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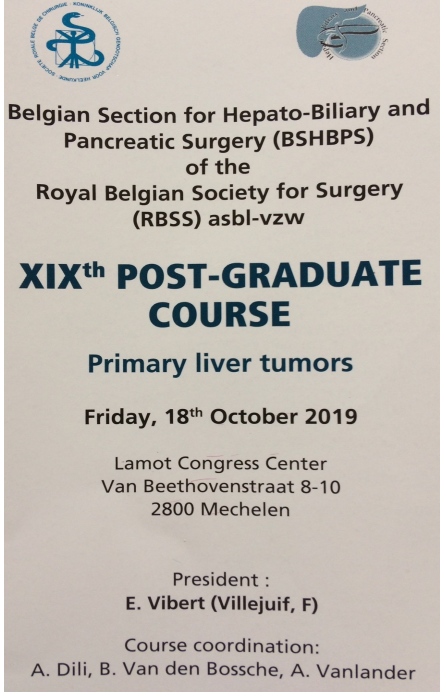

HCC on cirrhotic liver:
- Epidemiology
- Medical treatment guidelines
- Outcome

Prof Dr Isabelle COLLE

Hepatology and Gastroenterology A.S.Z. Aalst

Ghent University

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1. Epidemiology
2. Screening
3. Prevention
4. Diagnosis
5. Medical treatments

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1. **Epidemiology**
2. Screening
3. Prevention
4. Diagnosis
5. Medical treatments

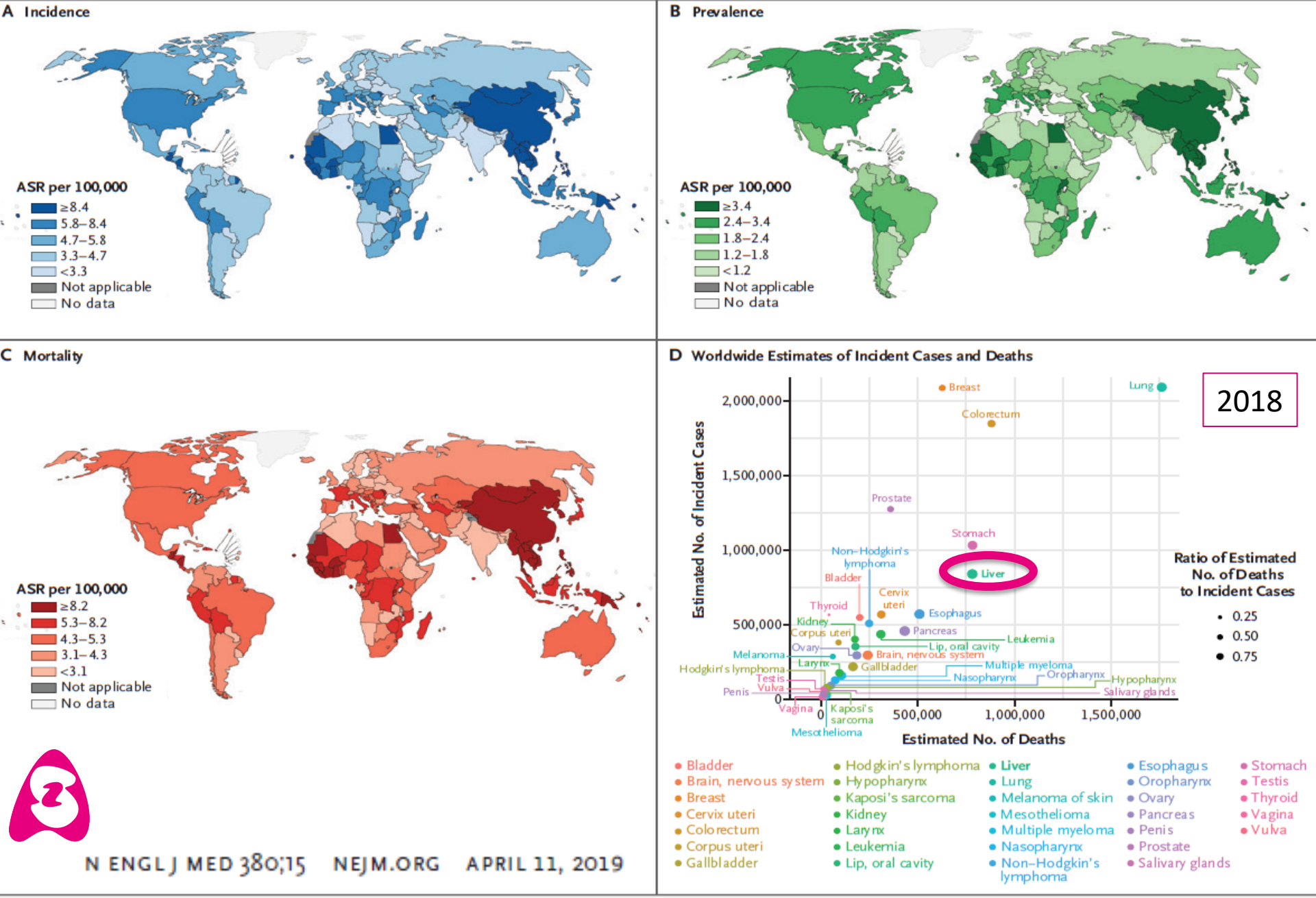
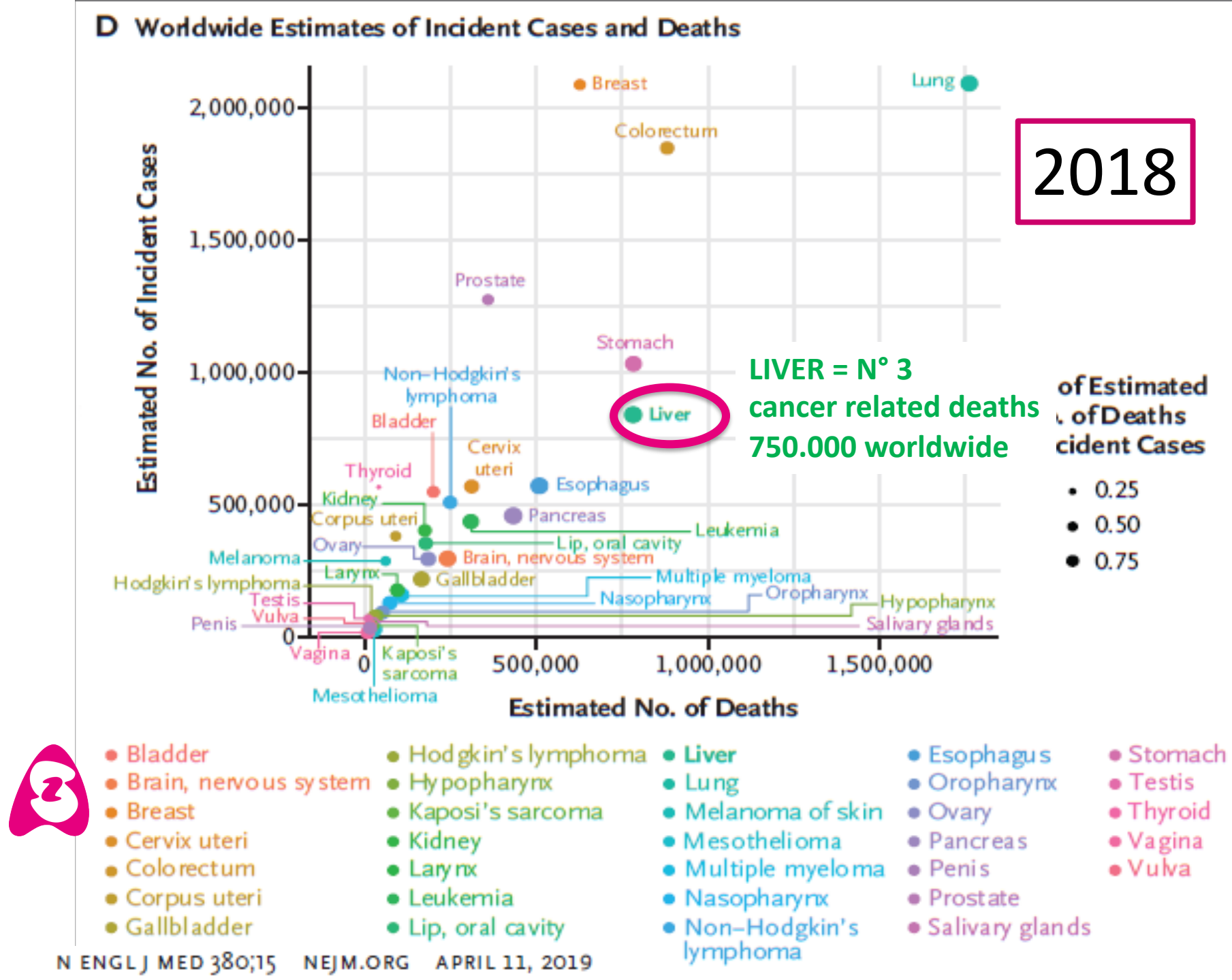


Figure 1. Worldwide Epidemiology of Liver Cancer in 2018.

Data are from the International Agency for Research on Cancer[1] (accessed on October 10, 2018). The incidence and prevalence of liver cancer are shown in Panels A and B, respectively, and associated deaths are shown in Panel C; data are expressed as the age-standardized rate (ASR) per 100,000 population. Panel D shows the worldwide estimates of incident cancer cases and deaths in 2018 for all tumor types.


D Worldwide Estimates of Incident Cases and Deaths
2018
LIVER = N° 3
cancer related deaths
750.000 worldwide
Estimated No. of Incident Cases
Estimated No. of Deaths
2,000,000
1,500,000
1,000,000
500,000
0
500,000
1,000,000
1,500,000
Breast
Lung
Colorectum
Prostate
Stomach
Non–Hodgkin's lymphoma
Liver
Bladder
Cervix uteri
Thyroid
Esophagus
Kidney
Pancreas
Corpus uteri
Leukemia
Ovary
Lip, oral cavity
Melanoma
Brain, nervous system
Larynx
Gallbladder
Hodgkin's lymphoma
Multiple myeloma
Testis
Nasopharynx
Oropharynx
Hypopharynx
Vulva
Penis
Salivary glands
Vagina
Kaposi's sarcoma
Mesothelioma
of Estimated
. of Deaths
cident Cases
0.25
0.50
0.75
Bladder
Brain, nervous system
Breast
Cervix uteri
Colorectum
Corpus uteri
Gallbladder
Hodgkin's lymphoma
Hypopharynx
Kaposi's sarcoma
Kidney
Larynx
Leukemia
Lip, oral cavity
Liver
Lung
Melanoma of skin
Mesothelioma
Multiple myeloma
Nasopharynx
Non–Hodgkin's lymphoma
Esophagus
Oropharynx
Ovary
Pancreas
Penis
Prostate
Salivary glands
Stomach
Testis
Thyroid
Vagina
Vulva

Epidemiology

VOLUME 34 · NUMBER 15 · MAY 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Future of Hepatocellular Carcinoma Incidence in the United States Forecast Through 2030

Jessica L. Petrick, Scott P. Kelly, Sean F. Altekruse, Katherine A. McGlynn, and Philip S. Rosenberg

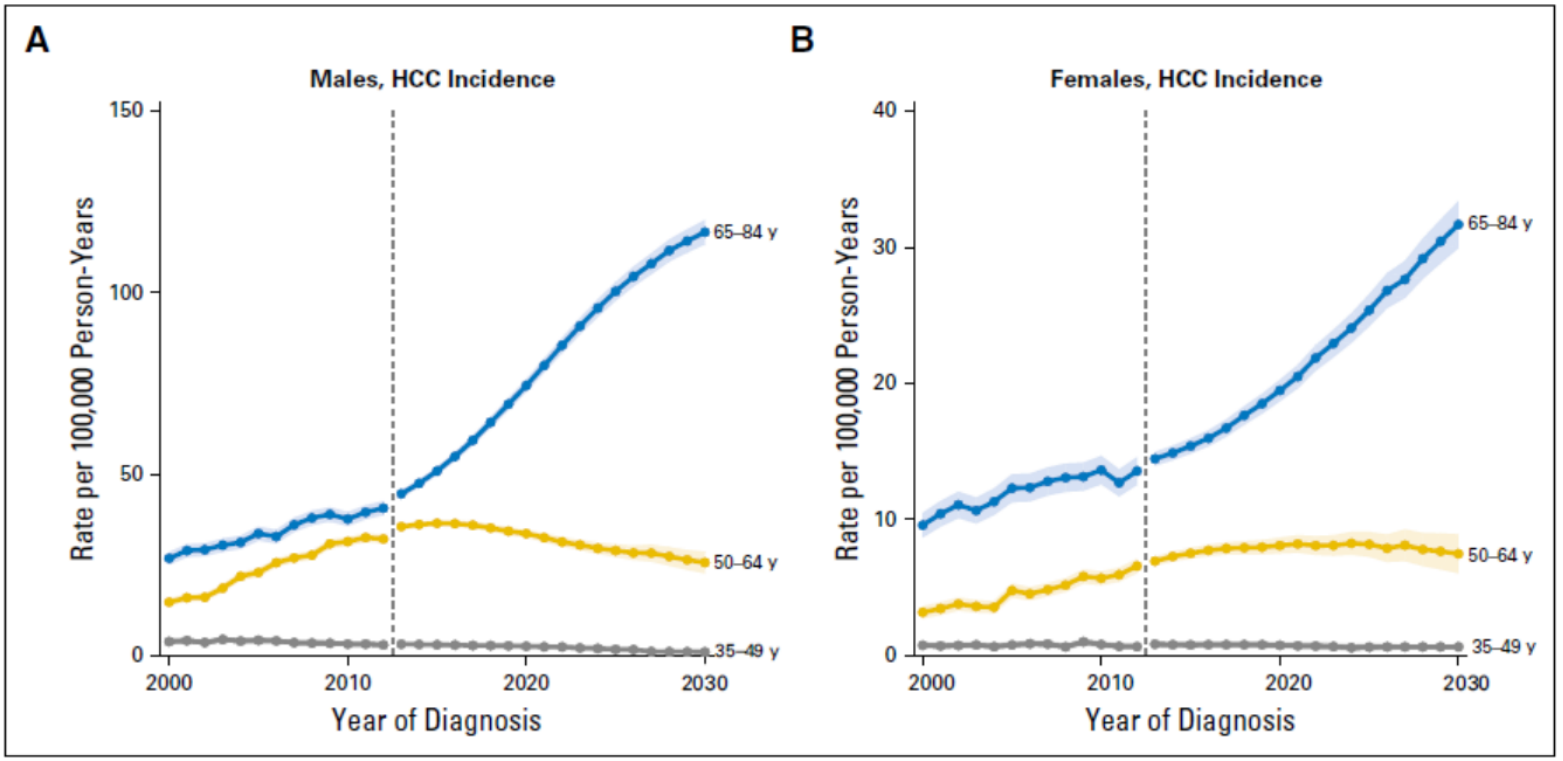


Fig 4. Observed and projected incidence of hepatocellular carcinoma (HCC; per 100,000 person-years) in SEER 18, by age group in (A) males, and (B) females. Shaded bands show point-wise 95% confidence limits.

Epidemiology

OBESITY: BMI > 30

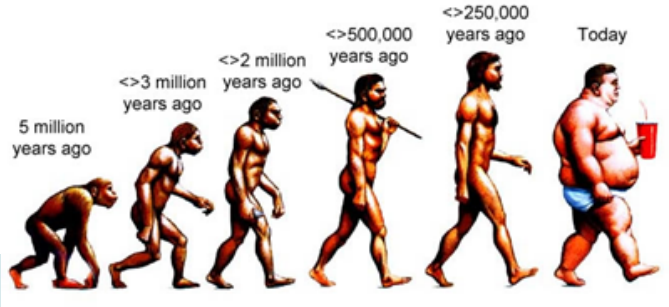
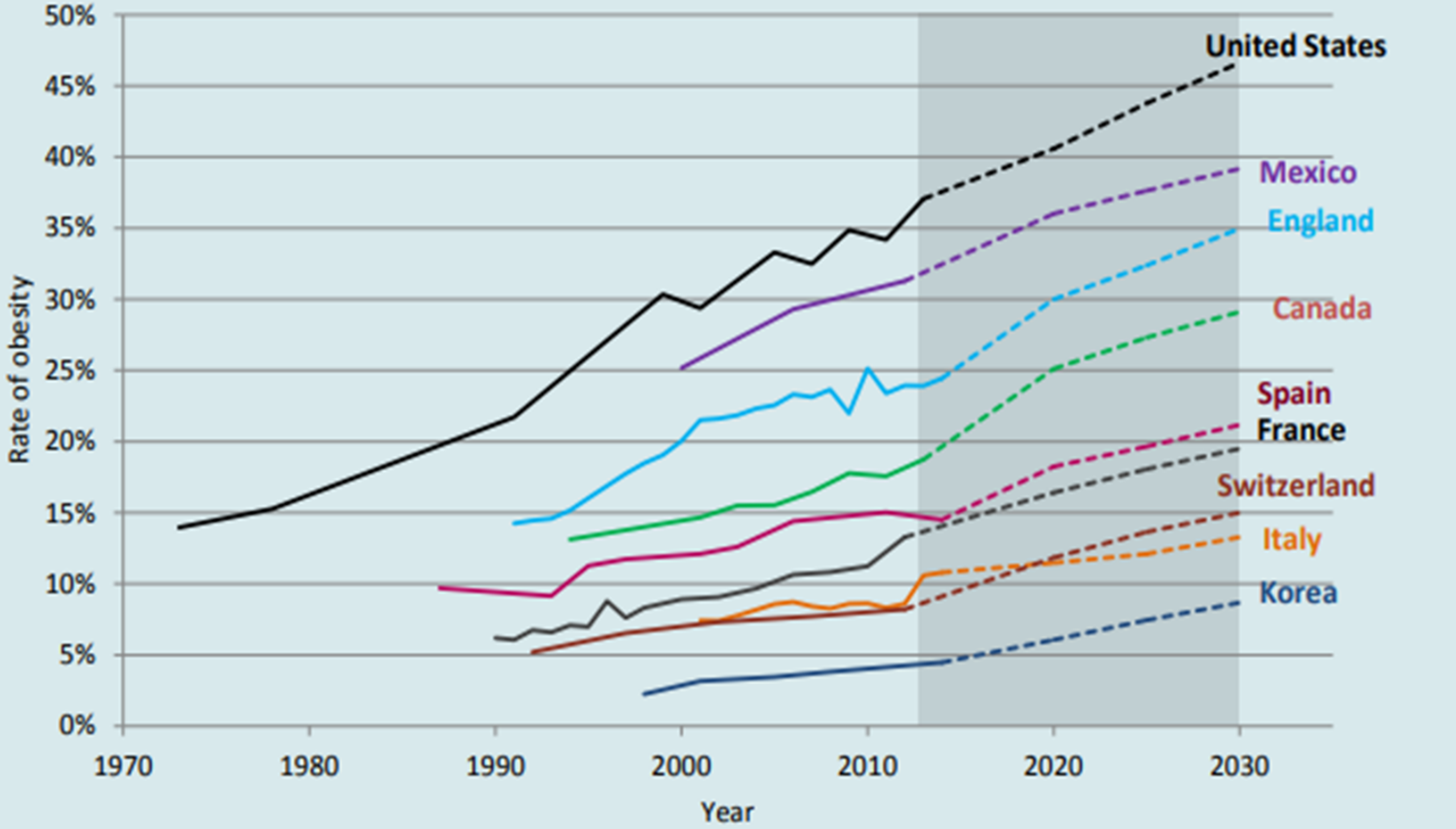


Figure 5: Projected rates of obesity



Body Mass Index and Risk of Primary Liver Cancer: A Meta-Analysis of Prospective Studies

YUQIN WANG, BAOCHAN WANG, FENG SHEN, JIANGAO FAN, HAIXIA CAO

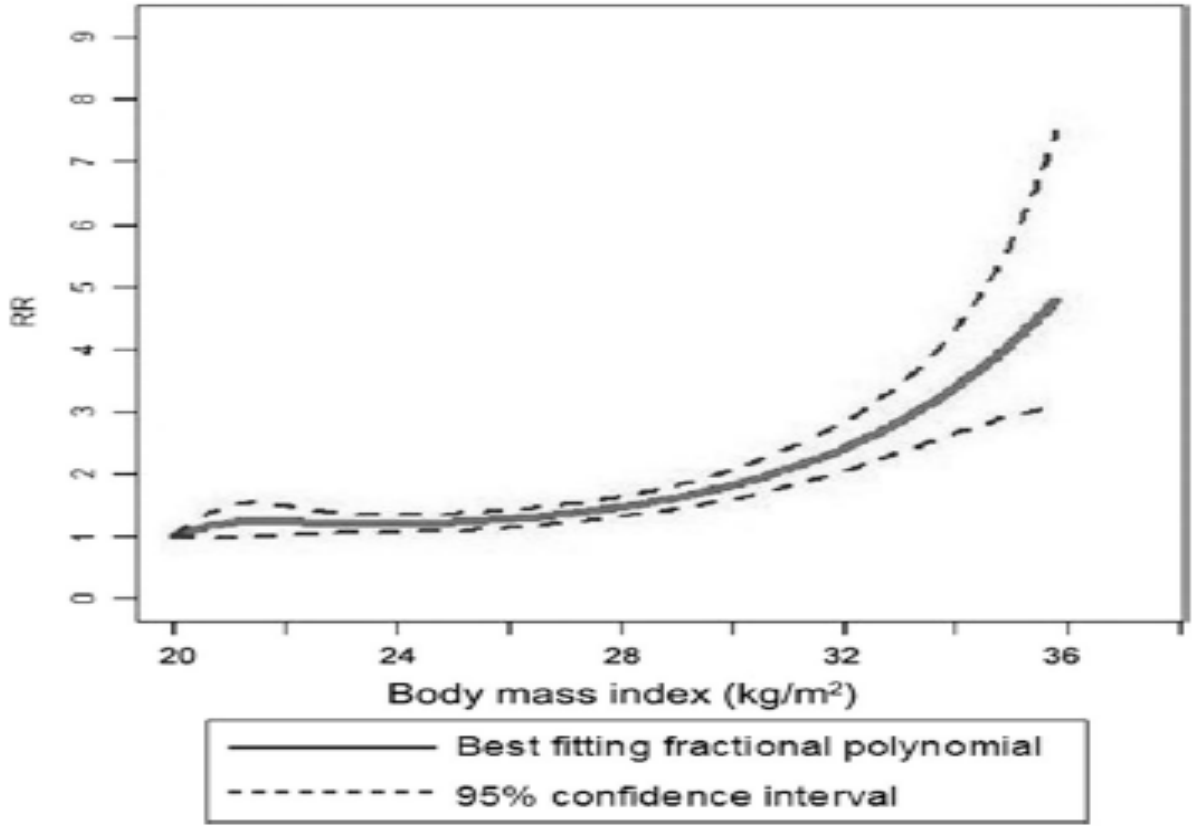
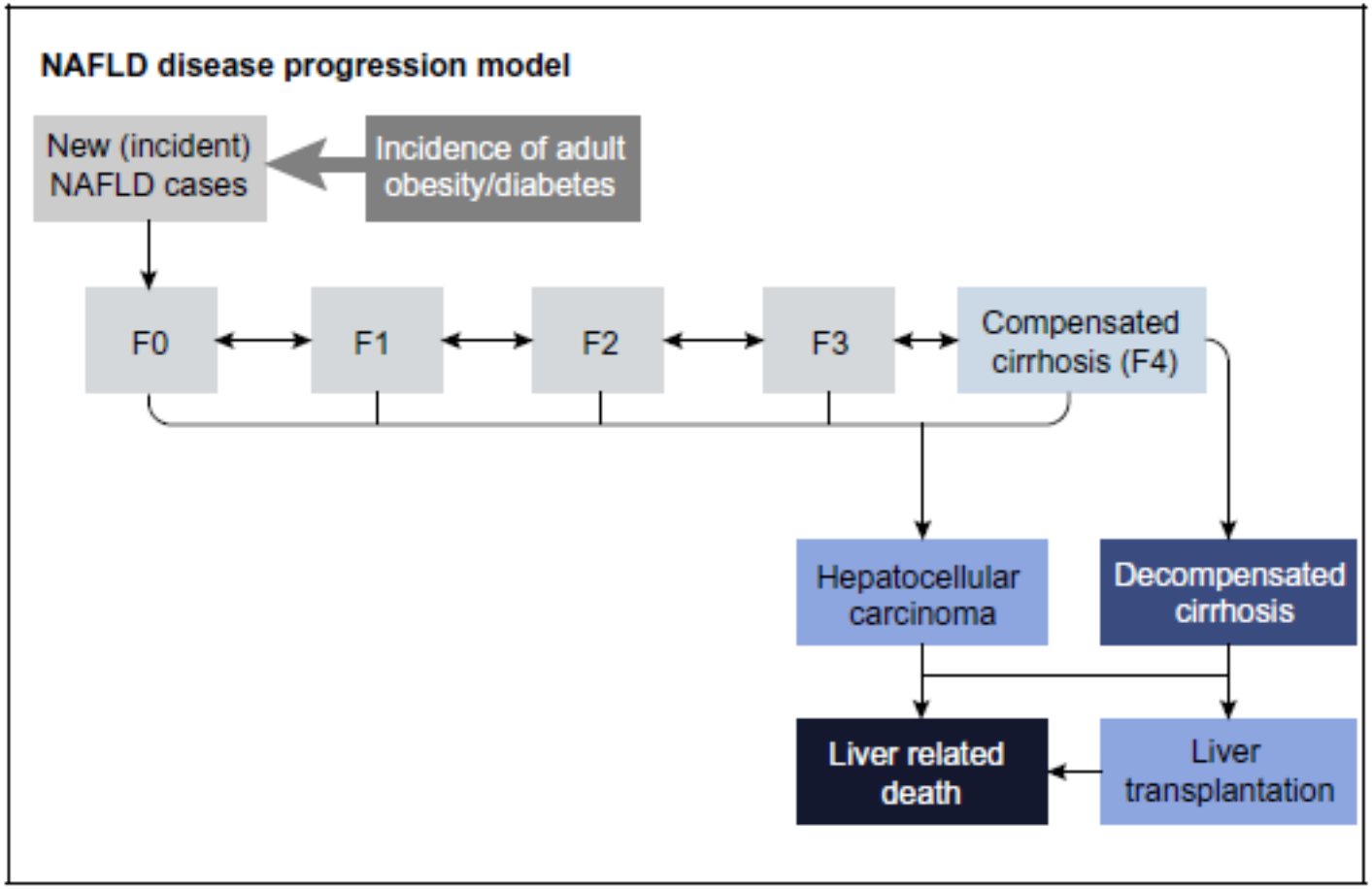


Figure 3. Body mass index and primary liver cancer risk, non-linear dose-risk relationship.
Abbreviation: RR, relative risk.

The Oncologist 2012;17:1461–1468 www.TheOncologist.com

Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030



Journal of Hepatology 2018 vol. 69 | 896–904

Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030

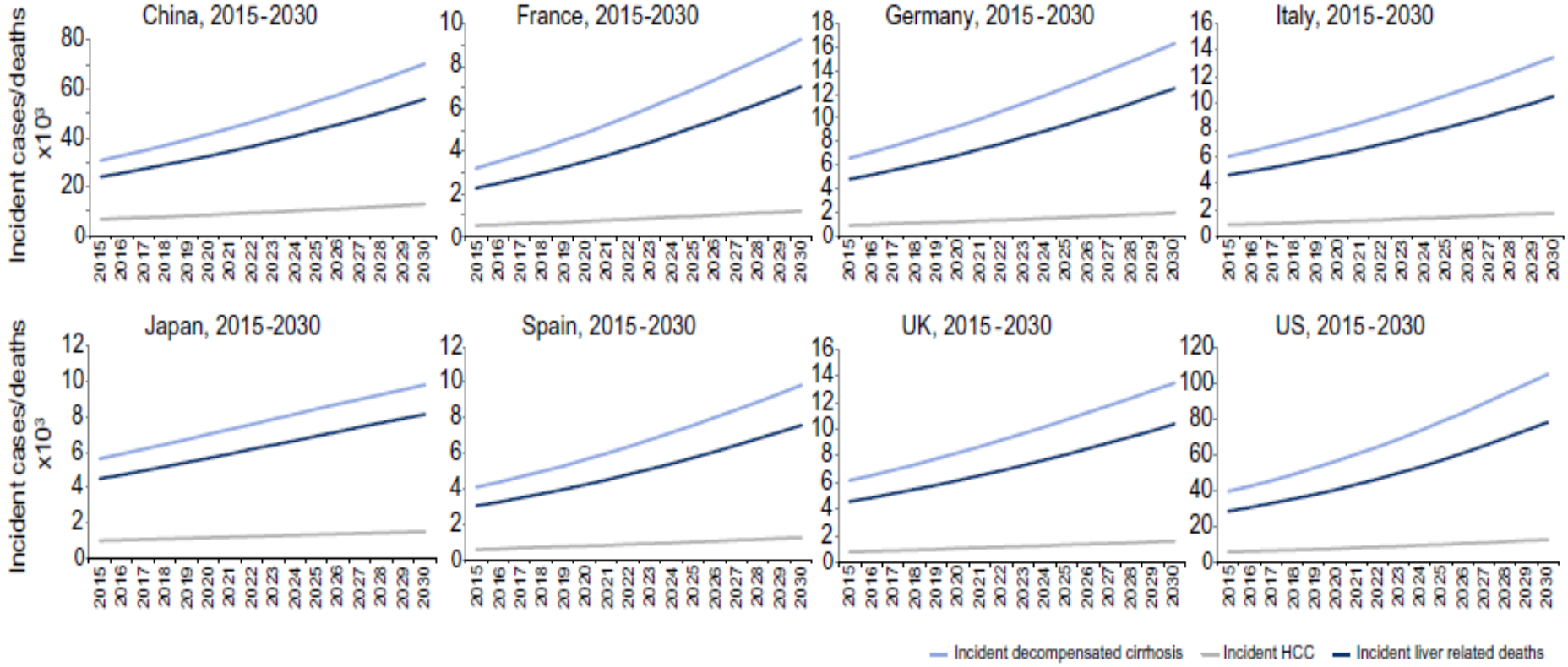


Fig. 3. Incident decompensated cirrhosis, HCC and liver-related deaths among prevalent NAFLD population – 2015–2030. HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease.

Journal of Hepatology **2018** vol. 69 | 896–904

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3. Prevention
4. Diagnosis
5. Medical treatments

Screening: US + lab + AFP every 6m

Table 3. Recommendations for HCC surveillance: Categories of adult patients in whom surveillance is recommended.

