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Hepatocellular Carcinoma

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Disclosures:

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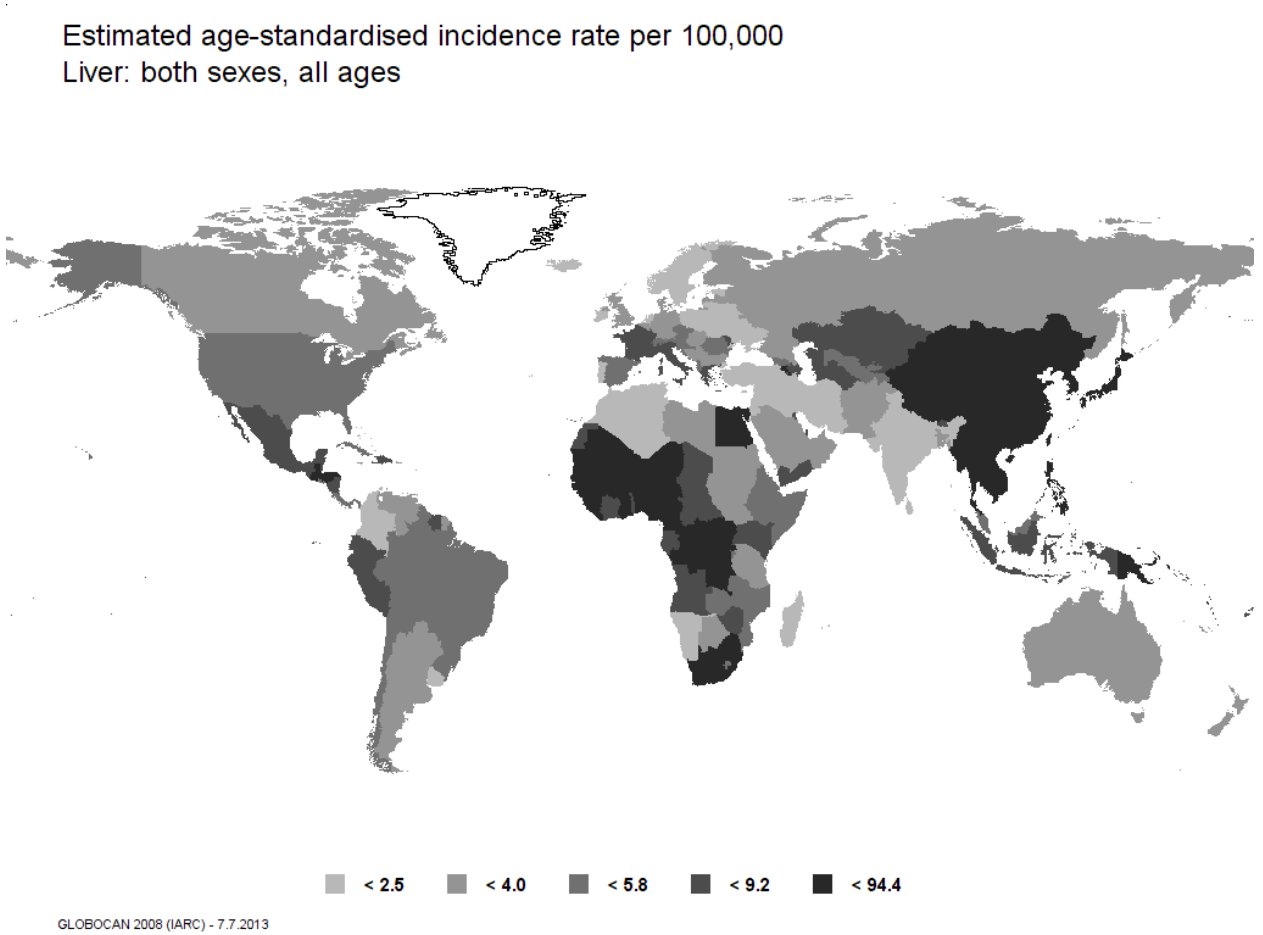
- Consulting: Eisai, Zymeworks
- Other Unpaid Affiliations: GI Cancer Alliance, ASCO, Fibrolamellar Cancer Foundation

HCC: Global incidence



3rd leading cause of global cancer related death
Incidence and mortality is rising in the United States

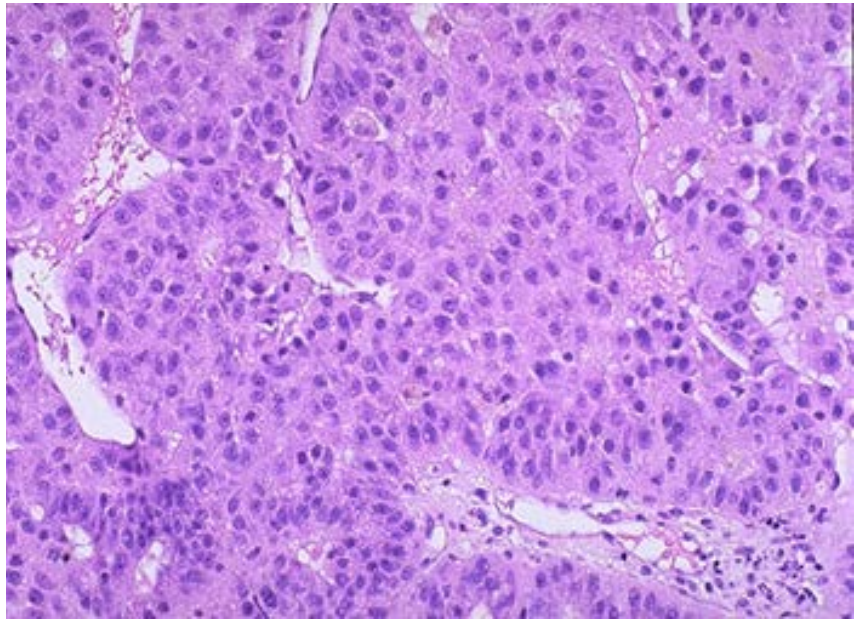
El-Serag HB. N Engl J Med 2011; 365:1118-1127.

Bray et al. Cancer 2018:68(6) 394-424

HCC: Risk Factors

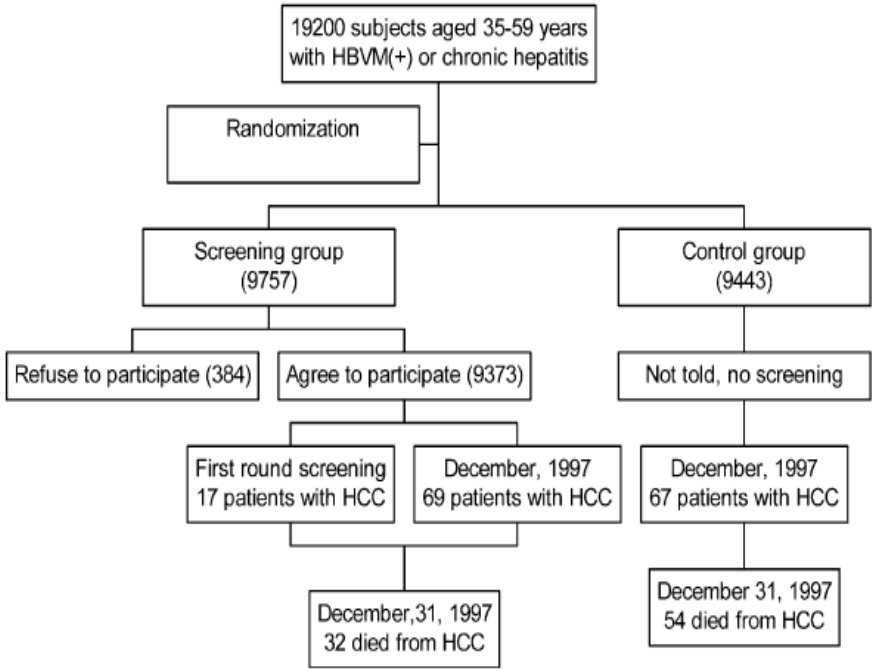
- **Cirrhosis from any cause**
  (3-4%annual risk of HCC)
  - HCV
  - HBV
  - Heavy alcohol consumption
  - Non-alcoholic steatohepatitis (NASH)
  - Aflatoxins
- **HBV Chronic Hepatitis**
  (0.4% annual risk of HCC)
- **Inherited metabolic diseases**
  - Hemochromatosis
  - Alpha-1 antitrypsin deficiency
  - Glycogen storage disease
  - Porphyria cutanea tarda
  - Tyrosinemia
  - Autoimmune hepatitis

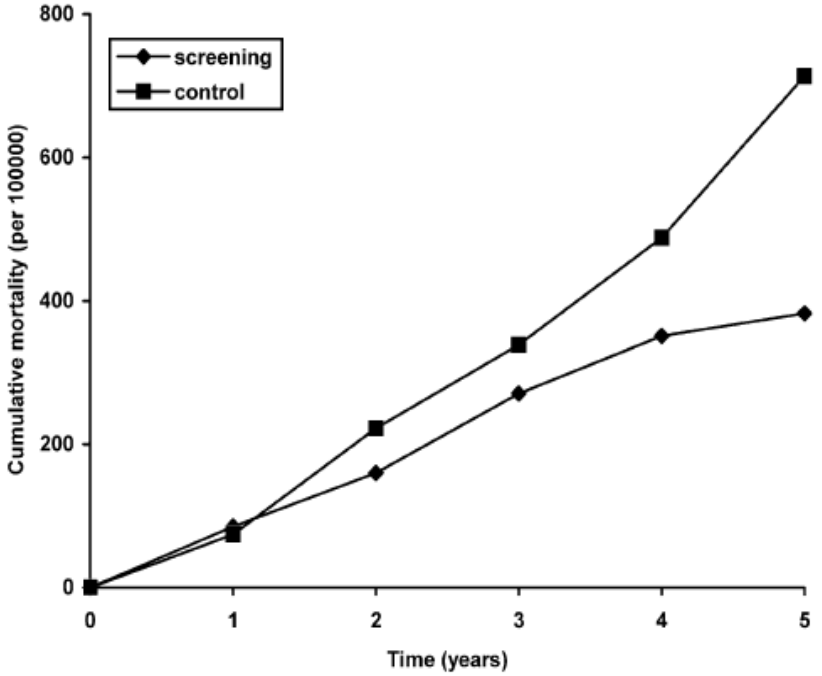
Diabetes Mellitus
Obesity



HCC: Screening and Early Detection

- Approximately 19,000 patients with chronic hepatitis/chronic HBV randomized to: Ultrasound every 6 months and AFP vs. control (no screening)
- **37% HCC mortality reduction** – **mortality rate ratio 0.63** (95% CI 0.41, 0.98)





Zhang BH et al. Randomized controlled trial of screening in hepatocellular carcinoma. *J Can Research Clin Oncol*. July 2004.

Who should be screened for HCC? AASLD Guidelines

TABLE 1. PATIENTS AT THE HIGHEST RISK FOR HCC

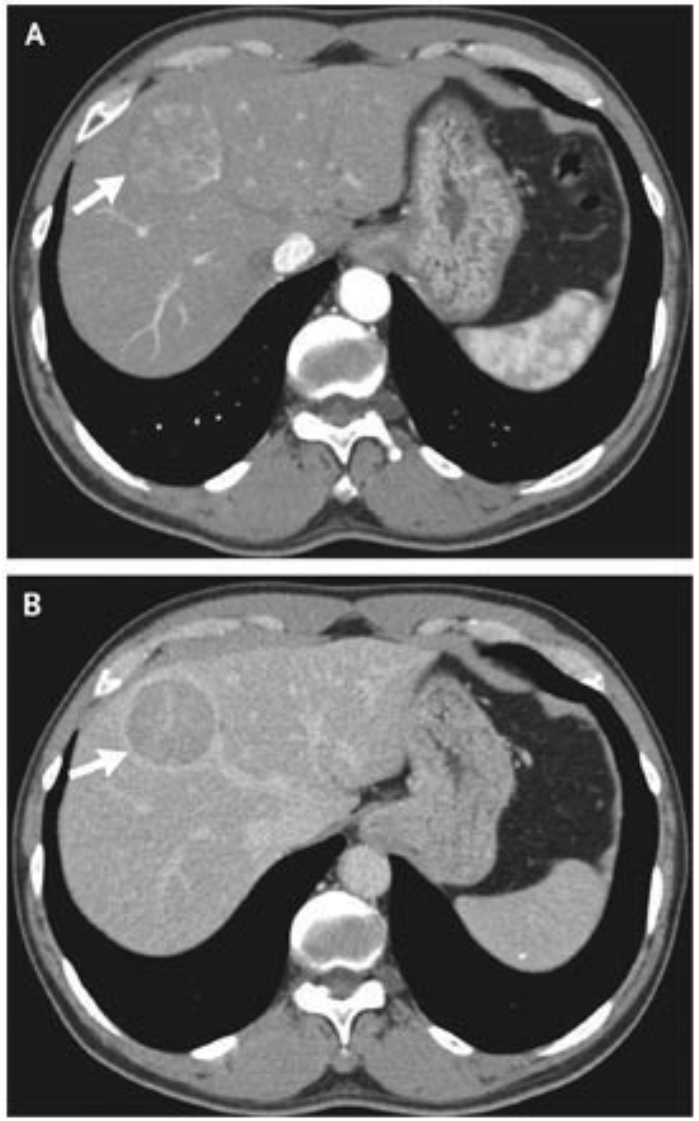
Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Incidence of HCC
Surveillance benefit		
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.6% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2-1.5	3%-8% per year
Hepatitis C cirrhosis	1.5	3%-5% per year
Stage 4 PBC	1.5	3%-5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	<0.2% per year
Hepatitis C and stage 3 fibrosis	1.5	<1.5% per year
NAFLD without cirrhosis	1.5	<1.5% per year

Abbreviation: LYG, life-years gained.

Marrerro et al. Hepatology 68(2) 2018.

Diagnosis

- **Diagnostic** imaging indicated for lesion 1 cm or greater or AFP > 20
- Typically no biopsy required
- LIRADS scoring system used to characterize lesions
  - Applies to patients with cirrhosis or chronic hepatitis B infection and incorporates:
    - Size of arterially enhancing lesion
    - Washout
    - Capsule
    - Threshold growth
- Contrast enhanced **multiphase** MRI or CT



Burrel et al. Hepatology 2003; 38
Marrerro et al. Hepatology 68(2) 2018

LIRADS: Standardized radiology reporting system

LR-1 = definitely benign LR-2 = probably benign

LR-3 = indeterminate LR-4 = suspicious LR-5 = definite

CT/MRI Diagnostic Table

Arterial phase hyperenhancement (APHE)		No APHE		APHE (not rim)		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count major features: • "Washout" (not peripheral) • Enhancing "capsule" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

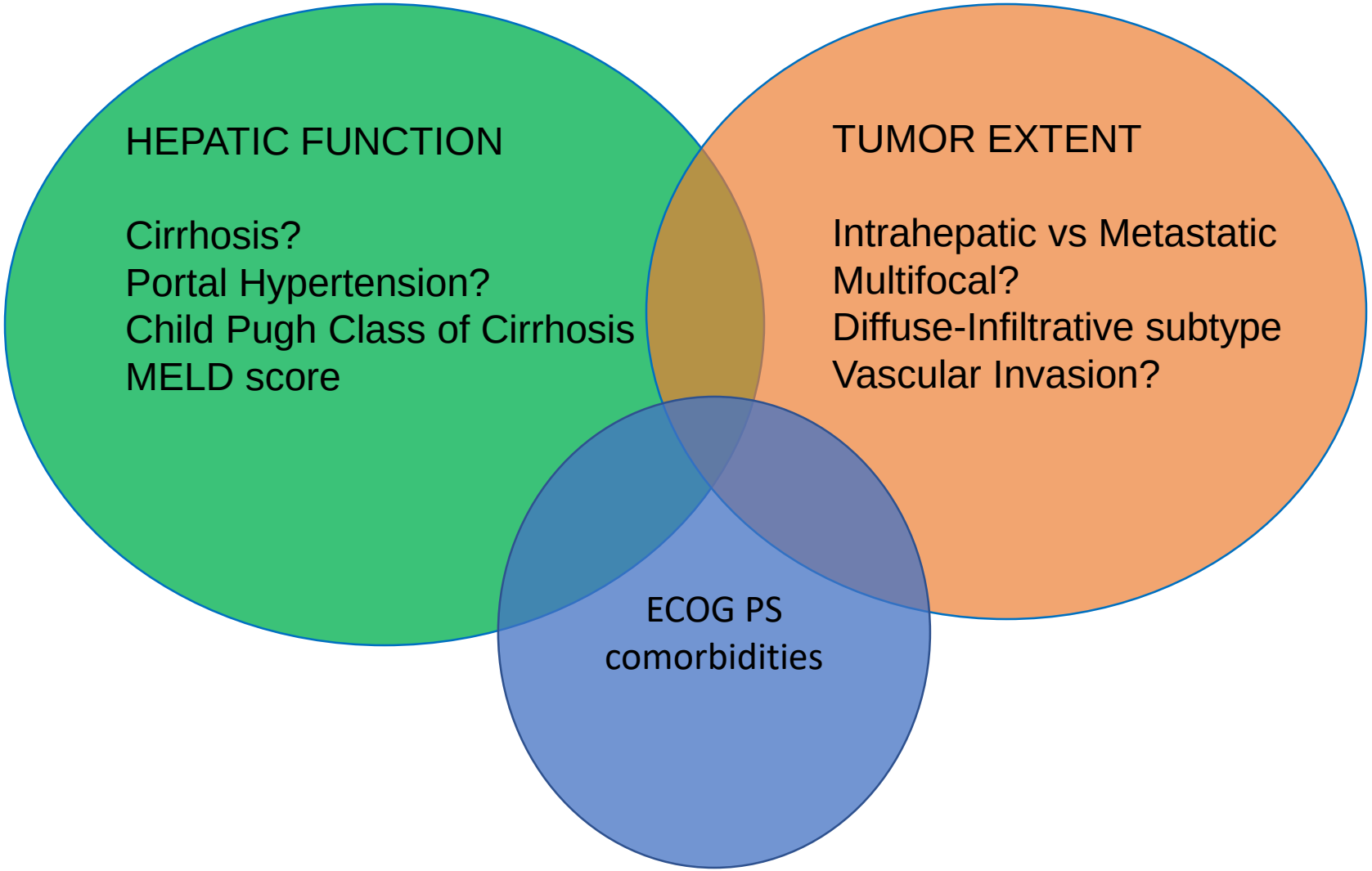
LR-4 / LR-5

Observations in this cell are categorized LR-4, except:
- LR-5g, if ≥ 50% diameter increase in < 6 months (equivalent to OPTN 5A-g)
- LR-5us, if "washout" and visibility at screening ultrasound (per AASLD HCC criteria)

