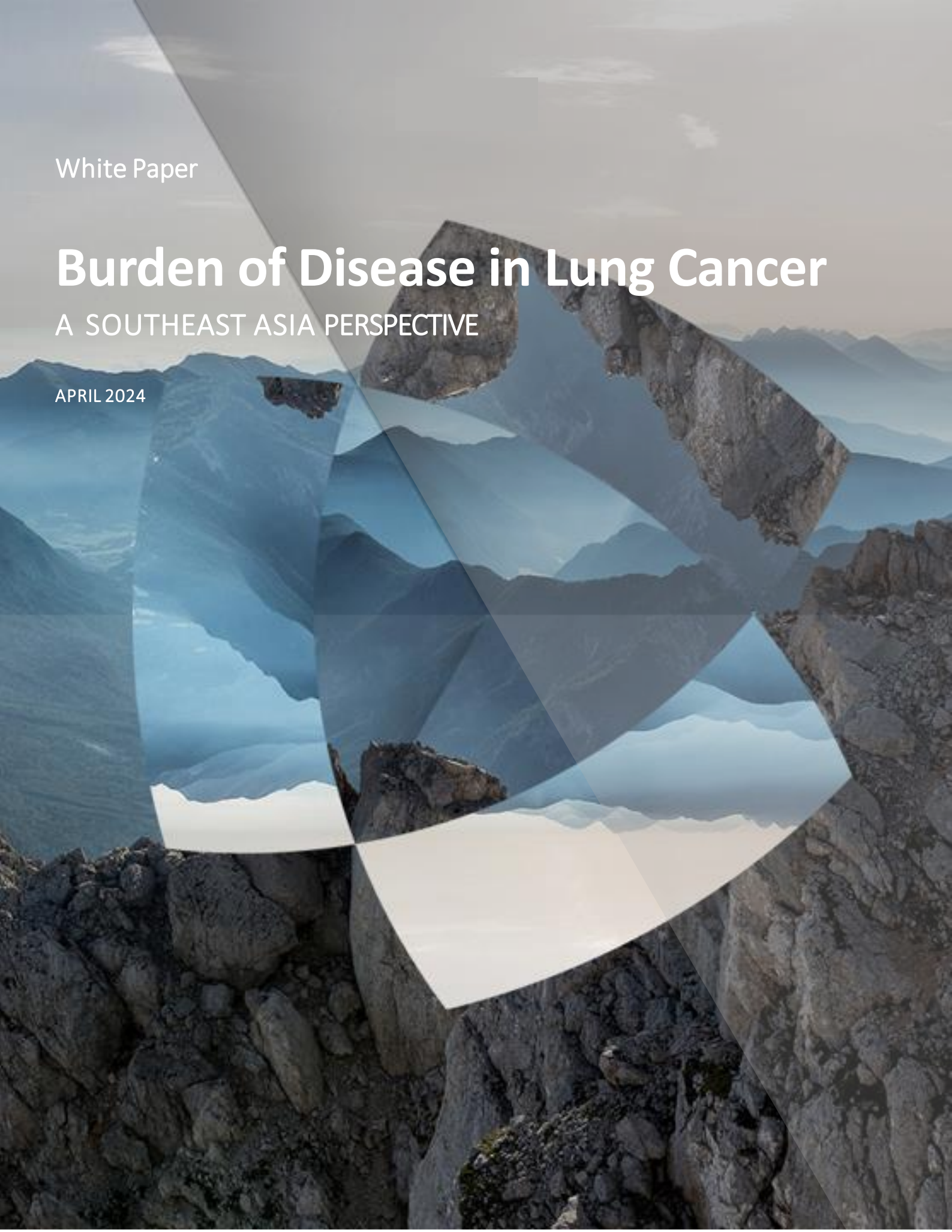

White Paper

Burden of Disease in Lung Cancer

A SOUTHEAST ASIA PERSPECTIVE

APRIL 2024

Johnson&Johnson

For Healthcare Professionals Only

With research and design support from Clarivate

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Executive summary

Lung cancer is a leading cause of cancer death in Southeast Asia (SEA). In recent years, precision oncology has transformed the diagnosis and treatment of advanced-stage non-small cell lung cancers (NSCLC). Targeted treatments have become increasingly available as oncogenic drivers are identified. Targeted therapy and molecular testing are now recognized as the future in lung cancer treatment. Most of these innovative medications have been shown to be both clinically effective and safe.

Targeted medicines, while offering great promise, present particular challenges. Toxicities, acquired resistance, access, and cost stand out as primary concerns to be addressed. Furthermore, there is a shortage of timely diagnosis and referral to competent care. This white paper highlights some of the significant problems in the use of targeted medicines in NSCLC in SEA, both in terms of disease burden and economic burden (with focus on managing AE costs) and urges for a united voice for change from the medical community to address these.

The 3 key themes covered in this white paper are:

DISEASE BURDEN

LUNG CANCER EPIDEMIOLOGY

The lung cancer burden in Asian regions is expected to double or more between 2020 and 2050, underscoring a pressing need for comprehensive preventive measures & healthcare interventions.

