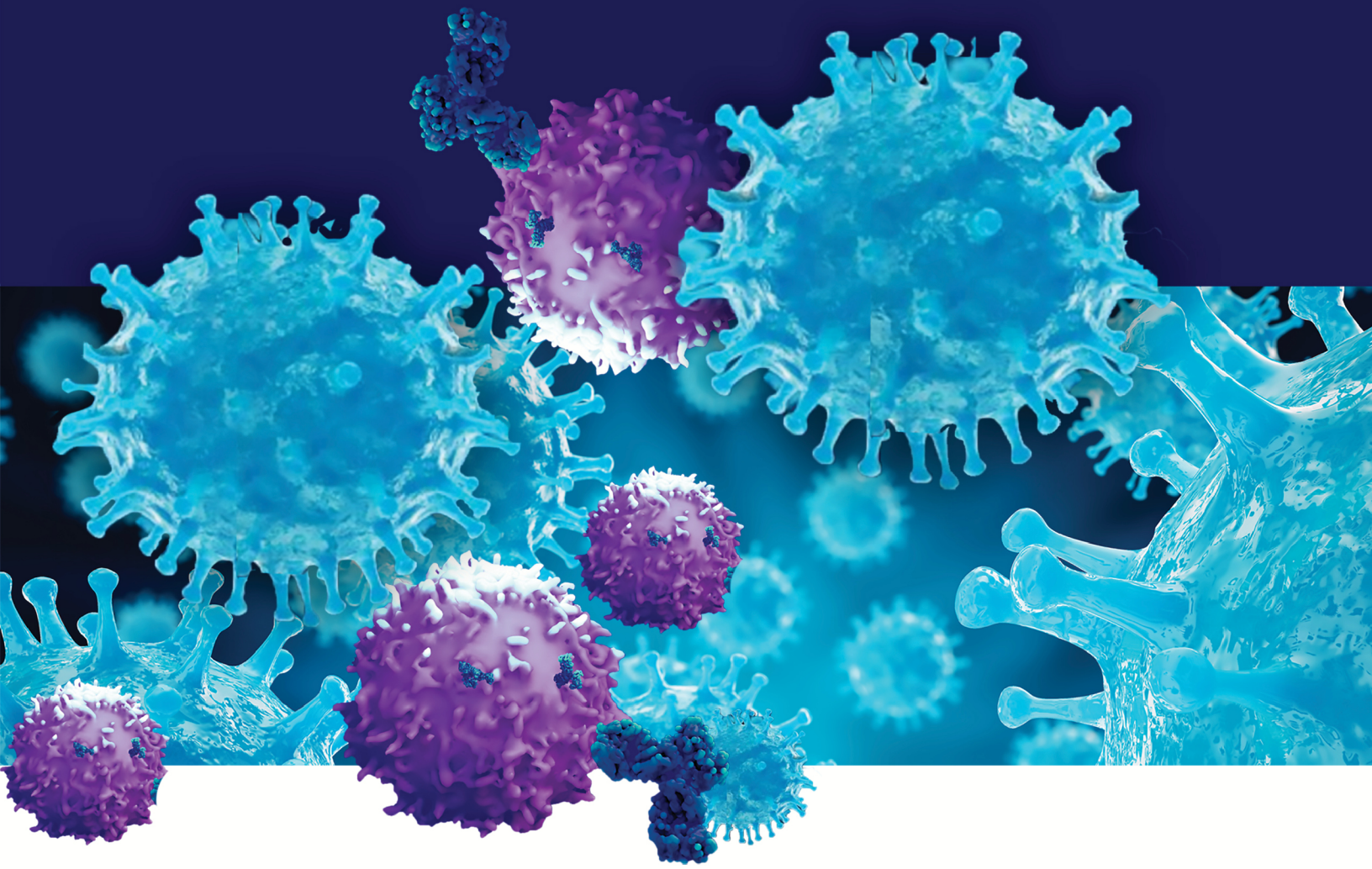
IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence and Management During the **COVID-19 Pandemic:**

IMMUNO-ONCOLOGY IN ADVANCED HEPATOCELLULAR CARCINOMA



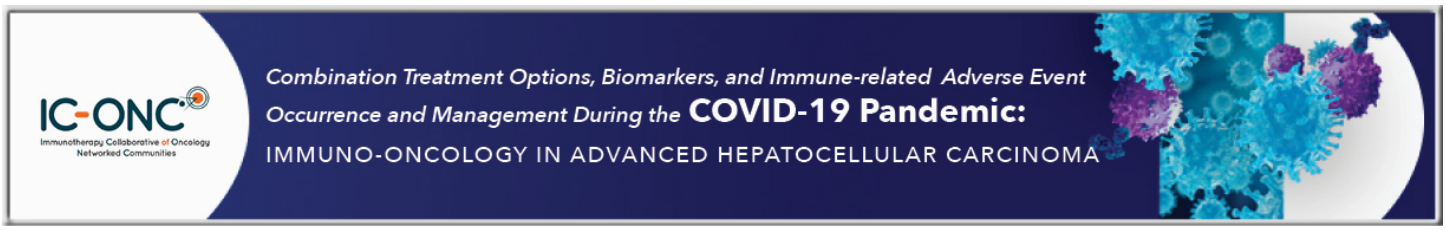
MEETING INFO

Tuesday, June 15, 2021
12:00 Noon to 1:00 PM Eastern

FACULTY

Robert G. Gish, MD, FAASLD, AGAF, FAST
Professor of Medicine, Loma Linda University, Liver Transplant Institute, Las Vegas, NV Principal, Robert G Gish Consultants, LLC
Adjunct Professor of Medicine, University of Nevada, Reno
Adjunct Professor of Medicine, University of Nevada, Las Vegas
Adjunct Professor of Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego
Medical Director, Hepatitis B Foundation, Doylestown, PA

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Bristol Myers Squibb.



Program Agenda

I. Introduction of IC-ONC Network - the Goals, Resources and Network Community Building Concept

a. Overview of IC-ONC Collaborative
b. Description of short and long-term goals and available resources that are available to the network community
c. Overview of the current scenario of new cancer immunotherapies for difficult-to-treat cancer malignancies (focus on advanced melanoma, NSCLC, RCC and HCC)
d. Rapidly changing treatment patterns and challenges in clinical practice due to the introduction of novel cancer immunotherapeutics

II. Available and Emerging Immuno-oncology Therapeutic Options for the Treatment of Advanced HCC

a. Mechanisms of action and clinical profiles of available immunotherapies used as monotherapies across lines of treatment for advanced HCC
b. Mechanisms of action and clinical profiles of available immunotherapies used as combination therapies across lines of treatment for advanced HCC
c. Mechanisms of action and clinical profiles of emerging immunotherapies alone and in combination across lines of treatment for advanced HCC

III. Immune-Related Adverse Events Secondary to ICI Therapy

a. Types of irAEs associated with immunotherapies for the treatment of advanced HCC
b. Pathophysiologic basis for irAEs
c. Surveillance and management of most common irAEs

IV. Immune- and Non-immune-related Biomarkers and Testing Methodologies

a. Prognostic and predictive biomarkers including alpha fetoprotein (Theme: MOAs biomarkers [i.e., PD-L1] on disease characteristics and response to treatment)
b. Evidence-based guidance on biomarker assessment
c. Incorporation of biomarker and genomic testing in the clinical practice setting

V. COVID-19 and Cancer

a. Malignancy as a risk factor for infection
b. Relationship between active or past cancer treatment and infection on outcomes
c. Effect of infection-risk on immunotherapy selection/initiation/continuation
d. COVID-19 vaccines and immunotherapy

VI. Multidisciplinary Oncology Team – Optimizing Patient Care and Survivorship Through Shared Decision Making

a. Educational strategies for the oncology patient
    1. Disease state, immuno-oncology medication use – dosing regimen (how and when to take, persistence/adherence, dosing options), potential adverse events and their management, review of treatment plan
b. Shared decision making in the care process – use of decision aids

c. Ongoing, routine communication between members of the multidisciplinary health care team throughout treatment
d. Team members and their respective roles

VII. Case Studies and Conclusions

VIII. Questions & Answers

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Track 4: Immuno-oncology in Advanced Hepatocellular Carcinoma

PROGRAM OVERVIEW

This case-based live virtual activity will cover the diagnosis, treatment, and management of patients with cancer who are treated or eligible for treatment with immunotherapy.

TARGET AUDIENCE

This initiative is designed to meet the educational needs of oncologists, oncology pharmacists, oncology nurses and other healthcare professionals and teams involved in the management of patients with cancer who are treated or eligible for treatment with immunotherapy.

LEARNING OBJECTIVES

Upon completion of the program, attendees should be able to:

• Review mechanisms of action and clinical profiles of immunotherapies used alone or in combination across lines of therapy for the treatment of HCC

• Recognize and manage side effects and toxicities associated with available and emerging immunotherapies used alone or in combination across lines of therapy for the treatment of HCC

• Discuss established and potential prognostic and predictive immune- and non-immune-related biomarkers for HCC and their impact on patient management strategies

• Summarize current recommendations and emerging evidence regarding the use of immunotherapies for patients with HCC during the COVID-19 pandemic including the management of irAEs and the utility of telemedicine

• Explain patient-centered SDM approaches aimed at optimizing cancer care and survivorship for those with HCC and the role of emergency care physicians as part of multidisciplinary teams in the diagnosis and management of irAEs associated with immunotherapies used alone or in combination

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Accreditation Statement
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Credit Designation Statement
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Nursing Credit Information
Purpose: This program would be beneficial for nurses involved in the management of patients with cancer who are treated or eligible for treatment with immunotherapy.
Credits: 1.0 ANCC Contact Hour

Accreditation Statement
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PROGRAM CHAIR

Robert G. Gish, MD, FAASLD, AGAF, FAST
Professor of Medicine, Loma Linda University, Liver Transplant Institute, Las Vegas, NV
Principal, Robert G Gish Consultants, LLC
Adjunct Professor of Medicine, University of Nevada, Reno
Adjunct Professor of Medicine, University of Nevada, Las Vegas
Adjunct Professor of Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego
Medical Director, Hepatitis B Foundation, Doylestown, PA

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Lauren Welch, MA, VP, Outcomes and Accreditation for Med Learning Group has nothing to disclose.
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We will start momentarily!

Your line will automatically be muted upon entry.

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- ✓ To receive credit, please visit **[insert QPro link here]**
- ✓ Please visit **www.ic-onc.org** for more information and resources
- ✓ To build a complimentary office poster, visit **immuneonc.posterprogram.com**
- ✓ ***To request a pair of glasses to view the 3D animations in this presentation, please email mjohnson@medlearninggroup.com***

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Combination Treatment Options, Biomarkers, and Immune-Related Adverse Event Occurrence and Management During the COVID-19 Pandemic

Immuno-oncology in Advanced Hepatocellular Carcinoma TeleECHO Series

Robert G. Gish, MD, FAASLD, AGAF, FAST

Professor of Medicine, Loma Linda University, Liver Transplant Institute, Las Vegas, NV Principal, Robert G Gish Consultants, LLC

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Disclosures

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Current activity with scientific/clinical advisory boards: Abbott, AbbVie, Merck, Arrowhead, Bayer, Dova, Eiger, Enyo, HepQuant, Intercept, and Janssen
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Minor stock shareholder: RiboScience and CoCrystal; **stock options**: Eiger, Genlantis, HepQuant, and AngioCrine
Expert testimony for pharma (intellectual property): Janssen and USP Pharma

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Learning Objectives

- Review mechanisms of action and clinical profiles of immunotherapies used alone or in combination across lines of therapy for the treatment of HCC
- Recognize and manage side effects and toxicities associated with available and emerging immunotherapies used alone or in combination across lines of therapy for the treatment of HCC
- Discuss established and potential prognostic and predictive immune- and non-immune-related biomarkers for HCC and their impact on patient management strategies
- Summarize current recommendations and emerging evidence regarding the use of immunotherapies for patients with HCC during the COVID-19 pandemic, including the management of irAEs.
- Explain patient-centered shared decision-making approaches aimed at optimizing cancer care and survivorship for those with HCC and the role of emergency care physicians as part of multidisciplinary teams in the diagnosis and management of irAEs associated with immunotherapies, used alone or in combination

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IC-ONC

- This program is part of the Immunotherapy Collaborative of Oncology Networked Communities (IC-ONC), a global information network in which multidisciplinary healthcare providers who are responsible for treating patients with cancer are connected via education.
- **IC-ONC.org** serves as the central location for educational resources and information pertinent to patients with cancer being treated with immunotherapy.
  - It is curated by global, national, and local oncology experts.
  - It provides dates and locations of upcoming live meetings.
  - It provides access to archived and enduring activities.
  - It identifies clinical articles.
  - It is a source of downloadable content and other inter-professional resources from more than 14 collaborative educational partners.
  - It provides access to our open-source immuno-oncology registry: **The Observatory**
- Its objective is to facilitate ongoing communication and collaboration among participating healthcare providers with the aim of providing optimal care for the patient with cancer.
- For more information, please visit **www.ic-onc.org**
- Supported by an educational grant from Bristol Myers Squibb.

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IC-ONC Observatory

- Through participation in this course, you will become a member of the IC-ONC Observatory
- Your login details will be emailed to you in the coming weeks
- For immediate information, please visit www.ic-onc.org

IC-ONC
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8

Introduction of the IC-ONC Network

IC-ONC = Immunotherapy Collaborative of Oncology Networked Communities.

