RIBOCICLIB

Henry L Gomez MD PhD
OncoSalud/Clínica Delgado-AUNA- Perú
Universidad Ricardo Palma –URP
Universidad Peruana Cayetano Heredia- UPCH
GECOPeru

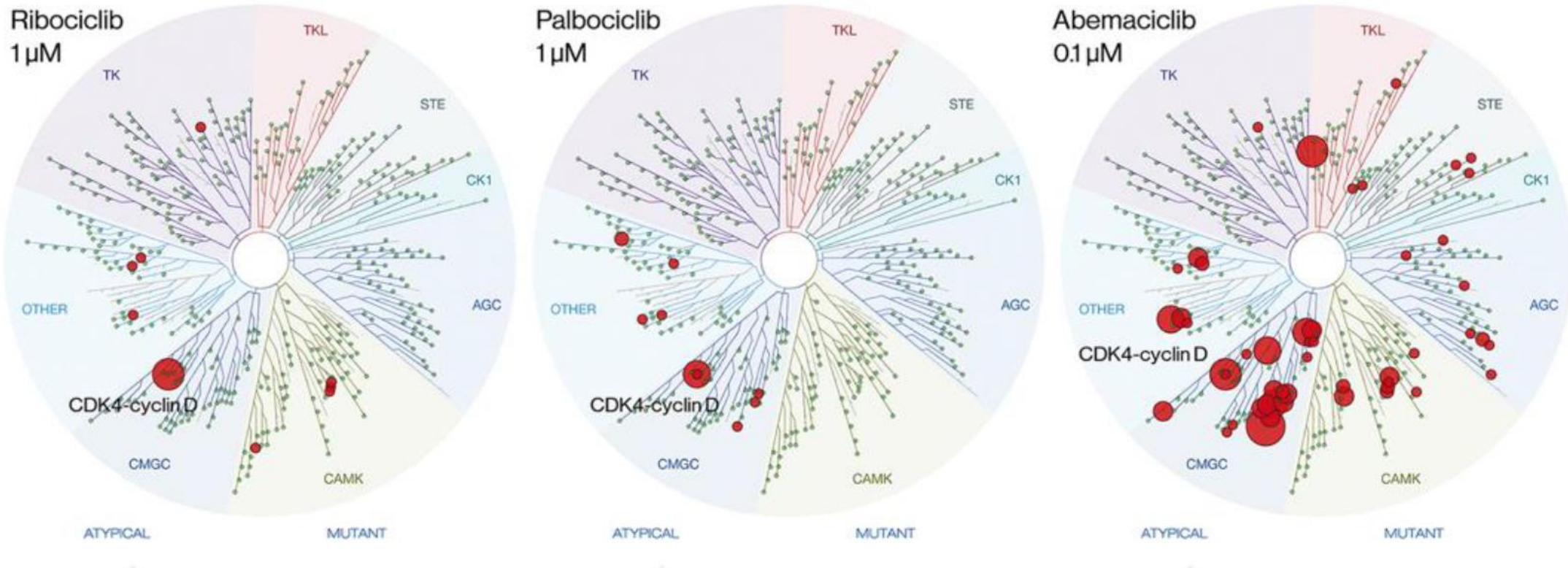
Declaración del Expositor

- ESTA PRESENTACIÓN SE FUNDAMENTA EN INFORMACIÓN PÚBLICAMENTE DISPONIBLE (INCLUYENDO INFORMACIÓN RELACIONADA CON PRODUCTOS O ENFOQUES NO-NOVARTIS)
- LAS OPINIONES EMITIDAS SON LAS DEL EXPOSITOR Y NO REPRESENTAN NECESARIAMENTE LAS OPINIONES DE NOVARTIS
- ESTAS DIAPOSITIVAS TIENEN UN PROPÓSITO EDUCACIONAL ÚNICAMENTE Y SON PARA EL USO PERSONAL DE LA AUDIENCIA. ESTAS DIAPOSITIVAS NO SON PARA DISTRIBUCIÓN FUERA DEL PROPÓSITO ANTES MENCIONADO SIN LA APROBACIÓN DEL EXPOSITOR
- EL CONTENIDO DE ESTAS DIAPOSITIVAS REFLEJA EL MEJOR CONOCIMIENTO DEL EXPOSITOR AL MOMENTO DE SU PRODUCCIÓN.
- DECLARA NO TENER NI POSEER IMPEDIMENTO O CONFLICTO DE INTERÉS ALGUNO AL MOMENTO DE LA PRESENTE EXPOSICIÓN POR LO QUE HACE CONSTAR QUE TIENE PLENO DERECHO, PODER, AUTORIDAD PARA EJECUTAR LOS SERVICIOS CONTRATADOS POR NOVARTIS BAJO SU CAPACIDAD INDIVIDUAL PROFESIONAL Y NO COMO EMPLEADO O AGENTE DE NINGUNA INSTITUCIÓN DE CARÁCTER PÚBLICO.”

BASES MOLECULARES

CDK4/6 inhibitors demonstrate differential target selectivity

Ribociclib and palbociclib have fewer interactions with off-target kinases than abemaciclib



References: Kim S et al. *Oncotarget*. 2018;9:35226-35240.

Ribociclib achieves highest levels of exposure in plasma relative to other CDK4/6 inhibitors at clinically relevant doses may result from differential CDK4 vs CDK6 inhibition

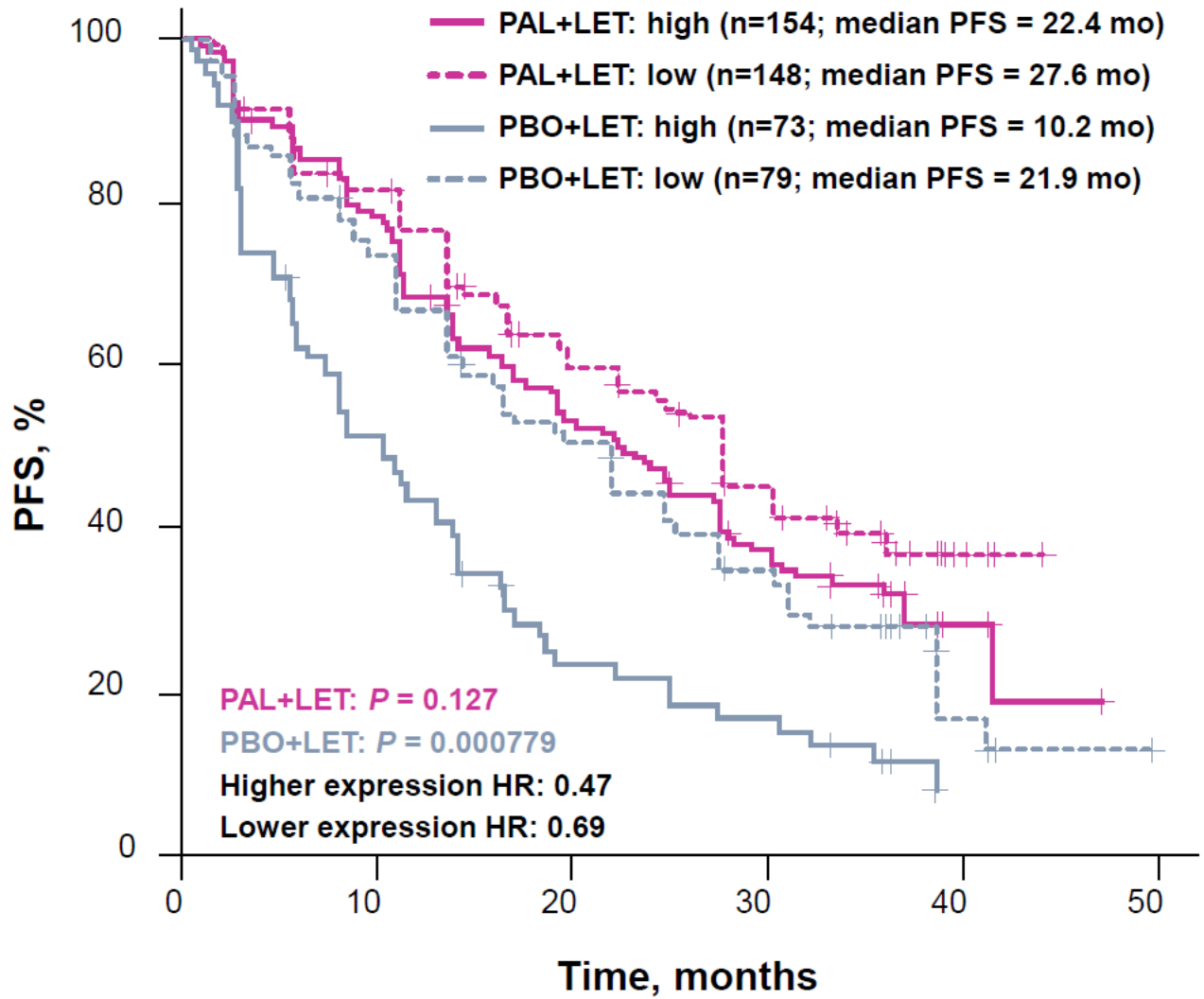
At clinically relevant doses and after adjustment for differences in potency against CDK4, ribociclib is expected to provide greater CDK4 inhibition than either palbociclib or abemaciclib in preclinical studies

	Ribociclib	Abemaciclib[a]	Palbociclib
	600 mg QD	200 mg q12h	125 mg QD
AUC_{0-24} steady state, h·ng/mL	**>20,000**[1]	5520[2]	1733[3,4]
AUC_{AVG} steady state, ng/mL	**>833**	230	72
AUC_{AVG} (free drug) steady state, nM	**>558**	18	25
Free drug exposure normalized to palbociclib	**>22x**	1x	1

[a] Recommended starting dose: abemaciclib + fulvestrant 150 mg BID, abemaciclib monotherapy 200 mg BID.

References: 1. Infante JR et al. *Clin Cancer Res.* 2016;22(23):5696-5705. 2. Patnaik A, et al. *Cancer Discov.* 2016;6:740-753. 3. Flaherty KT, et al. *Clin Cancer Res.* 2012;18:568-576. 4. Chen P et al. *Mol Cancer Ther.* 2016;15(10):2273-2281.

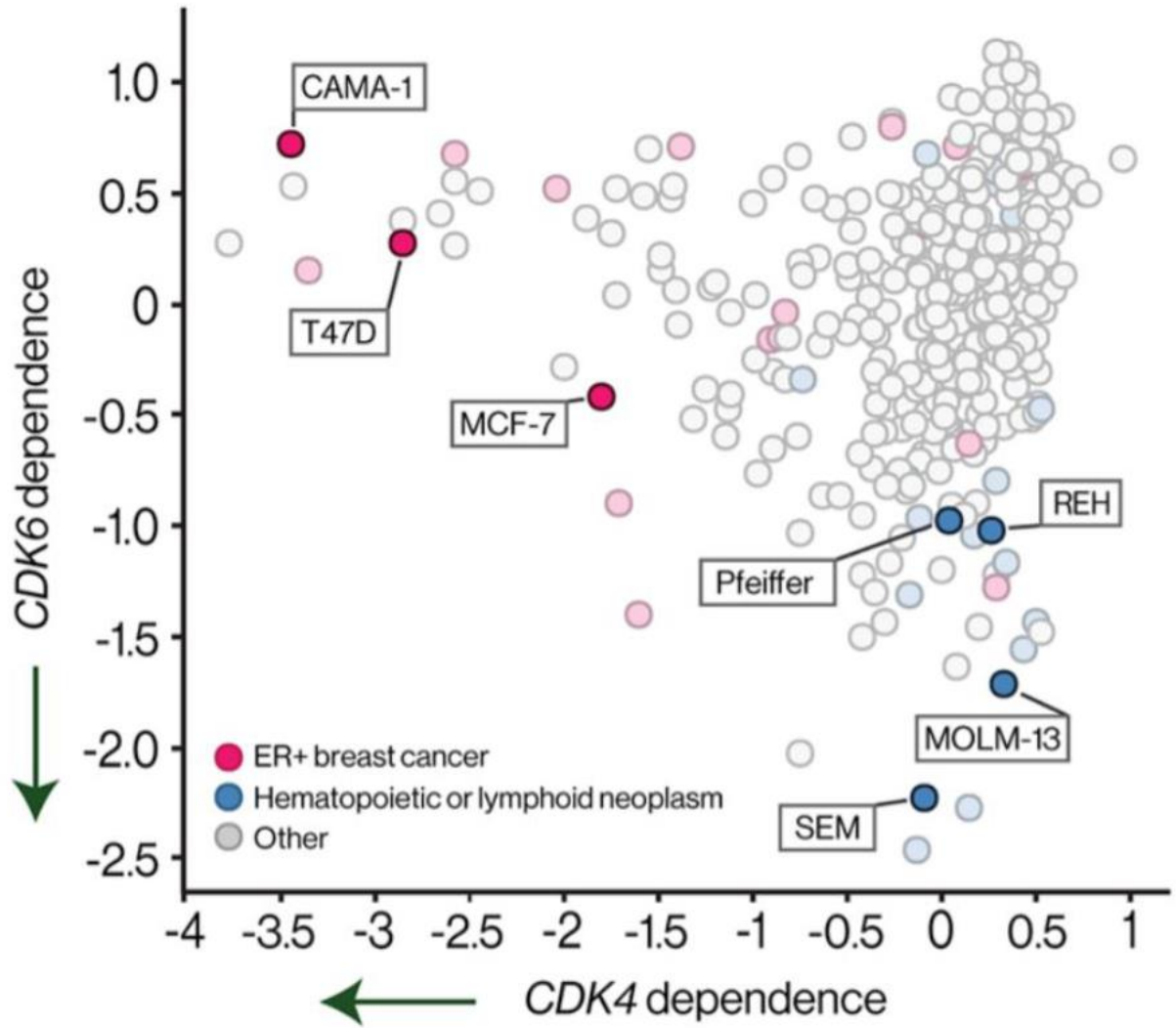
Higher expression of CDK4 is associated with ET resistance



PFS by CDK4 expression (PALOMA-2)

Reference: Finn RS et al. *Clin Cancer Res*. 2020;26:110-121.

CDK4 plays a more important role than CDK6 in ER+ breast cancer



CDK4-dependent lines were most commonly ER+ breast cancer lines, whereas **CDK6-dependent** lines were hematopoietic in origin

Reference: Kim S et al. *Oncotarget*. 2018;9:35226-35240.

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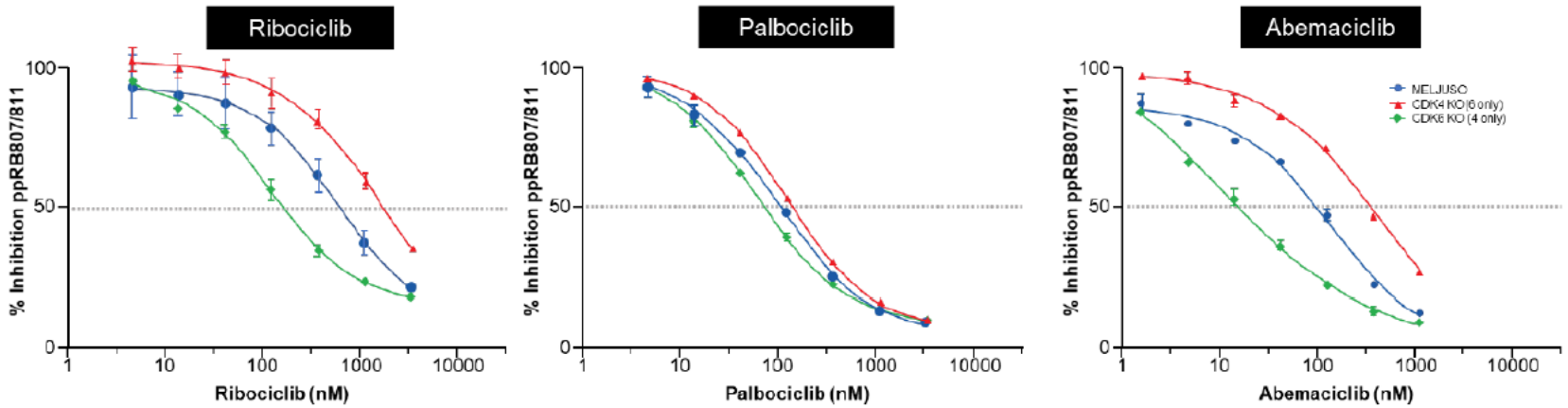
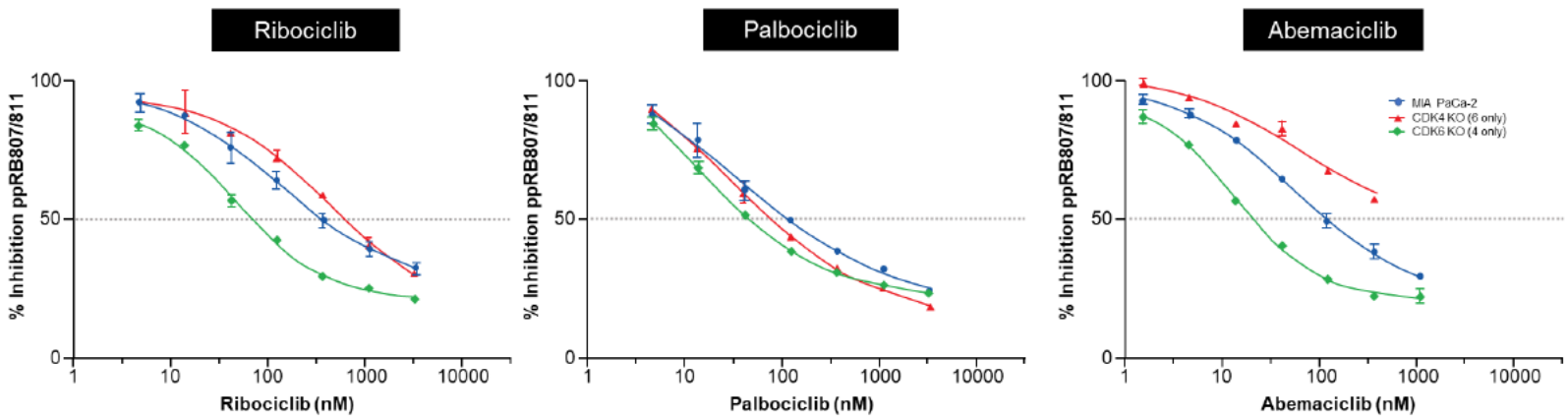
CDK4/6 inhibitors have differential activity toward their two targets

Fast Scan Phospho-RB807/811ELISA Analysis in MEL-JUSOCDK4 and CDK6 Knockout Clones



FastScanPhospho-RB807/811ELISA Analysis in MIA PaCa-2 CDK4 and CDK6 Knockout Clones



Ribociclib and **abemaciclib** are more active against CDK4 than CDK6

CDK4 > CDK6

Palbociclib inhibits CDK4 and CDK6 equally

CDK4 = CDK6

Reference: Delach S. SABCS 2020. Poster PS19-10.

KR2404175896

ESTUDIOS CLINICOS PIVOTALES

MONALEESA 2

MONALEESA 2:

Diseño del estudio: *Fase III- doble ciego, placebo controlado, multicéntrico.*
Objetivo*: Evaluar la eficacia y seguridad de la combinación de ribociclib + letrozole comparado a placebo + letrozole como terapia inicial en pacientes con cáncer de mama avanzado HR+, HER2-*

- Mujeres posmenopáusicas con HR+/ HER2- CMA
- Sin terapia previa para la enfermedad avanzada

N=668

R 1:1

***Estratificado por la presencia/ausencia de metástasis hepáticas y/o pulmonares

Ribociclib (600 mg/día)
3 semanas on/1 semana off
+
Letrozol (2,5 mg/día)
n=334

Placebo
+
Letrozol (2,5 mg/día)
n=334

Criterio de valoración primario
- SLP (evaluada localmente según RECIST 1.1)

Criterio secundario clave
- SG

Seleccionar variables secundarias
- ORR
- CBR
- Seguridad
- QOL

[Hortobagyi2016] Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(11):1738-1748.
[Hortobagyi2016a] Hortobagyi GN, Stemmer SM, Burris HA, et al. Protocol for: Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(Suppl):1-448.

CONTENT ID 449554 aprobado para distribución 22 Mayo2023

MONALEESA 2:

CARACTERISTICAS DE LOS PACIENTES

Demografía y línea de base

las características están bien equilibradas

entre ribociclib y placebo

brazos

Characteristic	Ribociclib + letrozole (n=334)	Placebo + letrozole (n=334)
Age, median (range)	62 (23–91)	63 (29–88)
Race, n (%)		
White	269 (80.5)	280 (83.8)
Asian	28 (8.4)	23 (6.9)
Black	10 (3.0)	7 (2.1)
Other or unknown	27 (8.1)	24 (7.2)
ECOG performance status, n (%)		
0	205 (61.4)	202 (60.5)
1	129 (38.6)	132 (39.5)
Disease stage, n (%)		
III	1 (0.3)	3 (0.9)
IV	333 (99.7)	331 (99.1)
HR status, n (%)		
Estrogen receptor–positive (ER+)	332 (99.4)	333 (99.7)
Progesterone receptor–positive (PR+)	271 (81.1)	278 (83.2)
Disease-free interval, n (%)		
Newly diagnosed disease	114 (34.1)	113 (33.8)
Existing disease	220 (65.9)	221 (66.2)
≤12 months	4 (1.2)	10 (3.0)
>12–≤24 months	14 (4.2)	15 (4.5)
>24 months	202 (60.5)	195 (58.4)
Unknown	0	1 (0.3)

Hortobagyi2016] Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(11):1738-1748. [

MONALEESA 2:

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Characteristic	Ribociclib + letrozole (n=334)	Placebo + letrozole (n=334)
Previous treatment, n (%)		
(Neo)adjuvant chemotherapy	146 (43.7)	145 (43.4)
(Neo)adjuvant endocrine therapy	175 (52.4)	171 (51.2)
Anastrozole	47 (14.1)	42 (12.6)
Exemestane	19 (5.7)	25 (7.5)
Goserelin	6 (1.8)	3 (0.9)
Letrozole	34 (10.2)	25 (7.5)
Tamoxifen	140 (41.9)	145 (43.4)
Other	2 (0.6)	4 (1.2)
Metastatic sites, n (%)		
0	2 (0.6)	1 (0.3)
1	100 (29.9)	117 (35.0)
2	118 (35.3)	103 (30.8)
≥3	114 (34.1)	113 (33.8)
Site of metastasis, n (%)		
Breast	8 (2.4)	11 (3.3)
Bone		
Any	246 (73.7)	244 (73.1)
Only	69 (20.7)	78 (23.4)
Visceral	197 (59.0)	196 (58.7)
Lymph nodes	133 (39.8)	123 (36.8)
Other	35 (10.5)	22 (6.6)

Hortobagyi2016] Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(11):1738-1748.

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MONALEESA 3

MONALEESA 3 :

Diseño del estudio: *Fase III- doble ciego, placebo controlado, multicéntrico.*
Objetivo*: Evaluar la eficacia y seguridad de la combinación de ribociclib más fulvestrant en comparación con placebo más fulvestrant en pacientes con HR+, HER2– aBC*

- Mujeres posmenopáusicas con HR+/ HER2- CMA
- ≤ 1 de terapia endocrina para enfermedad avanzada

N=726

R 2:1

- Ribociclib o placebo 1v/día 3 semanas con 1 semana de descanso por 28 días.
- Fulvestrant se administra el día 1 de cada ciclo de 28 días, con una dosis adicional el día 15 del ciclo.

Ribociclib 600 mg
+ Fulvestrant 500mg
n=484

Placebo +
Fulvestrant 500mg
n=242

Criterio de valoración primario

- SLP (evaluada localmente según RECIST 1.1)

Criterio secundario clave

- SG
- ORR
- CBR
- Seguridad
- QOL

[Slamon2018] Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor- Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018;36(24):2465-2472.

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MONALEESA 3:

CARACTERISTICAS DE LOS PACIENTES

Demografía y línea de base

las características están bien equilibradas

entre ribociclib y placebo

brazos

Characteristic	Ribociclib + fulvestrant (n=484)	Placebo + fulvestrant (n=242)
Gender, n (%)		
Female	484 (100)	242 (100)
Age, median (range)	63 (31–89)	63 (34–86)
Race, n (%)		
White	406 (83.9)	213 (88.0)
Asian	45 (9.3)	18 (7.4)
Native American	5 (1.0)	1 (0.4)
Black	3 (0.6)	2 (0.8)
Other	15 (3.1)	5 (2.1)
Unknown	10 (2.1)	3 (1.2)
ECOG performance status, n (%)		
0	310 (64.0)	158 (65.3)
1	173 (35.7)	83 (34.3)
Missing	1 (0.2)	1 (0.4)
Disease stage at study entry, n (%)		
II	2 (0.4)	0 (0.0)
III	4 (0.8)	2 (0.8)
IV	478 (98.8)	239 (98.8)
Missing	0 (0.0)	1 (0.4)
Hormone receptor status, n (%)		
ER+	481 (99.4)	241 (99.6)
PR+	353 (72.9)	167 (69.0)

[Slamon2018] Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor- Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018;36(24):2465-2472.

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Characteristic	Ribociclib + fulvestrant (n=484)	Placebo + fulvestrant (n=242)
Disease-free interval, months (%)		
Newly diagnosed disease*	97 (20.0)	42 (17.4)
Existing disease	387 (80.0)	199 (82.2)
≤12 months	22 (4.5)	9 (3.7)
>12 months	365 (75.4)	190 (78.5)
Missing	0 (0.0)	1 (0.4)
Prior endocrine therapy status, n (%)†		
Treatment naive	238 (49.2)	129 (53.3)
≤1 line of endocrine therapy	236 (48.8)	109 (45.0)
Prior endocrine therapy setting, n (%)		
(Neo)adjuvant	289 (59.7)	142 (58.7)
Advanced	110 (22.7)	40 (16.5)
Prior chemotherapy, n (%)		
Adjuvant	209 (43.2)	101 (41.7)
Neoadjuvant	65 (13.4)	30 (12.4)

*Newly diagnosed disease includes patients with no first recurrence/progression or with a first recurrence/progression within 90 days of diagnosis with no prior medication. For existing disease, disease-free interval is defined as the time from initial diagnosis to first recurrence /progression.

†Fourteen patients not included because of missing data or criteria not being met.

[Slamon2018] Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor- Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018;36(24):2465-2472.

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MONALEESA 7

MONALEESA 7 :

Diseño del estudio: *Fase III- doble ciego, placebo controlado, multicéntrico.*

Objetivo*: Evaluar la eficacia y seguridad de la combinación de ribociclib más terapia endocrina más supresión ovárica en mujeres premenopáusicas con HR+, HER2– aBC*

- Mujeres pre-peri menopáusicas con HR+/ HER2- CMA
- Sin terapia endocrina previa para el setting avanzado

N=672

R 1:1

Ribociclib 600 mg
+ Tamoxifeno 20mg o NSAI QD + goserelina (,3,6 mg)
n=335

Placebo + Tamoxifeno 20mg
o NSAI QD + goserelina (,3,6 mg)
n=337

- Ribociclib o placebo 1v/día 3 semanas con 1 semana de descanso por 28 días.
- tamoxifeno (20 mg) o un AINE (letrozol 2,5 mg o anastrozol 1 mg) una vez al día continuamente
- Goserelina (3,6 mg) se administra el día 1 de cada ciclo

Criterio de valoración primario

- SLP (evaluada localmente según RECIST 1.1)

Criterio secundario clave

- ORR
- CBR
- Tiempo de respuesta
- DOR
- Tiempo de deterioro ECOG
- Tiempo al 10% de deterioro del estado de salud global.
- Cambios en la linea de base de estado global de salud
- Seguridad- Tolerabilidad
- QOL

[Tripathy2018] Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormonereceptor- positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018;19(7):904-915.

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MONALEESA 7:

CARACTERISTICAS DE LOS PACIENTES

Demografía y línea de base

las características están bien equilibradas

entre ribociclib y placebo

brazos

Characteristic	Ribociclib + tamoxifen/NSAI + goserelin (n=335)	Placebo + tamoxifen/NSAI + goserelin (n=337)
Age, median (range)	43 (25–48)	45 (29–58)
Race, n (%)		
White	187 (56)	201 (60)
Asian	99 (30)	99 (29)
Black	10 (3)	9 (3)
Other or unknown	39 (12)	28 (8)
ECOG performance status, n (%)		
0	245 (73)	255 (76)
1	87 (26)	78 (23)
2	0	1 (<1)
Missing	3 (1)	3 (1)
Disease status at study entry, n (%)		
Locally advanced	1 (<1)	1 (<1)
Metastatic	334 (100)	336 (100)

[Tripathy2018] Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018;19(7):904-915.

MONALEESA 7:

CARACTERISTICAS DE LOS PACIENTES

Demografía y línea de base

las características están bien equilibradas

entre ribociclib y placebo

brazos

Characteristic	Ribociclib + tamoxifen/NSAI + goserelin (n=335)	Placebo + tamoxifen/NSAI + goserelin (n=337)
Hormone receptor status, n (%)		
ER+	331 (99)	335 (99)
PR+	290 (87)	288 (85)
Disease-free interval, months (%)		
Newly diagnosed disease*	136 (41)	134 (40)
Existing disease	199 (59)	203 (60)
≤12 months	23 (7)	13 (4)
>12 months	176 (53)	190 (56)
Prior (neo)adjuvant endocrine therapy, n (%)		
No	208 (62)	196 (58)
Yes	127 (38)	141 (42)
Progression ≤12 months after endocrine therapy	100 (30)	105 (31)
Progression >12 months after endocrine therapy	25 (7)	35 (10)
Missing	2 (1)	1 (<1)

*Newly diagnosed disease includes patients with no first recurrence/progression or with a first recurrence/progression within 90 days of diagnosis with no prior medication. For existing disease, disease-free interval is defined as the time from initial diagnosis to first recurrence /progression.

[Tripathy2018] Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018;19(7):904-915.

