Novel Targeted Agent for HCC Treatment

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Novel Targeted Agent for HCC Treatment

- Role of systemic treatment in HCC
- Molecular targets which is being explored in HCC
- Sorafenib: current evidence and its clinical implication
Position of systemic therapy in HCC

- **1st line systemic therapy for advanced HCC**
  - Unresectable, above Milan, TACE not feasible (gross vascular invasion/distant metastasis)
  - Sorafenib indicated

- **Rescue therapy in TACE failure**
  - Sorafenib indicated

- **Adjuvant therapy after resection**
  - Trial with sorafenib is now on-going
  - Adoptive Immunotherapy possible

- **Neoadjuvant setting: still no proven efficacy**
Challenges in systemic therapy in HCC

➢ Efficacy of sorafenib is modest and mainly cytostatic
  – 1\textsuperscript{st} line systemic therapy for advanced HCC: Sorafenib
    → Strong need for more efficacious systemic drug
  – TACE is still widely performed in Asia as a palliative treatment
    → Role of TACE + systemic treatment is being explored

➢ No consensus in the definition of TACE failure
  – Rescue therapy in TACE failure: Sorafenib

➢ No proven adjuvant therapy after resection
  – No consensus in treatment duration, High cost

• Huge need for new agent with better efficacy than sorafenib in HCC
Intracellular network circuits in HCC
Potential targets of molecular targeted agent

- Wnt/β-catenin
- RAS/RAF/MEK/ERK
- PI3K/Akt/mTOR
- Apoptosis
- Cell cycle
- Inflammatory pathway IL-6/STAT3, TNF-α, NF-κB, COX-2
- Angiogenesis

Semin Oncol 39:486-492
Molecular targets and targeted agents of several growth factors and receptors

Semin Oncol 39:486-492
Molecular targets and targeted agents in intracellular signaling in HCC

PI3K/Akt/mTOR

RAS/RAF/MEK/ERK

Semin Oncol 39:486-492
## Clinical trials of molecular targeted agents as a monotherapy