NSCLC is the most common cause of cancer related deaths in men and the second leading cause of cancer deaths in women worldwide.[1]

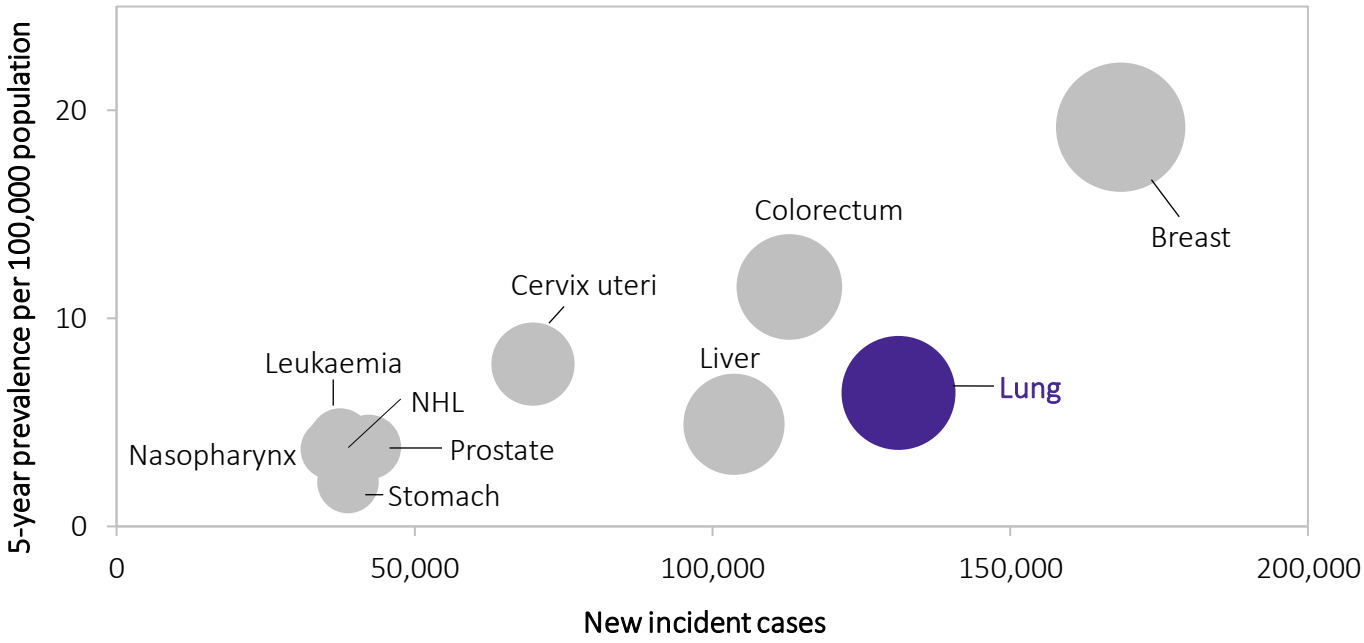
The burden of lung cancer in regions of Asia is expected to double or more between 2020 and 2050.[2]

East Asia is the leading region with the most incident cases and death. The most recent figures show that over 1.01 million new cases were recorded annually and more than 841,174 deaths.[2]

In addition, incidence and mortality in East Asia are expected to reach 1.7 million and 1.5 million, respectively by 2050,[2] making NSCLC a major public health issue with a growing impact on population and healthcare systems across the region.

In 2022, lung cancer is the second most common malignancy in SEA and the leading contributor to cancer-related fatalities.[3]

Top 10 Cancers in SEA[3]

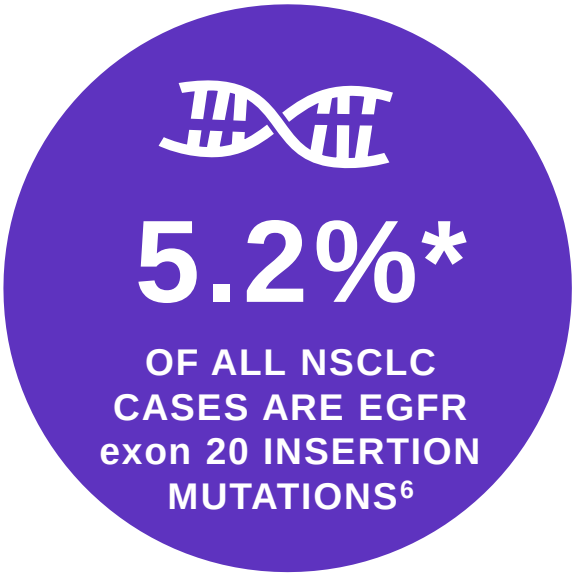


In SEA, lung cancer ranks as the second most frequent cancer, with an annual incidence of 131,184 new cases.[3] Additionally, the regional prevalence of lung cancer, at a rate of 6.4 cases per 100,000 population, highlights its significant impact and positions it as the fourth most prevalent cancer among the top 10 cancers in the region.[3] These statistics underscore the concerning burden of lung cancer in SEA and emphasize the necessity for effective approaches to prevention, early detection, and treatment to reduce its impact on public health in the region.

