Ongoing Clinical Trials in Hepatocellular Carcinoma

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APASL  Single Topic Conference on HCC
23rd Nov 2013, Cebu
HCC is a very Heterogeneous Disease

Table 1. Associations Between Transcriptomic Groups and Clinical, Pathological, and Genetic Variables

(Boyault, 2007)

Hierarchical clustering analysis of 6,712 probe sets

High level of association genetic alterations and clinical factors

SGH – Surgery
### Association analysis between clinical characteristics and genotype classification – European versus Asian patients

<table>
<thead>
<tr>
<th>Comparison</th>
<th>AFP &gt;100 IU/ml (n=63)</th>
<th>Gender (n=68)</th>
<th>Age &lt;60 (n=68)</th>
<th>Satellite Tumor (n=66)</th>
<th>HBV+ve (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 vs non-G1</td>
<td><strong>0.0009</strong>&lt;sup&gt;a&lt;/sup&gt; &lt;10&lt;sup&gt;-4&lt;/sup&gt;</td>
<td><strong>0.049</strong>&lt;sup&gt;b&lt;/sup&gt; &lt;10&lt;sup&gt;-2&lt;/sup&gt;</td>
<td>0.326</td>
<td>0.673</td>
<td>1</td>
</tr>
<tr>
<td>G2 vs non-G2</td>
<td>0.035</td>
<td>0.689</td>
<td>0.569</td>
<td>1</td>
<td>0.766 &lt;10&lt;sup&gt;-2&lt;/sup&gt; high HBV</td>
</tr>
<tr>
<td>G3 vs non-G3</td>
<td>0.329</td>
<td>0.678</td>
<td>0.203</td>
<td>0.679</td>
<td><strong>0.010</strong></td>
</tr>
<tr>
<td>G4 vs non-G4</td>
<td>0.207</td>
<td>0.102</td>
<td>0.573</td>
<td>1</td>
<td>0.561</td>
</tr>
<tr>
<td>G5 vs non-G5</td>
<td><strong>0.008</strong></td>
<td>1</td>
<td>0.089</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>G6 vs non-G6</td>
<td>0.637</td>
<td>0.479</td>
<td>0.117</td>
<td><strong>0.561</strong> &lt;10&lt;sup&gt;-2&lt;/sup&gt;</td>
<td>0.114</td>
</tr>
<tr>
<td>G1G2 vs non-G1G2</td>
<td>&lt;0.0001</td>
<td>0.076</td>
<td>0.138 &lt;10&lt;sup&gt;-2&lt;/sup&gt;</td>
<td>0.745</td>
<td>0.619</td>
</tr>
</tbody>
</table>

<sup>a</sup> Fisher’s exact test: *p*-values significant by Holm-Bonferroni multiple comparison test (adjusted to control family-wise error rate at α ≤0.05) in bold red type; *p*-values significant on a per test basis (*p* ≤ 0.05) in bold black type.

<sup>b</sup> Significant *p*-value (per test basis, *p* ≤ 0.05) in Boyault et al. indicated by green shading.

Zhu, Allen et al unpublished data
SHARP and Asia-Pacific Trials: Comparison of Results
(inoperable HCC, Child-Pugh A ECOG 0 -1)

|                               | SHARP                     | Asia-Pacific              |
|                               | Sorafenib | Placebo | Sorafenib | Placebo |
| Median overall survival (mo)  | 10.7       | 7.9     | 6.2        | 4.1     |
|                               | HR 0.69, p < 0.001        |                      | HR 0.68, p 0.14 |        |
|                               | 44% increase             |                      | 47% increase   |        |
| Median time to progression (mo) | 5.5       | 2.8     | 2.8        | 1.4     |
|                               | HR 0.58, p < 0.001        |                      | HR 0.57, p 0.0005 |    |
|                               | 73% increase             |                      | 74% increase   |        |

No differentiating biomarker

Cheng et al Lancet Oncol 2009
The Impact

The genetic diversity mandates specific identifiers for classification. It is necessary to select patients for specific targeted inhibiting therapies.

