BMJ Open

Role of CDK4/6 inhibitors in patients with hormone receptor (HR)-positive, human epidermal receptor-2 negative (HER-2) metastatic breast cancer study protocol for a systematic review, network meta-analysis and cost-effectiveness analysis

Qiancheng Hu,[1] Wenli Kang,[2] Qingfeng Wang,[1] Ting Luo [3]

To cite: Hu Q, Kang W, Wang Q, *et al*. Role of CDK4/6 inhibitors in patients with hormone receptor (HR)-positive, human epidermal receptor-2 negative (HER-2) metastatic breast cancer study protocol for a systematic review, network meta-analysis and cost-effectiveness analysis. *BMJ Open* 2022;**12**:e056374. doi:10.1136/bmjopen-2021-056374

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-056374).

QH and WK contributed equally.

Received 12 August 2021
Accepted 08 April 2022

For numbered affiliations see end of article.

Correspondence to
Dr Ting Luo; tina621@163.com

ABSTRACT

Introduction It is currently unclear which cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, combined with endocrine therapy, is the preferred treatment approach in patients with hormone receptor (HR)-positive, human epidermal receptor-2 (HER2) negative metastatic breast cancer. The aim of this study was to evaluate the existing evidence for the comparative efficacy, safety and cost-effectiveness of different CDK4/6 inhibitors for metastatic breast cancer in first-line and second-line settings.

Methods and analysis We will systematically conduct a literature search in Embase, PubMed and the Cochrane Library and additional searches by handsearching citations of previous systematic reviews. We will also screen major conference proceedings (American Society of Clinical Oncology, European Society of Medical Oncology and San Antonio Breast Cancer Symposium). Preliminary scoping searches were conducted in July 2021, but the search will be updated when new trials are available. The primary outcome was progression-free survival. The secondary outcomes were overall survival, objective response rates, grade 3–4 haematological and non-haematological toxicities, quality-adjusted life years and incremental cost-effectiveness ratios. The risk of bias will be assessed by Cochrane risk of bias tools, and the quality of evidence will be assessed by the Grading of Recommendations Assessment, Development and Evaluation. Subgroup analyses and sensitivity analyses will be performed to further confirm our findings. In addition, one-way sensitivity analysis and probabilistic sensitivity analyses will be conducted to determine uncertainty.

Ethics and dissemination This study does not require ethics approval as only secondary data will be collected. The results of our study will provide an overview of the current level of CDK4/6 inhibitors for patients with HR-positive, HER2-negative metastatic breast cancer, and undertake subgroup analyses to explore variables that might affect these effects. The results of this study will be presented at an international clinical conference and published in a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We will perform a cost-effectiveness analysis of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in patients with metastatic breast cancer from the perspective of the third-party payer in the USA based on the efficacy and safety of network meta-analysis.
⇒ Surface under the cumulative ranking (SUCRA) will be used to rank CDK4/6 inhibitors in terms of objective response rates, overall survival, progression-free survival, safety, quality-adjusted life years and incremental cost-effectiveness ratios, and a larger SUCRA indicates a more effective intervention.
⇒ The subgroup analyses will provide new important information regarding race differences for different CDK4/6 inhibitors in patients with hormone receptor-positive, human epidermal receptor-2-negative metastatic breast cancer in our network meta-analysis.
⇒ The Cochrane Risk of Bias tool will be used to assess the methodological quality of individual randomised controlled trials by two reviewers independently.
⇒ Phase III DAWNA-1 is limited by a short follow-up duration and a lack of data on patients with endocrine therapy-sensitive metastatic breast cancer.

PROSPERO registration number CRD42021266597.

INTRODUCTION

The global healthcare burden of breast cancer incidence and mortality is rapidly growing worldwide, with an estimated 2.3 million new cancer cases and 0.7 million cancer-related deaths in 2020.[1] Hormone receptor (HR)-positive and human epidermal growth factor receptor-2 (HER2) negative metastatic breast cancer represents the most frequent histologic subtype of invasive breast cancer

worldwide, accounting for approximately 80% of all cases in women.[2 3] Hormone-directed monotherapy, as well as its combinations, are the mainstay of treatments for HR-positive and HER2-negative metastatic breast cancer, substantially delaying the progression of disease and extending overall survival (OS).[4]

