Technology Guidance

Review of cancer drugs

for treating early or advanced HER2-positive breast cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended listing pertuzumab, pertuzumab plus trastuzumab fixed-dose subcutaneous (SC) injection, trastuzumab emtansine or tucatinib on the Medication Assistance Fund (MAF) for treating human epidermal growth factor receptor (HER2)-positive breast cancer due to unfavourable cost-effectiveness at the prices proposed by the manufacturer.

Clinical indications, subsidy class and MediShield Life claim limits for all drugs included in the evaluation are provided in the Annex.

Updated: 1 September 2023

Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of HER2-targeted therapies (pertuzumab, pertuzumab plus trastuzumab fixed dose SC injection, trastuzumab emtansine and tucatinib) for treating HER2-positive breast cancer. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for all drugs was considered in line with their registered indications. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE ascertain the clinical value of the drugs under evaluation and provided clinical advice on their appropriate and effective use based on the available clinical evidence.

1.2. The use of neratinib for extended adjuvant treatment of adults with early stage HER2-positive breast cancer was outside the scope of the evaluation following advice from local clinical experts and ODS members that there was currently no clinical need for this indication to be evaluated.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1. The Committee noted that approximately 480 patients are diagnosed with HER2-positive breast cancer each year in Singapore. While trastuzumab biosimilar is already on the Standard Drug List and used as routine first-line treatment for patients with HER2-positive breast cancer, the Committee agreed that there was a clinical need to consider other HER2-targeted therapies for subsidy to improve treatment affordability and ensure appropriate patient care.

2.2. HER2-positive early breast cancer (EBC)

The Committee noted that in local practice, pertuzumab in combination with trastuzumab is generally given in the neoadjuvant setting before surgery for three to six cycles, depending on the concurrent chemotherapy regimen administered. After surgery, trastuzumab with or without pertuzumab is continued as adjuvant treatment to complete one year of anti-HER2 blockade. Patients with residual disease after surgery usually receive trastuzumab emtansine monotherapy instead, up to a maximum of 14 cycles. The Committee acknowledged that the role of pertuzumab in the adjuvant setting was less clear given the shift towards treating high-risk patients in the neoadjuvant setting and the lack of data for adjuvant pertuzumab following neoadjuvant treatment.

2.3. HER2-positive advanced breast cancer (ABC)

The Committee heard that pertuzumab in combination with trastuzumab and a taxane is used locally for previously untreated ABC, in line with international clinical practice guidelines. However, there is no standard regimen recommended following disease progression on first-line therapy. Most patients receive trastuzumab emtansine monotherapy, while the remaining patients receive trastuzumab plus chemotherapy or lapatinib plus capecitabine.

2.4. The Committee noted that up to 50% of patients with HER2-positive ABC develop brain metastases and generally have very poor prognosis due to a lack of effective treatment options. Local clinicians confirmed that tucatinib could be considered for these patients after prior treatment with pertuzumab plus trastuzumab combination, in line with international clinical practice guidelines.

Clinical effectiveness and safety

3.1. HER2-positive EBC

Neoadjuvant setting

The Committee reviewed the available clinical evidence for pertuzumab used in the neoadjuvant setting from three phase II studies (NeoSphere, TRYPHAENA, BERENICE) and a phase III randomised controlled trial (RCT) conducted in Asia (PEONY). Compared with placebo or standard of care, pertuzumab consistently led to statistically significant higher pathological complete response (pCR) rates. The Committee heard that the studies were not designed to show survival outcomes, and the role of pCR as a surrogate endpoint for overall survival (OS) had not been definitively demonstrated.

3.2. *Adjuvant setting*

The Committee reviewed the available clinical evidence for HER2-targeted therapies used in the adjuvant setting. They noted that all patients receiving pertuzumab (APHINITY) had not had neoadjuvant therapy, whereas patients receiving trastuzumab emtansine (KATHERINE) had residual invasive disease after

neoadjuvant therapy. Adjuvant use of pertuzumab and trastuzumab emtansine led to statistically significant improvements in invasive disease-free survival (iDFS) at 6 years and 3 years respectively, compared to placebo and adjuvant trastuzumab. However, the Committee considered the magnitude of absolute benefit was modest for pertuzumab in both the intention-to-treat population (2.8%) and for lymph node positive patients (4.5%) and was unlikely to be clinically meaningful.

3.3. In the absence of mature OS data, the Committee recognised that the extent to which iDFS translates into a long-term OS benefit was unknown. They noted that further OS analyses were planned for pertuzumab and trastuzumab emtansine in 2022 and 2023, respectively.

3.4. Previously untreated HER2-positive ABC

Based on the available clinical evidence (CLEOPATRA), the Committee acknowledged that adding pertuzumab to trastuzumab and docetaxel led to statistically longer progression-free survival (PFS) and OS compared to trastuzumab and docetaxel alone for patients with previously untreated HER2-positive ABC.