ACR website: derived from LIRADS v2017

Separate LIRADS criteria for Contrast Enhanced Ultrasound exist

HCC: Considerations in staging and selection of therapeutic options



Hepatocellular Carcinoma: Staging

Multiple Complex staging systems incorporate:

- Size
- Multifocality
- Vascular invasion (e.g. portal vein tumor thrombus)
- Underlying liver function (Child-Pugh, MELD)
- Performance status
- Alpha fetoprotein levels

BCLC (Barcelona Clinic Liver Cancer) Staging

	BCLC stage				
	Very early stage (0)	Early stage (A)	Intermediate stage (B)	Advanced stage (C)	Terminal stage (D)
Child–Pugh classification	A	A–B	A–B	A–B	C
Performance status	0	0	0	1–2	3-4
Tumor status	1 HCC <2cm *Carcinoma in situ*	1 HCC or 3 nodules <3cm	Multinodular	Portal invasion or N1/ M1	Terminal stage

Llovet, JM et al. Design and Endpoints of Clinical Trials in Hepatocellular Carcinoma. *Journal of National Cancer Institute*. 100: 10, May 21, 2008

Modified BCLC Treatment Algorithm:
Early Stage Disease

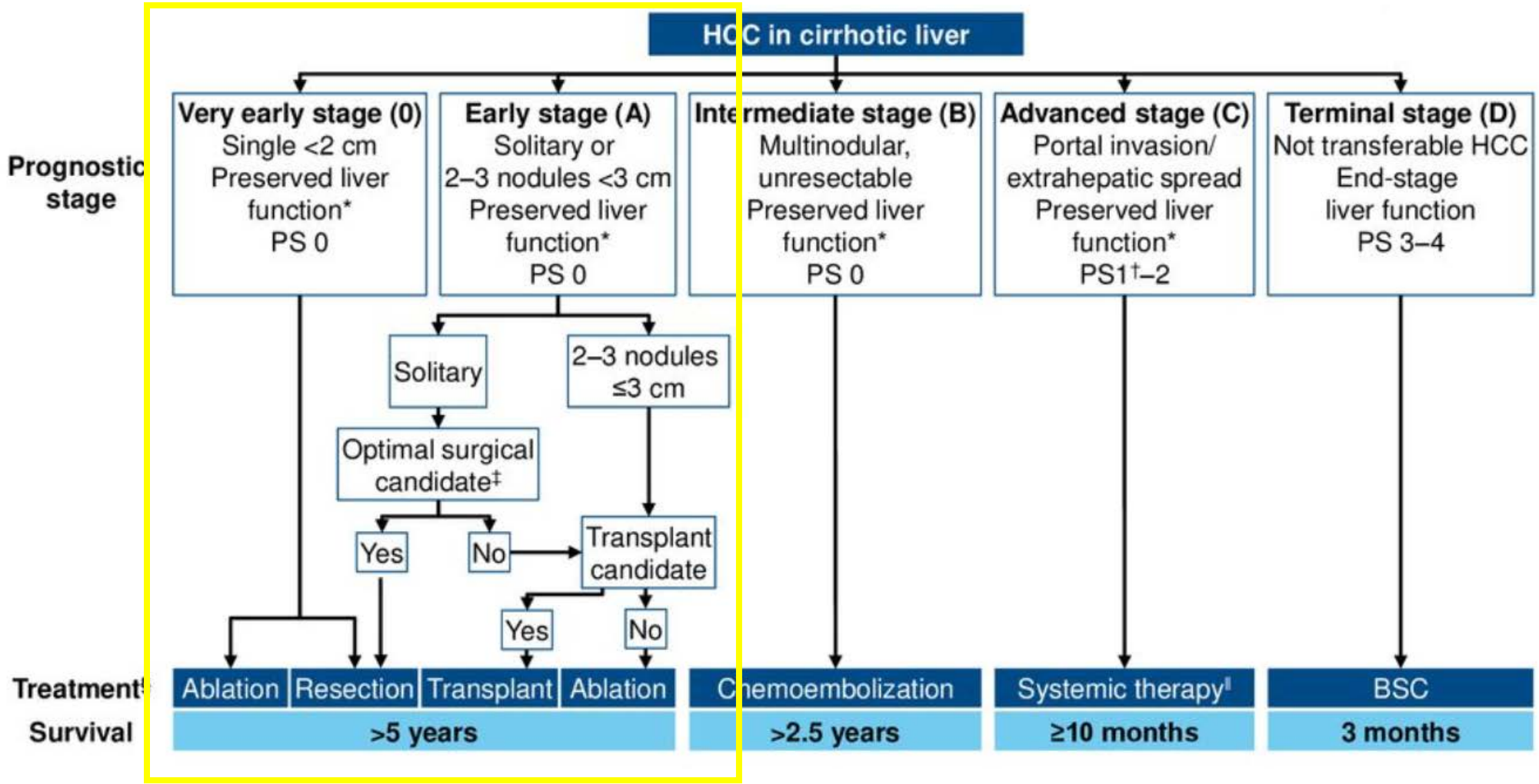


Figure: EASL CPG HCC. J Hepatol 2018

Early Stage Hepatocellular Carcinoma → BCLC Stage 0/A Local Options

Well-preserved liver function (non-cirrhotic, Child-Pugh A amenable to surgery)

- Surgical resection: no specific tumor size cut-off; no vascular invasion
- Accepted surgical outcome goal targets include:
  - Perioperative mortality 2-3%
  - 5-year overall survival of 60%

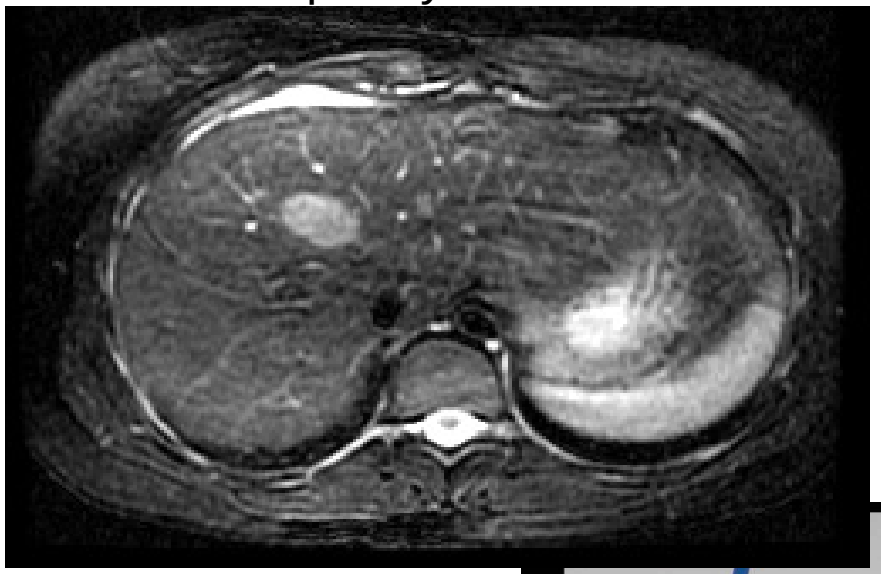
Underlying cirrhosis, poorer baseline liver function

- Liver transplantation: Milan criteria; strict eligibility criteria
- Radiofrequency ablation (RFA): Best in tumors < 3 cm; associated with similar survival to surgery.
- Stereotactic Radiation, focal radioembolization and other local interventions promising in multiple phase II trials

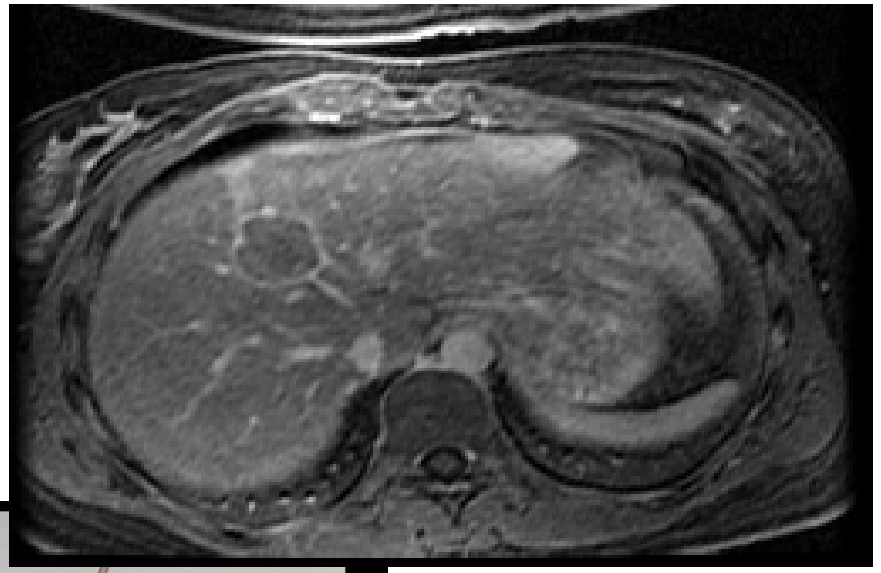
Hong SN, et al. Comparing the Outcomes of Radiofrequency Ablation and Surgery in Patients with a Single Small Hepatocellular Carcinoma and Well-Preserved Hepatic Function

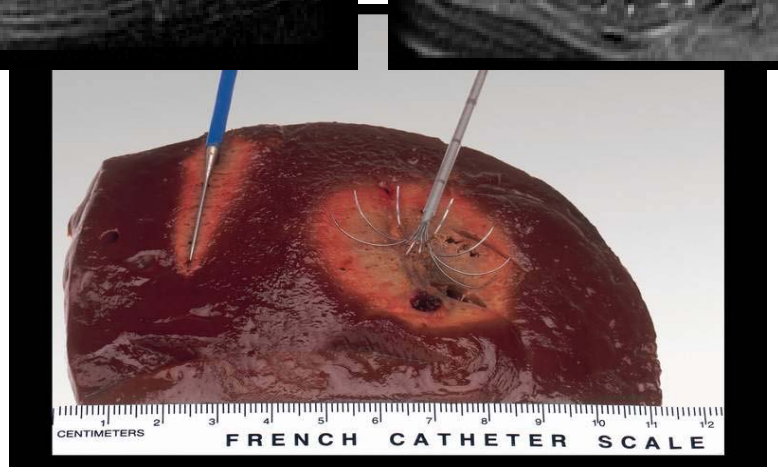
Local Treatment for Early Stage HCC: Radiofrequency Ablation

Pre-Radiofrequency Ablation



1-month post-RFA





Images from Dr. Siddharth Padia, UW Interventional Radiology

Early Stage Hepatocellular Carcinoma

- In well-selected patients with early stage HCC, 5-year survival 60-75% with local treatments.

  (Llovet JM et al. Hepatocellular Carcinoma. *Lancet*. December, 2003)

- No standard adjuvant chemotherapy following surgical resection, radiofrequency ablation (RFA) or other definitive local therapies

Orthotopic Liver Transplant: MELD Exception Points

Milan Transplant Criteria (1996)

- **Strict Criteria**
  - Solitary tumors ≤ 5cm

    or
  - 2-3 tumors all < 1-3 cm

    and
  - No macrovascular invasion/ mets

New Transplant Criteria (2017)

- **Downstaging to Milan allowed**
  - Solitary tumors 5-8 cm
  - 2-3 lesions
    - Each < 5 cm, sum < 8 cm
  - 4-5 lesions
    - Each < 3 cm, sum < 8 cm
- **AFP Criteria**
  - AFP > 1000 within Milan require locoregional therapy to achieve AFP < 500

Transplantation based on these guidelines has been shown to result in a 5-year post-transplant survival of ~80%

1) Llovet JM et al. Liver transplantation for small hepatocellular carcinoma: the tumor-node-metastases classification does not have prognostic power. *Hepatology*. June 1998. 2) Kalra A and Biggins SW. New paradigms for organ allocation and distribution in liver transplantation. Gastroenterology volume 34, 2018

Modified BCLC Treatment Algorithm:
Intermediate/Advanced Stage Disease

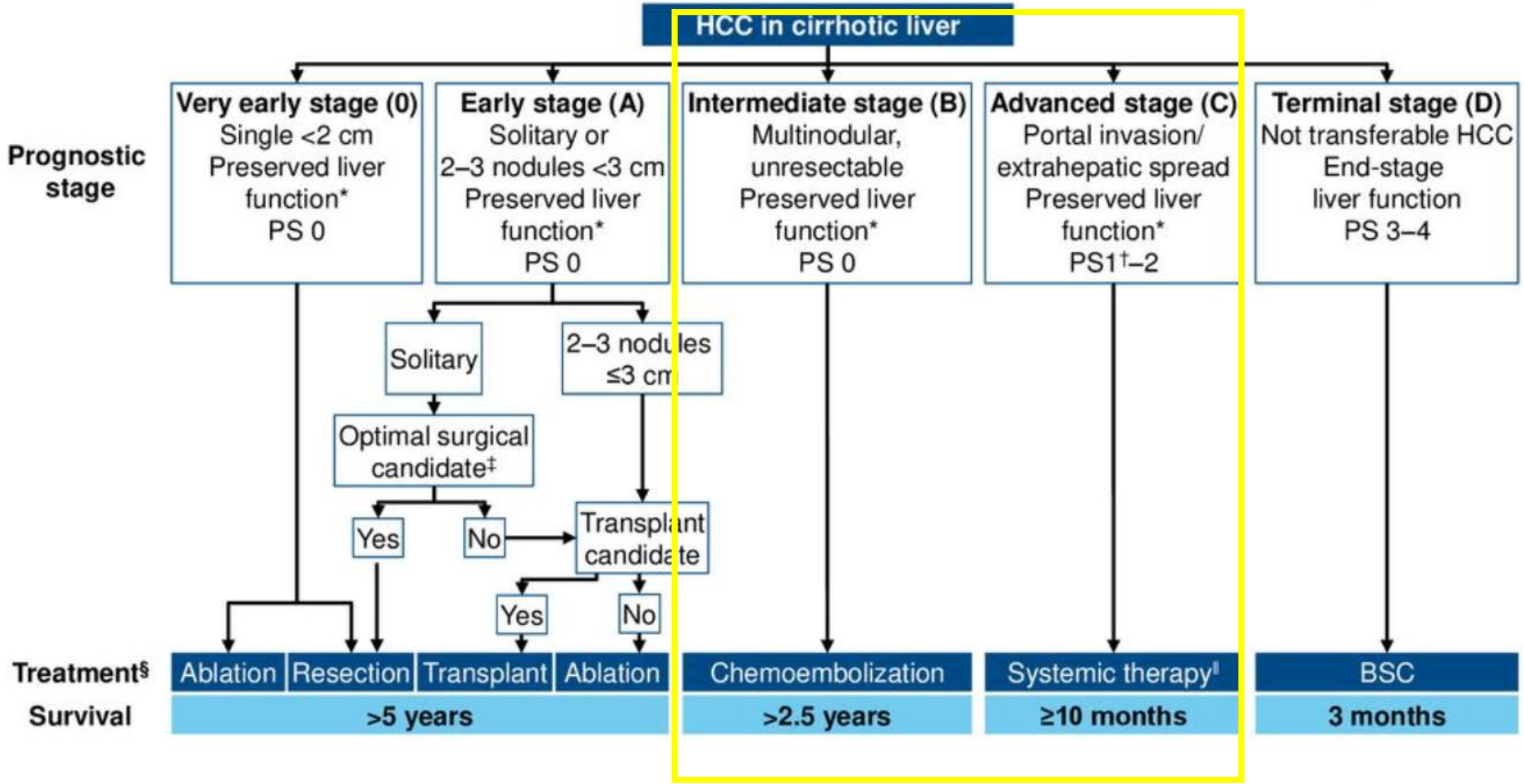


Figure: EASL CPG HCC. J Hepatol 2018

Intermediate/Advanced Hepatocellular Carcinoma: Standard Approaches

Liver-confined disease (tumors > 5cm, multifocal):

- Transarterial embolization (TAE/bland embolization) and chemoembolization (TACE)
- Radioembolization with Y^{90} beads (TARE, SIRT)
- External Beam Radiation (SBRT)
- Can be used as ‘bridge’ therapy while awaiting transplant

Metastatic disease or vascular invasion (BCLC C)

- Systemic therapy (boards answer); Y90 a consideration in less extensive portal venous invasion

