



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 sin tratamiento previo ¿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 sin tratamiento previo

Intervención: usar hormonoterapia+ inhibidores de CDK.

Comparación: usar solo hormonoterapia.

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

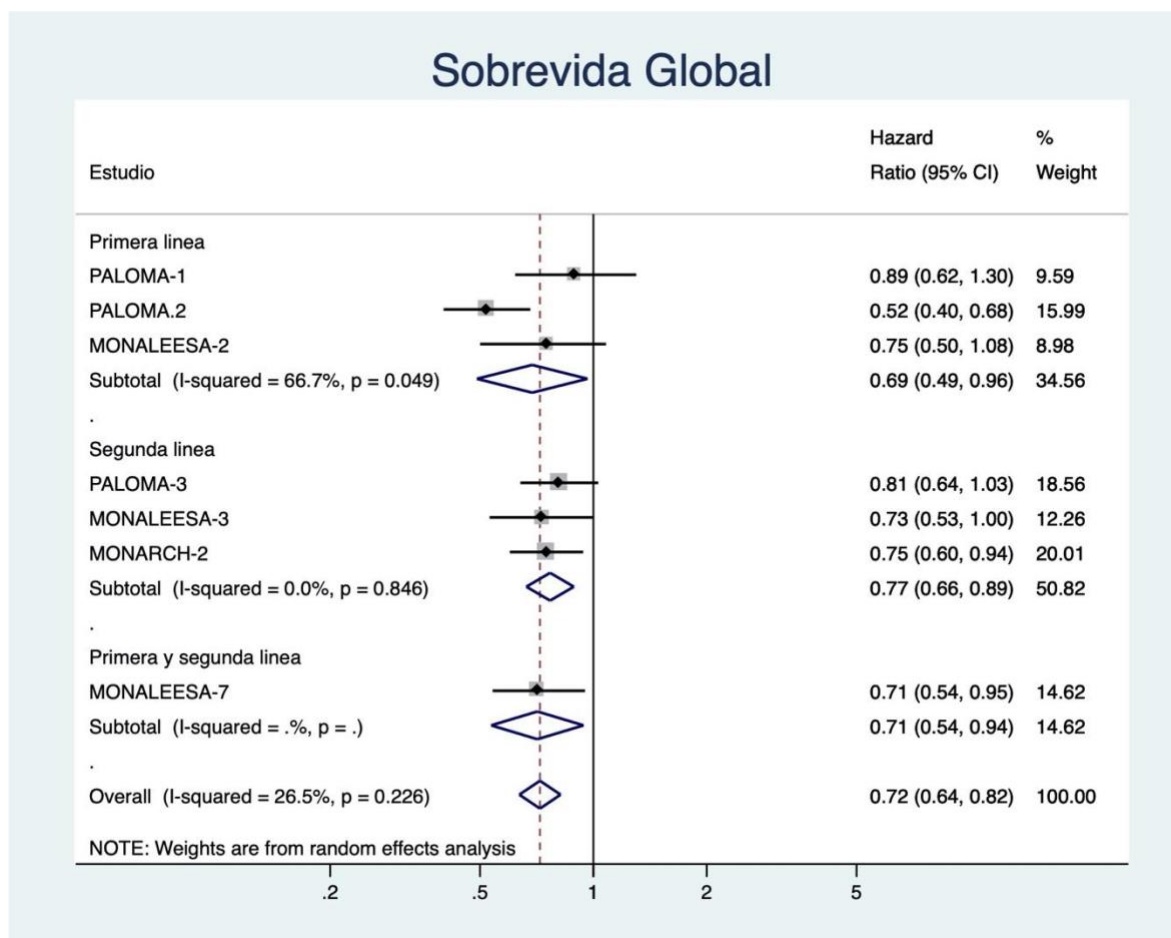
Al analizar la evidencia identificada, se concluyó que existe una revisión sistemática que [1]:

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

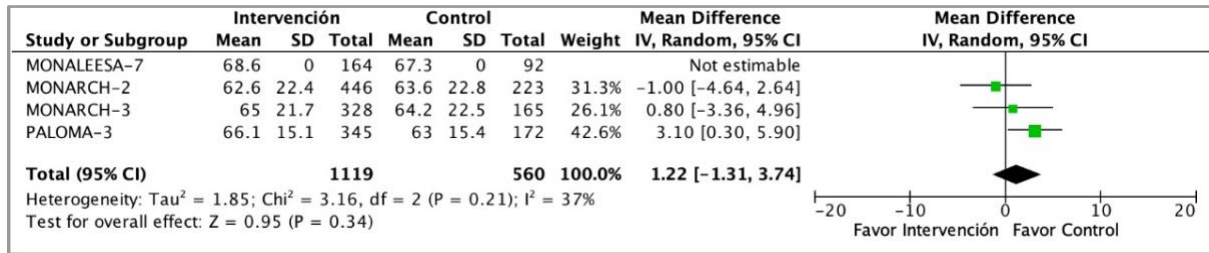
Por lo que se decidió utilizar su información para construir la tabla de resumen de resultados.