<table>
<thead>
<tr>
<th>Agent as monotherapy</th>
<th>Target</th>
<th>Design</th>
<th>Agent as monotherapy</th>
<th>Target</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sorafenib</strong> (Nexavar, BAY43-9006; Bayer)</td>
<td>BRAF, VEGFR-2, VEGFR-3, PDGFR-b, c-KIT, Flt3</td>
<td>Registered</td>
<td>Bevacizumab (Avastin; Genetech/Roche)</td>
<td>VEGF</td>
<td>Phase II</td>
</tr>
<tr>
<td>Regofarenib (fluoro-sorafenib, BAY73-4506; Bayer)</td>
<td>BRAF, VEGFR-2, VEGFR-3, PDGFR-b, c-KIT, Flt3, Tie2</td>
<td>Phase I/II</td>
<td>Erlotinib (Tarceva, OSI774; Genetech)</td>
<td>EGFR</td>
<td>Phase I/II</td>
</tr>
<tr>
<td><strong>Sunitinib</strong> (Sutent, SU11248; Pfizer)</td>
<td>VEGFR-1 VEGFR-2, PDGFR-α, PDGFR-b, c-KIT, Flt3, RET, CSF-1R</td>
<td>Phase III</td>
<td>Lapatinib (Tyverb, GW572016; GSK)</td>
<td>VEGFR, HER2/neu</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>Brivanib</strong> (BMS-582664; BMS)</td>
<td>VEGFR-2, VEGFR-3, FGFR-2, FGFR-3</td>
<td>Phase III</td>
<td>Gefitinib (Iressa, ZD1839; AstraZeneca)</td>
<td>EGFR</td>
<td>Phase II</td>
</tr>
<tr>
<td>Linifanib (ABT-869; Abbott)</td>
<td>VEGFR-2, PDGFR-b, CSF-1R</td>
<td>Phase II</td>
<td>Cetuximab (Erbitux, IMC-C225; BMS, Merck Serono)</td>
<td>EGFR</td>
<td>Phase II</td>
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<tr>
<td>Pazopanib (GW786034, Votrient; GSK)</td>
<td>VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-b, c-KIT</td>
<td>Phase I</td>
<td>OSI-906 (OSI Pharmaceuticals)</td>
<td>IGF-1R, IR</td>
<td>Phase II</td>
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<tr>
<td>TSU-68 (SU6668; Taiho)</td>
<td>VEGFR-2, PDGFR-β, FGFR-1</td>
<td>Phase I/II</td>
<td>Cixutumumab (IMC-A12; ImClone Systems Inc)</td>
<td>IGF-1R</td>
<td>Phase II</td>
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<tr>
<td>Foretinib (XL880, GSK1363089; GSK)</td>
<td>VEGFR-2; c-MET</td>
<td>Phase I/II</td>
<td>BIIB022 (Biogen-Idec)</td>
<td>IGF-1R</td>
<td>Phase I</td>
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<tr>
<td>E7080 (Eisai)</td>
<td>VEGFR-1, VEGFR-2, VEGFR-3</td>
<td>Phase I/II</td>
<td>AVE1642 (Sanofi-Aventis)</td>
<td>IGF-1R</td>
<td>Phase I/II</td>
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<td>BIBF 1120 (Vargatef; Boeringer Ingelheim)</td>
<td>VEGFR-2, PDGFR-b, FGFR</td>
<td>Phase II</td>
<td>Everolimus (RAD001; Novartis)</td>
<td>mTOR</td>
<td>Phase I/II</td>
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<tr>
<td>XL184 (BMS907351; BMS)</td>
<td>VEGFR-2; c-MET</td>
<td>Phase II</td>
<td>Temsirolimus (Torisel; Wyeth Pharmaceuticals, Inc)</td>
<td>mTOR</td>
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<tr>
<td>Dovitinib (TKI258; Novartis)</td>
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<td>Phase II</td>
<td>AZD8055 (AstraZeneca)</td>
<td>mTOR</td>
<td>Phase I/II</td>
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<tr>
<td>Cediranib (Recentin, AZD2171; AstraZeneca)</td>
<td>VEGFR-2</td>
<td>Phase II</td>
<td>ARQ197 (ArQule, Inc)</td>
<td>c-Met</td>
<td>Phase I/II</td>
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<tr>
<td>Vandetanib (Zactima, ZD6474; AstraZeneca)</td>
<td>VEGFR, RET, EGFR</td>
<td>Phase I/II</td>
<td>MK-2206 (Merck &amp; Co., Inc.)</td>
<td>Akt</td>
<td>Phase II</td>
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<tr>
<td>Foretinib (XL880, GSK1363089; GSK)</td>
<td>VEGFR-2; c-Met</td>
<td>Phase I</td>
<td>AZD6244 (ARRY-142886, Selumetinib; AstraZeneca)</td>
<td>MEK</td>
<td>Phase I/II</td>
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<td>Ramucirumab (IMC-1121B; ImClone Systems Inc)</td>
<td>VEGFR-2</td>
<td>Phase II/III</td>
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### Clinical trials of molecular targeted agents as a combination with other MTA or cytotoxic therapy

