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CLINICAL TRIAL LANDSCAPE OF CLL IN ASIA-PACIFIC

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Background

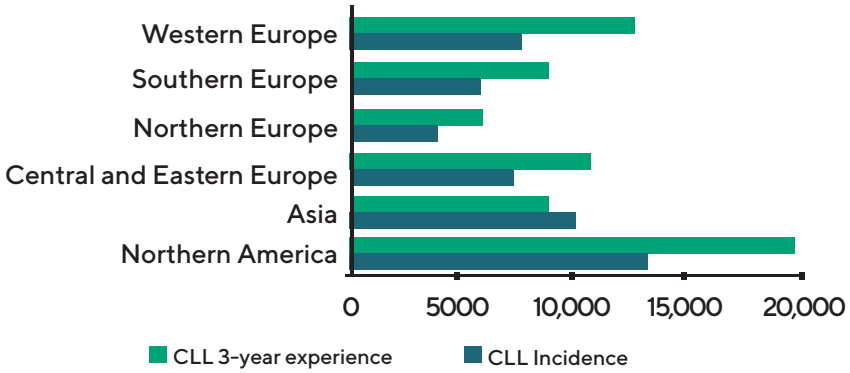
CLL (chronic lymphocytic leukaemia) is a blood and bone marrow cancer, and a slow growing leukaemia characterized by a progressive accumulation of functionally impaired B lymphocytes of monoclonal origin. CLL mostly affects older adults, with no apparent symptoms in the early stages of the disease. However, symptoms such as painless lymph node enlargement, fatigue, fever, upper left abdominal pain, night sweats, weight loss and recurrent infections develop as the cancer progresses. Factors such as increasing age, race, exposure to chemicals, familial history of blood and bone marrow cancers increase the risk of CLL. [1]

Prevalence

CLL is one of the most common forms of leukaemia, with the Asia Pacific region showing increasing incidence. Almost 70% of patients are older than 65 years at the time of diagnosis, and less than 2% are younger than 45 years.[2] CLL has a male predominance and are more likely to have disease progression and require therapy. [3]

CLL accounts for around 20% to 30% of all leukaemias worldwide. Figure 1 depicts the regional CLL incidence and 3-year prevalence, based on Globocan 2012 data. [4]

Figure1: CLL Incidence and 3-Year Prevalence Worldwide[a,b] [5]



[a] CLL incidence comprises the absolute number of cases annually. Three-year prevalence represents the number of CLL patients diagnosed and alive after 3 years.
[b] To determine CLL epidemiology, this analysis includes WHO GLOBOCAN 2012 data. The proportion of CLL case incidence and 3-year prevalence was calculated. CLL comprises approximately 30% of leukemia cases in Western countries and ~4% to 10% of leukemia cases in Asia.

CLL incidence trends at the global, regional and national level

A global study was conducted based on data from Global Burden of Disease online database, to quantify the trends of the age-standardized incidence rate (ASIR) of various types of leukemias from 1990 to 2017. Globally, the proportion of CLL from leukemia cases more than doubled between 1990 and 2017, increasing from 10% to around 18% during this period. The ASIR of CLL increased by 0.5% per year from 1990 to 2017. Between 1990 and 2017, most regions experienced a significant increase in the ASIR of CLL. At the regional level, the greatest increase was detected in East Asia, followed by Southeast Asia. At the national level, more than 85% of all countries experienced an increase in the ASIR of CLL between 1990 and 2017. China and South Korea were among the Asian locations showing the greatest increase. [6]

In China, CLL incidence is 0.3 per 100,000 [7]. Of the 4,174 individuals diagnosed with the four most common types of leukemias (AML, ALL, CML, CLL) studied (1952-1986) from Peking Union Medical College (PUMC), CLL was found in about 5% of the cases, while 23% had chronic myeloid leukaemia (CML); 50% had acute myeloid leukaemia (AML); and 22% had acute lymphoblastic leukaemia (ALL).[8]

EPIDEMIOLOGY OVERVIEW

In South Korea, CLL constitutes about 1.5% of all leukemias in the country. [9] Between January 1, 2006, and December 31, 2015, among the 19,500 newly diagnosed BNHL (B-cell Non-Hodgkin's Lymphoma) patients aged 18 years, CLL/SLL was the fourth most common cancer in South Korea between 2011 and 2015. [10]. Furthermore, for the period between 2005 and 2015, there were 52,757 new haematological malignancies, diagnosed by the National Health Insurance Service of Korea (Annual Report of Cancer Statistics for 2015), out of which lymphoid leukemia cases constituted 18% to 19% (n = 9759). Among these, the prevalence rates of CLL of B-cell type, showed an increasing trend over the ten-year period, with the incidence rate showing an APC of 0.5 between 2005 and 2015. (Refer table 1) [11]

