Current Standards of Care of Hepatocellular Carcinoma?

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Disclosures

Honoraria Received:

- Amgen, Astra Zeneca, Bohrengier, Hikma, Hospira,
- GSK, Lilly, Merck, MSD, Novartis, Pfizer,
- Pierre Fabre, Roche, Sandoz, Sanofi Avantis
Agenda

- Overview of Hepatocellular Carcinoma
- Very Early–Stage and Early-Stage HCC: Current Best Practices
- Advanced, Incurable HCC: Latest Developments in Treatment
The Many Challenges of HCC

- Common malignancy
  - Fifth most common cancer in men worldwide, second leading cause of cancer death
  - MOST COMMON IN EGYPT
- Complex malignancy
- 1 pt, 2 diseases
  - Cirrhosis leads to multifocal hepatocarcinogenesis, high recurrence rates
  - Portal HTN, thrombocytopenia
- Impaired hepatic function
- Complicated clinical trial design
- While transplant potentially curative, candidacy/access limited

AASLD Diagnostic Criteria for HCC

Mass on surveillance US or high AFP in a cirrhotic liver

- < 1 cm
  - Repeat US every 3-4 mos
  - Stable > 18-24 mos
  - Enlarging
  - Return to surveillance every 6-12 mos
  - Proceed according to lesion size

- 1-2 cm
  - 1 dynamic imaging study
  - Typical vascular pattern
  - Atypical vascular pattern with both techniques
  - Biopsy
  - Diagnostic of HCC
  - Nondiagnostic of HCC
  - Repeat biopsy or imaging follow-up
  - Change in size/profile
  - Repeat imaging and/or biopsy

- > 2 cm
  - 1 dynamic imaging technique
  - Atypical vascular pattern
  - Typical vascular pattern on dynamic imaging
  - Other diagnosis
  - Repeat biopsy or imaging follow-up
  - Change in size/profile
  - Repeat imaging and/or biopsy

Treat as HCC

ESMO GUIDELINES FOR HCC

Hepatocellular carcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up†
Very Early–Stage and Early-Stage HCC: Current Best Practices
Multidisciplinary Approach to the Pt With HCC

- Palliative care
- Medical oncology
- Hepatology
- Interventional radiology
- Nursing
- Clinical research
- Radiology
- Primary care provider
- Radiation oncology
- Surgery
## Curative Treatments

<table>
<thead>
<tr>
<th>Resection</th>
<th>Ablation</th>
<th>Transplant</th>
</tr>
</thead>
</table>
| ▪ Noncirrhotics  
  – Choice of therapy  
▪ Cirrhotics  
  – Reserved for CTP A  
  – Avoid R hepatectomy  
▪ Best for solitary HCC  
  ▪ < 30% eligible  
▪ Survival  
  – 5 yrs: 70%  
▪ Recurrence  
  – 5 yrs: 70% | ▪ Effective when < 3 cm  
  ▪ Multiple modalities  
  – Thermal  
  – Chemical  
  – Stereotactic radiation  
  ▪ Minimally invasive  
▪ Survival  
  – 5 yrs: 40% to 50%  
▪ Recurrence  
  – 5 yrs: 70% | ▪ Cures both  
  ▪ MELD exception  
  – Milan criteria  
  – Downsizing  
▪ Survival  
  – 5 yrs: > 70%  
▪ Recurrence  
  – 5 yrs: 15% |

