The Rapidly Evolving Treatment Landscape for Hepatocellular Carcinoma

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Courtney C. Cavalieri, PharmD, BCOP, has no financial relationships with commercial interests to disclose.

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Pharmacy Accreditation

Pharmacy Times Continuing Education™ is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

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Fee: Free
This activity is supported by educational grants from Bayer HealthCare Pharmaceuticals Inc.; Eisai Co.; Exelixis, Inc.; and Merck Sharp & Dohme Corp.
Educational Objectives

At the completion of this activity, participants will be able to:

• Identify characteristics, including risk factors, that would suggest a patient should be referred for potential evaluation for HCC

• Describe the current drug classes that are used in the treatment of patients with advanced HCC and their placement in guidelines

• Explain what therapies are currently being studied for the treatment of advanced HCC and their potential places in therapy

• Develop monitoring plans for patients undergoing treatment for advanced HCC, including management of dosing recommendations, drug interactions, and adverse effects
Instructions on accessing pretest questions:

1) Connect to the WiFi using the username and password printed out on table.
2) Open an Internet browser and navigate to access the program’s pre-test questions.
   www.tinyurl.com/HCC-pretest-2-18
3) Please enter your email address, first name, last name, and NAPB Number.
4) Complete the pretest questions.
Pretest Question 1

Before participating in the activity, how confident are you in current treatment strategies for patients with hepatocellular carcinoma?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely
Pretest Question 2

Which of the following is a biomarker that can be elevated in advanced hepatocellular carcinoma?

A. BRAF V600E
B. Hepatitis B surface antigen
C. Epidermal growth factor receptor
D. Alpha fetoprotein
Pretest Question 3

TM is a 61-year-old man with relapsed HCC who is about to begin cabozantinib. Oral kinase inhibitors and monoclonal antibodies that inhibit vascular endothelial growth factor (VEGF) require education and monitoring of mechanism-related toxicities. Which of these adverse effects should be included in his counseling?

A. Hypertension, proteinuria
B. Maculopapular rash, nausea
C. Decreased wound healing, hypothyroidism
D. Colitis, proteinuria
Pretest Question 4

KD is a 63-year-old man with advanced hepatocellular carcinoma that has progressed after sorafenib therapy. A new intravenous combination therapy is currently under review by the FDA for second-line treatment of advanced HCC. Select the appropriate mechanisms of action of this combination.

A. CTLA-4 inhibitor + PD-1 inhibitor
B. PARP inhibitor + PD-1 inhibitor
C. CTLA-4 inhibitor + VEGFR inhibitor
D. BRAF inhibitor + PD-L1 inhibitor
LJ is a 64-year-old man with previously treated advanced hepatocellular carcinoma with hepatitis C, cirrhosis, an alpha fetoprotein = 368 ng/mL. He is planned to start therapy with pembrolizumab. Which of the following is an important monitoring parameter to check regularly during pembrolizumab treatment?

A. Thyroid function tests
B. Blood pressure
C. Calcium
D. Urine protein
Liver Cancer Epidemiology

- Estimated 42,030 new cases diagnosed in the United States in 2019
  - Roughly 75% of liver cancers are hepatocellular carcinoma (HCC)
  - Most rapidly increasing cancer, with rates more than tripling since 1980
  - Median age at diagnosis = 64 years
- Estimated 31,780 US deaths in 2019
- HCC accounts for 2.4% of all new cancers in the United States

**HCC Risk Factors**

<table>
<thead>
<tr>
<th>Major Risk Factors</th>
<th>Minor Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis B virus</strong>&lt;br&gt;• Most common risk factor worldwide</td>
<td><strong>Aflatoxin B1 ingestion</strong>&lt;br&gt;• Mycotoxin from <em>Aspergillus</em> spp. fungus that affects grains, legumes in tropical/subtropical areas</td>
</tr>
<tr>
<td><strong>Hepatitis C virus</strong>&lt;br&gt;• Most common risk factor in United States&lt;br&gt;• Risk from unscreened blood products</td>
<td><strong>Cirrhosis-related</strong>&lt;br&gt;• Alcohol ingestion, HBV, and HCV&lt;br&gt;• Type 2 diabetes, NAFLD, and obesity&lt;br&gt;• Inherited syndromes: hereditary hemochromatosis</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong>&lt;br&gt;• Response to chronic liver injury&lt;br&gt;• All risk factors for HCC are directly associated with cirrhosis, except HBV and aflatoxin</td>
<td><strong>Other</strong>&lt;br&gt;• Gender (twice as common in men), smoking, HIV</td>
</tr>
</tbody>
</table>

Development of HCC


Alcoholic liver disease
Hepatitis C viral infection
Hepatitis B viral infection
Nonalcoholic steatohepatitis
HCC Screening

- **Average risk**
  - No effective screening

- **High risk** (cirrhosis, HBV, hereditary hemochromatosis)
  - Refer patient for HCC screening
  - Ultrasound ± alpha fetoprotein (AFP) every 6 months
  - AFP >100 ng/mL prompts need for computed tomography or magnetic resonance imaging

- **Alpha fetoprotein (AFP)**
  - Glycoprotein produced during gestation by the fetal liver and yolk sac
  - Tumor marker; can be elevated in HCC
    - AFP >400 ng/mL is diagnostic for HCC
    - Not all HCC tumors secrete AFP
      - ≈30% have a normal AFP at diagnosis

HCC Symptoms

- Weight loss/loss of appetite
- Abdominal pain
- Early satiety
- Nausea/vomiting
- Enlarged liver +/- spleen
- Ascites
- Jaundice

Common sites of metastatic HCC:
Lung, intra-abdominal lymph nodes, bone, and adrenal gland.

