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NÚCLEO DE QUITO

Desde 23 de Julio 1954

Impacto de los inhibidores de ciclina en la sobrevida global en la enfermedad metastásica luminal

Dr. Miguel Cedeño Vera
Medicina Interna
Onco Hematología
Solca Manabí

EXPOSITOR:

Dr. Miguel Cedeño

Oncología Clínica

* Especialista en Oncología y Hematología, Universidad de Guayaquil-Instituto Oncológico Nacional “Dr. Juan Tanca Marengo” (SOLCA Guayaquil).
* Especialista en Medicina Interna. Universidad de Guayaquil-Instituto Oncológico Nacional “Dr. Juan Tanca Marengo” (SOLCA Guayaquil).
* Investigador Principal, en Estudios Clínicos fase III, Multicéntricos.
* Miembro activo de la Sociedad Ecuatoriana de Oncología.
* Miembro activo de la Sociedad Americana de Oncología Clínica.
* Miembro de la Sociedad Europea de Oncología Clínica.
* Maestría Internacional Patología Mamaria.
* Miembro del Staff ManaHospital.
* Oncólogo Clínico Solca Manabí.

Conflictos de interés

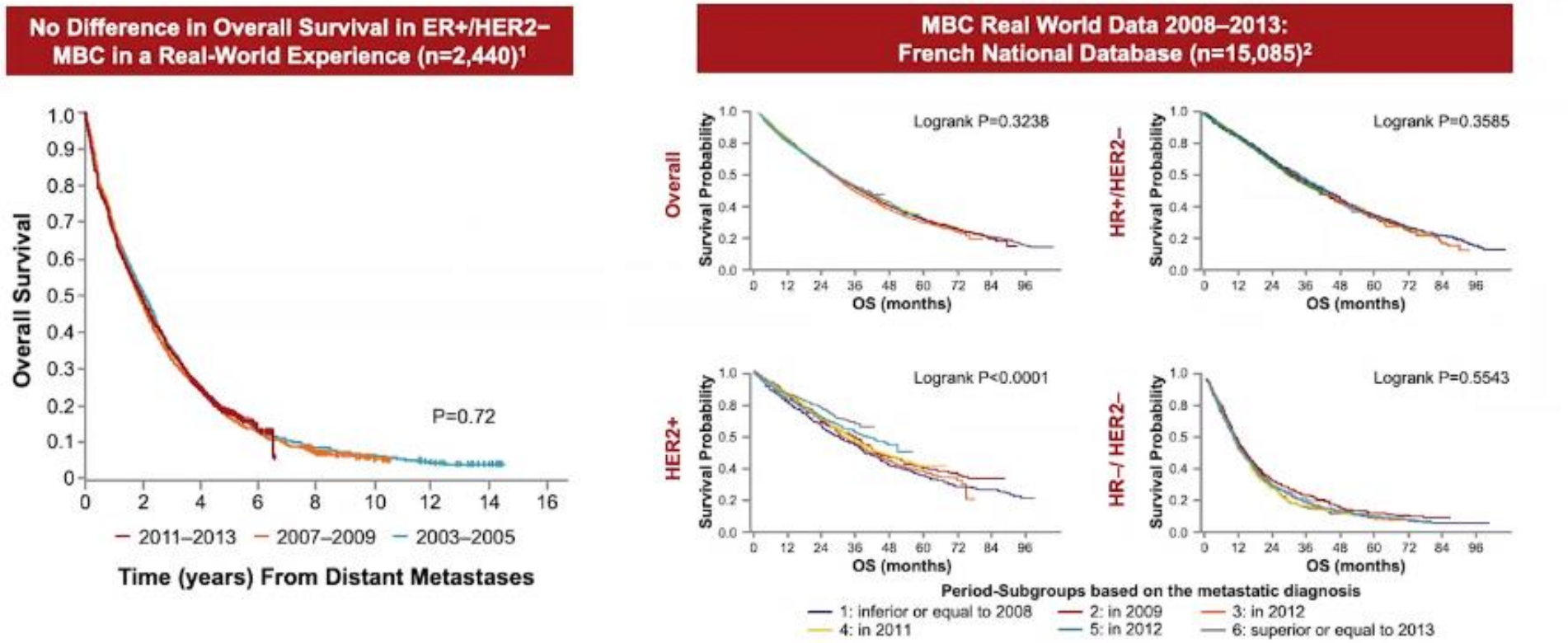
- Manifiesto que, dado mi trabajo como médico y consultor, mis potenciales conflictos de intereses son:

- Roche, Pfizer, AstraZeneca, Bayer, Tecnofarma, Merck, MSD, Novartis, Megalabs.

Contenidos

- Perspectiva de los iCDK4/6
- Primera línea SLP y SG con los iCDK4/6 en CMM
- Segunda línea SLP y SG con los iCDK4/6 en CMM
- Mantenimiento con un iCDK4/6
- Conclusiones

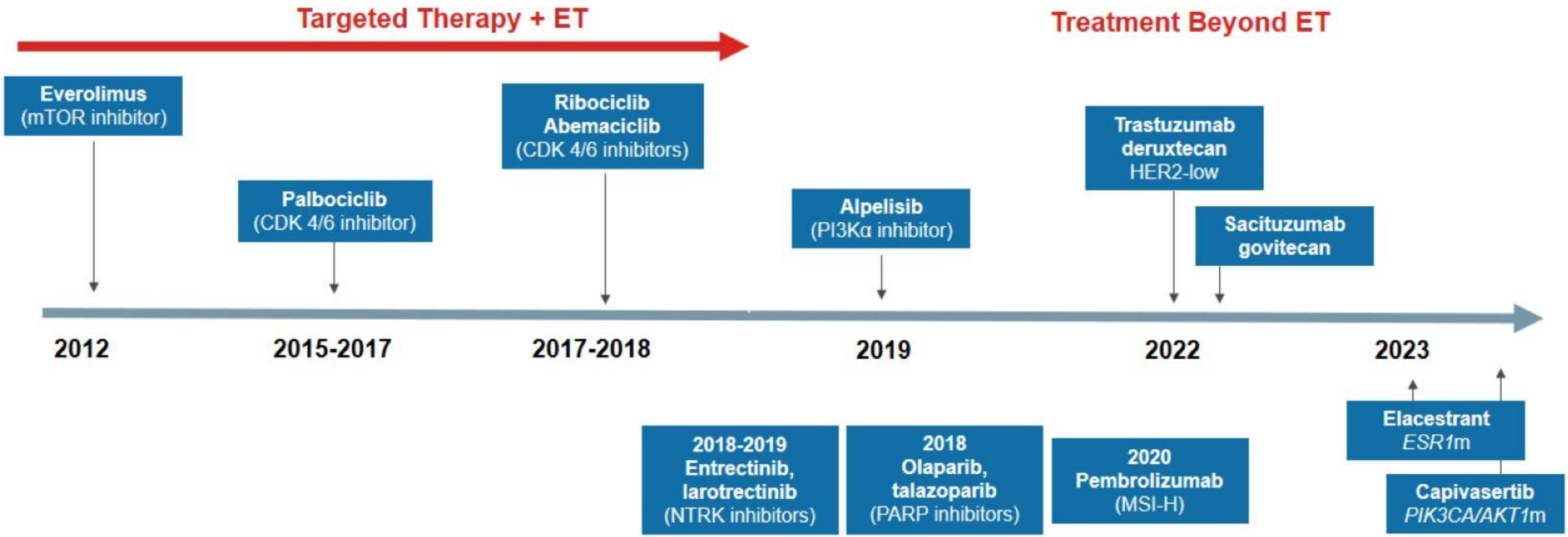
No se observaron mejoras en la SG entre los pacientes con CMM hasta 2013



- En 2014, la mediana de SG más larga reportada en CMM en ese momento fue de 56,5 meses, según lo informado en el estudio CLEOPATRA; estos pacientes fueron tratados con trastuzumab para CMM HER2+

References: 1. LeVasseur N. SABCS 2018. Abstract P1-16-05. 2. Gobbini E. *Eur J Cancer*. 2018;96:17-24. 3. Swain SM. *N Engl J Med*. 2015;372:724-734.

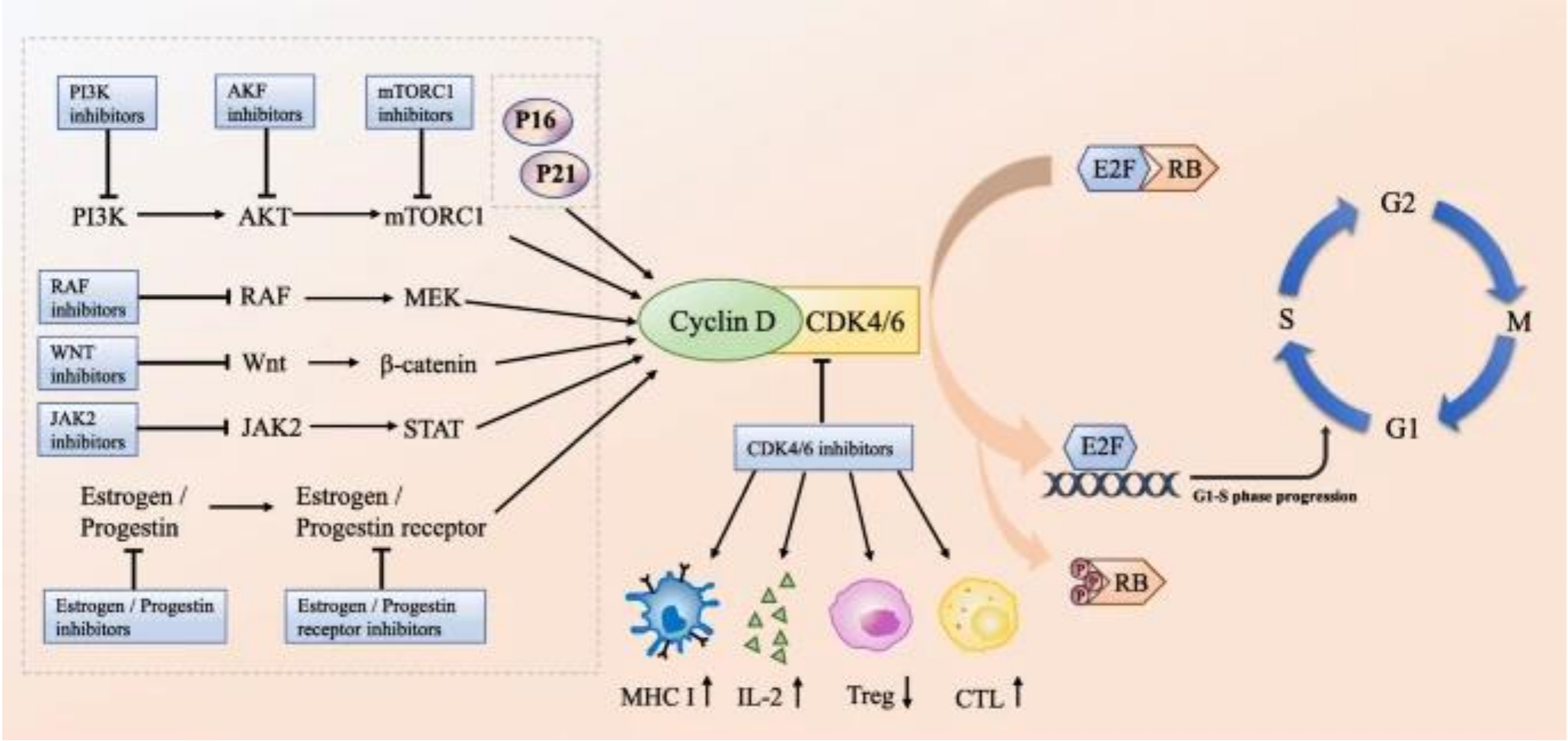
Timeline of FDA First Regulatory Approvals



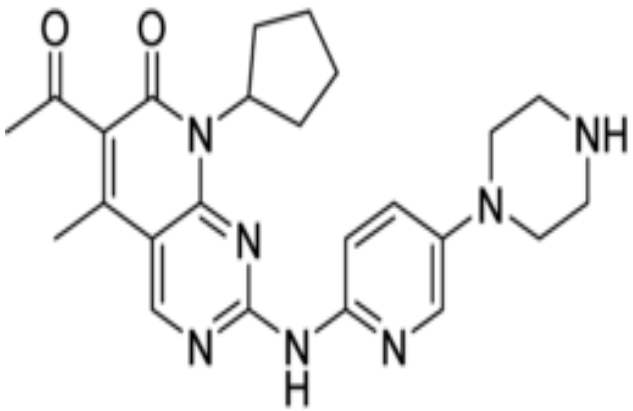
MSI-H, microsatellite instability-high; mTOR, mechanistic (mammalian) target of rapamycin; PI3Kα, phosphoinositide 3-kinase alpha.

Arora S, et al. Clin Cancer Res. 2022;28:1072-1086; Larotrectinib [PI]. Approved 2018. Revised November 2018; Entrectinib [PI]. Approved 2019. Revised October 2023; Fam-trastuzumab deruxtecan-nxki [PI]. Approved 2019. Revised August 2022; Sacituzumab govitecan [PI]. Approved 2020. Revised February 2023; Elacestrant [PI]. Approved 2023. Revised January 2023; Capivasertib [PI]. Approved 2023. Revised November 2023.

