Disclosures

• Bayer Pharmaceutical: Speaker’s bureau, consultant, research support
• Daiichi Pharmaceutical: Clinical trial research support
Management of HCC is challenging due to underlying liver disease, variable biologic behavior and variations in local expertise and available resources.

One such strategy is the establishment of multidisciplinary teams at academic centers and with community practice who collaborate on management decisions for their patients with HCC.
HCC Management
A Multidisciplinary Approach
Multidisciplinary Management

Management of Hepatocellular Carcinoma
Requires a Multidisciplinary Team Approach

Surgery
- Liver transplant
- Surgical Resection

Systemic Therapy
- Nexavar

Current HCC Treatment Options*

Locoregional Therapy
- PEI, RFA, TACE, TAE, Y-90

*Includes clinical trial

PEI = percutaneous ethanol injection; RFA = radiofrequency ablation; TACE = transarterial chemoembolization; TAE = transarterial embolization; Y-90 = Ytirium-90.

Aggressive multimodality treatment strategies adopted by multidisciplinary management of HCC patients can lead to improved patient surveillance.

Overall survival odds ratios after the establishment of a multidisciplinary treatment team at VA Medical Center in 2003:

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Survival Odds Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>1.44</td>
<td>0.12-17.92</td>
<td>NS</td>
</tr>
<tr>
<td>Stage II</td>
<td>15.50</td>
<td>2.82-85.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stage III</td>
<td>2.19</td>
<td>0.66-7.23</td>
<td>NS</td>
</tr>
<tr>
<td>Stage IV</td>
<td>21.00</td>
<td>1.83-240.66</td>
<td>0.01</td>
</tr>
<tr>
<td>Overall</td>
<td>7.10</td>
<td>3.46-14.52</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Data collected from 2000 to 2006. Total patients = 61 (from 2000 to 2003); 121 (from 2003 to 2006).
Treatment of Liver Tumors

- Surgical Resection
  - Lobectomy
  - Segmentectomy
  - Non Anatomic wedge resection
- Orthotopic Liver Transplantation
  - only for selected cases of hepatoma, hepatoblastoma, neuoroendocrine tumors
- Radiofrequency ablation
- Chemoembolization
- Microwave
- Therasphere \ Sirtex
- **Systemic chemotherapy trials**
- Ethanol injection
Barcelona Liver Clinics: Staging and Treatment

- **Very early stage**: single HCC mass <2 cm carcinoma in situ
  - 1 HCC
  - Portal pressure/bilirubin
  - Normal: Resection
  - High: OLT, PEI/RFA

- **Early stage**: 1 HCC or 3 nodules <3 cm, PS 0
  - 3 nodules ≤3 cm
  - Possible contraindication to transplant
    - NO: Resection
    - YES: OLT, PEI/RFA

- **Intermediate stage**: No portal vein thrombosis, Multinodular, PS 0
  - Chemoembolization

- **Advanced stage**: Portal invasion, Metastases, PS 0-2
  - Sorafenib

- **Terminal stage**: Symptomatic therapy

*Padma et al.* Liver Tumor Ablation: Percutaneous and Open Approaches. Journal of Surgical Oncology 2009;100:619–634
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>1-year survival (%)</th>
<th>3-year survival (%)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hasegawa et al. (2013)⁹</td>
<td>5361 5548</td>
<td>N/A</td>
<td>N/A</td>
<td>85.3 81.0</td>
</tr>
<tr>
<td>Tohme et al. (2013)¹⁰</td>
<td>50 60</td>
<td>88 86</td>
<td>68 50</td>
<td>47 35</td>
</tr>
<tr>
<td>Feng et al. (2012)¹¹</td>
<td>84 84</td>
<td>96.0 93.1</td>
<td>87.6 83.1</td>
<td>N/A N/A</td>
</tr>
<tr>
<td>Huang et al. (2010)¹²</td>
<td>115 115</td>
<td>98.2 88.9</td>
<td>92.1 69.5</td>
<td>75.6 54.7</td>
</tr>
<tr>
<td>Chen et al. (2006)¹³</td>
<td>90 71</td>
<td>93.3 95.8</td>
<td>73.4 71.4</td>
<td>N/A N/A</td>
</tr>
<tr>
<td>Lü et al. (2006)¹⁴</td>
<td>54 51</td>
<td>91.3 93.5</td>
<td>86.4 87.1</td>
<td>N/A N/A</td>
</tr>
<tr>
<td>Chen et al. (2005)¹⁵</td>
<td>65 47</td>
<td>93.2 92.8</td>
<td>67.3 64.5</td>
<td>N/A N/A</td>
</tr>
</tbody>
</table>

