CANCER CARE AND ACCESS TO CANCER DRUGS IN ASIA-PACIFIC

Patient access to innovative cancer drugs in Asia-Pacific

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PATIENT ACCESS TO INNOVATIVE CANCER DRUGS IN ASIA-PACIFIC

Sub-report 3 of the main report "Cancer care and access to cancer drugs in Asia-Pacific"

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Report summary

Cancer drugs are essential for improving patient outcomes. Almost 100 new cancer drugs have been launched over the last decade alone. While this is a welcome development for patients, not all drugs offer the same level of innovation. Constrained health care budgets could be aided by an increased focus on innovative cancer drugs that provide the greatest benefit to patients. Value frameworks, such as ESMO-MCBS, have been put forward to help classify cancer drugs with the aim to identify "*innovative*" cancer drugs (in this report defined as drugs with a "*substantial clinical benefit*" with an ESMO-MCBS score of 4 and 5 or B and A) that should be priorities for rapid reimbursement by national bodies from a clinical perspective.

Access to innovative cancer drugs through reimbursement is quite limited in Asia-Pacific. Of 38 innovative drug-indications approved by the US FDA in treatment of five major cancer types (breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, non-small cell lung cancer) between 1998 and 2020, 80% had received regulatory approval across Asia-Pacific in 2020. Yet only 35% of those indications were also reimbursed in 2020. The approved proportion of cancer drugs in general (141 indications in the five cancer types) was around 71% in Asia-Pacific compared to the US FDA, and the proportion of drug-indications with a positive reimbursement status was 39%.

A clear division in access to innovative cancer drugs exists between high-income and middle-income markets in Asia-Pacific. High-income markets achieve much higher proportions of both regulatory approval and reimbursement approval rates (91% and 59%, respectively) than middle-income markets (68% and 17%, respectively). Among the latter group, China, Indonesia, and Vietnam approve relatively fewer indications but at the same time reimburse a higher proportion of them. Among high-income markets, Japan sticks out due to its policy to reimburse all approved drugs essentially by default, which stands in stark contrast to the restrictive reimbursement policy observed in New Zealand.

Timely reimbursement of innovative cancer drugs is a major challenge in all markets in Asia-Pacific except in Japan. In high-income markets along with China, the median delay between regulatory approval and reimbursement approval was around 1.5 to 3 years. Yet a full assessment was not possible as reimbursement was still pending for many indications at the data cut-off. In all middle-income markets except China, delays could not be assessed, because there are essentially no recent innovative indications (launched globally during the last 10 years) that have ever achieved reimbursement listing.

The lack of timely reimbursement of innovative cancer drugs results in a great loss of patient life years. For every year of delay in reimbursement, almost 1 million patient life years are lost across

Asia-Pacific, drawing on a limited sample of only 10 innovative drug-indications. As cancer patients across Asia-Pacific typically face much longer delays in access to innovative cancer drugs than one year, their health outcomes could be greatly improved by faster reimbursement decisions.

Reasons for delayed reimbursement of innovative cancer drugs vary across markets in Asia-Pacific. In middle-income markets, they relate more to limited public health budgets as well as the organization of the reimbursement process with listings being infrequently reviewed and updated. In high-income markets, they relate more to the criteria applied in the reimbursement process (e.g., acceptance of surrogate endpoints, comparator in clinical trial reflective of current clinical practice, cost-effectiveness thresholds) and the lack of fast-track systems for innovative drugs (e.g., prioritized process with shorter timelines for drug-indications that lack a comparable alternative as in South Korea).

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1. Innovative cancer drugs

Cancer drugs are essential for improving patient outcomes (1). The last decade has seen a surge in the number of new cancer drugs being launched in the US (2). The situation is similar in Europe, where 92 new cancer drugs received marketing authorization between 2011 and 2020 compared to 35 new cancer drugs between 2001 and 2010; see Figure 1. New drugs offer new treatment options to patients, but they also represent a challenge for health care system. As the standard of care evolves rapidly in certain cancer types, medical staff needs to be trained continuously to be able to use the new treatments and clinical guidelines need to be updated frequently. In addition, health care budgets are constrained and health care payers around the world struggle to absorb the recent wave of new cancer drugs.

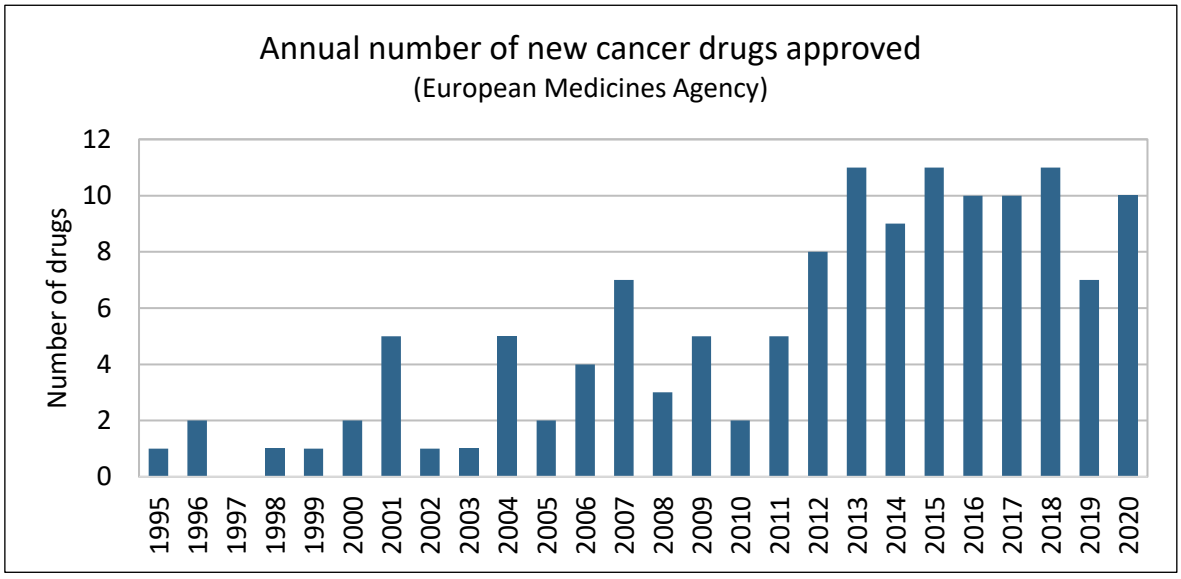

Figure 1: Annual number of new cancer drugs approved by the European Medicines Agency between 1995 and 2020

Source: EMA (3).

In fact, the price of new cancer drugs and the budget impact of cancer drugs as a whole are frequently debated topics. In the US, cancer patients might face financial hardship due to out-of-pocket expenses towards insurance co-payments, coinsurance, deductibles for prescription and non-prescription drugs, hospitalization, outpatient services and other medical care (4-9). It was estimated that 10%-20% of patients might decide to compromise on their treatment plan or not to take treatment due to considerations of these out-of-pocket expenses (10). In Europe, the debate focuses more on the sustainability of increasing public health expenditure on cancer drugs, because public payers (governments or sickness funds) cover the vast majority of the cost of cancer care (including cancer drugs) for the whole population (11, 12). In Asia-Pacific, the debate is also characterized by considerations of financial toxicity (see sub-report 2), especially in markets without comprehensive

universal health coverage, as well as of sustainability of publicly-funded health systems (13). Yet cancer drugs only account for between 1-22% of total pharmaceutical expenditure across markets in Asia-Pacific (see sub-report 4).

The value of a new cancer drug, as with any other new therapeutic intervention, is determined by its clinical benefit compared to its costs (14). Within budget-constrained health system, considerations of value can guide decision makers and help adopt new cancer drugs that are cost-effective and provide value-for-money. While costs of new cancer drugs may vary from country to country, the clinical benefit for an individual patient should be relatively constant across countries. In order to enable a meaningful discussion on the value of new cancer drugs, two major value frameworks to measure clinical benefit have been launched in recent years: the American Society of Clinical Oncology Value Framework (ASCO VF) and the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) (15, 16).

Clinical benefit in the context of the value frameworks refers to the added (i.e., relative) benefit compared with a control which, ideally, reflects the current standard of care. Consideration of the relative clinical benefit is important, as not all new drugs offer the same improvement over the existing treatment standard. In addition, value frameworks such as the ESMO-MCBS do not consider drugs at the molecular level but align with the specific indication and addressable patient population considered in pivotal clinical trials. This means that relative clinical benefit is closely geared to the use of a drug in a certain tumor type (e.g., lung cancer), tumor subtype (e.g., EGFR-positive non-small cell lung cancer), line of therapy (e.g., first line or later-line therapy), and treatment setting (curative or metastatic).

A scoring system for clinical benefit of cancer drugs can help national reimbursement bodies to distinguish between innovative and non-innovative drugs. Indeed, the ambition of the ESMO-MCBS is to be just that, a tool to inform the process of prioritization of access to cancer drugs when resources are limited (15, 17). It is also advantageous that this scoring system is provided directly by physicians through an international organization (European Society for Medical Oncology) which ensures objectivity and transparency and makes it less susceptible to the influence of external stakeholders with vested interests (e.g., individual country governments, pharmaceutical industry, patient organizations).

1.1 Aim of the sub-report

The aim of this sub-report is to describe patient access to innovative cancer drugs in Asia-Pacific.[1]

- Section 2 explores the regulatory approval and reimbursement status of cancer drugs.
- Section 3 examines the delay between regulatory and reimbursement decisions.
- Section 4 showcases the consequences for patients of delayed reimbursement.
- Section 5 discusses reasons for delayed reimbursement.