- Cirrhotic patients, Child-Pugh stage A and B **(evidence low; recommendation strong)**
- Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation (**evidence low; recommendation strong**)
- Non-cirrhotic HBV patients at intermediate or high risk of HCC* (according to PAGE-B† classes for Caucasian subjects, respectively 10–17 and ≥18 score points) (**evidence low; recommendation weak**)
- Non-cirrhotic F3 patients, regardless of aetiology may be considered for surveillance based on an individual risk assessment (**evidence low; recommendation weak**)

Page B: platelet, age, gender, hep B:

Sum ≤ 9 = low risk ≅ 0% HCC on 5y
Sum 10-17: intermediate ≅ 3 % HCC on 5y
Sum ≥ 18: high risk ≅ 17% HCC on 5y

Age (years)	Gender	Platelets (/mm³)
16-29: 0	Female: 0	≥200,000: 0
30-39: 2	Male: 6	100,000-199,999: 6
40-49: 4		<100,000: 9
50-59: 6		
60-69: 8		
≥70: 10		

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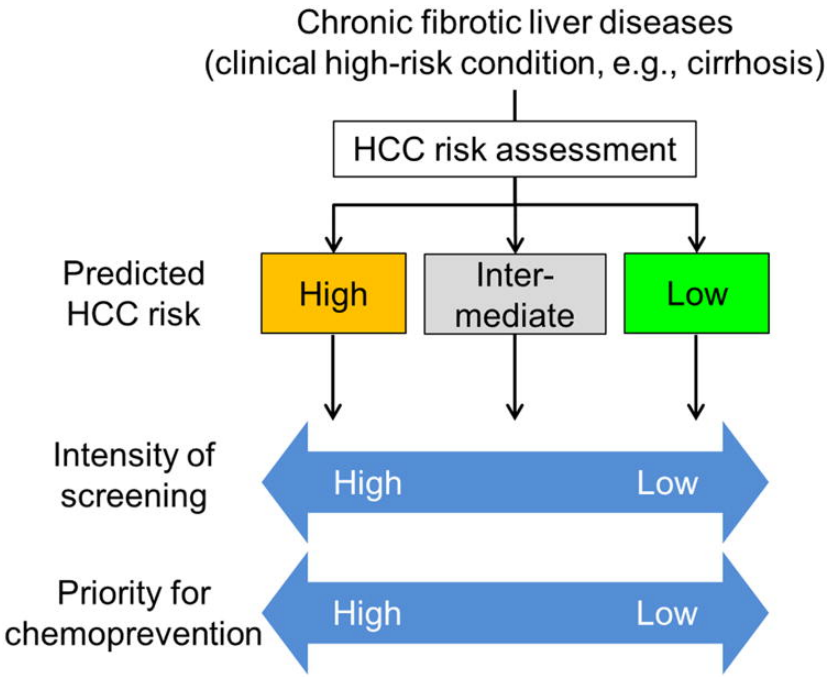
Screening: US + lab + AFP every 6m

Hcc risk stratification website => www.hccrisk.com

⇒ Risk based surveillance strategy = future

⇒ more frequently => 4/y ; abbreviated CE MRI (50%↓cost of N MRI) better than US when annual HCC incidence > 3%



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Prevention HCC

Stop alcohol, prevent obesity and NAFLD

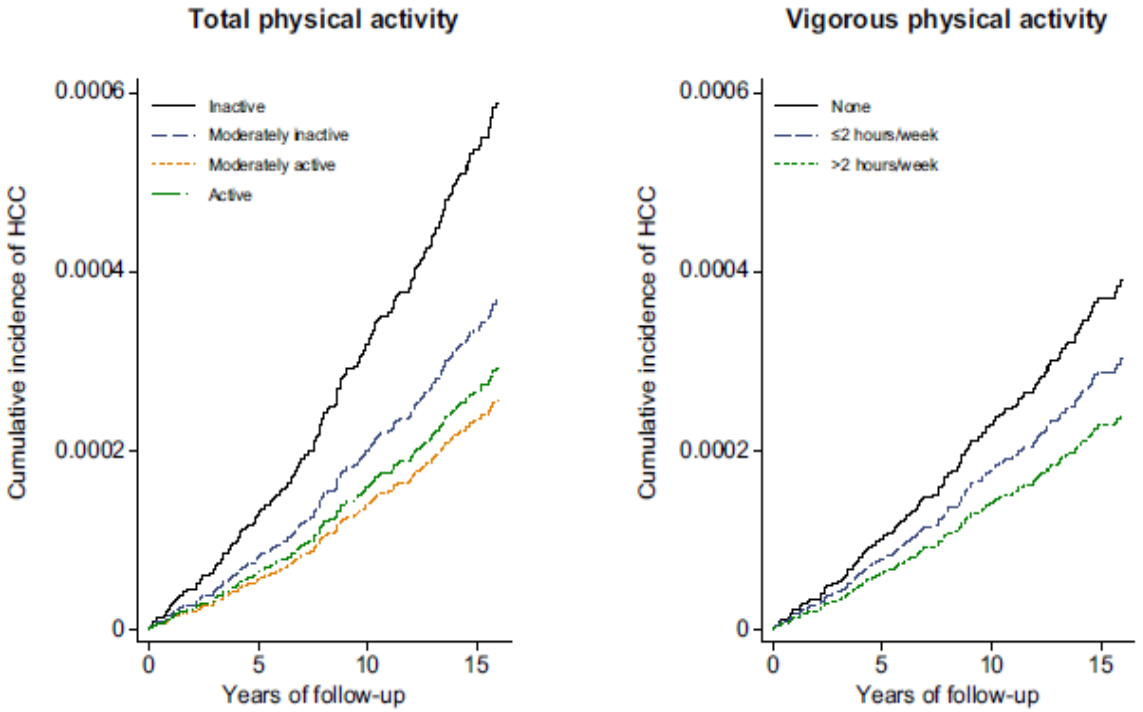
HBV: Vaccination and Nucleos(t)ide analogues NUCs

HCV: awareness and Direct acting antivirals DAAs

Exercise:

↓ All cause mortality

↓ Cancer risk 45%



Journal of Hepatology 2019 vol. 70 | 885–892

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Prevention HCC

Stop alcohol, prevent obesity and NAFLD

HBV: Vaccination and NUCs

HCV: awareness and DAAs

Exercise:

↓ All cause mortality

↓ cancer risk 45%

Coffee > tea: > 2 cups/d

Prevention HCC

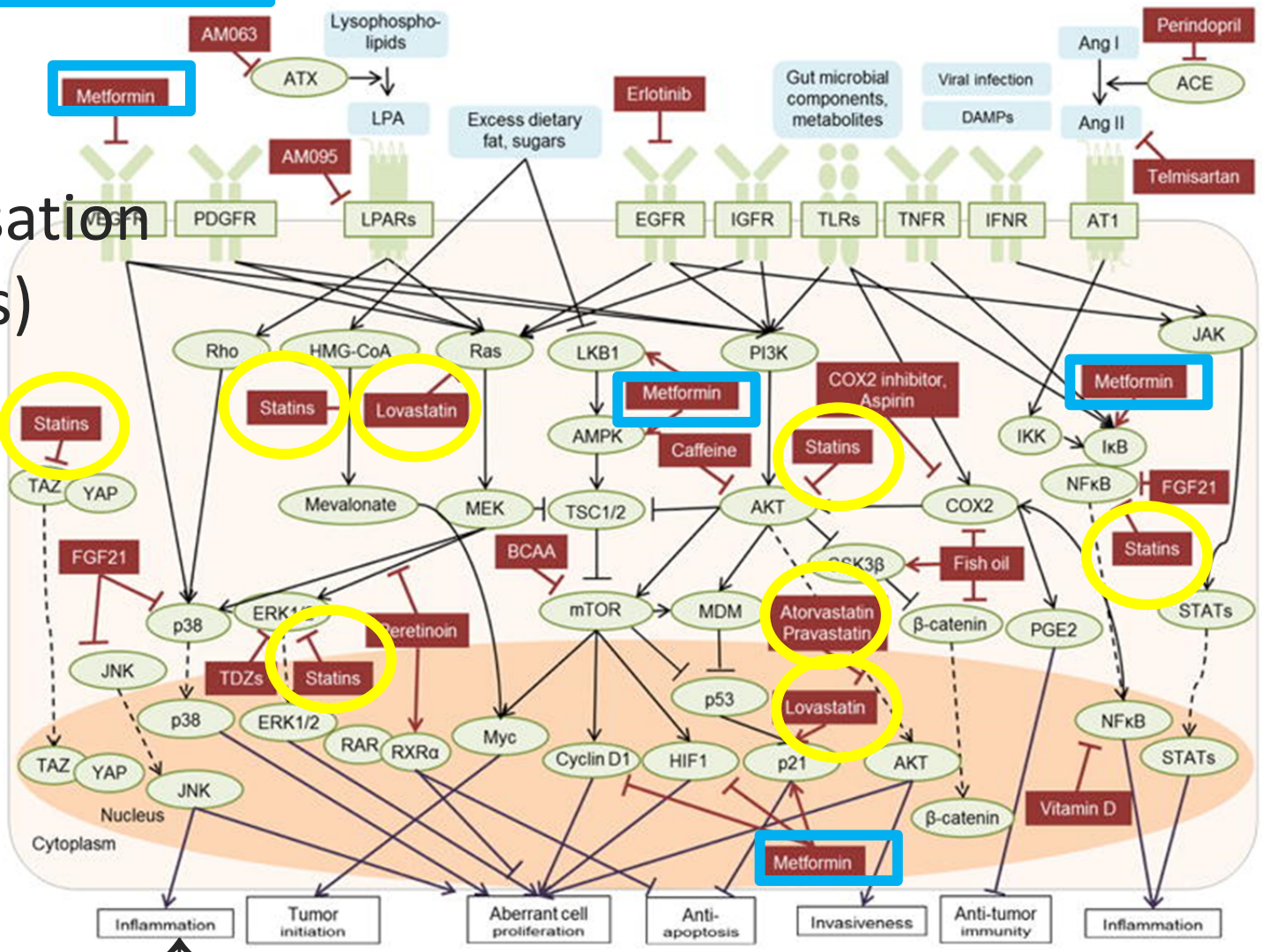
Statins and metformin:

↓ mortality

↓ HCC

↓ decompensation

↓ PHT (statins)



stop metformin => ↑ mortality

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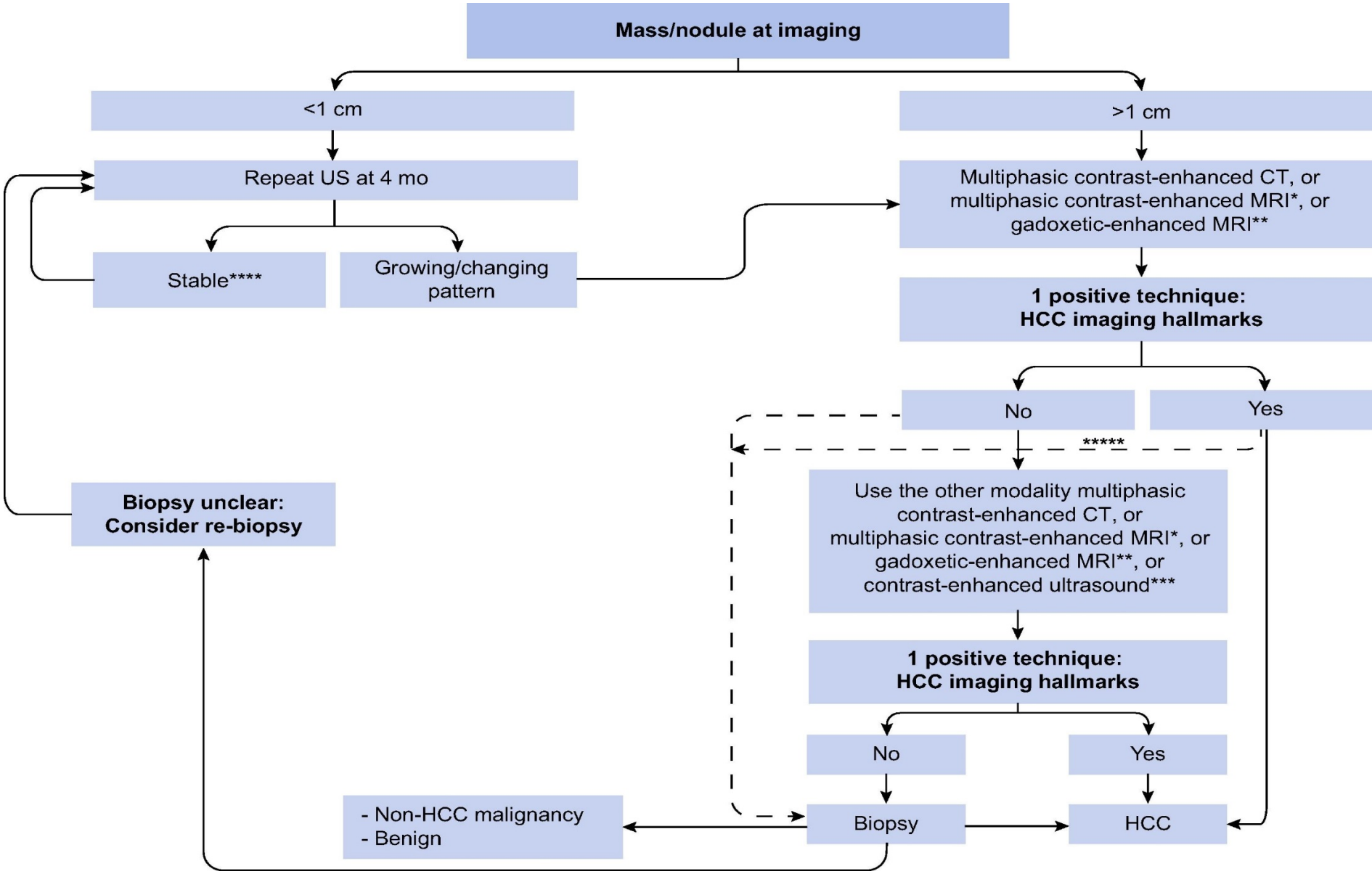
Journal of Hepatology
July 2018, 69: 182–236

DIAGNOSIS



US:

Sens: 61%

Spec 97%

Iso-echogenic

Hyper-echogenic

Hypo-echogenic

MRI: gadoxate

Sens: 70-100% Spec 97-100%

= as CT

=> Arterial substraction => detect small HCC

=> Hyperintensity on diffusion weighted MRI

CT scan

Sens: 53-68% Spec: 93-100%

Unenhanced: hypo- or isodense, capsule

Arterial phase: hyperdense, heterogeneous

Venous phase: iso- to hypodense: wash out

hyperdense: small hcc

heterogeneous

Delayed phase: hypodense,

scar/ pseudocapsule =hyperdense

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Assesment of the disease extension

- Prognosis is according EASL dependent upon
  - **Tumour stage**: size and extension of tumour?
    - CT lung
    - Bone scan
    - MR/CT liver
    - AFP
  - **General health** of the patient: general condition?

    ECOG

ECOG Performance status grades

ECOG	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair

ECOG: Eastern Cooperative Oncology Group

Assesment of the disease extension

- Prognosis is according EASL dependent upon
  - **Tumour stage**: size and extension of tumour?
    - CT lung
    - Bone scan
    - MR/CT liver
    - AFP
  - **General health** of the patient: general condition
    - ECOG
  - **Liver function**: Status of non-tumoural liver, PHT
  - **Treatment efficacy => BCLC stage**

Child Pugh score

Factor	Points		
	1	2	3
Serum bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Serum albumin (g/dL)	>3.5	3.0-3.5	<3.0
Prothrombin time			
Seconds prolonged	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Easily controlled	Poorly controlled
Hepatic encephalopathy	None	Minimal	Advanced

The Child-Pugh class can be A (a score of 5-6), B (7-9), or C (≥10).
INR: International normalized ratio

MELD score

MELD score range	90-day mortality rate
≤10	9% (1/11)
11-18	13% (6/45)
19-25	36% (8/22)
≥26	83% (19/23)

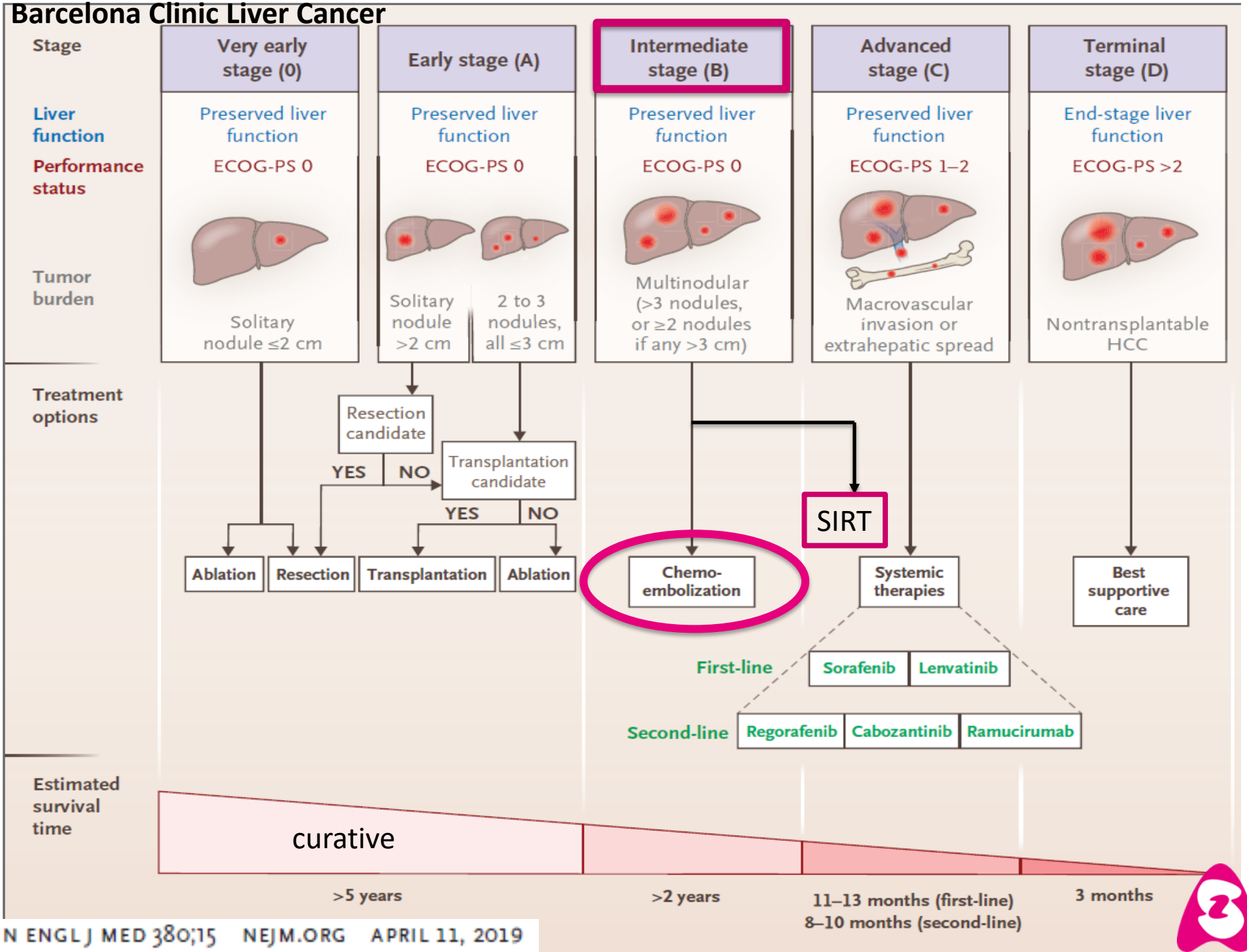
MELD: Model for End Stage Liver Disease. TIPS: transjugular intrahepatic portosystemic shunt.

MELD = 3.78 x $\log_e$ serum bilirubin (mg/dL) +
11.20 x $\log_e$ INR +
9.57 x $\log_e$ serum creatinine (mg/dL) +
6.43 (constant for liver disease etiology)

NOTES:
If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0

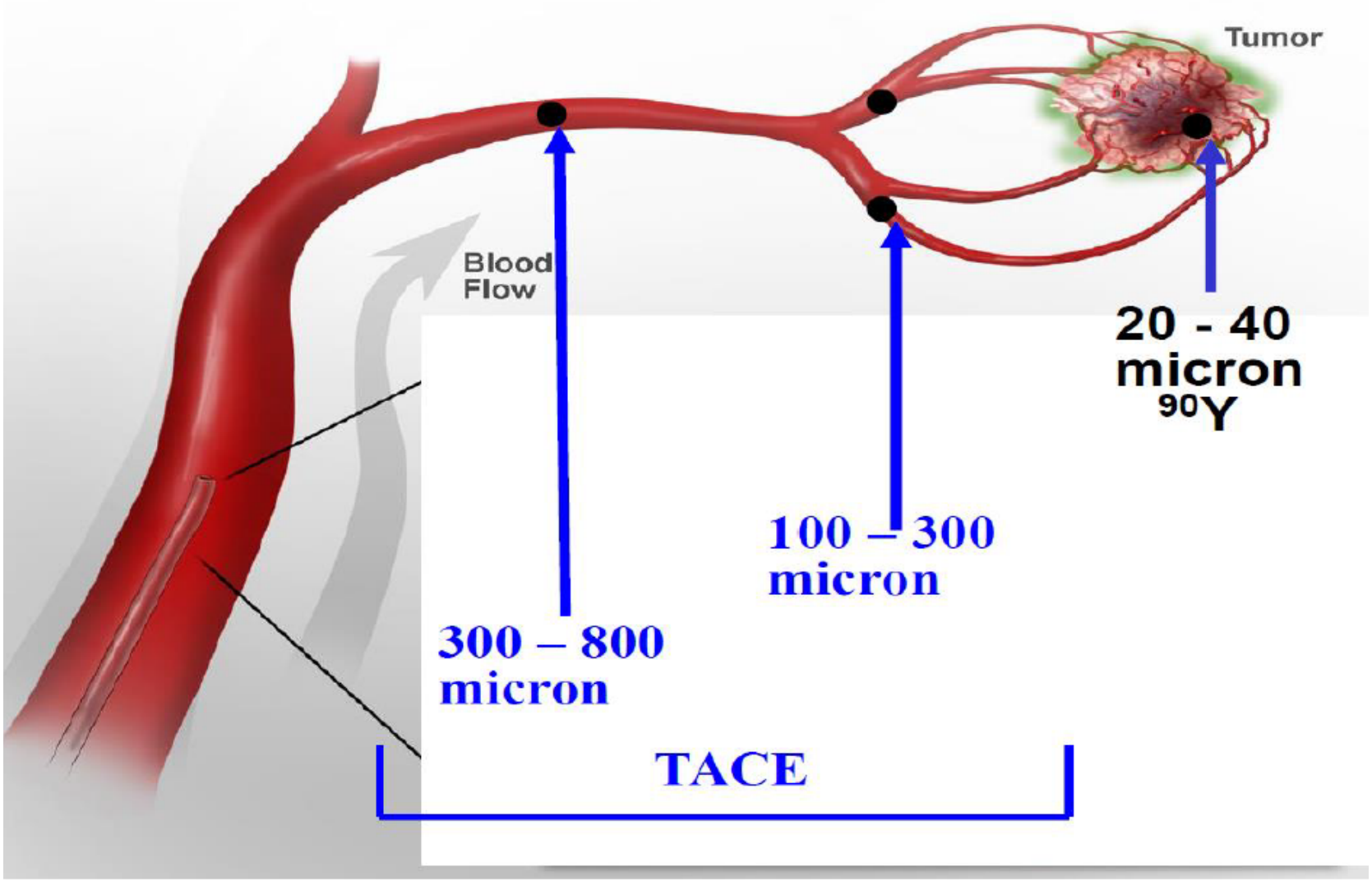
Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)

Barcelona Clinic Liver Cancer



Transarterial therapy: TACE – TARE/SIRT

BCLC-B stage



Morgan, Kennedy, Lewington et al. Nature Reviews in Clinical Oncology. October 2010

Transarterial therapies

TACE : transarterial chemoembolisation

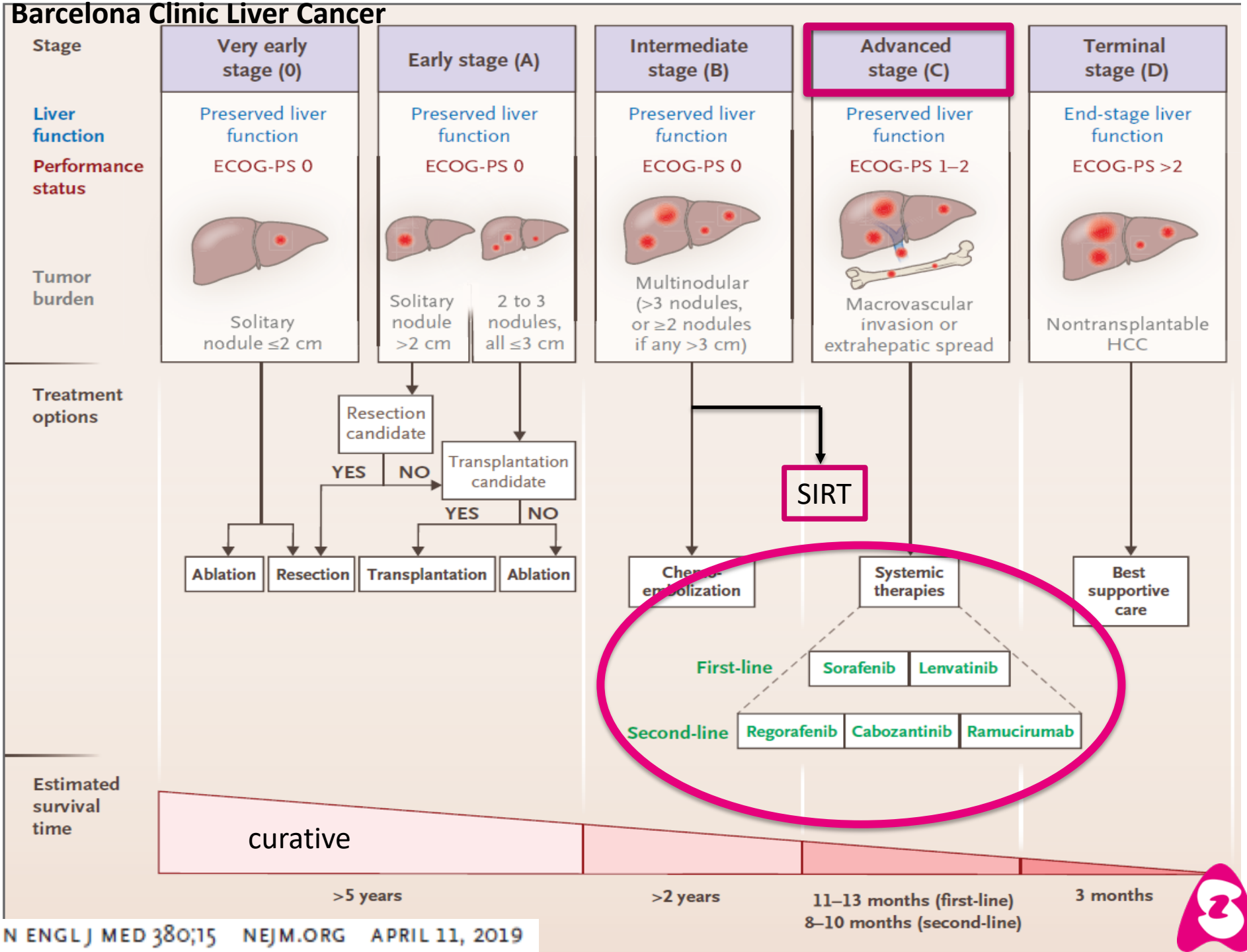
- IA infusion chemott + embolisation feeding vessel: cytotoxic + ischemic effect
- Doxorubicin, epirubicin, cisplatin, miriplatin, Doxo-DEB: OS 86% 1y; 57% 2y for all
- Superselective embolisation + conebeam CT
- Contra-Indications: bili > 2mg%; tumorburden > 50%; ECOG ≥ 2; vascular invasion PV; child B-C; cave biliary stents and biliary-enteric anastomosis => more abscesses
- Complications: postembolisationΣ, liver failure, alopecia

Transarterial therapies

TARE : transarterial radioembolisation = SIRT: selective internal radiation therapy

- Radio- Yttrium^{90}: β emittor, high E, low penetration, bound on resin (SIRs Sirtex®) or glass µ-spheres (Therasphere®)
- Lobar, sectorial or segmental approach
- Contra-Indications: bili > 2mg%; extrahepatic shunts => occluded; extrahepatic spread, child B/C
- Portal vein thrombosis is allowed ↔ TACE
- SIRT vs TACE???
  - Less toxicity, higher QOL
  - TTP and tumor control better, OS = same ≅ 16-20m

Barcelona Clinic Liver Cancer



First and second line therapies: BCLC-C

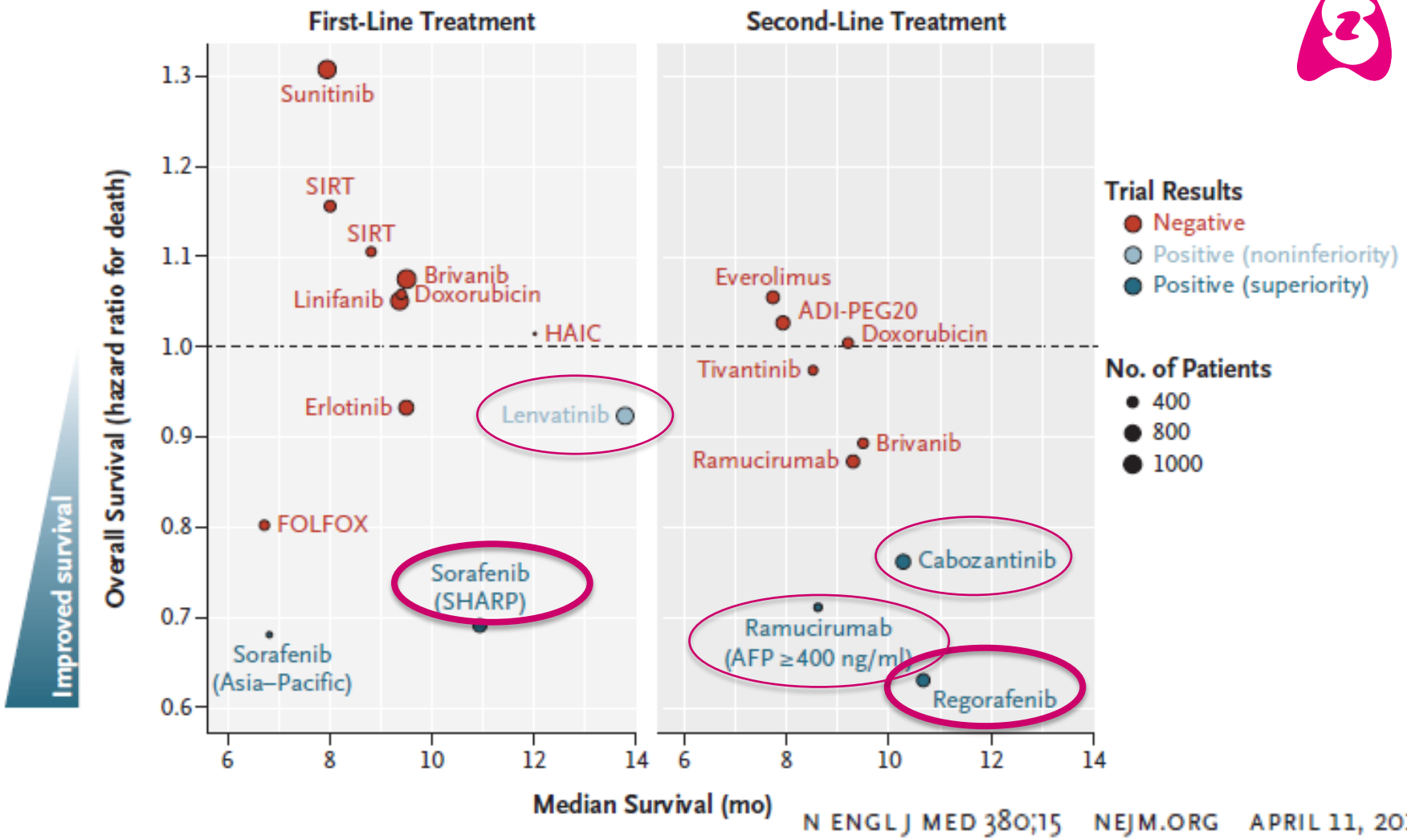


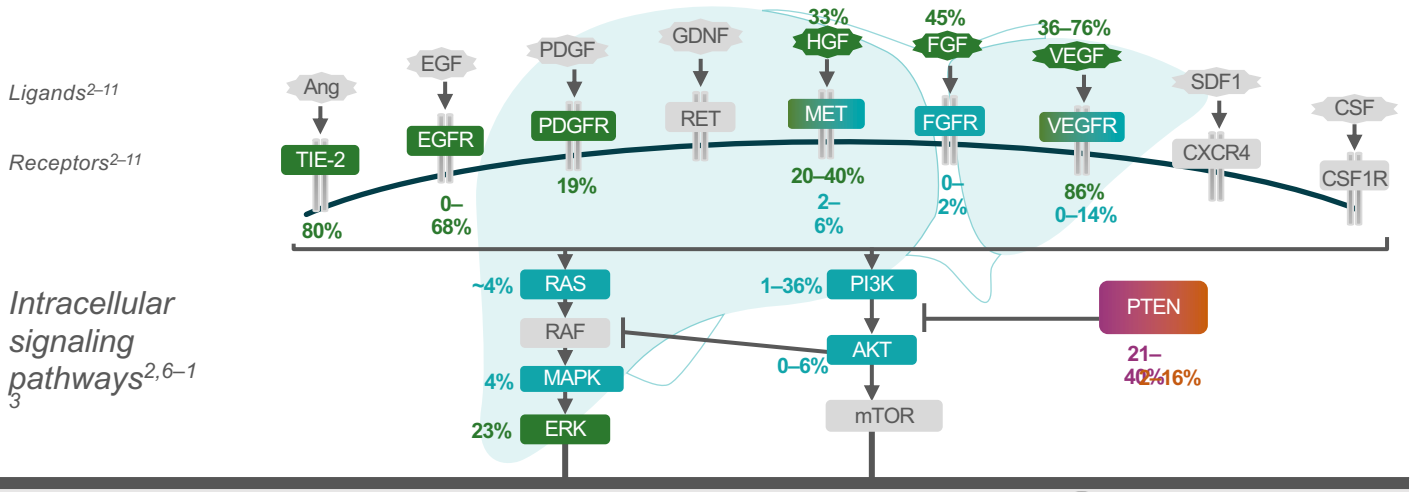
Figure 5. Systemic Therapies Tested in Phase 3 Trials for the Management of Advanced Hepatocellular Carcinoma.

ADI-PEG20 denotes pegylated arginine deiminase 20, HAIC hepatic arterial infusion chemotherapy, SHARP Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol, and SIRT selective internal radiation therapy.

CELL SIGNALING in HCC

Hepatocellular Carcinogenesis Involves Multiple Signaling Pathways

Development of hepatocellular carcinoma (HCC) is a complex, multistep process associated with altered activity of signaling pathways controlling cell division and survival[1–7]



Type of abnormality[2,4,6]

- Increased expression
- Activating mutation
- Deactivating mutation
- Decreased expression

Percentages indicate proportion of HCC cases harboring abnormality

Tumor immunity

- Tumor-associated macrophages support HCC progression and play key roles in suppressing immunological responses to tumor cells[7,14,15]
- CSF1R is involved in the recruitment of tumor-associated macrophages[7,14]

Tumor angiogenesis

- Blood vessels are required to satisfy the increasing metabolic needs of HCC[2,4]
- Liver cancers can overproduce the growth factor VEGF and overexpress its receptor (VEGFR), which are involved in angiogenesis[2]
- TIE-2, which mediates the angiogenic effects of angiopoietin, is overexpressed in HCC[4,16]

Oncogenesis

- Overexpression of tyrosine kinase receptors (e.g. PDGFR, MET) or their ligands (e.g. FGF19) can cause aberrant liver cell proliferation[2,6]

Metastasis

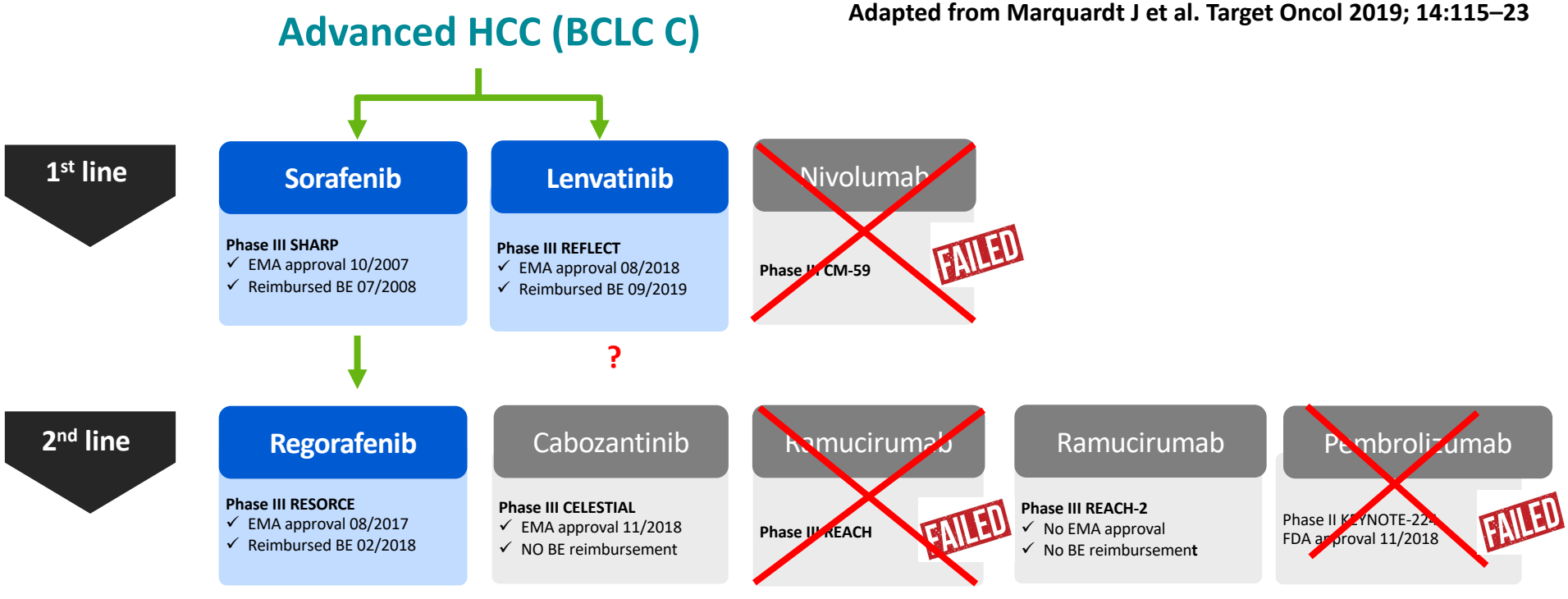
- Growth of new blood and lymph vessels promote liver tumor cells to spread from the original lesion[17]
- VEGF-C and its receptor VEGFR3 are involved in the formation of lymph vessels and are expressed in HCC[17,18]

References.
1. Llovet JM, et al. *Nat Rev Clin Oncol.* 2015;12:408–424. **2.** Marks EI & Yee NS. *Curr Cancer Drug Targets.* 2016;16:53–70. **3.** Zhong Z, et al. *Oncotarget.* 2016;7:36829–36841. **4.** Tanaka S, et al. *Hepatology.* 2002;35:861–867. **5.** Zhao Y & Adjei A. *Oncologist.* 2015;20:660–673. **6.** Wheeler D, et al. *Cell.* 2017;169:1327–1341. **7.** Cai H, et al. *OncoImmunology.* 2017;6:e1333213. **8.** Wilhelm S, et al. *Nat Rev Drug Discov.* 2006;5:835–844. **9.** Takahashi M. *Cytokine Growth Factor Rev.* 2001;12:361–373. **10.** eBioscience. Angiopoietin-TIE2 signaling. Accessible at http://www.ebioscience.com/resources/pathways/angiopoietin-tie2-signaling.htm. Accessed February 2018. **11.** Teicher BA & Fricker SP. *Clin Cancer Res.* 2010;16:2927–2931. **12.** Lim HY, et al. *Clin Cancer Res.* 2018;doi:10.1158/1078-0432.CCR-17-3588 (Epub ahead of print). **13.** Whittaker S, et al. Oncogene. 2010;29:4989–5005. **14.** Noy R, et al. *Immunity.* 2014;41:49–61. **15.** Wan S, et al. *Hepatology.* 2015;62:1304–1312. **16.** Pang R, et al. *Ann Surg Oncol.* 2010;15:962–971. **17.** Paduch R. *Cell Oncol. (Dordr).* 2016;39:397–410. **18.** Tanaka M & Iwakiri Y. *Cell Mol Gastroenterol Hepatol.* 2016;2:733–749. **19.** Abou-Elkacem L, et al. *Mol Cancer Ther.* 2013;12:1322–1331. **20.** Wilhelm SM, et al. *Int J Cancer.* 2011;129:245–255. **21.** Zopf D, et al. *Cancer Med.* 2016;5:3176–3185. **22.** Schmieder R, et al. *Int J Cancer.* 2014;135:1487–1496. **23.** Hoff S, et al. *Ann Oncol.* 2017;28(suppl_5):v403–v427. **24.** Daudigeos-Dubus E, et al. *PLoS One.*2015;10:e0142612. **25.** Takigawa H, et al. *Cancer Sci.* 2016;107:607–608.
26. Jost G, et al. *Invest Radiol.* 2013;48:715–721. **27.** Cyran CC, et al. *PLoS One.* 2013;8:e76009. **28.** Tai WT, et al. *Clin Cancer Res.* 2014;20:5768–5776. **29.** Kissel M, et al. *Oncotarget.* 2017;8:107096–107108.

