Hepatocellular Carcinoma

William P. Harris, MD

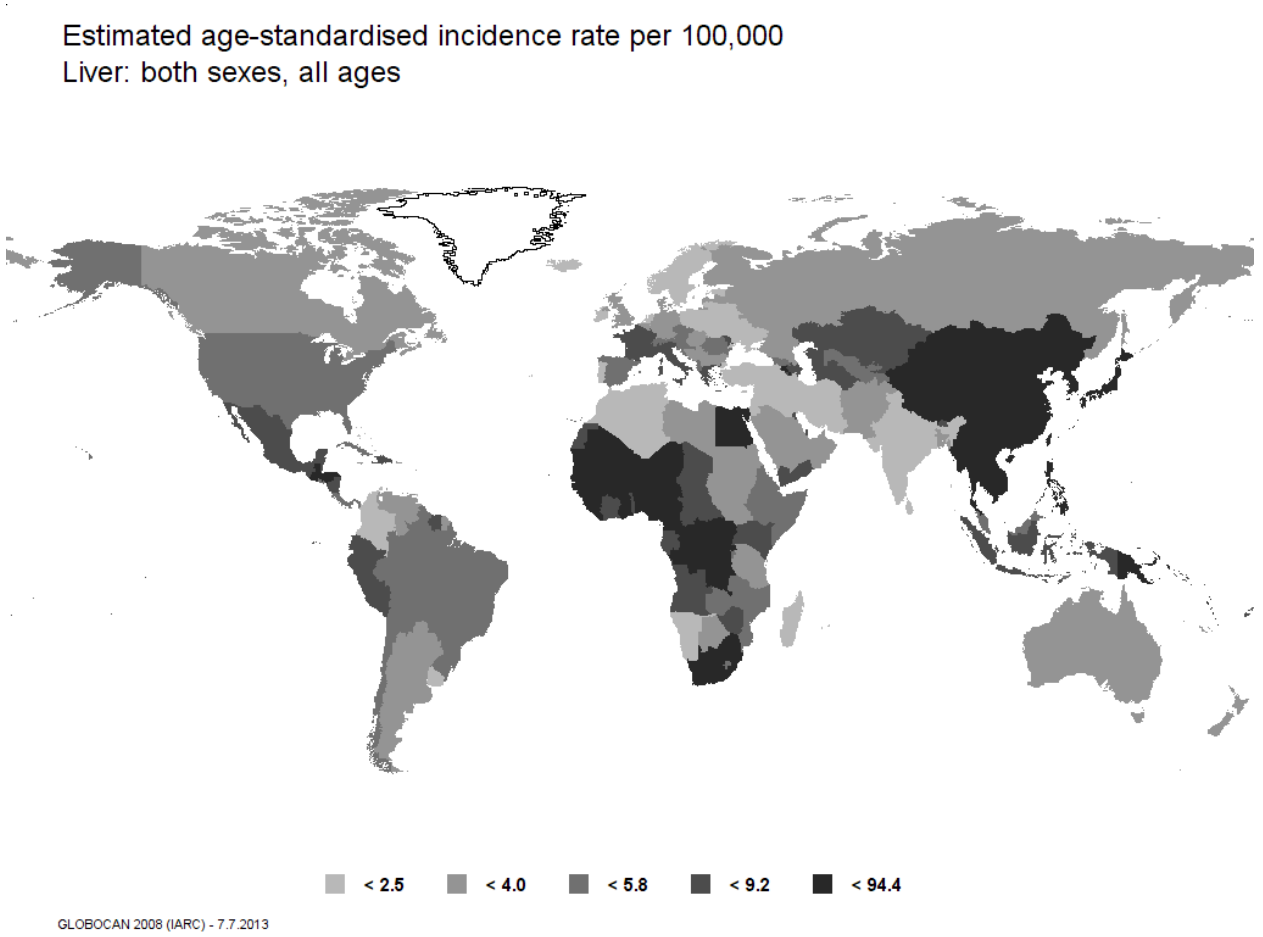
Associate Professor, Medical Oncology, University of Washington

Associate Professor, Clinical Research Division, Fred Hutchinson Cancer Research Center

Disclosures:

- Institutional Research Funding: Astra-Zeneca
- Consulting: Boston Scientific, Tallac Pharmaceuticals
- Other Unpaid Affiliations: GI Cancer Alliance, Fibrolamellar Cancer Foundation

HCC: Global incidence

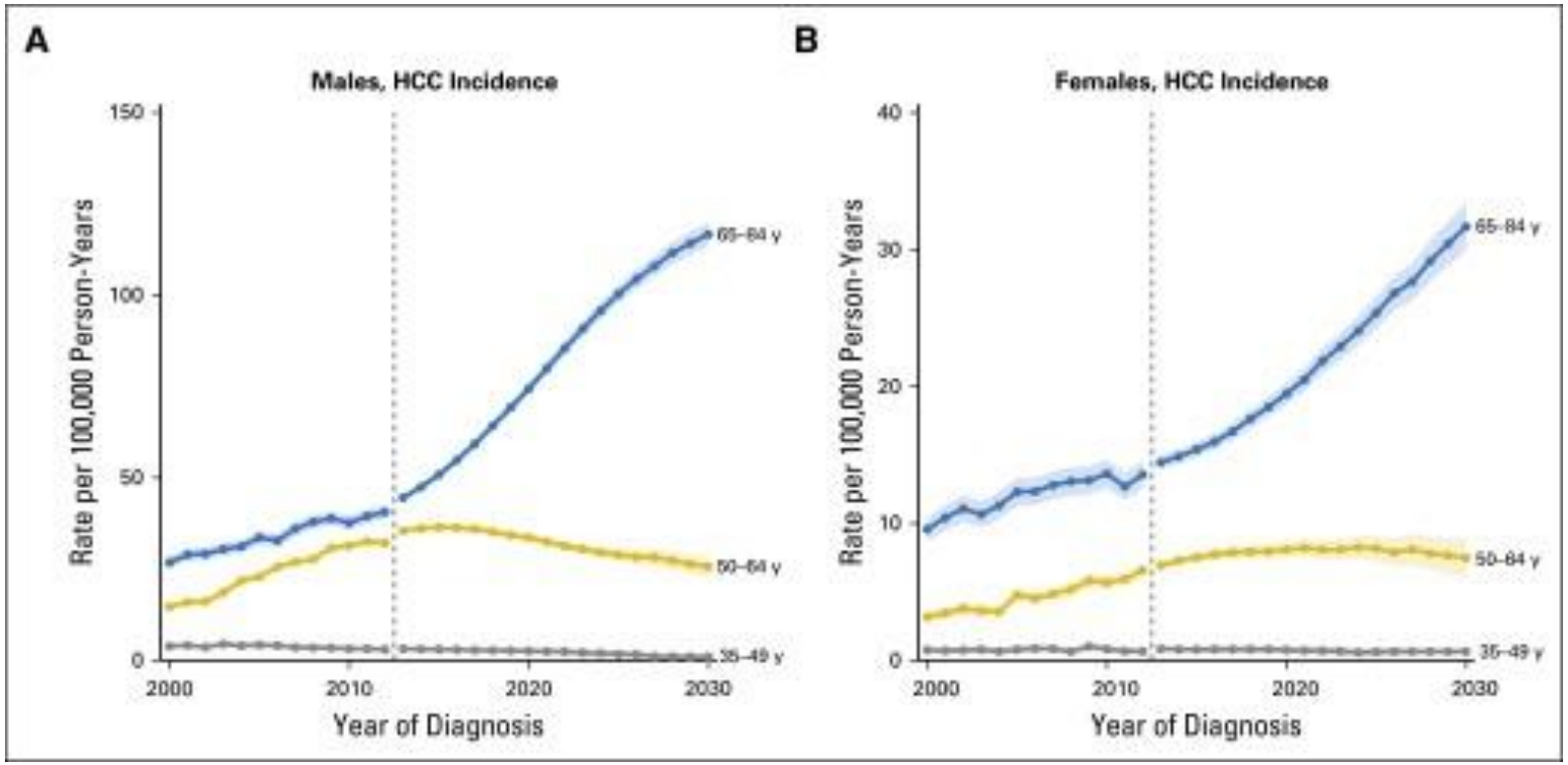


3rd leading cause of global cancer related death
Incidence and mortality is rising in the United States

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

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

HCC: US Incidence Trends



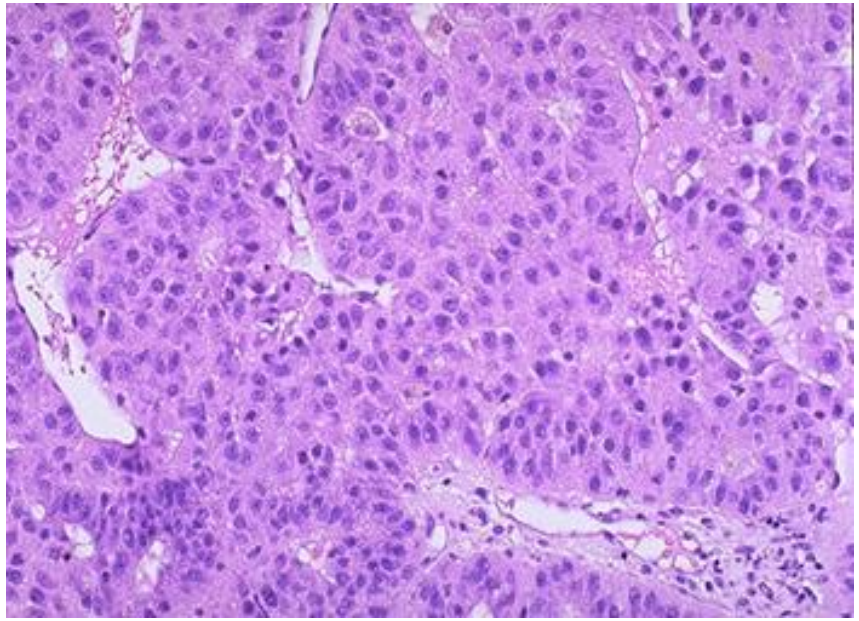
- **Projected increase in HCC incidence until at least 2030**
- **Aging population of patients with HCC**

Petrick et al. Future of Hepatocellular Carcinoma Incidence…*JCO* May 2016 34(15): 1787–1794.

HCC: Risk Factors

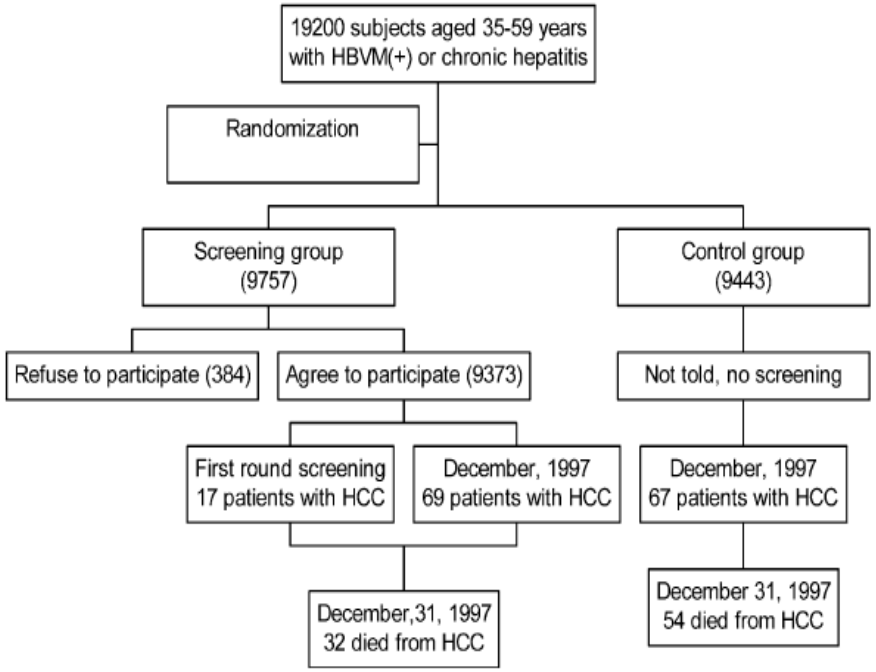
- **Cirrhosis from any cause**
  (3-4%annual risk of HCC)
  - HCV
  - HBV
  - Heavy alcohol consumption
  - Non-alcoholic steatohepatitis (NASH)
  - Aflatoxins
- **HBV Chronic Hepatitis**
  (0.4% annual risk of HCC)
- **Inherited metabolic diseases**
  - Hemochromatosis
  - Alpha-1 antitrypsin deficiency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

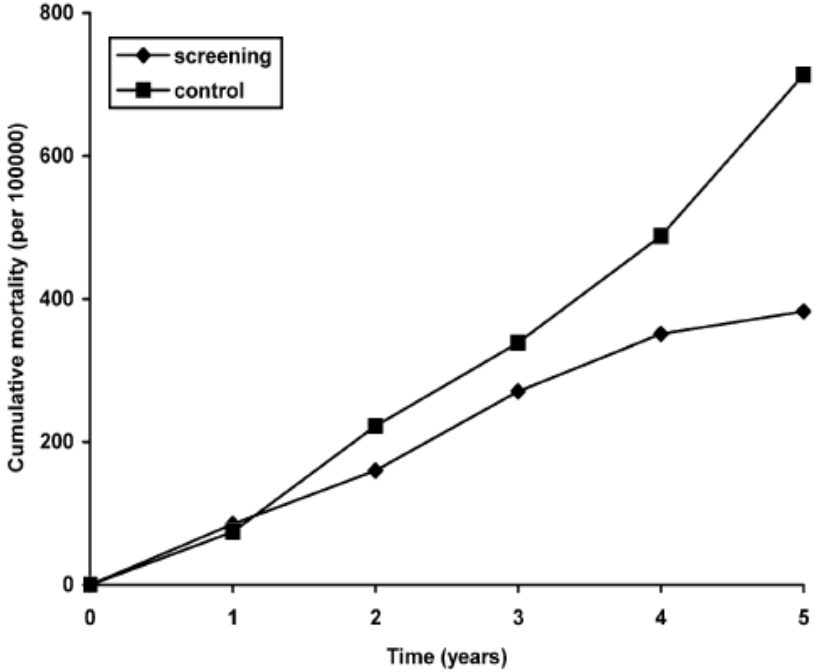
Diabetes Mellitus
Obesity



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

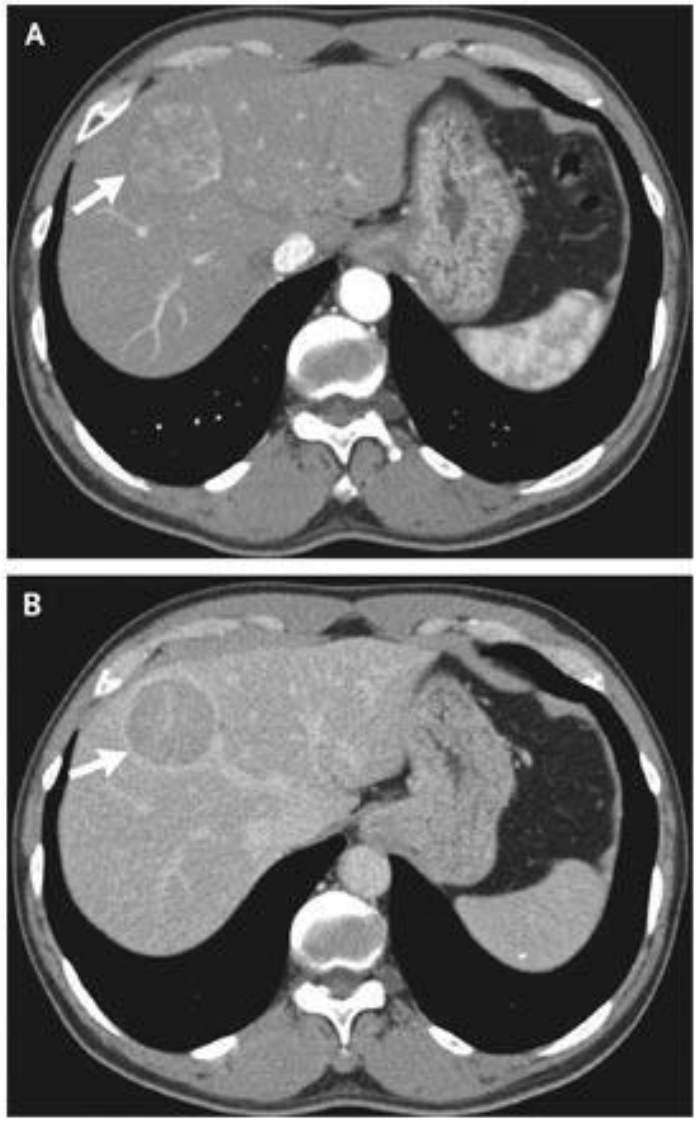
Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Incidence of HCC
Surveillance benefit		
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.6% per year
Hepatitis B carrier with family history 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