Hepatocellular Carcinoma: Updated Algorithms

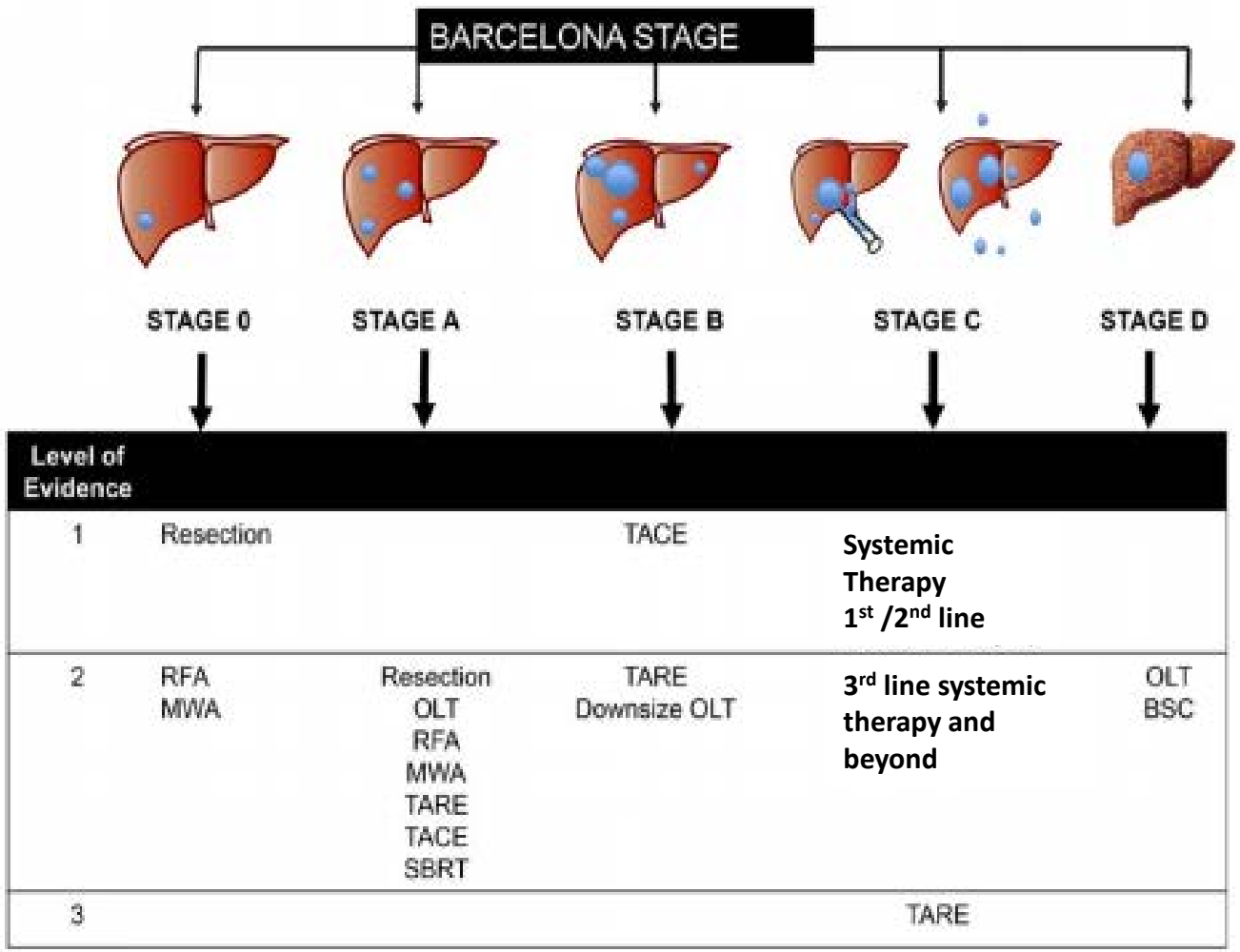


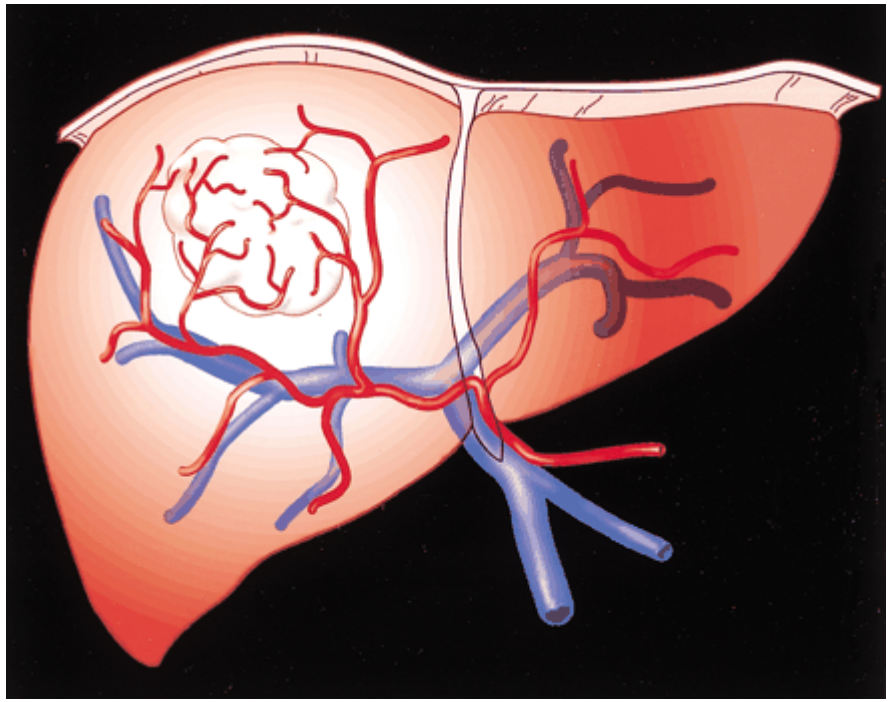
FIG. 3. Treatment recommendations according to BCLC Stage. Abbreviations: MWA, microwave ablation; BSC, best supportive care; 1L, first-line therapy; 2L, second-line therapy.

Modified from Marrero et al. Hepatology 68(2); 2018

Hepatocellular Carcinoma – Blood Supply to Tumor

Hepatocellular carcinomas derive 95% of their blood supply from branches of the hepatic artery.

Normal liver parenchyma: derives 75% of its blood supply from the portal vein

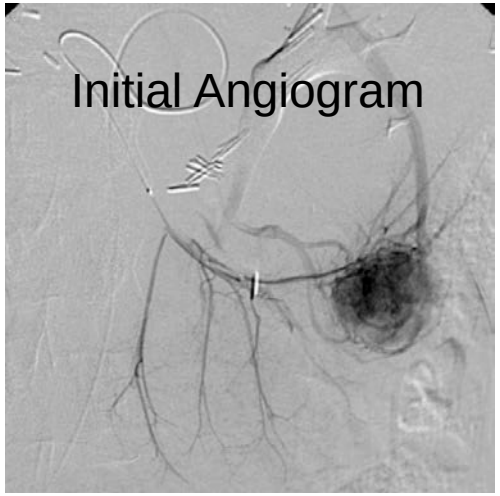


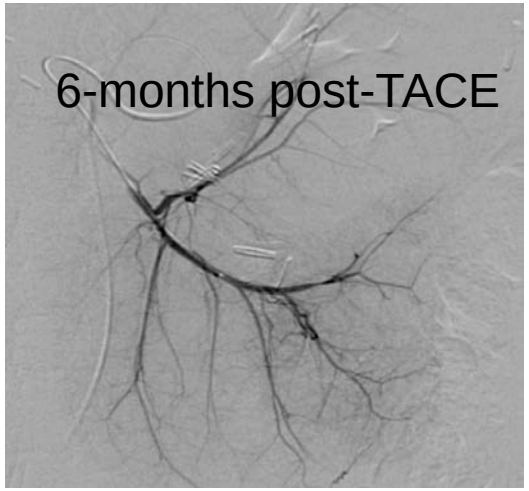
Intermediate/Advanced HCC: Transarterial Embolization

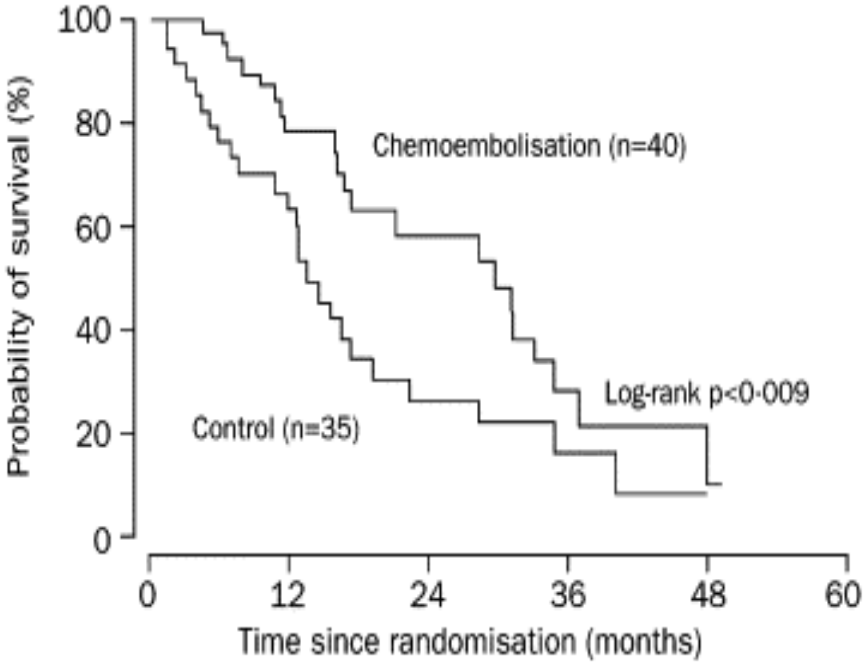
Two components of therapy:

1) Acute arterial obstruction

2) Local administration of chemotherapeutic agents







Llovet et al. Lancet 2002 359(9319)

TACE vs. Best Supportive Care – Asian vs. Western Population

	Lo et al *Hepatology* 2002		**Llovet et al *Lancet* 2002**	
Etiology	80% Hepatitis B		87% Hepatitis C	
Tumor characteristics	60% multinodular, mean tumor size 7cm		71% multinodular, mean tumor size 5cm	
Treatment (TACE)	Cisplatin (chemo) Gelatin sponge (embolic)		Doxorubicin (chemo) Gelatin sponge (embolic)	
Survival	TACE	BSC	TACE	BSC
1 year	57%	32%	82%	63%
2 year	**31%**	**11%**	**63%**	**27%**
3 year	26%	3%	29%	17%
HR for death TACE vs. BSC	**HR 0.49** (95% CI 0.28-0.81), p=0.006		**HR 0.45** (95% CI 0.25-0.81), p=0.02	

Lo C, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. May, 2002.

Llovett JM, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. May, 2002

TACE/TAE: Adverse Events

Expected toxicities:

- Post-embolization syndrome: Fatigue, nausea, pain, liver enzyme elevation, low grade fever
- Chemotherapy side effects: pancytopenia, alopecia, nausea

Contraindications:

- Bilirubin >3 mg/dL
- Main portal vein thrombosis – hepatic ischemia
- Child-Pugh C cirrhosis

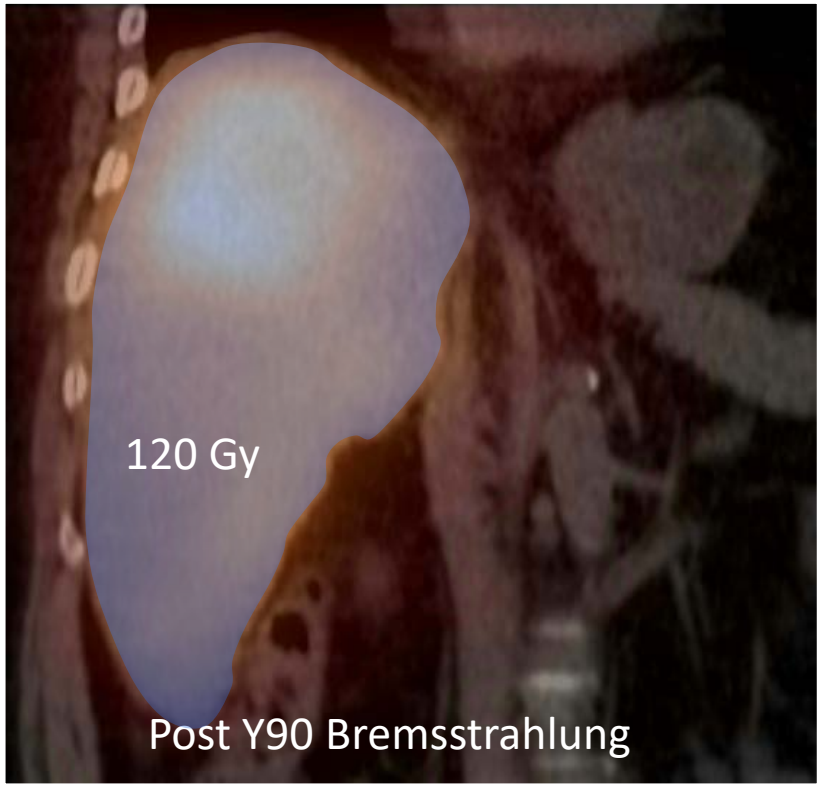
TACE/TAE – Conclusions and Questions

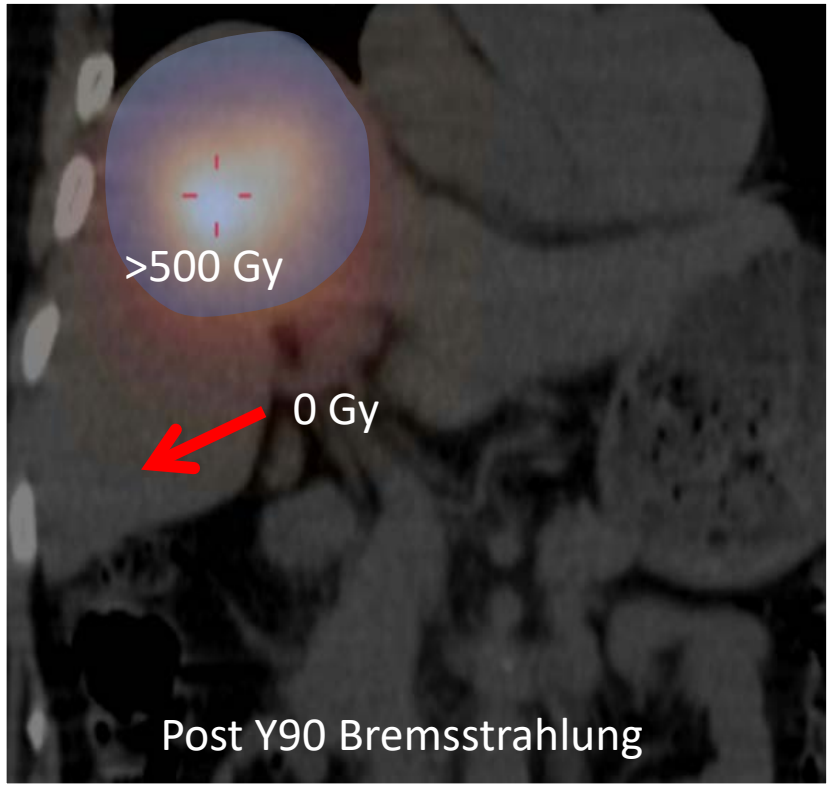
- Large systematic reviews / meta-analyses have demonstrated a benefit from TACE
  - Large contemporary series show median OS of 2.5-3.0 years with catheter-based therapy

(Bruix J et al. Chemoembolization for hepatocellular carcinoma. *Gastroenterology*. November, 2004).

- No definitive advantage of TACE over bland embolization.
- Is TACE/TAE superior to systemic therapy in BCLC B patients?
- How often should TACE/TAE be performed?
- When to move on to systemic therapy?

Y90 Radioembolization: Evolving Segmental Approaches for HCC

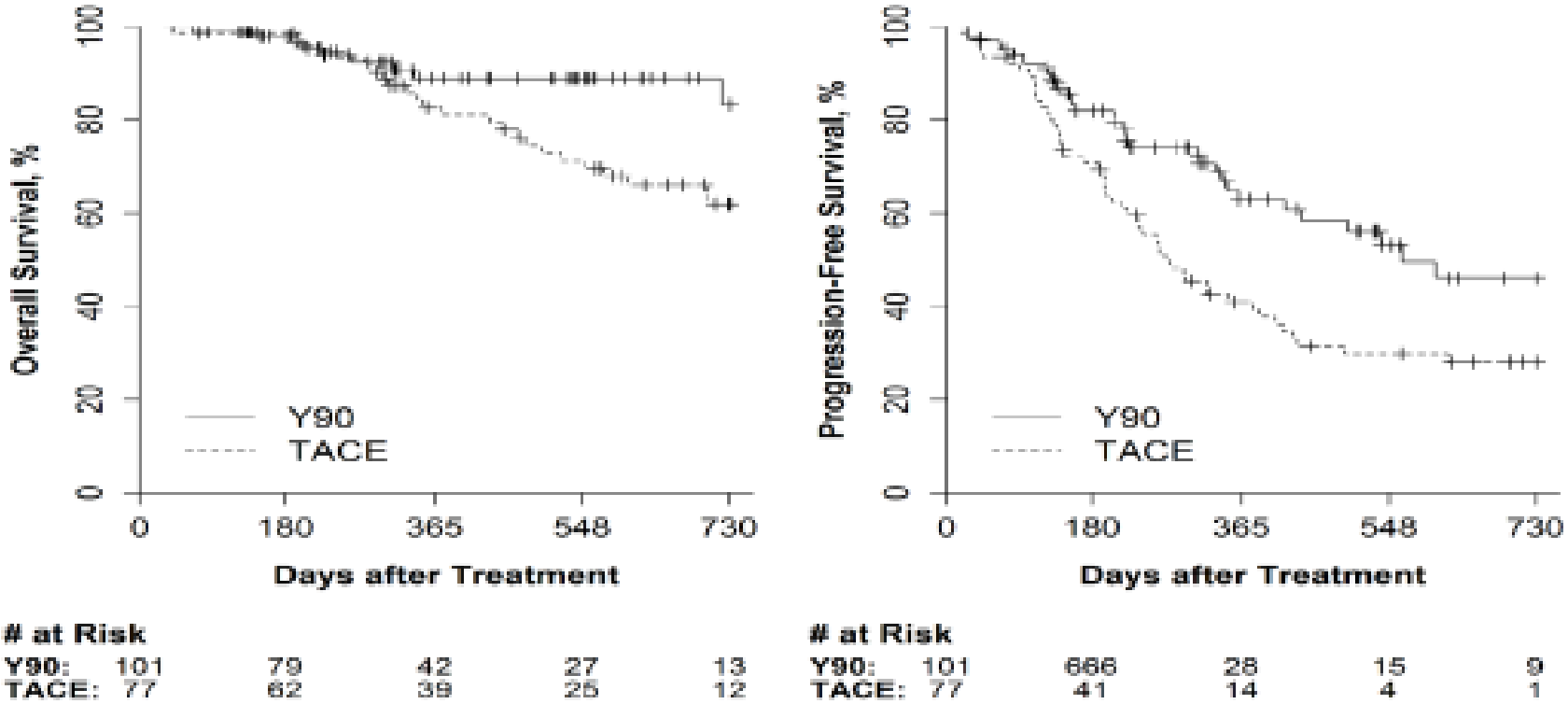




Improved targeting
Higher intra-tumoral radiation doses → Improved response?
Decreased collateral damage

High dose localized radioembolization: (radiation segmentectomy)

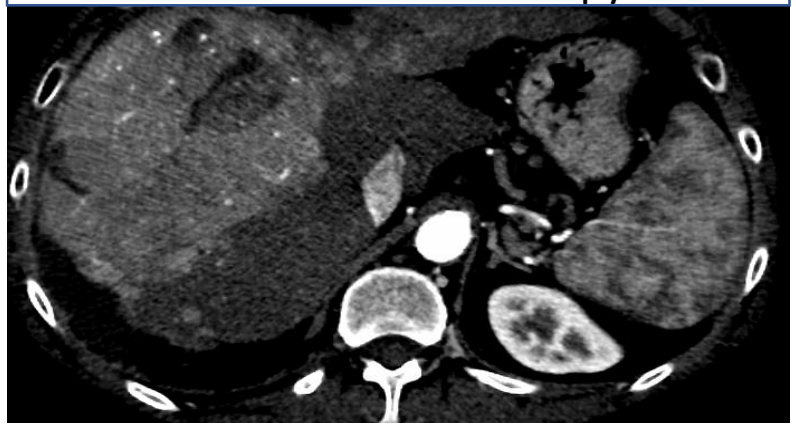
Figure 2. Kaplan-Meier curves of overall survival and progression-free survival.

