CANCER CARE AND ACCESS TO CANCER DRUGS IN ASIA-PACIFIC

Health spending on cancer drugs and unmet patient needs in Asia-Pacific

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Sub-report 4 of the main report "Cancer care and access to cancer drugs in Asia-Pacific"

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Report summary

Cancer drugs are an integral part of modern cancer care. The availability of targeted therapies and immunotherapies has changed the standard of care in many cancer types during the last two decades. While such clinical innovation helps address the growing burden of cancer, this poses challenges to health care systems and policy makers with finite health resources available.

Linking resource use in cancer care to patient outcomes is vital to inform funding decisions that strive to maximize value-for-money for patients, the health care system, and society. Expenditure on cancer drugs are a strong indicator of expenditure on cancer care services overall, due to their close links with diagnostics services and other physical infrastructure and manpower required to administer drugs. There is a clear positive relationship between the level of cancer drug expenditure and cancer patient survival across markets in Asia-Pacific. This suggests that patient outcomes are indeed associated with the amount of investment on cancer drugs and other cancer care services in general.

High-income markets in Asia-Pacific spent around 10-20% of total pharmaceutical expenditure – financed via public and private sources – on cancer drugs in 2019, whereas middle-income markets spent around 1-9%. These proportions directed to cancer are comparatively low in relation to the size of the disease burden of cancer. For example, the proportion of cancer deaths amounted to around 30% of all deaths in high-income markets and 9-25% of all deaths in middle-income markets in 2019.

In Asia-Pacific, Japan spent the most on cancer drugs per capita with over $90 in 2019, compared to around $110–$130 per capita in top-spending countries in Europe (Austria, Germany, Switzerland). South Korea spent the least on cancer drugs among high-income markets with around $30 per capita, which puts the market at the same level as European countries with lower GDP per capita than South Korea. In middle-income markets, per capita spending levels ranged from a mere $0.2 in India to $6.6 in Thailand. Higher list prices of drugs and higher numbers of cancer patients in high-income markets might explain some of the vast differences across Asia-Pacific. However, cancer drug expenditure per cancer case still ranged from less than $600 in India and Indonesia to $17,500 in Singapore.

Public spending on cancer drugs exhibits the same vast discrepancies between high-income markets and middle-income markets as observed with total spending. The differences in public spending were particularly pronounced among innovative cancer drugs (i.e., drugs with substantial clinical benefit according to ESMO-MCBS), with average spending of $7,300 per cancer case in high-income markets compared to $370 per cancer case in middle-income markets. Higher use of innovative drugs with much better patient accessibility via reimbursement might explain some of the differences.

Despite securing national reimbursement, patient access to the specific treatment might not necessarily be guaranteed. This could potentially be due to reasons such as the presence of high patient co-payments without a sufficient safety net for disadvantaged groups, sub-optimal level of health infrastructure and manpower, and government budget constraints that might limit accessibility.

Based on a case study of the cancer drug pemetrexed in non-small cell lung cancer, patient needs and actual access were compared (quantified by a comparison of the drug volume needed to treat all eligible patients with the actual drug volume administered). The analysis based on local data in markets such as Australia and Japan that reimburse the newer combination of pemetrexed with immunotherapy (pembrolizumab) seems to suggest that only about half of the patient needs were addressed despite reimbursement. Rigid clinical processes and narrow reimbursement criteria might explain this. Other markets that only reimburse the older combination of pemetrexed with cisplatin, were generally able to meet patient needs. The availability of generic versions of these drugs might have helped in this process, yet immunotherapy (without or in combination with chemotherapy) has now become standard of care, replacing platinum-based chemotherapy regimens. In middle-income markets with no reimbursement of pemetrexed, less than 10% of patient needs are met. This means that many patient life years have already been lost due to limited access and will continue to be so unless there is improved patient access to more effective treatment via reimbursement in a timely manner.

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1. Cancer drugs and unmet patient needs

Cancer drugs are an integral part of modern cancer care (1). Chemotherapy drugs and hormone therapy drugs were introduced in the 1940s-1970s and are still today a standard-of-care treatment modality during the treatment course of many cancer types (2). Chemotherapy can cause toxic side effects as it may damage normal healthy cells alongside malignant cells in the body (3). Targeted therapy drugs, introduced at the end of the 1990s, use a different mode of action and act on specific molecules (e.g., genes, proteins) that are involved in the growth and survival of cancer cells (4, 5). They have now become one of the main treatment options for some tumors. Since 2011, immunotherapy drugs, such as checkpoint inhibitor therapies and more recently CAR T-cell therapies that help the body's immune system to recognize and attack cancer cells, have been added to the therapeutic arsenal and they too have started to replace or complement chemotherapies (6).

As shown in sub-report 3, almost 100 new cancer drugs have been launched over the last decade alone, with many offering substantial clinical benefits to patients. While such clinical innovation helps address the growing burden of cancer, this poses challenges to health care systems and policy makers with finite health resources available.

Many new cancer drugs are given in combination with already existing drugs, and some new cancer drugs allow patient groups to be treated for which there was no drug treatment before. These circumstances render it difficult to maintain a constant level of spending on cancer drugs per patient over time. In fact, evidence from Europe shows that health expenditure on cancer drugs (based on list prices) tripled between 2005 and 2018, yet health expenditure on cancer care remained virtually constant in relation to total health expenditure (around 6%) during this period (7). What seems to have happened in Europe is that increasing expenditure on cancer drugs were largely offset by reductions in expenditure on inpatient care. These reductions stem from a transformation of cancer care from an inpatient to an outpatient setting, partly enabled by new cancer drugs that might lead to reductions in hospitalization due to better efficacy, easier management of side effects with reduced toxicity, or more convenient mode of administration. Importantly, patient outcomes have improved during this period in Europe (8), highlighting the importance of incorporating clinical innovation in clinical practice (6).

The availability and accessibility of cancer drugs differs substantially across Asia-Pacific (9). Sub-report 3 shows that high-income markets achieve much higher regulatory approval and

reimbursement approval rates of innovative[1] cancer drugs (91% and 59%, respectively) than middle-income markets (68% and 17%, respectively). Without reimbursement and insurance coverage, patients have to pay out-of-pocket for cancer drugs, which in practice severely limits accessibility (9). Limited accessibility because of delayed reimbursement results in almost 1 million patient life years lost across Asia-Pacific for each year of delay, based on a sample of only 10 innovative cancer drugs, as shown in sub-report 3. A prioritization of reimbursement of innovative drugs that provide the greatest benefits to patients is thus vital and could also help to accommodate these drugs in constrained health care budgets.

Access to drugs is a multi-dimensional issue that involves multiple stakeholders and sectors over the entire product life cycle, from research and development to quality assurance, supply chain management and use (10). Despite securing national reimbursement, patient access to the specific treatment might not necessarily be guaranteed. This could potentially be due to reasons such as the presence of high patient co-payments without a sufficient safety net for disadvantaged groups, sub-optimal level of health infrastructure and manpower, and government budget constraints that might limit accessibility. As emphasized in sub-report 2, all of these dimensions need to be addressed jointly to ensure adequate coverage of the provided services to meet patient needs.

1.1 Aim of the sub-report

The aim of this sub-report is to describe the extent of health spending on cancer drugs in Asia-Pacific[2].

- Section 2 describes total health spending on cancer drugs.
- Section 3 describes public health spending on cancer drugs.
- Section 4 examines the level of cancer drug spending in relation to patient needs.

[1] In this report, drug-indications with a “substantial clinical benefit” are called “innovative”. This follows the ESMO-MCBS scoring system. Drug-indications used in a curative setting receive a score of A, B, or C. A is the highest score and C is the lowest score. Drug-indications used in a non-curative setting receive a score of 5, 4, 3, 2, or 1. 5 is the highest score and 1 is the lowest score. An indication is said to have a “substantial magnitude of clinical benefit” if it receives a score of A or B in the curative setting or a score of 5 or 4 in the non-curative setting.

[2] Asia-Pacific consists in this report of 7 high-income markets – Australia, Hong Kong, Japan, New Zealand, Singapore, South Korea, Taiwan – and 7 middle-income markets – China, India, Indonesia, Malaysia, the Philippines, Thailand, Vietnam.

2. Total health spending on cancer drugs

This section explores the relative and absolute level of total health spending – public and private expenditure – on cancer drugs across all markets in Asia-Pacific. It aims to answer the following questions: What is the proportion of total health spending on cancer drugs in relation to all pharmaceuticals? What is the total health spending on cancer drugs per capita and per cancer patient?

2.1 Method and data

Information on drug expenditure for the treatment of different diseases are not routinely reported by most public authorities in the region. In some cases where such data is available, only the cost that was borne by the public payer would typically be reported and not drug expenditure through other financing mechanisms such as private insurance and out-of-pocket expenses. Data that include both public and private expenditure on cancer drugs were sourced from IQVIA, a global provider of pharmaceutical sales data, for 13 markets and from IPMG for Indonesia. Cancer drugs in groups L01 and L02 of the Anatomical Therapeutic Chemical (ATC) Classification System were included. This includes drugs of all different types of cancer therapy: chemotherapy, hormonal therapy, immunotherapy, and targeted therapy.

To put the size of the expenditure on cancer drugs into perspective, additional information on the total health expenditure (see sub-report 2) and total pharmaceutical expenditure were sourced from the WHO and IQVIA, respectively. Furthermore, cancer drug expenditure are compared across markets in Asia-Pacific in terms of per capita and per cancer incidence (i.e., number of newly diagnosed cases). The latter comparison is made due to differences between population demographics and the cancer incidence across markets (see sub-report 1). The lower reliability of cancer incidence data in middle-income markets and some high-income markets due to the absence of a nationwide high-quality cancer registries should be recalled here. Finally, cancer drug expenditure (serving as a proxy for total health expenditure on cancer care) are related to cancer patient outcomes in a similar manner as in sub-report 2. Linear regression analysis is used to examine the strength of the correlation between the two measures.

