TECHNOLOGY REVIEW (MINI-HTA)

TARGETED THERAPIES IN COMBINATION WITH HORMONAL THERAPY AS A FIRST-LINE TREATMENT FOR HR+ AND HER2- METASTATIC BREAST CANCER

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
013/2020

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Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my

e-ISBN: 978-967-2887-03-4

SUGGESTED CITATION: Balqis AG, Atikah S and Izzuna MMG. Targeted Therapies in Combination with Hormonal Therapy as a First-Line Treatment for HR+ and HER2- Metastatic Breast Cancer. Technology Review. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2020. 67 p. Report No.: 013/2020. e-ISBN: 978-967-2887-03-4

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

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EXECUTIVE SUMMARY

Background

Breast cancer is the most frequently diagnosed cancer worldwide, and it is the leading cause of cancer-related death among women.[1] The most common subtype of breast cancer is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), accounting for 68% of all diagnosed breast cancer. Oestrogen and oestrogen receptors are key drivers in breast cancer progression. Currently, endocrine or hormone therapy such as aromatase inhibitor (AI) is considered as the first-line treatment in postmenopausal women with HR+, HER2-, metastatic breast cancer. However, most patients have different resistance reaction to current endocrine therapy, which leads to disease progression. The introduction of targeted therapies such as inhibitors of cyclin dependant kinases 4 and 6 (CDK 4/6), inhibitors of mammalian target of rapamycin (mTOR), inhibitors of phosphatidylinositol-3-kinases (PI3K/AKT) pathways might overcome resistant reaction by targeting key intracellular signaling pathways in order to improve disease outcome. The combination of targeted agents with endocrine therapy has shown improvement in clinical outcomes such as progression-free survival (PFS). However, combination strategies may be restricted by the occurrence of adverse events and affordability constraints in the local settings. Therefore, this Technology Review was conducted following a request by an oncologist from Hospital Kuala Lumpur to review the evidence on targeted therapies in combination with hormonal therapy as a first-line treatment for HR+, HER2-, metastatic breast cancer.

Objective/ aim

To assess the safety, effectiveness, cost-effectiveness and organisational issues of targeted therapies in combination with hormonal therapy as a first-line treatment for HR+, HER2-, metastatic breast cancer.

Results and conclusion

A total of 986 records were identified through database and other sources. Fourteen studies were included in this review: three network meta-analysis, two systematic reviews with meta-analysis, one randomized control trial, six cost-effectiveness analyses, and two budget impact analysis. The evidence suggested that combination of CDK 4/6 inhibitors (palbociclib, ribociclib or abemaciclib) with AI resulted in longer PFS, higher overall response rate (ORR) and clinical benefit (CB) compared to AI monotherapy and fulvestrant-based therapies. When compared to chemotherapy agents, the combination treatment also showed improvement in PFS. Palbociclib, ribociclib and abemaciclib (in combination with AI) demonstrated similar efficacy as a first-line treatment for HR+, HER2-, metastatic breast cancer. In terms of safety, grade III or IV treatment-related side effects were significantly higher in patients who received combination treatment compared to AI monotherapy with commonly reported side effects of neutropaenia, leukopaenia, and anaemia. As for cost-effectiveness, ribociclib plus letrozole

was a cost-effective therapy option compared to palbociclib plus letrozole. The estimated ICER varied across countries for both treatment options with different perspectives and thresholds.

Methods

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1946 to present, EBM Reviews - Cochrane Central Register of Controlled Trials – October 2020, EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to October 2020, EBM Reviews - Health Technology Assessment – 4th Quarter 2016, EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2016. Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 2nd of November 2020.

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ABBREVIATION

AEs	:	Adverse Events or Adverse Effects
AI	:	Aromatase Inhibitor
ASCO	:	American Society of Clinical Oncology Guideline
CAD	:	Canadian Dollar
CASP	:	Critical Appraisal Skills Programme
CB	:	Clinical Benefit
CDK 4/6	:	Cyclin Dependant Kinases 4 and 6
CHF	:	Swiss Franc
CI	:	Confidence Interval
DES	:	Discrete Event Simulation
E2F	:	E2 Factor
ESMO	:	European Society for Medical Oncology
ET	:	Endocrine Therapy
EUR	:	Euro
GnRH	:	Gonadotropin-Releasing Hormone
GPCR	:	G-Protein-Coupled Receptors
HER2-	:	Human Epidermal Growth Factor Receptor 2-Negative
HR	:	Hazard Ratio
HR+	:	Hormone Receptor-Positive
ICER	:	Incremental Cost-Effectiveness Ratio
ILD	:	Interstitial Lung Disease
MA	:	Meta-Analysis
MBC	:	Metastatic Breast Cancer
MOH	:	Ministry of Health
mTOR	:	Mammalian Target Of Rapamycin
MYR	:	Malaysian Ringgit
NCCN	:	National Comprehensive Cancer Network
NMA	:	Network Meta-Analysis
NPRA	:	National Pharmaceutical Regulatory Agency
OR	:	Odd ratio
ORR	:	Overall Response Rate
OS	:	Overall Survival
PFS	:	Progression-Free Survival
PIK3/AKT	:	Phosphatidylinositol-3-Kinases
QALM	:	Quality Adjusted Life Months
QALY	:	Quality Adjusted Life Year
QAPFW	:	Quality-Adjusted Progression-Free Survival Weeks
QAPFY	:	Quality-Adjusted Progression-Free Years
QoL	:	Quality of Life
Rb	:	Retinoblastoma
RCT	:	Randomised Controlled Trial
RTK	:	Receptor Tyrosine Kinases
SERD	:	Selective Oestrogen Receptor Down-Regulator
SERM	:	Selective Oestrogen Receptor Modulators
SR	:	Systematic Review
US FDA	:	United States Food and Drug Administration
USD	:	US Dollar
WHO	:	World Health Organization
WTP	:	Willingness to Pay

1.0 BACKGROUND

Breast cancer is the most frequently diagnosed cancer worldwide, and it is the leading cause of cancer-related death among women.[1] The most common subtype of breast cancer is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), accounting for 68% of all diagnosed breast cancer. It is more frequently related to postmenopausal women and there is a five-year survival rate of 30.4% for metastatic breast cancer.[2] In Malaysia, the overall range of HR+ breast cancer cases were found to be high (50 to 65%). A study on incidence of breast cancer subtypes in Sarawak reported that 48% of diagnosed breast cancers were HR+ and HER2-.[3,4]

Oestrogen and oestrogen receptors are key drivers in breast cancer progression. Targeting oestrogen has been used for many years to inhibit the oestrogen signaling pathway in women with HR+ breast cancer.[5] Currently, endocrine therapy such as aromatase inhibitors (AI), selective oestrogen receptor modulators (SERM), and selective oestrogen receptor down-regulator (SERD) is considered as the first-line treatment in postmenopausal women with HR+, HER2-, metastatic breast cancer.[6] However, most patients have different resistance reaction to current endocrine therapy, which leads to disease progression.[7] The introduction of targeted therapies such as inhibitors of cyclin dependant kinases 4 and 6 (CDK 4/6), inhibitors of mammalian target of rapamycin (mTOR), inhibitors of phosphatidylinositol-3-kinases (PI3K/AKT) pathways might overcome resistant reaction by targeting key intracellular signaling pathways in order to improve disease outcome.[8]

In a first-line settings, CDK 4/6 inhibitors (palbociclib, ribociclib, abemaciclib) in combination with an AI has been approved as a treatment for postmenopausal women with HR+ and HER2-, metastatic breast cancer.[9,10] The combination of mTOR (everolimus) with exemestane, and PIK3 inhibitors (alpelisib) with fulvestrant, are approved for postmenopausal women with HR+ and HER2-, metastatic breast cancer following progression after an endorine-based treatment. [10] The combination of targeted agents with hormonal therapy has shown improvement in clinical outcomes such as progression-free survival (PFS). However, combination strategies may be restricted by the occurrence of adverse events and affordability constraints in the local settings.[3]

Therefore, this Technology Review was conducted following a request by an oncologist from Hospital Kuala Lumpur to review the evidence on targeted therapies in combination with hormonal therapy as a first-line treatment for HR+, HER2-, metastatic breast cancer.

2.0 OBJECTIVE / AIM

To assess the safety, effectiveness, cost-effectiveness and organisational issues of targeted therapies in combination with hormonal therapy as a first-line treatment for HR+, HER2-, metastatic breast cancer.

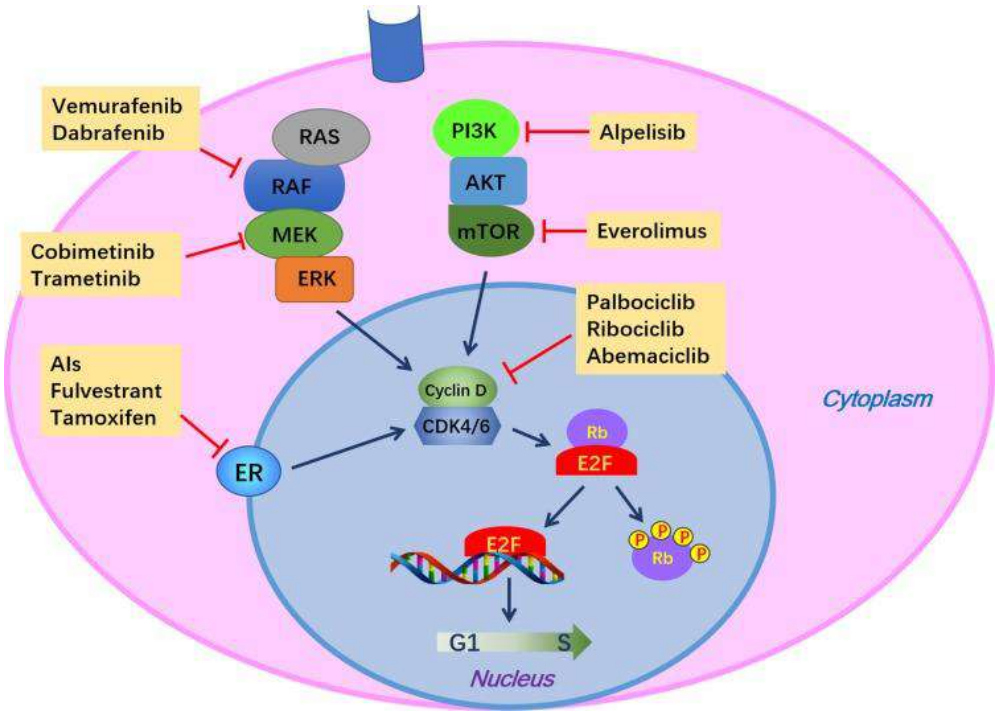
3.0 TECHNICAL FEATURES

3.1 Targeted Therapy

Targeted drugs are designed to block the growth and spread of cancer cells. These drugs work differently from chemotherapy drugs, which attack all cells that are growing quickly (including cancer cells).[11] Three types of targeted therapies used as a treatment for HR+, HER2-, metastatic breast cancer are listed in Table 1. The mechanisms of action are illustrated in Figure 1.

