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LUNG CANCER (NSCLC) – CLINICAL TRIALS LANDSCAPE – ASIA PACIFIC

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EPIDEMIOLOGY OVERVIEW

Disease Background

Lung cancer is the second most prevalent cancer and the primary cause of mortality in the world. Non-small cell lung cancer (NSCLC), which constitutes almost 85% of all lung cancers originates from larger cells, such as the epithelial cells lining the airways or mucus-producing cells. Small cell lung cancer (SCLC), the less common type, arises from small, hormone-producing cells and is more aggressive and fast-growing in comparison to NSCLC. Histologically, NSCLC is classified into three types: adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma.

About 30% of NSCLC patients are diagnosed with early stage (IIIIA) disease, often revealed only during an imaging procedure performed for an unrelated illness. Five-year recurrence rates are approximately 45%, 62% and 76% in Stage IB, Stage II, and Stage III respectively. Around 70% of patients have NSCLC that has progressed to an advanced stage (locally advanced or metastatic disease). While an estimated 35% of patients with locally advanced disease live for five years or longer, only 7% of those with metastatic illness show a similar survival rate. Nearly 50% of NSCLC cases are often linked with point mutations and biomarkers such as EGFR, KRAS, ALK, MET or ROS-1, whose prevalence varies across ethnic populations. [1,2]

Prevalence

In Asia, lung cancer ranks as the most prevalent cancer and the primary cause of mortality, with the region accounting for almost 60% of the global incidence of lung cancer. Age standardized rate of incidence (ASIR) in males (33 per 100,000 males) is more than twice higher compared to females (14 per 100,000 females). [3,4]

There is a notable genetic difference in the prevalence of activating driver mutations between Asian and non-Asian patients with NSCLC. The proportion of NSCLC patients with an EGFR mutation is much higher in Asia than in the US and Europe. Approximately half of Asian patients show this mutation, while its frequency only reaches 20% in Caucasian patients with adenocarcinoma histology. In contrast, European populations show a much higher frequency of KRAS mutations (about 30%) than Asian populations (less than10%). [5,6]

Around 85-90% of EGFR mutations comprise Exon 19 deletion and L858R point mutations of Exon 21 (classical EGFR mutations), while the remaining 10%-15% comprise uncommon mutations, such as the Exon 20 insertion (4–12%), L861Q (3%), G719X (2%) and S768I (1%). The Exon 20ins mutation represents the third most common type of EGFR mutation in NSCLC, next only to the Exon 19 deletions and Exon 21 L858R point mutations. [7]

In China, lung cancer is the most frequent cancer, and the leading cause of cancer-related death. The incidence rate has risen by 12% in the last ten years fuelled by an increasing tobacco consumption. [8,9] In 2020, China saw over 800,000 new lung cancer cases, with the region accounting for 37% of the global new lung cancer cases and showing the highest ASIR in Asia of 35 per 100,000 population.[10]

In India, lung cancer ranked as the fourth most common cancer by prevalence and mortality, with over 70,000 new cases diagnosed in 2020, representing about 3% of the global lung cancer cases. Diagnoses among men were nearly three times higher than women in 2020. [11]

In other locations such as Singapore, South Korea, Australia, New Zealand and the Philippines, we observed ASIRs of 27, 26, 25, 25, and 21 per 100,000 population respectively, with South Korea having the highest number of new cases (over 28,000) among these locations in 2020. [12]

According to Globocan, In the same year, Thailand had more than 20,000 new lung cancer cases diagnosed with an ASIR of 19 per 100,000, while Malaysia had more than 5,000 new lung cancer cases with an ASIR of 15 per 100,000.