SR surgical resection, RFA radiofrequency ablation, N/A not available
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>1-year survival (%)</th>
<th>3-year survival (%)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al. (2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT-UCSF</td>
<td>180</td>
<td>90</td>
<td>81</td>
<td>72</td>
</tr>
<tr>
<td>SLT</td>
<td>39</td>
<td>88</td>
<td>78</td>
<td>61</td>
</tr>
<tr>
<td>SLT-MC</td>
<td>N/A</td>
<td>89</td>
<td>83</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td>88</td>
<td>69</td>
<td>55</td>
</tr>
<tr>
<td>Wu et al. (2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT-MC</td>
<td>147</td>
<td>98.0</td>
<td>86.4</td>
<td>75.5</td>
</tr>
<tr>
<td>PLT-BMC</td>
<td>156</td>
<td>96.2</td>
<td>64.7</td>
<td>48.7</td>
</tr>
<tr>
<td>SLT</td>
<td>36</td>
<td>97.2</td>
<td>80.6</td>
<td>69.4</td>
</tr>
<tr>
<td>Facciuto et al. (2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT</td>
<td>32</td>
<td>87</td>
<td>69</td>
<td>60</td>
</tr>
<tr>
<td>Scatton et al. (2007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT</td>
<td>73</td>
<td>71</td>
<td>61</td>
<td>55</td>
</tr>
<tr>
<td>SLT</td>
<td>14</td>
<td>74</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Vennarecci et al. (2007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT</td>
<td>37</td>
<td>78</td>
<td>62.7</td>
<td>62.7</td>
</tr>
<tr>
<td>SLT</td>
<td>9</td>
<td>88.9</td>
<td>88.9</td>
<td>88.9</td>
</tr>
<tr>
<td>Margarit et al. (2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT</td>
<td>36</td>
<td>65</td>
<td>N/A</td>
<td>50</td>
</tr>
<tr>
<td>Adam et al. (2003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTL</td>
<td>195</td>
<td>N/A</td>
<td>N/A</td>
<td>61</td>
</tr>
<tr>
<td>SLT</td>
<td>17</td>
<td>N/A</td>
<td>N/A</td>
<td>41</td>
</tr>
</tbody>
</table>

PLT primary liver transplant, SLT salvage liver transplant, SLT-MC salvage liver transplant meeting Milan criteria, SLT-UCSF salvage liver transplant meeting UCSF criteria, PLT-MC primary liver transplant meeting Milan criteria, PLT-BMC primary liver transplant beyond Milan criteria, N/A not available.
### Randomized Studies on chemoembolization

<table>
<thead>
<tr>
<th>Study</th>
<th>Survival Rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-year</td>
</tr>
<tr>
<td><strong>Lo et al. (2002)</strong></td>
<td></td>
</tr>
<tr>
<td>Chemoembolization</td>
<td>57</td>
</tr>
<tr>
<td>Control</td>
<td>32</td>
</tr>
<tr>
<td><strong>Llovet et al. (2002)</strong></td>
<td></td>
</tr>
<tr>
<td>Chemoembolization</td>
<td>82</td>
</tr>
<tr>
<td>Control</td>
<td>63</td>
</tr>
</tbody>
</table>
Angiogenesis Role in Tumor Growth

Somatic mutation → Small avascular tumor

Initiation

Tumor secretion of angiogenic factors stimulates angiogenesis

Proliferation

Rapid tumor growth and metastasis

Maturation

Angiogenic switch

Molecularly Targeted Therapy in HCC

Zhu, Cancer, 2008
Phase III SHARP Trial
Study Design

- Multi-center, Phase III study
- Inclusion criteria
  - Histology proven HCC
  - Advanced, unresectable HCC
  - At least one measurable untreated lesion
  - ECOG ≤ 2
  - Child-Pugh class A
  - No prior systemic treatment
- Randomization
  - Double-blind placebo controlled trial (1:1)
  - Accrual: March 2005-April 2006

# Phase III SHARP Trial

## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sorafenib (n=299)</th>
<th>Placebo (n=303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr, median)</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>Male/Female (%)</td>
<td>87/13</td>
<td>87/13</td>
</tr>
<tr>
<td>Region (Europe/N America/others, %)</td>
<td>88/9/3</td>
<td>87/10/3</td>
</tr>
<tr>
<td>Etiology (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral Hepatitis (HCV/HBV)</td>
<td>29/19</td>
<td>27/18</td>
</tr>
<tr>
<td>Alcohol/Other</td>
<td>26/26</td>
<td>26/29</td>
</tr>
<tr>
<td>Child-Pugh (A/B, %)</td>
<td>95/5</td>
<td>98/2</td>
</tr>
<tr>
<td>Prior Therapies (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical Resection</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Loco-regional Therapies</td>
<td>39</td>
<td>41</td>
</tr>
</tbody>
</table>

Phase III SHARP Trial
Overall Survival (Intention to Treat)

Phase III SHARP Trial:
Time to Tumor Progression
(Independent Review)

- Nexavar:
  - Median: 24.0 weeks (5.5 months)
  - (95% CI, 18.0-30.0)
- Placebo:
  - Median: 12.3 weeks (2.8 months)
  - (95% CI, 11.7-17.1)

Progression-Free Probability

Hazard ratio (Nex/Pbo): 0.58
(95% CI, 0.45-0.74)

P=0.000007

Patients at risk
- Nexavar: 299
- Placebo: 303

Phase III SHARP Trial:
Maximum Percent Reduction in Tumor Measurement

Change in Target Lesion From Baseline to Smallest Tumor Size Post-Baseline
Based on Independent Radiological Assessment

Nexavar in HCC: Tumor Necrosis

- Central tumor necrosis was evident in many patients’ scans, despite the appearance of tumor growth.
- Tumor necrosis was assessed rigorously in 11 patients.

Representative sample of baseline and serial follow-up scans demonstrating tumor necrosis in a patient with HCC.

