The Rapidly Evolving Treatment Landscape for Hepatocellular Carcinoma

Courtney C. Cavalieri, PharmD, BCOP
Clinical Oncology Pharmacist
Gastrointestinal and Thoracic Oncology
Huntsman Cancer Institute at the University of Utah
Salt Lake City, Utah

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Content Development

Content for this program was developed by:

Laura R. Bobolts, PharmD, BCOP
Senior Vice President, Pharmacy
Oncology Analytics, Inc.
Plantation, Florida

Laura R. Bobolts, PharmD, BCOP, has no financial relationships with commercial interests to disclose.

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Fee: Free

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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

Pretest 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

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

American Cancer Society. *Cancer facts & figures 2019*. Atlanta: American Cancer Society; 2019. cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed July 8, 2019; SEER cancer stat facts: liver and intrahepatic bile duct cancer. National Cancer Institute. Bethesda, MD; seer.cancer.gov/statfacts/html/livibd.html. Accessed May 20, 2019.

HCC Risk Factors

Major Risk Factors

Hepatitis B virus
- Most common risk factor worldwide

Hepatitis C virus
- Most common risk factor in United States
- Risk from unscreened blood products

Cirrhosis
- Response to chronic liver injury
- All risk factors for HCC are directly associated with cirrhosis, except HBV and aflatoxin

Minor Risk Factors

Aflatoxin B1 ingestion
- Mycotoxin from *Aspergillus* spp. fungus that affects grains, legumes in tropical/subtropical areas

Cirrhosis-related
- Alcohol ingestion, HBV, and HCV
- Type 2 diabetes, NAFLD, and obesity
- Inherited syndromes: hereditary hemochromatosis

Other
- Gender (twice as common in men), smoking, HIV

Shariff MI, et al. *Expert Rev Gastroenterol Hepatol*. 2009;3(4):353-367.

Development of HCC

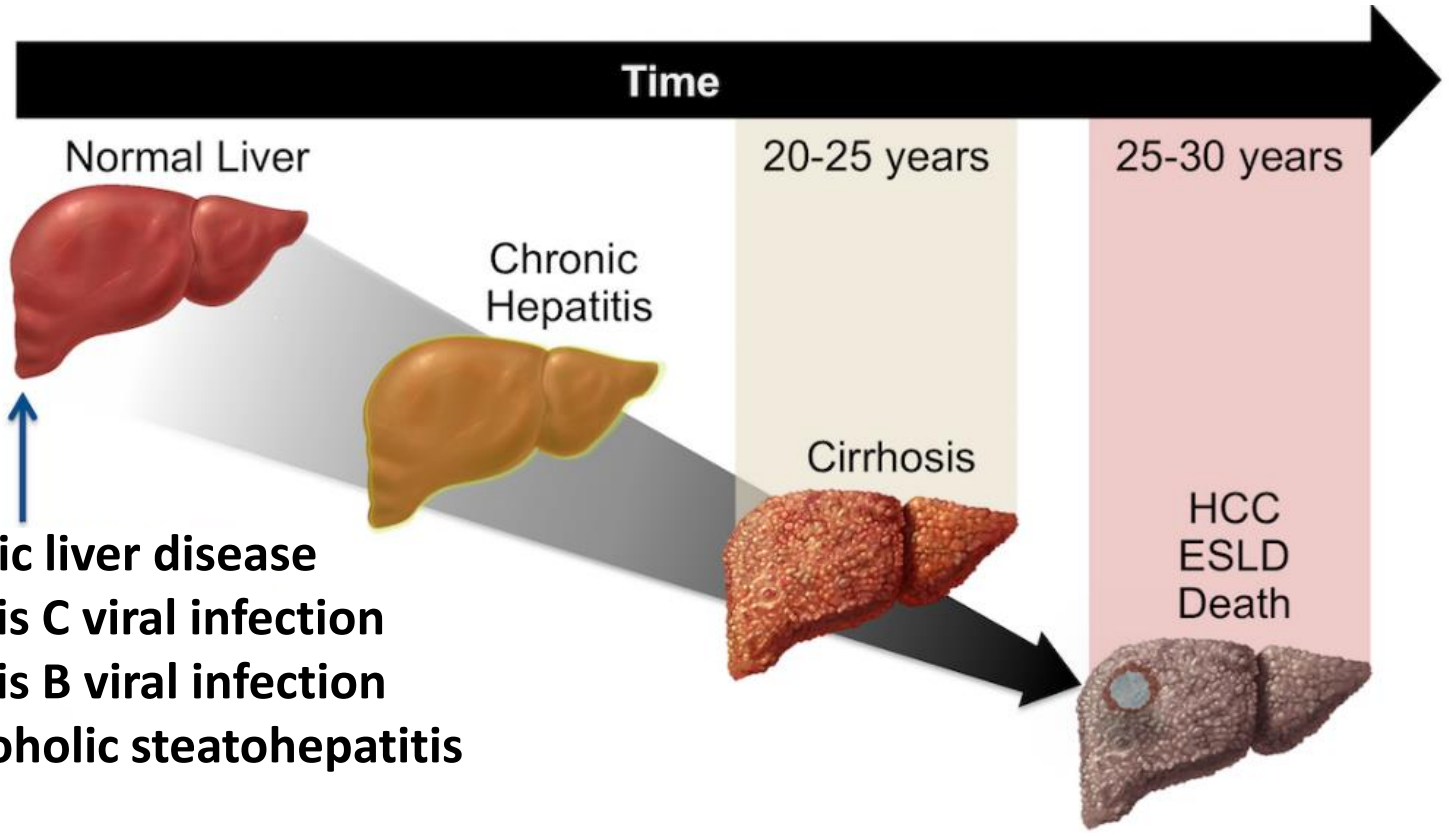


Illustration by David H. Spach, MD. Extrahepatic conditions related to hepatitis C. hepatitisc.uw.edu/go/evaluation-staging-monitoring/initial-evaluationchronic/core-concept/all. Accessed October 31, 2019. Republished with permission.

