Il carcinoma mammario metastatico HR+/HER2-: dagli inibitori di CDK 4/6 agli inibitori di PI3K

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Conflict of interest

- PF Roche
- PF Gilead
- PF Novartis
- PF Seagen
- PF Pfizer
- PF Lilly

HR+/HER2- MBC: an evolving scenario

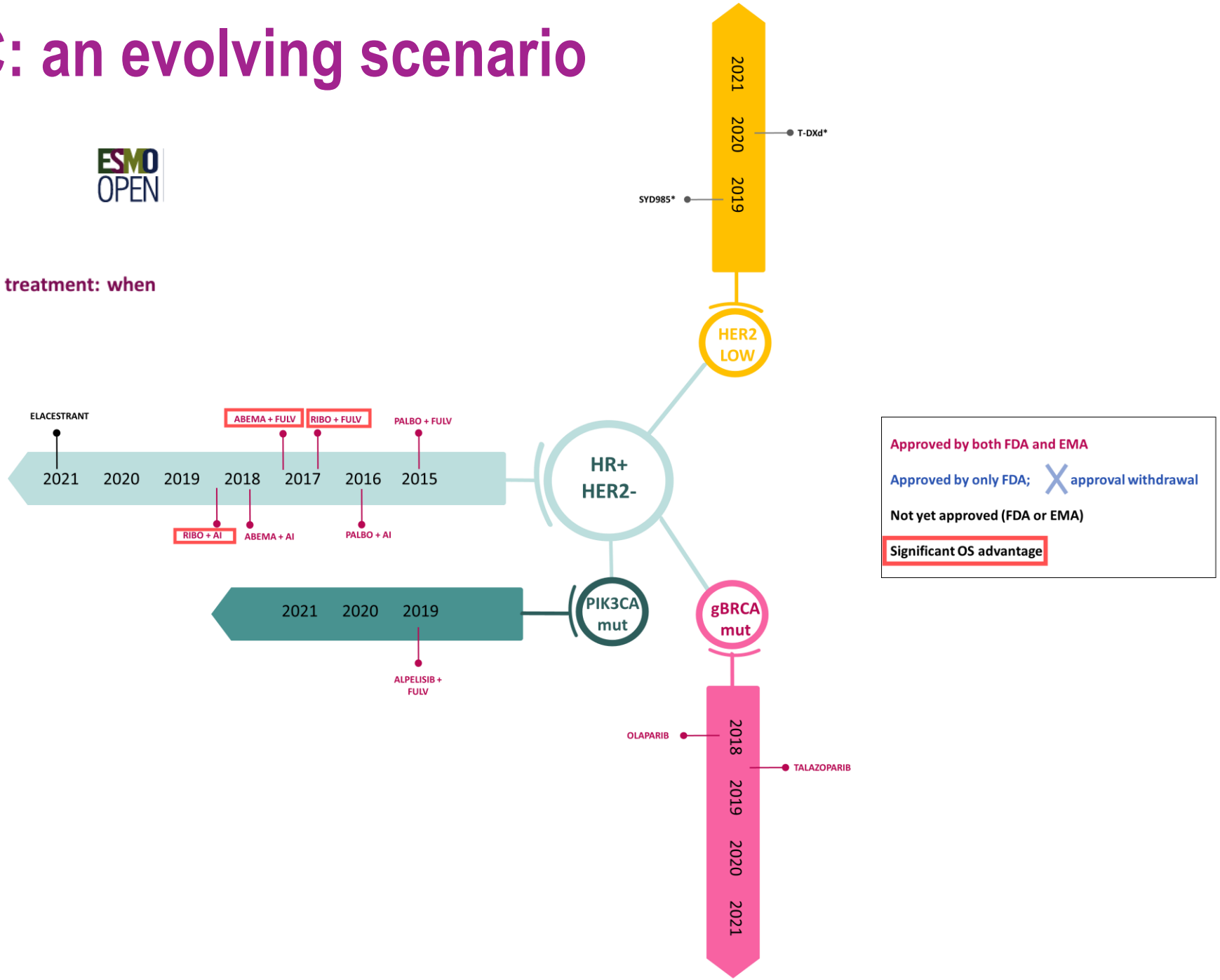
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN

REVIEW

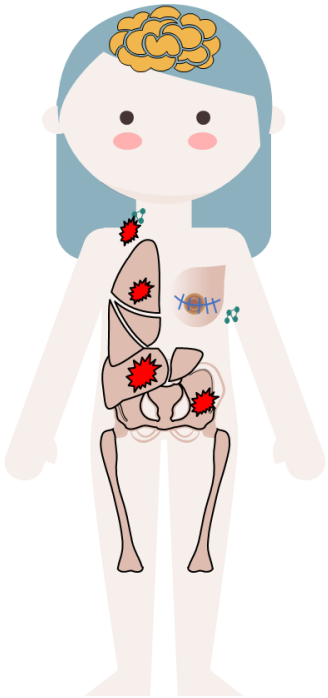
Major advancements in metastatic breast cancer treatment: when expanding options means prolonging survival

F. Miglietta[1], M. Bottosso[1], G. Griguolo[1,2], M. V. Dieci[1,2] & V. Guarneri[1,2*]



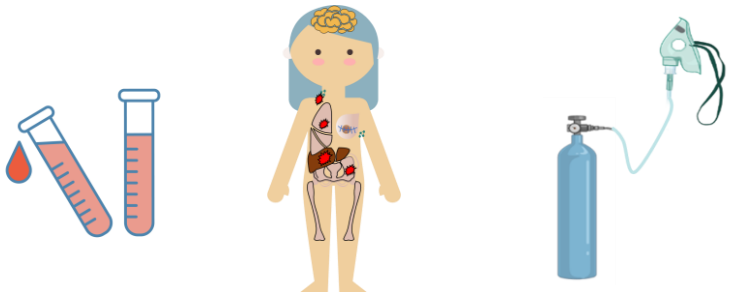
Modified from Miglietta F et al, ESMO Open 2022

HR+/HER2- MBC: choice of first-line therapy

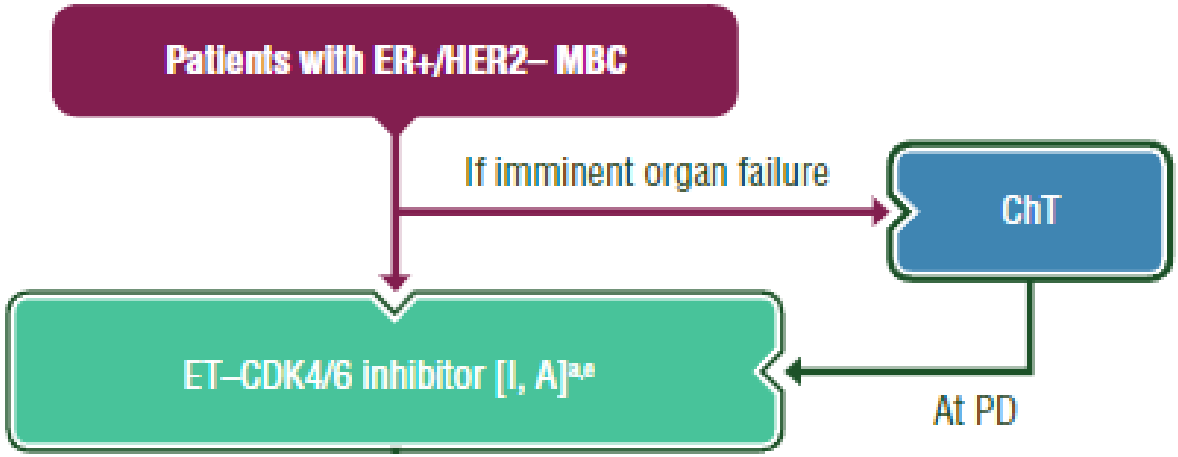


Standard approach → **endocrine-based treatment**

(imminent) organ failure

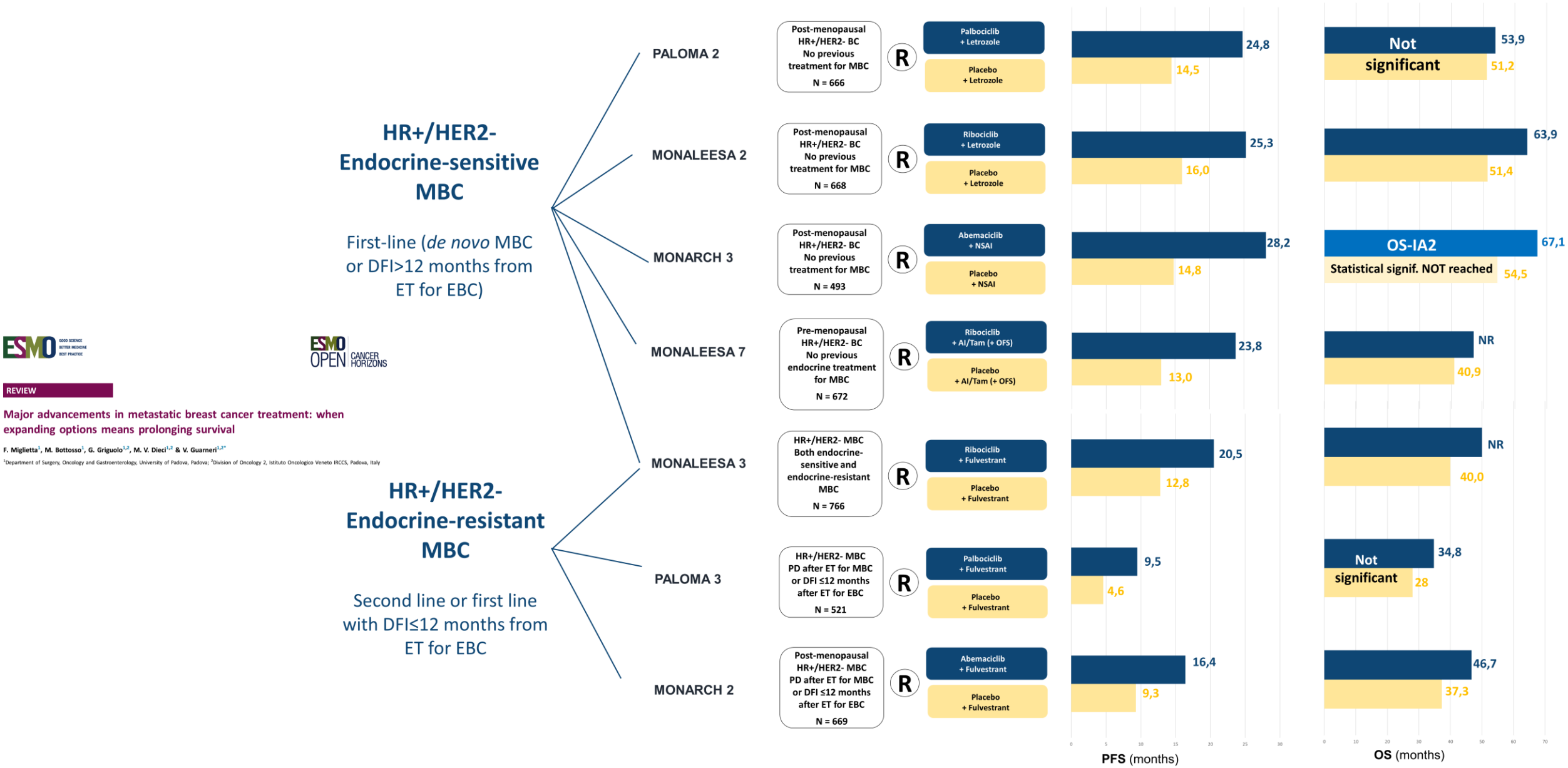


→ **chemotherapy**



Gennari et al, Ann Oncol 2021

HR+/HER2- MBC: CDK 4/6 inhibitors + ET



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

REVIEW

Major advancements in metastatic breast cancer treatment: when expanding options means prolonging survival