[1] 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. Innovative cancer drugs in national formularies

This section explores the regulatory approval status and the reimbursement status of cancer drugs across all markets in Asia-Pacific. It aims to answer the following question: What is the proportion of innovative cancer drugs in the national formulary?

2.1 Method and data

The following steps were taken to assess the availability of innovative cancer drugs in all 14 markets in Asia-Pacific. The first step involved the definition of a sample of innovative cancer drugs. We focused on drugs used in the same five cancer types (breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, non-small cell lung cancer (NSCLC)) as in sub-report 1. For all cancer types, we retrieved data on approved indications by the Food and Drug Administration (FDA) in the United States. The cut-off date was September 30, 2020. This yielded 141 indications of 72 drugs, approved between 1959 and 2020; see Table A1 in the Appendix for the full list. Figure 2 summarizes the proportion of the 141 indications across the five cancer types and shows that most approved indications are found in breast cancer (43%) and NSCLC (35%).

In the next step, we added information on the innovation status to the list of FDA-approved indications. To this end, we used the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS); see Box 1. Indications with an ESMO-MCBS score of 4 and 5 or A and B were classified as innovative; see Table A1 in the Appendix for the ESMO-MCBS score of each indication. The cut-off date was once again September 30, 2020. In total, 38 indications could be classified as "innovative", approved between 1998 and 2020.[2] NSCLC had the highest absolute number of innovative

Box 1: ESMO-MCBS and innovative drugs

Launched in 2015, the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) provides scores for new indications of cancer drugs used in solid tumors. The scale considers overall survival, progression-free survival, disease free survival, hazard ratio, response rate, quality of life, prognosis of the condition, and toxicity (18).

- Indications in a curative setting receive a score of A, B, or C. A is the highest score and C is the lowest score.
- Indications 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. In this report, indications with a "*substantial clinical benefit*" are called "*innovative*".

[2] It should be noted that most indications approved before 2010 lack an ESMO-MCBS score, because ESMO-MCBS was launched in 2015 and only few indications before that time were scored retroactively. Several indications approved in 2020 also lacked an ESMO-MCBS score at the time of data retrieval.

indications (18), whereas head and neck cancer the highest relative number of innovative indications (4 out of 11; 36%); see Figure 2.

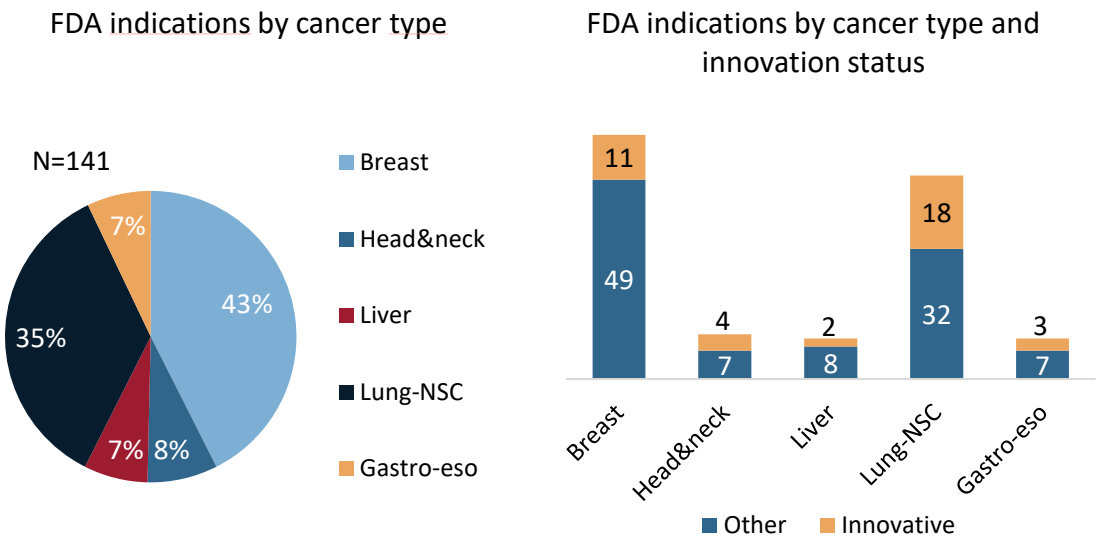

Figure 2: Overview of the sample of FDA-approved indications by cancer type

Notes: Breast = breast cancer, Head&neck = head and neck cancer, Liver = liver cancer, Lung-NSC is non-small cell lung cancer, Gastro-eso = gastro-esophageal cancer.
Source: FDA (19) and ESMO-MCBS (18).

In the final step, publicly available information [3] on the regulatory approval status and the reimbursement status of all 141 FDA-approved indications was retrieved in all 14 markets as of September 30, 2020. Table A2 in the Appendix provides an overview of the relevant national regulatory agencies responsible for drug approval (i.e., marketing authorization) as well as national reimbursement schemes for drugs (i.e., the national formulary) considered in the analysis. Analysis of reimbursement schemes are more complicated in certain markets and the following choices were made:

- India: A scheme for the entire population is lacking, partly due to its decentralized health system (20); the National List of Essential Medicines (NLEM) was used as a proxy for inferring reimbursement status instead.
- Singapore: Two schemes, Standard Drug List (SDL) and Medication Assistance Fund (MAF), were used to infer reimbursement status. In reality, three additional public health

[3] Table A3 in the Appendix provides an overview of the level of granularity in public information in the respective market. In general, information on the indication level was available in most markets. Information only at the drug level was available in (1) Hong Kong for regulatory approval status and reimbursement status in the Hospital Authority Drug Formulary, (2) India for reimbursement status inferred from the National List of Essential Medicines, (3) Japan for regulatory approval status and reimbursement status of drugs launched before 2004, (4) the Philippines for regulatory approval status, (5) Vietnam for reimbursement status.

insurance schemes (MediShield Life, MediSave, MediFund) can be used to cover treatment costs of approved cancer drugs (see Box 1 in sub-report 4) (21, 22).

- 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, and only the CSMBS, covering 8% of the population, through the Oncology Prior Authorization (OCPA) covers a slightly longer list of cancer drugs (23).

2.2 Results

To explore and compare the availability of cancer drugs in terms of regulatory approval status and reimbursement status within and across markets, results are presented with two different approaches. The first uses a common benchmark: approved indications by the US FDA. The second uses a local benchmark: approved indications by the national regulatory agency in the respective market. Results are also presented separately using either the whole sample of 141 indications across the five cancer types (breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, NSCLC) or the smaller sample of 38 innovative indications.

Sample of all indications

Figure 3 shows the proportions of drug-indications with positive regulatory approval status and positive reimbursement status compared to the US FDA benchmark as of Sep 30, 2020. Among the 141 drug-indications approved by the US FDA, around 71% had also received regulatory approval across Asia-Pacific. Across high-income markets, close to 80% of drug-indications had received regulatory approval, except for New Zealand at 65%. In middle-income markets, the average proportion was 62%, but there was great variation between markets ranging from around 50% in China and Indonesia to around 70% in India, Malaysia, and Thailand.

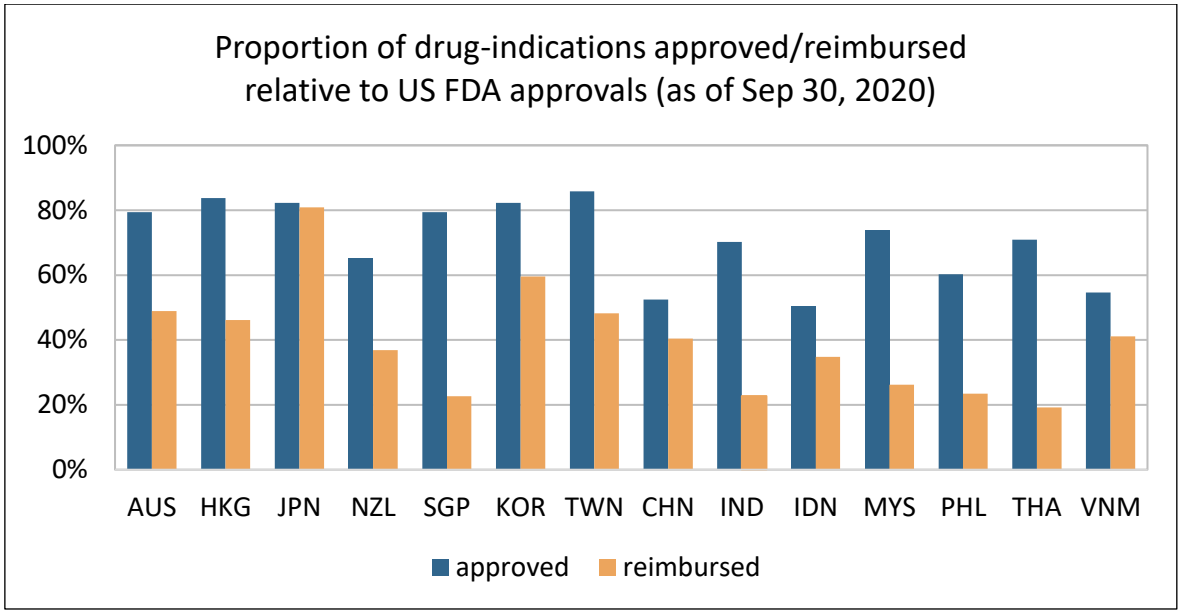

Figure 3: Proportion of drug-indications approved/reimbursed relative to US FDA approvals (as of Sep 30, 2020)

Notes: Numbers reflect the status on Sep 30, 2020. 100% refers to all 141 US FDA indications approved on Sep 30, 2020. Reimbursement in IND is based on the NLEM 2015. Reimbursement in SGP is underestimated as MediShield Life (MSL) can be used to cover most prescriptions.