HCC Screening

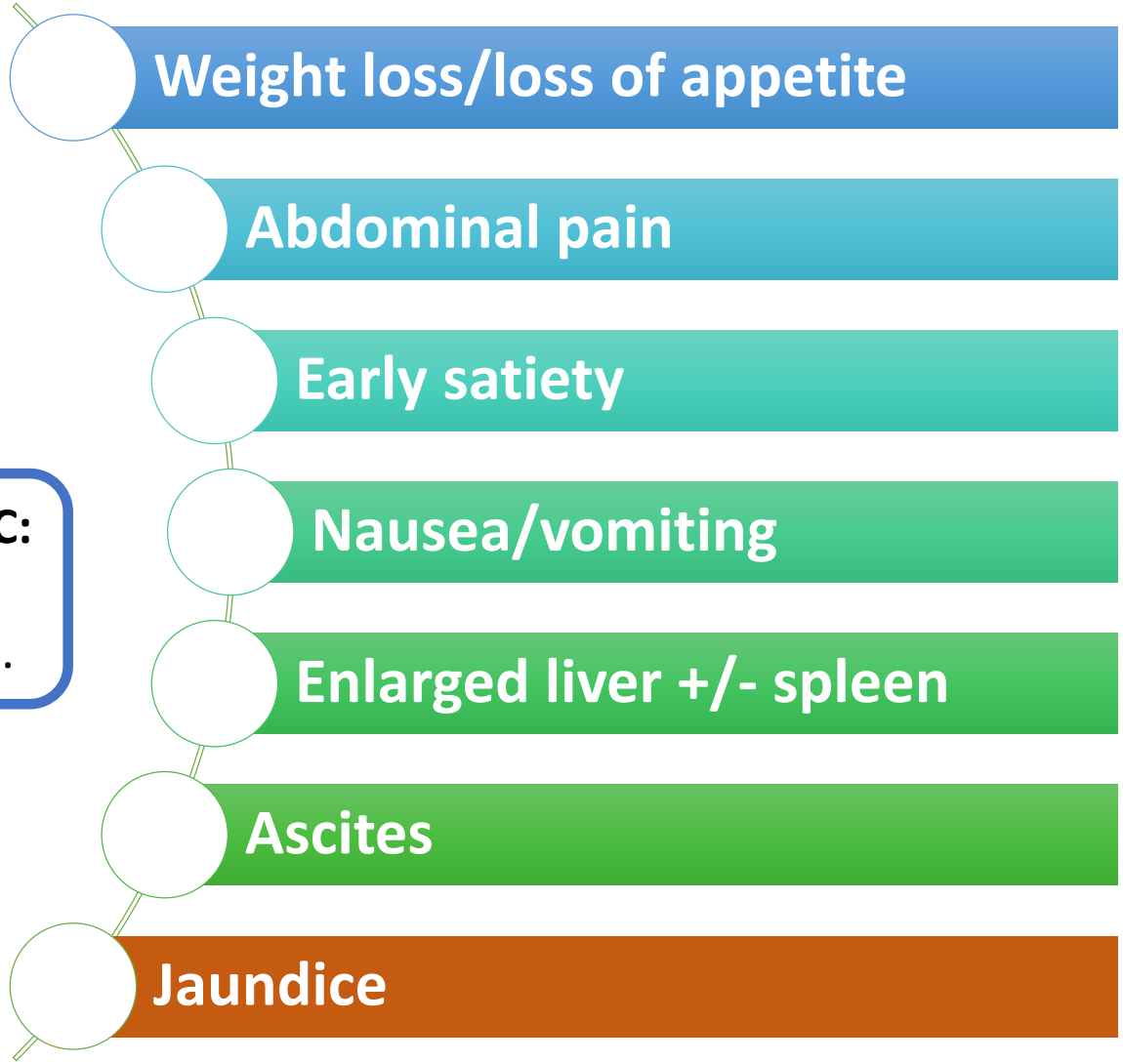
- Average risk
  - No effective screening
- High risk (cirrhosis, HBV, hereditary hemochromatosis)
  - Refer patient for HCC screening
  - Ultrasound ± alpha fetoprotein (AFP) every 6 months
  - AFP >100 ng/mL prompts need for computed tomography or magnetic resonance imaging

- 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

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Hepatobiliary Cancers. Version 3.2019 – August 1, 2019.
Bialecki ES, Di Bisceglie AM. *HPB (Oxford).* 2005;7(1):26-34.

HCC Symptoms

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



American Cancer Society. *Cancer facts & figures 2019*. cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed July 8, 2019; Schwartz JM, et al. uptodate.com. Published April 22, 2019. Accessed September 21, 2019.

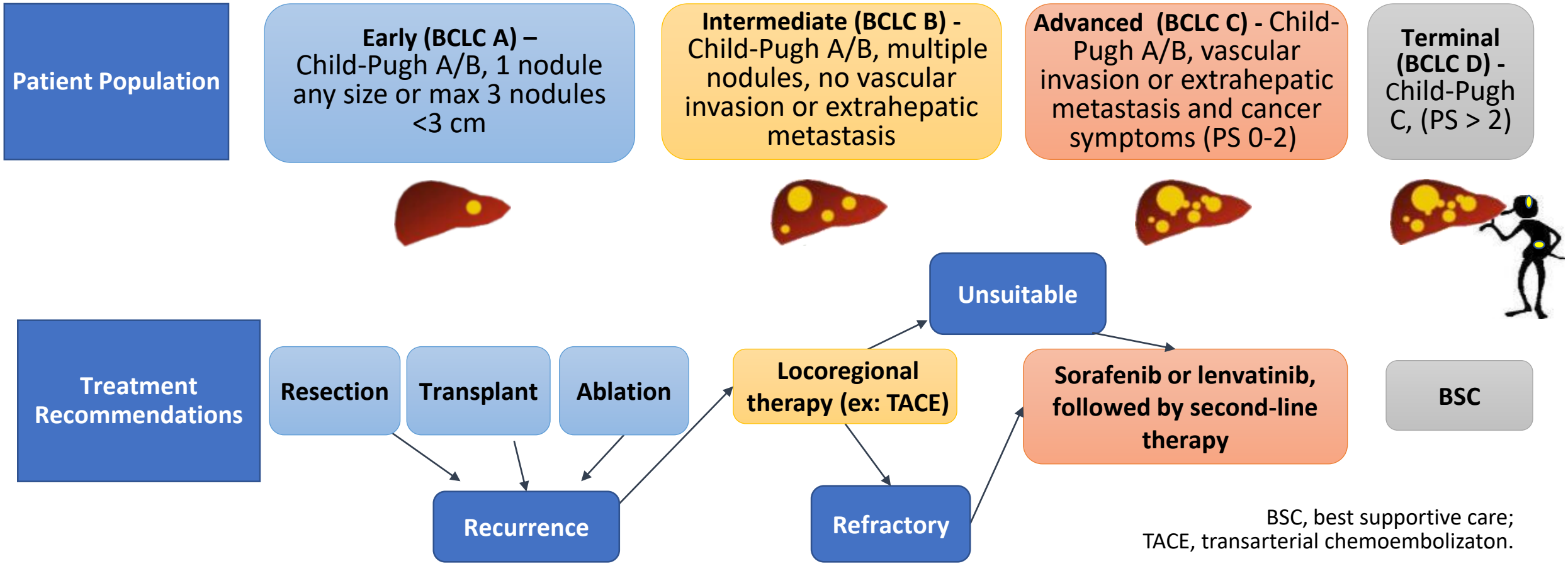
Child-Pugh Score

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

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

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Hepatobiliary Cancers. Version 3.2019 – August 1, 2019.

