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Systemic Therapies for HCC

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Disclosures

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Disclosures

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Consultant: AbbVie, Clinical Area – Hepatitis C
Consultant: Fuji-Film Wako, Clinical Area – HCC
Consultant: Gilead, Clinical Area – Hepatitis B, Hepatitis C, NASH
Consultant: Intercept, Clinical Area – PBC, NASH
Consultant: Salix, Clinical Area – Hepatic Encephalopathy
Hepatocellular Carcinoma (HCC)

- Common malignancy worldwide
  - 5th most common cancer worldwide
  - 2nd leading cause of cancer death ~600,000 deaths annually
- US incidence has more than tripled over the last three decades
  - Estimated new cases: ~40,000 new cases annually
  - Fastest rising cause of cancer related death in US, Dismal 5-year survival <15%
- 85%-95% of HCC cases occur in cirrhotic livers
  - Leading cause of death in cirrhosis
- Complex malignancy
  - Heterogeneous etiologies - HCV, HBV, NAFLD, Alcohol
  - Complex molecular carcinogenesis

Natural History of Untreated HCC in a US VA Cohort With HCV as the Predominant Etiology – Mortality by BCLC Stage (n=518)

UNOS/SRTR 2019 Report – Liver Transplants

More Candidates

More Liver Transplants

More ≥ 65

Less HCV

Transplant rates among waitlist candidates by sex and HCC status

Patient Survival by Diagnosis

HCC Screening

- Early diagnosis of HCC improves survival
- Screen patients with cirrhosis
  - HCV cirrhosis post-SVR
- Selected patients without cirrhosis
  - HBV
- **Ultrasound +/-AFP every 6 months recommended in patients with cirrhosis**
- Consensus lacking (benefit uncertain)
  - Hepatitis C and stage 3 fibrosis
  - NAFLD without cirrhosis
- Do not perform in Child’s class C cirrhosis unless on waiting list
- **Majority of patients (~80%) with cirrhosis are not receiving HCC surveillance as recommended by guidelines.**

4-AASLD, 5-EASL, 6-Asia-Pacific, 7-Japanese and *Expert opinion.
AASLD Diagnostic Criteria for HCC: Liver Nodule on Surveillance Ultrasound or High AFP in a Cirrhotic Liver

Available at [http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx](http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx).
Radiologic Diagnosis of HCC in Cirrhosis

Arterial phase enhancement

Venous phase “washout”

Liver Imaging Reporting and Data System (LI-RADS) Standardize Classification of Liver Nodules on Contrast Enhanced Cross-Sectional Imaging

- **Arterial phase hypo- or iso-enhancement**
  - **Diameter (mm):**
    - **< 20**
      - None: LR-3
      - One: LR-3
    - **≥ 20**
      - None: LR-3
      - One: LR-4
      - ≥ Two: LR-4

- **Arterial phase hyper-enhancement**
  - **< 10**
    - LR-3
  - **10-19**
    - LR-4
    - One: LR-4
    - ≥ Two: LR-4
  - **≥ 20**
    - LR-4
    - One: LR-4
    - ≥ Two: LR-4

**Observations in this cell are categorized based on one additional major feature:**
- LR-4 – if enhancing “capsule”
- LR-5 – if nonperipheral “washout” OR threshold growth growth

AASLD Guidelines: LI-RADS Diagnostic Algorithm for HCC

LOW-RISK LIVER LESIONS

- **LI-RADS 1** Definitely Benign
  - Return to surveillance imaging in 6 mo
  - Consider repeat diagnostic imaging in ≤ 6 mo

- **LI-RADS 2** Probably Benign
  - Return to surveillance imaging in 6 mo

INTERMEDIATE-RISK

- **LI-RADS 3** Intermediate
  - Repeat or alternative diagnostic imaging in 3-6 mo

HIGH-RISK LIVER LESIONS

- **LI-RADS 4** Probably HCC
  - Recommend multidisciplinary discussion for tailored workup that may include biopsy (select cases), or repeat or alternative diagnostic imaging in ≤ 3 mo
  - If biopsy
    - Pathology diagnosis

- **LI-RADS 5** Definitive HCC
  - HCC confirmed
  - If biopsy
    - Pathology diagnosis

- **LI-RADS M** Malignant, not definitively HCC
  - Recommend multidisciplinary discussion for tailored workup that may include biopsy (most cases), or repeat or alternative diagnostic imaging in ≤ 3 mo
  - If biopsy
    - Pathology diagnosis

**Multidisciplinary Liver Tumor Board & Transplant/HB Team**

Marrero JA et al. AASLD Practice Guideline HCC. 2018.
Diagnosis of HCC: To Biopsy or Not?