The proportion of drug-indications with a positive reimbursement status (39% across all markets) is generally much smaller compared to the regulatory approval status in Figure 3. The only exception is Japan. This is due to the Japanese system of including all drugs in the National Health Insurance (NHI) list once a drug is approved by the Pharmaceuticals and Medical Devices Agency (PMDA) (24). In other high-income markets, the proportion (compared to the US FDA benchmark) ranges from 37% in New Zealand to 60% in South Korea. Among the middle-income markets, China and Vietnam achieved the highest proportions of reimbursed indications of around 40%, thus exceeding New Zealand. The lowest proportion of only 19% was observed in Thailand. These proportions should also be interpreted against the backdrop of availability of generics/biosimilars in 2020. At the global level, generics/biosimilars were available for drugs that cover around 40% of all indications included in the analysis. Yet some of these older drugs might no longer be standard of care and their non-reimbursement will not affect patients as long as the newer drugs they were replaced with are reimbursed.

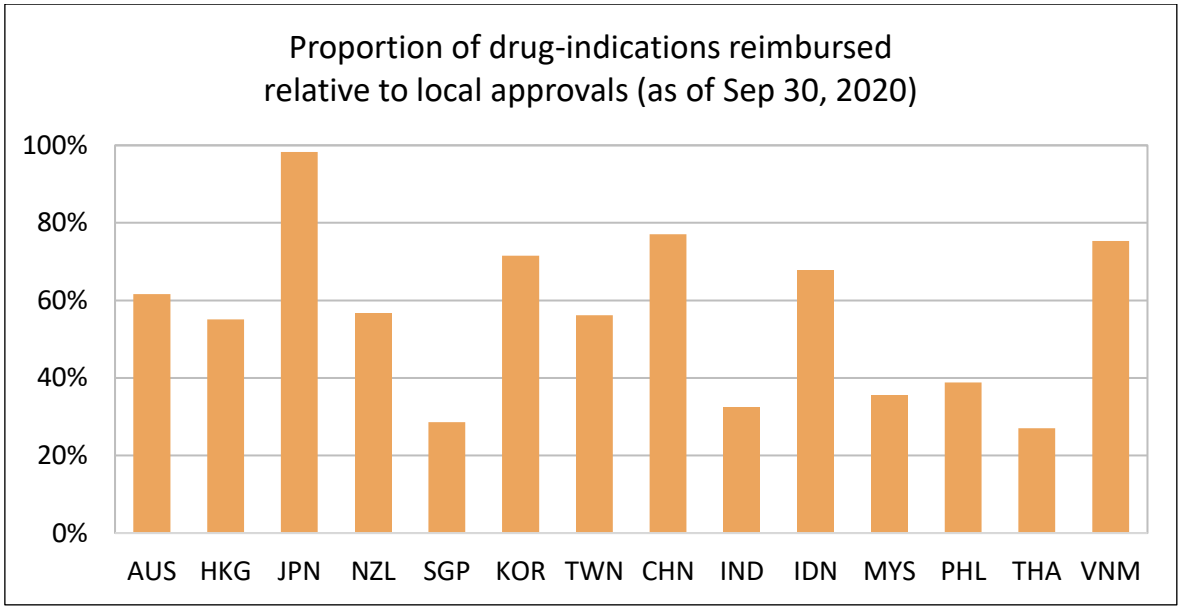

Figure 4: Proportion of drug-indications reimbursed relative to local approvals (as of Sep 30, 2020)

Notes: Numbers reflect the status on Sep 30, 2020. 100% refers to all locally approved indications (max = 141). Reimbursement in IND is based on the NLEM 2015. Reimbursement in SGP is underestimated as MediShield Life (MSL) can be used to cover most prescriptions.

In general, only locally approved drug-indications can be included in the local drug formulary. Therefore, Figure 4 shows the proportion of approved drug-indications that are made available to the general public through national reimbursement coverage in the respective local market.[4] Across Asia-Pacific, just more than half (56%) of locally approved indications were also reimbursed. Among the high-income markets, Japan (for reasons noted above) followed by South Korea achieved reimbursement proportions higher than the Asia-Pacific average. Middle-income markets fall into two categories; those that achieve a comparatively high reimbursement proportion (China, Indonesia, Vietnam, which at the same time are the three markets with the lowest regulatory approval proportion in Figure 3) and those that achieve a comparatively low proportion (India, Malaysia, Philippines, Thailand).

Sample of innovative indications

Innovative drugs are characterized by greater relative clinical benefit compared with the existing standard of care. Figure 5 shows the proportions of innovative drug-indications with positive regulatory approval status and positive reimbursement status compared to the US FDA benchmark as of Sep 30, 2020. Among the 38 innovative drug-indications approved by the US FDA, around

[4] Such a comparison eliminates the influence of factors related to the absence or delay of regulatory approval (e.g., differential timing of submissions for marketing authorization by pharmaceutical companies and length of the marketing authorization process) compared to the US FDA approval.

80% of them had received regulatory approval across Asia-Pacific. This is a higher proportion than the one observed for the whole sample of 141 drug-indications (71%). In high-income markets (average of 91%), the proportion is close to 100% in Australia, South Korea, and Taiwan, whereas it is the lowest in New Zealand at 76%. There is greater variation in the middle-income markets (average of 68%), with proportions ranging from 50% in Indonesia to 92% in Malaysia.

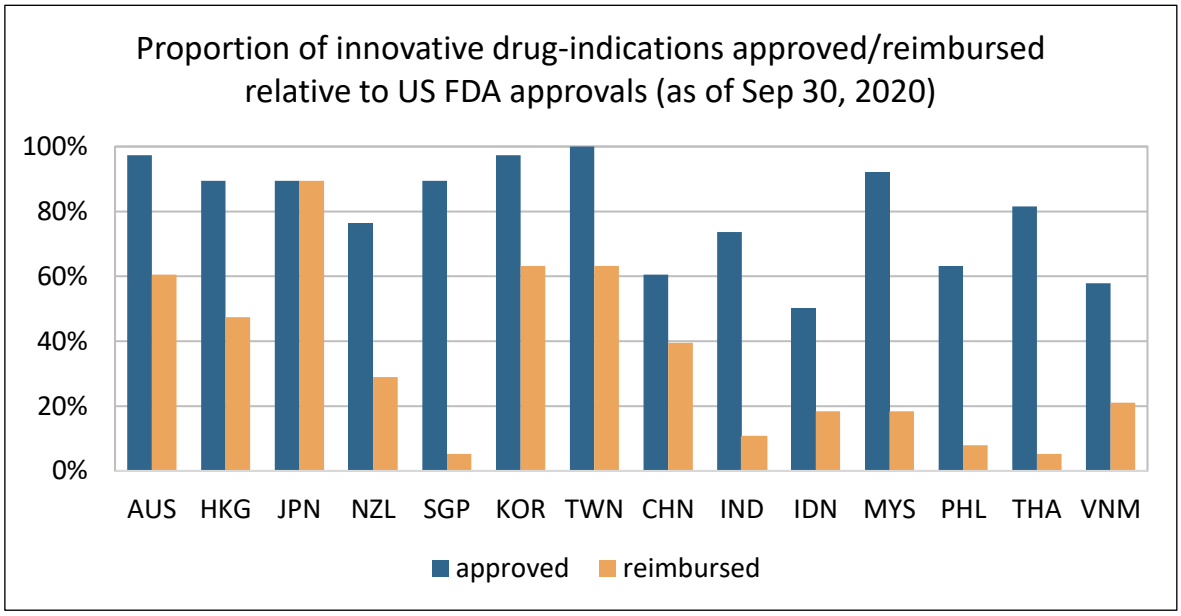

Figure 5: Proportion of innovative drug-indications approved/reimbursed relative to US FDA approvals (as of Sep 30, 2020)

Notes: Numbers reflect the status on Sep 30, 2020. 100% refers to all 38 US FDA indications approved on Sep 30, 2020. Reimbursement in IND is based on the NLEM 2015. Reimbursement in SGP is underestimated as MediShield Life (MSL) can be used to cover most prescriptions.

A defining feature of the considered innovative drug-indications is the big gap between regulatory approval status and reimbursement status in many markets. Figure 5 shows that the proportion of reimbursed indications (compared to the US FDA benchmark) is on average 35% across all markets. Yet in high income-markets it is 59% (excluding Singapore), ranging from 29% in New Zealand to 89% in Japan. In middle-income markets, it is merely 17% on average, ranging from 5% in Thailand to 39% in China. As noted above, these proportions should be interpreted against the backdrop of availability of generics/biosimilars in 2020. At the global level, generics/biosimilars were available for drugs that cover around 18% of all innovative indications included in the analysis.

A demarcation in terms of reimbursement of innovative drug-indications between high-income and middle-income markets can also be read off in Figure 6. Despite local regulatory approval, middle-income markets achieve only a reimbursement rate of 27%, ranging from 6% in Thailand to 65% in China. China, Indonesia (37%), and Vietnam (36%) have relatively higher reimbursement proportions than the other four middle-income markets, mirroring the pattern observed in Figure 4.

In comparison, around 64% of locally approved indications are reimbursed in high-income markets (excluding Singapore). Japan once again achieved 100% reimbursement of all locally approved innovative indications. For the other high-income markets, the proportion of reimbursed indications overall (Figure 4) and of innovative indications (Figure 6) is remarkably similar, suggesting no preferential treatment of innovative indications. An exception is New Zealand which reimburses distinctly fewer approved innovative indications (38%) than approved indications overall (57%).

