Liver Cancer: Still an Evolving Field!

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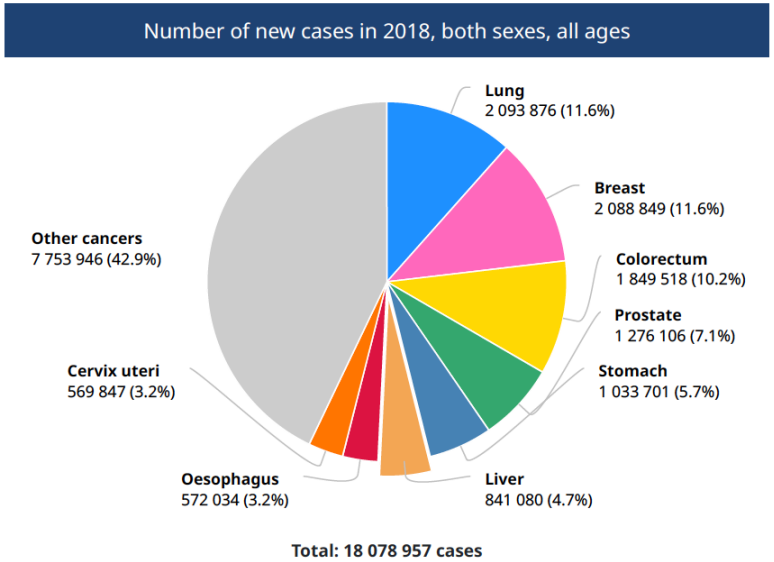
Disclosures

- Financial: Grifols, Durect, Salix, AbbVie, Gilead, Prometheus, Mallinckrodt, Novartis

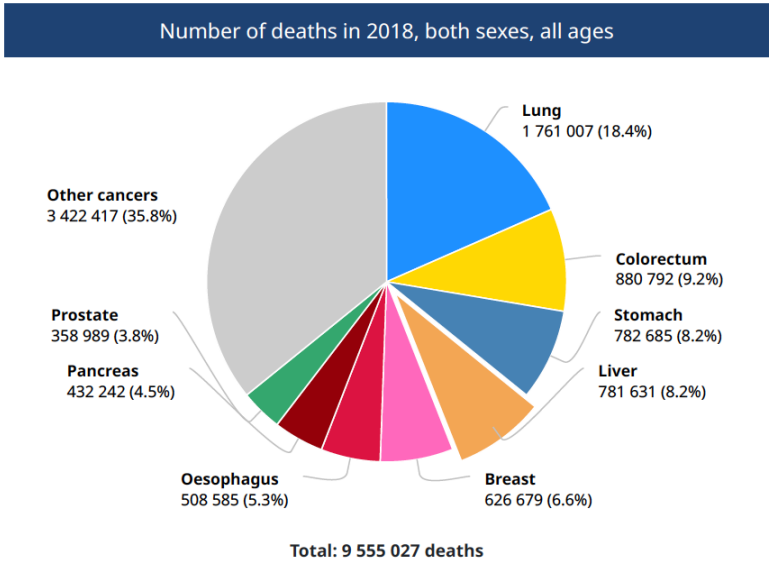
Global Data

HCC: New Cases and Mortality – 2018

6th most common tumor



4th most leading cause of cancer mortality

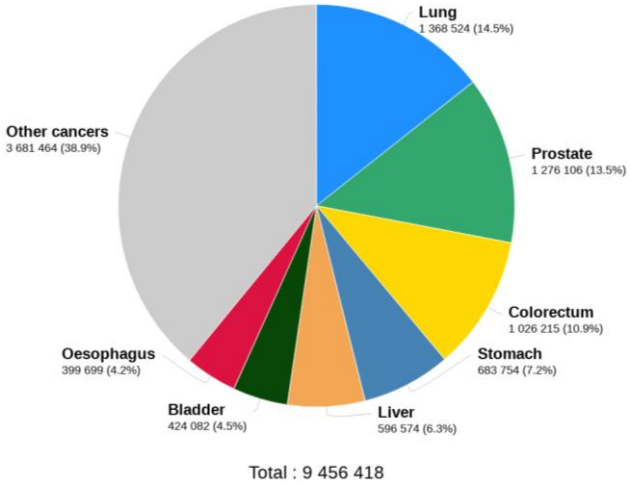


WHO. 2018. https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf.

HCC: Common in Both Men and Women

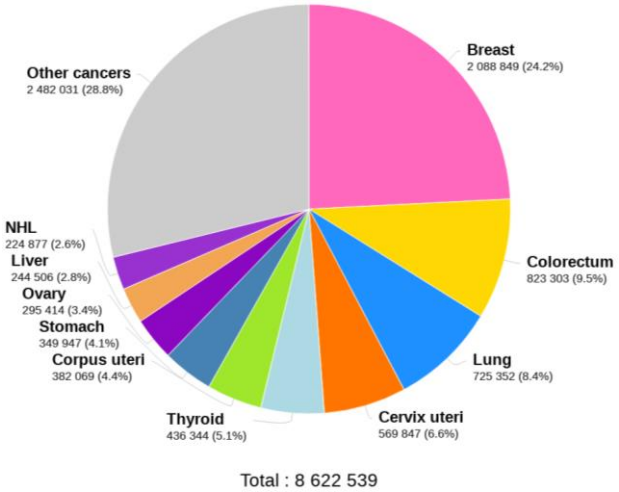
5th most common tumor

Men



9th most common tumor

Women

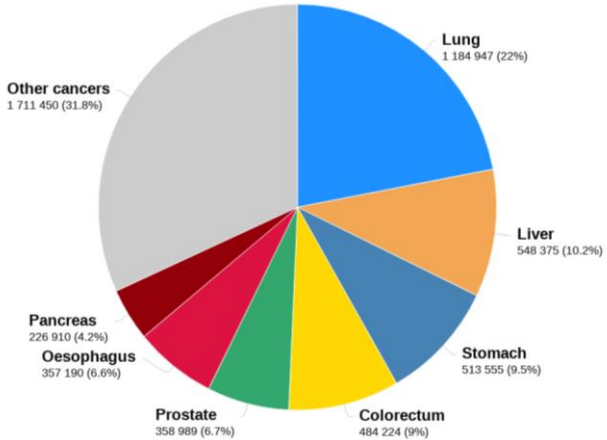


WHO. 2018. http://gco.iarc.fr/today/fact-sheets-cancers.

HCC: Common Cause of Mortality in Both Men and Women

2nd most common cause of cancer related death in men

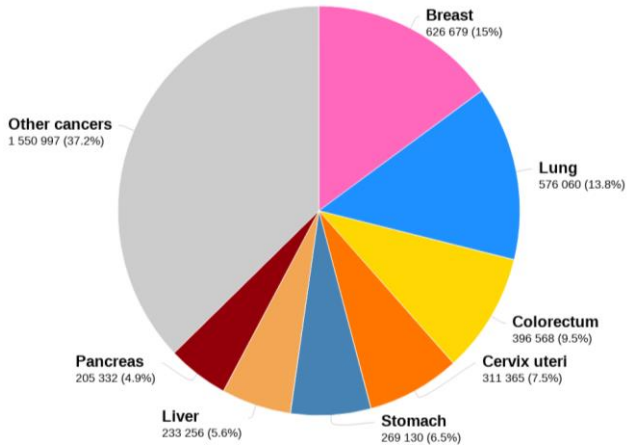
Men



Total : 5 385 640

6th most common cause of cancer related death in women

Women

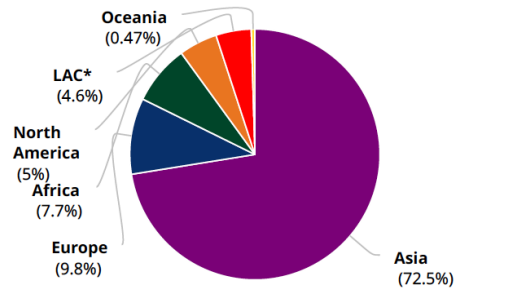


Total : 4 169 387

WHO. 2018. http://gco.iarc.fr/today/fact-sheets-cancers.

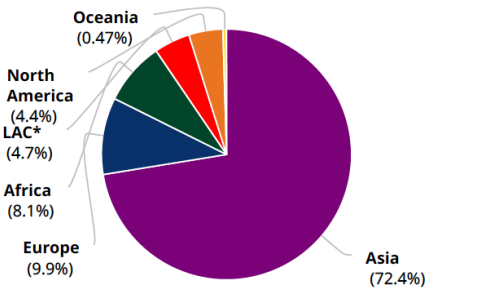
More than 70% of All HCC Cases Are in Asia

Incidence, both sexes



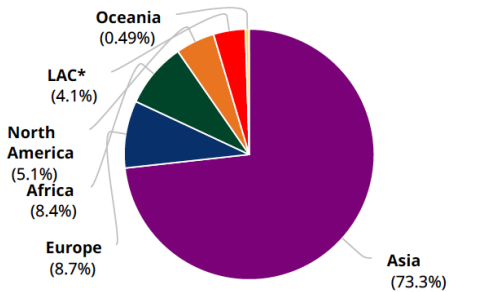
	Population	Number
	Asia	609 596
	Europe	82 466
	Africa	64 779
	North America	41 851
	*Latin America and the Caribbean	38 400
	Oceania	3 988
	Total	841 080

Mortality, both sexes



	Population	Number
	Asia	566 269
	Europe	77 375
	Africa	63 562
	*Latin America and the Caribbean	36 436
	North America	34 339
	Oceania	3 650
	Total	781 631

5-year prevalence, both sexes

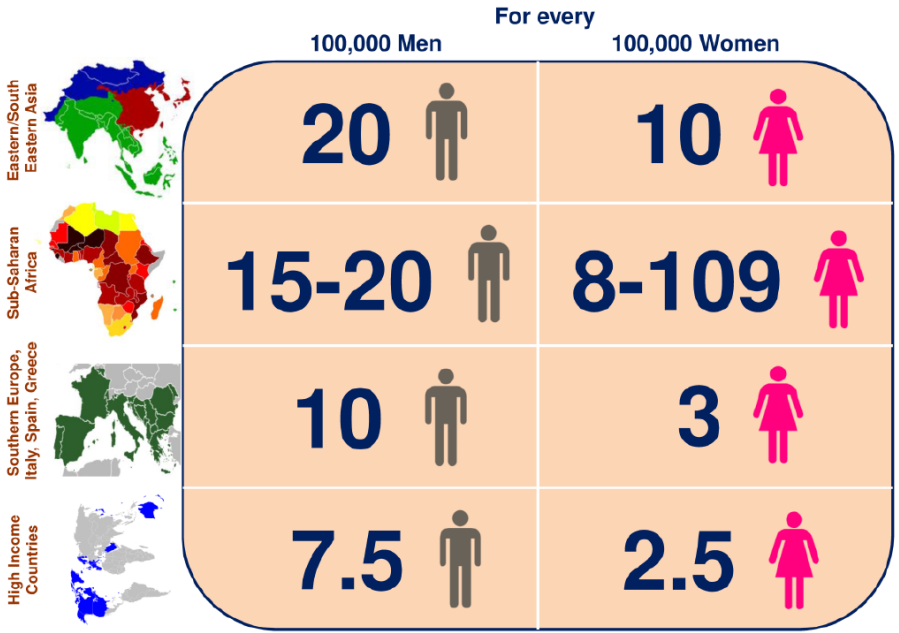


	Population	Number
	Asia	494 783
	Europe	58 477
	Africa	56 736
	North America	34 107
	*Latin America and the Caribbean	27 795
	Oceania	3 312
	Total	675 210

WHO. 2018. https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf.