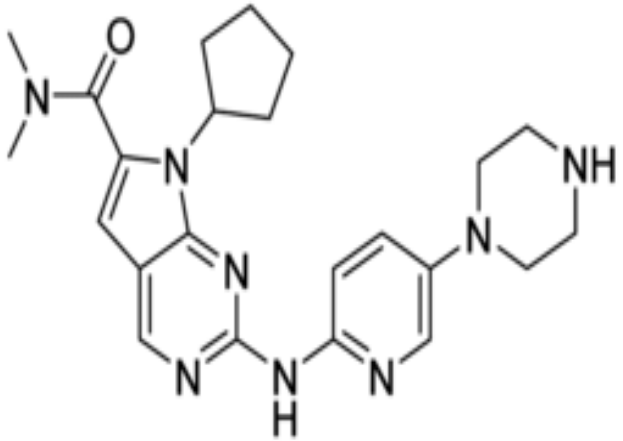
Mecanismo de acción de los inhibidores de las ciclinas



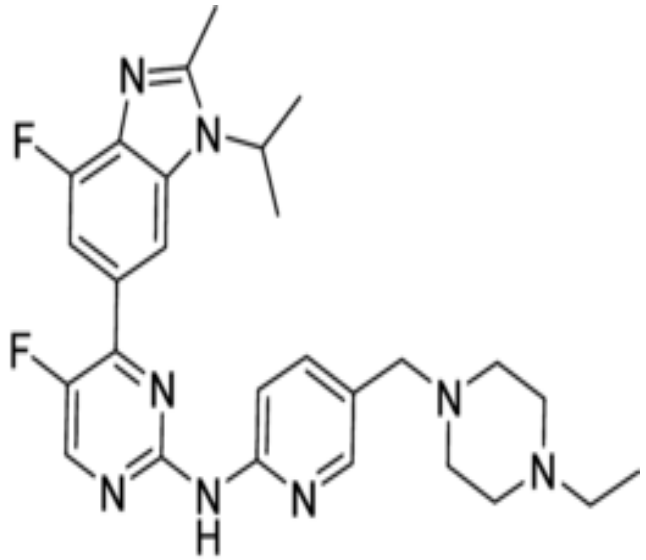
Estructura Química de los Inhibidores CDK4/6



Palbociclib



Ribociclib

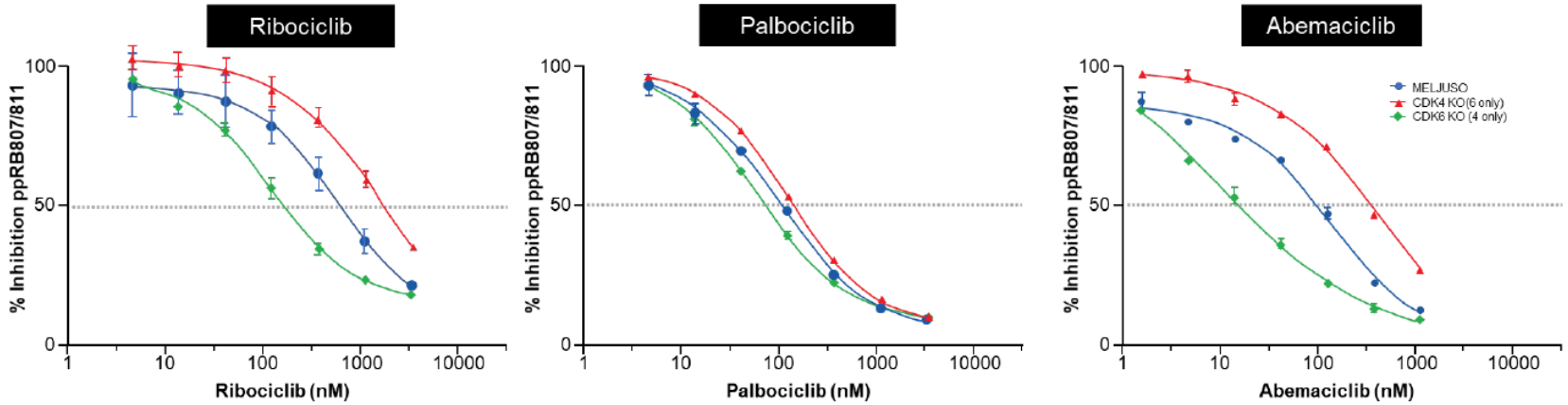


Abemaciclib

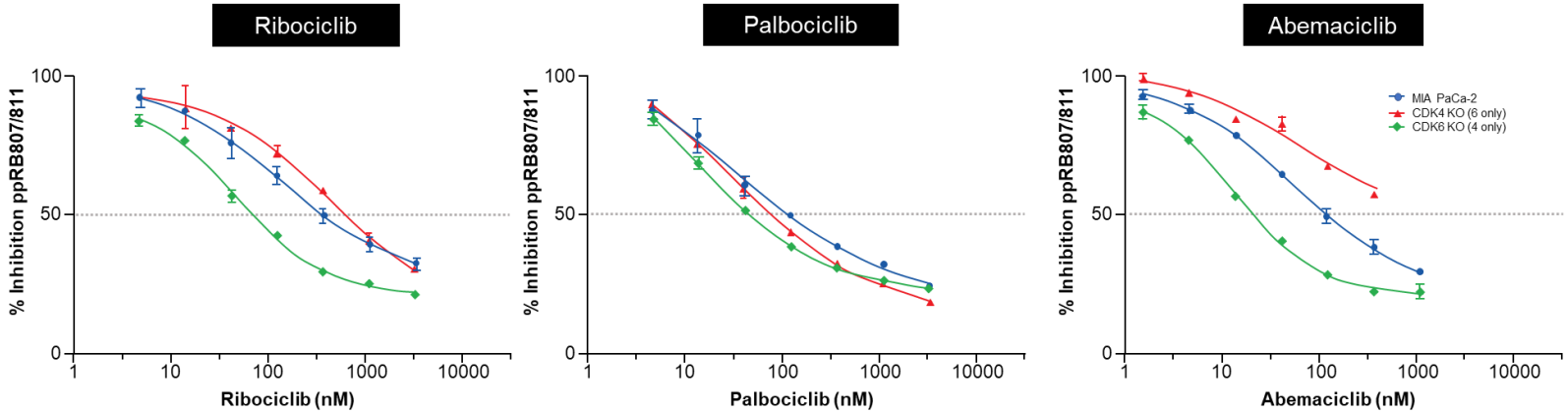
Solomon Tadesse March 2017Journal of Medicinal Chemistry 60(5):1892-1915

Los inhibidores de CDK4/6 tienen actividad diferencial hacia sus dos objetivos

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 y **abemaciclib** son más activos contra CDK4 que CDK6

CDK4 > CDK6

Palbociclib inhibe CDK4 y CDK6 igualmente

CDK4 = CDK6

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

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primera línea de tratamiento

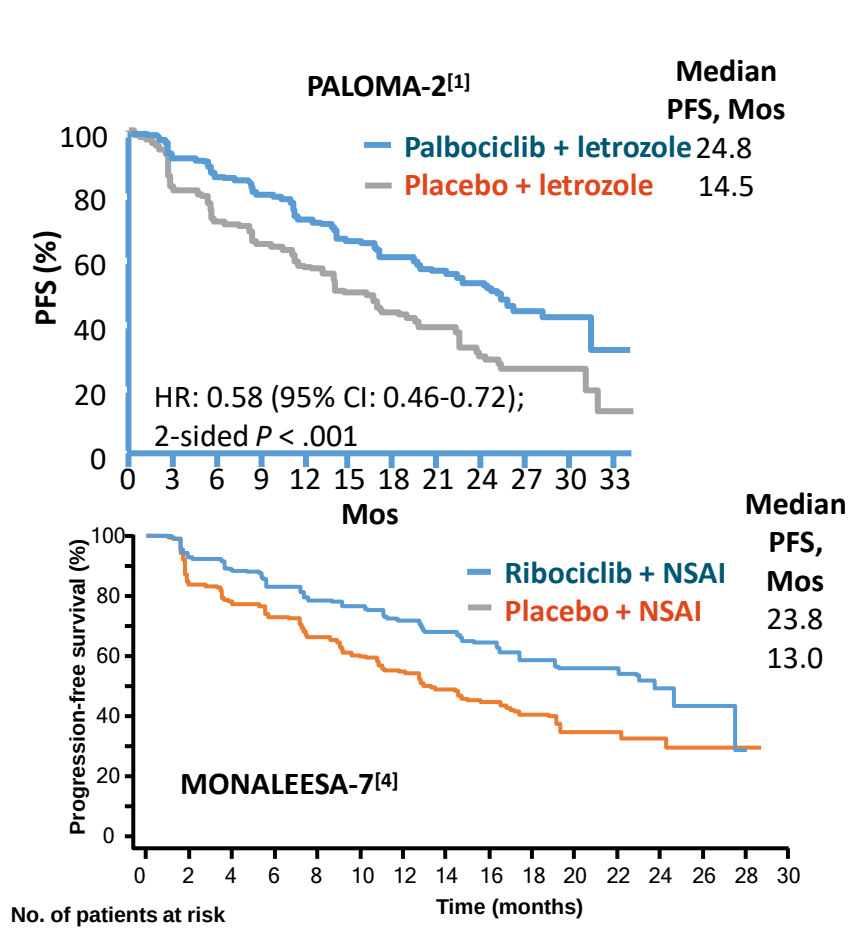
Los ensayos pivotales de fase 3 con inhibidores de CDK4/6 incluyeron una variedad de poblaciones de pacientes

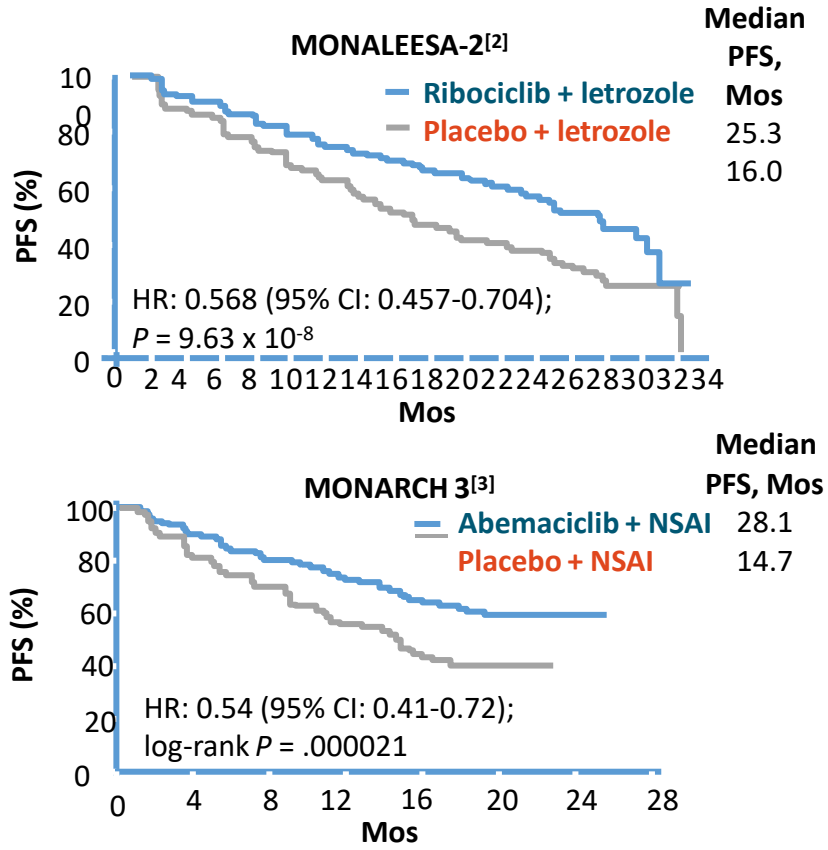
		No. Pacientes	R	Estado Menopáusico[a,b]	Factores de estratificación		QT previa para CMA
					Terapia endócrina	Sitio metastásico	
Primera línea	MONALEESA-2[1] Ribociclib + letrozole	668	1:1	Post	–	Hígado y/o pulmón	✘
	MONARCH 3[2,3] Abemaciclib + NSAI	493	2:1	Post	(Neo)adjuvante (IA, ninguna, u otra)	Visceral, solo hueso, otro	✘
	PALOMA-2[4] Palbociclib + letrozole	666	2:1	Post	Terapia hormonal previa	Visceral	✘
Recaída temprana y segunda línea	MONALEESA-7[5,6] Ribociclib + goserelin + tamoxifen/NSAI	672	1:1	Pre/peri	TE y en combinaciòn	Hígado y/o pulmón	Brazo tratamiento: 14% Brazo placebo: 14%
	MONALEESA-3[7,8] Ribociclib + fulvestrant	726	2:1	Post	TE previa para CMA	Hígado y/o pulmón	✘
	MONARCH 2[9,10] Abemaciclib + fulvestrant	669	2:1	Pre/peri y post	Resistencia TE primera vs secundaria	Visceral, solo hueso, otro	✘
	PALOMA-3[c,11,12] Palbociclib + fulvestrant	521	2:1	Pre/peri y post	Sensibilidad previa TE	Visceral	Brazo tratamiento: 31% Brazo placebo: 36%

[a] Symptomatic visceral disease was excluded in all trials. [b] CNS metastasis was excluded in all trials except for MONALEESA-3, which allowed stable CNS metastasis. [c] Second and later-lines of therapy.

References: 1. Hortobagyi GN et al. *N Engl J Med.* 2016;375:1738-1748. 2. Goetz MP et al. *J Clin Oncol.* 2017;35:3638-3646. 3. Johnston S. *NPJ Breast Cancer*. 2019;5:5. 4. Finn RS et al. *N Engl J Med*. 2016;375:1925-1936. 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. Slamon DJ et al. *J Clin Oncol.* 2018;36:2465-2472. 8. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524. 9. Sledge GW et al. *J Clin Oncol*. 2017;35:2875-2884. 10. Sledge GW et al. *JAMA Oncol.* 2020;6:116-124. 11. Turner NC et al. *N Engl J Med.* 2015;373:209-219. 12. Turner NC et al. *N Engl J Med.* 2018;379:1926-1936.

