

# Optimal management of HCC today (and tomorrow)

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INSERM 1162 - Paris 5 - Génomique fonctionnelle des tumeurs solides*

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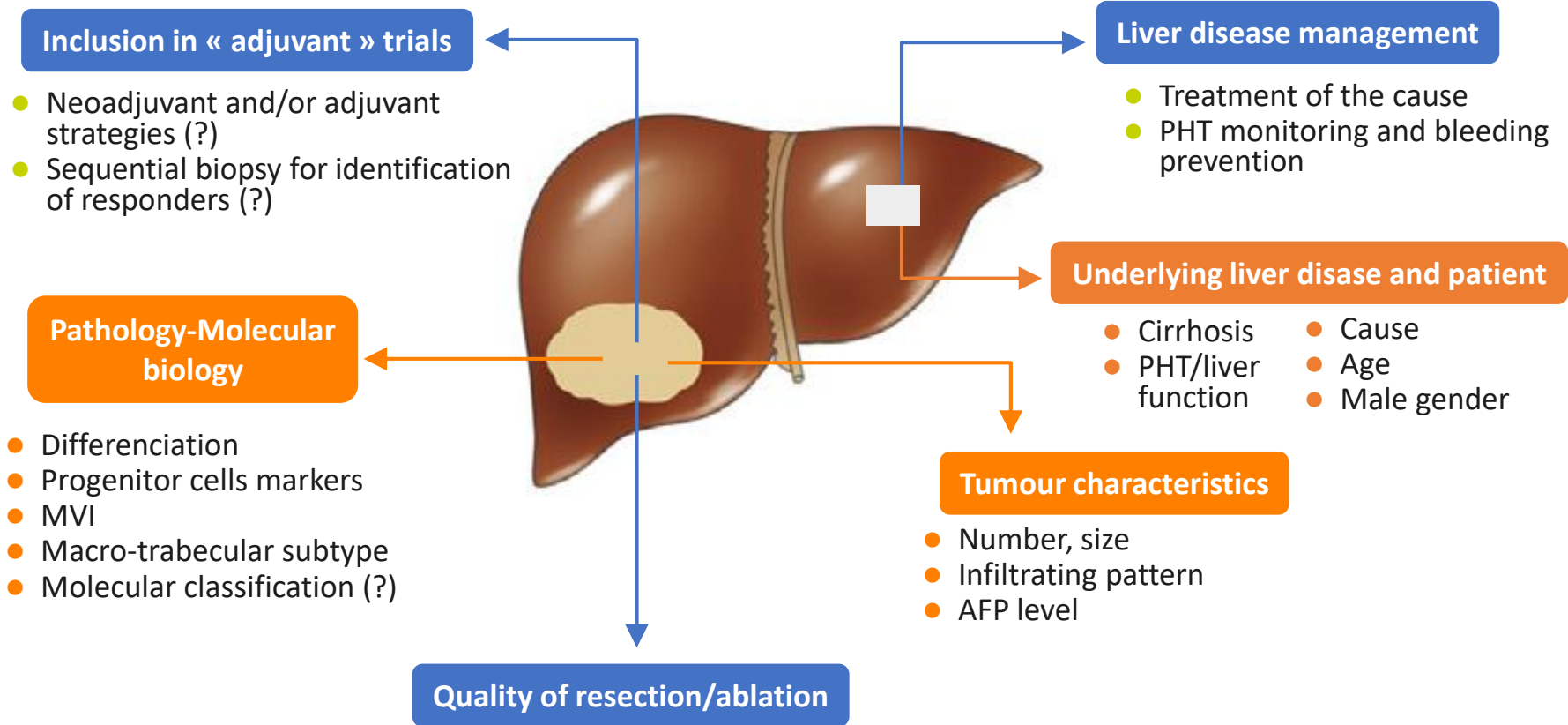
## ● Disclosures

- Abbvie, Astra Zeneca, Bayer, BMS, Gilead, Ipsen, Roche
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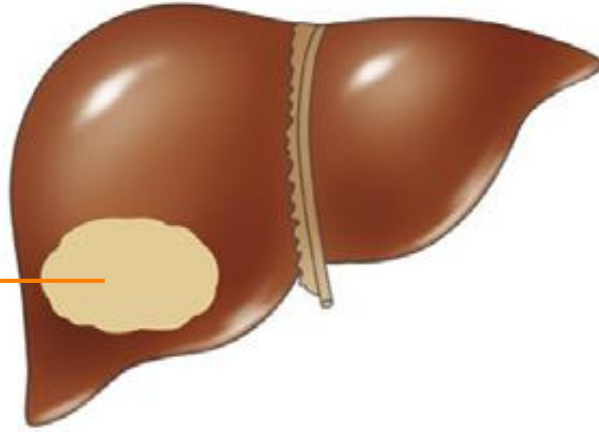
# Optimization goals differ according to tumour burden



# Optimizing curative management of HCC



# Optimizing curative management of HCC



## Pathology-Molecular biology

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

# ● 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



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

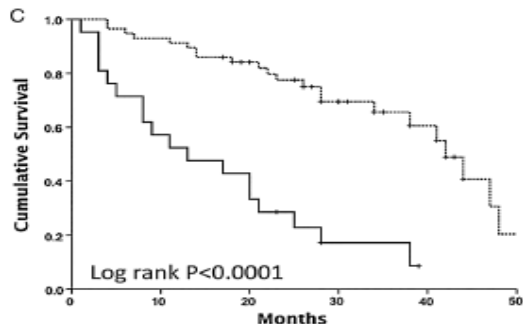
**Indeterminate 1-2-cm Nodules Found on Hepatocellular Carcinoma Surveillance: Biopsy for All, Some, or None?**

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

# Prognostic molecular signatures

## On biopsies

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

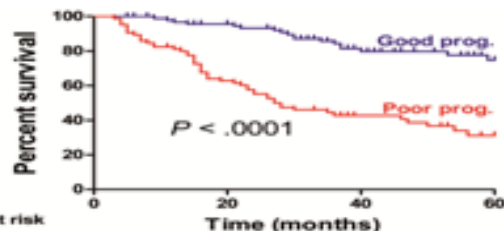


A five-gene transcriptomic hepatic signature including angiopoietin-2 (*ANGPT2*), delta-like ligand 4 (*DLL4*), neuropilin (NRP)/tolloid (TLL)-like 2 (*NETO2*), endothelial cell-specific molecule-1 (*ESM1*), and nuclear receptor subfamily 4, group A, member 1 (*NR4A1*) identifies with high sensitivity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

## On resections

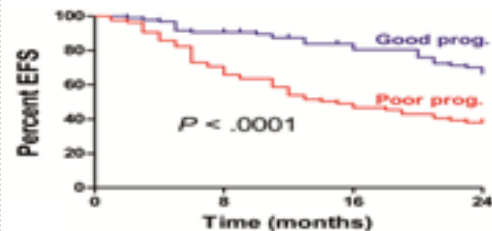
A hepatocellular carcinoma 5-gene score associated with survival of patients after liver resection