Table 1. Incidence, Mortality and 5 Year Prevalence of Lung Cancer (by region) in 2020

Location	Incidence			Mortality			Prevalence	
	New Cases	%	ASR[a]	New Deaths	%	ASR[b]	5-Year Prevalence	Prop[c]. Per 100,000
World	2,206,771	100	22.4	1,796,144	100	18.0	2,604,791	33.4
Asia	1,315,136	59.6	22.9	1,112,517	61.9	19.3	1,515,321	32.7
China	815,563	36.9	34.8	714,699	39.8	30.2	883,100	61.0
India	72,510	3.3	5.4	66,279	3.7	4.9	80,817	5.9
South Korea	28,651	1.3	25.5	20,505	1.1	16.5	46,967	91.6
Thailand	23,713	1.1	18.9	20,395	1.1	15.9	25,164	36.0
The Philippines	19,180	0.9	21.1	17,063	0.9	18.8	20,625	18.8
Australia	13,162	0.6	25.3	8,867	0.5	15.8	17,112	67.1
Malaysia	5,139	0.2	15.4	4,509	0.3	13.3	5,909	18.3
Singapore	2,916	0.1	26.5	2,626	0.1	23.7	3,722	63.6
New Zealand	2,425	0.1	24.8	1,924	0.1	18.4	3,177	65.9

Source: Globocan 2020
a age standardized rate of incidence; b age standardized rate of mortality; c proportions per 100,000;

STANDARD OF CARE

Treatment decisions for NSCLC are based on factors such as tumor histology, size and location, involvement of pleura, surgical margins, status and location of lymph nodes by station, tumor grade and lymphovascular invasion. Surgery, post-operative chemotherapy, radiation therapy, targeted therapy and immunotherapy are the various treatment options for NSCLC. Chemotherapy has improved disease-related symptoms in patients with advanced NSCLC in the short term. Chemotherapy's impact on tumor-related symptoms and quality of life has been studied in a number of clinical trials. Overall, these studies demonstrate that chemotherapy may control tumor-related symptoms without lowering overall quality of life; however, more research into the influence of chemotherapy on quality of life is needed. [13]

Table 2: Standard Treatment Options for NSCLC [13]

Stage (TNM Definitions)		Standard Treatment Options
Occult NSCLC		Surgery
Stage 0 NSCLC		Surgery
		Endobronchial therapies
Stages IA and IB NSCLC		Surgery
		Adjuvant therapy
		Radiation therapy
Stages IIA and IIB NSCLC		Surgery with or without adjuvant or neoadjuvant therapy
		Radiation therapy
Stage IIIA NSCLC	Resected or resectable disease	Surgery with neoadjuvant or adjuvant therapy
		Neoadjuvant therapy
		Adjuvant therapy
	Unresectable disease	Chemoradiation therapy
		Radiation therapy
	Superior sulcus tumors	Surgery
		Chemoradiation therapy followed by surgery
		Radiation therapy alone
	Tumors that invade the chest wall	Surgery
		Surgery and radiation therapy
		Radiation therapy alone
		Chemotherapy combined with radiation therapy and/or surgery
Stages IIIB and IIIC NSCLC		Sequential or concurrent chemotherapy and radiation therapy
		Radiation therapy alone

Stage (TNM Definitions)	Standard Treatment Options
Newly Diagnosed Stage IV, Relapsed, and Recurrent NSCLC	Cytotoxic combination chemotherapy
	Combination chemotherapy with monoclonal antibodies
	Maintenance therapy after first-line chemotherapy (for patients with stable or responding disease after four cycles of platinum-based combination chemotherapy)
	EGFR tyrosine kinase inhibitors
	ALK inhibitors (for patients with ALK translocations)
	BRAF V600E and MEK inhibitors (for patients with BRAF V600E mutations)
	ROS1 inhibitors (for patients with ROS1 rearrangements)
	NTRK inhibitors (for patients with NTRK fusions)
	RET inhibitors (for patients with RET fusions)
	MET inhibitors (for patients with MET exon 14 skipping mutations)
	Immune checkpoint inhibitors with or without chemotherapy
	Everolimus (for patients with unresectable, locally advanced or metastatic, progressive, well-differentiated, non-functional, neuroendocrine tumors)
	Local therapies and special considerations
Progressive Stage IV, Relapsed, and Recurrent NSCLC	Chemotherapy
	EGFR-directed therapy
	ALK-directed TKIs
	BRAF V600E and MEK inhibitors (for patients with BRAF V600E mutations)
	ROS1-directed therapy
	NTRK inhibitors (for patients with NTRK fusions)
	RET inhibitors (for patients with RET fusions)
	MET inhibitors (for patients with MET exon 14 skipping mutations)
	Immunotherapy
	Everolimus (for patients with unresectable, locally advanced, or metastatic, progressive, well-differentiated, non-functional, neuroendocrine tumors)