## SHARP: All-Grade Treatment-Emergent Adverse Events Reported in ≥10% of Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Nexavar n=297 (%)</th>
<th>Placebo n=302 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>98</td>
<td>39</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>Pain (abdomen)</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>Weight loss</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Anorexia*</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhage/bleeding</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>2</td>
</tr>
</tbody>
</table>

*Grade 5 events — 2 (<1%) in the Nexavar treatment arm.

NCI-CTC v3.0=National Cancer Institute–Common Toxicity Criteria version 3.0.
Nexavar Package Insert.
Toxicity
Hand-Foot Skin Reaction

• More than 90% of patients experience skin reactions on multi-targeted TKI therapy
  • Hand-foot reaction reported as high as 60%

Phase III: Sorafenib vs Placebo in Asian Patients with Advanced HCC

- Primary endpoint: Not specified
- Overall endpoints: OS, TTP time to symptomatic progression, disease control rate, and safety

Advanced HCC
ECOG PS 0 - 2
Child-Pugh Class A
No prior to systemic therapy
Life expectancy ≥ 12 weeks

Randomization
N = 226

Sorafenib 400 mg PO BID
n = 150

Placebo PO BID
n = 76

Asian Patients with Advanced HCC

Overall Survival

Survival Probability

HR (S/P): 0.68
95% CI: 0.50-0.93
P = 0.014

Sorafenib
Median: 6.5 weeks
(95% CI: 5.6-7.6)

Placebo
Median: 4.2 weeks
(95% CI: 3.7-5.5)

Asian Patients with Advanced HCC

**TTP**

---

**Progression-free Probability**

- **Sorafenib**
  - Median: 2.8 months
  - (95% CI: 2.6-3.6)

- **Placebo**
  - Median: 1.4 months
  - (95% CI: 1.3-1.5)

**HR (S/P): 0.57**

95% CI: 0.42-0.79

*P* <0.001


**Patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>150</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Asian (No. (%))</td>
<td>Non-Asian (No. (%))</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Total Patients, No. (%)</strong></td>
<td>36 (78)</td>
<td>10 (22)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>27 (75)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Mean Age, Years</td>
<td>65.4</td>
<td>58.4</td>
</tr>
<tr>
<td>Body Surface Area (BSA), m²</td>
<td>1.66</td>
<td>2.12</td>
</tr>
<tr>
<td><strong>Childs-Pugh Class, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>24 (67)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>B</td>
<td>11 (31)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>C</td>
<td>1 (3)</td>
<td>1 (10)</td>
</tr>
<tr>
<td><strong>Max Tolerated Dose, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (did not tolerate any dose)</td>
<td>5 (14)</td>
<td>0</td>
</tr>
<tr>
<td>200mg daily</td>
<td>5 (14)</td>
<td>0</td>
</tr>
<tr>
<td>200mg BID</td>
<td>25 (70)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>400mg/200mg daily</td>
<td>0</td>
<td>1 (10)</td>
</tr>
<tr>
<td>400mg BID</td>
<td>1 (3)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Did not tolerate 400 mg BID</td>
<td>35 (97)</td>
<td>6 (60)</td>
</tr>
<tr>
<td><strong>Dose Outcome, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued Early</td>
<td>14 (39)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Expired While on Treatment</td>
<td>8 (22)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Still Taking</td>
<td>14 (39)</td>
<td>5 (50)</td>
</tr>
</tbody>
</table>
Phase II Doxorubicin ± Nexavar: Study Design

- 1º endpoint: TTP
- 2º endpoints: OS, PFS, ORR, safety

Eligibility
- Child-Pugh A
- ECOG PS: 0, 1, 2

(1:1) Randomization (N~100)

6 cycles of:
- Doxorubicin 60 mg/m² IV*
  Day 1 in 21-day cycles
- Nexavar 400 mg po bid

Nexavar
400 mg po bid

6 cycles of:
- Doxorubicin 60 mg/m² IV*
  Day 1 in 21-day cycles
- Placebo 2 tablets po bid

Placebo
2 tablets po bid

Continue until withdrawal, PD, or death

Doxorubicin total allowed 360 mg/m² and in approved circumstances 450 mg/m², after which Nexavar vs placebo can be continued as single agent

*At physician discretion, doxorubicin was allowed up to a maximum accumulated dose of 450 mg/m².

Secondary Outcome
Overall Survival

Exploratory Comparison Per Protocol: Overall Survival

Median OS:
- Doxorubicin + sorafenib: 13.8
  (95% CI: 9.1-cannot be estimated)
- Doxorubicin + placebo: 6.5
  (95% CI: 4.9-11.3)

Hazard Ratio: 0.51
p = 0.0129
Total # of events: 51

Primary Outcome Results
Time to Progression

Exploratory Comparison Per Protocol: Time to Progression Based on Independent Tumor Assessment

Median TTP:
- Doxorubicin + sorafenib: 8.6 months (95% CI: 4.8-12.6)
- Doxorubicin + placebo: 4.8 months (95% CI: 2.2-8)

Hazard Ratio: 0.6
p = 0.076
Total # of events: 38
Phase II Doxorubicin ± Nexavar: Maximum Percent Reduction in Tumor Measurement