**Yes**
- Imaging is inconsistent with HCC
- Distinguish HCC from **Intrahepatic Cholangiocarcinoma (CCA)**
  - Poor prognosis
  - 5-year overall survival 8-50%
  - High recurrence rates 30-40%
- Avoids inappropriate treatment and misleading “cure”
- May be required for experimental treatments
- May permit personalized therapy

**No**
- Not always feasible
- Not needed if high diagnostic certainty based on imaging
- Risk
  - Hemorrhage
  - Tumor seeding (2.7% overall incidence)
- Risk of false negatives
  - Up to 1/3 of biopsies
  - May delay treatment
  - Continue to monitor lesion with imaging

**Biopsy is based on clinical picture**
No high-risk factors, normal AFP, non-classic radiographic features

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# HCC Staging and Treatments

## Staging

- **Very early Stage 0**: Child-Pugh A, Single < 2 cm, ECOG PS 0-1
- **Early Stage A**: Child-Pugh A-B, Single or 2-3 nodules < 3 cm, ECOG PS 0-1
- **Intermediate Stage B**: Multinodular, ECOG PS 0-1
- **Advanced Stage C**: Portal Vein invasion, N1, M1, ECOG PS 0-2
- **Terminal Stage D**: Any T, N or M, ECOG PS > 2

## Treatments

### Barcelona Stage

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>STAGE 0</th>
<th>STAGE A</th>
<th>STAGE B</th>
<th>STAGE C</th>
<th>STAGE D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Resection</td>
<td>TACE</td>
<td>Sorafenib (1L), lenvatinib (1L), regorafenib (2L), cabozantinib (2L), ramucirumab (2L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RFA, MWA</td>
<td>Resection, OLT, RFA, MWA, TARE, SBRT</td>
<td>TARE, Downsize OLT</td>
<td>Nivolumab (2L), pembrolizumab (2L)</td>
<td>OLT, BSC</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>TARE</td>
<td></td>
</tr>
</tbody>
</table>

### Estimated survival time

- >5 years
- >2 years
- 11-13 months (first-line)
- 8-10 months (second-line)
- 3 months
Multidisciplinary Care of Patients With HCC

- Palliative care
- Hepatology
- Radiology
- Medical oncology
- Primary care provider
- Interventional radiology
- Radiation oncology
- Nursing
- Clinical research
- Tumor Registry
- Surgery

Pt
What Is the Best Treatment Option?

**Surgery:**
- Liver Transplantation
- Resection

**Thermal Ablation:**
- Microwave (MWA)
- Radiofrequency (RFA)

**Transarterial:**
- Chemoembolization
- Y-90 microspheres

**Systemic Therapies:**
- Sorafenib
- Lenvatinib
- Regorafenib
- Nivolumab
- Cabozantinib
- Pembrolizumab
- Ramucirumab
- Clinical Trials
Management of Advanced HCC

BCLC C
Initial Systemic Therapy Options for Advanced HCC

Current Treatment Landscape - 1L Systemic Therapies with TKIs

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA Indication</th>
<th>Key Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>Unresectable HCC</td>
<td>SHARP</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>First-line treatment of patients with unresectable HCC</td>
<td>REFLECT</td>
</tr>
</tbody>
</table>
Palliation of Advanced HCC: Sorafenib

- 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
- First-line systemic therapy for unresectable/advanced HCC

Y90 vs Sorafenib in Locally Advanced HCC ± PVT (Stage B and C)

**Phase 3 SARAH, Europe/France**

- Median Overall Survival
  - Y90 /SIRT: 8.0 months
  - Sorafenib: 9.9 months
  - HR 1.15 (95% CI: 0.94-1.41; P=.18)

**Phase 3 SIRveNIB, Asia-Pacific**

- Median Overall Survival
  - Y90 /SIRT: 8.8 months
  - Sorafenib: 10.0 months
  - HR 1.12 (95% CI: 0.9-1.4; P=.36)

*Y90 versus Sor: Radioembolization has no clinical benefit versus sorafenib in advanced HCC.*
*SORAMIC Trial: Y90 plus Sorafenib (n=216) versus Sorafenib (n=208) alone did not improve OS.*
*SIRT + Sor, 12.1 months versus Sor alone 11.5 months (Presented EASL 2018, SORAMIC Trial).*
Lenvatinib vs Sorafenib in 1L Treatment in Advanced HCC

