

# **Punching Above Our Weight: Multi-Center Clinical Trials and *the Story of the AHCC Trials Group***

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Senior Consultant Surgeon, National Cancer Center, Singapore  
NMRC Senior Clinician- Scientist

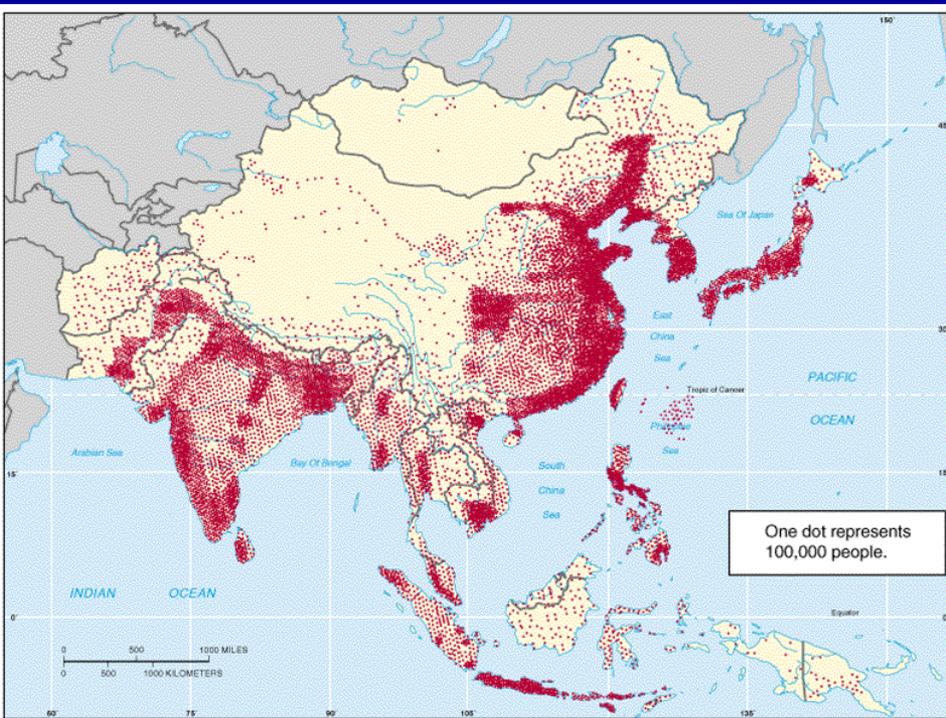
NMRC Research Symposium

Grand Copthorne, Singapore 19<sup>th</sup> March 2015



SGH – Surgery

# Singapore is a very small country in a very big continent



1	China	1,353,601,000	27	Azerbaijan	9,421,000
2	India	1,258,351,000	28	United Arab Emirates	8,106,000
3	Indonesia	244,769,000	29	Israel	7,695,000
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\*United Nations Population Division estimates for 1 Jul 2012

## If we are so small

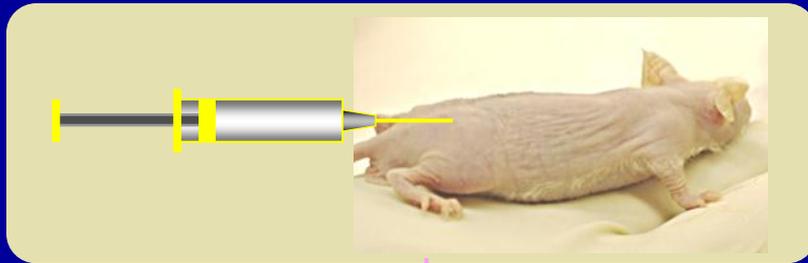
# Why should we bother to be thought-leaders in Bio-Medical Science?

- We need to develop the expertise to *achieve better outcomes for our own patients*
  - Copy from the west/other countries **OR**
  - Do the research to develop our own expertise
- We want to move up the *Bio-Medical value chain*
  - The Switzerland of South-east Asia (leader/producer) **OR**
  - The Bataam of South-east Asia (poor consumer)

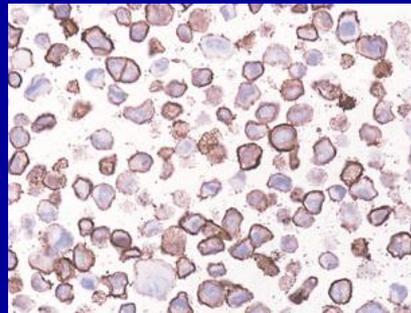
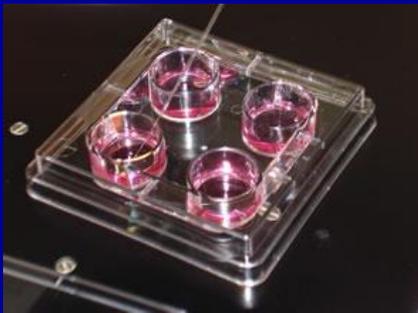
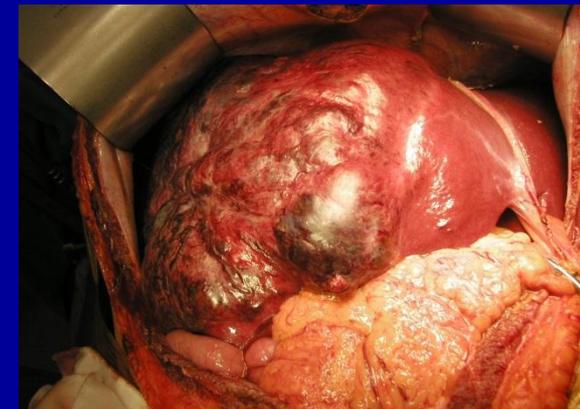
# Outline

- **Why multi-center clinical trials**
- **Why Hepatocellular Carcinoma (HCC)**
- **A short history of the Asia-Pacific HCC Trials Group**
- **The continuing challenges and how they are met**
- **The AHCC Trials Group infrastructure platform**

