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Disparities in Access to Systemic Treatment for Breast Cancer in Thailand and Major Asian Territories

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ABSTRACT

Purpose: Breast cancer (BC) treatment has shifted from chemotherapy to targeted therapy. Several targeted agents have demonstrated an improvement in survival. Given that national healthcare resources were correlated with the cancer mortality-to-incidence ratio, we compared access to BC drugs in Thailand with that in other Asian countries.
Methods: BC experts involved in the Breast International Group (BIG)-Asia in six representative groups for countries or special administrative region (SAR) in Asia (Hong Kong SAR, Japan, Korea, Taiwan, Thailand, and Singapore) were invited to participate in the survey. The questionnaire addressed national health reimbursement schemes, molecular testing for early BC (EBC), availability and accessibility of BC drugs. Accessibility and reimbursement of the drugs were reported based on their listing as essential medicines in the World Health Organization Model List of Essential Medicines (WHO-EML) and their nomination as effective drugs in the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS). The study was approved by all participating BIG-Asia organizations in November 2021.
Results: Genomic tests for EBC were non-reimbursable in all surveyed territories. Reimbursement and co-payment of BC drugs vary between and within these regions (particularly Thailand). Most drugs in the WHO-EML and ESMO-MCBS (A/B for EBC and 4/5 for advanced BC) were accessible in all surveyed territories. However, the accessibility of effective but costly WHO-EML and ESMO-MCBS drugs was not uniform in Thailand. There

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Conflict of Interest

SI received an honorarium from Novartis.

NP received honoraria from Novartis, AstraZeneca, Roche, Pfizer, and Lilly.

SB Kim received research grants from Novartis, Sanofi-Aventis, and DongKook Pharm Co. and served on the advisory boards of Novartis, AstraZeneca, Lilly, Dae Hwa Pharmaceutical Co. Ltd, ISU Abxis, Daiichi-Sankyo, and OBI Pharma. SB Kim owns stocks of Genopeaks and NeogeneTC.

YY received honoraria from AstraZeneca, Eisai, Lilly, Novartis, Pfizer, Roche, MSD, Inivata and Specialised Therapeutics. YY received travel, accommodation, and expenses AstraZeneca, Eisai, Lilly, Novartis, Pfizer, Roche, MSD, Inivata and Specialised Therapeutics.

JT received honorarium from Lilly, Pfizer, Novartis and Roche.

IS and YO have no conflicts of interest.

SO received research grant from Eisai and Taiho. He received honoraria from Chugai, Kyowa Kirin, MSD, Astra Zeneca, Eisai, Daiichi -Sankyo, Eli Lilly, Pfizer, Taiho, and Nipponkayaku. He serves as a consultant to Eli Lilly, Pfizer and MSD.

MO received research grants from Eisai, Astellas and Pfizer. She received honoraria from Pfizer, Eisai and Chugai.

JJ Chan serves as a consultant to Merck Sharp & Dohme, Novartis, GlaxoSmithKline, and AstraZeneca and received honoraria from AstraZeneca, Novartis, and DKSH Singapore. He received research Funding from OncoQuest (inst) and Bristol-Myers Squibb (inst).

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HCS Cheng has no conflicts of interest.

was an evident disparity for individuals covered by the Thai Social Security/Universal Health Coverage schemes.

Conclusion: Essential BC drugs are generally accessible in selected BIG-Asia countries or SAR. There is a disparity in accessing high-cost drugs in Thailand compared with other Asian territories.

Keywords: Antineoplastic Agents; Asians; Breast Neoplasms; Healthcare Disparity; Thailand

INTRODUCTION

The incidence of breast cancer (BC) has been increasing in Asia, and it is presently the most common cancer in Asian women. GLOBOCAN 2020 reported that the incidence of new BCs had exceeded that of lung cancers worldwide [1]. Although the age-standardized incidence rate of BC in Asia is much lower than that in Europe and the USA, the mortality-to-incidence ratio (MIR) in Asia is much higher [2]. The possible reasons for this inconsistency include differences in tumor biology, variations in health system policies, disparities in access to adequate medical care, absence of a screening policy, and cultural barriers [3].

