

Building an Investigator-led Clinical Research Network in Hepatocellular Carcinoma *an 18-year history*

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SCRI 2nd Annual Clinical Research Symposium 2016

1st September 2016 Raffles City



SGH – Surgery

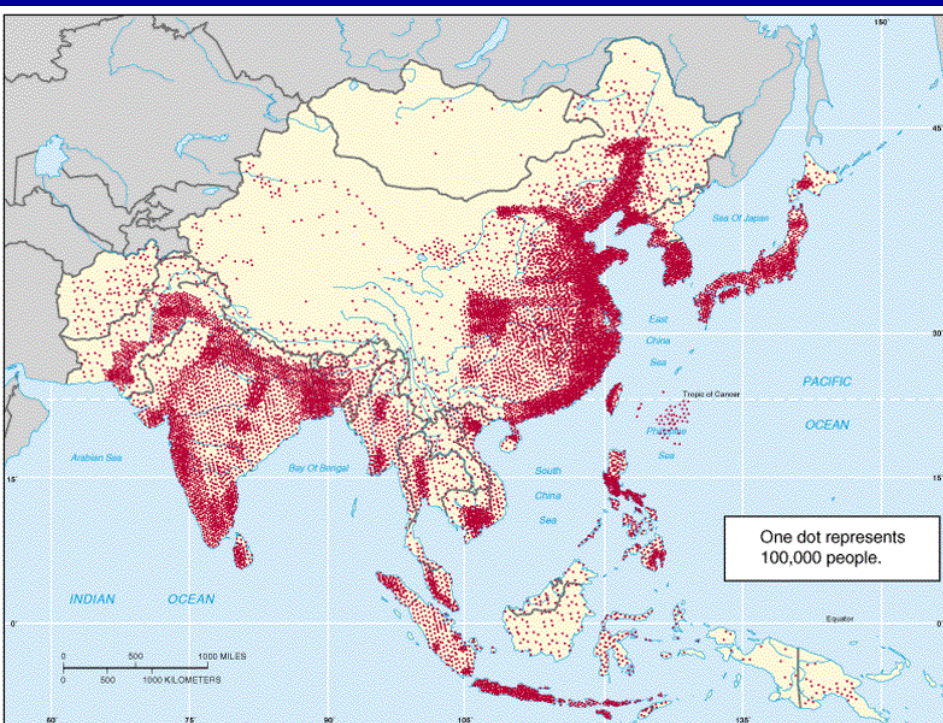


National Cancer
Centre Singapore
SingHealth

Why an Investigator-lead Asia-Pacific Research Network/Trials Group?



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
4	Pakistan	179,951,000	30	Hong Kong (China) ^[4]	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 ^[5]	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) ^[6]	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		Total	4,227,067,000

*United Nations Population Division estimates for 1 Jul 2012

If we are so small

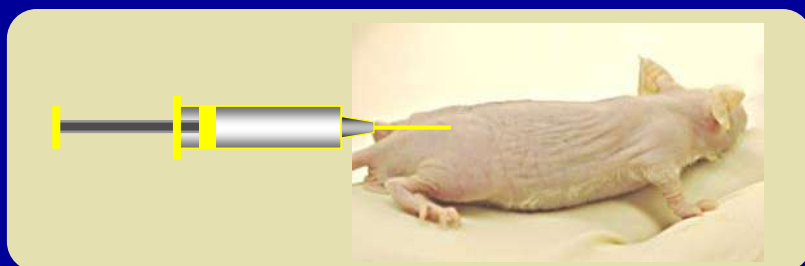
Why should we aspire to be thought- leaders in Bio-Medicine?

- 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*

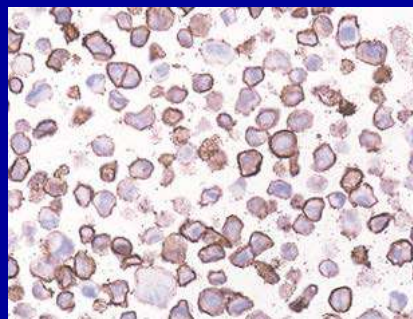


Biomedical Research:

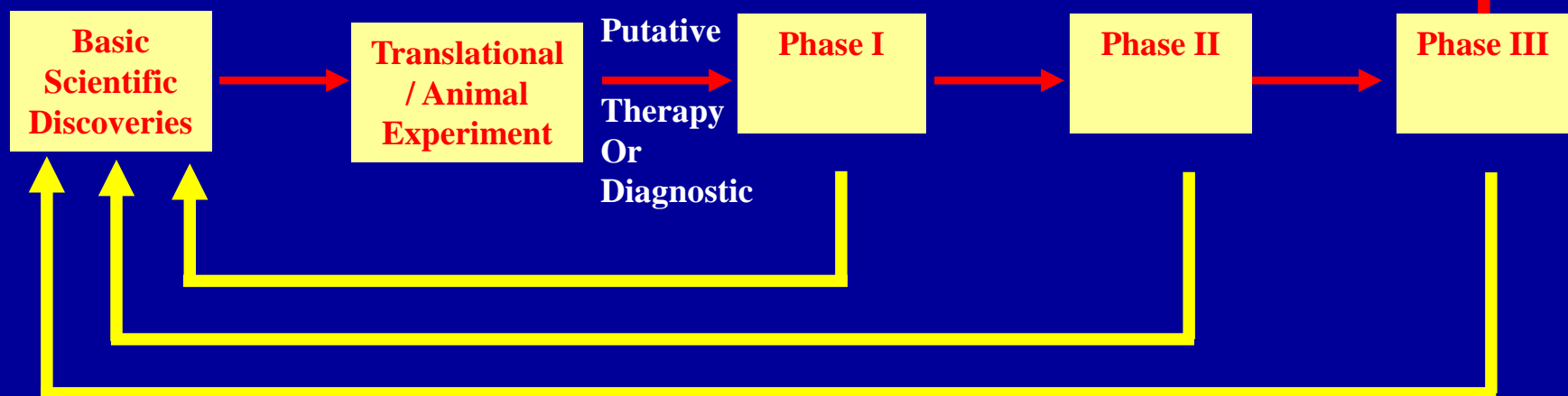
the only consistent way to achieve better outcomes in patients



