

# Practical Management Pearls for Immunotherapy for the Treatment of Hepatocellular Carcinoma

December 6, 2021

5:30 – 6:30 p.m. ET



*The Practical Management Pearls and Case Studies Webinars are part of the Cancer Immunotherapy Clinical Practice Guidelines Advanced Webinar Series supported, in part, by grants from Amgen and Merck & Co., Inc. (as of 9/15/2021)*

# Webinar faculty



**Tim F. Greten, MD**

*Expert Panel Chair*



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*Expert Panel Member*

# Learning objectives

- Appraise and classify liver-specific considerations for immunotherapy agents and associated toxicities/irAEs
- Appropriately assess and stage HCC for immunotherapy
- Appropriately manage liver-specific toxicities/irAEs associated with immunotherapy
- Discuss data on the integration of immunotherapies into treatment plans for early-stage HCC

# Webinar outline

- Development of the guideline
- Mechanism(s) of action of immunotherapy
- Staging and workup
- Toxicity management
- Sequencing of therapies
- Immunotherapy for early-stage disease
- Key takeaways

# Development of the guideline

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Position article and guidelines



Journal for  
ImmunoTherapy of Cancer

## Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of hepatocellular carcinoma

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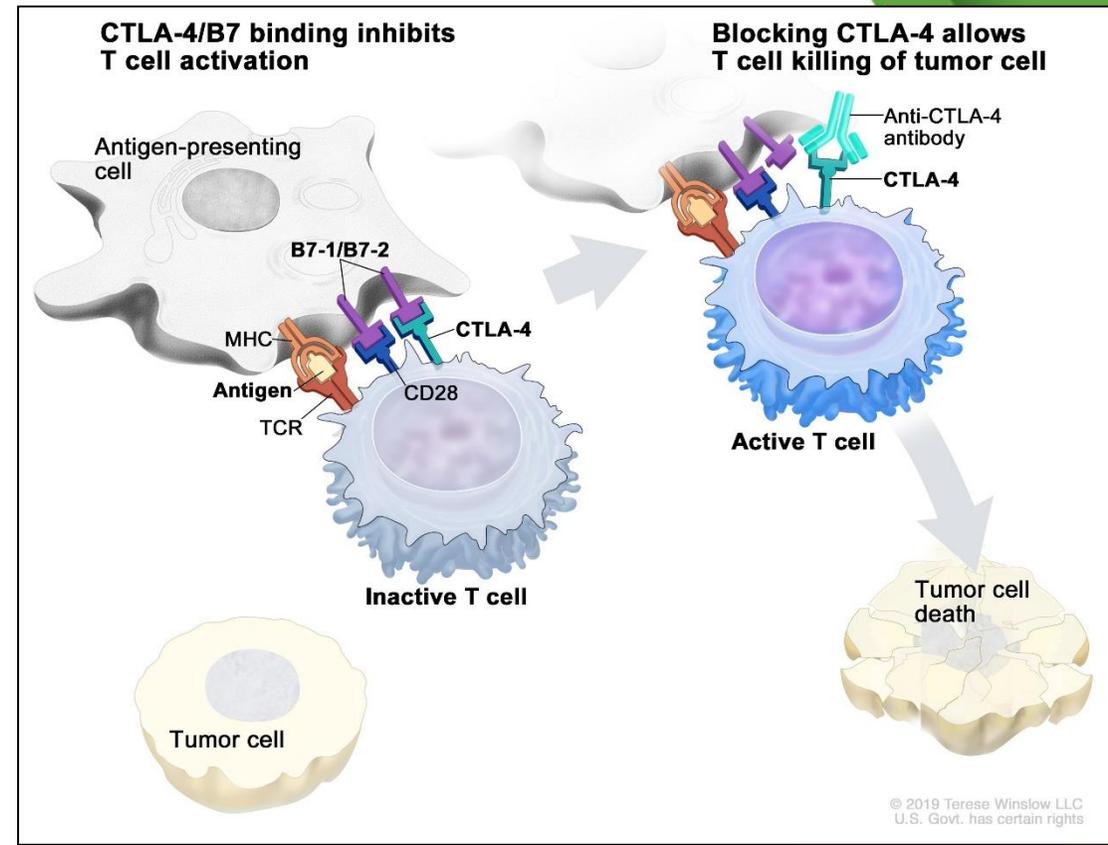
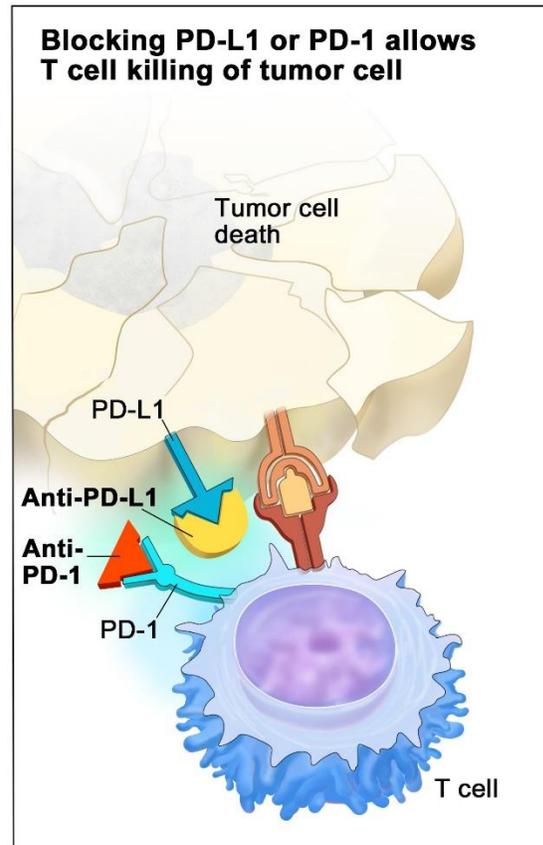
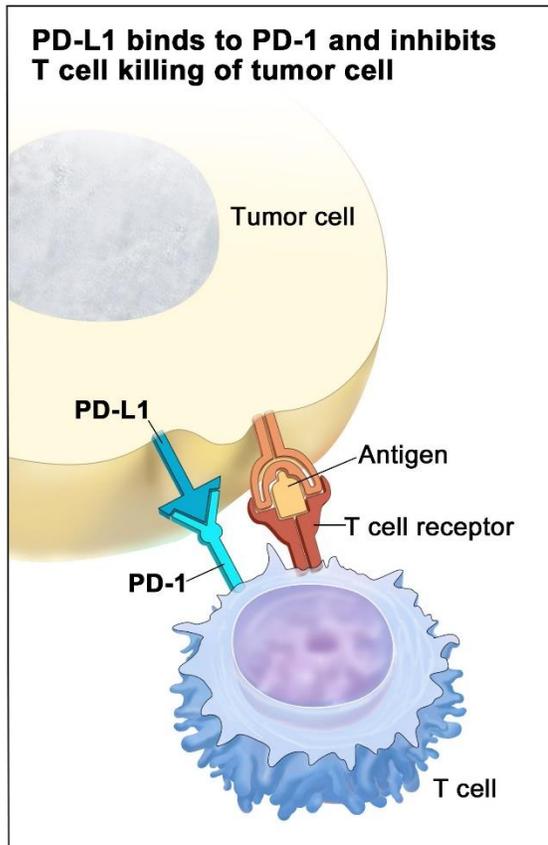
# Development of the guideline

- Developed according to the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines
- Panel consisted of 21 experts in the field
- Recommendations are based upon published literature evidence, or clinical evidence where appropriate
- Consensus was defined at 75% approval among voting members

# Webinar outline

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- **Mechanism(s) of action of immunotherapy**
- Staging and workup of patient candidates
- Toxicity management
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# Mechanism(s) of action of immune checkpoint inhibitors (ICIs)