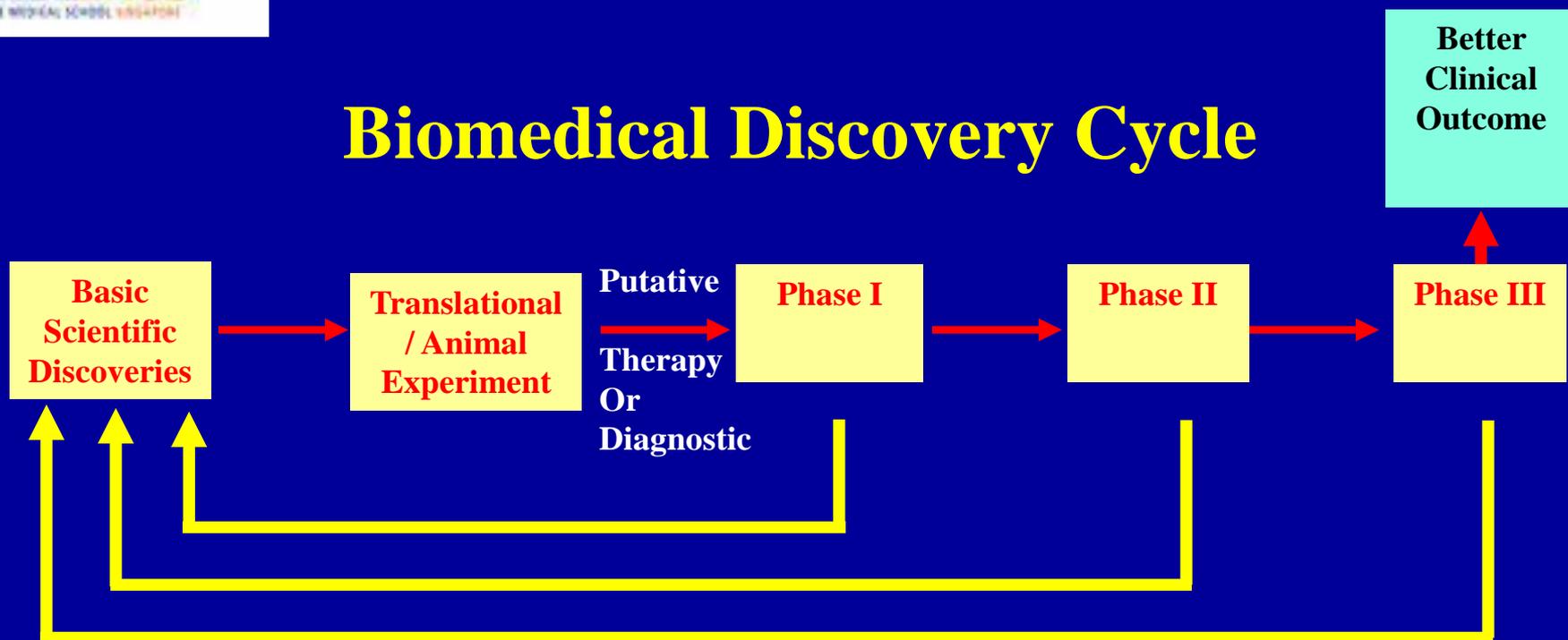
# Biomedical Research leads to better outcomes in patients



14 days



# Biomedical Discovery Cycle



## Clinical Insights

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

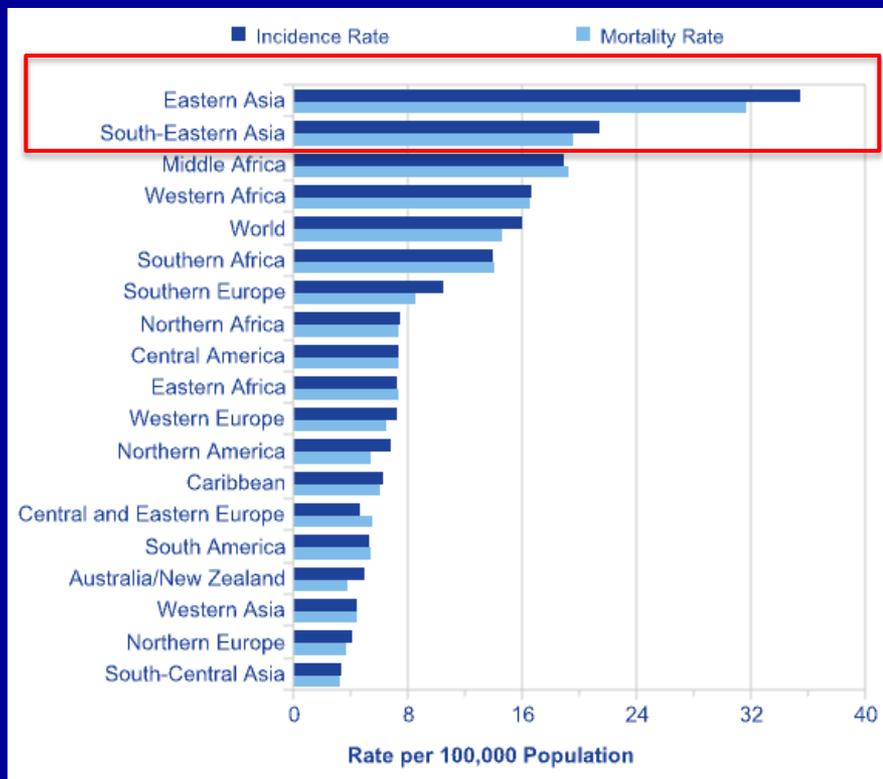
# Requirements of a good Phase III trial

- **Thought Leadership**
  - *Addresses a pivotal clinical issue the decision of which will impact significantly on clinical practice*
  - *Good scientific basis*
  - *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*

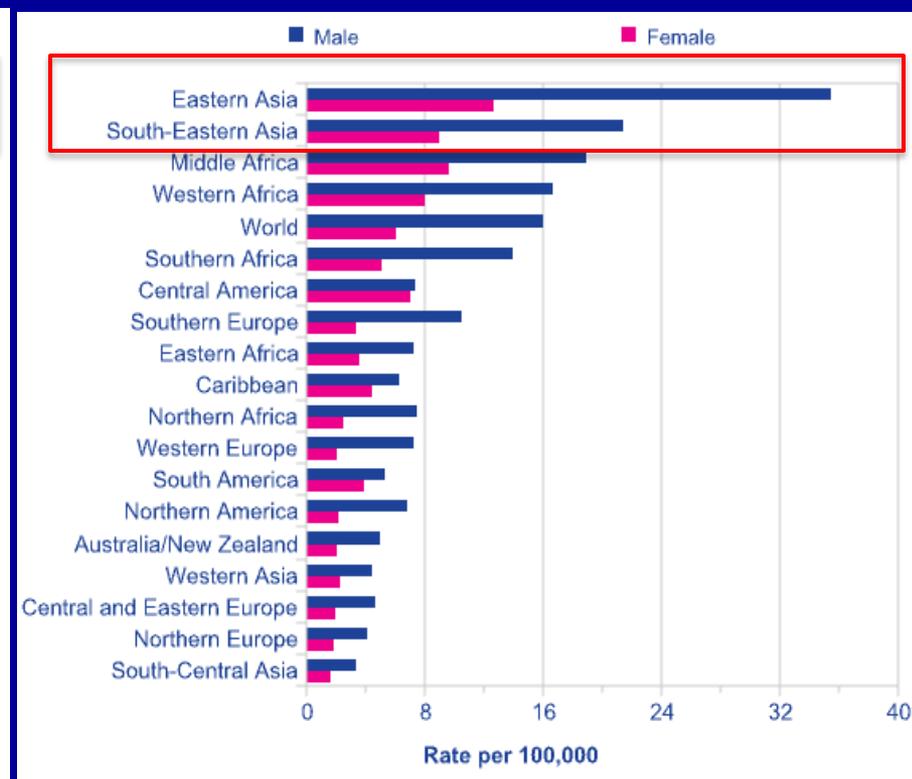
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# Hepatocellular Carcinoma: A Global Problem



