Advances in percutaneous ablation and systemic therapies for hepatocellular carcinoma

Paris Hepatology Congress 2019

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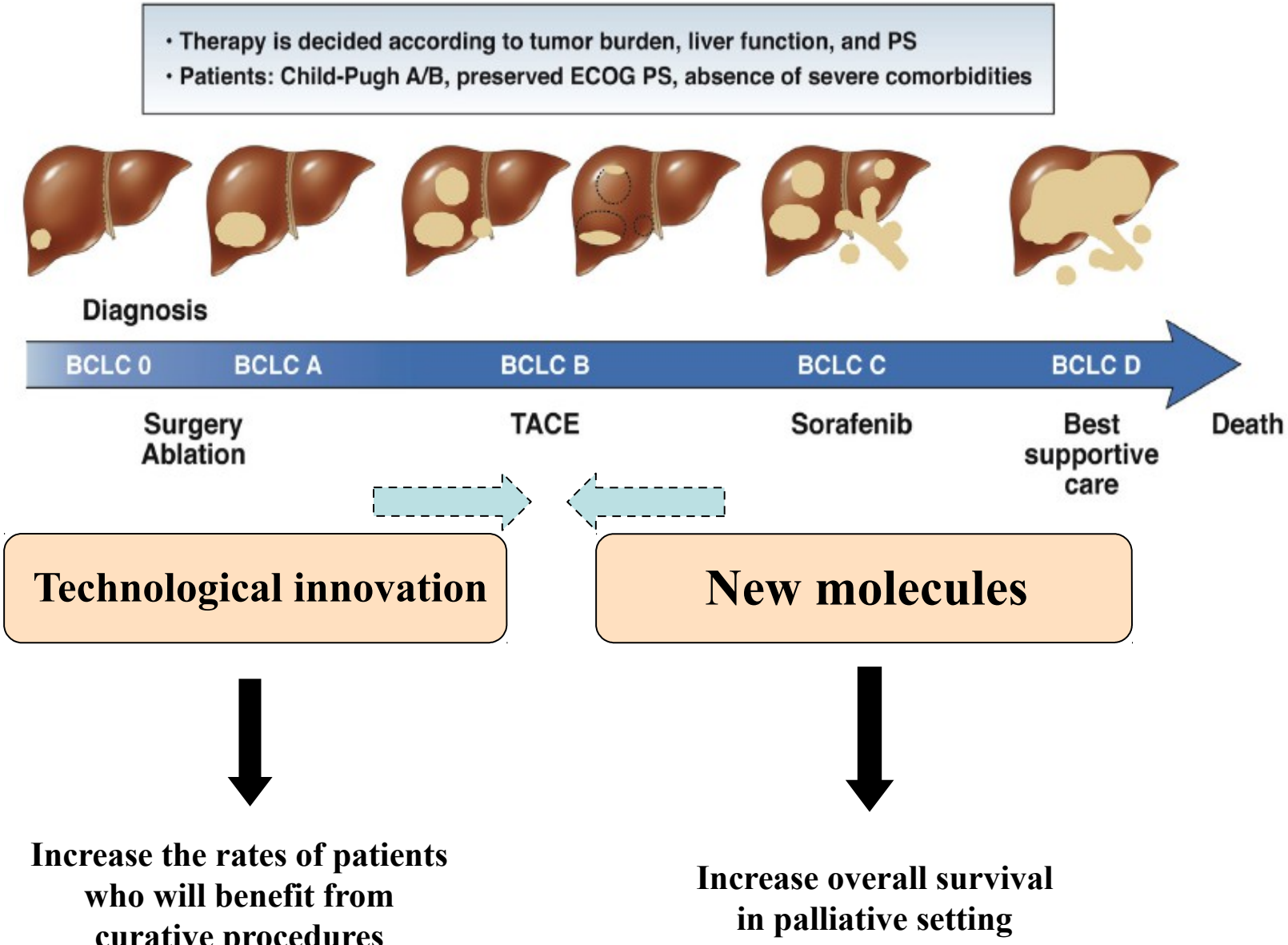
INSERM 1162 - Paris 5
Génomique fonctionnelle des tumeurs solides

Conflicts of interest

- Speaker for Abbvie, Bayer, BMS, Gilead, Ipsen
- Advisory board for Abbvie, Astra Zeneca, Bayer, BMS, Ipsen

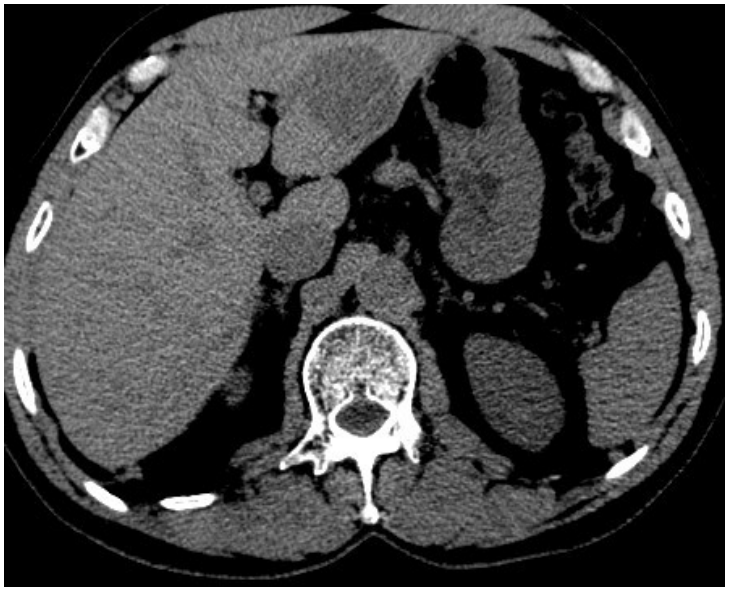


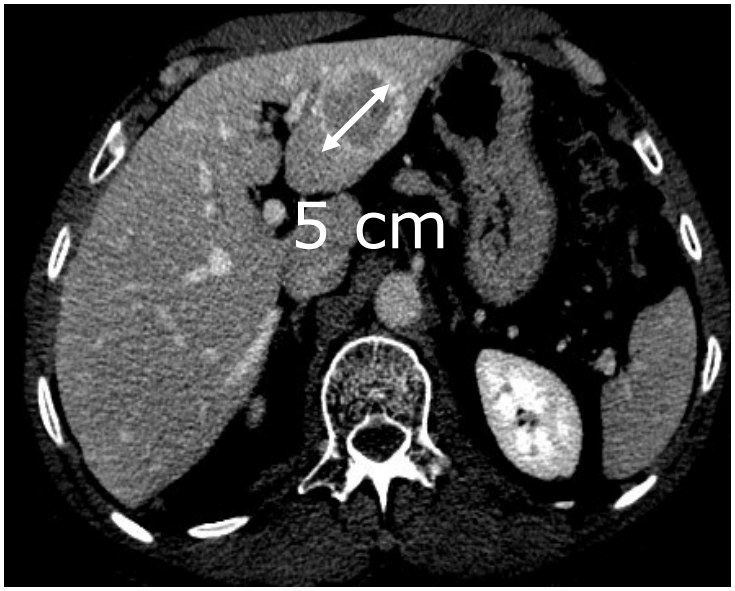
Bruix et al, Gastroenterology 2016

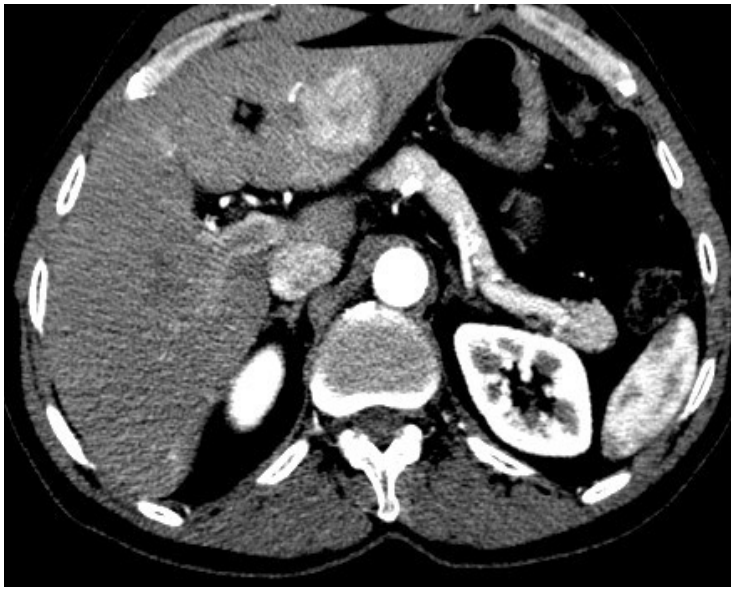
First case

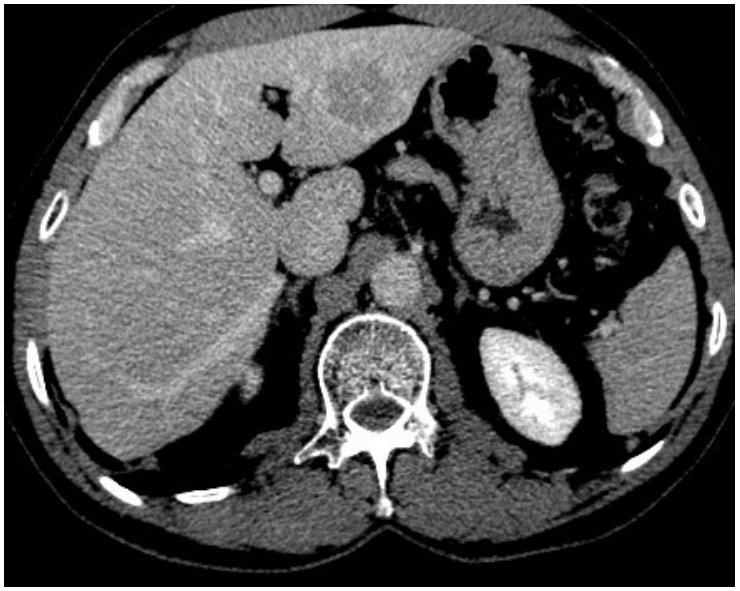
- 71 years old male
- Child-Pugh A6 HBV related cirrhosis (treated)
- Grade II esophageal varices
- Platelets count: 98 000 / mm3
- Bilirubin: 9 mg/L
- Albumin: 34 g/L
- Prothrombin time: 77%
- Liver stiffness: 22 Kpa
- Alpha-fetoprotein: 478 ng/ml
- PS 0, ECOG 0

Pretherapeutic imaging









Which treatment?

1. Transplantation
2. Resection
3. Ablation
4. TACE
5. Other

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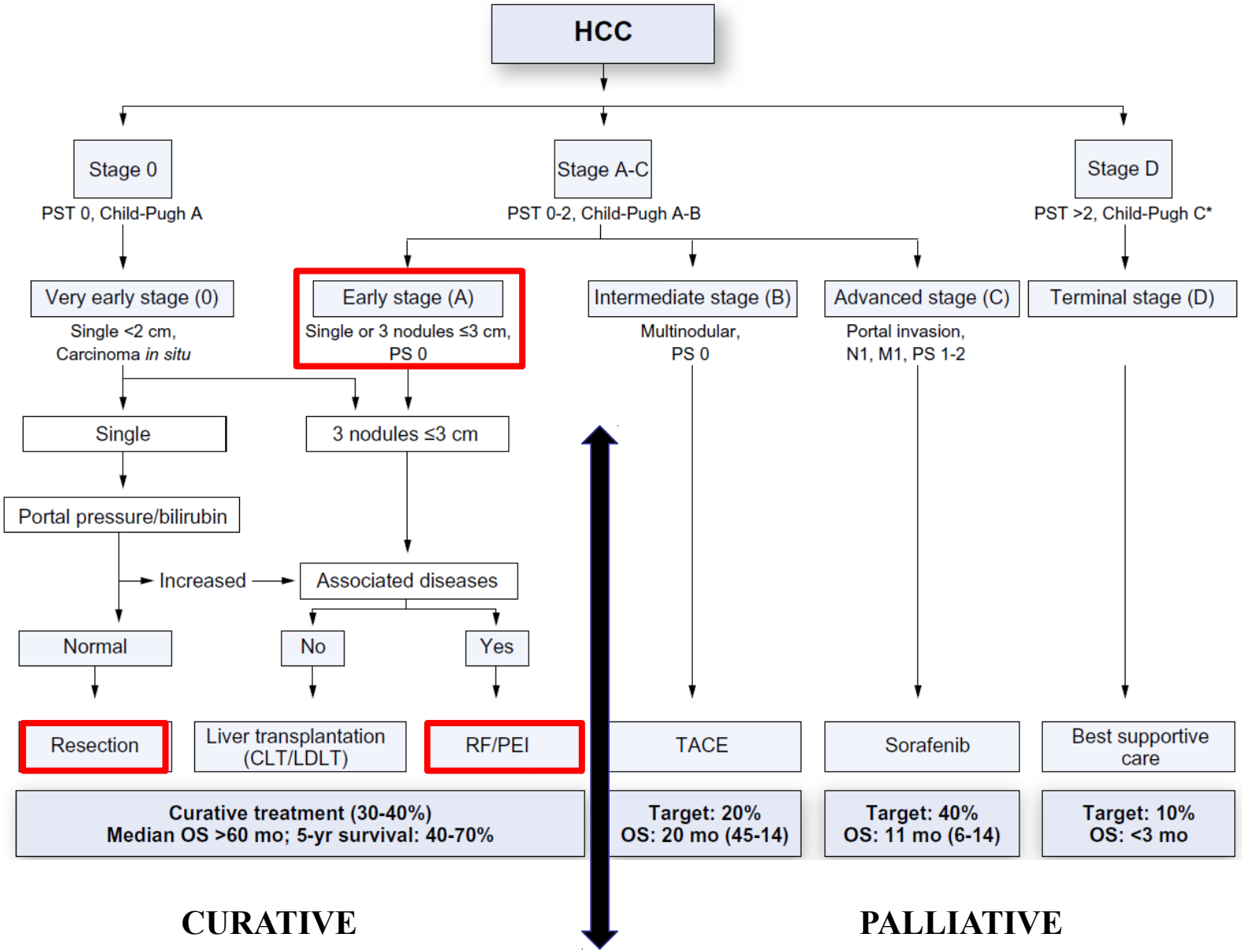
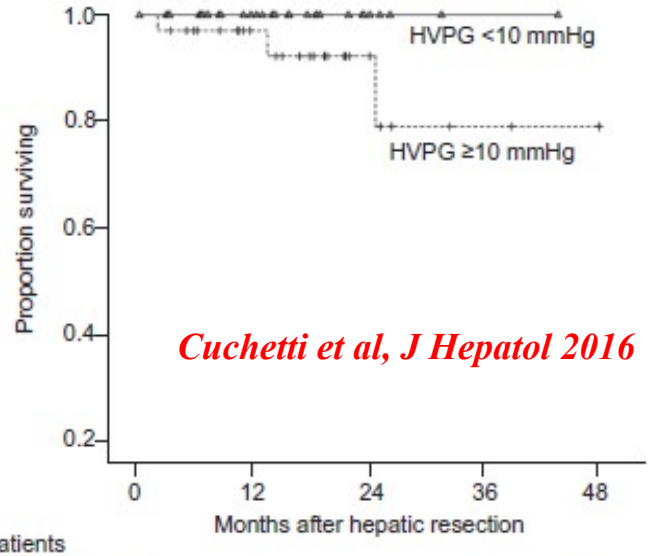
BCLC staging



Surgical Resection of Hepatocellular Carcinoma in Cirrhotic Patients: Prognostic Value of Preoperative Portal Pressure

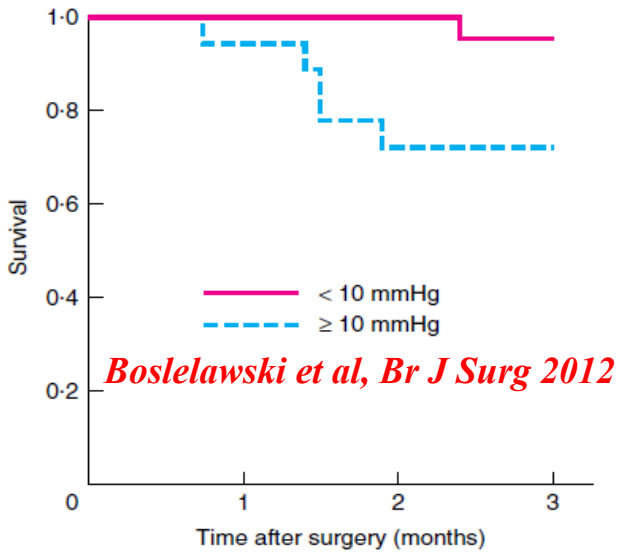
Gastroenterology 2006

Conclusions: Cirrhotics with increased portal pressure are at high risk of hepatic decompensation after resection of hepatocellular carcinoma. Surgical resection should therefore be restricted to patients without portal hypertension.



