19as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2024
MADRID 20 - 21 NOVIEMBRE 2024

Tratamiento del cáncer de mama luminal metastásico tras inhibidores de CDK 4/6

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GEICAM investigación en cáncer de mama

Conflictos de interés

- Consultancy/speaker fees from Novartis, Roche, Pfizer, Astra Zeneca, Daichi-Sankyo, Gilead, Exact Sciences, Seagen
- Institution research funding from Pfizer
- Travel support from Pfizer, Pierre Fabre, Lilly, Gilead

Patients with HR+/HER2– mBC

If imminent organ failure → Chemotherapy

↓

ET + CDK4/6i

↓

PD

SERDs	PI3K inh+ ET	AKT inh + ET	Everolimus + ET	Chemotherapy	ADCs

SERDS orales en el tratamiento del cáncer de mama precoz

Dra. Sara López-Tarruella, Hospital General Universitario Gregorio Marañón, Madrid

Capivasertib: una nueva opción para el cáncer de mama luminal metastásico

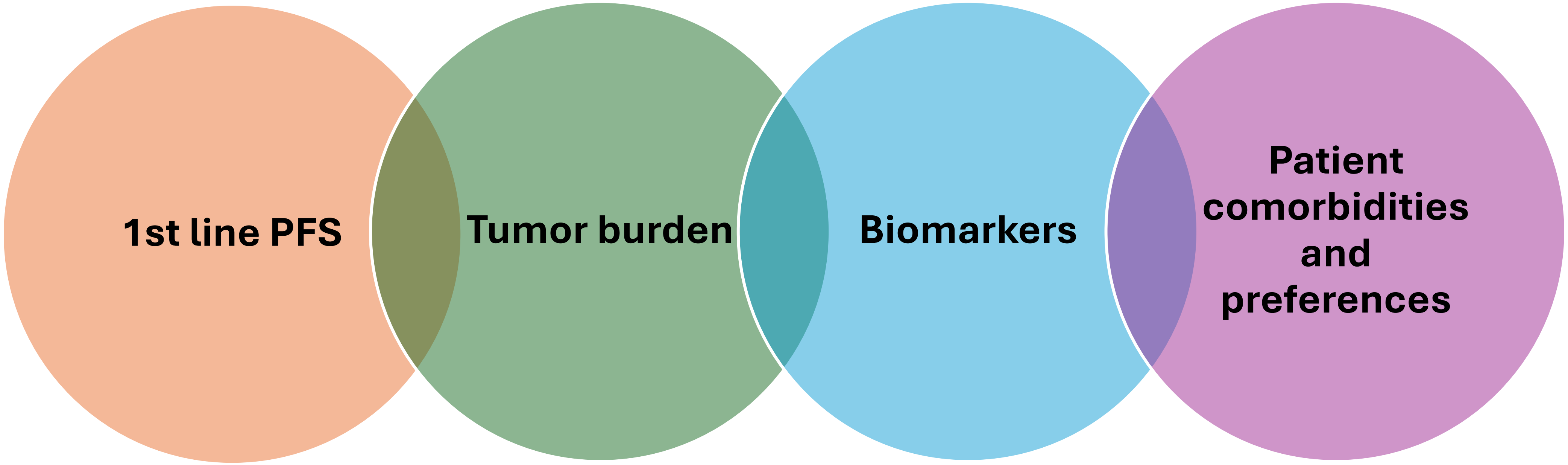
Dr. Jose Ángel García Sáenz, Hospital Universitario Clínico San Carlos, Madrid

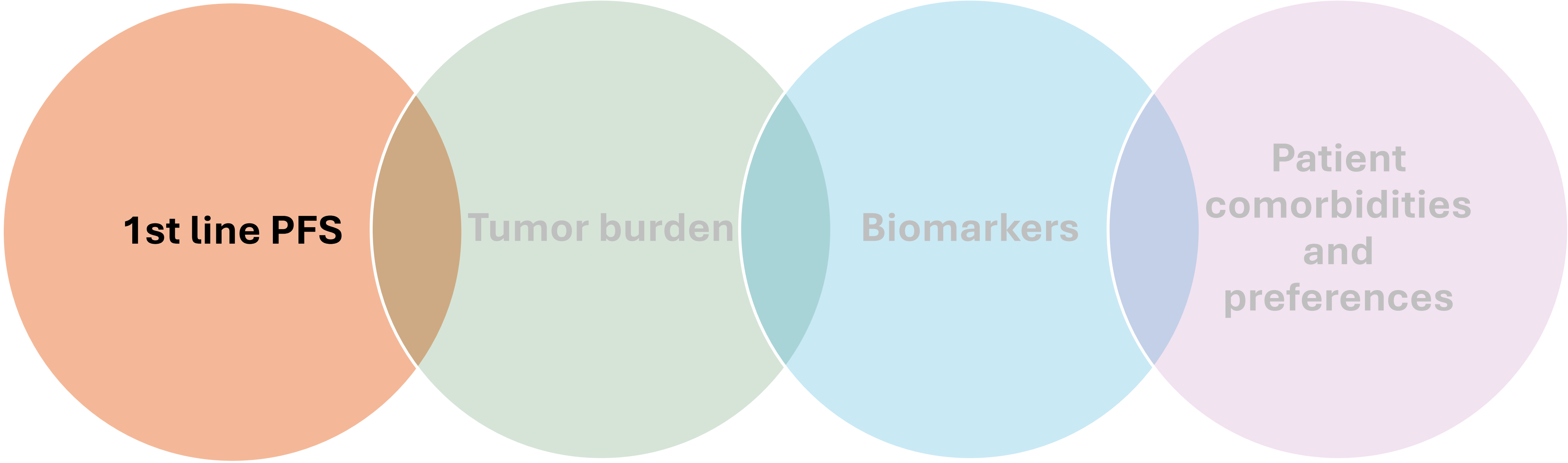
Nuevos horizontes en el cáncer de mama luminal metastásico inavolisib

Dra. Yolanda Jerez, Hospital General Universitario Gregorio Marañón, Madrid

Inmunoconjugados en el tratamiento del cáncer de mama her2 negativo

Dr. César A. Rodríguez, Presidente SEOM, Hospital Clínico Universitario de Salamanca - IBSAL


1st line PFS
Tumor burden
Biomarkers
Patient comorbidities and preferences


1st line PFS
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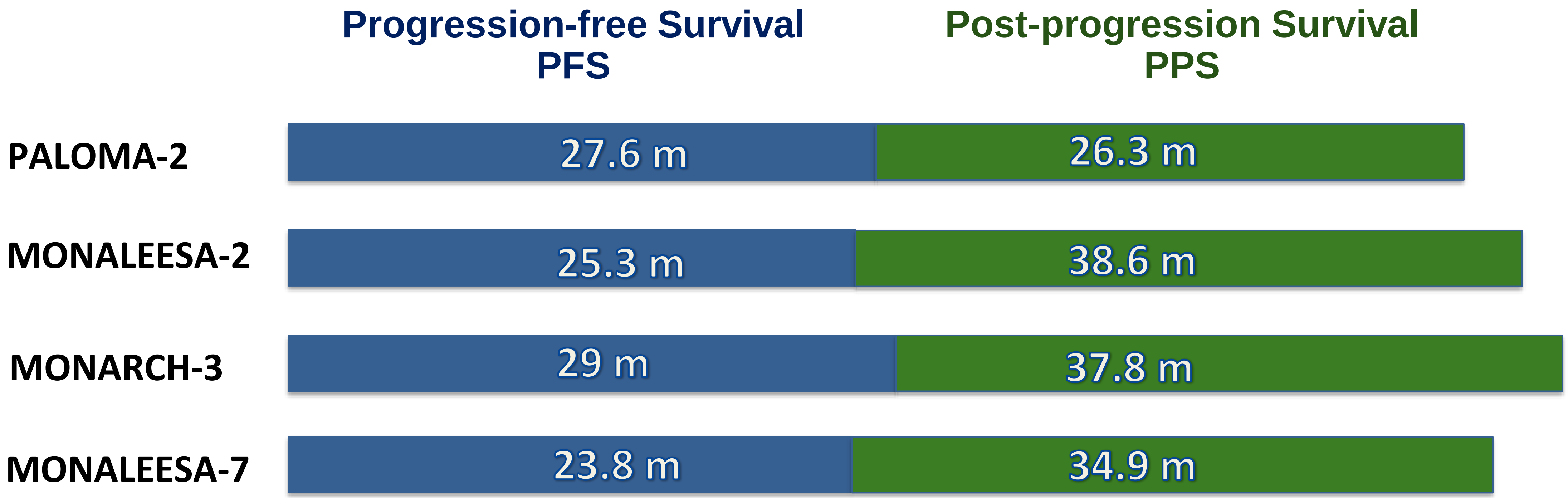
Contribution of the first and subsequent lines to overall survival