Disease specific survival  
Training cohort



Numbers at risk	0	20	40	60
Good prognosis	96	83	50	25
Poor prognosis	85	52	22	9

Early tumor recurrence-free survival  
Training cohort

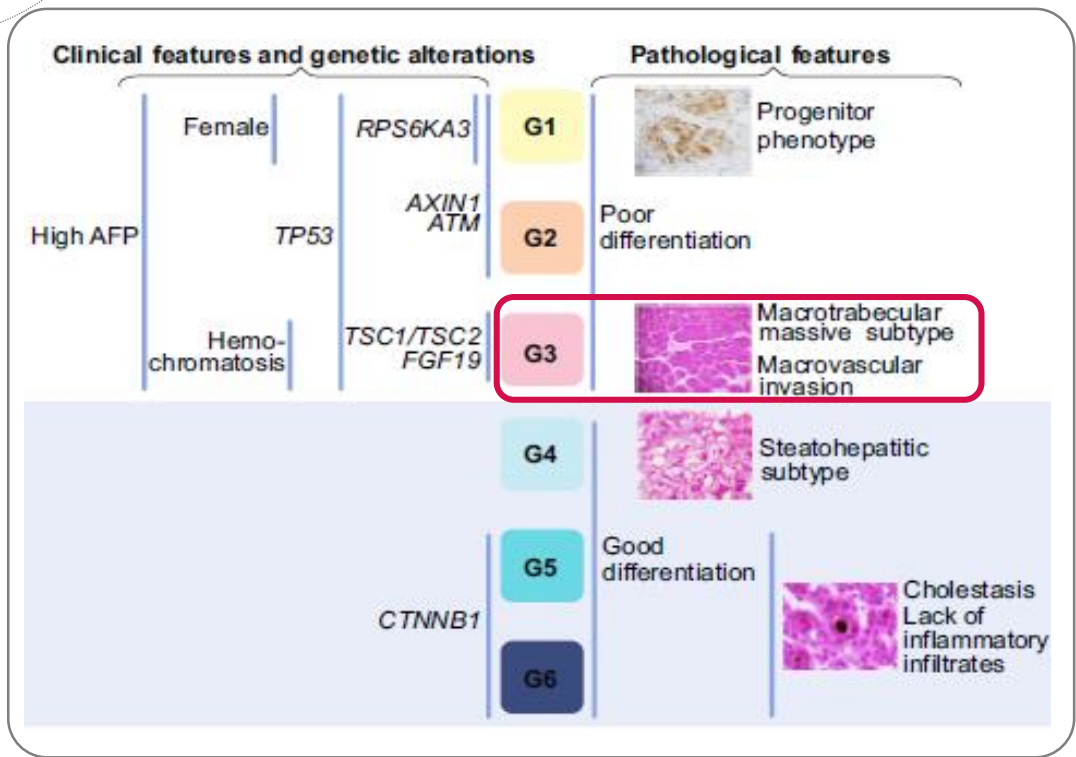


Numbers at risk	0	8	16	24
Good prognosis	96	85	74	60
Poor prognosis	85	60	40	29

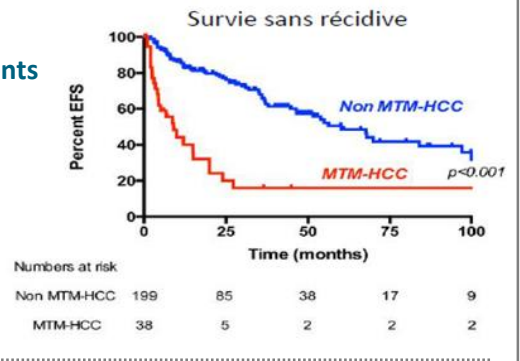
**TAF9 RAMP3 HN1 KRT19 RAN**

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)

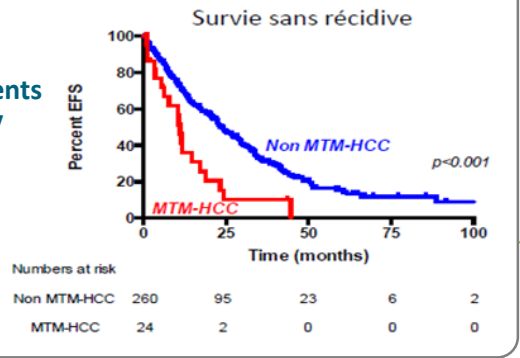
# Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification



237 HCC patients Treated by resection

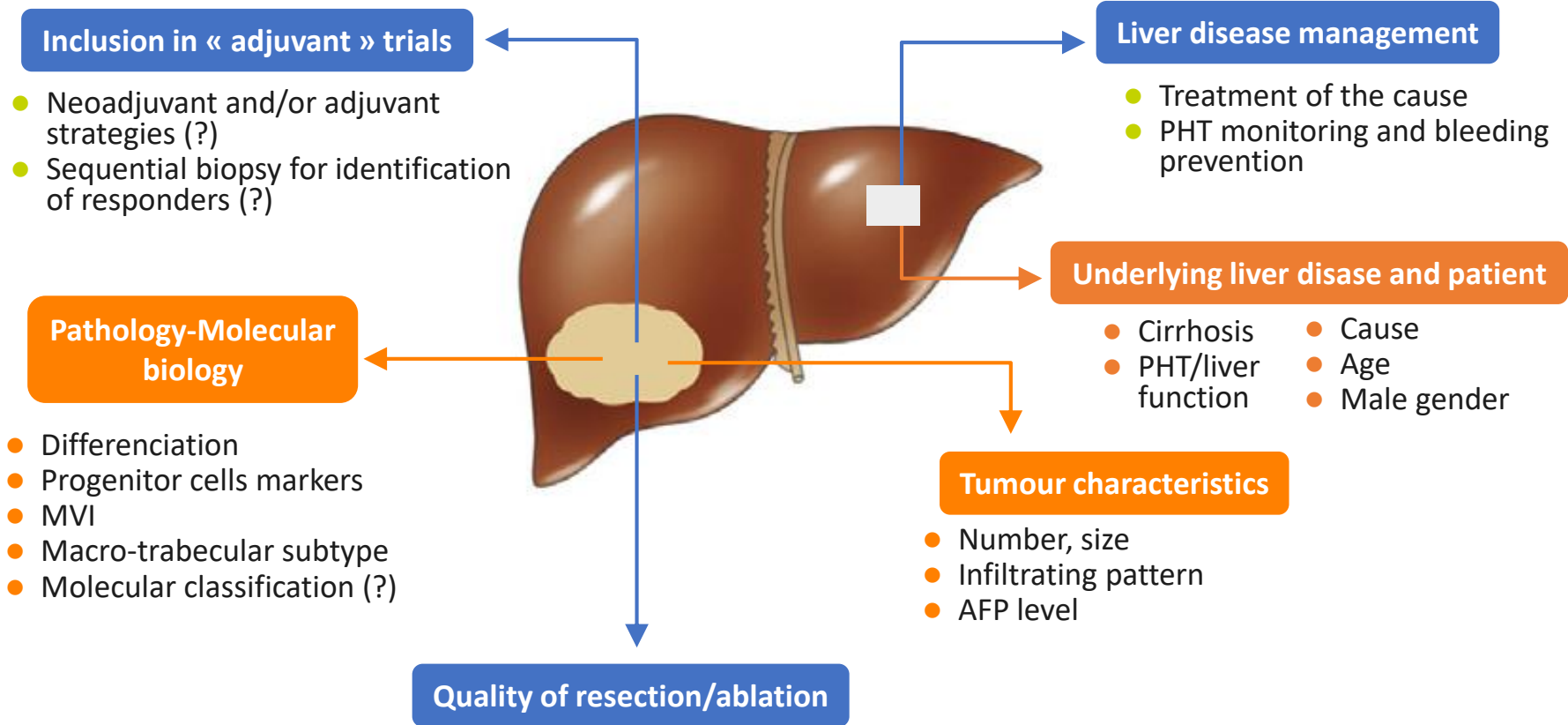


284 HCC patients Treated by ablation

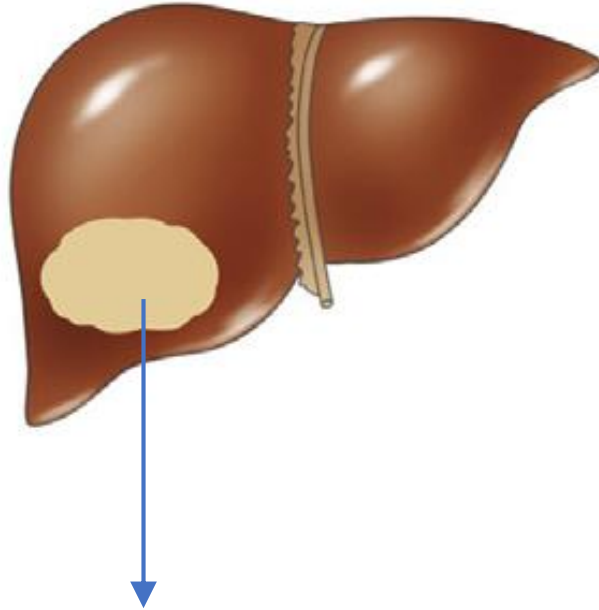




# Optimizing curative management of HCC



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Quality of resection/ablation

# Ablation or resection ?

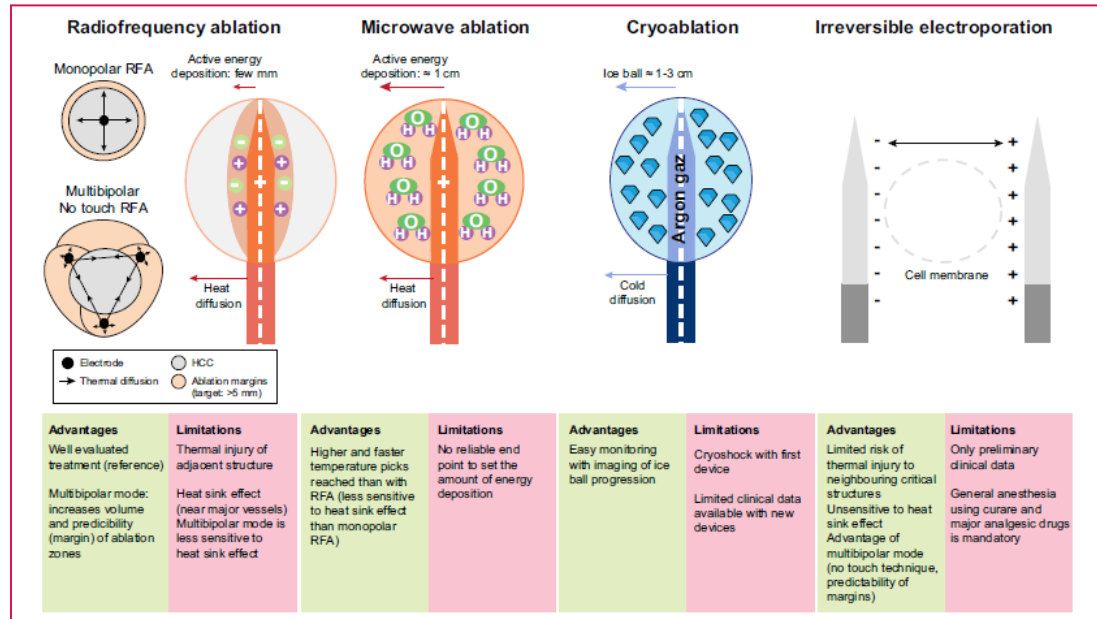
	Ablation	Resection
2 or 3 nodules	Distant	Same segment
Localization	Deep	Superficial
Liver function	Good <sup>a</sup>	<b>Excellent<sup>b</sup></b>
Portal Hypertension	Yes	<b>No</b>
Mortality	0.3%	1%
5-yrs survival	76% in patients eligible for resection	75%

*a Malades appartenant principalement à la classe A ou B de Child-Pugh*

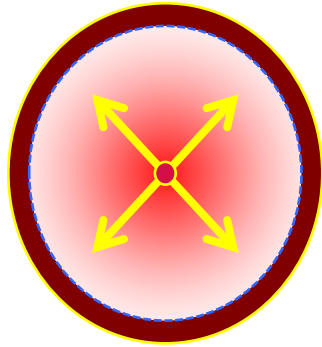
*b Malades appartenant principalement à la classe A de Child-Pugh, avec bilirubine normale et sans hypertension portale*

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

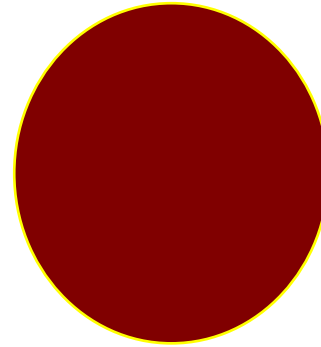
Jean-Charles Nault<sup>1,2,3,\*</sup>, Olivier Sutter<sup>4</sup>, Pierre Nahon<sup>1,2,3</sup>, Nathalie Ganne-Carrié<sup>1,2,3</sup>,  
Olivier Séror<sup>2,3,4,\*</sup>



# Principles for large ablations

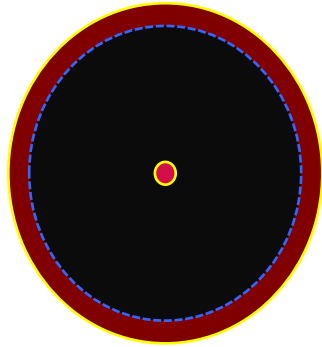


Monopolar RFA

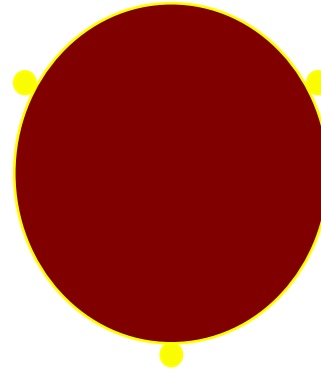


Multibipolar « no touch »

# Principles for large ablations

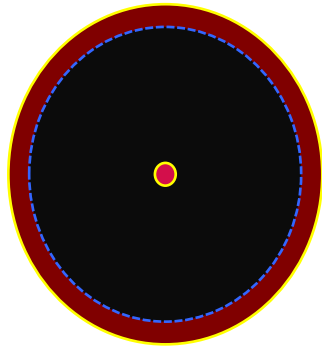


Monopolar RFA

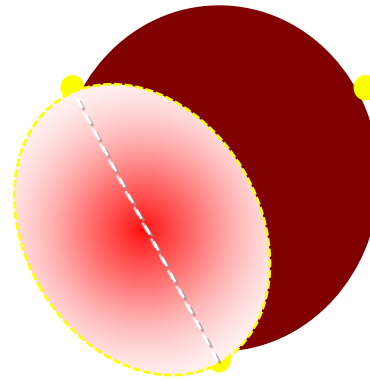


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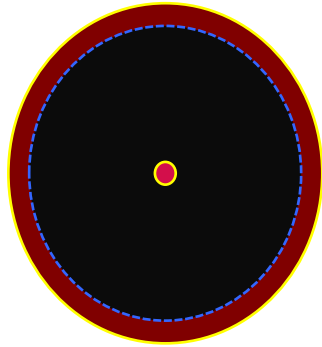


