Molecular Biology of Hepatocellular Carcinoma and Targeted Therapies

First International Course on Translational Hepatology: Focus on HCV Disease
March 9-11, 2011

Melanie B. Thomas, M.D.
Associate Director of Clinical Investigations
Grace E. DeWolff Chair in Medical Oncology
Associate Professor
Hollings Cancer Center    Charleston, SC
Hepatocellular Carcinoma (HCC) is a Challenging Cancer

• HCC is a complex malignancy:
  • Multiple etiologies:
    • HBV, HCV, alcohol, fatty liver,
    • hemochromatosis, alpha-1 anti-trypsin deficiency, other metabolic diseases,
    • exogenous hormones, autoimmune hepatitis, aflatoxin-B exposure.
  • Inflammatory environment of cirrhotic liver contributes to carcinogenesis.

• HCC is predicted to increase 4-fold in the U.S.

• Why is HCC Incidence Increasing?
  • Rising incidence of cirrhosis from multiple causes.
  • Large pool of >4,000,000 HCV+ individuals who acquired HCV prior to identification & screening, plus 38,000 new cases annually.
  • Increasing prevalence of obesity, fatty liver (non-alcoholic fatty liver disease, NAFLD).
  • Improved survival for patients with cirrhosis.
HCC Epidemiology

Obesity and Liver Cancer

BMI

- 35 to 39.9
- 30 to 34.5
- 20 to 29.9
- 18.5 to 25

Death Rate per 100,000

- Women
- Men

Caffo, et al, NEJM 2013
HCC Epidemiology

Mortality from Cancer in Obese US Men (n=900,053)

Type of Cancer (Highest BMI Category)

- Prostate (≥35) 1.34
- Non-Hodgkin’s Lymphoma (≥35) 1.49
- All Cancers (≥40) 1.52
- All Other Cancers (≥30) 1.68*
- Kidney (≥35) 1.70
- Multiple Myeloma (≥35) 1.71
- Gall Bladder (≥30) 1.76
- Colon and Rectum (≥35) 1.84
- Esophagus (≥30) 1.91*
- Stomach (≥35) 1.94
- Pancreas (≥35) 2.61*
- Liver (≥35) 4.52

Relative Risk of Death (95% Confidence Interval)


First International Course of Translational Hepatology, Florence, 2011
HCC is unique - one patient, two diseases:

Consequences of cirrhosis:

- Ascites
- Diffuse nodular, fatty liver
- Main portal vein thrombus

Portal hypertension leads to splenomegaly, varices.
HCC is unique - one patient, two diseases:

- HCC has multiple underlying etiologies > yields a molecularly complex tumor:
  - Cirrhosis = “field defect” - entire liver is a premalignant lesion
  - High recurrence rates after resection, locoregional therapy
  - Cirrhosis > portal HTN > thrombocytopenia > impaired synthetic function > GI bleeder risk.
  - Co-morbidities of cirrhosis complicate clinical trial design for new chemotherapeutic agents, patient recruitment.

HBV-related HCC:
- <50% develop in cirrhosis.
- Typically form large dominant masses with tumor capsule.
- Young patients, normal hepatic function.

HCV-related HCC:
- >90% in cirrhosis.
- Diffuse, infiltrative, multifocal HCC.
- Older patients, mild-severe hepatic dysfunction.
Liver Transplantation

- Current 5 year survival 65-75% for patients transplanted within Milan Criteria.
- No extrahepatic disease, no gross vascular invasion, 1 tumor < 5 cm, <3 tumors.

Hepatic resection

- Few patients eligible due to cirrhosis; contraindicated in portal HTN.
- Recurrence rate 50% at 18 months.

Regional therapy - field is rapidly evolving

- Trans-arterial selective delivery of embolic material +/-:
  - cytotoxic agent, drug-eluting beads, yttrium90-embedded microspheres.
- Level 1 evidence of benefit only for solitary tumors < 8 cm, normal bilirubin.
- Contraindicated when bilirubin >3, main PVT.