Marketing Authorizations differ from country to country.
Please check according to regorafenib's SmPC of your home country the approved indications as well as adverse reactions and contraindications.

Sequencing options in advanced HCC: 1st line

Adapted from Marquardt J et al. Target Oncol 2019; 14:115–23



TKIs

monoclonal antibody

	Sorafenib[1]	Regorafenib[2]	Lenvatinib[3]	Cabozantinib[4]	Ramucirumab[5]*
Specific targets	• PDGFR-β • C-RAF, B-RAF, and mutant B-RAF • FLT-3 • RET/PTC	• PDGFR • FGFR • CSF1R • B-RAF, B-RAF^{V600E} • RAF-1 • TIE2	• FGFR (1–4) • PDGFR-α	• MET • AXL • TIE2 • FLT3	• VEGFR2
Common targets	• VEGFR (1–3) • RET, (c-)Kit				

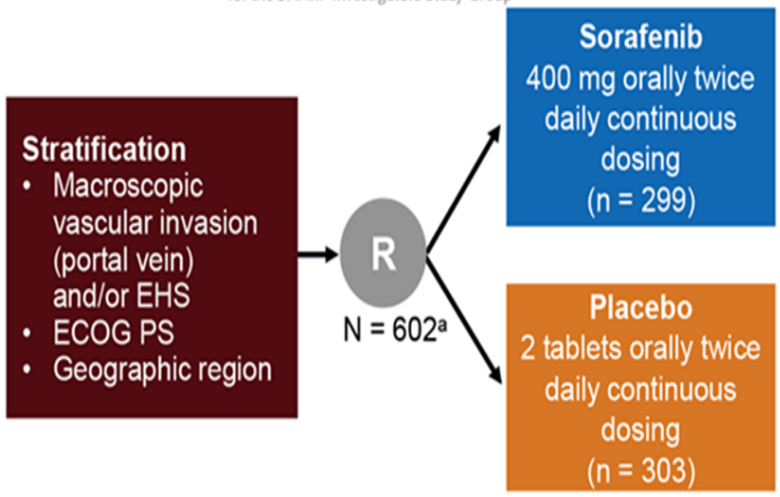
Llovet JM. NEJM 2008; 359: 378-390

Phase 3 SHARP Trial: Sorafenib Versus Placebo in Advanced HCC[1]

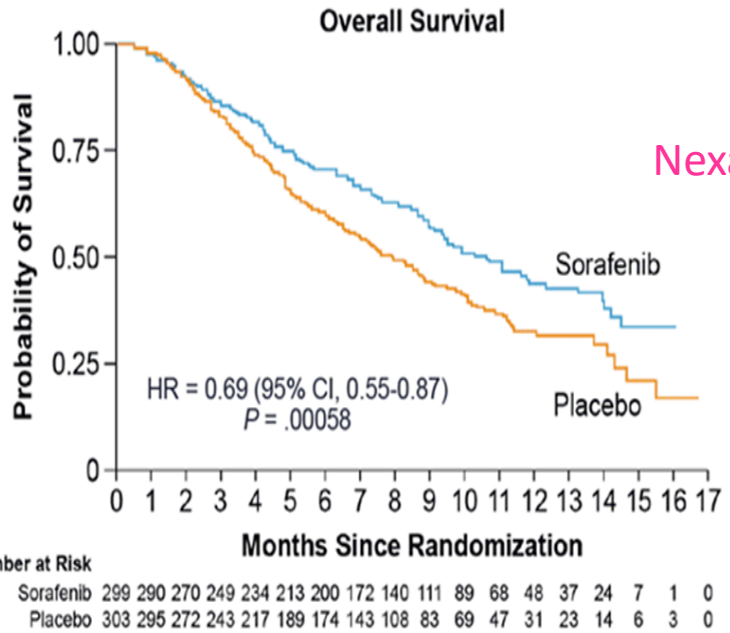
ORIGINAL ARTICLE

Sorafenib in Advanced Hepatocellular Carcinoma

Josep M. Llovet, M.D., Sergio Ricci, M.D., Vincenzo Mazzaferro, M.D., Philip Hilgard, M.D., Edward Gane, M.D., Jean-Frédéric Blanc, M.D., Andre Cosme de Oliveira, M.D., Armando Santoro, M.D., Jean-Luc Raoul, M.D., Alejandro Forner, M.D., Myron Schwartz, M.D., Camillo Porta, M.D., Stefan Zeuzem, M.D., Luigi Bolondi, M.D., Tim F. Greten, M.D., Peter R. Galle, M.D., Jean-François Seitz, M.D., Ivan Borbath, M.D., Dieter Häussinger, M.D., Tom Giannaris, B.Sc., Minghua Shan, Ph.D., Marius Moscovici, M.D., Dimitris Voliotis, M.D., and Jordi Bruix, M.D., for the SHARP Investigators Study Group*



[a] Majority of patients were Child–Pugh A.



Nexavar®

Sorafenib OS = 10.7 months
Placebo OS = 7.9 months

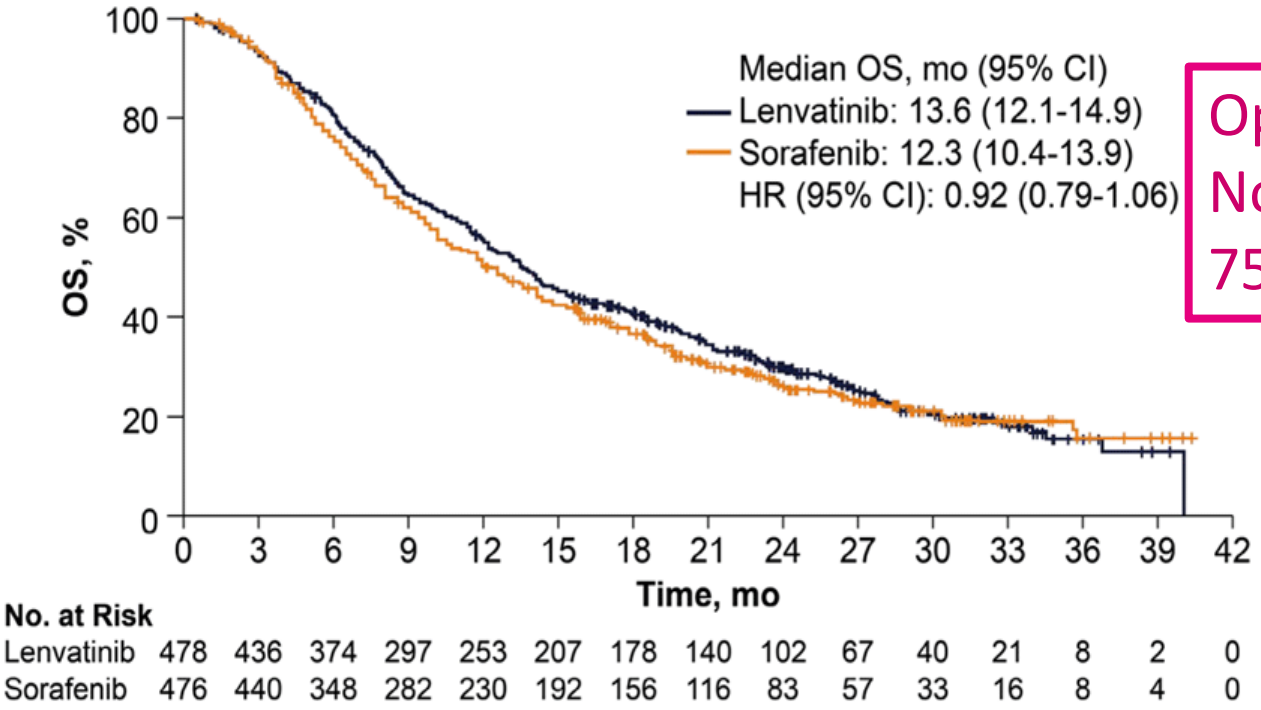
+3 months

Sorafenib is a protein kinase inhibitor with activity against many protein kinases, including VEGFR, PDGFR and RAF kinases.[2][3] Of the RAF kinases, Sorafenib is more selective for c-Raf than B-RAF

Kudo M. Lancet 2018; 391: 1163-1173: Phase 3 REFLECT trial

Lenvima®

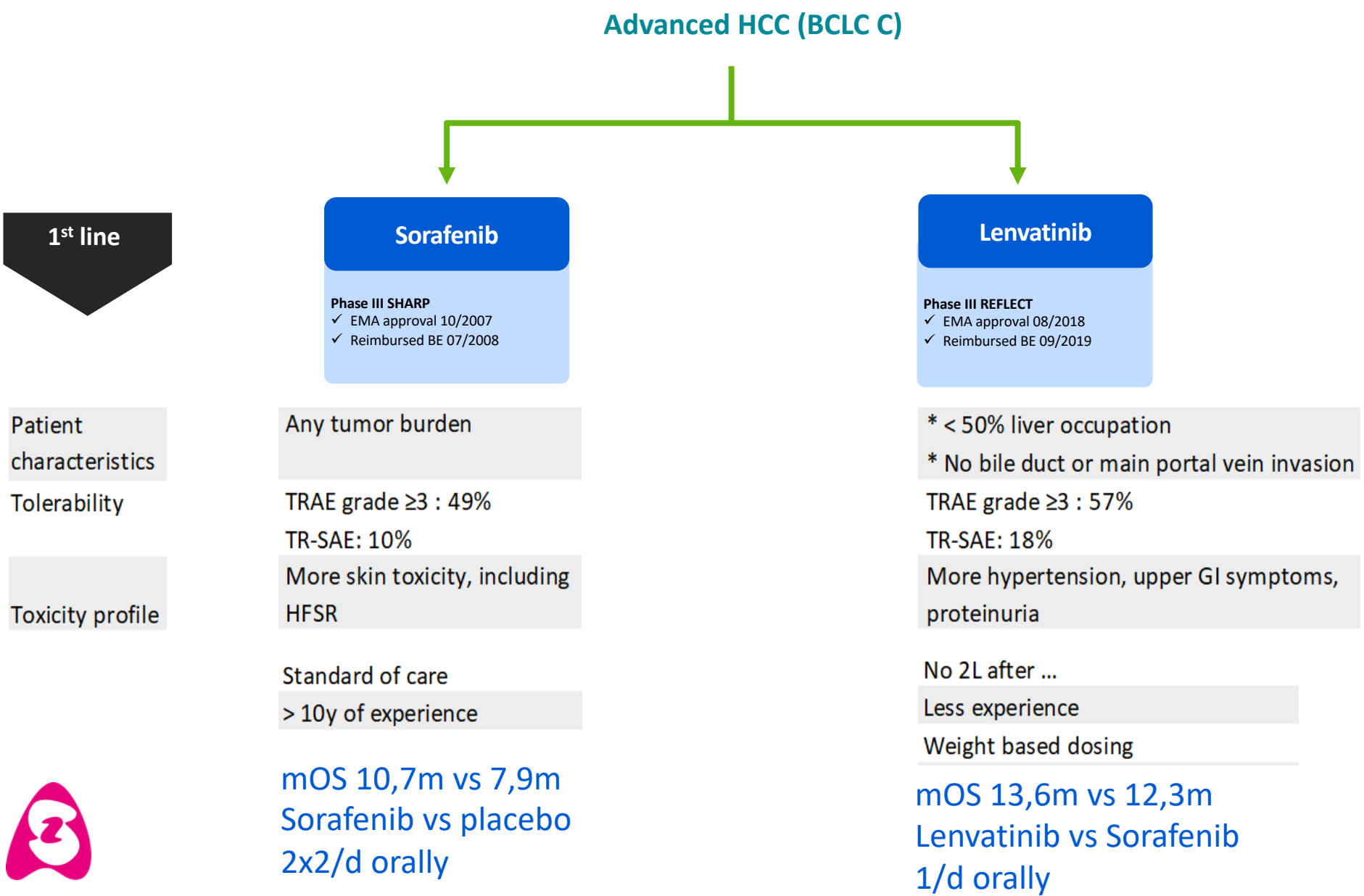
Lenvatinib Had Non-Inferior Overall Survival Compared to Sorafenib[1]



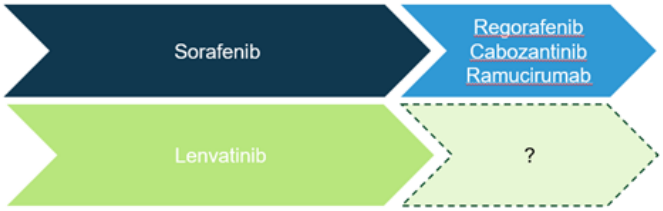
Open label
Non inferior
75% HBV

Lenvatinib acts as a multiple kinase inhibitor. It inhibits the three main vascular endothelial growth factor receptors VEGFR1, 2 and 3, as well as fibroblast growth factor receptors (FGFR) 1, 2, 3 and 4, platelet-derived growth factor receptor (PDGFR) alpha, c-Kit, and the RET proto-oncogene.

Selecting 1st line HCC systemic therapy



Sequencing options in advanced HCC: 2nd line



Advanced HCC (BCLC C)

1st line

Sorafenib

Phase III SHARP
- ✓ EMA approval 10/2007
- ✓ Reimbursed BE 07/2008

Lenvatinib

Phase III REFLECT
- ✓ EMA approval 08/2018
- ✓ Reimbursed BE 09/2019

Nivolumab ~~FAILED~~

Phase I/II CM-59

?

2nd line

Stivarga®

Regorafenib

Phase III RESORCE
- ✓ EMA approval 08/2017
- ✓ Reimbursed BE 02/2018

Cabozantinib

Phase III CELESTIAL
- ✓ EMA approval 11/2018
- ✓ NO BE reimbursement

Ramucirumab ~~FAILED~~

Phase III REACH

Ramucirumab

Phase III REACH-2
- ✓ No EMA approval
- ✓ No BE reimbursement

Pembrolizumab ~~FAILED~~

Phase II KEYNOTE-224
FDA approval 11/2018

Adapted from Marquardt J et al. Target Oncol 2019; 14:115–23

Adapted from Marquardt J et al. Target Oncol 2019; 14:115–23, 1. Nexavar (sorafenib) Full Prescribing Information, Bayer HealthCare Pharmaceuticals, Whippany, NJ, 2015; 2. Stivarga (regorafenib) Full Prescribing Information, Bayer HealthCare Pharmaceuticals, Whippany, NJ, 2018; 3. Lenvima (lenvatinib) Full Prescribing Information. Eisai Inc., Woodcliff Lake, NJ, 2018; 4. https://www.medicines.org.uk/emc/product/4331/smpc (accessed November 2018); 5. Zhu AX, et al. Lancet Oncol 2019;doi.org/10.1016/S1470-2045(18)30937-9

Sequencing options in advanced HCC: 2nd line

Advanced HCC (BCLC C)

1st line

- **Sorafenib**
  - Phase III SHARP
  - ✓ EMA approval 10/2007
  - ✓ Reimbursed BE 07/2008
- **Lenvatinib**
  - Phase III REFLECT
  - ✓ EMA approval 08/2018
  - ✓ Reimbursed BE 09/2019
- ~~Nivolumab~~
  - Phase I/II CM-59
  - FAILED

2nd line

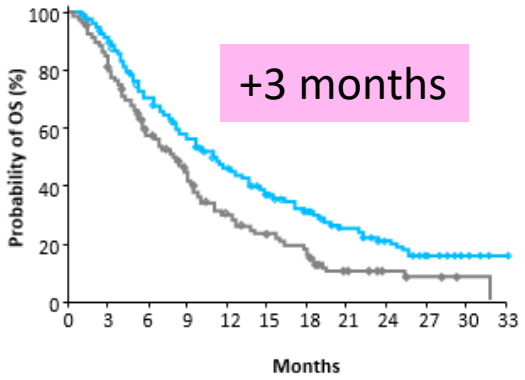
- **Regorafenib**
  - Phase III RESORCE
  - ✓ EMA approval 08/2017
  - ✓ Reimbursed BE 02/2018
- Cabozantinib
  - Phase III CELESTIAL
  - ✓ EMA approval 11/2018
  - ✓ NO BE reimbursement
- ~~Ramucirumab~~
  - Phase III REACH
  - FAILED
- Ramucirumab
  - Phase III REACH-2
  - ✓ No EMA approval
  - ✓ No BE reimbursement
- ~~Pembrolizumab~~
  - Phase II KEYNOTE-224
  - FDA approval 11/2018
  - FAILED

Sorafenib → Regorafenib / Cabozantinib / Ramucirumab

Lenvatinib → ?

RESORCE[1]

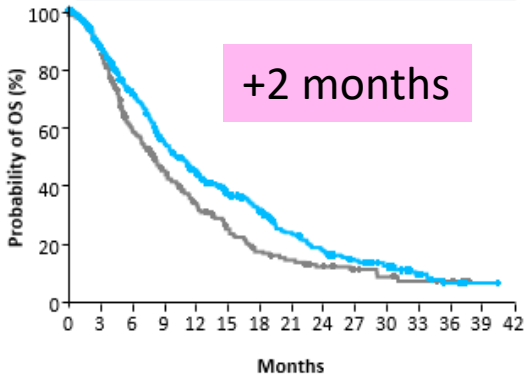
	Regorafenib n=379	Placebo n=194
mOS, (95% CI)	10.6 months (9.1–12.1)	7.8 months (6.3–8.8)
HR (95% CI)	0.63 (0.50–0.79); *P*<0.001	



+3 months

CELESTIAL[2]

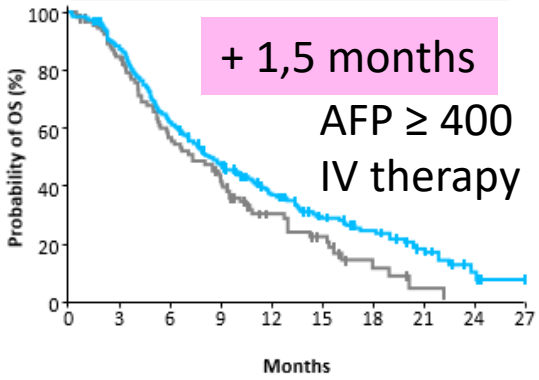
	Cabozantinib n=317	Placebo n=167
mOS (95% CI)	10.2 months (9.1–12.0)	8.0 months (6.8–9.4)
HR (95% CI)	0.76 (0.63–0.92); *P*=0.0049	



+2 months

REACH-2[3]

	Ramucirumab n=197	Placebo n=95
mOS (95% CI)	8.5 months (7.0–10.6)	7.3 months (5.4–9.1)
HR (95% CI)	0.71 (0.53–0.95); *P*=0.0199	



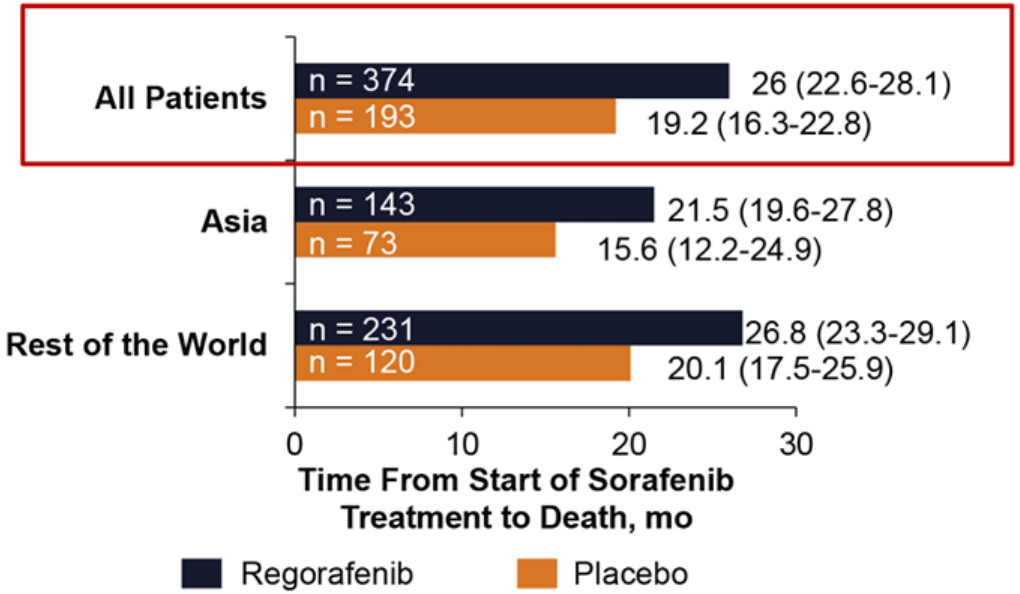
+ 1,5 months

AFP ≥ 400

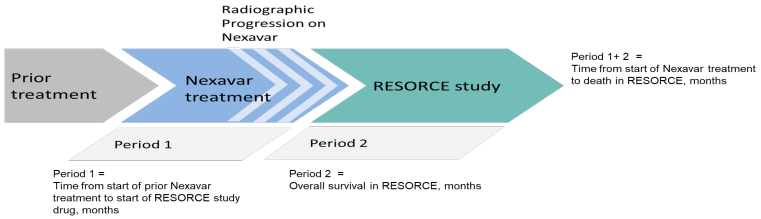
IV therapy

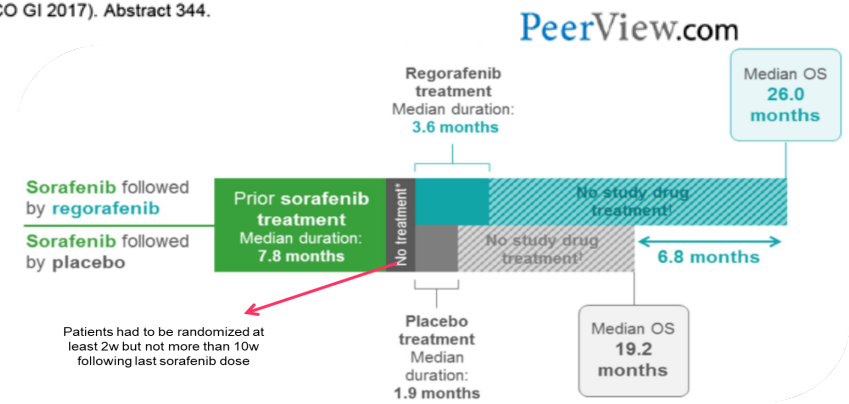
1. Bruix J et al. Lancet. 2017;389:56. 2. Abou-Alfa GK et al. N Engl J Med 2018;379:54. 3. Zhu AX et al. Lancet Oncol 2019;20:282

Sequencing Systemic Therapies Can Provide Meaningful Survival Exceeding 2 Years[1,2]



1. Finn RS et al. 2017 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI 2017). Abstract 344.
2. Finn RS et al. *J Hepatol*. 2018;69:353-358.





Patients who tolerate Sorafenib could potentially benefit from an average of **26 month OS** from the start of Sorafenib.

Sequencing options in advanced HCC: 2nd line

A.S.Z. ZIEKENHUIS

How to choose second line treatment?

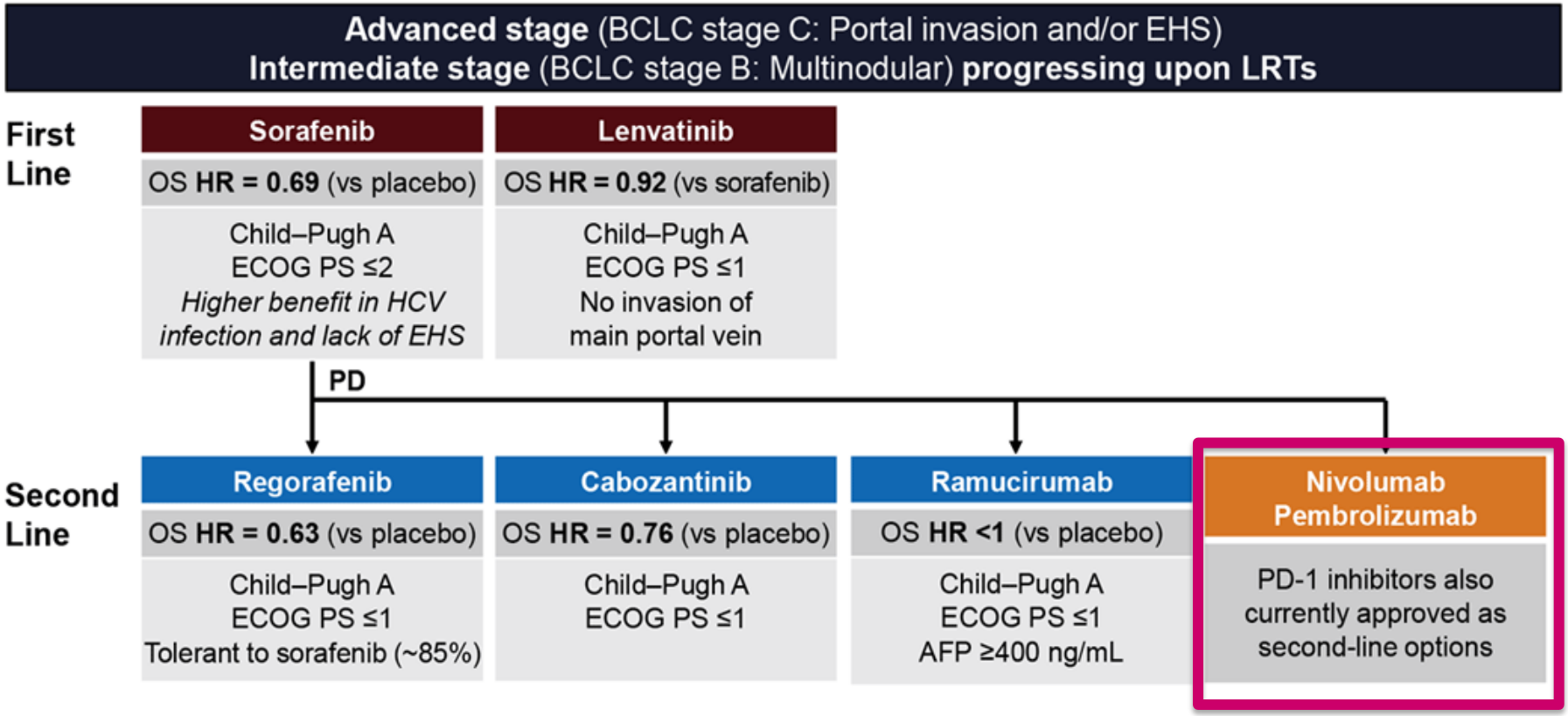
	Regorafenib	Cabozantinib	Ramucirumab
Level of evidence	Phase 3	Phase 3	Phase 3
Inclusion criteria	• Tolerated sorafenib but with radiographic progression	• Intolerant to sorafenib or with radiographic progression • Could have received an additional line of systemic therapy	• Intolerant to sorafenib or with radiographic progression • Patients with AFP ≥400 ng/mL
Efficacy	• Improved OS	• Improved OS	• Improved OS
AE profile	• Similar to AE profile of other TKIs	• Similar to AE profile of other TKIs	• Well tolerated with low rates of dose reductions or discontinuations
Logistics	• Orally daily for 3 weeks with 1-week holiday	• Orally once daily	• IV infusion every 2 weeks

FAILED for EMEA phase 3

Sequencing options in advanced HCC: 2nd line

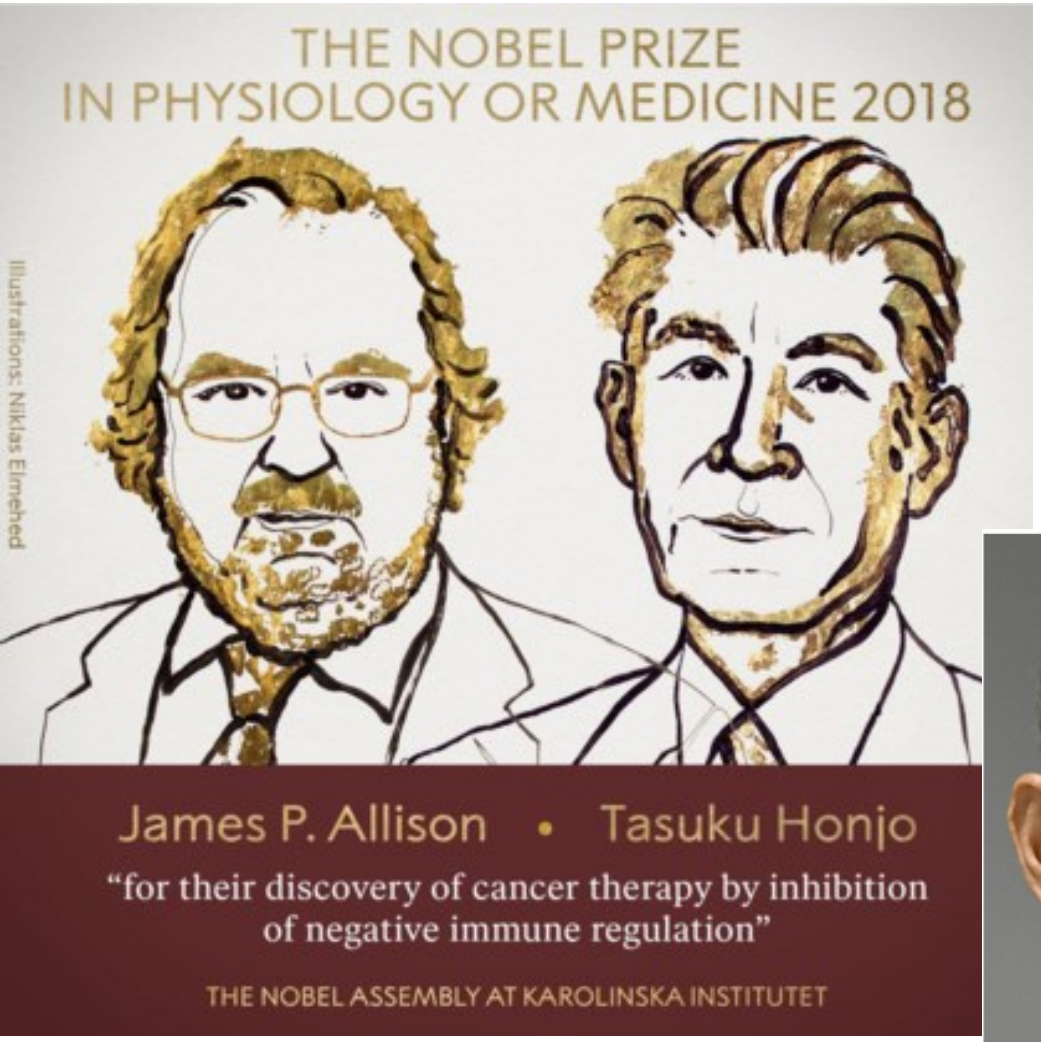
A.S.Z. ZIEKENHUIS

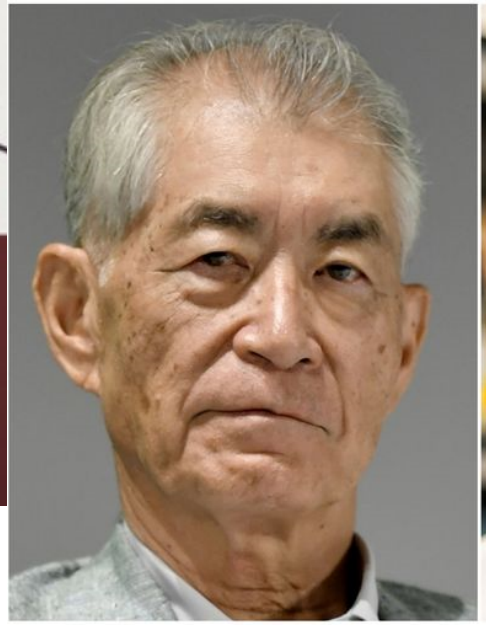
Treatment Strategy for Patients With Advanced HCC[1]

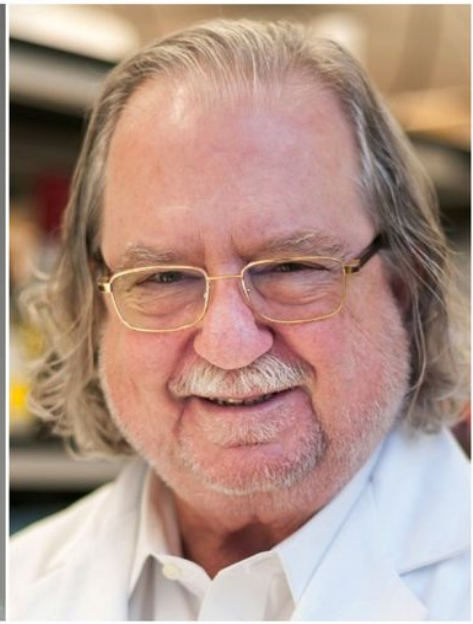


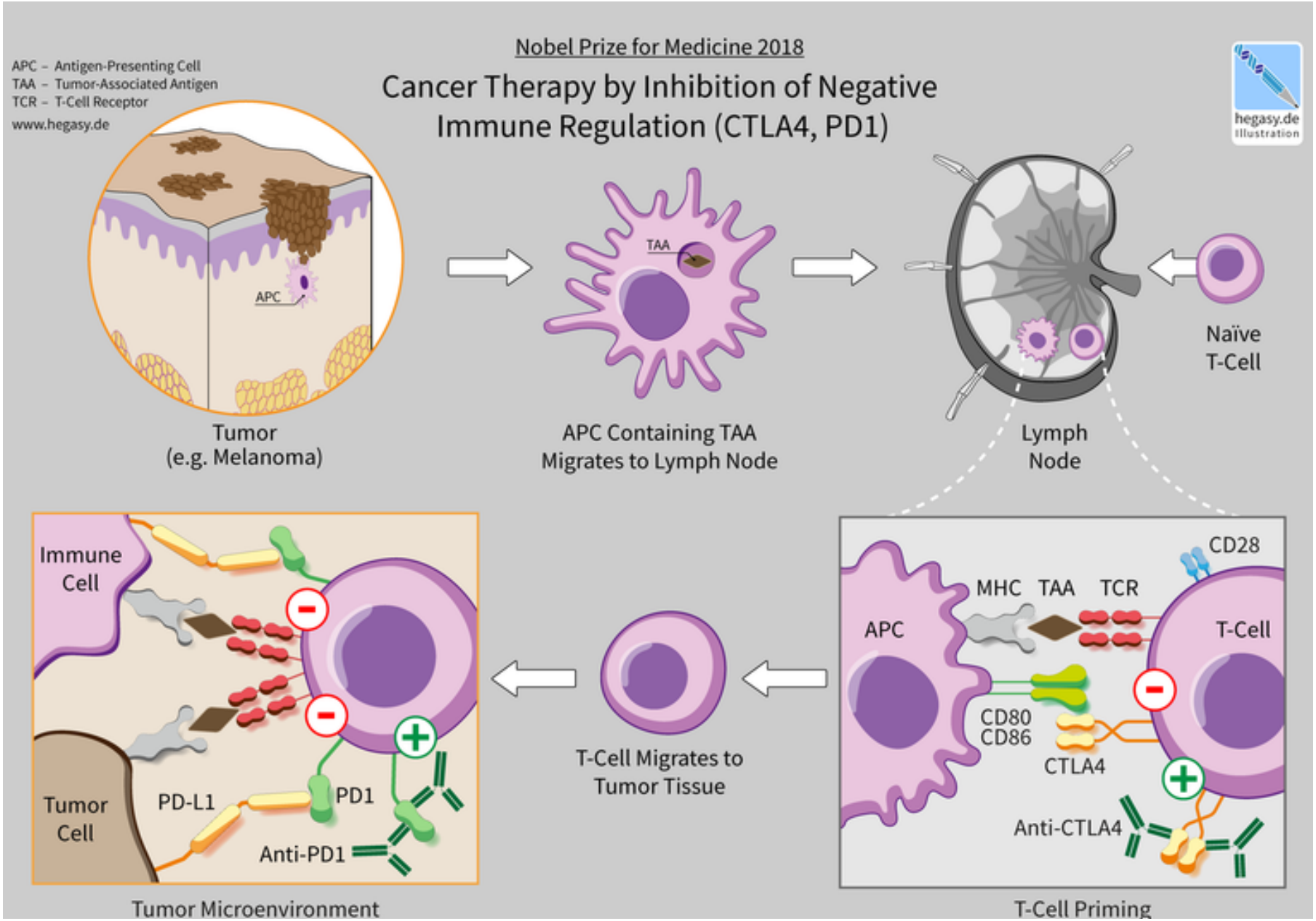
1. Llovet JM et al. *Nat Rev Clin Oncol*. 2018;15:599-616.