Monopolar RFA

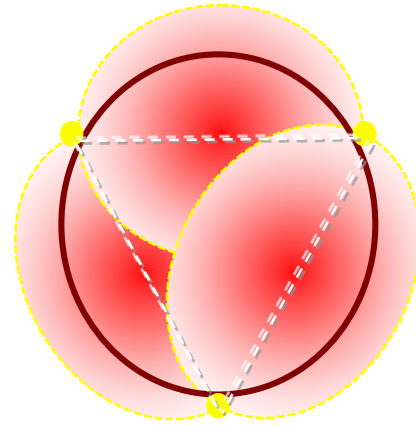


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# Principles for large ablations



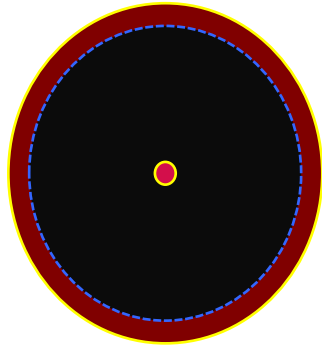
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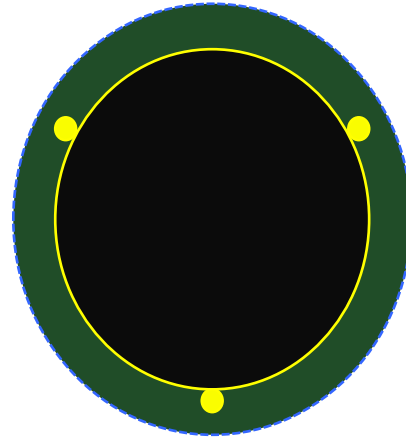
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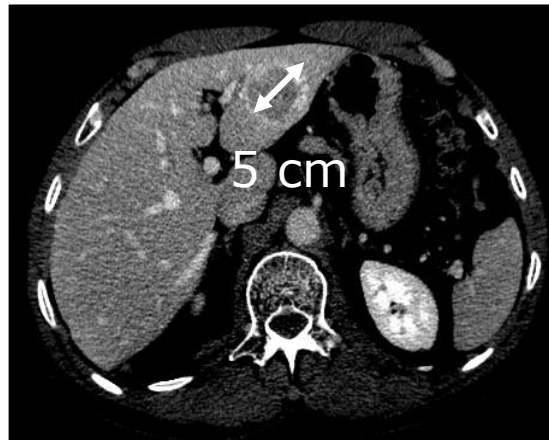
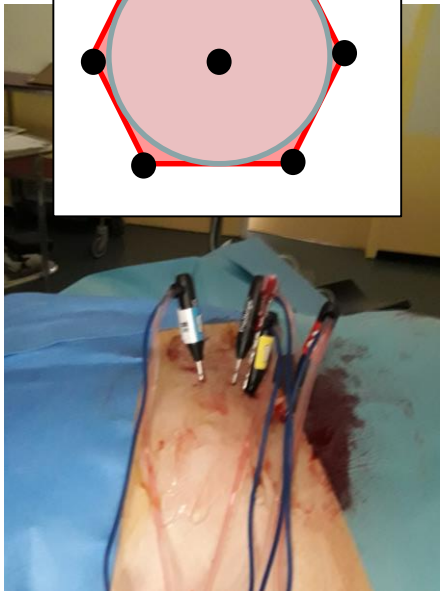
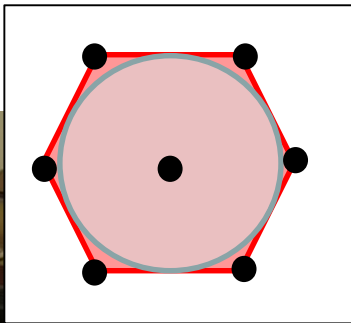
# Principles for large ablations



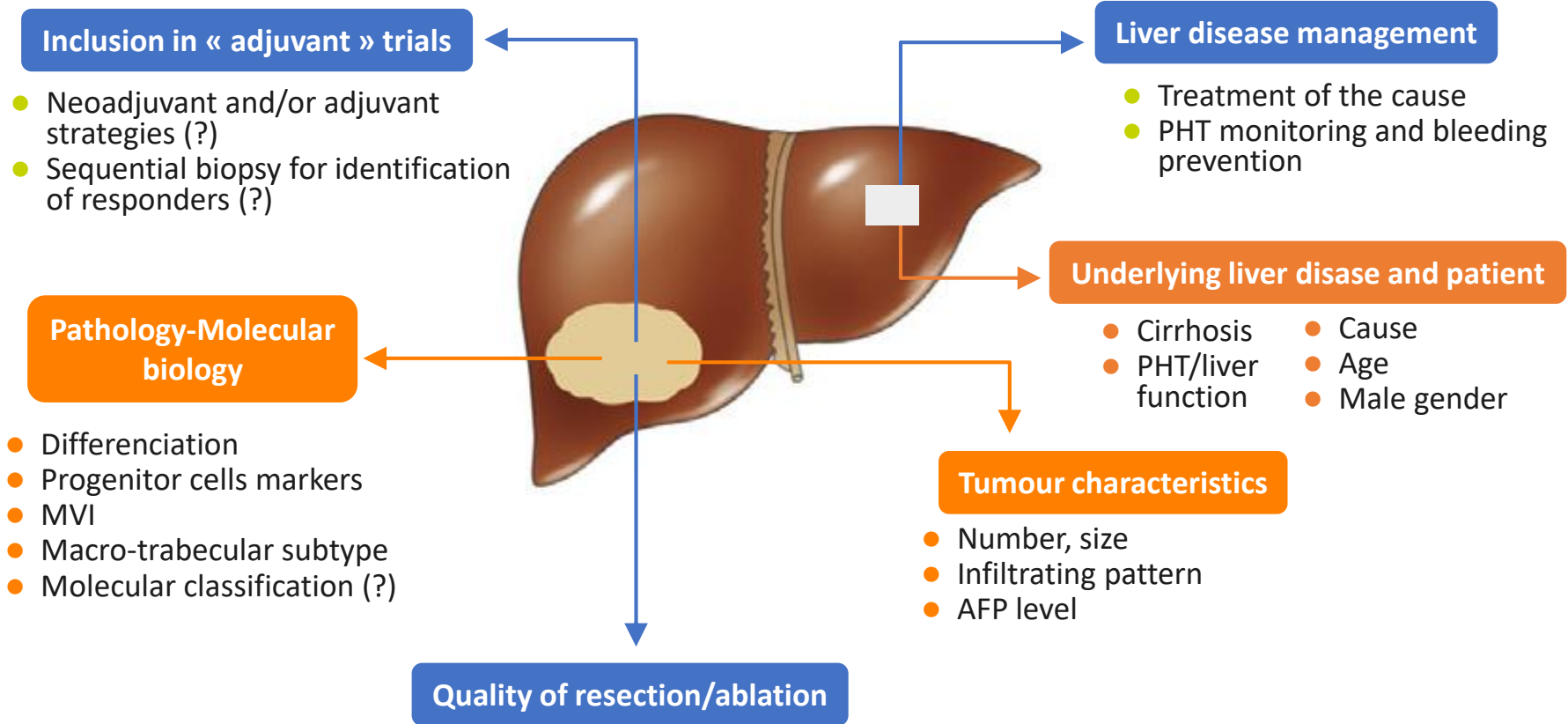
Monopolar RFA



Multibipolar « no touch »