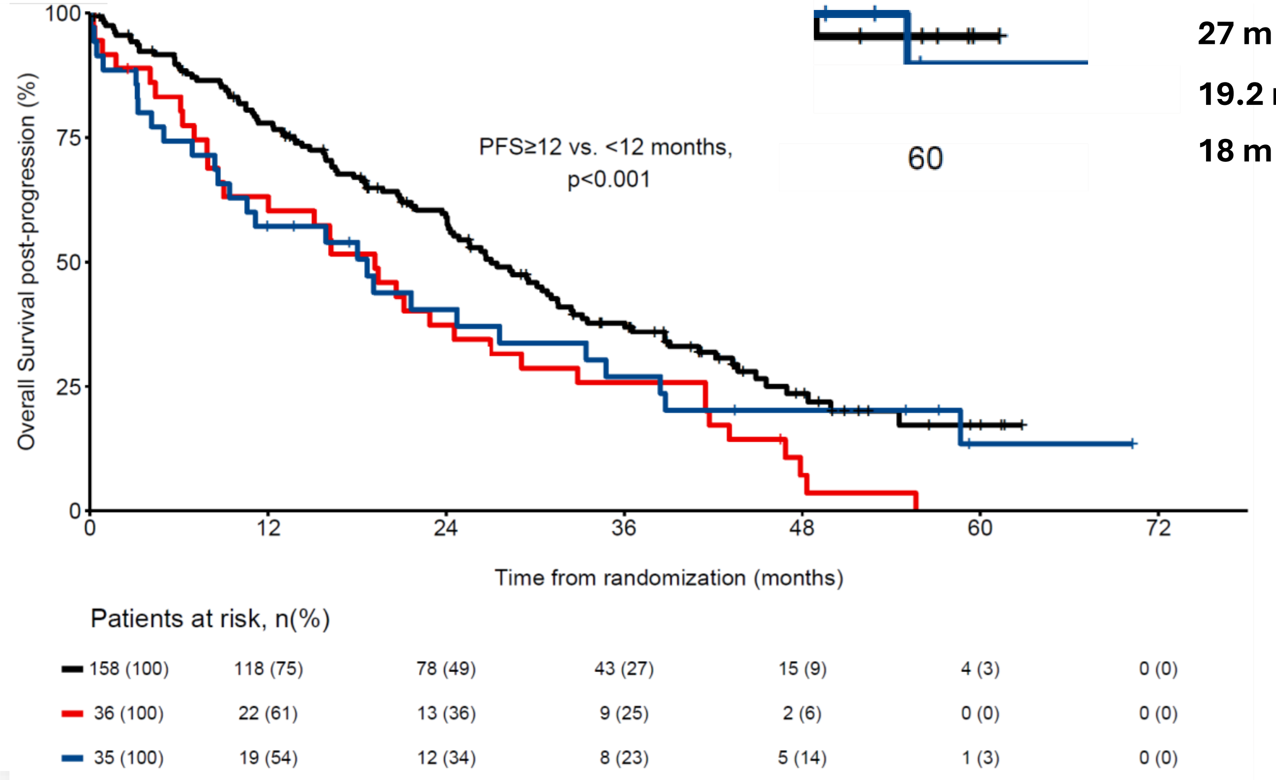


- **Progression-free survival in the first line is similar to post-progression overall survival**
- **Overall survival in HR+/HER2- breast cancer is largely influenced by the duration of response to the first-line treatment**

Goetz et al JCO 2017; Sledge et al JCO 2017; Finn et al NEJM 2016; Slamon et al JCO2024; Turner et al NEJM 2018; Hortobagyi et al NEJM 2016; ; Hortobagyi et al NEJM2022; Neven et al BCR2023; Tripathy et al Lancet Oncol 2018

The duration of progression-free survival in the first-line treatment is a strong clinical marker of outcome

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



27 m (95% CI: 24.1-31.1)

19.2 m (95% CI: 8.6-24.5)

18 m (95% CI: 8.6-24.7)

- **Early progression (<12 months) on a CDK4/6i regimen is a strong clinical marker of a less favorable outcome**
- **Overall survival after progression on iCDKs is similar to that of triple-negative breast cancers.**

Llombart A, SABCS 2023

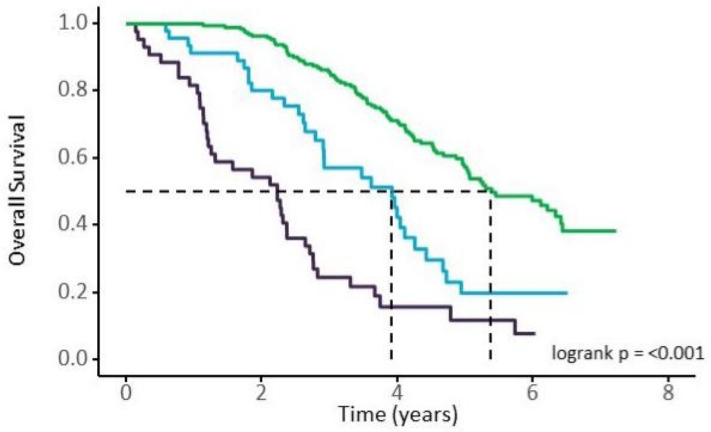
The duration of progression-free survival in the first-line treatment is a strong clinical marker of outcome

GEICAM spanish breast cancer group

GEICAM/2014-03_

_RegistEM study

ET-Sensitive patients OS by PFS to first-line



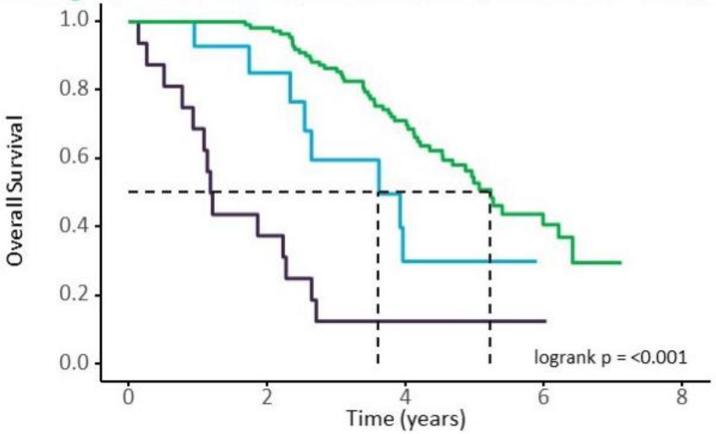
Number at risk

	0	2	4	6	8
PFS ≤ 6 m	44	24	5	1	0
PFS 6-12 m	47	36	14	2	0
PFS > 12 m	201	185	107	35	0

Time (years)

	PFS ≤6m	PFS 6-12m	PFS >12m
Definition	PFS to 1st line treatment equal or below 6 months.	PFS to 1st line treatment between 6 to 12 months.	PFS to 1st line treatment over 12 months.
N (%)	44	47	202
OS events	38 (86.4%)	30 (63.8%)	87 (43.1%)
mOS (years)	2.22	3.91	5.38
95% CI	1.25 - 2.7	2.89 - 4.41	5.01 - 6.42

ET-Sensitive patients OS by PFS to first-line (CDK4/6i + ET)