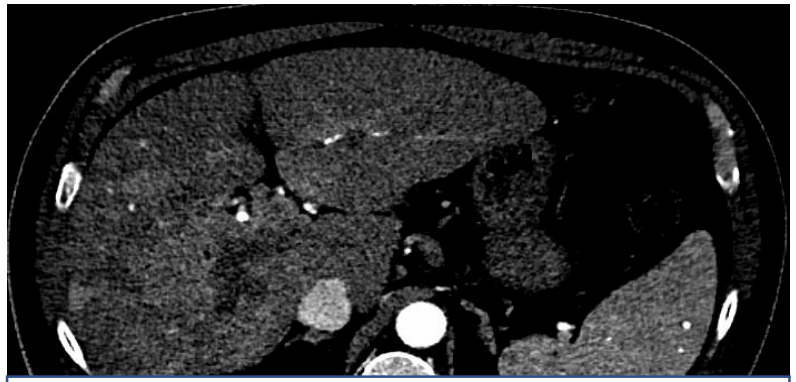


Padia et al. ASCO 2016 Poster, JCO 34, (suppl. Abstract 4084)

Background:
Systemic Therapy for Advanced Hepatocellular Carcinoma

BCLC B (ineligible/refractory to catheter-based therapy





BCLC C (Vascular Invasion/Metastatic Disease)

FDA APPROVED AGENTS

1st Line	2nd Line	3rd Line
Sorafenib SHARP/ASIA PACIFIC	Cabozantinib CELESTIAL TRIAL	Cabozantinib CELESTIAL TRIAL
Lenvatinib REFLECT TRIAL	Regorafenib (sorafenib tolerant) RESOURCE	
Atezolizumab + Bevacizumab IMBRAVE150 TRIAL	Ramucirumab (AFP>400) REACH-2	
	Nivolumab* CHECKMATE 040	
	Pembrolizumab* KEYNOTE 224	
	Nivolumab + Ipilimumab CHECKMATE 040	

*Accelerated Approval based upon ORR and DOR

Advanced/Metastatic Hepatocellular Carcinoma: SHARP Trial

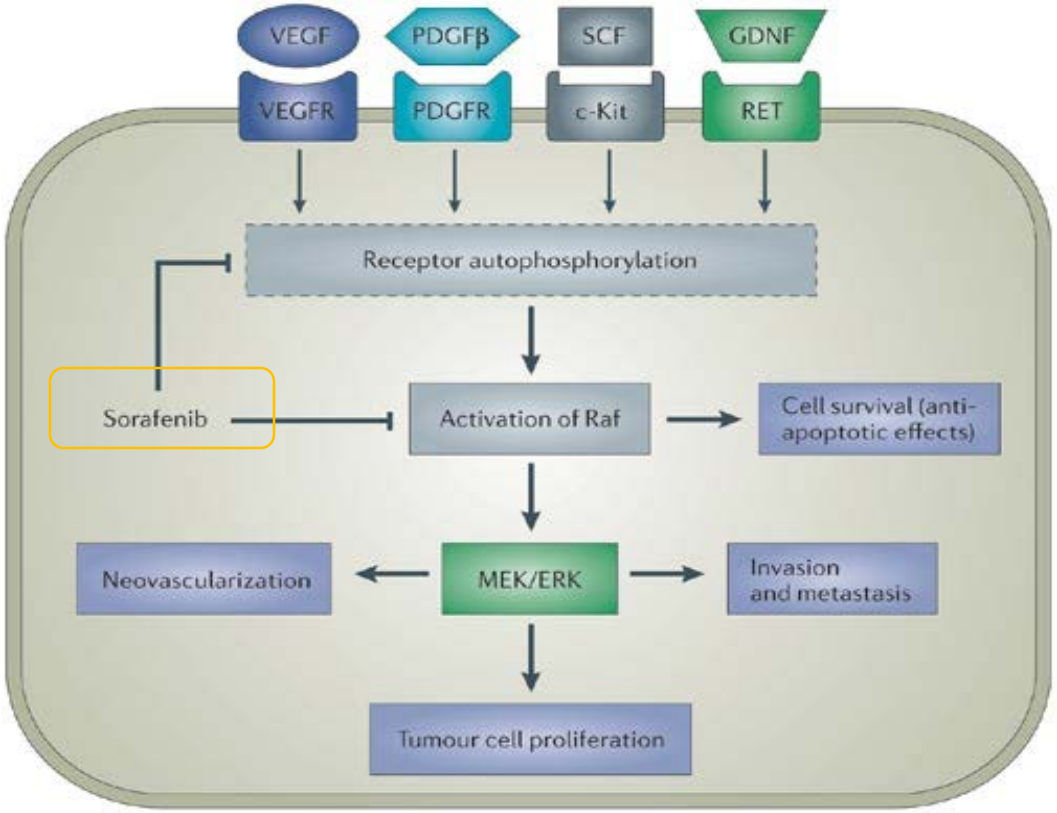
ORIGINAL ARTICLE

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*

Sorafenib approved by the FDA for advanced HCC in November 2007

Advanced/Metastatic HCC: Sorafenib



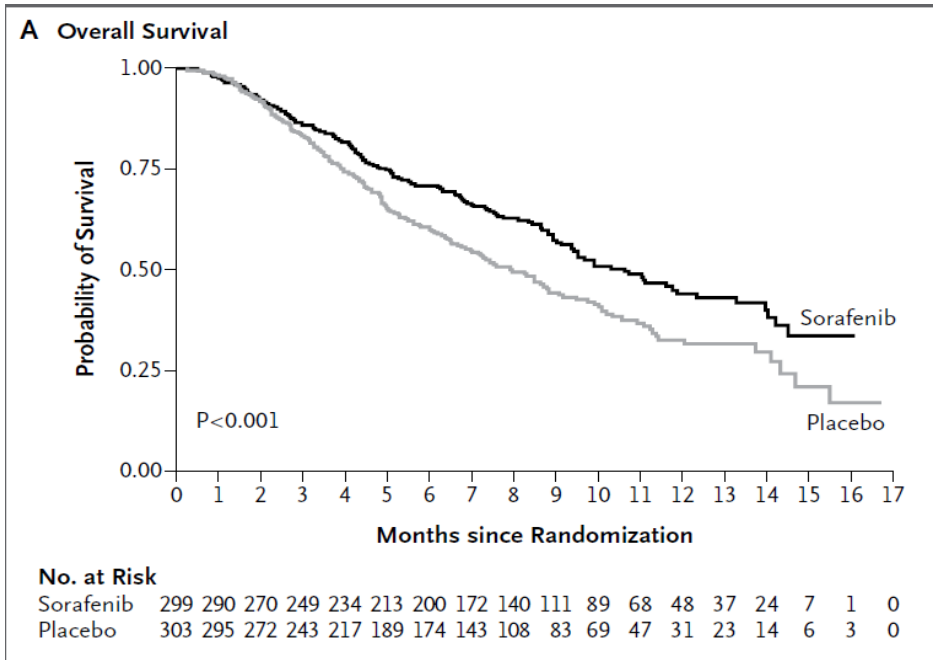
Wilhelm et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nature Reviews Drug Discovery*. October, 2006.

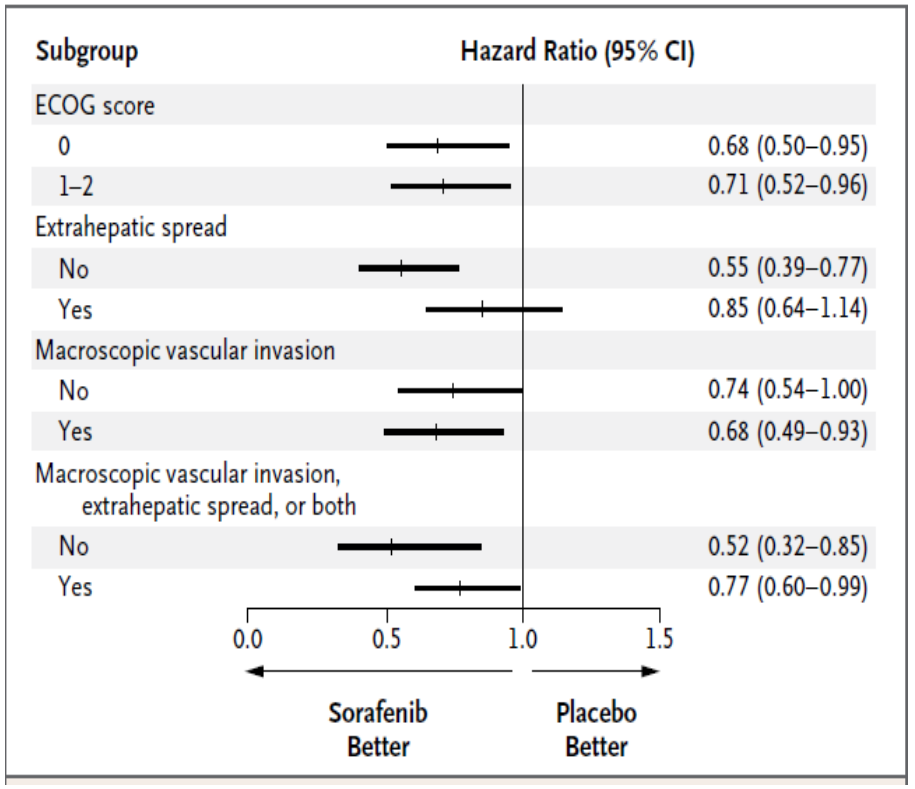
SHARP: Patient Characteristics

	Sorafenib (n=299)	Placebo (n=303)
Age	65	66
Male/Female	87/13	87/13
Region (Europe/N. America/Other %	88/9/3	87/10/3
Etiology (HCV/HBV)	29/19	27/18
(Alcohol/Other)	26/26	26/29
Child Pugh (A/B %)	95/5	98/2
Prior Therapies:		
Surgical resection	19%	21%
Loco-regional therapies	39%	41%
ECOG PS:		
O	54%	54%
1	38%	39%
2	8%	7%
Vascular Invasion/Extrahepatic spread		
Present	70%	70%
Absent	30%	30%

Llovet ASCO 2007

SHARP Trial: Results



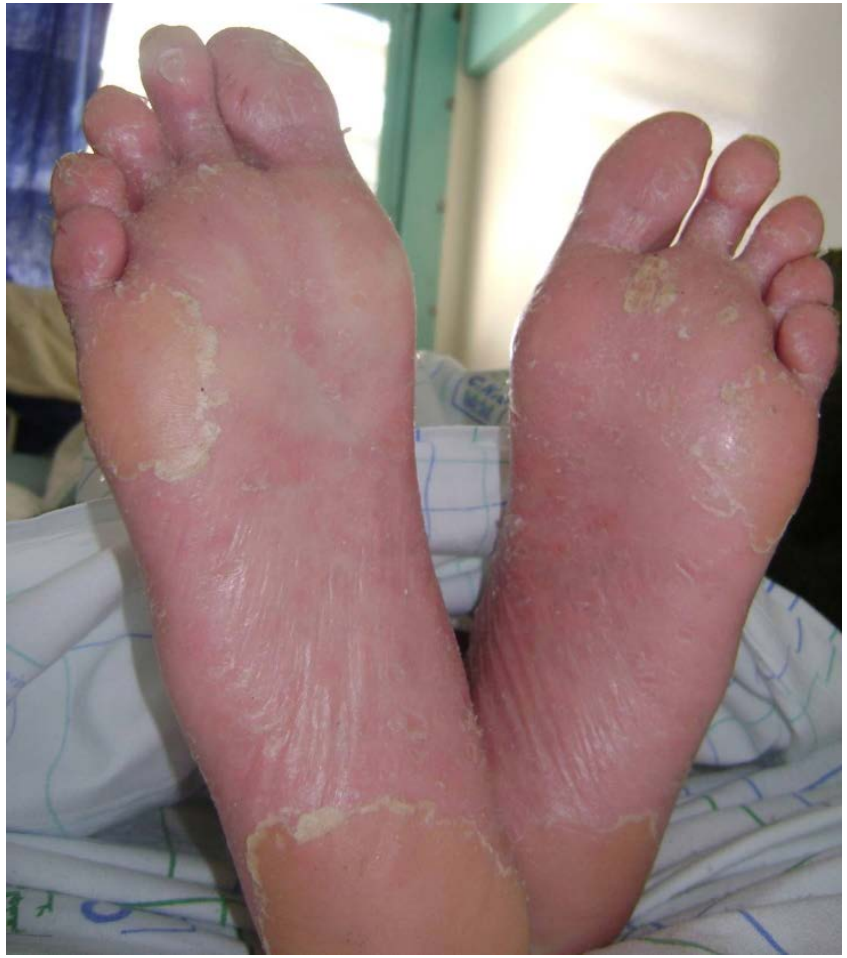


Median survival: 10.7 vs. 7.9 months
(HR 0.69 (95% CI 0.55, 0.87) p<0.001

Disease control rate: 43% vs. 32%
(p=0.002) – largely stable disease

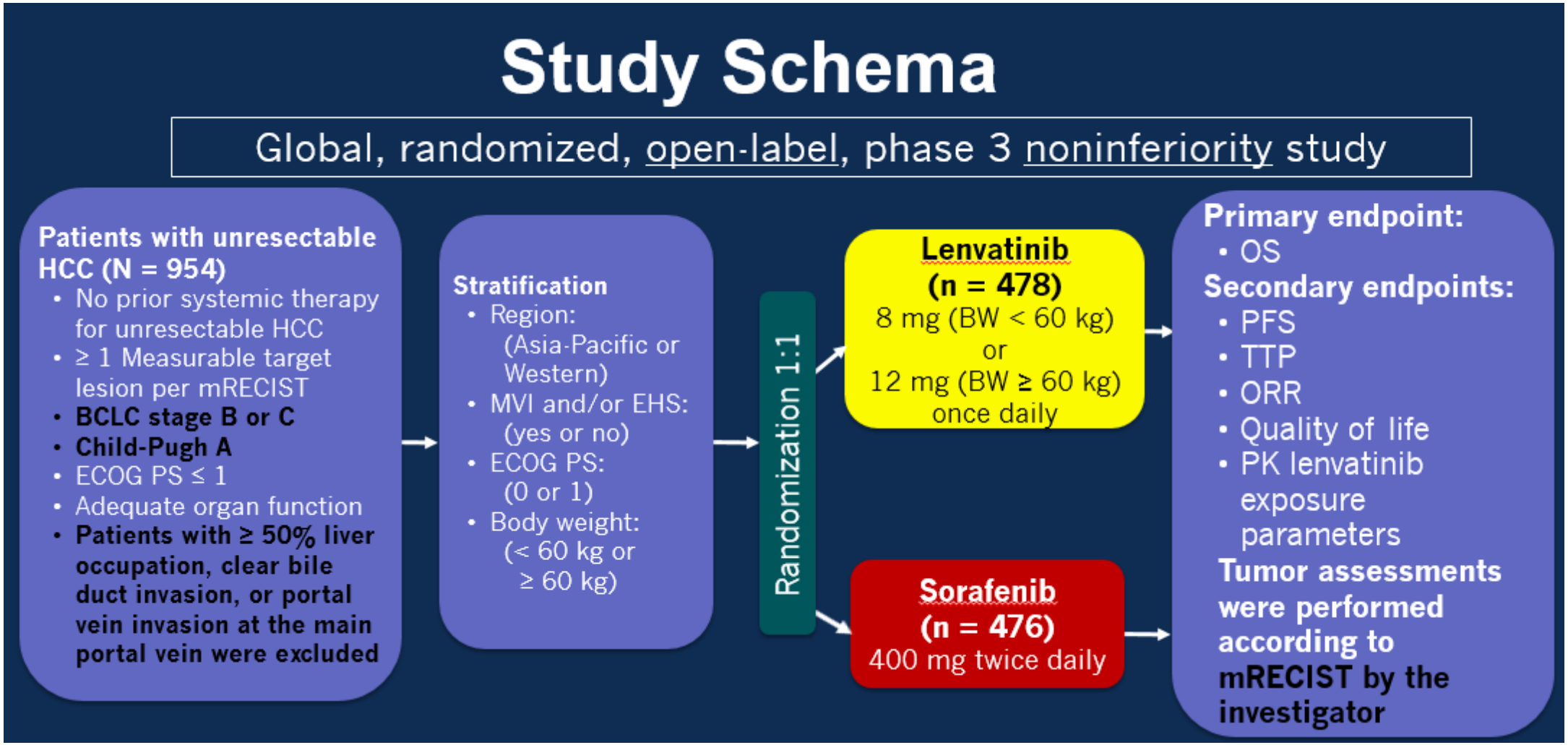
SHARP Trial: Safety

- Overall incidence of any grade adverse event: 80% (sorafenib) vs. 52% (placebo)
- Grade 3-4 toxicities: Hand-foot syndrome, diarrhea.
- Of note, prophylactic urea-based lotions decrease severity of hand-foot syndrome