Cuchetti et al, J Hepatol 2016

At risk patients					
HVPG <10 mmHg	36	21	5	2	0
HVPG ≥10 mmHg	34	22	8	3	2



Boslelawski et al, Br J Surg 2012

No. at risk				
HVPG < 10 mmHg	22	22	22	21
HVPG ≥ 10 mmHg	18	17	13	13

Portal hypertension (CSPH): Resection?

1108 patients (386 with *vs* 722 without HP) in **8** studies

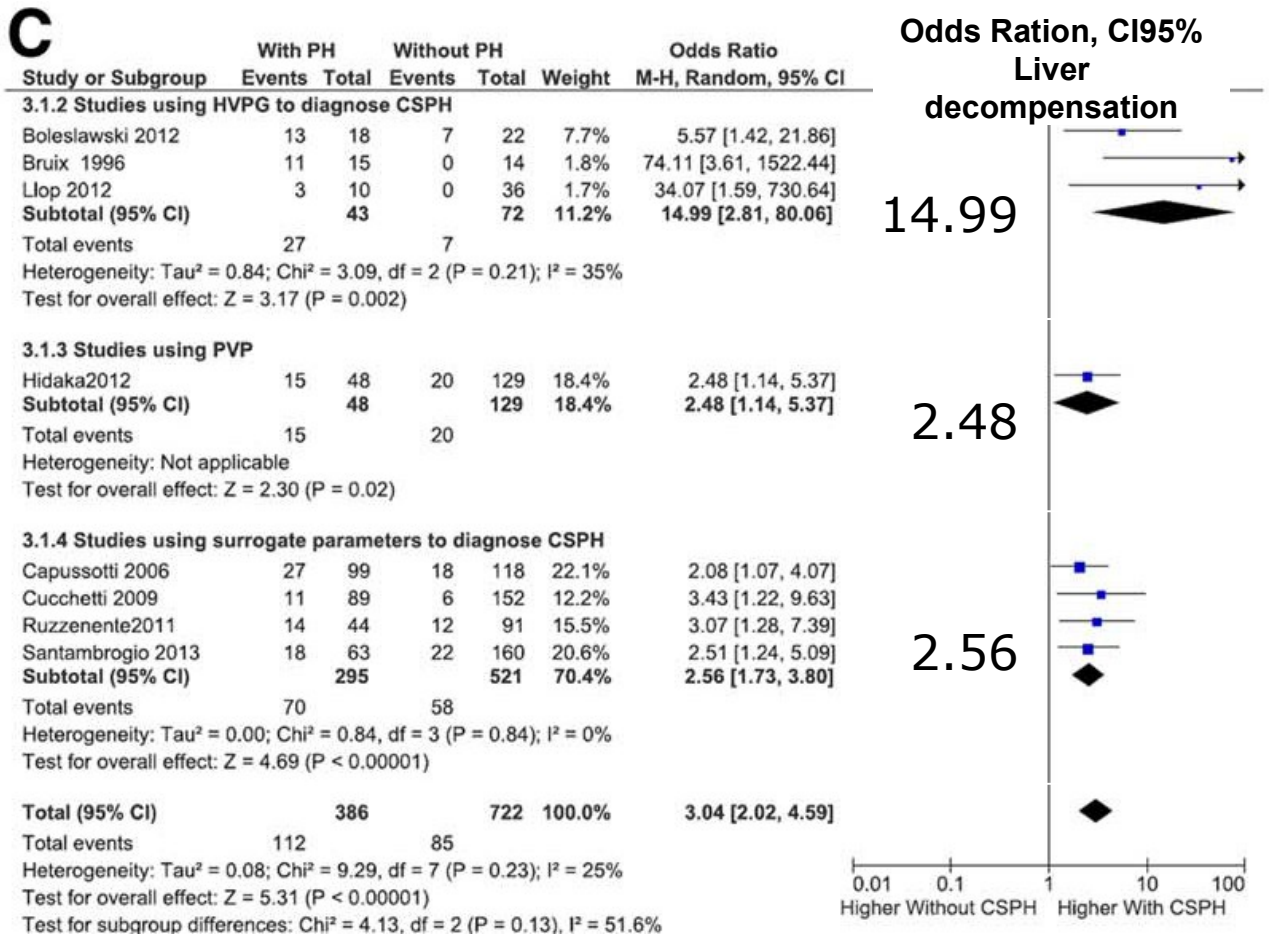
Berzigotti, Bruix, Hepatology 2015

HVPG:
≥ 10 mm Hg

PVP:
≥ 20 cm H2O

Surrogate:
GEV or
Plt.< 105/ml or
Spleen > 12 cm

Pooled

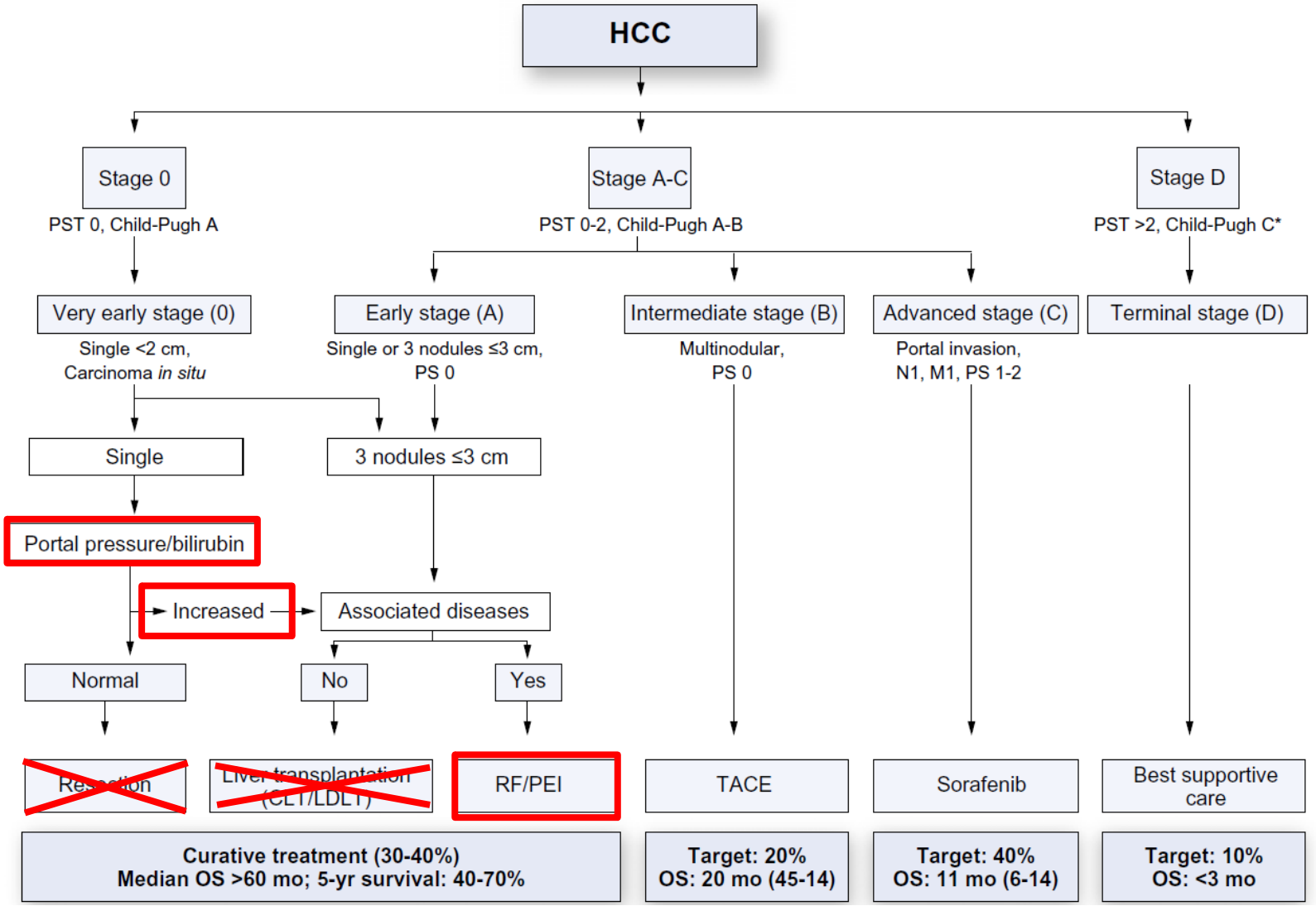


Ablation or resection ?

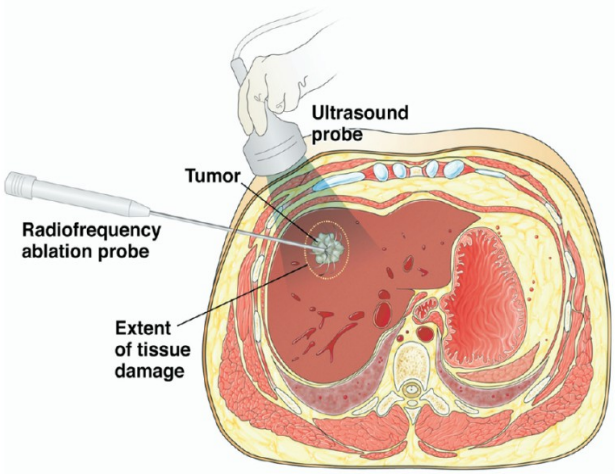
	Ablation	Resection
2 or 3 nodules	Distant	Same segment
Localization	Deep	Superficial
Liver function	**Gooda**	Excellentb
Portal Hypertension	**Yes**	No
Mortality	0.3%	1%
5-yrs survival	76% in patients eligible for resection	75%

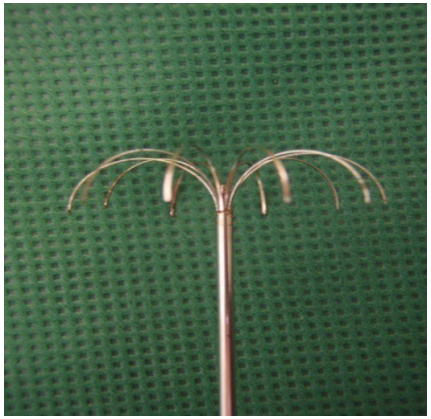
a Malades appartenant principalement à la classe A ou B de Child-Pugh
b Malades appartenant principalement à la classe A de Child-Pugh.avec bilirubine normale et sans hypertension portale

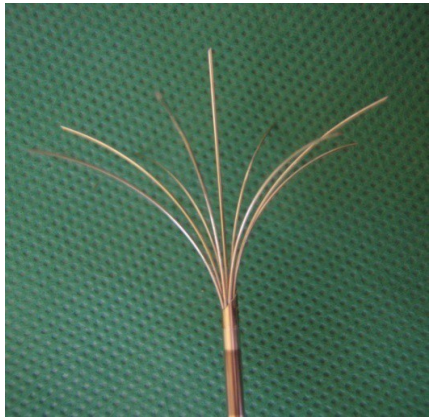
BCLC (AASLD/EASLD)