Sales data come with certain limitations. IQVIA sales data are based on list prices (i.e., ex-manufacturer prices), which means that they typically do not fully capture confidential rebates and arrangements between payers and drug manufacturers. The numbers reported in this section are thus upper bound estimates. Sales data for cancer drugs (but not for total pharmaceutical sales) for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total cancer

drug sales in China and <1% of total cancer drug sales in Taiwan). Sales data for cancer drugs (but not for total pharmaceutical sales) from IPMG for Indonesia lack most sales of generics/biosimilars.

2.2 Results

Pharmaceuticals are a cornerstone in the treatment of many diseases, including cancer. Figure 1 shows the proportion of total health expenditure spent on all pharmaceuticals (financed by public and private sources) across the 14 markets in Asia-Pacific in 2018. High-income markets tended to spend a lower proportion (average of 11%) on pharmaceuticals than middle-income markets (average of 22%). New Zealand spent the lowest proportion on pharmaceuticals which has partly been attributed to the single public payer (PHARMAC) operating on a capped budget (11, 12). The same general pattern as in Figure 1 has also been observed among wealthier and poorer countries of the OECD (13). One reason for this pattern are greater differences in relative prices of staff-based health care services (e.g., salaries of physicians, nurses) and pharmaceuticals in poorer countries. Staff-based health care services reflect domestic labor cost levels, whereas the prices of pharmaceuticals tend to lie within an international price corridor.

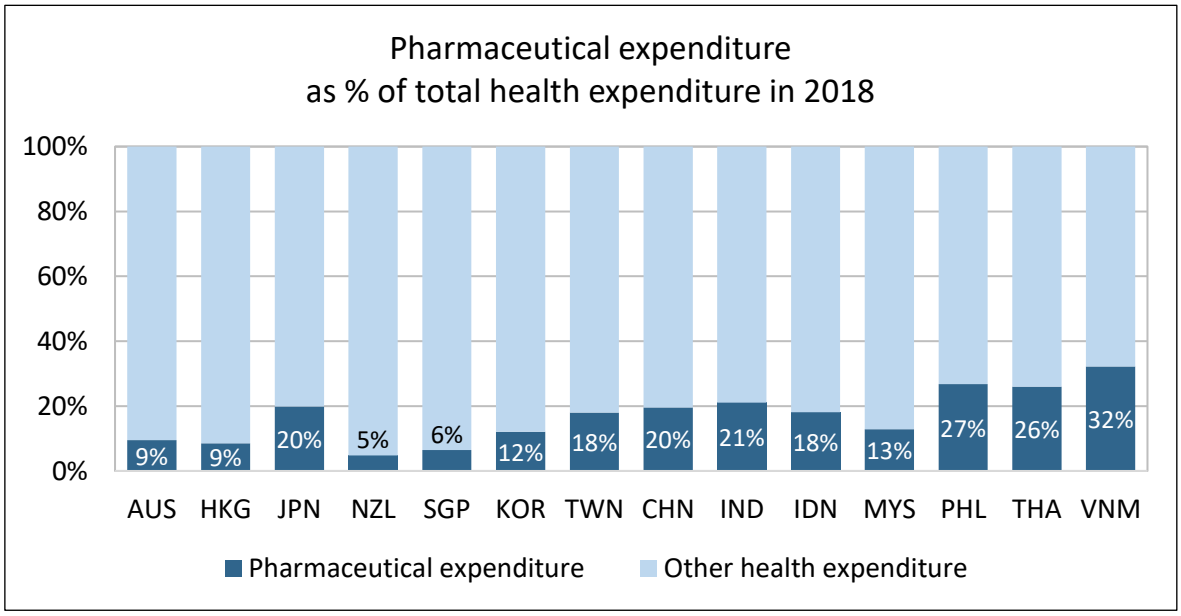

Figure 1: Expenditure on pharmaceuticals as % of total health expenditure, 2018

Notes: Expenditure include financing from public and private sources. Pharmaceutical expenditure were based on sales data based on list prices, which typically do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers. The proportions for pharmaceuticals reported here are thus upper bound estimates.
Source: WHO (14), Department of Health for HKG (15), and Ministry of Health and Welfare for TWN (16) for total health expenditure. IQVIA Market Prognosis Reports and OECD for NZL (17) for pharmaceutical expenditure.

Looking at cancer drugs specifically, Figure 2 shows that high-income markets in Asia-Pacific spent around 10-20% of total pharmaceutical expenditure on cancer drugs in 2019, whereas middle-income

markets spent around 1-9%. The proportions observed in high-income markets resemble the proportions in France, Germany, and the UK (6).

If we recall the burden of cancer mortality across respective markets, the analysis in sub-report 1 illustrated that around 30% of deaths in high-income markets are due to cancer. In comparison to the cancer burden observed, only 10-20% of total pharmaceutical spending has been directed to cancer to address this health issue. Similarly, in middle-income markets where 9-25% of deaths were attributed to cancer, only 1-9% of drug expenditure was on cancer.

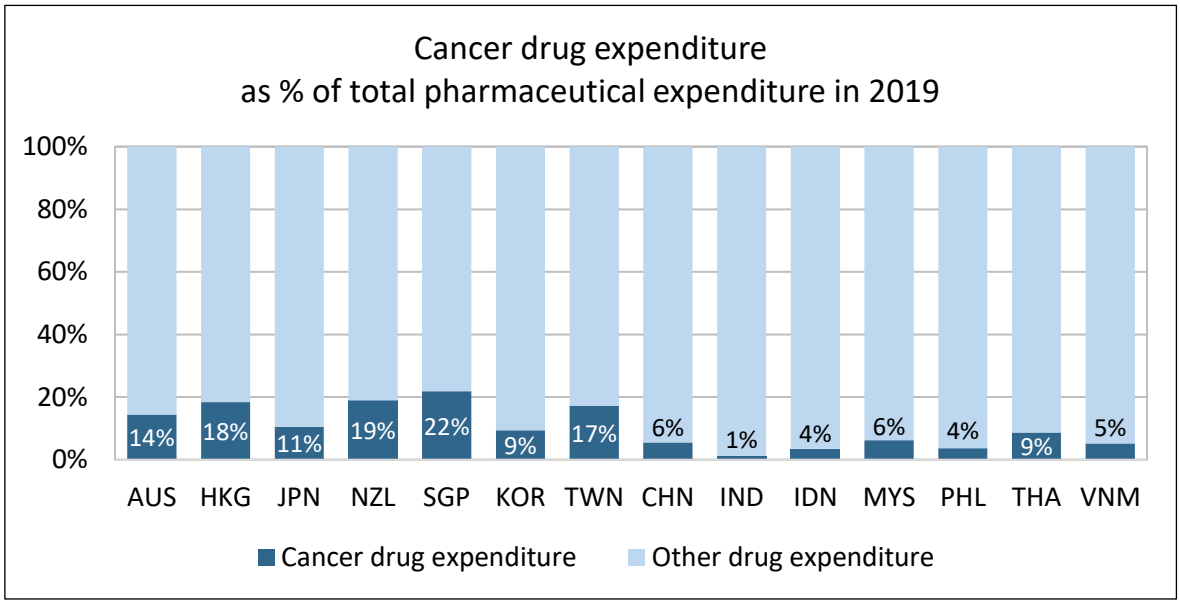

Figure 2: Expenditure on cancer drugs as % of total pharmaceutical expenditure, 2019

Notes: Expenditure include financing from public and private sources. Underlying sales data do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers, which would overestimate the proportion of cancer drug expenditure if the size of rebates for cancer drugs is greater than for other pharmaceuticals. Sales data for cancer drugs for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total cancer drug sales in China and <1% of total cancer drug sales in Taiwan). Sales data for cancer drugs for Indonesia lack most sales of generics/biosimilars. Sales of cancer drugs in ATC groups L01 and L02 are included.
Source: IQVIA Market Prognosis Reports and OECD for NZL (17) for total pharmaceutical expenditure. IQVIA MIDAS database for sales data of cancer drugs (18) and IPMG sales data of cancer drugs in IDN.

Cancer drug expenditure (based on list prices) in absolute terms are shown in Figure 3. Per capita spending levels on cancer drugs differ considerably across the region in 2019. Among high-income markets, Japan spent the most on cancer drugs per capita with over $90 while South Korea spent the least with around $30. Compared to the situation in Europe, Japan spent around as much as France on cancer drugs but not as much as the three top-spending countries (Austria, Germany, Switzerland) which spent around $110–$130 per capita in 2018 (6, 7). Cancer drug spending in South Korea was similar to that of poorer countries in Europe, such as Croatia, Hungary, and Portugal with lower GDP per capita than South Korea (6, 7).

Per capita spending levels on cancer drugs in middle-income markets range from a mere $0.2 in India to $6.6 in Thailand. These levels are exceptionally low compared to high-income markets in Asia-Pacific or countries in Europe. A potential explanation for lower national spending levels is the lower cancer incidence due to their relatively younger populations (see sub-report 1).

We then analyzed cancer drug expenditure per cancer incidence, which ranged from around $230 to $17,500 in the region as shown in Figure 3. While the cancer incidence might be underreported due to inadequate registration of patients in the national cancer registry (see also Box 2 in sub-report 1) and hence our estimates could be overstated, Singapore had the highest cancer drug expenditure per cancer incidence. Drug prices in Singapore are mainly driven by market forces with its free pricing policy even for generics, although tendering is practiced at public hospitals and government clinics (19). New Zealand and South Korea spent around 50% less on cancer drugs per cancer case compared to Australia, Hong Kong, and Japan. Strict price control due to PHARMAC's capped budgeting (20), along with the distinctly lower reimbursement rates of cancer drugs observed in sub-report 3, might explain the finding for New Zealand.