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# Unique immunologic features of HCC tumors

- HCC tumors are highly inflamed BUT highly immunosuppressive
  - M2 polarization of tumor associated macrophages (TAMs)
  - High levels of T cell exhaustion
  - Higher infiltration of Tregs
  - Higher infiltration of myeloid-derived suppressor cells (MDSCs)
  - Higher levels of dysfunctional NK cells

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# Expert Panel recommendations

## Staging and workup for HCC

- A multidisciplinary tumor board review of liver lesions is recommended for HCC diagnosis and the development of a management plan
- Notwithstanding that LI-RADS-5 is nearly 100% specific for HCC (LE: 1), histologic confirmation is recommended for patients with unresectable disease particularly prior to the initiation of systemic therapy. Histologic diagnosis is mandatory for non-cirrhotic patients.
- Despite the controversy regarding the scoring and staging systems that could be used, before initiation of systemic therapy, an evaluation of liver function, including aspartate transaminase (AST)/alanine aminotransferase (ALT), bilirubin, prothrombin time (PT)/international normalized ratio (INR), albumin, plus platelets, is critical (LE: 2).
- For patients being considered for immunotherapy, an HCC-specific staging system incorporating liver function assessment is suggested (LE: 2).
- To evaluate patients prior to receiving immunotherapy, Child-Pugh classification would be the most appropriate to date (LE: 1) to measure liver function.

# Staging systems for HCC

SYSTEM	PARAMETERS ASSESSED
Radiologic T-staging	Tumor size, Number of tumors, Portal vein invasion
Barcelona-Clinic Liver Cancer (BCLC)	Tumor size, ECOG PS, Nodular disease, Metastatic disease, Portal vein invasion, Liver function (Child-Pugh)
Cancer of the Liver Italian Program (CLIP)	Tumor size, Portal vein invasion, AFP, Liver function (Child-Pugh)
Japan Integrated Staging (JIS)	Tumor size, Nodular disease, Metastatic disease. Liver function (Child-Pugh)
Chinese University Prognostic Index (CUPI)	Tumor size, Nodular disease, Metastatic disease, AFP, Liver function (Bilirubin, ALK, ascites)
Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GETCH)	Karnofsky index, Portal vein invasion, AFP, Liver function (Bilirubin, ALK)

# *Poll Question*

**Rate your familiarity with the BCLC staging system:**

- Not familiar/Do not use
- Somewhat familiar/Use sometimes
- Very familiar/Use frequently

# BCLC staging for HCC

	Stage definition (BCLC 2018 update)	Estimated survival
<b>Stage 0—Very early-stage</b>	Single nodule $\leq 2$ cm; ECOG PS 0*; Preserved liver function	>5 years
<b>Stage A—Early-stage</b>	Single or up to three nodules $\leq 3$ cm; ECOG PS 0*; Preserved liver function	>5 years
<b>Stage B—Intermediate-stage</b>	Multinodular; ECOG PS 0*; Preserved liver function	>2 to 5 years
<b>Stage C—Advanced-stage</b>	Portal invasion; Extrahepatic spread; ECOG PS 1–2; Preserved liver function	>1 year
<b>Stage D—Terminal-stage</b>	ECOG PS 3–4; End-stage liver function	3 months

\*The American Association for the Study of Liver Disease (AASLD) recommends including ECOG PS 0 to 1 in stage 0, A and B, because of the significant overlap between PS 0 and PS 1  
BCLC, Barcelona-Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

# Imaging for diagnosis of HCC

- LI-RADS: Provides a standardized approach for radiologists to communicate with the treating physicians and provides a certain level of confidence that a lesion in a cirrhotic liver or a liver at risk for cirrhosis presents as HCC on imaging
  - Endorsed by the AASLD and OPTN/UNOS
  - Uses Radiographic T-staging:

Radiographic T-staging by LI-RADS and OPTN/UNOS

Stage	Definition
0	No HCC
1	One HCC <20 mm
2	One HCC ≥20 mm and ≤50 mm, or two or three HCCs, all ≤30 mm
3	One HCC >50 mm, or two or three HCCs, at least one >30 mm
4	4A. Four or more HCCs, regardless of size 4B. HCC + TIV

HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting And Data System; OPTN/UNOS, Organ Procurement and Transplantation Network/United Network for Organ Sharing; TIV, tumor in vein.

