

XV SIMPOSIUM BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

17, 18 Y 19 DE MAYO DE 2023



Inhibidores de Ciclinas en el tratamiento del CMM luminal. Supervivencia, calidad de vida y mucho más



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Disclosure Slide

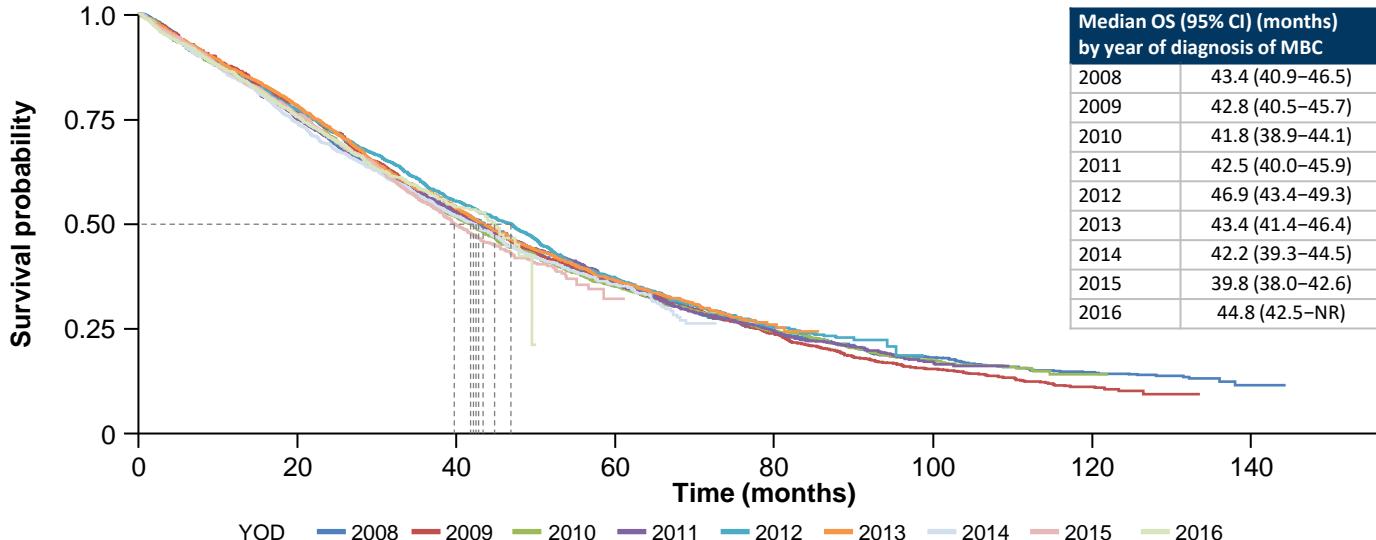
- **Scientific advisory board fees:** Novartis, Pfizer, Lilly
- **Consultancy training fees:** Roche, Novartis, MSD
- **Honoraria fees:** Roche, Novartis; Pfizer

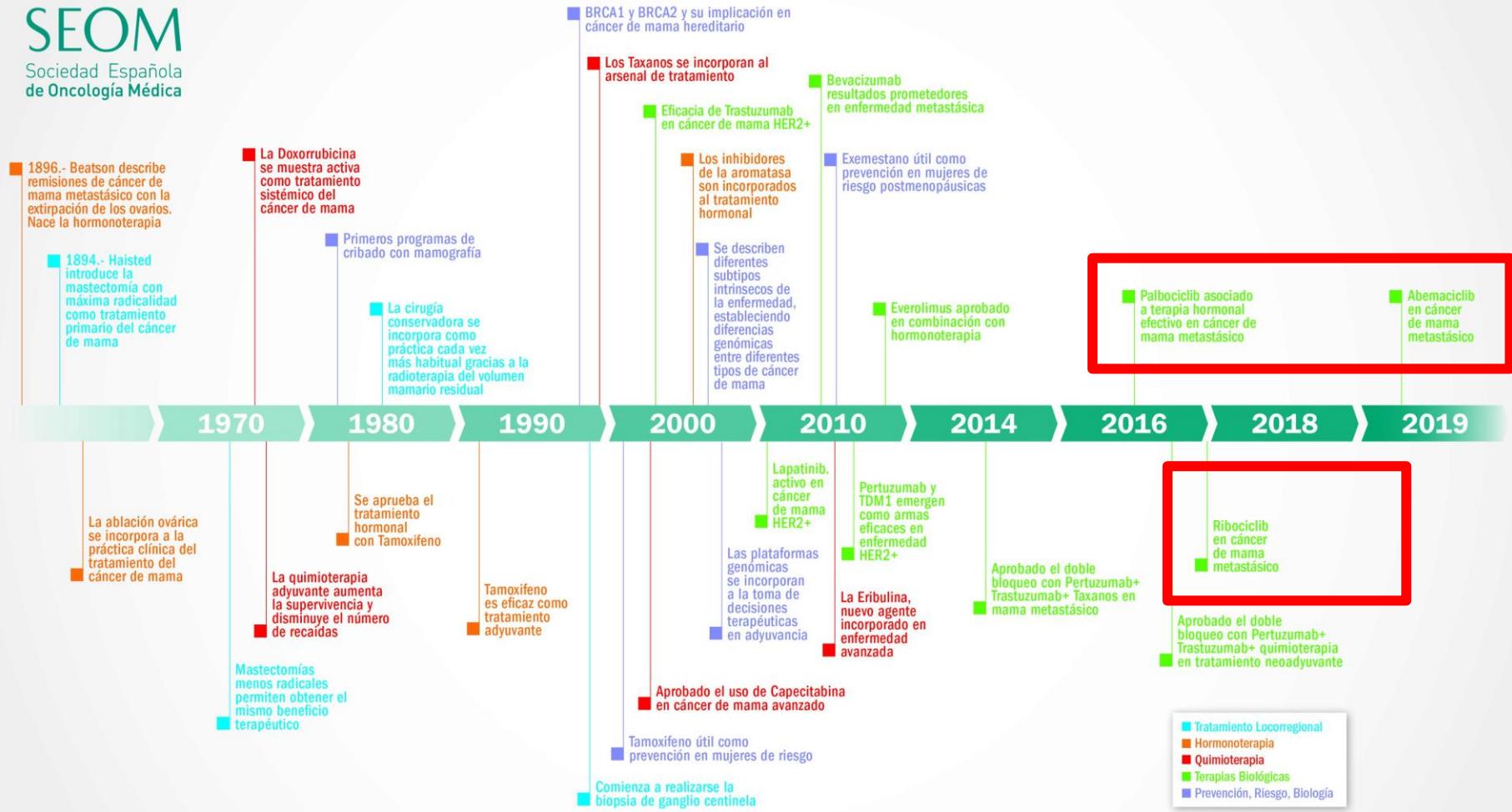


De dónde venimos??

2008–2017 – 18 French Cancer Centers

Overall survival in the HR+/HER2– subcohort according to the YOD
Based on KM estimates





¿Son todos los iCDK4/6 iguales?





¿Son todos los iCDKs iguales?

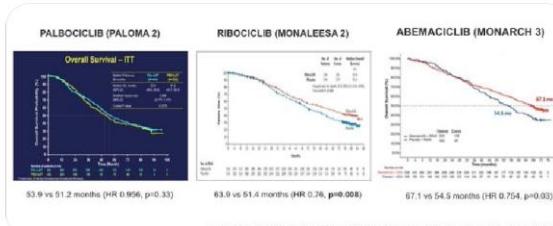
💊 CDK 4/6 inhibitors

OS results p3 recently reported

⭐ PALOMA2 (palbociclib): 🙅 significant OS advantage

⭐ MONALEESA2 (ribociclib): 🙌 significant OS advantage

⭐ MONARCH3 (abemaciclib): data immature, non-significant OS improvement



Finn RS et al. ASCO 2022; Hortobagyi GN et al. New Eng J Med 2022; Goetz M et al ESMO 2022

3

5

12

2.634



Paolo Tarantino @PTaranti... · 01 mar.

En respuesta a @PTarantinoMD

@TumorBoardTues y a @drsarahsam

12/24 #TumorBoardTuesday

骺 Mini tweetorial 5 🧑

💊 CDK 4/6 inhibitor

Despite similar PFS efficacy, three CDK4/6 inhibitors differ in toxicity profile

💊 Palbociclib: more neutropenia

💊 Ribociclib: more ↑ LFT

💊 can cause prolong QTc

💊 Abemaciclib: more GI tox, ↓ neutropenia

2

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Recomendable....

