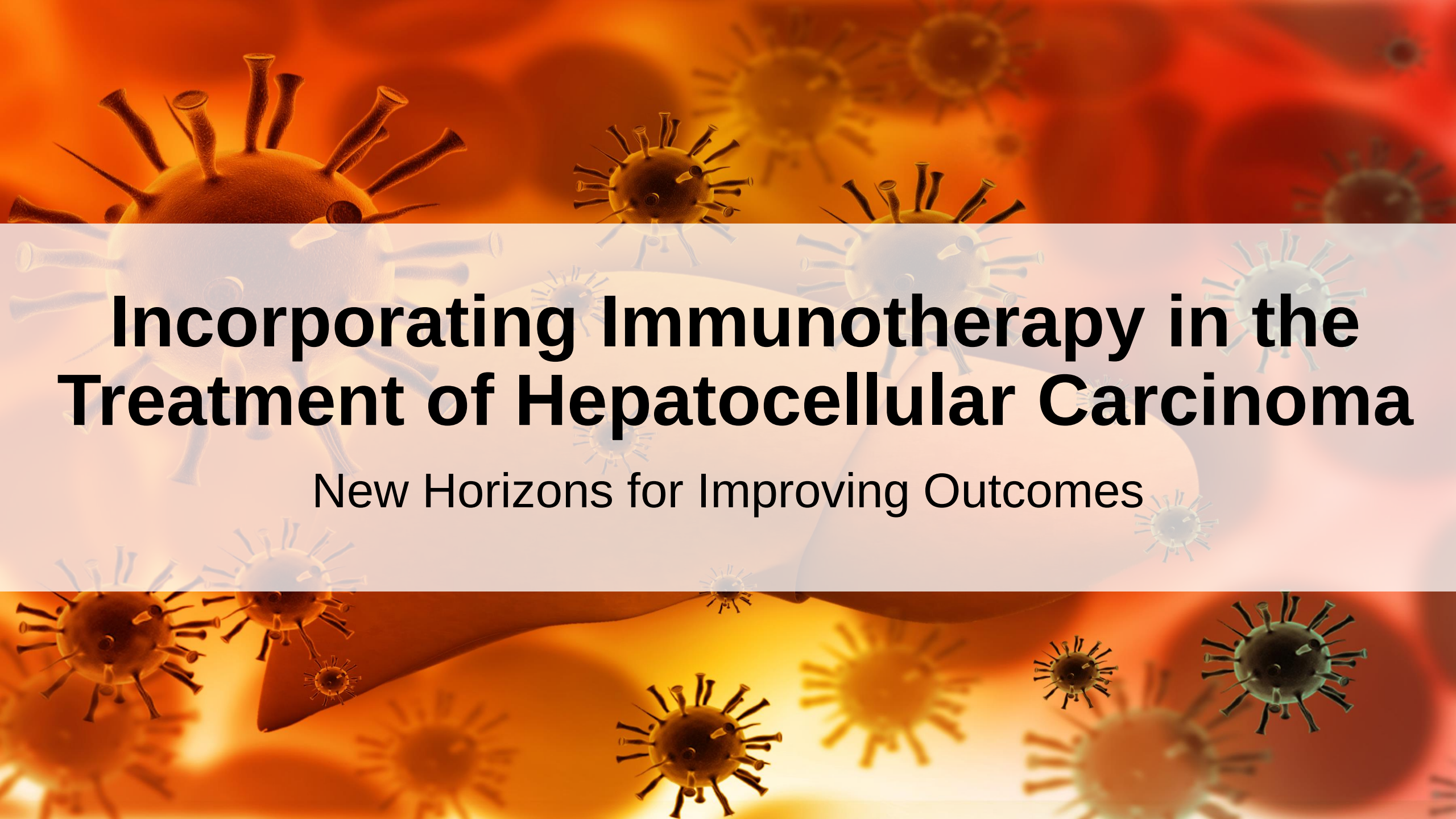

Incorporating Immunotherapy in the Treatment of Hepatocellular Carcinoma

New Horizons for Improving Outcomes

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Faculty

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Disclosures

Dr. Orr has disclosed that she has served as a consultant for Exelixis.

The clinical reviewer, Trang H. Au, PharmD, MPH, BCPS, has no actual or potential conflict of interest in relation to this program.

Susanne Batesko, RN, BSN, Robin Soboti, RPh, and Susan R. Grady, MSN, RN-BC, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education (PHE) continuing education activities hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.

Learning Objectives

- **Discuss** the rationale for use and place in therapy of approved immunotherapies in advanced hepatocellular carcinoma (HCC)
- **Appraise** the emerging data for immunotherapy combination regimens in the treatment of advanced HCC
- **Demonstrate** pharmacist-driven strategies to recognize and effectively prevent or manage immune-mediated toxicities

ARS Question #1

In your current practice, do you help care for patients with HCC?

