White Paper

DLBCL*: Asia-Pacific Insights and Experiences

Excerpts from an expert panel discussion from 8 Asia-Pacific Countries

JAN 2023

ALMA PANGANIBAN-PADRINAO - Senior Medical Director Head, Asia Medical
MARIA ROSELLE LUCAS - Senior Director, Medical Head, Oncology/Hematology
ANJU GOPAN - Medical Director Oncology/Hematology
JAIME ENRIQUE HILADO - Associate Medical Director Oncology
LARA KRISTINA DONATO - Associate Medical Director Hematology
ANISH SULE - Director, Integrated Market Access CSMS, Reviewer
VAISHNAVI KRISHNAN - MSL, CSMS, Asia Pacific Senior Author

* DLBCL: Diffuse Large B-Cell Lymphoma

Table of contents

Executive summary

Considering the rise in diffuse large B-cell lymphoma in the APAC region, there is a need to assess what more may be done in terms of treatment access and quality of life. Access to the right treatment at the right time with improvement in quality of life are essential for successful cancer treatment. With recent advancements in biomarker driven research and precision medicine, newer therapeutic options are now associated with fewer toxicities. As a result, physicians may aim to treat patients better and offer varied treatment options for patients with DLBCL. This is especially true for patients who have exhausted all SOC agents and for non-responders to therapy. In global trials (where APAC may not be involved initially), SOC is changed or added frequently which warrants the need to understand the impact of such changes for conduct of DLBCL trials in APAC region.

An optimum method to achieve access and better success with newer treatment is to have more clinical trials. The Asia-Pacific region has not always been considered for the conduct of the latest clinical trials, unlike the Americas and Europe have been. As a result, there is a delay in patients receiving newer therapies or participating in clinical trials as part of their management.

In order to understand the challenges and facilitate innovative ideas to drive clinical trials in the APAC region, IQVIA conducted an advisory board with a pre-meeting questionnaire involving key opinion leaders from 8 countries, including Australia, China, India, Japan, Malaysia, New Zealand, Singapore, and South Korea. By and large, Australia, Japan, and South Korea have more access to commercial CAR-T cell therapy and clinical studies. Although some companies in India can offer CAR-T cell therapies, largely, the conduct of clinical trials on CAR T-cell therapies remain low. There is, therefore, an incumbent need for more trials.

The consensus from the advisory board pointed towards the need for more clinical trials in the APAC region to facilitate patient access to new therapies and derive clinical data from the region.

Further, the current trend in the management of DLBCL with focus on perceived challenges for future clinical trials has been portrayed in this whitepaper, showcasing the potential of each country. Additionally, the advisory board has served to conclude that the region holds immense potential for the future of clinical research in DLBCL. No major challenges have been anticipated with respect to trial conduct and patient recruitment.

Data from the APAC region for clinical trials may be collected simultaneously with the rest of the world and this further facilitates real-time treatment approvals in the region and patient access to treatment. This will also help understand nuances for treatment with respect to safety and efficacy, specifically in patients with an Asian ethnicity.

Experts from the region, therefore, look forward to enrolling patients into clinical trials across all phases. Improving access to new therapies benefits patients immediately and will allow the region to contribute towards accelerating treatment innovation.

Why should Asia-Pacific be considered for clinical trials

- Strong expertise in translational assays and other novel techniques that are pertinent for newer clinical trials
- Strong KOL relationships with peers allow for direct communication of investigators with their colleagues that serve to facilitate referrals and is an important driver for recruitment
- Largely, streamlined regulatory processes are in place such that most APAC countries are efficient in securing approval and setting up trials
- DLBCL is the most common lymphoma in the region
- Presence of a large patient pool
- Less expensive to conduct trial here than in western countries

Country panelists

DR.KATHARINE LEWIS, AUSTRALIA

Clinical Trial and Lymphoma Fellow, Linear Clinical Research and Sir Charles Gairdner Hospital

DR. YUQIN SONG, CHINA

Professor of Medical Oncology, Deputy Director of Lymphoma Department,
President Assistant of Peking University Cancer Hospital

DR. REENA NAIR, INDIA

Head, Department of Medical Oncology, Tata Medical Center, Kolkata

Senior Consultant, Clinical Hematology, Tata Medical Center, Kolkata

DR. HIROKAZU NAGAI, JAPAN

Director, Clinical Research Center and Department of Advanced Medicine, Nagoya Medical Center

Chair, Lymphoma Study Group, Japan Clinical Oncology Society.

DR. GIN GIN GAN, MALAYSIA

Professor of Internal Medicine and Haematology, Faculty of Medicine, University of Malaya

DR. SAMAR ISSA, NEW ZEALAND

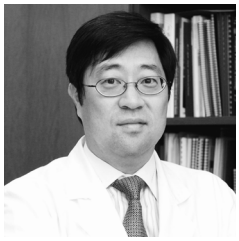
Clinical Head (Lymphoma Service) and Consultant Hematologist, Middlemore Hospital

Founding Chair, Lymphoma Network of New Zealand

DR. ANAND JEYASEKHARAN, SINGAPORE

Consultant Medical Oncologist, NCIS, NUH

Assistant Professor, Department of Medicine, NUS



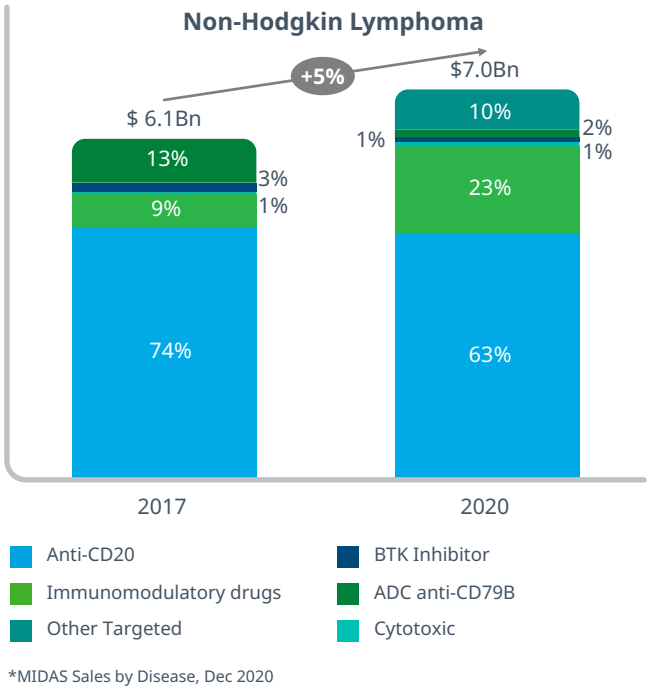
DR. WON-SEOG KIM, SOUTH KOREA

Professor and Director, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University, School of Medicine