14 days



Biomedical Discovery Cycle



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*

Requirements of a good prospective clinical study

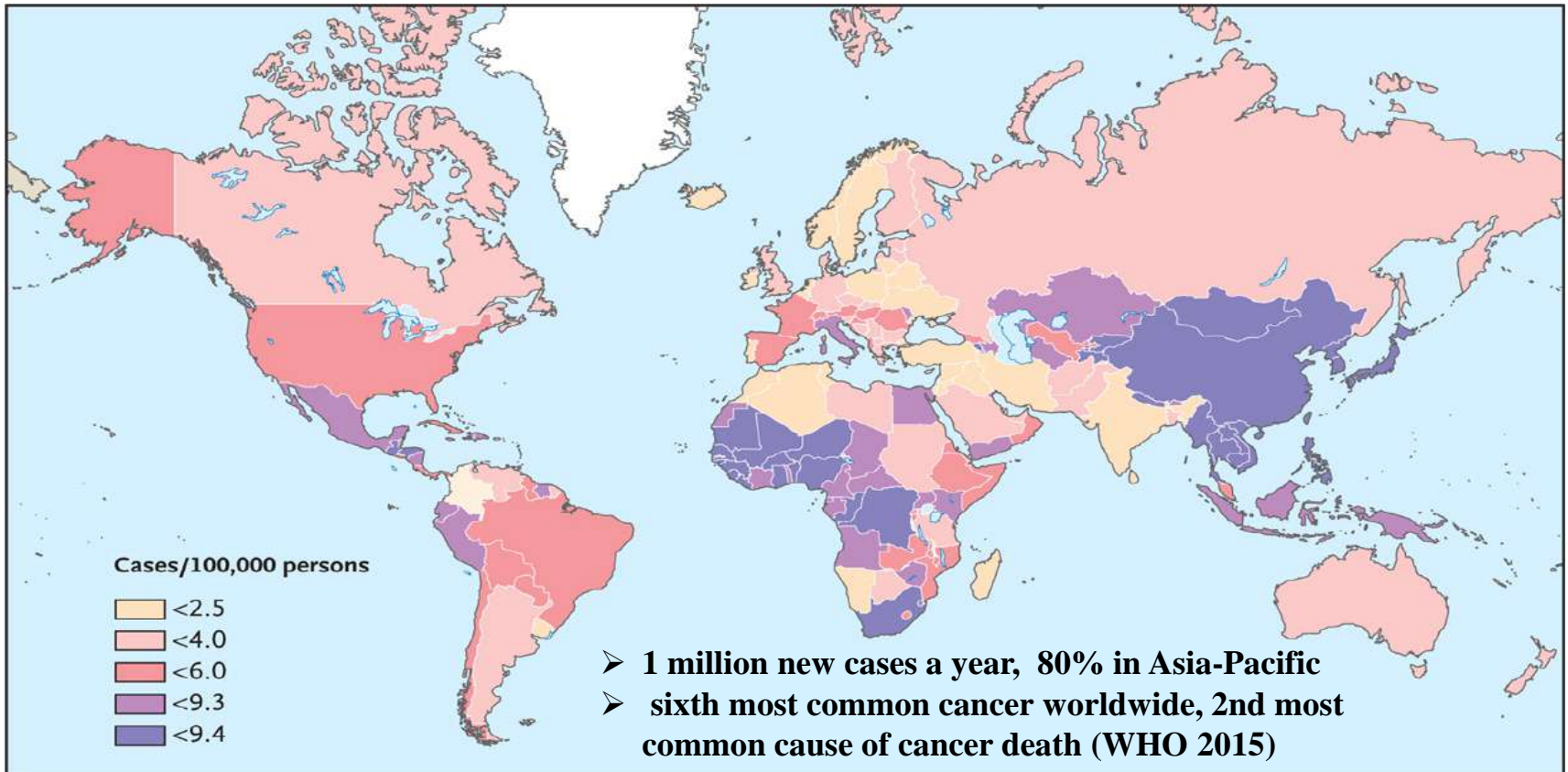
- **Thought Leadership**
 - *Addresses a pivotal clinical issue the decision of which will impact significantly on clinical practice*
 - *Good scientific rationale*
 - *Well thought out study design*
- **Organization**
 - *Good track record and excellent logistical ability to carry out a large trial*
- **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**



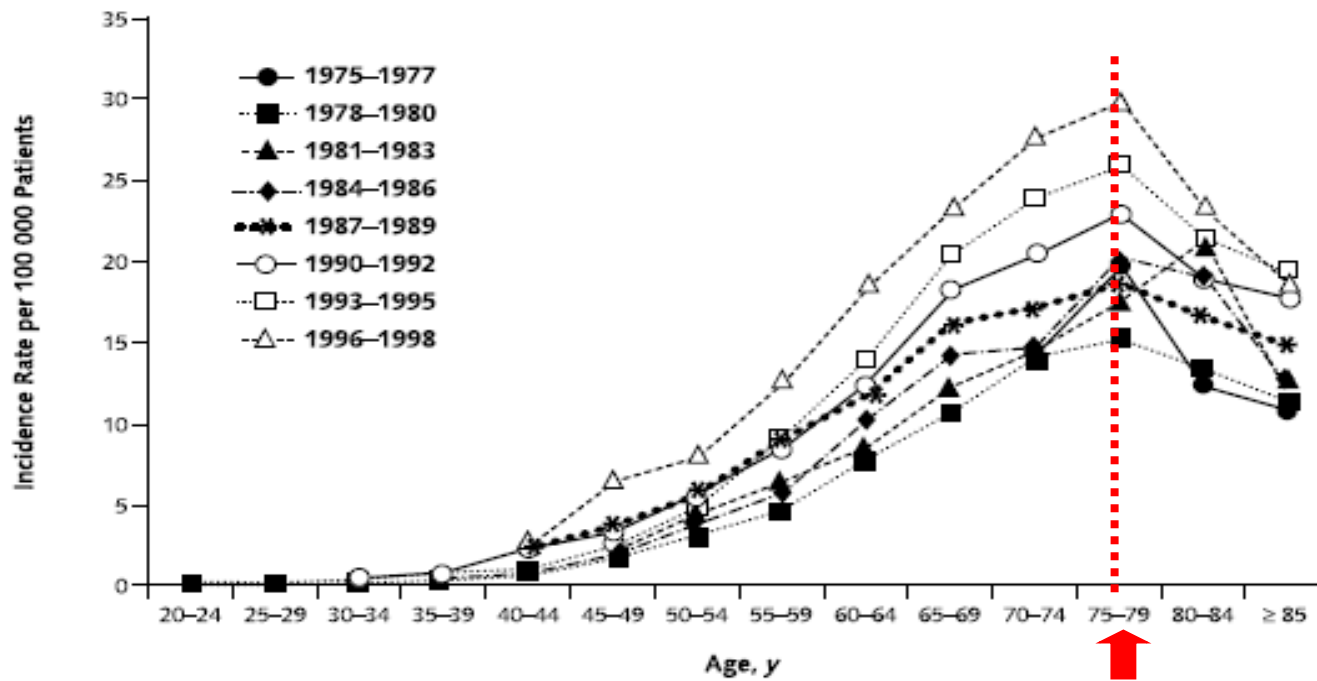
Regional Variation in the Estimated Age-Standardized Incidence Rates of Hepatocellular carcinoma.



El-Serag HB. N Engl J Med 2011;365:1118-1127.



THE NEW ENGLAND
 JOURNAL OF MEDICINE



Age-Specific HCC Incidences: USA

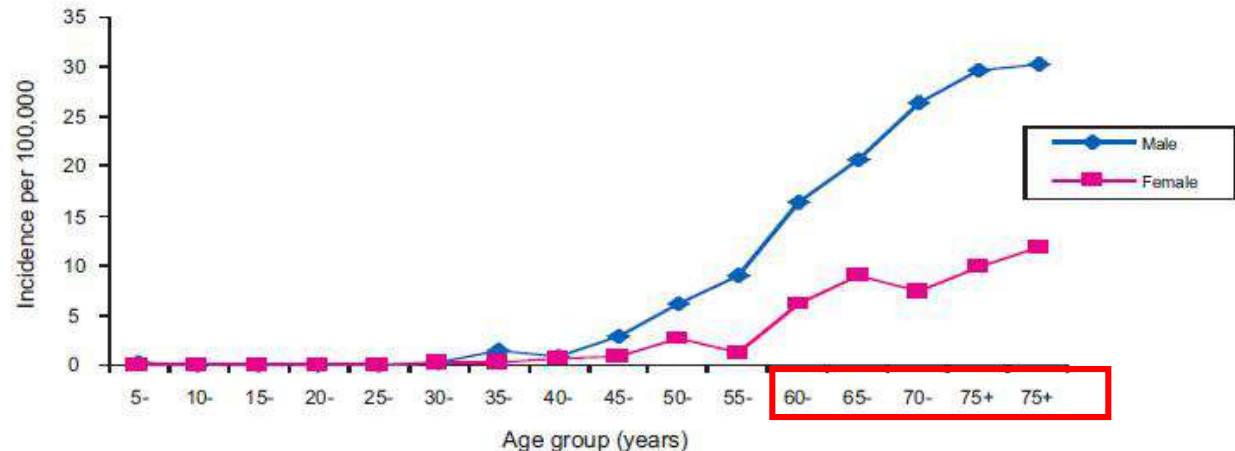
In the US, HCC incidences peak at the age of 77.