The dilemma of selecting a first line CDK4/6 inhibitor for hormone receptor-positive/HER2-negative metastatic breast cancer

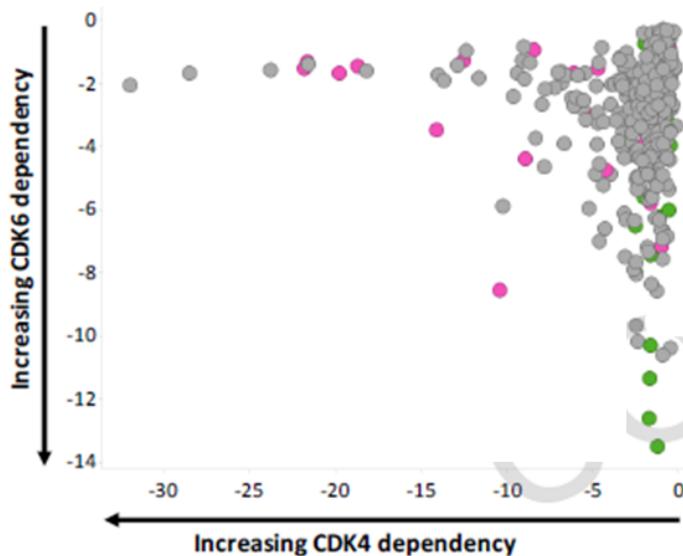
Albert Grinshpun ^{1,2,3}, Sara M. Tolaney ^{1,2,3}, Harold J. Burstein ^{1,2,3}, Rinath Jeselsohn ^{1,2,3} and Erica L. Mayer ^{1,2,3}

The combination of an endocrine agent with a CDK4/6 inhibitor is the standard of care in the first-line setting for patients with hormone receptor-positive, HER2-negative metastatic breast cancer. Randomized trials have demonstrated similar and significant improvements in progression-free survival using the three available CDK4/6 inhibitors and led to regulatory approval. However, mature overall survival data now suggest potential differences among the various agents, suggesting an evolution in selection preferences.

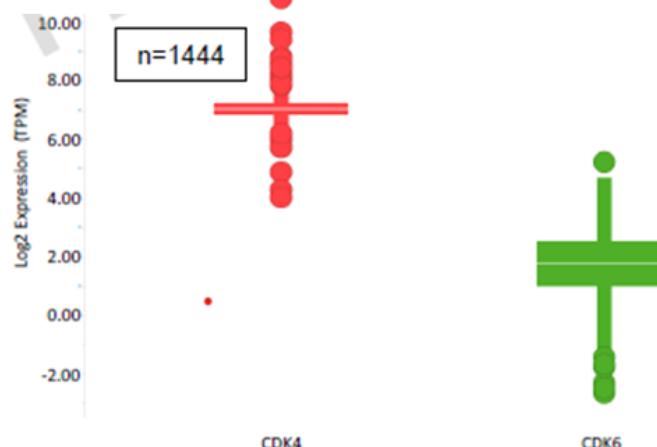
npj Breast Cancer (2023)9:15 ; <https://doi.org/10.1038/s41523-023-00520-7>

CDK4 juega un papel más importante que CDK6 en el CM

Breast cancer tumor-derived cell lines
are often uniquely CDK4-dependent

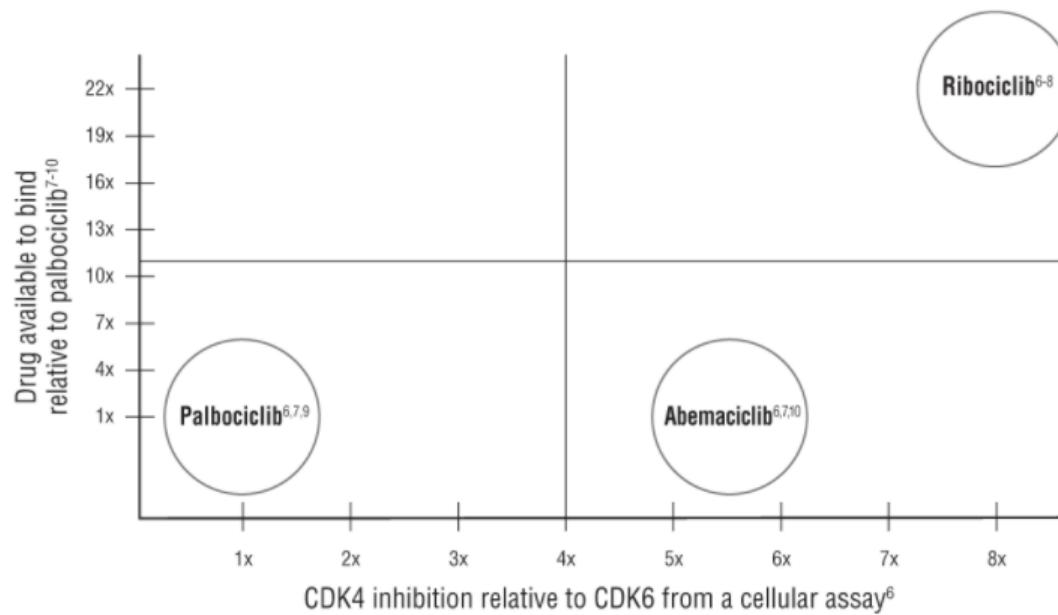


CDK4 mRNA is expressed at significantly
higher levels than CDK6 in ER+ BC



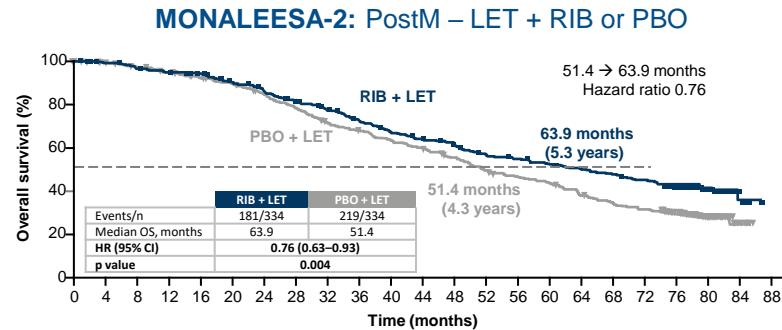
ICDK4/6 tienen actividad diferente sobre CDK4 y CDK6

Ribociclib tiene mayor inhibición sobre CDK4 que sobre CDK6 (x8 que palbociclib)
Ribociclib tiene mayores niveles de fármaco libre (x22)

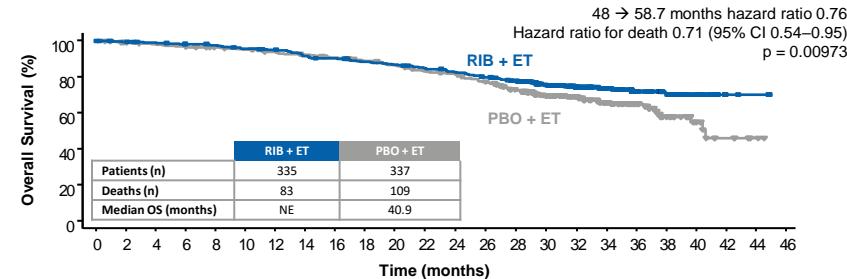


ICDK4/6: ¿Beneficio en Supervivencia Global?

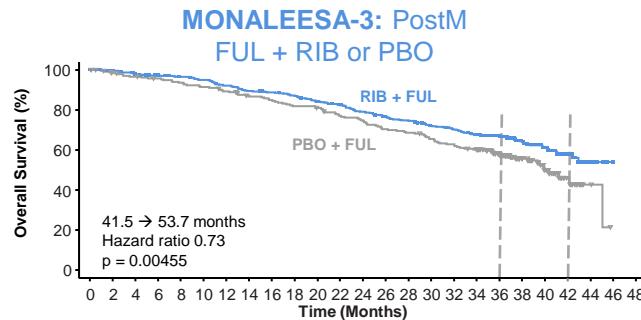
First line (median OS)



MONALEESA-7: PreM – Gos + NSAI/Tam + RIB or PBO



Second line or mixed (median OS)





¿Depende de la situación?

