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# CLINICAL TRIAL LANDSCAPE OF LIVER CANCER IN ASIA PACIFIC

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# EPIDEMIOLOGY OVERVIEW

**Background**

According to the Globocan 2020 report, liver cancer is the fourth most frequent cancer in Asia, with the region accounting for over 70% of all new liver cancer cases worldwide. Hepatocellular carcinoma (HCC) and bile duct malignancies are highly prevalent in Asia, especially in China and South Korea where the prevalence rate is about five times higher than in Western countries. Chronic viral hepatitis infections as well as fatty liver diseases (NASH in particular), which are endemic in this part of the world, are known to markedly increase the risk of developing HCC and explain the high rates observed in Asia. [1,2]

**Disease Prevalence**

There is wide geographical variation in the prevalence of primary liver cancers such as HCC. Eastern Asia and South-East Asia have the greatest incidence rates of this cancer in the Asian region. In general, it is more common in underdeveloped countries, which contribute to over 85% of cases. Men are far more likely than women to develop this malignancy. [3,4]

HCC and intrahepatic cholangiocarcinoma (ICC) are the two predominant histological forms of liver cancers, accounting for about 80% and 15% of liver cancer cases respectively. In 2018, Asia accounted for over a quarter of all incident cases and deaths, with China alone accounting for nearly half of the new cases and deaths worldwide. Furthermore, age-standardized rates for males and females in China were approximately three times higher than in the United States (28 vs. 10 per 100,000 for males and 9 vs. 3 per 100,000 for females). These figures mostly reflect regional differences in HBV infection rates, which have been reported to range from 18% in China to 1% in the United States. As a result, while lowering liver cancer incidence trends in Asia are encouraging, they continue to be a significant contributor to the worldwide liver cancer burden. [5]

In China, liver cancer is amongst the five most common cancers, with the ASR of incidence being 18 per 100,000 according to Globocan 2020 report. The 2020 liver cancer incidence in China constituted almost 45% of the global liver cancer cases. [6]

In Thailand, liver cancer is the most frequently occurring cancer type, with an ASIR of nearly 23 per 100,000 population, and the primary cause of cancer related mortalities, in 2020. In South Korea, liver cancer ranked as the sixth most common cancer with the 2020 ASIR being 14 per 100,000 population, and the second leading cause of cancer mortalities, according to Globocan report. In the Philippines, liver cancer is the fourth most common cancer with the 2020 ASIR being 11 per 100,000 population, and the second leading cause of cancer mortalities. [7,8,9]

Australia, New Zealand, Singapore and Malaysia show a lower prevalence compared to other Asia-Pacific locations. However, Singapore showed a relatively higher ASIR of 12 per 100,000 population according to Globocan 2020 report. In India, the ASR of incidence in 2020 was only one sixth that of China. However, chronic viral infections and alcohol abuse are expected to drive the number of cases up in the country.