BC treatment has evolved, with a steady shift from traditional chemotherapy to targeted therapy. Many newer targeted agents have shown a significant improvement in survival, both in early-stage and metastatic settings, and these agents have become the standard of care globally. However, access to many of these newer drugs varies between countries or regions, including those in Asia. National healthcare resources are correlated with cancer MIR. Countries with lower incomes have higher cancer MIRs than high-income countries [3]. Thailand, a Southeast Asian nation with a population of nearly 70 million, is currently classified by the World Bank as an upper-middle-income country. In a study by Batouli et al. [3], the MIR for cancer in Thailand was ranked 53rd (MIR, 0.6253). In contrast, the values for high-income countries in Asia, such as Japan, Singapore, South Korea, and Taiwan, were noticeably better, ranging between 0.4087 and 0.5564.

BC is the third most common type of cancer in Thailand. We hypothesized that the higher MIR for cancer in Thailand could be partly attributable to greater inequality in access to BC drugs than in other countries or territories in the region. We also explored the availability of BC drugs based on the World Health Organization Model List of Essential Medicines (WHO-EML) [4] and the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scores. Additionally, this study aimed to identify any unmet needs within representative Asian countries or special administrative region (SAR) to improve their reimbursement policies and, therefore, treatment outcomes.

The current study gathered information on access to BC drugs and healthcare systems in five Asian countries (Japan, Korea, Singapore, Taiwan, and Thailand) and one SAR, namely Hong Kong SAR, which are all involved in Breast International Group (BIG)-Asia. BIG-Asia was established to facilitate the development and performance of Asian-led clinical trials and research projects under the BIG umbrella. BIG-Asia also aims to expand international academic networking in BC care within the BIG framework. This study was one of the initial projects of BIG-Asia.

TD received honoraria from Novartis, Astra Zeneca, Roche, and Zeullig Pharmaceutical Thailand and served on the advisory boards of Novartis, AstraZeneca, Lilly, Eisai, Pfizer, and Merck Sharp & Dohme.

Author Contributions

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METHODS

BC experts involved in BIG-Asia from six representative Asian countries or regions were invited to participate in the survey. The authors also requested the related BIG-Asia organizations to nominate other experts to participate. They should be medical oncologists, clinical oncologists, breast surgical oncologists, or radiation oncologists. The organizations included the Thai Society of Clinical Oncology, Hong Kong Breast Oncology Group, Japan Breast Cancer Research Group, Korean Cancer Study Group, Singapore Cancer Therapeutics Research Group, and Taiwan Cooperative Oncology Group.

The survey form addressed national health reimbursement schemes and availability and accessibility of BC drugs and molecular testing for early breast cancer (EBC). The questionnaire was reviewed and approved by experts from all participating BIG-Asia organizations. The survey consisted of three parts. The first dealt with the territory's healthcare reimbursement system and any national "essential drug list" or equivalent. The second part focused on the availability of commercial BC multigene prognostic tests. The last part assessed the formulary of BC drugs for early and metastatic BC and whether the national healthcare authorities reimbursed these drugs for each indication. After excluding any basic or national health insurance coverage, reimbursement for each drug was classified as "non-reimbursed" (NR), "partially reimbursed" (PR), or "fully reimbursed" (FR). PR was defined as a ≥ 5% or higher co-payment for drug cost, while FR was defined as no drug cost or < 5% co-payment. The availability of original or generic/biosimilar drugs was also explored. Questionnaires and accompanying instructions were distributed to all participants. The responses were analyzed. Discordant responses were reviewed and crosschecked using publicly available online data for the concerned country. The data were refined through consultation with experts from the corresponding countries. The survey results were reviewed at a subsequent BIG-Asia meeting in February 2021, and a consensus was reached. All data were finalized and updated in November 2021.

Drug availability results are tabulated and color-coded. Pale red represents an NR item (fully self-paid), yellow signifies a PR item (partial funding support from the government), and blue denotes an FR item. Each BC drug was correlated with the 21st WHO-EML [4] and ESMO-MCBS [5,6]. A drug was deemed to be of therapeutic value or comparatively cost-effective if it was included in the WHO-EML or classified as ESMO-MCBS A/B or 4/5 in adjuvant and metastatic settings, respectively. We analyzed the comparative accessibility of BC drugs in participating Asian representative cooperative groups using the abovementioned criteria.

