



JOHNS HOPKINS
M E D I C I N E

Screening and Management of HCC:

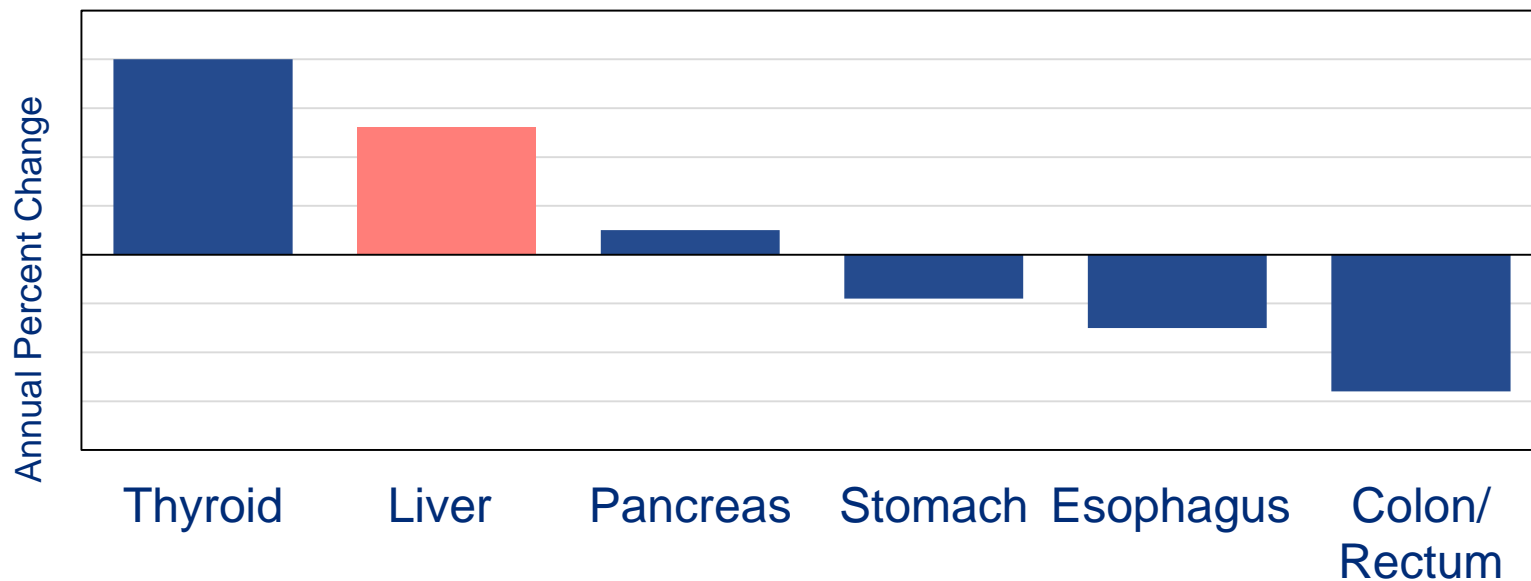
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June 7, 2018

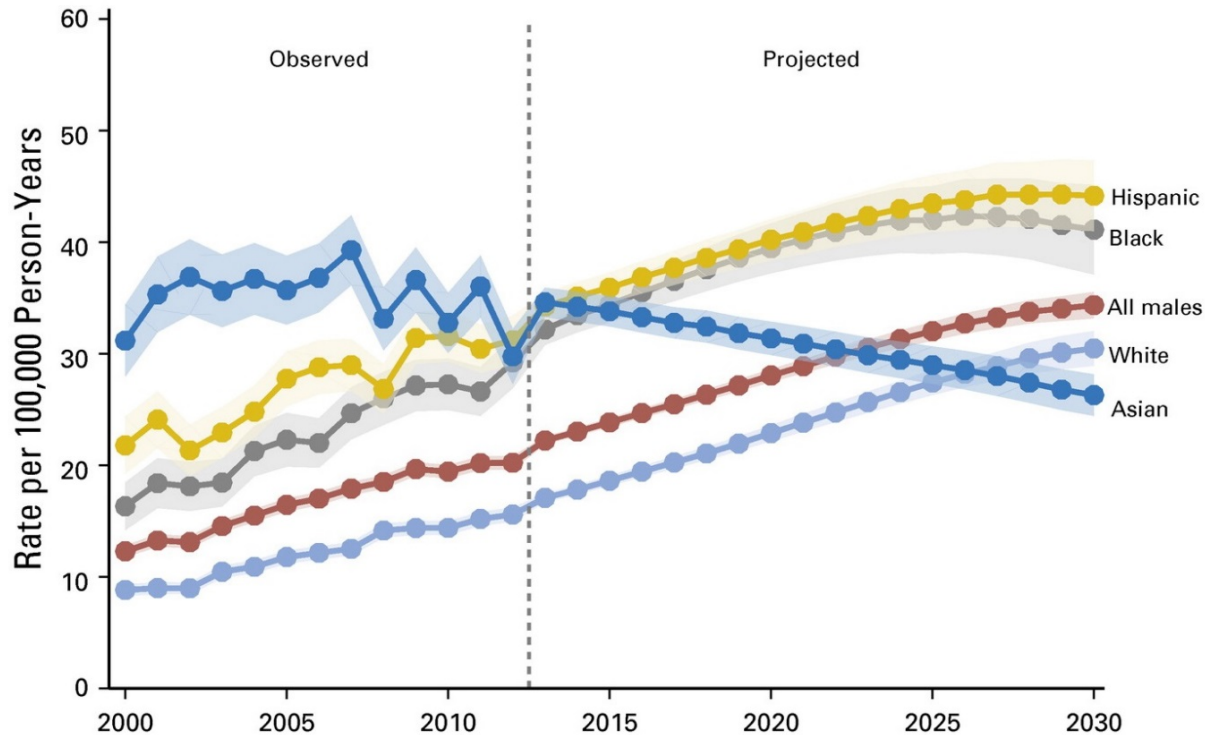
Outline

- Brief background of HCC treatment algorithm
- Role of screening for HCC
 - HBV, cirrhosis, treated HCV
- New *systemic* treatments for HCC
 - Clinical trials