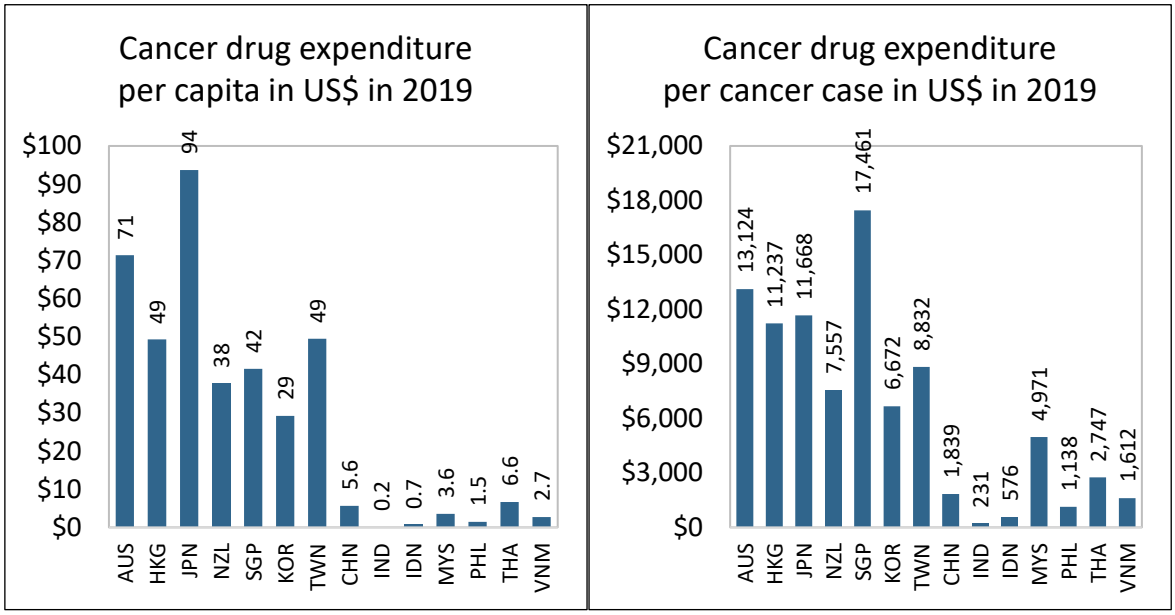

Figure 3: Cancer drug expenditure per capita and per cancer case in US$, 2019

Notes: Cancer drug expenditure include financing from public and private sources. They show current prices and are not adjusted for differences in purchasing power parity. Cancer drug expenditure are based on sales data based on list prices, which typically do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers. The absolute numbers reported here are thus upper bound estimates. Sales data for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total sales in China and <1% of total sales in Taiwan). Sales data for Indonesia do not contain most sales of generics/biosimilars. Sales of cancer drugs in ATC groups L01 and L02 are included. Cancer case is defined as cancer incidence (newly diagnosed cases) in 2018 in absence of data for 2019.
Source: IQVIA MIDAS database for sales data of cancer drugs (18) and IPMG sales data of cancer drugs in IDN, and national cancer registries and GLOBOCAN for cancer cases (see Table A1 in sub-report 1).

Among the middle-income markets, India and Indonesia spent the least with only $231 and $576 per cancer incidence respectively. In comparison, Malaysia spent almost $5,000 per cancer case but this number might be inflated as there could be an underestimation of patient numbers in Malaysia due to inadequate registration of patients in the national cancer registry (see also Box 1 in sub-report 1). However, previous studies have pointed to the free pricing policy in Malaysia's private healthcare sector as a reason for high drug prices and consequently high drug expenditure (20).

As emphasized in sub-report 2, linking resource use in cancer care to patient outcomes is vital to inform funding decisions that strive to maximize value-for-money for patients. Data on (public and private) expenditure on the universe of health care services used in cancer care are not systematically available markets across Asia-Pacific. However, overall spending on cancer care services is typically closely linked to spending on cancer drugs. Using cancer drug expenditure per capita as a proxy for total health expenditure on cancer care (resources use), Figure 4 shows how this correlates with the complement of the mortality-to-incidence ratio (1–MIR) (patient outcomes).

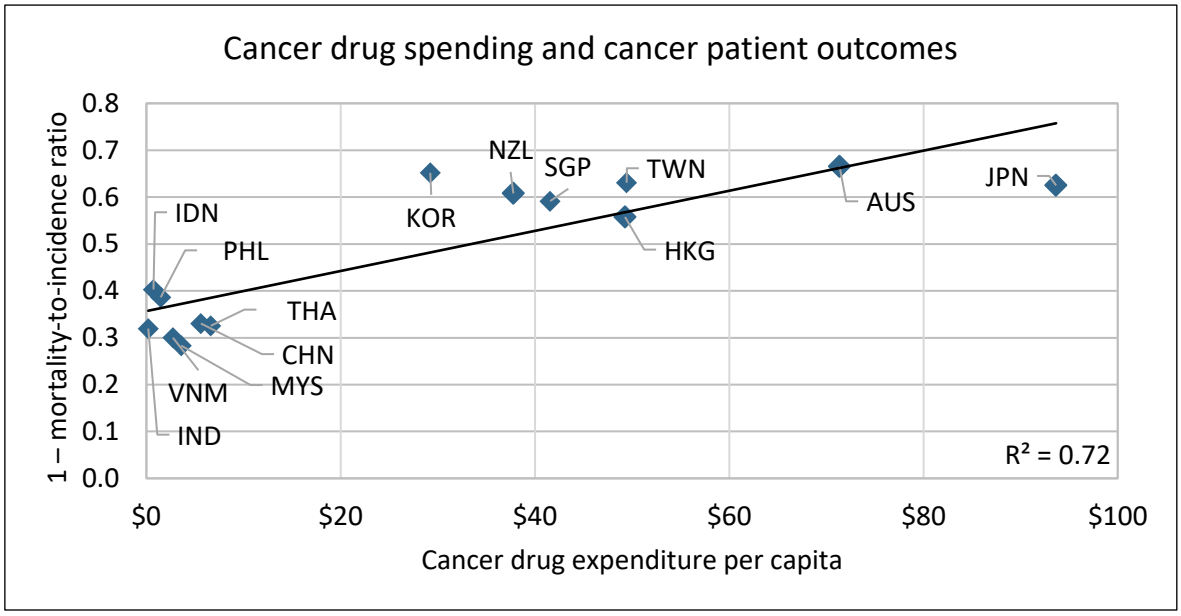

Figure 4: Total cancer drug expenditure per capita and complement of the mortality-to-incidence ratio of cancer, 2018

Notes: Cancer drug expenditure include financing from public and private sources. They are not adjusted for differences in purchasing power parity and refer to 2019 in absence of data for 2018. Cancer drug expenditure for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total sales in China and <1% of total sales in Taiwan). Cancer drug expenditure for Indonesia do not contain most sales of generics/biosimilars.
Source: National cancer registries and GLOBOCAN for mortality-to-incidence ratio (see sub-report 1) and IQVIA/IPMG sales data for cancer drug expenditure (see Figure 3).

Each dot in Figure 4 represents a market and the drawn (unweighted) line represents the relationship between resource use and outcomes inferred based on the 14 markets in Asia-Pacific. A strong positive correlation can be observed (correlation coefficient of 0.72; 0 is no correlation and 1 is

perfect correlation), which suggests that markets with higher spending on cancer drugs achieve better patient outcomes. A relationship of this kind does not need to be causal, but it suggests that the level of cancer drug spending (which should be closely related to spending on other cancer care services as well) might be a stronger driver of cancer patient outcomes. A similar analysis drawing on a set of countries in Europe has found a comparable association (21).

3. Public health spending on cancer drugs

This section explores the level of public health spending on innovative cancer drugs used in the treatment of five major cancer types – breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, non-small cell lung cancer – in Asia-Pacific. Innovation status was defined according to the ESMO-MCBS score (drug indications with a "substantial clinical benefit") (22), analogously to sub-report 3. The section aims to answer the following question: What is the level of public health spending on innovative cancer drugs?

3.1 Method and data

As described in section 2.1, public authorities typically do not report drug expenditure on the disease level. In this report, the following method was used to estimate cancer drug expenditure covered by public sources (i.e., the government) in 2019. The starting point was IQVIA quarterly sales data (and IPMG data for Indonesia) on drugs in 2019, covering both private and public sales. As in sub-report 3, cancer drugs used in the treatment of five cancer types – breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, non-small cell lung cancer – were included in the analysis; see Table A1 in the Appendix for the full list of 141 drug-indications.

In the first step, the reimbursement status of all indications of every drug in all quarters of 2019 was deduced from the date of inclusion in the respective national formularies (see Table A2 in the Appendix for an overview of the reimbursement schemes used).[3] Secondly, sales of drugs with multiple indications were split into different indications based on a proxy for potential patient numbers (incidence; see Table A1 in the Appendix of sub-report 1 for sources used), due to the limitation that IQVIA data do not capture sales by indication.[4] This allowed us to estimate the total public cancer drug expenditure on reimbursed indications only. A limitation of the sole consideration of the five cancer types is that some drugs may still have some reimbursed indications in other cancer

[3] India's health system is relatively fragmented and does not have a comprehensive national reimbursement scheme as yet; the National List of Essential Medicines (NLEM) was used as a proxy for inferring reimbursement status instead. In Singapore, two schemes, Standard Drug List (SDL) and Medication Assistance Fund (MAF), were used to infer reimbursement status, but in reality three additional public health insurance schemes (MediShield Life, MediSave, MediFund) can be used to cover treatment costs of approved cancer drugs. In Thailand, the National List of Essential Medicines (NLEM) was used as all three main public health insurance schemes (CSMBS, SSS, UCS) provide drugs on this list.