(Boyault, 2007)
The Impact

The genetic diversity mandates specific identifiers for classification. It is necessary to select patients for specific targeted inhibiting therapies.

...however treatment for HCC is frequently prescribed as if HCC were a homogenous disease...

(Boyault, 2007)
**Challenge:** Highly heterogeneous cancer with wide geographical and genetic diversity

- **Molecular Classification** of HCC through gene expression has been shown to correlate with different clinical features and prognosis there currently **NO** useful biomarkers for therapy and response.

- The absence of robustly-defined *molecular prognostic classifiers* has impacted negatively on:
  - the study of altered pathways
  - the development of targeted therapies
  - therapeutic decision making
  - patient directed therapy

(Boyault, 2007)

High level of association between genetic alterations and clinical factors
Hepatocellular Carcinoma: An Un-resolved Clinical Need

Surgery confers consistent long-term survival

But 80% are inoperable at time of diagnosis

High recurrence rates

Absence of robust therapeutic targets

Absence of robust molecular prognostic classifiers
Oncology Guidelines: HCC not amendable to resection, transplantation, RFA
Sorafenib opened the floodgates: many Phase III Trials in HCC

Molecular targeted RCT:
- with and without sorafenib

Loco-regional Therapy based RCT
- TACE-based RCT:
  - with and without sorafenib
- Yttrium-90 based RCT:
  - all phase III trials involve sorafenib
Molecular Therapy
Phase III Trials
Molecular Therapy
Phase III Trials

• Precedence of “molecular-targeted” agents over conventional cytotoxics

• Because of the:
  • molecular heterogeneity of HCC
  • and the absence of proven therapeutic targets

  – mono-therapy without predictive biomarker is unlikely offer more than modest survival benefits e.g. OS of 6.2 months versus 4.1 months in the Asia-Pacific sorafenib trial
Results of the phase III sorafenib Trial
(Western patients: SHARP) 2007
Child-Pugh A ECOG 0 -1

Overall Survival

Survival probability

Time from randomisation (months)

Sorafenib (n=299) = 0.7 months
Placebo (n=303) = 7.9 months

HR = 0.69 (95% CI: 0.55–0.87)
p<0.001

Time to Progression (independent central review)

Probability of radiologic progression

Time from randomisation (months)

Sorafenib (n=299) = 5.5 months
Placebo (n=303) = 2.8 months

HR = 0.58 (95% CI: 0.45–0.74)
p<0.001

Improvement in survival of 2.8 months

Results of the phase III sorafenib Trial (Asia-Pacific patients) 2009

Child-Pugh A ECOG 0 - 1

**Overall Survival**

<table>
<thead>
<tr>
<th>Survival probability</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nexavar</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Median: 6.5 mo (95% CI: 5.8-7.6)</td>
<td>Median: 4.2 mo (95% CI: 3.7-5.5)</td>
</tr>
<tr>
<td>HR (S/P): 0.68 (95% CI: 0.50-0.93)</td>
<td>HR (S/P): 0.68 (95% CI: 0.50-0.93)</td>
</tr>
<tr>
<td>(P = 0.014)</td>
<td>(P = 0.014)</td>
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</table>

**Time to Progression**

<table>
<thead>
<tr>
<th>Progression-free probability</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nexavar</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Median: 2.8 mo (95% CI: 2.6-3.6)</td>
<td>Median: 1.4 mo (95% CI: 1.3-1.5)</td>
</tr>
<tr>
<td>HR (S/P): 0.57 (95% CI: 0.42-0.79)</td>
<td>HR (S/P): 0.57 (95% CI: 0.42-0.79)</td>
</tr>
<tr>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
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</table>

**Patients at Risk**

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Nexavar</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nexavar 150</td>
<td>134</td>
<td>103</td>
</tr>
<tr>
<td>Placebo 76</td>
<td>62</td>
<td>41</td>
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</table>

**Improvement in survival of 2.3 months**

Cheng et al Lancet Oncol 2009
Molecular Therapy  
Phase III Trials

- Because of the:
  - molecular heterogeneity of HCC
  - and the absence of proven therapeutic targets