(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



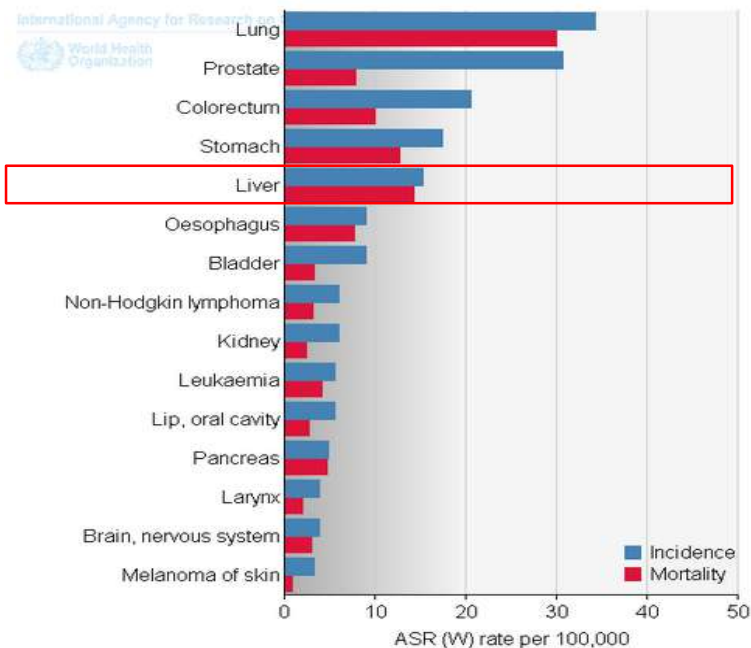
HCC: A Global Un-met Clinical Need

Mortality approximates incidence

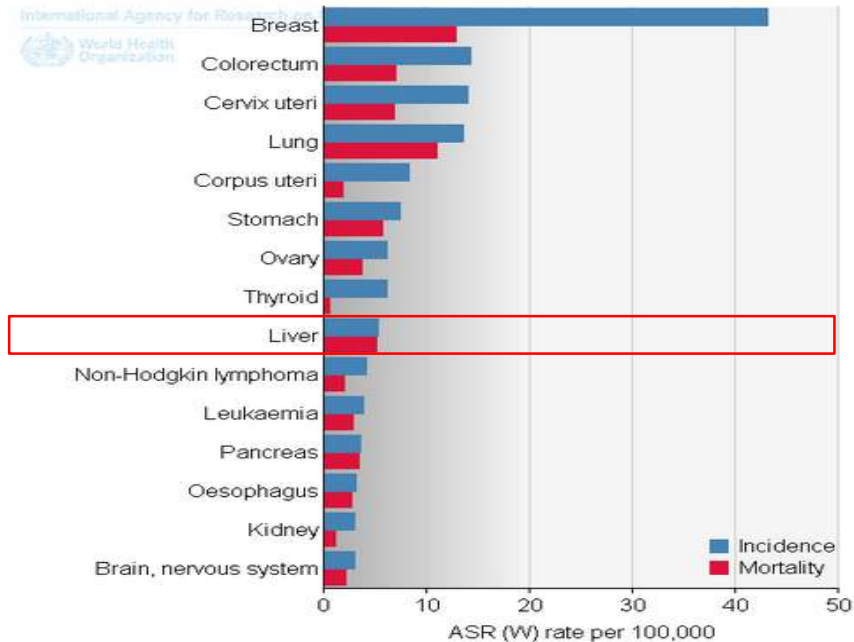
Men: 2nd cause of cancer deaths (previously 3rd)

Women: 5th cause of cancer deaths (previously 6th)

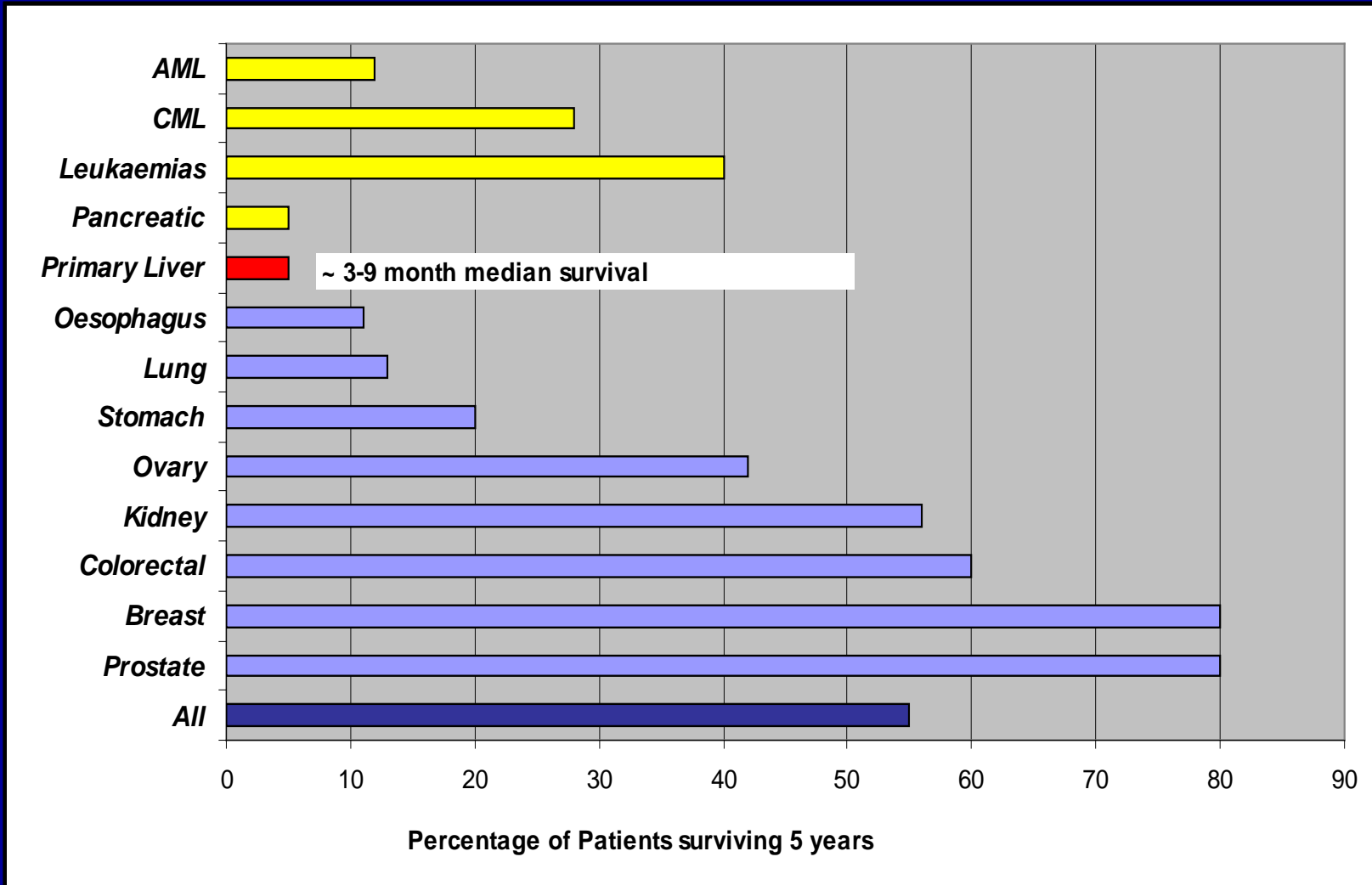
Estimated age-standardised incidence and mortality rates: men