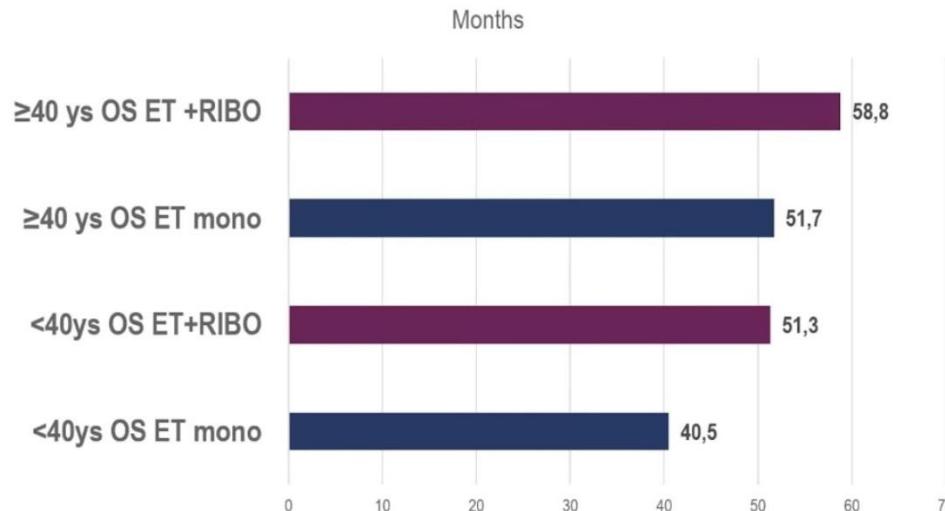


Eficacia en TODOS los Subgrupos

- Según Edad / Estado menopáusico
- Según Afectación visceral
- Según Criterios Hormono-sensibilidad
- Según Factores Biológicos

M-7: Subgrupos edad

PRESENTED MEDIAN OS RESULTS FROM THE ML-7 STUDY



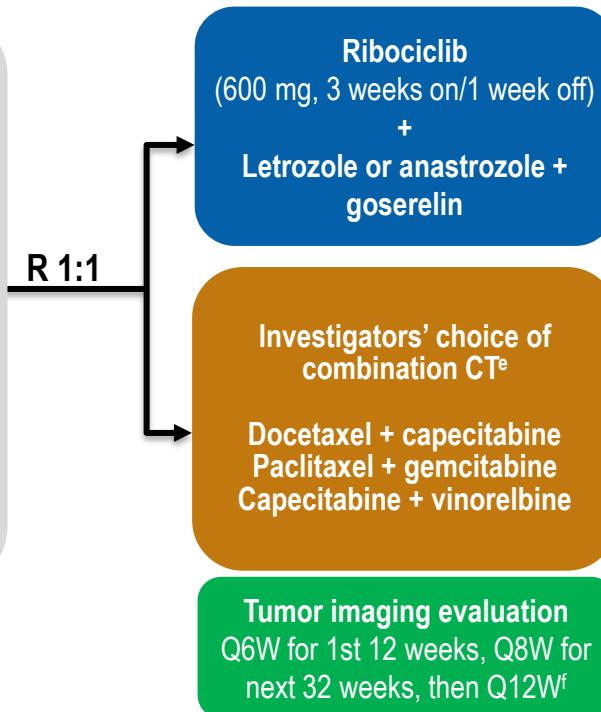
Eficacia en TODOS los Subgrupos

- Según Edad / Estado menopáusico
- **Según Afectación visceral**
- Según Criterios Hormono-sensibilidad
- Según Factores Biológicos

RIGHT Choice study design

- 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



ABC, advanced breast cancer; CBR, clinical benefit rate; CT, chemotherapy; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor positive; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QOL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response; ULN, upper limit of normal.
^a Where combination CT is clinically indicated by physician's judgment; ^b For patients with ECOG 2, the poor performance status should be due to breast cancer; ^c Patients were enrolled from Feb 2019 to Nov 2021; ^d Disease-free interval is defined as the duration from date of complete tumor resection for primary breast cancer lesion to the date of documented disease recurrence; ^e If one of the combination CT drugs had to be stopped because of toxicity, the patient was allowed to continue on the other, better-tolerated CT drug (monotherapy); ^f Until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision, and at end of treatment.

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

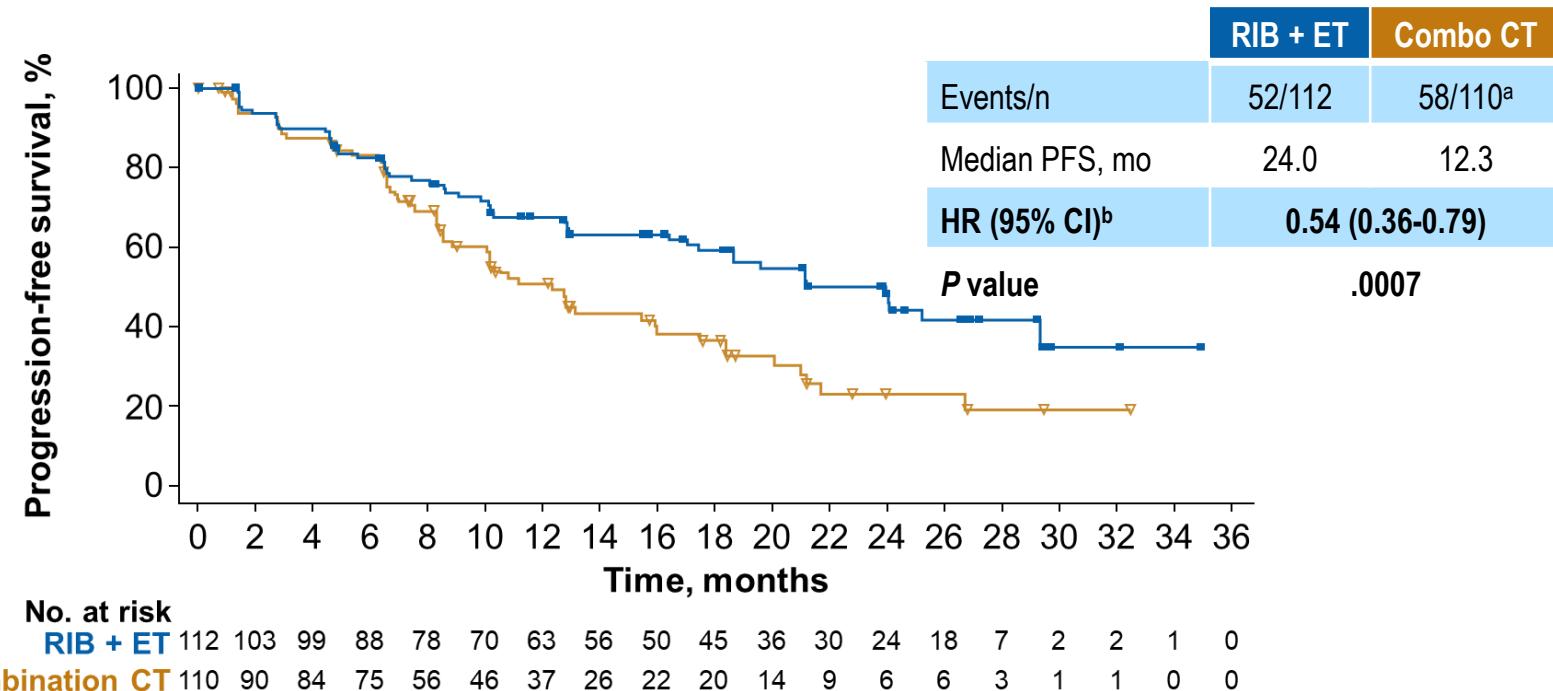
RIGHT Choice Baseline characteristics

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110	Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Median age, years	44.0	43.0	Disease status		
≥40 years	80 (71.4)	72 (65.5)	De novo	71 (63.4)	73 (66.4)
Race ^a			Visceral metastatic sites ^b		
Asian	60 (53.6)	58 (52.7)	Liver	56 (50.0)	57 (51.8)
White	51 (45.5)	52 (47.3)	Lung	63 (56.3)	58 (52.7)
Histological grade			Liver or lung	89 (79.5)	85 (77.3)
Grade 1	10 (8.9)	16 (14.5)	Aggressive disease characteristic		
Grade 2	66 (58.9)	61 (55.5)	Rapid progression	23 (20.5)	18 (16.4)
Grade 3	35 (31.3)	29 (26.4)	Symptomatic non-visceral disease	15 (13.4)	16 (14.5)
≥50% ER+	95 (84.8)	95 (86.4)	Symptomatic visceral metastases	74 (66.1)	76 (69.1)
PR+	99 (88.4)	102 (92.7)	Visceral crisis ^c	61 (54.5)	55 (50.0)

Combo CT, combination chemotherapy; ER+, estrogen receptor positive; ET, endocrine therapy; RIB, ribociclib.

