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Advocating for Action in HCC:

Delivering Impartial and Personalized Care

This transcript has been edited for style and clarity and includes all slides from the presentation.

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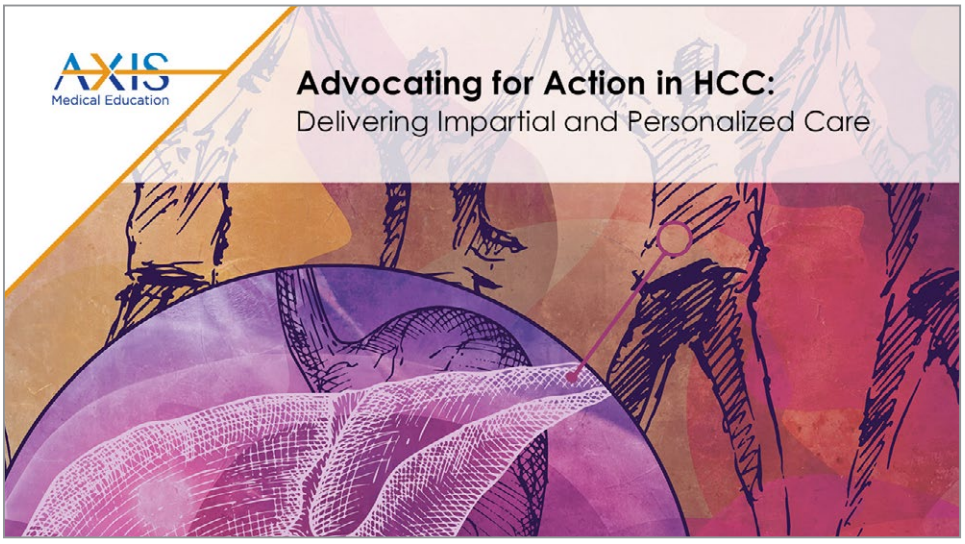
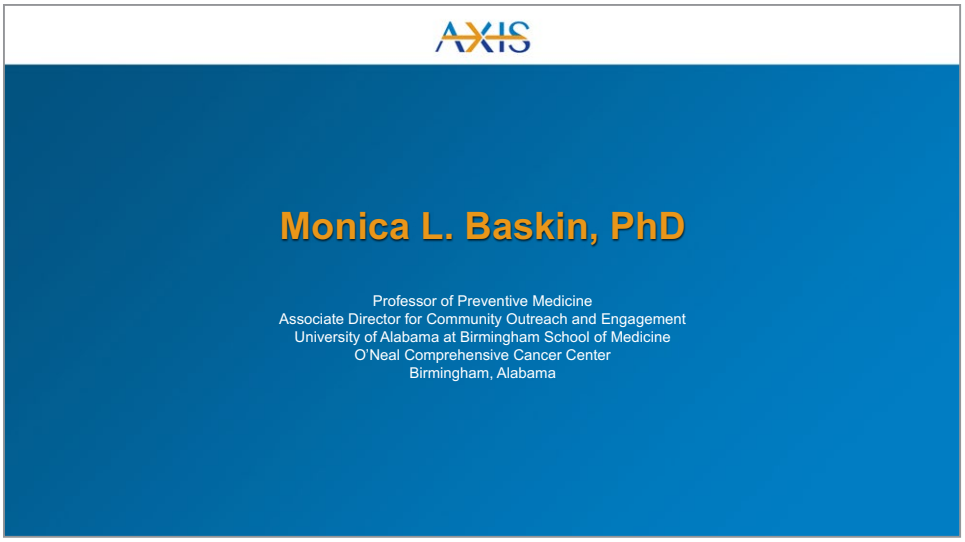
Advocating for Action in HCC: Delivering Impartial and Personalized Care

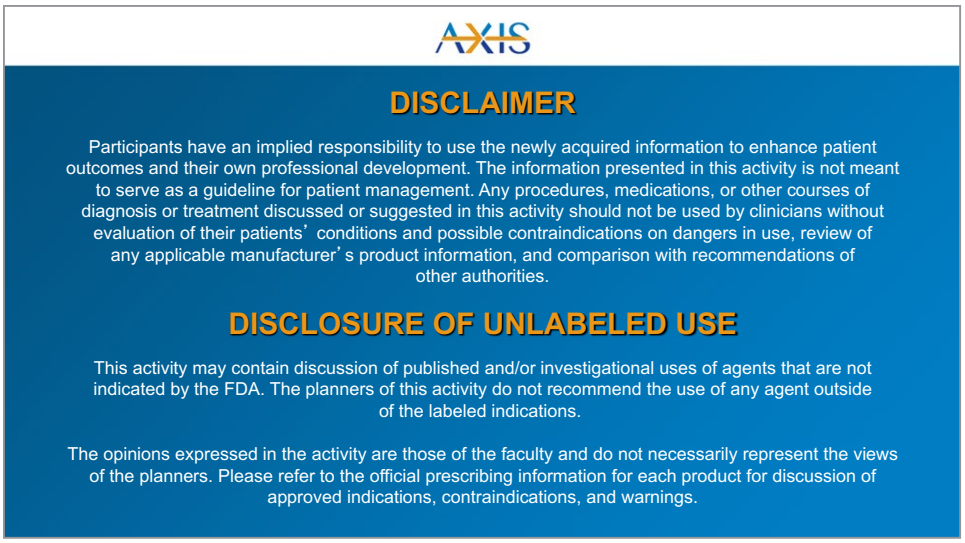
Monica L. Baskin, PhD and Josep M. Llovet, MD, PhD



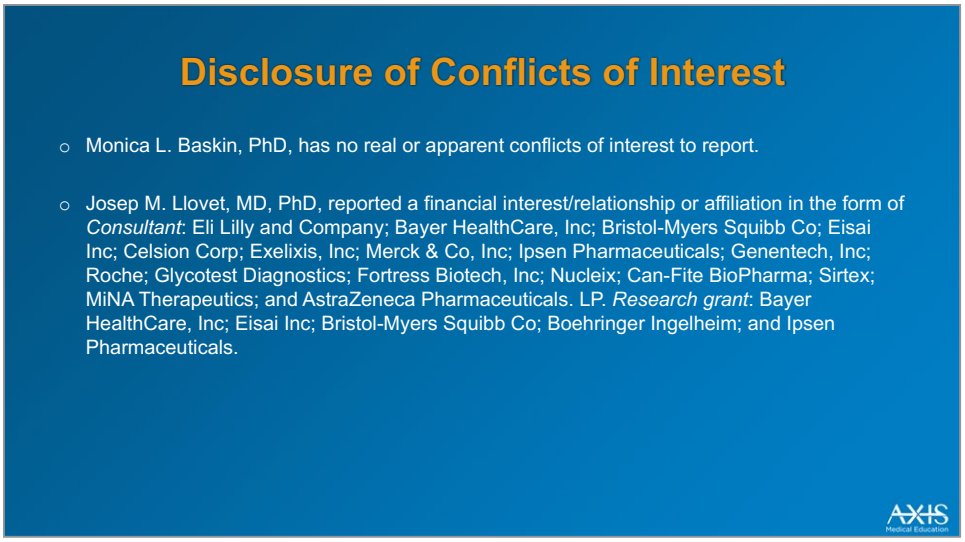
Monica L. Baskin, PhD: Hello and welcome to this educational activity, *Advocating for Action in HCC: Delivering Impartial and Personalized Care*.



I'm Dr. Monica Baskin. I'm delighted to present to you a little bit more about understanding health disparities and inequities in HCC. Dr. Llovet will then join us to discuss targeted therapies and a new era in HCC management — combination therapies.



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



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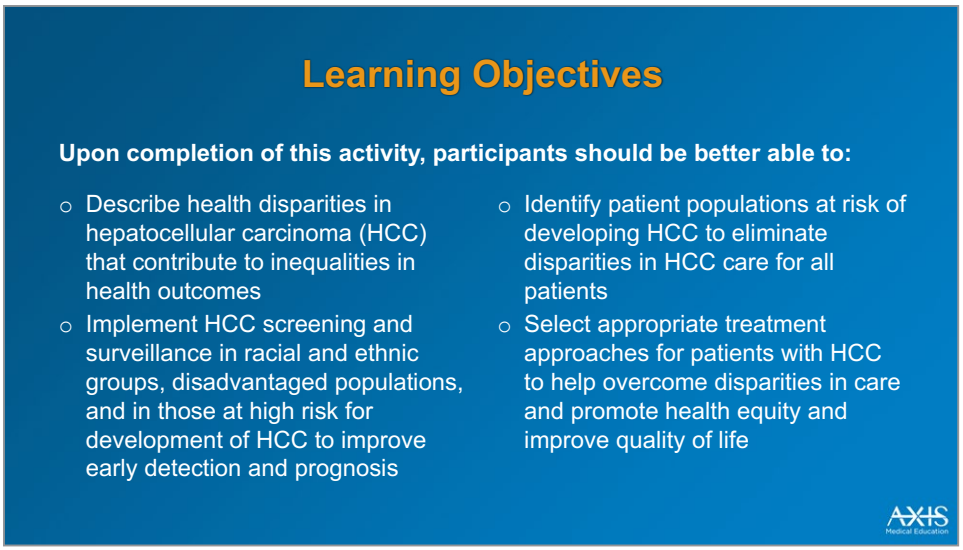
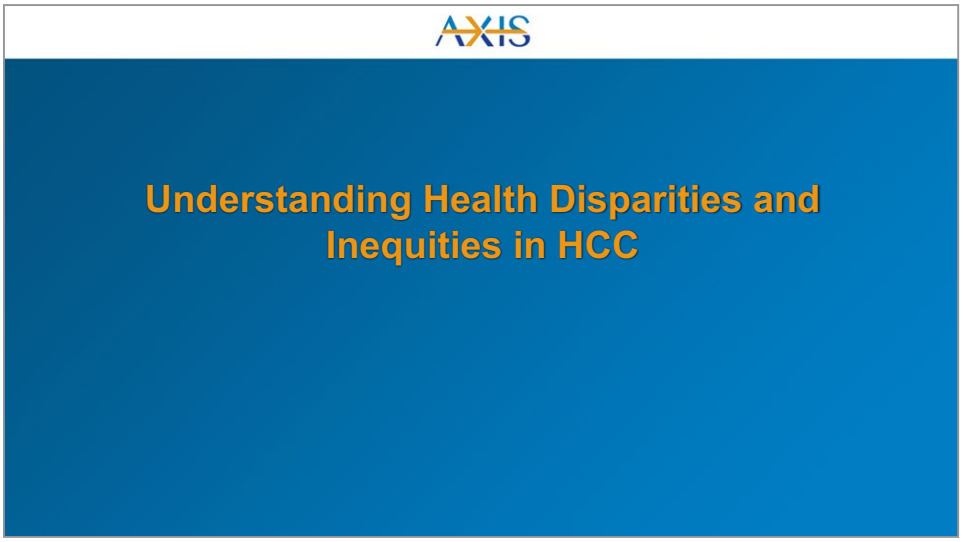


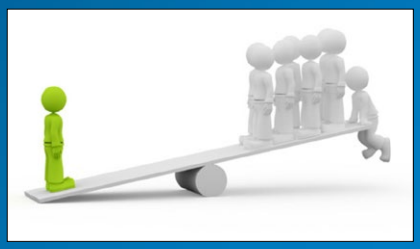
- And these are the learning objectives for this activity.



- To start, let's make sure we understand what is meant by health and healthcare disparities.

What Are Health and Healthcare Disparities?

- Health and healthcare disparities refer to differences in health and healthcare between groups that are closely linked with social, economic, and/or environmental disadvantage
  - Disparities occur across many dimensions, including race/ethnicity, socioeconomic status, age, location, sex, disability status, and sexual orientation



Artiga et al. 2020. https://www.kff.org/racial-equity-and-health-policy/issue-brief/disparities-in-health-and-health-care-five-key-questions-and-answers/.

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- So when we're talking about health and healthcare disparities, we're referencing the difference in health or healthcare between groups that are closely linked with social, economic, and environmental disadvantage. So these can be examples such as race and ethnicity, socioeconomic status, their physical location, sex, disability status, and sexual orientation.

What Are Cancer Health Disparities?

Cancer disparities (cancer health disparities) consist of differences in cancer measures such as:

- Incidence (new cases)
- Prevalence (all existing cases)
- Mortality (deaths)
- Morbidity (cancer-related health complications)
- Survivorship, including quality of life after cancer treatment
- Financial burden of cancer or related health conditions
- Screening rates
- Stage at diagnosis

National Cancer Institute. 2020. https://www.cancer.gov/about-cancer/understanding/disparities

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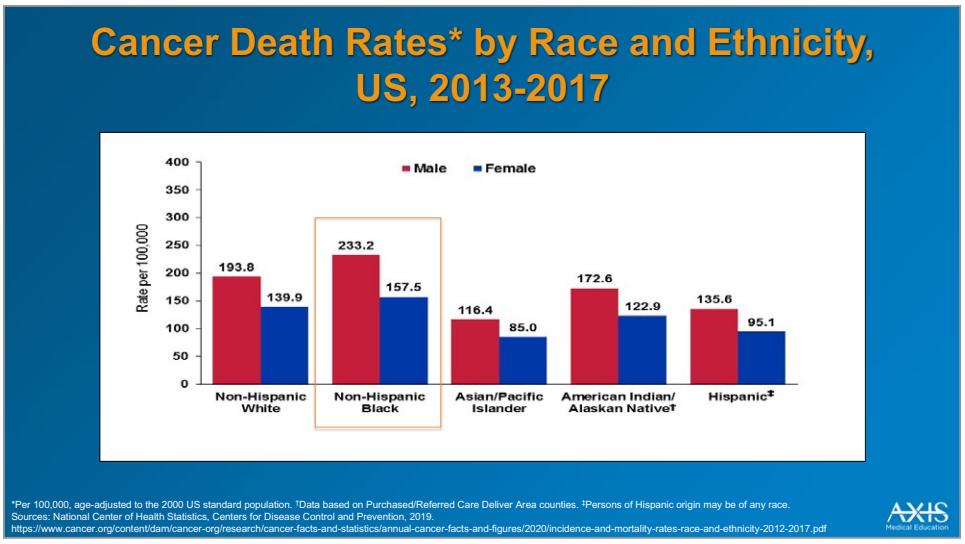
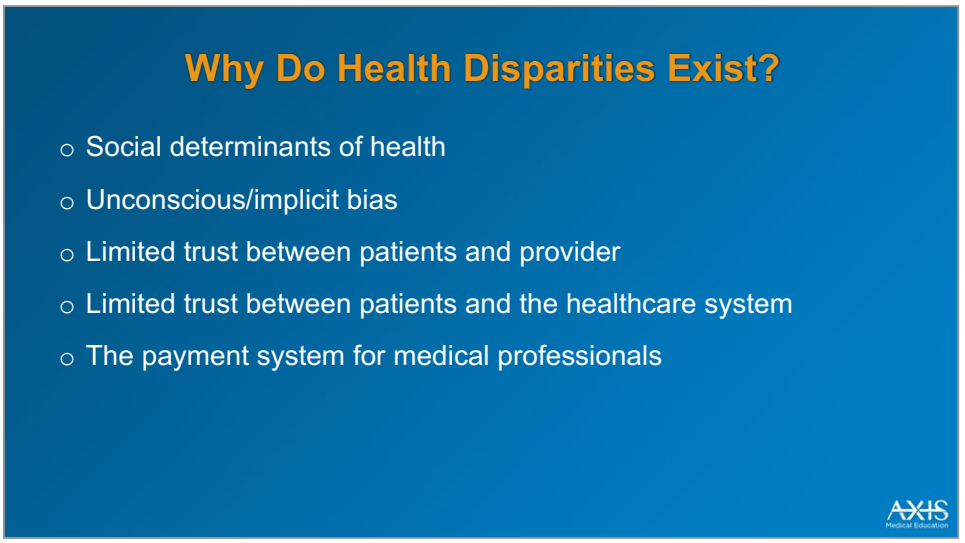
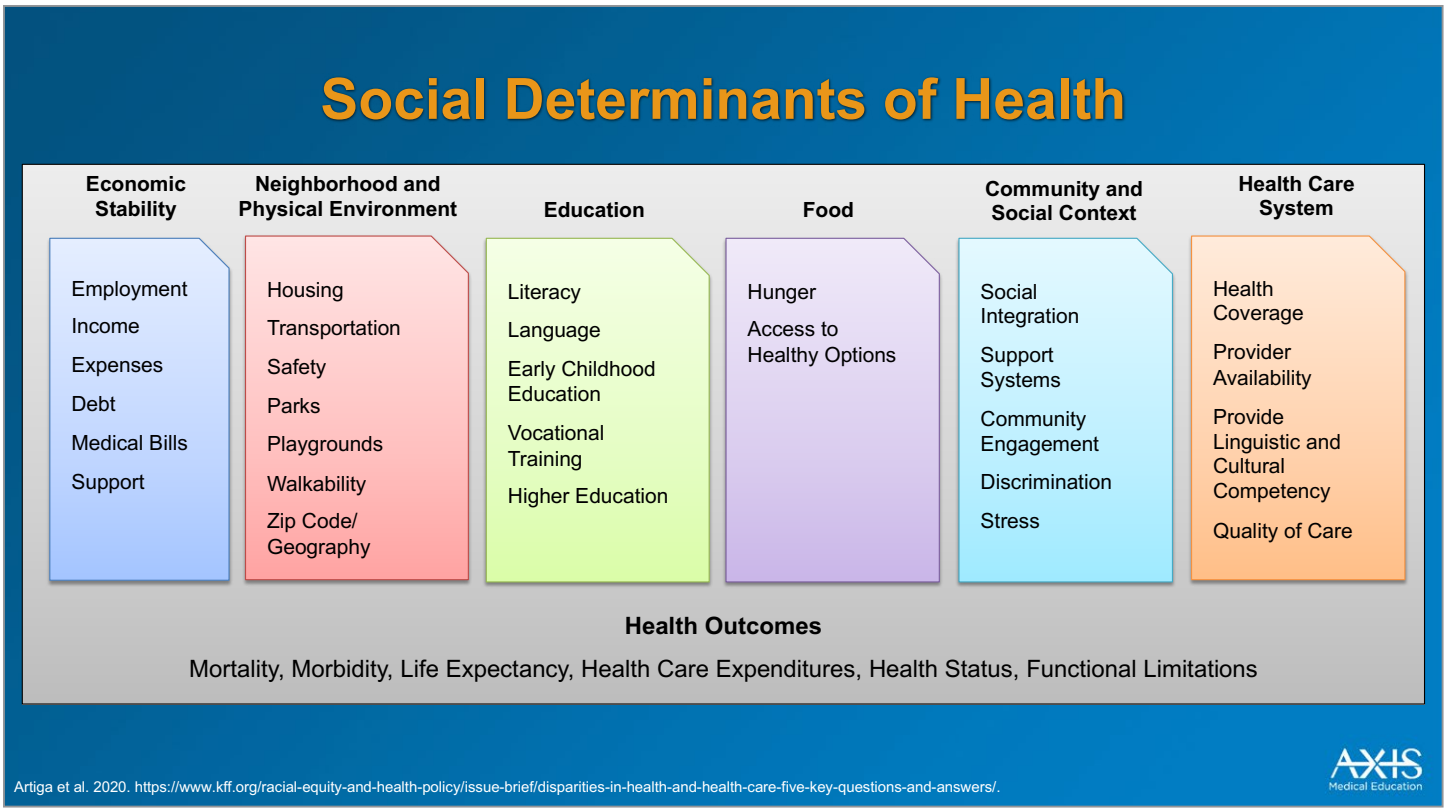
- More specifically, the National Cancer Institute defines cancer health disparities as differences in cancer measures such as the number of new cases, all existing cases, deaths, cancer-related health complications, survivorship, financial burden, screening rates, or stage at diagnosis.



- One such example is depicted here in this graph by the Centers for Disease Control and Prevention. It's looking at cancer death rates by race and ethnicity for the years 2013 to 2017. What you will see here is that the rates of cancer deaths do vary by race and ethnicity with non-Hispanic blacks, both male and female, having higher rates of cancer deaths during that period than any other racial and ethnic group. You might also notice the differences between males and females where overall, males were more likely to die from cancer than females across each of those groups.



- Why do these disparities exist? There are a number of reasons in the literature that suggest why we may see the differences in cancer health outcomes. There are social determinants of health so things beyond biology may be implicated in these disparities. We also know that unconscious or implicit bias has a role, as well as limitations in trust both between patients and providers as well as patients and the healthcare system, in general, and there may be implications of the way in which health systems and providers are paid that may play a role. So we'll briefly talk about each one of those now.



- First is social determinants of health. So we all probably easily recognize that our biology and our genetics play a role in our health and health outcomes. But what literature has shown is that there are these other things that are not related directly to our physiology that have implications for our health and outcomes. Those things include economic stability; ie, whether not an individual is employed, their income, and other kinds of things related to economics play a major role. We also know that the neighborhood and physical environment or, basically, where people live—you may have heard the phrase 'your zip code may be just as important as your genetic code in determining your health.' So where you live, your housing and transportation, all of that plays a role in terms of our health outcomes.