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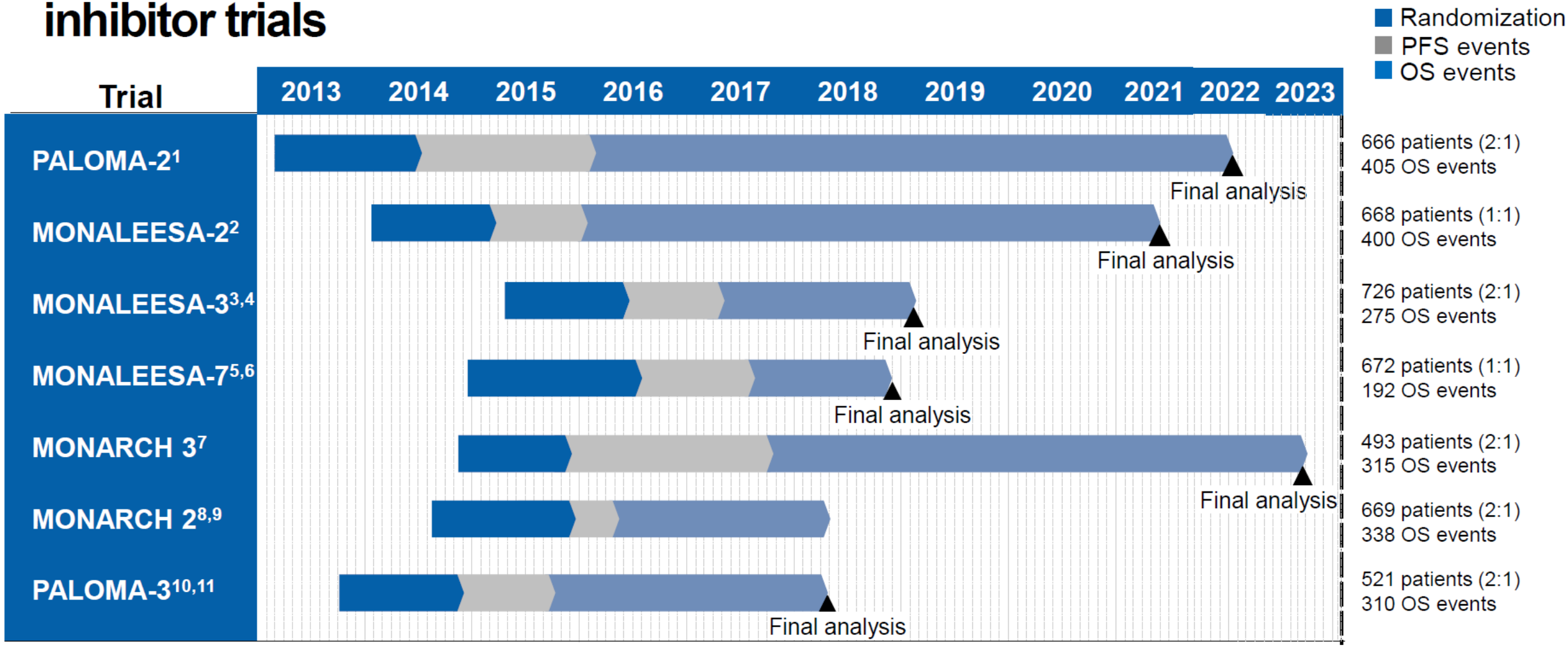
IMPACTO CLÍNICO

Timelines of reporting overall survival data in pivotal phase 3 CDK4/6 inhibitor trials



References: 1. Finn RS, et al. ASCO 2022. LBA1003. 2. Hortobagyi GN, et al. ESMO 2021. LBA17_PR [Oral]. 3. Slamon DJ et al. *J Clin Oncol*. 2018;36:2465-2472. 4. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524. 5. Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915. 6. Im SA, et al. *N Engl J Med*. 2019;381:307-316. 7. Goetz MP, et al. *J Clin Oncol*. 2017;35:3638-3646. 8. Sledge GW, et al. *J Clin Oncol*. 2017;35:2875-2884. 9. Sledge GW, et al. *JAMA Oncol*. 2020;6:116-124. 10. Cristofanili M, et al. *Lancet Oncol*. 2016;17:425-439. 11. Turner NC, et al. *N Engl J Med*. 2018;379:1926-1936.

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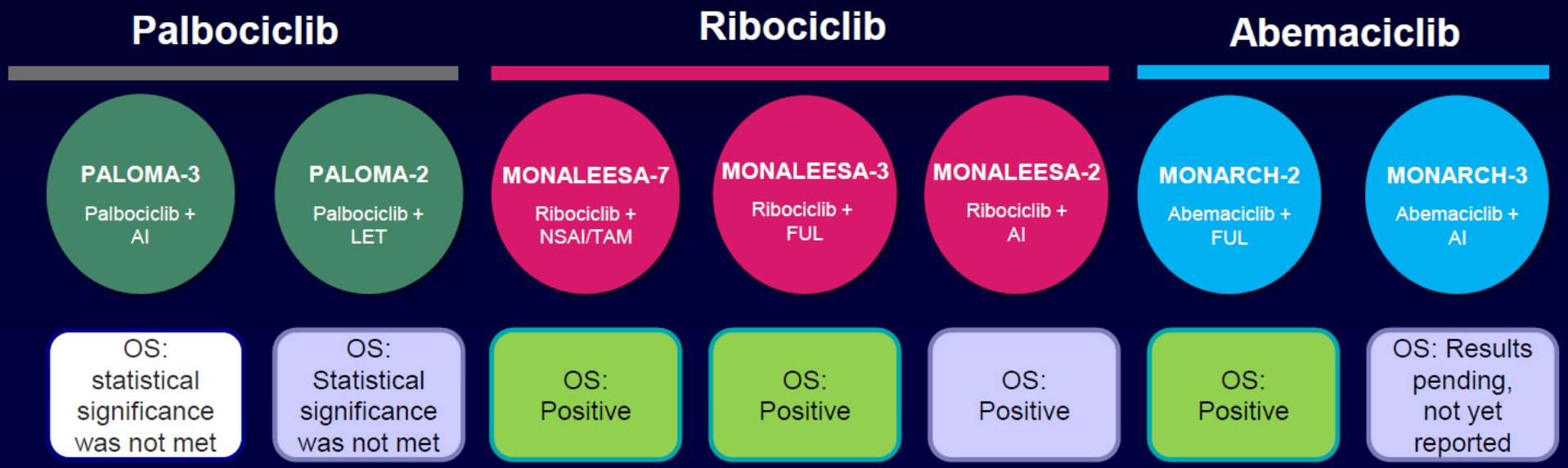
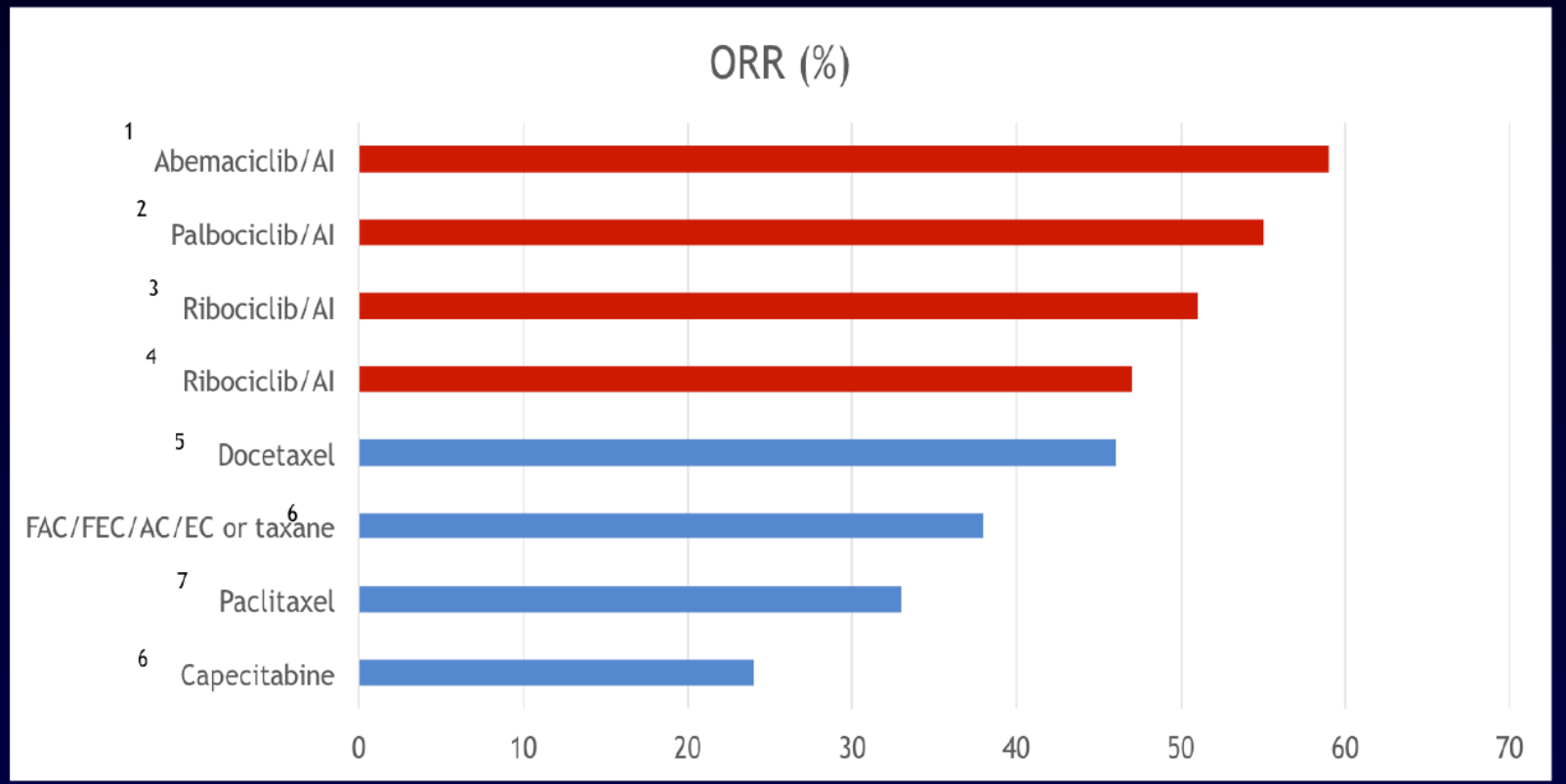
CDK4/6i Summary – Advanced Breast Cancer: Where Are We Now?

- The benefit of targeted therapy with CDK4/6 inhibitors demonstrated by statistically significant OS results in 4 ABC trials



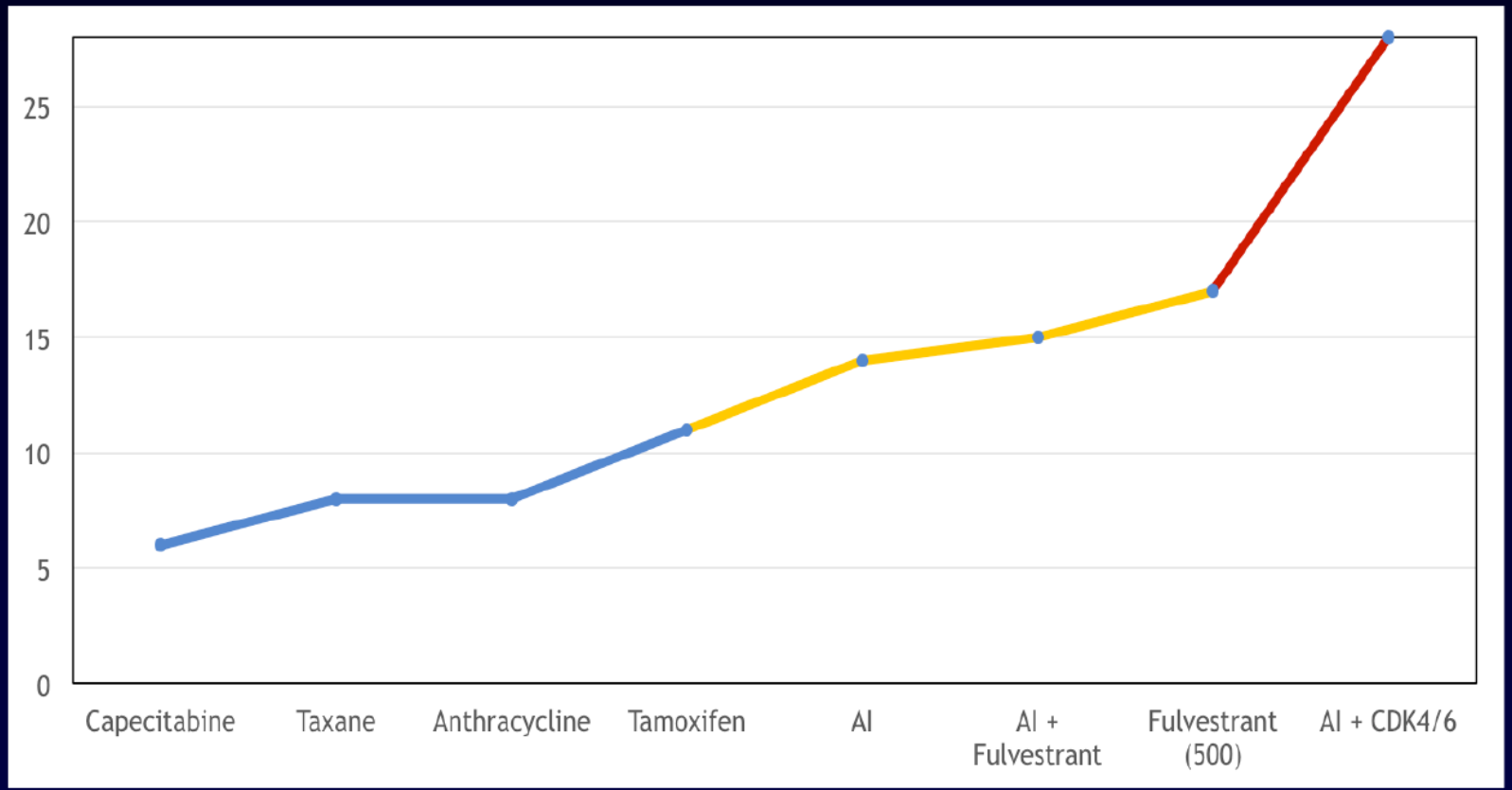
References: 1. Finn RS, et al. ASCO 2022. LBA1003. 2. Hortobagyi GN, et al. ESMO 2021. LBA17_PR [Oral]. 3. Slamon DJ et al. *J Clin Oncol*. 2018;36:2465-2472. 4. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524. 5. Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915. 6. Im SA, et al. *N Engl J Med*. 2019;381:307-316. 7. Goetz MP, et al. *J Clin Oncol*. 2017;35:3638-3646. 8. Sledge GW, et al. *J Clin Oncol*. 2017;35:2875-2884. 9. Sledge GW, et al. *JAMA Oncol*. 2020;6:116-124. 10. Cristofanili M, et al. *Lancet Oncol*. 2016;17:425-439. 11. Turner NC, et al. *N Engl J Med*. 2018;379:1926-1936.

ORR is better with front-line AI/CDK4/6i than with chemotherapy in modern studies of ER+/HER2- BC



1. MONARCH-3: Goetz M et al. J Clin Oncol. 2017;35:3638-46. 2. PALOMA-2: Finn RS et al. N Engl J Med 2016;375:1925-36. 3. MONALEESA-7: Tripathy D et al. Lancet Oncol. 2018. 4. MONALEESA-2: Hortobagyi GN et al. N Engl J Med. 2016;375:1738-48. 5. AVADO study: Miles D, et al J Clin Oncol. 2010;28:3239-47. 78% HR+; 6. RIBBON-1 study: Robert N et al. J Clin Oncol 2011;29:1252-60. 3/4 of patients with HR+ disease; 7. Meridian Study: Miles D et al. Eur J of Ca 2017;70:146-155. 83% HR+.

Highest PFS ever reported for ER+/HER2- MBC is with CDK4/6i-based therapy



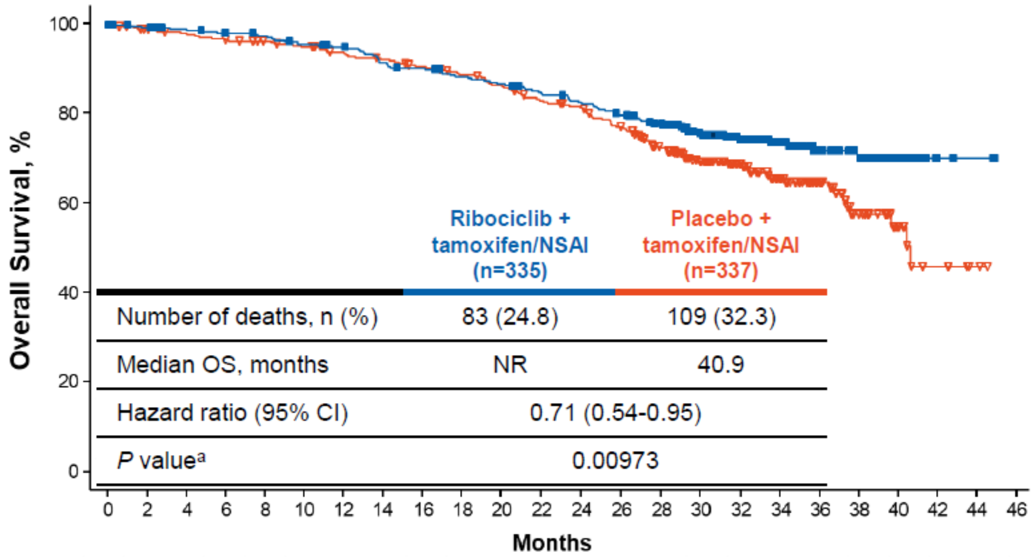
RIBBON-1 (capecitabine, taxane, anthracycline): Robert N et al. J Clin Oncol 2011;29:1252-60. MONALEESA-7 (tamoxife and AI): Tripathy D et al. Lancet Oncol. 2018. SWOG (AI + fulvestrant): Mehta R et al. N Engl J Med 2012;367:435-44. FALCON (Fulvestrant, AI) Robertson J et al. Lancet Oncol. 2016;388:2997-3005. PALOMA-2 (AI+CDK4/6i) Finn RS et al. N Engl J Med 2016;375:1925-36

SOBREVIDA GLOBAL CON RIBOCICLIB

MONALEESA-7: OS significantly improved in premenopausal women[1,2]

Planned OS Analysis[1]

OS | ITT (Median follow-up: 35 months)



	Ribociclib + tamoxifen/NSAI (n=335)	Placebo + tamoxifen/NSAI (n=337)
Number of deaths, n (%)	83 (24.8)	109 (32.3)
Median OS, months	NR	40.9
Hazard ratio (95% CI)	0.71 (0.54-0.95)	
P value[a]	0.00973	

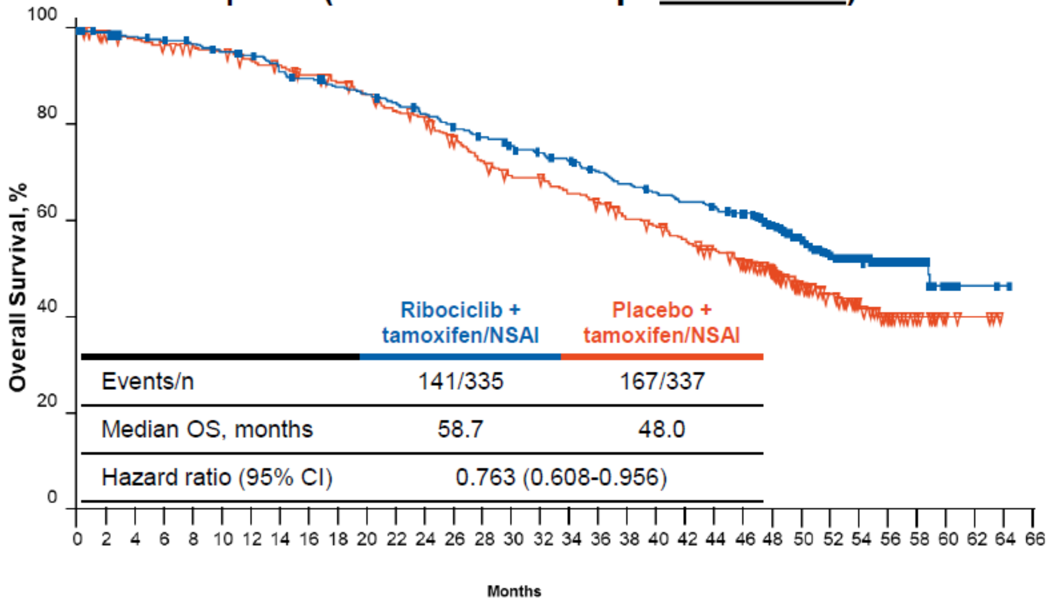
No. of Patients at Risk

Months	0	2	4	6	8	10	12	14	16	18	20	22
Ribociclib + tamoxifen/NSAI	335	330	325	320	316	309	304	292	287	279	274	266
Placebo + tamoxifen/NSAI	337	330	325	321	314	309	301	295	288	280	272	258

Months	24	26	28	30	32	34	36	38	40	42	44	46
Ribociclib + tamoxifen/NSAI	258	249	236	193	155	110	68	43	25	7	3	0
Placebo + tamoxifen/NSAI	251	235	210	166	122	92	62	33	19	7	2	0

Ad Hoc OS Analysis[2]

OS | ITT (Median follow-up: 54 months)



	Ribociclib + tamoxifen/NSAI	Placebo + tamoxifen/NSAI
Events/n	141/335	167/337
Median OS, months	58.7	48.0
Hazard ratio (95% CI)	0.763 (0.608-0.956)	

No. at Risk

Months	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Ribociclib + tamoxifen/NSAI	335	330	325	320	316	309	304	292	287	279	274	267	259	250	242	235	226
Placebo+ tamoxifen/NSAI	337	330	325	321	315	311	303	297	290	283	275	262	255	237	223	212	210

Months	34	36	38	40	42	44	46	48	50	52	54	56	58	60	62	64	66
Ribociclib + tamoxifen/NSAI	220	210	203	196	191	187	178	155	118	91	66	42	27	8	2	1	0
Placebo+ tamoxifen/NSAI	199	192	180	175	165	157	146	122	90	63	46	29	17	5	3	0	0

Nearly 5-year median OS; the longest survival benefit ever reported with a CDK4/6i trial exclusively focused on premenopausal patients with ABC

[a] The result crossed the prespecified stopping boundary for superior efficacy (1-sided stratified log-rank test, with a protocol-defined Lan-DeMets [O'Brien-Fleming] stopping boundary of *P*<.01018 for superior efficacy).

References: 1. Im SA et al. *N Engl J Med*. 2019;381(4):307-316; 2. Tripathy D, et al. Presented at SABCS 2020. Poster PD2-04.

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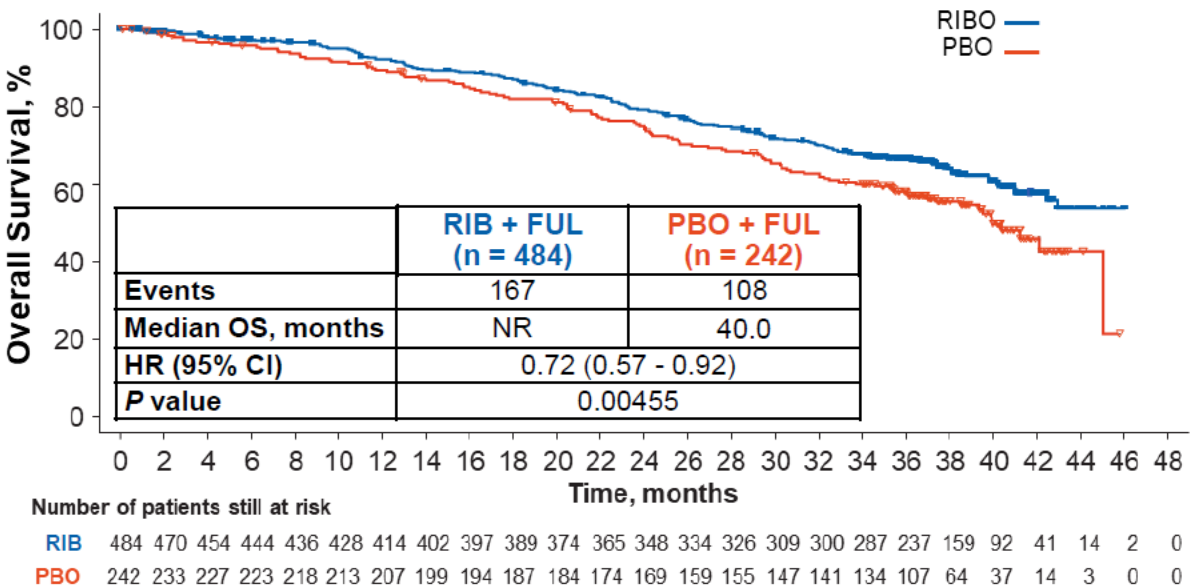
MONALEESA-3: OS significantly improved in postmenopausal women[1,2]

Planned OS Analysis[1]

OS | ITT population (Median follow-up: 39 months)



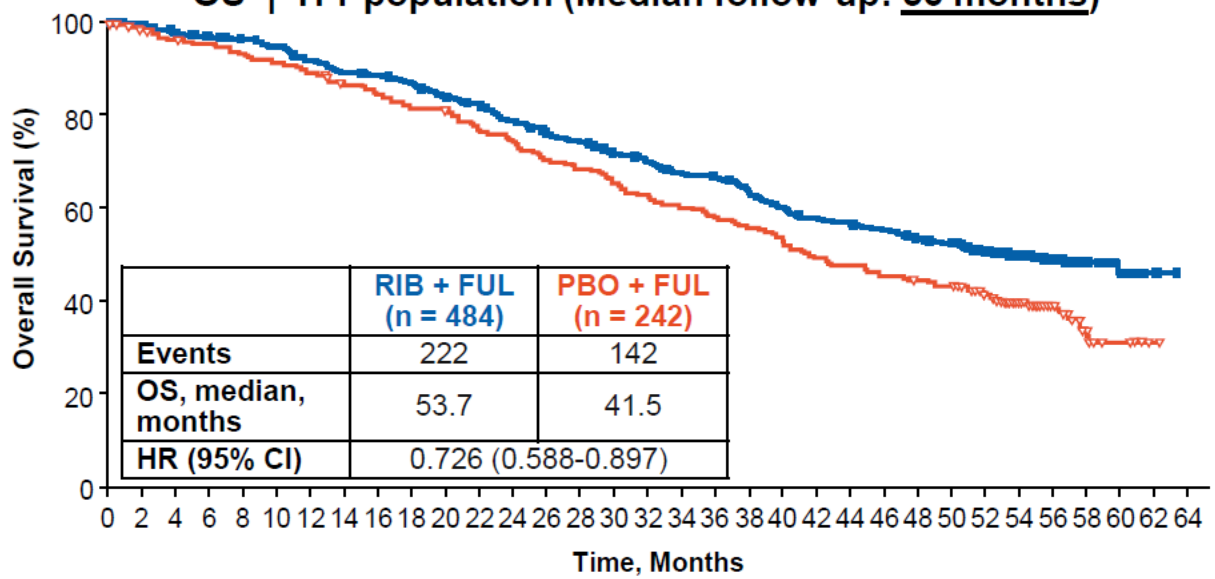
	RIB + FUL (n = 484)	PBO + FUL (n = 242)
Events	167	108
Median OS, months	NR	40.0
HR (95% CI)	0.72 (0.57 - 0.92)	
P value	0.00455	

Number of patients still at risk

RIB	484	470	454	444	436	428	414	402	397	389	374	365	348	334	326	309	300	287	237	159	92	41	14	2	0
PBO	242	233	227	223	218	213	207	199	194	187	184	174	169	159	155	147	141	134	107	64	37	14	3	0	0

Ad Hoc OS Analysis[2]

OS | ITT population (Median follow-up: 56 months)



	RIB + FUL (n = 484)	PBO + FUL (n = 242)
Events	222	142
OS, median, months	53.7	41.5
HR (95% CI)	0.726 (0.588-0.897)	

Number of patients still at risk

RIB	484	470	454	444	436	428	414	402	397	389	374	365	348	334	326	310	301	290	285	273	256	245	241	233	224	218	191	145	90	50	20	4	0
PBO	242	233	227	223	218	213	208	200	195	188	185	175	170	160	156	149	143	137	133	127	120	112	107	102	99	96	82	56	29	15	5	1	0

Nearly 4.5-year median OS; the longest survival benefit ever reported for a CDK4/6i in combination with fulvestrant[2]

[a]The result crossed the prespecified stopping boundary for superior efficacy (1-sided stratified log-rank test, with a protocol-defined Lan-DeMets [O'Brien-Fleming] stopping boundary of *P*<.01018 for superior efficacy).

References: 1. Slamon DJ, et al. *N Engl J Med*. 2020;382(6):514–524. 2. Slamon DJ, *Ann Oncol*. 2021;32:1015-1024.