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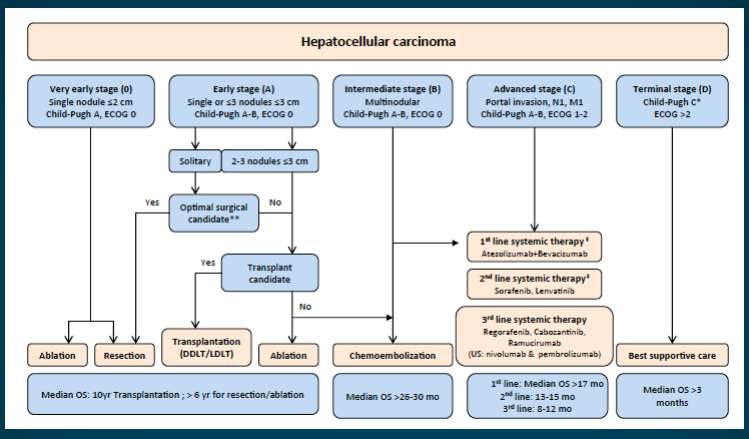
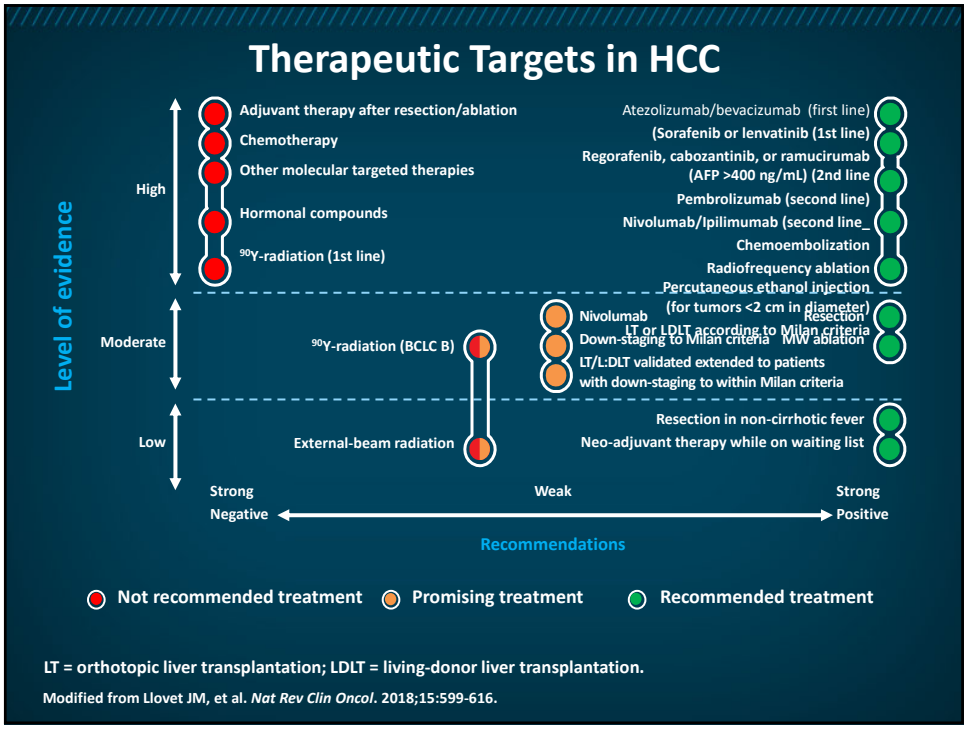
Modified BCLC Staging System



Llovet JM, et al. Hepatology,. 2021;73(S1).

10



LT = orthotopic liver transplantation; LDLT = living-donor liver transplantation.

Modified from Llovet JM, et al. *Nat Rev Clin Oncol*. 2018;15:599-616.

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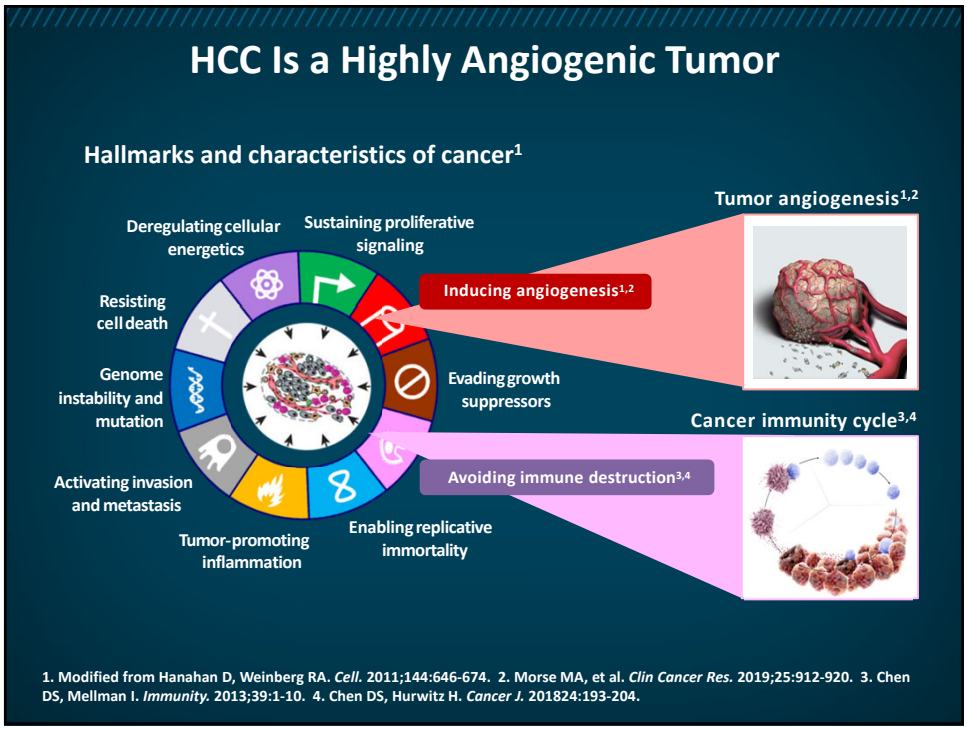
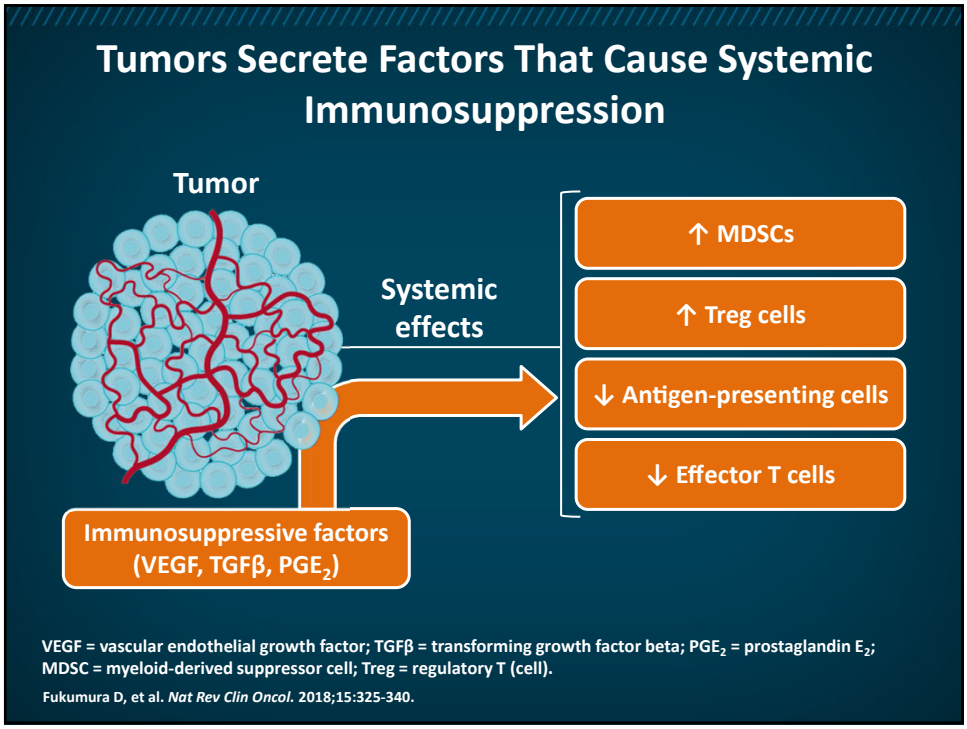
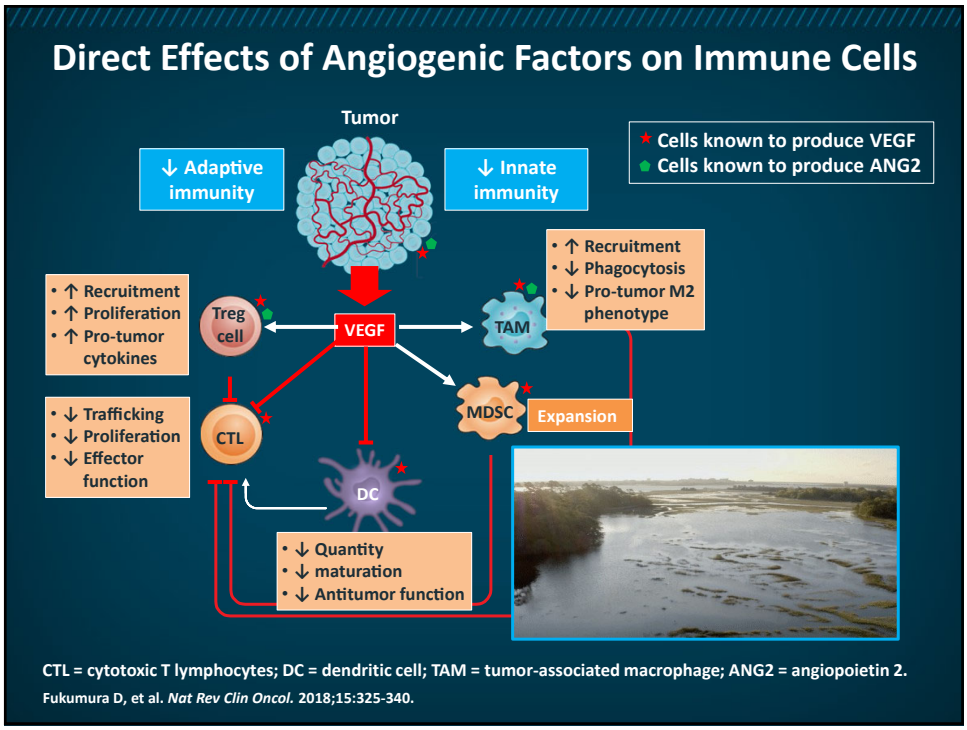


1. Modified from Hanahan D, Weinberg RA. *Cell.* 2011;144:646-674. 2. Morse MA, et al. *Clin Cancer Res.* 2019;25:912-920. 3. Chen DS, Mellman I. *Immunity.* 2013;39:1-10. 4. Chen DS, Hurwitz H. *Cancer J.* 201824:193-204.

12


Tumors Secrete Factors That Cause Systemic Immunosuppression
Tumor
Systemic effects
↑ MDSCs
↑ Treg cells
↓ Antigen-presenting cells
↓ Effector T cells
Immunosuppressive factors (VEGF, TGFβ, PGE2)
VEGF = vascular endothelial growth factor; TGFβ = transforming growth factor beta; PGE2 = prostaglandin E2; MDSC = myeloid-derived suppressor cell; Treg = regulatory T (cell).
Fukumura D, et al. Nat Rev Clin Oncol. 2018;15:325-340.

13


Direct Effects of Angiogenic Factors on Immune Cells
Tumor
↓ Adaptive immunity
↓ Innate immunity
Cells known to produce VEGF
Cells known to produce ANG2
• ↑ Recruitment
• ↑ Proliferation
• ↑ Pro-tumor cytokines
Treg cell
VEGF
TAM
• ↑ Recruitment
• ↓ Phagocytosis
• ↓ Pro-tumor M2 phenotype
• ↓ Trafficking
• ↓ Proliferation
• ↓ Effector function
CTL
MDSC
Expansion
DC
• ↓ Quantity
• ↓ maturation
• ↓ Antitumor function
CTL = cytotoxic T lymphocytes; DC = dendritic cell; TAM = tumor-associated macrophage; ANG2 = angiopoietin 2.
Fukumura D, et al. Nat Rev Clin Oncol. 2018;15:325-340.

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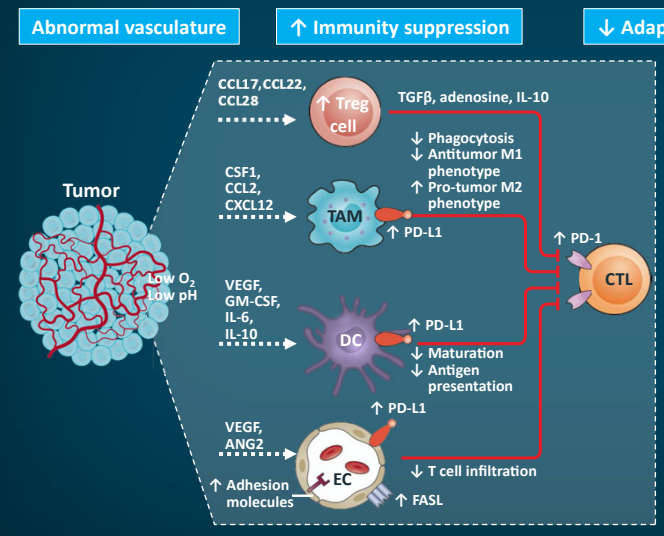
Abnormal Tumor Vasculature Contribution to Immunosuppression



IL = interleukin; PD-1 = programmed (cell) death 1; PD-Li = PD-1 ligand; GM-CSF = granulocyte-macrophage colony-stimulating factor; EC = endothelial cell; FASL = FAS antigen ligand.

Fukumura D, et al. *Nat Rev Clin Oncol.* 2018;15:325-340.