A. Yes, frequently
B. Yes, somewhat frequently
C. Yes, rarely
D. No

ARS Question #2

In your current practice, what are you seeing ordered for treatment of advanced HCC in the first-line setting?

A. Sorafenib
B. Lenvatinib
C. Nivolumab
D. Other

ARS Question #3

What are the providers at your institution utilizing for the treatment of advanced HCC in the second-line setting?

A. Regorafenib
B. Cabozantinib
C. Nivolumab
D. Pembrolizumab
E. Ramucirumab

Presentation Outline

- Overview of HCC
- Current systemic treatment options for advanced HCC
  - First-line
  - Second-line
- Therapeutic approaches with immunotherapy
- Emerging combination treatment options
- Management of immune-mediated toxicity
- HCC in the real-world setting

Epidemiology

- American Indian/Alaska Natives
  - Highest incidence and mortality rates
  - Double the incidence of Caucasians
- African Americans and Hispanics are expected to become the highest incident groups in the next 15 years
- Rates of HCC are increasing among those born between 1950 and 1959
  - Due to high rates of hepatitis C virus (HCV) infection in this age group

Islami F, et al. *CA Cancer J Clin*. 2017;67(4):273-89.;
Petrick JL, et al. *J Clin Oncol*. 2016;34(15):1787-94.

Risk Factors

- Viral infections caused by hepatitis B virus (HBV) or HCV
- Cirrhosis
- Inherited errors of metabolism
  - Hereditary hemochromatosis, porphyria cutanea tarda, and alpha-1 antitrypsin deficiency
- Wilson’s disease
- Excessive alcohol intake
- Environmental exposure to aflatoxin
  - Natural product of *Aspergillus* found in grains

Fattovich G, et al. *Gastroenterology*. 2004;127(Suppl 1):S35-50.;
Heimbach J, et al. *Hepatology*. 2018;67(1):358-80.

Diagnosis

- Initial workup
  - Evaluation of liver function
  - Hepatitis panel
  - Imaging for detection of metastatic disease
  - Assessment of comorbidities
- Staging
  - Classified into 1 of 4 categories:
    - Potentially resectable or transplantable, operable by performance status or comorbidity
    - Unresectable disease
    - Inoperable by performance status or comorbidity with local disease only
    - Metastatic disease

DeLeve LD, et al. *Hepatology*. 2009;49(5):1729-64.;
Heimbach J, et al. *Hepatology*. 2018;67(1):358-80.;
Miller G, et al. *Surg Oncol Clin N Am*. 2007;16(2):343-68.

Systemic Therapy for Unresectable or Advanced Disease

- Sorafenib
  - Oral multikinase inhibitor that suppresses tumor cell proliferation and angiogenesis
    - Category 1 recommendation for Child-Pugh Class A
    - Category 2A for Child-Pugh Class B7
- Lenvatinib
  - Oral inhibitor of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and other growth-signaling targets
    - Category 2A for Child-Pugh Class A only
- Cytotoxic chemotherapy has low response rates and lacks information on overall survival
  - Category 2B

Cheng AL, et al. *Lancet Oncol*. 2009;10(1):25-34.;
Kudo M, et al. *Lancet*. 2018;391(10126):1163-73.;
Llovet JM, et al. *N Engl J Med*. 2008;359(4):378-90.;
Thomas MB, et al. *Ann Surg Oncol*. 2008;15(4):1008-14.

Second-Line Treatment Options

- Regorafenib
- Cabozantinib
- Ramucirumab
- Nivolumab
- Pembrolizumab
- Sorafenib
  - If treated first-line with lenvatinib monotherapy

Abou-Alfa GK, et al. *N Engl J Med.* 2018;379(1):54-63.;
Bruix J, et al. *Lancet.* 2017;389(10064):56-66.;
El-Khoueiry AB, et al. *Lancet.* 2017; 389:2492-502.;
Zhu AX, et al. *J Clin Oncol* 2018;36(15_suppl):4003.;
Zhu AX, et al. *Lancet Oncol.* 2018;19(7):940-52.

Known Actionable Targets in HCC

Mechanism	Treatment options
Multikinase inhibitor	Sorafenib Lenvatinib Cabozantinib
VEGF inhibitor	Regorafenib
VEGFR2 inhibitor	Ramucirumab
PD-1 immune checkpoint inhibitor	Nivolumab Pembrolizumab

PD-1, programmed cell death protein 1.

Regorafenib

- VEGF inhibitor
- FDA approved for the treatment of patients with advanced HCC who have been previously treated with sorafenib
- Child-Pugh Class A only
- RESOURCE trial
  - January 2017
- Dosing: Regorafenib 160 mg PO daily days 1-21 of a 28-day cycle

FDA, United States Food and Drug Administration.