Cancer therapy by inhibition of negative immune regulation (CTLA4, PD1)





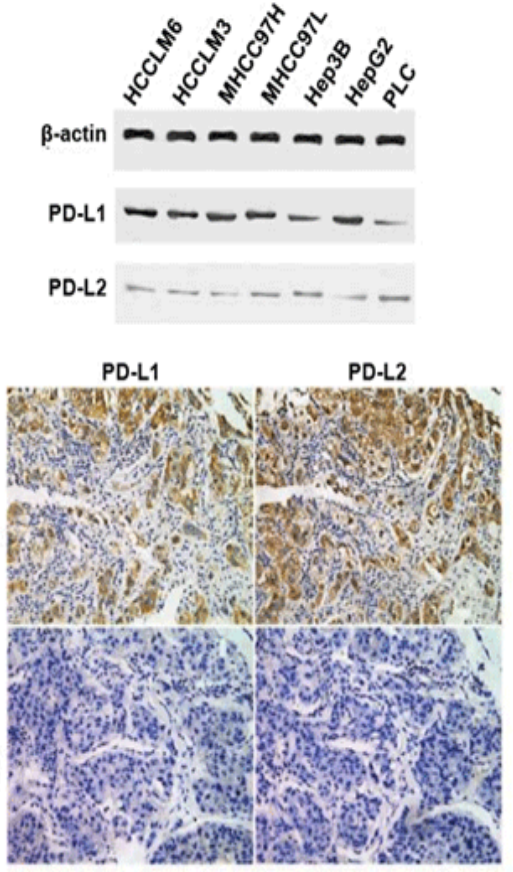


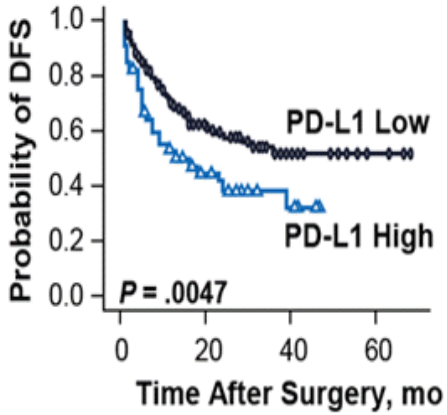


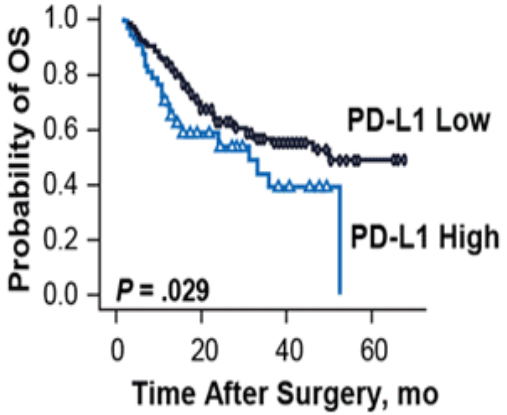
Programmed cell death 1 protein and ligand PD1 and PDL1 => regulates inflammation in tissue/tumor

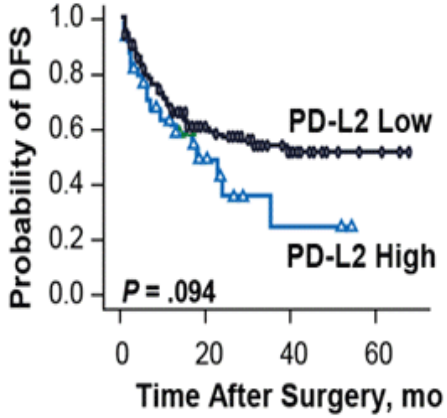
Cytotoxic T lymfocyte associated Ag 4 immune checkpoint => Dampener of T cell activation in ADP

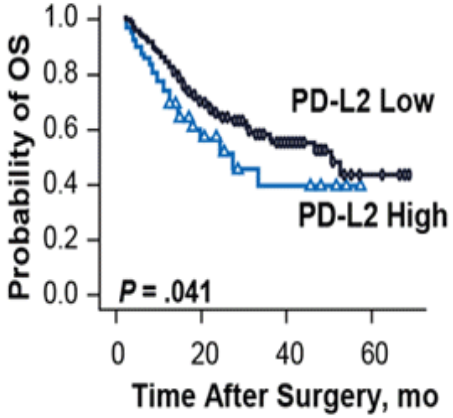
Rationale for Immunotherapy in HCC (Cont'd)[1,2]





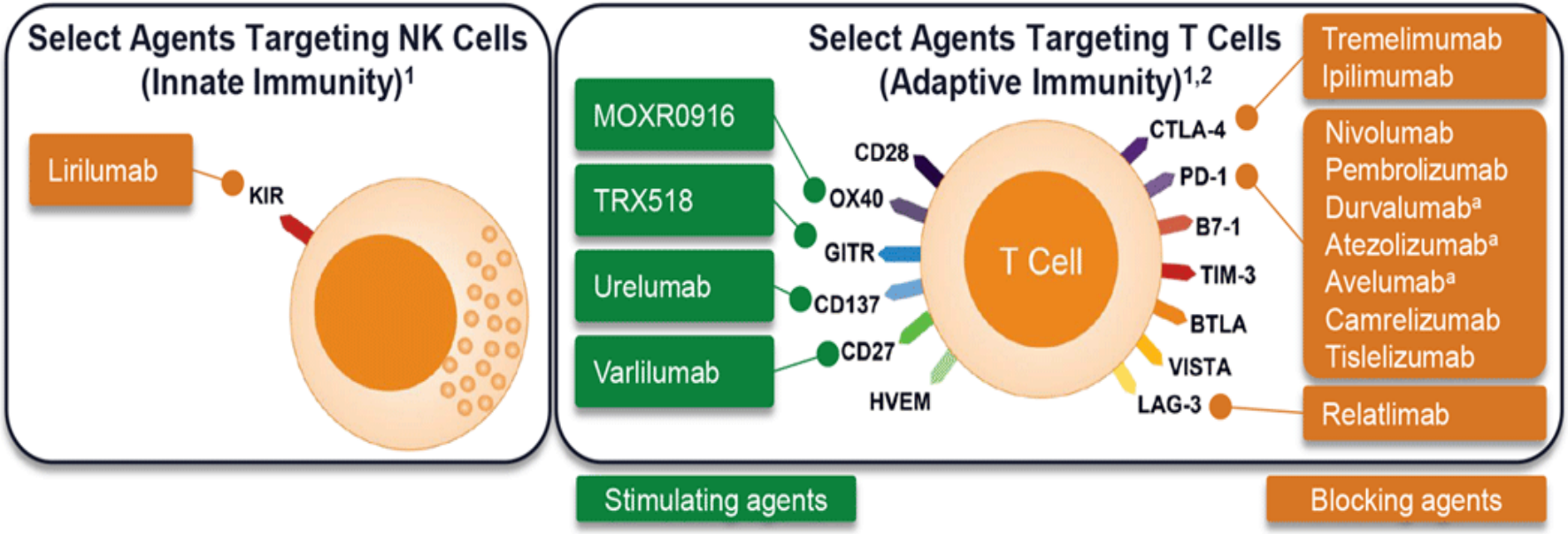






1. Umemoto Y et al. *J Gastroenterol*. 2015;50:65-75. 2. Gao Q et al. *Clin Cancer Res*. 2009;15:971-979.

Targeting Checkpoints as an Approach to Cancer Therapy



Not a complete list; several checkpoint-targeted agents are under investigation in the cancer setting[3]

[a] These agents target PD-L1.

1. Adapted from Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264. 2. Adapted from Mellman I et al. *Nature*. 2011;480:480-489.
3. http://www.clinicaltrials.gov. Accessed May 9, 2019.

Checkpoint Inhibitor Landscape for HCC in the United States

FDA Approved for Subsequent-Line Therapy if There Is Disease Progression[1]

Nivolumab	Pembrolizumab
Child–Pugh A or B7	Child–Pugh A

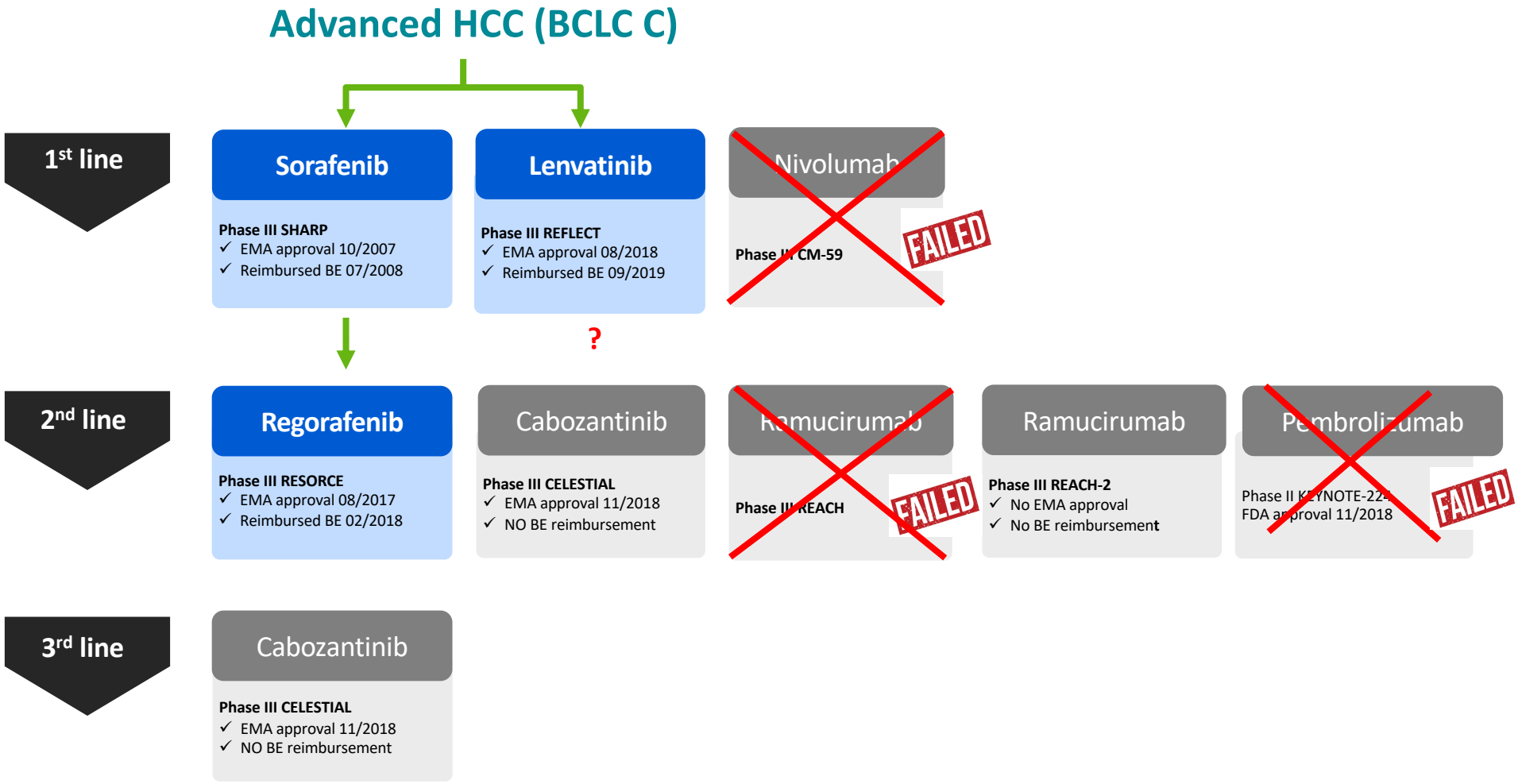
Emerging Checkpoint Inhibitors Under Investigation for HCC[2]

Nivolumab	Pembrolizumab	Tislelizumab
Targets PD-1 Phase 3: Monotherapy in first line	Targets PD-1 Phase 3: With lenvatinib in first line	Targets PD-1 Phase 3: Monotherapy in second line

Durvalumab	Atezolizumab
Targets PD-L1 Phase 3: With tremelimumab in first line	Targets PD-L1 Phase 3: With cabozantinib in first line Phase 3: With bevacizumab in first line

1. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers. V2.2019. Accessed May 10, 2019. 2. http://www.clinicaltrials.gov. Accessed May 13, 2019.

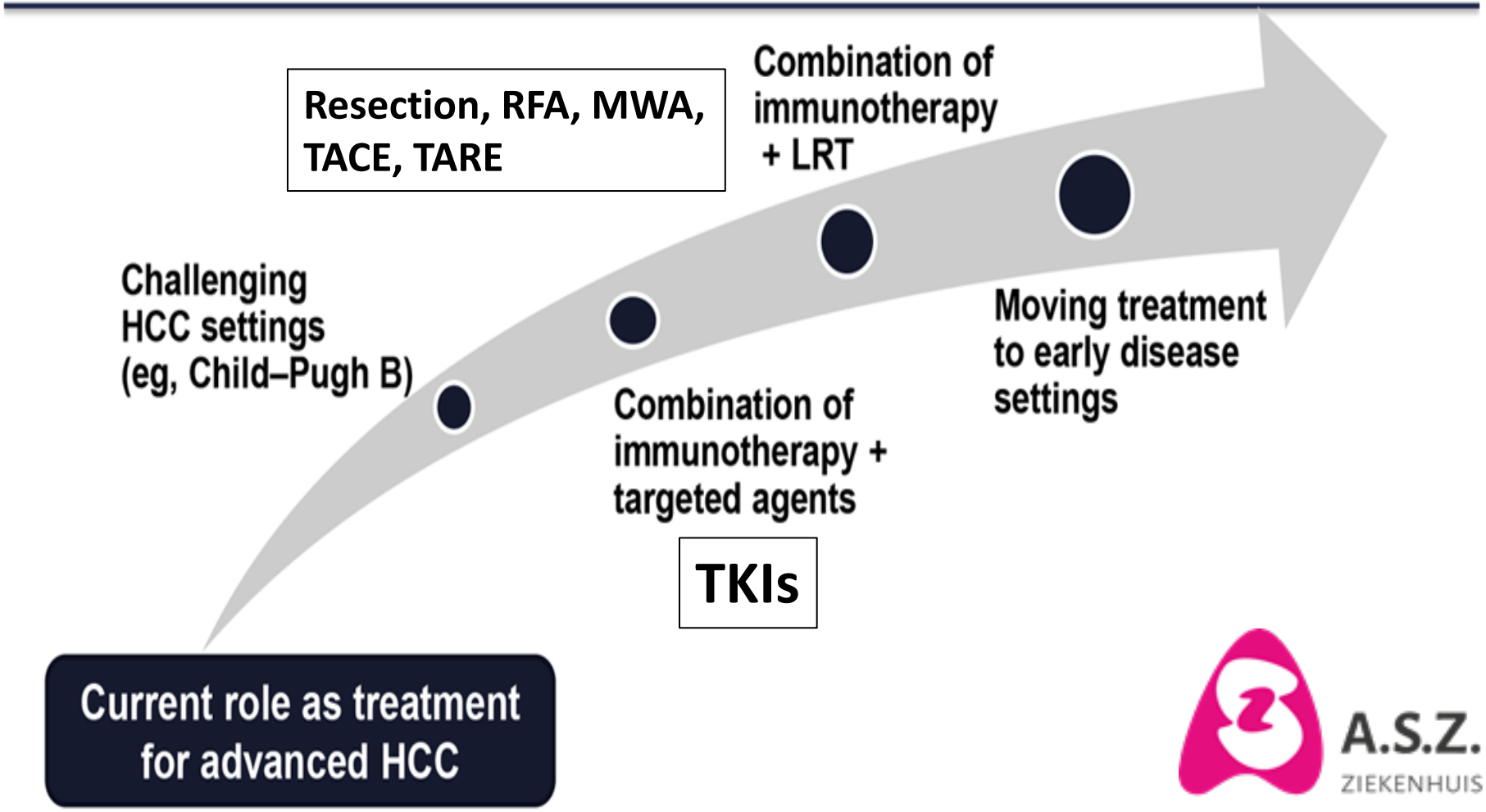
Sequencing options in advanced HCC: 3rd line



Adapted from Marquardt J et al. Target Oncol 2019; 14:115–23

CONCLUSIONS

Expanding the Role of Novel Therapeutics in HCC

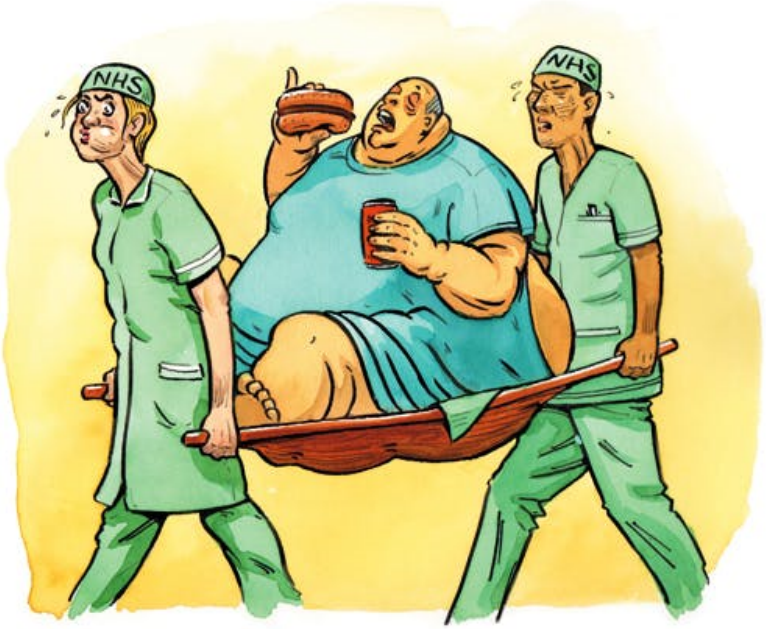


A.S.Z. ZIEKENHUIS

A.S.Z.
ZIEKENHUIS

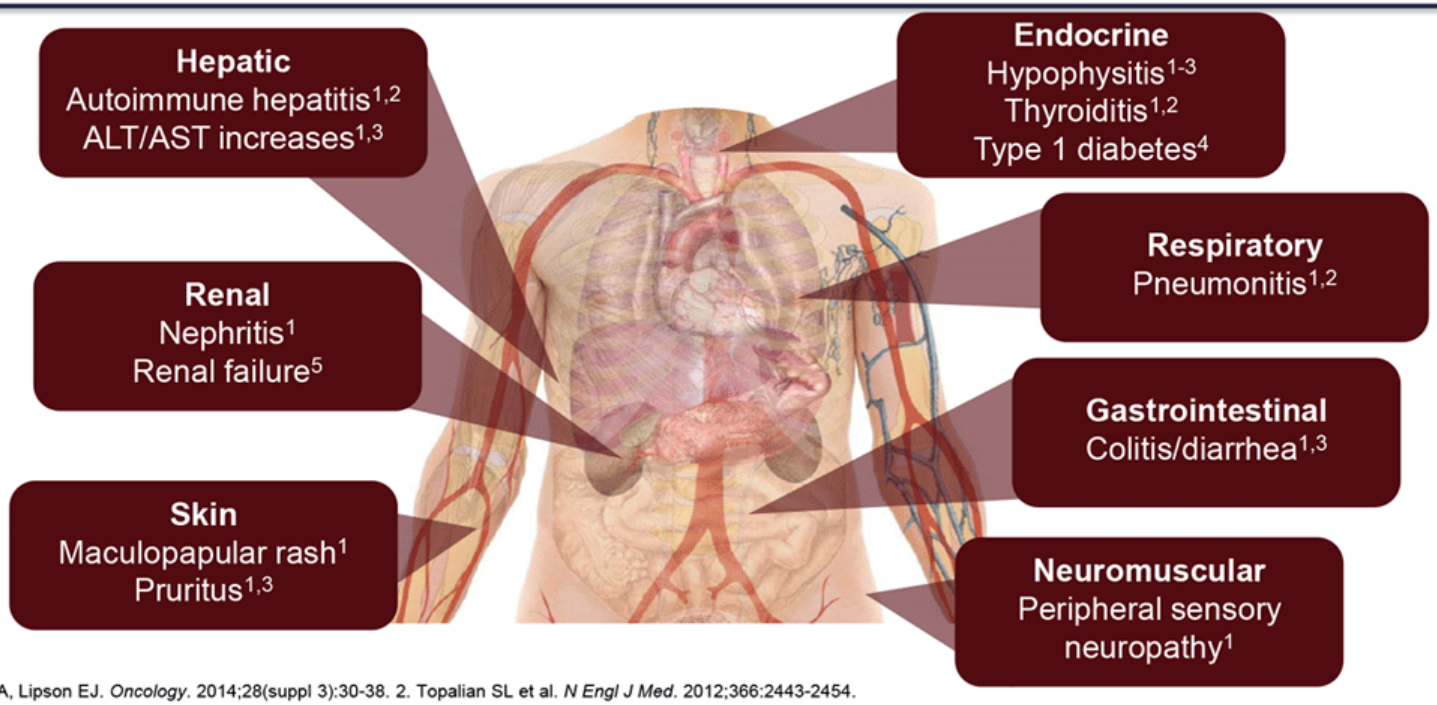
The future is *Bright!*

BEWARE



It is not as innocent as it seems

Immune-Related Adverse Events



1. Teply BA, Lipson EJ. *Oncology*. 2014;28(suppl 3):30-38. 2. Topalian SL et al. *N Engl J Med*. 2012;366:2443-2454.
3. Hodi FS et al. *N Engl J Med*. 2010;363:711-723. 4. Mellati M et al. *Diabetes Care*. 2015;38:e137-e138.
5. Forde PM et al. *Anticancer Res*. 2012;32:4607-4608.

General Algorithm for Managing Immune-Related Adverse Events[1-3]

Grade 1 (Minimal or No Symptoms; Diagnostic Changes Only)	Grade 2 (Mild to Moderate Symptoms)	Grade 3/4 (Severe or Life-Threatening Symptoms)
• Continue immunotherapy (or consider temporary delay) • Symptomatic therapy	• Withhold immunotherapy • Corticosteroids if symptoms do not resolve in 1 week (prednisone 0.5-1 mg/kg/d or equivalent) • Taper corticosteroids over ≥1 month to reduce recurrence • Re-dose if toxicity resolves to grade ≤1	• Discontinue immunotherapy • Hospitalization, multidisciplinary evaluation indicated • HD corticosteroids (prednisone 1-2 mg/kg/d or equivalent) • Taper HD corticosteroids over ≥1 month until toxicity resolves to grade ≤1 (prednisone 1-2 mg/kg/d or equivalent)

- If no improvement or progression, additional immunosuppressant treatment, such as infliximab, may be needed
- If >4 weeks of corticosteroids or other immunosuppressants needed, consider administration of antimicrobial/antifungal prophylaxis to prevent opportunistic infections

1. Postow MA. *Am Soc Clin Oncol Educ Book*. 2015:76-83. 2. Brahmer JR et al. *J Clin Oncol*. 2018;36:1714-1768. 3. Weber JS et al. *J Clin Oncol*. 2015;33:2092-2099.

EASL guidelines

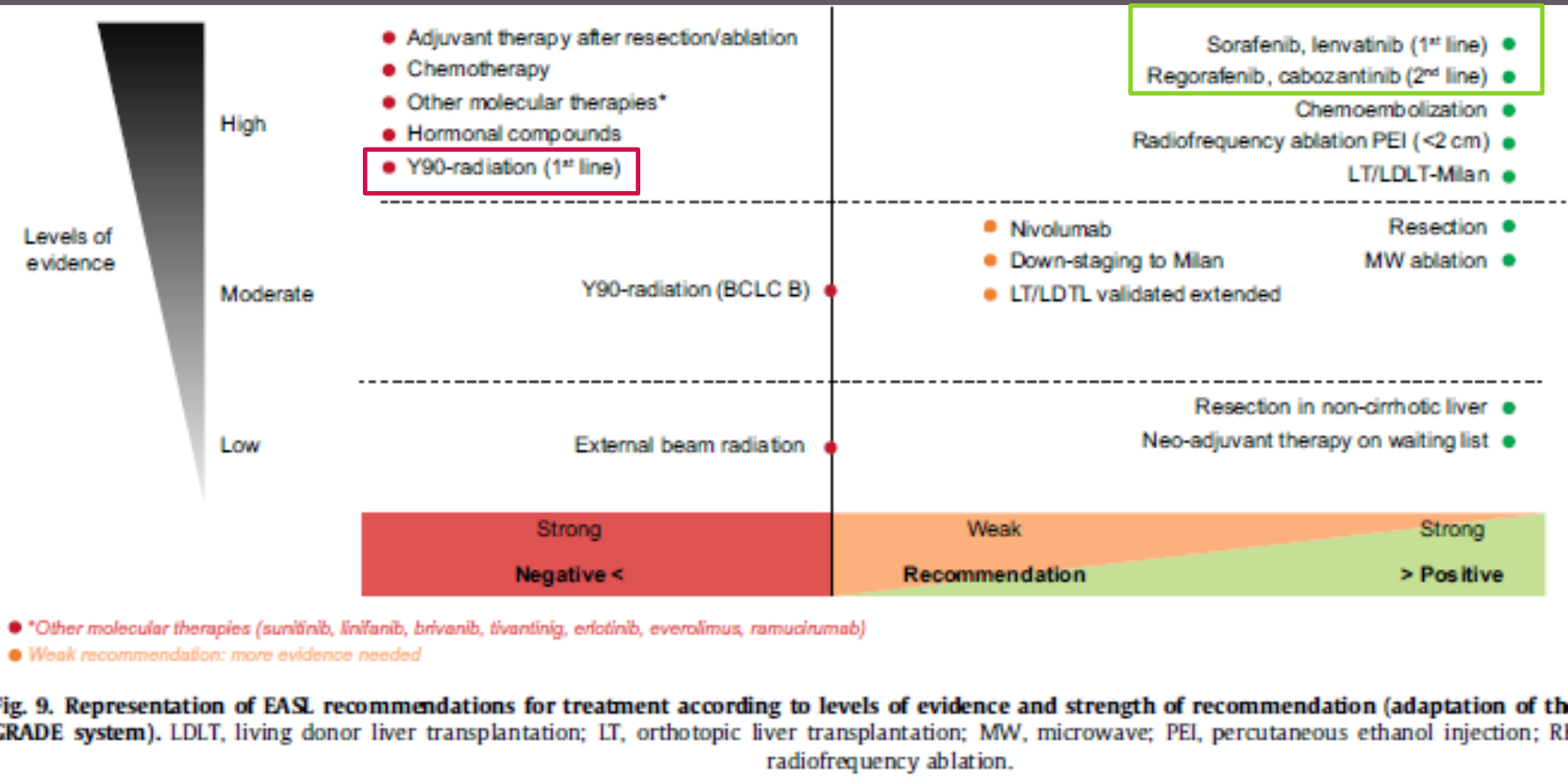


Fig. 9. Representation of EASL recommendations for treatment according to levels of evidence and strength of recommendation (adaptation of the GRADE system). LDLT, living donor liver transplantation; LT, orthotopic liver transplantation; MW, microwave; PEI, percutaneous ethanol injection; RF, radiofrequency ablation.

European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol (2018), https://doi.org/10.1016/j.jhep.2018.03.019

How I Have Adapted My Practice to the Immunotherapy Revolution in HCC

Professor Tim Meyer
Professor of Experimental Cancer Medicine
Research Department of Oncology
UCL Cancer Institute and Royal Free London Hospital
London, England

Go online to access full CME information, including faculty disclosures.

Expansion Phase: Baseline Patient Characteristics[1]

	Uninfected: Sorafenib Naive/Intolerant (n = 56)	Uninfected: Sorafenib Progressor (n = 57)	HCV (n = 50)	HBV (n = 51)	Total (N = 214)
Median age (range), y	66 (59-71)	65 (60–71)	65 (61–73)	55 (42–66)	64 (56–70)
Male, n (%)	48 (86)	42 (74)	42 (84)	39 (76)	171 (80)
Race, n (%)					
White	38 (68%)	34 (60%)	29 (58%)	4 (8%)	105 (49%)
Asian	16 (29%)	22 (39%)	18 (36%)	45 (88%)	101 (47%)
Black	1 (2%)	1 (2%)	2 (4%)	2 (4%)	6 (3%)
Other	1 (2)	0	1 (2)	0	2 (1)
Extrahepatic metastases, n (%)	36 (64%)	41 (72%)	25 (50%)	42 (82%)	144 (67%)
Vascular invasion, n (%)	13 (23%)	18 (32%)	17 (34%)	15 (29%)	63 (29%)
Child–Pugh score, n (%)					
5	43 (77%)	37 (65%)	27 (54%)	42 (82%)	149 (70%)
6	12 (21%)	20 (35%)	20 (40%)	9 (18%)	61 (29%)
7 – 9	1 (2%)	0	3 (6%)	0	4 (2%)
AFP >200 µg/L, n (%)	15 (27%)	22 (39%)	17 (34%)	25 (49%)	79 (37%)
Prior treatment type, n (%)					
Surgical resection	34 (61%)	36 (63%)	18 (36%)	40 (78%)	128 (60%)
Radiotherapy	9 (16%)	17 (30%)	4 (8%)	11 (22%)	41 (19%)
Local treatment for HCC	24 (43%)	28 (49%)	25 (50%)	40 (78%)	117 (55%)
Systemic therapy	23 (41%)	57 (100%)	32 (64%)	47 (92%)	159 (74%)
Sorafenib	15 (27%)	57 (100%)	30 (60%)	43 (84%)	145 (68%)

1. El-Khoueiry AB et al. *Lancet*. 2017;389:2492-2502.

Outcomes With Nivolumab in HCC[1,a]

	Uninfected, Untreated, or Intolerant (n = 56)	Uninfected Progressor (n = 57)	HCV (n = 50)	HBV (n = 51)	Total (N = 214)
OR[b]	13 (23%; 13-26)	12 (21%; 11-34)	10 (20%; 10-34)	7 (14%; 6-26)	42 (20%; 15-26)
CR	0	2 (4%)	0	1 (2%)	3 (1%)
PR	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
SD	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
PD	13 (23%)	18 (32%)	14 (28%)	23 (45%)	68 (32%)
NE	1 (2%)	4 (7%)	3 (6%)	0	8 (4%)
DOR[b]					
KM median	8.4 (8.3-NE)	NR	9.9 (4.5-9.9)	NR	9.9 (8.3-NE)
Ongoing, n/N (%)	8/13 (62%)	7/12 (58%)	8/10 (80%)	5/7 (71%)	28/42 (67%)
Disease control[b]	42 (75%; 62-86)	35 (61%; 48-74)	42 (75%; 62-86)	42 (75%; 62-86)	42 (75%; 62-86)
Disease control with SD for ≥6 mo	22 (39%; 27-53)	22 (39%; 26-52)	17 (34; 21-49)	18 (35%; 22-50)	79 (37%; 30-44)

The ORR by RECIST 1.1 in the post-sorafenib population was 14.3% (n = 154)

[a] Unless otherwise indicated, data are n (%; 95% CI); n (%); months (95% CI); or % (95% CI). [b] Determined by investigator assessment using RECIST version 1.1.