# Child-Pugh Score

<table>
<thead>
<tr>
<th>Measure</th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy (grade)</td>
<td>None</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>&lt;4</td>
<td>4-6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>• For primary biliary cirrhosis</td>
<td>&lt;4</td>
<td>4-10</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

Class A = 5-6 Points  
Class B = 7-9 Points  
Class C = 10-15 Points

The BCLC Staging System:
Linked to Treatment Recommendations

Patient Population
- Early (BCLC A) – Child-Pugh A/B, 1 nodule any size or max 3 nodules <3 cm
- Intermediate (BCLC B) - Child-Pugh A/B, multiple nodules, no vascular invasion or extrahepatic metastasis
- Advanced (BCLC C) - Child-Pugh A/B, vascular invasion or extrahepatic metastasis and cancer symptoms (PS 0-2)
- Terminal (BCLC D) - Child-Pugh C, (PS > 2)

Treatment Recommendations
- Resection
- Transplant
- Ablation
- Locoregional therapy (ex: TACE)
- Recurrence
- Refractory
- Unsuitable
- Sorafenib or lenvatinib, followed by second-line therapy
- BSC


BSC, best supportive care; TACE, transarterial chemoembolization.
Treatment Options for Advanced Unresectable HCC
Inhibiting Angiogenesis Is Important in HCC, a Vascular Tumor

Image republished from Levin PA, Dowell JE. *Onco Targ Ther.* 2017:10;2057-2066 and licensed under the terms of a Creative Commons BY-NC license (creativecommons.org/licenses/by-nc/3.0/).
Timeline of HCC FDA Approvals

Nov 2017: Nivolumab in HCC previously treated with sorafenib

Nov 2007: Sorafenib Unresectable HCC

April 2017: Regorafenib, HCC previously treated with sorafenib

Sept 2017: Nivolumab in HCC previously treated with sorafenib

Aug 2018: Lenvatinib first-line treatment unresectable HCC

Nov 2018: Pembrolizumab, HCC previously treated with sorafenib

May 2019: Ramucirumab, HCC previously treated with sorafenib and AFP ≥400 ng/mL

Jan 2019: Cabozantinib, HCC previously treated with sorafenib

Pharmacist contributions:
- Develop treatment plan
- Counsel patients
- Ensure dose is safe/effective
- Anticancer drug dispensing
- Promote adherence
- Develop plans to mitigate toxicities, admissions
- Utilization management
- Palliative care initiatives...

Image republished from canrefer.org.au/cancer-type/liver-cancer and licensed under the terms of a Creative Commons BY-ND license (creativecommons.org/licenses/by-nd/3.0/).
Approved First-Line Advanced HCC Treatment:  
**Sorafenib -or- Lenvatinib**
## First-Line Advanced HCC

<table>
<thead>
<tr>
<th></th>
<th><strong>Sorafenib</strong></th>
<th><strong>Lenvatinib</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCC Indication</strong></td>
<td>Unresectable HCC (first line and beyond; Child-Pugh A or B7)</td>
<td>First-line treatment unresectable HCC (first-line, Child-Pugh A only)</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Inhibits VEGFR-1, 2, 3, PDGFR-ß, c-CRAF, BRAF, mutant BRAF, KIT, FLT-3, RET, RET/PTC</td>
<td>Inhibits VEGFR-1, 2, 3, FGFR1, 2, 3, 4; PDGFRα, KIT, RET, FRS2α phosphorylation</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>400 mg (2 tabs) PO BID <strong>without food</strong> (1 hour before / 2 hours after meal) until disease progression or toxicity</td>
<td>12 mg (3 x 4-mg caps) PO daily <strong>if ≥60 kg</strong> or 8 mg (2 x 4-mg caps) PO daily <strong>if &lt;60 kg</strong> until disease progression or toxicity</td>
</tr>
</tbody>
</table>
| **Emetogenicity**              | Minimal (<10%) No prophylactic antiemetics                                   | **Moderate-High (≥30%)**  
**Prophylactic antiemetic needed.** Consider oral 5-HT₃ RA (eg, granisetron) prior to administration or granisetron patch |