The BCLC Staging System: Linked to Treatment Recommendations

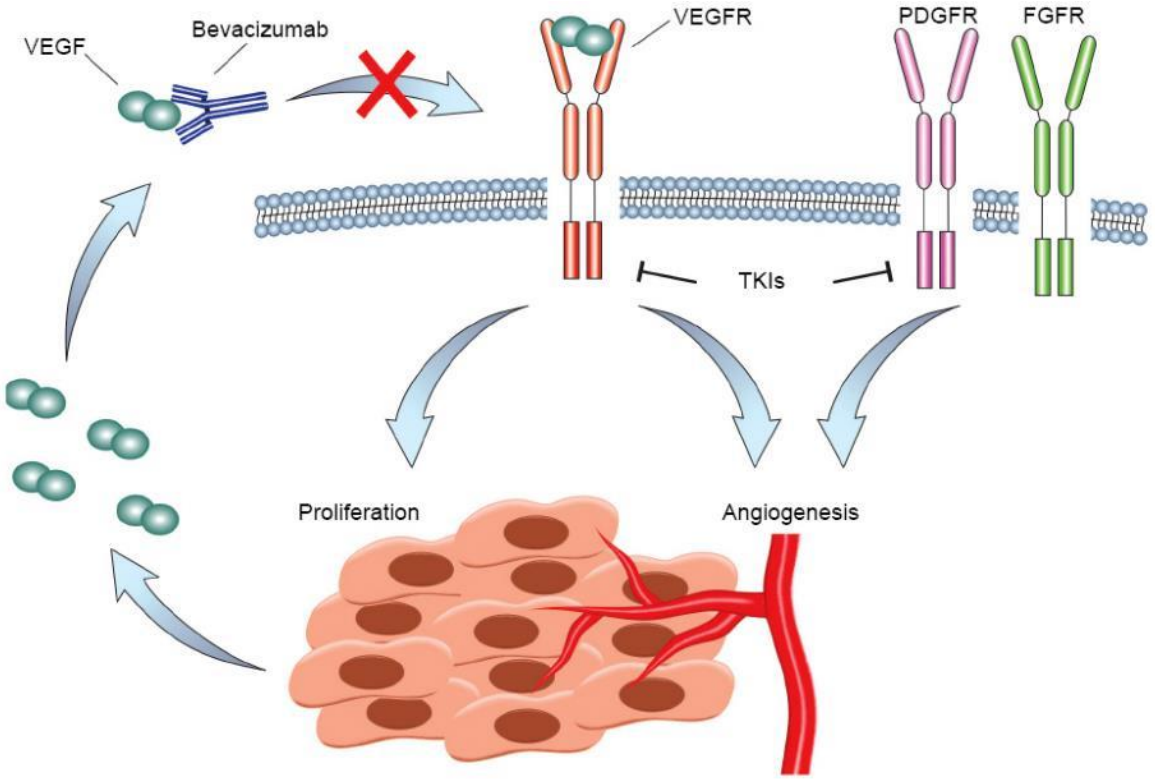


BSC, best supportive care;
TACE, transarterial chemoembolizaton.

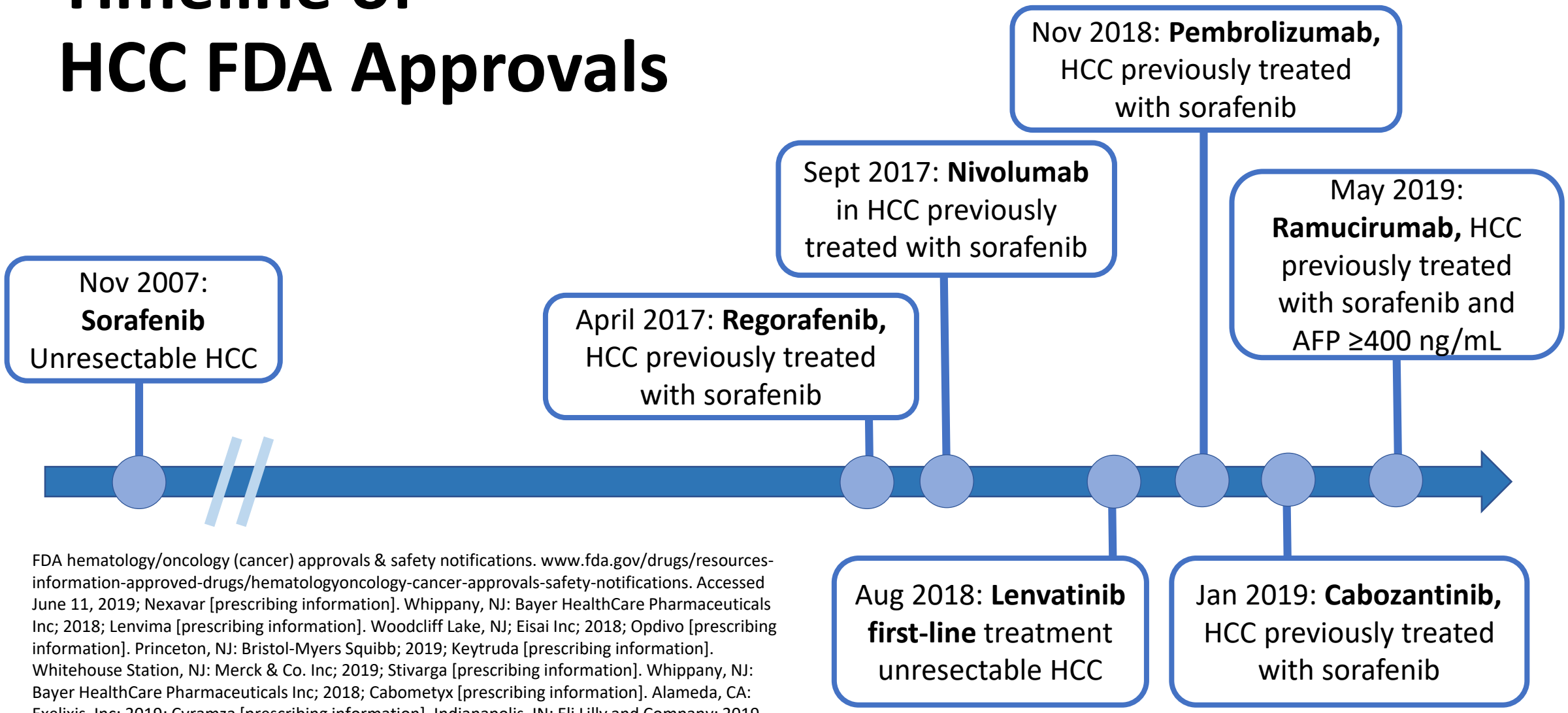
Marrero JA, et al. *Hepatology*. 2018;68(2):723-750; Kinoshita A, et al. *World J Hepatol*. 2015;7(3):406-424.