Metanálisis

Sobrevida global



Calidad de vida



Efectos adversos grados 3 y 4

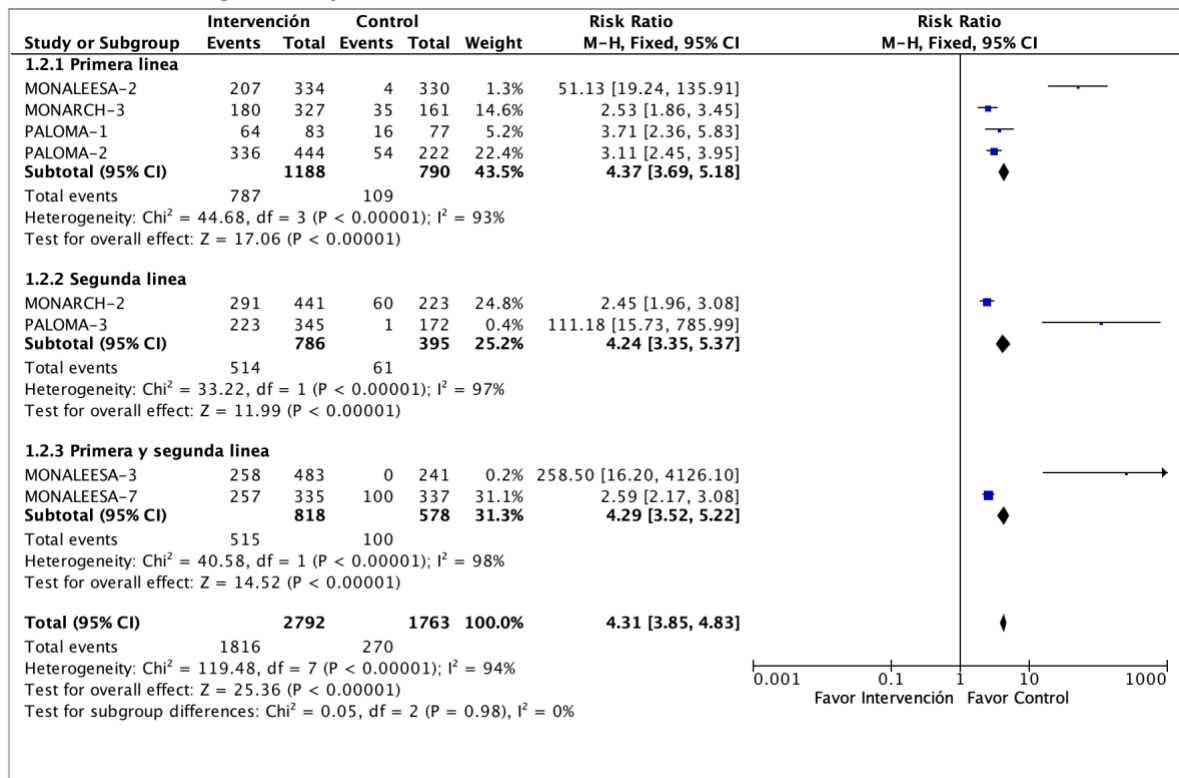


Tabla de Resumen de Resultados (Summary of Findings)

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 global¹	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 vida^{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%

¹La mediana de sobrevida se obtuvo del estudio PALOMA-3, al ser la mediana de la diferencia de medianas de los estudios incluidos.
²Evaluada con la encuesta de calidad de vida European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire Core 30 (QLQ-C30)
³Importancia 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 ($I^2=94%$)