MONALEESA-2 study design

Phase 3
- Postmenopausal women with HR+/ HER2– ABC
- No prior therapy for advanced disease
- Prior (neo)adjuvant ET, including TAM, allowed[a]
- N=668

R 1:1

Ribociclib (600 mg/day)
3 weeks on/1 week off
+
Letrozole (2.5 mg/day)
n=334

Placebo
+
Letrozole (2.5 mg/day)
n=334

Stratified by the presence/absence of liver and/or lung metastases

Primary endpoint
- PFS (locally assessed per RECIST 1.1)

Key secondary endpoint
- OS

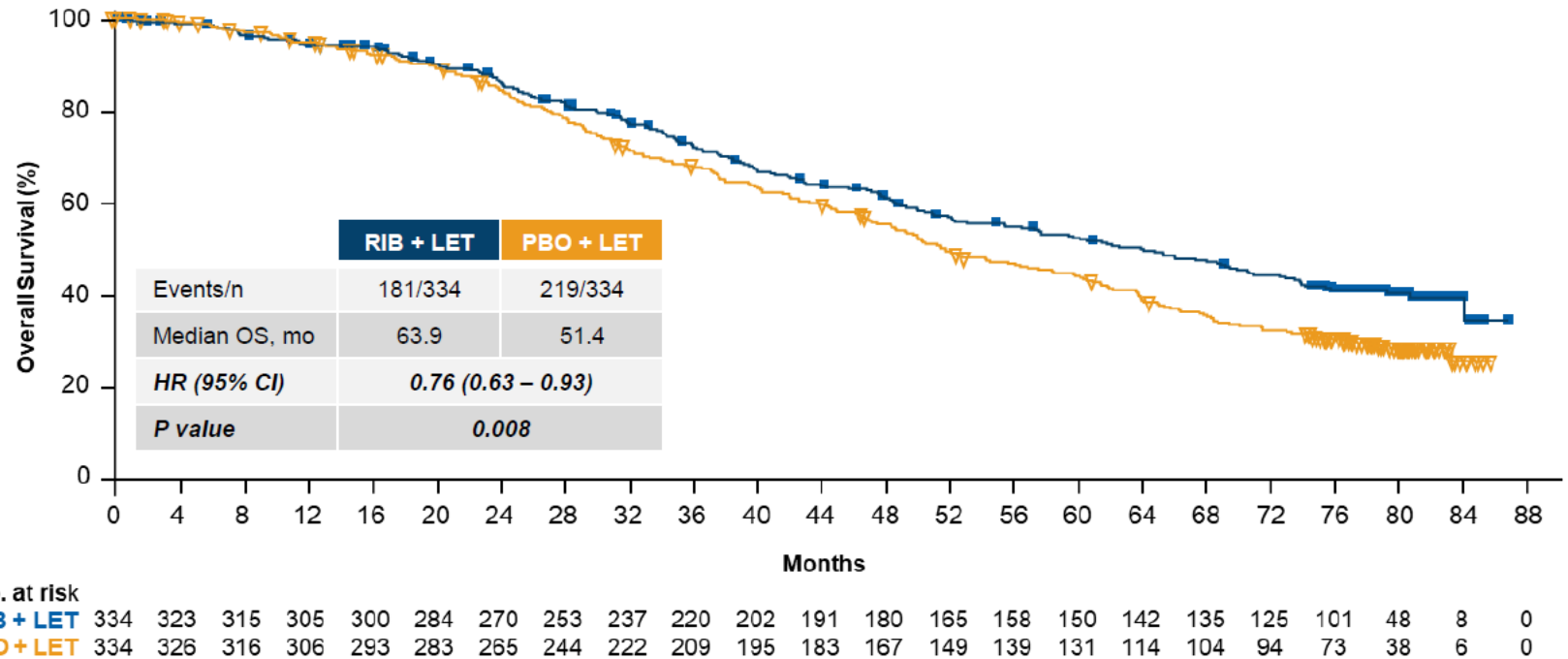
Select secondary endpoints
- ORR
- CBR
- Safety
- QOL

[a] Treatment-free interval > 12 months from completion of treatment until randomization required for prior NSAI use.

Reference: Hortobagyi GN, et al. *N Engl J Med.* 2016;375(18):1738-1748.

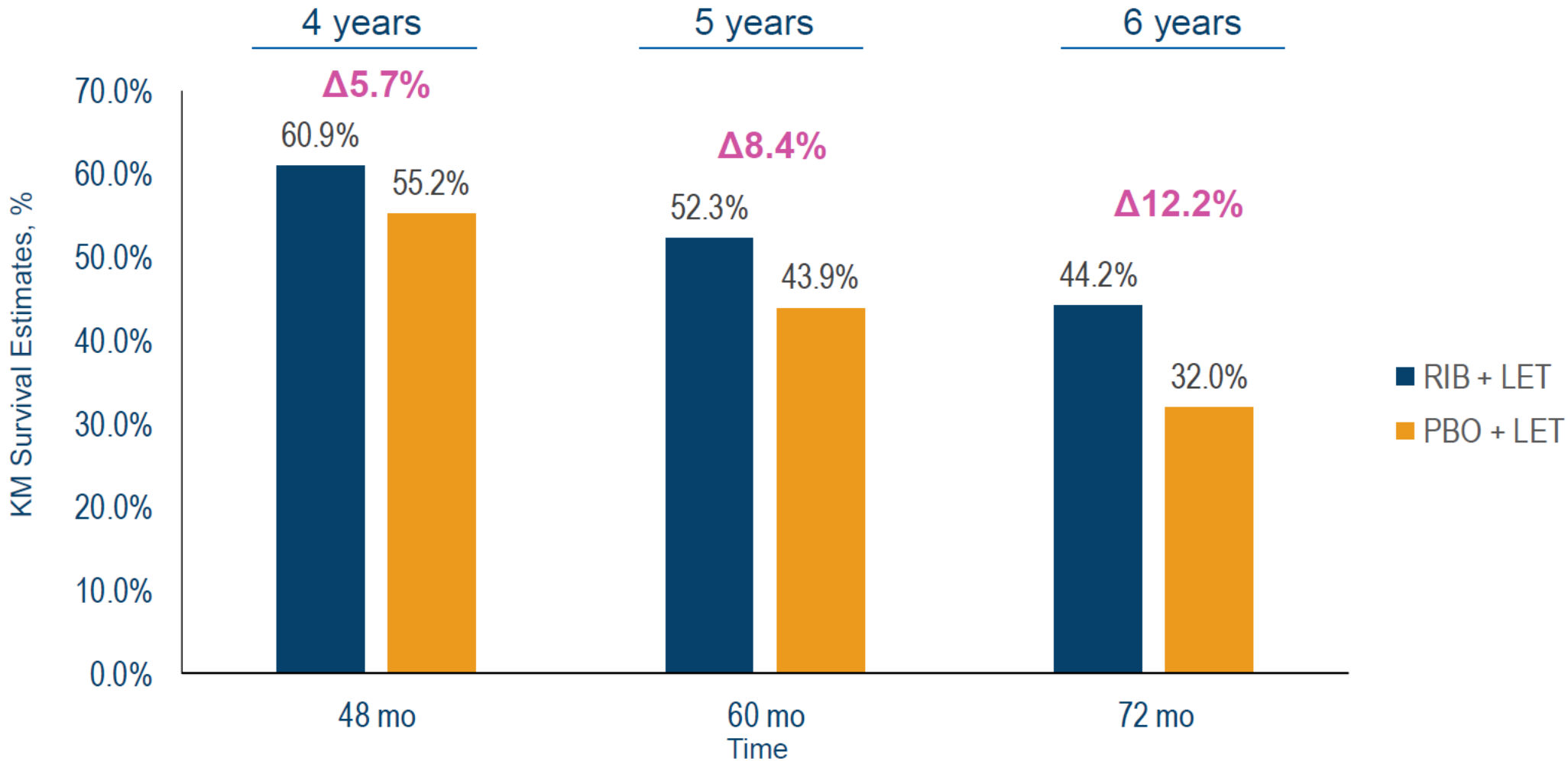
MONALEESA-2: Ribociclib achieved a statistically significant and clinically meaningful OS benefit

- Median follow-up time was 80 months (minimum, 75 months)
- Improvement in median OS was 12.5 months with RIB + LET compared with PBO + LET
- The *P* value of .008 crossed the prespecified boundary to claim superior efficacy



Reference: 1. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950.

MONALEESA-2: The OS benefit of ribociclib increased over time based on Kaplan-Meier estimates



2021 ESMO congress

Reference: Hortobagyi GN, et al. ESMO 2021. Oral LBA17_PR.

MONALEESA-2: Subsequent therapy after discontinuation

- Subsequent CDK4/6i use was higher in the PBO arm (34.4%) than the RIB arm (21.7%)
- Despite more subsequent CDK4/6i use in the PBO arm, the statistically significant benefit of 1L RIB was maintained

Parameter, n	RIB + LET n = 334	PBO + LET n = 334
Patients who discontinued study treatment, n	304 (91.0)	317 (94.9)
Patients who received first subsequent therapy, n (%)[a,b]	267 (87.8)	286 (90.2)
Hormone therapy alone	100 (32.9)	92 (29.0)
Hormone therapy + other therapy	74 (24.3)	94 (29.7)
Chemotherapy alone	53 (17.4)	61 (19.2)
Chemotherapy + hormone or other therapy	32 (10.5)	33 (10.4)
Patients who received a CDK4/6i in any subsequent line of therapy, n (%)[a,c]	66 (21.7)	109 (34.4)
Palbociclib	49 (16.1)	100 (31.5)
Ribociclib	14 (4.6)	6 (1.9)
Abemaciclib	8 (2.6)	12 (3.8)

[a] Percentages reported are based on the number of patients who discontinued study treatment. [b] Two patients (0.6%) in the ribociclib arm and 4 patients (1.2%) in the placebo arm received other therapies as the first subsequent antineoplastic therapy. [c] A patient with multiple occurrences of receiving a subsequent CDK4/6i is only counted once for the total row.

Reference: Hortobagyi GN, et al. *N Engl J Med.* 2022;386:942-950.

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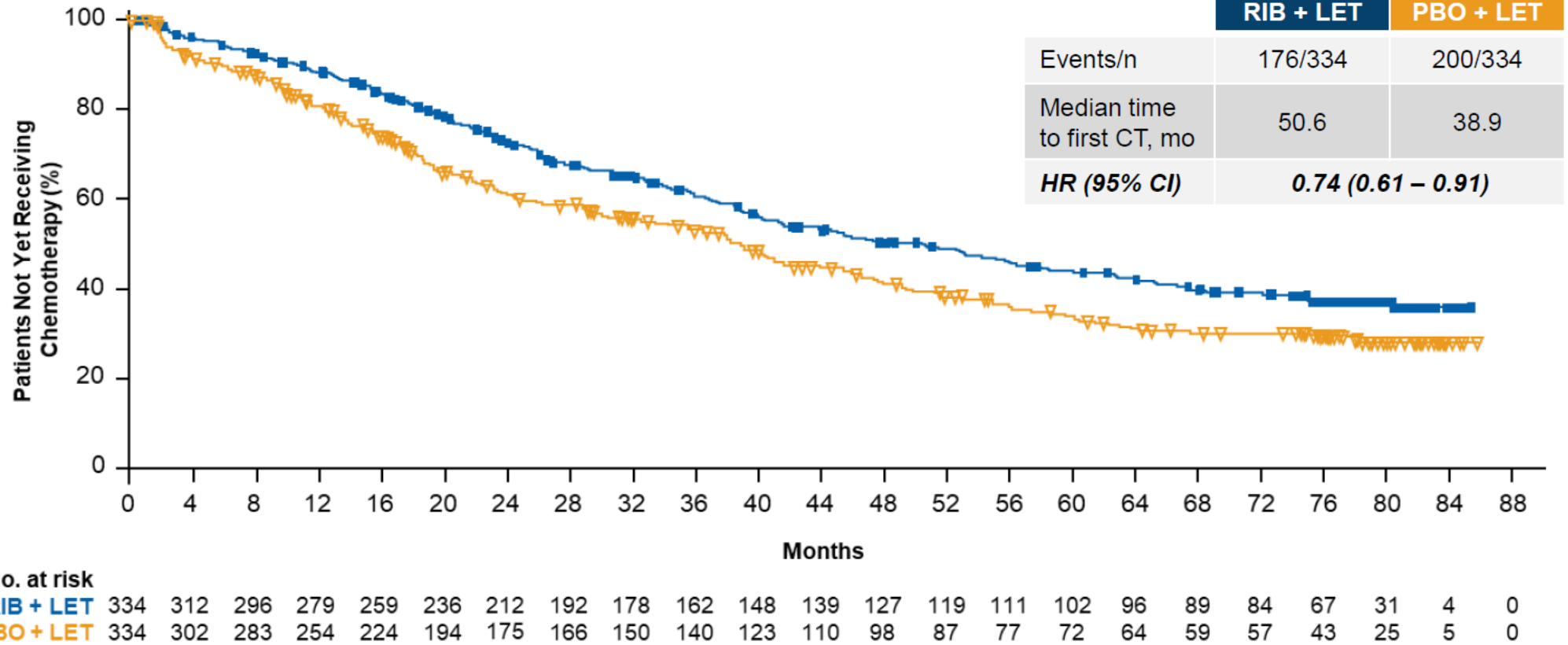
MONALEESA-2: Ribociclib + letrozole delayed time to first chemotherapy by approximately 1 year



	RIB + LET	PBO + LET
Events/n	176/334	200/334
Median time to first CT, mo	50.6	38.9
HR (95% CI)	***0.74 (0.61 – 0.91)***	

Time to first subsequent chemotherapy was defined as the time from randomization to the start of first chemotherapy following discontinuation of study treatment

Reference: Hortobagyi GN, et al. *N Engl J Med.* 2022;386:942-950.

Baseline characteristics were generally similar in MONALEESA-2, PALOMA-2 and MONARCH 3

Baseline characteristic, n (%)	MONALEESA-2[1,2]		PALOMA-2[3,4]		MONARCH 3[5]	
	RIB + LET, n=334	PBO + LET, n=334	PAL + LET, n=444	PBO + LET n=222	ABE + NSAI n=328	PBO + NSAI N=165
Disease site						
Visceral	197 (59.0)	196 (58.7)	214 (48.2)	110 (49.5)	172 (52.4)	89 (53.9)
Bone only	69 (20.7)	78 (23.4)	103 (23.2)	48 (21.6)	70 (21.3)	39 (23.6)
ECOG PS						
0	205 (61.4)	202 (60.5)	257 (57.9)	102 (45.9)	192 (58.5)	104 (63.0)
1	129 (38.6)	132 (39.5)	178 (40.1)	117 (52.7)	136 (41.5)	61 (37.0)
2[a]	-	-	9 (2.0)	3 (1.4)	-	-
Prior (neo)adjuvant treatment						
CT	146 (43.7)	145 (43.4)	213 (48.0)	109 (49.1)	125 (38.1)	66 (40.0)
ET	175 (52.4)	171 (51.2)	249 (56.1)	126 (56.8)	150 (45.7)	80 (48.5)
No. of disease sites						
1	100 (29.9)	117 (35.0)	138 (31.1)	66 (29.7)	96 (29.3)	47 (28.5)
2	118 (35.3)	103 (30.8)	117 (26.4)	52 (23.4)	76 (23.2)	42 (25.5)
≥3	114 (34.1)	113 (33.8)	189 (42.5)	104 (46.9)	154 (47.0)	75 (45.5)

[a] MONALEESA-2 and MONARCH 3 only included patients with ECOG PS of 0 or 1.

References: 1. Hortobagyi GN, et al. *N Engl J Med.* 2016;375:1738-1748. 2. Hortobagyi GN, et al. *N Engl J Med.* 2022;386:942-950. 3. Finn RS, et al. *N Engl J Med.* 2016;375:1925-1936. 4. Finn RS, et al. ASCO 2022. LBA1003. 5. Goetz MP, et al. *J Clin Oncol. 2017*;35:3638-3646.

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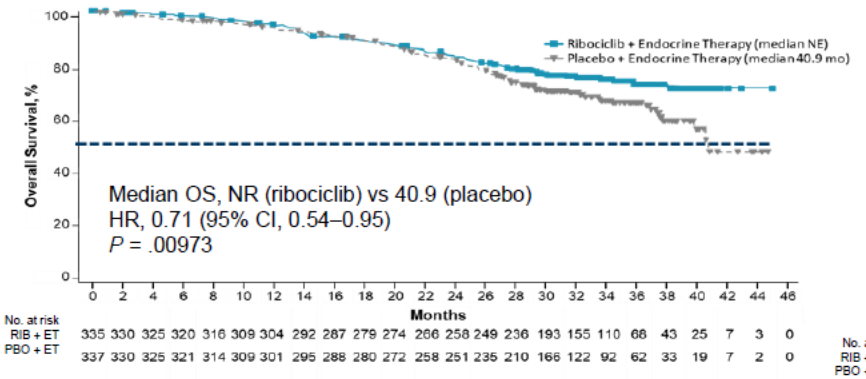
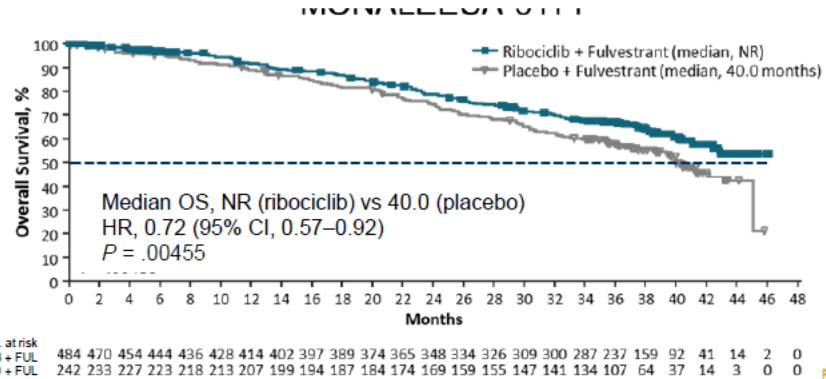
Ribociclib demonstrated significant OS benefit[a] regardless of menopausal status, ET partner, or line of therapy

MONALEESA-7 ITT[1]



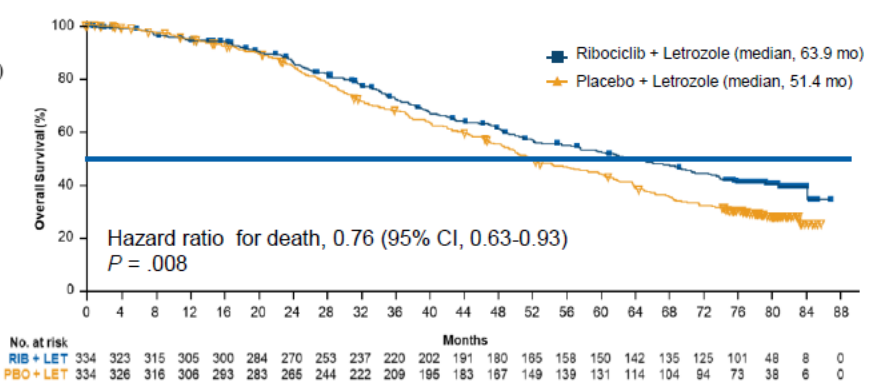
- Pre-/perimenopausal
- ET partner: NSAI/tamoxifen
- First-line treatment
  - 14% of patients received prior CT for ABC
- Updated ad hoc OS analysis[5]
  - Median follow-up: 53.5 mo (additional 18.9 mo of follow-up)
  - mOS: ribociclib, 58.7 mo; placebo, 48.0 mo
  - HR: 0.76 (95% CI, 0.61-0.96)

MONALEESA-3 ITT[2]



- Postmenopausal
- ET partner: fulvestrant
- First- and second-line treatment
  - Early relapsers were included in the second line
- Updated ad hoc OS analysis[6]
  - Median follow-up: 56.3 mo (additional 16.9 mo of follow-up)
  - mOS: ribociclib, 53.7 mo; placebo: 41.5 mo
  - HR: 0.73 (95% CI, 0.59-0.90)

MONALEESA-2 ITT[3,4]



- Postmenopausal
- ET partner: letrozole
- First-line treatment

Comparisons cannot be made in the absence of well-controlled, head-to-head studies

[a] Based on final protocol-specified OS analysis.

References: 1. Im SA et al. *N Engl J Med.* 2019;381:307-316. 2. Slamon DJ et al. *N Engl J Med.* 2020;382:514-524. 3. Hortobagyi GN, et al. *N Engl J Med.* 2022;386:942-950. 4. Hortobagyi GN, et al. ESMO 2021. Oral LBA17_PR. 5. Tripathy D. SABCS 2020. Poster PD2-04. 6. Slamon DJ. ASCO 2021. Oral 1001.

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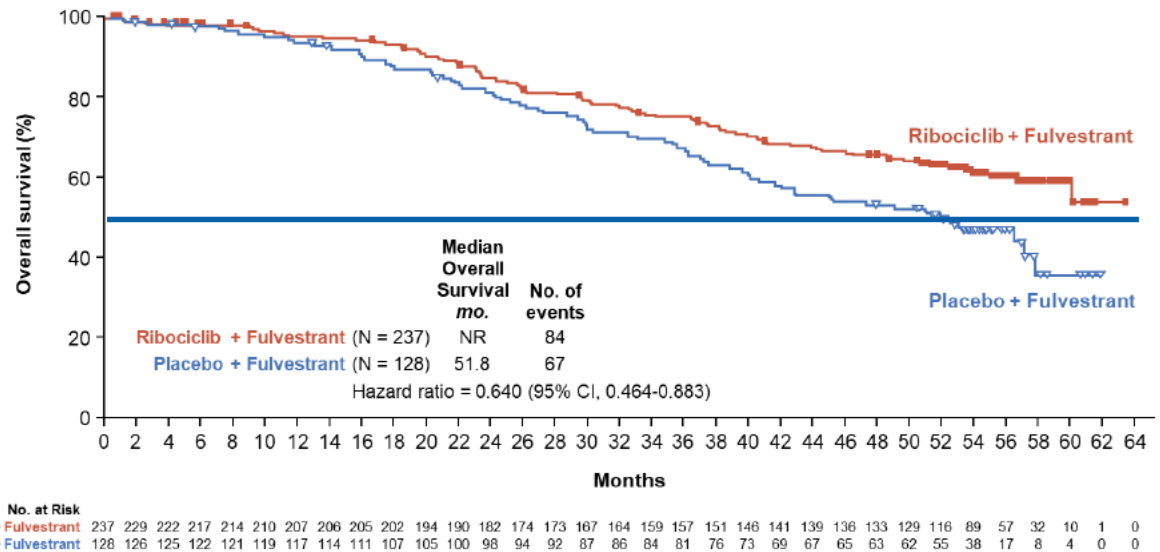
The OS benefit with ribociclib was maintained in the 1L and 2L settings in an ad hoc analysis[a] of MONALEESA-3

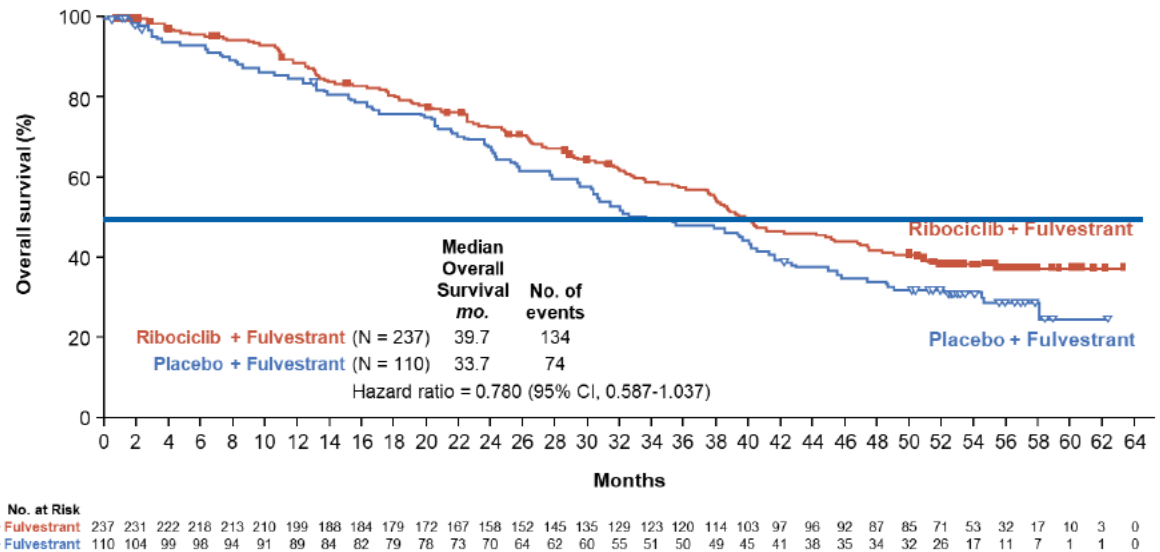
1L Setting[b]



No. at Risk

Ribociclib + Fulvestrant	237	229	222	217	214	210	207	206	205	202	194	190	182	174	173	167	164	159	157	151	146	141	139	136	133	129	116	89	57	32	10	1	0
Placebo + Fulvestrant	128	126	125	122	121	119	117	114	111	107	105	100	98	94	92	87	86	84	81	76	73	69	67	65	63	62	55	38	17	8	4	0	0

2L Setting[c]



No. at Risk

Ribociclib + Fulvestrant	237	231	222	218	213	210	199	188	184	179	172	167	158	152	145	135	129	123	120	114	103	97	96	92	87	85	71	53	32	17	10	3	0
Placebo + Fulvestrant	110	104	99	98	94	91	89	84	82	79	78	73	70	64	62	60	55	51	50	49	45	41	38	35	34	32	26	17	11	7	1	1	0

This analysis had an additional 16.9 months follow-up from the final protocol-specified analysis

[a] Median follow/up, 56.3 months. [b] De novo ABC or relapse > 12 months after completion of (neo)adjuvant ET with no treatment for ABC. [c] Early relapse on or ≤ 12 months from completion of (neo)adjuvant ET, no treatment for ABC, or relapse > 12 months from completion of (neo)adjuvant ET + PD on 1L ET for ABC, or ABC at diagnosis + PD on 1L ET for ABC.

Reference: Slamon DJ. ASCO 2021. Abstract 1001.

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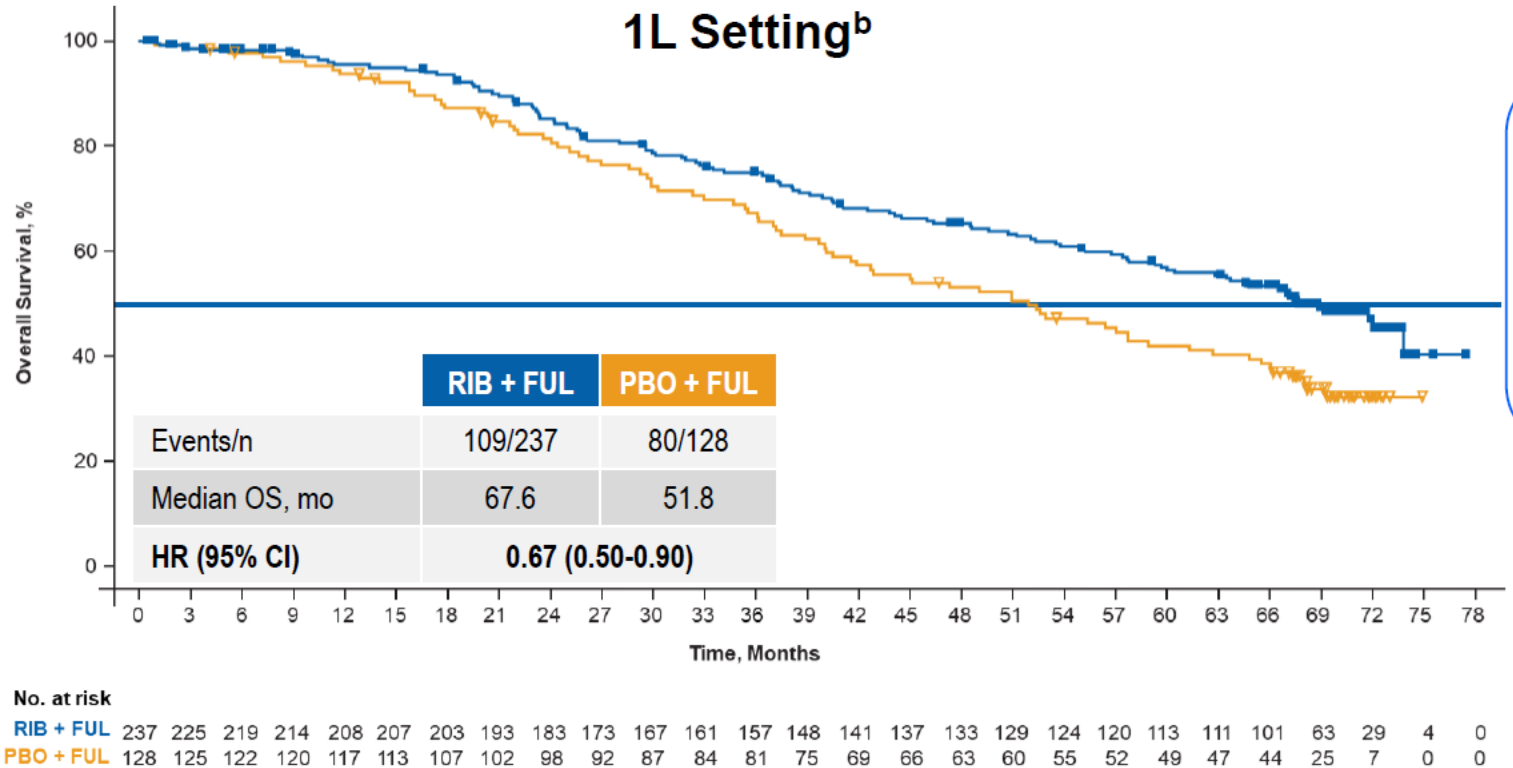
Median OS in the ribociclib arm has now been reached for the first-line population in MONALEESA-3[a]



A significant OS benefit was noted in the Ribociclib group as compared with the placebo group, with a 33% difference in the relative risk of death

- This analysis had an additional 31.4 months follow-up from the final protocol-specified analysis
- 1L ribociclib was associated with a 15.8-month improvement in OS vs placebo and a 33% relative reduction in risk of death
- At 5 years, the survival rates in the ribociclib vs placebo arms were 56.5% vs 42.1%, respectively

[a] Exploratory analysis with median duration between randomization and cut-off date of 70.8 months. [b] De novo ABC or relapse > 12 months after completion of (neo)adjuvant ET with no treatment for ABC.

Reference: Neven P. ESMO Breast 2022. Mini-Oral LBA4.

