Advanced Hepatocellular Carcinoma: The SEARCH trial

Discussant
Manfred P. Lutz
Caritasklinikum St. Theresia
Saarbrücken, Germany
Disclosure slide

Speaker / Advisory role

Bayer
Celgene
Clovis
Merck
Sanofi-Aventis
HCC

Major world health problem

• 90% of all primary liver cancers
• 3-7% of all cancers worldwide
• 3rd cause of cancer-related deaths
• Incidence rising (in the US x2 in 15 years)
HCC – Mortality rates

Adapted from:
El-Serag HB, Rudolph KL: Gastroenterology 2007, 132: 2557
HCC

Well defined risk factors

- Hepatitis B (50%)
- Hepatitis C
- Alcoholic liver disease
- Hemochromatosis
- Aflatoxin, Vinyl chloride
- NASH (non-alcoholic steatohepatitis)

Clinical situation

- Most Patients (90%) suffer from liver cirrhosis
- HCC is the leading cause of death in liver cirrhosis
HCC- treatment overview

Early and intermediate stage tumors:
• resection, liver transplant, local ablation (potentially curative)
• Chemo- or radioembolization (mOS 20 months)

Advanced tumors (BCLC C: portal invasion, N1, M1):
• No confirmed survival benefit in phase III trials e.g. for
  - chemotherapy
  - tamoxifen
  - immunotherapy
• 2008: Two positive trials for sorafenib

EASL-EORTC Clinical Practice Guideline
J Hepatol 2012; 56: 908
Sorafenib in advanced HCC

- **SHARP trial** (Llovet et al., NEJM 359:378, 2008)
  - N = 602, sorafenib vs. placebo
  - 10.7 vs. 7.9 months (HR 0.69, 95% CI 0.55-0.87)

- **Asia-Pacific trial** (Cheng et al. Lancet Oncol 10:25, 2009)
  - N = 271, 2:1 sorafenib vs. Placebo
  - median OS **6.5 vs. 4.2 months** (HR 0.68, 95% CI 0.50-0.93)
SEARCH
A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Sorafenib plus Erlotinib in Patients with Hepatocellular Carcinoma (HCC)

Andrew X. Zhu

Olivier Rosmorduc, T. R. Jeffrey Evans, Paul Ross, Armando Santoro, Flair Jose Carrilho, Marie-Aude Leberre, Markus Jensen, Gerold Meinhardt, Yoon-Koo Kang

1Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; 2Service d'hépatologie, hôpital Saint-Antoine, Paris, France; 3Beatson West of Scotland Cancer Centre, Institute of Cancer Sciences, University of Glasgow, Glasgow, UK; 4King’s College Hospital, London, UK; 5Humanitas Cancer Center, Milan, Italy; 6Department of Gastroenterology, University of São Paulo School of Medicine, São Paulo, Brazil; 7Bayer HealthCare Pharmaceuticals, Loos, France; 8Bayer Vital GmbH, Leverkusen, Germany; 9Bayer HealthCare Pharmaceuticals, Montville, NJ, USA; 10University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea
SEARCH: Trial summary

- Advanced HCC
- Child-Pugh A
- PS 0, 1

Inclusion criteria similar to SHARP and AP studies

Randomize

n = 720

1:1

Stratification:
- ECOG PS
- Geographic region
- Extrahepatic spread
- Smoking

Primary endpoint:
- OS

Secondary endpoints:
- TTP
- DCR
- Safety

Sorafenib 400 mg bid + Placebo 150 mg qd

Sorafenib 400 mg bid + Erlotinib 150 mg qd

The higher of the two approved erlotinib doses (100 mg; 150 mg) was selected
SEARCH: Rationale

- Sorafenib inhibits PDGFRβ, VEGFRs, c-Raf, B-Raf kinases
- Erlotinib inhibits EGFR, may thus be synergistic