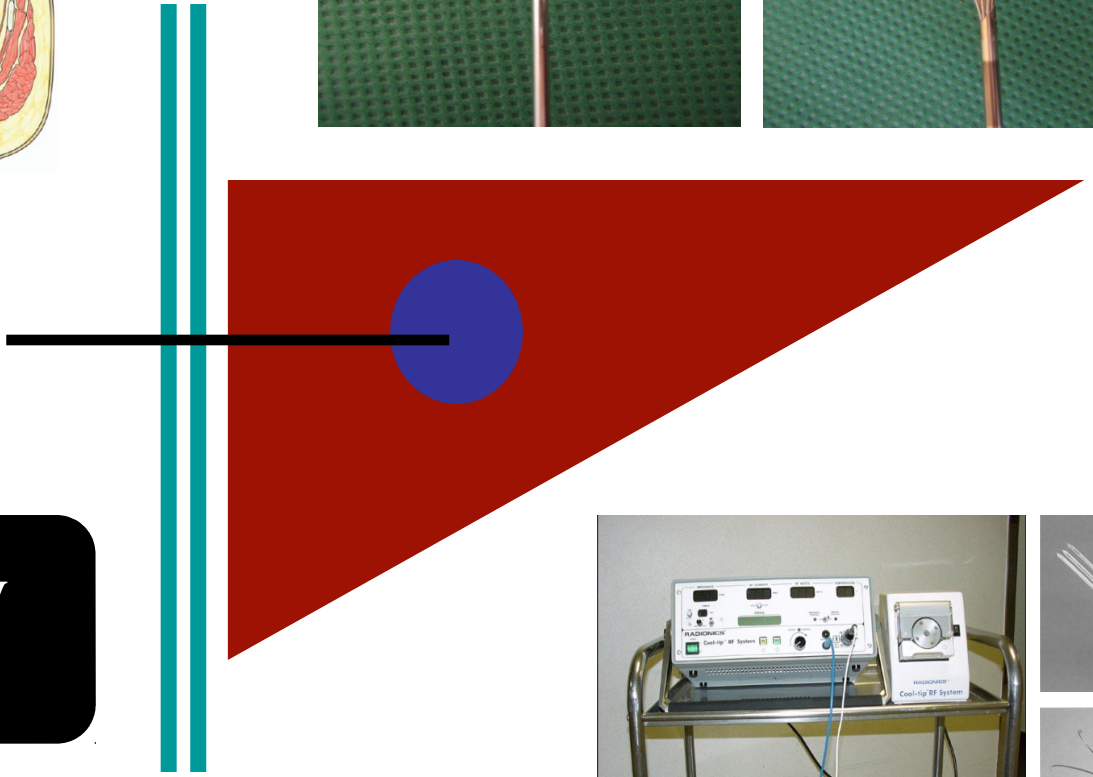
Percutanous ablation



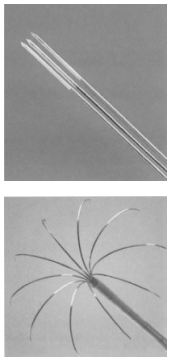




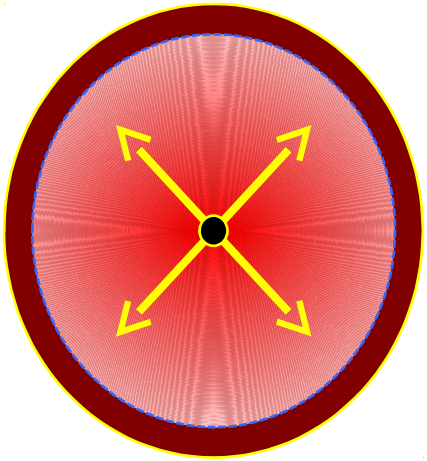
US control



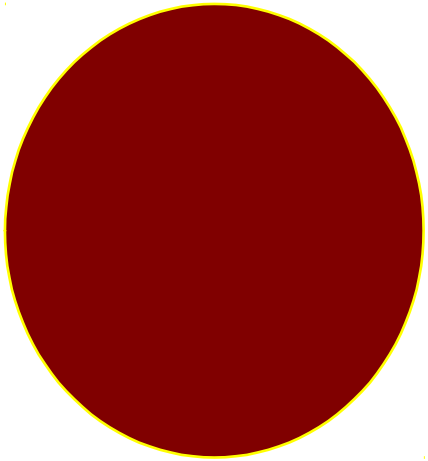
Radiofrequency ablation



Principles for large ablations

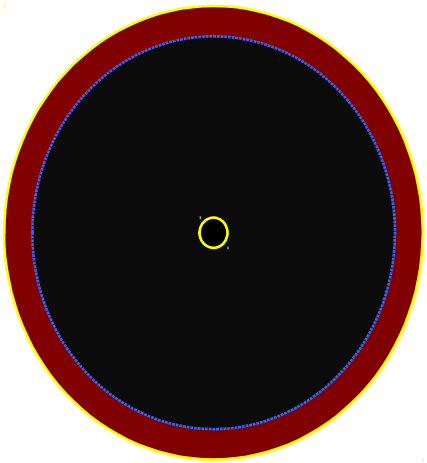


Monopolar RFA

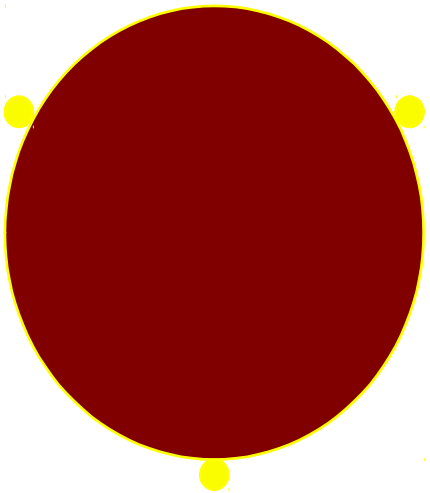


Multibipolar « no touch »

Principles for large ablations



Monopolar RFA



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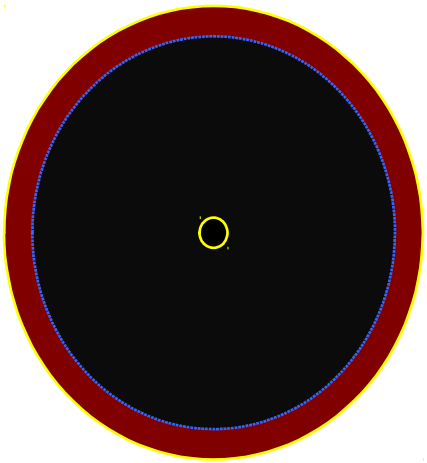
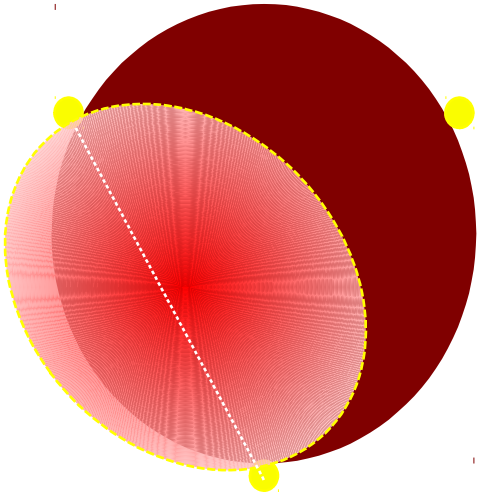


Monopolar RFA



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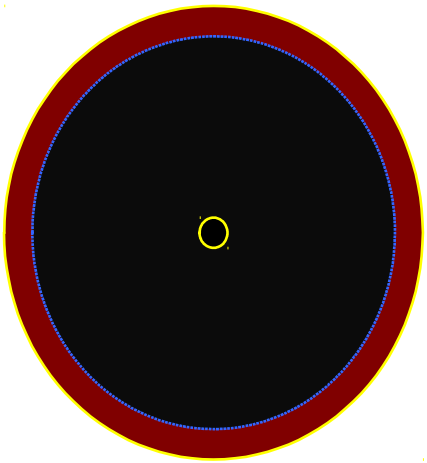
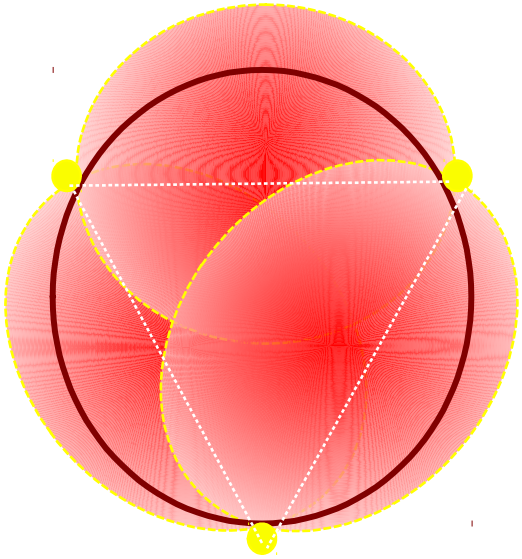


Monopolar RFA



Multibipolar « no touch »

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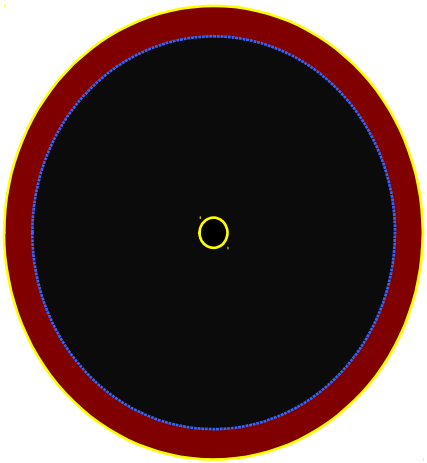
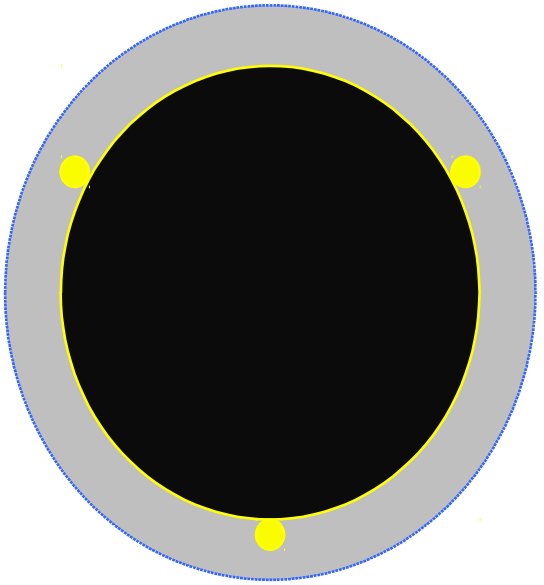


Monopolar RFA



Multibipolar « no touch »

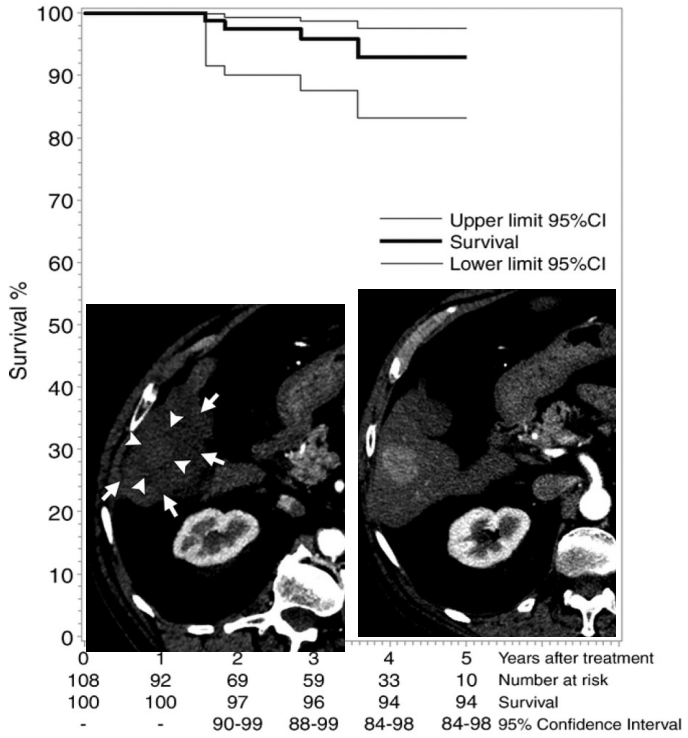
No touch multibipolar RFA for HCC

Radiology

Olivier Seror, MD, PhD
Gisèle N'Kontchou, MD
Jean-Charles Nault, MD
Yacine Rabahi, MD
Pierre Nahon, MD, PhD
Nathalie Ganne-Carrié, MD, PhD
Véronique Grando, MD
Nora Zentar, MD
Michel Beaugrand, MD
Jean-Claude Trinchet, MD, PhD
Abou Diallo, MD
Nicolas Sellier, MD

Radiology: Volume 280: Number 2—August 2016

Hepatocellular Carcinoma within Milan Criteria: No-Touch Multibipolar Radiofrequency Ablation for Treatment—Long-term Results[1]



a.

Large (≥5.0-cm) HCCs: Multipolar RF Ablation with Three Internally Cooled Bipolar Electrodes—Initial Experience in 26 Patients[1]

Seror et al, Radiology 2012

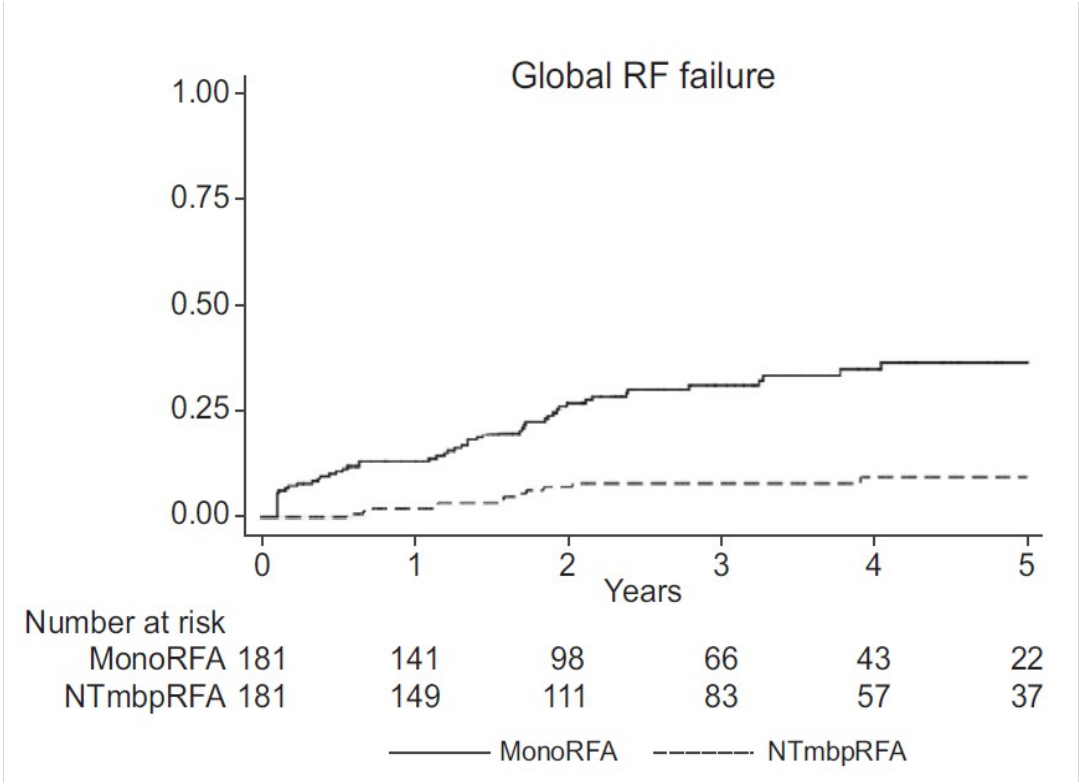
Research Article

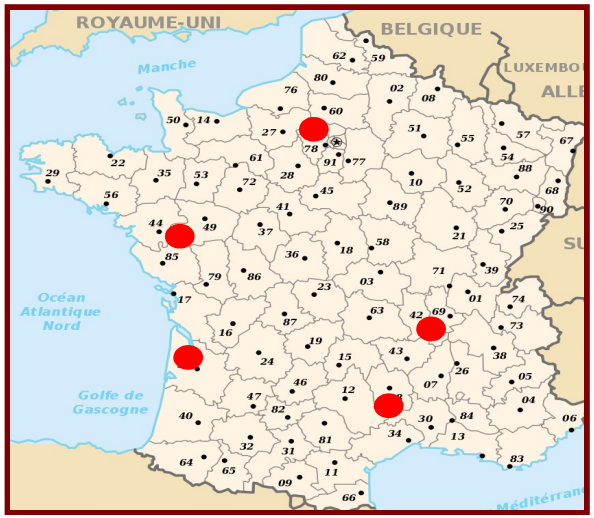
EASL JOURNAL OF HEPATOLOGY

http://dx.doi.org/10.1016/j.jhep.2016.07.010

Comparison of no-touch multi-bipolar *vs.* monopolar radiofrequency ablation for small HCC

Arnaud Hocquelet[1,2,*], Christophe Aubé[3,4], Agnès Rode[5], Victoire Cartier[3], Olivier Sutter[6,7], Anne Frederique Manichon[5], Jérome Boursier[4,8], Gisèle N'kontchou[9], Philippe Merle[10], Jean-Frédéric Blanc[11], Hervé Trillaud[1,2], Olivier Seror[6,7,12]