Bruix J, et al. *Lancet.* 2017;389(10064):56-66.;
Stivarga *(regorafenib)* [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2018.

RESOURCE

Outcome	Regorafenib (n=379)	Placebo (n=194)	p-value
Overall survival (OS)			
Number of deaths (%)	233 (61)	140 (72)	< 0.0001
Median OS in months (95% CI)	10.6 (9.1 – 12.1)	7.8 (6.3 – 8.8)	
Progression-free survival (PFS)*			
Number of events (%)	293 (77)	181 (93)	< 0.0001
Median PFS in months	3.1 (2.8 – 4.2)	1.5 (1.4 – 1.6)	
Overall response rate*	11%	4%	Not reported

*using mRECIST

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

RESOURCE

Adverse event (AE)	Regorafenib (n=374)			Placebo (n=193)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Hand-foot skin reaction	198 (53%)	47 (13%)	-	15 (8%)	1 (1%)	-
Diarrhea	155 (41%)	12 (3%)	0	29 (15%)	0	0
Fatigue	151 (40%)	34 (9%)	-	61 (32%)	9 (5%)	-
Hypertension	116 (31%)	56 (15%)	1 (< 1%)	12 (6%)	9 (5%)	0
Anorexia	116 (31%)	10 (3%)	0	28 (15%)	4 (2%)	0
Increased bilirubin	108 (29%)	37 (10%)	2 (1%)	34 (18%)	15 (8%)	6 (3%)
Abdominal pain	105 (28%)	13 (3%)	-	43 (22%)	8 (4%)	-

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

Cabozantinib

- Inhibits multiple tyrosine kinases, including VEGF, mesenchymal epithelial transition (MET), and the AXL receptor within the Tyro3-AXL-Mer (TAM) tyrosine kinase subfamily
- FDA approved for advanced HCC
- Child-Pugh Class A only
- CELESTIAL trial
  - July 2018
- Dosing: Cabozantinib 60 mg daily continuously until disease progression or unacceptable toxicity

Abou-Alfa GK, et al. *N Engl J Med.* 2018;379(1):54-63.;
Cabometyx (*cabozantinib*) [package insert]. Alameda, CA: Exelixis, Inc; 2019.

CELESTIAL

Outcome	Cabozantinib (n=467)	Placebo (n=237)	p-value
Median OS (months) (95% CI)	10.2 (9.1 – 12.0)	8.0 (6.8 – 9.4)	0.005
Median PFS* (months) (95% CI)	5.2 (4.0 – 5.5)	1.9 (1.9 – 1.9)	0.001
Objective response rate (ORR)*	4%	1%	Not reported
Disease control rate (DCR) (defined as partial response [PR] or stable disease [SD])	64%	33%	Not reported

*using mRECIST

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

CELESTIAL

Adverse event	Cabozantinib (n=467)			Placebo (n=237)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any AE	460 (99)	270 (58)	46 (10)	219 (92)	80 (34)	6 (3)
Diarrhea	251 (54)	45 (10)	1 (< 1)	44 (19)	4 (2)	0
Decreased appetite	225 (48)	27 (6)	0	43 (18)	1 (< 1)	0
Hand-foot syndrome	217 (46)	79 (17)	0	12 (5)	0	0
Fatigue	147 (31)	10 (2)	0	42 (18)	4 (2)	0
Nausea	147 (31)	10 (2)	0	42 (18)	4 (2)	0
Hypertension	137 (29)	73 (16)	1 (< 1)	14 (6)	4 (2)	0
Decreased PLT	45 (10)	13 (3)	4 (1)	7 (3)	2 (1)	0

PLT, platelet count.

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

Ramucirumab

- Human IgG1 monoclonal antibody; inhibits VEGF2
- FDA approved for advanced HCC
- REACH
  - Failed to show significant survival advantage
- REACH-2 trial
  - Follow-up study to confirm significant survival benefit in patients with baseline elevated alpha-fetoprotein (AFP)
- Category 1 recommendation for patient subset with an elevated AFP ≥ 400 ng/mL
- Dosing: 8 mg/kg IV over 1 hour every 2 weeks

Cyramza (*ramucirumab*) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2019.;
Zhu AX, et al. *Lancet Oncol.* 2015;16(7):859-70.;
Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-96.

REACH-2

Outcome	Ramucirumab (n=197)	Placebo (n=95)	p-value
Median OS (months)	8.5	7.3	0.0199
PFS (months)	2.8	1.6	< 0.0001
ORR	4.6%	1.1%	Not reported
DCR (ORR + SD)	59.9%	38.9%	Not reported

- Grade ≥ 3 AEs occurring in ≥ 5% of patients in the ramucirumab arm were
  - Hypertension (12.2%)
  - Hyponatremia (5.6%)

Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-96.