Change in Target Lesion From Baseline to Smallest Tumor Size Post-Baseline

- March 2007 data cut-off
- Based on independent radiological assessment population: subjects valid for ITT

SWOG Study Design

Eligibility
- CLIP 1, 2, 3
- Child-Pugh A
- ECOG PS: 0, 1, 2

(1:1) Randomization
(N=600-700)

Period 1
- 6 cycles of:
  - Doxorubicin 60 mg/m² IV*
  - Day 1 in 21-day cycles
  - Sorafenib 400 mg po bid

Period 2
- Sorafenib 400 mg po bid
- Continue until withdrawal, PD, or death

6 cycles of:
- Sorafenib 400 mg po bid
**Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermediate-stage hepatocellular carcinoma (HCC): Phase II, randomized, double-blind SPACE trial**

<table>
<thead>
<tr>
<th>Assessment (ITT)</th>
<th>TTP</th>
<th>OS**</th>
<th>Time to VI/EHS**</th>
<th>TTUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.8</td>
<td>0.9</td>
<td>0.6</td>
<td>1.6</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.6, 1.1</td>
<td>0.6, 1.3</td>
<td>0.3, 1.2</td>
<td>1.2, 2.1</td>
</tr>
<tr>
<td>P value (1 sided)*</td>
<td>0.07</td>
<td>0.295</td>
<td>0.076</td>
<td>0.999</td>
</tr>
</tbody>
</table>

*predefined alpha = 0.15;
**median was not reached in either group.

Median TTP was 169 v 166 days
A Phase III Randomized, Double-blind, Placebo-controlled Study of Sorafenib as Adjuvant Treatment for Hepatocellular Carcinoma After Surgical Resection or Local Ablation (STORM)

Primary Outcome Measures:
• Recurrence Free Survival

Secondary Outcome Measures:
• Time to recurrence
• Overall survival
• Patient-Reported Outcome (PRO) as assessed by FACT-Hep and EQ-5D questionnaire.
• Evaluation of biomarkers

Enrollment: 1115
Study Start Date: August 2008
Primary Study Completion Date: November 2012
March 2014
Primary endpoint not met
Bevacizumab MOA in HCC

- Recombinant humanized monoclonal antibody against VEGF
- Direct and indirect anti-angiogenic effects
- May enhance chemotherapy effect by:
  - Normalizing tumor vasculature
  - Decreasing interstitial pressure
# Phase II Bevacizumab in HCC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Pts</th>
<th>Dose (mg / kg)</th>
<th>ORR (%)</th>
<th>Median PFS / TTP (months)</th>
<th>6-Month PFS (%)</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab(^1)</td>
<td>24</td>
<td>5-10</td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bevacizumab(^2)</td>
<td>28</td>
<td>5-10</td>
<td>8</td>
<td>6.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GEMOX-B(^3)</td>
<td>33</td>
<td>10</td>
<td>20</td>
<td>5.3</td>
<td>48</td>
<td>9.6</td>
</tr>
<tr>
<td>CAPEOX-B(^4)</td>
<td>30</td>
<td>5</td>
<td>13</td>
<td>4.5</td>
<td>45</td>
<td>10.3</td>
</tr>
<tr>
<td>Cape-Bev(^5)</td>
<td>44</td>
<td>7.5</td>
<td>9</td>
<td>3.6*</td>
<td>-</td>
<td>8.2*</td>
</tr>
<tr>
<td>Bev-Erlotinib(^6)</td>
<td>34</td>
<td>10</td>
<td>21</td>
<td>9.0</td>
<td>-</td>
<td>19</td>
</tr>
</tbody>
</table>

GEMOX-B = gemcitabine, oxaliplatin, bevacizumab; CAPEOX-B = capecitabine, oxaliplatin, bevacizumab

\(^*\) In patients with CLIP score ≤ 3; For patients with CLIP = 4 Median PFS\(\frac{3}{4}\) 1.4 and OS = 3.3
Phase II Sunitinib in Advanced HCC European / Asian Experience

- Open-label single-agent study
- Primary endpoint: ORR by RECIST criteria

Sunitinib 50 mg PO daily x 4 weeks  N = 37

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asia</th>
<th>Europe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>1 (6.3%)</td>
<td>-</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Partial response</td>
<td>1 (6%)</td>
<td>-</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Stable disease ≥ 6 months</td>
<td>4 (25%)</td>
<td>9 (43%)</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8 (50%)</td>
<td>5 (24%)</td>
<td>13 (35%)</td>
</tr>
<tr>
<td>Clinical benefit (PR + stable disease &gt; 3 months)</td>
<td>5 (31%)</td>
<td>9 (43%)</td>
<td>14 (38%)</td>
</tr>
</tbody>
</table>

Continue until disease progression or unacceptable toxicity

A Multinational, Randomized, Open-Label, Phase 3 Study of Sunitinib Malate Versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma

**Table 4. Deaths During the Study or Within 28 Days After the Last Dose of Study Medication**

<table>
<thead>
<tr>
<th>Event</th>
<th>Sunitinib (n = 526)</th>
<th>%</th>
<th>Sorafenib (n = 542)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, all causes*</td>
<td>92</td>
<td>17.5</td>
<td>83</td>
<td>15.3</td>
</tr>
<tr>
<td>Cause†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td>70</td>
<td>76.1</td>
<td>71</td>
<td>85.5</td>
</tr>
<tr>
<td>Toxicity</td>
<td>17</td>
<td>18.5</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Dehydration with or without organ failure</td>
<td>3</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS hemorrhage</td>
<td>3</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Esophageal varices/GI hemorrhage‡</td>
<td>3</td>
<td>3.3</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Other/unknown cause</td>
<td>6</td>
<td>6.5</td>
<td>11</td>
<td>13.3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
<td>2.2</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Septic shock/sepsis</td>
<td>1</td>
<td>1.1</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Unknown reason</td>
<td>0</td>
<td>2.4</td>
<td>0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

*Patients may have more than one cause of death.
†Cause shown as number and percentage of total deaths: sunitinib, n = 92; sorafenib, n = 83.
‡Includes deaths attributed to tumor hemorrhage.
Brivanib: Open Label First Line Therapy

![Graph showing survival rates with Brivanib QD over months.]

- **Subjects at risk**
  - Brivanib QD: 55

- **Table showing progression rates**
<table>
<thead>
<tr>
<th>Group</th>
<th>No. progressed/No. treated subjects</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brivanib</td>
<td>48/55</td>
<td>2.7 (1.4, 3.0)</td>
</tr>
</tbody>
</table>
Brivanib: Open Label First Line Therapy

B

Proportion alive

Subjects at risk
Brivanib QD 55 47 39 31 26 23 22 18 15 10 6 0

Group No. died/No. treated subjects Median (95% CI)
Brivanib 35/55 10.0 (6.8, 15.2)
April 30, 2012

The experimental cancer drug brivanib did not lengthen overall survival for patients with hepatocellular carcinoma, but it did increase time to progression, demonstrating that it had anti-tumour activity, researchers reported at the 47th International Liver Congress (EASL 2012) last week in Barcelona.

July 19, 2012 04:30 PM Eastern Daylight Time

BRISK-FL Study with Investigational Compound Brivanib in Hepatocellular Carcinoma Does Not Meet Overall Survival Primary Endpoint
Ramucirumab (IMC-1121B): a fully human VEGFR2 antagonist

- Fully human anti-VEGFR-2 IgG₁ monoclonal antibody\(^1\)
- High affinity (KD = 50 \(\text{pM}\))\(^1\)
- Blocks VEGF binding to VEGFR-2 (IC\(_{50}\) 0.8-1.0 \(\text{nM}\))\(^1,3\)
- Biochemical and anti-tumor effects
  - Inhibits ligand-dependent VEGFR-2 activation and signaling\(^4\)
  - Inhibits growth & migration of human endothelial cells\(^1\)
  - Direct anti-tumor effect in NOD-SCID mice inoculated with VEGFR-2+ HL60\(^5\)

Ramucirumab

Waterfall Plot: Preliminary Response Data

Best Overall Percent Change from Baseline of Target Lesion Measurements by Child Pugh (evaluable population, n=38)

Response Rate*:
PR  4   10%
SD  25  60%

Preliminary mPFS*: 4.0 mos
Preliminary mOS*: 12.0 mos

* ITT population, n=42

Zhu et al ILCA, Montreal Sept 2010
### Current ongoing Phase 3 trial: REACH

A Randomized, Double-blind, Placebo-controlled Phase III Study of Ramucirumab + BSC vs. Placebo + BSC as 2\textsuperscript{nd}-line Treatment in Patients with Hepatocellular Carcinoma Following 1\textsuperscript{st}-line Therapy with Sorafenib

<table>
<thead>
<tr>
<th>RANDOMIZATION</th>
<th>RAMIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>1:1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best Supportive Care</th>
<th>Ramucirumab 8 mg/kg q2wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Supportive Care</td>
<td>Placebo q2wks</td>
</tr>
</tbody>
</table>

- Progressive Disease Or Unacceptable Toxicity Or Withdrawn Consent
- F/UP until Death or Study Completion

**Study Location:** North America/EU/ East Asia

**Stratification Factors:**
- North America vs Europe vs East Asia
- Etiology of liver disease (Hep B vs C vs Other Etiologies)
- Child Pugh score (A vs B [B7 or B8])

Company announced in July 2014, primary endpoint not met
CLINICAL PROTOCOL
A MULTICENTER, GLOBAL, RANDOMIZED, DOUBLE-BLIND STUDY OF AXITINIB VERSUS PLACEBO IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA FOLLOWING FAILURE OF ONE PRIOR ANTIANGIOGENIC THERAPY

ESMO: September 2014
Primary endpoint not met
Tivantinib (ARQ 197)

- A selective, oral MET inhibitor with a novel ATP-independent binding mechanism\(^1\)

- Broad spectrum anti-tumor activity as single agent and in combination in preclinical studies including MET+ HCC cell lines\(^2-4\)

- Promising phase 1b data in HCC as monotherapy and in combination with sorafenib\(^5\) (ASCO 2012 abstract #4117, poster #50D)

- Randomized, phase 2 data in NSCLC; ongoing phase 1, 2, and 3 trials in several cancers, including NSCLC and CRC\(^6-8\)

---

Study Design

Advanced HCC
Child Pugh A
Stratified by:
ECOG PS
Vascular Invasion

2:1 Randomization
107 pts

Tivantinib
PO BID
71 pts

Placebo
PO BID
36 pts

Crossover
AFTER Rx PD
23 pts

Endpoints
1° TTP
2° PFS, OS, ORR, DCR, crossover ORR, safety, PK
3° TTP, PFS, OS in subgroups by:
- MET Diagnostic status
- Viral infection (HBV, HCV)
- Duration of prior systemic therapy

* On ITT population. Efficacy assessment based on independent radiology review. Scans performed every 6 weeks.