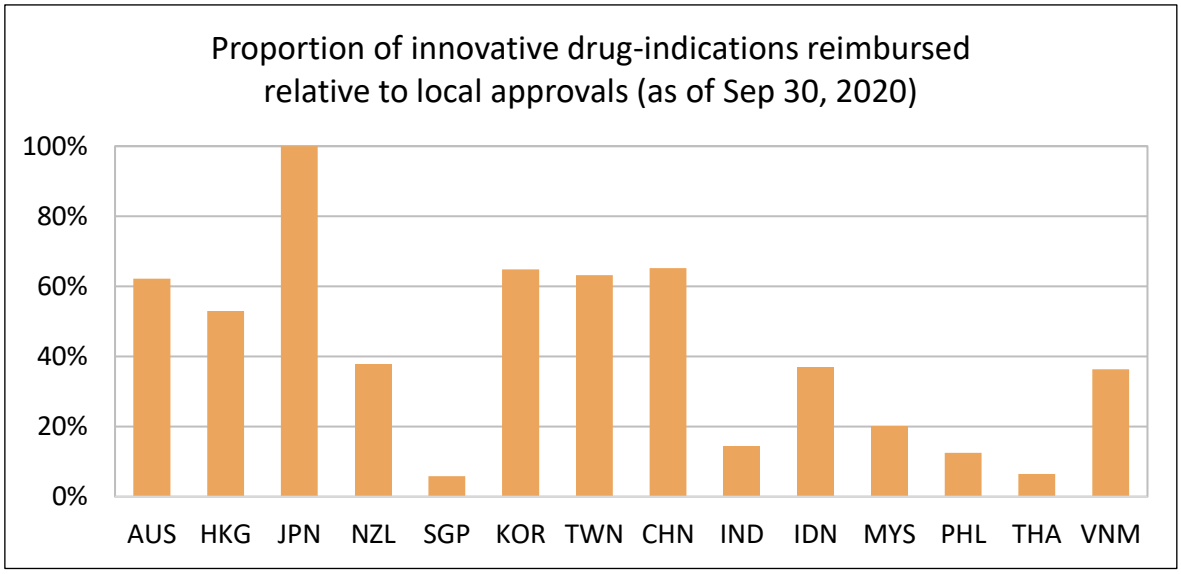

Figure 6: Proportion of innovative drug-indications reimbursed relative to local approvals (as of Sep 30, 2020)

Notes: Numbers reflect the status on Sep 30, 2020. 100% refers to all locally approved indications (max = 38). Reimbursement in IND is based on the NLEM 2015. Reimbursement in SGP is underestimated as MediShield Life (MSL) can be used to cover most prescriptions.

Figure 7 presents the same analysis as Figure 6 but separately for indications approved in breast cancer (left figure) and in NSCLC (right figure). The proportion of reimbursed innovative drug-indications for the treatment of these two cancer types varies between markets. All markets recorded higher proportions for NSCLC than for breast cancer, apart from China (same proportions) and New Zealand (higher proportion of breast cancer indications). Much of the lower proportion in breast cancer across markets is driven by a lack of reimbursement of the three CDK4/6 kinase inhibitors (abemaciclib, palbociclib, ribociclib) and the first PARP inhibitor (olaparib).

Advancement in medical research has enabled the use of precision medicines that target the abnormal biology of tumor cells or leverage biomarkers to predict response towards specific drugs (25, 26). For example, the discovery of specific oncogenic drivers in lung cancer (e.g., EGFR, ALK, etc.) along with the development of tyrosine kinase inhibitors have enabled significant improvements in the outcomes of patients with these activating mutations since the late 2000s. More recently, immunotherapy has further transformed the treatment landscape in lung cancer by offering

therapeutic options for patients without sensitizing mutations. Similar developments of personalized therapies could also be seen in other cancer types such as breast cancer.

With better understanding of tumor biology and the availability of innovative precision medicines that could offer significant benefits to specific patient sub-groups, it would be interesting to explore if there is sufficient access to address the clinical unmet needs of these different sub-groups.

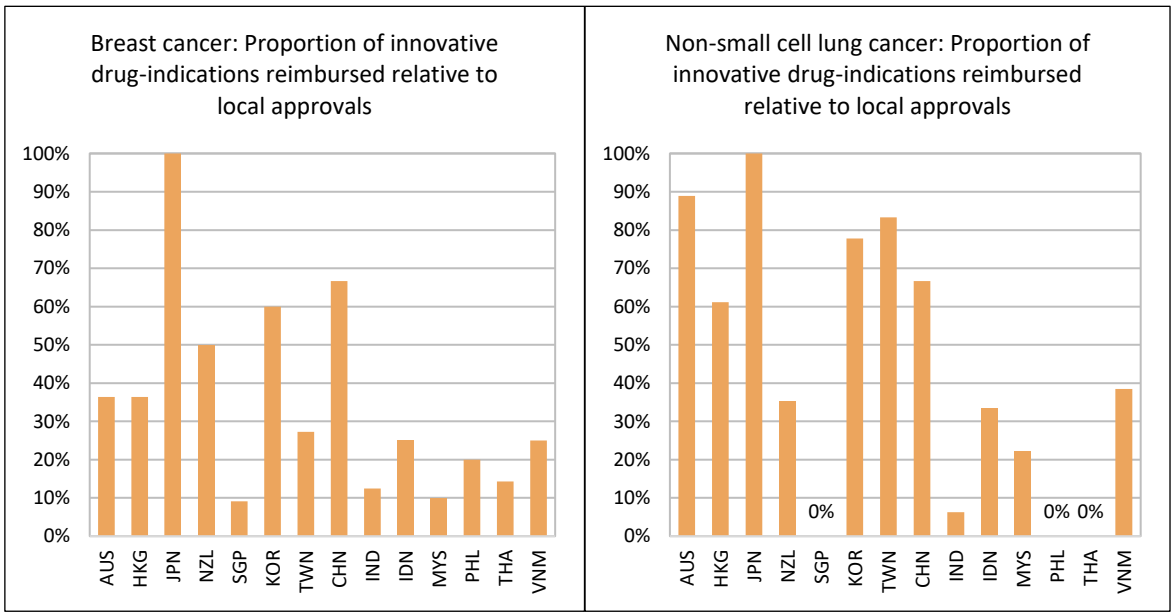

Figure 7: Proportion of innovative drug-indications reimbursed in breast cancer and NSCLC relative to local approvals (as of Sep 30, 2020)

Notes: Numbers reflect the status on Sep 30, 2020. 100% refers to all locally approved indications (max = 11 for breast cancer; max = 18 for NSCLC). Reimbursement in IND is based on the NLEM 2015. Reimbursement in SGP is underestimated as MediShield Life (MSL) can be used to cover most prescriptions.

Comparison with previous studies

There are few comparative studies looking at the issue of regulatory approval status and reimbursement status of cancer drugs. A recent study coordinated by ESMO assessed the availability of cancer drugs in most of the 14 markets considered in this report (13, 27). This study distinguished between drugs on the 2015 WHO Model List of Essential Medicines and newer drugs with an ESMO-MCBS score>2 not on the WHO list, with availability being assessed through survey answers in 2015.

The general finding for drugs on the WHO Model List of Essential Medicines (e.g., chemotherapy, trastuzumab, imatinib) was that accessibility in high-income countries and many upper-middle income countries was generally good. However, barriers to access were reported in some lower-middle income countries (especially in India and to a lesser extent in Indonesia, Philippines,

Vietnam) due to reasons such as the lack of reimbursement, budget capitation, and/or the lack of or unreliable suppliers.

For newer drugs with an ESMO-MCBS score>2, the study found that in most middle-income markets, drugs were hardly reimbursed or simply lacked regulatory approval. In high-income markets (including Australia, New Zealand, Japan, South Korea, and Singapore), the accessibility of these drugs varied. While most drugs were listed in the formulary and usually available in Japan followed by Australia, over half of them were not included in the formulary in New Zealand and Singapore. Interestingly, other barriers to access such as the lack of or unreliable suppliers and parallel exports were also reported for some instances (e.g., in New Zealand). Overall, the findings in this study align well with the patterns observed in this section.

Another study focusing on middle-income markets in Asia-Pacific assessed actual use of cancer drugs per patient, drawing on drugs listed on the 2017 WHO Model List of Essential Medicines (28). This study distinguished between traditional chemotherapy drugs, targeted drugs, and hormonal drugs. During most of the study period from 2007 to 2017, use of drugs of all three categories was the highest in Malaysia and Thailand, and distinctly lower in China, the Philippines and lastly Indonesia. The relatively higher level of access to cancer drugs in China reported in the current report study might be explained by the regular annual updates of the National Reimbursement Drug List (NRDL) since 2017, which is a promising sign of accelerated access as the list had remained unchanged in 2009-2017 (29, 30).

The analysis in this section has provided a snapshot of the approval and reimbursement status of innovative cancer drugs as of Sep 30, 2020. Clear differences in approval and reimbursement rates between markets could be observed in the region. Even though some high-income markets achieve relatively higher reimbursement rates than most middle-income markets, patient access can still be negatively affected by long delays between regulatory approval and reimbursement.

3. Delay in reimbursement of innovative cancer drugs

The previous section has established that there is a large gap between the proportion of drugs with positive regulatory approval status and positive reimbursement status. This section explores the delay between regulatory approval and positive reimbursement decision for innovative cancer drugs across all markets in Asia-Pacific. It aims to answer the following question: How long is the period from regulatory approval to reimbursement approval for innovative cancer drugs?

