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Multidisciplinary Perspectives in Advanced HCC:

A Focus on Immune Checkpoint Inhibitors

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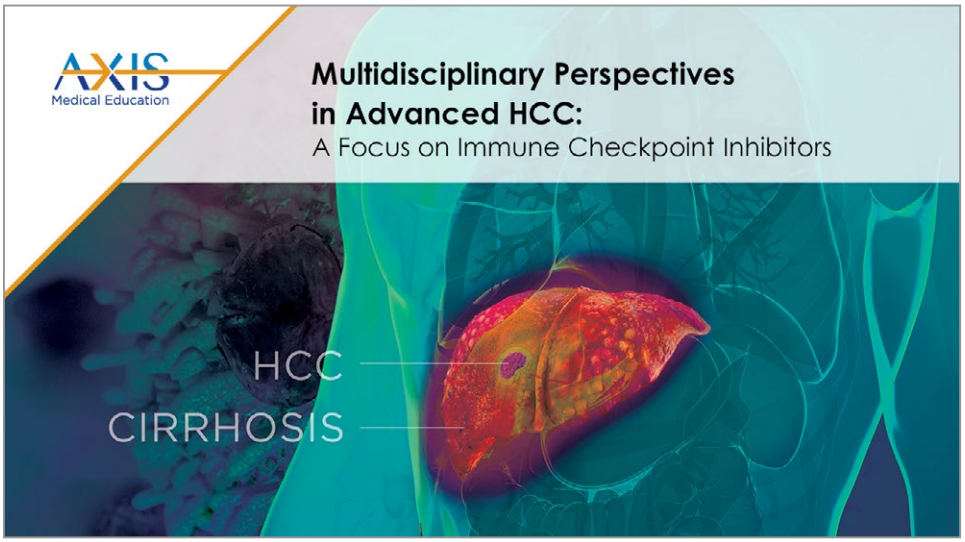
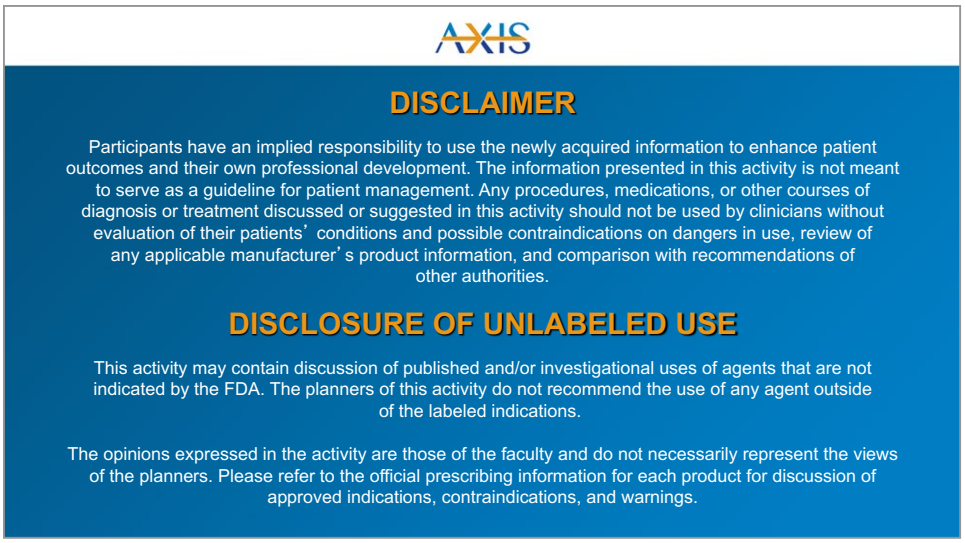
Multidisciplinary Perspectives in Advanced HCC: A Focus on Immune Checkpoint Inhibitors

Richard Finn, MD and Amit Singal, MD, MS

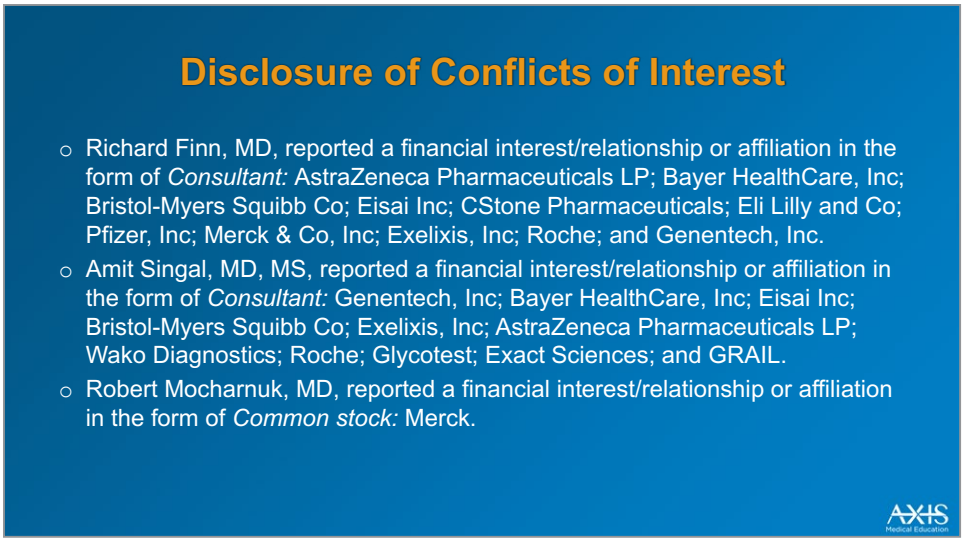


Robert Mocharnuk, MD: Hello, and welcome to this educational activity entitled, Multidisciplinary Perspectives in Advanced Hepatocellular Carcinoma, a Focus on Immune Checkpoint Inhibitors.

I am Dr. Robert Mocharnuk, Emeritus Professor of Clinical Medicine. I am joined today by Dr. Richard Finn, Professor of Medicine in the Division of Hematology/Oncology at the Geffen School of Medicine at UCLA, in Los Angeles; and Dr. Amit Singal, Professor of Medicine and Medical Director of the Liver Tumor Program at the University of Texas Southwestern Medical Center, in Dallas.



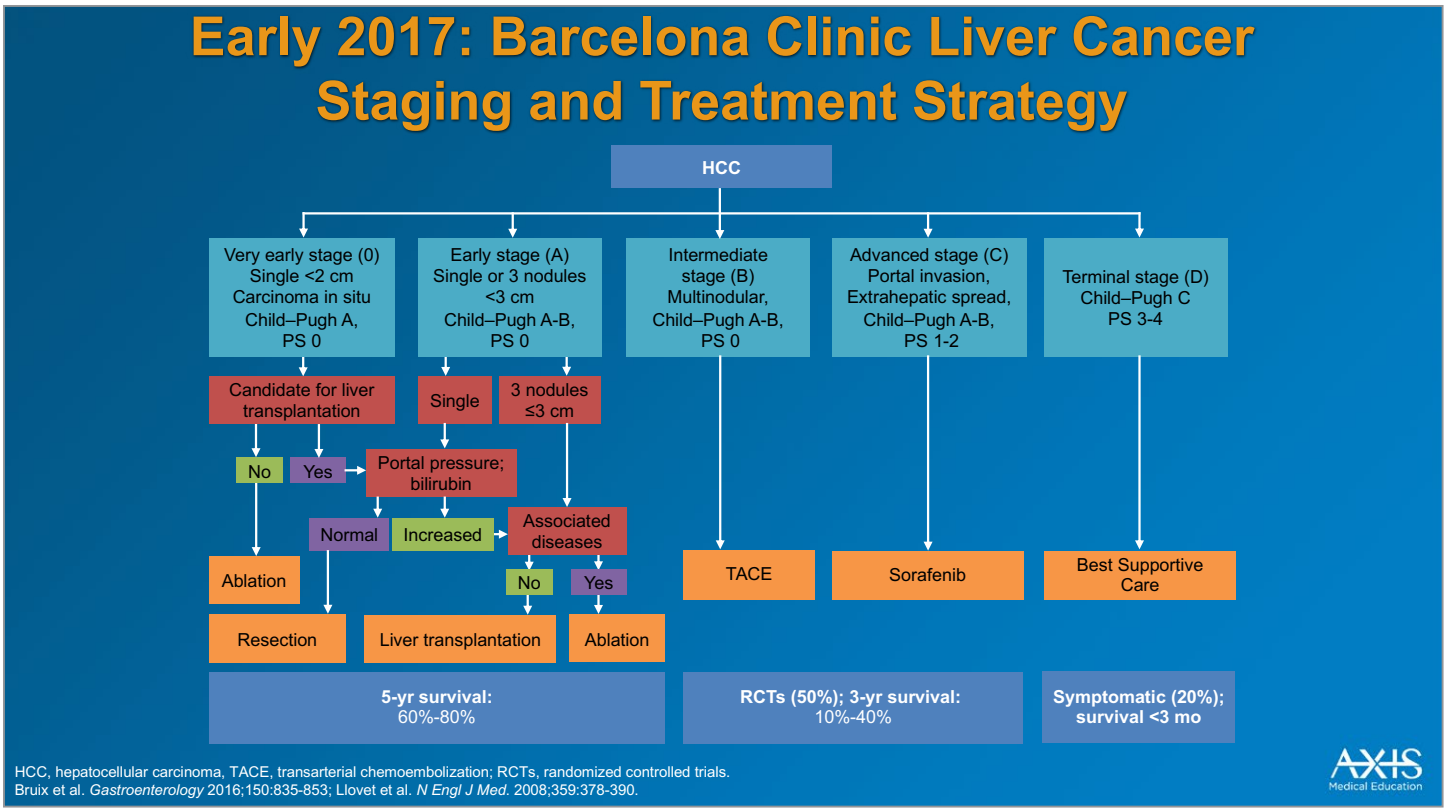
- Here is a disclaimer and disclosure indicating that we may be discussing off-label usage of approved agents or agents that are in development.



- Here is our financial disclosure information.

- Here are the learning objectives for this activity. Today we will review and evaluate the most recent clinical data and treatment recommendations, as well as providing expert insights on the use and management of immune checkpoint inhibitors for the treatment of advanced hepatocellular carcinoma (HCC).

- Let's start by discussing the current hepatocellular carcinoma treatment landscape. Dr. Finn, would you tell us what the treatment options are for advanced HCC, and why immunotherapy is so active in the treatment of HCC?

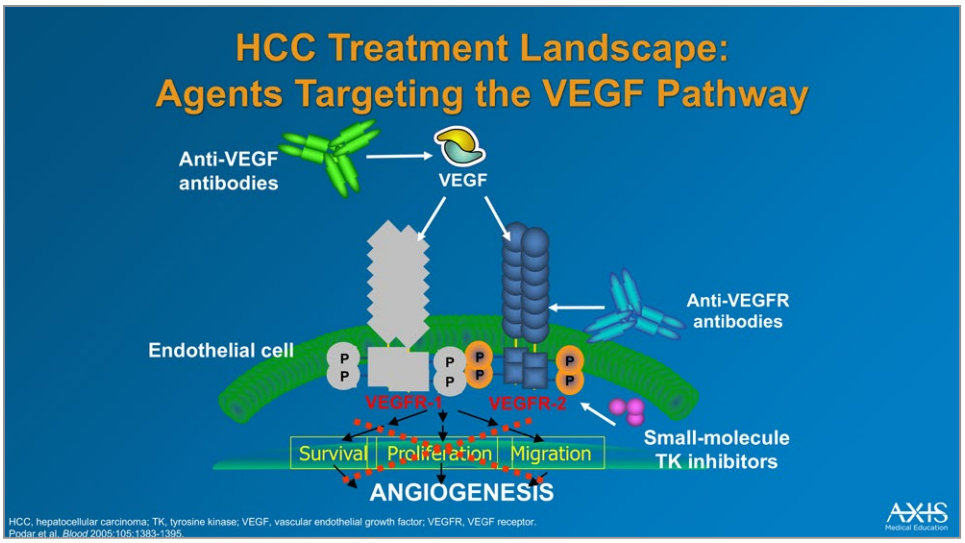


Richard Finn, MD: So when we think about systemic treatment of advanced liver cancer, we're really discussing the group of patients who, by the Barcelona or BCLC staging system, fall into the intermediate stage B or advanced stage C group. The Barcelona staging system is important in our assessment of patients with liver cancer because it takes into account the 2 competing risks for outcome. Specifically death—and that involves liver characteristics or liver physiology, the extent of their cirrhosis and its effect on their performance status, as well as tumor burden.

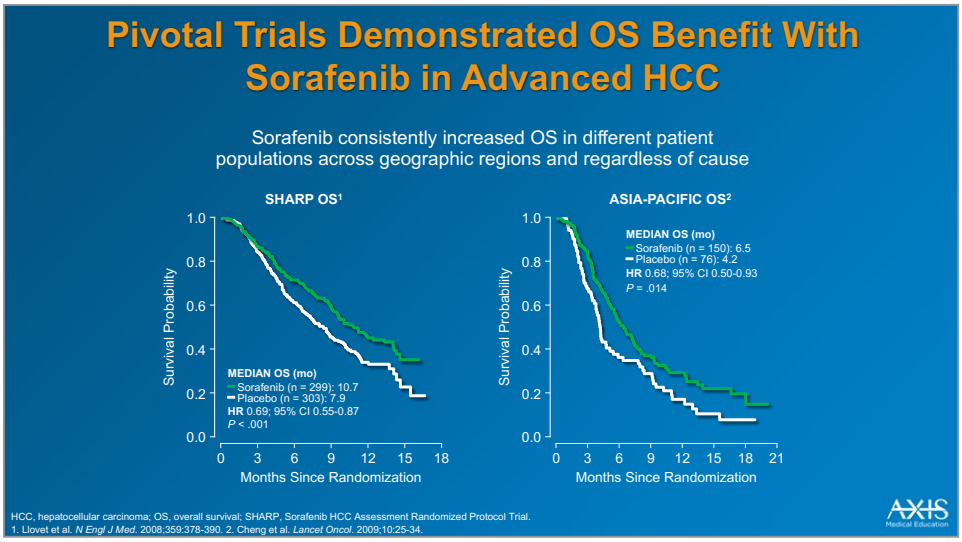
When we look at the BCLC, we see it exists with 5 stages, which on one side is the stage D patients who have very advanced decompensated liver disease. And these patients generally should be considered for supportive care because they're Child-Pugh C, they have ascites, elevated bilirubin, and poor performance status. The caveat is some patients will have a small enough tumor burden that they could be considered for liver transplant, which would be curative.

And on the other side—on the extremes—are those patients with earlier stage disease, who, if they have well-compensated liver function, can be considered for surgical resection. Or, which would be more likely the case in the United States, is that there are patients who have some evidence of portal hypertension or some medical contraindication to surgery, and these patients might receive local ablation with either microwave or radiofrequency ablation and eventually get listed for liver transplantation.

The majority of patients we see are this intermediate B or advanced stage C. In liver cancer, you can have advanced liver cancer and be a candidate for systemic treatment without having tumor outside the liver. This is for patients who have intermediate disease, who have received chemoembolization, but their tumor is progressing, despite transarterial chemoembolization, and it's progressing within the liver. Or vascular invasion develops. On imaging, they have tumor invading into the portal vasculature—either within or outside the liver—and this would also be considered a characteristic of advanced disease or a patient with metastatic spread.



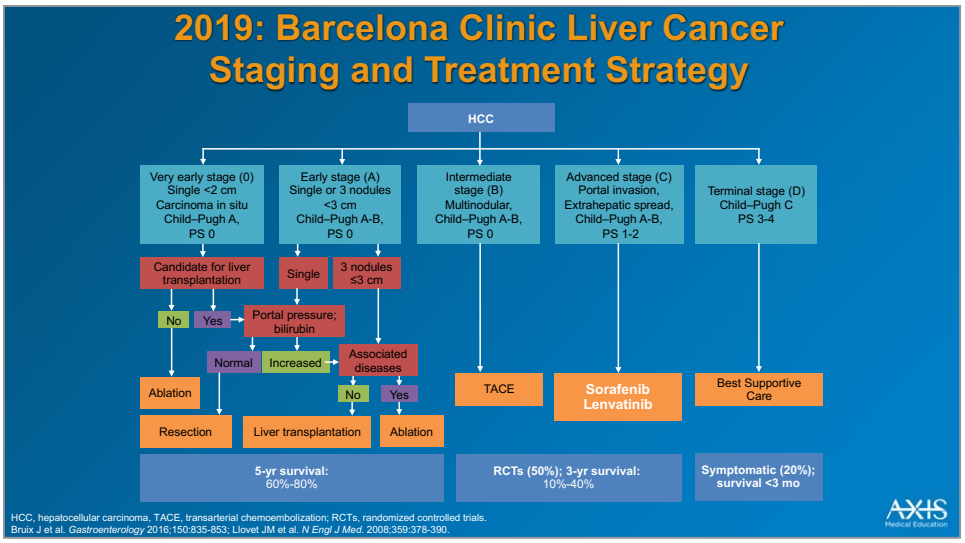
- Until 2017, the standard of care for these patients was sorafenib. And that's been changing. As we all know, there's a lot of interest in targeting the VEGF access in cancer medicine, and there are several ways to do that. There are monoclonal antibodies to the VEGF ligand such as bevacizumab. There are antibodies against the VEGF receptor such as ramucirumab—both of these are approved in various indications in liver cancer. For many years, the backbone of drug development has been small molecule inhibitors of the VEGF receptor kinase, as well as other intracellular kinases.