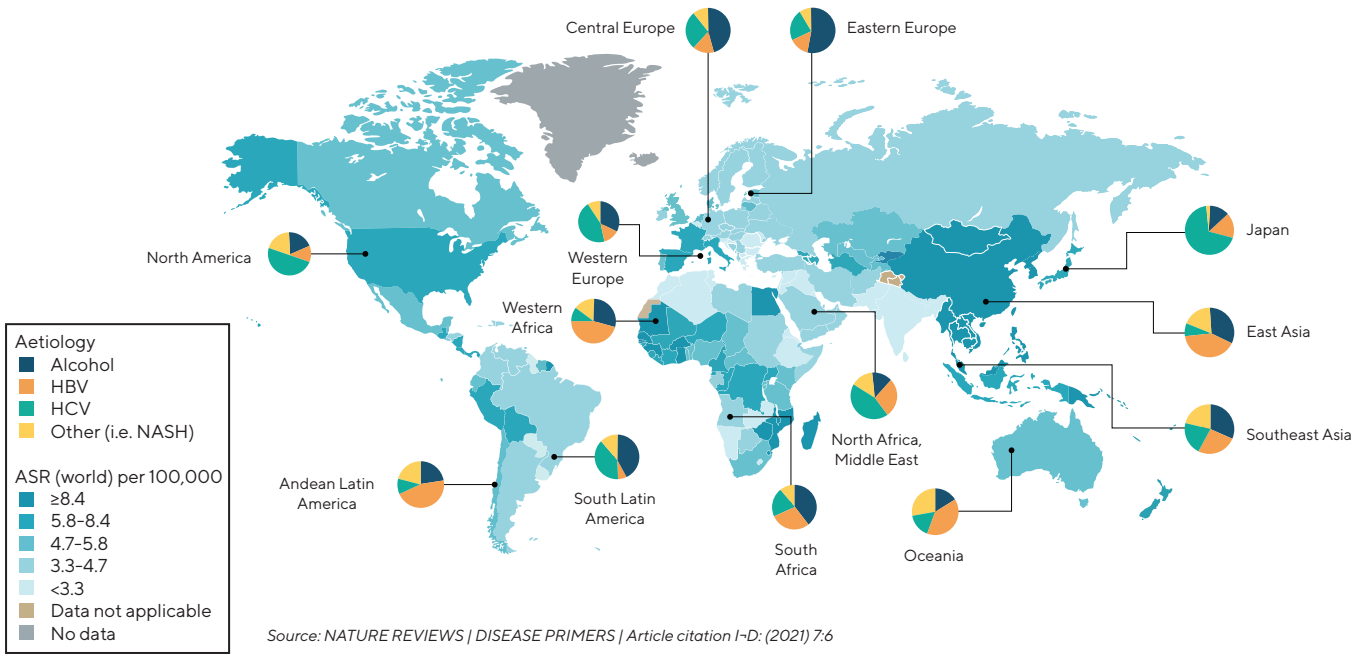
Table 1: Incidence, Mortality and 5-year Prevalence of Liver cancer in a selection of locations

| Region | Incidence | | | Mortality | | | 5-year prevalence (all ages) | |
|---|---|---|---|---|---|---|---|---|
| | Total New Cases | %* | ASR[a] | Total Deaths | %** | ASR[b] | Number | Prop[c] (Per 100,000) |
| **World** | 905,677 | 100 | 9.5 | 830,180 | 100 | 8.7 | 994,539 | 12.8 |
| **Asia** | 656,992 | 72.5 | 11.6 | 608,898 | 73.3 | 10.7 | 732,048 | 15.8 |
| **China^** | 410,038 | 45.3 | 18.2 | 391,152 | 47.1 | 17.2 | 422,633 | 29.2 |
| **US** | 42,284 | 4.7 | 6.9 | 31,078 | 3.7 | 4.7 | 45,341 | 13.7 |
| **India** | 34,743 | 3.8 | 2.6 | 33,793 | 4.1 | 2.5 | 38,602 | 2.8 |
| **Thailand** | 27,374 | 3.0 | 22.6 | 26,704 | 3.2 | 21.9 | 26,606 | 38.1 |
| **South Korea** | 14,788 | 1.6 | 14.3 | 11,158 | 1.3 | 9.9 | 29,908 | 58.3 |
| **The Philippines** | 10,594 | 1.2 | 11.4 | 9,953 | 1.2 | 10.8 | 10,964 | 10 |
| **Australia and New Zealand** | 3,344 | 0.4 | 6.1 | 2,503 | 0.3 | 4.1 | 3,578 | 11.8 |
| **Malaysia** | 2,149 | 0.2 | 6.4 | 2,050 | 0.2 | 6.1 | 2,267 | 7 |
| **Singapore** | 1,347 | 0.1 | 12.2 | 1,270 | 0.2 | 11.4 | 1,372 | 23.5 |

*Source: Globocan2020*
*Notes:*
**Calculated from world total liver cancer cases*
*** Calculated from world total liver cancer deaths*
*a – age standardized rate of incidence*
*b – age standardized rate of mortality*
*c – proportions per 100,000*
*^Includes Taiwan and Hong Kong*

The incidence and major aetiological factors involved in hepatocarcinogenesis are depicted in Figure 1. The highest incidence of hepatocellular carcinoma (HCC) is observed in East Asia.