EGFR exon 20 insertion mutations remain relatively rare in SEA countries.

Patients with EGFR exon 20 insertions generally experience a less favorable prognosis compared to individuals with common EGFR mutations.

Specifically, they face a 75% higher risk of mortality, with a median overall survival (mOS) of 16.2 months versus 25.5 months in those with common EGFR mutations. Additionally, there is a 93% increased risk of disease progression or death, reflected in a median progression-free survival (mPFS) of 5.1 months for patients with EGFR exon 20 insertions compared to 10.3 months for those with common EGFR mutations.[4,5]



Incidence of EGFR exon 20 Insertion mutations across selected SEA markets

	Malaysia	Philippines	Thailand	Singapore
Number of NSCLC cases[6]	5,647	11,898	23,426	4,673
Diagnosed cases	4,563	9,994	19,139	4,341
Diagnosis rate %[6]	80.8%	84.0%	81.7%	92.9%
Unresectable and metastatic cases	3,828	8,855	15,656	3,473
Unresectable metastatic rate%[6]	83.9%	88.6%	81.8%	80.0%
Non-squamous cases	2,902	6,136	11,742	2,733
Non-squamous rate %[6]	75.8%	69.3%	75.0%	78.7%
EGFR mutation cases	1,335	3,436	6,458	1,449
EGFR mutation Rate %[6]	46.0%	56.0%	55.0%	53.0%
EGFR Testing rate %[6]	99.0%	100.0%	96.0%	100.0%
Exon 20 insertion cases	67	258	181	79
Exon 20 insertion Rate %[6]	5.0%	7.5%	2.8%	5.4%
Treated cases	58	201	161	71
Treatment rate %[6]	87.5%	78.0%	89.0%	90.0%

*% refers to the average of 4 countries namely Malaysia, Philippines, Thailand, Singapore and does not include Vietnam and Indonesia.

CURRENT TREATMENT PRACTICE

Comprehensive overview of guidelines[7,8]

Comprehensive overview of the **first-line treatment options for NSCLC patients with specific genetic mutations, particularly sensitizing EGFR mutations (NCCN[7] and ESMO[8] commonly referred by HCPs)**

Molecular and biomarker-directed therapy for advanced or metastatic NSCLC

EGFR exon 19 deletion or exon 21 L858R mutations	EGFR S768I, L861Q, and/or G719X mutations	EGFR exon 20 insertion mutation
First-line therapy: • Osimertinib (preferred) • Osimertinib + pemetrexed + (cisplatin / carboplatin) • Afatinib • Erlotinib • Dacomitinib • Gefitinib • Erlotinib + ramucirumab / bevacizumab (non-squamous) **Subsequent therapy:** • Osimertinib (after progression on afatinib, dacomitinib, gefitinib or erlotinib-based regimen, and tested positive for T790M mutation after rebiopsy)	**First-line therapy:** • Afatinib (preferred) • Osimertinib (preferred) • Erlotinib • Dacomitinib • Gefitinib **Subsequent therapy:** • Osimertinib (after progression on afatinib, dacomitinib, gefitinib or erlotinib-based regimen, and tested positive for T790M mutation after rebiopsy)	**Subsequent therapy:** • Amivantamab-vmjw
• If EGFR mutation is discovered prior to first-line systemic therapy, osimertinib is the preferred 1L therapy • However, if EGFR mutation is discovered during first-line systemic therapy, physicians have the following options to consider: 1. Continue planned systemic therapy, including maintenance therapy 2. Interrupt systemic therapy and then transition to osimertinib (preferred) 3. Interrupt systemic therapy and then transition to afatinib, dacomitinib, gefitinib or erlotinib-based regimen	• If EGFR mutation is discovered prior to first-line systemic therapy, afatinib or osimertinib is the preferred 1L therapy • However, if EGFR mutation is discovered during first-line systemic therapy, physicians have the following options to consider: 1. Continue planned systemic therapy, including maintenance therapy 2. Interrupt systemic therapy and then transition to osimertinib (preferred) or afatinib (preferred) or erlotinib or gefitinib or dacomitinib	• Platinum-based chemotherapy is the preferred 1L therapy for advanced/metastatic NSCLC harbouring EGFR exon 20 insertion mutations • After the initial 1L treatment, tumor response is evaluated, if there is disease progression, the recommended subsequent treatment option is amivantamab

Key takeaway

For advanced/metastatic NSCLC harbouring sensitizing EGFR mutations, the guidelines recommend EGFR tyrosine kinase inhibitors as the first-line treatment option. Osimertinib is the preferred subsequent therapy for tumours that are tested positive for T790M mutation upon progression on afatinib, dacomitinib, gefitinib or erlotinib. Finally, amivantamab is recommended as a follow-up treatment option for patients with EGFR exon 20 insertion mutation-positive metastatic NSCLC after disease progression on systemic therapy.