Estimated age-standardised incidence and mortality rates: women



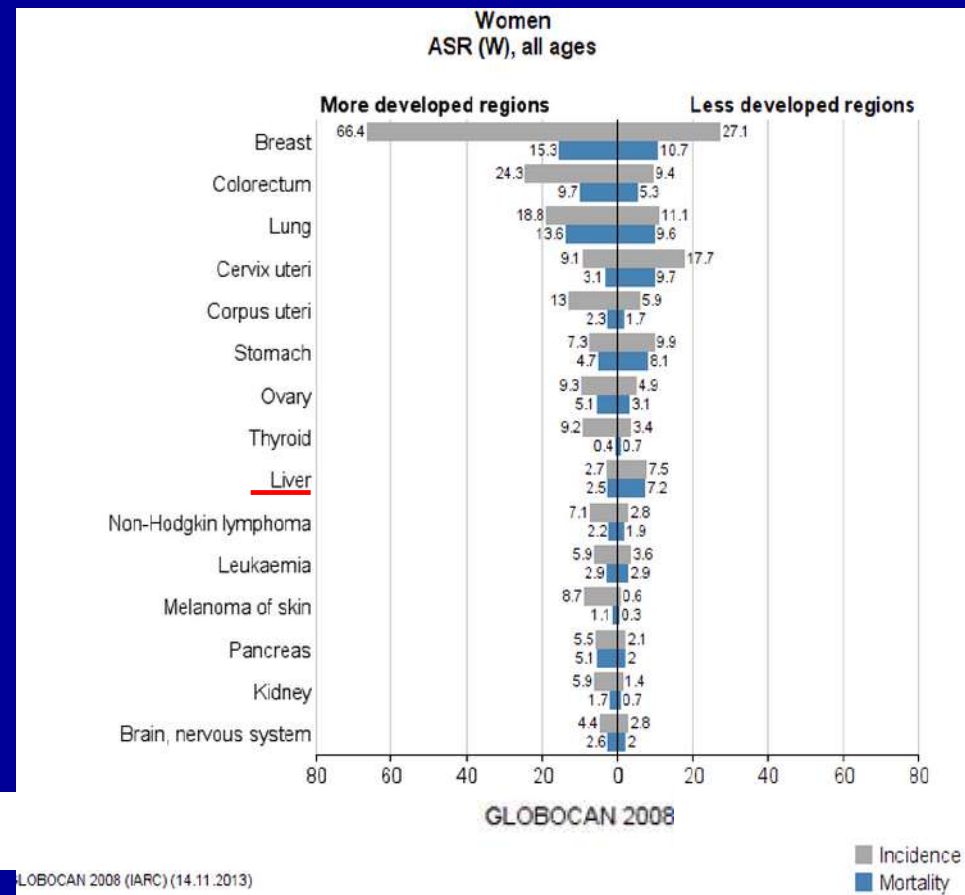
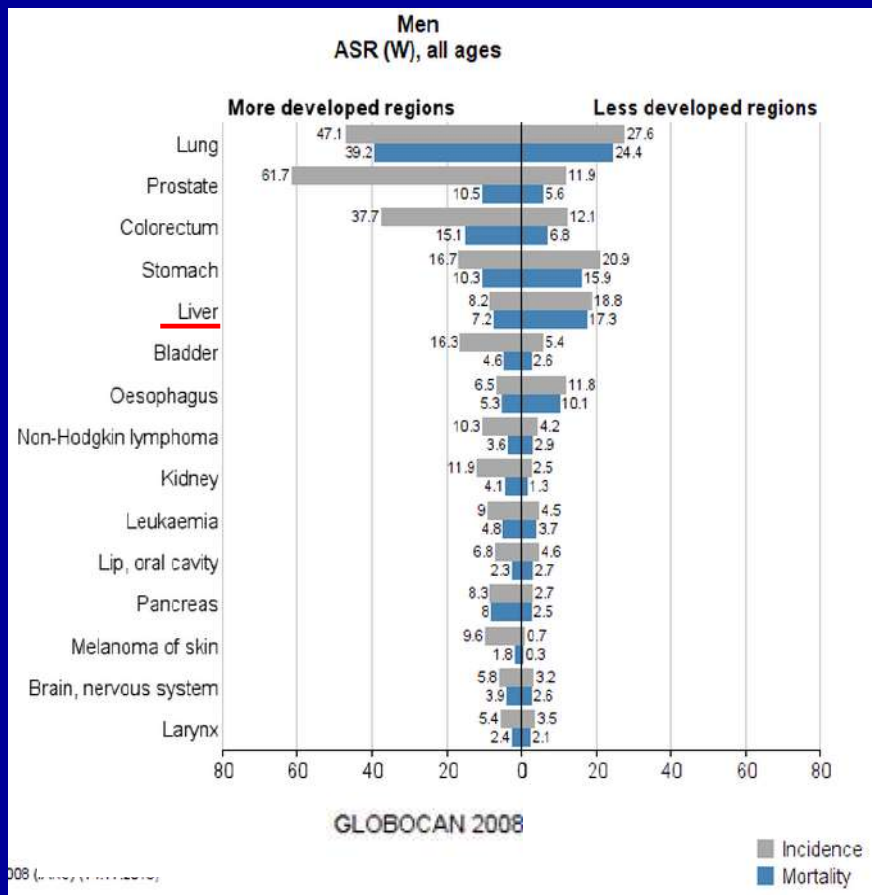
Median overall survival in HCC



Mortality worse in less develop 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**



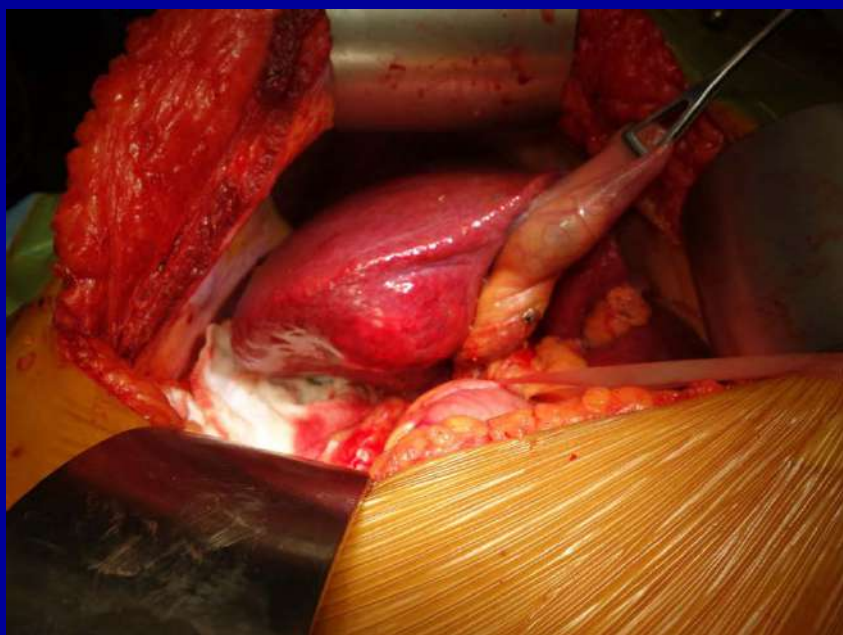
Significant Gaps in Hepatocellular Carcinoma

