Breast Cancer Debate of the Year

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BSMO

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Treatment of luminal MBC after exposure to CDK4/6 inhibitors

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Disclosures

Advisory role: Amgen, AstraZeneca, Bayer, Daiichi, EISAI, Genomic Health, Hengrui, Innate, Ipsen, Leo Pharma, Lilly, Merck, MSD, Novartis, Pfizer, Seattle Genetics

Speaker fees: Amgen, AstraZeneca, Bayer, Daiichi, EISAI, Genomic Health, Ipsen, Leo Pharma, Lilly, Merck, MSD, Novartis, Pfizer, Seattle Genetics

Research grants to my Institute: BMS, Roche

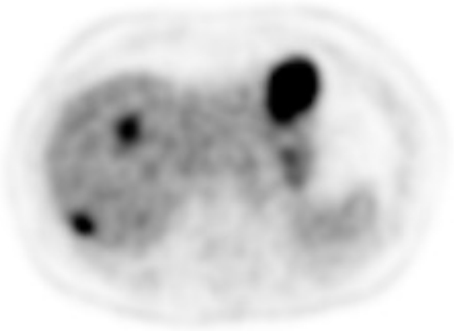
Clinical Case

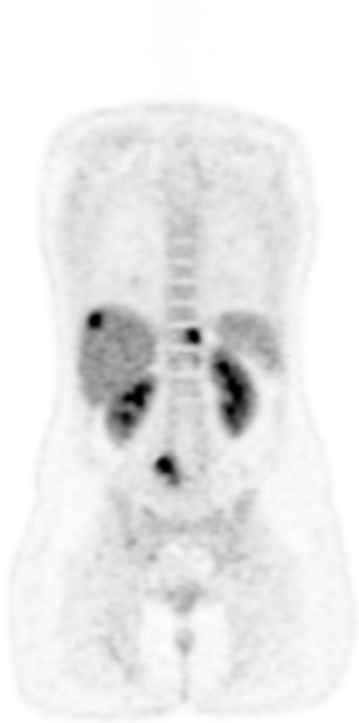
- Mme DG, née en 1964 (58 ans)
- Péri-ménopause
- Diagnostiquée en 2016 d'un carcinome canalaire infiltrant 18 mm de grade III, RO 8/8, RP 7/8, Neu négatif, Ki67 à 20%.
- Tumorectomie et ganglion sentinelle, pT1cN0, suivi d'une chimiothérapie adjuvante par 3 FEC - 3 Taxotère et radiothérapie adjuvante.
- Hormonothérapie : 2 mois de Femara puis switch pour intolérance en août 2017 vers Nolvadex (ménopause post chimiothérapie).

- En Mai 2020, douleur lombaire associée à une sciatalgie
- Augmentation de Ca15-3

FDG PET CT scan

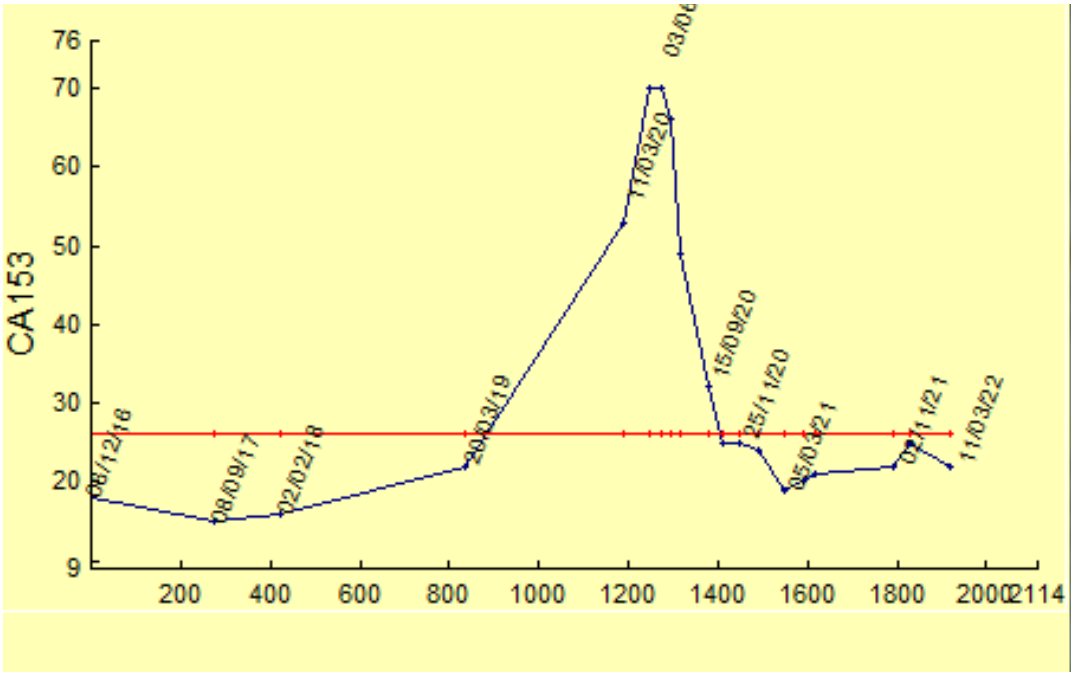
- Au moins 3 lésions hypermétaboliques hépatiques + centres nécrotiques
- Lésions hypermétaboliques osseuses Th11 et L4





