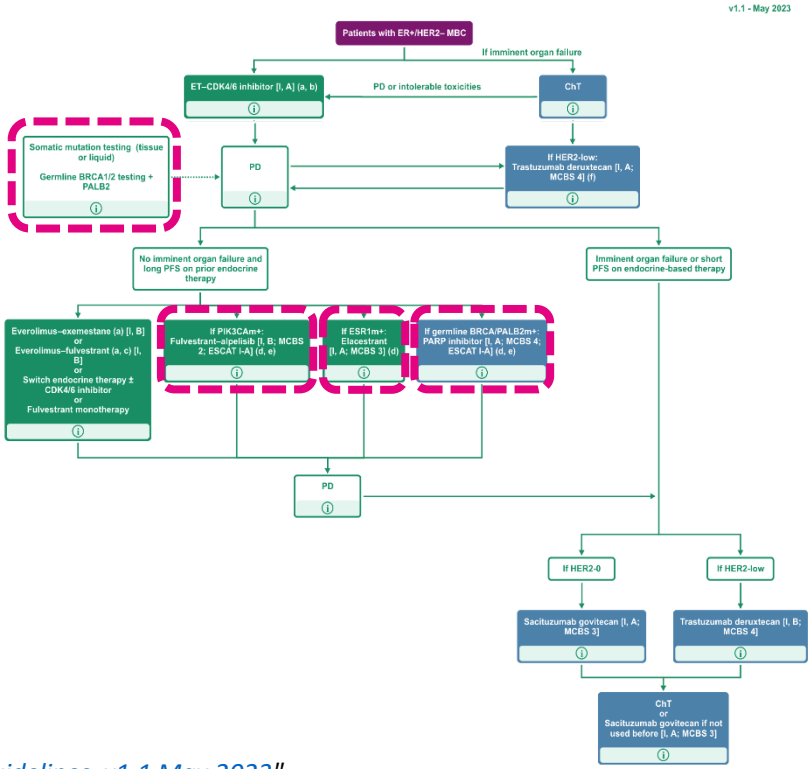
→ More pronounced effect if mESR1 and CDK4-6i therapy for at least 1 year

Kaklamani V al, SABCS 2022

4- Maintain a CDK4-6 inhibitor?

	PACE[1]	MAINTAIN[2]	PALMIRA[3]	POST MONARCH
Phase	II randomised	II randomised	III	III
N	166	120	198	
iCDK4/6 in 2e Line	Palbociclib + fulv **vs** Fulv **vs** Palbociclib + fulv + avelumab	Ribociclib + HT **vs** HT	Palbociclib + HT **vs** HT	Abémaciclib + Fulv vs Fulv
	Progression after CDK4/6 (≥6 months)	Progression after CDK4/6	Progression after CDK4/6 (≥12 months)	Progression after CDK4/6
Prior chemotherapy	0-1	≤ 1	0	0
1e iCDK 4/6 line	Palbociclib (91%)	Palbociclib (87%)	Palbociclib (100%)	
HT Preliminary	≤ 2	1	1	1
Impact ESR1 status		ESR1 wt		
Significant profit	No	Yes	No	Yes

Conclusion



Ann Oncol 2021;32(12): 1475-1495
ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023"

IUC

INSTITUT UNIVERSITAIRE DE CANCÉROLOGIE

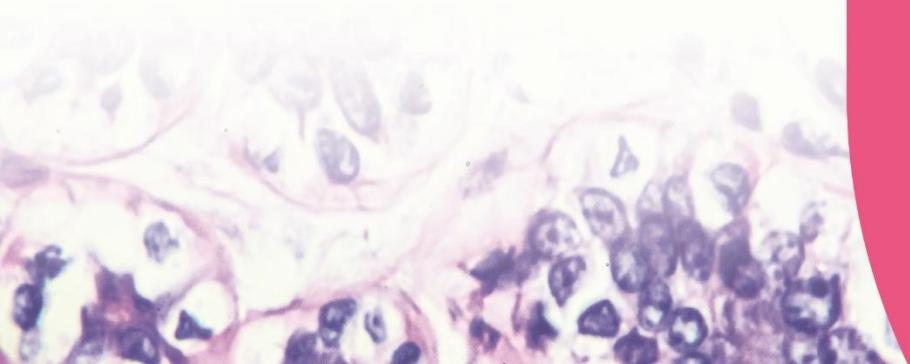
AP-HP. Sorbonne Université

Sciences & Humanités contre le cancer

Thanks

Global Breast Cancer Academy

Q&A



APTITUDE HEALTH

Objectives

Understand clinical and pathologic factors that influence first-line choice of therapy for patients with HR+ mBC

Discuss the role of biomarkers, molecular profiling, and resistance mechanisms in guiding treatment choices

Examine the role of targeted therapies following endocrine therapy failure

Gain insights into the care of patients with high-risk and endocrine-resistant HR+ mBC

Explore current and future sequencing strategies for HR+, HER2– mBC

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

Treatment options for high-risk and endocrine-resistant HR+ mBC

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Disclosures

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- **Stock, patents, and intellectual property** with MedSIR
- **Leadership** role for Eisai, Celgene-BMS, Lilly, Pfizer, Roche, Novartis, MSD, TESARO-GSK
- **Consultant/advisory board member** for Lilly, Roche, Pfizer, Novartis, Pierre-Fabre, Genomic-Health, TESARO-GSK
- **Speakers' bureau honoraria** from Lilly, AstraZeneca, MSD, Pfizer, Roche
- **Research funding to institution** from Roche, Foundation Medicine, Pierre-Fabre, Agendia
- **Travel, accommodations, and expenses paid or reimbursed** from Roche, Lilly, Novartis, Pfizer, AstraZeneca

Hormone receptors and endocrine sensitivity in BC

Breast cancer (BC) is a heterogenous disease encompassing a diverse range of biologically distinct tumours. Tumours can be classified by **molecular subtype**, **gene expression** and **stage**, which determines the type of treatment selected[1]

Subtype

Tumour molecular subtype is based on the expression of hormone receptors (**HR**; ie, estrogen receptors **[ER]** and/or progesterone receptors **[PgR]**) and human epidermal growth factor receptor 2 **(HER2)**.[1] Receptor expression enables tumours to grow in response to endogenous signalling molecules[1,2]

Endocrine sensitive (HR+) BC[3]

- Express ER and/or PgR
- ~70% of BCs
- **HER2 negative (–)**

HER2+ BC[3]

- Express HER2
- ~15–20% of BCs
- HR+ or HR–

Triple-Negative BC (TNBC)[4]

- Do not express ER, PgR or HER2
- ~10–15% of BCs
- Most aggressive, worst prognosis

Potentially targetable population:[6,7]

HER2-low

Luminal cancers[5]: HR+ tumours classified into luminal categories based on ER/PR, HER2, Ki-67, and tumor grade status:

Luminal A

- Low Ki-67 - Low tumour grade
- High ER/PR expression
- Better prognosis, tend to grow slowly
- Low sensitivity to CT, high to ET

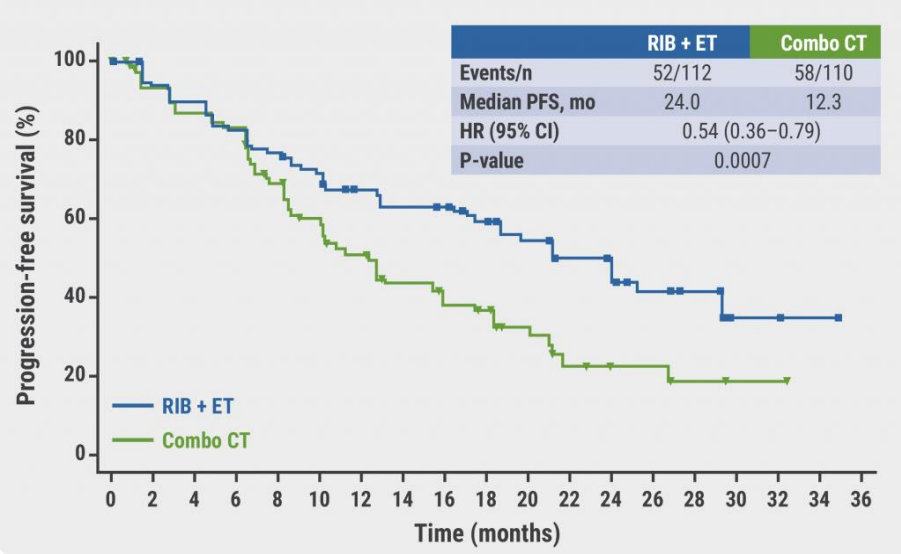
Luminal B[a]

- High Ki-67 – tumour grade
- Moderate – low ER/PR expression
- Worse prognosis more aggressive disease
- Moderate sensitivity to both CT and ET

*1. Tarantino P et al. J Clin Oncol. 2020;38(17):1951–1962. 2. Modi S et al. N Engl J Med. 2022;387(1):9–20. 3. American Cancer Society. Breast Facts & Figures 2019–2020. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf. Accessed June 23, 2023. 4. Guideline Summary: American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor HER2 Testing in Breast Cancer. J Oncol Pract. 2007;3(1):48–50.

CDK4/6i superior to CT in aggressive disease

RIGHT CHOICE - Randomised Phase 2 Study:
ER[+] HER2[-] MBC Patients with aggressive criteria to Ribociclib + ET vs Chemotherapy (doublets)



Lu YS, et al. SABCS 2022

ABIGAIL- Randomised Phase 2 Study:
ER[+] HER2[-] MBC Patients with aggressive criteria to Abema + ET vs weekly paclitaxel (12 weeks ORR)

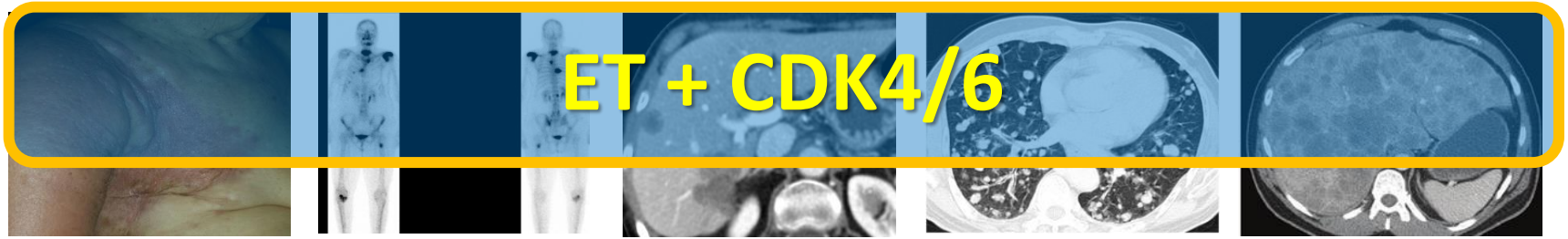
	Abemaciclib + ET *N* = 80	Paclitaxel *N* = 82	*P* value
12-week ORR (ITT)			
Complete response, partial response	**47 (58.8%)**	**33 (40.2%)**	0.02
Stable disease, progressive disease, or discontinuation	33 (41.2%)	49 (59.8%)	
Response at 12 weeks			
Complete response	0 (0%)	0 (0%)	
Partial response	47 (58.8%)	33 (40.2%)	
Stable disease	24 (30.0%)	37 (45.2%)	
Progressive disease	**1 (1.2%)**	**7 (8.5%)**	
Not evaluable	8 (10.0%)	5 (6.1%)	

Juan de la Haba-Rodríguez, MD, PhD. ESMO 2024

ER+/HER2- MBC in 2024: CDK4/6i cover almost all scenarios

Indolent disease → **Aggressive disease**

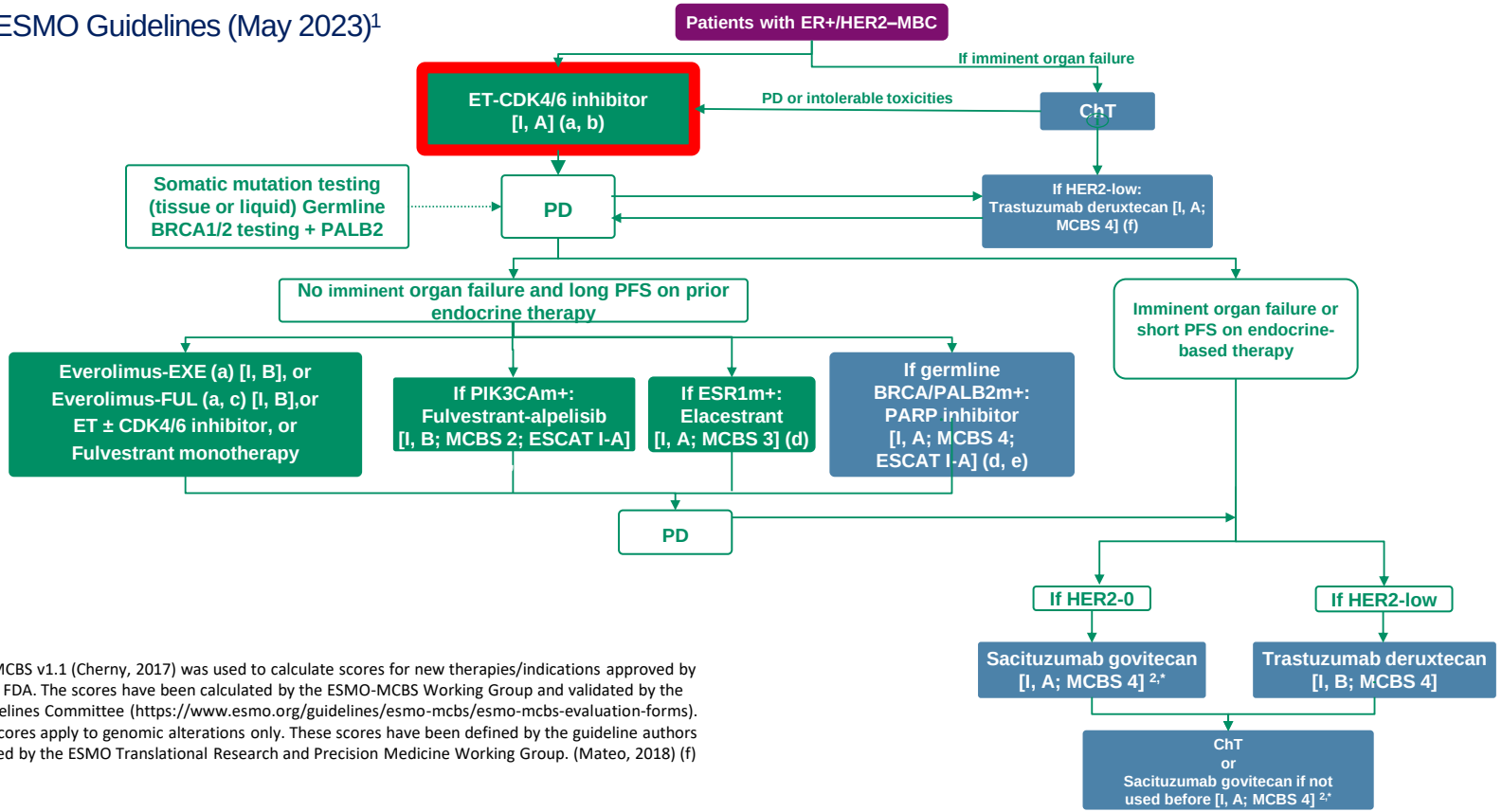
PROFILE Highly sensitive	PROFILE Sensitive	PROFILE Moderately sensitive	PROFILE Moderately sensitive and symptomatic	PROFILE Visceral crisis
"De novo" metastatic, or no prior ET, or very long DFI post-adjuvant	DFI post-adjuvant ET (>12 mo)	Short DFI post-adjuvant (<12 mo) or within adjuvant ET	Progression on adjuvant ET	Fast-progressing, life-threatening, aggressive disease
Exclusive bone / soft-tissue mets	Predominant bone or soft tissue mets	Visceral disease	More extensive visceral met(s)	Mets in high-risk sites requiring immediate medical intervention
Asymptomatic	No or minimal symptoms	No or minimal symptoms	Moderate symptoms	Highly symptomatic, requiring "fast response"



Antonio Llombart-Cussac, personal communication

Current ESMO HR+/HER2-negative mBC treatment algorithm: First-line treatment

Living ESMO Guidelines (May 2023)[1]



(d) ESMO-MCBS v1.1 (Cherny, 2017) was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
(e) ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group. (Mateo, 2018) (f)

1. ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023; original Clinical Practice Guideline *Ann Oncol* 2021;32(12):1475–1495.

Post-CDK Objective:

Maximize residual endocrine sensitivity before moving to “aggressive chemotherapy”

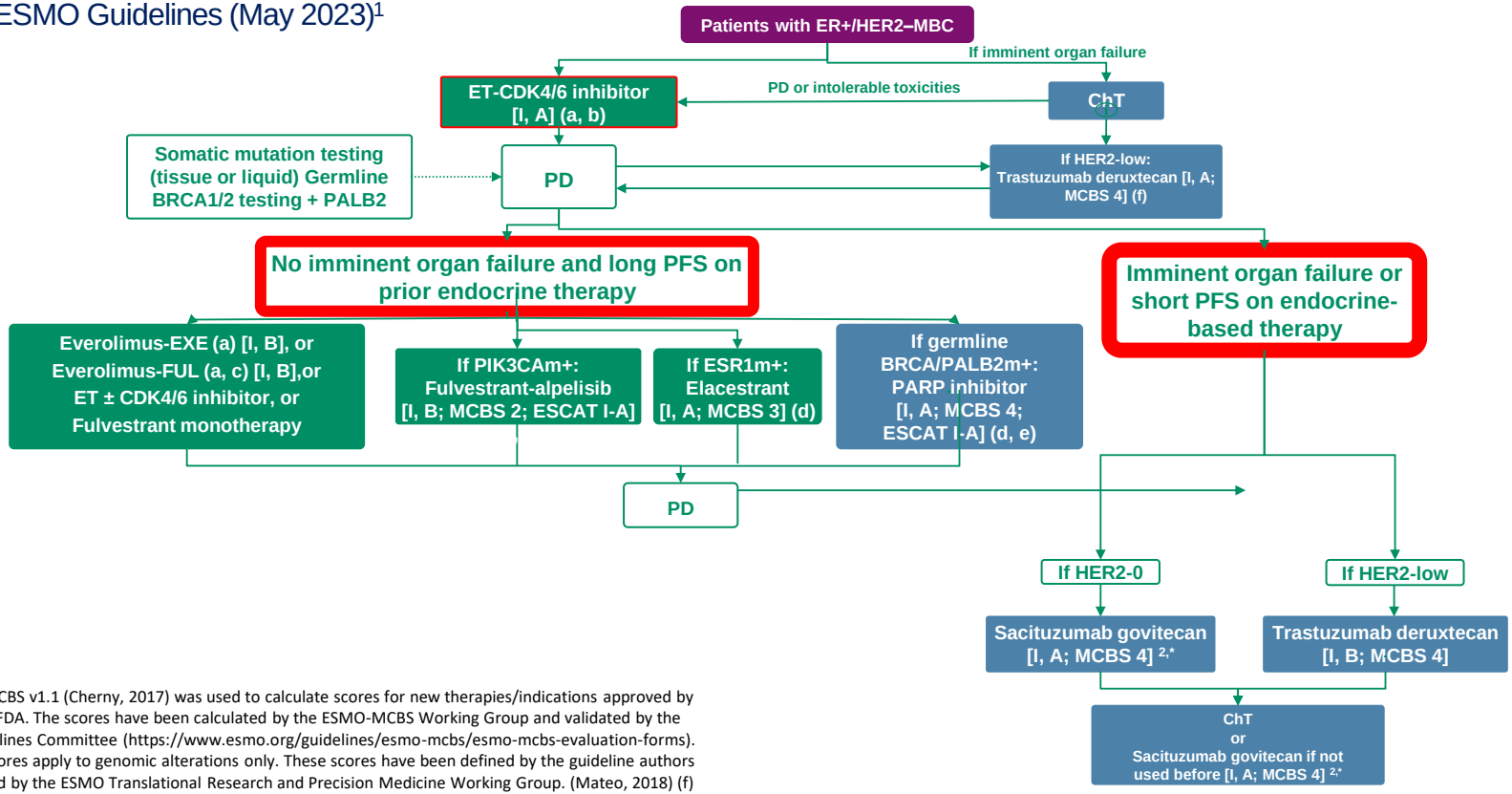
1. What ET options beyond CDK4/6i?

2. How do we define definitive endocrine resistance?

3. Optimal chemotherapy after ET exhaustion?

Current ESMO HR+/HER2-negative mBC treatment algorithm: Second-line treatment

Living ESMO Guidelines (May 2023)[1]



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1. ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023; original Clinical Practice Guideline *Ann Oncol* 2021;32(12):1475–1495.