REFERENCIAS

1. Y. M, J. L, H. W, Nie G. Incidence and risk of neutropenia with palbociclib in patients with cancer: A systematic review and meta-analysis. *J Clin Oncol* [Internet]. 2017;35(15 Supplement 1 PG-). Available from: <http://meetinglibrary.asco.org/record/144977/abstract> NS -
2. N. H, M. B, D. S, B. H, L. Z, E. R, et al. PCN28 cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced/metastatic breast cancer (A/MBC reservaste es por eso primera propina. *Value Heal* [Internet]. 2020;23(Supplement 1 PG-S27):S27.
3. A. R-E, G. H-R, Landaverde D U. Cyclin-dependent kinase 4/6 inhibitors in combination with fulvestrant for previously treated metastatic hormone receptor-positive breast cancer patients: A systematic review and meta-analysis of randomized clinical trials. *Cancer Treat Res Commun* [Internet]. 2020;23((Ramos-Esquivel) Departamento de Oncologia Medica. Hospital San Juan de Dios, San Jose, Costa Rica(Ramos-Esquivel, Hernandez-Romero, Landaverde) Escuela de Medicina, Universidad de Costa Rica, San Jose, Costa Rica(Landaverde) Departamento de Oncologia Med PG-100175):100175.
4. A. T, K.Z. T, Y.Y. T, A. N. Risk of gastrointestinal and hepatic toxicities in patients with hormone receptorpositive HER2-negative breast cancer treated with CDK 4/6 inhibitors: A systematic review and meta-analysis of randomized controlled trials. *J Clin Oncol* [Internet]. 2017;35(15 Supplement 1).
5. I.A. M, R. O, N.S. K. Targeted combination therapy with fulvestrant (FUL) for second-line (2L) treatment of hormone receptor-positive (HR+) advanced breast cancer (ABC). *J Clin Oncol* [Internet]. 2017;35(15 Supplement 1).
6. S. L, K.S. S, L. K, Abdel-Rahman O. AO - Lasheen Omar; ORCID: <http://orcid.org/0000-0002-5117-2502> SO <http://orcid.org/000-0002-7991-2701> AO-A-R. Fatigue, alopecia and stomatitis among patients with breast cancer receiving cyclin-dependent kinase 4 and 6 inhibitors: a systematic review and meta-analysis. *Expert Rev Anticancer Ther* [Internet]. 2017;17(9):851–6.
7. K.S. S, S. L, L. K. Gastrointestinal adverse effects of cyclin-dependent kinase 4 and 6 inhibitors in breast cancer patients: a systematic review and meta-analysis. *Ther Adv Drug Saf* [Internet]. 2017;8(11):337–47. Available from: <http://www.uk.sagepub.com/journals/Journal201944>
8. Z.H. X, H. Z, D. W, L. X. Cyclin-dependent kinase 4/6 inhibitor in combination with endocrine therapy versus endocrine therapy only for advanced breast cancer: A systematic review and meta-analysis. *Transl Cancer Res* [Internet]. 2020;9(2):657–68.
9. F. D, C. S, V. R, G. S, F. BA. CDK 4/6 inhibitors plus endocrine therapy in ER positive metastatic breast cancer (MBC): Systematic review and meta-analysis of randomized clinical trials. *Ann Oncol* [Internet]. 2019;30(Supplement 3).
10. J. L, F. F, L. Y, M. H, Y. L, Q. M, et al. Cyclin-dependent kinase 4 and 6 inhibitors in hormone receptor-positive, human epidermal growth factor receptor-2 negative advanced breast cancer: a meta-analysis of randomized clinical trials. *Breast Cancer Res Treat* [Internet]. 2020;180(1):21–32.
11. K.Z. T, S. B, M.H. Z, M. Q, F. H, S. A, et al. Risk of venous thromboembolism with abemaciclib based regimen versus other CDK 4/6 inhibitor containing regimens in patients with hormone receptor-positive HER2-negative metastatic breast cancer. *Cancer Res* [Internet]. 2019;79(4 Supplement 1).
12. K.Z. T, S. B, M.H. Z, A.M. T, M. Q, F. H, et al. Updated meta-analysis of randomized controlled trials (RCTs) to determine the CDK 4/6 inhibitors associated venous thromboembolism (VTE) risk in hormone receptor-positive breast cancer (BC) patients. *Ann Oncol* [Internet]. 2018;29(Supplement 8).
13. T.M. B, S. C. Treatment of advanced HR+/HER2- breast cancer with new targeted agents in combination with endocrine therapy: a review of efficacy and tolerability based on available randomized trials on everolimus, ribociclib, palbociclib and abemaciclib. *Acta Oncol (Madr)* [Internet]. 2019;58(2):147–53.
14. Y. D, G. M, W. L, T. W, Y. Z. CDK4/6 Inhibitors in Combination With Hormone Therapy for HR+/HER2- Advanced Breast Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Clin Breast Cancer* [Internet]. 2018;18(5):e943–53.
15. G. C, S. X, S. F, C. Y. The efficacy and safety of targeted therapy plus fulvestrant in postmenopausal women with hormone-receptor positive advanced breast cancer: A meta-analysis of randomized-control trials. *PLoS One* [Internet]. 2018;13(9):e0204202.
16. O. P-L, A.A. D, R. A, O. L, E. D, E. P, et al. Systematic literature review of clinical trials of endocrine therapies for premenopausal women with metastatic HR+ HER2- breast cancer. *Breast J* [Internet]. 2019;25(5):880–8.