F. Miglietta[1], M. Bottosso[1], G. Griguolo[1,2], M. V. Dieci[1,2] & V. Guarneri[1,2*]

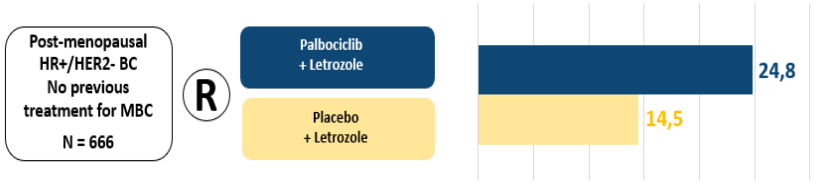
[1]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova; [2]Division of Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy

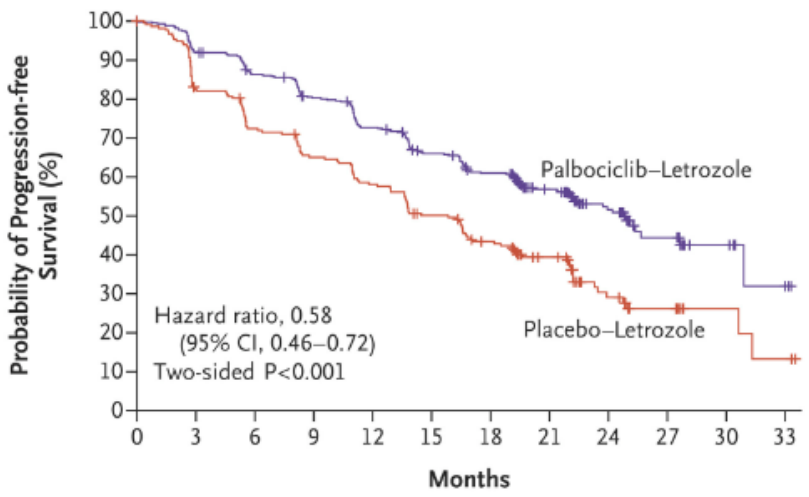
Modified from Miglietta et al, ESMO Open 2022

HR+/HER2- MBC: AI + CDK 4/6i in postmenopausal pts

Primary endpoint results: PFS

Palbociclib PALOMA-2





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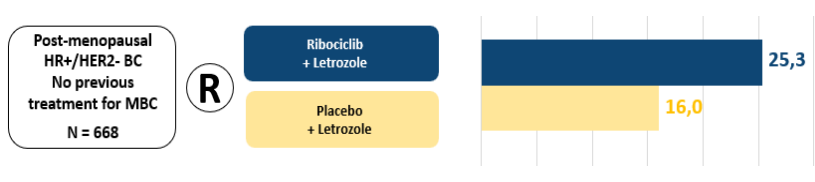

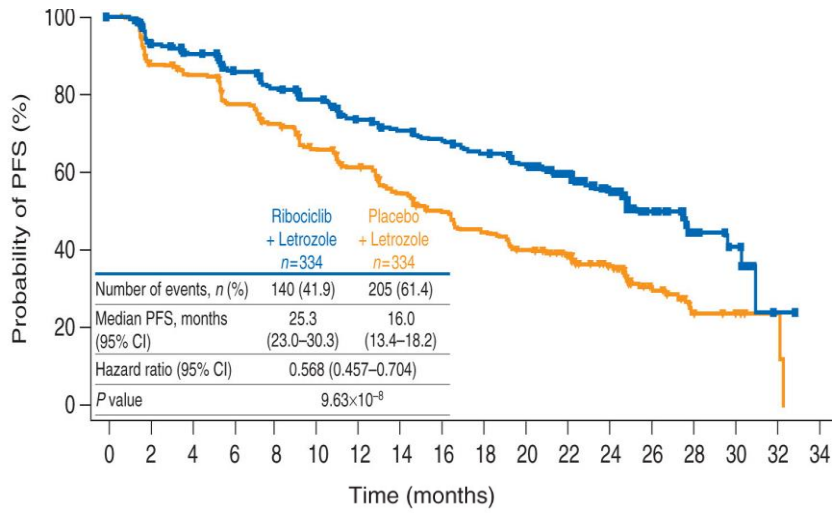

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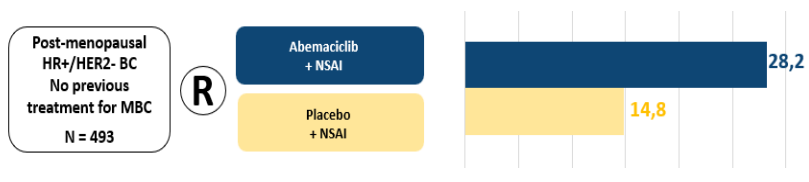
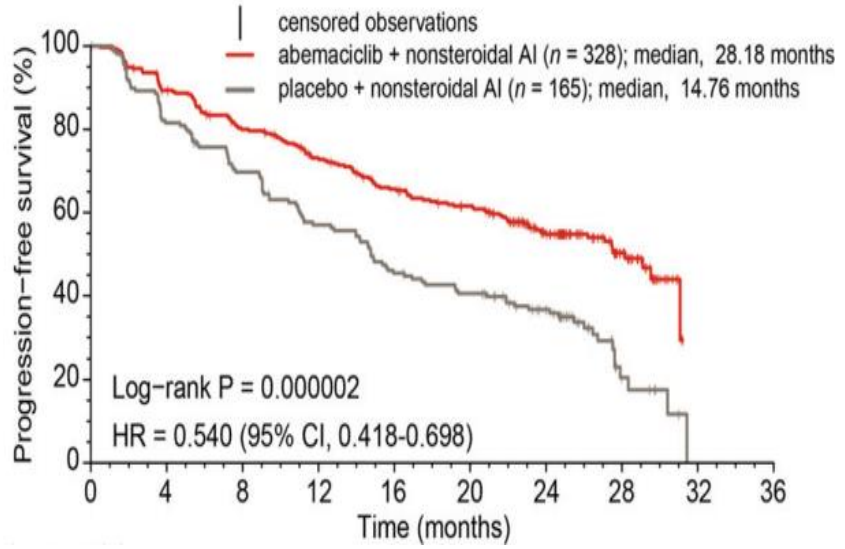


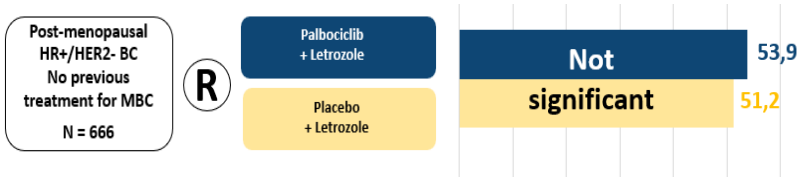


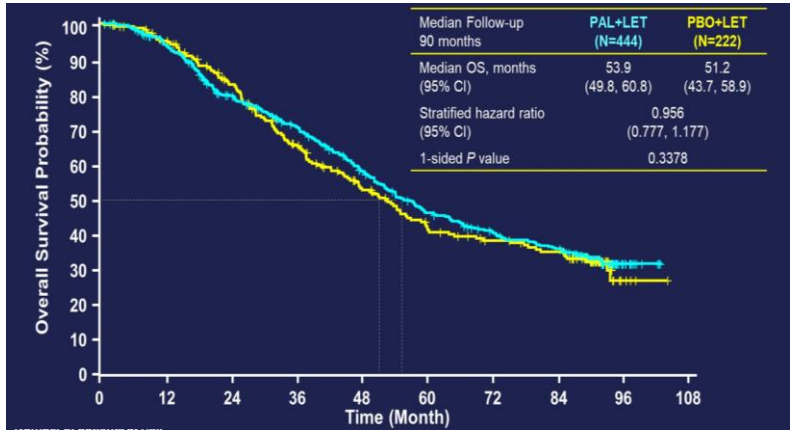
Finn RS et al, NEJM 2016; Hortobagyi G et al, NEJM 2016 and Ann Oncol 2018, Goetz MP et al, JCO 2017, Johnston et al NPJ BC 2019

HR+/HER2- MBC: AI + CDK 4/6i in postmenopausal pts

OS results

Palbociclib PALOMA-2





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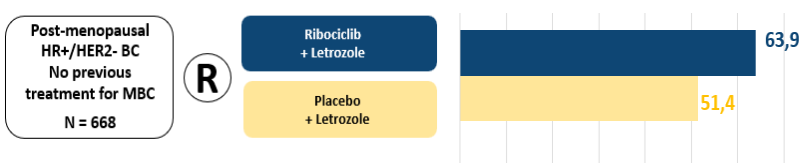