GLOBOCAN, 2008

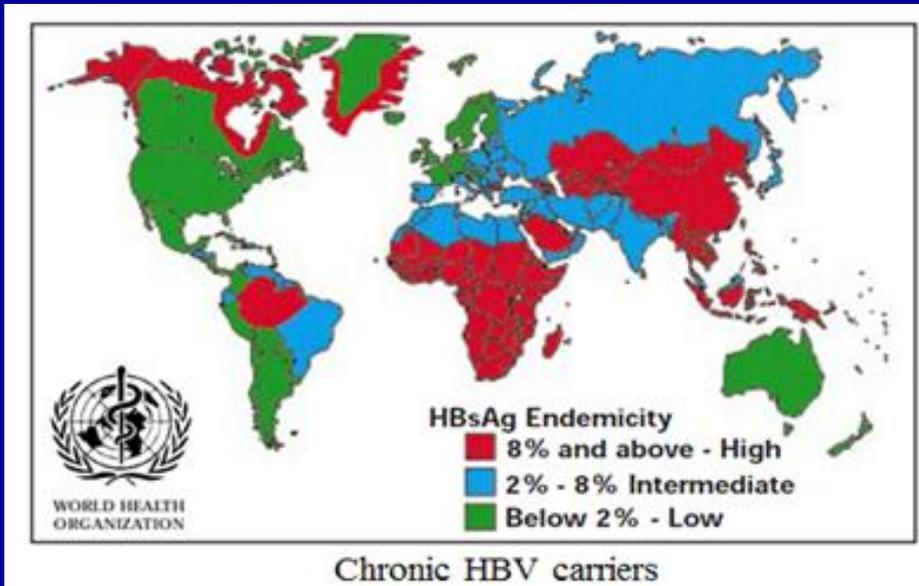


GLOBOCAN, 2008

sixth most common cancer worldwide, 3<sup>rd</sup> most common  
cause of cancer death

# HCC is **endemic** in the Asia-Pacific

75% to 80% of cases of HCC occur in the Asia-Pacific

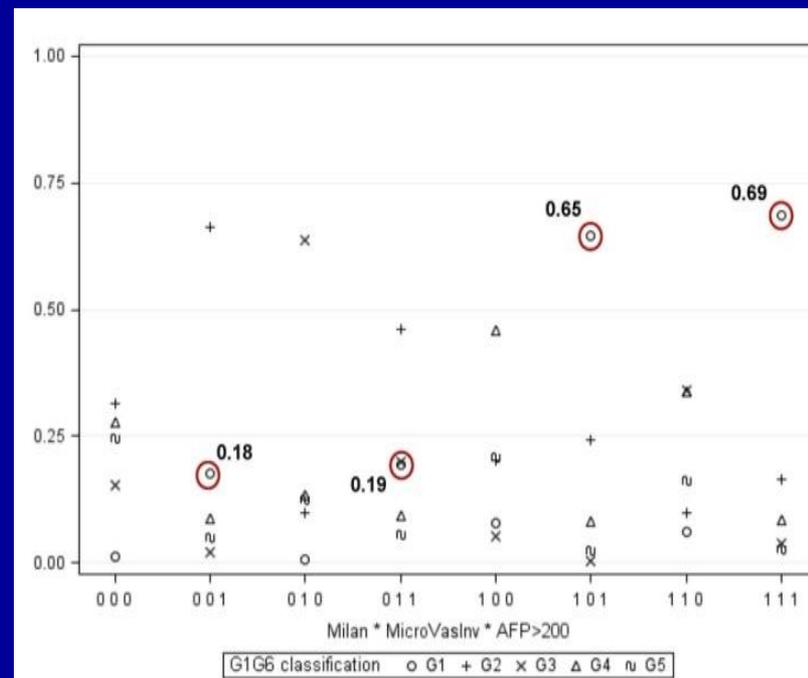


# Highly heterogeneous cancer Collaboration with INSERM

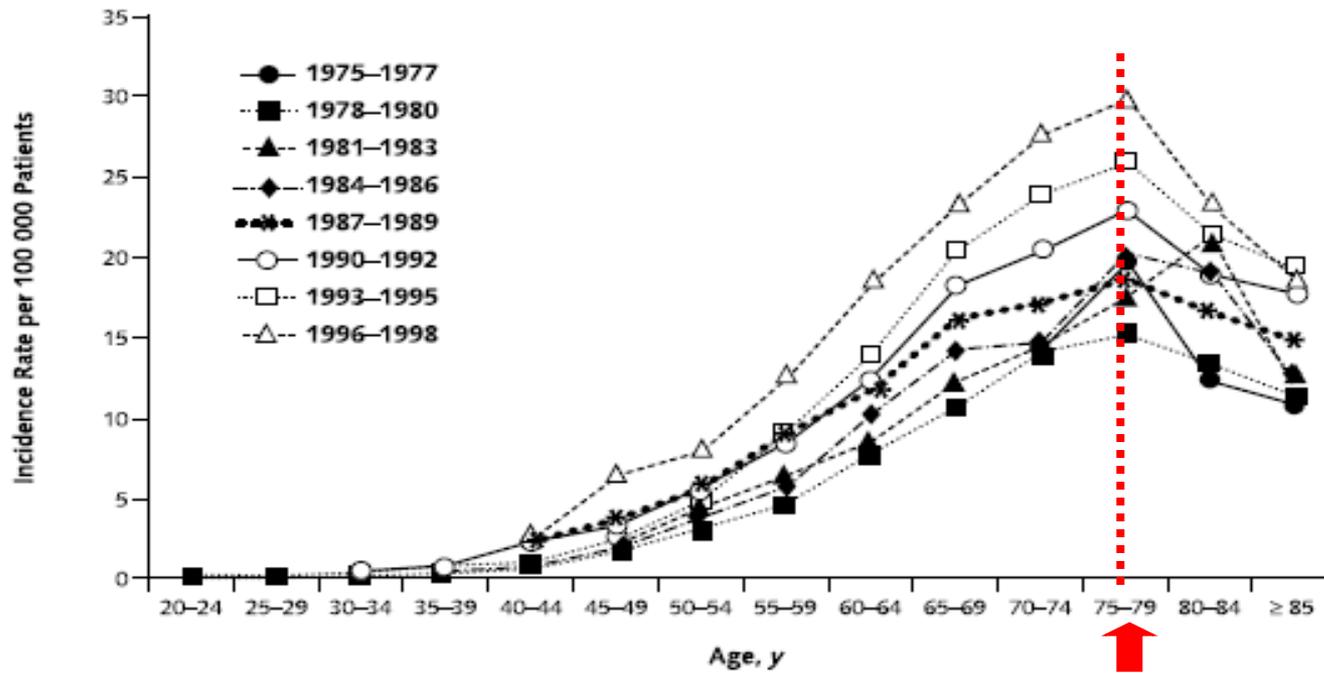


- Application of 100 samples of fresh frozen resected HCC from **South-east Asia** (Singapore) with a highly annotated database to *gene expression analysis*, suggest that proportions of European and Asian patients in the different sub-groups are different

Cannot depend on expertise  
from the west



JC Allen et al.