# Which patients are appropriate to evaluate with tumor biopsy?

- Histologic diagnosis is increasingly encouraged for the diagnosis of HCC, particularly for more advanced tumors requiring systemic therapy. It is required for non-cirrhotic patients.
  - May assist in the differential diagnosis
  - May uncover unknown genetic alterations
- Scenarios where no biopsy may be considered
  - In patients with cirrhosis and imaging characteristics consistent with HCC
  - In patients where liver transplants are being considered

# Liver function assessment in HCC

- Liver function assessment is a critical component of HCC treatment that is required for every patient
- Assessment tools:
  - Child-Pugh: Five-parameter staging system including three laboratory values (serum albumin, bilirubin, and prothrombin levels) and two clinical variables (presence and degree of ascites and hepatic encephalopathy)
  - Albumin-bilirubin (ALBI)

# *Poll Question*

**Which factors are prognostic for patient outcomes with advanced HCC?**

- a) Child-Pugh classification
- b) Tumor in vein (TIV)
- c) Extrahepatic metastasis
- d) All of the above

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- **Toxicity management**
- Sequencing of therapies
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- Key takeaways

# Expert Panel recommendations

## Toxicity management

- The panel recommends against the use of routine testing of biomarkers for predicting irAEs, which, at this point, remains exploratory.
- For management of irAEs in patients with HCC, refer to general principles in published guidelines.
- Patients should receive education on the expected toxicities associated with immunotherapies, including hepatitis, colitis, pneumonitis, and immune-related endocrinopathies. Detailed call parameters should be provided to promptly report signs and symptoms of irAEs.

# Toxicities reported in pivotal trials for HCC immunotherapy regimens

REPORTED ADVERSE EVENTS	IMMUNOTHERAPY REGIMEN		
	Atezolizumab + bevacizumab (IMbrave150 safety data)	Ipilimumab + nivolumab (CheckMate 040 safety data)	Pembrolizumab monotherapy (KEYNOTE-224 safety data)
Any grade	<p><b>98.2%</b></p> <p>Most common:</p> <ul style="list-style-type: none"> <li>- Hypertension (29.8%)</li> <li>- Fatigue (20.4%)</li> <li>- Proteinuria (20.1%)</li> </ul>	<p><b>94%</b></p> <p>Most common:</p> <ul style="list-style-type: none"> <li>- Pruritis (45%)</li> <li>- Rash (immune-mediated; 20.4%)</li> <li>- Rash (identified as treatment-related; 20.1%)</li> </ul>	<p><b>97%</b></p>
Grade 3-4	<p><b>56.5%</b></p> <p>Most common:</p> <ul style="list-style-type: none"> <li>- Hypertension (15.2%)</li> <li>- AST increase (7%)</li> <li>- ALT increase (3.6%)</li> </ul>	<p><b>53%</b></p> <p>Most common:</p> <ul style="list-style-type: none"> <li>- Hepatitis (immune-mediated; 29.8%)</li> <li>- AST increase (16%)</li> <li>- Lipase increase (20.1%)</li> </ul>	<p><b>25%</b></p> <p>Most common:</p> <ul style="list-style-type: none"> <li>- AST increase (7%)</li> <li>- Fatigue (4%)</li> <li>- ALT increase (4%)</li> </ul>