UNMET NEED IN TREATMENT

There is an urgent need for novel treatments for patients with NSCLC and EGFR exon 20 insertion mutations that offer a good efficacy and acceptable safety profile, allowing patients to live longer with an improved health-related quality of life (HRQoL).

Low Familiarity with Changes to Treatment Guidance: While clinical guidelines have recommended targeted therapies for exon 20 insertion mutations, recent introduction of these treatments and the mutation's infrequent occurrence could lead to physicians having less knowledge about these treatment options, resulting in a slower rate of adoption and potential treatment delays.

Suboptimal Efficacy: Due to suboptimal efficacy, there is currently no standard of care (SoC) for advanced/metastatic NSCLC harbouring EGFR exon 20 insertion mutations.

Patients with EGFR ex20ins have poor response to EGFR TKIs.[9] Chemotherapy does not provide durable treatment benefit (mPFS is 4.2 months with 1L chemotherapy).[10]

Unfavourable Safety Profile: Chemotherapy-based regimens comprise nonspecific, nonselective cytotoxic therapy, which provides modest increase in survival & causes significant toxicity; resulting in poor HRQoL.

PSYCHOSOCIAL DISEASE BURDEN

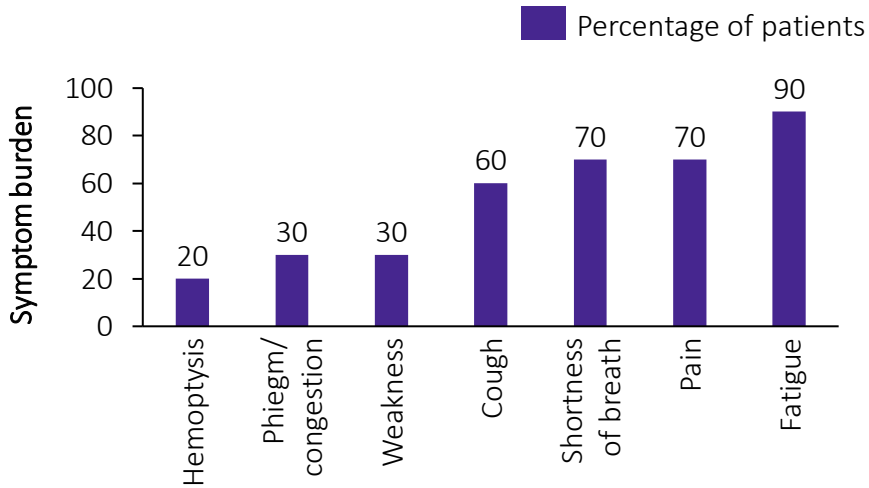
While overall survival remains the ultimate benchmark for lung cancer therapy, psychosocial care, which helps the patient to cope with the disease, is an increasingly important issue to patients and their everyday lives.

BURDEN ON QUALITY-OF-LIFE

NSCLC has been shown to have an impact on patient lives, with lower utility values and greater work and activity impairment. The burden on NSCLC patients has negative impact on caregivers, who report greater activity impairment and higher burden with worsening patient functionality.[11]

While there is no humanistic burden data available from SEA countries specific to EGFR exon 20 insertion, a US-based study[12,13] demonstrated a significant symptom, psychological, emotional, social, and physical impact on everyday life of patients with EGFR exon 20 insertion mutations.

Humanistic burden among patients with NSCLC and EGFR exon 20ins mutations[12,13]



Psychological impact

100%

Experienced a psychological or emotional impact

60%

Reported worry/anxiety about treatment, future, or finances

EGFR(m+) = epidermal growth factor receptor (mutation positive); exon 20ins = exon 20 insertions; NGS = next-generation sequencing; NSCLC = non-small cell lung cancer; PCR = polymerase chain reaction

DRUGS IN DEVELOPMENT FOR EXON 20 INS MUTATIONS

Current and emerging treatments for exon 20 insertion mutations[14]

Drug name	Highest status	Regulatory designations	Technology	Company
Amivantamab	Registered	Breakthrough Therapy; Orphan Drug	Bispecific Antibody SC Formulation	Johnson & Johnson Pharmaceuticals
Mobocertinib	Registered*	Breakthrough Therapy; Priority Review	TKI, Oral formulations	Takeda Pharmaceuticals
Zipalertinib (TAS6417)	Phase II-III	Breakthrough Therapy	TKI, Oral formulations	Taiho Pharma, Zai Lab
Sunvozertinib (DZD9008)	Phase II-III	Breakthrough Therapy	TKI, Oral formulations	Dizal Pharma
Furmonertinib	Phase II-III	FAST TRACK, Priority Review	TKI, Oral formulations	Arrivent Biopharma

Amivantamab: Amivantamab is the first and only bispecific antibody with immune cell-directing activity that targets both EGFR and MET. By binding extracellularly, amivantamab bypasses resistance mechanisms associated with secondary EGFR mutations and targets resistance from MET amplification.[15]