RESULTS

There were 20 respondents to the questionnaire. They came from six territories (five countries and one SAR) and comprised 12 medical oncologists, two clinical oncologists, four surgeons, and two radiation oncologists. According to the World Bank's 2020–2021 classification of countries by income level, Thailand is an upper-middle-income country, whereas the five other countries in this study are in the high-income category [7]. **Table 1** summarizes the healthcare reimbursement system for cancer treatment used in each territory. Except for Thailand, the surveyed territories had uniform basic healthcare coverage for cancer drug treatment and a single national cancer drug list or equivalent. Thailand has three national health insurance schemes, with beneficiaries from different sectors. All three Thai schemes allow the use

Table 1. Reimbursement schemes of representative Asian countries

Country/SAR	Reimbursement system	National essential drug list
Thailand	1. SSS: Private employees and the self-employed. 2. UCS: A basic governmental coverage. Items 1 and 2 cover cancer treatment in ED list, with extra coverage for a few non-ED drugs. 3. CSMBS: Expands the coverage to civil servants and their family, including some non-ED treatments.	Yes
Singapore	MediShield Life is a basic, government-administered, health insurance plan that covers cancer treatment. Singaporean individuals have to pay a premium from their Medisave savings to be covered by a compulsory basic health insurance scheme. Subsidies and financial assistance are provided for drugs included in the SDL and MAF. MAF is a financial assistance scheme to help pay for high-cost drugs that are not on the SDL, with co-payment by patients. However, the amount and financial assistance given depend on the household income.	Yes: SDL [8]
Hong Kong SAR	Government coverage for all drugs under the standard formulary. The public hospital drug formulary also includes drugs not under government coverage, i.e., SFI. Financial sponsorship is available for some expensive SFI drugs proportional to the patient's whole family income and assets via a "safety net" (the Samaritan Fund and the Community Care Fund).	Yes: Standard formulary/Generic drugs and special drugs under indicated conditions are considered equivalent to essential drug list [9]
Japan	Universal health insurance system covers 70%–90% of medical costs. Capped payments for higher health expenditure, depending on a policyholder's income.	Yes
Korea	Natural health insurance system covers 95% of anticancer drugs approved by HIRA. Co-payments for drugs on the national insurance list and Positive List Scheme are kept at a maximum of 5% for patients with cancer. Risk sharing agreement is also actively applied for partially reimbursed drugs.	Yes: national insurance list is considered as equivalent to essential drug list
Taiwan	National health insurance covers medical expenses for cancer treatment. Co-payment is < 10% if a citizen has a cancer diagnosis.	Yes

SAR = special administrative region; SSS = Social Security Scheme; UCS = Universal Coverage Scheme; ED = essential drug; CSMBS = Civil Servant Medical Benefit Scheme; SDL = Standard Drug List; MAF = Medication Assistance Fund; SFI = self-financed item; HIRA = Health Insurance Review & Assessment Service.

of drugs in the national list of essential medicines, with expanded benefits for individuals covered by one of the schemes (the Civil Servant Medical Benefit Scheme [CSMBS]). As nearly identical drug accessibility is afforded by the two other Thai schemes (Social Security Scheme [SSS] and Universal Coverage Scheme [UCS]), we combined them into a single category.

Availability and reimbursement of predictive genomic profiling tests for EBC

We surveyed only four comprehensive genomic profiling tests that are currently commercially available: Oncotype Dx®, MammaPrint®, Prosigna®, and EndoPredict®. Three of these tests, except EndoPredict®, were available for clinical use in all six territories. EndoPredict® was unavailable in Japan and Thailand. As of November 2021, none of the tests had been reimbursed in any country or SAR. All four tests were sent for processing by centers outside each territory.