Cyclin-dependent kinase 4/6 (CDK4/6), which are downstream agents in the oestrogen signalling pathway, drive G1-to-S phase progression and promote breast cancer cell proliferation.[5] CDK4/6 inhibitors block cell cycle progression by inactivating the retinoblastoma protein.[6] Three CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) in combination with hormone agents have been the US Food and Drug Administration-approved standard of care in patients with HR-positive and HER2-negative metastatic breast cancer.[7] Recently, published results from the DAWNA-1 have reported significant improvement in median progression-free survival (PFS) with dalpiciclib plus fulvestrant versus fulvestrant alone (15.7 vs 7.2 months; HR, 0.42; 95% CI, 0.31 to 0.58; p<0.001) in patients with HR-positive, HER2-negative metastatic breast cancer.[8] There are fundamental similarities between the four CDK4/6 inhibitors; however, they have different efficacy on OS and safety profiles according to the agent used.[8–15] A prior pairwise meta-analysis confirmed that CDK4/6 inhibitors in combination with hormone agents produced a significant OS improvement, both in aromatase inhibitor (AI)-resistant (HR 0.77, 95% CI, 0.67 to 0.89) and AI-sensitive patients (HR 0.75, 95% CI, 0.63 to 0.89).[16] Although all included studies had high evidence levels, the meta-analysis was limited by the relatively short follow-up period.[16 17] Updated efficacy results on OS with longer follow-up from PALOMA-3 and MONALEESA-3 were presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting.[18 19]

The use of CDK4/6 inhibitors comes not only with potential efficacy and toxicity but also with economic cost. Compared with fulvestrant alone, ribociclib plus fulvestrant as the first-line treatment for patients with HR-positive, HER2-negative metastatic breast cancer was estimated to result in gains of 1.19 life-years and 0.96 quality-adjusted life years (QALYs), at an incremental cost of $151 371 based on the MONALEESA-3 trial in Canada.[20] However, the addition of palbociclib or ribociclib to endocrine therapy in the treatment of HR-positive, HER2-negative metastatic breast cancer was unlikely to be cost-effective based on PALOMA-1, MONALEESA-2 and MONALEESA-7 in the USA, China and Singapore.[21–25] Furthermore, the findings based on the MONARCH 2 trial, MONALEESA-3 trial and PALOMA-3 trial suggested that abemaciclib plus fulvestrant might be cost-effective compared with ribociclib plus fulvestrant, but not cost-effective compared with palbociclib plus fulvestrant for second-line treatment of patients with HR-positive, HER2-negative metastatic breast cancer in the USA. A recent cost-effectiveness analysis confirmed that ribociclib was the less expensive of the three CDK4/6-inhibitors (palbociclib, ribociclib and abemaciclib) in patients with HR-positive, HER2-negative metastatic breast cancer.[26] Generally, to conduct full economic evaluations of each strategy, the study highlighted not only direct pharmacological costs, but also treatment, subsequent and indirect healthcare costs. However, the above results are considerably inconsistent with those of a single randomised controlled trial (RCT). Network meta-analysis is a useful method for comparing efficacy, safety and cost and obtaining relative rankings for multiple competing treatments simultaneously by combining direct evidence from head-to-head RCTs and indirect evidence from within a network.[27]

We will conduct a network meta-analysis and cost-effectiveness analysis to evaluate all comparisons of CDK4/6 inhibitors and recommend a rank order based on efficacy, safety and cost in patients with HR-positive, HER2-negative metastatic breast cancer.

METHODS

Our study was conducted following the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols[28 29] and the Consolidated Health Economic Evaluation Reporting Standards reporting guidelines.[30]

Eligility criteria

Type of participants

The study population is a cohort of patients with histologically or cytologically confirmed HR-positive, HER2-negative metastatic breast cancer. The eligible population in our network meta-analysis was classified into two groups: endocrine-sensitive and endocrine-resistant disease. Endocrine-resistant disease is defined as recurrence during or within 12 months after endocrine-based adjuvant treatment or pretreatment with endocrine therapy in a metastatic setting.[16 31 32]

Type of interventions and comparisons

All studies comparing four CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib and dalpiciclib) as single agents or in combination with endocrine therapy will be included in this study.

Types of outcome measures

The primary outcome is PFS, defined as the date of randomisation to the date of progression or death. The secondary outcome is OS (calculated from the time from randomisation to death from any cause), objective response rates (ORRs), grade 3–4 haematological and non-haematological toxicities, QALYs and incremental cost-effectiveness ratios (ICERs). Grade 3–4 haematological and non-haematological toxicities are performed in line with the Common Terminology Criteria for Adverse Events.[33 34] Studies should provide at least one of the above outcomes.