- The pivotal studies with sorafenib were done over a decade ago in the North American and European cohort, the SHARP study, and then a separate cohort done in Asia. Both of these studies came to the same conclusion—that compared to placebo, sorafenib improved overall survival both by the same hazard ratio, 0.69 or 0.68 in Asia, and that's an over 30% decrease in the risk for death.

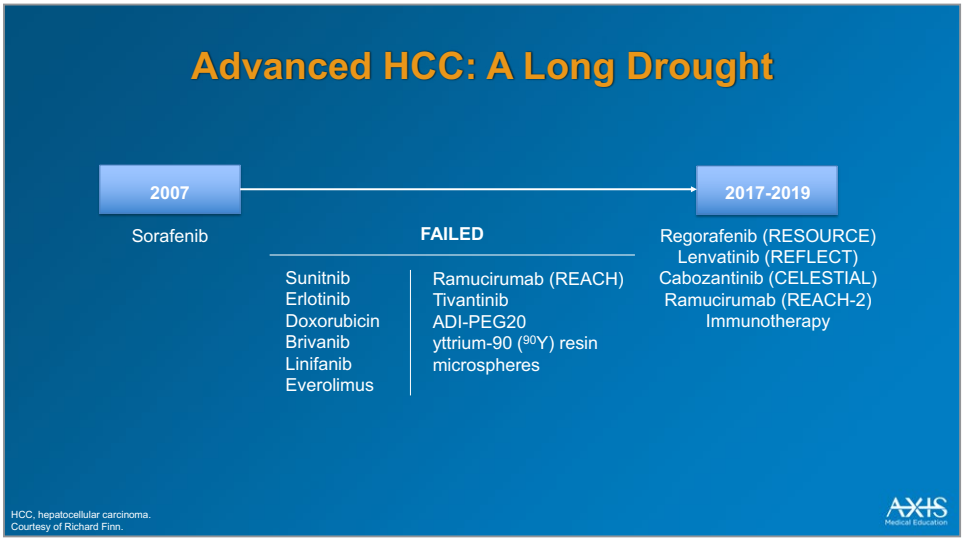
This was thought to be low-hanging fruit. To beat placebo appeared to be an easy thing.

With that being said, sorafenib was the first drug to do that. This year, 2020, heralded a regimen that actually beat sorafenib in terms of overall survival. What we learned from the sorafenib studies is that we can improve survival without inducing objective responses. That is to say sorafenib was cytostatic, it could generally slow progression, and it does have a side effect profile that was tolerable in this group of patients, 90% of whom have underling liver disease, that is, some degree of cirrhosis. All the patients accrued to liver cancer studies are Child-Pugh A, by design, to limit the effect of the underlying liver disease for the outcomes. Typically the primary outcome is always overall survival.



- Lenvatinib was approved in the frontline setting based on the REFLECT study, which was a noninferiority study that showed that lenvatinib, a potent VEGF receptor and FGFR receptor multikinase inhibitor, had a survival that was noninferior to sorafenib.

  Although the overall survival was noninferior, lenvatinib did improve response rates and significantly improved progression-free survival. In 2018, we had 2 options in frontline liver cancer, and a number of agents were being approved at the same time in second line after progression on sorafenib.



- There have been numerous failures over this decade from 2007 to 2017. In the past 3 years, we've seen a dramatic increase of drugs approved. Currently we have 9 different regimens approved in the United States to treat advanced liver cancer. That includes regorafenib, the first drug approved after sorafenib, and was the first drug approved in second line. We talked about lenvatinib. Cabozantinib, another small molecule VEGF cMET and axal inhibitor that was approved in second line.

  Ramucirumab, which initially failed in its second-line study, was then approved based on a repeat study focusing on this high alpha fetoprotein population. And then we've had a number of immunotherapy approvals—mostly accelerated approvals—but more recently, the approval of atezolizumab and bevacizumab in the frontline based on a positive phase 3 study.

NCCN Guidelines®: Systemic Therapy

Version 5.2020 – August 4, 2020

First-Line Therapy	Subsequent-Line Therapy if Disease Progression
Preferred Regimens • Sorafenib (Child-Pugh Class A or B7) • Lenvatinib (Child-Pugh Class A only) • Atezolizumab + bevacizumab (Child-Pugh Class A only)	• Regorafenib (Child-Pugh Class A only; category 1) • Cabozantinib (Child-Pugh Class A only; category 1) • Ramucirumab (AFP ≥400 ng/mL only; category 1) • Lenvatinib (Child-Pugh Class A only) • Nivolumab (Child-Pugh Class A or B) • Nivolumab + ipilimumab (Child-Pugh Class A only) • Sorafenib (Child-Pugh Class A or B7) • Pembrolizumab (Child-Pugh Class A only)
Useful in Certain Circumstances • Nivolumab (ineligible for TKI or other anti-angiogenic agents) • FOLFOX	

AFP, alpha fetoprotein; FOLFOX, fluorouracil, leucovorin, oxaliplatin; TKI, tyrosine kinase inhibitor.
Benson et al. NCCN Guidelines Hepatobiliary Cancers. Version 5.2020. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

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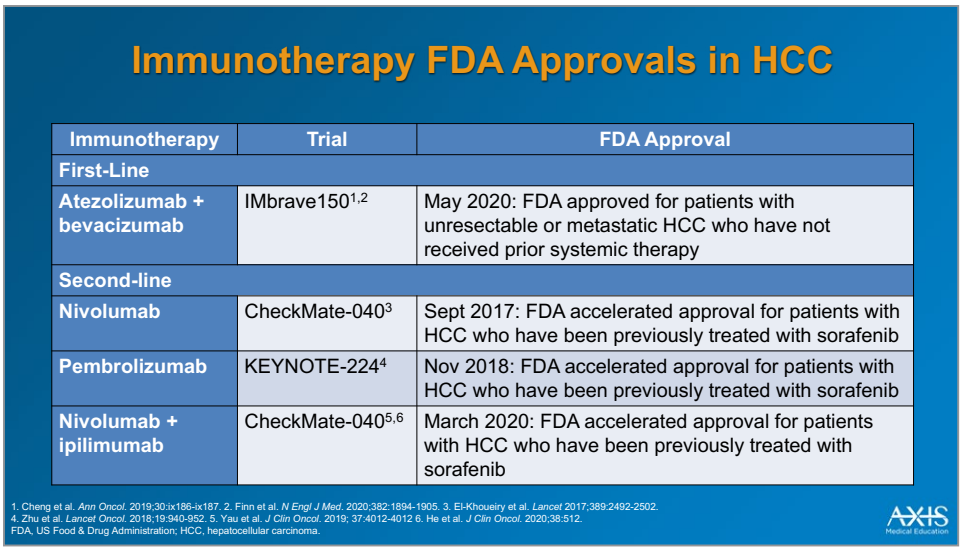
Here we see the NCCN Guidelines for system treatment. And most of these are supported by high level of evidence category 1. And in the frontline, sorafenib, lenvatinib, atezolizumab, and bevacizumab. Keep in mind that while these studies were only done in Child-Pugh A patients, many of our patients we see in the clinic will not be Child-Pugh A, they will not be clinical trial candidates. We need to adapt these data to best manage our patients.

The same thing can be said about second-line drugs. All of the second-line studies done to date have always followed sorafenib. So, then comes along lenvatinib and then, more recently, atezolizumab and bevacizumab—this is significant progress we're making. So, I don't think we necessarily throw out all the data we learned in the prior sorafenib era, but really say that we've proven that these drugs are anti-liver cancer drugs and figure out how best to sequence them in the clinic.

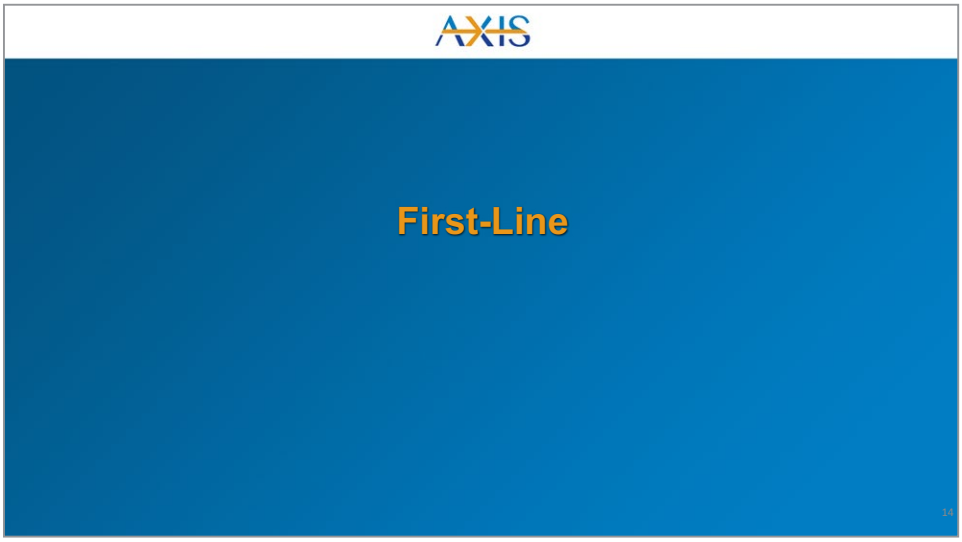
Interestingly, the NCCN Guidelines include nivolumab as a single agent, and I say in certain circumstances and specifically those patients who are not candidates for a TKI or for patients who cannot receive other antiangiogenic agents, and presumably this means bevacizumab. Nivolumab was approved on an accelerated basis for second-line liver cancer. Whereas in the frontline, it did not meet its endpoint versus sorafenib. But certainly the drug does have single-agent activity in a subset of patients. And survival in the phase 3 study with nivolumab, for that arm of the study, was 16 months. This may be something to consider, although we can't say there's high-level evidence supporting that.

And FOLFOX chemotherapy really is not used in the West.

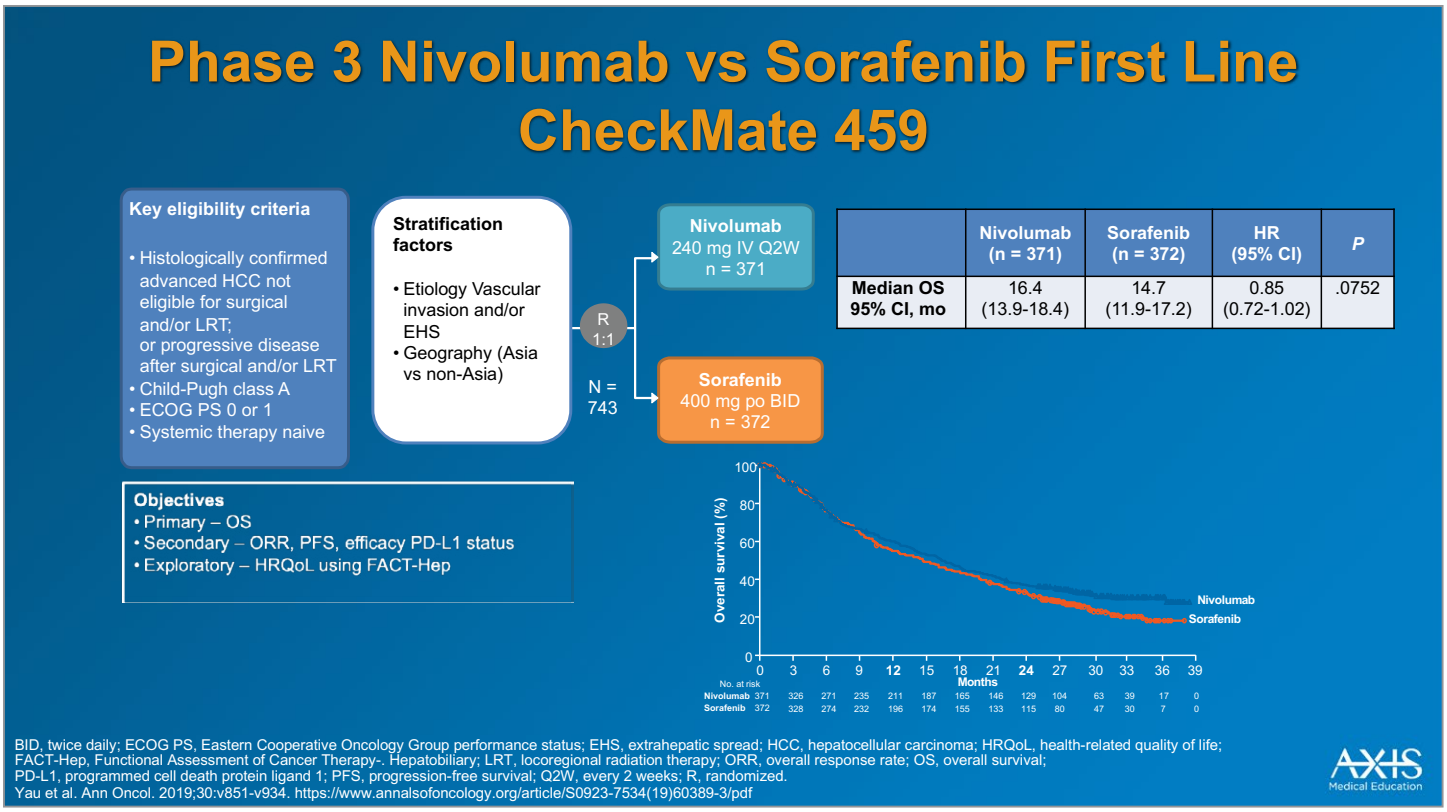


- Here we see the current immunotherapy approvals in liver cancer. The IMbrave150 study drove the approval of atezolizumab and bevacizumab because it was superior to sorafenib in overall survival, progression-free survival, as well as response rate and quality of life assessments. In second line, both nivolumab and pembrolizumab got accelerated approval based on single-arm phase 2 studies that showed response rates in the 15% to 20% range without any clear biomarker or clinical subgroup that benefited more or less.

  However, the phase 3 studies with these drugs didn't meet their endpoints. This year, nivolumab and ipilimumab were approved in second line based on accelerated approval. The phase 3 study of nivolumab and ipilimumab versus sorafenib is ongoing. We saw response rates with this combination of around 30%, though there were increased side effects. The need for steroids for autoimmune adverse events in this study was close to 50%.



- **Mocharnuk:** Thank you for that. Will you review the current and emerging immunotherapy options for the first-line treatment of HCC?



	Nivolumab (n = 371)	Sorafenib (n = 372)	HR (95% CI)	*P*
Median OS 95% CI, mo	16.4 (13.9-18.4)	14.7 (11.9-17.2)	0.85 (0.72-1.02)	.0752

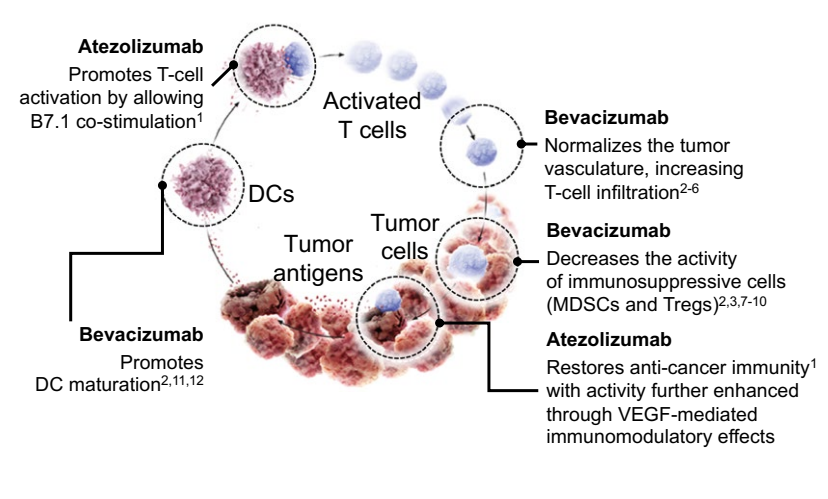
BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; FACT-Hep, Functional Assessment of Cancer Therapy-. Hepatobiliary; LRT, locoregional radiation therapy; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; R, randomized.
Yau et al. Ann Oncol. 2019;30:v851-v934. https://www.annalsofoncology.org/article/S0923-7534(19)60389-3/pdf

Finn: The phase 3 study, CheckMate 459, was to be the confirmatory study of nivolumab's activity in advanced liver cancer. This was an open-label study of nivolumab versus sorafenib in patients with Child-Pugh A liver function, good performance status with the primary endpoint of overall survival. This study was based on the phase 2 CheckMate 040 study, which again was the basis for the accelerated approval in second line.