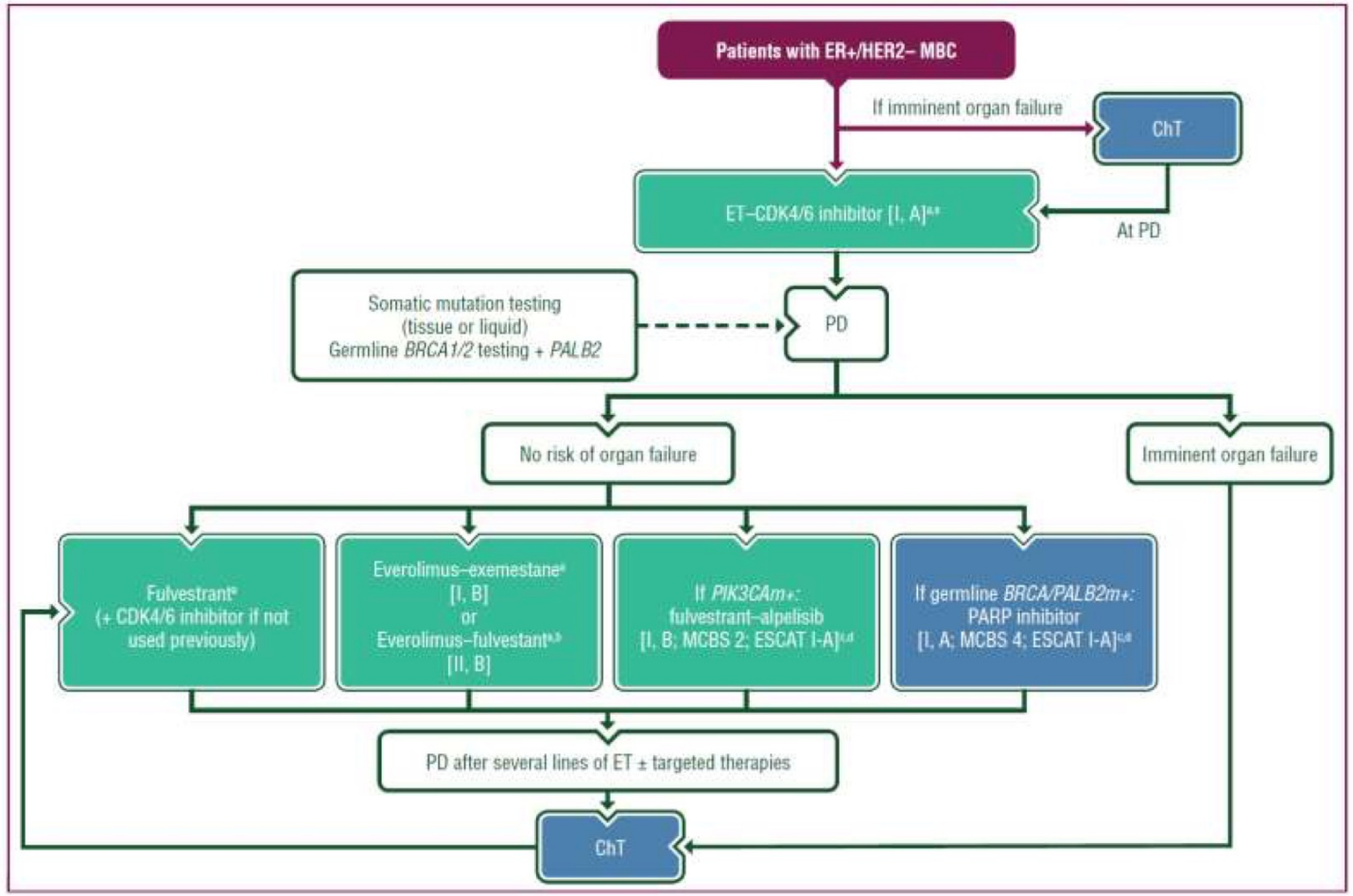
Clinical Case

- Inhibitor CDK4/6 + anastrozole 1 mg/jour débuté en juin 2020
- Sur le FDG PET CT scan de septembre 2020: réponse métabolique complète
- Normalisation du marqueur
- 06.2022: Progression osseuse et hépatique (Bil.N. légère cytolyse et cholestase hépatique)
- NGS: Mutations PI3K et ESR1
No BRCA mutations



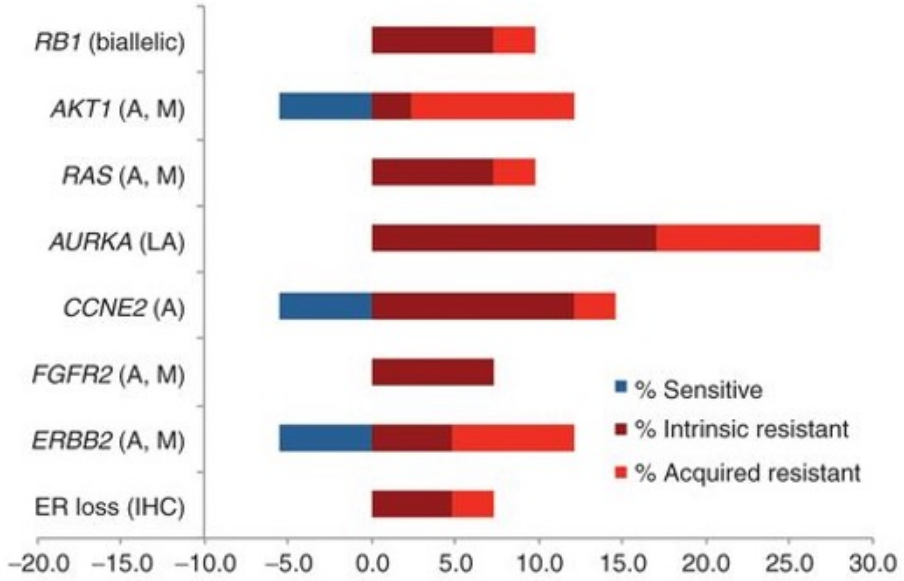
When to perform NGS in MBC?

HR+/HER2-



Gennarini et al.Ann Oncol 2021

The Genomic Landscape of Intrinsic and Acquired Resistance to Cyclin-Dependent Kinase 4/6 Inhibitors in Patients with Hormone Receptor–Positive Metastatic Breast Cancer



Wander SA, Cancer Discov. 2020;10(8):1174-1193.

Possible Post PD Treatments following AI+ CDK4/6 inhibitor?

- Fulvestrant alone
- Continue same CDKi + Fulvestrant
- Fulvestrant + another CDKi
- Exemestane + everolimus
- Fulvestrant + Alpelisib
- SERD or SERM
- New CDK inhibitor in a clinical trial
- ADC
- Metronomic chemo (ex: VEX) or capecitabine alone
- Other?