HCC Literature at a Glance

Trial	Llovet JM, et al. (SHARP)	Kudo M, et al.	Bruix J, et al. (RESOURCE)	Abou-Alfa, et al. (CELESTIAL)	Zhu AX, et al. (REACH-2)
Study drug	Sorafenib	Lenvatinib	Regorafenib	Cabozantinib	Ramucirumab
Patient population	aHCC with no prior therapy	aHCC with no prior therapy	aHCC previously treated with sorafenib	aHCC previously treated with sorafenib	aHCC previously treated with sorafenib and AFP ≥ 400 ng/mL
OS (months)	10.7	13.6	10.6	10.2	8.5

aHCC, advanced hepatocellular carcinoma.

Nivolumab

- PD-1 immune checkpoint inhibitor
- Currently FDA approved for use in HCC
- Child-Pugh Class A or B7
- Checkmate 040 trial
  - June 2017
- Checkmate 459
  - June 2019
- Dosing: 240 mg IV over 30 minutes every 2 weeks or 480 mg IV every 4 weeks

BMS announces results from CheckMate-459 [press release]. Bristol-Myers Squibb; June 24, 2019.;
El-Khoueiry AB, et al. *Lancet.* 2017; 389:2492-502.

Pembrolizumab

- PD-1 immune checkpoint inhibitor
- FDA approved for the treatment of patients with HCC who have previously been treated with sorafenib
- Child-Pugh Class A only
- KEYNOTE-224 trial
  - July 2018
- KEYNOTE-240 trial
  - February 2019
  - Missed primary endpoint
    - Pembrolizumab did not improve PFS or OS
- Dosing: 200 mg IV over 30 minutes every 3 weeks

Finn RS, et al. *J Clin Oncol.* 2019;37(suppl):4004.;
Zhu AX, et al. *Lancet Oncol.* 2018;19(7):940-52.

Combination

Noun: a joining or merging of different parts or qualities in which the component elements are individually distinct

Select Ongoing Clinical Trials
Immunotherapy in HCC

NCT number	Study treatment	Target	Phase
03298451	Durvalumab + tremelimumab	PD-L1 + CTLA-4	III
02423343	Nivolumab + galunisertib	PD-1 + TGFβ receptor 1	I - II
02988440	PDR001 + sorafenib	PD-1 + multikinase	I
02795429	PDR001 + capmatinib	PD-1 + c-Met	Ib - II
03418922	Nivolumab + lenvatinib	PD-1 + multikinase	I
03006926	Pembrolizumab + lenvatinib	PD-1 + multikinase	I
03434379	Atezolizumab + bevacizumab	PD-L1 + anti-VEGF	III
03289533	Averumab + axitinib	PD-L1 + multikinase	I - II
01658878	Nivolumab + ipilimumab + cabozantinib	PD-1 CTLA-4 + MET/VEGFR-2	I - II
02572687	Durvalumab + ramucirumab	PD-L1 + VEGFR-2	I

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-L1, programmed death ligand 1; TGF, transforming growth factor.

Kudo M. *Liver Cancer* 2019;8(3):143-54.

Pembrolizumab + Lenvatinib

Phase I open-label, multicenter study

Adults with unresectable HCC (uHCC), Child-Pugh Class A

n = 18

Primary endpoint: Safety

NONCOMPARATIVE

Part 1
Tolerability evaluation
Lenvatinib 12 mg or 8 mg PO daily
Pembrolizumab 200 mg IV q3weeks
n = 6

Part 2
Enrollment of additional patients with no prior systemic therapy

n = 7

Ikeda M, et al. *J Clin Oncol* 2018;36(15_suppl):4076.

Pembrolizumab + Lenvatinib

- Tumor assessments of complete response (CR) or PR were confirmed ≥ 4 weeks after initial response
- As of December 1, 2017, 18 patients had received lenvatinib plus pembrolizumab

Best response, n (%)	Part 1 (n=6)	Part 2 (n=7)	Total (n=13)
PR	4 (67)	2 (29)	6 (46)
SD	2 (33)	4 (57)	6 (46)
Progressive disease	0 (0)	0 (0)	0 (0)
Not evaluable	0 (0)	1 (14)	1 (8)

Ikeda M, et al. *J Clin Oncol* 2018;36(15_suppl):4076.

Pembrolizumab + Lenvatinib

- No dose-limiting toxicities were reported in Part 1
- Treatment emergent adverse events (TEAEs) occurred in 17 patients (94%)
- Most common TEAEs
  - Decreased appetite
  - Hypertension
- Preliminary study conclusion
  - Lenvatinib plus pembrolizumab was well tolerated with encouraging anti-tumor activity in patients with uHCC

Ikeda M, et al. *J Clin Oncol* 2018;36(15_suppl):4076.