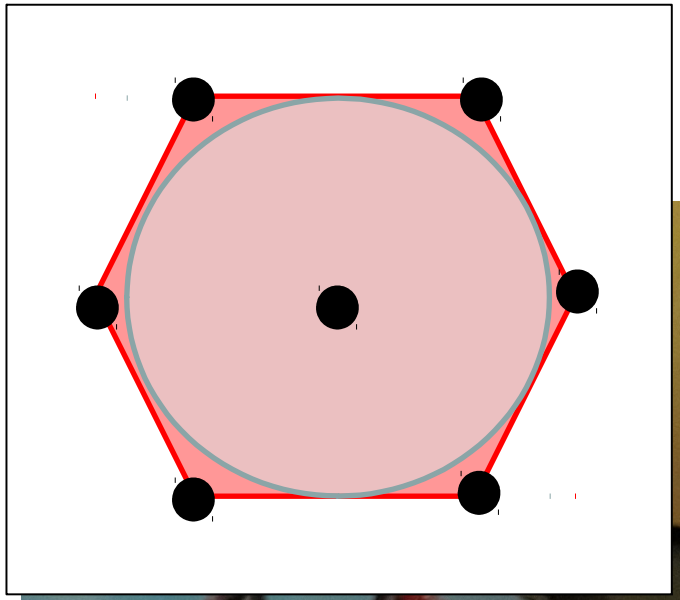




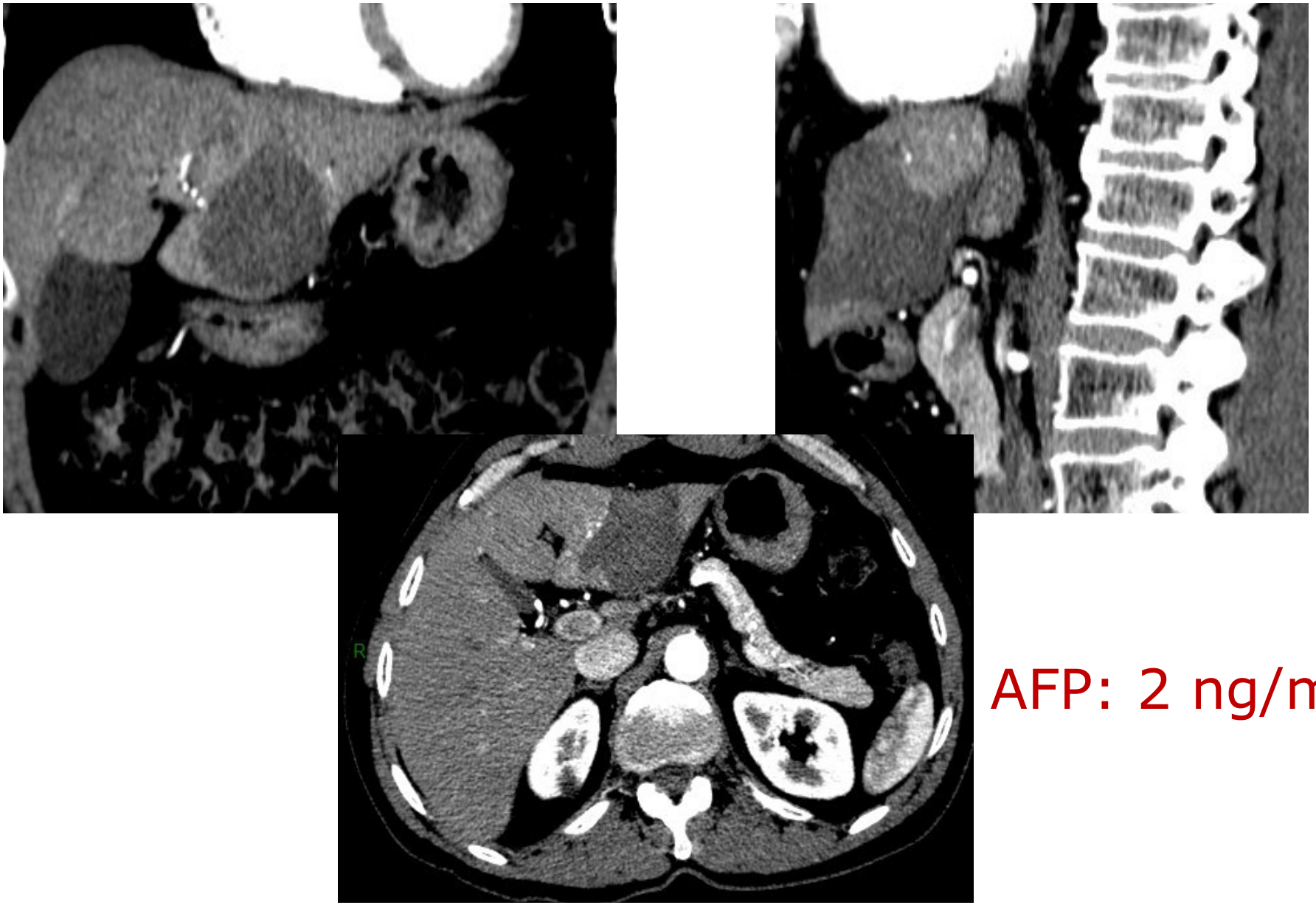
- Angers
- Bondy
- Bordeaux
- Lyon
- Montpellier

On October 2009 :

- Near no touch RFA consisting in inserting 7 straight electrodes with 4 cm active tips: 6 in square configuration at periphery of the tumor and 1 in its center.
- 200 kJ in 42’ minute of application time has been delivered
- 2 days of hospital stay

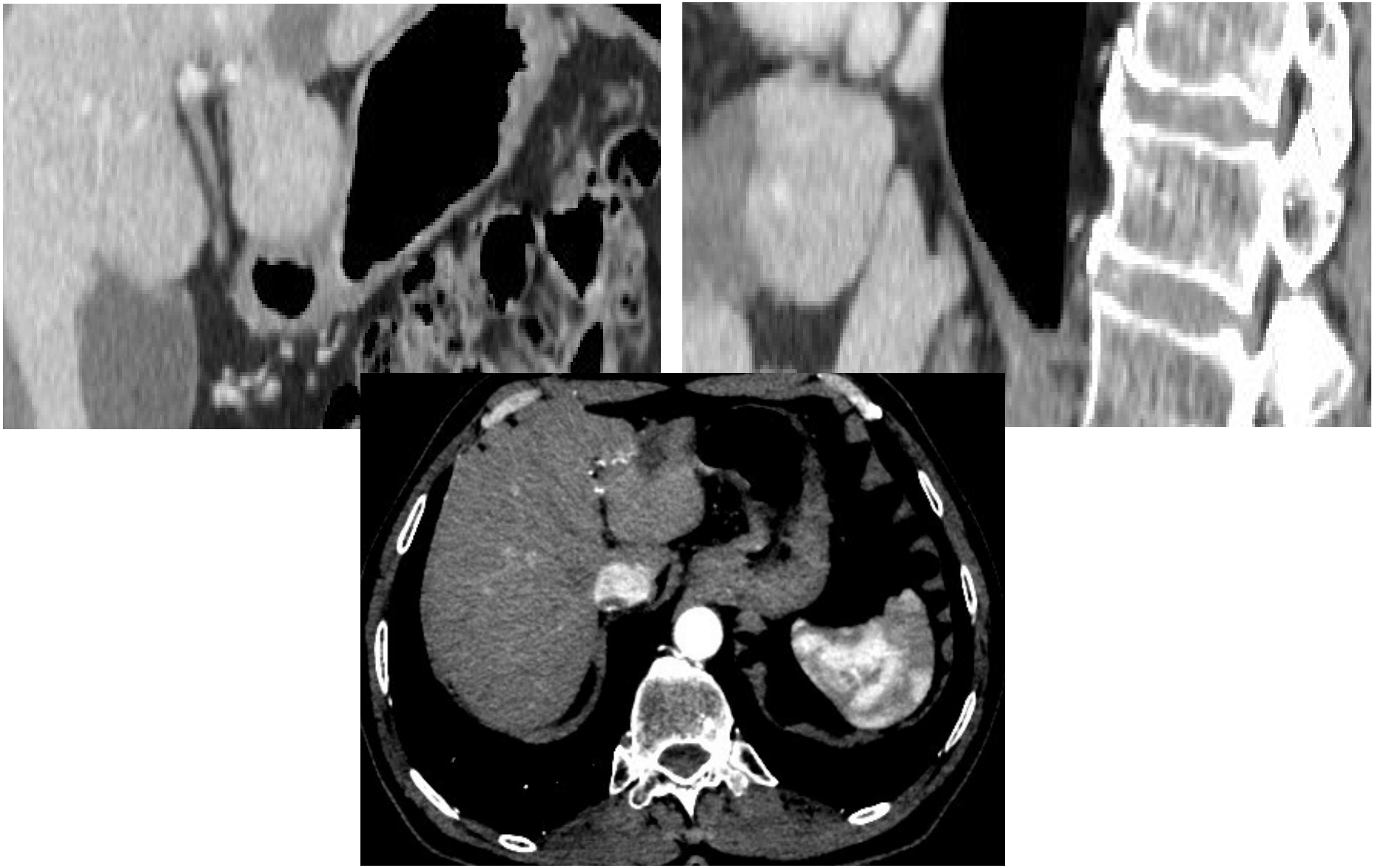


One month later



AFP: 2 ng/ml

5 years later

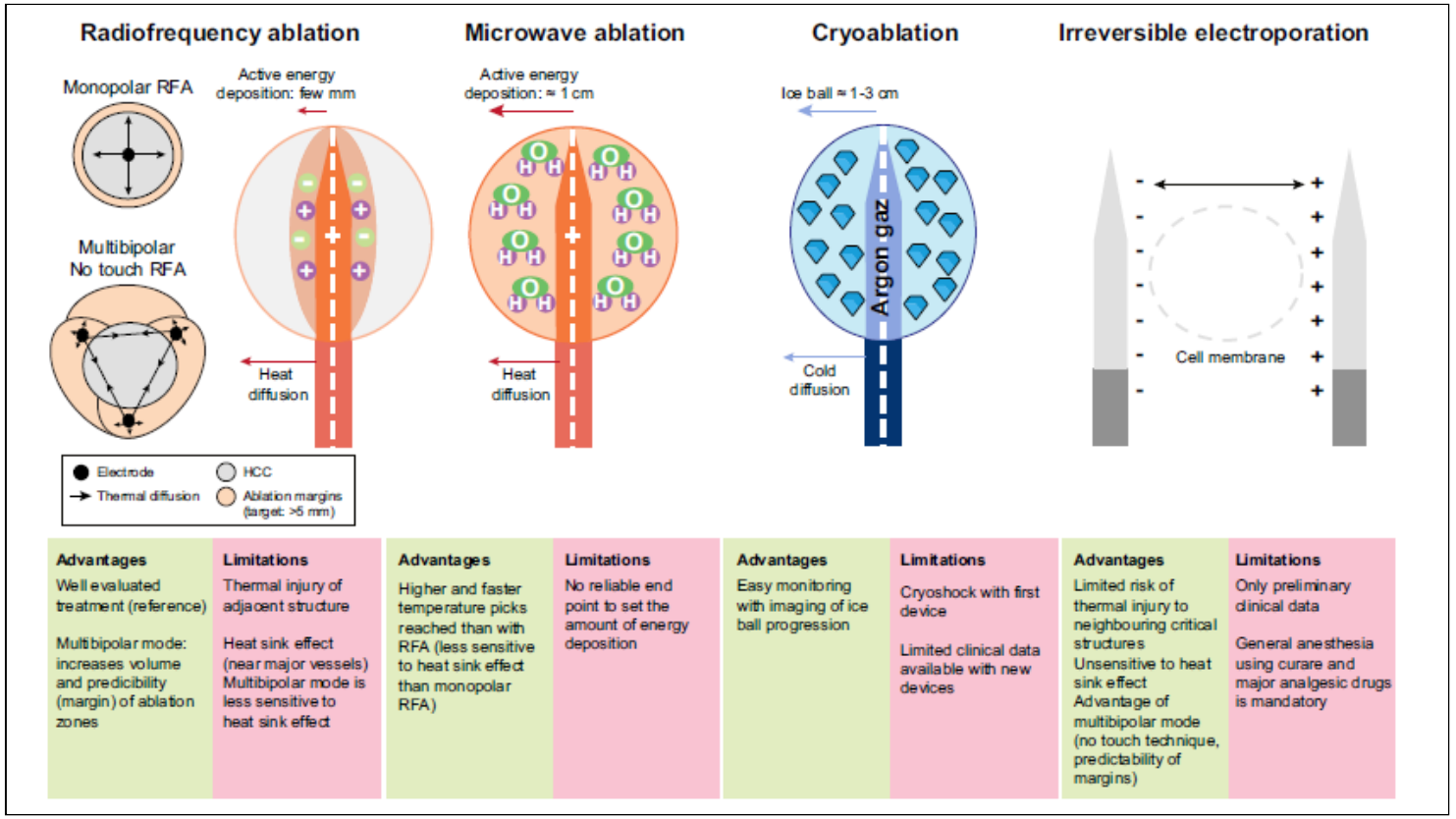


Review

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,*]

