Building an Investigator-led Clinical Research Network in Hepatocellular Carcinoma

*an 18-year history*

**Pierce Chow** FRCSE PhD
Professor, Duke-NUS Graduate Medical School
Senior Consultant Surgeon, National Cancer Center, Singapore
Senior Consultant Surgeon, Singapore General Hospital

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Why
an Investigator-lead Asia-Pacific Research Network/Trials Group?
Singapore is a very small country in a very big continent.

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**Population by Country**

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*United Nations Population Division estimates for 1 Jul 2012

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http://en.wikipedia.org/wiki/List_of_Aisan_countries_by_population
If we are so small
Why should we aspire to be thought-leaders in Bio-Medicine?

- We need to develop the expertise to achieve better outcomes for our own patients
  - Copy from the west/other countries OR
  - Develop expertise in our prevalent diseases

- We want to move up the Bio-Medical value chain
  - The Sweden of South-east Asia (leader/producer) OR
  - The powerless downstream consumer of South-east Asia
Biomedical Research: 
the only consistent way to achieve better outcomes in patients

14 days

5 – 8 mm Ø tumours
Biomedical Discovery Cycle

Basic Scientific Discoveries → Translational / Animal Experiment → Phase I → Phase II → Phase III → Better Clinical Outcome

Clinical Insights

Well-conducted *prospective clinical studies* on areas of *pivotal clinical importance* is the fastest and most direct way to bring clinical benefit to patients and *influence scientific direction*

*SGH – Surgery*  
*Adapted from KC Soo*
Requirements of a good prospective clinical study

• **Thought Leadership**
  - Addresses a pivotal clinical issue the decision of which will impact significantly on clinical practice
  - Good scientific rationale
  - Well thought out study design

• **Organization**
  - Good track record and excellent logistical ability to carry out a large trial

• **Large Population Catchment**
  - Large number of patients to provide scientifically robust results – *multi-center trials*
addresses an un-met need

An Asia-Pacific Hepatocellular Carcinoma Trials Group
Regional Variation in the Estimated Age-Standardized Incidence Rates of Hepatocellular carcinoma.


- 1 million new cases a year, 80% in Asia-Pacific
- sixth most common cancer worldwide, 2nd most common cause of cancer death (WHO 2015)
In the US, HCC incidences peak at the age of 77. (El-Serag et al., 2003)

Age-Specific HCC Incidences: Malaysia

(National Cancer Registry, Malaysia, 2008)
Men: 2nd cause of cancer deaths (previously 3rd)

Women: 5th cause of cancer deaths (previously 6th)
Median overall survival in HCC

Percentage of Patients surviving 5 years

- AML
- CML
- Leukaemias
- Pancreatic
- Primary Liver
- Oesophagus
- Lung
- Stomach
- Ovary
- Kidney
- Colorectal
- Breast
- Prostate
- All

~ 3-9 month median survival
Mortality worse in less developed countries

**Men:** 5th most Common
2nd cause of cancer deaths

**Women:** 9th most Common
6th cause of cancer deaths
Reasons for poor Clinical Outcomes in Hepatocellular Carcinoma

1. **Low research priority.** Historically a cancer of poor people in the 3rd world, previously of little interest to industry.

2. **Highly heterogeneous cancer,** wide geographical, genetic and etiological diversity (chronic Hep B vs Hep C vs NASH)

3. Underlying **molecular mechanisms poorly understood**
   - absence of proven therapeutic targets
   - absence of robust molecular prognostic classifiers

4. Few efficacious **therapeutics** other than surgery

5. Paucity of definitive **clinical trials**
More than 1 million new cases a year, 80% in the Asia-Pacific, but few efficacious therapies

- 20% of patients are diagnosed at an early stage and benefit from potentially curative therapies – resection, transplantation, radiofrequency ablation - recurrences common and limit long term survival