3.1 Method and data

The following steps were taken to assess the length of the delay between regulatory approval and positive reimbursement decision for innovative cancer drugs in all 14 markets in Asia-Pacific. The list of innovative indications described in section 2.1 was used as a starting point. Older innovative drugs that were approved by the US FDA between January 1, 1998 and January 1, 2010 were excluded. This reduced the number of innovative indications from 38 to 31; see Table A1 in the Appendix. This restriction was motivated by the fact that delays calculated in this section are supposed to be reflective of the current institutional setting and current standard of care. In addition, this restriction means that the analysis can capture a maximum delay of 10.75 years (Jan 1, 2010 to Sep 30, 2020).

Publicly available information on the exact dates of regulatory approval and/or reimbursement approval was retrieved in all 14 markets; see Table A2 in the Appendix for the relevant national regulatory agencies and national reimbursement schemes considered in the analysis. The level of granularity in public information regarding exact dates was sub-optimal in several markets; see Table A3 in the Appendix. These markets typically only provide dates of initial regulatory approval of a drug but no dates of subsequent extensions of the label to additional indications, whereas data availability for reimbursement approval dates by indication is generally better. An online search for company press releases was conducted to fill data gaps. Reimbursed indications with unclear regulatory approval dates or reimbursement approval dates were excluded from the analysis. India was excluded from the analysis as it lacks a reimbursement scheme for the entire population. In Singapore, no reimbursement dates were available although some older innovative indications were listed in the SDL or the MAF (31). In Hong Kong, only some indications in the

Box 2: Number of innovative drug-indications included in the analysis (see Table A4 in the Appendix)

AUS = 17	CHN = 8
HKG = 9	IND = 0
JPN = 27	IDN = 1
NZL = 5	MYS = 1
SGP = 0	PHL = 0
KOR = 16	THA = 0
TWN = 17	VNM 1

Community Care Fund (CCF) could be considered because of the lack of public information on reimbursement dates (32).

3.2 Results

Figure 8 presents the results of the analysis of the delay between regulatory approval and positive reimbursement decision. Across the innovative drug-indications, high-income markets generally record a median delay of 1.5 years (Australia and South Korea) to 3 years (Hong Kong and New Zealand). At the same time, the minimum delay is almost 1 year while the maximum delay is 4-6 years. Japan is the big exception. The median delay is 0 months in this analysis, because all new drugs with regulatory approval are in principal included within at most 60-90 days in the NHI list and all subsequent extensions of the drug's label to additional indications are reimbursed without any delay (24, 33, 34).

For middle-income markets, there is either no or very limited reimbursement. The delays in Indonesia (2.5 years), Malaysia (4.5 years), and Vietnam (1.5 years) are only based on a single indication and in no way reflective of a median delay. These numbers rather present the minimum reimbursement delay in these markets, as there remains no access to the other 30 innovative indications. The underlying sample for China is bigger and the median delay is 1.5 years, which is on par with some of the faster high-income markets. The Chinese numbers should also be interpreted in the light of the findings in section 2, where the emerging pattern was that comparatively few indications obtain regulatory approval (which suggests a long delay until regulatory approval), but relatively many of those are reimbursed. This is also influenced by the long delay in the update of the NRDL between 2009 and 2017 and more regular updates since then, as noted in section 2.

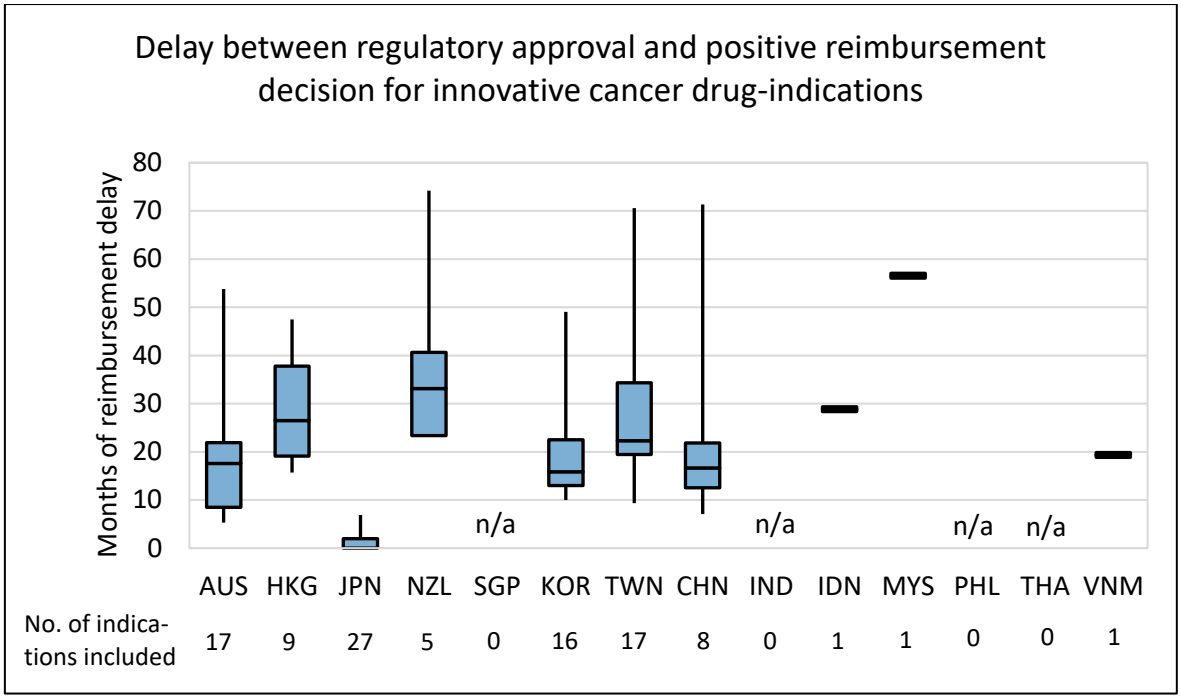

Figure 8: Delay between regulatory approval and positive reimbursement decision for innovative cancer drug-indications (in months)

Notes: The base sample contains 31 innovative drug-indications approved between Jan 1, 2010 and Sep 30, 2020 by the US FDA (see Table A1 in the Appendix), but local sample size differs (see Box 2). N/A = no innovative drugs approved or no information on regulatory/reimbursement approval dates available.
Interpretation of the boxplot: The lower/upper tips of the vertical lines denote the minimum and maximum delay, the borders of the blue boxes define the interquartile range (25th to 75th percentile), and the horizontal line inside the blue box denotes the median delay.

In general, all numbers in Figure 8 need to be interpreted with caution, especially those with few underlying indications (see Box 2). The main caveat is that only indications with a positive reimbursement decision were included in the analysis. An indication approved in 2012 still waiting for reimbursement in 2020 would have faced an 8-year delay but is not included. Delays of 8 years or longer are in fact the reality in many middle-income markets. Markets with fairly high regulatory approval rates (Malaysia, Philippines, Thailand) fail to reimburse innovative cancer drugs. This conclusion is in line with the report conducted by ESMO and described in section 2, which showed that even generic availability of cancer drugs does not entail a positive reimbursement decision (13, 27).

Comparison with previous studies

Previous studies assessing the delay between regulatory approval and reimbursement decision generally found similar results to this report. For Japan, the above-mentioned studies confirmed that new drugs are generally reimbursed within the timeframe of 60-90 days (24). For Taiwan, an analysis of the time from application submission to reimbursement listing found a median delay of 1.5 years (561 days, average delay of 742 days) for new cancer drugs approved between Jan 2013 and Sep

2017, compared to 2 years in this study (35). For South Korea, a recent analysis of 59 new cancer drugs approved between 2007 and 2018 found a median delay of 26 months. This is longer than the 16 months found in this report but might be partly explained by a different sample (all new cancer drugs vs. innovative indications of both new and existing cancer drugs for selected cancer types) and partly by the more recent time period studied here. The latter is important as the analysis here incorporates a longer time period since the introduction of the "risk-sharing agreement pathway" in 2014, a fast-track system for certain types of drugs including cancer drugs that has been shown to have reduced delays (36).

Studies comparing national formularies in Australia and New Zealand have repeatedly found that only around half of new drugs achieving reimbursement listing in Australia do so in New Zealand (37-39). They have also shown that reimbursement listing in New Zealand occurs on average 2.5 years after Australia. In this report, the methodology to calculate the gap between Australia and New Zealand is different but would suggest a shorter delay (18 months vs. 33 months). However, the real median delay in New Zealand is longer, as the current numbers are only based on 5 indications. For instance, the first indication in NSCLC of an immunotherapy drug (nivolumab) was approved in April 2016 but in September 2020 reimbursement listing was still pending, whereas in Australia it was reimbursed in August 2017 after a regulatory approval in January 2016.

Although Japan might appear as an outlier in the analysis of high-income markets in Asia-Pacific, some countries in Europe also have a reimbursement delay of only a few months. A survey, conducted by the European Federation of Pharmaceutical Industries and Associations (EFPIA), showed that the average delay between regulatory approval of all new cancer drugs approved by the European Medicines Agency (EMA) between 2015 and 2018 and patient access (defined as first sales of a drug in a local market, which typically coincides with reimbursement in the local market in Europe) was less than 6 months in Denmark and Germany (40).

4. Consequences of delayed reimbursement of innovative cancer drugs

The previous sections have established that many cancer drugs with regulatory approval lack positive reimbursement status. They have also shown that timely reimbursement is a major challenge and several years of delay is the rule rather than the exception. This section quantifies some of the consequences for patients with delayed reimbursement of innovative cancer drugs across all markets in Asia-Pacific. It aims to answer the following question: How many patient life years could be saved by faster reimbursement approval of innovative cancer drugs?

