Optimal management of HCC today (and tomorrow)

Pierre Nahon

Service d'Hépatologie - Hôpital Jean Verdier - Bondy - Université Paris 13
INSERM 1162 - Paris 5 - Génomique fonctionnelle des tumeurs solides

Disclosures

- Abbvie, Astra Zeneca, Bayer, BMS, Gilead, Ipsen, Roche

Optimization goals differ according to tumour burden

BCLC 0 | BCLC A | BCLC B | BCLC C

Resection/Ablation

Prognosis

- Safety
- Recurrence
- Transplant strategy

TACE

Adjuvant therapy?

Systemic therapy

Precision

- Treatment response
- Choice of a targeted therapy

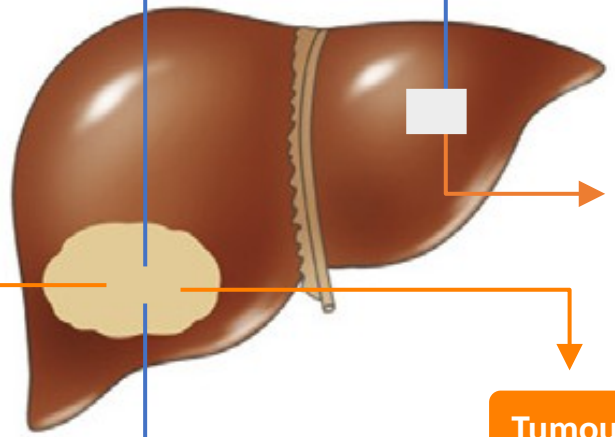
Optimizing curative management of HCC

Inclusion in « adjuvant » trials

- Neoadjuvant and/or adjuvant strategies (?)
- Sequential biopsy for identification of responders (?)

Liver disease management

- Treatment of the cause
- PHT monitoring and bleeding prevention



Underlying liver disase and patient

- Cirrhosis
- PHT/liver function
- Cause
- Age
- Male gender

Pathology-Molecular biology

- Differenciation
- Progenitor cells markers
- MVI
- Macro-trabecular subtype
- Molecular classification (?)

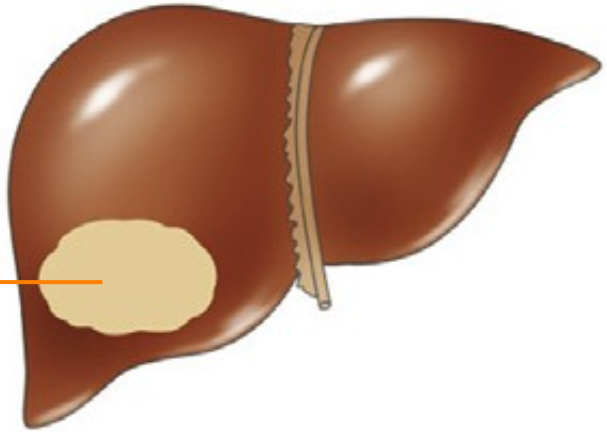
Tumour characteristics

- Number, size
- Infiltrating pattern
- AFP level

Quality of resection/ablation

Nahon P, Liver Int 2020

Optimizing curative management of HCC



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For many years, physicians were reluctant to perform HCC biopsy

Case in Point

Hepatocellular Carcinoma: To Biopsy or Not?

James M. Abraham, MD; and Christine Pocha, MD, PhD

GUT ONLINE

Diagnostic biopsy for hepatocellular carcinoma in cirrhosis: useful, necessary, dangerous, or academic sport?

J Schölmerich and D Schacherer

Gut 2004;53;1224-1226
doi:10.1136/gut.2004.040816

Should we biopsy each liver mass suspicious for HCC before liver transplantation?–No, please don't

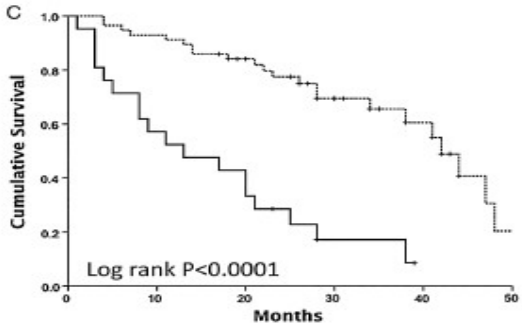
Indeterminate 1-2-cm Nodules Found on Hepatocellular Carcinoma Surveillance: Biopsy for All, Some, or None?

Biopsy for Liver Cancer: How to Balance Research Needs With Evidence-Based Clinical Practice

Prognostic molecular signatures

On biopsies

Neoangiogenesis-related genes are hallmarks of fast-growing hepatocellular carcinomas and worst survival. Results from a prospective study



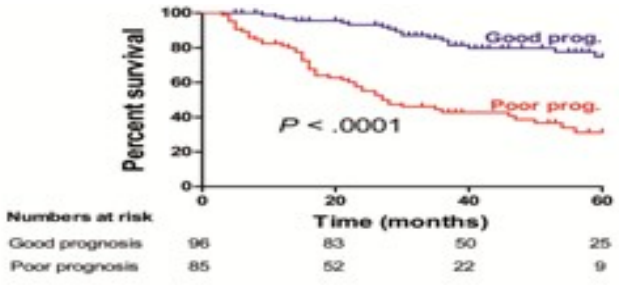
A five-gene transcriptomic hepatic signature including angiopoietin-2 (*ANGPT2*), delta-like ligand 4 (*DLL4*), neuropilin (NRP)/tolloid (TLL)-like 2 (*NETO2*), endothelial cell-specific molecule-1 (*ESM1*), and nuclear receptor subfamily 4, group A, member 1 (*NR4A1*) identifies with high sensitivity and specificity rapidly growing HCCs.

Villa E, Gut 2016

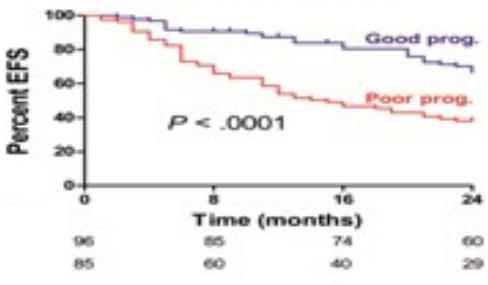
On resections

A hepatocellular carcinoma 5-gene score associated with survival of patients after liver resection