Low Income Countries Have a Disproportionate HCC Burden

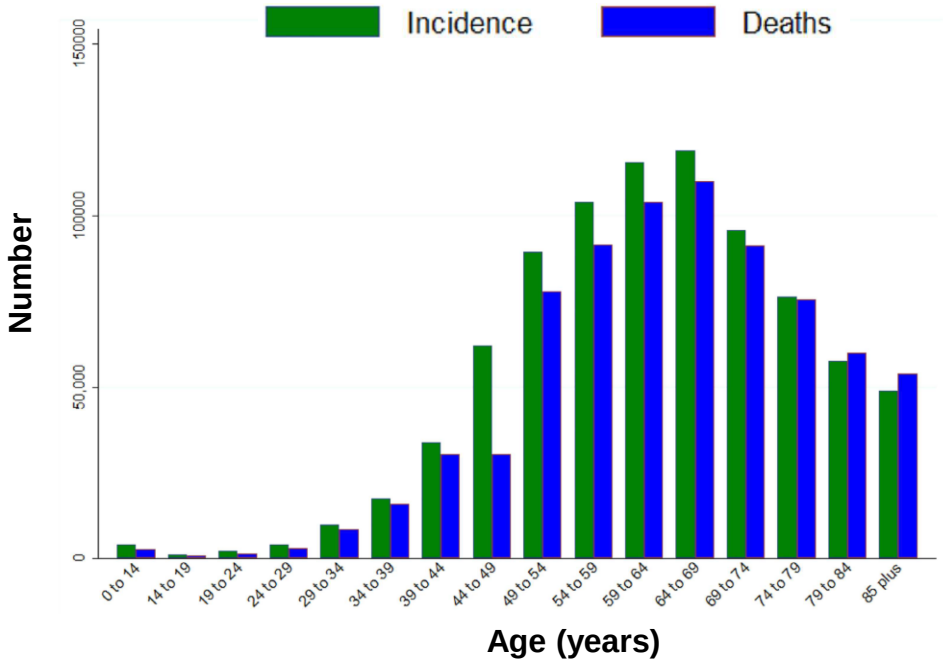
- Incidence rates of HCC in Eastern/South Eastern Asia, Sub-Saharan Africa, Southern Europe, Italy, Spain, Greece and high-income countries per 100,000 men and women



HCC, hepatocellular carcinoma.

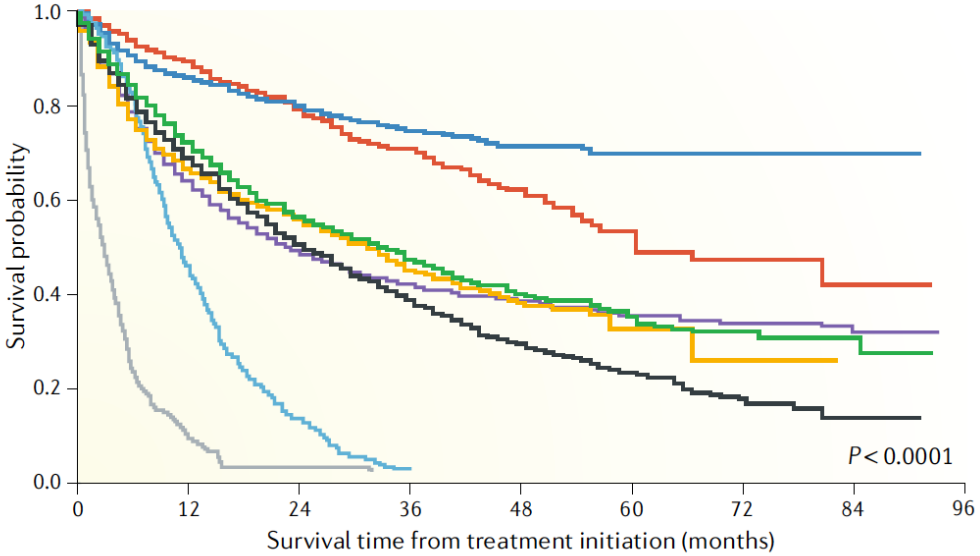
Raghunath A et al. *Cancers (Basel).* 2018;10(12):481.

HCC Incidence and Mortality: Patient Age



Sharma R et al. *Jpn J Clin Oncol*. 2020; hyaa130.

There Is Significant Geographic Variation in HCC Mortality



Countries	Median survival (months)
Taiwan	Not reached
Japan	60
North America	33
South Korea	31
Europe	24
China	23
Egypt	11
Other African countries	3

Yang JD et al. *Nat Rev Gastroenterol Hepatol*. 2019;16(10):589-604.

HCC Risk Factors

- Risk factors of hepatocellular carcinoma (HCC) and factors regulating HCC disparities.

Chronic Viral Hepatitis (HBV, HCV)

Cirrhosis

NAFLD/NASH

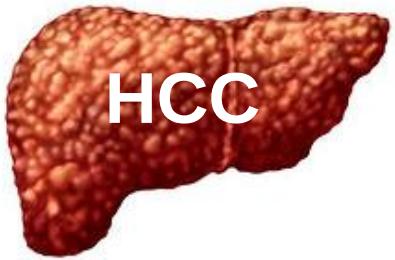
Metabolic Disease (Obesity and Diabetes mellitus)

Environment Toxins (Aflatoxin)

Genetic and Heredity disorders

Lifestyle Factors (Alcohol consumption and Smoking)

Dietary Factors



Factors influencing diagnosis and treatment

Socioeconomic Status

Health Care Access

Government Policies

Population Dynamics

HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH; nonalcoholic steatohepatitis.

Thylur RP et al. *JGH Open*. 2020;4(3):351-359.

United States Data

Incidence and Mortality

- In 2020, an estimated 42,810 new cases of liver cancer (including intrahepatic bile duct cancers) were diagnosed in the US and 30,160 people will die from the disease
- Approximately three-fourths of liver cancers are hepatocellular carcinoma (HCC)
- Liver cancer incidence is 3 times higher in men than in women
- The death rate for liver cancer has doubled from about 3 (per 100,000) during the 1980s to 6.6 during 2013-2017, but may have begun to stabilize in recent years
- The 5-year relative survival rate is 18%, up from 3% four decades ago
- Forty-four percent of patients are diagnosed with localized-stage disease, for which 5-year survival is still only 33%

Liver Cancer Mortality

Male

Lung & bronchus	72,500	23%
Prostate	33,330	10%
Colon & rectum	28,630	9%
Pancreas	24,640	8%
Liver & intrahepatic bile duct	20,020	6%
Leukemia	13,420	4%
Esophagus	13,100	4%
Urinary bladder	13,050	4%
Non-Hodgkin lymphoma	11,460	4%
Brain & other nervous system	10,190	3%
All sites	**321,160**	

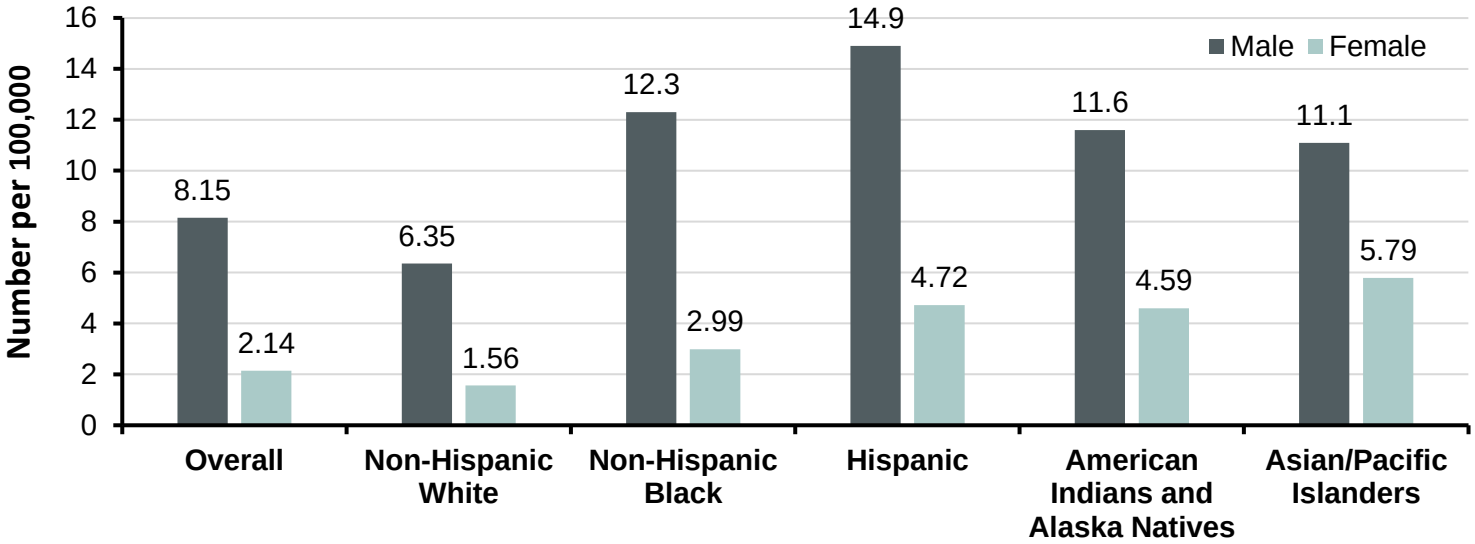
Female

Lung & bronchus	63,220	22%
Breast	42,170	15%
Colon & rectum	24,570	9%
Pancreas	22,410	8%
Ovary	13,940	5%
Uterine corpus	12,590	4%
Liver & intrahepatic bile duct	10,140	4%
Leukemia	9,680	3%
Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	7,830	3%
All sites	**285,360**	

ACS. 2020. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf.