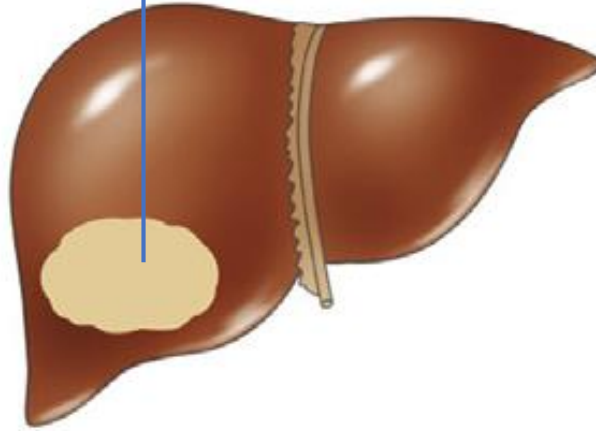
# Optimizing curative management of HCC

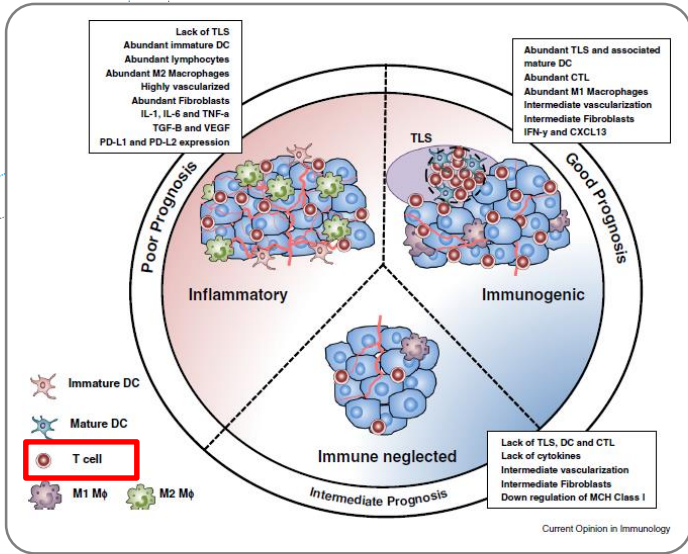


# Optimizing curative management of HCC

## Inclusion in « adjuvant » trials

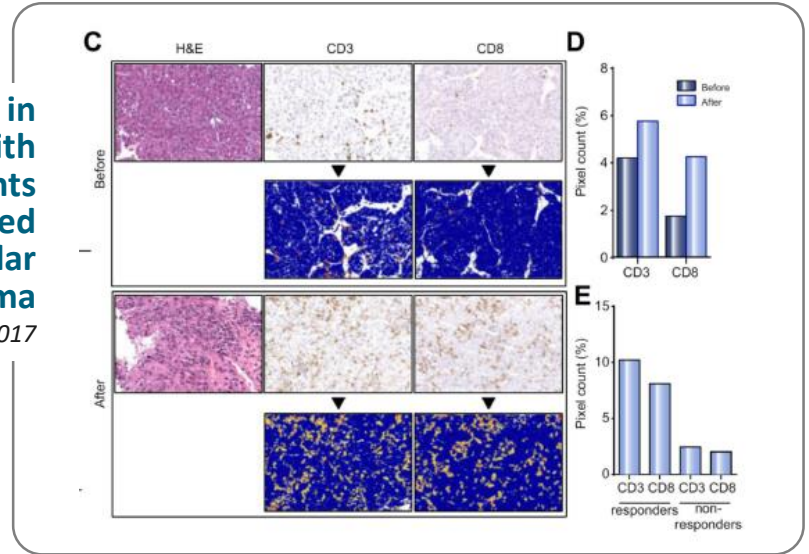
- Neoadjuvant and/or adjuvant strategies (?)
- Sequential biopsy for identification of responders (?)



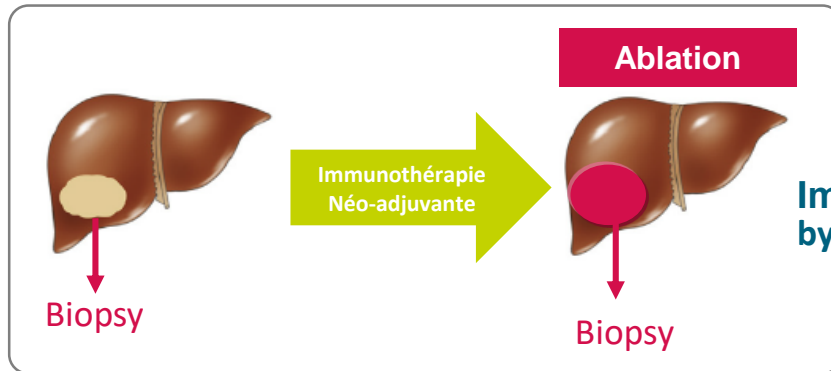


## Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma

Duffy AG, *J Hepatology* 2017



32 patients (tremelimumab and ablation at D36)



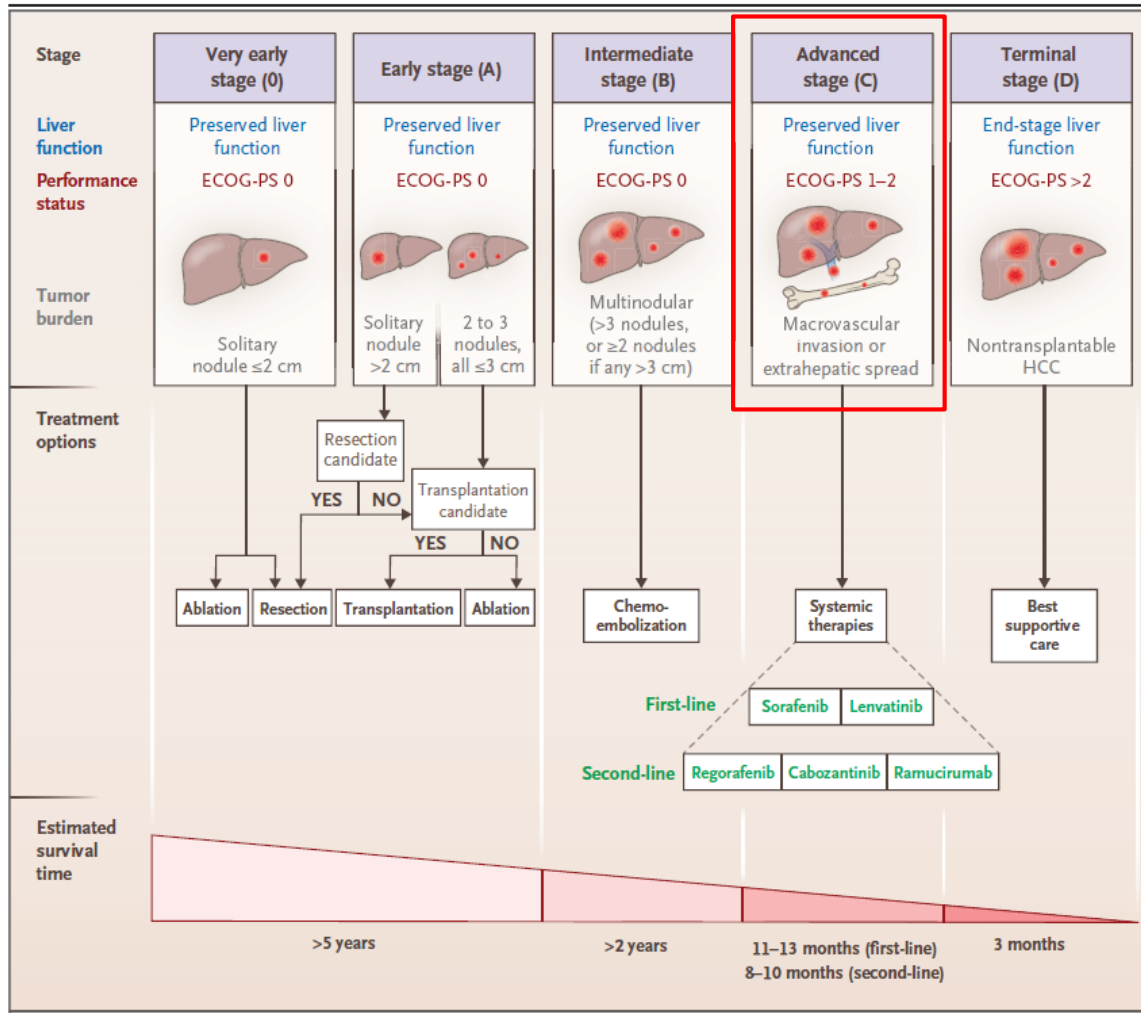
Immune stimulation induced by ablation and amplified by immunotherapy