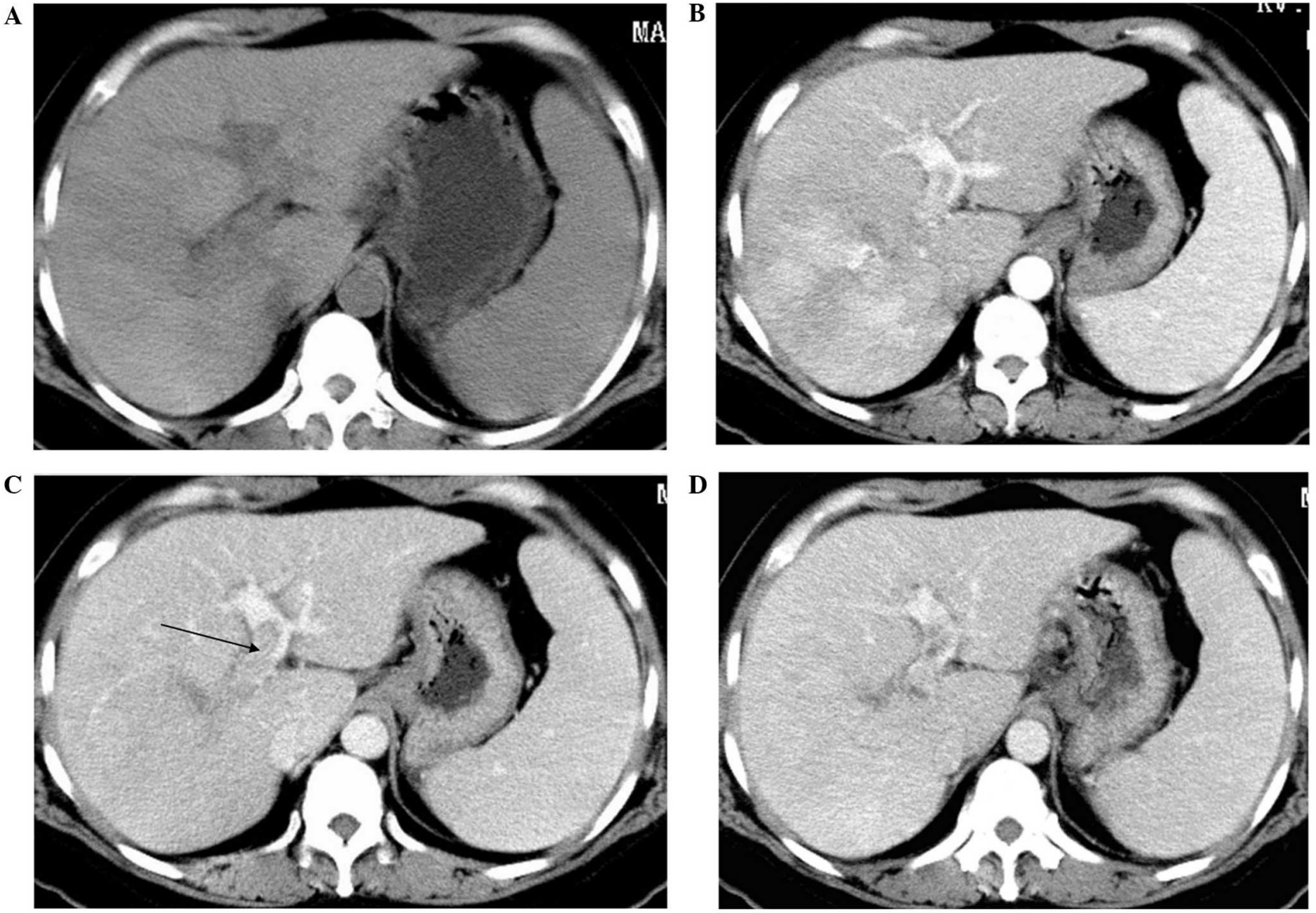


Advantages	Limitations	Advantages	Limitations	Advantages	Limitations	Advantages	Limitations
Well evaluated treatment (reference) Multibipolar mode: increases volume and predicibility (margin) of ablation zones	Thermal injury of adjacent structure Heat sink effect (near major vessels) Multibipolar mode 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

Second case

- 69 years old male
- Child-Pugh A6 alcohol-related cirrhosis
- Grade I esophageal varices
- Platelets count: 108 000 / mm3
- Bilirubin: 7 mg/L
- Albumin: 45 g/L
- Prothrombin time: 97%
- Liver stiffness: 62 Kpa
- Alpha-fetoprotein: 5ng/ml
- PS 0, ECOG 0

Imaging findings



Which treatment?

1. TACE
2. Radio-embolization
3. Sorafenib
4. Lenvatinib
5. Other systemic therapy

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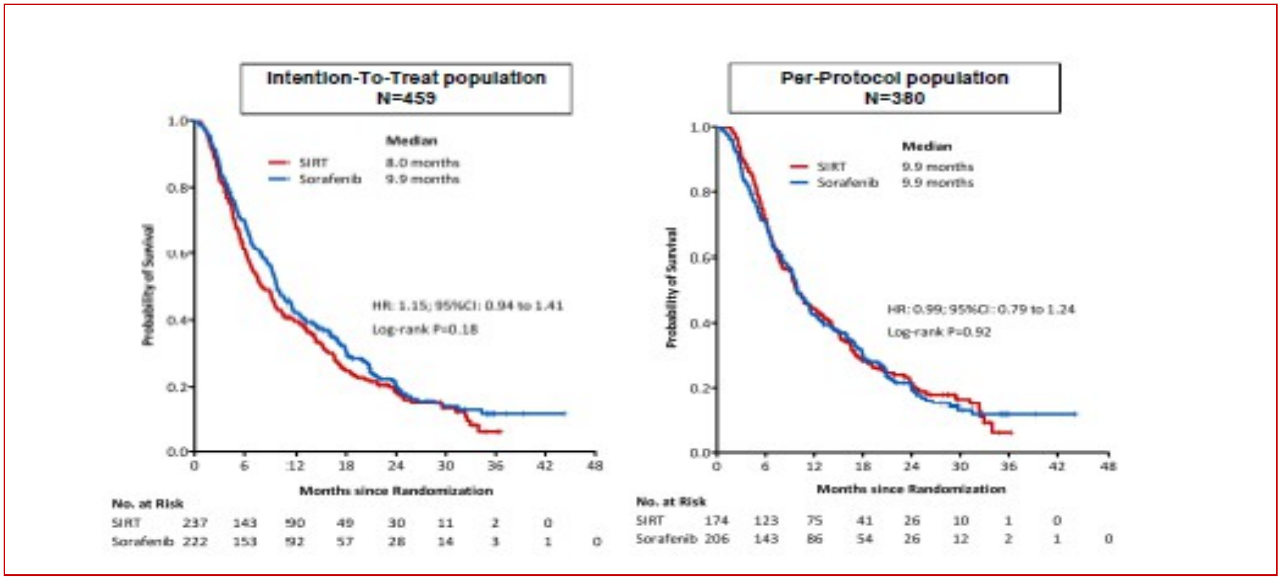
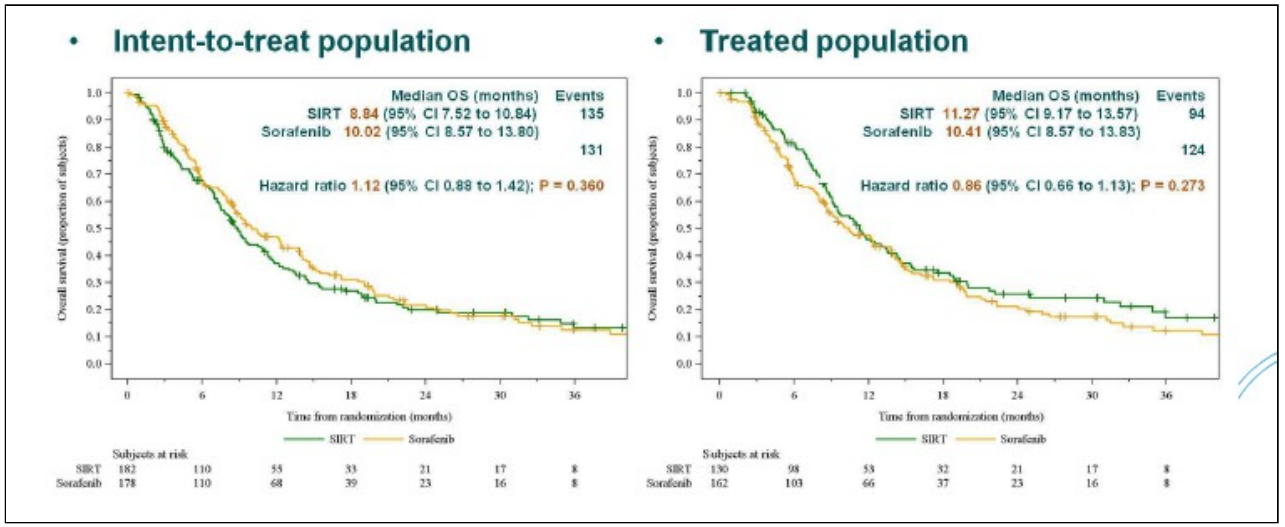
Radioembolization : negative trials



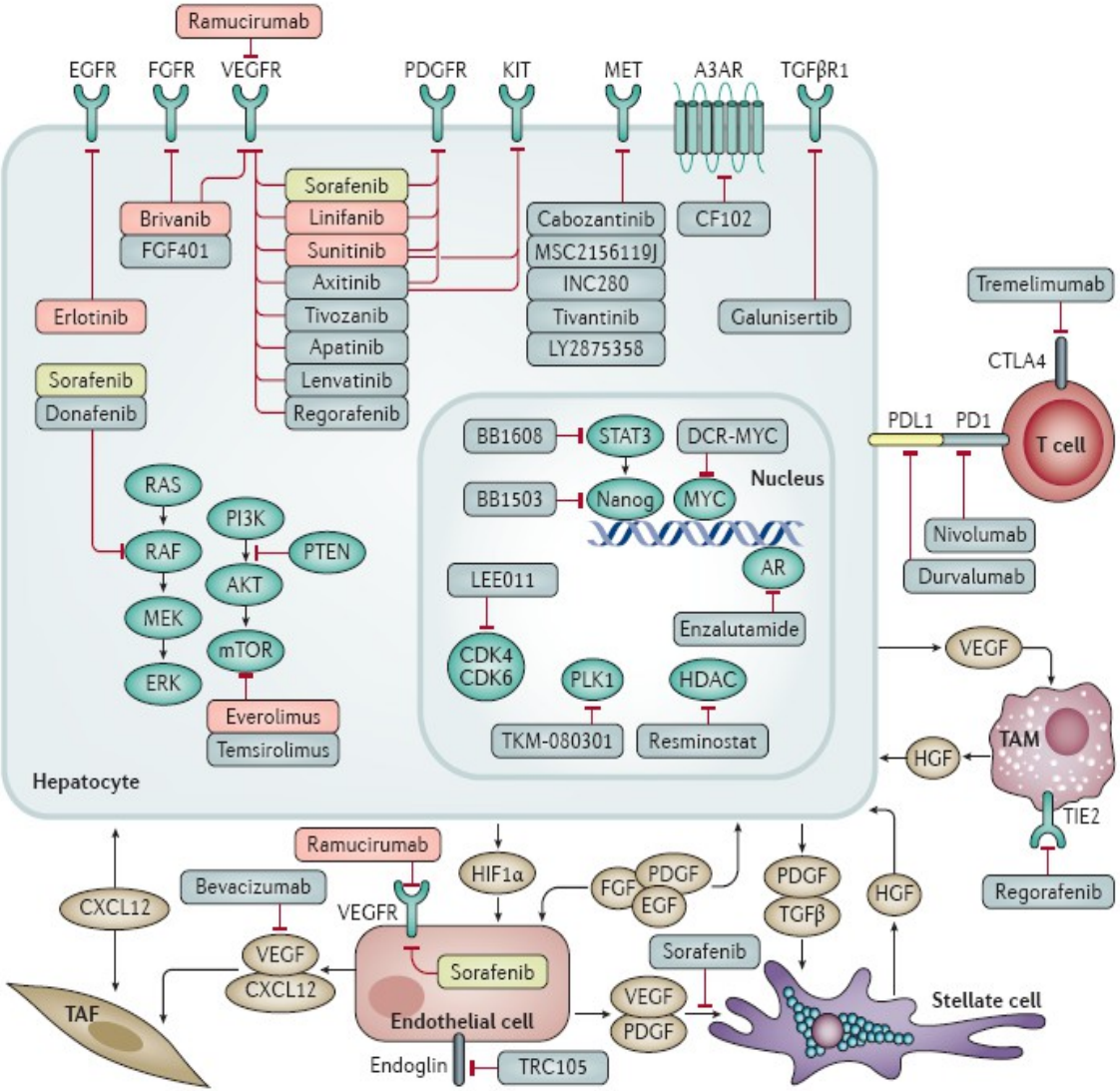
SARAH trial (West)
Vilgrain et al,
Lancet Oncol 2017



SIRveNIB trial (East)
Chow et al,
JCO 2018

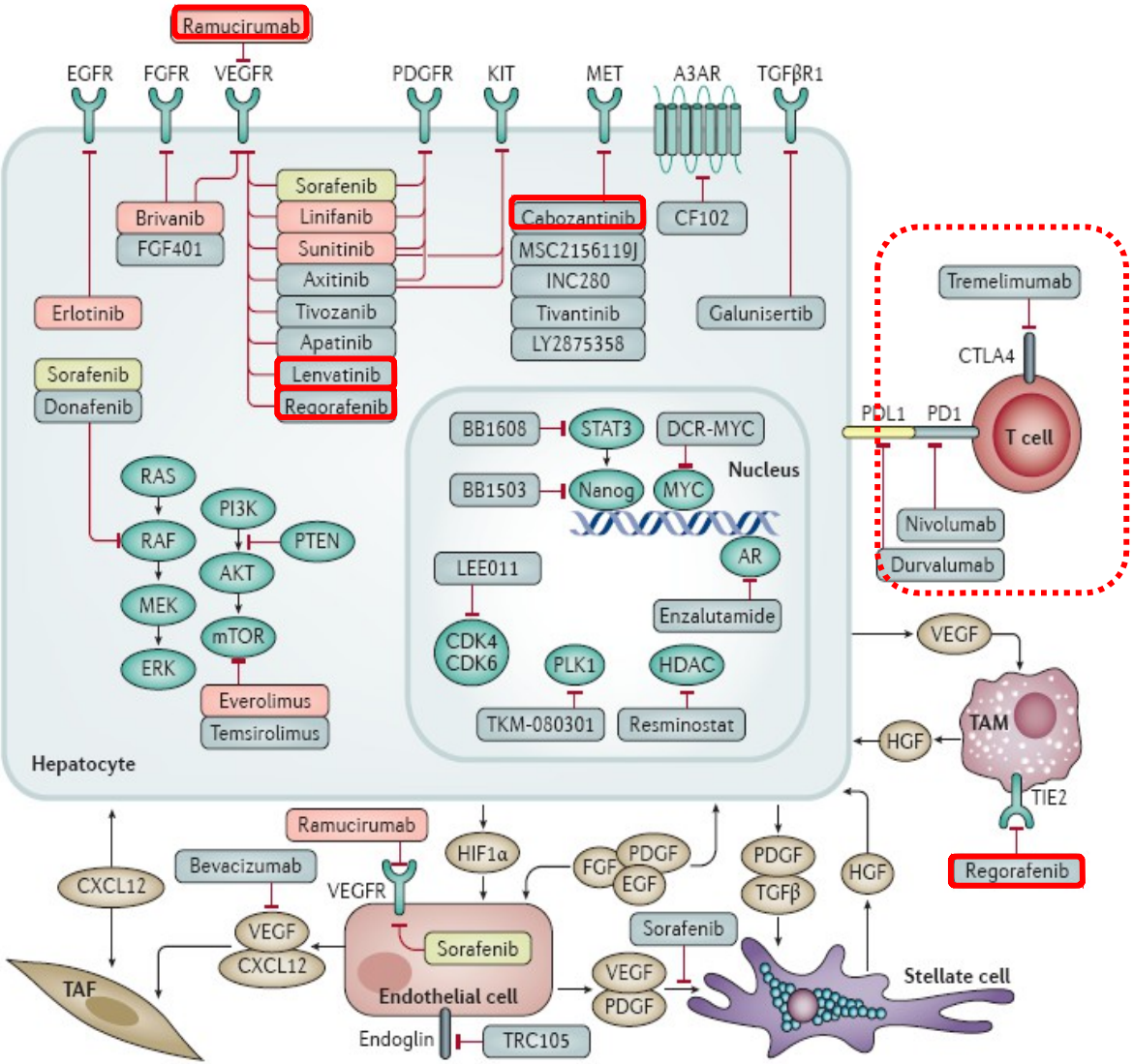
New molecules: where do we stand?