Background

The most common hematological malignancy reported has been malignant lymphoma. Lymphomas are solid tumors of the immune system.[1] Lymphoid malignancies are remarkable owing to the differences in epidemiology and etiology based on geography.[2] The most common type of B-cell non-Hodgkin lymphoma (BNHL) is diffuse large B-cell lymphoma (DLBCL) (Figure1), contributing to nearly 46% of all BNHL in Korea.[3]

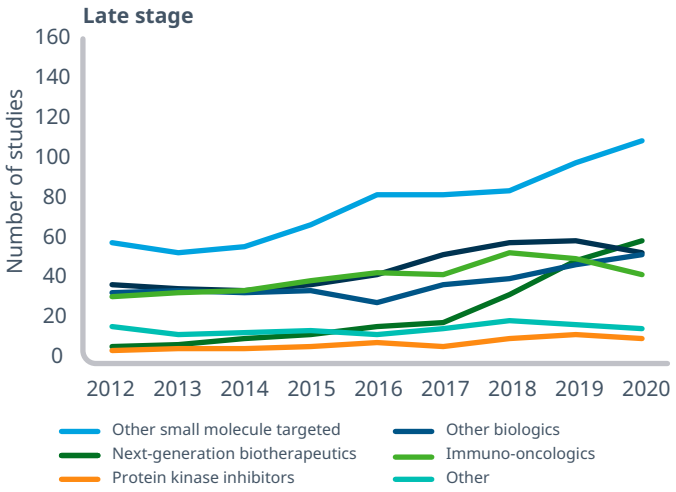
Figure 1: Lymphoma spending per drug class



*MIDAS Sales by Disease, Dec 2020

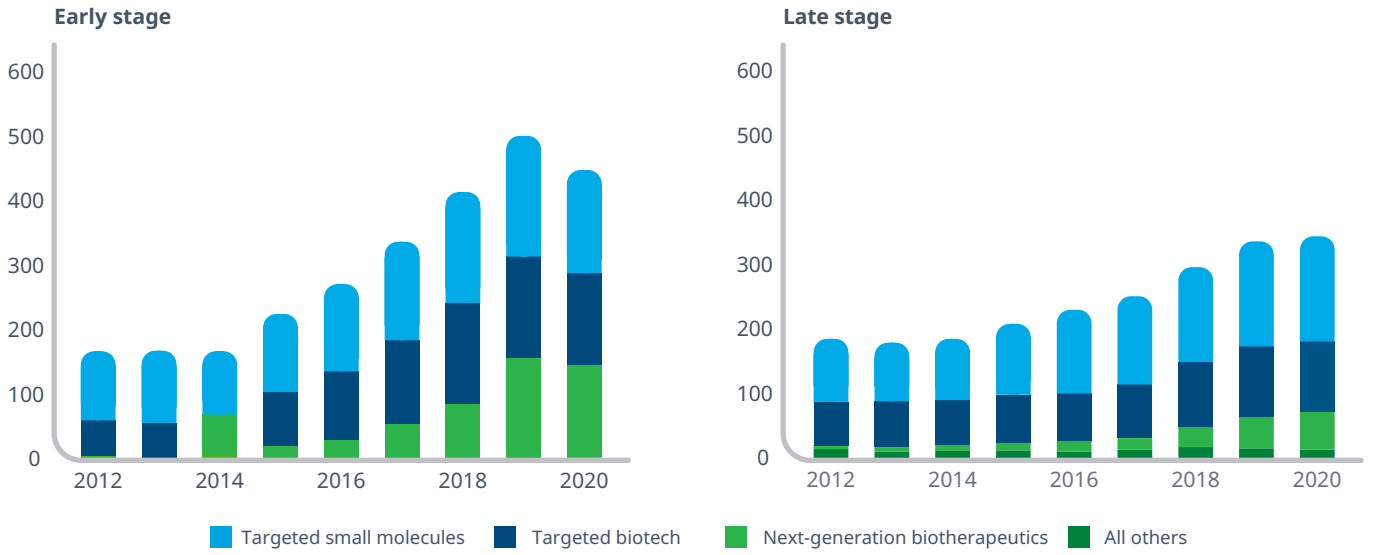
NHL is the seventh most prevalent cancer and globally it accounts for 3% of cancer diagnosis and death. The incidence of NHL has increased by 168% since 1975 and is common among males more than 65 years old.[4] Over the last few years, though the understanding of DLBCL and its pathology have improved, there is still a need for more targeted treatment. Approximately, 50%-70% of patients may be effectively treated with the standard first line therapy consisting of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[5] However, with R-CHOP, about 10% of patients are refractory and 40% experience relapse.[6] Several strategies such as dose intensification or novel agent addition have been implemented to improve the efficacy of the standard regimen, yet, about 50% of patients experience relapse after second line of treatment including salvage chemotherapy.[6] More recently, to overcome challenges to first-line treatment, therapies like chimeric antigen receptor (CAR) T-cells, bispecific T-cell engagers (BiTE), antibody-drug conjugates and new monoclonal antibodies offer novel treatment options for patients with DLBCL (Figures 2 and 3).[7]

Figure 2: Next generation biotherapeutic pipeline for hematology-oncology



*IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Dec 2021, Dec 2020; IQVIA Institute, Dec 2021

