

AHCC Trials Group

Newsletter 2019

Making a difference together



Members of the AHCC Trials Group at the 3rd Symposium of the Singapore Liver Cancer Consortium (SLCC), 3 May 2019

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Welcome to our AHCC Trials Group yearly newsletter.

The AHCC Trials Group met this year on 3 May 2019 for the 3rd symposium of the Singapore Liver Cancer Symposium (SLCC). This is followed by a series of meetings with the Investigators of the different studies under the Trials Group, namely the Translational and Clinical Research (TCR) Flagship Program in Liver Cancer (PLANet Study, AHCC07) and the HCC Registry in Asia (AHCC08). Similar to past meetings, the attendees, speakers for the symposium and our collaborators will round up the meetings with a networking meal. One of the very rewarding aspects of being in the Trials Group is the accessibility to the network of key opinion leaders (KOLs) in the region. In the recent 3 years, the Trials Group has grown to include more partners from the Asia Pacific and new members from China, Japan and possibly United States. Maintaining the close working relationship as a group for 22 years is one of the greatest feats of the AHCC Trials Group, and this is made possible with all the dedications, support and hard work of our members and study team. Thank you for pulling the AHCC Trials Group through these 22 years!

Trial Coordinating Centre:

3rd Symposium of the Singapore Liver Cancer Consortium 3rd May 2019

The Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group hosted its much anticipated 3rd Symposium of the Singapore Liver Cancer Consortium (SLCC) on 3 May 2019 at the Singapore National Eye Centre to a resounding success.

In attendance were international members of the AHCC Trials Group, other HCC researchers, healthcare professionals and industry collaborators. As in the last two symposiums, the latest treatments in hepatocellular carcinoma (HCC) were presented and discussed as were developments in pre-clinical and clinical studies on HCC in the Asia-Pacific.

Said Prof Pierce Chow, Protocol Chair of the AHCC Trials Group: "In pursuance of our aims to bring about better clinical outcomes for patients with HCC, the AHCC Trials Group is constantly exploring collaborations with investigators from both academic research institutes and industry partners."

The AHCC trials group has recently initiated 2 prospective studies on HCC in the Asia-Pacific. They are the TCR Flagship Program, Precision Medicine in Liver Cancer Asia-Pacific Network (the PLANet Study, AHCC07) and the HCC Registry in Asia (AHCC08).



The 3rd Symposium of the SLCC, 3 May 2019 at the Singapore National Eye Centre

AHCC07: Precision Medicine in Liver Cancer Asia-Pacific Network

High intra-tumoral heterogeneity exists in HCC and the AHCC07 study is a multi-centre, prospective genomics-immunomics study that leverages on a surgical cohort for multi-region sampling of resected HCC. Patients are followed up to disease recurrence when recurrent HCC are similarly sampled and their genomic and immunomic profiles compared with that of the index resections to identify actionable biomarkers.

A recent development has been the inclusion of a North American site at Duke Durham, which is expected to be initiated in Q3 this year. This new site will increase diversity and allow comparison of the genomic-immunomic profile of HCC in the Asia-Pacific with that of a separate population. The study has also expanded its scope (through successful grant applications), to include parallel epigenomic and metabolomic studies to further understand key mechanisms driving HCC.

AHCC08: Hepatocellular Carcinoma Registry in Asia

Separately the AHCC08 study is a multi-country prospective registry study of HCC patients from more than 30 sites in 9 countries of the Asia-Pacific. This registry will provide an insight into the different treatment journeys of HCC patients in Asia. To date, more than 1,500 patients have been recruited in the registry. Preliminary results have been presented in international conferences like ASCO GI 2019.

Local and overseas researchers on HCC including international key opinion leaders from Australia, Hong Kong and Japan presented treatment updates and early results of their studies. The AHCC Trials Group would like to thank all experts for sharing valuable insights and knowledge:

Heterogeneity of Hepatocytes in the Normal Liver and its Implication for Hepatocellular Carcinoma Molecular Subtypes

Dr Naiyang Fu, Duke-NUS Medical School, Singapore

Dr Fu shared his findings on an unexpected self-maintaining mode in hepatocyte regeneration and identified a defined subset of pericentral hepatocytes as major cells of origin in HCC development. Dr Fu's lab develops novel genetically engineered mouse models to study liver development, regeneration and cancer.