Option: CDK4/6*i* after CDK 4/6*i* – Pace Trial (Ph II)

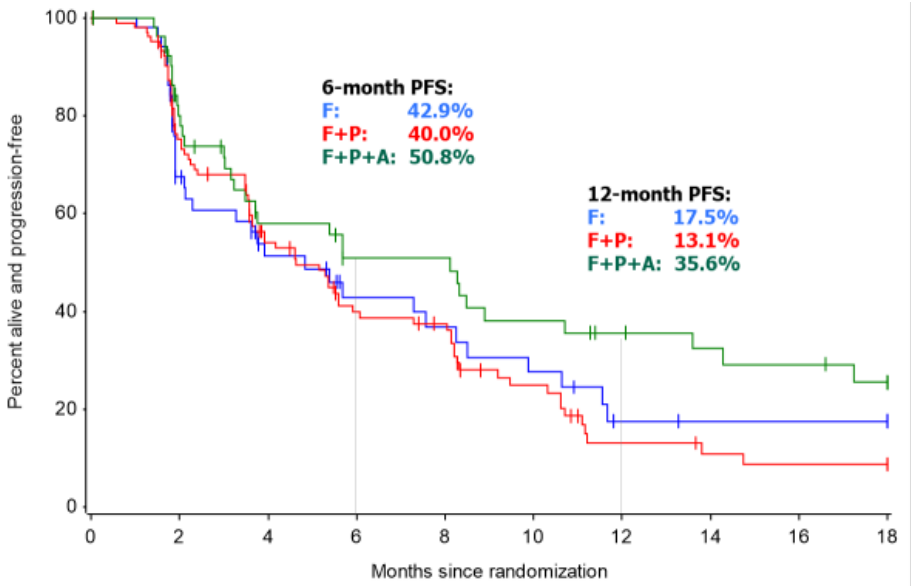
Aim: (1) Role of CDK4/6i beyond progression, with change of ET to fulvestrant, (2) adding ICPi

Eligibility Criteria
- HR+/HER2- MBC
- Progression on CDK4/6i and ET, with ≥6mo SD on prior regimen
- ≤2 prior lines ET for MBC
- No prior fulvestrant
- 0-1 prior chemo for MBC

N=220

RANDOMIZE

- Fulvestrant
- Fulvestrant Palbociclib
- Fulvestrant Palbociclib Avelumab



90% were pretreated with Palbociclib
77% pts: 2nd-line setting

	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

Combining palbociclib with fulvestrant beyond progression on prior CDK4/6i did not significantly improve PFS compared with using fulvestrant alone.

Mayer E et al. SABCS 2022, #GS3-06

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Option: CDK4/6*i* after CDK 4/6*i* - The MAINTAIN-trial (Ph II)

Key Entry Criteria

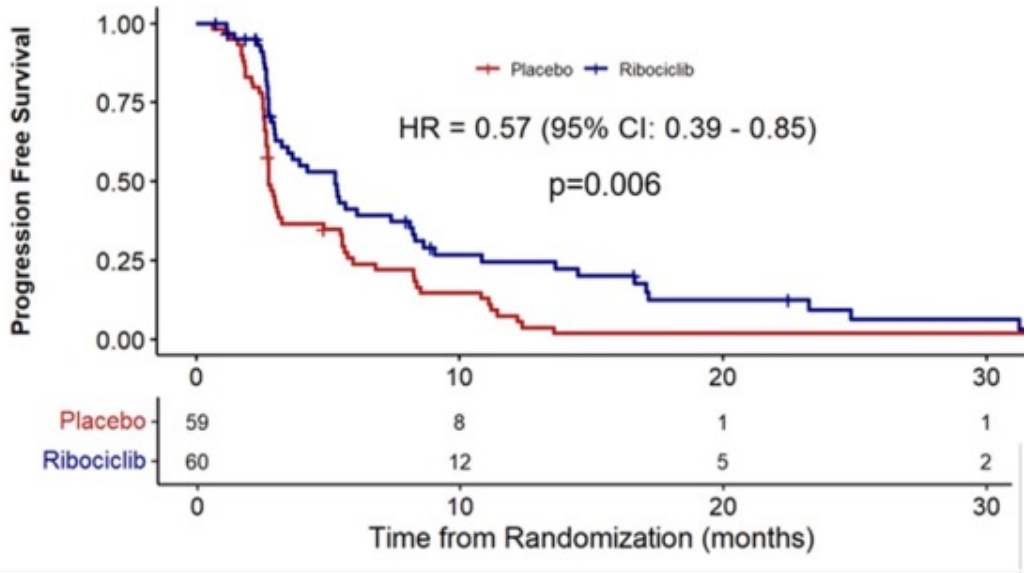
- **Progression on ET + any CDK 4/6 inhibitor**
- ER and/or PR ≥ 1%, HER2- MBC
- ≤ 1 line of chemo for MBC
- Measurable or non-measurable
- Postmeno or premeno and GnRHa

1:1

N=120

Arm 1
Ribociclib + Switch Endo Tx

Arm 2
Placebo + Switch Endo Tx



87% of the pts received prior palbociclib
83% of the pts switched to Fulvestrant
66% were treated prior with CDK 4/6i >12 mths

	ET+ Placebo	ET+ Ribo
Median PFS months (95% CI)	**2.76 (2.66-3.25)**	**5.29 (3.02-8.12)**
PFS rate at 6 months	23.9%	41.2%
PFS rate at 12 months	7.4%	24.6%

Kalinsky K et al ASCO 2022,#LBA1004;

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Data on exemestane and everolimus

Retrospective cohort studies of everolimus in combination with exemestane after progression with CDK4/6 inhibitors

	Design	Prior therapy	Post-CDKi therapy	N	Median rwPFS	mOS
Cook et al[l]	Retrospective cohort	Prior CDK4/6i No prior CDK4/6i	Eve + Exe	17 26	**3.6 mos** 4.2 mos	**15.6 mos** 11.3 mos
Rozenblit et al	Retrospective cohort	2L Eve + Exe: - CDK4/6i + ET - ET 3L Eve + Exe: - CDK4/6i + ET - ET	2L Eve + Exe 3L Eve + Ex	2L: - 54 - 192 3L: - 69 - 80	2L: *TTNT* - **4.3 mos** - 6.2 mos 3L: *TTNT* - **4.1 mos** - 5.6 mos	2L*: **37.7 mos** 32.7 mos 3L*: **59.2 mos** 40.8 mos
Giridhar et al	Retrospective cohort	Palbociclib 1st line	Isolated ET (29.7%) Eve + Exe (27%) Isolated ChT (21.7%)	37	3.1 mos (TTF) 13.2 mos (TTF) 4.1 mos (TTF)	
EVERMET et al	Retrospective cohort	CDK4/6i No CDK4/6i	Eve + Exe	25	**4.9 mos** 7.2 mos	
Xi et al	Retrospective cohort	Palbociclib (1st, 2nd and 3rd lines)	Capecitabine Eribulin Nab-pacli Exe + Eve	21 16 15 12	ChT 4.2 mos Eve + Exe **4.9 mos**	
Dhakal et al	Retrospective cohort	Palbociclib	Eve + Exe	41	**4.2 mos**	**18.7 mos**
Mo et al	Retrospective cohort	CDK4/6i No CDK4/6i	Eve + Exe	79 113	**3.8 mos** 5.4 mos	**22.6 mos** 24.3 mos