[4] In case a drug had only received regulatory approval for several indications, sales were split among those indications, whereas in case a drug had received reimbursement status for one or several indications, sales were only split among the reimbursed indications. This means that for drugs with multiple approved indications and where not all indications are reimbursed, sales in non-reimbursed indications cannot be discerned from remaining sales and are counted as reimbursed. The same applies to drugs with multiple approved indications within the same cancer type.

types, e.g., cetuximab and regorafenib may also be reimbursed for use in colorectal cancer. It was not possible to separate these sales from the ones included in the analysis. The estimates derived here for public drug expenditure on the five cancer types thus represent upper bounds of the true size of expenditure.

Thirdly, the total public expenditure were categorized under sales of innovative drug-indications and other drug-indications (see Table A1 in the Appendix). Innovation status was defined according to ESMO-MCBS score with a "substantial magnitude of clinical benefit", i.e. a score of A or B in the curative setting and 5 or 4 in the non-curative setting (22).

Another limitation of the IQVIA/IPMG data is that sales are based on the published list prices and volume of drugs sold. Thus, they do not capture confidential rebates and arrangements between public payers and pharmaceutical manufacturers, which leads to an overestimation of spending levels reported in this section. In addition, we are unable to separate any patient co-payments from the estimated public drug expenditure. Despite reimbursement status of a drug, patient co-payments (prescription fees) exist across markets in Asia-Pacific; see Appendix for examples. The amount of co-payment varies between markets and also depending on the specific drug within a specific market (e.g., higher co-payments on patent-protected drugs than on older drugs for which generic versions are available). Therefore, the estimates derived here for public drug expenditure are upper bounds.

3.2 Results

Public expenditure on cancer drugs used in the treatment of breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, and non-small cell lung cancer differ widely across markets in Asia-Pacific in 2019. Figure 5 shows that public spending (based on list prices) on the basket of 141 drug-indications in middle income markets was in the range of $0.1 to $2.9 per capita. By contrast, public spending ranged from $9 per capita in New Zealand to $58 in Japan in the high-income markets. As already observed in section 2, New Zealand's spending level is comparatively

Box 1: Public coverage of cancer drug expenditure in Singapore

In Singapore, cancer drug expenditure of patients are covered in several ways. At public health care institutions, older drugs with generic availability are often covered by the Standard Drug List (SDL) with 50% subsidies for all Singaporeans and the Medication Assistance Fund (MAF) with up to 75% subsidies for means-tested Singaporeans from lower to middle income households. There are also three public health insurance schemes, known as the "3M", MediShield Life (MSL), MediSave, and MediFund, for use at both public and private health care institutions that build on the already subsidized health care in public healthcare institutions (23). For cancer drug therapy, patients can draw up to SGD 3,000 per month under MSL, and up to SGD 1,200 per month under MediSave. MediFund is in place for low-income citizens who require further financial assistance (24).

low, and this might be partly due to the strict price control imposed via PHARMAC's capped budgeting (20).

Out of the 141 drug-indications, there were 38 classified as innovative according to the ESMO-MCBS scoring system. Figure 5 shows that public drug spending across these innovative drugs-indications was less than $1 per capita in all middle-income markets in 2019. Across high-income markets, this ranged from $7 in New Zealand to $34 in Japan. The relative difference in average spending between high-income and middle-income markets is thus larger for innovative drug-indications ($16 and $0.4, respectively) than for all drug-indications ($24 and $1.1, respectively).

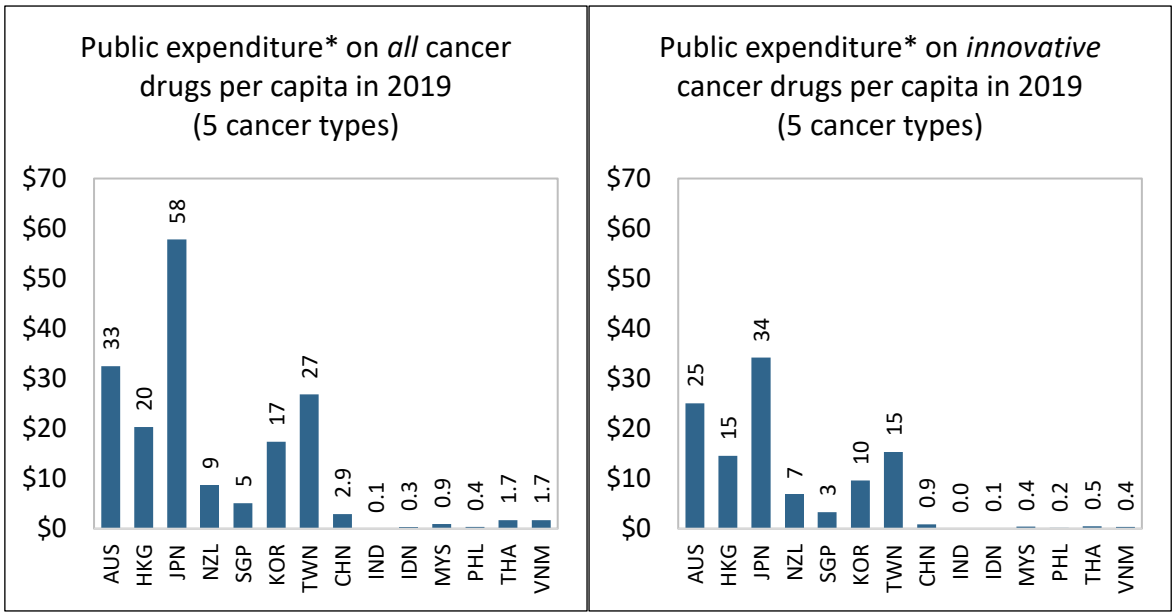

Figure 5: Public expenditure on cancer drugs of five selected cancer types per capita in US$, 2019

Notes: All cancer drugs refer to 141 indications and innovative cancer drugs to a subset of 38 indications used in the treatment of breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, and lung cancer; see Table A1 in the Appendix. * Including any OOP prescription fees for reimbursed drugs. Cancer drug expenditure are in current prices and are not adjusted for differences in purchasing power parity. Underlying sales data are based on list prices and do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers. The absolute numbers reported here are thus upper bound estimates, except for Singapore where expenditure covered by the public health insurance scheme MediShield Life (MSL) are not included. Sales data for cancer drugs for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total cancer drug sales in China and <1% of total cancer drug sales in Taiwan). Sales data for cancer drugs for Indonesia do not contain most sales of generics/biosimilars. Source: IQVIA MIDAS database (18) and IPMG sales data in IDN.

In Singapore, public expenditure on cancer drugs were based on the limited drugs and indications that have been listed on the SDL and MAF (see Box 1). Therefore, the current analysis indicated relatively low public expenditure on cancer drugs per capita at around $3-5. However, public health insurance schemes known as the "3M" (see Box 1) are available for patients to access cancer drugs beyond those listed on the SDL and MAF. For example, the government had spent SG$ 156.5 million in 2018 to provide financial assistance to low-income citizens via the MediFund (25). Such public

investment in cancer care in Singapore have not been captured in this analysis, as we are unable to distinguish between the different financing sources with IQVIA sales and other available data.

The relatively higher public spending on – both innovative and other – cancer drugs in high-income markets might be partly related to higher list prices in these markets compared to middle-income markets. Another reason are vast differences in reimbursement rates of drugs. Indeed, the analysis in sub-report 3 shows that the average reimbursement rate of the sample of innovative drug-indications was 59% in high-income markets and 17% in middle-income markets; in the sample of all drug-indications the rates were 53% and 30% respectively.

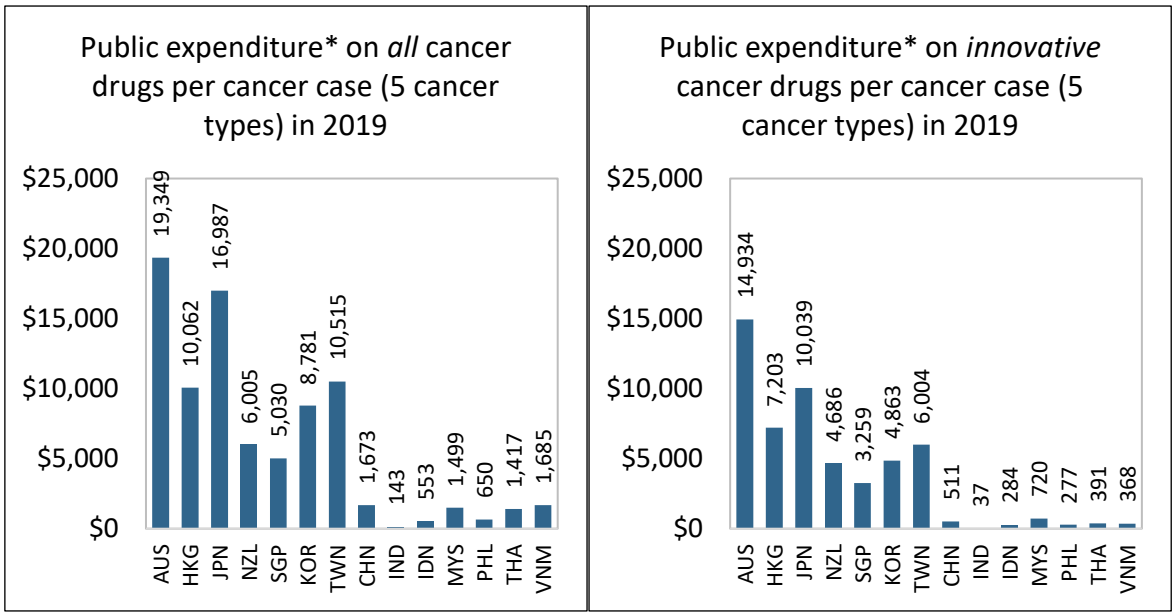

Figure 6: Public expenditure on (all and innovative) cancer drugs of five selected cancer types per cancer case in US$, 2019

Notes: * Including any OOP prescription fees for reimbursed drugs. Cancer drug expenditure are in current prices and are not adjusted for differences in purchasing power parity. Underlying sales data are based on list prices and do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers. The absolute numbers reported here are thus upper bound estimates, except for Singapore where expenditure covered by the public health insurance scheme MediShield Life (MSL) are not included. Sales data for cancer drugs for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total cancer drug sales in China and <1% of total cancer drug sales in Taiwan). Sales data for cancer drugs for Indonesia do not contain most sales of generics/biosimilars. Cancer drugs used in the treatment of breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, and lung cancer are included; see Table A1 in the Appendix of sub-report 1 for the full list. Cancer case is defined as cancer incidence (newly diagnosed cases) of the five included cancer types in 2018 in absence of data for 2019.
Source: IQVIA MIDAS database for sales data of cancer drugs (18), and national cancer registries and GLOBOCAN for cancer cases (see sub-report 1).