Incidence of HCC Varies By Race/Ethnicity

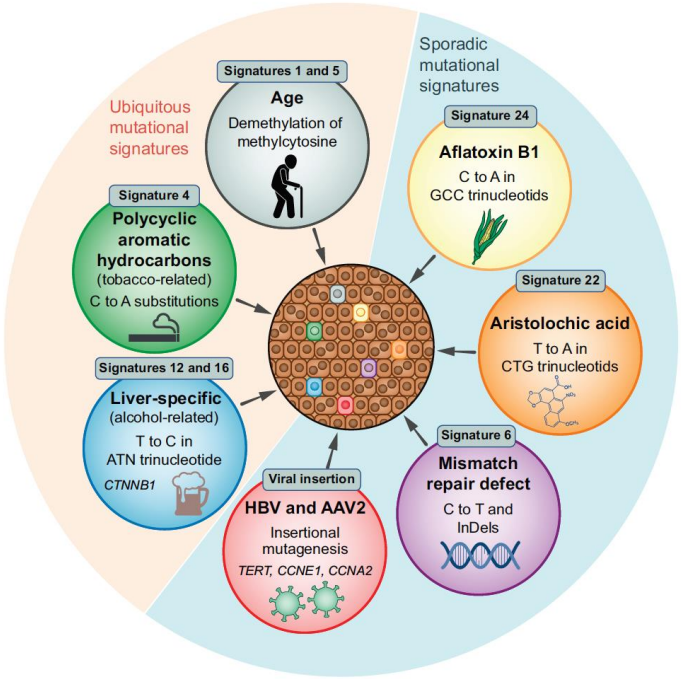
- Incidence of HCC –2001-2015



Zhang X et al. *Cancer Epidemiol Biomarkers Prev*. 2020;29(1):88-94.

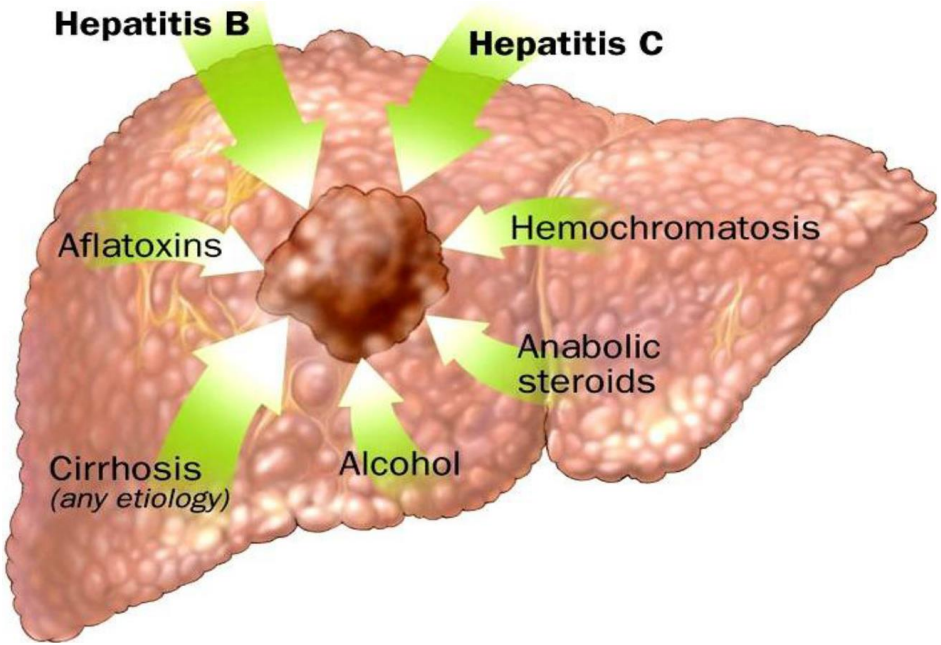
- Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death worldwide
- >80% of HCC cases occur in low- resource and middle- resource countries, particularly in Eastern Asia and sub-Saharan Africa, where medical and social care resources are often constrained
- Prevention and treatment of viral hepatitis and mitigation of exposure to aflatoxin and aristolochic acid, the main risk factors in high-incidence regions, are critical for decreasing the global burden of HCC

Mutational Processes and Common Driver Mutations in HCC



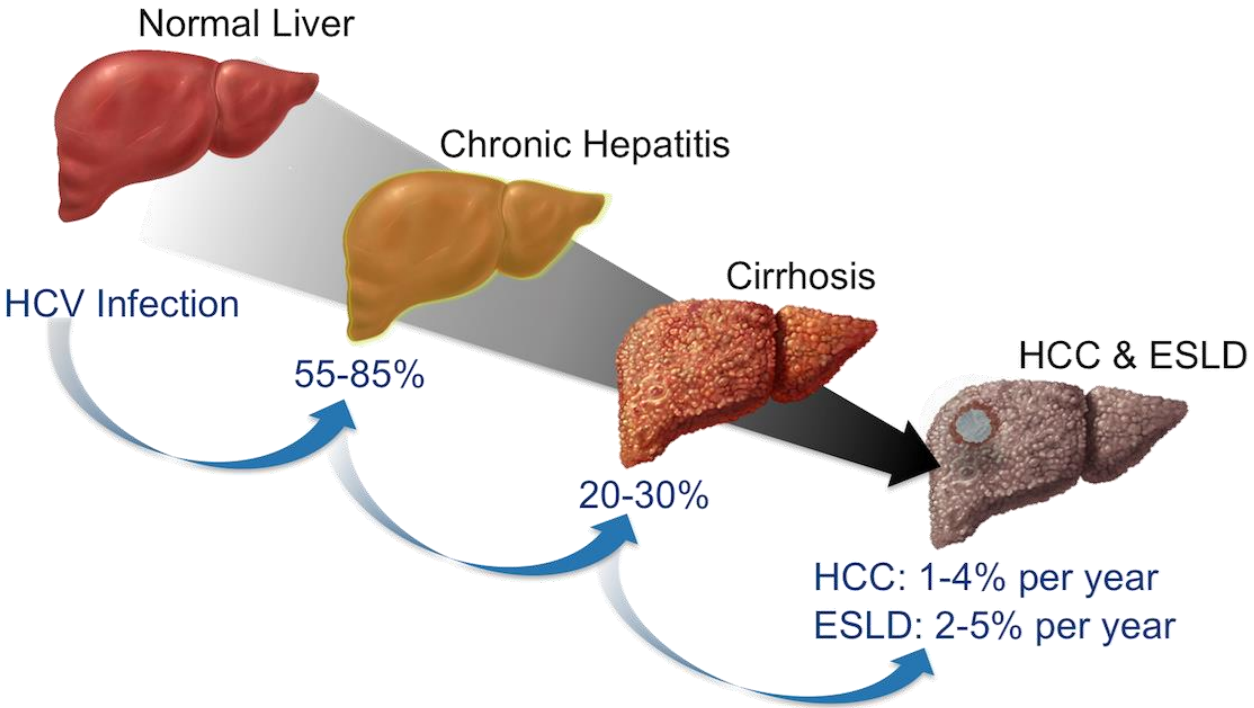
Mutations associated with HCC	Stage
Constitutional mutations/SNPs	
ATP7B	Wilson disease: cirrhosis/HCC predisposition
FAH	Tyrosinemia: cirrhosis/HCC predisposition
G6PC	Glycogenosis 1a: HCA-HCC predisposition
HFE	Haemochromatosis: cirrhosis/HCC predisposition
HNF1A	MODY 3 diabetes and HCA predisposition
HSD17B13 rs72613567	Cirrhosis/HCC predisposition (SNP)
PNPLA3 rs738409	Cirrhosis/HCC predisposition (SNP)
SERPINA1	Alpha-1 antitrypsin deficiency: cirrhosis/HCC predisposition
TM6SF2 rs58542926	Cirrhosis/HCC predisposition (SNP)
Somatic mutations	
TERT promoter	Tumour (early) (40–60%)
ACVR2A	Tumour (5%)
ARID1A	Tumour (5–15%)
ARID2	Tumour (3–15%)
AXIN1	Tumour (5–15%)
CTNNB1	Tumour (15–35%)
FGF19	Tumour (4–6%)
KEAP1	Tumour (2–8%)
KRAS	Tumour (1%)
MLL4	Tumour (5%)
NFE2L2	Tumour (3–6%)
RB1	Tumour (3–8%)
RPS6KA3	Tumour (2–9%)
SF3B1	Tumour (3%)
TP53	Tumour (15–45%)
VEGFA	Tumour (3–5%)

AAV, adeno-associated virus; HBV, hepatitis B, virus; HCC, hepatocellular carcinoma; SNP, single nucelotide polymorphism.
Müller M et al. *J Hepatol*. 2020;72(5):990-1002.



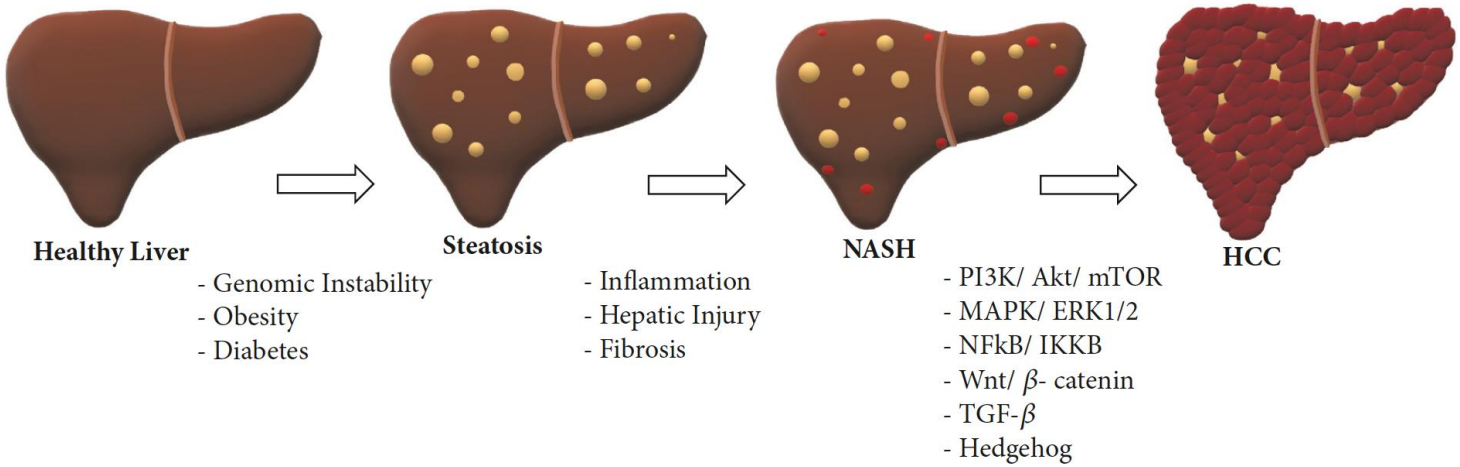
Ibrahim NE et al. *UK J Pharmaceutical and Biosciences*. 2018;6(5):48-55.

