

# Continuing cyclin-dependent kinase 4/6 inhibition in metastatic breast cancer patients previously treated with another cyclin-dependant kinase 4/6 inhibitor: a protocol for systematic review and meta-analysis

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# Abstract

Background: Breast cancer is the most common cancer among women worldwide. Most breast cancers are estrogen receptor-positive and epidermal growth factor receptor 2 negative (ER+/HER2-). A small proportion of these cases are metastatic, and cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are the mainstay of treatment in this scenario. Evidence supports the existence of differences between the three approved cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in preclinical and clinical settings. However, literature regarding the use of a CDK4/6i in metastatic breast cancer patients (MBC) previously treated with another CDK4/6i is scarce.

Methods: A search will be performed on the PubMed, Embase, and Web of Science databases following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. In addition, a manual search of the San Antonio Breast Cancer Conference, American Society of Clinical Oncology annual conference, European Society of Medical Oncology annual conference, and European Society of Medical Oncology Breast annual conference will be conducted.

Discussion: To our knowledge, no previous systematic review has evaluated the available evidence regarding the efficacy and safety of CDK4/6i treatment in MBC previously treated with another CDK4/6i. This systematic review and meta-analysis will synthesise existing data on the effectiveness and safety of using a CDK4/6i after prior exposure to another in MBC. It will also identify gaps in the literature for potential future research. The results of this study will focus on multiple audiences including patients, their families, caregivers, and healthcare professionals. These results will be published in a peer-reviewed journal.

Systematic review registration: PROSPERO CRD42022330355

## Introduction

Breast cancer is the most frequently diagnosed cancer in women globally and the second most significant cause of cancer-related death among women, followed by lung cancer (1). Approximately 70% of breast cancers express hormone receptors (HR), progesterone receptors (PRG), or estrogen receptors (ER), with metastatic breast cancer (MBC) being less common than early breast cancer (2). Estrogen receptor-positive and epidermal growth factor receptor 2 negative (ER+/HER2-) MBC is currently considered an incurable disease; however, in the past few years, the treatment paradigm has been shifting, and it is understood that a large number of sequential therapies can be used in most patients, with significant benefit and successful long-term disease control. Cyclin-dependent kinase 4 and 6

(CDK4/6) inhibitors have become the mainstay of treatment in these patients, inhibiting CDK4/CDK6-dependent phosphorylation of retinoblastoma (Rb), which subsequently blocks proliferation by inhibiting the progression of tumour cells from the G1 phase into the S phase of the cell cycle. Data supporting the use of CDK4/6 inhibitors (CDK4/6i) in combination with endocrine therapy in MBC come from several recent studies that have established the use of ribociclib, palbociclib, and abemaciclib as first- and second-line therapies (3).

These agents exhibit different activity patterns. In the case of abemaciclib, the inhibition of other targets, such as cyclin-dependent kinase 2 (CDK2/cyclin A/E) and cyclin-dependent kinase 1 (CDK1/cyclin B), leads to cell cycle arrest in the G1 phase as well as in the G2 phase. Moreover, both senescence and apoptosis occur earlier and at lower concentrations of abemaciclib when compared with palbociclib and ribociclib (4).

Acquired resistance to these therapies is a substantial clinical concern (5). Various mechanisms involving several cell cycle regulatory proteins have been described, including RB transcriptional corepressor 1 (RB1), cyclin E1 (CCNE1), cyclin E2 (CCNE2), cyclin-dependent kinase 6 (CDK6), and aurora kinases (AURKA). In addition, the activation of other oncogenic pathways, including Erb-B2 receptor tyrosine kinase 2 (ERBB2), fibroblast growth factor receptor (FGFR), serine/threonine kinase 1 (AKT), and RAS, appears to be relevant (5-10).

Considering the different patterns of action of CDK4/6i and the potential usefulness of continuing CDK4/6 inhibition after previous treatment with another CDK4/6i, we aim to design a protocol for a systematic review and meta-analysis to analyse the available evidence regarding the efficacy and safety of CDK4/6i treatment in this setting.

## **Objectives**

The main objective of this systematic review is to identify, critically evaluate, and synthesise existing studies that report overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and/or disease control rate (DCR) with the use of a CDK4/6i in MBC after prior exposure to another. The secondary objective is to assess the safety profile of CDK4/6i in this setting. The participants, interventions, comparators, and outcomes (PICO) framework used to formulate the research questions is provided below.

- Participants: ER+/HER2- MBC who have received a CDK4/6i.
- Interventions: CDK4/6i treatment in MBC who have previously received another CDK4/6i.
- Comparators: Studies that include a comparison/control group, a control group receiving no intervention, and a within-group comparison to baseline with no control or comparison groups will be considered for this review.