- 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**

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*



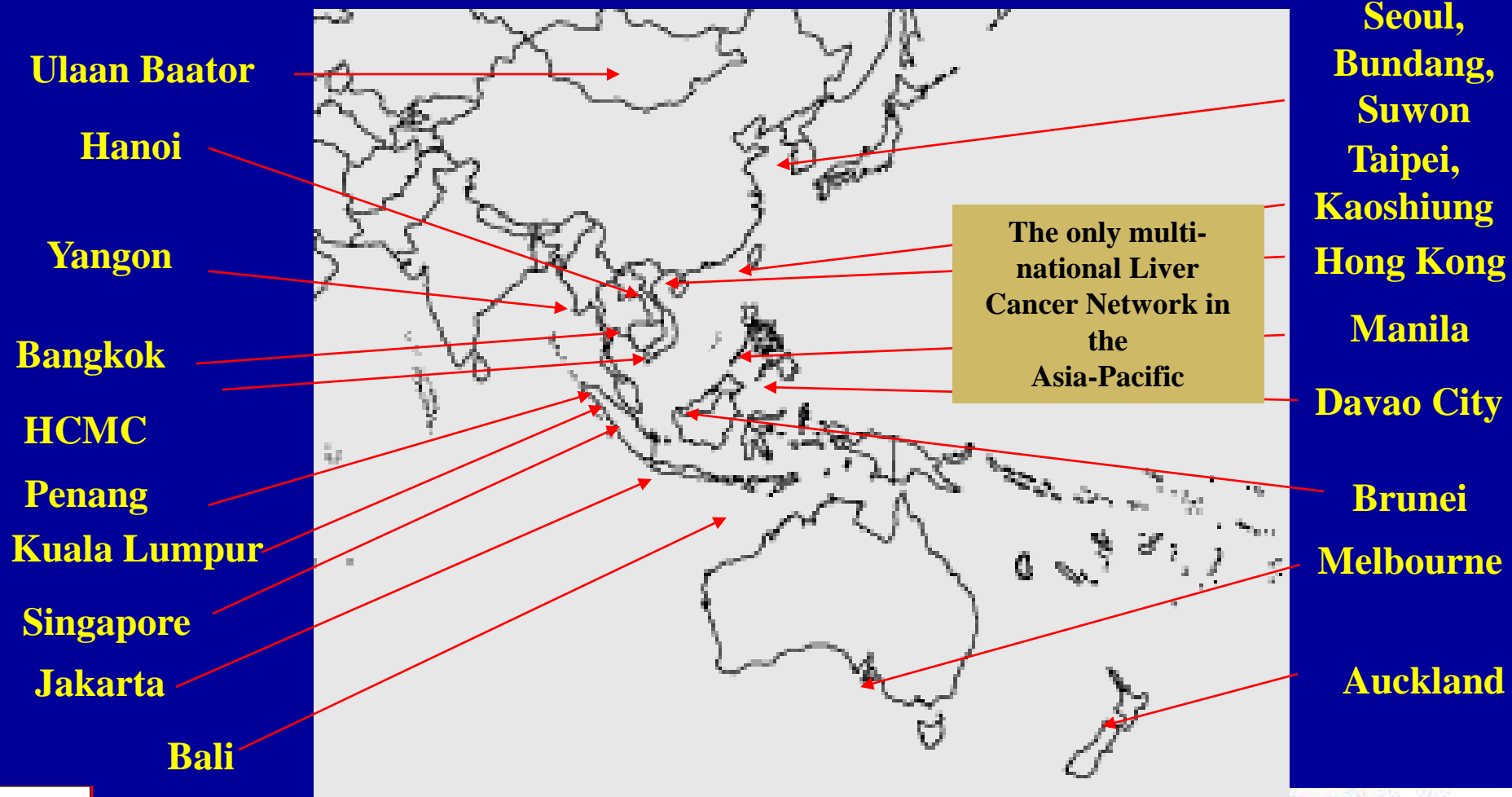
The Asia-Pacific HCC Trials Group

- **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



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 Liau	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

AHCC01:	NCT00003424. Randomised Trial of Tamoxifen Versus Placebo for the Treatment of Inoperable Hepatocellular Carcinoma.	1997 – 2000 <i>NMRC</i>
AHCC02:	NCT00041275. Randomized Double Blind Trial Of Megestrol Acetate Versus Placebo For The Treatment Of Inoperable Hepatocellular Carcinoma.	2002 – 2007 <i>NCC,</i> <i>SingHealth</i>
AHCC03:	NCT00027768. Randomised Trial of Adjuvant Hepatic Intra-Arterial Iodine-131-Lipiodol Following Curative Resection of Hepatocellular Carcinoma	2002 – 2008 <i>NMRC</i>
AHCC04:	NCT00247260. Phase II dose escalation trial of intra-tumoral Brachysil [®] in inoperable HCC	2005 – 2006 <i>PSiOncology</i>
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 <i>NMRC, Bayer,</i> <i>Sirtex</i>
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 <i>NMRC, Sirtex</i>

Challenges encountered and overcome 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*



