Advances in Systemic Therapy for Hepatocellular Carcinoma (HCC)

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Scope

• Background

• Staging and treatment strategies

• Current systemic therapy

• Future perspectives

• Conclusions
Background
HCC: A Deadly Tumour on the Rise

- HCC is the 6th most common cancer worldwide and is the 3rd leading cause of cancer-related mortality\(^1\)

- Most cases of HCC arise as a result of chronic liver inflammation or injury\(^2\)

- The incidence of HCC is increasing due to the long-term consequences of chronic hepatitis C and hepatitis B viral infections\(^3\)

- Most patients newly diagnosed with HCC are not candidates for curative treatment because of gross vascular invasion, extrahepatic metastases and/or poor liver function\(^4\)

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Staging and treatment strategies
HCC: BCLC Staging and Treatment Strategy

Barcelona Clinic Liver Cancer

Stage 0, PS 0, Child-Pugh A
- Very early stage (0)
  - Single < 2 cm
  - Carcinoma in situ

Stage 1-2, PS 0-2, Child-Pugh A-B
- Early stage (A)
  - Single or 3 nodules < 3 cm, PS 0
- Intermediate stage (B)
  - Multinodular, PS 0

Stage 3, PS > 2, Child-Pugh C
- Advanced stage (C)
  - Portal invasion, N1, M1, PS 1-2
- Terminal stage (D)

Resection
- Single
- Portal pressure/bilirubin
  - Normal
  - Increased
  - Associated diseases
  - No
  - Yes
- RFA/PEI

Liver transplantation
- 3 nodules ≤ 3 cm
- TACE
- Sorafenib
- Symptomatic (20%); survival < 3 mos

Curative treatments (30%); 5-yr survival: 40%-70%
RCTs (50%); 3-yr survival: 10%-40%

Historically

No Clear Benefit with Traditional Cytotoxic Therapies

Current systemic therapy
Sorafenib: Mechanism of action

Induces tumour cell apoptosis or inhibits tumour cell proliferation by targeting the RAF/MEK/ERK pathway at the level of RAF kinase.

Exerts an anti-angiogenic effect by targeting the receptor tyrosine kinases VEGFR-2, VEGFR-3 and PDGFR, and their associated signaling cascades.

Systemic Therapy for Advanced Disease
First-line sorafenib in HCC: Phase III SHARP and Asia-Pacific studies

SHARP Clinical Trial

**STUDY DESIGN**
- Stratification:
  - Macrorvascular invasion and/or extrahepatic spread
  - ECOG PS
  - Geographic region
- Randomization: N=602
- Nexavar *(n=298)*
  - 400 mg twice daily continuous oral dosing
- Placebo *(n=303)*
  - 2 tablets twice daily continuous oral dosing

End points:
- A primary end point was overall survival (OS)
- A secondary end point was time to tumor progression (TTP)

Asia-Pacific Study

**STUDY DESIGN**
- Stratification:
  - MVI and/or EHS
  - ECOG PS
  - Geographic region
- Randomization: N=226
  - 2:1
- Nexavar *(n=150)*
  - 400 mg twice daily
- Placebo *(n=76)*

End points:
- Overall survival (OS), time to progression (TTP), time to symptomatic progression (TTSP), disease control rate (DCR), and safety
- No predefined primary end point

Systemic Therapy for Advanced Disease
First-line sorafenib in HCC: Phase III SHARP and Asia-Pacific studies

<table>
<thead>
<tr>
<th>COMPARISON OF BASELINE PATIENT CHARACTERISTICS BETWEEN SHARP TRIAL AND AP STUDY</th>
<th>Asia-Pacific (n=150)</th>
<th>SHARP (n=299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>51</td>
<td>65</td>
</tr>
<tr>
<td>Hepatitis virus status (HBV/HCV), %</td>
<td>71/11</td>
<td>19/29</td>
</tr>
<tr>
<td>Sex (Male), %</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td>ECOG PS (0/1/2), %</td>
<td>25/69/5</td>
<td>54/38/8</td>
</tr>
<tr>
<td>Macrovascular invasion, %</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Extrahepatic spread, %</td>
<td>69</td>
<td>53</td>
</tr>
<tr>
<td>BCLC Stage C, %</td>
<td>95</td>
<td>82</td>
</tr>
<tr>
<td>Sites of disease, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>52</td>
<td>22</td>
</tr>
<tr>
<td>Lymph node</td>
<td>31</td>
<td>30</td>
</tr>
</tbody>
</table>