Treatment Options for Advanced Unresectable HCC

Inhibiting Angiogenesis Is Important in HCC, a Vascular Tumor

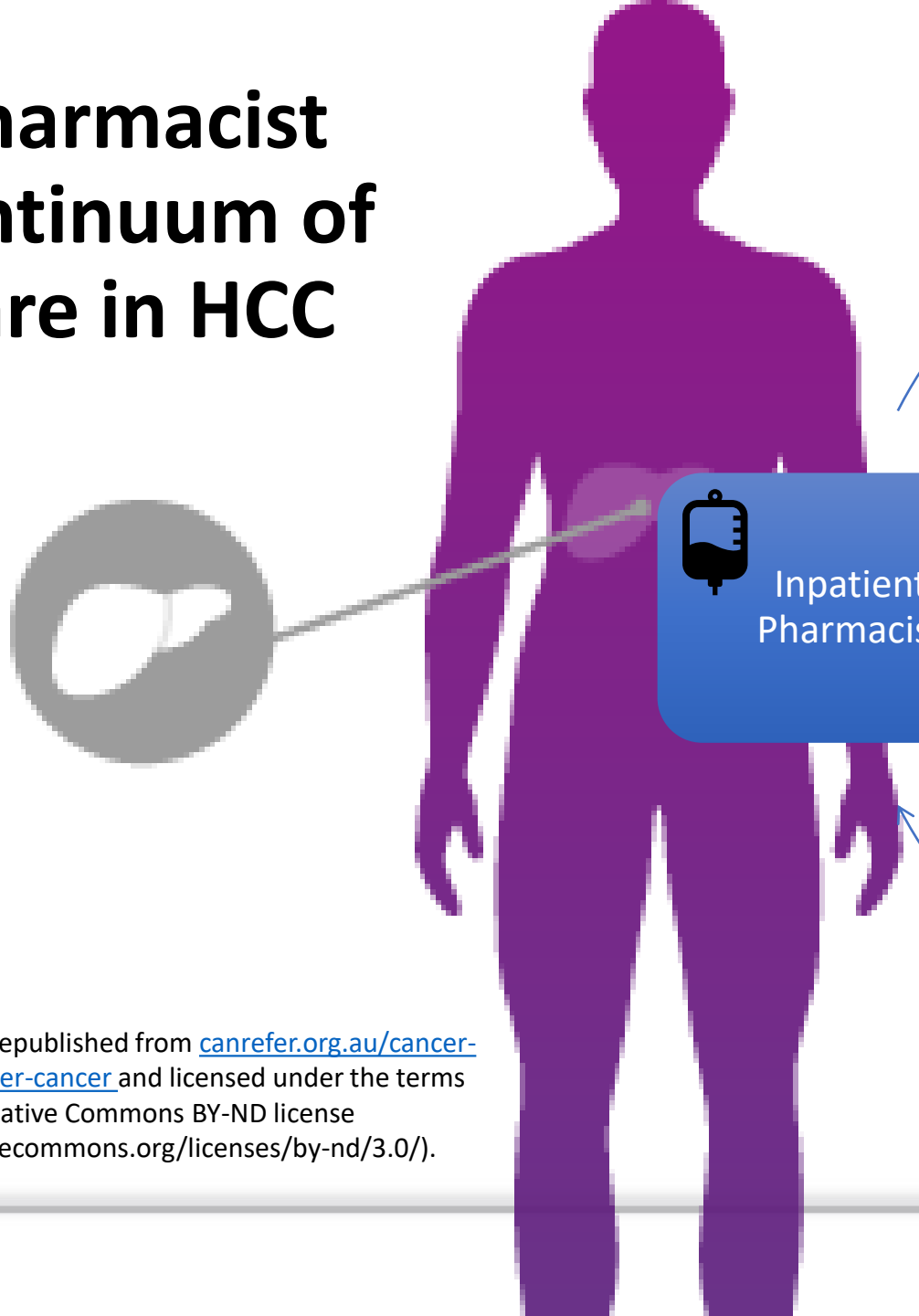


Timeline of HCC FDA Approvals



FDA hematology/oncology (cancer) approvals & safety notifications. www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications. Accessed June 11, 2019; Nexavar [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2018; Lenvima [prescribing information]. Woodcliff Lake, NJ; Eisai Inc; 2018; Opdivo [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2019; Keytruda [prescribing information]. Whitehouse Station, NJ: Merck & Co. Inc; 2019; Stivarga [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2018; Cabometyx [prescribing information]. Alameda, CA: Exelixis, Inc; 2019; Cyramza [prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2019.

Pharmacist Continuum of Care in HCC



Outpatient Clinic Pharmacist

Specialty Pharmacist

Infusion Center Pharmacist

Inpatient Pharmacist

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 …

Approved First-Line Advanced HCC Treatment: Sorafenib -or- Lenvatinib

First-Line Advanced HCC

	Sorafenib	Lenvatinib
HCC Indication	Unresectable HCC (first line and beyond; Child-Pugh A or B7)	First-line treatment unresectable HCC (first-line, Child-Pugh A only)
Mechanism	Inhibits **VEGFR**-1, 2, 3, PDGFR-ß, c-CRAF, BRAF, mutant BRAF, KIT, FLT-3, RET, RET/PTC	Inhibits **VEGFR**-1, 2, 3, FGFR1, 2, 3, 4; PDGFRα, KIT, RET, FRS2α phosphorylation
Dose	400 mg (2 tabs) PO BID **without food** (1 hour before / 2 hours after meal) until disease progression or toxicity	12 mg (3 x 4-mg caps) PO daily **if ≥60 kg** or 8 mg (2 x 4-mg caps) PO daily **if <60 kg** until disease progression or toxicity
Emetogenicity	Minimal (<10%) No prophylactic antiemetics	**Moderate-High (≥30%)** **Prophylactic antiemetic needed.** Consider oral 5-HT_3 RA (eg, granisetron) prior to administration or granisetron patch

VEGFR, vascular endothelial growth factor receptor. Nexavar [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2018; Lenvima [prescribing information]. Woodcliff Lake, NJ; Eisai Inc; 2018; Sorafenib. Lexicomp website. online.lexi.com. Updated September 16, 2019. Accessed September 23, 2019; Lenvatinib. Lexicomp website. online.lexi.com. Updated September 23, 2019. Accessed September 23, 2019.

First-Line Advanced HCC

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

AWP, average wholesale price; CBC, complete blood count; ECG, electrocardiogram; LFT, liver function test.

Nexavar [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2018; Lenvima [prescribing information]. Woodcliff Lake, NJ; Eisai Inc; 2018; Sorafenib. Lexicomp website. online.lexi.com. Updated September 16, 2019. Accessed December 18, 2019; Lenvatinib. Lexicomp website. online.lexi.com. Updated September 23, 2019. Accessed December 18, 2019.

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

Treatment	Median overall survival (OS)	Time to symptomatic progression	Time to radiologic progression	Disease-control rate (DCR)	Objective response rate (ORR)
Sorafenib	10.7 months [HR, 0.69; *P* <0.001]	4.1 months	5.5 months	43%	2%
Placebo	7.9 months	4.9 months	2.8 months	32%	1%

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

Llovet JM, et al. *N Engl J Med*. 2008;359(4):378-390.

REFLECT: First-Line Lenvatinib vs Sorafenib

REFLECT: Phase 3, randomized, open-label, multicenter trial, noninferiority study	
Treatment Arms:	• Lenvatinib 12 mg PO daily **if ≥60 kg** or 8 mg PO daily **if <60 kg** • Sorafenib 400 mg PO BID
Inclusion:	Advanced HCC, no prior systemic therapy, Child-Pugh A; Excluded: ≥50% liver occupation, invasion of bile duct, invasion at main portal vein

Treatment	Median OS	Median PFS	Median TTP	ORR
Lenvatinib (n = 478)	13.6 months	7.4 months	8.9 months	24.1%
Sorafenib (n = 476)	12.3 months	3.7 months	3.7 months	9.2%

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.

TTP, time to progression. Kudo M, et al. *Lancet*. 2018;391(10126):1163-1173.

Adverse Drug Reactions

Sorafenib & Lenvatinib	
Hand-foot syndrome	Hypertension
Diarrhea	Fatigue
Rash	Hypothyroidism
Weight loss	Proteinuria
Hemorrhage	Alopecia
Elevated LFTs	Dysphonia
Thromboembolic events*	Prolonged QTc*

*2% or less incidence.

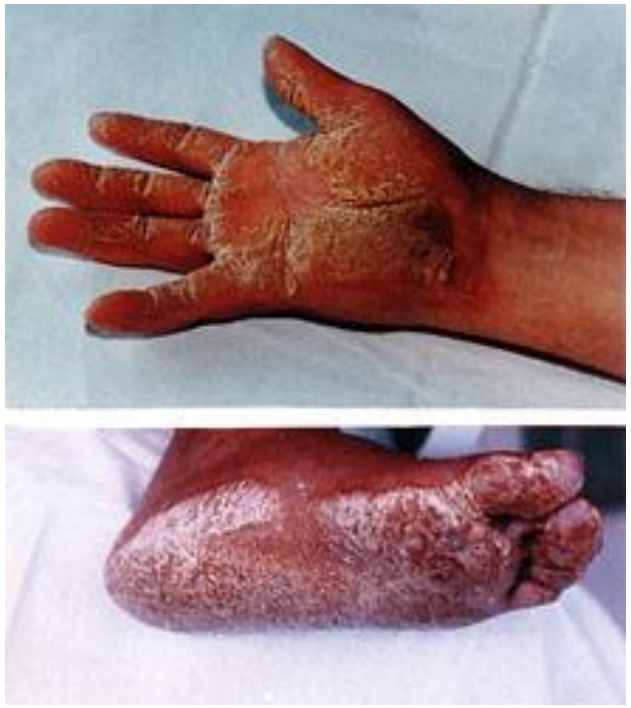
Sorafenib >
Hand-foot syndrome, diarrhea, alopecia, rash

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

Kudo M, et al. *Lancet*. 2018;391(10126):1163-1173; Llovet JM, et al. *N Engl J Med*. 2008;359(4):378-390.