Llovet et al, Nature Reviews 2016

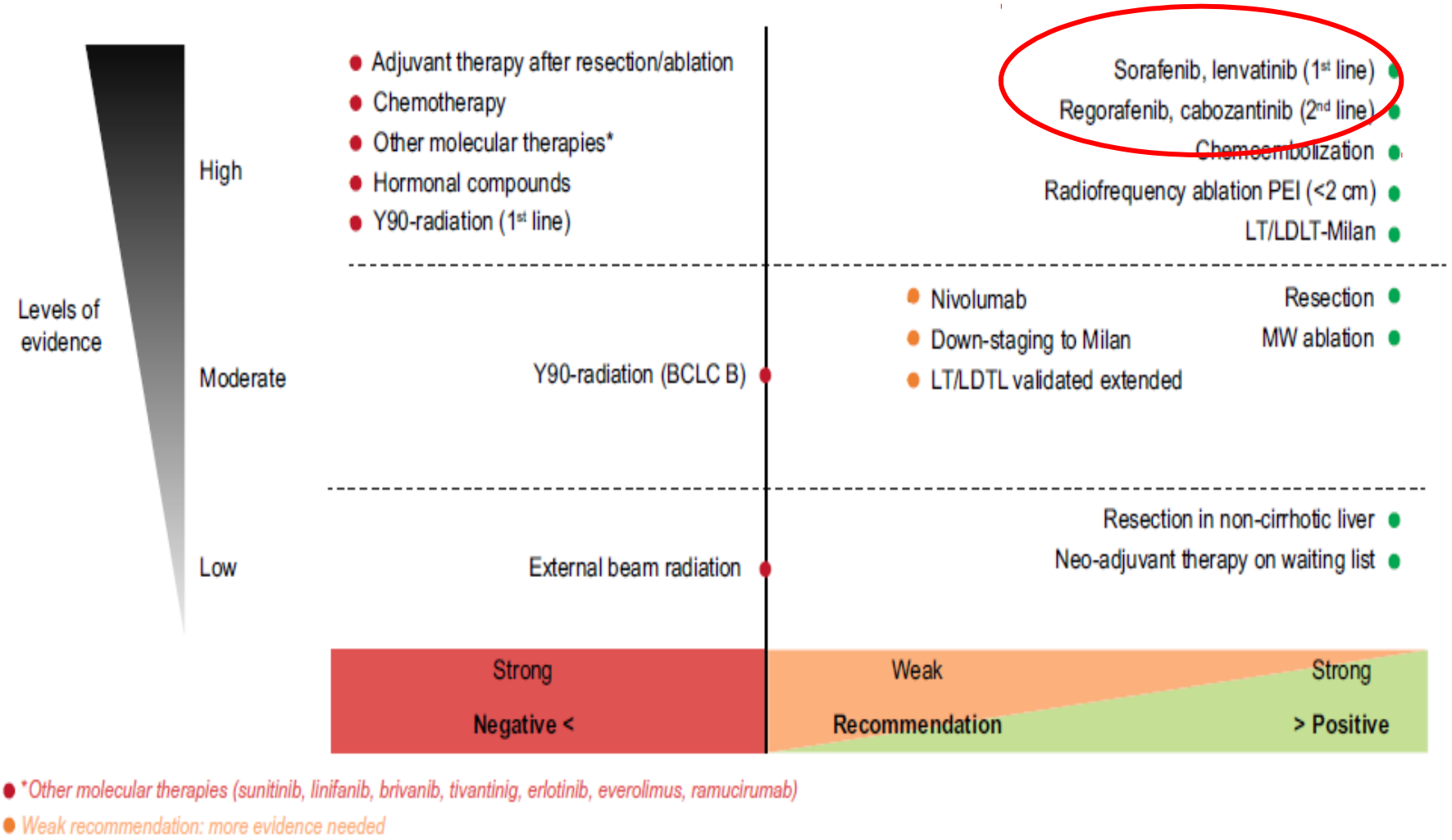


New molecules: where do we stand?

Llovet et al, Nature Reviews 2016



EASL 2018: recommandations for HCC management

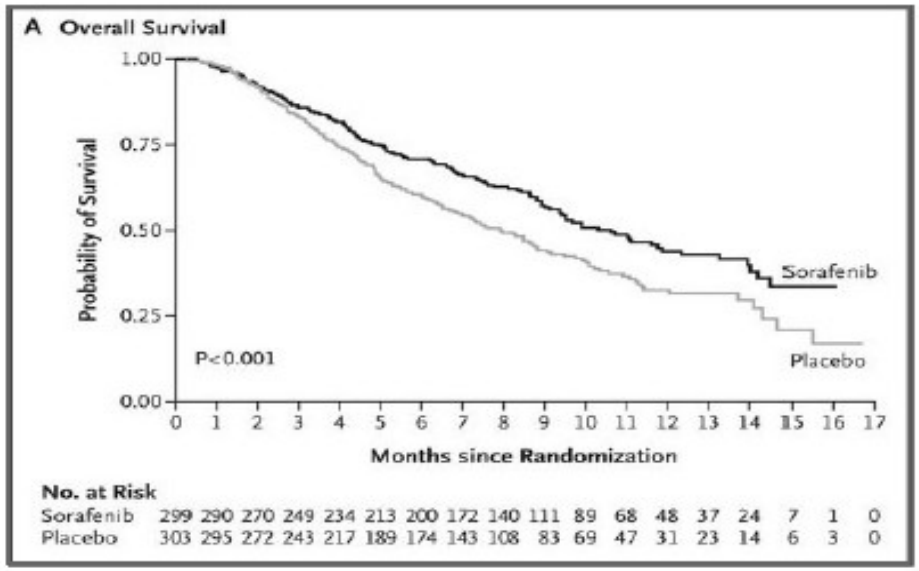


*Other molecular therapies (sunitinib, linifanib, brivanib, tivantinig, erlotinib, everolimus, ramucirumab)

Weak recommendation: more evidence needed

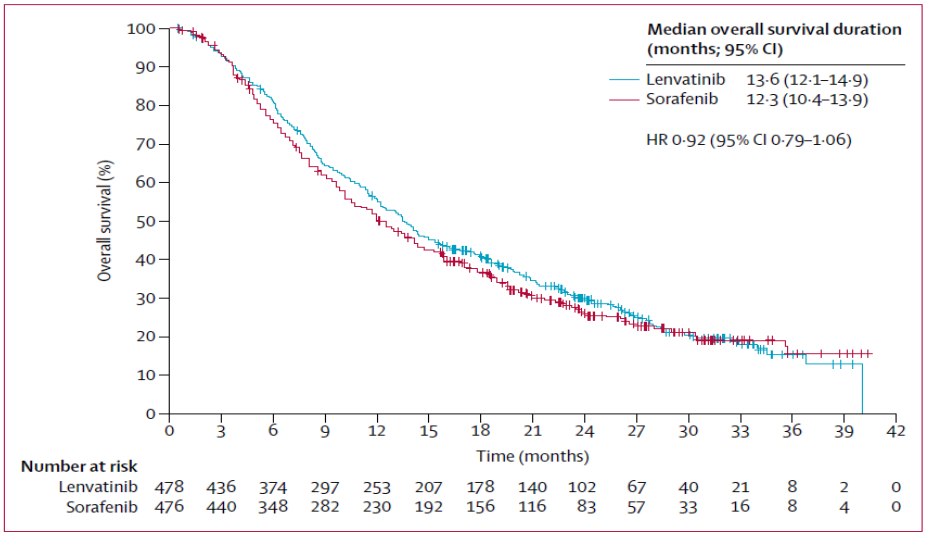
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol (2018),

Lenvatinib: an alternative to sorafenib in first line



SHARP trial

Llovet et al, NEJM 2008



Non-inferiority trial

Kudo et al, Lancet 2018

Second case (continued)

- The patient received sorafenib full dose
- Tolerance OK except asthenia grade I
- CT scan every 2 months: stable disease for 8 months
- Progression at month 9 with new hepatic lesions and one lung metastasis
- Liver function preserved

Which treatment?

1. Lenvatinib
2. Regorafenib
3. Cabozantinib
4. Nivolumab
5. Other

Which treatment?

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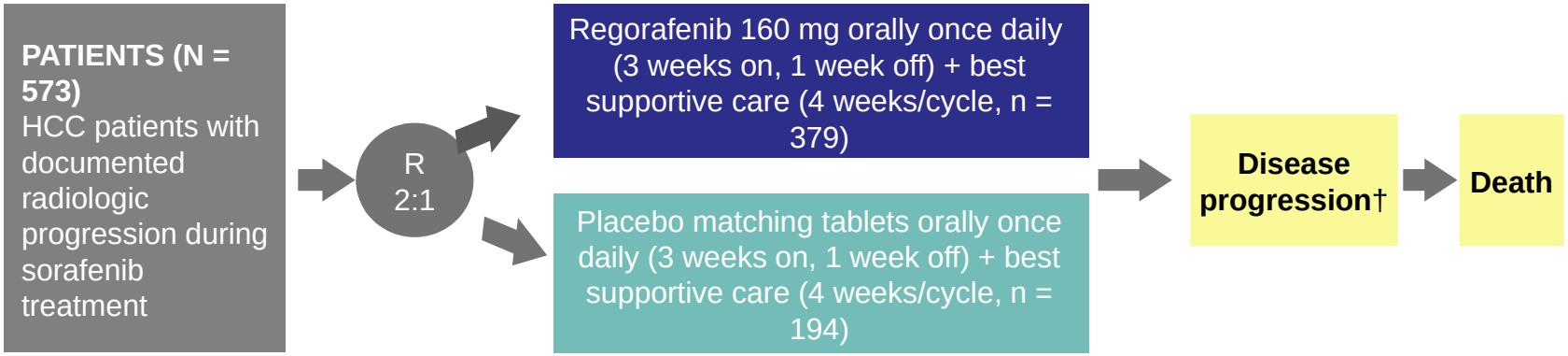
5. Other

Regorafenib : first approved systemic therapy in second line

RESORCE (NCT01774344)—a multinational,* randomized, double-blind, placebo-controlled phase III study that will evaluate the efficacy and safety of regorafenib in patients with advanced liver cancer who have progressed on prior sorafenib



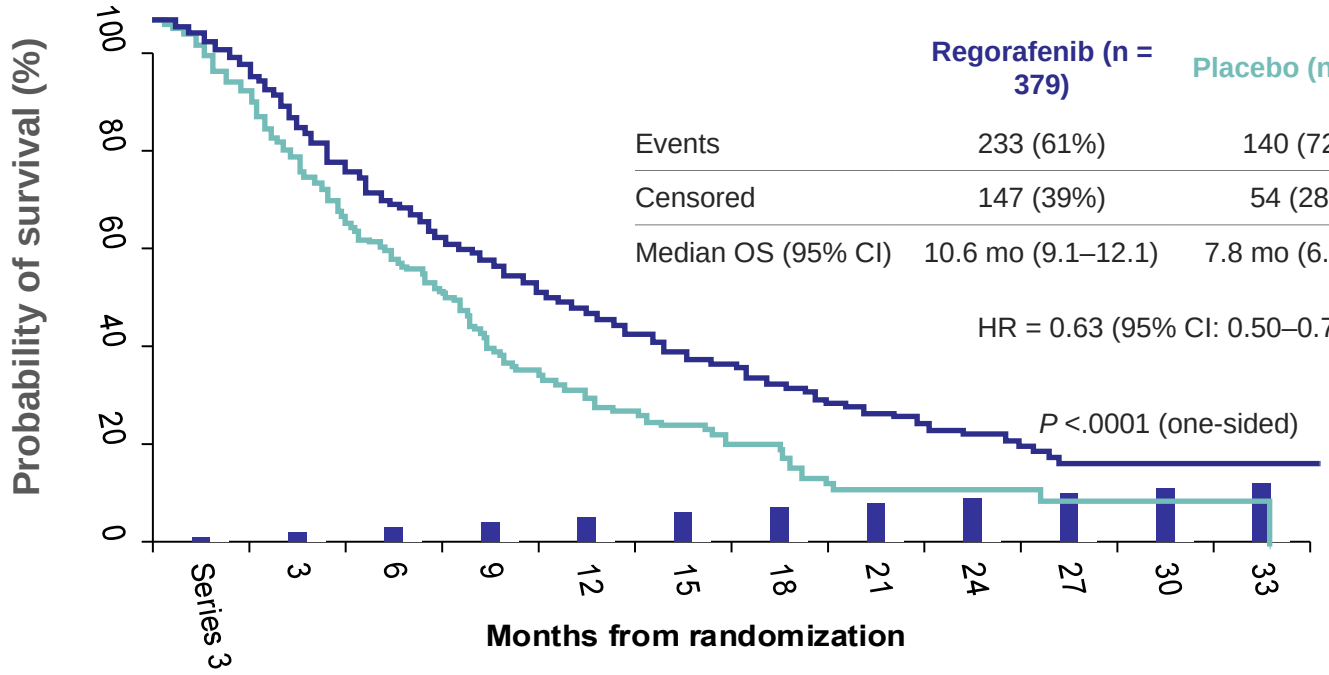
Stratification

- Geographic region (Asia vs ROW)
- Macrovascular invasion
- Extrahepatic disease
- ECOG PS (0 vs 1)
- AFP (<400 ng/mL vs ≥400 ng/mL)

L.FR.MA.04.2018.4754

*152 centers in 21 countries in North and South America, Europe, Australia, and Asia. †Including clinical progression, unacceptable toxicity, withdrawal of patient consent, or discontinuation of therapy by the treating physician.
AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; ROW, rest of world.
Adapted from Bruix J, et al. *Lancet.* 2017;389:56-66.