Disease specific survival
Training cohort



Early tumor recurrence-free survival
Training cohort

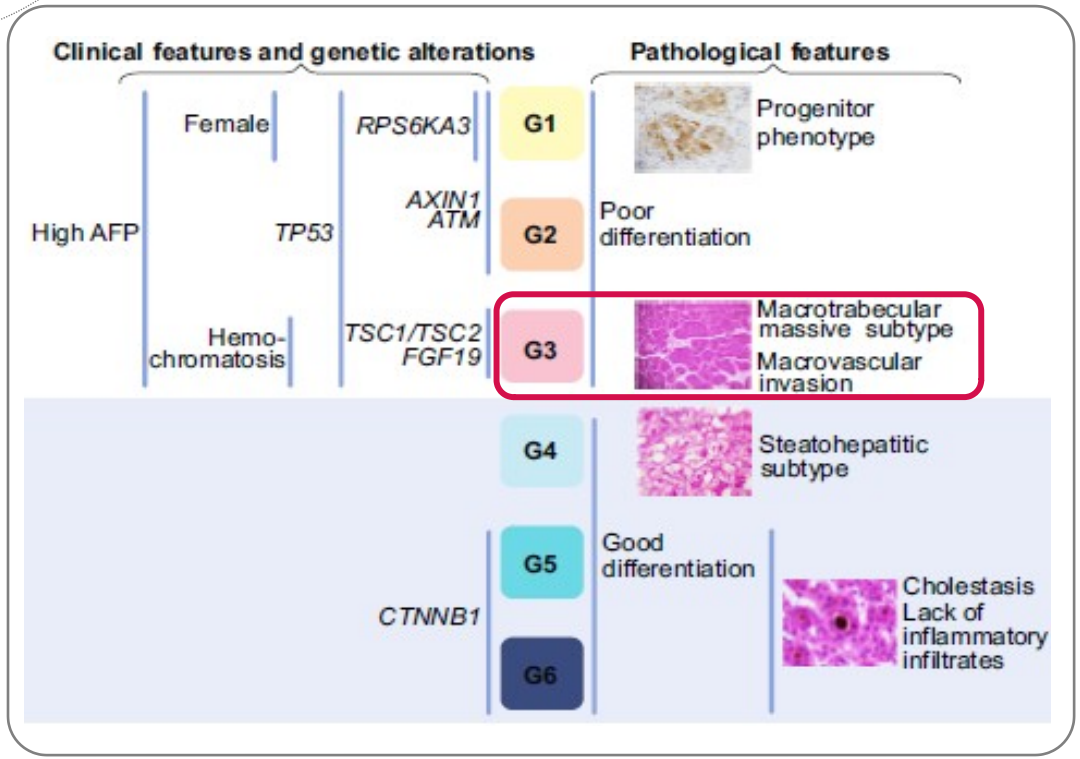


TAF9 RAMP3 HN1 KRT19 RAN

Score 5-gènes = ((log **TAF9** -1,3354874) X (-0,7)) + ((log **RAMP3** - 0,2179838) X 0,25587217)) + ((log **HN1** - 2,1549344)X(-0,14253598)) + ((log **KRT19**+2,2145301) X (-0,05104661)) + ((log **RAN** - 1,1360639) X 0,1859979)

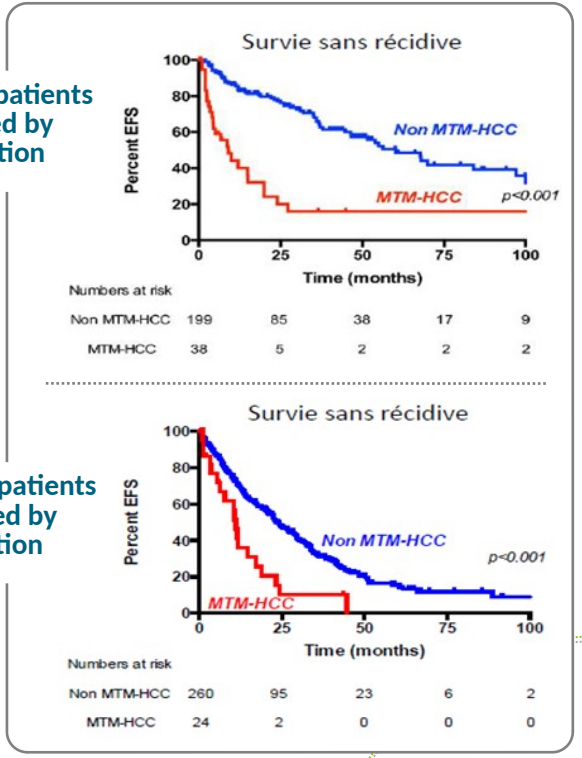
Nault JC, Gastroenterology 2013

Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification



237 HCC patients Treated by resection

284 HCC patients Treated by ablation



Calderaro J, J Hep 2017

Ziol, Hepatology 2018

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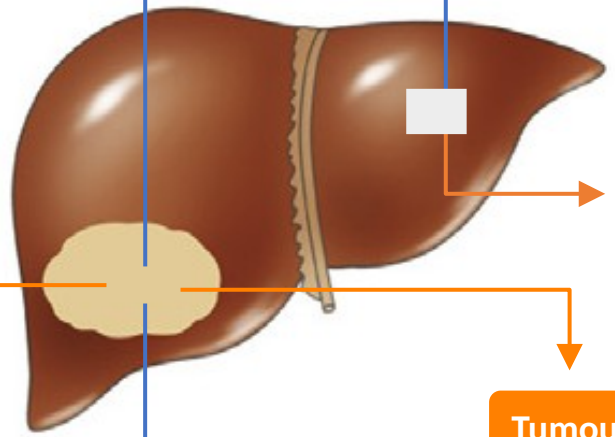

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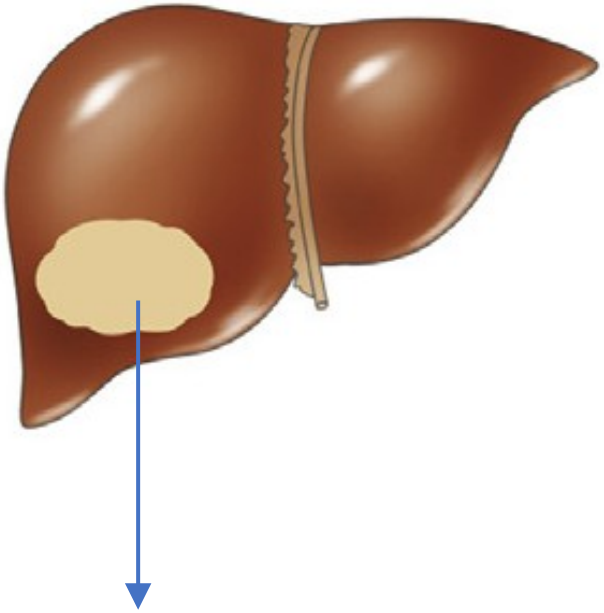
Quality of resection/ablation

Nahon P, Liver Int 2020

Optimizing curative management of HCC



Quality of resection/ablation

Nahon P, Liver Int 2020

Ablation or resection ?