Progression From HCV to HCC



ESLD, endstage liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.
Lingala S, Ghany MG, et al. *Gastroenterol Clin North Am*. 2015;44(4):717-734.

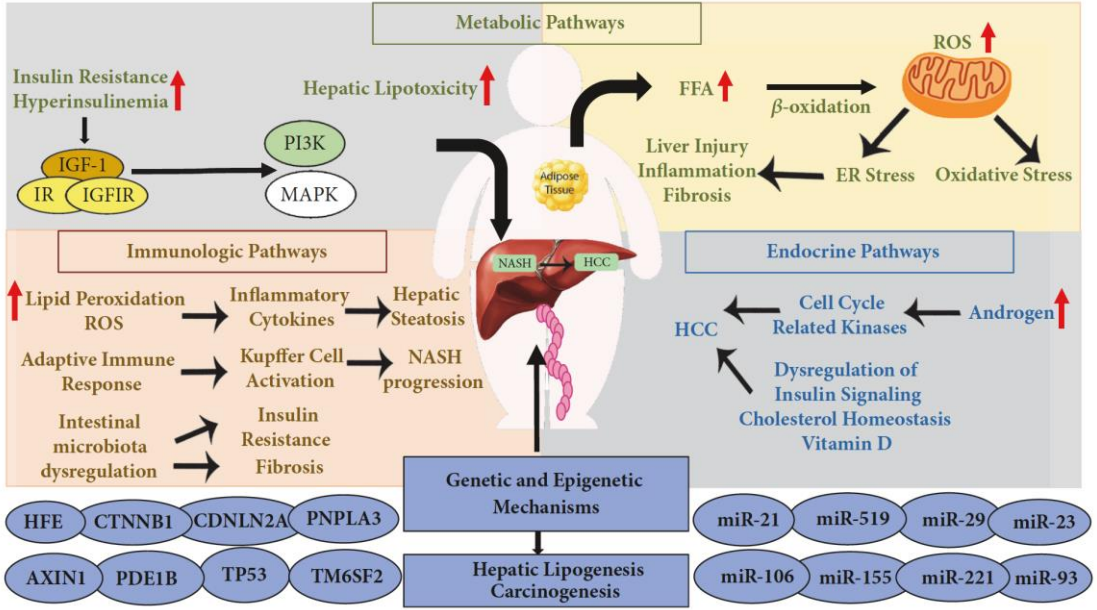
NAFLD and HCC



Akt, protein kinase B; ERK, extracellular signal-regulated kinase; HCC, hepatocellular carcinoma; IKKB, nuclear factor kappa-B kinase subunit β; mTOR, mammalian target of rapamycin; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NfKB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; TGF, transforming growth factor.

Kutlu O et al. *Can J Gastroenterol Hepatol*. 2018;2018:8543763.

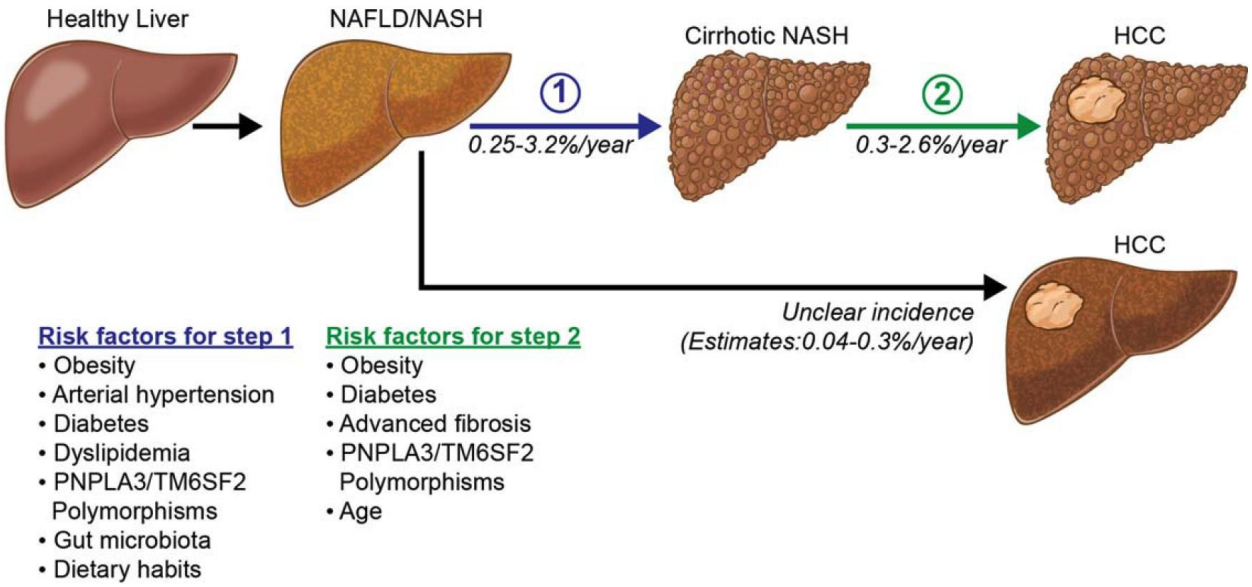
Proposed Mechanisms in NASH-Related HCC Progression.



ER, endoplasmic reticulum; FFA, free fatty acid; HCC, hepatocellular carcinoma; IGF-1, insulin-like growth factor-1; IGF1R, IGF-1 receptor; IR, insulin receptor; MAPK, mitogen activated protein kinase; miR, micro-ribonucleic acid; NASH, nonalcoholic steatohepatitis; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species.

Kutlu O et al. *Can J Gastroenterol Hepatol*. 2018;2018:8543763.

Natural History of NASH/NAFLD-Related HCC

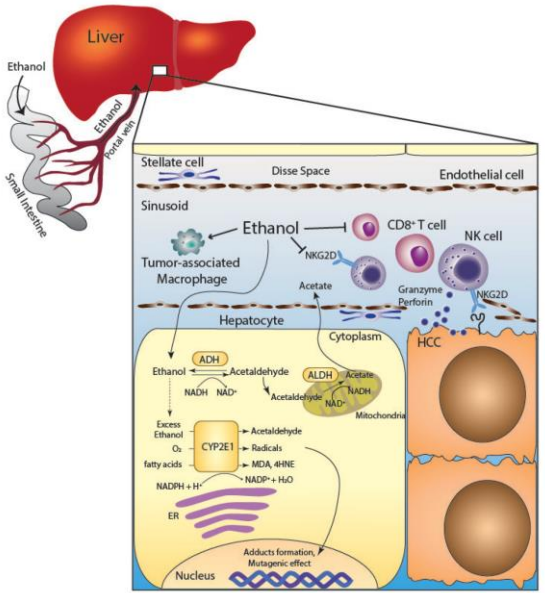


HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing protein 3; TM6SF2; transmembrane 6 superfamily member 2.

D'Avola D et al. *Clin Liver Dis* (Hoboken). 2016;8(4):100-104.

Mechanisms Associated With Alcohol-Associated HCC

- Alcohol is classified as a Group 1 carcinogen by the International Agency for Research on Cancer because it induces HCC (among other cancers) in humans
- Excessive alcohol intake may result in fatty liver, acute/chronic hepatitis, and cirrhosis and eventually lead to HCC
- Alcohol abuse increases the relative risk of hepatocellular carcinoma by 3- to 10-fold

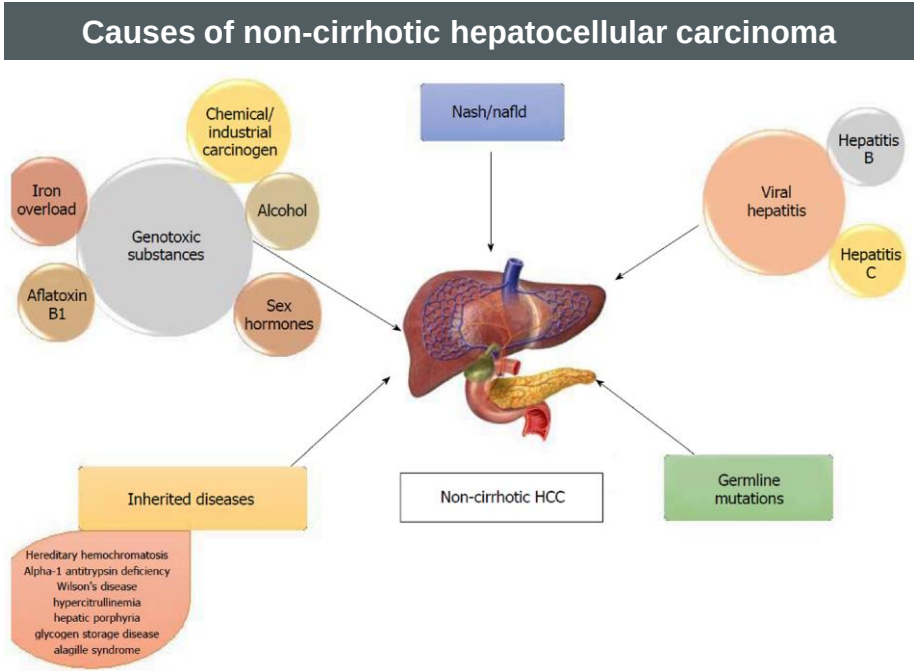


4-HNE, 4-hydroxynoneal; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CD, cluster of differentiation; CYP, cytochrome P450; ER, endoplasmic reticulum; HCC, hepatocellular carcinoma; MDA, malondialdehyde; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide hydrogen; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, NADP hydrogen; NK, natural killer; NKGD2, C-type lectin-like receptor expressed on NK cells.