The study did not meet its endpoint. Sorafenib had the longest survival we'd seen in a frontline liver cancer study of just under 15 months. Nivolumab also had the longest survival, at the time, that we had seen in a phase 3 liver cancer study with just over 16 months.

What was very interesting in this study is that we saw that close to 30% of the patients in the sorafenib arm with progression on sorafenib went on to receive immune checkpoint inhibitors or immunotherapy in the second-line setting. Now, the study did confirm the safety profile of nivolumab, and it also confirmed the response rate of nivolumab that we saw in the second-line setting, as a single agent.

Combining VEGF Inhibition and PD-1/PD-L1



- Bevacizumab (anti-VEGF) is an antiangiogenic agent with additional immunomodulatory effects
- In combination, bevacizumab may further enhance atezolizumab's efficacy by reversing VEGF-mediated immunosuppression to promote T-cell infiltration into the tumor

DC, dentritic cell; MDSCs, myeloid-derived suppressor cell; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.
1. Chen and Mellman. *Immunity* 2013;39:1-10. 2. Hegde et al. *Semin Cancer Biol*. 2018;52:117-124. 3. Wallin et al. *Nat Commun*. 2016;7:12624.
4. Goel et al. *Physiol Rev*. 2011;91:1071-1121. 5. Motz et al. *Nat Med*. 2014;20:607-615. 6. Hodi et al. *Cancer Immunol Res*. 2014;2:632-642.
7. Gabrilovich and Nagaraj. *Nat Rev Immunol*. 2009;9:162-174. 8. Roland et al. *PLoS One*. 2009;4:e7669. 9. Facciabene et al. *Nature* 2011;475:226-230.
10. Voron et al. *J Exp Med*. 2015;21:139-148. 11. Gabrilovich. *Nat Med*. 1996;2:1096-1103. 12. Oyama et al. *J Immunol*. 1998;160:1224-1232.
From Hsu et al. APASL 2019 Manila.

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▶ Now the interest for us, in research, has been to try to improve the response rate of single-agent immunotherapy. And that would require identifying a biomarker where we can enrich for the population of patients who get that benefit or look at combining immunotherapy with another target and mechanism of action. There's been a lot of interest in combining immunotherapy with VEGF inhibitors whether TKIs or antibodies. Our understanding of the mechanism of VEGF inhibition has grown scientifically, it's matured over time from when it was first approved with this idea that we can affect the flow of blood to a tumor and starve it of oxygen. And certainly, that is an important mechanism. However, as we've seen in some preclinical studies with bevacizumab, is that by normalizing the vasculature, you affect the immune infiltrate and microenvironment around the tumor. And you can actually promote a pro-immune antitumor environment, which with a drug like atezolizumab, can amplify that and therefore lead to more efficacy.

GO30140: Arm A Design
Atezolizumab + Bevacizumab

Advanced or metastatic and/or unresectable HCC

- No prior systemic therapy
- ECOG PS 0/1
- Child-Pugh **A-B7** (Arm A)

Arm A: unresectable or advanced HCC

Atezolizumab 1,200 mg IV q3w + bevacizumab 15 mg/kg IV q3w

(**n = 104**)

Arm F: randomized 1st-line HCC

Atezolizumab 1,200 mg IV q3w + bevacizumab 15 mg/kg IV q3w vs atezolizumab 1,200 mg IV q3w

Until disease progression, unacceptable toxicity or loss of clinical benefit

Primary endpoints	IRF-assessed ORR per RECIST v1.1 and safety
Key secondary endpoints	IRF-assessed ORR, DoR, PFS and TTRP per RECIST v1.1 (excl ORR) & HCC mRECIST
	INV-assessed ORR, DoR, PFS and TTRP per RECIST v1.1
	OS

Arm A: at clinical data cut-off (14 June 2019), 104 patients were evaluable with a **median follow-up of 12.4 months**

DoR, duration of response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; INV, investigator; IRF, independent review facility; mRECIST, modified Response Evaluation Criteria in Solid Tumours; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; TTRP, time to radiographic progression.
NCT02715531; Hsu et al. APASL 2019 Manila.

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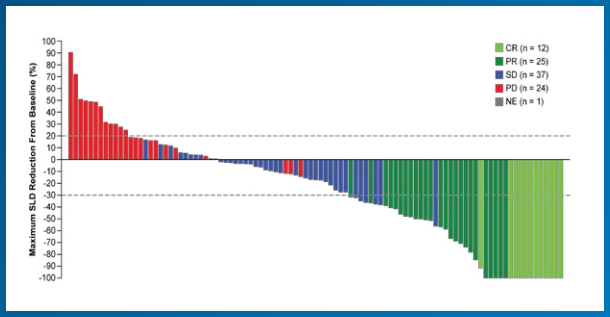
- There was initially a single-arm phase 1b/2 study of atezolizumab and bevacizumab. This study was a proof of concept type of study designed to assess safety. Very early on, there was a fairly high response rate seen with the combination of atezolizumab and bevacizumab in the single-arm component. And then, later on, there was a randomized component of atezolizumab and bevacizumab versus atezolizumab alone. And that confirmed the observation that the combination has a higher response rate in either drug alone.

  And if we go back, many of us, in the liver cancer space, for some time actually looked at bevacizumab in the early 2000s because we know liver cancer is a very hypervascular tumor. But there were some safety concerns, and there was not an overwhelming response with single-agent bevacizumab. By then, sorafenib was approved, and there were other drugs in this space. Bevacizumab never moved ahead into phase 3 trials until now in combination with atezolizumab.

GO30140: Arm A
Primary Efficacy Endpoint: ORR (IRF, R1.1)



Confirmed responses per IRF, R1.1, n (%)	(N = 104)
ORR 95% CI	37 (36) (26-46)
CR	12 (12)
PR	25 (24)
SD	37 (36)
DCR	74 (71)
PD	25 (24)

All CRs reached with systemic therapy only. Missing/unevaluable: 5 patients (5%), 99 patients showed on the plot Data cut-off: 14 June 2019
CR, complete response; DCR, disease control rate; IRF, independent review facility; ORR, objective response rate; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of the longest diameter.
NCT02715531; Hsu et al. APASL 2019 Manila.

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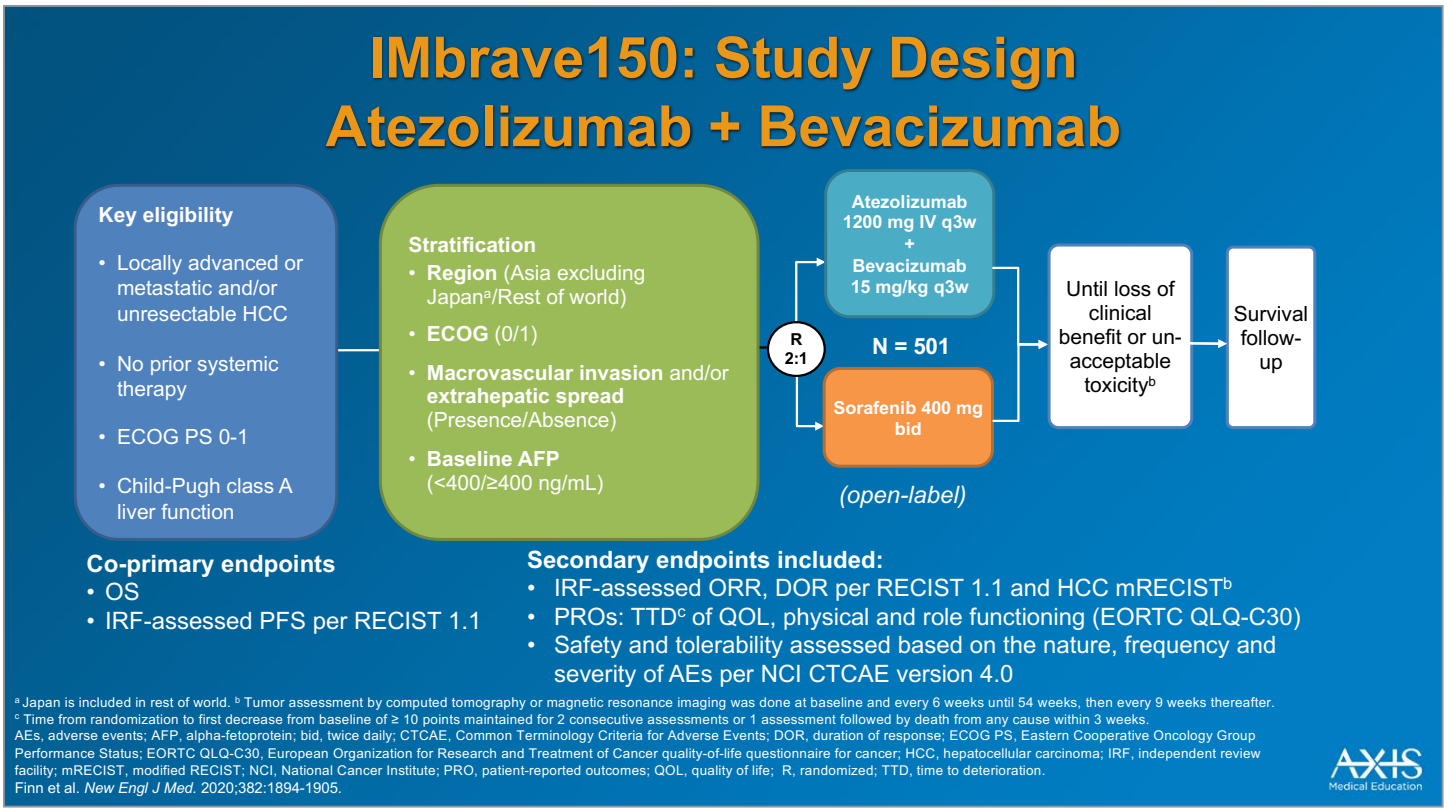
- Here you see the response rate from the single-arm component. You can see in over 100 patients, the response rate was 36% with 12% of patients having complete responses, 24% having partial responses, and a total disease control rate of 71%.



The IMbrave150 study, which was published in *The New England Journal of Medicine* in May of 2020, was an open-label, global study that looked at the combination of atezolizumab/bevacizumab given intravenously every 3 weeks versus sorafenib at the dose of 400 mg twice a day. The coprimary endpoints here were both overall survival and progression-free survival. We used very standard stratification factors, as well as selecting patients who are Child-Pugh A and good performance status.

Importantly, because of bevacizumab's activity on the VEGF axis and its association with bleeding and other malignancies, patients were required to have an upper endoscopy within 6 months of enrolling in the study. And if not having one, they would have to have that done because we know patients with chronic liver disease are at risk for varices.

IMbrave150: Patient Characteristics at Baseline

Characteristic	Atezolizumab + Bevacizumab (n = 336)	Sorafenib (n = 165)
Median age (IQR), y	64 (56-71)	66 (59-71)
Male, n (%)	277 (82)	137 (83)
Geographic region, n (%)		
Asia excluding Japan	133 (40)	68 (41)
Rest of the world[a]	203 (60)	97 (59)
ECOG performance status score, n (%)		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
Child-Pugh score, n (%)		
A5	239 (72)	121 (73)
A6	94 (28)	44 (27)
Barcelona Clinic Liver Cancer stage, n (%)		
A	8 (2)	6 (4)
B	52 (15)	26 (16)
C	276 (82)	133 (81)

Characteristic	Atezolizumab + Bevacizumab (n = 336)	Sorafenib (n = 165)
AFP at baseline ≥ 400 ng/mL	126 (38)	61 (37)
Macrovascular invasion and/or extrahepatic spread present, n (%)	258 (77)	120 (73)
Macrovascular invasion present, n (%)	129 (38)	71 (43)
Extrahepatic spread present, n (%)	212 (63)	93 (56)
Varices at baseline	88 (26)	43 (26)
Varices treated at baseline	36 (11)	23 (14)
Cause of hepatocellular carcinoma, n (%)		
Hepatitis B	164 (49)	76 (46)
Hepatitis C	72 (21)	36 (22)
Nonviral[b]	100 (30)	53 (32)
Prior local therapy for hepatocellular carcinoma, n (%)	161 (48)	85 (52)

- 501 patients enrolled from 111 sites in 17 countries between March 15, 2018 and January 30, 2019
- Median duration of follow-up was 8.6 mo
  - 8.9 mo in atezolizumab + bevacizumab group
  - 8.1 mo in sorafenib group

[a] The rest of the world includes the United States, Australia, New Zealand, and Japan.
[b] Includes alcohol, other and unknown non-hepatitis B and C causes.
Clinical data cut-off: August 29, 2019.
AFP, alpha fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status.
Finn et al. *N Engl J Med*. 2020;382:1894-1905.

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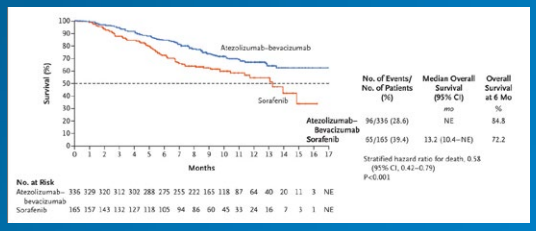
Here we see the breakdown characteristics of the patients enrolled in the study, and this is a very typical population, I think, for liver cancer patients—a little older. This study was stopped at its first interim analysis when it was presented that the survival curves separated early and remain separated through the course of follow-up. With a median follow-up of about 8.5 months, we see that the hazard ratio for death was 0.58. So this is a 42% decrease in the risk for death. As compared to the SHARP study with sorafenib versus placebo—that hazard ratio was 0.69, and that was versus placebo.

IMbrave 150
Co-primary Endpoint: OS (ITT Population)

- OS longer with atezolizumab + bevacizumab vs sorafenib (*P*<0.001)
- Estimated 6-month survival rates:
  - Atezolizumab + bevacizumab: 84.8% (95% CI 80.9-88.7)
  - Sorafenib: 72.2% (95% CI 65.1-79.4)
- Estimated 12-month survival rates:
  - Atezolizumab + bevacizumab: 67.2% (95% CI 61.3-73.1)
  - Sorafenib: 54.6% (95% CI 45.2-64.0)



Factors included in the stratified *P* value and Cox model were geographic region (Asia [excluding Japan] vs the rest of the world), AFP level at baseline (<400 ng/mL vs ≥400 ng/mL), and macrovascular invasion, extrahepatic spread, or both (yes vs no).
Tick marks indicate censored data.
ITT, intention to treat; OS, overall survival; NE, could not be evaluated.
Finn et al. *N Engl J Med*. 2020;382:1894-1905.

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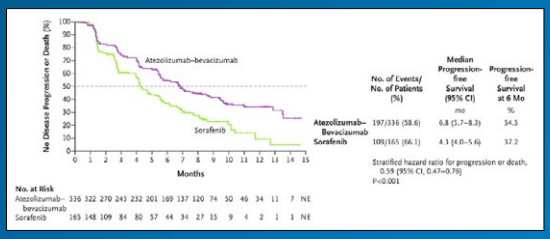
Here versus an active control for the first time we're seeing in the frontline setting a significant improvement in overall survival. Sorafenib had a median survival of about 13 months, which again is comparable to modern studies with sorafenib. At the time of this readout, we still had not reached the median survival in the combination arm. This study is ongoing, and we'll wait to see updated data in the future.

IMbrave 150
Co-Primary Endpoint: PFS[a] (ITT Population)

PFS longer with atezolizumab + bevacizumab vs sorafenib ($P < .001$)



[a] As assessed at an independent review facility according to RECIST 1.1.
Factors included in the stratified P value and Cox model were geographic region (Asia [excluding Japan] vs the rest of the world), AFP level at baseline (<400 ng/mL vs ≥400 ng/mL), and macrovascular invasion, extrahepatic spread, or both (yes vs no).
Tick marks indicate censored data.
ITT, intention to treat; NE, not evaluated; PFS, progression-free survival.
Adapted from Finn et al. *N Engl J Med*. 2020;382:1894-1905.

- The study also met its primary endpoint of improving progression-free survival, again, with a similar hazard ratio of 0.59 with an improvement of 4.3 to 6.8 months.