Figure 1: The incidence and aetiology of HCC per region [10,11]




*Source: NATURE REVIEWS | DISEASE PRIMERS | Article citation I-D: (2021) 7:6*

# STANDARD OF CARE

Surgery, ablation, embolization therapy, radiation, targeted therapy, chemotherapy, and immunotherapy are the various options for treating liver cancer. The stage of liver cancer determines the treatment choice.

**Surgery, device based and radio oncology methods:**
Since the early 2010s, the management of HCC has vastly improved. The Barcelona Clinic Liver Cancer (BCLC) staging method is used to assign treatment based on tumour stages. Patients with early-stage HCC tumours are the best prospects for hepatic resection, liver transplantation, and local ablation, whereas patients with intermediate-stage HCC tumours are best treated with TACE (Transarterial chemoembolization), and those with advanced disease undergo systemic therapy first.

Of these procedures, the predominant curative therapy in HCC cases have been hepatic resection and liver transplantation. For tumours down-staged beyond Milan criteria, refinements in patient selection have led to improved surgical resection outcomes and outstanding 10-year post-liver transplantation survival rates. However, for non-surgical early-stage HCC, radiofrequency ablation remains the backbone of image-guided ablation despite advancements in alternative approaches.

Adjuvant therapies to prevent relapse post these potentially curative methods, are an unmet medical need, as randomised controlled trials (RCTs) have so far given poor results. TACE has been the most frequently used treatment and standard of care for intermediate-stage HCC for the past two decades. TARE (transarterial radioembolization) has been demonstrated to be effective in phase II studies, but guidelines have not yet established it as a primary standard of care. In the immediate term, other loco-regional devices or radiation oncology methods are unlikely to improve the intermediate therapy arsenal.

**Systemic therapies:**
With regards to systemic therapies, categories like immune-checkpoint inhibitors (ICIs), tyrosine kinase inhibitors (TKIs), and monoclonal antibodies are the primary drug categories. Nearly 60% of patients with HCC are predicted to be exposed to systemic therapy throughout their lives, especially in advanced stages of the disease. In the last five years, there has been significant progress in the development of systemic medicines, with studies indicating a significant increase in overall survival and patient quality of life.

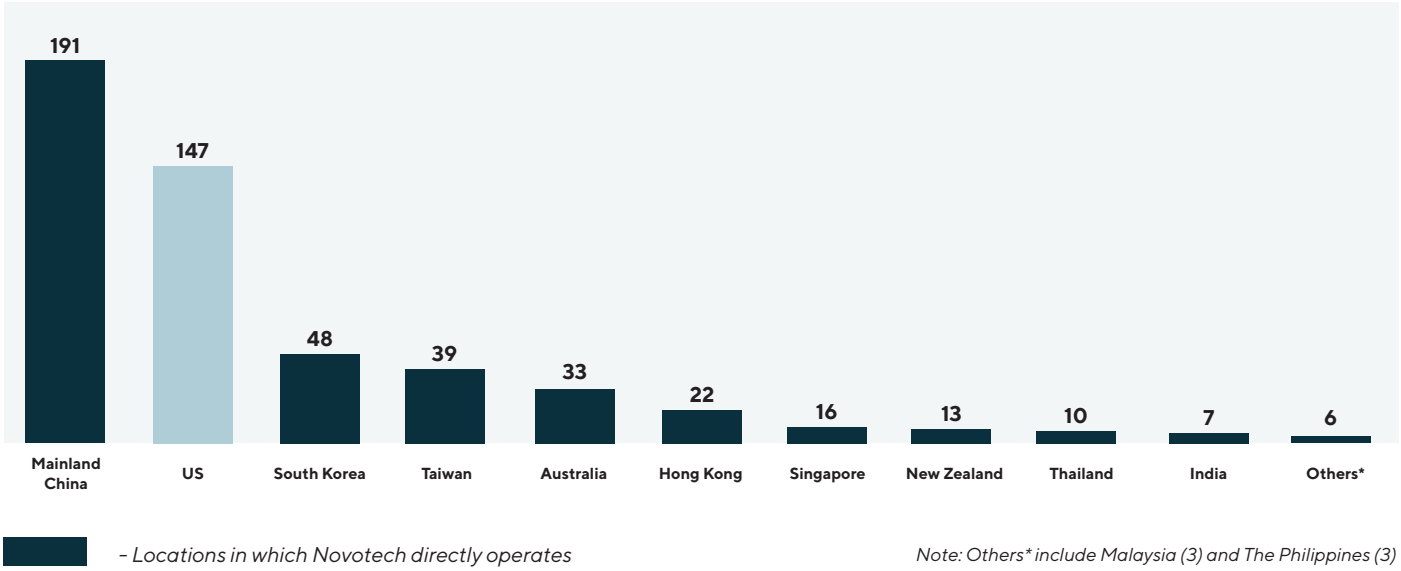
The natural history of advanced-stage HCC cases, for instance, includes a median survival of ~8 months. The FDA-approved combination of atezolizumab (anti-PDL1 antibody) plus bevacizumab (anti-VEGF antibody) has increased this life expectancy by more than twofold and improved patient-reported outcomes in advanced-stage HCC cases. The most effective single-drug therapies are still sorafenib and lenvatinib. Others like regorafenib, cabozantinib, and ramucirumab have also shown to improve survival when treatment is switched to single-agent regimens. Single-agent ICIs have been reported to deliver significant therapeutic advantages, but biomarkers have so far failed to identify this patient group.