	Ablation	Resection
2 or 3 nodules	Distant	Same segment
Localization	Deep	Superficial
Liver function	Good[a]	**Excellent[b]**
Portal Hypertension	Yes	**No**
Mortality	0.3%	1%
5-yrs survival	76% in patients eligible for resection	75%

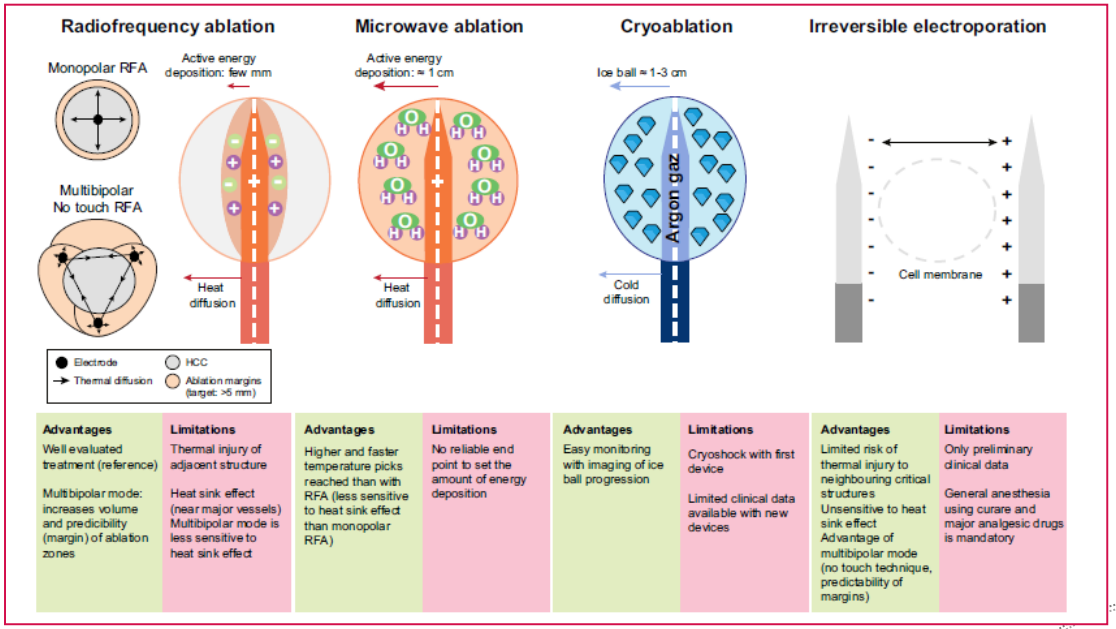
a Malades appartenant principalement à la classe A ou B de Child-Pugh
b Malades appartenant principalement à la classe A de Child-Pugh.avec bilirubine normale et sans hypertension portale

Review

JOURNAL
OF HEPATOLOGY

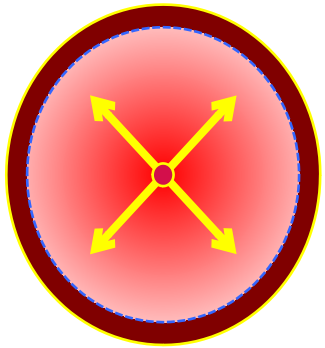
Percutaneous treatment of hepatocellular carcinoma: State of the art and innovations

Jean-Charles Nault[1,2,3,*,†], Olivier Sutter[4], Pierre Nahon[1,2,3], Nathalie Ganne-Carrié[1,2,3], Olivier Séror[2,3,4,*]

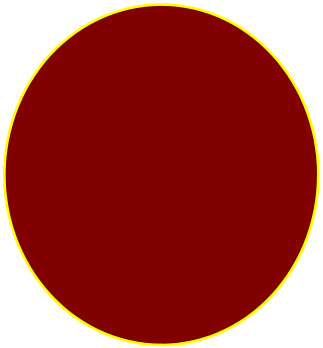


Radiofrequency ablation		Microwave ablation		Cryoablation		Irreversible electroporation	
Advantages	**Limitations**	**Advantages**	**Limitations**	**Advantages**	**Limitations**	**Advantages**	**Limitations**
Well evaluated treatment (reference) Multibipolar mode: increases volume and predicibility (margin) of ablation zones	Thermal injury of adjacent structure Heat sink effect (near major vessels) Multibipolar mode is less sensitive to heat sink effect	Higher and faster temperature picks reached than with RFA (less sensitive to heat sink effect than monopolar RFA)	No reliable end point to set the amount of energy deposition	Easy monitoring with imaging of ice ball progression	Cryoshock with first device Limited clinical data available with new devices	Limited risk of thermal injury to neighbouring critical structures Unsensitive to heat sink effect Advantage of multibipolar mode (no touch technique, predictability of margins)	Only preliminary clinical data General anesthesia using curare and major analgesic drugs is mandatory

Principles for large ablations



Monopolar RFA



Multibipolar « no touch »

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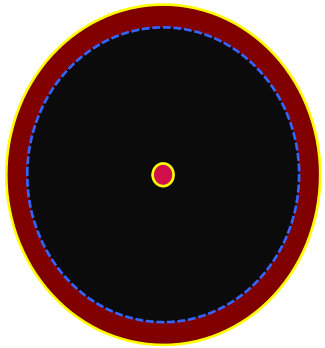

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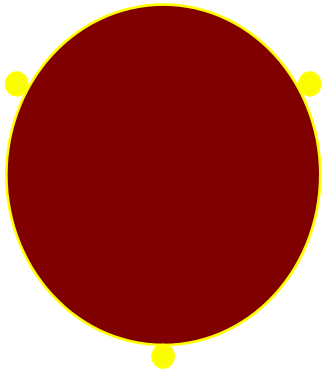

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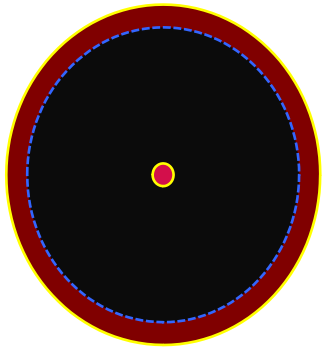

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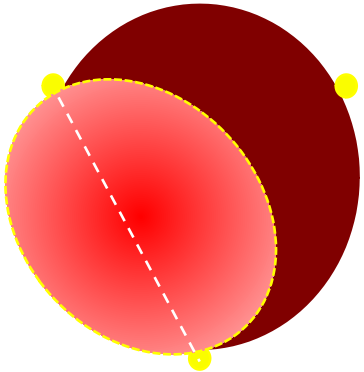

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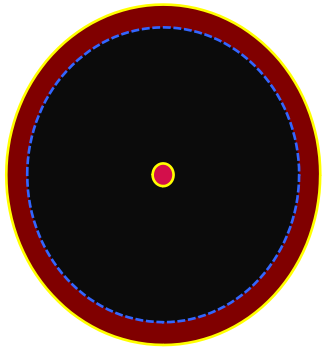

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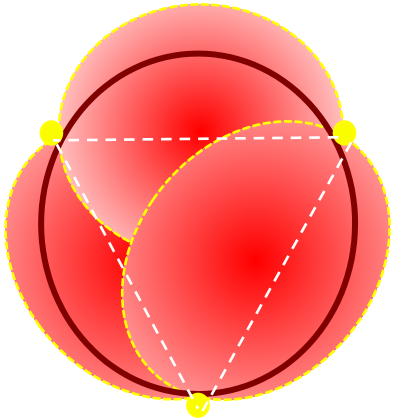

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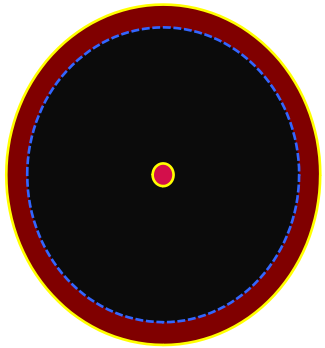