IMbrave 150: Secondary Efficacy Outcomes

Variable	IRF RECIST 1.1[a]			IRF HCC-specific mRECIST[b]		
	Atezolizumab + Bevacizumab (n = 326)	Sorafenib (n = 159)	Difference (P)[c]	Atezolizumab + Bevacizumab (n = 325)	Sorafenib (n = 158)	Difference (P)[c]
Confirmed[d] objective response, n (% [95% CI])	89 (27.3 [22.5-32.5])	19 (11.9 [7.4-18.0])	15.4 (<.001)	108 (33.2 [28.1-38.6])	21 (13.3 [8.4-19.6])	19.9 (<.001)
Complete response, n (%)	18 (5.5)	0		33 (10.2)	3 (1.9)	
Partial response, n (%)	71 (21.8)	19 (11.9)		75 (23.1%)	18 (11.4)	
Stable disease, n (%)	151 (46.3)	69 (43.4)		127 (39.1%)	66 (41.8)	
Disease control rate[e], n (%)	240 (73.6)	88 (55.3)		235 (72.3)	87 (55.1)	
Progressive disease, n (%)	64 (19.6)	39 (24.5)		66 (20.3)	40 (25.3)	
Could not be evaluated, n (%)	8 (2.5)	14 (8.8)		10 (3.1)	14 (8.9)	
Data missing, n (%)	14 (4.3)	18 (11.3)		14 (4.3)	17 (10.8)	
Ongoing objective response at data cutoff, n/N (%)	77/89 (86.5)	13/19 (68.4)		84/108 (77.8)	13/21 (61.9)	

[a] Based on patients who presented at baseline with measurable disease per IRF RECIST criteria. [b] Based on patients who presented at baseline with measurable disease per HCC mRECIST criteria.
[c] Between-group difference (atezolizumab + bevacizumab minus sorafenib) in the percentage of patients with confirmed response, expressed in percentage points. The P value was derived from a Cochran–Mantel–Haenszel test. Randomization, which was performed through an interactive voice-response or Web-response system, included as stratification factors geographic region (Asia excludingJapan vs. the rest of the world), alpha-fetoprotein level (<400 ng per milliliter vs. ≥400 ng per milliliter) at baseline, and macrovascular invasion, extrahepatic spread, or both (yes vs. no). [d] Defined as a response (complete response or partial response) seen at two consecutive tumor assessments at least 28 days apart. [e] Calculated from the sum of complete response, partial response and stable disease.
IRF, independent review facility.
Finn et al. *N Engl J Med*. 2020;382:1894-1905.

- If we look at the secondary readout of response rate, and again what we're seeing here are response rates of 27%, and that is a fairly high response rate when we think of where we were with the TKIs. Here we have a response rate that is fairly high, and patients who do respond have a long response.

KEYNOTE-524/Study 116
Lenvatinib + Pembrolizumab

Summary of Efficacy Outcomes			
Parameter	Lenvatinib + Pembrolizumab (N=100)		
	mRECIST per IIR	RECIST Version 1.1 per IIR	mRECIST per IR
ORR (confirmed responses), n (%) (95% CI)	46 (46) (36.0–56.3)	36 (36) (26.6–46.2)	41 (41) (31.3–51.3)
Best overall response, n (%)			
Complete response	11 (11)	1 (1)	5 (5)
Partial response	35 (35)	35 (35)	36 (36)
Stable disease	42 (42)	52 (52)	45 (45)
Progressive disease	7 (7)	7 (7)	7 (7)
Unknown/not evaluable	5 (5)	5 (5)	7 (7)
Median DOR for confirmed responders, months (95% CI)	8.6 (6.9–NE)	12.6 (6.9–NE)	12.6 (6.2–18.7)
Median TTR for confirmed responders, months (range)	1.9 (1.2–5.5)	2.8 (1.2–7.7)	2.7 (1.2–11.8)
Disease control rate, n (%) (95% CI)	88 (88) (80.0–93.6)	88 (88) (80.0–93.6)	86 (86) (77.6–92.1)

- Phase 1b, open-label, single-arm trial
- 100 patients with unresectable HCC with no prior systemic therapy
- July 2019: FDA Breakthrough Therapy Designation
- Phase 3 LEAP-002 trial ongoing (NCT03713593)
  - Lenvatinib in combination with pembrolizumab versus lenvatinib as first-line therapy in patients with advanced HCC

FDA, US Food & Drug Administration; DOR, duration of response; HCC, hepatocellular carcinoma; IIR, independent imaging review; NE, not evaluable; ORR, objective response rate; TTR, time to response.
Finn et al. *J Clin Oncol*. 2020;38: abstract 4519.

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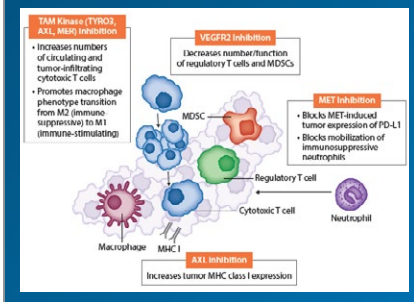
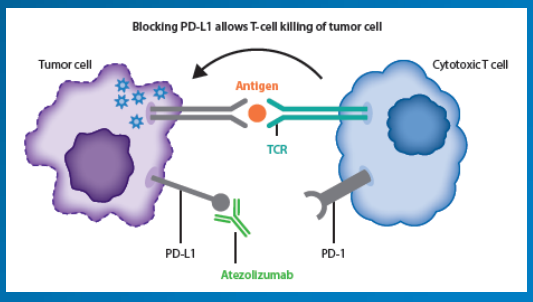
There are other studies ongoing in this space of combining VEGF inhibition with TKIs. KEYNOTE-524 or the -116 study is looking at lenvatinib in combination with pembrolizumab. Very similar to the phase single-arm study with atezolizumab/bevacizumab, we're seeing response rates in the 36% range by conventional RECIST by independent review; and, by mRECIST also higher, 46%. And again, here some of these being complete responses, the majority being partial responses.

Disease control rates are very high in the high 80% range and duration of response by RECIST of over 1 year. This study is building the story around dual inhibition of checkpoint inhibition and VEGF receptor plus inhibition. This led to the LEAP-002 study, which is ongoing, looking at the combination of pembrolizumab and lenvatinib versus lenvatinib alone; this is a phase 3 placebo-controlled study.

COSMIC-312 Trial
ICI + TKI: Atezolizumab + Cabozantinib

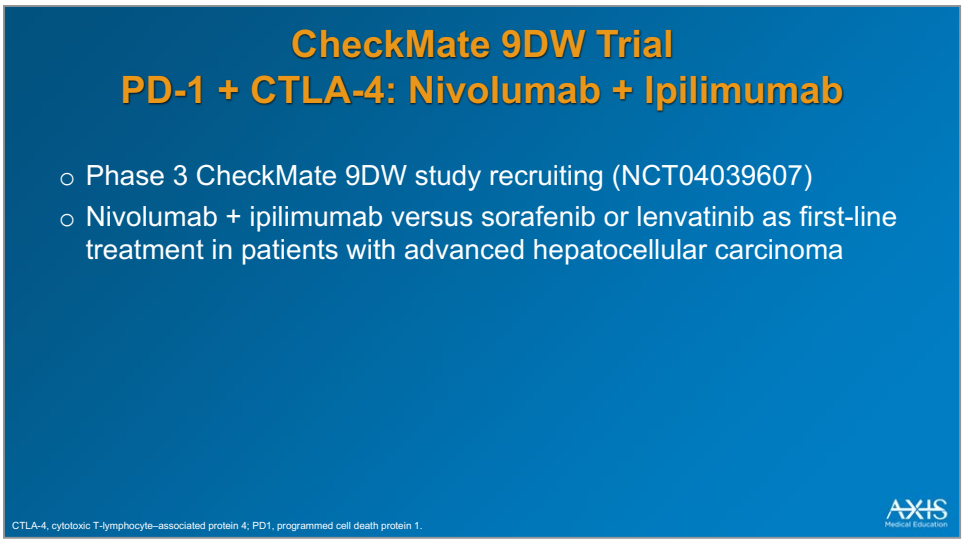




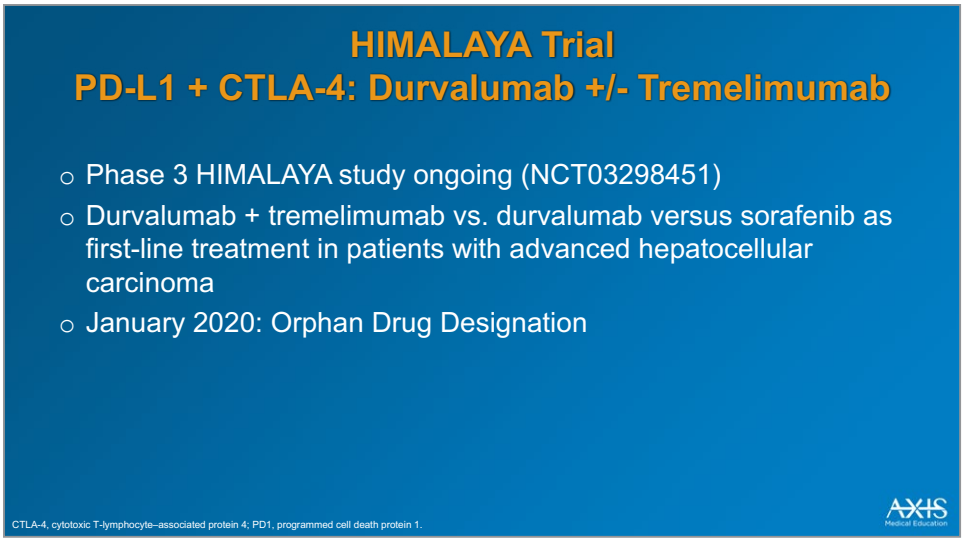
ICI, immune checkpoint inhibitor; MDSCs, myeloid-derived suppressor cells; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TKI, tyrosine kinase inhibitor.
Kelley et al. *J Clin Oncol*. 2019;37(15_suppl): abstract TPS4157.

AXIS Medical Education

Atezolizumab is also being evaluated with cabozantinib. Cabozantinib is approved in second line. It's a multikinase inhibitor, which hits the VEGF receptor, which has been validated as being important in combination with immunotherapy. However, it also hits other receptors such as the TAM kinases, specifically AXL, cMET (the hepatocyte growth factor), and builds on this idea that you can affect the immune microenvironment around the tumor that in combination with a checkpoint inhibitor, such as atezolizumab, can improve response rates.



- What about dual checkpoint inhibition? Nivolumab and ipilimumab—nivolumab inhibiting PD-1, ipilimumab targeting the CTLA-4 protein—is approved in liver cancer based on an accelerated approval mechanism. This ongoing phase 3 study is evaluating this combination versus either sorafenib or lenvatinib as first-line treatment. We are anxious to see the results when that's ready. The combination in second line was giving response rates of around 30%.



- Along those lines is the HIMALAYA trial. This study is looking at the PD-L1 antibody, durvalumab, plus tremelimumab versus sorafenib. This initially was a 4-arm study but now is a 3-arm study once the dose of the combination was established; it's durvalumab versus durvalumab plus tremelimumab versus sorafenib. This study has completed accrual, and we're awaiting results. At ASCO, we saw some data of durvalumab and tremelimumab in a single-arm study in second line, and we saw response rates of around 24% with an acceptable safety profile. Now we're waiting for results from this phase 3 study.

Mocharnuk: That was great, Dr. Finn. Is the IMbrave150 data practice-changing? How have you integrated the combination approach of VEGF inhibition with immunotherapy into your practice?

Finn: I think the approval of atezolizumab and bevacizumab in the frontline treatment of liver cancer is really a game changer. For so long, we've wanted something that improved survival versus sorafenib, and we've got that. Given that we need to pay attention to its side effect profile specifically, I think, asking ourselves why we shouldn't use this for a patient.

This has become the frontline standard of care, unless there are patients who have some definite contraindication to immunotherapy or to bevacizumab. Keep in mind that the VEGF receptor inhibitors, lenvatinib and sorafenib, do have overlapping side effect profiles with bevacizumab. It's really the high response rate and maintained quality of life or even improved quality of life for this combination that will make it the standard of care.

Mocharnuk: Dr. Singal, let's now turn to you for a minute. What are your thoughts on where we are with first-line therapy for advanced HCC? And what would you recommend for a patient with both cirrhosis and HCC?

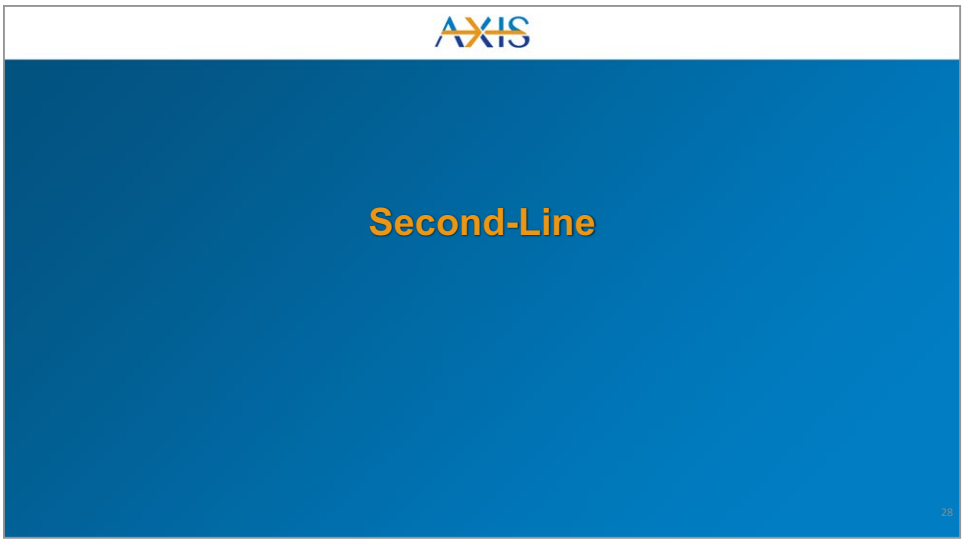
Amit Singal, MD, MS: That's a great question, and very important in clinical practice because the majority of HCC in the western world presents in the setting of cirrhosis. In fact, in the United States and Europe, we can say that more than 80%, if not over 90%, of cases of advanced HCC occur in the setting of cirrhosis.

When we consider cirrhosis, it's not just one big bucket. There are different gradations of how severe someone's cirrhosis can be. We typically classify this going from Child-Pugh A to Child-Pugh B to Child-Pugh C, depending on how sick somebody's liver is at the time of clinical presentation.

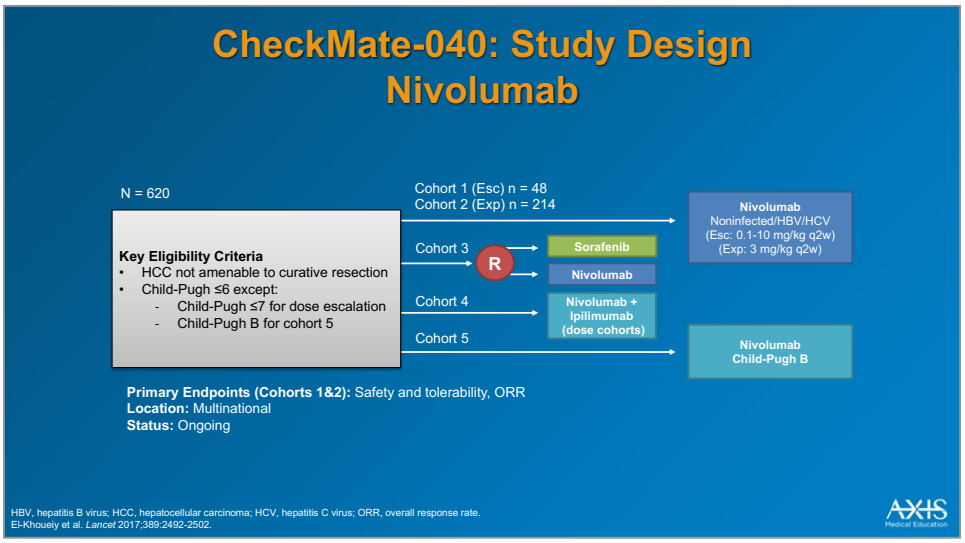
As you've already heard from Dr. Finn, when we think of atezolizumab and bevacizumab, this was restricted to patients with well-compensated liver disease. That is, Child-Pugh A cirrhosis with minimal symptoms. However, there are many patients who present with advanced HCC, who may have more significant liver dysfunction, whether this is portal hypertension, or Child-Pugh B cirrhosis.

In those patients, we have to consider alternative therapies that have been evaluated in patients with more advanced liver dysfunction, such as sorafenib or nivolumab. We know that sorafenib has been evaluated in many real-world clinical experience studies, such as GIDEON. We also know that nivolumab was evaluated in a small subset of Child-Pugh B patients as part of the CheckMate 040 study.