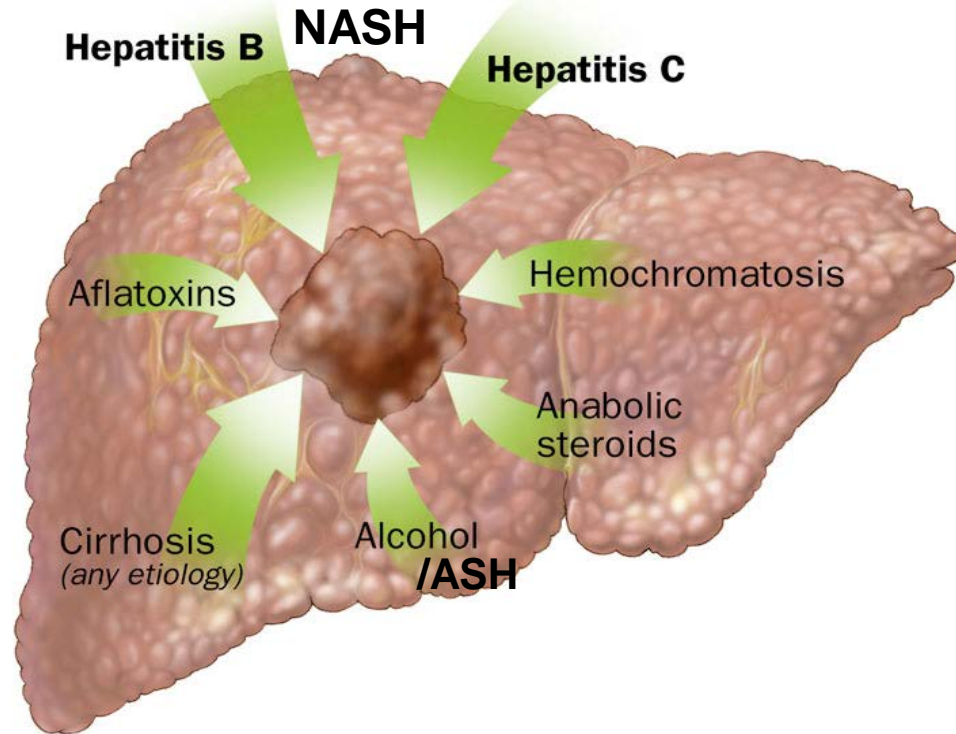
Rising Incidence of Liver Cancer 2005-2014



HCC incidence is rising in all US racial/ethnic groups except Asians

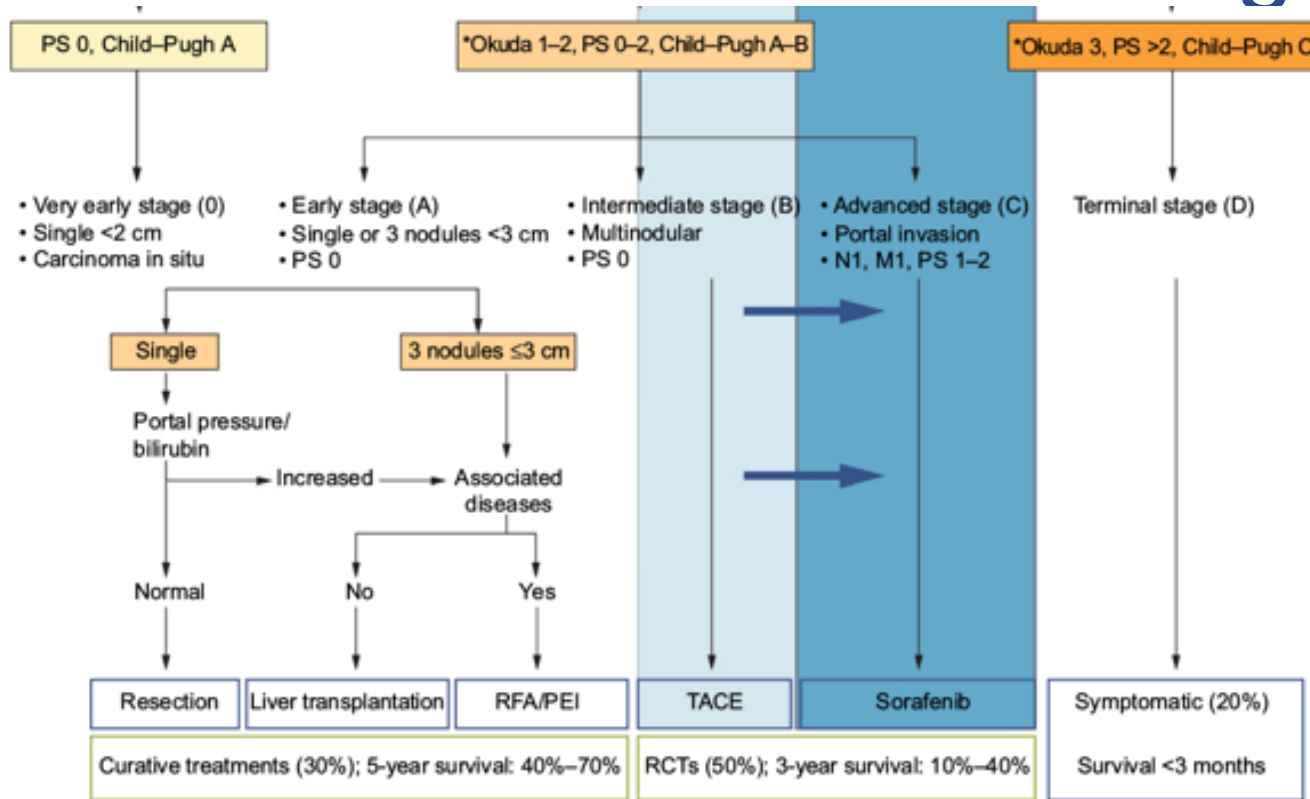


Etiology of HCC in the US

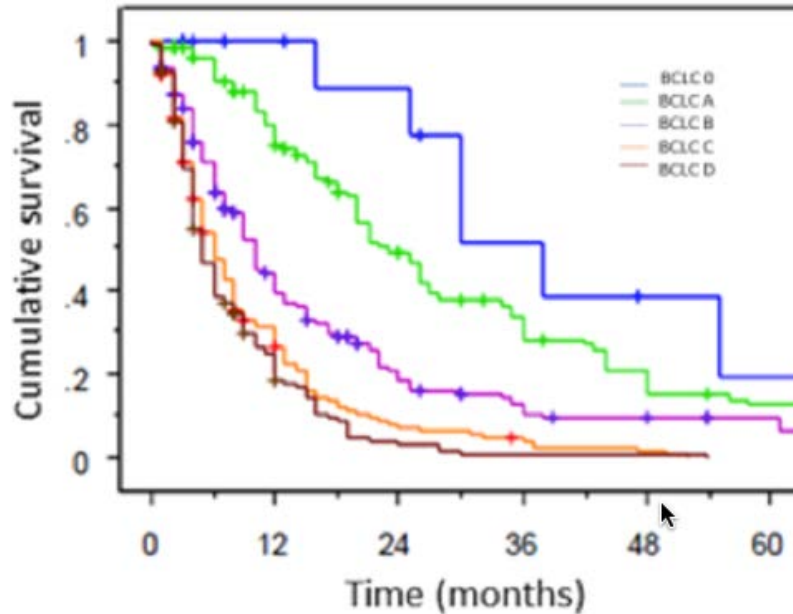


Cirrhosis

Barcelona Clinic Liver Cancer Staging



Survival by natural course of HCC

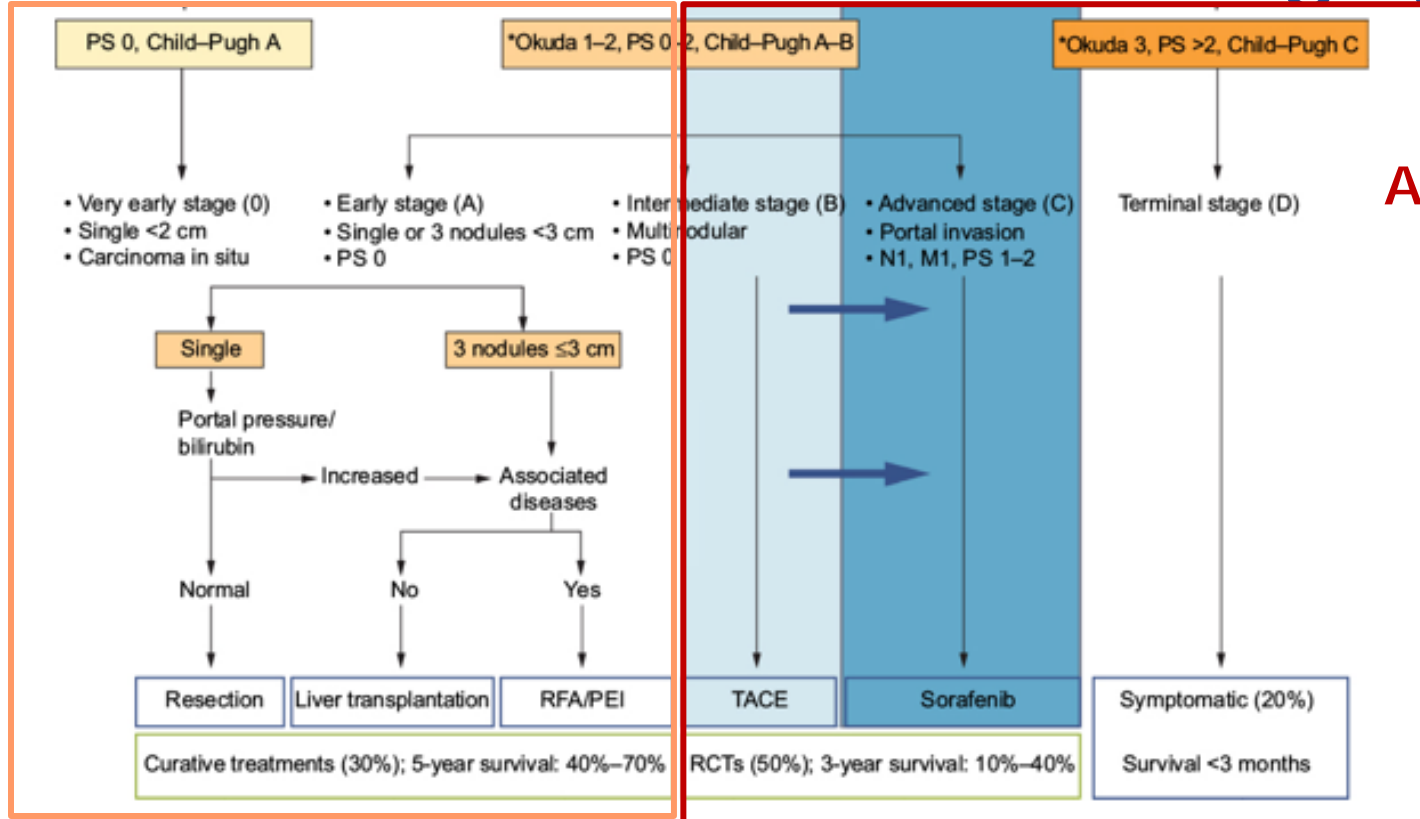


Two-disease process:

- Cancer
- Cirrhosis

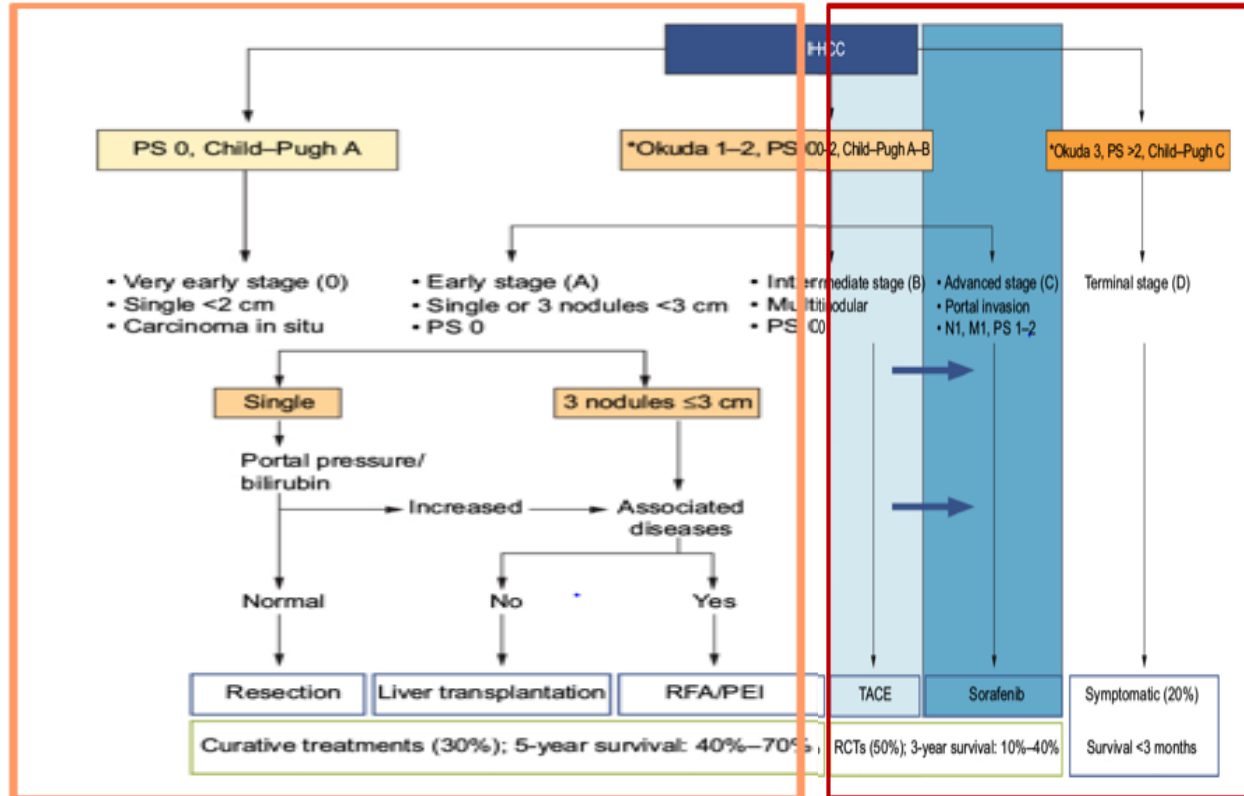
Barcelona Clinic Liver Cancer Staging

Early



Advanced
70%

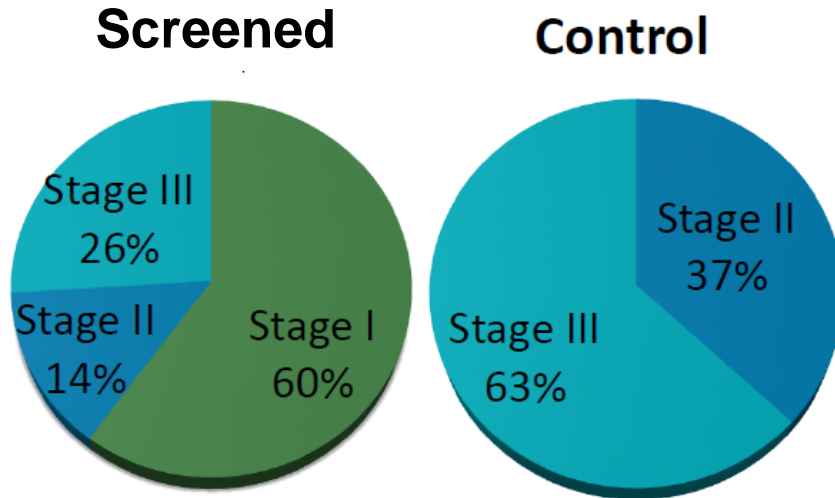
Barcelona Clinic Liver Cancer Staging



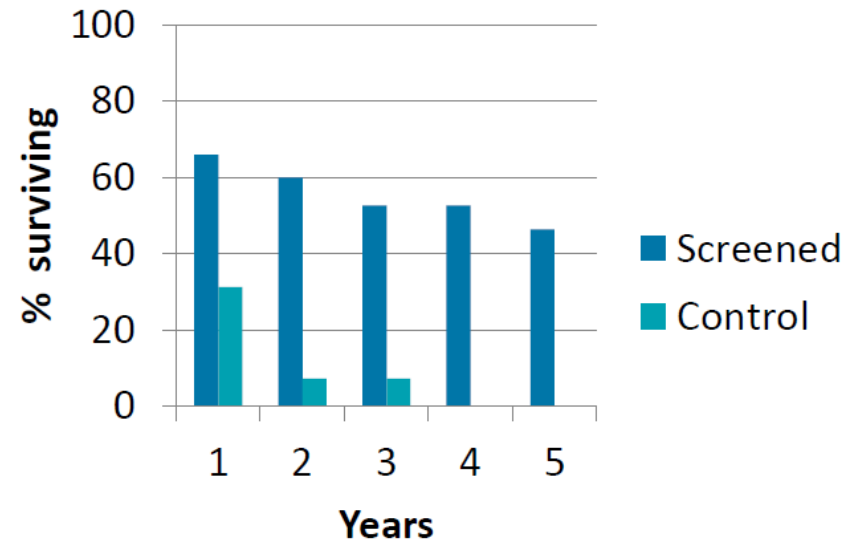
SCREENING & EARLY DIAGNOSIS

HCC screening improves survival

Stage at diagnosis in the screened and control groups



1-5 year survival of the screened and control groups

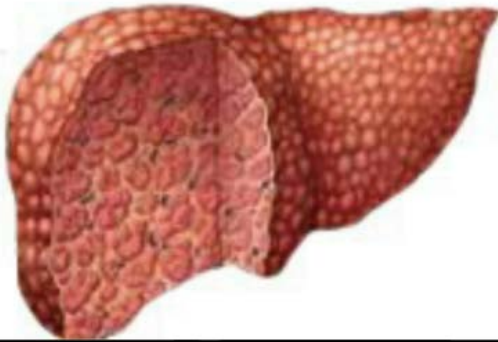


Screening improves detection

- Early detection achieved 70 vs. 30%
 - Early detection improved survival
 - At risk population and implementation
- Screening tests
 - Alpha feto-protein and Ultrasound

Target Population for Screening

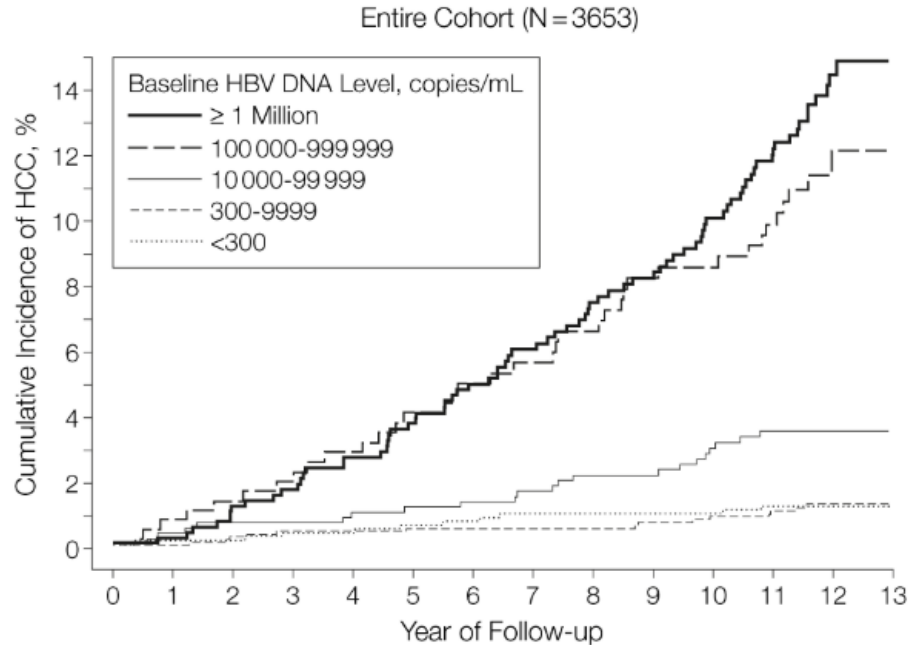
CIRRHOSIS



HBV

- Carriers with family history of HCC
- Asian men age >40, women >50
- African/ African-American male

HBV viral load and HCC



- Biological gradient of HCC risk by level of HBV DNA
 - Starting at 10k copies/mL
- *Without cirrhosis*

AFP screening in HCC

	Sensitivity	Specificity	PPV
<u>Case-control studies</u>			
Trevisani 2001	60%	91%	25%*
<u>Cohort Surveillance studies</u>			
Tanaka 1990	64%		
Pateron 1994	50%	86%	33%
Borzio 1995	47%		
Sherman 1995	64%	91%	9%
Solmi 1996	54%		
Zoli 1996	62%		
Mc Mahon 2000	97%	95%	31%
Bolondi 2001	41%	82%	46%
Tong 2001	59%	91%	11%

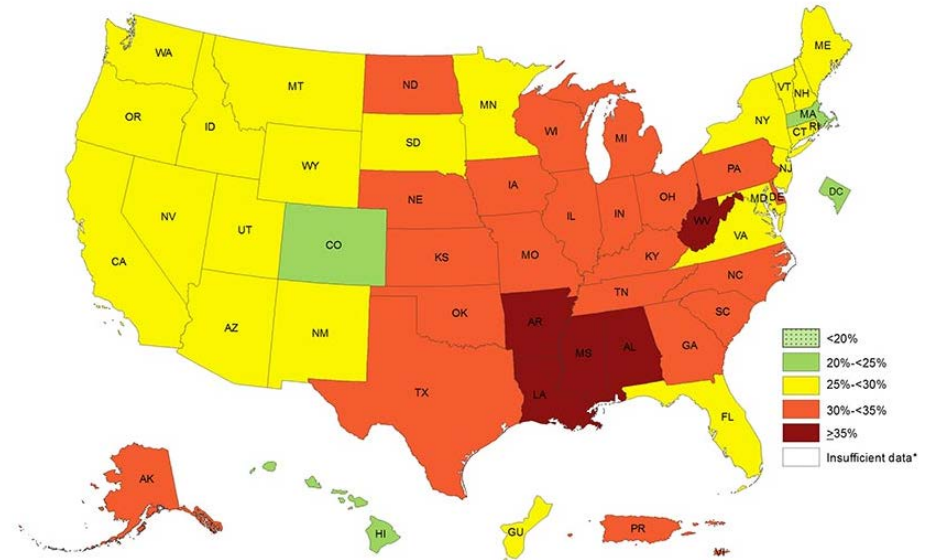
*5% prevalence

AFP and US combined improves sensitivity for HCC detection

Surveillance Test	Sensitivity	Specificity
Ultrasound	92.0 (89.2 – 94.8)	74.2 (71.8 – 76.7)
AFP >20	52.9 (47.8 – 58.0)	93.3 (91.9 – 94.7)
Ultrasound and AFP >20	99.2 (98.2 – 100)	68.3 (65.7 – 70.9)
Ultrasound and AFP >20 and >2* from nadir	99.2 (98.2 – 100)	71.6 (69.0 – 74.0)

Limitations with Ultrasound

- Operator dependent
- Patient dependent
 - Western population
 - Obesity
 - Nodular liver



CDC report 2016

HCC screening recommendation

Society	Guidelines
AASLD	US every 6 months
EASL	US every 6 months
APASL	AFP+US every 6 months
NCCN	AFP+US every 6-12 months
VA	AFP+US every 6-12 months

1. Bruix J, Sherman M. [http://www.aasld.org/practiceguidelines/Documents/Bookmarked Practice Guidelines/HCCUpdate2010.pdf](http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf). Accessed January 31 2012.

2. Bruix J et al. J Hepatology 2001;35:421-430 3. Omata M et al. Hepatol Int 2010;4:439-474.

4. Adapted from NCCN Practice Guidelines: http://www.nccn.org/professionals/physician_gis/hepatobiliary.pdf. (Jan 31,2012)

5. <http://www.hepatitis.va.gov/pdf/2009HCC-guidelines.pdf>. Accessed Jan 31,2012

Biomarkers being evaluated in Phase II/III

- AFP-L3
- Osteopontin
- Des-gamma carboxy prothombin
- Circulating miRNA
- Circulating tumor cells
- Circulating tumor DNA (CancerSeek, TEC-seq)



NEW SYSTEMIC TREATMENT

HCC Treatment in 2016

Line of Treatment	TKIs/Anti-VEGF	Immunotherapies
First Line	Sorafenib (2008)	
Second Line		

HCC Treatment in 2018

Line of Treatment	TKIs/Anti-VEGF	Immunotherapies
First Line	Sorafenib (2008) Lenvatinib (2017)	
Second Line	Regorafenib (2017) Cabozantinib (2018) Ramucirumab (2018, High AFP only)	Nivolumab (2017)

THE LANCET

Volume 389, Issue 10088, 24–30 June 2017, Pages 2492–2502

THE LANCET

THE LANCET
The Lancet is a peer-reviewed medical journal published weekly by the British Medical Association. It is one of the four major medical journals in the world, alongside the New England Journal of Medicine, the New York Times, and the British Medical Journal.

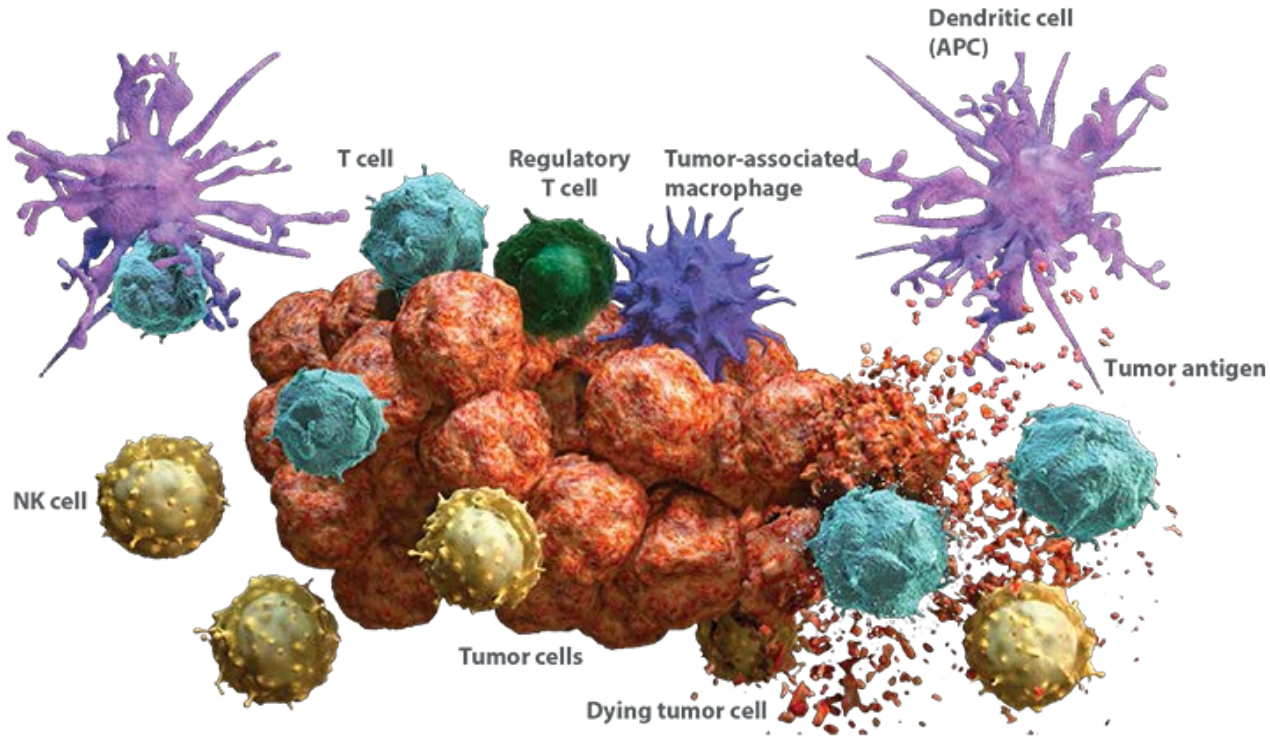
THE LANCET
The Lancet is a peer-reviewed medical journal published weekly by the British Medical Association. It is one of the four major medical journals in the world, alongside the New England Journal of Medicine, the New York Times, and the British Medical Journal.

Articles

Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

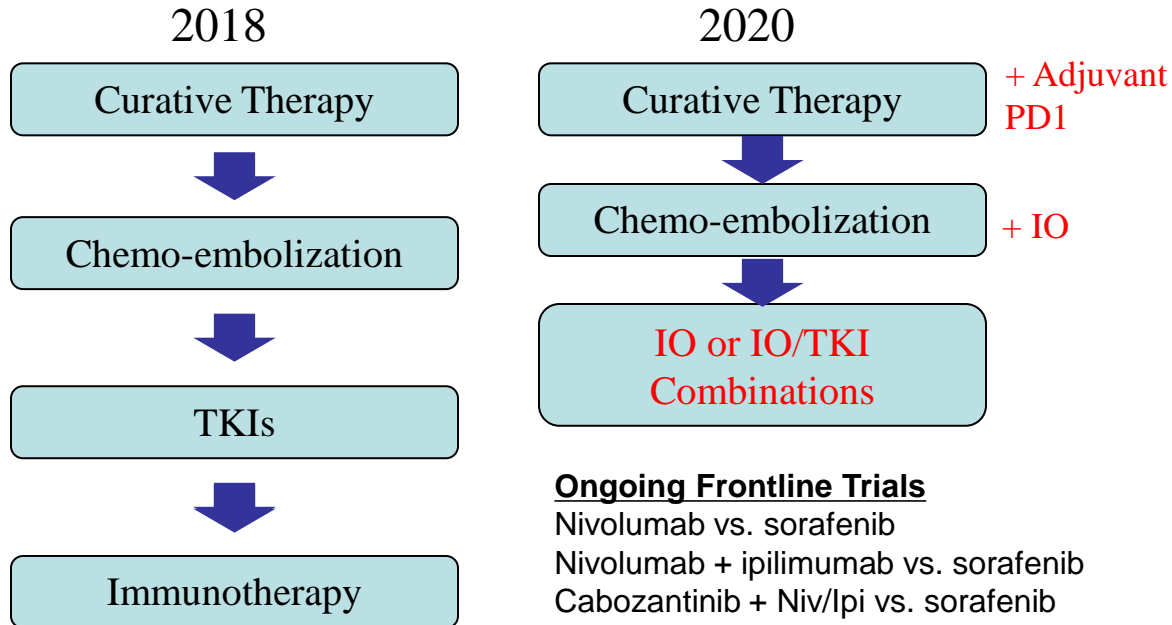
Dr Anthony B El-Khoueiry MD ^{a, *}, Bruno Sangro MD ^{b, †}, Thomas Yau MD ^{c, †}, Todd S Crocenzi MD ^d, Masatoshi Kudo MD ^e, Chiun Hsu MD ^f, Tae-You Kim MD ^g, Su-Pin Choo BMBS ^h, Jörg Trojan MD ⁱ, Thomas Brodeur MD ^j, G. Umberto S. MD ^k, T. M. MD ^l, M. MD ^m, M. MD ⁿ, M. MD ^o, M. MD ^p, M. MD ^q

Adaptive immune response



Dranoff G. *Nat Rev Cancer*. 2004;4:11-22. 2. Fernandez NC et al. *Nature Med*. 1999;5(4):405-411. 3. Ramarathinam L et al. *J Exp Med*. 1994;179(4):1205-1214.

HCC Treatment (2018 vs. 2020)



Ongoing Frontline Trials

Nivolumab vs. sorafenib

Nivolumab + ipilimumab vs. sorafenib

Cabozantinib + Niv/Ipi vs. sorafenib

Lenvatinib + pembrolizumab vs. sorafenib

Durvalumab vs. sorafenib

Durvalumab/tremelimumab vs. sorafenib

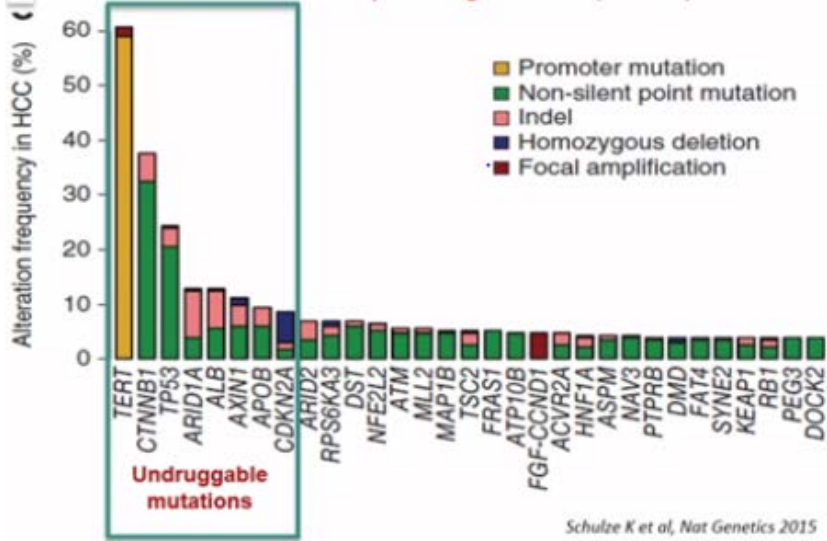
6/7/2018

Clinical Trials at JHH

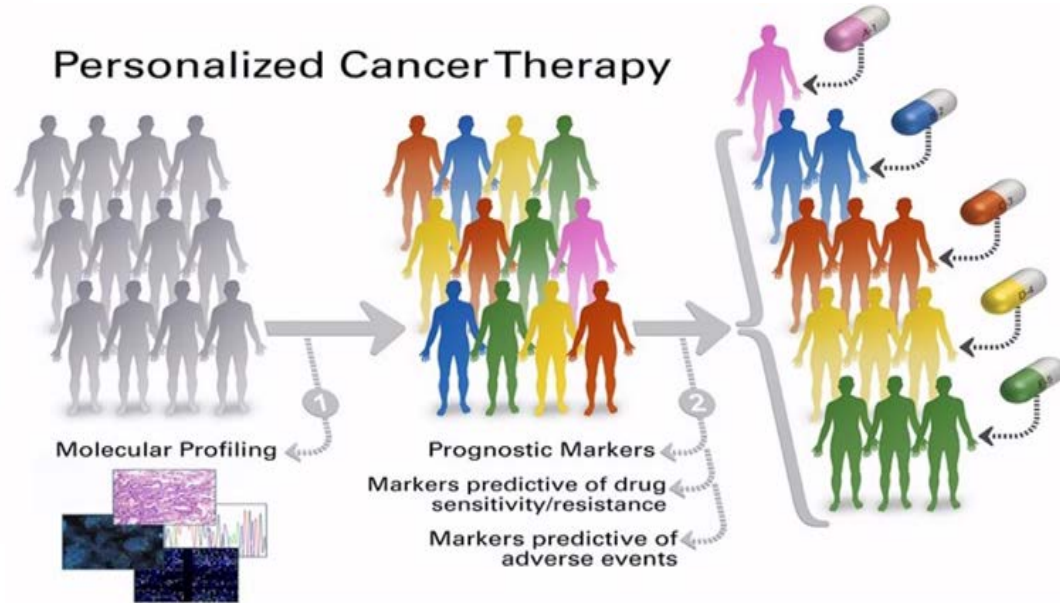
1. Nivolumab with Cabozantinib as neoadjuvant therapy for surgical resection (BMS)
2. Combination of tremelimumab/durvalumab with intra-arterial treatment in intermediate stage HCC (AZ)

Future of HCC

Genome sequencing in HCC (n=250)



Personalized Cancer Therapy



Summary

- Demographics of HCC is changing
- Early detection improves survival in patients with HCC
- Improved screening methods are in development
- Several new systemic treatments are approved and more combinatorial treatments in plan
- Personalized approach to HCC treatment is needed

Thank you!