Type of studies

All eligible RCTs published from the time of database inception to 31 July 2021 will be included. There are no

Table 1 Search strategy used in PubMed

Number	Search terms
#1	(Breast Neoplasm [mesh]) or (Neoplasm, Breast(ti/ab)) or (Breast Tumors(ti/ab)) or (Breast Tumor(ti/ab)) or (Tumor, Breast(ti/ab)) or (Tumors, Breast(ti/ab)) or (Neoplasms, Breast(ti/ab)) or (Breast Cancer(ti/ab)) or (Cancer, Breast(ti/ab)) or (Mammary Cancer(ti/ab)) or (Cancer, Mammary(ti/ab)) or (Cancers, Mammary(ti/ab)) or (Mammary Cancers(ti/ab)) or (Malignant Neoplasm of Breast(ti/ab)) or (Breast Malignant Neoplasm(ti/ab)) or (Breast Malignant Neoplasms(ti/ab)) or (Malignant Tumor of Breast(ti/ab)) or (Breast Malignant Tumor(ti/ab)) or (Breast Malignant Tumors(ti/ab)) or (Cancer of Breast(ti/ab)) or (Cancer of the Breast(ti/ab)) or (Mammary Carcinoma, Human(ti/ab)) or (Carcinoma, Human Mammary(ti/ab)) or (Carcinomas, Human Mammary(ti/ab)) or (Human Mammary Carcinomas(ti/ab)) or (Mammary Carcinomas, Human(ti/ab)) or (Human Mammary Carcinoma(ti/ab)) or (Mammary Neoplasms, Human(ti/ab)) or (Human Mammary Neoplasm(ti/ab)) or (Human Mammary Neoplasms(ti/ab)) or (Neoplasm, Human Mammary(ti/ab)) or (Neoplasms, Human Mammary(ti/ab)) or (Mammary Neoplasm, Human(ti/ab)) or (Breast Carcinoma(ti/ab)) or (Breast Carcinomas(ti/ab)) or (Carcinoma, Breast(ti/ab)) or (Carcinomas, Breast(ti/ab))
#2	(palbociclib(ti/ab)) or (ribociclib(ti/ab)) or (abemaciclib(ti/ab)) or (dalpiciclib(ti/ab))
#3	(Randomized Controlled Trials as Topic (mesh)) or (Clinical Trials, Randomized(ti/ab)) or (Trials, Randomized Clinical(ti/ab)) or (Controlled Clinical Trials, Randomized(ti/ab))
#4	#1 and #2 and #3

limitations in nationality distribution. The studies will be limited to results published in English.

Data sources and search strategy

The comprehensive literature search will be divided into two stages. In the first stage, electronic searches will be used to identify potentially relevant RCTs in PubMed, Embase, the Cochrane Library and Web of Science as well as meeting abstracts from the ASCO, European Society of Medical Oncology and San Antonio Breast Cancer Symposiums. In the second stage, a hand search will be performed in the references from relevant systematic reviews, meta-analyses and cost-effectiveness analyses. Preliminary scoping searches were conducted in July 2021, but the search will be updated when new trials are available. Two reviewers will conduct literature screening and data extraction independently. We will use EndNote V.X7 software to conduct the search strategy and remove duplicates. The latest or larger one will be included in our network meta-analysis when studies have multiple publications. Any discrepancies between reviewers will be resolved by consensus or by consulting with a third reviewer. Full details of the search strategies in PubMed are outlined in more detail in table 1. The search strategies used for Embase and the Cochrane Library are supplied in online supplemental search strategies (online supplemental appendix 1).

A standardised data extraction form created in Microsoft Excel 2010 (Microsoft Corp, Redmond, Washington, USA, www.microsoft.com) will be used to collect data of interest. Relevant information such as the first author, study name, study design, publication time, total sample size, population, line of treatment, treatment arm, control arm, primary endpoint and outcomes (ORR, cost and grade 3–4 haematological and non-haematological toxicities, HR for OS and PFS) will be extracted. We will contact authors or pharmaceutical companies for further information on unpublished or incomplete trials, if possible.

Risk of bias

The Cochrane Risk of Bias tool will be used to assess the methodological quality of individual RCTs by two reviewers independently. Each domain could obtain a high-risk, unclear-risk and low-risk, depending on random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting and other sources of bias.[35] Any disagreement will be resolved by the third researcher.