# Liver-specific considerations for toxicity management: drug-induced hepatotoxicity

## Cirrhosis-related disorders that should be considered in workup of irAEs

Organ	irAE	Chronic liver disease
Skin	<ul style="list-style-type: none"> <li>▶ Pruritus</li> <li>▶ Rash</li> <li>▶ Erythema multiforme, psoriasis, urticaria and rosácea</li> <li>▶ Severe cutaneous adverse reactions</li> </ul>	<ul style="list-style-type: none"> <li>▶ Pruritus</li> <li>▶ Skin disorders, including lichen planus, polyarteritis nodosa, cryoglobulinemic vasculitis, and porphyria cutanea tarda (HCV- and HBV-related)</li> </ul>
GI tract	<ul style="list-style-type: none"> <li>▶ Diarrhea</li> <li>▶ Colitis</li> </ul>	<ul style="list-style-type: none"> <li>▶ Small intestine bacterial overgrowth</li> <li>▶ Chronic pancreatitis</li> </ul>
Liver	<ul style="list-style-type: none"> <li>▶ Hepatitis</li> </ul>	<ul style="list-style-type: none"> <li>▶ Flares or viral infection</li> </ul>
Lung	<ul style="list-style-type: none"> <li>▶ Pneumonitis</li> </ul>	<ul style="list-style-type: none"> <li>▶ Hepatopulmonary syndrome</li> <li>▶ Porto-pulmonary hypertension</li> </ul>
Thyroid	<ul style="list-style-type: none"> <li>▶ Hypothyroidism</li> <li>▶ Hyperthyroidism</li> <li>▶ Graves' disease</li> </ul>	<ul style="list-style-type: none"> <li>▶ Reduced peripheral conversion of T4 to T3</li> <li>▶ Thyroid dysfunction</li> </ul>
Adrenal glands and pituitary glands	<ul style="list-style-type: none"> <li>▶ Adrenal insufficiency</li> <li>▶ Hypophysitis</li> </ul>	<ul style="list-style-type: none"> <li>▶ Hypogonadism</li> <li>▶ Hypothalamic-pituitary dysfunction</li> <li>▶ Relative adrenal insufficiency</li> </ul>

# Liver-specific considerations for toxicity management: drug-induced hepatotoxicity

## Cirrhosis-related disorders that should be considered in workup of irAEs

Organ	irAE	Chronic liver disease
Kidney	<ul style="list-style-type: none"> <li>▶ Nephritis</li> </ul>	<ul style="list-style-type: none"> <li>▶ Hepatorenal syndrome</li> <li>▶ Mixed cryoglobulinemia (HCV-related)</li> <li>▶ HBV-related nephropathy</li> <li>▶ IgA nephropathy</li> </ul>
Nervous system	<ul style="list-style-type: none"> <li>▶ Encephalitis</li> <li>▶ Aseptic meningitis</li> <li>▶ Peripheral neuropathy</li> <li>▶ Myasthenia gravis</li> <li>▶ Guillain-Barre syndrome</li> <li>▶ Autonomic neuropathy</li> <li>▶ Transverse myelitis</li> </ul>	<ul style="list-style-type: none"> <li>▶ Porto-systemic encephalopathy (typical and atypical)</li> <li>▶ Viral-related peripheral neuropathy</li> <li>▶ Wernicke's encephalopathy</li> <li>▶ Autonomic neuropathy (HCV-related)</li> </ul>
Blood and bone marrow	<ul style="list-style-type: none"> <li>▶ Cytopenias</li> <li>▶ Hemolytic anemia</li> <li>▶ Red cell aplasia</li> <li>▶ Bone marrow failure</li> <li>▶ Hemophilia A</li> <li>▶ Hemophagocytic lymphohistiocytosis</li> <li>▶ Macrophage activation syndrome</li> </ul>	<ul style="list-style-type: none"> <li>▶ Hypersplenism and bone marrow depression</li> <li>▶ Anemia due to folate or iron deficiency</li> <li>▶ Hemolytic anemia</li> <li>▶ Viral-related thrombotic thrombocytopenic purpura and aplastic anemia</li> <li>▶ Immune thrombocytopenia (HCV-related)</li> <li>▶ Lymphopenia related to HCC therapies</li> </ul>