SLP en estudios de primera línea con iCDK4/6





1. Finn RS, et al. N Engl J Med. 2016;375:1925-1936. 2. Hortobagyi GN, et al. Ann Oncol. 2018;29:1541-1547. 3. Goetz MP, t al. J Clin Oncol. 2017;35:3638-3646.4. Tripathy D et al. Lancet Oncol. 2018;19:904-915

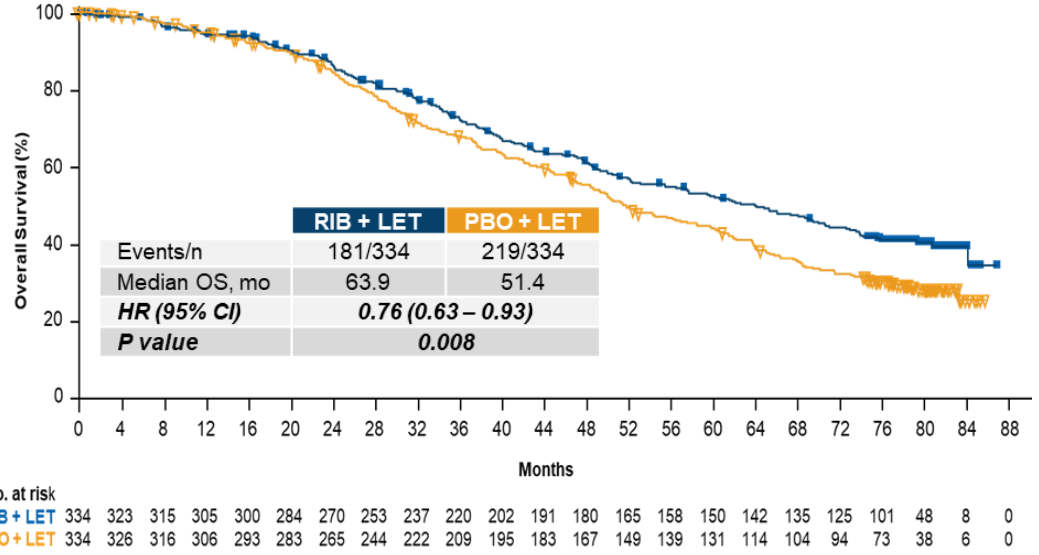
Impacto inhibidores de ciclina en primera línea: SLP

Phase III Study	PALOMA-2[1,2]	MONALEESA-2[3,4]	MONARCH-3[5,6]	MONALEESA-3[7,8]	MONALEESA-7[9]
Setting	1st line	1st line	1st line	1st and 2nd line	1st line*
Endocrine partner	Letrozole	Letrozole	Letrozole or anastrozole	Fulvestrant	Tamoxifen, letrozole, or anastrozole
CDK4/6 inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Ribociclib
No. patients	666	668	493	365	672
HR	0.563	0.56	0.54	0.55	0.55
PFS, mos	27.6 vs 14.5	25.3 vs 16	28.18 vs 14.76	33.6 vs 19.2	23.8 vs 13.0
ORR, %	55.3 vs 44.4	52.7 vs 37.1	59 vs 44	40.9 vs 28.7†	41 vs 30

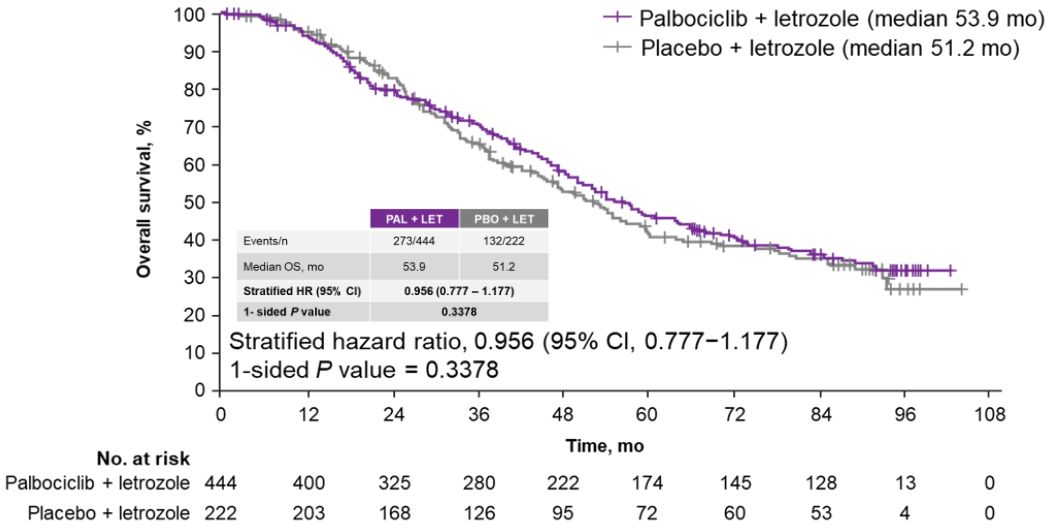
1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Hortobagyi. NEJM. 2016;375:1738. 4. Hortobagyi. Ann Oncol. 2018;29:1541. 5. Goetz. JCO. 2017;35:3638. 6. Johnston. NPJ Breast Cancer. 2019;5:5. 7. Slamon. JCO. 2018;36:2465. 8. Slamon. NEJM. 2020;382:514. 9. Tripathy. Lancet Oncol. 2018;19:904.

SG en estudios de primera línea con iCDK4/6

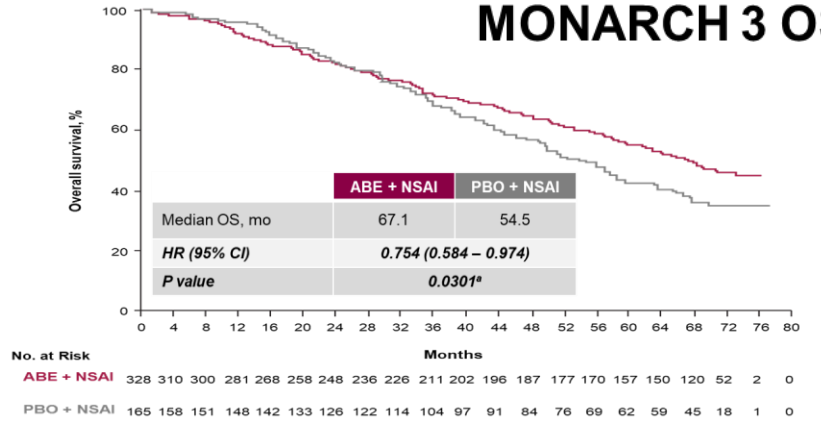
MONALEESA-2 OS ITT



PALOMA-2 OS ITT

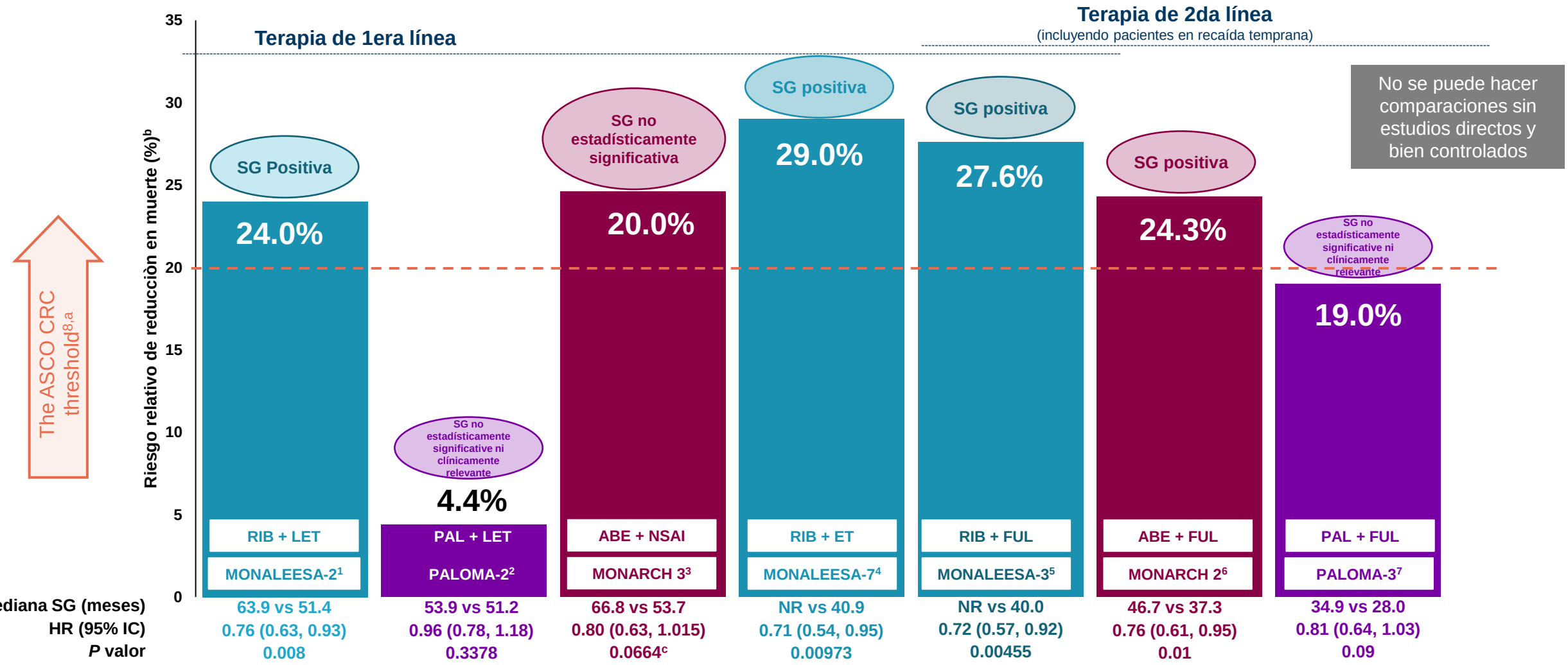


MONARCH 3 OS ITT[1]



1. Finn RS, et al. N Engl J Med. 2016;375:1925-1936. 2. Hortobagyi GN, et al. Ann Oncol. 2018;29:1541-1547. 3. Goetz MP, t al. J Clin Oncol. 2017;35:3638-3646.4. Tripathy D et al. Lancet Oncol. 2018;19:904-915

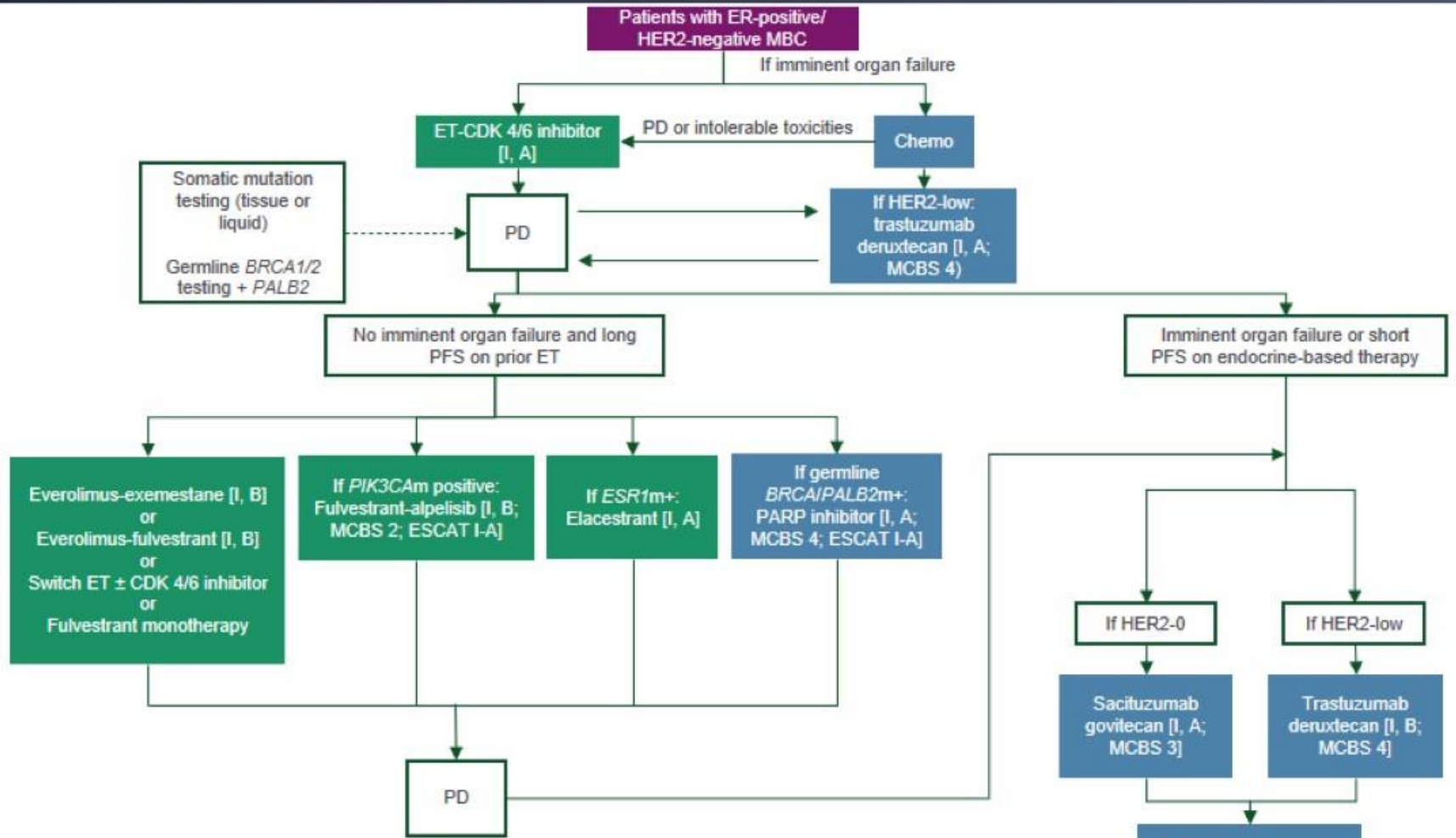
SG con el uso de los iCDK4/6: estudios pivotales



[a] The ASCO Cancer Research Committee defined incremental improvements in HR of OS ≥ 20% over standard therapy as a clinically meaningful outcome; the magnitude of benefit is based on hazard ratios and refers to the proportional improvement achieved with the addition of CDK4/6 inhibitors in comparison to the respective control groups. [b] As measured by 1 minus HR multiplied by 100.[c] P value did not reach threshold for statistical significance at this interim analysis of MONARCH 3

References: 1. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950. 2. Finn RS, et al. ASCO 2022. LBA1003. 3. Goetz, et al. ESMO 2022. LBA15. 4. Im SA, et al. *N Engl J Med*. 2019;38:307-316. 5. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524. 6. Sledge GW, et al. *JAMA Oncol*. 2020;6:116-124. 7. Turner NC, et al. *N Engl J Med*. 2018;15;379:1926-1936. 8. Ellis LM, et al. *J Clin Oncol*. 2014;32:1277-80.