<table>
<thead>
<tr>
<th>Combination of targeted agents</th>
<th>Design</th>
<th>Targeted agents in combination with cytotoxic therapy</th>
<th>Design</th>
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</thead>
<tbody>
<tr>
<td>Sorafenib + Erlotinib</td>
<td>Phase III</td>
<td>Erlotinib + Gemcitabine- Oxaliplatin (GEMOX)</td>
<td>Phase II</td>
</tr>
<tr>
<td>Sorafenib + AVE1642</td>
<td>Phase I/II</td>
<td>Erlotinib + Docetaxel</td>
<td>Phase II</td>
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<tr>
<td>Sorafenib + BIBF 1120</td>
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<td>Cetuximab + Capecitabine- Oxaliplatin (CAPEOX)</td>
<td>Phase II</td>
</tr>
<tr>
<td>Sorafenib + Panobinostat (LBH589, Novartis)</td>
<td>Phase I</td>
<td>Bevacizumab + TACE</td>
<td>Phase II</td>
</tr>
<tr>
<td>Sorafenib + Cixutumumab</td>
<td>Phase I</td>
<td>Bevacizumab + Gemcitabine- Oxaliplatin (GEMOX)</td>
<td>Phase II</td>
</tr>
<tr>
<td>Sorafenib + OSI-906</td>
<td>Phase III</td>
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<td>Sorafenib + BIIB022</td>
<td>Phase I</td>
<td></td>
<td></td>
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<tr>
<td>Sorafenib + Temsirolimus</td>
<td>Phase I/II</td>
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<td>Sorafenib + ARQ197</td>
<td>Phase I</td>
<td></td>
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<tr>
<td>Sorafenib + AZD6244</td>
<td>Phase I/II</td>
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<tr>
<td>Erlotinib + Bevacizumab</td>
<td>Phase II</td>
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<tr>
<td>Erlotinib + AVE1642</td>
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<tr>
<td>Erlotinib + Celecoxib</td>
<td>Phase I/II</td>
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</tr>
<tr>
<td>Bevacizumab + Everolimus</td>
<td>Phase II</td>
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</tbody>
</table>
Sorafenib: current evidence and its clinical implication

- Sorafenib: an unique approved MTA in HCC

- After SHARP trial, all the trials of MTA have to use it as a reference in their trials.
Sorafenib: the first systemic targeted therapy to show significant survival benefit in advanced HCC

Results from pivotal trials demonstrated that sorafenib consistently increased overall survival in different patient populations across geographic regions and etiologies\textsuperscript{1,2}

BCLC staging and AASLD guideline

HCC

Stage 0
PST 0, Child–Pugh A

Stage A–C
PST 0–2, Child–Pugh A–B

Stage D
PST > 2, Child–Pugh C

Very early stage (0)
1 HCC < 2 cm
Carcinoma in situ

Early stage (A)
1 HCC or 3 nodules < 3 cm, PST 0

Intermediate stage (B)
Multinodular, PST 0

Advanced stage (C)
Portal invasion, N1, M1, PST 1–2

End stage (D)
Symptomatic treatment (20%)
Survival < 3 months

Resection
Liver transplantation
PEI/RFA
TACE
Sorafenib

Curative treatments (30%)
5-year survival (40–70%)
Palliative treatments (50%)
Median survival 11–20 months

Associated diseases
Yes
No

Portal pressure/bilirubin
Increased
Associated diseases

Normal

Hepatology 2011;53:1020–1022
BCLC is not applicable in all the cases...

- Sorafenib is indicated in advanced HCC as a 1\textsuperscript{st} line Tx and TACE refractory HCC as a rescue therapy
  1) Response is mainly cytostatic and modest (3 mon benefit)
  2) High cost is another obstacle of sorafenib
  3) Combination of other treatment to sorafenib in advanced HCC is another option to be explored
    - Sorafenib + TACE, sorafenib + other molecular targeted therapy
  4) Definition of TACE failure/refractoriness?
Research direction after sorafenib

• Developing new drug

• Extending role of sorafenib
  – Combination with other targeted agent or cytotoxic chemotherapy
  – Combination with TACE
  – Adjuvant treatment
1st line therapy in advanced HCC
Phase III Sunitinib vs Sorafenib

SUN1170 HCC – Study Design

Enrollment Criteria
- Advanced histologically confirmed HCC
- No prior systemic chemotherapy
- ECOG PS 0–1
- Child-Pugh group A

Stratification
- Region (Asia vs Ex-Asia)
- Prior TACE (≤3 vs. >3 courses)
- Tumor invasion (presence vs. absence of vascular invasions and/or extrahepatic spread)

Randomization

Sunitinib
37.5 mg/day CDD (N=600)

Sorafenib
400 mg BID (N=600)

