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The Asia Pacific CRO

ESOPHAGEAL CANCER – CLINICAL TRIALS LANDSCAPE – ASIA PACIFIC

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Disease Background

According to Globocan, Esophageal cancer (EC) is the ninth most prevalent cancer and the sixth leading cause of cancer-related mortality in the world. In Asia, EC is the sixth most common cancer, with the region constituting almost 80% of the new EC cases globally. Etiologically there are two main histological subtypes: esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC), which account for 90% and 10% of cases respectively. EC is a complex disease with many causes, although often linked with alcohol and tobacco consumption. Nearly 80% of all ECs are diagnosed in less developed nations. Esophageal cancer is often characterized by a poor prognosis and a rapid progression, with a 5-year survival rate of less than 20%. [1,2,3]

Epidemiology

In terms of regional distribution, the highest standardized incidence rate has been observed in East Asia (12 per 100,000). [4] In the most populated countries of China and India, EC ranks as the fifth most common cancer by incidence in 2020.

China which reported over 300,000 new cases of EC in 2020 according to Globocan, with an ASIR of 14 per 100,000, accounted for more than half the global share of new EC cases.

India which reported over 60,000 new EC cases in 2020 according to Globocan, with an ASIR of 5 per 100,000 accounted for about 10% of the new EC cases globally.

Thailand and South Korea reported a little over 3,500 and 2,500 cases respectively, with ASIRs of 3 and 2 per 100,000 respectively in 2020 according to Globocan. Australia and the Philippines both reported over 1,000 cases each in 2020 according to Globocan. Malaysia, New Zealand and Singapore together reported close to 1,000 cases in 2020 according to Globocan, with New Zealand showing the highest ASIR of 4 per 100,000 among them.

Table 1: Esophageal Cancer Incidence, mortality and 5-Year Prevalence by region (2020)

Region	Incidence			Mortality			5-Year Prevalence (all ages)	
	Number	%	ASR*	Number	%	ASR**	Number	Prop#. (per 100 000)
World	604,100	100	6.3	544,076	100	5.6	666,388	8.6
Asia	481,552	80	8.5	434,363	80	7.6	523,122	11.3
China^	324,422	54	13.8	301,135	55	12.7	347,912	24.0
India	63,180	10	4.7	58,342	11	4.4	68,607	5.0
United States	18,309	3	2.8	16,209	3	2.4	23,062	7.0
Thailand	3,447	0.6	2.9	3,176	0.6	2.7	3,698	5.3
South Korea	2,615	0.4	2.4	1,571	0.3	1.3	3,282	6.4
Australia	1,554	0.3	3	1,302	0.2	2.4	1,924	7.6
The Philippines	1,144	0.2	1.2	1,122	0.2	1.2	1,228	1.1
Malaysia	398	0.07	1.2	386	0.07	1.2	490	1.5
New Zealand	362	0.06	3.6	262	0.05	2.5	437	9.1
Singapore	234	0.04	2.1	320	0.06	2.0	302	5.2

Source: *Globocan 2020; Note: *age standardized rate of incidence; **age standardized rate of mortality; # proportion per 100,000; ^includes Taiwan and Hong Kong*

Histologically, the incidence of ESCC is higher in Asian countries like China, India, Thailand and South Korea, than in other countries. ESCC therefore is the predominant type in Asia, whereas EAC remains rare. [5, 6, 7]. As an exception, Australia and New Zealand, have both shown a higher incidence of EAC than ESCC among males in 2018. In the same year, males showed the highest ASRs of ESCC in China (ASR 18.8), while the same gender showed the highest ASRs of EAC in New Zealand (ASR 4.2). [8]

Table 2: Incidence and ASR of Esophageal Cancer, by Histological Subtype and Gender, 2018, by locations (2018). [8]

Country	Male				Female			
	EAC		ESCC		EAC		ESCC	
	ASR	N	ASR	N	ASR	N	ASR	N
China	0.9	9,488	18.8	204,602	0.4	3,737	7.8	89,532
India	0.4	2,726	5.1	31,164	0.1	864	2.8	17,642
Thailand	0.4	185	5.5	2,836	0.1	49	0.8	493
South Korea	0.2	92	5.0	2,260	0.0	27	0.4	214
The Philippines	0.7	253	1.5	566	0.1	62	0.4	178
Australia	3.5	790	1.9	439	0.5	132	1.0	316
Singapore	0.4	24	3.6	183	0.1	6	0.7	55
Malaysia	0.8	121	1.1	177	0.3	42	0.5	82
New Zealand	4.2	191	1.6	72	0.6	34	1.3	74