In addition, phase III trials examining the efficacy of combination therapy, such as combining ICIs with TKIs or PD1/PDL1 axis inhibitors with CTLA4 inhibitors, are now underway. The findings of these studies are expected to alter the landscape of HCC management at all stages of progression. [12]
Others forms of cancer immunotherapy that go beyond checkpoint inhibition are still at a preclinical or early clinical stage. Examples of such immunotherapies are chimeric antigen receptor (CAR-) T cells, allogeneic NK cells, and oncolytic viruses.[13]

# CLINICAL TRIAL LANDSCAPE

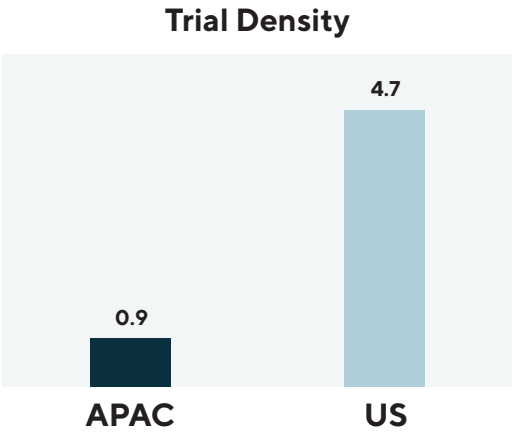
Biopharma companies have initiated over 500 clinical trials in liver cancer since 2018, with the Asia Pacific region involved in 50% of the trials. Clinical trials in Asia Pacific predominantly involve Mainland China, South Korea, Taiwan, Australia, Hong Kong and Singapore with fewer competing trials compared to the US. (Figure 2). Nearly 90% of the trials are related to Hepatocellular carcinoma.

**Figure 2: Top locations in the US and Asia Pacific, based on the number of studies in Liver cancer initiated by Biopharma companies since 2018 [14].**




Due to its large population and lower volume of studies, the Asia Pacific region has lower competing trial risk with a trial density about 5 times lower than the US (Figure 3).

**Figure 3. Comparison of the trial density* for industry-sponsored Liver cancer clinical trials in the US and Asia Pacific [14]**




*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 35% shorter than trials in the US (Figure 4). In addition, these trials in the Asia Pacific region recruit, on average, four times faster than the US (1.5 and 0.4 patients per site per month respectively) (Figure 5).

**Figure 4. Comparison of median patient enrolment duration (in months) for Liver cancer clinical trials in the US and Asia Pacific since 2018 [14]**