- Outcomes: OS (defined as the time from treatment initiation to death) and/or PFS (defined as the time from treatment initiation to disease progression or death from any cause) and/or ORR (defined as the proportion of patients who had a partial or complete response to therapy) and/or DCR (defined as the percentage of patients with advanced or metastatic cancer who achieved complete response, partial response, and stable disease) and/or adverse events (AEs).

### **Primary question**

What are the OS, PFS, ORR, and DCR of CDK4/6i treatment in MBC after prior exposure to another CDK4/6i?

### **Secondary question**

What is the safety profile of CDK4/6i treatment for MBC after prior exposure to another CDKi?

## **Methods**

To our knowledge, no previous systematic reviews and meta-analyses have evaluated the available evidence regarding the efficacy and safety of CDK4/6i treatment in MBC patients previously treated with another CDK4/6i. Therefore, a specific protocol for a new systematic review and meta-analysis was developed. The present protocol has been registered in the PROSPERO database (registration number: CRD42022330355) and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (11).

### **Ethics**

No ethical approval is required for the performance of this work.

### **Study identification/information sources**

PubMed and Web of Science will be searched from their inception date to 15 July 2022. In addition, the reviewers will perform a manual search of gray literature, including the San Antonio Breast Cancer Conference, American Society of Clinical Oncology annual conference, European Society of Medical Oncology annual conference, and European Society of Medical Oncology Breast annual conference. Finally, the reviewers will examine the citation lists of the reviewed documents to identify possible additional articles of relevance.

## Search strategy

Our PubMed search strategy is the following:

(abemaciclib OR ribociclib OR palbociclib OR cyclin-dependent kinase inhibitor OR cyclin-dependent kinase inhibitor OR iCDK OR CDKi OR CDK inhibitor OR CDK4/6i OR CDK4/6 inhibitor) AND (Rechallenge OR previous OR prior OR after OR retreatment OR readministration OR restart OR resume OR reinduction OR reintroduction OR continuing) AND (breast cancer OR breast malignancy OR breast neoplasm).

The reviewers will adapt this search strategy for the Web of Science database.

## Study selection

Studies will be included in this systematic review if they meet the following eligibility criteria:

1. Human studies.
2. ER+/HER2- MBC patients previously treated with CDK4/6i now undergoing CDK4/6 inhibition treatment with another CDKi.
3. Any observational retrospective or prospective study and any RCT will be eligible for inclusion.
4. Reporting of a hazard ratio (HR) for OS, PFS, and/or survival curves, allowing estimation of the HR for OS or PFS and/or reporting of ORR, DCR, and/or AEs.
5. English language publication.
6. Other criteria: there will be no limitations on the year of publication.

Studies will be excluded in this systematic review if they meet the following criteria:

1. Age group below 18
2. Letter to editors, review articles, case studies, non-human studies.
3. Studies without full accessibility.
4. Duplicate studies.
5. Articles written in other languages, not English.

Six reviewers (JBA, RS, MA, CF, ALL, CT) will independently screen the titles and abstracts of these studies for potential inclusion. Potentially eligible studies will be confirmed by an evaluation of the full text. A third-party investigator (FM or JA) will resolve any uncertainty or discrepancy. References of all articles included or excluded at the full-text review stage will be entered into EndNote 20.2. Details of the study screening and selection process will be shown in *Figure 1*.

## **Data Extraction**

A standardised data extraction template for the study will be developed using Microsoft Excel. Six reviewers will apply data extraction separately (JBA, RS, MA, CF, ALL, and CT). Whenever possible, the original authors will be contacted for any missing data. The following information will be retrieved:

- Studies: publication year, name of the first author, study design, sample size, country, whether single-center or multicentre, follow-up length, follow-up method, and quality of the study.
- Participants: age, sex, ethnicity, performance status, menopausal status, tumour pathology characteristics (histological type, hormone receptor, HER2 status, Ki67), extent of disease, presence of visceral metastases, previous lines of treatment with start and finish date, previous chemotherapy use, time until CDK4/6i use since prior CDK4/6i, PFS obtained with prior CDK4/6i, best response achieved with prior CDK4/6i, and previous AEs with these treatments.
- Interventions: CDK4/6i treatment start and finish date and dosage.
- Outcome measures: HR for OS, PFS, and/or survival curves, allowing estimation of the HR for OS and/or PFS, ORR, DCR, and AEs.

The reviewers will also collect other information regarding the data extraction process (e.g. reviewer, date of data extraction, record number, and missing data). The capacity of this procedure to collect the intended data will be tested in a few studies before performing complete data extraction of all included studies.

Once data extraction is completed, reviewers will compare their results, and a third author (FM or JG) will mediate in case of disagreement.