A Paradigm Shift in Cancer Imaging: A Study of Tumour/Normal Boundaries in Hepatocellular Carcinoma using Next Generation Imaging Mass Spectrometry

Dr Glenn Bonney, National University Hospital, Singapore

Dr Bonney presented early results from a study he had initiated in cancer imaging of tumour/normal boundaries in HCC using next generation mass spectrometry imaging. His latest findings suggest that there are molecular species that are uniquely and consistently expressed within the tumour margins of HCC. These consistent changes represent a paradigm shift and an opportunity for greater understanding in tumour biology, diagnostic and therapeutic targets. Dr Bonney has an avid interest in using next generation proteomic platforms in real time to affect clinical and surgical endeavours.

Considerations in Liver Transplantation for NASH-related Hepatocellular Carcinoma

Assoc Prof Simone Strasser, Royal Prince Alfred Hospital, Australia

Prof Strasser from the AW Morrow Gastroenterology and Liver Centre, the Australian National Liver Transplant Unit at Royal Prince Alfred Hospital (RPAH) and the University of Sydney presented the latest considerations in liver transplantation for NASH-related HCC. She is also a steering committee member and a site investigator of the AHCC08 (HCC Registry in Asia) study.

Immunotherapy in Hepatocellular Carcinoma – An Update

Dr Thomas Yau, The University of Hong Kong, Hong Kong

Dr Yau, a well-known clinical researcher from the University of Hong Kong and Queen Mary Hospital, Hong Kong developed the Hong Kong Liver Cancer classification and is a global pioneer of a drug development program hepatocellular carcinoma. Dr Yau presented the latest developments in immunotherapy in HCC.

The Evolving Roles of Targeted Therapy in Hepatocellular Carcinoma

Prof Kudo Masatoshi, Kindai University, Japan

Prof Kudo Masatoshi, Chairman of the Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan, spoke on the evolving roles of targeted therapy in HCC. Systemic therapy for HCC has markedly advanced since the survival benefit of a molecular targeted agent, sorafenib, were demonstrated in the SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) and Asia Pacific trials in 2007. In the last 2 years, clinical trials of 4 agents (regorafenib, lenvatinib, cabozantinib, and ramucirumab) were positive in succession between 2017 and 2018, and FDA has approved the use of regorafenib, lenvatinib and cabozantinib in clinical practice. Phase 3 clinical trials of immune checkpoint inhibitors and a combination therapy of immune checkpoint inhibitors and molecular targeted agents are also ongoing, which suggests that the treatment paradigm of HCC in all stages (early, intermediate and advanced), is expected to be changed drastically in the very near future.

Realizing Personalized Therapy in Hepatocellular Carcinoma - The Singapore-Samsung Initiative

Dr Shin Yong Jae, Samsung Medical Center, South Korea

Dr Shin is the Chief Research Scientist of the Institute of Refractory Cancer Research (IRCR), Samsung Medical Center (SMC) and Research Professor at the School of Medicine, Sungkyunkwan University. He holds a joint appointment at NCCS as Deputy Director of the PuRPOSE Joint Laboratory Programme at A*STAR-IMCB. The PuRPOSE program aims to develop a personalized, targeted patient-specific diagnostic and predictive next-generation AVATAR system in HCC through multi-institutional collaborative efforts in Singapore. The platform provides reliable and patient-specific diagnostic and predictive data in a clinically relevant timeframe of three or four weeks. Patient-derived HCC tumor samples are leveraged upon for genomic correlation and for in vivo studies and drug screening. This platform is being validated to deliver precision analysis and revolutionise cancer treatment to improve clinical outcomes in patients with HCC.