  Education is another one of those areas that's considered to be a social determinant of health. Not only your formal education, but also related to issues of literacy—your basic understanding of what's happening specifically around your health. Food is another one of the social determinants—so whether you have appropriate or adequate food or are experiencing hunger, if you have access to healthy options in your community. The community and social context that's also been identified as an implication in the disparity. So whether you have appropriate social supports to help you through your cancer and other issues, whether you're experiencing a significant amount of stress or discrimination, and how well you're integrated with your neighbors and your community are also implicated here.

  And finally, the healthcare system has a role to play in terms of determinants of health. This could be something as broad as whether individuals have healthcare coverage but also the issue of whether the providers are linguistically and culturally competent in the overall quality of care being received.

Implicit Bias

- Racial bias can involve explicit or negative thoughts and feelings about individuals of another race
- Implicit racial bias is automatically activated and operates at a nonconscious level
- Non-black (i.e., white, Asian, and Hispanic/Latino) health-care providers display substantial implicit racial bias toward blacks at levels comparable to the general public

Higher implicit racial bias of oncologists associated with:

- Shorter patient interactions
- Less patient-centered and supportive care
- More patient difficulty remembering contents of the interaction
- Less patient confidence in recommended treatments and greater perceived difficulty completing them

Penner et al. *J Clin Oncol.* 2016;34(24):2874-2880.

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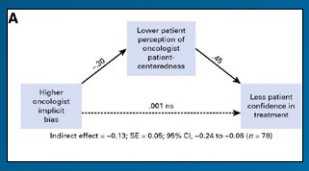
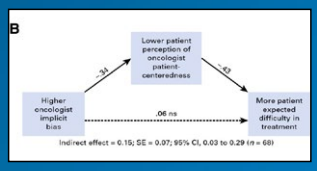
- Implicit biases are also implicated in cancer health disparities. These are our unconscious thoughts about individuals based on their membership in a particular group. What the literature indicates specifically around cancer is that higher implicit racial bias of oncologists is associated with shorter patient interactions between that provider and the patient. It's also associated with less patient-centered and supportive care, more patient difficulty remembering the contents of the interaction, and less patient confidence in being able to follow through with the recommendations of that provider.

Indirect Effects Of Oncologist Implicit Bias On Patient Treatment Expectations

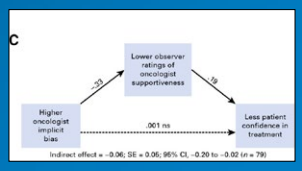
Patients' perceptions of oncologist patient centeredness and confidence in treatment



Patients' perceptions of oncologist patient centeredness and expected difficulty in treatment



Observers' ratings of oncologist supportiveness and patient confidence in treatment



Significant indirect effects of oncologist implicit racial bias on patients' degree of confidence in recommended treatments and perceptions of difficulty in completing them

Penner et al. *J Clin Oncol.* 2016;34(24):2874-2880.

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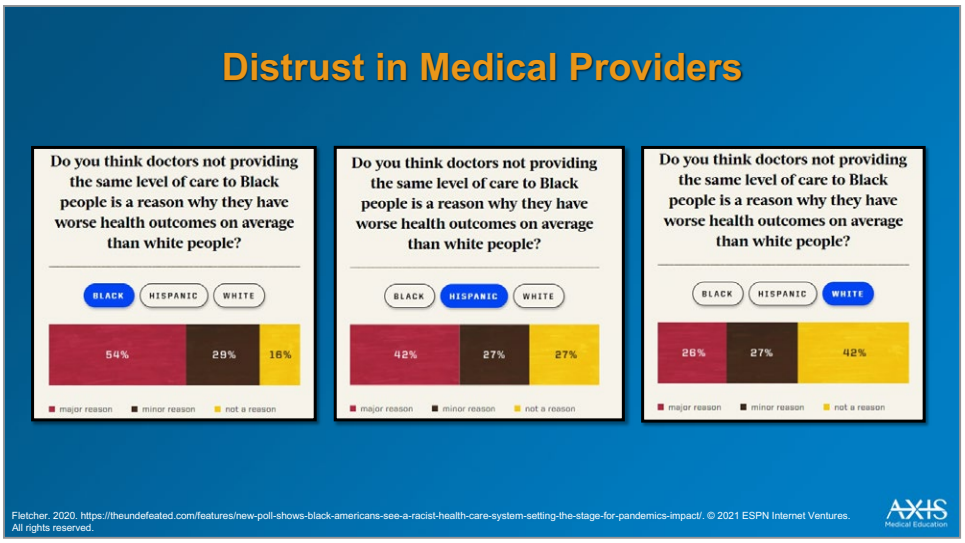
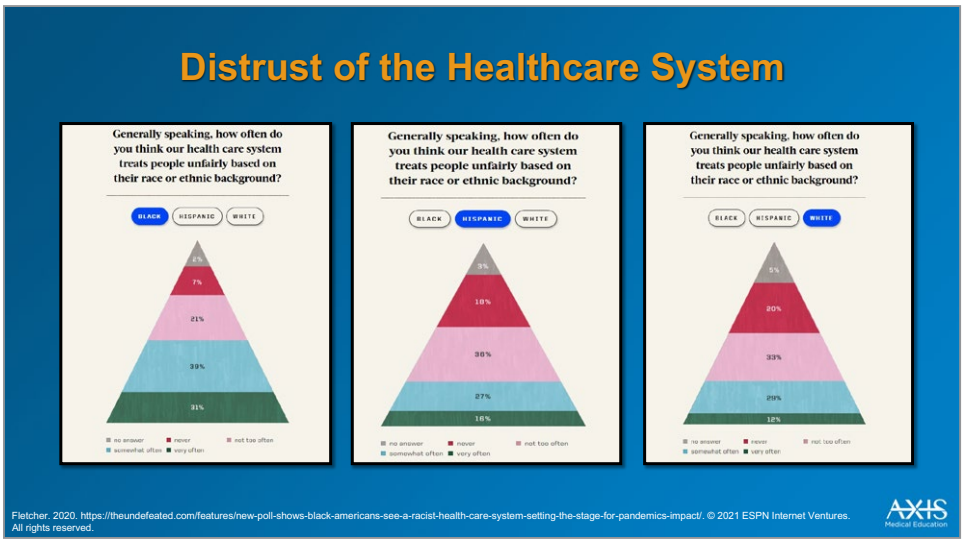
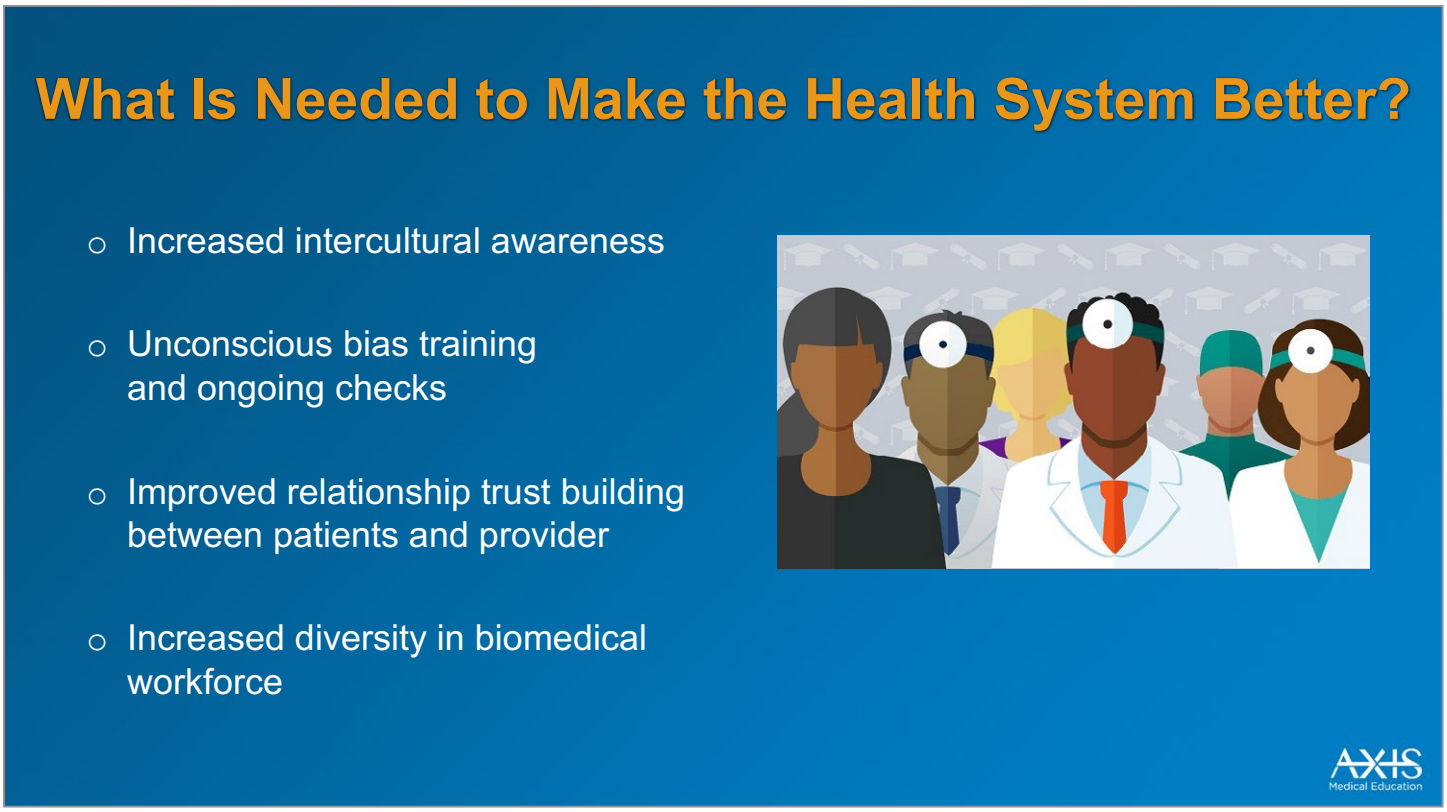
- These are some data looking at the direct quantifiable implications of those different biases on patient treatment outcomes.



- Another area that is implicated for cancer health disparities is issues around trust. This recent poll looked at the distrust in medical providers. What they asked in the poll was 'Do you think doctors not providing the same level of care to Black people is a reason why they have worse health outcomes, on average, than White people?' And through these 3 different charts, you'll see the responses by individuals who identified as being Black, Hispanic, and White. There's a notable difference in terms of those groups and considering whether this distrust is related to either a major reason for those worse health outcomes to not a reason at all.

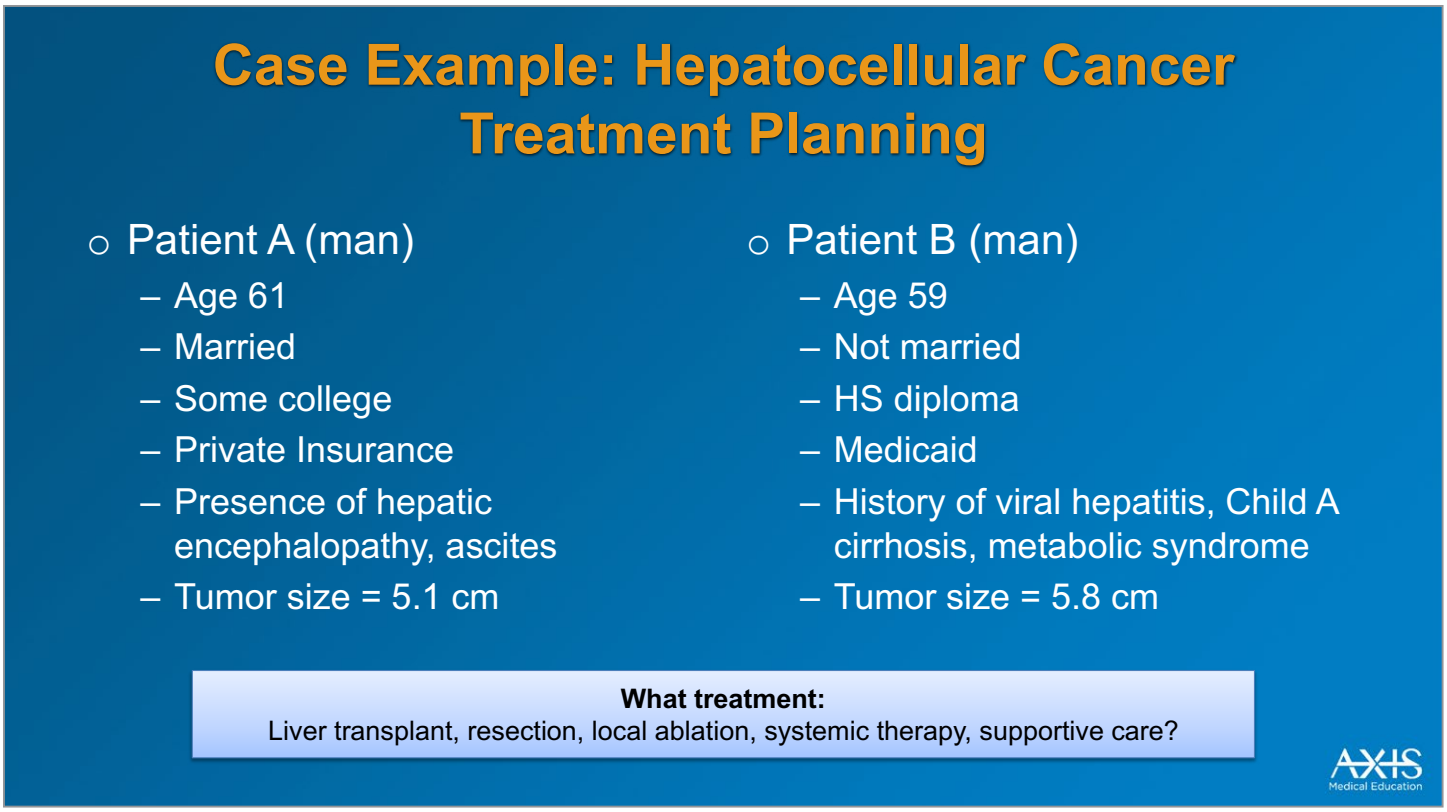


- The poll similarly asked the question as it related to trust in the healthcare system. So it asked, 'How often do you think our healthcare system treats people unfairly based on their race or ethnic background?' And just as before, there are 3 charts here; they represent the responses by individuals identifying as Black, Hispanic, or White with the green color (at the bottom) being individuals that felt as though very often that was the case on up to the gray (at the top of the pyramid) individuals either did not answer or just below that the response was never. So again, a considerable variability between those who believe that there is a role to play from our healthcare system in terms of the poor or unfair treatment that individuals from racial and ethnic backgrounds receive.



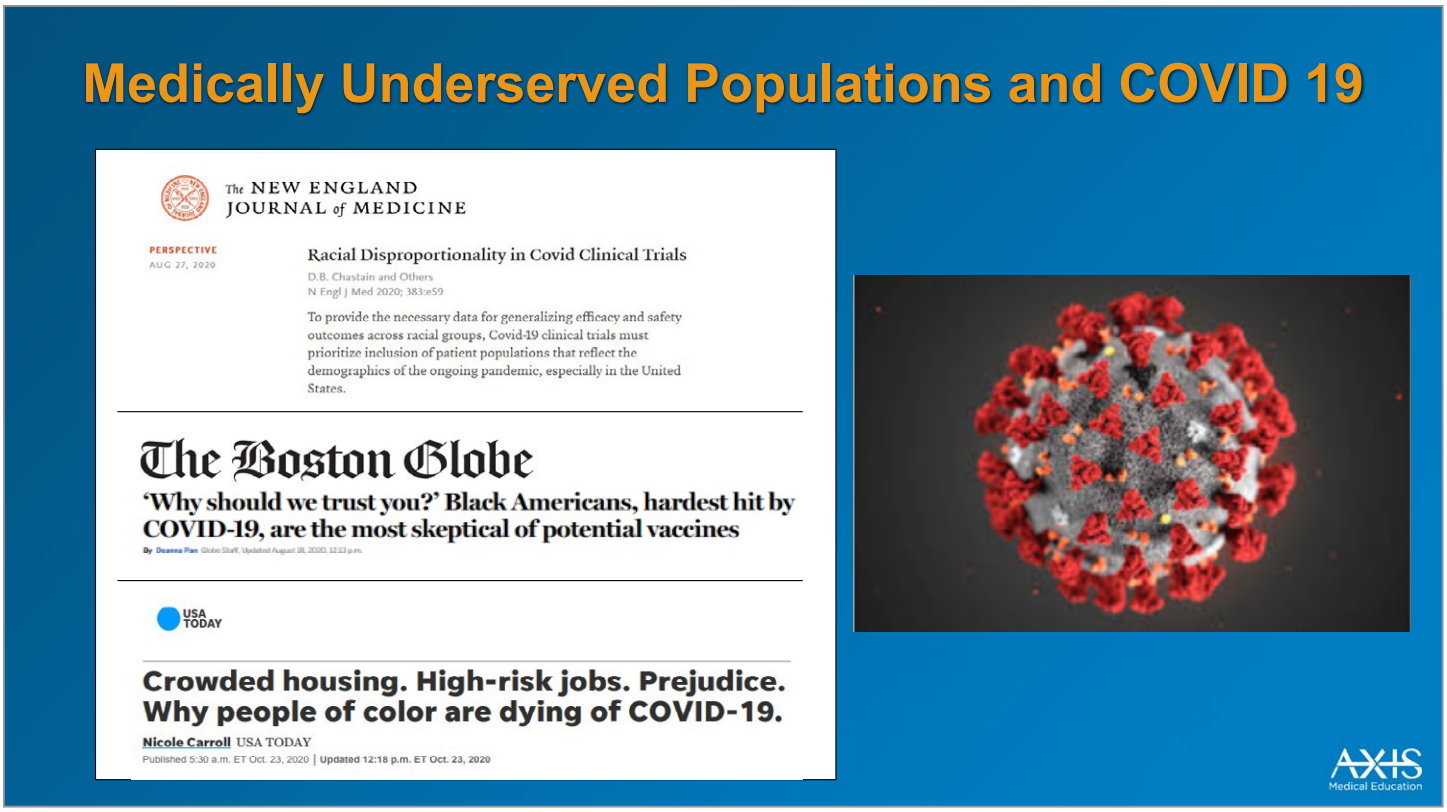
So that's a little bit about what some of the challenges are. We've proposed a few things that we think are very much achievable. First, I think there's a need for increased intercultural awareness and certainly being aware of the different groups that come for our care and what some of the unique needs may be. A second recommendation is around unconscious bias training and ongoing checks for that. So being able to realize what may be some of those biases that we bring into the healthcare system and how they may be having a negative impact on patient outcomes and treatment. Being able to bring those into the conscious minds, so that we can do something about them, particularly in terms of making sure those biases don't negatively impact the patients that we're caring for. And oftentimes checking in. So it's not just you do the one-time training, but we need to have, on an ongoing basis, some way to check back in to make sure that those biases aren't creeping back up.

A third recommendation is trying to move toward improved relationships and trust building between patients and providers. We see that there is a direct negative impact when patients and providers don't have that trusting relationship. We also saw from the poll that there's some variability in terms of how people rate those relationships. So we need to improve that relationship between patients and providers, so that our patients do have a sense of trust in the providers that they're seeing. And lastly, is increasing diversity in the biomedical workforce. We've also seen literature that suggests that many folks of color, particularly, prefer to have providers that look like them or have a similar background. And therefore, that may be one of the things that might help to build up the trust in both providers and the medical system. But we also know our biomedical workforce currently does not represent the overall population.



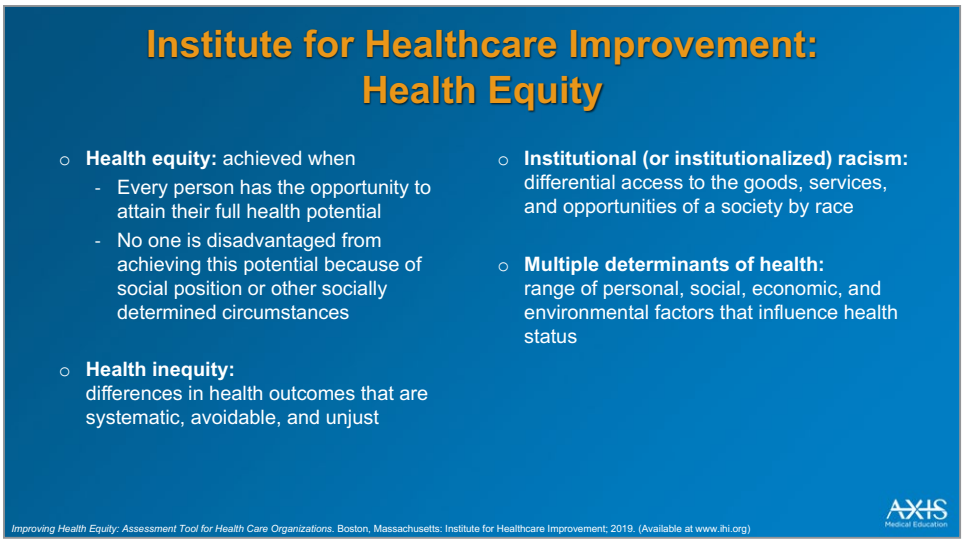
Here's an example of where some of the biases and challenges may show up in terms of HCC treatment and planning. There are 2 patients presented here, both males. Patient A is age 61, married, has gone to college, has private insurance, has a few symptoms in terms of clinical presentation for their cancer. Patient B is very similar in age. This person is, however, not married, did not go onto college, and they have Medicaid or government insurance. And their clinical presentation is a little bit different but still presenting with symptoms. So the question here is what do you think would be the treatment of choice for each of these patients? So I'll pause just a second for you to think about that.