Patients in the Asia-Pacific Study also had more prior locoregional therapies.
Systemic Therapy for Advanced Disease
First-line sorafenib in HCC: Phase III SHARP and Asia-Pacific studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patient No.</th>
<th>Objective response</th>
<th>Median Survival (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RR: 2.3%</td>
<td>OS: 10.7, TTP: 5.5</td>
</tr>
<tr>
<td>Llovet et al</td>
<td>299</td>
<td>SD: 71%</td>
<td>p &lt; 0.001, p &lt; 0.001</td>
</tr>
<tr>
<td>Sorafenib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>303</td>
<td>RR: 0.7%</td>
<td>7.9, 2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD: 67%</td>
<td>p &lt; 0.001, p &lt; 0.001</td>
</tr>
<tr>
<td>Cheng et al</td>
<td>150</td>
<td>RR: 3.3%</td>
<td>6.5, 2.8</td>
</tr>
<tr>
<td>Sorafenib</td>
<td></td>
<td>SD: 54.0%</td>
<td>p = 0.014, p &lt; 0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>76</td>
<td>RR: 1.3%</td>
<td>4.2, 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD: 27.6%</td>
<td></td>
</tr>
</tbody>
</table>

Systemic Therapy for Advanced Disease
First-line sorafenib in HCC: Phase III SHARP and Asia-Pacific studies

One-third of patients required dose reductions due to toxicity

## Systemic Therapy for Advanced Disease

Failed Phase III studies

<table>
<thead>
<tr>
<th>Indication / Target Population</th>
<th>Acronym</th>
<th>Phase III Comparison (Active vs Control)</th>
<th>Primary Outcome</th>
<th>Child-Pugh</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line / Advanced HCC</strong></td>
<td>BRISK-FL</td>
<td>Brivanib vs Sorafenib</td>
<td>OS</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linifanib vs Sorafenib</td>
<td>OS</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sunitinib vs Sorafenib</td>
<td>OS</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>SEARCH</td>
<td>Sorafenib + Erlotinib vs Sorafenib</td>
<td>OS</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>SECOX</td>
<td>Sorafenib + Cisplatin + 5FU vs Sorafenib</td>
<td>OS</td>
<td>A/B(7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib + Capecitabine + Oxaliplatin vs Sorafenib</td>
<td>OS</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib + Doxorubicin vs Sorafenib</td>
<td>OS</td>
<td>A</td>
</tr>
<tr>
<td><strong>Second line / Advanced HCC</strong></td>
<td>EVOLVE-1</td>
<td>Everolimus vs Placebo</td>
<td>OS</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>BRISK</td>
<td>Brivanib vs Placebo</td>
<td>OS</td>
<td>A/B(7)</td>
</tr>
<tr>
<td></td>
<td>BRISK-APS</td>
<td>Brivanib vs Placebo</td>
<td>OS</td>
<td>A/B(7)</td>
</tr>
<tr>
<td></td>
<td>REACH</td>
<td>Ramucirumab vs Placebo</td>
<td>OS</td>
<td>A/B(8)</td>
</tr>
<tr>
<td><strong>Adjuvant / Early HCC post resection or ablation</strong></td>
<td>STORM</td>
<td>Sorafenib vs Placebo</td>
<td>RFS</td>
<td>A</td>
</tr>
</tbody>
</table>
**Systemic Therapy for Advanced Disease**

**Second-line regorafenib: Phase III RESORCE study**

- **Pts with BCLC stage B or C HCC; documented PD on sorafenib ≥ 20 days at ≥ 400 mg/day; Child-Pugh A liver function; ECOG PS 0-1 (N = 573)**

- **Randomized 2:1**

  - **Regorafenib + BSC**
    - 160 mg PO daily Wks 1-3 (n = 379)
  - **Placebo + BSC**
    - PO daily Wks 1-3 (n = 194)

- **4-wk cycles**

- **All pts treated until PD, death, or unacceptable toxicity**

**Primary endpoint:** OS (ITT)

**Secondary endpoints:** PFS, TTP, RR, DCR

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*BSC, best supportive care; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; ITT, intent to treat; PD, progressive disease; PS, performance status; TTP, time to progression, RR, response rate.*

Systemic Therapy for Advanced Disease
Second-line regorafenib: Phase III RESORCE study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Regorafenib (n = 379)</th>
<th>Placebo (n = 194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos</td>
<td>10.6</td>
<td>7.8</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>3.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Median TTP</td>
<td>3.2*</td>
<td>1.5*</td>
</tr>
<tr>
<td>ORR, %</td>
<td>10.6†</td>
<td>4.1†</td>
</tr>
</tbody>
</table>

*HR 0.44; 95% CI: 0.36-0.55; P < .001; †P = .005

38% reduction in risk of death (HR: 0.62; 95% CI: 0.50-0.78; P < .001)
54% reduction in risk of progression or death (HR: 0.46; 95% CI: 0.37-0.56; P < .001)

DCR (CR + PR + SD): 65.2% vs 36.1% (P < .001)

DCR, disease control rate; SD, stable disease; TTP, time to progression.