Data on PIK3CA and AKT inhibitors

ALPELISIB + Fulvestrant in HR+, HER2- MBC
Results of the phase III SOLAR-1 Trial

André F. et al
ESMO 2018 - NEJM 2019

Men or postmenopausal women, with HR+, HER2– ABC

- Recurrence/progression on/after prior AI
- Identified *PIK3CA* status (in archival or fresh tumor tissue)
- Measurable disease or ≥1 predominantly lytic bone lesion
- ECOG performance status ≤1

(N=572)

PIK3CA-mutant cohort (n=341)

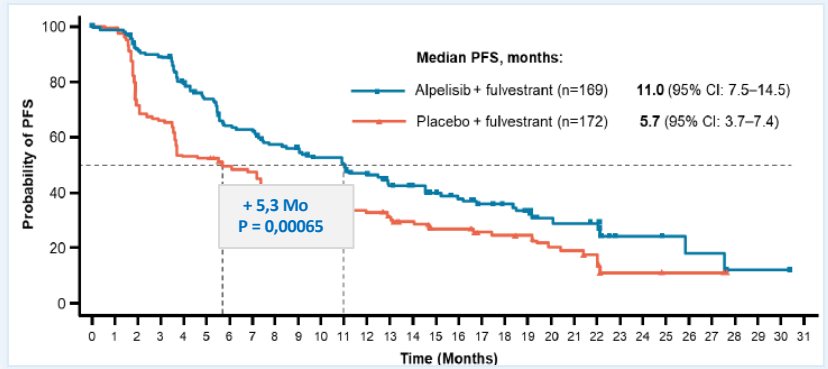
R

ALP 300 mg QD PO + FUL 500 mg IM* n=169

PBO + FUL 500 mg IM* n=172

Primary endpoint

- **PFS in *PIK3CA*-mutant cohort**



Efficacy of Alpelisib after progression on CDK4/6i

	Design	Prior therapy	Post-CDKi therapy	N	mPFS	mOS
BYLieve	Phase 2 (PI3KCAmut)	CDKi + AI (Cohort A) CDKi + Ful (Cohort B) (≤ 1L ChT)	Alpelisib + Fulvestrant (Cohort A) Alpelisib + Letrozol (Cohort B)	127 81	7.3 mos 5.7 mos	17.3 mos
SOLAR1	Phase 3 (PIK3CAmut)	ET-resistant and prior CDK4/6i (sub-analysis)	Alpelisib + Fulvestrant	20	5.5 mos	

CAPItello-291 trial (PH III): Fulvestrant +/- Capivasertib

(n=708 pts progressed on prior aromatase inhibitor+/-CDK 4/6*i, no AKT pathway mutation required*)

Pretreatment: 69% CDK4/6i; 80% ET for ABC; 18% CTX for ABC

Cohorts	Treatment	PFS in mths (investigator-assessed)	△PFS in mths	; i	
Overall population	FUL+Cap	7.2 (5.5 - 7.4)	3.6	0.60 (0.51-0.71)	p<0.001
	FUL	3.6 (2.8 - 3.7)			
AKT pathway mutated (44%)*	FUL+Cap	7.3 (5.5 - 9.0)	4.2	0.50 (0.38-0.65)	p<0.001
	FUL	3.1 (2.0 - 3.7)			
Non-mutated / unknown (56%)	FUL+Cap	7.2 (4.5 – 7.4)	3.5	0.70 (0.56-0.88)	
	FUL	3.7 (3.0 – 5.0)			

*PIK3CA, AKT1 and / or PTEN alteration

Benefit from Capivasertib was consistent across clinically relevant subgroups including in patients with prior CDK 4/6*i* treatment; **OS data immature**

Turner NC et al. SABCS 2022, G3-04;