NCCN now differentiates Ribociclib as the only Category 1 Preferred 1L treatment option in combination with an AI for patients with HR+/HER2- mBC

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens

First-Line Therapy

- Aromatase inhibitor + CDK4/6 inhibitor[b]
  - Aromatase inhibitor + ribociclib (category 1)[c]
  - Aromatase inhibitor + abemaciclib
  - Aromatase inhibitor + palbociclib
- Fulvestrant[d] + CDK4/6 inhibitor[b]
  - Fulvestrant + ribociclib (category 1)[e]
  - Fulvestrant + abemaciclib (category 1)[e]
  - Fulvestrant + palbociclib

Second- and Subsequent-Line Therapy

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[f,g]
- For *PIK3CA* or *AKT1* activating mutations or PTEN alterations, see targeted therapy options, see BINV-Q (6)[h]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[i,j]

Other Recommended Regimens

First- and/or Subsequent-Line Therapy

- Selective ER down-regulator
  - Fulvestrant[k]
  - For *ESR1* mutated tumors, see BINV-Q (6)
- Selective ER down-regulator (fulvestrant) + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[k]
- Non-steroidal aromatase inhibitor
  - Anastrozole
  - Letrozole
- Selective ER modulator
  - Tamoxifen
- Steroidal aromatase inactivator
  - Exemestane

Useful in Certain Circumstances

Subsequent-Line Therapy

- Megestrol acetate
- Estradiol
- Abemaciclib[l]
- Targeted therapy options, see BINV-Q (6)

HER2-Positive and Postmenopausal[m,n] or Premenopausal Receiving Ovarian Ablation or Suppression

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

Reference: NCCN Guidelines version 1.2024 Breast Cancer

High ESMO Magnitude of Clinical Benefit Scale scores[1] reflect the positive benefit of treatment with ribociclib

Agent	Trial	Menopausal Status	Treatment Setting	ET Partner	Outputs Reported to Date	MCBS Agent Score[1]
Ribociclib[2-4]	MONALEESA-7	Premenopausal	1L	NSAI or TAM	PFS, OS, QOL	5
Ribociclib[5-7]	MONALEESA-3	Postmenopausal	1L or 2L	Fulvestrant	PFS, OS, QOL	4
Abemaciclib[8-10]	MONARCH 2	Pre-/peri- and postmenopausal	2L	Fulvestrant	PFS, OS, QOL	4
Palbociclib[11-13]	PALOMA-3	Pre- and postmenopausal	2L	Fulvestrant	PFS, OS, QOL	4
Ribociclib[14-16]	MONALEESA-2	Postmenopausal	1L	Letrozole	PFS, **OS**, QOL	**4**
Abemaciclib[17,18]	MONARCH 3	Postmenopausal	1L	NSAI	PFS, QOL	3
Palbociclib[19,20]	PALOMA-2	Postmenopausal	1L	Letrozole	PFS, QOL	3

Bold endpoints are those that are associated with an increase in MCBS score from previous assigned score (ABC6 vs ABC5).

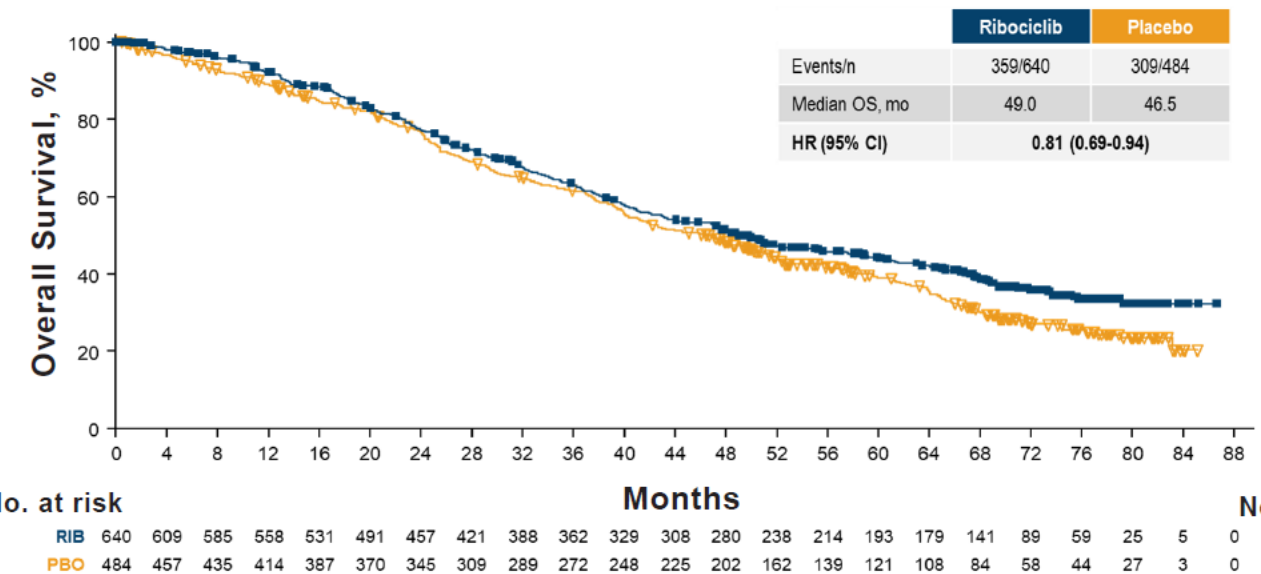
ESMO MCBS scoring details: 4 and 5 = substantial clinical benefit; 3 = moderate benefit

References: 1. https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards Accessed September 19, 2023. 2. Tripathy D, et al. *Lancet Oncol*. 2018;7:904-915. 3. Im SA, et al. *N Engl J Med*. 2019;381:307-316. 4. Harbeck N, et al. *Ther Adv Med Oncol*. 2020;12:1-8. 5. Slamon DJ, et al. *J Clin Oncol*. 2018;24:2465-2472. 6. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524. 7. Fasching PA, et al. *Breast*. 2020;54:148-154. 8. Sledge GW, et al. *J Clin Oncol*. 2017;35:2875-2884. 9. Sledge GW, et al. *JAMA Oncol*. 2020;6:116-124. 10. Kaufman PA, et al. *Oncologist*. 2020;25(2):e243-e251. 11. Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439. 12. Turner NC, et al. *N Engl J Med*. 2018;379:1926-1936. 13. Harbeck N, et al. *Ann Oncol*. 2016;27:1047-1054. 14. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541-1547. 15. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950. 16. Verma S, et al. *Breast Cancer Res Treat*. 2018;170(3):535-545. 17. Goetz M, et al. *J Clin Oncol*. 2017;35:3628-3646. 18. Goetz MP, et al. *Oncologist*. 2020;9999:1-13. 19. Finn RS, et al. *N Engl J Med*. 2016;375:1925-1936. 20. Rugo HS, et al. *Ann Oncol*. 2018;29:888-894.

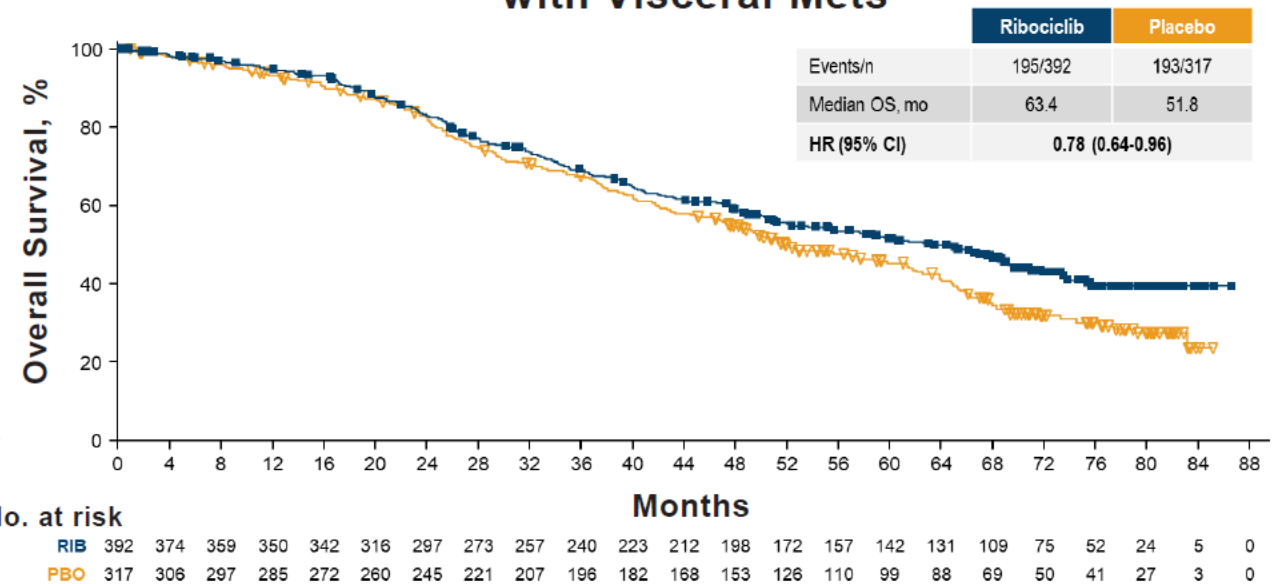
Ribociclib demonstrated a clinically meaningful survival benefit in a pooled ML visceral mets analysis

- All patients with visceral mets, including 1L patients, derived significant OS benefit with RIB + ET vs PBO + ET
  - In 1L patients, a 12-month improvement in OS was observed with RIB + ET vs PBO + ET
- Approximately 58% of 1L patients had visceral metastases in the MONALEESA program

OS in all Patients with Visceral Mets



OS in 1L Patients with Visceral Mets

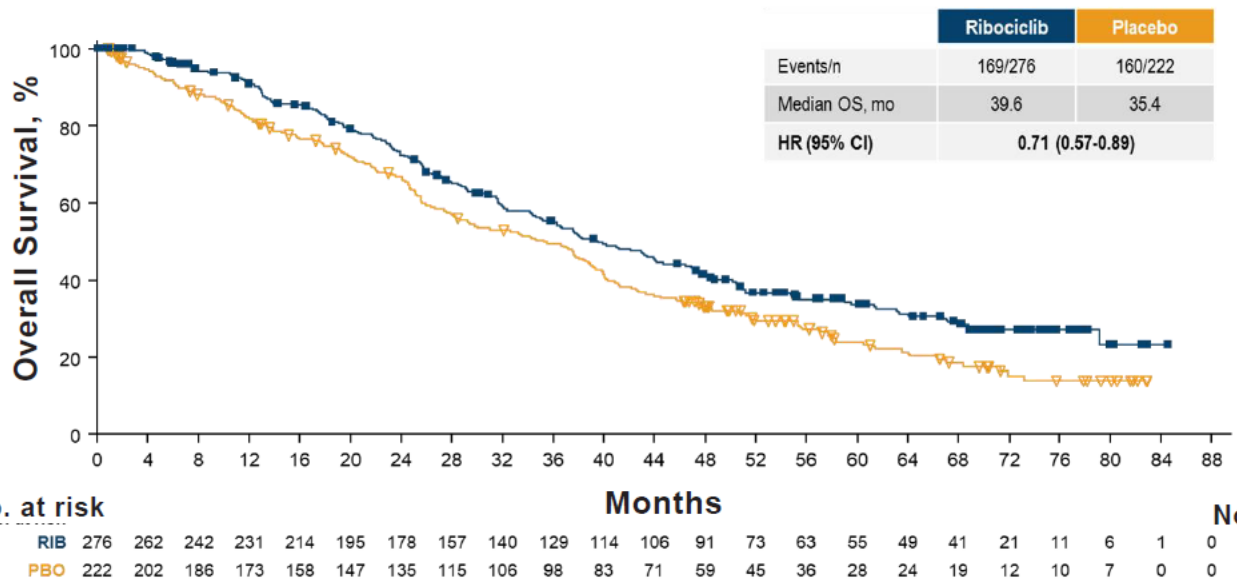


Reference: Yardley D, et al. ESMO 2022. Poster 205P.

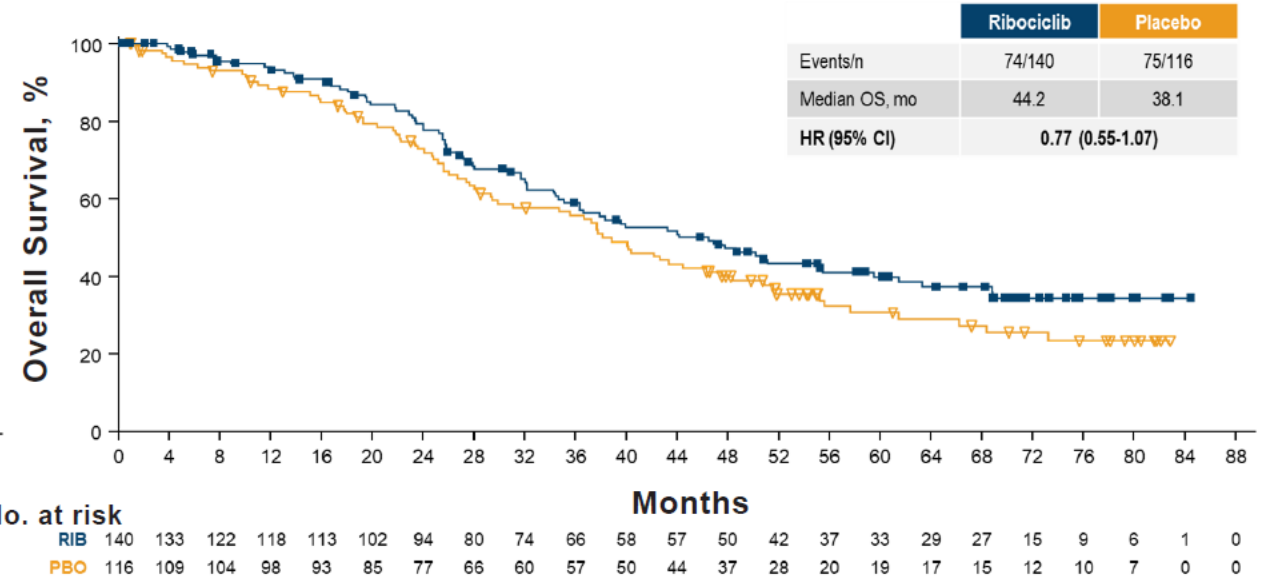
The significant benefit of ribociclib is extended to patients with liver metastases in a pooled ML analysis

- Patients with liver mets derived significant OS benefit with RIB + ET vs ET
  - In 1L patients, mOS numerically favored RIB + ET
- Approximately 21% of 1L patients had liver metastases

OS in all Patients with Liver Mets



OS in 1L Patients with Liver Mets

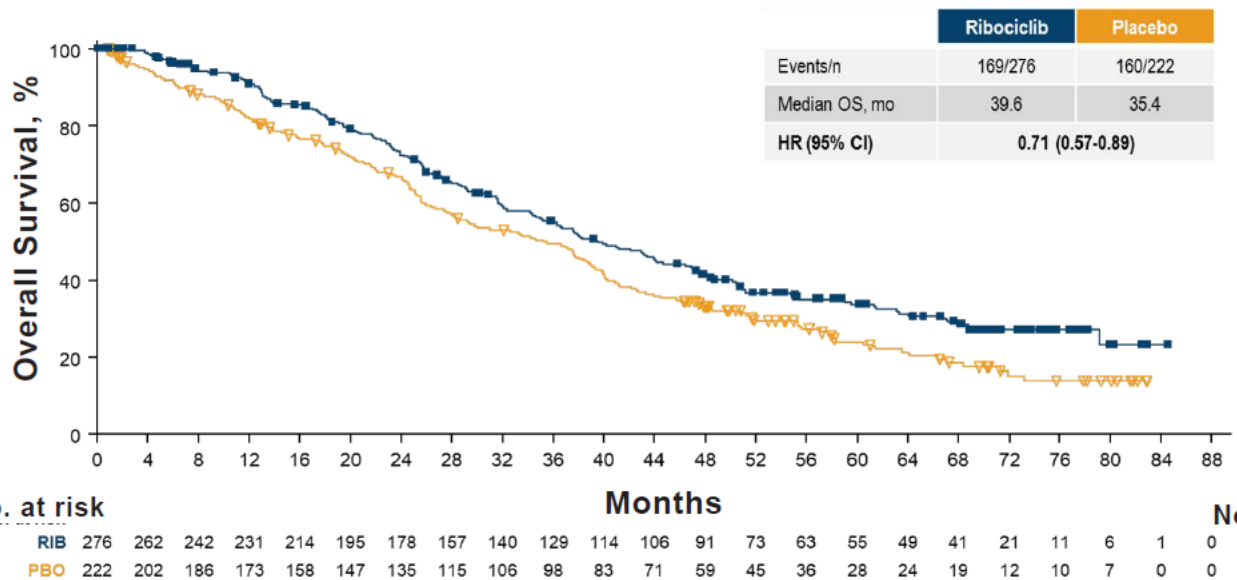


Reference: Yardley D, et al. ESMO 2022. Poster 205P.

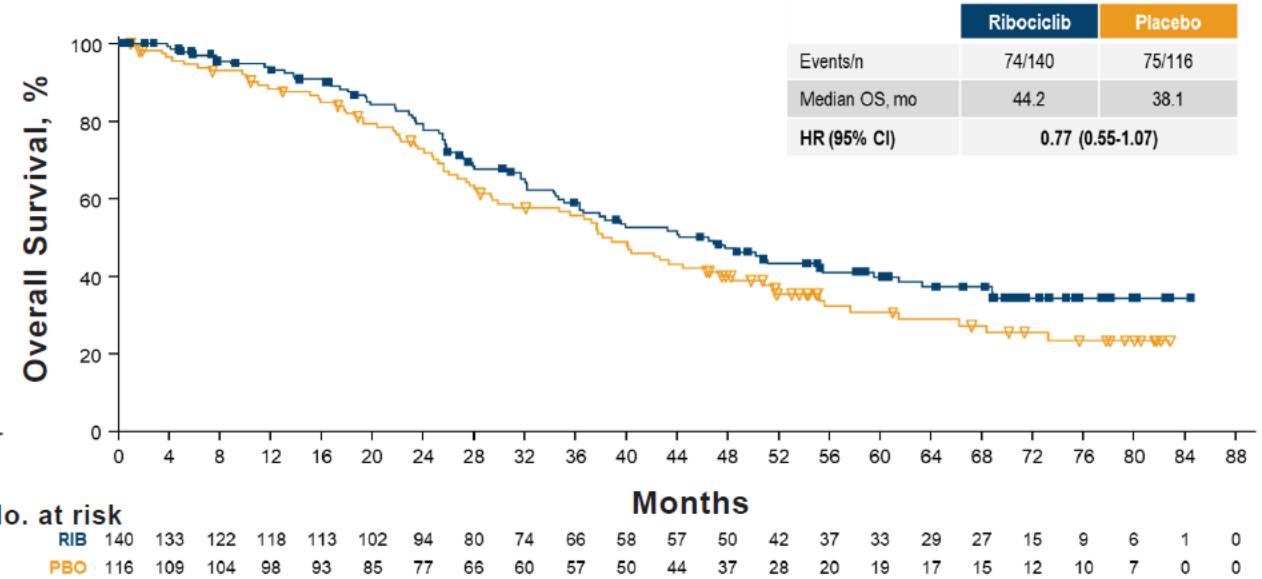
The significant benefit of ribociclib is extended to patients with liver metastases in a pooled ML analysis

- Patients with liver mets derived significant OS benefit with RIB + ET vs ET
  - In 1L patients, mOS numerically favored RIB + ET
- Approximately 21% of 1L patients had liver metastases

OS in all Patients with Liver Mets



OS in 1L Patients with Liver Mets

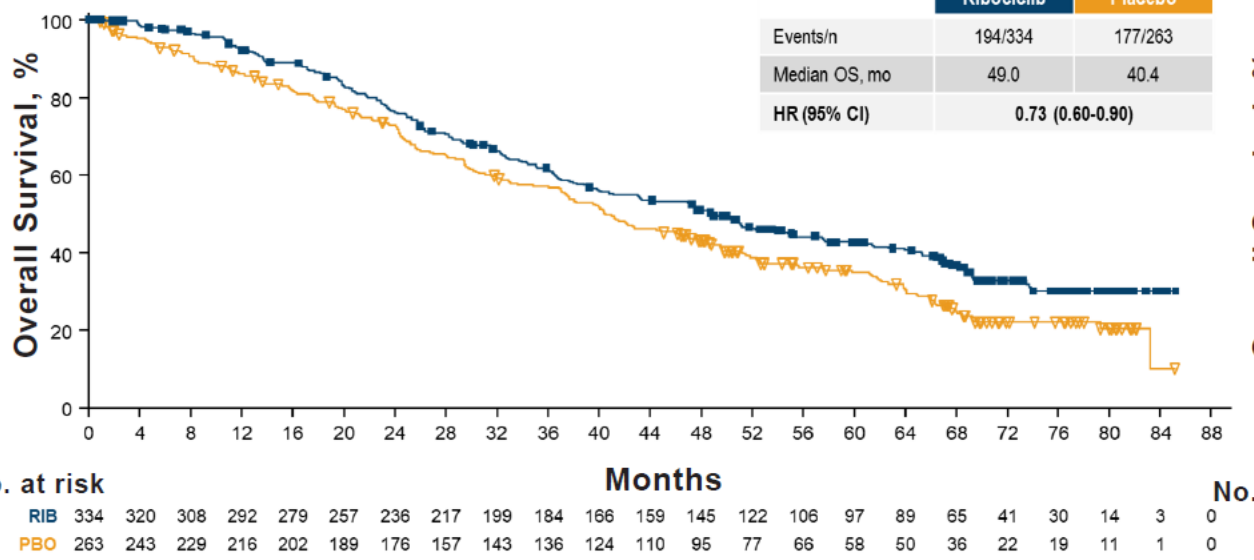


Reference: Yardley D, et al. ESMO 2022. Poster 205P.

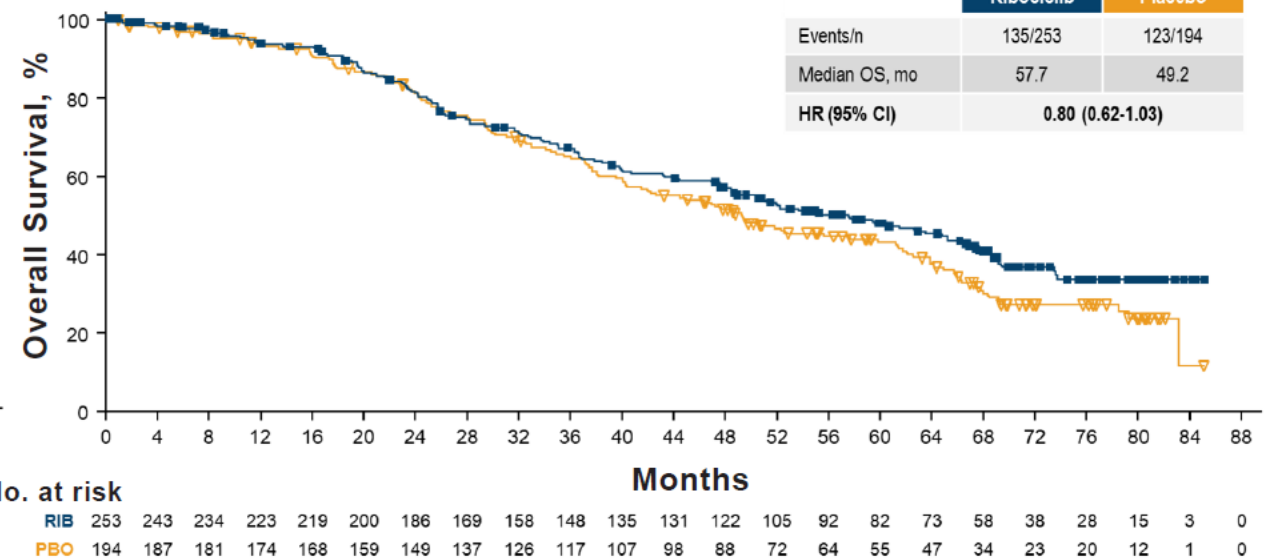
Pooled ML visceral mets analysis: Patients ≥ 3 metastatic sites also significantly benefit from ribociclib

- Patients with ≥ 3 met sites derived significant OS benefit with RIB + ET vs ET
  - In 1L patients, mOS numerically favored RIB + ET
- In all patients with ≥ 3 met sites, including 1L patients, a >10-month mPFS improvement with RIB + ET was seen

OS in all Patients with ≥ 3 Met Sites



OS in 1L Patients with ≥ 3 Met Sites



Reference: Yardley D, et al. ESMO 2022. Poster 205P.

Consistent improvement in long-term survival at 5 and 6 years with ribociclib across all subgroups analyzed in an exploratory analysis of MONALEESA-2

	OS Rate at 5 Years, %		OS Rate at 6 Years, %	
	RIB + FUL	PBO + FUL	RIB + FUL	PBO + FUL
Bone-only metastases				
Yes	58.6	47.1	50.2	33.8
No	50.6	43.0	42.6	31.5
Liver metastases				
Yes	37.2	28.4	31.0	18.9
No	55.2	48.3	46.8	35.7
Liver or lung metastases				
Yes	48.2	45.4	40.5	31.2
No	57.1	41.9	48.6	33.2
No. of metastatic sites				
<3	54.8	46.9	47.4	36.1
≥3	47.4	38.1	37.9	24.2
Prior CT				
Yes	44.1	37.3	39.7	25.1
No	59.3	48.9	47.9	37.3
Prior ET				
NSAI and others	53.8	43.4	46.1	14.5
Tamoxifen +/- NSAI	45.6	43.9	40.3	31.5
None	58.6	44.0	47.6	35.2

Reference: O'Shaughnessy J, et al. SABCS 2021. Oral GS2-01.

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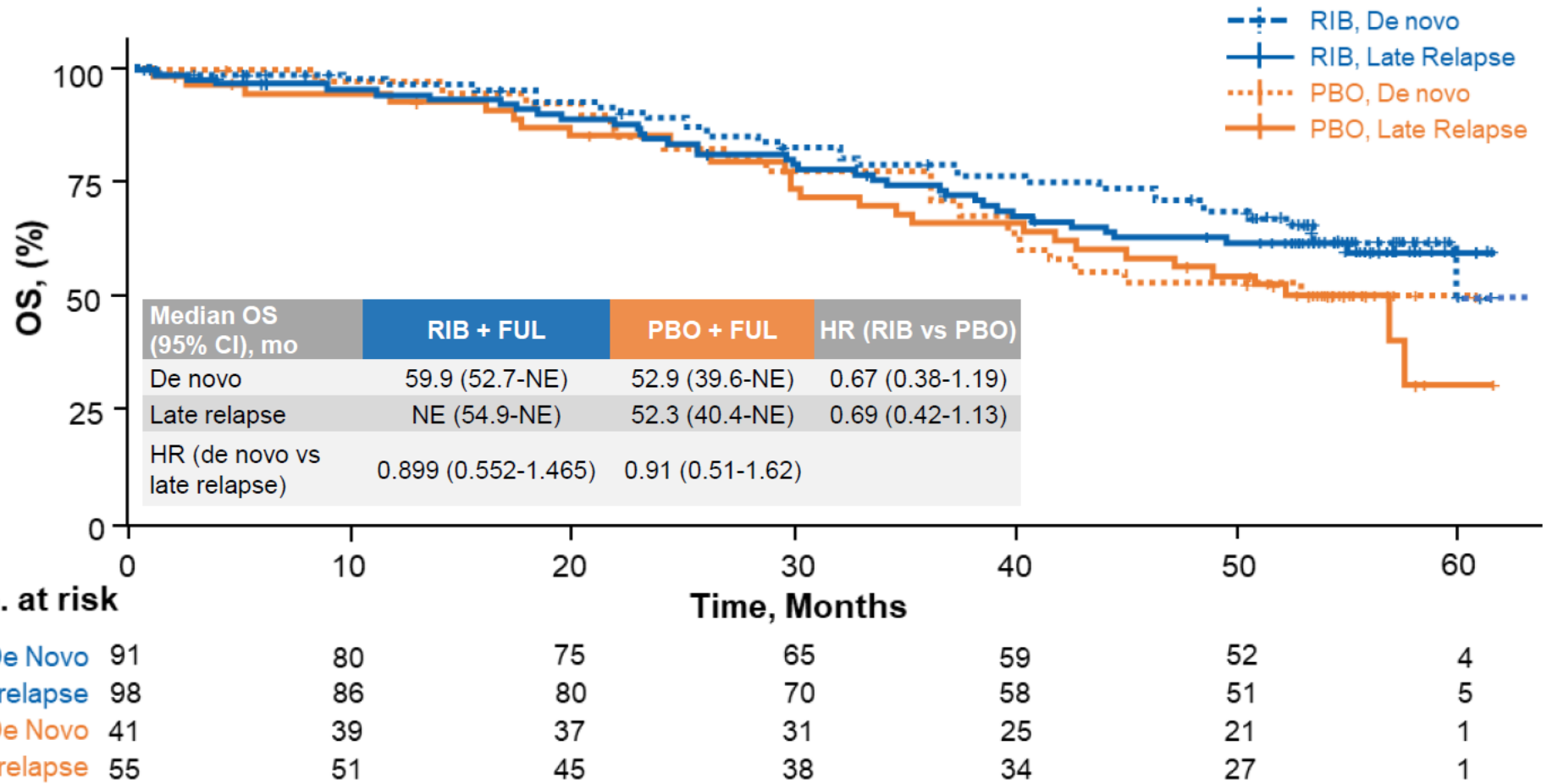
OS benefit maintained in patients with de novo disease and late relapse in MONALEESA-3



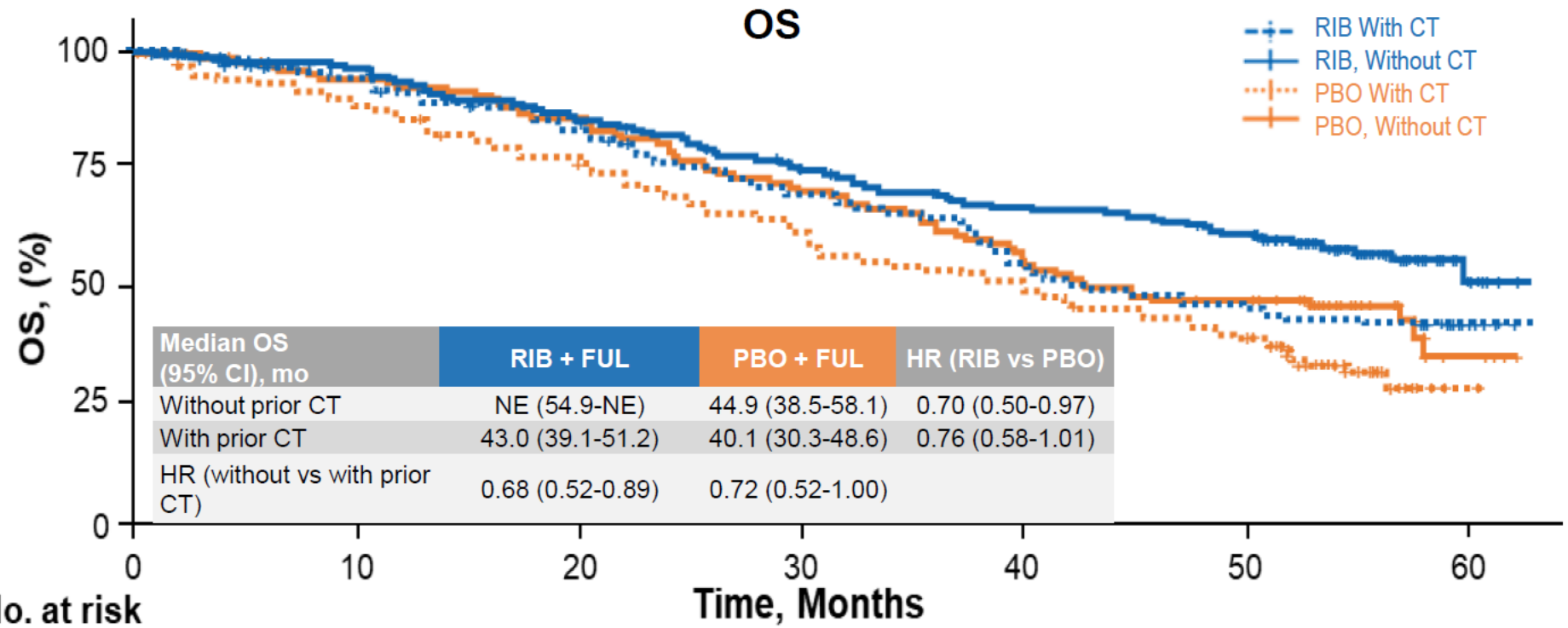
Median OS (95% CI), mo	RIB + FUL	PBO + FUL	HR (RIB vs PBO)
De novo	59.9 (52.7-NE)	52.9 (39.6-NE)	0.67 (0.38-1.19)
Late relapse	NE (54.9-NE)	52.3 (40.4-NE)	0.69 (0.42-1.13)
HR (de novo vs late relapse)	0.899 (0.552-1.465)	0.91 (0.51-1.62)	

No. at risk

RIB, De Novo	91	80	75	65	59	52	4
RIB, Late relapse	98	86	80	70	58	51	5
PBO, De Novo	41	39	37	31	25	21	1
PBO, Late relapse	55	51	45	38	34	27	1

Reference: De Laurentiis M, et al. SABCS 2021. Poster P1-18-11.