Survival After Resection for HCC

- Of 1265 HCC pts evaluated, only 35 were ideal candidates for resection

## Liver Embolo Therapy Techniques

<table>
<thead>
<tr>
<th>Technique</th>
<th>Mechanism</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAE</td>
<td>Ischemic necrosis induced at arteriolar level via permanent embolic (eg, small particles)</td>
<td>▪ Low cost, no chemotherapy adverse events</td>
<td>▪ Postembolization syndrome may cause PEs</td>
</tr>
<tr>
<td>Conventional TACE (cTACE)</td>
<td>Intrahepatic chemotherapy with embolization by ethiodized oil</td>
<td>▪ Strongest evidence supporting benefit from RCT data</td>
<td>▪ Intraoperator technical variation (cTACE) ▪ Systemic release of chemotherapy (cTACE) ▪ Postembolization syndrome</td>
</tr>
<tr>
<td>DEB-TACE</td>
<td>Intrahepatic chemotherapy + embolization with slow-release drug-eluting beads</td>
<td>▪ More standardized than cTACE, less systemic release of chemotherapy</td>
<td>▪ More expensive than cTACE ▪ Postembolization syndrome</td>
</tr>
<tr>
<td>Radioembolization</td>
<td>Radiation necrosis induced by beta-emitting Yttrium-90 microspheres</td>
<td>▪ May improve TTP ▪ Fewer sessions required ▪ No postembolization syndrome ▪ May be safer in adv disease with PVT ▪ Radiation segmentectomy may be curative ▪ FLR hypertrophy from radiation lobectomy can provide tumor control and facilitate resection</td>
<td>▪ Cost: 2-3x more expensive ▪ Requires multidisciplinary coordination ▪ Nontarget delivery may cause severe ulceration ▪ Potential biliary toxicity ▪ Radiation-induced liver disease</td>
</tr>
</tbody>
</table>
Palliative TACE Prolongs Survival in Unresectable HCC

Phase III SARAH: SIRT vs Sorafenib in Progressive, Inoperable HCC After 2x TACE

- Selective internal radiation therapy
- SIRT comprises yttrium-90 resin microspheres injected into the tumors, delivering up to 40 times more radiation than would be possible using standard radiation therapy.
- Because SIRT is directly delivered to the tumor, surrounding healthy tissue is spared radiation exposure.

Patients with locally advanced or inoperable HCC who did not respond to other treatments or who had 2 failed rounds of transarterial chemoembolization.

<table>
<thead>
<tr>
<th>SIRT</th>
<th>(n=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>400 mg BID</td>
</tr>
<tr>
<td>(n = 222)</td>
<td></td>
</tr>
</tbody>
</table>

Phase III SARAH: SIRT vs Sorafenib in Progressive, Inoperable HCC After 2x TACE

ITT Population (N = 459)

Probability of Survival

mOS, Mos

SIRT 8.0
Sorafenib 9.9

HR: 1.15 (95% CI: 0.94-1.41; log-rank P = .179)

Mos Since Randomization

Per Protocol Population (n = 380)

Probability of Survival

mOS, Mos

SIRT 9.9
Sorafenib 9.9

HR: 0.99 (95% CI: 0.79-1.24; log-rank P = .92)

Mos Since Randomization

Management of Advanced HCC
Advanced HCC: Challenges

- Competing causes of death
  - Cirrhosis vs HCC
- Unreliable hepatic function
  - Variable metabolism
- Inherent drug resistance?
  - Function of liver
Prior to 2007, no therapy was of benefit in advanced HCC

SHARP trial: CTP A pts with advanced HCC randomized to sorafenib 400 BID vs placebo

Sorafenib delayed progression and prolonged survival from 7.9 to 10.7 mos

Led to approval by the FDA in 2007 for palliation of advanced-stage HCC

It remains the only approved first-line systemic therapy for HCC

## First-line Randomized Phase III Trials in HCC

<table>
<thead>
<tr>
<th>Phase III Trial</th>
<th>Targets</th>
<th>Median TTP, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib vs sorafenib(^{[1]})</td>
<td>VEGFRs, PDGFRs, c-KIT, FLT3, RET(^{[2]})</td>
<td>4.1 vs 3.8</td>
<td>7.9 vs 10.2</td>
</tr>
<tr>
<td></td>
<td>HR: 1.13 (95% CI: 0.98-1.31; (P = .8312))</td>
<td>HR: 1.30 (95% CI: 1.13-1.50; 2-sided (P = .0014))</td>
<td></td>
</tr>
<tr>
<td>Brivanib vs sorafenib (BRISK-FL)(^{[3]})</td>
<td>VEGFR2, FGFR(^{[4]})</td>
<td>4.2 vs 4.1</td>
<td>9.5 vs 9.9</td>
</tr>
<tr>
<td></td>
<td>HR: 1.01 (95% CI: 0.88-1.16; (P = .8532))</td>
<td>HR: 1.07 (95% CI: 0.94-1.23; (P = .3116))</td>
<td></td>
</tr>
<tr>
<td>Linifanib vs sorafenib(^{[5]})</td>
<td>VEGFR, PDGFR</td>
<td>5.4 vs 4.0</td>
<td>9.1 vs 9.8</td>
</tr>
<tr>
<td></td>
<td>HR: 0.759 (95% CI: 0.643-0.895; (P = .001))</td>
<td>HR: 1.046 (95% CI: 0.896-1.221; (P = \text{NS}))</td>
<td></td>
</tr>
<tr>
<td>Sorafenib + erlotinib vs sorafenib + placebo(^{[6]})</td>
<td>VEGFR1/2/3, PDGFR, Ras, Raf, EGFR(^{[6,7]})</td>
<td>3.2 vs 4.0</td>
<td>9.5 vs 8.5</td>
</tr>
<tr>
<td></td>
<td>HR: 1.135 (95% CI: 0.944-1.366; (P = .18))</td>
<td>HR: 0.929 (95% CI: 0.781-1.106; (P = .408))</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin + sorafenib vs sorafenib (CALGB 80802)(^{[8]})</td>
<td>VEGFR1/2/3, PDGFR, Ras, Raf(^{[7]})</td>
<td>4.0 vs 3.9*</td>
<td>8.9 vs 10.5</td>
</tr>
<tr>
<td></td>
<td>HR: 0.9 (95% CI: 0.72-1.20; (P = .98))</td>
<td>HR: 1.06 (95% CI: 0.8-1.4; (P = .24))</td>
<td></td>
</tr>
</tbody>
</table>
Lenvatinib: Mechanism of Action