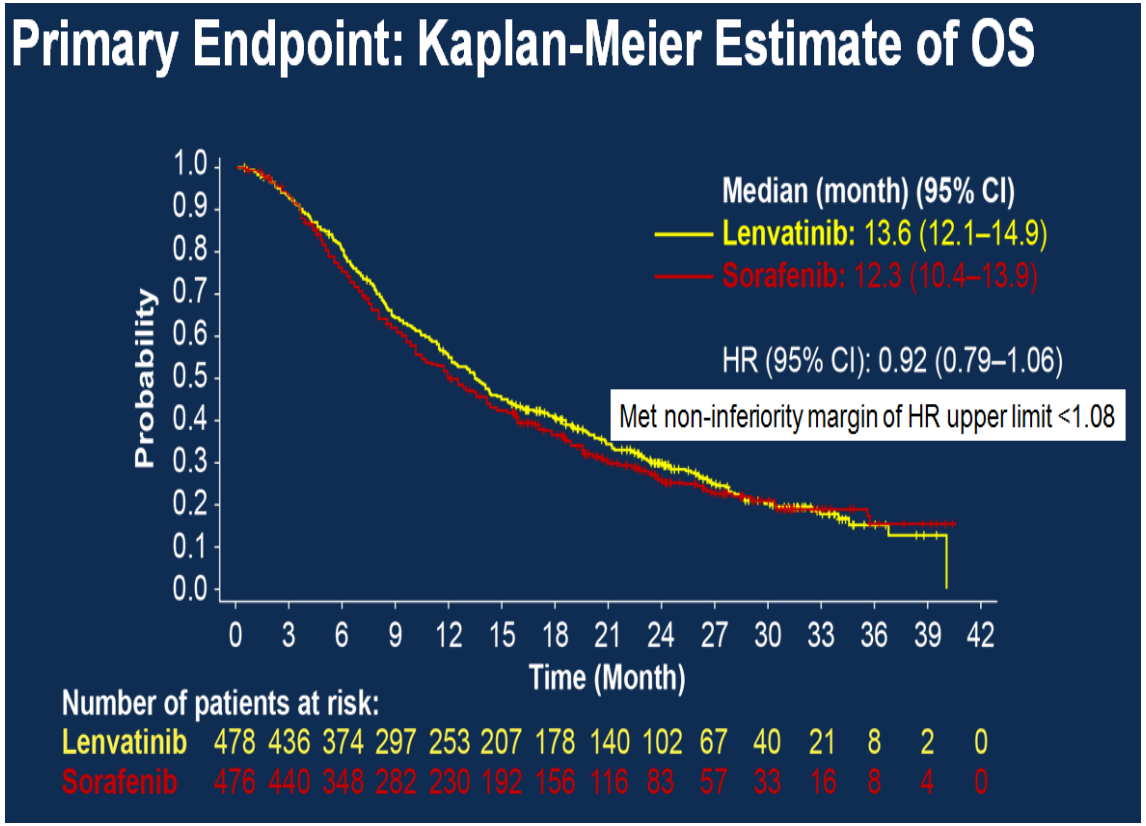
Benomar, et al. *Dermatology online journal*. Nov 2008

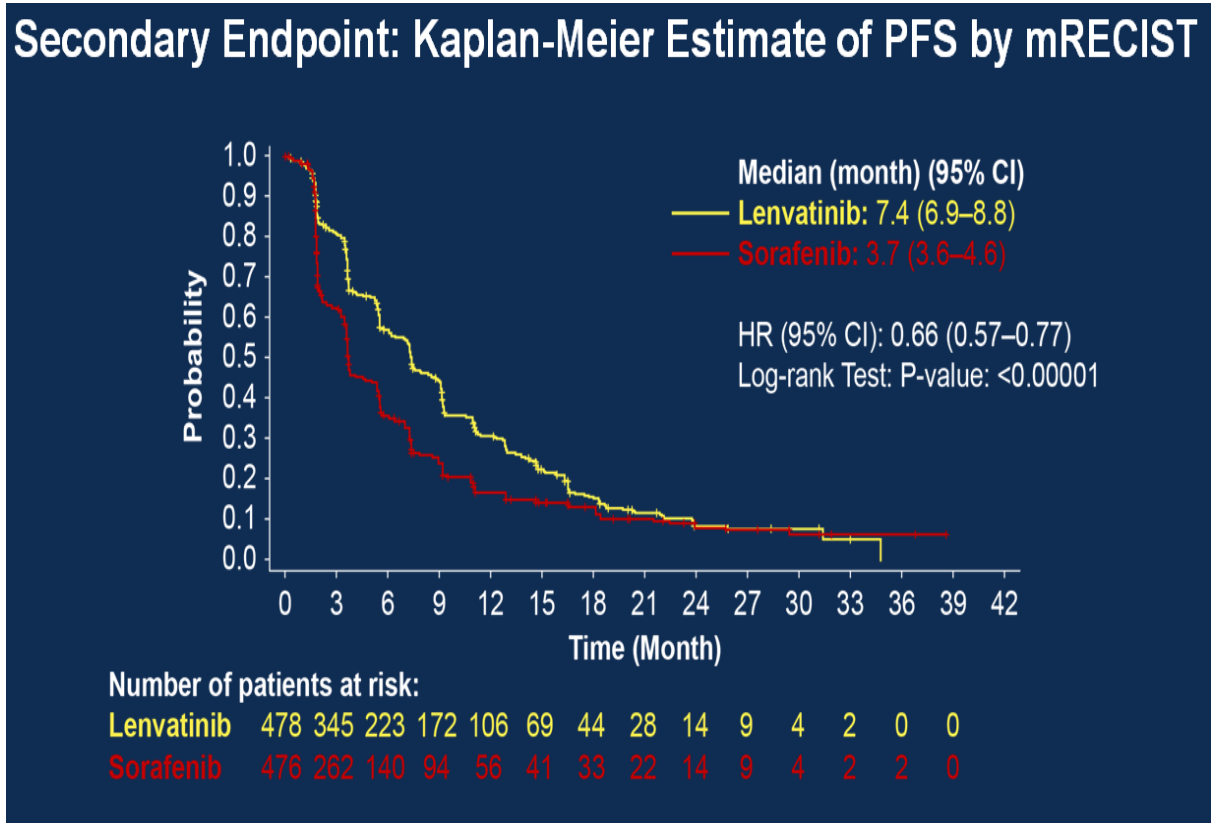
Lenvatinib: First-Line HCC Trial



Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial [published online February 9, 2018]. *Lancet.* doi:10.1016/S0140-6736(18)30207-1.

Lenvatinib First-Line HCC Trial





Lenvatinib non-inferior to sorafenib as 1st line therapy

- Multi-TKI: anti VEGF, FGFR, PDGFRα, RET, KIT
- FDA approved August 2018 for Child-Pugh A patients
- ORR: 24% vs 9% by mRECIST

Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial [published online February 9, 2018]. *Lancet.*

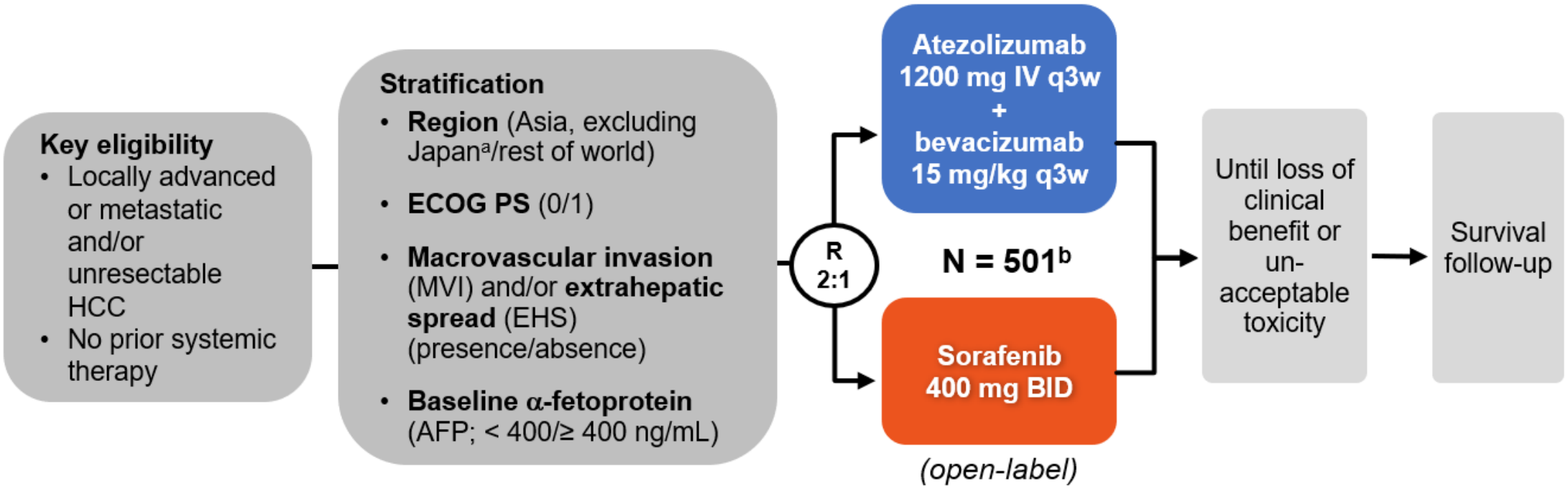
Lenvatinib: First-Line HCC Trial

Adverse event, n (%)	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hypertension	201 (42)	111 (23)	144 (30)	68 (14)
Diarrhea	184 (39)	20 (4)	220 (46)	20 (4)
Decreased appetite	162 (34)	22 (5)	127 (27)	6 (1)
Decreased weight	147 (31)	36 (8)	106 (22)	14 (3)
Fatigue	141 (30)	18 (4)	119 (25)	17 (4)
Palmar-plantar erythrodysesthesia	128 (27)	14 (3)	249 (52)	54 (11)
Proteinuria	117 (25)	27 (6)	54 (11)	8 (2)
Dysphonia	113 (24)	1 (0)	57 (12)	0 (0)
Nausea	93 (20)	4 (1)	68 (14)	4 (1)
Decreased platelet count	87 (18)	26 (6)	58 (12)	16 (3)
Abdominal pain	81 (17)	8 (2)	87 (18)	13 (3)
Hypothyroidism	78 (16)	0 (0)	8 (2)	0 (0)
Vomiting	77 (16)	6 (1)	36 (8)	5 (1)
Constipation	76 (16)	3 (1)	52 (11)	0 (0)
Elevated aspartate aminotransferase	65 (14)	24 (5)	80 (17)	38 (8)
Rash	46 (10)	0 (0)	76 (16)	2 (0)
Alopecia	14 (3)	0 (N/A)	119 (25)	0 (N/A)

Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial [published online February 9, 2018]. *Lancet.* doi:10.1016/S0140-6736(18)30207-1.

Practice Changing Trial: IMBRAVE 150 Trial

Atezolizumab + Bevacizumab for 1st Line HCC



Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

Slide modified from Cheng, AL et al. ESMO ASIA 2019 Oral Presentation

Key Inclusion/Exclusion Criteria

Notable Inclusion Criteria

- Child Pugh A hepatic function
- Advanced HCC (not a candidate for surgery or transplant)
- ECOG 0-1
- Extensive portal vein and hepatic venous invasion allowed
- AST/ALT < 5x ULN
- Platelet count >75,000

Notable Exclusion Criteria

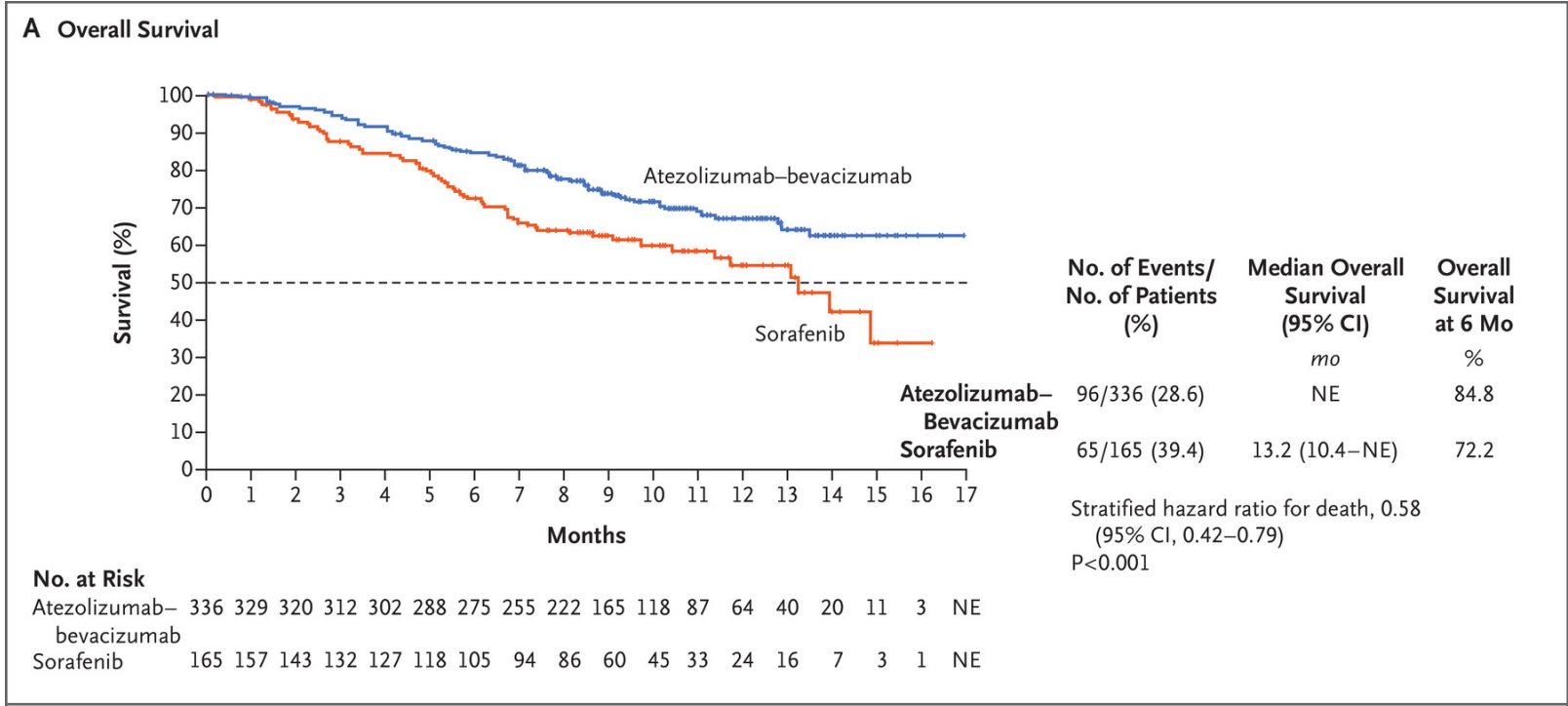
- Untreated/incompletely treated esophageal/gastric varices
- History of autoimmune disease
- Hepatitis B/C co-infection
- Anticoagulation or antiplatelet therapy (ASA 81 mg allowed)
- Uncontrolled hypertension (>150/100)

IMBRAVE 150 RESULTS

Comments:

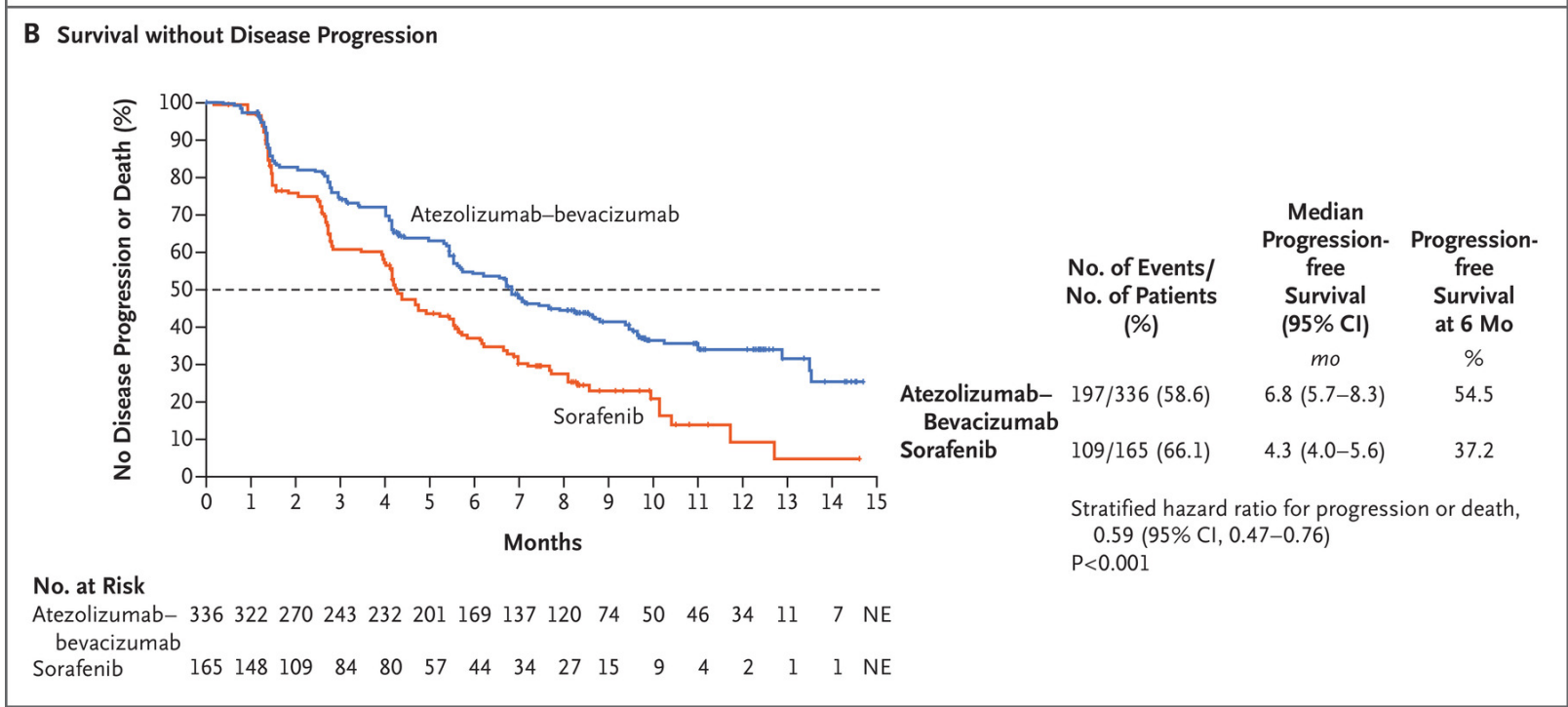
- Trial stopped at first interim analysis due to clear efficacy
- Met both co-primary endpoints
  - **OS HR 0.58 p<.001**
  - **PFS HR .59 p<.001**
- mOS not yet reached, longer follow-up needed
- ORR 27.3% vs 11.9%
- Favorable mPFS of 6.8 months

Finn et al. NEJM 2020 382:1894-1905



	No. of Events/ No. of Patients (%)	Median Overall Survival (95% CI)	Overall Survival at 6 Mo
		mo	%
Atezolizumab–Bevacizumab	96/336 (28.6)	NE	84.8
Sorafenib	65/165 (39.4)	13.2 (10.4–NE)	72.2

Stratified hazard ratio for death, 0.58 (95% CI, 0.42–0.79)
P<0.001

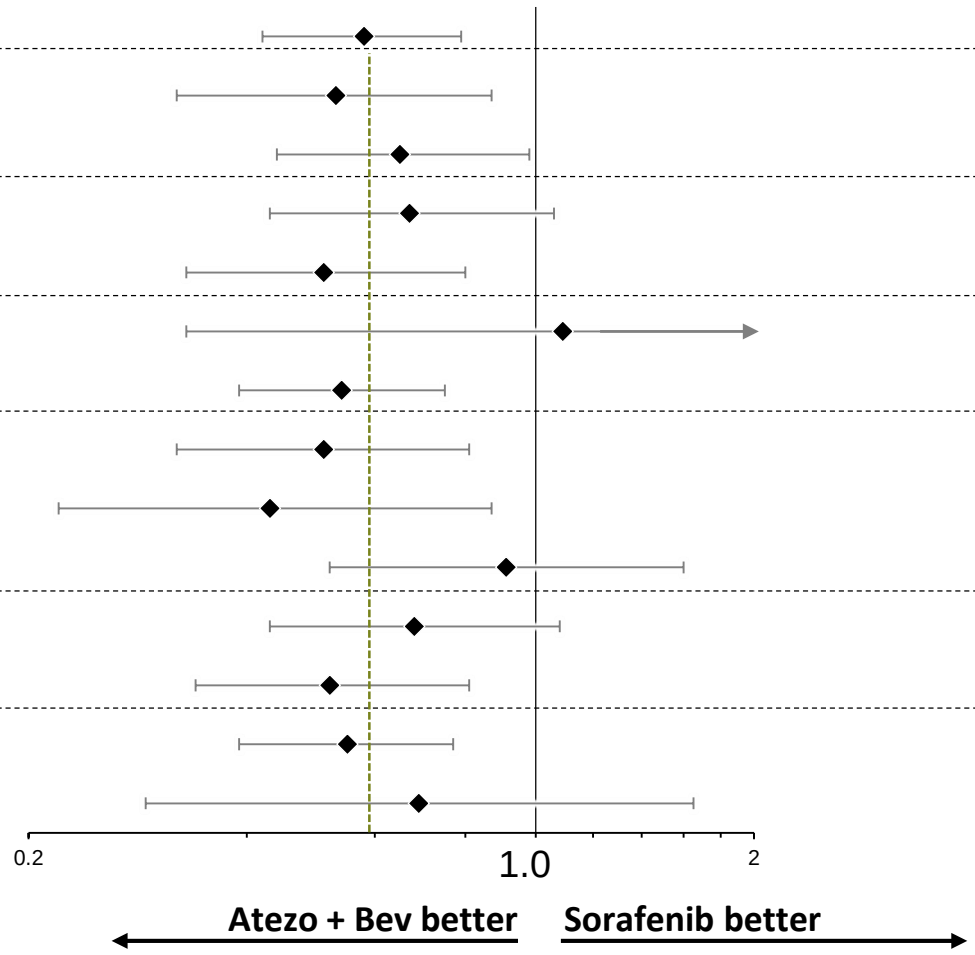


	No. of Events/ No. of Patients (%)	Median Progression-free Survival (95% CI)	Progression-free Survival at 6 Mo
		mo	%
Atezolizumab–Bevacizumab	197/336 (58.6)	6.8 (5.7–8.3)	54.5
Sorafenib	109/165 (66.1)	4.3 (4.0–5.6)	37.2

Stratified hazard ratio for progression or death, 0.59 (95% CI, 0.47–0.76)
P<0.001

OS subgroups

Characteristic (n)	Atezo + Bev mOS, mo (n = 336)	Sorafenib mOS, mo (n = 165)	HR (95% CI)[a]
All patients (501)	NE	13.2	0.58 (0.42, 0.79)
Asia (excluding Japan[b]) (201)	NE	13.1	0.53 (0.32, 0.87)
Rest of world (300)	NE	13.2	0.65 (0.44, 0.98)
ECOG PS 0 (312)	NE	13.9	0.67 (0.43, 1.06)
ECOG PS 1 (189)	NE	7.4	0.51 (0.33, 0.80)
BCLC stage B[c] (78)	NE	14.9	1.09 (0.33, 3.53)
BCLC stage C[c] (409)	NE	11.4	0.54 (0.39, 0.75)
HBV HCC (240)	NE	13.9	0.51 (0.32, 0.81)
HCV HCC (108)	NE	13.1	0.43 (0.22, 0.87)
Non-viral HCC (153)	NE	14.9	0.91 (0.52, 1.60)
AFP ≥ 400 ng/mL (187)	12.8	9.1	0.68 (0.43, 1.08)
AFP < 400 ng/mL (314)	NE	13.9	0.52 (0.34, 0.81)
EHS and/or MVI (378)	NE	10.4	0.55 (0.39, 0.77)
No EHS and MVI (123)	NE	14.9	0.69 (0.29, 1.65)



NE, not estimable.
[a] Unstratified HR shown for all characteristics except for "All patients," where stratified HR is shown. [b] Japan is included in rest of world.
[c] BCLC stage A not shown, as there were only 14 patients; thus, estimation is not meaningful.
Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Slide derived from Cheng, AL et al. ESMO ASIA 2019 Oral Presentation

IMBRAVE 150 - AEs

Comments:

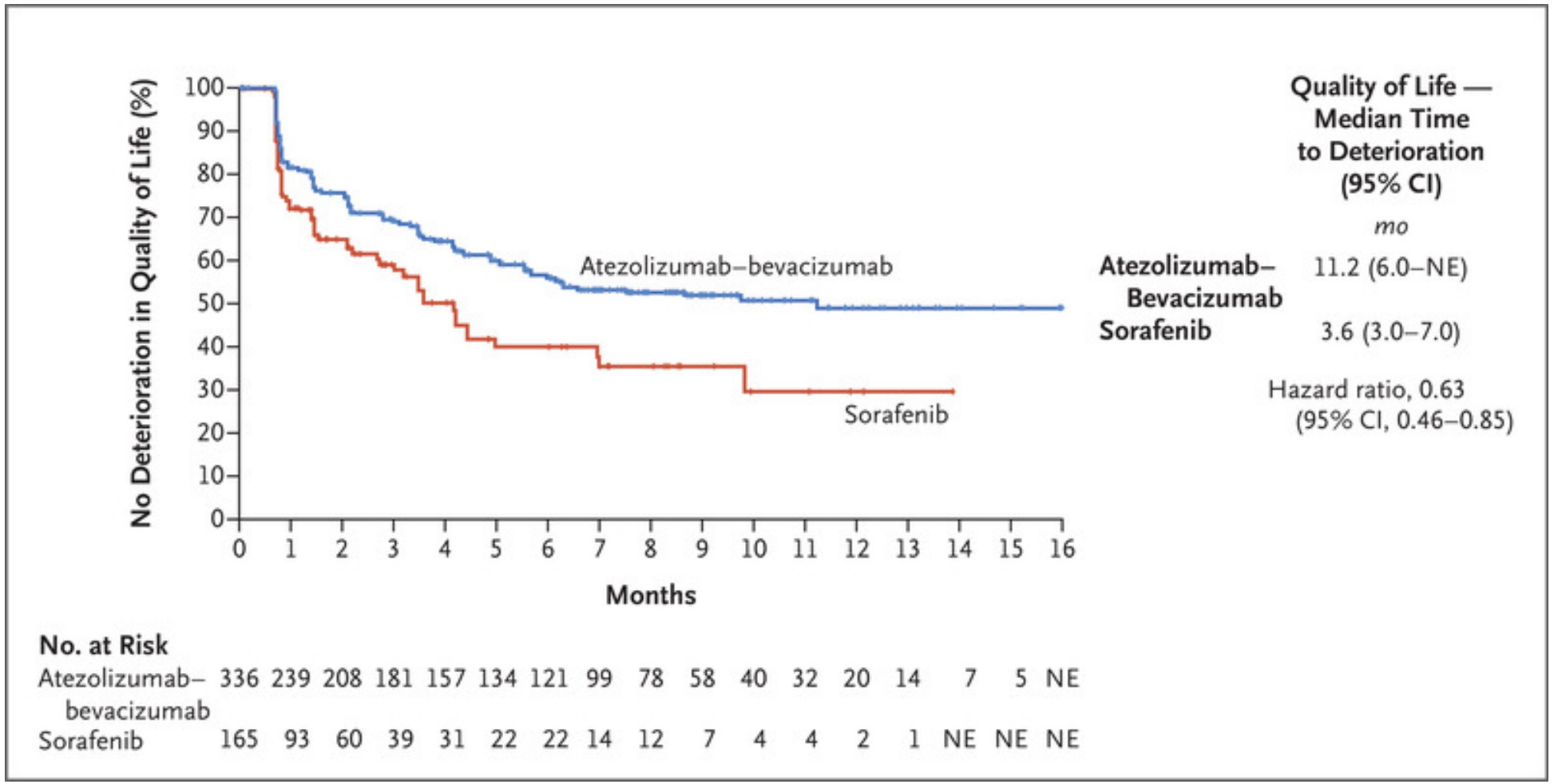
- Serious Adverse Events increased in Atezo/Bev arm slightly (38% vs. 30.8%)
    - No one clear toxicity stands out
    - Less PPE, severe diarrhea, asthenia noted
- Gastrointestinal (usually variceal) bleeding rates consistent with known risk
    - 7% vs 4.5% overall
    - Fatal bleeding/Perforation Atezo/Bev (n=6) vs sorafenib (n=1)

Finn et al. NEJM 2020 382:1894-1905

Table 4. Adverse Events with an Incidence of More Than 10% in Either Group.

Event	Atezolizumab–Bevacizumab (N=329)		Sorafenib (N=156)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number (percent)			
Hypertension	98 (29.8)	50 (15.2)	38 (24.4)	19 (12.2)
Fatigue	67 (20.4)	8 (2.4)	29 (18.6)	5 (3.2)
Proteinuria	66 (20.1)	10 (3.0)	11 (7.1)	1 (0.6)
Aspartate aminotransferase increase	64 (19.5)	23 (7.0)	26 (16.7)	8 (5.1)
Pruritus	64 (19.5)	0	15 (9.6)	0
Diarrhea	62 (18.8)	6 (1.8)	77 (49.4)	8 (5.1)
Decreased appetite	58 (17.6)	4 (1.2)	38 (24.4)	6 (3.8)
Pyrexia	59 (17.9)	4 (1.2)	15 (9.6)	2 (1.3)
Alanine aminotransferase increase	46 (14.0)	12 (3.6)	14 (9.0)	2 (1.3)
Constipation	44 (13.4)	0	22 (14.1)	0
Blood bilirubin increase	43 (13.1)	8 (2.4)	22 (14.1)	10 (6.4)
Rash	41 (12.5)	0	27 (17.3)	4 (2.6)
Abdominal pain	40 (12.2)	4 (1.2)	27 (17.3)	4 (2.6)
Nausea	40 (12.2)	1 (0.3)	25 (16.0)	1 (0.6)
Cough	39 (11.9)	0	15 (9.6)	1 (0.6)
Infusion-related reaction	37 (11.2)	8 (2.4)	0	0
Weight decrease	37 (11.2)	0	15 (9.6)	1 (0.6)
Platelet count decrease	35 (10.6)	11 (3.3)	18 (11.5)	2 (1.3)
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Asthenia	22 (6.7)	1 (0.3)	21 (13.5)	4 (2.6)
Alopecia	4 (1.2)	0	22 (14.1)	0
Palmar–plantar erythrodysesthesia syndrome	3 (0.9)	0	75 (48.1)	13 (8.3)

IMBRAVE 150 – Quality of Life Assessments



Finn et al. NEJM 2020 382:1894-1905

SUMMARY: FIRST-LINE SYSTEMIC THERAPY FOR HCC

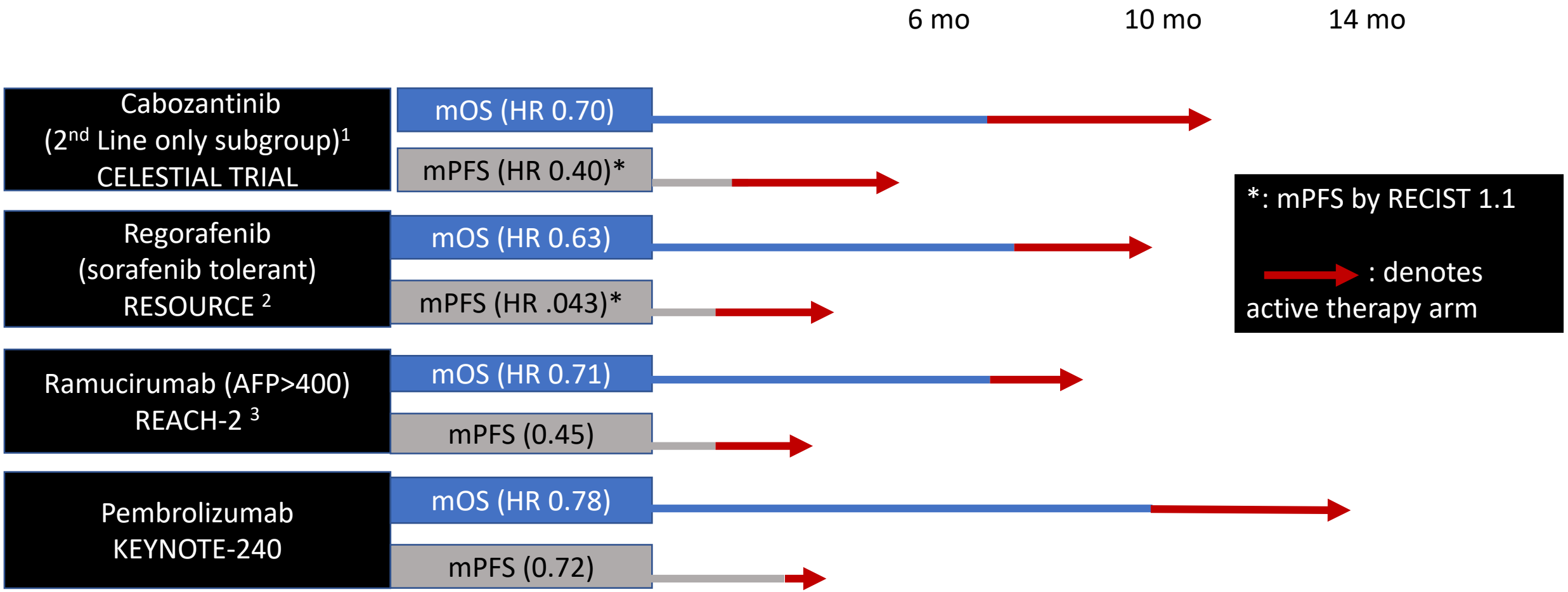
- Atezolizumab and Bevacizumab represents the favored 1st line therapy for advanced HCC for eligible patients
    - **Patients require EGD for variceal screening and treatment as indicated prior to initiation of therapy**

- In patients with advanced, unresectable HCC with Child-Pugh A cirrhosis, treatment with sorafenib resulted in a 3-month survival benefit compared to placebo.

- Lenvatinib demonstrated non-inferiority to sorafenib as 1st line therapy, with superior response rates, TTP and PFS.