^aOne patient (0.9%) in the RIB arm was African American; ^bThe same patient may have multiple visceral metastatic sites. ^cBased on PI's judgment, which followed ABC3 and NCCN guidelines, which were available at the time of study design.

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



ABC, advanced breast cancer; Combo CT, combination chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; HR, hazard ratio; IRT, interactive response technology; PFS, progression-free survival; RIB, ribociclib.

^a Ten patients in CT arm did not receive any treatment; ^b HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT.

Eficacia en TODOS los Subgrupos

- Según Edad / Estado menopáusico
- Según Afectación visceral
- **Según Criterios Hormono-sensibilidad**
- Según Factores Biológicos



¿Qué hacer en 1^a línea?

Renata Arakelian @RenataArakelian

Replying to @PTarantinoMD and @AlbertGrinshpun @AlbertGrinshpun, what are your considerations about abema X ribo in 1 line?

6:31 AM · 23 Mar 23 · 60 Views

Followed by some Tweeters you follow

Albert Grinshpun @AlbertGrinshpun · 1h

Replying to @RenataArakelian and @PTarantinoMD

Until monarch-3 data is out, probably ribo

Renata Arakelian @RenataArakelian · 1h

Thank you! Looking forward to your answer after monarch-3 publication!



Paciente con CMm HER2-negativo y posmenopáusicas o premenopáusicas que reciben ablación o supresión ovárica	
PAUTAS PREFERIDAS	OTRAS PAUTAS RECOMENDADAS
<p>Tratamiento de primera línea</p> <ul style="list-style-type: none">• Inhibidor de la aromatasa + inhibidor de CDK4/6^a<ul style="list-style-type: none">- Inhibidor de la aromatasa + ribociclib (categoría 1)^c- Inhibidor de la aromatasa + abemaciclib- Inhibidor de la aromatasa + palbociclib• Fulvestrant^d + inhibidor de CDK4/6^a<ul style="list-style-type: none">- Fulvestrant + ribociclib (categoría 1)^c- Fulvestrant + abemaciclib (categoría 1)^c- Fulvestrant + palbociclib	<p>Tratamiento de primera línea y/o de líneas posteriores</p> <ul style="list-style-type: none">• Degradador selectivo del receptor de estrógeno (SERD)<ul style="list-style-type: none">- Fulvestrant^e- Para los tumores con mutación en <i>ESR1</i>, ver BINV-Q (6)• Degradador selectivo del receptor de estrógeno^f• Inhibidor no esteroideo de la aromatasa<ul style="list-style-type: none">- Anastrozol- Letrozol• Modulador selectivo de los RE<ul style="list-style-type: none">- Tamoxifeno• Inactivador esteroideo de la aromatasa<ul style="list-style-type: none">- Exemestano
<p>Tratamiento de segunda línea y posteriores</p> <ul style="list-style-type: none">• Fulvestrant + inhibidor de CDK4/6 (abemaciclib, palbociclib o ribociclib) si no se ha utilizado previamente un inhibidor de CDK4/6 (categoría 1)^g• Para los tumores con mutación en <i>PIK3CA</i>, consultar las opciones adicionales del tratamiento dirigido; ver BINV-Q (6)^h• Everolimus + tratamiento endocrino (exemestano, fulvestrant, tamoxifeno)ⁱ	<p>ÚTIL EN DETERMINADAS CIRCUNSTANCIAS</p> <p>Tratamiento de líneas posteriores</p> <ul style="list-style-type: none">• Acetato de megestrol• Estradiol• Abemaciclib^j• Opciones adicionales de tratamiento dirigido, ver BINV-Q (6)

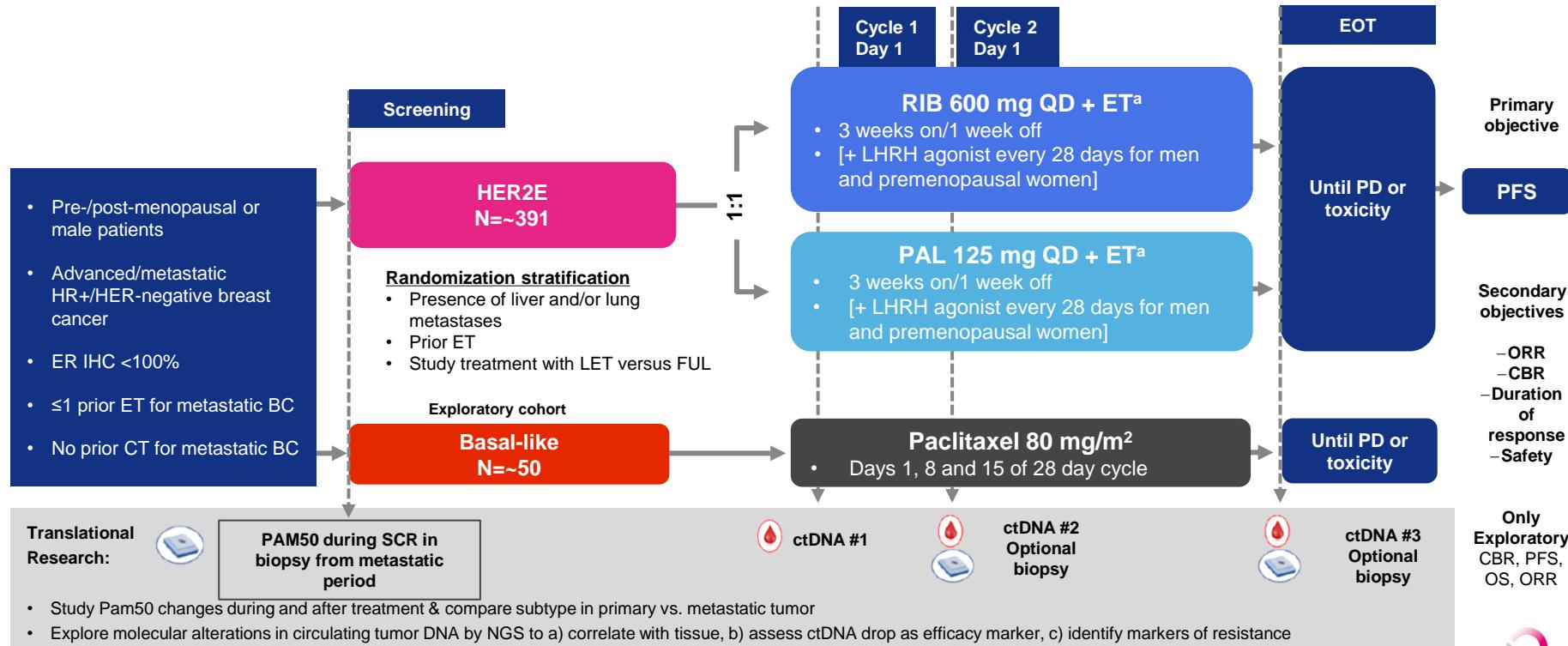
Las guías NCCN® diferencian ribociclib (KISQALI®) como la única opción de tratamiento de primera línea preferida con Categoría 1 en combinación con un IA para pacientes con CMm RH+/HER2-.¹

Eficacia en TODOS los Subgrupos

- Según Edad / Estado menopáusico
- Según Afectación visceral
- Según Criterios Hormono-sensibilidad
- **Según Factores Biológicos**

HARMONIA - a Solti sponsored H2H trial in collaboration with AFT and NVS

This international, multicenter, open-label Phase III trial will be conducted in men and pre-/post-menopausal women with HR+/HER2-, non-luminal BC who have not received any prior chemotherapy agent for the treatment of advanced disease



^aFor premenopausal women and men: LET 2.5 mg (orally QD) for 28 days OR FUL 500 mg (intramuscularly two injections) on days 1, 15, 29 and once monthly thereafter; for postmenopausal women: LET 2.5 mg (orally QD) for 28 days OR FUL 500 mg (intramuscularly two injections) on days 1, 15, 29 and once monthly thereafter.