1. El-Khoueiry AB et al. *Lancet*. 2017;389:2492-2502.

Nivolumab CheckMate -040 Study: Response and PD-L1 Expression[1]

Best Change in Target Lesion From Baseline[a]
Tumor-Cell PD-L1 Expression

Overall, the ORR by RECIST 1.1 in the post-sorafenib population was 14.3% (n = 154)

Sorafenib Naive ESC + EXP

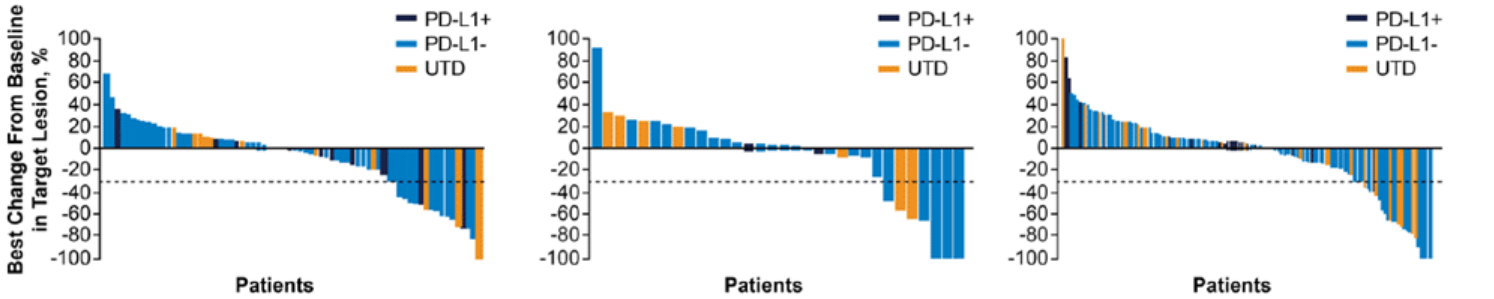
	PD-L1+	PD-L1-	UTD
ORR, n / N (%)	3 / 11 (27)	11 / 56 (20)	2 / 13 (15)

Sorafenib Experienced ESC

	PD-L1+	PD-L1-	UTD
ORR, n / N (%)	2 / 9 (22)	5 / 26 (19)	0 / 2 (0)

Sorafenib Experienced EXP

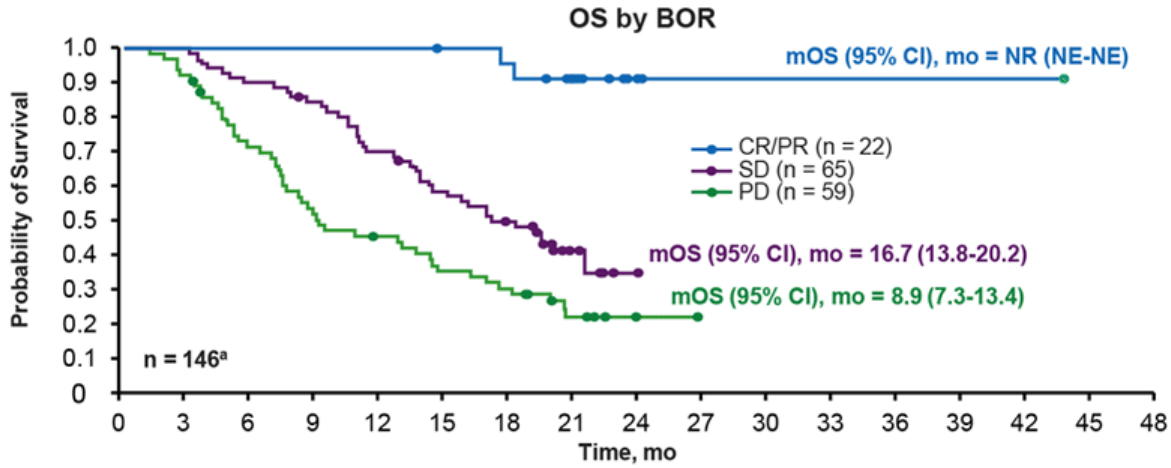
	PD-L1+	PD-L1-	UTD
ORR, n / N (%)	7 / 25 (28)	13 / 102 (13)	1 / 18 (6)



[a] Tumor response assessed by BICR using RECIST v1.1; plots include patients evaluable for tumor response and had ≥1 post-baseline target lesion assessment [sorafenib naive, n = 72; sorafenib experienced [ESC], n = 32; sorafenib experienced [EXP], n = 135). PD-L1+: ≥1% tumor cells expressing PD-L1; PD-L1-: <1% tumor cells expressing PD-L1.

1. Crocenzi T et al. ASCO 2017. Abstract 4013.

CheckMate -040: Overall Survival by Best Overall Response or Change in Target Lesion Size[1]



OS Rate, % (95% CI)	CR/PR (n = 22)	SD (n = 65)	PD n = 59
12 month	100 (100-100)	67 (55-77)	41 (28-53)
18 month	100 (100-100)	45 (33-57)	26 (15-38)

[a] Best overall response was unable to be determined in 8 patients.

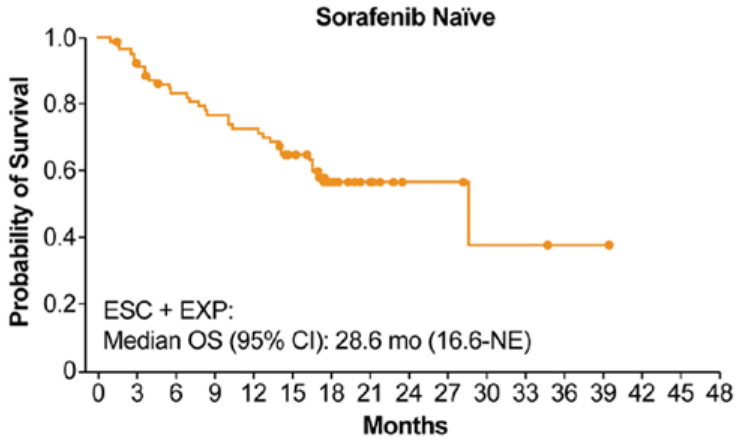
1. El-Khoueiry A et al. *J Clin Oncol*. 2018;36:4(suppl): Abstract 475.

Nivolumab Dose Expansion: Treatment-Emergent Adverse Events[1]

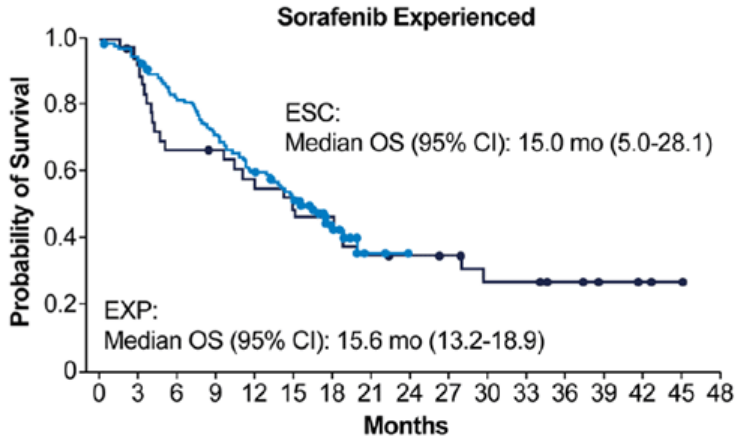
	Uninfected (n = 113)		HCV (n = 57)		HBV (n = 50)		Total (N = 214)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4	Any Grade	Grades 3-4	Any Grade	Grades 3-4
Patients with any TRAE, n (%)	9 (8)	4 (3)	5 (10)	4 (8)	2(4)	1(2)	16 (7)	9(4)
Symptomatic TRAEs reported in >4% of all patients								
Rash	16 (14)	2 (1)	9 (18)	0	8 (16)	0	33 (15)	2 (1)
Pruritus	18 (15)	0	14 (28)	1 (2)	13 (25)	0	45 (21)	1 (<1)
Diarrhea	19 (16)	2 (1)	5(10)	0	3 (6)	1 (2)	27 (13)	3 (10
Decreased Appetite	6 (5)	0	2 (4)	1 (2)	3 (6)	0	11 (5)	1 (<1)
Fatigue	34 (30)	2 (1)	8 (16)	1 (2)	7 (14)	0	49 (23)	3 (1)
Nausea	10 (8)	0	6 (12)	0	1 (2)	0	17 (8)	0
Dry mouth	9 (8)	0	2 (4)	0	2 (4)	0	13 (6)	0
Laboratory-value TRAEs reported in >4% of all patients								
↑ AST	9 (8)	4 (3)	6 (12)	5 (10)	1 (2)	0	16 (7)	9 (4)
↑ ALT	7 (6)	2 (1)	7 (14)	3 (6)	3 (6)	0	17 (8)	5 (2)

1. El-Khoueiry AB et al. *Lancet*. 2017;389:2492-2502.

Nivolumab: Survival Update Based on Sorafenib Exposure[1,a]



OS Rate (95% CI), %	ESC + EXP
12 months	73 (61.3-81.3)
18 months	57 (44.3-67.1)



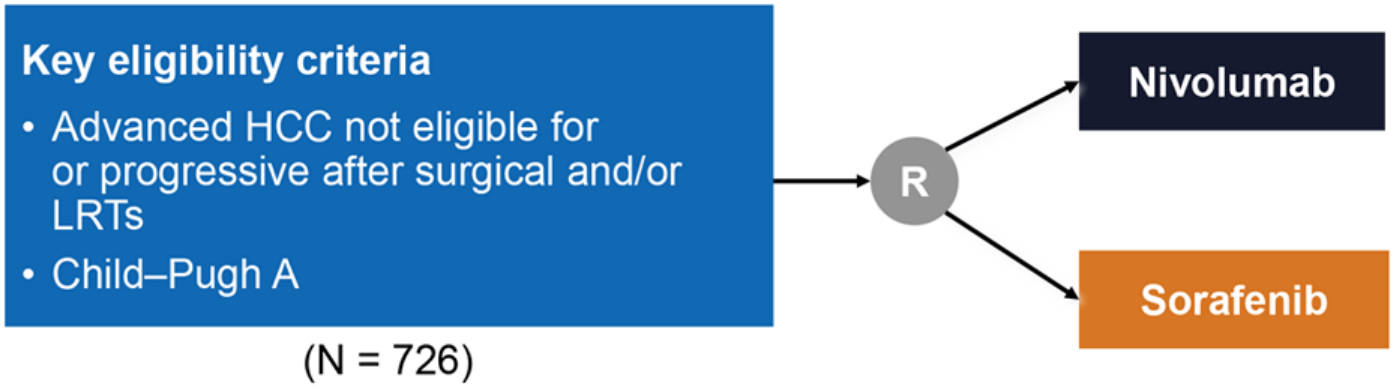
OS Rate (95% CI), %	ESC	EXP
12 months	58 (40.2-72.2)	60 (51.4-67.5)
18 months	46 (29.5-61.7)	44 (35.3-51.9)

[a] KM method; closed circles denote censored patients.

1. Crocenzi T et al. ASCO 2017. Abstract 4013.

CheckMate -459: Nivolumab Versus Sorafenib in Advanced HCC[1]

Phase 3



- **Primary endpoints:** TTP, OS
- **Other endpoints:** ORR, PFS, and biomarkers

1. https://clinicaltrials.gov/ct2/show/NCT02576509. Accessed May 9, 2019.

KEYNOTE-224: Phase 2 Study of Pembrolizumab in Previously Treated HCC[1]

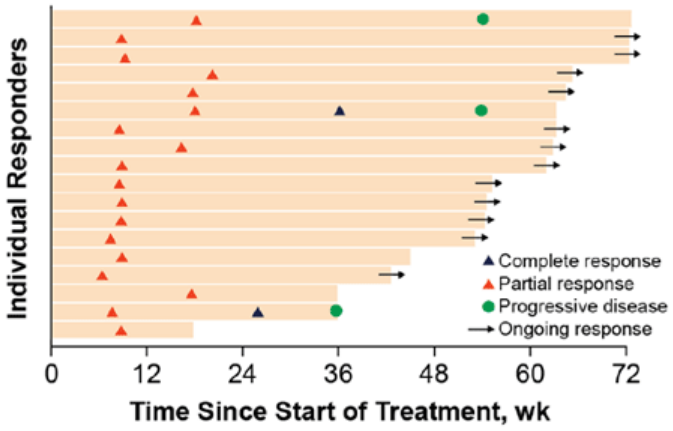
- **KEYNOTE-224:** Nonrandomized, multicenter, open-label, phase 2 trial assessing PD-1 inhibitor pembrolizumab 200 mg every 3 weeks
- Patients (N = 104) with HCC previously treated with sorafenib who were either intolerant to this treatment or showed radiographic progression after treatment[a]
- The primary endpoint was objective response

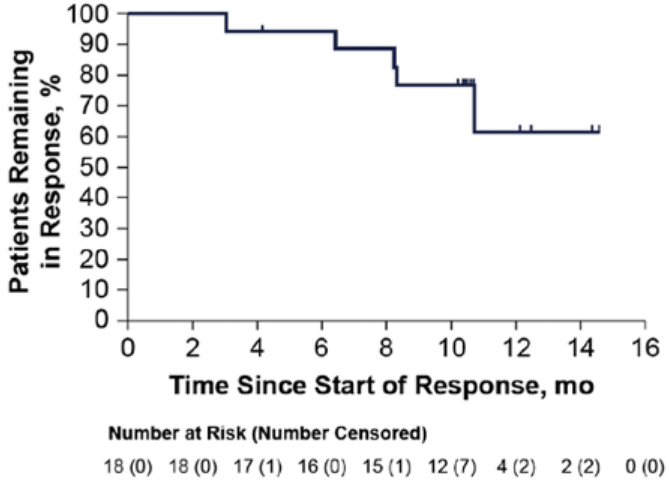
[a] ECOG PS of 0-1; adequate organ function, Child–Pugh class A.

1. Zhu AX et al. *Lancet Oncol*. 2018;19:940-952.

KEYNOTE-224: Phase 2 Study of Pembrolizumab in Previously Treated HCC (Cont'd)[1]

Median DOR not reached
Objective response: 17%





1. Zhu AX et al. *Lancet Oncol*. 2018;19:940-952.

KEYNOTE-224: Selected Adverse Events[1]

AE, n (%)	Grade 1-2	Grade 3	Grade 4	Grade 5
Fatigue	18 (17)	4 (4)	0	0
Pruritus	12 (12)	0	0	0
Diarrhea	11 (11)	0	0	0
Rash	10 (10)	0	0	0
Nausea	8 (8)	0	0	0
Asthenia	7 (7)	0	0	0
Increased AST	7 (7)	7 (7)	0	0
Decreased appetite	6 (6)	1 (1)	0	0
Myalgia	6 (6)	1 (1)	0	0
Hypothyroidism	6 (6)	0	0	0
Increased ALT	5 (5)	4 (4)	0	0
Arthralgia	5 (5)	0	0	0
Maculopapular rash	5 (5)	0	0	0
Hyperbilirubinemia	3 (3)	1 (1)	1 (1)	0
Dyspnea	4 (4)	1 (1)	0	0
Anemia	2 (2)	1 (1)	0	0
Adrenal insufficiency	1 (1)	2 (2)	0	0

1. Zhu AX et al. *Lancet Oncol*. 2018;19:940-952.

KEYNOTE-240: Pembrolizumab Versus BSC as Second-Line Therapy[1]

Phase 3

Key eligibility criteria

- Histologically or cytologically confirmed advanced HCC
- BCLC stage B or C, not amenable to LRT or refractory to LRT
- Child–Pugh A
- Untreated HCV or >4 weeks of successful HCV treatment
- No prior systemic therapy for HCC other than sorafenib

(N = 408)

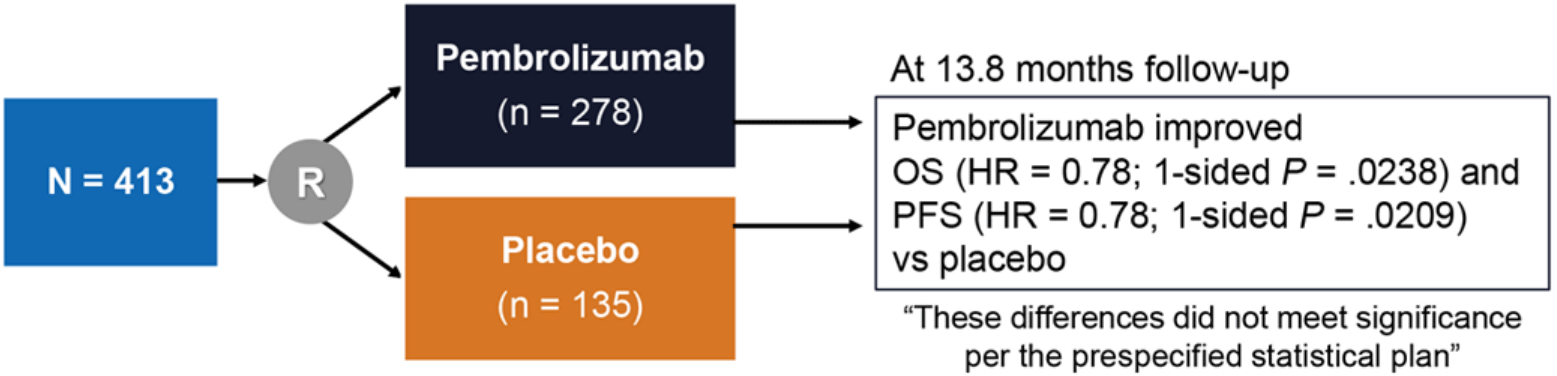
R

- **Pembrolizumab + BSC**
- **Placebo + BSC**

- **Primary endpoints:** PFS, OS
- **Other endpoints:** ORR, DCR, TTP, and DOR

1. https://clinicaltrials.gov/ct2/show/NCT02702401. Accessed May 9, 2019.

KEYNOTE-240: Pembrolizumab Versus BSC as Second-Line Therapy (Cont'd)[1]



Pembrolizumab reduced the risk of death by 22% and improved PFS over placebo

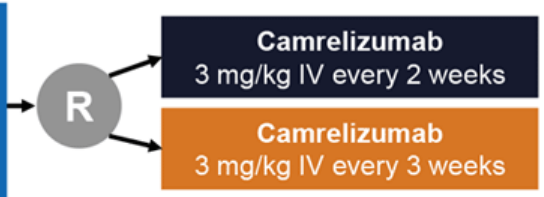
1. Finn RS et al. ASCO 2019. Abstract 4004.

PD-1 Inhibitor: Camrelizumab in Advanced HCC[1]

- Camrelizumab (SHR-1210): novel humanized high-affinity IgG4 monoclonal antibody against PD-1
- Tested in phase 2 study in advanced HCC

Key eligibility criteria

- Histologically or cytologically confirmed advanced HCC
- Progression on or intolerance to ≥1 prior systemic therapy
- Not amenable to surgery or local treatment for HCC
- Child–Pugh A or B (≤7)
- ≥1 measurable lesion
- ECOG PS 0 or 1



- **Primary endpoints:** ORR, and 6-month OS rate
- **Other endpoints:** Efficacy (DCR, DOR, TTP, PFS, OS) and safety

	All (N = 217)	Every-2–Week Group (n = 109)	Every-3–Week Group (n = 108)
ORR, n (%)	30 (13.8)	12 (11.0)	18 (16.7)
CR	0	0	0
PR	30 (13.8)	12 (11.0)	18 (16.7)
SD	67 (30.9)	40 (36.7)	27 (25.0)
PD	98 (45.2)	44 (40.4)	54 (50.0)
NE	22 (10.1)	13 (11.9)	9 (8.3)
6-month OS, %	74.7	76.1	73.1

1. Qin SK et al. *Ann Oncol.* 2018;29:5(suppl): Abstract LBA27.

PD-1 Inhibitor: Tislelizumab in Advanced HCC[1]

Phase 3: RATIONALE-301: Tislelizumab Versus Sorafenib as First-Line Therapy

Key eligibility criteria
- Histologically confirmed advanced HCC
- BCLC stage B or C, not amenable to LRT and to curative treatment approach
- Child–Pugh A
- ECOG PS ≤1
- No prior systemic therapy for HCC

(N = 660)

- **Primary endpoint:** OS
- **Other endpoints:** ORR, PFS, DOR, and TTP

1. https://clinicaltrials.gov/ct2/showNCT03412773. Accessed May 8, 2019.

Combining CTLA-4 and PD-1/PD-L1 Inhibitors in HCC

CheckMate -040: Nivolumab Plus Ipilimumab[1]

- 148 sorafenib-treated patients were randomized
  - 88% had vascular invasion or EHS
  - 91% had BCLC stage C
  - 84% discontinued sorafenib due to disease progression
  - 14% discontinued due to toxicity
- 3 treatment arms

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses)	**Nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (4 doses), each followed by nivolumab 240 mg every 2 weeks**	**Nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks**

1. Yau T et al. ASCO 2019. Abstract 4012.

CheckMate -040: Nivolumab Plus Ipilimumab (Cont'd)[1]

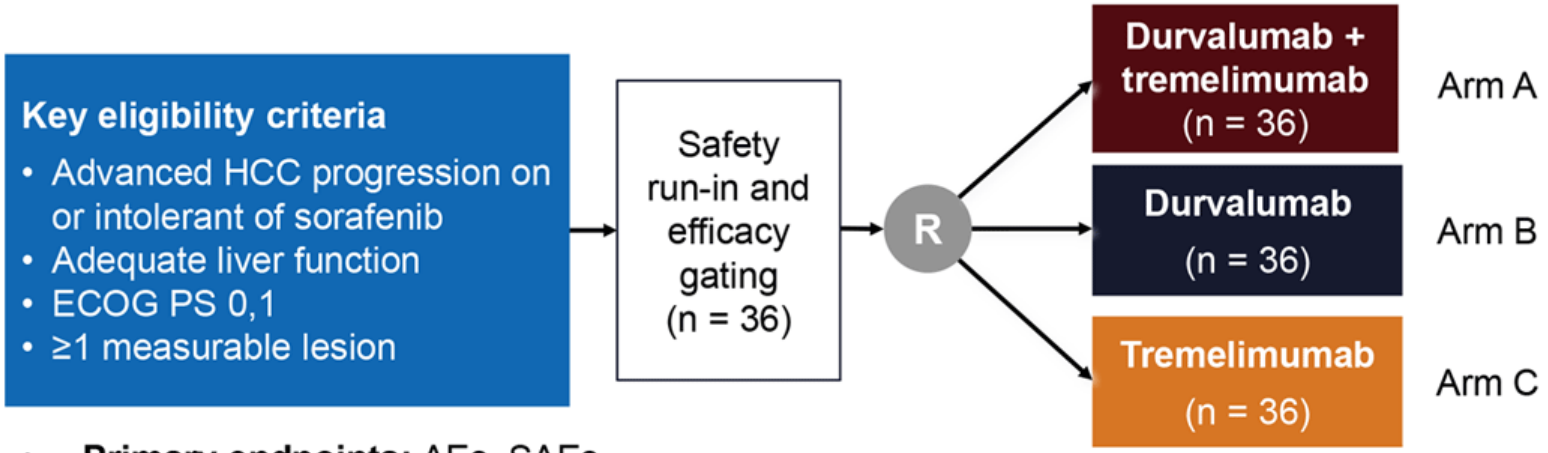
	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Every 3 Weeks (n = 50)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Every 3 Weeks (n = 49)	Nivolumab 3 mg/kg Every 2 Weeks + Ipilimumab 1 mg/kg Every 6 Weeks (n = 49)
ORR, n (%)	16 (32)	15 (31)	15 (31)
CR	4 (8)	3 (6)	0
PR	12 (24)	12 (24)	15 (31)
SD	9 (18)	5 (10)	9 (18)
PD	20 (40)	24 (49)	21 (43)
DCR, % (95% CI)	54 (39-68)	43 (29-58)	49 (34-64)
mOS, mo (95% CI)	23 (9-NA)	12 (8-15)	13 (7-33)
12-mo OS rate, % (95% CI)	61 (46-73)	56 (41-69)	51 (36-64)
24-mo OS rate, % (95% CI)	48 (34-61)	30 (18-44)	42 (28-56)

37% of patients had grade 3-4 pruritus and rash

Nivolumab plus ipilimumab led to meaningful responses with an ORR twice that of nivolumab monotherapy

1. Yau T et al. ASCO 2019. Abstract 4012.

Phase 1/2 Study: Durvalumab Plus Tremelimumab[1]



- **Primary endpoints:** AEs, SAEs, and dose-limiting toxicities
- **Secondary endpoints:** ORR, DOR, OS, PD-L1 expression, TTP, PFS, DCR, and TTR

In each arm:
- 12 patients uninfected
- 12 patients with HBV
- 12 patients with HCV

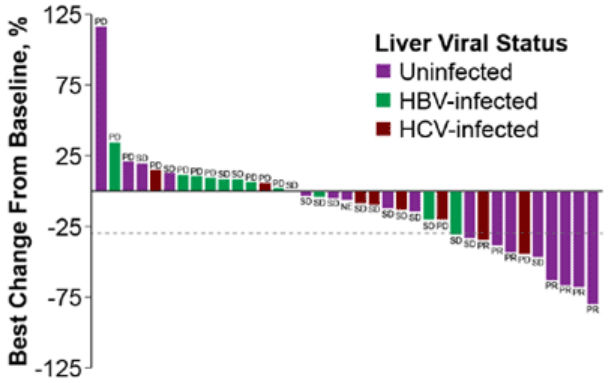
1. https://clinicaltrials.gov/show/NCT02519348. Accessed May 9, 2019.

Durvalumab Plus Tremelimumab: Efficacy and Safety Data[1]

Investigator-Assessed Response

	HBV+ (n = 11)	HCV+ (n = 9)	Uninfected (n = 20)	All (N = 40)
Confirmed ORR, % (95% CI)	0 (0.0-28.5)	11.1 (0.3-48.2)	30.0 (11.9-54.3)	17.5 (7.3-32.8)
CR + PR, (confirmed + unconfirmed), % (95% CI)	9.1 (0.2-41.3)	11.1 (0.3-48.2)	40.0 (19.1-63.9)	25.0 (12.7-41.2)
DCR at week 16, % (95% CI)	45.5 (16.7-76.6)	44.4 (13.7-78.8)	70.0 (45.7-88.1)	57.5 (40.9-73.0)

Antitumor Activity



Most common AEs were fatigue, pruritus, and elevated liver enzymes

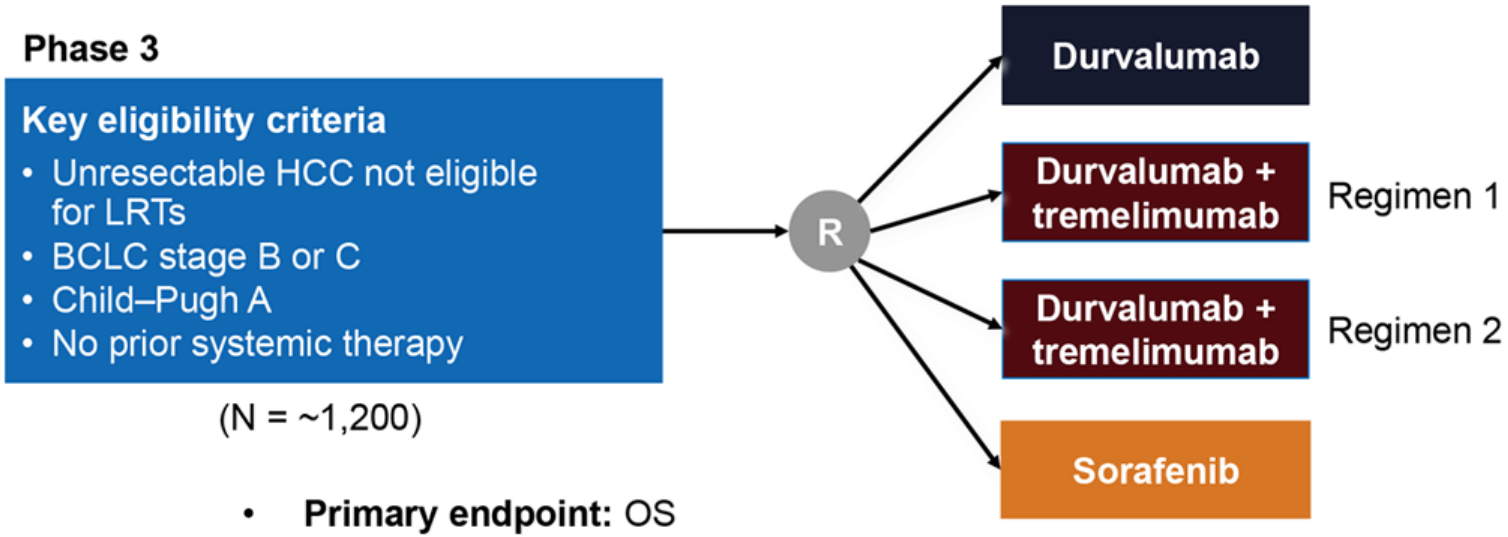
1. Kelley RK et al. ASCO 2017. Abstract 4073.

Durvalumab Plus Tremelimumab: Efficacy and Safety Data (Cont'd)[1]

Preferred Term	HBV+ (n = 11)	HCV+ (n = 9)	Uninfected (n = 20)	Total (N = 40)	
				Any	Grade 3/4
Pruritus	3 (27.3)	3 (33.3)	3 (15.0)	9 (22.5)	0
Elevated ALT	3 (27.3)	3 (33.3)	2 (10.0)	8 (20.0)	2 (5.0)
Elevated AST	3 (27.3)	2 (22.2)	2 (10.0)	7 (17.5)	4 (10.0)
Elevated lipase	2 (18.2)	1 (11.1)	3 (15.0)	6 (15.0)	4 (10.0)
Rash	2 (18.2)	1 (11.1)	2 (10.0)	5 (12.5)	0
Diarrhea	3 (27.3)	2 (22.2)	0	5 (12.5)	1 (2.5)
Elevated amylase	2 (18.2)	0	1 (5.0)	3 (7.5)	1 (2.5)
Colitis	0	2 (22.2)	0	1 (2.5)	1 (2.5)
Pneumonitis	1 (9.1)	0	0	1 (2.5)	1 (2.5)
Pancreatitis	0	1 (11.1)	0	1 (2.5)	1 (2.5)
Hypertransaminasemia	0	1 (11.1)	0	1 (2.5)	1 (2.5)

1. Kelley RK et al. ASCO 2017. Abstract 4073.

HIMALAYA: Durvalumab Plus Tremelimumab Versus Sorafenib[1]



- **Primary endpoint:** OS
- **Other endpoints:** TTP, PFS, ORR, DCR, DOR, and QOL

1. https://clinicaltrials.gov/ct2/show/NCT03298451. Accessed May 9, 2019.

Managing Immune-Related Adverse Events

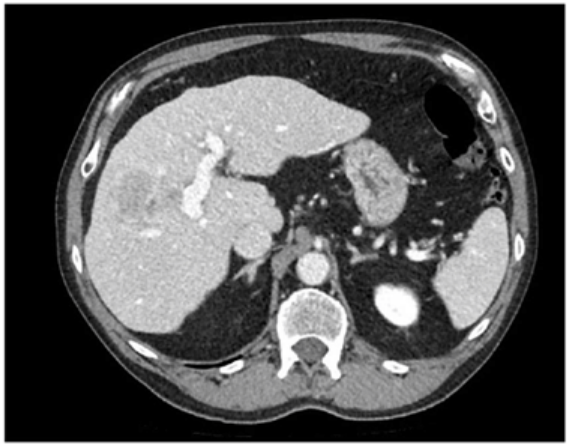
Summary and Future Directions

- Anti–PD-1/PD-L1 therapy shows favorable safety and early efficacy in HCC
- How to expand the benefit of immunotherapy to more patients with HCC?
  - Biomarker development (enhance patient selection, minimize unnecessary exposure)
  - Moving to frontline setting
  - Combination therapies
- Expand the safety experience to patients with moderate liver dysfunction

How I Think, How I Treat

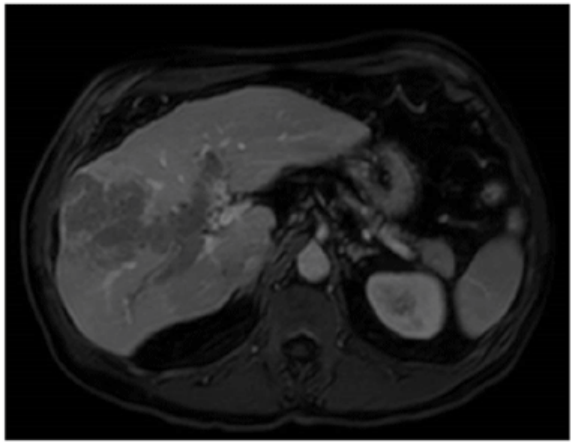
My Decision-Making Process: Patient Case Example

65-year-old male Stage IV hemochromatosis with liver cirrhosis, diabetes, and WHO PS 0	HCC screening program: AFP 12 US liver: ill-defined area ~3 cm	Started on sorafenib



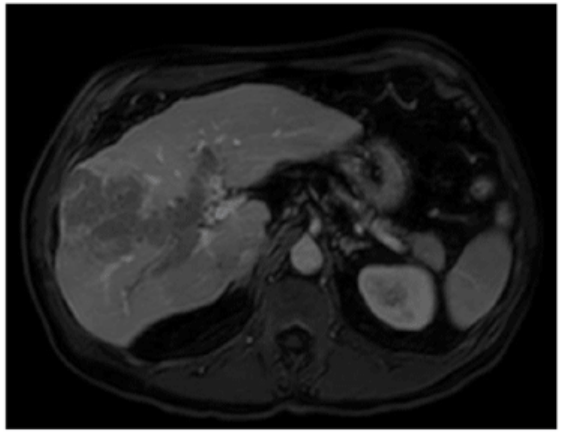
Jan 2015

6 months later



June 2015

My Decision-Making Process: Patient Case Example (Cont'd)



June 2015

What are the options?

- Second-line systemic treatment
- Clinical trial on immunotherapy

My Considerations

- Regorafenib
- Cabozantinib
- Ramucirumab
- Nivolumab
- Pembrolizumab

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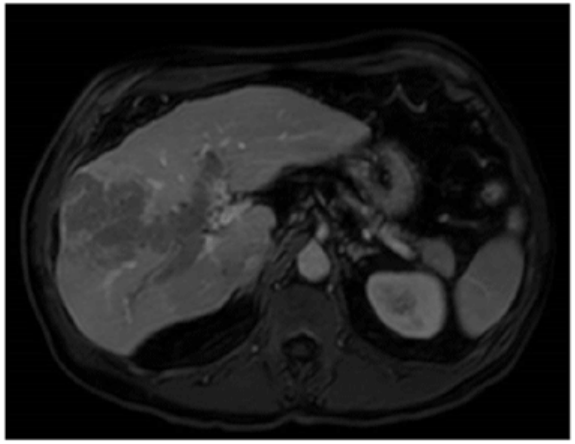
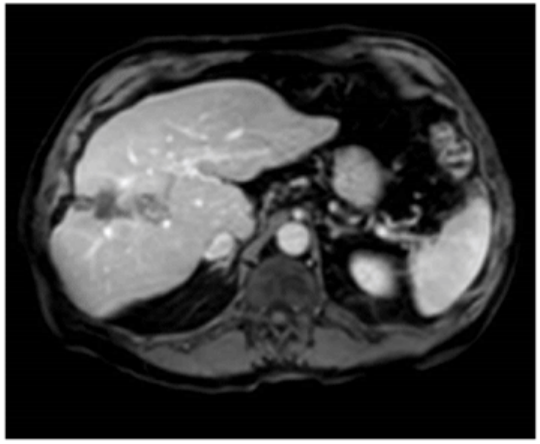
My Decision-Making Process: Patient Case Example (Cont'd)

He was eligible for the CheckMate -040 trial → I recommended clinical trial enrollment



June 2015

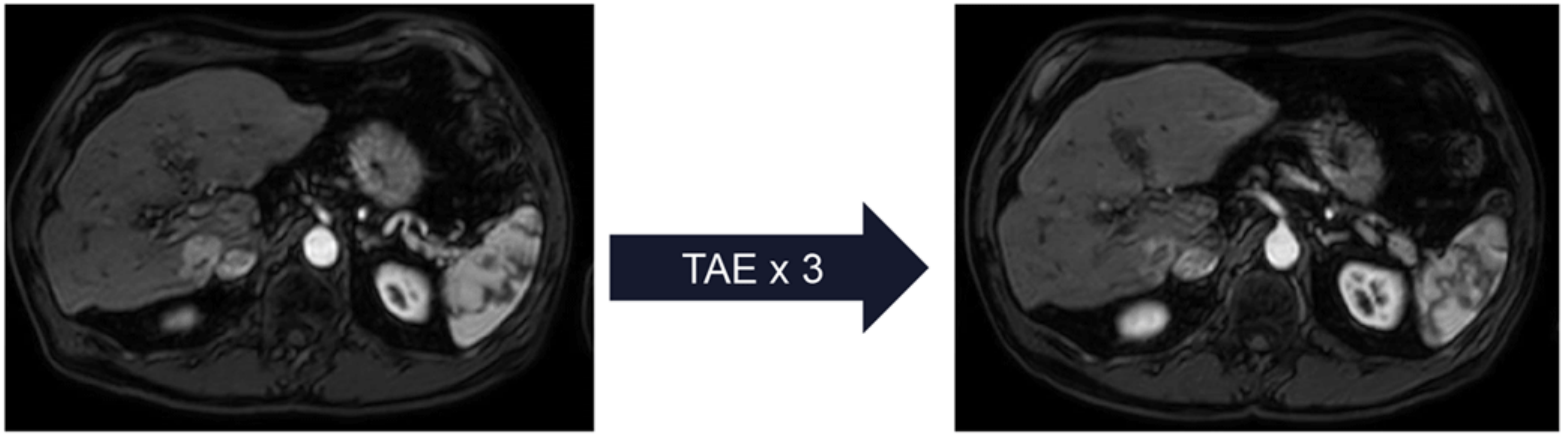
4 months later



Oct 2015

My Decision-Making Process: Patient Case Example (Cont'd)

Moving right to left on the BCLC algorithm



March 2018

March 2019

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Preparing for the Future

Thoughts on Innovative Approaches to HCC Using Targeted Agents and Immunotherapy as Building Blocks for Multimodal Care

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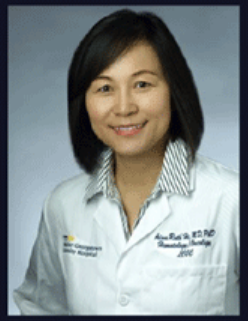


Go online to access full CME information, including faculty disclosures.