Table 1. List of Targeted Therapy for HR+, HER2- Metastatic Breast Cancer

Targeted Therapies	Mechanism of Action	Drugs
Cyclin dependant kinases 4 and 6 (CDK 4/6) Inhibitors	CDK 4/6, which combines with cyclin D1 and phosphorylate retinoblastoma protein (Rb), promotes cell cycle entry in G1/S phase. CDK 4/6 inhibitor dephosphorylates Rb and activates E2F; then produce G1/S cell cycle arrest and apoptosis.[9]	Palbociclib (Ibrance®) Ribociclib (Kryxana®) Abemaciclib (Yulareb®)
Mammalian target of rapamycin (mTOR) inhibitors	mTOR is a downstream effector of the PI3K/AKT pathway and comprised of two multi-protein complexes; mTOR complex 1 and 2. mTOR inhibitors binds to intracellular FK506 binding protein 12 kDA (FKBP-12) and inhibits mTOR protein kinase activity and thus, inhibits cell growth.[12]	Everolimus (Afinitor®) Temsirolimus (Torisel®) Sirolimus (Rapamune®)
Phosphatidylinositol-3-kinases (PIK3) inhibitors	The PI3K pathway integrates extracellular signals that activate receptor tyrosine kinases (RTKs) and G-protein-coupled receptors (GPCRs) and is necessary for normal growth and proliferation. By inhibiting these enzymes, PI3K inhibitors cause cell death, inhibit the proliferation of malignant cells, and interfere with several signaling pathways.[13]	Alpelisib (Trezilent®) Buparlisib Pictilisib Taselisib



Abbreviations: Rb, retinoblastoma; ER, oestrogen receptor; E2F, E2 factor

Figure 1. Mechanism of Action for Targeted Therapy and Hormone Therapy[14]

3.2 Hormone Therapy

Hormone therapy, also known as endocrine therapy slows or stops the growth of hormone-sensitive tumours by blocking the body's ability to produce hormones or by interfering with effects of hormones on breast cancer cells. Table 2 described the list of endocrine therapy available for treatment of breast cancer.

Table 2. List of Hormone Therapy for Breast Cancer

Endocrine Therapy	Mechanism of Action	Drugs
Aromatase Inhibitor (AI)	AI blocks the activity of an enzyme called aromatase, which the body uses to make oestrogen in the ovaries and in other tissues. There are two general categories of aromatase inhibitors: the nonsteroidal inhibitors, which bind competitively with aromatase, and the steroidal inhibitors, which bind irreversibly.[15,16]	Anastrozole (Arimidex®) Letrozole (Femara®) Exemestane (Aromasin®)
Selective oestrogen receptor modulators	SERM bind to oestrogen receptors, preventing oestrogen from binding. It	Tamoxifen (Nolvadex®) Toremifene (Fareston®)

(SERM)	also mimics the effects of oestrogen, depending on where they are expressed in the body.[15]	
Selective oestrogen receptor down-regulator (SERD)	Like SERMs, SERD binds to the oestrogen receptor and functions as an oestrogen blocker. However, it does not mimic oestrogen and known as pure anti-oestrogen.[15]	Fulvestrant (Faslodex®)
Gonadotropin-releasing hormone (GnRH) agonists	GnRH interferes with signals that stimulate the ovaries to produce oestrogen.[15]	Goserelin (Zoladex®) Leuprolide (Lupron®)

4.0 METHODS

4.1 SEARCHING

Electronic databases were searched through the Ovid interface:

- Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1946 to present
- EBM Reviews - Cochrane Central Register of Controlled Trials – October 2020
- EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to October 2020
- EBM Reviews - Health Technology Assessment – 4th Quarter 2016
- EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2016

Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 2nd of November 2020.

Appendix 2 shows the detailed search strategies.

4.2 SELECTION

Two reviewers (BAG and AS) independently screened the titles and abstracts against the inclusion and exclusion criteria as shown below and evaluated the selected full-text articles for final article selection.

Inclusion criteria:

Population	HR+, HER2-, metastatic breast cancer.
Interventions	Targeted therapy in combination with endocrine therapy in first-line setting
Comparators	Endocrine therapy alone / Chemotherapy / Placebo / any comparator
Outcomes	Efficacy/Effectiveness: • Progression-free survival (PFS) • Overall survival (OS) • Overall response rate (ORR) • Clinical benefit (CB) Safety: • Adverse events related to treatment such as haematological, non-haematological, and lung toxicity Economic Implication • Cost-effectiveness
Study design	Health Technology Assessment (HTA) reports, Systematic review (SR) and Meta-analysis, Randomised

	Controlled Trials (RCT), Non-randomised controlled trials (NRCT), cohort studies, cross-sectional studies

Exclusion criteria:

i. Animal / laboratory / case series / case report
ii. Narrative review

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and were graded according to US/Canadian preventive services task force (Appendix 1). Data were extracted and summarised in evidence table as in Appendix 3.

5.0 RESULTS

5.1 SELECTION OF THE INCLUDED STUDIES

A total of 980 records were identified through Ovid interface and six records were identified from other sources (references of retrieved articles). All the records were screened and 922 records were excluded. Of these, 64 relevant abstracts were retrieved in full text. After applying inclusion and exclusion criteria, 50 articles were excluded with reasons (Figure 2).

There were 14 studies included in this review: three network meta-analysis (NMA), two SR with meta-analysis, one RCT, six cost-effectiveness analyses, and two budget impact analysis. The studies were conducted in United States (US), Spain, Italy, Switzerland and Canada. The selection of the studies was shown on Figure 2.

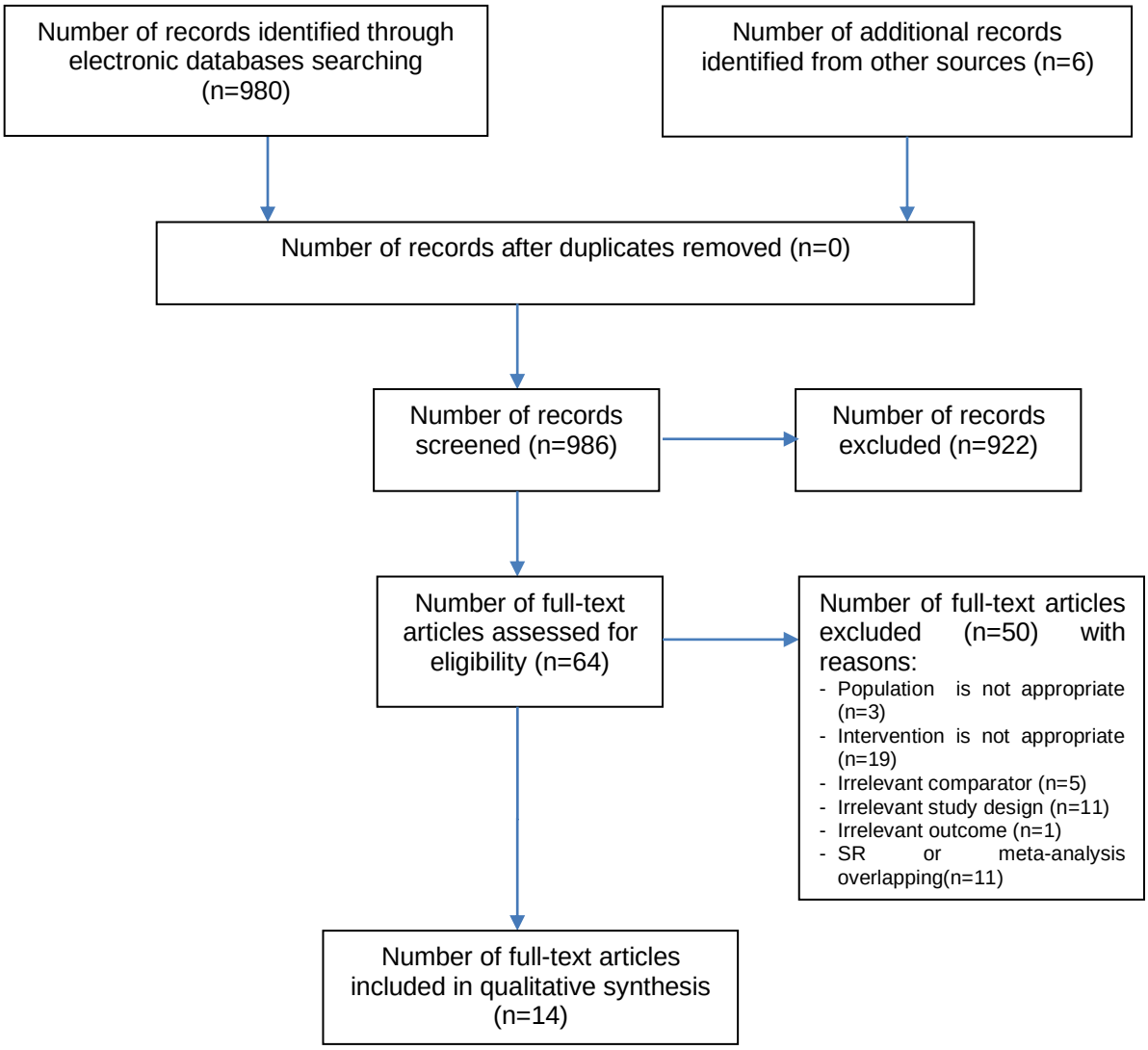


Figure 2. Flow chart of study selection

5.2 RISK OF BIAS ASSESSMENT

Both reviewers (BAG and AS) independently appraised relevant articles using the Critical Appraisal Skills Programme (CASP) checklist and Cochrane risk-of-bias tool. Review authors' judgements involved answering pre-specified questions and discrepancies were resolved by consensus.

Assessment for Systematic Review Studies using Critical Appraisal Skills Programme (CASP) Checklist

Five systematic reviews were included in this assessment and the risk of bias is summarised in figure 3. Only one study was at low risk of bias for all domains assessed. Wilson et al. and Li et al. did not explained on the quality of assessment used in their included studies, thus were judged to have high risk of bias for the third domain.

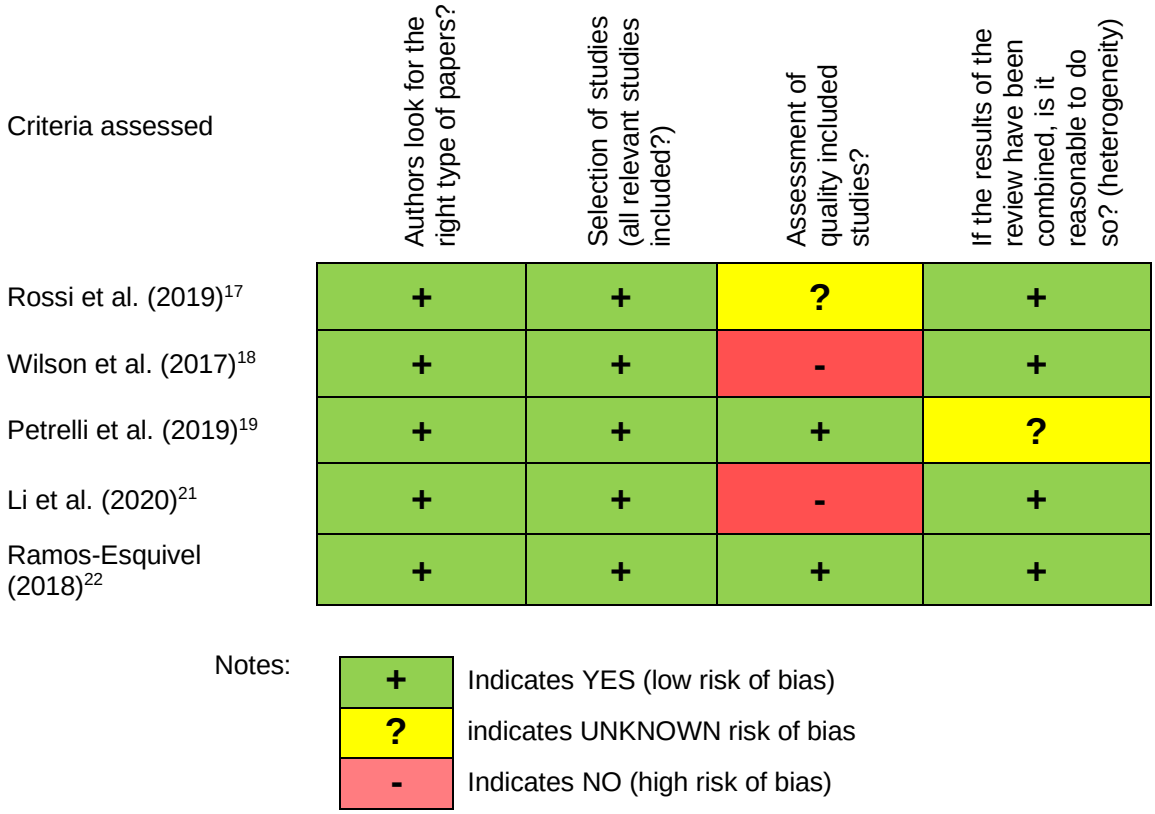


Figure 3. Risk of Bias Summary for Systematic Review (SR)

Assessment for Randomised Control Trial (RCT) using Revised Cochrane Risk of Bias Tool

One RCT were included in this assessment and the risk of bias is shown in figure 4. Blinding was not clearly explained in this study, thus was judged to have some concern of bias for the second domain.