- Multitargeted, PO small molecular TKI
  - Potent against VEGFR2 and VEGFR3
  - Also targets VEGFR1, FGFR1-3, PDGFRα, RET, and KIT

REFLECT: Study Design

- Multicenter, randomized, open-label phase III noninferiority study

  **Stratified by region (Asia-Pacific vs Western), MVI and/or EHS (yes vs no), ECOG PS (0 vs 1), and BW (< vs ≥ 60 kg)**

  Pts with unresectable HCC, no prior systemic therapy, ≥ 1 measurable target lesion, BCLC stage B/C, Child-Pugh A, ECOG PS 0/1, and adequate organ function (N = 954)

- Primary endpoint: OS
  - Noninferiority margin 1.08; criteria met if upper limit of 2-sided 95% CI for HR < 1.08

- Secondary endpoints: PFS, TTP, ORR, QoL, lenvatinib PK

- Other endpoints: DCR, CBR, exploratory biomarker analysis

REFLECT: PFS and OS

Median, mos (95% CI)
- Lenvatinib: 7.4 (6.9−8.8)
- Sorafenib: 3.7 (3.6−4.6)

HR: 0.66 (95% CI: 0.57-0.77)
Log-rank test: $P < 0.00001$

Median, mos (95% CI)
- Lenvatinib: 13.6 (12.1−14.9)
- Sorafenib: 12.3 (10.4−13.9)

HR: 0.92 (95% CI: 0.79-1.06)

- Conclusion: lenvatinib noninferior to sorafenib in OS in first-line setting for unresectable HCC
- Statistically significant improvements in PFS, TTP, and ORR for lenvatinib vs sorafenib

### Second-line Phase III Randomized Trials in HCC

<table>
<thead>
<tr>
<th>Phase III Trial</th>
<th>Target(s)</th>
<th>Median TTP, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab vs placebo&lt;sup&gt;[1]&lt;/sup&gt;</td>
<td>IgG1 Ab to VEGFR2</td>
<td>3.5 vs 2.6</td>
<td>9.2 vs 7.6</td>
</tr>
<tr>
<td></td>
<td>HR: 0.59 (95% CI: 0.49-0.72; P &lt; .0001)</td>
<td>HR 0.87 (95% CI: 0.72-1.05; P = .14)</td>
<td></td>
</tr>
<tr>
<td>Brivanib vs placebo&lt;sup&gt;[2]&lt;/sup&gt;</td>
<td>VEGFR2, FGFR&lt;sup&gt;[3]&lt;/sup&gt;</td>
<td>4.2 vs 2.7</td>
<td>9.4 vs 8.2</td>
</tr>
<tr>
<td></td>
<td>HR: 0.56 (95% CI: 0.42-0.76; P &lt; .001)</td>
<td>HR: 0.89 (95% CI: 0.69-1.15; P = .3307)</td>
<td></td>
</tr>
<tr>
<td>Everolimus vs placebo&lt;sup&gt;[4]&lt;/sup&gt;</td>
<td>mTOR</td>
<td>3.0 vs 2.6</td>
<td>7.6 vs 7.3</td>
</tr>
<tr>
<td></td>
<td>HR: 0.93 (95% CI: 0.75-1.15; P = NR*)</td>
<td>HR: 1.05 (95% CI: 0.86-1.27; P = .68)</td>
<td></td>
</tr>
<tr>
<td>Tivantinib vs placebo&lt;sup&gt;[5]&lt;/sup&gt;</td>
<td>cMet&lt;sup&gt;[6]&lt;/sup&gt;</td>
<td>2.4 vs 3.0</td>
<td>8.4 vs 9.1</td>
</tr>
<tr>
<td></td>
<td>HR: 0.96 (95% CI: 0.74-1.25; P = .76)</td>
<td>HR 0.97 (95% CI 0.75-1.25; P = .81)</td>
<td></td>
</tr>
</tbody>
</table>