Real World Data on Hepatocellular Carcinoma in the Asia-Pacific - Interim Analysis of the Hepatocellular Carcinoma Registry in Asia

Dr Mihir Gandhi, Singapore Clinical Research Institute, Singapore

Dr Mihir Gandhi from the Singapore Clinical Research Institute (SCRI) applied his extensive experience in statistical and clinical research and in the planning and designing of phase I to III clinical trials, to the analysis of the Liver Cancer Registry (AHCC 08). He presented the initial data of the AHCC08 study which reveals considerable variation in presentation and management patterns in HCC between different countries in the Asia-Pacific namely China, Singapore, South Korea and Japan.

Updates on the study - A Phase II Open-Label, Single Centre, Non-Randomised Trial of Y90-Radioembolization in Combination with Nivolumab in Asian Patients with Advanced Hepatocellular Carcinoma

Dr David Tai, National Cancer Centre, Singapore

Dr Tai presented the updated analysis of an open label, single arm, phase 2 trial investigating the efficacy and safety of Radio-embolization with yttrium-90 combined with the immunotherapeutic nivolumab in HCC. Yttrium-90 radioembolization (RE) has emerged as an efficacious therapeutic option for intermediate stage hepatocellular carcinoma (HCC) while nivolumab, an anti-programmed death 1 (anti-PD1) monoclonal antibody, has been approved by FDA for use in the second line treatment of advanced HCC. Research in Singhealth has previously shown that RE significantly up-regulates systemic T cells and tumor-infiltrating lymphocytes and this was the basis of the hypothesis that the addition of nivolumab to RE will be synergistic.

The SLCC aims to create an internationally competitive HCC platform to develop disruptive technologies for precision medicine in HCC. The symposium was attended by more than 120 attendees, including 30 overseas investigators. The next symposium and meeting will be next year. The AHCC Trials Group thanks all investigators and collaborators for their constant support over the last 22 years.



The Investigators at the AHCC08 Investigators' Meeting



AHCC07 Precision Medicine in Liver Cancer across an Asia-Pacific Network (NCT03267641)