Now if you've got that in mind what you'd recommend, one of the things that the literature suggests is that the patient on the right, patient B, would be more likely to go in and have invasive treatment versus the patient on the left. And that may be attributed to particular biases around whether this person may, in fact, go on to follow the treatment recommendations. It may also be about whether the insurance that the person has may be more equipped to pay for some of the other more invasive treatments. There are a lot of things out there to be considered about this example. What we see in the literature is that typically, individuals who have government insurance or no insurance that may not have some of the social support are often recommended for different treatments than individuals who seem to have a little bit more of those resources as in patient A.

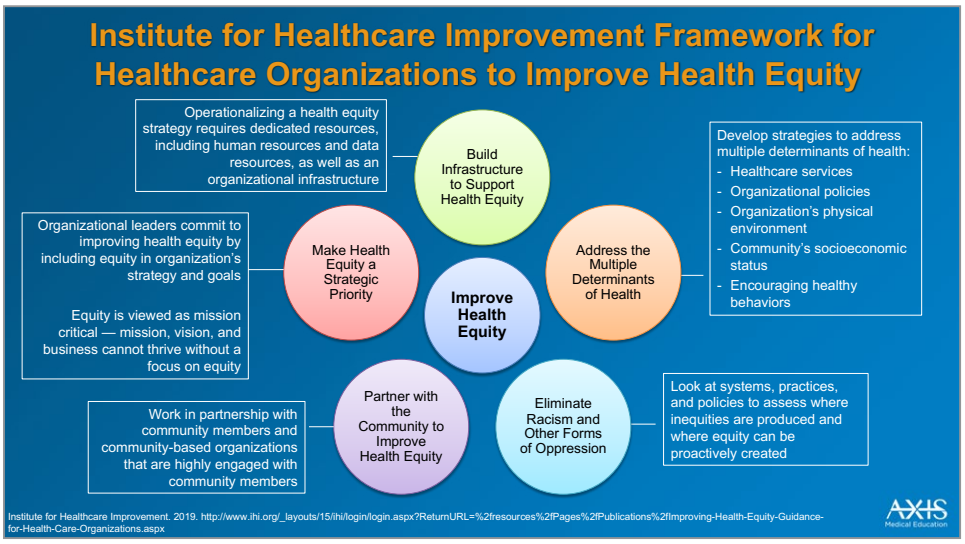


- It goes without saying that the COVID-19 pandemic has certainly impacted a lot of what we do across the healthcare system. We also know that the medically underserved, in addition to cancer, are also those populations that are significantly impacted by the pandemic. These are just a couple of the headlines that have come out in the last year about the challenges in terms of reaching those who are most vulnerable from either a racial and ethnic standpoint, socioeconomic standpoint, or even a geographic standpoint and really highlighting some of the things that have been mentioned before.

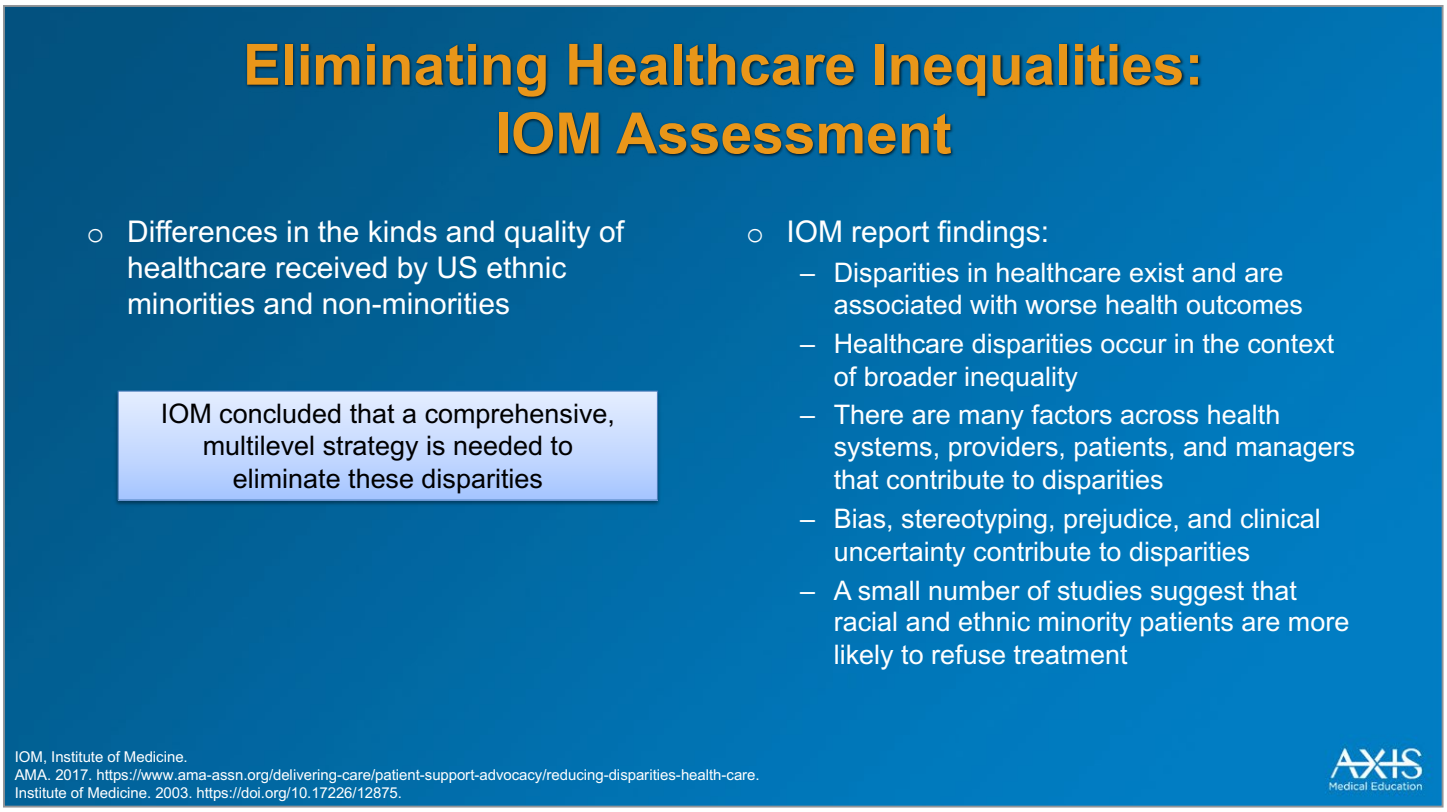
  So Black individuals, for example, asking why should we trust you when it comes down to COVID-19 and may be even more hesitant or skeptical around vaccines. Other folks are highlighting the racially disproportionate number of individuals who are in those clinical trials that are related to the vaccine, as well as the higher rates of deaths for COVID-19. So we can't discount some of the challenges that already exist that are outside of the treatment that we have in cancer to think about how they may, in fact, influence our patients as they're coming in for their cancer treatment.



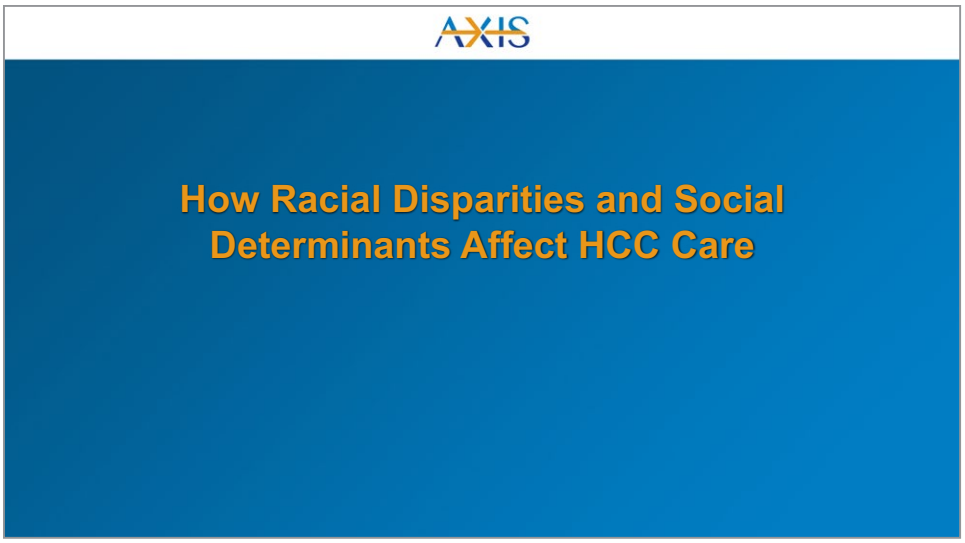
- In thinking about the way forward, the Institute for Healthcare Improvement identifies health equity in a sense of trying to make sure that people have an equal opportunity to attain their full health potential. And then, you know, on the flipside of that, inequity will be that there are differences. Often those are at a systemic level, but they are avoidable, and they are certainly unjust. These issues can happen at the institutional level, particularly around racism. We're not speaking about individual people. As an individual, I have these racial views or biased views against another individual. Institutionally, we are talking about things that are baked into the system that really do make a difference for one group versus the other just by virtue of their identification with that group. And we've talked about these multiple determinants of health before referencing them as social determinants and how they also influence the health status.



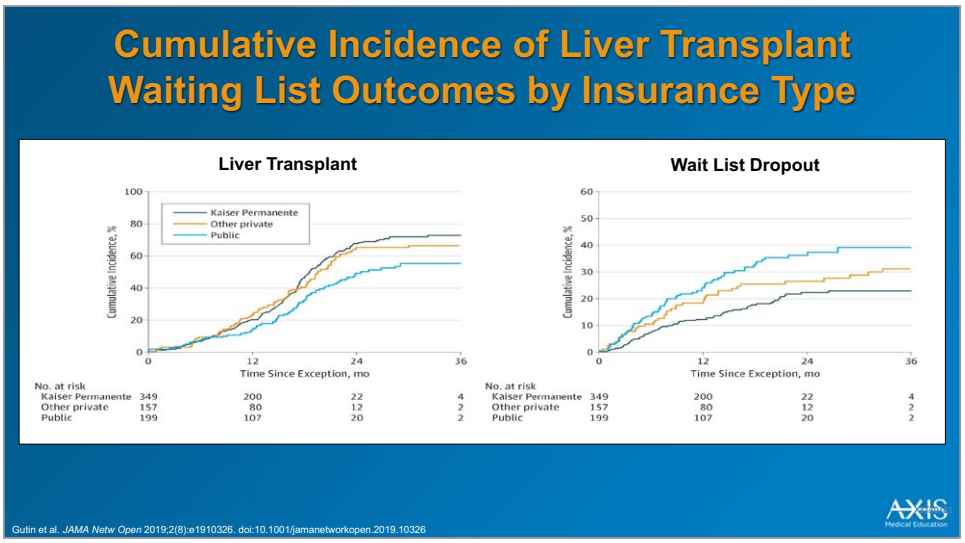
- This graph highlights how to improve that health equity. There are lots of ways to do that. Building infrastructure, addressing those multiple determinants or social determinants, eliminating racism and other forms of oppression particularly at the systemic level. Partnering with communities and doing community engagement, and then making health equity a strategic priority—all of these strategies are what we can do, as a member of the healthcare system, to advance health equity.



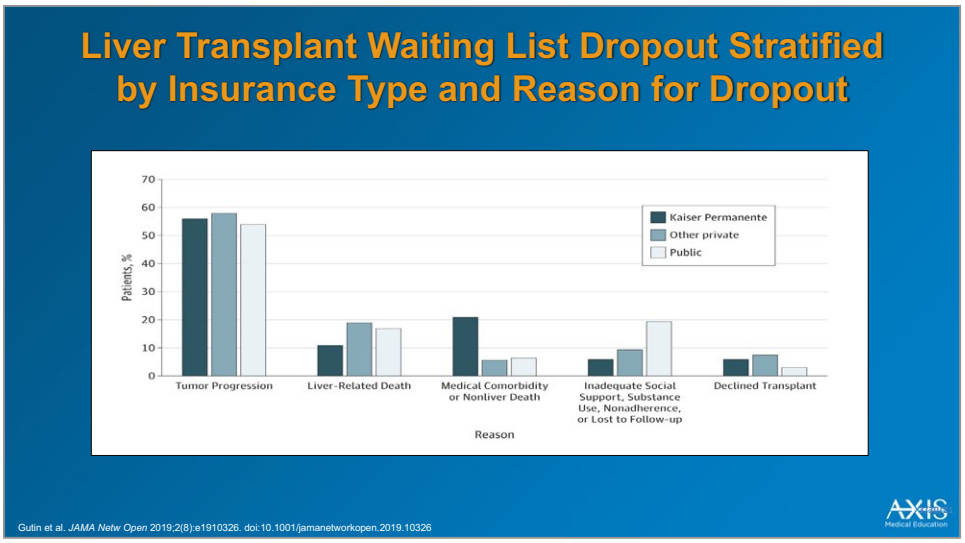
▶ More recently, the Institute of Medicine did this assessment about eliminating healthcare inequities. What they found were differences in the kinds and qualities of healthcare received by individuals in the US, particularly minorities and non-minorities, in this report. They found that disparities exist, and they are associated with worse health outcomes. They also found that healthcare disparities occur in the context of the broader inequality that we've been talking about, so again, outside in those social determinants. There are certainly multiple factors that are involved. And biases, stereotypes, prejudice, and so forth also contribute to those disparities. This report also found that a small number of studies are suggesting that racial and ethnic minority patients were more likely to refuse treatment. However, that's probably the case because of some of the other things that we talked about—the poll about distrust both in the provider and the medical care system—may also play into the smaller number of individuals refusing treatment.



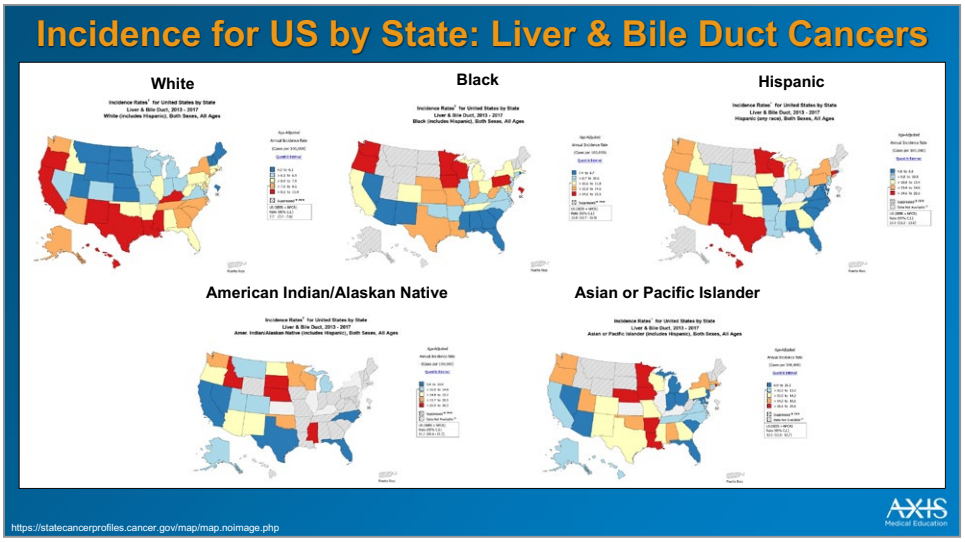
- So let's move on to discussing how racial disparities and social determinants affect the care of our hepatocellular cancer (HCC) patient.



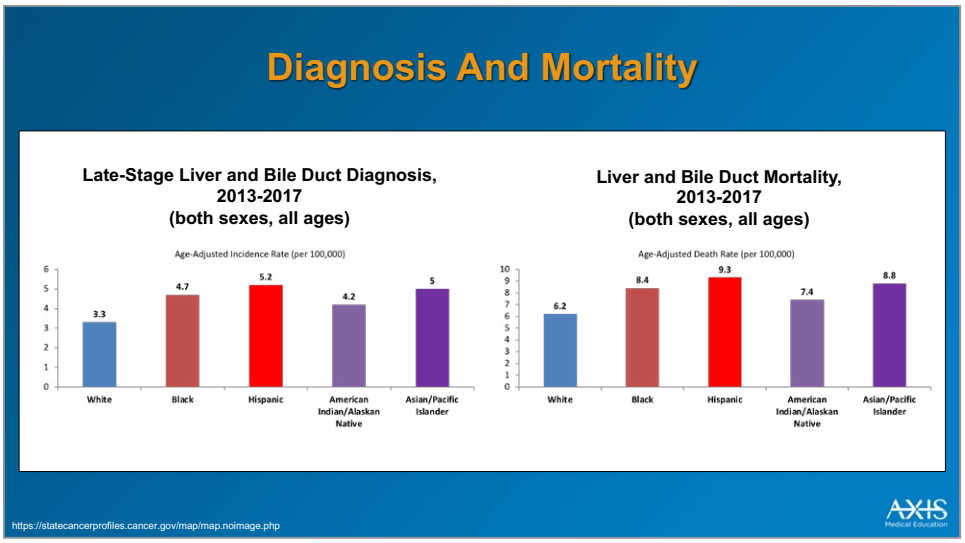
- The literature presented here present the cumulative incidence of liver transplant waiting list outcomes by insurance type. As you look at the graph, one of the take-aways points is that individuals who have public insurance are less likely to be moved up earlier on those transplant waiting lists. So those who have private insurance—in this dataset looking at the Kaiser Permanente versus other private—those individuals are spending less and less time on the transplant list, and their likelihood of actually moving forward to transplant is not much higher.



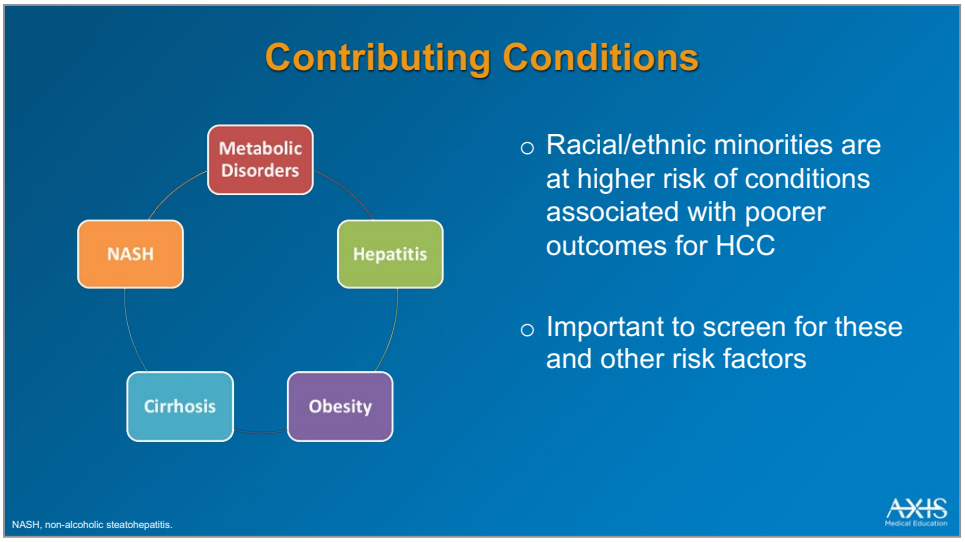
- Similarly, this study looked at the liver transplant dropout stratified by insurance type and reason. Again, looking at the same cohort of Kaiser Permanente insured individuals versus other private insurance versus public, you'll see that there is some difference in terms of both the reason that individuals and the percentage of those who were on that wait list or dropped off of the waiting list.



- This slide looks across the country at the incidence by state for liver and bile duct cancers. Again, you should draw your attention to the red in each of these maps indicate individuals who have the highest degree of incidence for the liver and bile duct cancers. The blue represents individual states that have a lower incidence. And then a white or grayed out—that's typically those states where we don't have sufficient data, or the data were so small that it was suppressed. What you might notice is that there are some geographic patterns in terms of who has the incidence of liver and bile cancer, and then there are also disparities as exists by race and ethnicity.



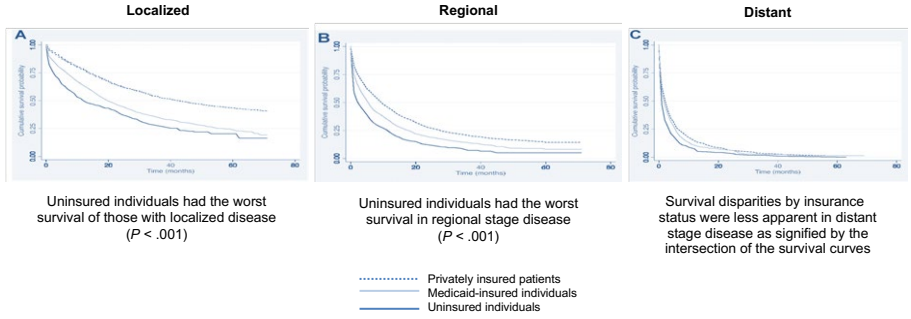
- These graphs represent diagnosis and mortality. On the left is late-stage liver and bile duct diagnoses between 2013 and 2017. Again, you can see some of the similar patterns of racial and ethnic disparities. On the right, it's looking at liver and bile duct mortality between 2013 and 2017. Again, racial and ethnic disparities are shown typically in both of these where you have a higher rate of Hispanic and Black individuals, both in terms of diagnosis and death.