STANDARD OF CARE

Esophageal cancer (EC), which includes ESCC and EAC, is one of the world's deadliest cancers. The therapeutic choices for EC patients are quite diverse and include endoscopic resection, surgery, chemotherapy (CT), radiotherapy (RT), chemoradiotherapy (CRT), and targeted therapy. [9] However, as the two subtypes, ESCC and EAC, have very little in common in terms of risk factors and genetic mutation profiles, they are considered as two separate diseases, such that their treatment, and prognosis are expected to be significantly different. Until recently, the most effective treatment for EC patients has been a combination of esophagectomy and lymphadenectomy; as a result, early screening and diagnosis for EC patients is critical. Most EC patients are currently diagnosed late, with local or distant metastases, and many accessible medicines, including targeted therapy and immunotherapy, do not provide satisfying survival benefits for these patients, as they do for other cancer populations. Combining multiple medications in the future are thought of as a successful strategy for late-stage EC patients, while substantial clinical trials in a randomized, multi-center fashion are warranted. [9]

Table 3: The types of medications used for Esophageal cancer [9]

Treatment type	Options
Surgery	a. Endoscopic resection b. Esophagestomy combined with lymphadenectomy
Radiation and chemotherapy	a. Neoadjuvant chemotherapy b. Neoadjuvant chemoradiotherapy c. Chemotherapy d. Radiotherapy e. Chemoradiotherapy
Targeted therapy	a. Anti-EGFR therapy b. Anti-PI3K/mTOR therapy
Immunotherapy	a. Anti-PD-1 therapy b. Anti-PD-L1 therapy c. Anti-CTLA-4 therapy

Table 4: Recent approvals of immunotherapeutic agents for Esophageal cancer [10]

Adenocarcinoma				Squamous Cell Carcinoma			
Treatment	Trial Name	Setting	Approval	Treatment	Trial Name	Setting	Approval
Nivolumab	CHECK-MATE-577	Adjuvant (after neo-adjuvant chemora-diation + surgery with residual pathological disease)	2021 (FDA, EMA)	Nivolumab	CHECK-MATE-577	Adjuvant (after neo-adjuvant chemora-diation + surgery with residual pathological disease)	2021 (FDA, EMA)
Nivolumab + platine or fluoropyrim-idine-based chemother-apy	CHECK-MATE-649	1st line, metastatic, recurrent or inoperable	2021 (FDA)	Pembroli-zumab + platine or fluoropyrim-idine-based chemother-apy	KEY-NOTE-590	1st line metastatic, recurrent or inoperable	2021 (FDA, EMA for CPS ≥ 10)
Pembroli-zumab + platine or fluoropyrim-idine-based chemother-apy	KEY-NOTE-590	1st line, metastatic, recurrent or inoperable	2021 (FDA, EMA for CPS ≥ 10)	Nivolumab	ATTRAC-TION-3	2nd and further-line metastatic, recurrent or inoperable	2020 (FDA, EMA)
				Pembroli-zumab	KEY-NOTE-181	2nd and further-line metastatic, recurrent or inoperable, CPS ≥ 10	2019 (FDA)

Pan-Asian adapted ESMO guidelines for EC

Table 5: Summary of Asian recommendations for patients with metastatic Esophageal cancer [11]

Recommendation	Description
Management of advanced disease	Patients with metastatic esophageal cancer can be considered for different palliative treatment options depending on the clinical situation. External radiotherapy, single-dose brachytherapy, gastrostomy/jejunostomy or metal stent placement may be considered [A5100% and V, B].
	Chemotherapy is indicated for palliative treatment in selected patients, particularly for patients with adenocarcinoma who have a good performance status [A¼100% and IIIB].
	In squamous cell esophageal cancer, combination chemotherapy is the preferred option in clinical practice for fit patients [A5100%].
	BSC or palliative monotherapy should be considered for unfit patients [A5100% and II, B].
Personalized medicine	Trastuzumab–containing treatment is recommended for HER2-positive GEJ adenocarcinomas. It is an option for patients with HER2-positive pure esophageal adenocarcinomas despite their rarity [A5100% and I, A].

NOTE: BSC, BEST SUPPORTIVE CARE; GEJ, GASTROESOPHAGEAL JUNCTION; HER2, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2.

Table 6: Summary of drug approvals and reimbursement, By Asian Locations [11]