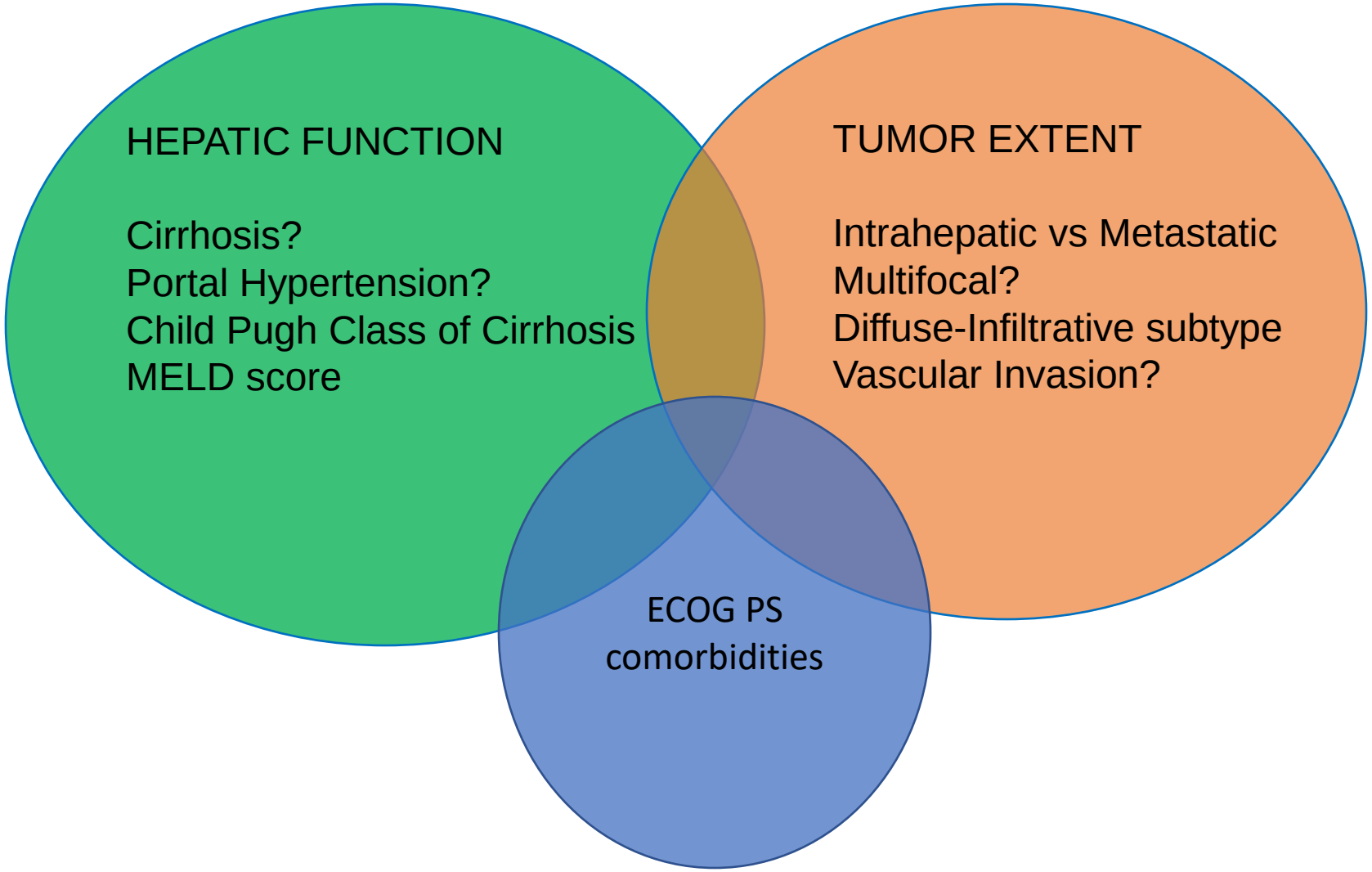
LR-4 / LR-5

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

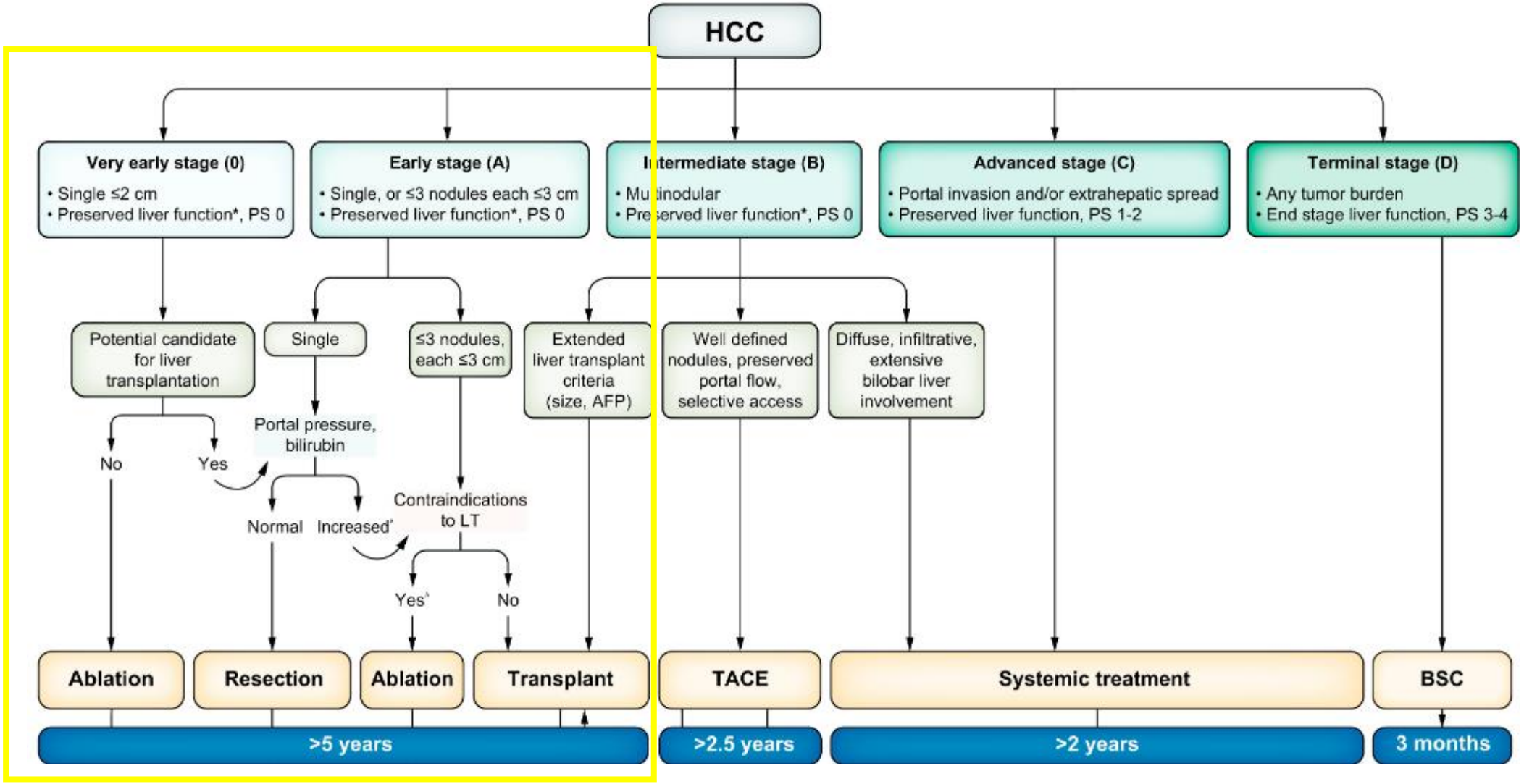


Figure derived from Reig M. et al. J hepatology March 2022 76(3) 681-693

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

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

- Surgical resection: Typically unifocal, 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%

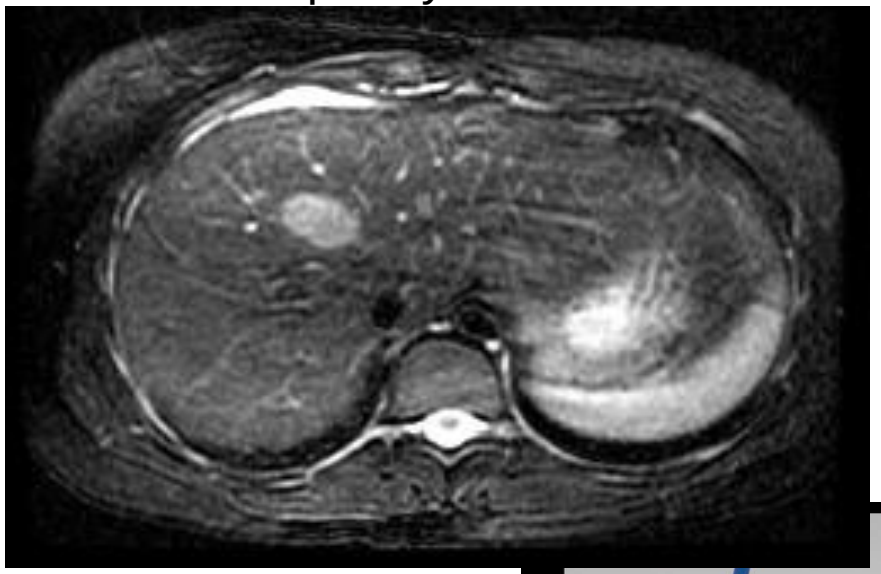
Underlying cirrhosis, poorer baseline liver function

- 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

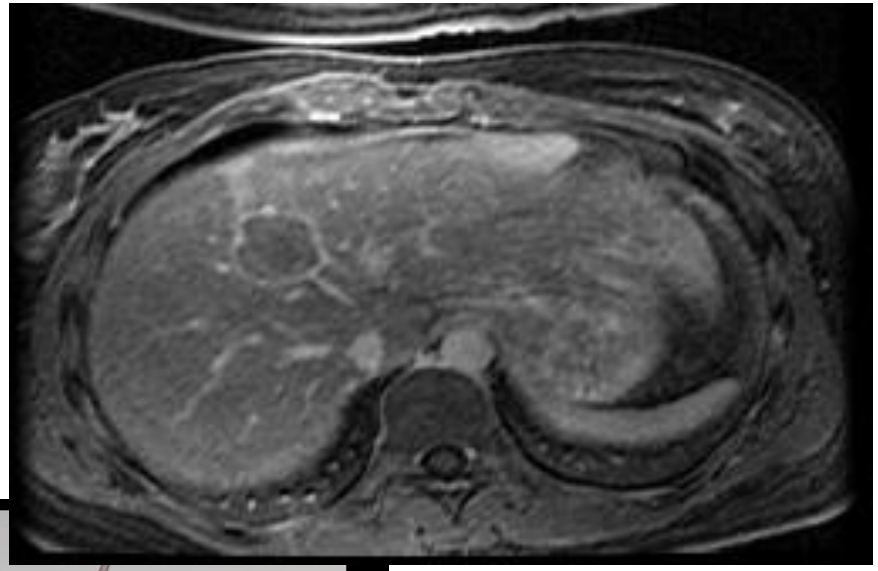
Hong SN, et al. Comparing the Outcomes of Radiofrequency Ablation and Surgery in Patients with a Single Small Hepatocellular Carcinoma and Well-Preserved Hepatic Function

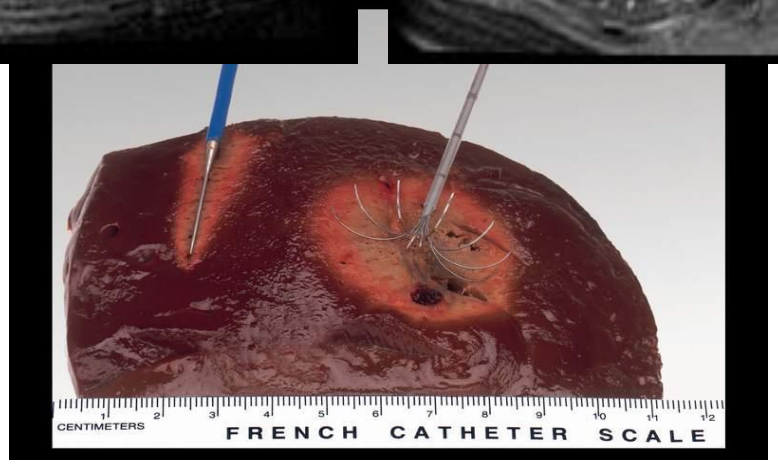
Local Treatment for Early-Stage HCC: Radiofrequency Ablation

Pre-Radiofrequency Ablation



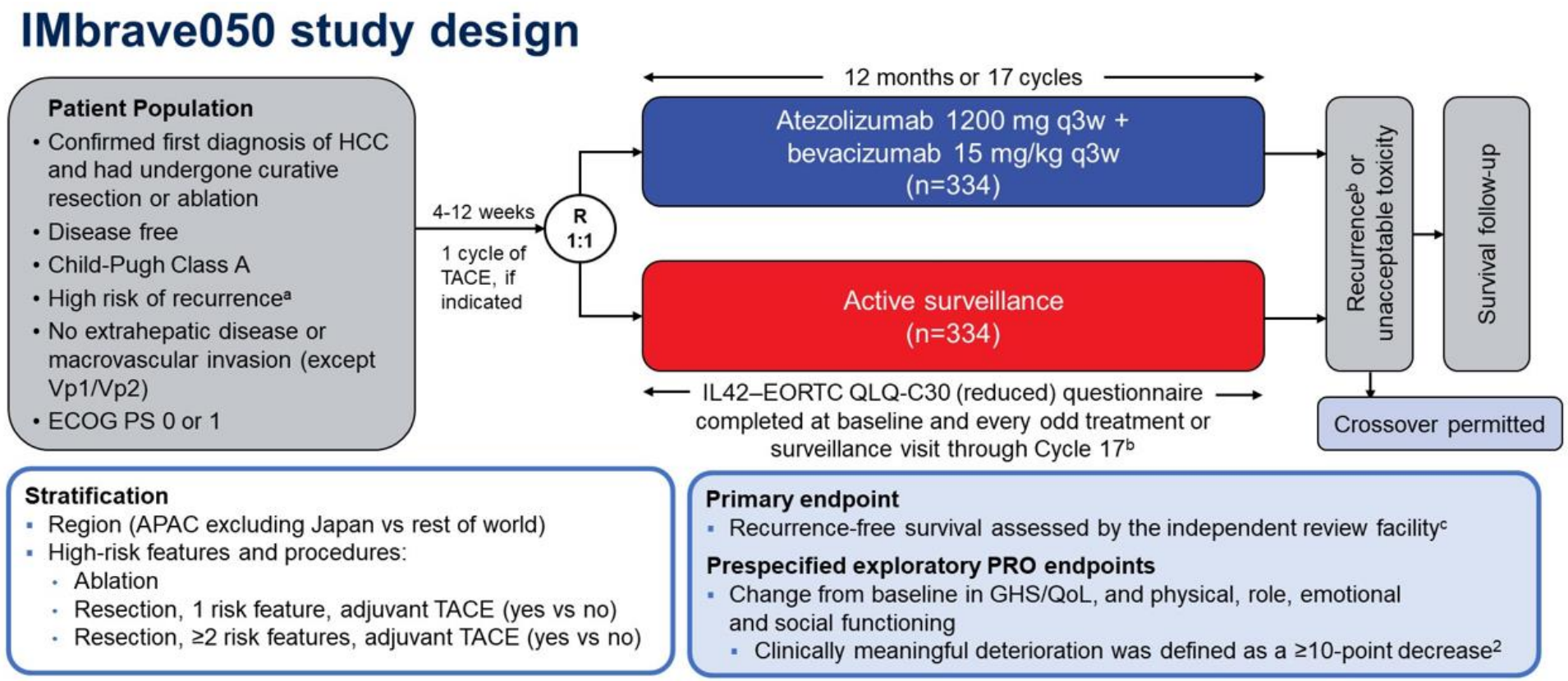
1-month post-RFA





Images from Dr. Siddharth Padia, UW Interventional Radiology

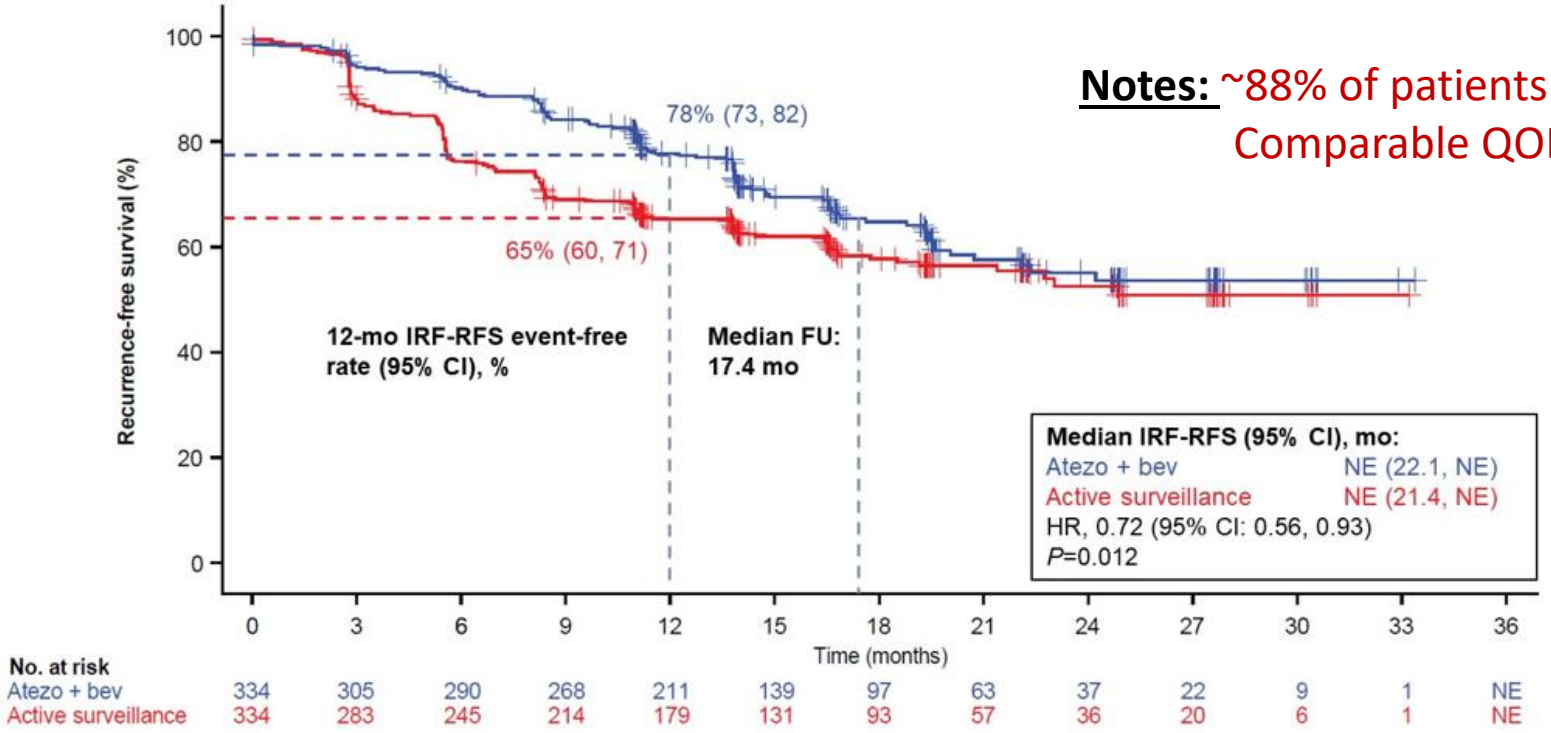
Phase 3 Data from ASCO 2023: Promise for Adjuvant Therapy in Resected or Ablated High-Risk HCC