3.5. Previously treated HER2-positive ABC

The Committee reviewed the available clinical evidence (EMILIA) comparing trastuzumab emtansine with capecitabine plus lapatinib in patients with HER2-positive ABC, whose disease had progressed on pertuzumab plus trastuzumab and taxane combination treatment. While acknowledging that trastuzumab emtansine resulted in significantly longer PFS and OS, the Committee noted that only 9.5% of patients in EMILIA had received prior pertuzumab, which was too small to determine its treatment effect in patients whose disease had progressed following pertuzumab. The Committee further noted the clinical benefits of trastuzumab emtansine observed in EMILIA were supported by the TH3RESA trial that evaluated its use versus physician's choice treatment in a more heavily treated (3rd line or greater) population.

3.6. The Committee reviewed the available clinical evidence for tucatinib from a double-blind, randomised controlled trial (HER2CLIMB) in patients with HER2-positive ABC previously treated with trastuzumab, pertuzumab and trastuzumab emtansine. Approximately 50% of patients in the trial had brain metastases. After a median follow-up of 14.0 months, the addition of tucatinib to trastuzumab plus capecitabine led to statistically significant improvements in PFS and OS compared to trastuzumab plus capecitabine alone. Subgroup analyses of patients with brain metastases also showed consistent results with statistically significant improvements in PFS and OS.

3.7. Pertuzumab plus trastuzumab fixed-dose SC injection

The Committee reviewed the available evidence for pertuzumab plus trastuzumab fixed-dose SC injection from a phase III, open-label, non-inferiority trial (FeDeriCA) conducted in patients with EBC (neoadjuvant-adjuvant setting). They noted that the fixed-dose combination was non-inferior to intravenous infusions of pertuzumab and trastuzumab on basis of pharmacokinetic endpoints, with similar pCR rates between treatment groups.

3.8. Overall, the Committee agreed that HER2-targeted therapies were generally tolerable in the trials.

Cost effectiveness

4.1. The manufacturers of all drugs under evaluation were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration.

4.2. HER2-positive EBC

Neoadjuvant setting

In the absence of local cost-effectiveness evaluations, the Committee reviewed results from overseas reference HTA agencies for the use of pertuzumab in the neoadjuvant setting and agreed that there was high uncertainty associated with cost-effectiveness estimates because they relied on the clinical assumption that an absolute increase in the rate of pCR could lead to improvement in OS, which has not been definitively proven.

4.3. *Adjuvant setting*

Based on overseas cost-effectiveness analyses, the Committee noted that the cost-effectiveness of pertuzumab or trastuzumab emtansine in the adjuvant setting remained uncertain given there were no statistically significant OS benefits demonstrated in their respective trials.

4.4. Previously untreated HER2-positive ABC

The Committee considered an analysis conducted by ACE which assessed the cost-effectiveness of adding pertuzumab to trastuzumab biosimilar and docetaxel in patients with previously untreated HER2-positive ABC. They noted that the base-case incremental cost-effectiveness ratio (ICER) was more than SG$105,000 per quality adjusted life year (QALY) gained, and was sensitive to the price of pertuzumab used in the model. Based on the analyses, the Committee considered that pertuzumab did not represent a cost-effective use of healthcare resources for previously untreated HER2-positive ABC at the price proposed by the manufacturer.

4.5. Previously treated HER2-positive ABC

The Committee reviewed the cost-effectiveness analyses submitted to overseas HTA agencies for trastuzumab emtansine, and noted that in most instances, it was only considered cost-effective contingent on commercial discounts or with risk-share arrangements in place. The Committee noted that the price proposed by the manufacturer was higher than in overseas reference jurisdictions, therefore, it was unlikely that trastuzumab emtansine would be cost-effective in the local setting.

4.6. The Committee considered an analysis conducted by ACE which assessed the cost-effectiveness of adding tucatinib to trastuzumab biosimilar and capecitabine in patients who have received one or more prior anti-HER2-based regimens for ABC. The Committee noted that the base-case ICER was more than SG$105,000 per QALY

gained and considered that tucatinib did not represent a cost-effective use of healthcare resources at the price proposed by the manufacturer.

4.6. Pertuzumab plus trastuzumab fixed-dose SC injection

Taking into account the prices of intravenous infusions of pertuzumab and trastuzumab biosimilar, the Committee considered that pertuzumab plus trastuzumab fixed-dose SC injection was unlikely to be cost-effective at the prices proposed by the manufacturer.

Estimated annual technology cost

5.1. Based on local epidemiology rates and estimated drug utilisation in the public healthcare institutions, the Committee noted that the annual cost impact in the first year of listing each drug on the MAF was estimated to be:

HER2-positive EBC

- Pertuzumab (neoadjuvant and adjuvant): between SG$1 million to less than SG$3 million;
- Trastuzumab emtansine (adjuvant): between SG$1 million to less than SG$3 million;

HER-positive ABC

- Pertuzumab: between SG$5 million to less than SG$10 million;
- Trastuzumab emtansine: between SG$3 million to less than SG$5 million; and
- Tucatinib: between SG$3 million to less than SG$5 million.