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Placeholder slide for PD-1/PD-L1 animation

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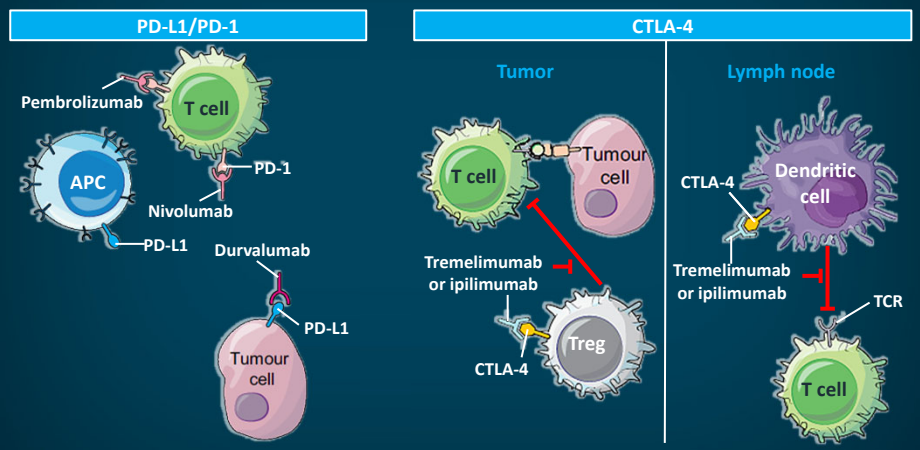
Immune Checkpoint Inhibitors: MOA

PD-1 is key for effector phase of immune response, expressed by CD8+ and CD4+ T cells and APCs. Cancer cells expressing PD-L1 escape from immunosurveillance.

CTLA-4 necessary for activation of CD4+ T cells and priming phase of immune response. Also induces Treg activation and differentiation.



MOA = mechanism of action; CD = cluster of differentiation; APC = antigen-presenting cell; CTLA-4 = cytotoxic T Lymphocyte antigen 4; TCR = T cell receptor.

Modified from Greten TF, Sangro B. *J Hepatol.* 2018;68:157-166.

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Immunotherapy Monotherapy

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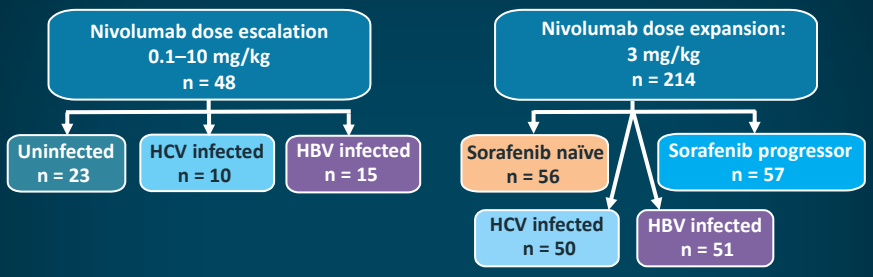
CheckMate-040: Study Scheme and Survival



% (95% CI)	Sorafenib naive	Sorafenib progressor	HCV infected	HBV infected	All patients
OS, % (95% CI) 6 mos 9 mos K-M median	 89% (77–95) 82% (68–90) NR	 75% (62–85) 63% (49–74) **13.2** (8.6–NE)	 85% (72–93) 81% (66–90) NR	 84% (71–92) 70% (55–81) NR	 83% (78–88) 74% (67–79) NR
PFS, mos (95% CI) K-M median	5.4 (3.9–8.5)	4.0 (2.6–6.7)	4.0 (2.6–5.7)	4.0 (1.3–4.1)	4.0 (2.9–5.4)

HCV = hepatitis C virus; HBV = hepatitis B virus; OS = overall survival; PFS = progression-free survival; K-M = Kaplan-Meier, CI = confidence interval; mo(s) = month(s); NR = not reached; NE = not estimable/evaluable.

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

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Nivolumab in Patients with Child-Pugh B Advanced HCC in CheckMate-040

Objective

- To assess the safety and efficacy of the PD-1 inhibitor nivolumab in the Child-Pugh B cohort of the CheckMate-040 study, the first prospective study of immunotherapy in patients with Child-Pugh B advanced HCC (aHCC)

Methods

- Sorafenib-naive (n = 25) or -experienced (n = 24) patients with Child-Pugh B (B7–B8) aHCC received nivolumab 240 mg IV for 30 min Q2W (flat dose) until unacceptable toxicity or disease progression; primary endpoints were ORR by investigator (INV) assessment and DoR

Main findings

- INV-assessed ORR = 10.2%; disease control rate = 55.1%
- Median DoR = 9.9 months; 2 patients had ongoing responses
- Median overall survival = 7.6 months

Conclusions

- Nivolumab demonstrated durable responses and a manageable safety profile in patients with Child-Pugh B aHCC.

IV = intravenous; Q2W = every 2 weeks; ORR = overall/objective response rate; DoR = duration of response.

Kudo M, et al. *J Clin Oncol*. 2019;37(4 suppl): abstract 327.

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Nivolumab in Patients with Child-Pugh B aHCC
CheckMate-040

Safety profile of nivolumab in patients with Child-Pugh B status and Child-Pugh A status in CheckMate-040

	Cohort 5 Child-Pugh B status Nivolumab 240 mg n = 49		Cohorts 1 and 2 Child-Pugh A status Nivolumab 0.1–10 mg/kg in ESC 3 mg/kg in EXP n = 262	
Total patients with an event, n (%)	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Drug-related AEs	25 (51.0)	12 (24.5)	206 (78.6)	59 (22.5)
Hepatobiliary disorders	3 (6.1)	3 (6.1)	Not reported	Not reported
Drug-related SAEs	2 (4.1)	2 (4.1)	23 (8.8)	13 (5.0)
DRAEs leading to discontinuation	2 (4.1)	2 (4.1)	11 (4.2)	5 (1.9)
Drug-related select hepatic events	4 (8.2)	2 (4.1)	27 (10.3)	18 (6.9)
AST increased	2 (4.1)	2 (4.1)	38 (14.5)	15 (5.7)
ALT increased	1 (2.0)	0	26 (9.9)	10 (3.8)
Hyperbilirubinemia	1 (2.0)	0	3 (1.1)	0
Liver function test increased	1 (2.0)	0	1 (0.4)	1 (0.4)
IMAEs — hepatitis	1 (2.0)	1 (2.0)	14 (5.3)	12 (4.6)

AE = adverse event; SAE = serious AE; DRAE = drug-related AE; ESC = dose-escalation phase; EXP = dose-expansion phase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; IMAE = immune-mediated AE.

Kudo M, et al. American Association for the Study of Liver Diseases (AASLD), 2018: abstract LB-2.

21

KEYNOTE 224: Pembrolizumab for Second-Line Treatment in HCC

Study design

Key eligibility criteria
- ≥18 years of age
- Pathologically confirmed HCC
- Progression on or intolerance to sorafenib treatment
- Child Pugh class A
- ECOG PS 0–1
- BCLC Stage C or B disease
- Predicted life expectancy >3 mos

→ **Pembrolizumab 200 mg Q3W for ~2 years or until PD, intolerable toxicity, withdrawal of consent, or investigator decision** → **Survival follow-up**

Response assessed Q9W

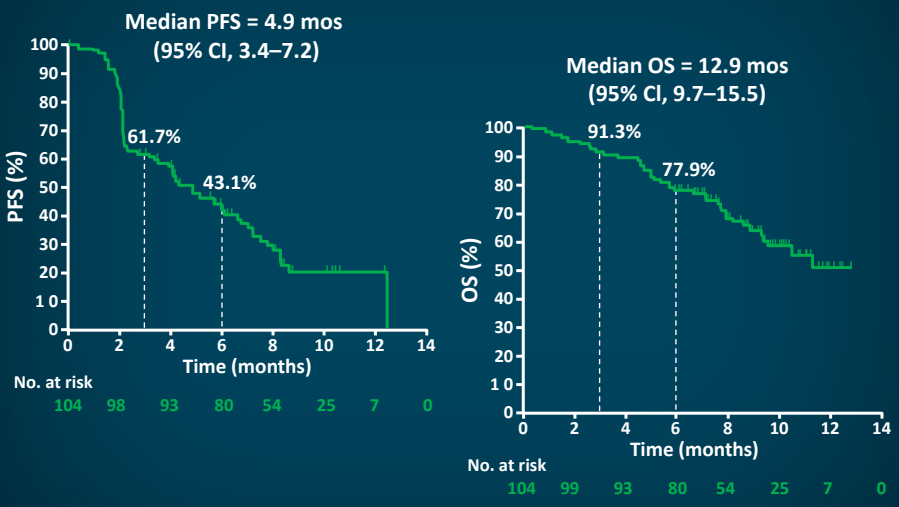
- Primary endpoint: ORR (RECIST v1.1, central review)
- Secondary endpoints: DoR, DCR, TTP, PFS, OS, safety, and tolerability

Q3W = every 3 weeks; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors; DCR = disease control rate; TTP = time to progression.

Zhu AX, et al. *Lancet Oncol*. 2018;19:940-952.

22

KEYNOTE 224: PFS and OS



Based on RESIST v1.1 by central radiology review. Data cutoff date: Aug 24, 2017.

Zhu AX, et al. *J Clin Oncol.* 2018;36(4 suppl): abstract 209. Zhu AX, et al. *Lancet Oncol.* 2018;19:940-952.

23

KEYNOTE 224

Treatment-related adverse events*

Adverse events	Total N = 104 n (%)
≥1 event	76 (73)
≥Grade 3	27 (26)
Led to discontinuation	7 (7)
Led to death	1 (1)
Occurred in ≥10% of all patients (all grades)	
Fatigue	22 (21)
AST increased	14 (13)
Pruritus	12 (11)
Diarrhea	11 (11)
Rash	10 (10)
Hepatic related	
Immune-mediated	3 (3)
Viral flare	0 (0)

Zhu AX, et al. *Lancet Oncol.* 2018;19:940-952. Zhu AX, et al. *J Clin Oncol.* 2018;36(4 suppl): abstract 209.

24

Molecularly Targeted Therapy in Advanced HCC

CHALLENGES	OPPORTUNITIES
No data for 2nd-line therapy after failure of lenvatinib or IO therapy	Synergism between IO and TKI
Toxicity and tolerance of TKI therapy	Combination or sequential therapy?
Area of unmet need in Child-Pugh B7	Change HCC treatment paradigm
$$$	↑ drug options, ↓ drug cost

IO = immuno-oncology; TKI = tyrosine-kinase inhibitor.

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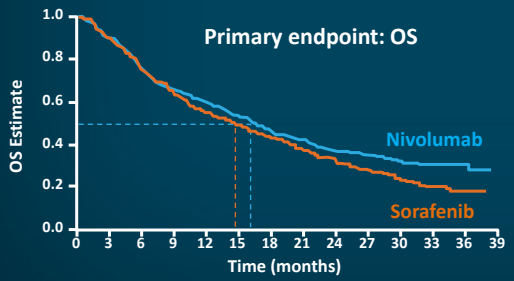
Single-Agent Immunotherapy: Improved Outcomes
But...Did Not Meet Predetermined Endpoints

1L nivolumab: CheckMate-459 (phase 3)

- Advanced HCC not eligible for surgical and/or LRT, or PD after surgical and/or LRT
- No prior systemic therapy
- Child-Pugh class A
- ECOG PS 0/1

R 1:1 (N = 743)

- Nivolumab 240 mg IV Q2W (n = 371)
- Sorafenib 400 mg PO BID (n = 372)



	Nivo	Sora
Median OS, (95% CI) mos	16.4 (13.9–18.4)	14.7 (11.9–17.2)
HR = 0.85 (95% CI, 0.72–1.02), *P*= .0752		

1L = first line; LRT = locoregional therapy; PO = orally; Sora = sorafenib; Nivo = nivolumab.

Yau T, et al. *Ann Oncol.* 2019;30(suppl 5): abstract LBA38_PR.

26

Single-Agent Immunotherapy: Improved Outcomes Without Meeting Predetermined Endpoints

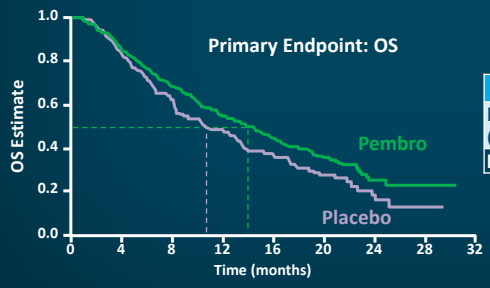
2L pembrolizumab: KEYNOTE-240 (phase 3)

- Advanced HCC
- Prior sorafenib therapy
- BCLC stage B/C
- Child-Pugh class A
- ECOG PS 0/1

R 2:1

(N = 413)

- Pembrolizumab 200 mg Q3W + BSC (n = 278)
- Placebo Q3W + BSC (n = 135)



	Pembro	Placebo
Median OS, (95% CI) mos	13.9 (11.6–16.0)	10.6 (8.3–13.5)
HR = 0.78 (95% CI, 0.611–0.998), *P*= .0238		

2L = second line; BSC = best supportive care.