ESMO Guidelines for ER-Positive/HER2-Negative MBC



CDK 4/6, cyclin-dependent kinase 4/6; chemo, chemotherapy; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO, European Society for Molecular Oncology; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; MBC, metastatic breast cancer; MCBS, ESMO-Magnitude of Clinical Benefit Scale; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFS, progression-free survival.

ESMO. Accessed January 25, 2024. https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer

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segunda línea de tratamiento

Los ensayos pivotales de fase 3 con inhibidores de CDK4/6 varían en su definición y criterios de inclusión para TE previa.

		Primera Línea		Recaída Temprana y Segunda Línea	
		Sin TE en etapa avanzada	Recaída > 12 Meses desde finalizar T.E (Neo) adjuvante	Recaída en o ≤ 12 Meses después de finalizar la T.E (Neo)adjuvant ET	Recaída en primera línea T.E para CMA
Primera Línea	**MONALEESA-2**[1] Ribociclib + letrozole	✓	✓ (NSAI only)[e]	✓ (non-NSAI)[f]	
	MONARCH 3[2] Abemaciclib + NSAI	✓	✓	X (no early relapsers)[g]	
	PALOMA-2[3] Palbociclib + letrozole	✓	✓ (NSAI only)[e]	✓ (non-NSAI)[h]	
	MONALEESA-7[4] Ribociclib + goserelin + tamoxifen/NSAI	✓	✓	✓ i	
Recaída Temprana y 2da línea	**MONALEESA-3**[5,a] Ribociclilb + fulvestrant	✓	✓	✓	✓
	MONARCH 2[6,b] Abemaciclib + fulvestrant			✓	✓
	PALOMA-3[7,c,d] Palbociclib + fulvestrant			✓	36% tenía ≥2 líneas previas de terapia para CMA

[a] MONALEESA-3 also included de novo ABC. [b] MONARCH-2 recruited an ET-naive population; however, this population was not included in the primary or updated OS analysis. [c] PALOMA-3 allowed ≥ 1 line of ET in ABC and ≤ 1 line of prior chemotherapy for ABC. [d] Second and later-lines of therapy. [e] Time since the last dose of nonsteroidal aromatase inhibitors must have been greater than 12 months. [f] In MONALEESA-2, patients with DFI (defined as the time from initial diagnosis to disease recurrence) ≤ 12 months were allowed if not on NSAI in the (neo)adjuvant setting. [g] MONARCH 3 exclude all patients with a DFI ≤ 12 months regardless of prior ET. [h] PALOMA-2 included patients with a DFI (time from end of [neo]adjuvant treatment to disease recurrence) ≤ 12 months. [i] Patients who relapsed on 1 ET partner < 12 month
ET arm.

References: 1. Hortobagyi GN et al. *N Engl J Med*. 2016;375:1738-1748. 2. Goetz MP et al. *J Clin Oncol*. 2017;35:3638-3646. 3. Finn RS et al. *N Engl J Med*. 2016;375:1925-1936. 4. Tripathy D et al. *Lancet Oncol*. 2018;19:904-915. 5. Slamon DJ et al. *J Clin Oncol*. 2018;36:2465-2472. 6. Sledge GW et al. *J Clin Oncol*. 2017;35:2875-2884. 7. Turner NC et al. *N Engl J Med*. 2015;373:209-219.

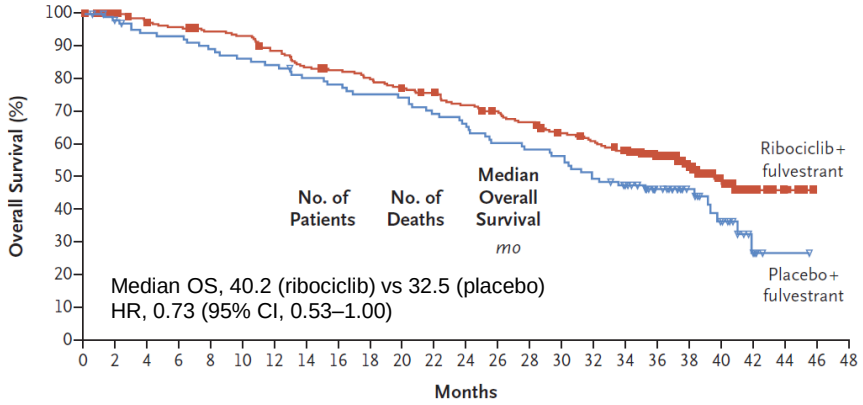
iCDK4/6 + Terapia Endócrina, mejoran la SLP en 1era/2da línea en CMM

Study/Arms	[1]PALOMA-1	[2]PALOMA-2	[3]MONALEESA-2	[4]MONARCH 3	[5]MONALEESA-7	[6]PALOMA-3	[7]MONARCH 2	[8]MONALEESA-3
Phase	2	3	3	3	3	3	3	3
CDK4/6i ET partner	Palbo AI	Palbo AI	Ribo AI	Abema AI	Ribo AI/tam + OS	Palbo Fulvestrant	Abema Fulvestrant	Ribo Fulvestrant
N	165	666	668	493	642	521	669	726
Median PFS (placebo), mo	10.2	14.5	16	14.7	13.0	4.6	9.3	12.8
Median PFS (CDK4/6i), mo	20.2	27.6	25.3	28.1	23.8	11.2	16.4	20.5
HR 95% CI	0.48 0.31-0.74	0.56 0.46-0.69	0.54 0.41-0.69	0.55 0.44-0.69	0.55 0.44-0.69	0.50 0.40-0.62	0.553 0.45-0.68	0.593 0.480-0.732
P value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

1. Finn R et al. *Lancet Oncol*. 2015;16:25-35. 2. Rugo H et al. SABCS. 2017. 3. Hortobagyi GN, et al. ASCO. 4. Goetz MP et al. *J Clin Oncol*. 2017;35:3638-3646.
5. Tripathy D et al. *Lancet Oncol*. 2018;19:904-915. 6. Turner NC et al. *N Engl J Med*. 2015;373:209-219. 7. Sledge GW et al. *J Clin Oncol*. 2017;35:2875-2884.
8. Slamon DJ et al. *J Clin Oncol*. 2018;36:2465-2472.

SG en segunda línea con los iCDK4/6

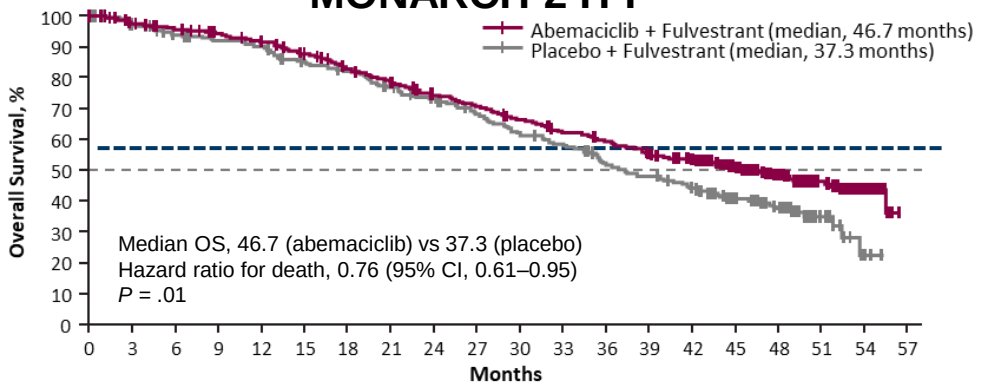
MONALEESA-3 2L Subgroup[1,b]



No. at Risk

Ribociclib+fulvestrant	237	231	222	218	213	210	199	188	184	179	172	167	158	152	145	135	129	122	94	63	36	17	7	1	0
Placebo+fulvestrant	109	103	98	97	93	90	88	83	81	78	77	72	69	63	61	59	54	49	35	23	15	6	1	0	0

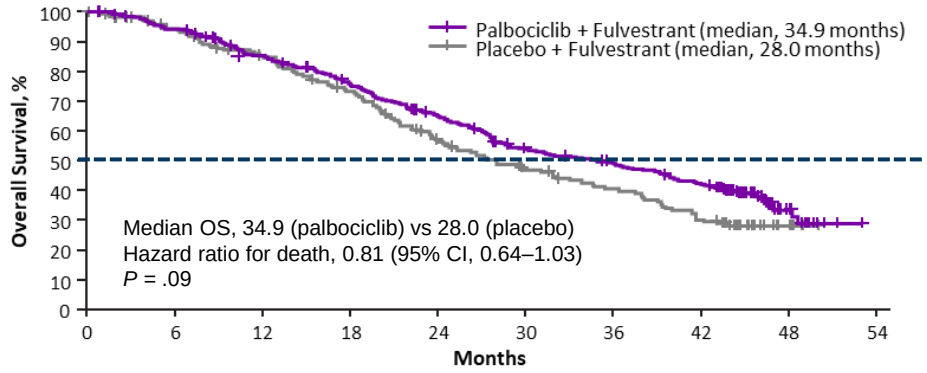
MONARCH 2 ITT[2]



No. at risk

Abemaciclib + fulvestrant	446	422	410	397	384	364	339	321	302	284	265	246	234	214	202	157	101	58	23	0
Placebo + fulvestrant	223	214	201	195	191	178	170	158	148	135	122	115	99	92	82	62	42	15	3	0

PALOMA-3 ITT[3]



No. at risk

Palbociclib + fulvestrant	347	321	286	247	209	165	148	126	17	0
Placebo + fulvestrant	174	155	135	115	86	68	57	43		

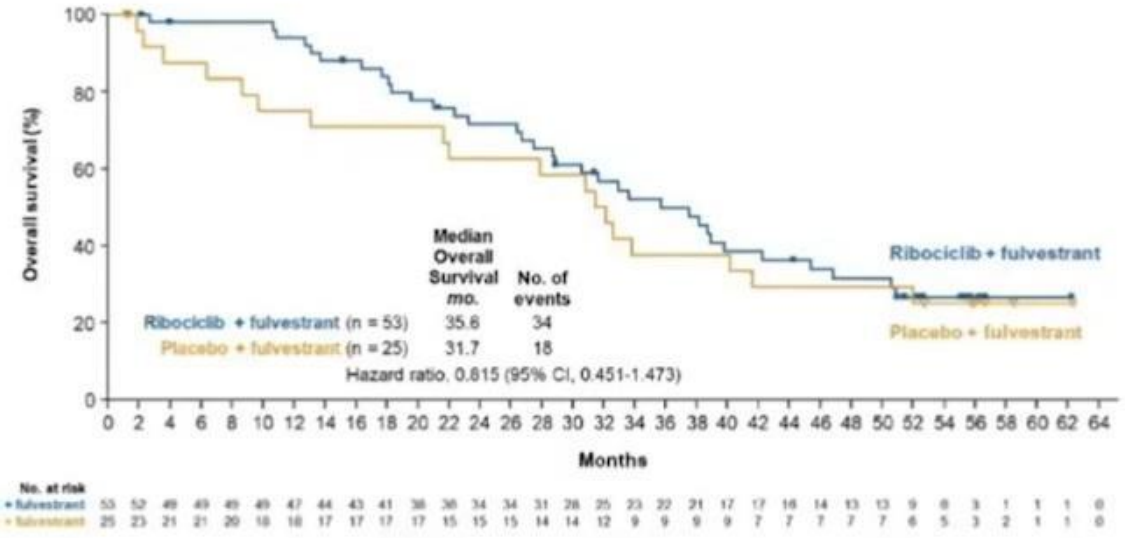
Comparisons cannot be made in the absence of well-controlled, head-to-head studies

[a] Based on final protocol-specified OS analysis. [b] This is a subgroup analysis, the trial was not powered for this ananlysis.

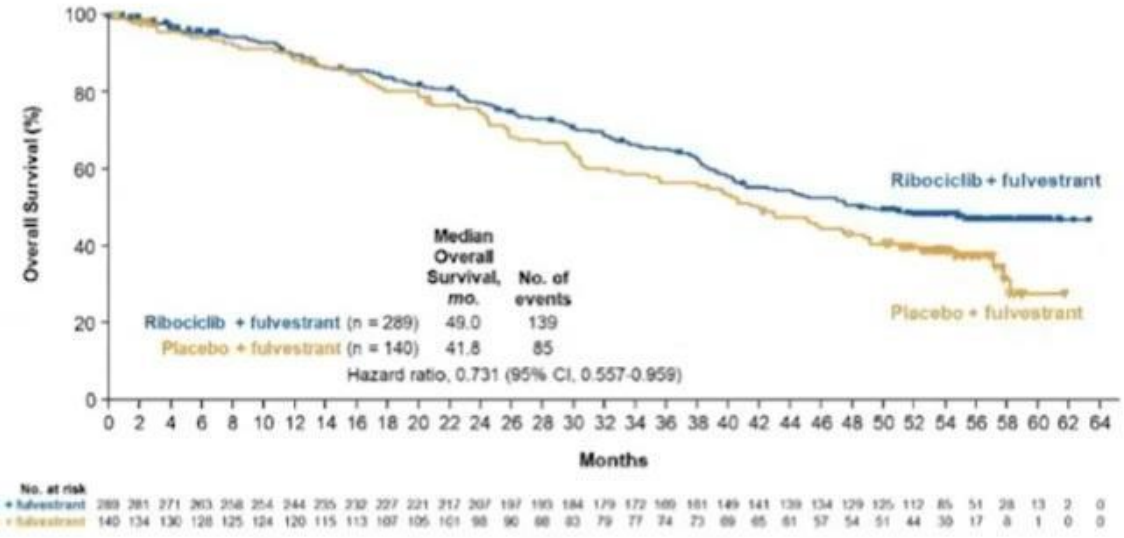
References: 1. Slamon DJ et al. *N Engl J Med.* 2020;382:514-524. 2. Sledge GW et al. *JAMA Oncol.* 2020;6:116-124. 3. Turner NC et al. *N Engl J Med.* 2018;379:1926-1936.