Challenges

- Only one useful systemic therapy, sorafenib – no useful adjuvant therapy
  - in 1998 – no sorafenib, no RFA, TACE was not proven
- Highly heterogeneous genome
  - between patients (etiology, geography, ethnicity)
  - Significant intra-tumoral heterogeneity
- No validated predictive bio-markers
  - to match potentially useful therapeutics to the individual patient
Hepatocellular Carcinoma: An Unmet Need Globally and in Asia

Surgery is potentially curative in early stage HCC

But 80% are inoperable at time of diagnosis

High recurrence rates

Paucity of therapeutic targets

Lacks molecular prognostic classifiers

SGH – Surgery
A short history
How we started the Asia-Pacific Hepatocellular Carcinoma Trials Group
The Beginning of the AHCC

• Created in 1998 when clinicians from:
  - The Chinese University of Hong Kong
  - The Undayana University, Bali, Indonesia
  - The University Kebangsaan in Malaysia

• Joined a RCT in HCC proposed by:
  - the Dept of General Surgery, Singapore General Hospital (SGH) – no NCCS then
  - NMRC Clinical Trials and Epidemiology Research Unit (CTERU) - SCRI

• The 1st collaborative oncology trial in the region - became truly Asia-Pacific with centers from: Myanmar, Thailand, Australia, Korea and New Zealand
The Asia-Pacific HCC Trials Group

• **Aim:** to carry out definitive multi-centre trials and other research on HCC in the Asia-Pacific where the disease is endemic

• In 1998 - very few therapeutic options for HCC
  • *relatively few large clinical studies in HCC*

• Clinicians looking after HCC patients in the Asia-Pacific were bonded by a common need:
  • *for a trials group that seek efficacious treatment for a common cancer that had few therapeutic options*
Asia-Pacific HCC Trials Group 2016

40 sites, 17 countries, 1000 patients

6 randomized controlled trials since 1998
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<th>Country</th>
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Multi-disciplinary KOLS looking after patients with HCC in the Asia-Pacific*

*Outside of China and Japan*

Kong et al 2013
### Multi-center Clinical Trials of the AHCC

| AHCC01: | NCT00003424. Randomised Trial of Tamoxifen Versus Placebo for the Treatment of Inoperable Hepatocellular Carcinoma. | 1997 – 2000 | NMRC |
| AHCC02: | NCT00041275. Randomized Double Blind Trial Of Megestrol Acetate Versus Placebo For The Treatment Of Inoperable Hepatocellular Carcinoma. | 2002 – 2007 | NCC, SingHealth |
| AHCC04: | NCT00247260. Phase II dose escalation trial of intra-tumoral Brachysil® in inoperable HCC | 2005 – 2006 | PSiOncology |
| AHCC05: | NCT00712790. Phase I/II Study of SIR-Spheres Plus Sorafenib as First Line Treatment in Patients With Non-Resectable Primary Hepatocellular Carcinoma | 2008 – 2009 | NMRC, Bayer, Sirtex |
| AHCC06: | NCT01135056. Phase III Multi-Centre Open-Label Randomized Controlled Trial of Selective Internal Radiation Therapy (SIRT) Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (SIRveNIB) | 2010 – 2016 | NMRC, Sirtex |
Challenges encountered and overcame in building an Investigator-led Clinical Research Network in Hepatocellular Carcinoma

In the Asia-Pacific
Asia-Pacific is Highly Heterogenous

- Highly diverse geographical region
- Disparate levels of socio-economic development
- Different ethnic populations
- Main burden of HCC
  - high incidences of chronic HBV and HCV

SGH – Surgery
Inherent Advantages in Conducting HCC Clinical Trials in Asia

- Heterogeneity reflects the clinical reality of the disease
  - Highly representative, achieve definitive outcomes

- Large number of potential research participants

- Directly benefit patients who otherwise would have no access to new therapies - Economically disadvantaged nations

- Prognostic biomarkers

- Understand various genetic and environmental influences that affect pathology and treatment response
  - Across different ethnicity and populations
The Challenges