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

27

Rationale For Combining Antiangiogenic Therapy with Immune Checkpoint Inhibitor

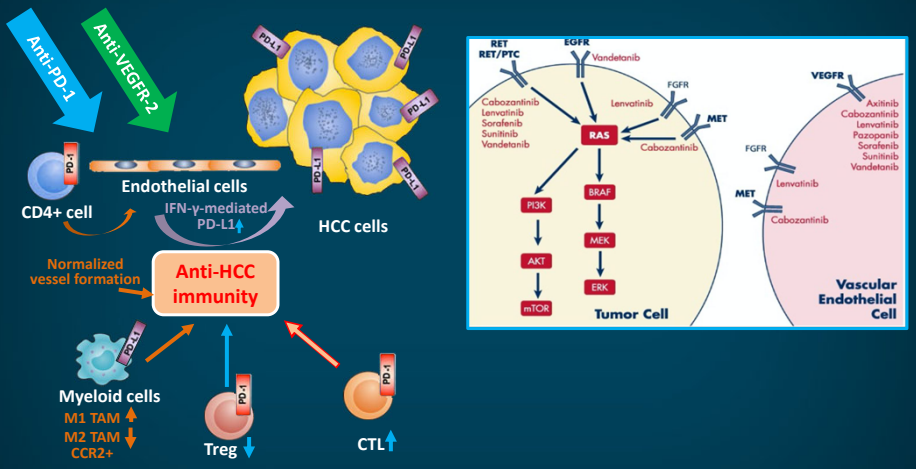
- Abnormalities in the TME contribute to immunosuppression
- Reprogramming specific facets of the immune compartment, such as immunosuppressive myeloid and lymphoid cell subsets, may overcome microenvironment-induced resistance mechanisms and enhance antitumor immunity
- Targeting nonimmune components of the TME by normalizing or decompressing the vasculature can overcoming resistance to ICBs and other immunotherapies

TME = tumor microenvironment; ICB = immune checkpoint blockade.

Datta M, et al. *ASCO Educational Book.* 2019;39:165-174.

28

Mechanism of Interaction Between Anti-PD-1 and Anti-VEGFR-2 Therapy in HCC



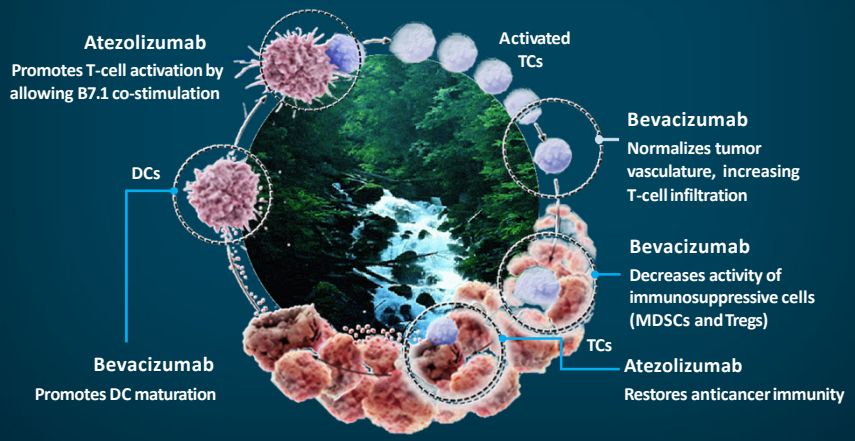
IFN = interferon; EGFR = epidermal growth factor receptor; PI3K = phosphoinositide-3 kinase; ERK = extracellular signal-regulated kinase; AKT = serine-threonine protein kinase; mTOR = mammalian target of rapamycin; VEGFR = VEGF receptor.

Shigeta K, et al. *Hepatology.* 2020;71:1247-1261.

29

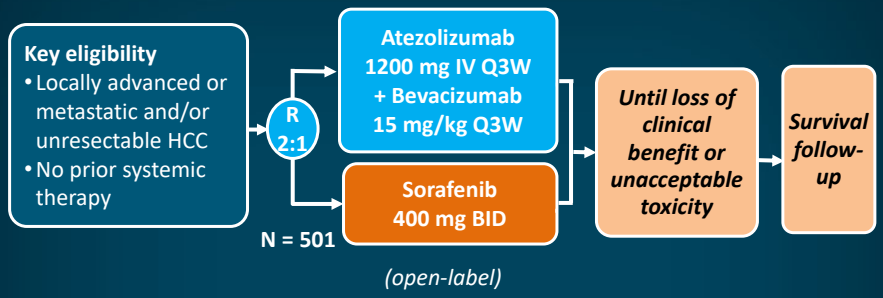
Atezolizumab + Bevacizumab

- Bevacizumab (anti-VEGF) is an antiangiogenic agent with additional immunomodulatory effects
- Adding bevacizumab may enhance atezolizumab's efficacy by reversing VEGF-mediated immunosuppression to promote anticancer T-cell activity



30

IMbrave150 Study Design



- **Co-primary endpoints:** OS and IRF-assessed PFS per RECIST 1.1
- **Key secondary endpoints** (in testing strategy): IRF-assessed ORR per RECIST 1.1 and per HCC mRECIST, DoR, time to deterioration of QoL and functioning
- **Stratification factors:** region (Asia, excluding Japan vs rest of world), ECOG PS (0 vs 1), macrovascular invasion (MVI) and/or extrahepatic spread (EHS) (presence vs absence), and baseline α-fetoprotein (AFP <400 vs ≥400 ng/mL)

IRF = independent review facility; mRECIST = HCC-specific modified RECIST; QoL = quality of life.

Finn RS, et al. *N Engl J Med.* 2020;382:1894-1905.

31

IMbrave150: Updated OS Data

Description: global, randomized, OL, phase 3 study of atezolizumab + bevacizumab vs sorafenib in patients with unresectable HCC

Results

- At data cut-off (8/31/2020), median FU was 15.6 months with 280 OS events
- Median OS: Atezo + Bev = 19.2 months and Sora = 13.4; HR = 0.66 (95% CI, 0.52–0.85); *P*= .0009)
- Survival benefit of Atezo + Bev vs Sora was generally consistent with primary analysis and across subgroups
- Safety was consistent with the primary analysis

Conclusions

- IMbrave150 showed consistent clinically meaningful efficacy and safety in the additional 12-month FU. Atezo + Bev demonstrated the longest survival seen in front-line phase 3 studies in advanced HCC, confirming it as SOC for previously untreated unresectable HCC

OL = open-label; FU = follow-up; SOC = standard of care.

Finn R, et al. *Liver Cancer Summit.* 2021: abstract O05

32

IMbrave150: Updated Outcomes

Updated analysis	RECIST 1.1		mRECIST for HCC	
	Atezo + Bev (n = 326)	Sora (n = 159)	Atezo + Bev (n = 325)	Sora (n = 158)
Confirmed ORR, % (95% CI)	**30 (25–35)**	**11 (7–17)**	**35 (30–41)**	**14 (9–20)**
CR, n (%)	25 (8)	1 (<1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DoR, mos (95% CI)	18.1 (14.6–NE)	14.9 (4.9–17.0)	16.3 (13.1–21.4)	12.6 (6.1–17.7)

CR = complete response; PR = partial response; SD = stable disease.

Finn R, et al. *Liver Cancer Summit.* 2021: abstract O05

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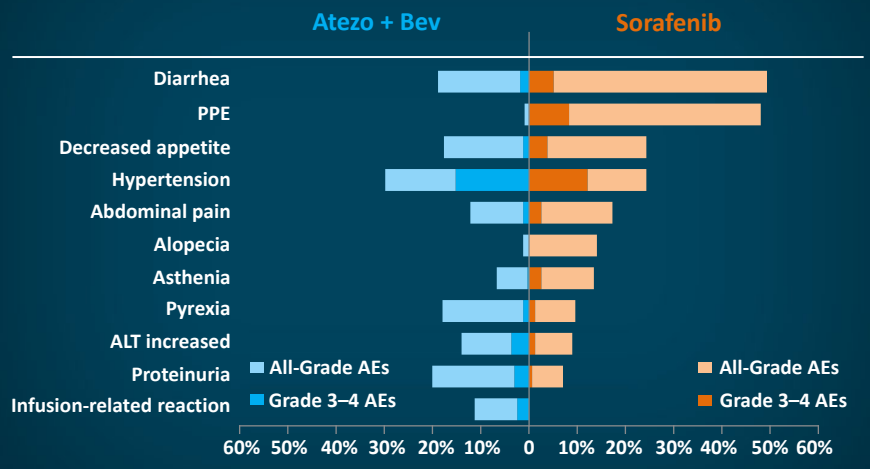
IMBrave 150: Safety*

≥10% frequency of AEs in either study arm and >5% difference between arms



*Safety-evaluable population

PPE = palmar-plantar erythrodysesthesia.

Finn R, et al. *Liver Cancer Summit.* 2021: abstract O05

34

Investigational Monotherapy and Combination Immunotherapy Regimens for HCC*

Phase 3	Phase 2/3	Phase 1b/2	Phase 1/2a
• Experimental PD-1 inhibitor + sorafenib • Pexa-Vec vaccine + sorafenib	• Nivolumab + lenvatinib (1L) • Cobolimab + dostarlimab • Vaccinia + sorafenib (PHOCUS) • Nivolumab monotherapy vs sorafenib (1L) • Nivolumab + sorafenib • Nivolumab + ipilimumab • Nivolumab + cabozantinib • Durvalumab + tremelimumab • Durvalumab + bevacizumab • Durvalumab monotherapy • Tremelimumab monotherapy	• Atezolizumab + bevacizumab • Atezolizumab + bevacizumab + tiragolumab or tocilizumab	• Pexa-Vec + Nivolumab (1L)

*Studies in patients with progressive disease after prior treatment unless otherwise noted.

Clinicaltrials.gov. searched March 16, 2021.

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Lenvatinib + Pembro in 1L+ Unresectable HCC
Phase 1b Trial

- Unresectable HCC
- BCLC stage B (not suitable for TACE) or C
- Child-Pugh A
- ECOG PS 0/1
- ≥1 measurable lesion per mRECIST (N = 104)

→ Lenvatinib 8 or 12 mg QD + Pembro 200 mg IV Q3W

- Part 1: DLT evaluation Patients ineligible for other therapies
- Part 1: Expansion No prior systemic therapy

- **Primary endpoints:** safety and tolerability (DLT); ORR and DoR (expansion)
- **Secondary endpoints:** PFS, TTP, OS, TTR, ADAs

Parameter		Overall (N = 100*)
Median age, years (range)		67 (47–86)
Sex, n (%)	Male	81 (81)
	Female	12 (17.9)
Race, n (%)	White	51 (51)
	Asian	28 (28)
	Black	2 (2)
	Other	5 (5)
ECOG PS, n (%)	0	62 (62)
	1	38 (38)
BCLC stage, n (%)	B	29 (29)
	C	71 (71)
Serum AFP, n (%)	<200 ng/mL	61 (61)
	≥200 ng/mL	36 (36)
	Missing	3 (3)
Child-Pugh score, n (%)	5	71 (71)
	6	27 (27)
	7	2 (2)
HCC etiology, n (%)	HBV+	19 (19)
	HCV+	36 (36)
	Alcohol	28 (28)
	Other	22 (22)
MVI+		20 (20)
EHS+		52 (52)

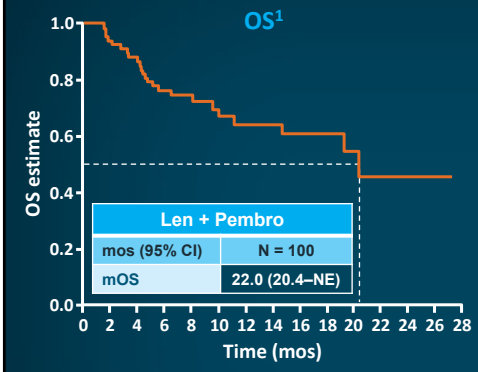
*4 patients excluded from DLT phase due to prior sorafenib treatment.

ADA = anti-drug antibody; DLT = dose-limiting toxicity; QD = once daily; IIR = independent imaging review; TACE = transarterial chemoembolization; TTP = time to response.

Finn RS, et al. *J Clin Oncol*. 2020;38:2960-2970.

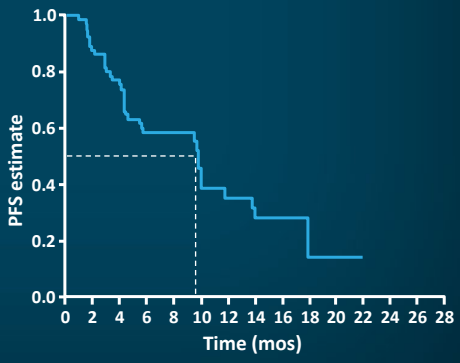
36

Lenvatinib + Pembrolizumab: OS and PFS



PFS (IIR mRECIST)[1]

mos (95% CI)	Len + Pembro		
	mRECIST		RECIST 1.1
	INV	IIR	IIR
mPFS	8.2 (7.4–9.7)	9.3 (5.6–9.7)	8.6 (7.1–9.7)



In July 2019, the FDA granted breakthrough therapy designation to this combination for 1L treatment of advanced unresectable HCC not amenable to locoregional therapy[2]

1. Finn RS, et al. *J Clin Oncol*. 2020;38:2960-2970. 2. Columbus G. *OncLive* (www.onclive.com/view/fda-grants-breakthrough-designation-to-frontline-pembrolizumablenvatinib-for-hcc). Accessed 3/27/2021.