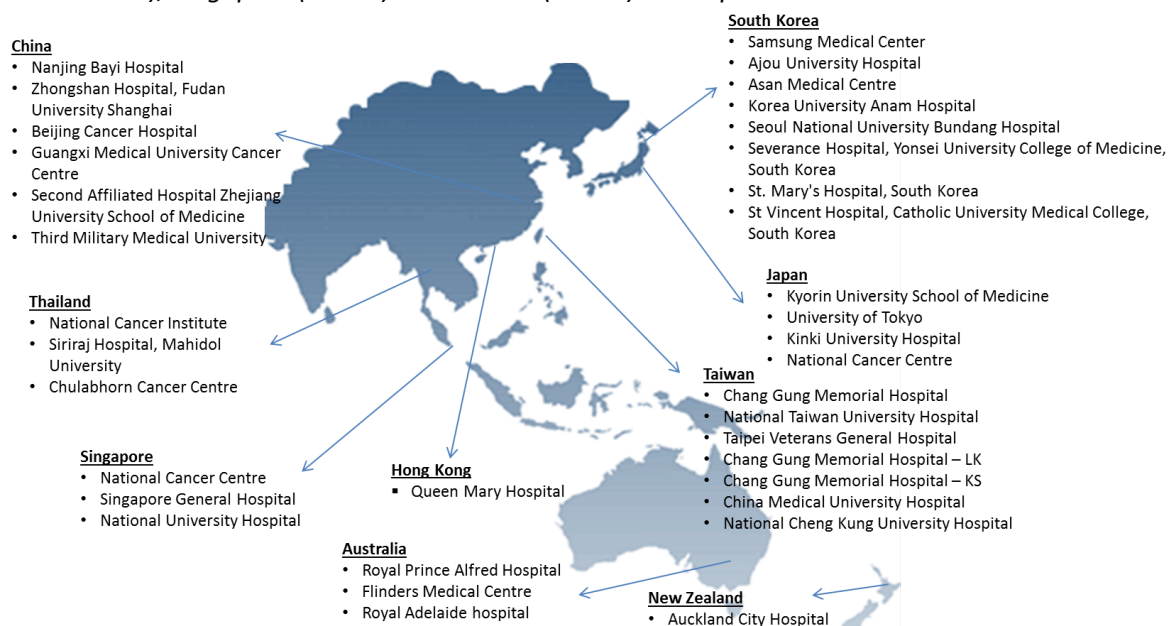
- Protocol Chair: Prof Pierce Chow
- Status: Recruitment in progress. Target recruitment of 100 patients. Preliminary results were published in 6 papers journals.
 1. Zhao, Y., Shuen, T.W.H., Toh, T.B., Chan, X.Y., Liu, M., Tan, S.Y., Fan, Y., Yang, H., Lyer, S.G., Bonney, G.K., Loh, E., Chang, K.T.E., Tan, T.C., Zhai, W., Chan, J.K.Y., Chow, E.K., Chee, C.E., Lee, G.H., Dan, Y.Y., Chow, P.K., Toh, H.C., Lim, S.G., and Chen, Q. (2018). **Development of a New Patient-Derived Xenograft Humanised Mouse Model to Study Human-Specific Tumour Microenvironment and Immunotherapy.** *Gut*. 10.1136/gutjnl-2017-315201.
 2. Lim, C.J., Lee, Y.H., Pan, L., Lai, L., Chua, C., Wasser, M., Lim, T.K.H., Yeong, J., Toh, H.C., Lee, S.Y., Chan, C.Y., Goh, B.K., Chung, A., Heikenwalder, M., Ng, I.O., Chow, P., Albani, S., and Chew, V. (2018). **Multidimensional Analyses Reveal Distinct Immune Microenvironment in Hepatitis B Virus-Related Hepatocellular Carcinoma.** *Gut*. 10.1136/gutjnl-2018-316510.
 3. Chew, V., Lee, Y.H., Pan, L., Nasir, N.J.M., Lim, C.J., Chua, C., Lai, L., Hazirah, S.N., Lim, T.K.H., Goh, B.K.P., Chung, A., Lo, R.H.G., Ng, D., Filarca, R.L.F., Albani, S., and Chow, P.K.H. (2018). **Immune Activation Underlies a Sustained Clinical Response to Yttrium-90 Radioembolisation in Hepatocellular Carcinoma.** *Gut*. 10.1136/gutjnl-2017-315485.
 4. Fong, E.L.S., Toh, T.B., Lin, Q.X.X., Liu, Z., Hooi, L., Mohd Abdul Rashid, M.B., Benoukraf, T., Chow, E.K., Huynh, T.H., and Yu, H. (2018). **Generation of Matched Patient-Derived Xenograft in Vitro-in Vivo Models Using 3d Macroporous Hydrogels for the Study of Liver Cancer.** *Biomaterials* 159, 229-240.
 5. Chew, V., Lai, L., Pan, L., Lim, C.J., Li, J., Ong, R., Chua, C., Leong, J.Y., Lim, K.H., Toh, H.C., Lee, S.Y., Chan, C.Y., Goh, B.K.P., Chung, A., Chow, P.K.H., and Albani, S. (2017). **Delineation of an Immunosuppressive Gradient in Hepatocellular Carcinoma Using High-Dimensional Proteomic and Transcriptomic Analyses.** *Proc Natl Acad Sci U S A* 114, E5900-E5909. 10.1073/pnas.1706559114.
 6. Zhai, W., Lim, T.K., Zhang, T., Phang, S.T., Tiang, Z., Guan, P., Ng, M.H., Lim, J.Q., Yao, F., Li, Z., Ng, P.Y., Yan, J., Goh, B.K., Chung, A.Y., Choo, S.P., Khor, C.C., Soon, W.W., Sung, K.W., Foo, R.S., and Chow, P.K. (2017). **The Spatial Organization of Intra-Tumour Heterogeneity and Evolutionary Trajectories of Metastases in Hepatocellular Carcinoma.** *Nat Commun* 8, 4565. 10.1038/ncomms14565.