Treatment options beyond CDK4/6 inhibitors

Almost all ABC patients on CDK4/6i will progress

Endocrine sensitivity compromise – Fulvestrant single agent achieves mPFS of 1.8–4.5 mo

Endocrine strategies based on actionable mutations and/or doublets

- mTORi: **everolimus** and second-generation mTOR
- PI3K*mut*: **alpelisib, inavolisib**
- AKT/PI3K/PTEN: **Capivasertib,** ipatasertib
- g*BRCA1/2*mut: **Olaparib, talazoparib**
- *ESR1*mut: **Elacestrant, camizestrant, giredestrant**/PROTAC/Progestagens
- CDK4/6i rechallenge: Ribociclib, abemaciclib, and new CDK4/6i
- CDK2 / CDK4 selective inhibitors

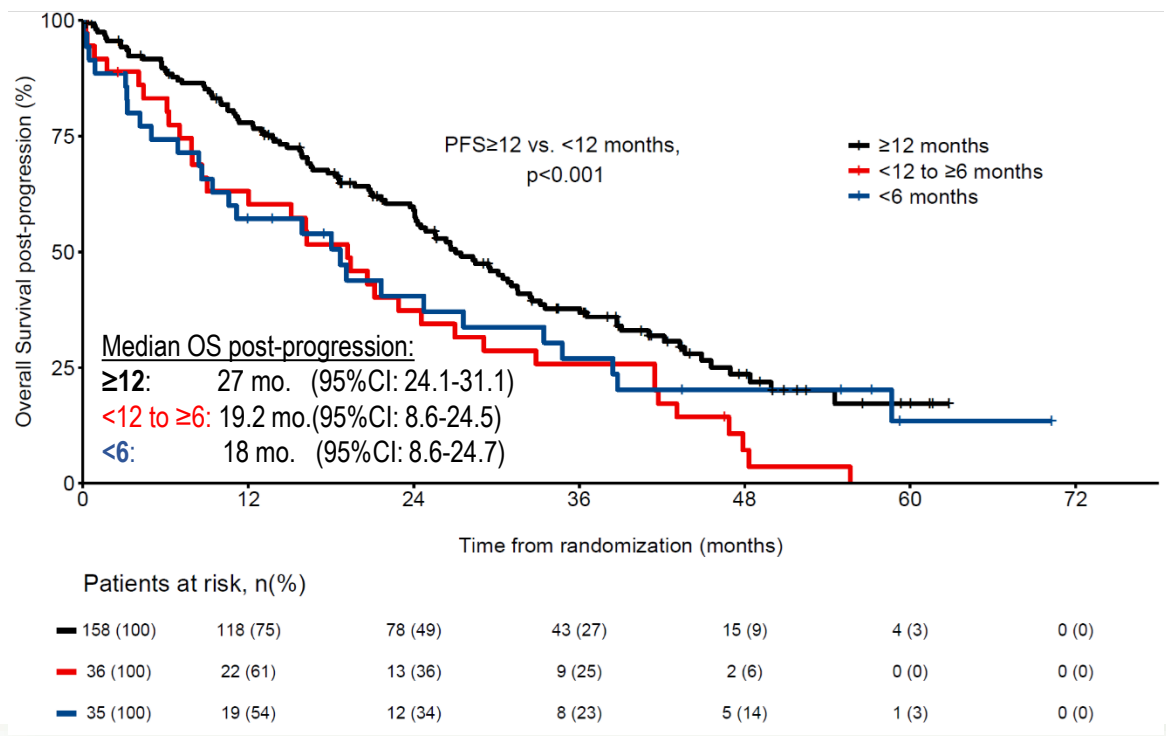
Non-endocrine approaches = ADCs

- HER2-low: **Trastuzumab deruxtecan**
- TROP2: **Sacituzumab govitecan, datopotamab deruxtecan**

Median PFS for endocrine strategies after CDK4/6i therapy

Second Line (post-CDK4/6i+ IA)	Clinical Trial	Study	Prior CDk4/6i	Target	Median PFS in Months
FUL + alpelisib	BYLieve	II	100%	*PI3K*mut	7.3
FUL + abemaciclib	postMONARCH	III	100%	no	6.0
FUL + capivasertib	CAPItello-291	III	100% *	All (wt/mut)	5,5
FUL + ribociclib	MAINTAIN	II	100%	no	5.3
Camizestrant	SERENA-2	II	60%	*ESR1*mut/wt	5.5
Elacestrant	EMERALD	III	100%	*ESR1*mut	3.8
FUL	Several	III	100%	no	1.9–5.3

Early progression on CDK4/6i is a strong prognostic factor: PARSIFAL long subanalysis



Events per cohort:

≥12:	103 (65.2%)
<12 to ≥6:	34 (94.4%)
<6:	27 (77.1%)

n (%), number of patients (percentage based on N); N: number of patients; mo.: months; OS: overall survival; PFS: progression-free survival

Llombart A, et al. SABCS 2023

Benefits on second-line ET are modulated by the duration - sensitivity to the prior CDK4/6i therapy – EMERALD-3

Duration on CDK4/6i in the metastatic setting	At Least 6 Months (92.3%)		At Least 12 Months (71.6%)	
	Elacestrant (n=103)	SOC Hormonal Therapy (n=102)	Elacestrant (n=78)	SOC Hormonal Therapy (n=81)
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 6 months, % (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
PFS rate at 18 months, % (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)	

Modified from **Kaklamani V** et al., GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting. Abstract GS3-01; SABCS 2022

Benefits on second-line ET are modulated by the duration - sensitivity to the prior CDK4/6i therapy – METALLICA

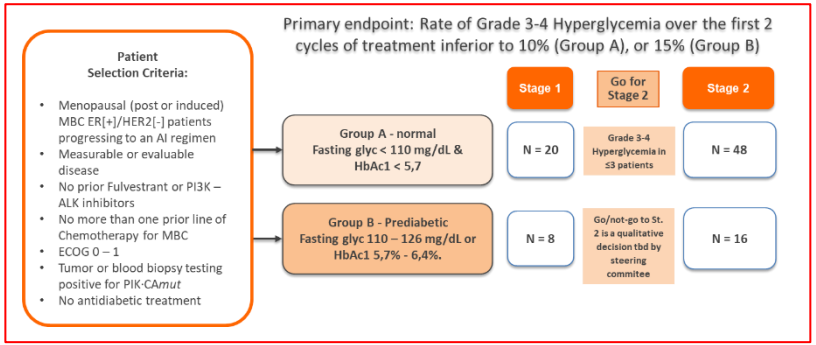
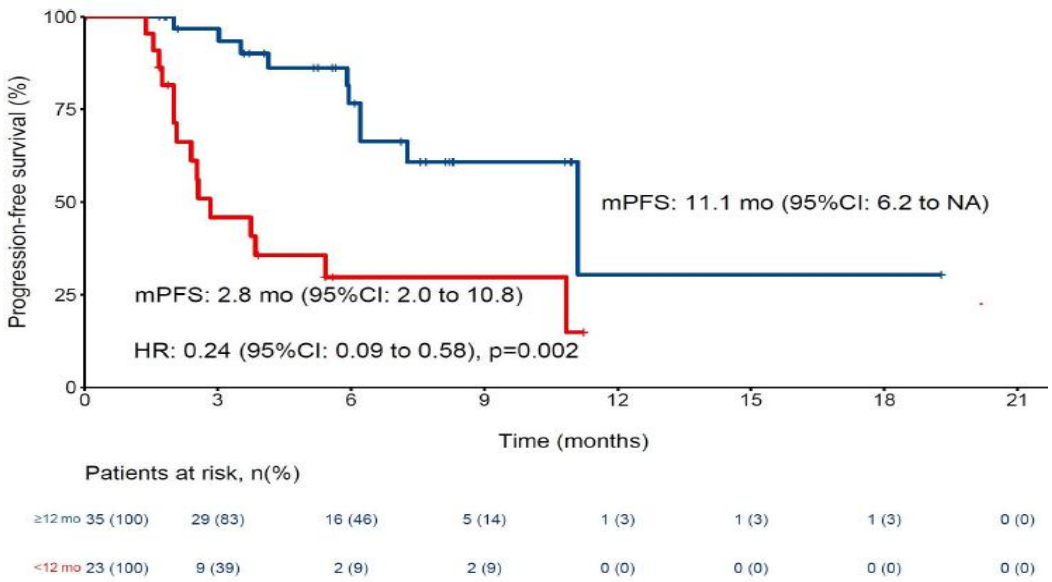


Figure 3. Progression-free survival rate in HR+/HER2-/*PIK3CA*-mutated ABC patients treated with ALP+ET by duration of prior CDK4/6i.



Llombart A, et al. EClinicalMedicine 2024 Apr 11:71:102520. doi: 10.1016/j.eclinm.2024.102520

DESTINY-Breast04: Study Design

Patients[a]
- HER2-low (IHC 1+ vs 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)

HR+ = 494
HR− = 63

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

Primary endpoint
- PFS by BICR (HR+)

Secondary endpoints[d]
- PFS by BICR (all patients)
- OS (HR+ and all patients)
- PFS (investigator)
- ORR (BICR and investigator)
- DOR (BICR)
- Safety
- Patient-reported outcomes (HR+)[e]

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

Exploratory analysis subgroups (all patients)
- Prior CDK4/6i use (**HR+ cohort**; yes, no)
- Disease burden (low = 0-2; high = 3+ sites)
- Rapid progression (disease progression ≤6 months of neo/adjuvant therapy)
- HER2 status (IHC 1+, IHC 2+/ISH−)
- Number of prior lines of chemotherapy (1, 2)
- Age (<65, ≥65 years)
- Baseline CNS metastases (yes, no)
- Prior anthracycline treatment (yes, no)

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system. [c]TPC was administered according to the label. [d]Efficacy in the HR− cohort was an exploratory endpoint. [e]The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

1. Modi S et al. *N Engl J Med*. 2022;387(1):9-20. 2. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

DB-04: Prior therapies

Characteristic	Hormone receptor-positive		All patients (HR+ and HR−)	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy[a] (metastatic setting)				
Median number of lines (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Median number of lines (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0

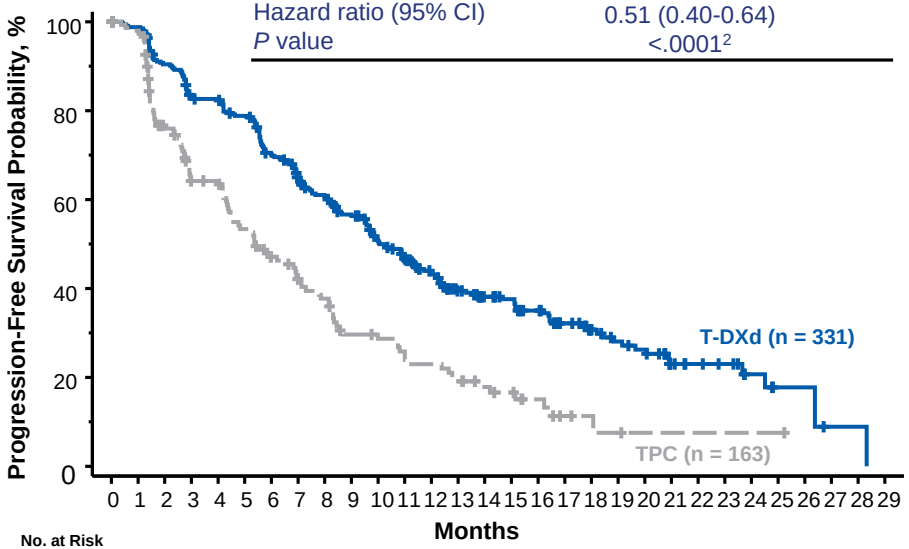
Based on derived data, which includes protocol deviations.

[a]Systemic therapy refers to any type of treatment that targets the entire body.[2]

1. Modi S et al. Presented at American Society of Clinical Oncology (ASCO) 2022, June 2022, LBA3. 2. Dictionary of Cancer Terms, National Cancer Institute. Accessed September 7, 2022. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/systemic-therapy

DB-04: PFS in HR+ and all patients

	Hormone receptor-positive	
	T-DXd (n = 331)	**TPC** (n = 163)
mPFS (95% CI), mo	10.1 (9.5-11.5)	5.4 (4.4-7.1)
Hazard ratio (95% CI)	0.51 (0.40-0.64)	
P value	<.0001[2]	

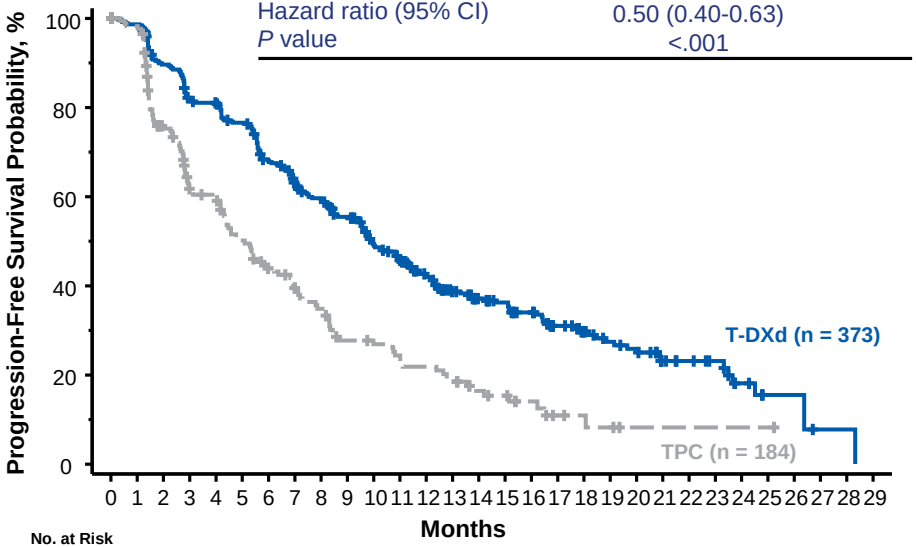


No. at Risk

T-DXd (n = 331): 331 324 290 265 262 248 218 198 182 165 142 128 107 89 78 73 64 48 37 31 28 17 14 12 7 4 4 1 1 0

TPC (n = 163): 163 146 105 85 84 69 57 48 43 32 30 27 24 20 14 12 8 4 3 2 1 1 1 1 1 1 0

	All patients (HR+ and HR−)	
	T-DXd (n = 373)	**TPC** (n = 184)
mPFS (95% CI), mo	9.9 (9.0-11.3)	5.1 (4.2-6.8)
Hazard ratio (95% CI)	0.50 (0.40-0.63)	
P value	<.001	



No. at Risk

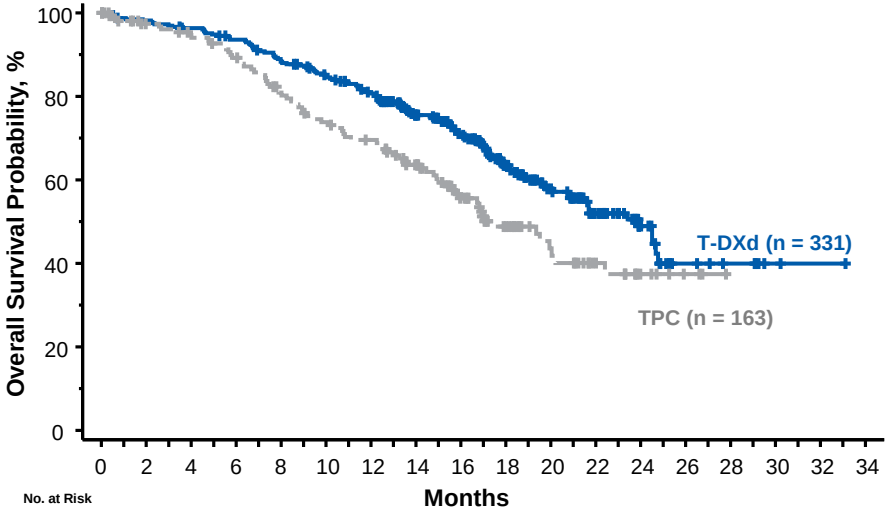
T-DXd (n = 373): 373 365 325 295 290 272 238 217 201 183 156 142 118 100 88 81 71 53 42 35 32 21 18 15 8 4 4 1 1 0

TPC (n = 184): 184 166 119 93 90 73 60 51 45 34 32 29 26 22 15 13 9 5 4 3 1 1 1 1 1 1 0

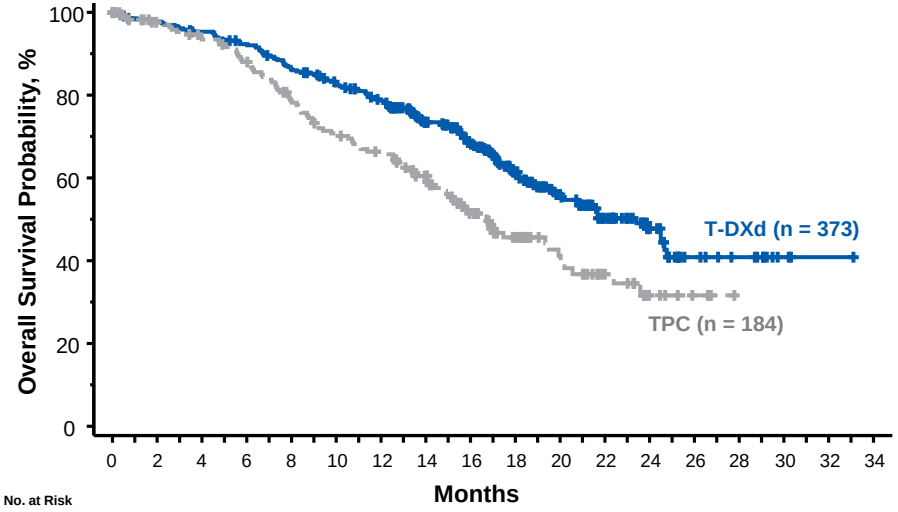
1. Modi S et al. *N Engl J Med*. 2022;387(1):9-20. 2. Modi S et al. Presented at American Society of Clinical Oncology (ASCO) 2022, June 2022, LBA3.

DB-04: OS in HR+ and all patients

	Hormone receptor-positive	
	T-DXd (n = 331)	**TPC** (n = 163)
mOS (95% CI), mo	23.9 (20.8-24.8)	17.5 (15.2-22.4)
Hazard ratio (95% CI)	0.64 (0.48-0.86)	
P value	.003	



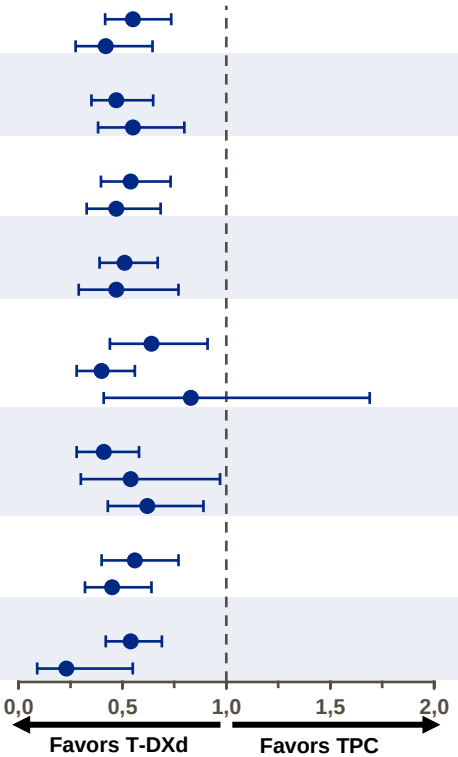
	All patients (HR+ and HR−)	
	T-DXd (n = 373)	**TPC** (n = 184)
mOS (95% CI), mo	23.4 (20.0-24.8)	16.8 (14.5-20.0)
Hazard ratio (95% CI)	0.64 (0.49-0.84)	
P value	.001	



Modi S et al. *N Engl J Med*. 2022;387(1):9-20.

DB-04: Subgroup analysis – PFS in HR+ patients

	No. of Events/No. of Patients		mPFS, months (95% CI)		Hazard ratio (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6i					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH−	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)
Prior lines of chemotherapy					
1	129/203	63/93	10.9 (8.5-12.3)	6.8 (4.5-8.2)	0.54 (0.40-0.73)
≥2	81/127	47/69	9.9 (8.3-11.7)	4.6 (2.8-6.2)	0.47 (0.33-0.68)
Age					
<65 years	170/260	79/120	9.8 (8.4-11.3)	5.4 (4.1-7.8)	0.51 (0.39-0.67)
≥65 years	41/71	31/43	12.0 (9.5-14.7)	5.6 (4.3-10.8)	0.47 (0.29-0.77)
Race					
White	100/156	43/78	10.0 (8.5-12.2)	7.1 (4.0-10.0)	0.64 (0.44-0.91)
Asian	83/131	54/66	11.0 (8.4-13.8)	4.8 (4.2-6.4)	0.40 (0.28-0.56)
Other	25/37	11/16	6.0 (5.4-10.5)	7.0 (1.4-11.0)	0.83 (0.41-1.69)
Region					
Asia	81/128	48/60	10.9 (8.4-14.7)	5.3 (4.2-6.8)	0.41 (0.28-0.58)
Europe and Israel	90/149	44/73	10.8 (8.5-13.0)	7.1 (3.0-10.7)	0.62 (0.43-0.89)
North America	40/54	18/30	8.5 (6.3-11.3)	4.5 (2.9-8.2)	0.54 (0.30-0.97)
ECOG performance status					
0	116/187	55/95	10.9 (9.5-13.0)	7.0 (4.2-8.5)	0.56 (0.40-0.77)
1	95/144	55/68	9.7 (7.3-11.5)	4.6 (2.9-6.2)	0.45 (0.32-0.64)
Visceral disease at baseline					
Yes	196/298	100/146	9.8 (8.5-11.1)	5.8 (4.4-7.1)	0.54 (0.42-0.69)
No	15/33	10/17	17.9 (10.9-26.4)	4.5 (1.6-12.4)	0.23 (0.09-0.55)



[a]PFS by blinded independent central review. Based on derived data that includes protocol deviations.
Modi S et al. *N Engl J Med*. 2022;387(1):9-20.

DESTINY-Breast06: Study Design

A randomised, multicentre, open-label trial (NCT04494425)

POPULATION

- Advanced/metastatic HR+ BC
- HER2 IHC >0<1+ or 1+ or 2+ (determined based on central IHC assessment of archival tissue collected at time of diagnosis of first metastatic disease or later)

Prior lines of therapy in MBC:

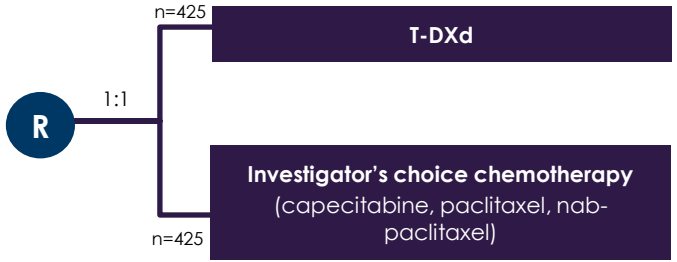
- Progression after 2 prior ET ± targeted therapy **or** within 6 months of 1L ET + CDK4/6i*

Stratification factors:

- Prior CDK4/6i
- HER2 IHC 2+ v. 1+ v. >0<1+
- Prior taxane in non-metastatic setting

- First subject in: July 2020
- 791 patients enrolled
- 310 sites open

TREATMENT



- Treatment continues until progressive disease or toxicity
- HER2 IHC >0<1+ defined by tumour membrane expression characterised as faint or barely perceptible and incomplete membrane staining that is seen in 10% or fewer tumour cells†

ENDPOINTS

Primary:

- PFS (BICR) in HER2-low population†

Key Secondary:

- OS in HER2-low population
- PFS (BICR) in ITT population
- OS in ITT population

Secondary:

- PFS (investigator assessed) in HER2-low population
- ORR and DOR of HER2-low and ITT populations
- Safety and tolerability
- Symptoms, functioning and HRQoL

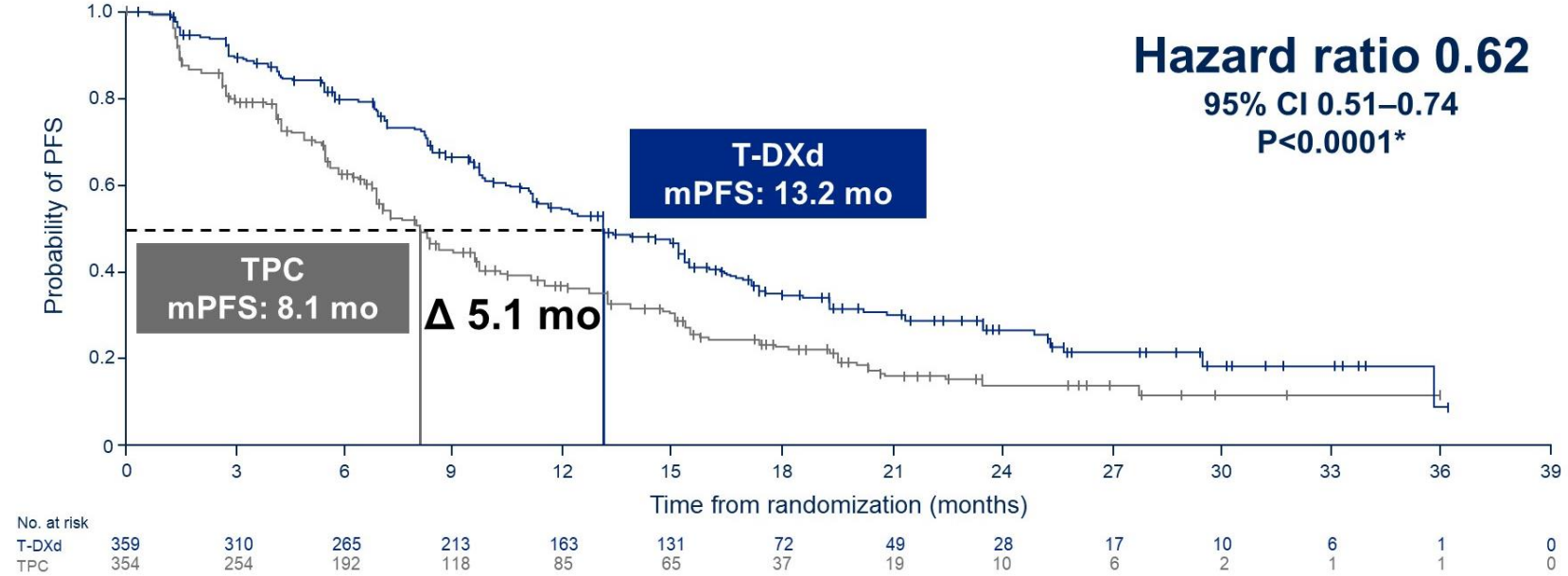
Exploratory:

- Protein expression
- ctDNA
- Patient Reported Outcomes

*Disease progression on ET + CDK4/6i <6 months of starting 1L metastatic treatment and considered appropriate for chemotherapy as the next treatment by the investigator or disease recurrence while on the first 24 months of adjuvant ET †N=150 IHC >0<1+ patients agreed with FDA and EMA: Futility analysis passed in December 2022. ‡456 events are required to perform PFS analysis.