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Immune-Related Adverse Events Secondary to ICI Therapy

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Placeholder slide for irAE animation

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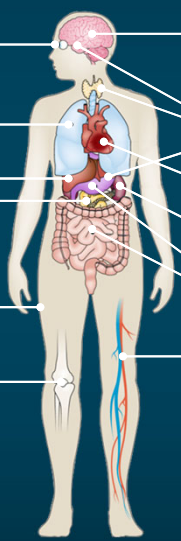
Autoimmune Organ Targets and Disease From ICI Therapy



- Uveitis
- Sjögren syndrome
- Conjunctivitis and/or blepharitis
- Episcleritis and/or scleritis
- Retinitis

- Pneumonitis
- Pleuritis
- Sarcoid-like granulomatosis

- Hepatitis

- Pancreatitis
- Autoimmune diabetes

- Skin rash
- Pruritus
- Vitiligo
- DRESS
- Psoriasis
- Stevens-Johnson syndrome

- Arthralgia
- Arthritis
- Myositis
- Dermatomyositis

- Encephalitis
- Meningitis
- Polyneuropathy
- Guillain-Barré syndrome
- Subacute inflammatory neuropathies

- Hypophysitis
- Thyroiditis
- Adrenalitis

- Myocarditis
- Pericarditis

- Interstitial nephritis
- Glomerulonephritis

- Colitis
- Enteritis
- Gastritis

- Anemia
- Neutropenia
- Thrombocytopenia
- Thrombotic microangiopathy
- Acquired hemophilia
- Vasculitis

Modified from Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.

ICI = immune checkpoint inhibitor; DRESS = drug reaction with eosinophilia and systemic symptoms.

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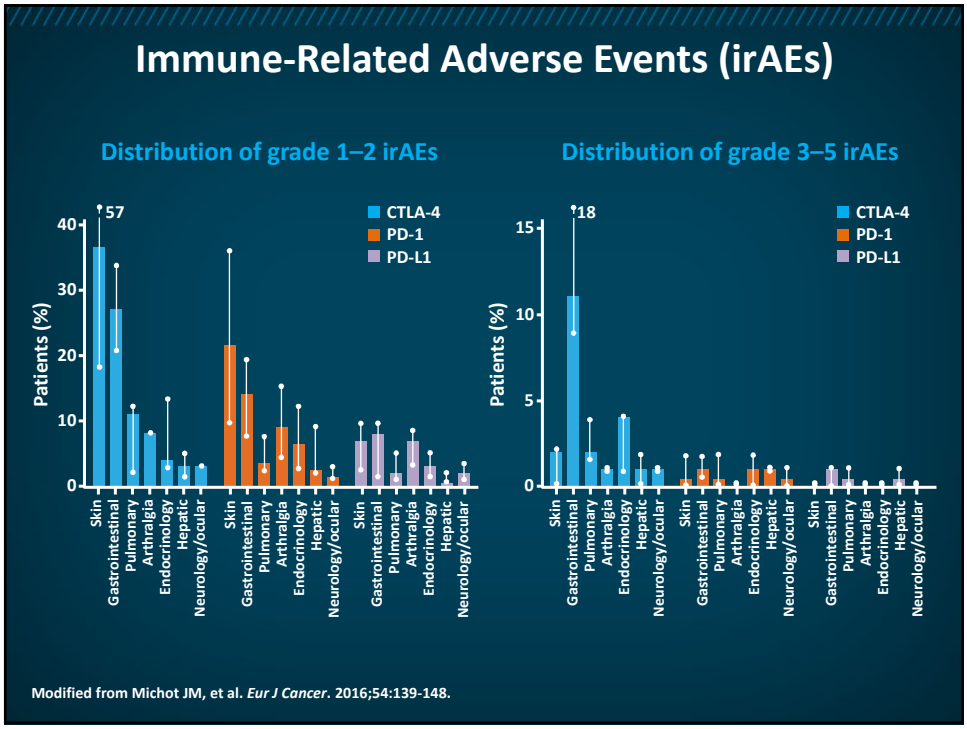
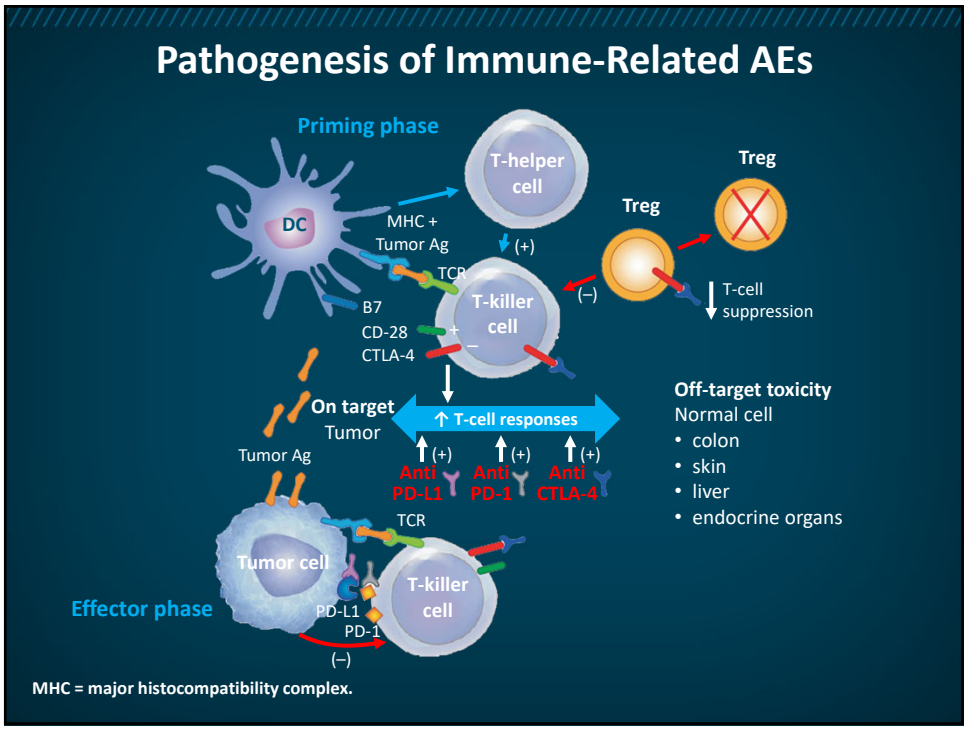

Immune-Related Adverse Events (irAEs)
Distribution of grade 1–2 irAEs
Distribution of grade 3–5 irAEs
CTLA-4
PD-1
PD-L1
Patients (%)
57
18
Skin
Gastrointestinal
Pulmonary
Arthralgia
Endocrinology
Hepatic
Neurology/ocular
Modified from Michot JM, et al. Eur J Cancer. 2016;54:139-148.

41


Pathogenesis of Immune-Related AEs
Priming phase
DC
MHC +
Tumor Ag
TCR
B7
CD-28
CTLA-4
T-helper cell
T-killer cell
Treg
T-cell suppression
On target
Tumor
Tumor Ag
↑ T-cell responses
Anti PD-L1
Anti PD-1
Anti CTLA-4
Off-target toxicity
Normal cell
• colon
• skin
• liver
• endocrine organs
Tumor cell
Effector phase
PD-L1
PD-1
MHC = major histocompatibility complex.

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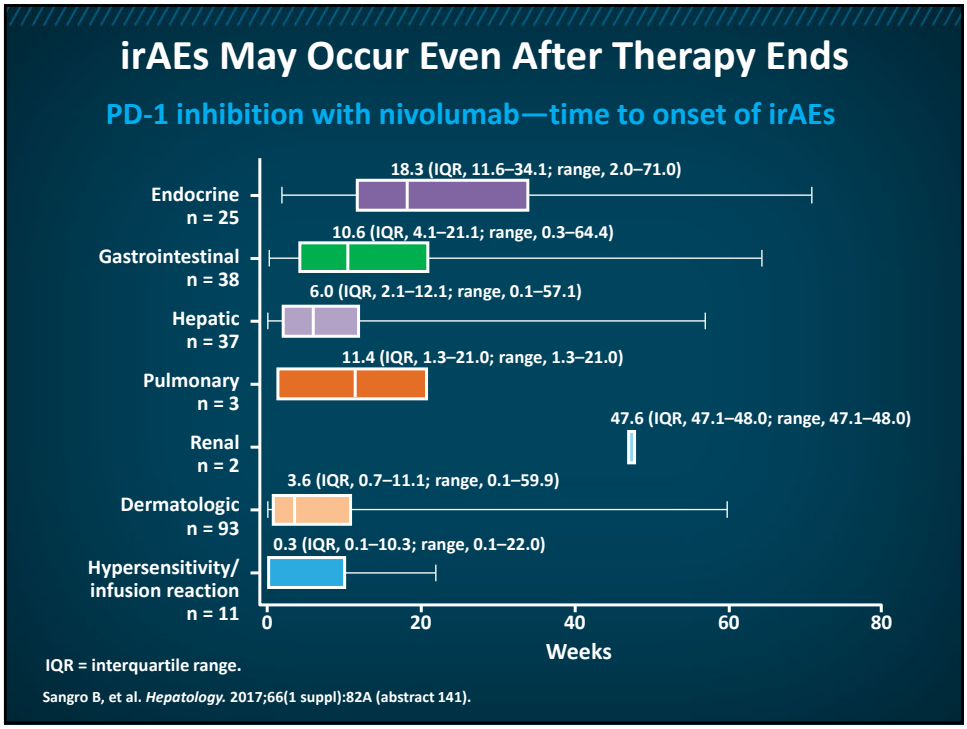
irAEs May Occur Even After Therapy Ends
PD-1 inhibition with nivolumab—time to onset of irAEs
Endocrine n = 25
18.3 (IQR, 11.6–34.1; range, 2.0–71.0)
Gastrointestinal n = 38
10.6 (IQR, 4.1–21.1; range, 0.3–64.4)
Hepatic n = 37
6.0 (IQR, 2.1–12.1; range, 0.1–57.1)
Pulmonary n = 3
11.4 (IQR, 1.3–21.0; range, 1.3–21.0)
Renal n = 2
47.6 (IQR, 47.1–48.0; range, 47.1–48.0)
Dermatologic n = 93
3.6 (IQR, 0.7–11.1; range, 0.1–59.9)
Hypersensitivity/ infusion reaction n = 11
0.3 (IQR, 0.1–10.3; range, 0.1–22.0)
0
20
40
60
80
Weeks
IQR = interquartile range.
Sangro B, et al. Hepatology. 2017;66(1 suppl):82A (abstract 141).

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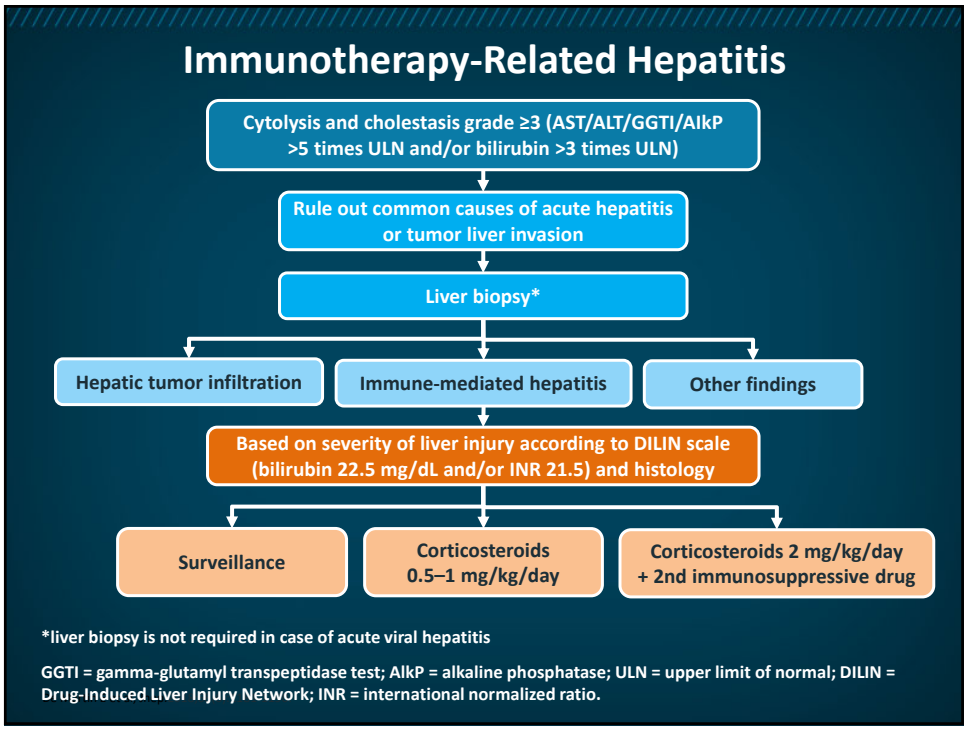
Immunotherapy-Related Hepatitis
Cytolysis and cholestasis grade ≥3 (AST/ALT/GGTI/AlkP >5 times ULN and/or bilirubin >3 times ULN)
Rule out common causes of acute hepatitis or tumor liver invasion
Liver biopsy*
Hepatic tumor infiltration
Immune-mediated hepatitis
Other findings
Based on severity of liver injury according to DILIN scale (bilirubin 22.5 mg/dL and/or INR 21.5) and histology
Surveillance
Corticosteroids 0.5–1 mg/kg/day
Corticosteroids 2 mg/kg/day + 2nd immunosuppressive drug
*liver biopsy is not required in case of acute viral hepatitis
GGTI = gamma-glutamyl transpeptidase test; AlkP = alkaline phosphatase; ULN = upper limit of normal; DILIN = Drug-Induced Liver Injury Network; INR = international normalized ratio.