Quality of evidence

Two reviewers will independently assess the quality of synthetic evidence for each outcome by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[36] Quality of evidence will consider five items involving risk of bias, inconsistency, imprecision, indirectness and publication bias. The overall quality of evidence is classified into four levels: high, moderate, low or very low. RCTs are initially categorised as high quality and could be downgraded by one or two levels for the items mentioned above. Two review authors will independently make judgments about the quality of the included studies using GRADEprofiler software (GRADEpro, V.3.6.1) (available at www.gradeworkinggroup.org).

Assessment of publication bias

If there are up to 10 studies included in the network meta-analysis, we will use a comparison-adjusted funnel plot with Egger's test to examine any potential publication bias.[35]

Statistical analysis

We will draw the network plot, contribution graph, inconsistency check chart and comparison-adjusted funnel plot in our network meta-analysis. A traditional pairwise meta-analysis for direct comparisons with at least two studies will be conducted, using Stata V.13.0 (StataCorp). For each type of CDK4/6 inhibitor in patients with metastatic breast cancer, network meta-analysis will be mainly performed using OpenBUGS (V.3.2.3). Dichotomous

outcomes, including ORR and grade 3–4 haematological and non-haematological toxicities, are expressed as ORs with 95% CIs/credible intervals (CrIs). Additionally, the pooled HRs with 95% CIs/CrIs for survival outcomes will be calculated using fixed effects and random effects models.[37] We will select a random-effect model or fixed-effect model to pool the data based on the lowest deviance information criterion.[38 39] The design-by-treatment inconsistency model, the loop-specific approach and the node-splitting approach will be using to evaluate the global inconsistency, the local inconsistency and the inconsistency for each comparison, respectively.[40] A consistency model will be adopted only when there is no inconsistency between loops or designs.[41] Surface under the cumulative ranking (SUCRA) will be used to rank CDK4/6 inhibitors in terms of ORR, OS, PFS, safety, QALYs and ICERs, and a larger SUCRA indicates a more effective intervention.[42] The results regarding the comprehensive efficacy, tolerability and cost-effectiveness of CDK4/6 inhibitors will be visualised using a multidimensional cluster analysis based on SUCRA data.[43] Statistical heterogeneity across studies will be assessed using the I^2 statistic, where a cut-off of ≥50% is considered indicative of substantial heterogeneity.[44] In network meta-analysis and traditional pairwise meta-analysis, a p value <0.05 is considered statistically significant (two-sided).

Cost-effectiveness analysis

We will perform a cost-effectiveness analysis of CDK4/6 inhibitors in patients with metastatic breast cancer from the perspective of the third-party payer in the USA. All modelling and calculations will be implemented using TreeAge Pro 2009 software (TreeAge Software, Williamstown, Massachusetts, USA). The structure of the Markov model comprises three mutually exclusive health states: PFS, progression and death (figure 1). The expected total costs, QALYs and ICERs will be estimated over a lifetime horizon (10 years). The model inputs of clinical data, cost and utility estimates will be collected from the network meta-analysis and published literature. The drug costs of maintenance therapy will be obtained from the wholesale prices paid by the pharmacy of West China Hospital. All costs will be adjusted to represent 2020 US$ using Tom's Inflation Calculator (https://www.halfhill.com/inflation_js.html 2020). Costs and outcomes will be discounted at 3% annually.[45] One-way sensitivity analysis and probabilistic sensitivity analyses will be performed to assess the potential drivers of economic outcomes. Subgroup analysis will also be performed in patients categorised by menopausal status and prior lines of endocrine therapy. The cost-effectiveness of CDK4/6 inhibitors will be evaluated in comparison with each other to determine the relative effectiveness of the interventions, from most cost-effective to least cost-effective.

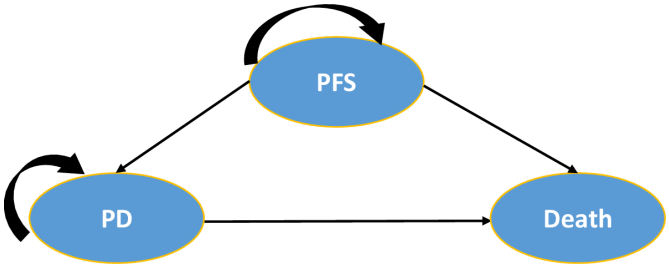

Figure 1 Three-state diagram of Markov model is showed in figure. The initial health state for individuals is progression-free survival. Once patients enter in progressed disease, the cohort either remain in the same health state or transition to death, the absorbing state. Blue circles represent Markov health states, and solid arrows denote possible transitions among the three health states in the diagram. Abbreviations: PD, progressed disease; PFS, progression-free survival.