- **mono-therapy** without predictive biomarker is unlikely offer more than modest survival benefits e.g. OS of 6.2 months versus 4.1 months in the Asia-Pacific sorafenib trial

- **Trials of new molecular-targeted therapies on unselected HCC patients** have low chance of success
# Systemic therapy phase III trials against placebo/BSC

<table>
<thead>
<tr>
<th>Trial no</th>
<th>Sponsor</th>
<th>Size</th>
<th>Centers</th>
<th>Therapy 1</th>
<th>Therapy 2</th>
<th>PO</th>
<th>Start</th>
<th>End</th>
<th>Status</th>
<th>Protocol Chair</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00825955</td>
<td>BMS (BRISK PS)</td>
<td>414</td>
<td>116</td>
<td>Brivanib</td>
<td>Placebo</td>
<td>OS</td>
<td>Feb-09</td>
<td>May-12</td>
<td>not recruiting (Negative)</td>
<td>BMS</td>
</tr>
<tr>
<td>NCT01035229</td>
<td>Novartis (EVOLVE-1)</td>
<td>531</td>
<td>168</td>
<td>Everolimus</td>
<td>Placebo</td>
<td>OS</td>
<td>Apr-10</td>
<td>Mar-13</td>
<td>not recruiting (Negative)</td>
<td>Novartis</td>
</tr>
<tr>
<td>NCT01140347</td>
<td>ImClone LLC (REACH)</td>
<td>544</td>
<td>235</td>
<td>Ramucirumab DP</td>
<td>Placebo</td>
<td>OS</td>
<td>Oct-10</td>
<td>Apr-13</td>
<td>Active, not recruiting</td>
<td>ImClone LLC</td>
</tr>
<tr>
<td>NCT01755767</td>
<td>Daiichi Sankyo</td>
<td>303</td>
<td>EU +US</td>
<td>Tivantinib</td>
<td>Placebo</td>
<td>OS</td>
<td>Dec-12</td>
<td>Sep-15</td>
<td>Recruiting</td>
<td>Giovanni Abbadessa</td>
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<tr>
<td>NCT00692770</td>
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<td>234</td>
<td>Sorafenib (Adjuvant)</td>
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<td>May-09</td>
<td>Dec-12</td>
<td>Active, not recruiting</td>
<td>Bayer</td>
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<tr>
<td>NCT01405573</td>
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<td>10</td>
<td>Sorafenib (Child-Pugh B)</td>
<td>BSC</td>
<td>OS</td>
<td>Jul-2011</td>
<td>Jul-13</td>
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<td>B Daniele</td>
</tr>
<tr>
<td>NCT01438450</td>
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<td>1</td>
<td>Thalidomide + Capecitabine</td>
<td>BSC</td>
<td>OS</td>
<td>Oct-07</td>
<td>Sep-14</td>
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<td>S Acharya</td>
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<tr>
<td>NCT01774344</td>
<td>Bayer</td>
<td>530</td>
<td>World</td>
<td>Regorafenib</td>
<td>Placebo</td>
<td>OS</td>
<td>May 2013</td>
<td>October 2016</td>
<td>Recruiting</td>
<td>Bayer</td>
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</table>
# Systemic therapy phase III trials against sorafenib