# First-Line Advanced HCC

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Sorafenib</th>
<th>Lenvatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Electrolytes, LFTs, thyroid function tests; blood pressure; ECG (if risk QT prolongation)</td>
<td>Renal function; calcium (≥ monthly), urine protein</td>
</tr>
<tr>
<td></td>
<td>CBC with diff; lipase and amylase</td>
<td></td>
</tr>
<tr>
<td>Drug Interactions</td>
<td><strong>Substrate</strong> CYP3A4 (minor), UGT1A9; <strong>Inhibits</strong> BSEP/ABCB11, UGT1A1, UGT1A9</td>
<td><strong>Substrate</strong> BCRP/ABCG2, CYP3A4 (minor), P-glycoprotein/ABCB1; <strong>Inhibits</strong> UGT1A4, UGT1A9</td>
</tr>
<tr>
<td></td>
<td>May ↑ warfarin, avoid strong 3A4 inducers (rifampin, St. John’s wort)</td>
<td>May ↑ QTc-prolonging effect of drugs such as amiodarone, azithromycin, citalopram</td>
</tr>
<tr>
<td>Monthly Cost</td>
<td>$23,077 (AWP)</td>
<td>$22,049 (AWP)</td>
</tr>
</tbody>
</table>

AWP, average wholesale price; CBC, complete blood count; ECG, electrocardiogram; LFT, liver function test.
SHARP: First-Line Sorafenib

**SHARP: Phase 3, randomized, double-blind, placebo-controlled, multicenter trial**

**Treatment Arms:** Sorafenib 400 mg PO BID versus placebo

**Inclusion:** Advanced HCC (not eligible for or disease progression after surgical/locoregional therapies), no prior systemic therapy, ECOG PS ≤2, Child-Pugh Class A

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median overall survival (OS)</th>
<th>Time to symptomatic progression</th>
<th>Time to radiologic progression</th>
<th>Disease-control rate (DCR)</th>
<th>Objective response rate (ORR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>10.7 months [HR, 0.69; (P &lt; 0.001)]</td>
<td>4.1 months</td>
<td>5.5 months</td>
<td>43%</td>
<td>2%</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.9 months</td>
<td>4.9 months</td>
<td>2.8 months</td>
<td>32%</td>
<td>1%</td>
</tr>
</tbody>
</table>

**Conclusion:** Sorafenib increased OS over placebo in untreated advanced HCC.

REFLECT: First-Line Lenvatinib vs Sorafenib

REFLECT: Phase 3, randomized, open-label, multicenter trial, noninferiority study

<table>
<thead>
<tr>
<th>Treatment Arms:</th>
<th>Lenvatinib 12 mg PO daily if ≥60 kg or 8 mg PO daily if &lt;60 kg</th>
<th>Sorafenib 400 mg PO BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion:</td>
<td>Advanced HCC, no prior systemic therapy, Child-Pugh A; Excluded: ≥50% liver occupation, invasion of bile duct, invasion at main portal vein</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
<th>Median PFS</th>
<th>Median TTP</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib (n = 478)</td>
<td>13.6 months</td>
<td>7.4 months</td>
<td>8.9 months</td>
<td>24.1%</td>
</tr>
<tr>
<td>Sorafenib (n = 476)</td>
<td>12.3 months</td>
<td>3.7 months</td>
<td>3.7 months</td>
<td>9.2%</td>
</tr>
</tbody>
</table>

**Median duration of study treatment:** 5.7 months lenvatinib vs 3.7 months sorafenib

**Conclusion:** Lenvatinib was noninferior to sorafenib in OS in untreated advanced HCC.

Adverse Drug Reactions

### Sorafenib & Lenvatinib

<table>
<thead>
<tr>
<th>Condition</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-foot syndrome</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Rash</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Elevated LFTs</td>
<td>Dysphonia</td>
</tr>
<tr>
<td>Thromboembolic events*</td>
<td>Prolonged QTc*</td>
</tr>
</tbody>
</table>

*Sorafenib >  Hand-foot syndrome, diarrhea, alopecia, rash

*Lenvatinib > Hypertension, dysphonia, proteinuria, hypothyroidism, QT prolongation

*2% or less incidence.

Hand-Foot Syndrome (HFS) (Palmar-Plantar Erythrodysesthesias)

- Redness, swelling, pain, blistering at the palms of hands and soles of feet
  - Common with sorafenib, regorafenib > lenvatinib, cabozantinib
  - If HFS on one of above, likely to experience it with another
- Surrogate for drug efficacy?
  - HFS while on sorafenib = up to 60% reduction in risk of death
- Median time to onset: 30 days
- Early and effective management necessary to prevent a reduction in the quality of life

Hand-Foot Syndrome

• Prevention is key!
  • Avoid sources of heat: hot water, sunbathing
  • Avoid friction of hand/feet (eg, running, tennis, vacuuming)
  • Wear loose-fitting shoes
  • Keep hands/feet well moisturized with emollient-based creams

• Management
  • Topical pain relievers containing lidocaine
  • Topical corticosteroids for blisters
  • Apply emollient-based creams without friction
  • Ice pack under the hands/feet
  • May need pain reliever (acetaminophen, ibuprofen, naproxen sodium)

First-Line Nivolumab Failed vs Sorafenib

• **CheckMate-459**: Phase 3 study found NO overall survival (HR, 0.85; [95% CI, 0.72-1.02]; \(P = 0.0752\)) benefit for nivolumab over sorafenib in the first-line management of advanced unresectable HCC
  
  • *Trial teaches us to exercise caution in moving agents up a line in therapy based on early-phase, open-label trials with limited sample sizes*

• However, if a patient is not a candidate or cannot tolerate sorafenib or lenvatinib therapy, nivolumab may be an alternative to consider