Source: www.cancer.gov
Note: ALK = anaplastic lymphoma kinase; BRAF = v-raf murine sarcoma viral oncogene homolog B1; EGFR = epidermal growth factor receptor; MEK = MAPK kinase 1; NSCLC = non-small cell lung cancer; NTRK = neurotrophic tyrosine receptor kinase; PD-L1 = programmed death-ligand 1; RET = rearranged during transfection proto-oncogene; TKIs = tyrosine kinase inhibitors; TNM = T, size of tumor and any spread of cancer into nearby tissue; N, spread of cancer to nearby lymph nodes; M, metastasis or spread of cancer to other parts of body.

Locally Advanced -Stage III NSCLC – Treatment in Asia-Pacific

In Asia-Pacific, treatment guidelines formulated and laid by the ESMO (European Society for Medical Oncology) have been followed for the effective treatment of advanced NSCLC. The ESMO 2017 Guidelines for treatment of unresectable LA-Stage III NSCLC have been formulated and adapted for Asian patients, by considering the potential differences related to their ethnicity, cancer biology and standard practices of the treatment. These guidelines represent the consensus opinions reached by the lung cancer treatment experts who represented the oncology societies of Korea (KSMO), China (CSCO), India (ISMPO), Japan (JSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS).[14]

Table 3: Asian drug approvals and reimbursements for unresectable locally-advanced stage III NSCLC, by Asian locations and ESMO Magnitude of Clinical Benefit Score (MCBS) [14,16]

Drugs Approval Status		Cisplatin	Carboplatin	Etoposide	Vinorelbine	Docetaxel	Paclitaxel	Pemetrexed	Durvalumab
CSCO	Approved	Y	Y	Y	Y	Y	Y	Y	N
	Reimbursed	Y	Y	Y	Y	Y	Y	Y	N
ISMPO	Approved	Y	Y	Y	Y	Y	Y	Y	N
	Reimbursed	Y	Y	Y	Y	Y	Y	Y	N
JSMO	Approved	Y	Y	N	Y	Y	Y	Y	Y
	Reimbursed	Y	Y	N	Y	Y	Y	Y	Y
KSMO	Approved	Y	Y	Y	Y	Y	Y	Y	Y
	Reimbursed	Y	Y	Y	Y	N	Y	N	N
MOS	Approved	Y	Y	Y	Y	Y	Y	Y	Y
	Reimbursed	Y	Y	Y	Y	Y	Y	Y[a]	N
SSO	Approved	Y	Y	Y	Y	Y	Y	Y	Y
	Reimbursed	Y	Y	Y	Y	Y	Y	Y	N
TOS	**Approved**	Y	Y	Y	Y	Y	Y	Y	Y
	Reimbursed	Y	Y[a]	Y	Y	Y	Y	Y	N
MCBS[b]		NA	NA	NA	NA	NA	NA	NA	A

Source: Annals of Oncology; K. Park et al; Volume 31 - Issue 2 – 2020
NOTE: CSCO, Chinese Society of Clinical Oncology; ESMO, European Society for Medical Oncology; HCC, hepatocellular carcinoma; ISMPO, Indian Society of Medical and Paediatric Oncology; JSMO, Japanese Society of Medical Oncology; KSMO, Korean Society of Medical Oncology; MOS, Malaysian Oncology Society; NA, not applicable; NSCLC, non-small-cell lung cancer; SSO, Singapore Society of Oncology; TOS, Taiwan Oncology Society; a Reimbursable for second line advanced adenocarcinoma of NSCLC; b Only for drugs approved by the EMA since 2016.