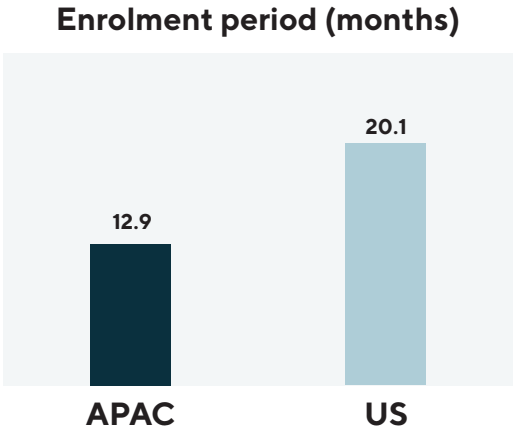
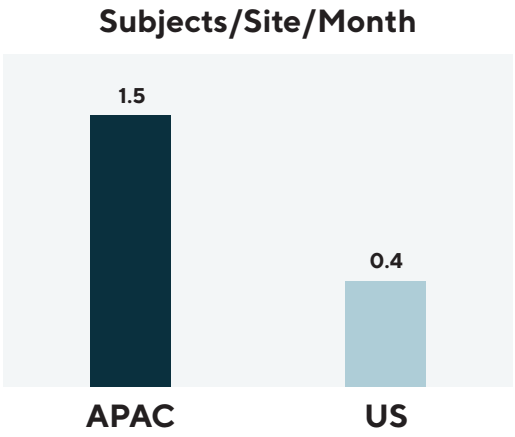



**Figure 5. Comparison of median patient recruitment rates (in subjects per site per month) for Liver cancer clinical trials in the US and Asia Pacific since 2018 [14]**



# KEY OPINION LEADERS IN LIVER CANCER

**Prof. JACOB GEORGE**
Westmead Hospital – AUSTRALIA

Jacob George is Professor of Gastroenterology and Hepatic Medicine, Faculty of Medicine, University of Sydney. He is Head of Department of Gastroenterology and Hepatology at Westmead Hospital and Director of Gastroenterology and Hepatology Services, Sydney West Area Health Service and Director of the Storr Liver Unit, Westmead Millennium Institute, Westmead. His work on human hepatic cytochrome P450 expression was the first to demonstrate the existence of disease-specific alterations in hepatic drug metabolism in cirrhosis.

Professor George has published seminal papers on the pivotal role of transforming growth factor beta (TGF beta) in fibrogenesis. His major contribution to date has been on the role of insulin resistance in NASH, chronic hepatitis C and to the pathogenesis and progression of liver diseases in general. His research interests include the cellular and molecular basis of liver cancer. He has participated as a Principal Investigator for over seven trials and has worked with sponsors such as Pfizer Inc, AbbVie Inc, and Gilead Sciences Inc. He has more than 100 publications to his credit.

**Prof. EDWARD GANE**
Auckland Hospital – NEW ZEALAND

Edward Gane is a Professor of Medicine at the University of Auckland (New Zealand) and Chief Hepatologist, Transplant Physician and Deputy Director of the New Zealand Liver Transplant Unit at Auckland City Hospital. He is the co-author of over 100 publications including in The Lancet and The New England Journal of Medicine and serves on the editorial committee for several journals. Dr. Gane serves on the Executive Committee of the NZ Society of Gastroenterology and is a member of several international organizations including APASL, AASLD, ILCA and ILTS. He was involved in 175 clinical studies including 8 in liver cancer for Amgen, Bayer, and Onyx Pharmaceuticals.

**Prof. YOUNG-SUK LIM**
Asan Medical Center – SOUTH KOREA

Young-Suk Lim is a Professor at the University of Ulsan College of Medicine, (S. Korea), and head of the Asan clinical trial center. Professor Lim is co-author of over 150 scientific publications and was involved in about 40 clinical trials, primarily for pivotal and phase IV trials. Professor Lim more specifically worked on both hepatitis and HCC trials for Gilead, BMS, AbbVie, GSK, Celltrion, Altimmune, Roche or Ildong.

**Prof. RONNIE POON**
Hong Kong Integrated Oncology Center – HONG KONG

Ronnie Poon is Honorary Clinical Professor at the Li Ka Shing Faculty of Medicine (Hong Kong) and has been involved in about 50 clinical trials on both first-in-human testing and pivotal studies. He collaborated with major pharmaceutical and biotech companies such as Novartis, Bayer, Amgen, and GSK and was involved in 8 studies with Novartis alone. Professor Poon has been actively involved in academic research as well and is the co-author of over 300 scientific publications including in the J Clin Oncol and Cancer Cell.