Availability and reimbursement of medical treatment

The list of BC drugs in the survey was drawn from the recommended drugs in the evidence-based clinical practice guidelines of the ESMO and the National Comprehensive Cancer Network. Each drug was labeled according to whether it was in the WHO-EML or scored in the ESMO-MCBS. The reimbursement status of each drug was presented in a color-coded format. Regarding drugs for Singapore, the three respondents from that country agreed that medicine costs should be categorized as PR, despite the drugs being listed in Singapore's standard drug list.

Drugs for EBC

Twenty drugs were included in this survey. In the case of trastuzumab, intravenous and subcutaneous preparations were considered separate items. Gonadotropin-releasing hormone (GnRH) agonists were counted as a group without specifying the names of the individual drugs. **Figure 1** summarizes the results for drugs included in WHO-EML or ESMO-MCBS A or B. **Figure 2** presents the drugs that were not listed in the WHO-EML or ESMO-MCBS.

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Breast cancer drugs	WHO-EML	ESMO-MCBS	Thailand		Singapore	Hong Kong SAR	Japan	Korea	Taiwan
			CSMBS	SSS/UC	ML				
Anastrozole	Y	NA	FR	NR	PR	FR	FR	FR	FR
Letrozole	Y	NA	FR	FR	PR	FR	FR	FR	FR
Tamoxifen	Y	NA	FR	FR	PR	FR	FR	FR	FR
GnRH agonist	Y	NA	FR	NR	PR	PR	FR	FR	PR
Cyclophosphamide	Y	NA	FR	FR	PR	FR	FR	FR	FR
Methotrexate	Y	NA	FR	FR	PR	FR	FR	FR	FR
5FU	Y	NA	FR	FR	PR	FR	FR	FR	FR
Docetaxel	Y	NA	FR	FR	PR	FR	FR	FR	FR
Doxorubicin	Y	NA	FR	FR	PR	FR	FR	FR	FR
Paclitaxel	Y	NA	FR	FR	PR	FR	FR	FR	FR
Trastuzumab iv (LN+)	Y	A	FR	FR	PR†	PR†	FR	FR	FR
Trastuzumab iv (LN−)	Y	A	FR*	NR	PR	PR†	FR	FR	NR
T-DM1 in residual disease	NA	A	NR	NR	PR	PR	FR	NR	NR
Pertuzumab (adjuvant)	NA	B	NR	NR	PR	NR	FR	NR	NR
Zoledronate	NA	B	FR	NR	PR	NR	NR	FR	FR

Figure 1. Access to systemic treatment for early BC using drugs in the WHO-EML or with ESMO-MCBS scores of A or B.
BC = breast cancer; WHO-EML = World Health Organization Model List of Essential Medicines; ESMO-MCBS = European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; ER = estrogen receptor; CSMBS = Civil Servant Medical Benefit Scheme; SSS = Social Security Scheme; UCS = Universal Coverage Scheme; ML = MediShield Life; SAR = special administrative region; GnRH = gonadotropin-releasing hormone; FU = fluorouracil; LN = lymph node; Y = yes; NA = not available; FR = fully reimbursed; NR = non-reimbursed; PR = partially reimbursed.
*Only for ER-negative BC; †Only for biosimilar drugs.

Most chemotherapeutic agents and hormonal therapies for EBC were not evaluated in ESMO-MCBS but were listed in the WHO-EML. The drugs were relatively accessible in all countries, with a few exceptions. GnRH agonists were PR in Hong Kong SAR, Taiwan, and Singapore but NR in Thailand (SSS/UCS subgroups). Although the Thai SSS/UCS system did not cover anastrozole, letrozole could be substituted for the same indications.

Breast cancer drugs	ESMO-MCBS	Thailand		Singapore	Hong Kong SAR	Japan	Korea	Taiwan
		CSMBS	SSS/UC	ML				
Exemestane	NA	FR	NR	PR	PR	FR	FR	FR
Epirubicin	NA	FR	NR	PR	FR	FR	FR	FR
Capecitabine	NA	FR	NR	PR	FR	PR	FR	FR
Carboplatin	NA	FR	FR	PR	FR	PR	FR	PR
Cisplatin	NA	FR	FR	PR	FR	NR	FR	FR
Trastuzumab sc (any stage)	NA	FR	NR	PR	PR	NA	FR	FR†
Pertuzumab (neoadjuvant)	C	FR*	NR	PR	PR	FR	PR	NR
Denosumab	A	NR	NR	PR	NR	NR	FR	FR