Subsequent Therapy for Advanced HCC Treatment
Targeted Therapy for Advanced HCC

1st Line
- Sorafenib (Child-Pugh A & B7)
- Lenvatinib (Child-Pugh A)

2nd Line
- Nivolumab (Child-Pugh A & B7)
- Pembrolizumab (Child-Pugh A; NCCN 2B)
- Ramucirumab (AFP ≥400 ng/mL & Child-Pugh A)
- Sorafenib* (Child-Pugh A & B7)
- Regorafenib (Child-Pugh A)
- Cabozantinib (Child-Pugh A)

3rd Line
- Cabozantinib* (Child-Pugh A)

*If not previously received. All options are NCCN category 1 or 2A unless otherwise noted.
Second-Line HCC Immunotherapy

<table>
<thead>
<tr>
<th>Nivolumab &amp; Pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>HCC previously treated with sorafenib</td>
</tr>
<tr>
<td>Drug Class</td>
</tr>
<tr>
<td>PD-1 Inhibitor / Immune Checkpoint Inhibitor Monoclonal Antibody</td>
</tr>
</tbody>
</table>

**Mechanism:**
Binds to PD-1 receptor, blocking its interaction with PD-L1 and PD-L2, releasing PD-1 pathway inhibition of the immune response, turning the immune system on to recognize the cancer as foreign.

# Second-Line HCC Immunotherapy

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>240 mg IV q2wk or 480 mg IV q4wk until progression or toxicity</td>
<td>200 mg IV q3wk until disease progression or toxicity*</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Hepatic and renal function, thyroid function; blood glucose; monitor for signs/symptoms of immune-related adverse effects and infusion reactions</td>
<td></td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>Consider minimizing the use, duration, and dose of immunosuppressant agents (including systemic corticosteroids – prednisone ≥10 mg/day), if can prior to start</td>
<td></td>
</tr>
<tr>
<td><strong>Monthly Cost</strong></td>
<td>$14,329 (ASP+6%)</td>
<td>$14,208 (ASP+6%)</td>
</tr>
</tbody>
</table>

* sBLA filed pembrolizumab 400 mg IV q 6 weeks → **NOT** FDA indicated today but decision expected by February 18, 2020.

Immune-Related Adverse Effect Management for Immune Checkpoint Inhibitors

Management varies according to organ. Below are general recommendations; refer to prescribing information or national guidelines (ASCO, NCCN, ESMO) for more details.

- **Grade 1**: Continue drug with close monitoring
  - Exception of some neurologic, hematologic, and cardiac toxicities

- **Grade 2**: Consider holding drug; resume with caution when toxicity is grade ≤1
  - May start corticosteroids (initial dose of 0.5-1 mg/kg/day prednisone or equivalent)

- **Grade 3**: Hold drug; start high-dose corticosteroids
  - Prednisone 1-2 mg/kg/day or methylprednisolone IV at 1-2 mg/kg/day; taper over 4-6 weeks

- **Grade 4**: Permanently discontinue drug
  - Exception of endocrinopathies controlled by hormone replacement

CheckMate-040: Second-Line Nivolumab

CheckMate-040: Phase 1/2, open-label, noncomparative, dose escalation and expansion trial

Treatment Arms:
- Nivolumab 0.1-10 mg/kg IV q2wk (Dose Escalation)
- Nivolumab 3 mg/kg IV q2wk (Dose Expansion)

Inclusion:
- Advanced HCC, sorafenib progression/intolerance, Child-Pugh A (or B7 dose-escalation), HCV, HBV receiving effective antivirals. Excluded prior PD-1/ PD-L1/CTLA-4 inhibitors; significant ascites; hepatic encephalopathy, liver transplant

End Point (Dose Expansion)  Uninfected sorafenib untreated/ intolerant (n = 56)  Uninfected sorafenib progressor (n = 57)  HCV infected (n = 50)  HBV infected (n = 51)  All patients (n = 214)

ORR 23% 21% 20% 14% 20%
PFS 5.4 months 4 months 4 months 4 months 4 months
OS NR 13.2 months NR NR NR

KEYNOTE-224: Second-Line Pembrolizumab

**KEYNOTE-240: Phase 2, open-label, nonrandomized trial**

**Treatment:** Pembrolizumab 200 mg IV q3wk x 2 years or until toxicity/progression

**Inclusion:** Advanced unresectable HCC, progression after sorafenib or intolerance, Child-Pugh A; HBV receiving effective antiviral therapy (viral load <100 IU/mL); antiviral therapy not required for patients with HCV; no prior PD-1/PD-L1 inhibitors or organ transplant

<table>
<thead>
<tr>
<th>End Point</th>
<th>Pembrolizumab (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>17%</td>
</tr>
<tr>
<td>DOR</td>
<td>NR (3.1-14.6+)</td>
</tr>
<tr>
<td>DCR</td>
<td>62%</td>
</tr>
</tbody>
</table>

February 9, 2018: FDA issued **accelerated approval** for pembrolizumab in HCC previously treated with sorafenib based on these ORR data