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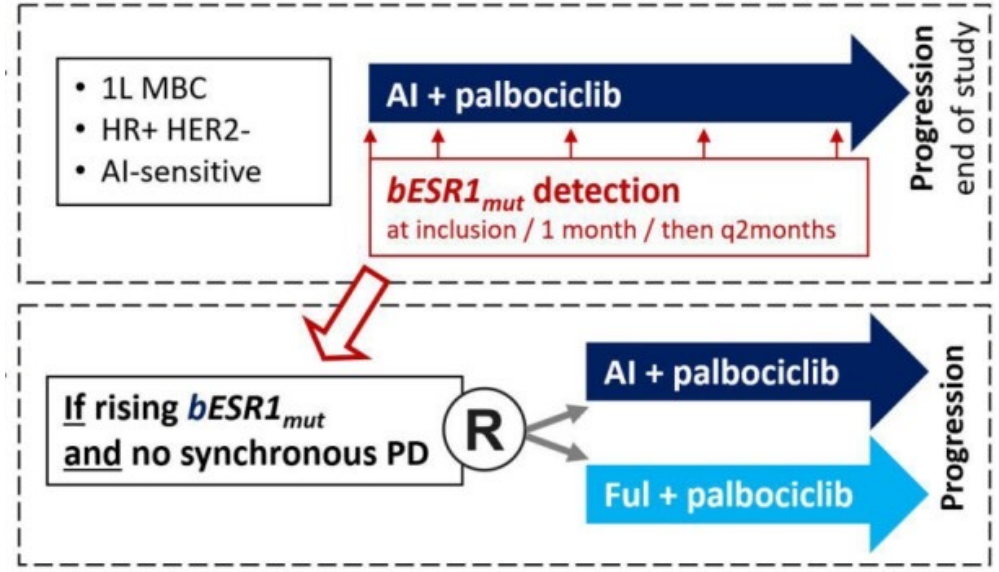
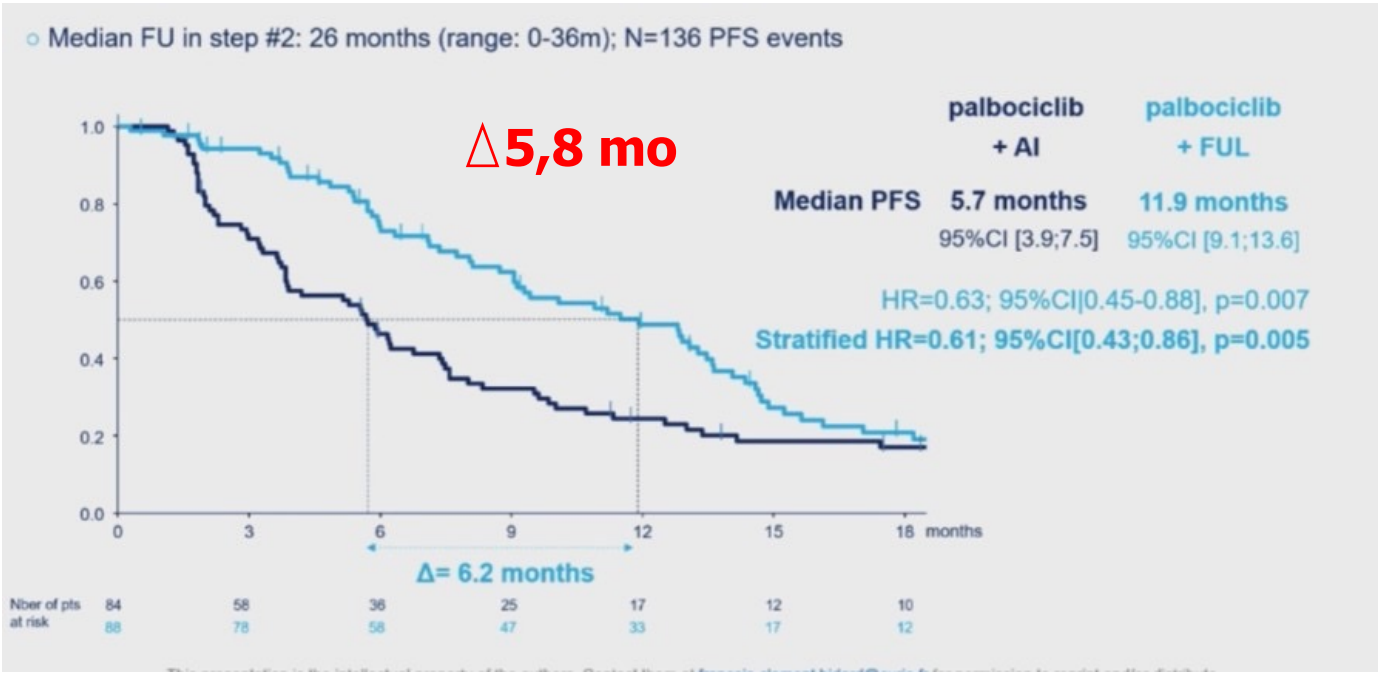
ESR1 mutations in advanced luminal disease: An emerging entity following exposure to AIs (30-40% of pts)

Option: CDK4/6*i* after CDK 4/6*i* – PADA-1Trial

Changing treatment at the onset of the ESR1 mutation by dynamically monitoring ctDNA

PADA1-trial:
Phase III; n=136





A switch from AI/palbociclib to fulvestrant/palbociclib in patients with rising ESR1 mutations despite the absence of clinical or radiological disease progression was associated with improved mPFS.

Bidard F-C et al. SABCS 2021 GS3-05

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New treatment option: SERDs

Oral SERDS currently under investigations in phase II/ III trials for **pts (>=2nd line)**

Trial	Phase	Oral SERD	Standard arm	Result
acelERA BC	II	Giredestrant	PC ET	**Negative trial (No PFS-benefit)[1]**
evERA BC	III	Giredestrant + EVE	Exemestane+ EVE	ongoing
SERENA-2	II	Camizestrant	Fulvestrant	**Positive trial (PFS-benefit)[2]**
SERENA-6 (ESR-1 mut)	III	Camizestrant + CDK 4/6i	AI + CDK 4/6i	ongoing
AMEERA-3	II	Amcenestrant **(stopped)**	PC ET	**Negative trial (No PFS-benefit)[3]**
EMERALD	III	Elacestrant	SOC	**Positive trial (PFS-benefit)[4]**
EMBER-3	III	Imlunestrant +/- abemaciclib	PCET	ongoing

[1] Martin MM et al, ESMO 2022;MO211, [2]Oliveira M et al. SABCS 2022;GS3-02, [3]Tolaney S et al, ESMO 2022;MO212; [4]Bardia A et al. SABCS 2022;GS3-01

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SERDs as monotherapy in the 2nd/3rd line setting

	EMERALD (PH III) *	SERENA-2 (PH II)	
Oral SERD	Elacestrant	Camizestrant	
Standard arm	AI or FUL	Fulvestrant	
Pretreatment	1-2 ETX, 1 CTX	1 ETX, 1 CTX	
Prior CDK 4/6i / prior CTX (in ABC)	100% / 20-25%	51%/19%	
Fulvestrant (standard arm)	69% FUL by PC	100%	
Dose	400 mg	75 mg	150 mg
PFS mths	2.8 vs.1.9 mths 0.70 (0.55-0.88) **Δ 1.0 mths**	7.2 vs. 3.7 mths *0,58 (0.41-0.91)* **Δ 3.5 mths**	7.7 vs. 3.7 mths *0,67(0.48-0.92)* **Δ 4.0 mths**
PFS in mths **(prior CDK 4/6i)**	See above	5.5 vs. 2.1 mths *0,49 (0.31-0.75)* **Δ 3.4 mths**	3.8 vs. 2.1 mths *0,68 (0.44-1.04)* **Δ 1.7 mths**
PFS in mths (**ESR-1mutated**)	3.78 vs. 1.82 mths 0,55 (0.39-0.77) **Δ 2.0 mths**	6.3 vs. 2.2 mths *0,33 (0.18-0.58)* **Δ 4.1 mths**	9.2 vs. 2.2 mths *0,55 (0.33-0.89)* **Δ 7.0 mths**

***Duration of CDK4/6*i* was correlated with PFS on the EMERALD trial!**

The longer the duration of prior CDK4/6i, the longer PFS on elacestrant as compared with SOC:
mPFS in the ESR-1 mutated cohort / CDK 4/6i>=12 mo: 8.6 mo with elacestrant vs 2 mo with SOC

