Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

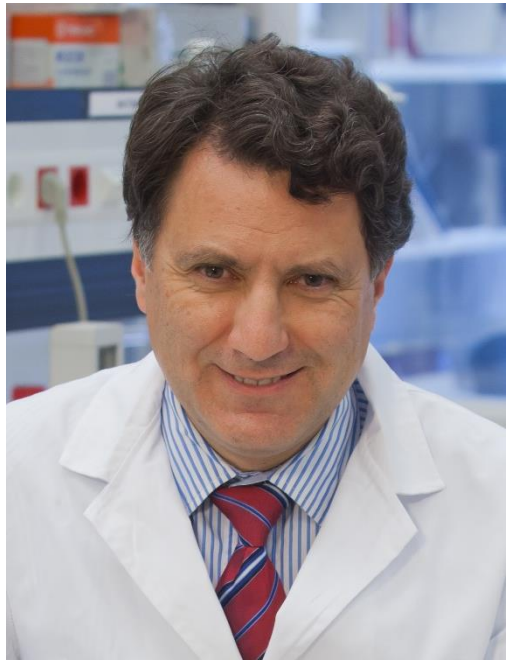
Immunotherapy for the Treatment of Hepatocellular Carcinoma

November 8, 2021

10 – 11 a.m. ET

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

Webinar faculty



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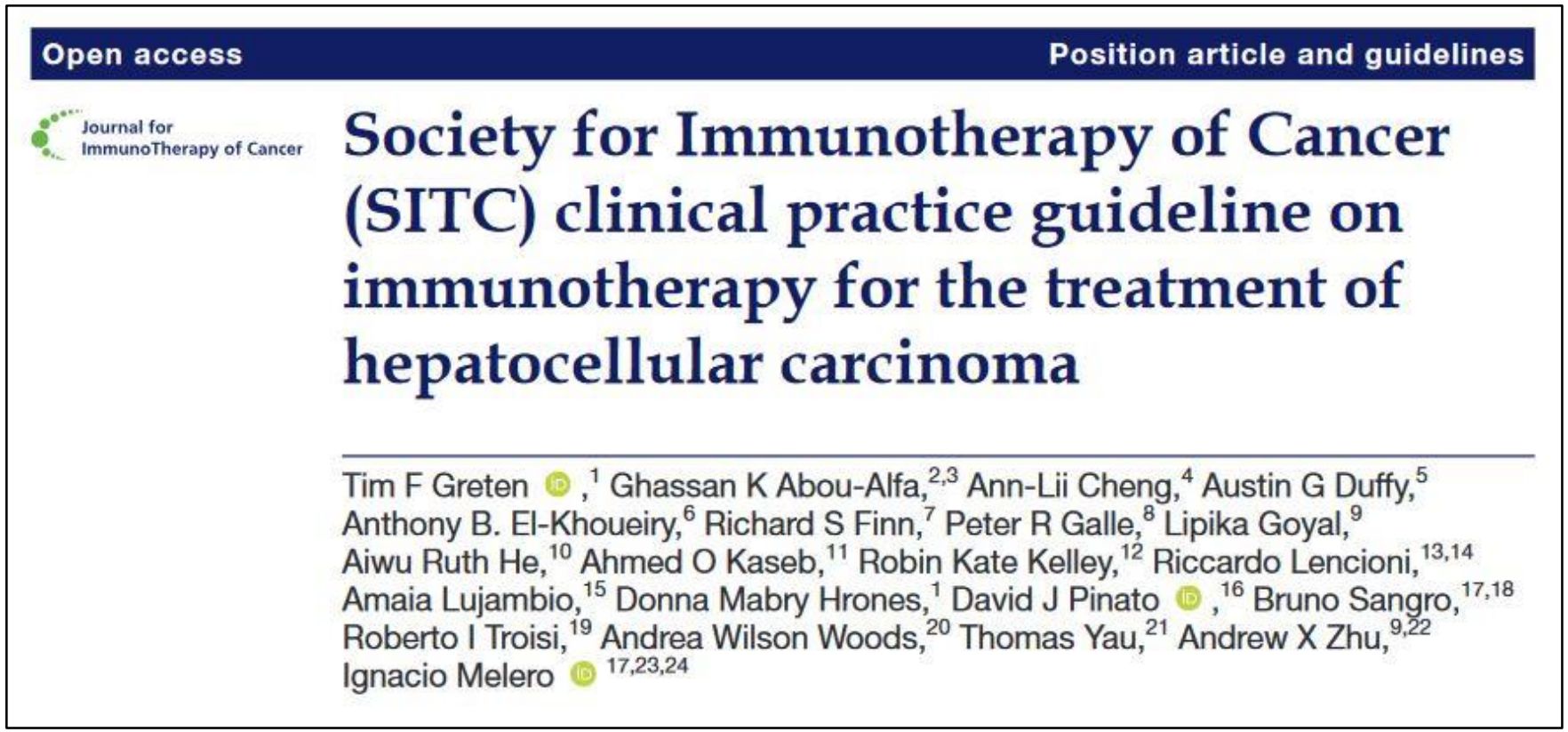
Learning objectives