Table 1: Incidence and Prevalence of CLL of B-cell type, 2005-2015, South Korea [11]

Lymphoid leukemias												
Year	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**Total**
Male	496	516	474	473	469	487	524	527	485	548	581	**5,580**
Female	315	371	350	342	365	353	433	405	394	424	427	**4,179**
ASIRa and APCb off CLL of B-cell type, by year	**ASIR**											**APC(2005-2015)**
	0.27	0.26	0.25	0.23	0.24	0.22	0.26	0.26	0.25	0.28	0.26	**0.48**
Prevalence rate in CLL of B-cell type by year	0.8	0.95	1.06	1.12	1.23	1.31	1.41	1.58	1.72	1.89	2.11	

a – age standardised incidence rate *b – annual percentage change*

In Australia over 1,000 people are diagnosed with CLL each year. CLL is the most common type of leukemia diagnosed in Australia with the 5-year survival rate being 79%. [12]

In New Zealand around 270 people are diagnosed with CLL every year. It is the most common form of leukaemia in New Zealand. [13] Between 1993 and 2002, there were a total of 4,253 leukemia patients identified from the NZCR, out of which CLL constituted the majority (40%, n = 1,691). [14]

In India, CLL is less prevalent than other kinds of leukaemia, with the incidence rate being 0.4 per 100,000 people. However, the number of incident cases is estimated to be 5,000 per year, with a prevalence of 25,000 patients. (Global Burden of Disease Results Tool). [15]

In Singapore, about 20 to 30 new cases of CLL are reported each year. [16] Malaysia has an annual incidence rate of 0.1 per 100,000 population, one of the lowest in Asia Pacific. [17]

In Thailand, the incidence of leukemia is relatively low by world standard. It is the eighth most common cancer in males and tenth in females. The estimated ASIR for Thailand is 4 per 100,000 in males and 3 per 100,000 in females [18]. Between 1963-1998, 184 CLL patients were identified at a single largest institution in Bangkok, Thailand, with the highest number of cases diagnosed in the 60 plus age group. [19]

According to the Philippines Cancer Facts & Estimates study from 2015, around 4 to 5 Filipinos per 100,000 may get leukaemia. According to the data, 4,270 new cases of leukaemia were detected in 2015, with 3,386 leukemia-related deaths. Lymphocytic leukaemia is the most common kind of leukaemia in Filipino children and those over the age of 70. [20]

STANDARD OF CARE

The therapy of CLL patients is determined by several criteria, including the patient's age, genetic profile, illness stage, and response to previous treatments. Drug therapy, surgery, radiation, leukapheresis and stem cell transplant are the various treatment options.

Drug Therapy

For CLL, a variety of drugs (monoclonal antibodies, other targeted drugs, chemotherapy) and drug combinations are employed. A key factor in deciding treatment options is whether there is a 17p deletion or TP53 mutation. NCCN (National Comprehensive Cancer Network, Inc) experts recommend clinical trials, especially if leukemia cells have 17p deletion or a TP53 mutation.

Even with newer treatments, outcomes for CLL with either marker are worse than other CLL types. Clinical trials are thus key to finding better treatments. [21]

Table 2: NCCN Recommendations for First-line and Second-line treatments for CLL, 2021 [21]