<table>
<thead>
<tr>
<th>Trial no</th>
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<th>Centers</th>
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<th>End</th>
<th>Status</th>
<th>Protocol Chair</th>
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<tr>
<td>NCT00699374</td>
<td>Pfizer</td>
<td>1075</td>
<td>World</td>
<td>Sunitinib</td>
<td>Sorafenib</td>
<td>OS</td>
<td>Jul-08</td>
<td>Dec-11</td>
<td>(2010) Terminated</td>
<td>Cheng AL</td>
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<tr>
<td>NCT00901901</td>
<td>Bayer (SEARCH)</td>
<td>731</td>
<td>163</td>
<td>Sorafenib + Erlotinib</td>
<td>Sorafenib + placebo</td>
<td>OS</td>
<td>May-09</td>
<td>Dec-12</td>
<td>Not recruiting</td>
<td>Bayer</td>
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<tr>
<td>NCT00858871</td>
<td>BMS (BRISK FL)</td>
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<td>175</td>
<td>Brivanib + Placebo</td>
<td>Sorafenib + placebo</td>
<td>OS</td>
<td>May-09</td>
<td>Dec-12</td>
<td>Not recruiting</td>
<td>BMS</td>
</tr>
<tr>
<td>NCT01009593</td>
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<td>1100</td>
<td>163</td>
<td>Linifanib</td>
<td>Sorafenib</td>
<td>OS</td>
<td>Jan-10</td>
<td>May-12</td>
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<td>J Ricker</td>
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<tr>
<td>NCT01214343</td>
<td>Japan gov</td>
<td>190</td>
<td>30</td>
<td>Sorafenib + low dose FP</td>
<td>Sorafenib</td>
<td>OS</td>
<td>Oct-10</td>
<td>Sep-13</td>
<td>Recruiting</td>
<td>M Kudo</td>
</tr>
<tr>
<td>NCT01015833</td>
<td>NCI</td>
<td>480</td>
<td>290</td>
<td>Doxorubicin + sorafenib</td>
<td>Sorafenib</td>
<td>OS</td>
<td>Feb-10</td>
<td>Sep-11</td>
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<td>Abou-Alfa</td>
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<tr>
<td>NCT01075555</td>
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<td>474</td>
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<td>Sorafenib + Pravastin</td>
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<td>Sep-13</td>
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<td>Jean-Louis</td>
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<tr>
<td>NCT01761266</td>
<td>Eisai</td>
<td>940</td>
<td>World</td>
<td>Lenvatinib</td>
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<td>OS</td>
<td>Feb-13</td>
<td>Feb-15</td>
<td>Recruiting</td>
<td>Eisai</td>
</tr>
</tbody>
</table>
HCC that has become resistant to sorafenib is more aggressive

The Enhanced Metastatic Potential of Hepatocellular Carcinoma (HCC) Cells with Sorafenib Resistance

Ariel Ka-Man Chow¹,², Lui Ng³, Colin Siu-Chi Lam³, Sunny Kit-Man Wong³, Timothy Ming-Hun Wan², Nathan Shiu-Man Cheng³, Thomas Chung-Cheung Yau³, Ronnie Tung-Ping Poon¹,², Roberta Wen-Chi Pang¹,²*

¹Centre for Cancer Research, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China. ²Department of Surgery, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

Abstract

Acquired resistance towards sorafenib treatment was found in HCC patients, which results in poor prognosis. To investigate the enhanced metastatic potential of sorafenib resistance cells, sorafenib-resistant (SorR) cell lines were established by long-term exposure of the HCC cells to the maximum tolerated dose of sorafenib. Cell proliferation assay and qPCR of ABC transporter genes (ABCC1-3) were first performed to confirm the resistance of cells. Migration and invasion assays, and immunoblotting analysis on the expression of epithelial to mesenchymal transition (EMT) regulatory proteins were performed to study the metastatic potential of SorR cells. The expression of CD44 and CD133 were studied by flow cytometry and the gene expressions of pluripotency factors were studied by qPCR to demonstrate the enrichment of cancer stem cells (CSCs) in SorR cells. Control (CTL) and SorR cells were also injected orthotopically to the livers of NOD-SCID mice to investigate the development of lung metastasis. Increased expressions of ABCC1-3 were found in SorR cells. Enhanced migratory and invasive abilities of SorR cells were observed. The changes in expression of EMT regulatory proteins demonstrated an activation of the EMT process in SorR cells. Enriched proportion of CD44⁺ and CD44⁺CD133⁺ cells were also observed in SorR cells. All (8/8) mice injected with SorR cells demonstrated lung metastasis whereas only 1/8 mouse injected with CTL cells showed lung metastasis. HCC cells with sorafenib resistance demonstrated a higher metastatic potential, which may be due to the activated EMT process. Enriched CSCs were also demonstrated in the sorafenib resistant cells. This study suggests that advanced HCC patients with acquired sorafenib resistance may have enhanced tumor growth or distant metastasis, which raises the concern of long-term sorafenib treatment in advanced HCC patients who have developed resistance of sorafenib.
Because of the:

- molecular heterogeneity of HCC
- and the absence of proven therapeutic targets

- *mono-therapy* without predictive biomarker is unlikely offer more than modest survival benefits e.g. OS of 6.2 months versus 4.1 months in the Asia-Pacific sorafenib trial

- Trials of molecular-targeted therapies on unselected HCC patients have low chance of success
- Trials of molecular-targeted therapies on unselected HCC patients who have failed sorafenib have low chance of success
### Randomized trials for second-line therapy after failure with first-line therapy (Sorafenib)

<table>
<thead>
<tr>
<th>Trial no</th>
<th>Sponsor</th>
<th>Size</th>
<th>Centers</th>
<th>Therapy 1</th>
<th>Therapy 2</th>
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<td>BMS</td>
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<td>531</td>
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<td>Everolimus</td>
<td>Placebo</td>
<td>OS</td>
<td>Apr-10</td>
<td>Mar-13</td>
<td>not recruiting (Negative)</td>
<td>Novartis</td>
</tr>
<tr>
<td>NCT01101906</td>
<td>Astellas Pharma Inc</td>
<td>23</td>
<td>World</td>
<td>OSI-906</td>
<td>Placebo</td>
<td>TTP</td>
<td>Oct-10</td>
<td>Dec-11</td>
<td>Terminated</td>
<td>Astellas Pharma</td>
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<td>NCT00687596</td>
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<td>1</td>
<td>TAC 101</td>
<td>Placebo</td>
<td>OS</td>
<td>Jun-08</td>
<td>May-10</td>
<td>Terminated (Fabio Benedetti)</td>
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<td>Oct-16</td>
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<td>Ramucirumab DP</td>
<td>Placebo</td>
<td>OS</td>
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<td>Apr-13</td>
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<td>Placebo</td>
<td>OS</td>
<td>Dec-10</td>
<td>Nov-13</td>
<td>Recruiting</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>
Impact of systemic therapy phase III trials on practice

• Any improvements in OS over sorafenib with newer systemic agents or combination of agents however marginal, may replace sorafenib mono-therapy as standard of care in systemic disease

• In the absence of predictive biomarkers, the impact on locally advanced disease may be minimal especially in the Asia-Pacific where loco-regional therapy is widely used.

• Positive trials with sorafenib + loco-regional combinations will help maintain a role for sorafenib
Loco-regional Therapy based Phase III Trials

- TACE-based RCT:
  - with and without sorafenib
- Yttrium-90 based RCT:
  - all phase III trials involve sorafenib
# TACE-based phase III trials involving molecular targeted agents

<table>
<thead>
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<th>End</th>
<th>Status</th>
<th>Protocol</th>
<th>Chair</th>
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<tbody>
<tr>
<td>NCT00494299</td>
<td>Bayer</td>
<td>458</td>
<td>75 (Japan, Korea)</td>
<td>TACE + sorafenib</td>
<td>TACE + placebo</td>
<td>TTP</td>
<td>Apr-06</td>
<td>Nov-10</td>
<td>Completed (negative)</td>
<td>Bayer</td>
<td>Pierce Chow FRCS, PhD</td>
</tr>
<tr>
<td><strong>Phase II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>NCT00855218</td>
<td>Bayer SPACE</td>
<td>307</td>
<td>107</td>
<td>DC-Beads + sorafenib</td>
<td>DC-BEADS + placebo</td>
<td>TTP</td>
<td>Mar-09</td>
<td>Mar-12</td>
<td>completed</td>
<td>Bayer</td>
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<tr>
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<td>8 (UK)</td>
<td>DC-Beads + sorafenib</td>
<td>DC-BEADS + placebo</td>
<td>PFS</td>
<td>Nov-10</td>
<td>Nov-14</td>
<td>Recruiting</td>
<td>Tim Meyer</td>
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<td>NCT01004978</td>
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<td>128 (US)</td>
<td>TACE + sorafenib</td>
<td>TACE + placebo</td>
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<td>Oct-09</td>
<td>Sep-12</td>
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<td>John Kauh</td>
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<td>398</td>
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<td>Sorafenib</td>
<td>OS</td>
<td>Sep-12</td>
<td>Mar-16</td>
<td>Recruiting</td>
<td>Guohong Han</td>
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<tr>
<td>NCT01829035</td>
<td>NCC, Korea</td>
<td>338</td>
<td>1 (Korea)</td>
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<td>Feb-13</td>
<td>Jul-16</td>
<td>Recruiting</td>
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<td>OS</td>
<td>Jul-10</td>
<td>Jul-13</td>
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<tr>
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<td>OS</td>
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<td>NCT00908752</td>
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<td>870</td>
<td>102</td>
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<td>Mar-15</td>
<td>Recruiting</td>
<td>BMS</td>
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</table>
Sorafenib or Placebo in combination with TACE for intermediate stage HCC