- Select appropriate diagnostics and biomarker testing for a patient with HCC being considered for immunotherapy based on the expert panel recommendations in the SITC Clinical Practice Guideline (CPG)
- Implement immunotherapy treatments for HCC effectively and appropriately for according to the recommendations in the CPG
- Appraise patterns of response to immunotherapy in order to appropriately monitor and manage patients with HCC during treatment
- Describe considerations and available tools to assess and support patient quality of life during immunotherapy treatment for HCC

Webinar outline

- Guideline Development
- Diagnostics and staging
- Recommended immunotherapies
- Patient selection and response monitoring
- Quality of life support and patient education

Development of the Guideline



Open access 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

- Guideline Development
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Expert Panel recommendations on staging 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.

Expert Panel recommendations on staging for HCC

- 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.

Expert Panel recommendations on biomarker testing for HCC

- The panel recommends against the use of routine testing of biomarkers for predicting immunotherapy efficacy, which, at this point, remains exploratory

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Table 4 Landmark trials leading to FDA approvals for immunotherapy for HCC

Trial (NCT#)	Phase	Agent(s) evaluated	Study population	Patients	Outcomes
CheckMate 040 (NCT01658878)	I/II	Nivolumab*†	Patients with histologically confirmed advanced HCC with or without HCV or HBV infection. Previous sorafenib treatment was allowed. CP A or B7 disease for dose escalation; CP A disease for dose expansion.	262	ORR 20% (95% CI 15% to 26%) in dose-expansion phase ORR 14.3% (95% CI 6% to 28%) in population with progressive disease on/intolerance to sorafenib
KEYNOTE-224 (NCT02702414)	I	Pembrolizumab*	Patients with disease progression on or after sorafenib or intolerant to sorafenib, and measurable CP A disease.	104	ORR 17% (95% CI 11% to 26%)
CheckMate 040 (NCT01658878)	I/II	Nivolumab+ipilimumab*	Patients with histologically confirmed advanced HCC with or without HCV or HBV infection. Previous sorafenib treatment was allowed.	148	ORR 33% (95% CI 20% to 48%)
IMbrave150‡	III	Atezolizumab+ bevacizumab vs sorafenib	Patients with unresectable HCC who had received no prior systemic therapy and had well-compensated liver disease.	501	OS HR 0.58 (95% CI 0.42 to 0.79; p<0.001) ORR 27.3% vs 11.9% (p<0.001)