Study Enrollment: 85% patients had 2 prior ET+/- targeted therapy; 15% post 1L ET + CDK4/6i, 15% patients are IHC >0<1+ (vs ~30% in RW), ~30% capecitabine treated

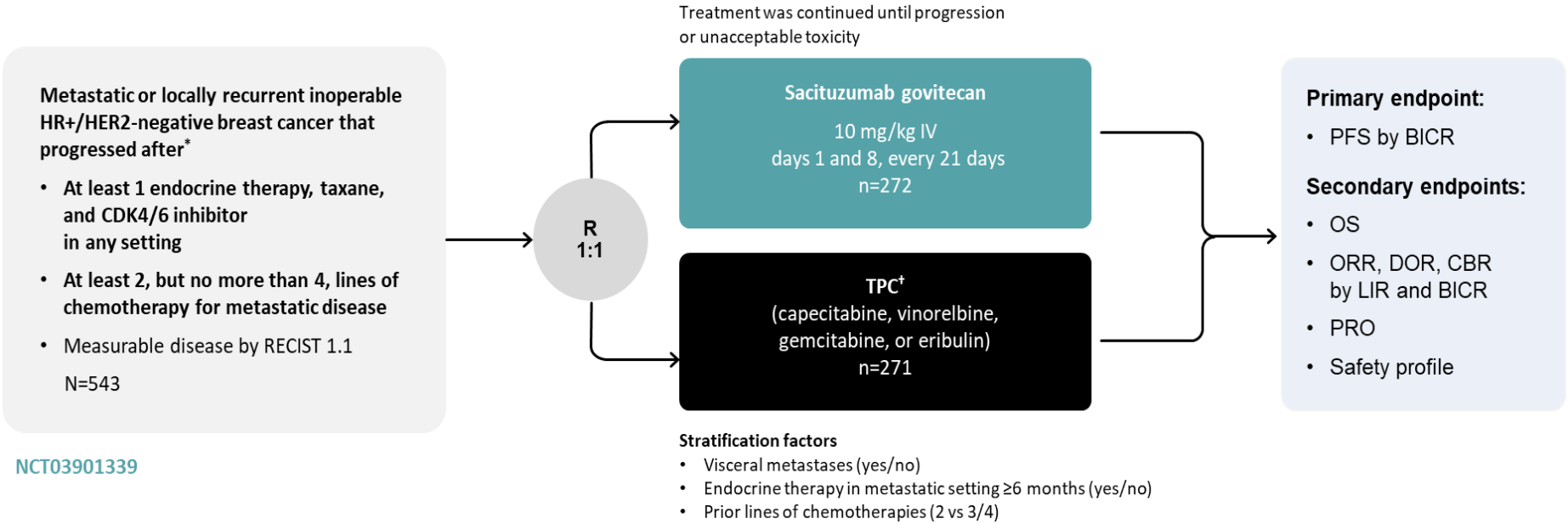
DB-06: PFS in HER2-low (ITT, primary endpoint)



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

*P-value of <0.05 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

TROPICS-02: A Phase 3 study of SG in pre-treated HR+/HER2-negative (IHC0, IHC1+, IHC2+/ISH−)



NCT03901339

1. Rugo HS, et al. *J Clin Oncol*. 2022;40:3365−3376 (Supp).

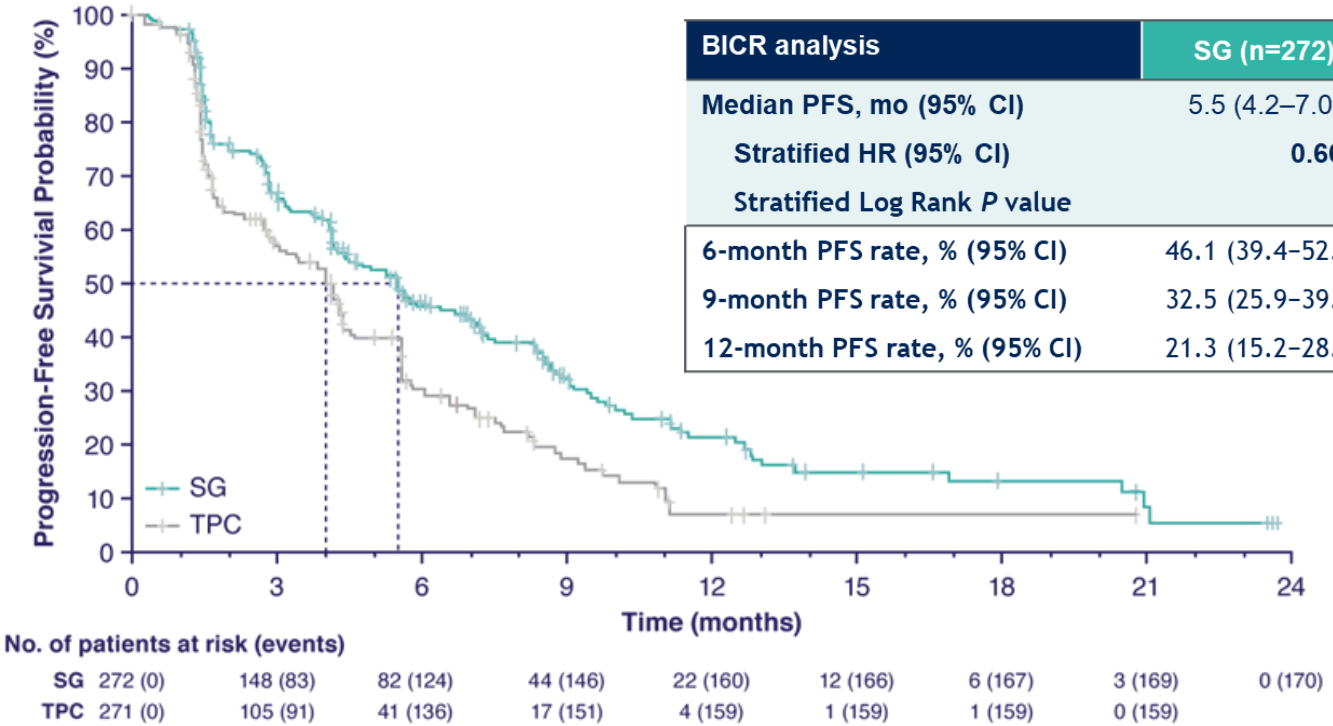
TROPICS-02: Demographics and baseline characteristics

	SG (n=272)	TPC (n=271)
Female, n (%)	270 (99)	268 (99)
Median age, y (range)	57 (29–86)	55 (27–78)
<65 years, n (%)	199 (73)	204 (75)
≥65 years, n (%)	73 (27)	67 (25)
Race or ethnic group, n (%)		
White	184 (68)	178 (66)
Black	8 (3)	13 (5)
Asian	11 (4)	5 (2)
Other[a]/Not reported[b]	69 (25)	75 (28)
ECOG PS, n (%)		
0	116 (43)	126 (46)
1	156 (57)	145 (54)
Visceral metastases at baseline, n (%)	259 (95)	258 (95)
Liver metastases,[c] n (%)	229 (84)	237 (87)
De novo metastatic breast cancer, n (%)	78 (29)	60 (22)

	SG (n=272)	TPC (n=271)
Median time from initial metastatic diagnosis to randomization, months (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 months, 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)

1. Rugo HS, et al. *J Clin Oncol*. 2022;40:3365–3376 (Supp).

TROPICS-02: Primary endpoint: BICR-assessed PFS in the ITT population

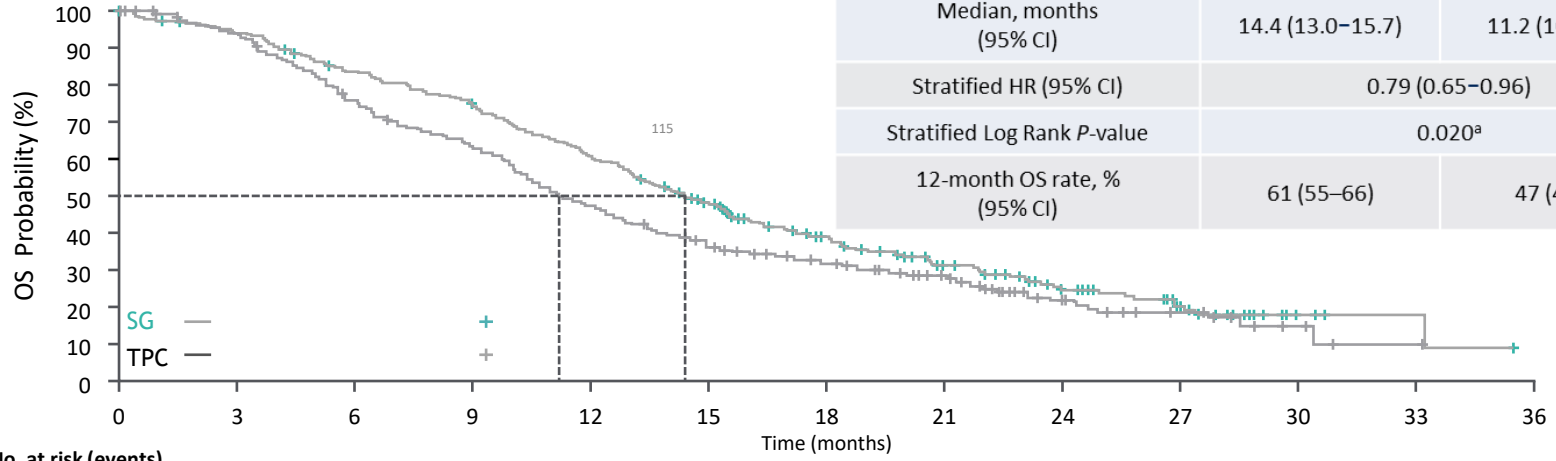


BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2–28.1)	7.1 (2.8–13.9)

1. Rugo HS, et al. *J Clin Oncol*. 2022;40:3365−3376 (Supp).

TROPICS-02: Secondary endpoint: OS – ITT population at IA2

	SG (N=272)	TPC (N=271)
Number of events/censored	191/81	199/72
Median, months (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	0.020[a]	
12-month OS rate, % (95% CI)	61 (55–66)	47 (41–53)



No. 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)

1. Rugo HS, et al. *J Clin Oncol*. 2022;40:3365–3376 (Supp).

TROPION-Breast01: Study design

Randomized, 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)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Secondary endpoints included:** ORR, PFS (investigator assessed), TFST, safety, PROs

Randomization stratified by:

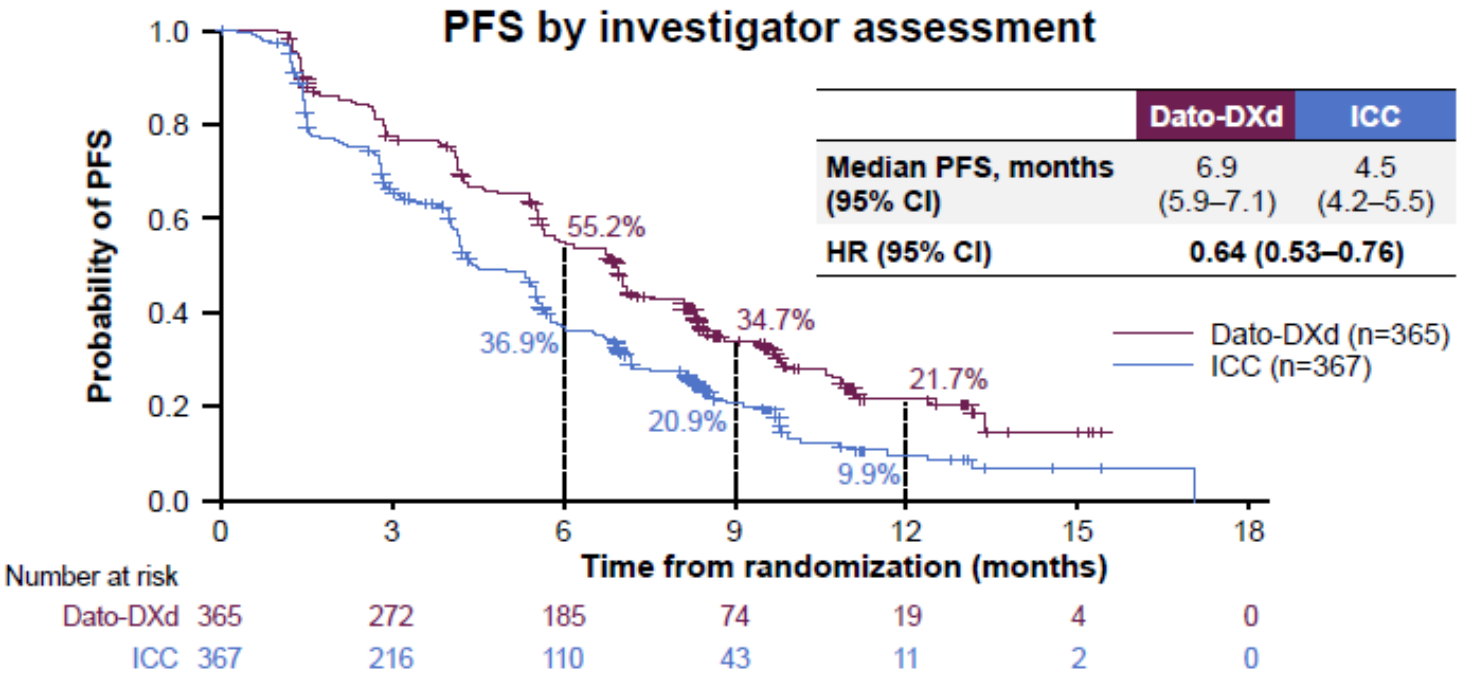
- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m² IV on Days 1 and 8, Q3W; vinorelbine, 25 mg/m² IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m² IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m² orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice). CDK4/6, cyclin-dependent kinase 4/6; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IHC, immunohistochemistry; ISH, in-situ hybridization; IV, intravenous; PD, progressive disease; PROs, patient-reported outcomes; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world; TFST, time to first subsequent therapy

1. Bardia A, et al. *Future Oncol* 2023;

TROPION-Breast01: PFS by ITT



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	**0.64 (0.53–0.76)**	

PFS by BICR (primary endpoint)[1]: Median 6.9 vs 4.9 months; HR 0.63 (95% CI 0.52–0.76); P<0.0001

Data cut-off: 17 July 2023.

1. Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

Median PFS for cytotoxic agents after endocrine therapy

	Clinical Trial	Study	Prior CDK4/6i	Prior CT regimens	Target	Median PFS in months
Trastuzumab deruxtecan	DB-06	III	100%	0	HER2-low	**13**
Trastuzumab deruxtecan*	DB-04	III	70%	1–2	HER2-low	**10.1**
Datopotamab deruxtecan	TROPION-1	III	82%	1–2	no	**6.7**
Sacituzumab govitecan	TROPICS-2	III	100%	>2	no	**5.5**
Capecitabine*	PEARLs	II/II	0%	0	no	**14.4–9.4**

Can we reasonably define endocrine exhaustion in mBC?

1st **Requires progression on a prior CDK4/6i regimen**

- CDK4/6i have shown strong PFS and OS benefits in mBC and clinically relevant DFS in early BC
- Reasonable to consider them as the backbone of endocrine guidance

Primary Resistance

- mBC relapse on adjuvant CDK4/6i or <1 year (weak)
- Progression within the first 6 (strong) to 12 (modest) months on first line CDK4/6i

Secondary Resistance

- Relapse after 12 months of completing adjuvant CDK4/6i (strong)
- PD ≥12 months after initiating CDK4/6i for mBC (modest)

Define the progression pattern on prior CDK4/6i **2nd**

- *ESR1*
- PI3K, AKT, PTEN
- g*BRCA1/2 – PALB2*

Determine biomarkers **3rd**

4th **Disease burden – patient situation**

- ECOG
- Symptoms
- Visceral involvement

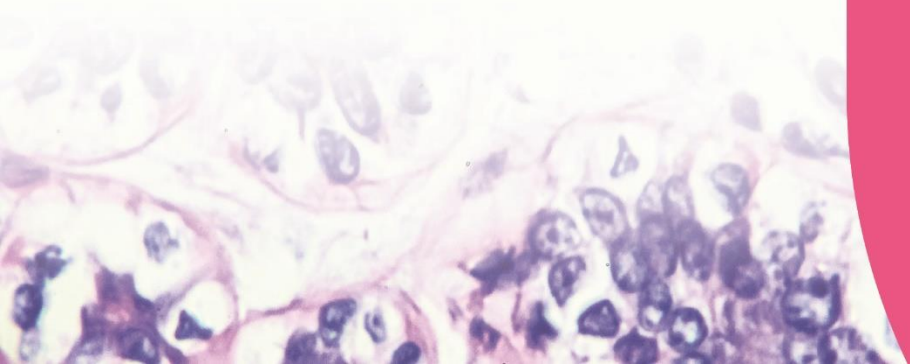
The optimal sequence of ET dependent also on patient preference and treatment availability

- ADCs, and particularly trastuzumab-deruxtecan have shown significant OS gain over standard CT in Endocrine Resistant patients
- **Patients must arrive on good performance to these options**
- **HER2-low/0 status is a new essential biomarker**

Endocrine resistance is not the end **5th**

Global Breast Cancer Academy

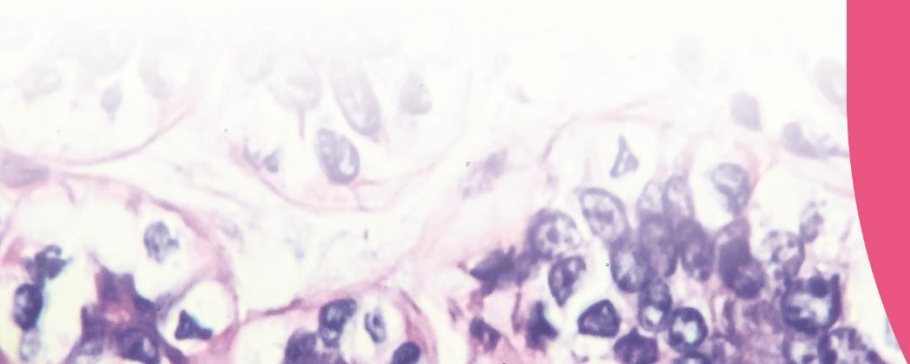
Q&A



APTITUDE HEALTH

Global Breast Cancer Academy

Break



APTITUDE HEALTH

Objectives

Understand clinical and pathologic factors that influence first-line choice of therapy for patients with HR+ mBC

Discuss the role of biomarkers, molecular profiling, and resistance mechanisms in guiding treatment choices

Examine the role of targeted therapies following endocrine therapy failure

Gain insights into the care of patients with high-risk and endocrine-resistant HR+ mBC

Explore current and future sequencing strategies for HR+, HER2– mBC

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

Global Breast Cancer Academy

Panel discussion: What is the optimal sequencing strategy for HR+, HER2– mBC?

Nadia Harbeck and all faculty

APTITUDE HEALTH

Interactive Discussion

1. What is the optimal sequencing strategy for HR+, HER2– mBC?
2. What drives the sequencing decisions?

We encourage our audience to ask questions using the Q&A box

Objectives

Understand clinical and pathologic factors that influence first-line choice of therapy for patients with HR+ mBC

Discuss the role of biomarkers, molecular profiling, and resistance mechanisms in guiding treatment choices

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Gain insights into the care of patients with high-risk and endocrine-resistant HR+ mBC

Explore current and future sequencing strategies for HR+, HER2– mBC

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

How bright is the future of HR+, HER2- mBC ?