Number at risk

	0	2	4	6	8
PFS ≤6 m	16	6	1	1	0
PFS 6-12 m	15	11	3	0	0
PFS >12 m	119	110	58	13	0

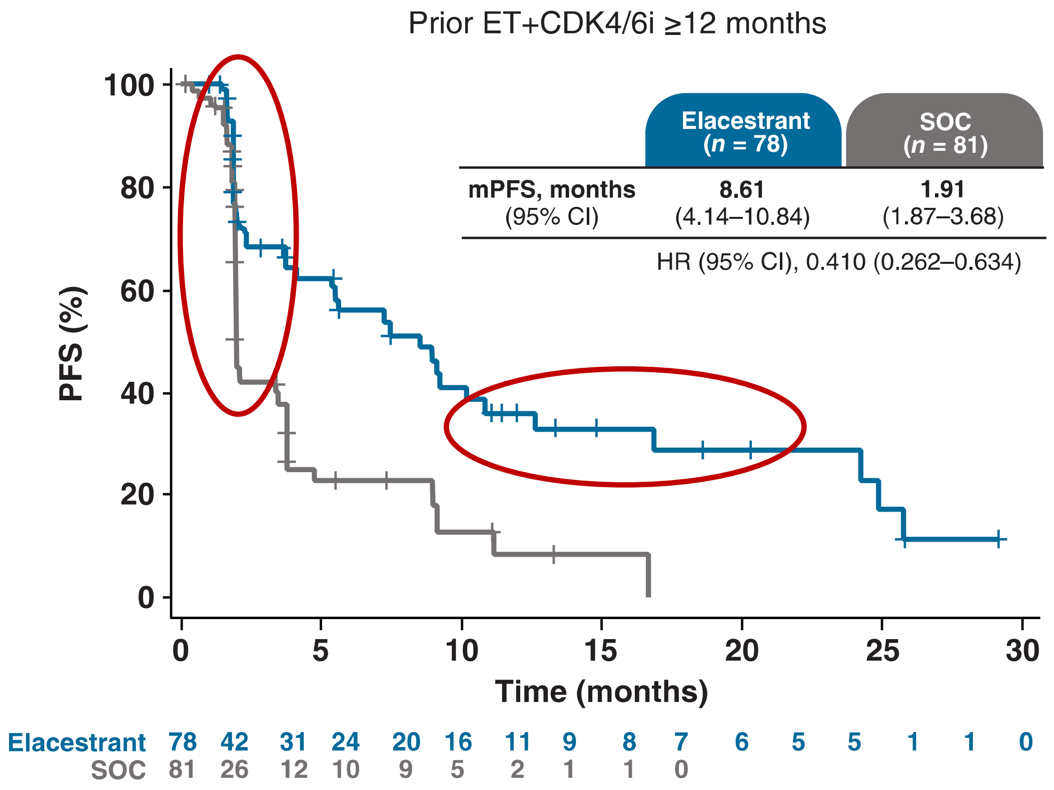
Time (years)

	PFS ≤6m	PFS 6-12m	PFS >12m
Definition	PFS to 1st line treatment equal or below 6 months.	PFS to 1st line treatment between 6 to 12 months.	PFS to 1st line treatment over 12 months.
N (%)	16	15	119
OS events	14(87.5%)	8(53.3%)	50(42%)
mOS (years)	1.19	3.6	5.22
95% CI	0.93 - 2.7	2.53 - NA	4.67 - NA

Guerrero-Zotano A, ASCO 2024

The duration of PFS in the first-line treatment with CDK 4/6i influences the response to Elacestrant

		median PFS months (95% CI)	HR (95% CI)
At least 6 mo	Elacestrant (n=103)	4.14 (2.20-7.79)	0.51 (0.36-0.73)
	SOC (n=102)	1.87 (1.87-3.29)	
At least 12 mo	Elacestrant (n=78)	8.61 (4.14-10.8)	0.41 (0.26-0.63)
	SOC (n=81)	1.91 (1.87-3.68)	
At least 18 mo	Elacestrant (n=55)	8.61 (5.45-16.89)	0.46 (0.27-0.79)
	SOC (n=56)	2.1 (1.87-3.75)	

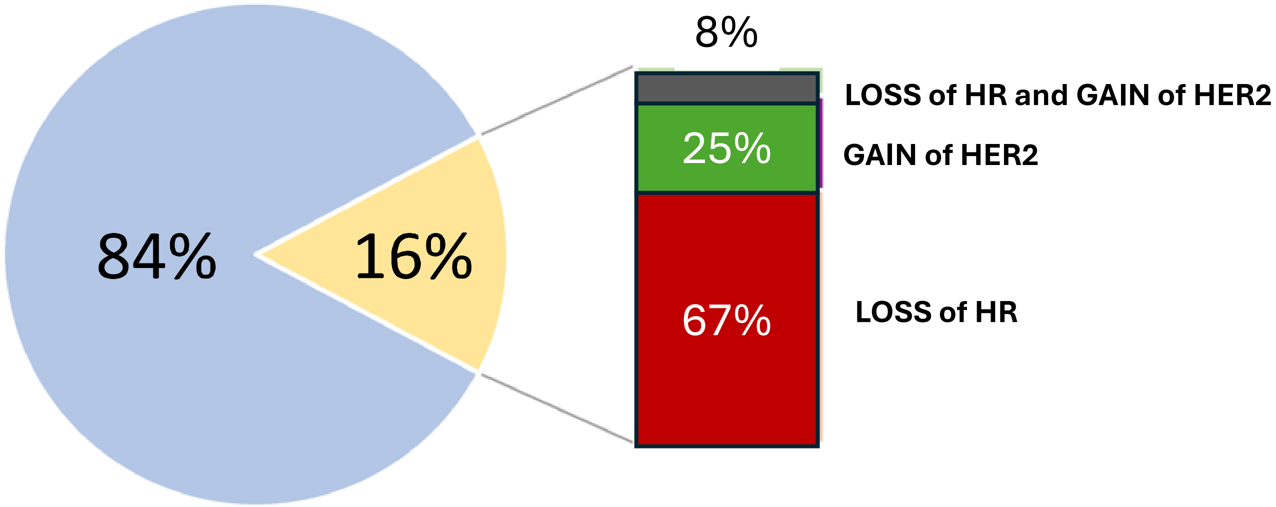


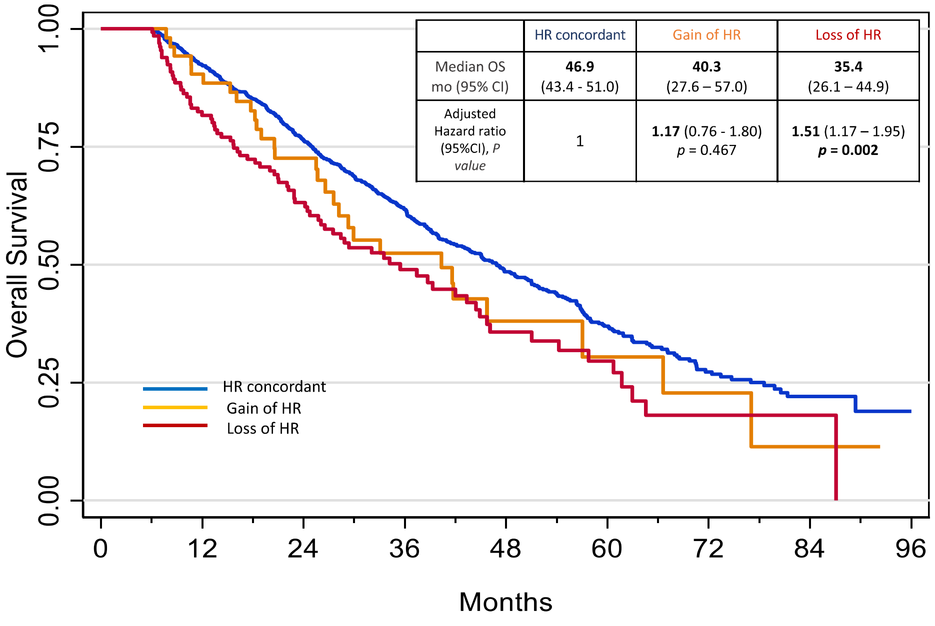
Early progression on CDK 4/6 is a marker of resistance to further endocrine treatment