Among post-platinum patients, the median OS for amivantamab is 22.8 months and the median PFS is 8.3 months.[15]

Amivantamab has a tolerable safety profile. Treatment-related AEs were primarily grade 1-2 (16% grade ≥ 3).[15] Transient infusion-related reaction (IRR) are common after the first infusion (66%) and do not tend to recur.[15]

Amivantamab has a low rate of treatment-related discontinuation (4%); patients stay on treatment and achieve durable response to delay progression (mDOR 11.1 months).[15]

Mobocertinib: Mobocertinib is first in class oral TKI indicated for exon 20 insertion mutations (SoC). It has an oral mode of administration which is usually preferred by patients and HCPs.

These treatments have the potential to provide physicians and patients with innovative options for managing non-small cell lung cancer featuring EGFRm exon 20 insertion mutations.

*Voluntary withdrawal of mobocertinib globally on 3 Oct 2023.

ECONOMIC BURDEN

HEALTH FINANCING CHALLENGES IN THE SEA MARKETS

Healthcare spending in the SEA countries (Indonesia, Malaysia, the Philippines, Singapore, Thailand, and Vietnam), which was estimated at $420 billion in 2017, **is expected to rise by 70% over the next two decades.**[16]

This trend will be driven by the ageing of these countries' populations, high rates of smoking in some countries, and the adoption of more sedentary lifestyles and poor diets, which result in a lack of exercise and rising rates of obesity.

Four SEA nations, **Indonesia, Malaysia, Philippines, and Vietnam, currently have relatively low levels of government spending on health, ranging from 1.1% to 3.8% of GDP.** Singapore and Thailand spend more, at 4.9% and 4.1% of GDP. Even so, this increased spending is less than the global average of 6%, or 7.7% among OECD countries.[16] **Nonetheless, most SEA governments have been attempting to restrain the rise in health-care expenses at a time when demand is beginning to rise quickly**.

To minimize **substantially higher treatment and care expenses later on, there has been a shift in focus on early diagnosis and effective treatment for chronic diseases especially cancers.** Governments in many SEA countries now engage in preventive and early diagnostic capacity building, as well as ensuring access to care is decentralized to local communities rather than centralized in expensive hospitals.

Healthcare sector-wide costs and efficient resource utilization are crucial, including systematic monitoring of the costs associated with managing adverse events and their impact on productivity. **Given that adverse events (AEs) can potentially disrupt scheduled cancer treatments, leading to severe clinical implications for patients and increased disease and economic burden, a comprehensive evaluation of cancer care expenses should extend beyond the costs of therapy.** It should encompass the economic impact linked to AEs, as addressing these aspects not only optimizes resource allocation but also ensures the sustainability and effectiveness of cancer care delivery.

Public-private collaborations have the potential to have the largest impact. The private sector can make a significant contribution, to not only attract much-needed funds, but also help to build capacity for quality healthcare services.

Finally, **developing effective solutions necessitates both improved communication among partners** and innovation in institutional frameworks to assure accountability, value for money, and risk and profit sharing.

IMPORTANCE OF AE MANAGEMENT

The ACTION study (Asian CosTs In ONcology) evaluated the economic impact of lung cancer diagnoses in SEA countries Malaysia, Thailand, Philippines, Indonesia, Vietnam, Cambodia, Laos, and Myanmar.[17]

48% of patients in the study faced-out-of-pocket expenses over one year that equal or exceeded 30% of their annual household income;[17] these expenses cover both hospital and non-hospital healthcare costs, which patients directly incur at the point of service and are not reimbursed by insurance.

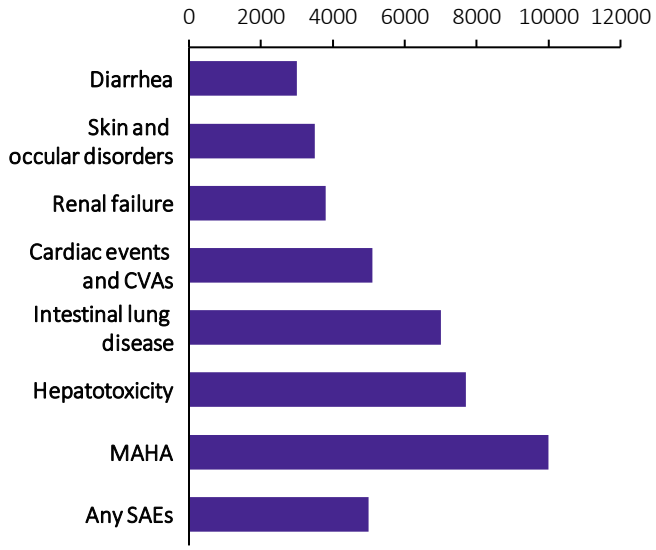
Furthermore, for NSCLC patients carrying classical EGFR mutations, the management of serious adverse events (SAEs) remains a primary driver of healthcare resource utilization and cost.[18]

This economic burden in NSCLC encompasses all direct[19] and indirect[11] expenses, including treatment costs, the loss of work productivity, and costs incurred by caregivers.