Data cut-off: 21 Oct 2011 (18 Apr 2012 for OS)
**OS Results (ITT Population)**

![Survival Curves]

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tivantinib</td>
<td>6.6 mos</td>
<td>71</td>
<td>56</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.2 mos</td>
<td>36</td>
<td>30</td>
</tr>
</tbody>
</table>

HR: 0.90 (95% CI: 0.57-1.40) Log Rank: P=0.63

![Survival Curves]

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tivantinib 240mg</td>
<td>7.5 mos</td>
<td>33</td>
<td>21</td>
</tr>
<tr>
<td>Tivantinib 360mg</td>
<td>6.4 mos</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.2 mos</td>
<td>36</td>
<td>30</td>
</tr>
</tbody>
</table>

240mg vs Placebo HR: 0.71 (95% CI: 0.41-1.25) Log Rank P=0.24

360mg vs Placebo HR: 1.00 (95% CI: 0.78-1.27) Log Rank P=0.98
Improved OS in MET Diagnostic High Group

- **Tivantinib**: Median OS = 7.2 mos, Patients = 22, Events = 17
- **Placebo**: Median OS = 3.8 mos, Patients = 15, Events = 15

HR: 0.38 (95% CI: 0.18-0.81) Log Rank: P=0.01

*8 MET Dx High patients crossed-over, 5 remained on open-label tivantinib for at least 6 weeks (1 non-evaluable at cut-off date)
A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY OF TIVANTINIB (ARQ 197) IN SUBJECTS WITH MET DIAGNOSTIC-HIGH INOPERABLE HEPATOCellular CARCINOMA (HCC) TREATED WITH ONE PRIOR SYSTEMIC THERAPY

SIV Presentation

Protocol Version: 3, dated 09Sep2013
Study Centers and Countries

- 120 sites
- 303 patients

**Europe**
- Austria
- Belgium
- Portugal
- France
- Germany
- Sweden
- Switzerland
- Spain
- Italy
- Netherlands

**North America**
- Canada
- United States

**South America**
- Argentina
- Brazil

**Asia/Pacific**
- Australia
- New Zealand
Study Objectives

**Primary:** Evaluate *overall survival* (OS) among all subjects in the intent-to-treat (ITT) population compared to placebo.

**Secondary:**
- Evaluate *progression free survival* (PFS) at central, independent radiology review among all subjects treated with tivantinib compared to placebo.
- Further evaluate *safety* of tivantinib in the treated HCC subjects.
METIV-HCC - Screening and Randomization

**Patient Consented**
IRT Contacted

- Ship Tumor Sample to LabCorp (biopsy if needed)
- Medical History
- SAEs (if applicable)

**MET HIGH Confirmed**

**IRT Contacted:**
Receive blinded drug allocation number

**Screening Procedures Within 14 days**

**Screening:**
Within 21 days of Randomization
- CT/MRI (Chest, Abdomen, Pelvis)
- Tumor Assessment (RECIST)

**Within 14 Days of Randomization**
- Eligibility Criteria
- Medical History
- Physical Exam
- ECOG PS
- Child Pugh Score
- Vital Signs, including height, weight, and temperature
- Central lab tests, including AFP, Hepatitis, serum pregnancy (if applicable)
- Local Hematology
- Triplicate 12-Lead ECG
- Con meds / SAEs

**Randomization**
(Blend Cycle 1/Day 1):
- Patient Questionnaires
- PE and vital signs
- ECOG PS
- Child-Pugh score
- Local Hematology
- Central Lab tests including PK & PG
- Triplicate 12-lead ECG
- Con meds / AEs
- Study Medication Dispensing
- Send Baseline scan to Icon

**Confirmation of progression or intolerance to sorafenib**

**Obtain MET status results (2-7 days after receipt)**
Pexa-Vec: Targeted & Armed Vaccinia
Engineered for Enhanced Tumor Selectivity & Immune Response Induction

Thymidine kinase gene:
- Enables replication in normal cells

lac-Z insertion
- For monitoring

GM-CSF insertion
- Drives active immunity

TK disruption:
- Selective targeting of cancer cells and tumor vasculature

Wyeth vaccine strain

Pexa-Vec
Pexa-Vec: Mechanisms-of-action

Multiple, complementary anti-tumor effects

Kirn et al, Nature Reviews Cancer 2009
Pexa-Vec clinical development overview

- >300 patients have received intratumoral and/or intravenous Pexa-Vec (>1,200 treatments)
- Pexa-Vec treatment generally well-tolerated
  - Transient flu-like symptoms
  - Transient hypotension
- Phase 2 trial in front-line HCC positive
- Phase 2b trial in second-line HCC did not meet primary endpoint
Randomized Phase 2: Enrollment Complete

N= 30

N. America & Korea

Eligibility Criteria
• Advanced, unresectable HCC
• Tumor progression during or following at least one prior HCC regimen
• 1-5 hepatic tumors ≥ 1 cm
  Child-Pugh A or B