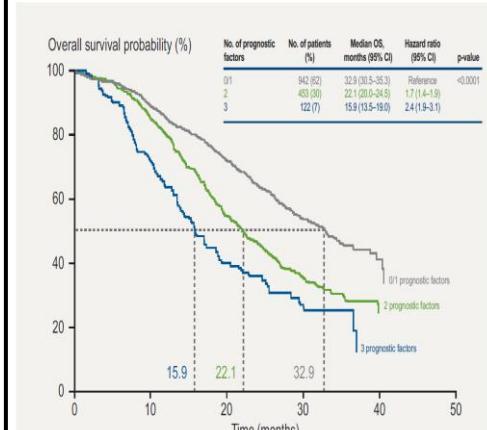
ABC, advanced breast cancer; BC, breast cancer; CT, chemotherapy; ET, endocrine therapy; EOT, end of trial; ER, estrogen receptor; FUL, fulvestrant; HER2E, HER2-enriched; HR, hormone-receptor; IHC, immunohistochemistry; LET, letrozole; PD, disease progression; QD, once daily; RIB, ribociclib



¿Cómo tratamos las recidivas en curso de HT adyuvante?

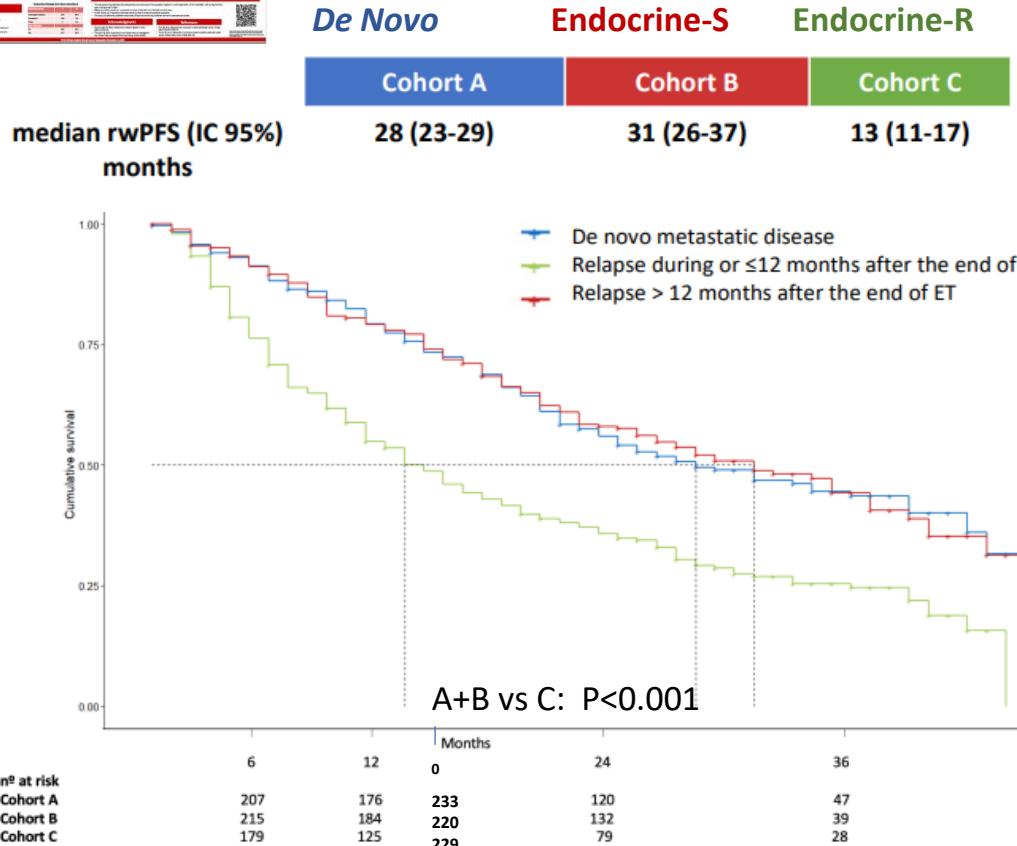
Enfermedad Luminal... ¿Mal Pronóstico?

Figure 5. Overall survival in the hormone receptor-positive subgroup (n=1517) according to number of prognostic factors present



- Poor-prognosis population if at least two of the following criteria:
 - Liver involvement and/or ≥ 3 metastatic sites
 - Prior neo/adjuvant anthracyclines and/or taxanes
 - DFI ≤ 24 months

De Nov2017-Nov2019, 762 pacientes, 80% >50 años,
30% IV de novo, 78% postmenop, 55% viscerales , TFI<12 meses 30%



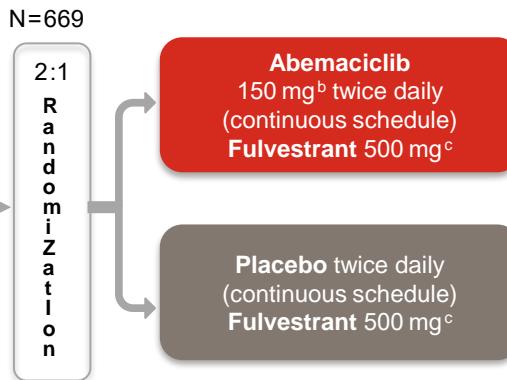
- PalboSPAIN is the most extensive European RWD study of Palbociclib in 1st line therapy
- The median rwPFS times are generally consistent PALOMA-2
 - 24m (CI 95%: 21-27) in the entire population.
 - 28m (CI 95%: 23-39) in **de novo** cohort.
 - 31m (CI 95%: 26-37) in patients with **>12months** Treatment Free Interval (TFI)
 - 13m (CI 95%: 11-17) in population with **≤12monthsTFI**
- OS is still immature
- Safety profile agrees with previous data.
- Number of patients with reductions are higher than in PALOMA2 but without impacting negatively on rwPFS.



MONARCH-2 Study design

Inclusion Criteria

- ER+/HER2- MBC
- Pre/peri^a or postmenopausal
- ET resistant:
 - Relapsed on neoadjuvant or on/within 1 yr of adjuvant
 - Progressed on first-line ET
- No chemo for MBC
- No more than 1 ET for MBC
- ECOG PS ≤1



Primary endpoint:

Investigator-assessed PFS

Secondary endpoints:

OS, response, clinical benefit rate, safety

Stratification factors:

- Metastatic site
- ET resistance (primary vs secondary)^{2,3}

Study Population at Baseline¹:

- Bone-only disease – 27%
- Visceral disease – 56%
- Primary ET resistance – 25%
- De novo metastatic – 20%