Post Approval Pembrolizumab Failure

• **KEYNOTE-240**: The phase 3 confirmatory study found **NO** OS or PFS benefit for pembrolizumab over placebo in advanced HCC with prior sorafenib (press release February 19, 2019)

<table>
<thead>
<tr>
<th><strong>KEYNOTE-240 Results</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td><strong>HR, 0.78 [95% CI, 0.611-0.998]; P = 0.0238: not statistically significant</strong></td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td><strong>HR, 0.78 [95% CI, 0.61-0.99]; P = 0.0209: not statistically significant</strong></td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td><strong>16.9% (95% CI, 12.7%-21.8%) for pembrolizumab vs 2.2% (95% CI, 0.5%-6.4%) for placebo (nominal 1-sided; P = 0.00001)</strong></td>
</tr>
<tr>
<td><strong>DOR</strong></td>
<td><strong>13.8 months pembrolizumab</strong></td>
</tr>
</tbody>
</table>

Does shrinking of a tumor (↑ ORR) lead to an improvement in survival (OS)???
# Second-Line Oral VEGFR Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib</th>
<th>Cabozantinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>HCC previously treated with sorafenib</td>
<td></td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Inhibits VEGFR-1, 2, 3, RET, KIT, PDGFR-α, PDGFR-β, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, Abl, CSF1R</td>
<td>Inhibits VEGFR-1, 2, 3, MET, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, TIE-2.</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>160 mg (4 x 40-mg tabs) PO after low-fat meal daily for 21 days of 28-day cycle until toxicity or progression</td>
<td>60-mg tab PO without food (1 hour before or 2 hours after meal) daily until toxicity or disease progression</td>
</tr>
<tr>
<td><strong>Emetogenicity</strong></td>
<td>Minimal (&lt;10%) &lt;br&gt;No prophylactic antiemetics</td>
<td><strong>Moderate-High (≥30%)</strong> Prophylactic antiemetic needed. Consider oral 5-HT₃ RA (eg, granisetron) prior to administration or granisetron patch</td>
</tr>
</tbody>
</table>

# Second-Line Oral VEGFR Inhibitors

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Regorafenib</th>
<th>Cabozantinib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LFTs; CBC with diff (monitor platelets); electrolytes; blood pressure; hand-foot syndrome</td>
<td>Renal function; proteinuria; osteonecrosis of the jaw (oral exam prior to start)</td>
</tr>
<tr>
<td></td>
<td>INR if on warfarin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Regorafenib</th>
<th>Cabozantinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Substrate</strong> CYP3A4 (major), UGT1A9; <strong>Inhibits</strong> BCRP/ABCG2, UGT1A1, UGT1A9</td>
<td>Avoid grapefruit juice - ↑s concentration; Avoid strong CYP3A4 inducers &amp; inhibitors</td>
<td><strong>Substrate</strong> CYP2C9 (minor), CYP3A4 (major)</td>
</tr>
<tr>
<td></td>
<td>Avoid grapefruit juice - ↑s concentration; Avoid strong CYP3A4 inducers &amp; inhibitors</td>
<td>Avoid grapefruit juice - ↑s concentration; Avoid strong CYP3A4 inducers &amp; inhibitors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monthly Cost</th>
<th>Regorafenib</th>
<th>Cabozantinib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$20,839 (AWP)</td>
<td>$23,030 (AWP)</td>
</tr>
</tbody>
</table>

AWP, average wholesale price; CBC, complete blood count; INR, international normalized ratio; LFT, liver function test; VEGFR, vascular endothelial growth factor receptor.

RESORCE: Second-Line Regorafenib

RESORCE: Multicenter, phase 3, randomized, double-blind, placebo-controlled trial

<table>
<thead>
<tr>
<th>Treatment Arms:</th>
<th>Regorafenib 160 mg PO daily for 21 days; repeated q 28 days or placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion:</td>
<td>Advanced HCC, progression on sorafenib, no prior systemic therapy other than sorafenib, Child-Pugh A; <strong>Excluded if discontinued sorafenib for toxicity</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
<th>Median PFS</th>
<th>Median TTP</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regorafenib (n = 379)</td>
<td>10.6 months</td>
<td>3.1 months</td>
<td>3.2 months</td>
<td>11%</td>
</tr>
<tr>
<td>Placebo (n = 194)</td>
<td>7.8 months</td>
<td>1.5 months</td>
<td>1.5 months</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Median duration of study treatment:** 3.6 months regorafenib

**Dose interruptions or reductions:** 54% regorafenib

**Conclusion:** Regorafenib increases OS over placebo in previously treated advanced HCC.

# CELESTIAL: Second-Line+ Cabozantinib

## CELESTIAL: Phase 3, randomized, double-blind, placebo-controlled trial

<table>
<thead>
<tr>
<th>Treatment Arms:</th>
<th>Cabozantinib 60 mg PO daily or placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion:</td>
<td>Advanced HCC, prior sorafenib, <strong>progression after 1 or 2 prior systemic therapies</strong>, Child-Pugh A; <strong>Excluded if</strong> moderate-severe ascites, on <strong>anticoagulation</strong>, unstable brain metastases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
<th>Median PFS</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib (n = 470)</td>
<td>10.2 months</td>
<td>5.2 months</td>
<td>4%</td>
</tr>
<tr>
<td>Placebo (n = 237)</td>
<td>8 months</td>
<td>1.9 months</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

**Median duration of study treatment:** 3.8 months cabozantinib  
**Conclusion:** Cabozantinib increases OS and PFS over placebo in previously treated advanced HCC.