17. A. G, C. S, V. R, F. D. Efficacy of CDK 4/6 inhibitors in ER positive metastatic breast cancer: Systematic review and meta-analysis of randomized clinical trials. *J Clin Oncol* [Internet]. 2018;36(15 Supplement 1).
18. K. R, G. F, C. DA, X. L, M.V. T, Ekinci E. AO - Trivedi Ekim; ORCID: <http://orcid.org/0000-0002-8606-6179> MV. O <http://orcid.org/0000-0002-0585-5580> AO-E. Ribociclib in HR+/HER2- Advanced or Metastatic Breast Cancer Patients. *Ann Pharmacother* [Internet]. 2019;53(5):501–9.
19. L. K, K.S. S, S. L, O. A-R. Hematological adverse effects in breast cancer patients treated with cyclin-dependent kinase 4 and 6 inhibitors: a systematic review and meta-analysis. *Breast Cancer* [Internet]. 2018;25(1):17–27.
20. Y. W, Y. Y, S. L, Q. O. Cyclin-dependent kinases 4 and 6 inhibitors in HR+/HER2- advanced breast cancer. *J Clin Oncol* [Internet]. 2018;36(15 Supplement 1).
21. C. M, C. C, G. B, L. C, E. Z, M. M, et al. CDK4/6 inhibitors in advanced hormone receptor-positive/HER2-negative breast cancer: a systematic review and meta-analysis of randomized trials. *Breast Cancer Res Treat* [Internet]. 2018;172(1):9–21.
22. R. Y, K. T, S. S, A. S, S. B, M. Q, et al. A systematic review and meta-analysis of randomized controlled trials to evaluate the risk of health-related quality of life events in patients with hormone receptor-positive her2-negative metastatic breast cancer treated with CDK 4/6 inhibitors. *JNCCN J Natl Compr Cancer Netw* [Internet]. 2019;17(3–5).
23. L. G, Y. H, X. C, Q. L, B. W, Ma X. AO - Ma XO <http://orcid.org/0000-0002-9148-5001>. Safety and efficacy profile of cyclin-dependent kinases 4/6 inhibitor palbociclib in cancer therapy: A meta-analysis of clinical trials. *Cancer Med* [Internet]. 2019;8(4):1389–400.
24. M. Z, K.Z. T, A. T, M.M. H, S. R, F.L. H. Risk of hematological toxicities and febrile neutropenia in patients with hormone receptor-positive HER2-negative metastatic breast cancer treated with CDK 4/6 inhibitors: A systematic review and meta-analysis of randomized controlled trials. *J Clin Oncol* [Internet]. 2017;35(31 Supplement 1):207.
25. F.R. W, A. V, D. M, C. C. Systematic review and network meta-analysis comparing palbociclib with chemotherapy agents for the treatment of postmenopausal women with HR-positive and HER2-negative advanced/metastatic breast cancer. *Breast Cancer Res Treat* [Internet]. 2017;166(1):167–77.
26. K.G.M. B, E.J.A. M. The effect of addition of cyclindependent kinase 4 & 6 (CDK 4/6) inhibitor to endocrine therapy in the cardiovascular toxicity in advanced breast cancer patients: A systematic review and metaanalysis. *J Glob Oncol* [Internet]. 2019;5(Supplement):134.
27. M. Z, K.Z. T, A. T, M.M. H, Y.Y. T, A. N. A systematic review and meta-analysis of randomized controlled trials to evaluate the risk of gastrointestinal and hepatic toxicities in patients with hormone receptor-positive HER2-negative metastatic breast cancer treated with CDK 4/6 inhibitors. *J Clin Oncol* [Internet]. 2017;35(31 Supplement 1):209.
28. S. S, A. S, S. B, F. M-D, N. A, Y.M. M, et al. CDK 4/6 inhibitor-associated hematologic toxicities and febrile neutropenia in patients with hormone receptor-positive HER2-negative metastatic breast cancer. *JNCCN J Natl Compr Cancer Netw* [Internet]. 2019;17(3–5).
29. T. L, A. F, E. L, L. M. Efficacy of abemaciclib, palbociclib and ribociclib among the older compared with younger women in HR-positive/HER2- negative, advanced breast cancer. *J Clin Oncol* [Internet]. 2018;36(15 Supplement 1).
30. K.Z. T, M.H. Z, A.M. T, C. J, S. R, F. H. Incidence of venous thromboembolism in patients with hormone receptor-positive HER2-negative metastatic breast cancer treated with CDK 4/6 inhibitors: A systematic review and meta-analysis of randomized controlled trials. *Cancer Res* [Internet]. 2018;78(4 Supplement 1).
31. M.M. H, K.Z. T, M. Z, A. T, P. D, F.L. H. Risk of health-related quality of life events from pain and fatigue among patients with hormone receptor-positive HER-2 negative metastatic breast cancer treated with CDK 4/6 inhibitor. *J Clin Oncol* [Internet]. 2017;35(31 Supplement 1):215. Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.31_suppl.215
32. L. W, S. G, D. L, X. R, Z. S, W. W, et al. CDK4/6 inhibitors plus endocrine therapy improve overall survival in advanced HR+/HER2- breast cancer: A meta-analysis of randomized controlled trials. *Breast J* [Internet]. 2019;
33. A. T, M. V, I. S, E. M, C. I, E. B, et al. First-Line Treatment for Endocrine-Sensitive Bone-Only Metastatic Breast Cancer: Systematic Review and Meta-analysis. *Clin Breast Cancer* [Internet]. 2019;19(6):e701–16. Available from: <http://www.journals.elsevier.com/clinical-breast-cancer>