Systemic Therapy for Advanced Disease
Second-line regorafenib: Phase III RESORCE study

<table>
<thead>
<tr>
<th>Adverse Events, %</th>
<th>Regorafenib (n = 379)</th>
<th>Placebo (n = 194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ≥ grade 3 adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Hypertension</td>
<td>15.2</td>
<td>4.7</td>
</tr>
<tr>
<td>▪ Hand–foot syndrome</td>
<td>12.6</td>
<td>0.5</td>
</tr>
<tr>
<td>▪ Fatigue</td>
<td>9.1</td>
<td>4.7</td>
</tr>
<tr>
<td>▪ Diarrhea</td>
<td>3.2</td>
<td>0</td>
</tr>
<tr>
<td>Dose modifications due to adverse events</td>
<td>68.2</td>
<td>31.1</td>
</tr>
<tr>
<td>Deaths occurring ≤ 30 days after last dose</td>
<td>13.4</td>
<td>19.7</td>
</tr>
</tbody>
</table>

Future perspectives
Cancer Immunotherapy

Cancer evades immune cell recognition and destruction via several mechanisms\textsuperscript{1-5}

\begin{enumerate}
\item **A** Reduced presentation of tumour antigens to the immune system
  \begin{itemize}
  \item Downregulation of MHC expression
  \item Suppression of APC
  \end{itemize}

\item **B** Release of immunosuppressive factors
  \begin{itemize}
  \item Factors/enzymes directly or indirectly suppress immune response
  \end{itemize}

\item **C** Recruitment of immunosuppressive cells
  \begin{itemize}
  \item Tregs
  \item MDSCs
  \end{itemize}

\item **D** T-cell immune checkpoint modulation

\end{enumerate}


BTLA = B- and T-lymphocyte attenuator; GITR = glucocorticoid induced tumour necrosis factor-related protein; HVEM = herpes virus entry mediator; LAG-3 = lymphocyte-activation gene 3; MDSC = myeloid-derived suppressor cell; TIM-3 = T-cell immunoglobulin domain and mucin domain-3; VISTA = V-domain immunoglobulin-containing suppressor of T-cell activation.

Cancer Immunotherapy

Immune checkpoint inhibition: CTLA-4 and PD-1/PD-L1

MHC = major histocompatibility complex; TCR = T-cell receptors; CTLA-4 = cytotoxic T-lymphocyte associated protein 4; PD-1 = programmed death protein 1; PD-L1 = programmed death protein ligand 1.


Ipilimumab (Yervoy®)

Pembrolizumab (Keytruda®)
Nivolumab (Opdivo®)
Atezolizumab (Tecentriq®)
Immunotherapy for Advanced Disease

Immune checkpoint inhibition with PD-1 antibodies

**Background:** Overexpression of PD-L1 in HCC has a poor prognosis. Safety and preliminary antitumor efficacy of nivolumab, a fully human IgG4 monoclonal antibody PD-1 inhibitor, was evaluated in a multi-arm ascending-dose, phase I/II study in patients (pts) with HCC.

**Methods:** Pts with histologically confirmed advanced HCC with Child-Pugh (CP) score ≤ B7 and progressive disease (PD) on, intolerant of, or refusing sorafenib were enrolled. Dose escalation occurred in parallel cohorts based on etiology: no active hepatits virus infection or virus-infected HCC pts. Pts received nivolumab 0.1 – 10 mg/kg intravenously for up to two years. The primary endpoint was safety. Secondary endpoints included antitumor activity using mRECIST criteria, pharmacokinetics, and immunogenicity.