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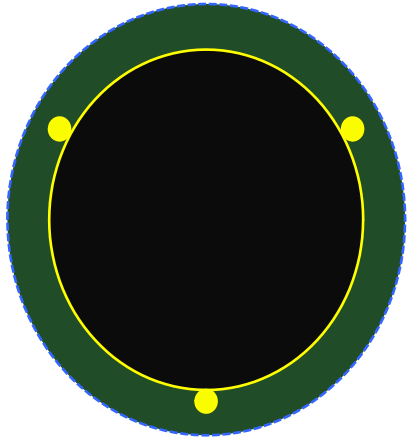

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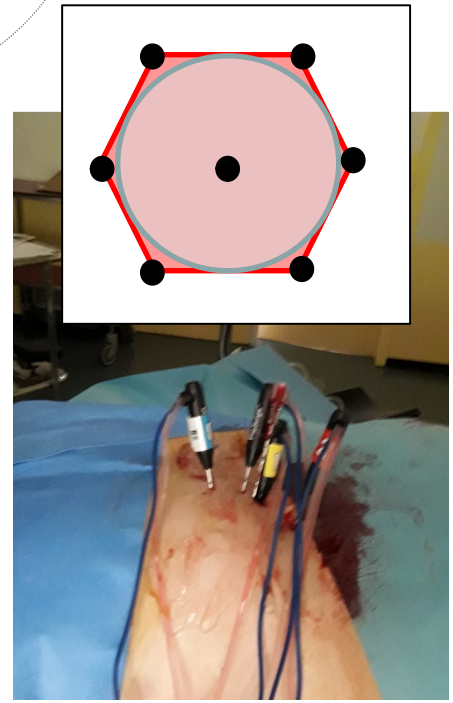

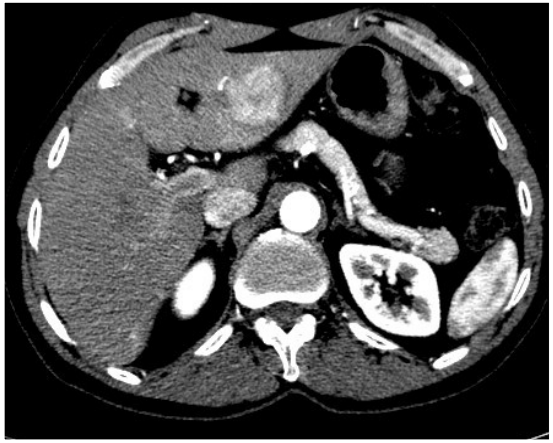


5 cm

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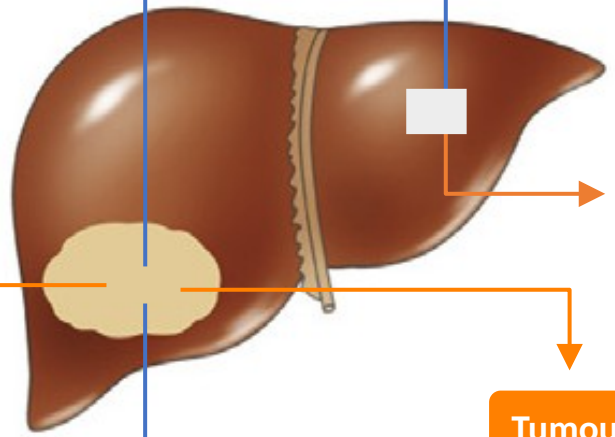

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Nahon P, Liver Int 2020

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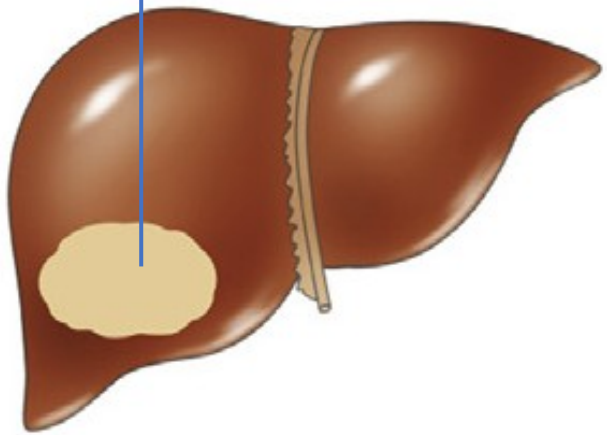
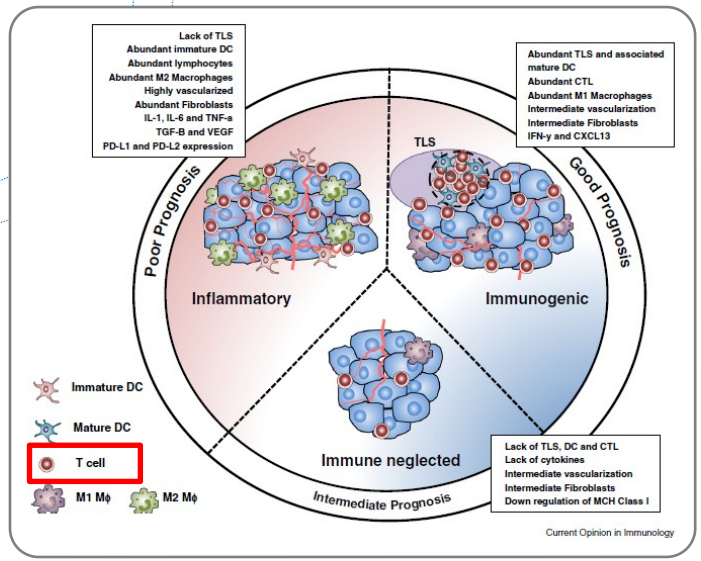
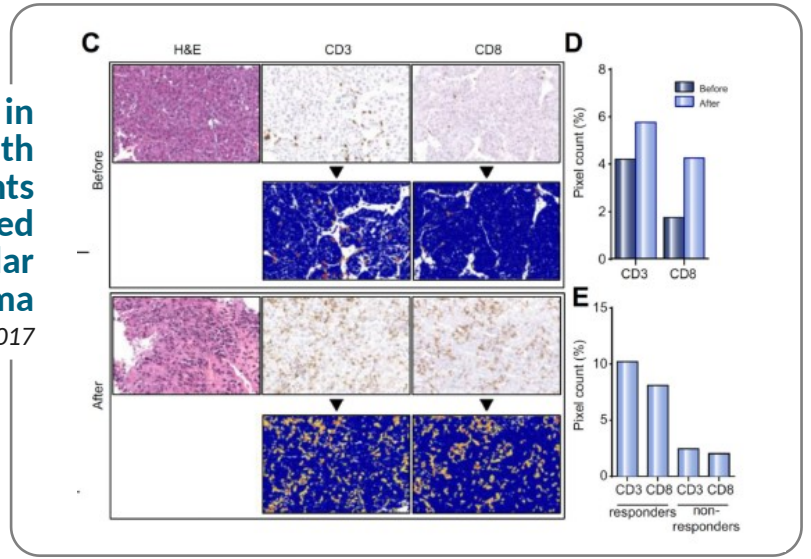