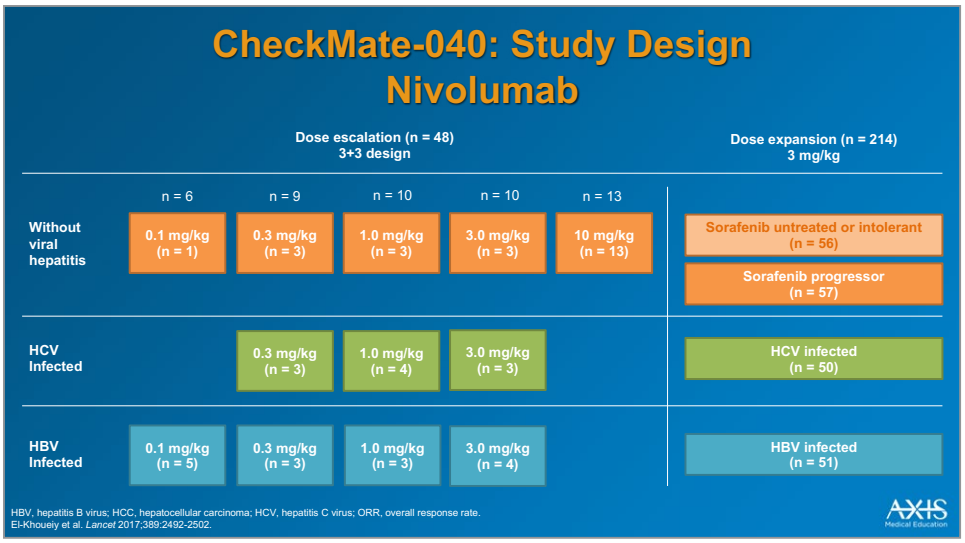
Of course, we hope that more and more real-world data will be available for other agents so we can start to consider them in Child-Pugh B cirrhosis, or those patients with portal hypertension. But at least right now, that's how I consider it, where atezolizumab and bevacizumab is first-line therapy for most patients with Child-Pugh A cirrhosis and no portal hypertension, but we have to consider alternative therapies in patients with more advanced liver dysfunction.



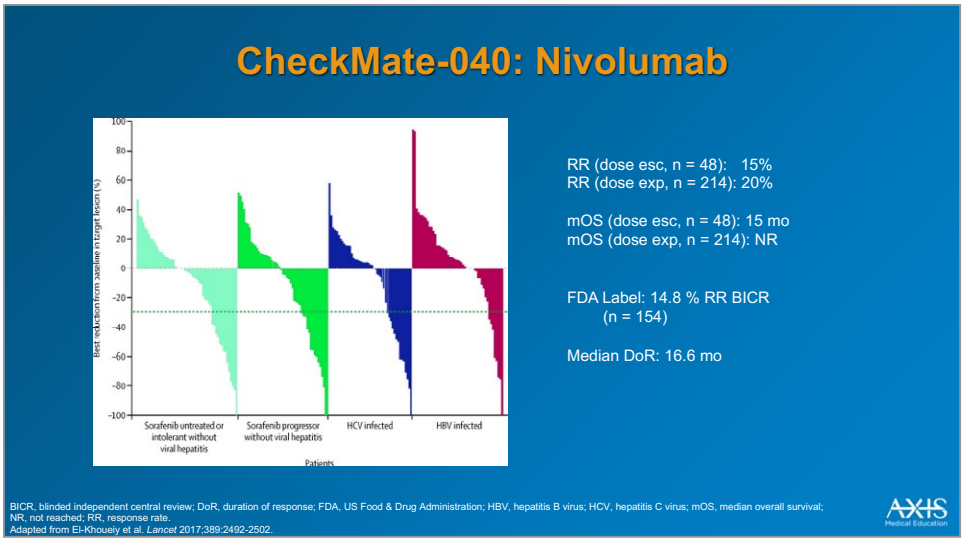
Mocharnuk: Thanks, Dr. Singal. Now, let's turn to second-line treatment. Dr. Finn, will you please discuss the available data for immunotherapy as second-line treatment?



Finn: As exciting as things have been in the frontline setting, we actually have a lot of developments in the second-line setting, which will influence how we sequence drugs moving forward. CheckMate 040, the 040 study, was the first study with a PD-1 inhibitor to look at how these drugs work in liver cancer populations. This has grown over time to have multiple arms to it. However, the initial arm was a dose escalation phase and expansion phase to make sure that PD-1 inhibition would be safe in a population of patients with underlying liver disease.

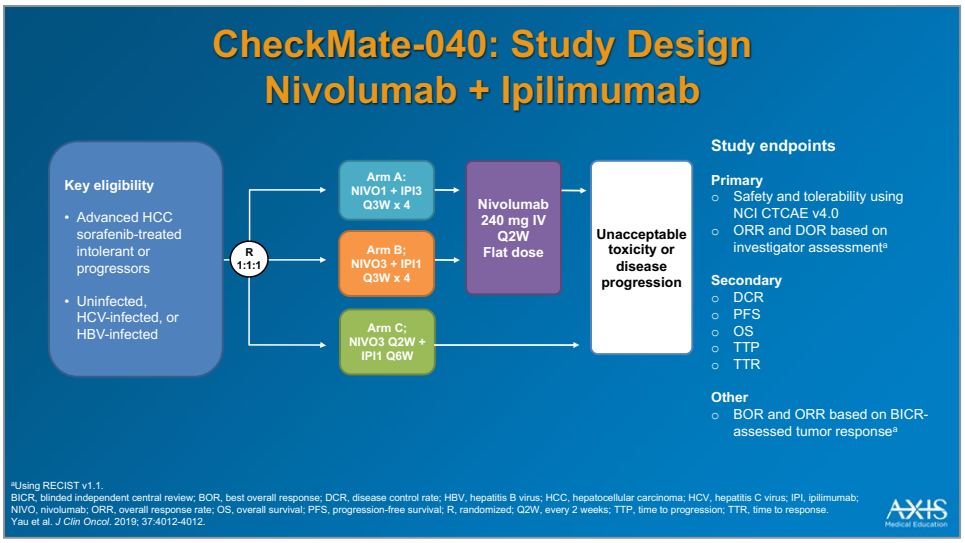


- The dose escalation was looked at in hepatitis B–infected versus hepatitis C–infected versus those patients who don't have viral hepatitis.



- The results of this study formed the basis for the accelerated approval of nivolumab, and we saw response rates of around 15%. What was striking is that the responders had a long duration of response, over 16 months. And if you look at these waterfall plots, we see that the percentage of responders really didn't differ from the etiology of their liver disease whether they had hepatitis C, hepatitis B, or nonviral etiology for their liver cancer. We also saw that in the frontline setting, the responses were significant as well.

  Based on these results, nivolumab received accelerated approval in the second line with the phase 3 confirmatory study CheckMate 459, which we discussed earlier. CheckMate 040 established the safety profile of this drug in liver cancer patients.



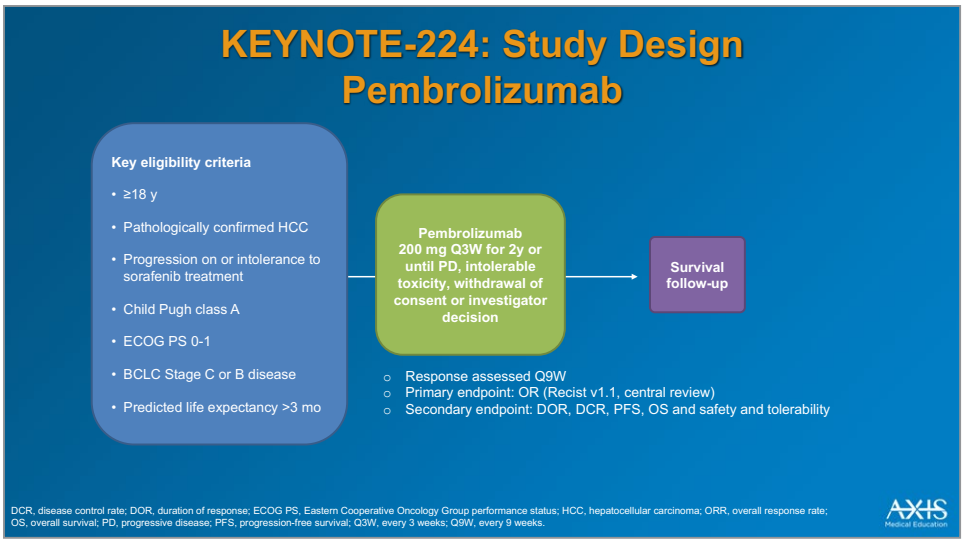
- CheckMate 040 also had an arm evaluating various doses of nivolumab and the CTLA-4 antibody, ipilimumab. And as it turns out, this study became the basis for accelerated approval of this combination in second line, and that was really based on what we see here as response rates of over 30% regardless of the dosing regimen. Arm A is what did get approval, which was nivolumab 1 mg/kg and ipilimumab 3 mg/kg for 4 doses every 3 weeks and then followed by the standard dose of nivolumab in this population of 240 every 2 weeks.

CheckMate-040: Nivolumab + Ipilimumab

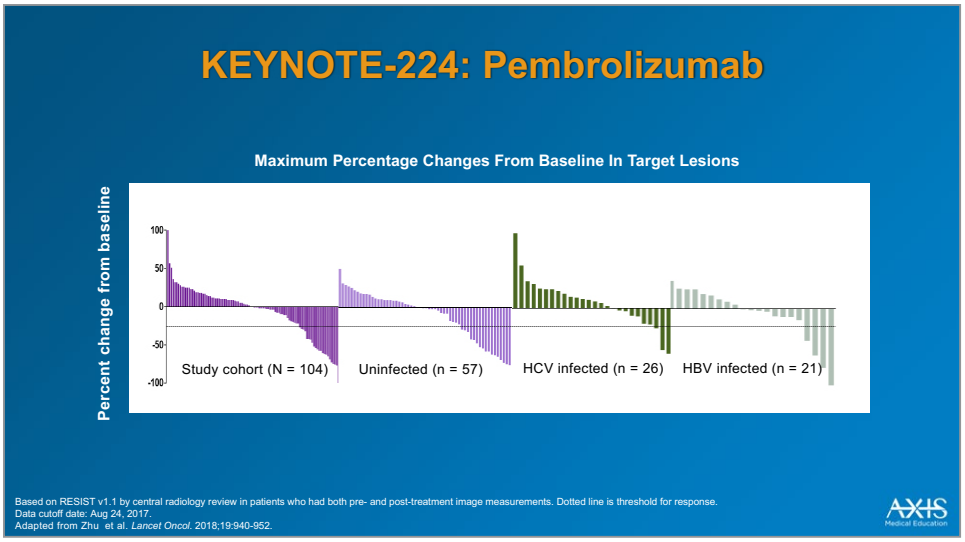
Result	Arm A Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Q3W (4 doses) followed by Nivolumab 240 mg Q2W n = 50	Arm B Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W (4 doses) followed by Nivolumab 240 mg Q2W n = 49	Arm C Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W n = 49
ORR by BICR, n (%)	16 (32)	15 (31)	15 (31)
BOR, n (%)			
CR	4 (8)	3 (6)	0
PR	12 (24)	12 (24)	15 (31)
SD	9 (18)	6 (10)	9 (18)
PD	20 (40)	24 (49)	21 (43)
Unable to determine	3 (6)	4 (8)	4 (8)
DCR, n (%)	27 (54)	21 (43)	24 (49)
Median TTR, mo	2.0	2.6	2.7
Median DOR, mo	17.5	22.2	16.6
ORR by investigator assessment, n (%)	16 (32)	13 (27)	14 (29)
Median OS, mo	22.8	12.5	12.7

BICR, blinded independent control review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, overall response rate; PD, progressive disease; PR, partial response; Q, every; W, weeks; SD, stable disease; TTR, time to response.
Yau et al. *J Clin Oncol*. 2019; 37:4012-4012. He et al. *J Clin Oncol*. 2020;38:512.

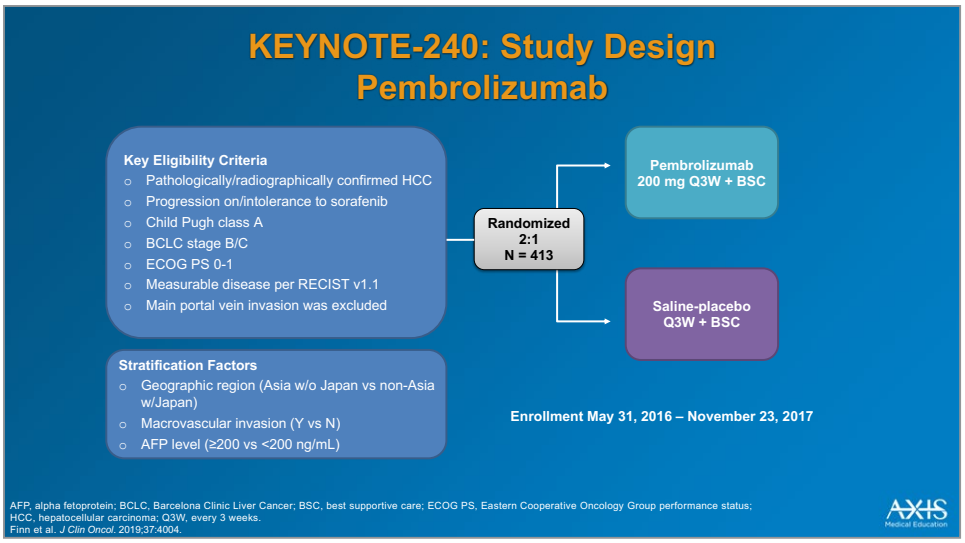
- The reason this arm was selected was while the response rates were very similar, the survival for this arm of the study was quite longer than the others—we see up to 23 months. Keeping in mind that this is a single-arm study, overall 150 patients or so, but Arm A alone was only 50 patients. As mentioned, this combination is now being evaluated in a phase 3 study versus sorafenib or lenvatinib.



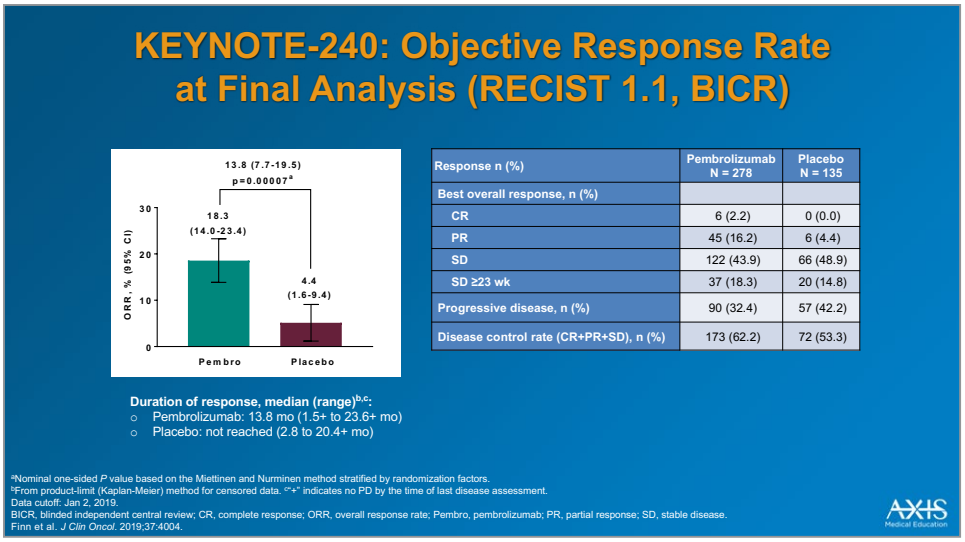
- Similarly, pembrolizumab was evaluated in a single-arm phase 2 study in a cohort of liver cancer patients who had Child-Pugh A liver disease that had progressed on sorafenib.



- And we saw a very similar observation—regardless of etiology, there were a number of patients who received a benefit from the drug, as measured by response or stable disease. Based on this dataset, pembrolizumab received accelerated approval.



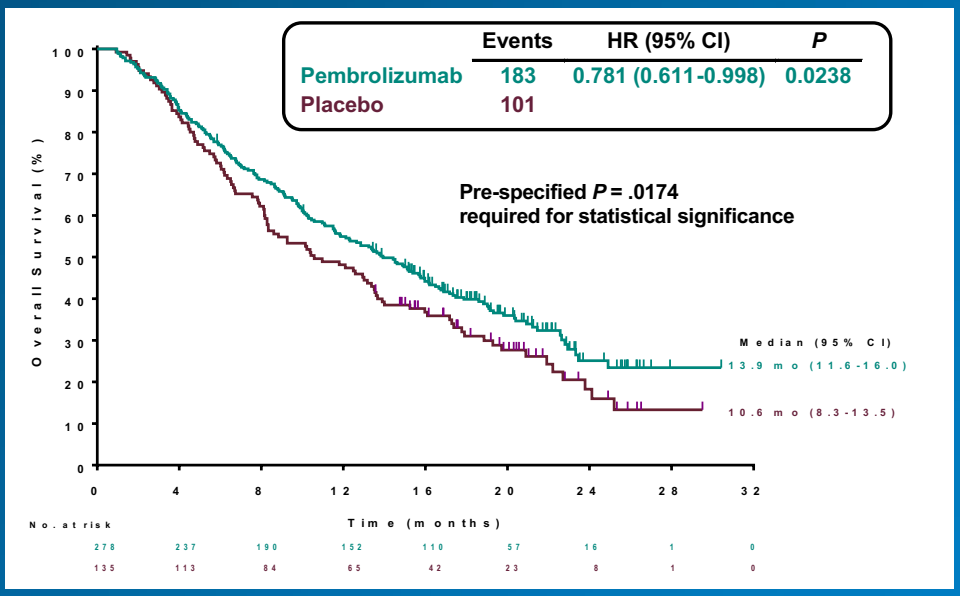
- The confirmatory study for pembrolizumab was KEYNOTE-240, which was a phase 3 study in second line. And this is probably the last phase 3 study we'll see versus placebo in second line because we have so many drugs approved. In this study, we took patients who had prior sorafenib and randomized them 2:1 of pembrolizumab versus placebo. And importantly, it had 2 coprimary endpoints—overall survival and progression-free survival.