The higher number of cancer patients also contributes to the relatively higher public spending on cancer drugs in high-income markets. Therefore, Figure 6 shows spending levels per cancer case, defined as the sum of newly diagnosed cases of the five specific cancer types included. Public spending on all cancer drugs (based on list prices) ranged from $6,000 per cancer case in New Zealand to around $20,000 in Australia in the high-income markets (excluding Singapore; see Box

1). In middle-income markets public spending ranged from just above $140 per cancer case in India to around $1,700 in China and Vietnam.

Public spending on innovative drugs in high-income markets was on average $7,300 compared to $370 in middle-income markets. For all drugs, the corresponding averages were $11,000 and $1,100, respectively. The greater differences for innovative drugs might be related to the lower numbers of innovative cancer drugs being reimbursed in middle-income markets as noted above.

4. Patient needs in relation to cancer drug spending

The previous sections have established that spending on cancer drugs differs widely across markets in Asia-Pacific, even after considering differences in patient numbers. Reimbursement plays an important role here. Yet, despite securing national reimbursement, patient access to the specific treatment might not necessarily be guaranteed, e.g., due to the presence of high patient co-payments. This section quantifies to what extent the level of cancer drug spending meets patient needs. It aims to answer the following question: Is health spending on cancer drugs sufficient to meet patient needs?

4.1 Method and data

A case study of the cancer drug pemetrexed was conducted to illustrate how well spending on cancer drugs meets patient needs. The period of analysis was the third quarter of 2020 (Q3, July to September).

Pemetrexed is a chemotherapy drug and has been in use globally since 2004. It was available in all 14 markets across Asia-Pacific in 2020. Other than Japan, it had already lost its patent protection and faced generic competition (see sub-report 5). It is predominantly[5] used in the treatment of non-small cell lung cancer (NSCLC) and had received the following approved indications by the US FDA:

- August 2004: Second line after prior chemotherapy, as monotherapy, in locally advanced or metastatic disease. The approval was based on clinical trial data showing non-inferiority to docetaxel (26).
- September 2008: First line, in combination with cisplatin, in locally advanced or metastatic non-squamous disease. The approval was based on clinical trial data showing superiority to gemcitabine + cisplatin in patients with non-squamous disease but not with squamous disease (27).
- July 2009: Second line after four cycles of platinum-based chemotherapy (maintenance treatment in non-progressing disease), as monotherapy, in locally advanced or metastatic non-squamous disease. The approval was based on clinical trial data showing superiority to placebo (28).

[5] It is also used together with cisplatin in the treatment of mesothelioma, a relatively rare cancer type.

- May 2017: First line, in combination with pembrolizumab and carboplatin (or cisplatin since August 2018), in metastatic non-squamous disease with no EGFR or ALK genomic tumor aberrations. The approval was based on clinical trial data showing superiority to pemetrexed + carboplatin (later also to pemetrexed + cisplatin) (29).

The initial second-line indication, approved in 2004, was later limited to the treatment of patients with non-squamous disease by the US FDA. The bottom three indications of pemetrexed for first-line treatment and second-line maintenance are all innovative indications, each with an ESMO-MCBS score of 4 (22).

Analysis of drug volume needed

Several steps were taken to assess the drug volume of pemetrexed required to meet patient needs. First, the patient target population was defined as "*first-line therapy for non-squamous disease in stage IIIB+IIIC+IV NSCLC*". With advancement in research, pemetrexed in combination with cisplatin is no longer standard of care (SoC) in some patient segments. This concerns EGFR+ and ALK+ patients where tyrosine kinase inhibitors are SoC, EGFR/ALK wild type patients with high PD-L1 expression where immunotherapy drugs as monotherapy are SoC, and EGFR/ALK wild type patients without strong PD-L1 expression where the combination of immunotherapy and chemotherapy drugs is SoC, based on NCCN guidelines (30).

Table 1: Reimbursement status of first-line treatment options in advanced non-squamous NSCLC in the third quarter of 2020 across Asia-Pacific

		Pemetrexed	EGFR-TKI	ALK-TKI	IO mono for PD-L1 TPS≥50	IO chemo combo
High-income markets	Australia	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
	Hong Kong	**Yes**	**Yes**	**Yes**	**Yes**	No
	Japan	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
	New Zealand	**Yes**	**Yes**	**Yes**	No	No
	Singapore	*	*	*	*	*
	South Korea	**Yes**	**Yes**	**Yes**	No	No
	Taiwan	**Yes**	**Yes**	**Yes**	**Yes**	No
Middle-income markets	China	**Yes**	**Yes**	**Yes**	No	No
	India	No	No	No	No	No
	Indonesia	**Yes**	**Yes**	No	No	No
	Malaysia	No (2L only)	**Yes**	No	No	No
	Philippines	No	No	No	No	No
	Thailand	No	No	No	No	No
	Vietnam	**Yes**	**Yes**	No	No	No

Notes: * In Singapore, pemetrexed is not on the SDL or MAF but patients are covered through the 3M schemes (see Box 1). In Thailand, the information here is based on the NLEM. TKI = tyrosine kinase inhibitor, IO = immunotherapy, TPS = tumor proportion score, mono = monotherapy, chemo combo = in combination with chemotherapy, 2L = second line.
Source: Retrieved from sources listed in Table A2 in the Appendix.

Therefore, the estimated addressable population for pemetrexed would reduce in size when (i) an EGFR inhibitor, (ii) an ALK inhibitor, and/or (iii) immunotherapy in monotherapy for PD-L1 TPS≥50% was reimbursed in first-line therapy in the local market in Q3 2020; see Table 1. This was based on the assumption that these three types of treatment would replace pemetrexed in their respective patient segments. The final patient target population in each market is shown in Table 2.

Second, the average drug volume needed per patient was calculated for pemetrexed. The general dosage schedule for pemetrexed (both if given as monotherapy or in combination) is 500 mg/m^2 on day 1 of each 21-day cycle. A body surface area of 1.8 m^2 was assumed. In markets where the combination of pemetrexed and pembrolizumab was reimbursed, this combination was assumed to be the SoC, based on NCCN guidelines (30). The following average treatment duration with pemetrexed was assumed:

- If pemetrexed is given in combination with cisplatin, it is administered for up to 6 cycles in the absence of disease progression or unacceptable toxicity. The average treatment duration in the pivotal clinical trial (H3E-MC-JMDB) was 3.0 months (27).
- If pemetrexed is given in combination with pembrolizumab and carboplatin/cisplatin, it is administered until disease progression or unacceptable toxicity. The average treatment duration in the pivotal clinical trial (KEYNOTE-189) was 8.1 months (31).

Third, the total volume of pemetrexed needed (in milligram) was derived by combining the number of patients in the target population with the average drug volume needed per patient.

Analysis of drug volume administered

The drug volume of pemetrexed administered to patients was defined as the drug volume sold in Q3 2020.[6] Data on volume sold (in milligrams) was obtained from the IQVIA MIDAS database for each market in Asia-Pacific (18). For Indonesia, IPMG data did not contain sales of generic versions and sales of the originator drugs were zero, which is why this market was excluded from the analysis. The IQVIA data available do not provide a split by public and private channels across all markets, and neither by indication nor by line of therapy.[7] However, the latter issues are less problematic for pemetrexed than for most other cancer drugs because of its narrow use in clinical practice for NSCLC only.

[6] Despite the COVID-19 pandemic, sales volumes of pemetrexed do not show any noticeable increases or decreases in Q3 2020 compared to quarters throughout 2019 in all markets in the IQVIA MIDAS database.
[7] Use of pemetrexed in the treatment of mesothelioma was assumed to be negligible. Note that pemetrexed is typically not used in second-line or later-line therapy if it is already used in first-line therapy.