## Age-Specific HCC Incidences: USA

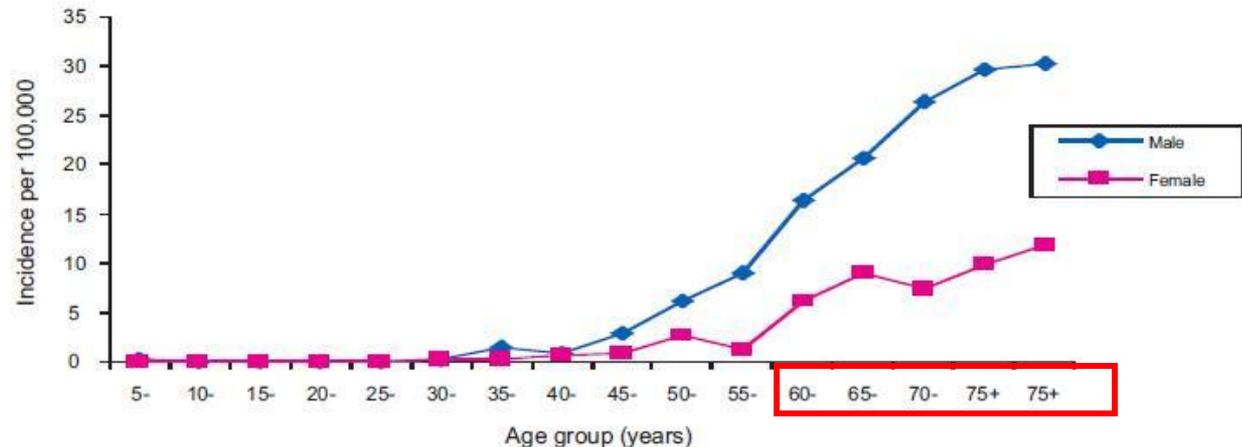
In the US, HCC incidences peak at the age of 77.

(El-Serag et al., 2003)

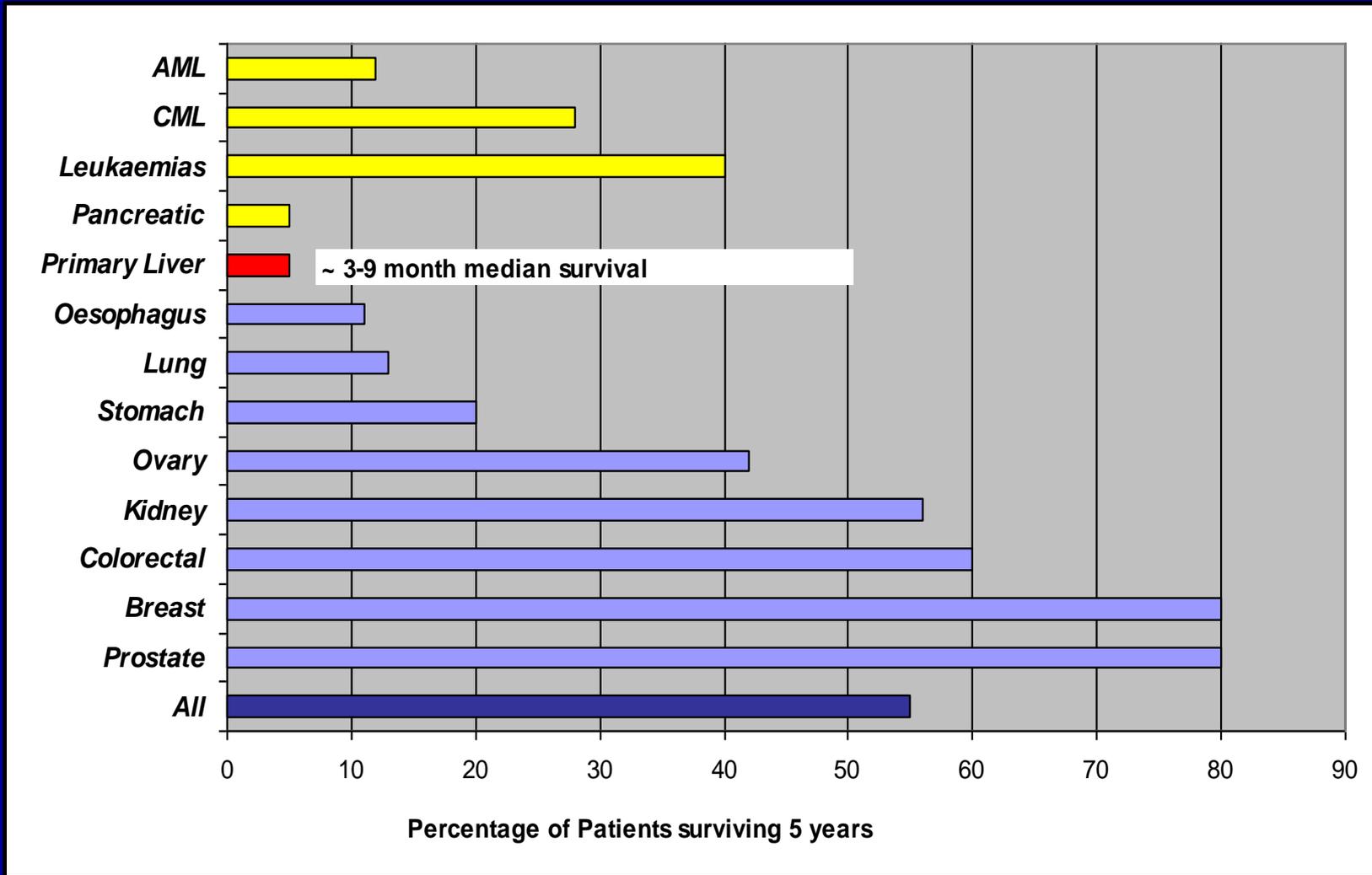
## Age-Specific HCC Incidences: Malaysia

(National Cancer Registry, Malaysia, 2008)

Figure 36: Liver. Age specific Cancer Incidence per 100,000 population by sex, Malaysia 2007