DIRECT COSTS

All-cause healthcare cost difference between patients with vs. without SAEs during first-line monotherapy with an EGFR TKI[18]

Adjusted mean cost difference (2017 USD)



* Statistical significance at the 5% level

CVA = cerebrovascular accident; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; exon 20 insertion mutations = exon 20 insertions; MAHA = microangiopathic haemolytic anaemia; NSCLC = non-small cell lung cancer; SAE = serious adverse event; SLR = systematic literature review; TKI = tyrosine kinase inhibitor

INDIRECT COSTS

Patients overall[11]

37% Work impairment

53% Activity impairment

Patients with ECOG PS* 3/4

81% Work impairment

74% Activity impairment

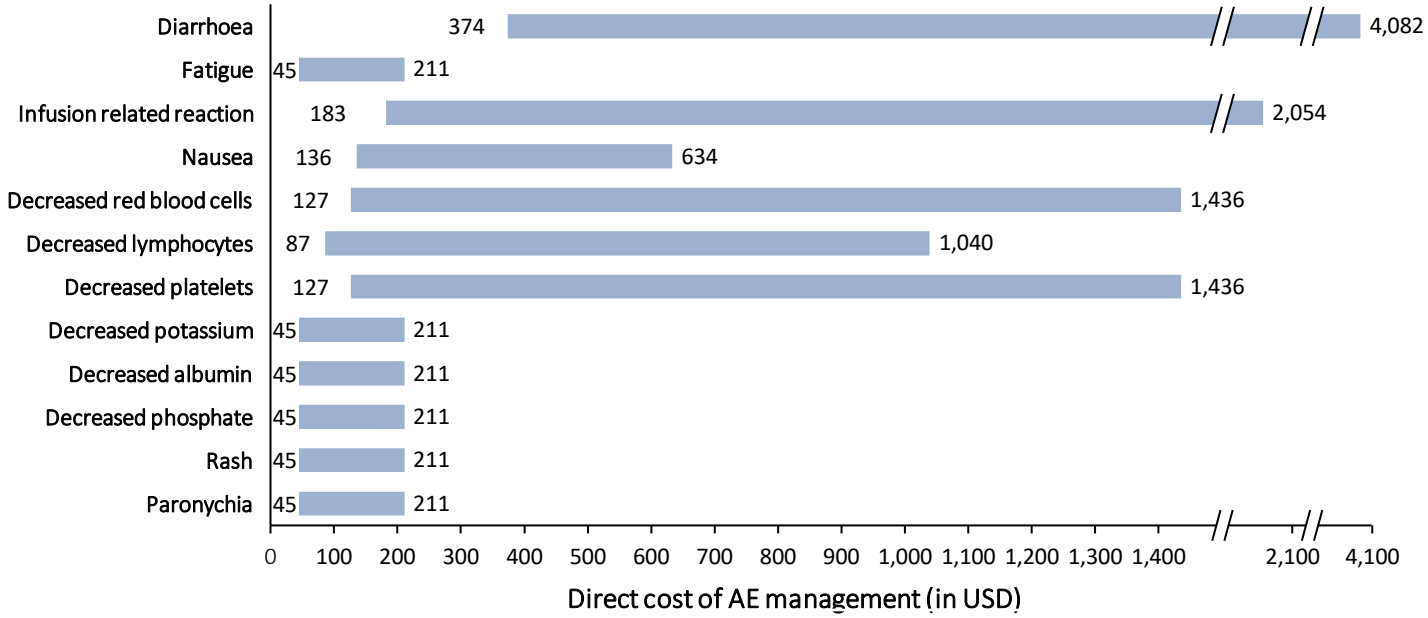
The indirect cost burden of wage loss in patients with advanced NSCLC increases with disease stage

DIRECT & INDIRECT COSTS OF AE MANAGEMENT

As an illustration of adverse event (AE) management costs, we evaluated the associated costs for two recently FDA approved drugs - amivantamab and mobocertinib with distinct AE profiles for the treatment for EGFR exon 20 insertion mutant NSCLC in adults.

Incidence rates of Grade 3/4 AEs		
AE description	Amivantamab[19]	Mobocertinib[20]
Diarrhoea	3%	22%
Infusion related reaction	3%	
Decreased red blood cells		4%
Decreased lymphocytes	8%	15%
Decreased platelets		1%
Fatigue	2%	4%
Nausea	0%	4%
Decreased potassium	6%	5%
Decreased albumin	8%	2%
Decreased phosphate	8%	
Rash	4%	2%
Paronychia	3%	1%

Est. per-patient direct cost to manage AEs in private setting in SEA markets (in USD)[21]



Less severe side effects such as fatigue, nausea, rash, paronychia, and certain lab abnormalities like low potassium, albumin, and phosphate levels are typically manageable through outpatient care. The extent of outpatient management vary by country, with Singapore having relatively higher direct AE costs.