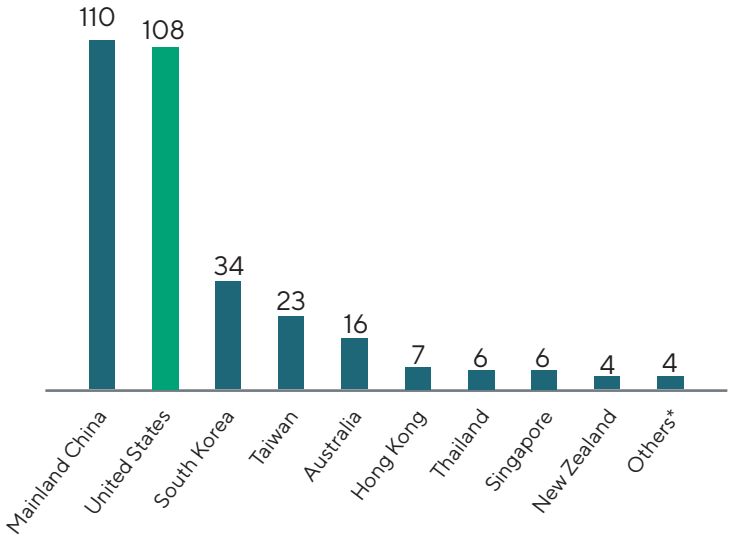
Location wise drug status			5-FU	Cisplatin	Nedaplatin	Docetaxel	Paclitaxel
CSCO	**China**	Approval	Y	Y	Y	Y	Y
		Reimbursement	Y	Y	Partially reimbursed or with restriction	Partially reimbursed or with restriction	Y
JSMO	**Japan**	Approval	Y	Y	Y	Y	Y
		Reimbursement	Y	Y	Y	Y	Y
KSMO	**Korea**	Approval	Y	Y	N	Y	a
		Reimbursement	Y	Y	N	Y	a
MOS	**Malaysia**	Approval	Y	Y	N	Y	Y
		Reimbursement	Y	Y	N	Y	Y
SSO	**Singapore**	Approval	Y	Y	N	Y	Y
		Reimbursement	Y	Y	N	Y	Y
TOS	**Taiwan**	Approval	Y	Y	N	N	N
		Reimbursement	Y	Y	N	N	N

NOTE: 5-FU, 5-FLUOROURACIL; Y – approved or reimbursed; N – not approved or reimbursed; a - Only reimbursed in treatment of oesophageal adenocarcinomas; CSCO - Chinese Society of Clinical Oncology; JSMO - Japanese Society of Medical Oncology; KSMO - Korean Society of Medical Oncology; MOS - Malaysian Oncological Society; SSO - Singapore Society of Oncology; TOS - Taiwan Oncology Society

CLINICAL TRIAL LANDSCAPE

Biopharma companies have initiated over 350 clinical trials in Esophageal cancer since 2018, with the Asia Pacific region involved about half of the trials. Clinical trials in Asia Pacific predominantly involve Mainland China, South Korea, Taiwan and Australia, with fewer competing trials compared to the US. (Figure 1).

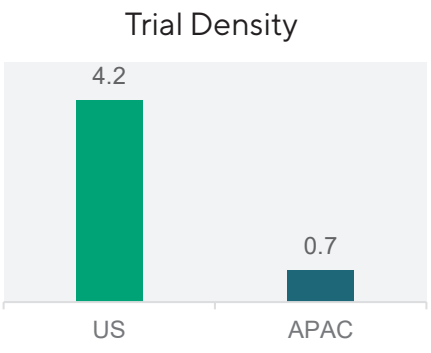
Figure 1: Top locations in Asia Pacific and the US, based on the number of studies in Esophageal cancer initiated by Biopharma companies since 2018 [12].



- Locations in which Novotech directly operates
Note: Others include India (2), Malaysia (1) and The Philippines (1)*

Due to its large population and lower volume of studies, the Asia Pacific region has lower competing trial risk with a trial density about 6 times lower than the US (Figure 2).

Figure 2. Comparison of the trial density* for industry-sponsored Esophageal cancer clinical trials in the US and Asia Pacific [12]



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

Trials running in the Asia-Pacific region since 2017, show median recruitment durations about 20% shorter than trials in the US (Figure 3). In addition, these trials in the Asia-Pacific region recruit, on average, twice faster than the US (0.3 and 0.6 patients per site per month respectively) (Figure 4)

Figure 3. Comparison of median patient enrolment duration (in months) for Esophageal cancer clinical trials in the US and Asia-Pacific since 2017 [12]

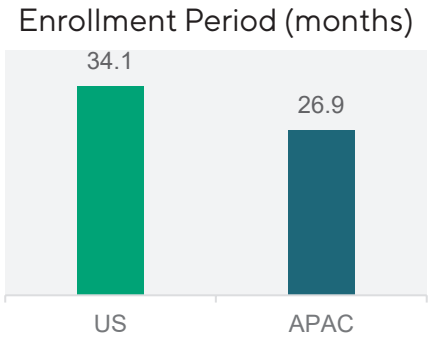
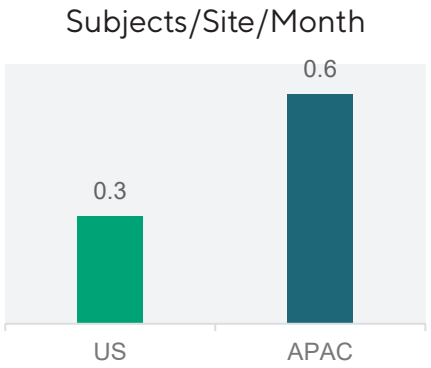