Transitivity, homogeneity and consistency assumption

Before conducting the network meta-analysis, we will assess three major assumptions: transitivity, homogeneity and consistency.[46] We will conduct a descriptive comparison of the baseline patient-level and study-level characteristics of the included studies. We will then explore the possible sources of obvious heterogeneity by performing network meta-regression analysis. If the results from indirect evidence are not compatible with the results from direct evidence, we will calculate the difference between direct and indirect evidence through the z test in the network.[47 48]

Subgroup analysis

A meta-regression analysis will be undertaken for primary outcomes to analyse influencing factors. In addition, we categorised four CDK4/6 inhibitor therapy regimens into the following subgroups when possible: age (<65 years vs ≥65 years), visceral metastases (yes vs no), progesterone receptor (positive vs negative), bone-only metastases (yes vs no), liver-only metastases (yes vs no), treatment-free interval (<36 months vs ≥36 months) and ethnicity (Asian vs non-Asian).

Sensitivity analysis

We plan to conduct sensitivity analysis on the results of efficacy and safety according to the results of the risk of bias assessment. If studies have a high risk of bias, we will exclude these studies and perform meta-analysis within the remainder of the included studies. Where appropriate, sensitivity analyses will be conducted by varying key model inputs (for example, random-effect and fixed-effect models). In addition, we will conduct the following sensitivity analyses to explore possible causes of heterogeneity, such as study design, study size, year of publication and length of follow-up.[49]

Patient and public involvement

No patients or the public were involved in the study design and will be involved in the actual conduct of the review.

Ethics and dissemination

No ethics review committee approval will be required given the nature of the network meta-analysis. The findings will be submitted for publication in an international

peer-reviewed scientific journal and presented at academic conferences.

DISCUSSION

CDK4/6 inhibitors for HR-positive metastatic breast cancers are exciting new classes of targeted therapies.[50] Recently, apart from dalpiciclib, the efficacy and safety of CDK4/6 inhibitors in comparison to endocrine therapies have been studied in many network meta-analyses.[51–54] It might be interesting to compare CDK4/6 inhibitors for HR-positive, HER-2 negative metastatic breast cancer by incorporating a network meta-analysis and cost-effectiveness analysis into a single analysis.

The CDK4/6 inhibitors that induced cell cycle arrest at the G1/S phase transition were related to cancer aggressiveness.[55] Three CDK4/6 inhibitors with endocrine therapy (an AI or fulvestrant) were recommended as first-line or second-line treatment for HR-positive, HER2-negative metastatic breast cancer by several international treatment guidelines.[32 56 57] Palbociclib, as well as abemaciclib and ribociclib, are the highly-selective oral CDK4/6 inhibitors to be introduced into clinical practice when combined with AIs or fulvestrant in HR-positive, HER2-negative metastatic breast cancer based on pivotal randomised clinical trials. In fact, no difference in PFS was detectable between palbociclib, ribociclib and abemaciclib, but large differences in the safety and tolerability are apparent in the different CDK4/6 inhibitors.[58] A novel, highly selective, small molecule CDK4/6 inhibitor dalpiciclib is currently under active investigation.[59] The results from the phase III DAWNA-1 trial showed that dalpiciclib plus fulvestrant improved PFS compared with fulvestrant alone in patients with HR positive, HER2-negative metastatic endocrine-resistant breast cancer. However, the most common grade 3–4 adverse events in the dalpiciclib plus fulvestrant group were haematologic toxicities,[60] which was consistent with palbociclib and ribociclib but different from abemaciclib.[61]

The mean age at diagnosis of breast cancer in Asian countries was considerably younger than that in western countries.[62–64] Compared with non-Asian populations, premenopausal Asian women had even better outcomes in the MONALEESA-7.[65] However, this correlation was not found when the whole Asian population was analysed through horizontal comparisons of DAWNA-1 and MONARCH 2.[60 66] A limitation is that there were no RCTs specifically designed to assess the use of CDK4/6 inhibitors in Asian and non-Asian patients with HR-positive, HER-2 negative metastatic breast cancer.[67] Therefore, the subgroup analyses will provide new important information regarding race differences in our network meta-analysis.

The results of our study will provide an overview of the current level of CDK4/6 inhibitors for patients with HR-positive, HER-2 negative metastatic breast cancer, and undertake subgroup analyses to explore variables that might affect these effects. The findings might aid clinicians, health policymakers and governments in identifying patients with metastatic breast cancer who can benefit from one of four CDK inhibitors.