**DR. LIM HO YEONG**
Samsung Medical Center – SOUTH KOREA

Dr. Lim is the co-author of over 50 scientific publications and was involved in almost a hundred clinical trials including for Sanofi, Pfizer, Eli Lilly, Amgen, Transgene, PharmAbcine and Merck. Dr Lim is a Research Fellow from Johns Hopkins University Oncology Center and is an active member of several academic societies including the American Society of Clinical Oncology and the American Association for Cancer Research.

**Dr. YOON KOO KANG**
ASAN Medical Center – SOUTH KOREA

Dr. Kang is Assistant Professor at UUCM AMC and a Research Fellow in Medicine Branch from the National Cancer Institute. Dr. Kang is one the most active clinical investigators in South Korea. He is the co-author of over 200 scientific publications and was involved in over 140 clinical studies in numerous solid tumor indications. Prof. Kang is currently involved in ongoing pivotal studies for BMS, EMD, AstraZeneca and MacroGenics.

**A/Prof. YAU CHUNG CHEUNG, THOMAS**
Queen Mary Hospital – HONG KONG

Dr. Yau Chung Cheung is a Clinical Associate Professor, Department of Medicine, University of Hong Kong. Dr. Yau's main research interests are gastrointestinal oncology, early phase clinical trials and translational research. He pioneered Hong Kong Liver Cancer classification and is one of the global pioneers in hepatocellular carcinoma drug development program. He is actively involved in cancer immunotherapy drug development and has also led few global ground-breaking immunotherapy trials for liver cancer some of which have led to global drug approval for advanced hepatocellular carcinoma. He has published more than 140 peer-reviewed publications in various leading oncology journals, namely Lancet, JAMA Oncology, Gastroenterology, and Journal of Hepatology.

**A/Prof. STEPHEN L. CHAN**
Prince of Wales Hospital, The Chinese University of Hong Kong – HONG KONG

Dr. Stephen L. Chan is an Associate Clinical Professor at the Chinese University of Hong Kong's Department of Clinical Oncology. His main research focus is on gastrointestinal cancers, particularly hepatobiliary and pancreatic tumours, in both clinical and traditional settings. Dr. Chan has over 100 publications under his belt, including five first-author articles in the Journal of Clinical Oncology and comments in the Lancet. He has served as the Principal Investigator for a variety of clinical trials, including those supported by the Hong Kong Government's General Research Fund, University Grant Committee, Innovation and Technology Fund, and Hong Kong Health and Research Fund. He has worked for industry sponsors such as AstraZeneca Plc, Pfizer Inc, Acrotech Biopharma LLC and F. Hoffmann-La Roche Ltd to name a few.

**Prof. LI-TZONG CHEN**
National Institute of Cancer Research - TAIWAN

Professor Li-Tzong Chen is the Chief Executive Officer of Center for Cancer Research, Kaohsiung Medical University and the Chairperson, Research and Development Committee, Kaohsiung Medical University Chung-Ho Memorial Hospital. He has served as the Principal Investigator for more than 25 trials and has worked with sponsors such as AstraZeneca Plc, Pfizer Inc, BridgeBio Pharma Inc, Elevation Oncology Inc and Ipsen SA to name a few. Prof Chen. is the co-author of over 200 publications and was involved in 60 clinical studies, including 10 in gastric cancer.

**Prof. CHENG ANN-LII**
National Taiwan University College of Medicine – TAIWAN

Professor Cheng Ann Lii is a distinguished Professor, Attending Physician, Vice superintendent and Director of the NTU Cancer Center at National Taiwan University. His topics of interest include oncology, internal medicine and general medicine, nuclear medicine, hematology, and translational research for endemic cancers. Dr.Cheng has actively contributed towards basic and translational research in hepatocellular carcinoma and has co-authored over 300 peer reviewed publications. He was involved in 85 clinical studies, including 40 solid tumor studies for Celgene, Boehringer Ingelheim, MSD, BeiGene, Innopharmax, and Taiwan Liposome Company.