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
EMERALD 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

# Optimization goals differ according to tumour burden



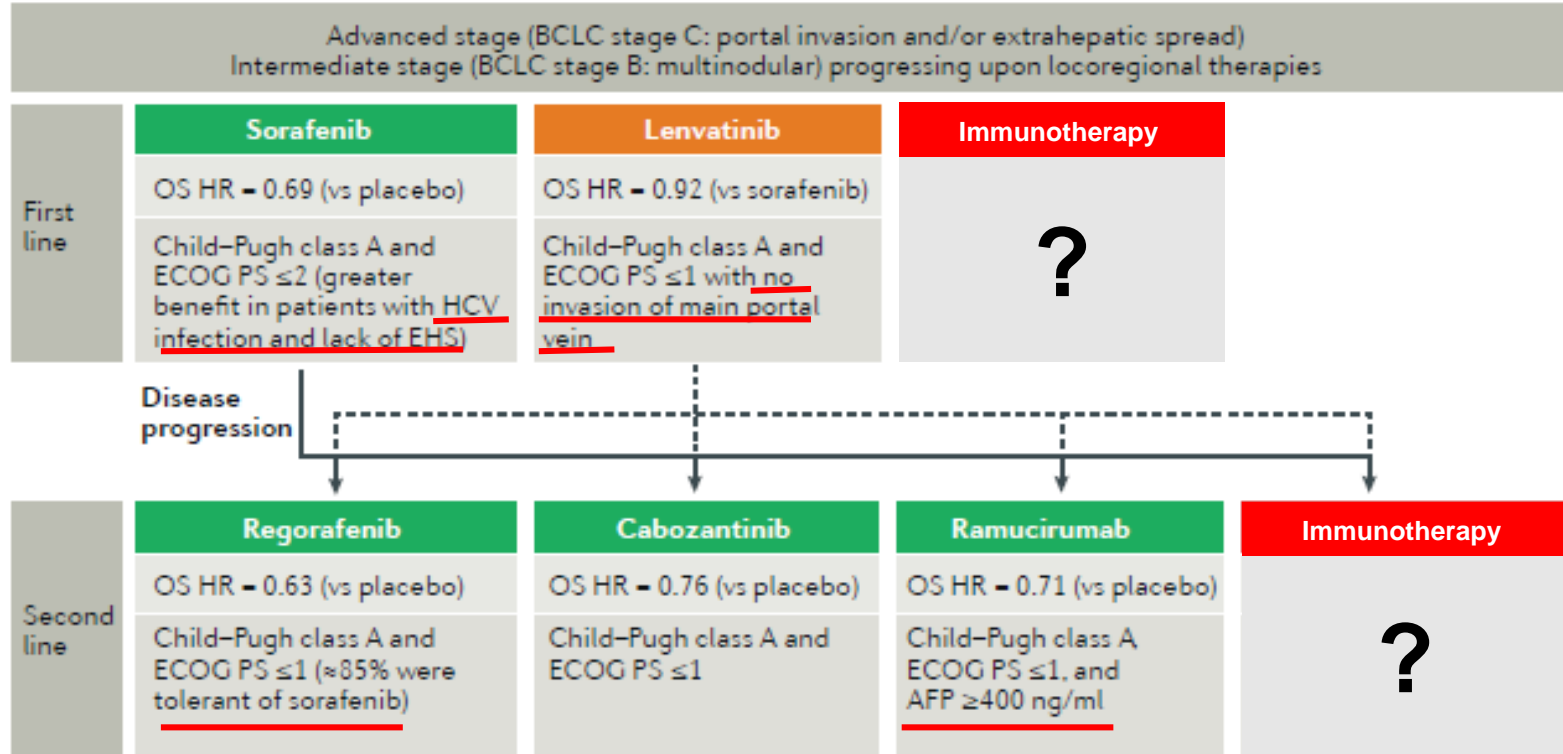


A broader therapeutic landscape with 5 approved systemic therapies