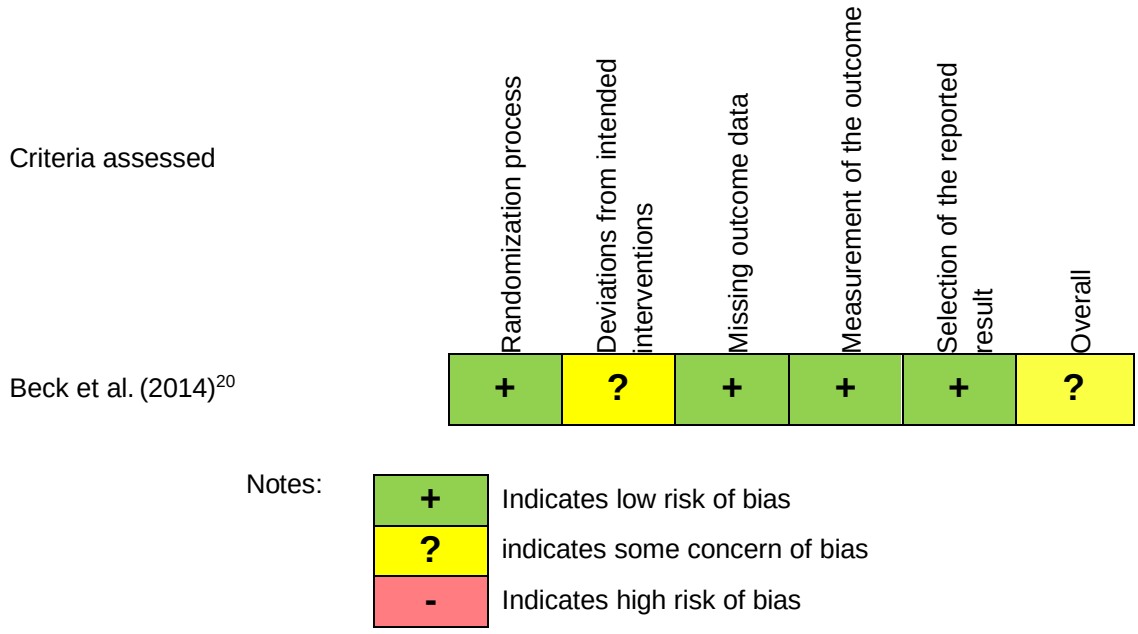


Figure 4. Risk of Bias for Randomised Control Trial

Assessment for Economic Evaluation Studies using Critical Appraisal Skills Programme (CASP) Checklist

Six cost-effectiveness analyses and two budget impact studies were included in this assessment and the risk of bias is summarised in figure 5. All studies were at low risk of bias for all domains accessed.

Criteria assessed	Mamiya et al. (2017)[24]	Raphael et al. (2017)[25]	Mattler-Walstra et al. (2016)[26,27]	Zhang et al. (2018)[28]	Mistry et al. (2018)[29]	Galve-Calvo et al. (2018)[30]	Mistry et al. (2018)[31]	Diaby et al. (2014)[32]
A well-define question posed?	+	+	+	+	+	+	+	+
Comprehensive description of competing alternative given?	+	+	+	+	+	+	+	+
Effectiveness established?	+	+	+	+	+	+	+	+
Effects of intervention identified, measured and valued appropriately?	+	+	+	+	+	+	+	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	+	+	+	+	+	+	+	+
Costs and consequences adjusted for different times at which they occurred (discounting)?	+	+	+	+	+	+	+	+
Results of the evaluation?	+	+	+	+	+	+	+	+
Incremental analysis of the consequences and costs of alternatives performed?	+	+	+	+	+	+	+	+
Sensitivity analysis performed?	+	+	+	+	+	+	+	+

Notes:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

Figure 5. Risk of Bias Summary for Economic Evaluation

5.3 EFFICACY/ EFFECTIVENESS

Five studies reported the effectiveness of targeted therapy in combination with hormonal therapy as a first-line treatment for HR+, HER2-, metastatic breast cancer, of which three were NMA and two were systematic reviews with meta-analysis. The results were presented based on outcomes as follow; PFS, overall response rate (ORR), clinical benefit (CB) and overall survival (OS). For each outcome, results will be divided into four types of comparison; combination of CDK 4/6 inhibitor with AI versus endocrine therapy, combination of CDK 4/6 inhibitor with AI versus chemotherapy, comparison between

CDK 4/6 inhibitors, and combination of everolimus plus exemestene versus exemestene alone.

Progression-Free Survival (PFS)

Combination of CDK 4/6 Inhibitors with Aromatase Inhibitor (AI) versus Endocrine Therapy

Rossi et al. conducted a study to indirectly compare the combination of CDK 4/6 inhibitors plus AI (letrozole or anastrozole) with fulvestrant-based therapies and AI monotherapy in patients with HR+, HER2-, metastatic breast cancer. Databases were searched from November 2011 to June 2019 focusing on phase III RCTs that reported the comparison of CDK 4/6 inhibitors plus endocrine therapy, or fulvestrant plus or less endocrine therapy, versus endocrine therapy treatment alone in a first-line setting. Seven RCTs were included, whereby four RCTs compared CDK 4/6 inhibitors plus AI with AI monotherapy (PALOMA-2, MONALEESA-2, MONALEESA-7, MONARCH-3; n=1441), while three RCTs compared fulvestrant plus or less AI, with AI monotherapy (FALCON, SWOG, FACT, n=837). A NMA was performed using the Bayesian hierarchical arm-based model. The CDK 4/6 inhibitors combination treatments resulted in longer PFS (median PFS: 23.8 to 25.3 months) when indirectly compared to fulvestrant-based therapies (median PFS: 10.8 to 16.6 months) as shown in figure 6 (HR: 0.68; 95% CI: 0.53, 0.8 for palbociclib plus AI, HR: 0.65; 95% CI: 0.53, 0.79 for ribociclib plus AI, HR:0.63; 95% CI: 0.47, 0.86 for abemaciclib plus AI). In a subgroup analysis, PFS were consistent in patients with bone-only disease, non-visceral sites, no prior endocrine therapy, no chemotherapy, and Asian population.[17, level I]

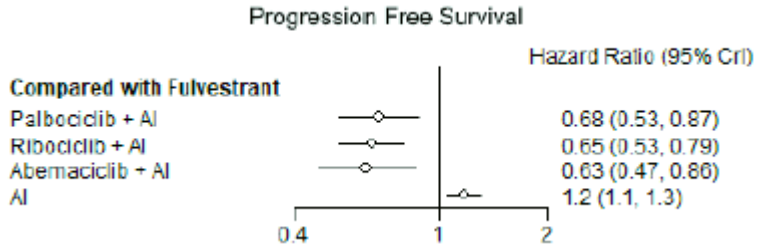


Figure 6. Forest plot with direct comparisons against fulvestrant for PFS

Combination of CDK 4/6 Inhibitors with Aromatase Inhibitor (AI) versus Chemotherapy Agents

Wilson et al. (2017) conducted a Bayesian NMA and pairwise meta-analysis (MA) to compare the combination of palbociclib plus letrozole with chemotherapy agents as a first-line treatment in post-menopausal women with HR+, HER2-, metastatic breast cancer. Databases were searched from January 2000 to January 2016 focusing on RCTs of chemotherapy agents, chemotherapy plus biological therapies, and endocrine-based therapies used to treat postmenopausal women with HR+, HER2-, metastatic

breast cancer. A total of 22 studies that enrolled 8152 patients were included. Palbociclib plus letrozole significantly improved PFS compared to capecitabine (HR:0.28; 95% CI: 0.11, 0.72), and mitoxantrone (HR:0.28; 95% CI: 0.13, 0.61). Improvement was also shown in palbociclib plus letrozole when compared to paclitaxel (HR: 0.59; 95% CI: 0.19, 1.96), docetaxel (HR: 0.51; 95% CI: 0.14, 0.23), and other monotherapy or chemotherapy agents (HR ranging from 0.24 to 0.99). Sensitivity analysis conducted was aligned with the findings, where treatment with palbociclib plus letrozole improved PFS relative to all other treatment.[18, level I]

Comparison between CDK 4/6 Inhibitors

Petrelli et al. (2019) compared the effectiveness between palbociclib, ribociclib, and abemaciclib for treatment of HR+, HER2-, metastatic breast cancer via NMA. Databases were searched up to October 2018. The searched focus on phase III RCTs that reported the comparison of CDK 4/6 inhibitors plus AI with AI alone. Three RCTs (PALOMA-2, MONARCH-3, MONALEESA-2) that enrolled 1827 patients in a first-line setting were included. Three comparison were made; a) palbociclib versus ribociclib, b) palbociclib versus abemaciclib, and c) ribociclib versus abemaciclib as shown in figure 7, 8, and 9. Palbociclib, ribociclib and abemacicilib demonstrated similar efficacy in terms of PFS (HR: 1.04; 95% CI: 0.73, 1.46 for palbociclib versus ribociclib; HR: 1.07; 95% CI: 0.75, 1.54 for palbociclib versus abemaciclib; and HR: 1.04; 95% CI: 0.71, 1.52 for ribociclib versus abemaciclib).[19, level I]

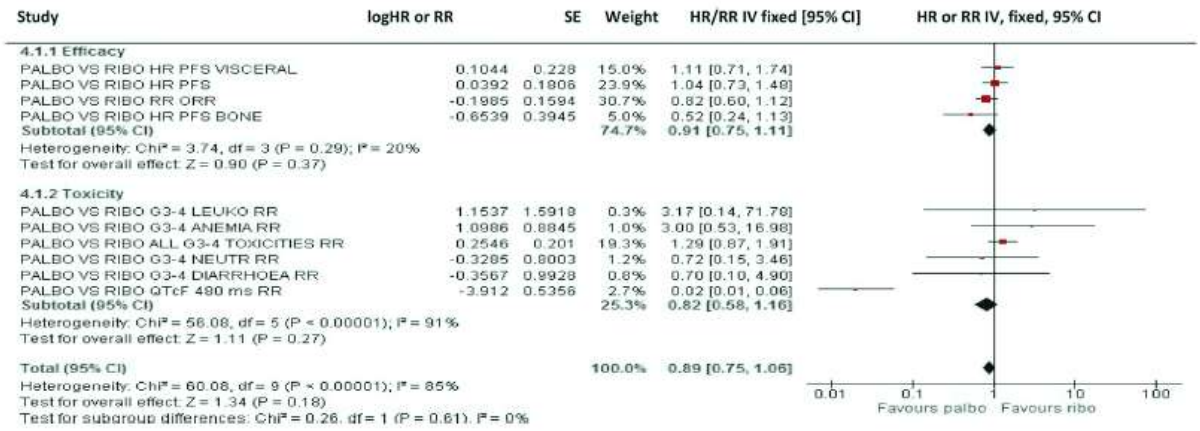


Figure 7. Forest plots for all indirect comparisons among CDK 4/6 inhibitors: palbociclib versus ribociclib