Moreover, patients with advanced NSCLC experience substantial indirect cost, which increases with worsening functional status such as productivity loss due to work / activity impairment and additional cost incurred for receiving informal care or having a caregiver.

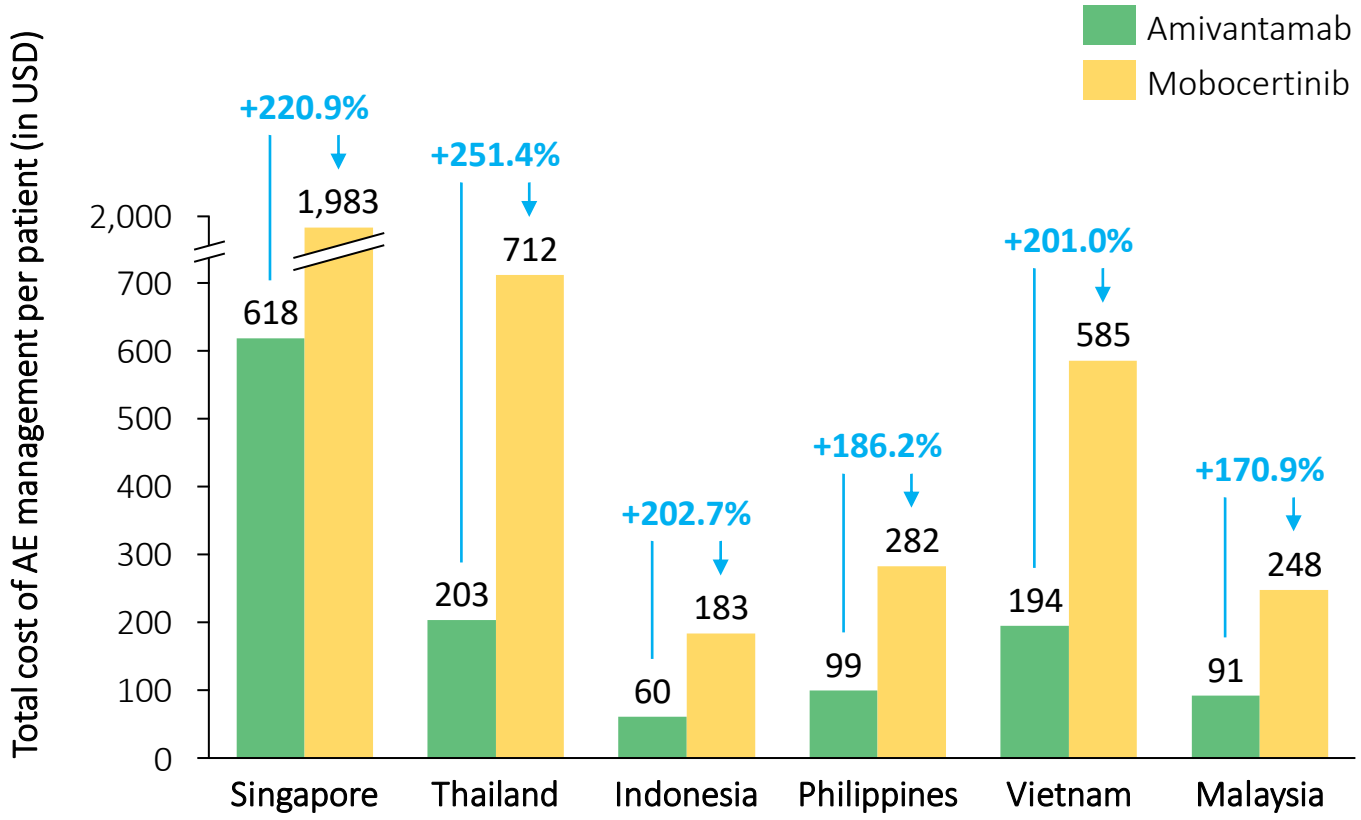
COST OF AE MANAGEMENT & VARIATION ACROSS MARKETS

Comparative total direct and indirect cost of adverse event (AE) management in private setting for amivantamab vs mobocertinib, by country[21]

Methodology:

The analysis gathered data on the occurrence of grade 3 or 4 AEs associated with two treatments, amivantamab and mobocertinib, using information provided in their respective prescribing documents. These adverse events encompassed laboratory abnormalities (including anemia, lymphopenia, thrombocytopenia, hypoalbuminemia, hypophosphatemia, and hypokalemia), as well as diarrhea, fatigue, infusion-related reactions, nausea, rash, and paronychia. For the purposes of our analysis, it was assumed that all 12 of these key AEs considered would require either specialist visits or inpatient care.