Atezolizumab + Bevacizumab

Phase Ib study

Adults with previously untreated unresectable or metastatic HCC

n = 68

Primary endpoints:
Safety
Investigator-assessed ORR

NONCOMPARATIVE

Atezolizumab 1200 mg + bevacizumab 15 mg/kg IV q3weeks

Pishvaian MJ, et al. Presented at: European Society for Medical Oncology. October, 2018; Munich, Germany.

Atezolizumab + Bevacizumab

Endpoint	Outcome
ORR; n (%) CR PR	23 (34) 1 (1) 22 (32)
SD; n (%)	30 (44)
DCR (CR+PR+SD); % 16-week DCR 24-week DCR	78% 68% 50%
Progression of disease (PD); n (%)	11 (16%)
Median PFS; months Range; months	14.9 0 to 23.9+

Pishvaian MJ, et al. Presented at: European Society for Medical Oncology; October, 2018; Munich, Germany.

Atezolizumab + Bevacizumab

- Safety results (n = 68)
  - Any grade treatment-related AEs
    - Occurred in 49 patients (72%)
  - Grade 3-4 AEs
    - Seen in 17 patients (25%)
  - Most common AE
    - Hypertension
  - Immune-related AEs requiring systemic corticosteroids
    - Occurred in 4 patients (6%)

Pishvaian MJ, et al. Presented at: European Society for Medical Oncology. October, 2018; Munich, Germany.

Atezolizumab + Bevaziumab
IMbrave150

Open label, multicenter Phase III trial

Adults with locally advanced, metastatic, and/or unresectable HCC with no prior systemic therapy and Child-Pugh Class A liver function

n = 480 (planned)

Co-primary endpoints:
OS, ORR

RANDOMIZE

2:1

Atezolizumab 1200 mg + bevacizumab 15 mg/kg IV q3weeks

Sorafenib 400 mg PO BID

Finn RS, et al. *J Clin Oncol* 2018;.36(15_suppl):4141.

Nivolumab + Ipilimumab
Checkmate 040

Phase I/II trial
Cohort 4

Adults with aHCC who were previously treated with sorafenib

n = 120

Primary endpoint:
Safety and tolerability

RANDOMIZE

1:1

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3weeks (4 doses)

n = 50

Nivolumab 3 mg/kg + ipilimumab 1 mg/kg q3weeks (4 doses)

n = 49

Nivolumab 3 mg/kg q2weeks + ipilimumab 1 mg/kg q6weeks

n = 49

Both followed by nivolumab 240 mg q2weeks

Yau T, et al. *J Clin Oncol. 2019;*37(15_suppl):4012.

Nivolumab + Ipilimumab

Secondary endpoints	NIVO1/IPI3 Q3W (n=50)	NIVO3/IPI1 Q3W (n=49)	NIVO3 Q2W/IPI1 Q6W (n=49)
ORR, n (%)	16 (32)	15 (31)	15 (31)
CR	4 (8)	3 (6)	0
PR	12 (24)	12 (24)	15 (31)
SD	9 (18)	5 (10)	9 (18)
PD	20 (40)	24 (49)	21 (43)
DCR, % (95% CI)	54 (39 – 68)	43 (29 – 58)	49 (34 – 64)
mOS, mo (95% CI)	23 (9 – NA)	12 (8 – 15)	13 (7 – 33)
12-mo OS, % (95% CI)	61 (46 – 73)	56 (41 – 69)	51 (36 – 64)
24-mo OS, % (95% CI)	48 (34 – 61)	30 (18 – 44)	42 (28 – 56)

Yau T, et al. *J Clin Oncol. 2019;*37(15_suppl):4012.

Nivolumab + Ipilimumab

- Tolerability
  - 37% of patients had grade 3 or 4 AEs
    - Most common: pruritus and rash
  - 5% had grade 3 or higher AE leading to discontinuation
- Study conclusion
  - Nivolumab plus ipilimumab led to clinically meaningful response and has an acceptable safety profile

Yau T, et al. *J Clin Oncol. 2019;*37(15_suppl):4012.

Durvalumab + Tremelimumab

Phase I/II open label trial

Adults with uHCC who had prior sorafenib treatment or refused sorafenib treatment

n = 40

Primary endpoint:
Safety

NONCOMPARATIVE

Phase 1
Safety run-in

Phase 2
Duvarulmab 20 mg/kg + tremelimumab 1 mg/kg IV q4weeks
for 4 doses
Followed by durvalumab 20 mg/kg q4weeks alone

Kelley RK, et al. *J Clin Oncol.* 2017;35(15_suppl):4073.

Durvalumab + Tremelimumab

n (%)	HBV + (n=11)	HCV + (n=9)	Uninfected (n=20)	All (n=40)
Confirmed ORR (all PR)	0	0	6 (30)	6 (15)
CR + PR (confirmed + unconfirmed)	1 (9.1)	0	7 (35)	8 (20)
DCR 16 (CR + PR + SD ≥ 16 weeks)	5 (45.5)	4 (44.4)	14 (70)	23 (57.5)

Kelley RK, et al. *J Clin Oncol.* 2017;35(15_suppl):4073.