- **Advanced HCC >75% of patients:**
  - Median survival 6-8 months
  - Sorafenib improves median survival from 7.9 to 10.7 months, but with chronic side effects.
Systemic chemotherapy for patients with advanced HCC

- HCC is a highly chemotherapy-resistant tumor.
- Hepatocytes and HCC cells produce over express multi-drug resistance (mdr1) gene > produce cellular efflux pumps.
- Numerous classes of conventional cytotoxic drugs have been studied in HCC:
  - Anthracyclines
  - Taxanes
  - Anti-metabolites
  - Interferons
  - Cell cycle inhibitors

Despite 30 years of clinical trials of numerous chemotherapy agents, no drug or combination showed patient benefit.
# Negative Randomized Chemotherapy Clinical Trials in HCC

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Phase</th>
<th>N</th>
<th>RR%</th>
<th>MS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeo JNCI 2005</td>
<td>*PIAF vs adriamycin</td>
<td>III</td>
<td>94/94</td>
<td>20.9 vs 10.5</td>
<td>8.6 vs 6.83</td>
</tr>
<tr>
<td>Posey et al ASCO 2005</td>
<td>T13067 vs adriamycin</td>
<td>II/III</td>
<td>169/170</td>
<td>NA</td>
<td>5.7 vs 5.6</td>
</tr>
<tr>
<td>Gish et al JCO 2007</td>
<td>Nolatrexed vs doxorubicin</td>
<td>II</td>
<td>37/17</td>
<td>0</td>
<td>4.9 vs 3.7</td>
</tr>
<tr>
<td>Mok et al JCO</td>
<td>Nolatrexed vs doxorubicin</td>
<td>III</td>
<td>444</td>
<td>1.4 vs 4.0</td>
<td>5.5 vs 8 (p=.0068)</td>
</tr>
<tr>
<td>Barbare</td>
<td>Tamoxifen vs BSC</td>
<td>II</td>
<td>210/210</td>
<td>NA</td>
<td>4.8 vs 4.0</td>
</tr>
<tr>
<td>Dollinger et al ASCO 2008</td>
<td>Thymosin vs placebo</td>
<td>III</td>
<td>65/68</td>
<td>NA</td>
<td>5.0 vs 5.2</td>
</tr>
<tr>
<td>SUN 1170</td>
<td>Sunitinib vs sorafenib</td>
<td>III</td>
<td>NA</td>
<td></td>
<td>Trial closed at 1st interim analysis</td>
</tr>
</tbody>
</table>
TARGETED THERAPY FOR HCC
The Dawn of a New Era