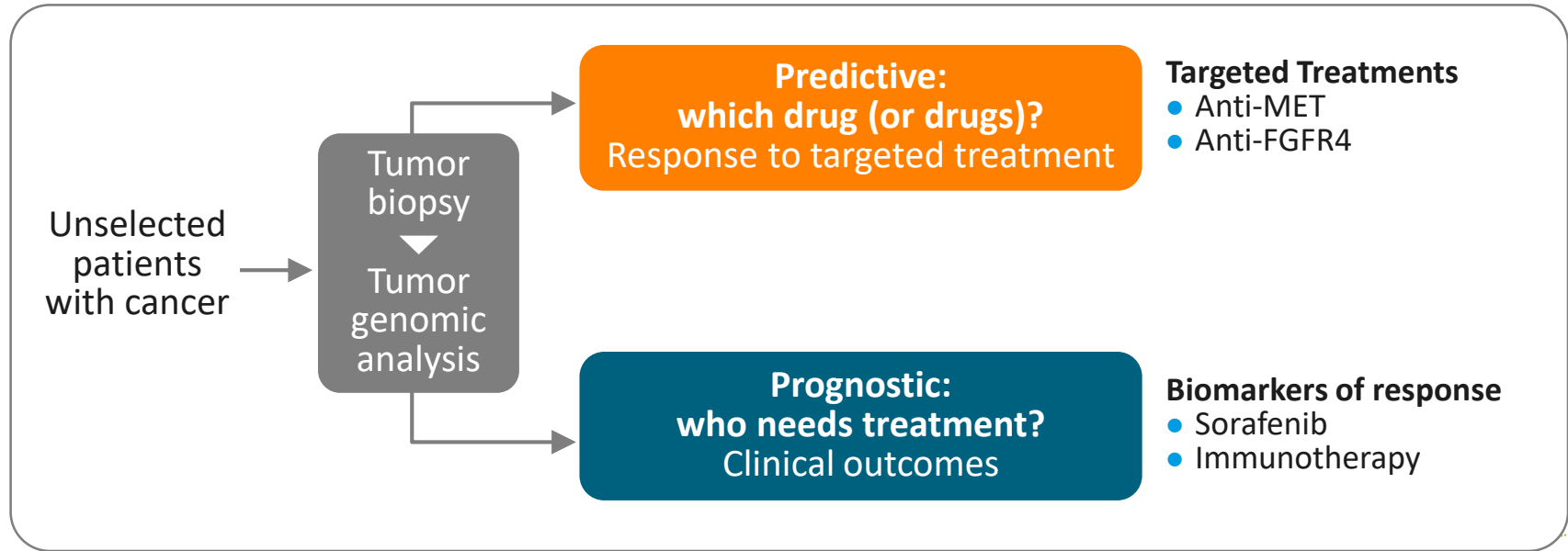
Villanueva A, NEJM 2019



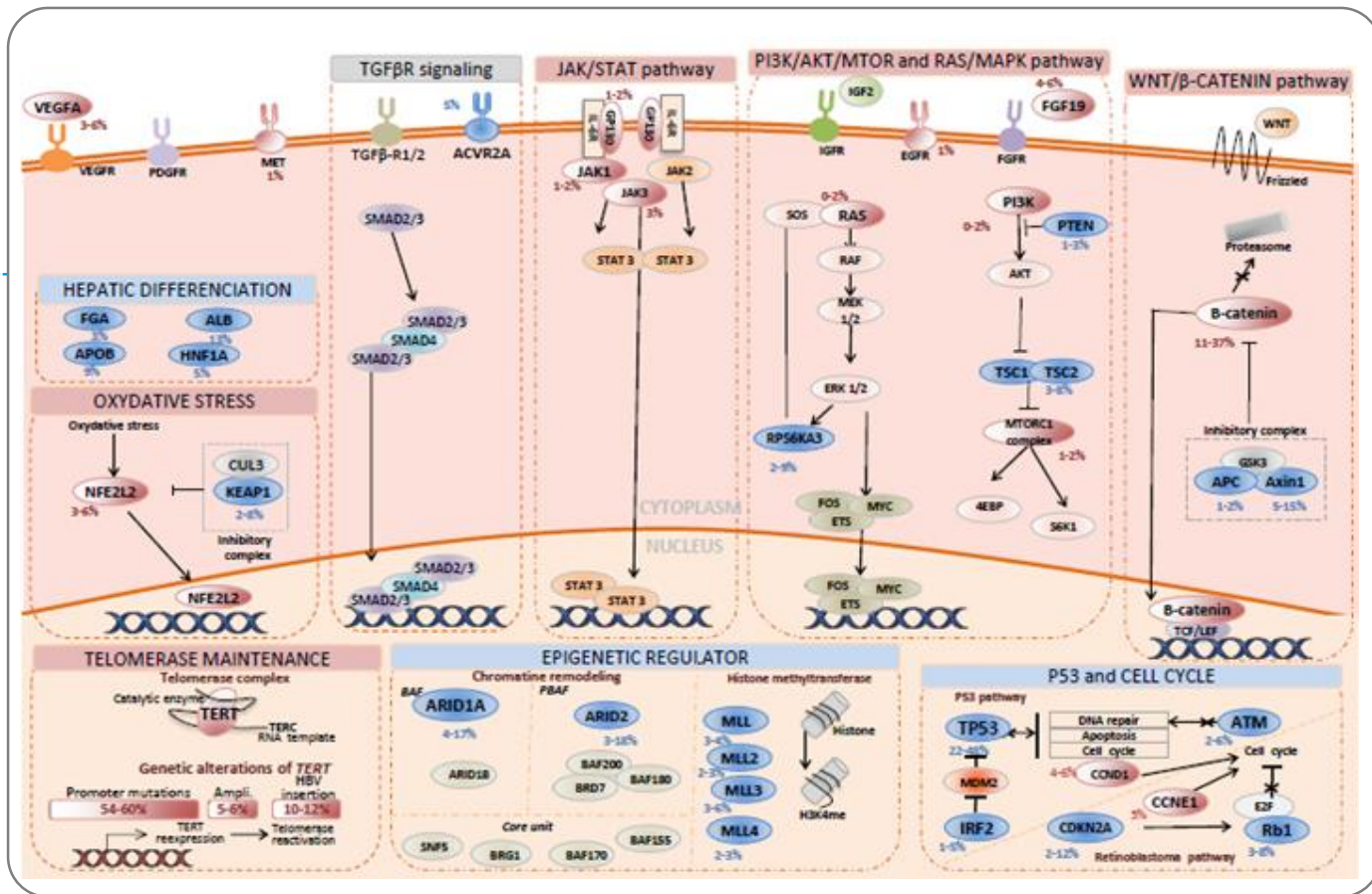
# How to choose in 2020?



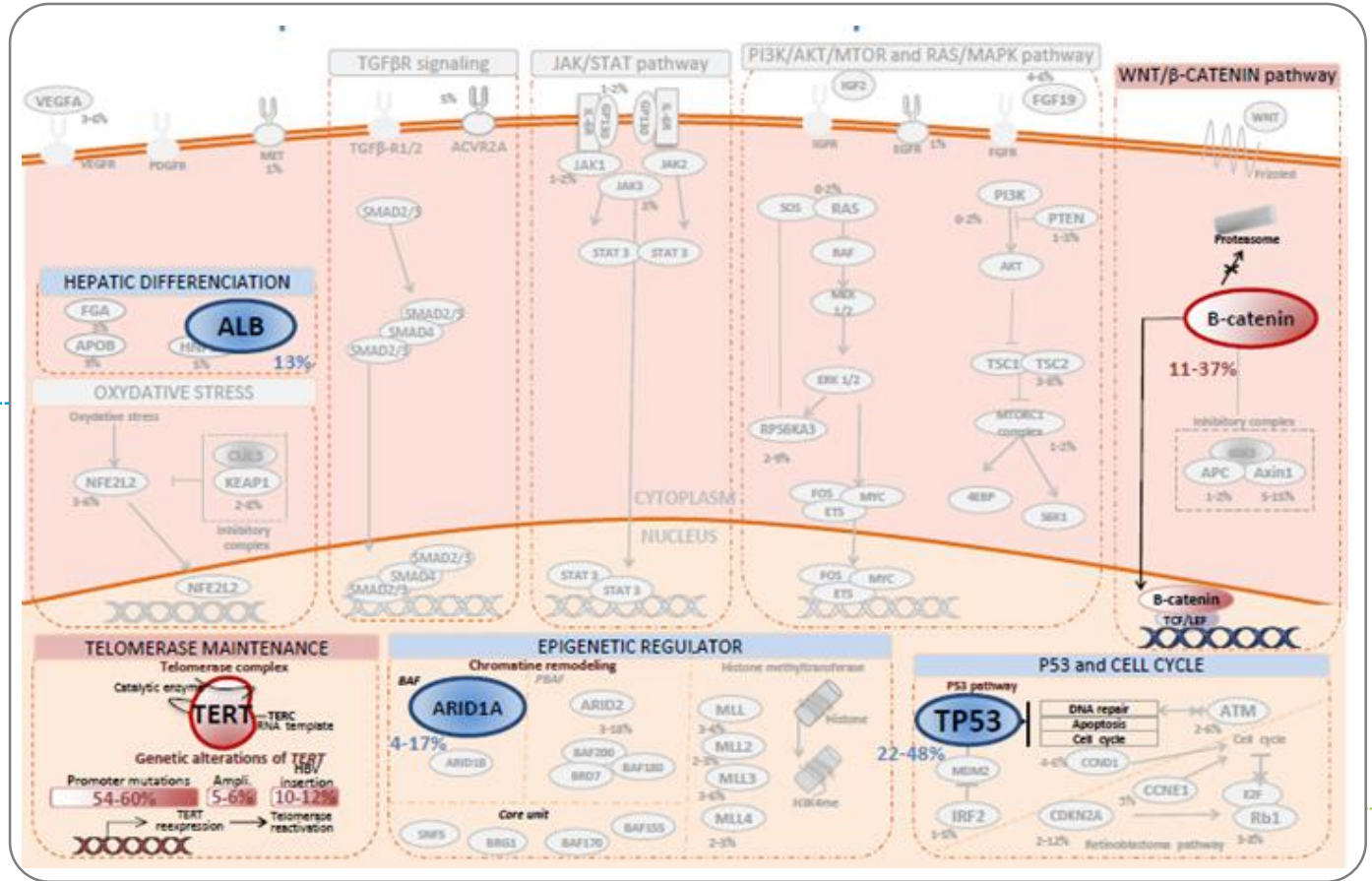
# ● Can we implement tumour genomics in decision making process?