Figure 3: Advancement in hematology-oncology pipeline

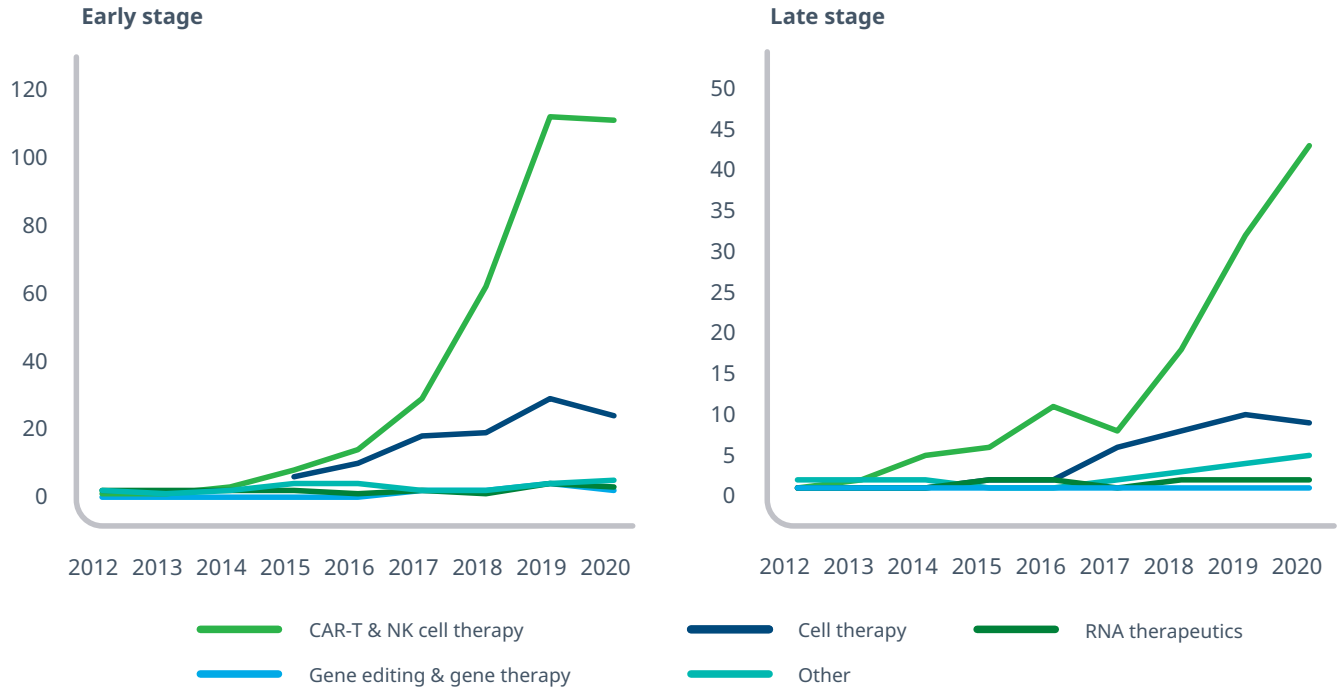


*IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Dec 2021

Clinical trials landscape of newer therapeutic modalities for DLBCL — A global scenario

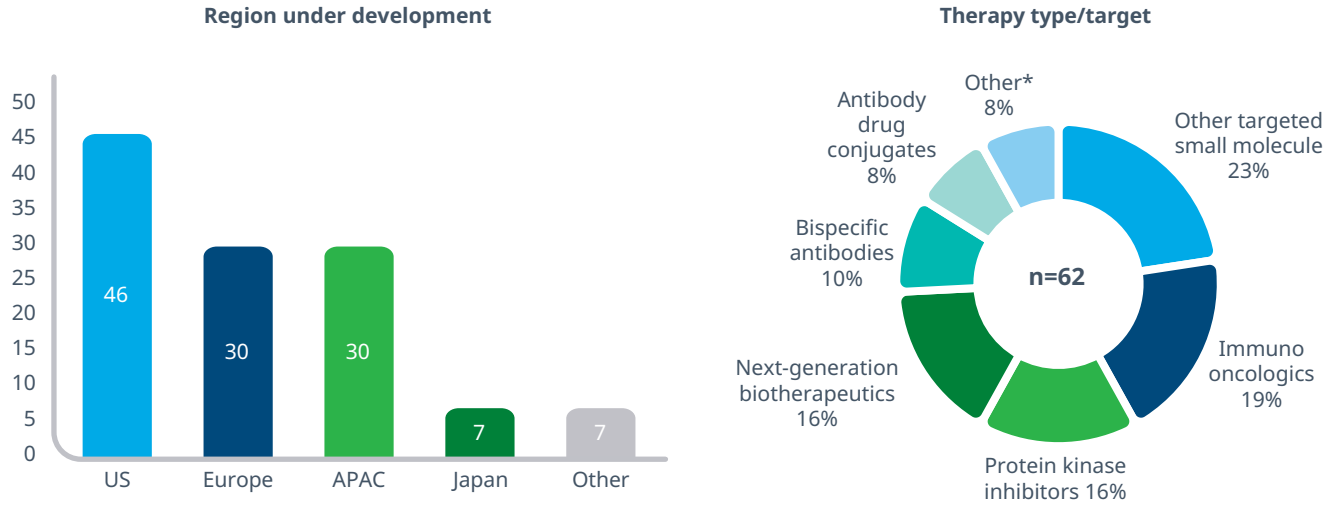
The pieline for next-generation biotherapeutics is focused on CAR-T and cell therapies (Figure 4) and represents 16% of the products under development for DLBCL (Figure 5) .[8,9]

Figure 4: DLBCL novel therapeutics pipeline



*IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Dec 2021

Figure 5: DLBCL novel therapeutics pipeline



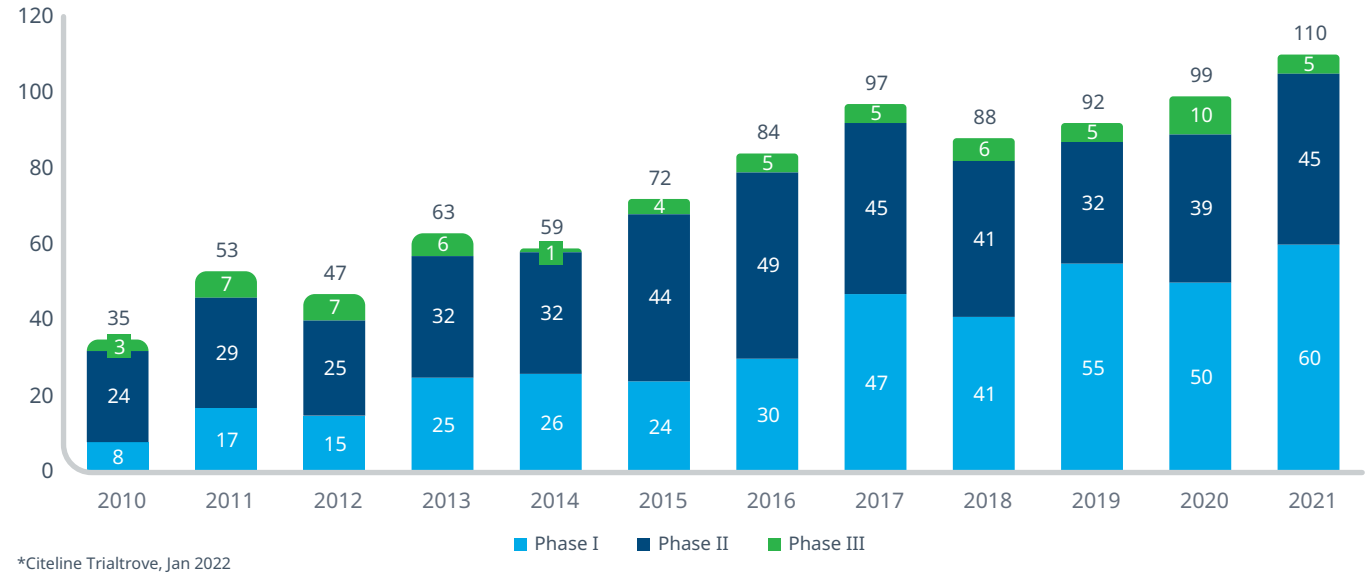
*IQVIA Pipeline Intelligence, Dec 2021; IQVIA Institute, Feb 2022; *Other includes cytotoxics, radiotherapeutics and biologics not otherwise shown

According to recent data, from 2018 to 2020, 314 NHL trials were conducted in USA while 166 trials were conducted collectively in Australia, New Zealand, South Korea, Taiwan, Singapore, India, Hong Kong, and Thailand.[4] Furthermore, clinical trials for DLBCL have doubled in the last decade. However, phase III trials remain low (Figure 6). The APAC region, in this regard, may not have always been considered in the latest DLBCL clinical trials. As a result, patients lack the opportunity to participate in such trials leading to delay in access to such novel therapies.