Endpoints
- Primary: OS
- Secondary
  - PFS
  - TTP
  - Safety

Statistics
- Superiority/non-inferiority design
- Hypothesis: increase in median OS from 10.7 to 13.3 months
- Non-inferiority boundary of median OS (9.5, 11.5 months)
- 1-sided log-rank test; α=0.025, 90% power

BID: twice daily; CDD: continuous daily dosing; ECOG PS: Eastern Cooperative Oncology Group performance status; PFS: progression-free survival; TACE: transarterial chemoembolization
OS – Primary Endpoint
(ITT Population)

- **Sunitinib**
  - Median 7.9 months (95% CI: 7.4–9.2)
  - Hazard Ratio (HR) 1.30 (95% CI: 1.13–1.50)
  - P-value: 0.0010

- **Sorafenib**
  - Median 10.2 months (95% CI: 8.9–11.4)

**Patients at risk**

<table>
<thead>
<tr>
<th>Months</th>
<th>Sunitinib</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>530</td>
<td>544</td>
</tr>
<tr>
<td>5</td>
<td>354</td>
<td>388</td>
</tr>
<tr>
<td>10</td>
<td>208</td>
<td>245</td>
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<tr>
<td>15</td>
<td>112</td>
<td>139</td>
</tr>
<tr>
<td>20</td>
<td>41</td>
<td>61</td>
</tr>
<tr>
<td>25</td>
<td>8</td>
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<td>30</td>
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<td>35</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

P-value based on stratified log-rank test; CI: confidence interval; HR: hazard ratio
## Deaths on Study*

*(All Causes; As-treated Population)*

<table>
<thead>
<tr>
<th>Event</th>
<th>Sunitinib (N=526)</th>
<th>Sorafenib (N=542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (all causes; n, %)</td>
<td>92 (17%)</td>
<td>83 (15%)</td>
</tr>
<tr>
<td>Cause (% of total deaths: SU n=92; SO n=83)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td>76%</td>
<td>86%</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydration ± organ failure</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td>CNS hemorrhage</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td>Esophageal varices/GI hemorrhage†</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Other/unknown cause</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Septic shock/sepsis</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Unknown reason</td>
<td>0</td>
<td>2%</td>
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</table>

*Deaths during the study or within 28 days after the last dose of study medication. Subjects may have more than one cause of death; †includes deaths attributed to tumor hemorrhage. CNS: central nervous system; GI: gastrointestinal; SU: sunitinib; SO: sorafenib*
## Phase III 2nd line therapy Brivanib vs Placebo (BRISK-PS)

<table>
<thead>
<tr>
<th></th>
<th>Brivanib (n=263)</th>
<th>Placebo (n=132)</th>
<th>Brivanib vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>9.4 mon</td>
<td>8.2 mon</td>
<td>0.89</td>
</tr>
<tr>
<td>Median TTP</td>
<td>4.2 mon</td>
<td>2.7 mon</td>
<td>0.56</td>
</tr>
<tr>
<td>DCR</td>
<td>71.2%</td>
<td>49.1%</td>
<td>NA</td>
</tr>
<tr>
<td>ORR</td>
<td>11.5%</td>
<td>1.9%</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Brivanib vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.89</td>
</tr>
<tr>
<td>OR</td>
<td>NA</td>
</tr>
<tr>
<td>P</td>
<td>0.3307</td>
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<td>0.56</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>0.0001</td>
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<tr>
<td></td>
<td>2.69</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>5.75</td>
</tr>
<tr>
<td></td>
<td>0.0032</td>
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</table>

Llovet et al. ILCA 2012

## Phase III Randomized 1st line Brivanib vs Sorafenib (BRISK-FL)

- Press release, July 19, 2012 04:30 PM Eastern Daylight Time
- BRISK-FL Study with Investigational Compound Brivanib in HCC does Not Meet Overall Survival Primary Endpoint
1st line combination therapy in advanced HCC
Phase III sorafenib + erlotinib vs sorafenib + placebo

ESMO LBA2 | SEARCH: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Sor Plus Erlotinib in Pts with HCC  A.X. Zhu, et al.