Cetuximab
Bevacizumab

Gefitinib
Erilotinib
AZD2171
AZD6474
Sunitinib
Lapatinib

Sorafenib

Approved in 2007 by FDA, EMEA based on prolonged survival

First International Course of Translational Hepatology, Florence, 2011
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Phase</th>
<th>Sample size</th>
<th>RR%</th>
<th>PFS/TTP</th>
<th>Median survival (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>2</td>
<td>137</td>
<td>2.2</td>
<td></td>
<td>9.3</td>
<td>Abou Alfa et al JCO 2006</td>
</tr>
<tr>
<td>Sorafenib vs placebo (“SHARP” trial)</td>
<td>3</td>
<td>602</td>
<td>2.3</td>
<td>5.5 (T)</td>
<td>10.7 (vs 7.9 placebo, p=0.00058)</td>
<td>Llovet et al NEJM 2008</td>
</tr>
<tr>
<td>Sorafenib vs placebo</td>
<td>3</td>
<td>150/76</td>
<td></td>
<td>TTP 2.8 vs 1.4 PFS 2.8 vs 1.4</td>
<td>6.2 (vs 4.1 placebo)</td>
<td>Cheng et al Lancet Oncology 2009</td>
</tr>
<tr>
<td>Sorafenib + doxorubicin vs doxorubicin placebo</td>
<td>RII</td>
<td>47/49</td>
<td>4/2</td>
<td>8.6/4.8 (T)</td>
<td>13.7/6.5</td>
<td>Abou Alfa et al</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2</td>
<td>46</td>
<td>13</td>
<td>6.9 (P)</td>
<td>12.4</td>
<td>Seigel et al JCO 2008</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>2</td>
<td>21</td>
<td>4.7</td>
<td></td>
<td>6.5</td>
<td>Rizell et al 2008</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2</td>
<td>38</td>
<td>9</td>
<td>3.2 (P)</td>
<td>13</td>
<td>Philip et al JCO 2005</td>
</tr>
<tr>
<td>Erlotinib vs placebo</td>
<td>2</td>
<td>40</td>
<td>0</td>
<td>6.3 (P)</td>
<td>10.75</td>
<td>Thomas et al Cancer 2007</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>2</td>
<td>32</td>
<td>0</td>
<td>1.4</td>
<td>9.6</td>
<td>Zhu et al Cancer 2007</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>2.8 (P)</td>
<td>6.5</td>
<td>O’Dwyer et al ASCO 2006</td>
</tr>
<tr>
<td>Sunitinb</td>
<td>2</td>
<td>34</td>
<td>2.9</td>
<td>3.9</td>
<td>9.8</td>
<td>Zhu et al JCO 2009</td>
</tr>
<tr>
<td>Sunitinb vs placebo</td>
<td>2</td>
<td>37</td>
<td>2.7</td>
<td>5.2</td>
<td>11.2</td>
<td>Faivre et al ASCO 2007</td>
</tr>
<tr>
<td>Bevacizumab + erlotonib</td>
<td>2</td>
<td>55</td>
<td>2.8 (T)</td>
<td></td>
<td>10</td>
<td>Raoul et al 2009</td>
</tr>
<tr>
<td>Bevacizumab + erlotonib</td>
<td>2</td>
<td>40</td>
<td>25</td>
<td>9.0 (T)</td>
<td>15.65</td>
<td>Thomas et al JCO 2009</td>
</tr>
<tr>
<td>Bevacizumab + erlotonib</td>
<td>2</td>
<td>59</td>
<td>27.5</td>
<td></td>
<td></td>
<td>Kaseb, Garrett-Meyer, Thomas et al 2011 (in press)</td>
</tr>
</tbody>
</table>

**Recent Trials of Molecular-Targeted Agents in HCC**

*First International Course of Translational Hepatology, Florence, 2011*
<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Tumor type</th>
<th>Effect</th>
<th>Target Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>HER2 receptor, HER1-2 heterodimers</td>
<td>Her2-overexpressing breast cancer</td>
<td>Improves survival, Decreases recurrence as adjuvant therapy</td>
<td>yes</td>
</tr>
<tr>
<td>Lapatinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>mAB binds serum VEGF A ligand</td>
<td>Metastatic colorectal, lung, breast cancers</td>
<td>Improves survival, TTP in metastatic colon, lung, breast cancers</td>
<td>no</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Extra-cellular domain EGFR</td>
<td>Irinotecan-refractory colorectal cancer</td>
<td>Improves survival, TTP in metastatic colon</td>
<td>Kras mutants do not benefit from EGFR mAb</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Intracellular phosphorylation site</td>
<td>non-small cell lung pancreatic</td>
<td>Improves survival, NSCLLA, 2nd line</td>
<td>EGFR mutations in minority of patients predict benefit</td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
<td>Improves PFS in pancreatic ca by &lt;2 wks</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Raf-ras pathway VEGF</td>
<td>RCC, HCC</td>
<td>Improves survival, TTP</td>
<td>no</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Raf-ras pathway VEGF</td>
<td>GIST, RCC</td>
<td>Improves survival, TTP</td>
<td>no</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>mTOR</td>
<td>Myeloma</td>
<td>Improves survival, decreases transfusions</td>
<td>no</td>
</tr>
<tr>
<td>Imatinib</td>
<td>C-kit</td>
<td>GIST, CML</td>
<td>Improves RR, survival, Decreases recurrence</td>
<td>yes</td>
</tr>
</tbody>
</table>
Evidence for the Critical Role of Angiogenesis in HCC:

- HCC are highly vascularized, propensity for vascular invasion
- Growth factors EGF, TGFβ, HGF, VEGF all involved in normal liver regeneration
- Increased growth factors expression seen in chronic hepatitis, cirrhosis, dysplastic nodules, HCC cell lines and tissue
- VEGF over-expression and increased microvessel density (MVD) common in HCC
- VEGF gene is transcribed, expressed and VEGF secreted by HCC
- High VEGF expression in HCC measured by immunohistochemistry (IHC) tissue significantly associated with:
  - increased arterialization
  - poorer tumor differentiation
  - high proliferative index
  - poor tumor encapsulation
Angiogenesis in HCC Progression

- Angiogenic factors implicated in HCC include
  - VEGFs (vascular endothelial growth factors)
  - PDGFs (platelet-derived growth factors)
  - PIGF (placental growth factor)
  - TGF-α, TGF-β (transforming growth factors-alpha, -beta)
  - bFGF (basic fibroblast growth factor)
  - EGF (epidermal growth factor)
  - HGF (hepatocyte growth factor)
  - ANGs (angiopoietins)
  - IL-4, IL-8 (interleukins-4, -8)

HCC Pathogenesis

Angiogenic Signaling in Cancer

Autocrine stimulation

Ras  
PI3-K  
STATs

Proliferation, metastasis

HIF

Tumor cell

Endothelial cell

Ras  
PI3-K  
STATs

Proliferation and migration

IGF  
HGF  
PDGF  
VEGF

FGF  
PIGF  
Ang-2  
PDGF  
VEGF

Pericyte

VEGF
<table>
<thead>
<tr>
<th>Factor</th>
<th>Role in hepatocellular carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGF (hepatocyte growth factor)</td>
<td>Known pro-angiogenic growth factor, acts via c-met. Common in hepatocyte regeneration; predicts poor prognosis.</td>
</tr>
<tr>
<td>EGF (epidermal growth factor receptor)</td>
<td>Known mitogen in multiple tumor types; Increases HCC proliferations in multiple cell line. EGF over-expression common in chronic hepatitis, cirrhosis and HCC (40-80%).</td>
</tr>
<tr>
<td>FGF (fibroblast growth factor receptor)</td>
<td>Upregulates DNA synthesis. Mitogenic for hepatocytes, potent inducer of angiogenesis. Interacts with EGFR; Frequent in hepatitis, cirrhosis, HCC; not in normal liver</td>
</tr>
<tr>
<td>IGF (insulin-like growth factor family)</td>
<td>Common in fetal liver; declines after birth; highly prevalent in HCC IGF pro-carcinogenic in many tumor types. May be link between fatty liver and HCC. Preclinical data shows anti-IGF-1 tyrosine kinase inhibitors induce growth inhibition, apoptosis, cell cycle arrest in HCC cell lines.</td>
</tr>
<tr>
<td>PDGF (platelet-derived growth factor)</td>
<td>An angiogenic molecule promotes endothelial cell migration. May be potent stimulator of angiogenesis in HCC.</td>
</tr>
</tbody>
</table>
mAb to extracellular receptor domaine