- International (Europe, Americas, Asia–Pacific), Phase II, randomised, double-blind study of Sorafenib® or placebo with TACE with DC Bead and doxorubicin

Eligibility criteria
- Unresectable HCC
- Multinodular HCC
- Child–Pugh A
- ECOG PS 0

Exclusion criteria
- EHS/MVI
- Contraindication to TACE

Randomisation 1:1 (n=300)

Endpoints
Primary
- TTP

Secondary
- OS
- TTUP
- Time to vascular invasion
- Time to EHS

DC-TACE + Sorafenib 400mg b.i.d.

DC-TACE + placebo

ECOG PS = Eastern Cooperative Oncology Group Performance Status
MVI = macrovascular invasion; TTUP = time to untreatable progression

Earlier TACE trial in Japan negative

SGH – Surgery
# TACE-based phase III trials not involving molecular targeted agents

<table>
<thead>
<tr>
<th>Trial no</th>
<th>Sponsor</th>
<th>Size</th>
<th>Centers</th>
<th>Therapy 1</th>
<th>Therapy 2</th>
<th>PO</th>
<th>Start</th>
<th>End</th>
<th>Status</th>
<th>Protocol Chair</th>
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<tbody>
<tr>
<td>NCT00501813</td>
<td>Sun Yat-sen</td>
<td>160</td>
<td>1 (China)</td>
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<td>Jul-17</td>
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<td>shi ming</td>
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<td>NCT01872988</td>
<td>Chinese University of Hong Kong</td>
<td>144</td>
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<td>Hepatectomy + TACE</td>
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<td>NCT01512407</td>
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<td>NCT01676194</td>
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<td>BSC</td>
<td>OS</td>
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<td>Aug-17</td>
<td>Recruiting</td>
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<td>OS</td>
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<td>Apr-13</td>
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<td>Dec-15</td>
<td>Recruiting</td>
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<td>OS</td>
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<td>TACE + distilled water</td>
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<td>NCT01387932</td>
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<td>23</td>
<td>HepaSphere/QuadraSphere</td>
<td>Conventional TACE</td>
<td>OS</td>
<td>Apr-11</td>
<td>Sep-14</td>
<td>Recruiting</td>
<td>Michael Soulen</td>
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Impact of TACE-based phase III trials on Practice

• Any positive trial with OS as primary end-point will be likely to establish that combination as being superior to TACE alone in locally advanced disease

• TACE has little efficacy in HCC with PVT
Loco-regional Therapy based Phase III Trials

- TACE-based RCT:
  - with and without sorafenib
- Yttrium-90 based RCT:
  - all phase III trials involve sorafenib
# SIRT Yttrium-90 phase II & III trials

<table>
<thead>
<tr>
<th>Trial no</th>
<th>Sponsor</th>
<th>Size</th>
<th>Centers</th>
<th>Therapy 1</th>
<th>Therapy 2</th>
<th>PO</th>
<th>Start</th>
<th>End</th>
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<td>Mar-12</td>
<td>Oct-16</td>
<td>Recruiting</td>
<td>Riad Saleem</td>
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<td>Oct-15</td>
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<td>NCT00712790</td>
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<td>Jun-09</td>
<td>Completed</td>
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<td>34</td>
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<td>RFA – Sorafenib</td>
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<td>Sep-14</td>
<td>Recruiting</td>
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<td>Sorafenib &amp; Y-90 Toxicity</td>
<td>Sep-13</td>
<td>Sep-17</td>
<td>Recruiting</td>
<td>Ahmed Kaseb</td>
</tr>
</tbody>
</table>
Asia-Pacific HCC Trials Group 2013