Author affiliations
[1]Department of Abdominal Oncology, Cancer Center, Sichuan University West China Hospital, Chengdu, Sichuan, China
[2]Department of International Medical Center, Sichuan University West China Hospital, Chengdu, Sichuan, China
[3]Department of Head, Neck and Mammary Gland Oncology, Cancer Center, Sichuan University West China Hospital, Chengdu, Sichuan, China

Contributors QH and TL conceived the idea and initiated this protocol. QH and WK contributed to the development of the search strategy for this review protocol. QH prepared and wrote the manuscript. TL and QW participated in critical revision of the manuscript. All authors read and approved the final version of the manuscript.

Funding This work was supported by the Project of Sichuan Department of Science and Technology (grant number 2021YES0235).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Ting Luo http://orcid.org/0000-0002-2923-9344

REFERENCES

1 Sung H, Ferlay J, Siegel RL, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
2 Sørlie T, Perou CM, Tibshirani R, *et al*. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 2001;98:10869–74.
3 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687–717.
4 Loibl S, Poortmans P, Morrow M, *et al*. Breast cancer. *Lancet* 2021;397:1750–69.
5 Asghar U, Witkiewicz AK, Turner NC, *et al*. The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nat Rev Drug Discov* 2015;14:130–46.
6 Finn RS, Dering J, Conklin D, *et al*. Pd 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Res* 2009;11:R77.
7 Nasrazadani A, Brufsky AM. Cdk4/6 inhibitors: taking the place of chemotherapy? *Lancet Oncol* 2019;20:1329–30.
8 Xu B, Zhang Q, Zhang P. Dalpiciclib versus placebo plus fulvestrant in HR+/HER2- advanced breast cancer that relapsed or progressed on previous endocrine therapy (DAWNA-1): a multicenter, randomized, phase 3 study. 2021 American Society of clinical oncology (ASCO) annual meeting.Abstract 1002.