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

- 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



Grieb BC, et al. American Society of Clinical Oncology Educational Book 39 (May 17, 2019) 248-260.

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)

Hand-foot syndrome or palmar-plantar erythrodysesthesia. Cancer.net website. cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/hand-foot-syndrome-or-palmar-plantar-erythrodysesthesia. Accessed June 15, 2019.

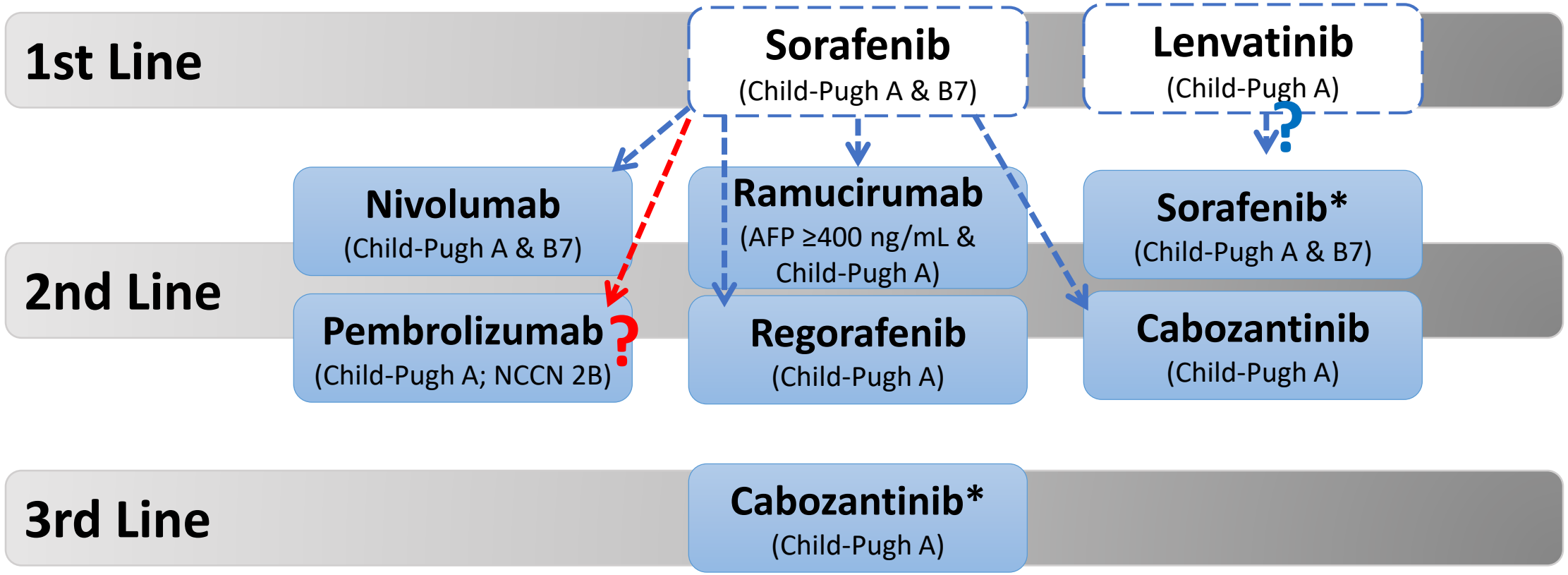
First-Line Nivolumab Failed vs Sorafenib

- **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

Bristol-Myers Squibb announces results from CheckMate-459 study evaluating Opdivo (nivolumab) as a first-line treatment for patients with unresectable hepatocellular carcinoma [news release]. Bristol-Myers Squibb; Princeton, NJ: June 24, 2019. news.bms.com/press-release/bmy/bristol-myers-squibb-announces-results-checkmate-459-study-evaluating-opdivo-nivol. Accessed July 8, 2019.

Subsequent Therapy for Advanced HCC Treatment

Targeted Therapy for Advanced HCC



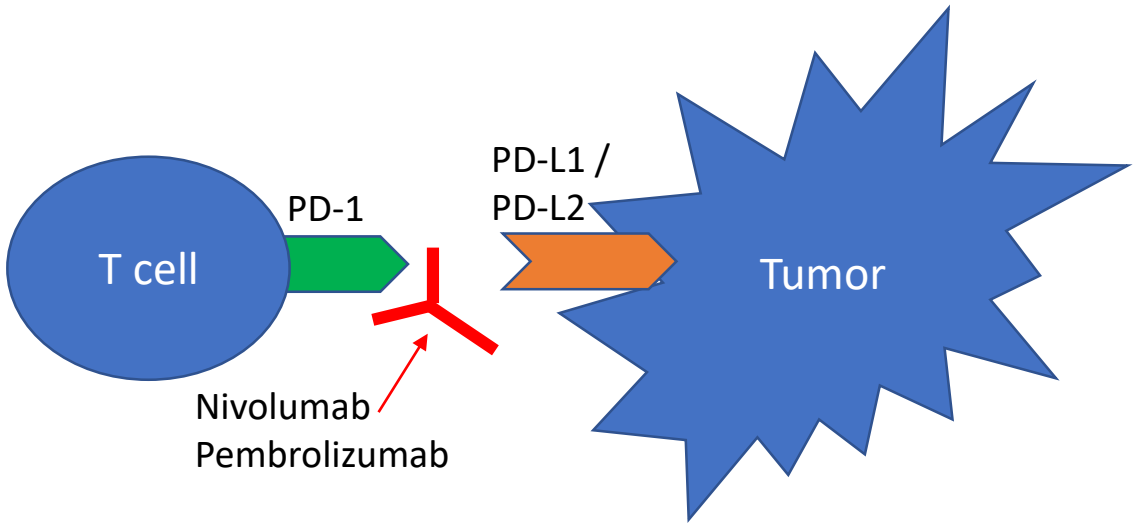
*If not previously received. All options are NCCN category 1 or 2A unless otherwise noted.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Hepatobiliary Cancers. Version 3.2019 – August 1, 2019.

Second-Line HCC Immunotherapy

Nivolumab & Pembrolizumab	
Indication	HCC previously treated with sorafenib
Drug Class	PD-1 Inhibitor / Immune Checkpoint Inhibitor Monoclonal Antibody

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



Opdivo [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2019; Keytruda [prescribing information]. Whitehouse Station, NJ: Merck & Co. Inc; 2019.

Second-Line HCC Immunotherapy

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

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

ASP, average sales price; Opdivo [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2019; Keytruda [prescribing information]. Whitehouse Station, NJ: Merck & Co. Inc; 2019; Centers for Medicare & Medicaid Services. January 2020 ASP pricing file. cms.gov/apps/ama/license.asp?file=https%3A//edit.cms.gov/files/zip/january-2020-asp-pricing-file. Updated December 10, 2019. Accessed December 18, 2019; FDA Accepts Merck's Supplemental Biologics License Applications for KEYTRUDA (pembrolizumab) Six-Week Dosing Schedule for Melanoma and Multiple Other Indications. BioSpace. Released July 9, 2019. Accessed September 25, 2019.

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

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-1768; NCCN Guidelines for Management Immunotherapy-Related Toxicities V2.2019 – April 8, 2019.

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

El-Khoueiry AB, et al. *Lancet*. 2017;389(10088):2492-2502.