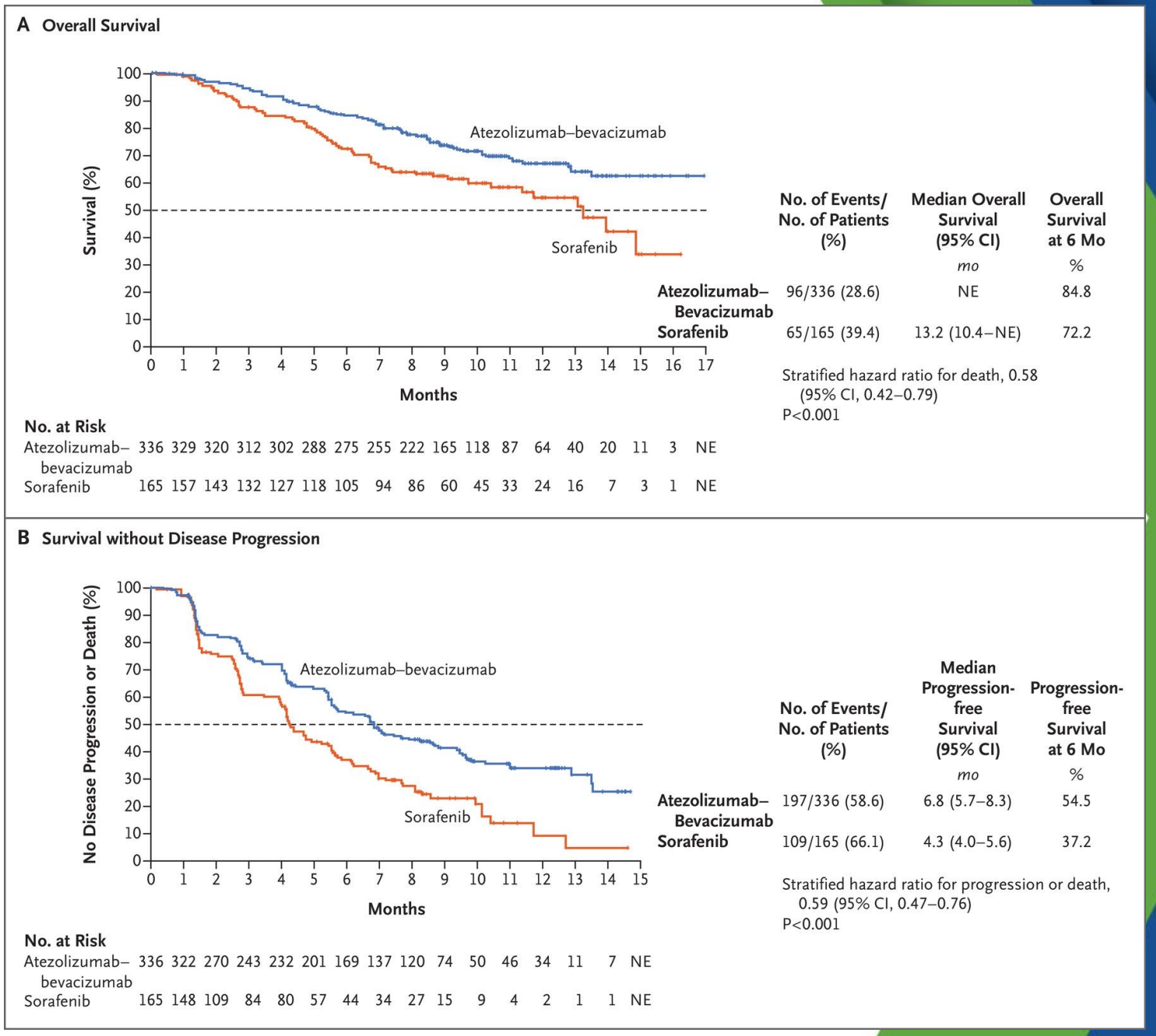
*Accelerated approval contingent on confirmatory trials
†Indication voluntarily withdrawn July 2021
‡Updated data with 12 additional months of follow-up found ORR of 29.8% (95% CI 24.8% to 35.0%) for atezolizumab+bevacizumab versus 11.3% (95% CI 6.9% to 17.3%) for sorafenib[66]
CI, confidence interval; CP, Child-Pugh; FDA, US Food and Drug Administration; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ORR, overall response rate; OS, overall survival.

Greten TF, et al. JITC 2021;9:e002794.

Expert Panel recommendations on first-line immunotherapy treatment for 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).