First line regimens for CLL without 17p deletion and TP53 mutation	
Preferred regimens	• Acalabrutinib with or without obinutuzumab • Ibrutinib • Venetoclax and obinutuzumab
Other regimens for people who are frail, 65 years of age and over, or who are sick	• Bendamustine and an anti-CD20 monoclonal antibody if not frail • Chlorambucil and Obinutuzumab • HDMP and rituximab • Ibrutinib and Obinutuzumab • Obinutuzumab
Other regimens for people who are under 65 years of age and fairly healthy	• Bendamustine and an anti-CD20 monoclonal antibody • FCR (preferred among other regimens for CLL with IGHV mutations) • Fludarabine and rituximab • HDMP and rituximab • Ibrutinib and rituximab
First line regimens for CLL with 17p deletion and TP53 mutation	
Preferred regimens	• Acalabrutinib with or without obinutuzumab • Ibrutinib • Venetoclax and obinutuzumab
Other regimens	• Alemtuzumab with or without rituximab • HDMP and rituximab • Obinutuzumab • Zanubrutinib if the patient can not take other BTK inhibitors
Second line regimens for CLL without 17p deletion and TP53 mutation	
Preferred regimens	• Acalabrutinib • Ibrutinib • Venetoclax and rituximab • Duvelisib • Idelalisib and rituximab
Other regimens for people who are frail, 65 years of age and over, or who are sick	• Alemtuzumab with or without rituximab • Chlorambucil and rituximab • Reduced-dose FCR • HDMP and rituximab • Idelalisib • Lenalidomide with or without rituximab • Obinutuzumab • Ofatumumab • Reduced-dose pentostatin, cyclophosphamide and rituximab • Venetoclax • Zanubrutinib • Bendamustine and rituximab • Bendamustine, rituximab and ibrutinib

STANDARD OF CARE

Other regimens for people who are under 65 years of age and fairly healthy	• Alemtuzumab with or without rituximab • Bendamustine and rituximab • Fludarabine, cyclophosphamide and ofatumumab • FCR • HDMP and rituximab • Idelalisib • Lenalidomide with or without rituximab • Obinutuzumab • Ofatumumab • Pentostatin, cyclophosphamide and rituximab • Venetoclax • Zanubrutinib • Bendamustine, rituximab and ibrutinib • Bendamustine, rituximab and idelalisib
Second line regimens for CLL with 17p deletion and TP53 mutation	
Preferred regimens	• Acalabrutinib • Ibrutinib • Venetoclax and rituximab • Duvelisib • Idelalisib and rituximab • Venetoclax
Other regimens	• Alemtuzumab with or without rituximab • HDMP and rituximab • Idelalisib • Lenalidomide with or without rituximab • Ofatumumab • Zanubrutinib

Source: NCCN Guidelines for CLL, 2021

Targeted therapies such as Tyrosine Kinase Inhibitors (TKI) are Registered and available across APAC. Access to these newer therapies is limited in a number of APAC countries as they are not funded by governments or health insurance. As such, access to these newer therapies is prohibited due to cost. This limitation in availability of newer therapies makes APAC an ideal region to conduct trials as patient and Investigator engagement is significantly higher as compared to other countries where these therapies are more accessible.

Surgery and radiation

Localized treatment with low-dose radiation therapy may be chosen if the primary concern is an enlarged spleen or swollen lymph nodes in one part of the body. If the enlarged spleen is producing symptoms, splenectomy (splenectomy surgery) is another possibility.

Leukapheresis

When the quantity of CLL cells in the blood is extremely high, it might pose issues with regular circulation, a medical condition called Leukostasis. As chemo may not reduce the number of cells until a few days after the initial dose, some of the cells may need to be removed from the blood by a treatment called leukapheresis before the chemo is given. This treatment immediately reduces blood counts. Although the effect is only temporary, it may be helpful until the chemo takes action.

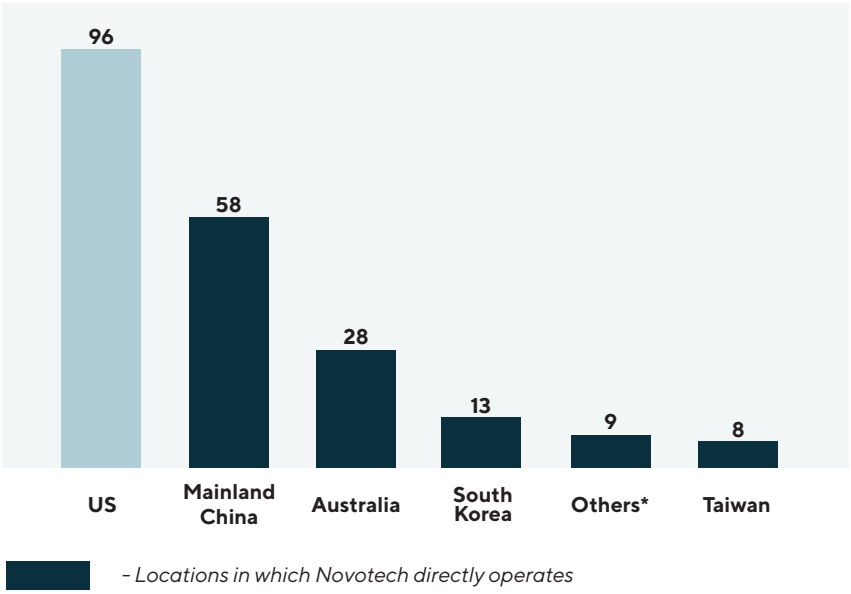
Stem cell transplant

People with very high-risk disease (based on prognostic factors) may be chosen for possible stem cell transplant (SCT) as an early treatment modality. [22]