Figure 2. Access to other early BC systemic treatments not listed in the WHO-EML or not provided an ESMO-MCBS score of A or B.
BC = breast cancer; WHO-EML = World Health Organization Model List of Essential Medicines; ESMO-MCBS = European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; CSMBS = Civil Servant Medical Benefit Scheme; SSS = Social Security Scheme; UCS = Universal Coverage Scheme; ML = MediShield Life; SAR = special administrative region; NA = not available; FR = fully reimbursed; NR = non-reimbursed; PR = partially reimbursed.
*With specific conditions; †Only for node-positive BC.

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The accessibility of human epidermal growth factor receptor 2 (HER2)-targeted agents was lower than that of chemotherapy and endocrine therapy. Trastuzumab was listed in the WHO-EML and scored as A or B in the ESMO-MCBS. Nevertheless, the survey revealed disparities in terms of access (reimbursement), especially in lymph node (LN)-negative patients. In LN-negative HER2-positive EBC, trastuzumab was NR in Taiwan and Thailand (SSS/UCS) but PR in Hong Kong SAR and Singapore. Regarding CSMBS in Thailand, trastuzumab was FR for LN-negative, HER2-positive, and estrogen receptor (ER)-negative patients. Furthermore, only 6-month trastuzumab treatment was allowed. Interestingly, the subcutaneous trastuzumab preparation was reimbursed in a manner similar to the intravenous form in most countries, except Japan, where this preparation was unavailable (**Figure 2**).

T-DM1 for adjuvant treatment of residual disease after neoadjuvant therapy and pertuzumab for adjuvant treatment were scored as A and B in the ESMO-MCBS, respectively, but these drugs were not included in the WHO-EML. Even though T-DM1 and pertuzumab were available in all territories, neither drug was easily accessible. T-DM1 for the treatment of residual disease after neoadjuvant therapy was somewhat more accessible. It was FR in Japan and PR in Hong Kong SAR and Singapore but NR in Korea, Taiwan, and Thailand. In Japan, adjuvant T-DM1 and pertuzumab are considered FR. However, adjuvant pertuzumab was PR in Singapore and NR in the remaining four territories. Pertuzumab use in neoadjuvant settings (rated C in the ESMO-MCBS; not listed in the WHO-EML) was FR only in Japan. Although the drug was also FR in Thailand, this level of reimbursement was only available to patients covered by the CSMBS. In Hong Kong SAR, Korea, and Singapore, pertuzumab was PR, whereas it was NR in Taiwan and SSS/UCS subgroups in Thailand.

In the case of non-targeted drugs for EBC that were not included in the WHO-EML (**Figure 2**), access was generally good in most territories. In Thailand, most drugs in **Figure 2** were NR for the SSS/UCS subgroups but FR under CSMBS.

Drugs for advanced BC

Generally, the accessibility of chemotherapy and endocrine agents for advanced BC was uniform among the six countries or territories for drugs included in the WHO-EML. In the case of drugs for advanced BC with MCBS scores of 4 and 5, most were newer targeted drugs, not in WHO-EML. The accessibility of these drugs was limited, particularly in Hong Kong SAR and Thailand. These drugs included CDK 4/6 inhibitors, PARP inhibitors, T-DM1, and pertuzumab (**Figure 3**). The situation in Thailand was similar to that encountered in adjuvant settings, in which the accessibility of effective drugs in WHO-EML and ESMO-MCBS was not uniform. There was a marked disparity for SSS/UCS patients, with drugs such as trastuzumab, pertuzumab, vinorelbine, and ribociclib classified as NR, whereas they were classified as FR for individuals under CSMBS. Thailand was the only country where T-DM1 was NR in a metastatic setting. Olaparib was NR in Korea and Thailand, while talazoparib was available only in Singapore and Taiwan.