Cetuximab
Bevacizumab

Gefitinib
Erlotinib
AZD2171
AZD6474
Sunitinib
Lapatinib

GRB
SOS
Prenylated Ras

Raf
P

MEK 1/2
P

MAPK
P

Cell growth

Receptor Tyrosine Kinase

Farnesyl Transferase

Ras

Farnesyl Transferase inhibitors

Courtesy of Dr. Lewis Roberts, with permission
### Recent Trials of Molecular-Targeted Agents in HCC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Phase</th>
<th>Sample size</th>
<th>RR%</th>
<th>PFS, TTP</th>
<th>Median survival (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>2</td>
<td>137</td>
<td>2.2</td>
<td></td>
<td>9.3</td>
<td>Abou Alfa et al JCO 2006</td>
</tr>
<tr>
<td>Sorafenib vs placebo</td>
<td>3</td>
<td>602</td>
<td>2.3</td>
<td>5.5 (T)</td>
<td>10.7 (vs 7.9 placebo, p=0.00058)</td>
<td>Llovet et al NEJM 2008</td>
</tr>
<tr>
<td>Sorafenib vs placebo</td>
<td>3</td>
<td>150/76</td>
<td></td>
<td>TTP 2.8 vs 1.4</td>
<td>6.2 (vs 4.1 placebo)</td>
<td>Cheng et al Lancet Oncology 2009</td>
</tr>
<tr>
<td>Sorafenib + doxorubicin vs doxorubicin + placebo</td>
<td>RII</td>
<td>47/49</td>
<td>4/2</td>
<td>8.6/4.8 (T)</td>
<td>13.7/6.5</td>
<td>Abou Alfa et al</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2</td>
<td>46</td>
<td>13</td>
<td>6.9 (P)</td>
<td>12.4</td>
<td>Seigel et al JCO 2008</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>2</td>
<td>21</td>
<td>4.7</td>
<td></td>
<td>6.5</td>
<td>Rizell et al 2008</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2</td>
<td>38</td>
<td>9</td>
<td>3.2 (P)</td>
<td>13</td>
<td>Philip et al JCO 2005</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2</td>
<td>40</td>
<td>0</td>
<td>6.3 (P)</td>
<td>10.75</td>
<td>Thomas et al Cancer 2007</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>2</td>
<td>32</td>
<td>0</td>
<td>1.4</td>
<td>9.6</td>
<td>Zhu et al Cancer 2007</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>2.8 (P)</td>
<td>6.5</td>
<td>O'Dwyer et al ASCO 2006</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>2</td>
<td>34</td>
<td>2.9</td>
<td>3.9</td>
<td>9.8</td>
<td>Zhu et al JCO 2009</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>2</td>
<td>37</td>
<td>2.7</td>
<td>5.2</td>
<td>11.2</td>
<td>Faivre et al ASCO 2007</td>
</tr>
<tr>
<td>Brivinib</td>
<td>2</td>
<td>55</td>
<td>2.8 (T)</td>
<td>10</td>
<td></td>
<td>Raoul et al 2009</td>
</tr>
<tr>
<td>Bevacizumab + erlotinib</td>
<td>2</td>
<td>40</td>
<td>25</td>
<td>9.0 (T)</td>
<td>15.65</td>
<td>Thomas et al JCO 2009</td>
</tr>
<tr>
<td>Bevacizumab + erlotinib</td>
<td>2</td>
<td>59</td>
<td>27.5</td>
<td></td>
<td></td>
<td>Kaseb, Garrett-Meyer, Thomas et al 2011 (in press)</td>
</tr>
</tbody>
</table>

First International Course of Translational Hepatology, Florence, 2011
Phase II trial of bevacizumab and erlotinib in HCC

- **Trial based on:**
  - Importance of VEGF and EGF in HCC carcinogenesis.
  - Improved survival of bevacizumab, erlotinib in multiple other tumor types.

- **Single-arm, open label trial of B+E in unresectable HCC**
  - Bevacizumab (humanized mAb against VEGF-A ligand)
  - Erlotinib (oral tyrosine kinase inhibitor TKI binds EGF)

- **Primary Endpoint progression-free survival at 16 weeks therapy >50%**
  - Based on “historical controls” from small Phase II trials (pre-SHARP trial results)
  - Goal: identify meaningful “biologic signal” of drug activity
  - Evaluate safety of dual targeted agents in HCC.

- **Eligibility criteria:**
  - One prior systemic therapy allowed; unlimited regional treatments
  - Performance Status 0-2
  - Childs-Pugh A, B; bilirubin <2, transaminases ≤ 5 XULN, platelets ≥ 60,000
  - Portal vein thrombus allowed
  - No fibrolamellar HCC
  - Prior variceal bleeding allowed if >3 months.
## Summary of Survival Data: ITT Analysis

<table>
<thead>
<tr>
<th>Prior treatment history</th>
<th>PFS in months Median (95% CI)</th>
<th>OS in months Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior treatment (n=44)</td>
<td>8.8 (5.5, 10.1)</td>
<td>15.6 (9.5, 19.5)</td>
</tr>
<tr>
<td>Prior treatment with sorafenib (n=8)</td>
<td>7.9 (4.2, 13.3)</td>
<td>13.3 (4.2, 22.3)</td>
</tr>
<tr>
<td>Prior treatment with other systemic therapy (n=6)</td>
<td>6.6 (1.9, 11.0)</td>
<td>14.4 (1.9, Inf*)</td>
</tr>
</tbody>
</table>

*Upper limit is infinite because of the small number of patients with prior treatment with regimens not including sorafenib.*
Radiographic evidence of tumor responses in HCC patients treated with bevacizumab and erlotinib
Computed tomography of the abdomen of a 76 year old man with multi-focal hypervascular HCC in right lobe liver, baseline.