# Median overall survival in HCC



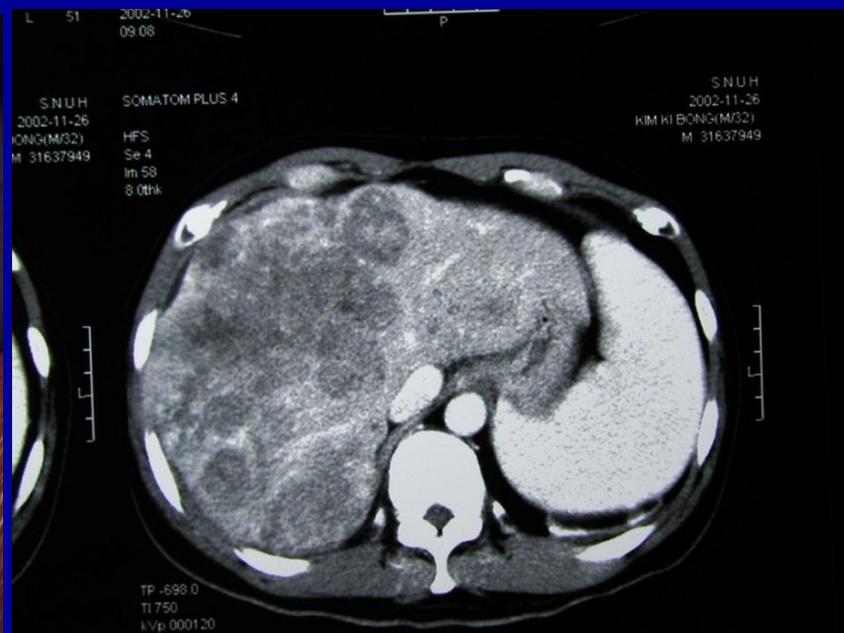
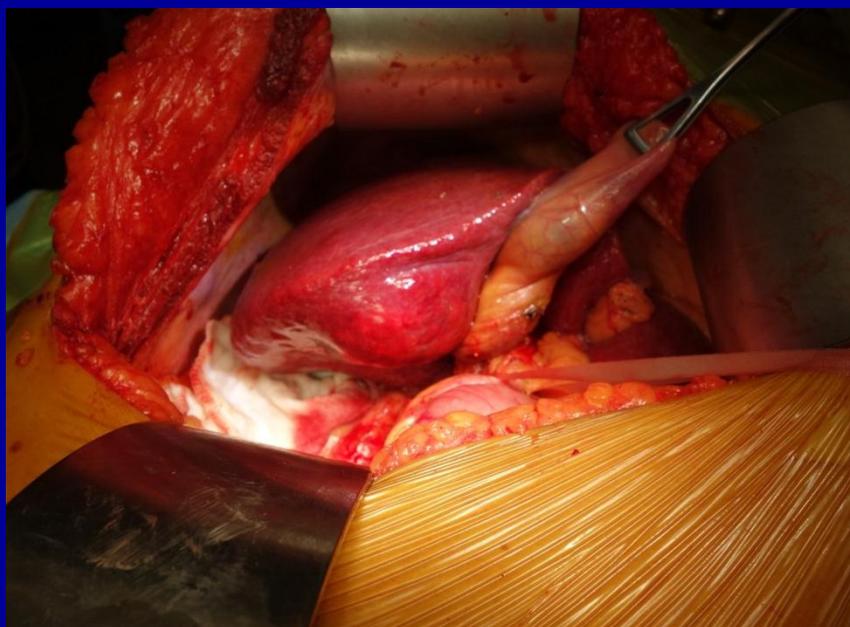
# Reasons for poor Clinical Outcomes in Hepatocellular Carcinoma

1. **Low research priority**. Historically a cancer of poor people in the 3<sup>rd</sup> world, previously of little interest to industry.
2. **Highly heterogeneous cancer**, wide **geographical and genetic** diversity (chronic Hep B vs Hep C?)
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**

# 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

# Rapid Evolution in the Management of HCC

- *The last decade has seen better approaches and more efficacious therapies for HCC e.g.*
  - *Better survival with improved surgical approaches*
  - *Selective internal radiation therapy with ytium-90*
  - *Radio-frequency and microwave ablation*
  - *New systemic therapies*
- *Resulted in significant improvement in clinical outcomes*
- *New clinical trials will lead to additional changes in management over the next few years*



**NEED + EVOLUTION**  
**= OPPORTUNITY (TO DO**  
**GOOD)**



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# The Beginning of the AHCC

- Created in **1997** when clinicians from:
  - *The Chinese University of Hong Kong*
  - *The Undayana University, Bali, Indonesia*
  - *The University Kebangsaan in Malaysia*
  
- Joined an **NMRC supported 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 1<sup>st</sup> collaborative oncology trial in the region - became truly Asia-Pacific with centers from : *Myanmar, Thailand, Australia, Korea and New Zealand*

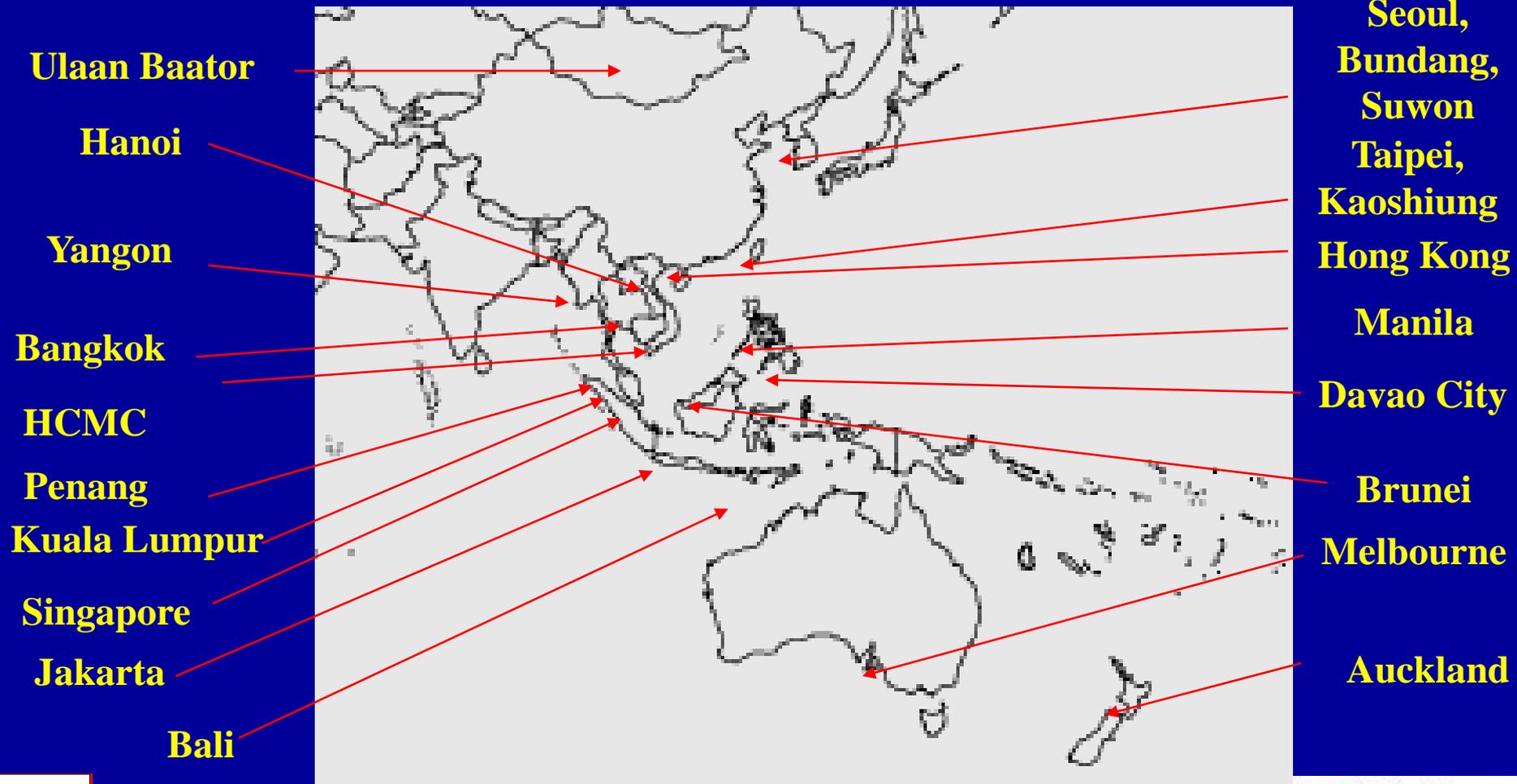


# The Asia-Pacific HCC Trials Group

- **Aim:** to carry out definitive multi-centre trials and other research on HCC in the Asia-Pacific where the disease is endemic
- In 1997 - 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