Regorafenib and OS Benefit Compared With Placebo in patients with HCC Who Have Progressed on Sorafenib



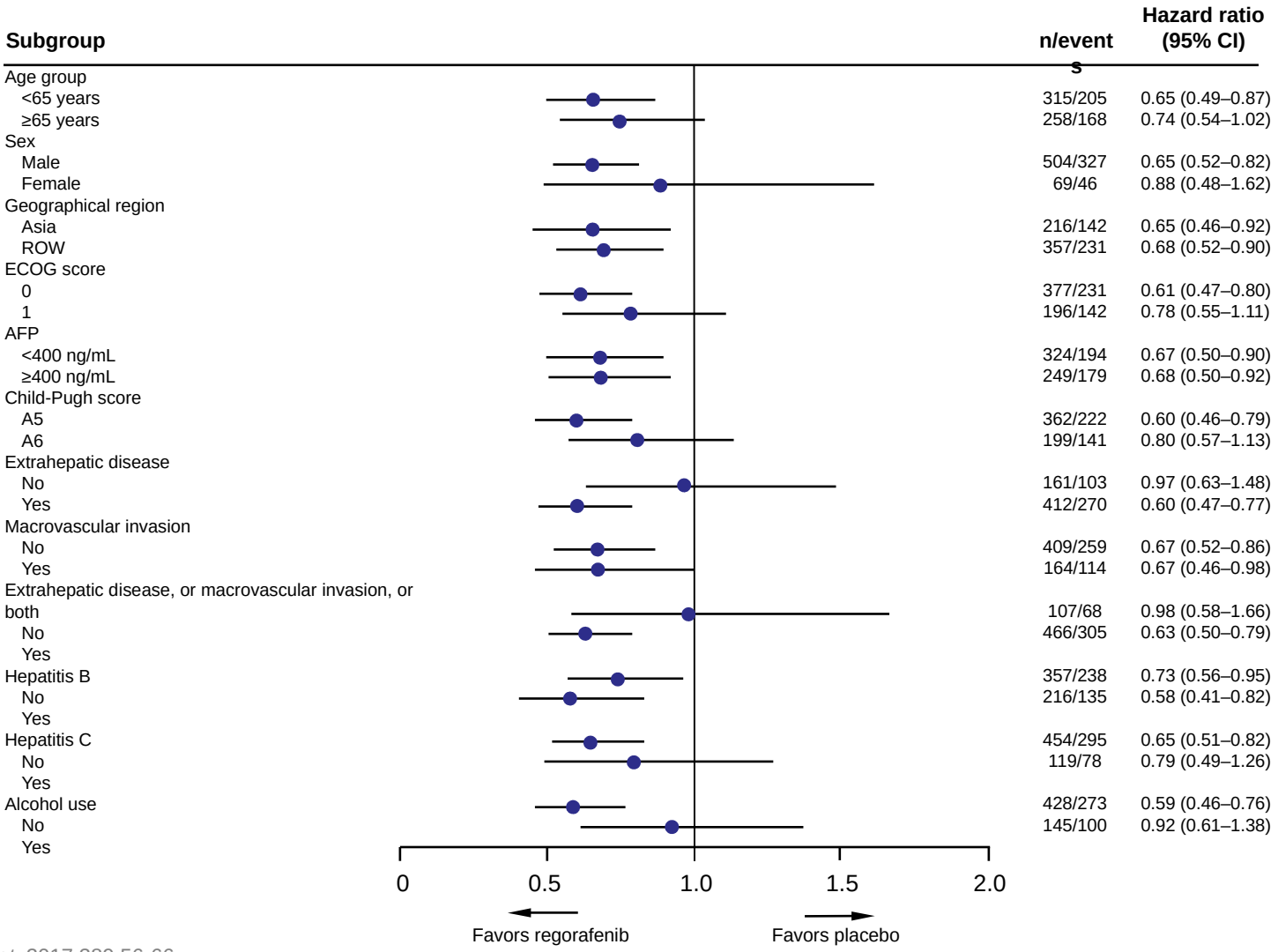
Number at risk

Regorafenib	379	316	224	170	122	78	54	34	21	10	4	0
Placebo	194	149	95	62	37	26	16	8	5	3	1	0

L.FR.MA.04.2018.4754

Bruix J, et al. *Lancet.* 2017;389:56-66.

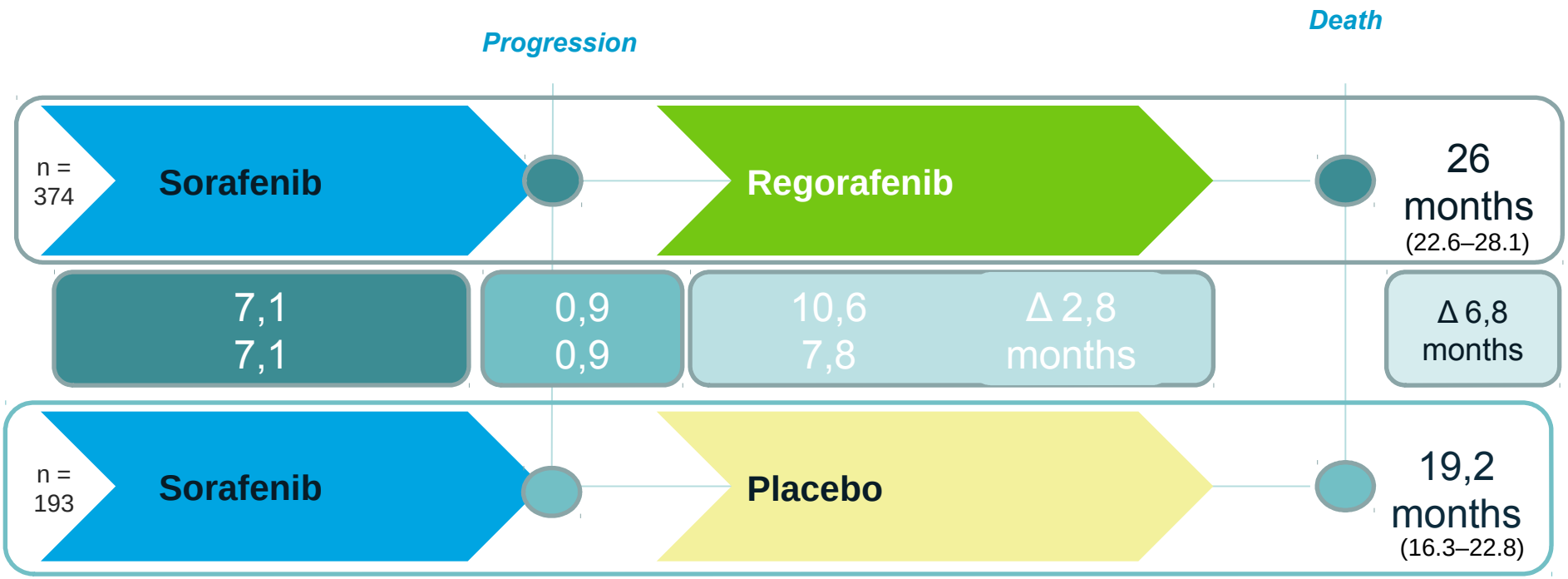
Improvement in OS With Regorafenib Was Maintained in All Preplanned Subgroups



L.FR.MA.04.2018.4754

Bruix J, et al. *Lancet.* 2017;389:56-66.

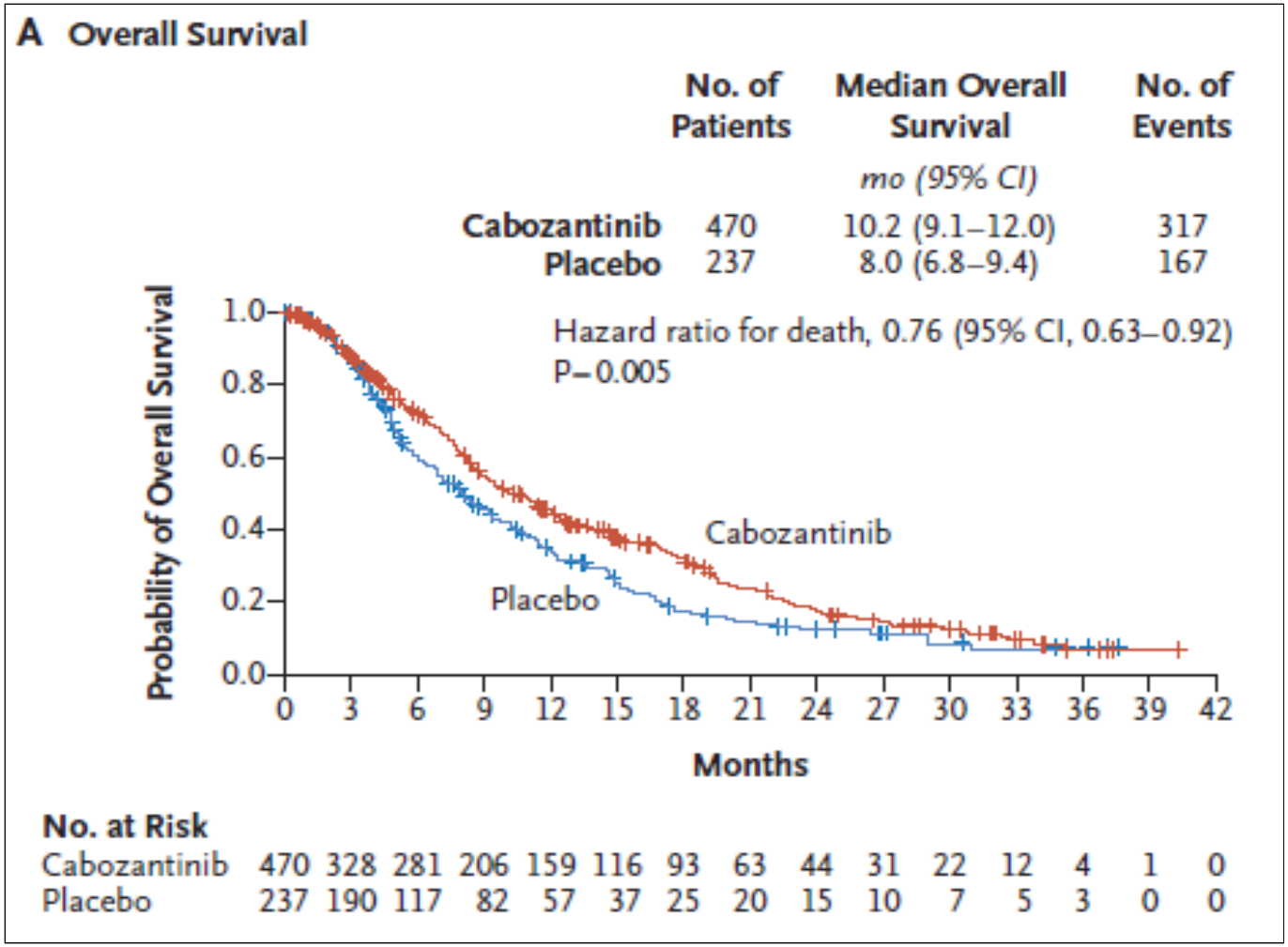
Sequential treatment with sorafenib and regorafenib: effet on survival



L.FR.MA.04.2018.4754

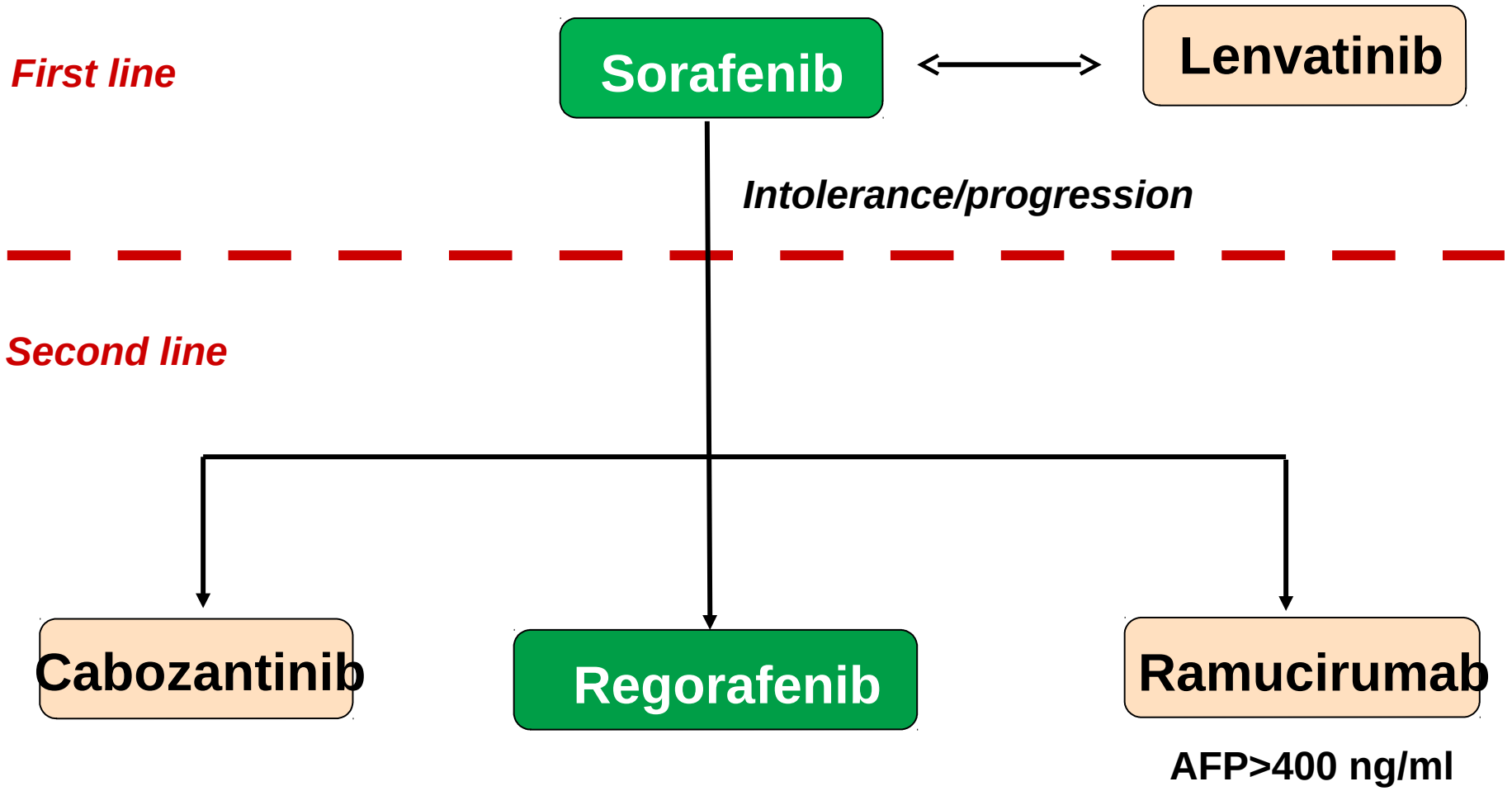
Adapted from Finn R, et al. ASCO GI 2017. Abstract 344.

Cabozantinib : another option in second line (and beyond?)

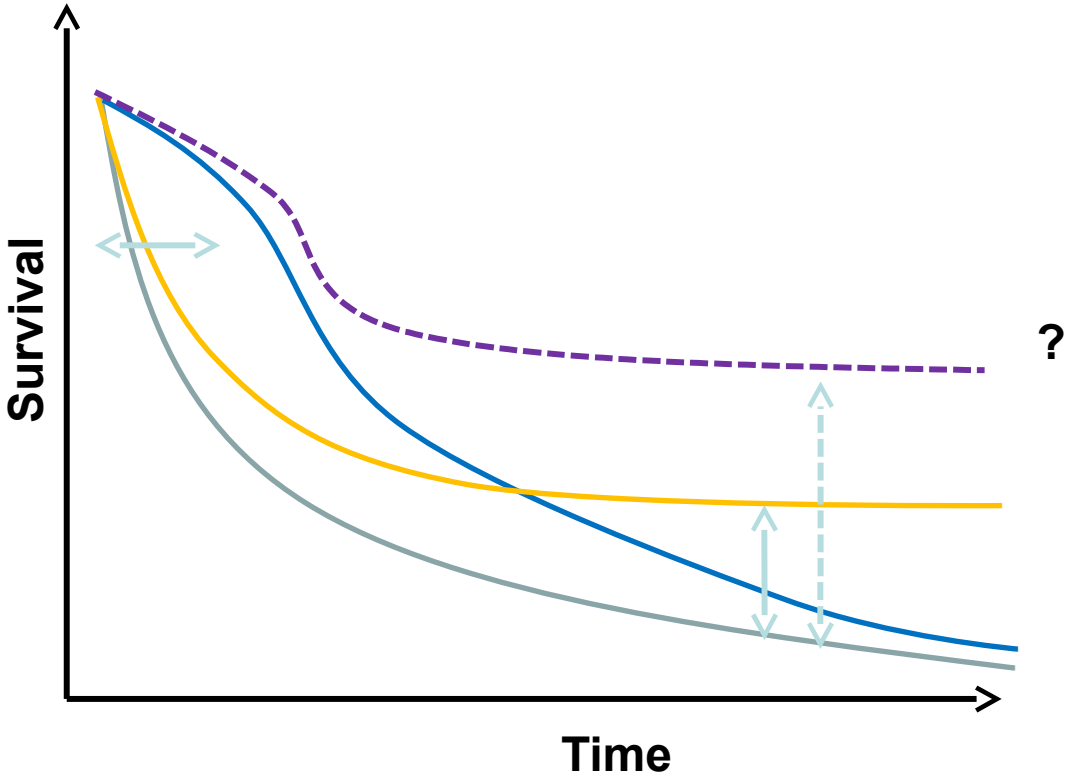


Abou-Alfa et al, NEJM 2018

Towards new recommandations?