9 Turner NC, Slamon DJ, Ro J, *et al*. Overall survival with Palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med* 2018;379:1926–36.
10 Hortobagyi GN, Stemmer SM, Burris HA, *et al*. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016;375:1738–48.
11 Hortobagyi GN, Stemmer SM, Burris HA, *et al*. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol* 2018;29:1541–7.
12 Slamon DJ, Neven P, Chia S, *et al*. Overall survival with Ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med* 2020;382:514–24.
13 Sledge GW, Toi M, Neven P, *et al*. The effect of Abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-Negative breast cancer that progressed on endocrine Therapy-MONARCH 2: a randomized clinical trial. *JAMA Oncol* 2020;6:116-124.
14 Finn RS, Boer K, Bondarenko I, *et al*. Overall survival results from the randomized phase 2 study of palbociclib in combination with letrozole versus letrozole alone for first-line treatment of ER+/HER2-advanced breast cancer (PALOMA-1, TRIO-18). *Breast Cancer Res Treat* 2020;183:419–28.
15 Desnoyers A, Nadler MB, Kumar V, *et al*. Comparison of treatment-related adverse events of different cyclin-dependent kinase 4/6 inhibitors in metastatic breast cancer: a network meta-analysis. *Cancer Treat Rev* 2020;90:102086.
16 Piezzo M, Chiodini P, Riemma M, *et al*. Progression-Free survival and overall survival of CDK 4/6 inhibitors plus endocrine therapy in metastatic breast cancer: a systematic review and meta-analysis. *Int J Mol Sci* 2020;21. doi:10.3390/ijms21176400. [Epub ahead of print: 03 09 2020].
17 Guo Q, Lin X, Ye L, *et al*. Comparative efficacy of Cdk4/6 inhibitors plus aromatase inhibitors versus fulvestrant for the first-line treatment of hormone receptor-positive advanced breast cancer: a network meta-analysis. *Target Oncol* 2019;14:139–48.
18 Cristofanilli M, Rugo HS, Im S-A. Overall survival (OS) with palbociclib (pal) + fulvestrant (FUL) in women with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): updated analyses from PALOMA-3. American Society of clinical oncology (ASCO) annual meeting. Abstract 1000 2021.
19 Slamon DJ, Neven P, Chia SKL. Updated overall survival (OS) results from the phase III MONALEESA-3 trial of postmenopausal patients (PTS) with HR+/HER2- advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (rib). 2021 American Society of clinical oncology (ASCO) annual meeting. Abstract 1001.
20 Stellato D, Thabane ME, Park J, *et al*. Cost effectiveness of Ribociclib in combination with fulvestrant for the treatment of postmenopausal women with HR+/HER2- advanced breast cancer who have received no or only one prior line of endocrine therapy: a Canadian healthcare perspective. *Pharmacoeconomics* 2021;39:1045-1058.
21 Zhang B, Long EF. Cost-Effectiveness analysis of palbociclib or ribociclib in the treatment of advanced hormone receptor-positive, HER2-negative breast cancer. *Breast Cancer Res Treat* 2019;175:775–9.
22 Jeong E, Wang C, Wilson L, *et al*. Cost-Effectiveness of adding Ribociclib to endocrine therapy for patients with HR-positive, HER2-negative advanced breast cancer among premenopausal or perimenopausal women. *Front Oncol* 2021;11:658054.
23 Loke L, Lee S-C, Pearce F, *et al*. Cost-Effectiveness of ribociclib as initial treatment for premenopausal women with advanced breast cancer in Singapore. *Cancer Rep* 2021;4:e1308.
24 Yang J, Han J, Tian M, *et al*. Cost-Effectiveness of Ribociclib for hormone receptor-positive HER2-negative advanced breast cancer. *Cancer Manag Res* 2020;12:12905–13.
25 Huang X, Lin S, Rao X, *et al*. First-Line treatment with Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive advanced breast cancer: a cost-effectiveness analysis. *Clin Breast Cancer* 2021;21:e479-e488.
26 Giuliani J, Bonetti A. The introduction of a third CDK4/6 inhibitor does not change the cost-effectiveness profile in first and subsequent-lines after progression or relapse during previous endocrine therapy in patients with hormone receptor positive (HR+)/human epidermal receptor-2 negative (HER-2) advanced or metastatic breast cancer. *J Oncol Pharm Pract* 2020;26:1486–91.
27 Higgins JPT, Welton NJ. Network meta-analysis: a norm for comparative effectiveness? *Lancet* 2015;386:628–30.
28 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
29 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
30 Husereau D, Drummond M, Petrou S, *et al*. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health* 2013;16:231–50.
31 Nagaraj G, Ma CX, . Clinical challenges in the management of hormone receptor-positive, human epidermal growth factor receptor 2-Negative metastatic breast cancer: a literature review. *Adv Ther* 2021;38:109–36.
32 Cardoso F, Paluch-Shimon S, Senkus E, *et al*. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol* 2020;31:1623–49.
33 Trotti A, Colevas AD, Setser A, *et al*. Patient-reported outcomes and the evolution of adverse event reporting in oncology. *J Clin Oncol* 2007;25:5121–7.
34 Thor M, Deasy JO, Paulus R, *et al*. Tolerance doses for late adverse events after hypofractionated radiotherapy for prostate cancer on trial NRG Oncology/RTOG 0415. *Radiother Oncol* 2019;135:19–24.
35 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
36 Guyatt G, Oxman AD, Akl EA, *et al*. Grade guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
37 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
38 Cameron C, Coyle D, Richter T, *et al*. Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation. *BMJ Open* 2014;4:e004301.
39 Qiu Z, Song PXK, Tan M. Bayesian hierarchical models for multi-level repeated ordinal data using WinBUGS. *J Biopharm Stat* 2002;12:121–35.
40 Veroniki AA, Vasiliadis HS, Higgins JPT, *et al*. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol* 2013;42:332–45.
41 Zintzaras E, Ioannidis JPA. Heterogeneity testing in meta-analysis of genome searches. *Genet Epidemiol* 2005;28:123–37.
42 Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
43 Haldar P, Pavord ID, Shaw DE, *et al*. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218–24.
44 Higgins JPT, Jackson D, Barrett JK, *et al*. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3:98-110.
45 Bosetti R, Tabatabai L, Naufal G, *et al*. New model of integrated care for uncontrolled type 2 diabetes in a retrospective, underserved adult population in the USA: a study protocol for an effectiveness and cost-effectiveness analysis. *BMJ Open* 2020;10:e038084.
46 Sanders GD, Neumann PJ, Basu A, *et al*. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA* 2016;316:1093–103.
47 Song F, Loke YK, Walsh T, *et al*. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. *BMJ* 2009;338:b1147.
48 Dias S, Welton NJ, Caldwell DM, *et al*. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932–44.
49 Chootrakool H, Shi JQ, Yue R. Meta-Analysis and sensitivity analysis for multi-arm trials with selection bias. *Stat Med* 2011;30:1183–98.
50 Treating ER+ breast cancer with CDK4/6 inhibitors. *Cancer Discov* 2017;7:OF4.
51 Leung JH, Leung HWC, Wang S-Y, *et al*. Efficacy and safety of Cdk4/6 and PI3K/Akt/mTOR inhibitors as second-line treatment in postmenopausal patients with hormone receptor-positive, HER-2-negative metastatic breast cancer: a network meta-analysis. *Expert Opin Drug Saf* 2021;20:949-957.
52 Rugo HS, Haltner A, Zhan L, *et al*. Matching-adjusted indirect comparison of palbociclib versus ribociclib and abemaciclib in hormone receptor-positive/HER2-negative advanced breast cancer. *J Comp Eff Res* 2021;10:457–67.
53 Rossi V, Berchialla P, Giannarelli D, *et al*. Should all patients with HR-positive HER2-negative metastatic breast cancer receive CDK 4/6 inhibitor as first-line based therapy? A network meta-analysis of data from the PALOMA 2, MONALEESA 2, MONALEESA 7, monarch