Overall and Progression-Free Survival with First-Line Atezolizumab + Bevacizumab in IMbrave150



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

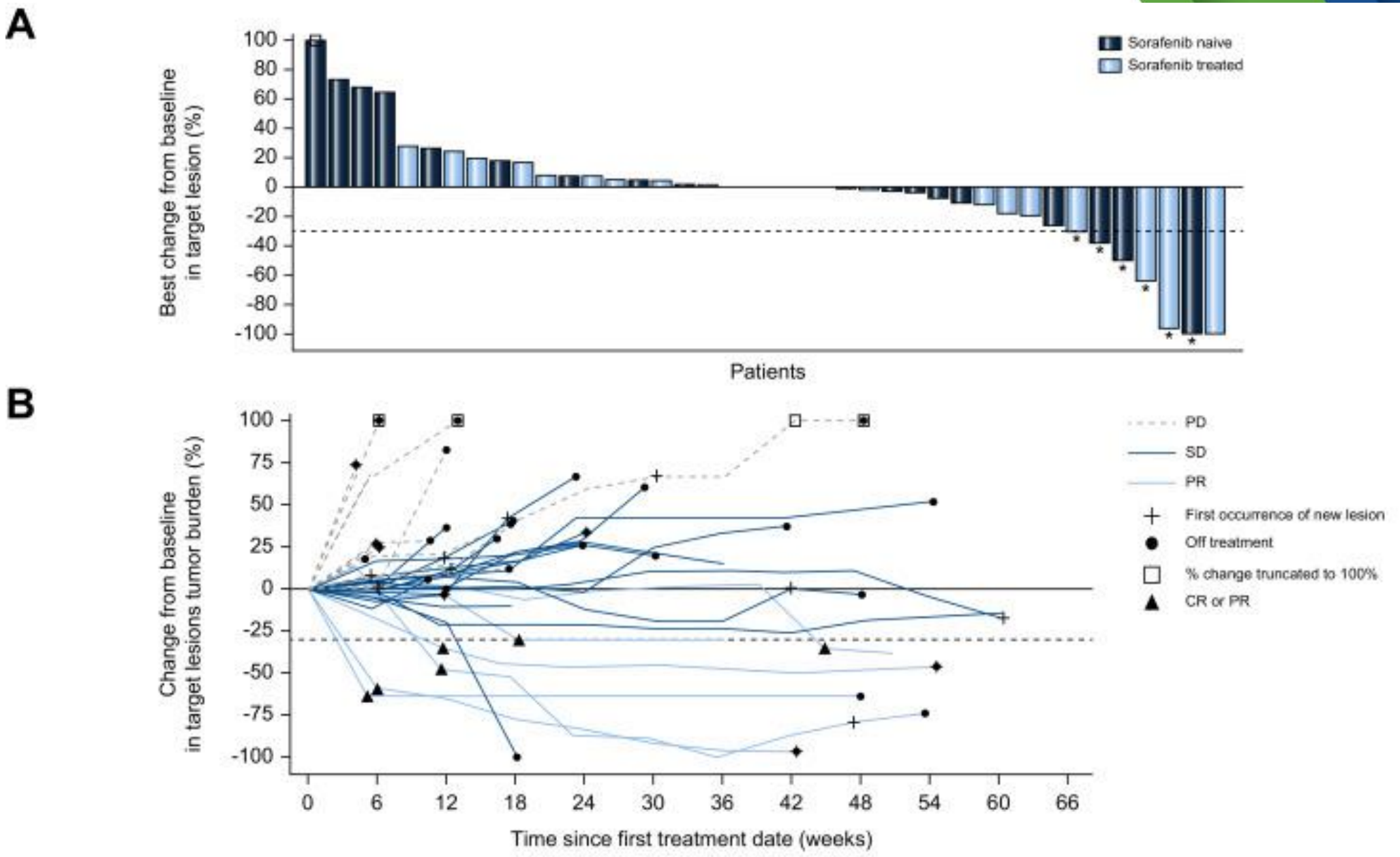
Expert Panel recommendations for patients with contraindications to atezolizumab + bevacizumab

- 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).