Is There a Role for Immunotherapy in Child–Pugh B HCC?[1-7]

- An acute need for new options for Child–Pugh B HCC
- Child–Pugh B associated with a worse prognosis than Child–Pugh A
- Patients with Child–Pugh B often excluded from advanced HCC clinical trials

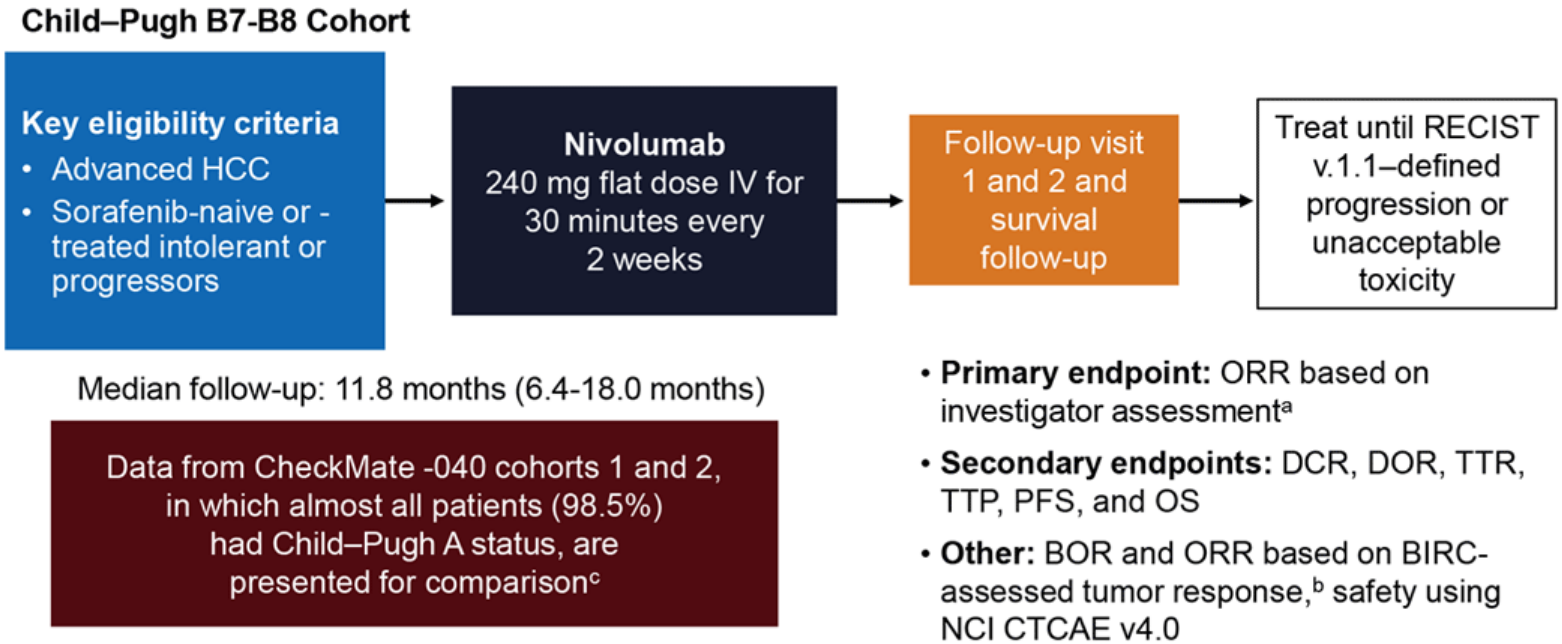
Historical OS for patients with advanced HCC and Child–Pugh B status treated with sorafenib was ~4 months

No definitive data on benefit of sorafenib and other TKIs in Child–Pugh B HCC

A role for immunotherapy? CheckMate -040 included Child–Pugh B cohort[8]

1. Greten TF et al. *Br J Cancer*. 2005;92:1862-1868. 2. Abou-Alfa G et al. *Gastrointest Cancer Res*. 2011;4:40-44. 3. DA Fonseca LG et al. *Mol Clin Oncol*. 2015;3:793-796. 4. Pressiani T et al. *Ann Oncol*. 2013;24:406-411. 5. Chiu J et al. *Cancer*. 2012;118:5293-5301. 6. Marrero JA et al. *J Hepatol*. 2016;65:1140-1147. 7. Federico A et al. *Oncol Lett*. 2015;9:1628-1632. 8. El-Khoueiry AB et al. *Lancet*. 2017;389:2492-2502.

CheckMate -040: Child–Pugh B Cohort[1]



- **Primary endpoint:** ORR based on investigator assessment[a]
- **Secondary endpoints:** DCR, DOR, TTR, TTP, PFS, and OS
- **Other:** BOR and ORR based on BIRC-assessed tumor response,[b] safety using NCI CTCAE v4.0

[a] Using RECIST v1.1. [b] Using mRECIST. [c] Direct comparisons between cohorts cannot be made.

1. Kudo M et al. ASCO GI 2019. Abstract 327.

CheckMate -040: Nivolumab Efficacy by Child–Pugh Status[1]

Outcome	Child–Pugh B (n = 49)	Child–Pugh A (n = 262)
	Median	Median
TTR, mo	2.7	2.7
DOR, mo	9.9	12.4

- TRAEs were reported in 25 (51%) patients; 4 (8.2%) patients had select hepatic TRAEs
- Investigator ORR was 10.2%; DCR was 55.1%
- mOS = 7.6 months in Child–Pugh B
- NCCN recommendation as second-line therapy for Child–Pugh Class A or B7[2]

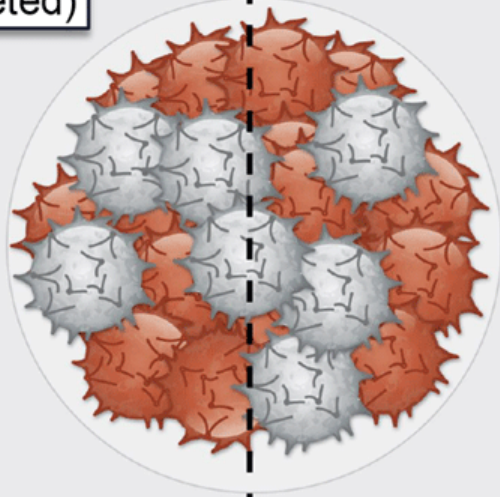
1. Kudo M et al. ASCO GI 2019. Abstract 327. 2. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers. Version 2.2019. Accessed May 9, 2019.

Rationale Behind Combination Approaches[1,2]

Systemic Therapy
(anti-angiogenic, multi-targeted)

Systemic therapy induces:

- Hypoxia
- Treg population
- ↑ PD-L1 expression



Tumor Microenvironment

1. Chen Y et al. *Hepatology*. 2015;61:1591-1602. 2. Greten TF et al. *Rev Recent Clin Trials*. 2008;3:31-39.

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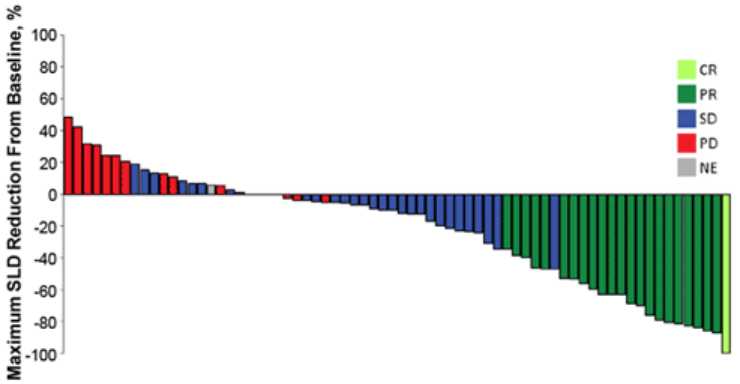
Atezolizumab Plus Bevacizumab in Advanced HCC: Response[1]

ORR	
Overall, n (%)[a]	23/73 (32)
CR	1/73 (1)
PR	22/73 (30)
SD	33/73 (45)
PD	13/73 (18)
By region, n/n (%)[b]	
Asia excluding Japan	12/41 (29)
Japan/USA	10/31 (32)
By etiology, n/n (%)	
HBV	11/36 (31)
HCV	10/23 (43)
Nonviral	2/14 (14)
By baseline AFP, n/n (%)[c]	
<400 ng/mL	12/41 (29)
≥400 ng/mL	11/27 (41)
By EHS/MVI, n/n (%)[d]	
EHS and/or MVI	18/64 (28)
MVI negative	13/32 (41)
EHS negative	9/22 (41)
Neither EHS nor MVI	5/8 (63)

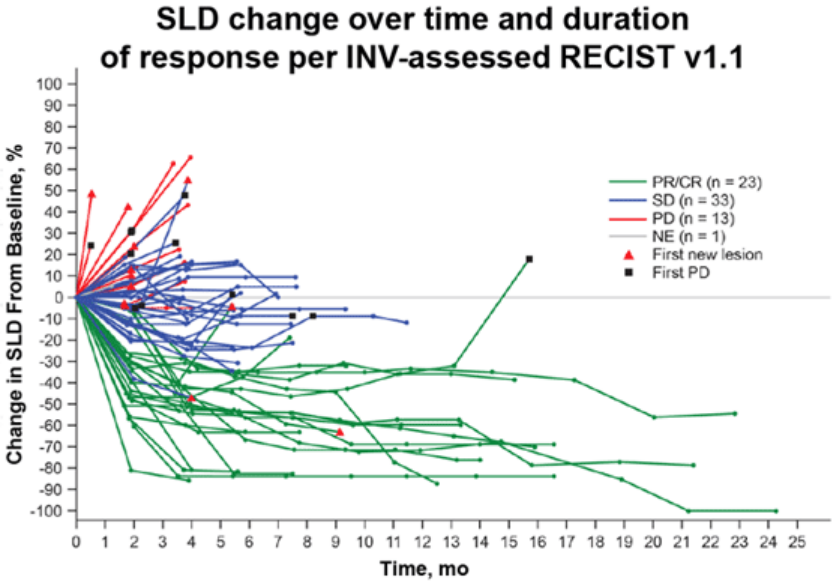


[a] Four patients were unevaluable. [b] Region data from one patient are missing. [c] Baseline AFP data from five patients are missing.
[d] EHS and MVI baseline data from two patients are missing.

1. Pishvaian MJ et al. European Society for Medical Oncology Congress 2018 (ESMO 2018). Abstract LBA26.

Atezolizumab Plus Bevacizumab in Advanced HCC: Response (Cont'd)[1]

Other Responses	
DCR (CR+PR+SD), n/n (%)	**56/73 (77)**
≥ 16 wks	48/73 (66)
≥ 24 wks	34/73 (47)
Median DOR (range), mo	**NR (1.6+ to 22.0+)**
≥ 6 mo, n/n (%)	12/23 (52)
≥ 12 mo, n/n (%)	6/23 (26)
Ongoing response, n/n (%)	**19/23 (83)**
Median follow-up, mo	7.2



Median PFS was 14.9 mo

1. Pishvaian MJ et al. ESMO 2018. Abstract LBA26.

Atezolizumab Plus Bevacizumab in Advanced HCC: Safety[1]

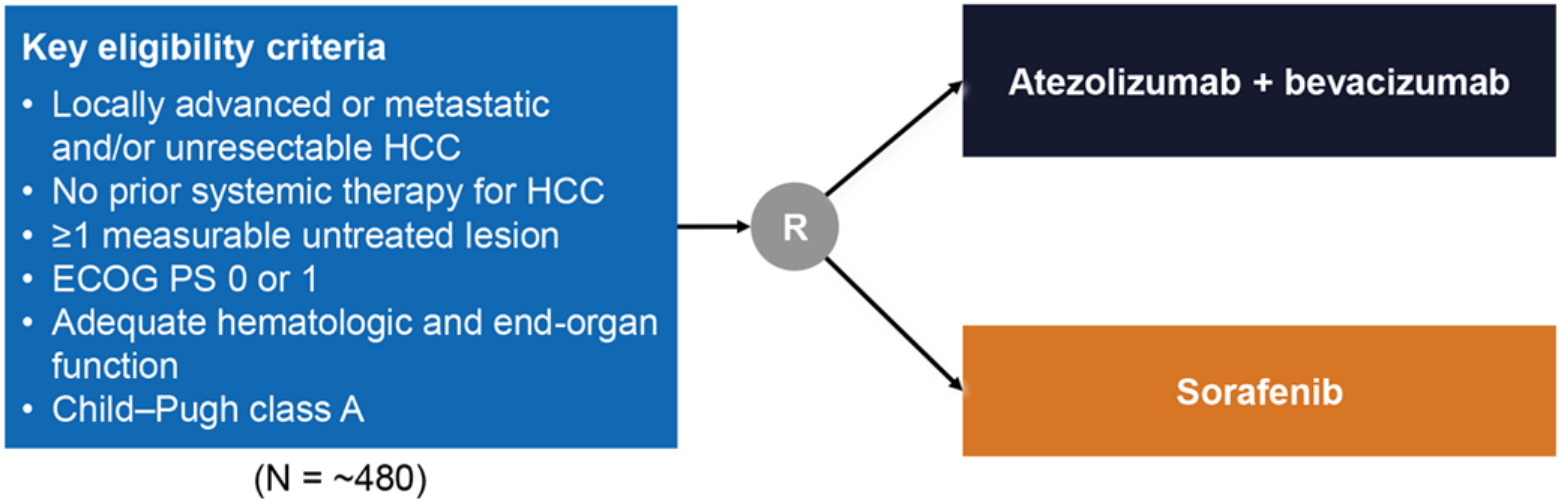
Most Common AEs (≥20% of Patients); n = 103	n (%)
Decreased appetite	29 (28)
Fatigue	21 (20)
Rash	21 (20)
Pyrexia	21 (20)

Grade 3/4 TRAEs (≥5% of Patients); n = 103	n (%)
Hypertension	10 (10)

Grade ≥3 Atezolizumab AESIs Requiring Systemic Corticosteroids	n (%)
Pneumonitis	2 (2)
Encephalitis autoimmune	1 (1)
Drug-induced liver injury	1 (1)
Colitis	1 (1)
AST increased	1 (1)
Gamma-glutamyltransferase increased	1 (1)
Diabetes mellitus	1 (1)
Pancreatitis	1 (1)

1. Pishvaian MJ et al. ESMO 2018. Abstract LBA26.

Phase 3 IMbrave150 Study: Atezolizumab Plus Bevacizumab Versus Sorafenib in Untreated Patients[1]



- **Primary endpoints:** PFS and OS
- ***Fully accrued in 2018***

1. https://clinicaltrials.gov/ct2/show/NCT03434379. Accessed May 13, 2019.

Phase 1b Study: Lenvatinib Plus Pembrolizumab in Unresectable HCC[1]

Summary of TEAEs: Safety Analysis Set

Parameter, n (%)	Lenvatinib + Pembrolizumab		
	Part 1 (n = 6)	Part 2 (n = 24)	Overall (N = 30)
TEAEs	6 (100.0)	24 (100.0)	30 (100.0)
Treatment-related TEAEs	6 (100.0)	22 (91.7)	28 (93.3)
TEAEs ≥ grade 3	5 (83.3)	13 (54.2)	18 (60.0)
Serious AEs	2 (33.3)	6 (25.0)	8 (26.7)
Fatal AEs[a]	0	3 (12.5)	3 (10.0)
Dose modifications			
LEN or PEM dose interruptions due to TEAEs	5 (83.3)	13 (54.2)	18 (60.0)
LEN dose reductions due to TEAEs	5 (83.3)	13 (54.2)	18 (60.0)
Discontinuation of LEN or PEM due to TEAE(s)[b]	0	5 (20.8)	5 (16.7)

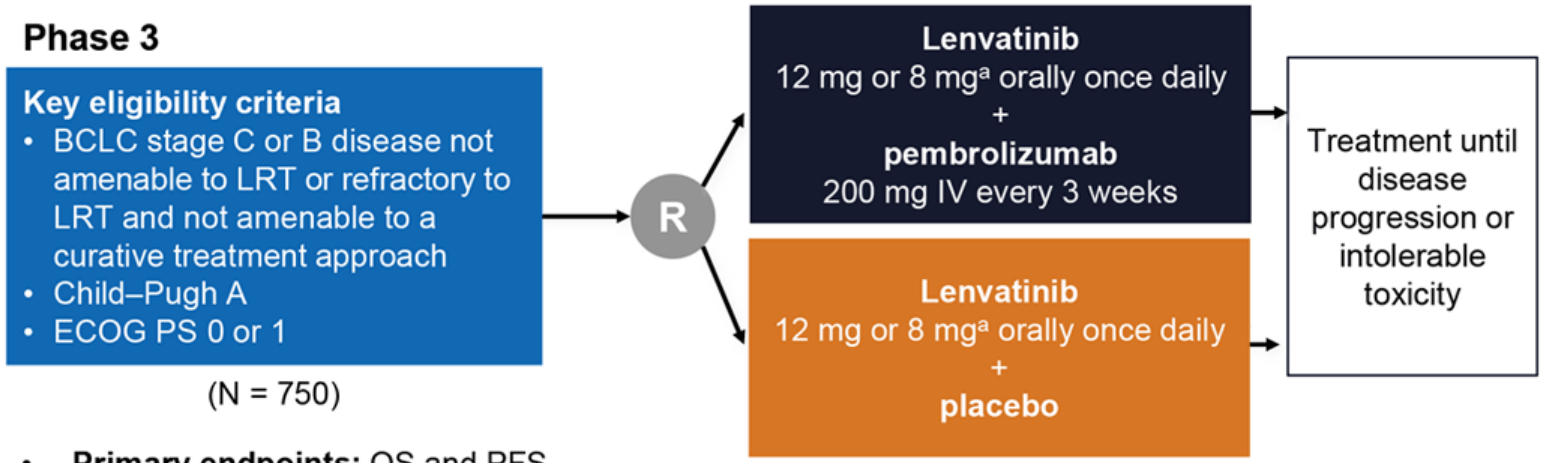
Summary of Tumor Response: Investigator Assessment by mRECIST; Efficacy Analysis Set[c]

	Lenvatinib + Pembrolizumab		
	Part 1 (n = 6)	Part 2 (n = 24)	Overall (N = 30)
BOR, n (%)			
CR[d]	0	1 (5.0)	1 (3.8)
PR[e]	4 (66.7)	6 (30.0)	10 (38.5)
SD	2 (33.3)	13 (65.0)	15 (57.7)
PD	0	0	0
ORR (including unconfirmed responses), n (%)	4 (66.7)	7 (35.0)	11 (42.3)
95% CI	22.3-95.7	15.4-59.4	23.4-63.1
ORR (excluding unconfirmed responses), n %	3 (50.0)	4 (20.0)	7 (26.9)
95% CI	11.8-88.2	5.7-43.7	11.6-47.8

[a] Acute respiratory distress syndrome (n = 1); intestinal perforation (n = 1); bacterial peritonitis (n = 1). [b] Two TEAEs leading to discontinuation (acute respiratory distress syndrome and acute respiratory failure) were reported in the same patient. [c] Patients with postevaluable tumor assessment. [d] Zero CR confirmed.
[e] Seven PR confirmed.

1. Ikeda M et al. ASCO 2018. Abstract 4076.

LEAP-002: First-Line Lenvatinib Plus Pembrolizumab Versus Lenvatinib Plus Placebo in Advanced HCC[1]



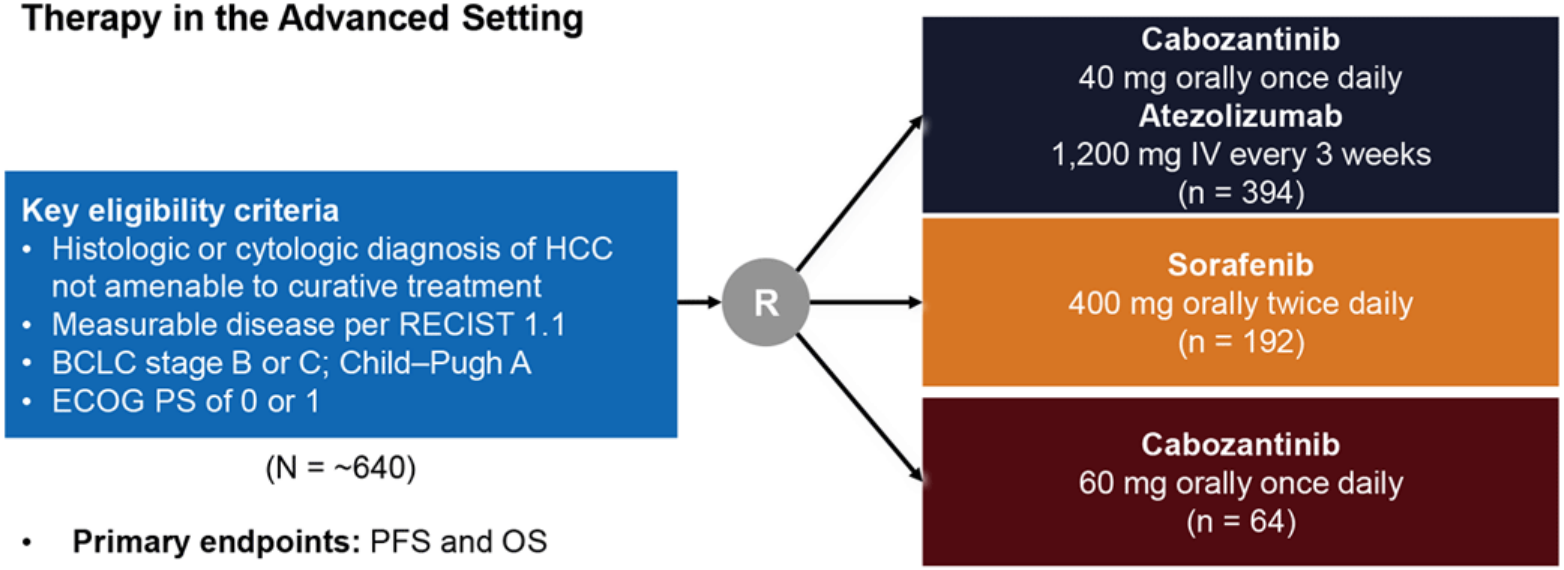
- **Primary endpoints:** OS and PFS
- **Secondary endpoints:** ORR, DOR, DCR, and safety

[a] 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg).

1. https://clinicaltrials.gov/ct2/show/NCT03713593. Accessed May 13, 2019.

Phase 3 COSMIC-312 Study: Cabozantinib ± Atezolizumab Versus Sorafenib in Advanced HCC[1]

Study in Adults With Advanced HCC Who Have Not Received Prior Systemic Anticancer Therapy in the Advanced Setting



- **Primary endpoints:** PFS and OS

1. https://clinicaltrials.gov/ct2/show/NCT03755791. Accessed May 13, 2019.

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Selected Ongoing, Early Phase Trials of Immune Checkpoint Inhibitors in Combination[1-3]

Phase	Target	Agent
2	PD-1 + multi-kinase	Nivolumab + lenvatinib
2	PD-1 + multi-kinase	Nivolumab + sorafenib
1b/2	PD-1 + TGF-β receptor I	Nivolumab + galunisertib (LY2157299)
1/2	PD-1 + multi-kinase	Nivolumab + cabozantinib
1/2	PD-1 + CTLA-4 + multi-kinase	Nivolumab + ipilimumab + cabozantinib
1	PD-1 + VEGF	Nivolumab + bevacizumab
1b	PD-L1 + VEGF/PDGF	Avelumab + axitinib[a]
1/2	PD-1 + c-Met	PDR001 + capmatinib (INC280)
1	PD-1 + multi-kinase	PDR001 + sorafenib
1	PD-1 + multi-kinase	Pembrolizumab + lenvatinib
1	PD-1 + multi-kinase	Pembrolizumab + nintedanib
1	PD-L1 + VEGFR2	Durvalumab + ramucirumab

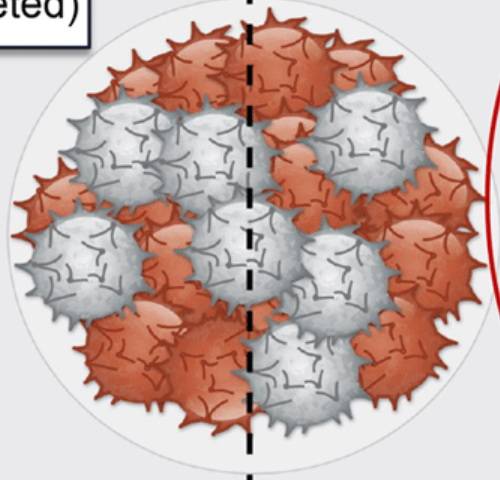
[a] Results presented at ASCO 2019.

1. https://clinicaltrials.gov. Accessed May 13, 2019. 2. Kelley RK et al. *J Clin Oncol*. 2017;35:15(suppl): Abstract 4073.
3. Kudo M et al. *Oncology*. 2017;93(suppl 1):147-159.

Rationale Behind Combination Approaches[1,2]

Systemic Therapy
(anti-angiogenic, multi-targeted)

Localized Therapy
(TACE/RFA/PEI)



Systemic therapy induces:

- Hypoxia
- Treg population
- ↑ PD-L1 expression

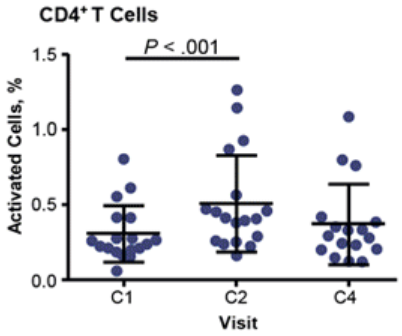
Localized therapy induces:

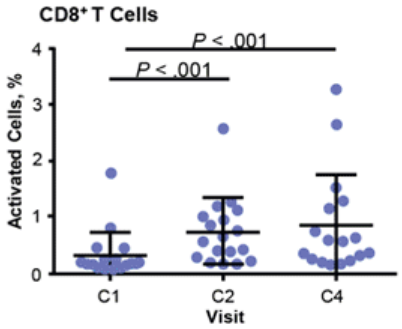
- High antigen load
- Damage to liver cells
- Tumor-specific T-cell response

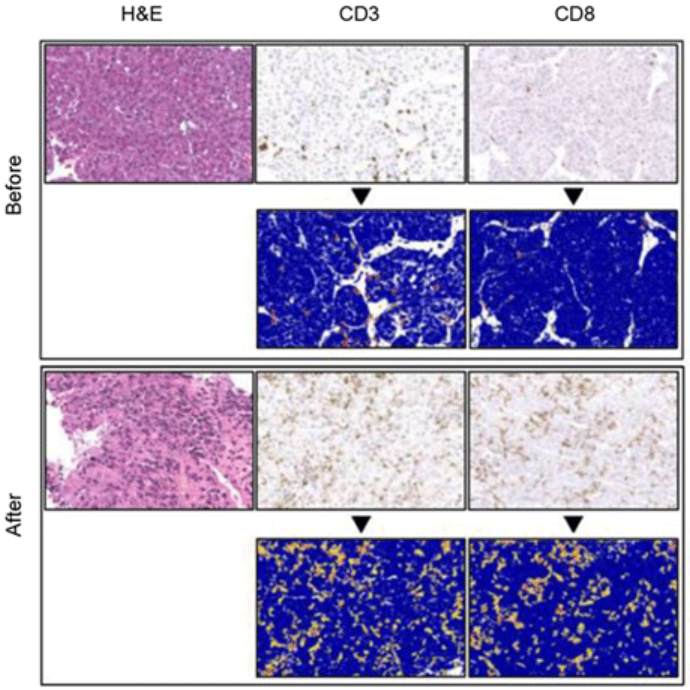
Tumor Microenvironment

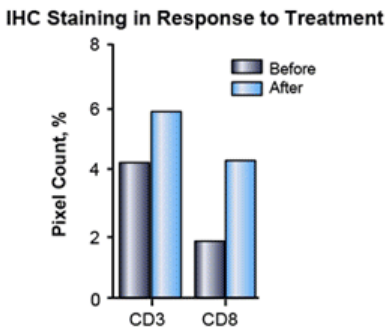
1. Chen Y et al. *Hepatology*. 2015;61:1591-1602. 2. Greten TF et al. *Rev Recent Clin Trials*. 2008;3:31-39.

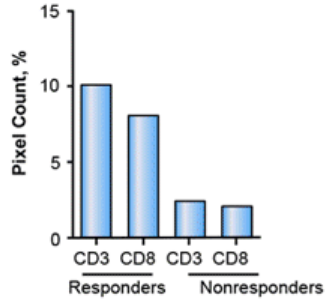
Tremelimumab in Combination With Ablation in Patients With Advanced HCC[1]











1. Duffy AG et al. *J Hepatol*. 2017;66:545-551.

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Concurrent Nivolumab Plus LRT[1]

- Patients (N = 13) received concurrent nivolumab (Child–Pugh A = 12; BCLC stage A = 1; BCLC stage B: 7; and BCLC stage C = 5)

Targeted Tumor and ORR (mRECIST)		Side Effects
LRT targeted tumor response: 19/20 patients		5 patients changed from Child–Pugh A to B
ORR (based on LRT received)		
TARE	1/6 patients	2 patients had grade 2 pneumonitis and transaminitis
TACE	5/13 patients	
RFA	0/1 patients	No grade 3 or higher AEs

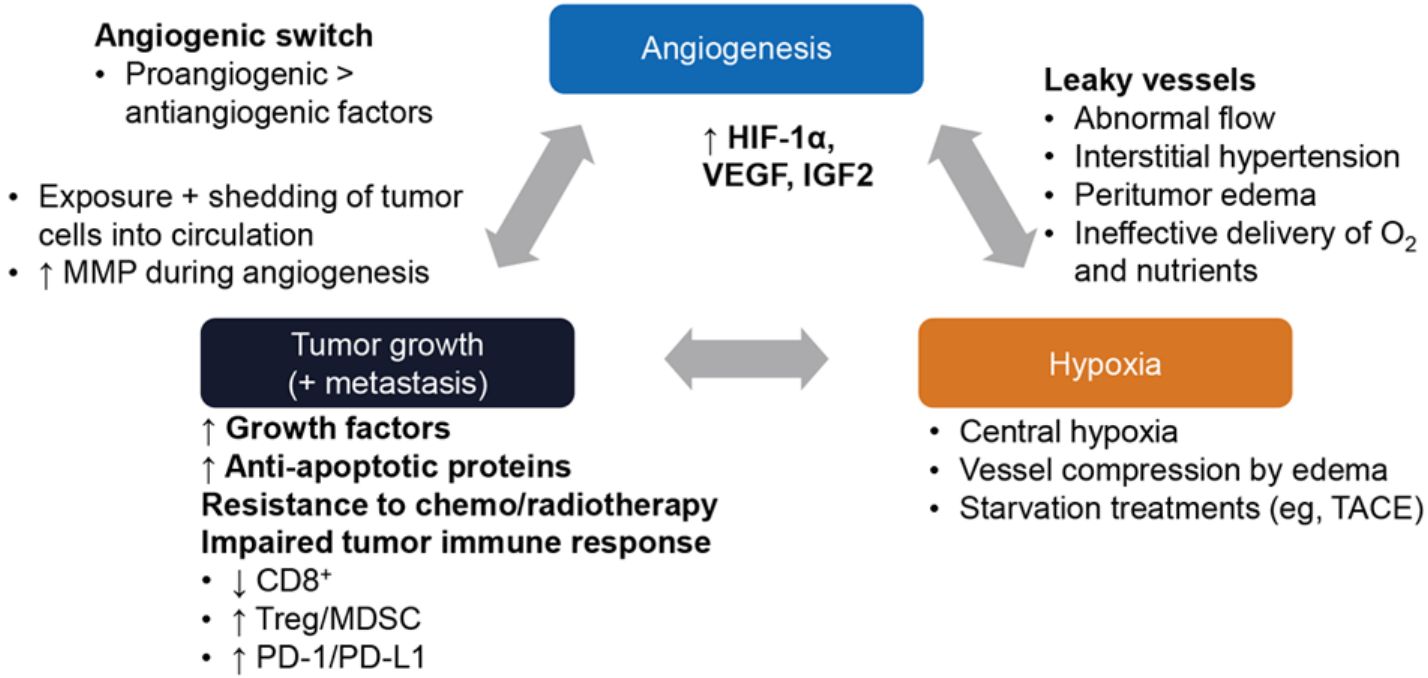
1. Marinelli B et al. *J Vasc Interv Radiol*. 2019;30(suppl 3):s143.

Ongoing Trials
Combining Local and Immune-Based Therapy[1]

Study Arms	Phase	Patient Population	NCT Identifier
Nivolumab + TACE (IMMUTACE)	2	Intermediate stage HCC	NCT03572582
Durvalumab + tremelimumab + DEB-TACE	2	Intermediate stage HCC	NCT03638141
Pembrolizumab + TACE	1,2	Intermediate stage HCC	NCT03397654
DEB-TACE + nivolumab	1	BCLC B	NCT03143270
Pembrolizumab + local ablation	2	Candidates for local ablation	NCT03753659
Nivolumab after SIRT (Y90)	2	Candidates for locoregional therapy	NCT03380130
Durvalumab + bevacizumab + TACE (EMERALD-1)	3	Patients with locoregional HCC	NCT03778957
Durvalumab + tremelimumab + radiation	2	Locally advanced/unresectable or metastatic HCC	NCT03482102
Durvalumab + tremelimumab with TACE, RFA, or cryoablation	1, 2	Locally advanced/advanced HCC	NCT02821754
Pembrolizumab + Y90	1	Locally advanced, high-risk HCC	NCT03099564
SBRT then nivolumab ± ipilimumab	1	Unresectable HCC	NCT03203304

1. http://www.clinicaltrials.gov. Accessed May 13, 2019.

Moving to Earlier Stage Disease: Rationale and Early Evidence[1]



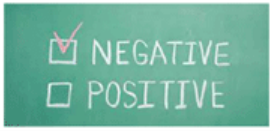
1. Liu K et al. *Clin Transl Gastroenterol.* 2017;8:e98.