## **Risk of Bias Assessment**

- For non-randomised studies, the risk of bias tool in non-randomised studies of interventions (ROBINS-I) will be used if non-randomised studies are included (12). Seven domains will be

evaluated: confounding, selection of study participants, classification of interventions, bias from deviations of intended interventions, missing data, measurement of outcomes, and selection of the reported outcome. The overall bias will be estimated for these seven domains. Each individual study will be assessed as having a low, moderate, severe, and critical risk of bias. If crucial information for determining the risk of bias is missing, such studies will be considered non-informative.

- For randomised studies, the risk-of-bias tool from the Cochrane Handbook V.5.1.0 will also be used if random controlled trials are included (13). Six domains of the risk of bias will be evaluated: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Eligible studies will be judged to have a low or high risk of bias.

The risk of bias in all included studies will be evaluated by six reviewers independently (JBA, RS, MA, CF, ALL, and CT). Disagreements will be reported and resolved by a third reviewer (FM or JG).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) will be used to rate the quality of the body of evidence retrieved in this systematic review, assessed initially by two reviewers (JB, AL) (14). The overall evidence for each outcome will be rated as very low, low, moderate, or high quality, based on the study design and limitations, consistency of effect, and the directness or generalizability of evidence [15].

### **Data synthesis and statistical analysis**

Statistical analysis will be conducted using Stata software version 16.1 (Stata Corp., College Station, Texas). The Kolmogorov-Smirnov test will be used to check the normality of the extracted data. Descriptive statistics will be used to describe the characteristics of all eligible studies. Normally distributed data will be presented as mean (standard deviation), and non-parametric data will be expressed as median (interquartile range). Categorical data will be presented as proportions (%).

If the studies retrieved report quantitative data that can be combined, the extracted data will be aggregated into a meta-analysis. Heterogeneity will be assessed using the  $Q$  and  $I^2$  statistics. A  $p$ -value  $<0.10$  or an  $I^2 >50\%$  suggests that statistical heterogeneity may exist (16). Publication bias will be assessed using the funnel plot and Begg's and Egger's tests (17, 18). A fixed-effects model will be used when the effects are assumed to be homogenous ( $p > 0.05$ ,  $I^2 \leq 50\%$ ), and a random-effects model will be used when they are heterogeneous ( $p < 0.05$ ,  $I^2 > 50\%$ ). Confidence intervals will be set at 95%, and two-sided  $p$ -values  $< 0.05$  will be considered statistically significant. If heterogeneity is detected, a subgroup analysis will be conducted to judge the source of heterogeneity. The criteria for subgroup analysis will potentially include age, ethnicity, performance status, extent of disease, presence of visceral metastases,

previous lines of treatment, previous chemotherapy use, time until CDK4/6i use since prior CDK4/6i, PFS obtained with prior CDK4/6i, and best response achieved with prior CDK4/6i.

Pearson's Chi-square and Fisher's exact tests will be used for categorical variables, while the t-test or Mann-Whitney tests will be applied for continuous variables, if applicable. OS and PFS will be estimated by Kaplan-Meier analysis. Log-rank tests will be employed to compare differences in OS and PFS between subgroups.

## Discussion

There has been an increasing interest and evidence regarding the potential of CDK4/6 inhibition after previous treatment with CDK4/6i. With this hypothesis in mind, a phase III clinical trial in patients who have progressed with a combination of CDK4/6i and an aromatase inhibitor is underway. This population will then be randomised to receive fulvestrant with abemaciclib or placebo (19,20). In addition, other studies are investigating the efficacy of different targeted therapies, such as enobosarm and lasofoxifene, in conjunction with abemaciclib in patients with ER+/HER2- MBC who have progressed with previous CDK4/6i (21,22). Another study is evaluating the efficacy of fulvestrant or exemestane plus ribociclib or placebo in patients with ER+/HER2- MBC whose cancer previously progressed on any CDK 4/6i plus any endocrine therapy (23).

The proposed review will serve several purposes. First, it will synthesise and consolidate evidence on the use of continuing CDK4/6 inhibition in patients with ER+/HER2- MBC who have received another CDK4/6i. Aggregating relevant studies, their efficacy, and the quality of evidence can help inform clinical decision making in this challenging setting, while the standard of care recommendations and further research are being developed. Second, this review may reveal target populations specific to particular settings, age groups, or other clinically relevant criteria that are more suitable for continuing CDK4/6 inhibition after a previous CDK4/6i. Third, it will serve as a source of information on adverse events in this setting.

Beyond informing clinical care, the review also seeks to identify opportunities to improve the methodological quality of future intervention research in this population to develop an appropriate standard of care. In addition, it may lead researchers to identify and test intervention paradigms to improve the outcomes in this population.

This systematic review will be conducted according to recommended standards, including explicit eligibility criteria, independent assessment of eligibility, and a comprehensive search. To our knowledge, this will be the first systematic review on continuing CDK4/6 inhibition in metastatic breast cancer patients previously treated with another CDKi.