- Looking a little bit more in terms of what might be contributing conditions that also show up. We know that racial and ethnic minorities are at higher risk of other conditions that are associated with outcomes for HCC. So metabolic disorders, hepatitis, obesity, cirrhosis, and nonalcoholic steatohepatitis (NASH) are all of those combinations that may be contributing to the poorer outcomes that we see here. The point is being able to screen for these other conditions that may have a negative impact on HCC treatment. So finding out whether they have a history as well as trying to identify and address issues around metabolic disorders and obesity in particular.

Relationship Between Insurance Type at Diagnosis and Survival

Kaplan–Meier Survival Analysis of Patients with HCC, Stratified by Stage



Uninsured individuals had the worst survival of those with localized disease ($P < .001$)

Uninsured individuals had the worst survival in regional stage disease ($P < .001$)

Survival disparities by insurance status were less apparent in distant stage disease as signified by the intersection of the survival curves

Privately insured patients
Medicaid-insured individuals
Uninsured individuals

Adapted from Adler Jaffe et al. *Cancer Epidemiol Biomarkers Prev.* 2020;29:300-307.

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- This slide describes a study looking at the relationship between insurance type at diagnosis and survival. Similar to the presentation before, we see that there is a difference between those individuals who have private insurance versus those with public insurance (the middle line) and then those who are uninsured. So uninsured individuals have the worse survival of all of those with localized disease. We also see that uninsured individuals have the worse survival at the regional stage. And then, thinking of more distant survival disparities by insurance status were less apparent in that case. But certainly, localized and regional, we see a clear difference in terms of survival based on whether you have insurance and what type of insurance it is.

Patient Populations at Increased Risk of Developing HCC

- Metabolic disorders associated with increased risk of HCC:
  - Obesity
  - Diabetes
  - NAFLD
  - NASH
- HCC incidence expected to increase in older populations due to rise in comorbid conditions
  - Hepatitis C, cirrhosis, obesity, diabetes, and NASH
- Liver cirrhosis and hepatic dysfunction often complicate treatment of HCC
  - ~80% of patients diagnosed with HCC have preexisting cirrhosis
  - Can be caused by HBV, HCV, alcohol, and NAFLD

Underlying chronic liver disease and cirrhosis underscores importance of health equity to ensure accurate and timely screening, diagnosis, and treatment that is evidence-based and personalized for all HCC patients

HBV, hepatitis B virus, HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
Benson et al. NCCN Guidelines 2020; Marrero et al. *Hepatology* 2018;68:723-750.

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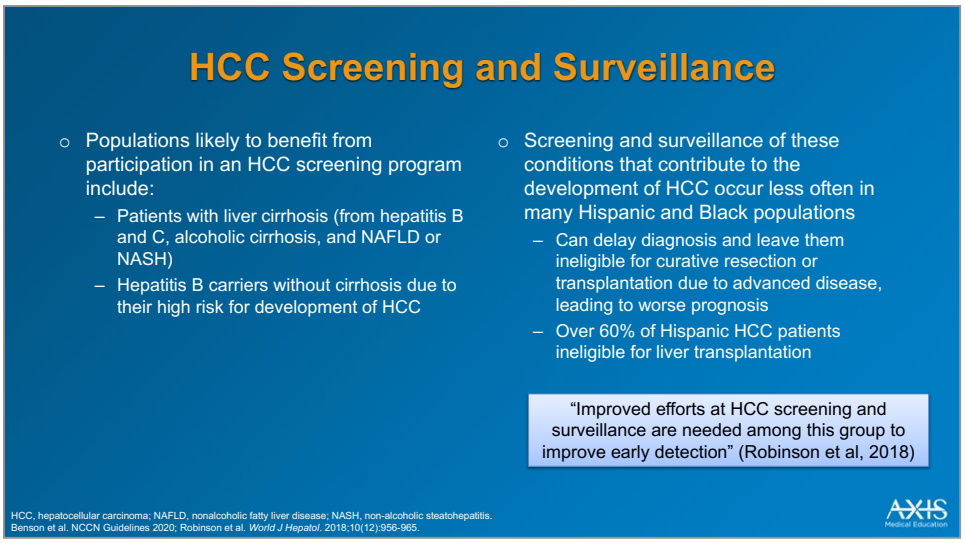
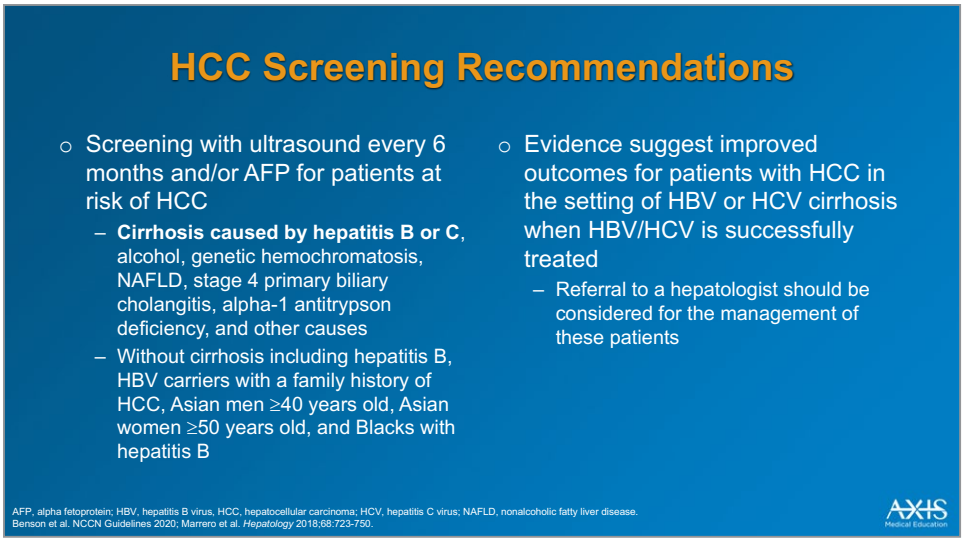
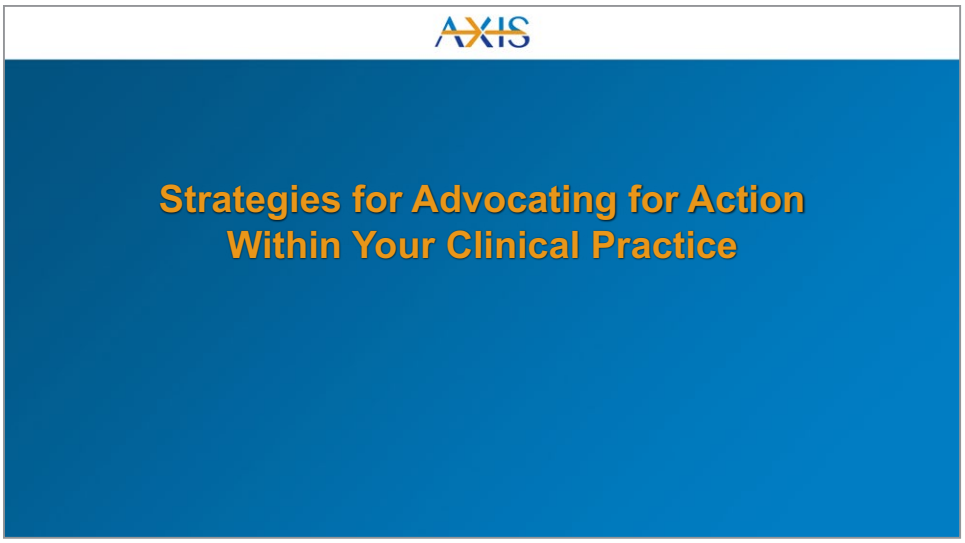
- We previously mentioned metabolic disorders—all of those things listed there—may increase the risk for HCC. We also know that HCC incidence is expected to increase in older populations, and that liver cirrhosis and hepatic dysfunction often complicate treatment.



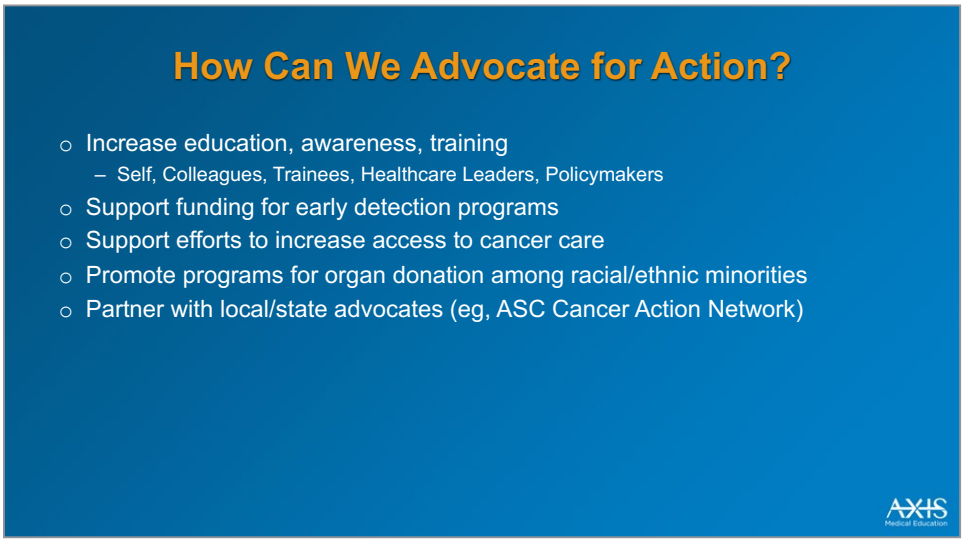
- For screening and surveillance, we understand that populations likely to benefit from participation in the screening program include those folks who are at higher risk. We should make sure that these individuals are prioritized for screening. We also know that screening and surveillance of these conditions often lead to identifying many more Hispanic and Black populations who are at risk. That's necessary so that we won't delay their diagnosis and leave them ineligible for some of the treatments that we know are much more likely to lead to longer-term survival.



- The screening recommendations are to screen with ultrasound every 6 months and/or an alpha fetoprotein (AFP) for patients at risk. And then, the other recommendation is around looking at the evidence that suggests improved outcome for patients with HCC in the setting of hepatitis B virus or hepatitis C virus cirrhosis when either one of those is successfully treated.



- So we'll move on to strategies for advocating for action within your clinical practice.



- How can we advocate for action? There are several things that are really important for us, as members of the healthcare system, to advocate. So first, increase education, awareness, and training. That education and training is for both ourselves, our colleagues, our trainees, healthcare leaders, and policymakers. Making sure that we're all aware of these issues and that we can point to solutions that we can lead in this area. The second is to support funding for early detection programs. We know that early detection often mean the difference between being able to get an effective in and long-term survival. So making sure that we can come in and detect cancers early, so that we can have individuals with the most opportunities to get the appropriate care.

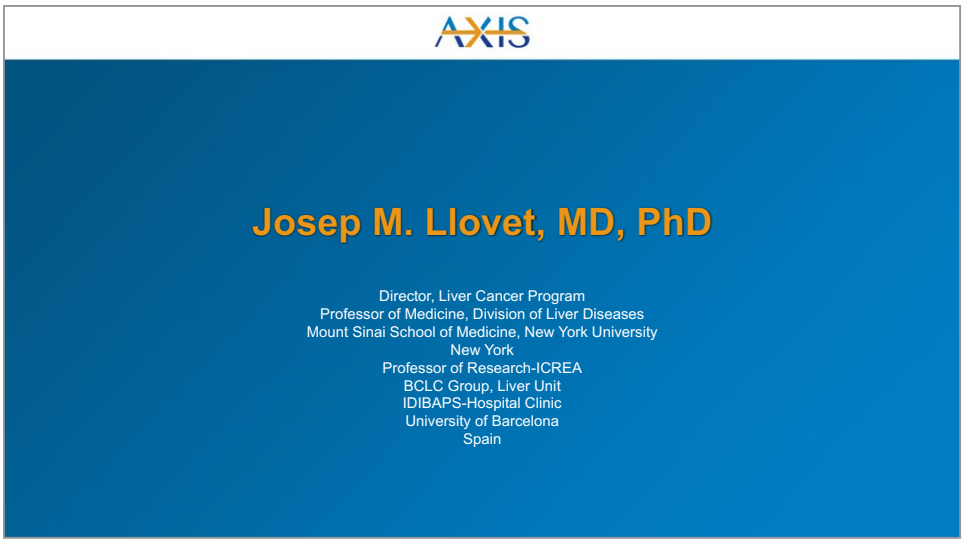
  The third recommendation is supporting efforts to increase access to cancer care. We still have a number of individuals who don't have easy access to cancer care. So whether it's by geographic challenges in terms of those who may be in rural areas or not able to access oncologists or other types of cancer care, but we've got to do our part to make sure that everyone who needs cancer care has access. We can also promote programs for organ donation, particularly around Blacks, Hispanics, and other racial/ethnic minorities who tend to have rates of organ donation that are much lower than those of other populations. And then, lastly, partnering with local/state advocates like the American Cancer Society Cancer Action Network, which is always advocating for more resources for individuals who have cancer.

We can also improve communication and promote awareness among underserved populations at higher risk. And so, part of it is training individuals, both those who already have cancer and their support systems and loved ones. We want to make sure that we have culturally competent training and information, that we are utilizing patient modalities like motivational interviewing in which the provider is speaking directly with the patient and identifying that person's values and connecting that with care and treatment. And then we also want to make sure that, again, we're aware of and checking implicit biases that may pop up in the clinical encounter.

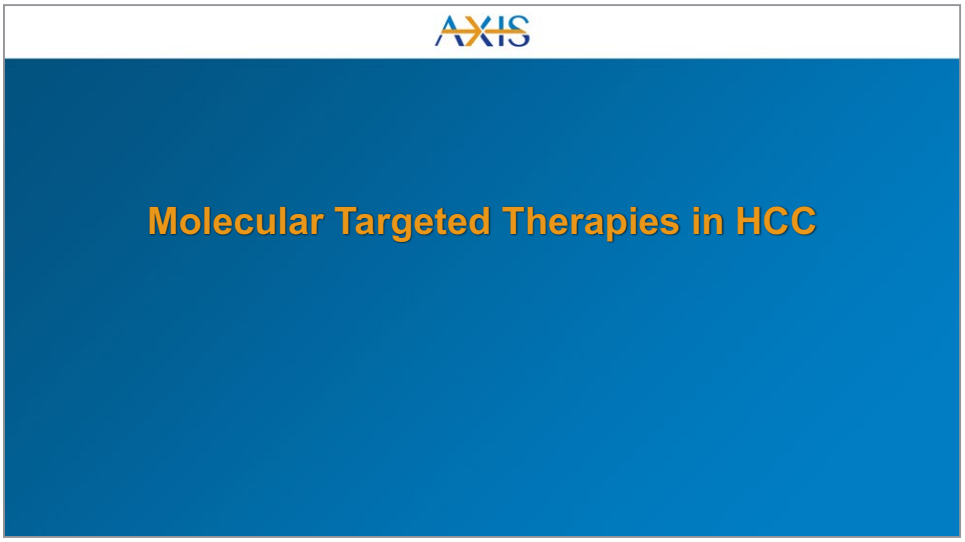
We want to actively work to reduce and eliminate those biases. We also want to invest in community engagement. So we often find that there's greater trust in the medical system when the healthcare system and providers are going as a community and helping to serve and recognize what the community's needs are. We can also employ staff with training and social work and case management in individuals who have a specialty to identify where the barriers and challenges are for individuals to get the appropriate care. And then being able to have those resources to address those challenges.

We want to also utilize patient navigators; they have been found to be very effective in one-on-one relationships with patients to identify those barriers and then link them to things like social work and case management if those barriers are particularly at the social determinants level. And then lastly, you know, a number of facilities have employed community health workers. These are individuals who are steeped in the community that are very aware of the cultural context. And they are interfacing and working with the healthcare system, in addition to working with individuals in the community, and they have been shown to be quite effective in working with underserved populations.

Now I'd like to welcome Dr. Josep Llovet, who will highlight the latest emerging evidence in HCC and how this impacts current clinical practice.



- **Josep M. Llovet, MD, PhD:** Hello, I am Dr. Josep Maria Llovet. I am professor of medicine and director of the liver cancer program at Mount Sinai, New York, and professor of medicine at the University of Barcelona. Thank you Dr. Baskin for your important work in minority health, health disparities, and cancer care. You nicely defined for us how racial disparities and social determinants affect HCC care.



- Now, I'm going to talk about molecular-targeted therapies in HCC.

Molecular Pathogenesis and Targeted Therapies in HCC

- **Epidemiology**
- Molecular pathogenesis and drivers
- Targeted therapies
  - First and second line standard of care
  - Immunotherapy
- Combination therapies: new era in HCC management
  - Atezolizumab + bevacizumab and beyond
  - Ongoing combinations and emerging treatments

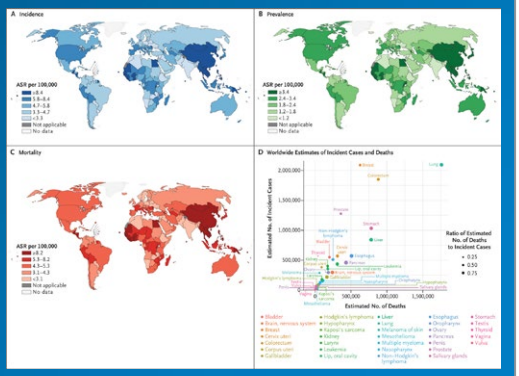
HCC, hepatocellular carcinoma.

AXIS Medical Education

- And here, you have the outline of my presentation. We'll talk about epidemiology, pathogenesis, targeted therapies, and combination therapies.

Incidence and Mortality of HCC

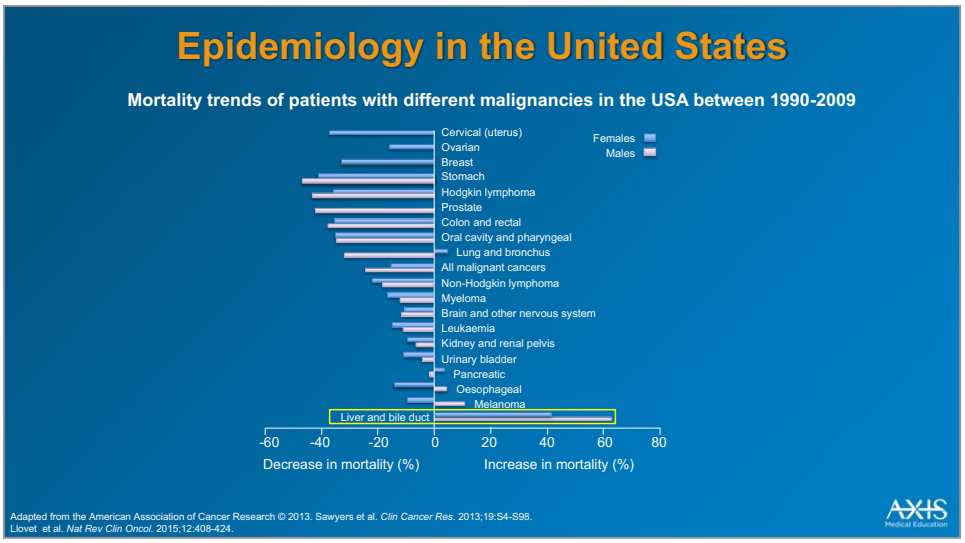
- 6th most common cancer globally
- 4th leading cause of cancer-related mortality
- >850,000 new cases of liver cancer (2018)
  - Eastern Asia: 570,000
  - Europe: 68,000
  - United States: 37,000
- Leading cause of death in cirrhotic patients
- Incidence increasing globally and will reach **1M cases** by 2025



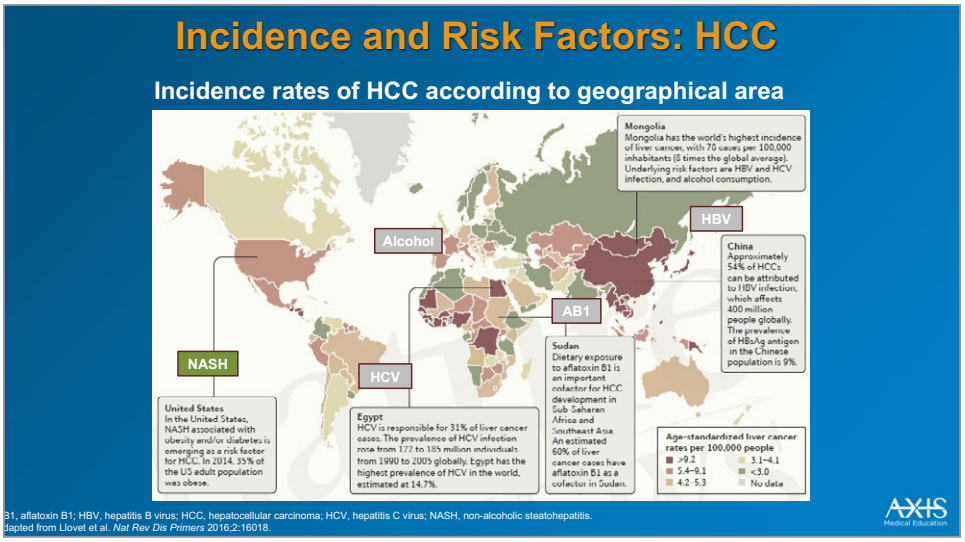
HCC, hepatocellular carcinoma.
IARC, https://gco.iarc.fr/today/home
WHO, http://www.who.int/healthinfo/global_burden_disease/projections/en/
Villanueva A, NEJM 2019.