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# FDA-approved immunotherapy agents and indications for HCC

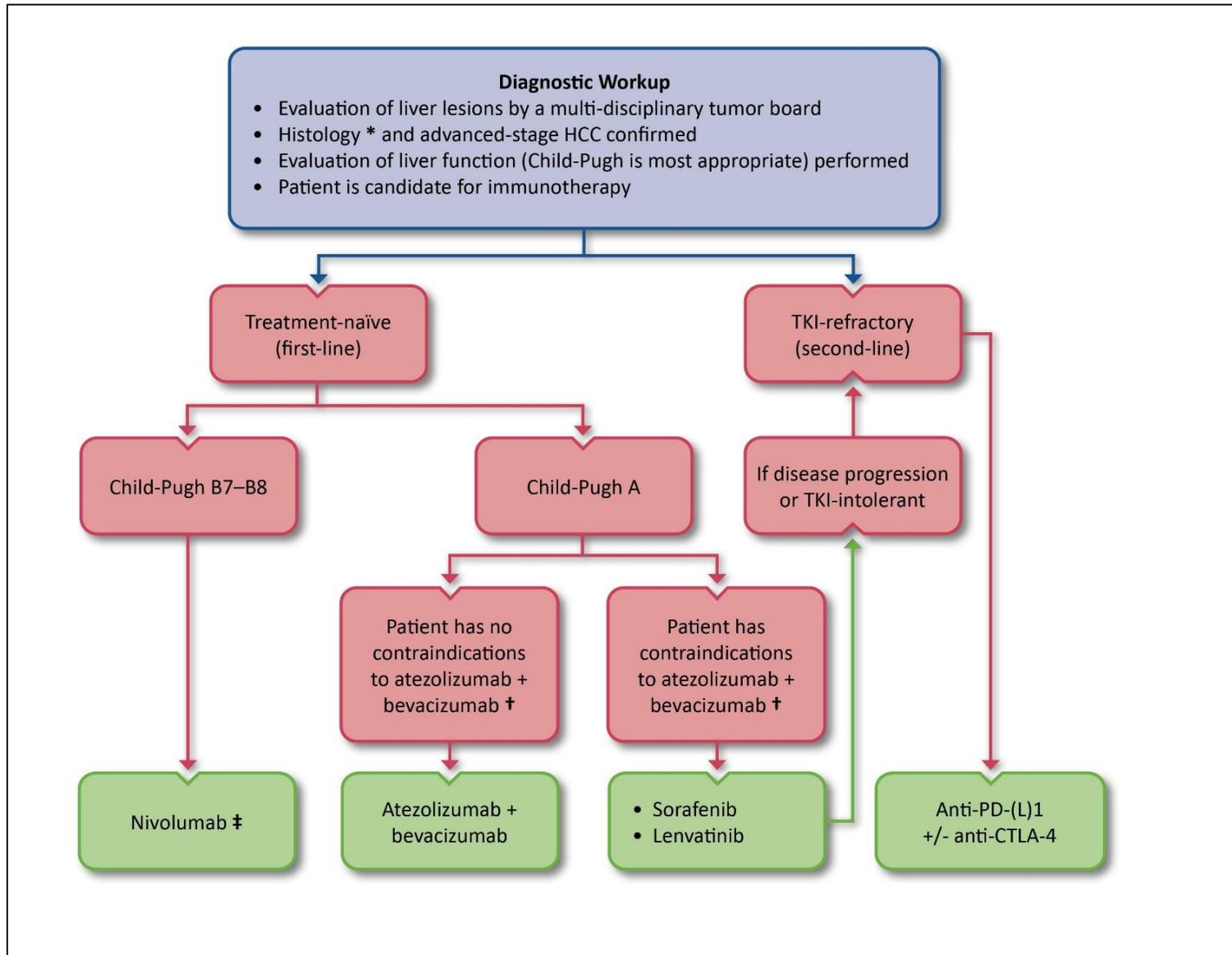
- First-line immunotherapy for HCC
  - Atezolizumab + bevacizumab: for patients with unresectable or metastatic HCC who have not received prior systemic therapy
- Second-line and later immunotherapy for HCC
  - Nivolumab + ipilimumab: for patients with HCC who have previously been treated with Sorafenib
  - Pembrolizumab monotherapy: for patients with HCC who have previously been treated with sorafenib