Combination of Intra-Arterial Therapy Plus Sorafenib[1]

- **Goal:**
  - Extend the period of tumor control induced by cytotoxic effects of intra-arterial therapy
  - Preserve liver function by reducing frequency of intra-arterial therapy
- **Sequential:**
  - TACE/Y90 → sorafenib
- **Interrupted:**
  - Sorafenib ⨯ → TACE/Y90 → sorafenib
- **Continuous:**
  - Sorafenib → TACE/Y90 → sorafenib

1. Haydur AA et al. *Gastrointest Cancer Res*. 2014;7:98-102.

SORAMIC Trial[1]



Phase 2 trial

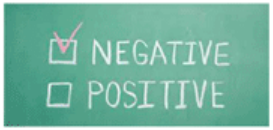
- Primary endpoint: OS

	Sorafenib + Y90 (n = 216)	Sorafenib (n = 208)	HR; *P*
OS: ITT, mo	12.1	11.5	1.018; .25
	n = 114	n = 174	
OS: per protocol, mo	14.1	11.1	0.86; .25

- Subgroup analysis of the patients treated per-protocol identified improved OS in the sorafenib + Y90 arm in patients:
  - Aged <65 years (HR = 0.652)
  - With nonalcoholic etiology of liver disease (HR = 0.632)
  - Without cirrhosis (HR = 0.465)
- Increased AEs, grade ≥3, noted in the combination group (73%) compared with sorafenib alone (65%)

1. Ricke J et al. 2018 Annual Meeting of the European Association for the Study of the Liver (ILC 2018). Abstract LBO-005.

TACE + Systemic Therapy (TKI)[1]



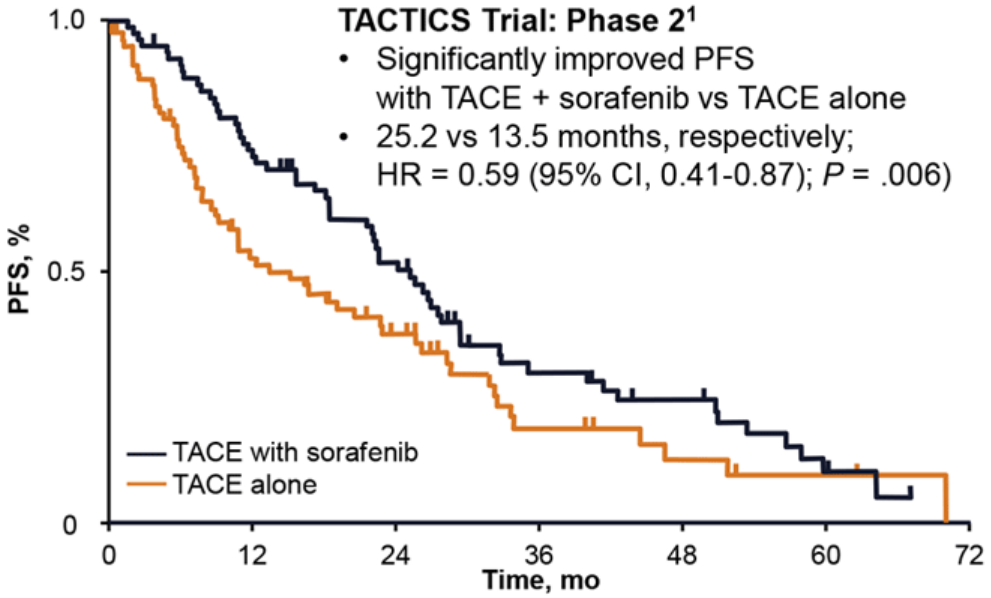
	Post-TACE (N = 458)		BRISK-TA (N = 502)		SPACE (N = 307)		ORIENTAL (N = 888)		TACE-2 (N = 313)	
	Sorafenib (n = 229)	Placebo (n = 227)	Brivanib (n = 249)	Placebo (n = 253)	Sorafenib (n = 154)	Placebo (n = 153)	Orantinib (n = 444)	Placebo (n = 444)	Sorafenib (n = 157)	Placebo (n = 156)
Phase	3		3 (immature/ terminated)		2		3 (terminated due to interim analysis)		3 (terminated due to interim analysis)	
mOS, mo	29.7	NR	26.4	26.1	NR	NR	31.1	32.3	21.1	19.7
HR (95% CI)	1.06 (0.69-1.64)		0.90 (0.66-1.23)		0.898 (0.606-1.330)		1.090 (0.878-1.352)		0.91 (0.67-1.24)	
P	.79		.528		.295		.435		.57	
mTTP, mo	5.4	3.7	8.4	4.9	5.6	5.5	ND	ND	7.9[a]	7.8[a]
HR (95% CI)	0.87 (0.70-1.09)		0.61 (0.48-0.77)		0.797 (0.588-1.080)		ND		0.99 (0.77-1.27)	
P	.252		< .0001		.072		ND		.94	
Primary endpoint	TTP		OS		TTP		OS		PFS	
Definition of progression	RECICLE		mRECIST		mRECIST		TACE discontinuation criteria		RECIST 1.1	
Median DOT of study drug	17 wk		24 wk		21 wk		43.6 wk		17.1 wk	

[a] PFS was used in the TACE-2 study.

1. Kudo M, Arizumi T. *Oncology*. 2017;93(suppl 1):127-134.

Lessons Learned as Part of Combinations

- Different populations, including earlier-stage HCC
- Timing of sorafenib
- Dose of sorafenib
- Duration of sorafenib
- Early termination of study based on other studies
- Study design has conservative stopping rules



No. at Risk							
TACE with sorafenib	80	56	36	17	12	3	0
TACE alone	76	37	22	8	4	2	0

1. Kudo M et al. ASCO GI 2018. Abstract 206.

PeerView.com

Phase 3 CheckMate -9DX Study: Adjuvant Nivolumab in High-Risk Resected HCC[1]

Key eligibility criteria

- First diagnosis of HCC with curative resection or ablation
- Nonviral-related HCC, HBV-HCC, or HCV-HCC
- Child–Pugh score = 5 or 6
- ECOG PS ≤1
- No evidence of tumor metastasis or co-existing malignant disease
- No prior therapy for HCC
- No prior liver transplantation and not on waitlist for transplantation

(N = 530)

- **Primary endpoint:** RFS
- **Other endpoints:** OS and TTR

1. https://clinicaltrials.gov/ct2/show/NCT03383458. Accessed May 13, 2019.

Phase 3 KEYNOTE-937 Study: Adjuvant Pembrolizumab[1]

Key eligibility criteria

- Diagnosis of HCC by radiologic criteria and/or pathologic confirmation
- No radiologic evidence of disease prior to enrollment
- Child–Pugh score = 5 or 6
- ECOG PS 0
- AFP concentration <400 ng/mL

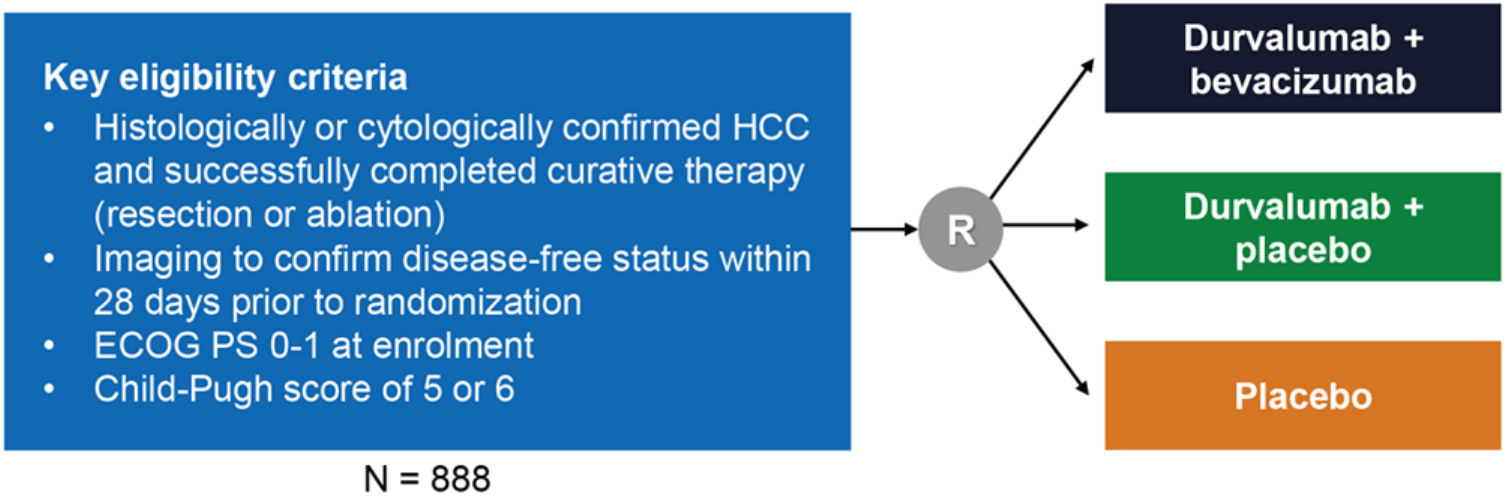
(N = 950)

- **Primary endpoints:** RFS and OS

1. https://clinicaltrials.gov/ct2/showNCT03867084. Accessed May 13, 2019.

Phase 3 EMERALD-2 Study: Adjuvant Durvalumab and Bevacizumab[1]

Trial of Durvalumab as Monotherapy or in Combination With Bevacizumab as Adjuvant Therapy in Patients Who Are at High Risk of Recurrence After Curative Hepatic Resection or Ablation



1. https://clinicaltrials.gov/ct2/show/NCT03847428. Accessed May 13, 2019.

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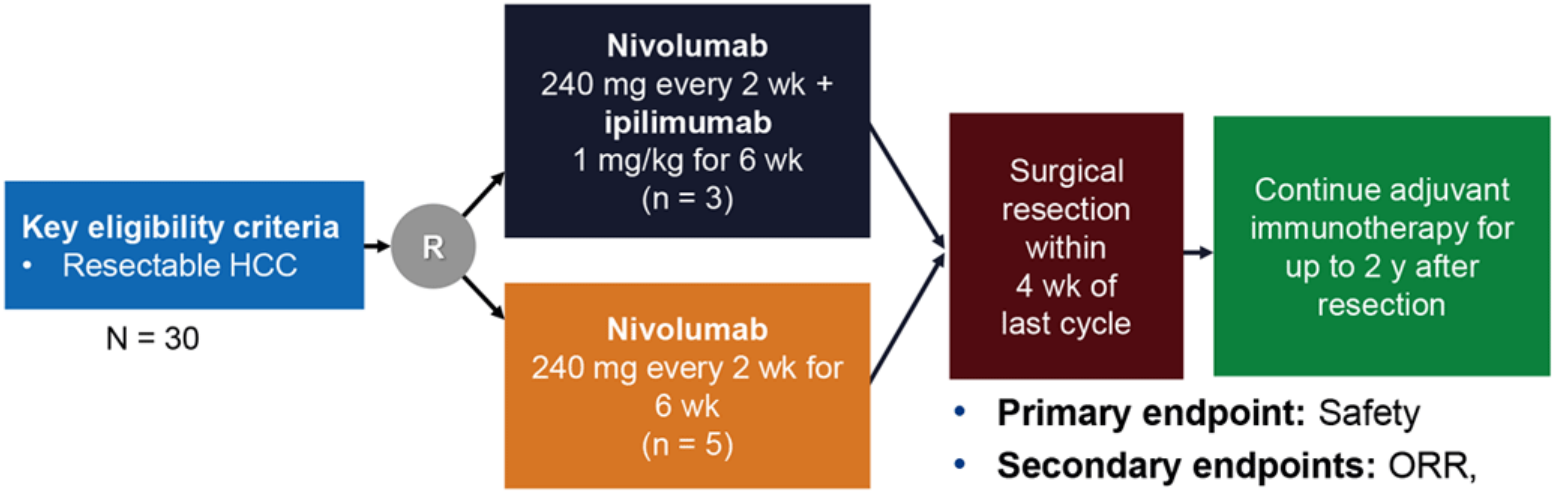
Perioperative Phase 2 Study: Nivolumab ± Ipilimumab in Resectable HCC[1]



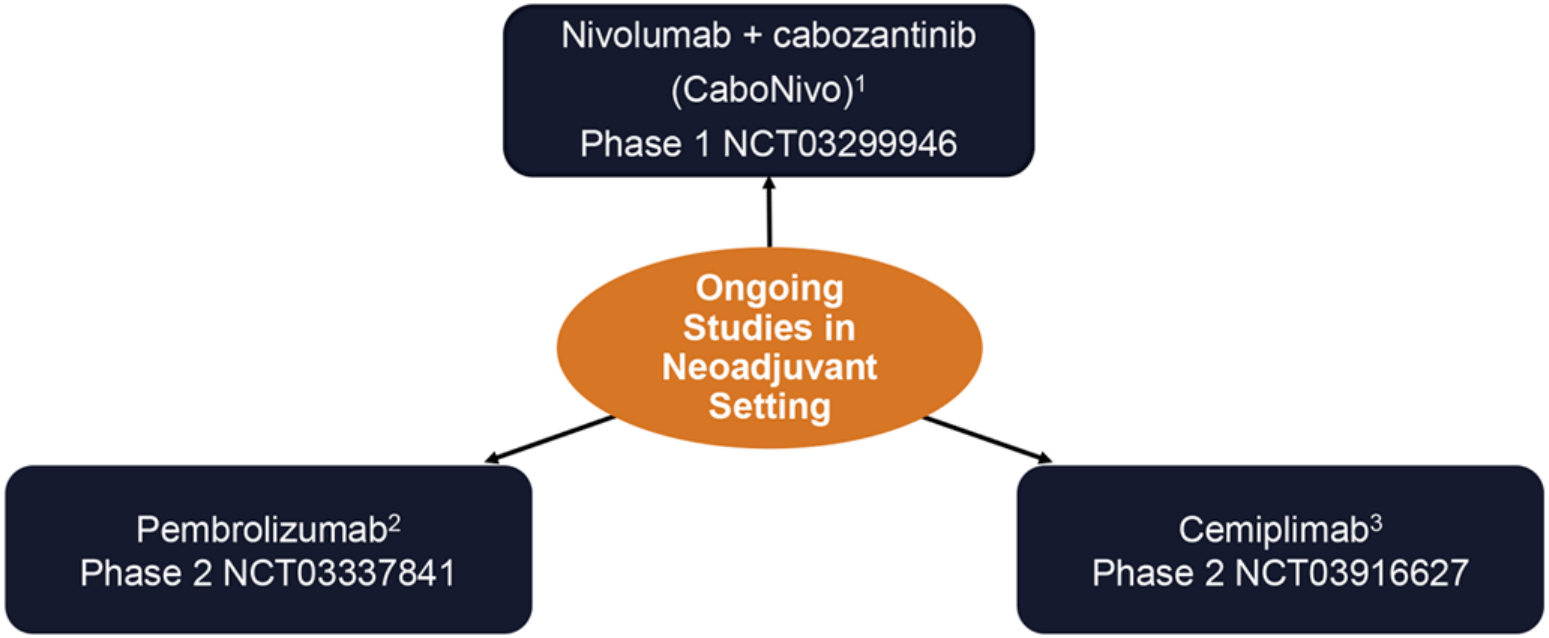
- **Primary endpoint:** Safety
- **Secondary endpoints:** ORR, pCR, and TTP

- pCR was demonstrated in 3 of 8 patients (37.5%)
- Perioperative nivolumab + ipilimumab generally well tolerated; no delays in surgical resection in this interim analysis

1. Kaseb AO et al. ASCO GI 2019. Abstract 185.

PeerView.com

Ongoing Studies in Neoadjuvant Setting



1. https://clinicaltrials.gov/ct2/show/NCT03299946. Accessed May 27, 2019. 2. https://clinicaltrials.gov/ct2/show/NCT03337841. Accessed May 27, 2019.
3. https://clinicaltrials.gov/ct2/show/NCT03916627. Accessed May 27, 2019.

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Take a Peek at the Future

- Combination treatment strategies may replace single-agent treatment
- The sequence of the lines of therapy will be determined, and it is possible that the exposure of one type of therapy may make HCC more sensitive or resistant to another type of therapy given the complex effect of TKIs and IO on the tumor microenvironment
- The use of systemic therapy will be moved to the earlier stages of HCC, which could extend the life of patients by improving the efficacy of current therapy strategies (surgery, transplant, RFA, TACE, etc.) and preserving liver function
- Biomarkers may be discovered to prioritize the treatment for HCC patients

How I Think, How I Treat

My Recommendations for Customizing Care Across the Spectrum of HCC (1)

Bring HCC patients to a multidisciplinary team for a comprehensive treatment plan

Assess patients' prognosis by determining the extensiveness of disease, biomarker AFP, and liver reserve (Child–Pugh Score)

My Recommendations for Customizing Care Across the Spectrum of HCC (2)

Provide supportive care to treat the underlying liver dysfunction in collaboration with GI and hepatology colleagues

Treat the varices, give beta blockers, and treat ascites and encephalopathy

My Recommendations for Customizing Care Across the Spectrum of HCC (3)

Maximize the patient's exposure to new treatments by offering clinical trials if possible

Patients across the disease spectrum of HCC are candidates for clinical trial-based therapy that includes TKIs or immunotherapy

Examples:

- Patients with resectable disease may be eligible for CheckMate -9DX, KEYNOTE-937, or EMERALD-2
- Patients with advanced HCC may be eligible for LEAP-002, IMbrave150, or COSMIC-312

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My Recommendations for Customizing Care Across the Spectrum of HCC (4)

Educate patients on their cancer, underlying liver disease, treatment options, and possible side effects of treatment

Many patient resources are available, including the American Liver Foundation (ALF), among others

Closing Remarks and Audience Q&A

Ghassan Abou-Alfa, MD, MBA
Memorial Sloan Kettering Cancer Center
Weill Medical College at Cornell University
New York, New York

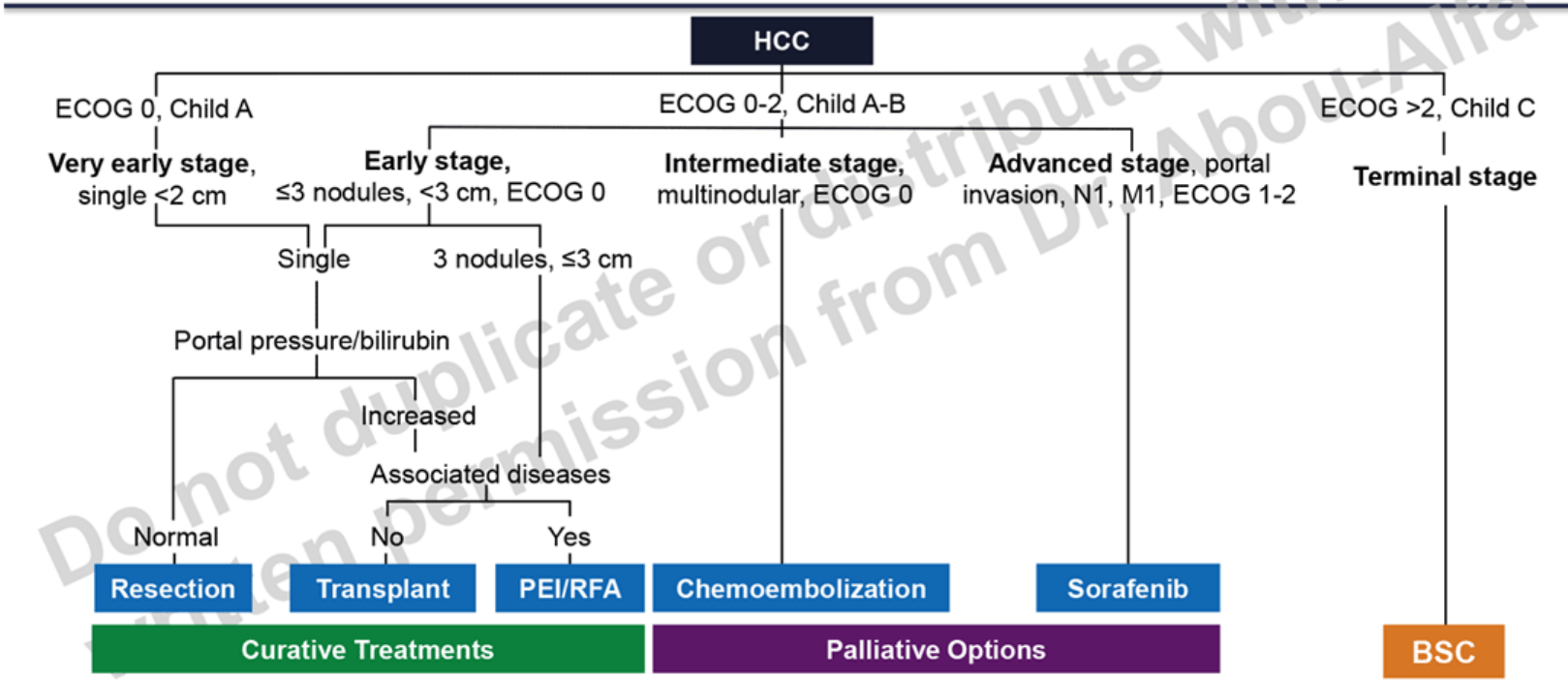
Aiwu Ruth He, MD, PhD
Georgetown University
Washington, District of Columbia

Professor Tim Meyer
UCL Cancer Institute and
Royal Free London Hospital
London, England

Amit Singal, MD, MS
UT Southwestern Medical Center
Dallas, Texas

Go online to access full CME information, including faculty disclosures.

Barcelona Clinic Liver Cancer Staging[1]

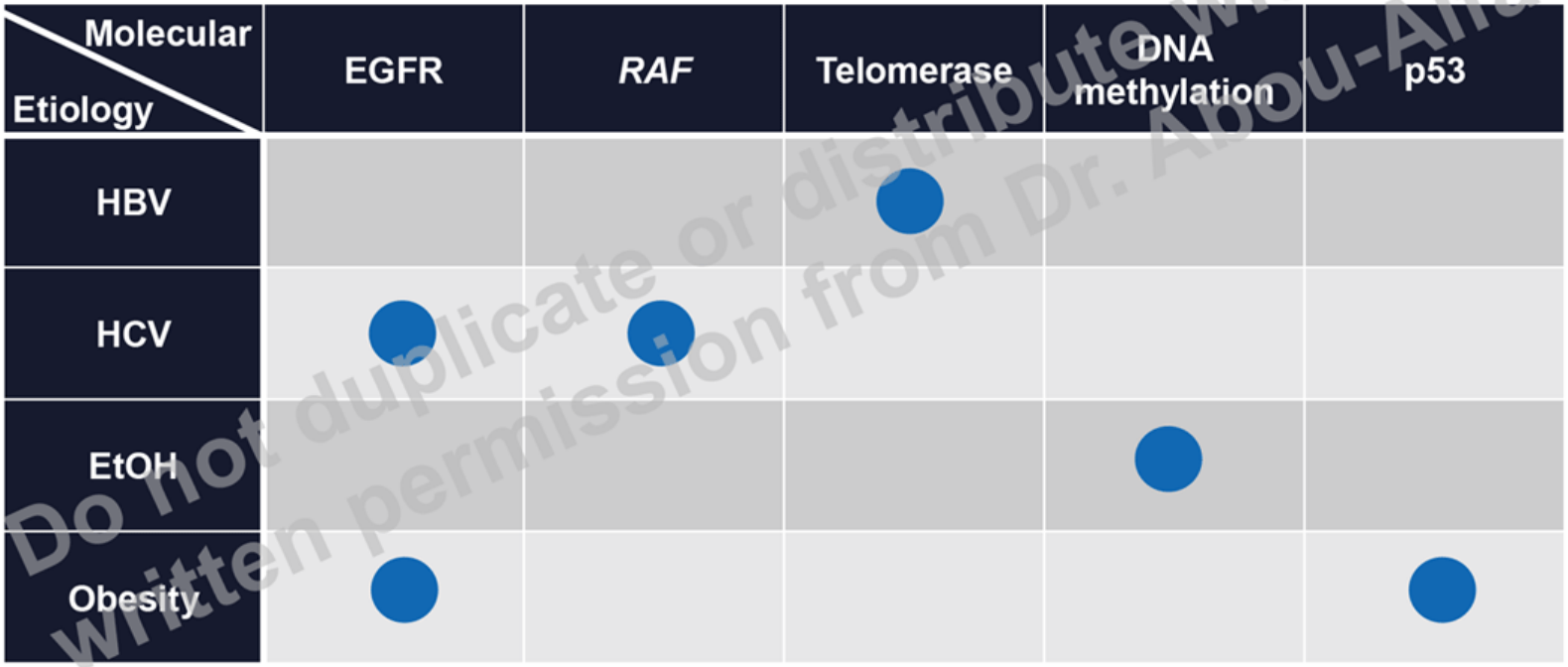


1. Adapted from Forner A et al. *Semin Liver Dis*. 2010;30:61-74.

The Big Picture Different Scenarios

	First Line	Second Line	Third Line
Classic	Sorafenib	Regorafenib	Checkpoint inhibitor
Novel	Lenvatinib	Cabozantinib	Checkpoint inhibitor
Nivolumab before classic first line	Nivolumab	Sorafenib	Regorafenib
Nivolumab before novel first line	Nivolumab	Lenvatinib	Cabozantinib
Nivolumab as first line	Nivolumab	Cabozantinib	–
Pembrolizumab after TKI	Sorafenib	Regorafenib	Pembrolizumab
Pembrolizumab in the midst of TKI	Lenvatinib	Pembrolizumab	Cabozantinib
AFP ≥400	–	Ramucirumab	–

Etiology of HCC at the Molecular Level[1]



1. Thorgeirsson S et al. *Nat Genet*. 2002;31:339-346.

Understood and Expected Genetic Pathways

Understood and Expected Genetic Pathways

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Audience Q&A: Question 1

What toxicities would you worry most about when using checkpoint inhibitors?

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Audience Q&A: Question 2

Do you use biopsy and/or cell-free DNA to understand biomarkers as well as to determine a diagnosis?

Audience Q&A: Question 3

What are your thoughts on the combination of SBRT or radiation therapy with immunotherapy?

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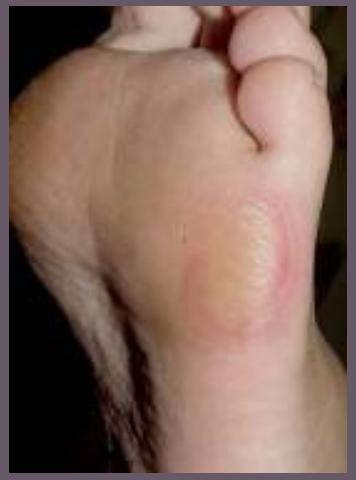
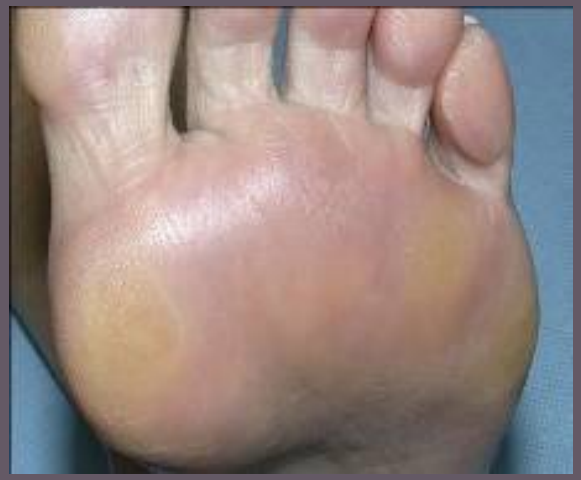
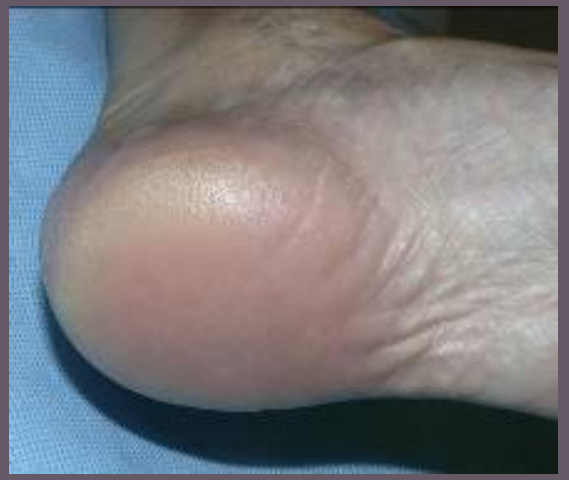
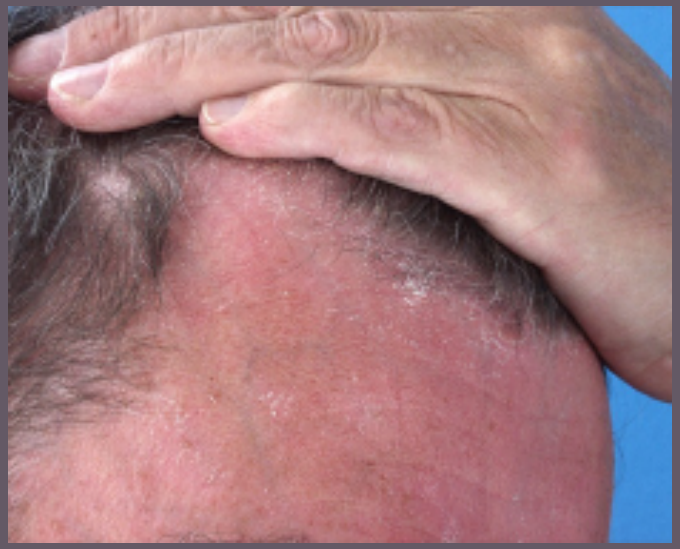
Hand-voet-syndroom: meest ernstig thv drukzones

- Hyperkeratotische gebieden
- Let op de zone met erytheem aan de rand van het letsel op de linker foto.

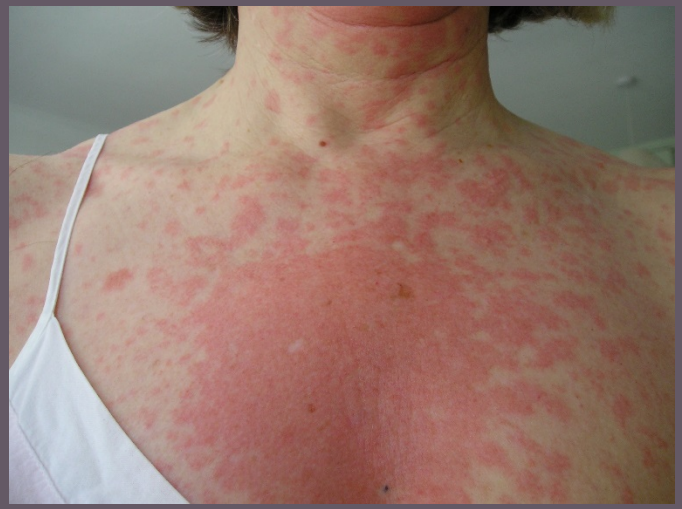




Huiduitslag: symptomen

- Uitslag in het gezicht: schilfering rond de haargrens



- Maculopapulaire uitslag op het lichaam



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FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

Radiolabeled microspheres treatment

Karen Geboes

October 2010

Universitair Ziekenhuis Gent

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Radiolabeled microspheres treatment

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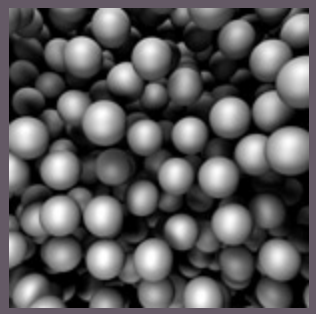
- Practical aspects
- Data on outcome
- Complications

radiolabeled microspheres



- *glass* microspheres
  - Therasphere, Nordion, Canada
  - No randomized data available
  - Mainly applied for HCC

- *resin* microspheres (20-60 µm)
  - SIRspheres, Sirtex, Australia
  - Some randomized data available
  - Mainly applied for mCRC and HCC

^{90} Yttrium

- Pure beta-emittor (Emax: 2.27 MeV, average 0.94 MeV)
- Maximum range in human tissue: 11mm, mean 2.5mm
- Half life: 64h

Comparison of the Two ^{90}Y Microsphere Devices

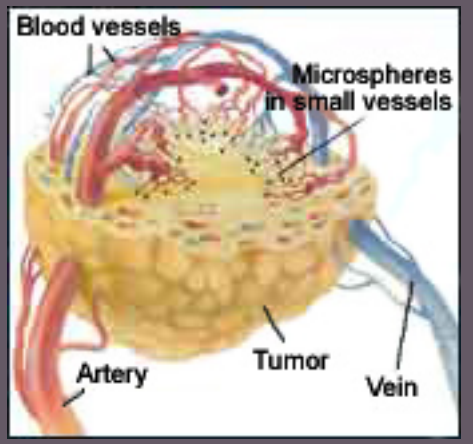
Characteristic	Glass Microsphere Device	Resin Microsphere Device
Number of spheres per dose		
Range	$3–8 \times 10^6$	$30–60 \times 10^6$
Mean	4×10^6	50×10^6
Specific gravity	High	Low
Specific activity (Bq per sphere)	2500	50
Institutional review board oversight	Required	Not required
FDA approval category	Humanitarian device exemption	Premarket approval
Dose variation with tumor volume	No	Yes
Hepatopulmonary shunt upper limit (%)	10	20
Solution used for suspension of spheres	Normal saline	Sterile water
Adjuvant chemotherapy	No	Yes

1 treatment: 5 GBq/2M spheres 2 GBq/50M spheres

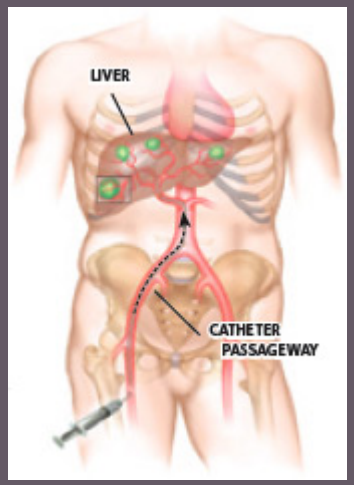
SIRspheres:

- patient tailored activity can be taken from vials
- lower specific gravity for SIRspheres:
- more homogeneous distribution of activity?

Intra-arterial administration



Rationale:
liver's double blood supply:
- Liver tumors > 3mm are vascularised mainly (80 – 100%) by the hepatic artery while normal tissue is fed by the portal vein



Advantages:
<> External radiation: higher activity to tumor + surrounding parenchyma
limited exposure of other organs
<> RFA: targets tumor but not limited to tumor
- minimally invasive: less stringent criteria compared to surgery
- additional diagnostic information

Patient selection

- Karnofsky at least 70%
- No ascites
- Bilirubine < 2mg/dL (3 mg/dL if a single segment is treated)
- Child-Pugh not exceeding B7
- Liver dominant tumor burden
- (No radiation upper abdomen)

Procedure

1. Angiography of liver and IA injection of Tc-MAA as tracer to simulate the treatment
   - Check for excessive lung shunt
   - Check for tracer deposition GI tract, pancreas, falciform
2. Actual treatment with Yttrium-90 about 2 weeks later
3. Post therapy scan

! 24h admission in hospital at each occasion (1 and 2: MAA, maybe even treatment of each lobe separately)

No (limited) specific radioprotective guidelines needed (in contrast to 131-I Lipiodol)

! No general anaesthesia

Reimbursed

Procedure

1. Angiography of liver and IA injection of ^{99}Tc-MAA as tracer to simulate the treatment

    Check for excessive lung shunt

    Check for tracer deposition GI tract, pancreas, falciform

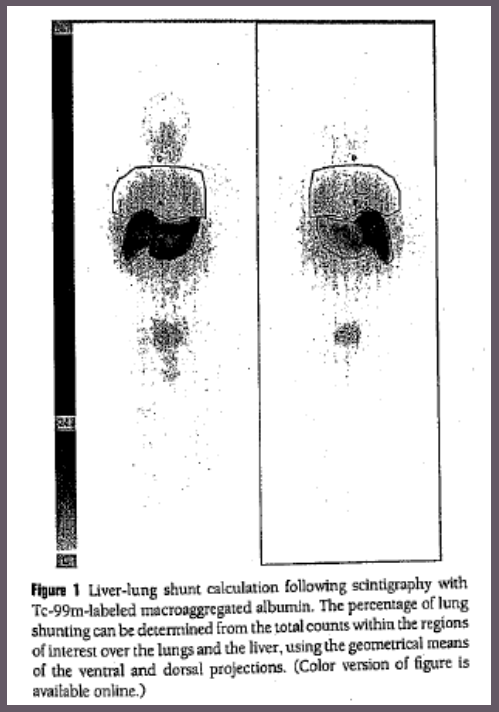


Figure 1 Liver-lung shunt calculation following scintigraphy with Tc-99m-labeled macroaggregated albumin. The percentage of lung shunting can be determined from the total counts within the regions of interest over the lungs and the liver, using the geometrical means of the ventral and dorsal projections. (Color version of figure is available online.)