Metastatic NSCLC – Treatment in Asia-Pacific

The ESMO 2016 Guidelines for the treatment of metastatic NSCLC cancer in Asian patients have been formulated and adapted by taking into account the differences of ethnicity, cancer biology and standard treatment differences. These guidelines represent the consensus opinions reached by metastatic NSCLC patient treatment experts, representing the oncological societies of China (CSCO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS). [15]

Table 4: Summary of drug approvals and reimbursement for mNSCLC, by Asian locations and ESMO Magnitude of Clinical Benefit Score (MCBS) [15,17]

Drugs	CSCO China		JSMO Japan		KSMO Korea		MOS Malaysia		SSO Singapore		TOS Taiwan		ESMO MCBS V1.1 [278, 279]
	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement	
Pemetrexed 1st-line													4
Pemetrexed maintenance													ND
Pemetrexed 2nd-line													4
Gemcitabine													ND
Vinorelbine													ND
Nab-paclitaxel													ND
Docetaxel													ND
Cisplatin													ND
Carboplatin													ND
Bevacizumab													2
Ramucirumab													1
Nintedanib													ND
Cetuximab													ND
Necitumumab													1
Gefitinib													4
Erlotinib													4
Afatinib					*	*							4 or 2
Osimertinib													4
Crizotinib													4
Alectinib 1st-line													ND
Alectinib 2nd-line													ND
Ceritinib 1st-line													ND
Ceritinib 2nd-line													ND
Nivolumab 2nd-line													5
Pembrolizumab 1st-line													5
Atezolizumab			**								**		ND
Denozumab													ND
Zoledronic acid													ND

*First-line only, **Second-line only; ND, not done.

Approved or reimbursed

Partially reimbursed or with restriction

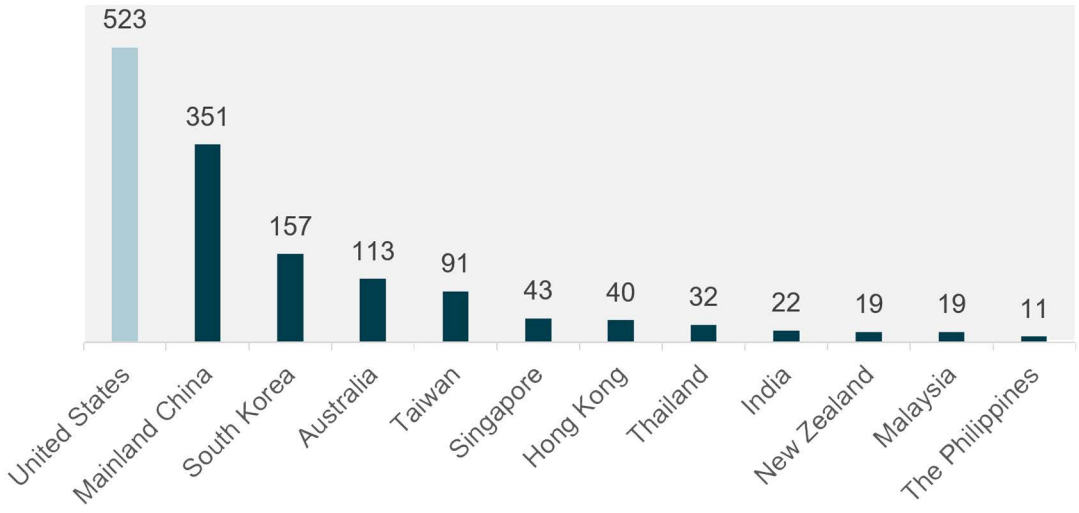
Not approved or reimbursed

Source: Annals of Oncology, Wu et al. Volume 30 | Issue 2 | 2019

CLINICAL TRIAL LANDSCAPE

Biopharma companies have initiated over 1,800 ongoing clinical trials in lung cancer since 2017, with the Asia-Pacific region involved in about 40% of the trials. The majority of the trials are related to the NSCLC subtype. Clinical trials in Asia-Pacific predominantly involve Mainland China, South Korea, Australia, Taiwan, Singapore and Hong Kong, with fewer competing trials compared to the US. (Figure 1).