The costs associated with specialist visits, hospitalization (both in the ICU and non-ICU settings), were determined based on information extracted from various academic papers and journals. The unit cost and frequency of each event were used to calculate the total cost of managing each adverse event in the context of each treatment. Costs include indirect cost of productivity losses and informal care for the patient. It should be noted that these AE management costs were considered as one-time expenses and the date of onset of the adverse events was not factored into the calculations. Additionally, all costs were adjusted to reflect the inflation to 2023 USD.



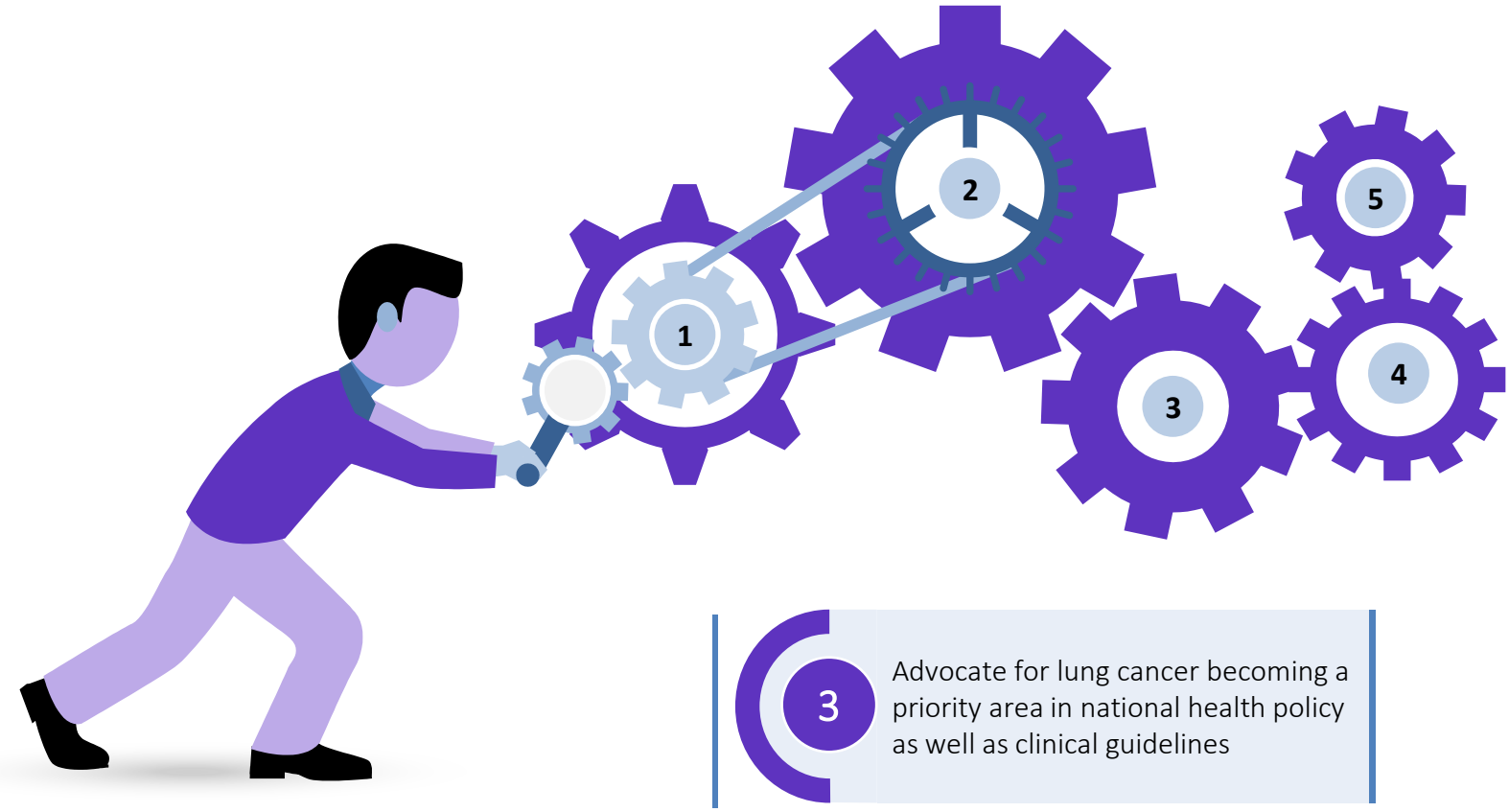
Amivantamab demonstrates a less costly AE profile compared to mobocertinib in the treatment of locally advanced or metastatic NSCLC patients harboring ex20ins mutation whose disease progressed despite platinum-based chemotherapy.

CALL TO ACTION

We believe that a united voice from the SEA medical community is critical to drive change to improve the support and care of lung cancer patients

1. Increase public awareness of lung cancer and its impact through stakeholder and community education

2. Improve health care delivery and consistency of management of lung cancer and shared decision making between patients and their healthcare professionals



3. Advocate for lung cancer becoming a priority area in national health policy as well as clinical guidelines

4. Increase awareness of the importance of testing for lung cancer, especially in the early stages

5. Unite the SEA medical community, to drive change that not only improves patient care but also makes healthcare systems more cost-efficient

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