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

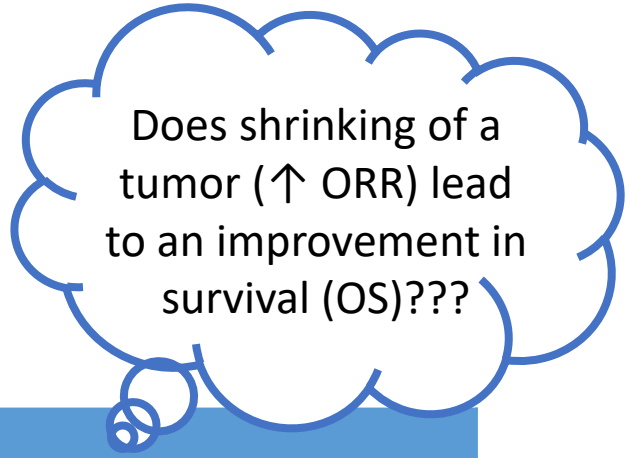
End Point	Pembrolizumab (n = 104)
ORR	**17%**
DOR	NR (3.1-14.6+)
DCR	62%

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

DOR, duration of response. Zhu AX, et al. *Lancet Oncol*. 2018;19(7):940-952.

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)



KEYNOTE-240 Results	
OS	**HR, 0.78** [95% CI, 0.611-0.998]; *P* = 0.0238: **not statistically significant**
PFS	HR, 0.78 [95% CI, 0.61-0.99]; *P* = 0.0209: **not statistically significant**
ORR	**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)
DOR	13.8 months pembrolizumab

Finn RS, et al. *J Clin Oncol.* 2019;37(suppl):Abstract 4004.

Second-Line Oral VEGFR Inhibitors

	Regorafenib	Cabozantinib
Indication	HCC previously treated with sorafenib	
Mechanism	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	Inhibits **VEGFR**-1, 2, 3, MET, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, TIE-2.
Dose	160 mg (4 x 40-mg tabs) PO **after low-fat meal daily** for 21 days of 28-day cycle until toxicity or progression	60-mg tab PO **without food** (1 hour before or 2 hours after meal) daily until toxicity or disease progression
Emetogenicity	Minimal (<10%) No prophylactic antiemetics	**Moderate-High (≥30%)** **Prophylactic antiemetic needed.** Consider oral 5-HT_3 RA (eg, granisetron) prior to administration or granisetron patch

Cabometyx [prescribing information]. Alameda, CA: Exelixis, Inc; 2019; Cabozantinib. Lexicomp website. online.lexi.com. Updated 9/9/2019. Accessed 9/16/2019; Stivarga [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2018; Regorafenib. Lexicomp website. online.lexi.com. Updated 9/13/19. Accessed 9/15/2019.

Second-Line Oral VEGFR Inhibitors

	Regorafenib	Cabozantinib
Monitoring	LFTs; CBC with diff (monitor platelets); electrolytes; blood pressure; hand-foot syndrome	
	INR if on warfarin	Renal function; proteinuria; osteonecrosis of the jaw (oral exam prior to start)
Drug Interactions	**Substrate** CYP3A4 (major), UGT1A9; **Inhibits** BCRP/ABCG2, UGT1A1, UGT1A9 Avoid grapefruit juice - ↑s concentration; Avoid strong CYP3A4 inducers & inhibitors	**Substrate** CYP2C9 (minor), CYP3A4 (major) Avoid grapefruit juice - ↑s concentration; Avoid strong CYP3A4 inducers & inhibitors
Monthly Cost	$20,839 (AWP)	$23,030 (AWP)

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

Cabometyx [prescribing information]. Alameda, CA: Exelixis, Inc; 2019; Cabozantinib. Lexicomp website. online.lexi.com. Updated September 9, 2019. Accessed December 18, 2019; Stivarga [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2018; Regorafenib. Lexicomp website. online.lexi.com. Updated September 13, 2019. Accessed December 18, 2019.

RESORCE: Second-Line Regorafenib

RESORCE: Multicenter, phase 3, randomized, double-blind, placebo-controlled trial	
Treatment Arms:	Regorafenib 160 mg PO daily for 21 days; repeated q 28 days or placebo
Inclusion:	Advanced HCC, progression on sorafenib, no prior systemic therapy other than sorafenib, Child-Pugh A; **Excluded if discontinued sorafenib for toxicity**

Treatment	Median OS	Median PFS	Median TTP	ORR
Regorafenib (n = 379)	10.6 months	3.1 months	3.2 months	11%
Placebo (n = 194)	7.8 months	1.5 months	1.5 months	4%

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.

Bruix J, et al. *Lancet*. 2017;389(10064):56-66.

CELESTIAL: Second-Line+ Cabozantinib

CELESTIAL: Phase 3, randomized, double-blind, placebo-controlled trial	
Treatment Arms:	Cabozantinib 60 mg PO daily or placebo
Inclusion:	Advanced HCC, prior sorafenib, **progression after 1 or 2 prior systemic therapies,** Child-Pugh A; **Excluded if** moderate-severe ascites**, on anticoagulation,** unstable brain metastases

Treatment	Median OS	Median PFS	ORR
Cabozantinib (n = 470)	10.2 months	5.2 months	4%
Placebo (n = 237)	8 months	1.9 months	<1%

Median duration of study treatment: 3.8 months cabozantinib

Conclusion: Cabozantinib increases OS and PFS over placebo in previously treated advanced HCC.

Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63.

Adverse Drug Effects

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

Regorafenib* > Hand-foot syndrome, hemorrhage

* Regorafenib's adverse effects mimic those of sorafenib

Cabozantinib > diarrhea, fatigue, nausea/vomiting

Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63; Bruix J, et al. *Lancet*. 2017;389(10064):56-66.

Second-Line IV VEGFR2 Inhibitor

Ramucirumab	
Indication	Patients with HCC who have an **AFP ≥400 ng/mL** previously treated with sorafenib
Drug Class	VEGFR2 Inhibitor/Monoclonal Antibody
Dose	8 mg/kg IV q2wk until disease progression or toxicity
Monitoring	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
Drug Interactions	Angiogenesis inhibitors (systemic) may enhance the adverse/toxic effect of bisphosphonate derivatives. Risk for osteonecrosis of the jaw may be increased.
Monthly Cost	$16,597 (ASP+6%)

GI, gastrointestinal; IV, intravenous.

Cyramza [prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2019; Centers for Medicare & Medicaid Services. January 2020 ASP pricing file. cms.gov/apps/ama/license.asp?file=https%3A//edit.cms.gov/files/zip/january-2020-asp-pricing-file. Updated December 10, 2019. Accessed December 18, 2019.