*Difference not statistically tested per prespecified analysis plan.

**Phase III RESORCE: Second-line Regorafenib vs Placebo in HCC With Progression**

- 152 centers in 21 countries in North/South America, Europe, Australia, Asia

*Randomized 2:1*

*Stratified by geography (Asia vs other), macrovascular invasion, extrahepatic disease, ECOG PS (0 vs 1), AFP (< 400 ng/mL vs ≥ 400 ng/mL)*

**Pts with HCC with documented radiologic progression on sorafenib** (N = 573)

- **Regorafenib 160 mg PO QD**
  - Days 1-21 of 28-day cycle
  - + BSC
  - (n = 379)

- **Placebo**
  - Days 1-21 of 28-day cycle
  - + BSC
  - (n = 194)

**Until PD, unacceptable toxicity, or withdrawal**

RESORCE: Efficacy

mOS, mos

Regorafenib (n = 379) | Placebo (n = 194)
10.6 | 7.8
(HR: 0.63; 95% CI: 0.50-0.79; 1-sided P < .0001)

mPFS, mos

Regorafenib (n = 379) | Placebo (n = 194)
3.1 | 1.5
(HR: 0.46; 95% CI: 0.37-0.56; 1-sided P < .0001)

Modified RECIST

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>Regorafenib (n = 379)</th>
<th>Placebo (n = 194)</th>
<th>Regorafenib (n = 379)</th>
<th>Placebo (n = 194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>11*</td>
<td>4</td>
<td>6.6*</td>
<td>2.6</td>
</tr>
<tr>
<td>DCR</td>
<td>65*</td>
<td>36</td>
<td>65.7*</td>
<td>34.5</td>
</tr>
</tbody>
</table>

*P < .05 vs placebo.

Emerging Drugs for HCC

- MET signaling inhibitors
  - Cabozantinib (second line phase III)
- FGFR inhibitors
  - Pan-FGFR inhibitor (erdafitinib)
  - Selective FGFR4 inhibitor (FGF401)
- TGF-β signaling
  - Galunisertib

- Antiangiogenic and antiproliferative TKIs
  - Donafenib (first line phase III under way: NCT02645981)
- Immune checkpoint inhibitors
Cabozantinib versus placebo in patients with advanced HCC phase 3 CELESTIAL trial.

- Celestial was a Ph 3 HCC study in analyzing cabozantinib vs placebo in patient post-sorafenib.
- The study showed that the overall survival had significantly improved (10.2 mo) vs over placebo (8.0 mo) in HCC patients in the 2L setting.
- Progression free survival (5.2 mo vs 1.9 mos) and objective response rates (4.0% vs. 0.4%) were improved as well.
- Six grade 5 adverse events
Ramicirumab in HCC breaking news

- REACH-2 phase III trial improves PFS and OS versus placebo as a second-line treatment of patients with HCC and elevated baseline AFP
Rationale for Immunotherapy in HCC

- HCC is a classical inflammation-induced tumor type
- Spontaneous immune responses are frequently observed
- Independent of liver function (no metabolism)
- Can be combined with ablative therapies

PD-L1 expression (observed in ~74% of HCC cases) predicts recurrence/survival in HCC patients after resection\(^1,2\)

Phase I/II CheckMate 040: Nivolumab in Advanced HCC

**Study Endpoints**

**Primary**
- Safety and tolerability (ESC)
- ORR (EXP)\(^b\)

**Secondary**
- ORR (ESC)\(^b\)
- Disease control rate
- Time to response
- Duration of response
- Overall survival

**Other**
- Biomarker assessments

\(^a\) Median follow-up calculated from first dose to last known date alive or death.
\(^b\) Using RECIST v1.1.
ESC, dose-escalation phase; EXP, dose-expansion phase.