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ICI Immune-Mediated Hepatitis in Clinical Trials

Class and Author	Study type (Phase)	Indication	No. of Patients	Additional therapy	All grade ALT (or AST*) elevation (%)	Grade 3–4 ALT (or AST*) elevation (%)
CTLA-4						
Ipilimumab						
Hodi et al. (2010)[1]	3	Melanoma	131	—	5 (3.8%)	0 (0%)
Hodi et al. (2010)[1]	3	Melanoma	380	gp100 peptide vaccine	2 (1.5%)	2 (0.5%)
Robert et al. (2011)[2]	3	Melanoma	247	Dacarbazine	72 (29.1%)	51 (20.6%)
Lynch et al. (2012)[3]	2	NSCLC	138	Paclitaxel and carboplatin	73 (52.9%)	4 (2.9%)
Reck et al. (2013)[4]	2	SCLC	84	Paclitaxel and carboplatin	39 (46.4%)	22 (26.2%)
Kwon et al. (2014)[5]	3	Prostatic cancer	393	Radiation therapy	20 (5.0%)	6 (2.0%)
Eggermont et al. (2015)[6]	3	Melanoma	471	—	102 (21.7%)	25 (5.3%)
Tremelimumab						
Ribas et al. (2013)[7]	3	Melanoma	325	—	2 (0.6%)	2 (0.6%)
Anti-PD-1						
Nivolumab						
Robert et al. (2015)[8]	3	Melanoma	206	—	2 (1.0)	1 (0.5%)
Weber et al. (2017)[9]	3	Melanoma	452	—	28 (6.2%)	5 (1.1%)
Brahmer et al. (2015)[10]	3	Squamous-cell NSCLC	131	—	2 (1.5%)	0 (0%)
Borghaei et al. (2015)[11]	3	Non-squamous-cell NSCLC	287	—	16 (5.6%)	1 (0.3%)

*AST if only reported elevation.

NSCLC = non-small-cell lung cancer; SCLC = small cell lung cancer.

Jennings JJ, et al. *Expert Opin Drug Metab Toxicol.* 2019;15:231-244. 1. Hodi FS, et al. *N Engl J Med.* 2010;363:711-723. 2. Robert C, et al. *N Engl J Med.* 2011;364:2517-2525. 3. Lynch TJ, et al. *J Clin Oncol.* 2012;30:2046-2054. 4. Reck M, et al. *Ann Oncol.* 2013;24:75-83. 5. Kwon ED, et al. *Lancet Oncol.* 2014;15:700-712. 6. Eggermont AM, et al. *Lancet Oncol.* 2915;16:522-530. 7. Ribas A, et al. *J Clin Oncol.* 2013;31:616-622. 8. Robert C, et al. *N Engl J Med.* 2015;372:320-330 and supplement. 9. Weber J, et al. *N Engl J Med.* 2017;377:1824-1835. 10. Brahmer J, et al. *N Engl J Med.* 2015;373:123-135 and supplement. 11. Borghaei H, et al. *N Engl J Med.* 2015;373:1627-1639 and supplement.

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ICI Immune-Mediated Hepatitis in Clinical Trials (continued)

Class and Author	Study type (Phase)	Indication	No. of Patients	Additional therapy	All grade ALT (or AST*) elevation (%)	Grade 3–4 ALT (or AST*) elevation (%)
Anti-PD-L1						
Atezolizumab						
Rosenberg et al. (2016)[1]	2	Urothelial carcinoma	310	—	10 (3%)	2 (0.6%)
Jotte et al. (2020)[2]	3	Squamous-cell NSCLC	334	nabPaclitaxel and carboplatin	59 (17.7%)	18 (5.4%)
Combination Therapy						
Postow et al. (2015)[3]	2	Melanoma	94	Ipi + Nivo	21 (22.3%)	10 (10.6%)
Larkin et al. (2015)[4]	3	Melanoma	313	Ipi + Nivo	55 (17.6%)	26 (8.3%)
Wolchok et al. (2013)[5]	1	Melanoma	53	Ipi + Nivo	11 (21.0%)	6 (11%)

*AST if only reported elevation.

Ipi = ipilimumab.

Jennings JJ, et al. *Expert Opin Drug Metab Toxicol.* 2019;15:231-244. 1. Rosenberg JE, et al. *Lancet.* 2016;387:1909-1920. 2. 3. Postow MA, et al. *N Engl J Med.* 2015;372:2006-2017. 4. Larkin J, et al. *N Engl J Med.* 2015;373:23-34. 5. Wolchok JD, et al. *N Engl J Med.* 2013;369:122-133.

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Recognizing Immune-Related Hepatotoxicity

1. No uniform definition
2. Hepatotoxicity ranges from asymptomatic increases in aminotransferases to acute hepatitis
3. Minority of patients have fever
4. Median time to onset: 5 weeks (1–49)
   Median of 2 (1–12) doses
5. Dose dependent
   7% vs 25% with ipilimumab 3 mg vs 10 mg/kg
6. Increased with combination
   ALT increase in 3.8% (monotherapy) vs 17.6% (nivolumab + ipilimumab)

HCC connect
POWERED BY COR2ED

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Grading for Hepatotoxicity

Utilize common terminology criteria of AEs: CTCAE—NCI

- Severity based on peak abnormalities of liver biochemistry AST/ALT/ALP/GGT
- Higher grades of severity—3 and 4
- INR not included
- Always check bilirubin, including direct bilirubin.
  ALT and AST are not liver-function tests

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute;
Colevas D, Setser A. *J Clin Oncol*. 2004;22(14 suppl): abstract 6098.

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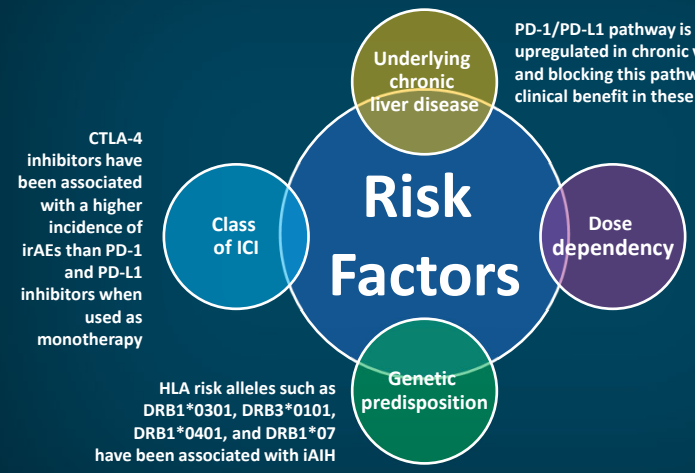
Risk Factors That May Predispose to Checkpoint Inhibitor-Induced Hepatotoxicity



PD-1/PD-L1 pathway is known to be upregulated in chronic viral hepatitis and blocking this pathway may have a clinical benefit in these diseases

CTLA-4 inhibitors have been associated with a higher incidence of irAEs than PD-1 and PD-L1 inhibitors when used as monotherapy

In dose-ranging study of ipilimumab for retreating advanced melanoma, no grade 3–4 hepatic AEs observed at dose of 0.3 mg/kg, but these toxicities increased to 30% with 10 mg/kg dose

HLA risk alleles such as DRB1*0301, DRB3*0101, DRB1*0401, and DRB1*07 have been associated with iAIH

iAIH = idiopathic autoimmune hepatitis.

Jennings JJ, et al. *Expert Opin Drug Metab Toxicol.* 2019;15:231-244.

49

Clinicopathologic Features and Outcomes of Hepatic Injury

Feature	ICI-IMH	iAIH	DI-AIH
Onset following drug exposure	3–9 weeks	Not applicable	Months to years
Presence of other autoimmune disorders	Data unavailable	25–40%	21%
Mean peak liver enzymes, including jaundice	Usually <5 ULN, Less than 2% >10 ULN	AST: 154–1031 IU; ALT: 185–1141 IU; Bili: 2–4 mg	ALT: 291–956 AST: 255–1141; Bili: 4–13 mg
Clinical presentation	Most commonly asymptomatic on routine monitoring	20% present with acute hepatitis; others are insidious	Insidious
Autoimmune serology	Absent or rare	Type I: ANA (70–80%); SMA (34–45%); Anti-LKM1 (3%)	ANA positivity 83% SMA (16–50%)
Histology	**CTLA-4:** panlobular hepatitis with centrilobular necrosis, granulomatous hepatitis with fibrin ring granulomas, central vein endothelitis **PD-1/L1:** lobular hepatitis with centrilobular necrosis, periportal inflammation; however, no fibrin-ring granulomas. Rare cholestatic injury with ductopenia	Interface hepatitis with lymphocytic/lymphoplasmacytic infiltrate, rosettes, and emperipolesis (presence of intact cell within cytoplasm of another cell)	Indistinguishable from iAIH
Immunohistochemistry	Usually CD3+ and CD8+	Usually CD4+ and CD20+	Indistinguishable from iAIH
Response to steroids	88% for grade 3 or 4 hepatitis	20% achieve complete remission; 80% require ongoing immunosuppression due to relapse on withdrawal	Resolves on withdrawal of agent in 40% patients; 60% required steroids but rarely relapsed after withdrawal

ICI-IMH = immune-mediated hepatitis from ICIs; DI-AIH = drug-induced AIH; ANA = antinuclear antibodies; SMA = smooth-muscle antibodies; LKM1 = liver kidney microsomal-1.

Jennings JJ, et al. *Expert Opin Drug Metab Toxicol.* 2019;15:231-244.

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Immunotherapy-Related Hepatitis
ASCO Guidelines for Treatment

	Immunotherapy Recommendations and Monitoring	Treatment
AST/ALT <3x ULN **Total bilirubin <1.5x ULN**	• Continue therapy • Monitor labs 1–2x/week	• None
AST/ALT 3–5x ULN **Total bilirubin 1.5–3x ULN**	• Hold therapy until recovered • Monitor labs every 3 days	• Prednisone 0.5–1 mg/kg/d if persists more than 3–5 days • Taper over at least 1 month
AST/ALT 5–20x ULN **Total bilirubin 3–10x ULN**	• Permanently discontinue • Monitor labs every 1–2 days	• Methylprednisolone 1–2 mg/kg • If no improvement after 3 days, consider mycophenolate mofetil or azathioprine (test for TPMT deficiency) • Taper steroids around 4–6 weeks
AST/ALT >20x ULN **Total bilirubin >10x ULN** **Decompensated liver function**	• Permanently discontinue • Inpatient monitoring • Consider transfer to tertiary care facility	• Methylprednisolone 2 mg/kg • If no improvement after 3 days, consider mycophenolate mofetil • Taper steroids around 4–6 weeks

ASCO = American Society of Clinical Oncology; TPMT = thiopurine methyltransferase.

Brahmer JR, et al. *J Clin Oncol.* 2018;36:1714-1768.

51

Clinically Significant Hepatotoxicity Often Leads to Treatment Discontinuation

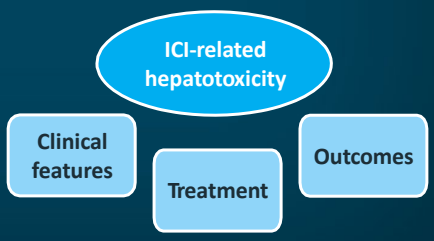
Background

- Immune checkpoint inhibitors are efficacious in advanced cancer
- Hepatotoxicity can impact ICI-based therapy
- Limited information about features of ICI hepatotoxicity (ICI-HT)

Design

- Retrospective
- ICI exposure
- ICI-HT ALT >5x ULN
- January 2010–March 2018

Objectives



Miller ED, et al. *Am J Gastroenterol.* 2020;115:251-261. Abu-Sbeih H, et all. *Hepatology*. 2018;68(suppl 1):25A-26A(abstract 39).

52

Clinical Profiles of Patients with Immune-Related ICI-Related Hepatic AEs

Characteristics	Steroids n = 67	No steroids n = 33	P-value
ALT, median U/L (IQR)	540 (300–2100)	408 (297–1188)	.075
Underlying liver disease, n (%)	27 (40)	11 (33)	.768
ICI discontinued, n (%)	49 (73)	20 (61)	—
Time from liver injury to ALT improvement, days (IQR)	23 (14–35)	14 (8–27)	.043

Miller ED, et al. *Am J Gastroenterol.* 2020;115:251-261. Abu-Sbeih H, et al. *Hepatology*. 2018;68(suppl 1):25A-26A(abstract 39).

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Conclusions and Takeaway Points

Conclusions

- Incidence of ICI-HT was rare (2%)
- Incidence higher for combination (9.2%) vs monotherapy (1.1–1.7%)
- Clinical features similar for ICI regimens
- ICI interrupted in all cases of ICI-HT
- ICI restarted in some, most cases without recurrent HT
- No liver failure or death was attributed to ICI hepatotoxicity

Key Takeaway Points

- Be aware of possible liver injury in ICI recipients
- Coordinate care with oncologists
- Minimize liver injury and maximize impact of ICI against cancer

Miller ED, et al. *Am J Gastroenterol.* 2020;115:251-261. Abu-Sbeih H, et al. *Hepatology*. 2018;68(suppl 1):25A-26A(abstract 39).