- **Evident gaps** in experiences – *RCT experience*
- Feasibility of conducting good GCP-standard clinical trials
- **Rudimentary** medical facilities, infrastructure and indemnity assurance
- **Differences** in the standard of care and cultural practices
  - affect implementation of study protocol
- **Funding and Sponsorship Model**
Meeting the Challenges

• Helping sites to be GCP-compliant
  – *E.g. helping sites to set up IRBs*

• Training of clinical trials teams:
  – *Significant investment in time and resources to train, update and familiarize local staff with study protocol and GCP guideline*

• Thorough audits
  – *E.g. 100% audits for AHCC02 trial*

• Outsource clinical services to privately run institutions outside of the trial centres
  – *E.g. CT scan imaging to meet inclusion criteria*
Extensive Site visits, training, audits

Thailand
Korea
Myanmar
Phillipines
Vietnam
Continual Dialogue, Frequent one-to-one meetings and Open Channels of Communications are vital

AHCC06 2\textsuperscript{nd} IM 16/11/12
AHCC03 3\textsuperscript{rd} IM 10/07/14

Challenges are very different in the different countries – one size does not fit all
Examples of issues Identified by Members at AHCC06 Investigator’s Meetings

1. Patients at many sites especially in the 3rd World (e.g. Indonesia, Philippines, Myanmar) had problems paying for follow-up investigations – CT scans, blood tests

2. Results in non-compliance, protocol deviations and patient drop-outs

3. In other sites e.g. Taiwan, hospital expects the trial to pay for follow-up investigations once patients enter trial

4. Dis-incentivizes the sites from recruiting patients
Funding and Paradigm Shift in Clinical Research
In the Asia-Pacific
Paradigm Shift: Conducting Clinical Trials in Asia-Pacific

Over the last 18 years

Due to:

• Rapid expansion of pharmaceutical industry
• Potential of new markets in the Asia-Pacific
• Cost effectiveness
  • Relatively cheaper costs of conducting clinical trials
• Improving medical infrastructure
• Reduced amount of regulatory barriers compared to the past

Kong, Chow 2013
## Multi-center Clinical Trials of the AHCC

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Funding

• Model of co-funding: academic and industrial sources of funding
  – *Maintain the independence of an investigator-initiated trial*
  – *Increase the quantum of funding available by tapping on industry*

• AHCC05 (SirSA) - 2008
  – NMRC $487,000
  – Therapeutics from Bayer ($1mil) and Sirtex ($1 mil)

• AHCC06 (SirveNIB) - 2010
  – NMRC $1.67 mil
  – Sirtex $8.5 mil + $1.9 mil
Sponsorship Model: Inter-site Agreement

8 TRIAL DATABASE

8.1 The Participating Institutions shall provide such Trial data in the form and manner as advised by the Study Steering Committee to a central data base (“Trial Database”) to be established and maintained in Singapore.

8.2 Ownership of Trial data shall reside with the Participating Institution providing such Trial data (“Contributing Participating Institution”) to the Trial Database. For the avoidance of doubt, no claim shall be made by the Contributing Participating Institution on or over Trial analysis and Trial results (“Trial Analysis and Results”) derived from Trial data.

8.3 The Trial data maintained in the Trial Database and Trial Analysis and Results shall be used in accordance with the direction of the Study Steering Committee.

8.4 Use of Trial data provided to the Trial Database may be used for purposes other than the Trial only with the prior written consent of the Contributing Participating Institution.

9 MISCELLANEOUS

9.1 The Parties’ relationship one with the other under this Agreement shall be that of an independent contractor and no Party has authority to assume or create any obligation on behalf of any other Party, save as is herein expressly provided. Any Party may provide such support to any other Party as may be agreed between them to facilitate the successful implementation of the Trial. Each Party assumes its obligations hereunder on a several basis.