Pr Joseph Gligorov

Disclosures

Affiliations/ disclosures	
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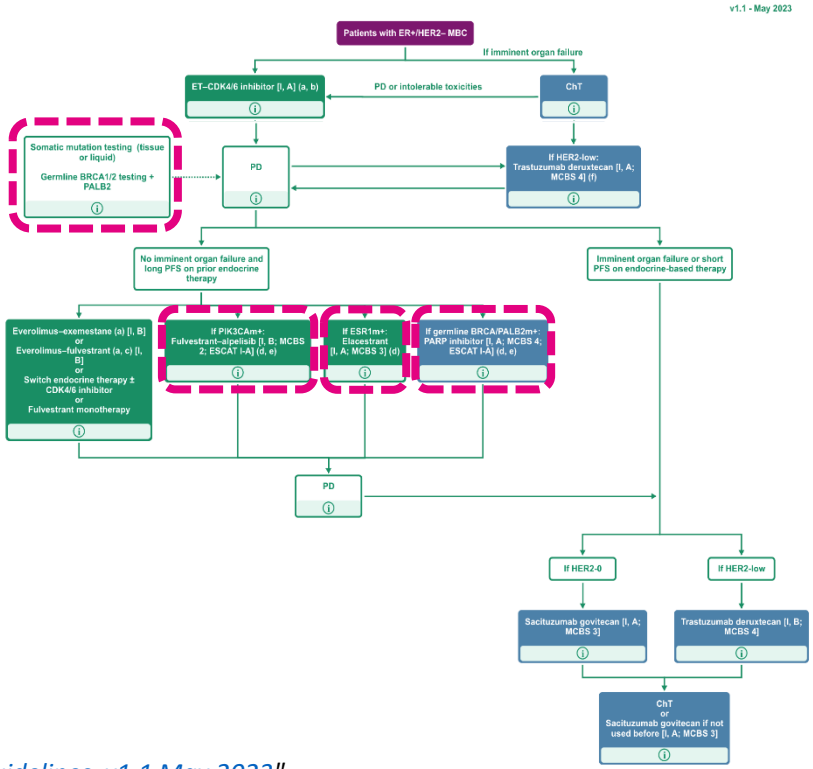
Stock options	Non
Family relationship	Non
Other (institutions & associations)	Sorbonne Université, AP-HP, Inserm (Employeurs et affiliations principales) Cours de Nice St Paul de Vence (responsabilité de programme de formation continue et de recommandations) ESMO, ESO, ABC, AROME, SoFOM, SFMPP, SPCC (membre de sociétés savants et associations médicales) Alliance Contre le Cancer, Vaincre le Cancer (associations de soutien à la recherche et aux soins)

Hypothesis

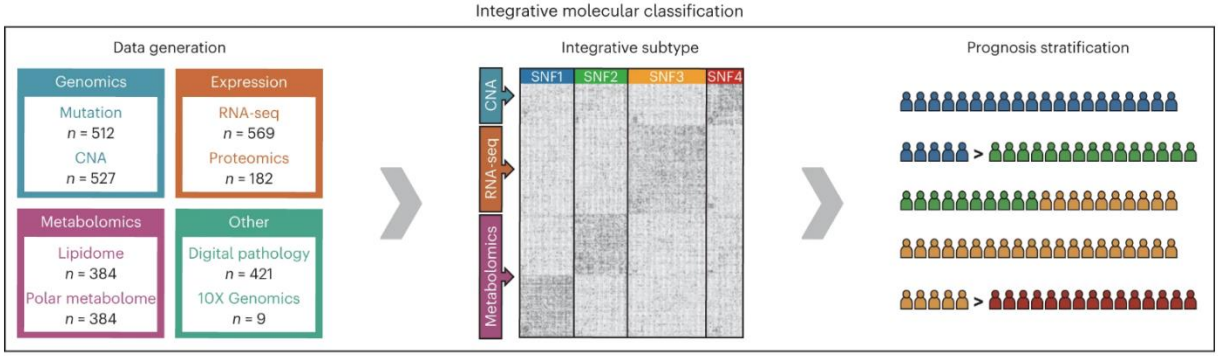
Our current standard

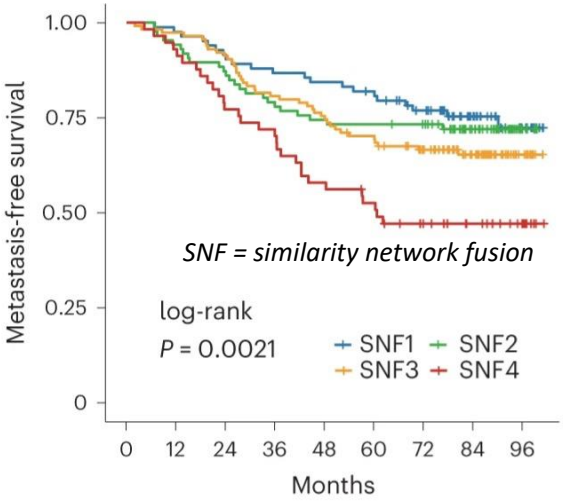


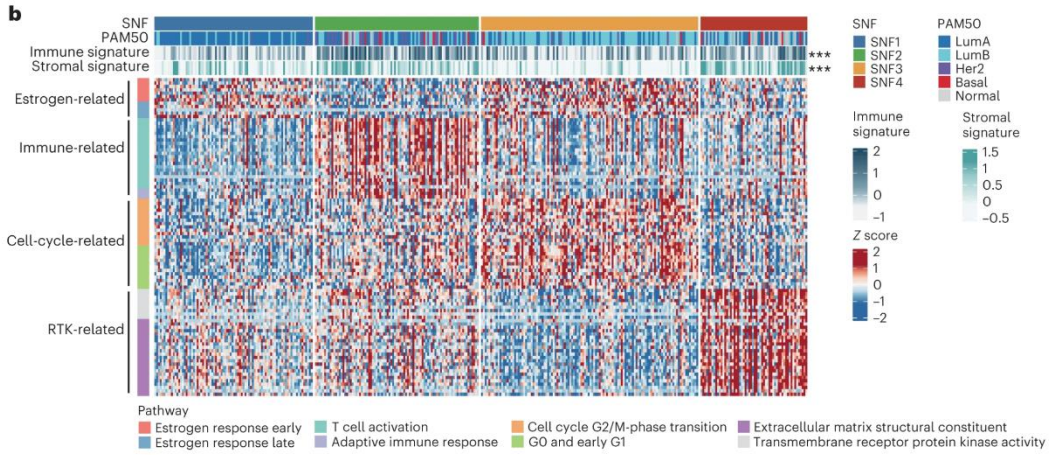
Ann Oncol 2021;32(12): 1475-1495
ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023"

Where are we going ?

Personalised enough? / HR+HER2-: a heterogeneous disease







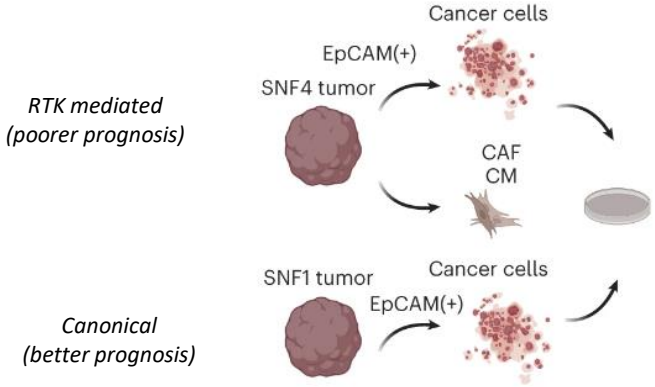
SNF1 = Canonical

SNF2 = Immunogenic

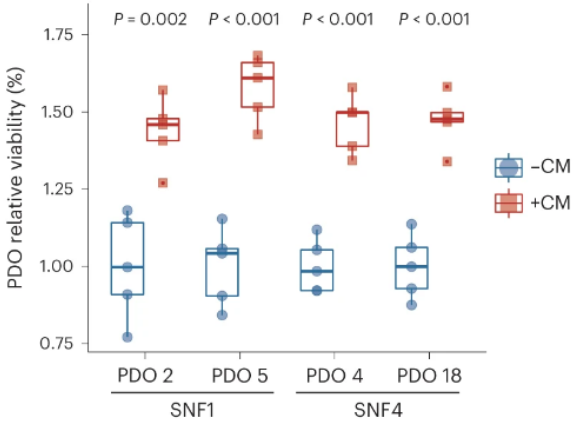
SNF3 = Proliferative

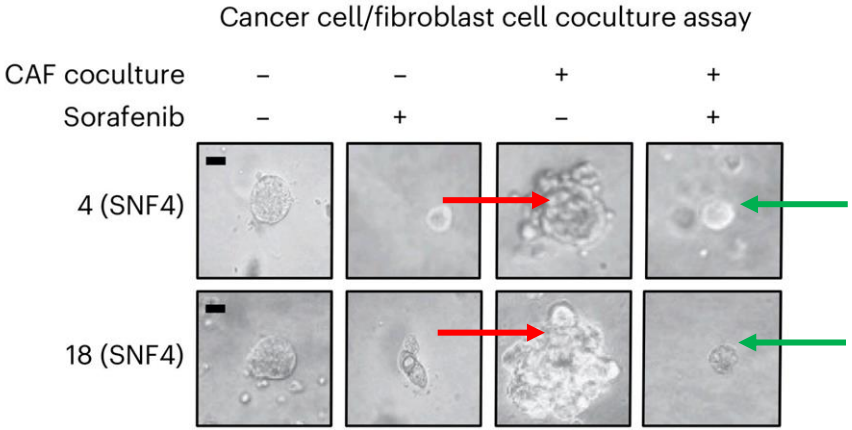
SNF4 = Mediated by RTKs

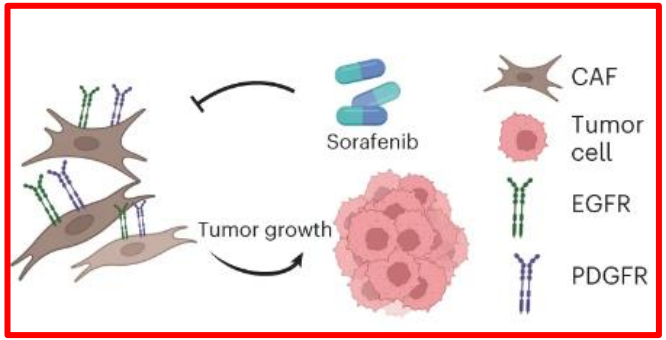
Jin *et al.* Nature Genetics 2023



CAF = cancer-associated fibroblasts
CM = conditioned culture medium



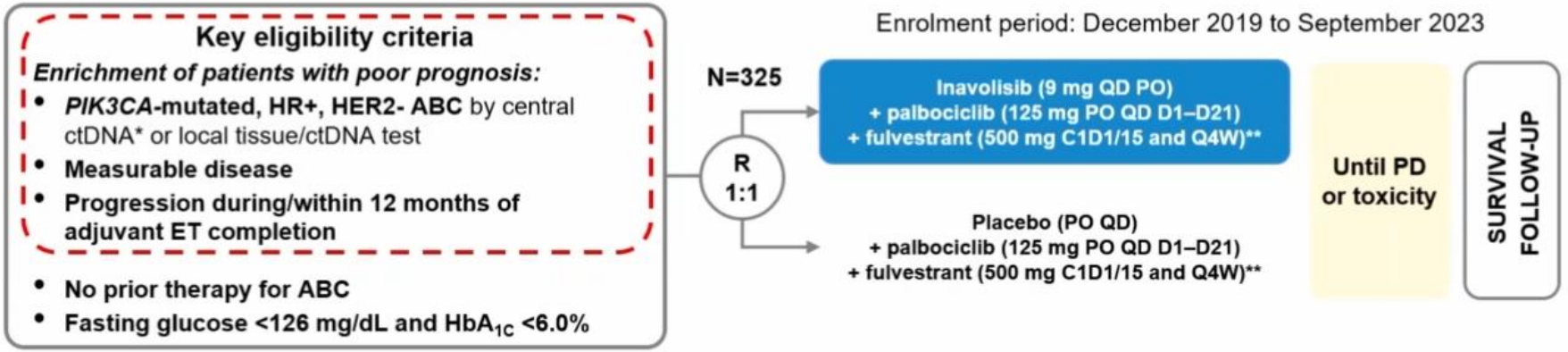




SNF4 target: tumour microenvironment >> C Cancer?

Jin *et al.* Nature Genetics 2023

INAVO120 - Phase III 1L MBC endocrine resistant *PIK3CAmut*



Stratification factors:

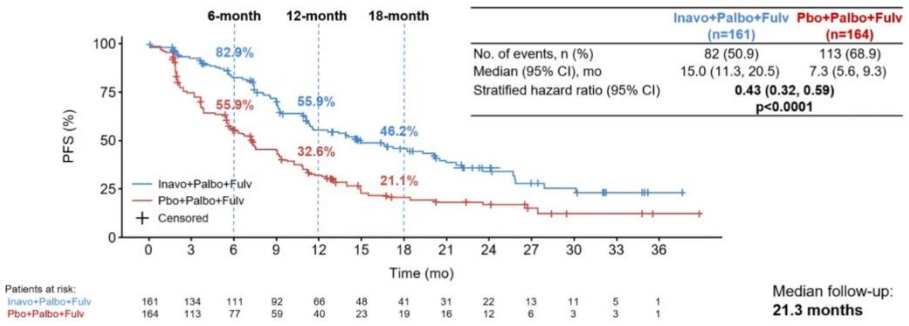
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints

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

INAVO120 - Phase III L1 meta hormonoresitant mPI3K

Primary endpoint: PFS (investigator-assessed)

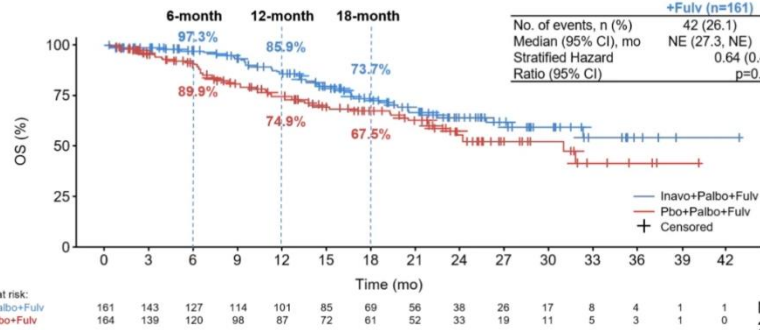


	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	0.43 (0.32, 0.59) p<0.0001	

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.

Key secondary endpoint: Overall survival (interim analysis)



	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	

Median follow-up: **21.3 months**

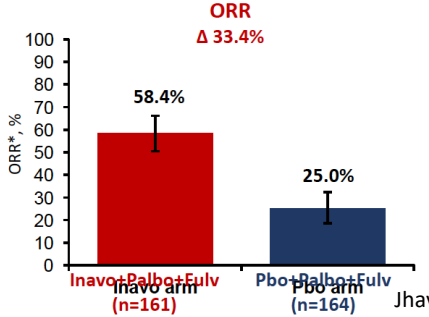
The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; NE, not estimable; OS, overall survival; Palbo, palbociclib; Pbo, placebo.

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Number of organ sites, n (%)		
1	21 (13.0)	32 (19.5)
2	59 (36.6)	46 (28.0)
≥3	81 (50.3)	86 (52.4)
Visceral disease, n (%)*	132 (82.0)	128 (78.0)
Liver	77 (47.8)	91 (55.5)
Lung	66 (41.0)	66 (40.2)
Bone only†	5 (3.1)	6 (3.7)
ER‡ and PgR status, n (%)		
ER+/PgR+	113 (70.2)	113 (68.9)
ER+/PgR-	45 (28.0)	45 (27.4)
Endocrine resistance, n (%)**		
Primary	53 (32.9)	58 (35.4)
Secondary	108 (67.1)	105 (64.0)

Within 2 years of adjuvant ET

After 2 years or within 12 months of stopping



Jhaveri *et al.* SABCS 2023

INAVO120 - AE with incidence ≥ 20% - EI with incidence ≥ 20% - EI with incidence ≥ 20% - EI with incidence ≥ 20

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Neutropenia	**144 (88.9%)**	**130 (80.2%)**	**147 (90.7%)**	**127 (78.4%)**
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	**83 (51.2%)**	**9 (5.6%)**	**43 (26.5%)**	**0**
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
Hyperglycemia	**95 (58.6%)**	**9 (5.6%)**	**14 (8.6%)**	**0**
Diarrhea	**78 (48.1%)**	**6 (3.7%)**	**26 (16.0%)**	**0**
Nausea	**45 (27.8%)**	**1 (0.6%)**	**27 (16.7%)**	**0**
Rash	**41 (25.3%)**	**0**	**28 (17.3%)**	**0**
Decreased Appetite	38 (23.5%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

6% grade 3 hyperglycaemia

(33% in SOLAR1)

Patient selection +++

Fasting blood glucose <1.26g/L & HbA1c < 6

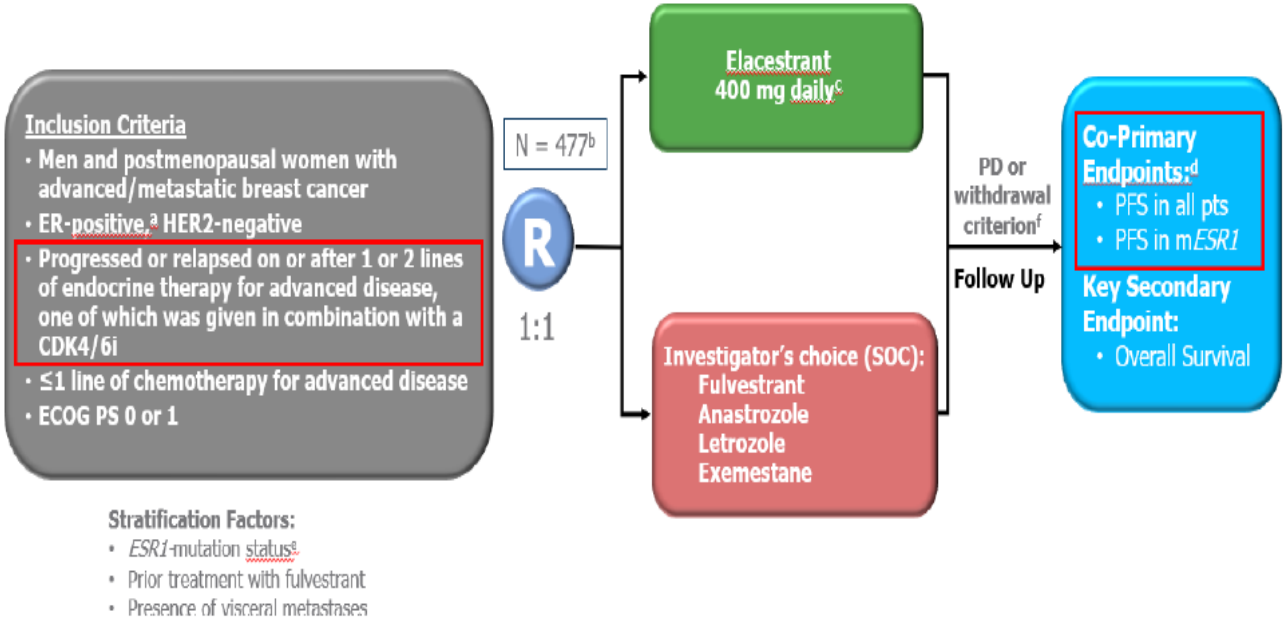
Low stoppage rate for IE: 6.8

INNAVO121 : Inavolisib + fulvestrant *vs.* Alpelisib + fulvestrant post CDK4/6

INAVO122: Inavolisib + trastu/pertu vs. trastu/pertu alone in L1 HER2+

maintenance

EMERALD phase III rando
Elacestrant *vs.* SOC in L2 or L3 after HT and CDK4/6

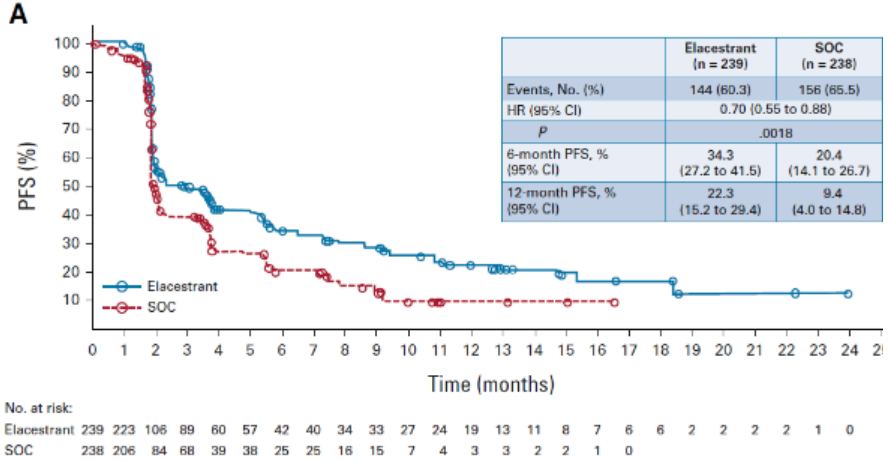


Patients included in the elacestrant arm: 48% mESR1; 68% meta visceral; 46% with 2 L HT and 20% with CT

Bidard FC *et al.* JCO 2022

EMERALD phase III rando
Elacestrant *vs.* SOC in L2 or L3 after HT and CDK4/6

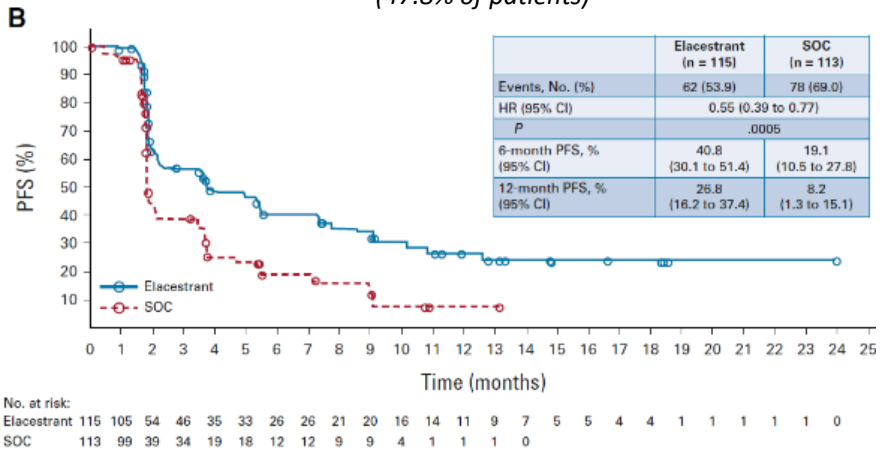
All patients



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

PFS = 1.9 *versus* 2.8 months

ESR1mt
(47.8% of patients)



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

PFS = 1.9 *versus* 3.8 months

Bidard FC *et al.* JCO 2022

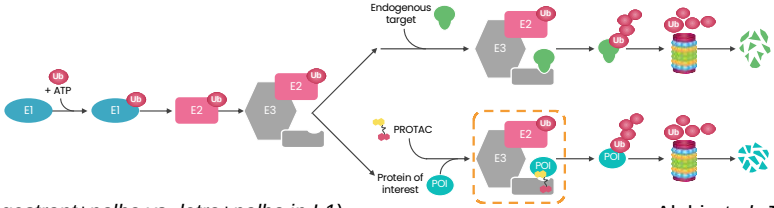
Trials evaluating oral SERDs

Trial	Oral SERD	Phase	N	ET line	Invest Arm	Comp Arm	Hiking	Primary Endpoint	Design	
persevERA	Giredestrant	III	978	I	Giredestrant 30 mg + Palbociclib[a]	Letrozole + Palbociclib[a]	1:1	PFS	Double-blind, placebo controlled	NCT04546009
SERENA-4	Camizestrant	III	1342	I	Camizestrant 75 mg + Palbociclib[a]	Anastrozole + Palbociclib[a]	1:1	PFS	Double-blind, placebo controlled	NCT04711252
SERENA-6	Camizestrant	III	302	I (ESR I^{mut} ctDNA)	Camizestrant 75 mg + Palbociclib/Abemaciclib[a]	AI (letrozole/anastrozole) + Palbociclib/Abemaciclib[a]	1:1	PFS	Double-blind, placebo controlled	NCT04964934
EMBER-3	Imlunestrant	III	800	2 (prior AI alone or with CDK4/6i)	Imlunestrant 400 mg vs Imlunestrant + Abemaciclib[a]	Physician's choice ET (fulvestrant / exemestane)[a]	1:1:1	PFS	Open-label	NCT04975308
SERENA-2 POSITIVE	Camizestrant	II	240[b]	2	Camizestrant 75/150/300 mg	Fulvestrant	1:1:1:1	PFS	Open-label	NCT04214288
EMERALD POSITIVE	Elacestrant	III	477[b]	2-3, post CDK4/6i	Elacestrant 400 mg	Physician's choice ET (Fulvestrant/ AI)	1:1	PFS in all patients and in ESRI^{mut}	Open-label	NCT03778931
acelERA NEGATIVE	Giredestrant	II	303[b]	2-3	Giredestrant 30 mg	Physician's choice ET (Fulvestrant/ AI)	1:1	PFS	Open-label	NCT04576455