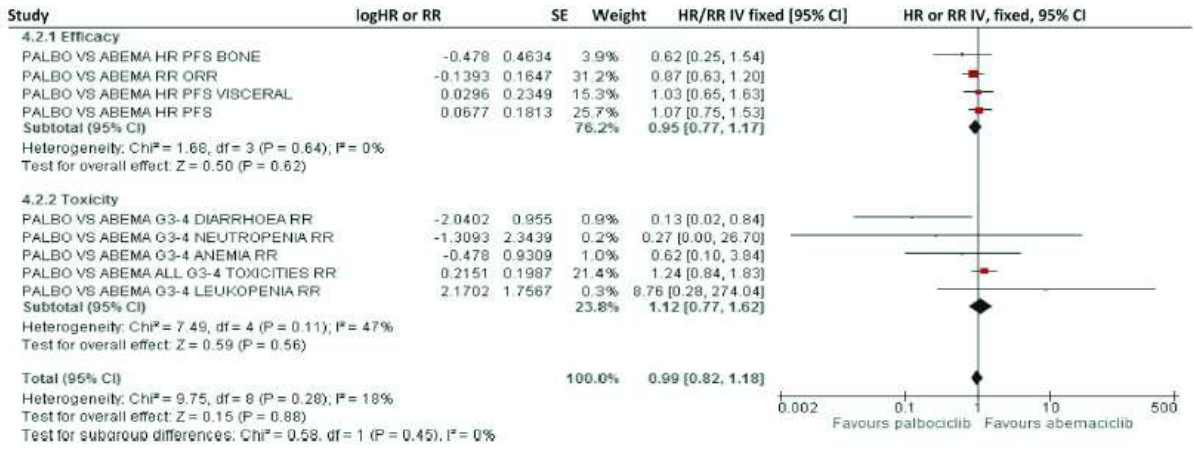


Figure 8. Forest plots for all indirect comparisons among CDK 4/6 inhibitors: palbociclib versus abemaciclib

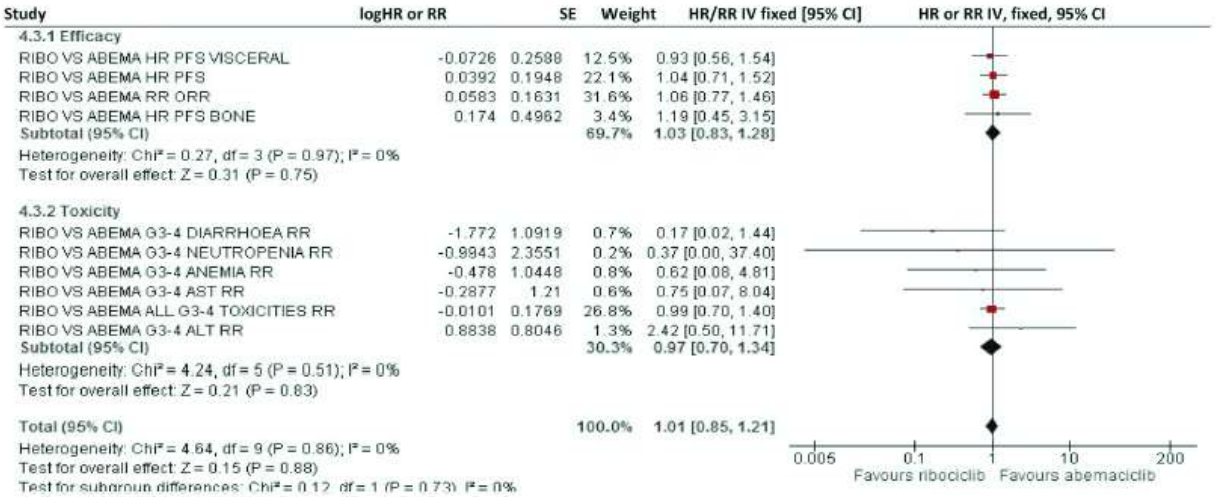


Figure 9. Forest plots for all indirect comparisons among CDK 4/6 inhibitors: ribociclib versus abemaciclib

Combination of Everolimus with Aromatase Inhibitor (AI) versus AI alone

Beck et al. (2014) evaluated the effectiveness of everolimus plus exemestene in the subgroup of patients in the BOLERO-2 trials who received this regimen as first-line treatment for HR+, HER2-, metastatic breast cancer. The BOLERO-2 trial was a phase III, multicenter, randomised, double blind, placebo-controlled trial. Patients were randomised to receive either everolimus (10mg/day) plus exemestene 25mg/day) (n=100) or placebo plus exemestene (25mg/day)(n=37). The median PFS with everolimus plus exemestane were nearly tripled compared to placebo plus exemestane (11.5 versus 4.1 months, HR: 0.39; 95% CI: 0.25, 0.62). The results were consistent with central assessment (15.2 versus 4.2 months; HR: 0.32; 95% CI: 0.18, 0.57).[20, level II-1]

Overall Response Rate (ORR)

Combination of CDK 4/6 Inhibitors with Aromatase Inhibitor (AI) versus Endocrine Therapy

Rossi et al. reported a higher response rate in patients receiving CDK 4/6 inhibitors combination strategies when indirectly compared to fulvestrant-based therapies (OR:1.3; 95% CI: 0.81, 2.0 for palbociclib plus AI, OR:1.6; 95% CI: 1.1, 2.5 for ribociclib plus AI, OR:1.6; 95% CI: 1.1, 2.4 for abemaciclib plus AI) as shown in figure 10.[17, level I]

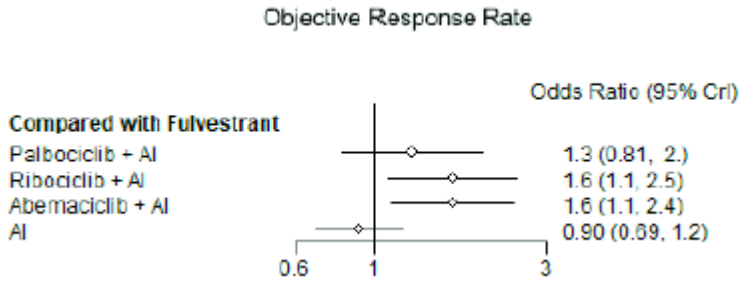


Figure 10. Forest plot with direct comparisons against fulvestrant for ORR

Comparison between CDK 4/6 Inhibitors

In a meta-analysis by Petrelli et al, there was no significant different in ORR among the three comparisons; relative risk (RR):0.82; 95% CI: 0.6, 1.09, RR: 0.87; 95% CI: 0.63, 1.19, and RR: 1.06; 95% CI: 0.77, 1.47, for palbociclib versus ribociclib, palbociclib versus abemaciclib, and ribociclib versus abemaciclib, respectively (figure 7, 8, 9).[19, level I]

Clinical Benefit (CB)

Combination of CDK 4/6 Inhibitors with Aromatase Inhibitor (AI) versus Endocrine Therapy

Rossi et al. reported higher CB in patients receiving CDK 4/6 inhibitor combination strategies when indirectly compared to fulvestrant-based therapies (OR: 2.1; 95% CI: 1.3, 3.3 for palbociclib plus AI, OR: 1.3; 95% CI: 0.92, 1.8 for ribociclib plus AI, OR: 1.2; 95% CI: 0.81, 1.8 for abemaciclib plus AI as shown in figure 11.[17, level I]

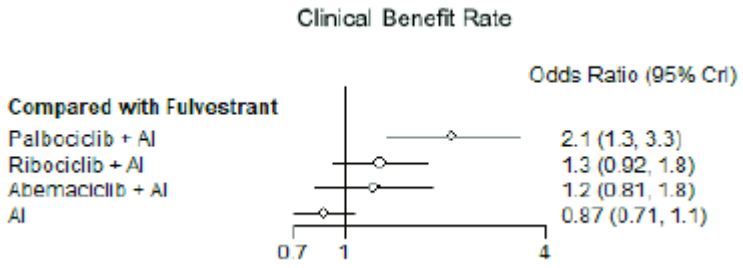


Figure 11. Forest plot with direct comparisons against fulvestrant for CB

Overall Survival (OS)

Combination of CDK 4/6 Inhibitors with Aromatase Inhibitor (AI) versus Endocrine Therapy

Li et al. (2020) reported the association of CDK 4/6 inhibitors plus AI, compared with AI alone, with overall survival (OS) in patients with HR+, HER2-, metastatic breast cancer. Databases were searched up to March 2020. Three RCTs (PALOMA-1, MONARCH-2, and MONALEESA-7) that reported survival outcomes were included. Compared to AI alone (median OS: 33.3 to 37.3 months), CDK 4/6 inhibitors plus AI (median OS: 37.5 to 46.7 months) was associated with significant improvement in OS in the first-line setting (HR: 1.35; 95% CI: 1.18, 1.54; p<0.01), with low heterogeneity across studies (I^2=0%, p=0.99).[21], level I

5.4 SAFETY

Three studies reported the safety of targeted therapy in combination with hormonal therapy as a first-line treatment for HR+, HER2-, metastatic breast cancer.

Combination of CDK 4/6 Inhibitors with Aromatase Inhibitor (AI) versus Endocrine Therapy

Ramos-Esquivel et al. (2018) reported the toxicity of CDK 4/6 inhibitors plus AI combination treatment versus AI alone in a first-line setting. A meta-analysis were conducted which included three RCTs (PALOMA-2, MONARCH-3, MONALEESA-2). Mantel-Haenszel method was used to calculate the pooled OR for treatment-related side-effects. The odds of having any grade III or IV treatment-related side effect were significantly higher in patients receiving the combination treatment (Mantel–Haenszel OR: 7.51; 95% CI: 6.01, 9.38) as shown in figure 12. The most common all-grade toxicity was neutropaenia; ranging from 21.1% (abemaciclib) to 66.5% (palbociclib), followed by leukopaenia; ranging from 7.6% (abemaciclib) to 24.8% (palbociclib), and anaemia; ranging from 1.2% (ribociclib) to 5.8% (abemaciclib). The rates of febrile neutropaenia were low, ranging from 0.3% (abemaciclib) to 1.8% (palbociclib).[22], level I

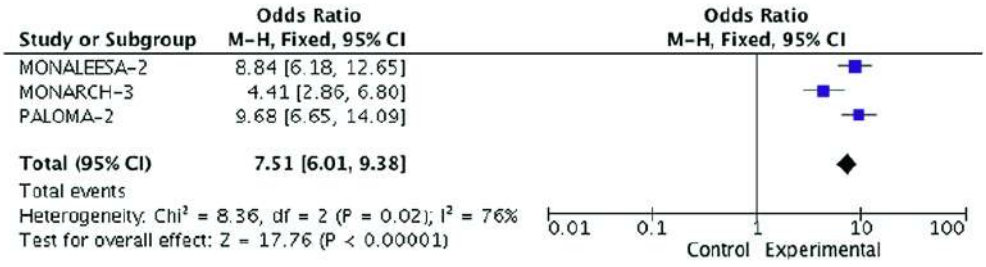


Figure 12. Forest plot of treatment related side-effects

Comparison between CDK 4/6 Inhibitors

Petrelli et al. compared the safety between palbociclib, ribociclib, and abemaciclib via an indirect adjusted analysis as shown in figure 7,8, and 9. There were no difference found among CDK 4/6 inhibitors for all grade III and IV toxicities, except less incidence of grade III and IV diarrhoea with palbociclib compared with abemaciclib (RR:0.13; 95% CI: 0.02, 0.92), and reduced risk of QTc prolongation with palbociclib compared to ribociclib (RR:0.02; 95% CI:0, 0.15). Palbociclib and ribociclib, in combination with letrozole demonstrated similar time to deterioration in quality of life (HR:0.94; 95% CI:0.72, 1.24; p=0.73).[19], level I

Combination of Everolimus with Aromatase Inhibitor (AI) versus AI alone

Beck et al. reported the safety of everolimus plus exemestene in the subgroup of patients in the BOLERO-2 trials. Most reported adverse events with treatment group were stomatitis (68%), diarrhoea (40%), and rash (37%). Most common adverse events of grade III or IV intensity in treatment group were hyperglycaemia (8%), stomatitis (4%), diarrhoea (4%) and fatigue (3%). Treatment discontinuation due to adverse events was slightly higher in treatment group (10%) compared to control group (8%). Dose reductions or interruptions were higher in treatment group (74% patients had everolimus dose reduction) compared to control group (32% had placebo dose reduction).[20], level II-1

FDA Warning

US Food and Drug Administration (US FDA) in 2019 warned the used of palbociclib, ribociclib and abemaciclib in patients with advanced breast cancer may cause rare but severe inflammation of the lungs. Serious and fatal cases of interstitial lung disease (ILD) and pneumonitis have been identified in clinical trials and post-marketing reports related to CDK 4/6 inhibitors used. From the clinical trials, one to three percents of patients had ILD or pneumonitis of any grade, and less than one percent had fatal outcomes.[23]

5.5 ECONOMIC IMPLICATION

5.5.1 Cost-effectiveness

Six cost-effectiveness studies and two budget impact analyses were retrieved on the use of targeted therapies in combination with hormonal therapies as a first-line treatment in patients with HR+, HER2-, metastatic breast cancer. The results were presented based on the types of targeted therapy used; palbociclib, ribociclib and everolimus. No retrievable evidence found on the cost-effectiveness of abemaciclib for this population.