Matsushita H, Takaki A, et al. *BMJ Open Gastroenterol*. 2019;6(1):e000260.

Non-Cirrhotic HCC

- HCC typically arises in the setting of cirrhosis
- However, approximately 20% of HCC's develop in a non-cirrhotic liver
- This sub-group of HCC often presents at advanced stages because surveillance is not performed in a non-cirrhotic liver



HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
Desai A et al. *World J Hepatol*. 2019;11(1):1-18.

Screening Guidelines

Guideline	EASL	AASLD	JSH	APASL

Definition of high-risk population	• Pts with cirrhosis, Child-Pugh stage A and B
	• Pts with cirrhosis, Child-Pugh stage C awaiting liver transplant
	• Pts without cirrhosis with HBV and an intermediate or high risk of HCC (PAGE-B score ≥10)
	• Pts without cirrhosis with chronic HCV and bridging
	• fibrosis
		• Pts with cirrhosis, Child-Pugh stage A and B
		• Pts with cirrhosis, Child-Pugh stage C awaiting liver transplant
		• Pts without cirrhosis with HBV
			• Extremely high-risk pts:
			  • Pts with cirrhosis and HBV or HCV
			• High-risk pts:
			  • Nonviral cirrhosis
			  • Pts without cirrhosis with HBV or HCV
				• Pts with cirrhosis
				• Pts without cirrhosis with HBV:
				  • Asian females >50 y
				  • Asian males >40 y
				  • Africans >20 y
				  • Family history of HCC

Screening interval	• Every 6 mo	• Every 4-8 mo	• Every 3-4 mo in extremely high-risk pts • Every 6 mo in high-risk pts	• Every 6 mo
Imaging modality	• US (performed by • experienced personnel)	• US	• US • CT/MRI optional every 6-12 mo in extremely high-risk pts	• US
Biomarkers	• Not recommended	• At discretion of physician	• AFP • AFP-L3 fractions • DCP	• AFP

AASLD, American Association for the Study of Liver Diseases; AFP, α-fetoprotein; APASL, Asian Pacific Association for the Study of the Liver; CT, computed tomography; DCP, des-gamma carboxyprothrombin; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; JSH, Japan Society of Hepatology; mo, month; MRI, magnetic resonance imaging; PAGE-B, platelets, age, gender, hepatitis B; pts, patients; US, ultrasound.

Frenette CT et al. *Mayo Clin Proc Innov Qual Outcomes*. 2019;3(3):302-310.

Groups At High Risk For HCC

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Incidence of HCC
Surveillance benefit		
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.6% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2-1.5	3%-8% per year
Hepatitis C cirrhosis	1.5	3%-5% per year
Stage 4 PBC	1.5	3%-5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	<0.2% per year
Hepatitis C and stage 3 fibrosis	1.5	<1.5% per year
NAFLD without cirrhosis	1.5	<1.5% per year

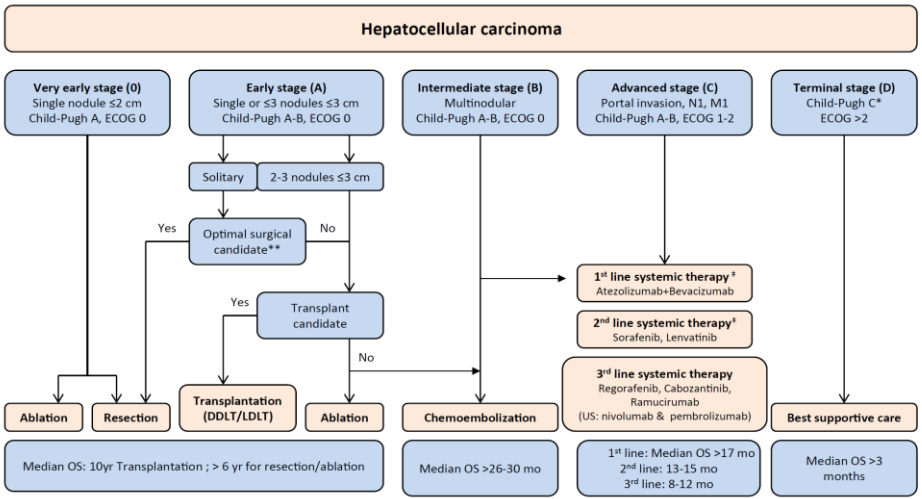
Abbreviation: LYG, life-years gained.

HCC, hepatocellular carcinoma; LYG, life years gained; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis.

Marrero JA et al. *Hepatology*. 2018 Aug;68(2):723-750.

The Barcelona Clinic Liver Cancer Staging System

Modified BCLC Staging - AASLD 2020 Consensus Conference Update



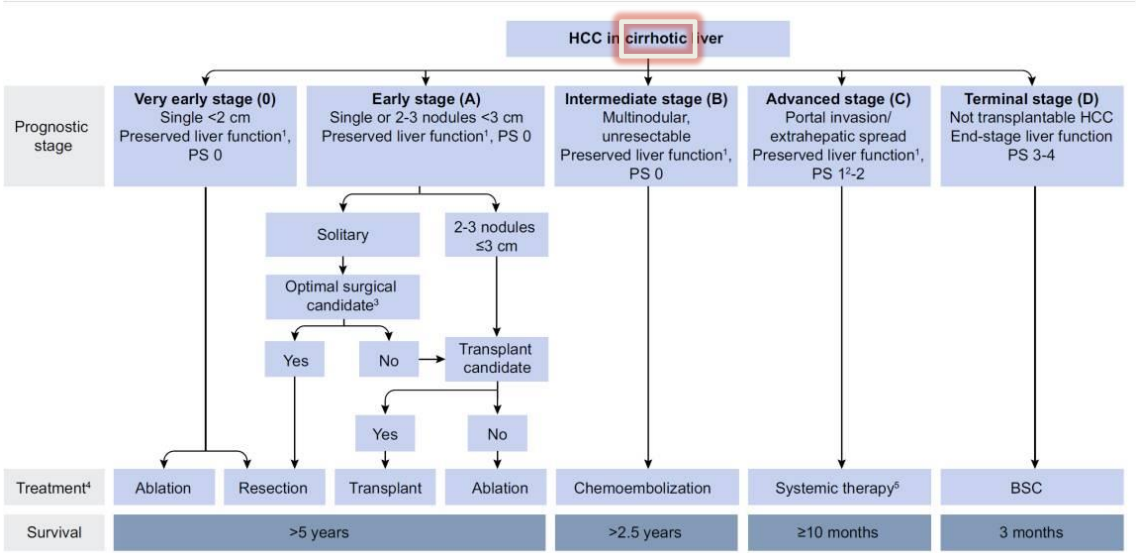
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; AASLD, American Association for the Study of Liver Diseases; DDLT, deceased donor liver transplantation; ECOG, Eastern Cooperative Oncology Group; LDLT, living donor liver transplantation; M1, distant metastasis; N1, lymph node metastasis; PS, performance status; OS, overall survival.

Llovet JM et al. *Hepatology*. 2020. [Epub ahead of print].

EASL Clinical Practice Guidelines – Management of HCC

Modified BCLC Staging System 2018

- Patients with cirrhosis form the primary at-risk cohort for HCC in the developed world
- Cirrhosis is the end-stage result of any chronic liver injury, whether this is due to viral hepatitis, alcohol abuse, non-alcoholic steatohepatitis or any other cause
- Patients with cirrhosis have an annual incidence rate of 2-4%
- Over 90% of HCC in the United States occur in the setting of cirrhosis



Abbreviations: ASCO, American Society of Clinical Oncology; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; EASL, European Association for the Study of the Liver; EMA, European Medicines Agency; FDA, Food and Drug Administration; MELD, model for end-stage liver disease; PS, performance status; OS, overall survival.

EASL Clinical Practice Guidelines: Management of Hepatocellular Carcinoma. *J Hepatol*. 2018;69(1):182-236.

Management of HCC

- Liver transplantation
- Resection
- Tumor ablation
  - Radiofrequency thermal ablation
  - Alcohol injection
  - Chemoembolization
- Targeted molecular therapy
- Chemotherapy
  - Regional/systemic

Potentially curative

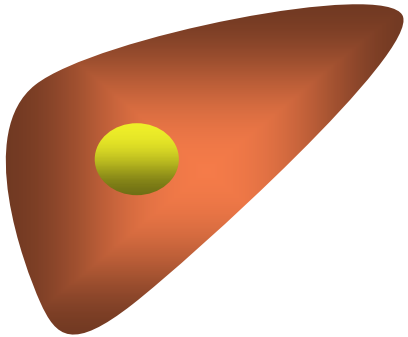
Curative Treatments for Early Stage HCC

- Liver transplantation
  - Milan criteria
  - 5 yr survival > 70%
  - Recurrence reportedly as high as 40% after transplantation (UNOS 7.5 %)

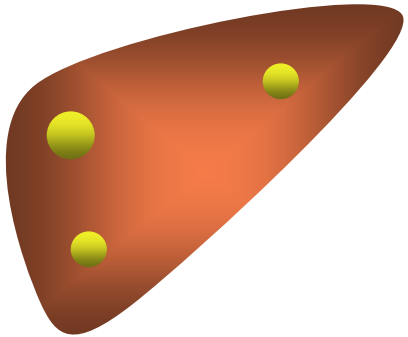
Mazzaferro V et al. *N Engl J Med.* 1996;334:693-699.