## Adverse Drug Effects

<table>
<thead>
<tr>
<th>Regorafenib</th>
<th>Cabozantinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-foot syndrome (52%)</td>
<td>Diarrhea (54%)</td>
</tr>
<tr>
<td>Diarrhea (33%)</td>
<td>Decreased appetite (48%)</td>
</tr>
<tr>
<td>Fatigue (29%)</td>
<td>Hand-foot syndrome (46%)</td>
</tr>
<tr>
<td>Anorexia (24%)</td>
<td>Fatigue (45%)</td>
</tr>
<tr>
<td>Hypertension (23%)</td>
<td>Nausea (31%)</td>
</tr>
<tr>
<td>Increased bilirubin (19%)</td>
<td>Hypertension (29%)</td>
</tr>
<tr>
<td>Increased AST (13%)</td>
<td>Vomiting (26%)</td>
</tr>
<tr>
<td>Hemorrhage (8%, grade ≥3)</td>
<td>Increased AST (22%)</td>
</tr>
<tr>
<td>Increased ALT (8%)</td>
<td>Increased ALT (17%)</td>
</tr>
<tr>
<td>Hypophosphatemia (6%)</td>
<td>Thrombocytopenia (11%)</td>
</tr>
<tr>
<td>Thrombocytopenia (5%)</td>
<td>Increased bilirubin (10%)</td>
</tr>
</tbody>
</table>

**Regorafenib** > Hand-foot syndrome, hemorrhage

* Regorafenib’s adverse effects mimic those of sorafenib

**Cabozantinib** > diarrhea, fatigue, nausea/vomiting

# Second-Line IV VEGFR2 Inhibitor

<table>
<thead>
<tr>
<th><strong>Ramucirumab</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Patients with HCC who have an <strong>AFP ≥400 ng/mL</strong> previously treated with sorafenib</td>
</tr>
<tr>
<td><strong>Drug Class</strong></td>
<td>VEGFR2 Inhibitor/Monoclonal Antibody</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>8 mg/kg IV q2wk until disease progression or toxicity</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>LFTs; urine protein; thyroid function; blood pressure; monitor for infusion-related reactions, arterial thromboembolic events, bleeding/hemorrhage, GI perforation, wound healing impairment, reversible posterior leukoencephalopathy syndrome</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>Angiogenesis inhibitors (systemic) may enhance the adverse/toxic effect of bisphosphonate derivatives. Risk for osteonecrosis of the jaw may be increased.</td>
</tr>
<tr>
<td><strong>Monthly Cost</strong></td>
<td>$16,597 (ASP+6%)</td>
</tr>
</tbody>
</table>

Gl, gastrointestinal; IV, intravenous.

# REACH-2: Second-Line Ramucirumab

**REACH-2: Multicenter, phase 3, randomized, double-blind, placebo-controlled trial**

<table>
<thead>
<tr>
<th>Treatment Arms</th>
<th>Ramucirumab 8 mg/kg IV q2wk or placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion:</td>
<td>Advanced HCC, progression or intolerance to sorafenib, <strong>AFP ≥400 ng/mL</strong>, Child-Pugh A; Excluded: brain metastases, liver transplants</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
<th>Median PFS</th>
<th>Median TTP</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab (n = 197)</td>
<td>8.5 months</td>
<td>2.8 months</td>
<td>3 months</td>
<td>5%</td>
</tr>
<tr>
<td>Placebo (n = 95)</td>
<td>7.3 months</td>
<td>1.6 months</td>
<td>1.6 months</td>
<td>1%</td>
</tr>
</tbody>
</table>

**Median duration of study treatment:** 12 weeks ramucirumab  
**Ramucirumab adverse effects:** hypertension, liver injury/failure, proteinuria, infusion reactions, bleeding  
**Conclusion:** Ramucirumab ↑s OS in previously treated patients with advanced HCC with an AFP ≥400 ng/mL

Why does ramucirumab need a biomarker? Failed to provide benefit in REACH trial in those with any AFP level...
Drug-induced Hypertension

- Common with sorafenib, lenvatinib, regorafenib, cabozantinib, ramucirumab
- Conduct risk assessment
- Address any preexisting hypertension
- Monitor blood pressure regularly and manage elevations aggressively

Figure republished from Touyz RM, et al. J Am Soc Hypertens. 2018;12(6):409-425 and licensed under the terms of a Creative Commons BY license (creativecommons.org/licenses/by/4.0/).
Hypertension Management

- BP $\geq$140/90 mm Hg or 20 mm Hg ↑ diastolic higher from baseline: initiate antihypertensive, titrate current therapy, or add another agent
- No one antihypertensive class is superior
- Avoid CYP450 inhibitors: verapamil, diltiazem