Nahon P, Liver Int 2020

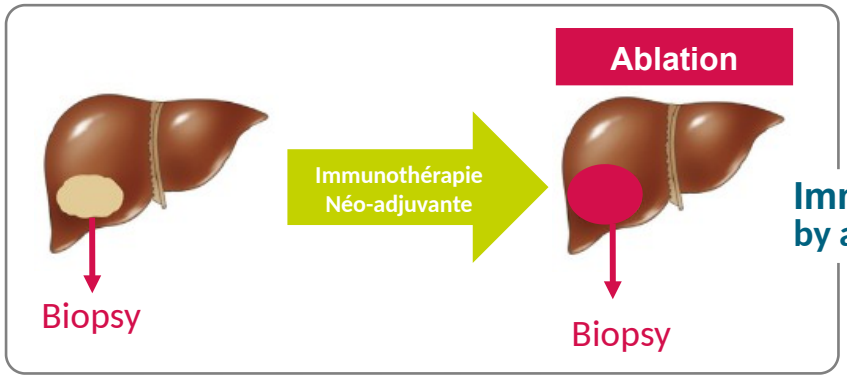


Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma

Duffy AG, J Hepatology 2017



32 patients (tremelimumab and ablation at D36)



Immune stimulation induced by ablation and amplified by immunotherapy

Several trials in adjuvant setting, with immune checkpoint inhibitors, are ongoing for patients with high risk of recurrence after curative treatment of HCC

Phase III Trial	Experimental Arm	Control Arm	Primary endpoint	Secondary endpoints	Planned participant recruitment
ChekMate 9 DX (NCT03383458)	Nivolumab	Placebo	Recurrence-free survival	Overall survival Time to recurrence	530
KEYNOTE-937 (NCT03867084)	Pembrolizumab	Placebo	Recurrence-free survival overall survival	Adverse event QoL	950
EMRALD 2 (NCT03847428)	Durvalumab Bevacizumab	Placebo	Recurrence-free survival	Overall survival Time to recurrence	888
IMbrave050 (NCT04102098)	Atezolizumab Bevacizumab	Active surveillance	Recurrence-free survival	Overall survival Time to recurrence	662

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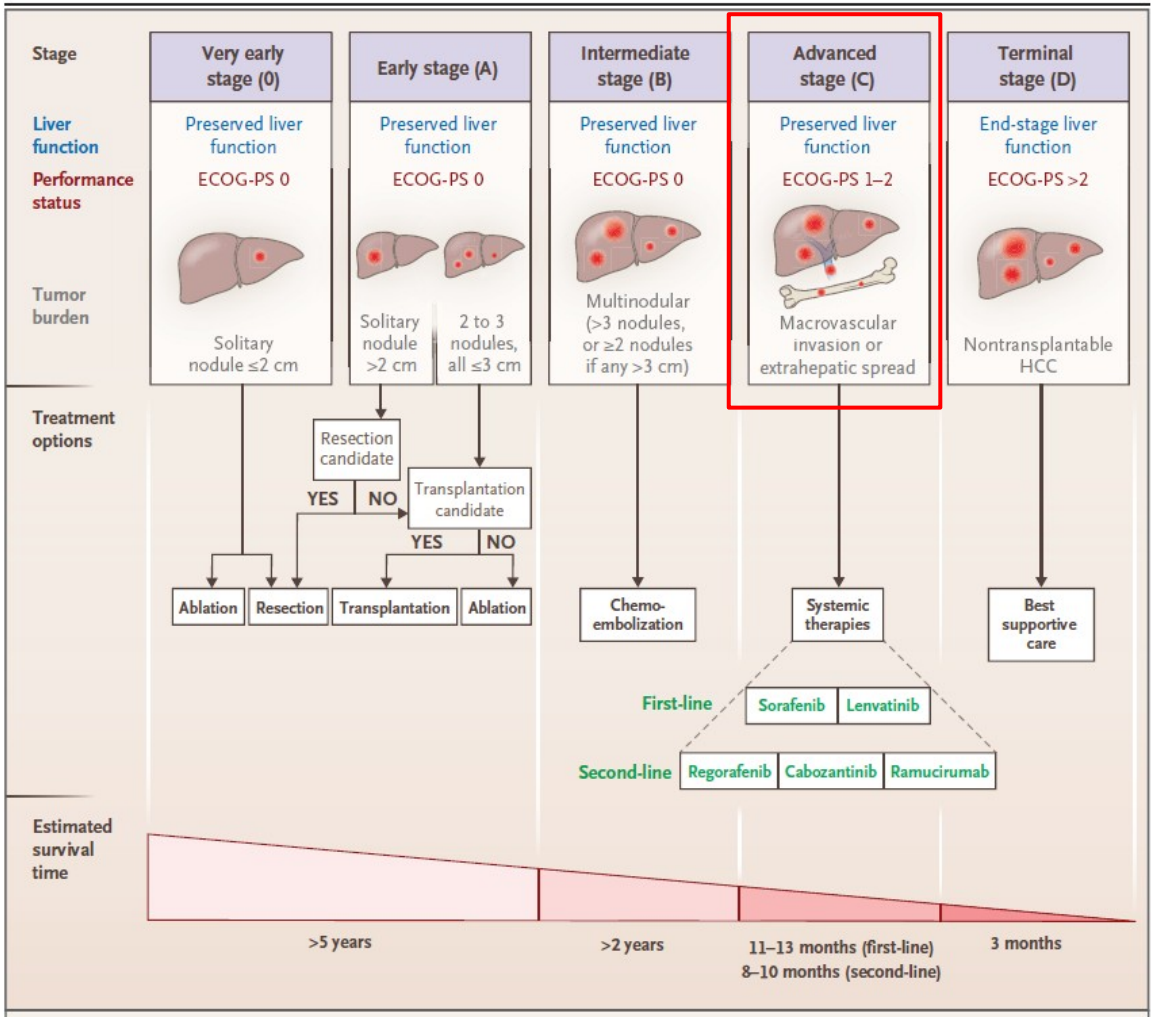
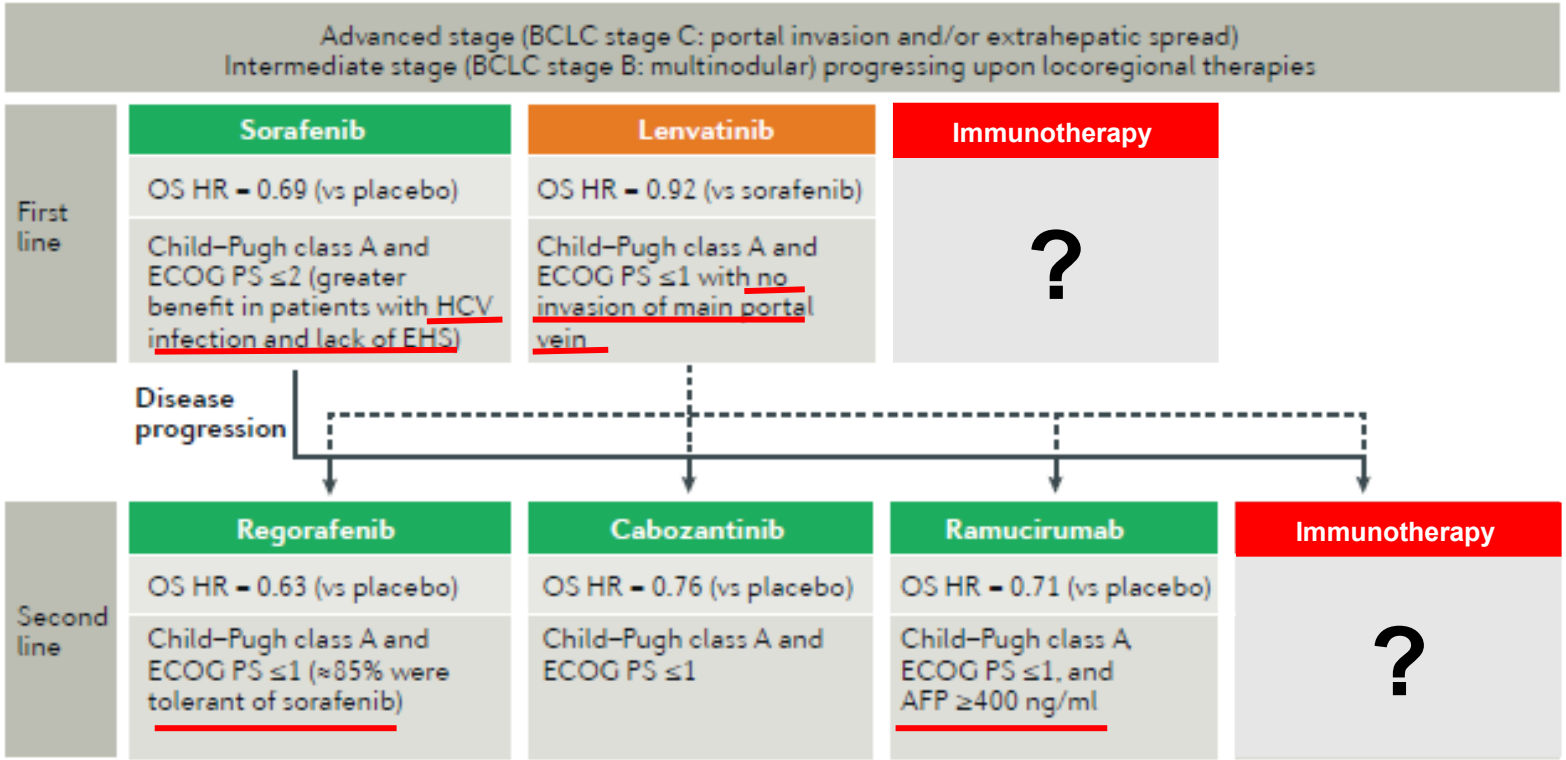