9.2 No Party shall use the names, logos, trade marks or service marks of any other Party for any purpose whether in relation to any advertisement or other form of publicity without obtaining the prior written consent of the other Party, save as required by any applicable law or governmental regulation.
The Structure of the Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group
Structure of the AHCC
A Collaborative Trial Network

- AHCC Trials Group – a collaborative trials group
- Membership by participation in trials
- Trials governed by a Steering Committee
- Trials managed by an Academic Research Organization (ARO) – Singapore Clinical Research Institute (SCRI), Network Executives and the Protocol Chair
Investigator-Initiated Trials: 
*The AHCC Trials Group Model*

Structure introduces accountability and reduces potential conflict.
While trials are initiated by individual PIs they are built from the ground up. Input from sites are crucial important to ensure buy-in
Strategic Advantages of a Collaborative Trials Network

- Allows industry to access PIs of different countries from the region
- Facilitates support and broadens collaborations
- Fosters positive relationships among clinician-investigator
- Increases opportunity for scientific breakthrough in future collaborations
Developing a collaborative platform

• By 2014 the AHCC has reached a stage in its development where it was meaningful to develop a collaborative platform with industrial partners.
• To realize this strategic initiative, a collaborative partnership was developed to facilitate:
  – clinical projects with industry partners
  – funding mechanisms that supports the scientific and administrative infrastructure of the trials group
  – access to the collective expertise of the group on scientific and clinical matters pertaining to HCC
Scientific Forum and General Meeting
31st Oct 2014

Funded through a collaborative platform with industry to become a regular 6-monthly event
Where are we today in the AHCC Trials Group? 18 years later
Asia-Pacific, Phase III, open-label, randomized-controlled study

**UPDATE:** closure of AHCC06 trial

SIRT Yttrium-90 versus Sorafenib in patients with locally advanced HCC (SIRveNIB)

Closed on 25th May 2016

**Eligibility criteria**
- Locally advanced HCC
- Child–Pugh <8 pts
- ECOG PS 0 – 1

**Exclusion criteria**
- Distant metastases
- Complete main portal vein thrombosis

**Randomisation** 1:1 (n=360)

**Endpoints**
- Primary
  - OS
- Secondary
  - TTP
  - QoL
  - Downstaging to curative therapies

**Sorafenib**
400mg b.i.d.

**SIRT Yttrium-90**

ECOG PS = Eastern Cooperative Oncology Group Performance Status
OS = overall survival; TTP = time to tumour progression

Eligible: Previous surgery, RFA, TACE
Clinical Trajectory and Translational Clinical Trial

Recurrence
Biopsy or resection tissue samples, cfDNA, CTC

Therapeutics selected on the basis of discoveries in this study

Tumor genomics and heterogeneity

Preop scans, bloods, multi-region tissue samples, cfDNA, CTC

100 patients
5 Asia-Pac centers

3-monthly follow-up: scans, bloods, cfDNA, CTC

Adjunct Adjuvant Therapy Trial

Surgical Resection

Translational Immunomics

UPDATE: investigator meeting AHCC07
The Planet Study

PRECISION MEDICINE IN LIVER CANCER ACROSS AN ASIAN PACIFIC NETWORK

NMRC TCR Grant awarded April 2016

Asia-Pacific HCC Trials Group
Program Overview

Multi-national Study Sites:
- NUHS (KK Madhavan)
- SingHealth (Brian Goh)
- National Cancer Center, Bangkok (Rawisak)
- Medical City, Manila (Vanessa De Villa)
- UMMC, KL (Yoong Boon Koon)

Personalized Genomics for drug development
Theme Lead: Zhai Wei Wei
- Intratumoural Heterogeneity (Zhai Wei Wei, Axel Hillmer)
- Cell-free DNA (Iain Tan)
- CTC & single cell omics (Zhai Wei Wei, Roger Foo)

Immune-modulation and therapy
Theme Lead: Salvatore Albani
- Immuno-microenvironment (Valerie Chew)
- Immuno-profile of Peripheral T-cells (Valerie Chew)
- Genomics and epigenomics of immune subsets in tumour

Longitudinal study and Clinical trials
Theme Lead: Pierce Chow
1. Adjuvant (P Chow)
2. Recurrence (Toh Han Chong)