**40 sites, 17 countries, 1000 patients**



Country	Site	Principal investigator	AHCC trial
Australia	Austin and Repatriation Medical Centre	Jonathan Cebon	01
Brunei	Raja Isteri Pengiran Anak Saleha Hospital	Kenneth Kok	06
Hong Kong	Prince of Wales Hospital	Philip Johnson	01
	Queen Mary Hospital	Ronnie Poon	06
Indonesia	Cipto Mangunkusumo Hospital	Laurentius Lesmana	06
	Rumah Sakit Sanglah	Tjakra Manuaba	02, 06
Malaysia	Hospital Universiti Kebangsaan	A. Haron	01
	Penang Adventist Hospital	Aloysius Raj	06
	Selayang Hospital	Harjit Singh	05
Mongolia	National Cancer Center of Mongolia	Ariunaa Khasbazar	06
Myanmar	Yangon General Hospital	Khin-Maung Win	01, 02, 05, 06
New Zealand	Auckland Hospital	Michael Findlay	01
		Paul Thompson	02
Philippines	Davao Doctors Hospital	Rolley Lobo	02
	Makati Medical Center	Catherine Teh	06
	St Luke's Medical Centre	Ian Chua	06
	The Medical City	Janus Ong	06
Singapore	Changi General Hospital	Jessica Tan	06
		Khoon-Hean Tay	02, 03
	Khoo Teck Puat Hospital	Jude Lee, Tzu Zen Tan	06
	Mount Elizabeth Hospital	Richard Guan	04
	National Cancer Centre	Donald Poon	05
		Khee-Chee Soo	01,02
		Kian-Fong Foo, Susan Loong	04
		London Ooi	03
		Su-Pin Choo	06
	National University Hospital	Stephan Chang	06
	Singapore General Hospital	Alexander Chung	05
		Anthony Goh	04
		Khee-Chee Soo	01, 02
		Peng-Chung Cheow	06
	Tan Tock Seng Hospital	Kui-Hin Liao	04
		S. C. Chia	01
		Soo Ping Chew	03
South Korea	St. Vincent's Hospital	Mo-Yang Jin	02, 06
		Si-Hyun Bae	01
	Asan Medical Center	Hyun-Ki Yoon	06
	Korea University Anam Hospital	Yun-Hwan Kim	06
	Seoul National University Bundang Hospital	Ho-Seong Han	05, 06
	St. Mary's Hospital	Si-Hyun Bae	06
	Yonsei University Severance Hospital	Jong-Yun Won	06
Taiwan	Chang Gung Memorial Hospital	Chien-Fu Hung	06
	China Medical University Hospital	Cheng-Yuan Peng	06
	Kaohsiung Chang Gung Memorial Hospital	Chao-Long Chen	06
	National Taiwan University Hospital	Po-Chin Liang	06
	Taipei Veterans General Hospital	Rhuen-Chuan Lee	06
Thailand	Ramathibodi Hospital, Bangkok	Thiravud Khuaprema	02
Vietnam	National Cancer Institute, Hanoi	Ba-Duc Nguyen	02
	Cho Ray Hospital	Hoa-Hai Hoang,	02, 04
		Van-Viet Truong	02

# 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

<b>AHCC01:</b>	<b>NCT00003424.</b> Randomised Trial of Tamoxifen Versus Placebo for the Treatment of Inoperable Hepatocellular Carcinoma.	1997 – 2000 <i>NMRC</i>
<b>AHCC02:</b>	<b>NCT00041275.</b> Randomized Double Blind Trial Of Megestrol Acetate Versus Placebo For The Treatment Of Inoperable Hepatocellular Carcinoma.	2002 – 2007 <i>NCC,</i> <i>SingHealth</i>
<b>AHCC03:</b>	<b>NCT00027768.</b> Randomised Trial of Adjuvant Hepatic Intra-Arterial Iodine-131-Lipiodol Following Curative Resection of Hepatocellular Carcinoma	2002 – 2008 <i>NMRC</i>
<b>AHCC04:</b>	<b>NCT00247260.</b> Phase II dose escalation trial of intra-tumoral Brachysil® in inoperable HCC	2005 – 2006 <i>PSiOncology</i>
<b>AHCC05:</b>	<b>NCT00712790.</b> Phase I/II Study of SIR-Spheres Plus Sorafenib as First Line Treatment in Patients With Non-Resectable Primary Hepatocellular Carcinoma	2008 – 2009 <i>NMRC, Bayer,</i> <i>Sirtex</i>
<b>AHCC06:</b>	<b>NCT01135056.</b> Phase III Multi-Centre Open-Label Randomized Controlled Trial of Selective Internal Radiation Therapy (SIRT) Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (SIRveNIB)	2010 – 2015 <i>NMRC, Sirtex</i>

# Asia-Pacific Hepatocellular Carcinoma Trials Group 6<sup>th</sup> General Meeting



31<sup>st</sup> October 2014



SGH – Surgery

# Paradigm Shift: Conducting Clinical Trials in Asia-Pacific *Over the last 16 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

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# 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*



# The Advantages of 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*
- Opportunities to detect 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**

# Continual Dialogue, Frequent one-to-one meetings and Open Channels of Communications are vital

**AHCC06 2<sup>nd</sup> IM 16/11/12**

**AHCC06 3<sup>rd</sup> IM 10/07/14**



**Challenges are very different in the different countries –  
one size does not fit all**

# 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



Phillipines

Korea



Vietnam



Myanmar



# Challenges

- **External Challenges**
  - Financial, logistical, training, technical,
  - Can be *overcome* with innovation, determination, hard work
  - *Clarity of Vision, Consistency of Purpose*
- **Internal Challenges**
  - Internal challenges are very difficult to overcome
  - Administrative, philosophical, structural, cultural, fiscal
  - Only *senior leadership* aligned with the mission can resolve them

# 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

# AHCC06 : SIRT versus Sorafenib in patients with locally advanced HCC (**SirveNIB**)

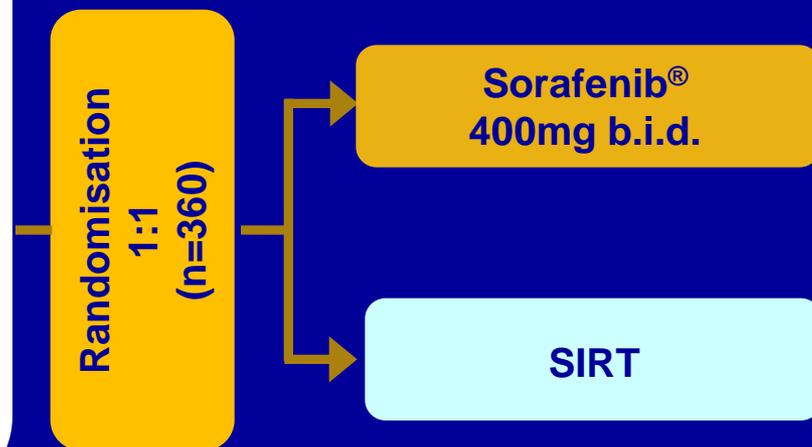
Asia-Pacific, Phase III, open-label, randomised-controlled study