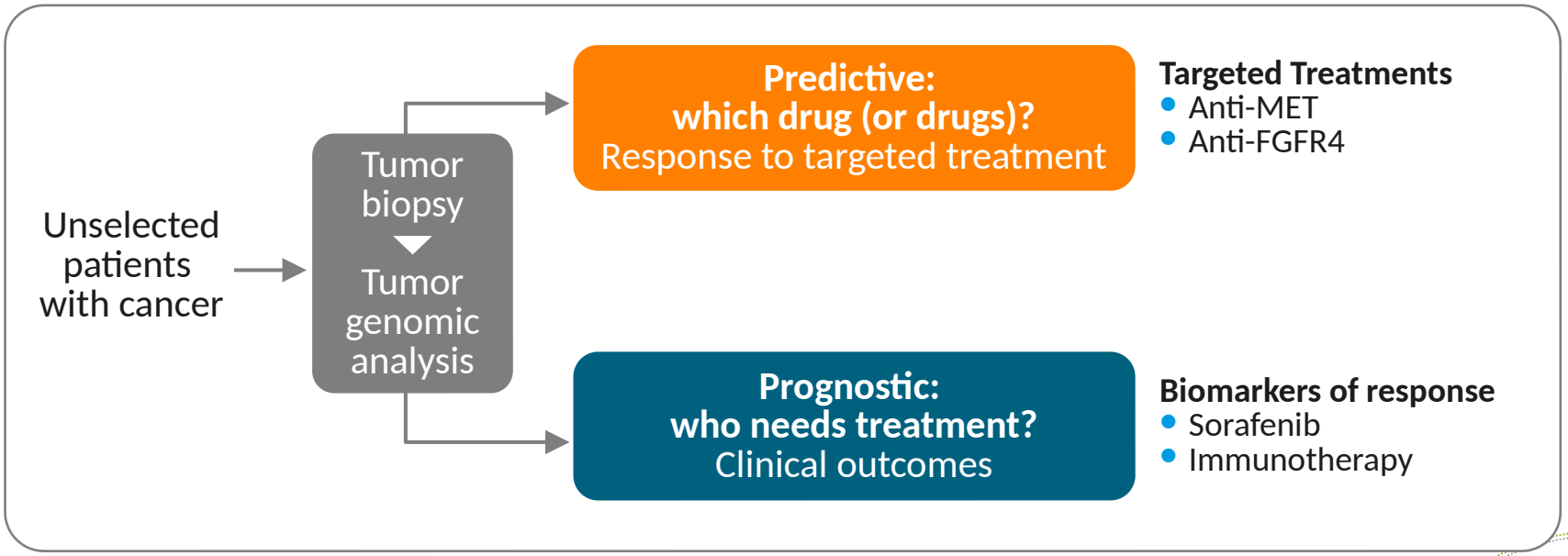
A broader therapeutic landscape with 5 approved systemic therapies

Villanueva A,
NEJM 2019

How to choose in 2020?