Bardia A, CCR 2024

Loss of Hormone Receptors in Metastatic Evolution

Primary HR+ HER2-





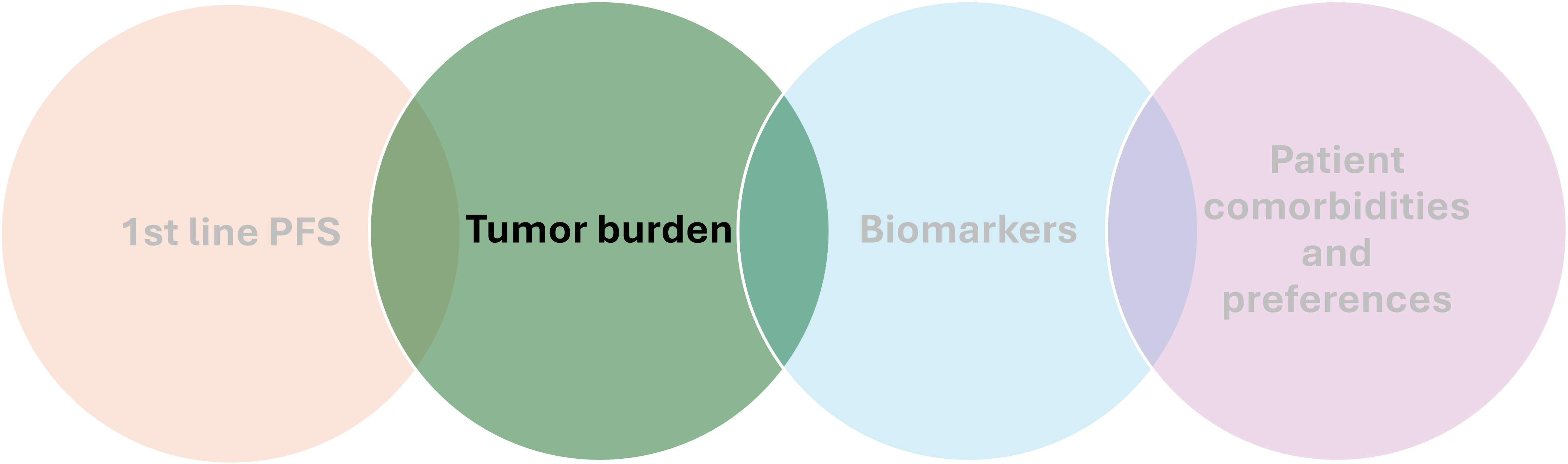
HR concordant	1199	1078	744	447	245	129	55	16	1
Gain of HR	53	47	32	17	6	4	2	1	0
Loss of HR	131	106	71	38	20	13	4	1	0

Strongly consider rebiopsy in cases of early progression!!!

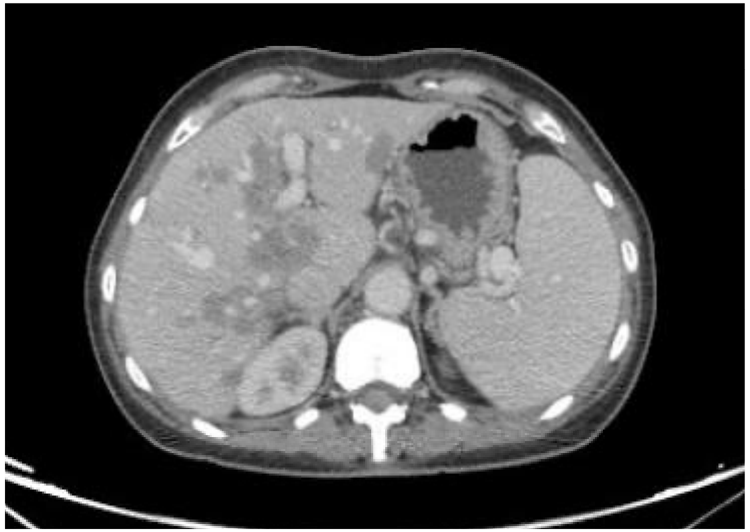
Grinda T, NPJ Breast Cancer 2021

Selection of 2nd line Treatment according to First-line PFS

> 12 months	6-12 months	< 6 months
Elacestrant (if ESR1 mut)		
Fulvestrant + Targeted therapy	**Fulvestrant + Targeted therapy**	
		Chemotherapy
		Trastuzumab Deruxtecan (if HER2 low or ultralow)


1st line PFS
Tumor burden
Biomarkers
Patient comorbidities and preferences

Tumor burden


The percentage of objective responses is not a regulatory objective, but it can be a clinically relevant objective in symptomatic patients with a high tumor burden

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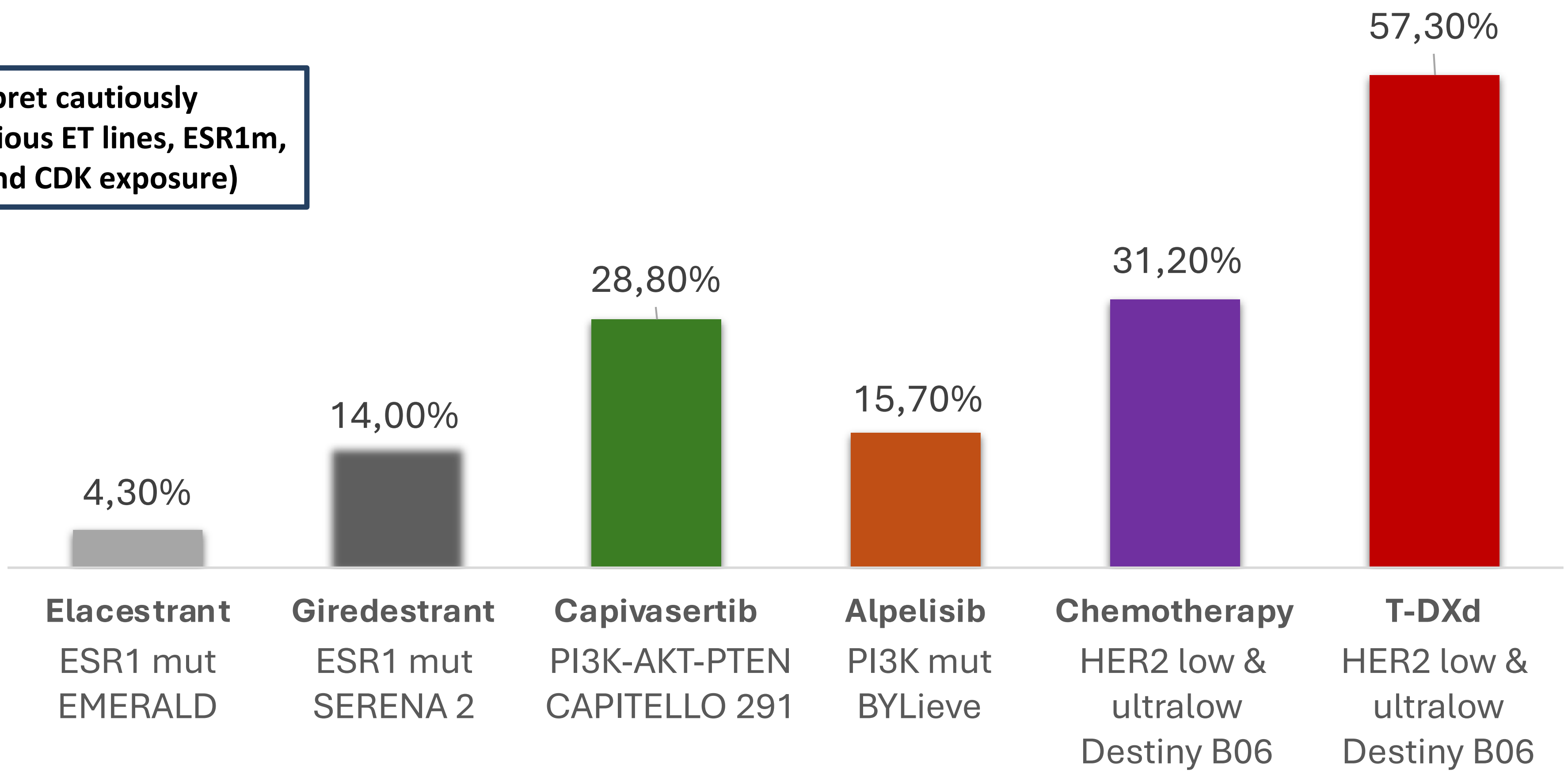
Response Rate in Endocrine-resistant mBC

To interpret cautiously (different previous ET lines, ESR1m, PI3K mut and CDK exposure)



Bidard FC, J Clin Oncol 2022; Martin M, J Clin Oncol 2023; Turner NC, NEJM 2023; Rugo HS, Ann Oncol 2020; Curigiliano G, ASCO 2024