Oliveira M et al. SABCS 2022,GS3-02; Bardia A et al. SABCS 2022,GS3-0

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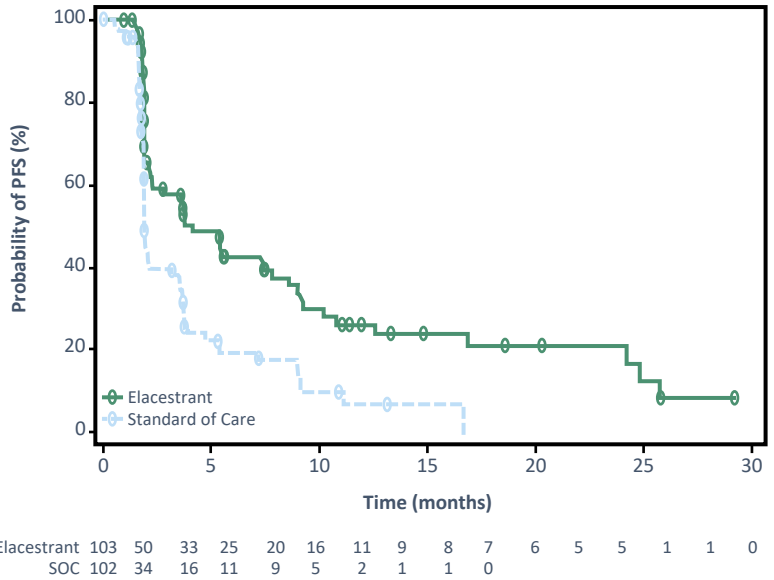
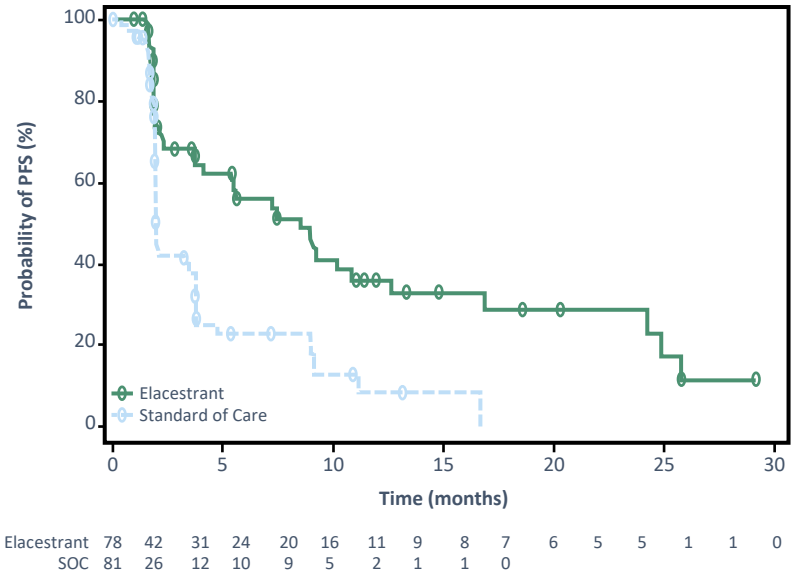
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



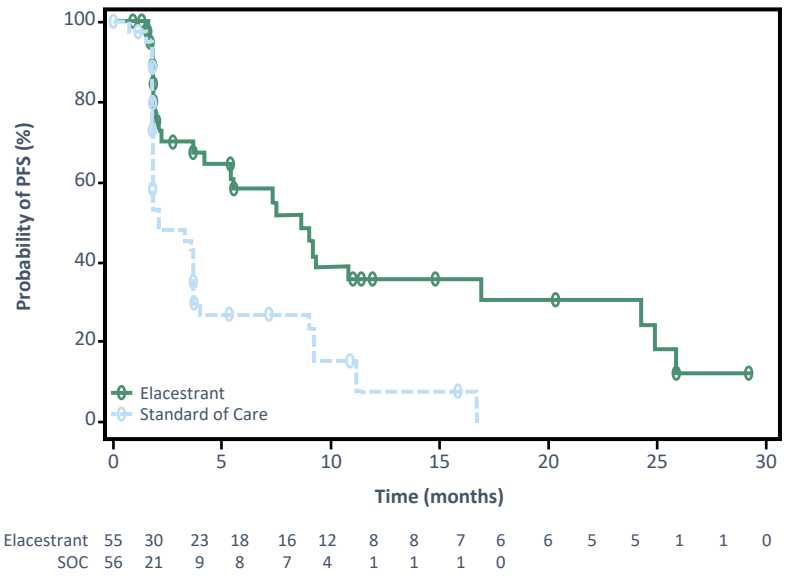
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

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)	