- Lenvatinib targets VEGFR axis as well as FGFR 1-3
- Compared lenvatinib to sorafenib in the front line setting with a non-inferiority design (Phase 3 REFLECT)
- Patients with unresectable HCC randomized 1:1
  - Len (n=478: <60kg 8mg, >60kg 12 mg)
  - Sor (n=476)
- Excluded patients with Main PV
- BCLC Stage B/C
  - Len 22% / 78%
  - Sor 19% / 81%
- Lenvatinib is noninferior to sorafenib in OS
  - Statistically significant improvements in PFS, TTP, and ORR for lenvatinib vs sorafenib
- First phase 3 trial in HCC to be positive since sorafenib 2007 (SHARP trial)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lenvatinib (n = 478)</th>
<th>Sorafenib (n = 476)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mos (95% CI)</td>
<td>13.6 (12.1-14.9)</td>
<td>12.3 (10.4-13.9)</td>
<td>0.92 (0.79-1.06)</td>
</tr>
<tr>
<td>mPFS, mos (95% CI)</td>
<td>7.4 (6.9-8.8)</td>
<td>3.7 (3.6-4.6)</td>
<td>0.66 (0.57-0.77)</td>
</tr>
<tr>
<td>mTTP, mos (95% CI)</td>
<td>8.9 (7.4-9.2)</td>
<td>3.7 (3.6-5.4)</td>
<td>0.63 (0.53-0.73)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>115 (24.1)</td>
<td>44 (9.2)</td>
<td></td>
</tr>
</tbody>
</table>

1L= 1st Line.
Select Treatment-Emergent AEs (Lenvatinib vs Sorafenib)

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Lenvatinib (n = 476)</th>
<th>Sorafenib (n = 475)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Total</td>
<td>99</td>
<td>75</td>
</tr>
<tr>
<td>HFSR</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>24</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

RESORCE Phase 3: Regorafenib vs Placebo in 2L Advanced HCC

- Pts with HCC with documented radiologic progression on sorafenib (N= 573)
- Randomized 2:1 to Rego (n=379) vs Placebo (n=194)
- Tolerated sorafenib > 400 mg/day for at least 20 of the last 28 days of treatment
- Rego 160 mg PO QD, Days 1-21 of 28-day cycle
- Approved by FDA on April 2017 for HCC previously treated with sorafenib (2L)

**Outcomes of the Sequence of Sorafenib Followed by Regorafenib or Placebo**

<table>
<thead>
<tr>
<th>Outcomes From start of sorafenib</th>
<th>Regorafenib (n=374)</th>
<th>Placebo (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival, months</td>
<td>26.0</td>
<td>19.2</td>
</tr>
<tr>
<td>Estimated survival, at 3 yrs</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>Estimated survival, at 5 yrs</td>
<td>16%</td>
<td>3%</td>
</tr>
</tbody>
</table>

CELESTIAL Phase 3: Cabozantinib vs Placebo in 2L Advanced HCC

- Cabozantinib targets VEGFR axis and MET.
- Pts with advanced HCC radiologic progression on sorafenib
- No more than 2 prior systemic therapies
- Randomized 2:1 to cabozantinib 60 mg QD (n=470) vs placebo (n=237)
- BCLC Stage C: 85% and 84%
- Cabozantinib significantly prolonged OS in patients with previously treated advanced HCC.
- Corresponding to this survival benefit, a longer duration of PFS was also observed
- Positive Phase 3 in 2L setting for advanced HCC with OS and PFS benefit

2L = second line.
Abou-Alfa GK et al. NEJM July 2018.
REACH-2 Phase 3: Ramucirumab for Patients With Previously Treated HCC and Higher AFP (≥400ng/ml) Advanced HCC

- Ramucirumab anti-VEGR2 monoclonal antibody
- Pts with advanced HCC, AFP > 400 ng/mL, BCLC stage B/C, Child-Pugh A, PS 0/1, prior sorafenib
- Randomized 2:1 to ramucirumab 8 mg/kg IV Q2W (n=197) vs placebo (n=95)
- Ramucirumab prolonged OS in patients with previously treated advanced HCC.
- Positive Phase 3 in 2L setting for advanced HCC with OS and PFS benefit
- FDA approved 2L setting

2L = second line.
Immunotherapy as Second Line for Advanced HCC

Both received conditional FDA approval based on Phase 2 non-controlled studies.

