TARGETED THERAPIES IN COMBINATION WITH HORMONAL THERAPY AS A FIRST-LINE TREATMENT FOR HR+ AND HER2- METASTATIC BREAST CANCER
EXECUTIVE SUMMARY
(Adapted from the report by BALQIS ABDUL GHANI)

Authors:
Balqis Abdul Ghani
Atikah Shaharudin
Dr. Izzuna Mudla Mohamed Ghazali

External Reviewer:
Dr (Ms) Nor Aina binti Emran
Head of Breast & Endocrine Surgery, MOH

Dr Ros Suzanna binti Ahmad Bustamam
Head of Radiotheraphy & Oncology, MOH

For further information, please contact:

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590 Putrajaya.

htamalaysia@moh.gov.my
Tel: 603 8883 1229

Available at the following website:
http://www.moh.gov.my

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Background
Breast cancer is the most frequently diagnosed cancer worldwide, and it is the leading cause of cancer-related death among women. 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
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.

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.

Results and conclusion:

Effectiveness
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.

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.

Economic implication

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.