**Objective**
- To compare the efficacy and safety of sorafenib plus erlotinib with sorafenib plus placebo as first-line treatment in patients with advanced/unresectable HCC

**Design**
- Randomized, double-blind, placebo-controlled phase III trial conducted in 26 countries in Europe, North and South America, and Asia Pacific
- Study aim: show a 33% increase in median OS compared to sorafenib + placebo using a one-sided alpha of 0.025; a total of 521 events are required to achieve 90% power

The addition of erlotinib to sorafenib did not significantly prolong OS (HR 0.929) or TTP (HR 1.135).
Sorafenib is the first and unique targeted therapy to significantly prolong survival in HCC patients.

- Although efficacy of Sorafenib is not considered to be enough, there is still no other options as a 1st line systemic therapy in HCC.

- There is still no systemic combination regimen superior to sorafenib monotherapy.

- Huge number of clinical trials of different MTA are now on-going.
Sorafenib + TACE combination therapy in HCC

- TACE could have benefit in subgroup of advanced HCC
- TACE is still widely performed in advanced HCC
  → searching for synergistic effect of sorafenib + TACE

- Enrolment criteria and study design
  - Intermediate stage or TACE eligible advanced stage

- Difficulties in clinical trials of TACE combination treatment
  - Efficacy evaluation
    - “Treatment failure” is not well defined
    - Progression by mRECIST is not always treatment failure, but rather could be “an indication” for further TACE treatment
  - Standardization of TACE procedure
    - No standard in TACE interval, chemotherapeutic agents, and decision of next sessions of TACE
Phase III Study of Sorafenib in Patients in Japan and South Korea with Advanced Hepatocellular Carcinoma Treated After Transarterial Chemoembolization (TACE)

Stratification factors:
- Response to TACE (CR vs non-CR)*
- ECOG PS (0 vs 1)
- Number of prior TACE (1 vs 2)

TACE
N=552

Median 9.3 wks
(≤3 months)

CT scan

Median 5.4 wks
(>4 wks)

Median 3.6 wks
(<6 wks)

Randomization
N=458

1:1

CT scan

n=229

Sorafenib
400 mg bid

n=229

Placebo

TTP by central review
- Primary endpoint
  - 324 PD events

OS
- Secondary endpoint

TTP by Central Review
Primary Endpoint

Progression-Free Probability

Days from Randomization

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib (n=229)</th>
<th>Placebo (n=229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at risk</td>
<td>229</td>
<td>229</td>
</tr>
<tr>
<td>Days from Randomization</td>
<td>1200</td>
<td>1200</td>
</tr>
<tr>
<td>0</td>
<td>70</td>
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<td>1000</td>
<td>1</td>
<td>0</td>
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<tr>
<td>1200</td>
<td>0</td>
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</tbody>
</table>

HR (S/P): 0.87
95% CI: 0.70, 1.09
P=0.252 (2-sided)

Sorafenib (n=229) Median: 164 days (5.4 mo)
(95% CI: 116, 220)

Placebo (n=229) Median: 112 days (3.7 mo)
(95% CI: 106, 122)
Overall Survival
Secondary Endpoint

Survival Probability

Days from Randomization

HR (S/P): 1.06
95% CI: 0.69, 1.64
P=0.790 (2-sided)

Sorafenib (n=229) Censored
Median: 903 days (29.7 mo)
(95% CI: 872, NE)

Placebo (n=229) Censored
Median: NE
(95% CI: NE, NE)

Patients at risk

<table>
<thead>
<tr>
<th></th>
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<tbody>
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<td>20</td>
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<tr>
<td></td>
<td>3</td>
<td>0</td>
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</table>

NE=not estimable due to immaturity of data.
TTP (Central Review): Japanese and S. Korean Patients
Exploratory Subgroup Analysis

Japanese Patients
- Sorafenib (n=196)
  Median: 119 days (3.9 mo)
- Placebo (n=191)
  Median: 112 days (3.7 mo)