Several potential limitations may affect this review. Publication bias and restriction of this review to English-language publications may limit the generalizability and strength of the recommendations. In addition, studies may have significant heterogeneity, precluding statistical pooling and meta-analysis results.

The results of this review will be made available for publication in a peer-reviewed journal.

## Declarations

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**Declaration of conflicting interests:** José A. García-Sáenz: Eli Lilly & Co., Novartis, Pfizer, Celgene, Daiichi Sankyo, Eisai, AstraZeneca (C/A), AstraZeneca (RF), and Roche-Genentech (other). The remaining authors have no potential conflicts of interest to declare.

(C/A) Consulting/advisory relationship, (RF) research funding, (E) employment, (ET) expert testimony, (H) Honoraria received, (OI) Ownership interests, (IP) Intellectual property rights/inventor/patent holder, (SAB) Scientific advisory board.

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## Figures

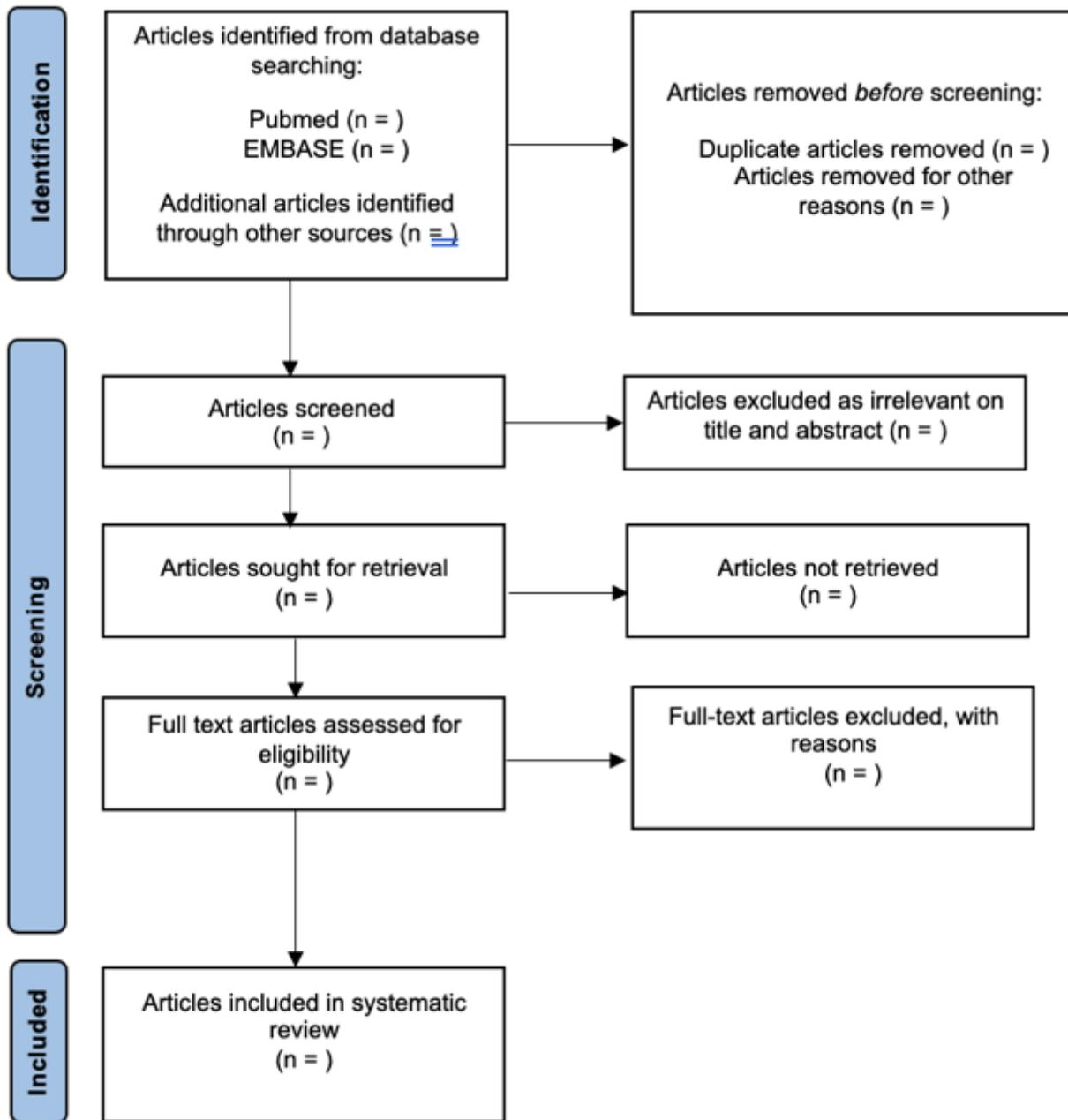


Figure 1

Flow diagram of the study selection process.