Maitland ML, et al. J Natl Cancer Inst. 2010;102(9):596-604; Figure republished from Touyz RM, et al. J Am Soc Hypertens. 2018;12(6):409-425 and licensed under the terms of a Creative Commons BY license (creativecommons.org/licenses/by/4.0/).
HCC Treatment-Related Adverse Effects

**Diarrhea**

- Consider antidiarrheals (eg, loperamide)
- If immune mediated, may need corticosteroids or if refractory, infliximab
- Dietary modifications
- Increase hydration
- Replete of electrolytes as needed
- Discontinue medications that may contribute (ie, lactulose), if possible

**Fatigue**

- Evaluate for hypothyroidism or immune-mediated endocrinopathies
- Rule out electrolyte disturbances
- Encourage physical activity


Photo by unknown author republished from dogkisses.wordpress.com/2011/03/04/pain-fatigue-and-dogs/) and licensed under the terms of a Creative Commons BY-NC license (creativecommons.org/licenses/by-nc/3.0/).
Promising Future: Advanced HCC Therapies
Second-Line Nivolumab + Ipilimumab

Synergistic effect of ipilimumab on nivolumab

Figure republished from de Mello Ra, et al. *Onco Targ Ther*. 2016;10:21-30 and licensed under the terms of a Creative Commons BY-NC license (creativecommons.org/licenses/by-nc/3.0/).
## CheckMate-040: Second-Line Nivolumab + Ipilimumab Cohort *Preliminary data*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Arm A: Nivolumab 1 mg/kg, Ipilimumab 3 mg/kg IV q3wk x 4, then nivolumab 240 mg IV q2wk</th>
<th>Arm B: Nivolumab 3 mg/kg, Ipilimumab 1 mg/kg IV q3wk x 4, then nivolumab 240 mg IV q2wk</th>
<th>Arm C: Nivolumab 3 mg/kg IV q2wk, Ipilimumab 1 mg/kg IV q6wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>32%</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>DOR</td>
<td>17.5 months</td>
<td>22.2 months</td>
<td>16.6 months</td>
</tr>
<tr>
<td>TTR</td>
<td>2 months</td>
<td>2.6 months</td>
<td>2.7 months</td>
</tr>
<tr>
<td>OS</td>
<td>22.8 months</td>
<td>12.5 months</td>
<td>12.7 months</td>
</tr>
</tbody>
</table>

**Conclusion:** Arm A had the longest median OS at 22.8 months (95% CI, 9.4, N/A); 30-month OS, 44%.

*Preliminary data: Not supported for coverage yet; FDA review anticipated early 2020.*

### CheckMate-040:
Nivolumab + Ipilimumab Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction, %</th>
<th>Arm A: Nivo1 + Ipi3 q3wk x 4 → Nivo</th>
<th>Arm B: Nivo3 + Ipi1 q3wk x 4 → Nivo</th>
<th>Arm C: Nivo3 q2wk + Ipi1 q6wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td>Any grade</td>
</tr>
<tr>
<td>Rash</td>
<td>35%</td>
<td>6%</td>
<td>29%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>20%</td>
<td>20%</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea/colitis</td>
<td>10%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>10%</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>AST increase</td>
<td>20%</td>
<td>16%</td>
<td>20%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>45%</td>
<td>4%</td>
<td>33%</td>
</tr>
</tbody>
</table>

**Conclusion:** Although Arm A had the best survival data, it also had the highest toxicity.

*Preliminary data: Not supported for coverage yet; FDA review anticipated early 2020.*

**First-Line Breakthrough Therapies**

**Pembrolizumab + Lenvatinib**  
(KEYNOTE-524: Ongoing Phase 1b)  
• ORR: 44.8% (n = 67)  
• Median DOR: 18.7 months  
• Phase 3 LEAP-002 trial is ongoing

**Atezolizumab + Bevacizumab**  
(IMbrave-150: Ongoing Phase 3)  
• Atezolizumab plus bevacizumab reduced risk of death by 42% and reduced risk of disease progression or death by 41% versus sorafenib in untreated HCC  
  • mOS not reached for atezolizumab + bevacizumab vs 13.2 mo sorafenib (P = 0.0006)  
  • mPFS 6.8 mo atezolizumab + bevacizumab vs 4.3 mo sorafenib (P <0.0001)

# Ongoing Trials

<table>
<thead>
<tr>
<th>Clinical Trial Identifier</th>
<th>Study</th>
<th>Primary End Point(s)</th>
<th>Estimated Primary Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03298451</td>
<td>HIMALAYA: Durvalumab +/- tremelimumab vs sorafenib first-line advanced HCC</td>
<td>Overall survival</td>
<td>June 30, 2020</td>
</tr>
<tr>
<td>NCT03755791</td>
<td>COSMIC-312: Cabozantinib + atezolizumab vs sorafenib first-line advanced HCC</td>
<td>Overall survival Progression-free survival</td>
<td>August 1, 2020</td>
</tr>
<tr>
<td>NCT03412773</td>
<td>RATIONALE-301: Tislelizumab (PD-1i) vs sorafenib first-line advanced HCC</td>
<td>Overall survival</td>
<td>January 2022</td>
</tr>
<tr>
<td>NCT03713593</td>
<td>LEAP-002: Lenvatinib + pembrolizumab vs lenvatinib first-line advanced HCC</td>
<td>Overall survival Progression-free survival</td>
<td>July 23, 2022</td>
</tr>
</tbody>
</table>