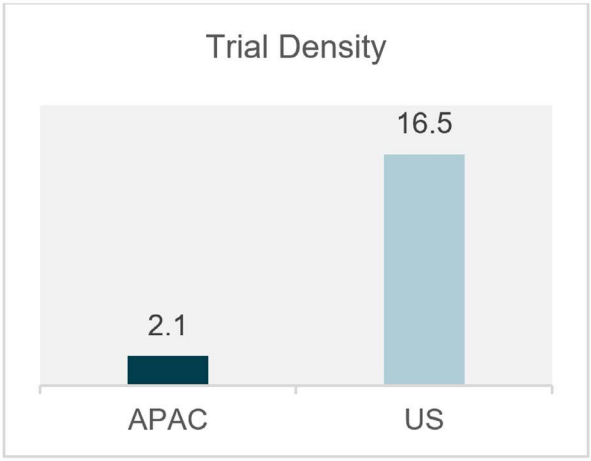
Figure 1: Top locations in Asia-Pacific and the US, based on the number of studies in NSCLC initiated by Biopharma companies since 2017 [18].



- Locations in which Novotech directly operates

Due to its large population and lower volume of studies, the Asia-Pacific region has lower competing trial risk with a trial density about 8 times lower than the US (Figure 2).

Figure 2. Comparison of the trial density* for industry-sponsored NSCLC clinical trials in the US and Asia-Pacific [18]



**Trial density is the number of recruiting sites for industry-initiated trials per million urban population*

Trials running in the Asia-Pacific region since 2018, show median recruitment durations about 30% shorter than trials in the US (Figure 3). In addition, these trials in the Asia-Pacific region recruit, on average, about 50% faster than the US (0.4 and 0.6 patients per site per month respectively) (Figure 4)

Figure 3. Comparison of median patient enrolment duration (in months) for NSCLC clinical trials in the US and Asia-Pacific since 2018 [18]

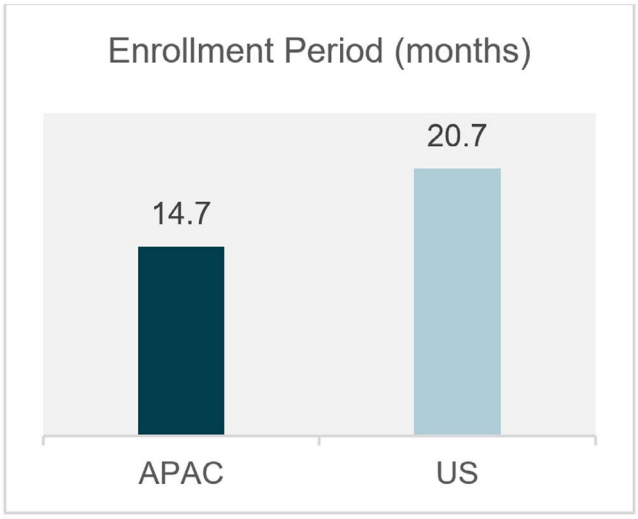
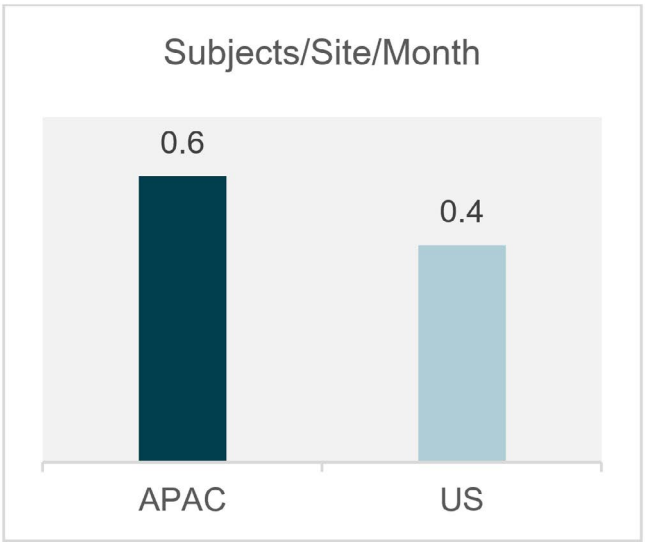


Figure 4. Comparison of median patient recruitment rates (in subjects per site per month) for NSCLC clinical trials in the US and Asia-Pacific since 2018 [18]