OS benefit maintained in patients with vs without prior CT in MONALEESA-3



Median OS (95% CI), mo	RIB + FUL	PBO + FUL	HR (RIB vs PBO)
Without prior CT	NE (54.9-NE)	44.9 (38.5-58.1)	0.70 (0.50-0.97)
With prior CT	43.0 (39.1-51.2)	40.1 (30.3-48.6)	0.76 (0.58-1.01)
HR (without vs with prior CT)	0.68 (0.52-0.89)	0.72 (0.52-1.00)	

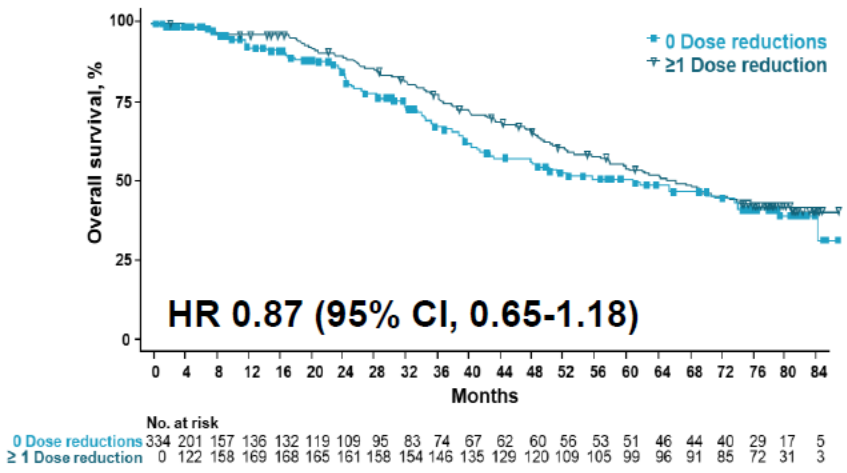
No. at risk

RIB, With CT	265	231	202	164	128	102	9
RIB, Without CT	219	197	172	146	128	116	11
PBO, With CT	126	109	91	73	60	46	1
PBO, Without CT	116	104	94	76	60	50	4

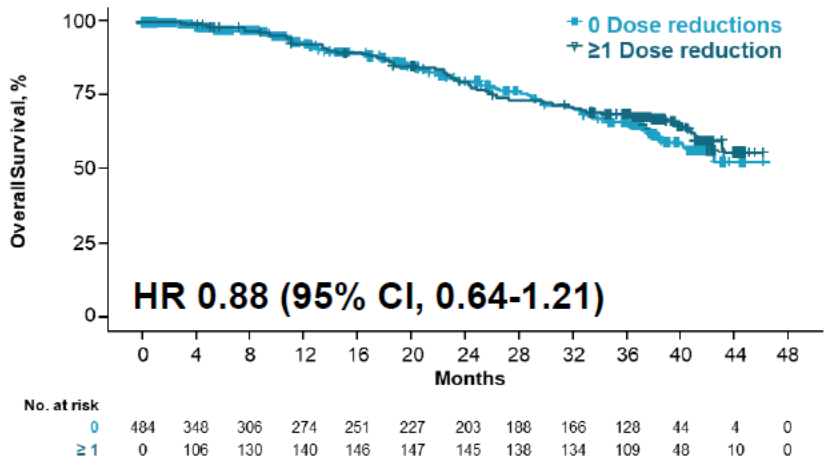
Reference: De Laurentiis M, et al. SABCS 2021. Poster P1-18-11.

Dose reductions of ribociclib do not compromise OS benefit in the advanced setting

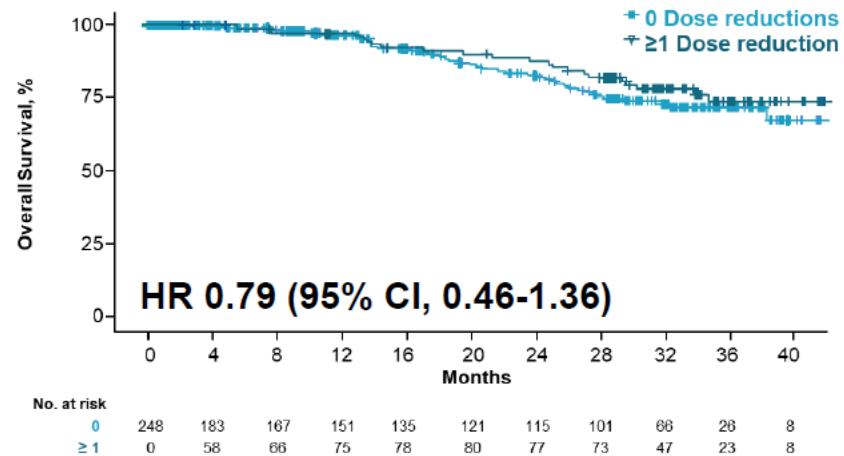
MONALEESA-2[1]



MONALEESA-3[2]



MONALEESA-7[2]



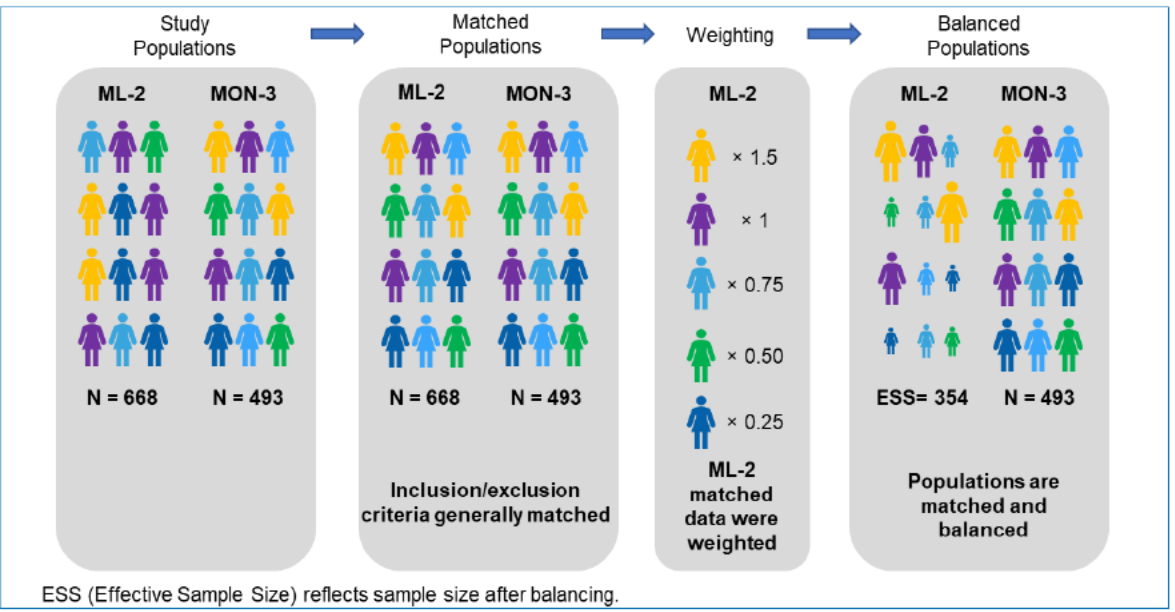
- In pooled **MONALEESA** studies, median PFS was similar between patients with and without ≥1 dose reduction[3]
- An analysis of **PALOMA-3** showed a similar PFS benefit of palbociclib in patients with or without dose reductions[4]
- According to data from **MONARCH** studies, ABE dose reduction did not impact PFS[5]

Comparisons cannot be made in the absence of well-controlled, head-to-head studies.

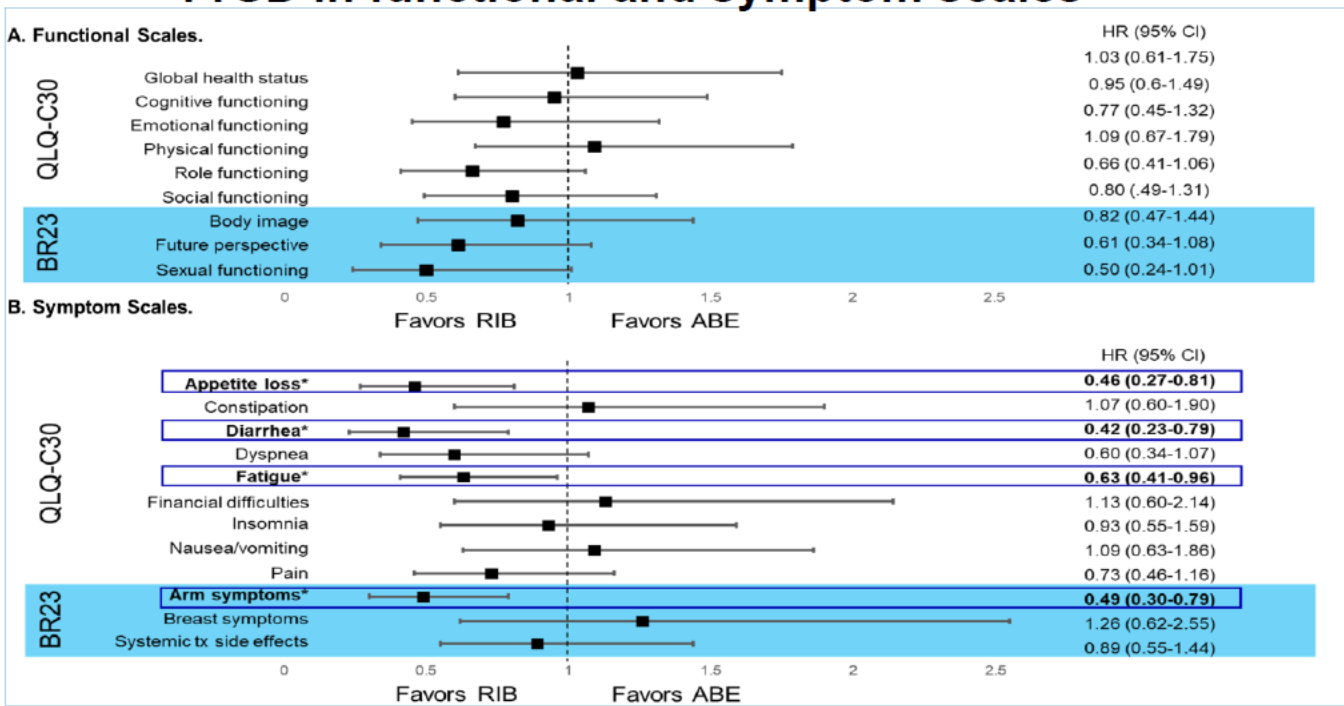
References: 1. Hart L, et al. ASCO 2022. Poster 1017. 2. De Laurentiis M, et al. ESMO 2020. Poster 331P; 3. Beck JT, et al. SABCS 2018. Poster P6-18-06. 4. Verma S, et al. *Oncologist.* 2016;21:1165-1175. 5. Rugo H, et al. *J Clin Oncol.* 2018;36(15 suppl 1):Abstract 1053.

MAIC analysis of QOL in MONALEESA-2 vs MONARCH 3 significantly favored RIB vs ABEMA for diarrhea, fatigue, appetite loss, and arm symptoms

MAIC overview and attrition



TTSD in functional and symptom scales



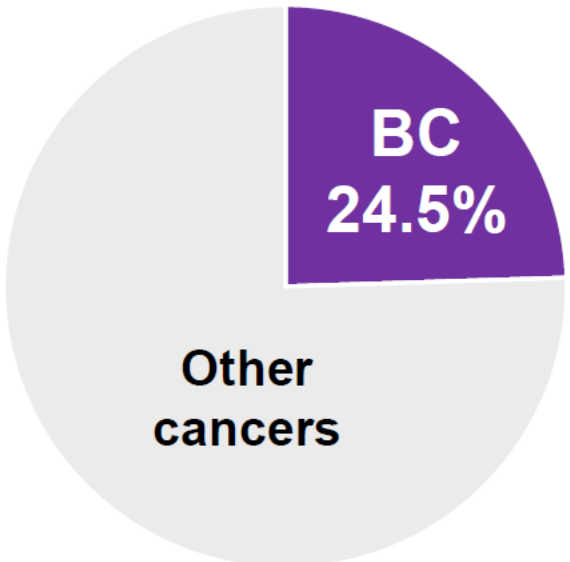
- 1L RIB + AI was associated with better symptom-related QOL compared with 1L ABE + AI in postmenopausal patients with HR+/HER2− ABC

Reference: Ther Adv Med Oncol. 2023; 15

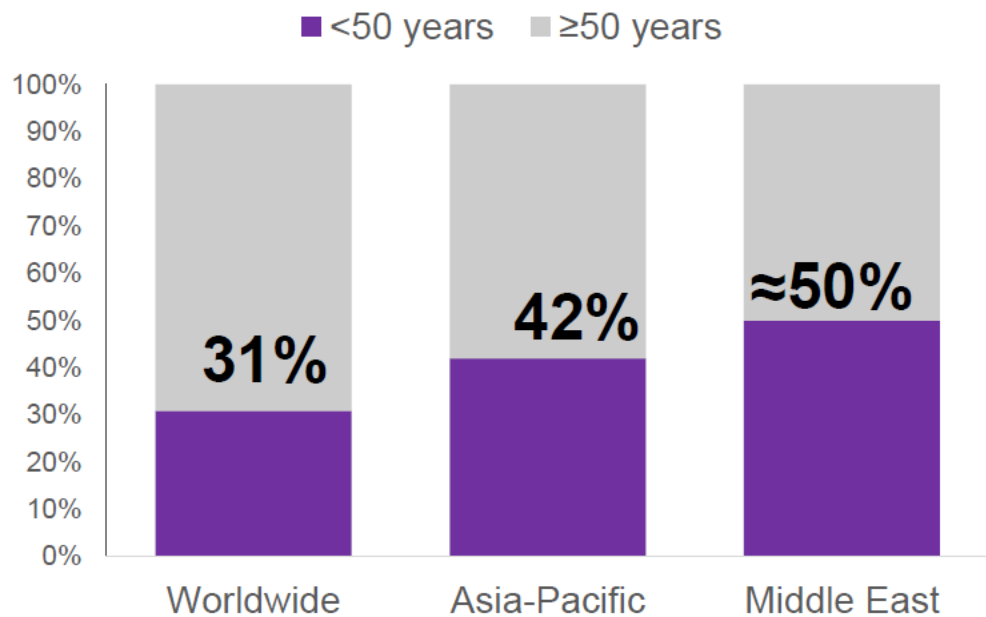
TRATAMIENTO DE CÁNCER DE MAMA AGRESIVO CON RIBOCICLIB

Premenopausal BC

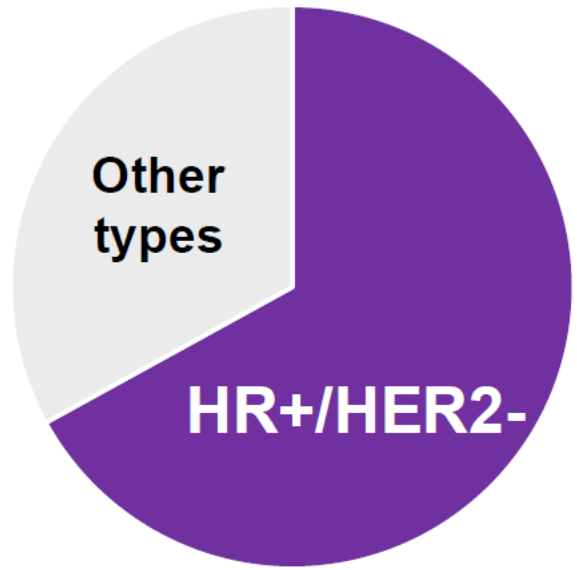
BC is the most frequently diagnosed cancer among women worldwide[1]



Premenopausal (<50 years old) are a higher proportion of patients in Asia-Pacific and Middle Eastern regions[2-4]



≈2/3 of premenopausal women with breast cancer have the HR+/HER2-subtype[5]



- Premenopausal women tend to have more aggressive disease and poorer prognosis compared with postmenopausal women[5]

References: 1. Lei S et al. *Cancer Commun (Lond)*. 2021;41:1183-1194. 2, Heer E et al. *Lancet Global Health*. 2020;8:E1027. 3. Youlden DR, *Cancer Biol Med*. 2014;11:101. 4. Safiri S et al. *Arch Public Health*. 2022;80:168. 5. Shah AN et al. *Oncologist*. 2020;25:e900-e908.

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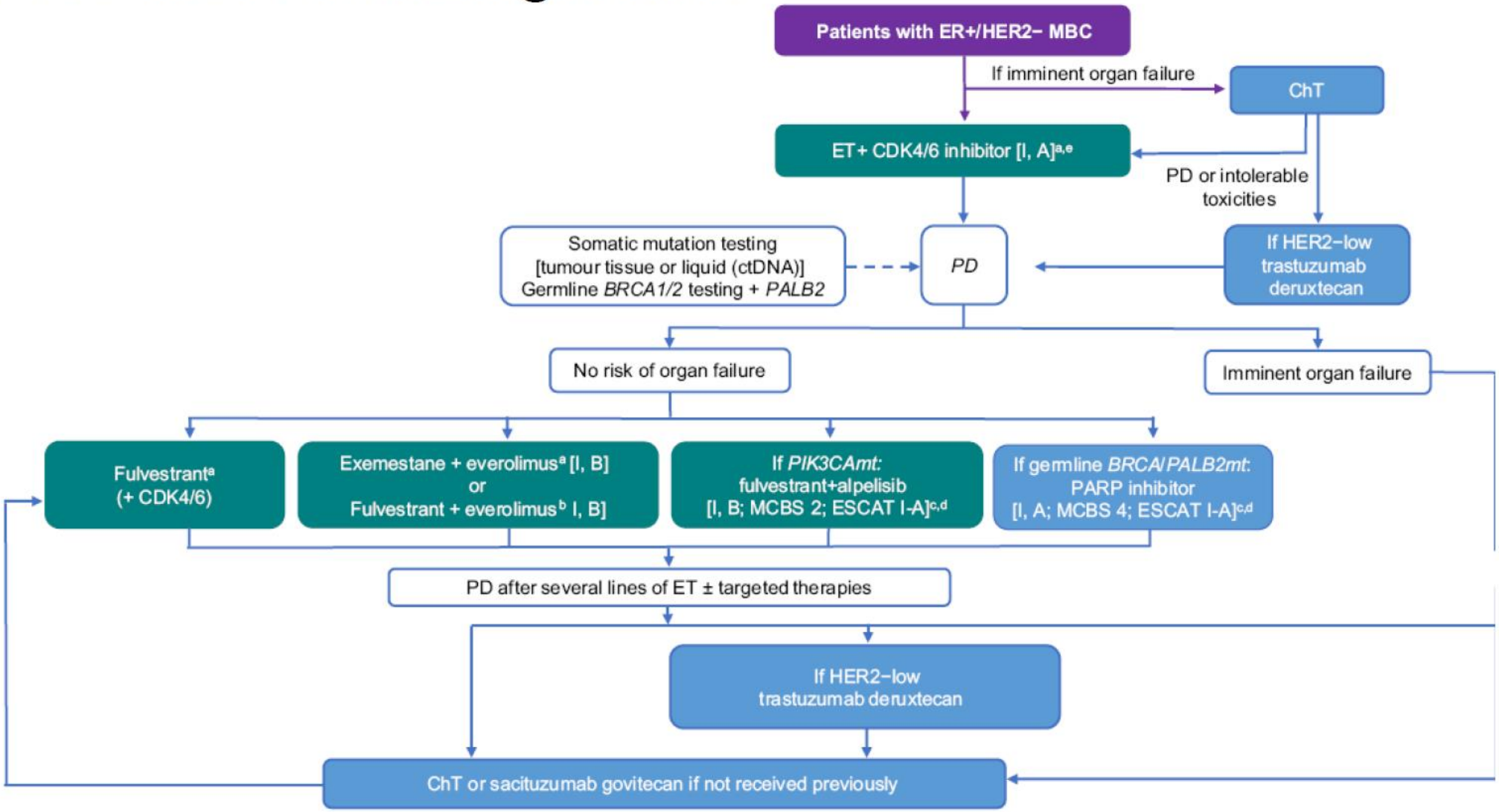
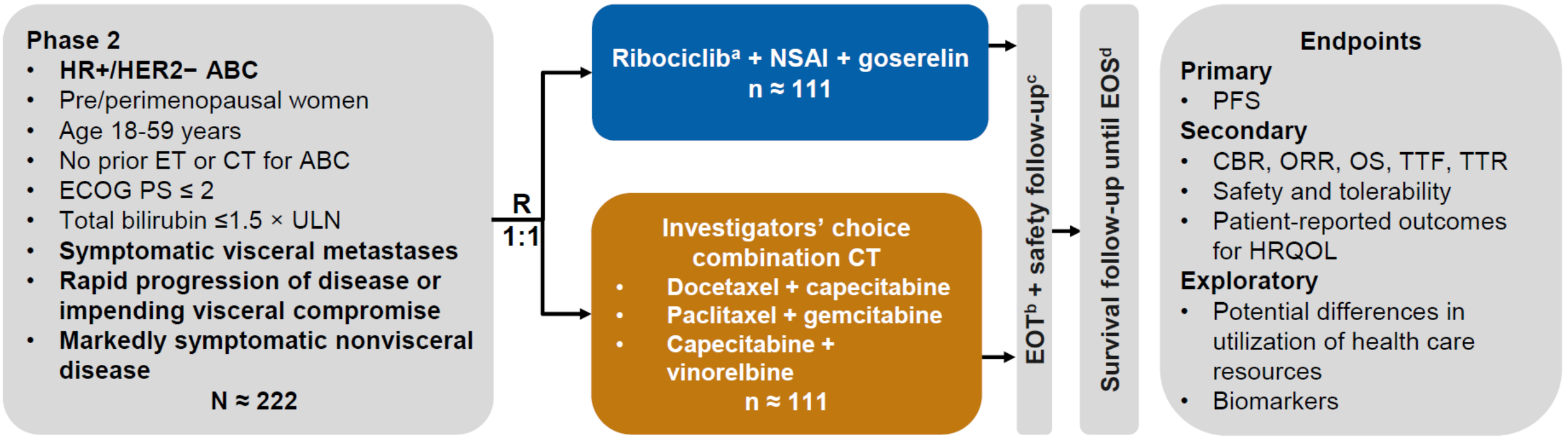
HR+/HER2- MBC treatment guideline



ESMO pan-Asian guideline 2023

RIGHT Choice Study Design

- There is no published clinical study to date investigating the population of patients with aggressive HR+/HER2− disease, including those with visceral crisis
- RIGHT Choice study is the first and only prospective study comparing CDK4/6i + ET vs combination chemotherapy in advanced BC patients with aggressive disease, including those with visceral crisis



[a] Ribociclib will be administered on a 28-day cycle, combination CT on a 21-day cycle. [b] EOT, defined as until diseae progression, unacceptable toxicity, death, or discontinuation for any reason. [c] After discontinuation of study treatment, patients will be followed for safety for at least 30 days except in case of death, lost to follow-up, or withdrawl of consent. [d] Survival follow-up will be done every 16 (± 4) wks until EOS, which is defined by the following: at least 44 months from first patient first visit or when required numbers of OS events have been reached (80% of patients have died), whichever comes first. **Reference:** Lu Y-S et al. SABCS 2022. abstract GS1-10.

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Current ESMO Treatment Guidelines for HR+/HER2− ABC

The definition of Visceral Crisis has evolved

3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3)[1]

ABC IMPORTANT DEFINITIONS

VISCERAL CRISIS is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication from a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.

5th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 5)[2]

Section I. ABC definitions

Guideline statement

Visceral crisis is defined as severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy.

Examples: ***Liver visceral crisis***: rapidly increasing bilirubin >1.5 x ULN in the absence of Gilbert's syndrome or biliary tract obstruction. ***Lung visceral crisis***: rapidly increasing dyspnoea at rest, not alleviated by drainage of pleural effusion.

The inclusion criteria in RIGHT Choice study was based on the definition of visceral crisis in ABC3

References: 1. Cardoso F, et al. Ann Oncol. 2017;28:16-33. 2. Cardoso F, et al. Ann Oncol. 2020;28:1623.

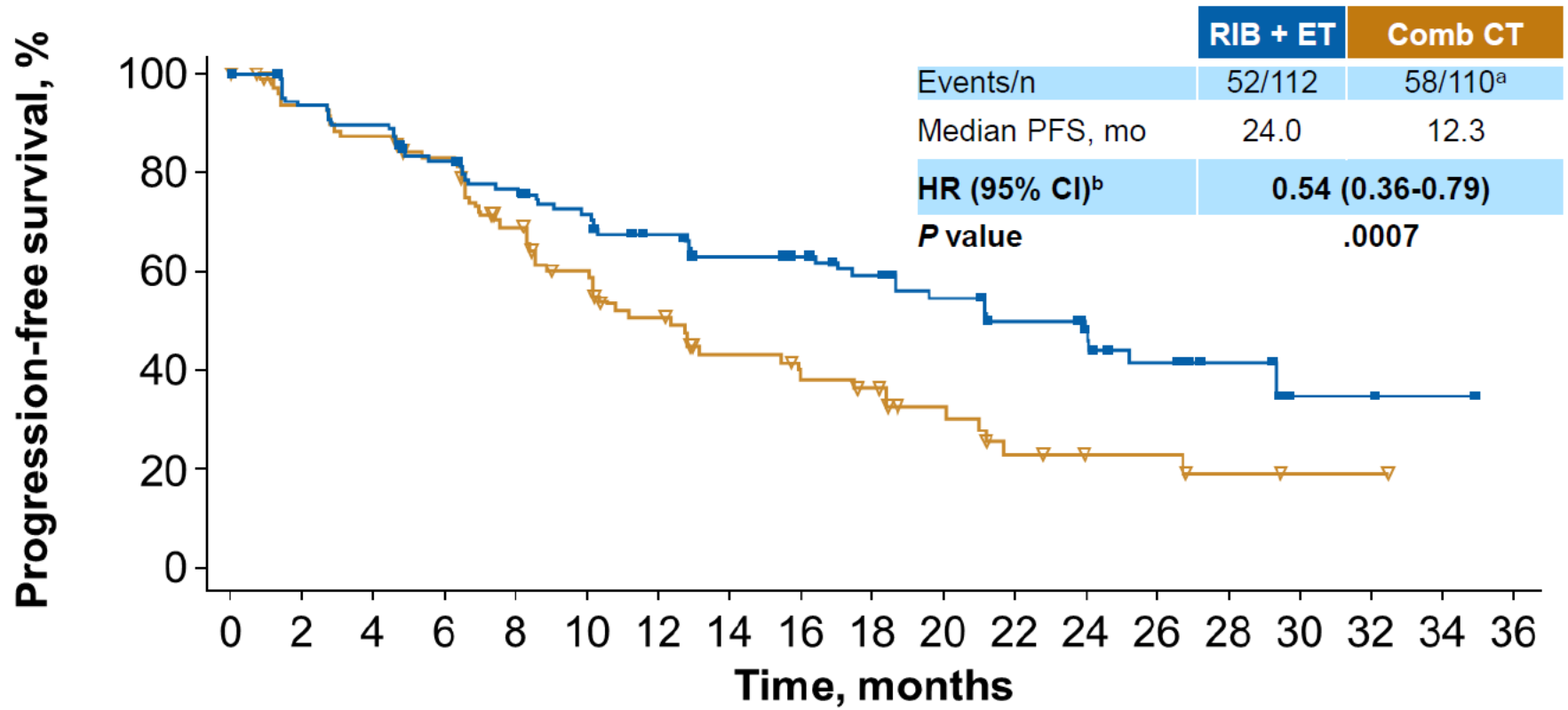
RIGHT Choice: Treatment was ongoing in 46% of patients in the RIB + ET arm

- Baseline characteristics were well balanced between arms
- In the RIB+ET arm
  - Median age was 44 years
  - 53.6% were Asian
  - 66.1% had visceral metastases
  - 54.5% were in visceral crisis

Parameter, n (%)	RIB + ET n = 112	Combination CT n = 110[a,b]
Patients treated		
Treatment ongoing[c,d]	51 (45.5)	26 (23.6)
Reason for end of treatment		
Progressive disease	50 (44.6)	58 (52.7)
Adverse event	8 (7.1)	3 (2.7)
Death	1 (0.9)	0
Physician decision	1 (0.9)	5 (4.5)
Subject decision	1 (0.9)	8 (7.3)

[a] Ten patients in CT arm did not receive any treatment; [b] 24 patients received docetaxel/capecitabine, 34 patients received paclitaxel/gemcitabine, and 42 patients received capecitabine/vinorelbine combination; [c] Patients continued study treatment at the time of the cutoff (12 Apr 2022); [d] The median rime from randomization to data cut-off date was 24.1 months. **Reference:** Lu Y-S et al. SABCS 2022. abstract GS1-10.