Response n (%)	Pembrolizumab N = 278	Placebo N = 135
Best overall response, n (%)		
CR	6 (2.2)	0 (0.0)
PR	45 (16.2)	6 (4.4)
SD	122 (43.9)	66 (48.9)
SD ≥23 wk	37 (18.3)	20 (14.8)
Progressive disease, n (%)	90 (32.4)	57 (42.2)
Disease control rate (CR+PR+SD), n (%)	173 (62.2)	72 (53.3)

- We confirmed the single-agent activity of pembrolizumab. Here you see a response rate of 18%, and a disease control rate of 62%. If a patient responded to pembrolizumab, there was a long median duration of response of over 13 months.

KEYNOTE-240: Overall Survival



Data Cutoff: Jan 2, 2019.
Finn et al. *J Clin Oncol*. 2019;37:4004.

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Here you see the overall survival curves. Median survival with placebo was 10.6 months, which was the longest we've seen in a control arm, and perhaps that's related to the ability of patients to go on to drugs at progression. In addition, we excluded patients with main portal vein invasion, which wasn't always an exclusion in other phase 3 studies. But the median survival with pembrolizumab was 13.9 months.

This was a hazard ratio of 0.78. The confidence interval is less than 1.0, and the *P* value is .0238. However, we cannot say this was a positive study because based on the statistical design, we needed a *P* value of .0174. However, many of us think that this study confirmed that in a subset of patients, pembrolizumab clearly has clinical activity. The next generation of studies will be combining these drugs in the frontline setting.

Mocharnuk: So we have a lot more immunotherapy approaches in the second line for patients previously treated with sorafenib. Doctors Finn and Singal, are there nuances among these immunotherapy options that would help you to choose treatment? And what would you do for a patient who was treated with atezolizumab and bevacizumab in the first line?

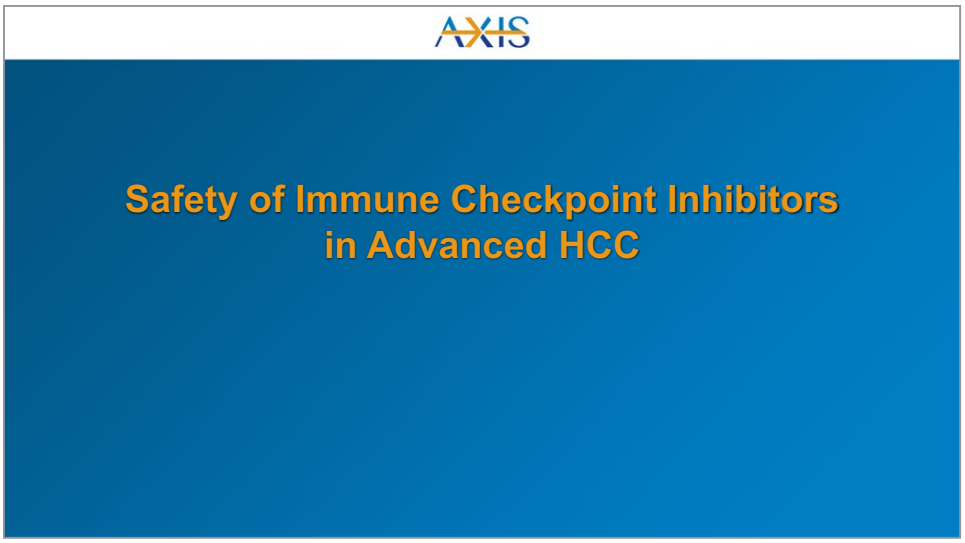
Finn: All the drugs approved in second line were approved in patients who had received sorafenib. For a patient who receives lenvatinib frontline, then the single-agent immunotherapy option certainly would be an option at progression, as well as some of the TKIs that are approved. I think single-agent immunotherapy after prior atezolizumab and bevacizumab might be a little harder sell because of the overlapping mechanism of action.

It will be very exciting to see how the combination of ipilimumab and nivolumab might come into play here, although we'll need more data in the liver cancer space. There has been some data in other malignancies—essentially phase 2 data—that this combination might have activity after prior single-agent immunotherapy such as in the renal cell population or in melanoma.

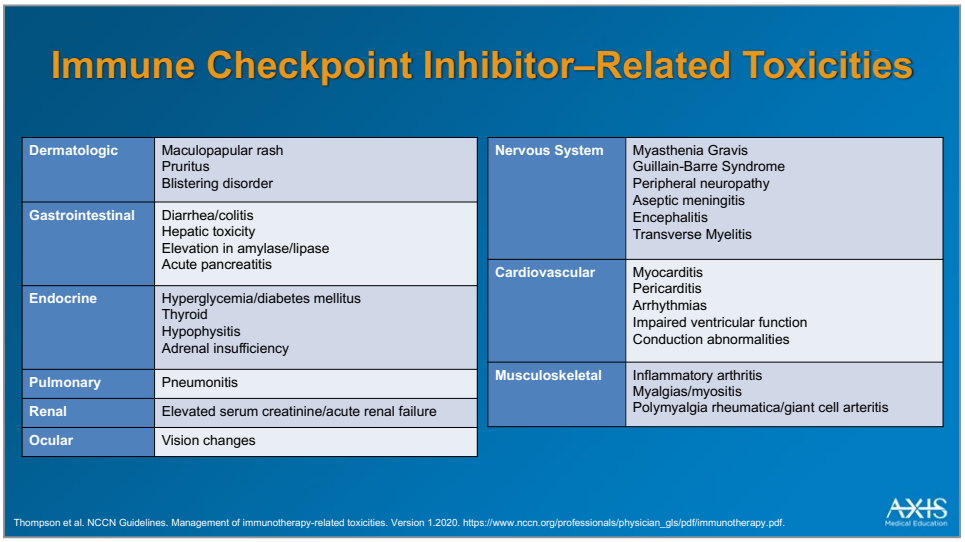
Singal: We don't have any data for any therapy after atezolizumab and bevacizumab. And so, we're really in an arena where we have to apply old data and assume these therapies would be effective after atezolizumab and bevacizumab. As you've heard from Rich, many of us would really prefer the TKIs in this setting for several of the reasons that you've already heard. It's possible that by using a more pure VEGF, that some of the escape mechanisms that you experience in the first-line setting could be acted upon by using a broader TKI such as sorafenib, lenvatinib, or cabozantinib, that really act on multiple pathways.

There is some appeal to using combination immunotherapy agents, a PD-1 in combination with a CTLA-4, such as ipilimumab/nivolumab, which has been approved in the second-line setting. Although, once again, we don't have any data in HCC to see if any of these therapies would be effective after atezolizumab and bevacizumab.

As we're going through and selecting between these therapies, ideally we would have a treatment selection biomarker, that is, a biomarker that would say, for example, lenvatinib or cabozantinib, or using a CTLA-4 inhibitor would be more effective in this setting. But unfortunately, that biomarker currently doesn't exist, and so we have to use small differences between these agents to select between them in clinical practice.



Mocharnuk: You know, it's exciting that so many drugs have been approved recently for the treatment of HCC. However, as we know, many of these new agents can cause unique adverse side effects that must be addressed by physicians and other cancer care providers. Would you please summarize some of the more common side effects and how you address these in your clinical practices?



Finn: We're all very excited about the data we're seeing with immune checkpoint inhibitors in liver cancer, specifically now in the frontline setting the survival advantage and its single-agent activity in the second-line setting and the upcoming combinations. All that needs to be balanced against safety and adverse events. What's interesting in the liver cancer population, when done in Child-Pugh A patients, is that we're not seeing any new toxicities that we don't see in other malignancies.

Clearly when we consent patients for the use of these drugs, it's a very broad consent that really any organ system can be affected with these drugs but some things being more common such as dermatologic reactions, certainly thyroid disorders. But again, any organ system can be affected, and therefore we need to watch patients closely. One of the big concerns in the liver cancer population is autoimmune hepatitis given these patients have cirrhosis. That is not necessarily a common event in the liver cancer population.

Immune-related Adverse Events Guideline Recommendations

Guidelines for the management of immune-related adverse events have been developed:

- ASCO[1]
- ESMO[2]
- NCCN[3]
- SITC[4,5]

Grade	American Society of Clinical Oncology Clinical Practice Guideline (2018) Immune Checkpoint Inhibitor Therapy General Recommendations[1]
1	• Continued with close monitoring • Exception: some neurologic, hematologic, and cardiac toxicities
2	• Suspended for most, with consideration of resuming when symptoms revert to grade 1 or less • Corticosteroids may be administered
3	• Suspended • Initiation of high-dose corticosteroids - prednisone 1-2 mg/kg/d - methylprednisolone 1-2 mg/kg/d • Corticosteroids should be tapered over the course of at least 4-6 weeks • Some refractory cases may require infliximab or other immunosuppressive therapy
4	• Permanent discontinuation • Exception: endocrinopathies that have been controlled by hormone replacement

1. Brahmer et al. *J Clin Oncol*. 2018;36(17):1714-1768; 2. Haanen et al, 2017; 3. Thompson et al, 2019; 4. Puzanov et al, 2017; 5. Ernstoff et al, 2019.

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- There are a lot of guidelines, and this table comes from various guidelines that have been put out. But I think the take-home message is that we need to monitor our patients closely. Certainly the use of steroids will be required for more serious events.

NCCN Guidelines® Routine Monitoring for Immune-Checkpoint Inhibitors

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Comprehensive pt history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency) • Infectious disease screening as indicated	Clinical exam at each visit with adverse event symptom assessment	Follow-up testing based on findings, symptoms
Imaging • Cross-sectional imaging • Brain magnetic resonance imaging if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General bloodwork • CBC with differential • Comprehensive metabolic panel	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6-12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Monitor affected BSA and lesion type; photographic documentation Skin biopsy if indicated
Pancreatic • Baseline testing is not required	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis

BSA, body surface area; CBC, complete blood cell count; CT, computed tomography; TSH, thyroid-stimulating hormone; MRCP, magnetic resonance cholangiopancreatography; PFTs, pulmonary function tests.
[a]Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs).
[b]Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.
[c]After first four doses of immunotherapy, only as clinically indicated.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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- Again, these NCCN monitoring guidelines are not unique to liver cancer patients. Performing a thorough clinical examination, a good review of systems, and certainly looking at GI toxicity. In a liver cancer population, diarrhea can cause volume challenges, which again in this group of patients who don't have as much reserve as an otherwise "healthy" patient with cancer. All of these patients will have some degree of liver dysfunction.

NCCN Guidelines® Routine Monitoring for Immune-Checkpoint Inhibitors (cont.)

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Thyroid • TSH, free thyroxine (T4)[c]	Every 4-6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	Total T3 and free T4 if abnormal thyroid function suspected.
Adrenal/Pituitary • Adrenal: Serum cortisol (morning preferred)[c] • Pituitary: TSH, free thyroxine (T4)[c]	Repeat prior to each treatment or every 4 weeks during immunotherapy, then follow-up every 6-12 weeks	Luteinizing hormone (LH), follicle-stimulating hormone (FISH), testosterone (males), estradiol (females), adrenocorticotropic hormone (ACTH)
Pulmonary • Oxygen saturation (resting and with ambulation) • PFTs for high-risk pts	Repeat oxygen saturation tests based on symptoms	Chest CT with contrast to evaluate for pneumonitis, biopsy if needed to exclude other causes.
Cardiovascular • Consider baseline electrocardiograph • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal • Joint examination/functional assessment as needed for pts with pre-existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine phosphokinase (CPK)

CT, computed tomography; PFTs, pulmonary function tests; TSH, thyroid-stimulating hormone.
[a]Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs). See Principles of Immunotherapy Patient Education (IMMUNO-B).
[b]Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.
[c]After first four doses of immunotherapy, only as clinically indicated.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

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NCCN Guidelines®
Immunotherapy: Healthcare Provider Information

Prior to Starting ICI Therapy
Assess patient's understanding of disease and recommendations for treatment
Educate patients about MOA and rationale for use of ICIs
Document any underlying medical conditions affecting any organ system (eg, pulmonary, cardiac, neurologic, musculoskeletal)
Take a history of any autoimmune diseases
Record all medications, including OTC medications and herbal supplements
Patients of reproductive age should be advised to use effective birth control during and for at least 5 months after final dose of ICI • Effect of ICI on human reproductive function is unknown • Consider fertility preservation and reproductive endocrinology referral
Breast feeding is contraindicated during and for at least 5 months after the final dose of ICI
Provide patient with and instruct them to carry a **wallet card** that outlines: • Type of ICI they are receiving • Potential irAEs • Contact numbers for their oncology health care team
Assess patient's ability to monitor and report potential irAEs. Engagement of caregiver may be necessary
Assess patient for potential for home care support service needs during therapy
Educate patient about potential toxicity profile of ICI therapy, including presenting symptoms and timing
Inform patient of existing educational resources (see following slide)

ICI, immune checkpoint inhibitor; MOA, mechanism of action; OTC, over the counter; irAE, immune-related adverse events.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

NCCN Guidelines®
Immunotherapy: Healthcare Provider Information

Instruct Patients to Notify Oncology Health Care Team If:
Any new signs or symptoms develop, including: • Severe fatigue • Headache • Rash • Cough • Shortness of breath • Chest pain • Abdominal bloating • Change in bowel pattern • Weight loss • Vision changes or eye pain • Severe muscle weakness • Severe muscle or joint pains • Mood changes
Patients should monitor symptoms for at least 2 years following conclusion of ICI therapy
Patient is evaluated by other HCPs or admitted to hospital
Any new medications are prescribed
Prior to receiving any immunization or vaccinations

Inform Patient of Existing Educational Resources:	
Understanding Immunotherapy Side Effects	https://www.nccn.org/images/pdf/Immunotherapy_Infographic.pdf
Oncology Nursing Society Immunotherapy Wallet Cards	https://www.ons.org/sites/default/files/2019-01
Society for Immunotherapy of Cancer Understanding Cancer Immunotherapy	https://www.sitcancer.org/HigherLogic/System/DownloadDocumentFile.ashx?DocumentFileKey=567abb47-c7f1-2fa3-b008-053953020940&forceDialog=0#page=1&zoom=auto,-91,783
AIM with Immunotherapy	https://aimwithimmunotherapy.org

HCPs, healthcare providers; ICI, immune checkpoint inhibitor.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

NCCN Guidelines®
Immunotherapy: Healthcare Provider Information

Review patient medications for potential drug interactions (eg, QT prolongation) when administering agents to manage ICI-related toxicity

Toxicity Management	
Mild to moderate AEs	• Provide symptomatic management • Delay in ICI may be recommended if unclear if irAE is developing or until AEs resolve to grade 1 or pre-treatment baseline • Corticosteroids may be required if AE does not improve • If hormone replacement required: usually for lifetime & may continue beyond completion of ICI
Severe AEs	• Discontinue ICI • Initiate corticosteroid therapy immediately • IV methylprednisolone should be considered until evidence of improvement in toxicity • Additional immunosuppressant therapy may be required for steroid-refractory AEs • Inpatient care and additional supportive care may be required
Supportive care during immunosuppressant therapy may include:	• Monitoring of blood glucose levels • PPIs or H2 blockers to prevent gastritis • Antimicrobial and antifungal prophylaxis to prevent opportunistic infections • Vitamin D and calcium supplementation to prevent osteoporosis

AEs, adverse events; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; PPIs, proton pump inhibitors.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

NCCN Guidelines®: Immunotherapy Patient Education

Immunotherapy Background	• One of the functions of the immune system is to distinguish healthy cells from abnormal cells • Tumor cells have proteins on their surface that bind to immune cells, blocking ability of immune cells to recognize them as foreign • ICIs are a class of medications that prevent tumors from "hiding" or "evading" the body's natural immune system • ICIs block these proteins, "releasing the brakes" on the immune system's WBCs • ICI therapy may be given in combination with other ICIs, chemotherapy, or targeted therapy
Side Effects	• AEs from ICI differ from those of other types of cancer treatment • Can affect one or several different organ systems • Amplifying immune system can cause T cells to attack healthy cells in the body, causing inflammatory conditions that mimic a range of autoimmune conditions, some can be serious. Known as irAEs • irAEs can occur at any time during treatment or after treatment is completed • irAE rebound during steroid taper can also occur, which may impact steroid taper • Severity of AEs can range from asymptomatic to severe or life-threatening; may be cumulative over the course of therapy • Combination therapy may increase severity of AEs

Educational efforts must consider patient's primary language and literacy level

Education should be provided at start of therapy and at regular intervals as the trajectory of irAEs is variable

Reinforcement of educational concepts is essential

AEs, adverse events; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; WBC, white blood cells.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

NCCN Guidelines®: Immunotherapy Patient Education

Monitoring and Treatment Response

• Therapy with ICI requires close communication between patient/family and treating center
• Symptoms that patients may think are unrelated are often signs of ICI toxicity
  ○ Diarrhea or nausea
• Educate patients to notify all HCPs (esp. PCPs) that they are receiving/have received immunotherapy
• Regular monitoring will be conducted to detect any potential irAEs and to assess treatment response
• Laboratory tests should be obtained prior to each treatment and at regular intervals after completion of immune checkpoint blockade to assess for organ function
  ○ Complete metabolic panel; kidney, liver, thyroid, pancreas
• Physical exams will include monitoring of organ function
  ○ Cardiac, pulmonary, neurologic, skin
• Assess for significant shifts in weight, as they may be indicative of fluid balance disorders
• Treatment response time differs from standard cancer therapy; may take longer to see a response
• Most irAEs can be managed effectively if detected and treated early

HCPs healthcare professionals; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; PCPs, primary care providers.
Adapted from Thompson et al. NCCN Guidelines. Management of immunotherapy-related toxicities. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

Some of these drugs now can be dosed monthly or every 6 weeks. In the context of a liver cancer population, that doesn't mean you don't see them in between. It's very important to see patients in close follow-up certainly when they start their treatment, and also educate patients about what to look for as far as side effects are concerned.