- The benefit/safety of current 1st line therapy for routine use in Child-Pugh B cirrhosis is unclear.

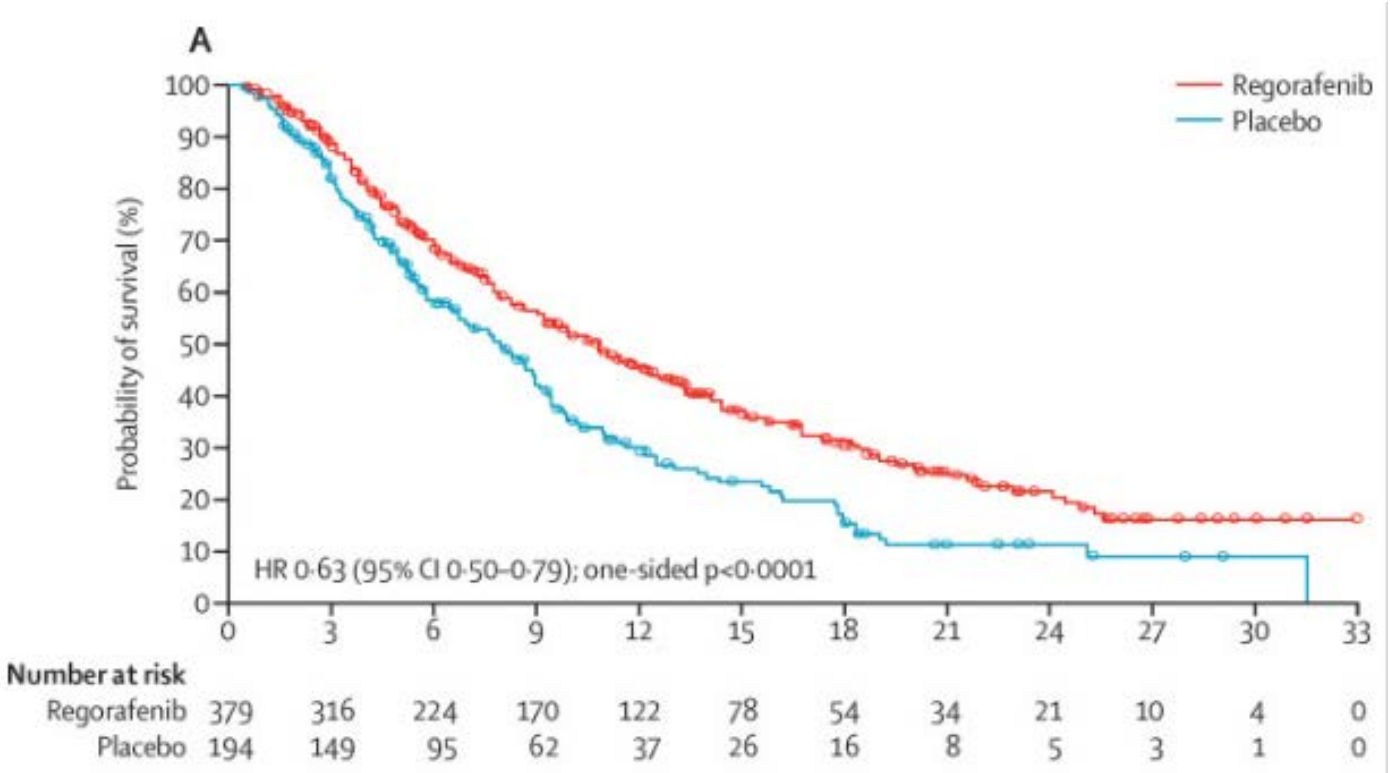
Phase III HCC Trials: Second-Line Therapy Outcomes



1. Kelley et al. ASCO 2018 Abstract 4088
2. Bruix et al. Lancet 2017 389(10064):56-66
3. Zhu et al. Lancet Oncology 2019 20(2):282-292

Regorafenib vs. Placebo (2nd line) Positive Phase III Trial Results

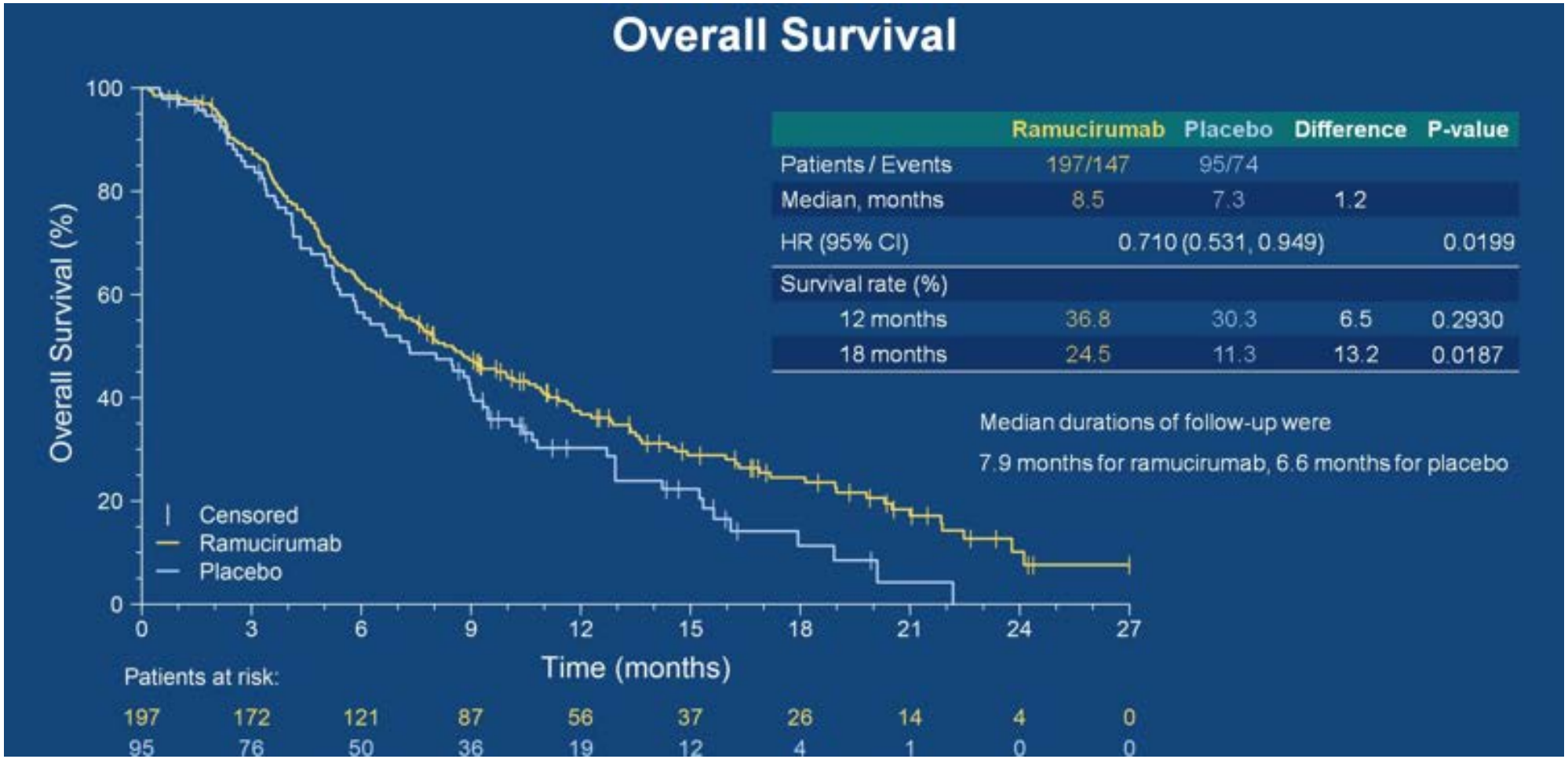
- Multi-TKI with broad activity
  - VEGFR1-3, TIE2
  - FGFR1, PDGFR-B, KIT, RET
  - C-RAF, B-RAF
- Key Patient Characteristics
  - Child Pugh A, ECOG 0-1
  - **Tolerant but progressing on sorafenib**
- Design
  - 2:1 randomized placebo-controlled trial
  - Regorafenib 160 mg days 1-21 monthly
  - Primary endpoint: improved OS
- Outcome
  - **mOS 10.6 vs 7.8 months (HR .63, p<.0001)**
  - Grade >3 Toxicity compared to placebo:
    - 10% increased HTN
    - 12% hand-foot syndrome
    - 4% fatigue
    - 3% diarrhea



FDA approved for second line HCC

Bruix J et al. Lancet Jan 2017. 389(10064):56-66

Ramucirumab as 2L therapy for HCC (in patients with AFP >400)



	Ramucirumab	Placebo	Difference	P-value
Patients / Events	197/147	95/74		
Median, months	8.5	7.3	1.2	
HR (95% CI)	0.710 (0.531, 0.949)			0.0199
Survival rate (%)				
12 months	36.8	30.3	6.5	0.2930
18 months	24.5	11.3	13.2	0.0187

FDA approved as second line therapy if AFP > 400

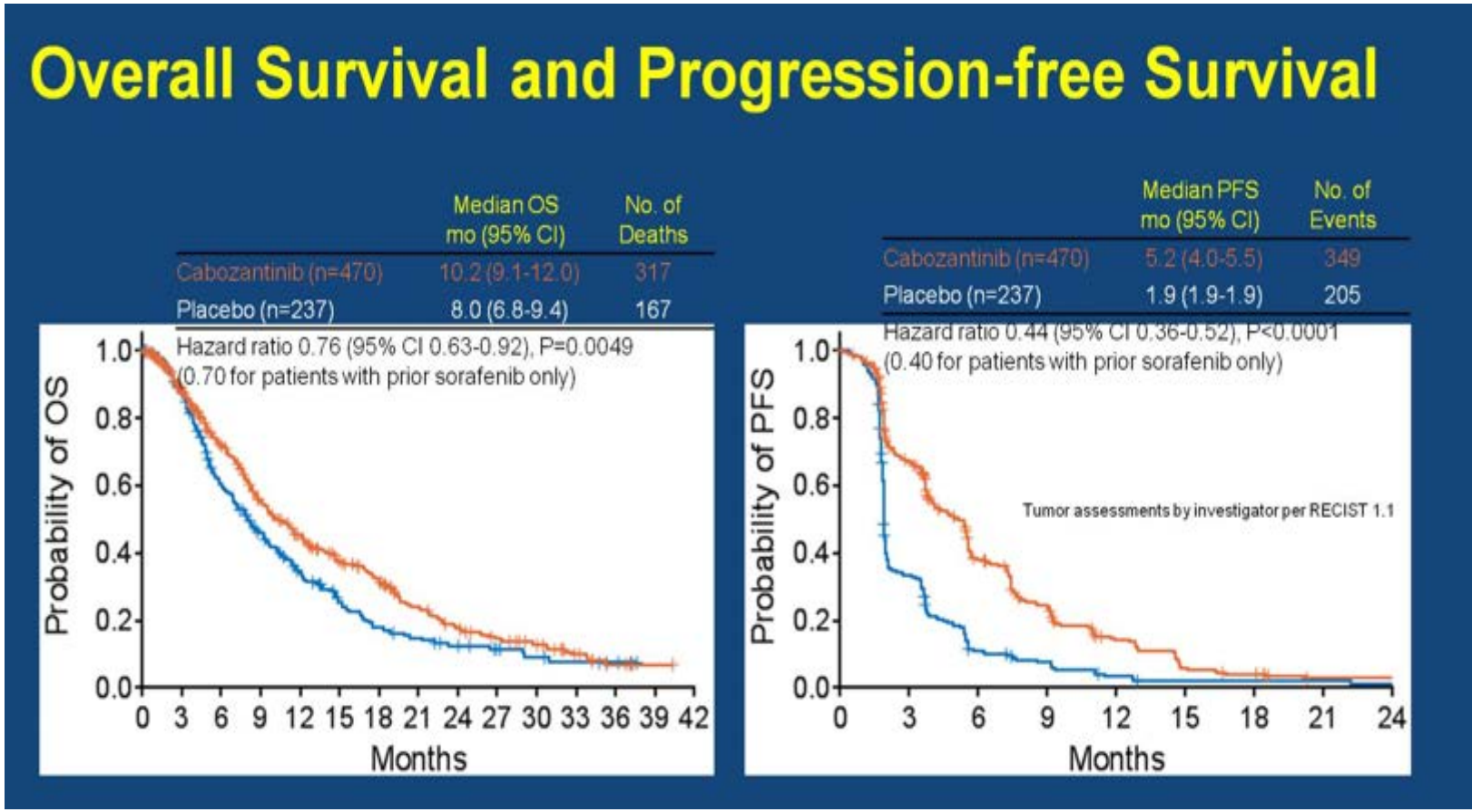
Main Grade 3-4 Toxicities: HTN (12%), Ascites (4%), encephalopathy (3%)

Zhu et al. REACH-2 Trial Oral Presentation, ASCO 2018 Annual Meeting

Cabozantinib in Refractory HCC
Positive Phase III Data in 2nd / 3rd line

Randomized Phase III trial of cabozantinib vs. placebo
→ sorafenib refractory / intolerant patients with HCC

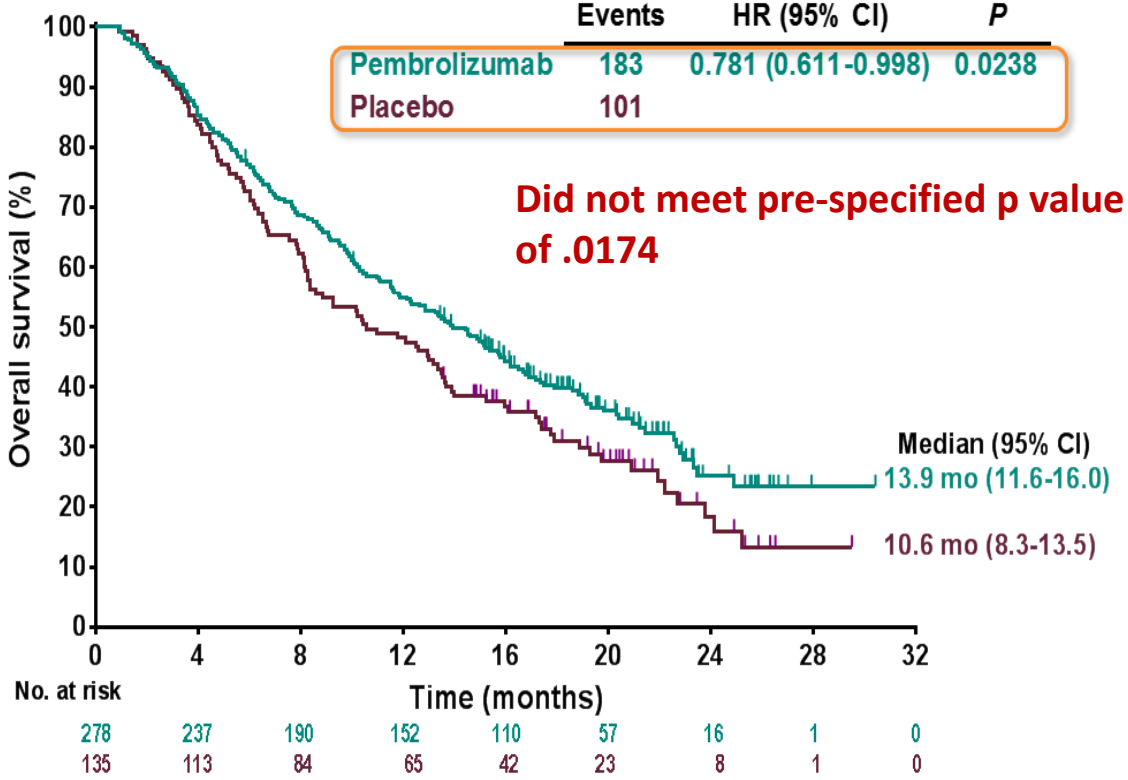
- 707 patients randomized 2:1 against placebo
- 2nd /3rd line therapy; Child-Pugh A
- mOS 10.2 vs 8.0 months (HR .76, p=.005)
- Not selected based upon c-met status
- FDA approved



Abou-Alfa GK et al. GI ASCO 2018 oral presentation; JCO 36:4s Abstr 207

Recent results: KEYNOTE-240 Trial (2nd Line Pembrolizumab vs. Placebo)