Decreased tumor vascularity, partial tumor response after 6 months bevcizumab and erlotinib.
62 yo man with multifocal recurrent HCC, PVT 4 mos after extended rt hepatectomy
Baseline alpha-fetoprotein (AFP) 214,046

After 16 weeks B+E, partial response, AFP 287
Sustained PR after 10 mos
29 yo man with cirrhosis, metabolic syndrome, massive HCC. Baseline, AFP 70,000

Restaging CT after 16 weeks bevacizumab + erlotinib decreased tumor vascularity, AFP 30,000
50 yo man with recurrent HCC in right portal vein (tumor thrombus) and adjacent liver. Tumor effacing IVC. Baseline AFP 2,073

PR after 8 weeks B+E, improved IVC flow. AFP 482
63 year old woman with hypervascular HCC, right lobe. Significant portal HTN precluded resection.

Decreased tumor vascularity after 8, 16 weeks treatment with B+E.
Radiographic Evidence of Tumor Response to B+E in Second-Line Setting After Progression on Sorafenib
48 yo woman presented with ruptured 9 cm HCC 8/05, underwent primary resection. Developed recurrent multiple abdominal implants 3/06; failed 5FU/IFN

Patient treated with B+E off-protocol; significant radiographic response after 6 mos. 2/07 underwent resection of prior incision, port sites, residual implants. No tumor detected in any specimen=pCR. Free of disease June 2008

Thomas et al Journal of Surgical Oncology Oct 2007
An exciting time in hepatocellular carcinoma...

- SHARP trial established sorafenib as standard of care systemic therapy for advanced disease patients

- Explosion of interest and clinical research in HCC-
  - 156 actively recruiting, phase II or III interventional trials in HCC listed on [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
  - Broad international recruitment
  - Multiple trials for each stage of disease

- Numerous targeted agents are now in clinical trials

- .......However - are the “right” agents being studied?
## Current Randomized Trials in HCC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Study Phase</th>
<th>Rationale</th>
</tr>
</thead>
</table>
| Sorafenib vs Sunitinib                      | III         | OS Sorafenib 10.7 months Ph III  
OS Sunitinib 8-9.8 months in 2 Ph II  
Closed at 1st interim analysis for futility |
| Sorafenib vs Erlotinib + Sorafenib          | III         | OS Sorafenib 10.7 months Ph III                                          |
| Sorafenib vs Bevacizumab+Erlotinib          | Randomized Ph II | OS Sorafenib 10.7 months Ph III  
TTP 5.5. vs 2.8 months  
Response rate 28%  
OS B+E 15.6 months (n=58)  
TTP 8.8 months |
| Sorafenib vs Brivinib                       | III         | OS Sorafenib 10.7 months Ph III  
OS 10 months Ph II |
| Sorafenib vs doxorubicin+sorafenib          | III         | OS Sorafenib 10.7 mos Ph III  
OS Dox+S 13.8 mos Randomized Ph II |
| Sorafenib vs ABT869                         | I/II        | OS Sorafenib 10.7 mos Ph III  
OS 9.7 months Ph II |
Conclusions:

- HCC is a highly molecularly complex tumor...
- ...Yet a single agent sorafenib, that targets ras-raf-signaling pathway is the first chemotherapy agent to improve patient survival.
- The prominent role of growth factor dysregulation in HCC provides opportunities to develop potent, combination targeted therapy strategies.
- It is essential to develop molecular characterization systems of all stages and etiologies of HCC.
Molto grazie

Please come visit Charleston, South Carolina.