## Eligibility criteria

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

## Exclusion criteria

- Distant metastases
- Complete main portal vein thrombosis



## Endpoints

### Primary

- OS

### Secondary

- TTP
- QoL
- **Downstaging to curative therapies**

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

Eligible: *Previous surgery, RFA, TACE*

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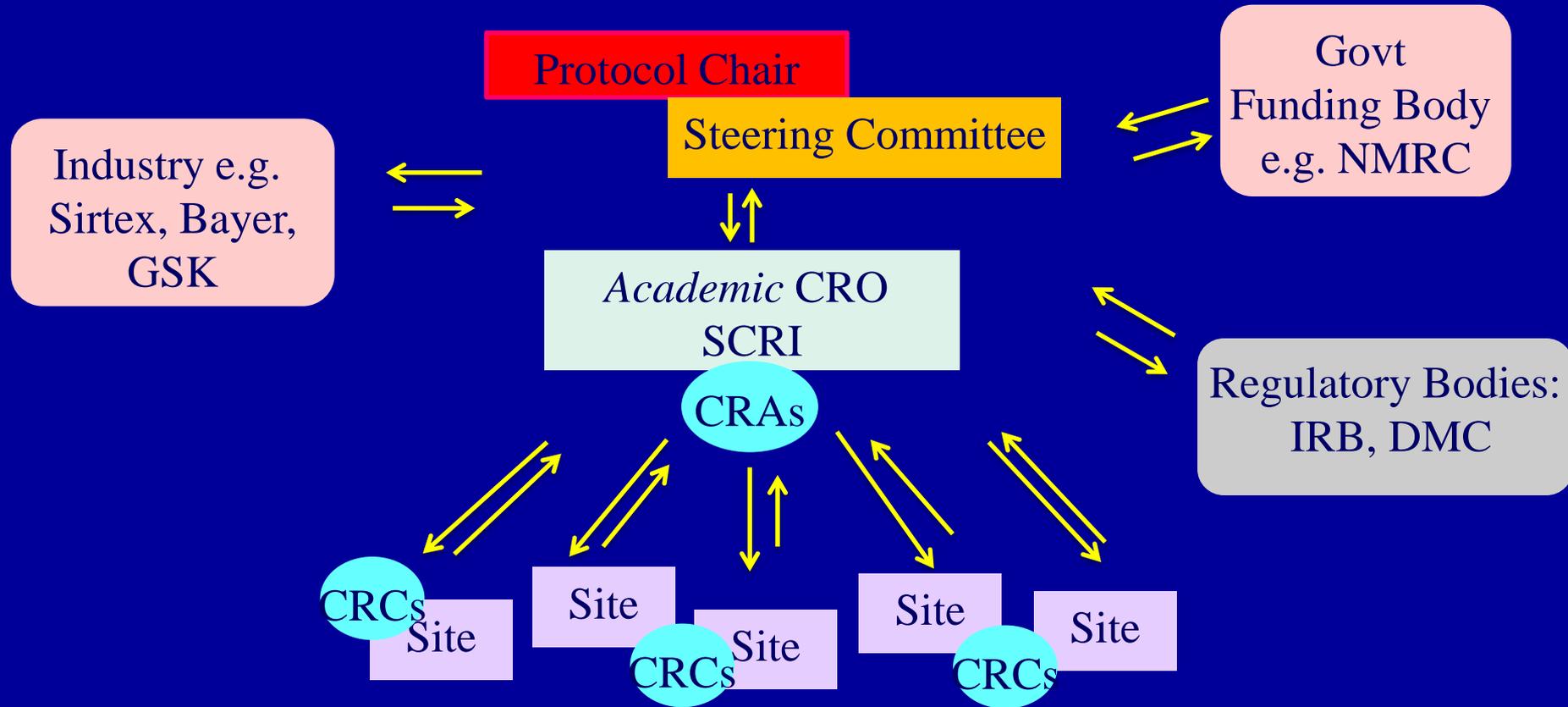
# Structure of the AHCC

## 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

# General Meetings

## 5<sup>th</sup> General Meeting



## 6<sup>th</sup> General Meeting



While trials are initiated by individual PIs they are built from the ground up. Input from sites are crucial important to ensure buy-in

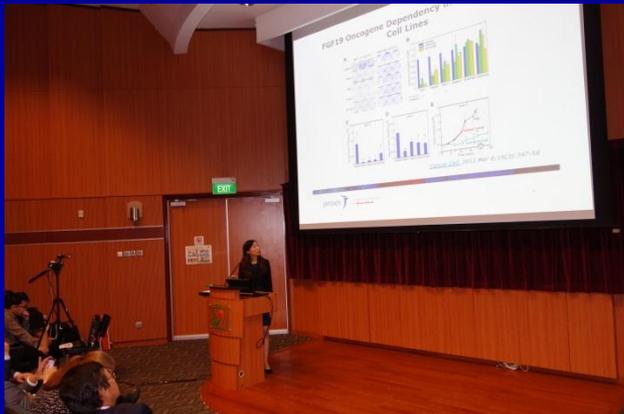
# Developing a collaborative platform

- The AHCC has reached a stage in its development where it is meaningful to develop a collaborative platform with industrial partners.
- To realize this strategic initiative, a collaborative partnership has been 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

## 31<sup>st</sup> Oct 2014



Funded through a collaborative platform with industry  
to become a regular 6-monthly event

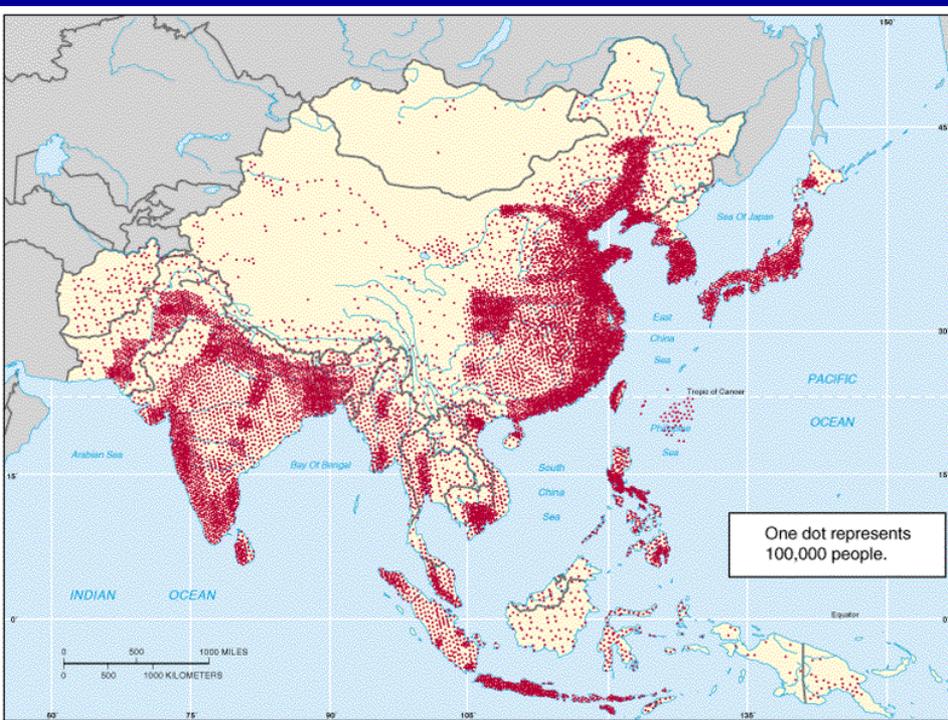


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National Cancer  
Centre Singapore  
SingHealth