Therefore, more clinical trials are required in the APAC region as treatment options are evolving and are becoming more biomarker driven. With more clinical trials, treatment options for patients are expected to increase.

An advisory board was thus carried out to identify and mitigate gaps regarding availability of clinical trial options and access to patients in line with global clinical trials/SOC. This white paper shares critical insights gathered from an expert panel-led advisory board on the current state, challenges, and opportunities for strengthening the management of DLBCL and conduct of clinical trials in the APAC region.

Figure 6: Clinical trials development in DLBCL



*Citeline Trialtrove, Jan 2022

Expert opinion on the Asia-Pacific potential

CLINICAL TRIAL EXPERIENCE IN THE REGION

With a small number of trials open in the region, patient access to these innovative treatments remains low. Because of this, the consensus from the panelists was that there is a need for more trials in the region. One of the challenges noted amongst most panelists was the availability of relevant lab evaluations on evolving biomarkers and laboratory evaluations used in present clinical trials.

Newer therapies like CAR-T cells and bispecific antibodies are available by means of patient access programs and a few clinical trials. An issue with lack of access to CAR-T cell therapy were noted in some countries especially in India, Malaysia, and New Zealand, where patients were unable to access such new therapies due to fewer clinical trials. In countries such as Japan, Australia, and South Korea, commercial CAR-T therapy was available, and a few clinical trials have been conducted. However, there is still a need for more trials in the region.

More trials in the region will allow for an increase in the number of treatment options for patients with DLBCL, especially for those who have exhausted all available SOC agents and those who are non-responders to standard therapy. In Singapore, bispecific antibody trials are currently underway, and these are showing promise for patients with refractory or relapsed disease.

Dr. Anand Jeyasekharan, a leading consultant oncologist at NCIS, NUH, Singapore, stated that,

"We would love to have more trials largely because DLBCL is the most common subtype of lymphoma. It is still the biggest unmet need, even though there are other types of lymphomas that often do worse. So, we still feel that our immediate requirement is in the setting of refractory or relapsed disease, particularly for those patients who are unfit for transplant and elderly patients."

Additionally, Dr. Samar Issa, Clinical Head (Lymphoma Service) and Consultant Hematologist, Middlemore Hospital, New Zealand, also opined that,

"I think in the relapse setting, especially in patients who are older, with co-morbidities, not fit for high dose therapy, there is an unmet need. We do have access to bispecific trials. And I also think that there is room for first-line treatment, targeted therapies and, basically new molecules that help us overcome the high-risk patients up-front rather than wait for them to relapse."

USE OF BIOSIMILARS

Biosimilars were noted to be popular in South Korea, with several drugs already in the market and with about 3 biotechnology companies continuing to show interest in developing biosimilars for other molecules. Further, in clinical practice, biosimilars for rituximab are commercially available, with patients benefiting from lower costs of treatment.

However, in New Zealand, biosimilars are not yet widely used in clinical practice, and as such, there is limited experience in their use. Even with clinical trials of novel molecules are underway, the interest remains high where biosimilars are concerned. Overall, panelists are of the opinion that biosimilar trials are welcome in their countries.

THE CAR-T CELL EXPERIENCE IN THE REGION

Considering the evolution in CAR-T cell therapy, panelists from across the region offered expert insights. There has been CAR-T cell therapy experience seen in Australia, while Malaysia and New Zealand do not have access to these therapies. In India, on the other hand, while there is limited access to clinical studies on CAR-T cells and bispecific agents, local CAR-T cell manufacturing and clinical trials have begun in one institute in the country so far. Countries such as South Korea, China and Japan do have CAR-T cell clinical studies, but the general consensus among all KOLs remain that there is a need for more such trials for DLBCL in the region.

The CAR-T cell team in Singapore have specifically stated that patients <70 years of age are preferred for single infusion.

Dr. Hirokazu Nagai, Director, Clinical Research Center and Department of Advanced Medicine, Nagoya Medical Center, Japan, further added that,

"In Japan also, CAR-T is becoming very popular. The number of patients who are treated with CAR-T treatment is still restricted and there will be around 40 institutes over Japan who can use CAR-T. I think CAR-T therapy is very effective, but the efficacy and safety are somewhat limited in the DLBCL."

Although, immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in China in CAR-T cell trials, the South Korean panelist voiced that cytokine-release syndrome (CRS) and ICANS were not very challenging to treat and can be managed. The consensus here remains that while there are some challenges that need investigation and management, the region showcased adequate expertise and experience to manage any adverse event that may be expected with the novel therapeutic agents.

INTERNATIONAL PROGNOSTIC INDEX

With respect to the use of International Prognostic Index (IPI) for DLBCL, panelists from Singapore and Australia stated that they prefer to use the basic IPI as it is the most relevant to the first line setting that can further aid to stratify stage of disease. Age-adjusted IPIs are used relatively less frequently.

UNMET NEED THAT REQUIRES CLINICAL TRIALS

Drugs available today are much more effective than previously available therapies. In this scenario, the preference would be to bring them into earlier salvage therapy. Since patients are responding well to first line therapy with a large percentage of them in long term remission, trials on first line therapy are not urgently needed at the moment.

The real issue lies for those patients who have refractory disease. It has become increasingly challenging to treat these patients, where response rates are lower and second-line chemotherapy does not seem to benefit these patients much. Therefore, clinical trials for more effective second line therapies using multiple drug combinations that may work better for refractory patients has been identified as an unmet need.

For those patients where the disease relapses after a long period of time (about more than a year), existing drug combinations may still be used, especially high-dose chemotherapy followed by rescue procedures.

For patients with reasonable disease-free intervals, fourth or fifth lines of therapy may be considered. However, for refractory patients recurring within 3 months of completing frontline therapy, the risk for adverse events may increase with continuing chemotherapy alone. For these cases, changing the modality of treatment to an agent that is different from conventional chemotherapy would be ideal.