MONALEESA 3: Sobrevida global por sensibilidade endócrina

População endócrina-resistente



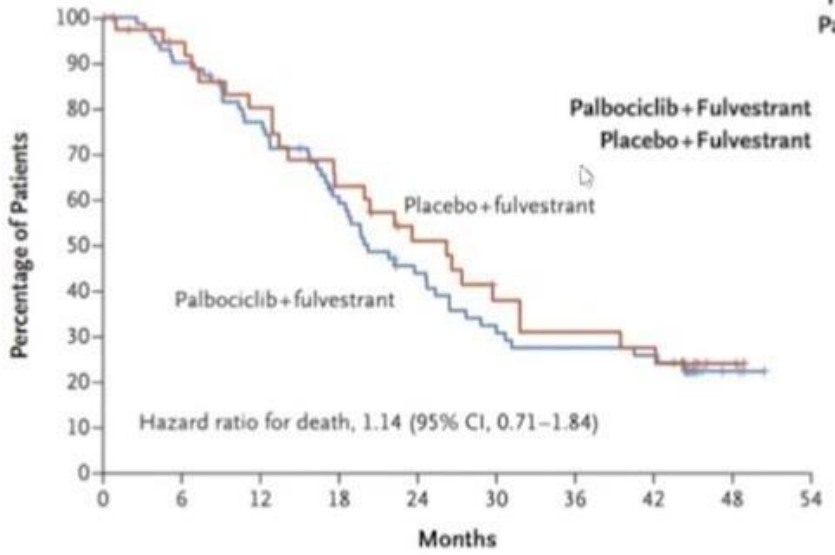
População endócrina-sensível



- Ribociclibe + fulvestranto prolongaram SG mediana em relação a placebo + fulvestranto em pacientes que eram sensíveis à TE, bem como naqueles que eram resistentes à TE.

PALOMA 3: Sobrevida global por sensibilidade endócrina

População endócrina-resistente

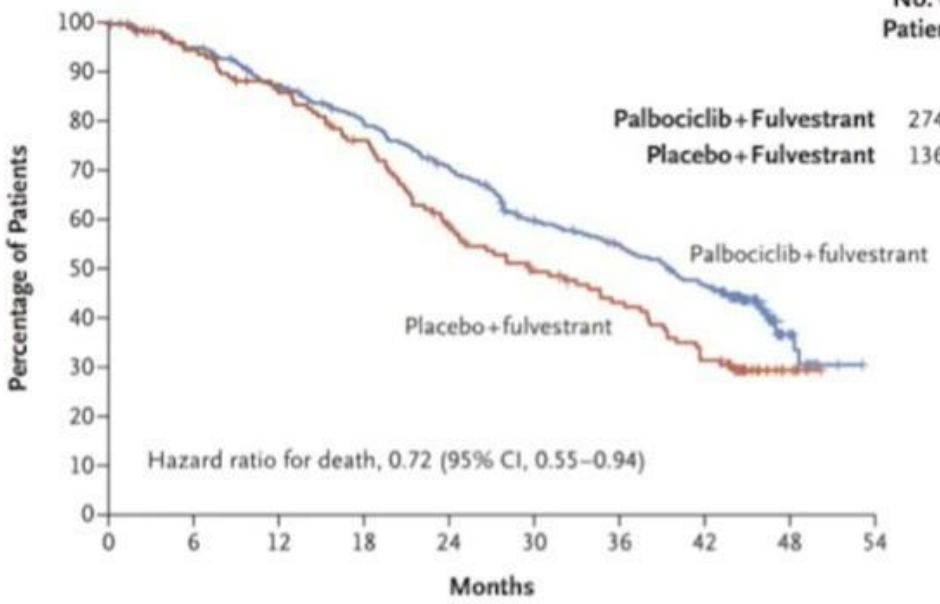


	No. of Patients	Median Overall Survival (95% CI)
		mo
Palbociclib + Fulvestrant	73	20.2 (17.2–26.4)
Placebo + Fulvestrant	38	26.2 (17.5–31.8)

No. at Risk

Palbociclib + fulvestrant	73	64	53	39	27	19	17	16	3	—
Placebo + fulvestrant	38	33	28	22	16	11	9	8	2	—

População endócrina-sensível



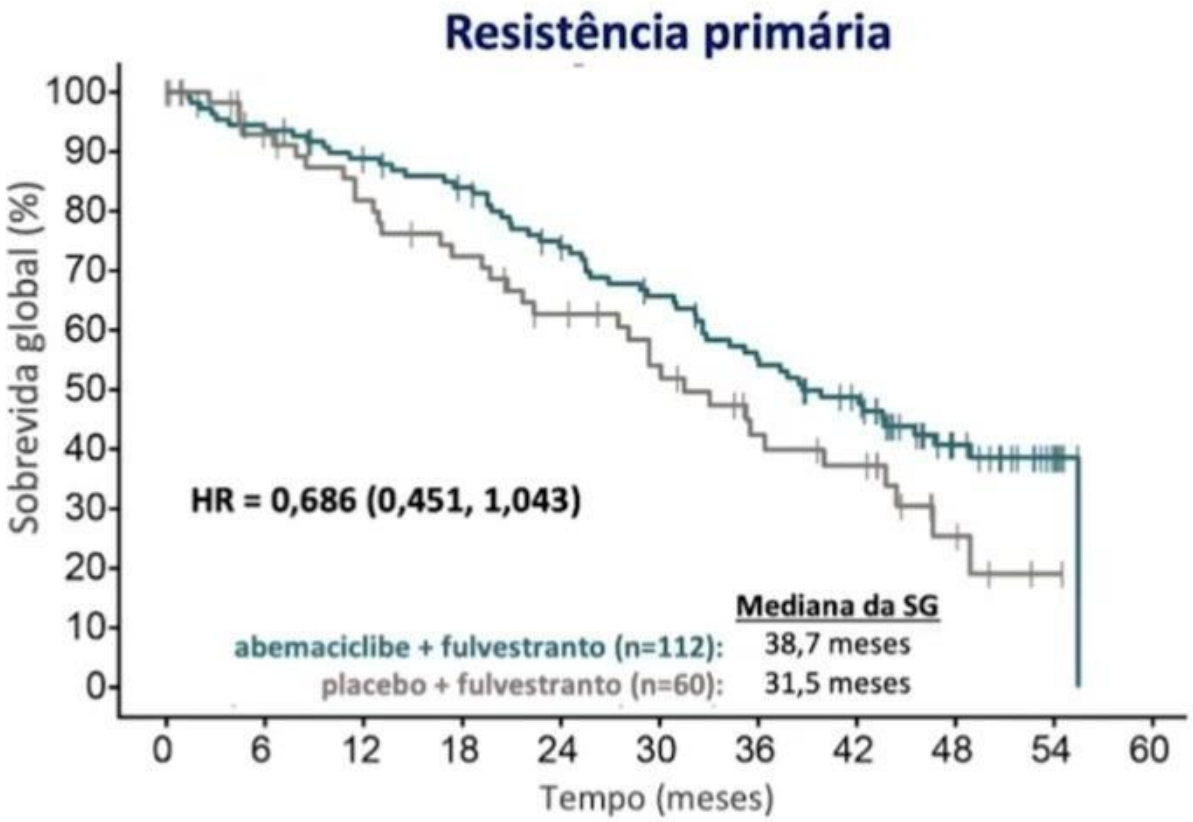
	No. of Patients	Median Overall Survival (95% CI)
		mo
Palbociclib + Fulvestrant	274	39.7 (34.8–45.7)
Placebo + Fulvestrant	136	29.7 (23.8–37.9)

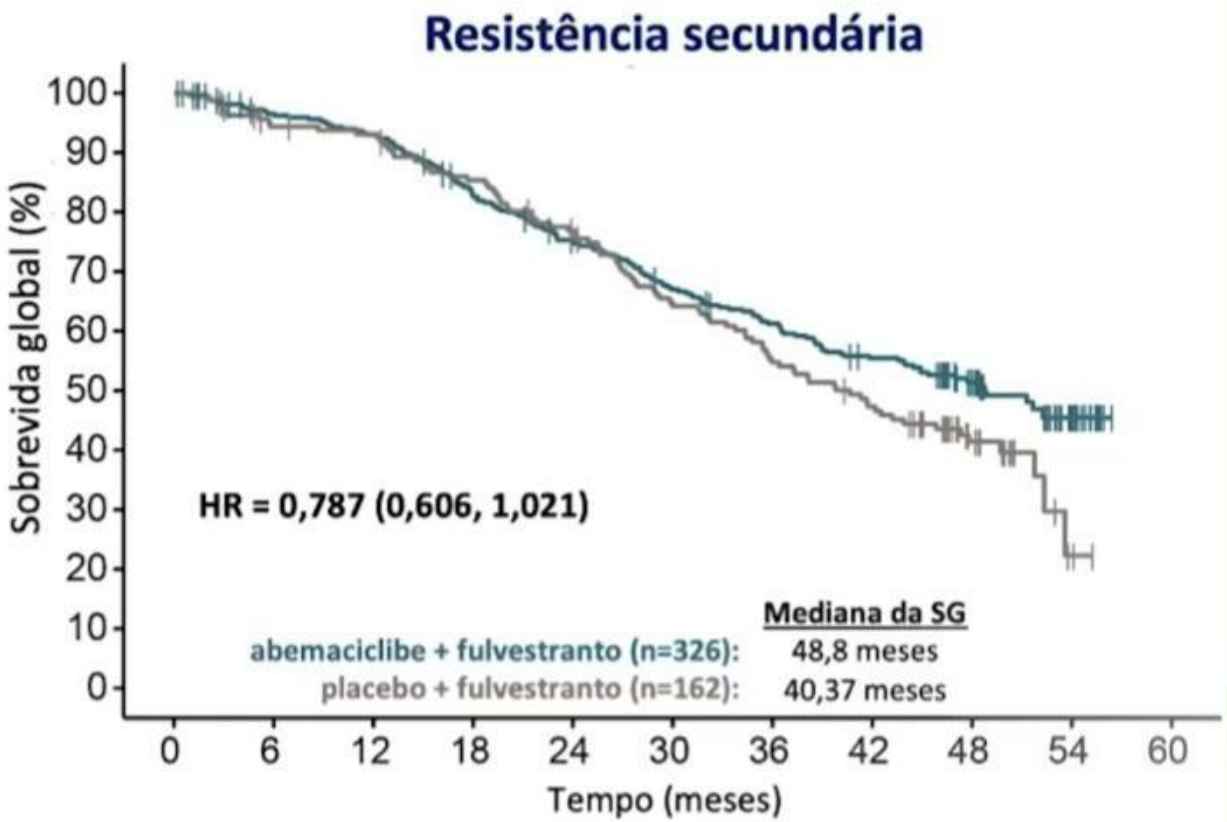
No. at Risk

Palbociclib + fulvestrant	274	257	233	208	182	146	131	110	14	—
Placebo + fulvestrant	136	122	107	93	70	57	48	35	5	—

Adaptado de Turner NC, et al. N Engl J Med 379:1926, 2018 - Permission for reuse Only [Internet]. https://www.nejm.org/doi/full/10.1056/nejmoa1810527

MONARCH2: Sobrevida global (SG) por resistência à terapia endócrina





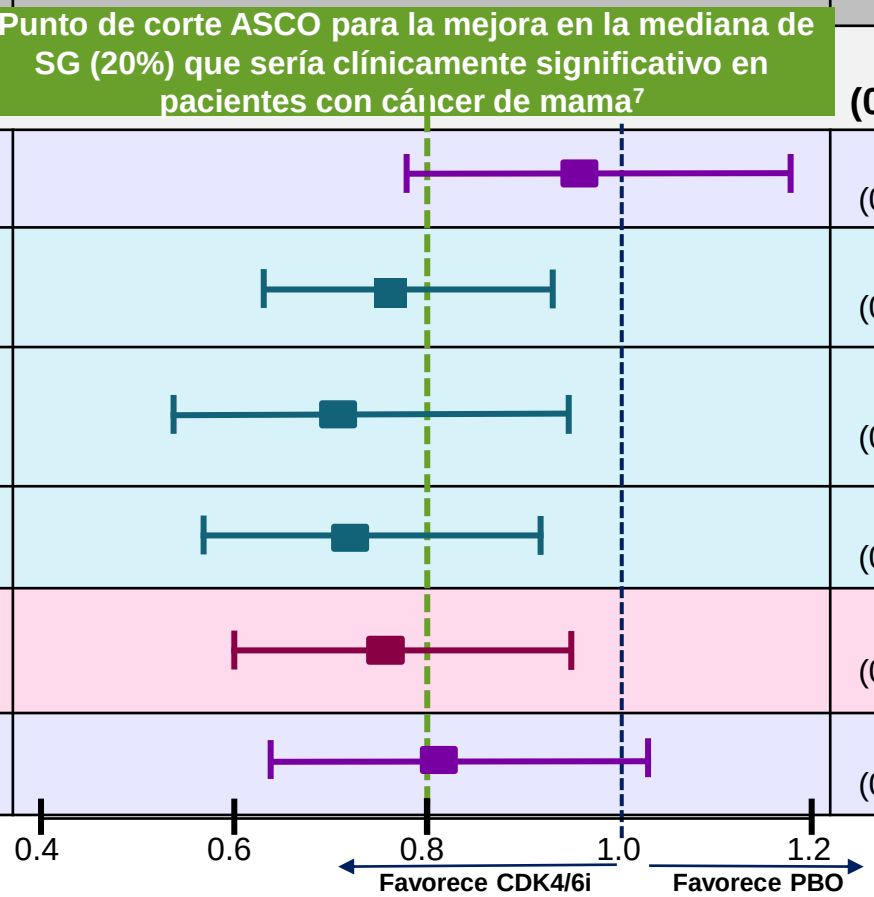
[a]*Valor P de interação: 0,588*

Adaptado de Sledge et al., JAMA Oncol. Publicado online em 29 de setembro de 2019.

Resultados finales de SG especificados por el protocolo en pacientes tratados con inhibidores de CDK4/6

No se pueden hacer comparaciones sin estudios directos bien controlados.