*Table 2: Estimation of eligible patients for first-line treatment of advanced non-squamous NSCLC with pemetrexed in 2020**

		Lung cancer incidence	NSCLC in lung cancer	Non-squamous in NSCLC	EGFR+ in non-squamous	ALK+ in non-squamous	PD-L1 TPS≥50% in EGFR- ALK-	Disease stage IIIB+IIIC+IV	Eligible patients
		[a]	[b]	[c]	[d]	[e]	[f]	[g]	[h]
High-income markets	Australia	12,712	85%	74%	19%	3%	25%	70%	3,266
	Hong Kong	5,252	85%	74%	48%	3%	30%	70%	795
	Japan	125,100	85%	74%	48%	3%	30%	70%	18,932
	New Zealand	2,255	85%	74%	19%	3%	25%	70%	772
	Singapore ^	1,556	85%	74%	48%	3%	30%	70%	235
	South Korea	26,985	85%	74%	48%	3%	30%	70%	5,834
	Taiwan	16,023	85%	74%	48%	3%	30%	70%	2,425
Middle-income markets	China	774,323	85%	74%	48%	3%	30%	70%	167,399
	India	67,795	85%	74%	31%	3%	25%	75%	31,982
	Indonesia	30,023	85%	74%	48%	3%	30%	70%	6,887
	Malaysia	4,686	85%	74%	48%	3%	30%	70%	1,075
	Philippines	17,255	85%	74%	48%	3%	30%	70%	7,597
	Thailand	23,957	85%	74%	48%	3%	30%	70%	10,548
	Vietnam	23,667	85%	74%	48%	3%	30%	70%	5,429

Notes: Eligible patients [h] are obtained by multiplying column [a] with [b], [c], [g] and – depending on information provided in Table 1– with (1-[d]), (1-[e]), (1-[f]).
* Eligible patient numbers are later divided by 4 in the actual calculations to match sales in Q3 2020.
^ For Singapore it was assumed that patients have access to EGFR/ALK and IO mono for PD-L1 TPS≥50%.
Sources: [a] national cancer registries and GLOBOCAN cited in sub-report 1, with numbers for 2018 used as a proxy for 2020. [b] (32, 33). [c] (34). [d] (32, 35, 36). [e] (37). [f] (37). [g] (32, 33).

4.2 Results

Medical treatment of many cancer types has changed radically during the last two decades with the availability of targeted therapy and immunotherapy. Yet unmet patient needs are still high in most cancer types. Non-small cell lung cancer is a cancer type characterized by high unmet needs, as evidenced by a 5-year survival rate of around 20% (see sub-report 1). The chemotherapy drug pemetrexed together with cisplatin has offered the subset of patients with non-squamous disease the prospect of prolonged survival compared to previous first-line therapy since 2009. With US FDA approval in 2017, the addition of the immunotherapy drug pembrolizumab to pemetrexed and cisplatin/carboplatin has further improved survival prospects in EGFR/ALK wild type patients.

Table 3 shows to what extent patient needs for treatment with pemetrexed was met based on information on the volume of pemetrexed sold in Q3 2020 and the patient segment addressed by pemetrexed. For Australia, Japan, and Singapore, the volume needed was based on use in EGFR/ALK wild type patients without high PD-L1 expression and the combination therapy with pembrolizumab and cisplatin/carboplatin for on average 8.1 months per patient. In all other markets, the volume needed was based on use in the combination therapy with cisplatin only for on average 3.0 months per patient in the respective patient population, see Table 1 and Table 2.

In Australia and Japan, around half (47% and 48%, respectively) of the patient needs of pemetrexed was met compared to over 80% in Singapore. For Japan, previous studies on drug use in advanced NSCLC have also pointed to a large proportion of patients (around 32%) not receiving any first-line systemic treatment, as well as suboptimal testing for genomic alterations required to administer targeted therapies (38, 39). For Australia, an explanation of the gap in unmet patient needs might be the limitation of reimbursement of the combination of pemetrexed and pembrolizumab to patients with ECOG performance status (PS) 0 and 1, thus denying patients with PS 2-4 this treatment (40, 41). Treatment guidelines by the European Society for Medical Oncology (ESMO) recommend systemic treatment to metastatic NSCLC patients with PS 0-2 (42). Previous studies indicated that around one third of lung cancer patients might have PS 2-4 in Australia (43).

In the other high-income markets, patient needs seem to be fully met in Hong Kong, South Korea, and Taiwan. In fact, the achievement of 100% patient need is unrealistic, as there are patients with poor performance status who cannot receive systemic treatment. An explanation for the high numbers in these three markets might be the use of pemetrexed for longer than the average treatment duration observed in the pivotal clinical trial, which was 3.0 months and capped at six cycles (27), due to

ensuing maintenance therapy. In the control arm of the pivotal clinical trial of pemetrexed and pembrolizumab, the average treatment duration of pemetrexed was 5.7 months without capping (31).

Table 3: Drug volume needed vs. drug volume administered of pemetrexed in the third quarter of 2020

		Reimbursement status of pemetrexed in first-line non-squamous NSCLC	Addressable patient group	Proportion of pemetrexed volume sold relative to estimated patient needs
High-income markets	Australia	Yes (combo with pembrolizumab)	EGFR/ALK wild type TPS<50%	47%
	Hong Kong	Yes (combo with cisplatin)	EGFR/ALK wild type TPS<50%	100%
	Japan	Yes (combo with pembrolizumab)	EGFR/ALK wild type TPS<50%	48%
	New Zealand	Yes (combo with cisplatin)	EGFR/ALK wild type	51%
	Singapore	Yes* (combo with pembrolizumab)	EGFR/ALK wild type TPS<50%	81%
	South Korea	Yes (combo with cisplatin)	EGFR/ALK wild type	100%
	Taiwan	Yes (combo with cisplatin)	EGFR/ALK wild type TPS<50%	100%
Middle-income markets	China	Yes (combo with cisplatin)	EGFR/ALK wild type	84%
	India	No	All non-squamous	7%
	Indonesia	Yes (combo with cisplatin)	EGFR wild type	n/a
	Malaysia	No (second line only)	EGFR wild type	28%
	Philippines	No	All non-squamous	2%
	Thailand	No	All non-squamous	5%
	Vietnam	Yes (combo with cisplatin)	EGFR wild type	75%

Notes: * In Singapore, pemetrexed is not on the SDL or MAF but it is assumed patients have access through the 3M schemes (see Box 1). n/a = no sales of the originator drug or generic versions recorded in the IQVIA MIDAS database.

Unmet patient needs are high in most middle-income markets. China and Vietnam are the only markets that seem to be able to meet patient needs. They are also the only markets (except for Indonesia with missing data) where pemetrexed is reimbursed. Co-payments apply in both China and Vietnam, see Appendix. In Vietnam, a 50% patient co-payment applies to pemetrexed, which might explain the higher proportion of unmet need compared to China where co-payments tend to be a bit lower but might vary across the country. In Malaysia, pemetrexed is only reimbursed as a second-line treatment and the total sales recorded (which include private sales) would have only been sufficient to meet the needs of less than a third of patients. In India, the Philippines, and Thailand there was no national reimbursement of pemetrexed in any line of therapy. Sales are thus predominantly financed by private sources. Limited access via self-pay in these markets means that fewer than 5% of eligible patients see their clinical needs being met.

Even though the analysis in this section is only based on the case of pemetrexed, several conclusions can be drawn. First, reimbursement of drugs is vital for the vast majority of patients to gain access. Without reimbursement, patients are forced to pay the full price out-of-pocket. This exceeds the financial means of most patients even if there might already by generic versions available, such as for pemetrexed. Second, high-income markets may struggle to meet patient needs in the initial years after a new medical treatment is introduced. In Australia and Japan, the combination therapy of pemetrexed and pembrolizumab had been approved for 7 months and 18 months, respectively, before Q3 2020. Slow uptake of new treatments can either be caused by factors within the health system (such as rigid clinical processes) or outside the health system (such as restrictions in use imposed by narrow reimbursement criteria). Lastly, markets that do not yet reimburse the combination of pemetrexed with immunotherapy (let alone markets that do not yet reimburse pemetrexed with cisplatin only) continue to amass staggering numbers of patient life years lost until reimbursement, as shown in sub-report 3 due to significant delays or the lack of reimbursement of innovative cancer treatment.

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Appendix

Table A1: List of US FDA-approved indications and ESMO-MCBS score (Sep 30, 2020)

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Abemaciclib	BC	2L, combo with fulvestrant, HR+ HER2-, advanced or metastatic	28-Sep-2017	4	Innovative
Abemaciclib	BC	1L, combo with aromatase inhibitor, HR+ HER2-, advanced or metastatic	26-Feb-2018	3	Others
Abemaciclib	BC	2L, mono, HR+ HER2-, advanced or metastatic	28-Sep-2017		Others
Afatinib	LUC	1L, mono, EGFR+, metastatic	12-Jan-2018 (12-Jul-2013)	4	Innovative
Afatinib	LUC	2L, mono, SQ, metastatic	15-Apr-2016	2	Others
Alectinib	LUC	1L, mono, ALK+, metastatic	6-Nov-2017	4	Innovative
Alectinib	LUC	2L, mono, ALK+, metastatic	11-Dec-2015	4	Innovative
Alpelisib	BC	2L, combo with fulvestrant, HR+ HER2- PIK3CA+, advanced or metastatic	24-May-2019	3	Others
Anastrozole	BC	2L, mono, advanced	27-Dec-1995		Others
Anastrozole	BC	1L, mono, HR+, advanced or metastatic	1-Sep-2000		Others
Anastrozole	BC	Adjuvant, HR+	5-Sep-2002		Others
Atezolizumab	LUC	2L, mono, metastatic	18-Oct-2016	5	Innovative
Atezolizumab	BC	1L, combo with nab-paclitaxel, triple-negative, PD-L1+, advanced or metastatic	8-Mar-2019	3	Others
Atezolizumab	LIC	1L, combo with bevacizumab, HCC, metastatic	29-May-2020		Others
Atezolizumab	LUC	1L, combo with bevacizumab + paclitaxel + carboplatin, NSQ, EGFR- ALK-, metastatic	6-Dec-2018	3	Others
Atezolizumab	LUC	1L, combo with nab-paclitaxel + carboplatin, NSQ, EGFR- ALK-, metastatic	3-Dec-2019	3	Others
Atezolizumab	LUC	1L, mono, PD-L1+ EGFR- ALK-, metastatic	18-May-2020		Others
Bevacizumab	LIC	1L, combo with atezolizumab, HCC, metastatic	29-May-2020		Others
Bevacizumab	LUC	1L, combo with carboplatin + paclitaxel, NSQ, metastatic	11-Oct-2006	2	Others
Bleomycin	HNC	1L, mono, SCCHN, metastatic	31-Jul-1973		Others
Brigatinib	LUC	1L, mono, ALK+, metastatic	22-May-2020 (2-Oct-2017)	3	Others
Cabozantinib	LIC	2L, mono, HCC, metastatic	14-Jan-2019	3	Others
Capecitabine	BC	2L/3L, mono, metastatic	30-Apr-1998		Others
Capecitabine	BC	2L, combo with docetaxel, metastatic	7-Sep-2001		Others
Capmatinib	LUC	1L, mono, MET+, metastatic	6-May-2020		Others
Ceritinib	LUC	1L, mono, ALK+, metastatic	26-May-2017 (29-Apr-2014)	4	Innovative
Cetuximab	HNC	1L, combo with radiation therapy, SCCHN, advanced	1-Mar-2006		Others
Cetuximab	HNC	2L, mono, SCCHN, metastatic	1-Mar-2006		Others
Cetuximab	HNC	1L, combo with platinum + fluorouracil, SCCHN, metastatic	7-Nov-2011	3	Others
Crizotinib	LUC	1L, mono, ALK+ or ROS1+, metastatic	21-Jul-2017 (26-Aug-2011)	4 / 3	Innovative