4.1 Method and data

To quantify the consequences of delayed reimbursement, patient life years lost was used as a metric. The following steps were taken to calculate the number of patient life years lost. The first step involved the definition of a sample of innovative drug-indications, drawing from the pool of innovative indications identified in section 2. For each of the five cancer types in scope, two innovative indications were selected. All 10 drug-indications were considered in every market, even if regulatory approval in a market was still pending in September 2020 as this is a prerequisite for reimbursement. Table 1 provides an overview of the 10 selected indications.

In the second step, the annual number of eligible patients was calculated. Eligibility was defined according to the approved label (using the local approved label or the US FDA label in case of no local approval). The exact calculation of patient numbers was done in the following top-down manner. Newly diagnosed cases (incidence) in 2018 of the selected tumor type (breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, lung cancer) served as the starting point (see sub-report 1). These numbers were then adjusted for the proportion of tumor subtype (e.g., non-small cell lung cancer), genomic alterations (e.g., HER2-positive in breast cancer), disease stage (e.g., metastatic disease), and line of therapy; see Table 1 for the level of detail used. Market-specific estimates were retrieved for these adjustment factors; in case these were not available, Asia-specific (Europe-specific for Australia and New Zealand) or global estimates were used.

In the third step, median survival gain per eligible patient was calculated. The survival gain was based on the gain in overall survival (OS) observed in key clinical trials; see Table 1. In cases when the comparator drug used in the key clinical trial lacked regulatory approval in a specific market, an indirect comparison was made, based on the key clinical trial of the comparator drug and the current standard of care.

Table 1: Innovative cancer drug-indications and their clinical benefit

Cancer type	Drug	Indication	ESMO-MCBS	Comparator drug	OS gain (months)	Clinical trial
Breast cancer	Abemaciclib	2nd line, combo with fulvestrant, HR+ HER2-, metastatic	4	Fulvestrant	9.4	(41)
Breast cancer	Pertuzumab	1st line, combo with trastuzumab + docetaxel, HER2+, metastatic	4	Trastuzumab + docetaxel	15.7	(42)
Esophageal cancer	Nivolumab	2nd line, mono, ESCC, metastatic	4	Paclitaxel or docetaxel	2.5	(43)
Gastric cancer	Trifluridine & tipiracil	3rd line, mono, gastric or GEJ AC, metastatic	3*	Placebo (best supportive care)	2.1	(44)
Head and neck cancer	Cetuximab	1st line, combo with platinum + fluorouracil, HNSCC, metastatic	3*	Platinum + fluorouracil	2.7	(45)
Head and neck cancer	Pembrolizumab	1st line, combo with platinum + fluorouracil, HNSCC, metastatic	4	Cetuximab + platinum + fluorouracil	2.3	(46)
Liver cancer	Atezolizumab^	1st line, combo with bevacizumab, HCC, Child-Pugh class A, advanced	5	Sorafenib	9.6	(47)
Liver cancer	Regorafenib	2nd line, mono, HCC, Child-Pugh class A, advanced	4	Placebo (best supportive care)	2.8	(48)
Lung cancer	Osimertinib	1st line, mono, NSCLC, EGFR+, metastatic	4	Erlotinib or gefitinib	6.8	(49)
Lung cancer	Pembrolizumab	1st line, combo with pemetrexed + platinum, NSCLC, NSQ, EGFR- ALK-, metastatic / 1st line, combo with carboplatin + (nab-)paclitaxel, NSCLC, SQ, EGFR- ALK-, metastatic	4 / 4	Pemetrexed + carboplatin / carboplatin + (nab-)paclitaxel	11.3 / 5.5	(50, 51)

Notes: AC = adenocarcinoma, ESCC = esophageal squamous cell carcinoma, GEJ = gastroesophageal junction, HCC = hepatocellular carcinoma, NSQ = non-squamous, OS = overall survival, SCCHN = squamous cell carcinoma of the head and neck, SQ = squamous.

* Indications with ESMO-MCBS score of 3 (moderate clinical benefit) used in the absence of other GEJ and head & neck drug-indications with higher scores of 4/B+

^ Indication received ESMO-MCBS score after main data collection.

Clinical trials for indirect comparison were used in some markets for osimertinib (average of erlotinib (52) and gefitinib (53)), for atezolizumab (sorafenib (54)), and for pembrolizumab in head and neck cancer (cetuximab (45)).

In the final step, information on the delay between regulatory approval and reimbursement approval was added (see section 3). However, as shown in the previous section, the median delay differs greatly between markets and many markets had failed to reimburse most of the 10 indications considered here by September 2020. In order to obtain comparable estimates of the consequences of delayed reimbursement, the following strategy was used. The annual number of eligible patients and the median survival gain per patient was first combined. This yielded number patient life years lost. This number also presents the patient life years lost *per year*, as it is based on the *annual* number of eligible patients. In instances when the actual delay between regulatory approval and reimbursement approval was shorter than one year (in Japan for all 10 indications, in Australia for 2 indications[5], and in South Korea for 1 indication[6]), the actual delay was used rather than one year of delay.

4.2 Results

Reimbursement of cancer drugs to facilitate patient access is vital. Timely reimbursement of new innovative drug-indications is important to improve survival outcome and avoid the loss of patient life years. Figure 9 presents the results of the analysis of patient life years lost due to delayed reimbursement. Across the 14 markets in Asia-Pacific, 928,000 patient life years are lost for every year of reimbursement delay of only 10 innovative indications across 5 cancer types. Compared to the number of eligible patients of 1.53 million diagnosed every year, this equals more than 7 months of life lost per patient.

The lion's share of the total loss in patient life years in Asia-Pacific occurs in China with 635,000 life years lost per year of delay, corresponding to more than two thirds of the total loss. This is naturally owed to the large cancer patient population in China (see sub-report 1), both in absolute terms and in relative terms for the five cancer types considered. At the other end of the spectrum are the two markets with the smallest cancer patient populations, Singapore and New Zealand, with 1,500 to 2,000 life years lost.

Japan is the only market where the numbers in Figure 9 present actual loss of patient life years due to delay as all 10 indications had received reimbursement by September 2020. There were minimal delays of around 2 months between regulatory approval and reimbursement of the breast cancer indications, which were new drugs listed on NHI within the 60-90 days period as mentioned previously. In the other 13 markets in Asia-Pacific, the numbers in Figure 9 would need to be multiplied with the actual time period it took (or will take) to receive reimbursement to get

[5] Trifluridine & tipiracil and pembrolizumab in lung cancer (squamous type).
[6] Regorafenib.

comparable numbers to Japan. For example, section 3 showed that the median reimbursement delay of innovative indications is around 2 years in Taiwan. The annual life years lost here amounts to 12,600, but the final number might be around 25,000 assuming a 2-year delay. For markets where reimbursement might take 10 years or more, such as the Philippines as shown in section 3, the final number would amount to ten times the numbers presented here – 230,000 patient life years lost in the case of the Philippines.

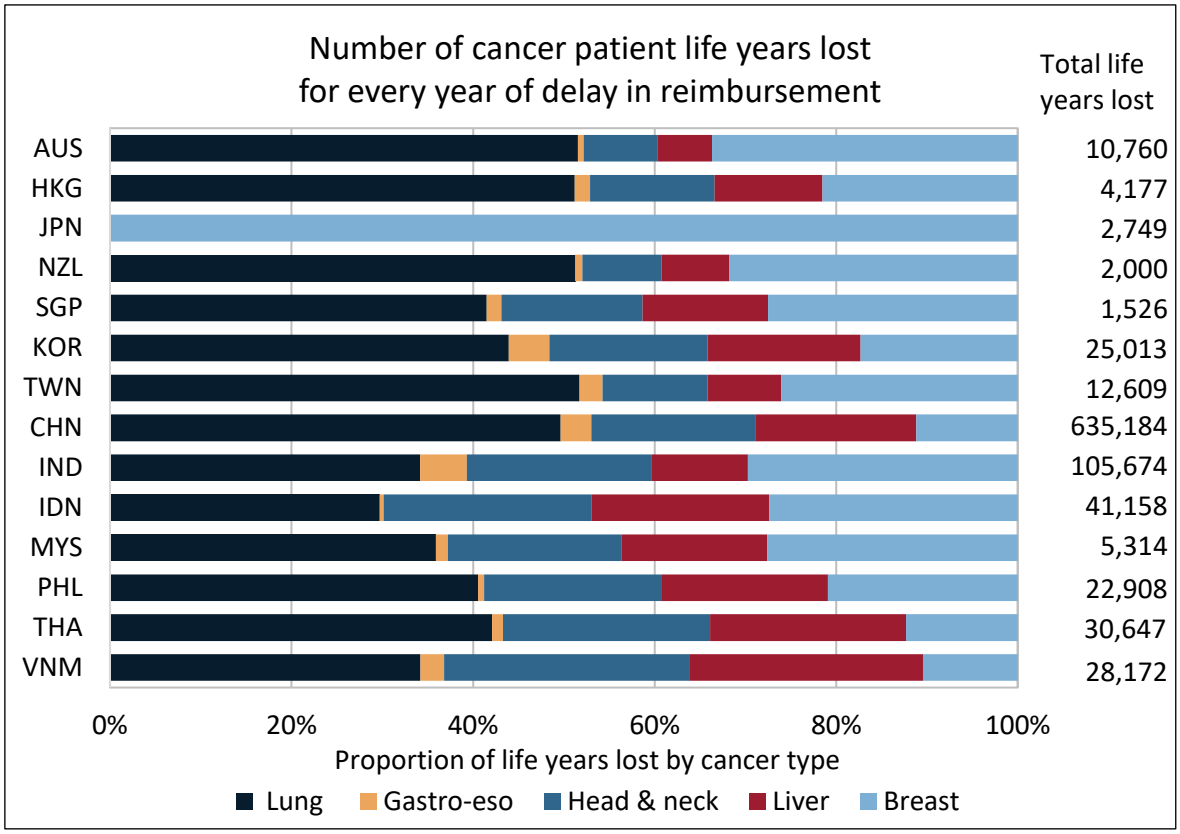

Figure 9: Number (right side) and proportion (left side) of patient life years lost for every year of delay in reimbursement of 10 innovative indications in 5 cancer types

Notes: Lung = NSCLC, Gastro-eso = gastro-esophageal cancer, Head & neck = head and neck cancer, Liver = liver cancer, Breast = breast cancer.