Durvalumab + Tremelimumab

- Tolerability
  - 60% had ≥ 1 treatment-related AE
  - 20% had ≥ 1 grade 3 or higher AE
  - Most common (> 15%) AE of any grade
    - Fatigue
    - Increase ALT
    - Pruritus
    - Increased AST
  - Most common grade 3 or higher AE
    - Asymptomatic increased AST
  - 3 patients discontinued treatment due to treatment-related AE
    - Grade 3 pneumonitis; grade 3 colitis; grade 4 AST/ALT elevations

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Kelley RK, et al. *J Clin Oncol.* 2017;35(15_suppl):4073.

Durvalumab + Tremelimumab
HIMALAYA Study

Phase 3 open-label, multicenter study

Adults with uHCC who have not received prior treatment

Primary endpoint:
OS

Secondary endpoints:
ORR, duration of response, DCR, PFS, and time to progression

RANDOMIZED

- **Durvalumab monotherapy**
- **Durvalumab + tremelimumab**
- **Sorafenib monotherapy**

Abou-Alfa GK, et al. *J Clin Oncol.* 2018;36(15_suppl):4144.

Adverse Effect

Noun: a secondary, typically undesirable effect of a drug or medical treatment

Medication Review

Select Approved Agents

Adverse event	Regorafenib	Cabozantinib	Ramucirumab	Nivolumab	Pembrolizumab
Hand-foot syndrome	++	++	-	-	-
Diarrhea	++	++	+	++	+
Fatigue	++	++	-	++	+
Hypertension	++	+	+	-	-
Rash	-	+	-	++	+
Nausea	+	++	-	+	+
Myalgia	-	-	-	+	+
Decreased appetite	++	++	-	+	+

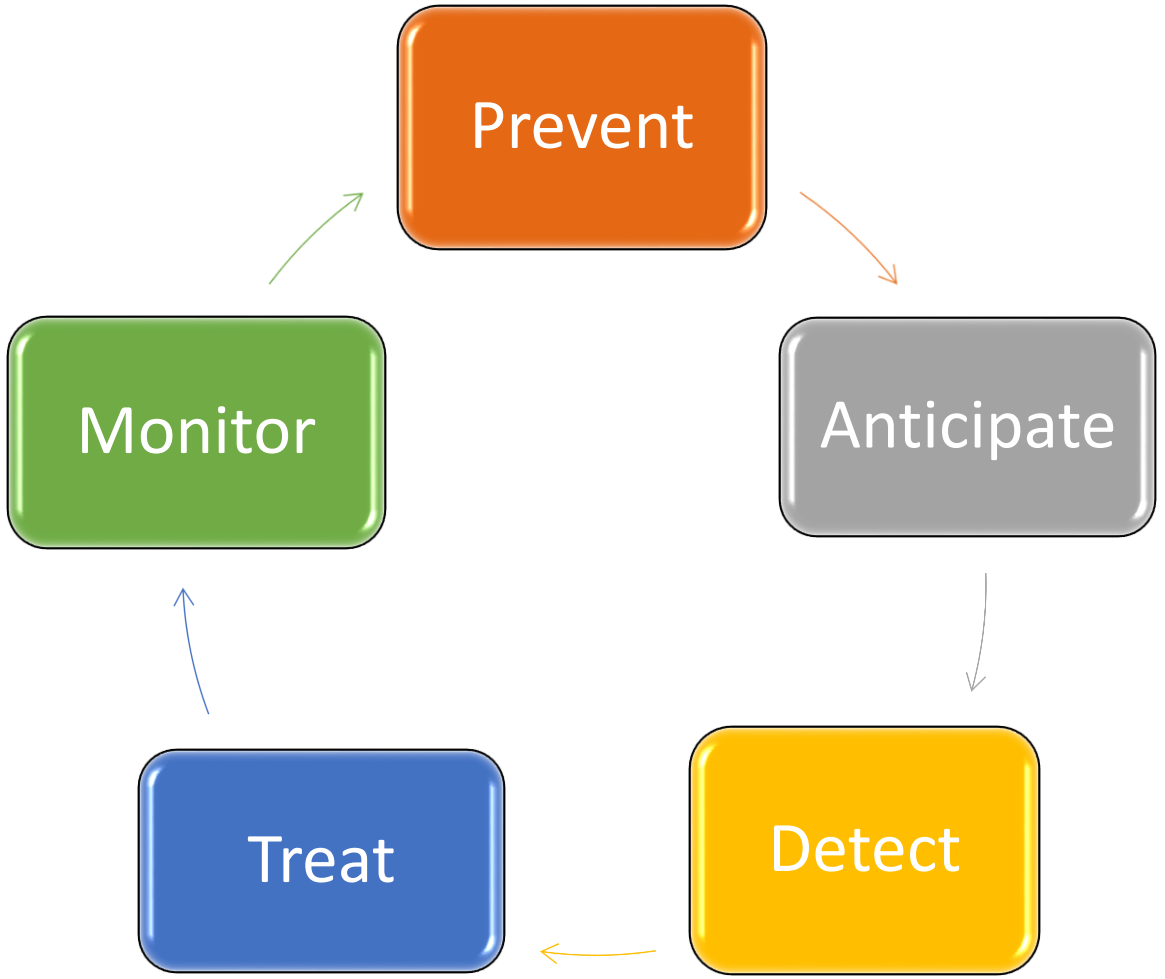
++ = > 30% incidence
+ = 10% – 29% incidence
- = < 10% incidence