Liver Transplant for HCC in Cirrhosis
Milan Criteria

Single, not > 5cm



Up to 3, none > 3cm



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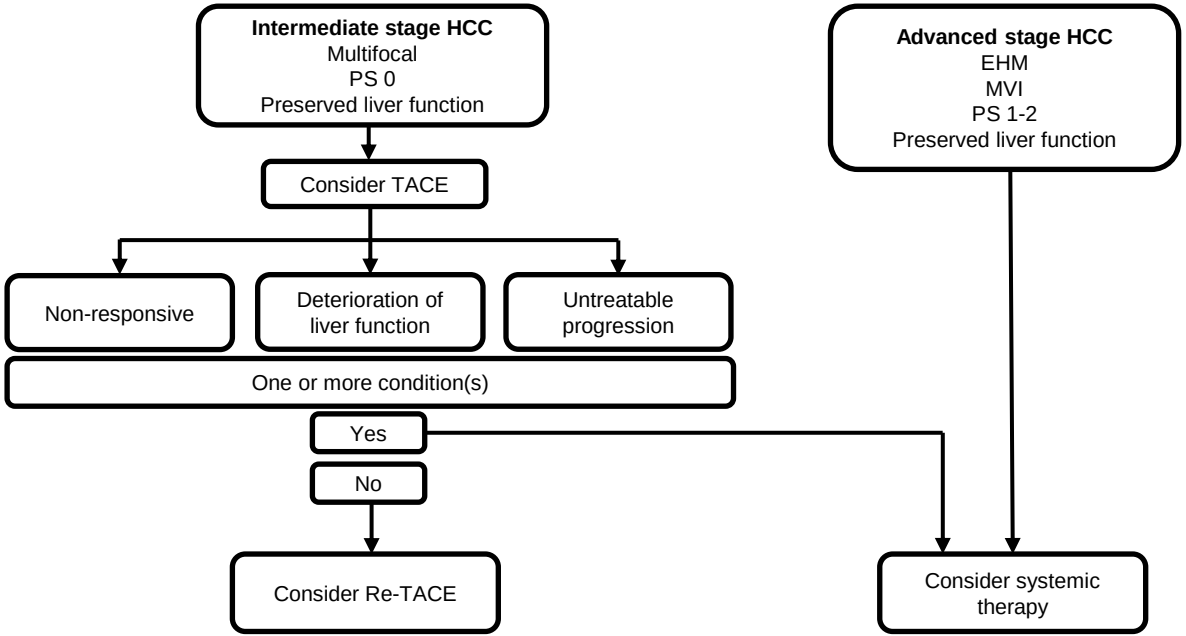
Absence of Macroscopic Vascular Invasion
Absence of Extrahepatic Spread

Mazzaferro V et al. *N Engl J Med.* 1996;334:693-699.

Systemic Treatment of HCC



EHM = extrahepatic metastases; MVI = macrovascular invasion.
Pinter & Peck-Radosavljevic. 2018.

Treatment for Advanced HCC – 2007-2017

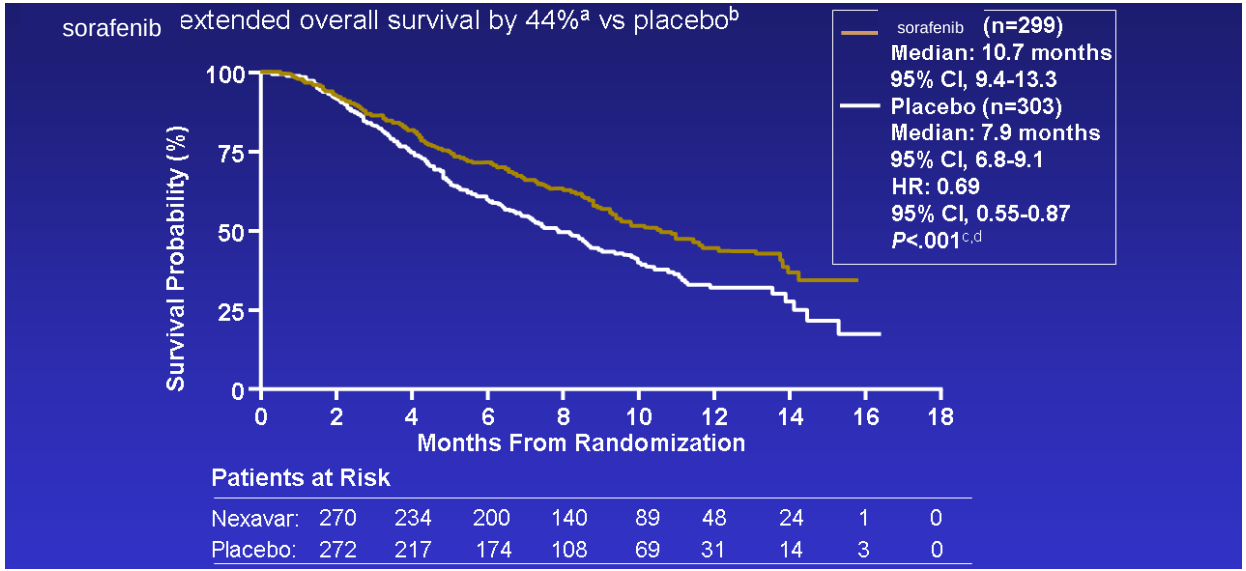
Line of Treatment	Targeted therapies	Targeted/ Immunotherapy combinations	Immunotherapies
First Line	Sorafenib		
Second Line			

Treatment for Advanced HCC – 2020

Line of Treatment	Targeted therapies	Targeted/ Immunotherapy combinations	Immunotherapies
First Line	Sorafenib Lenvatinib	Bevacizumab+ Atezolizumab	
Second Line	Regorafenib Cabozantinib Ramucirumab		Nivolumab Pembrolizumab *Nivolumab+ Ipilimumab

Phase 3 SHARP Trial

Overall Survival (Intention-to-Treat)



[a]Based on HR of 0.69, overall survival improvement calculated as follows: (1.0/0.69 – 1) x 100% = 44%.
[b]Intent-to-treat population. [c]Statistically significant because the P value was below the prespecified O'Brien-Fleming stopping boundary of α=0.0077. [d]Based on the 321 deaths as of the October 2006 cut-off date.
Llovet JM et al. N Engl J Med. 2008;359(4):378-390.

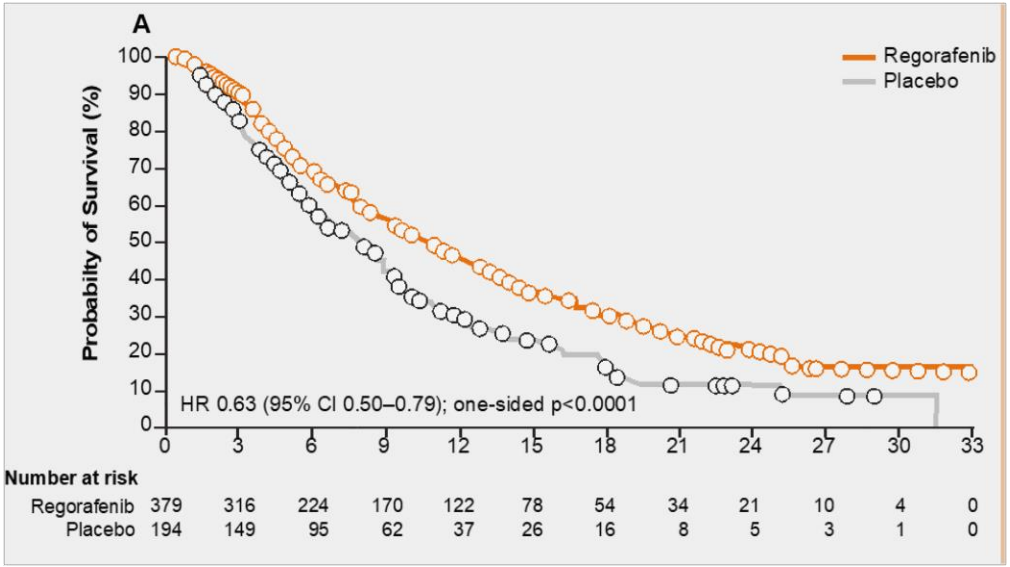
Regorafenib (RESORCE)

- 573 were enrolled and randomised
- (379 to regorafenib and 194 to placebo), and
- 567 initiated treatment (374 received regorafenib and 193 received placebo)
- Regorafenib improved overall survival with a hazard ratio of 0·63 (p<0·0001)
- median survival was 10·6 months (95%) for regorafenib versus 7·8 months

The Lancet. V 389. No 10064. p 56-66. Jan 2017.

Overall Survival (OS)

Primary Endpoint



	Regorafenib n=379	Placebo n=194
Events	232 (61%)	140 (72%)
Censored	147 (39%)	54 (28%)
Median OS (95% CI)	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
HR 0.62 (95% CI: 0.50, 0.78)		
P<0.001 (2-sided)		

Bruix et al. *Lancet*. 2017.

Lenvatinib vs Sorafenib Phase III

- Lenvatinib is an:
  - Oral multiple tyrosine kinase inhibitor
  - Mainly active against VEGFR1, VEGFR2, and VEGFR3
  - Also inhibits FGFR1, 2, 3, and 4, PDGFR, KIT, RET
- Study examined lenvatinib 8 mg or 12 mg daily (based on body weight) vs sorafenib
- 954 patients enrolled globally
- BCLC B or C, Child-Pugh A, ECOG PS ≤1
- No prior systemic therapy
- Primary endpoint OS with target of non-inferiority

Cheng et al. *ASCO*. 2017.

Lenvatinib vs Sorafenib Phase III

Outcomes	LEN	SOR	HR
Median OS, mos (95% CI)	13.6 (12.1−14.9)	12.3 (10.4−13.9)	0.92 (0.79−1.06)
Median PFS, mos (95% CI)*	7.4 (6.9−8.8)	3.7 (3.6−4.6)	0.66 (0.57−0.77)
Median TTP, mos (95% CI)*	8.9 (7.4−9.2)	3.7 (3.6−5.4)	0.63 (0.53−0.73)
ORR, n (%)*	115 (24)	44 (9)	

- Similar number of patients in each arm had AEs
- 13% LEN patients and 9% SOR patients discontinued due to AEs

*p<0.0001

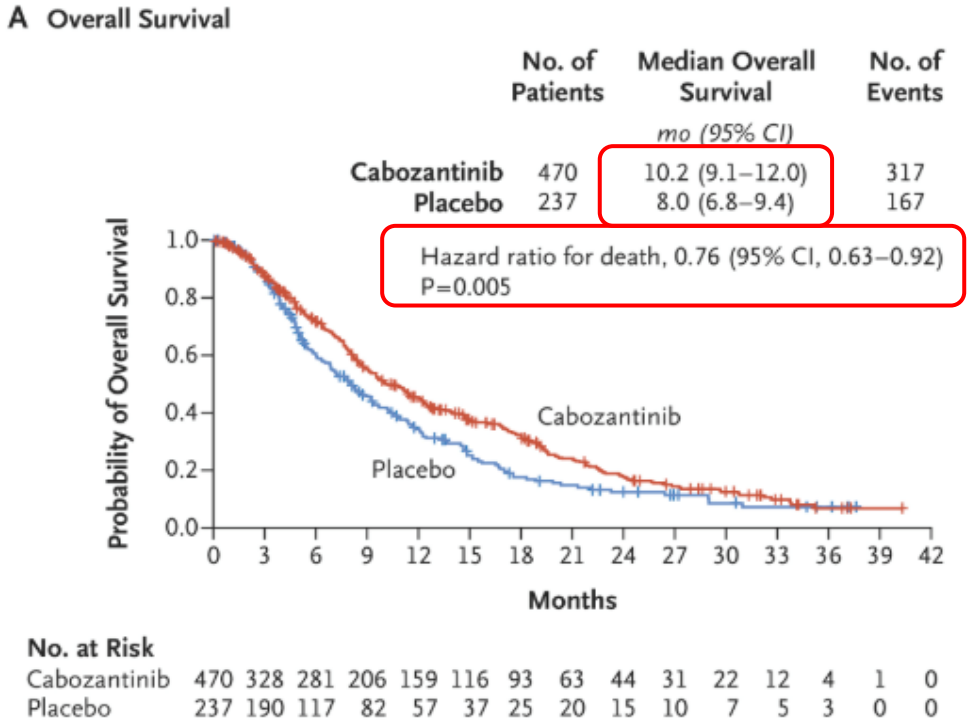
Cheng et al. *ASCO*. 2017.

Cabozantinib (C) Versus Placebo (P) in Patients (pts) With Advanced Hepatocellular Carcinoma (HCC) Who Have Received Prior Sorafenib: Results From The Randomized Phase III CELESTIAL Trial.

- Median OS 10.2 mo for C vs 8.0 mo for P
  - (p = 0.0049)
- Median PFS was 5.2 mo for C vs 1.9 mo for P
  - (p < 0.001)
- ORR was 4% vs 0.4% (p = 0.0086)

CELESTIAL: Cabozantinib (After Sorafenib Failure)

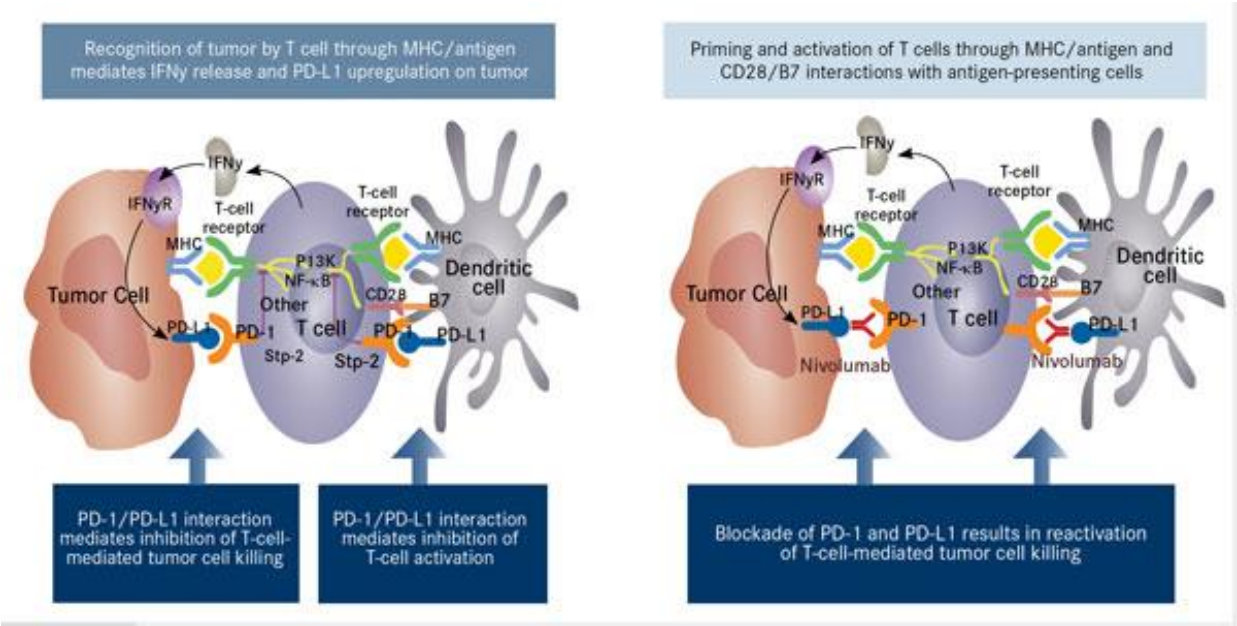
Results



Abou-Alfa et al. 2018.

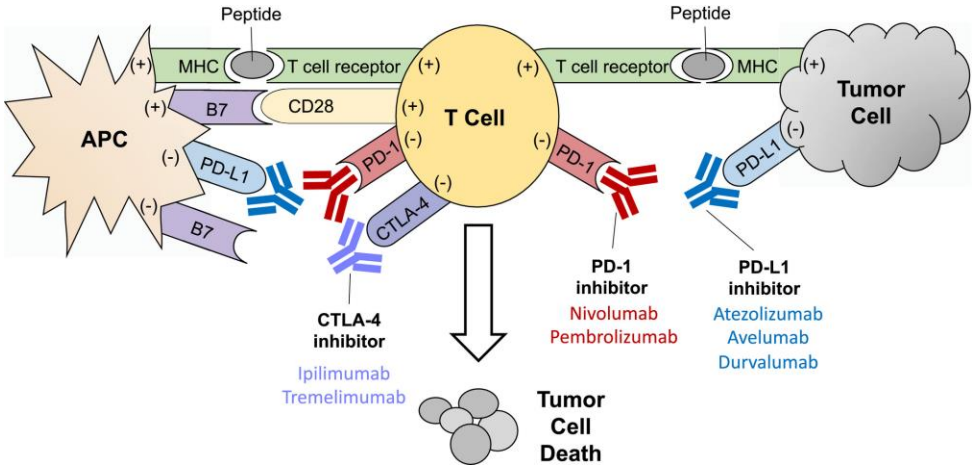
Immunotherapy

Immunotherapy in Malignancy: PD-1 Inhibition



PD-1, “Programmed Death-1”.

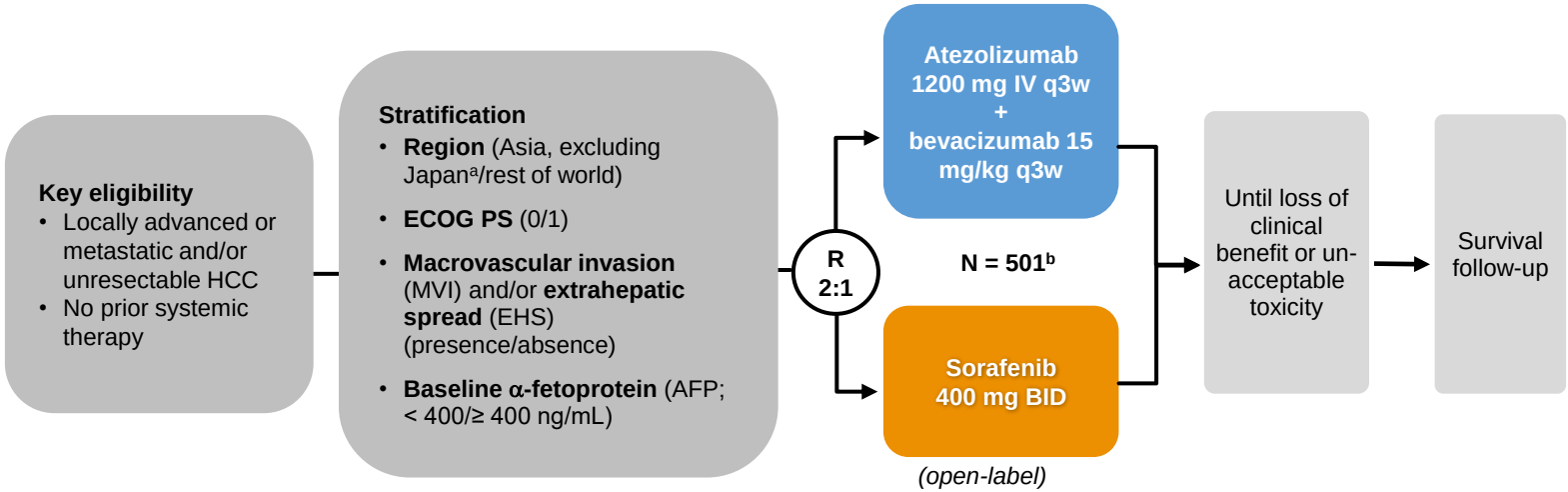
Nourkeyhani et al. *J Targeted Ther Cancer*. 2014.



T cell activation is mediated by the interaction of the T cell receptor with the MHC and the CD28 receptor with the B7 costimulatory molecule on the APC. Activating interactions are noted with a plus sign (+). T cell inhibition is mediated by the interaction of PD-L1 and PD-1, as well as CTLA-4 and B7. Inhibitory interactions are noted with a minus sign (−). Inhibitors of PD-1, PD-L1, and CTLA-4 prevent the inactivation of T cells, thus allowing the T cells to destroy the tumor cell more effectively

https://doi.org/10.1002/cld.879.