Figure 9 also presents a split of the loss in patient life years by cancer type. In all markets (except Japan), the greatest number of life years that could be saved was in lung cancer followed by breast cancer (except in Vietnam) with better access to innovative treatment. These numbers partly reflect larger numbers of eligible patients in these two cancer types (see sub-report 1), but also greater absolute survival gains that could be offered by the select drug-indications based on pivotal trial data (see Table 1). Japan has only patient life years lost from delays in reimbursement of both breast cancer drug-indications, as these were the initial indications approved for these drugs, which comes along with some delay (at most 60-90 days as noted above).

Comparison with previous studies

Comparable studies on the topic of patient life years lost due to delays in reimbursement of cancer drugs are scarce in Asia-Pacific.[7] In Europe, a recent study used two cancer drugs – abiraterone and ipilimumab – to study life years lost during the delay between approval by the European Medicines Agency and initial patient access (defined as first sales registered in the IQVIA MIDAS database) in a large sample of countries (57). The approach to use first sales as a proxy for patient access (thought of in terms of reimbursement) makes more sense in the European health care systems, where few sales occur before reimbursement. However, this is different in Asia-Pacific (see sub-report 4). In terms of conclusion, the European study echoes the findings in this report that cancer patients face long delays in access to innovative cancer drugs in most markets and their health outcomes could be greatly improved by faster reimbursement decisions.

It should also be noted that the estimated number of almost 1 million patient life years lost in this report is only based on 10 innovative drug-indications. As explained in section 3, there were 31 innovative drug-indications approved by the US FDA between 2010 and 2020 for the five cancer types considered in this report. For other cancer types, there are also innovative cancer drugs available, and they might face similar challenges with reimbursement delays. Thus, the estimate of almost 1 million patient life years lost per year of reimbursement delay is likely a great underestimation of the actual loss across all innovative cancer drugs and cancer types.

[7] There is a vast literature on the topic of years of life lost (YLL) due to premature death of cancer and other diseases. The WHO regularly provides statistics on this measure for countries around the globe (55). Recently, studies on COVID-19 and YLL have been published (56), and they are closer to the topic considered here, as they indirectly quantify the YLL due to delay in access to an effective vaccine.

5. Reasons for delayed reimbursement of innovative cancer drugs

This section discusses reasons for delayed reimbursement of innovative cancer drugs across all markets in Asia-Pacific. It aims to answer the following question: What are the reasons for the delay in access to innovative cancer drugs in the different markets in Asia-Pacific and also compared to the situation in Europe?

5.1 Method

An ad-hoc literature search was performed to extract relevant articles and reports published in the grey literature. Material reviewed during the data collection of regulatory approval and reimbursement dates, described in section 3.1, was also used.

5.2 Results

Delays in patient access to innovative cancer drugs is not just a challenge in Asia-Pacific. Countries in Europe share the same challenge, despite a more favorable basis to start from. In Europe, the European Medicines Agency (EMA) was established in 1995 and has taken over the responsibility for regulatory approval of most new drugs, including all cancer drugs. However, individual countries are responsible for the reimbursement decision. The time for these decisions varies considerably. The survey by EFPIA mentioned in section 3, showed that the average delay between regulatory approval by the EMA and patient access ranged from less than 6 months in Denmark and Germany to over 2 years in many (less wealthy) Eastern European countries, for cancer drugs approved between 2015 and 2018 (40).

Similar to Asia-Pacific, Europe also consists of countries of different sizes and with varying economic wealth (although the variations are distinctly smaller), which provides them with different means to make reimbursement decisions for innovative cancer drugs. A recent survey among different European stakeholders has uncovered 9 key factors that are causing delay to innovative cancer drugs (58); see Table 2. These factors generally relate to three broad categories: the organization of the reimbursement process, the criteria applied in this process, and the readiness of the health care system to absorb the drugs. A description of these three categories applied to the different markets in Asia-Pacific is provided below.

Table 2: Factors delaying patient access to innovative cancer drugs in Europe

Category	Factors causing delay	Description
Process	Late start of the process	Late company submission or late start of the national process after EMA approval
	Lack of clearly defined national timelines	Absence of (or no compliance with) a maximum duration of the process
	Multiple layers of decision-making	Subnational enforcement or financing of a reimbursement decision
Value assessment criteria	Misalignment of evidence requirements	Differences between EMA and national HTA bodies, and between HTA bodies (endpoints, comparator, population, etc.)
	Unpredictability of requirements	Unclear or inconsistently applied evidence requirements and pricing and reimbursement thresholds
	Limited compatibility of existing HTA and value assessment methodology with innovation	More evidence gaps arising from latest innovations (novel endpoints, trial designs, etc.)
Health system readiness	Limited resources to implement decisions	Resource and budget insufficiency hampering prescription and use
	Lack of up-to-date clinical guidelines	Latest innovations are often not included in the guidelines
	Suboptimal health care infrastructure and care pathways	Care organization hampers optimal prescription and use

Notes: EMA = European Medicines Agency, HTA = health technology assessment. Source: (58).

Reimbursement process

An exact description of the reimbursement process in every market goes beyond the scope of this report. However, there are some institutional features worth highlighting in relation to patient access. Even if the process leading up to a reimbursement decision is carried out at different times for different drugs, patient access is only realized once the decision comes into force. This typically coincides with the time when the reimbursement scheme (national formulary) is updated. Table 2 provides an overview of the frequency at which reimbursement schemes used in this report are usually updated.

Table 3: Reimbursement schemes and frequency of update

	Market	Reimbursement scheme	Frequency of reimbursement scheme update*
HIGH-INCOME MARKETS	Australia	Pharmaceutical Benefits Scheme (PBS) list	Monthly
	Hong Kong	Hospital Authority Drug Formulary (HADF), Samaritan Fund (SF), Community Care Fund (CCF)	Every 2-4 months
	Japan	National Health Insurance (NHI) list	Every 1-3 months
	New Zealand	Pharmaceutical Management Agency (PHARMAC) list	Monthly
	Singapore	Standard Drug List (SDL), Medication Assistance Fund (MAF)	Every 3-4 months
	South Korea	National Health Insurance (NHI) list	Monthly
	Taiwan	National Health Insurance (NHI) list	Monthly
MIDDLE-INCOME MARKETS	China	National Reimbursement Drug List (NRDL)	Most recent updates in Feb 2017 and Aug/Nov 2019, Dec 2020
	India	(no scheme for entire population)	n/a
	Indonesia	National Formulary (Fornas)	Most recent updates Apr 2018, Apr 2019, Apr 2020
	Malaysia	Ministry of Health Medicines Formulary (MOHMF)	≈3 times per year
	Philippines	Philippine National Formulary (PNF)	8th edition of PNF-EML in 2017 and full PNF update in Sep 2019
	Thailand	National List of Essential Medicines (NLEM)	Most recent updates Jul 2018, Mar 2019, Oct 2020
	Vietnam	Reimbursement Drug List (RDL)	Most recent updates Jan 2015, Jan 2019

Notes: * Reimbursement committees could meet at different intervals across the markets than the cited update of the reimbursement scheme. n/a = not applicable.

In high-income markets, reimbursement listings tend to be updated every 1-4 months. This limits the potential delay between the actual reimbursement decision and the decision to come into effect.

By contrast, reimbursement listings are reviewed and updated much less frequently across most middle-income markets; see Table 3. For instance, China got its first national formulary in 2000 (back then called the China National Formulary, CNF), which was subsequently updated in 2004, in 2009, and in 2017 (29). During the update in 2009 and 2017, around 70 new cancer drugs were launched in Europe alone (see Figure 1), but without inclusion in the CNF/NRDL none of them could reach patients in China on a large scale. Since 2017, China has significantly improved on the frequency of updates and now aims for updates on an annual basis (59, 60).

The fast-paced development of new cancer drugs coming into the market in the recent decade together with the infrequent updates of reimbursement listings means that there could be growing numbers of cancer patients with limited access to the latest treatment options in many middle-income markets. For instance, during the four years between the two most recent updates of the RDL in 2015 and 2019 in Vietnam, 42 new cancer drugs were launched in Europe alone (see Figure 1). Removing these kinds of institutional barriers is an important step towards driving change and improving patient outcomes in middle-income markets.