Adapted from: Downton T, et al. Drug Des Devel Ther. 2022;16:2933-2948

New generation therapeutics targeting ER

Proteolysis Targeting Chimera (PROTACs)
E3 ubiqutin ligase and ER = ubiquitination and degradation of the ER via the proteasome

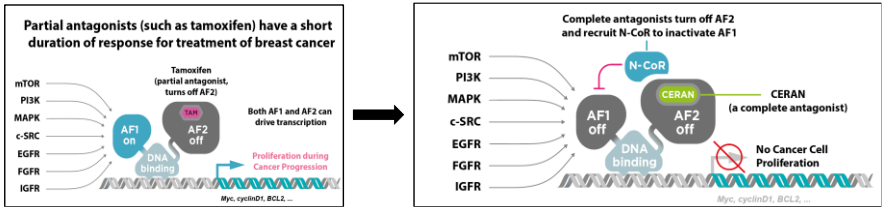


Phase II VERITAC with Vepdegestrant CBR 37.1 to 51.2
2 phase III: VERITAC-2 (vepdegestrant in L2 post CDK4/6 vs. fulvestrant) / VERITAC-3 (vepdegestrant+palbo vs. letro+palbo in L1)

Alabi *et al.* J Biol Chem. 2021

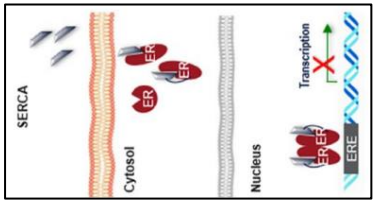
CERAN: blocks transcriptional activity in the ER
Direct antagonistic action on AF2
Recruitment of corepressors to inactivate AF1

Phase I/II OP-1250 palazestrant: mPF 7.2 months in 2/3L CBR 40% to 52



Hodges-Gallagher *et al.* ENA 2020

Selective Estrogen Receptor Covalent Antagonists (SERCAs)
Blocks transcriptional activity in the ER by binding a specific cysteine residue (H3B-6545)

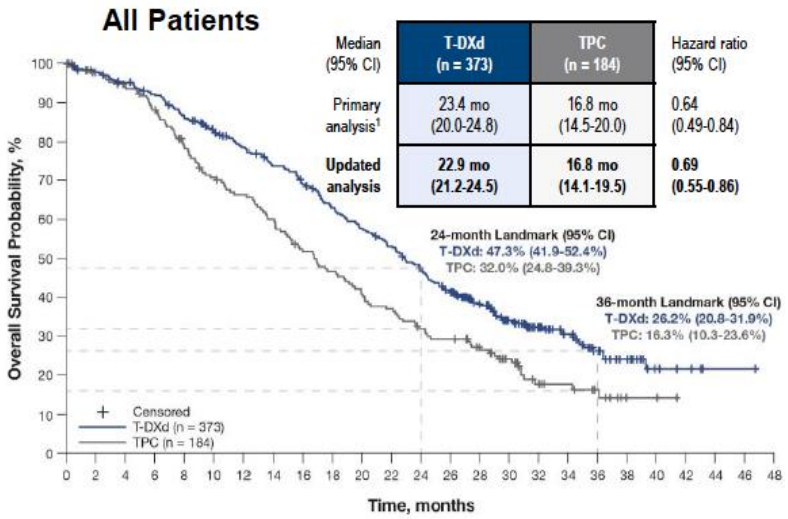


Shastry *et al.* Cur Treat Option in Oncol 2023

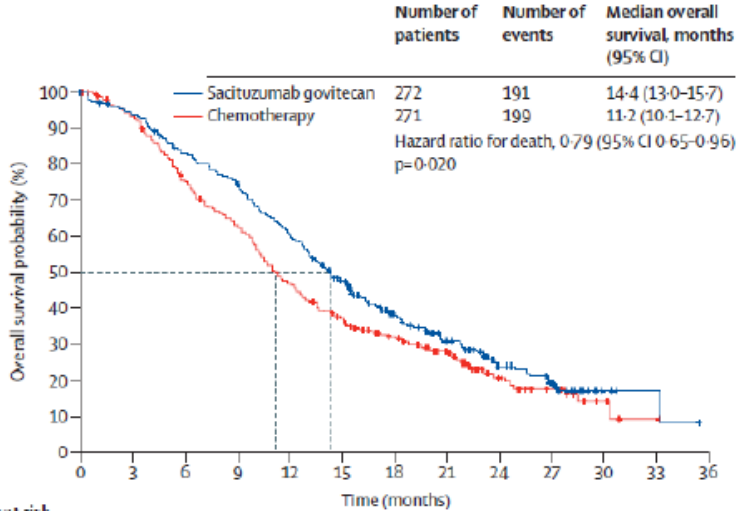
When to start chemotherapy and which chemotherapy?

1L = Standard CT; 2L & 3L = ADC

Destiny-breast 04 T-DXd vs. SoC
2L HER2-low (1+, 2+/ISH-)



TROPICS 02 SG vs. SoC
3L HER2-neg (0, 1+, 2+/ISH-)



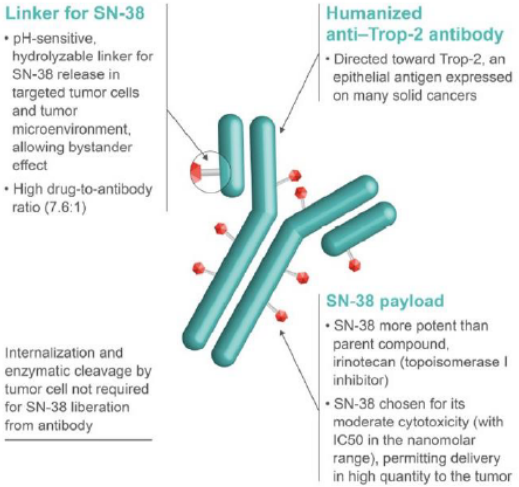
Overall survival benefits

Rugo *et al.* Lancet 2023

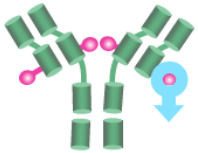
Anti-TROP2 ADCs in mBC HR+/HER2-

	Sacituzumab-gov. (n=272)	Datopotamab-DXd (n=365)	SKB264 (MK-2870) (n=38)
Payload	Anti-TOPO1	Anti-TOPO1	Anti-TOPO1
DAR	7.6	4	7.8
Trial	Ph3 RCT (TROPiCS-02)	**Ph3 RCT (TROPION-Breast01)**	**Single arm Ph1-2**

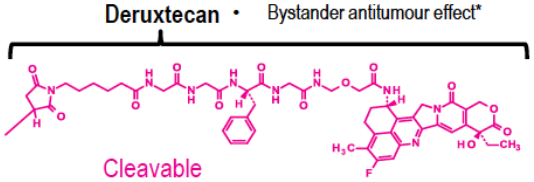
Sacituzumab govitecan



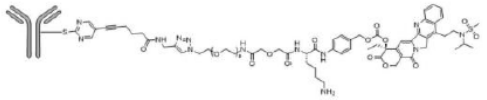
Datopotamab deruxtecan



- Payload mechanism of action: Topo-I inhibitor*
- High potency payload*
- Optimised drug to antibody ratio ≈4*†
- Payload with short systemic half-life*†
- Stable linker-payload*
- Tumour-selective cleavable linker*
- Bystander antitumour effect*



SKB264 (MK-2870)



- anti-TROP2 ADC
- Sulfonyl pyrimidine-CL2A-carbonate linker
- **Payload**: belotecan-derivative topoisomerase I inhibitor
- **DAR**: 7.4

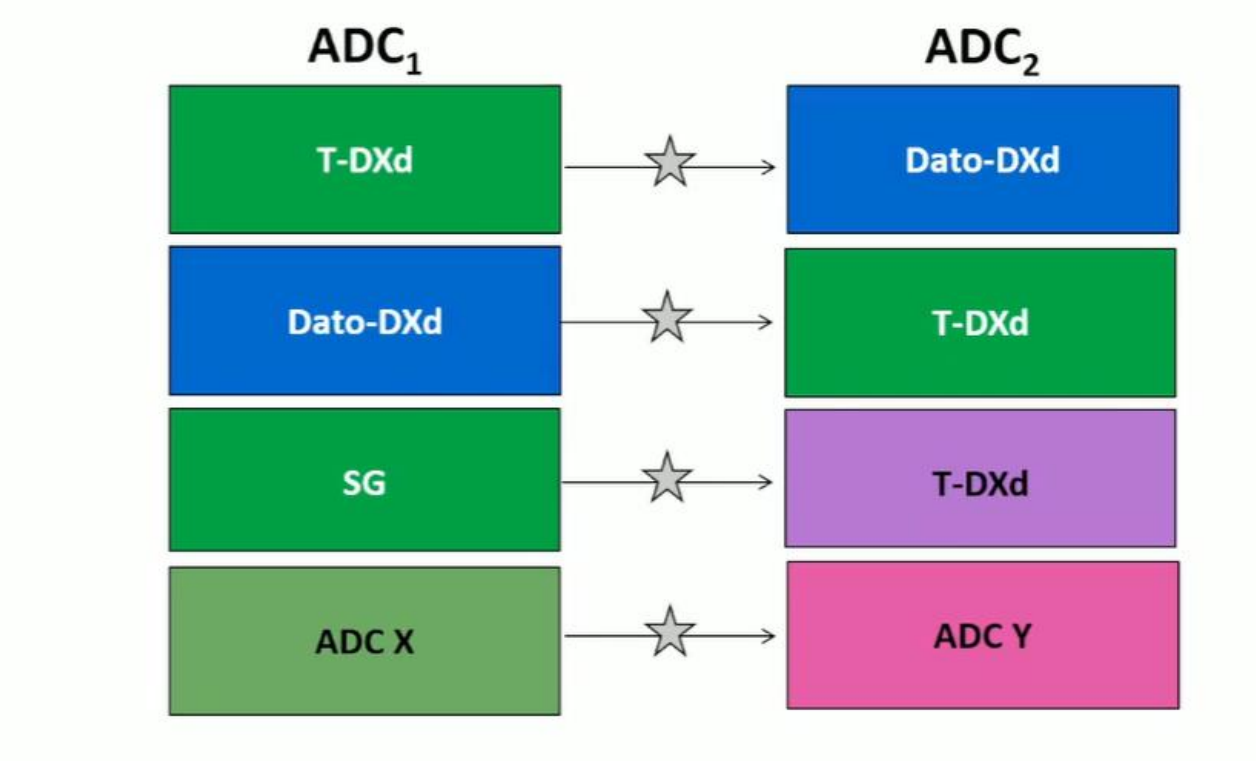
Giuseppe Curigliano discussion ESMO 2023

Anti-TROP2 ADCs in mBC RH+/HER2-

	Sacituzumab-gov. (n=272)	Datopotamab-DXd (n=365)	SKB264 (MK-2870) (n=38)
Payload	Anti-TOPO1	Anti-TOPO1	Anti-TOPO1
DAR	7.6	4	7.8
Trial	Ph3 RCT (TROPiCS-02)	Ph3 RCT (TROPION-Breast01)	Single arm Ph1-2
Age, median (range), years	57 (29-86)	56 (29–86)	50 (34-66)
ECOG PS 0, %	43%	54%	40%
Prior lines of chemotherapy, median	**3**	**1**	**2**
Prior CDK4/6 inhibitor, %	98%	82%	66%
Prior taxane and/or anthracycline, %	64%	65%	100%
ORR, %	**21%**	**36%**	**37%**
Median PFS, months - HR	**5.5 vs. 4.0** HR: 0.65 (95% CI 0.53-0.81)	**6.9 vs. 4.9** HR: 0.63 (95% CI 0.52–0.76)	11.1
Median OS, months - HR	14.5 vs. 11.2 HR 0.79 (0.65-0.95)	**Not mature** HR 0.84 (95% CI 0.62–1.14)	NR
Median FUP, months	12.7	10.8	8.2
Treatment discontinuation due to TRAE, %	**6%**	**3%**	**0%**
Oral mucositis/stomatitis - all grades | G3, %	NA	59% | 7%	46% | 2%
Drug-related ILD - all grades | G3, %	NA	3% | 1%	0% | 0%

Giuseppe Curigliano discussion ESMO 2023

Critical questioning of sequences



Tomorrow: HR+/HER2- mBC

gBRCA/PALB2mut ➜ PARPi

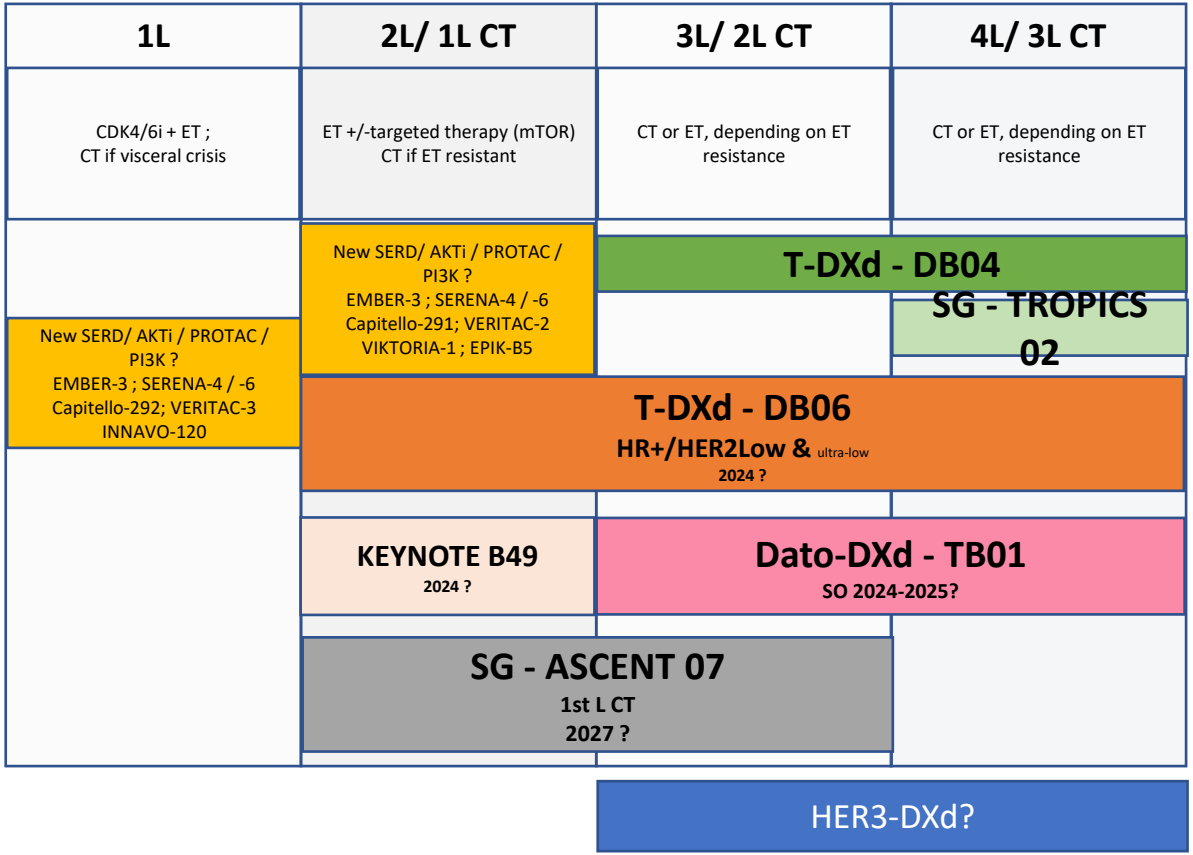
ESR1mut ➜ Elacestrant?

PI3Kmut ➜ Fulv + Innavolisib ? Alpelisib ?

AKTmut/PTEN ➜ Fulv + capi?

Visceral crisis / HT primary resistance ➜ Ctie/ADC (DB06) ?

The role of immunoassays (**Keynote B49**)



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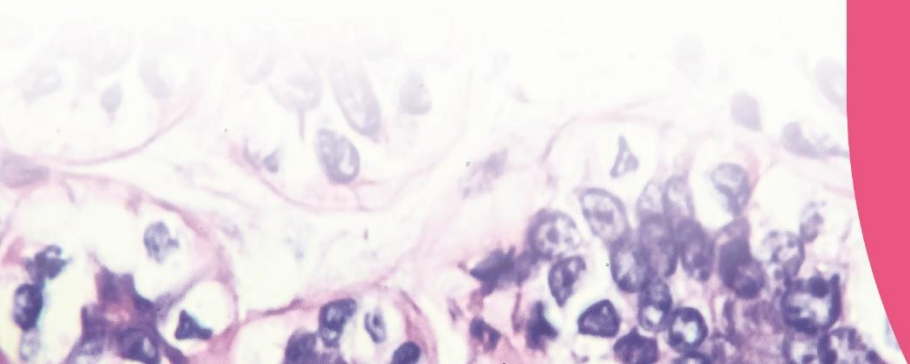
AP-HP. Sorbonne Université

Sciences & Humanités contre le cancer

Thanks

Global Breast Cancer Academy

Q&A



APTITUDE HEALTH

Objectives

Understand clinical and pathologic factors that influence first-line choice of therapy for patients with HR+ mBC

Discuss the role of biomarkers, molecular profiling, and resistance mechanisms in guiding treatment choices

Examine the role of targeted therapies following endocrine therapy failure

Gain insights into the care of patients with high-risk and endocrine-resistant HR+ mBC

Explore current and future sequencing strategies for HR+, HER2– mBC

Engage in patient case-based panel discussions and comprehensively discuss available treatment options

Global Breast Cancer Academy

BC case-based panel discussion

Case 1: Alexander König

Case 2: Lauren Seknazi

Case 3: Paula Llor

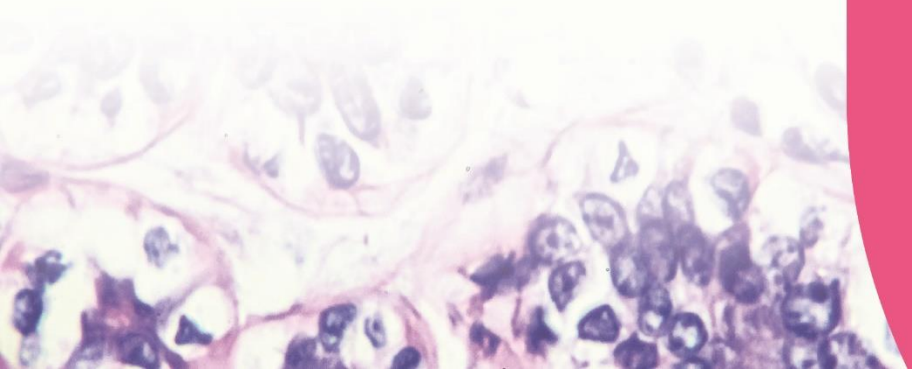
Moderator: Nadia Harbeck

APTITUDE HEALTH

Global Breast Cancer Academy

Case 1: HR+, HER2– mBC – what should be the 1L therapy after progression on adjuvant therapy with AI + CDK4/6 inhibitor?

Alexander König



APTITUDE HEALTH

LMU KLINIKUM
Klinik und Poliklinik für
Frauenheilkunde und Geburtshilfe

Global Breast Cancer Academy Europe
How does HR+ mBC look Today and Tomorrow

Casereport

Brustzentrum LMU Klinikum | 26.11.2024 | Alexander König

Brustzentrum im LMU Klinikum

CCC MÜNCHEN COMPREHENSIVE CANCER CENTER
TZM - TUMORZENTRUM

DKTK German Cancer Consortium

Offenlegung
Potentielle Interessenskonflikte

- Daiichi-Sankyo
- RG Gesellschaft für Information und Organisation mbH, Gräfelfing
- MEDEA GmbH, Saarbrücken

Casereport
HR+ mBC

LMU KLINIKUM

BC case-based panel discussion

Case 1

HR+, HER2- mBC

What shouhld be the **Firstline Therapy** after progression on adjuvant therapy with AI and CDK4/6 inhibitor?

Casereport 1
HR+ mBC

Female patient, 69 year old

Diagnosis Breast Cancer 11/2021 (66 year)

Metastatic disease since 01/2024

Casereport 1
HR+ mBC

- 66 year old female patient, unremarkable medical history, no chronical disease
- First diagnosis Breast cancer **11/2021**
- suspicious finding in mammography screening (right breast), cT1c (1,8 cm), cN0
- Biopsy: NST, G3, ER 95%, PR 80%, Her2: Score 0, ki67: 15%

Casereport 1
HR+ mBC

Treatment:

Operation Resection tumor and SLNE (12/2021): pT1c, pN1a (1/3), G3, L0, V0, R0

Tumor Biology:

NST, G3, ER 95%, PR 80%, Her2: Score 0

Staging: No metastasis

Adjuvant **Chemotherapy**:

6x Docetaxel, Cyclophosphamid (01/2022 – 05/2022)

Radiotherapy (06/2022 – 07/2022)

Casereport 1
HR+ mBC

After radiotherapy:

Start **Exemestane and Abemaciclib**

Casereport 1
HR+ mBC

Approval **Abemaciclib** in Europe **04/2022**

Corresponding to data from **monarchE Trial**:

Early Breast Cancer Pat. HR+, Her2-, nodal pos., with high risk of relapse:

Inclusion criteria:

≥ 4 pALN (positive axillary lymphe nodes) or

1 – 3 pALN and one of the following criteria: Tumorsize ≥ 5 cm or Grading 3

Casereport 1
HR+ mBC

Dosage **Abemaciclib**: **150 mg** twice per day,

Reduction of dosage to **100 mg** or **50 mg**, if it is necessary

Tabelle 1. Empfehlungen zur Dosisanpassung bei Nebenwirkungen

	Verzenios-Dosis Kombinationstherapie
Empfohlene Dosis	150 mg zweimal täglich
Erste Dosisanpassung	100 mg zweimal täglich
Zweite Dosisanpassung	50 mg zweimal täglich

Source: Fachinformation Abemaciclib (German technical information about the medication)

Casereport 1
HR+ mBC

The patientin started Abemaciclib 150 mg 1-0-1 in 08/2022

Most frequently side effects:

diarrhoea, changing blood count, increasing transaminases, changing electrocardiogram

With our patient: blood count was stable,

but development Diarrhoea Grading 3; changing dosage to 100 mg 1-0-1,

after dosage reduction: normal rate of defecation; continuation treatment

Casereport 1
HR+ mBC

- once per month the patient had a visit in our outpatient clinic (control Blood levels, prescription medication)
- **01/2024**: Patient has dry cough; no infection, no expectoration
- CT scan: suspicious findings for pulmonary metastasis

- Bronchoscopy and biopsy: **Infiltration by adenocarcinoma, consistent with metastasis breast cancer**,
  ER 90%, PR 10%, Her2: Score 2+, FISH negative
  PIK3CA: Wildtyp., ESR1: pos.