Figure 4. Comparison of median patient recruitment rates (in subjects per site per month) for Esophageal cancer clinical trials in the US and Asia-Pacific since 2017 [12]



KEY OPINION LEADERS IN ESOPHAGEAL CANCER

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Dr. Ruihua Xu is currently a Professor and President in the Department of Medical Oncology at Sun Yat-Sen University (SYSU) Cancer Center, Guangzhou, China. His primary research interests include the development of novel drugs for GI cancer, the design and conduct of phase I and II clinicals, in addition to transnational research aimed at developing prognostic and predictive markers in GI cancer patients. He served as a Steering Committee member in several global trials, working with several sponsors such as Pfizer Inc, Ampo Biotechnology Inc, Innovent Biologics Inc and KeyMed Biosciences Inc among others. He is now leading several clinical trials in China and has published more than 150 peer-reviewed papers, in renowned journals such as Journal of Clinical Oncology, Hepatology, Cancer Research, Leukemia, Clinic Cancer Research and Cancer

Dr. LORRAINE CHANTRILL
Wollongong Hospital – AUSTRALIA

Dr Lorraine Chantrill is Head of Medical Oncology, Illawarra Cancer Care Centre at Wollongong Hospital and Head of Service for Medical Oncology across the Illawarra Shoalhaven Local Health District (ISLHD), and Area Clinical Director of Clinical Trials. Dr.Chantrill is also the Chair of the AGITG (Australian and New Zealand Gastro-Intestinal Trials Group), in addition to being the Chair of the Scientific Advisory Committee. She has served on the AGITG Upper GI Working Party since 2011 and has chaired the Working Party since August 2014. Dr.Chantrill has garnered extensive experience towards management of Oncology Clinical Trials and served as the Principal Investigator for several clinical trials in gastrointestinal cancers. Dr.Chantrill looks forward to building the region's clinical trial portfolio to enhance patients' access to some new and emerging therapies. She has worked with sponsors such as Amgen Inc, Bristol-Myers Squibb Co and F. Hoffmann-La Roche Ltd among others.

Prof. JOO-HANG KIM
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Joo-Hang Kim is a Professor at the Cha University and the Director of the Institute for Cancer Research and Chief of Hemato-Oncology, Yonsei University College of Medicine. He specializes in lung cancer, head and neck cancer, and esophageal cancer. He has participated in more than 40 clinical trials serving as the Principal Investigator in over 10 of them. He has worked for sponsors such as F. Hoffmann-La Roche Ltd, Genosco Inc and AstraZeneca Plc to name a few and has more than 80 publications to his credit.

PROF. JANG-MING LEE
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Dr. Jang-ming Lee is a Professor of Surgery, Department of Thoracic Surgery, National Taiwan University Hospital, Taipei, Taiwan. His top areas of expertise are Esophageal Cancer, Squamous Cell Skin Carcinoma, Collapsed Lung, and Squamous Cell Lung Carcinoma. His clinical research consists of co-authoring over a 100 peer reviewed articles and participating in 4 clinical trials in the past 15 years. He has worked with sponsors such as Exelixis Inc, Merck & Co Inc and F. Hoffmann-La Roche Ltd.

Dr. MATTHEW NG
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Dr. Matthew Ng is a Senior Consultant Medical Oncologist who specialises in experimental therapies. In the Division of Medical Oncology, he directs the Upper GI Cancer Clinical Service and Research Program. His current research focuses on the creation of biomarker-driven, early-phase clinical studies, notably in oesophageo-gastric malignancies. He has participated in more than 20 clinical trials serving as a Principal Investigator in more than 10 trials. He has worked for a wide range of sponsors such as Pfizer Inc, F. Hoffmann-La Roche Ltd, Bristol-Myers Squibb Co, MacroGenics Inc and Genentech USA Inc among others.

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Dr Brigette Ma is currently a Professor and Honorary Consultant at the Department of Clinical Oncology, Chinese University of Hong Kong (CUHK). She is also the Medical Director of the Phase I Clinical Trial Centre (Oncology) and Co-Director of the Cancer Drug Testing Unit at the Department of Clinical Oncology, Prince of Wales Hospital, CUHK. Her specific areas of interest in new drug development and clinical research include the design and conduct of phase I clinical trials, novel therapies for nasopharyngeal carcinoma, colorectal cancer and other gastrointestinal cancers. She has severed as a Principal Investigator in over 15 trials and has worked with sponsors such as Pfizer Inc, AstraZeneca Plc and Millennium Pharmaceuticals Inc among others. She has published over 110 peer-reviewed papers and serves in the editorial board of the Asian-Pacific Journal of Clinical Oncology.

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