Palbociclib

Mamiya et al. (2017) developed discrete event stimulation (DES) model to evaluate the cost-effectiveness of adding palbociclib to letrozole in treatment of HR+, HER2-, metastatic breast cancer based on data from PALOMA-1 trial. The analysis was conducted from the societal perspective and a lifetime horizon was used. Estimated costs for one-month treatment of palbociclib and letrozole alone were USD 9850 and USD 655, respectively. The addition of palbociclib increased quality-adjusted life expectancy (QALY) of 0.31 at incremental cost of USD 244,326. The estimated incremental cost-effectiveness ratio (ICER) was USD 768,498 per additional QALY gained. Sensitivity analysis demonstrated that adding palbociclib has a 0% chance of being cost-effective at a willingness-to-pay (WTP) threshold of USD 100 000 per quality adjusted life year (QALY).[24]

Raphael et al. (2017) assessed the cost-utility of palbociclib from the Canadian healthcare perspective through a DES model by using data from PALOMA-1 and 2 trials. A time horizon of 15 years was used in the base case with costs and effectiveness discounted at 5% annually. The addition of palbociclib provided an additional 14.7 quality-adjusted life months (QALMs) at an incremental cost of CAD 161,508. The resulting incremental cost-effectiveness ratio (ICER) was CAD 10,999 per additional QALM gained. The probability of palbociclib to be cost-effective was 0% at a WTP threshold of CAD 4167 per QALM. Sensitivity analysis showed that at a WTP threshold of CAD 11,000 per QALM, the probability of palbociclib to be cost-effective was 50%.[25]

Matter-Walstra et al. (2016) conducted a cost-effectiveness analysis of palbociclib and letrozole from the Swiss healthcare system perspective. A Markov model simulation was developed by using data from PALOMA-1. A lifetime horizon was adopted to capture related costs and outcomes. The addition of palbociclib provided an additional 1.14 QALYs at an incremental cost of CHF 156,251. The resulting ICER was CHF 137,063 per additional QALY gained. The probability of palbociclib to be cost-effective were 19% at a WTP threshold of CHF 100,000 per QALY.[26,27]

Ribociclib

Zhang et al. (2019) assessed the cost-effectiveness of ribociclib or palbociclib for the treatment of HR+, HER2-, metastatic breast cancer in the United States. A Markov model simulation was developed using data from published clinical trials evaluating palbociclib (PALOMA-1) and ribociclib (MONALEESA-2). Three simulated treatments strategies were conducted that includes: a) ribociclib plus letrozole, b) palbociclib plus letrozole, and c) letrozole alone. The average lifetime costs for each treatment were described in table 3 below:

Table 3. Average lifetime cost for each treatment strategies

Treatment	Average lifetime costs (USD)	QALYs
Ribociclib + Letrozole	549,164	2.94
Palbociclib + Letrozole	475,339	2.56
Letrozole alone	170,289	2.08

Compared to letrozole alone, treatment with ribociclib plus letrozole resulted in additional 0.86 QALYs (average) with an ICER of USD 440,000 per QALY gained; while palbociclib plus letrozole resulted in additional 0.48 QALYs (average) with an ICER of USD 634,000 per QALY gained. At a WTP threshold of USD 100 000 per QALY, neither ribociclib nor palbociclib was cost-effective. To reach such a cost-effectiveness threshold, palbociclib and ribociclib prices need to be decreased by approximately 70%.[28]

Mistry et al. (2018) evaluated the cost-effectiveness of ribociclib plus letrozole versus palbociclib plus letrozole and versus letrozole monotherapy from a US private third-party payer perspective. A partitioned survival model was developed from published clinical trials evaluating palbociclib (PALOMA-1), ribociclib (MONALEESA-2), and Bayesian network meta-analysis. A 40-year lifetime horizon with a one month cycle length was used. The treatment costs were described in table 4 below:

Table 4. Average lifetime cost for each treatment strategies

Treatment	Average lifetime costs (USD)	QALYs
Ribociclib + Letrozole	432,095	3.07
Palbociclib + Letrozole	475,132	2.99
Letrozole alone	287,180	2.38

Compared to palbociclib plus letrozole, treatment with ribociclib plus letrozole was associated with a cost reduction of USD 43,037 and 0.086 QALYs gained. When compared to letrozole alone, ribociclib plus letrozole was associated with a cost reduction of USD 144,915 at an incremental QALY of 0.689, equating to an ICER of USD 210,369 per additional QALY gained. The authors concluded that ribociclib plus letrozole is a cost-effective alternative to palbociclib plus letrozole for the first-line treatment of postmenopausal women with HR+, HER2-, metastatic breast cancer. Ribociclib plus letrozole is also cost-effective versus letrozole alone at WTP thresholds greater than USD 198,000 per QALY.[29]

Galve-calvo et al. (2018) evaluate the cost-effectiveness of ribociclib compared to palbociclib, both in combination with letrozole, from the perspective of the Spanish National Health System (NHS). A partitioned survival model was developed from published clinical trials evaluating palbociclib (PALOMA-1) and ribociclib (MONALEESA-2). A 15-year lifetime horizon with a one month cycle length was used. Compared to palbociclib plus letrozole, treatment with ribociclib plus letrozole was associated with an incremental cost of EUR 439.86 with incremental life-years (LYs) gained of 0.437 and 0.285 QALY. The resulting ICER and incremental cost-utility ratio (ICUR) were EUR 1,007.69 per LY gained and EUR 1,543.62 per QALY gained, respectively. Considering WTP threshold of EUR 20,000 to 30,000 per QALY gained, ribociclib plus letrozole would be a cost-effective treatment option compared to palbociclib plus letrozole. The results of the multiple sensitivity analyses showed limited dispersion of the outcomes, thus corroborating their robustness.[30]

Mistry et al. (2018) in another study conducted a budget impact analysis of ribociclib plus letrozole as a first-line treatment option for postmenopausal women with HR+, HER2-, metastatic breast cancer, from a US payer perspective. A cohort-based budget impact model was used to calculate the incremental cost of introducing ribociclib plus letrozole over three years for the target population. Of one million insured members, 263 were eligible for CDK 4/6 inhibitor treatment. Cumulative total savings with ribociclib plus letrozole were USD 3,010,000 over three years, attributing to reduce costs (drug acquisition, USD 2,720,000; subsequent therapy, USD 96,000; adverse events, USD 82,000). Savings per year increased over the time horizon with increased market share of ribociclib: USD 125,000, USD 1,040,000, and USD 1,850,000 in every year (year one to three), respectively. The introduction of ribociclib yielding a cumulative incremental cost saving of USD 318.11 per member treated per month. The authors concluded that ribociclib plus letrozole was a cost-saving first-line treatment option for postmenopausal women with HR+, HER2- metastatic breast cancer.[31]

Everolimus

Diaby et al. (2014) performed a cost-effectiveness analysis of everolimus plus exemestene from the US payer perspective. A Markov model simulation was developed using data from BOLERO-2. A time horizon of 120 weeks was adopted. The total cost for everolimus plus exemestane (USD 63,584) was higher than exemestane alone (USD 3,010). When compared to exemestane alone, everolimus plus exemestane had an incremental benefit of 11.88 quality-adjusted progression-free survival weeks (QAPFW) [0.22 quality-adjusted progression-free years (QAPFY)] and an incremental cost of USD 60,574. This translated into an ICER of USD 265,498/QAPFY. The univariate sensitivity analysis showed the important variations of the ICER, ranging between USD 189,836 and USD 530,947/QAPFY. The authors concluded that everolimus plus exemestane was not cost-effective compared to exemestane alone.[32]

5.6 ORGANISATIONAL

5.6.1 Approval of CDK 4/6 inhibitors and mTOR

Palbociclib, ribociclib, abemaciclib and everolimus has received FDA approval for treatment in post-menopausal women or men with HR+, HER2-, metastatic breast cancer. These drugs were also registered under National Pharmaceutical Regulatory Agency (NPRA) and only ribociclib was listed in MOH Formulary Medicines.[33,34] Table 6 summarised the indications approved by FDA for each drugs.[35,36,37,38]

Table 6. Indication approved for CDK 4/6 inhibitor and mTOR

Drugs	Year of approval	Population	Indication Approved by FDA	
			First-line treatment for HR+, HER2-, METASTATIC BREAST CANCER	Second- or later-line treatment for HR+, HER2-, METASTATIC BREAST CANCER
Palbociclib	2015	Post-menopausal women	Palbociclib + AI	Palbociclib + Fulvestrant
	2019	Men	Palbociclib + AI	-
Ribociclib	2017	Pre- or Post-menopausal women	Ribociclib + AI Ribociclib + Fulvestrant	Ribociclib + Fulvestrant
Abemaciclib	2017	Post-menopausal women	Abemaciclib + AI	Abemaciclib + Fulvestrant
Everolimus	2012	Post-menopausal women	-	Everolimus + Exemestene

5.6.2 Guidelines / Recommendations

Endocrine therapy is a standard first-line treatment in patients with HR+, HER2-, metastatic breast cancer. Nevertheless, guidelines and recommendation by several organizations have suggested the option of targeted therapies in combination with hormonal therapies in this population.

American Society of Clinical Oncology Guideline (ASCO)
The ASCO in 2016 developed recommendations about endocrine therapy for women with HR+, METASTATIC BREAST CANCER. Combination treatment of palbociclib and AI was recommended as one of the first-line treatment options in post-

menopausal women with HR+, HER2-, metastatic breast cancer. Combination of palbociclib plus fulvestrant may be offered to post-menopausal women who exposed to prior hormone therapy and up to one line of chemotherapy. Everolimus plus exemestane may be offered to post-menopausal women who experience progression during treatment with AI.[39]

National Comprehensive Cancer Network (NCCN)

A clinical guideline on breast cancer was developed by NCCN in 2020. For post-menopausal women with HR+, HER2-, metastatic breast cancer, combination of CDK 4/6 inhibitor with AI or fulvestrant were among the first-line treatment options recommended. For second-line treatment, CDK 4/6 in combination with fulvestrant, and everolimus with either an AI, tamoxifen, or fulvestrant, were among the preferred choice of treatment.[40]

European Society for Medical Oncology (ESMO)

International consensus guideline on metastatic breast cancer was developed by ESMO in 2020. Combination of CDK 4/6 inhibitors with AI were the preferred first-line treatment in patients with HR+, HER2-, METASTATIC BREAST CANCER. Similar to NCCN guideline, CDK 4/6 in combination with fulvestrant, and everolimus with either an AI, tamoxifen, or fulvestrant were recommended as the second-line treatment.[41]

Ministry of Health Malaysia

Latest guideline on Management of Breast Cancer (third edition) published in 2019 recommended endocrine therapy as a first-line treatment in HR+, HER2-, metastatic breast cancer unless there is evidence of visceral crisis or endocrine resistance. Nevertheless, the guideline acknowledged that combination of endocrine therapy with CDK 4/6 inhibitors has shown promising results in pre- and post-menopausal, endocrine-naive HR+, HER2-, metastatic breast cancer.[6]

5.7 SOCIAL/ ETHICAL / LEGAL

There was no retrievable evidence on the societal issues of using targeted therapy in combination with hormonal therapy in patients with HR+, HER2-, metastatic breast cancer.

5.8 LIMITATION

This technology review has several limitations. This review has been prioritized to include only first-line treatment for HR+, HER2-, metastatic breast cancer despite other treatment line used in this population. A few studies that did not provide control group to the combination treatment were being excluded. Some systematic review and meta-analysis that combined results from both first-line and second-line settings were also excluded.