Casereport 1
HR+ mBC

LMU KLINIKUM

Recommendation Tumorboard:
changig treatment to **Elacestrant**

Casereport 1
HR+ mBC

Elacestrant: **345 mg once per day** (1 Tablet)

Dose modification 258 mg per day (3x 86 mg Tablet)

Most frequently side effects:

Nausea, vomiting, diarrhoea, constipation,

Increasing triglycerides, increasing cholesterol, increasing transaminases,

fatigue, arthralgia, hot flashes

Casereport 1
HR+ mBC

Treatment with Elacestrant **since 02/2024**

- Staging by CT Scan every 3 months: stable disease
- No side effects
- Pat. has a good quality of life

Casereport 1
HR+ mBC

Summary:

- Patient develops metastatic disease after adjuvant treatment by AI and CDK4/6 inhibitor
- Mutation ESR1 Gene
- Decision treatment by Elacestrant
- Since 10 months stable disease and a good quality of life

LMU Frauenklinik

Münchner Symposium ’24

13.–14.12.2024 · Hilton Munich Park

JETZT ANMELDEN!

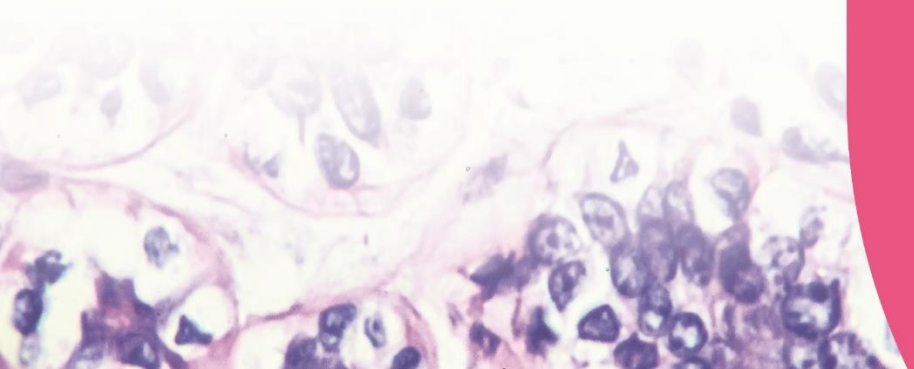
Gynäkologische Tumoren und Brustkrebs
Neues aus San Antonio
State of the Art Gynäkologie und Geburtshilfe

www.muenchner-symposium.de

Global Breast Cancer Academy

Case 2: HR+, HER2– mBC – 2L therapy after early progression in metastatic disease

Lauren Seknazi



APTITUDE HEALTH

HR+, HER2-, mBC: 2nde line therapy after early progression in metastatic disease

Dr Lauren Seknazi

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Sciences & Humanités contre le cancer
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS
SORBONNE UNIVERSITÉ

Clinical case

- Patient aged 69
- Married, 2 children, retired
- Medical past history: Hypertension, Diabetes (metformine)

➢ **1999: HR+ HER2- right breast cancer**

➢ **pT2N2M0 IDC grade 2 (2+2+2), ER100%, PgR 70%,**

- Right total mastectomy - axillary curage, adjuvant chemotherapy (6 FEC), adjuvant RT, tamoxifen 6 years

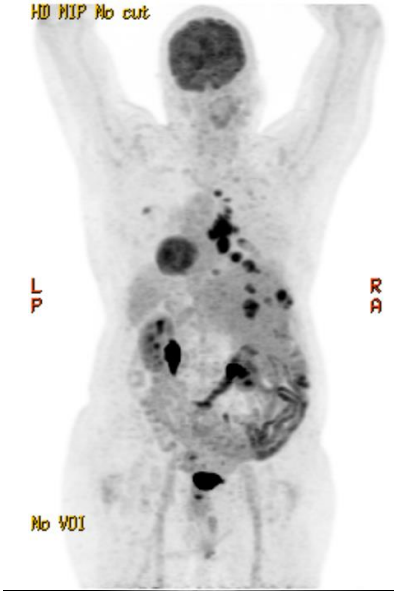
➢ **June 2020: multi-metastatic recurrence**

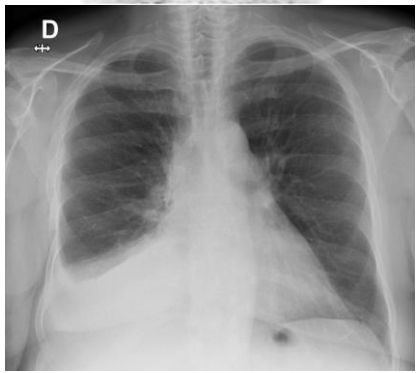
- **PET scan** in the context of dyspnoea: left breast nodule, plurifocal right pleural extension and mediastino-hilar lymph nodes

- **Lymph node biopsy**: grade 1 NST infiltrating carcinoma, RO 100%, RP 20%, HER2 negative (0), Ki67 30%.

⇒ **1st line AI + CDK4/6i starting in june 2020**

⇒ **Request for oncogenetic investigation**



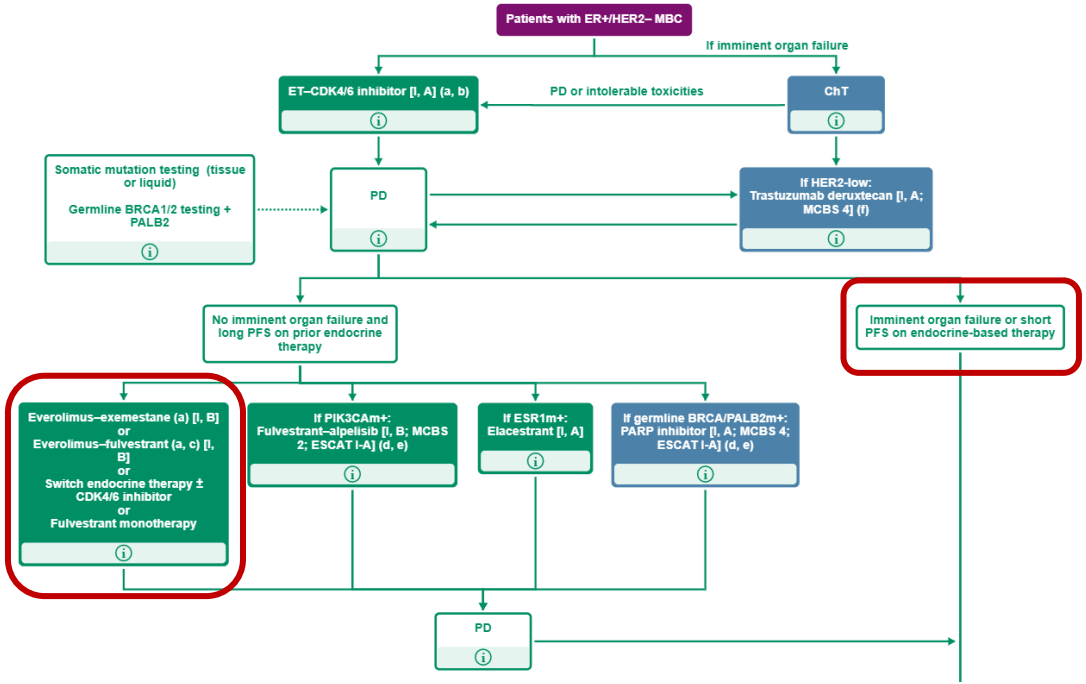


Clinical case- situation 1

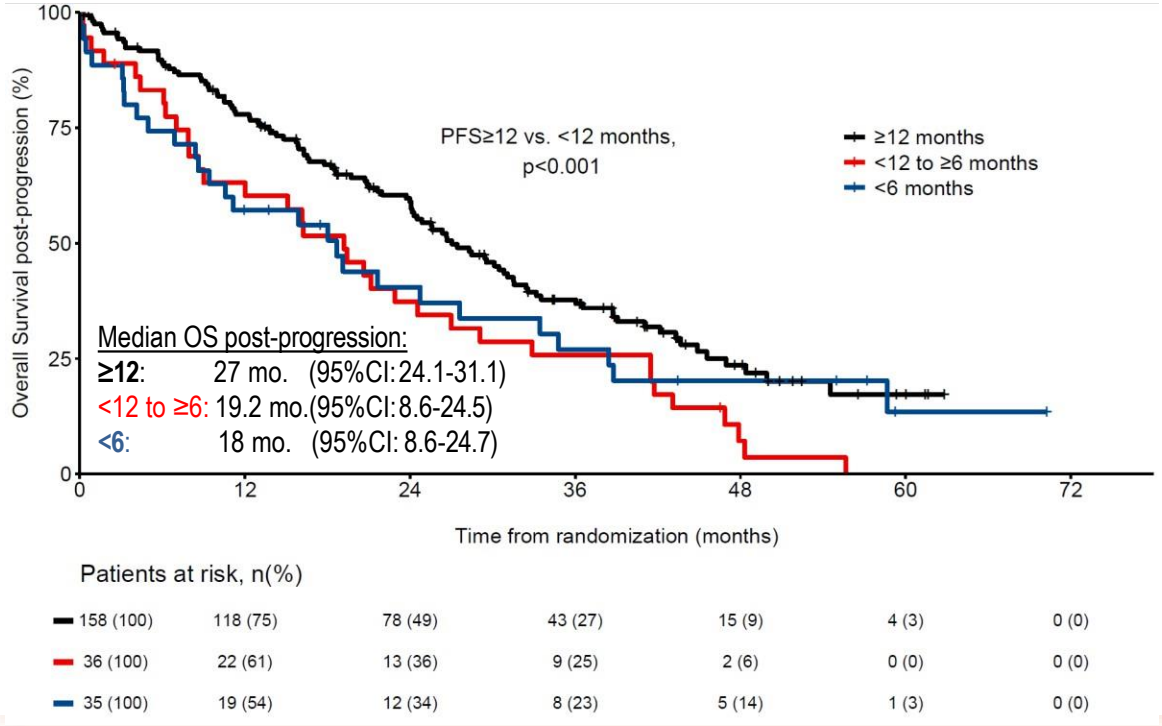
❖ March 2021 (+ 9 months): lymph node progression (PET-FDG), asymptomatic

- **Negative oncogenetic investigation**

- **What is the 2ème line treatment?**
  - Fulvestrant alone
  - Tamoxifen alone
  - Fulvestrant + everolimus
  - Tamoxifene + everolimus
  - Monochemotherapy
  - Polychemotherapy



Parsifal: Post-progression Survival by PFS duration (< 6, 6 - 12, and ≥12 months) for progressing patients (n=229)



Events per cohort:

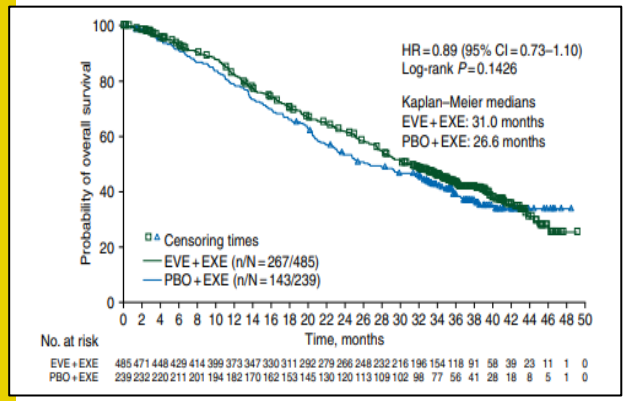
≥12:	103 (65.2%)
<12 to ≥6:	34 (94.4%)
<6:	27 (77.1%)

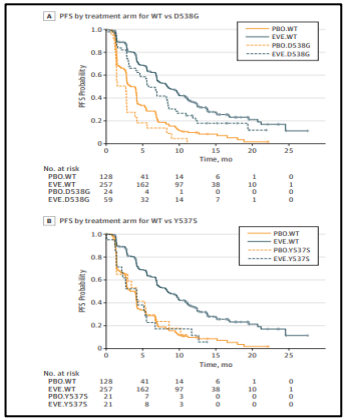
n (%), number of patients (percentage based on N); N: number of patients; mo.: months; OS: overall survival; PFS: progression-free survival

Fulvestrant / Exemestane + Everolimus

BOLERO 2 study, phase III

N= 724 postmenopausal patients, R 2:1 (everolimus vs placebo)
One line of stage IV CT admitted
Before the era of CDK4-6 inhibitors
PFS: 3.2 → 7.8 months (HR 0.46; p<0.0001)





Baselga J et al, NEJM 2012; Piccart M et al, Ann Oncol, 2014
Chandarlapaty et al. Jama Oncol;, 2026

MANTA study, phase II

Table. Primary and Key Secondary Efficacy End Points

End Point	Fulvestrant Plus Daily Vistusertib (n = 101)	Fulvestrant Plus Intermittent Vistusertib (n = 95)	Fulvestrant (n = 66)	Fulvestrant Plus Everolimus (n = 64)
PFS, median (95% CI), mo	7.6 (5.9-9.4)	8.0 (5.6-9.9)	5.4 (3.5-9.2)	12.3 (7.7-15.7)
HR vs fulvestrant (95% CI)	0.88 (0.63-1.24)	0.79 (0.55-1.12)	NA	NA
P value	.46	.16	NA	NA
HR vs fulvestrant plus everolimus (95% CI)	0.63 (0.45-0.90)	0.71 (0.49-1.01)	0.63 (0.42-0.92)	NA
P value	.01	.06	.01	NA
Objective response rate, % (95% CI)	31.6 (21.4-43.3)	28.6 (18.8-40.0)	26.0 (14.6-40.3)	41.2 (27.6-55.8)
Clinical benefit rate, % (95% CI)	44.7 (33.3-56.6)	39.0 (28.0-50.8)	38.0 (24.7-52.8)	56.9 (42.2-70.7)
Duration of response median (95% CI), mo	11.8 (8.4-13.7)	9.4 (5.9-14.5)	16.7 (10.8-19.3)	17.6 (9.1-19.1)
Duration of clinical benefit median (95% CI), mo	11.9 (10.9-13.7)	13.4 (11.2-18.9)	16.7 (12.8-20.2)	14.3 (12.2-18.6)
Overall survival median (95% CI), mo	27.1 (20.0-NR)	24.2 (20.6-NR)	24.4 (17.3-NR)	NR

Abbreviations: HR, hazard ratio; NA, not applicable; NR, not reached; PFS, progression-free survival.

Schmid P et al. JAMA Oncol, 2019

PrE0102 : Randomized Phase II Trial of **Fulvestrant Plus Everolimus** or Placebo in Postmenopausal Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy:

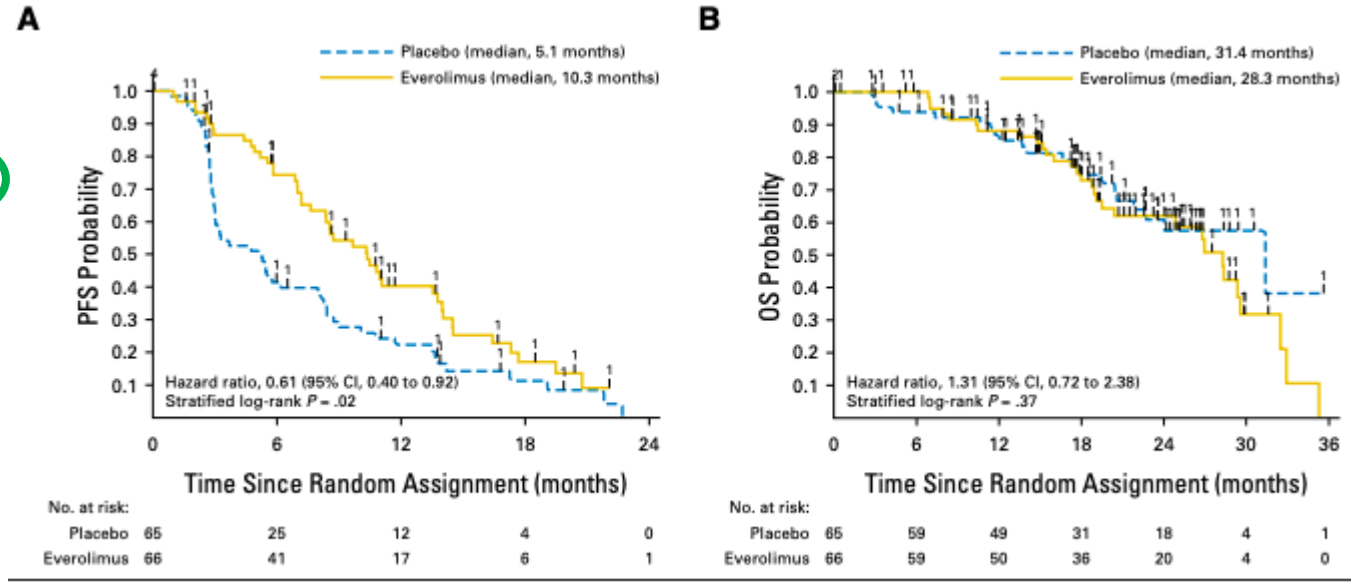


Fig 2. Kaplan-Meier estimates of investigator-assessed (A) progression-free survival (PFS) and (B) overall survival (OS) in the intent-to-treat (ITT) population.

Tamoxifen or fulvestrant can also be combined with everolimus.
(LoE/GoR : II/B) (80%)

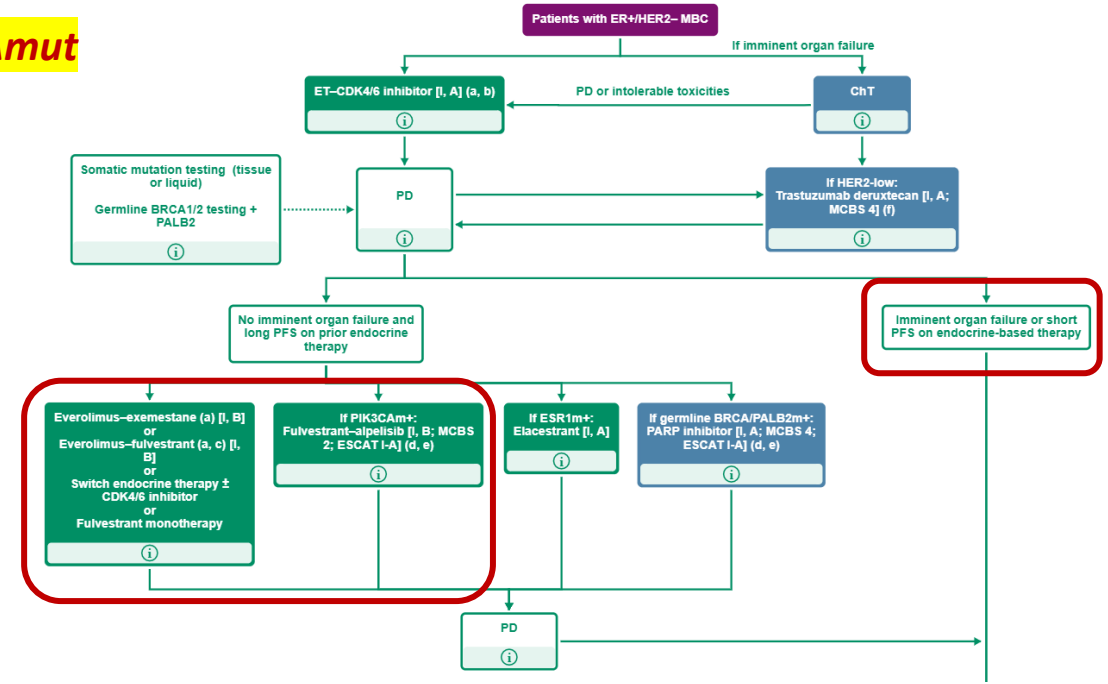
Kornblum et al. JCO 2018

Clinical case- situation 2

❖ March 2021 (+ 9 months): lymph node progression (PET-FDG), asymptomatic

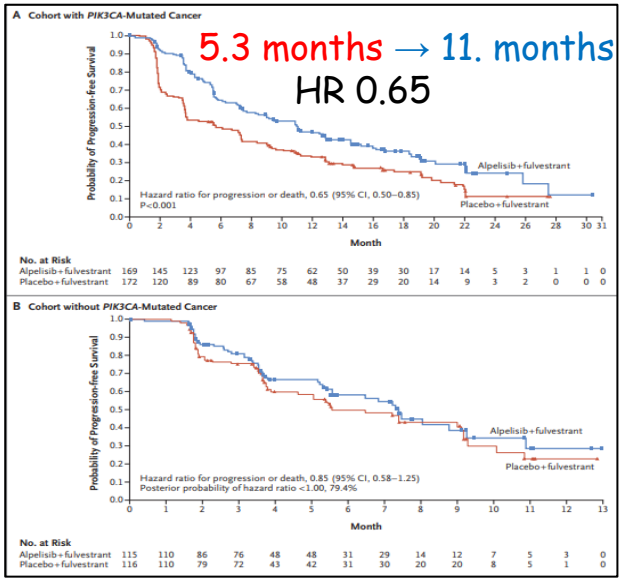
- **oncogenetic investigation: *PIK3CAmut***

- **What is the 2ème line treatment?**
  - Fulvestrant alone
  - Tamoxifen alone
  - Fulvestrant + everolimus
  - Tamoxifene + everolimus
  - Fulvestrant + alpelisib
  - Fulvestrant + capivasertib
  - Monochemotherapy
  - Polychemotherapy



Targeting *PIK3CA* mutations (Alpelisib, not reimbursed in France)

SOLAR-1 study: PFS



PIK3CA mutation (n=341)

No *PIK3CA* mutation (n=331)

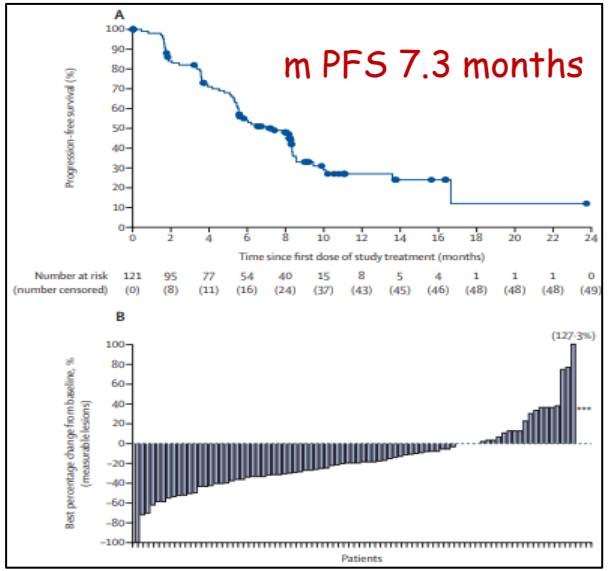
6% of patients had an i CDK4-6

Negative study in OS but + 7.9 months

André F et al, NEJM 2019 and Ann Oncol, 2021

BYLieve study (post CDK)