AXIS Medical Education

- HCC is the sixth most common cancer globally, the fourth leading cause of cancer-related death with more than 850,000 new cases diagnosed every year—around 40,000 in the US. It's the leading cause of death in cirrhotic patients, and there is an increasing incidence globally. And it's expected to reach 1,000,000 cases by 2025.



- This slide summarizes the morality trends of patients with different malignancies in the US between 1990 and 2009. As you can see, for almost all solid tumors, there has been a significant decrease in mortality with two exceptions—melanoma in males and liver and bile duct cancers both in males and females, with an increasing mortality ranging from 40% to 60%.



- What are the main risk factors for the development of HCC? We know almost all of them. Hepatitis B virus infection represents at this point 54% of the attributable fraction of HCCs globally. Hepatitis C virus infection still is the main cause of HCC in the West, accounting for 31% of the cases. Then we have alcohol-related HCC, 20%. And NASH is associated with obesity and diabetes is a risk factor that is vastly increasing at this point in the West, particularly in the US where 35% to 40% of the adult population is obese.

Molecular Pathogenesis and Targeted Therapies in HCC

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- Targeted therapies
  - First and second line standard of care
  - Immunotherapy
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HCC, hepatocellular carcinoma.

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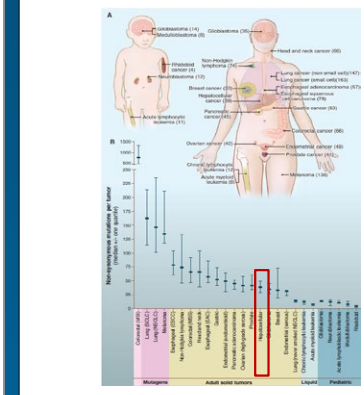
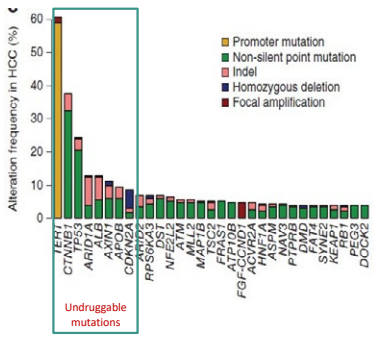
- In terms of molecular pathogenesis, HCC is one of the tumors with around 40 to 60 mutations per tumor. But only a small proportion of these mutations are known as oncogenic drivers.

Landscape of Mutations in HCC

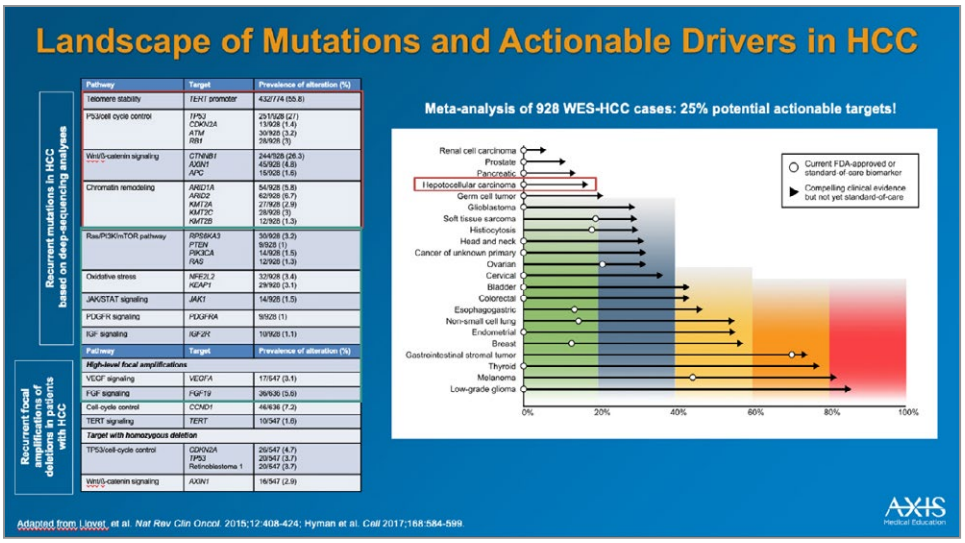




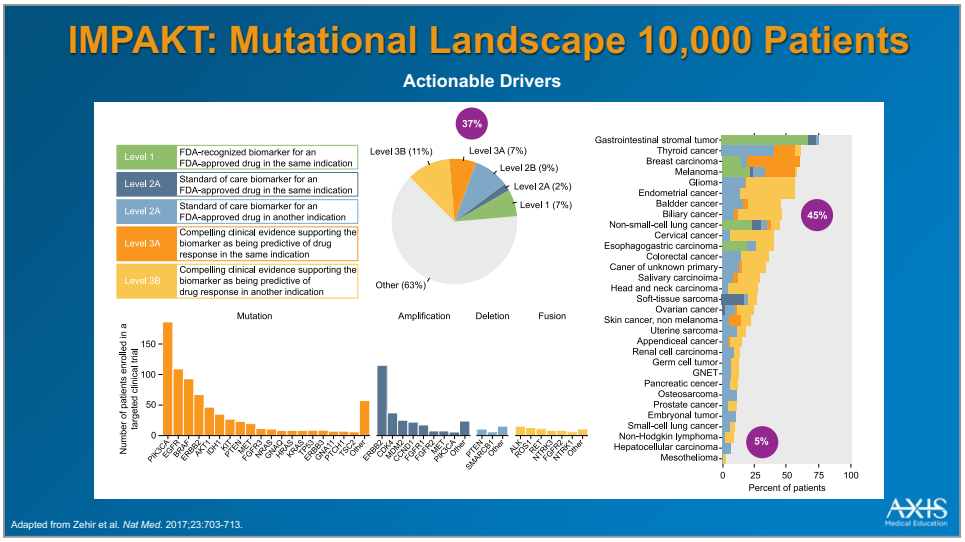
Vogelstein et al. *Science* 2013;339:1546-1558; Schulze et al. *Nat Genet.* 2015;47(5):505-511.

AXIS Medical Education

- As you can see, on the right-hand side, we have TERT, beta-catenin, P53, ARID1A, and others above 10%. And unfortunately, the most prevalent mutations in HCC are undruggable at this point.



- This is a meta-analysis we conducted in close to 1,000 cases of HCC for which whole exome sequencing was available. And, again, you have in red undruggable, unactionable mutations—*TERT* 55%, *TP53* 27%, beta-catenin 26%, and so on and so forth. And in green, you have actionable mutations. And you only have *VEGF* amplification, *FGF19* amplification, and also mutations in *JAK*1, platelet-derived—all of those less than 10% in prevalence.



- Overall, 25% of HCCs have actually at least one potential actionable target. And this falls in the low range of the potential actionable targets in oncology, as you can see in this slide where you have thyroid cancer or melanoma with 80% of the drivers that are potentially actionable. And on the other end of the spectrum, you have prostate, pancreatic cancer, and HCC with 20% or less of the drivers that are actionable.

  This is a study from Memorial Sloan Kettering Cancer Center. They sequenced 10,000 patients, and as a result of this analysis, they were able to treat, based on the mutations identified, 37% of the patients, providing that these patients have any drug available for these targets. And this goes up to 45% as you can see in biliary tract cancer. But, unfortunately, in HCC, only 5% of the patients were able to receive this type of personalized oncology.

Molecular Pathogenesis and Targeted Therapies in HCC

- Epidemiology
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HCC, hepatocellular carcinoma.

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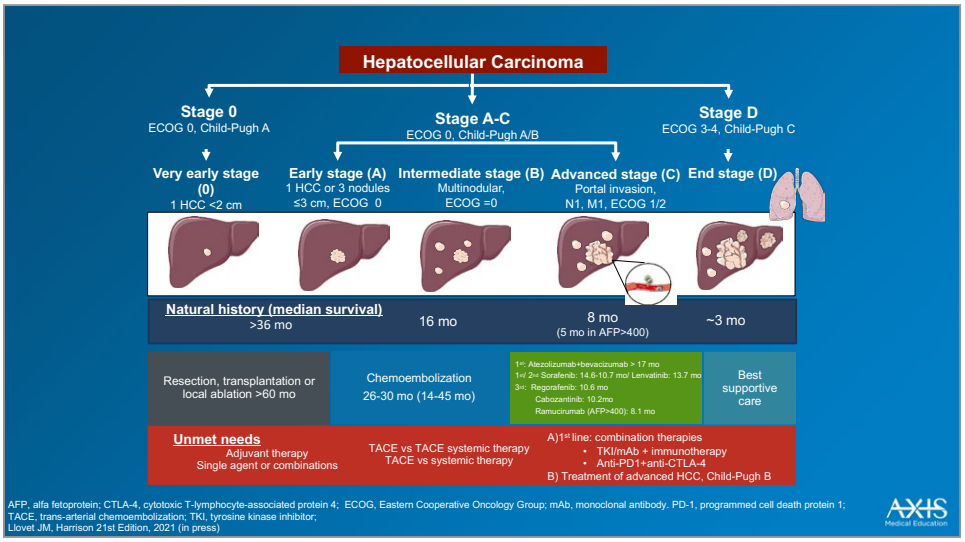
- Let's talk about the therapies that are currently available for this disease.



AFP, alfa fetoprotein; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECOG, Eastern Cooperative Oncology Group; mAb, monoclonal antibody. PD-1, programmed cell death protein 1; TACE, trans-arterial chemoembolization; TKI, tyrosine kinase inhibitor;
Llovet JM, Harrison 21st Edition, 2021 (in press)

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- This is just a summary of what we know about the disease. The natural history in blue at the early stages—without treatment 36 months, intermediate 16 months, advanced stage 8 months or median survival. While moving that to up to 60 month median survival with resection, transplantation, or local ablation at the early stages. Up to 26 to 30 months for chemoembolization at intermediate. And in advanced, at this point, with atezolizumab/bevacizumab in frontline, recently reported at ASCO GI, 19-month median survival.

  Then, we have sorafenib and lenvatinib with survivals around 13, 14 months. And in second line, regorafenib, cabozantinib, and ramucirumab with survivals around 10 months.

  Unmet needs are certainly adjuvant therapies after resection, local ablation, and combination therapies throughout all the stages of the disease.

Molecular Therapies for Advanced HCC (2020)

	Positive	Non-inferior	Negative
First-line	Sorafenib vs placebo (SHARP[1], Asia-Pacific[2])	Sorafenib vs lenvatinib (REFLECT[3,4])	Sorafenib +/- erlotinib
			Sorafenib vs brivanib
			Sorafenib vs sunitinib
			Sorafenib vs linifanib
	Atezolizumab + bevacizumab (IMbrave150[5])		Sorafenib +/- doxorubicin
			Sorafenib vs Y90
			Sorafenib vs nivolumab
Second-line	Ramucirumab vs placebo (AFP ≥ 400 ng/mL) (REACH-2[6])	-	Brivanib vs placebo
			Everolimus vs placebo
	Regorafenib vs placebo (RESOURCE[7])		Tivantinib vs placebo
			Pembrolizumab vs placebo
	Cabozantinib vs placebo (CELESTIAL[8])		

1. Llovet et al. *N Engl J Med.* 2008;359:378-390. 2. Cheng et al. *Lancet Oncol.* 2009;10:25-34. 3. Kudo et al. *Lancet.* 2018;391:1163-1173. 4. Alsina et al. *J Clin Oncol.* 2019;37:371-371. 5. Finn et al. *N Engl J Med.* 2020;382:1894-1905. 6. Zhu et al. *J Clin Oncol.* 2018;36:4003. 7. Bruix et al. *Lancet.* 2017;389:56-66. 8. About-Alfa et al. *N Engl J Med.* 2018;379:54-63.

AXIS Medical Education

- What trials have been reported up to 2020? Well, we have on the left-hand side the positive trials. Sorafenib in SHARP in the Asia-Pacific. Atezolizumab/bevacizumab—the IMbrave recently reported in 2020 in frontline.

  In second-line, we have ramucirumab, the REACH-2; regorafenib, the RESOURCE; and cabozantinib, CELESTIAL. These are the positive phase 3 trials.

  Then, you can see the noninferior trials. The REFLECT trial, which compared lenvatinib versus sorafenib shows noninferiority. And in the second watch for superiority, it was not reached. Therefore, lenvatinib was identified as a drug with similar efficacy as compared to sorafenib.

  And then, on the right-hand side, you have all these drugs that have been discarded for the management of HCC—erlotinib, brivanib, sunitinib, linifanib, doxo, Y90 at least for advanced. And then, we'll talk about nivolumab and brivanib, everolimus, tivantinib, and pembrolizumab.

NCCN Guidelines®: Systemic Therapy
Version 5.2020 – August 4, 2020

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

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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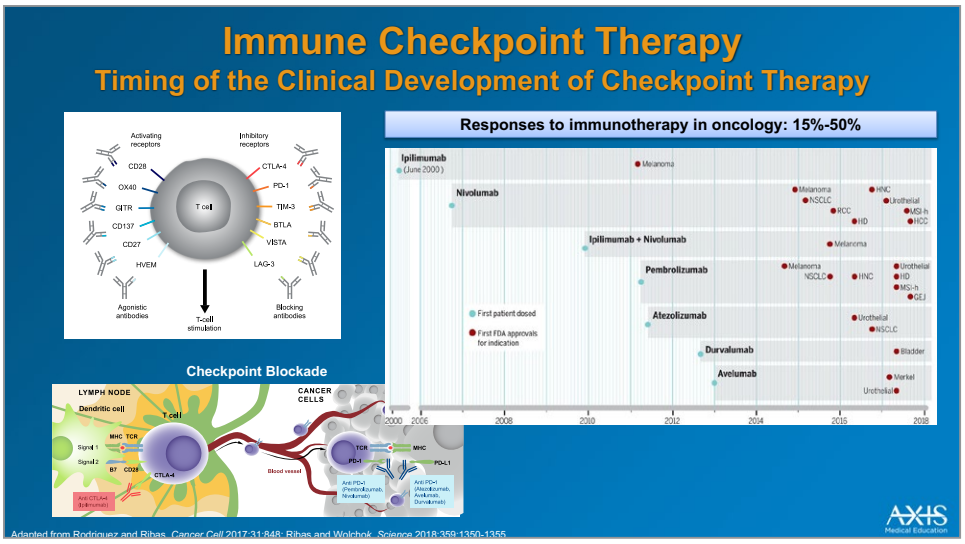
- Here you have the NCCN Guidelines, and the recently updated recommendations for systemic treatment. And the preferred regimens in frontline, sorafenib, lenvatinib, and atezolizumab plus bevacizumab. Whereas in subsequent lines of therapy, you have the drugs that have shown efficacy certainly – regorafenib, cabozantinib, ramucirumab, lenvatinib. And then you have nivolumab, nivolumab plus ipilimumab, and pembrolizumab. These drugs have been approved by FDA based on phase 2 data, and therefore, are recommended by these guidelines based on accelerated program.



- Let's talk a bit about immunotherapy. You're very familiar with all types of anti–programmed cell death ligand 1 (PD-L1), particularly atezolizumab, avelumab, and durvalumab; anti–programmed cell death protein (PD-1)—mostly pembrolizumab and nivolumab—in HCC; and anti-CTLA4—for instance, ipilimumab. These drugs are leading to 15% to 50% objective responses. In HCC, it's between 15% and 20%.

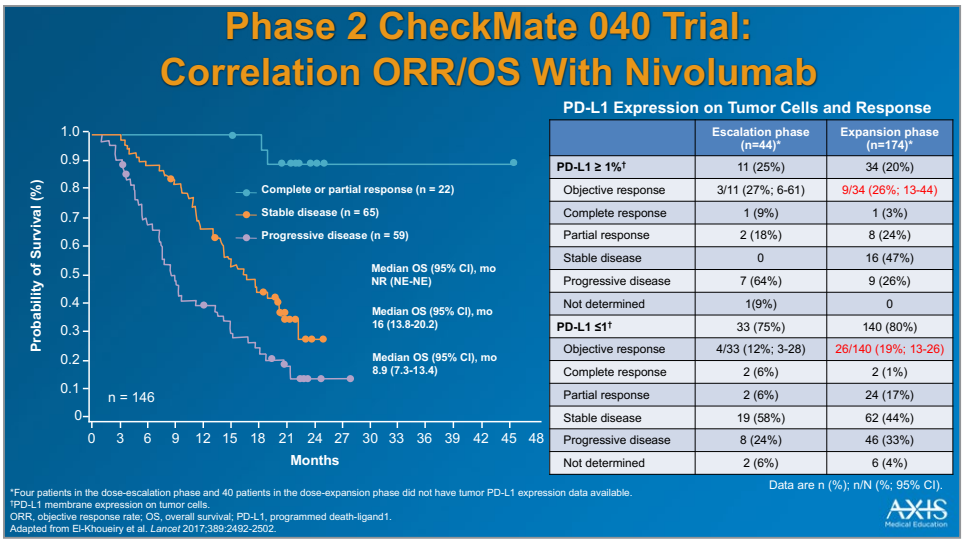
Overview of Immunotherapy FDA Approvals in HCC

Immunotherapy	Trial	FDA Approval
First-Line		
Atezolizumab + bevacizumab	IMbrave150[1,2]	May 2020: patients with unresectable or metastatic HCC who have not received prior systemic therapy
Second-line		
Nivolumab	CheckMate-040[3]	Sept 2017 (accelerated approval): patients with HCC who have been previously treated with sorafenib
Pembrolizumab	KEYNOTE-224[4]	Nov 2018 (accelerated approval): patients with HCC who have been previously treated with sorafenib
Nivolumab + ipilimumab	CheckMate-040[5,6]	March 2020 (accelerated approval): patients with HCC who have been previously treated with sorafenib

1. Cheng et al. *Ann Oncol*. 2019;30:ix186-ix187. 2. Finn et al. *N Engl J Med*. 2020;382:1894-1905. 3. El-Khoueiry et al. *Lancet* 2017;389:2492-2502.
4. Zhu et al. *Lancet Oncol*. 2018;19:940-952. 5. Yau et al. *J Clin Oncol*. 2019; 37:4012-4012 6. He et al. *J Clin Oncol*. 2020;38:512.
FDA, US Food & Drug Administration; HCC, hepatocellular carcinoma.

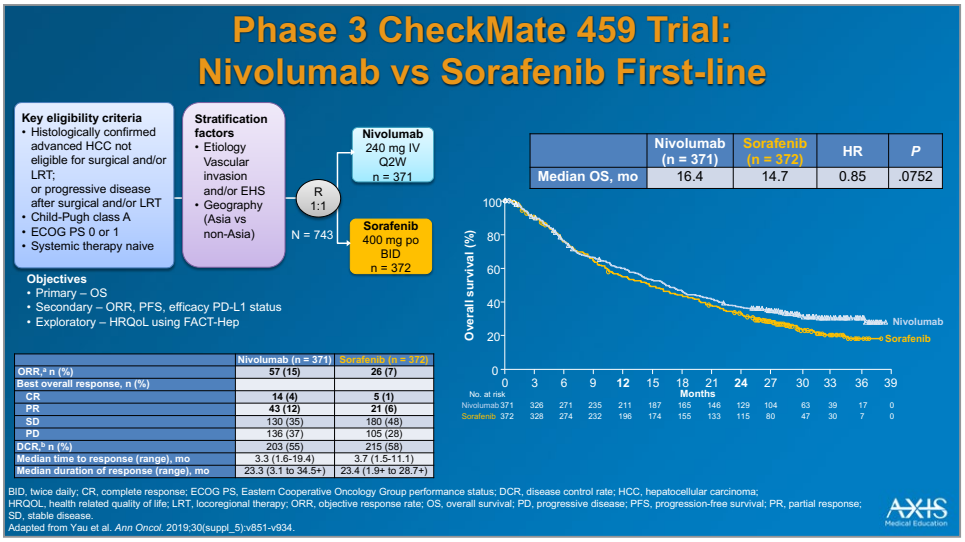
AXIS Medical Education

- And here, you have an overview of the approvals by FDA. In frontline, we have atezolizumab plus bevacizumab that was approved in May 2020 for patients in frontline advanced HCC. And then, as I mentioned before, you have nivolumab, pembrolizumab, and nivolumab/ipilimumab that were approved based on phase 2 data between September 2017 to March 2020. This is for nivolumab/ipilimumab combination based on phase 2 data that got first breakthrough designation and then accelerated approval.