*High Risk Features include: Tumor >5 cm, >3 tumors, microvascular invasion on pathology, Minor macrovascular invasion (Vp1/Vp2) or high-grade pathology (grade 3/4)

Figure modified from Kudo et al. ASCO 2023 Oral Abstract Presentation. J Clin Oncol 41, 2023 (suppl 16; abstr 4002)

IMBRAVE 050: Adjuvant Therapy In Resected/Ablated High Risk HCC



Notes: ~88% of patients underwent resection
Comparable QOL between arms

Updated Analysis as of May 2024:

- RFS benefit seen in first interim analysis above **not** sustained
- OS remains immature but no benefit currently
- Use of adjuvant Atezolizumab/Bevacizumab is **not** recommended

Figure modified from Kudo et al. ASCO 2023 Oral Abstract Presentation. J Clin Oncol 41, 2023 (suppl 16; abstr 4002)

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)

- Initial promising results for adjuvant systemic therapy following surgical resection and radiofrequency ablation (RFA) in patients at high risk of recurrence now updated: no clear benefit of adjuvant therapy noted

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

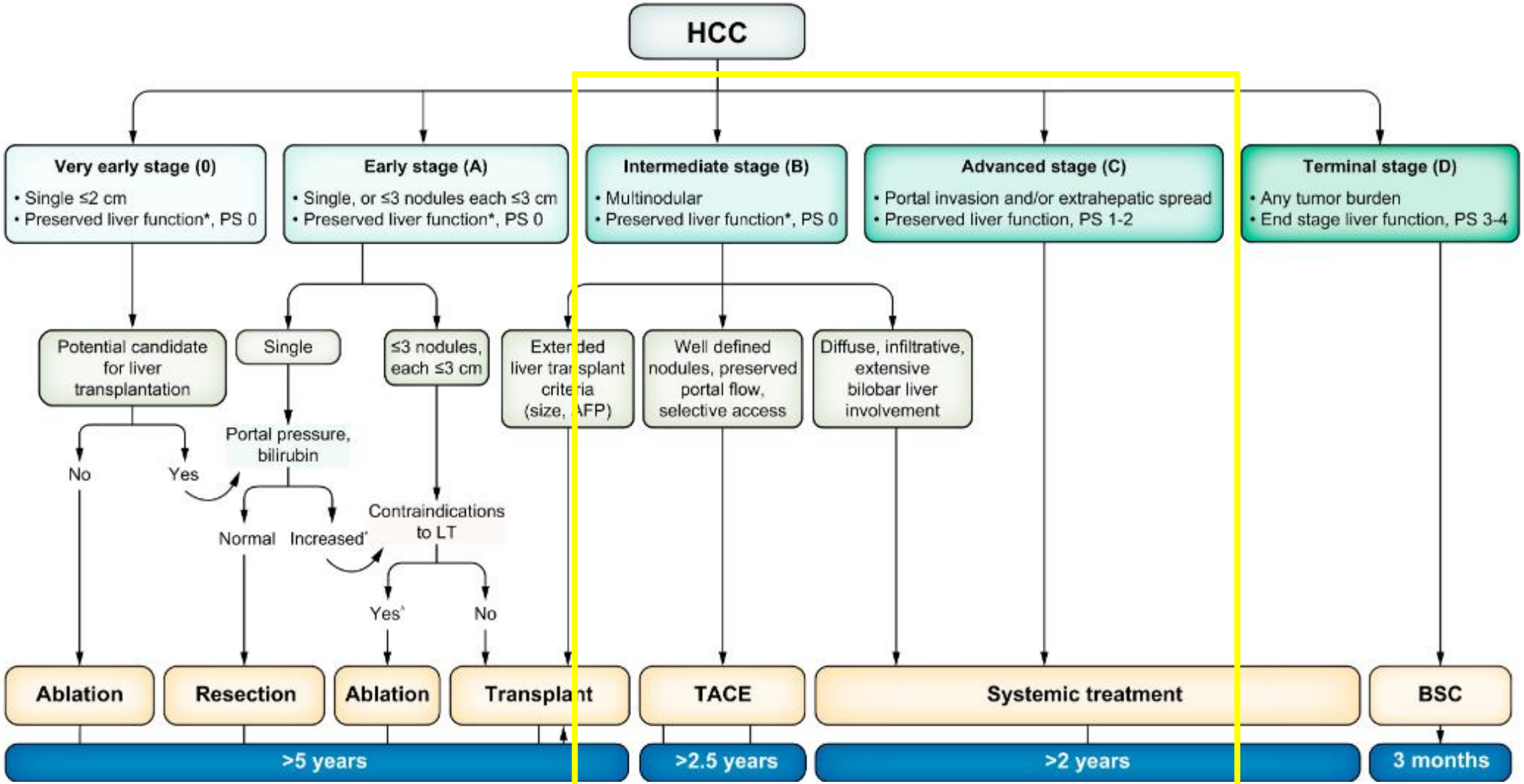


Figure derived from Reig M. et al. J hepatology March 2022 76(3) 681-693

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 or to downstage to transplant

Metastatic disease or vascular invasion (BCLC C)

- Systemic therapy (most commonly); Y90 a consideration in select cases with less extensive portal venous invasion

Hepatocellular Carcinoma: Updated Algorithms

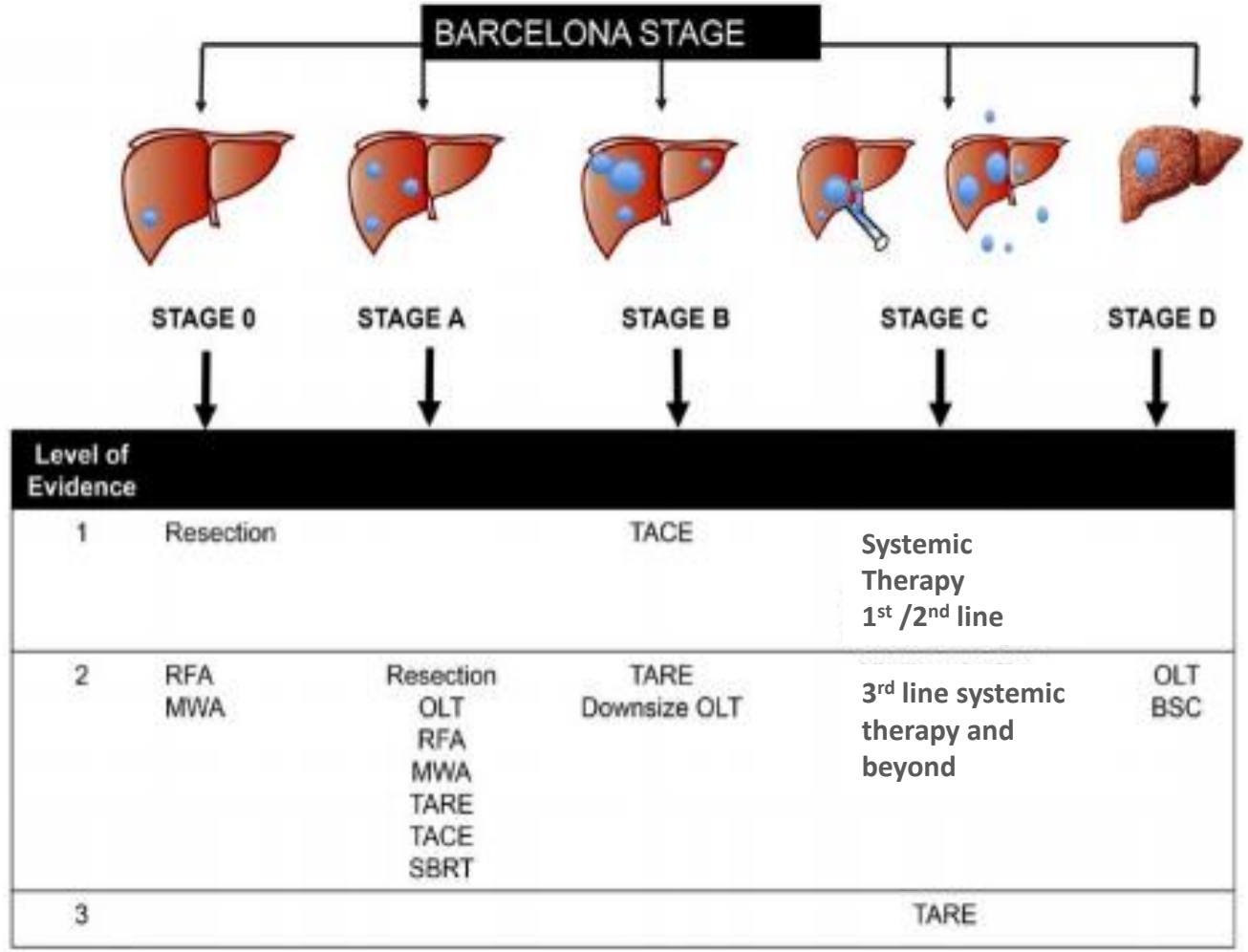


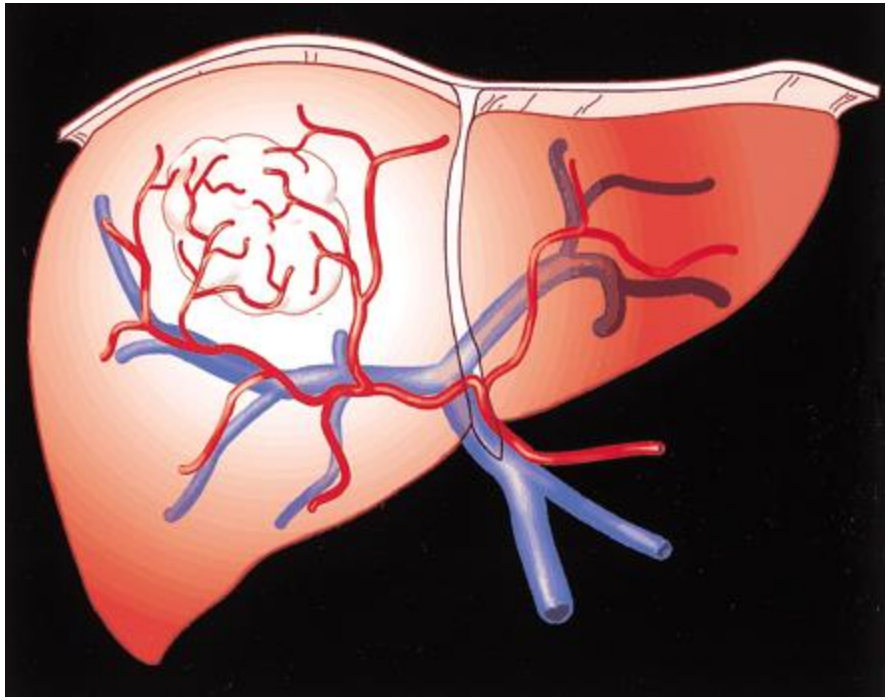
FIG. 3. Treatment recommendations according to BCLC Stage. Abbreviations: MWA, microwave ablation; BSC, best supportive care; 1L, first-line therapy; 2L, second-line therapy.

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

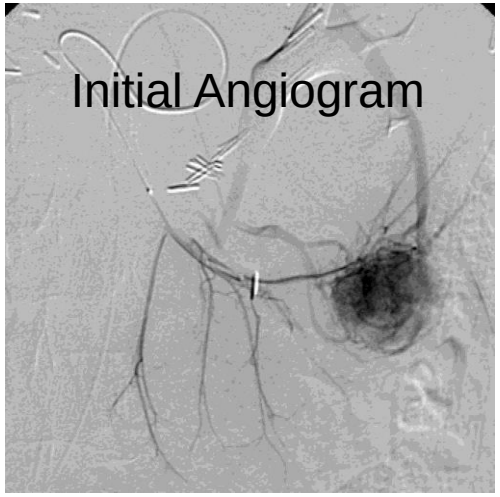


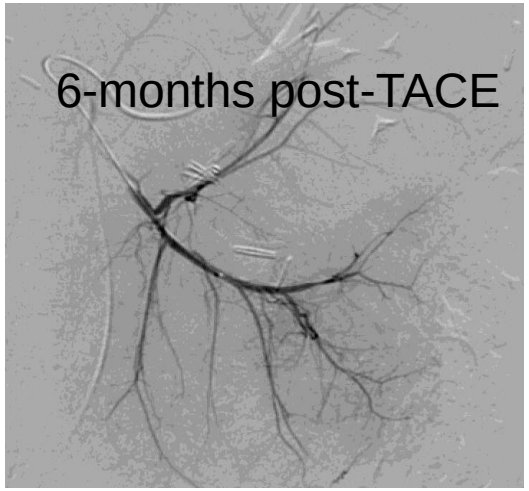
Intermediate/Advanced HCC: Transarterial Embolization

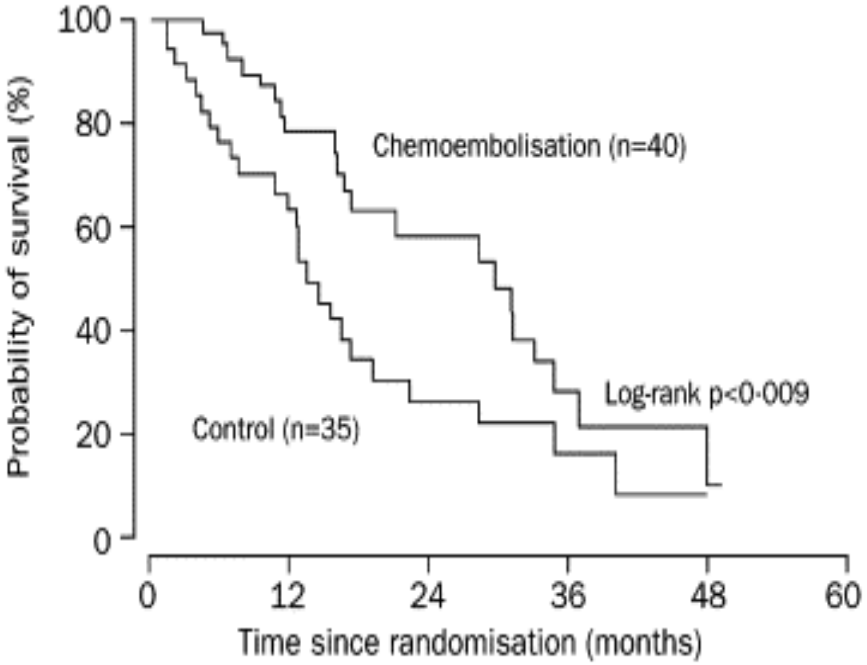
Two components of therapy:

1) Acute arterial obstruction

2) Local arterial 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

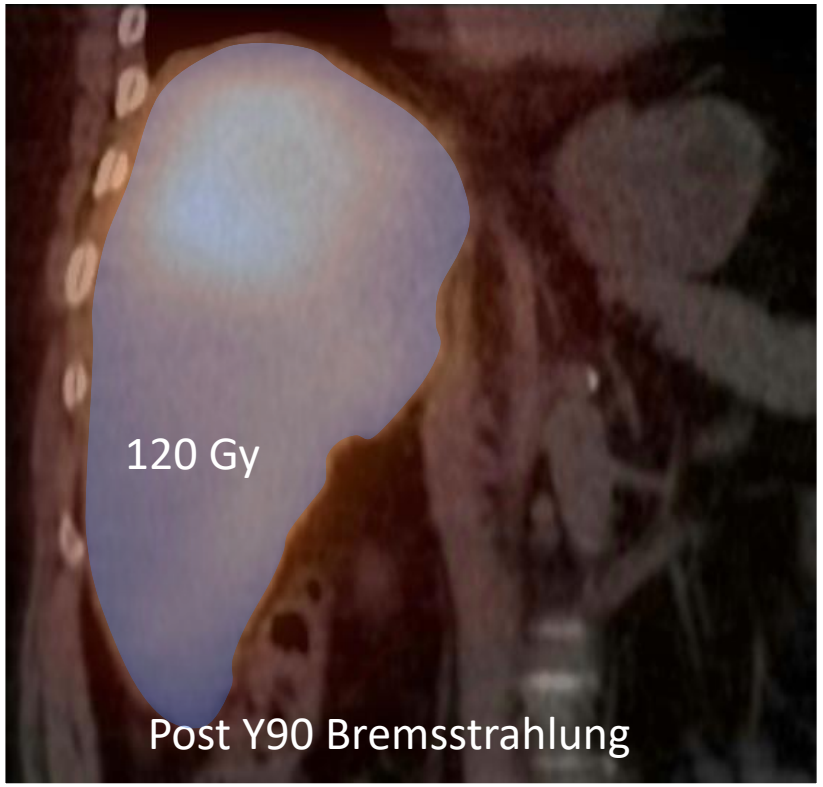
TACE/TAE – Conclusions and Questions

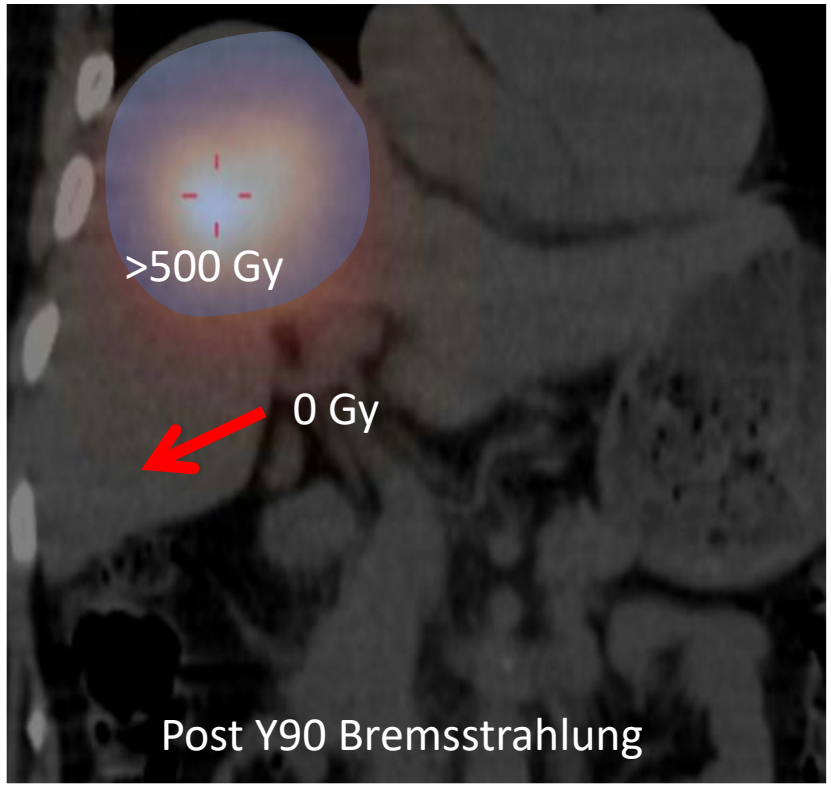
- Large systematic reviews / meta-analyses have demonstrated a benefit from TACE
  - Large series show median OS of 2.5-3.0 years with catheter-based therapy

(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

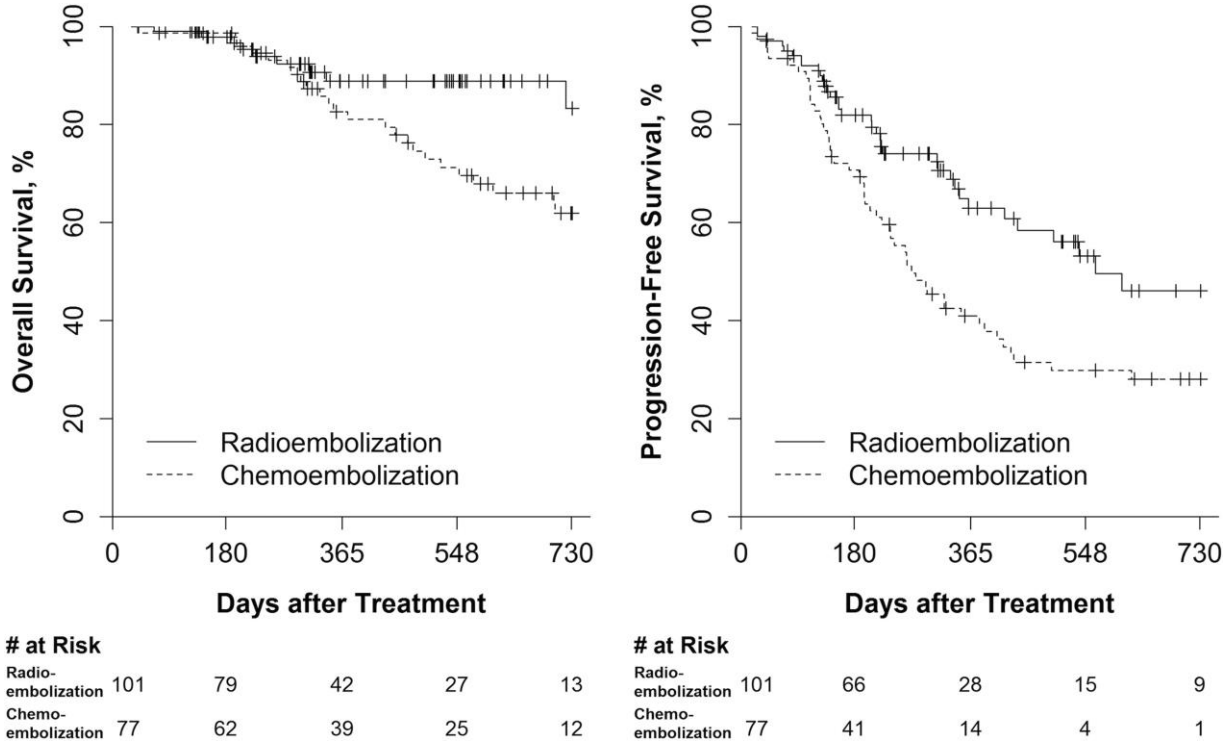




Improved targeting
Higher intra-tumoral radiation doses → Improved response?
Decreased collateral damage

High dose localized radioembolization: (radiation segmentectomy)

Promising data from large UW Retrospective Series: radiation segmentectomy vs. TACE



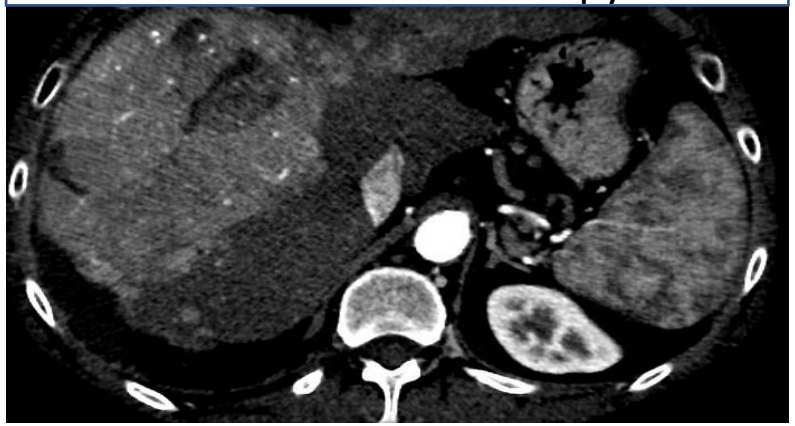
LEGACY STUDY: High-dose radioembolization in single tumors up to 8 cm

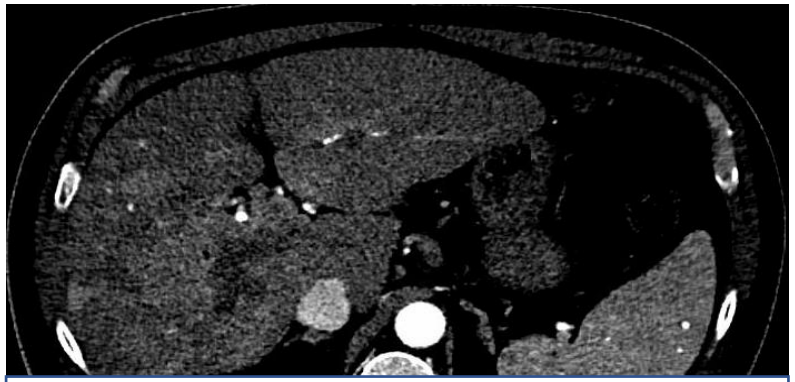
- ORR: 88.3%
- Durable response Rate (>6 months): 62%

Padia et al. *JVIR* Jun 2017, PMID 28365172
Salem et al. *Hepatology* March 2021, PMID 33739462

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	
Durvalumab + Tremelimumab HIMALAYA TRIAL	~~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*

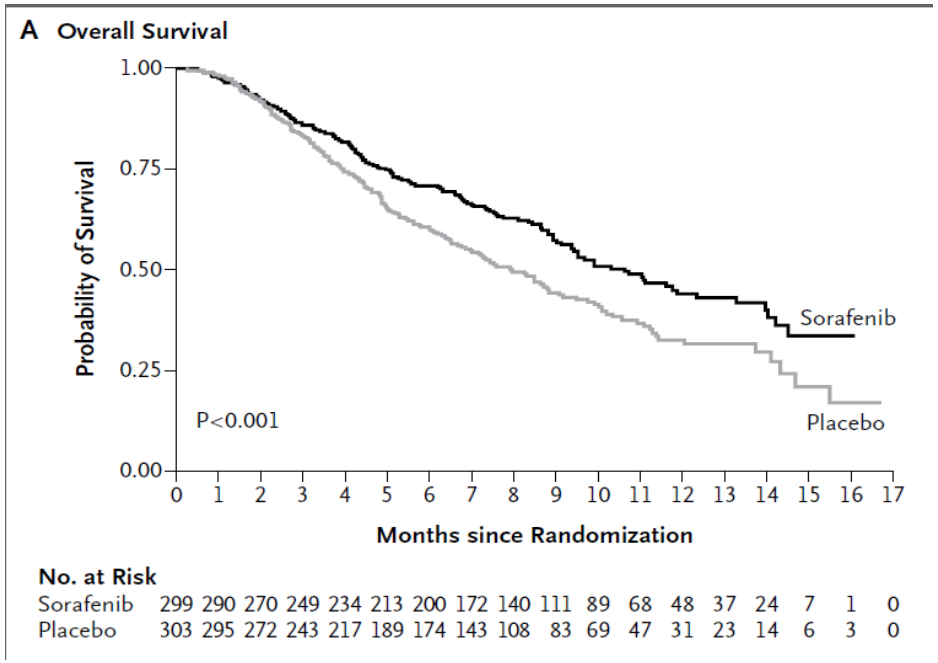
Sorafenib approved by the FDA for advanced HCC in November 2007