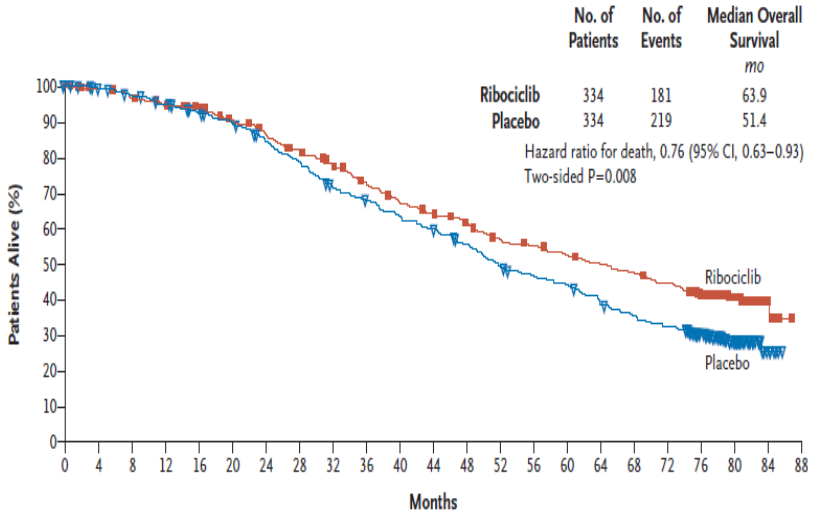

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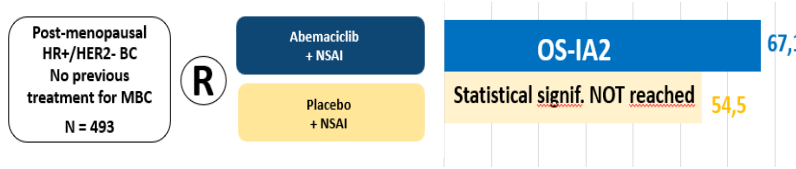
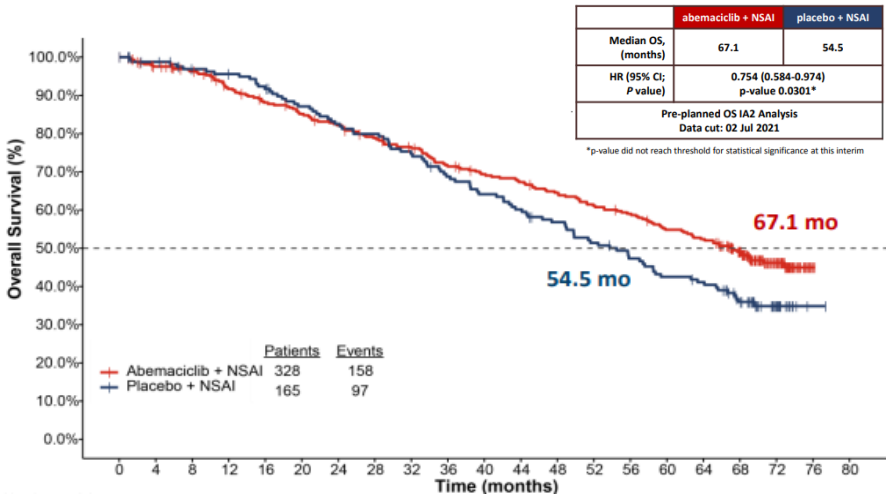




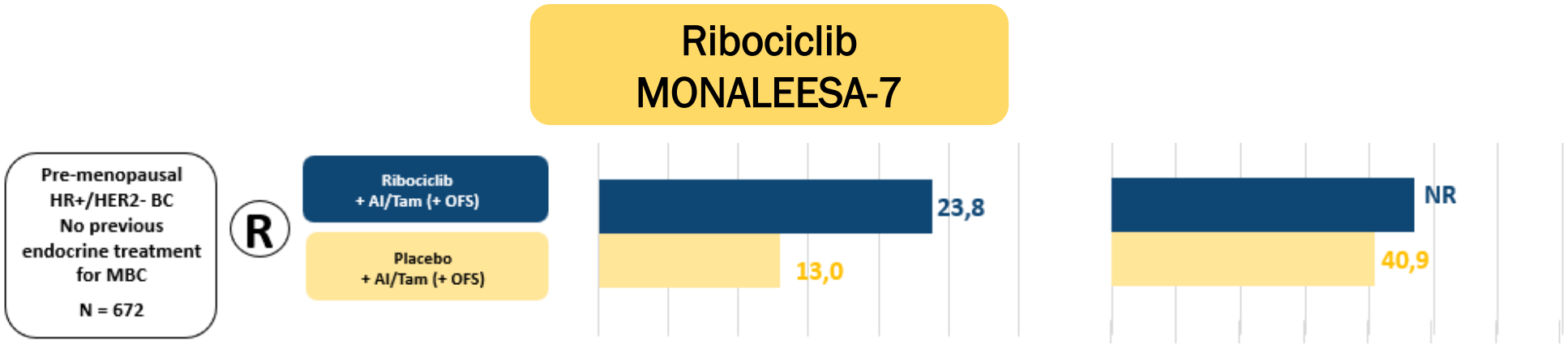
OS-IA2 significance not formally reached

Finn RS et al, ASCO 2022; Hortobagyi G et al, NEJM 2022; Goetz M et al, ESMO 2022

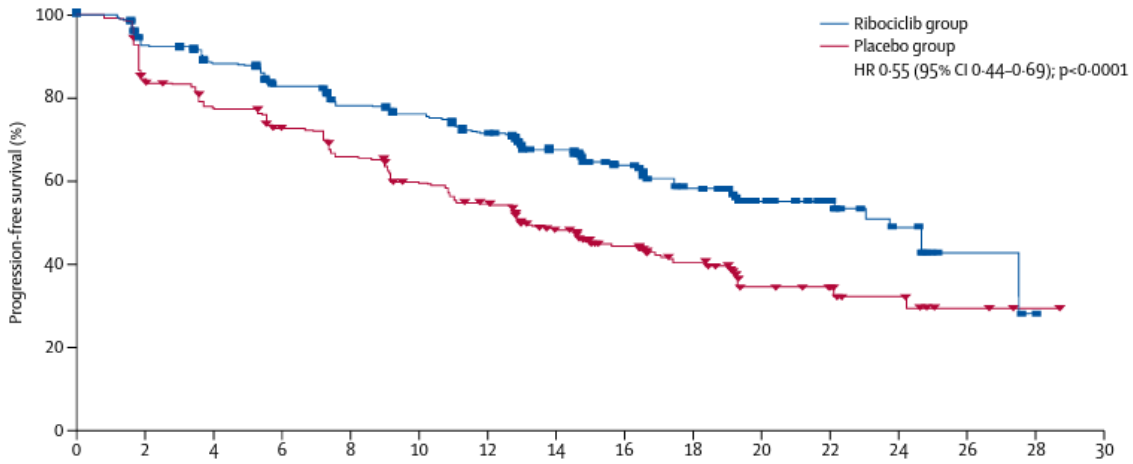
HR+/HER2- MBC: CDK 4/6i + ET in premenopausal pts

PFS and PS results

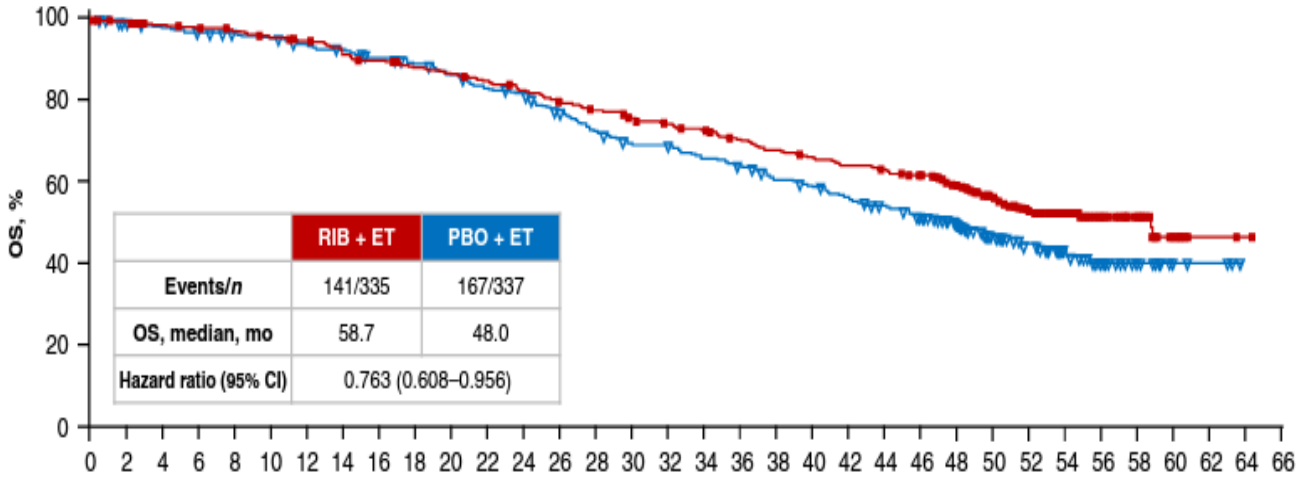
Ribociclib
MONALEESA-7



PFS



OS (all pts)



	RIB + ET	PBO + ET
Events/*n*	141/335	167/337
OS, median, mo	58.7	48.0
Hazard ratio (95% CI)	0.763 (0.608–0.956)	

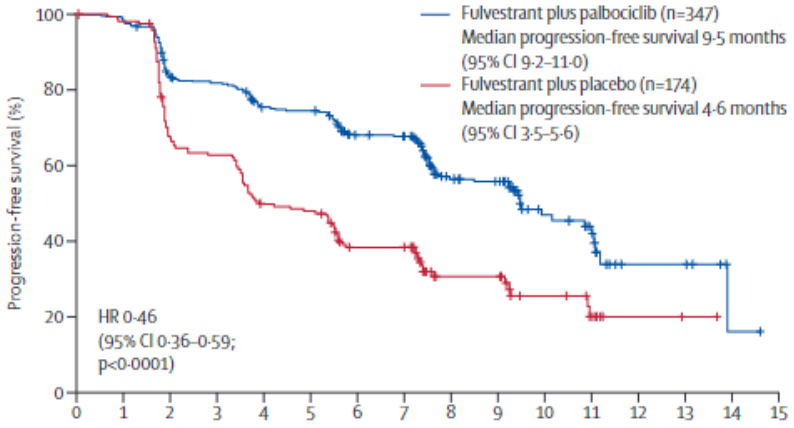
PATIENTS RECEIVING AI: HR 0,798 (95%CI 0,615-1,035)

Tripathy et al, Lancet Oncol 2018; Im SA et al, NEJM 2019; Lu YS et al, Ann Oncol 2022