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>154 sorafenib-treated patients</td>
<td>104 sorafenib-treated patients</td>
</tr>
<tr>
<td>Patient features</td>
<td>2L or 3L</td>
<td>2L</td>
</tr>
<tr>
<td></td>
<td>Sorafenib-intolerants allowed</td>
<td>Sorafenib-intolerants allowed</td>
</tr>
<tr>
<td></td>
<td>Effective therapy for HBV+ve patients</td>
<td>Effective therapy for HBV+ve patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No involvement of portal vein trunk</td>
</tr>
<tr>
<td>Response rate</td>
<td>14% regardless of etiology or AFP levels</td>
<td>17% regardless of etiology or AFP levels</td>
</tr>
<tr>
<td>Duration of response</td>
<td>16.6 months in HCV patients, not reached in other etiologies</td>
<td>≥ 6 months in 77%</td>
</tr>
<tr>
<td>mOS</td>
<td>15.1 months (95% CI 13.2–18.8)</td>
<td>12.9 months (95% CI 9.7–15.5)</td>
</tr>
</tbody>
</table>

- Lack of predictive biomarker for response: No difference in response by tumor PDL1 expression. MSI high rare (<2%) in HCC.

# HCC Treatment Landscape: Second-Line Options

<table>
<thead>
<tr>
<th>Agent</th>
<th>Key Trial</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>CELESTIAL</td>
<td>Child-Pugh A</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>CheckMate-40</td>
<td>Child-Pugh A/B7</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>KEYNOTE-224</td>
<td>Child-Pugh A</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>REACH-2</td>
<td>Child-Pugh A, AFP ≥ 400 ng/mL</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>RESORCE</td>
<td>Child-Pugh A, tolerated first-line sorafenib</td>
</tr>
</tbody>
</table>
Key eligibility

- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy

Stratification

- Region (Asia, excluding Japan\(^a\)/rest of world)
- ECOG PS (0/1)
- Macrovascular invasion (MVI) and/or extrahepatic spread (EHS) (presence/absence)
- Baseline \(\alpha\)-fetoprotein (AFP; < 400/\(\geq\) 400 ng/mL)

Atezolizumab 1200 mg IV q3w + bevacizumab 15 mg/kg q3w

Sorafenib 400 mg BID

Until loss of clinical benefit or unacceptable toxicity

Survival follow-up

Co-primary endpoints

- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)

- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

\(^a\) Japan is included in rest of world.

\(^b\) An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.
OS: Co-Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI), mo$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + Bev</td>
<td>NE</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>13.2 (10.4, NE)</td>
</tr>
</tbody>
</table>

HR, 0.58 (95% CI: 0.42, 0.79)$^b$

$^a$ Median OS (95% CI), mo$^a$; 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. $^b$ HR and P value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. $^c$ The 2-sided P value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.
**Confirmed PFS\(^a\): Co-Primary Endpoint**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (95% CI), mo(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + Bev</td>
<td>6.8 (5.7, 8.3)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>4.3 (4.0, 5.6)</td>
</tr>
</tbody>
</table>

HR, 0.59 (95% CI: 0.47, 0.76)\(^c,d\)

\(P < 0.0001\)^\(^d\)

\(^a\) Assessed by IRF per RECIST 1.1. \(^b\) 197 patients (59%) in the Atezo + Bev arm vs 109 (66%) in the sorafenib arm had an event. \(^c\) HR and P value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. \(^d\) The 2-sided P value boundary is 0.002. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.
Safety

≥ 10% Frequency of AEs in Either Arm and > 5% Difference Between Arms

- Diarrhoea
- PPE
- Decreased appetite
- Hypertension
- Abdominal pain
- Alopecia
- Asthenia
- Pyrexia
- ALT increased
- Proteinuria
- Infusion-related reaction

PPE, palmar-plantar erythrodysesthesia.

a Safety-evaluable population.
Algorithm of Treatment for Advanced HCC

Front-line

- **Sorafenib**
  - Progressive disease or intolerance

- **Atezo/Beva**
  - Progressive disease or intolerance

- **Levatinib**
  - Progressive disease or intolerance

Second-line

- **Regorafenib**
- **Cabozantinib**
- **Ramucirumab**
- **Nivolumub**
- **Pembrolizumab**

Beyond

- One of the agents the patient has not yet received

Progressive disease or intolerance
Conclusions

- Burden of HCC is increasing
- Screen your at-risk patients with cirrhosis for HCC with ultrasound and AFP every 6 months for early detection
- Early-stage HCC (BCLC A) may be cured with thermal ablation, resection and/or liver transplantation
- Intermediate-stage HCC (BCLC B) palliated with TACE and Y90
- Local measures often fail in tumors with aggressive biology
- Advanced-stage HCC (BCLC C) palliated with sorafenib
  - Newer 1L (lenvatinib) and 2L therapies (regorafenib, cabozantinib, ramucirumab, nivolumab, pembrolizumab)
- Application of therapies may be limited by severity of cirrhosis
- Multidisciplinary collaboration is paramount for optimal outcome