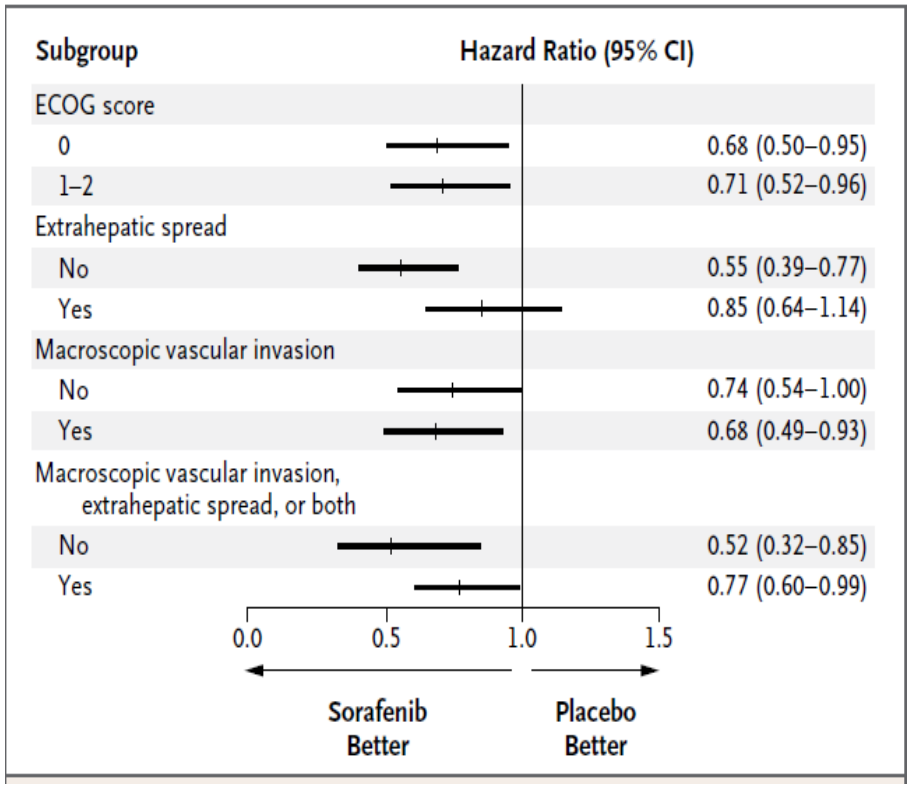
SHARP: Patient Characteristics

	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



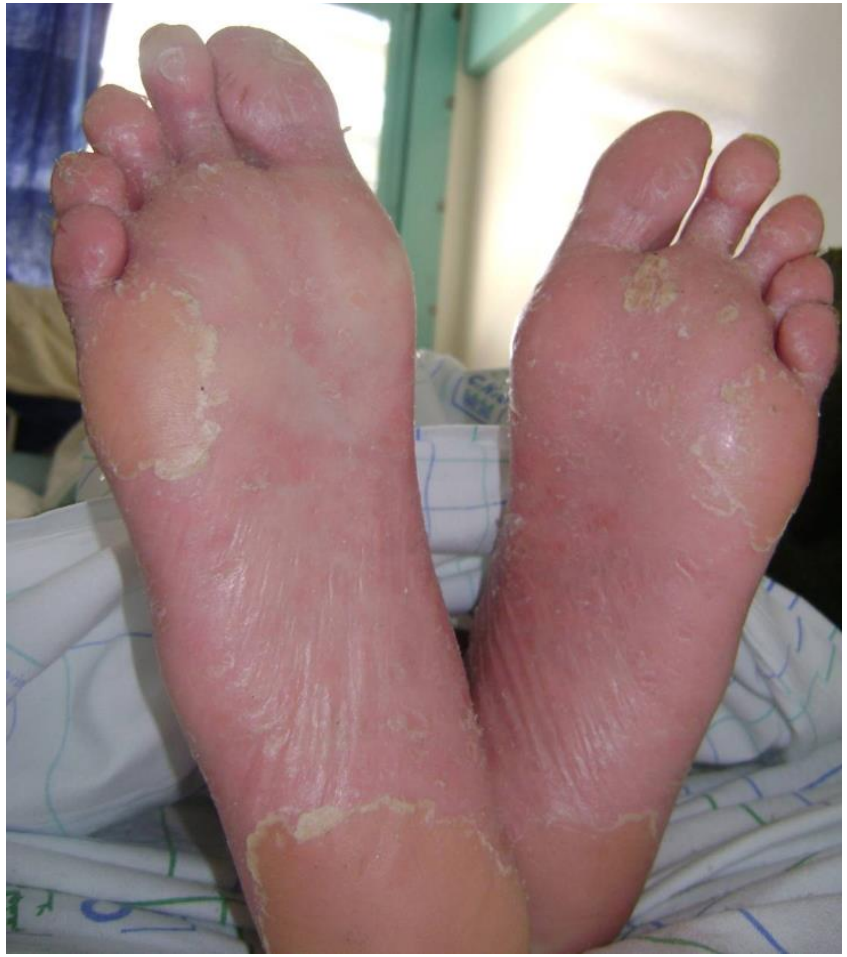


Median survival: 10.7 vs. 7.9 months
(HR 0.69 (95% CI 0.55, 0.87) p<0.001

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

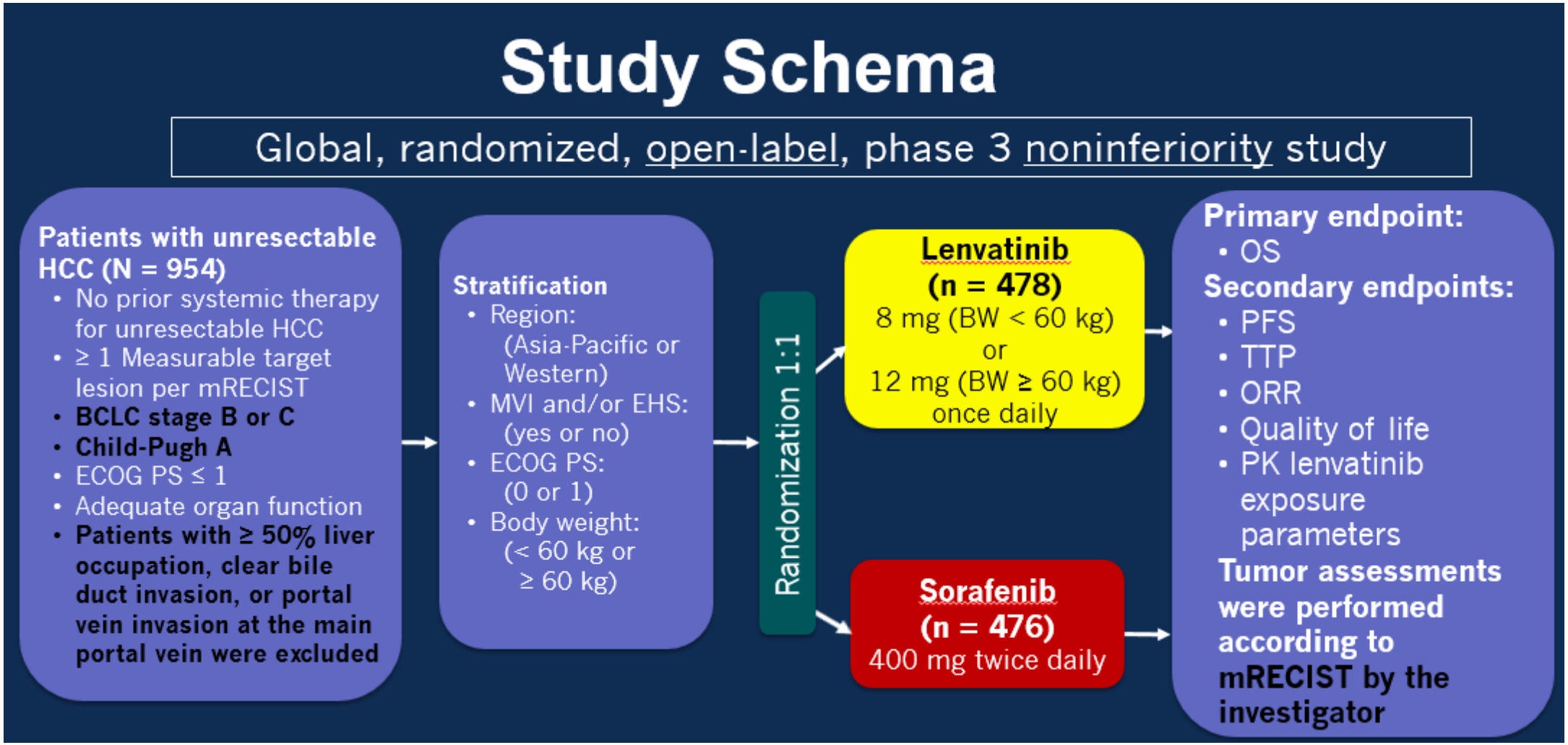
SHARP Trial: Safety

- 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



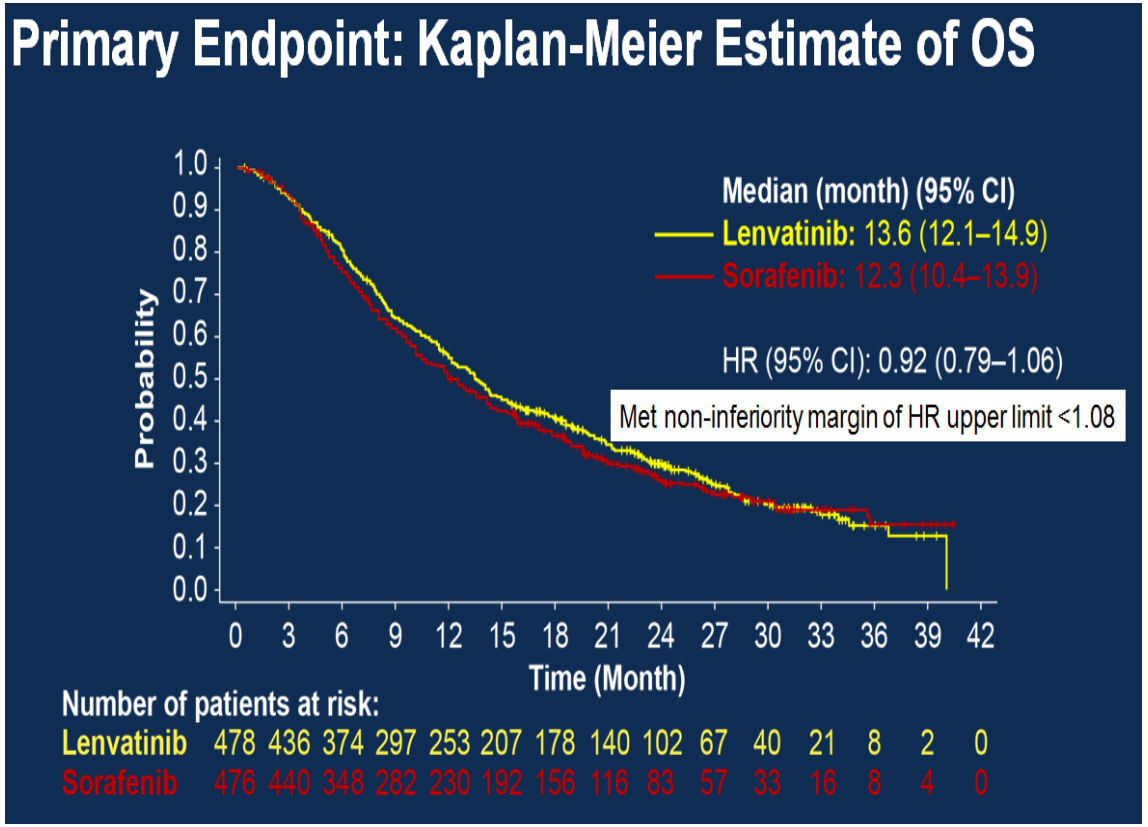
Benomar, et al. *Dermatology online journal*. Nov 2008

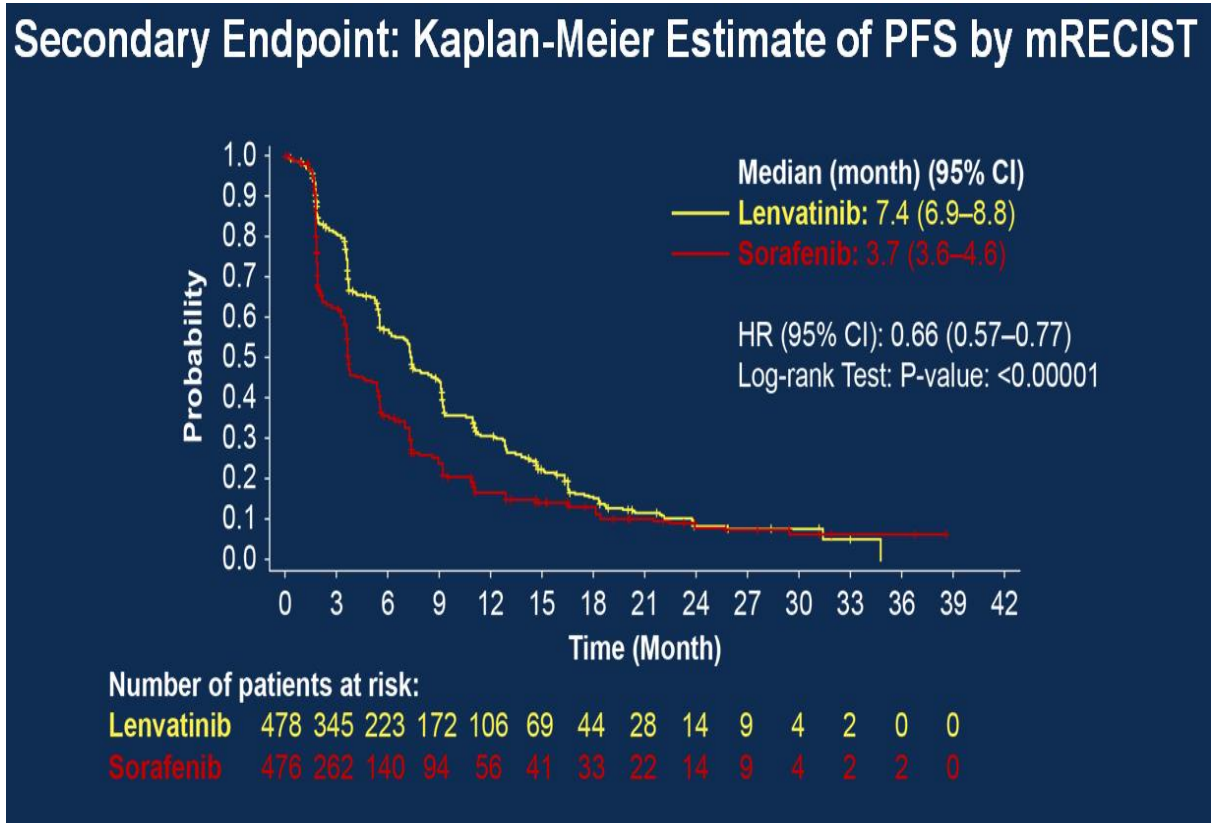
Lenvatinib: First-Line HCC Trial



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.*

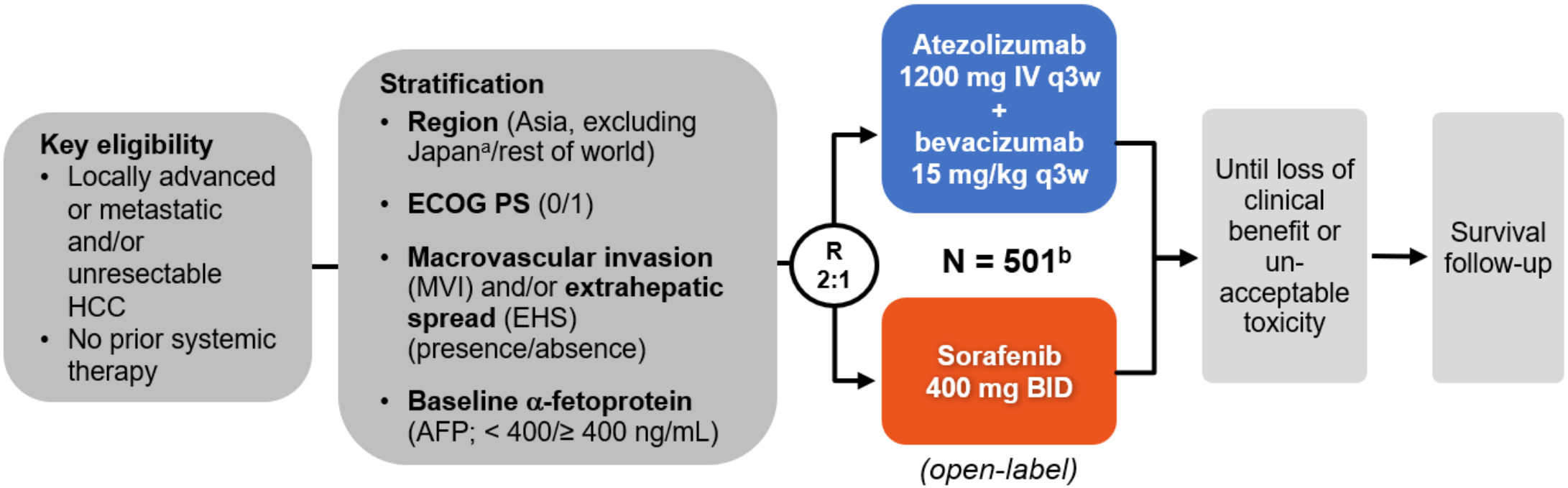
Lenvatinib: First-Line HCC Trial

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.

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

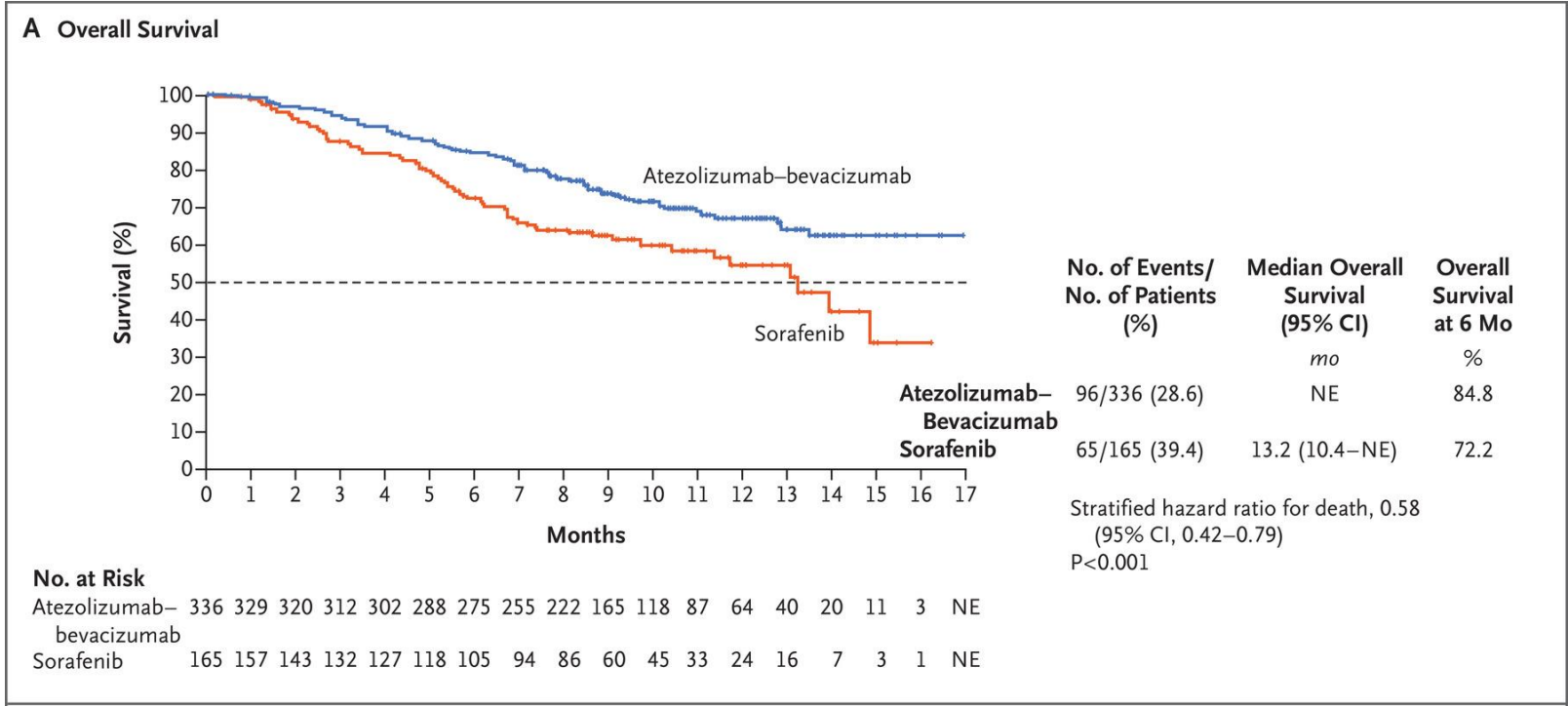
- Untreated/incompletely treated esophageal/gastric varices
- History of autoimmune disease
- Hepatitis B/C co-infection
- Anticoagulation or antiplatelet therapy (ASA 81 mg allowed)
- Uncontrolled hypertension (>150/100)
- Recent GI bleeding event