Efficacy of single-agent nivolumab for Child Pugh B7-B8 HCC

	Child-Pugh B			Child-Pugh A*
	Sorafenib naive (n=25)	Sorafenib treated (n=24)	All patients (n=49)	Cohorts 1 and 2 (n=262)
Objective response using RECIST v1.1, n (%)	3 (12)	3 (13)	6 (12)	53 (20)
95% CI	3–31	3–32	5–25	16–26
Best overall response				
Complete response, n (%) [95% CI]	0 [0–14]	0 [0–14]	0 [0–7]	8 (3) [1–6]
Partial response, n (%) [95% CI]	3 (12) [3–31]	3 (13) [3–32]	6 (12) [5–25]	45 (17) [13–22]
Stable disease, n (%)	12 (48)	9 (38)	21 (43)	107 (41)
Progressive disease, n (%)	7 (28)	8 (33)	15 (31)	88 (34)
Unable to determine, n (%)	3 (12)	4 (17)	7 (14)	14 (5)
Disease control rate, n (%) [95% CI]	15 (60) [39–79]	12 (50) [29–71]	27 (55) [40–69]	160 (61) [55–67]
Time to response, months				
Median	2.7	1.4	2.7	2.7
Range	2.7–10.3	1.2–4.2	1.2–10.3	1.2–16.4
IQR	2.7–10.3	1.2–4.2	1.4–4.2	1.4–4.1
Median duration of response, months	9.8	9.9	9.9	12.4
Range	1.4+ to 9.9	4.2+ to 9.9	1.4+ to 9.9	2.8 to 51.1+
95% CI	9.7–9.9	Not applicable	9.7–9.9	9.4–18.7

Kudo M, et al. J Hep 2021; 75(3):600-609



Kudo M, et al. J Hep 2021; 75(3):600-609

FDA ODAC review of checkpoint inhibitors for HCC: PEMBROLIZUMAB

On April 29, 2021, FDA ODAC voted 8 to 0 in favor of maintaining the accelerated approval of pembrolizumab for patients with HCC who have previously been treated with sorafenib.

Sponsor Position:

- Pembrolizumab monotherapy represents an important option for the significant proportion of patients with HCC who cannot receive first-line bevacizumab and whose disease progresses after sorafenib
- The incremental benefit of second-line pembrolizumab is analogous to the approved second-line TKIs, and the toxicities associated with pembrolizumab monotherapy are largely manageable
- Durable responses seen with pembrolizumab monotherapy are clinically meaningful

FDA Position:

- ORR with pembrolizumab monotherapy was low in the registration trial KEYNOTE-244 and the confirmatory trial KEYNOTE-240
- Recognizing that the bevacizumab-ineligible population represents a significant unmet need, patients at high risk for bleeding with bevacizumab were not included in KEYNOTE-244 and KEYNOTE-240

Public Comment:

- HCC is associated with very poor prognosis and significant unmet need, especially for the patients with poor underlying liver function or who cannot receive first-line atezolizumab + bevacizumab due to bleeding risk
- Removing options for second-line therapies is not in the best interest of patients with HCC

FDA ODAC review of checkpoint inhibitors for HCC: NIVOLUMAB*

In a 4 to 5 vote, ODAC recommended rescinding the indication for nivolumab for the treatment of patients with HCC and prior sorafenib therapy.

Sponsor Position:

- Nivolumab fills an unmet medical need for the patients who cannot receive bevacizumab in the first-line and whose disease progresses after TKI therapy
- Nivolumab monotherapy is well-tolerated in patients with HCC and associated with fewer toxicities than the ipilimumab-containing combination regimen
- Exploratory analyses in CheckMate 459 favor benefit for healthcare-related quality of life with nivolumab
- Delayed benefit was seen at longer follow-up in CheckMate 459, possibly due to subsequent systemic therapy use in sorafenib arm, including immunotherapy

Public Comment:

- Nivolumab monotherapy is an important option for many HCC patients, especially given the increased potential for toxicity with ipilimumab-containing combinations
- The safety and adverse event profile of nivolumab is favorable compared to other available second-line therapies for HCC

FDA Position:

- Availability of first-line atezolizumab + bevacizumab (in addition to other second-line options, including combination ipilimumab + nivolumab) has changed the HCC treatment landscape
- Statistically significant OS benefit with nivolumab monotherapy was not shown in the designated confirmatory trial, CheckMate 459
- Alternative confirmatory trials CheckMate 9DX (adjuvant nivolumab) and CheckMate 9DW (first-line ipilimumab + nivolumab) will not provide evidence for benefit with second-line monotherapy
- Data are lacking on efficacy of the monotherapy in the population of patients who cannot tolerate first-line bevacizumab as well as those deemed ineligible for other second-line therapies, such as ipilimumab + nivolumab

***In July 2021, the nivolumab monotherapy indication for HCC was voluntarily withdrawn.**

Expert Panel recommendations on second-line and later immunotherapy options for HCC

- 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).