HR+/HER2- MBC: Fulv + CDK 4/6i in postmenopausal pts

Primary endpoint results: PFS

Palbociclib PALOMA-3



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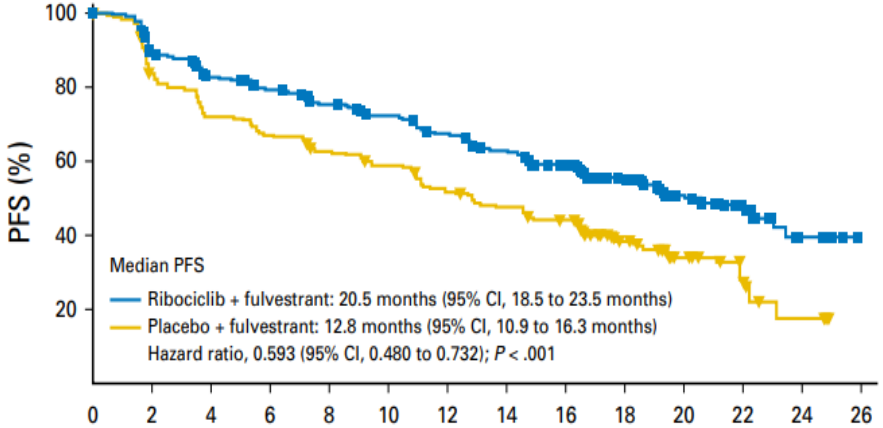

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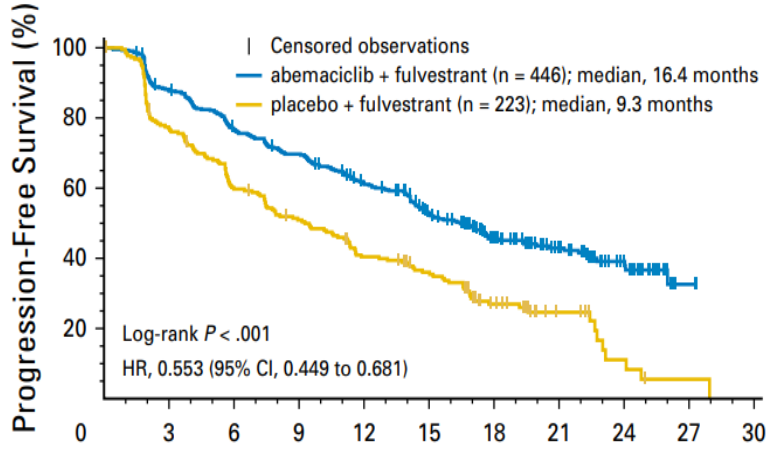
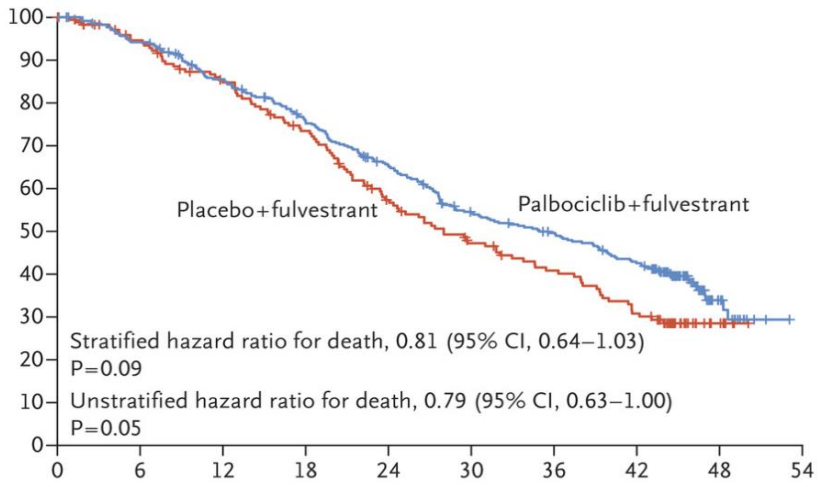


Cristofanilli et al, Lancet Oncol 2016; Slamon et al, JCO 2018; Sledge et al, JCO 2017

HR+/HER2- MBC: Fulv + CDK 4/6i in postmenopausal pts

OS results

Palbociclib PALOMA-3



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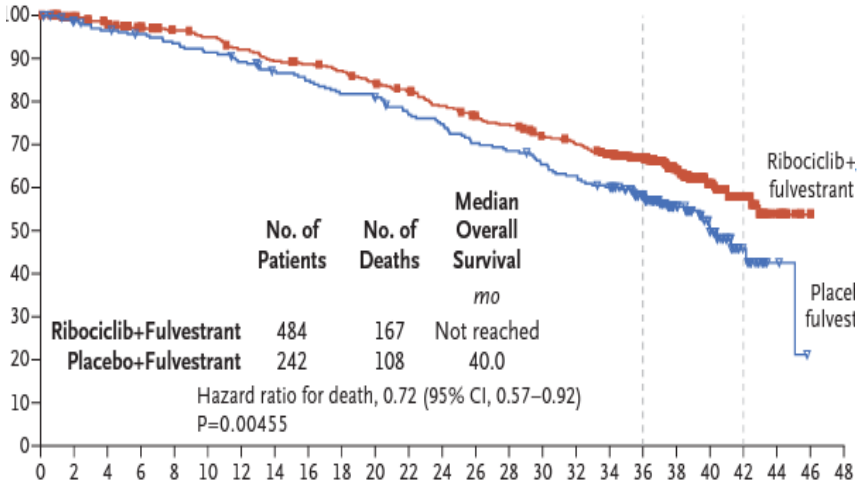

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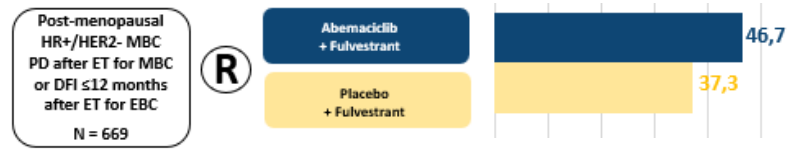
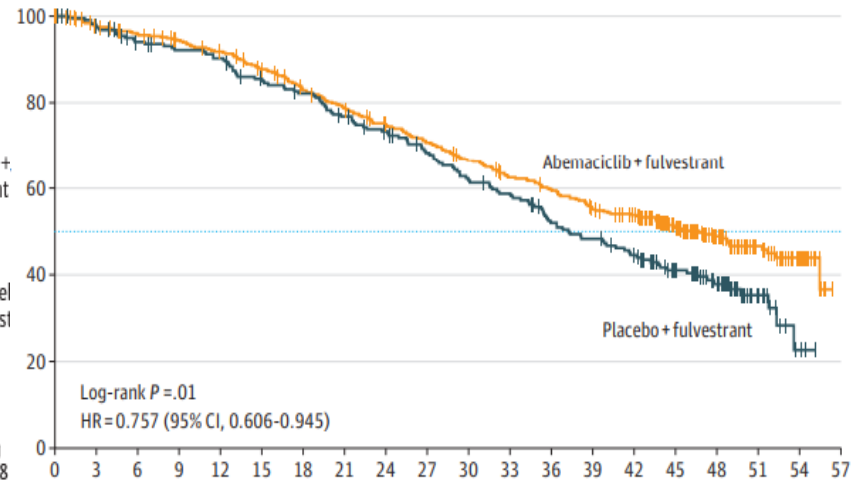