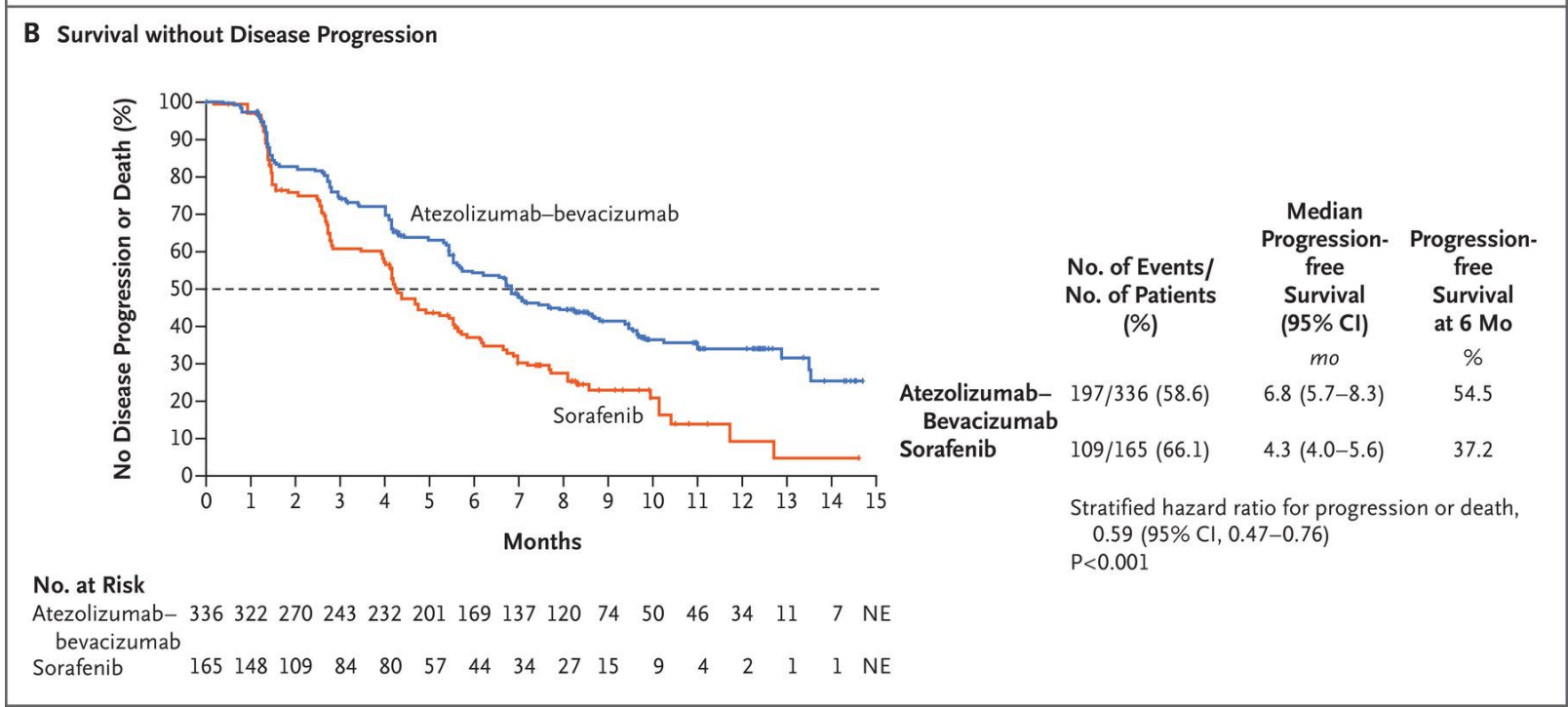
IMBRAVE 150 RESULTS

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

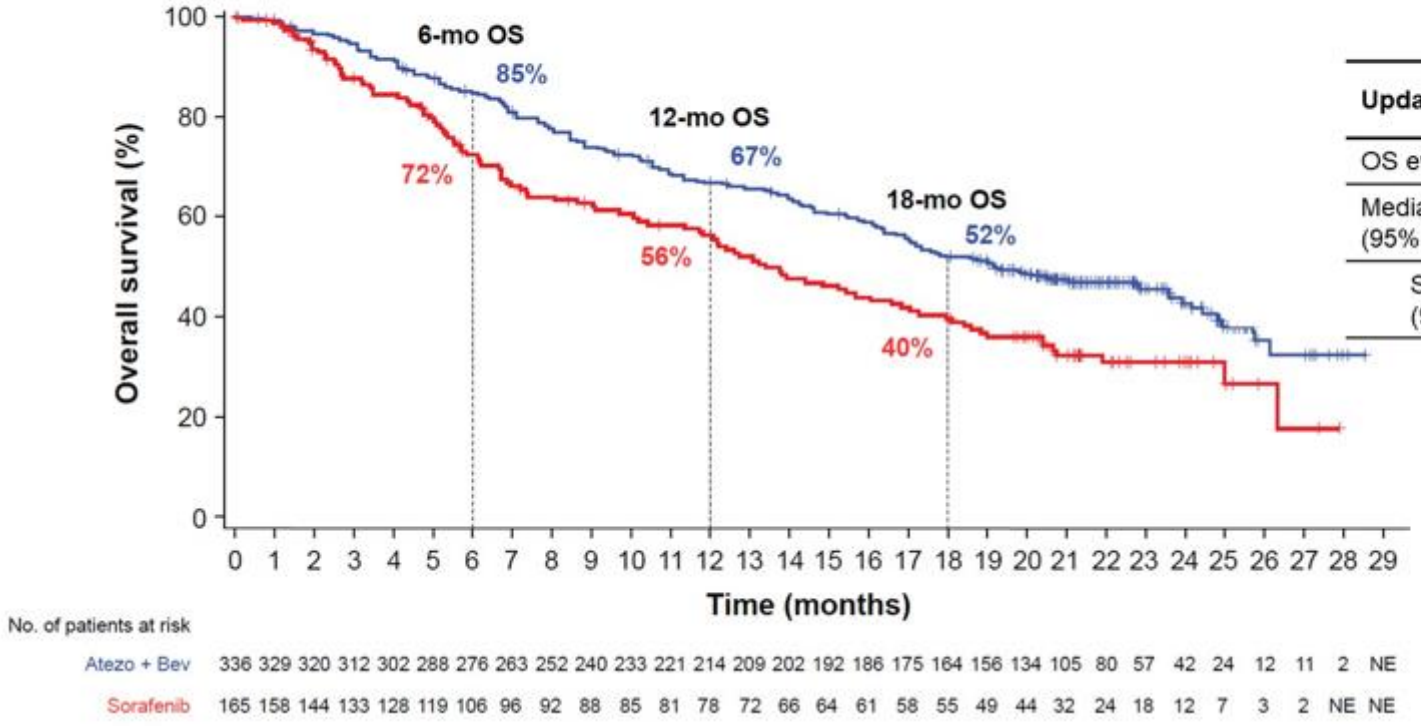
Finn et al. NEJM 2020 382:1894-1905





Updated Final Results Atezolizumab/Bevacizumab IMBRAVE 150 Trial

Updated OS



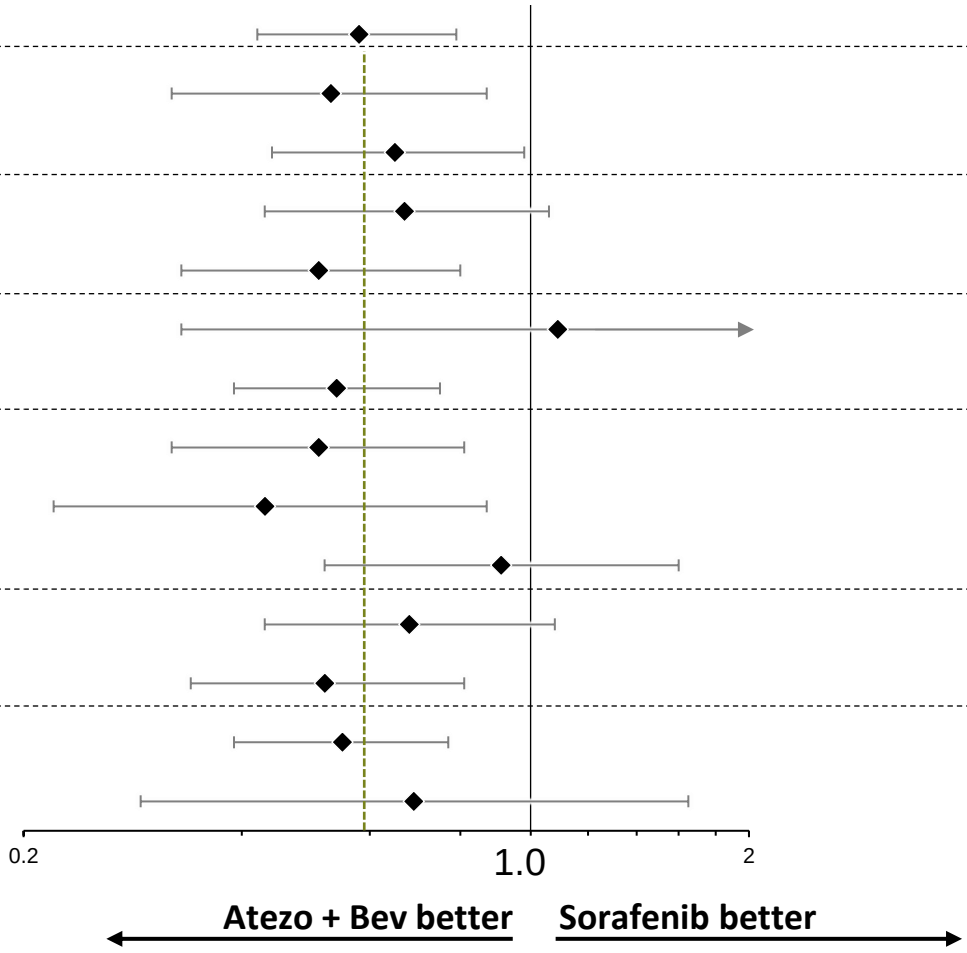
Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

Median OS: 19.2 months
Response Rate: 30%
Disease Control Rate: 74%
mDOR: ~18 months

Finn et al. GI ASCO 2021, J Clin Oncol 39, 2021 (suppl 3; abstr 267)

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:

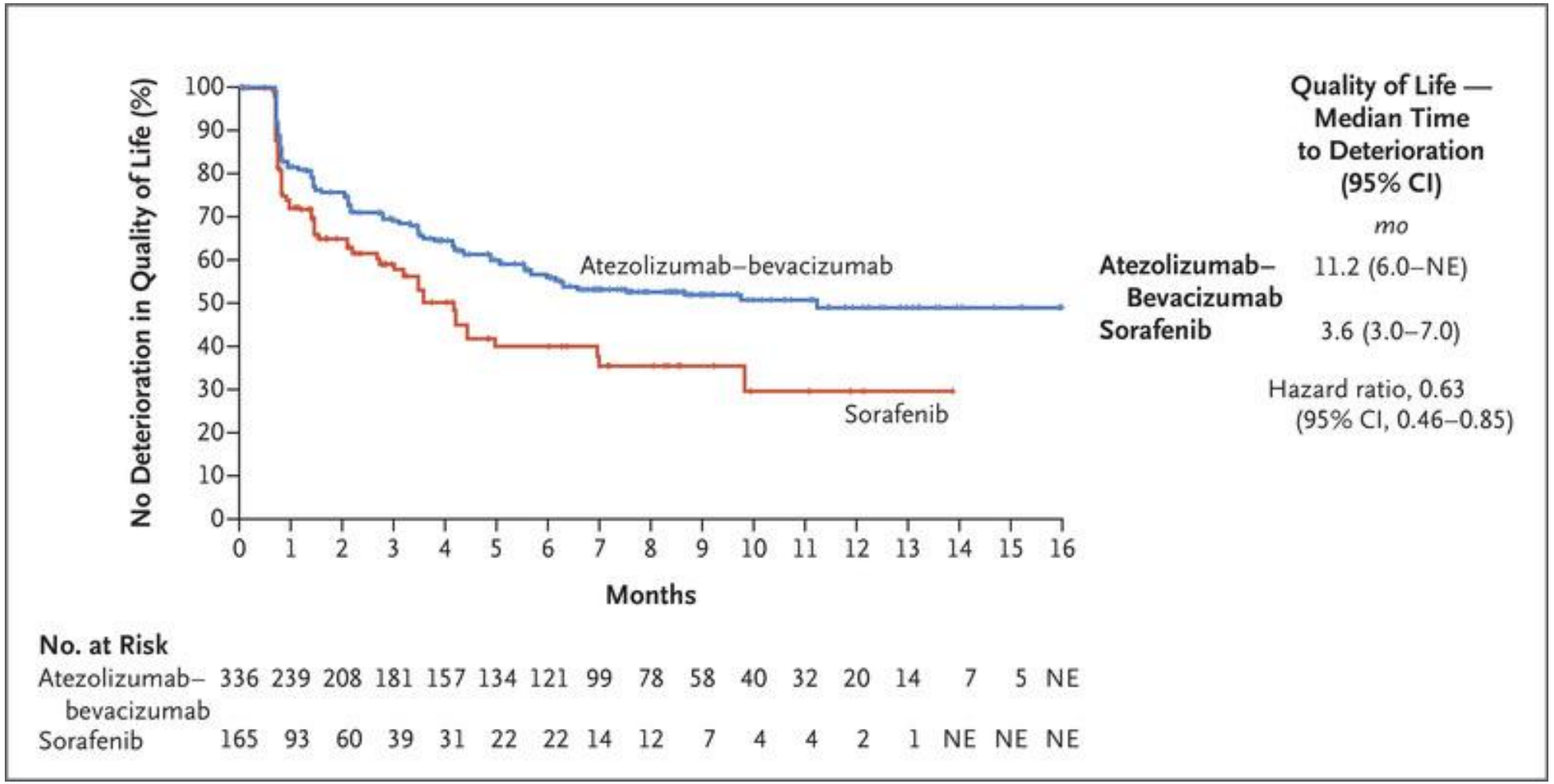
- Serious Adverse Events increased in Atezo/Bev arm slightly (38% vs. 30.8%)
    - No one clear toxicity stands out
    - Less PPE, severe diarrhea, asthenia noted
- Gastrointestinal (usually variceal) bleeding rates consistent with known risk
    - 7% vs 4.5% overall
    - Fatal bleeding/Perforation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

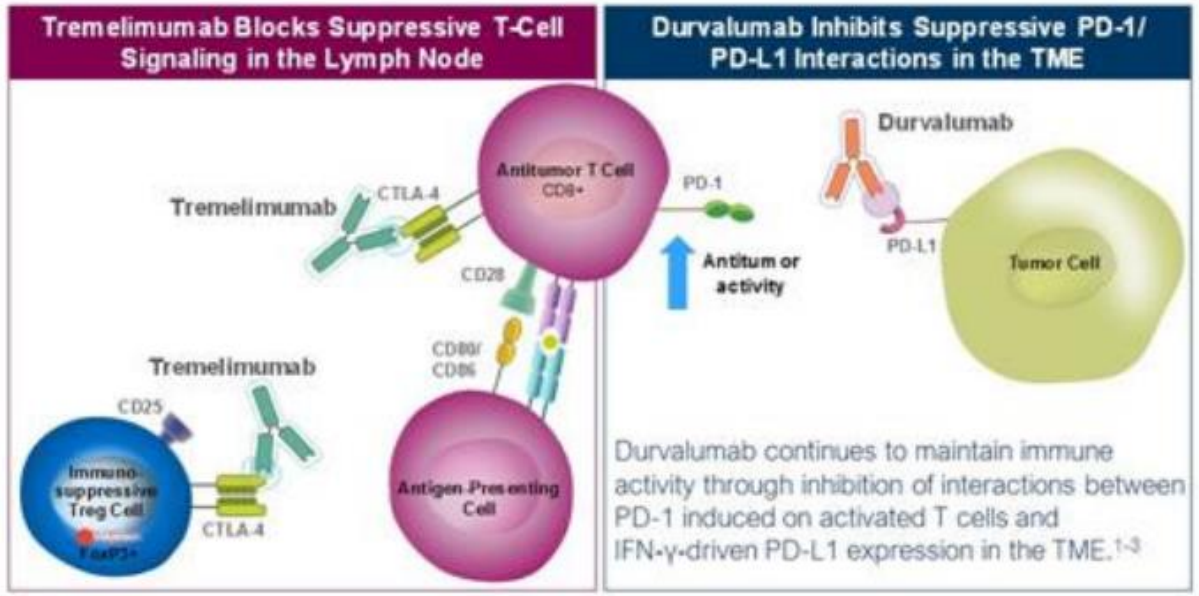
Event	Atezolizumab–Bevacizumab (N=329)		Sorafenib (N=156)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number (percent)			
Hypertension	98 (29.8)	50 (15.2)	38 (24.4)	19 (12.2)
Fatigue	67 (20.4)	8 (2.4)	29 (18.6)	5 (3.2)
Proteinuria	66 (20.1)	10 (3.0)	11 (7.1)	1 (0.6)
Aspartate aminotransferase increase	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



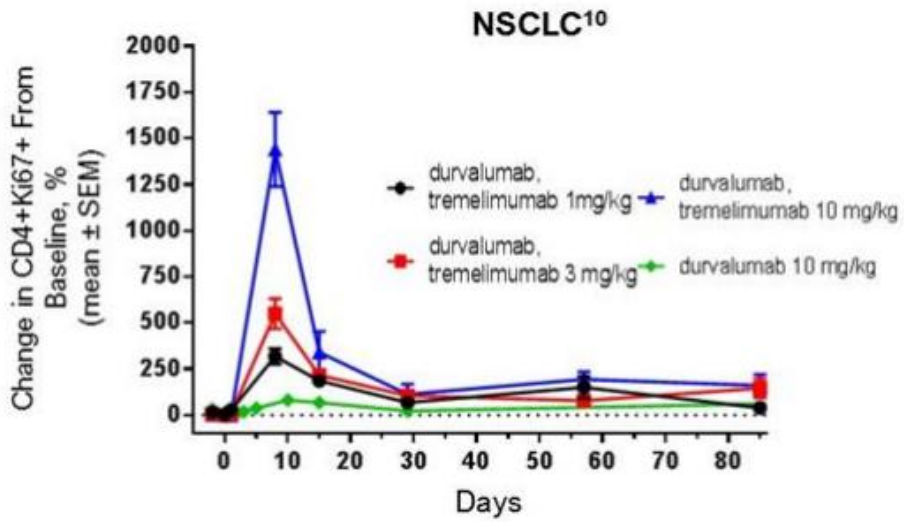
Finn et al. NEJM 2020 382:1894-1905

HIMALAYA TRIAL: STRIDE Regimen
Single Priming Dose CTLA4 + Continued αPD-1



Primary strategy with anti-CTLA4

Increased activity with higher doses of anti-CTLA4 combined with anti-PD-1/PD-L1



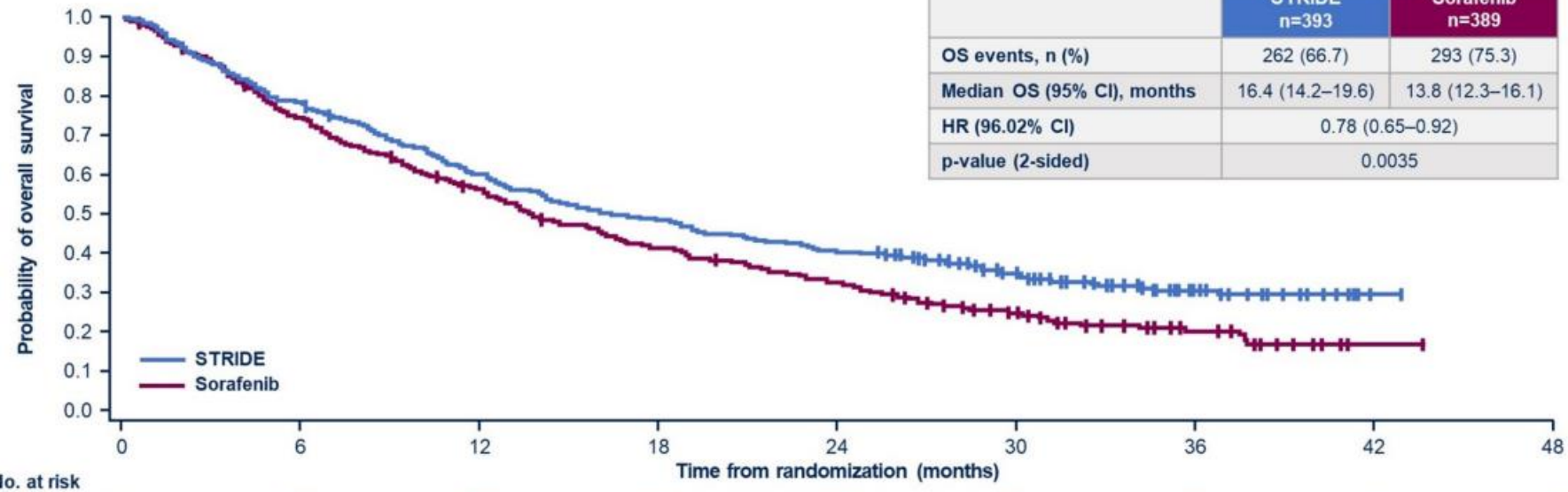
CTLA4 inhibitor leads to initial burst of peripheral T cells in NSCLC and melanoma

1. Antonia et al. Lancet Oncol 2016;299. 2. Souza et al. Cancer Res 2018;abstr CT 104.

Phase III HIMALAYA Study: 1st Line Durvalumab/Tremelimumab vs Sorafenib

Primary objective: overall survival for STRIDE vs sorafenib

	STRIDE n=393	Sorafenib n=389
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI), months	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (96.02% CI)	0.78 (0.65–0.92)	
p-value (2-sided)	0.0035	