N = 127



Rugo HS et al, Lancet Oncol 2021

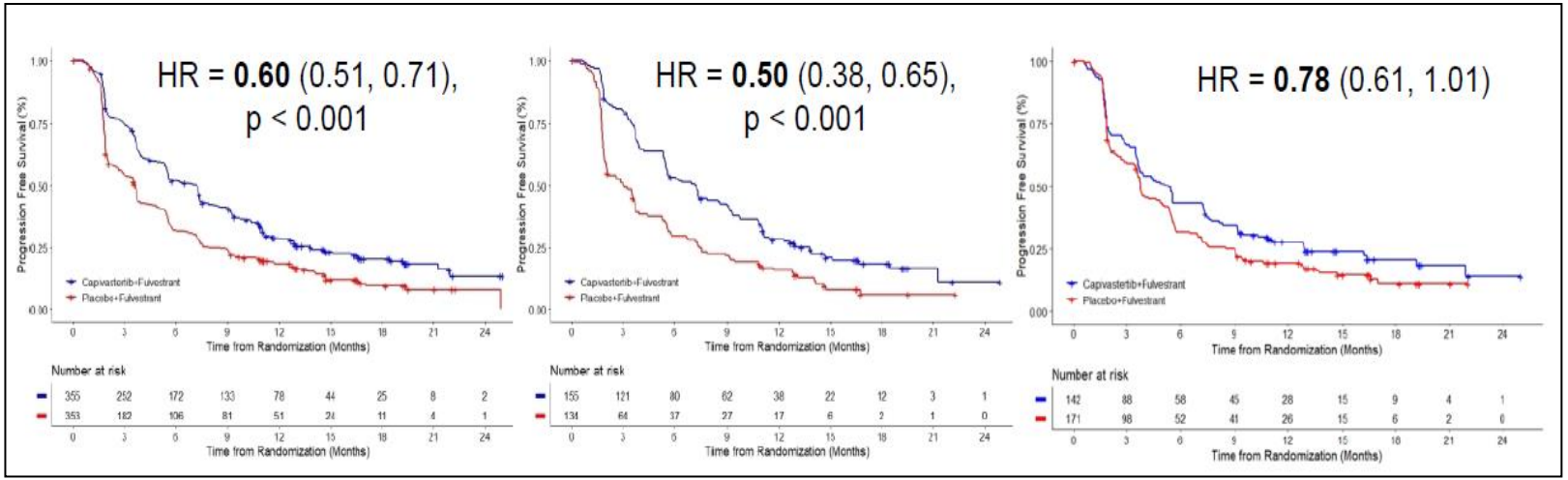
Capivasertib

CAPITELLO-291 study: results

Total population n=708

Population pathway activation n= 289

Population without activation of the track n= 313 (exploratory)



mPFS 3.6 → 7.2 months

3.1→ 7.3 months

3.7→ 5.3 months

Turner N et al, NEJM 2023

Capivasertib

CAPITELLO-291 study: Side effects

Table 2. Most Frequent Adverse Events in the Overall Population (Safety Population).*

Event	Capivasertib–Fulvestrant (N=355)					Placebo–Fulvestrant (N=350)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)									
Any adverse event	343 (96.6)	52 (14.6)	139 (39.2)	139 (39.2)	9 (2.5)	288 (82.3)	115 (32.9)	118 (33.7)	44 (12.6)	10 (2.9)
Diarrhea	257 (72.4)	164 (46.2)	60 (16.9)	33 (9.3)	0	70 (20.0)	60 (17.1)	9 (2.6)	1 (0.3)	0
Rash†	135 (38.0)	57 (16.1)	35 (9.9)	43 (12.1)	0	25 (7.1)	19 (5.4)	5 (1.4)	1 (0.3)	0
Nausea	123 (34.6)	85 (23.9)	35 (9.9)	3 (0.8)	0	54 (15.4)	42 (12.0)	10 (2.9)	2 (0.6)	0
Fatigue	74 (20.8)	49 (13.8)	23 (6.5)	2 (0.6)	0	45 (12.9)	35 (10.0)	8 (2.3)	2 (0.6)	0
Vomiting	73 (20.6)	54 (15.2)	13 (3.7)	6 (1.7)	0	17 (4.9)	10 (2.9)	5 (1.4)	2 (0.6)	0
Headache	60 (16.9)	47 (13.2)	12 (3.4)	1 (0.3)	0	43 (12.3)	33 (9.4)	8 (2.3)	2 (0.6)	0
Decreased appetite	59 (16.6)	37 (10.4)	21 (5.9)	1 (0.3)	0	22 (6.3)	11 (3.1)	9 (2.6)	2 (0.6)	0
Hyperglycemia	58 (16.3)	24 (6.8)	26 (7.3)	7 (2.0)	1 (0.3)	13 (3.7)	8 (2.3)	4 (1.1)	1 (0.3)	0
Stomatitis	52 (14.6)	24 (6.8)	21 (5.9)	7 (2.0)	0	17 (4.9)	15 (4.3)	2 (0.6)	0	0
Asthenia	47 (13.2)	29 (8.2)	14 (3.9)	4 (1.1)	0	36 (10.3)	31 (8.9)	3 (0.9)	2 (0.6)	0
Pruritus	44 (12.4)	32 (9.0)	10 (2.8)	2 (0.6)	0	23 (6.6)	19 (5.4)	4 (1.1)	0	0
Anemia	37 (10.4)	15 (4.2)	15 (4.2)	7 (2.0)	0	17 (4.9)	4 (1.1)	9 (2.6)	4 (1.1)	0
Urinary tract infection	36 (10.1)	8 (2.3)	23 (6.5)	5 (1.4)	0	23 (6.6)	2 (0.6)	21 (6.0)	0	0

* The safety population included all the patients who received at least one dose of capivasertib, fulvestrant, or placebo. The listed events were reported as a single term (or for rash, as a group term) in at least 10% of the patients for any grade in the capivasertib–fulvestrant group. Adverse events are reported regardless of the relationship to capivasertib, fulvestrant, or placebo.

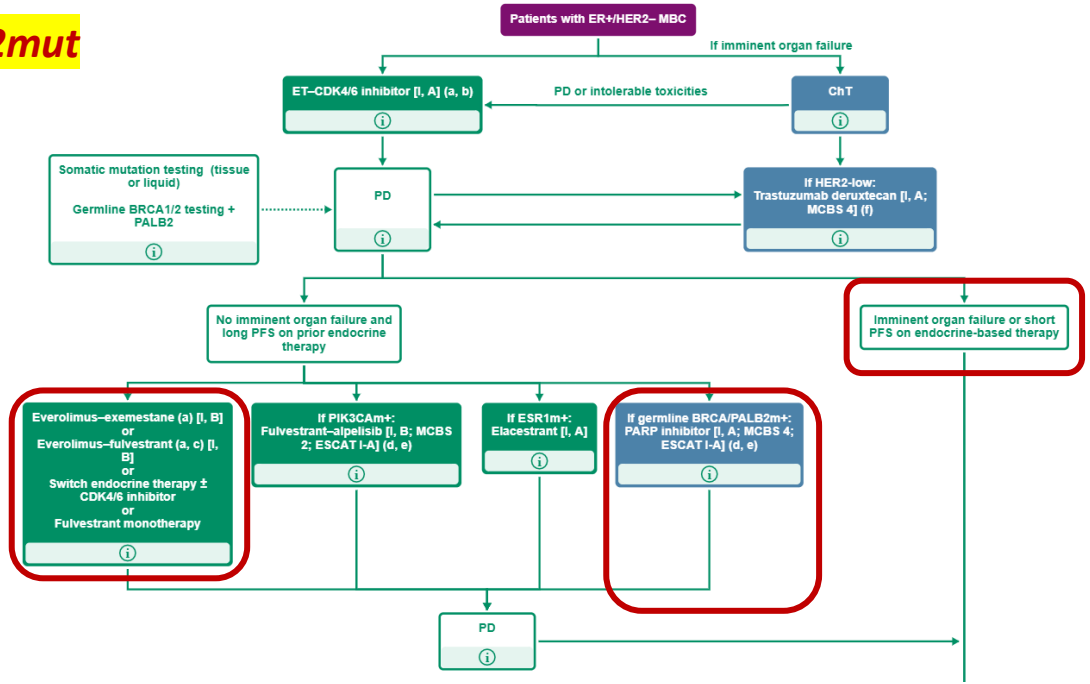
† The group term of rash includes the preferred terms of rash, rash macular, maculopapular rash, rash papular, and rash pruritic.

Clinical case- situation 3

❖ March 2021 (+ 9 months): lymph node progression (PET-FDG), asymptomatic

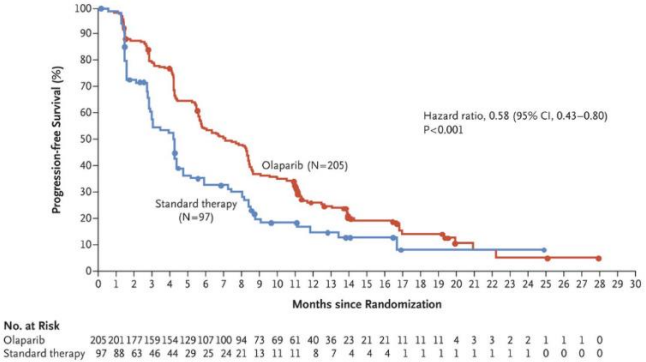
- **oncogenetic investigation: *gBRCA2mut***

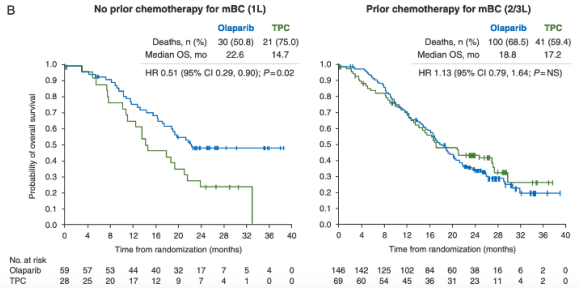
- **What is the 2ème line treatment?**
  - Fulvestrant alone
  - Tamoxifen alone
  - Fulvestrant + everolimus
  - Tamoxifene + everolimus
  - Olaparib
  - Talazoparib
  - Monochemotherapy
  - Polychemotherapy

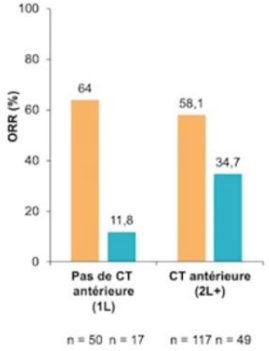


In the case of a *BRCA1/BRCA2* mutation, when should PARPi be prescribed?

OLYMPIAD

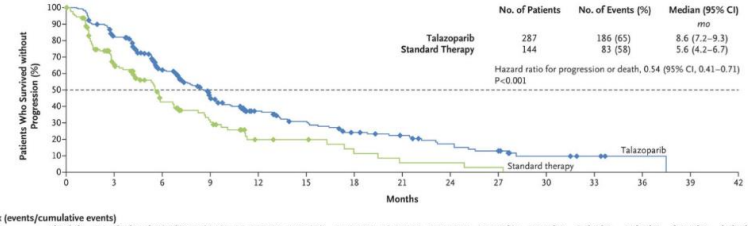


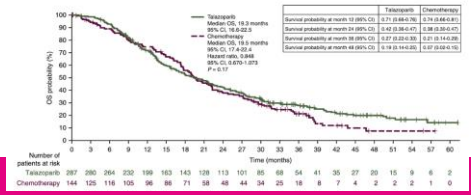


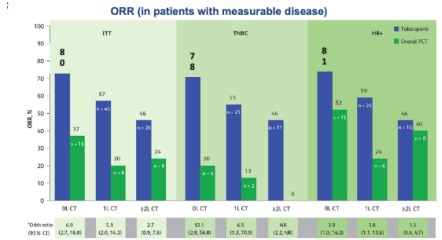


Robson et al, NEJM 2017
Robson et al, NEJM 2019

EMBRACA







DOR (in patients with objective response)

	ITT			TNBC			HR+		
mDOR (n) (95% CI), mo	0L CT	1L CT	≥2L CT	0L CT	1L CT	≥2L CT	0L CT	1L CT	≥2L CT
TALA	6.2 (66) 5.0–9.5	4.2 (45) 2.9–7.0	4.5 (26) 2.7–6.3	5.4 (31) 3.6–6.2	4.1 (21) 2.8–4.2	4.4 (11) 1.4–15.2	9.5 (35) 5.9–14.4	6.7 (24) 2.9–11.2	4.5 (15) 2.3–6.3
Overall PCT	3.0 (15) 1.4–7.6	3.4 (8) 1.2–7.8	3.1 (8) 1.4–5.6	1.4 (4) 1.4–2.4	5.6 (2) 3.5–7.8	0 (0)	6.4 (11) 1.0–NR	3.1 (6) 1.2–9.6	3.1 (8) 1.4–5.6

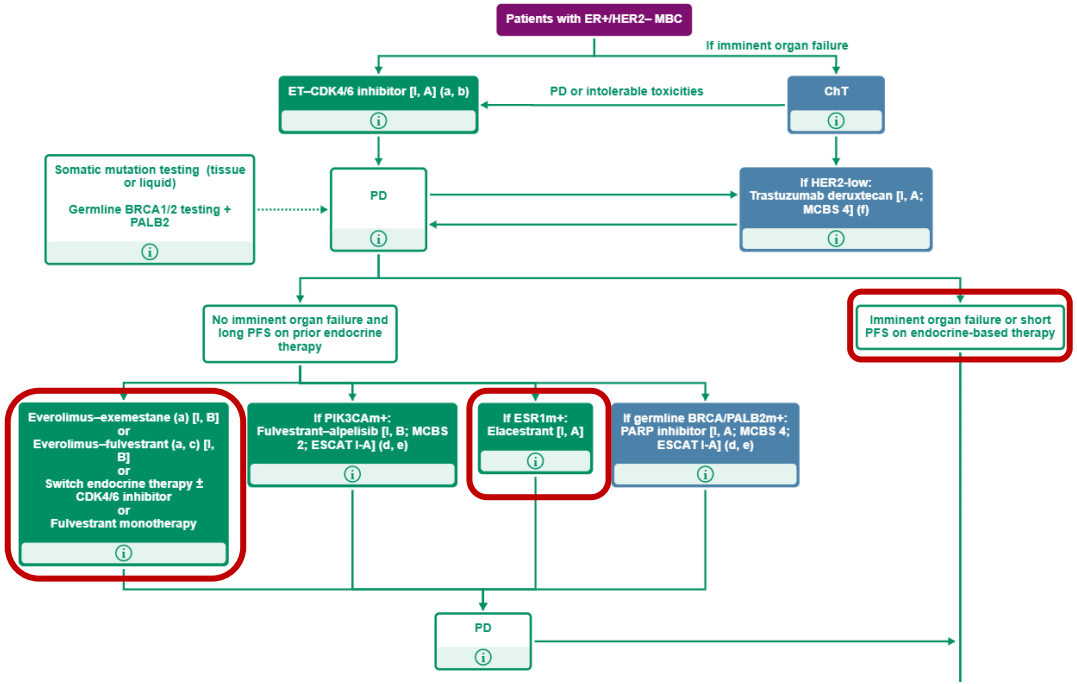
Litton et al, Ann Oncol 2020

Clinical case- situation 4

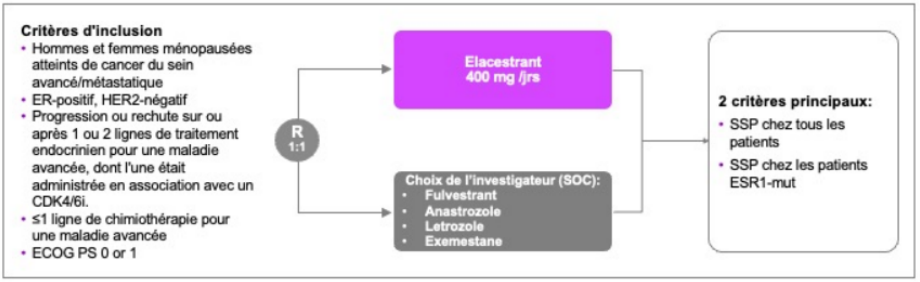
❖ March 2021 (+ 9 months): lymph node progression (PET-FDG), asymptomatic

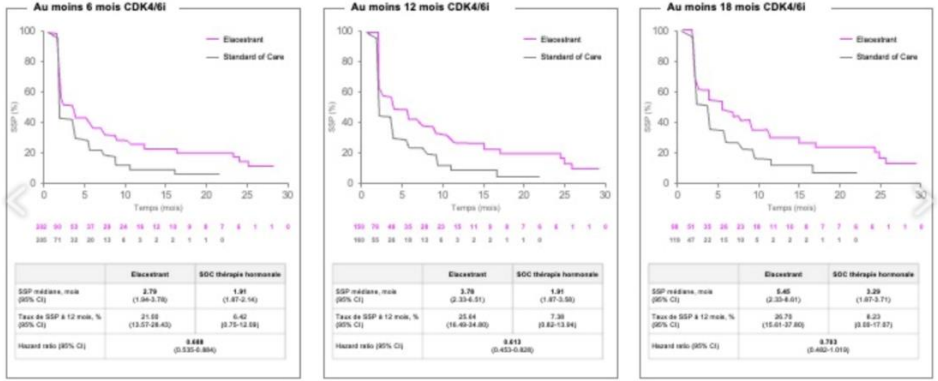
- **oncogenetic investigation: *ESR1mut***

- **What is the 2ème line treatment?**
  - Fulvestrant alone
  - Elacestrant alone
  - Fulvestrant + everolimus
  - Monochemotherapy
  - Polychemotherapy



Elacestrant more effective in cases of *ESR1* mutation and duration of exposure to an iCDK4/6 in L1 > 12 months



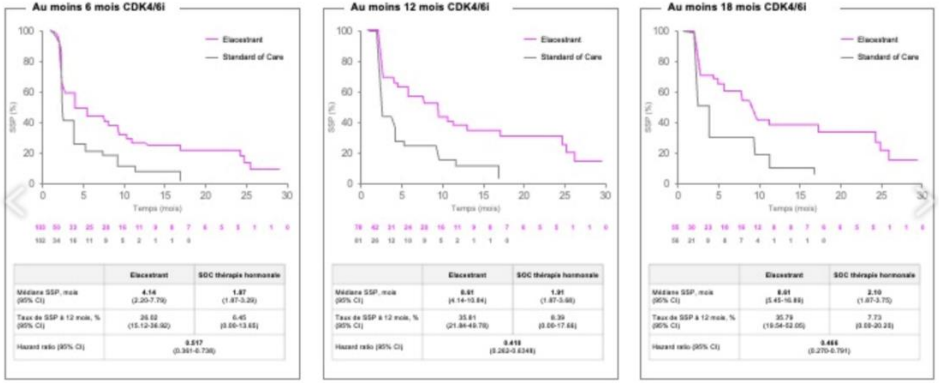


All patients: PFS as a function of duration of ttmt with iCDK4/6

Efficacy of SERD with PFS on iCDK4/6 < 12 months

Duration on CDK4/6i in the metastatic setting	<6 months		6- 12 months	
ESR1-mut	Elacestrant (n=9)	SoC (n=8)	Elacestrant (n=25)	SoC (n=21)
Median PFS (months)	1.87 (1.64 - .)	1.87 (1.68 - 5.55)	1.91 (1.87 - 2.79)	1.84 (1.68 - 3.45)
Hazard ratio	1.565 (0.424 - 5.769)		1.122 (0.547 - 2.347)	

⇒ **Less effective SERD in 2ème lines after exposure to an iCDK4/6 + HT < 12 months in 1ère lines?**



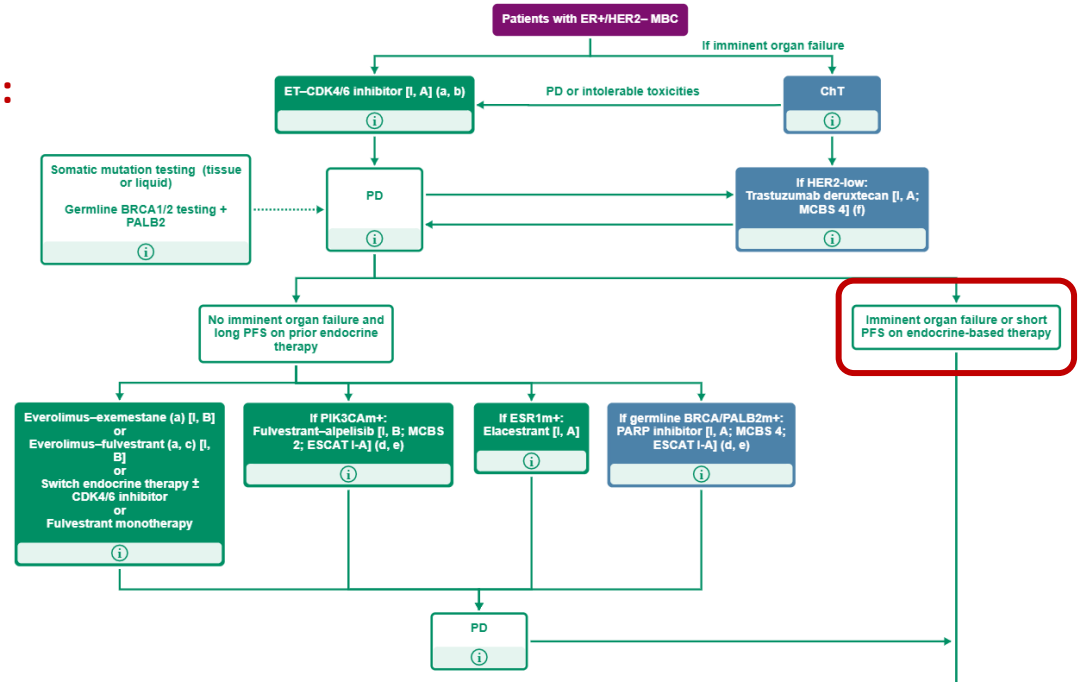
ESR1 mutated tumours: PFS as a function of duration of ttmt with iCDK4/6

Clinical case- situation 5

❖ March 2021 (+ 9 months): hepatic and lung progression (PET-FDG), symptomatic (O_2), pain, ECOG2

- **Negative oncogenetic investigation:**
- ***But HER2 was considered as 1+ on the biopsy***

- **What is the 2ème line treatment?**
  - Monochemotherapy
  - Polychemotherapy
  - Trastuzumab-deruxtecan
  - Sacituzumab-govitecan