Patient derived models

Experimental models, PDX, cell lines – Dan Yock Yong, Tam Wai Leong, Edward Chow, Dan Tenen

Radiomics: Invitrocue, David Townsend
Investigator Meeting 2016:
AHCC07: The PLANET Study
**Study Design**: Multi-centre, longitudinal cohort study

**Sample Size**: 2000 – 2500 (Retrospective vs Prospective Cases = 30 : 70)

**Patient HCC Diagnosis Period**: 1\(^{st}\) Jan 2013 - 30\(^{th}\) Jun 2018 (Phase 1)

**Start of Registry**: 1\(^{st}\) Oct 2016
List of Invited Sites Across Asia – 1st Phase

**China**
- Nanjing Bayi Hospital
- Zhongshan Hospital, Fudan University Shanghai
- Beijing Cancer Hospital
- Sun Yat Sen University Cancer Centre, Guangzhou
- Guangxi Medical University Cancer Centre
- Hunan Province Xiang Ya Hospital
- Jiangsu Cancer Centre
- Tongji Medical University, Wuhan
- Second Affiliated Hospital Zhejiang University School of Medicine
- The Eastern Hepatobiliary Surgery Hospital, Shanghai
- Third Military Medical University

**South Korea**
- Ajou University Hospital
- Asan Medical Centre
- Korea University Anam Hospital
- Seoul National University Bundang Hospital

**Japan**
- Kyorin University School of Medicine
- University of Tokyo
- Kinki University Hospital
- National Cancer Centre

**Taiwan**
- Chang Gung Memorial Hospital
- National Taiwan University Hospital
- Taipei Veterans General Hospital
- Chang Gung Memorial Hospital – LK
- Chang Gung Memorial Hospital – KS
- China Medical University Hospital
- National Cheng Kung University Hospital

**Thailand**
- National Cancer Institute
- Siriraj Hospital, Mahidol University
- Chulabhorn Cancer Centre

**Hong Kong**
- Queen Mary Hospital

**Singapore**
- National Cancer Centre
- Singapore General Hospital
- National University Hospital

**Australia**
- Royal Prince Alfred Hospital
- University of Adelaide
- Austin Hospital

**New Zealand**
- Auckland City Hospital
Investigator Meeting:
AHCC08: Asia-Pacific HCC Registry
Now includes sites from China and Japan
AHCC General Meetings

9th General Meeting

26th August 2016, The Academia, SingHealth
Asia-Pacific HCC Trials Group 2016

40 sites, 17 countries, 1000 patients

Ulaan Baator
Hanoi
Yangon
Bangkok
HCMC
Penang
Kuala Lumpur
Singapore
Jakarta
Bali

The only multinational Liver Cancer Network in the Asia-Pacific

Seoul, Bundang, Suwon
Taipei, Kaoshiung
Hong Kong
Manila
Davao City
Brunei
Melbourne
Auckland

SGH – Surgery

6 randomized controlled trials since 1998
AHCCC Trials Group 2016

Now includes members from China and Japan
It is possible to build multi-center Research Networks.

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<th>Rank</th>
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*United Nations Population Division estimates for 1 Jul 2012

http://en.wikipedia.org/wiki/List_of_Asian_countries_by_population
- Thought Leadership
- Organization
- Large population

[Map showing population distribution in Asia]

http://en.wikipedia.org/wiki/List_of_Asian_countries_by_population

*United Nations Population Division estimates for 1 Jul 2012
It is a Virtuous Cycle

Phase III trials are long and tough battles. *I would like to thank all our participating PIs who believe in our science and our vision of what is possible and trust that we can do this. And to the numerous others who have tried to made this easier.*
......when the going gets tough .........

The tough gets going!
Thank You!
Acknowledgement: Rachel Choi BSc (Hons) for assistance with the slides
Asia-Pacific Hepatocellular Carcinoma Trials Group

6th General Meeting

31st October 2014
AHCC General Meetings
8th General Meeting
29th Jan 2016, The Academia, SingHealth