Immune-Related Adverse Event (irAE)

- Immunotherapy vs. chemotherapy
  - Delayed onset
  - Prolonged duration of toxicity
- CTLA-4 inhibitors
  - Tend to have higher rates of toxicity
  - Timing is more predictable
- Risk factors
  - Combination immunotherapy regimens
  - Personal history of autoimmune disorders

Myers G. *Curr Oncol*. 2018;25(5):342-7.

5 Pillars of irAE Management



Champiat S, et al. *Ann Oncol.* 2016;27(4):559-74.

Prevent: Know the Possibilities

Organ system	Common AEs	Rare AEs
Cardiac	-	Cardiomyopathy, myocarditis, pericarditis
Dermatologic	Rash, pruritus, vitiligo	Bullous dermatitis, Stevens-Johnson syndrome, toxic epidermal necrosis, DRESS
Endocrine	Hypothyroidism, hyperthyroidism, thyroiditis	Autoimmune type 1 diabetes, primary adrenal insufficiency
Gastrointestinal	Diarrhea, colitis, lichenoid mucositis	Enteritis, gastritis, pancreatitis
Hematologic	-	Aplastic anemia, hemolytic anemia, ITP, lymphopenia, hemophilia
Hepatic	Transaminitis, hepatitis	-
Neurologic	Sensorimotor neuropathy	Meningitis, encephalitis, facial nerve palsy, Guillain-Barre syndrome, myasthenia gravis
Ophthalmic	-	Uveitis, conjunctivitis, scleritis, retinitis
Renal	Increase serum creatinine, nephritis	-
Respiratory	Pneumonitis	Pleuritis, sarcoidosis
Rheumatic	Arthralgia, myalgia	Dermatomyositis, myositis, vasculitis

DRESS, drug reaction with eosinophilia and systemic symptoms; ITP, immune thrombocytopenic purpura.

Myers G. *Curr Oncol*. 2018;25(5):342-7.

Anticipate

- Baseline assessment
  - Physical exam, labs, and imaging to use as references during treatment
- During treatment
  - Assess new symptoms or increase of pre-existing symptoms
  - Monitor labs routinely
- After treatment
  - Monitor every 3 months for the first year, and then every 6 months

Champiat S, et al. *Ann Oncol.* 2016;27(4):559-74.;
Thompson JA, et al. *J Natl Compr Canc Netw.* 2019;17(3)255-89.

Detect

- When an AE is detected, consider 3 potential etiologies
  - Disease progression
  - Treatment-related immune toxicity
  - Unrelated event
- Toxicities can develop at any time
  - Majority occur within the first 4 months
  - Median onset varies depending on the type of toxicity

Champiat S, et al. *Ann Oncol.* 2016;27(4):559-74.;
Thompson JA, et al. *J Natl Compr Canc Netw.* 2019;17(3)255-89.

Treat

- Primary questions to answer when treating an irAE:
  - Outpatient versus inpatient treatment?
  - Continue, hold, or discontinue immunotherapy?
  - Is therapy with a corticosteroid necessary?
  - What therapy is warranted for a steroid-refractory irAE?
  - What symptomatic treatment is needed?
  - What information does the patient need to know for monitoring?

Champiat S, et al. *Ann Oncol.* 2016;27(4):559-74.;
Thompson JA, et al. *J Natl Compr Canc Netw.* 2019;17(3)255-89.

General Treatment Guidelines

- Grade 1 toxicity
  - Continue immunotherapy
- Grade 2 toxicity
  - Consider suspension; patient and AE dependent
- Grade 3 toxicity
  - Suspend and discuss resumption based on risk/benefit ratio
- Grade 4 toxicity
  - Discontinue immunotherapy permanently

Champiat S, et al. *Ann Oncol.* 2016;27(4):559-74.;
Thompson JA, et al. *J Natl Compr Canc Netw.* 2019;17(3)255-89.