Conclusion

• 2 FDA-approved options first-line advanced HCC: sorafenib or lenvatinib
  • Choice must be individualized, and toxicity considered as efficacy is noninferior
  • No data to guide second-line treatment if lenvatinib used first line (too new)

• Multiple options second-line advanced HCC
  • Nivolumab offers different adverse effect profile
  • Confirmatory pembrolizumab trial failed to provide benefit over placebo
  • Ramucirumab requires a biomarker → only for AFP ≥400 ng/mL

• Limited guidance for Child-Pugh B patients
  • Only data in Child-Pugh score = B7 are with sorafenib or nivolumab, with limited data
Additional Resources


• Association of Community Cancer Centers, Patient Assistance and Reimbursement Guide. accc-cancer.org/home/learn/publications/patient-assistance-and-reimbursement-guide
## Supplemental Information: Monitoring Summary

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib</th>
<th>Lenvatinib</th>
<th>Regorafenib</th>
<th>Cabozantinib</th>
<th>Ramucirumab</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure</td>
<td>q 1-2 weeks for ≤8 weeks, then monthly</td>
<td>q 1-2 weeks for ≤8 weeks, then monthly</td>
<td>q 1-2 weeks for ≤8 weeks, then monthly</td>
<td>q 1-2 weeks for ≤8 weeks, then monthly</td>
<td>q 2 weeks</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>TSH</td>
<td>Baseline, then q 2-3 months</td>
<td>Baseline, then q 2-3 months</td>
<td>Baseline, then q 2-3 months</td>
<td>Baseline, then q 2-3 months</td>
<td>---</td>
<td>Baseline, q 4-6 weeks on drug; q 6-12 weeks after drug</td>
<td>Baseline, q 4-6 weeks on drug; q 6-12 weeks after drug</td>
</tr>
<tr>
<td>ECG</td>
<td>Baseline, week 2-4, q 3 months</td>
<td>Baseline, week 2-4, q 3 months</td>
<td>Baseline, week 2-4, q 3 months</td>
<td>Baseline, week 2-4, q 3 months</td>
<td>Baseline, week 2-4, q 3 months</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Regularly</td>
<td>Regularly</td>
<td>Regularly</td>
<td>Regularly</td>
<td>Regularly</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

TSH, thyroid stimulating hormone; ECG, electrocardiogram.

Instructions on accessing posttest questions:

1) Navigate to the link below to access the program’s posttest questions.

www.tinyurl.com/HCC-posttest-2-18

2) Complete the posttest questions.
Posttest Question 1

After participating in the activity, how confident are you in current treatment strategies for patients with hepatocellular carcinoma?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely
Posttest Question 2

Which of the following is a biomarker that can be elevated in advanced hepatocellular carcinoma?

A. BRAF V600E
B. Hepatitis B surface antigen
C. Epidermal growth factor receptor
D. Alpha fetoprotein
Posttest Question 3

TM is a 61-year-old man with relapsed HCC who is about to begin cabozantinib. Oral kinase inhibitors and monoclonal antibodies that inhibit vascular endothelial growth factor (VEGF) require education and monitoring of mechanism-related toxicities. Which of these adverse effects should be included in his counseling?

A. Hypertension, proteinuria
B. Maculopapular rash, nausea
C. Decreased wound healing, hypothyroidism
D. Colitis, proteinuria
Posttest Question 4

KD is a 63-year-old man with advanced hepatocellular carcinoma that has progressed after sorafenib therapy. A new intravenous combination therapy is currently under review by the FDA for second-line treatment of advanced HCC. Select the appropriate mechanisms of action of action of this combination.

A. CTLA-4 inhibitor + PD-1 inhibitor  
B. PARP inhibitor + PD-1 inhibitor  
C. CTLA-4 inhibitor + VEGFR inhibitor  
D. BRAF inhibitor + PD-L1 inhibitor
Posttest Question 5

LJ is a 64-year-old man with previously treated advanced hepatocellular carcinoma with hepatitis C, cirrhosis, an alpha fetoprotein = 368 ng/mL. He is planned to start therapy with pembrolizumab. Which of the following is an important monitoring parameter to check regularly during pembrolizumab treatment?

A. Thyroid function tests  
B. Blood pressure  
C. Calcium  
D. Urine protein
Question and Answer Session
To complete the evaluation and request credit, please follow the instructions below:

1. Go to: www.pharmacytimes.org and log in to your account.
2. If you do not have an account, create one here: www.pharmacytimes.org/signup
3. Once logged in, go to: www.pharmacytimes.org/requestcredit
4. Enter code: **1753** and click “Submit”.
5. Complete the activity evaluation.
6. Verify your NABP and date of birth, then click “Submit”.

Your credit will be uploaded to CPE Monitor. You may view your credit within 48 hours at www.mycpemonitor.net

NOTE: Participation data will not be uploaded into CPE monitor if your do not have your NABP (e-profile ID) number and date of birth entered.
All participants must request credit by April 18, 2020.
Thank You!