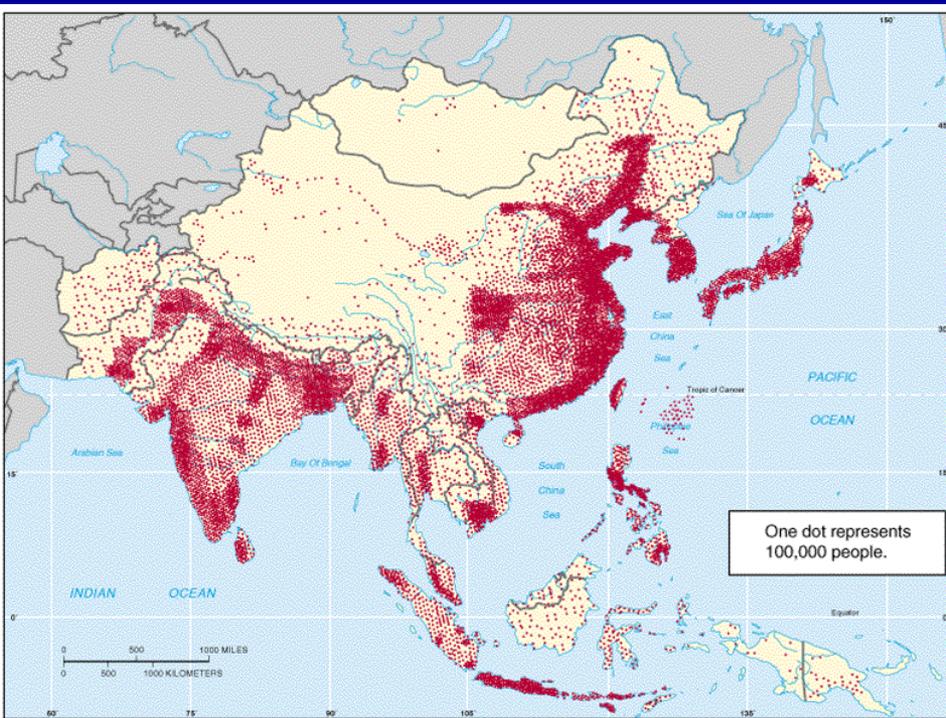
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- Thought Leadership
- Organization
- Large population



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3	Indonesia	244,769,000	29	Israel	7,695,000
4	Pakistan	179,951,000	30	Hong Kong (China) <sup>[4]</sup>	7,196,000
5	Bangladesh	152,409,000	31	Tajikistan	7,079,000
6	Japan	126,435,000	32	Jordan	6,457,000
7	Philippines	96,471,000	33	Laos	6,374,000
8	Vietnam	89,730,000	34	Kyrgyzstan	5,448,000
9	Iran	75,612,000	35	Singapore	5,256,000
10	Turkey	74,509,000	36	Turkmenistan	5,170,000
11	Thailand	69,892,000	37	Georgia	4,304,000
12	Myanmar	48,724,000	38	Lebanon	4,292,000
13	South Korea	48,588,000	39	Palestinian territories <sup>[5]</sup>	4,271,000
14	Iraq	33,703,000	40	Armenia	3,109,000
15	Afghanistan	33,397,000	41	Oman	2,904,000
16	Nepal	31,011,000	42	Kuwait	2,892,000
17	Malaysia	29,322,000	43	Mongolia	2,844,000
18	Saudi Arabia	28,705,000	44	Qatar	1,939,000
19	Uzbekistan	28,077,000	45	Bahrain	1,359,000
20	Yemen	25,569,000	46	Timor-Leste	1,187,000
21	North Korea	24,554,000	47	Cyprus	1,129,000
22	Taiwan	—	48	Bhutan	750,000
23	Sri Lanka	21,224,000	49	Macau (China) <sup>[6]</sup>	567,000
24	Syria	21,118,000	50	Brunei	413,000
25	Kazakhstan	16,381,000	51	Maldives	324,000
26	Cambodia	14,478,000		<b>Total</b>	<b>4,227,067,000</b>

\*United Nations Population Division estimates for 1 Jul 2012

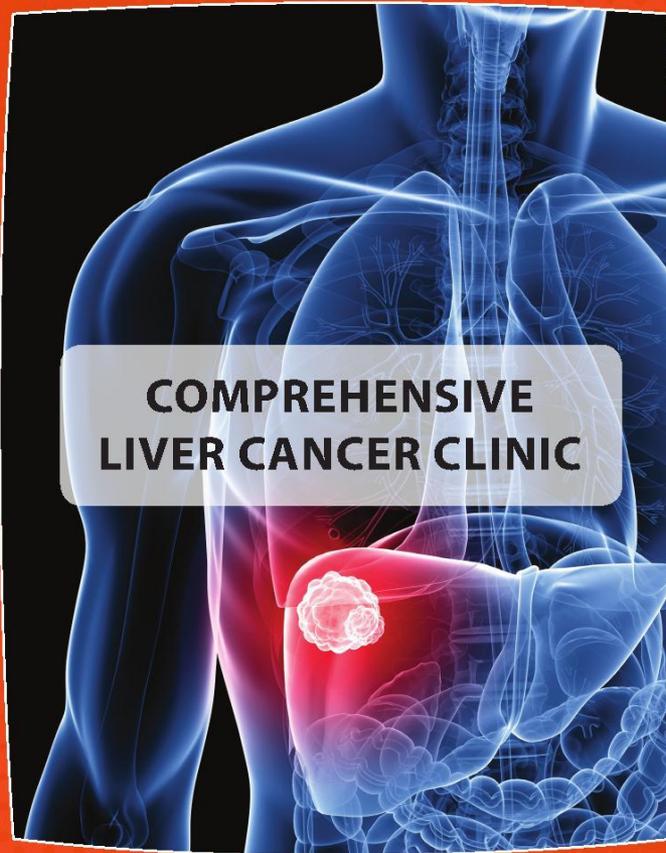
# It is a Virtuous Cycle

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

**But unless we can resolve internal  
structural and philosophical hurdles**

**We will be downsized to LIGHT WEIGHT  
– which is what we really are**





*Thank  
You!*

**Acknowledgement:** Rachel  
Choi BSc (Hons) for  
assistance with the slides