3, falcon, SWOG and fact trials. *Cancers* 2019;11. doi:10.3390/cancers11111661. [Epub ahead of print: 26 10 2019].
54 Giuliano M, Schettini F, Rognoni C, *et al*. Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis. *Lancet Oncol* 2019;20:1360–9.
55 Malumbres M, Barbacid M. Cell cycle, Cdks and cancer: a changing paradigm. *Nat Rev Cancer* 2009;9:153–66.
56 Gradishar WJ, Anderson BO, Abraham J, *et al*. Breast cancer, version 3.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2020;18:452–78.
57 Breast Cancer Expert Committee of National Cancer Quality Control Center, Breast Cancer Expert Committee of China Anti-Cancer Association, Cancer Drug Clinical Research Committee of China Anti-Cancer Association. [Guidelines for clinical diagnosis and treatment of advanced breast cancer in China (2020 Edition)]. *Zhonghua Zhong Liu Za Zhi* 2020;42:781–97.
58 Kwapisz D. Cyclin-Dependent kinase 4/6 inhibitors in breast cancer: palbociclib, ribociclib, and abemaciclib. *Breast Cancer Res Treat* 2017;166:41–54.
59 Zhang P, Xu B, Gui L, *et al*. A phase 1 study of dalpiciclib, a cyclin-dependent kinase 4/6 inhibitor in Chinese patients with advanced breast cancer. *Biomark Res* 2021;9:24.
60 Dalpiciclib extends progression-free survival in HR+/HER2– advanced breast cancer. *Oncologist* 2021;26:S9–10.
61 Gao JJ, Cheng J, Bloomquist E, *et al*. Cdk4/6 inhibitor treatment for patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer: a US food and drug administration pooled analysis. *Lancet Oncol* 2020;21:250–60.
62 Fan L, Strasser-Weippl K, Li J-J, *et al*. Breast cancer in China. *Lancet Oncol* 2014;15:e279–89.
63 Youlden DR, Cramb SM, Yip CH, *et al*. Incidence and mortality of female breast cancer in the Asia-Pacific region. *Cancer Biol Med* 2014;11:101–15.
64 Nobel TB, Asumeng CK, Jasek J, *et al*. Disparities in mortality-to-incidence ratios by race/ethnicity for female breast cancer in New York City, 2002-2016. *Cancer Med* 2020;9:8226–34.
65 Tripathy D, Im S-A, 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;19:904–15.
66 Sledge GW, 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;35:2875-2884.
67 Dawood S, Chiu JW-Y, Huang C-S, *et al*. Palbociclib and beyond for the treatment of HR + HER2- metastatic breast cancer: an Asian-Pacific perspective and practical management guide on the use of CDK4/6 inhibitors. *Curr Med Res Opin* 2020;36:1363–73.

P1:

Embase

#1: breast cancer/

#2: breast ancer.mp.

#3: #1 OR #2

#4: palbociclib/

#5: palbociclib.mp.

#6: #4 OR #5

#7: ribociclib/

#8: ribociclib.mp.

#9: #7 OR #8

#10: abemaciclib/

#11: abemaciclib.mp.

#12: #10 OR #11

#13: dalpiciclib.mp.

#14: #6 OR #9 OR #12 OR #13

#15: "randomized controlled trial (topic)"/

#16: Randomized Controlled Trials.mp.

#17: #15 OR #16

#18:#3 AND #14 AND #17

P2: Cochrane Library

#1: MeSH descriptor: [Breast Neoplasms] explode all trees

#2: (palbociclib):ti,ab,kw OR (ribociclib):ti,ab,kw OR (abemaciclib):ti,ab,kw OR (dalpiciclib):ti,ab,kw

#3: MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees

#4: #1 AND #2 AND #3