Figure 4 summarizes the data of the drugs that were not in the WHO-EML, had ESMO-MCBS scores < 4, or had not been evaluated by ESMO-MBCS. The accessibility of the drugs was variable. Many were classified as NR or PR, even in the high-income countries in this study. Reimbursement for some high-cost drugs was allowed based on specific indications. For example, denosumab was PR in Hong Kong SAR for patients with chronic kidney disease. Likewise, atezolizumab was only allowed in Japan for patients with PDL1-positive triple-negative advanced BC.

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Breast cancer drugs	WHO-EML	ESMO-MCBS	Thailand		Singapore	Hong Kong SAR	Japan	Korea	Taiwan
			CSMBS	SSS/UC	ML				
Anastrozole	Y	NA	FR	NR	PR	FR	FR	FR	FR
Letrozole	Y	NA	FR	FR	PR	FR	FR	FR	FR
Tamoxifen	Y	NA	FR	FR	PR	FR	FR	FR	FR
GnRH agonist	Y	NA	FR	NR	PR	PR	FR	FR	PR
Zoledronate	Y	NA	FR	FR	PR	FR	FR	FR	FR
Capecitabine	Y	NA	FR	FR	PR	FR	FR	FR	FR
Cyclophosphamide	Y	NA	FR	FR	PR	FR	FR	FR	FR
Methotrexate	Y	NA	FR	FR	PR	FR	FR	FR	FR
5FU	Y	NA	FR	FR	PR	FR	FR	FR	FR
Docetaxel	Y	NA	FR	FR	PR	FR	FR	FR	FR
Doxorubicin	Y	NA	FR	FR	PR	FR	FR	FR	FR
Paclitaxel	Y	NA	FR	FR	PR	FR	FR	FR	FR
Vinorelbine IV	Y	NA	FR	NR	PR	FR	FR	FR	FR
Trastuzumab IV	Y	NA	FR	NR	PR	PR	FR	FR	FR
Ribociclib	N	5	FR*	NR	PR	PR	NA	FR	FR
Palbociclib	N	4	NR	NR	PR	PR	FR	FR	FR
Abemaciclib	N	4	NR	NR	PR	PR	FR	FR	NR
Pertuzumab	N	4	FR	NR	PR	PR	FR	FR	FR
T-DM1	N	4	NR	NR	PR	PR	FR	FR	FR†
Olaparib	N	4	NR	NR	PR	NR	FR	NR	FR‡
Talazoparib	N	4	NA	NA	PR	NA	NA	NA	FR

Figure 3. Access to systemic treatment for advanced BC using drugs in the WHO-EML or with ESMO-MCBS scores of 4 or 5.
BC = breast cancer; WHO-EML = World Health Organization Model List of Essential Medicines; ESMO-MCBS = European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; CSMBS = Civil Servant Medical Benefit Scheme; SSS = Social Security Scheme; UCS = Universal Coverage Scheme; ML = MediShield Life; SAR = special administrative region; FU = fluorouracil; IV = intravenous form; Y = yes; N = no; NA = not available; FR = fully reimbursed; NR = non-reimbursed; PR = partially reimbursed.
*Reimbursable only for first-line treatment; †For specific conditions; ‡For patients with *BRCA*-mutated triple-negative BC.

Availability of generic and original BC drugs

Original and generic versions of most BC drugs surveyed were available (**Supplementary Table 1**). Notably, many drugs were not available in Japan, such as ribociclib, oral vinorelbine, and subcutaneous trastuzumab. As previously mentioned, ixabepilone is no longer available in many countries or regions. Talazoparib is only available in Taiwan and Singapore.

DISCUSSION

In this study, we report the findings of the first survey on the accessibility of BC drugs in major Asian countries and SAR, including five countries and the Hong Kong SAR. We also compared the accessibility of BC drugs in Thailand with that of other Asian countries or SAR involved in BIG-Asia. The availability of genomic tests and BC drugs did not differ between the major territories; however, the accessibility and reimbursement of cancer drugs varied. Overall, drug accessibility in the selected BIG-Asia countries or territories was adequate, especially for drugs in the WHO-EML or with a high value in ESMO-MCBS. However, variable accessibility and reimbursement were evident for newer targeted agents. Many of these