That means having a broad differential for what these drugs can do. In addition, if a patient is taking steroids, watching them closely and doing a taper that's appropriate so you don't induce a flare. With that being said, many patients can be rechallenged once they're off steroids, depending on the toxicity and its severity.

Singal: I think there's a broad difference between the immunotherapies and TKIs in terms of adverse events and their management. When we take a look at the TKIs, adverse events tend to be common, although they tend to be mild, and they tend to be easily manageable with dose reductions or dose interruptions.

In contrast, when we take a look at the checkpoint inhibitors, these tend to be very well tolerated and patients tend to maintain a higher quality of life. As shown by some of the trials that have been presented, both the CheckMate 459 trial as well as the IMbrave 150 trial, where you see patients generally do quite well with high quality of life, and very few adverse events.

However, when these adverse events occur, although rare, they can be quite serious. And so, you can actually have adverse events that land people in the hospital, or even in rare cases can lead to treatment discontinuation or even death in very rare cases.

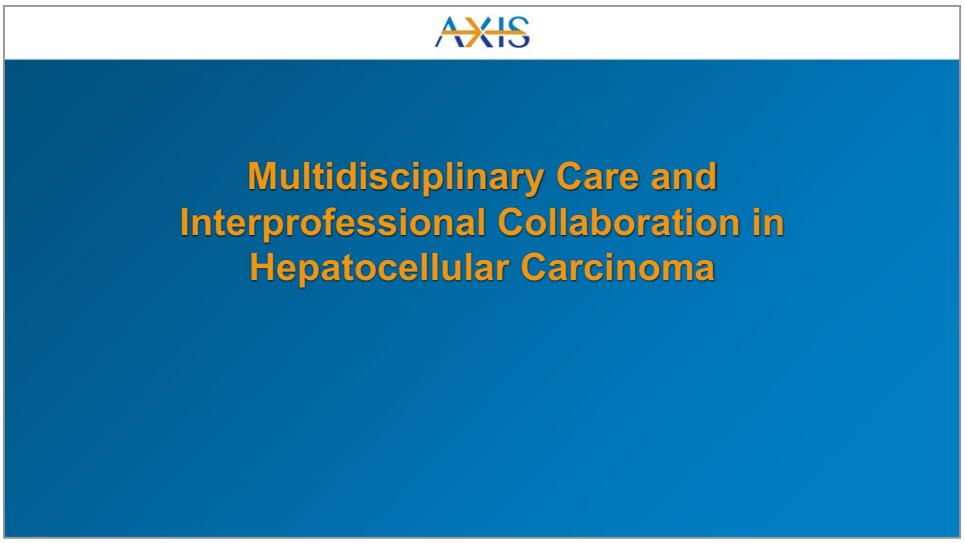
So it's important that, because these adverse events tend to be very rare, although can be serious if not detected early, it's important that we have a high level of suspicion, so we can identify these adverse events early and act upon them. Whether that's by dose interruption, or that's by treating with steroids.

The two that really stick out in my mind when you're thinking about HCC patients would be to have a high level of suspicion for immune-mediated hepatitis, and endocrinopathies. Because those can actually be quite easily overlooked if you don't have that high level of suspicion.

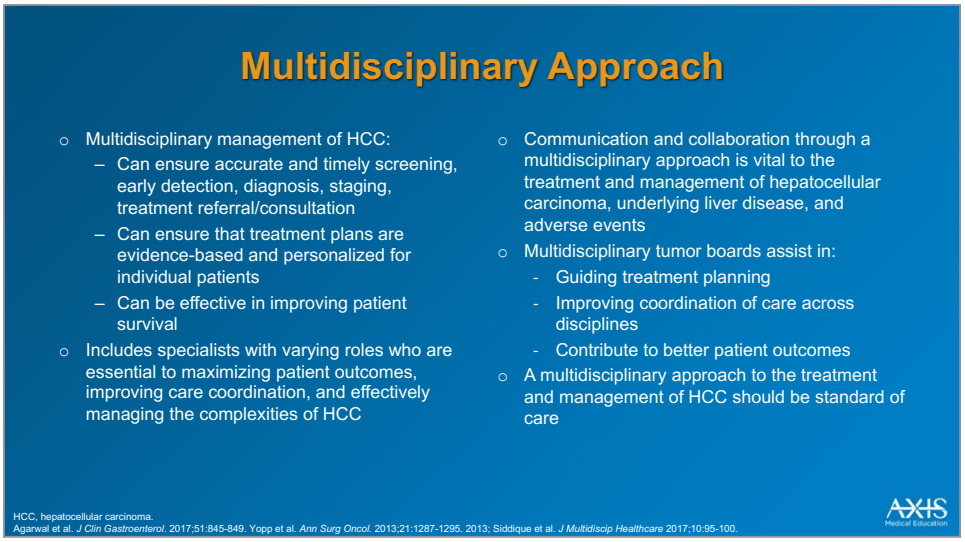
Patients with HCC tend to have underlying chronic liver disease and will have elevated liver enzymes. And so, you can't ignore mild elevations or moderate elevations in liver enzymes as being related to the underlying liver disease. If you see a steady elevation in those liver enzymes, I think it's worth considering and asking yourself, is this the onset of immune-mediated hepatitis, and should I withhold the checkpoint inhibitor?

Likewise, if a patient's presenting with increased fatigue or malaise, this could be the cirrhosis, but it could be early signs of an endocrinopathy related to the checkpoint inhibitor. And once again, at that point it's worth asking yourself, could this be related to thyroid dysfunction or adrenal insufficiency? And should I withhold the drug or delay the drug, or should I treat with steroids?

Overall these drugs are very safe. But once again, we must have a high level of suspicion for adverse events so we can act early and prevent them from becoming significant.

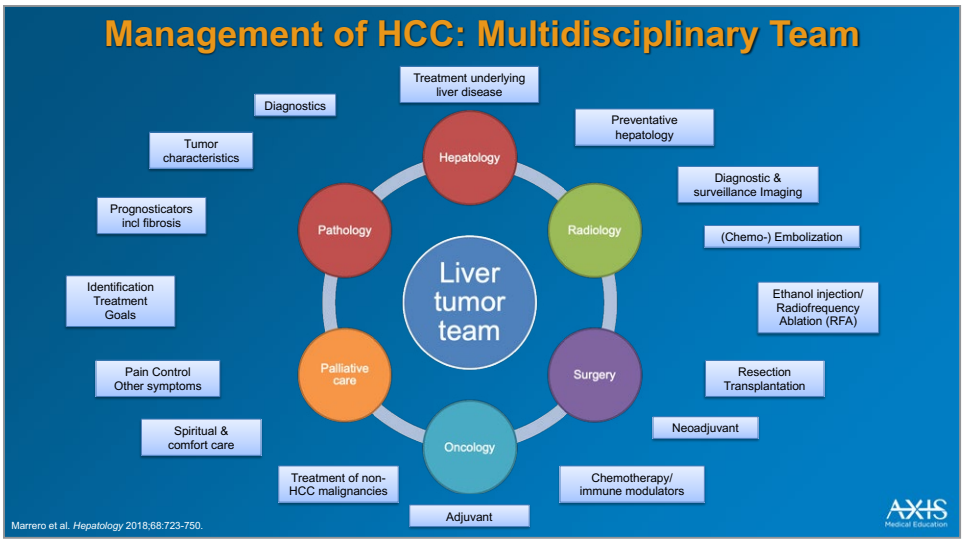


Mocharnuk: Thanks for those insights. Given the complexities inherent to patients with HCC and the wealth of treatments now available, it seems that multiple specialists are needed to manage these patients. Dr. Singal, would you speak to this point?

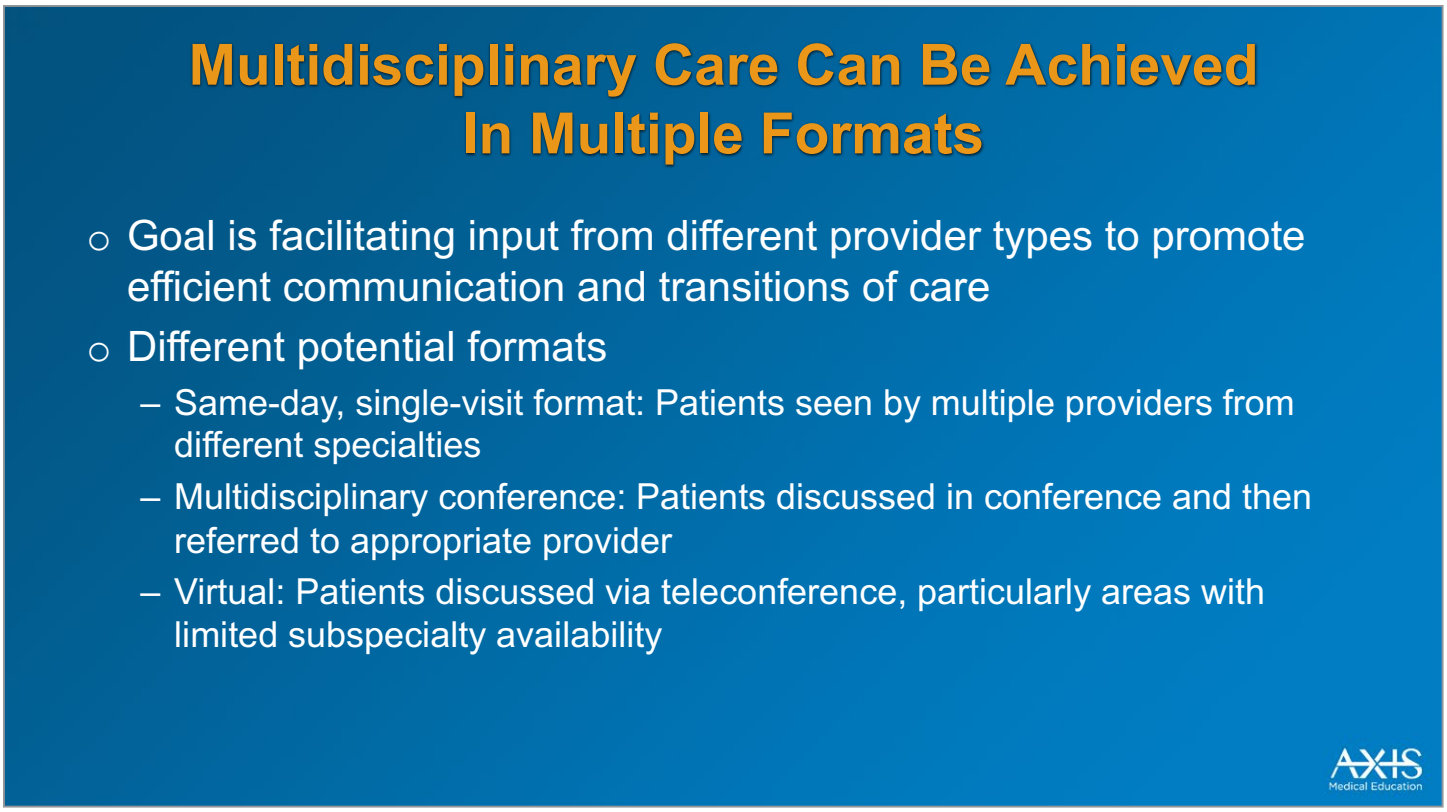


Singal: This is a very important point, and something that we really have to consider when we manage patients with HCC. There are two key points. The first is that most patients who present with HCC actually have chronic liver disease, if not cirrhosis. So this is a disease within a disease. And this really highlights up front the importance of involving a hepatologist throughout the care of all patients with HCC.

The second is that when we think about the management of HCC, this really is a broad treatment landscape that goes all the way from surgical therapies to local regional therapies to systemic therapies. And these therapies are all delivered by different providers.



- So when you think of the multidisciplinary format, you really involve providers from surgery—that includes transplant surgery and surgical oncologists. You involve interventional radiologists who can do things like ablation, chemoembolization, radioembolization. We see radiation oncologists who can do things like stereotactic body radiation therapy. And then, of course, medical oncologists who can give systemic therapy.



Now when we traditionally think about the management of an HCC patient, we think of one provider giving one single therapy at one point. But we've become more and more cognizant that oftentimes we're thinking of sequential therapies or even combination therapies. So for example, somebody who's listed for transplant often needs bridging therapies while they're on the transplant list.

There are more and more trials evaluating combination therapies of systemic therapy when used in combination with surgical therapy or in combination with loco-regional therapy. These trials are ongoing but are highly promising. This is really where the field is going. And so, this once again highlights the importance of constant communication between these providers to not only think of the optimal treatment up front, but the optimal treatments as patients either respond or don't respond to treatments, so we can continue having them be on the best therapy at each individual point.

When we think of multidisciplinary care, the traditional format has been to do this in a multidisciplinary conference. And I think many of us have these at our centers, where we work with radiology, we present imaging, and you discuss as a group to determine the best up-front therapy. But more and more centers are also building in other formats.

For example, fluid referral systems, where people can go between clinics on the same days easily, or even co-located clinics, that is, a one-stop shop where a patient can come in and see multiple providers that same day. This makes it the most convenient for a patient, also maximizing communication between providers, once again optimizing treatment choices, not only in the beginning but also along the entire treatment continuum.

Multidisciplinary Care Improves HCC Outcomes

Study	No. of Patients	Description	Outcomes
Sinn 2019	6,619	Single day MDT conference	Improves survival
Serper 2017	3,988	Multi-specialty evaluation or tumor board	Increases HCC treatment receipt and improves survival
Yopp 2014	355	Single day MDT clinic and conference	Improves early detection, curative treatment, time to treatment, and survival
Zhang 2013	343	Single day MDT clinic	Changes imaging/pathology interpretation and therapy plan
Chang 2008	183	Fluid referrals and joint conference	Improves early detection, curative treatment, and survival

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

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- Now as we start to think about this, multidisciplinary care obviously sounds like a great option for patients, and it sounds very enticing. But one of the things in HCC is that we actually have very good data showing that this significantly improves outcomes. So we have several studies, as you can see here, that show different formats of multidisciplinary care actually improves outcomes. Whether that's increasing treatment received, increasing guideline concordance, increasing curative treatment. But most importantly, it improves survival.

  And once again, this has been shown consistently across studies that have evaluated the importance or the benefits of multidisciplinary care.