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



Phillipines

Korea



Vietnam



Myanmar



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

AHCC06 2nd IM 16/11/12



AHCC03 3rd 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

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



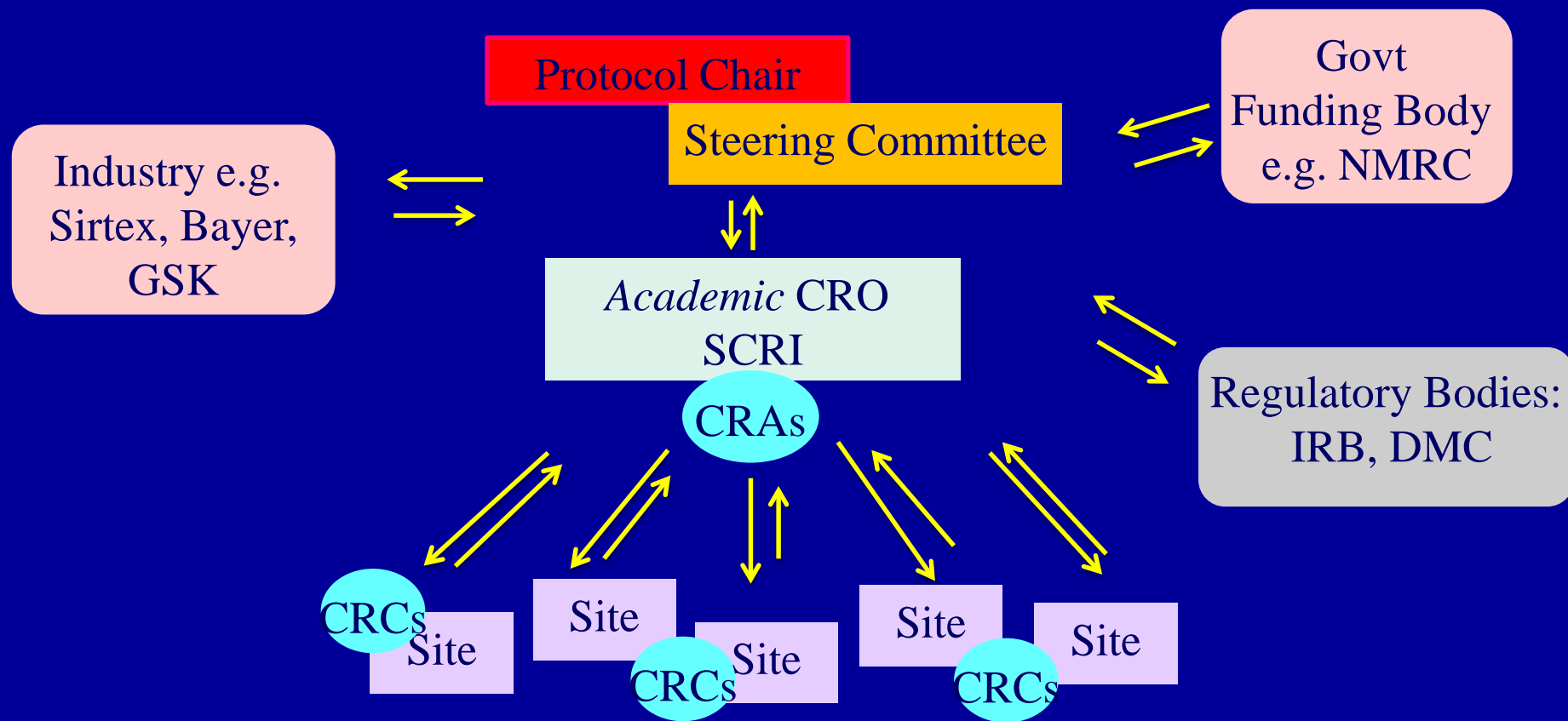
Structure of the AHCC

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

General Meetings

5th General Meeting



6th 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

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



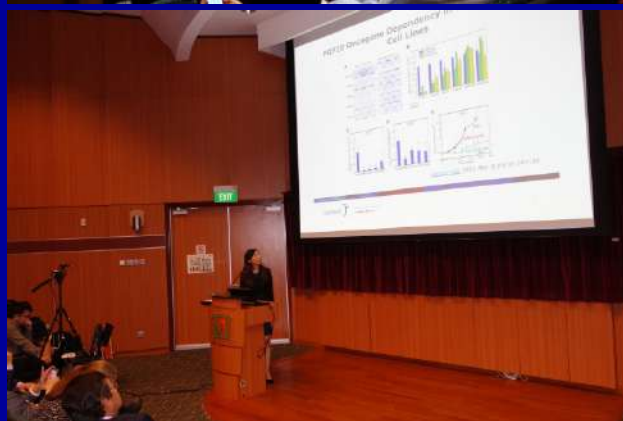
Developing a collaborative platform

- 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



SGH – Surgery



Where are we today
in the AHCC Trials Group?
18 years later



UPDATE: closure of AHCC06 trial

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

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

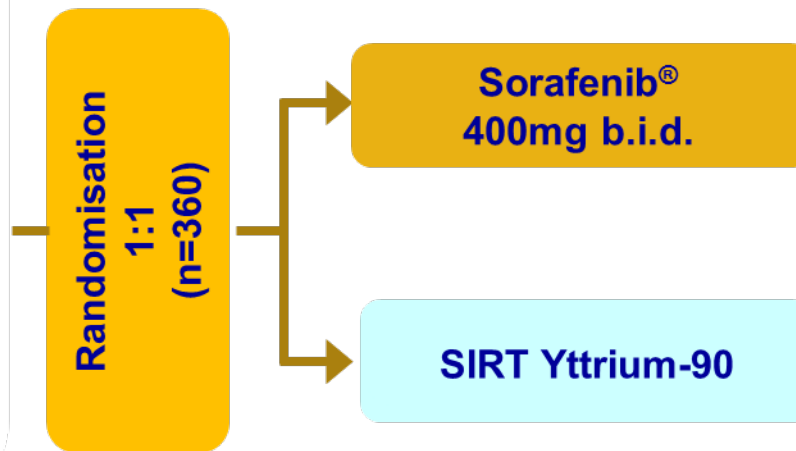
Closed on 25th May 2016

Eligibility criteria

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

Exclusion criteria

- Distant metastases
- Complete main portal vein thrombosis



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*

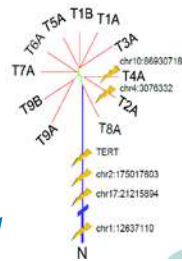
UPDATE: investigator meeting AHCC07

The Planet Study

PRECISION MEDICINE IN LIVER CANCER ACROSS AN ASIAN PACIFIC NETWORK

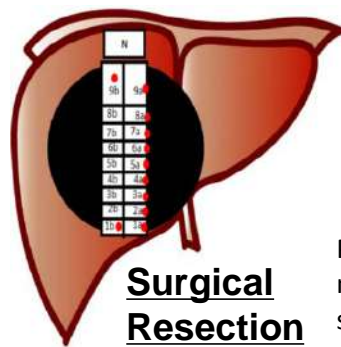
NMRC TCR Grant awarded April 2016

Tumor genomics and heterogeneity



Clinical Trajectory and Translational Clinical Trial

Adjunct Adjuvant Therapy Trial

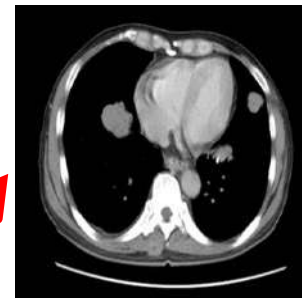


Surgical Resection

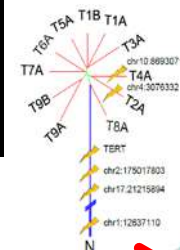
100 patients
5 Asia-Pac centers

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

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

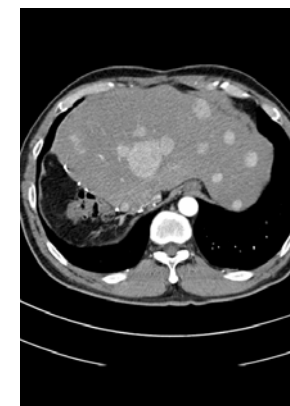
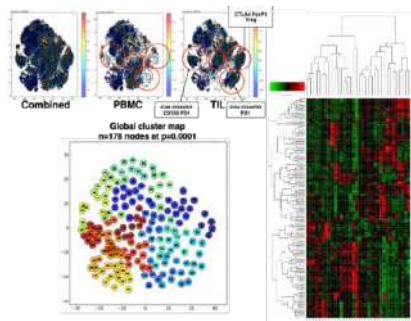


Recurrence
Biopsy or resection tissue samples, cfDNA, CTC



Therapeutics selected on the basis of discoveries in this study

Translational Immunomics



Asia-Pacific HCC Trials Group



ancer igapore

PATIENTS. AT THE HEART OF ALL WE DO.

Program Overview

Multi-national Study Sites:

NUHS
(KK Madhavan)

SingHealth
(Brian Goh)

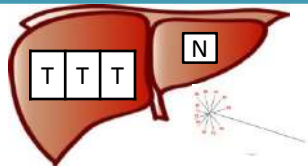
National Cancer Center, Bangkok
(Rawisak)

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

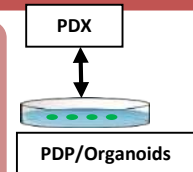
Function and mechanisms

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**

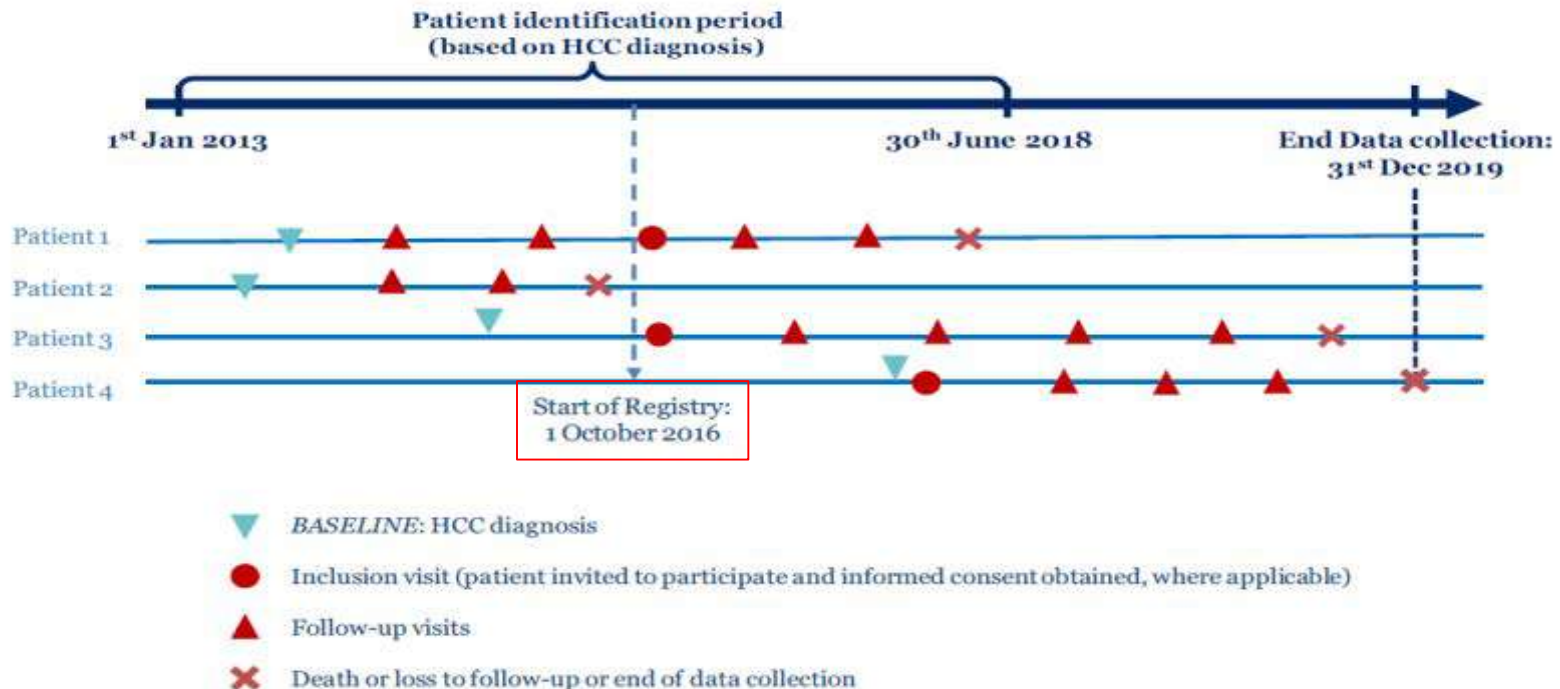
Investigator Meeting 2016: AHCC07: The PLANET Study