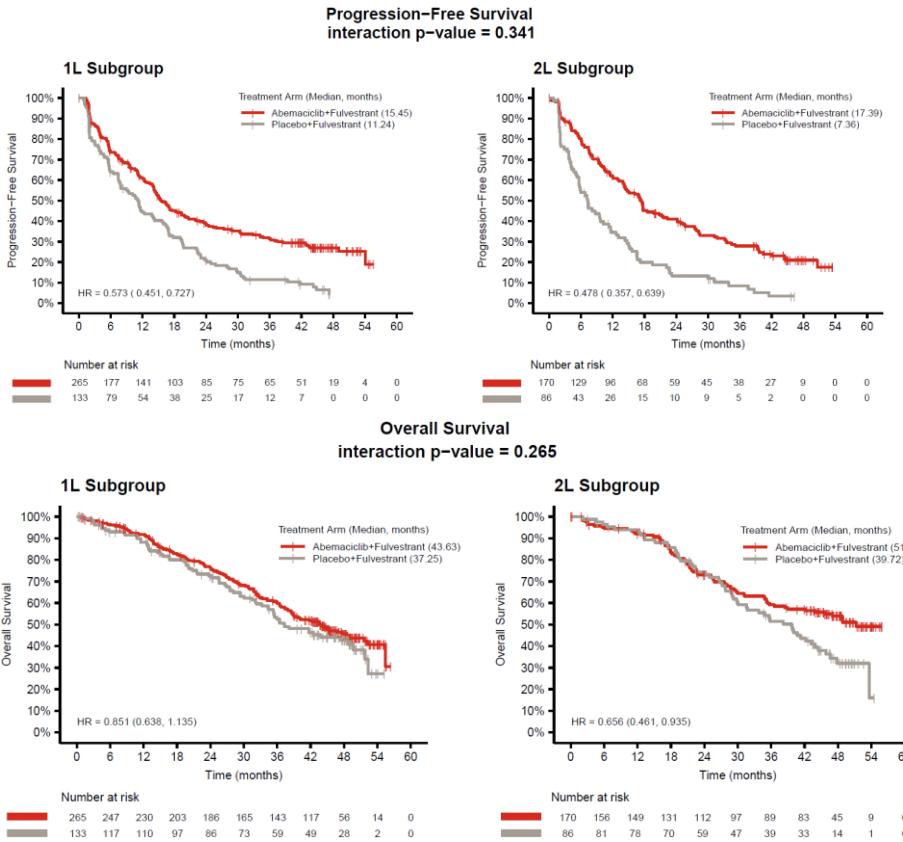
MONARCH-2 First Line Patients

n (%)	Abemaciclib + Fulvestrant N=446	Placebo + Fulvestrant N=223		
Most Recent line of endocrine therapy				
1L Subgroup	265 (59.4)	133 (59.6)		
2L Subgroup	170 (38.1)	86 (38.5)		
n (%)	1L Subgroup	2L Subgroup		
	Abemaciclib + Fulvestrant N=265	Placebo+ Fulvestrant N=133	Abemaciclib + Fulvestrant N=170	Placebo+ Fulvestrant N=86
Metastatic site^a				
Visceral	147 (55.5)	78 (58.6)	95 (55.9)	49 (57.0)
Bone only	77 (29.1)	36 (27.1)	44 (25.9)	20 (23.3)
Other ^b	41 (15.5)	19 (14.3)	31 (18.2)	17 (19.8)
Endocrine therapy resistance^a				
Primary ^c	71 (26.8)	39 (29.3)	39 (22.9)	18 (20.9)
Secondary ^d	194 (73.2)	94 (70.7)	131 (77.1)	68 (79.1)



MONARCH-2 First Line PFS /OS

1. Neven P et al. MONARCH 2: subgroup analysis of patients receiving abemaciclib + fulvestrant as first- and second-line therapy for HR+, HER2- advanced breast cancer (Abstract Number 1061). 2020 ASCO

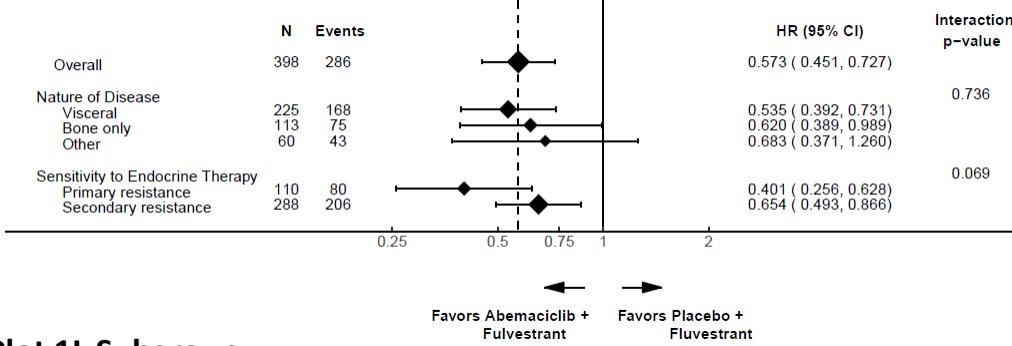


*Analyses were not adjusted for multiplicity, and the study was not powered to test the effect of Verzenios + fulvestrant among subgroups.

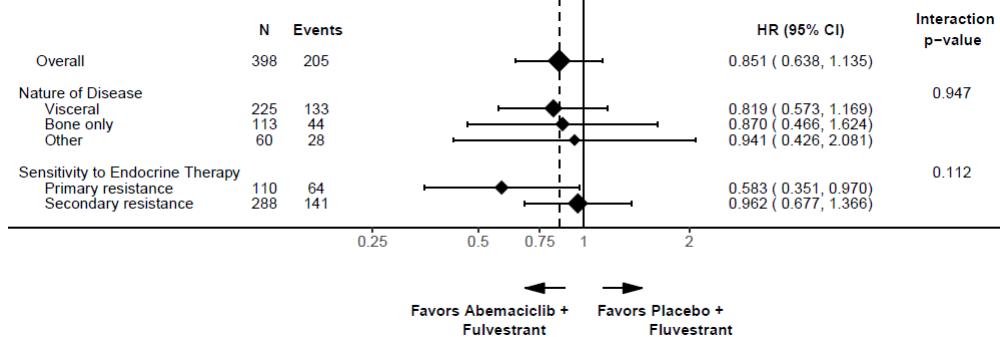


MONARCH-2 First Line PFS /OS

PFS Forest Plot 1L Subgroup



OS Forest Plot 1L Subgroup





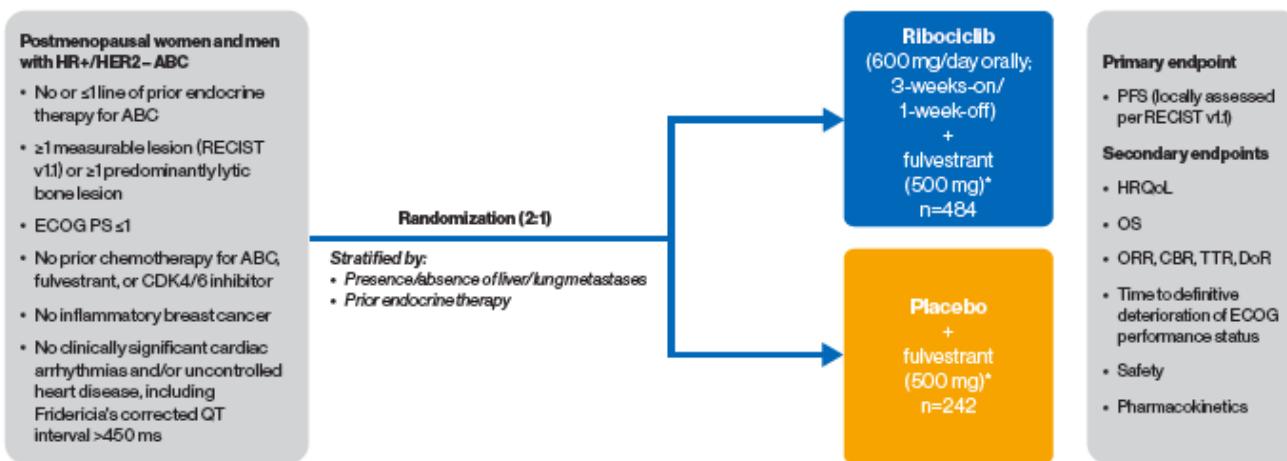
ML 2-3-7 Early Relapse Subgroup

ESTUDIO	ML-2	ML-3	ML-7
% PACIENTES RECIDIVA EN CURSO ADYUVANCIA / FIN<12 M	18%	28.3%	30%

460 PACIENTES CON RECIDIVA EN CURSO ADYUVANCIA / FIN <12 M FUERON TRATADAS CON RIBOCICLIB EN LOS ESTUDIOS MONALEESA



ML 3 Early Relapse subgroup



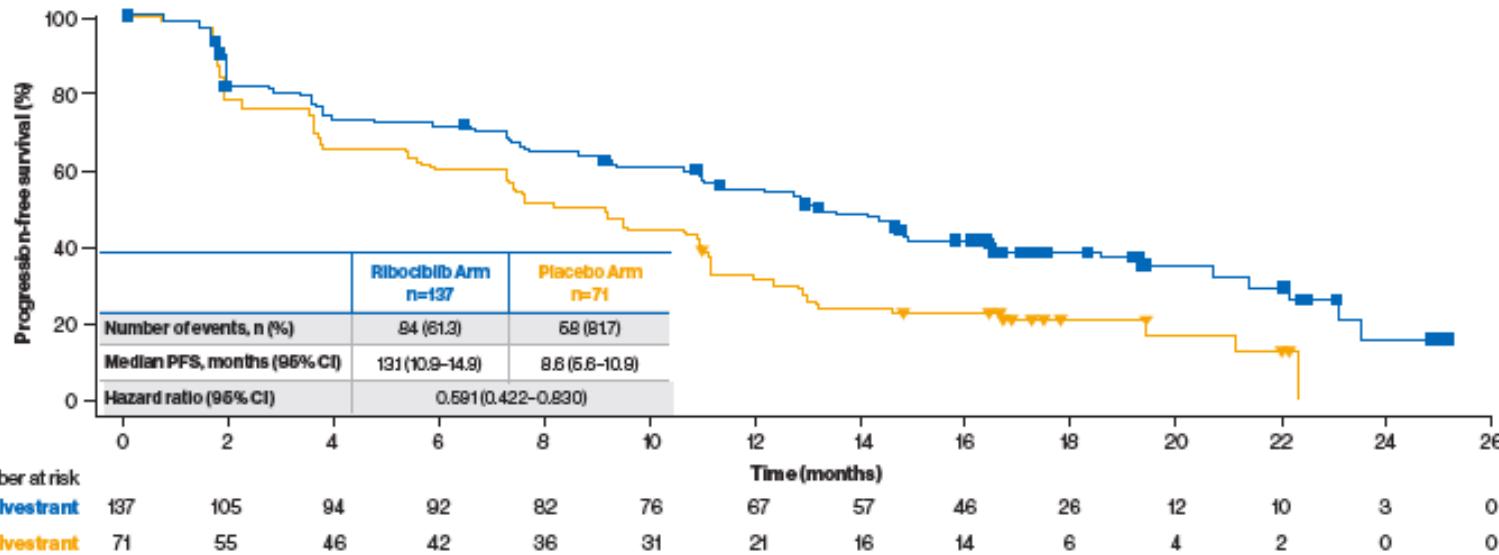
ABC, advanced breast cancer; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinases 4 and 6; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; HRQoL, health-related quality of life; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

*Fulvestrant was administered intramuscularly on Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of every 28-day cycle thereafter.