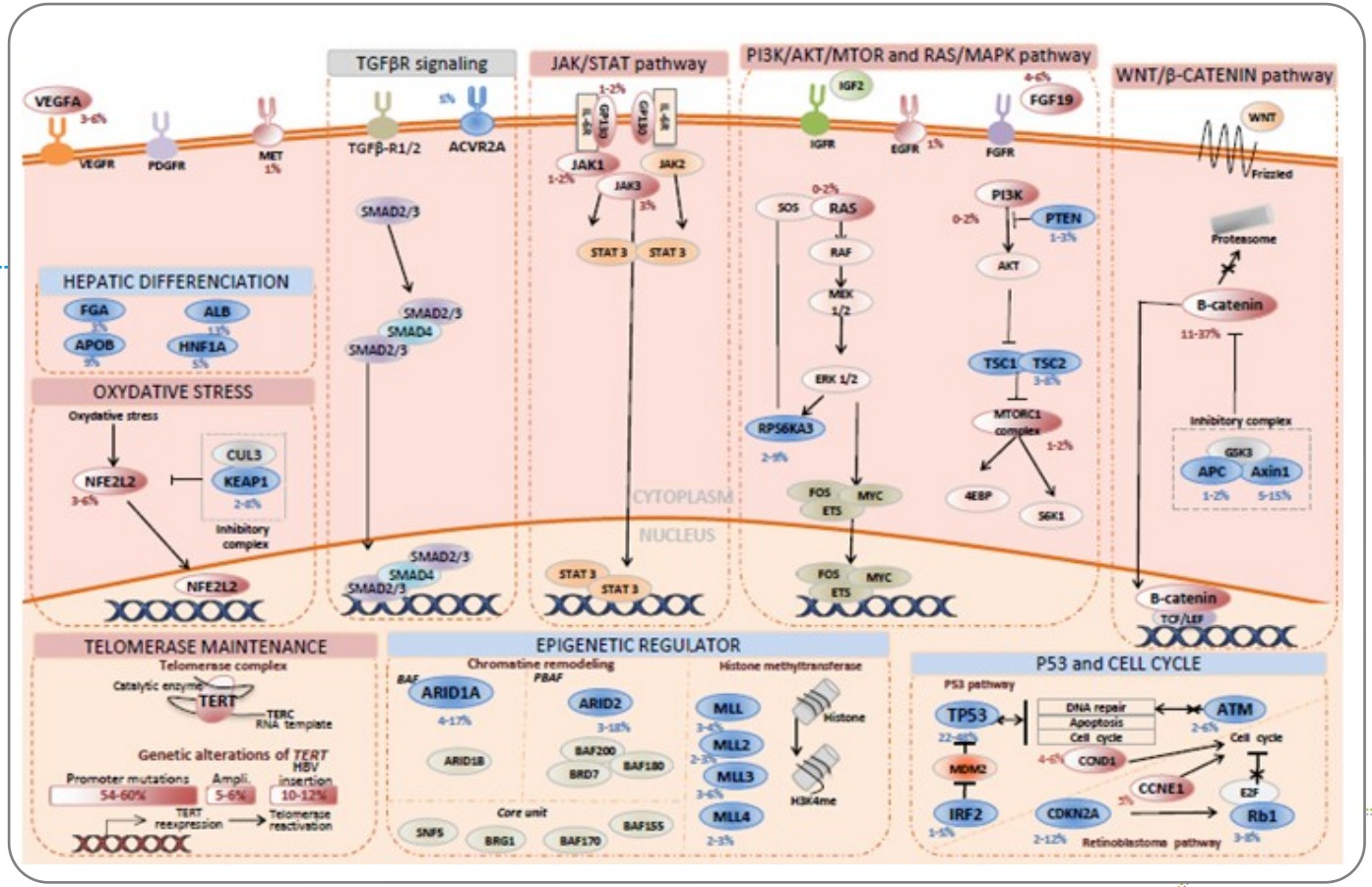


Can we implement tumour genomics in decision making process?



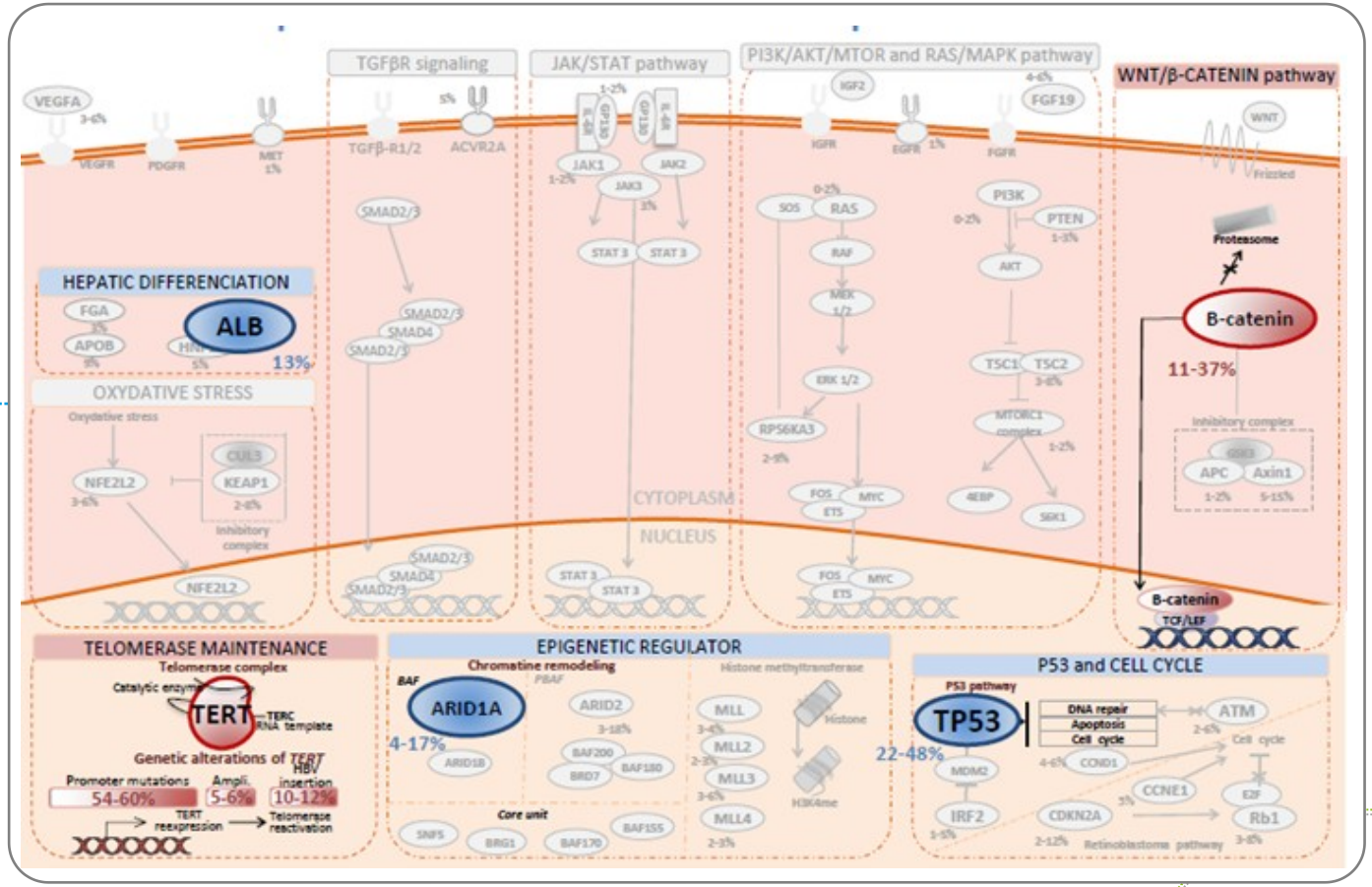
Simon R, Nature Reviews 2013

HCC genetic landscape



Schultze K, Nat Genet 2015

But most genetic mutations are not targetable...



...only 20-30% are.