	Brazo de tratamiento: SG, mediana, meses	Brazo placebo: SG, mediana, meses	Hazard ratio	Hazard ratio (95% CI)	*P* valor	Significancia encontrada vs placebo[a]
MONARCH 3 Abemaciclib + NSA	**66.8**	**53.7**		**0.80 (0.63-1.01)**	**.0664**	X
PALOMA-2[1] Palbociclib + letrozole	53.9	51.2		0.96 (0.78-1.18)	.3378	✘
MONALEESA-2[2] Ribociclib + letrozole	63.9	51.4		0.76 (0.63-0.93)	.008	✓
MONALEESA-7[3] Ribociclib + goserelin + tamoxifen/NSAI	NR	40.9		0.71 (0.54-0.95)	.00973	✓
MONALEESA-3[4] Ribociclib + fulvestrant	NR	40.0		0.72 (0.57-0.92)	.00455	✓
MONARCH 2[5] Abemaciclib + fulvestrant	46.7	37.3		0.76 (0.61-0.95)	.01	✓
PALOMA-3[6] Palbociclib + fulvestrant	34.9	28.0		0.81 (0.64-1.03)	.09	✘



[a] The red × denotes trials that did not report significant median OS compared with placebo.

References: 1. Finn RS, et al. ASCO 2022. LBA1003. 2. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950. 3. Im SA, et al. *N Engl J Med*. 2019;381:307-316. 4. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524. 5. Sledge GW, et al. *JAMA Oncol*. 2020;6:116-124. 6. Turner NC, et al. *N Engl J Med*. 2018;379:1926-1936. 7. Ellis LM, et al. *J Clin Oncol*. 2014;32(12):1277-1280.

SONIA: Phase III Trial Assessing the Optimal Therapeutic Position of CDK4/6 Inhibitors for Patients With HR+/HER2- Advanced Breast Cancer

CCO Independent Conference Highlights*

of the *2023 ASCO Annual Meeting, June 2-6, 2023, Chicago, Illinois*

*CCO is an independent medical education company that provides state-of-the-art medical information to healthcare professionals through conference coverage and other educational programs.

Supported by educational grants from AstraZeneca, Daiichi Sankyo, Gilead, and Merck Sharp & Dohme Corp.

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2023 ASCO ANNUAL MEETING

SONIA

Primary outcome of the phase 3 SONIA trial (BOOG 2017-03)

Gabe Sonke, Annemiek van Ommen - Nijhof, Noor Wortelboer, Vincent van der Noort, Astrid Swinkels, Hedwig Blommestein, Aart Beeker, Karin Beelen, Lisanne Hamming, Joan Heijns, Aafke Honkoop, Paul de Jong, Quirine van Rossum - Schornagel, Christa van Schaik - van de Mheen, Jolien Tol, Cathrien Tromp - van Driel, Suzan Vrijaldenhoven, Elise van Leeuwen - Stok, Inge Konings, Agnes Jager

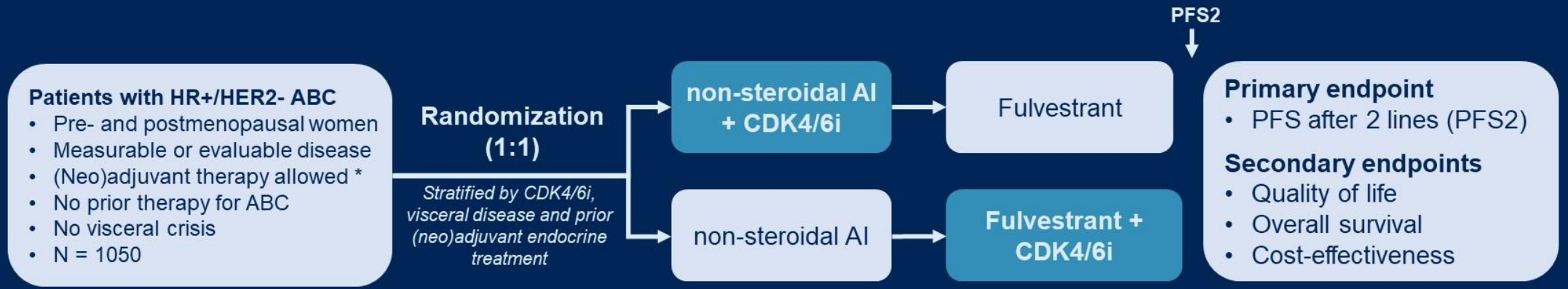
PRESENTED BY: Prof. Gabe S. Sonke, MD, PhD

SONIA: racional

- La adición de inhibidores de CDK4/6 a la terapia endocrina mejora la SSP y la SG en pacientes con cáncer de mama avanzado, tanto como tratamiento inicial como después de la monoterapia endocrina.
  - A pesar de la falta de evidencia de superioridad del uso de primera línea sobre la segunda línea, la mayoría de las guías recomiendan en el ámbito de primera línea.
- El estudio actual evaluó la eficacia y seguridad del inhibidor de CDK4/6 agregado a la terapia endocrina de primera o segunda línea en pacientes con cáncer de mama avanzado HR+/HER2- que no han recibido terapia previa en el entorno avanzado.

1. Finn. NEJM. 2016;375:1925. 2. Hortobagyi. NEJM. 2016;375:1738. 3. Goetz. JCO. 2017;35:3638. 4. Cristofanili. Lancet Oncol. 2016;17:425. 5. Slamon. JCO. 2018;36:2465. 6. Sledge. JCO. 2017;35:2875. 7. NCCN Breast v4.2023. 8. Burstein. JCO. 2021;35:3959. 9. Gennari. Ann Oncol. 2021;32:1475. 10. Sonke. ASCO 2023. Abstr LBA1000.

SONIA trial design



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

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

Baseline characteristics

SONIA

		First-line CDK4/6i N=524	Second-line CDK4/6i N=526
Median age, years (range)		64 (24-88)	63 (25-87)
WHO PS, n (%)	0	257 (49)	257 (49)
	≥1	267 (51)	269 (51)
Menopausal status, n (%)	Pre- / perimenopausal	69 (13)	76 (14)
	Postmenopausal	455 (87)	450 (86)
Disease-free interval, n (%)	Newly diagnosed	182 (35)	182 (35)
	≤24 months	96 (18)	98 (19)
	>24 months	246 (47)	246 (47)
Prior (neo)adjuvant therapy, n (%)	Chemotherapy	212 (40)	210 (40)
	Endocrine therapy	258 (49)	254 (48)
Metastatic site, n (%)	Visceral disease	291 (56)	292 (56)
	Bone-only disease	91 (17)	91 (17)
Measurable disease, n (%)		315 (60)	312 (59)
Type of CDK4/6i, n (%)	Palbociclib	479 (91)	479 (91)
	Ribociclib	42 (8)	44 (8)
	Abemaciclib	3 (1)	3 (1)

Trial overview

SONIA

Inclusion period: November 23, 2017 - September 1, 2021

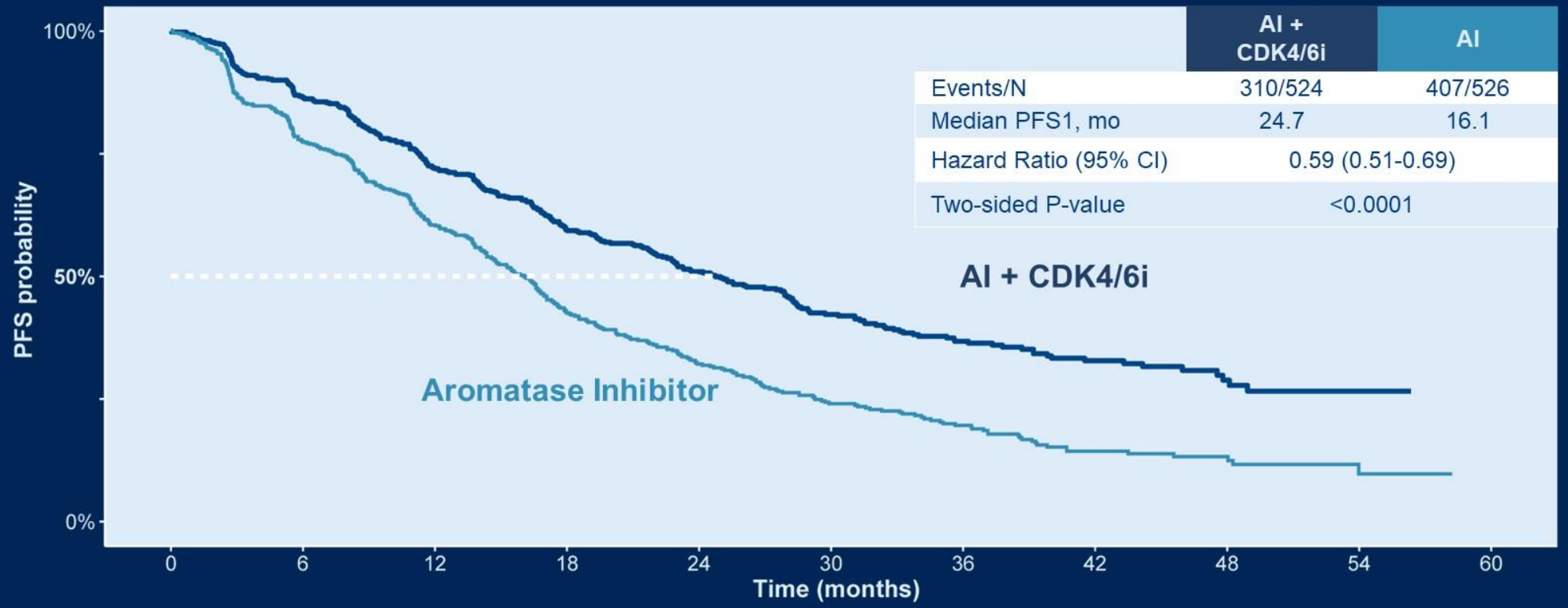
Data cut-off date: December 1, 2022

Median follow-up: 37.3 months

		First-line CDK4/6i N=524	Second-line CDK4/6i N=526
Patient status, n	First-line treatment ongoing	207	122
	Second-line treatment ongoing	16	82
	Follow-up	117	134
Number of events, n	PFS1	310	407
	PFS2	281	310
	OS	184	188
Median duration on CDK4/6i, months		24.6	8.1

Progression-free survival in first line

SONIA



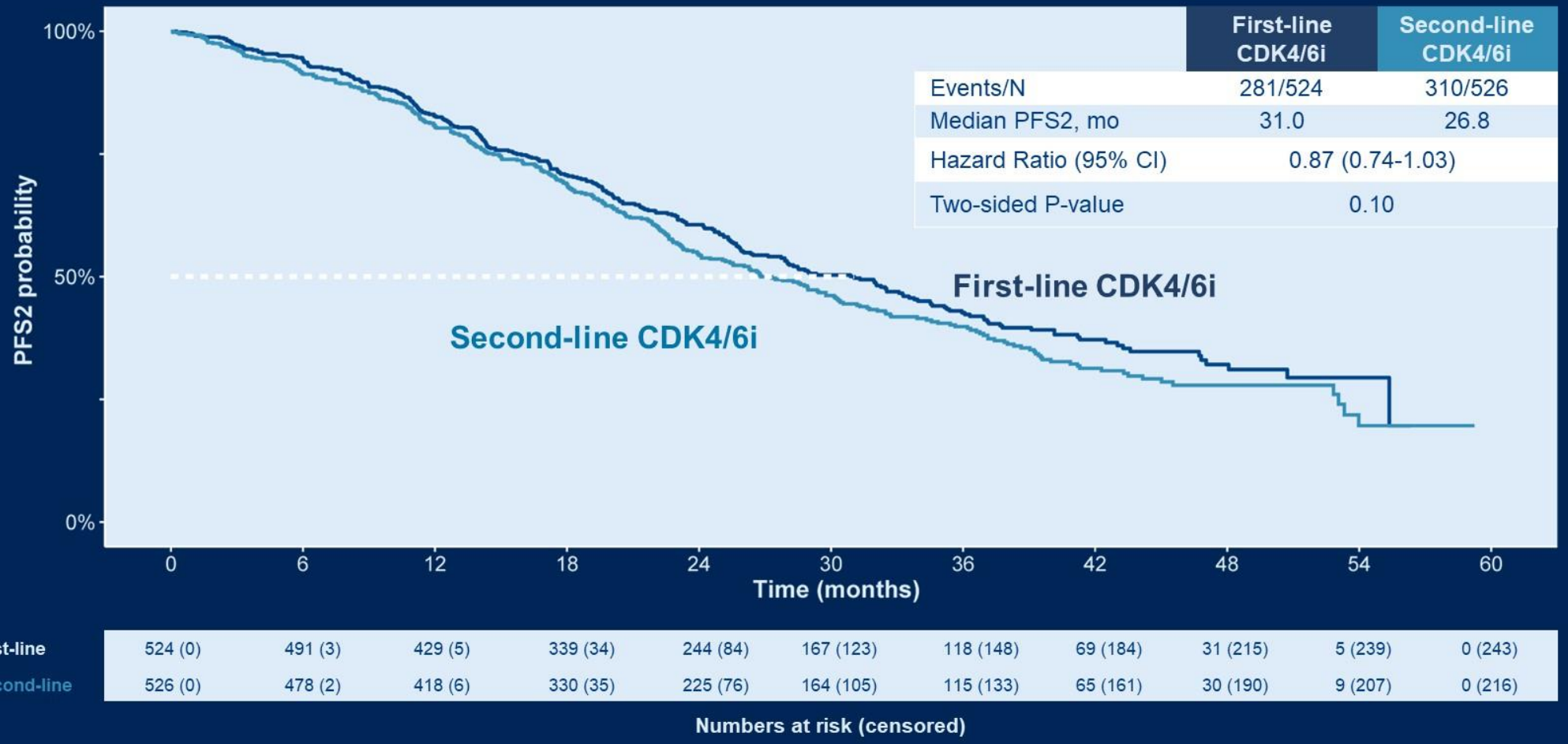
	AI + CDK4/6i	AI
Events/N	310/524	407/526
Median PFS1, mo	24.7	16.1
Hazard Ratio (95% CI)	0.59 (0.51-0.69)	
Two-sided P-value	<0.0001	

AI + CDK4/6i	524 (0)	451 (3)	374 (4)	285 (30)	202 (76)	137 (110)	101 (129)	63 (158)	27 (189)	4 (210)	0 (214)
AI	526 (0)	406 (2)	315 (4)	203 (25)	128 (54)	84 (68)	57 (81)	31 (93)	17 (105)	5 (114)	0 (119)