No. at risk								
STRIDE	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for STRIDE and 32.23 (95% CI, 30.42–33.71) months for sorafenib.
CI, confidence interval; HR, hazard ratio; OS, overall survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

ORR 20.1% vs 5.1%
DCR 60.1% vs 60.7%
~20% required steroids
Did not allow for main PV invasion

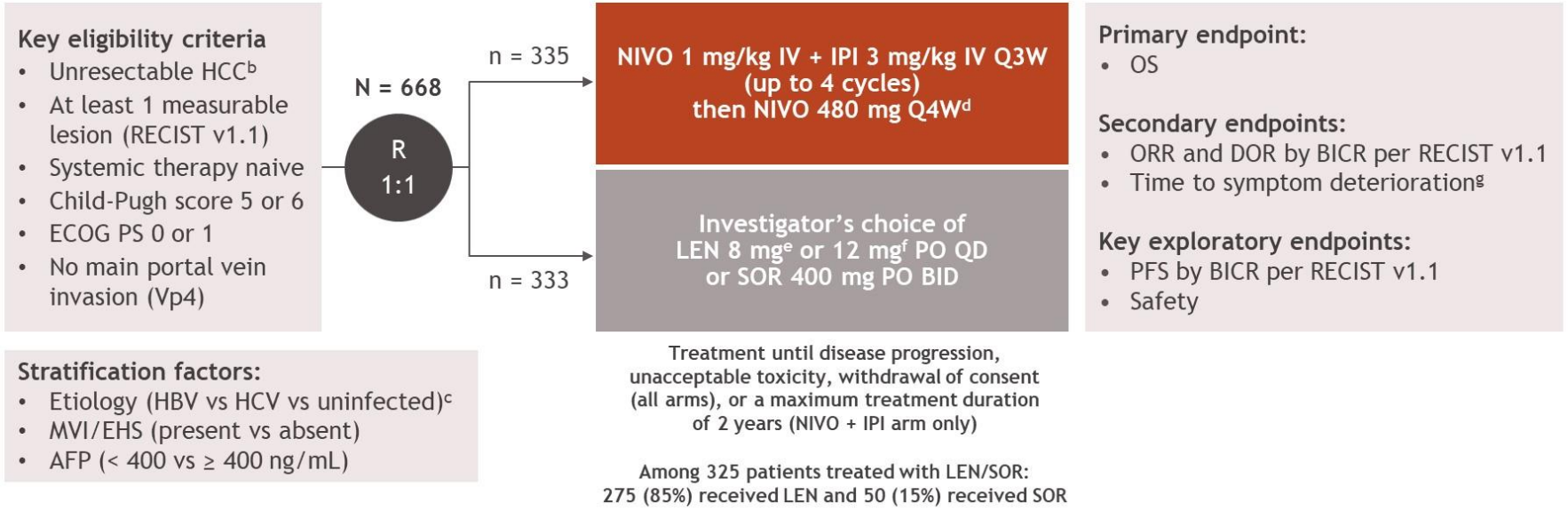
FDA Approved First-Line Option: Single dose Tremelimumab → ongoing Durvalumab q28 days

Abou-Alfa et al. J Clin Oncol 2022;40:suppl 379. GI ASCO 2022 Oral Presentation

New First Line Data from ASCO 2023 (under FDA Review)

CheckMate 9DW study design

- CheckMate 9DW is a global, phase 3, randomized, open-label study of NIVO in combination with IPI compared with LEN or SOR as 1L treatment in patients with unresectable HCC[a]



- At data cutoff (January 31, 2024), median (range) follow-up[h] was 35.2 (26.8-48.9) months

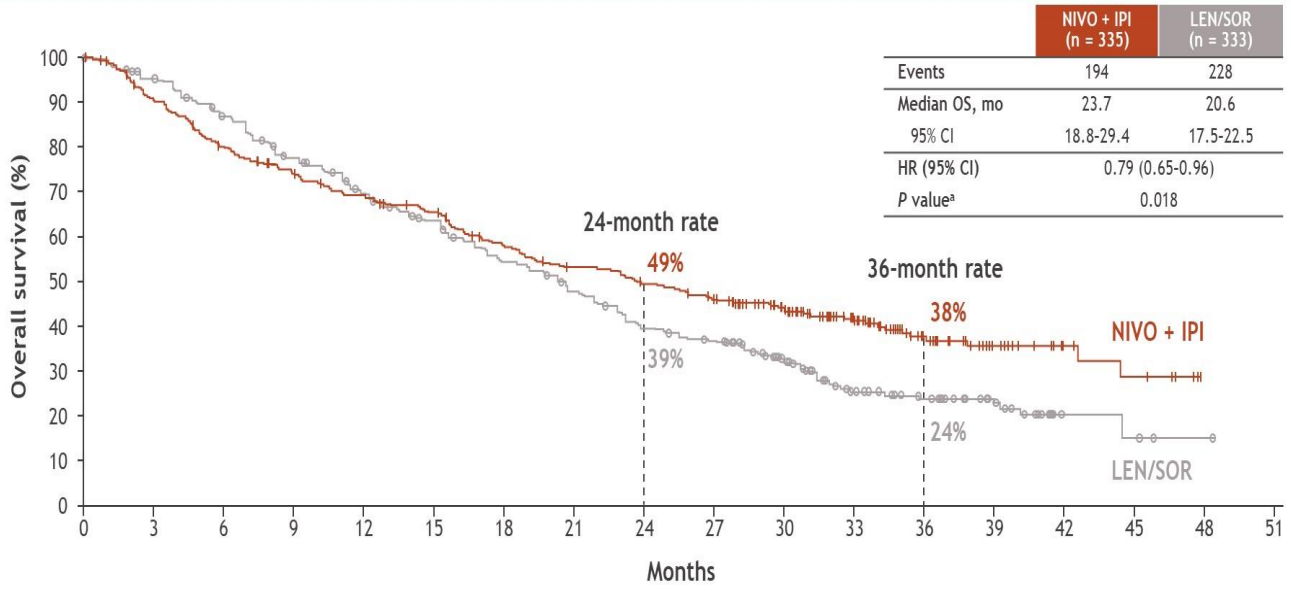
[a]ClinicalTrials.gov: NCT04039607. [b]Disease not eligible for, or progressive disease after, curative surgical and/or locoregional therapies. [c]Based on central lab serology results for stratification purpose. [d]Minimum of 1 dose of NIVO + IPI is required before proceeding to NIVO monotherapy. [e]If body weight < 60 kg. [f]If body weight ≥ 60 kg. [g]HCS subscale score of the FACT-Hep. [h]Time between randomization date and cutoff date.

Galle et al. J Clin Oncol 2024;42:suppl 17 LBA4008. GI ASCO 2024 Oral Presentation

Checkmate 9DW Data: 1L Nivo + Ipi

CheckMate 9DW

Overall survival



	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	194	228
Median OS, mo	23.7	20.6
95% CI	18.8-29.4	17.5-22.5
HR (95% CI)	0.79 (0.65-0.96)	
P value[a]	0.018	

No. at risk

NIVO + IPI	335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
LEN/SOR	333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

- Statistically significant and clinically meaningful OS benefit with NIVO + IPI vs LEN/SOR
  - Longer median OS and long-term survival benefit with higher OS rates at 24 and 36 months

Median (range) follow-up, 35.2 (26.8-48.9) months. Median OS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a]Two-sided *P* value from stratified log-rank test. Boundary for statistical significance: *P* value ≤ 0.0257.

6

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
ORR,[a] %	36	13
95% CI	31-42	10-17
P value[b]	< 0.0001	
Best overall response,[a] %		
Complete response	7	2
Partial response	29	11
Stable disease[c]	32	62
Progressive disease	20	14
Not evaluable	12	11
Median TTR (range),[a] mo	2.2 (1.1-11.6)	3.7 (0.6-11.2)

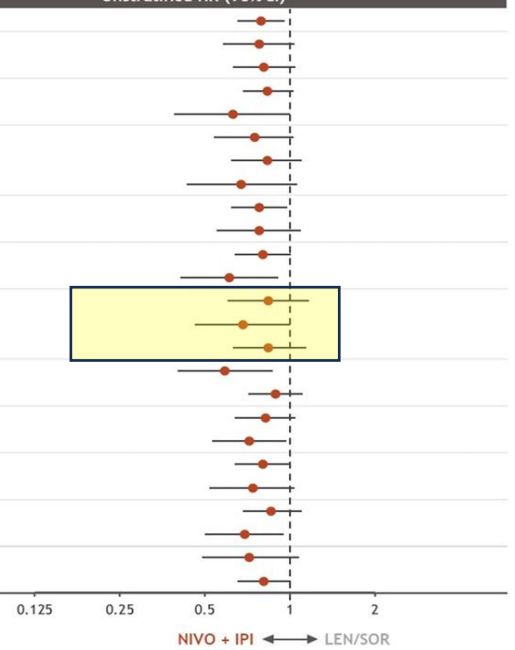
Galle et al. J Clin Oncol 2024;42:suppl 17 LBA4008. GI ASCO 2024 Oral Presentation

Checkmate 9DW: Subgroup Analysis

CheckMate 9DW

Overall survival subgroup analysis

Category	Subgroup	Median OS, mo		Unstratified HR
		NIVO + IPI	LEN/SOR	
Overall (N = 668)		23.7	20.6	0.79
Age, years	< 65 (n = 311)	26.8	22.7	0.78
	≥ 65 (n = 357)	18.8	18.2	0.81
Sex	Male (n = 548)	23.0	21.1	0.83
	Female (n = 120)	26.9	17.3	0.63
Region	Asia (n = 280)	34.0	22.5	0.75
	North America/Europe (n = 289)	22.9	19.8	0.83
	Rest of world (n = 99)	18.8	12.4	0.67
ECOG PS[a]	0 (n = 476)	27.9	22.5	0.78
	1 (n = 191)	16.4	15.3	0.78
Child-Pugh score[b]	5 (n = 517)	27.9	23.2	0.80
	6 (n = 130)	18.3	10.3	0.61
Etiology[c,d]	HBV (n = 229)	23.5	22.3	0.84
	HCV (n = 186)	33.0	17.8	0.68
	Uninfected (n = 243)	19.3	18.4	0.84
MVI[c]	Yes (n = 169)	22.9	15.4	0.59
	No (n = 499)	23.9	21.9	0.89
EHS[c]	Yes (n = 360)	18.7	16.6	0.82
	No (n = 308)	33.5	22.5	0.72
MVI/EHS[c]	Yes (n = 438)	19.4	17.7	0.80
	No (n = 230)	33.5	23.0	0.74
Baseline AFP, ng/ml	< 400 (n = 447)	25.9	23.8	0.86
	≥ 400 (n = 221)	16.4	12.1	0.69
BCLC at baseline[e]	≤ B (n = 177)	33.5	27.1	0.72
	C (n = 488)	20.3	17.8	0.81



Median (range) follow-up, 35.2 (26.8-48.9) months. HRs and 95% CIs from unstratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. HR is not computed for subset categories with 10 or less patients per treatment arm. [a]Not reported, n = 1. [b]Score ≥ 7, n = 20; not reported, n = 1. [c]Per CRF. [d]Reported as having both HBV and HCV as risk factors for HCC, n = 10; these patients did not have active co-infection with HBV and HCV. [e]Unknown, n = 3.

7

Galle et al. J Clin Oncol 2024;42:suppl 17 LBA4008. GI ASCO 2024 Oral Presentation

Cross Trial Comparisons: Current 1L HCC combination options

	Atezo/Bev	STRIDE	Nivo/Ipi
OS	HR 0.58	HR 0.78	HR 0.79*
PFS	HR 0.59	HR 0.9	HR 0.87*
ORR	30% (5.5% CR)	20% (3.1% CR)	36% (7% CR)

* 85% lenvatinib

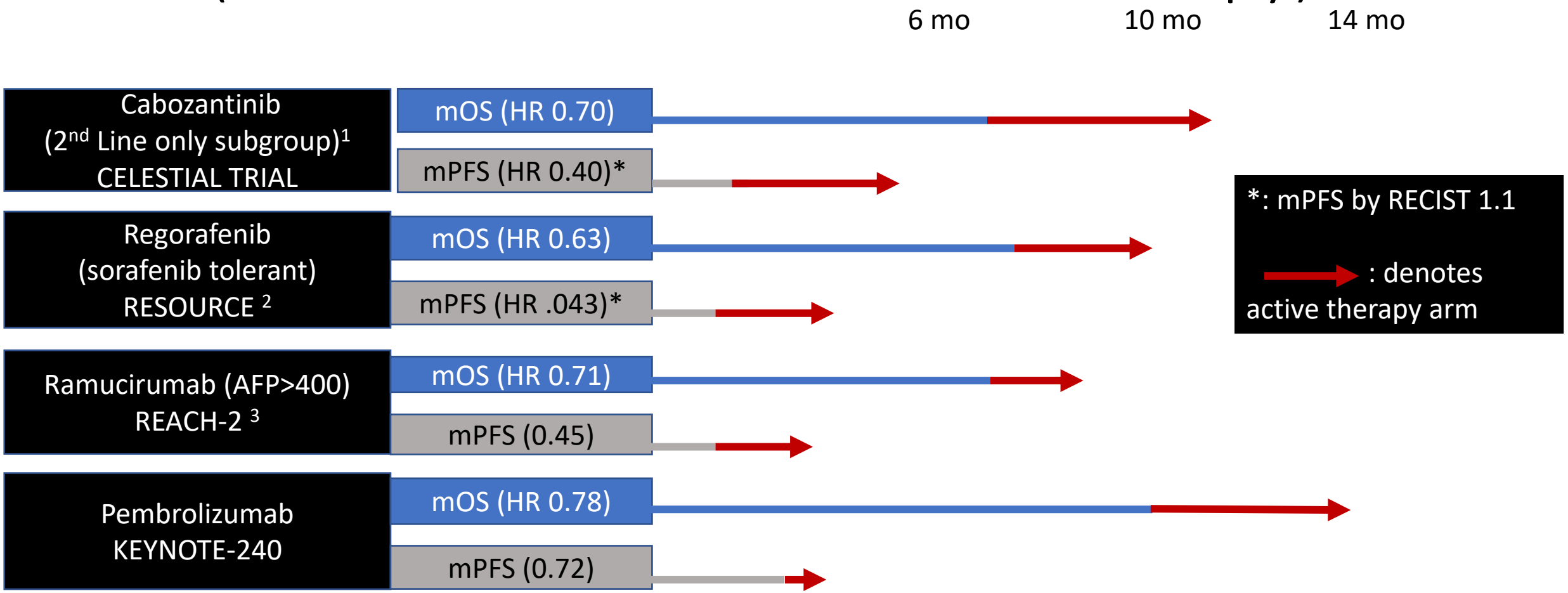
Median OS TKI	13.2 months	13.8 months	20.6 months
Median OS Doublet	NE (updated 19 months)	16.4 months	23.7 months

% Patients requiring steroid rescue	Not reported	20%	30%

SUMMARY: FIRST-LINE SYSTEMIC THERAPY FOR HCC

- Atezolizumab and Bevacizumab OR Durvalumab/Tremelimumab represent the favored FDA approved 1st line therapy for advanced HCC for eligible patients
    - **Atezolizumab/Bevacizumab:**
        - **Patients require EGD for variceal screening and treatment as indicated prior to initiation of therapy**
        - **Note: Trial included patients with Main Portal Vein Invasion**
    - **Single Priming dose Tremelimumab + ongoing Durvalumab:**
        - **Ideal for patients with high risk of bleeding or thrombosis**
        - **Note: Trial did not include patients with Main Portal Vein Invasion**
- Nivolumab and Ipilimumab 1L data under FDA review
    - Higher response rates at the expense of increased immune mediated toxicity
    - Future consideration in patients who cannot receive atezo/bev who have bulky disease and need for palliation or for future neoadjuvant trials
- Sorafenib or Lenvatinib remain additional (albeit inferior) options if contraindications to immune checkpoint inhibition exist
- Data in Child-Pugh B cirrhosis is limited; exact safety and benefit remain unclear