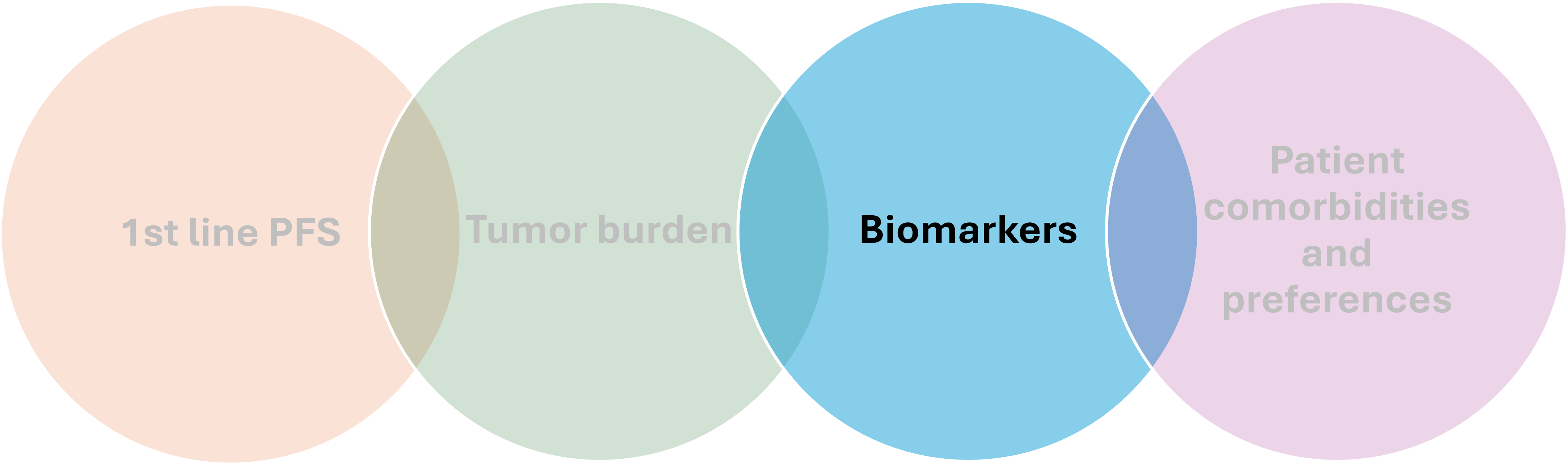
Selection of 2nd line Treatment according to tumor burden

Elacestrant (if ESR1 mut)

Fulvestrant + Targeted therapy

Chemotherapy

Trastuzumab Deruxtecan (if HER2 low or ultralow)


1st line PFS
Tumor burden
Biomarkers
Patient comorbidities and preferences

Mutational status

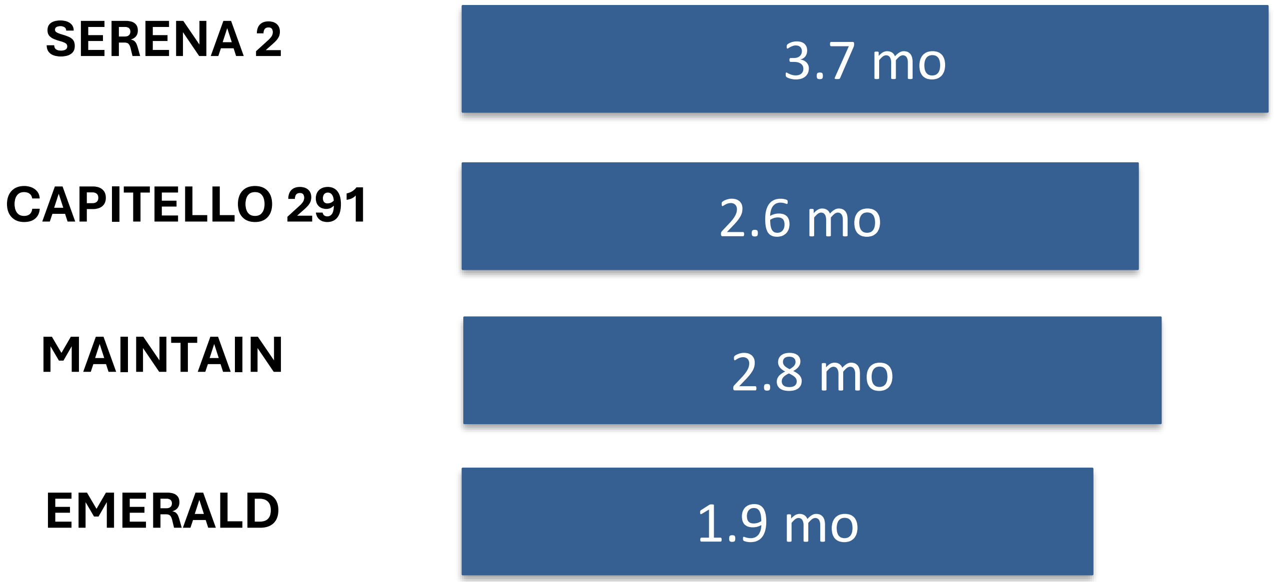
Wild-type or unknown	BRCA mut	ESR1 mut	PI3K pathway mut

Mutational status

Wild-type or unknown	BRCA mut	ESR1 mut	PI3K pathway mut

PFS with Fulvestrant in CDK4/6i naive patients

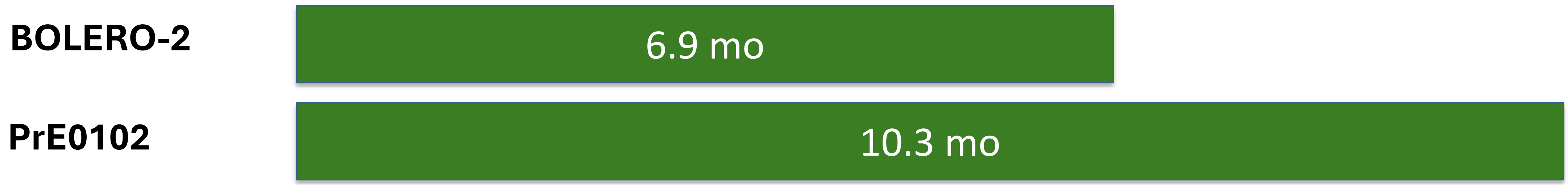
PFS with Fulvestrant in CDK4/6i pre-treated patients



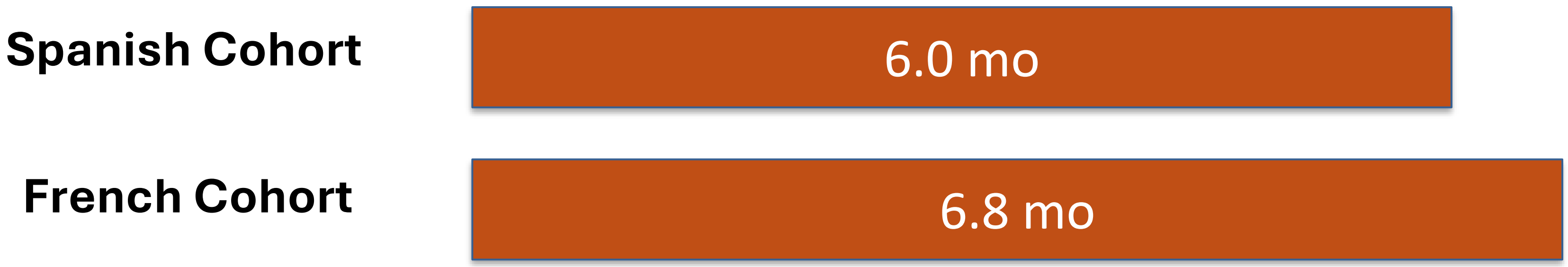
To interpret cautiously (different previous ET lines, ESR1m and CDK exposure)

Di Leo, J Clin Oncol 20210; Sledge G, J Clin Oncol 20217; , Bidard F. JCO 2022; Turner N. ESMO Breast 2023; Llombart A, ASCO 2023; Olivera M SABCS 2022