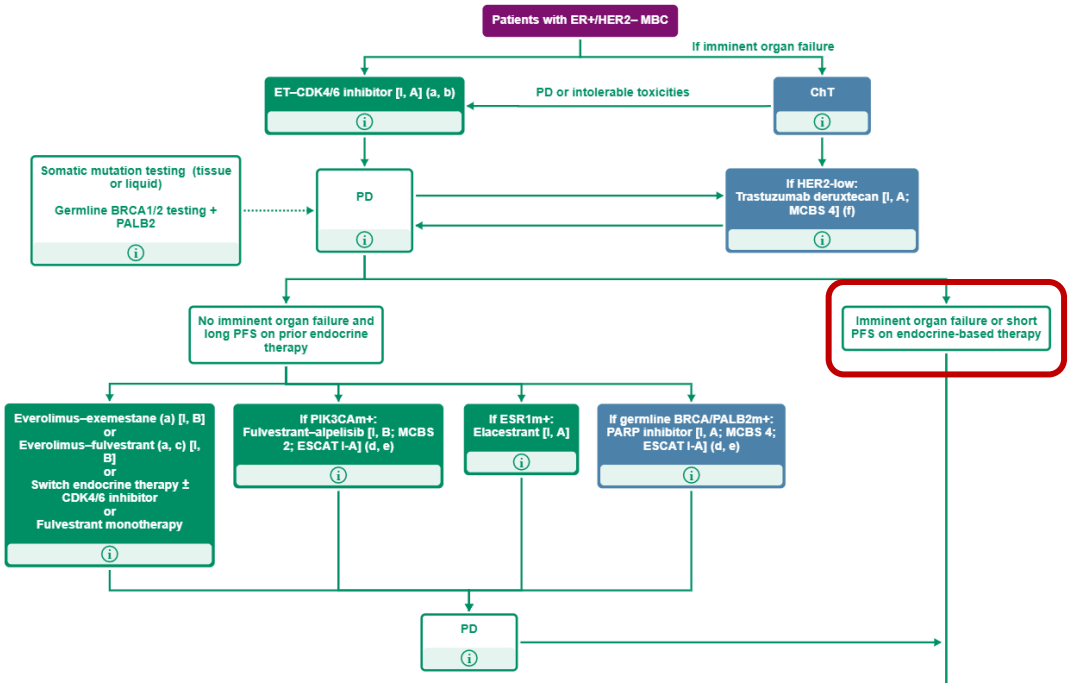


Clinical case- situation 6

❖ March 2021 (+ 9 months): hepatic and lung progression (PET-FDG), symptomatic (O_2), pain, ECOG2

- **Negative oncogenetic investigation:**

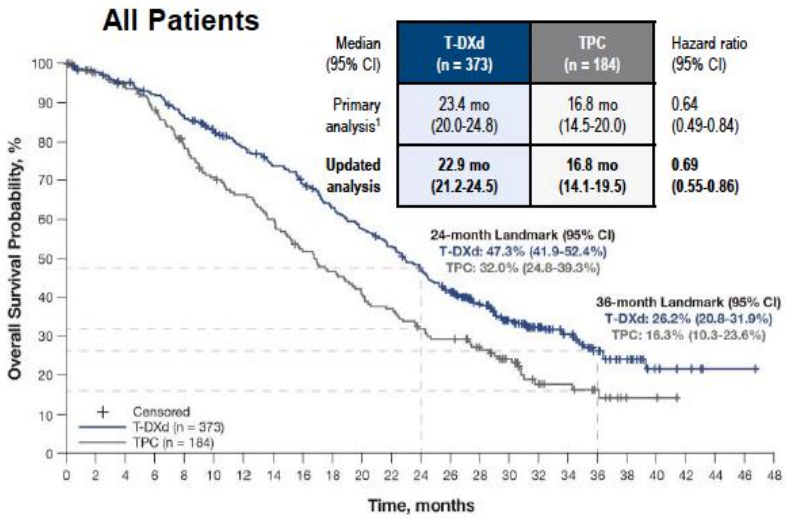
- **What is the 2ème line treatment?**
  - Monochemotherapy
  - Polychemotherapy
  - Sacituzulmab-govitecan



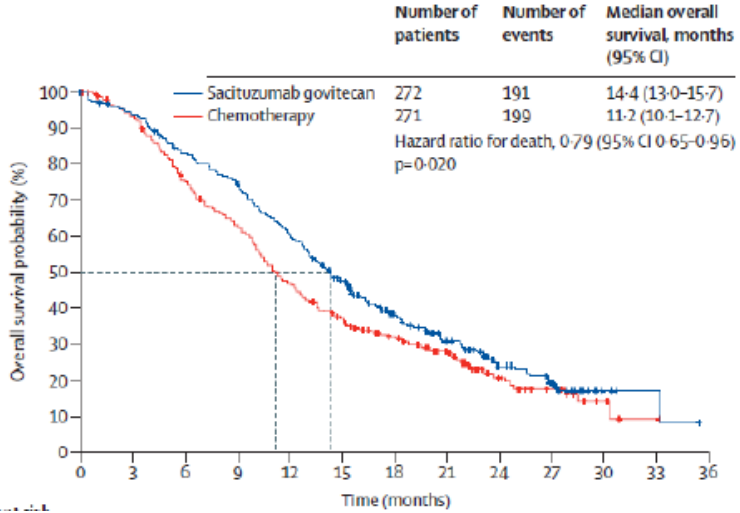
Place of ADCs in ER+ Breast cancers

1L = CT standard ; 2L & 3L = ADC

Destiny-breast 04 T-DXd vs. SoC
2L HER2-faible (1+, 2+/ISH-)



TROPICS 02 SG vs. SoC
3L HER2-neg (0, 1+, 2+/ISH-)



OS benefits

S. Modi *et al.*, ESMO 2023

Rugo *et al.* Lancet 2023

IUC

INSTITUT UNIVERSITAIRE DE CANCÉROLOGIE

AP-HP. Sorbonne Université

Sciences & Humanités contre le cancer

Thanks

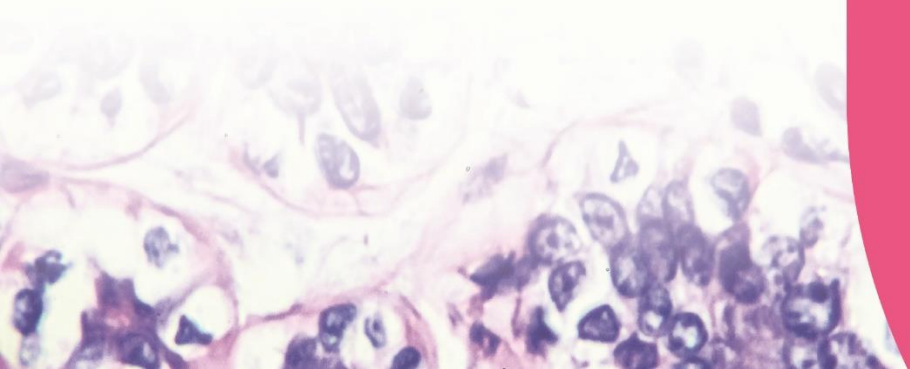
Global Breast Cancer Academy

Case 3: HR+, HER2– mBC – 2L therapy after long exposure to ET ± CDK4/6 inhibitor

Paula Llor, MD

Arnau de Vilanova Hospital, Valencia, Spain

26 November 2024



APTITUDE HEALTH

Declaration of interests

No disclosures
No conflict of interests

Global Breast Cancer Academy

2015

Case introduction

- 45-year-old woman
- No medical history
- Locally advanced right breast cancer stage IIB (cT3N0M0)
- g*BRCA* WT

→ Invasive ductal carcinoma G3
- ER 90% PR 0%
- HER2 2+ FISH negative
- Ki-67 40%

  - **Neoadjuvant chemotherapy**:
    - Epirubicin + cyclophosphamide q3w x4 cycles → Docetaxel q3w x4 cycles
  - **Surgery: Segmental mastectomy + selective axillary lymphadenectomy:**
    - ypT1bN0 Ki67 10%
    - No metastasis in 2 sentinel lymph nodes
  - **Adjuvant RT:** 50 Gy 22-07-2016 and 02-09-2016
  - **Adjuvant HT:** Tamoxifen since October 2016

Locally advanced breast cancer HR+ HER2-

2015

4 YEARS

Aug 2020

Follow-up visit:

- Asthenia, weight loss, and hyporexia
- Elevated CEA level

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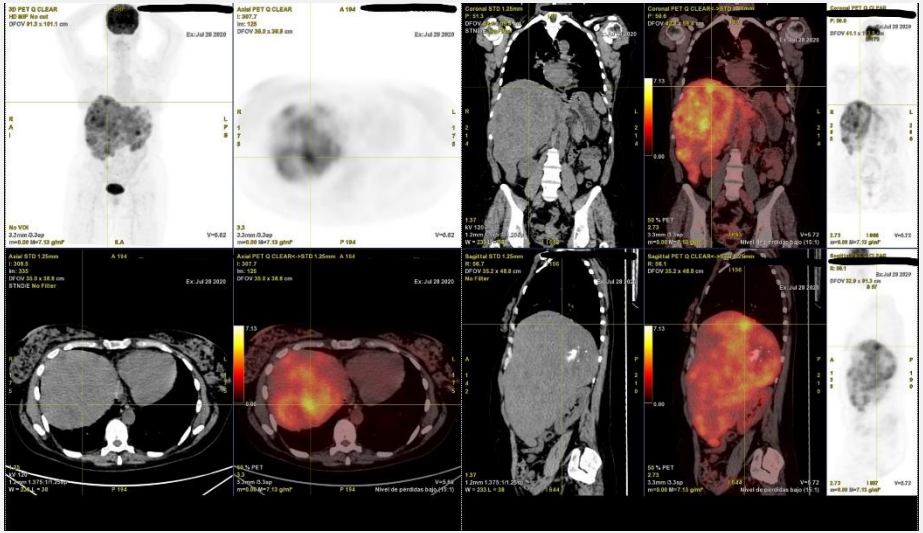
DISEASE-FREE INTERVAL: 4 YEARS

Aug 2020

- Asthenia, weight loss, and hyporexia
- Elevated CEA level

- PET-CT: severe metastatic liver infiltration



Liver biopsy

↓

Infiltration by breast carcinoma

HR+, HER2 2+ FISH negative

DISEASE-FREE INTERVAL: 4 YEARS

Aug 2020

Metastatic breast cancer HR+ HER2– with severe liver infiltration:

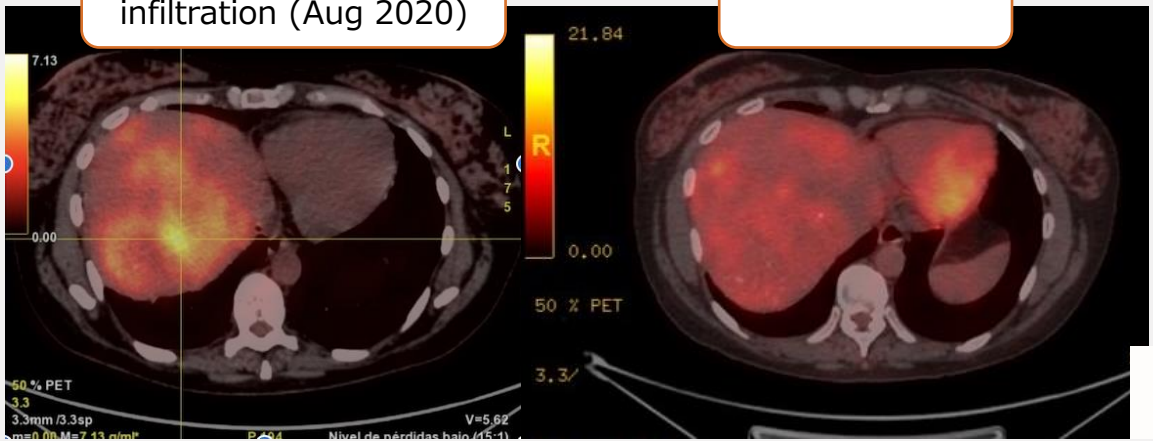
FIRST LINE TREATMENT:

CDK4/6i (Palbociclib) + Letrozole + LHRH analogs

- G4 Neutropenia in spite of dose reduction after 2 months of treatment → switch to Abemaciclib

Extensive hepatomegaly due to metastatic infiltration (Aug 2020)

Partial response in PET-CT Nov 2020



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Locally advanced breast cancer
cT3N0M0
Hormonal receptor positive
HER2 negative

2015

4 YEARS

Aug 2020

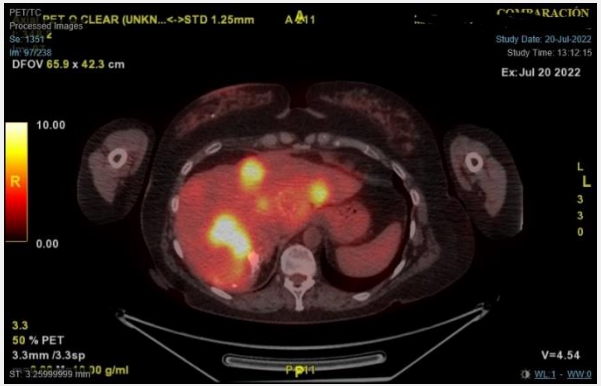
Metastatic breast cancer HR+ HER2−:

1L Treatment
CDK4/6i (Palbociclib) + Letrozole + LHRH analogs

2 YEARS

Slow increase of tumor markers and CTCs

Aug 2022



- PET-CT: Liver PD

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- **Plasma NGS:**

Pathogenic

Name	Therapeutical Impact
MAP2K1 p.C121S	Tier IID
NRAS p.G12R	Tier IID
PIK3CA p.E542K	Tier IA
TP53	

Aug 2022

SECOND LINE TREATMENT: Alpelisib + Fulvestrant

AEs: G3 Maculopapular rash in the first 2 weeks of treatment –> **Stop alpelisib + oral corticosteroids**

↓ Restart Alpelisib with a lower dose

AEs: Recurrence of G3 rash and onset of hyperglycemia G3

↓

SWITCH TO Everolimus + Fulvestrant

Nov 2022
- CTCs: 13 (previous 25)
- PET-CT Nov 2022: partial response

Locally advanced breast cancer
cT3N0M0
Hormonal receptor positive
HER2 negative

2015

4 YEARS

Aug 2020

1L Treatment
CDK4/6i (Palbociclib) + Letrozole
+ LHRH analogs

2 YEARS

Aug 2022

2L Treatment
Everolimus + Fulvestrant

9 MONTHS

Jun 2023

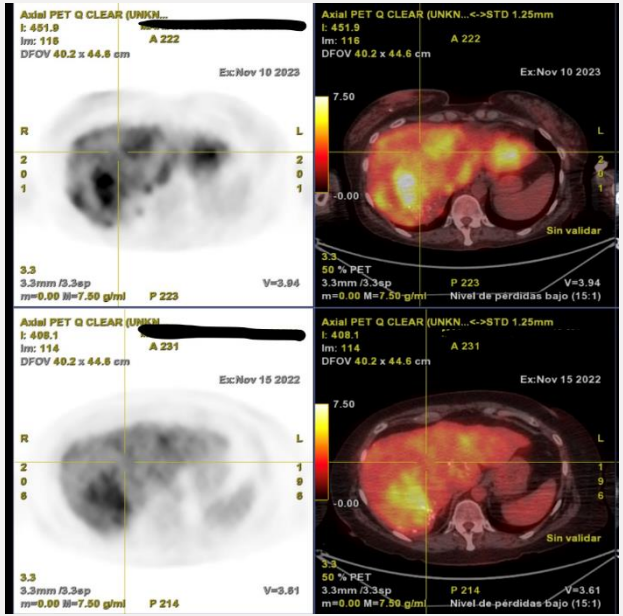
Metastatic breast cancer HR+
HER2–:

- **Asthenia, weight loss**
- **Liver failure:**
  - Bilirubin 3,05
  - GGT 576
  - LDH 710
- **Tumor markers increase**
- **CTCs: 944**

GBC Global Breast Cancer Academy

Jun 2023

- PS – ECOG 3. Jaundice
- PET-CT: Liver progressive disease



EXCLUSIVE PALLIATIVE CARE

OR

THIRD LINE TREATMENT?

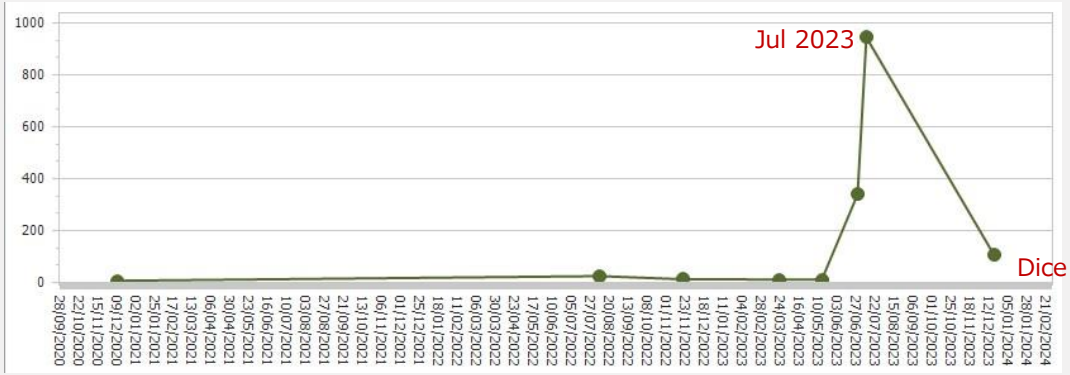
Capecitabine reduced doses (liver failure)

- Serum bilirubin Aug 2023: 1.0

Global Breast Cancer Academy

Dec 2023

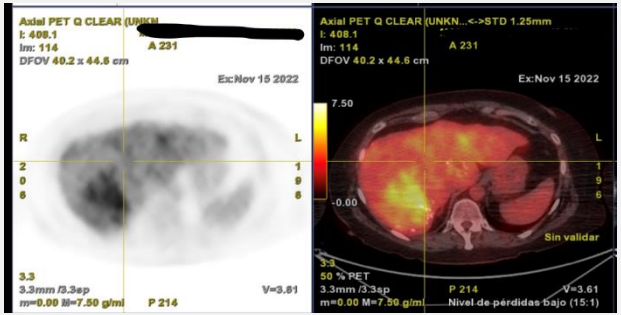
- CTCs levels

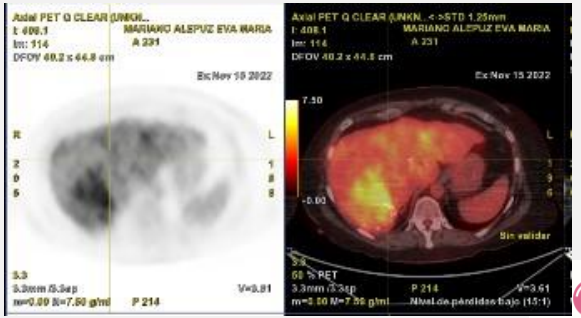


- PET-CT

Extensive hepatomegaly due to metastatic infiltration (Aug 2023)

Stable disease at PET-CT Dec 2023





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Locally advanced breast cancer
cT3N0M0
Hormonal receptor positive
HER2 negative

2015

4 YEARS

Aug 2020

Metastatic breast cancer HR+ HER2−:

1L Treatment
CDK4/6i (Palbociclib) + Letrozole + LHRH analogs

2 YEARS

Aug 2022

2L Treatment
Everolimus + Fulvestrant

9 MONTHS

Jun 2023

3L Treatment
Capecitabine

7 MONTHS

Jan 2024

- Headache, nausea, photophobia

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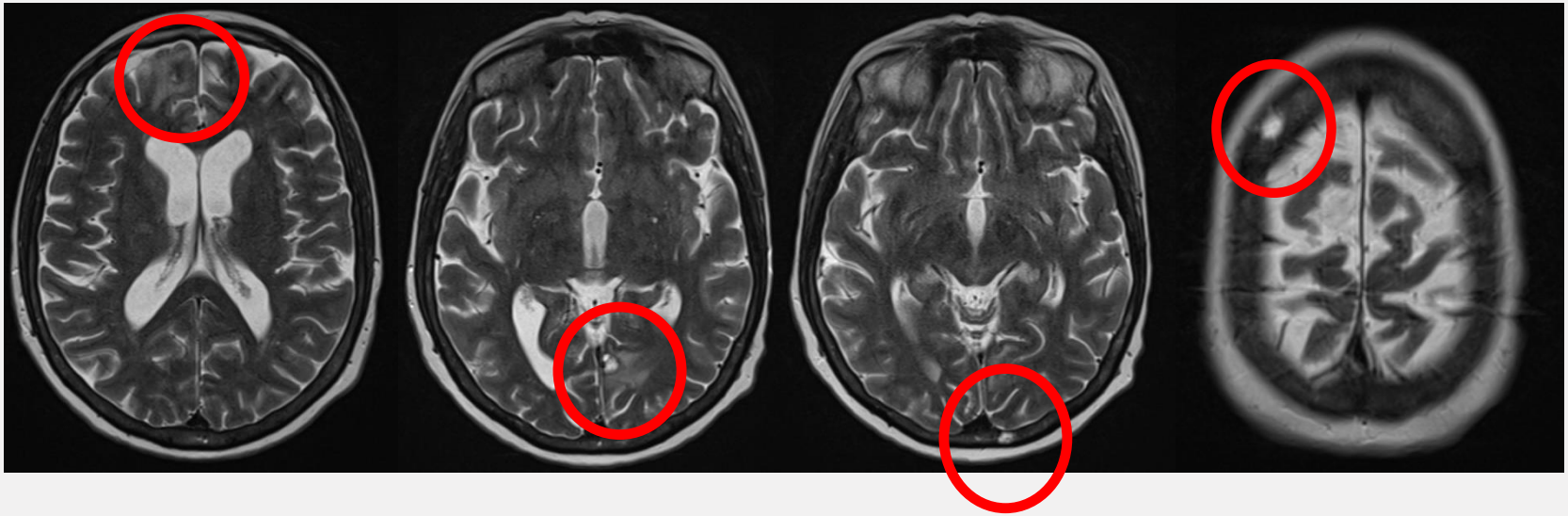
- Brain MRI: right frontal and left occipital metastases. Leptomeningeal lesions



Jan 2024

FOURTH-LINE TREATMENT: CLINICAL TRIAL – Patritumab deruxtecan

The patient is currently undergoing treatment

Discussion

- Which frontline treatment would you have chosen for this kind of patient: HR+, HER2– ABC with aggressive disease characteristics?
- What factors would you take into account in choosing the second line of treatment for this patient?
- If the case were today: Do you think your decision would be different?

Thank you for your attention!

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ARS questions

Nadia Harbeck

APTITUDE HEALTH

Question 3 [REPEATED]

According to the current ESMO guidelines, which of the following biomarkers should be tested after progression on ET + CDK4/6 inhibitor? *(Select all that apply.)*

A. Germline *BRCA1/2*
B. Germline *PALB2*
C. *PIK3CA* mutation
D. *ESR1* mutation
E. *PTEN* mutation
F. *AKT1* mutation

Question 4 [REPEATED]

How does an *ESR1* mutation affect endocrine therapy in HR+ mBC?

A. Enhances CDK4/6 inhibitor activity
B. Causes endocrine sensitivity
C. Promotes HER2 overexpression
D. Leads to endocrine resistance

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Session close

Nadia Harbeck

APTITUDE HEALTH

Thank you!

- Thank you to our sponsor, expert presenters, and to you for your participation
- Please complete the **evaluation** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the website within a few weeks

THANK YOU!

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