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



	RIB + ET	Comb 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

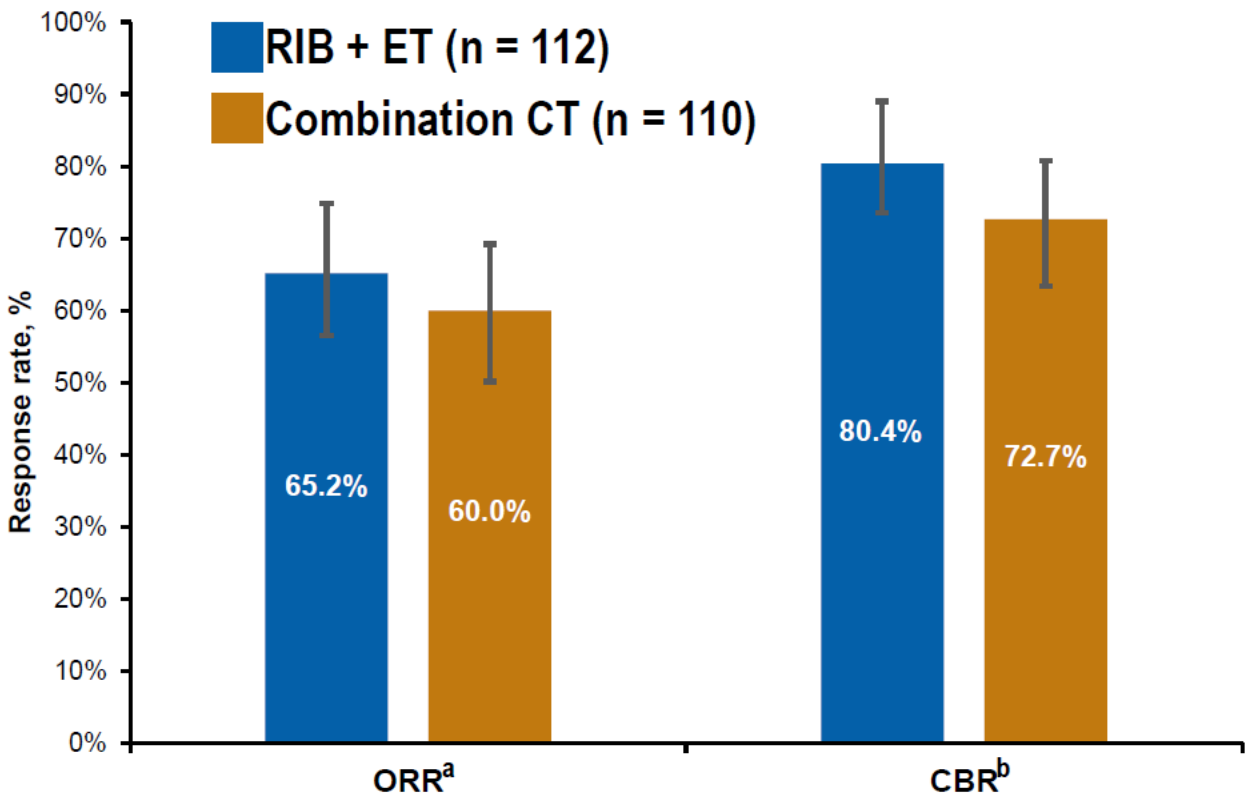
RIB + ET	112	103	99	88	78	70	63	56	50	45	36	30	24	18	7	2	2	1	0
Combination CT	110	90	84	75	56	46	37	26	22	20	14	9	6	6	3	1	1	0	0

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

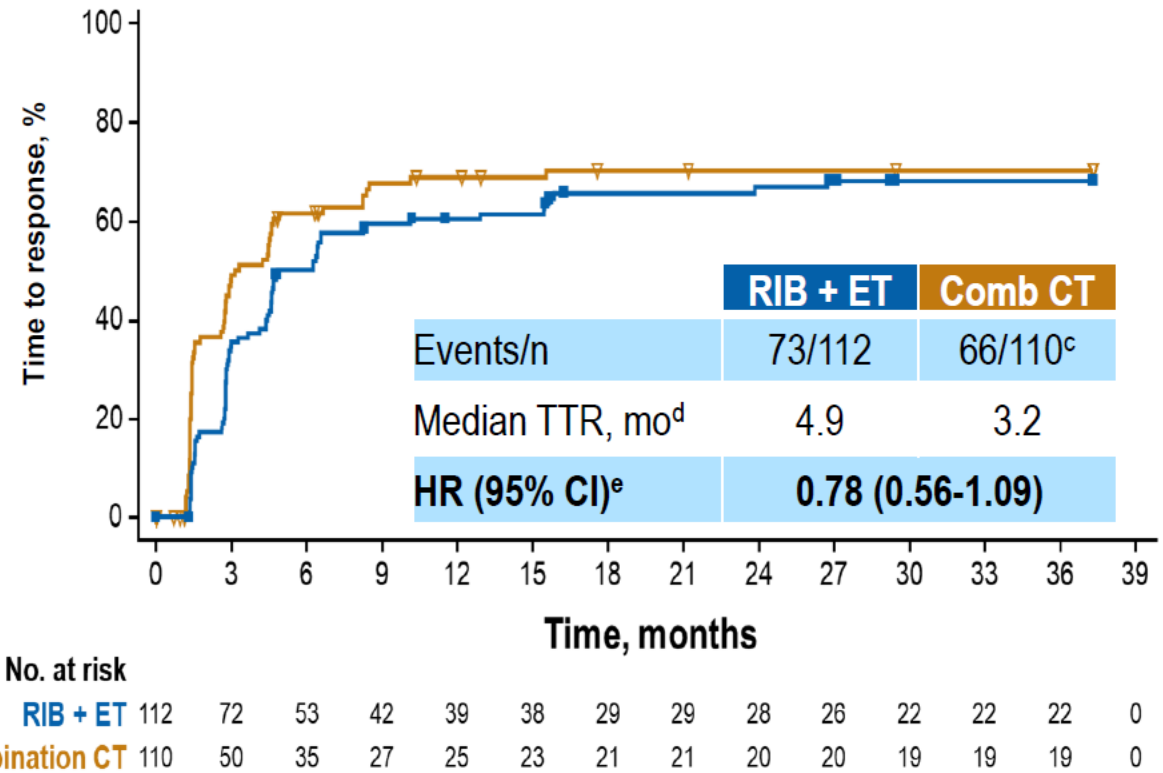
Reference: Lu Y-S et al. SABCS 2022. abstract GS1-10.

RIGHT Choice: Time to treatment response and objective response rate

ORR and CBR were comparable between RIB + ET and combination CT arm



Median TTR with RIB + ET was similar to combination CT

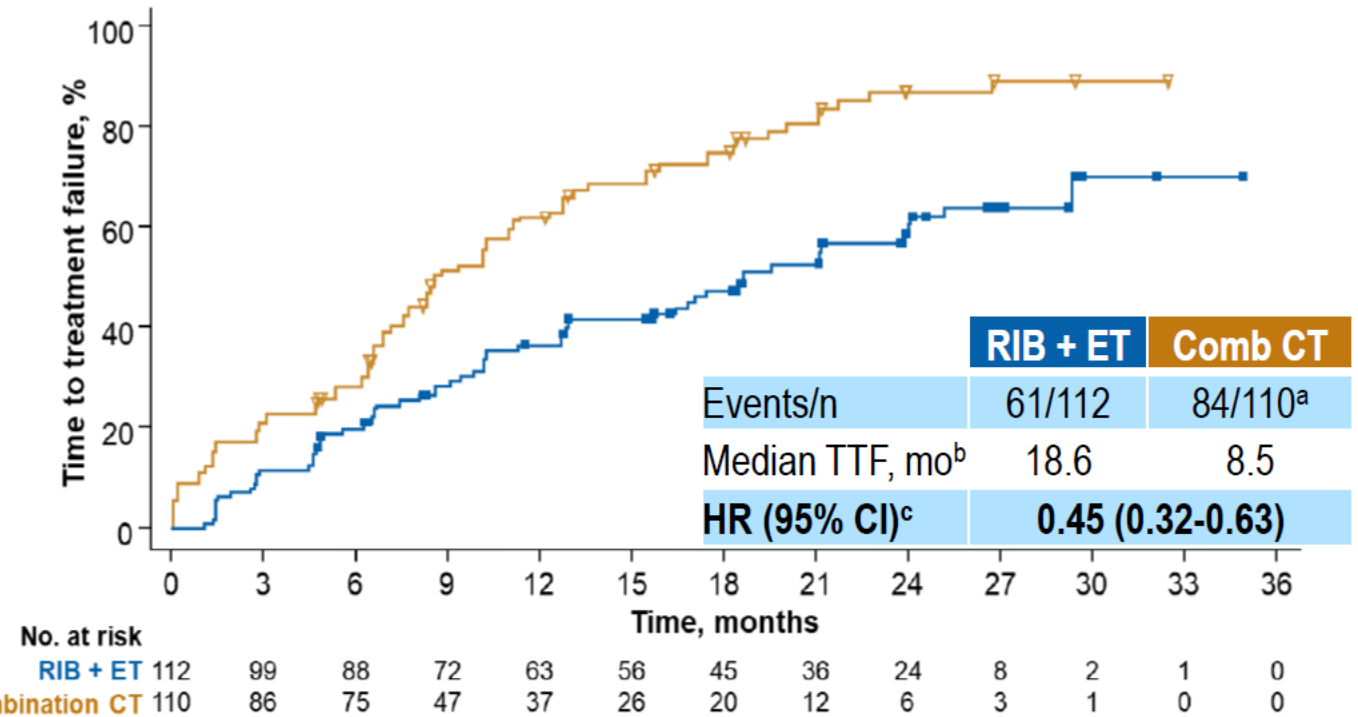


[a] Proportion of patients with CR or PR without confirmation or SD or non-CR/non-PD ≥24 weeks; [b] Proportion of patients with CR or PR without confirmation or SD or non-CR/non-PD ≥24 weeks; [c] Ten patients in CT arm did not receive any treatment; [d] Defined as the time from the date of randomization to the first documented complete or partial response; [e] HR is obtained from Cox PH model stratified by liver metastasis and disease-free interval per IRT.

Reference: Lu Y-S et al. SABCS 2022. abstract GS1-10.

RIGHT Choice: Time to treatment failure and 3-month treatment failure rate

Median TTF was longer with RIB + ET versus combination CT



- The 3-month treatment failure rate[d] for the RIB arm was ≈ half (n=13, 11.6%; 95% CI, 6.3-19.0) of combination CT arm (n=24, 21.8%; 95% CI, 14.5-30.7)

[a] Ten patients in CT arm did not receive any treatment; ; [b] Defined as the time from randomization to progression, death, change to other anticancer therapy, or discontinuation; [c] HR is obtained from Cox PH model stratified by liver metastasis and disease-free interval per IRT; [d] The proportion of patients who discontinued study treatment due to progressive disease, death, change to other anti-cancer therapy, or discontinuation due to reasons other than protocol violation. **Reference:** Lu Y-S et al. SABCS 2022. abstract GS1-10.

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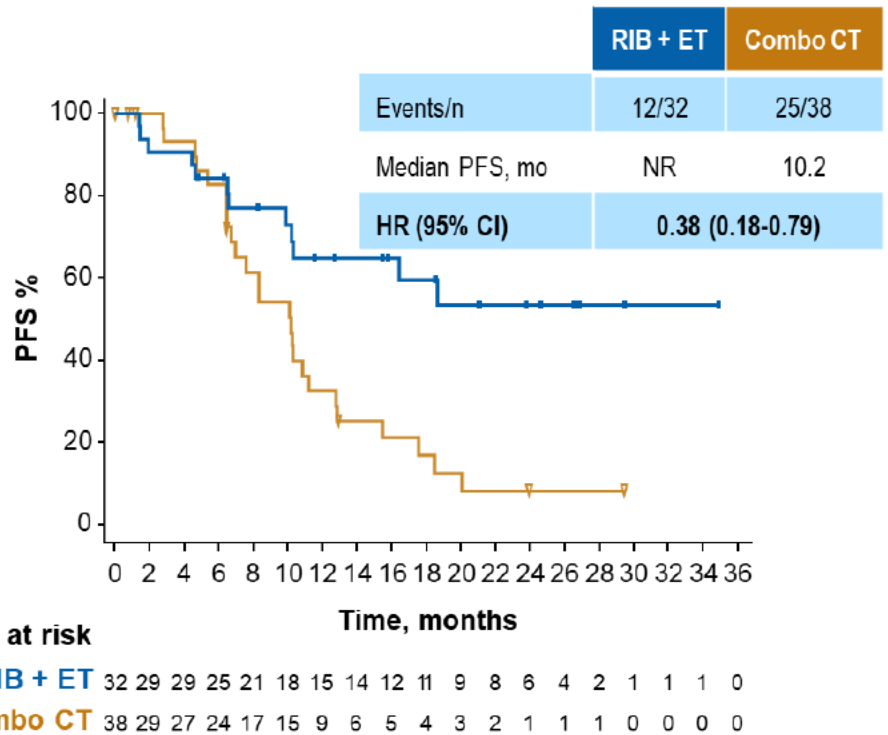
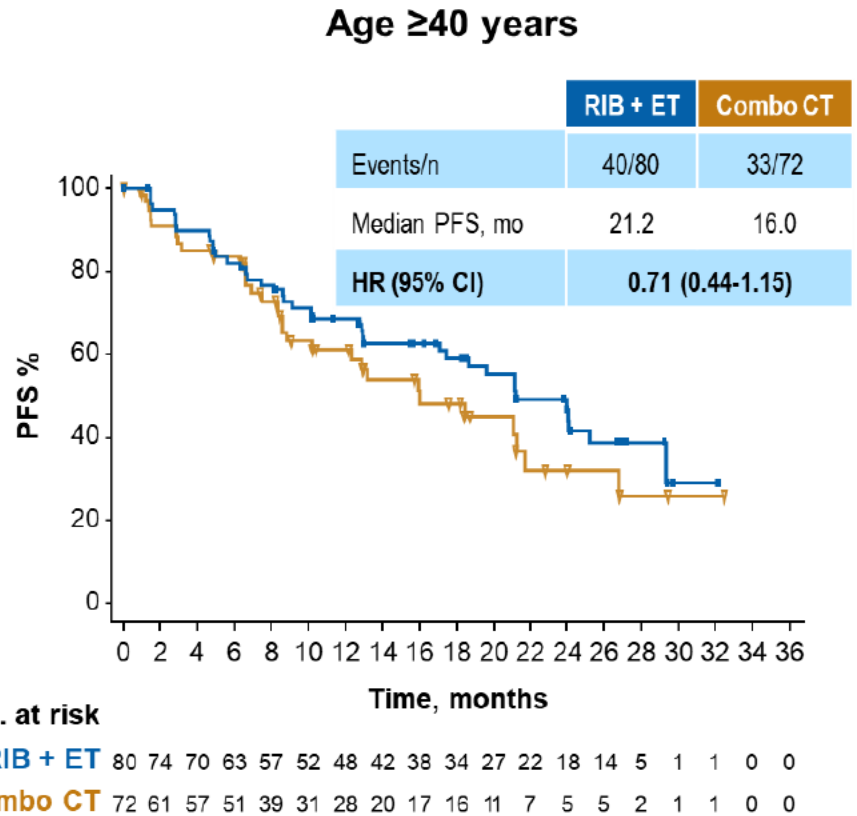
RIGHT Choice: Reduction of disease progression risk in the RIB + ET arm was greater in patients <40 vs ≥40 years of age

Age <40 years



Age ≥40 years



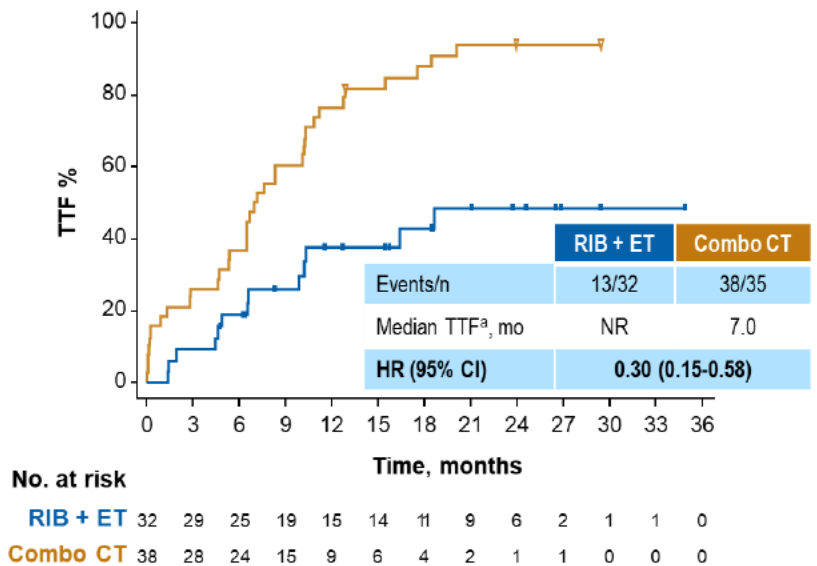
- In patients <40 years, RIB + ET was associated with a 62% relative reduction in risk of disease progression or death than combo CT
- PFS with combo CT was shorter for patients <40 vs ≥40 years of age

- In patients ≥40 years, RIB + ET was associated with a 29% relative reduction in risk of disease progression or death than combo CT

Reference: El Saghir NS, et al. ASCO 2023. abstract 1063.

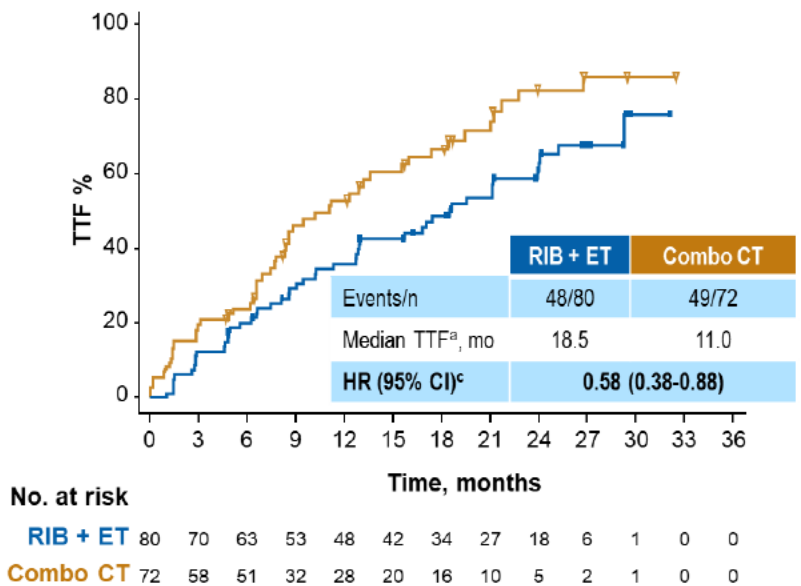
RIGHT Choice: Reduction in TTF risk in the RIB + ET arm was greater in patients <40 vs ≥40 years of age

Age <40 years



- In patients <40 years, there was a 70% relative reduction in risk of treatment failure with RIB + ET vs combo CT
  - The 3-month TFR with RIB + ET was 16.8% lower than with combo CT
- In the <40 year age group, combo CT had shorter TTF and higher 3-month TFR vs ≥40 years

Age ≥40 years



- In patients ≥40 years, there was a 42% relative reduction in risk of treatment failure with RIB + ET vs combo CT
  - The 3-month TFR with RIB + ET was 6.9% lower than with combo CT

[a] TTF is defined as the time from randomization to progression, death, change to other anticancer therapy, or discontinuation.

Reference: El Saghir NS, et al. ASCO 2023. abstract 1063.

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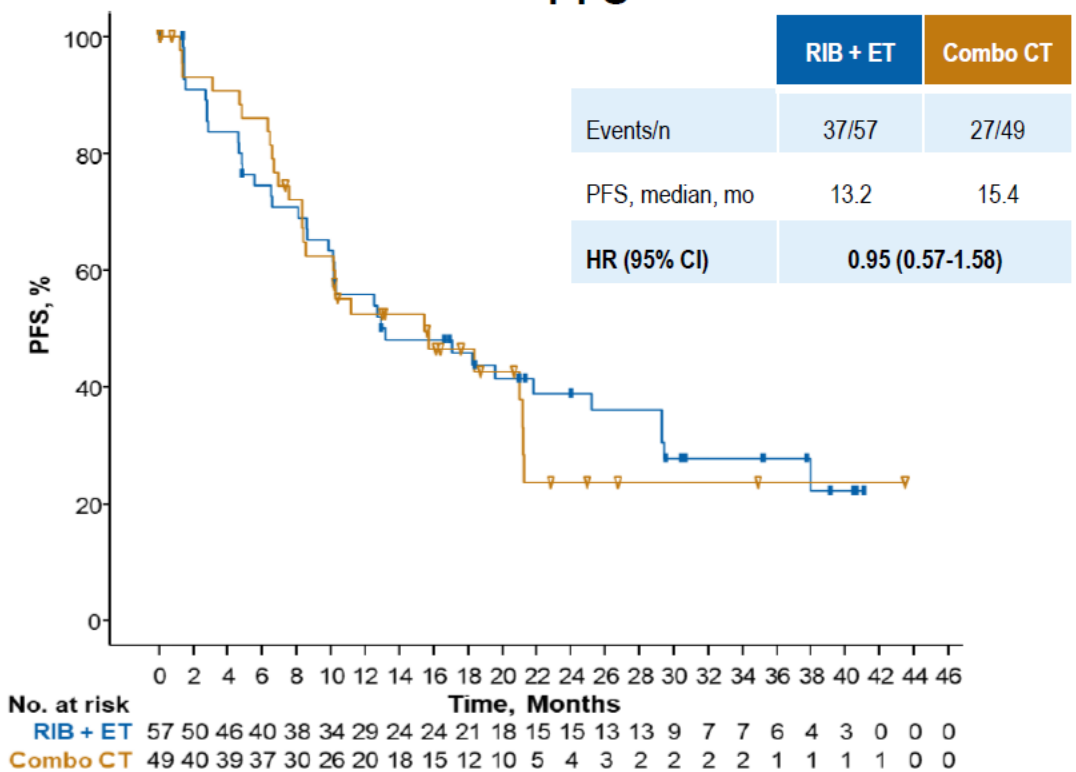
RIGHT Choice: PFS, ORR, and CBR patients with visceral crisis treated with RIB + ET vs combination CT

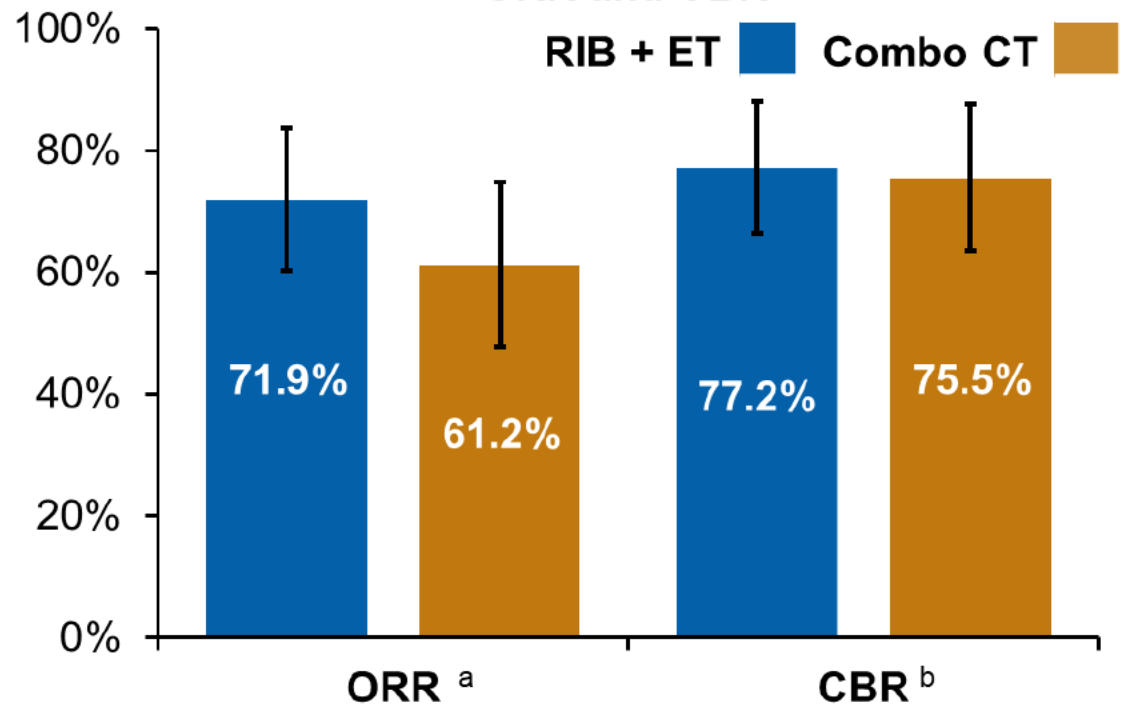
Data cutoff date: May 10, 2023

PFS



	RIB + ET	Combo CT
Events/n	37/57	27/49
PFS, median, mo	13.2	15.4
HR (95% CI)	**0.95 (0.57-1.58)**	

ORR and CBR



- In patients with visceral crisis, PFS was similar between arms
- In patients with visceral crisis, ORR was numerically higher with RIB + ET vs combo CT, while CBR was similar in both arms

[a] Proportion of patients with CR or PR without image confirmation; [b] Proportion of patients with CR or PR without image confirmation or stable disease or non-CR/non–progressive disease for ≥24 weeks.

Reference: Azim H, et al. ESMO 2023. Poster 402P.

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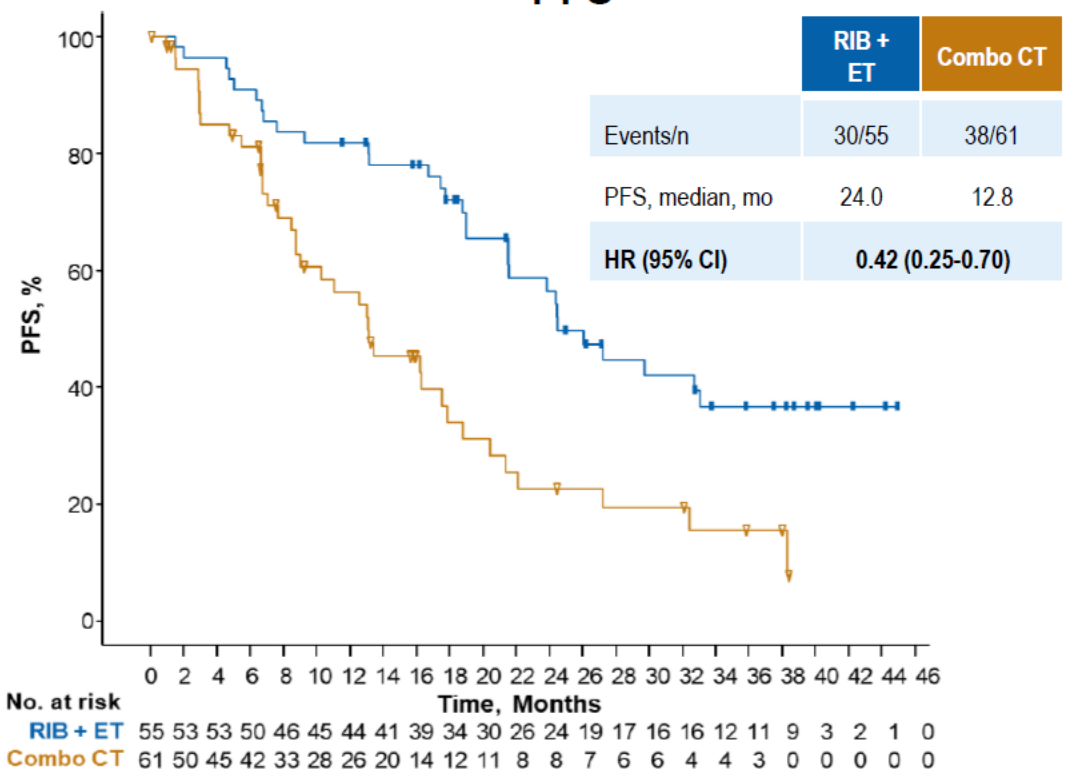
RIGHT Choice: PFS, ORR, and CBR in patients without visceral crisis treated with RIB + ET vs combination CT

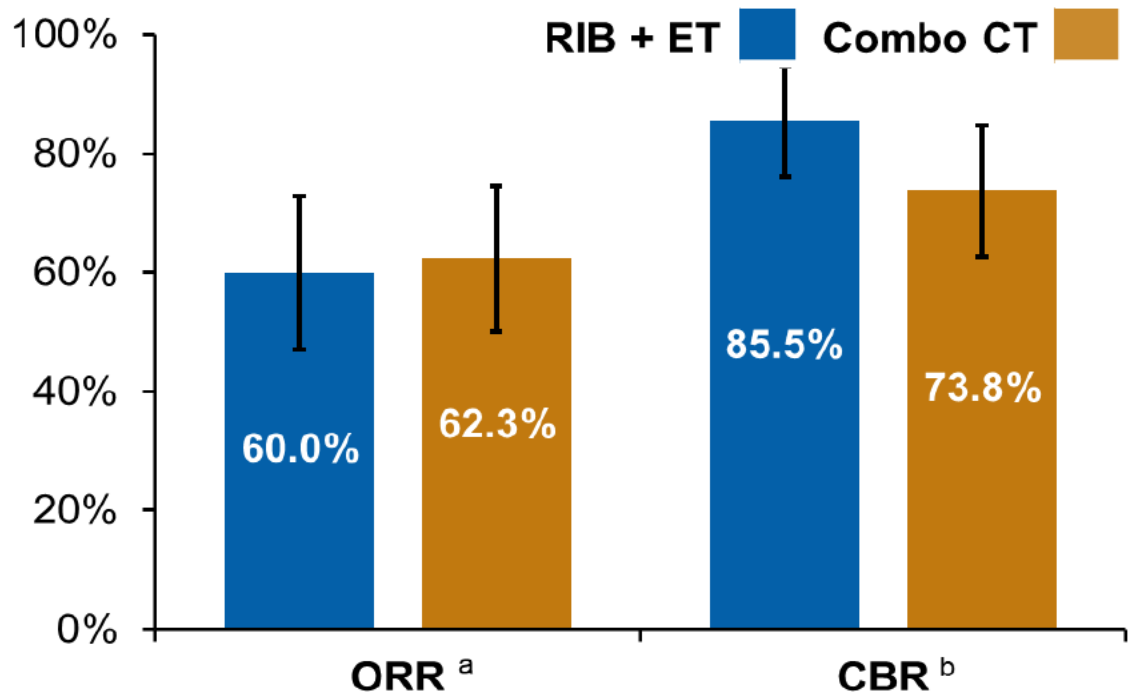
Data cutoff date: May 10, 2023

PFS



	RIB + ET	Combo CT
Events/n	30/55	38/61
PFS, median, mo	24.0	12.8
HR (95% CI)	**0.42 (0.25-0.70)**	

ORR and CBR



- In patients without visceral crisis, there was a 58% relative reduction in risk of disease progression or death with RIB + ET vs combo CT
- In patients without visceral crisis, the ORR was similar in both treatment arms and CBR was numerically higher RIB + ET than with combo CT

[a] Proportion of patients with CR or PR without image confirmation; [b] Proportion of patients with CR or PR without image confirmation or stable disease or non-CR/non–progressive disease for ≥24 weeks.