PFS with everolimus + ET in CDK4/6i naive patients

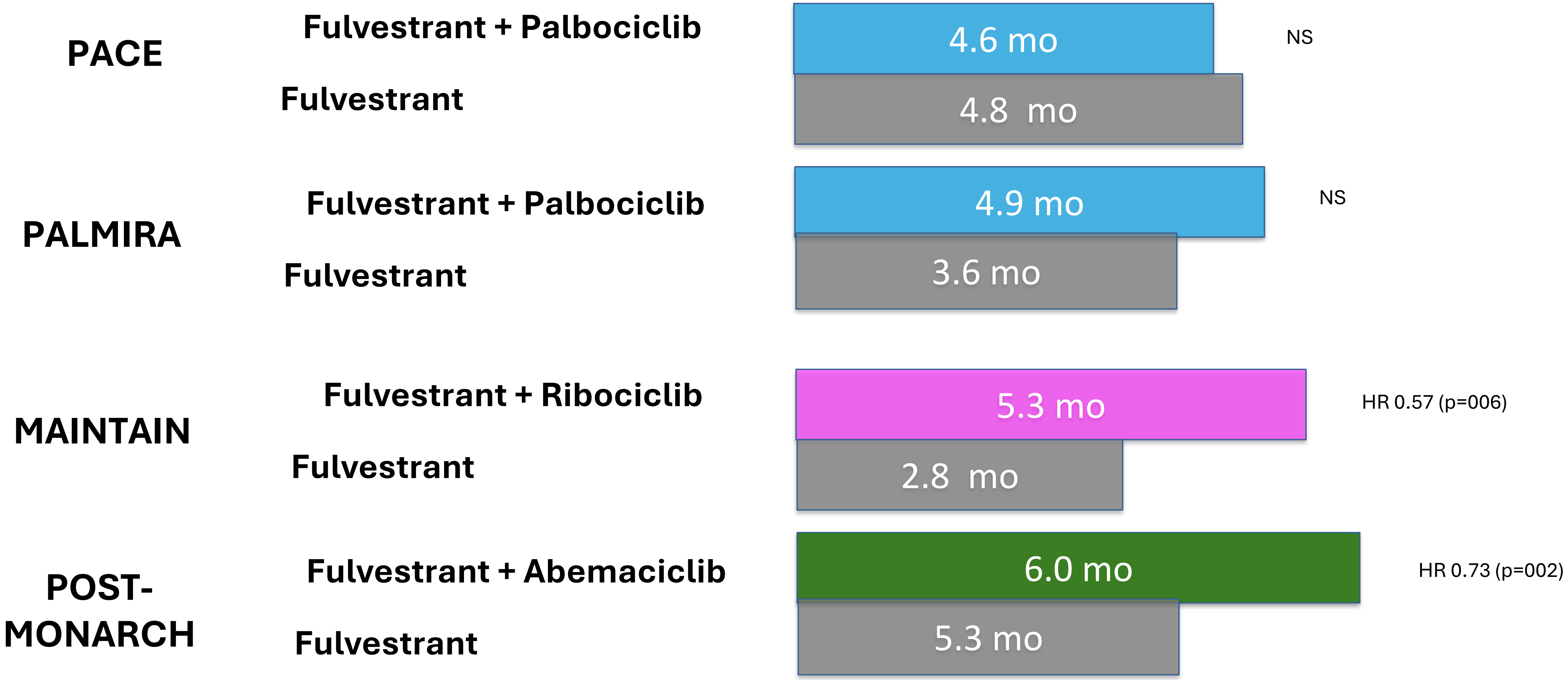


PFS with everolimus + ET in CDK4/6i pretreated patients



Baselga et al NEJM 2012; Piccart et al Ann Oncol 2014; Kornblum et al JCO 2019; Vasseur et al Onccogene 2024; Sanchez-Bayona et al BCRT 2024

PFS with CDK 4/6i + Fulvestrant in CDK4/6i + AI pretreated patients

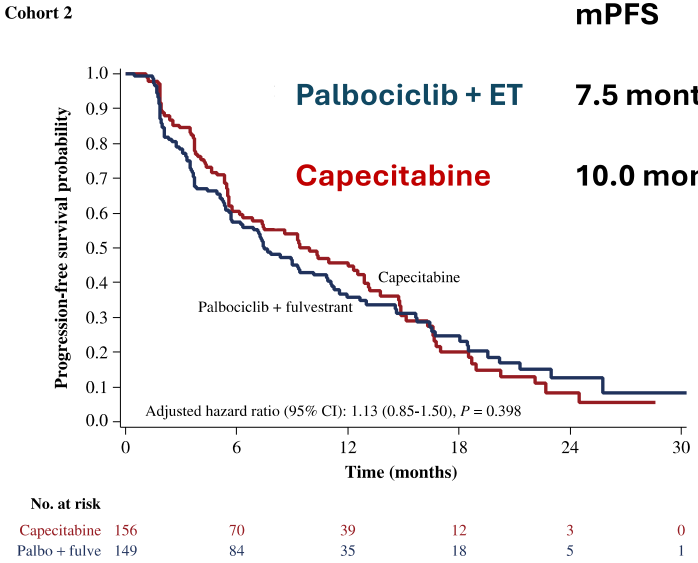


Kalinsky et al ASCO 2024: Giordano et al Ann Oncol 2024; Kalinski et al JCO 2023; Mayer et al JCO 2024; Damodaran et al Ann Oncol 2023; Albanell et al CCR 2023; Llombart-Cussac et al ASCO 2023; Kalinsky et al, ASCO 2024

Targeted therapy + ET vs Capecitabine in endocrine- resistant mBC

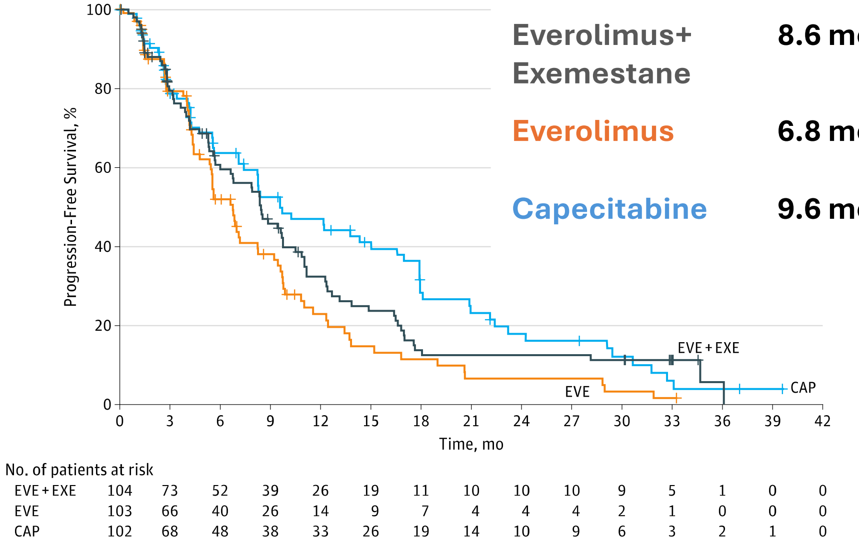
PEARL Study
ET + Palbociclib vs capecitabine

	mPFS
Palbociclib + ET	7.5 months
Capecitabine	10.0 months



BOLERO 6 Study
Everolimus + exemestane vs Everolimus vs capecitabine

	mPFS
Everolimus+ Exemestane	8.6 months
Everolimus	6.8 months
Capecitabine	9.6 months



No targeted therapy in combination with endocrine therapy has demonstrated superiority over capecitabine in endocrine-resistant breast cancer

Martin M, Ann Oncol 2020; Jerusalem G, JAMA Oncol 2018

Mutational status

Wild-type or unknown	BRCA mut	ESR1 mut	PI3K pathway mut
Everolimus + ET			
Fulvestrant			
Switch ET +/- iCDK			
Capecitabine			

Mutational status

Wild-type	**BRCA mut**	ESR1 mut	PI3K pathway mut
	≈5%		

Outcomes with CDK4/6i therapy in HR-positive and *gBRCAmut* MBC patients

Author	Results/Conclusions
Frenel et al.	BRCA/PALB2 mutated patients with shorter PFS (14.3 vs. 26.7m)
Collins et al.	BRCA mutated patients with shorter OS (26 vs. 51m)
Bruno et al.	BRCA/CHECK/ATM mutated patients with worse outcomes
Safonov et al.	BRCA2 mutations with worse PFS
Fuentes Antras, et al.	BRCA1/2 and PALB2 mutations with shorter PFS (9.9 vs. 26.8m)

- **Mostly retrospective and subgroup analyses data**
- **Unmet need for specific treatment approaches for HR+/BRCA-mutated patients**
- **Prospective data and combinations need to be explored**

Frenel J, et al. Ann Oncol 2020.
Bruno L, et al. JCO Precision Oncol, 2022.
Safonov A, et al. Cancer Res 2022.
Collins J, et al. Oncol Therapy, 2021.
Fuentes Antras J, et al. ASCO 2023.