54

Key Points

- Initial reported rates of hepatotoxicity due to ICIs show that it is not uncommon—occurring in 2–30% of patients; however, severe cases remain very rare
- Liver injury due to ICIs most often presents with hepatocellular biochemical pattern, but cholestatic injury has also been reported
- Risk of hepatotoxicity increases when using multiple ICIs and in patients who develop other immune-related adverse events
- Other risk factors for hepatotoxicity include underlying chronic liver disease, higher dosages of ICIs, and utilizing anti-CTLA-4 agents as opposed to anti-PD-1 or anti-PD-LI agents
- Patients started on ICIs should have serial monitoring (ie, at least monthly) of their liver-associated enzymes to monitor for hepatotoxicity
- Liver biopsy can be useful in establishing diagnosis of ICI-IMH, especially when fibrin-ring granulomas are found in patients receiving anti-CTLA-4 therapy

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Action Items to Consider When ICI Autoimmune Relate AE—Specifically Liver iAIH—Is Diagnosed

- Consultation with a liver specialist should be considered for any patient who develops grade 2 hepatotoxicity or greater
- Liver biopsy may be useful in a subset of patients to identify those with less severe inflammation who may be able to avoid steroids and alternatively be managed with close monitoring of liver-associated enzymes and temporarily holding the ICI
- Corticosteroids, when indicated based on the grade of hepatotoxicity, can be used either orally or intravenously, depending on severity
- Limited data are available on additional or alternative agents (eg, budesonide, tacrolimus, mycophenolate mofetil, azathioprine) that may be needed if injury is refractory to corticosteroids
- Guidelines from multiple groups agree on need for permanent discontinuation of ICI therapy for grade 4 injury; however, restarting ICI treatment has been increasing for patients with less-severe grade 3 injury

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Liver Enzyme Elevations and Hepatotoxicity in Patients Treated with ICI Immunotherapy

Background & Aims

- Common liver irAEs (L-irAEs) resulting from ICI immunotherapy are poorly characterized
- Aim was to better understand causes of liver enzyme elevation (LEE), frequency of L-irAEs, and resulting impact on patient management

Methods

Aug 2012–Dec 2018
Patients from phase 1/2 clinical trials (Tumor Immunotherapy Program*)

↓

Clinical records reviewed for patients with clinically significant LEE (ALT/AST >3x ULN and/or bilirubin >1.5x ULN)

Results

Patient demographics	Patients treated with ICI (%) (N = 472)
Therapy type	
Anti-PD-1	65.2
Combination ICIs	6.1
Clinically significant LEE	21.6
Diagnostic evaluation	
Liver imaging	71.6
HBV/HCV serology	16.7
Autoimmune serology	13.7
Liver biopsy	2.9
LEE attributed to:	
Disease progression	54.9
Other drugs/toxins	6.9
Surgery	4.9
Other	16.7
L-irAE	16.7 of LEE (3.6% of total cohort)

*At the Princess Margaret Cancer Centre, Toronto, Canada.

Cunningham M, et al. International Liver Congress (ILC) 2019: abstract PS-139.

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Liver Enzyme Elevations and Hepatotoxicity

Results (continued)

- L-irAEs associated with:
  - Prior ICI exposure in 41.2% of patients with vs 15.4% in patients without L-irAEs; *P*= .011
  - Other irAEs in 76.5% of patients with vs 19.2% without L-irAEs; *P* <.001
- 15/17 patients with L-irAEs received steroids, and liver enzymes normalized after a median of 37 days (IQR 21–52); 4 patients received further ICI, with recurrent L-irAE in 1 patient

Variable	Patients (N = 472)
Follow-up, median (IQR)	7.5 months (3.6–16.2)
Total disease progression, n (%)	421 (89.2)
Patients with L-irAE (%)	52.9 } ***P*= .001**
Patients without L-irAE (%)	86.7 }
Death, n (%)	292 (61.9)
Death due to complications from L-irAE	0

Conclusions

- LEE may be unrelated to cancer/ICI.
- L-irAEs were more common in patients with previous ICI exposure and other irAEs.
- Lower incidence of disease progression seen in those with L-irAE

Cunningham M, et al. ILC 2019: abstract PS-139

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Management of Hepatotoxicity Associated with ICIs

Hepatotoxicity CTCAE grade of severity	General Recommendations
Grade ≥2 **AST and/or ALT >3–5 times ULN and/or total bilirubin >1.5–3 times ULN**	1. Start corticosteroids (Minimum 0.5–1.0 mg/d prednisone equivalent) **AND** 2. Withhold ICI (Do not restart until return to Grade 1 or baseline) **AND** 3. Monitor for changes in liver function; general principals include: a. Recheck liver tests/INR/albumin every 3 days b. Review all potential hepatotoxic medications c. Rule out alternative viral or autoimmune etiologies
Grade ≥3 **AST and/or ALT >5 times ULN and/or total bilirubin >3 times ULN**	1. Institute corticosteroids (1–2 mg/kg/d prednisone equivalent) **AND** 2. Permanent discontinuation

Brahmer JR, et al. *J Clin Oncol.* 2018;36:1714-1768.

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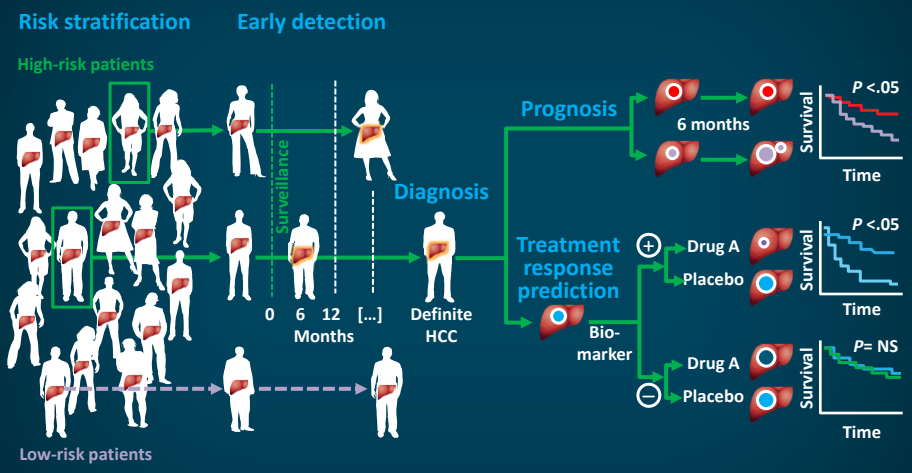
Immune-Related and Non-immune-Related Biomarkers and Testing Methodologies

60

Biomarker Development in HCC



NS = not significant.

Singal AG, et al. *Gastroenterology.* 2021;Mar 8: Epub ahead of print.

61

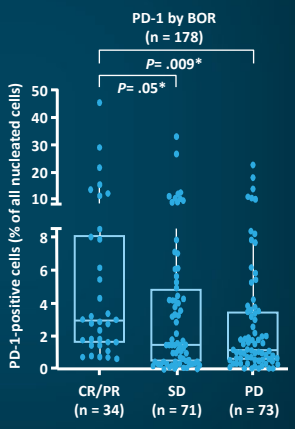
Biomarkers of Response to Checkpoint Inhibitors

Nivolumab Phase 2 Trial

Gene expression signatures

Gene expression signatures and clinical response			
Gene signatures	Genes included	ORR *P*-value	OS *P*-value
Inflammatory	CD274 (PD-L1), CD8A, LAG3, STAT1	0.05	0.01
Cytolytic activity	GZMA, PRF1	0.1	0.2
Gajewski 13-gene inflammatory	CCL2, CCL3, CCL4, CD8A, CXCL10, CXCL9, GZMK, HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, ICOS, IRF1	0.04	0.05
6-gene interferon gamma	CXCL10, CXCL9, HLA-DRA, IDO1, IFNG, STAT1	0.05	0.009
Antigen-presenting cells	CMKLR1, HLA-DQA1, HLA-DRB1, PSMB10	0.6	0.08
Interferon gamma biology	CCL5, CD27, CXCL9, CXCR6, IDO1, STAT1	0.07	0.008
T-cell exhaustion	CD274 (PD-L1), CD276, CD8A, LAG3, PDCD1LG2, TIGIT	0.03	0.04
T/NK	HLA-E, NGK7	0.3	0.04
Ribas 10-gene interferon gamma	CCR5, CXCL10, CXCL11, CXCL9, GZMA, HLA-DRA, IDO1, IFNG, PRF1, STAT1	0.07	0.02
Immune class, n	104	0.15	0.29

PD-1 expression



*CR/PR vs SD vs PD were compared using a continuous model based on available data.

Sangro B, et al. *J Hepatol.* 2020;73:1460-1469.

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Assessment of Inflammation Biomarkers in Relation to Clinical Outcomes in Nivolumab-Treated Patients With Advanced Hepatocellular Carcinoma in CheckMate 040

Ignacio Melero,[1] Jaclyn Neely,[2] Bruno Sangro,[3] Richard S. Finn,[4] Ghassan K. Abou-Alfa,[5] Ann-Lii Cheng,[6] Thomas Yau,[7] Junji Furuse,[8] Joong-Won Park,[9] Samir Wadhawan,[2] Hao Tang,[2] Christine Delacruz,[2] Carlos Baccan,[2] Zachary Boyd,[2†] Anthony El-Khoueiry[10†]

1. Universidad de Navarra, Pamplona, Spain; 2. BristoMyers Squibb, Princeton, NJ, USA; 3. Clinica Universidad de Navarra and CIBEREHD, Pamplona, Spain: 4. University of California, Los Angeles, CA, USA; 5. Memorial Sloan Kettering Cancer Center, and Weill Medical College at Cornell University, New York, NY, USA; 6. National Taiwan University Hospital, Taipei, Taiwan; 7. University of Hong Kong, Hong Kong, China: 8. Kyorin University Faculty of Medicine, Tokyo, Japan; 9. National Cancer Center, Goyang, South Korea; 10. USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Melero I, et al. *Cancer Res.* 2019; 79(13): abstract 2675 (American Association for Cancer Research [AACR]).

63

CheckMate-040: Patients Receiving Nivolumab

Gene expression signatures and clinical response		
Gene signatures	**ORR *P*-value**	**OS *P*-value**
Inflammatory signature	.05	.01
Cytolytic activity signature	.1	.2
Gajewski 13-gene inflammatory signature	.04	.05
6-gene interferon gamma signature	.05	.009
Antigen-presenting cells signature	.6	.08
Interferon gamma biology signature	.07	.008
T-cell exhaustion signature	.03	.04
T/NK cell signature	.3	.04
Ribas 10-gene interferon gamma signature	.07	.02

For a subset of patients in CheckMate-040 for whom RNA sequencing data were available (n = 37), several gene signatures (eg, inflammatory signature, Gajewski, 6-gene interferon gamma, interferon gamma biology, and T-cell exhaustion signatures) correlated with improved response and/or OS

RNA = ribonucleic acid.

Sangro B, et al. *J Hepatol.* 2020;73:1460-1469.

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COVID-19 and HCC

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Treatment of Advanced HCC in COVID-19 ERA
Key Questions and Considerations

1. Are patients with HCC at increased risk for infection and/or complications from COVID-19?
2. Does immunotherapy increase the risk for more severe disease or death from COVID-19?
3. What are the current recommendations for use of immunotherapy in patients with HCC to mitigate risks related to COVID-19?
4. What are some additional considerations for COVID-19 risk mitigation in the care of HCC patients?
   - Risk mitigation measures
   - Role of telemedicine
   - Impact on practice patterns

COVID-19 = coronavirus disease 2019.

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Cancer and COVID-19 Risk

Literature review including >10 studies focused on COVID-19 in cancer patients[1]

Key findings/conclusions

- Data suggest an **increased risk of acquiring SARS-CoV-2 infection** compared with general population[1]
  - Individuals with cancer comprised a larger proportion of COVID-19 patients in both the United States (6%)[2] and China (1%)[3]
- Compared with COVID-19 patients without cancer, those with cancer appeared to have an **increased risk for severe outcomes, including intubation and death,** after adjusting for other COVID-19 risk factors[1]
- Overall case fatality rates among cancer patients range from 11% to 28%, with disproportionately higher rates in some subgroups[1]:
  - Lung cancer (18% to 55%)
  - Hematologic malignancy (33% to 41%)

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1. Fung M, Babik JM. *Clin Infect Dis*. 2020; Jun 27:Epub ahead of print. 2. Miyashita H, et al. *Ann Oncol*. 2020;31:1088-1089. 3. Liang W, et al. *Lancet Oncol.* 2020;21:335-337.

67

Theoretical Concerns About ICI Use During COVID-19 Outbreak

Effects on cellular immunity or immune-related neutropenia may impair immune response to virus[1]

- Hematologic irAEs are uncommon
- Limited data on viral infections or reactivations as a complication to ICIs
  - However, few cases of infections secondary to irAE treatment have been reported

Possible negative interference of ICI in pathogenesis of COVID-19[2,3]

- Synergistic immune hyperactivation (ie, treatment-induced cytokine-release syndrome plus infection-related cytokine storm)

Potential overlap between coronavirus-related interstitial pneumonia and pulmonary toxicity from anti-PD-1/PD-L1 agents[2,3]

1. Kattan J, et al. *Immunotherapy.* 2020;12:351-354. 2. Bersanelli M. *Immunotherapy*. 2020;12:269-273. 3. Rossi E, et al. *J Immunother Cancer*. 2020;8:e000952.

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Risk of COVID-Related Mortality in Larger Cohorts of Patients Receiving Cancer Therapy

800 patients in prospective observational UK Coronavirus Cancer Monitoring Project, who were diagnosed 3/18 to 4/26/2020[1]

- After adjusting for age, gender, and comorbidities, chemotherapy in past 4 weeks had no significant effect on mortality from COVID-19 disease, compared with cancer patients who had not received recent chemotherapy
- No significant effect on mortality for patients with cancer receiving immunotherapy (6%), hormonal therapy (8%), targeted therapy (9%), radiotherapy (10%) within 4 weeks of COVID-19 diagnosis

Observational study of 890 patients at 19 centers in UK, Italy, Spain, and Germany, who were recruited 2/26 to 4/1 (censored 5/11/2020)[2]

- Active treatment with chemotherapy (23.1%), targeted therapy (10.4%), and immunotherapy (6.3%) at time of COVID-19 diagnosis did not worsen mortality

1. Lee LY, et al. *Lancet.* 2020;395:1919-1926. 2. Pinato DJ, et al. *Cancer Discov.* 2020;10:1465-1474.

69

Guidance Regarding ICI Treatment During COVID-19

ASCO

- Consider less frequent dosing intervals
- Where possible, COVID-19 testing prior to therapy with these agents is reasonable
- Special precautions/considerations
  - Some agents are associated with a risk of inflammatory reactions and complications (eg, pneumonitis)
  - Immunosuppression for serious irAEs may not be advisable

"The potential harms and benefits of therapy should be carefully considered for each patient"

NCCN

- In all stages/settings, consider lowest-frequency dosing schedule of available regimens
- For stage IV disease, single-agent anti-PD-1 is recommended over combination ipilimumab/ nivolumab due to:
  - More substantial inflammation/possible exacerbation of COVID-19
  - Need for steroids/other immunosuppressants that may adversely affect SARS-CoV-2–infected individuals
  - Increased resource utilization for visits related to toxicities/monitoring

"Decisions…should be individualized, with preference for agents with the lowest toxicity profile"

ASCO (www.asco.org/asco-coronavirus-resources/care-individuals-cancer-during-covid-19/cancer-treatment-supportive-care). National Comprehensive Cancer Network (NCCN) (www.nccn.org/covid-19/pdf/Melanoma.pdf). Accessed 3/3/2021.