Erlotinib

- EGFR is overexpressed in hepatic fibrosis, early HCC
- The ligands EGF and TGFβ are mitogenic for hepatocytes
- EGF expression has been demonstrated in HCC cell lines
- Two single agent phase II trials with encouraging results
  - mOS 10.75 months and 13 months
  - no correlation with EGFR expression (68% and 52%)

Yamaguchi K et al. J Surg Oncol 1995, 58: 240
SEARCH: Statistics

• N=720 pts with advanced HCC
• Primary end point:
  33% increase in median OS
  521 events (90% power, α one-sided 0.025)
• Current Analysis:
  Database lock 7th June 2012
  523 deaths (72.6% of 720 pts)
Overall Survival*

HR: 0.929
95% CI: 0.781, 1.106
P = 0.204 (1-sided)

Sorafenib + Erlotinib
Median: 289 days – 9.5 mo

Sorafenib + Placebo
Median: 259 days – 8.5 mo

*ITT Population
Overall Survival*

**Sorafenib + Erlotinib**
Median: 289 days – 9.5 mo

**Sorafenib + Placebo**
Median: 259 days – 8.5 mo

*ITT Population*

- HR for OS: 0.93 (p=0.2)
- OS gain of 30 days = 12% (aim: 33%)
- DCR better in control arm (p=0.01)

> Negative trial!
Obvious Reasons?

- **Backbone Sorafenib > well supported**
  - 2 phase III trials

- **Rationale > can be defended**

- **Trial Design > solid**
  - standard dose of inhibitors
  - sufficiently powered two arm phase III
  - completed in time with expected event number
  - aim 33% probably too enthusiastic (SHARP 36%)

- **Patient population > standard**

- **Toxicity > fairly similar in both arms**
Can we leave it there?

- OS in the control arm (S) of SEARCH is less than in SHARP (8.5 vs. 10.7 months)

- Sorafenib/Erlotinib
  - Trend for better OS
  - More Responses (p 0.051)

- Sorafenib/Placebo
  - Better disease control (p 0.01)
# SEARCH: Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>SEARCH (S ± Erlot) N=720</th>
<th>SHARP (S vs. Placebo) N=602</th>
<th>Asia/Pacific (S vs. Placebo) N=226</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>61y</td>
<td>65y</td>
<td>51y</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>81%</td>
<td>87%</td>
<td>86%</td>
</tr>
<tr>
<td><strong>Europe/Americas vs. Asia</strong></td>
<td>75/25</td>
<td>100/--</td>
<td>--/100</td>
</tr>
<tr>
<td><strong>ECOG PS 0/1/2</strong></td>
<td>61/39</td>
<td>54/38/8</td>
<td>26/68/5</td>
</tr>
<tr>
<td><strong>Child Pugh A</strong></td>
<td>97</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td><strong>BCLC Stage B/C</strong></td>
<td>15/85</td>
<td>18/82</td>
<td>4/96</td>
</tr>
<tr>
<td><strong>Hepatitis B/C</strong></td>
<td>35/27</td>
<td>18/28</td>
<td>74/9</td>
</tr>
<tr>
<td><strong>Prior Embolization (TACE)</strong></td>
<td>29%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td>8%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td><strong>OS Sorafenib arm</strong></td>
<td>8.5</td>
<td>10.7</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Llovet et al. NEJM 2008, 359: 378
Cheng et al. Lancet Oncol 2009, 10: 25
Can we leave it there?

- OS in the control arm (S) of SEARCH is less than in SHARP (8.5 vs. 10.7 months)

- Sorafenib/Erlotinib
  - Trend for better OS
  - More Responses (p 0.051)

- Sorafenib/Placebo
  - Better disease control (p 0.01)
### SEARCH: efficacy?