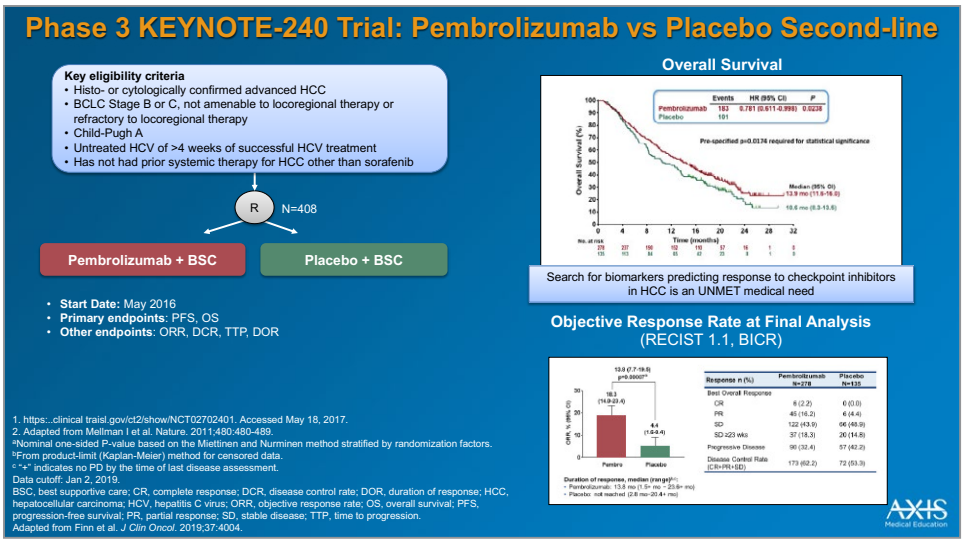


So, what do we know about these drugs? Here you have the subgroup analysis according to type of response for nivolumab. Patients who were achieving complete or partial responses have an outstanding outcome with overall survival beyond 36 months. Whereas patients achieving stable disease have a median survival of 16 months. And patients with a best response as progressive disease, median survival of around 9 months.

And it seems that this is not associated with a status of PD-L1 immunostaining assessed by more than 1% of the cells in the histological analysis.



This is the trial that was designed based on the phase 2 results of nivolumab comparing nivolumab versus sorafenib—CheckMate 459. It was a head-to-head comparison. Nivolumab led to 15% objective responses as opposed to 7% in sorafenib. But the nivolumab was not able to hit the primary endpoint of overall survival significant differences despite that median survival for a patient receiving nivolumab as single agent in frontline was 16.4 months—at that time, the best survival ever reported in frontline—compared to 14.7 months for patients receiving sorafenib. The hazard ratio was 0.85.



- A similar issue happened with pembrolizumab versus placebo. This is the KEYNOTE 240 study comparing pembrolizumab versus placebo in second line. Again, pembrolizumab was reported to induce 18% objective response rate as opposed to 4% in placebo. And in survival, the hazard ratio was 0.78 with a substantial difference—13.9 months for second line as opposed to 10.6 months for placebo. But the *P* value did not hit superiority because the prespecified *P* value was .017 and the achieved *P* value was .23.

KEYNOTE-240: Updated Results

	Pembrolizumab (n=278)	Placebo (n=135)
Median OS	13.9 months	10.6 months
OS HR	0.77	
24-month OS rate	28.8%	20.4%
36-month OS rate	17.7%	11.7%
Median PFS	3.3 months	2.8 months
PFS HR	0.70	
24-month PFS rate	11.8%	4.8%
36-month PFS rate	9%	0%
ORR	18.3%	4.4%
Median TTR	2.7 months	2.9 months
Median DOR	13.9 months	15.2 months
DCR	61.9%	53.3%

Median follow-up:39.6 months pembrolizumab, 39.8 months placebo.
DCR, disease control rate; DOR, duration of response; ORR, objective response rate; TTP, time-to-progression.
Merle et al. *J Clin Oncol*. 2021;39(suppl 3):268.

- So, as you can see on this slide, the KEYNOTE-240 trial, the median survival for pembrolizumab was 13.9 months versus 10.6 months for placebo. In terms of objective response, it was 18.3% for pembrolizumab and 4.4% for placebo, with a median duration of response of close to 14 months for pembrolizumab and 15 months for placebo. The disease control rate was close to 62% in the pembrolizumab arm.

Phase 2 KEYNOTE-224 Trial: Pembrolizumab Second-line

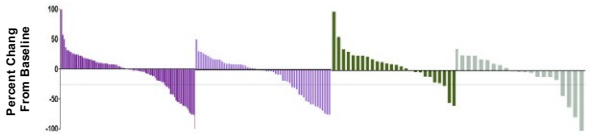
Key eligibility criteria
- ≥18 y
- Pathologically confirmed HCC
- Progression on or intolerance to sorafenib treatment
- Child Pugh class A
- ECOG PS 0-1
- BCLC Stage C or B disease
- Predicted life expectancy >3 mo

Pembrolizumab 200 mg Q3W for 2y or until PD, intolerable toxicity, withdrawal of consent or investigator decision

Survival follow-up

- Response assessed Q9W
- Primary endpoint:
  - OR (Recist v1.1, central review)
- Secondary endpoints:
  - DOR, DCR, PFS, OS and safety and tolerability

Maximum Percentage Changes From Baseline in Target Lesions



Study cohort (N = 104) Uninfected (n = 57) HCV infected (n = 26) HBV infected (n = 21)

BCLC, Barcelona-Clinic Liver Cancer; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; Q9W, every 9 weeks.
Based on RESIST v1.1 by central radiology review in patients who had both pre- and post-treatment image measurements. Dotted line is threshold for response.
Data cutoff date: Aug 24, 2017.
Adapted from Zhu et al. *Lancet Oncol.* 2018;19:940-952.

AXIS Medical Education

Certainly, this indicates that these drugs as single-agent have activity, probably very strong activity in a subgroup of patients. And there is an unmet need to identify those patients.

And here, you have also with pembrolizumab the phase 2 study and the breakdown of response according to etiology in a cohort of 104 patients, also supporting the fact that pembrolizumab is inducing objective response—either complete or partial response—in a proportion of patients that at the end will benefit in terms of overall survival.

Biomarkers for Checkpoint Inhibitor Immunotherapy

Factors that predict response to immune checkpoint inhibitor therapy

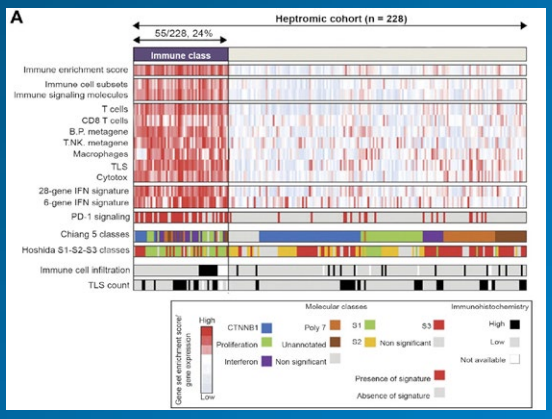
Factor	Association with favorable clinical outcome	Validated in phase 3 clinical trial?	Predictive vs prognostic	Cancer type	Tissue type for biomarker assessment	Possible assay type for biomarker assessment
Tumor mutation burden	**Positive**	**Yes**	**Predictive**	**Multiple**	**Blood or tumor tissue**	**NGS WES or targeted gene panel sequencing**
PD-L1 expression	**Positive**	**Yes**	**Predictive**	**Multiple**	**Tumor tissue**	**Immunohistochemistry**
Copy number variation	Negative	TBD	Prognostic, predictive or both	Multiple	Tumor tissue	NGS WES or targeted gene panel sequencing
HLA class I diversity	Positive	TBD	Predictive	Melanoma NSCLC	Blood	NGS WES or PCR-based typing
LOH at HLA class I alleles	Negative	TBD	Predictive	Melanoma	Tumor tissue	TBD
T cell repertoire clonality change	Positive	TBD	Predictive	Melanoma	Tumor tissue or blood	TBD
T cell-inflamed microenvironment	Positive	TBD	Prognostic, predictive or both	Multiple	Tumor tissue	NGS RNA-seq or immunostaining
SERPINB3 or *SERPINB4* mutations	Positive	TBD	Predictive	Melanoma	Tumor tissue	NGS WES
Gut microbial diversity	Positive	TBD	Predictive	Melanoma	Oral or gut	PCR or NGS
Specific gut microbial species	Positive or negative	TBD	Predictive	Melanoma	Oral or gut	PCR or NGS
TGFß expression	Negative	TBD	Predictive	Melanoma	Tumor tissue or blood	NGS, WES, targeted gene panel sequencing or RNA-seq
Mutations in the ß-catenin pathway	Negative	TBD	Predictive	Melanoma	Tumor tissue or blood	NGS WES, targeted gene panel sequencing or RNA-seq
JAK2 mutations (rare)[c]	Negative	TBD	Predictive	Melanoma	Tumor tissue or blood	NGS WES or targeted gene panel sequencing
B2M mutations (rare)	Negative	TBD	Predictive	Melanoma	Tumor tissue or blood	NGS WES or targeted gene panel sequencing
STK11 mutations (common)	Negative	TBD	Predictive	NSCLC	Tumor tissue or blood	NGS WES or targeted gene panel sequencing

NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death protein ligand 1; TBD, to be determined.
Adapted from Havel et al. *Nat Rev Cancer* 2019;19:133-150.

AXIS Medical Education

Well, which are these biomarkers for checkpoint inhibitor immunotherapy to identify responders? Generally, tumor mutational burden and PD-L1 expression are the two biomarkers accepted by regulatory agencies in certain solid tumors.

Predictors of Response/Primary Resistance to ICIs



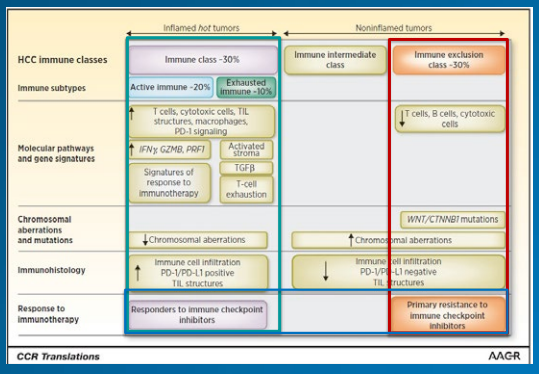
ICIs, immune checkpoint inhibitors.
Sia et al. *Gastroenterology* 2017;153:812-826.

- In HCC, we identified years ago what we called the immune class that involves 24% of HCCs. And these tumors are somehow inflamed tumors or hot tumors with enrichment of T cells, CD8s, TLS, cytotoxic, lytic activity, and signatures that predict response in other tumors such as melanoma.

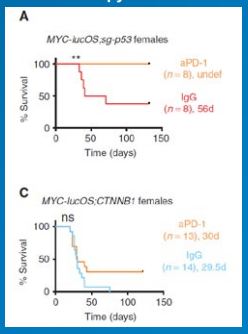
  So, the actual classification suggests that there are the inflamed hot tumors and the noninflamed tumors. The inflamed tumors eventually are those that may respond to checkpoint inhibitors, and the noninflamed tumors are those that eventually will not respond to checkpoint inhibitors.

HCC Immune Subclass

Molecular characterization of the immune subclass



ß-Catenin Activation Promotes Immune Escape and Resistance to Anti-PD-1 Therapy in HCC

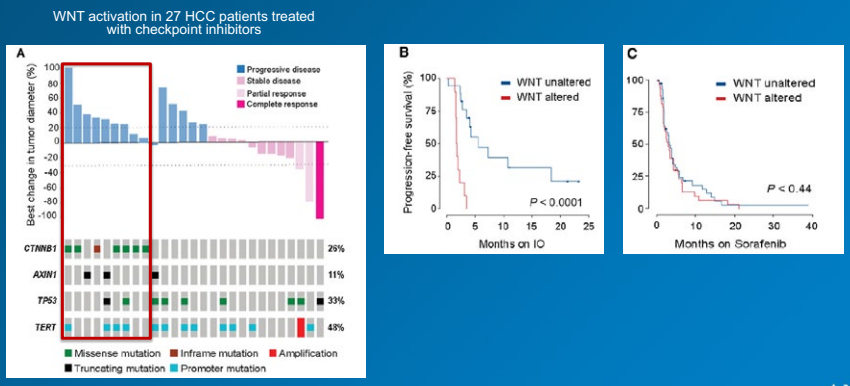


HCC, hepatocelular carcinoma; PD-1, programmed cell death protein 1; TIL, tumor-infiltrating lymphocytes.
Pinyol et al. *Clin Cancer Res.* 2019;25:2021-2023.
De Galarreta et al. *Cancer Discov.* 2019;9:1124-1141.

- And certainly, in experimental models, it seems that one of the mechanisms of exclusion, as it happens with melanoma, is the presence of beta-catenin mutations. Experimental models in this nice study in Cancer Discovery—when animals with *MYC* and *TP53* mutations were treated with *PD-L1*, they respond. Conversely, they were resistant if the tumor was driven by MYC and beta-catenin.

HCC Immune Subclass

Biomarkers predicting response to checkpoint inhibitors- WNT activation



HCC, hepatocellular carcinoma.
Harding et al. *Clin Cancer Res*. 2019;25:2116-2126.

AXIS Medical Education

- And in humans, we have very few data. Only this study suggests that those patients that are resistant to checkpoint inhibitors, certainly have an enrichment of mutations with beta catenin and AXIN1. And this is a concept that we need to follow.

Molecular Pathogenesis and Targeted Therapies in HCC

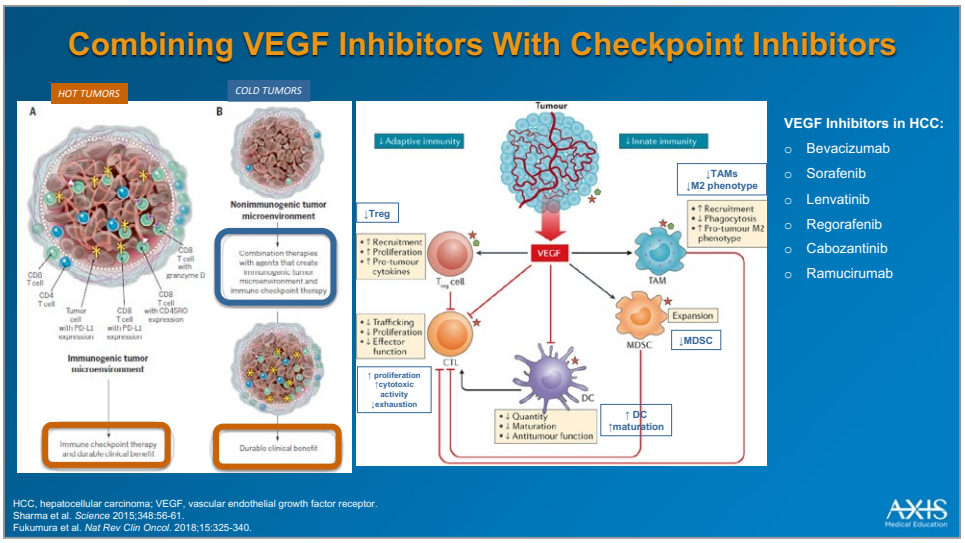
- Epidemiology
- Molecular pathogenesis and drivers
- Targeted therapies
  - First and second line standard of care
  - Immunotherapy
- **Combination therapies: new era in HCC management**
  - **Atezolizumab + bevacizumab and beyond**
  - Ongoing combinations and emerging treatments

HCC, hepatocellular carcinoma.

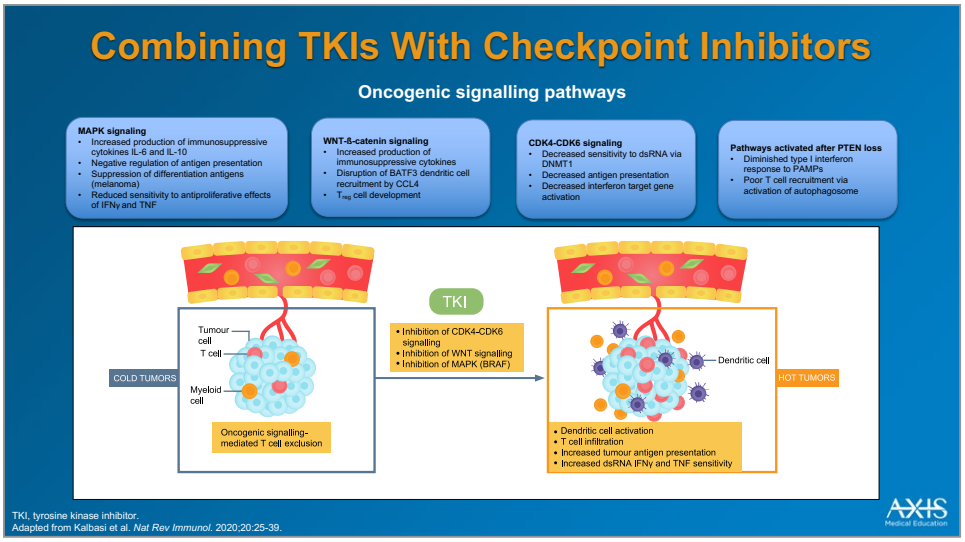
AXIS Medical Education

- Now, I'm moving to combination therapies that represent a breakthrough in the management of the disease after 12 years of primacy of sorafenib and later on lenvatinib as well as single agents.

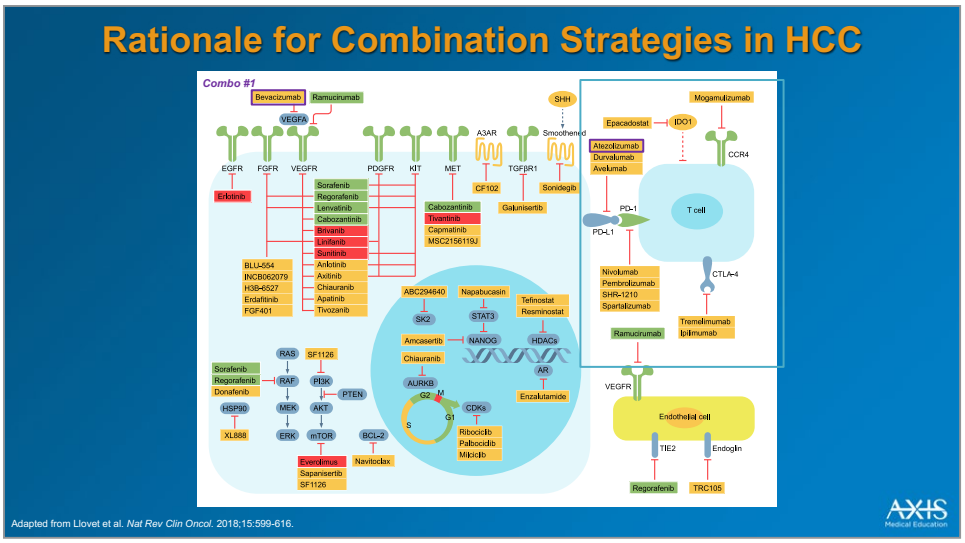
  Well, the concept of hot tumors is very clear—tumors that have an immune tumor microenvironment enriched with CD8ts and tumors that express PD-L1, CD4, and so on. And these are more prone to respond. Whereas cold tumors are those that have a nonimmunogenic tumor microenvironment and that need another drug to switch these nonimmunogenic to immunogenic transforming these cold tumors into hot tumors to achieve durable clinical benefit from checkpoint inhibitors.



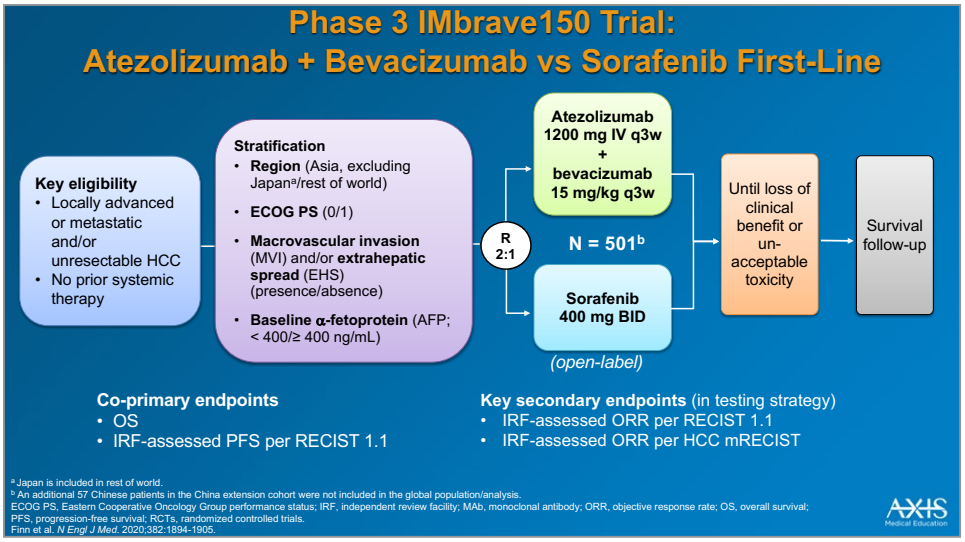
- And this certainly might be achieved with VEGF inhibitors that have been widely studied: bevacizumab, sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab. These drugs might be able to decrease T reg cells; increase dendritic cells and maturation of dendritic cells; decrease M2 macrophages, TAMs, and MDSCs; and certainly, favor the immune response to checkpoint inhibitors.