HR (S/P): 0.94
95% CI: 0.75, 1.19

Korean Patients
- Sorafenib (n=33)
  Median: NE
- Placebo (n=38)
  Median: 166 days (5.5 mo)

HR (S/P): 0.38
95% CI: 0.18, 0.81

<table>
<thead>
<tr>
<th></th>
<th>Japan Sorafenib</th>
<th>Japan Placebo</th>
<th>S. Korea Sorafenib</th>
<th>S. Korea Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of treatment, weeks</td>
<td>16.1</td>
<td>19.6</td>
<td>30.9</td>
<td>33.3</td>
</tr>
<tr>
<td>Median daily dose, mg</td>
<td>381.8</td>
<td>786.0</td>
<td>402.6</td>
<td>766.1</td>
</tr>
</tbody>
</table>
SPACE trial
Study Schema

**Inclusion Criteria**
- Unresectable, multinodular, HCC
- Child-Pugh A without ascites or encephalopathy
- ECOG PS of 0

**Exclusion Criteria**
- Vasc. invasion, extrahepatic spread (VI/EHS)
- Planned liver transplantation
- Previous local therapy to target lesion
- Prior TACE, prior systemic therapy

**Randomize**

- First TACE with DEBDOX performed 3-7 days after start of treatment with sorafenib or placebo
- Subsequent TACE with DEBDOX performed on day 1 (±4 days) of cycles 3, 7, and 13, and every 6 cycles thereafter
- Patients allowed optional TACE with DEBDOX sessions between cycles 7 and 13 and cycles 13 and 19, if deemed necessary by the investigator

**Primary Endpoint**
- Time to progression (by central review)

**Secondary Endpoints**
- Overall survival
- Time to VI/EHS
- Time to untreatable progression
- Safety

**Randomize**

- Imaging
  - TACE (optional)
  - Cycle no (±4 weeks)

- Sorafenib 400mg bid
  - n=154

- Matching Placebo
  - n=153
TTP by Central Review
Primary Endpoint

HR: 0.797
95% CI: 0.588, 1.08
P = 0.072

Sorafenib
Median: 169 days
95% CI: 166, 219 days

Placebo
Median: 166 days
95% CI: 113, 168 days

Patients at Risk
Sorafenib 154
Placebo 153
Interim analysis

Overall Survival
Secondary Endpoint

Survival Probability

HR: 0.898
95% CI: 0.606, 1.33
P = 0.295

Sorafenib
Median: NR
95% CI: 554 days, NR

Placebo
Median: NR
95% CI: 562 days, NR

Patients at Risk
Sorafenib 154  143  126  111  74  44  23  5  0
Placebo 153  142  127  109  73  44  23  4  0
Sorafenib + TACE combination is still attractive strategy in HCC treatment.

Sorafenib combined to TACE was relatively well tolerated, but did not show robust survival benefit over TACE alone until now.

In future clinical trials of TACE combination, difference of clinical practice such as TACE procedure and TACE failure definition, should be considered.
Sorafenib as adjuvant treatment in the prevention of recurrence of hepatocellular carcinoma

- International (Europe, America, Asia-Pacific), double-blind, placebo-controlled phase III adjuvant trial

Prior treatment
- Resection
- RFA
- PEI

Eligibility criteria
- Child–Pugh score 5–7
- Intermediate or high risk of recurrence

Randomisation
1:1

Stratification
- Prior curative treatment
- Geographical region

Primary endpoint
- Recurrence-free survival

Secondary endpoints
- Time to recurrence
- OS
- Biomarkers
- Other

n=1,100

Sorafenib 400 mg bid

Placebo

This study is now on-going

http://clinicaltrials.gov. NCT00692770
Summary and conclusions

- Systemic therapy is indicated in advanced HCC and TACE refractory cases.
- **Sorafenib** is the only approved targeted therapy in this setting.
- There is still no systemic combination regimen superior to sorafenib monotherapy.
- **TACE combination with molecular targeted agent** could be still attractive strategy in HCC treatment.
- Huge number of clinical trials of different MTAs are now on-going.
Thank you for your kind attention