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib + Placebo</th>
<th>Sorafenib + Erlotinib</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>4%</td>
<td>7%</td>
<td>0.051</td>
</tr>
<tr>
<td>Overall survival</td>
<td>8.5 mo</td>
<td>9.5 mo</td>
<td>0.2</td>
</tr>
<tr>
<td>Time to progression</td>
<td>4.0 mo</td>
<td>3.2 mo</td>
<td>0.9</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>53 %</td>
<td>44%</td>
<td>0.01</td>
</tr>
<tr>
<td>(CR + PR + SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## SEARCH: toxicity and treatment

<table>
<thead>
<tr>
<th>SAEs</th>
<th>Sorafenib  + Placebo</th>
<th>Sorafenib  + Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment emergent</td>
<td>194</td>
<td>210</td>
</tr>
<tr>
<td>Deaths during first 30 days tx</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Deaths up to 30 days after tx</td>
<td>65</td>
<td>76</td>
</tr>
</tbody>
</table>

### Selected AEs (all grade)

<table>
<thead>
<tr>
<th>AE</th>
<th>Sorafenib + Placebo</th>
<th>Sorafenib + Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>40%</td>
<td>52%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>37%</td>
<td>43%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59%</td>
<td>76%</td>
</tr>
</tbody>
</table>

### Study drug administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sorafenib + Placebo</th>
<th>Sorafenib + Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>Interruptions</td>
<td>80%</td>
<td>83%</td>
</tr>
<tr>
<td>Median Tx duration</td>
<td>4.0 months</td>
<td>2.8 months</td>
</tr>
</tbody>
</table>
Toxicity and DFS ?

• Number of reported AEs are slightly higher in the experimental arm
• Treatment duration is shorter

> Increased toxicity per time period !!
> Impact on disease control rate likely:
  - no tumor measurements at end of study;
  - in case of termination for toxicity, the date of the previous measurement was used for definition of confirmed DC
Overall Survival*

- HR for OS: 0.93 (p=0.2)
- OS gain of 30 days = 12% (aim: 33%)
- RR improved with Erlotinib (p = 0.051)
- DCR better in control arm ??

> Negative trial ?!
> Rationale ??
HCC
HCC

EGF-R
Kit
FGF-R
cMET
PDGF-R
Ras
Raf
Mek
Erk
PI3K
Akt
mTor
S

STAT
Jak

www.esmo2012.org
HCC

• Highly vascularized tumor
• Dependent on angiogenesis
• Gene signature as in liver regeneration
• Develops in cirrhotic liver
  - loss of liver mass
  - Macroenvironment of growth factor activity
  - mainly angiogenic factors
  - mesenchymal stimulation through HGF/met
  - less expression of EGF
Sorafenib

**Triple action (at least)**

- Inhibits angiogenesis through the VEGFR/PDGFR
- Inhibits met-stimulated epithelial-mesenchymal transition through Raf
- Decreases paracrine secretion of HIF-1α / VEGF

Nagai T et al. Mol Cancer Ther 2011; 10: 169
Erlotinib

Action in HCC?

• Erlotinib induces VEGF mRNA, thus stimulating endothelial cell migration and vascular sprouting.

• Erlotinib downregulates ERK phosphorylation without effect on cell viability (in contrast to Sorafenib, which inhibits both).

• But: Erlotinib is effective in some Sorafenib-resistant cell lines.

Ezzoukhry Z et al. Int J Cancer; 2012 epub
Sieghart et al. J Hepatol 2012; 57: 592

www.esmo2012.org
HCC are highly heterogeneous

Zhang Z. Nature Genetics 2012, 10: 1075
HCC are highly heterogeneous

Zhang Z. Nature Genetics 2012, 10: 1075
Summary

• The combination of Sorafenib/Erlotinib as compared to Sorafenib/Placebo did not significantly improve overall survival in a mixed population of HCC

• Erlotinib treatment increased the toxicity in the experimental arm which likely influenced the statistical evaluation of TTP and DCR

• Subgroups of HCC may profit from Erlotinib treatment
Conclusion

- Sorafenib remains the standard treatment for advanced HCC
- Combinations with less toxicity needed
- Subgroup analysis necessary
  - Hep B vs. Hep C vs. other causes
  - Extention of disease (local vs. metastatic?)
  - EGFR copy number, mutation
  - EGFR downstream target (Ras, Raf)
  - VEGFR and Ligands
  - HGF/met
  - Epiregulin/Amphiregulin