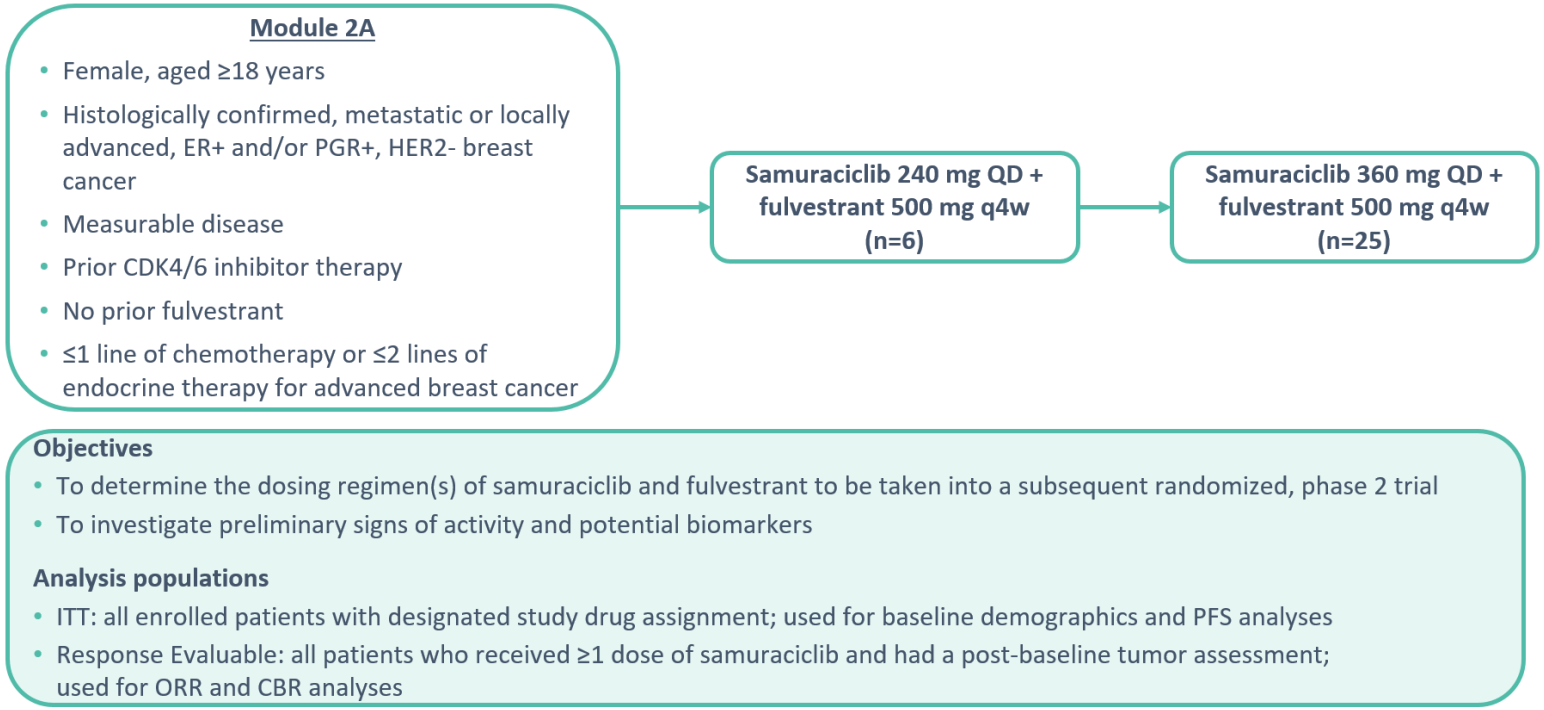
At least 18 mo CDK4/6i



	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)	

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

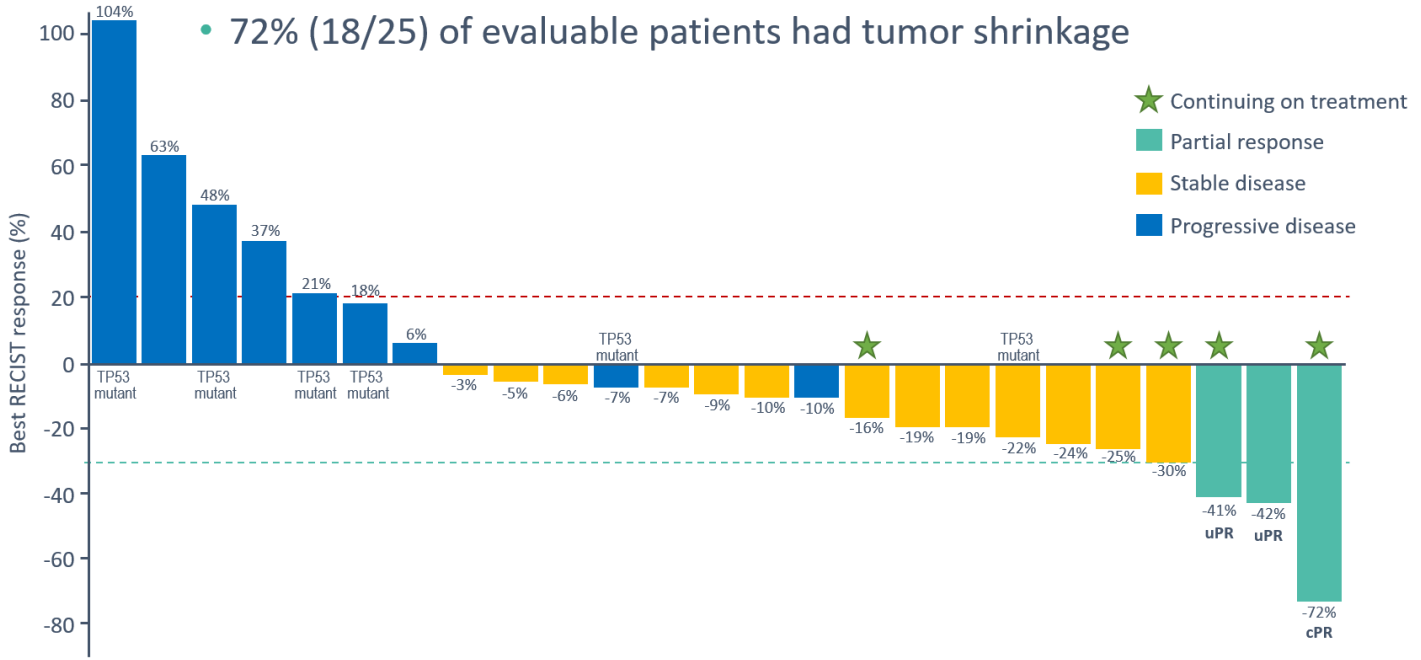
New CDK inhibitor : Samuraciclib (CDK7inhibitor)
Study design and objectives (NCT03363893)



CBR, clinical benefit rate; ITT, intent to treat; ORR, objective response rate; PFS, progression-free survival; PGR, progesterone receptor; QD, once daily

Coombes C et al, SABCS 2021, GS3-10

Best RECIST response confirms that samuraciclib-based therapy is active



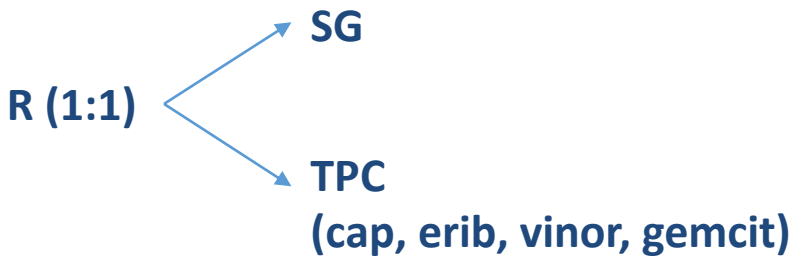
cPR, confirmed partial response; uPR, unconfirmed partial response, based on RECIST criteria
Data cut-off: September 25, 2021

Coombes C et al, SABCS 2021, GS3-10

Antibody drugs conjugates

TROPiCS-02: A randomized ph 3 trial of Sacituzumab Govitecan vs TPC in HR+/HER2- MBC
Study Design

MBC
PS 0-1
2-4 prior CT for MBC
1 prior CT if PD ≤ 12mo after (Neo)adj
Prior taxane
Prior CDK4/6 inh