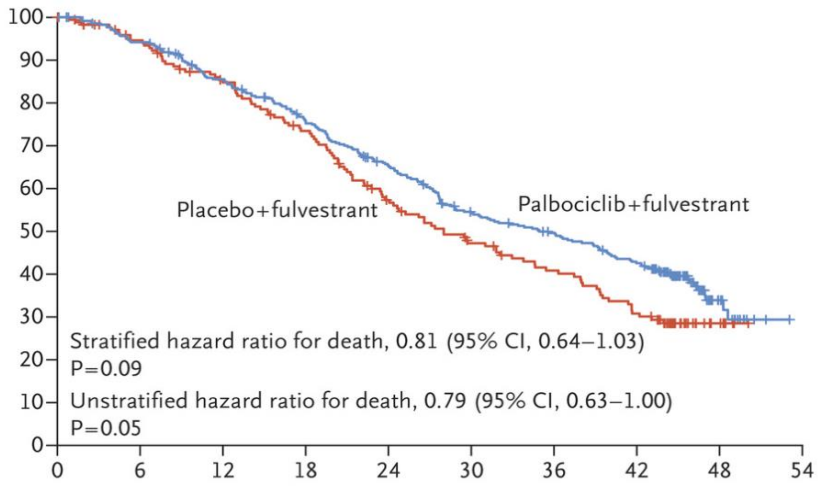
NOT SIGNIFICANT

Turner et al, NEJM 2018; Slamon et al, NEJM 2020; Sledge et al, JAMA Oncol 2018

HR+/HER2- MBC: Fulv + CDK 4/6i in postmenopausal pts

OS results

Palbociclib PALOMA-3



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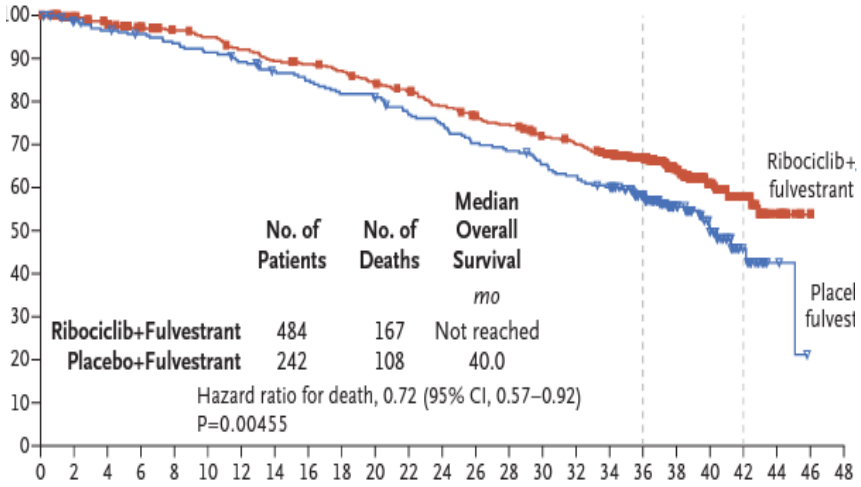
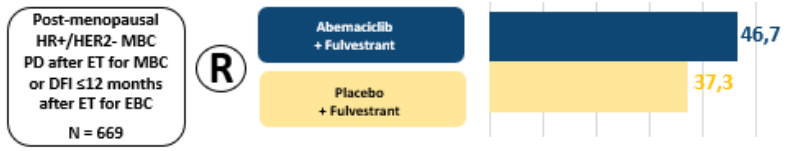
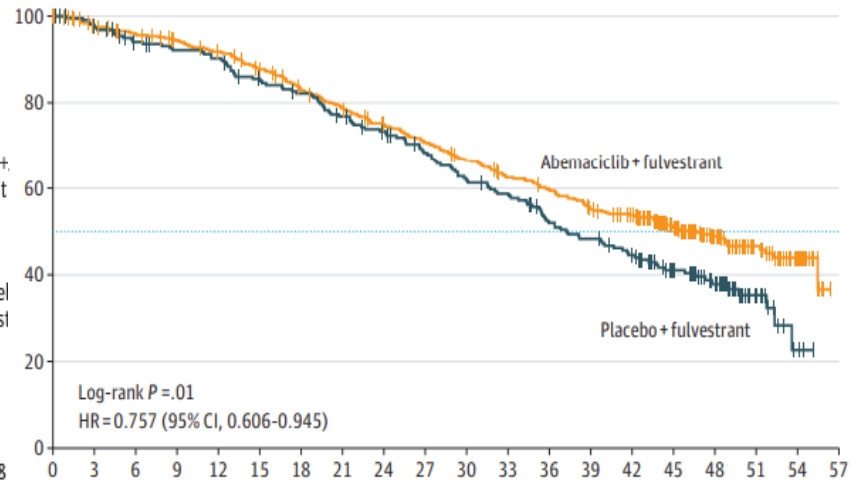


Extension of the regulatory positioning of Ribociclib + FULV also in endocrine sensitive pts

Abemaciclib MONARCH-2





Turner et al, NEJM 2018; Slamon et al, NEJM 2020; Sledge et al, JAMA Oncol 2018

HR+/HER2- MBC: Challenging the role of CT even in patients with aggressive clinical features

RIGHT Choice trial

- Pre-/perimenopausal women
- HR+/ HER2– ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease[a]
  - Symptomatic visceral metastases
  - Rapid disease progression or impending visceral compromise
  - Markedly symptomatic non-visceral disease
- ECOG PS ≤ 2[b]
- Total bilirubin ≤ 1.5 ULN
- N = 222[c]

Stratified by (1) the presence or absence of liver metastases and by (2) DFI[d] < or ≥2 years

R 1:1

- **Ribociclib** (600 mg, 3 weeks on/1 week off) + **Letrozole or anastrozole + goserelin**
- **Investigators' choice of combination CT[e]**: Docetaxel + capecitabine; Paclitaxel + gemcitabine; Capecitabine + vinorelbine

Tumor imaging evaluation Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W[f]

Primary endpoint
- PFS (locally assessed per RECIST 1.1)

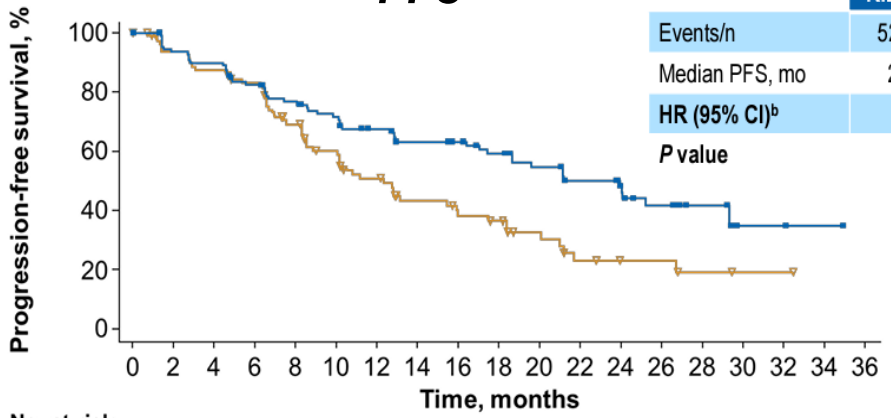
Secondary endpoints
- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QOL

Exploratory endpoints
- Biomarker analyses
- Healthcare resource utilization

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Median age, years	44.0	43.0
≥40 years	80 (71.4)	72 (65.5)
Race[a]		
Asian	60 (53.6)	58 (52.7)
White	51 (45.5)	52 (47.3)
Histological grade		
Grade 1	10 (8.9)	16 (14.5)
Grade 2	66 (58.9)	61 (55.5)
Grade 3	35 (31.3)	29 (26.4)
≥50% ER+	95 (84.8)	95 (86.4)
PR+	99 (88.4)	102 (92.7)

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Disease status		
De novo	71 (63.4)	73 (66.4)
Visceral metastatic sites[b]		
Liver	56 (50.0)	57 (51.8)
Lung	63 (56.3)	58 (52.7)
Liver or lung	89 (79.5)	85 (77.3)
Aggressive disease characteristic		
Rapid progression	23 (20.5)	18 (16.4)
Symptomatic non-visceral disease	15 (13.4)	16 (14.5)
Symptomatic visceral metastases	74 (66.1)	76 (69.1)
Visceral crisis[c]	61 (54.5)	55 (50.0)

PFS

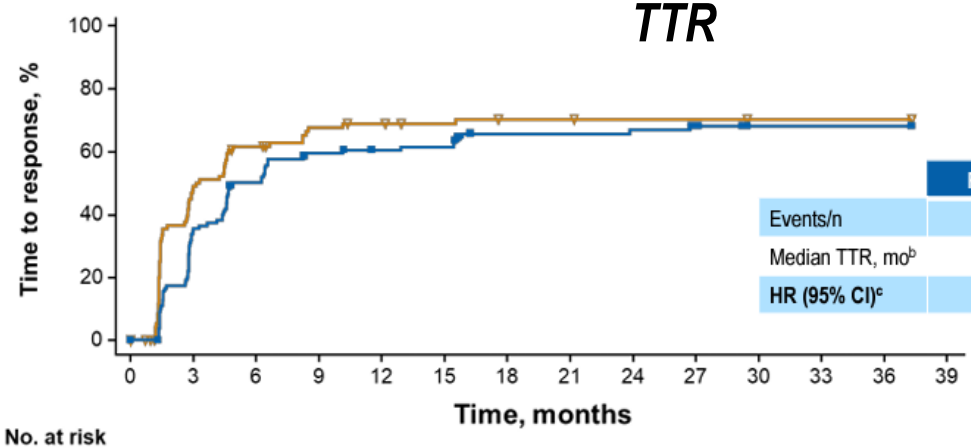


	RIB + ET	Combo CT
Events/n	52/112	58/110[a]
Median PFS, mo	24.0	12.3
HR (95% CI)[b]	**0.54 (0.36-0.79)**	
***P* value**	**.0007**	

No. at risk

RIB + ET	112	103	99	88	78	70	63	56	50	45	36	30	24	18	7	2	2	1	0
Combination CT	110	90	84	75	56	46	37	26	22	20	14	9	6	6	3	1	1	0	0

TTR



	RIB + ET	Combo CT
Events/n	73/112	66/110[a]
Median TTR, mo[b]	4.9	3.2
HR (95% CI)[c]	**0.78 (0.56-1.09)**	

No. at risk

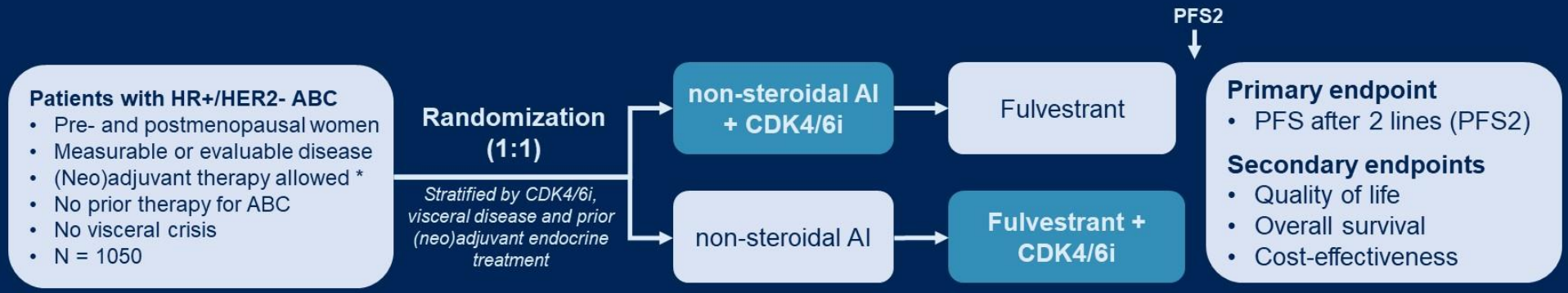
RIB + ET	112	72	53	42	39	38	29	29	28	26	22	22	22	0
Combination CT	110	50	35	27	25	23	21	21	20	20	19	19	19	0

Lu et al, SABCS 2022

HR+/HER2- MBC: can we challenge CDK 4/6i in the first line?