- Also, tyrosine kinase inhibitors (TKIs) are able to transform these cold tumors, that oncogenic signaling-mediated T cell excluded, into hot tumors that have dendritic cell activation, T-cell infiltration, and increased tumor antigen presentation. These TKIs—at least the ones that have demonstrated to be able to switch—are those that are blocking MAP signaling, particularly BRAF, CDK4, and CDK6 signaling, and also WNT signaling.

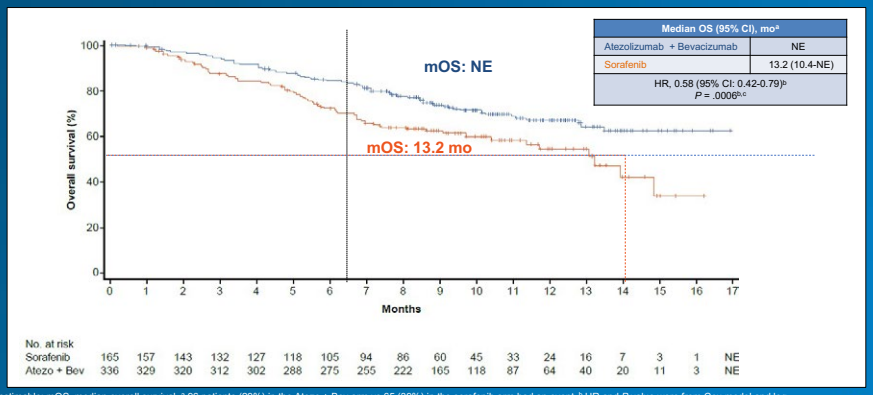


- In terms of HCC, I'm going to talk about some combinations that have made an impact in the disease.



- And the most important one is atezolizumab plus bevacizumab. This is the IMbrave150 trial where this combination was compared 2 to 1 to sorafenib as single agent and a standard of care with a co-primary endpoint of overall survival (OS) and progression-free survival.

Phase 3 IMbrave150 Trial: Overall Survival (Co-primary endpoint)



NE, not estimable; mOS, median overall survival. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (<400 vs ≥400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is .0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.
Finn et al. *N Engl J Med*. 2020;382:1894-1905.

- And as you can see here, the trial was stopped at the first interim with a hazard ratio of 0.58.

IMbrave150: Updated OS

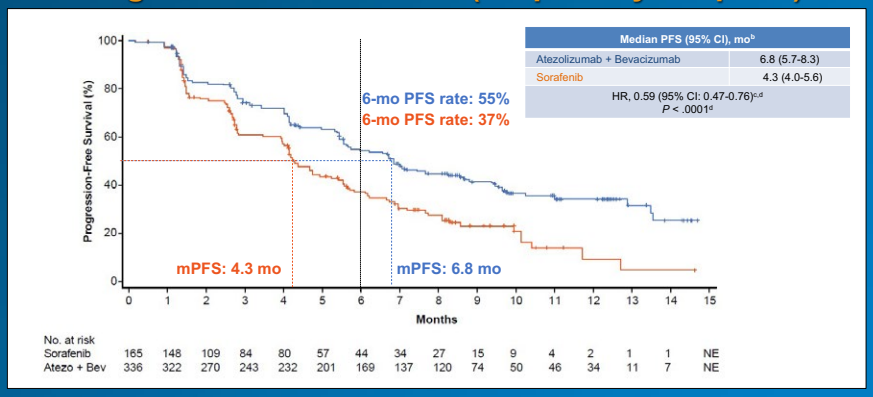
OS longer with atezolizumab + bevacizumab vs sorafenib (*P* < .001)

	Atezolizumab + Bevacizumab (n=336)	Sorafenib (n=165)
Primary Analysis (8.6 months median follow-up)		
Median OS	NE	13.2 months
OS HR	0.58	
Estimated 6-month survival rate	84.8% (95% CI 80.9-88.7)	72.2% (95% CI 65.1-79.4)
Estimated 12-month survival rate	67.2% (95% CI 61.3-73.1)	54.6% (95% CI 45.2-64.0)
Updated Analysis (15.6 months median follow-up)		
Median OS	19.2 months	13.4 months
OS HR	0.66	

OS, overall survival; NE, could not be evaluated.
Finn et al. *N Engl J Med*. 2020;382:1894-1905; Finn et al, 2021.

- And now, we have a follow-up of this study, which recently reported at ASCO GI with a hazard ratio of 0.66. Median survival for atezolizumab/ bevacizumab now has been reported to be 19.2 months and for sorafenib 13.4 months.

Phase 3 IMbrave150 Trial: Progression-free Survival (Co-primary endpoint)



[a] Assessed by IRF per RECIST 1.1. [b] 197 patients (59%) in the Atezo + Bev arm vs 109 (66%) in the sorafenib arm had an event. [c] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [d] The 2-sided *P* value boundary is .002. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.
mPFS, median progression-free survival.
Finn et al. *N Engl J Med*. 2020;382:1894-1905.

- This is a substantial difference achieved by this combination therapy that also had an impact in progression-free survival, with a strong difference of 6.8 for atezolizumab/bevacizumab compared to 4.3 for sorafenib.

IMbrave150: Updated PFS

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

	Atezolizumab + Bevacizumab (n=336)	Sorafenib (n=165)
Primary Analysis (8.6 months median follow-up)		
Median PFS	6.8 months	4.3 months
PFS HR	0.59	
Updated Analysis (15.6 months median follow-up)		
Median PFS	6.9 months	4.3 months
PFS HR	0.65	

PFS, progression-free survival.
Finn et al. *N Engl J Med*. 2020;382:1894-1905; Finn et al. 2021.

- The updated information points to 6.9 months for atezolizumab + bevacizumab versus 4.3 months for sorafenib with a hazard ratio of 0.65.

Phase 3 IMbrave150 Trial: Response Rate

	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezolizymab + Bevacizumab (n = 326)	Sorafenib (n = 159)	Atezolizumab + Bevacizumab (n = 325)[a]	Sorafenib (n = 158)
Confirmed ORR, n (%) (95% CI)	89 (27)	19 (12)	108 (33)	21 (13)
CR	18 (6)	0	33 (10)	3 (2)
PR	71 (22)	19 (12)	75 (23)	18 (11)
Stratified *P* value[b]	<.0001		<.0001	
SC, n (%)	151 (46)	69 (43)	127 (39)	66 (42)
PD, n (%)	64 (20)	39 (25)	66 (20)	40 (25)
DCR, n (%)	240 (74)	88 (55)	235 (72)	87 (55)
Ongoing response, n (%)[c]	77 (87)	13 (68)	84 (78)	13 (62)
Median DOR, mo (95% CI)	NE	6.3	NE	6.3
Event-free rate at 6 months, n (%)	88	59	82	63

[a] IRF HCC mRECIST–evaluable population was based on patients who presented with measurable disease at baseline per HCC mRECIST criteria.
[b] Stratification factors included geographic region (Asia vs rest of world, including Japan), AFP level (<400 vs ≥400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS.
[c] Denominator is patients with confirmed CR/PR. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.
CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response.
Finn et al. *N Engl J Med*. 2020;382:1894-1905.

AXIS Medical Education

- Also, differences in terms of objective response assessed by RECIST—27% for atezolizumab/bevacizumab; 33% by modified RECIST.

IMbrave150: Updated Secondary Efficacy Outcomes

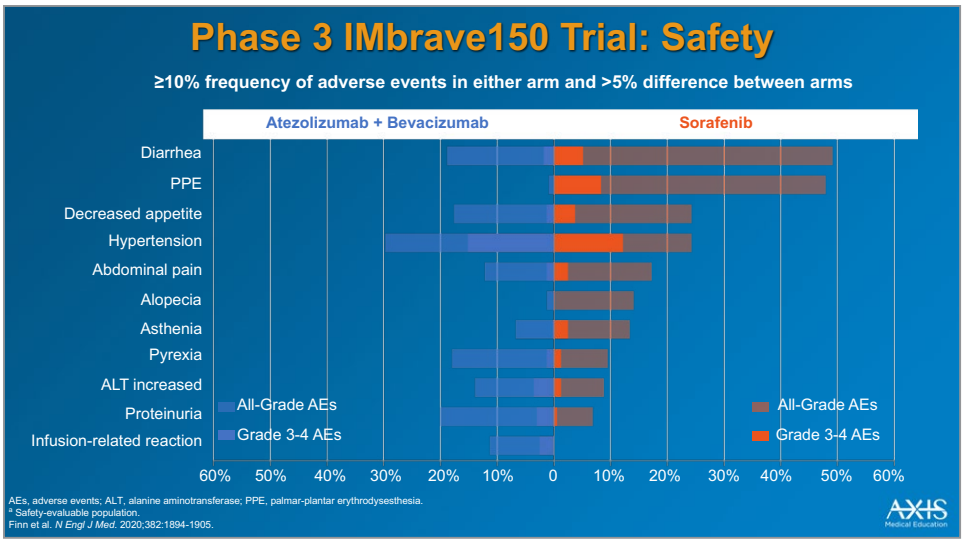
	Atezolizumab + Bevacizumab (n=326)	Sorafenib (n=159)
Confirmed ORR	30%	11%
CR, n (%)	25 (8)	1 (<1)
PR, n (%)	72 (22)	17 (11)
SD, n (%)	144 (44)	69 (43)
Ongoing response, n (%)	54 (56)	5 (28)
	Atezolizumab + Bevacizumab (n=97)	**Sorafenib (n=18)**
Median DOR	18.1 months	14.9 months

CR, complete response; DOR, duration of response; NE, not estimable; ORR, objective response rate; PFS, progression free response; PR, partial response; SD, stable disease.
Finn et al. *N Engl J Med*. 2020;382:1894-1905; Finn et al, 2021.

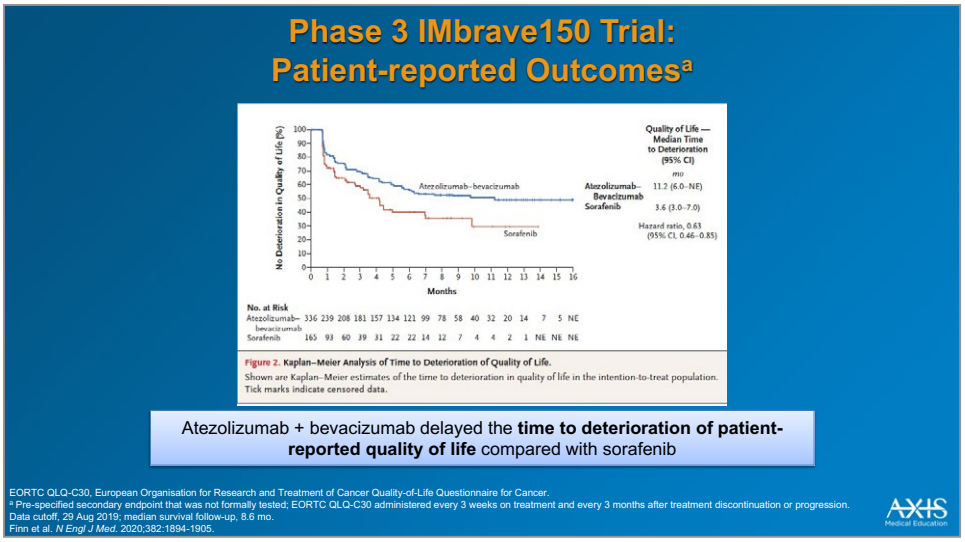
AXIS Medical Education

- And with a recent update at ASCO GI, we have for modified RECIST, it was 36%, and for RECIST, 30% for atezolizumab/bevacizumab—significantly different compared to sorafenib.

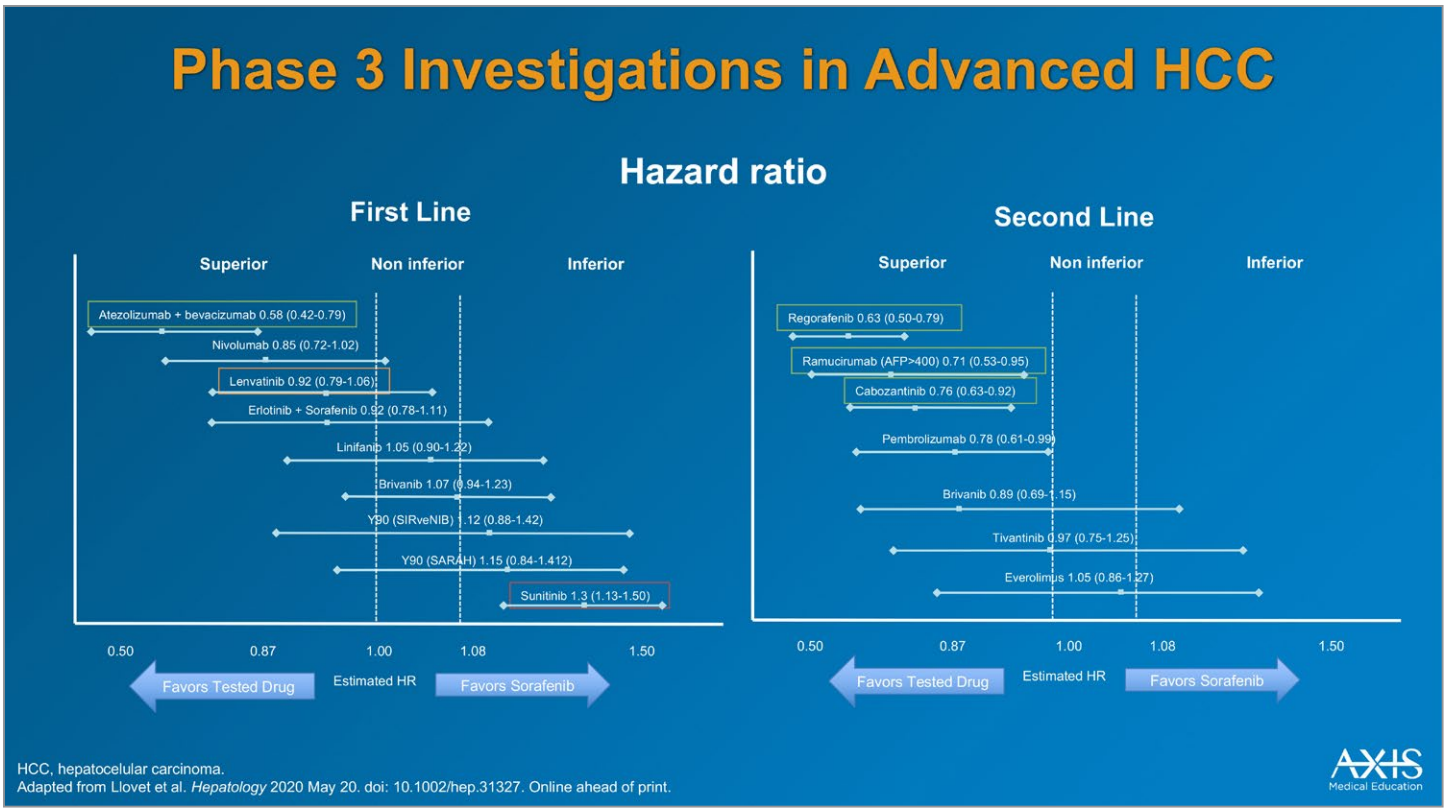
  Also, in terms of disease control rate overall, we're talking about 75% disease control rate with the combination compared to 55% for sorafenib.



- In terms of adverse events, overall, the grade 3/4 treatment-related adverse events accounted for 37% of the cases in atezolizumab/bevacizumab and 55% for sorafenib. The most remarkable grade 3/4 were hypertension, certainly, for atezolizumab/bevacizumab and also ALT increase and proteinuria. And for sorafenib, the well-known hypertension and hand-foot skin reaction and also diarrhea were remarkable.



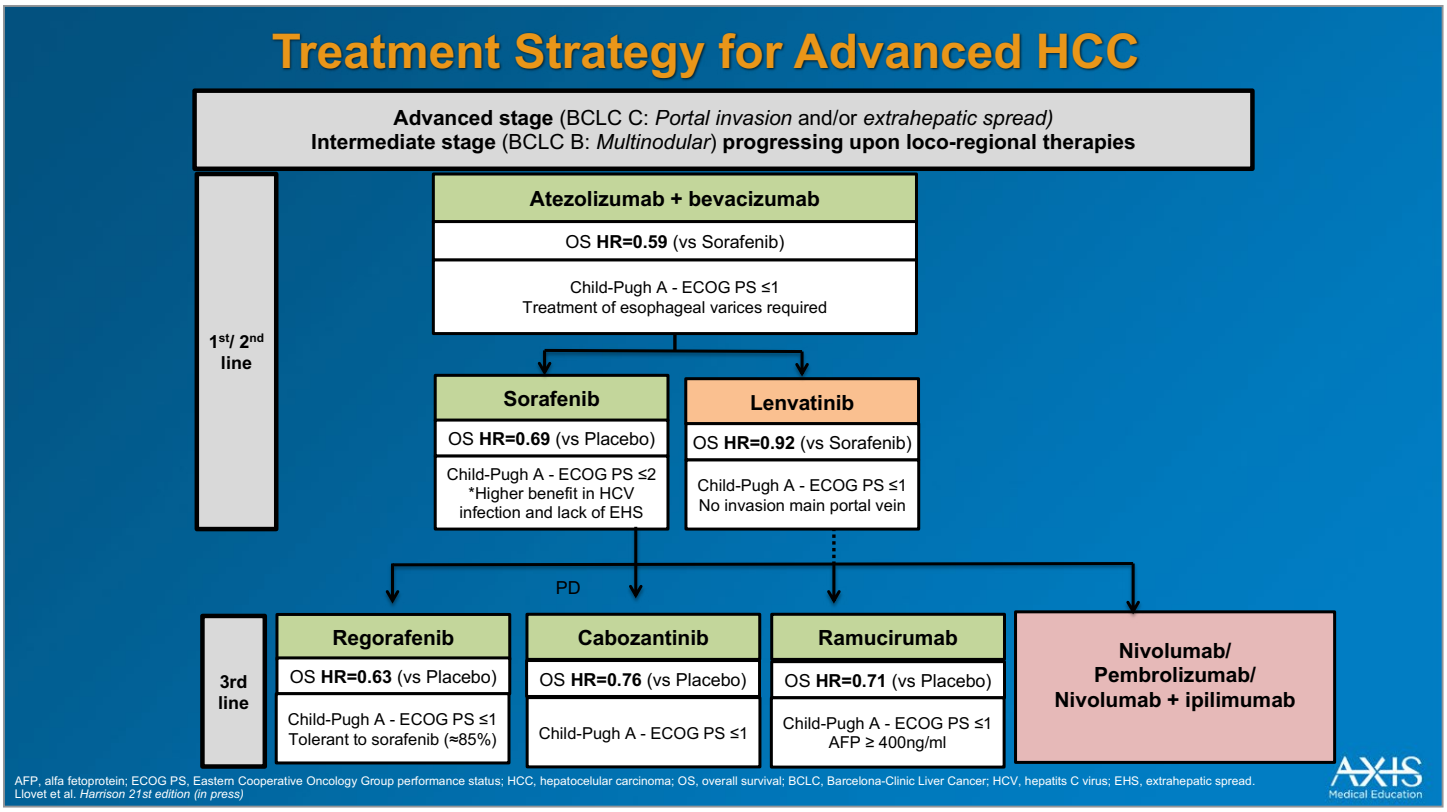
- Finally, this trial also assessed patient-reported outcomes. That is increasingly an endpoint that the FDA is very interested to assess. And certainly, time to deterioration of the quality of life was significantly longer for atezolizumab/bevacizumab—11.2 months' time to deterioration compared to 3.6 months for sorafenib with a substantial difference.



- So, on this slide, you have a summary of all of the trials—the phase 3 investigations in advanced HCC. Certainly, on the left-hand side, you have in frontline atezolizumab/bevacizumab superior to sorafenib. All these figures represent comparisons with sorafenib.

  Lenvatinib, as you can see in orange, is noninferior. It's crossing the one, but below the upper boundary of 1.08 defined as the limit for noninferiority.

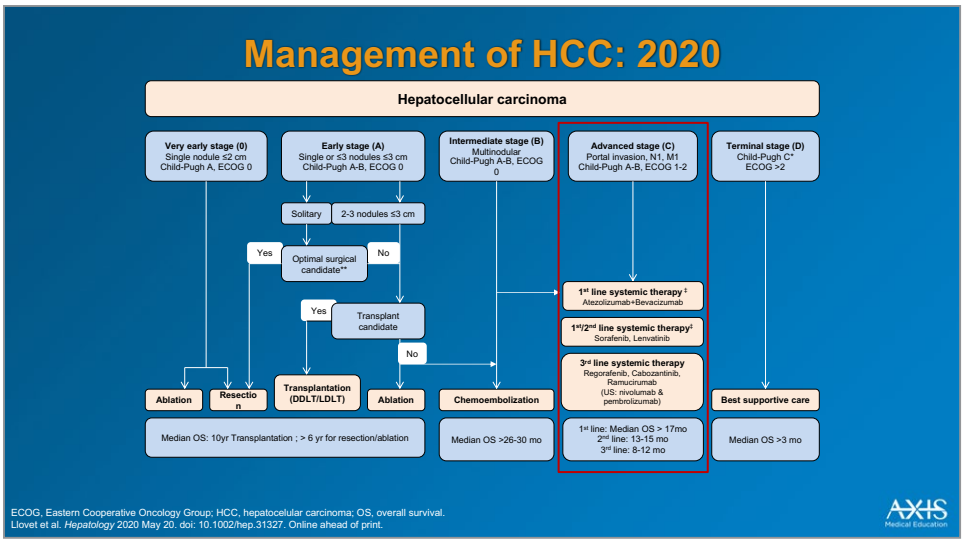
  And then, on the right-hand side, you have regorafenib, cabozantinib, and ramucirumab—all of them in green—where you have superiority versus placebo. And on the left-hand side, you have nivolumab crossing the one. And on the right-hand side, you have pembrolizumab that despite it's below the one in terms of upper boundary did not reach statistical significance. And, therefore, for single-agent checkpoint inhibitors, we need biomarkers to guide the strategy of treatment.