Primary endpoint: PFS

Rugo HS LBA 1001, ASCO 2022

TROPiCS-02: A randomized ph 3 trial of Sacituzumab Govitecan (Trop2) vs TPC in HR+/HER2- MBC Results

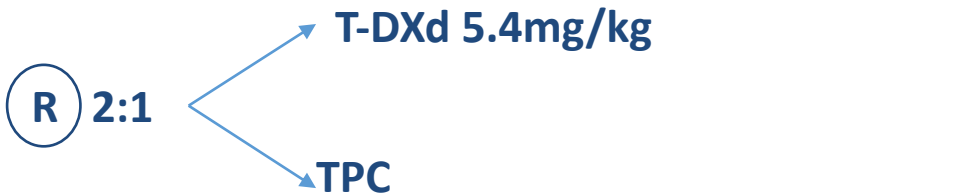
Characteristics	SG	TPC	HR
N° of pts	272	271	
Med prior CT (MBC)	3	3	
Med PFS (mo.)	5.5	4.0	0.66 (P=0.003) (95% CI, 0.53-0.83)
PFS (6mo)	46%	30%	
PFS (12mo)	21%	7%	
OS (mo)	13.9	12.3	0.84 (P=0.143)
ORR	21%	14%	
CBR	34%	22%	

Visceral Metastases : 95%

Rugo HS LBA 1001, ASCO 2022

DESTINY Breast 04: T-DXd vs TPC in pts with HER2-low MBC
Study Design

MBC
HER-2 low (IHC 1+ or 2+/ISH-)*
1-2 prior lines of CT for MBC



Primary endpoint: PFS (BICR) in HR+
Secondary endpoint: PFS (BICR) in full analysis set (FAS)

Full Analysis Set: HR+ and –
***Centrally confirmed**

Modi S LBA3, ASCO 2022

H.U.B

DESTINY Breast 04: T-DXd vs TPC in pts with HER-2 low MBC Results

Characteristics		T-DXd	TPC
N° of pts (total)		373	184
HR+		88.7%	88.6%
mPFS mo	HR+	10.1	5.4
	FAS	9.9	5.1
	HR-	6.6	2.9
m OS mo	HR+	23.9	17.5
	FAS	23.4	16.8
	HR-	16.6	10.3
ILD (n=45)	G1/2	10%	
	G3/4	1.3%	
	G5	0.8%	

Modi S LBA 3, ASCO 2022

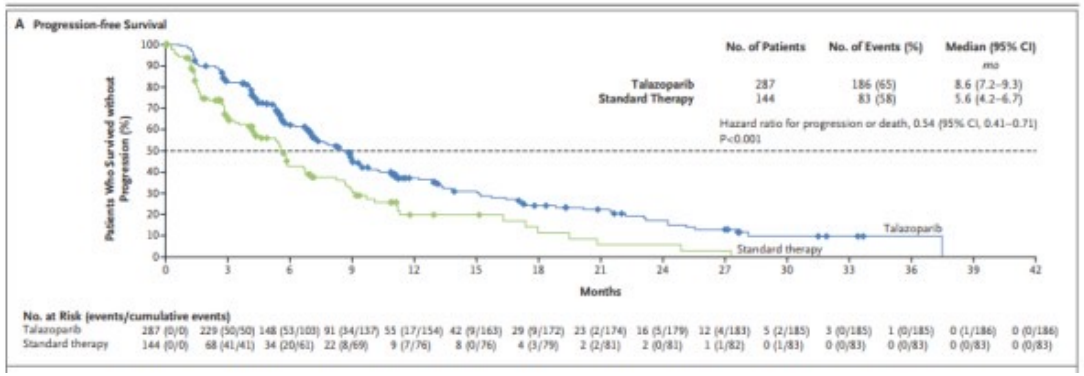
H.U.B

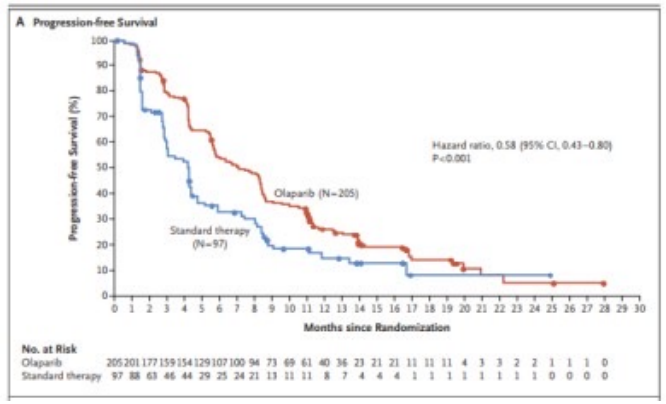
Option for patients with BRCA1/2 germline mutations: PARP*i*

EMBRACA[1]: n=431
Talazoparib versus PC
PFS: 8.6 months vs. 5.6 months
HR 0.54; 95%-CI, 0.41-0.71; P<0.001)

TPC: capecitabine, vinorelbine, eribulin gemcitabine (only EMBRACA)

OlympiAD[2] n=302
Olaparib versus PC
PFS: 7.0 months vs. 4.2 months,
HR 0,58 (95%-CI: 0,43 -0,80); p< 0.001





None of patients had prior CDK 4/6 inhibitor or other endocrine combination therapies.
No survival benefit reported [3,4]

[1]Litton K et al. NEJM 2018; [2]Robson M et al. NEJM 2017;[3]Litton JK et al Ann Ocol 2020; [4]Robson ME et al. Ann Oncol 2019

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Post SABCS 2022 : Algorithm for discussion
RH+/HER2-

To be considered

- **Prior ET**
- **Type and response to prior CDKi**
- **Germline or somatic mutations**
- **Load of CTC? or tumor?**

AI + CDK4/6i
(Metastatic disease)

AI + Abema
(Adjuvant/Recurrence on or within 6 mo?
One year? of stopping Abema.)

1)Mild PD, tumor response to palbo → Fulv+ribo (or abema)

2)ESR1 mutation, prior CDKi> 12 mo. → Elacestrant (Fulv + CDKi if no PD on AI+CDKi)

3) PIK3CA mutation → Fulv + Alpelisib

4) AKT mutated pathway → Fulv + Capivasertib

5) gBRCA mutation → PARPi

6) No mutations, response to prior Therapy → Exem+Everolimus

7) Imminent organ failure → chemo (including ADCs)

8) HER-2 low, ET failure → T-DXd

9) HER2 0, ET failure → Sacituzumab Govitecan

H.U.B

THANK YOU