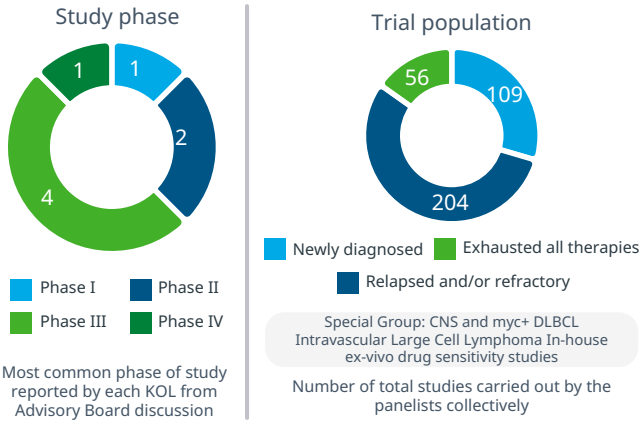
Dr. Reena Nair, Head of Department, Medical Oncology, Tata Medical Center, Kolkata, India stated that,

"We look forward to all of it coming in clinical trials through from phase I to phase III, we are also open to phase IV because a lot of work that we do is phase IV when the drugs are already in the market and come into the country, we have a chance to use them before it goes into general therapeutics."

INCLUSION OF UNIQUE PATIENT GROUPS IN CLINICAL TRIALS

The experience of our KOLs with respect to the most common study phase and most common type of patient treated are noted below (Figure 7).

Figure 7: DLBCL trial experience



The introduction of rituximab has improved response rates, even in patients with CNS involvement. Additionally, there has also been an increasing experience with CNS relapse. A large unmet need is among those with leptomeningeal seeding, wherein it is known that PI3K inhibitors cannot penetrate the CNS. However, even with existing therapies such as rituximab, the extent of its benefits in those with CNS involvement is not fully known. With new trials, where eligibility criteria are concerned, CNS cases are excluded. There is, therefore, an evident need for clinical trials where secondary CNS disease is concerned.

Dr. Won-Seog Kim, Professor and Director, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University, South Korea, states

"I think there are two reasons as to why majority of trials exclude patients with historical CNS involvement. The first reason is that not every new compound has its own pharmacokinetic (PK) data and CNS penetration data. The other reason is that from the beginning, the outcome for patients with CNS involvement is quite poor."

Another issue noted by KOLS was that there might be limited pre-clinical data on CNS penetration. In phase I studies, CNS penetration data is not usually determined as well.

In Japan, enrollment for patients with intravascular large cell lymphoma was noted to be challenging as it took 3-4 years for one phase II study.

In Australia, there was a recent study that was started with novel agents and small-molecule therapy. About 5-6 patients from referral centers have already been benefitting from this study. Despite being a relatively rare condition, there is a strong unmet need in the treatment of CNS lymphoma patients, especially since they are indeed challenging to treat. Also, this would be the ideal group of patients to obtain PK data from, since CSF analysis is a routine investigation in this population.

If there is data available about agents crossing the blood brain barrier from phase I studies, then more CNS patients with de novo or relapse or refractory disease may be evaluated in a small subset, with design modification made to the trial design as necessary.

One of the main considerations for this group of patients may be flexibility in eligibility criteria, modifying ECOG status depending on the safety profile of the molecules and including the elderly age group accordingly. There was a general thought among KOLs that patients with ECOG 3 might benefit from BTK inhibitors and other small molecules, where the side effect profile is already well-established. It might, therefore, be helpful that this population be included in clinical trials.

ENROLLMENT CHALLENGES FOR DLBCL CLINICAL TRIALS

Dr. Anand Jeyasekharan from Singapore offered the opinion that number of biopsies required as per study protocol may be a deterring factor for patients to refuse trial entry. This is especially true for elderly patients who do not prefer having to come multiple times for biopsies, and hence decline to participate in the clinical trials. Dr. Reena Nair from India further agreed on this opinion.

Another deterring factor was discussed by Dr. Reena Nair from India, who opined that distance from home to the site determines whether the patient would want to enroll. The limitation was observed to arise when a patient resides far away from the clinical trial site. In these scenarios, it becomes challenging for the physician to convince the patient of multiple visits, owing to logistics. Also, in the case of older patients who are accompanied by caregivers, employment and the number of leaves that the caregivers can avail for purpose of these multiple visits becomes another limiting factor.

However, enrollment was less challenging in institutes that cater to the local population, where logistics is not a concern.

PROGRAMS AND STRATEGIES TO MITIGATE RECRUITMENT CHALLENGES

Weekly meetings on lymphoma, word of mouth, and direct communication between principal investigators and referring physicians have proven most effective in mitigating patient recruitment challenges, specifically in New Zealand, Australia, and Malaysia.

In China, media and social groups have also been commonly used.

In Australia, although a patient recruitment referral app exists, it is not commonly used throughout the country. **Dr. Katherine Lewis, Clinical Trial and Lymphoma Fellow, Linear Clinical Research and Sir Charles Gairdner Hospital, Australia further states that,**

"Where I am based, over on the west coast of Australia, the app is not widely used and I think that this is not a negative comment on the app, but more about the sort of relationships between centers that we already have. It would very much be person to person. The other big center is known and there is a lot of kind of cross center respect and access just by knowing each other so that is more why the app is not used so much."

Further, in Malaysia, the list of available trials made available on the society website has been an added advantage. **Dr. Gin Gin Gan, Chair of the Hematology Block and Head of the Hematology Unit, Department of Medicine, University of Malaya Medical Center stated that,**

"We have a platform where we can post it on our society website, so that is another way for us to try to inform our colleagues from all over the country that there is a clinical trial and if they have any patients that they think could be included in clinical trials."

SITUATIONS WHERE BONE MARROW BIOPSIES ARE DONE AFTER BASELINE

Panelists generally agreed that bone marrow biopsies are done in patients with prior bone marrow involvement and not necessary otherwise. Keeping in line with the new guidelines, upfront bone marrow biopsies have not been carried out. However, in patients who are refractory to treatment who might need high dose chemotherapy, those requiring autologous transplants and for those requiring a response assessment prior to salvage therapy, bone marrow biopsy has been considered across the region.

POPULATION WHERE NEXT GENERATION SEQUENCING (NGS) IS HELPFUL

In South Korea, NGS is more routinely done, considering specimen availability. It was noted that NGS may not be useful in front-line treatment. Next generation sequencing has been done in the highly relapsed setting, if the MCD subtype is being considered. For this, there is a need for data on increased activity for BTK inhibitors.

RARE ADVERSE EVENTS WITH IMMUNO-ONCOLOGY (IO) THERAPY: INFECTIONS AND INFLAMMATION

In a patient who has received bispecific antibodies, one patient developed fatal pan-system inflammatory disease along with CMV reactivation.

On the other hand, many patients were seen to have COVID-19 persistence and are unable to clear COVID-19.