Pruritus

Assessment	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3)
• Total body exam • Evaluate dermatologic history	• Continue immunotherapy • Oral antihistamines • Moderate-potency topical steroids	• Continue immunotherapy with intensified antipruritic therapy • Oral antihistamines • High-potency topical steroids • Dermatology consult	• Hold immunotherapy • Oral antihistamines • Prednisone or methylprednisolone 0.5-1 mg/kg/day • Consider GABA agonists • Urgent dermatology consult

GABA, gamma aminobutyric acid.

Champiat S, et al. *Ann Oncol.* 2016;27(4):559-74.;
Thompson JA, et al. *J Natl Compr Canc Netw.* 2019;17(3)255-89.

Colitis

Assessment	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3/4)

• Rule out infectious causes
• Consider CT of abdomen/pelvis
• Consider GI consult
	• Consider holding immunotherapy
	• Loperamide or diphenoxylate/atropine
	• Hydration
	• Close monitoring
		• Hold immunotherapy
		• Prednisone/ methyprednisolone 1 mg/kg/day
		• No response in 2-3 days:
		  • Increase dose to 2 mg/kg/day
		  • Consider adding infliximab
			• Grade 3:
			  • Discontinue anti-CTLA-4; consider resuming PD-1/PD-L1 after resolution
			• Grade 4:
			  • Permanently discontinue
			• IV methylprednisolone 2 mg/kg/day
			• If no response in 2 days:
			  • Continue steroids, add infliximab
			  • If infliximab-refractory, consider vedolizumab

CT, computed tomography; GI, gastroenterology.

Champiat S, et al. *Ann Oncol.* 2016;27(4):559-74.; Thompson JA, et al. *J Natl Compr Canc Netw.* 2019;17(3)255-89.

Pneumonitis

Mild (grade 1)	Moderate (grade 2)	Severe (grade 3/4)

• Consider holding immunotherapy
• Reassess in 1-2 weeks
• Consider chest CT
	• Hold immunotherapy
	• Pulmonary consult
	• Infectious workup
	• Consider bronchoscopy and chest CT
	• Consider empiric antibiotics if infection has not be ruled out
	• Prednisone/methylprednisolone 1-2 mg/kg/day
		• Permanently discontinue immunotherapy
		• Inpatient care with infectious workup
		• Pulmonary and infectious disease consults
		• Bronchoscopy with BAL
		• Empiric antibiotics if infection has not been ruled out
		• Methylprednisolone 1-2 mg/kg/day
		  • Assess response after 48 hours, taper over 6 weeks or more
		• Consider the following if no improvement at 48 hours:
		  • Infliximab
		  • Mycophenolate mofetil
		  • IVIG

BAL, bronchoalveolar lavage; IVIG, intravenous immunoglobulin.

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Monitor

- Time to resolution is highly variable
  - Gastrointestinal, renal, and hepatic irAEs may rapidly improve
  - Skin and endocrine irAEs may take more time
- Long-term immunosuppressive treatments
  - Corticosteroids, anti-TNF
  - Increased risk of opportunistic infections

TNF, tumor necrosis factor.

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Thompson JA, et al. *J Natl Compr Canc Netw.* 2019;17(3)255-89.

Real World

Noun: the existing state of things, as opposed to one that is imaginary, simulated, or theoretical

Clinical Trial vs. Real-World Practice

Clinical trial patients

- Inclusion and exclusion criteria
- Strict monitoring for adherence and AEs
- Treated based on pre-specified study protocol
- Study treatment likely provided by sponsor or practice site
- Frequent follow-up at predetermined intervals
- Regular documentation at each follow-up visit with study staff

Real-world patients

- Monitored for adherence and AEs on the basis of clinical opinion
- Treatment coverage required through the patient's insurance plan or charitable drug program
- Follow-up likely dictated by clinic availability and clinician opinion (more variability)
- Clear protocol not always available
- Documentation dependent on institution requirements

Benefits Investigation

- Commercially insured
  - Prior authorization likely required
  - Industry assistance potentially available
- Medicare or Medicaid
  - Additional assistance may be restricted
  - Step-therapy may play a role in decision-making
  - Medical versus prescription coverage
    - Alphabet soup – Part B vs. Part D

Clinical Presentation Challenges

- Child-Pugh Classification
  - Class A
    - Numerous treatment options available, but not as many patients
  - Class B
    - Not as much data, but more patients in this category
  - Class C
    - Almost no data to support systemic treatment in this patient population
- Comorbidities
  - HCV/HBV infection, cirrhosis, non-alcoholic fatty liver disease

Pharmacist Involvement

- Treatment decision-making
- Medication procurement/coverage
- Drug information and education
  - For clinic staff and patients
- Drug-drug and drug-food interaction review
- Ongoing adherence assessment
- AE monitoring and management
- Documentation

Summary

- HCC treatment is expanding to include novel immunotherapy options
- Emerging combination regimens may be used to improve outcomes in this complicated disease state
- Pharmacists play a large role in immune-mediated toxicity identification and management

Thank You!