SONIA trial design

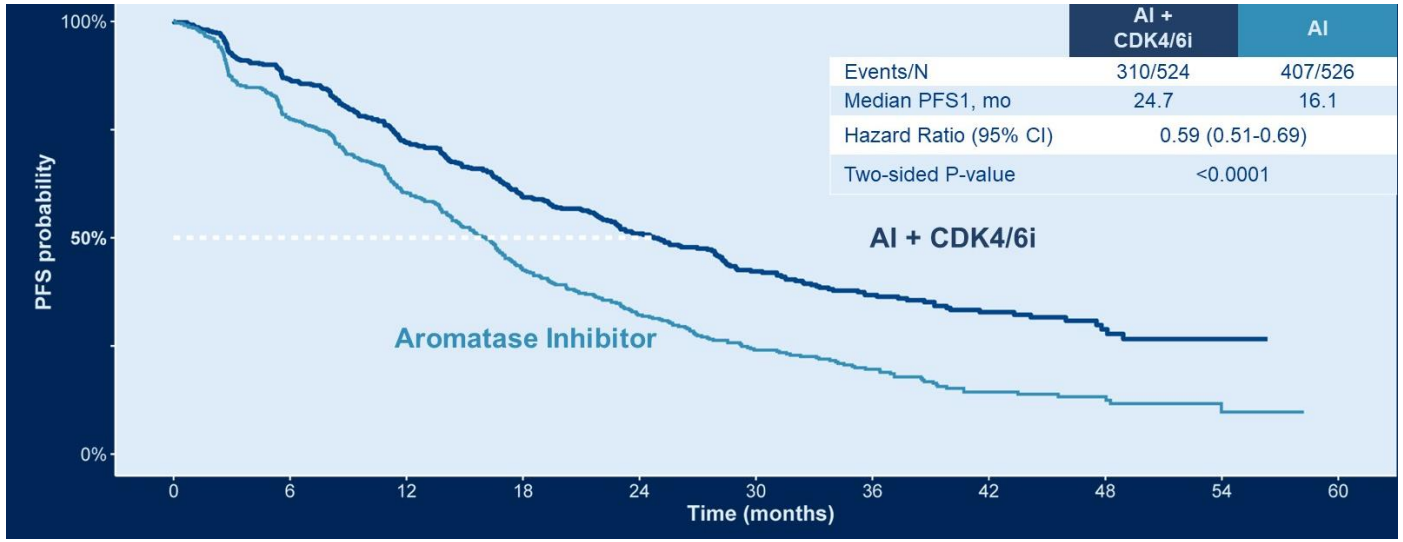
SONIA



- Tumor assessments every 12 weeks
- PFS locally assessed per RECIST v1.1
- Primary analysis planned after 574 PFS2 events
  - 89% power to detect superiority according to ESMO MCBS (HR lower limit CI ≤0.65 and Δ ≥3 months) with two-sided α=5%[1]

HR+, hormone receptor positive; HER2- , HER2 negative; ABC, advanced breast cancer; AI, aromatase inhibitor; PFS, progression-free survival
* disease-free interval after non-steroidal aromatase inhibitor >12 months. CllinicalTrials.gov (NCT03425838)
1. Cherny NI, et al. Ann Oncol 2017

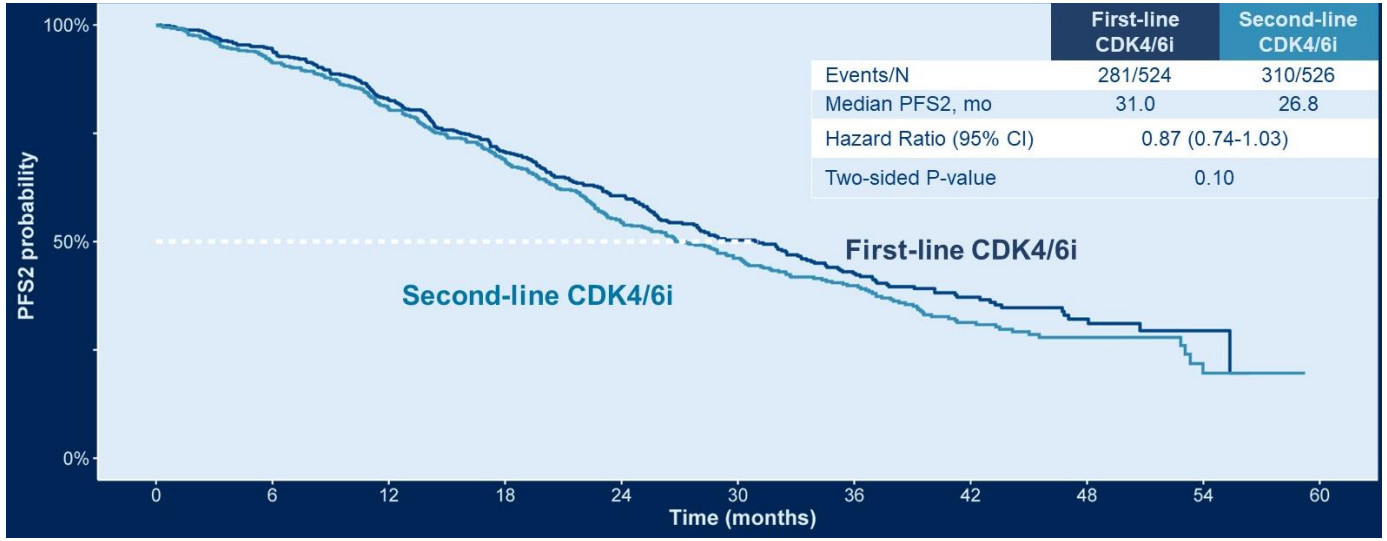
HR+/HER2- MBC: can we challenge CDK 4/6i in the first line?