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Cyclophosphamide	BC	1L, mono	[16-Nov-1959]		Others
Dabrafenib	LUC	1L, combo with dabrafenib, BRAF V600E+, metastatic	22-Jun-2017	2	Others
Dacomitinib	LUC	1L, mono, EGFR+, metastatic	27-Sep-2018	3	Others
Docetaxel	GEC	1L, combo with cisplatin + fluorouracil, gastric or GEJ AC, advanced	22-Mar-2006	A	Innovative
Docetaxel	BC	2L, mono, advanced or metastatic	22-Jun-1996 (14-May-1996)		Others
Docetaxel	BC	Adjuvant, combo with doxorubicin and cyclophosphamide, node-positive	18-Aug-2004		Others
Docetaxel	HNC	1L, combo with cisplatin + fluorouracil, SCCHN, advanced	28-Sep-2007 (17-Nov-2006)		Others
Docetaxel	LUC	2L, mono, advanced or metastatic	23-Dec-1998		Others
Docetaxel	LUC	1L, combo with cisplatin, advanced or metastatic	27-Nov-2002		Others
Doxorubicin	BC	1L, mono, metastatic	[7-Aug-1974]		Others
Doxorubicin	BC	Adjuvant, combo	8-May-2003		Others
Doxorubicin	GEC	1L, mono, gastric, metastatic	[7-Aug-1974]		Others
Durvalumab	LUC	2L, mono, stage III	16-Feb-2018	4	Innovative
Entrectinib	LUC	1L, mono, ROS1+, metastatic	15-Aug-2019	3	Others
Epirubicin	BC	Adjuvant, combo	15-Sep-1999		Others
Eribulin	BC	3L, mono, metastatic	15-Aug-2010	2	Others
Erlotinib	LUC	1L or laterL, mono, EGFR+, metastatic	18-Oct-2016 (18-Nov-2004)	4	Innovative
Everolimus	BC	2L, combo with exemestane, HR+ HER2-, advanced	20-Jul-2012	2	Others
Exemestane	BC	2L, mono, advanced	21-Oct-1999		Others
Exemestane	BC	Adjuvant after tamoxifen, ER+	5-Oct-2005		Others
Fluorouracil	GEC	Perioperative, combo with cisplatin, gastric or GEJ or esophageal AC, resectable	[25-Apr-1962]	A	Innovative
Fluorouracil	BC	1L, mono, AC	[25-Apr-1962]		Others
Fulvestrant	BC	2L, mono, HR+, advanced	25-Aug-2017 (25-Apr-2002)	2	Others
Fulvestrant	BC	2L, combo with palbociclib or abemaciclib, HR+ HER2-, advanced or metastatic	14-Nov-2018 (2-Mar-2016)		Others
Fulvestrant	BC	1L, mono, HR+ HER2-, advanced	25-Aug-2017	2	Others
Fulvestrant	BC	1L/2L, combo with ribociclib, HR+ HER2-, advanced or metastatic	11-Mar-2019		Others
Gefitinib	LUC	1L, mono, EGFR+, metastatic	13-Jul-2015 (3-May-2003)	4	Innovative
Gemcitabine	BC	1L, combo with paclitaxel, metastatic	19-Mar-2010 (19-May-2004)		Others
Gemcitabine	LUC	1L, combo with cisplatin, metastatic	19-Mar-2010 (25-Aug-1998)		Others
Goserelin	BC	1L, mono, advanced	31-Aug-2009 (1989)		Others
Hydroxyurea	HNC	1L, combo with chemoradiation, SCCHN, advanced	[7-Dec-1967]		Others
Ipilimumab	LIC	2L, combo with nivolumab, HCC, metastatic	10-Mar-2020		Others
Ipilimumab	LUC	1L, combo with nivolumab, PD-L1+ EGFR- ALK-, metastatic	15-May-2020		Others
Ipilimumab	LUC	1L, combo with nivolumab + Pt-based chemo, EGFR- ALK-, metastatic	26-May-2020		Others

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Ixabepilone	BC	3L, combo with capecitabine, metastatic	16-Oct-2007		Others
Ixabepilone	BC	4L, mono, metastatic	16-Oct-2007		Others
Lapatinib	BC	2L, combo with capecitabine, HER2+, advanced or metastatic	13-Mar-2007	3	Others
Lapatinib	BC	1L, combo with letrozole, HR+ HER2+, metastatic	29-Jan-2010		Others
Larotrectinib	LUC	1L, mono, NTRK+, metastatic	26-Nov-2018	3	Others
Lenvatinib	LIC	1L, mono, HCC, unresectable	15-Aug-2018	4	Innovative
Letrozole	BC	1L/2L, mono, HR+, advanced	2-Mar-2010 (25-Jul-1997)		Others
Letrozole	BC	Adjuvant after tamoxifen	29-Oct-2004		Others
Letrozole	BC	Adjuvant, HR+	28-Dec-2005		Others
Lorlatinib	LUC	2L/3L, mono, ALK+, metastatic	2-Nov-2018	3	Others
Methotrexate	BC	1L, mono	[10-Aug-1959]		Others
Methotrexate	HNC	1L, mono, epidermoid	[10-Aug-1959]		Others
Methotrexate	LUC	1L, mono, SQ	[10-Aug-1959]		Others
Mitomycin	GEC	1L, combo with chemo, gastric AC, metastatic	1-Jan-1974		Others
Necitumumab	LUC	1L, combo with gemcitabine + cisplatin, SQ, metastatic	24-Nov-2015	1	Others
Neratinib	BC	Adjuvant-extended, mono, HER2+	1-Oct-2018 (17-Jul-2017)	A	Innovative
Neratinib	BC	3L, combo with capecitabine, HER2+, metastatic	25-Feb-2020		Others
Nivolumab	HNC	2L, mono, SCCHN, metastatic	10-Nov-2016	4 / 5	Innovative
Nivolumab	LUC	2L, mono, metastatic	9-Oct-2015 (4-Mar-2015)	5	Innovative
Nivolumab	LIC	2L, mono or combo with ipilimumab, HCC, metastatic	10-Mar-2020 (22-Sep-2017)		Others
Nivolumab	LUC	1L, combo with ipilimumab, PD-L1+ EGFR- ALK-, metastatic	15-May-2020		Others
Nivolumab	LUC	1L, combo with ipilimumab + Pt-based chemo, EGFR- ALK-, metastatic	26-May-2020		Others
Nivolumab	GEC	2L, mono, ESCC, metastatic	10-Jun-2020	4	Innovative
Olaparib	BC	2L, mono, gBRCAm+ HER2-, metastatic	12-Jan-2018	4	Innovative
Osimertinib	LUC	2L, mono, EGFR-T790M+, metastatic	13-Nov-2015	4	Innovative
Osimertinib	LUC	1L, mono, EGFR+, metastatic	18-Apr-2018	4	Innovative
Paclitaxel	BC	2L, mono, metastatic	13-Apr-1994		Others
Paclitaxel	BC	Adjuvant, combo with doxorubicin-based chemo, node-positive	25-Oct-1999		Others
Paclitaxel	LUC	1L, combo with cisplatin, metastatic	30-Jun-1998		Others
Paclitaxel-nab	BC	2L, mono, metastatic	7-Jan-2005		Others
Paclitaxel-nab	LUC	1L, combo with carboplatin, advanced or metastatic	11-Oct-2012		Others
Palbociclib	BC	2L, combo with fulvestrant, HR+ HER2-, advanced or metastatic	19-Feb-2016	4	Innovative
Palbociclib	BC	1L, combo with aromatase inhibitor, HR+ HER2-, advanced or metastatic	31-Mar-2017 (3-Feb-2015)	3	Others
Pembrolizumab	HNC	1L, mono, SCCHN, PD-L1+, metastatic	17-Jun-2019	4 / 5	Innovative
Pembrolizumab	HNC	1L, combo with platinum + fluorouracil, SCCHN, metastatic	17-Jun-2019	4	Innovative
Pembrolizumab	HNC	2L, mono, SCCHN, metastatic	5-Aug-2016	4	Innovative
Pembrolizumab	LUC	2L, mono, PD-L1+, metastatic	24-Oct-2016 (2-Oct-2015)	5	Innovative
Pembrolizumab	LUC	1L, mono, PD-L1+ EGFR- ALK-, stage III or metastatic	11-Apr-2019 (24-Oct-2016)	5	Innovative