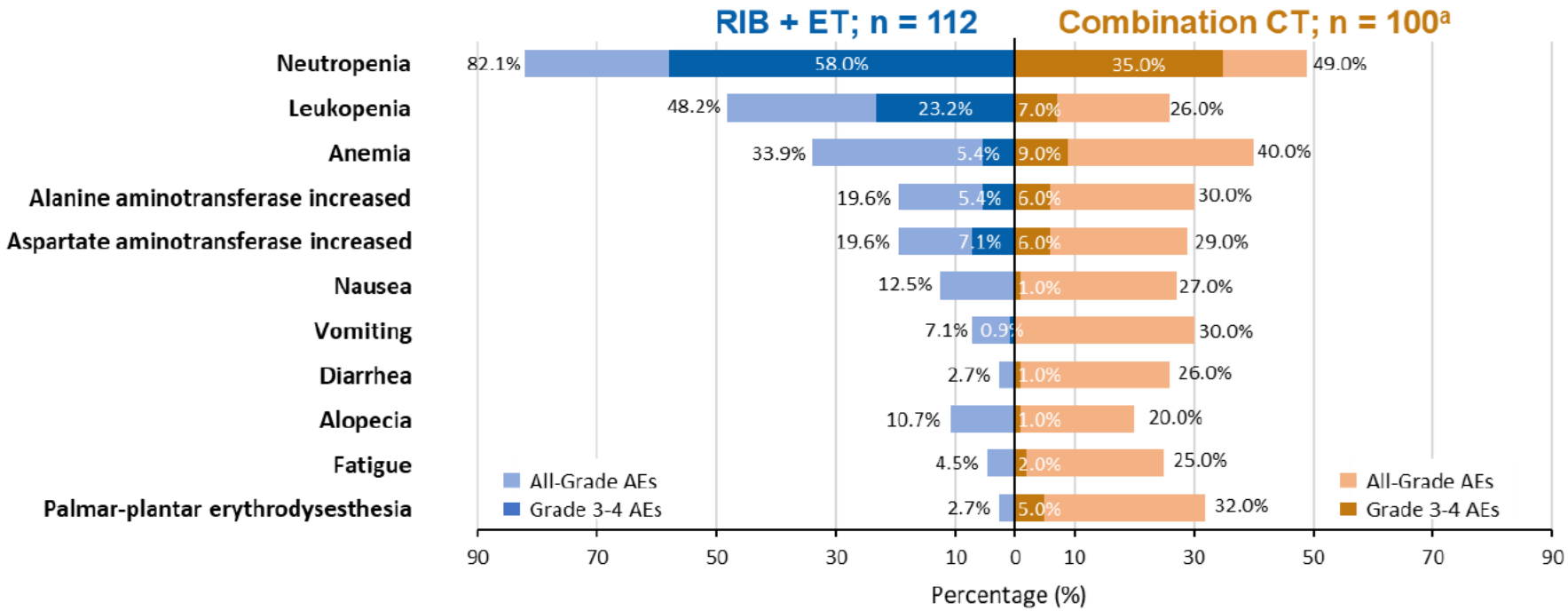
Reference: Azim H, et al. ESMO 2023. Poster 402P.

KR2404175896

RIGHT Choice: RIB safety was consistent with MONALEESA trials

n (%)	RIB + ET; n = 112		Combination CT; n = 100[a]	
	All Grade	≥Grade 3	All Grade	≥Grade 3
Total AEs	112 (100)	84 (75)	100 (100)	71 (71)
Treatment-related serious AEs	2 (1.8)	1 (0.9)	8 (8.0)	7 (7.0)
Treatment-related AEs leading to discontinuation	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)



[a] Ten patients in CT arm that did not receive any treatment were not included in the safety set. **Reference:** Lu Y-S et al. SABCS 2022. abstract GS1-10.

Indication

For the treatment of hormonereceptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine based therapy in pre/peri-, or postmenopausal women;
- fulvestrant, for the treatment of postmenopausal women, as initial endocrine based therapy or following disease progression on endocrine therapy

Reimbursement criteria

Treatment	Patients	Line of Therapy	Clinical Study
Ribociclib + NSAI + Goserelin	Premenopausal or perimenopausal metastatic/recurrent BC that satisfies all of the following criteria: ①HER2-negative ②Hormonereceptor(HR)-positive *Reimbursement expansion of M7 early relapse: Recurrence during or within 1 year of adjuvant therapy with endocrine therapy (excluding NSAI) or neoadjuvant chemotherapy	≥1L	**MONALEESA 7**
Ribociclib + NSAI	Postmenopausal metastatic/recurrent BC that satisfies all of the following criteria: ①HER2-negative ②Hormonereceptor(HR)-positive ③Not treated nonsteroidal aromatase inhibitor	1L	**MONALEESA 2**
Ribociclib + Fulvestrant	Postmenopausal metastatic/recurrent BC that satisfies all of the following criteria: ①HER2-negative ②Hormonereceptor(HR)-positive	≥2L	**MONALEESA 3**

Reference: 1. Kisqali label in Korea, MFDS 2. HIRA announcement #2021-220 (Sep1.2021).

Conclusiones:

- En enfermedad avanzada, los inhibidores de CDK4/6 + ET tiene beneficios de PFS y OS en HR+ HER2- BC.

- Actualmente se utilizan tres inhibidores de CDK4/6 en la práctica clínica habitual que muestran una PFS muy consistentes, aunque en el caso de los resultados de sus OS son disimiles.

- El perfil de toxicidad varía entre los diferentes inhibidores de CDK4/6, lo que permite un grado de adaptación del tratamiento en función de las necesidades de cada paciente.

- Ribociclib es el único inhibidor de CDK4/6 que muestra beneficios tanto estadísticos de PFS como de SG en pacientes pre y posmenopáusicas en combinación con NSAI
  - En la evaluación preclínica, CDK4 desempeña un papel más importante en HR+ BC. Ribociclib logra altas exposiciones totales y libres al fármaco en relación con otros CDKi. La alta exposición lograda puede ser el resultado de una mayor selectividad por CDK4.
  - Ribociclib + ET podría considerarse como una opción de tratamiento válida de primera línea en pacientes premenopáusicas con HR+/HER2-ABC clínicamente agresivos, incluidas aquellas con crisis visceral. La evidencia del mundo real respalda el resultado del ensayo clínico.

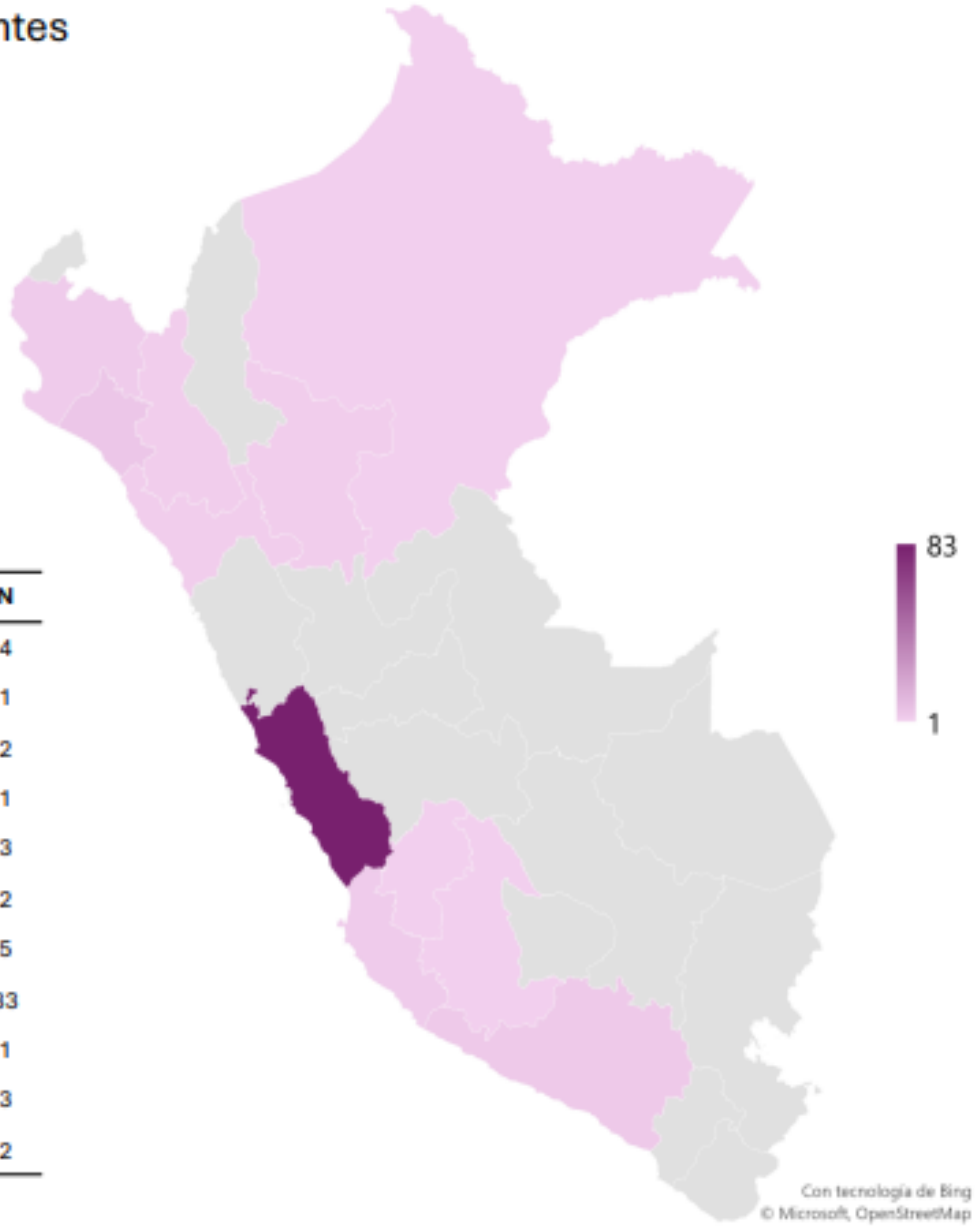
An Overview of the Safety Profile and Clinical Impact of CDK4/6 Inhibitors in Breast Cancer—A Systematic Review of Randomized Phase II and III Clinical Trials - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10526227/
Efficacy of CDK4/6 inhibitors combined with endocrine therapy in HR+/HER2- breast cancer: an umbrella review - https://pubmed.ncbi.nlm.nih.gov/38240835/

EXPERIENCIA ONCOSALUD CON RIBOCICLIB 2020-2023

Datos demográficos

N= 107 pacientes

Departamento	N
Arequipa	4
Ayacucho	1
Cajamarca	2
Huancavelica	1
Ica	3
La Libertad	2
Lambayeque	5
Lima	83
Loreto	1
Piura	3
San Martin	2



Datos clínico-patológicos

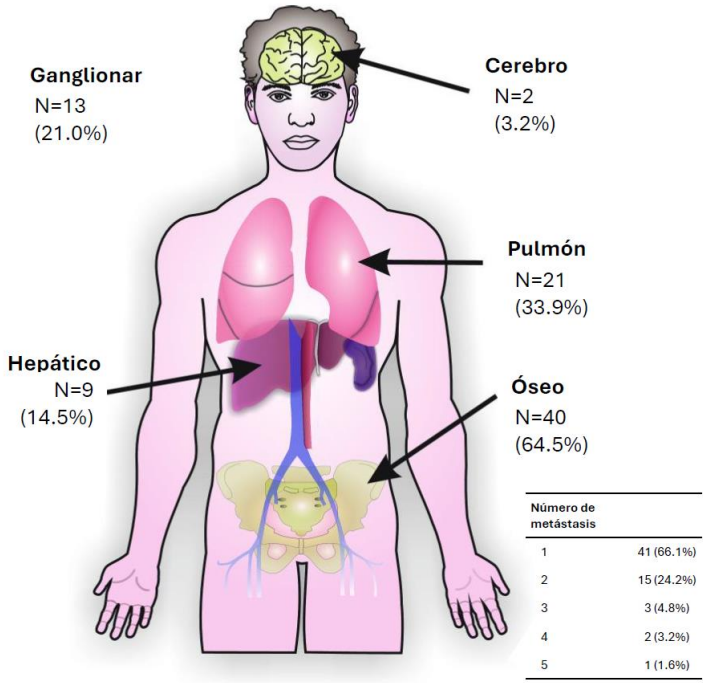
Características	Total, N = 107
Edad	52 (44, 64)
Estatus menopaúsico	
Premenopaúsica	48 (44.9%)
Postmenopáusica	59 (55.1%)
Antecedentes de cáncer de mama/ovario	
Si	41 (38.3%)
No	66 (61.7%)
Tipo histológico	
Ductal	87 (81.3%)
Lobulillar	14 (13.1%)
Mixto	1 (0.9%)
Otro	5 (4.7%)
Tamaño tumoral (cm)	3.20 (2.00, 5.00)
No reportado	8
T	
T1	19 (19.0%)
T2	38 (38.0%)
T3	14 (14.0%)
T4	29 (29.0%)
No reportado	7
N	
N0	17 (16.8%)
N1	57 (56.4%)
N2	11 (10.9%)
N3	16 (15.8%)
No reportado	6
Grado histológico	
II	58 (58.6%)
III	41 (41.4%)
No reportado	8
HER2 estatus	
0	85 (83.3%)
+	13 (12.7%)
++	4 (3.9%)
No reportado	5
Ki67 (%)	30 (20, 50)
No reportado	10

[1] Median (IQR); n (%)

Fuente: Oncosalud - AUNA

Clinic Features

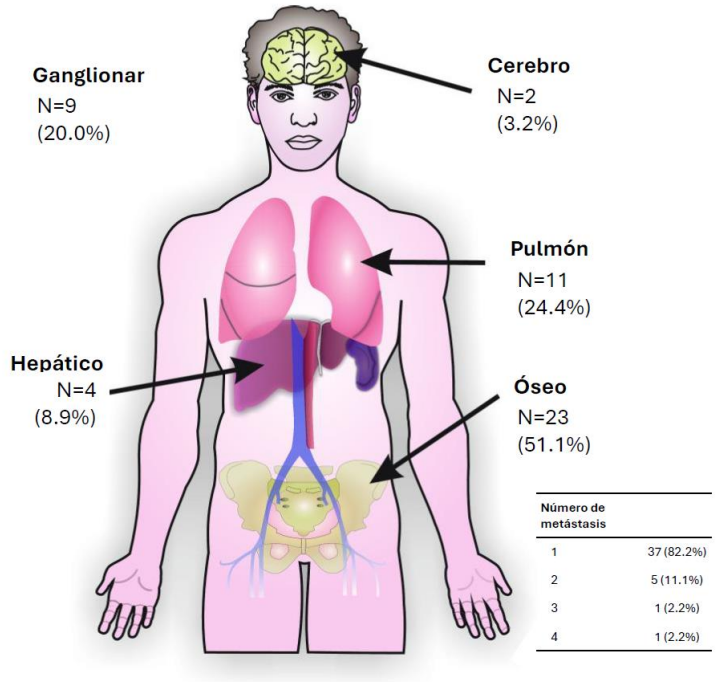
Metástasis al debut (N=62)



Número de metástasis	
1	41 (66.1%)
2	15 (24.2%)
3	3 (4.8%)
4	2 (3.2%)
5	1 (1.6%)

Oligometástasis= 21.0% (N=13)

Metástasis a distancia (N=45)



Número de metástasis	
1	37 (82.2%)
2	5 (11.1%)
3	1 (2.2%)
4	1 (2.2%)

Imagen de referencia: De-la-Cruz-Ku et al., 2020

Datos clínico-patológicos

Características	Total, N = 107
Edad	52 (44, 64)
Estatus menopaúsico	
Premenopaúsica	48 (44.9%)
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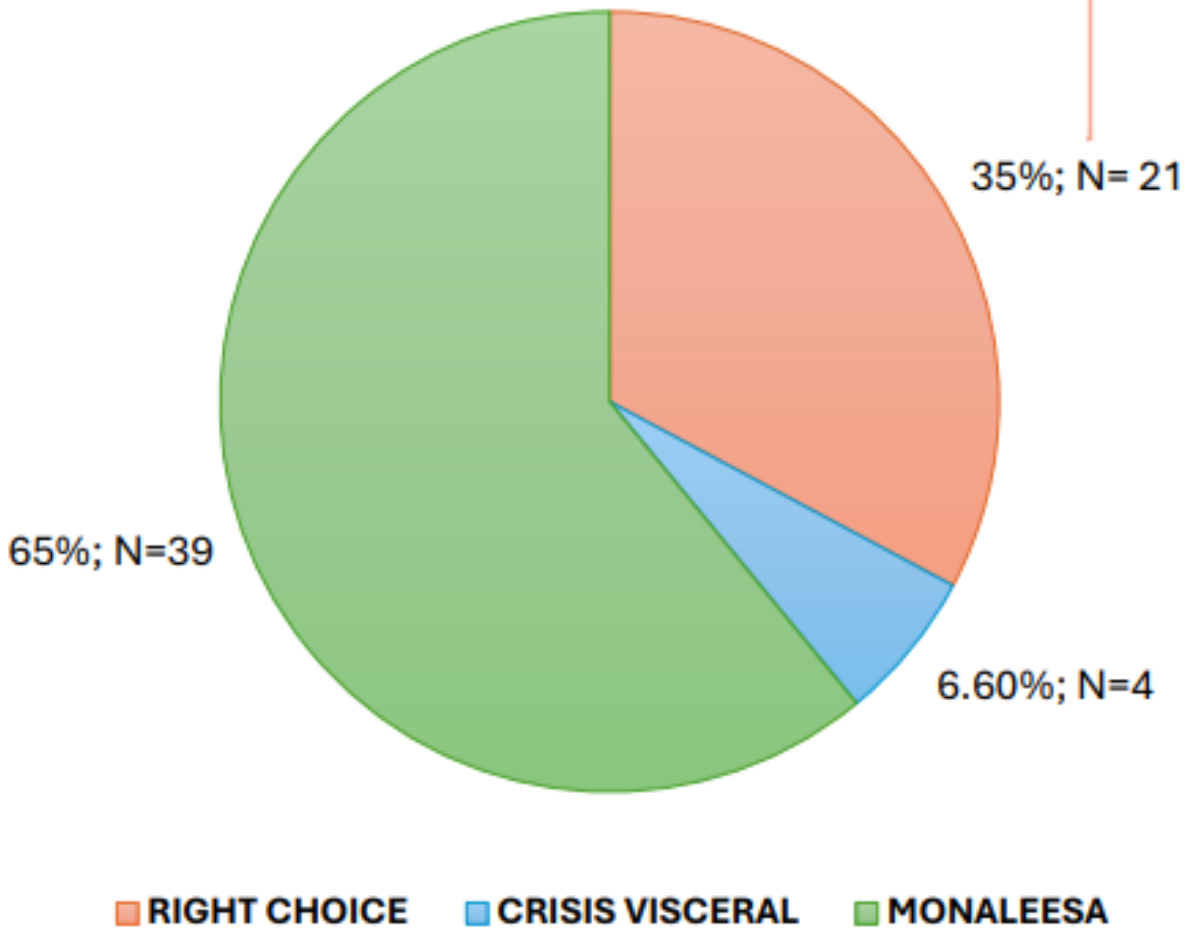
Ki67 (%)	30 (20, 50)
No reportado	10

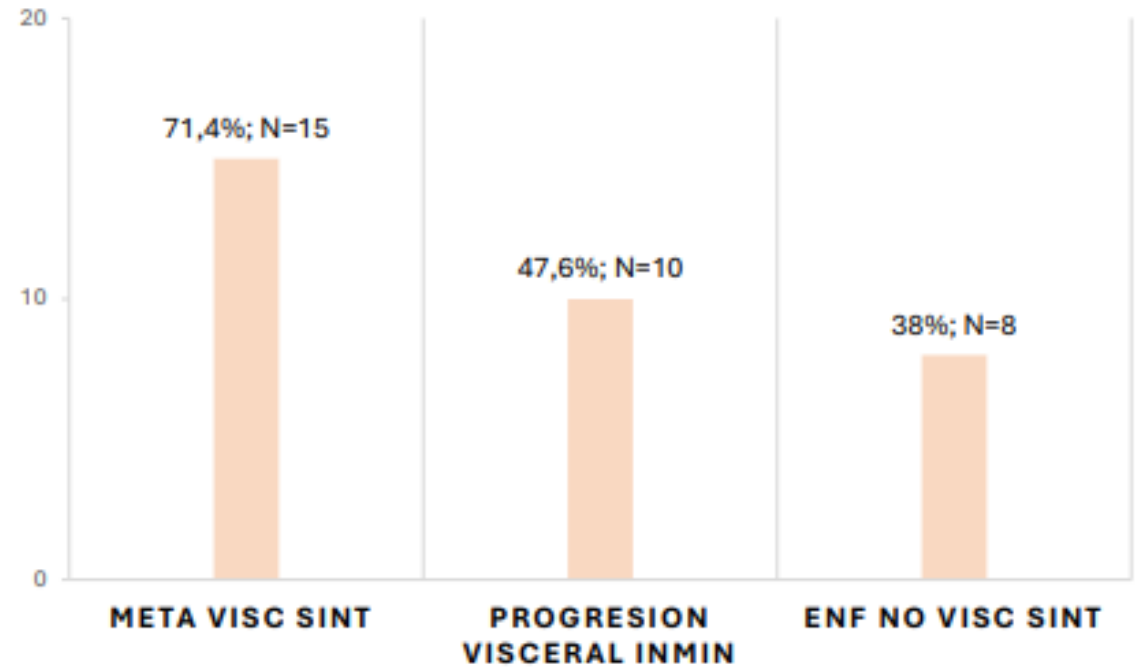
[1] Median (IQR); n (%)

Fuente: Oncosalud - AUNA

RIGHT Choice (N=21) **vs. Monaleesa trials - iCDK 4/6** (N=39)



RIGHT Choice (N=21) → Aggresive disease

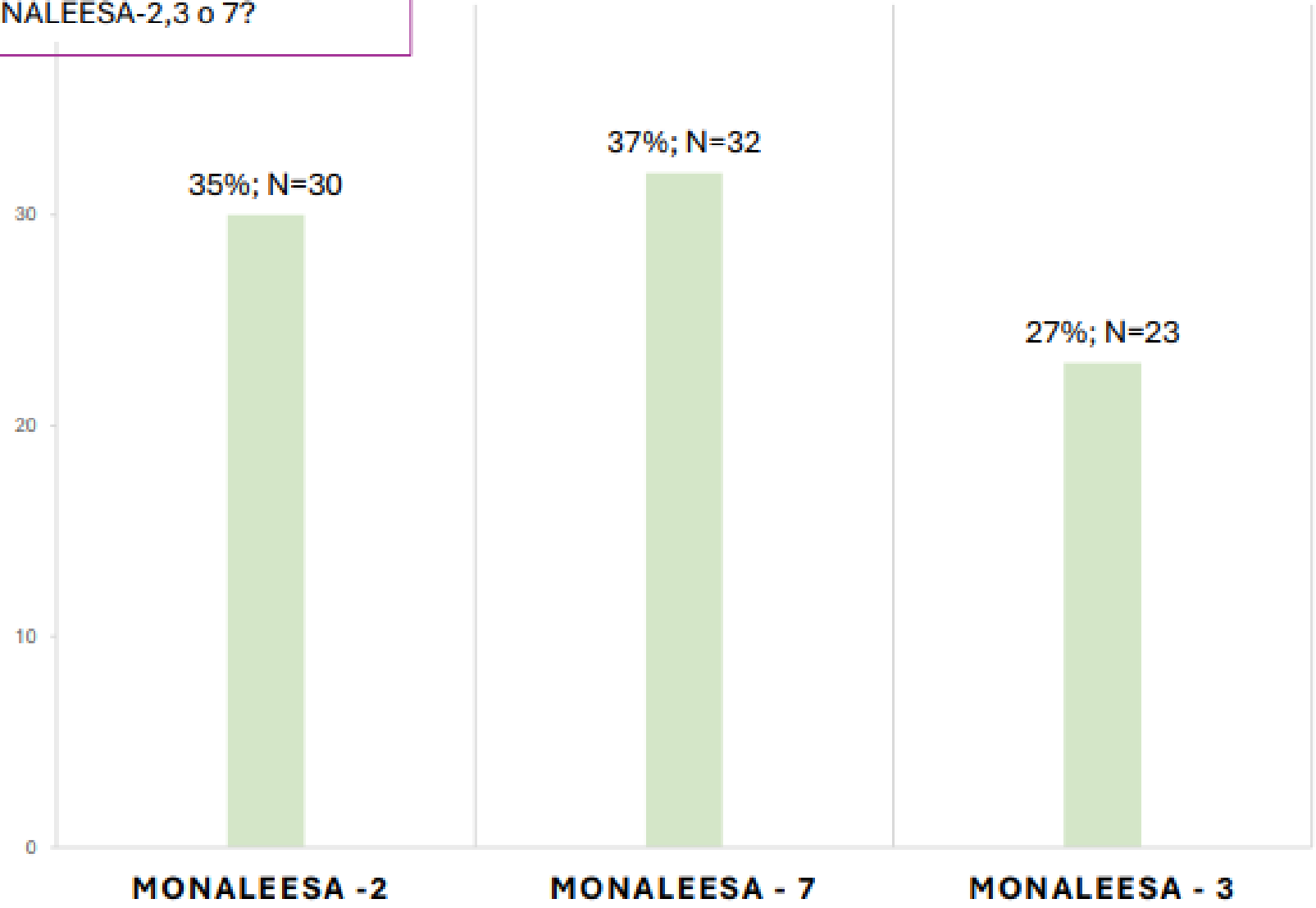


Aproximadamente, 35% de los pacientes cumplen con los criterios de "agressive disease" según **RIGHT Choice Trial**

65% recibió tratamiento con iCDK 4/6 usados en **Monaleesa Trial**

MONALEESA trials

¿Cuántos pacientes cumplieron con los criterios de los estudios de MONALEESA-2,3 o 7?



Fuente: Oncosalud - AUNA

Esquema de tratamiento

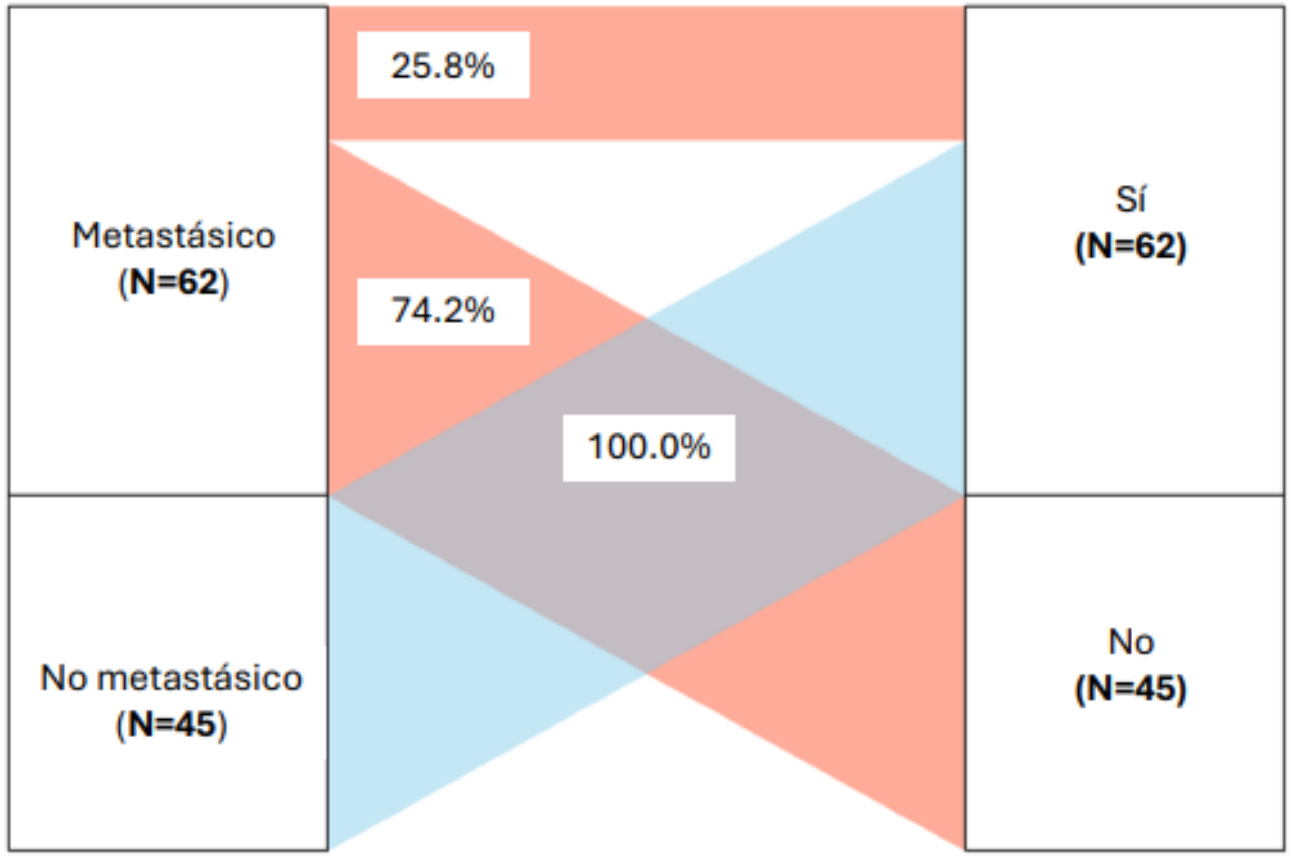
1L

AC/AC-T	2 (3.4%)
FULVESTRANT	1 (1.7%)
PABOCICLIB	1 (1.7%)
PACLITAXEL	1 (1.7%)
RIBOCICLIB	**55 (91.7%)**

ANASTROZOL	7 (12.7%)
EXEMESTANE	1 (1.8%)
FULVESTRANT	2 (3.6%)
LETROZOL	43 (78.2%)
TAMOXIFENO	1 (1.8%)

Tratamiento completo	21 (35.6%)
Tiempo de tratamiento (meses)	12 (7, 20)

Diagnóstico



¿Desarrolló progresión/ recurrencia?