# HCC genetic landscape



But most genetic mutations are not targetable...



...only 20-30% are.

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



134 CHC (127 patients)

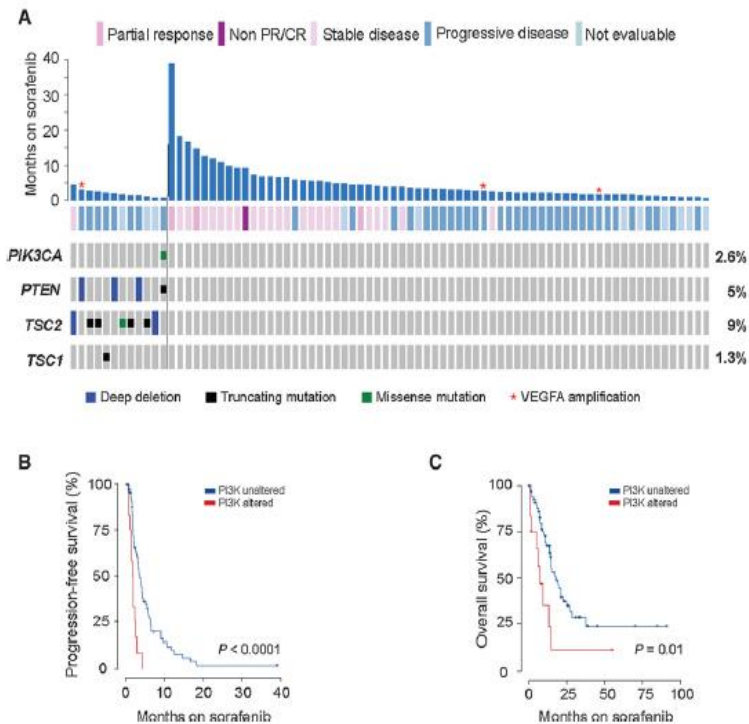
NGS (FFPE, 63% biopsies)

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

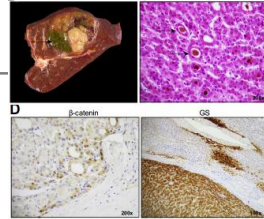
## Sorafenib



**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 PIK3-mTOR-activated tumors ( $N = 12$ ) versus non-PIK3-mTOR tumors ( $N = 67$ ), demonstrating shorter PFS in PIK3-mTOR-activated HCCs. **C**, Kaplan-Meier OS on first-line sorafenib therapy for patients with PIK3-mTOR-activated tumors ( $N = 12$ ) versus non-PIK3-mTOR tumors ( $N = 67$ ), demonstrating a shorter OS in PIK3-mTOR-activated HCCs.

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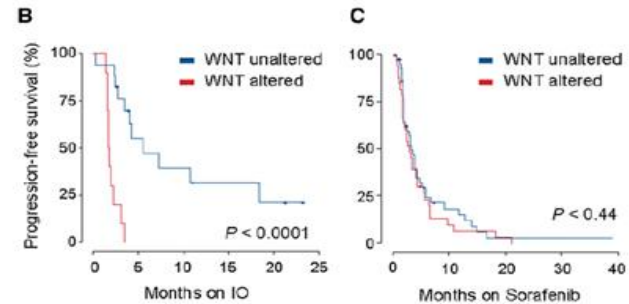
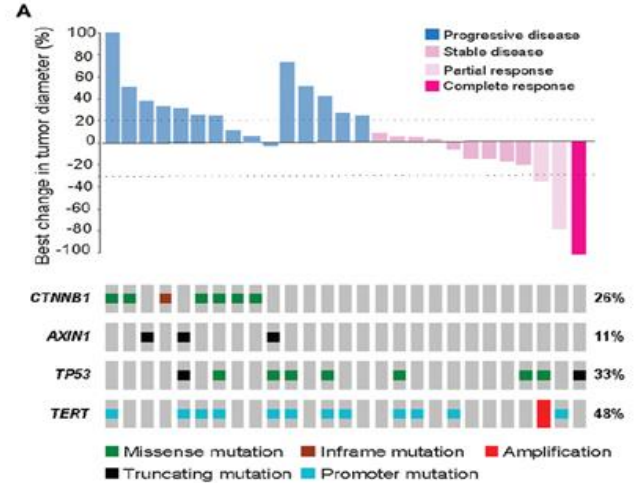
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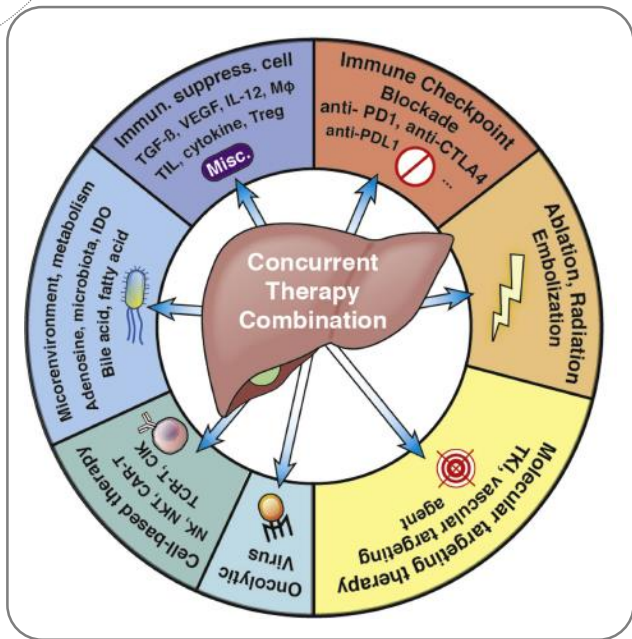
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Immunotherapy, N (%)	
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+ Anti-CTLA-4	1
+ Anti-LAG3	2
+ Anti-KIR	2

## Immunotherapy



# 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 biomarkers/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**