Additional considerations

6.1. The Committee acknowledged that most patients who receive treatment with pertuzumab, pertuzumab plus trastuzumab fixed-dose SC injection or trastuzumab emtansine are currently able to obtain financial assistance in the public healthcare institutions through the manufacturer-sponsored ARiSE programme that limits the amount that patients have to pay for their treatment each month.

Recommendations

7.1. Based on available evidence, the Committee recommended not listing pertuzumab, pertuzumab plus trastuzumab fixed-dose SC injection, trastuzumab emtansine and tucatinib on the MAF for treating HER2-positive breast cancer due to unfavourable cost-effectiveness at the prices proposed by the manufacturer.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
HER2-positive early breast cancer			
Pertuzumab 420 mg/14 mL concentrate for solution for infusion plus trastuzumab powder for IV infusion (440 mg) or trastuzumab solution for SC injection (600 mg/5 mL)	Pertuzumab in combination with trastuzumab and chemotherapy for neoadjuvant treatment of HER2-positive locally advanced, inflammatory or early stage (tumour >2 cm in diameter or node positive) breast cancer for 4 to 6 cycles. Following surgery, patients may continue with trastuzumab with or without pertuzumab for a total of 1 year of anti-HER2 treatment.	Not recommended for subsidy	$2400 (1 Sep 2022)
Pertuzumab 420 mg/14 mL concentrate for solution for infusion plus trastuzumab powder for IV infusion (440 mg) or trastuzumab solution for SC injection (600 mg/5 mL)	Pertuzumab in combination with trastuzumab and chemotherapy for adjuvant treatment of high-risk (with positive nodes) HER2-positive early breast cancer for a maximum duration of 1 year.	Not recommended for subsidy	$2400 (1 Sep 2022)
Pertuzumab/ trastuzumab 600 mg/600 mg and 1200 mg/600 mg solution for subcutaneous injection	In combination with chemotherapy for neoadjuvant treatment of HER2-positive locally advanced, inflammatory or early stage (tumour >2 cm in diameter or node positive) breast cancer for 4 to 6 cycles. Following surgery, patients may continue with trastuzumab with or without pertuzumab for a total of 1 year of anti-HER2 treatment.	Not recommended for subsidy	$2400 (1 Sep 2022)
Pertuzumab/ trastuzumab 600 mg/600 mg and 1200 mg/600 mg solution for subcutaneous injection	In combination with chemotherapy for adjuvant treatment of high-risk (with positive nodes) HER2-positive early breast cancer for a maximum duration of 1 year.	Not recommended for subsidy	$2400 (1 Sep 2022)
Trastuzumab emtansine 100 mg and 160 mg powder for concentrate for	Adjuvant treatment of HER2-positive early breast cancer in patients with residual invasive disease, after neoadjuvant treatment with trastuzumab and a taxane.	Not recommended for subsidy	$2400 (1 Sep 2022)

infusion solution	Maximum 14 cycles.		
HER2-positive advanced breast cancer			
Pertuzumab 420 mg/14 mL concentrate for solution for infusion plus trastuzumab powder for IV infusion (440 mg) or trastuzumab solution for SC injection (600 mg/5 mL)	Pertuzumab in combination with trastuzumab and chemotherapy for HER2-positive metastatic or locally recurrent breast cancer, in patients without prior treatment for metastatic disease. Treatment with pertuzumab should be stopped if disease progresses.	Not recommended for subsidy	$2400 (1 Sep 2022)
Pertuzumab/ trastuzumab 600 mg/600 mg and 1200 mg/600 mg solution for subcutaneous injection	Fixed-dose pertuzumab and trastuzumab subcutaneous injection in combination with chemotherapy for treating HER2-positive metastatic or locally recurrent breast cancer, in patients without prior treatment for metastatic disease. Treatment with pertuzumab should be stopped if disease progresses.	Not recommended for subsidy	$2400 (1 Sep 2022)
Trastuzumab emtansine 100 mg and 160 mg powder for concentrate for infusion solution	Treatment of HER2-positive, locally advanced, unresectable, or metastatic breast cancer in patients who have received prior treatment with trastuzumab and chemotherapy.	Not recommended for subsidy	$2400 (1 Sep 2022)
Tucatinib 50 mg and 150 mg tablets plus trastuzumab powder for IV infusion (440 mg) or trastuzumab solution for SC injection (600 mg/5 mL)	Treatment of locally advanced unresectable or metastatic HER2-positive breast cancer in combination with trastuzumab and capecitabine in patients who have received one or more prior anti-HER2-based regimens in the metastatic setting.	Not recommended for subsidy	$2400 (1 Sep 2022)

Abbreviations: MAF, Medication Assistance Fund.

VERSION HISTORY

Review of cancer drugs for treating early or advanced HER2-positive breast cancer

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

Publication of guidance

Date of publication 12 July 2022

Guidance updated with the following changes:

- Clinical criteria for pertuzumab plus trastuzumab and fixed dose pertuzumab and trastuzumab (in Annex) revised to replace “combination with a taxane” with “combination with chemotherapy”
- Clinical criteria for trastuzumab emtansine (in Annex) revised to replace “prior treatment with trastuzumab and a taxane” with “prior treatment with trastuzumab and chemotherapy”.

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