**Prof. CHUN-JEN LIU**
National Taiwan University Hospital - TAIWAN

Chun-Jen Liu is a professor at the National Taiwan University College of Medicine's Graduate Institute of Clinical Medicine. Professor Liu's research focuses on the role of host and viral factors in chronic hepatitis B and C aetiology and natural/treatment outcomes. Professor Liu is also the Principal Investigator in a number of multicenter clinical trials treating patients with chronic viral hepatitis B and C. He has worked with sponsors such as AbbVie Inc, TaiGen Biotechnology Co Ltd, Assembly Biosciences Inc and F. Hoffmann-La Roche Ltd among others. He has published more than 170 peer-reviewed research articles.

**Prof. RYU MIN-HEE**
Asan Medical Center – SOUTH KOREA

Ryu Min-Hee is a professor in the Division of Oncology at the Asan Medical Center, University of Ulsan College of Medicine Seoul, South Korea. He specializes in stomach cancer, liver cancer, and GIST, an orphan cancer. He has published over 180 papers. He has served as the Principal Investigator in more than 5 trials and has participated in more than 40 trials and 35 publications. He has worked with sponsors such as AstraZeneca Plc, F. Hoffmann-La Roche Ltd and Bristol-Myers Squibb Co, among others.

**Prof. JUNG-HWAN YOON**
Seoul National University Hospital – SOUTH KOREA

Jung Hwan Yoon is a professor at the Seoul National University College of Medicine. His focus areas include Acute liver failure, Ascites, Benign hepatic tumour, Chronic hepatitis, Cirrhosis, Esophageal vein, Fatty liver, Hepatic coma, Hepatocellular carcinoma, Liver fibrosis, Liver transplantation, Viral hepatitis, hepatitis, jaundice and peritonitis. Prof. Yoon has participated in more than 40 trials, serving as a Principal Investigator for more than 20, and has worked with sponsors such as Assembly Biosciences Inc, F. Hoffmann-La Roche Ltd, Bristol-Myers Squibb Co and Sillajen Biotherapeutics to name a few. He has more than 30 publications to his credit.

**Dr. YONG WEI PENG**
National University Cancer Institute Singapore (NCIS) – SINGAPORE

Dr. Yong Wei Peng is a senior Consultant, Department of Haematology-Oncology, National University Cancer Institute. He leads the therapeutic arm (NUH module) of the Singapore Gastric Cancer Consortium. His clinical interest is in gastrointestinal cancers and his research interests are pharmacogenetics and epigenetics in cancer. He is the Chairman of the National Healthcare Group Domain-Specific Ethics Review Board. He has participated in close to 40 trials and as a Principal Investigator in more than 20. He has worked for sponsors such as AstraZeneca Plc, BridgeBio Pharma Inc, Moderna Inc, Pfizer Inc and Arbutus Biopharma Corp among others.

**Dr. MATTHEW NG**
National Cancer Centre Singapore (NCCS) - SINGAPORE

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. Through genetic profiling of patients' tumours and the examination of pharmacodynamic indicators of oncogenic pathway modification, 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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References:


1. https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf
2. IPD. Kumar V, Fausto N, Abbas A, eds. (2015). Robbins & Cotran Pathologic Basis of Disease (9th ed.). Saunders.pp. 870–873. ISBN 978-1455726134.
3. https://www.wcrj.net/wp-content/uploads/sites/5/2018/06/e1082-Liver-cancer-in-the-world-Epidemiology-incidence-mortality-and-risk-factors.pdf
4. https://www.medscape.com/answers/197319-39196/what-is-the-global-incidence-of-hepatocellular-carcinoma-hcc-worldwide
5. https://www.frontiersin.org/articles/10.3389/fonc.2020.00171/full
6. https://gco.iarc.fr/today/data/factsheets/populations/160-china-fact-sheets.pdf
7. https://gco.iarc.fr/today/data/factsheets/populations/764-thailand-fact-sheets.pdf
8. https://gco.iarc.fr/today/data/factsheets/populations/410-korea-republic-of-fact-sheets.pdf
9. https://gco.iarc.fr/today/data/factsheets/populations/608-philippines-fact-sheets.pdf
10. https://www.nature.com/articles/s41572-020-00240-3.pdf; https://www.nature.com/articles/s41572-020-00240-3
11. https://www.nature.com/articles/s41572-020-00240-3/figures/1
12. https://www.nature.com/articles/s41572-020-00240-3
13. https://doi.org/10.3390/cancers13081962
14. Globaldata, Extracted date: 5th September 2021