**Results:** The study has enrolled 41 pts with a CP score of 5 (n = 35) or 6 (n = 6), ECOG score of 0 (n = 26) or 1 (n = 15), 73% with extrahepatic metastasis and/or portal vein invasion, and 77% with prior sorafenib use. Eighteen pts remain on study, and 23 discontinued treatment due to PD (n = 17), complete response (CR; n = 2), drug-related adverse events (AEs; n = 2) and non-drug–related AEs (n = 2). Drug-related AEs of any grade occurred in 29 pts (71%; 17% grade 3/4), with ≥ 10% of pts experiencing aspartate aminotransferase (AST) increase and rash (each 17%), alanine aminotransferase(ALT) and lipase increase (each 15%), and amylase increase (12%). Grade 3 and 4 AEs ≥ 5% were AST increase (12%), ALT increase (10%) and lipase increase (5%). A dose-limiting toxicity occurred in an uninfected pt at 10 mg/kg; no maximum tolerated dose was defined in any cohort. Response was evaluable in 39 pts: 2 CR (5%) and 7 partial responses (PR; 18%). Response duration was 14–17+ months for CR, < 1–8+ months for PR, and 1.5–17+ months for stable disease (SD). Overall survival (OS) rate at 6 months is 72%.

**Conclusions:** Nivolumab has a manageable AE profile and produced durable responses across all dose levels and HCC cohorts, with a favorable 6-month OS rate. Updated safety, antitumor activity, and biomarker data will be presented.

Clinical trial information: NCT01658878

Immunotherapy for Advanced Disease

Immune checkpoint inhibition with PD-1 antibodies

Randomized, open-label, multicenter phase III trial

Stratified by etiology, vascular invasion and/or extrahepatic spread, and geography

Advanced HCC; no prior systemic therapy; not eligible for/progressed after locoregional therapy; C-P A; ECOG PS 0-1 (planned N = 726)

Nivolumab
30 min IV Q2W

Sorafenib
PO BID

All pts treated until PD, unacceptable toxicity, or withdrawal of consent

*Nonviral HCC, HBV-HCC (HBV infection resolved or controlled), or HCV- HCC (resolved or active HCV infection)

Primary endpoint: time to progression, OS
Secondary endpoints: ORR, PFS, PD-L1 expression

ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; OS, overall survival; ORR, overall response rate; PFS, progression free survival.

## Select Ongoing First-line Phase III Trials in Advanced HCC

<table>
<thead>
<tr>
<th>First-Line Study</th>
<th>N</th>
<th>Population</th>
<th>Primary Endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib vs sorafenib (NCT01761266)</td>
<td>954</td>
<td>Unresectable HCC</td>
<td>OS</td>
<td>Open label</td>
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<tr>
<td>Nivolumab vs sorafenib (NCT02576509)</td>
<td>726</td>
<td>Unresectable or progressive advanced HCC</td>
<td>TTP, OS</td>
<td></td>
</tr>
<tr>
<td>Sorafenib ± SBRT (RTOG 1112; NCT01730937)</td>
<td>368</td>
<td>HCC with ≥ 1 liver lesion or vascular tumor thrombosis</td>
<td>OS</td>
<td>Biomarker analysis</td>
</tr>
<tr>
<td>Sorafenib ± TACE (NCT01906216)</td>
<td>246</td>
<td>Advanced HCC (BCLC Stage C)</td>
<td>OS</td>
<td>Analysis of prognostic value of AFP response</td>
</tr>
<tr>
<td>Sorafenib vs Y90 (NCT01135056)</td>
<td>360</td>
<td>Locally advanced HCC (BCLC stage B or C without extrahepatic disease</td>
<td>OS</td>
<td></td>
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</table>
## Select Ongoing Second-line Phase III Trials in Advanced HCC

<table>
<thead>
<tr>
<th>Second-Line Study</th>
<th>N</th>
<th>Population</th>
<th>Primary Endpoint(s)</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tivantinib vs BSC (NCT01755767)</td>
<td>368</td>
<td>Unresectable HCC after 1 prior therapy</td>
<td>OS</td>
<td></td>
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<tr>
<td>Tivantinib vs placebo (NCT02029157)</td>
<td>160</td>
<td>c-MET high HCC after sorafenib</td>
<td>OS</td>
<td>“All comers” with no c-MET selection</td>
</tr>
<tr>
<td>Cabozantinib vs BSC (NCT01908426)</td>
<td>760</td>
<td>HCC with prior sorafenib</td>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>Ramucirumab vs BSC (REACH-2; NCT02435433)</td>
<td>399</td>
<td>HCC with elevated baseline AFP after first-line sorafenib</td>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab vs BSC (KEYNOTE-240; NCT02702401)</td>
<td>408</td>
<td>HCC with progression on sorafenib</td>
<td>PFS, OS</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions
Conclusions

• Sorafenib is the only systemic agent approved for the first-line treatment of advanced HCC

• Regorafenib improves survival in patients with disease progression following sorafenib

• Immune checkpoint inhibition is an exciting therapeutic strategy

• Many Phase III studies are ongoing