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Breast cancer drugs	ESMO-MCBS	Thailand		Singapore	Hong Kong SAR	Japan	Korea	Taiwan
		CSMBS	SSS/UC	ML				
Exemestane	NA	FR	NR	PR	FR	FR	FR	FR
Fulvestrant	NA	FR	NR	PR	NR	FR	FR	FR
Megestrol	NA	FR	FR	PR	FR	FR	FR	FR
Everolimus	2	FR	NR	PR	PR	FR	FR	FR
Denosumab	NA	NR	NR	PR	PR*	FR	FR	FR
Pamidronate	NA	FR	FR	PR	FR	FR	FR	FR
Carboplatin	NA	FR	FR	PR	FR	PR	FR	FR
Cisplatin	NA	FR	FR	PR	FR	NR	FR	FR
Epirubicin	NA	FR	NR	PR	FR	FR	FR	FR
Eribulin	2	FR	NR	PR	FR	FR	FR	FR
Gemcitabine	NA	FR	NR	PR	FR	FR	FR	FR
Ixabipilone	NA	FR	NR	PR	NA	NA	NA	FR
Liposomal doxorubicin	NA	FR	NR	PR	PR	NR	PR	FR
Nab-paclitaxel	NA	NR	NR	PR	NR	PR	FR	NR
Vinorelbine oral	NA	FR	NR	PR	NR	NA	NR	FR
Trastuzumab sc	NA	FR	NR	PR	PR	NA	FR	FR
Lapatinib	3	FR	NR	PR	PR	FR	FR	FR‡
Atezolizumab	NA	NR	NR	PR	PR	PR†	NR	NR
Bevacizumab	2	NR	NR	PR	NR	FR	NR	NR

Figure 4. Access to systemic treatment for advanced BC using drugs that are not in the WHO-EML or with ESMO-MCBS scores < 4 or unscored.
BC = breast cancer; WHO-EML = World Health Organization Model List of Essential Medicines; ESMO-MCBS = European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; CSMBS = Civil Servant Medical Benefit Scheme; SSS = Social Security Scheme; UCS = Universal Coverage Scheme; ML = MediShield Life; SAR = special administrative region; SC = subcutaneous form; NA = not available; FR = fully reimbursed; NR = non-reimbursed; PR = partially reimbursed.
*Only for patients with chronic kidney disease; †For PDL1-positive triple-negative BC; ‡For brain metastasis.

agents are in the ESMO-MCBS high-score category, which is more up-to-date than the WHO-EML. Even in some high-income countries, variability was observed, with many agents not classified as FR. The disparities in their accessibility and reimbursement suggest that the price of innovative drugs was prohibitively out of proportion to the magnitude of the benefits perceived by the healthcare systems in Asia.

Among the six participating cooperative groups in this survey, all except Thailand are classified as high income, while Thailand is in the upper-middle-income category. Patients in the high-income countries or regions mostly needed to pay a small sum for all drugs, for example, 10%–30% (with capping) in Japan or < 5% co-payment in Korea and Taiwan. This approach provides the opportunity to receive more expensive but more efficacious drugs.

The reimbursement system in Thailand is complex and fragmented, with two extremes. At one extreme is the CSMBS. It is an open-ended budget system that covers a minority of the population (7.7%) [10], with relatively liberal access. At the other extreme are the SSS and UCS, which apply to the majority of the population. They have closed-end budgets and are capitation-based, leading to a more substantial financial burden on patients than on those covered by CSMBS. Although SSS/UCS covers all essential drugs on the national list without out-of-pocket payments, self-pay is in force for excluded drugs. Consequently, there is a stark difference in the accessibility of the treatment afforded by the two systems.

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The reimbursement of cancer drugs in Thailand operates on a no-payment policy but with access to only a limited range and number of drugs. In comparison, the concept of reasonable co-payment with broad accessibility for approved drugs is used in Singapore, and a small co-payment, with or without cost capping, is required in Japan, Korea, and Taiwan. The Hong Kong SAR system falls between that in force in Thailand and elsewhere, with many PR items and more NR items than in other countries. The advantage of Thailand's reimbursement system is that coverage of essential and cost-effective drugs is provided to all patients regardless of their economic status. However, the main limitation of the Thai system is that only a small minority of patients can access newer, more efficient, and more costly drugs through CSMBS. This restriction may negatively affect the national BC outcomes.