Numbers at risk (censored)

Primary endpoint: PFS2

SONIA



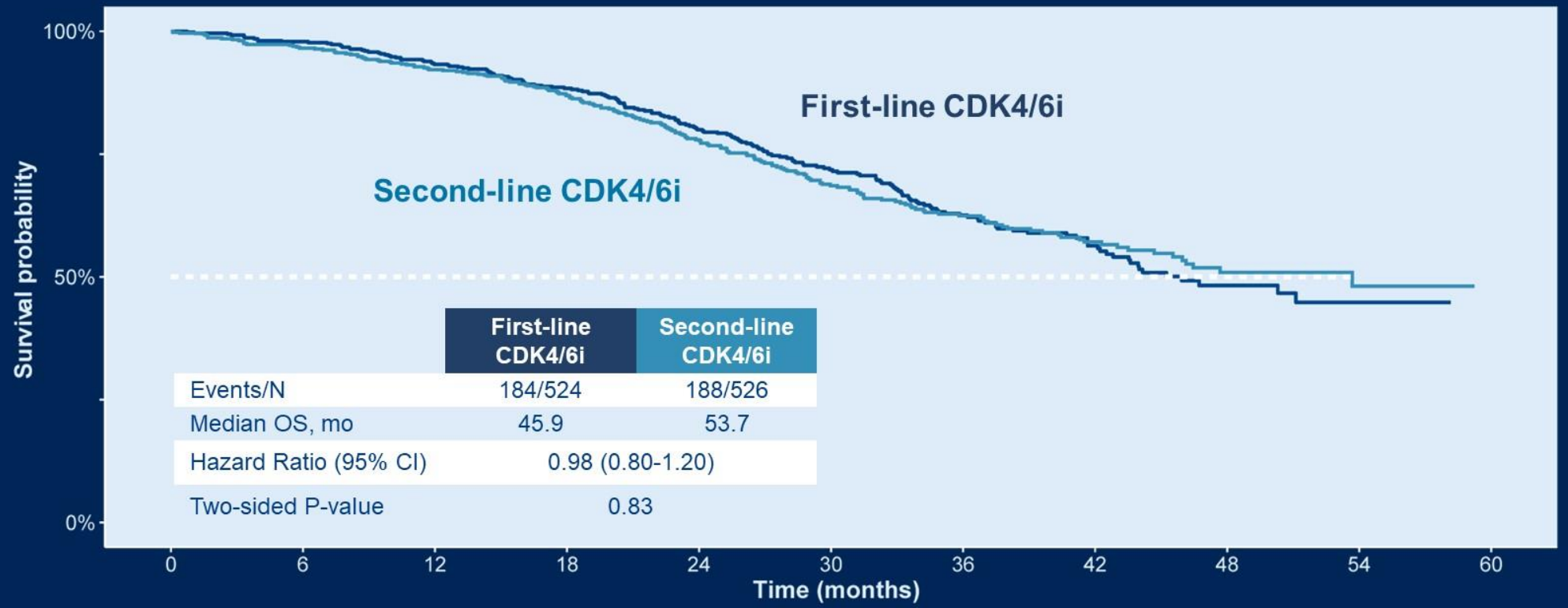
	First-line CDK4/6i	Second-line CDK4/6i
Events/N	281/524	310/526
Median PFS2, mo	31.0	26.8
Hazard Ratio (95% CI)	0.87 (0.74-1.03)	
Two-sided P-value	0.10	

First-line	524 (0)	491 (3)	429 (5)	339 (34)	244 (84)	167 (123)	118 (148)	69 (184)	31 (215)	5 (239)	0 (243)
Second-line	526 (0)	478 (2)	418 (6)	330 (35)	225 (76)	164 (105)	115 (133)	65 (161)	30 (190)	9 (207)	0 (216)

Numbers at risk (censored)

Overall survival

SONIA



	First-line CDK4/6i	Second-line CDK4/6i
Events/N	184/524	188/526
Median OS, mo	45.9	53.7
Hazard Ratio (95% CI)	0.98 (0.80-1.20)	
Two-sided P-value	0.83	

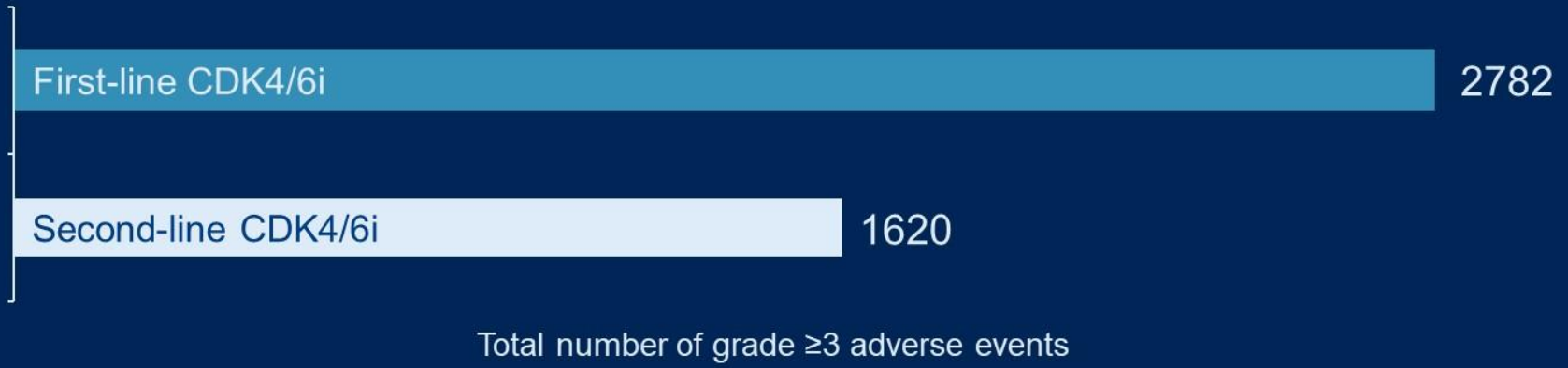
First-line	524 (0)	510 (3)	485 (4)	427 (37)	324 (103)	240 (157)	171 (197)	104 (250)	42 (300)	7 (333)	0 (340)
Second-line	526 (0)	506 (2)	483 (2)	426 (32)	328 (89)	242 (139)	175 (186)	112 (236)	52 (287)	16 (322)	0 (338)

Numbers at risk (censored)

Safety summary

SONIA

- The safety profile was characteristic for CDK4/6i
  - neutropenia, liver function abnormalities, anemia, thrombocytopenia
- 42% more grade ≥3 adverse events when CDK4/6i was used in first-line



Summary of the main findings

SONTA

CDK4/6 inhibition in first-line compared to second-line

- Does not improve Progression-Free Survival
- Does not improve Overall Survival
- Does not improve Quality of Life
- Extends time on CDK4/6i by 16.5 months
- Increases incidence of grade 3-4 toxicity by 42%
- Increases drug expenditure by $200,000 per patient[1]

1. CMS drug prices: CMS.gov, Centers for Medicare & Medicaid Services

PRESENTED BY: Prof. Gabe S. Sonke, MD, PhD

SONIA: Conclusión de los investigadores

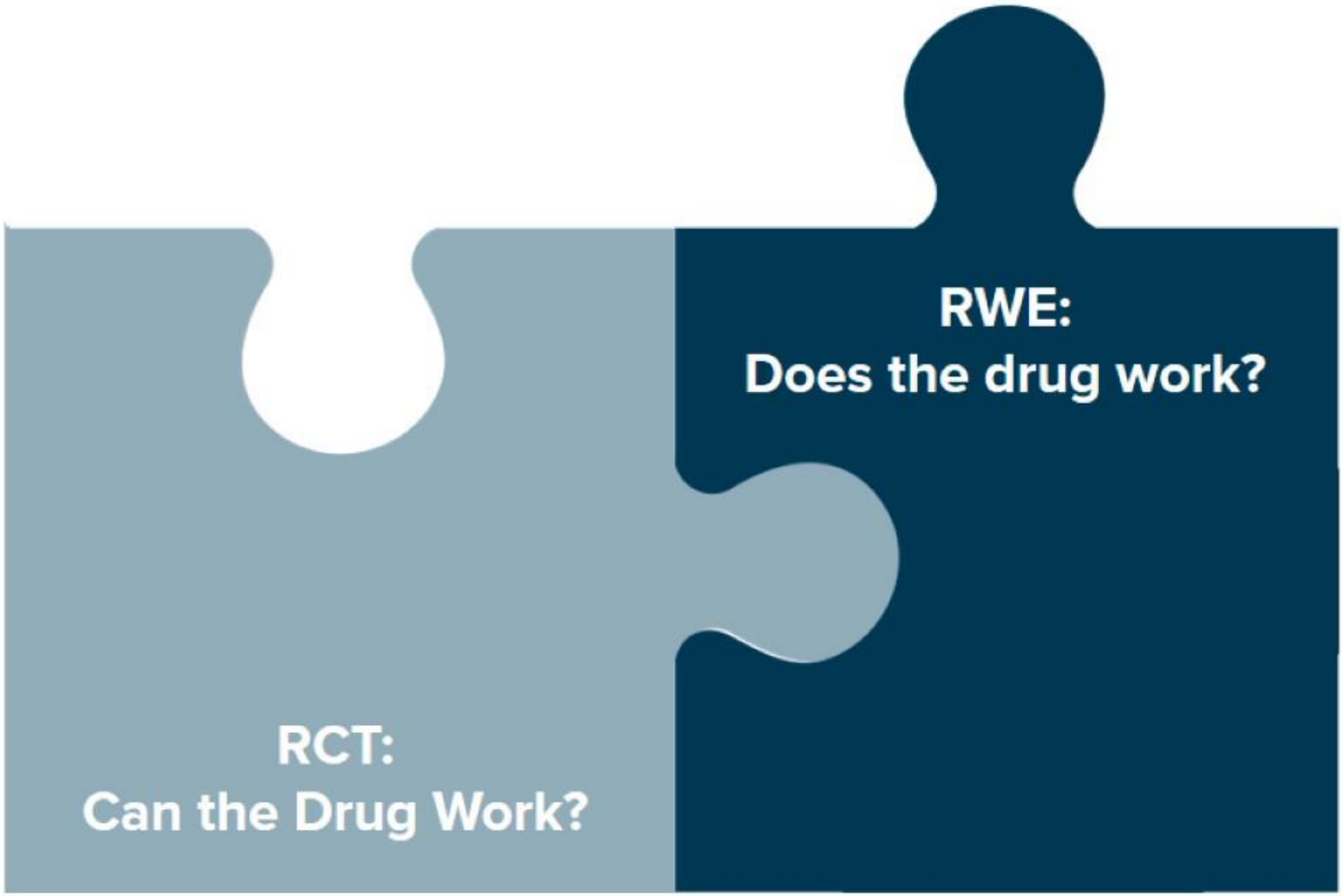
- El uso en primera línea de iCDK4/6 + TE no proporciona un beneficio estadísticamente significativo ni clínicamente significativo en la SSP en comparación con el uso en segunda línea en mujeres con CMM HR+, HER2-.
  - El uso en primera línea prolonga el tiempo de CDK4/6i en 16,56 meses y aumenta la toxicidad y los costos.
- Por lo tanto, el uso en segunda línea puede ser una opción preferida para la mayoría de las pacientes. (Financiado por la Organización Holandesa para la Investigación y el Desarrollo en Salud y las Aseguradoras de Salud Holandesas; número ClinicalTrials.gov, NCT03425838).

Sonke. ASCO 2023. Abstr LBA1000.

SOLCA
NÚCLEO DE QUITO

vida real (Real World)

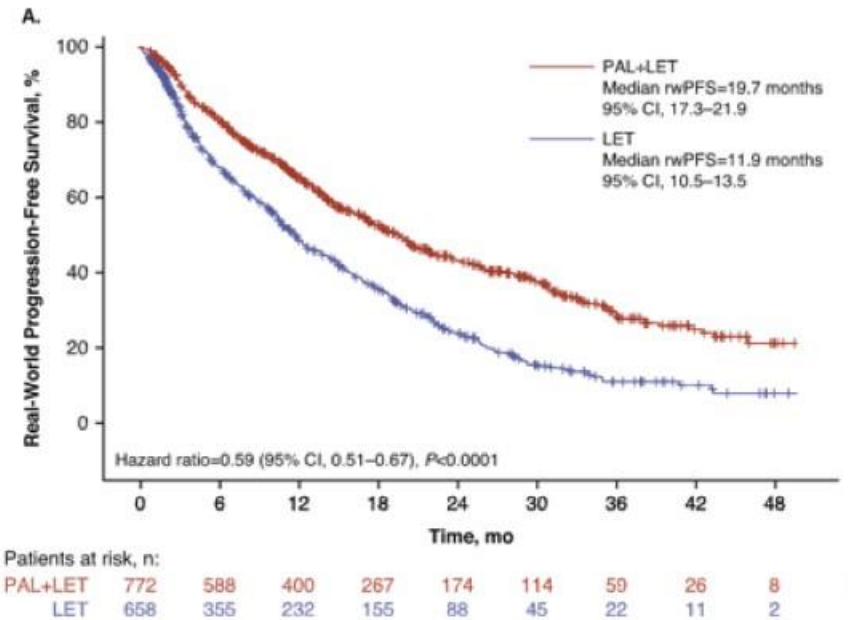
Randomized Trials vs Real World Studies



First-Line Palbociclib + Letrozole vs Letrozole Alone for HR+/HER2- MBC in Real-World Clinical Practice

