RECOMENDACIÓN TRATAMIENTO

BÚSQUEDA Y SÍNTESIS DE EVIDENCIA DE EFECTOS DESEABLES E INDESEABLES

Guía de Práctica Clínica Cáncer de Mama

A. PREGUNTA CLÍNICA

Mujeres con cáncer de mama RH (+) HER2 (-)metastasico que han progresado a otra línea de tratamiento hormonal ¿Se debe "usar hormonoterapia+ inhibidores de CDK" en comparación a "sólo hormonoterapia"?

Análisis y definición de los componentes de la pregunta en formato PICO

Población: Pacientes con cáncer de mama RH (+) HER2 (-) metastasico que han progresado a otra línea de tratamiento hormonal

Intervención: usar hormonoterapia+ inhibidores de CDK.

Comparación: usar solo hormonaterapia.

Desenlaces (outcomes): Sobrevida global, calidad de vida, efectos adversos, sobrevida libre de progresión

B. BÚSQUEDA DE EVIDENCIA

Se realizó una búsqueda general de revisiones sistemáticas asociadas al tema de cáncer de mama (ver Anexo 1: estrategia de búsqueda). Las bases de datos utilizadas fueron: Cochrane database of systematic reviews (CDSR); PubMed; EMBASE. No se aplicaron restricciones en base al idioma o estado de publicación. Dos revisores de manera independiente realizaron la selección de los títulos y los resúmenes, la evaluación del texto completo y la extracción de datos. Un tercer miembro del equipo resolvió cualquier discrepancia entre los distintos revisores. Finalmente, se seleccionaron las revisiones sistemáticas (y los estudios incluidos en éstas) correspondientes a la temática y se clasificaron en función de las preguntas a las que daban respuesta.

C. RESULTADOS

Resumen de la evidencia identificada

Se buscaron revisiones sistemáticas que analizan estudios en pacientes con cáncer de mama metastásico que han progresado a otra línea de tratamiento hormonal, los cuales comparan usar la adición de inhibidores de CDK a la terapia hormonal en segunda línea de tratamiento. Se identificaron 37 revisiones sistemáticas que incluyeron 8 ensayos clínicos, de los cuales todos corresponden a ensayos aleatorizados.

Tabla 1: Resumen de la evidencia identificada

Revisión Sistemática	37 [1-37]
Estudios primarios	8 ensayos clínicos [38-45]

Selección de la evidencia

Se realizó un análisis de las revisiones sistemáticas y de los ensayos clínicos considerándose relevantes ya que abordan específicamente los componentes de la pregunta priorizada por el panel.

Estimador del efecto

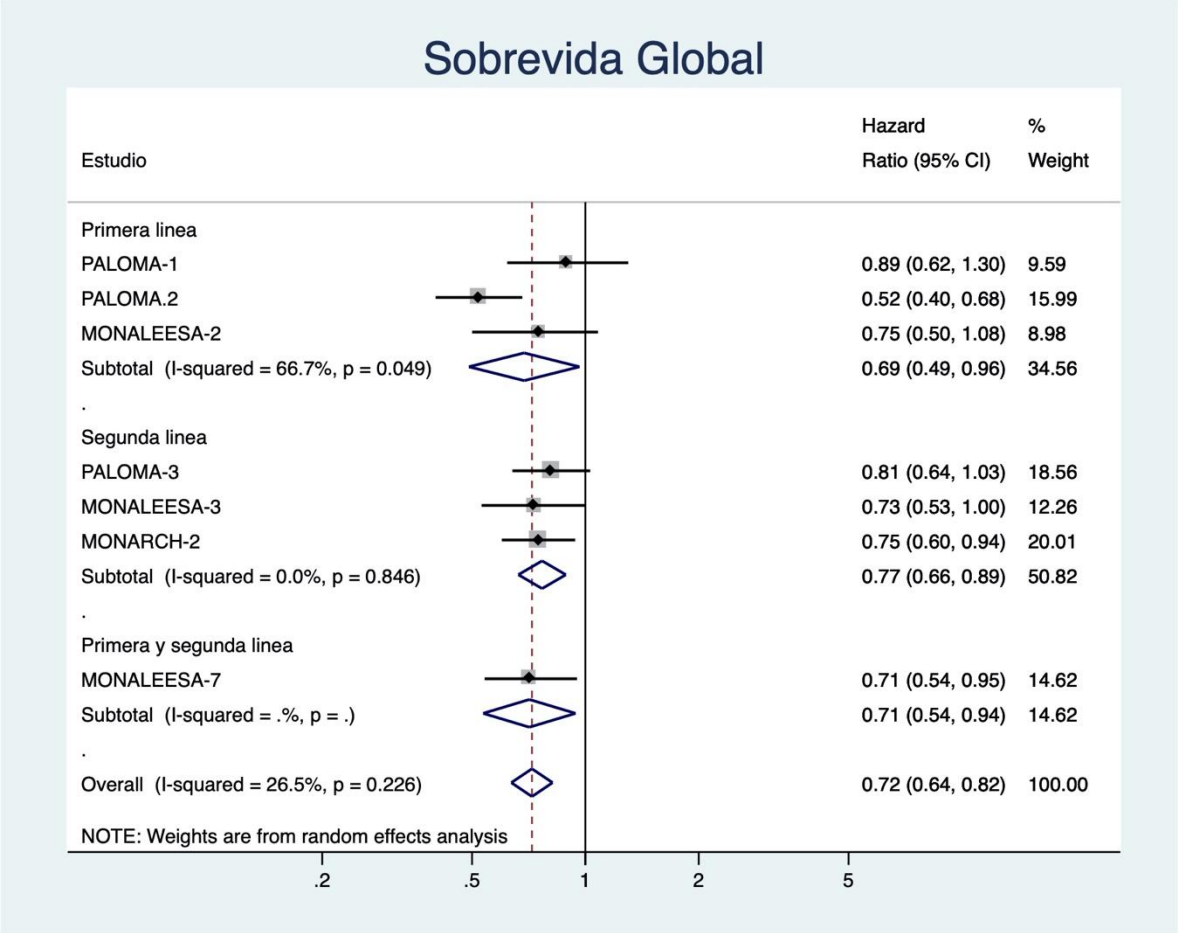
Al analizar la evidencia identificada, se concluyó que existe una revisión sistemática que [1]:

1. Incluye el total de los estudios posiblemente relevantes [38-45].
2. Entrega un estimador agregado del efecto (metanálisis) para los desenlaces de interés.

Por lo que se decidió utilizar su información para construir la tabla de resumen de resultados.

Metanálisis

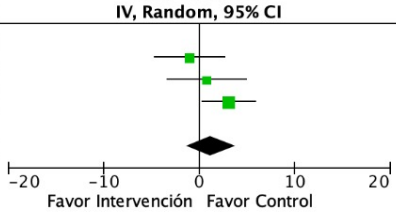
Sobrevida global



Calidad de vida

Study or Subgroup	Intervención Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
MONALEESA-7	68.6	0	164	67.3	0	92		Not estimable
MONARCH-2	62.6	22.4	446	63.6	22.8	223	31.3%	-1.00 [-4.64, 2.64]
MONARCH-3	65	21.7	328	64.2	22.5	165	26.1%	0.80 [-3.36, 4.96]
PALOMA-3	66.1	15.1	345	63	15.4	172	42.6%	3.10 [0.30, 5.90]
Total (95% CI)			**1119**			**560**	**100.0%**	**1.22 [-1.31, 3.74]**

Heterogeneity: $Tau^2 = 1.85$; $Chi^2 = 3.16$, df = 2 (P = 0.21); $I^2 = 37\%$
Test for overall effect: Z = 0.95 (P = 0.34)



Efectos adversos grados 3 y 4

Study or Subgroup	Intervención Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Primera linea						
MONALEESA-2	207	334	4	330	1.3%	51.13 [19.24, 135.91]
MONARCH-3	180	327	35	161	14.6%	2.53 [1.86, 3.45]
PALOMA-1	64	83	16	77	5.2%	3.71 [2.36, 5.83]
PALOMA-2	336	444	54	222	22.4%	3.11 [2.45, 3.95]
Subtotal (95% CI)		**1188**		**790**	**43.5%**	**4.37 [3.69, 5.18]**
Total events	787		109			
Heterogeneity: $Chi^2 = 44.68$, df = 3 (P < 0.00001); $I^2 = 93\%$						
Test for overall effect: Z = 17.06 (P < 0.00001)						
1.2.2 Segunda linea						
MONARCH-2	291	441	60	223	24.8%	2.45 [1.96, 3.08]
PALOMA-3	223	345	1	172	0.4%	111.18 [15.73, 785.99]
Subtotal (95% CI)		**786**		**395**	**25.2%**	**4.24 [3.35, 5.37]**
Total events	514		61			
Heterogeneity: $Chi^2 = 33.22$, df = 1 (P < 0.00001); $I^2 = 97\%$						
Test for overall effect: Z = 11.99 (P < 0.00001)						
1.2.3 Primera y segunda linea						
MONALEESA-3	258	483	0	241	0.2%	258.50 [16.20, 4126.10]
MONALEESA-7	257	335	100	337	31.1%	2.59 [2.17, 3.08]
Subtotal (95% CI)		**818**		**578**	**31.3%**	**4.29 [3.52, 5.22]**
Total events	515		100			
Heterogeneity: $Chi^2 = 40.58$, df = 1 (P < 0.00001); $I^2 = 98\%$						
Test for overall effect: Z = 14.52 (P < 0.00001)						
Total (95% CI)		**2792**		**1763**	**100.0%**	**4.31 [3.85, 4.83]**
Total events	1816		270			
Heterogeneity: $Chi^2 = 119.48$, df = 7 (P < 0.00001); $I^2 = 94\%$						
Test for overall effect: Z = 25.36 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 0.05$, df = 2 (P = 0.98), $I^2 = 0\%$						