Multidisciplinary Care Associated With Improved Survival

Variable (N = 3,988)	HR (95% CI)
BCLC stage (vs BCLC 0)	
A	1.13 (0.94-1.36)
B	1.63 (1.36-1.96)
C	2.50 (2.05-3.05)
Child Pugh B	1.5 (1.37-1.64)
Type of HCC therapy	
Liver transplant	0.22 (0.16-0.31)
Resection	0.38 (0.28-0.52)
Ablation	0.63 (0.52-0.76)
Transarterial therapies	0.83 (0.74-0.92)
Systemic therapies	1.99 (1.80-2.20)
MDC tumor board	0.83 (0.77-0.90)
Specialist within 1 month	
Hepatology	0.70 (0.63-0.78)
Medical oncology	0.82 (0.74-0.91)
surgery	0.79 (0.71-0.89)

- Cohort study of national VA from Jan 2008 to Dec 2014
- Multi-specialty evaluation was associated with HCC therapy (HR 1.60, 95% CI 1.15-2.21)
- Review by MDC tumor board was associated with reduced mortality (HR 0.83, 95% CI 0.77-0.90)

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; MDC, multidisciplinary committee.
Serper et al. *Gastroenterology* 2017;152:1954-1964

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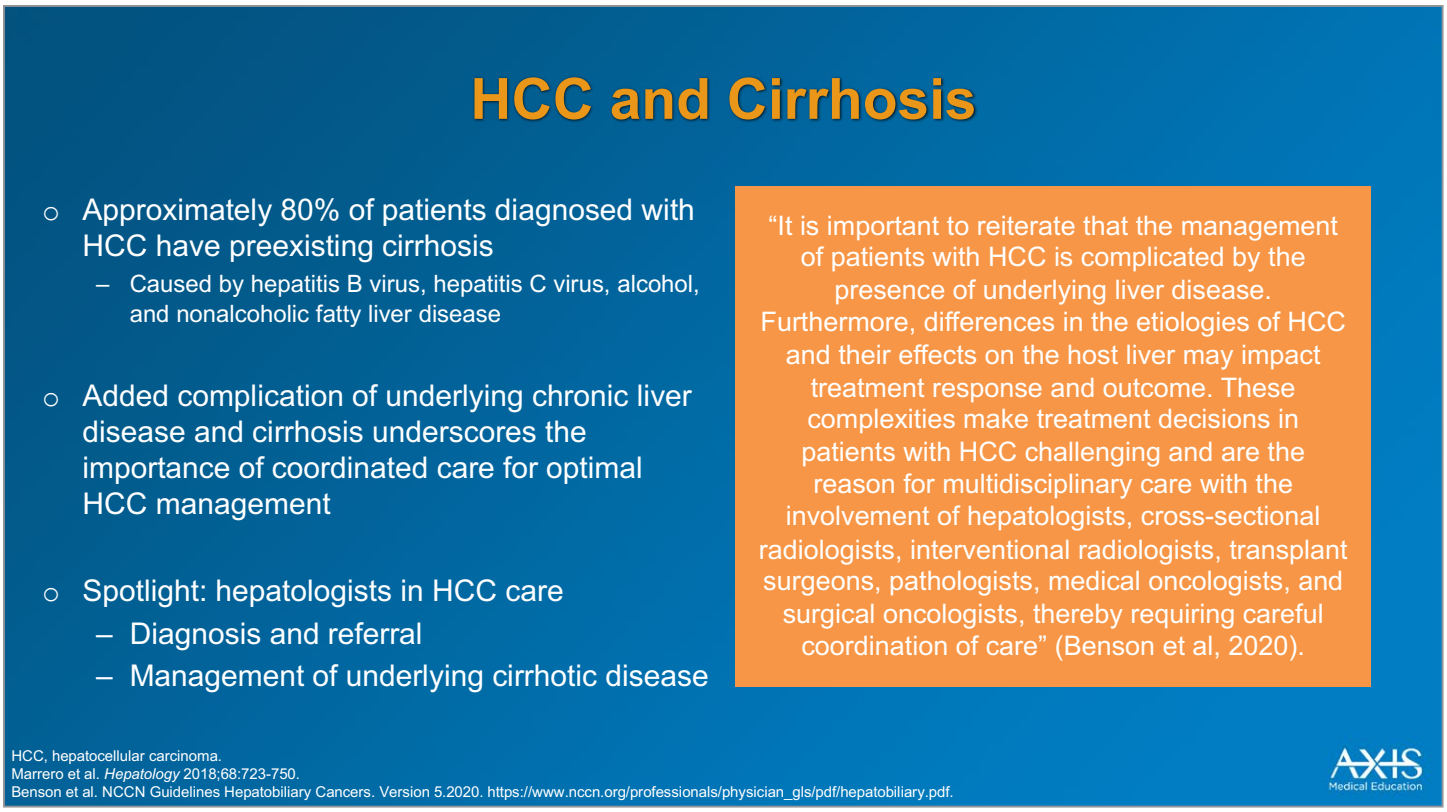
- Now when we take a look at all of those studies, here you can see probably one of the largest studies that's evaluated multidisciplinary care in just under 4,000 patients. This was a cohort study that came out of the National Veterans' Affairs in the United States, taking a look at patients with HCC diagnosed between 2008 and 2014.

  And when we look at the associations within this study, we see that multi-specialty evaluation was associated with the receipt of HCC therapy with an odds ratio of 1.6. And most importantly, review by a multidisciplinary tumor board was associated with reduced mortality, a 17% reduction in mortality, statistically and clinically significant.

  This really highlights that multidisciplinary care is not only something that sounds good, but also improves outcomes and should be considered the standard of care for all patients with HCC receiving care in clinical practice.



Mocharnuk: We appreciate both of your insights on this issue. Our time is drawing short, so Dr. Finn, would you please summarize the important points of today's presentation?

Finn: Thank you very much for having me in the program. It's important to take away a few important points. One is that liver cancer is really 2 diseases. It's a tumor and it's an underlying liver disease. In that context, the importance of a multidisciplinary approach is paramount. For patients who present with intermediate disease and get treated with things such as locoregional treatment, it's important to keep in mind that patients are not cured with that, and eventually the disease will progress.

Now that we have so many options in frontline and second line that are improving survival, it's important that we transition patients at the right time.

To maximize the benefit from systemic treatment, we need to get patients before they're decompensated. As the patients go through their natural history of cirrhosis or locoregional treatment, we can see them start to decline in their performance status, as well as their liver function, which might limit our ability to treat them with the drugs that we have available. Again, it's important to work in the context of a multidisciplinary program.

Key Takeaways

- After nearly a decade, 4 positive phase 3 studies have resulted in FDA approval of 4 new drugs in HCC that improve survival
  - Lenvatinib non-inferior to sorafenib, HR 0.92
  - Regorafenib vs placebo, second line, HR 0.62
  - Cabozantinib vs placebo, second and third line (HR 0.70 prior sorafenib)
  - Ramucirumab vs placebo, second line, high AFP
- For the first-time, there is a highly active regimen that is superior to sorafenib first-line (practice changing)
- Level 1 Evidence for single agent checkpoint inhibitors?
  - Nivolumab vs sorafenib first-line: did not meet endpoint
  - Pembrolizumab vs placebo second-line: did not meet stats
- Ongoing studies looking at novel combinations
  - Checkpoint inhibitors and TKIs
  - PD-1+ CTLA-4

Immunotherapy	Trial	FDA Approval
First-Line		
Atezolizumab + bevacizumab	IMbrave150	May 2020: FDA approved for patients with unresectable or metastatic HCC who have not received prior systemic therapy
Second-line		
Nivolumab	CheckMate-040	Sept 2017: FDA accelerated approval for patients with HCC who have been previously treated with sorafenib
Pembrolizumab	KEYNOTE-224	Nov 2018: FDA accelerated approval for patients with HCC who have been previously treated with sorafenib
Nivolumab + ipilimumab	CheckMate-040	March 2020: FDA accelerated approval for patients with HCC who have been previously treated with sorafenib

AFP, alpha fetoprotein; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; FDA, US Food & Drug Administration; HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1; TKIs, tyrosine kinase inhibitors.

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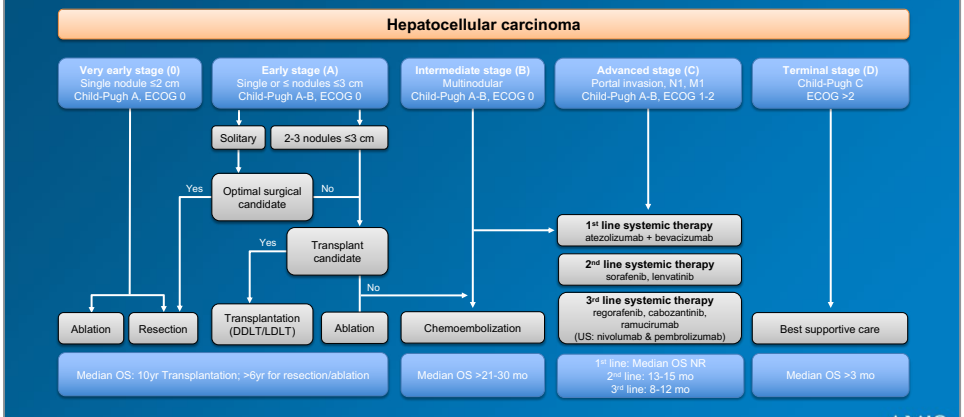
When we look at the drugs we have now, after a decade of no drugs newly approved, we have a number of drugs approved with high levels of evidence, including in frontline atezolizumab and bevacizumab, as well as lenvatinib for its noninferiority to sorafenib and improving secondary endpoints. In second line, regorafenib and cabozantinib—small molecules approved after sorafenib. We also have ramucirumab, which was approved as a monoclonal antibody single agent for patients who progress on sorafenib but have a high alpha fetoprotein (>400).

That's one of the drugs in liver cancer that we have a biomarker for to select patients. Given all of these new agents, it's important for us to figure out how best to sequence them in clinical practice. At the same time, there are a lot of new exciting things coming along. So, just as we're getting settled in with this dataset, perhaps, there will be changes in the near future.

So, thank you very much for the opportunity to participate in the program.

Treatment Strategy in the Management of HCC 2020



ECOG, Eastern Cooperative Oncology Group; OS, overall survival.
Adapted from Llovet et al. *Hepatology* 2020 May 20. doi: 10.1002/hep.31327. Online ahead of print.

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Mocharnuk: Thank you, Dr. Finn and Dr. Singal, for this excellent review. And thank you to our audience for your participation in this activity.

REFERENCES

Agarwal PD, Phillips P, Hillman L, et al. Multidisciplinary management of hepatocellular carcinoma improves access to therapy and patient survival. *J Clin Gastroenterol.* 2017;51:845-849.

Benson et al. NCCN Guidelines Hepatobiliary Cancers. Version 5.2020. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.

Brahmer J, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2018;36(17):1714-1768.

Bruix J, Reig M, Sherman M, et al. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology* 2016;150:835-853.

Chang TT, Sawhney R, Monto A, et al. Implementation of a multidisciplinary treatment team for hepatocellular cancer at a Veterans Affairs Medical Center improves survival. *HPB (Oxford)* 2008;10:405-411.

Chen DS and Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013;39:1-10.

Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2009;10:25-34.

Cheng AL, Qin S, Ikeda M, et al. IMbrave150: Efficacy and safety results from a phase III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). *Ann Oncol*. 2019;30:ix186-ix187.

El-Khoueiy AB, Sangro B, Yau T et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017;389:2492-2502.

Ernstoff MS, Puzanov I, Robert C, Diab A, Hersey P, eds. *SITC's Guide to Managing Immunotherapy Toxicity*. New York: demosMEDICAL; 2019.

Facciabene A, Peng X, Hagemann IS, et al. Tumour hypoxia promotes tolerance and angiogenesis via CCL28 and T(reg) cells. *Nature* 2011;475:226-230.

FDA News Release. September 22, 2017. FDA grants accelerated approval to nivolumab for HCC previously treated with sorafenib. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm577166.htm.

FDA News Release. November 9, 2018. FDA grants accelerated approval to pembrolizumab for hepatocellular carcinoma. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm625705.htm.

FDA News Release. March 10, 2020. FDA grants accelerated approval to nivolumab and ipilimumab combination for hepatocellular carcinoma. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma.

FDA News Release. May 29, 2020. FDA approves atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-plus-bevacizumab-unresectable-hepatocellular-carcinoma.

Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med.* 2020;382:1894-1905.

Finn et al. A phase Ib study of lenvatinib (LEN) plus pembrolizumab (PEMBRO) in unresectable hepatocellular carcinoma (uHCC). *J Clin Oncol.* 2020;38: abstract 4519.

Finn RS, Ryoo B-Y, Merle P, et al. Results of KEYNOTE-240: phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). *J Clin Oncol.* 2019;37:4004.

Gabrilovich DI and Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol.* 2009;9:162-174.

Gabrilovich DI, Chen HL, Girgis KR, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. *Nat Med*. 1996;2:1096-1103.

Goel S, Duda DG, Xu L, et al. Normalization of the vasculature for treatment of cancer and other diseases. *Physiol Rev.* 2011;91:1071-1121.

Haanen J, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines. *Ann Oncol.* 2017;28: iv119-iv142.

He AR, Yau T. Hsu C, et al. Nivolumab + ipilimumab combination therapy in patients with advanced hepatocellular carcinoma: subgroup analysis from CheckMate 040. *J Clin Oncol.* 2020;38:512.

Hegde PS, Wallin JJ, Mancao C, et al. Predictive markers of anti-VEGF and emerging role of angiogenesis inhibitors as immunotherapeutics. *Semin Cancer Biol.* 2018;52:117-124.

Hodi FS, Lawrence D, Lezcano C, et al. Bevacizumab plus ipilimumab in patients with metastatic melanoma. Cancer *Immunol Res.* 2014;2:632-642.

Hsu C-H, Lee MS, Ryoo B-Y, et al. Safety and clinical activity results from atezolizumab + bevacizumab in hepatocellular carcinoma: updates from a phase 1b study. Presented at APASL 2019; Manila. https://medically.roche.com/content/dam/pdmahub/non-restricted/oncology/hepatocellular-carcinoma/apasl-2019/Atezo_APASL_PhIb_HCC_Hsu_oral_FINAL_2019FEB21.pdf.

Kelley RK, Cheng A-L, Braiteh FS, et al. Phase 3 (COSMIC-312) study of cabozantinib (C) in combination with atezolizumab (A) versus sorafenib (S) in patients (pts) with advanced hepatocellular carcinoma (aHCC) who have not received previous systemic anticancer therapy. *J Clin Oncol.* 2019;37(15_suppl): abstract TPS4157. https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.TPS4157.

Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359:378-390.

Llovet JM and Lencioni R. mRECIST for HCC: performance and novel refinements. *J Hepatol* 2020;72(2):288-306.

Marrero JA, Kulik LM, Sirlin C, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018;68:723-750.

Motz GT, Santoro SP, Wang LP, et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. *Nat Med.* 2014;20:607-615.

Oyama T, Ran S, Ishida T, et al. Vascular endothelial growth factor affects dendritic cell maturation through the inhibition of nuclear factor-kappa B activation in hemopoietic progenitor cells. *J Immunol.* 1998;160:1224-1232.

Podar K and Anderson KC. The pathophysiologic role of VEGF in hematologic malignancies: therapeutic implications. *Blood* 2005;105:1383-1395.

Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378:159-168.

REFERENCES

Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 2017;5:95.

Roland CL, Lynn KD, Toombs JE, et al. Cytokine levels correlate with immune cell infiltration after anti-vegf therapy in preclinical mouse models of breast cancer. *PLoS One* 2009;4:e7669.

Serper M, Tadderi TH, Mehta R, et al. Association of provider specialty and multidisciplinary care with hepatocellular carcinoma treatment and mortality. *Gastroenterology* 2017;152:1954-1964.

Siddique O, Yoo ER, Perumpail RB, et al. The importance of a multidisciplinary approach to hepatocellular carcinoma. *J Multidiscip Healthcare* 2017;10: 95–100.

Thompson JA, Schneider BJ, Brahmer J, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Management of immunotherapy-related toxicities. Version 1.2020. © 2019 National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

Voron T, Colussi O, Marcheteau E, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. *J Exp Med.* 2015;21:139-148.

Wallin JJ, Bendell JC, Funke R, et al. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. *Nat Commun.* 2016;7:12624.

Yau T, Kang Y, Kim T, et al. Nivolumab + ipilimumab combination therapy in patient with advanced hepatocellular carcinoma: Results from CheckMate 040. *J Clin Oncol.* 2019; 37:4012-4012.

Yau T, Park JW, Finn RS, et al. CheckMate 459: a randomized, multi-center phase 3 study of nivolumab (nivo) vs sorafenib (sor) as first-line (1l) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). *Ann Oncol.* 2019;30: v851-v934. 10.1093/annonc/mdz394. https://www.annalsofoncology.org/article/S0923-7534(19)60389-3/pdf.

Yopp AC, Mansour JC, Beg MS, et al. Establishment of a multidisciplinary hepatocellular carcinoma clinic is associated with improved clinical outcome. *Ann Surg Oncol.* 2013;21:1287-1295. 2014;21:1287-1295.

Zhang J, Mavros MN, Cosgrove D, et al. Impact of a single-day multidisciplinary clinic on the management of patients with liver tumours. *Curr Oncol.* 2013;20:e123-e131.

Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomized, open-label phase 2 trial. *Lancet Oncol.* 2018;19:940-952.

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