6.0 CONCLUSION

The evidence suggested that combination of CDK 4/6 inhibitors with AI resulted in longer PFS, higher ORR and CB compared to AI monotherapy and fulvestrant-based therapies. When compared to chemotherapy agents, the combination treatment also showed improvement in PFS. Palbociclib, ribociclib and abemaciclib (in combination with AI) demonstrated similar efficacy as a first-line treatment for HR+, HER2-, metastatic breast cancer.

In terms of safety, grade III or IV treatment-related side effects were significantly higher in patients who received combination treatment compared to AI monotherapy with commonly reported side effects of neutropaenia, leukopaenia, and anaemia.

As for cost-effectiveness, ribociclib plus letrozole was a cost-effective therapy option compared to palbociclib plus letrozole. The estimated ICER varied across countries for both treatment options with different perspectives and thresholds.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS / DIAGNOSTIC STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomised controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: SEARCH STRATEGY

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to November 2, 2020>

Search Strategy:

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1. breast cancer/
2. cyclin dependent protein kinases.tw.
3. protein kinase inhibitor.tw.
4. CYCLIN-DEPENDENT KINASE 6/
5. cdk6 protein.tw.
6. CYCLIN-DEPENDENT KINASE 4/
7. cdk4 protein.tw.
8. abemaciclib.tw.
9. ribociclib.tw.
10. palbociclib.tw.
11. everolimus.tw.
12. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 1 and 12

APPENDIX 3: EVIDENCE TABLE

Evidence Table : Efficacy and Safety
Question : Is targeted therapies in combination with hormonal therapy effective and safe as a first-line treatment for HR+ , HER-, Metastatic Breast Cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. 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 (Basel). 2019;11(11):1661. Italy	Network Meta-Analysis (NMA) Objective: To indirectly compared between the combination strategy, including CDK 4/6 inhibitors plus AI, and fulvestrant-based therapies for the first-line treatment of HR+/HER2- metastatic breast cancer. Method: MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trial were searched from November 2011 to June 2019. The searched focus on phase III RCT that reported the comparison of CDK 4/6 inhibitors plus endocrine therapy (ET) or fulvestrant (F) plus or less ET *versus* ET treatment alone as first-line therapy in metastatic HR+, HER2- breast cancer. A NMA was performed using the Bayesian hierarchical arm-based model which provides the estimates for various effect sizes.	I	N=7 RCTs 4 RCTs: CDK 4/6 inhibitor+AI vs AI alone (n=1441) PALOMA-2 MONARCH-3 MONALEESA-2 MONALEESA-7 3 RCTs: Fulvestrant+AI vs AI alone (n=837) FALCON SWOG FACT	CDK 4/6 inhibitors (Palbociclib, Ribociclib, Abemaciclib)+ AI (Lestrozole/Anastrozole) Fulvestrant or Anastrozle + Fulvestrant	Placebo + AI (Lestrozole/Anastrozole) Anastrozole		<u>Effectiveness</u> Four RCT comparing CDK 4/6 inhibitors+AI with AI alone were identified. Three RCT comparing fulvestrant alone or fulvestrant+anastrozole with anastrozole were identified. Progression-Free Survival (PFS) • CDK 4/6 inhibitors combination strategies resulted in longer PFS when indirectly compared to F-based therapies [HR: 0.68 (95% CI: 0.53, 0.8) for Palbociclib + AI, HR: 0.65(95% CI: 0.53, 0.79) for ribociclib + AI, HR:0.63 (95% CI: 0.47,0.86) for abemaciclib + AI) • In a subgroup analysis, PFS were consistent in patients with bone-only disease, non-visceral sites, no prior endocrine therapy, no chemotherapy and Asian population. Objective Response Rate (ORR) • CDK 4/6 inhibitors combination strategies resulted in higher response rate when indirectly compared to F-based therapies [OR:1.3 (95% CI: 0.81, 2.0) for palbociclib + AI, OR:1.6 (95% CI: 1.1, 2.5) for ribociclib + AI, OR:1.6 (95% CI: 1.1, 2.4) for abemaciclib + AI) Clinical Benefit (CB) • CDK 4/6 inhibitors combination strategies resulted in higher CB when indirectly compared to F-based therapies [OR:2.1 (95% CI: 1.3, 3.3) for palbociclib + AI, OR:1.3 (95% CI: 0.92,	

Evidence Table : Efficacy and Safety
Question : Is targeted therapies in combination with hormonal therapy effective and safe as a first-line treatment for HR+ , HER-, Metastatic Breast Cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							1.8) for ribociclib + AI, OR:1.2 (95% CI: 0.81, 1.8) for abemaciclib + AI) Overall survival (OS) • Indirect comparison was not performed by Rossi et al. as most of the studies were not completely matured at the time the NMA was conducted. • MONALEESA-7 study estimated OS at 42 months was 70.2% (95% CI: 63.5, 76.0) in the CDK 4/6 inhibitor arm versus 46% (95%CI:32, 58.9) in the AI alone arm. Author's conclusion: CDK 4/6 inhibitors have similar efficacy when associated with an AI in the first-line treatment of HR+ metastatic breast cancer, and are superior to either fulvestrant or AI monotherapy, regardless of any other patients or tumours characteristic.	

Evidence Table : Efficacy and Safety
Question : Is targeted therapies in combination with hormonal therapy effective and safe as a first-line treatment for HR+ , HER-, Metastatic Breast Cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Wilson FR, Varu A, Mitra D, et al. 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. 2017;166(1):167-177. US	Network Meta-Analysis (NMA) Objective: To compare palbociclib+letrozole and palbociclib+fulvestrant with chemotherapy agents as a first-line or second-line treatment in postmenopausal women with HR+/HER2-, metastatic breast cancer. Method: MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trial and PubMed were searched from January 2000 to January 2016. The searched focus on RCTs of chemotherapy agents, chemotherapy plus biological therapies, and endocrine-based therapies used to treat postmenopausal women with HR+/HER2-, metastatic breast cancer. Bayesian NMAs and pairwise meta-analysis were conducted to pool RCT results. Two separate evidence networks were generated to stratify studies by first and second lines of therapies.	I	N=8152 (22 studies on first-line treatment)	Palbociclib + Letrozozle	Chemotherapy agents		Progression-Free Survival (PFS) • In the first line treatment, palbociclib+letrozole significantly improved PFS compared to capecitabine [HR:0.28 (95% CI:0.11,0.72)], and mitoxantrone [HR:0.28 (95% CI:0.13,0.61)]. • Improvement was also shown in palbociclib+letrozole when compared to paclitaxel [HR:0.59 (95% CI:0.19,1.96)], docetaxel [HR:0.51 (95% CI:0.14,0.23)], and other monotherapy or chemotherapy agents (HR ranging from 0.24 to 0.99). • Sensitivity analysis as conducted to include PALOMA-2 study. Palbociclib+letrozole was associated with improved PFS relative to all other tratement. Author's conclusion: Palbociclib+letrozole demonstrated trends in incremental efficacy compared with chemotherapy agents.	

Evidence Table : Efficacy and Safety
Question : Is targeted therapies in combination with hormonal therapy effective and safe as a first-line treatment for HR+ , HER-, Metastatic Breast Cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Petrelli F, Ghidini A, Pedersini R et al. Comparative efficacy of palbociclib, ribociclib and abemaciclib for ER+ metastatic breast cancer: an adjusted indirect analysis of randomized controlled trials. *Breast Cancer Res Treat.* 2019;174(3):597-604. Italy	Network Meta-analysis Objectives: To compare the effectiveness of palbociclib, ribociclib, and abemaciclib in HR+ HER2- metastatic breast cancer via an indirect adjusted analysis. Method: MEDLINE, EMBASE and the Cochrane Library were searched up to October 2018. The searched focus on phase III RCT that reported the comparison of CDK 4/6 inhibitors plus ET with ET alone, with or without placebo in metastatic HR+, HER2- breast cancer. The results were compared with an adjusted indirect analysis of RCTs.	I	N=1827 PALOMA-2 MONARCH-3 MONALEESA-2	Palbociclib Palbociclib Ribociclib	Ribociclib Abemaciclib Abemaciclib		Three RCTs included patients who received CDK 4/6 inhibitors+AI as first line therapy for metastatic breast cancer. Baseline characteristics were similar and comparable. Three comparison were made: Palbociclib vs Ribociclib, Palbociclib vs Abemaciclib, and Ribociclib vs Abemaciclib. <u>Effectiveness</u> Progression-Free Survival (PFS) • In indirect comparisons, all three first-line treatments were similar in terms of PFS; HR:1.04 (95% CI: 0.73, 1.46), 1.07 (95% CI:0.75, 1.54), 1.04 (95% CI:0.71, 1.52) for Palbociclib vs Ribociclib, Palbociclib vs Abemaciclib, and Ribociclib vs Abemaciclib, respectively. Objective Response Rate (ORR) • No significant different among the three comparisons; RR:0.82 (95% CI:0.6, 1.09), 0.87 (95% CI: 0.63, 1.19), and 1.06 (95% CI: 0.77, 1.47) for Palbociclib vs Ribociclib, Palbociclib vs Abemaciclib, and Ribociclib vs Abemaciclib, respectively. <u>Safety</u> • No difference among CDK 4/6 inhibitors were found except less incidence of G3-4 diarrhoea with palbociclib compared with abemaciclib [RR:0.13, (95% CI:0.02,0.92)], and reduced risk of QTcF prolongation with palbociclib compared to ribociclib	

Evidence Table : Efficacy and Safety
Question : Is targeted therapies in combination with hormonal therapy effective and safe as a first-line treatment for HR+ , HER-, Metastatic Breast Cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							[RR:0.02, (95% CI:0,0.15)]. • Palbociclib and ribociclib, in combination letrozole demonstrated similar time to deterioration in quality of life (HR:0.94; 95% CI:0.72, 1.24; p=0.73). Author's conclusion: Based on PFS and ORR results of this indirect meta-analysis, palbociclib, ribociclib, and abemaciclib are equally effective in first line treatment for HR+ HER2- metastatic breast cancer.	

Evidence Table : Efficacy and Safety
Question : Is targeted therapies in combination with hormonal therapy effective and safe as a first-line treatment for HR+ , HER-, Metastatic Breast Cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Beck JT, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane as first-line therapy in HR$^+$, HER2$^-$ advanced breast cancer in BOLERO-2. Breast Cancer Res Treat. 2014;143(3):459-467. US	Randomized Control Trial Objective: To evaluate the safety, efficacy and health-related quality of life (HRQoL) effects of everolimus plus exemestene in the subgroup of patients in the BOLERO-2 trials who received this regimen as first-line treatment for advanced breast cancer. Method: The BOLERO-2 trial is a phase III, multicenter, randomized, double blind, placebo controlled trial. Between June 2009 and January 2011, 724 post-menopausal women with HR+, HER2- advanced or metastatic breast cancer recurring or progressing during or after letrozole or anastrozole were randomized at a 2:1 ratio to receive either everolimus (10mg/day) + exemestene 25mg/day) or placebo + exemestene (25mg/day). The primary endpoint was PFS.	II-1	n=724 Post-menopausal women with HR+, HER2- advanced or metastatic breast cancer Treatment group, n=485 Control group, n=239	everolimus (10mg/day) + exemestene (25mg/day)	placebo + exemestene 25mg/day)	18 months	<u>Effectiveness</u> • Overall, 19% of patients (137 of 724) entered the trial having received neo-adjuvant therapy as their last systemic treatment before study entry. • These patients received treatment (100 of 485) or control (37 of 239) as first-line treatment for advanced breast cancer. • The efficacy data from this subset were consistent with outcomes in the overall trial population. Median PFS by local investigator assessment nearly tripled to 11.5 months with everolimus + exemestene from 4.1 months with placebo + exemestene (hazard ratio = 0.39; 95 % CI 0.25–0.62). This was confirmed by central assessment (15.2 vs 4.2 months; hazard ratio = 0.32; 95 % CI 0.18–0.57). • Baseline mean Global Health Status was similar between treatment arms (62.8 vs 63.4). Median time to definitive deterioration (TDD) was longer with treatment group (11.1 vs 7.2 months; hazard ratio = 0.69; 95% CI 0.39–1.22). <u>Safety</u> • Most reported AE with treatment group were stomatitis (68%), diarrhoea (40%), and rash (37%). • Most common AE of grade 3 or 4 intensity in treatment group were hyperglycemia (8%), stomatitis (4%), diarrhoea (4%) and fatigue (3%). • Treatment discontinuation due to AE was slightly higher in treatment group (10%) compared to control group (8%).	