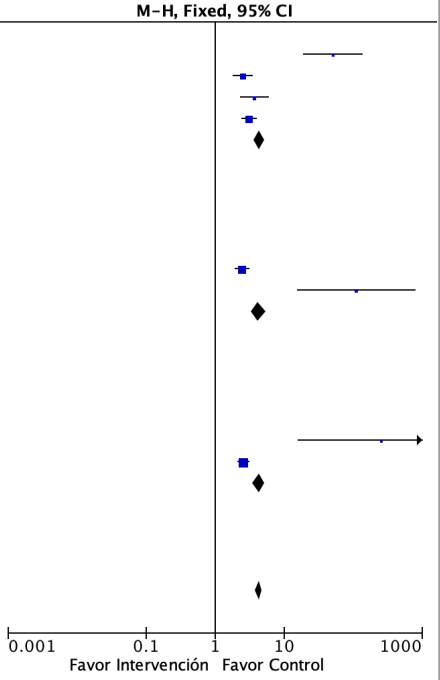


Tabla de Resumen de Resultados (Summary of Findings)

Desenlaces	Efecto relativo (IC 95%)	Efecto absoluto estimado			Certeza de la evidencia (GRADE)	Mensajes clave en términos sencillos
		CON Inhibidor de CDK	SIN Inhibidor de CDK	Diferencia (IC 95%)		
Sobrevida global[1]	**HR 0,72** (0,64 a 0,82) 7 estudios 4. 062 personas	**34,9 meses**	**28 meses**	**6,9 meses más**	⨁⨁⨁⨁ **Alta**	El uso de inhibidores del CDK aumenta la sobrevida global.
Calidad de vidal[2,3]	**DM 1,22** (-1,31 a 3,74) 3 estudios 1.423 personas	**1,22 puntos más** (1,31 menos a 3,74 más)			⨁⨁⨁◯[a] **Moderada**	El uso de inhibidores de la CDK probablemente no tiene impacto en la calidad de vida.
Efectos adversos grado 3 y 4	**RR 4.31** (3.85 a 4.83) 8 estudio 4.555 personas	**660** Por cada 1000	**153** por cada 1000	**507 más por 1000** (de 436 más a 587 más)	⨁⨁⨁◯[b] **Moderada**	El uso de inhibidores de la CDK probablemente aumenta los efectos adversos.

RR: Riesgo relativo.
IC: Intervalo de confianza del 95%

[1]La mediana de sobrevida se obtuvo del estudio PALOMA-3, al ser la mediana de la diferencia de medianas de los estudios incluidos.
[2]Evaluada con la encuesta de calidad de vida European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire Core 30 (QLQ-C30)
[3]Importancia mínima clínica importante para la calidad de vida medida con la EORTC QLQ-C30 es de 5 puntos.

EXPLICACIONES

a. Se disminuyó la certeza de la evidencia por imprecisión, dado que los extremos del intervalo de confianza en torno al efecto absoluto probablemente cruzan los umbrales de decisión para considerar la intervención como beneficiosa o perjudicial.

b. Se disminuyó un nivel de certeza en la evidencia ya que los estudios son heterogéneos (I^2=94%)

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ANEXO 1: ESTRATEGIA DE BÚSQUEDA

EMBASE y Pubmed vía Ovid	
1. systematic review/ 2. meta-analysis/ 3. (meta analy* or metanaly* or metaanaly*).ti,ab. 4. ((systematic or evidence) adj2 (review* or overview*)).ti,ab. 5. (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. 6. (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. 7. cochrane.jw. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. exp Breast Neoplasms/ 10. Carcinoma, Lobular/ 11. exp Carcinoma, Intraductal, Noninfiltrating/ 12. ((breast$ or mammar$) adj3 (neoplas$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or malignanc$ or dcis or duct$ or infiltrating or intraduct$ or lobul$ or medullary or tubular)).tw. 13. ((lobul$ or ductal$ or intraduct$ or medullary or tubular) adj2 (carcin$ or cancer$ or tumo?r$ or neoplasm$ or adenocarcin$)).tw. 14. exp Breast/ or exp Breast Diseases/ or (breast$ or mammar$).tw. 15. 9 or 10 or 11 or 12 or 13 or 14 16. palbociclib.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui, sy] 17. "PD 0332991".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui, sy] 18. abemaciclib.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui, sy] 19. LY2835219.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui, sy] 20. ribociclib.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui, sy] 21. LEE011.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui, sy] 22. CDK inhibitor.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui, sy] 23. 16 or 17 or 18 or 19 or 20 or 21 or 22 24. 8 and 15 and 23 25. limit 24 to yr="2014 -Current" 26. remove duplicates from 25	Hits: 145