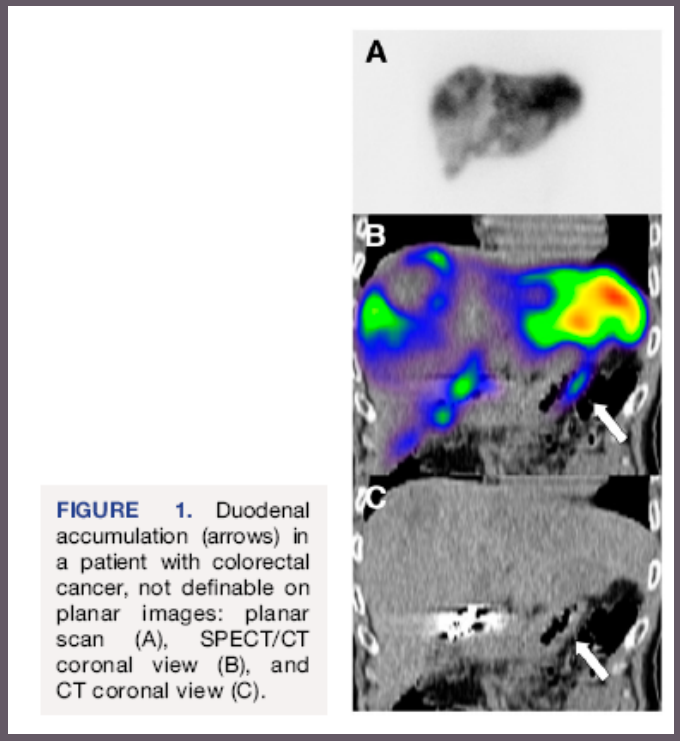


FIGURE 1. Duodenal accumulation (arrows) in a patient with colorectal cancer, not definable on planar images: planar scan (A), SPECT/CT coronal view (B), and CT coronal view (C).

Activity calculation for SIR-Spheres

1. Empirical

Empirical Dose Calculations for Resin Microspheres	
A: Calculation of Dose	
Liver Involvement by Tumor (%)	Recommended Dose (GBq)
<25	2.0
25–50	2.5
>50	3.0

Standard dose ~ size of tumor in liver

BSA method ~ size of tumor in liver, but corrected for size of patient

2. BSA method

A(GBq)= (BSA-0,2)+relative liver involvement
activities between 1,3-2,5 GBq

Partition model ~ MAA activity: higher doses in tumor, lower in other tissues – correction for LFT

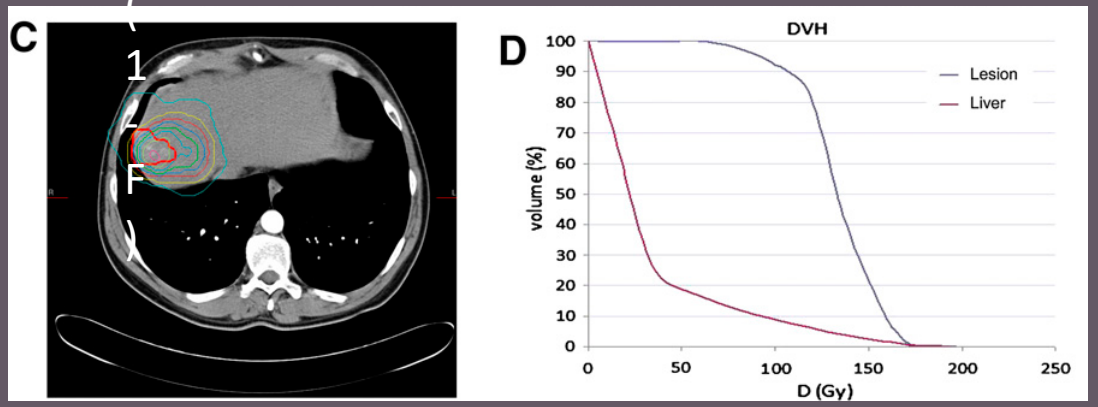
3. Partition model

Mass liver, mass tumor, T/N, dose parenchym (40-70 Gy), LSF

Activity calculation for Therasphere

$$A\ (GBq) = \frac{D\ (Gy) \times M\ (kg)}{49.8 \times \left(1 - \frac{F}{100}\right)}$$

D: nominal target dose liver incl tumor (150 Gy)
M: patient specific liver mass, CT derived
49.8 Gy.Kg.GBq-1 equilibrium accumulated dose constant for ^{90}Y
F: lung shunt



Recommendations for SIR-Spheres

- When there is 10 % or more lung shunting, the patient dose would be further reduced, according to the following table 2.

Table 2 – Dose Reduction Factors for Patients with Lung Shunting

% Lung Shunting	Reduction Factor
< 10 %	No reduction
10 % - 15 %	20 % reduction
15 % - 20 %	40 % reduction
> 20 %	No Treatment

Recommendations for Therasphere

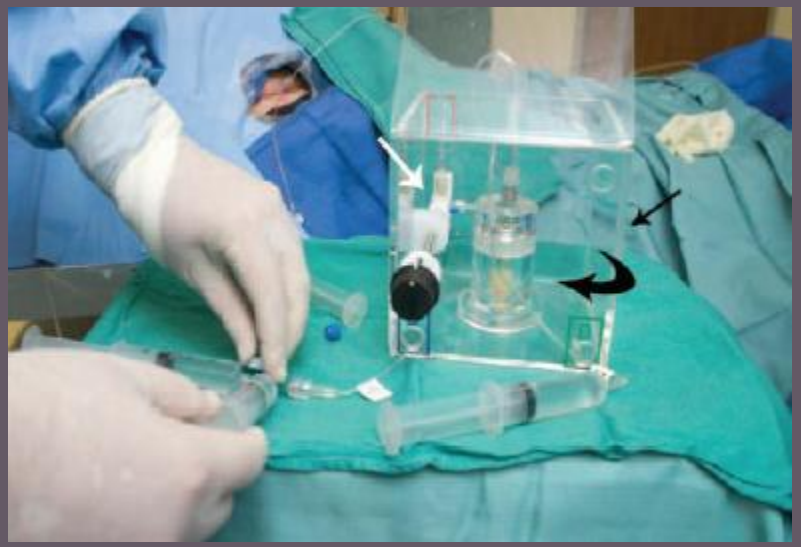
Do not exceed 610 MBq to the lungs
30 Gy single session or 50 Gy cumulative

Procedure

2. Actual treatment with Yttrium-90 about 2 weeks later

Pure beta-emittor (Emax: 2.27 MeV, average 0.94 MeV)
Maximum range in human tissue: 11mm
Half life: 64h

plastic protection material (no lead) - bremsstrahlung



No photons in waste material

No isolation

24h in hospital because of angiography

No strict rules in contact at home

Procedure

3. Post therapy scan

'brehmsstrahlung scintigraphy' within 24h to document extrahepatic spread of microspheres.

Procedure

How to distinguish necrosis/ fibrosis/ edema/ hemorrage < treatment and recurrence

Response evaluation

- RECIST?

CT: decreased attenuation in affected areas ~ edema, congestion, microinfarction

Changes noted at 8 weeks, diminished at 16 weeks (≠ recurrence)

- PET?

Total SUV of axial slice or of individual lesions

No prospective data on PET response and outcome

- (diffusion-weighted) MRI?

Dynamic vascular assessment: necrosis, vascularity, volume, blood marker reduction and water diffusion

Procedure

Response evaluation

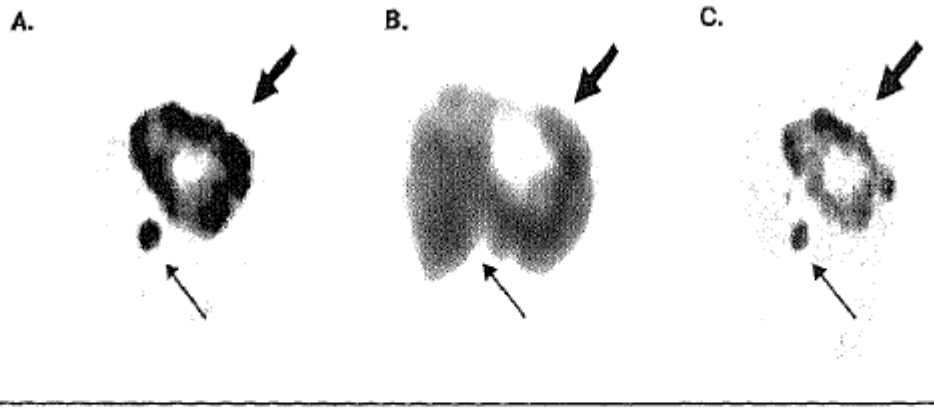


Figure 1. Integrated multimodality fluorodeoxyglucose positron emission tomography (FDG-PET) and macroaggregates of albumin single photon emission computed tomography (MAA-SPECT) imaging allows prediction of the selective internal radiation therapy (SIRT) response. A. The baseline FDG-PET scan: a coronal slice through the liver shows a large necrotic metastasis of the left lobe (thick arrow) and a smaller hypermetabolic lesion of the left lobe (thin arrow). **B.** The same coronal slice of the MAA-SPECT (pretherapeutic ^{90}Y-RE simulation): the small lesion does not show any uptake of MAA whereas the large necrotic lesion shows a moderate and heterogeneous uptake at the periphery and absence of perfusion at the central (necrotic) part. **C.** The FDG-PET scan performed 6 weeks after ^{90}Y-RE. On the same coronal slice a non-response of the small lesion (stable SUV) is observed; and a partial response (SUV reduction

Conclusions on practical aspects:

- Dose calculation is being optimised (120 Gy in tumor typically)

(also in treatment with chemotherapy: similar but slightly different regimens are used)

- Response evaluation is being optimised

(also in treatment with chemotherapy: response evaluation after bevacizumab treatment)

SIRT for liver metastases of CRC

Numerous prospective non-randomized studies
in first-line, second-line or salvage therapy
with or without chemotherapy

response rates: 26 – 100%
median overall survival: 10.8 – 29.4 months

Vente et al, Eur Radiol 2009
Sharma et al, JCO 2007
Lim et al, Intern Med J 2005
Lim et al, BMC Cancer 2005
Wong et al, J Nucl Med 2004

Multicentric, retrospective analysis in 208 chemorefractory CRC pts

Excluded: bili > 2mg/dL, ALT/AST> 5 x UNL, platelets < 60.000
Bilobar disease: half of these patients treated in 2 sessions
Toxicity:

- Fatigue and abdominal pain
- 5% rise in bili (grade 2 – 3)
- 5% ulceration

At 3 m 10% showed progression, rest SD or PR
Responders (CT/PET/CEA…) median survival 10.5 m vs 4.5 m for non-responders

Heterogeneous data – CT & RECIST probably suboptimal for response evaluation

Kennedy et al, Int J Radiat Oncol Biol Phys 2006

Randomized trial IA floxuridine vs IA floxuridine plus SIR-Spheres in 74 patients with bilobar CRC liver mets

	HAC + SIRS	HAC	
RR	44%	18%	p=0.01
TTP	15.9m	9.7m	p=0.04
mOS	17m	15.9m	(HR 1.41 0.86 – 2.34)

- Floxuridine 12 days IA
- SIR-Spheres single session mean 2.4 GBq
- >> chemo naive patients
- No added toxicity
- Significant difference in time to liver progression
- No statistical power to prove difference in survival

No classical evaluation of response: tumour to liver-ratio

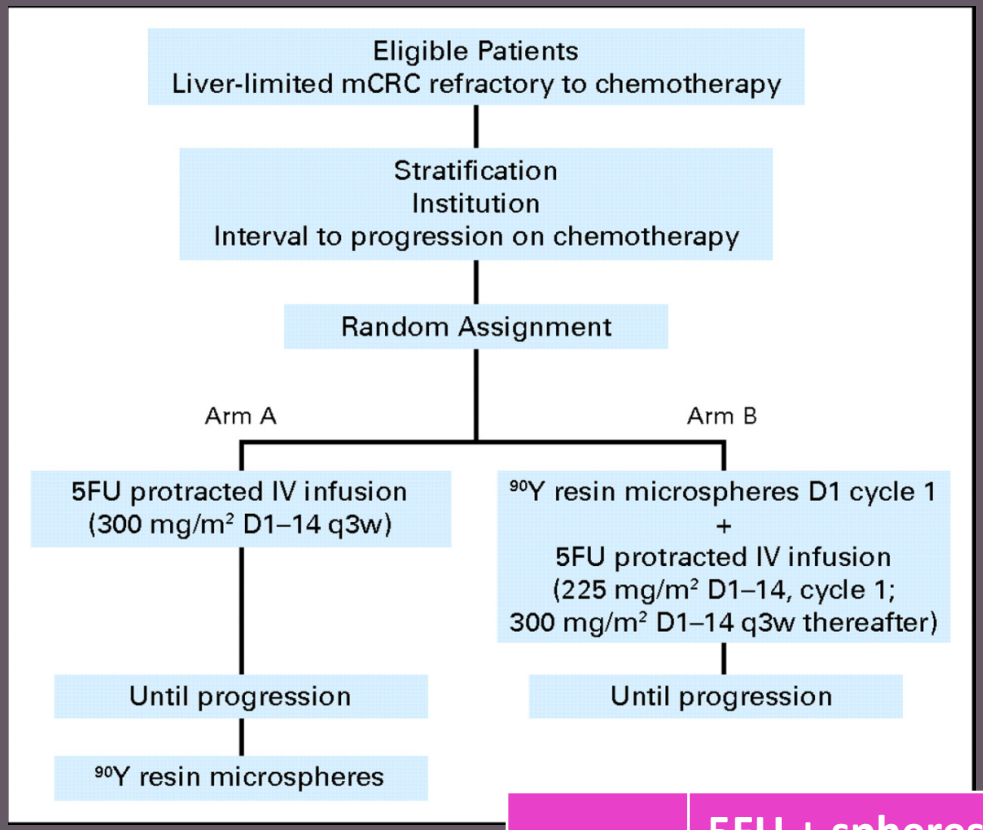
Gray et al. Ann Oncol 2001

Microspheres in mCRC: results

Phase II study: 21 chemo-naive pts: 5FU +/- ^{90}Y-microspheres

	5FU + spheres	5FU	
RR	90.9%	0%	P<0.001
TTP	18.6m	3.6m	P<0.0005
OS	29.4m	14.1m	HR 0.39 (0.14 – 1.13)

Van Hazel et al. J Surg Oncol 2004



N=46
Chemorefractory CRC liver mets

Cross over possible

	5FU + spheres	spheres	
RR	38%	17%	
TTP	5m	2.25m	HR 0.51 (0.28 – 0.94)
OS	10.75m	8m	HR 0.92 (0.47 – 1.78)

Hendlisz et al, JCO 2010

SIRFLOX study

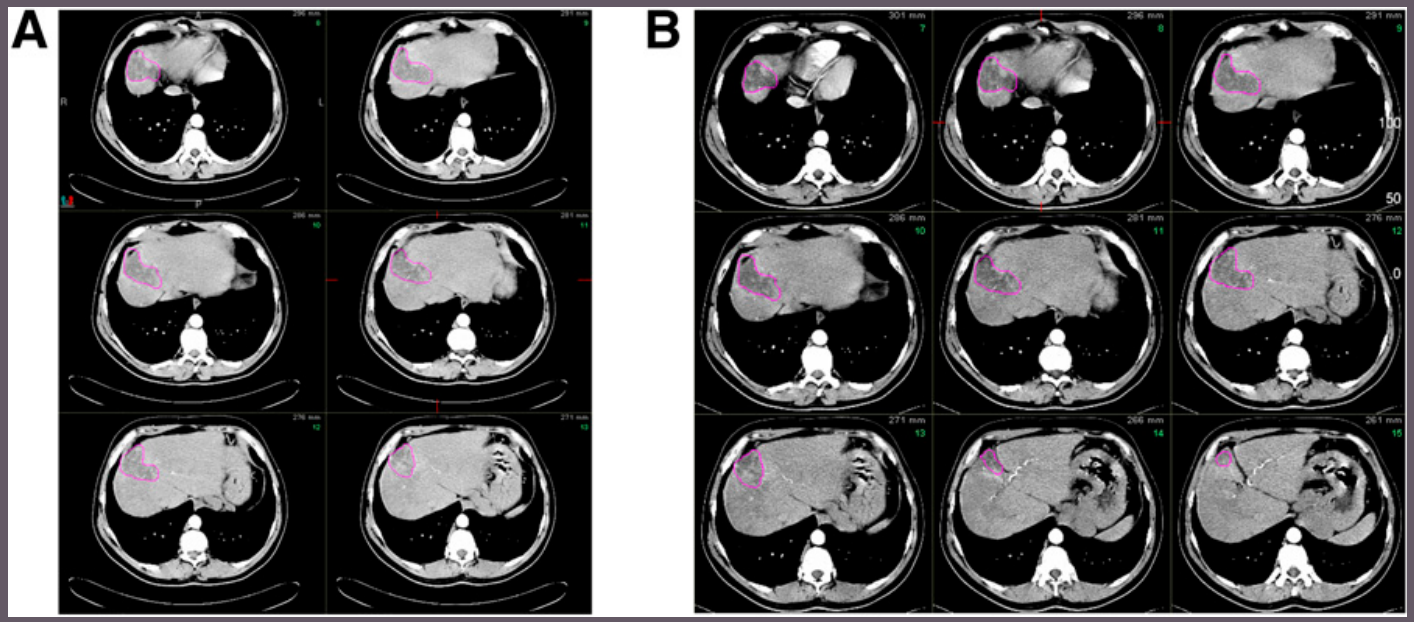
FIRST LINE in CRC liver mets:

Randomized FOLFOX vs FOLFOX plus single session SIR-Spheres

Protocol amendment: + avastin

Hepatocellular Carcinoma

Multicentric European study with SIR-Spheres for HCC
Sangro et al. ILCA 2009



252 patients
Median survival
- Child-Pugh A: 16,8 months
- Child-Pugh B: 10,3 months
- BCLC B: 20,8 months
- No extrahep disease: 15,3 months

- Lewandowski et al. Am J Transplant. 2009

- "A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization."

- Cohort study comparing chemo-embolisation vs Yttrium-90 in 86 UNOS T3 HCC pts
- more downstagings achieved with Yttrium-90
- better survival
- pitfall: different tumour biology?

Table 6: Imaging findings–progression analyses

Characteristic		TACE N = 35	Y90 N = 43	p-Value
WHO	PD	9 (26)	4 (9)	0.07
1-year progression rate (%)		25	11	0.008
Median time to WHO PD (95% CI) (months)		19.6 (12.4, -)	48.6 (30.8, -)	
EASL	PD	7 (20)	3 (7)	0.10
1-year progression rate (%)		40	8	0.01
Median time to EASL PD (95% CI) (months)		19.6 (11.6, -)	- (25.9, -)	
UNOS	Progressed	11 (31)	10 (23)	0.45
1-year progression rate (%)		28	19	0.098
Median time to UNOS progression (95% CI) (months)		18.2 (17.3–19.6)	33.3 (15.3, -)	
UNOS/new lesion	Progressed	12 (34)	12 (28)	0.63
1-year progression rate (%)		36	22	0.096
Median time to UNOS/new lesion progression (95% CI) (months)		17.3 (7–22.6)	32.6 (13.8–33.3)	
Overall progression	Progressed	11 (31)	7 (16)	0.45
1-year progression rate (%)		32	15	0.005
Median time to overall progression (95% CI) (months)		12.8 (7.9–19.6)	33.3 (17.8–33.9)	

PD = progressive disease.

- Salem R. Gastroenterology 2009

"Radioembolization for Hepatocellular Carcinoma Using Yttrium-90 Microspheres: A Comprehensive Report of Long-term Outcomes."

- Single center prospective longitudinal study
- n= 291 HCC patients; 526 treatments
- Toxicity
  - Fatigue 57%, pain 23%, nausea/vomiting 20%, bilirubine gr III/IV 19%
- Response
  - WHO 42%, EASL 57%
- TTP 8 m
- Survival
  - Child-Pugh A 17 m, Child-Pugh B 8 (B+PVT 6m)

- Rhee et al: 42 pts

~ 90% PR or SD/6 months

- Kennedy et al: 148 pts with 185 procedures

SD 23%, PR 60%, CR 3%

- King et al: symptomatic responses in 18/33 pts at 3 months and 16/32 pts at 6 months

18% CR, 32% PR, mOS 29.4 ± 3.4 months

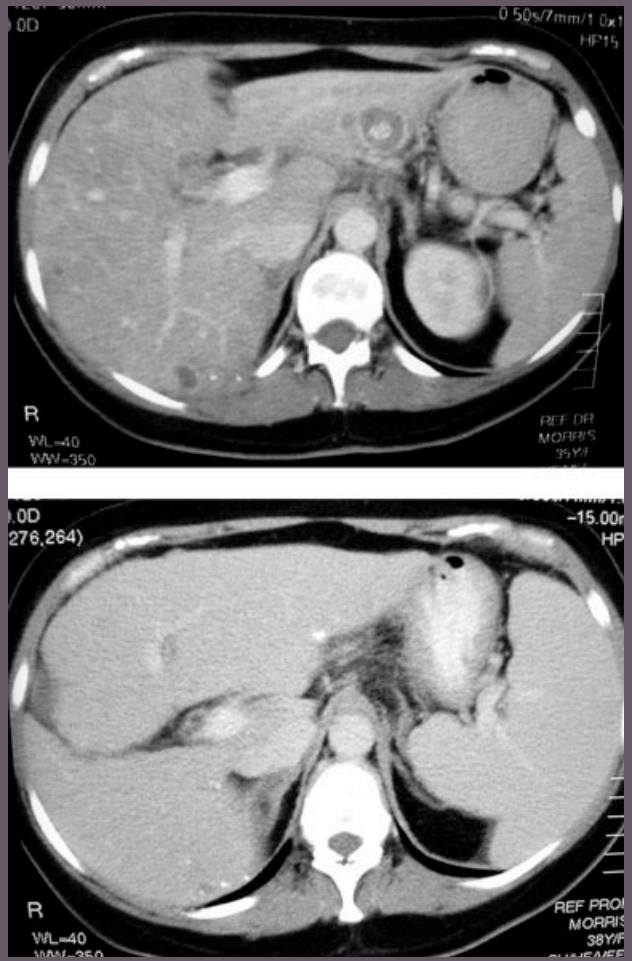


TABLE 1
Characteristics of Patients the With Best Liver Response to Yttrium-90 Radioembolization by Response Evaluation Criteria in Solid Tumors

CT Response in Liver	Primary Site	Prior Liver Treatments	Prior Extrahepatic Disease	% Hepatic Replacement	Follow-up, mo	SIR-Spheres: Dose Delivered, GBq	Yttrium 90 Estimated Tumor Dose, Gy	CgA Fall, %
CR	Pancreas	LR	Nil	30	42	1.9	79	−93
CR	Small bowel	LR	Nil	1	42	1.6	62	−63
CR	Small bowel	Nil	+	10	33	2	16	−48
CR	Medullary thyroid	Nil	Nil	50	48	2	46	−60
CR	Small bowel	Nil	Nil	10	28	0.9	19	−70
PR	Small bowel	Nil	Nil	60	26	2.3	18	−23
PR	Small bowel	Nil	Nil	50	4*	1.9	45	Nil baseline
PR	Small bowel	Nil	Nil	40	8*	1.9	60	−31
PR	Unknown	Nil	Nil	50	11*	2.3	40	−14
PR	Small bowel	IV	+	30	24*	1.9	55	−68
PR	Pancreas	LR	Nil	10	45	1.5	65	−77
PR	Glucagonoma	Nil	Nil	10	41	2	125	−63
PR	Unknown	Nil	+	30	41	2.1	36	−20
PR	Unknown	Nil	+	20	35	1.6	55	−25
PR	Somatostatinoma	LR	Nil	10	39	1.8	50	−12.5
PR	Pancreas	Nil	+	25	29	2.1	61	−25
PR	Small bowel	Nil	Nil	40	12*	2	52	Nil baseline
SD	Bronchus	Nil	Nil	10	8	2	105	−55
SD	Small bowel	LR	+	20	20*	2.3	52	−86
SD	Small bowel	IV	+	50	39*	2.1	65	−79
SD	Vipoma	LR	+	20	18*	2.1	89	No change
SD	Small bowel	LR	+	25	24*	1.9	40	−75

CT indicates computed tomography; SIR, selective internal radiation; GBq, gigabecquerel; Gy, grays; CgA chromogranin A; CR, complete response; LR, liver resection; +, positive; PR, partial response; IV, systemic chemotherapy; SD, stable disease.
*Deceased.

Microspheres in NET: results

- Data in cholangiocarcinoma
- Data in breast cancer
- Data in melanoma
- Report in GIST

Conclusions on possible treatment options:

- Valid option in mCRC in liver predominant disease after progression on conventional treatment
- Neo-adjuvant treatment in HCC

(conversion therapy in mCRC? Sirflox)

- Local ablative therapy in non-operable HCC
- Symptomatic NET

(not considered for PRRT?)

Pitfall

Most large studies published by a few groups with a lot of expertise.

Low number of complications!

Postembolisation syndrome: corticosteroids?

Toxicity:

Fatigue (56-61%)

Anorexia

Nausea (21-23%)

Abdominal pain (25%)

Elevated liver function tests (10.2 – 17.5%)

Radiation pneumonitis

GI ulcerations (9-12%?)

REILD (radioembolisation induced liver disease)

Radiation pneumonitis

- When there is 10 % or more lung shunting, the patient dose would be further reduced, according to the following table 2.

Table 2 – Dose Reduction Factors for Patients with Lung Shunting

% Lung Shunting	Reduction Factor
< 10 %	No reduction
10 % - 15 %	20 % reduction
15 % - 20 %	40 % reduction
> 20 %	No Treatment

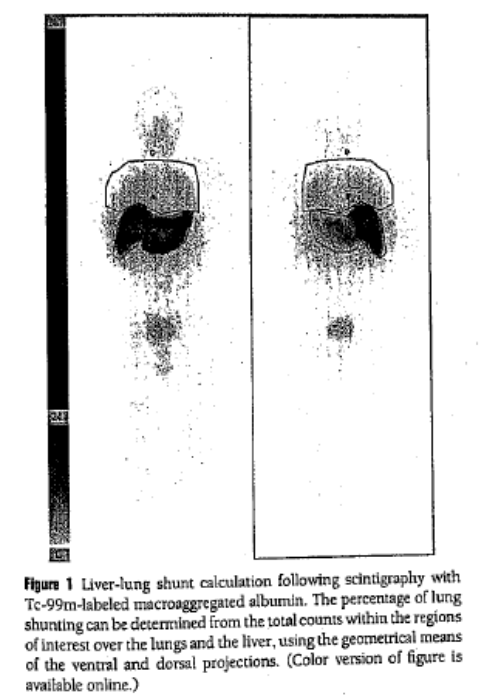
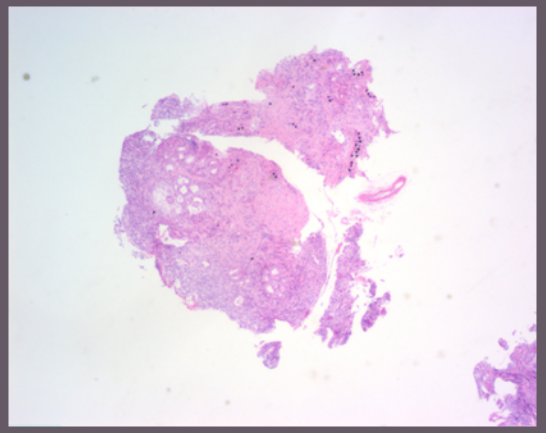


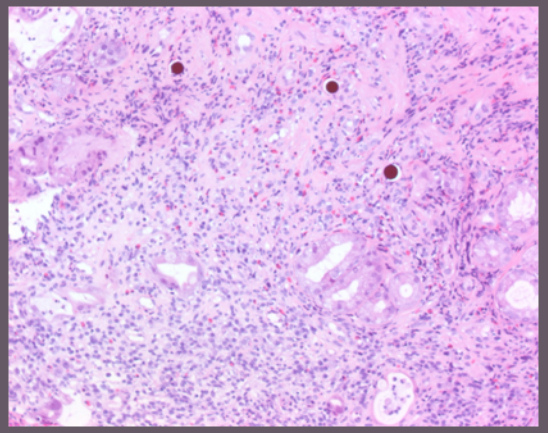
Figure 1 Liver-lung shunt calculation following scintigraphy with Tc-99m-labeled macroaggregated albumin. The percentage of lung shunting can be determined from the total counts within the regions of interest over the lungs and the liver, using the geometrical means of the ventral and dorsal projections. (Color version of figure is available online.)

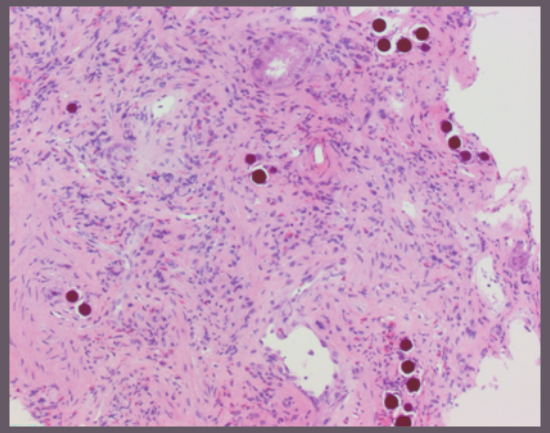
Recommendations for Therasphere

Do not exceed 610 MBq to the lungs
30 Gy single session or 50 Gy cumulative

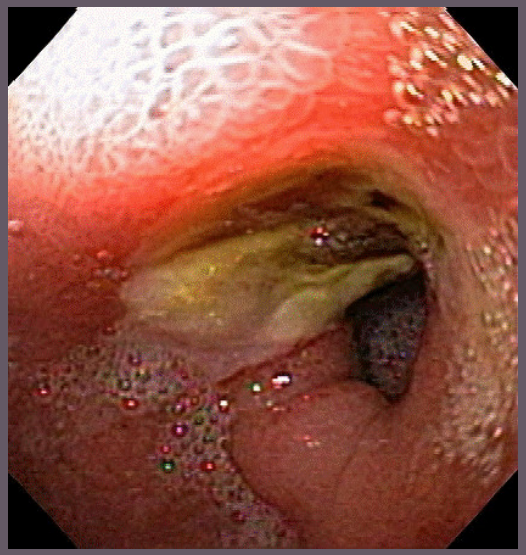
GI ulcerations (9-12%?)

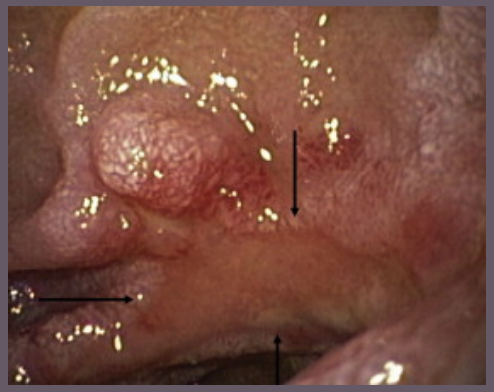


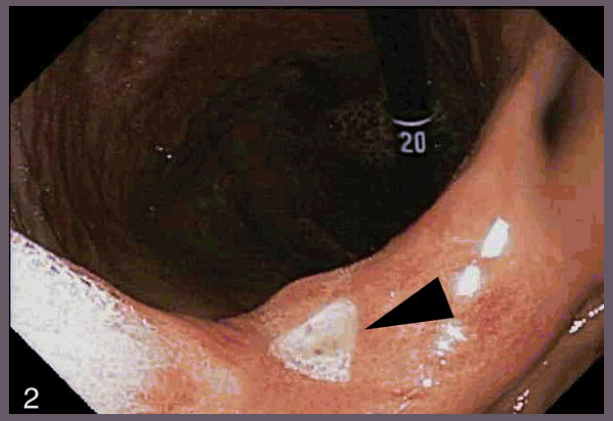




GI ulcerations (9-12%?)







Mucosal ischemia due to mechanical occlusion of mucosal arterioles or submucosal arteries
Radiation injury to the vessels
Radiation injury to the mucosa

South CD et al, World J Surg Oncol. 2008
Zimmerman L et al, Gastrointestinal Endoscopy 2008
Ogawa F et al, Archives of Pathology and Laboratory Medicine 2008

GI ulcerations (9-12%?)

-deliver high-energy, low-penetrating therapeutic doses of radiation

-variant hepatic arterial anatomy, collateral vessels, and changes in flow dynamics during treatment can affect particle dispersion and lead to nontarget particle distribution and subsequent gastrointestinal morbidity.

-awareness of these variances and techniques to prevent gastrointestinal tract microsphere delivery is essential in mitigating this serious complication.

- to increase the understanding of the role of various imaging and preventative techniques in minimizing this undesired effect.

Murthy R et al, J Vasc Interv Radiol 2007

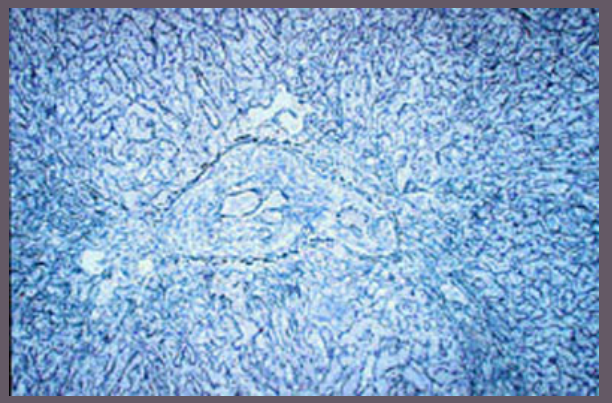
REILD (radioembolisation induced liver disease) (4%?)

Radiation doses > 40 Gy

After 4 weeks – 4 months

Ascites/anicteric hepatomegaly/elevated liver enzymes

Veno-occlusive disease



Heavily pretreated patients

(chemotherapy, radiation upper abdomen, volume reductive surgery)

Conclusions on complications:

- Need for specialised centra
- Need for communication: between radiologists and oncologists, but also between centers
- Careful selection of patients:

- Be aware of possible complications in heavily pretreated patients
- *And thus as well in patients that are treated palliatively but with an expected long OS?*

Don't forget: complications for certain chemotherapies and also in surgery

- Take home messages

- Very well controlled local treatment option for liver tumors
- Little randomized data
- Valid option in chemorefractory patients
- Randomised studies ongoing
- Dose calculation and response evaluation studied
- Complication rate may be underestimated – complications may be severe – well trained staff is needed; communication is needed!