Value assessment criteria – the role of HTA

The reimbursement process of a new drug is typically informed by an analysis of the clinical benefits and costs of treatment. The systematic evaluation of the properties and effects of a new drug, typically also including a comparison with the existing standard of care, is called health technology assessment (HTA). Evaluations of clinical trials data naturally hold a level of uncertainty around a drug's performance in the real world, which in turn can cause delays in reimbursement decisions by HTA bodies. To address this issue, health care payers, HTA bodies, and the pharmaceutical industry have adopted formal arrangements, called risk-sharing agreements (RSA), patient access schemes (PAS), or managed entry agreements (MEA), to share the financial risks associated with new drugs when their value is not fully observable at the time of launch (61). Many European countries have adopted RSA, although success is mixed due to their complexity and administrative burden (62, 63). The use and comprehensiveness of HTA to inform reimbursement decisions as well as of RSA differs across markets in Asia-Pacific.

Japan did not use to carry out any HTA, but after conducting a pilot-program between 2016 and 2019, the submission of cost-effectiveness evidence to the Central Social Insurance Medical Council (Chuikyo) has become mandatory for selected drugs (33). The evaluation of this evidence only informs pricing decisions and happens *after* the reimbursement decision and thus will not delay the latter. By contrast, Australia, New Zealand, South Korea, and Taiwan perform HTA routinely and carry out their assessments *before* reimbursement. The speed of these assessments thus crucially influences delay in access to innovative cancer drugs.

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) bases its recommendations for reimbursement on a number of criteria, but cost-effectiveness is imperative. Most applications are initially declined and have to be revised several times, according to information from the public registry of PBAC (64). In New Zealand, the Pharmaceutical Management Agency (PHARMAC) also conducts a thorough review and is doing broad consultations with different stakeholders, but this also causes significant delays. A review of the public registry of PHARMAC and major immunotherapy

drugs (e.g., nivolumab or pembrolizumab) shows that consultations have been going on since 2016 but no decisions have been reached by the end of 2020 (65). These delays have potentially resulted in thousands of patient life years lost, as shown in section 4.

In South Korea, HTA has been performed by the Health Insurance Review and Assessment service (HIRA) since 2006, and drugs are assessed in different tracks depending on whether an alternative drug is available or not. In 2014, a special RSA fast-rack pathway to improve patients' access to cancer drugs (and drugs for rare disease) was introduced, which was shown to have reduced reimbursement delays (36, 66). In Taiwan, HTA has been performed since 2007 by the Center for Drug Evaluation (CDE) to inform inclusion of drugs on the National Health Insurance list (67). RSA to reduce reimbursement delay and manage financial impact were announced to be piloted for cancer drugs in September 2018 by the Ministry of Health and Welfare (68, 69).

In Singapore, HTA has been conducted to a limited extent by the Agency for Care Effectiveness (ACE) since 2015 (22). ACE seems to apply a comparatively strict approach, as evidenced by an evaluation of first-generation and second-generation EGFR inhibitors for NSCLC in 2018 (70). In its evaluation ACE did not recommend inclusion in the Medial Assistance Fund, because the drugs provided "*uncertain clinically meaningful benefits for patients*" and have "*unacceptable cost-effectiveness*", despite being reimbursed in all other high-income markets and even some middle-income markets.

Some middle-income markets have also started to adopt HTA to inform reimbursement decisions. In Thailand, the use of HTA in facilitating decision making started with the revision of the 2004 NLEM, which included economic aspects as a criterion for drug selection (71). The Health Intervention and Technology Assessment Program (HITAP) was established in 2007, yet resources to conduct proper HTA remain limited (71). In Malaysia, the Malaysian Health Technology Assessment Section (MaHTAS) carries out HTA and has also strengthened its capacity to conduct economic evaluations since 2015 (72). In China, HTA efforts are underway but have not been formally implemented (66). The Philippines launched its first HTA process and methods guidelines in September 2020 (73). By contrast, in Indonesia and in Vietnam HTA is not yet used to guide the selection of drugs to be listed in the national formulary (74, 75).

Health system readiness

As shown in sub-report 2, all middle-income markets in Asia-Pacific invest comparatively little in health care – both in relation to GDP and in absolute terms. Budgetary restrictions and the resulting lack of reimbursement have been pointed out as the root cause for low patient access to newer cancer drugs in middle-income markets, in the survey by ESMO described in section 2 (13). Limited

resources delay positive reimbursement decisions. However, as pointed out by the WHO, the wealth of a country is just a general determinant of health spending whereas political commitment to allocate sufficient investment for the provision of high-quality health care (which includes access to innovative drugs) also matters (76). The latter might explain why New Zealand incurs comparatively long delays in reimbursement of innovative cancer drugs among high-income markets.

All health care payers, albeit by different extent potentially, face the same challenges in allocating limited health resources. Therefore, there is a need for clear prioritization of drugs with high clinical benefit to achieve an allocation of resources that maximizes patient outcomes. The analysis in section 4 of this report has demonstrated the positive impact on patient survival outcomes that could potentially be achieved by investing in innovative treatment options and ensuring timely patient access.

Reimbursement decisions of innovative drugs also have to be well thought through in terms of the auxiliary health services needed to administer them. Sub-optimal health care infrastructure can hamper the use of innovative drugs. For instance, to administer targeted therapies in NSCLC, an assessment of genomic alterations is a prerequisite. Drugs targeting EGFR, ALK, ROS1, BRAF, NTRK, RET, and MET mutations have been approved by the US FDA during the last decade (see Table A1 in the Appendix). Sequential testing for these alterations is challenging due to the number of different tests warranted, resulting in depletion of tumor tissue samples and incomplete assessments. Extensive mutational profiling using next generation sequencing (NGS) has emerged as the main alternative to meet the clinical need, but this technology is still relatively costly as compared to other more traditional molecular methods. In Europe, this is one of the reasons why countries with limited economic means also provide limited access to drugs targeting these mutations (77).

The analysis in this report offers a nuanced view on reimbursement of cancer drugs, emphasizing the need to focus on innovative drugs that provide clear clinical benefits to patients. Yet access to innovative cancer drugs through reimbursement is quite limited in Asia-Pacific and a clear division between high-income and middle-income markets is noticeable. Even in markets with greater access, patients have to wait for several years to get access due to delays in reimbursement decisions, resulting in a great loss of patient life years. Reasons for delayed reimbursement of innovative cancer drugs vary across markets in Asia-Pacific. In middle-income markets they relate more to the budgetary readiness of the health care system to absorb new drugs (see sub-report 5 for potential solutions) as well as the organization of the reimbursement process. In high-income markets, they relate more to the criteria applied in the reimbursement process and the lack of fast-track systems for innovative drugs.

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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.

Table A3: Level of granularity available in public databases of regulatory agencies and reimbursement schemes

	MARKET	REGULATORY APPROVAL		REIMBURSEMENT APPROVAL	
		Current status	**Exact date**	**Current status**	**Exact date**
HIGH-INCOME MARKETS	Australia	I	I	I	I
	Hong Kong	D (except IO)	D (except most innovative indications in CCF)	I (CCF+SF) D (HADF)	I (CCF+SF partly) X (HADF)
	Japan	I (after 2004)	I (after 2004)	I (after 2004)	I (after 2004 partly)
	New Zealand	I	I	I	I
	Singapore	I	I (after 2016)	I	X
	South Korea	I	I	I	I
	Taiwan	I	D (except IO and most innovative indications)	I	I
MIDDLE-INCOME MARKETS	China	I	D (except IO and most innovative indications)	I	I
	India	I	I	D	X
	Indonesia	I	D (except some indications)	I	I
	Malaysia	I	I	I	I
	Philippines	D (except IO)	D	I	I
	Thailand	I	D (except some indications)	I	I
	Vietnam	I	D	D*	D

Notes: I = by indication; D = by drug only; X = no information. IO = immunotherapy drugs information provided by MSD or retrieved through company press releases. CCF = Community Care Fund; SF = Samaritan Fund; HADF = Hospital Authority Drug Fund. * All approved indications are usually reimbursed when a drug is on the Reimbursement Drug List.

Table A4: Sample of innovative drug-indications analyzed in calculations of delay between regulatory approval and reimbursement

AUS	HKG	JPN	NZL	KOR	TWN
Afatinib	Alectinib	Abemaciclib	Alectinib (x2)	Abemaciclib	Afatinib
Alectinib	Ceritinib	Afatinib	Palbociclib	Afatinib	Alectinib (x2)
Atezolizumab	Durvalumab	Alectinib (x2)	Pertuzumab	Alectinib (x2)	Atezolizumab
Ceritinib	Lenvatinib	Atezolizumab	Trastuzumab emtansine	Atezolizumab	Ceritinib
Crizotinib	Osimertinib	Ceritinib		Ceritinib	Crizotinib
Durvalumab	Pembrolizumab	Crizotinib		Crizotinib	Lenvatinib
Lenvatinib	Pertuzumab	Durvalumab		Durvalumab	Nivolumab (x2)
Nivolumab (x2)	Ribociclib	Lenvatinib		Lenvatinib	Osimertinib (x2)
Osimertinib (x2)	Trastuzumab emtansine	Nivolumab (x3)		Nivolumab	Pembrolizumab (x3)
Pembrolizumab (x3)		Olaparib		Osimertinib	Pertuzumab
Pertuzumab		Osimertinib (x2)		Palbociclib	Regorafenib
Ribociclib		Palbociclib		Pembrolizumab	Ribociclib
Trastuzumab emtansine		Pembrolizumab (x7)		Pertuzumab	
		Pertuzumab (x2)		Regorafenib	
		Regorafenib		Trastuzumab emtansine	
		Trastuzumab emtansine			

CHN	IDN	MYS	VNM
Afatinib	Afatinib	Afatinib	Afatinib
Alectinib (x2)			
Ceritinib			
Crizotinib			
Osimertinib			
Pertuzumab			
Regorafenib			

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