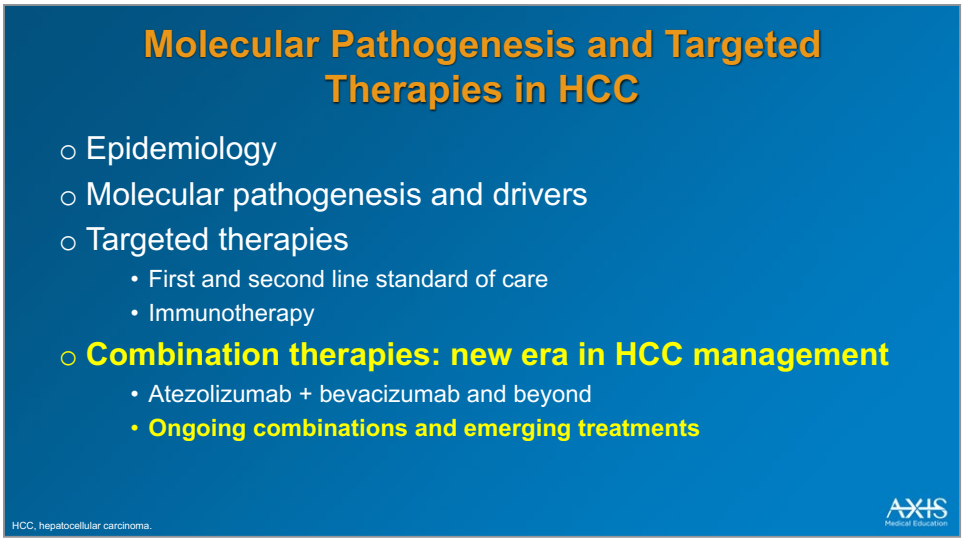
- This is the strategy. Certainly, recently reported in several papers. Atezolizumab/ bevacizumab will be frontline. And then sorafenib and lenvatinib might be also frontline in patients that either do not tolerate the drugs—either atezolizumab or bevacizumab—or have any autoimmune disease or have any contraindication.

Do not have, for instance, a GI endoscopy. An upper GI endoscopy is required before starting atezolizumab/ bevacizumab to rule out esophageal varices or at least if there these varices, those varices need to be treated before starting this combination.

And then, if sorafenib and lenvatinib are not used in frontline, they certainly might be used in second line followed regorafenib, cabozantinib, and ramucirumab. And then you have the three drugs involving single agent checkpoint—nivolumab, pembrolizumab, or the combination of nivolumab/ ipilimumab—that are also approved by FDA in second line.

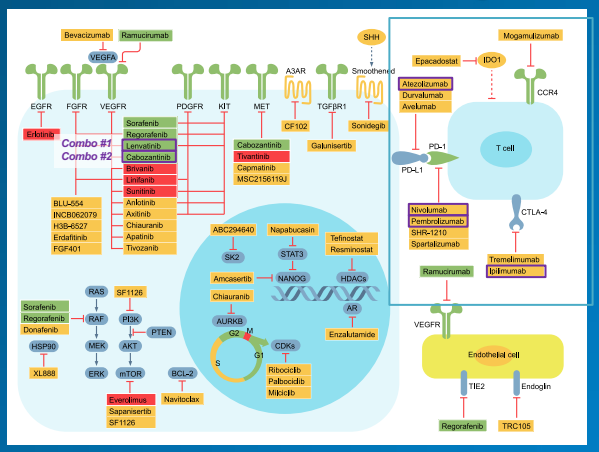


- This is another scheme that was recently reported by the American Association for the Study of Liver Disease in Hepatology about the recommendation of frontline and second-line and third-line treatment therapies.



- Finally, very briefly, I'm going to talk about other common combinations.

Rationale for Combination Strategies in HCC



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

AXIS Medical Education

- And one of those is certainly lenvatinib/pembrolizumab. But also, now, more increasingly, there are triplets in place in terms of trials with cabozantinib combined with nivolumab and ipilimumab.

Phase 1b KEYNOTE-524 Trial (Study 116): Lenvatinib + Pembrolizumab

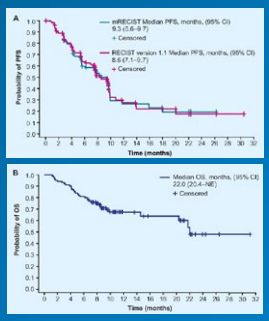
Lenvatinib (8mg [bodyweight <60 kg] or 12 mg [bodyweight ≥60 kg] PO QD) + pembrolizumab (200mg or placebo IV Q3W)

Inclusion criteria:
- uHCC
- BCLC Stage B or C
- Child-Pugh class A
- ECOG PS 0-1

Expansion (part 1&2)
- N = 6+ 98
- No prior systemic therapy
- **Overall: 100 patients evaluable**

TABLE 3. Summary of Efficacy Outcomes in Those Receiving Lenvatinib Plus Pembrolizumab (N = 100)

	mRECIST	
Parameter	Investigator Review	IIR
ORR (confirmed responses only)	41 (41)	46 (46)
95% CI*	31.3 to 51.3	36.0 to 56.3
ORR (confirmed and unconfirmed responses)	46 (46)	53 (53)
95% CI*	36.0 to 56.3	42.8 to 63.1
Best overall response		
CR	5 (5)	11 (11)
PR	36 (36)	35 (35)
SD^b^	45 (45)	42 (42)
PD	7 (7)	7 (7)
DCR	86 (86)	88 (88)



CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
Finn et al. *J Clin Oncol.* 2020;38:2960-2970.

AXIS Medical Education

- So, this is the KEYNOTE-524 or 116—lenvatinib/pembrolizumab as a single-arm, phase 2, 100 patients. Interestingly enough, objective responses were here at the level of 46% by modified RECIST with disease-control rates that also are unprecedented up to 90%.

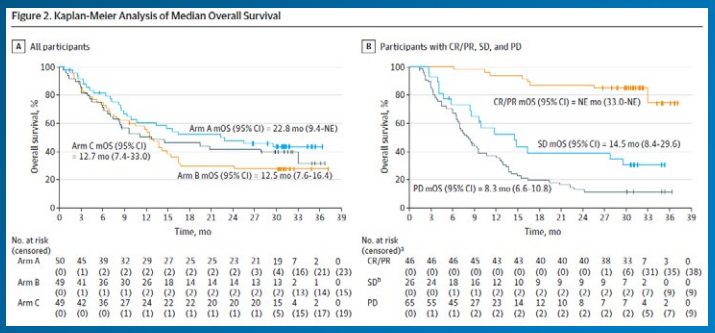
  In this phase 2 study or phase 1b/2 study, the median survival was 22 months, and the progression-free survival was 9.3 months with this combination.

  And now, we have the LEAP-002 as the phase 3 trial comparing lenvatinib/pembrolizumab versus lenvatinib alone.

Phase 1/2 CheckMate 040 Trial: Nivolumab + Ipilimumab

Survival by Treatment Arm

Overall Population Survival Stratified By Best Overall Response



CR, complete response; HCC, hepatocellular carcinoma; mOS, median overall survival; ; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
Yau *et al. JAMA Oncol.* 2020;6:e204564.

- Another trial that has been reported in JAMA with nivolumab plus ipilimumab, and certainly, one of the combinations was able to achieve median survival of 22.8 months in second line. And those patients achieving objective response—either complete or partial response—was around 30% of the patients. Had an outstanding outcome. The median was not reached, but certainly, it was beyond 33 months.

Phase 1/2 CheckMate 040 Trial: Nivolumab + Ipilimumab +/- Cabozantinib

CheckMate 040 is a Phase 1/2, open-label, non-comparative, dose escalation and expansion trial of nivolumab in adults (≥18 years) with histologically confirmed advanced HCC with or without hepatitis C or B (HCV or HBV) infection[1]

- Aged ≥ 18 years with advanced HCC
- Sorafenib naive or progression after or intolerance to sorafenib
- HBV, HCV, or non-viral HCC
- Child-Pugh score A5 or A6

1:1

Doublet arm
Nivolumab 240 Q2W IV + cabozantinib 40 QD PO

Triplet arm
Nivolumab 3 Q2W IV + Ipilimumab 1 Q6W IV + cabozantinib 40 QD PO

Primary endpoints:
- Safety and tolerability
- ORR by investigator assessment

Secondary endpoints:
- DCR, DOR, TTR, TTP, PFS, OS

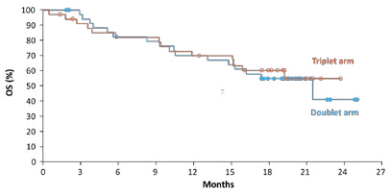
DCR, disease control rate; DOR, duration of response; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

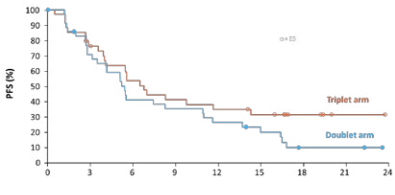
- Another study that was conducted was the combination of nivolumab/ipilimumab with cabozantinib.

Phase 1/2 CheckMate 040 Trial: Nivolumab + Ipilimumab +/- Cabozantinib

OS	Doublet arm n = 36	Triplet arm n = 35
Median OS (95% CI), mo	21.5 (13.1-NR)	NA (15.1-NR)
Patients with an event, n	15 (44)	14 (40)
15-month OS rate, % (95% CI)	64 (45-78)	70 (51-83)

PFS	Doublet arm n = 36	Triplet arm n = 35
Median PFS (95% CI), mo	5.4 (3.2-10.9)	6.8 (4.0-14.3)
Patients with an event, n (%)	30 (83)	22 (63)





HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival.
Yau et al. *J Clin Oncol*. 2020;38:478.

- As you can see, as a triplet, median overall survival was not achieved, but the median progression-free survival was remarkable at 6.8 months.

Phase 1/2 CheckMate 040 Trial: Nivolumab + Ipilimumab +/- Cabozantinib

Efficacy	Doublet arm n = 36		Triplet arm n = 35	
	Investigator assessment	BICR	Investigator assessment	BICR
ORR* using RECIST v1.1, n (%)	7 (19)†	5 (14)	10 (29)†	11 (31)
BOR, n (%)				
CR	0	1 (3)	0	2 (6)
PR	7 (19)	4 (11)	10 (29)	9 (26)
SD	20 (56)	20 (56)	19 (54)	16 (46)
PD	8 (22)	7 (19)	4 (11)	4 (11)
Unable to determine‡	1 (3)	1 (3)	2 (6)	3 (9)
DCR**, n (%)	27 (75)	28 (78)	29 (83)	28 (80)
Median TTR (range), months	4.8 (2.7–20.7)	NA	3.5 (1.3–9.9)	NA
Median DOR (range), months	8.3 (0.0–NR)	NA	NA	NA
Safety	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Any TRAE, n (%)	32 (89)	17 (47)	33 (94)	25 (71)
Continuing treatment, n (%)	7 (19)		10 (29)	

BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; HCC, hepatocellular carcinoma; PD, progressive disease; PR, partial response; SD, stable disease; TRAE, treatment-related adverse event; TTR, time to response.
Yau et al. *J Clin Oncol*. 2020;38:478.

- In terms of adverse events, certainly, the triplet doesn't seem to have an unmanageable adverse event profile despite that certainly the grade 3/4 are slightly higher than with the doublet arm.

New Targets and Agents in Phase 1/2 Trials

Trial name/ identifier	Setting	Treatment	Primary endpoints	Study type	Planned enrollment, n
Phase 1/2 trials					
GO30140 NCT02715531	Advanced HCC/first-line	Bevacizumab + atezolizumab	Safety, ORR, PFS	Phase 1b	430 (across all cohorts)
NCT03006926	Advanced HCC/first-line	Lenvatinib + pembrolizumab	Dose escalation: Safety, DLTs Dose expansion: ORR, DOR	Phase 1b (dose-escalation and dose-expansion)	97
NCT03418922	Advanced HCC/first-line	Lenvatinib + nivolumab	Part1: DLTs, safety Part2: Safety	Phase 1b (part 1 and part 2)	26
NCT03895970	Advanced hepatobiliary tumors/second-line	Lenvatinib + pembrolizumab	ORR, DCR, PFS	Phase 1b	50
CheckMate 040 NCT01658878	Advanced HCC/first- or second-line	Cabozantinib + nivolumab +/- ipilimumab	Safety, ORR	Phase 1/2 (dose-escalation, dose-expansion)	620 (across all cohorts)
COSMIC-021 NCT03170960	Advanced solid tumors, HCC/first-line	Cabozantinib + atezolizumab	Dose escalation: MTD, Recommended dose Dose expansion: ORR	Phase 1b (dose-escalation and dose-expansion)	1000 (across all cohorts)
CaboNivo NCT03299946	Locally advanced HCC/neoadjuvant	Cabozantinib + nivolumab	Safety, number of patients who complete preoperative treatment and proceed to surgery	Phase 1b	15
CAMILLA NCT03539822	Advanced GI tumors, HCC/second-line	Cabozantinib + durvalumab	MTD	Phase 1b	30
NCT03347292	Advanced HCC/first-line	Regorafenib + pembrolizumab	Safety, DLTs	Phase 1b (dose-escalation and dose-expansion)	40
REGOMUNE NCT03475953	Advanced GI tumors, HCC/second-line	Regorafenib + avelumab	Part 1: Recommended phase II dose of regorafenib Part 2: ORR	Phase 1/2 (part 1 and part 2)	212
NCT02572687	Advanced solid tumors, HCC/second-line and AFP ≥1.5x upper limit of normal	Ramucirumab + durvalumab	DLTs	Phase 1	114
NCT02082210	Advanced solid tumors, HCC/second-line	Ramucirumab + emibetuzumab	Part A: DLTs Part B: ORR	Phase ½	97
NCT02423343	Advanced solid tumors, HCC/second-line and AFP ≥200 ng/mL	Galunisertib + nivolumab	Phase Ib: MTD	Phase 1b/2 (dose escalation and cohort expansion)	75

HOT Issue: Combination therapies!

DCR, disease control rate; DLTs, dose-limiting toxicities; HCC, hepatocellular carcinoma; ORR, objective response rate; PFS, progression-free survival
Adapted from Faivre et al. *J Hepatol*. 2020;72:342-352.

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- So, in terms of new agents, here you have a list of new agents that are currently tested in combination with checkpoint inhibitors. And, of course, you have regorafenib here, and you have galunisertib, also a TGF-beta inhibitor that is currently in place.

  I have to say that the combination therapies are now the hot topic. And really, we're now in a new era of treatment in HCC where we will probably not see any more trials with single agents. We know the first in class is certainly atezolizumab/bevacizumab, but we need to know if this is also the best in class or if other combinations may even have a better outcome when treating patients in frontline HCC.

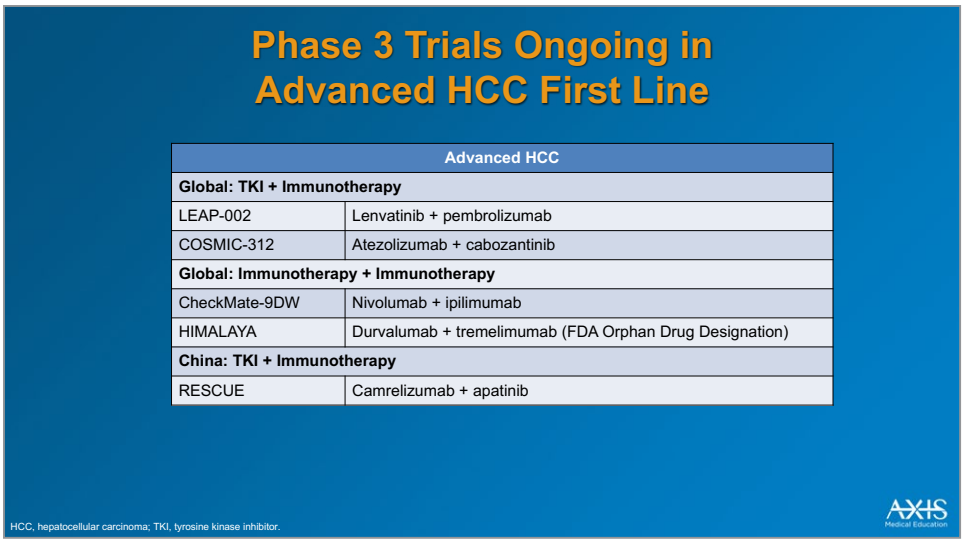
Phase 3 Trials Ongoing With Immunotherapies in HCC

Adjuvant Therapies in Early HCC (After Resection/Ablation)	
CheckMate 9DX	Nivolumab vs placebo
KEYNOTE-937	Pembrolizumab vs placebo
IMbrave 050	Atezolizumab + pembrolizumab vs placebo
EMERALD-2	Durvalumab + bevacizumab vs placebo
Intermediate HCC	
EMERALD-1	TACE + bevacizumab + durvalumab vs TACE
LEAP 012	TACE + lenvatinib + pembrolizumab vs TACE
CheckMate 74W	TACE + nivolumab + ipilimumab vs TACE
REGONIVO	TACE vs regorafenib + nivolumab
TACE-3	TACE + nivolumab vs TACE

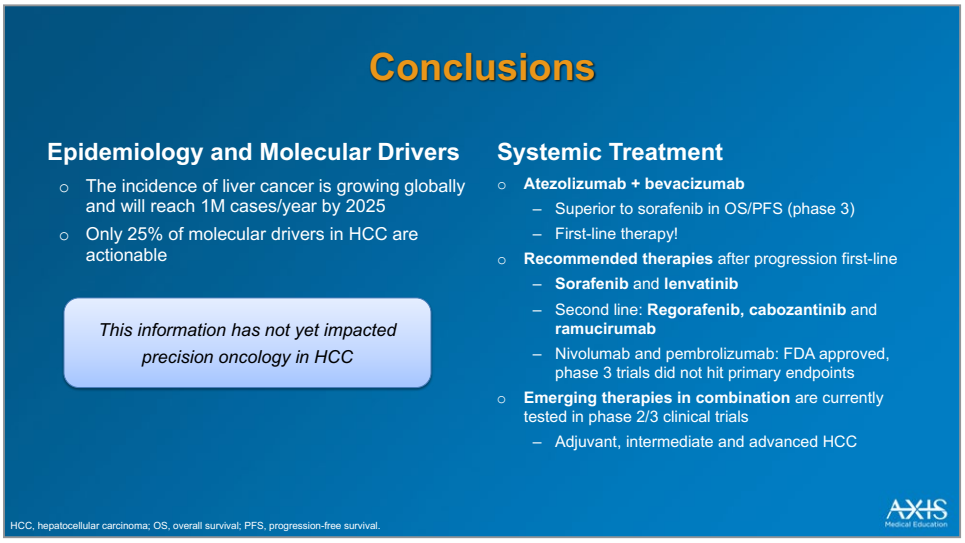
HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

AXIS Medical Education

- And here, you have a summary of how these immunotherapies now are currently being tested in the adjuvant settings.



In advance, again, we know the first in class. Let's see if this is the best therapy, or the new trials—LEAP-002 testing lenvatinib/pembrolizumab, COSMIC-312 testing atezolizumab/cabozantinib, CheckMate-9DW testing nivolumab/ipilimumab, the HIMALAYA trial testing durvalumab plus tremelimumab, or the RESCUE trial of camrelizumab plus apatinib. Let's see if they will have a different outcome or even an improved outcome.



So, in conclusion, in terms of epidemiology and molecular drivers, the incidence of liver cancer is growing globally and will reach 1,000,000 cases by 2025. And only 25% of molecular drivers in HCC are actionable. And, unfortunately, these data have not yet impacted precision oncology in HCC because most of the most prevalent drivers are undruggable.

In terms of systemic treatment, now atezolizumab plus bevacizumab is unquestionably the standard of care in frontline. It shows superiority to sorafenib. Sorafenib and lenvatinib can be also still frontline in patients with any contraindications for atezolizumab/bevacizumab or with esophageal varices. Otherwise, it will be second line.

And then, those patients who progress with these regimens may be treated with regorafenib. And particularly, regorafenib in case a patient receives sorafenib as prior therapy, or cabozantinib, ramucirumab in patients with AFP of more than 400.

And finally, we have that nivolumab alone, pembrolizumab alone or even nivolumab/ipilimumab are FDA approved based on phase 2 data and got accelerated approval. And the emerging therapies now are mostly all of them in combination. And phase 2/phase 3 trials are currently conducted in adjuvant, intermediate, and advanced HCC with certainly most of the instances with immune therapies in the set of drugs that are currently tested.

Dr. Baskin and I thank you for your attention.

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