PARP inhibitors in advanced gBRCA mut BC

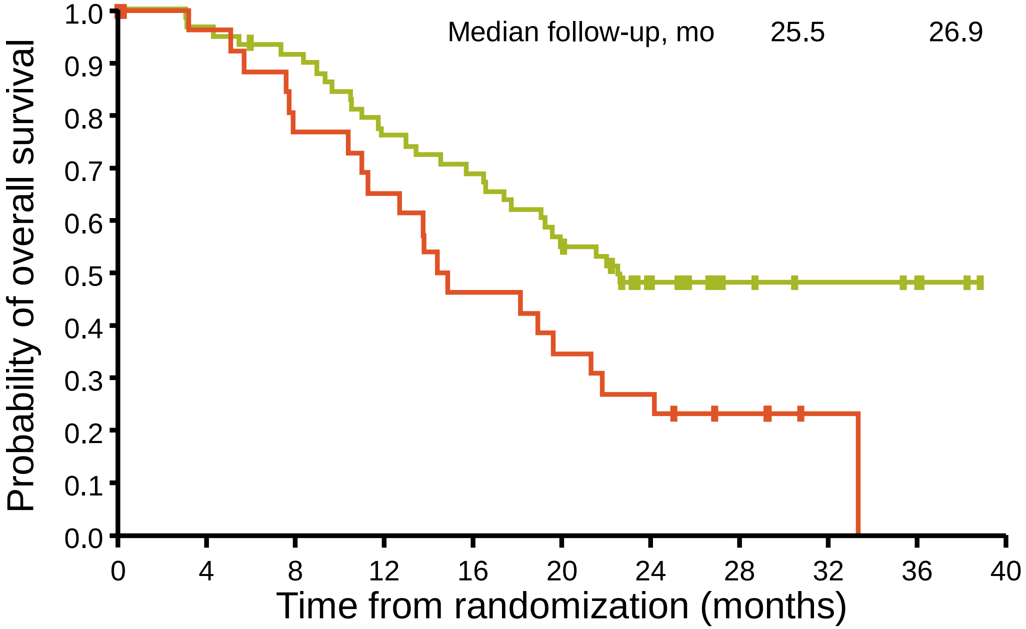
OLYMPIA Trial

gBRCA1/BRCA2 Advanced anthracycline/taxane resistant breast cancer

- Olaparib
- Physician Choice with SOC options

Overall Survival
No prior chemotherapy for mBC (1L)

	Olaparib	TPC
Deaths, n (%)	30 (50.8)	21 (75.0)
Median OS, mo	22.6	14.7
HR 0.51 (95%CI 0.29–0.90; *P*=0.02)		
Alive at 6 mo, %	93.2	88.5
Alive at 18 mo, %	62.1	46.2
Median follow-up, mo	25.5	26.9



Robson et al. AACR, 2018

Mutational status

Wild-type	BRCA mut	ESR1 mut	PI3K pathway mut
	PARP inhibitors		

Mutational status

Wild-type

BRCA mut

ESR1 mut

PI3K pathway mut

ESR1 ≈30 %

PIK3CA ≈38 %

AKT1 ≈7%

PTEN ≈5%

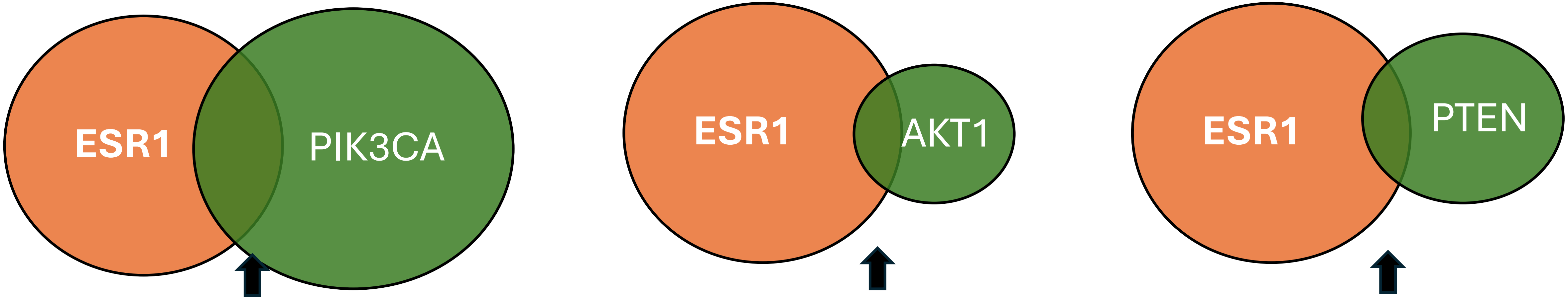
Medford A, ASCO 2023; Tolaney SM, Clin Cancer Res 2022; Dempsey N, ASCO 2023

Mutational status

Wild-type	BRCA mut	ESR1 mut	PI3K pathway mut
		Elacestrant	Fulvestrant + Alpelisib. (only PIK3CA)
			Fulvestrant + Capivasertib

Mutational status

Wild-type	BRCA mut	ESR1 mut	PI3K pathway mut



10-49%
PIK3CA & ESR1

5%
AKT & ESR1

7%
PTEN & ESR1

The optimal sequence in patients with coexisting mutations in ESR1 and the PI3K pathway is not known.

The combination of SERDs and new inhibitors of the PI3K pathway should be explored

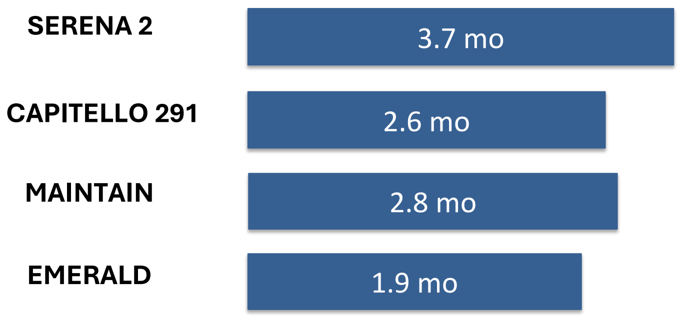
Medford A, ASCO 2023; Tolaney SM, Clin Cancer Res 2022; Dempsey N, ASCO 2023

Limitations of targeted therapy after iCDKs: Efficacy

Registry studies must compare the experimental treatment with the standard treatment

Considering the activity of fulvestrant after CDK 4/6 inhibitors..

PFS with Fulvestrant in CDK4/6i pre-treated patients



1- Can fulvestrant be considered a standard treatment?

2- Are SERDS or PI3K/AKT inhibitors better options than everolimus + endocrine therapy or capecitabine in patients with ESR1 mutations or activation of PIK3 pathway?