REACH-2: Second-Line Ramucirumab

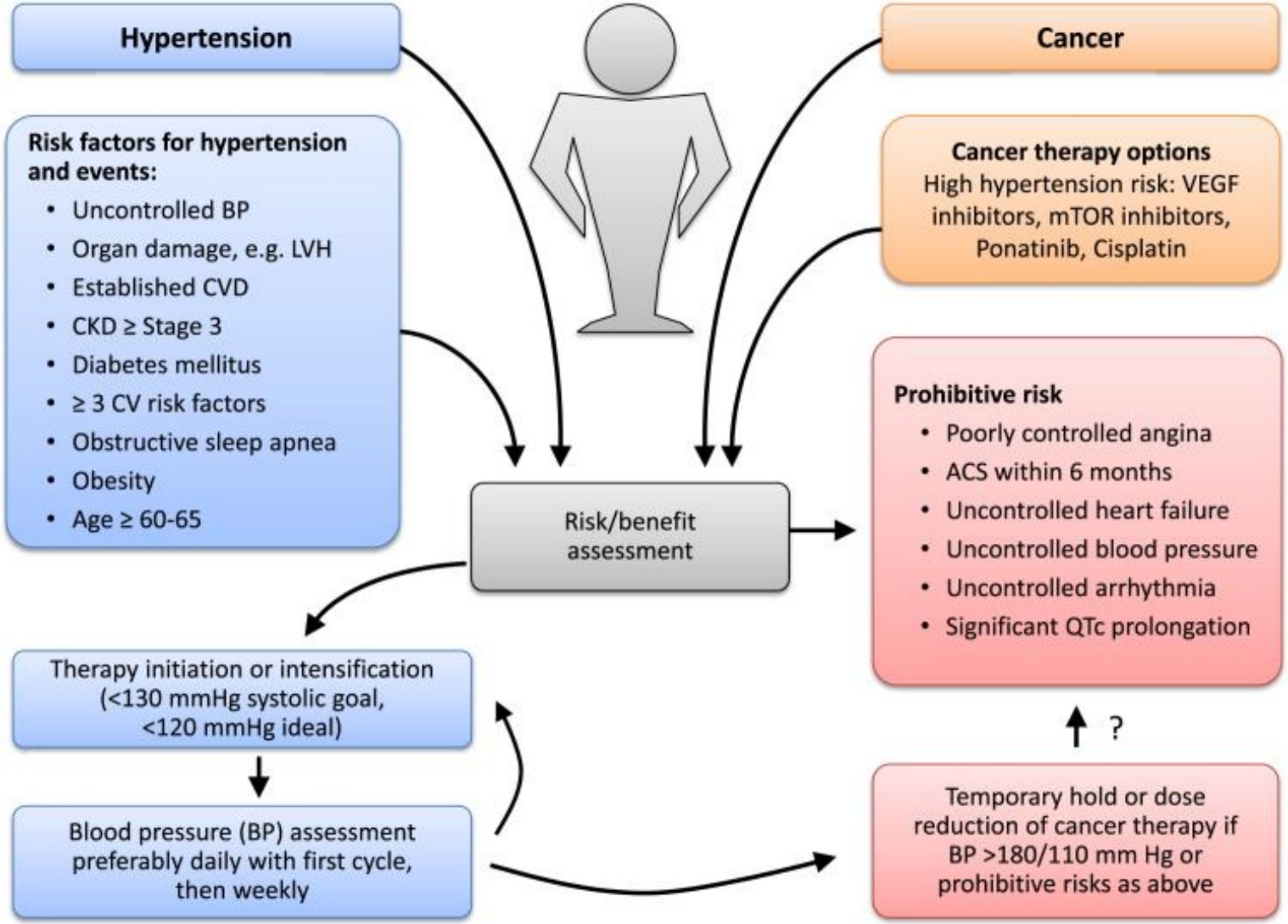
Why does ramucirumab need a biomarker? Failed to provide benefit in REACH trial in those with any AFP level

REACH-2: Multicenter, phase 3, randomized, double-blind, placebo-controlled trial	
Treatment Arms:	Ramucirumab 8 mg/kg IV q2wk or placebo
Inclusion:	Advanced HCC, progression or intolerance to sorafenib, **AFP ≥400 ng/mL**, Child-Pugh A; Excluded: brain metastases, liver transplants

Treatment	Median OS	Median PFS	Median TTP	ORR
Ramucirumab (n = 197)	8.5 months	2.8 months	3 months	5%
Placebo (n = 95)	7.3 months	1.6 months	1.6 months	1%

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

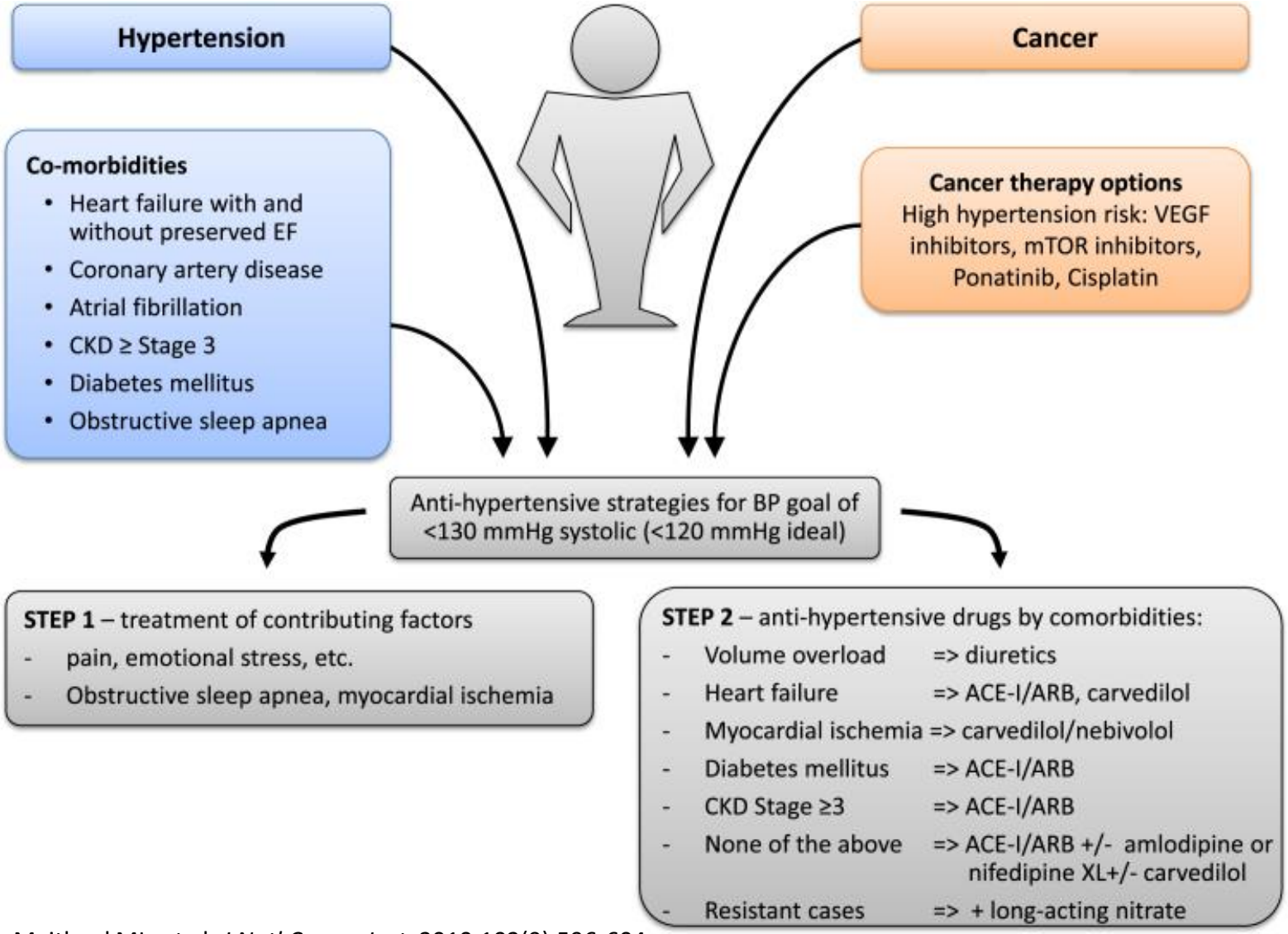
Zhu AX, et al. *Lancet Oncol*. 2015;16(7):859-870. Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-296.



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

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/).