Evidence Table : Efficacy and Safety
Question : Is targeted therapies in combination with hormonal therapy effective and safe as a first-line treatment for HR+ , HER-, Metastatic Breast Cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							• Dose reductions or interruptions were higher in treatment group (74% patients had everolimus dose reduction) compared to control group (32% had placebo dose reduction). Author's conclusion: The marked PFS improvement in patients receiving everolimus plus exemestene as first-line therapy for disease recurrence during or after neo-adjuvant therapy supports the efficacy of this combination in the first-line setting. Furthermore, the results highlight the potential benefit ofearly introduction of everolimus plus exemestene in the management of HR+, HER2- advanced breast cancer in post-menopausal patients.	

Evidence Table : Efficacy and Safety
Question : Is targeted therapies in combination with hormonal therapy effective and safe as a first-line treatment for HR+ , HER-, Metastatic Breast Cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
5. Li J, Huo X, Zhao F, et al. Association of Cyclin-Dependent Kinases 4 and 6 Inhibitors With Survival in Patients With Hormone Receptor-Positive Metastatic Breast Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(10):e2020312.	Systematic review and meta-analysis Objective: To evaluate the association of CDK 4/6 inhibitors plus AI, compared with AI alone, with overall survival (OS) in patients with HR+, HER2-, metastatic breast cancer. Method: Pubmed, Embase and few other databases were searched up to March 2020. The searched focus on phase II or III RCT that reported survival outcome and PFS in patients who received CDK 4/6 inhibitors plus AI for HR+, HER2- metastatic breast cancer.	I	N=2539 PALOMA-1 MONALEESA-2 MONALEESA-7	CDK 4/6 inhibitors and NSAI PALOMA-1: Palbociclib 125mg/day + letrozole 2.5mg/day MONALEESA-2&7: Ribociclib 600mg/day + letrozole 2.5mg/day	NSAI alone letrozole 2.5mg/day letrozole 2.5mg/day		<u>Overall Survival (OS)</u> • Compared to AI alone, CDK 4/6 inhibitors plus AI was associated with significant improvement in OS in the first-line setting (HR: 1.35; 95% CI: 1.18, 1.54; p<0.01), with low heterogeneity across studies (I^2=0%, p=0.99).	

Evidence Table : Efficacy and Safety
Question : Is targeted therapies in combination with hormonal therapy effective and safe as a first-line treatment for HR+ , HER-, Metastatic Breast Cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
6. Ramos-Esquivel A, Hernández-Steller H, Savard MF et al. 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. 2018;25(4):479-488. US	Systematic review and meta-analysis Objective: To compare the efficacy and toxicity of the combination of cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors and nonsteroidal aromatase inhibitors (AI) versus AI alone as first-line therapy for patients with metastatic hormone receptor positive breast cancer. Method: MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trial were searched from October 2007 up to October 2017. The searched focus on phase III RCT that reported the comparison of CDK 4/6 inhibitors plus hormonal treatment alone as first-line therapy in metastatic HR+, HER2- breast cancer.	I	n=1106 post-menopausal women with HR+, HER2- breast cancer	CDK 4/6 inhibitors and NSAI PALOMA-2: Palbociclib 125mg/day + letrozole 2.5mg/day MONALEESA-2: Ribociclib 600mg/day + letrozole 2.5mg/day MONARCH -3: Abemaciclib 150mg BD + anastrozle 1mg/day or letrozole 2.5mg/day	NSAI alone letrozole 2.5mg/day letrozole 2.5mg/day anastrozle 1mg/day or letrozole 2.5mg/day	-	<u>Safety</u> • The odds of having any grade 3 or 4 treatment-related side effect were significantly higher in patients receiving the experimental combination (Mantel–Haenszel OR: 7.51;95% CI 6.01,9.38) • The most common all-grade toxicity was neutropaenia ranging from 66.5% (palbociclib) to 21.1% (abemaciclib), followed by leukopaenia and anaemia. The rates of febrile neutropaenia were low, ranging from 1.8% (palbociclib) to 0.3% (abemaciclib).	Evidence on effectiveness is Included in NMA by Rossi et al.

Evidence Table : Cost-effectiveness
Question : Is targeted therapies in combination with hormonal therapy cost-effective as a first-line treatment for HR+, HER-, metastatic breast cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Mamiya H, Tahara RK, Tolaney SM, et al. Cost-effectiveness of palbociclib in hormone receptor-positive advanced breast cancer. Ann Oncol. 2017 Aug 1;28(8):1825-1831. US	Cost-effectiveness analysis Objective: To assess the cost-effectiveness of adding palbociclib to usual care in treatment of advanced breast cancer. Method: A discrete event simulation (DES) model was developed to simulate time to cancer progression and to compare lifetime clinical benefit and cost of alternative treatment strategies for patients with metastatic disease from societal perspective. Endocrine treatment naive patients were assigned to palbocicli+ letrozole or letrozole alone. Drug cost was obtained from Micromedex® RED BOOK. Estimated costs for one-month treatment of Palbociclib and letrozole alone were $9850 and $655, respectively. All costs and QALYs were discounted at a 3% annual rate.		Hypothetical cohort of 10,000 patients with baseline characteristic similar to those observed in PALOMA 1 & 3	Palbociclib (125mg orally for 21 days, followed by 1-week off) plus Letrozole (2.5mg orally daily for 28 days)	Letrozole (2.5mg orally daily for 28 days)	Time horizon: Lifetime	• For patients who received letrozole alone, the average quality-adjusted life expectancy was 1.82 QALYs, with an average lifetime expenditure of USD 128,435. • For patients who received palbociclib+letrozole, the average quality-adjusted life expectancy was 2.13 QALYs, with an average lifetime expenditure of USD 372,761. • Therefore, compared to letrozole alone, Palbociclib+letrozole resulted in an ICER of USD 768,498 per additional QALY gained. • Sensitivity analyses demonstrated adding palbociclib has a 0% chance of being cost-effectiveness at a willingness-to-pay threshold of USD 100 000 per QALY. • At a 75% discount, Palbociclib+letrozle has a 26% probability of being cost-effective. Author's conclusion: From a societal perspective, palbociclib is highly unlikely to be cost-effective compared with the usual care in the US.	Societal perspective

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Question : Is targeted therapies in combination with hormonal therapy cost-effective as a first-line treatment for HR+, HER-, metastatic breast cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Raphael J, Helou J, Pritchard KI, et al. Palbociclib in hormone receptor positive advanced breast cancer: A cost-utility analysis. Eur J Cancer. 2017;85:146-154. Canada	Cost-utility analysis Objective: To assess the cost-utility of Palbociclib from the Canadian healthcare perspective. Method: A discrete event simulation (DES) model was developed by using data from PALOMA-1 and 2 trials. Two strategies were compared; Palbociclib plus letrozole versus letrozole alone. A time horizon of 15 years was used in the base case with costs and effectiveness discounted at 5% annually. The incremental cost per quality-adjusted life-month (QALM) was calculated. Utility costs estimated for each healthcare state were derived from published literature. Drug costs were obtained from Pan-Canadian Oncology Drug Review.		PALOMA-1 & 2 Costs: Palbociclib (28 days course)-Canadian Dollars $6250 Letrozole (28 days course)-Canadian Dollars $38.58	Palbociclib (125mg orally for 21 days, followed by 1-week off) plus Letrozole (2.5mg orally daily for 28 days)	Letrozole (2.5mg orally daily for 28 days)	Time horizon: 15 years	• Average costs for palbociclib+letrozole (CAD 383,858) were higher compared to letrozle alone (CAD 222,350). • Palbociclib+letrozole had a higher effectiveness (41.25 QALMs) compared to letrozle alone (26.47 QALMs) • The addition of Palbociclib provided an additional 14.7 QALMs at an incremental cost of CAD 161,508. The resulting ICER was CAD 10,999 per additional QALM gained. • Assuming a WTP threshold of CAD 4167 per QALM, the probability of Palbociclib to be cost-effective were 0%. • Sensitivity analysis showed that a WTP threshold of CAD 11,000 per QALM, the probability of Palbociclib to be cost-effective were 50%. Author's conclusion: The addition of palbociclib to letrozle is unlikely to be cost-effective for the treatment of METASTATIC BREAST CANCER from a Canadian healthcare perspective with its current price.	Canadian Healthcare perspective

Evidence Table : Cost-effectiveness
Question : Is targeted therapies in combination with hormonal therapy cost-effective as a first-line treatment for HR+, HER-, metastatic breast cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Matter-Walstra K, Ruhstaller T, Klingbiel D, et. al. Palbociclib as a first-line treatment in ooestrogen receptor-positive, HER2-negative, advanced breast cancer not cost-effective with current pricing: a health economic analysis of the Swiss Group for Clinical Cancer Research (SAKK). Breast Cancer Res Treat. 2016;158(1):51-57. (Update) Matter-Walstra K, Schwenkglenks M, Dedes KJ. Cost-effectiveness of palbociclib plus letrozole versus letrozole alone as a first-line treatment in women with ooestrogen receptor-positive, HER2-negative,	Cost-effectiveness analysis Objective: To examine the cost-effectiveness of combined palbociclib and letrozole from the Swiss healthcare system perspective. Method: A Markov model simulation was developed using data from PALOMA-1. The model consists of three states; progressive-free disease (PF), progressive disease (PD) and death. A lifetime horizon was adopted to capture related costs and outcomes. Drug cost was obtained from current Swiss price (letrozole) and USA price (palbociclib). All costs and QALYs were discounted at a 3% and 6% annual rate.		PALOMA-1	Palbociclib (125mg orally for 21 days, followed by 1-week off) plus Letrozole (2.5mg orally daily for 28 days)	Letrozole (2.5mg orally daily for 28 days)	Time horizon: Lifetime	• Palbociclib+letrozole had a higher effectiveness (3.33 QALYs) compared to letrozle alone (2.19 QALYs) • The addition of Palbociclib provided an additional 1.14 QALYs at an incremental cost of CHF156,251. The resulting ICER was CHF137,063 per additional QALY gained. • At discount rate of 3% and 6%, the ICER increases to CHF143,585 and CHF150,341 per QALY gained, respectively. • Assuming a WTP threshold of CHF100,000 per QALY, the probability of Palbociclib to be cost-effective were 19%. Author's conclusion: Palbociclib+ letrozole cannot be considered cost-effective for the first-line treatment of patients with metastatic breast cancer in the Swiss healthcare system.	Swiss healthcare system perspective

Evidence Table : Cost-effectiveness
Question : Is targeted therapies in combination with hormonal therapy cost-effective as a first-line treatment for HR+, HER-, metastatic breast cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
advanced breast cancer. Revised results for the Swiss health care setting. Breast Cancer Res Treat. 2017;163(3):635. Switzerland								

Evidence Table : Cost-effectiveness
Question : Is targeted therapies in combination with hormonal therapy cost-effective as a first-line treatment for HR+, HER-, metastatic breast cancer?

<table>
<tr><th>Bibliographic citation</th><th>Study Type / Methodology</th><th>LE</th><th>Number of patients and patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow up (if applicable)</th><th>Outcome measures/ Effect size</th><th>General comments</th></tr>
<tr>
<td>4. 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(3):775-779.

US</td>
<td>Cost-effectiveness analysis

Objective:
To evaluate the cost-effectiveness of palbociclib or ribociclib for the treatment of advanced HR+, HER2- metastatic breast cancer in the United States.