Limitations of targeted therapy after iCDKs: Toxicity

	Capivasertib + Fulvestrant CAPITELLO-291	Alpelisib + Fulvestrant BYLieve	Elacestrant EMERALD	Everolimus + Exemestane BOLERO-2	Capecitabine PEARL
Diarrhea	76.8%	85%	13.9%	35%	55.5%

Bidard F. JCO 2022; Rugo HS, Ann Oncol 2020 ; Bidard FC, J Clin Oncol 2022 ; Baselga J, NEJM 2012; Martin M, Ann Oncol 2020

Limitations of targeted therapy after iCDKs: Toxicity

	Capivasertib + Fulvestrant CAPITELLO-291	Alpelisib + Fulvestrant BYLieve	Elacestrant EMERALD	Everolimus + Exemestane BOLERO-2	Capecitabine PEARL
Diarrhea	76.8%	85%	13.9%	35%	55.5%
Nausea	34.8%	54.8%	35%	36%	37.7%
Vomiting	20.6%	24.6%	19%	27%	29.1%

Bidard F. JCO 2022; Rugo HS, Ann Oncol 2020 ; Bidard FC, J Clin Oncol 2022 ; Baselga J, NEJM 2012; Martin M, Ann Oncol 2020

Limitations of targeted therapy after iCDKs: Toxicity

	Capivasertib + Fulvestrant CAPITELLO-291	Alpelisib + Fulvestrant BYLieve	Elacestrant EMERALD	Everolimus + Exemestane BOLERO-2	Capecitabine PEARL
Diarrhea	76.8%	85%	13.9%	35%	55.5%
Nausea	34.8%	54.8%	35%	36%	37.7%
Vomiting	20.6%	24.6%	19%	27%	29.1%
Stomatitis	17.4%	34.1%	NA	14%	25%
Rash	40.6%	31%	NA	56%	NA
Hyperglycaemia	16.8%	63.5%	NA	13%	NA

Bidard F. JCO 2022; Rugo HS, Ann Oncol 2020 ; Bidard FC, J Clin Oncol 2022 ; Baselga J, NEJM 2012; Martin M, Ann Oncol 2020

Limitations of targeted therapy after iCDKs: Biomarker analysis

Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group

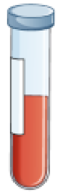
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

- **It is recommended to perform tumour NGS of a tumour (or plasma) sample from a patient with HR+/HER2- ABC as standard of care.**
- **The NGS testing should be done after resistance to endocrine therapy to optimise the likelihood of detecting ESR1 mutations**

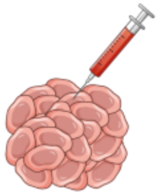
Time to results

Liquid

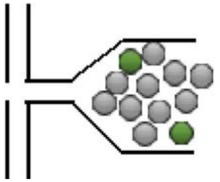


or

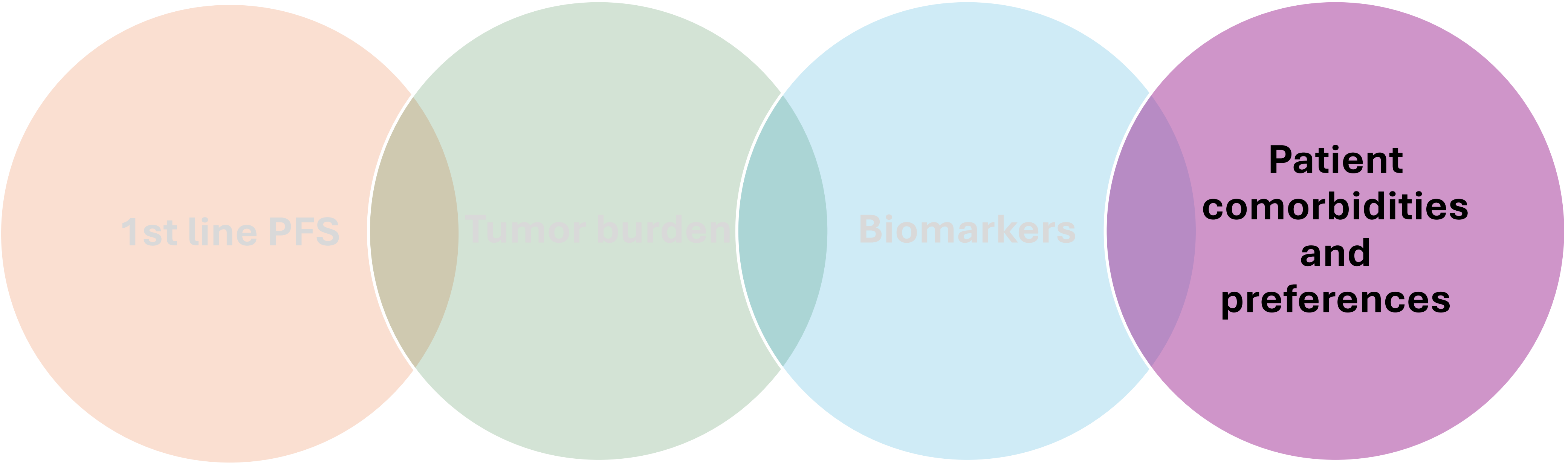
Tissue



ddPCR



NGS


1st line PFS
Tumor burden
Biomarkers
Patient comorbidities and preferences

Comorbidities

- Diabetes mellitus
- Gastrointestinal disorders
- Previous toxicity from iCDKs (Neumonitis, neutropenia)

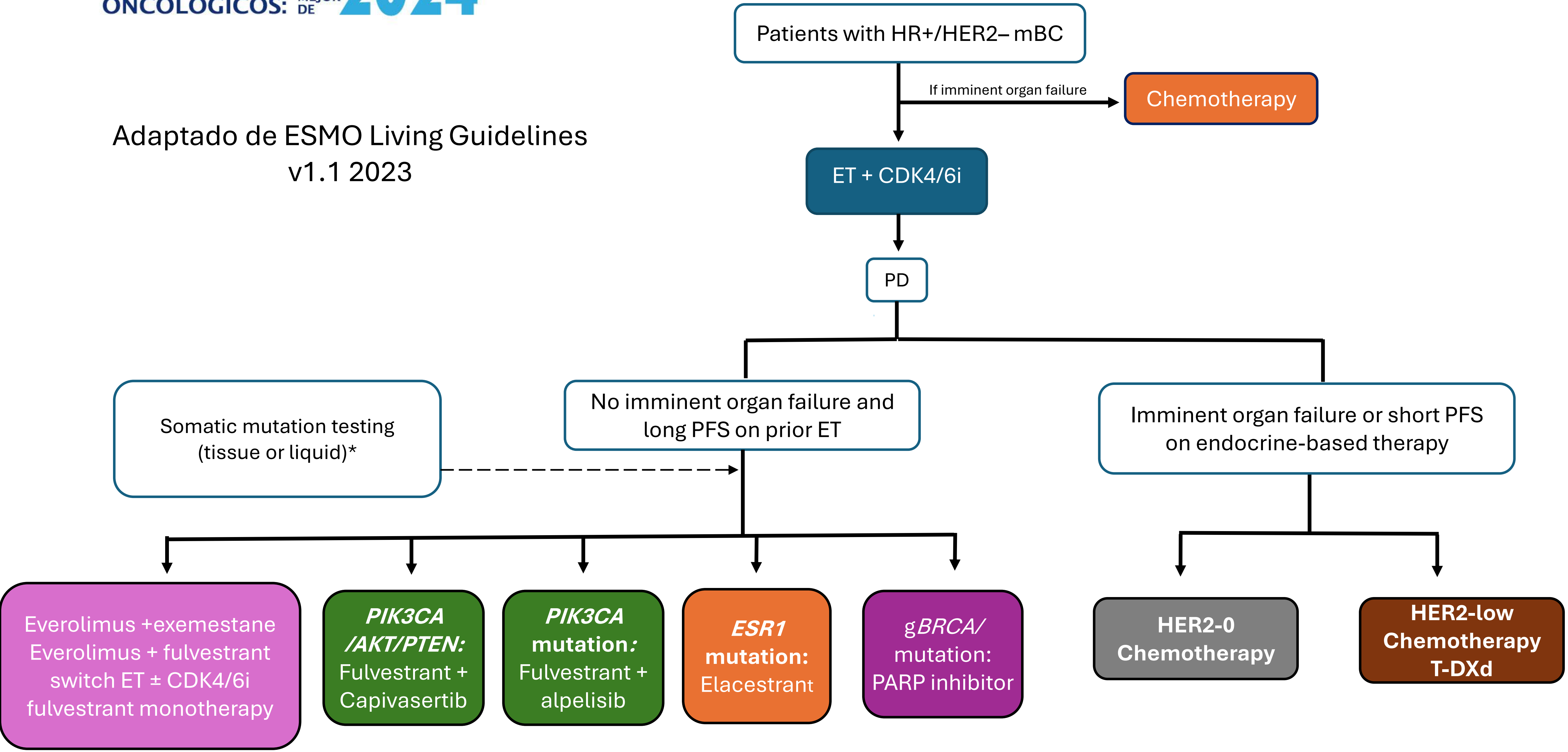
Pharmacogenomics

- DPYD deficiency

Patient preference

- Alopecia
- Need for monitoring and visits
- Oral vs iv vs im route of administration

Adaptado de ESMO Living Guidelines v1.1 2023



*Germline *BRCA1/2* testing if high likelihood of harbouring germline BRCA1/2