34. C. M, M. M, G. B, C. C, L. C, M.M. L, et al. CDK inhibitors in advanced HR+ Her 2- breast cancer: A systematic review and metaanalysis of randomized trials. *J Clin Oncol* [Internet]. 2018;36(15 Supplement 1).
 35. K.F. H, P. R. First-line CDK4/6 inhibitor treatment for HR+, HER2-negative metastatic breast cancer (MBC). *Cancer Res* [Internet]. 2018;78(13 Supplement 1). Available from: http://cancerres.aacrjournals.org/content/78/13_Supplement/1615
 36. A. T, M. V, I. S, C. I, E. B, F. P, et al. First-line treatment for endocrine sensitive bone-only metastatic breast cancer: Is more always better? *Ann Oncol* [Internet]. 2018;29(Supplement 8).
 37. A. R-E, H. H-S, M.-F. S. Cyclin-dependent kinase 4/6 inhibitors as first-line treatment for post-menopausal metastatic hormone receptor-positive breast cancer patients: a systematic review and meta-analysis of phase III randomized clinical trials. *Breast Cancer* [Internet]. 2018;25(4):479–88.
- Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol*. 2015;16(1):25-35. doi:10.1016/S1470-2045(14)71159-3
- Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med*. 2016;375(20):1925-1936. doi:10.1056/NEJMoa1607303
- Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial [published correction appears in *Lancet Oncol*. 2016 Apr;17 (4):e136] [published correction appears in *Lancet Oncol*. 2016 Jul;17 (7):e270]. *Lancet Oncol*. 2016;17(4):425-439. doi:10.1016/S1470-2045(15)00613-0
- Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer [published correction appears in *N Engl J Med*. 2018 Dec 27;379(26):2582]. *N Engl J Med*. 2016;375(18):1738-1748. doi:10.1056/NEJMoa1609709
- 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. doi:10.1200/JCO.2018.78.9909
- 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. doi:10.1016/S1470-2045(18)30292-4
- Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. *J Clin Oncol*. 2017;35(25):2875-2884. doi:10.1200/JCO.2017.73.7585
- Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *J Clin Oncol*. 2017;35(32):3638-3646. doi:10.1200/JCO.2017.75.6155

ANEXO 1: ESTRATEGIA DE BÚSQUEDA

EMBASE y Pubmed vía Ovid	
<ol style="list-style-type: none"> 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 tumor?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 tumor?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 	<p>Hits: 145</p>