# Expert Panel recommendations

## Immunotherapy for the treatment of HCC

- For first-line treatment of patients with advanced Child-Pugh A HCC, atezolizumab plus bevacizumab is recommended, unless either medication is contraindicated (LE: 2).
- General contraindications to bevacizumab include high risk of cardiac disease, stroke, hemorrhage, hemoptysis, gastrointestinal perforation, or non-healing wounds (LE: 1). Consideration should be given to timing of prior events. Additional contraindications specifically relevant to HCC include untreated or incompletely treated gastroesophageal varices at risk for bleeding (LE: 2).
- For patients with contraindications to atezolizumab plus bevacizumab treatment, lenvatinib or sorafenib should be considered as standard first-line therapy (LE: 2).
- Nivolumab monotherapy has demonstrated activity in Child-Pugh B7-B8 HCC for both first-line treatment of sorafenib-naïve patients and for second-line treatment of patients who were intolerant to or progressed on sorafenib (LE: 3).
- For patients with good performance status who have progressed on first-line therapy and have not received prior immunotherapy, other non FDA-approved or conditionally approved anti-PD-1 checkpoint inhibitors may be considered as immunotherapeutic options (LE: 3).

# HCC Immunotherapy treatment algorithm\*



\* Updated since guideline publication

# Expert Panel recommendations

## Emerging biomarkers and immunotherapy strategies

- Clinicians should encourage patients' participation in clinical trials.
- Future biomarker development might help to select a subgroup of patients benefitting from single-agent nivolumab treatment. Designing a biomarker strategy based on pretreatment and on-treatment tissue and blood samples to assess immune cell changes and other correlatives is critical to elucidate mechanisms of response or resistance to immunotherapy in combination with local therapy in early-stage HCC.
- Studies evaluating combinations of other immunotherapies with ICIs should be based on solid scientific rationale.

# Emerging biomarkers approaches

- While there is an urgent need in this area, no biomarkers predictive of benefit with ICIs are routinely used at this time
- Biomarkers in development
  - Alpha-fetoprotein (AFP)
  - Glypican 3 (GPC3)
  - Tumor infiltrating immune cells
    - M2 tumor-associated macrophages (TAMs)
  - Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR)
  - PD-L1 expression
  - Gut microbiota

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# Expert Panel recommendations

## Immunotherapy in early-stage disease

- For patients with advanced-stage HCC and for patients with earlier-stage disease where liver-directed therapies are not considered appropriate or who have progressed after liver-directed therapy, the data at present supports first-line and subsequent-line ICI therapy use (LE: 2). Further studies are needed to confirm the efficacy of immunotherapy in the curative setting (neoadjuvant/adjuvant/perioperative) or in conjunction with intra-arterial therapies.
- The panel recommends against the use of immunotherapy in the post-transplant setting (LE: 4) due to the high risk of graft failure, given known mechanisms of ICIs.
- Additional studies are needed to assess the potential risks and benefits of immunotherapy in the pretransplant setting.
- Future randomized studies to compare local therapy alone to local therapy combined with immunotherapy are essential to assess the expected synergy and favorable treatment outcome of the combination strategy.

# Key Takeaways

- HCC is a disease within a disease
- A complex interplay of liver disease and the tumor determine outcomes
- Underlying liver disease not only impacts assessment of toxicity and response to immunotherapy but also treatment decisions and sequencing of agents

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