PFS

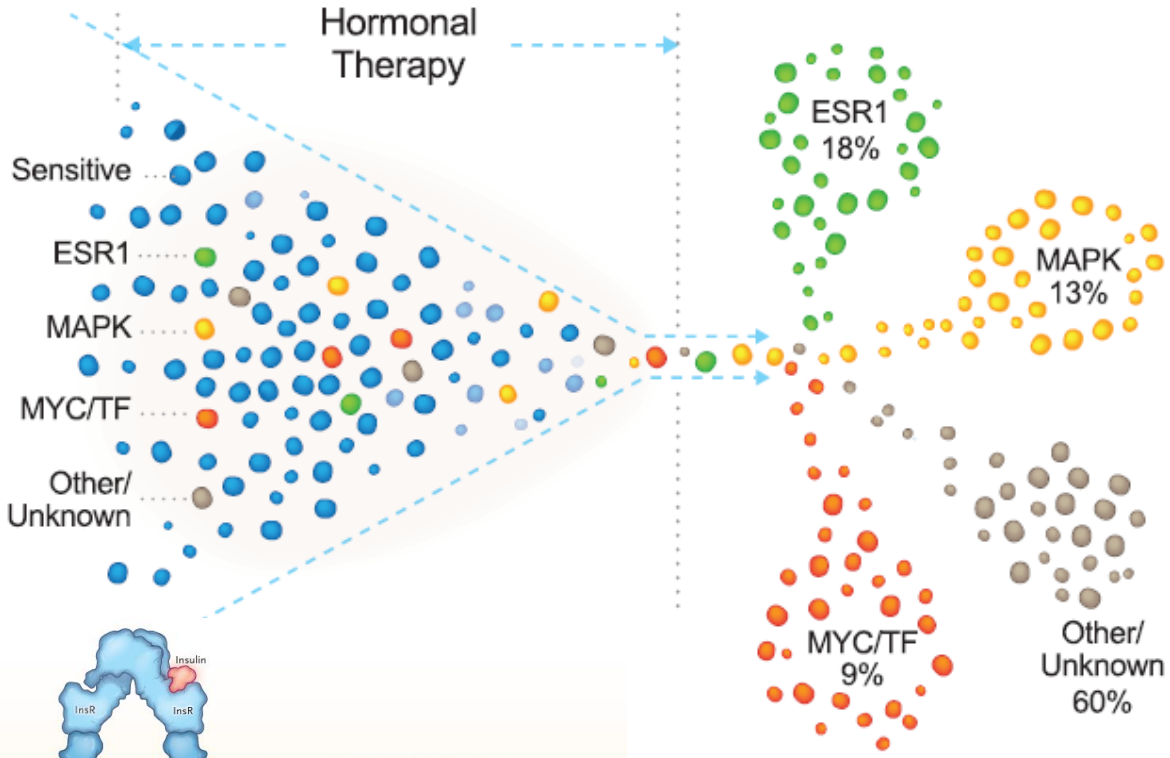
Similar OS

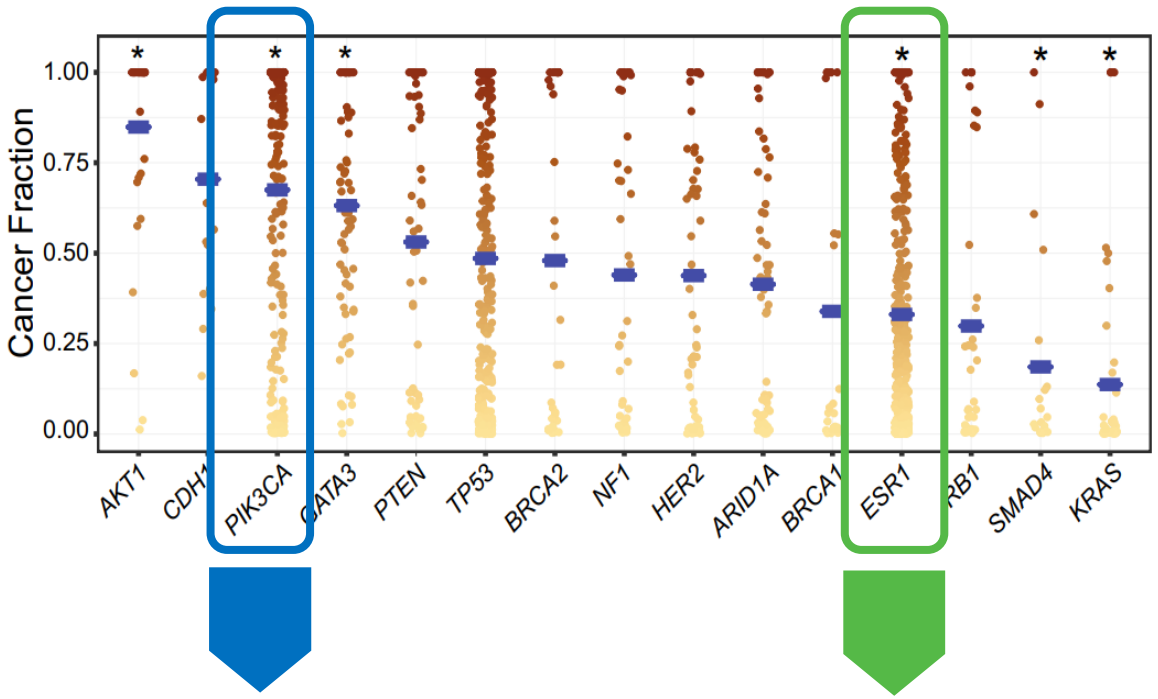
PFS2

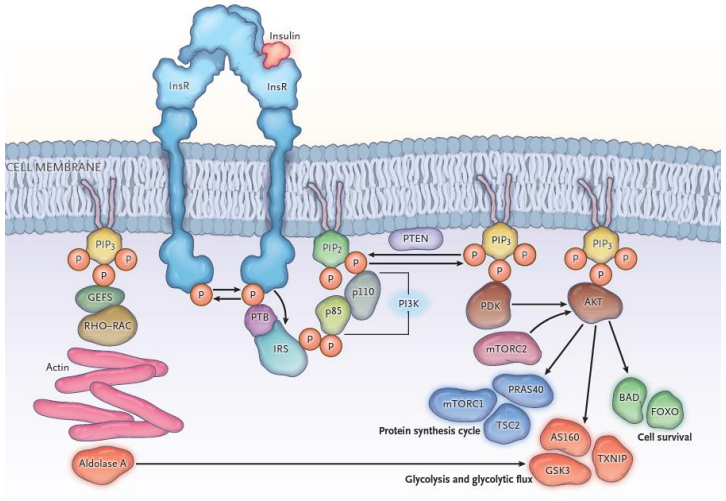


Sonke et al, ASCO 2023

Endocrine-resistance is virtually an inevitable phenomenon

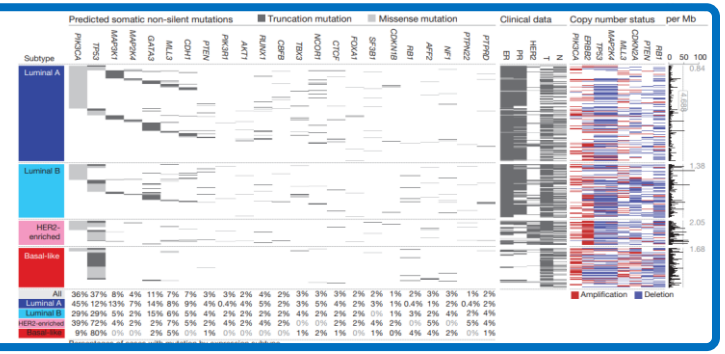






PIK3CA

30-50% of HR+/HER2- BC



ESR1 mutation

ESR1 mutant BC could define a subset of patients with ER-driven resistance

Razavi et al, Cancer Cell 2018; Toi et al, Nat Genet 2013; Kingston et al, Nat Comm, 2021; Goncalves et al, NEJM 2018; TCGA Nature 2012

HR+/HER2- MBC: PI3K-AKT-i in HR+/HER2- endocrine resistant pts

SOLAR-1 (III)

HR+/HER2- ABC
Prior ET (AI)

N=572

R

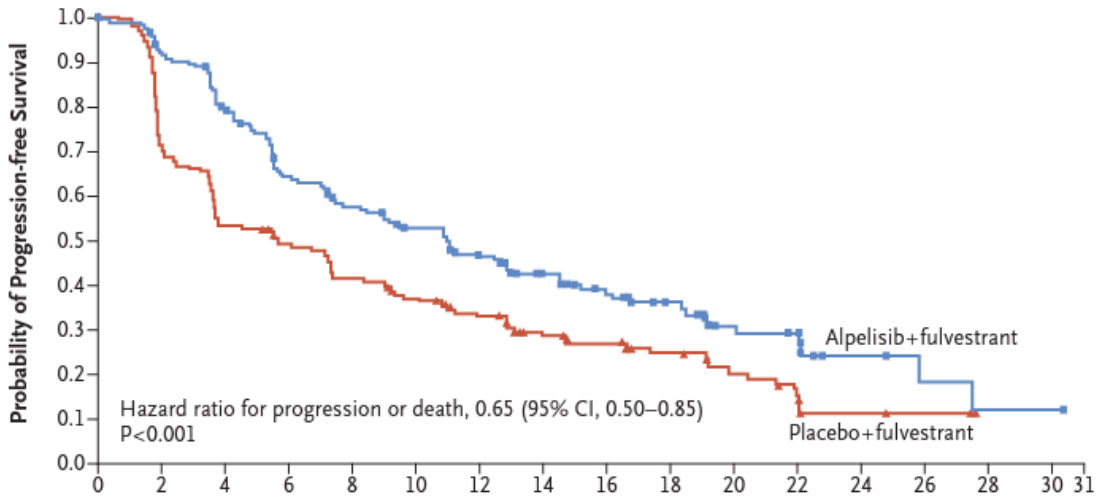
ALPELISIB
+ Fulvestrant

Placebo
+ Fulvestrant

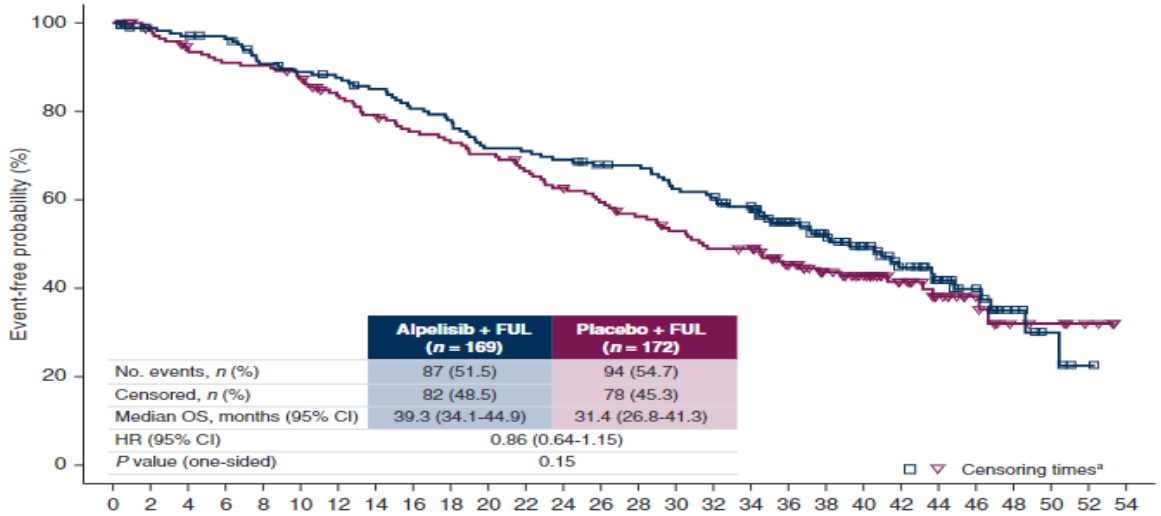
Primary endpoint: PFS in PIK3CA mutated cohort

Hyperglicemia (permanent discontinaution >6%)
rash and diarrhea

PFS in PIK3CA-mut



OS in PIK3CA-mut



	Alpelisib + FUL (*n* = 169)	Placebo + FUL (*n* = 172)
No. events, *n* (%)	87 (51.5)	94 (54.7)
Censored, *n* (%)	82 (48.5)	78 (45.3)
Median OS, months (95% CI)	39.3 (34.1-44.9)	31.4 (26.8-41.3)
HR (95% CI)	0.86 (0.64-1.15)	
P value (one-sided)	0.15	

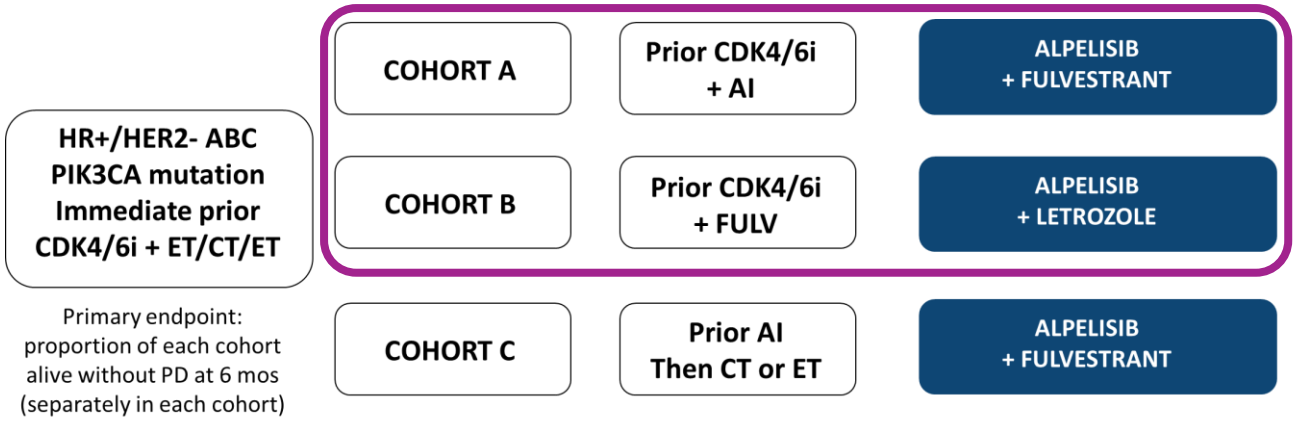
No benefit of alpelisib in the PIK3CA-WT cohort

7.9-month numeric improvement in median OS

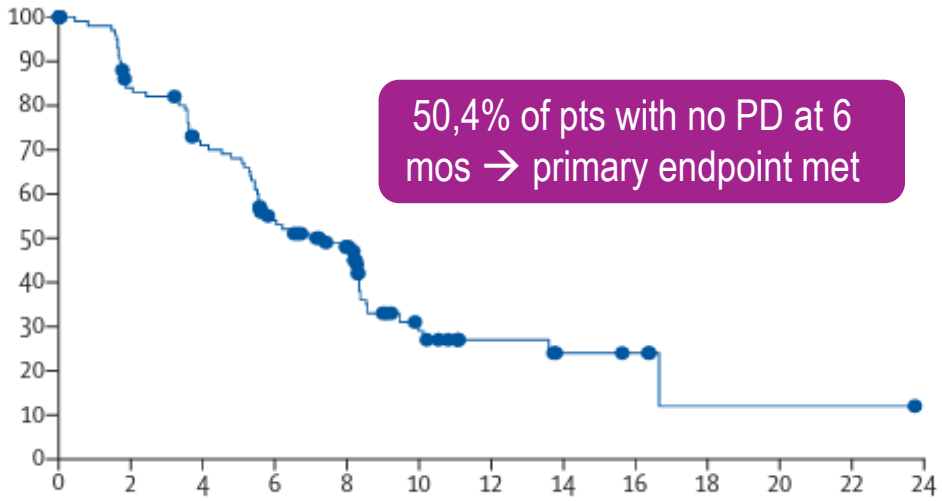
André et al, NEJM 2019, Andrè et al, Ann Oncol 2021