CLINICAL TRIAL LANDSCAPE

Biopharma companies have initiated over 250 clinical trials in CLL since 2018, with the Asia Pacific region involved in about 40% of the trials. Clinical trials in Asia Pacific predominantly involve Mainland China, Australia and South Korea with fewer competing trials compared to the US. (Figure 2).

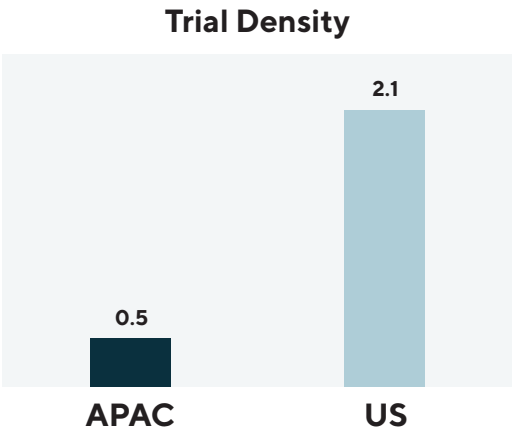
Figure 2: Top locations in Asia Pacific and the US based on the number of studies in CLL initiated by Biopharma companies since 2018 [23].



Note: Others include Singapore (4), New Zealand (2), India (1), Thailand (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 4 times lower than the US (Figure 3).

Figure 3. Comparison of the trial density* for industry sponsored CLL clinical trials in the US and Asia Pacific [23]



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

CLINICAL TRIAL LANDSCAPE

Leukemia trials conducted in the Asia Pacific region since 2018, show median recruitment durations about 40% shorter than trials in the US (Figure 4). In addition, these trials in the Asia Pacific region recruit, on average, twice as fast than in the US (1.1 and 0.5 patients per site per month respectively) (Figure 5).

Figure 4. Comparison of the median patient enrolment duration (in months) for leukemia clinical trials in the US and Asia Pacific since 2018 [24]

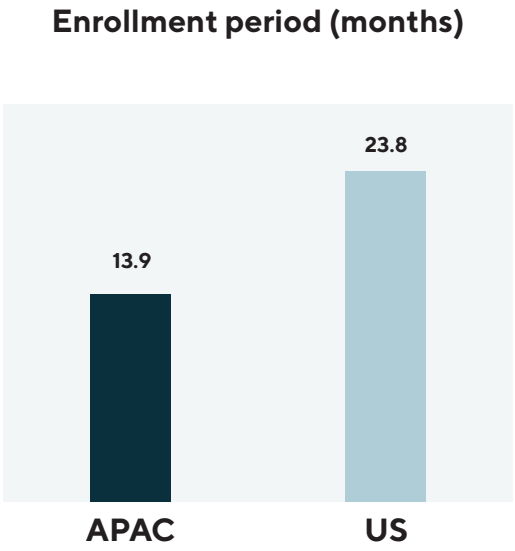
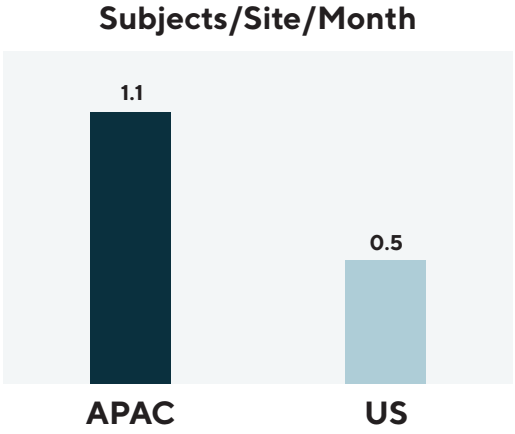


Figure 5. Comparison of the median patient recruitment rates (in subjects per site per month) for leukemia clinical trials in the US and Asia Pacific since 2018 [24]



KEY OPINION LEADERS IN CLL

Prof. JIAN-YONG LI
The First Affiliated Hospital of Nanjing Medical University - CHINA