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Pembrolizumab	LUC	1L, combo with pemetrexed + carboplatin, NSQ, EGFR- ALK-, metastatic	30-Oct-2018 (17-May-2017)	4	Innovative
Pembrolizumab	LUC	1L, combo with carboplatin + (nab-)paclitaxel, SQ, metastatic	30-Oct-2018	4	Innovative
Pembrolizumab	LIC	2L, mono, HCC, metastatic	9-Nov-2018		Others
Pembrolizumab	GEC	3L, mono, gastric or GEJ AC, PD-L1+, metastatic	22-Sep-2017		Others
Pembrolizumab	GEC	2L, mono, ESCC, PD-L1+, metastatic	30-Jul-2019		Others
Pemetrexed	LUC	2L maintenance, NSQ, advanced or metastatic	2-Jul-2009	4	Innovative
Pemetrexed	LUC	1L, como with cisplatin, NSQ, advanced or metastatic	11-Oct-2017 (26-Sep-2008)	4	Innovative
Pemetrexed	LUC	2L, mono, NSQ, metastatic	11-Oct-2017 (19-Aug-2004)		Others
Pemetrexed	LUC	1L, combo with pembrolizumab + carboplatin, NSQ, EGFR- ALK-, metastatic	30-Jan-2019 (4-Jun-2018)		Others
Pertuzumab	BC	1L, combo with trastuzumab + docetaxel, HER2+, metastatic	8-Jun-2012	4	Innovative
Pertuzumab	BC	Adjuvant, combo with trastuzumab + chemotherapy, HER2+	20-Dec-2017	B	Innovative
Pertuzumab	BC	Neoadjuvant, combo with trastuzumab + chemotherapy, HER2+	20-Dec-2017 (30-Sep-2013)	C	Others
Pralsetinib	LUC	1L, mono, RET+, metastatic	4-Sep-2020		Others
Ramucirumab	LIC	2L, mono, HCC, metastatic	10-May-2019	1	Others
Ramucirumab	LUC	2L, combo with docetaxel, metastatic	12-Dec-2014	1	Others
Ramucirumab	LUC	1L, combo with erlotinib, EGFR+, metastatic	29-May-2020	3	Others
Ramucirumab	GEC	2L, mono or combo with paclitaxel, gastric or GEJ AC, metastatic	12-Dec-2014 (21-Apr-2014)	2	Others
Regorafenib	LIC	2L, mono, HCC, metastatic	27-Apr-2017	4	Innovative
Ribociclib	BC	1L, combo with aromatase inhibitor, HR+ HER2-, advanced or metastatic	18-Jul-2018 (13-Mar-2017)	3 / 5	Innovative
Ribociclib	BC	1L or 2L, combo with fulvestrant, HR+ HER2-, advanced or metastatic	18-Jul-2018	4	Innovative
Sacituzumab govitecan	BC	3L, mono, triple-negative, metastatic	22-Apr-2020		Others
Selpercatinib	LUC	1L, mono, RET+, metastatic	8-May-2020		Others
Sorafenib	LIC	1L, mono, HCC, metastatic	16-Nov-2007		Others
Talazoparib	BC	1L, mono, gBRCAm+ HER2-, advanced or metastatic	16-Oct-2018	4	Innovative
Tamoxifen	BC	1L, mono, metastatic	29-Oct-1998 (30-Dec-1977)		Others
Tamoxifen	BC	Adjuvant, mono	29-Oct-1998 (30-Dec-1977)		Others
Thiotepa	BC	1L, mono, metastatic	9-Mar-1959		Others
Toremifene	BC	1L, mono, ER+, metastatic	20-Nov-1997		Others
Trametinib	LUC	1L, combo with dabrafenib, BRAF V600E+, metastatic	22-Jun-2017		Others
Trastuzumab	BC	Adjuvant / 1L / laterL, mono/combo, HER2+, all stages	18-Jan-2008 (25-Sep-1998)	A	Innovative
Trastuzumab	GEC	1L, mono, gastric or GEJ AC, metastatic	20-Oct-2010		Others
Trastuzumab deruxtecan	BC	3L, mono, HER2+, metastatic	20-Dec-2019	2	Others
Trastuzumab emtansine	BC	2L, mono, HER2+, metastatic	19-Aug-2013	4	Innovative

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Trastuzumab emtansine	BC	Adjuvant, mono, HER2+	3-May-2019		Others
Trifluridine & tipiracil	GEC	3L, mono, gastric or GEJ AC, metastatic	22-Feb-2019	3	Others
Tucatinib	BC	2L, combo with trastuzumab and capecitabine, HER2+, advanced or metastatic	17-Apr-2020	3	Others
Vinblastine	BC	2L, metastatic	[25-Nov-1965]		Others
Vinorelbine	LUC	1L, mono, metastatic	14-Mar-2014 (23-Dec-1994)		Others
Vinorelbine	LUC	1L, combo with cisplatin, advanced or metastatic	14-Mar-2014 (23-Dec-1994)		Others

Notes: BC = breast cancer, GEC = gastro-esophageal cancer, HNC = head and neck cancer, LIC = liver cancer, LUC = non-small cell lung cancer. AC = adenocarcinoma, ESCC = esophageal squamous cell carcinoma, GEJ = gastroesophageal junction, HCC = hepatocellular carcinoma, NSQ = non-squamous, SCCHN = squamous cell carcinoma of the head and neck, SQ = squamous. FDA approval dates in parenthesis () indicate original date of approved indication that has been replaced by the current one, and brackets [] indicate drug approval date in absence of information on indication approval date.

Table A2: National regulatory drug agencies and national drug reimbursement schemes

	MARKET	REGULATORY AGENCY	REIMBURSEMENT SCHEME
HIGH-INCOME MARKETS	Australia	Therapeutic Goods Administration (TGA)	Pharmaceutical Benefits Scheme (PBS) list
	Hong Kong	Drug Office (DO)	Hospital Authority Drug Formulary (HADF), Samaritan Fund (SF), Community Care Fund (CCF)
	Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	National Health Insurance (NHI) list
	New Zealand	Medicines and Medical Devices Safety Authority (Medsafe)	Pharmaceutical Management Agency (PHARMAC) list
	Singapore	Health Sciences Authority (HSA)	Standard Drug List (SDL), Medication Assistance Fund (MAF)
	South Korea	Ministry of Food and Drug Safety (MFDS)	National Health Insurance (NHI) list
	Taiwan	Food and Drug Administration (FDA)	National Health Insurance (NHI) list
MIDDLE-INCOME MARKETS	China	National Medical Products Administration (NMPA)	National Reimbursement Drug List (NRDL)
	India	Central Drugs Standard Control Organisation (CDSCO)	(no scheme for entire population)*
	Indonesia	National Agency of Drug and Food Control (BPOM)	National Formulary (Fornas)
	Malaysia	National Pharmaceutical Regulatory Agency (NPRA)	Ministry of Health Medicines Formulary (MOHMF)
	Philippines	Food and Drug Administration (FDA)	Philippine National Formulary (PNF)
	Thailand	Food and Drug Administration (FDA)	National List of Essential Medicines (NLEM)
	Vietnam	Drug Administration of Vietnam (DAV)	Reimbursement Drug List (RDL)

Notes: * In the analysis, inclusion in the National List of Essential Medicines (NLEM) in its latest version from 2015 was used as a proxy for inferring reimbursement status.

Out-of-pocket payments on reimbursed cancer drugs

Co-payments for prescribed cancer drugs are common across Asia-Pacific; see below for a list of examples. Different sizes in co-payment need to be taken into consideration when interpreting the size of public expenditure on cancer drugs shown in Figure 5 and Figure 6 in this report, as co-payments are included in the presented numbers.

High-income markets:

- **Australia**: Most drugs on the Pharmaceutical Benefits Scheme (PBS) require a co-payment of AUD 41.30 per prescription (or AUD 6.60 for special groups with a concession card) (44). Notably, the number of treatment cycles with patent-protected cancer drugs is typically restricted on the PBS. For example, the number packs of osimertinib is restricted to five (45), enough for five months of treatment, which can be compared to over 20 months of treatment in the key clinical trial of osimertinib in first-line EGFR-positive non-small cell lung cancer (46). After the co-payment of AUD 41.30 for each of the five packs paid via the PBS, patients would face a dispense price of AUD 7,971.16 per pack.
- **Japan**: Co-payments of 10% to 30% (depending on income level and age) apply to prescription drugs on the National Health Insurance (NHI) list. Two safety nets, Tokutei Shikkan Iryo Hojo and Kogaku Ryoyohi Seido, exists to protect from excessive amounts of co-payments (47).
- **New Zealand**: There is a NZD 5 co-payment per prescription drug listed with PHARMAC, yet drugs administered directly in hospitals come with no co-payment (48).
- **Singapore**: As described in Box 1 above, several public schemes exist to cover costs of cancer drugs. According to the Ministry of Health, the coverage they provided every month was enough to fully cover drug treatment costs for 9 out of 10 patients in 2017 (23).

Middle-income markets:

- **China**: Drug co-payments and deductibles vary by insurance scheme, by province/city and by drug (49). Drugs included on A List of the National Reimbursement Drug List (NRDL) are free of co-payment nationwide for insured persons of the UEBMI or URBMI scheme. The level of reimbursement for drugs on the B list of the NRDL is set by local authorities and varies across the country. Previous studies noted that patients might not be able to afford the high co-payment rates in order to access targeted therapies on the B list of the NRDL (50). For instance, the average co-payment rate in tertiary hospitals for patients enrolled in urban and rural medical insurance systems was 40.7% for trastuzumab. The absolute size of

the co-payment for annual treatment with trastuzumab (around $6,600) exceeded the average disposable income per capita (around $4,300) in 2018 (50).

- **Vietnam**: For most targeted therapies (including tyrosine kinase inhibitors like Afatinib, Gefitinib, Sorafenib and monoclonal antibodies such as Bevacizumab, Cetuximab, Trastuzumab) on the latest Reimbursement Drug List (RDL) issued in 2018, health insurance will pay 50% of the costs (51). Co-payment might also differ depending on the indication of a specific drug (e.g., trastuzumab has a coverage ratio of 60% in breast cancer and 50% in gastric cancer). For most chemotherapies, health insurance will cover all costs.

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