Benefits of immunotherapy for cancer treatment



Chemotherapy

Targeted therapy

Immunotherapy

Combo or sequential with immuno

Check-point inhibitors

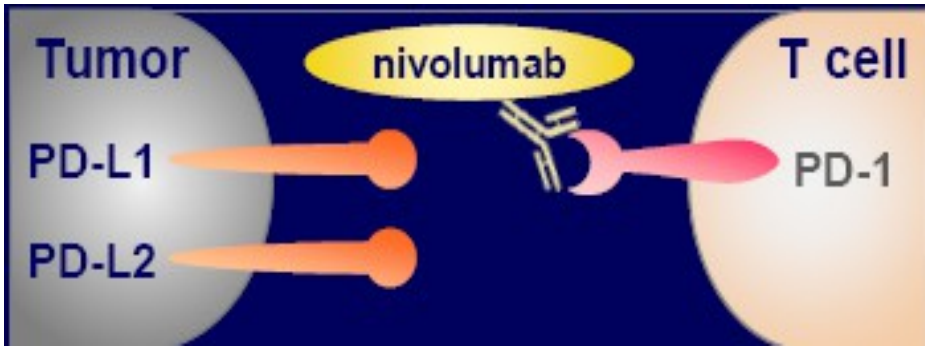
NIVOLUMAB

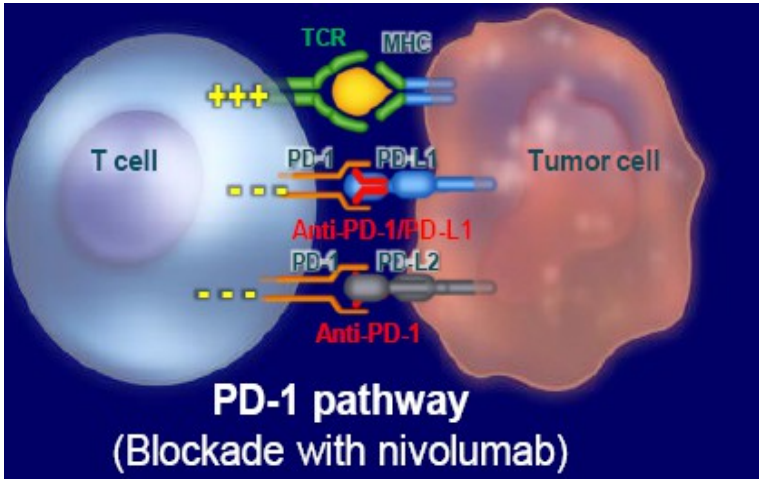
Nivolumab (anti-PD-1; BMS-936558; ONO-4538)

- Fully human, IgG4 PD-1 receptor-blocking monoclonal antibody[1-3]
- Inhibits a major immunosuppressive mechanism directly at the tumor site
  - Prevents inactivation or reactivates ability of T cells to attack the tumor[2]
- Binds to PD-1 receptors on T cells with high affinity
  - Selectively disrupts inhibitory signalling triggered by PD-L1 and PD-L2
  - Restores normal T-cell antitumor function[1,3]

Pardoll DM, Nat Rev Cancer 2012

PD1-PDL1 pathway

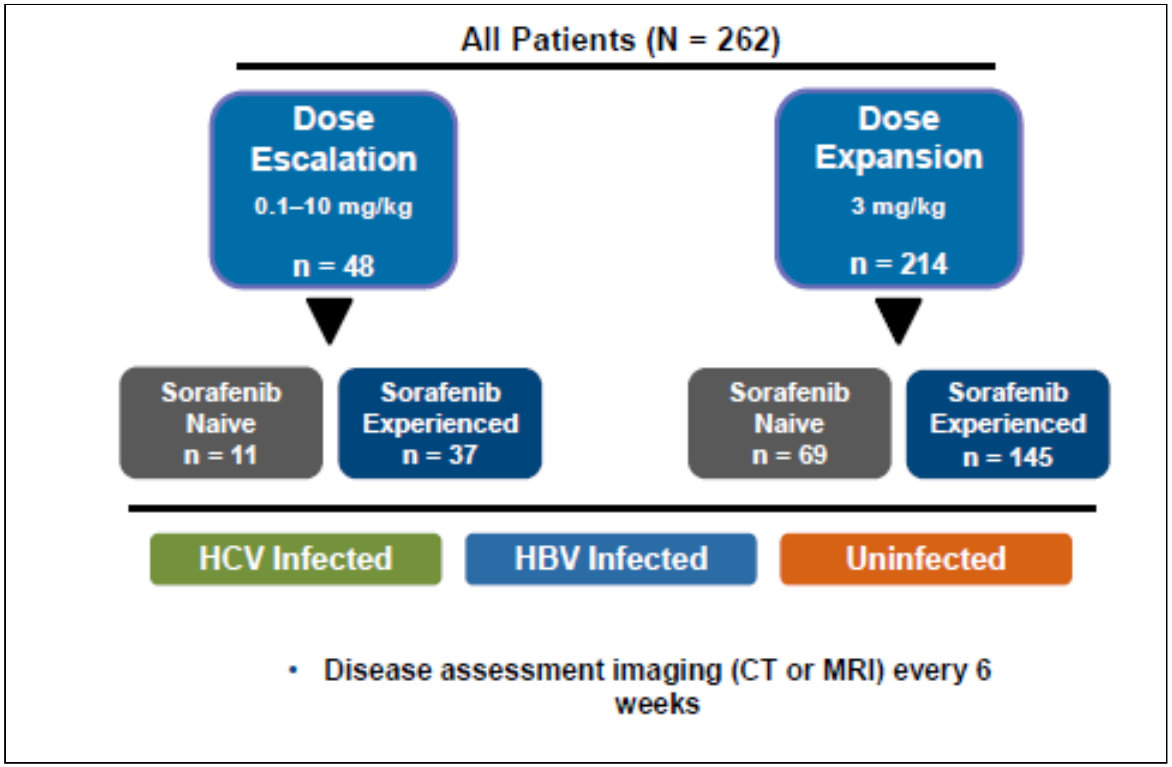


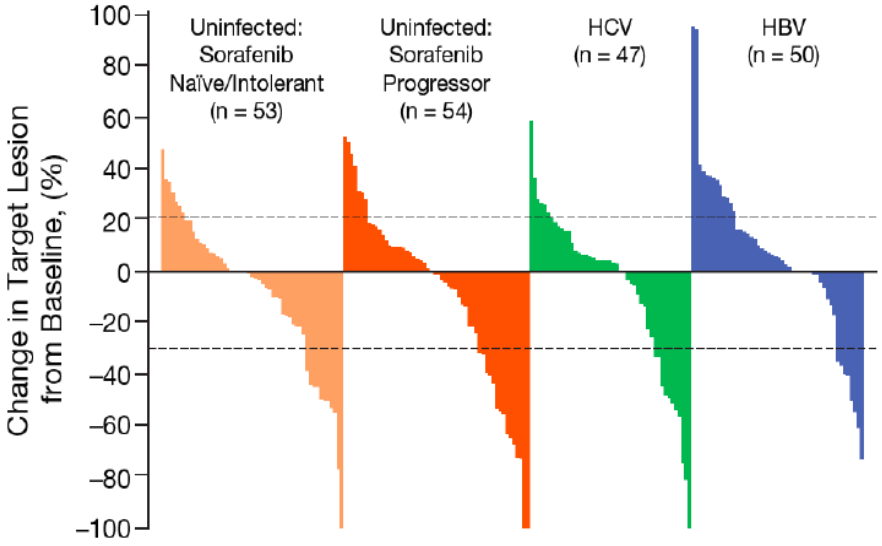


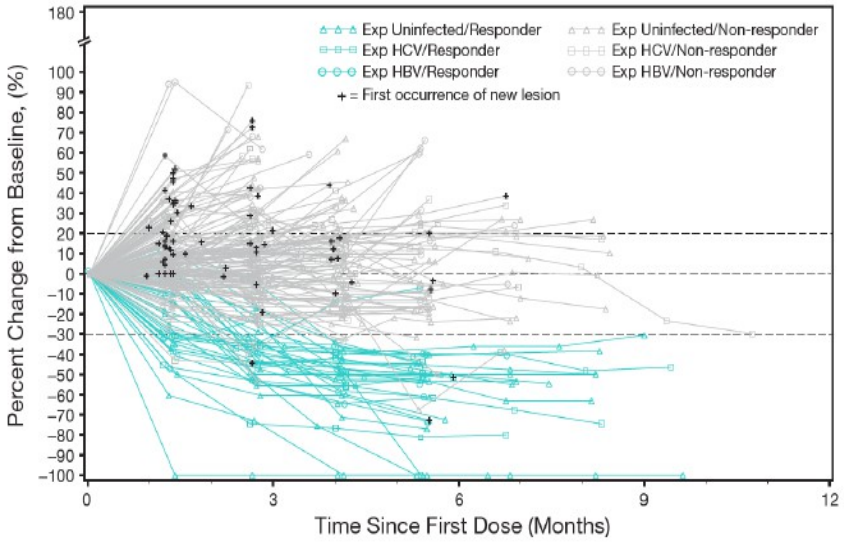
Lancet. 2017 Apr 20. [Epub ahead of print].

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

Anthony B El-Khoueiry, Bruno Sangro,* Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan, Theodore H Welling 3rd, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely, Hao Tang, Homa B Dastani, Ignacio Melero*







- **Tumour reduction: 45% patients**
- **Reduction at least 30%: 22% patients**

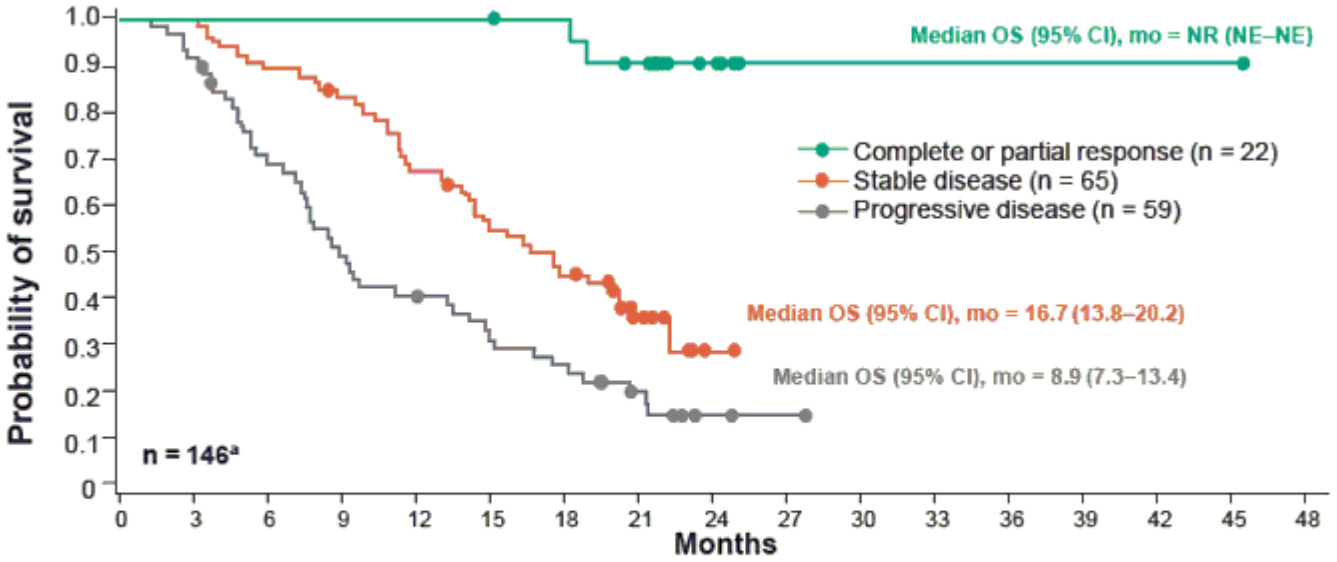
- AEs 3-4: 18% patients

Survival rate, % (95% CI)[a]	Uninfected: Sorafenib Naïve/ Intolerant (n = 54)	Uninfected: Sorafenib Progressors (n = 58)	HCV (n = 51)	HBV (n = 51)	Total (N = 214)
6-Month	89.8 (77.1, 95.6)	75.6 (61.5, 85.2)	82.1 (61.3, 92.4)	83.3 (67.6, 91.8)	82.5 (75.8, 87.5)
9-Month	79.8 (50.6, 92.8)	NC	NC	NC	70.8 (56.6, 81.1)

El-Khoueiry et al, Lancet 2017

Translation into survival benefit ?

Overall Survival by Best Overall Response in All Patients



OS rate (95% CI), %	Complete/partial response n = 22	Stable disease n = 65	Progressive disease n = 59
12 month	100 (100–100)	67 (55–77)	41 (28–53)
18 month	100 (100–100)	45 (33–57)	26 (15–38)

- Median OS was 15.1 months (95% CI, 13.2–18.8) in the overall analysis population (N = 154)

Meyer et al, EASL 2018

Summary

- ✓ Advances in ablative techniques offer new aggressive therapeutic managements for large and locally advanced tumors which can be treated in a curative approach.

- ✓ Several systemic therapies are now available and allow management of patients in first and second lines. However, no biomarkers are available to predict response and select the optimal candidates for a given molecule.

- ✓ Immunotherapy is emerging and might become the backbone for combined therapy.

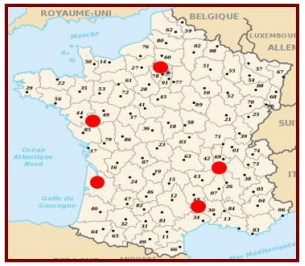
French phase 2 trial

- Academic trial supported by **BMS**
- Coordinating investigator: **Pr Pierre Nahon**

Nivolep trial

ClinicalTrials.gov ID: NCT03630640

- n=50
- 5 centres



« Curative intent »

(Every 30 days)

Primary Endpoint:
local recurrence-free survival