Journal impact factors: *Gut* (16.658), *Nat Commun* (12.124), *Proc Natl Acad Sci* (9.661), *Biomaterials* (8.402).
- Number of participating centres: 6



AHCC08 Hepatocellular Carcinoma Registry in Asia (NCT03233360)

- Protocol Chair: Prof Pierce Chow
- Status: Recruitment in progress. Target recruitment of 2,500 patients from 9 countries. Preliminary results were presented at ASCO 2018, ILCA 2018, ASCO GI 2019 and APPLE 2019.
- Number of participating centres: 32 recruiting and 3 pending
- As of 16 Sep 2019, the registry has recruited 2,139 patients.
- Outcomes:
 1. *Online publication at ASCO 2018, Chicago*
Differences in presentation and management patterns in patients with hepatocellular carcinoma (HCC) between China and Singapore: Initial data from the HCC Registry in Asia
 Results on 174 patients from China (4 sites) and Singapore (2 sites) until 31 Dec 2017
 Poster presentation at ASCO GI 2019, San Francisco
 2. *E-poster presentation at ILCA 2018, London*
Differences in presentation and management patterns in patients with hepatocellular carcinoma (HCC) between China and Singapore: Initial data from the HCC Registry in Asia
 Results on 174 patients from China (4 sites) and Singapore (2 sites) until 31 Dec 2017
 3. *Poster presentation at ASCO GI 2019, San Francisco*
Differences in Presentation and Management Patterns in Patients with Hepatocellular Carcinoma (HCC): Data from HCC Registry in Asia
 Results on 657 patients from China (5 sites), South Korea (4 sites), Singapore (3 sites) and Japan (2 sites) until 30 Aug 2018
 4. *Poster presentation at 10th APPLE Congress 2019, Aug 29-31, 2019, Hokkaido, Japan*
Variations in cancer stages at diagnosis and management strategies in Hepatocellular Carcinoma (HCC): Data from the HCC Registry in Asia (AHCC08)
 Results on 951 patients from Australia (2 sites), China (6 sites), Japan (4 sites), South Korea (6 sites), Singapore (3 sites) and Taiwan (4 sites) until Apr 2019



About the AHCC Trials Group

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and the SLCC

The Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group is a collaborative group formed in 1997 by clinicians treating HCC in major medical centres in the Asia-Pacific region. The aims of the trials group are to conduct preventive and therapeutic trials in HCC, to carry out basic and translational research in this field and to develop training and educational programmes pertaining to HCC. With these objectives, the trials group holds annual general meetings and symposia that bring together international experts to create opportunities to network and share updates and research ideas.

The Trials Group holds regular General Meetings to align the group's mission and to discuss current and new therapies available for HCC. These meetings were often attended by more than 20 overseas site representatives and the valuable inputs often conceive ideas of new clinical designs. Common practices is also shared to have an overall picture of the HCC treatment in Asia-Pacific. In conjunction with the general meetings, the Trials Group will have its scientific forum to share new updates on the research and treatments on HCC. The forum is complimentary to the all medical professionals and industry partners. This is in line with the group's mission on the education to HCC.

From 2017, the scientific forum is renamed to the Symposium of the Singapore Liver Cancer Consortium (SLCC). This is subsequent to the group's flagship program, the AHCC07 study (Precision Medicine in Translational). The members of the SLCC are the study members of the AHCC07 study which is a collaboration with A*Star GIS and STIIC. In 2016, the study was awarded the Translational & Clinical Research (TCR) Flagship Programme grant by Singapore's National Medical Research Council (NMRC). This allows the Trials Group together with the study team to integrate, coordinate and leverage on the strength of the network and this collaborators. The Trials Group continuously works with academic researchers and industry partners. This leverages on complementary strengths, to design and plan clinical trials and studies that lead to a better understanding of HCC and improve clinical outcomes of patients with HCC.

Contact Details

For further queries, please contact the AHCC Trials Group at

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Read more about all trials
under AHCC Trials Group at

<http://www.scri.edu.sg>

Our current studies:

