

Best of EASL - Addis Ababa, Ethiopia 29 Sep to 01 Oct, 2016

Inaugural meeting of the Sub Saharan GI-Hepatology Working Group Incorporating Best of AGA and Best of EASL

NEW TRENDS IN THE SCREENING, DIAGNOSIS AND TREATMENT OF HEPATOCELLULAR CARCINOMA

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www.ucl.ac.uk/medicine/liver-and-digestive-health

Hepatocellular Carcinoma: HCC

- Worldwide
 - HCC is the 5th most common cancer
 - 700,000 new cases and 600,000 deaths in 2012.¹
 - 2nd leading cancer related cause of death worldwide.²
- United States
 - ~30,640 new cases and 21,620 deaths in 2013.
 - HCC five-year survival rate is 15%.⁴
 - Early HCC recurrence: important cause of post-transplant mortality

1. <http://www.cancer.org/cancer/livercancer/detailedguide/liver-cancer-what-is-key-statistics>; revised 09/25/2013

2. http://www.iarc.fr/en/media-centre/pr/2014/pdfs/pr224_E.pdf.

3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11-30.

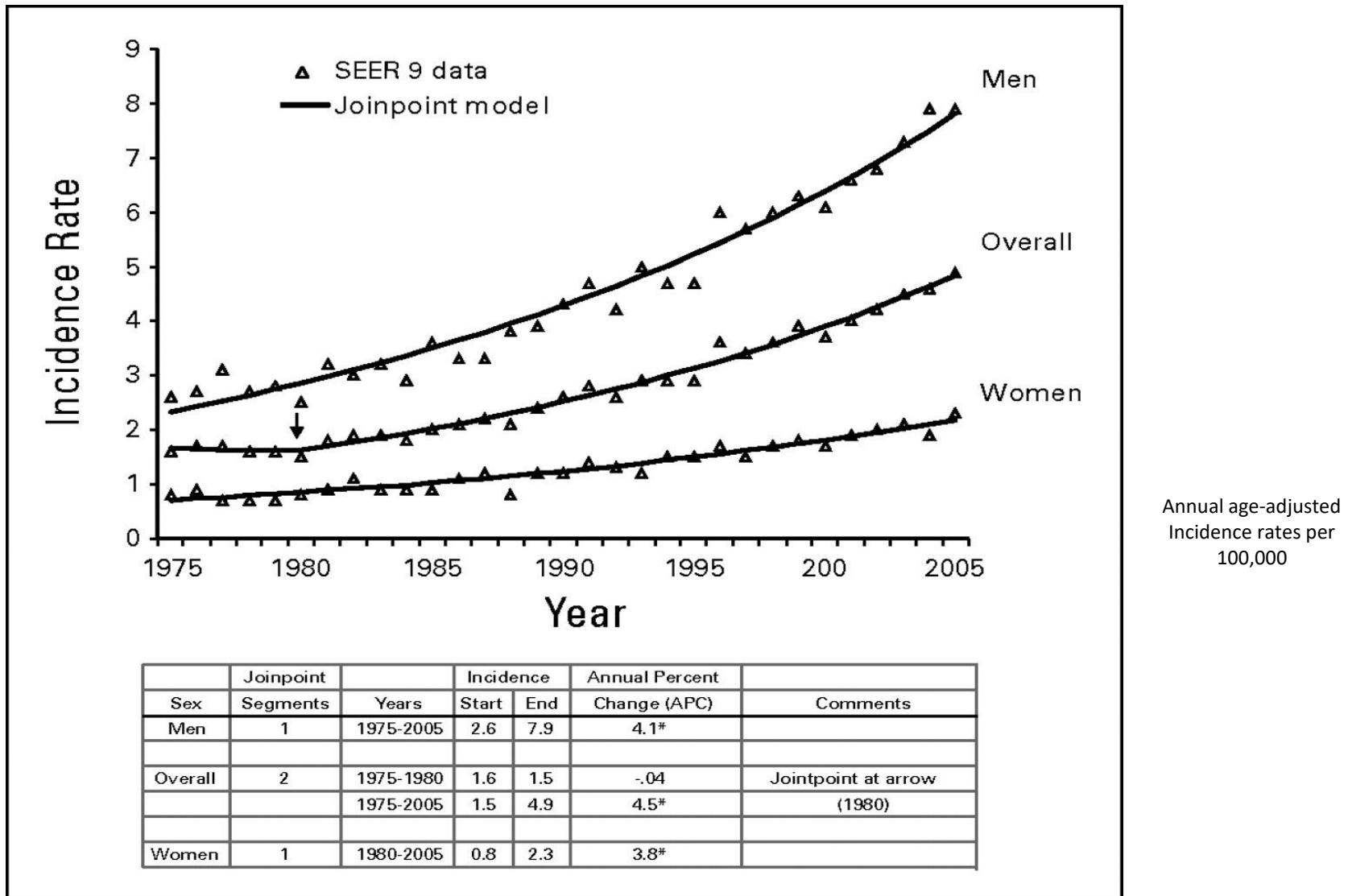
4. American Cancer Society. Survival rates for liver cancer. 2013. Available at:
<http://www.cancer.org/cancer/livercancer/detailedguide/liver-cancer-survival-rates>, revised 01/22/2014



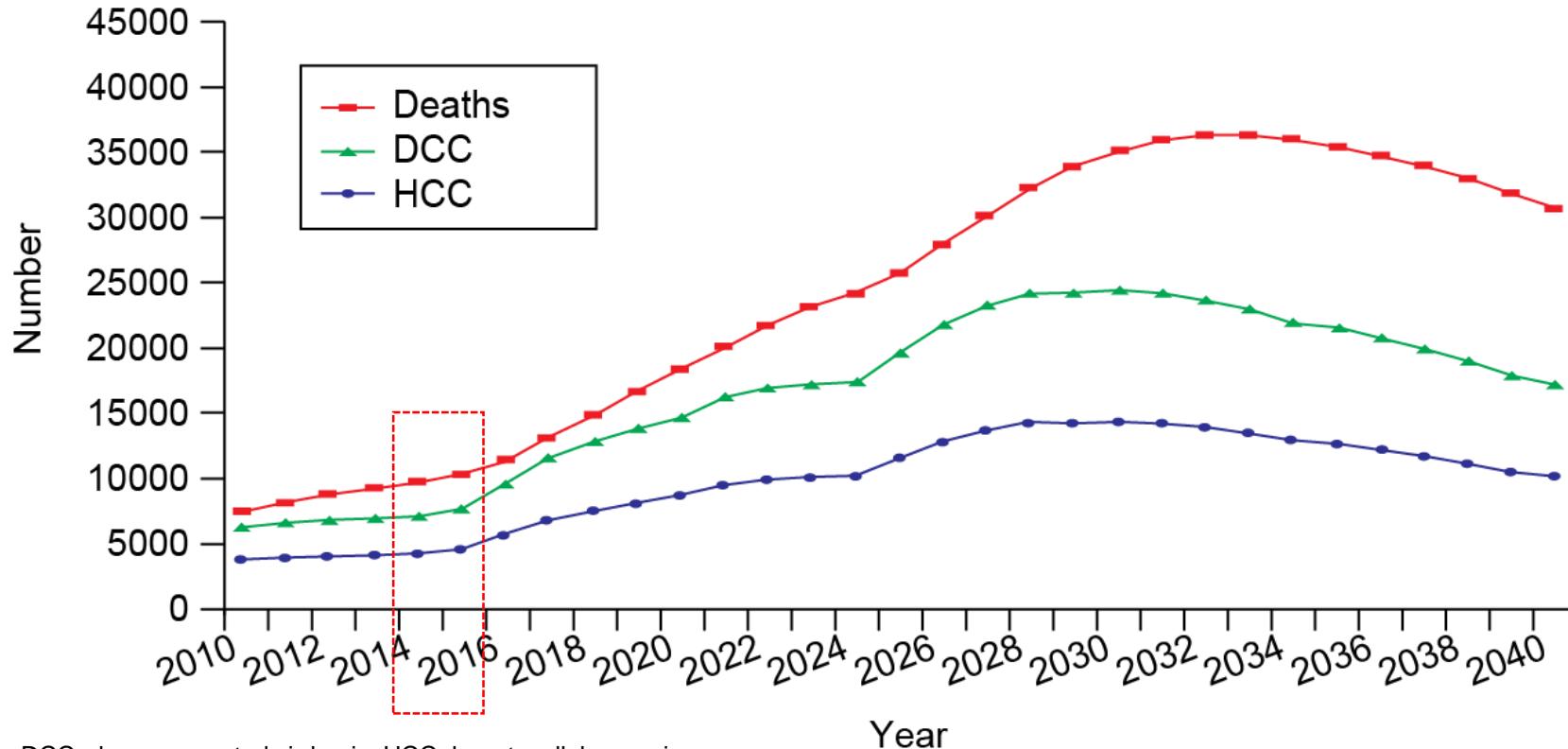
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HCC Incidence Rate Tripled Over 30 Years in USA

SEER: NCI's Surveillance, Epidemiology and End Results Program
Provides Cancer Statistics on the US population



Projected Incidence of HCV Related Liver Cancer and Death



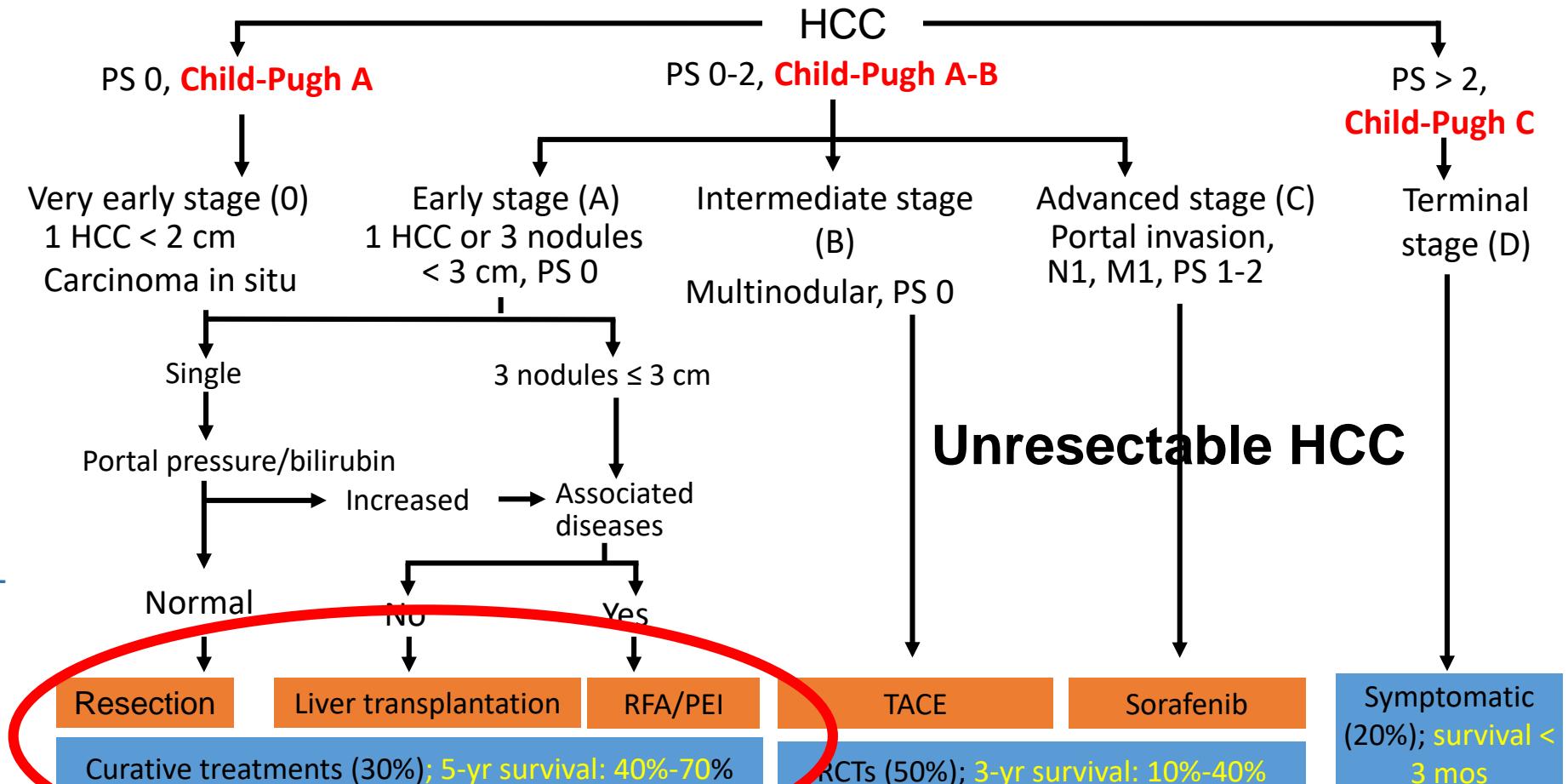
DCC=decompensated cirrhosis; HCC=hepatocellular carcinoma

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Liver Cancer 3rd Most Lethal Cancer By 2030

1. Rein DB, et al. *Dig Liver Dis.* 2011;43(1):66-72.
2. Biggins SW, et al. *Liver Transpl.* 2012;18(12):1471-1478.
2. The American Association for Cancer Research has published a [report in its journal Cancer Research, published online on May 19, 2014](#) *Cancer Res.* 1–9. 2014 AACR.

BCLC Staging and Treatment Strategy



“Is it Time for Molecular Profiling in Liver Cancers: personalized decision Making?”

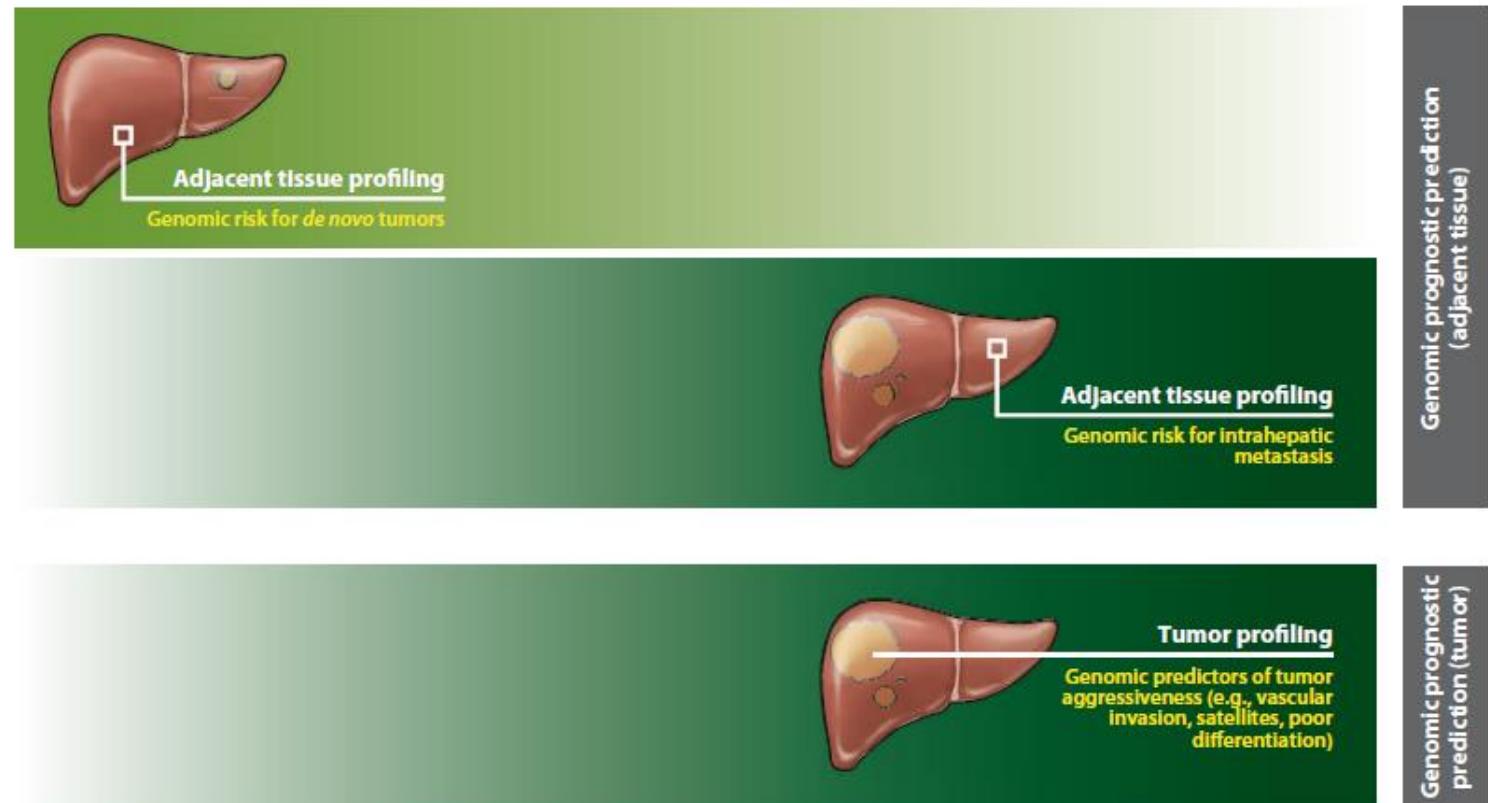


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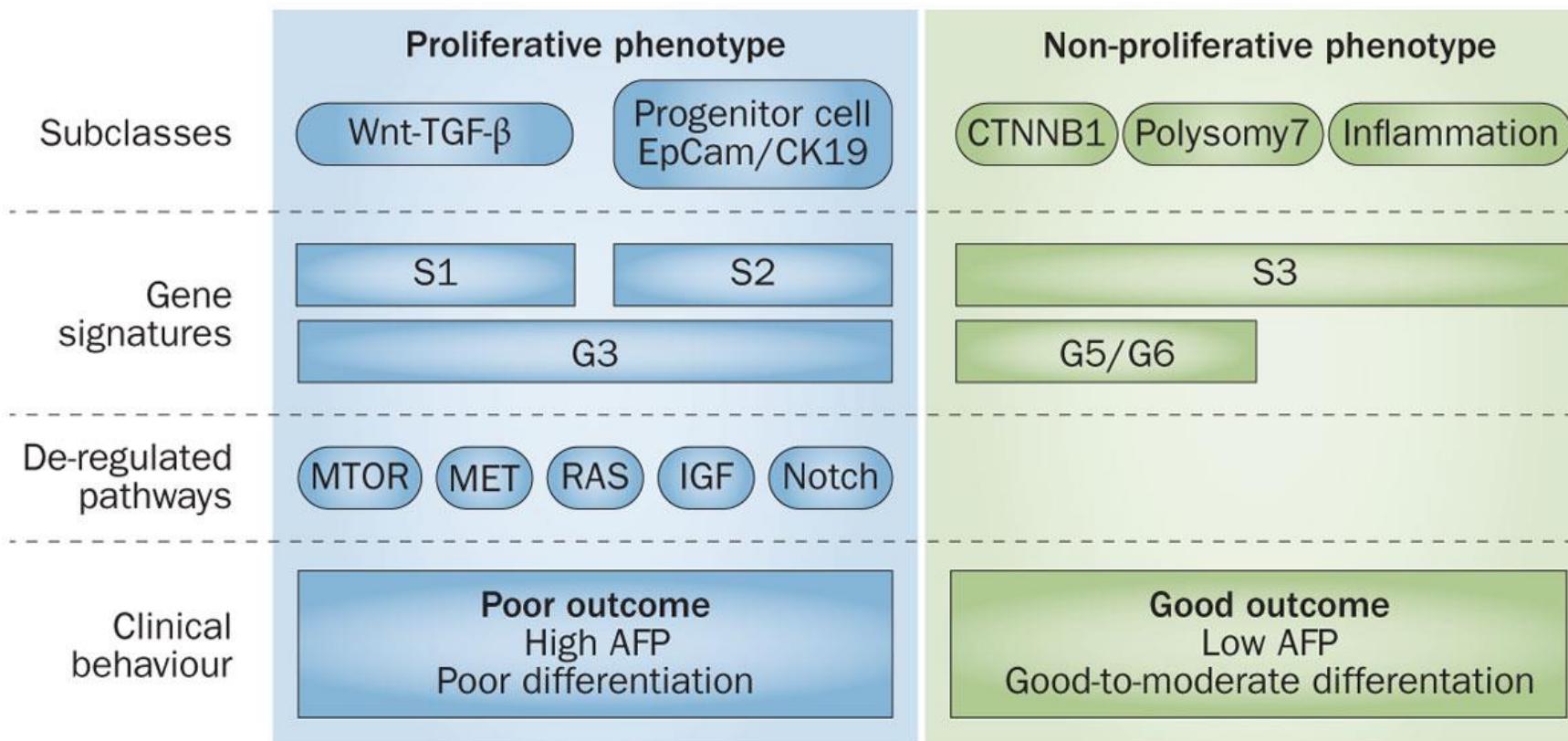
Prognosis in HCC: Clinical & Genomic Data

Villanueva *et al.*, Annu Rev Med 2010; 61: 317

	Very early / Early stage (BCLC-0/A)	Intermediate stage (BCLC-B)	Advanced stage (BCLC-C)	Terminal stage (BCLC-D)	Clinical prognostic prediction
STANDARD THERAPY	Curative treatments	Chemoembolization	Sorafenib	Symptomatic	
PREDICTED SURVIVAL	> 60 months	~ 20 months	~ 11 months	< 3 months	



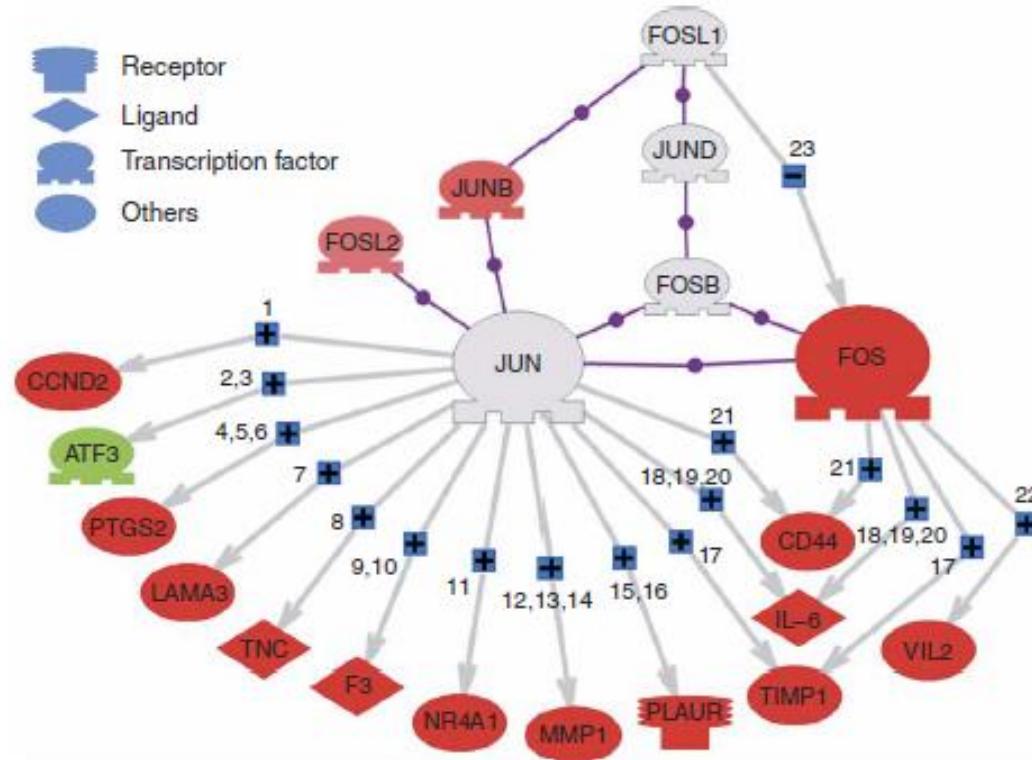
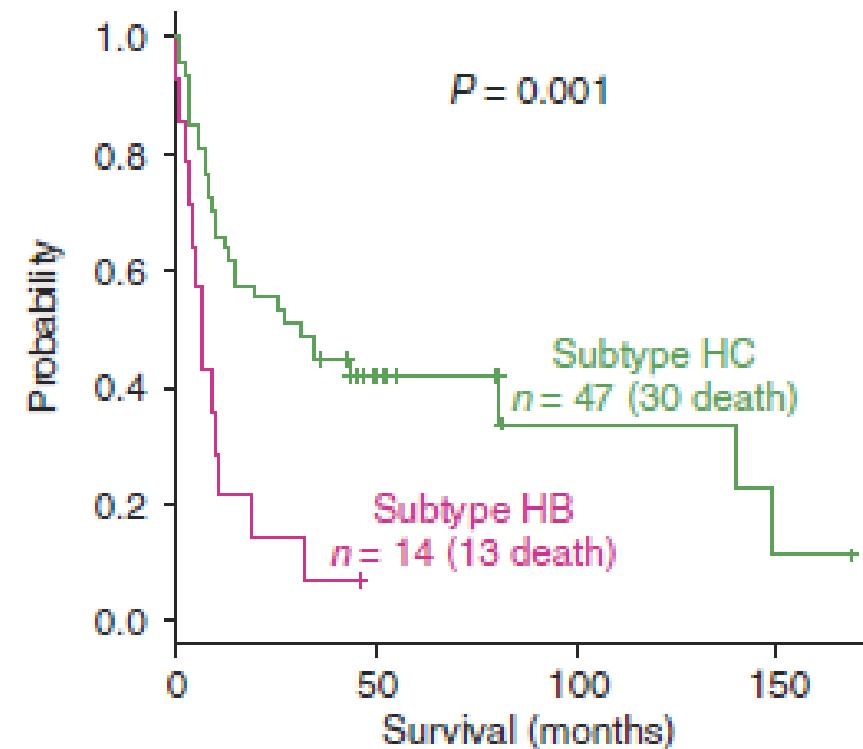
Schematic representation of molecular classification of patients with HCC using gene signatures



Progenitor Cell Signature & Survival

Lee et al., Nature Medicine 2006; 12: 410

- Gene expression analysis (hierachial clustering) of fetal hepatoblasts & 61 Chinese hHCC
- Validated with 78 Caucasian hHCC
- Progenitor Cell “poor survival signature”: CK7, CK19, VIM → AP-1↑ (c-jun)



Summary: Molecular Classification HCC

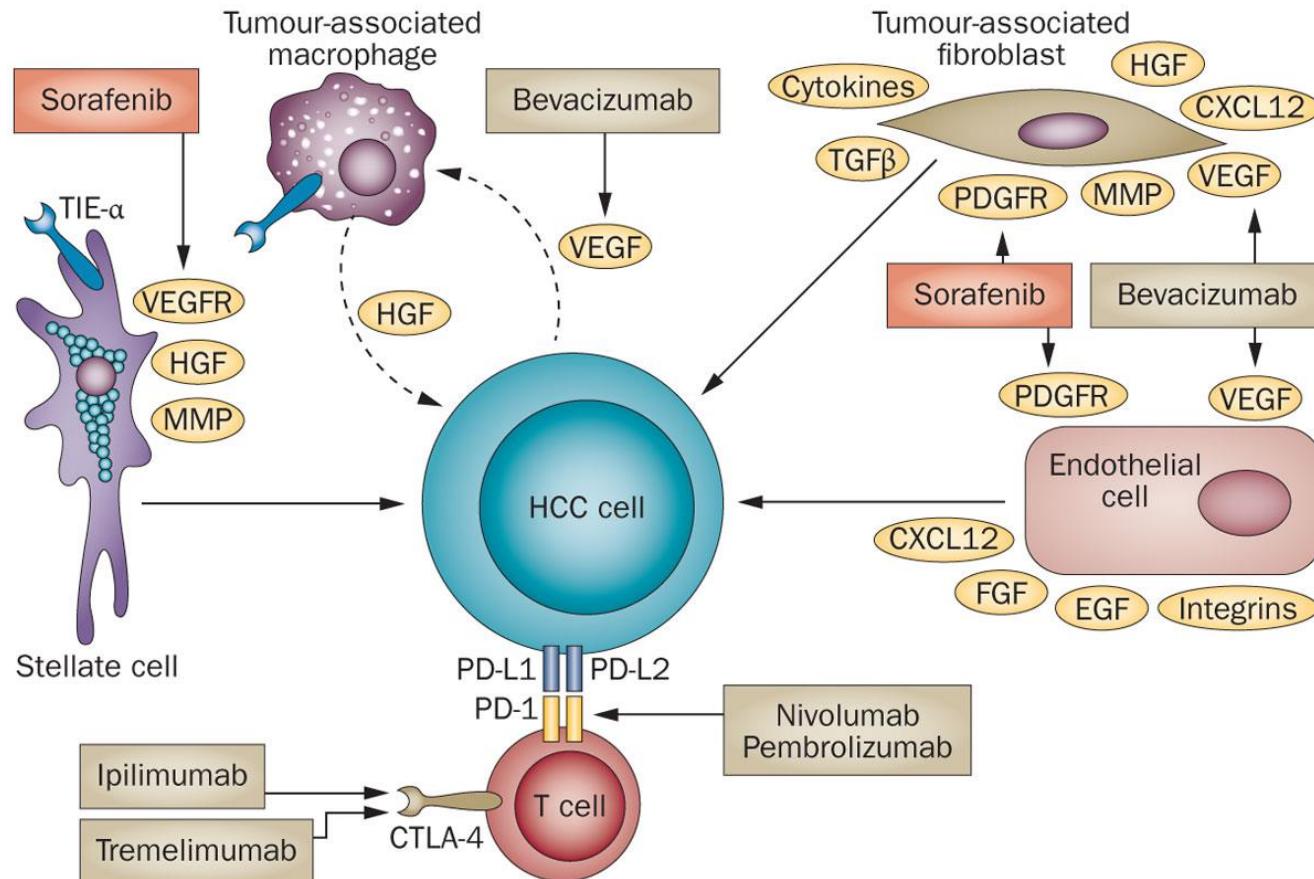
Zucman-Rossi *et al.*, GE 2015; 149: 1226

	PROLIFERATION CLASS		NON-PROLIFERATION CLASS
CELL LINEAGE FEATURES	Progenitor-like	Hepatocyte-like	Hepatocyte-like
PROGNOSTIC GENE SIGNATURES	EpCAM	Late TGF-β	
	S2	S1	
	Hepatoblastoma-C2		
	Hepatoblast-like		S3
	Cluster A		Cluster B
	Vascular invasion signature	WNT / CTNNB1	Poly 7
	G1-3 / 5-gene signature	G5-6	Immune related
DNA SOMATIC ALTERATIONS	Chr 11q13 amplif. (FGF19 / CCND1)	CTNNB1 mut.	DNA ampl. Chr7
SIGNALING PATHWAY ACTIVATION	NOTCH	TGFβ	
	IGF2	Liver-WNT	Classical WNT
	RAS / MAPK		
	MET		
	AKT / MTOR		
EPIGENETIC-BASED SUBTYPES	36 CpG DNA methylation signature	miRNA Class C2 (C19MC)	miRNA Class B
CLINICAL FEATURES	miRNA Class C3		
	HBV	HCV, Alcohol	
	High AFP levels	Low AFP levels	
	Poor differentiation	Well-Mod differentiation	
	Vascular invasion (+++)	Vascular invasion (+)	
	Worse outcome (recurrence / survival)	Better outcome	

Molecular therapies acting on immune checkpoints and the microenvironment



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Nature Reviews | Clinical Oncology

HCC Pharmacological Treatment: Current Status

- Sorafenib remains SOC for advanced disease
- No second line therapy
- No adjuvant therapy
- Await data from
 - Ongoing Phase III trials
 - Stratified approaches
 - Immunotherapy



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Reasons learned from HCC unsuccessful studies

- Liver related toxicities of new medications
- Poor understanding of tumor biology and disease natural progression, absence of good prognostic score
- Tumor heterogeneity
- Poorly methodology to assess in vitro efficacy
- End points reassessment



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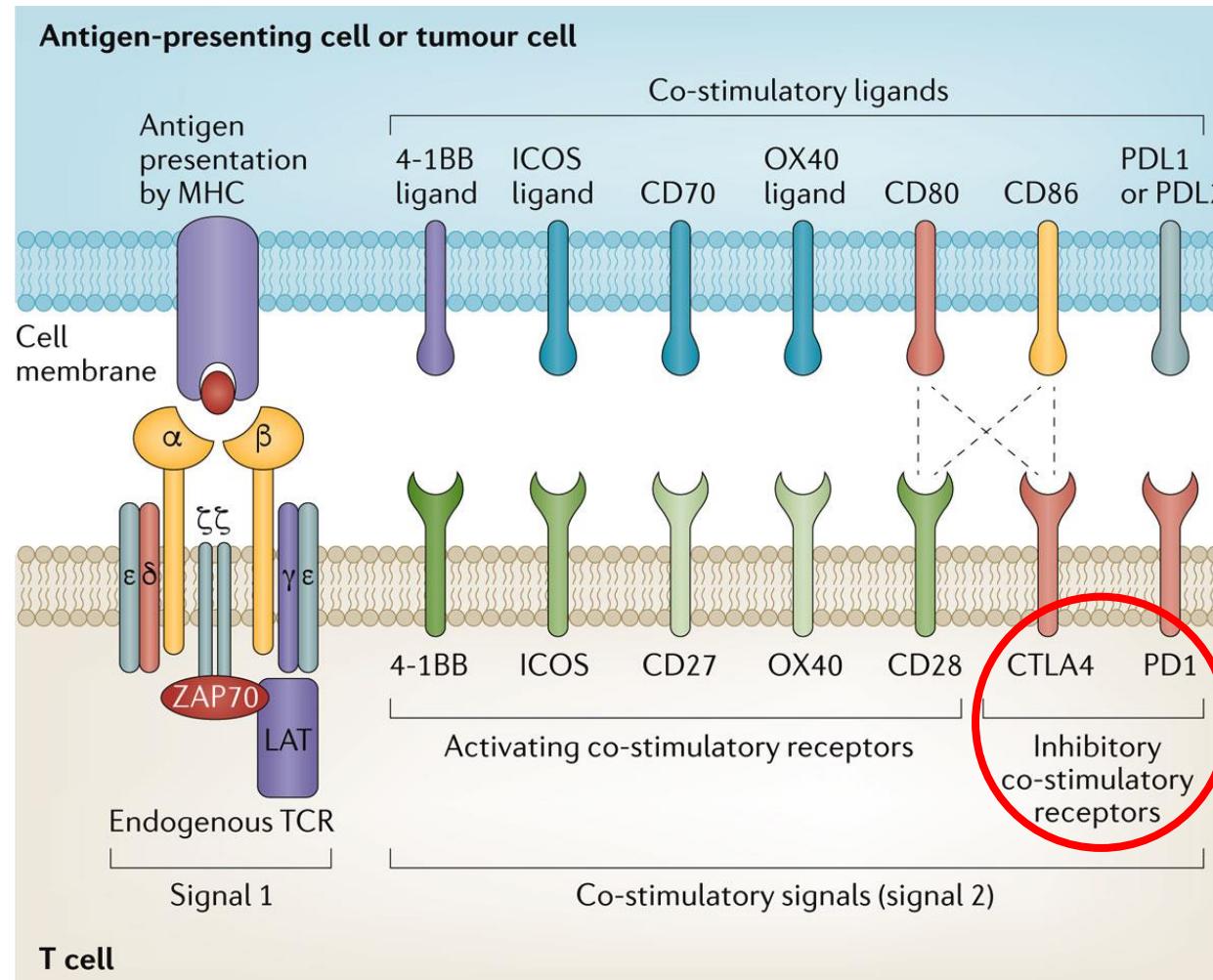
Immunotherapy for HCC



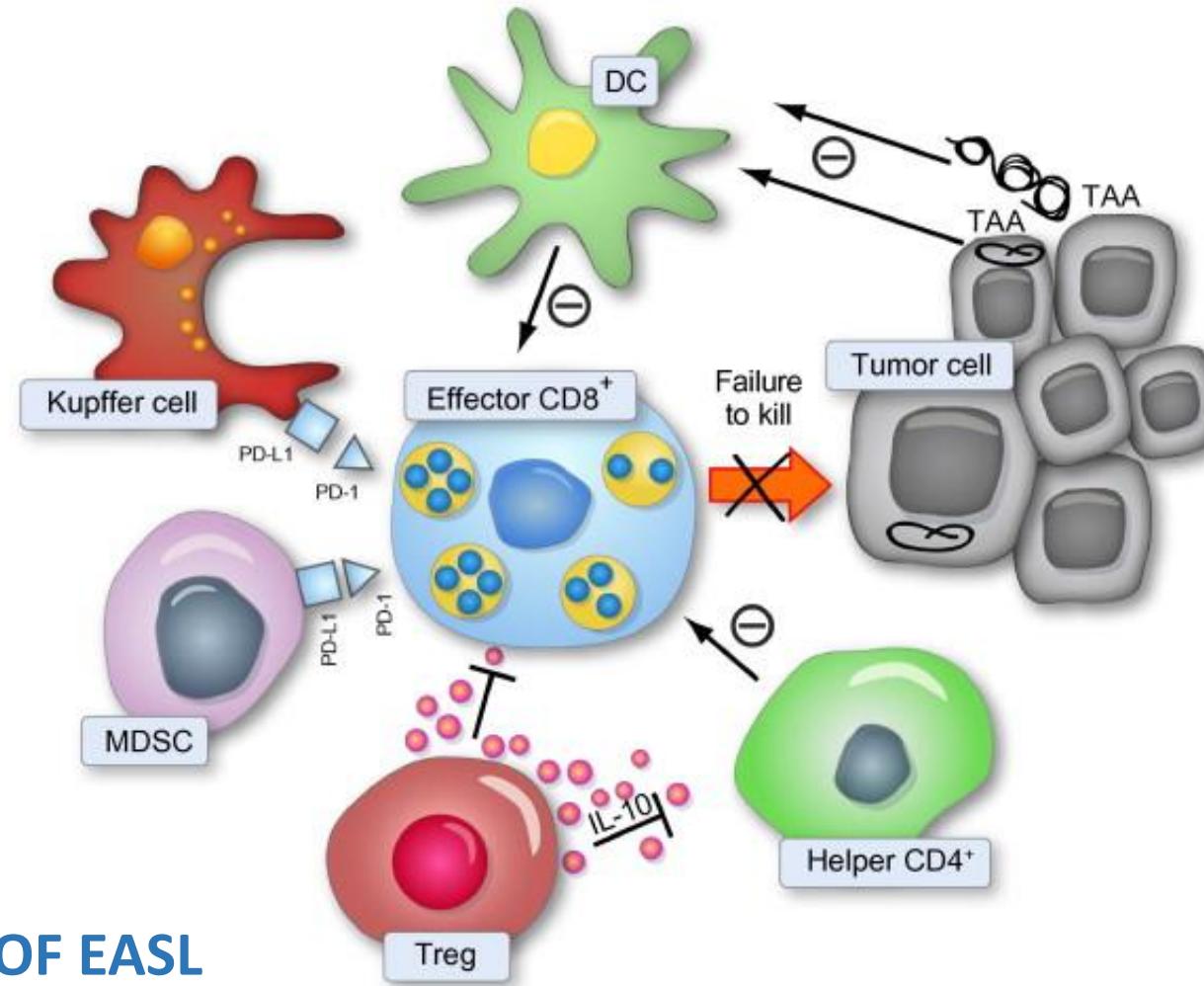
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T-Cell Receptors & Costimulation

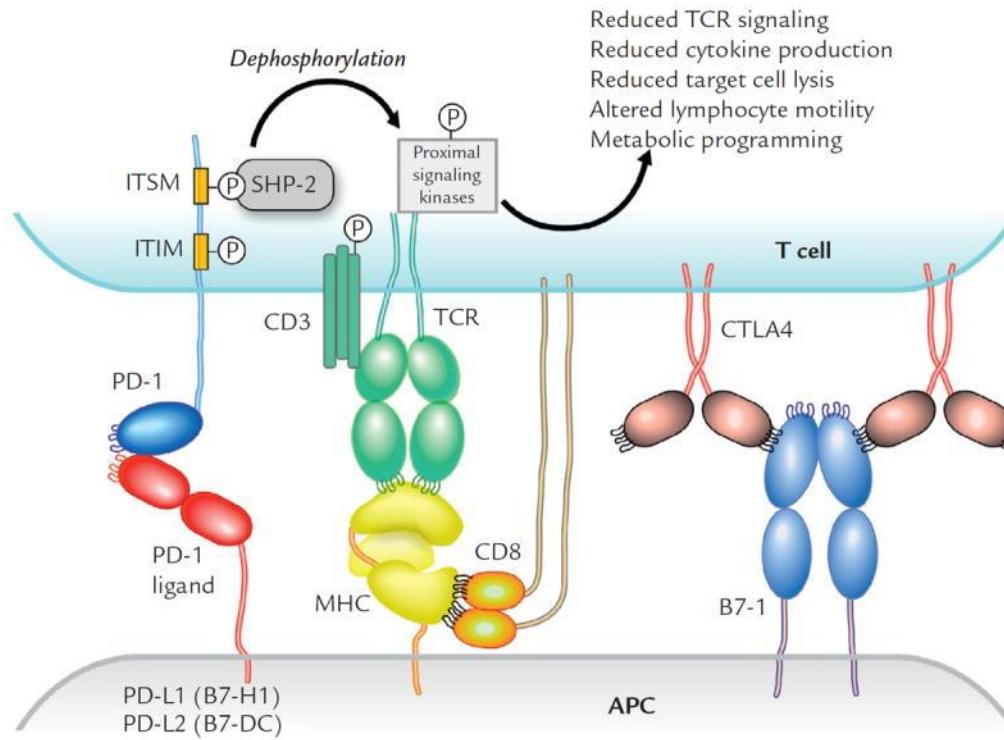
Fesnak *et al.*, Nature Rev. Cancer 2016; 16: 566



Multiple mechanism limits TAA-specific CD8+ T cell immune responses in HCC (JHepatology, 2011, 54: 830-834)



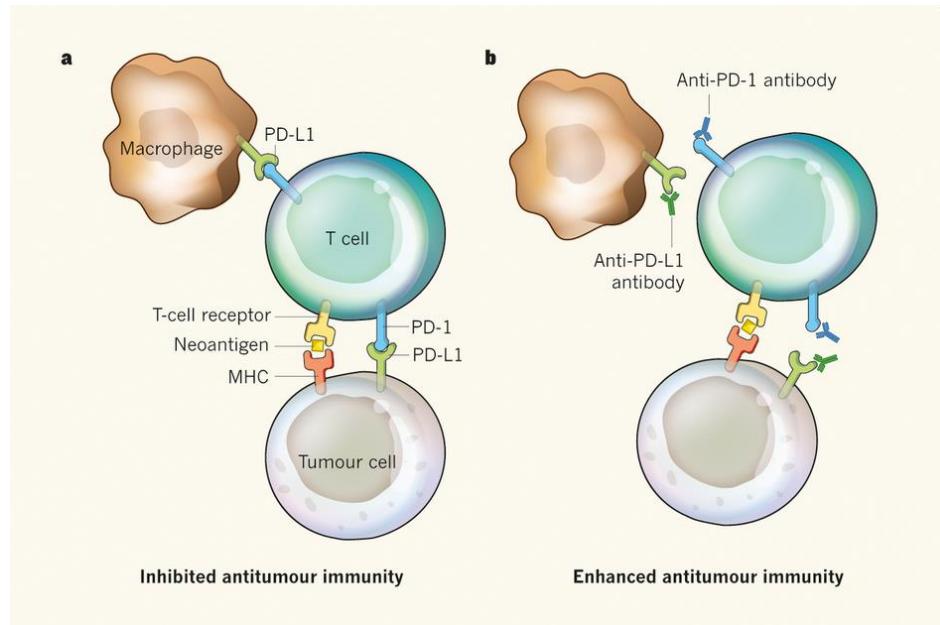
The Next Immune-Checkpoint Inhibitors: PD-1/PD-L1 Blockade



PD1-Blockade in Solid Tumors

Wolchok *et al.*, Nature 2014; 515: 496

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Signals from macrophages / other (T-) cells can inhibit CTL-response against tumor neoantigens

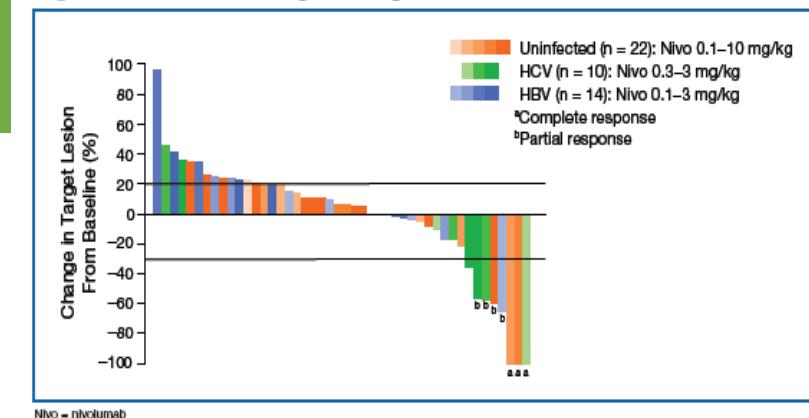
Nivolumab PI/II, CA209-040: Response

El-Khoueiry et al., ASCO 2015. Abstract LBA101, ASCO 2016, P4012

- PD-1 and PD-L1 overexpression associated with poor HCC prognosis
- HBV & HCV infections associated with PD-1 upregulation and immune exhaustion
- Nivolumab: fully human IgG4 antibody selectively inhibiting interaction PD-1 – PD-1L

Best Response in Evaluable Pts, %	Uninfect ed (n = 21)	HCV Infected (n = 11)	HBV Infected (n = 10)	Total (N = 42)
ORR	14	36	10	19
■ CR	10	0	0	5
■ PR	5	36	10	14
■ SD	48	45	50	48
■ PD	38	18	40	33

Figure 2. Maximal change in target lesions from baseline



- DoR in 8 pts with objective response: ~ 3-18+ mos
- Duration of SD in 20 evaluable pts: 1.1-17.3 mos
- Preliminary 12-mo OS: 62%
 - 12-mo OS in phase III regorafenib trial after sorafenib failure: ~ 45%



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