Method:
A Markov model simulation was developed using data from published clinical trials evaluating palbociclib (PALOMA-1) and ribociclib (MONALEESA-2). Three simulated treatments strategies included were palbociclib+letrozole, ribociclib+letrozole and letrozole alone. The model consists of three states; progressive-free disease (PF), progressive disease (PD) and death. The main outcomes were simulated PFS, OS, quality-adjusted life-years (QALY), and incremental cost-effectiveness ratio (ICER). ICER was compared against a willingness-to-pay threshold of $100,000 per QALY gained.

Drug costs were obtained from Micromedex® RED BOOK. Estimated costs for one-month treatment of palbociclib, ribociclib, and letrozole alone were USD13,155, USD 13,140, and USD 544, respectively. All costs and QALYs were discounted at a 3% annual rate.</td>
<td></td>
<td>PALOMA-1

MONALEESA-2</td>
<td>Palbociclib (125mg orally for 21 days, followed by 1-week off) plus Letrozole (2.5mg orally daily for 28 days)

Ribociclib (600mg orally for 21 days, followed by 1-week off) plus Letrozole (2.5mg orally daily for 28 days)</td>
<td>Letrozole (2.5mg orally daily for 28 days)</td>
<td>Time horizon: Lifetime</td>
<td>• Simulated median OS was 38.9 months for palbociclib+letrozole and 33.0 months for letrozole alone. Simulated median OS for ribociclib+letrozole was 43.3 months.
• The average lifetime costs for each treatment were describe below:

<table>
<tr><th>Treatment</th><th>Average lifetime costs (USD)</th><th>QALYs</th></tr>
<tr><td>Letrozole alone</td><td>170,289</td><td>2.08</td></tr>
<tr><td>Palbociclib+ Letrozole</td><td>475,339</td><td>2.56</td></tr>
<tr><td>Ribociclib+Letrozole</td><td>549,164</td><td>2.94</td></tr>
</table>

• Compared to letrozole alone, treatment with palbociclib+letrozole resulted in additional 0.48 QALYs, on average, with an ICER of USD 634,000 per QALY gained; while ribociclib+letrozole resulted in additional 0.86 QALYs, on average, with an ICER of USD 440,000 per QALY gained.
• At current prices, neither palbociclib nor ribociclib was cost-effective, assuming a willingness-to-pay threshold of USD 100,000 per QALY gained.
• To reach such a cost-effectiveness threshold, palbociclib and ribociclib prices must decrease by approximately 70%.

Author's conclusion:
The addition of palbociclib or ribociclib in the treatment of HR+, HER2- metastatic breast cancer is not cost-effective in the US given current drug prices.</td>
<td></td>
</tr>
</table>

Evidence Table : Cost-effectiveness
Question : Is targeted therapies in combination with hormonal therapy cost-effective as a first-line treatment for HR+, HER-, metastatic breast cancer?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
5. Mistry R, May JR, Suri G, et al. Cost-Effectiveness of Ribociclib plus Letrozole Versus Palbociclib plus Letrozole and Letrozole Monotherapy in the First-Line Treatment of Postmenopausal Women with HR+/HER2- Advanced or Metastatic Breast Cancer: A U.S. Payer Perspective. J Manag Care Spec Pharm. 2018;24(6):514-523. United States	Cost-effectiveness analysis Objective: To evaluate the cost-effectiveness of ribociclib plus letrozole versus palbociclib plus letrozole and versus letrozole monotherapy in the first-line treatment of postmenopausal women with HR+/HER2- advanced or metastatic breast cancer from a U.S. private third-party payer perspective. Method: A partitioned survival model was developed from published clinical trials evaluating palbociclib (PALOMA-1), ribociclib (MONALEESA-2), and Bayesian network meta-analysis. The model, which consists of three states; progressive-free disease (PF), progressive disease (PD) and death, simulated lifetime costs and outcomes over a 40-year lifetime horizon with a 1-month cycle length. Health care costs included drug acquisition and monitoring, disease management, subsequent therapies, and serious drug-related adverse events.		PALOMA-1 MONALEESA-2	Palbociclib (125mg orally for 21 days, followed by 1-week off) plus Letrozole (2.5mg orally daily for 28 days) Ribociclib (600mg orally for 21 days, followed by 1-week off) plus Letrozole (2.5mg orally daily for 28 days)	Letrozole (2.5mg orally daily for 28 days)	Time horizon: 40 years	• All treatment cost were describe below: Treatment / Average lifetime costs (USD) / QALYs Letrozole alone: 287,180 / 2.38 Palbociclib+ Letrozole: 475,132 / 2.99 Ribociclib+L etrozole: 432,095 / 3.07 • Compared to palbociclib+letrozole, treatment with ribociclib+letrozole was associated with a cost reduction of 43,037 and 0.086 QALYs gained. • When compared to letrozole alone, ribociclib+letrozole were associated with a cost reduction of USD 144,915 at an incremental QALY of 0.689, equating to an ICER of USD 210,369 per additional QALY gained. • Sensitivity analysis demonstrated the probabilities of ribociclib+letrozole being cost-effective vs letrozole alone at WTP threshold of USD 50,000, USD 100,000 and USD 200,000 per QALY gained were 1.6%, 6.3% and 50.5%, respectively. Author's conclusion: In the United States, ribociclib+ letrozole is a cost-effective alternative to palbociclib+ letrozole for the first-line treatment of postmenopausal women with HR+/HER2- advanced or metastatic breast cancer. Ribociclib+letrozole is also cost-effective	US Payer perspective

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<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>versus letrozole monotherapy at WTP thresholds greater than USD 198,000 per QALY.</td><td></td></tr>
<tr><td>6. Galve-Calvo E, González-Haba E, et al. Cost-effectiveness analysis of ribociclib versus palbociclib in the first-line treatment of HR+/HER2- advanced or metastatic breast cancer in Spain. Clinicoecon Outcomes Res. 2018;10:773-790.

Spain</td><td>Cost-effectiveness study

Objective:
To evaluate the cost-effectiveness of ribociclib compared to palbociclib, both in combination with letrozole, in the first-line treatment of postmenopausal women with HR+, HER2- metastatic breast cancer from the perspective of the Spanish National Health System (NHS).

Method:
A partitioned survival model was developed from published clinical trials evaluating palbociclib (PALOMA-1) and ribociclib (MONALEESA-2). The model, consists of three states; progressive-free disease (PF), progressive disease (PD) and death. The Spanish NHS perspective was adopted, taking into account exclusively direct health costs from 2017 expressed in Euros. Drug prices used were the reported ex-factory prices.</td><td></td><td>PALOMA-1
MONALEESA-2</td><td>Palbociclib (125mg orally for 21 days, followed by 1-week off) plus Letrozole (2.5mg orally daily for 28 days)

Ribociclib (600mg orally for 21 days, followed by 1-week off) plus Letrozole (2.5mg orally daily for 28 days)</td><td>Letrozole (2.5mg orally daily for 28 days)</td><td>Time horizon: 15 years</td><td>• The treatment costs as below:
<table>
<tr><th>Treatment</th><th>Average costs (EUR)</th><th>QALYs</th></tr>
<tr><td>Palbociclib+ Letrozole</td><td>91,895</td><td>3.028</td></tr>
<tr><td>Ribociclib+Letrozole</td><td>90,923</td><td>3.313</td></tr>
</table>
• Compared to palbociclib+letrozole, treatment with ribociclib+letrozole was associated with an incremental cost of EUR 439.86 together with incremental life-years (LYs) gained of 0.437 and 0.285 QALY.
• The resulting ICER and ICUR were EUR 1,007.69 per LY gained and EUR 1,543.62 per QALY gained, respectively.
• Considering WTP threshold of EUR 20,000 to 30,000/QALY gained, ribociclib+letrozole would be a cost-effective treatment option compared to palbociclib+letrozole.
• The results of the multiple sensitivity analyses showed limited dispersion of the outcomes, thus corroborating their robustness.

Author's conclusion:
From the NHS perspective, considering the most commonly established WTP thresholds in the Spanish setting, ribociclib+letrozole would represent a cost-effective therapeutic option compared to palbociclib+letrozole in the first-line treatment of HR+, HER2- metastatic</td><td>Spanish National Health System's perspective</td></tr>
</table>

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							breast cancer in postmenopausal women.	
7. Mistry R, Suri G, Young K, et al. Budget impact of including ribociclib in combination with letrozole on US payer formulary: first-line treatment of post-menopausal women with HR+/HER2- advanced or metastatic breast cancer. Curr Med Res Opin. 2018;34(12):2143-2150. US	Budget Impact Analysis Objectives: To evaluate the budget impact of using the ribociclib plus letrozole as a first-line treatment option for postmenopausal women with HR+, HER2- metastatic breast cancer, from a United States (US) payer perspective. Method: A cohort-based budget impact model was used to calculate the incremental cost of introducing ribociclib plus letrozole over three years for the target population. The model compared two scenarios: treatment options excluding or including ribociclib plus letrozole. Market shares were derived from market research and the assumption was the introduction of ribociclib plus letrozole would only displace existing CDK 4/6-based therapies. Acquisition costs were based on wholesale acquisition costs and considered co-payment. Costs for drug administration and monitoring, subsequent therapy, and relevant adverse events were included.		Hypothetical cohort of 1,000,000 health plan member	Ribociclib (600mg orally for 21 days, followed by 1-week off) plus Letrozole (2.5mg orally daily for 28 days)	Letrozole (2.5mg orally daily for 28 days)	3 years	• Of 1 million insured members, 263 were eligible for CDK 4/6 inhibitor treatment. • Cumulative total savings with ribociclib plus letrozole were USD 3.01M over three years, attributing to reduced costs (drug acquisition, USD 2.72M; subsequent therapy, USD 96K; AEs, USD 82K). • Savings per year increased over the time horizon with increased market share of ribociclib: USD 125K, USD 1.04M, and USD 1.85M in Years 1-3, respectively. • The introduction of ribociclib yielding a cumulative incremental cost saving of USD 318.11 per member treated per month. Author's conclusion: In the US, ribociclib plus letrozole represents a cost-saving first-line treatment option for postmenopausal women with HR+, HER2 metastatic breast cancer.	

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8. Diaby V, Adunlin G, Zeichner SB, et.al. Cost-effectiveness analysis of everolimus plus exemestane versus exemestane alone for treatment of hormone receptor positive metastatic breast cancer. Breast Cancer Res Treat. 2014;147(2):433-41. US	Cost-effectiveness analysis Objective: To determine the cost-effectiveness of everolimus+exemestane compared to exemestane alone in postmenopausal women with HR+, HER2- metastatic breast cancer. Method: A Markov model simulation was developed using data from BOLERO-2. The model consists of three states; stable (progressive-free) without adverse events, stable with adverse events, and progression. A time horizon of 120 weeks (final progressive-free analysis of BOLERO-2) was adopted. Costs were obtained from Medicare Services drug payment table and physician fee schedule. Benefits were expressed as quality-adjusted progression-free survival weeks (QAPFW) and quality-adjusted progression-free years (QAPFY), with utilities/disutilities derived from the literature. A WTP threshold between USD 49,965 and USD 149,895 was considered based on US per capita GDP in 2013.		BOLERO-2	Everolimus (10mg daily for 6 weeks) plus Exemestane (25mg daily for 6 weeks)	Exemestane (25mg daily for 6 weeks)	Time horizon: 120 weeks (2.5 years)	• The total cost for everolimus+exemestane (USD 63,584) was higher than exemestane alone (USD 3,010). • When compared to exemestane alone, everolimus+exemestane had an incremental benefit of 11.88 QAPFW (0.22 QAPFY) and an incremental cost of USD 60,574. This translated into an ICER of USD 265,498/QAPFY. - Univariate sensitivity analyses showed important variations of the ICER, ranging between USD 189,836 and USD 530,947/QAPFY. Author's conclusion: Everolimus+exemestane is not cost-effective compared to exemestane alone. Further research is needed to investigate the cost-effectiveness of the drug combination within sub-groups of the population studied in BOLERO-2.	

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e ISBN 978-967-2887-03-4