- Early relapse subgroup: patients with disease that relapsed on or ≤12 months from completion of (neo)adjuvant endocrine therapy.



ML 3 Early Relapse subgroup



In the early relapse setting alone, median PFS was 13.1 months (95% CI: 10.9–14.9) for the ribociclib + fulvestrant arm vs 8.6 months (95% CI: 5.6–10.9) for the placebo + fulvestrant arm (hazard ratio: 0.591; 95% CI: 0.422–0.830);

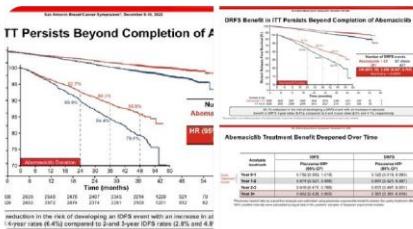


¿Cómo trataremos las recidivas tras iCDK4/6 adyuvante?



Hope Rugo @hoperugo · 06 dic. 22

#SABCS2022 MonarchE 42 mo FU data presented by Johnston with ongoing greater benefit - suggesting a marked carryover effect. Great for our patients! Honored to participate. [@OncoAlert](#)



1



14



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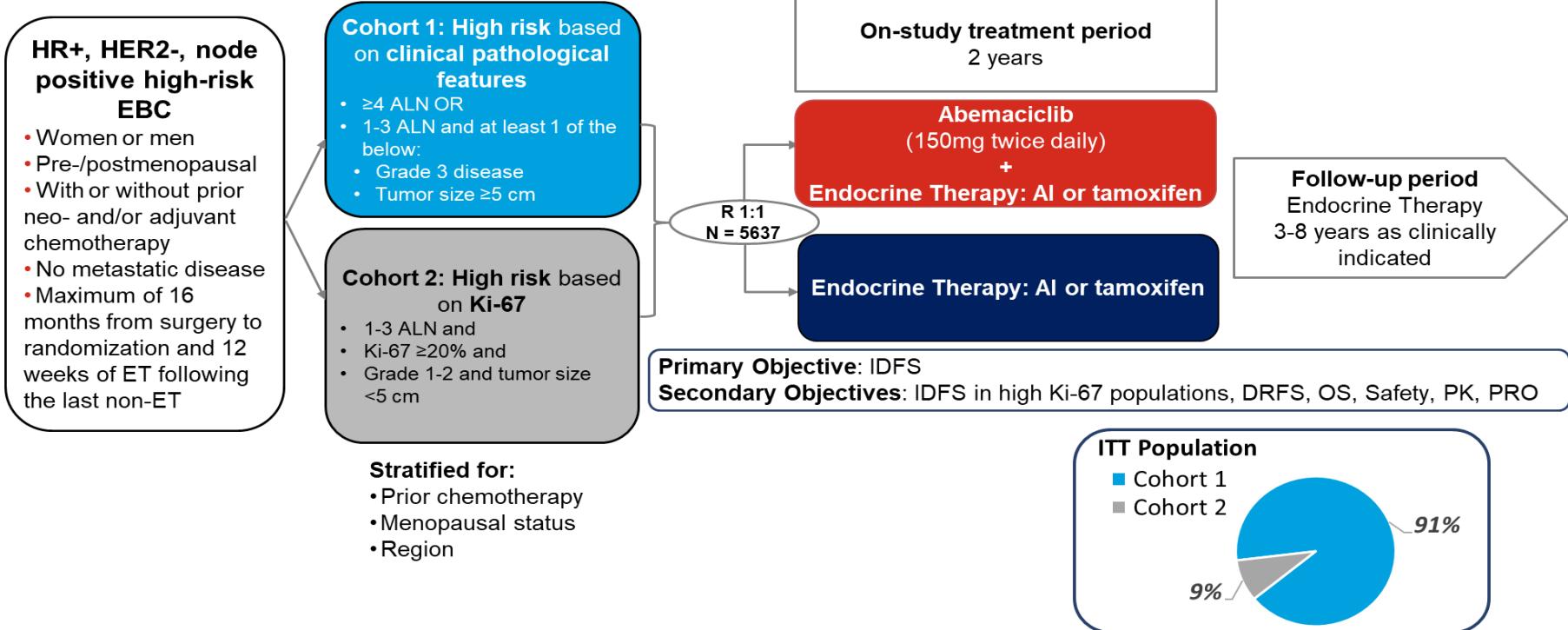


Lucette Veen
@lucetteveen

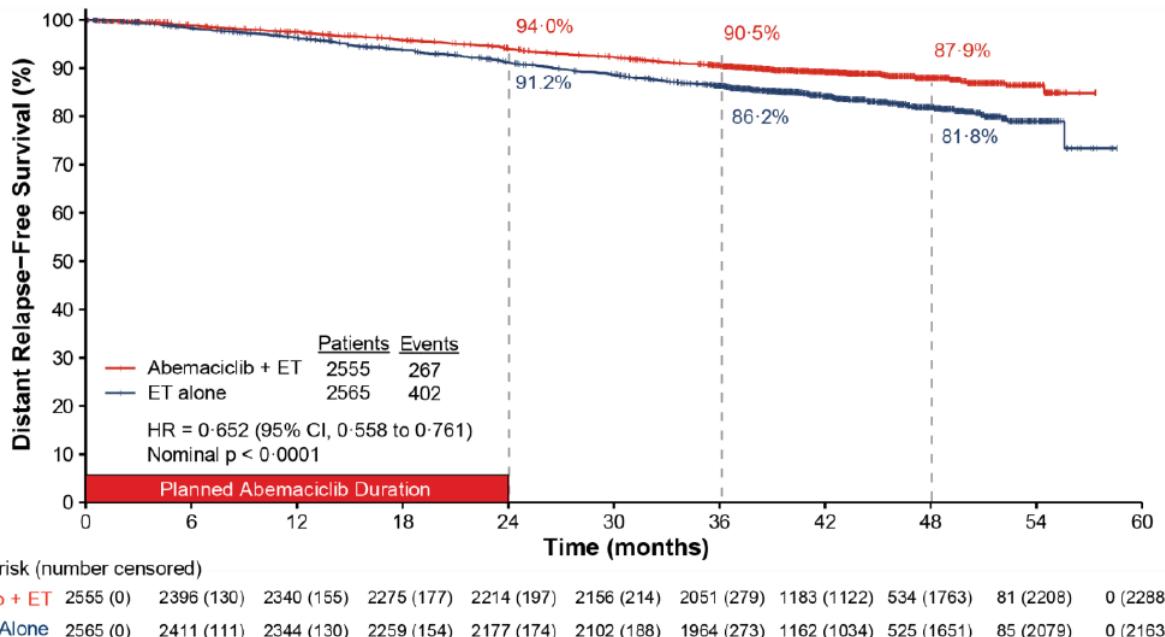
Respondiendo a [@hoperugo](#) y a [@OncoAlert](#)

What's the treatment for those patients that do become metastatic? Presumably not CDK4/6i?