Stratification:
• +/- viral etiology

Arm A: High Dose
Pexa-Vec 1x10⁹ pfu¹

Arm B: Low Dose
Pexa-Vec 1 x 10⁸ pfu²

Endpoints:
Clinical: tumor response, overall survival, safety
MOA: Necrosis, vascular disruption, active immunotherapy

Visit Week                        0         1         2         3         4         5         6         7        8        Wk 12         Wk 18
IT
IT
IT

1 - Phase 1 MTD
2 - 10% of high dose; activity observed in Phase 1 trials

Heo et al, Nature Medicine 2013
High vs. Low Dose Pexa-Vec in HCC

Statistically significant dose-related increase in overall survival for Pexa-Vec

Overall Survival:
14.1 vs. 6.7 mos.,
HR = 0.39, n = 29
p = 0.020

Historical reference (sorafenib vs. placebo)
SHARP: 10.7 vs 7.9 mos.
HR = 0.69, n = 602
Asia/Pac: 6.5 vs 4.2 mos.
HR = 0.68, n = 226

Pexa-Vec IT Injections into tumors
Days 1, 15, 29

- High-dose Pexa-Vec resulted in greater systemic exposure
- Tumor responses observed in both treatment arms

Heo et al, Nature Medicine 2013
Pexa-Vec Phase 2b Second-line HCC Trial (TRAVERSE)

Sorafenib failure/intolerant

**N=120 (129 enrolled)**

**Asia, N.America, Europe**

**Eligibility Criteria**
- Advanced, unresectable HCC
- Failed or intolerant of Sorafenib
- BCLC B or C
- Child-Pugh A or B7
- ECOG 0-2

**Stratification:**
- Asian vs Non-Asian region
- Intolerant vs Sorafenib failure
- Extrahepatic HCC

**Randomized 2:1**

**Arm A**
- Pexa-Vec $10^9$ IV → IT x 5 + Best Supportive Care

**Arm B**
- Best Supportive Care

**Primary Endpoint**
- OS

**Secondary Endpoints**
- RR (mRECIST), TTP, TTSP, QOL, safety

**Visit Week**
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- Wk 12
- Wk 18
Overall Study Conclusions

• No benefit in overall survival observed in the study
  – Advanced patient population may have resulted in an observed short life expectancy that could have impaired the treatment effect of Pexa-Vec
  – Median survival in control arm shorter than expected

• Overall, TRAVERSE confirmed an acceptable safety profile for Pexa-Vec, characterized by transient adverse events that are mostly preventable or manageable

• Taken in combination with the results from previous Pexa-Vec studies in HCC (HEP007), further development of Pexa-Vec in HCC earlier stages of the disease is planned

• Final results for TRAVERSE to be published later this year
N=600

Asia, N. America, Europe

Eligibility Criteria
- Post LCR or metastatic
- BCLC B or C
- No previous systemic therapy
- Histo Dx
- CP A
- ECOG(PS) 0-1
- Measurable and injectable tumors

Randomized 1:1

Arm A
- 3 x IT Pexa-Vec $10^9$
- followed by sorafenib 400 mg BID

Arm B
- Sorafenib 400 mg BID

Primary Endpoint
- OS

Secondary Endpoints
- RR (mRECIST), TTP, TTSP, QOL, safety

Visit Week

Arm A

0 1 2 3 4 5 6 7 8 Wk 12 Wk 18

Arm B

Sorafenib

Sorafenib naïve
Study endpoints

- **Primary**
  - Overall survival in Arm A vs Arm B

- **Secondary**
  - Time to tumor progression (TTP)
  - Progression free survival (PFS)
  - Overall response rate (ORR)
  - Disease control rate (DCR)
  - Safety
  - Time to symptomatic progression (TSP)
  - Quality of life (QoL)
Key Inclusion criteria

1. Male or female patients, age ≥18 years old
2. Histological/cytological diagnosis of primary HCC
3. Advanced stage HCC (Barcelona Clinic Liver Cancer [BCLC] Stage C or B per American Association for the Study of Liver Disease [AASLD] guidelines) eligible for systemic therapy excluding cholangiocarcinoma, hepatocellular carcinoma, fibrolamellar carcinoma and hepatoblastoma.
4. Tumor status (as determined by radiology evaluation): At least one measurable viable tumor in the liver (≥1 cm LD and enhancing on arterial phase of triphasic CT scan or MRI), and injectable under imaging-guidance (CT and/or ultrasound)
5. At least one tumor that has not received prior local-regional treatment, or that has exhibited >25% increase in viable tumor size since prior local-regional treatment
6. Child-Pugh Class A. **NOTE:** paracentesis, albumin infusion or diuretic treatment cannot be used to downgrade Child-Pugh score (e.g., to improve from severe to moderate/mild or from moderate-to-mild ascites)
7. Performance status 0 or 1 on the ECOG scale
Key Exclusion Criteria

1. History of moderate or severe ascites, bleeding esophageal varices, hepatic encephalopathy or pleural effusions related to liver insufficiency within 6 months of Screening
2. Bulky disease patients- tumors encompassing >50% of the liver volume and or inferior vena cava invasion.
3. Known significant immunodeficiency due to underlying illness (e.g., HIV/AIDS) and/or immune-suppressive medication including high-dose corticosteroids (defined as ≥20 mg/day prednisone or equivalent which is ongoing at the time of randomization and/or was taken for more than 4 weeks within the preceding 2 months of study treatment)
Exclusion Criteria (continued)