HR+/HER2- MBC: PI3K-AKT-i in HR+/HER2- endocrine resistant pts

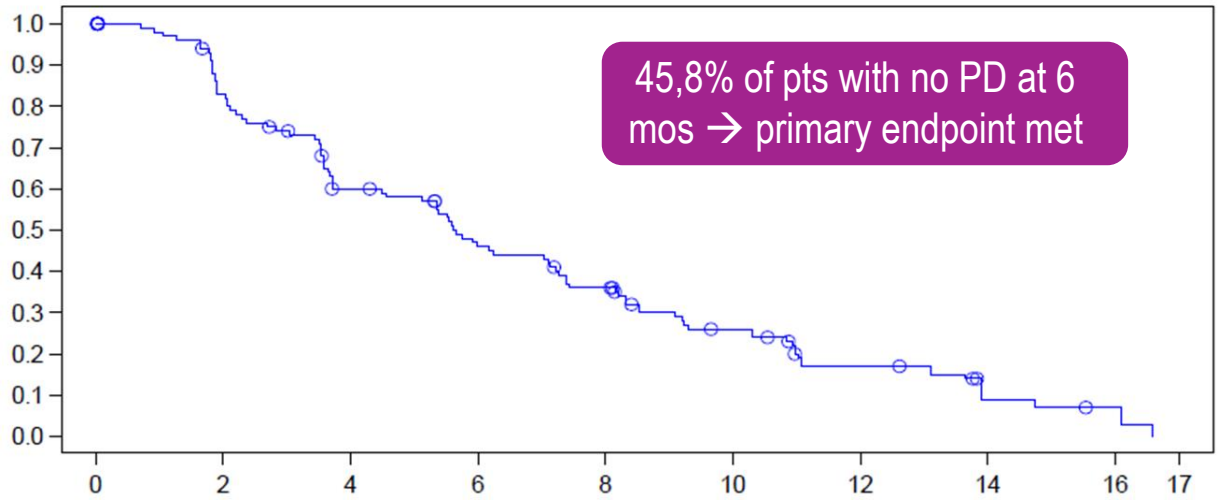
ByLIEVE (II)



PFS in Cohort A



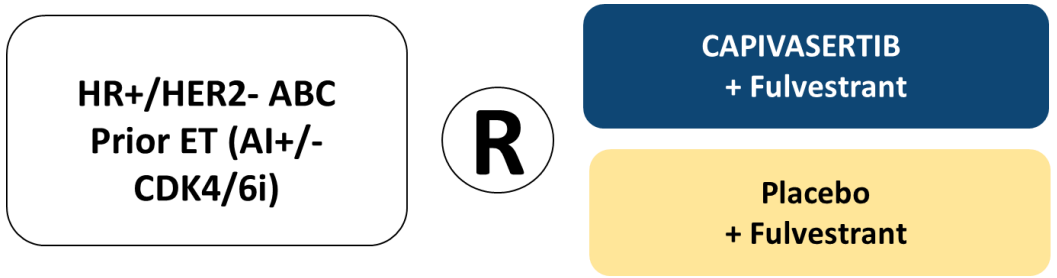
PFS in Cohort B



Rugo et al, Lancet Oncol 2021; Rugo et al, SABCS 2020

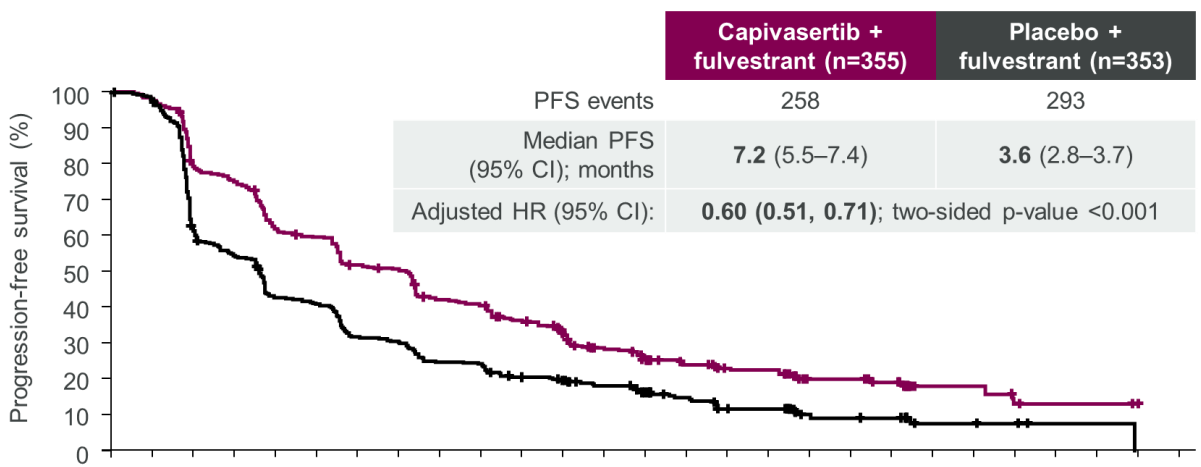
HR+/HER2- MBC: PI3K-AKT-i in HR+/HER2- endocrine resistant pts

CAPItello-291



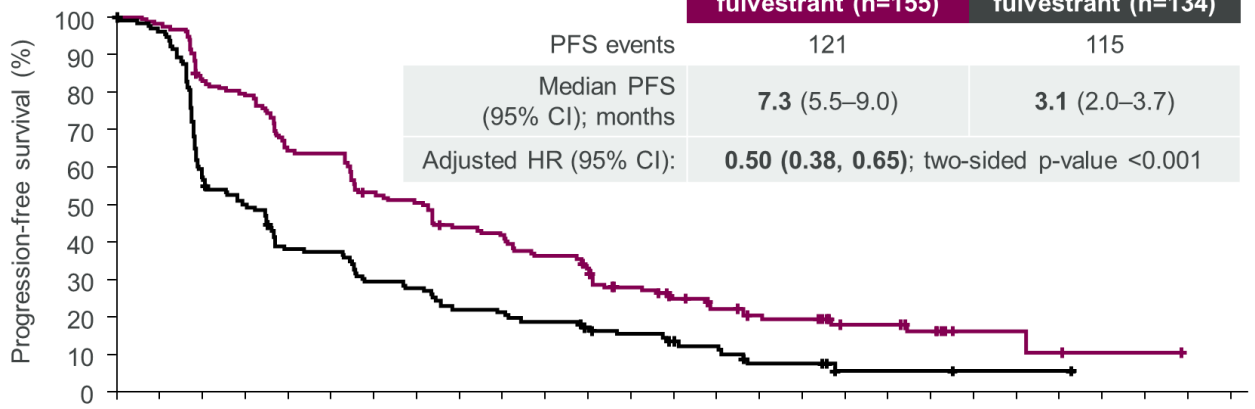
Primary endpoint: PFS in ITT and in AKT-altered

PFS in ITT



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

PFS in AKT-altered



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

Jones et al, ASCO 2022; Howell et al, Lancet Oncol 2022

HR+/HER2- MBC: oral SERDs

EMERALD	SERENA-2	AMEERA-3	acelERA
ELACESTRANT*	**CAMIZESTRANT***	**AMCENESTRANT**	**GIREDESTRANT**
vs Fulvestrant/AI	*vs* Fulvestrant	*vs* Fulvestrant/AI/tam	*vs* Fulvestrant/AI
Phase III (478)	Phase II (240)	Phase II (367)	Phase II (303)
I[ary]: PFS in ITT/ESR1+	I[ary]: PFS in ITT	I[ary]: PFS in ITT	I[ary]: PFS in ITT
Prior CDK4/6i 100%	**Prior CDK4/6i 46.6%**	**Prior CDK4/6i 78.9%**	**Prior CDK4/6i 42%**
Prior Fulvestrant 30.3%	Prior Fulvestrant 0%	Prior Fulvestrant 9.6%	Prior Fulvestrant 19%
Prior CT (≤1) 22.3%	Prior CT (≤1) 19.2%	Prior CT (≤1) 11.4%	Prior CT (≤1) 32%
Visceral 69.7%	Visceral 58.3%**	Visceral 63.8%	Visceral 68%
ESR1mut: 47.7%**	**ESR1mut***: 36.7%**	**ESR1mut*: 41.4%**	**ESR1mut: 39%**
POSITIVE (median PFS: 2.8 vs 1.9 mos)	**POSITIVE** (median PFS: 7.2-7.7 vs 3.7 mos)	**NEGATIVE** (median PFS: 3.6 vs 3.7 mos)	**NEGATIVE** (median PFS: 5.6 vs 5.4 mos)
*Elacestrant is both a ER degrader and inhibithor of estradiol-dependent ER-directed gene trascription **Gaurdant 360	*The dose of 75 mg will go forward **lung and/or liver disease ***GuardantOMNI™	*digital PCR ***AMCENESTRANT DEVELOPMENT: STOPPED***	*FoundationOne liquid CDx

Bidard et al, JCO 2022; Bardia et al, SABCS2022; Oliveira et al, SABCS2022; Tolaney et al, ESMO 2022; Martin et al, ESMO 2022

HR+/HER2- MBC: CDK 4/6i remarks

- **CDK 4/6i represent the current standard of care for the front-line therapy of HR+/HER2- BC**
  - both in postmenopausal and premenopausal setting
  - both in endocrine sensistive and endocrine resistant setting
- **In the absence of head-to-head comparisons and by acknowledging the questionability of direct cross-trial comparisons, in the everyday treatment decision process it is reasonable to base the choice across the three CDK4/6 inhibitors on:**
  - country-specific availability & regulatory/reimbursement policies
  - agent-specific toxicity spectrum falling outside the overlapping class-effect AEs
  - efficacy information progressively maturing and getting released, especially in terms of OS impact
    - possible confounding role of treatment crossover and post-progression therapies → possible mitigation of the peremptoriness of not statistically significant OS results
- **Evolving scenario**
  - Challenging the role of CT even in highly symptomatic patients
  - Not all patients may need CDK 4/6i in the first-line → be aware of finencial toxicity

HR+/HER2- MBC: beyond CDK 4/6i

- **The clinical value of PI3Ki inhibitors in PIK3CA mutated patients with endocrine-resistant disease is established**
  - The regulatory scenario of alpelisib (+fulv) currently precludes patients with PIK3CA-mutated disease progressing to AI+CDK4/6i to get access to this treatment strategy → since almost all patients receive CDK 4/6i in the first-line setting, alpelisib + fulv is only a virtual option, with no actual clinical positioning → waiting for EPIK-B5 trial
- **The CAPITELLO trial (III) demonstrated the clinical value of capivasertib (+fulv) in endocrine-resistant patients, including those pre-treated with CDK 4/6i**
- **Oral SERDs are going to represent an option in patients for whom endocrine-resistance is driven (at least in part) by ESR1 mut.**

Grazie

Federica Miglietta