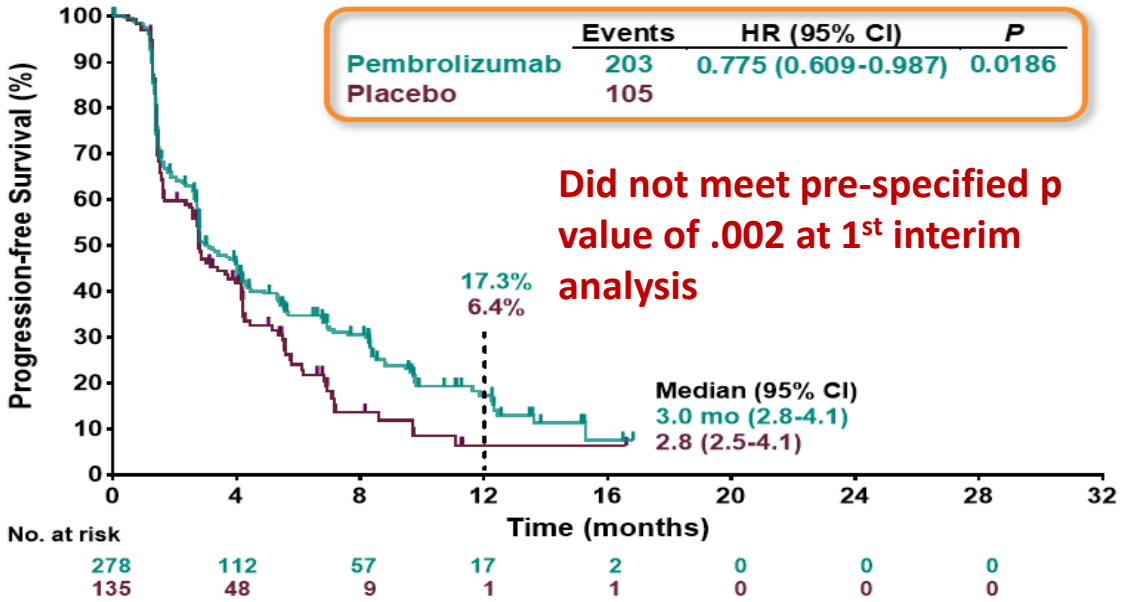
Overall Survival



Did not meet pre-specified p value of .0174

Progression-free Survival

First interim analysis



Did not meet pre-specified p value of .002 at 1st interim analysis

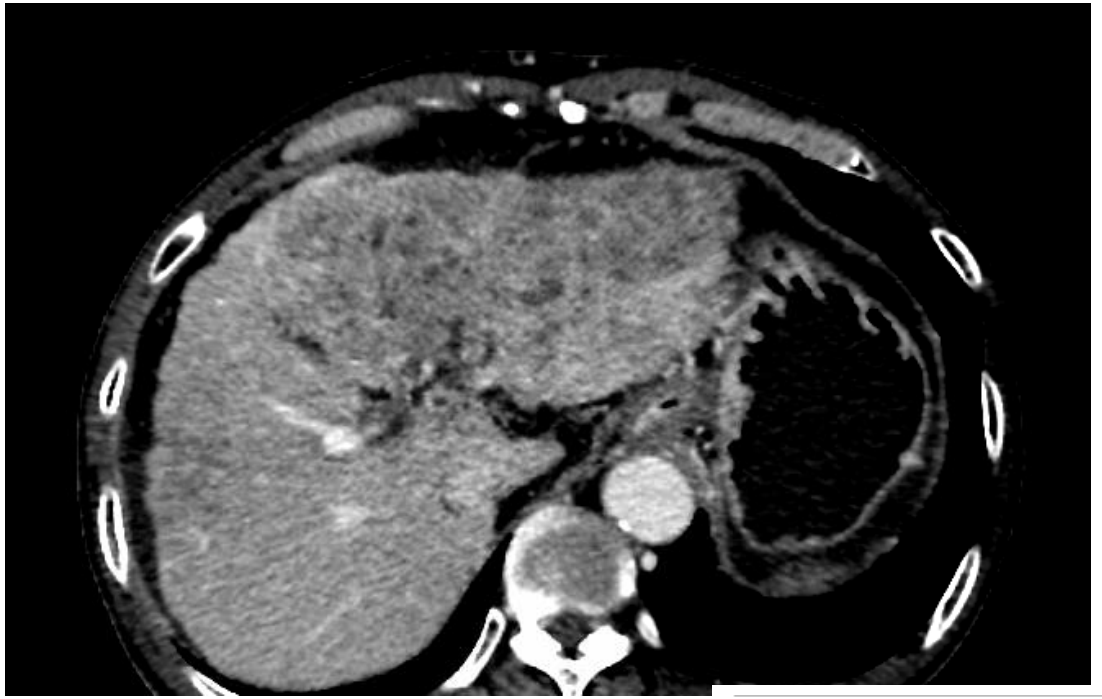
FDA approved 2nd Line irrespective of PD-L1 status despite just missing statistical endpoints in Phase III trial.

ORR 18.3% by RECIST 1.1 **Median DOR 13.8 months** **mOS 13.9 months**

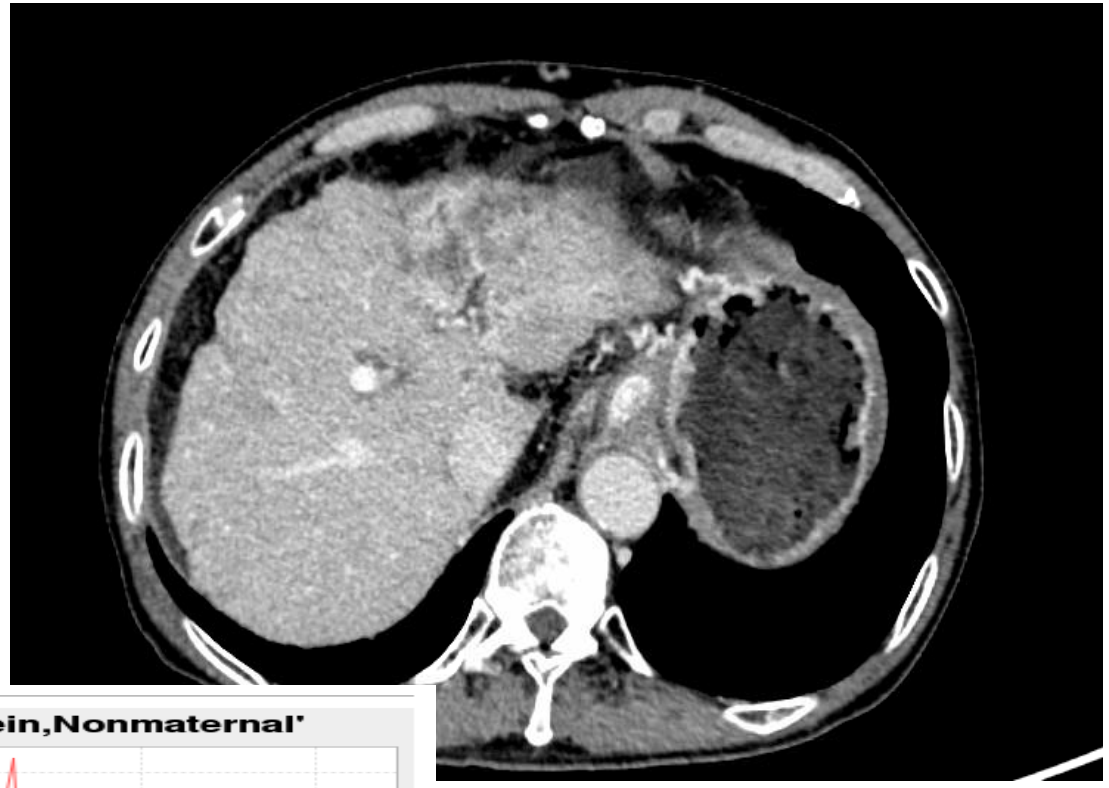
Finn et al. ASCO 2019 JCO 37(suppl; abstr 4004)

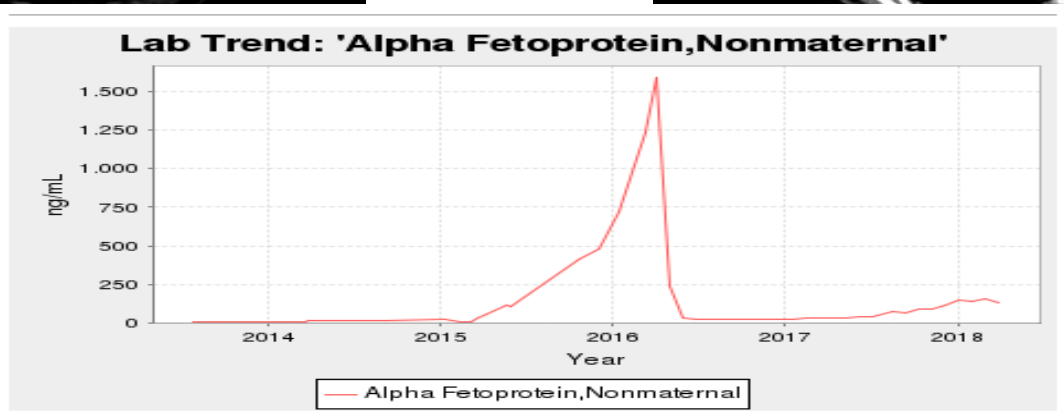
Second-Line Systemic Therapy: Case

Progressive Disease 1 year after sorafenib initiation



Scans 2 years after PD1 inhibition



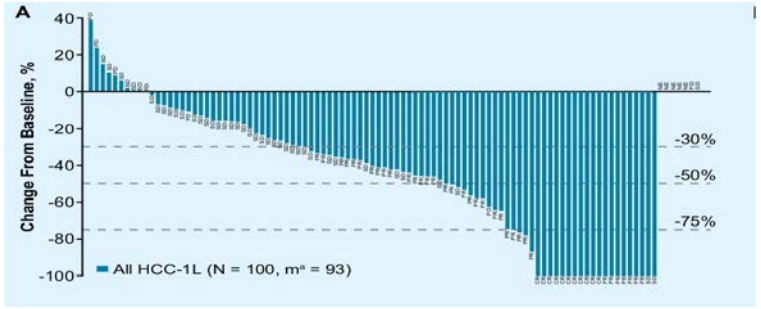


Future Directions/Questions: HCC

- **Optimal sequencing of currently approved agents unclear**
  - **Especially with no data to guide next steps after atezo/bev 1st line therapy**
- **Optimizing Immunotherapy approaches**

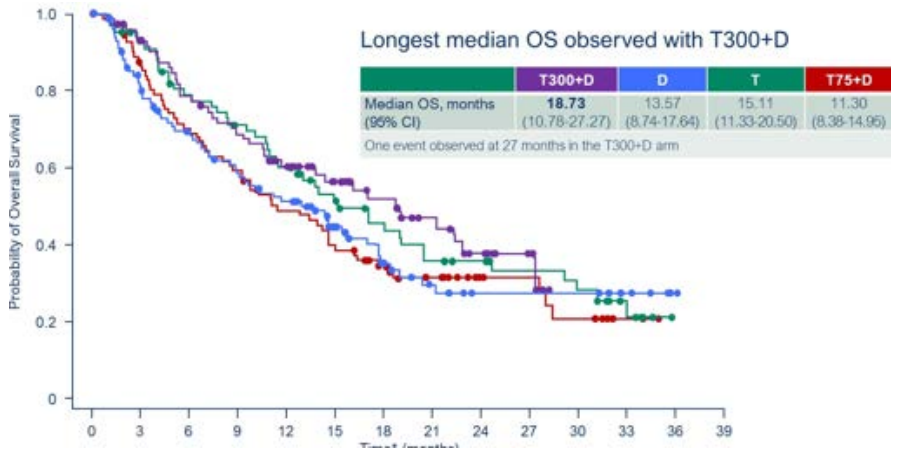
Promising combination strategies show high response rates in early phase trials; Phase III 1st line trials ongoing

TKI + α-PD1/PDL1 (n=100)
Lenvatinib + Pembro: 36% ORR
88% DCR, mPFS 8.6 mo.



α-CTLA4 + α-PD1/PDL1 (2nd Line)
Nivo(1)/Ipi(3): 32% ORR
8% CR; 23-month mOS

One Priming Dose α-CTLA4 + α-PDL1
Tremelimumab + Durvalumab



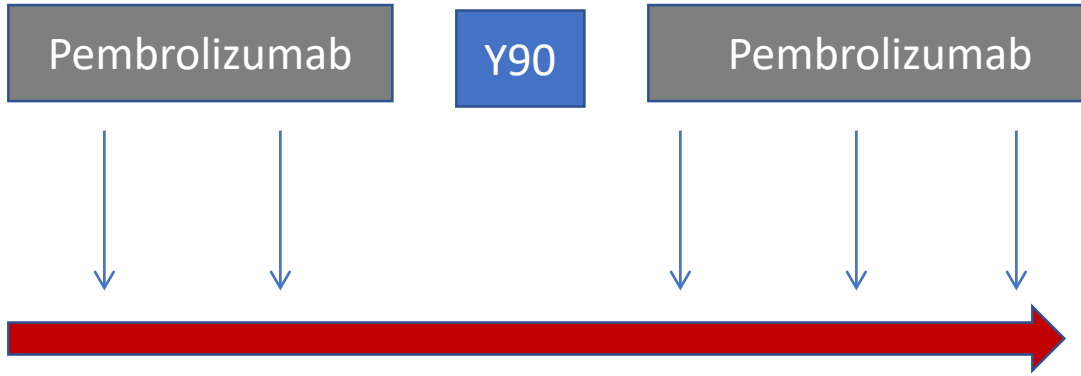
1. Zhu et al. ASCO 2020 Abstr 4519
2. Kelley et al ASCO 2020 Abstr 4508.
3. Yau et al. ASCO 2019 J Clin Oncol. 2019; 37(suppl) Abstr 4012

Future Directions: Local Interventions + Immune Checkpoint Inhibition

Phase II: SBRT + PD1 inhibitor (NCT03316872)
Phase II: Radioembolization + PD1 inhibitor (NCT03099564)
Phase III: TACE + PD-L1 inhibitor (+/- Bevacizumab) (NCT03778957)

Ongoing phase 2 Single arm Pilot study (n=30), 3 institution study

- **HCC not amenable to Resection/Transplant**
- **No prior radioembolization**
- **Child Pugh A, ECOG 0-1**
- **BCLC Stage B/C**

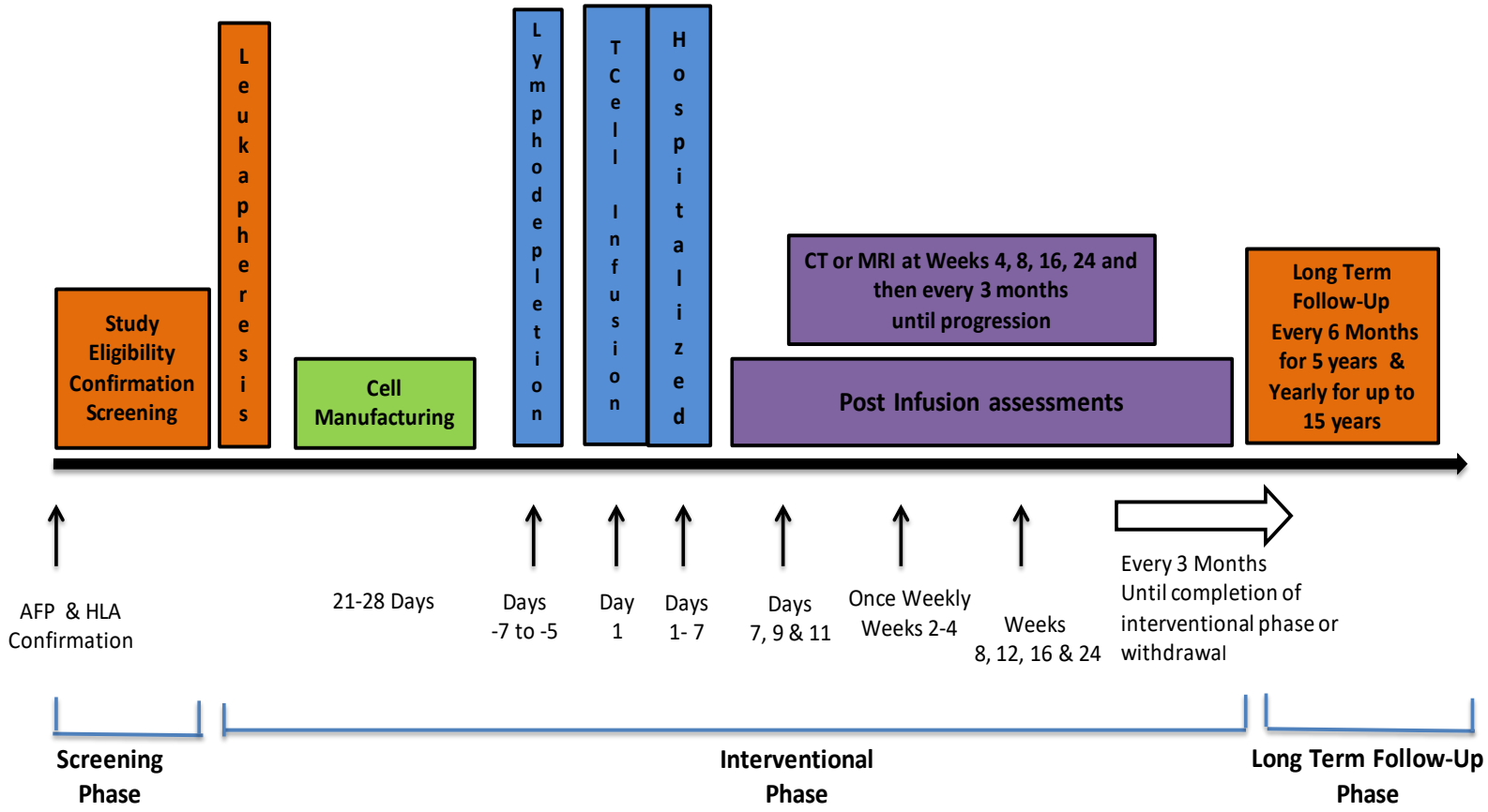


<u>Outcomes:</u>
Immunologic correlates
Toxicity assessment
Response rates, mOS, TTP

Future Directions: Adoptive T-cell Therapy
AFP-directed chimeric T-cell Receptor Therapy (TCR)

- Advanced HCC, any-line
- Child Pugh A
- ECOG 0-1
- HLA-A*02:01 + (~35%)
- Tumor AFP + by IHC (~40%) or elevated serum AFP
- Liver Parenchyma AFP – by IHC (most)
- Mandatory biopsies
- Requires chemotherapy conditioning

First in Human Studies, currently accruing



HCC: Final Take-home messages

- Localized therapy and liver transplantation for early stage disease (BCLC stage A) can be curative
- For Child-Pugh A/B unresectable HCC (without vascular involvement or metastatic disease): TACE has been shown to prolong survival compared with best supportive care
- For vascular involvement/metastatic HCC or select patients with bulky intermediate stage disease (Child-Pugh A), atezolizumab and bevacizumab is standard of care as first-line therapy.
- For advanced/metastatic HCC (Child-Pugh B), the benefit of systemic therapy is less defined but may be considered in select patients.
- Multiple recently FDA approved systemic therapies in the refractory setting, with no current consensus regarding optimal selection. Many GI Oncologists would attempt TKI (Lenvatinib, sorafenib) after atezo/bev.