UPDATE: investigator meeting AHCC08 2016

The Asia-Pacific Hepatocellular Carcinoma Registry – Phase 1

- **Study Design** : Multi-centre, longitudinal cohort study
- **Sample Size** : **2000 – 2500** (**Retrospective** vs **Prospective** Cases = **30 : 70**)
- **Patient HCC Diagnosis Period** : 1st Jan 2013 - 30th Jun 2018 (Phase 1)
- **Start of Registry** : 1st 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

Thailand

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

Singapore

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

Hong Kong

- Queen Mary Hospital

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

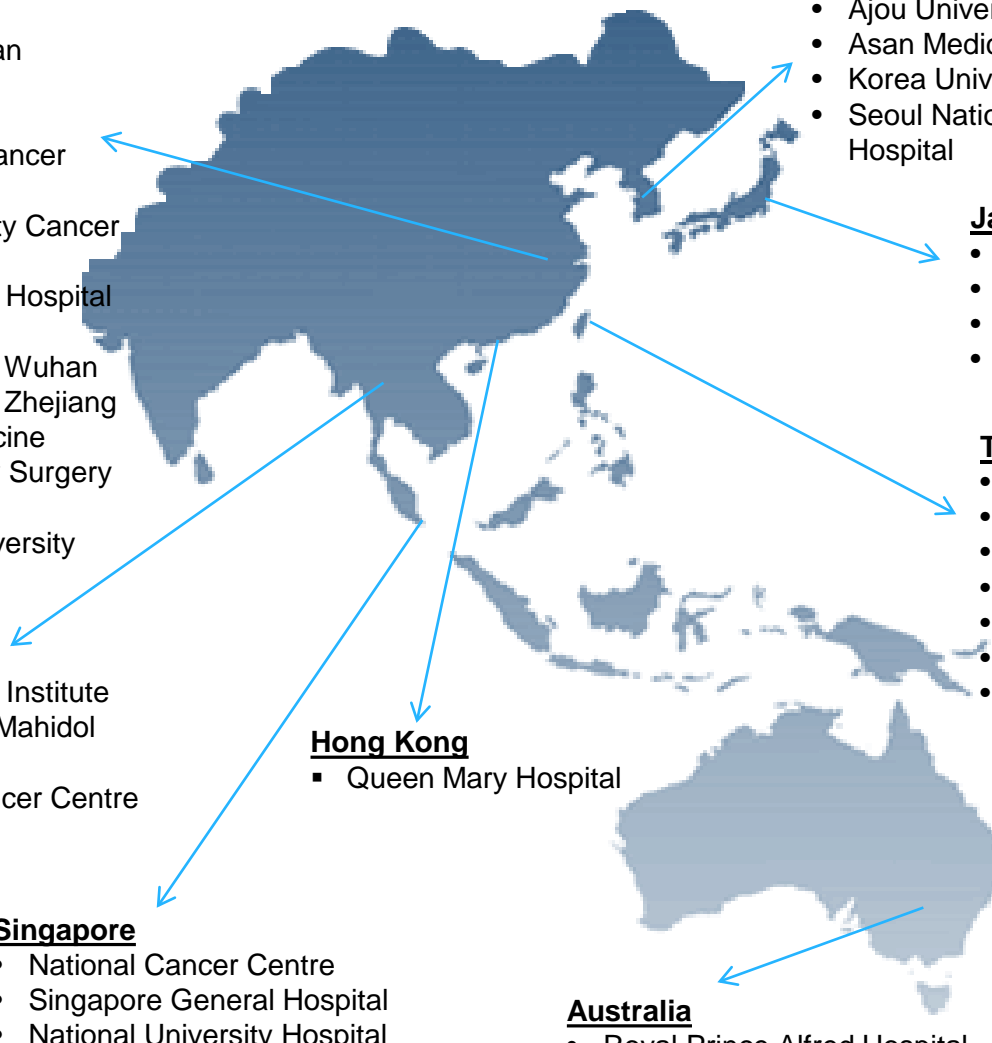
- Chang Gung Memorial Hospital
- National Taiwan University Hospital
- Taipei Veterans General Hospital
- Chang Gung Memorial Hospital – LK
- Chang Gung Memorial Hospital – KS
- China Medical University Hospital
- National Cheng Kung University Hospital

New Zealand

- Auckland City Hospital

Australia

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



Investigator Meeting:

AHCC08: Asia-Pacific HCC Registry

Now includes sites from China and Japan



AHCC General Meetings

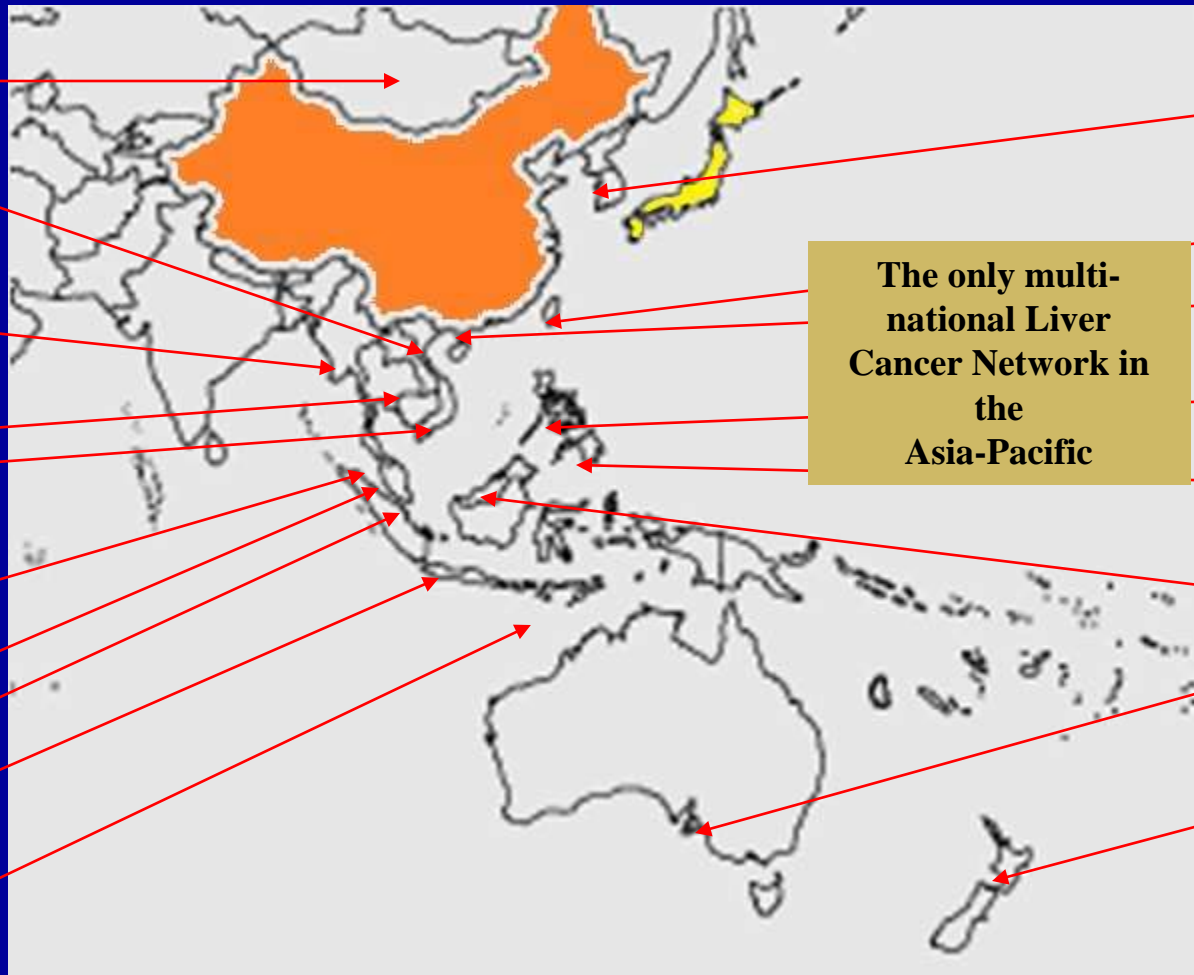
9th General Meeting

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

Seoul,
Bundang,
Suwon

Taipei,
Kaoshiung

Hong Kong

Manila

Davao City

Brunei

Melbourne

Auckland

The only multi-national Liver Cancer Network in the Asia-Pacific

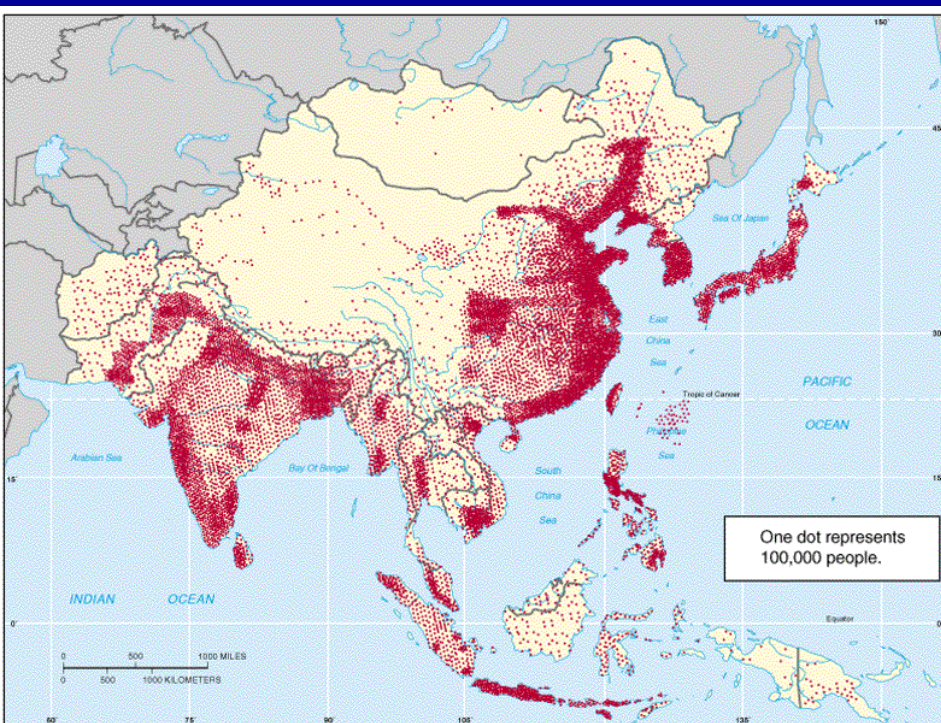


AHCC Trials Group 2016

Now includes members from China and Japan



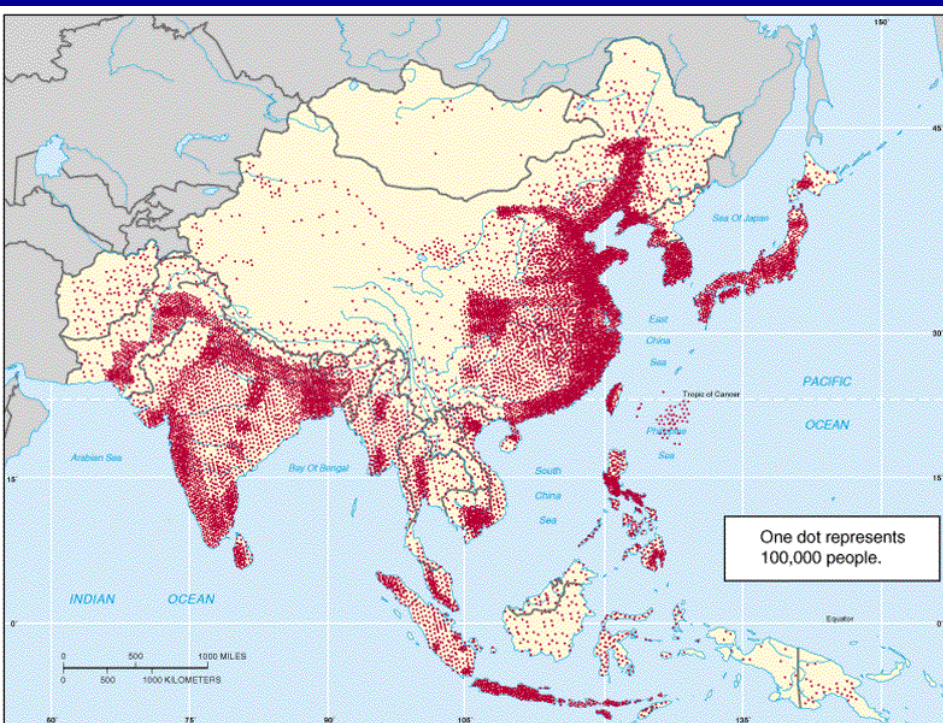
It is possible to build multi-center Research Networks



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
4	Pakistan	179,951,000	30	Hong Kong (China) ^[4]	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 ^[5]	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) ^[6]	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		Total	4,227,067,000

*United Nations Population Division estimates for 1 Jul 2012

- Thought Leadership
- Organization
- Large population



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*United Nations Population Division estimates for 1 Jul 2012

It is a Virtuous Cycle

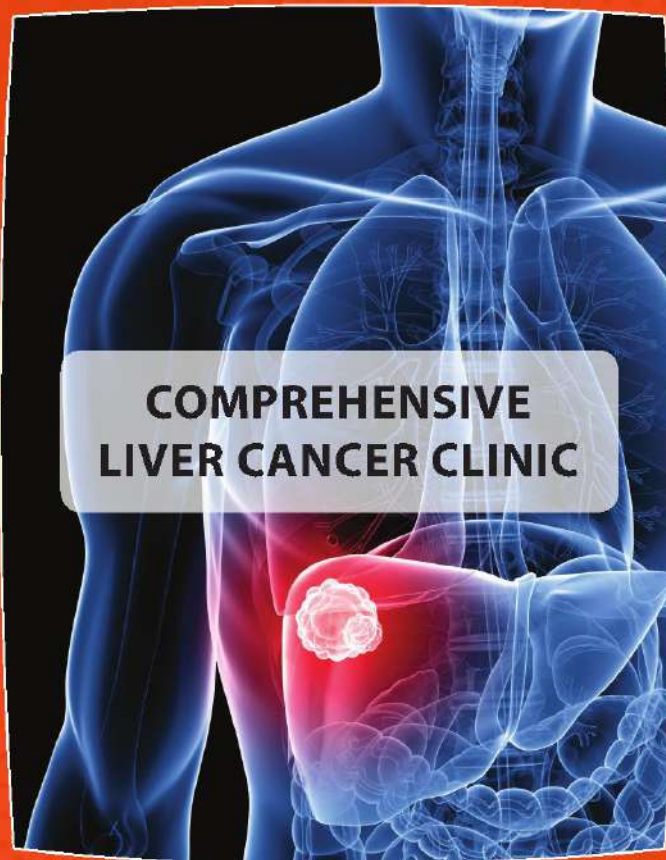
Phase III trials are long and tough battles.
*I would like to thank all our participating PIs
who believe in our science and our vision of
what is possible and trust that we can do this*
And to the numerous others who have tried to
made this easier



.....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



SGH – Surgery



AHCC General Meetings

8th General Meeting

29th Jan 2016, The Academia, SingHealth