Hypertension Management

- BP ≥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

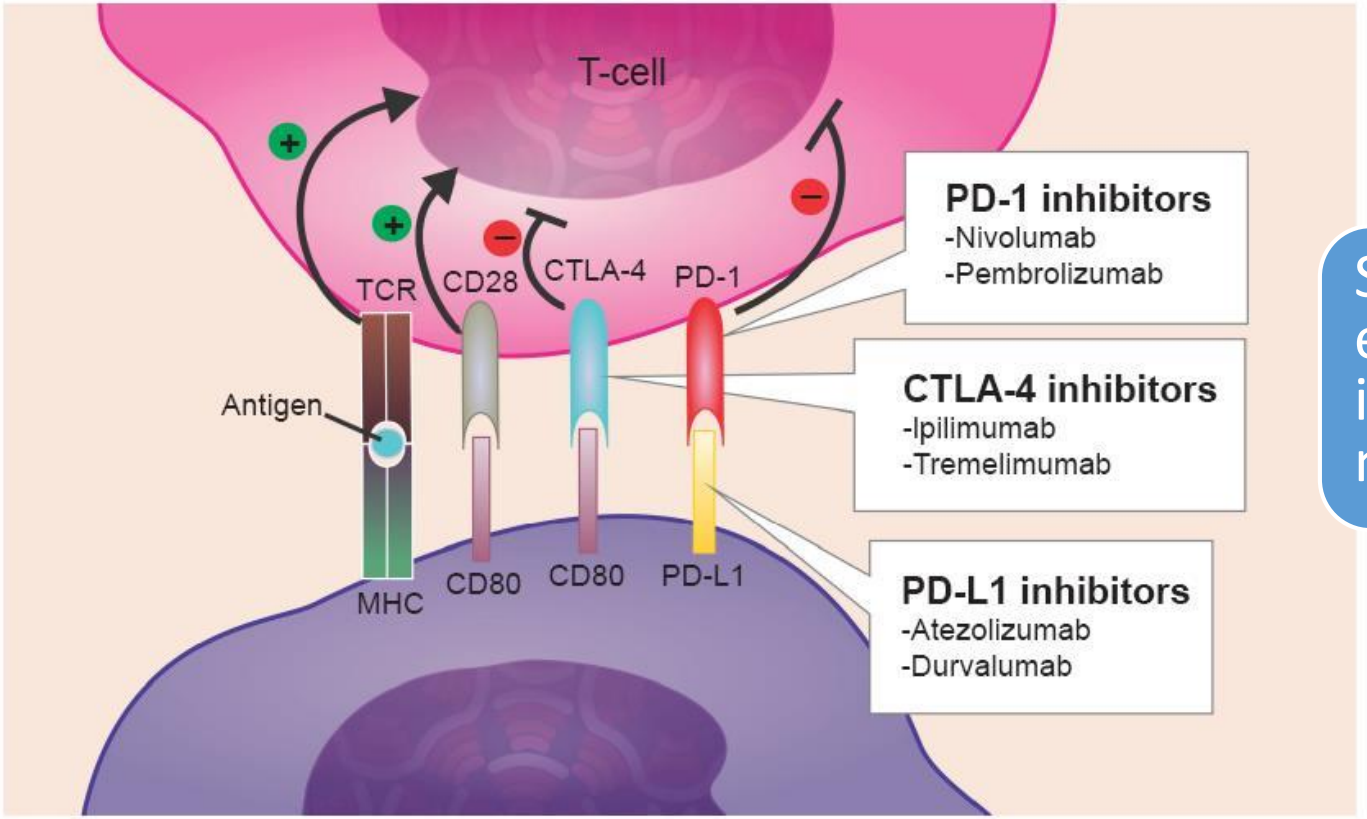
Fatigue

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

Grieb BC, et al. American Society of Clinical Oncology Educational Book 39 (May 17, 2019) 248-260.

Promising Future:
Advanced HCC Therapies

Second-Line Nivolumab + Ipilimumab



Synergistic effect of ipilimumab on nivolumab

CheckMate-040: Second-Line Nivolumab + Ipilimumab Cohort *Preliminary data*

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

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.

Yau T, et al. Poster presented at: 2019 ASCO Annual Meeting; June 3, 2019; Chicago, IL. abstracts.asco.org/239/AbstView_239_250641.html. Accessed July 8, 2019.

CheckMate-040: Nivolumab + Ipilimumab Adverse Drug Reactions

Adverse Reaction, %	Arm A: Nivo1 + Ipi3 q3wk x 4 → Nivo		Arm B: Nivo3 + Ipi1 q3wk x 4 → Nivo		Arm C: Nivo3 q2wk + Ipi1 q6wk	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Rash	35%	6%	29%	4%	17%	0
Hepatitis	20%	20%	12%	10%	6%	6%
Diarrhea/colitis	10%	6%	2%	2%	2%	2%
Pneumonitis	10%	6%	0	0	0	0
AST increase	20%	16%	20%	8%	13%	4%
Pruritus	45%	4%	33%	0	29%	0

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.

Yau T, et al. Poster presented at: 2019 ASCO Annual Meeting; June 3, 2019; Chicago, IL. abstracts.asco.org/239/AbstView_239_250641.html. Accessed July 8, 2019.

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)

Combination of Immunotherapy and VEGF Inhibitor Improves Survival in Hepatocellular Carcinoma [ESMO Asia 2019 Press Release]. November 22, 2019. esmo.org/Press-Office/Press-Releases/ESMO-Asia-Congress-2019-IMbrave150-atezolizumab-bevacizumab-hepatocellular-carcinoma-HCC-Cheng. Accessed December 18, 2019; Kunzmann V. *Ann Oncol*. 2019;30 (suppl 5):v253-v324.

Ongoing Trials

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

National Institutes of Health (NIH) National Library of Medicine (NLM) Clinicaltrials.gov. clinicaltrials.gov/ct2/home. Accessed December 18, 2019.

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

- NCCN Guidelines. Hepatobiliary Cancers. Version 3.2019 – August 1, 2019. nccn.org
- Villanueva A. Hepatocellular carcinoma. *N Engl J Med.* 2019;380(15):1450-1462.
- AASLD Guidelines for the Treatment of Hepatocellular Carcinoma. *Hepatology.* 2018;67(1):358-380. aasld.org/sites/default/files/2019-06/HCC-Guideline-2018.pdf
- Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2018;29(suppl 4):iv238-iv255. esmo.org/Guidelines/Gastrointestinal-Cancers/Hepatocellular-Carcinoma/eUpdate-Treatment-Recommendations
- 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

	Sorafenib	Lenvatinib	Regorafenib	Cabozantinib	Ramucirumab	Nivolumab	Pembrolizumab
Blood Pressure	q 1-2 weeks for ≤8 weeks, then monthly	q 1-2 weeks for ≤8 weeks, then monthly	q 1-2 weeks for ≤8 weeks, then monthly	q 1-2 weeks for ≤8 weeks, then monthly	q 2 weeks	---	---
TSH	Baseline, then q 2-3 months	Baseline, then monthly	Baseline, then q 2-3 months	Baseline, then q 2-3 months	---	Baseline, q 4-6 weeks on drug; q 6-12 weeks after drug	Baseline, q 4-6 weeks on drug; q 6-12 weeks after drug
ECG	Baseline, week 2-4, q 3 months	Baseline, week 2-4, q 3 months	Baseline, week 2-4, q 3 months	Baseline, week 2-4, q 3 months	Baseline, week 2-4, q 3 months	---	---
Urinalysis	Regularly	Regularly	Regularly	Regularly	Regularly	---	---

TSH, thyroid stimulating hormone; ECG, electrocardiogram.

Grieb BC, et al. American Society of Clinical Oncology Educational Book 39 (May 17, 2019) 248-260.

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 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!