KEY OPINION LEADERS IN LUNG CANCER AND NSCLC

Prof. LI ZHANG
Sun Yat-Sen University Cancer Centre ***– CHINA***

Dr. Zhang is Professor of Medical Oncology, Deputy Director of Lung Cancer Research Centre of Sun Yat-Sen University, Chief of the Department of Clinical Research, Department of Medical Oncology and Phase I Unit at the Centre. Dr. Zhang has served as the Principal Investigator for several international phase III clinical trials. He is also a member of the NCCN Clinical Practice Guidelines in Oncology™ for the Lung Cancer, Colon/Rectal Cancer and Head and Neck Cancer Panel. Dr. Zhang has served an Editorial Board member in addition to publishing more than 90 clinical research papers in the Journal of Clinical Oncology, Lancet Oncology, Cancer, Cancer Gene Therapy, Journal of Thoracic Oncology, Lung Cancer, Cancer Chemotherapy and Pharmacology, Oncology, Clinical Lung Cancer, and Medical Oncology.

Prof. AHN MYUNG-JU
Samsung Medical Center ***– SOUTH KOREA***

Prof. Ahn is Professor in the Department of Hematology and Oncology at the Samsung Medical Center. She is a member of the International Association Society of Lung Cancer, and a member of the American Society of Oncology. She is the co-author of over 200 publications and was involved in over 100 clinical studies, including more than 60 in solid tumors trials, for Novartis, Roche, Curis, BeiGene, and Ignyta.

Dr. MOK SHU KAM TONY
Chinese University of Hong Kong ***– HONG KONG***

Dr. Mok is Chairman of the Department of Clinical Oncology at the Chinese University of Hong Kong and serves on the Board of Director at the American Society of Clinical Oncology. He participated in over 90 clinical studies, including 69 in Lung cancer, for Roche, Boehringer Ingelheim, BMS, AstraZeneca, ImmvaRx, AVEO Bio, Ono Pharma, and Xcovery.

Prof. MICHAEL MILLWARD
Sir Charles Gairdner Hospital ***– AUSTRALIA***

Professor Michael Millward is the foundation Chair of Clinical Cancer Research at the University of Western Australia and a Consultant Medical Oncologist at Sir Charles Gairdner Hospital and Linear Clinical Research, Perth, Western Australia. He has a strong track record in delivering clinical trial outcomes, particularly with novel therapeutics and phase I/II studies. He has extensive clinical and research interests in lung cancer and melanoma. He has published more than 190 original papers and 300 abstracts at international meetings. He has conducted 87 clinical trials in various indications in oncology.

Dr. DANIEL TAN
National Cancer Centre Singapore (NCCS) ***– SINGAPORE***

Dr. Tan is a senior consultant at the Division of Medical Oncology at National cancer Centre Singapore. His research interests are in drug development and molecular biology of thoracic cancers and drug development in phase I trials, specifically in drug resistance, with particular emphasis on lung cancer and the PI3K pathway. He is directly involved in developing protocols testing new drug targets and combinations in various cancers. He is the Principal Investigator for the National Medical Research Council Lung Cancer Large Collaborative Grant (2019-2023). He has published several papers in leading journals such as Nature, Nature Medicine, The New England Journal of Medicine, The Lancet, The Lancet Oncology and Journal of Clinical Oncology. He serves as Associate Editor for the Journal of Thoracic Oncology and is the conference chair for the World Conference in Lung Cancer.

Prof. YANG JAMES CHIH HSIN
National Taiwan University Hospital ***– TAIWAN***

Prof. Yang is the Director of the Graduate Institute of Oncology at the National Taiwan University (Taiwan). He served on the editorial board of Annals of Oncology and Lung Cancer Journals and is the current associate editor of the Journal of Thoracic Oncology and Nature Scientific Report. He is the co-author of over 100 scientific publications, and he was involved in over 80 clinical studies, including 65 in Lung cancer for AstraZeneca, Novartis, Eli Lilly, Incyte Corporation, BMS, Takeda, and Hutchinson MediPharma.

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