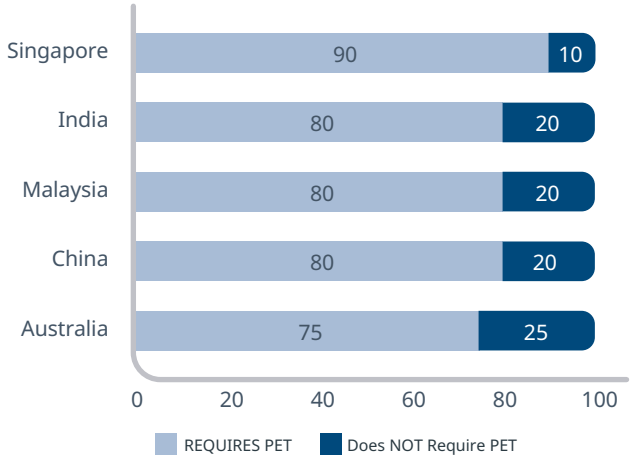
In India, in some cases of mild or asymptomatic COVID-19, the next dose of rituximab was given, and severe lung injuries were noted in these patients. This was indicative that rituximab maintenance may be an area for additional attention in COVID patients.

CONCERNS ABOUT FREQUENCY OF PET USE IN TRIALS

There have been some concerns raised over the frequency of PET scans in trials. Even for patients with relapse, the frequency of PET scans may need to be spaced out, especially considering that PET uses high dose radiation, and most patients may have already done multiple CT and PET scan by the time of relapse.

Due to these concerns, KOLs offered the opinion that non-invasive testing could be considered and is needed as a means of monitoring disease, such as use of ctDNA, thereby minimizing the need to repeat PET scans. Figure 8 summarizes proportion of clinical trials where PET scans are required versus not required for the APAC region.

Figure 8: PET Scans for efficacy assessments



STAFF RESOURCING AT CLINICAL TRIAL SITES

Staff resourcing may not be an issue with the availability of investigators and experts as per the need of clinical trials in all regions. In India, for lymphomas, a majority of investigators are interested in participating in clinical trials. There are also several centers of lymphoma across the country that have been good at managing patients. Therefore, resourcing staff for clinical trial sites in India is not an issue, and resources for clinical trials such as coordinators is not as expensive as in other countries. There are also large coordinator groups available within the clinical centers.

RECOMMENDED APPROACH FOR PSEUDO-PROGRESSION CASES ESPECIALLY IN IO THERAPIES

Clinically differentiating true progression from pseudo-progression may be challenging. Communicating with medical monitors on an individual trial basis in cases where pseudo-progression is a possibility may be useful. Routinely, treatment may be continued until pseudo-progression is confirmed on further scans, based on clinical evaluation of patient and final decision of principal investigator/treating oncologist.

SPATIAL IMMUNOPHENOTYPING AS A POTENTIAL BIOMARKER

With the advent of new technologies such as spatial transcriptomics and the more complex immunophenotyping, multicolor flow in paraffin tissue can now be achieved. The ability to then look at types of macrophages and T cells that are present may have bearing especially as we move into IO-based treatments (such as CD47-based combinations). While this may be very useful for clinicians for immediate results, pathologists may take longer to be convinced in the implementation of such technology.

In the US, several pathology groups in solid cancer immunology are working towards bringing these technologies into standard practice and this may soon be available for hematologic oncology as well.

CACHEXIA AS A BIOMARKER

In India, cachexia is a geography-specific issue, not just because of the illness or co-morbidities but also due to malnutrition over the years. Patients are evaluated using a validated questionnaire known as Subjective Global Assessment. Here, the patient answers questions about their diet, weight loss and other physical activities over the last 3 weeks and the last 3 months. Data was then correlated with the IPIs and it was seen that long-term cachexia had a major impact on the following: response to therapy, completion of therapy, and overall survival.

NOVEL METHODS FOR PATIENT SELECTION

In Singapore, more platform-based approaches are being investigated, not only for DLBCL, but other cancers as well. In terms of trial design, more adaptive designs are needed where one can shift from one agent to another rather quickly. It may be interesting to see how industry partners can work with us and incorporate these large platforms into large phase III trials.

DISCORDANCE IN LOCAL INTERPRETATIONS VERSUS CENTRAL IMAGING ANALYSIS

In China, a difference of above 15% is not acceptable. This is observed because the independent review committee and investigator's evaluation are completely independent. In Singapore, such events are allowed if physician discretion is maintained. Insights from Japan suggests that such discordances could happen and needs to be managed efficiently. In contrast, the occurrence of such discordance in South Korea, Australia, and New Zealand is unlikely and rare. In Australia, communication with the sponsor to ascertain the reasons for the differences by principal investigator (PI) are captured, if patient treatment decisions are affected as a result.

PREFERRED THERAPEUTIC REGIMEN FOR FIRST LINE STAGE IV DLBCL (WITH RESPONSE RATE AND DURATION OF RESPONSE)

R-CHOP is the most common first line treatment noted in the APAC region in line with global guidelines (reference: NCCN and ESMO). Along with R-CHOP, the first line regimen for stage IV DLBCL is R-miniCHOP for elderly patients and R-DA-EPOCH for MYC+ DLBCL. Details are shown in Table 1.

Overall, the ORR was noted to be ranging from 50-95%, long-term cure in 60-70% and relapse in 3%-40% of patients. The panelists further offered the opinion that the better indicator is 2-year progression-free survival (PFS), which is estimated to be ~ 65-70%.

PREFERRED THERAPEUTIC REGIMEN FOR SECOND LINE STAGE IV DLBCL (WITH RESPONSE RATE AND DURATION OF RESPONSE)

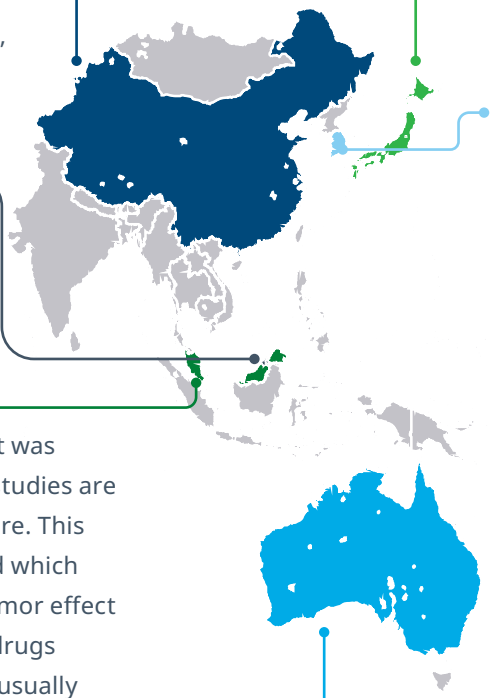
As per Prof. Song from China, the preferred regimen was DICE for patients intending to SCT; or GDP/GemOx for elderly patients as a second line therapeutic regimen.