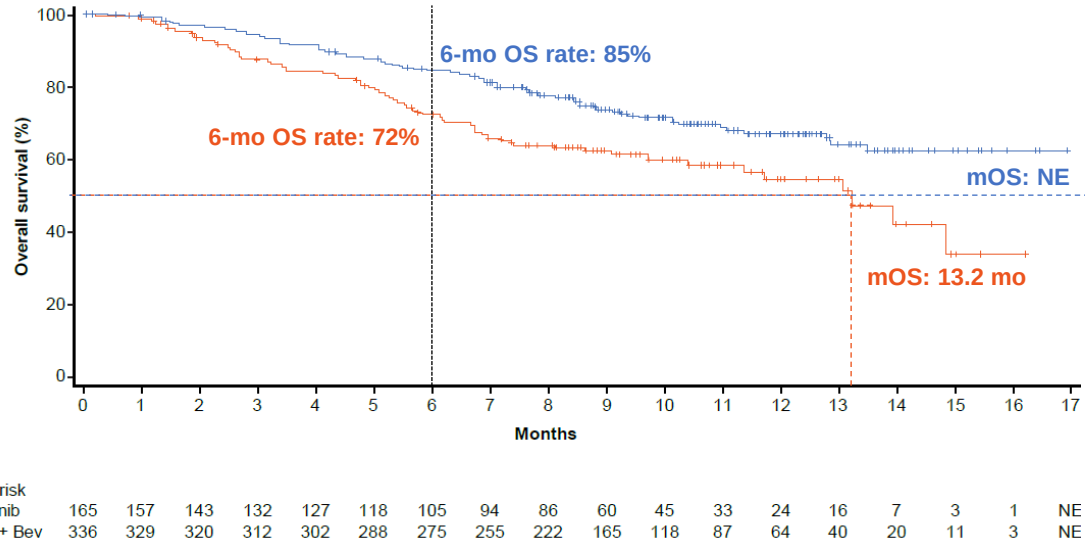
IMbrave150 Study Design



Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

A. Japan is included in rest of world.
B. An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

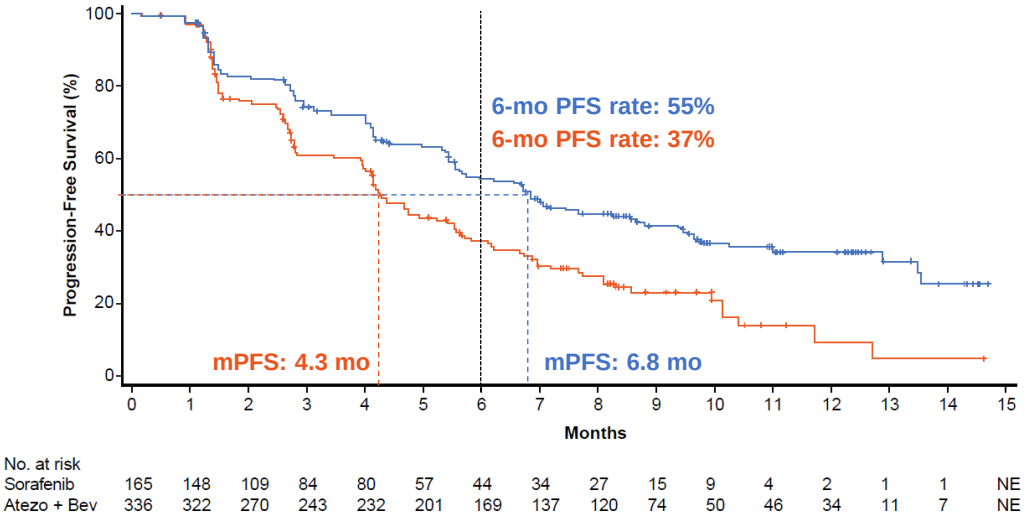
Overall Survival: Co-Primary Endpoint



Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b] *P* = 0.0006[b,c]	

NE, not estimable. 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 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Confirmed Progression Free Survival: Co-Primary Endpoint

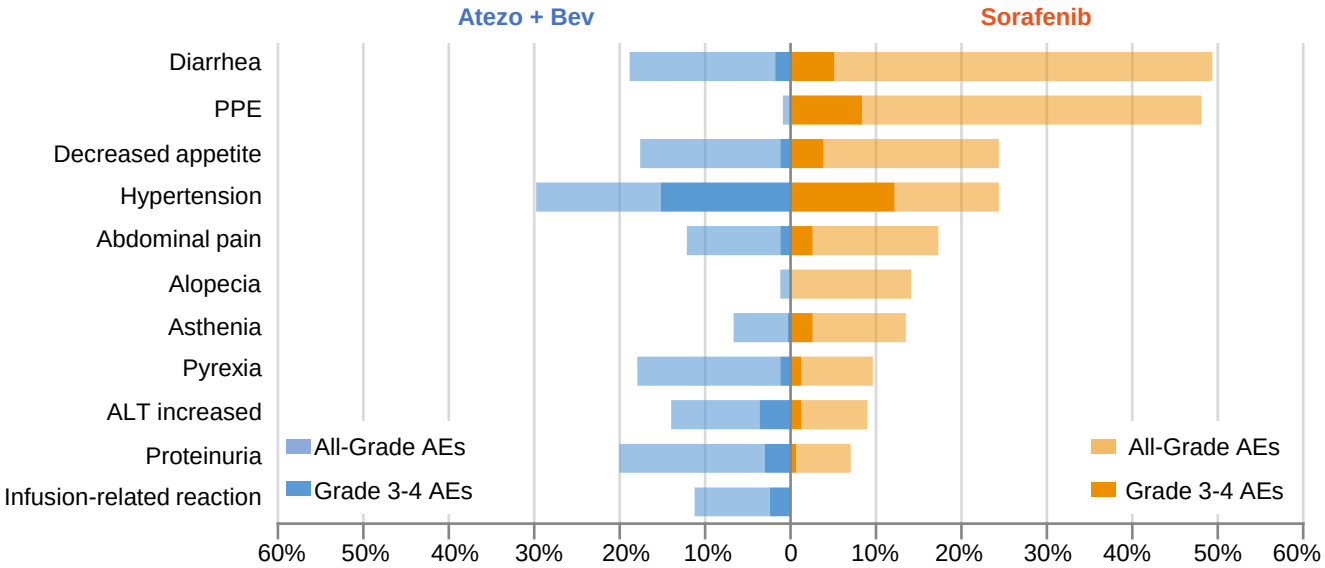


Median PFS (95% CI), mo[b]	
Atezo + Bev	6.8 (5.7, 8.3)
Sorafenib	4.3 (4.0, 5.6)
HR, 0.59 (95% CI: 0.47, 0.76)[c,d] *P* < 0.0001[d]	

[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 0.002. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Safety[a]

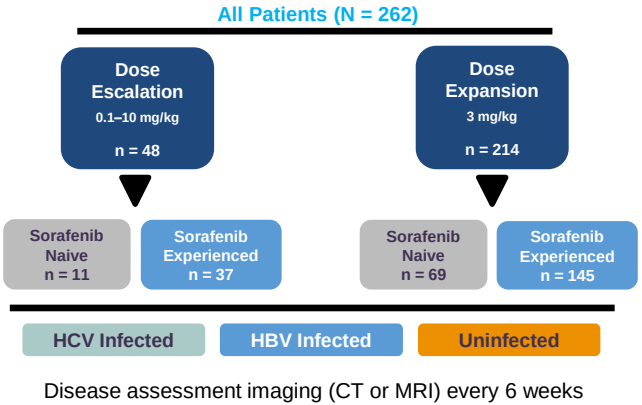
≥ 10% frequency of AEs in either arm and > 5% difference between arms



PPE, palmar-plantar erythrodysaesthesia.
[a] Safety-evaluable population.

Nivolumab in Patients With Advanced Hepatocellular Carcinoma (CheckMate 040): An Open-Label, Non-Comparative, Phase 1/2 Dose Escalation and Axpansion Trial

Nivolumab is FDA approved for patients with HCC who have previously failed sorafenib (accelerated approval)



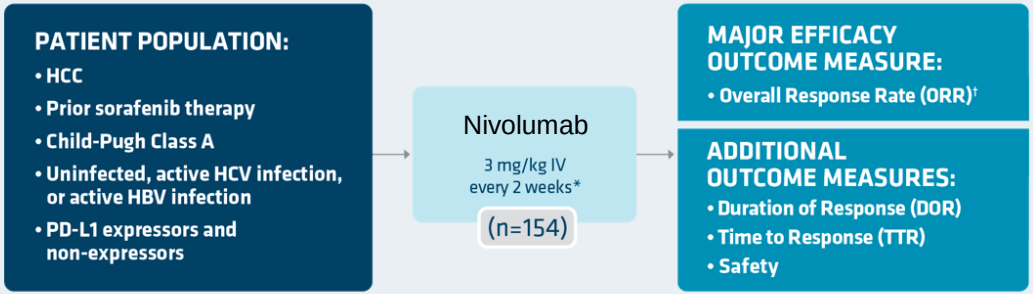
Disease assessment imaging (CT or MRI) every 6 weeks

- **Study Endpoints**
  - **Primary**
    - Safety and tolerability (escalation)
    - ORRa (expansion)
  - **Secondary**
    - ORRa (escalation)
    - Disease control rate
    - Time to response
    - Duration of response
    - Overall survival
  - **Other**
    - Biomarker assessments
    - Viral kinetics on treatment

ORR, objective response rate.
a RECIST v1.1.
Sangro et al. *EASL*. 2017.

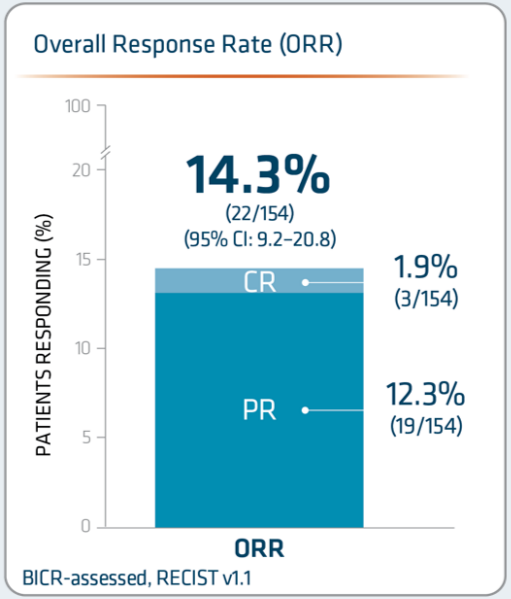
CheckMate 040 Study Design

CheckMate 040 Study: In patients previously treated with sorafenib



- Included a phase 1/2, multicenter, open-label study conducted in patients with HCC who progressed on or were intolerant to sorafenib
- The trial excluded patients with infection with HIV and active co-infection with HBV/HCV or HBV/HDV
- Patients were required to have an AST and ALT of no more than five times the ULN and total bilirubin of less than 3 mg/dL

Best Overall Response
Sorafenib-Experienced Patients – Dose-Expansion Phase



Median time to onset of response

2.8 months

(range: 1.2–7.0 months)

- Overall responses were observed in both PD-L1 non-expressors and expressors
- ORR based on mRECIST was 18.2% (28/154; 95% CI: 12.4-25.2). CR: 3.2% (5/154); PR: 14.9% (23/154)

Select Important Safety Information

Serious Adverse Reactions

- In Checkmate 040, serious adverse reactions occurred in 49% of patients (n=154). The most frequent serious adverse reactions reported in at least 2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, and pneumonia.

Nivolumab Summary and Conclusions

- In sorafenib-naïve and sorafenib-experienced patients with or without viral hepatitis, nivolumab demonstrated:
  - Improved survival and durable objective responses with extended follow up that were consistent across etiologies
- Safety profiles of nivolumab in patients with or without viral hepatitis were similar to what has been observed in other tumor types
  - Hepatic safety events, including AST/ALT elevations, were manageable and reversible
  - No new safety signals observed

Q&A/Panel Discussion