Estudio MONARCH-E: Diseño del Estudio



Estudio MONARCH-E: Beneficio DRFS en Cohorte 1

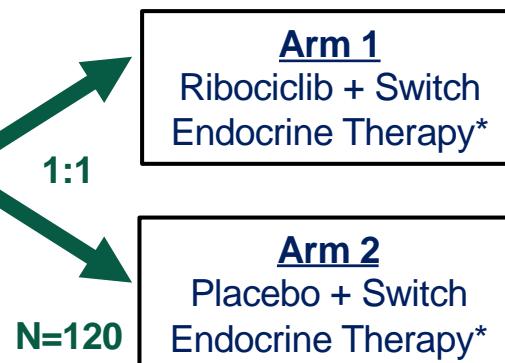


35% reduction in the risk of developing a DRFS event with an increase in absolute benefit in DRFS 4-year rates (6.1%), compared to 2-and 3-year rates (2.8% and 4.3%, respectively)

MANTAIN: Ribociclib tras Inh CDK4/6

Key Entry Criteria

- Men or Women age \geq 18 yrs
- ER and/or PR \geq 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- \leq 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
 - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed



Primary Endpoint

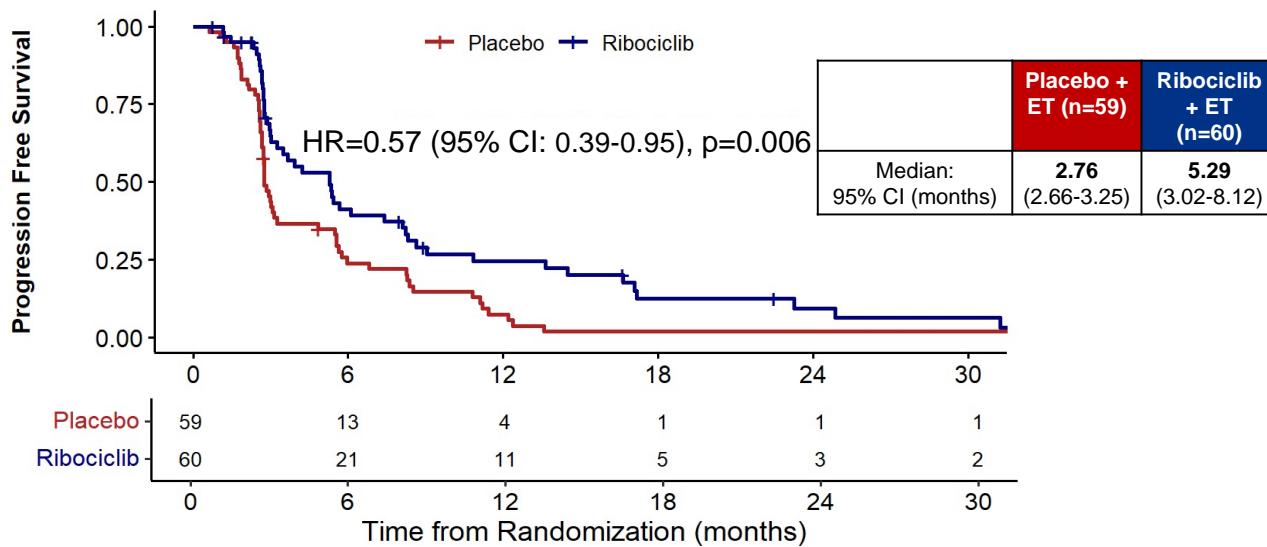
- Progression free survival
 - Locally assessed per RECIST 1.1

Secondary Endpoints

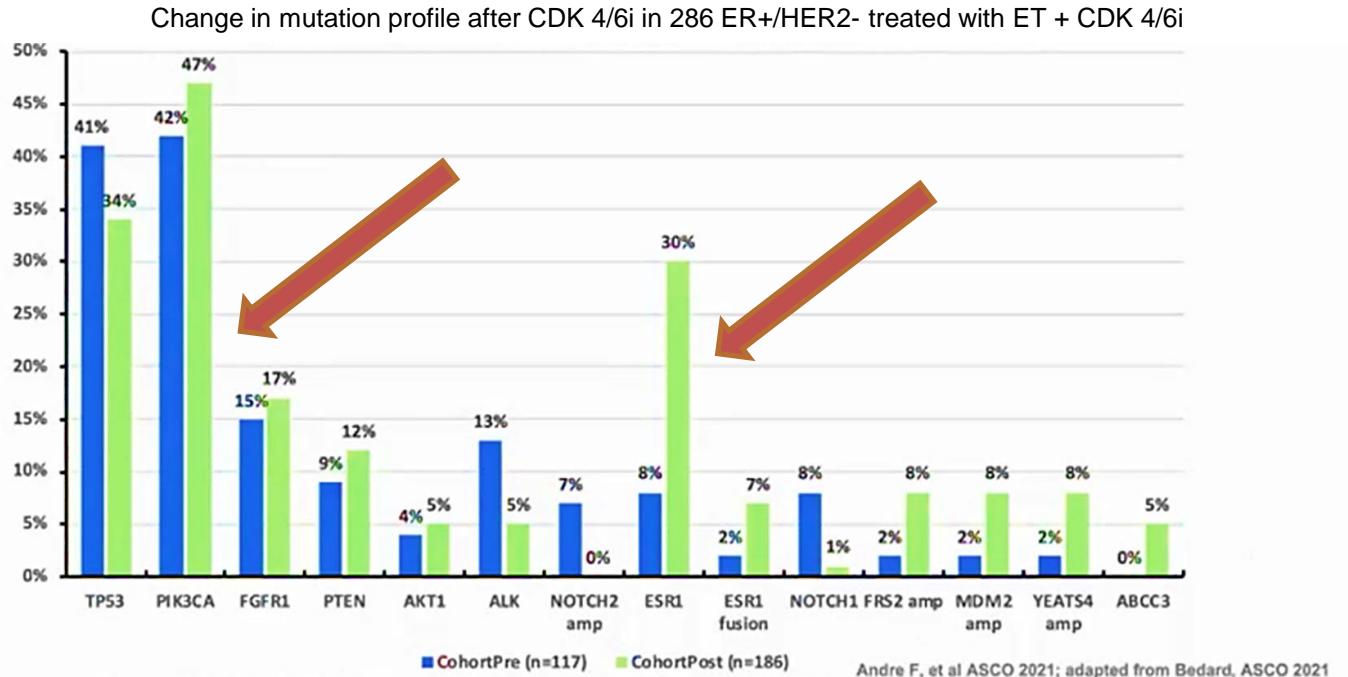
- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

MANTAIN: Ribociclib tras Inh CDK4/6

Primary Endpoint: Progression Free Survival (PFS)



Cambios en el perfil mutacional tras iCDK4/6





Conclusiones



Paolo Tarantino
@PTarantinoMD

Ribociclib was announced to improve iDFS in the adjuvant setting (NATALEE phase 3 trial), where palbociclib failed in two phase 3 trials.

Does this increase your confidence in preferring 1st line ribociclib over palbociclib in the metastatic setting?

[Traducir Tweet](#)

Yes, supports 1L ribo	46%
No, unrelated settings	25%
Other (comment)	2%
See results	27%

670 votos • Resultados finales

16:36 · 27 mar. 23 · 18,4K Visualizaciones



Dr Sarah Sammons @drsa... · 01 mar.

En respuesta a @stage4kelly
@PTarantinoMD y a @TumorBoardTues

Complicated question but the three inhibitors are markedly different. The best we can do is discuss the available OS data and AE profiles with patients.

1 1 2 401



Dr. Kelly Shanahan @stag... · 01 mar.

Isn't there a proposed head to head? RWE paper suggests palbo also significantly ↑ OS, right?
#TumorBoardTuesday

2 1 2 364

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Paolo Tarantino @PTaranti... · 01 mar.

En respuesta a @stage4kelly
@TumorBoardTues y a @drsarahsam

Control arms help. All control arms had approximately an OS of 51-54 months, suggesting not too different populations enrolled in the three trials.

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Conclusiones

ESTUDIO	ML-2	ML-3	ML-7
% PACIENTES RECIDIVA EN CURSO ADYUVANCIA / FIN<12 M	18%	28.3%	30%

460 PACIENTES CON RECIDIVA EN CURSO ADYUVANCIA / FIN <12 M FUERON TRATADAS CON RIBOCICLIB EN LOS ESTUDIOS MONALEESA



Conclusiones



Paolo Tarantino
@PTarantinoMD

En respuesta a @PTarantinoMD,
@TumorBoardTues y 20 más
23/24 #TumorBoardTuesday
#BreastCancer

Multiplicity of potential treatment options are becoming available for patients progressing to 1L ET + CDK4/6-inh
expected to improve outcomes in near future for this large population of patients

Check this algorithm by @drsarahsam



POST-CDK 4/6: Second-line ET Options in 2023 *PENDING FDA APPROVAL