Dr. Jian Yong Li is the Professor and Director of Department of Hematology, First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China. His research work focuses on the clinical and biologic characteristics of lymphoproliferative disorders including CLL, lymphoma and myeloma. He has participated in more than 60 clinical trials and served as the Principal Investigator in more than 20. He has worked with multiple sponsors such as AstraZeneca Plc, Cellular Biomedicine Group Inc, Legend Biotech Corp, Nanjing Bioheng Biotech Co Ltd, Pfizer Inc, Beijing Sunbio Biotech Co Ltd and Shanghai Longyao Biotechnology Co Ltd among others. He is also the president of the Society of Hematological Malignancy of Chinese Anti-Cancer Association, Director of Hematology Society of Jiangsu Province and the Editorial Boards of many journals and has contributed to about 30 publications.

Prof. CONSTANTINE TAM
Peter MacCallum Cancer Centre – AUSTRALIA

Dr Constantine Tam is the Director of Haematology at the St Vincent's Hospital (Melbourne, Australia) and leads the Low-Grade Lymphoma and CLL Stream at Victorian Comprehensive Cancer Centre. He is an internationally recognized expert in targeted therapies for B-cell malignancies and leads multiple clinical trials for the novel BTK inhibitor BGB-3111, as well as the first clinical trial in the world to combine ibrutinib and venetoclax. He is a member of the Australasian Leukemia and Lymphoma Group as well as the editorial board of Leukemia & Lymphoma having authored more than 100 research papers, along with his work cited over 2000 times in the literature. Dr Tam's clinical focus is the development of targeted drug combinations for treatment of CLL and NHL, with a long-term goal of achieving cure in these diseases.

Prof. HO S LEE
Kosin University Gospel Hospital – SOUTH KOREA

Dr Ho S Lee is a Professor of the Department of Internal Medicine, Koson University College of Medicine, South Korea. Lee was a Principal Investigator in 6 cancer trials including B Cell Lymphomas with sponsors such as Millennium Pharmaceuticals Inc, Biogen Inc and Celltrion Inc. His speciality areas include multiple myeloma, malignant lymphoma, acute and chronic leukemias. He has more than 80 co-authored publications.

Prof. KWONG YOK LAM
University of Hong Kong – HONG KONG

Professor Kwong is Chief of the Division of Haematology, Oncology and Bone Marrow Transplantation at the Department of Medicine, University of Hong Kong. He is specialized in haematology and hematopathology. His clinical work focuses on the management of haematological malignancies, with special interests in the treatment of leukemias, T-cell and natural killer cell lymphomas, which are neoplasms prevalent in Asian populations. Kwong and his team also pioneered the development and use of oral arsenic trioxide in the treatment of acute promyelocytic leukaemia and other blood cancers. He has been a principal investigator on 17 trials and has co-authored 25 publications.

Prof. DARYL T C LUNG
Raffles Medical Group Ltd - SINGAPORE

Dr Daryl Tan is the Director of Research at Raffles Hospital and a haematologist at Raffles Cancer Centre and Mount Elizabeth Novena Hospital, Singapore. His areas of interest are lymphoid malignancies including high-grade and low-grade lymphoma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma and myelodysplastic syndromes (MDS). He spearheaded several clinical trials examining novel approaches in treating lymphoma and multiple myeloma and was the Principal Investigator of more than 40 investigator-initiated and industry-sponsored clinical studies in haematological cancers. He has worked with sponsors such as AstraZeneca Plc, Bristol-Myers Squibb Co and Secura Bio Inc. His research has resulted in several international presentations and more than 100 publications in high-impact factor scientific journals including first-authored articles in the Lancet Oncology, Blood and the *Annals of Oncology.*

Prof. YING-JAN L. WANG
National Cheng Kung University (NCKU) - TAIWAN

Dr. Ying Jan L Wang is the Professor, Department of Environmental and Occupational Health, NCKU. His top areas of expertise are Mantle Cell Lymphoma (MCL), Chronic Lymphocytic Leukemia (CLL), Chronic B-Cell Leukemia, and Leukemia chemoprevention and therapy, in addition to radiotherapy combined with chemotherapy and molecular mechanisms of environmental toxicants and is one of the top-rated experts in these indications. His clinical research spans overseeing clinical studies of patients undergoing new therapies and co-authoring more than 200 peer reviewed articles in the past 15 years including 15 articles specifically in CLL.

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