- Median follow-up:\(^a\) 16.4 months in sorafenib-naive patients
  - 14.3 months in sorafenib-naive patients (ESC)
  - 14.9 months in sorafenib-experienced patients (EXP)

**CheckMate 040 Best Overall Response**

*Blinded Independent Central Review*

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Sorafenib Naive ESC + EXP n = 80\textsuperscript{a}</th>
<th>Sorafenib Experienced ESC n = 37\textsuperscript{a}</th>
<th>Sorafenib Experienced EXP n = 145</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response using RECIST v1.1</strong></td>
<td>16 (20)</td>
<td>7 (19)</td>
<td>21 (14)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (1)</td>
<td>1 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Partial response</td>
<td>15 (19)</td>
<td>6 (16)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>25 (31)</td>
<td>12 (32)</td>
<td>60 (41)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>32 (40)</td>
<td>13 (35)</td>
<td>56 (39)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>5 (6)</td>
<td>4 (11)</td>
<td>8 (6)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Two sorafenib-naive patients and 1 sorafenib-experienced (ESC) patient had a best overall response reported as non-CR/non-PD by BICR.

- 15% of sorafenib progressors and 23% of patients who were intolerant of sorafenib achieved an objective response.
- Disease control rates were 54% in sorafenib-naive patients and 55% in all sorafenib-experienced patients.

CheckMate 040 Overall Survival

Sorafenib Naive (ESC + EXP):
Median OS (95% CI), mo = 28.6 (16.6–NE)

Sorafenib Experienced (EXP):
Median OS (95% CI), mo = 15.6 (13.2–18.9)

Sorafenib Experienced (ESC):
Median OS (95% CI), mo = 15.0 (5.0–28.1)

KEYNOTE-224: Pembrolizumab in Patients with Advanced HCC Previously Treated with Sorafenib.

- Keynote-224 was a Phase 2 HCC single arm study analyzing pembrolizumab in a patient population post-sorafenib. Data presented with 8 months follow-up.
- Disease control rate was 61.5%, median duration of response was 8.2 mo, median time for response and overall survival was NR (9.4-NE).
- 1 treatment related death was reported during the study.

Zhu AX, et al. ASCO GI January 18-20, 2018; San Francisco, Calif. Abstract 209
### Ongoing Immunotherapy Clinical Trials in HCC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Trial Identifier</th>
<th>Planned Enrollment</th>
<th>Therapy Line</th>
<th>Enrollment Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (anti–PD-1) vs sorafenib</td>
<td>NCT02576509</td>
<td>726</td>
<td>First</td>
<td>11/2015</td>
</tr>
<tr>
<td>Pexastimogene devacirepvec (Pexa-Vec) + sorafenib vs sorafenib</td>
<td>NCT02562755</td>
<td>600</td>
<td>First</td>
<td>10/2015</td>
</tr>
<tr>
<td>Pembrolizumab (anti–PD-1) vs BSC</td>
<td>NCT02702401</td>
<td>408</td>
<td>Second</td>
<td>5/2016</td>
</tr>
<tr>
<td>Durvalumab (anti–PD-L1) + tremelimumab (anti–CTLA-4)</td>
<td>NCT02519348</td>
<td>144</td>
<td>Second</td>
<td>10/2015</td>
</tr>
</tbody>
</table>
How to treat pts with advanced disease?

First line

- Sorafenib
- Lenvatinib?
- Immunotherapy?
  - Ongoing phase III trial of nivolumab vs sorafenib

Second line

- Regorafenib
- Nivolumab
- Immunotherapy?
  - Ongoing phase III study of pembrolizumab vs BSC

Third line
RAP UP

- Early-stage HCC may be cured with
  - Thermal ablation
  - Resection
  - Liver transplantation

- Advanced-stage HCC may be palliated with
  - TACE or XRT
  - Sorafenib
  - Experimental therapies

- Local measures often fail in tumors with aggressive biology
- Application of therapies may be limited by severity of cirrhosis
- Choosing the optimal treatment requires collaboration of multiple specialties
THANK YOU