Schultze K, Nat Genet 2015

Precision Medicine and Imaging

Clinical Cancer Research

Prospective Genotyping of Hepatocellular Carcinoma: Clinical Implications of Next-Generation Sequencing for Matching Patients to Targeted and Immune Therapies

134 CHC (127 patients)

NGS (FFPE, 63% biopsies)

81 Sorafenib

31 Immunotherapy

Immunotherapy, *N* (%)	
Anti–CTLA-4 monotherapy	1
Anti–PD/PD-L1 monotherapy	25
Anti–PD-1/PD-L1 + immune checkpoint inhibitor	5
+ Anti–CTLA-4	1
+ Anti-LAG3	2
+ Anti-KIR	2

Sorafenib

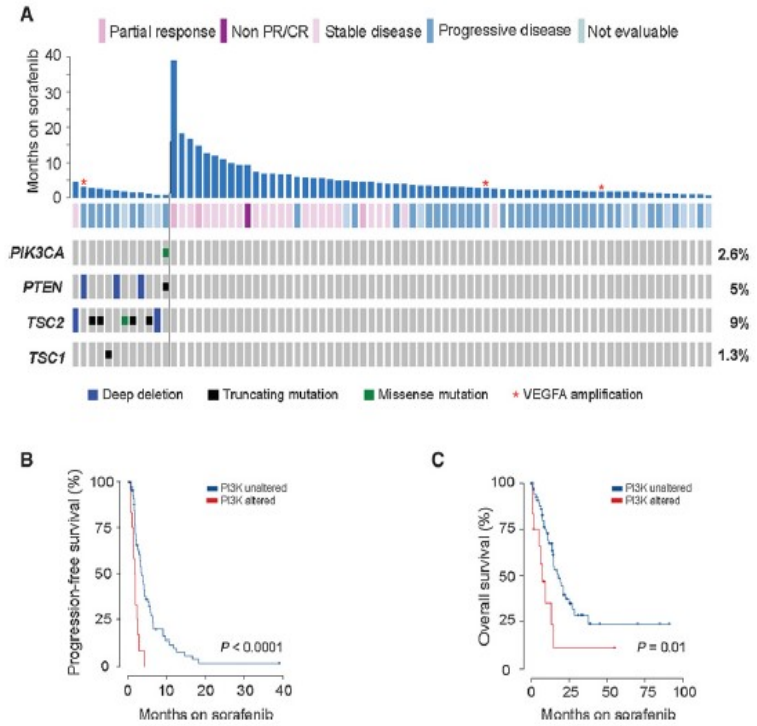


Figure 2.
Genomic determinants of response to sorafenib in patients with advanced HCC. **A,** Months of treatment (*y*-axis) for each patient annotated with gene alteration and objective response. **B,** Kaplan–Meier PFS on sorafenib therapy for patients with PI3K–mTOR-activated tumors ($N = 12$) versus non-PI3K–mTOR tumors ($N = 67$), demonstrating shorter PFS in PI3K–mTOR activated HCCs. **C,** Kaplan–Meier OS on first-line sorafenib therapy for patients with PI3K–mTOR-activated tumors ($N = 12$) versus non-PI3K–mTOR tumors ($N = 67$), demonstrating a shorter OS in PI3K–mTOR-activated HCCs.

Harding JJ, Clin Cancer Res 2019

Immunotherapy

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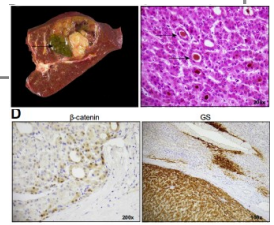

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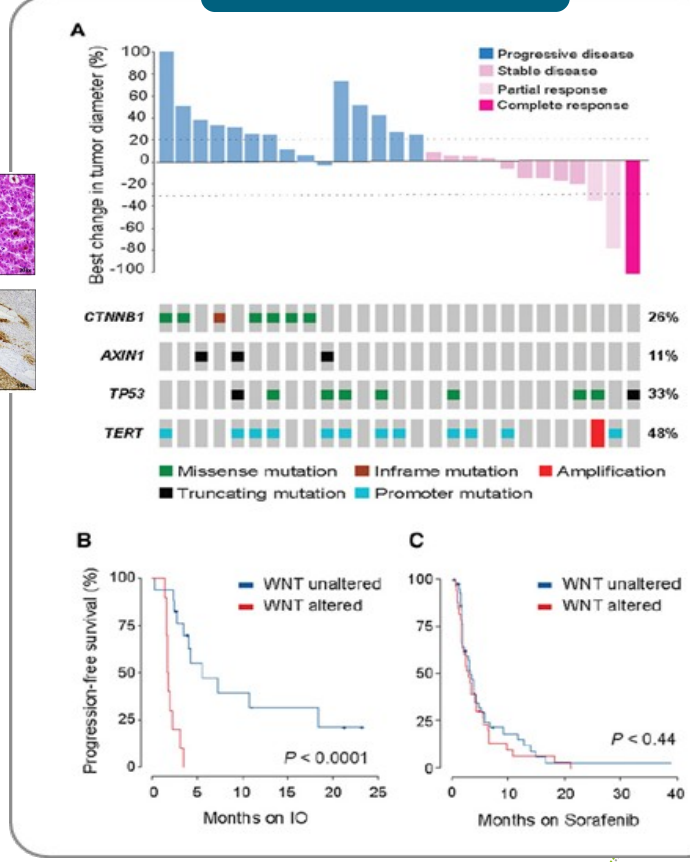
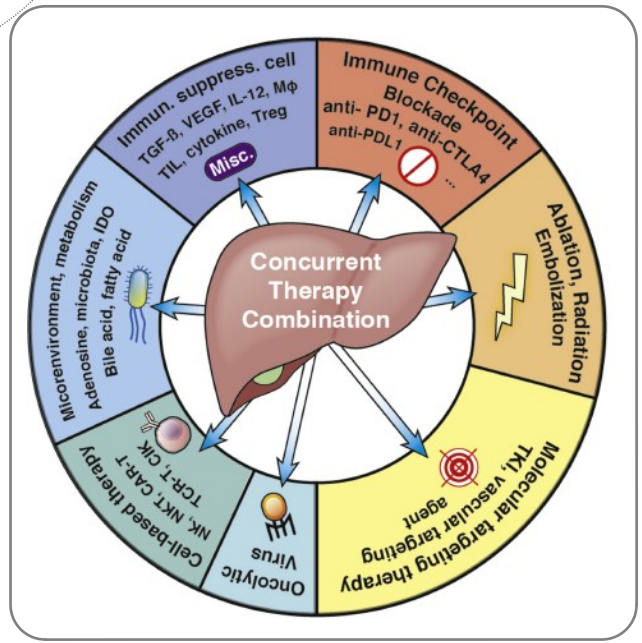


Harding JJ, Clin Cancer Res 2019

Perspectives : towards more complex associations and strategies



- Small HCC biopsy reveals prognostic information useful to refine therapeutic strategy
- Technological advances in surgery/ablation allow safe curative option in a broader range of patients
- Adjuvant strategies using Immunotherapy are promising to maintain long-term remission in patients with high-risk of recurrence
- Molecular biomakers/signatures associated with anti-tumoural response will be key when considering the growing number of approved molecules

Sequential biobanking has become pivotal in academic and industrial trials

Greten T, Gastro 2019