4. Ongoing severe inflammatory skin condition (as determined by the Investigator) requiring medical treatment
5. History of severe eczema (as determined by the Investigator) requiring prior medical treatment
6. Clinically significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions. Mild ascites that does not preclude safe IT injection of Pexa-Vec is allowed at the discretion of the treating physician.
7. Symptomatic cardiovascular disease, including but not limited to significant coronary artery disease (e.g., requiring angioplasty or stenting) or congestive heart failure within the preceding 12 months
8. Current or past history of cardiovascular disease (e.g., past history of myocardial infarction, ischemic cardiomyopathy) unless cardiology consultation and clearance has been obtained for study participation
9. Prior systemic therapy for HCC. **NOTE:** Patients receiving 7 days or less exposure to systemic therapy are allowed.
10. Hepatitis C virus therapy including interferon/pegylated interferon or ribavirin that cannot be discontinued within 14 days prior to any Pexa-Vec injection. Medical Monitor should be consulted if the patient is taking any other anti-viral medications to determine eligibility.
11. Inability to suspend treatment with anti-hypertensive medication (including but not limited to: diuretics, beta-blockers, angiotensin converting enzyme [ACE] inhibitors, aldosterone antagonists, etc.) for 48 hours prior to and 48 hours after each Pexa-Vec injection.
Study Treatment

- **Arm A: Pexa-Vec + Sorafenib**
  - Pexa-Vec (1 x 10⁹ pfu): 3 intratumoral injections of 1 x 10⁹ pfu suspended in sterile normal saline buffered in sodium bicarbonate. *Intrahepatic tumors only* (Day 1, Day 15, Day 29)
  - Sorafenib (400 mg BID): Treatment will be initiated at visit Week 6, or 2 weeks after the third Pexa-Vec IT (*whichever is later*).

- **Arm B: Sorafenib**
  - Sorafenib dosing of 400 mg (oral, BID) will be started on Day 1
Multipronged Injection Needle
Quadra-Fuse (QF) / Quadra-Fuse ST (REX Medical)
Irreversible Electroporation (IRE)

Intact Cell Membrane → Electroporation → Disruption of Cell Membrane

Application of short pulse high-voltage DC current
What is the NanoKnife
NanoKnife

- Approved by the FDA under a 510K for soft tissue ablation.
- Cell death is caused by microelectrical pulses that cause irreversible damage to cell membranes.
- Although the vascular smooth muscle cells of arteries are affected by IRE, the actual blood vessel (which is not cellular) remains unaffected.
## NanoKnife Generator Specifications

<table>
<thead>
<tr>
<th>Specification</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Probe Outputs</td>
<td>1-6</td>
</tr>
<tr>
<td>Number of Pulses*</td>
<td>90</td>
</tr>
<tr>
<td>Pulse Amplitude</td>
<td>100 to 3000 V</td>
</tr>
<tr>
<td>Pulse Length</td>
<td>20 - 100 $\mu$Sec</td>
</tr>
<tr>
<td>Pulse Amplitude Precision</td>
<td>$\pm$5%</td>
</tr>
<tr>
<td>Pulse Length Precision</td>
<td>$\pm$2 $\mu$Sec or 2%</td>
</tr>
<tr>
<td>Maximum Current</td>
<td>50 A</td>
</tr>
</tbody>
</table>

* Number of pulses for each pair of electrodes.
Animal Studies: Liver

- Sharp demarcation between IRE-ablated zone and normal liver is shown.
- Intact vessels and bile ducts are seen in area of ablation.
Dear Dr. Imagawa:

The Food and Drug Administration (FDA) has reviewed your investigational device exemptions (IDE) application. We regret to inform you that your application to conduct a clinical investigation is disapproved and you may not begin your investigation. Our disapproval is based on the following safety deficiencies:
UCI Patient #7

Pre op

POD #1

POD #30

POD# #90
UCI: Patient #4

POD #1

POD #37

POD #158
Edema Zone Following Nanoknife Ablation of Liver Lesions

Average Percentage Change in Tumor Volume
Post-operative Day over Baseline

- Percent
- 0
- 1000
- 2000

n=21  n=20  n=8  n=14  n=3  n=3  n=5  n=6

Day 0  Day 1  Day 7  Day 30  Day 60  Day 90  Day 120  Day 180

Post-operative Day
UCI: Patient #4

- New Tumor
- Necrotic appearing tissue around ablation site
- Hole at old nanoknife site
UCI: Patient #4
UCI Experience: Minimum one year follow up

- 18 patients
  - 12 liver
  - 2 porta hepatis
  - 3 pancreas
  - 1 retroperitoneum
- Median survival not yet achieved
- Complications
  - 2 bile leaks
  - 1 portal vein thrombosis
  - 1 chylous leak
  - 1 hepatic vein thrombosis
Conclusions

- Curative modalities for HCC are rare
  - Transplant
  - Resection
  - RFA
- Multiple modalities exist for the treatment of unresectable HCC
- A multidisciplinary approach leads to better survival outcomes