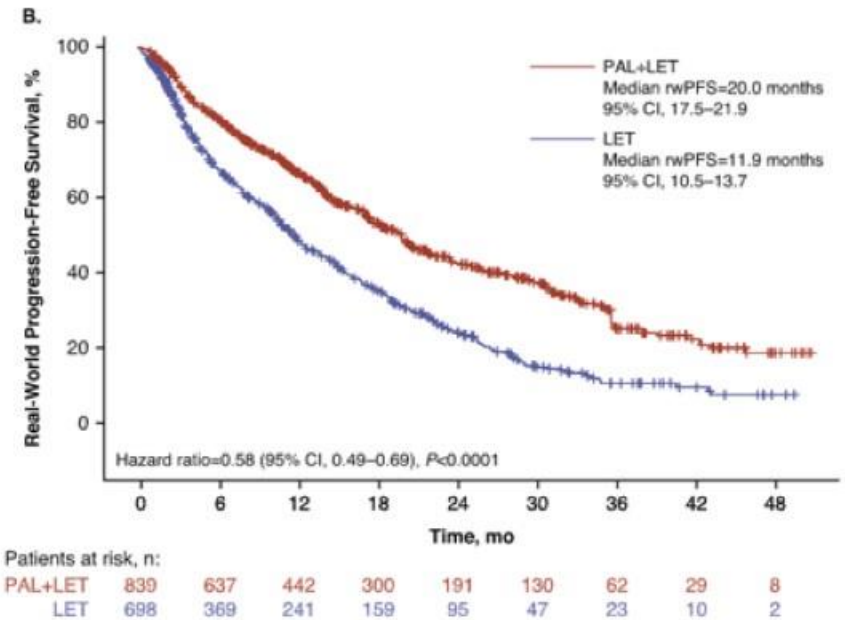
Kaplan-Meier Curves of Real-World PFS

Unadjusted Analysis (No. of Pts at Risk)



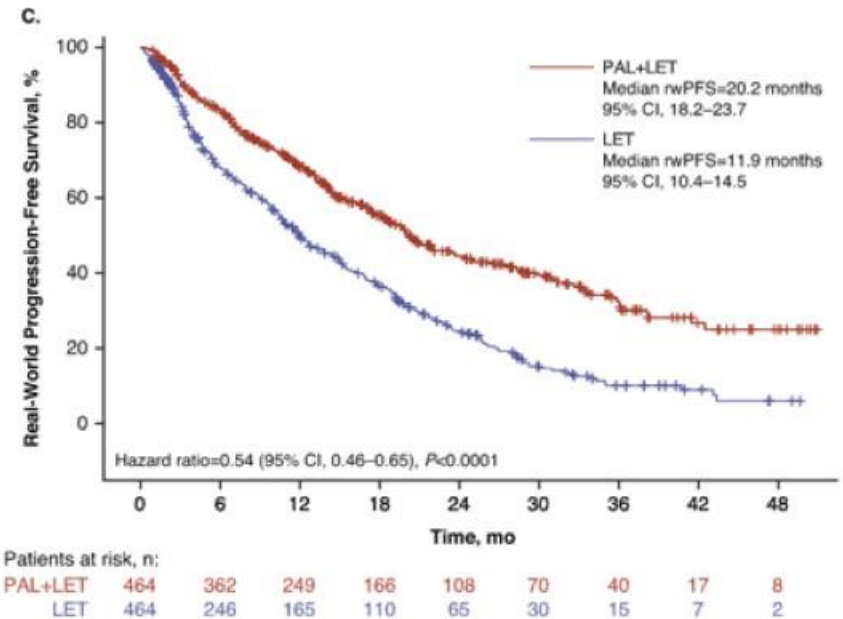
Patients at risk, n:									
PAL+LET	772	588	400	267	174	114	59	26	8
LET	658	355	232	155	88	45	22	11	2

sIPTW Adjusted Analysis



Patients at risk, n:									
PAL+LET	839	637	442	300	191	130	62	29	8
LET	698	369	241	159	95	47	23	10	2

After PSM



Patients at risk, n:									
PAL+LET	464	362	249	166	108	70	40	17	8
LET	464	246	165	110	65	30	15	7	2

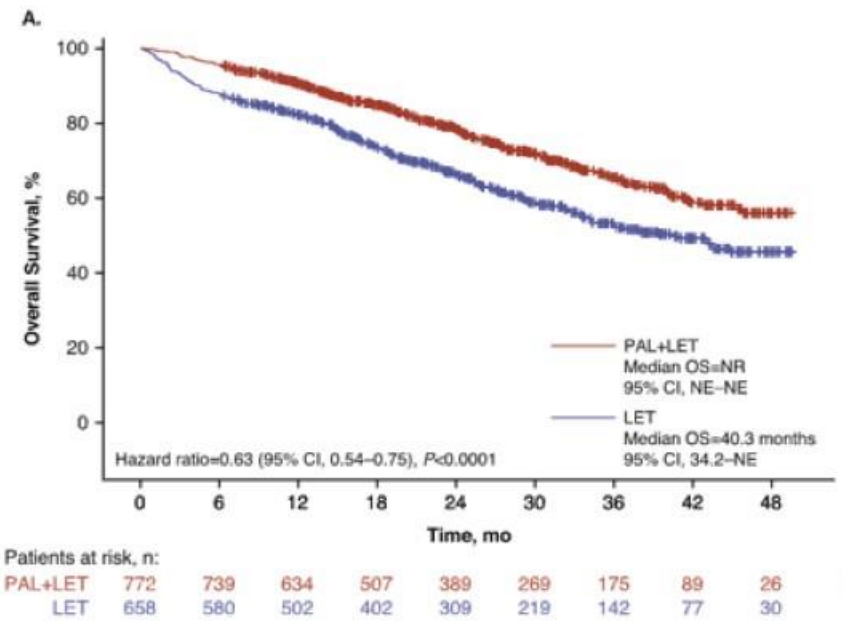
LET, letrozole; PAL, palbociclib; PSM, inverse probability treatment weighting; rwPFS, real-world progression-free survival; sIPTW, stabilized inverse probability treatment weighting.

DeMichele A, et al. Breast Cancer Research. 2021:23:37.

First-Line Palbociclib + Letrozole vs Letrozole Alone for HR+/HER2- MBC in Real-World Clinical Practice (cont)

Kaplan-Meier Curves of Real-World OS

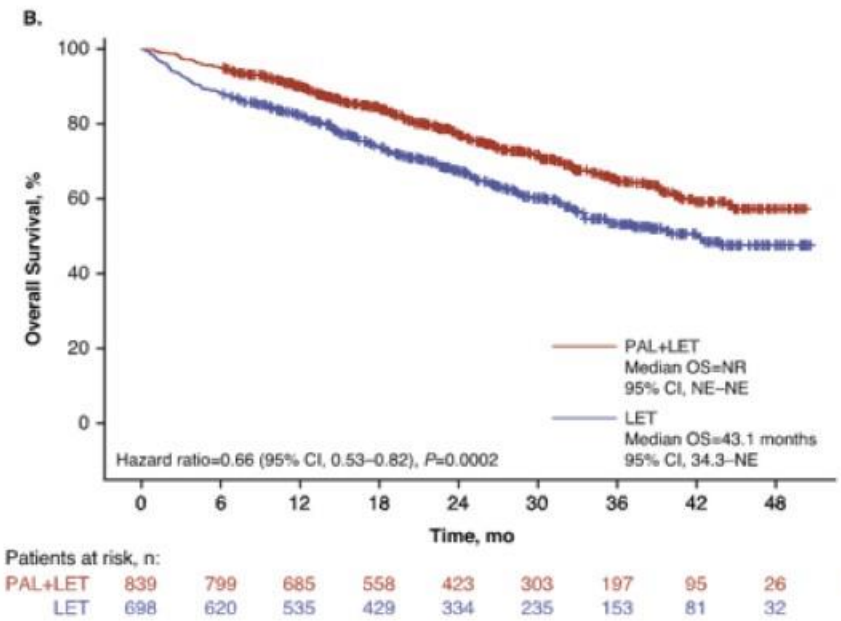
Unadjusted Analysis (No. of Pts at Risk)



Patients at risk, n:

PAL+LET	772	739	634	507	389	269	175	89	26
LET	658	580	502	402	309	219	142	77	30

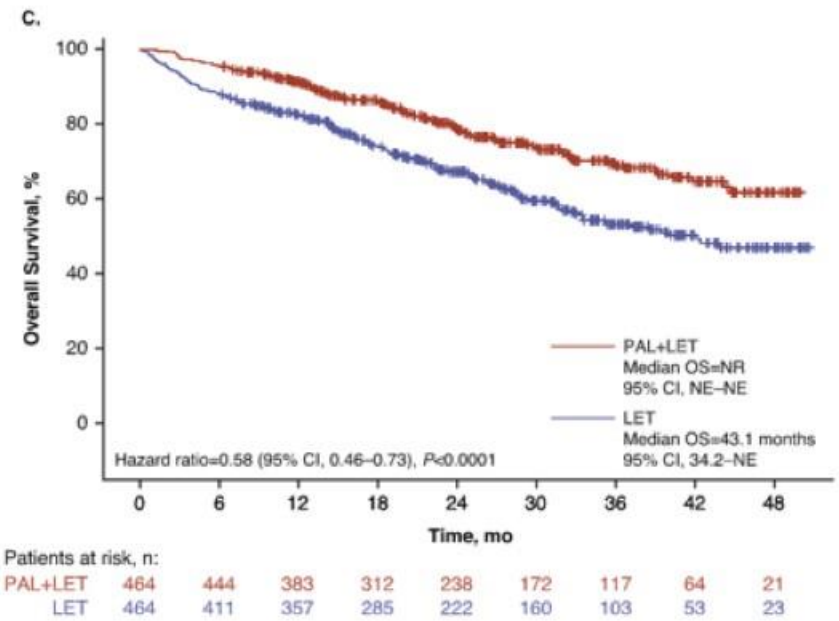
sIPTW Adjusted Analysis



Patients at risk, n:

PAL+LET	839	799	685	558	423	303	197	95	26
LET	698	620	535	429	334	235	153	81	32

After PSM



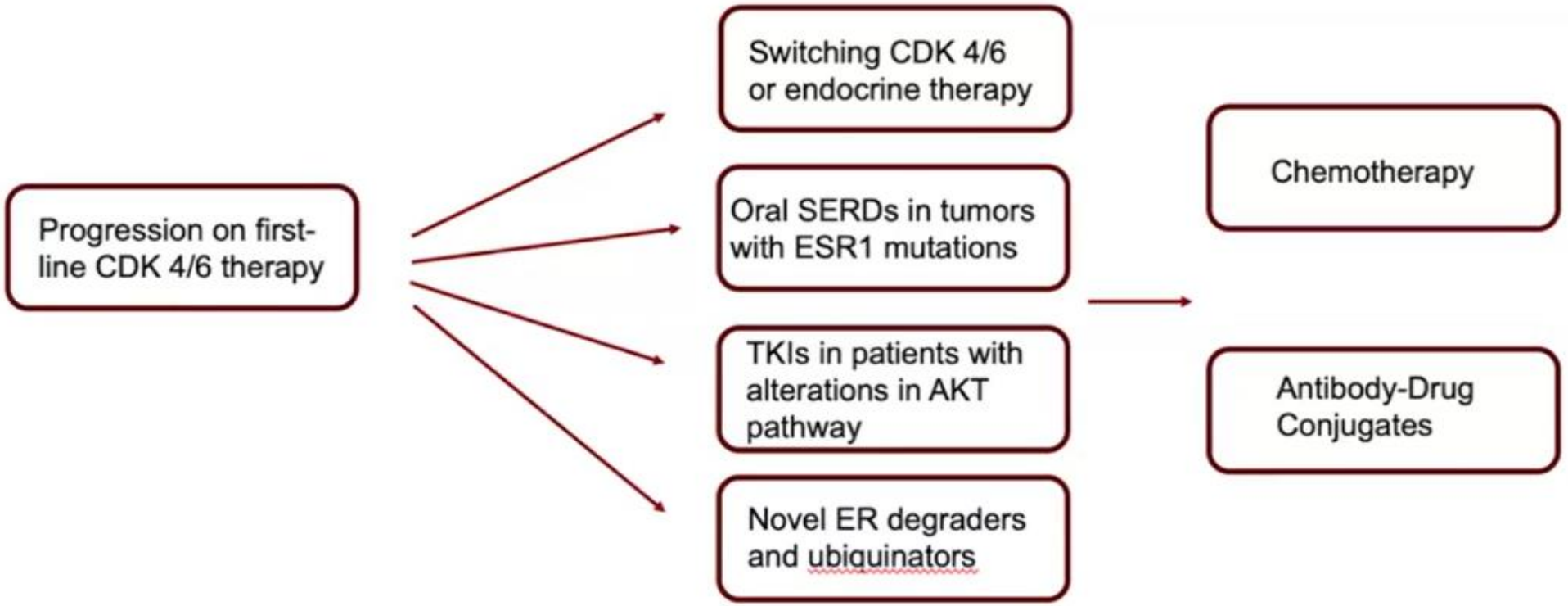
Patients at risk, n:

PAL+LET	464	444	383	312	238	172	117	64	21
LET	464	411	357	285	222	160	103	53	23

DeMichele A, et al. Breast Cancer Research. 2021:23:37.

Switching CDK 4/6

	MAINTAIN	PACE	PostMONARCH
Patient Population	Advanced HR+ progression after prior CDK 4/6 + ET	Advanced HR+ progression after prior CDK 4/6 + ET	Advanced HR+ progression after prior CDK 4/6 + ET
Treatment	Fulvestrant (83%) or Exemestane +/- Ribociclib	Arm A: Fulvestrant Arm B: Fulvestrant + Palbociclib	Fulvestrant +/- Abemaciclib
Sample Size	120	220	350
Prior CDK 4/6	Palbociclib 84%	Palbociclib 90%	Palbociclib 59%
Current CDK 4/6	Ribociclib	Palbociclib	Abemaciclib
mPFS ET + CDK 4/6 vs ET + placebo	5.3m vs 2.8m HR 0.56	4.6m vs 4.8m HR 1.11	6.m vs 5.3m HR 0.73


Progression on first-line CDK 4/6 therapy
Switching CDK 4/6 or endocrine therapy
Oral SERDs in tumors with ESR1 mutations
TKIs in patients with alterations in AKT pathway
Novel ER degraders and ubiquinators
Chemotherapy
Antibody-Drug Conjugates

Conclusiones

- iCDK4/6 han impactado favorablemente la SLP y SG en el CMM en 1era o 2da línea
- Hace falta tener más evidencia si es mejor iniciarlo a la progresión a la TE
- Esperamos a futuro tener más dato de la relevancia del switch con los iCDK4/6 o de la TE