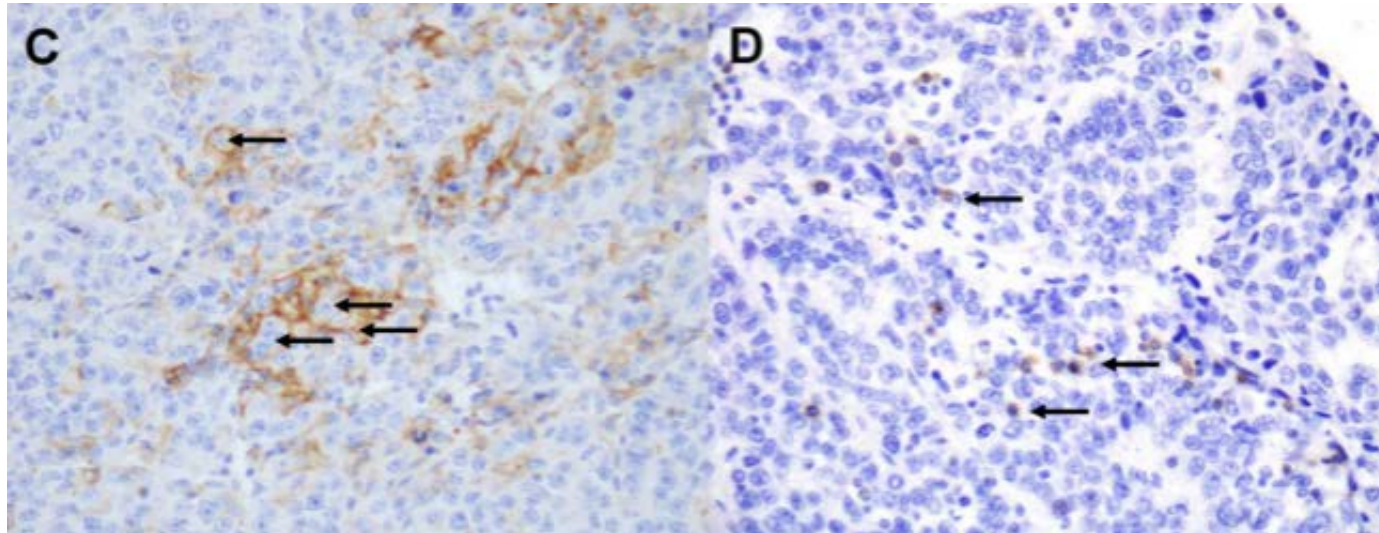


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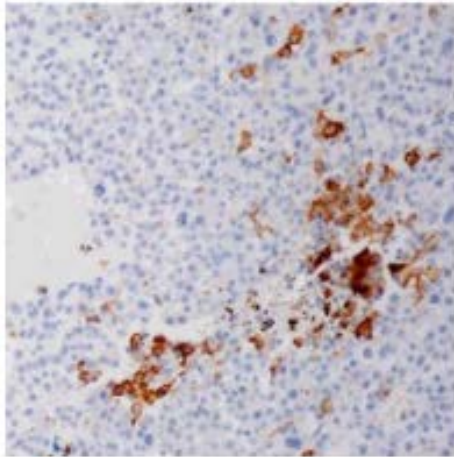
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- Associated with:
 - **Early detection** (OR 2.11)
 - 70.9% vs. 29.9%
 - **Receipt of curative treatment** (OR 2.24)
 - 51.6% vs 23.7%

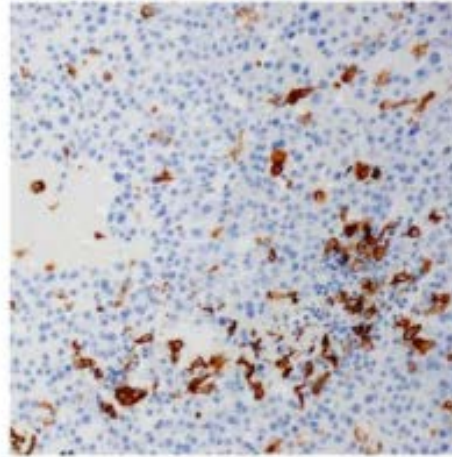
PD-L1 in HCC tumor



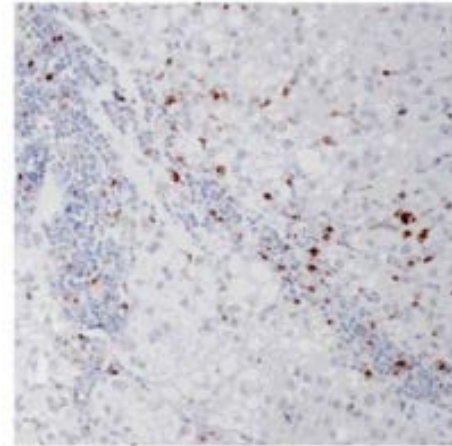
PD-L1 and LAG3 in HCC



PD-L1 in tumor (83%)

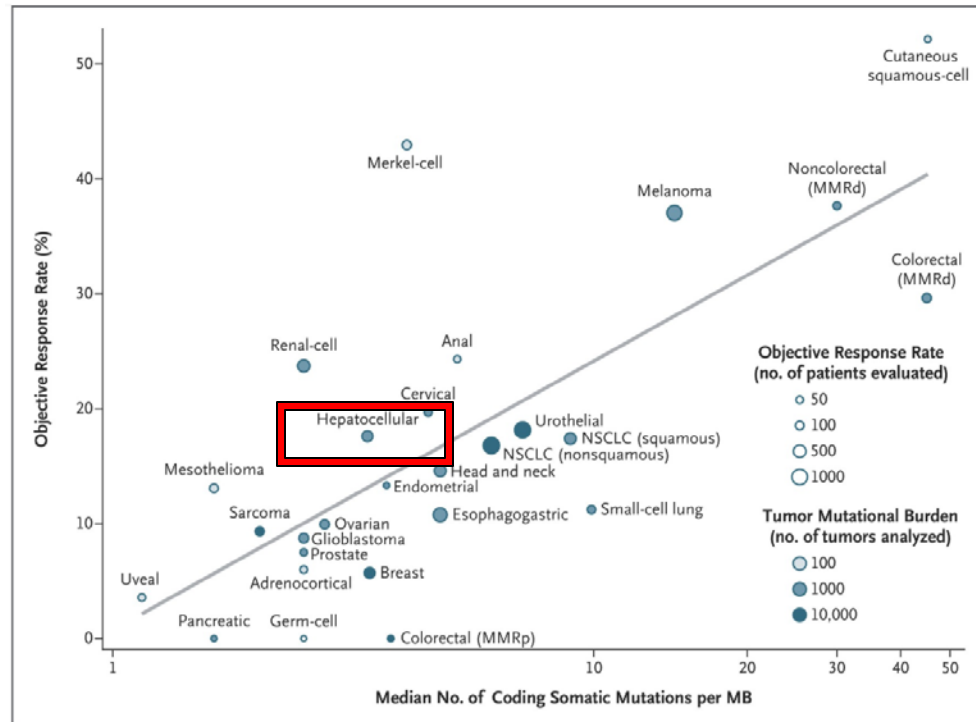


CD163+ tumor-associated
macrophages



LAG+ tumor-infiltrating
Lymphocytes (14%)

Tumor mutational Burden and response to immunotherapy



Systemic therapies in 2018

- Sorafenib – 1st line since 2007
- Regorafenib – FDA-approved 2017
 - Median OS 10.6 mo vs 7.8 months for placebo
- Lenvatanib – phase III trial (FDA pending)
 - Non-inferior to Sorafenib, OS 13.6 vs 12.3 mo
- Nivolumab – PD-1 inhibitor. 20% objective response (FDA approved 2017)