Across the region however, R-ICE regimens were more commonly preferred. The RR reported by panelists ranged from 80% and DOR at 12-18 months. R-DHAP was considered as alternative second line therapy, especially in those who cannot tolerate R-ICE.

Table 1: Preferred treatment options per lines of therapy

	FIRST LINE	SECOND LINE	THIRD LINE	FOURTH LINE	FIFTH LINE
REGIMEN	• R-CHOP • R-CHOP interchelated with IV HD-MTX	• R-DHAC • R-DHAP • R-ICE	• R-GDP • R-ICE • R-DHAC	• R-GDP • R-ICE • R-DHAC	• R-GDP • R-ICE • R-DHAC
RESPONSE RATE (%)	• 50-95	• 50-80	• 30-70	• 30-50	• 50
ALTERNATIVE	• CEOP or mini-CHOP or CVP ± R	• R-DHAP • R-GDP • R-ICE	• Pola-BR • GDP • GEMOX after DICE	• GDP • PEPC	• GDP • PEPC

Figure 10: Additional considerations for conduct of DLBCL clinical trials



CHINA

Hepatitis B virus, Hepatitis C virus and HIV are routine tests done in China for all patients. For those who are HBsAg, or HBV DNA positive, antiviral treatment is given.

MALAYSIA

Ki67 is done routinely for DLBCL for an idea of how aggressive the lymphoma is

SINGAPORE

From the panel discussion, it was noted that drug-sensitivity studies are being carried out in Singapore. This helps physicians understand which drugs might have an anti-tumor effect for a certain patient. Some drugs might be those that are not usually used for lymphomas (e.g., everolimus and palbociclib).

AUSTRALIA

HBV and HCV tests are also routinely done. Vitamin D deficiency noted to be very common (roughly 20% of patients). This is addressed together with the lymphoma or even before chemotherapy if needed.

JAPAN

Ki67 is a routine test. EBERish is expensive, so how widely it is used would depend on the institution. At the Nagoya Medical Center, EBERish is done for almost all patients.

SOUTH KOREA

In some institutes, there is routine HBV DNA follow-up like the way it is done in Japan. HB surface antigen, antibody, IgG core-antibody are being checked routinely. In case of HB surface antigen carriers, antiviral therapy is being given in routine practice. For core positive cases, some clinicians prescribe antiviral agents prophylactically. Next-generation sequencing is ideally performed in all patients, subject to availability of enough tissue. Actionable mutations not identified often.

NEW ZEALAND

MYD88 is now being done more often, especially in patients with suspected CSF involvement as a way of detecting CNS disease in aggressive lymphomas. This is in addition to flow cytometry and/or cytology and has been helpful in identifying these patients in the diagnostic as well as follow-up settings. Therefore, the test has now been incorporated within routine CSF and vitreous fluid testing for CNS lymphoma patients.

Importance of using Mini Mental State Exam (MMSE) in trials: MMSE is a widely used test of cognitive function among the elderly. The use of MMSE is important in patients who have impaired cognitive function, are elderly and are frail and they need to have different treatment considerations and follow up when enrolled into clinical trials or any treatment.

RECIL Criteria: Only one trial with the RECIL criteria was seen, hence not much experience with this system. The consensus among panelists was that LUGANO is more commonly used.

Use of Routine Flow Cytometry: Majority of the panelists indicated that flow cytometry is performed routinely.

The future of DLBCL trials in APAC region

The main focus of the advisory board was to understand if the Asia-Pacific region is at par with other countries globally where conducting clinical trials is concerned, with respect to expertise and patient access to latest treatments for DLBCL. It is pertinent to understand where and why the Asia-Pacific region lags in conducting clinical trials. The advisory board has also served to understand that the APAC region has adequate expertise to be part of global evolving oncology trials, regional trials, and more local clinical trials.

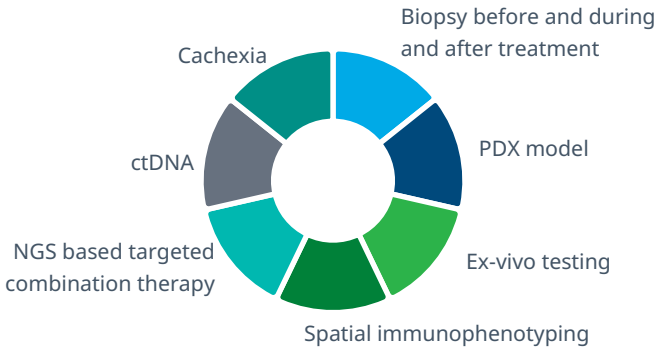
As trials in APAC are initiated at the end or in the middle of US or European trials, there is a need to understand what factors will enable the Asia-Pacific, as a region, to be considered in tandem with other regions for DLBCL clinical trials.

One of the ways this need could be addressed is by partaking in collaborative knowledge sharing across the region. It is expected that this advisory board will be a stepping-stone to exploring and showcasing the region's expertise and experience in managing DLBCL.

Assessing capabilities in the region increases our chances to be part of global clinical trials and will enable us to offer more treatment options for patients in real time.

Considering that future treatments may be more biomarker-driven, the advisory board found that the region has the necessary interest, patient pool, and capabilities that may be further enhanced as necessary (Figure 11).