Previous studies on cancer drug availability reported that essential medicines in the WHO-EML were available only at full price (i.e., NR) in nearly one-third of the low- and middle-income countries [11,12]. In contrast, some essential agents, such as trastuzumab, were classified as FR in both early and advanced settings, even in middle-income countries in Eastern Europe [11]. Our survey was reassuring in that this disparity was not present among the BIG-Asia countries surveyed in the current investigation. Nevertheless, continuous improvement in access to more efficient medicines is needed to achieve better outcomes.

According to a 2020 GLOBOCAN report, Thailand had the highest MIR among the countries involved in the present survey (Japan, Korea, and Singapore). An MIR similar to that of Thailand has been reported for other upper-middle-income countries in Asia and Europe, such as China, Malaysia, Romania, and Russia [1]. BC is the leading cause of cancer-related death in Thai women; therefore, lowering BC mortality could potentially improve the country's MIR. Many factors affect BC mortality, such as the stage at presentation, effectiveness of screening policies, and other treatment modalities. More than three-quarters of Thai patients access BC drugs through the UCS/SSS scheme, which does not cover many innovative targeted agents that have been proven to prevent recurrence, delay progression, and death. Presumably, full access to BC drugs may significantly contribute to BC mortality in the country. In keeping with recent findings of situational analysis of BC in Thailand [13], the extent to which other factors might contribute to BC mortality was unclear. However, access to medicines is particularly important. Our results demonstrated a relative disparity in access to BC drugs in Thailand compared to other major Asian countries or regions and a disparity within the country. This survey provides a better understanding of the disparity and limited accessibility of systemic BC treatment in Thailand. This study represents a step toward improving drug accessibility and reducing disparities among Thai patients with BC. In recognition of financial constraints, selecting highly efficacious and cost-effective drugs is key to equal access for all patients. For instance, trastuzumab, one of the drugs in the WHO-EML, should be listed as an essential drug in Thailand based on its substantial benefits and recent availability of biosimilar formulations. Tiered pricing, choosing one drug in each category at the most reasonable price, improving the approval of biosimilar/generic drugs, and using health technology assessments are potential strategies to sustainably overcome disparities in BC treatment [14-16].

The clinical utility of genomic testing in predicting the benefits of chemotherapy for HR-positive HER2-negative EBC has been established, and several commercially available genomic profiling assays are presently available. It has been widely accepted in the USA and several European countries for routine clinical decisions. However, in all six Asian participating cooperative groups surveyed, the limitations on the reimbursement of commercial genomic testing are extremely challenging. Additionally, our survey showed that these genomic tests need to be sent

to centralized testing centers outside the territory, further increasing out-of-pocket expenses for patients. Moreover, there is evidence that multigene assays developed for Western populations may not be well applied to Asian populations [17,18]. Therefore, some countries, such as Taiwan, have established national molecular profiling databases for comparison with Oncotype Dx® and explored the performance and cost-effectiveness of their local populations [19,20].

The strength of the survey is that it represents the first comprehensive review of BC drugs in Asian countries or SAR. The study categorized BC drugs according to the WHO-EML and ESMO MCBS, which contain expensive drugs with clinical benefits. The survey results were validated during a meeting of the BIG-Asia group. Moreover, we explored and reported the reimbursement systems in each country. This information can serve as a reference for policymakers in guiding decisions related to reducing disparities and improving drug accessibility. However, as with all surveys that reflect a snapshot of information at one timepoint, the information in this report may no longer be current. The analyses were based on survey data obtained in 2020, when the results of many drug studies were unavailable.

In conclusion, essential BC drugs are generally well accessible in the BIG-Asia countries. A disparity in access to high-cost BC drugs is evident in Thailand compared with other Asian countries. Limited access to drugs may be a potential factor contributing to a worse BC MIR. Establishing equal access and affordable drug prices to reduce disparity remains the key to improving BC outcomes in Thailand.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Availability of generic and original BC drugs in representative Asian countries

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