1L

CAPECITABINA	2 (4.6%)
CARBOPLATINO	1 (2.3%)
DOCETAXEL	1 (2.3%)
FULVESTRANT	2 (4.6%)
LETROZOL	1 (2.3%)
PACLITAXEL	2 (3.9%)
PERTUZUMAB	1 (2.3%)
RIBOCICLIB	**41 (62.1%)**

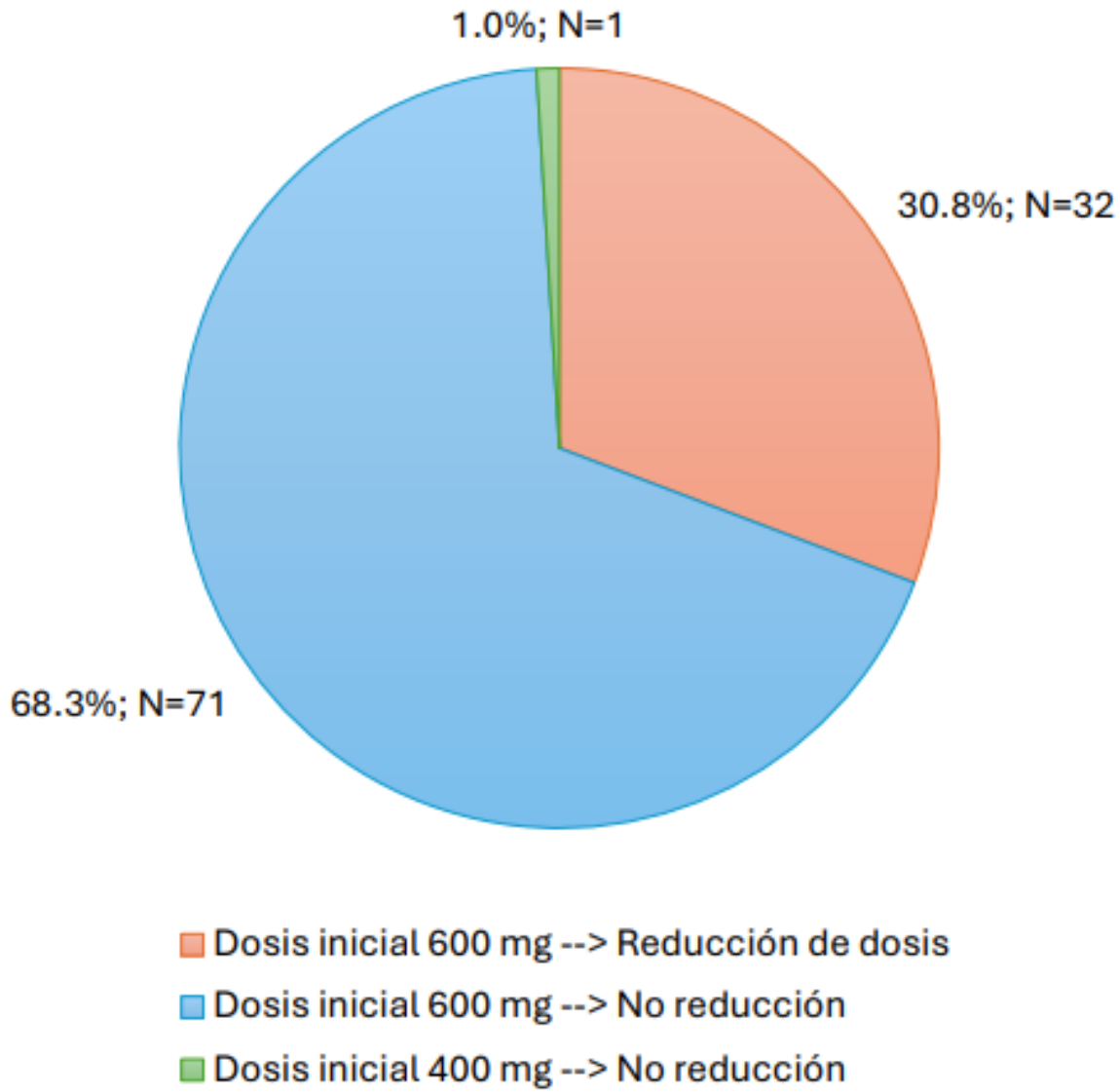
RIBOCICLIB en otras líneas de tratamiento

2L	5 (11.4%)
3L	0 (0.0%)
4L	2 (4.6%)
5L	0 (0.0%)

Tratamiento completo	23 (37.1%)
Tiempo de tratamiento (meses)	5 (3, 11)

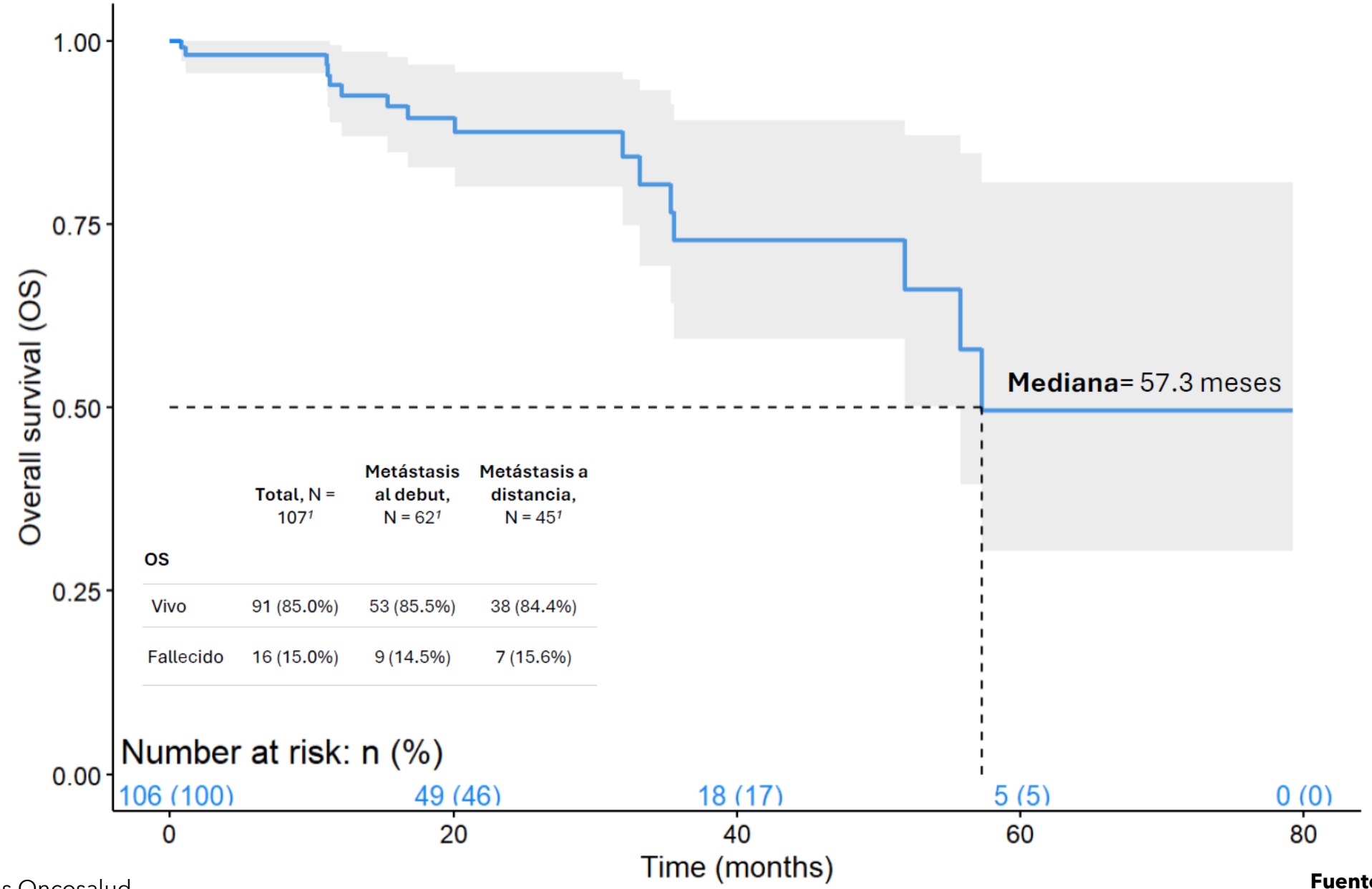
Fuente: Oncosalud - AUNA

Detalles sobre la dosis



Fuente: Oncosalud - AUNA

Análisis sobrevida global



	Total, N = 107[1]	Metástasis al debut, N = 62[1]	Metástasis a distancia, N = 45[1]
OS			
Vivo	91 (85.0%)	53 (85.5%)	38 (84.4%)
Fallecido	16 (15.0%)	9 (14.5%)	7 (15.6%)

Referencia Datos Oncosalud

Fuente: Oncosalud - AUNA

GRACIAS

Abstract submitted to ESMO Congress 2024 (September 13-17, Barcelona, Spain)

Treatment patterns and outcomes in first-line (1L) therapy in Peruvian patients (pts) with hormone receptor (HR)-positive HER2-negative advanced breast cancer (ABC)

Guillermo Valencia, Patricia Rioja, Miguel Chirito, Olenka Peralta, Jorge Sánchez, Connie Rabanal, Zaida Morante, Hugo Fuentes, Carlos Castaneda, Tatiana Vidaurre, Silvia Neciosup, Cristian Pacheco, Henry L Gómez

Medical Oncology Department. Instituto Nacional de Enfermedades Neoplásicas (INEN). Lima, Peru

Background

Advanced breast cancer (ABC) is an incurable neoplasm with a median overall survival (OS) of 3 years. Although endocrine therapy (ET) is recommended for HR (+)/HER2 (-) ABC, chemotherapy (CT) is reserved in some cases and is often used as first-line (1L)treatment in many countries. In this work, we evaluated the 1L treatment and the factors influencing this selection and patients' outcomes in a public institution.

Methods

Retrospective review of HR (+)/HER2 (-) ABC patients (including *de novo*, recurrent/progressive disease) diagnosed at the Instituto Nacional de Enfermedades Neoplásicas (INEN) during the 2021-2023 period. The type of first-line (1L) regimens and clinicopathological factors that influence this selection were evaluated. Overall survival (OS) was evaluated with the Kaplan-Meier method.

Results

145 patients were included with a median follow-up of 41 months. Regarding to characteristic of patients, the median age was 53.9 years (range: 24-85); 63.4% were post-menopausal, 29.2% with *de novo* diagnosis, 93.1% had ECOG 0-1 and 69.0% where luminal B. CT was selected as 1L treatment in 43.4% of cases.

In univariate analysis, the presence of visceral metastases (most frequent lung metastases) (OR 2.31, 1.07-5.09, p=0.034) and *de novo* ABC (OR 2.15, 1.04-4-52, p=0.039) were associated with a higher use of CT, while lymph node metastases were associated with ET choice (OR 0.36, 0.12-0.92, p=0.044). **The 1L progression-free survival (PFS) with ET was 18 months.**

Multivariate analysis showed that patients with *de novo* diagnosis were more likely to receive CT as 1L therapy (OR=2.26, CI95%:1.02-5.07). In patients treated with ET, 71.1% and 28.9% received in second line (2L) ET and CT, respectively.

Overall survival (OS) rates at 1, 3 and, 5 years were 98.5%, 82.0% and 64.5%, respectively.

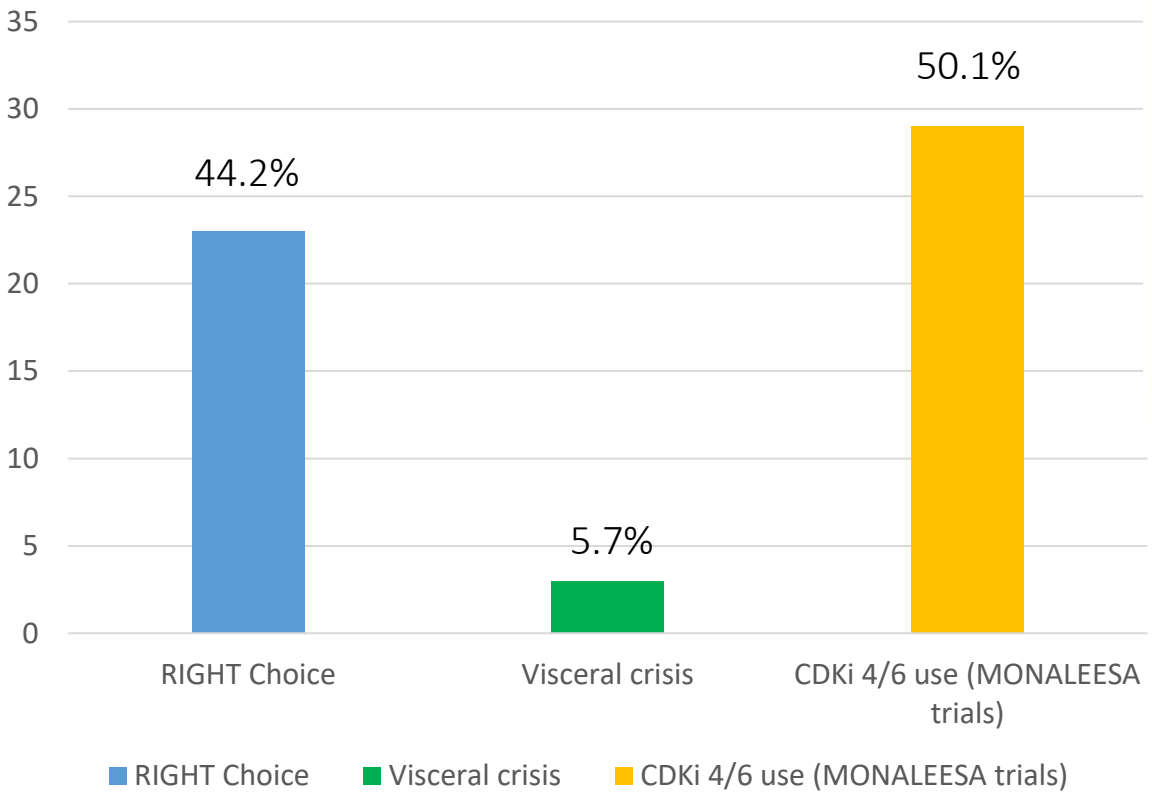
Peruvian patients (pts) who received chemoterapy (CT) as first-line (1L) vs. MONALEESA trials vs. RIGHT Choice trial

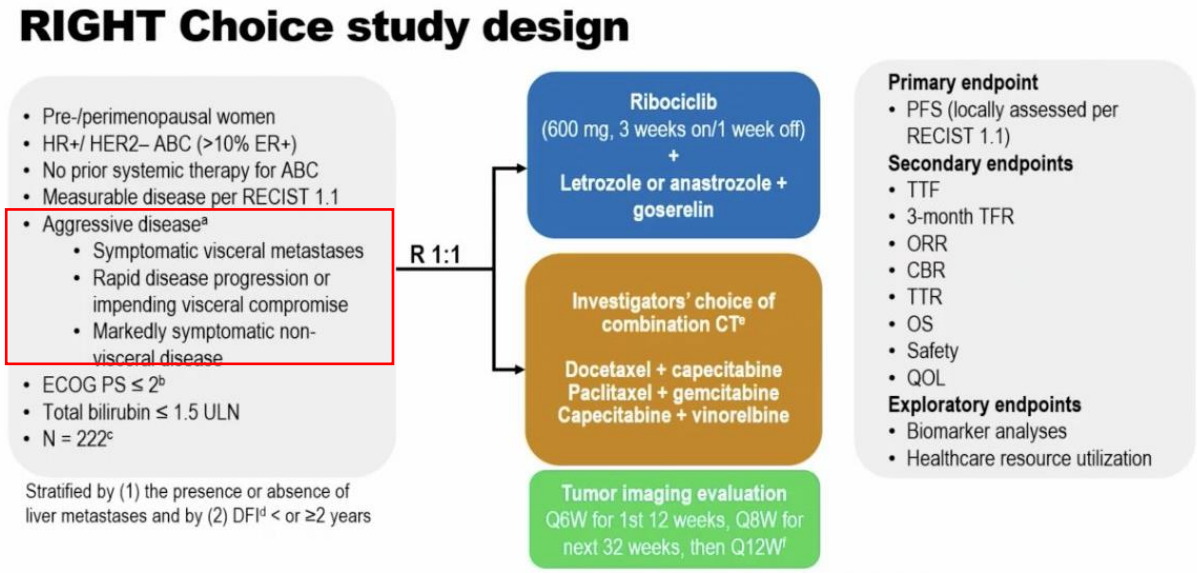
Patients (pts) received 1L CT52.1%		Peruvian pts	MONALEESA trials	RIGHT Choice trial
Median age		52 (24-80) year	55 year	Premenopausal
Postmenopausal		54%	80%	0%
Premenopausal		46%	20% ML-2 20% ML-3 100% ML-7	100%
De novo (diagnosis)		44%	35%	ND
ECOG 0-1		95%	99%	99%
Luminal B subtype		55%	ND	ND
Visceral metastases		37%	60%	50%
Visceral crisis		5.7%	0%	50%
Aggressive disease (RIGHT Choice definition)		44.2%	ND	100%
"Aggresive disease" definition	Symptomatic visceral metastases	30.4%	ND	67.6%
	Rapid disease progression	78%	ND	18.5%
	Markedly symptomatic non-visceral metastases	52%	ND	14%

ML: MONALEESA, ND: no data

Patients (pts) who received 1L chemotherapy (CT) (n=52)

- Pts met the criteria for:

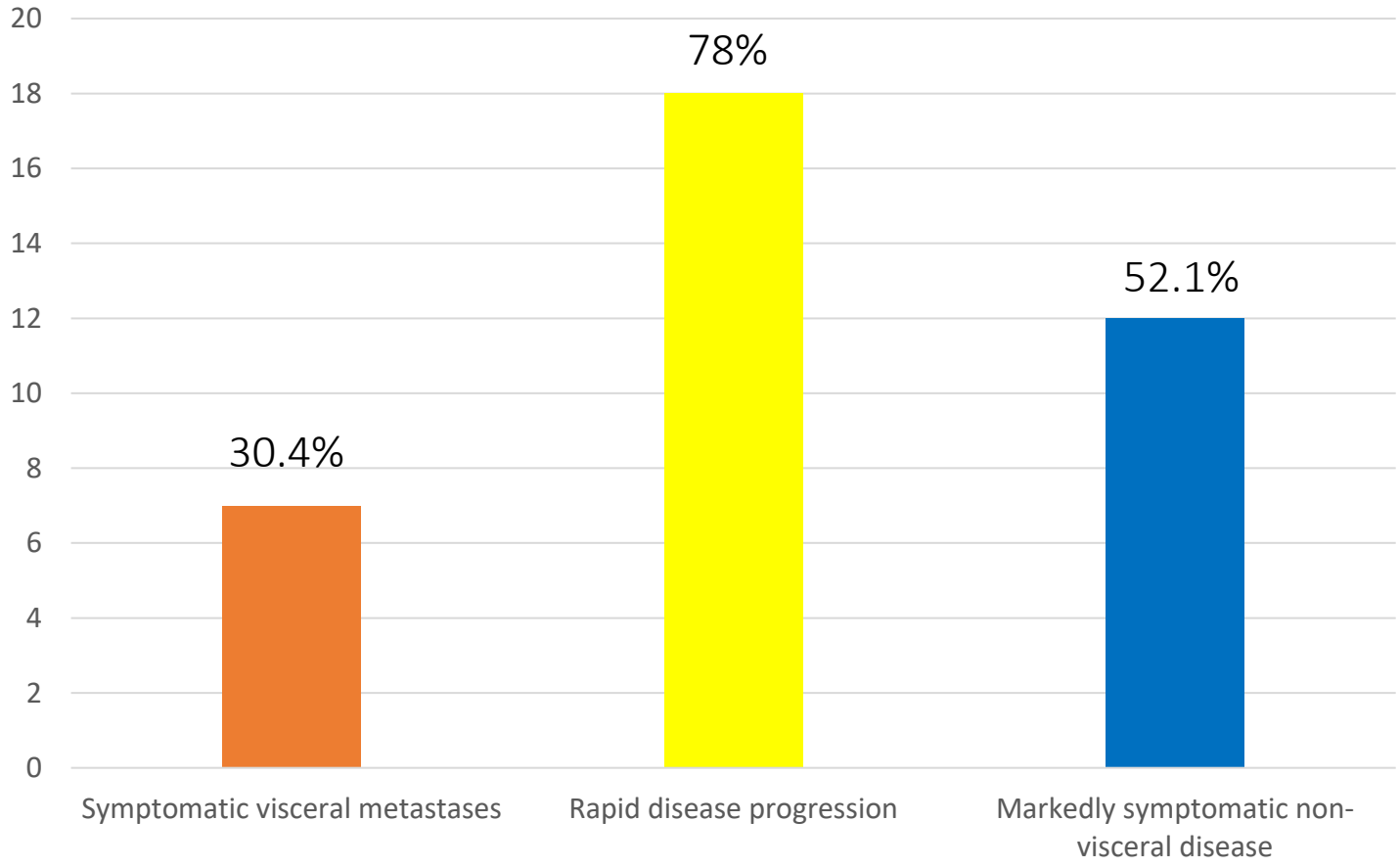




- Approximately **half** of the pts had **"aggressive disease"** as defined by RIGHT Choice trial
- Half of the pts were not no receive CT **(no access to CDK 4/6 inhibitors)**

Patients (pts) who met RIGHT Choice criteria (n=23) “aggresive disease”

- Of the total of pts who met criteria for RIGHT Choice, they met any of the following definitions for “aggressive disease”:



- **Most pts** presented **“rapid disease progression”** for decisión to use CT
- **Half** of the pts had **markedly symptomatic non-visceral metastases** (most frequent: multiple bone with spinal cord compression requiring palliative radiotherapy)

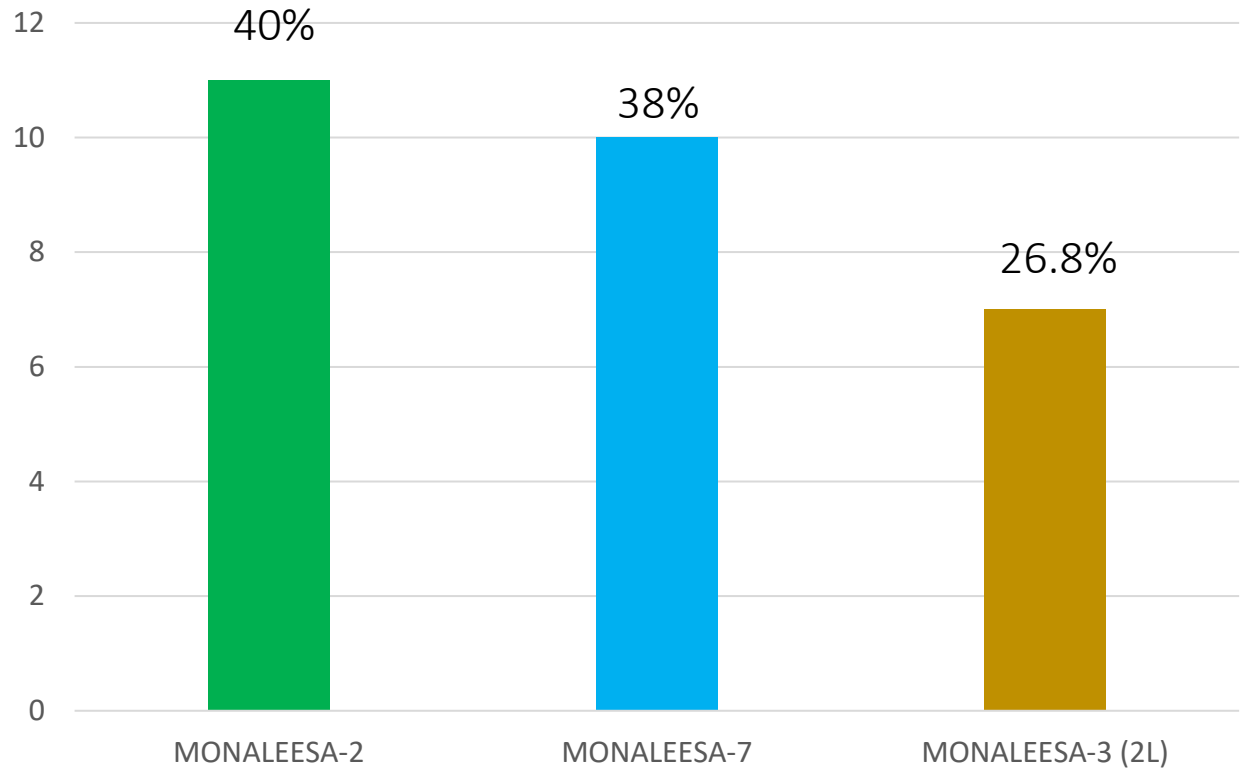
Peruvian pts received 1L CT who met RIGHT Choice criteria (n=23) vs. who met MONALEESA criteria (n=26)

Patients (pts) received 1L CT52.1%		Peruvian pts who met RIGHT Choice criteria	Peruvian pts who met MONALEESA criteria
Median age		51 (29-71) year	53 (24-80) year
Postmenopausal		66%	62%
Premenopausal		34%	38%
De novo (diagnosis)		60%	38%
ECOG 0-1		83%	100%
Luminal B subtype		56%	65%
Visceral metastases		50%	38%
Visceral crisis		5.7%	0%
Aggressive disease (RIGHT Choice definition)		44.2%	0%
"Aggresive disease" definition	Symptomatic visceral metastases	30.4%	ND
	Rapid disease progression	78%	ND
	Markedly symptomatic non-visceral metastases	52%	ND

ML: MONALEESA, ND: no data

Pts who met criteria for CDK 4/6 inhibitors use (n=26)

- Of the total number of pts who met criteria for CDKi 4/6 use (MONALEESA-2, 3 or 7) met the study definitions for:



- 40% were 1L postmenopausal (met criteria for ML-2)
- About 40% were 1L premenopausal (met criteria for ML-7)
- Approximately 30% of pts relapsed during adjuvant treatment (met criteria for 2L ML-3)

Valencia G, et al. Treatment patterns and outcomes in first-line (1L) therapy in Peruvian patients (pts) with hormone receptor (HR)-positive HER2-negative advanced breast cancer (ABC). 2024

diagnostics

MDPI

Systematic Review

Somatic Mutations in Latin American Breast Cancer Patients: A Systematic Review and Meta-Analysis

Gabriela A. Martínez-Nava [1,†], Laura Keren Urbina-Jara [2,†], Saúl Lira-Albarrán [3], Henry L. Gómez [4], Erika Ruiz-García [5], María Tereza Nieto-Coronel [6], Rocio Ortiz-Lopez [2,7], Kenia Nadiezhda Martínez Villalba [8], Mariana Muñoz-Sánchez [9], Dione Aguilar [10], Liliana Gómez-Flores-Ramos [11], Sara Aileen Cabrera-Nieto [9], Alejandro Mohar [8] and Marlid Cruz-Ramos [12,*]

1 Laboratorio de Gerociencias, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Calz. México-Xochimilco 289, Tlalpan, Mexico City 14389, Mexico; ameria.justice@gmail.com
2 Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey 64710, Mexico; lauraqcb@gmail.com (L.K.U.-J.); rortizl@tec.mx (R.O.-L.)
3 Departamento de Gestión Académica e Investigación, Hospital Escuela, Tegucigalpa 11101, Honduras; saul.lira@hospitalescuela.edu.hn
4 Departmento de Medicina Oncológica, Instituto Nacional de Enfermedades Neoplásicas, Av. Angamos Este 2520, Lima 15023, Peru; hgomez@inen.sld.pe
5 Laboratorio de Medicina Traslacional, Instituto Nacional de Cancerologia, Mexico City 14080, Mexico; betzabe100@yahoo.com.mx
6 Departamento de Medicina Oncológica, Centro Oncopalia, Universidad Mayor de San Andrés, La Paz P.O. Box 8635, Bolivia; maytemtnc2@gmail.com
7 Tecnologico de Monterrey, Institute for Obesity Research, Monterrey 64849, Mexico
8 Unidad de Epidemiologia e Investigación Biomédica en Cáncer, Instituto de Investigaciones Biomédicas, UNAM-Instituto Nacional de Cancerologia, Mexico City 14080, Mexico; kenia28nadiezhda@gmail.com (K.N.M.V.); mohar@iibiomedicas.unam.mx (A.M.)
9 Facultad de Ciencias de la Salud, Universidad Anáhuac México, Mexico City 52786, Mexico; mariana.munozsa@anahuac.mx (M.M.-S.); sara.cabrera32@anahuac.mx (S.A.C.-N.)
10 Tecnologico de Monterrey, Centro de Cáncer de Mama, Hospital Zambrano Hellion, San Pedro Garza Garcia 66278, Mexico; oncogenetica.monterrey@gmail.com
11 CONAHCYT/Center for Population Health Research, National Institute of Public Health, Universidad No. 655, Cuernavaca 62100, Mexico; liliana.gomez@insp.mx
12 Programa Joven y Fuerte/CONAHCYT, Instituto Nacional de Cancerologia, Av. San Fernando 22, Belisario Dominguez Sección 16, Tlalpan, Mexico City 14080, Mexico
* Correspondence: marlid.cruz@gmail.com
† Authors: Gabriela A. Martinez-Nava and Laura Keren Urbina-Jara should be considered as first author.

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