70

ASCO Guidance Regarding Initiating/Resuming Anticancer Therapy After COVID-19 Infection

After "symptoms of COVID-19 have resolved and there is some certainty the virus is no longer present (eg, a negative SARS-Cov-2 test), unless the cancer is rapidly progressing and the risk:benefit assessment favors proceeding with cancer treatment"

"…once transmission-based precautions are no longer necessary would be reasonable"

- Recommended strategy for determining duration of transmission-based precautions depends on whether patient is considered immunocompromised
- Conditions causing a high degree of immunocompromise:
  - Receipt of chemotherapy for cancer
  - Untreated HIV infection with CD4 T lymphocyte count <200/mm^3
  - Combined primary immunodeficiency disorder
  - Receipt of the equivalent of prednisone >20 mg/day for more than 14 days

HIV = human immunodeficiency virus.

ASCO (www.asco.org/asco-coronavirus-resources/care-individuals-cancer-during-covid-19/cancer-treatment-supportive-care. Centers for Disease Control and Prevention (CDC) (www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html). Accessed 3/3/2021.

71

ASCO Guidance Regarding COVID-19 Vaccines in Cancer Patients*

- The Pfizer and Moderna vaccines were shown to be safe and effective for the general population and there was no evidence that they would not be safe for most cancer patients, although it should be noted that patients receiving immunosuppressive and cytotoxic treatments were excluded from participation in the vaccine trials to date so there is little to no data on the safety and efficacy of the Pfizer and Moderna vaccines in cancer patients.
- At this time, patients with cancer may be offered vaccination against COVID-19 as long as components of that vaccine are not contraindicated.

***Statement issued prior to authorization of Janssen/Johnson & Johnson vaccine on 2/27/2021.**

ASCO. COVID-19 vaccine and patients with cancer (www.asco.org/asco-coronavirusresources/covid-19-patient-care-information/covid-19-vaccine-patients-cancer). Accessed 3/3/2021

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Multidisciplinary Oncology Team

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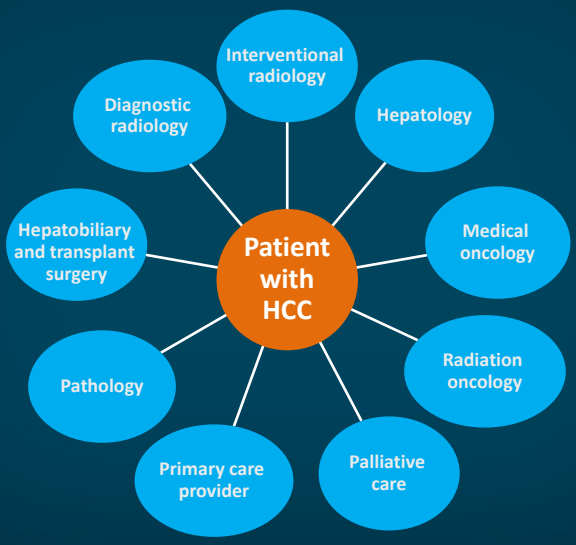
Multidisciplinary Management Is Important



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Multidisciplinary Care Improves HCC Outcomes

Study	Patients N	Description	Outcomes
Serper et al. 2017	3988	Multi-specialty evaluation or tumor board review	Increase in HCC treatment but not tumor board review improved survival
Yopp et al. 2014	355	Single-day MDT clinic and conference	Improve early detection, curative treatment, time to treatment, and survival
Zhang et al. 2013	343	Single-day MDT clinic	Changed imaging/pathology interpretation and therapy plan
Chang et al. 2008	121	Fluid referrals and joint conference	Improve early detection, curative treatment, and survival

MDT = multidisciplinary treatment.

Serper M, et al. *Gastroenterology*. 2017;152:1954-1964. Yopp AC, et al. *Ann Surg Oncol*. 2014;21: 1287-1295. Zhang J, et al. *Curr Oncol*. 2013;20:e123-e131. Chang TT, et al. *HPB* (Oxford). 2008;10:405-411.

75

5 Essential Steps of SDM: SHARE Approach

It's all about communication!

AHRQ. Share approach factsheet (www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf). Accessed 3/18/2021.

76

Strategies for Effective Communication

Evidence-Based Recommendations on Handling Information
• Ask patients what types of information and level of detail they wish to have
• Offer information about quality-of life issues as well as anticancer therapy
• Use the number of patient concerns as a marker for distress and poor adjustment
• Recognize that patient misunderstandings about clinical trials are common.
• In transitions to hospice care, avoid using phrases such as "*there is nothing more that can be done*"

Evidence-Based Recommendations on Dealing with Patient Emotions
• Do not assume that patients will request help for emotional issues
• Consider the patient-physician encounter as providing both cognitive data about patient understanding and emotional data about patient feelings
• Explicitly solicit emotional data from patients about their mood in order to detect distress

Back A. *Oncology* (Williston Park). 2006;20:67-74.

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Case Studies

78

Case 1: Second-Line Immunotherapy

- 74-year-old man with NASH cirrhosis and liver lesion.
- MELD score 9, Bili = 1.3, Alb = 3.4, INR = 1.1, no ascites, no encephalopathy
- AFP = 12,645
- Diagnosed with 6 cm HCC in posterior right lobe with branch portal vein invasion
- ECOG PS = 0
- BCLC = D
- Underwent radioembolization (Y90), which resulted in partial response on imaging, with persistent enhancement in 25% of lesion; AFP = 4259
- CT chest showed new 1 cm lung nodule. Biopsied and confirmed metastatic disease
- Started on sorafenib 400 mg BID

NASH = nonalcoholic steatohepatitis; CT = computed tomography (scan); MELD = model of end-stage liver disease; Bili = bilirubin; Alb = albumin; INR = international normalized ratio; AFP = alpha-fetoprotein; HCC = hepatocellular cancer; ECOG = Eastern Cooperative Oncology Group; PS = performance status; BCLC = Barcelona Clinic Liver Cancer; BID = twice daily.

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Case (Continued)

- Patient developed severe diarrhea on sorafenib, despite dose reduction and multiple antidiarrheal therapies
- Sorafenib discontinued and nivolumab started
- After nivolumab initiation, lung nodule disappeared, liver nodule stabilized, and AFP decreased to 109
- Patient has now been on nivolumab for 18 months with stable disease

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What is the best next step for this patient?

1. Hospice
2. Continue nivolumab until progress.
3. Switch to atezolizumab + bevacizumab
4. Stop nivolumab and monitor for progression.

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B. Continue nivolumab until progression.

Rationale: The patient is doing well on nivolumab; there is no reason to switch.

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Case 2: Possible Immune-related Adverse Events

- 65 yo male w/metastatic HCC with adrenal and bone metastasis (AFP 16,388 ng/mL, biopsy moderately differentiated)
- Bilobar hepatomas with extrinsic compression by masses at porta hepatis. Possible partial malignant thrombosis of PV.
- Participated in clinical trial:
  - 1500mg (PD-L1) in combination with tremelimumab (CTLA4-i) 300mg for 1 dose; then investigational PD-L1; 1500mg q4 weekly
- Developed diarrhea associated with G3 transaminitis
- Elevated transaminases already present pre-treatment but worsened after first dose.

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Case 2 Continued

- The clinical impression was that the elevated liver enzymes were due to cell death from HCC in the liver
- The clinical team continued with targeted therapy
- AFP 16,388 -> 8.4 ng/mL
- Improvement in disease with LiRADs 5 T; possible residual disease and recurrence in a different area.

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Polling Question

What to do next for this patient?

1. Continue dual therapy with double ICI treatment and reassess if disease progresses.
2. Stop treatment and monitor for disease progression.
3. Add a TKI inhibitor such as cabozantinib and monitor for disease progression.
4. Move to hospice.

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Answer: A

Continue dual therapy with double ICI treatment and reassess if disease progresses.

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Key Learning Points

- Be aware of the various forms of liver injury and their severity in ICI recipients
- Coordinate care with gastro/hepatologists and oncologists
- Minimize and manage liver injury with immune suppression and/or dose discontinuation
- Maximize impact of ICI against HCC with coordinated and informed approach

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Immuno-oncology in Advanced Hepatocellular Carcinoma

Project ECHO®

Med Learning Group
New York

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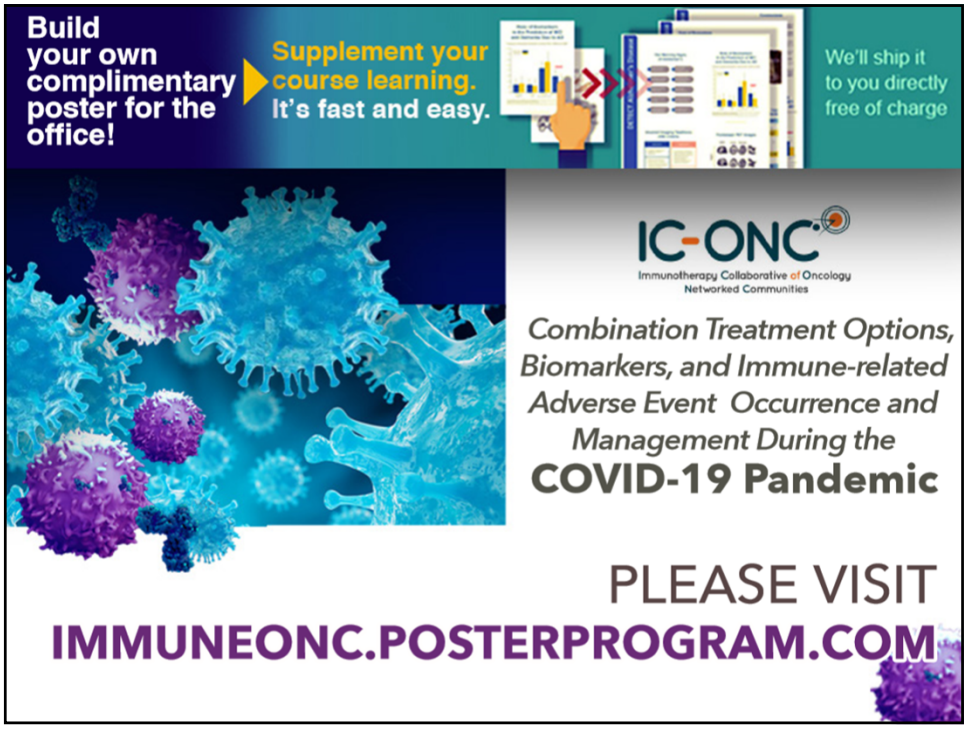
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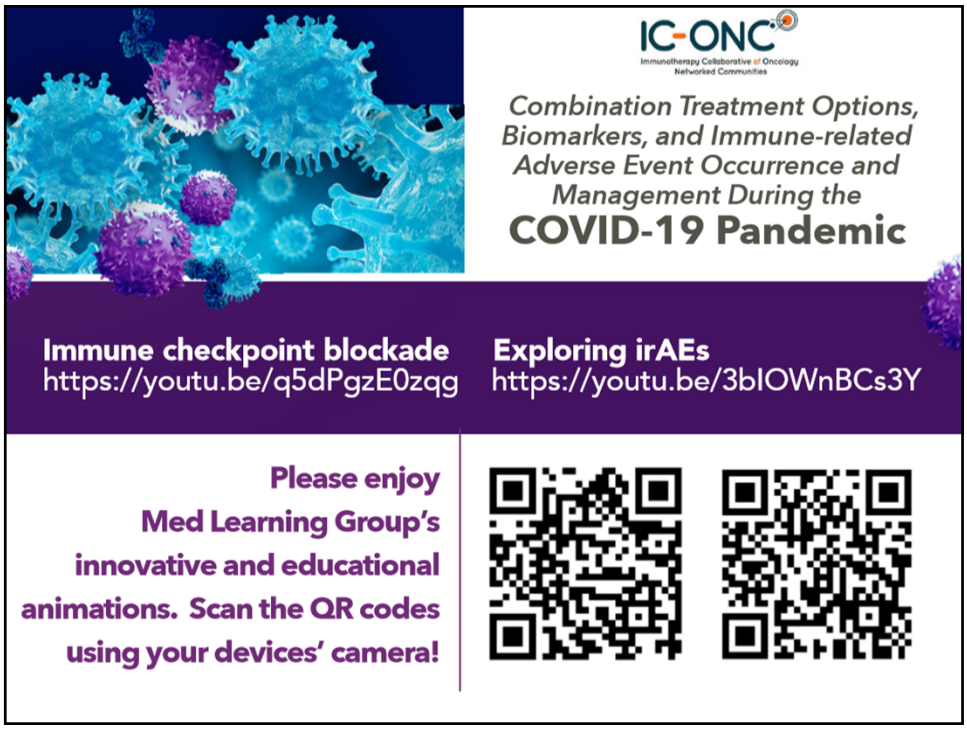
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Questions and Answers

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