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Expert Panel recommendations on patient selection for immunotherapy

- 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.
- In patients with HCC with cirrhosis, the data supports the use of immunotherapy in patients with underlying synthetic liver function consistent with well-compensated cirrhosis, specifically Child-Pugh A (LE: 2). The panel recognizes, however, that some **carefully selected patients with Child-Pugh B** may derive benefit (LE: 3).
- Patients who have contraindications for the use of TKIs or anti-VEGF therapies (eg, cardiovascular comorbidities) may be suitable for anti-PD-1 monotherapy (LE: 1).

Expert Panel recommendations on special patient populations

- The panel agrees that patients can be considered for immunotherapy treatment **irrespective of hepatitis viral etiology** (LE: 3), though it is strongly recommended that patients with HBV be on concomitant antiviral medication and adherent.
- While patients living with **HIV** have not been included in clinical trials to date, the panel believes that this **is not an absolute contraindication** to treatment with immunotherapy as long as the appropriate HIV therapy is instituted as per expert guidance (LE: 2), while further dedicated studies to assess such therapies in patients living with HIV remain critical.
- Historical disparities in access to clinical trial participation for underrepresented groups should be considered, with **efforts made to support diversity, equity, and inclusion**.

Expert Panel recommendations on response monitoring for immunotherapy for HCC

- Limited data are available concerning the value of **mRECIST** and immune-related RECIST (**irRECIST**) criteria in the setting of HCC response assessment, especially in the context of ICI therapy. **Further studies are needed** to compare outcomes between patients with response to treatment by mRECIST versus irRECIST.
- Caution should be exercised in translating response assessment models developed for clinical trials into clinical practice.

Expert Panel recommendations on atypical patterns of response to immunotherapy

- Pseudoprogression, while a real phenomenon, occurs rarely (LE: 4). **A comprehensive assessment is encouraged**. In published trials, treatment beyond progression has been allowed.
- Hyperprogression may occur (LE: 4). It is uncommon, cannot be anticipated, and remains poorly understood.

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Expert Panel recommendations on patient education

- Patients must know which provider is coordinating their treatment, and they need to have **clear instructions** to promptly report any signs or symptoms of potential immune-related toxicities.
- 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.

Call parameters for patients with HCC being treated with immunotherapy

You should contact your healthcare providers for any of the following symptoms (or call 911 or seek emergency services as indicated)*:

- Abdominal pain
- Change in stool (blood or mucus in stool, change in color, light or clay colored)
- Increase in bowel movements, >3 movements above a patient's baseline
- Diarrhea, >3 watery stools
- Nausea or vomiting
- Jaundice (yellowish skin color)
- Difficulty breathing, shortness of breath, or chest tightness
- New non-productive dry cough
- Mental status changes
- New visual disturbances
- Headache
- New or worsening fatigue
- Fever with temperature >100.4°F (38°C)
- New weakness, muscle or joint pains
- Unintentional weight loss >3 lbs (1.5 kg)
- Significant weight gain with obvious abdominal swelling
- Rash which may or may not be accompanied by tenderness or itching

*Note to providers: Call parameters for patients highlight the following conditions: colitis, pneumonitis, endocrinopathies, dermatologic toxicities. It should be noted that many conditions have overlapping symptoms.

Greten TF, et al. JITC 2021;9:e002794.

Expert Panel recommendations on QOL support

- Assessment of patients' **physical function and symptoms** should be performed before, during, and after therapy.
- Patients should be referred to a **treatment team** including a social worker and a financial manager to assist in navigating healthcare costs and identifying support systems.
- Conversations should be initiated with patients about how the **costs** of immunotherapy treatment will be covered, including contributions from private insurance, Medicare and Medicaid, clinical trials, patient assistance programs, or compassionate use as needed.
- Patients should be provided information about local advocacy and **support groups specific to primary liver cancer**.

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Cancer Immunotherapy GUIDELINES

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https://www.sitcancer.org/CPG-webinars

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December 6, 2021, 5:30 – 6:30 p.m. ET

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November 15, 2021, 11:30 a.m. – 12:30 p.m. ET

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