Figure 11: Biomarker evaluation capability



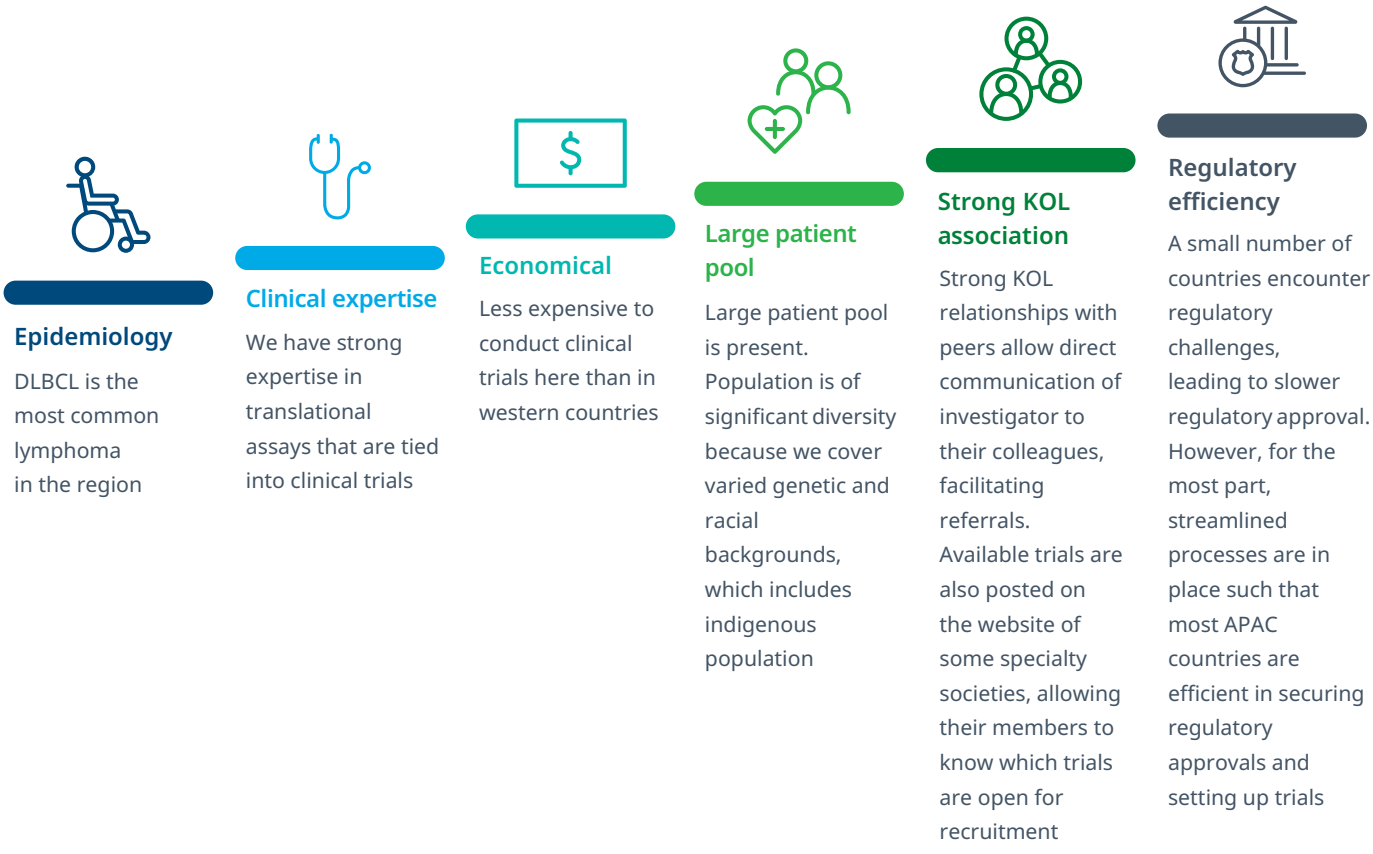
*Data adapted from pre-ad board questionnaire

The discussion with panelists across the region served to reconfirm that, as a region, adequate facilities and expertise for these evolving personalized trials and treatment are available.

These valuable resources must then be utilized to improve trial design and conduct more clinical trials in the region. Additional advantages for DLBCL clinical trials in the APAC region have been detailed in Figure 12.

It is therefore evident that pre-requisites for clinical trials such as conducive regulatory environment, adequate patient pool, and well-equipped clinical trial sites with access to biomarker evaluation capabilities are available in the region. With the evident need to boost DLBCL trials in the region, this panel discussion has further highlighted the APAC region's largely uncovered potential for conducting global clinical trials.

Figure 12: Advantages of conducting DLBCL clinical trials in the APAC region



References

1. Shankland KR, et al. Lancet. 2012 Sep 1;380(9844):848-57.
2. Epidemiology of Lymphoid Malignancy in Asia. In (Ed.), Epidemiology Insights. Intech Open; 2012.
3. Kim JS, Liu Y, Ha KH, et al. Increasing Incidence of B-Cell Non-Hodgkin Lymphoma and Occurrence of Second Primary Malignancies in South Korea: 10-Year Follow-up Using the Korean National Health Information Database. Cancer Res Treat. 2020;52(4):1262-1272.
4. Thandra KC et al. Med Sci (Basel). 2021;30;9(1):5.
5. Coiffier B, Sarkozy C. Diffuse large B-cell lymphoma: R-CHOP failure-what to do? Hematology Am Soc Hematol Educ Program. 2016;2016(1):366-378.
6. Ernst M, Oeser A, Besiroglu B et al. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. Cochrane Database Syst Rev. 2021; 13;9(9):CD013365.
7. Diffuse Large B-Cell Lymphoma (DLBCL) Therapeutics Market by Product and Geography - Forecast and Analysis 2022-2026. Available from: https://www.technavio.com/report/diffuse-large-b-cell-lymphoma-dlbcl-therapeutics-market-industry-analysis Accessed on: 6 Jun 2022
8. IQVIA Pipeline Intelligence, Dec 2021; IQVIA Institute, Feb 2022
9. Citeline Trialtrove, Jan 2022

About the authors

DR. MARIA ROSELLE LUCAS
Senior Medical Director, IQVIA

Dr. Maria Roselle Lucas has more than 18 years of experience in clinical and medical affairs and medical monitoring. She is a hematologist by profession and has been involved in numerous hematology and oncology clinical trials. She has provided strategic medical support for product launches and clinical development within IQVIA and in her previous role, also conducting advisory board meetings and leading discussion with key opinion leaders during this time. Her therapeutic expertise includes lymphoproliferative disorders, leukemias and solid tumors, among others.

DR. ANJU GOPAN
Medical Director, IQVIA

Dr. Anju Gopan has been with IQVIA for 4 years as a therapeutic medical expert in medical oncology and hematology. She has conducted oncology advisory boards, presented in webinars and conferences and has authored whitepapers and co-authored articles in oncology in the last 16 years. She has expertise in clinical trials including the latest evolving oncology therapeutic drugs classes like CAR T-cells, antibody-drug conjugates, and immunotherapy agents. She served as sub-investigator for multiple international oncology clinical trials since 2006 and then later on served as a therapeutic medical expert for numerous clinical trials in clinical research organizations.

DR. JAIME ENRIQUE HILADO
Associate Medical Director, IQVIA

Dr. Jaime Enrique Hilado completed his specialty training in medical oncology last 2013 and was a sub-investigator in numerous clinical trials at that time. Thereafter, he joined the medical affairs division of a leading global pharmaceutical company in oncology.

Having joined IQVIA 4 years ago, he serves as a therapeutic medical expert in medical oncology and hematology. He has conducted advisory board and steering committee meetings during his tenure. His current field of interest is on the leukemias and lymphomas and gastric cancers, among others.

THANKS FOR THE SUPPORT TO IQVIA TEAM MEMBERS:

Dr. Marlowe Imperial – MSL Oncology;
Dr. Edwin Gumafelix – Therapeutic Medical Advisor (TMA) Onco Hematology;
Dr. Ashok Kumar Deenabandu – TMA Onco Hematology;
Dr. Xinbin Qui – Medical Director;
Sarang Vinze, Atsushi Fujita & Xiujie Li – Patient and Site Service Support;
Sujata Routray - Trend analysis;
Emma Jumali, Vanita Nayak & Juraidah Mohd Jahari – Admin Support.

CONTACT US
iqvia.com