Ulaan Baator
Hanoi
Yangon
Bangkok
Penang
Kuala Lumpur
Singapore
Jakarta
Bali

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

SGH – Surgery
AHCC06: SIRT versus Sorafenib in patients with locally advanced HCC SIRveNIB

Asia-Pacific, Phase III, open-label, open-labelled study

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

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

Eligible: Previous surgery, RFA, TACE

SGH – Surgery
Study Design

• Investigator-initiated – supported by grants from NMRC Singapore and Sirtex

• Multi-center

• Open-label

• Randomized controlled

• **Target:** 360 subjects / 26 centers + 3
Excludes extra-hepatic metastases

Milan
SIRT: Survival by BCLC Stage

Salem et al. Gastroenterology 2010; 138: 52–64

SGH – Surgery
Asia-Pacific Sorafenib Trial
Overall Survival with and without Major Vascular Invasion and/or Extra Hepatic Disease in Child-Pugh A patients

With Major Vascular Invasion/Extra-hepatic disease

- **Nexavar (n=118)**
  - Median: 5.6 months
  - (95% CI: 4.8, 6.7)
- **Placebo (n=61)**
  - Median: 4.1 months
  - (95% CI: 3.4, 4.8)

**Survival Distribution Function**

- **HR (S/P): 0.75**
  - 95% CI: 0.54, 1.05

Without Major Vascular Invasion/Extra-hepatic disease

- **Nexavar (n=32)**
  - Median: 14.3 months
  - (95% CI: 10.8, NR)
- **Placebo (n=15)**
  - Median: 8.0 months
  - (95% CI: 3.3, NR)

**Survival Distribution Function**

- **HR (S/P): 0.45**
  - 95% CI: 0.19, 1.06

The SARAH Study

To determine whether radioembolisation with SIR-Spheres® microspheres is more effective on overall survival in advanced HCC than sorafenib

**Design:** Prospective open-label, multi-centre, national (France) RCT

### Eligible Patients:
- Unresectable HCC
- BCLC stage C or
- BCLC stage A/B:
  - New lesions post-radical therapy and unsuitable for further radical therapy or
  - No objective response after ≤2 TACE sessions
- Child-Pugh class A or B ≤7 points
- ECOG performance status 0–1
- Fit for sorafenib and SIRT

### Randomise

1:1

n = 400

**Primary endpoint:** Overall survival

**Secondary endpoints:** Safety and toxicity
- Quality of life
- Healthcare costs
- Progression-free survival at 6 months

**Sponsor:** Assistance Publique – Hôpitaux de Paris (AP-HP)

**PI:** Prof. Valérie Vilgrain

**Status:** Currently enrolling
A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients with Unresectable Hepatocellular Carcinoma: STOP-HCC¹

- PI: Riad Salem

- Randomized Phase III
  - Multicenter; international
  - N=400 approximately
  - Unresectable HCC

- Kinase Inhibitor +/- TheraSphere

- Endpoints
  - Primary
    - Overall survival (OS)
  - Secondary
    - Safety

¹Nordion Phase III Clinical Trials:
  - conducted under Investigational Device Exemption (IDE)
Impact of SIRT yttrium-90 phase III trials on Practice

- There is no completed phase III SIRT yttrium-90 trials yet
- All 3 on-going phase III trials have Overall Survival (OS) as primary outcome.
- All 3 trials have sorafenib as comparator
- SIRT yttrium-90 is efficacious in PVT
- Any positive trial will establish SIRT yttrium-90 as standard of care in HCC with PVT and at least an equal alternative to TACE in HCC without PVT

SGH – Surgery

Pierce Chow FRCSE PhD
Many ongoing Phase III Trials for HCC

The results of these trials will significantly impact practice over the next 5 years.
Thank You!