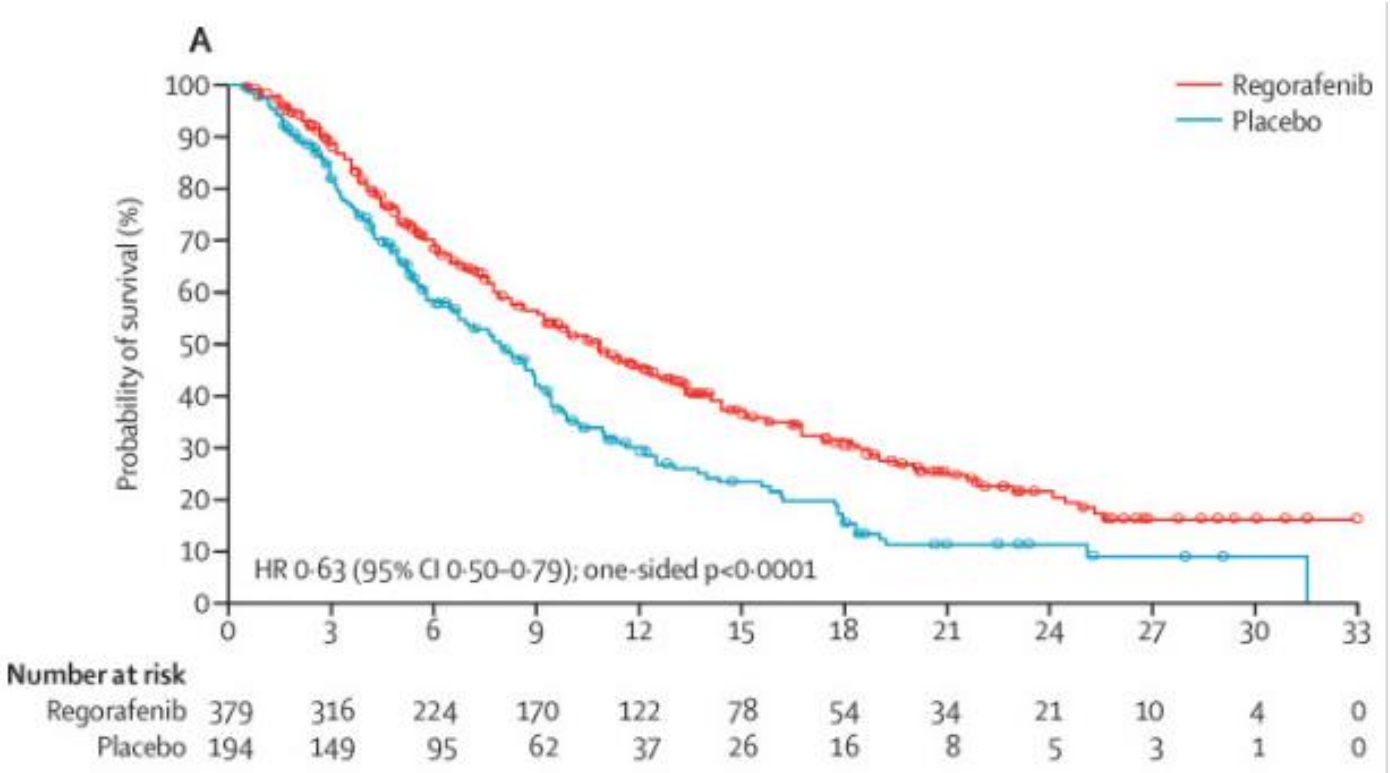
Phase III HCC Trials: Second-Line Therapy Outcomes (data after 1st line Sorafenib Therapy)



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

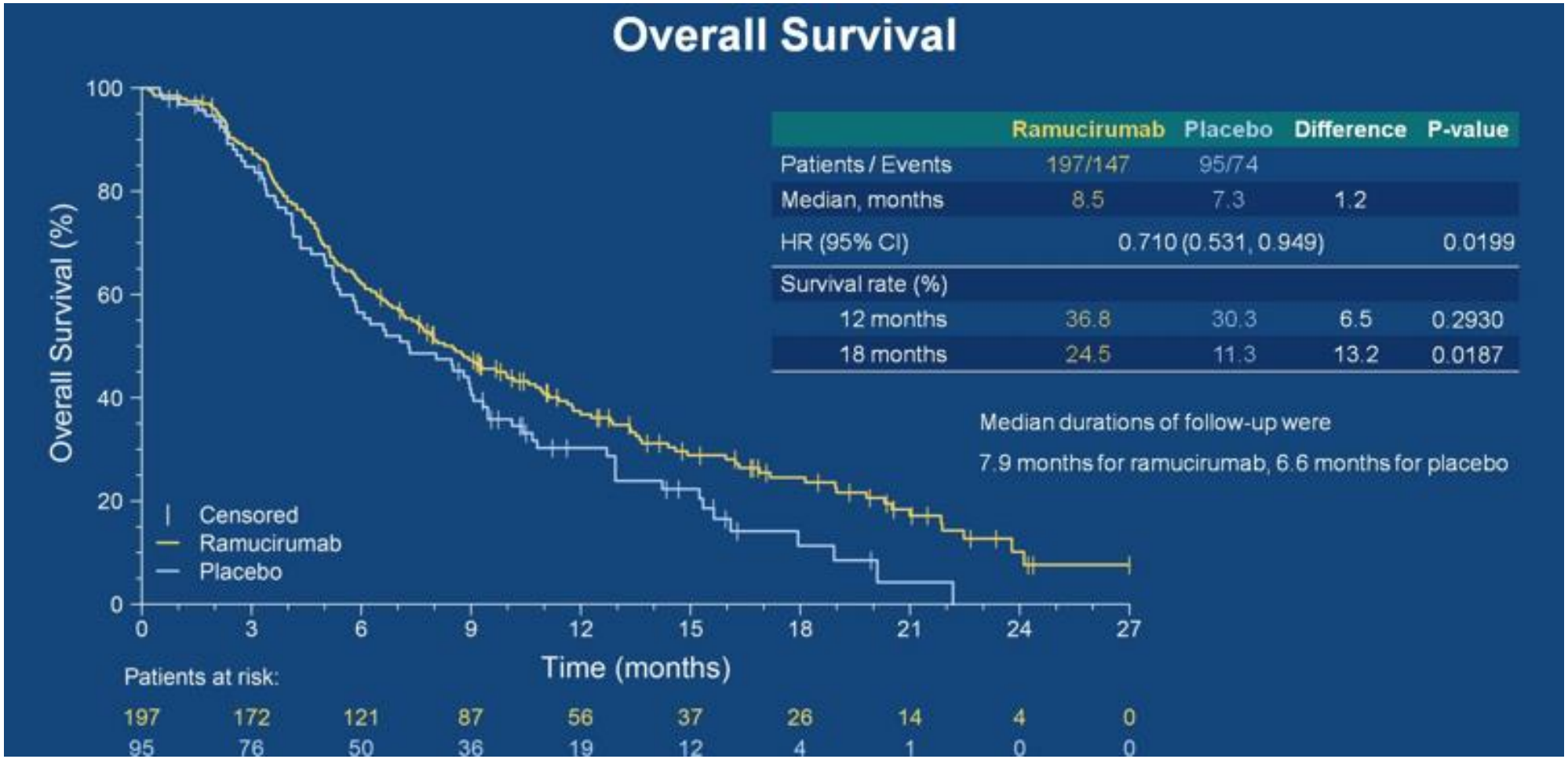
- Multi-TKI with broad activity
  - VEGFR1-3, TIE2
  - FGFR1, PDGFR-B, KIT, RET
  - C-RAF, B-RAF
- Key Patient Characteristics
  - Child Pugh A, ECOG 0-1
  - **Tolerant but progressing on sorafenib**
- Design
  - 2:1 randomized placebo-controlled trial
  - Regorafenib 160 mg days 1-21 monthly
  - Primary 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)



FDA approved as second line therapy if AFP > 400

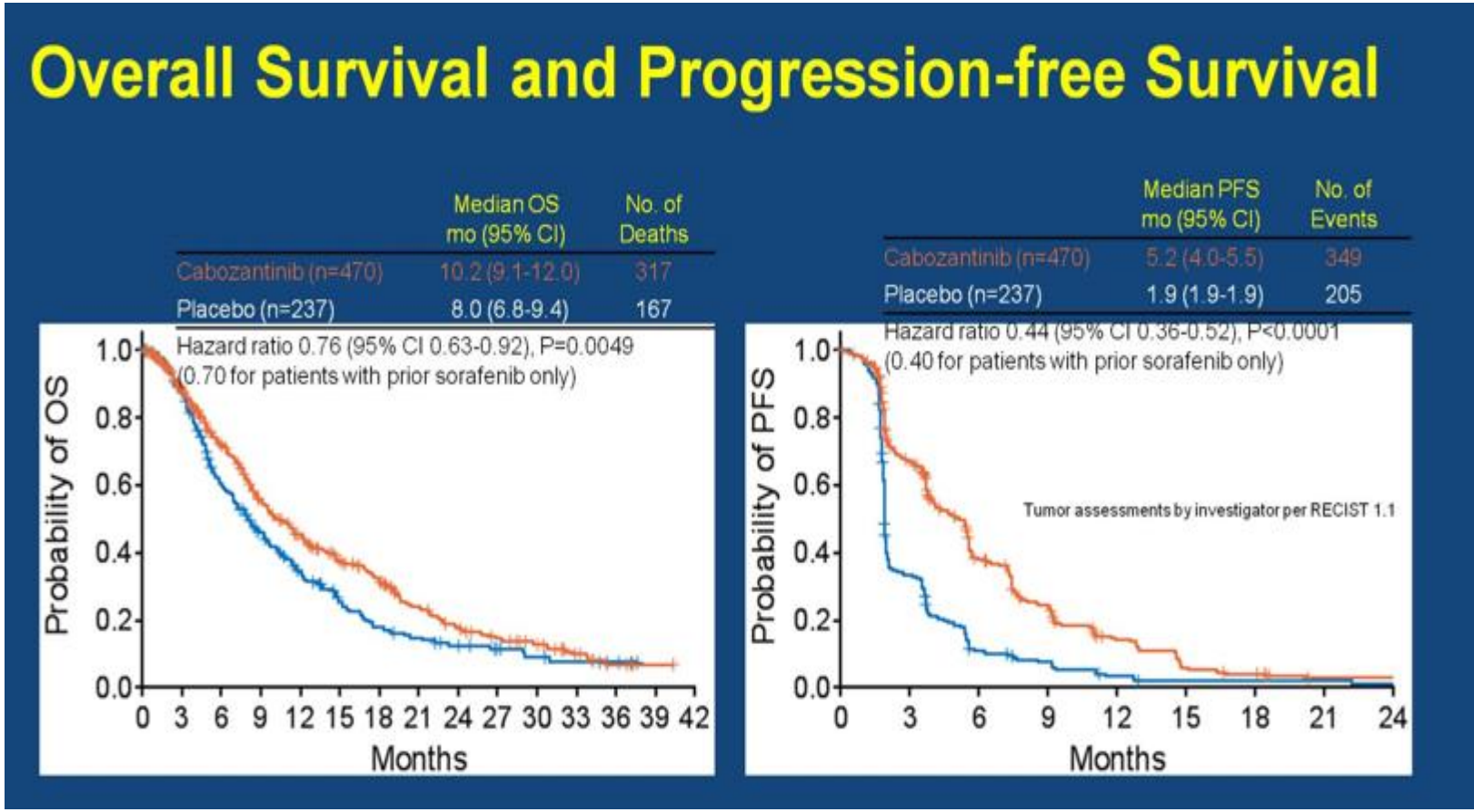
Main Grade 3-4 Toxicities: HTN (12%), Ascites (4%), encephalopathy (3%)

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

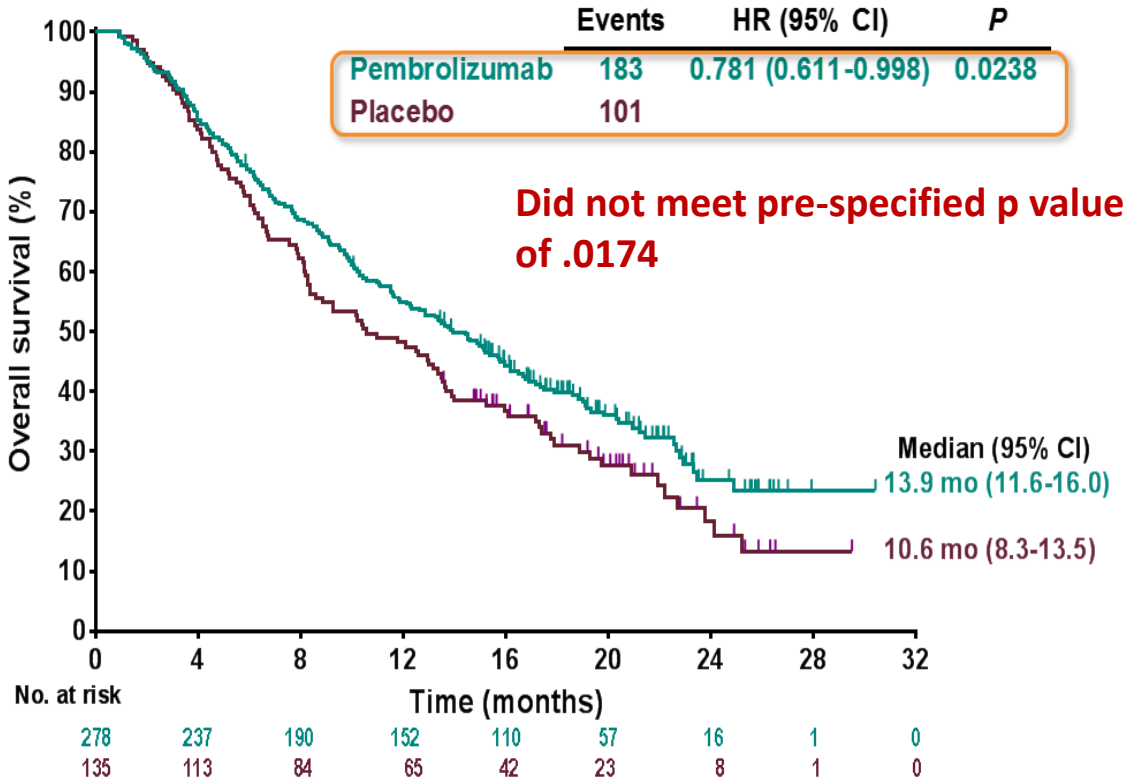
- 707 patients randomized 2:1 against placebo
- 2nd /3rd line therapy; Child-Pugh A
- mOS 10.2 vs 8.0 months (HR .76, p=.005)
- Not selected based upon c-met status
- FDA approved



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

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

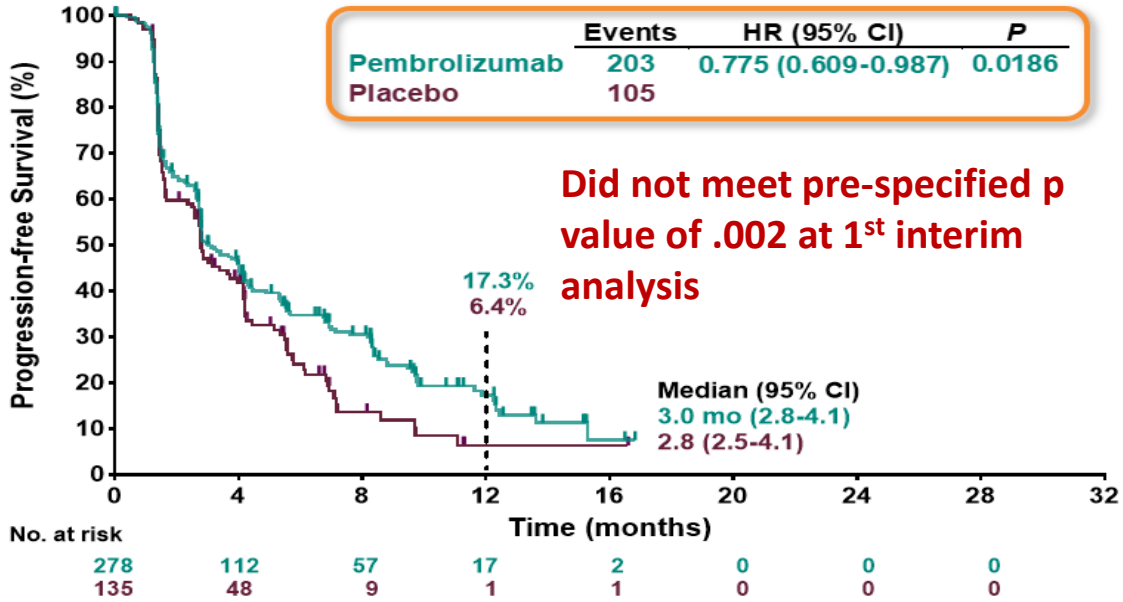
Overall Survival



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

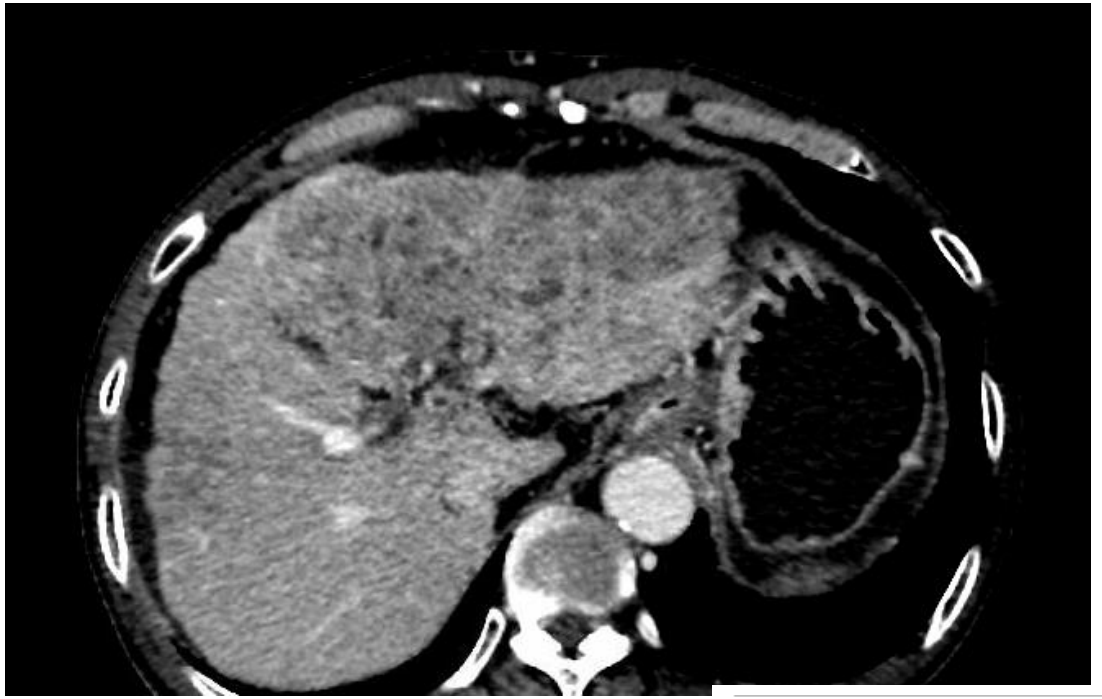
FDA approved 2nd Line irrespective of PD-L1 status despite just missing statistical endpoints in Phase III trial.

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

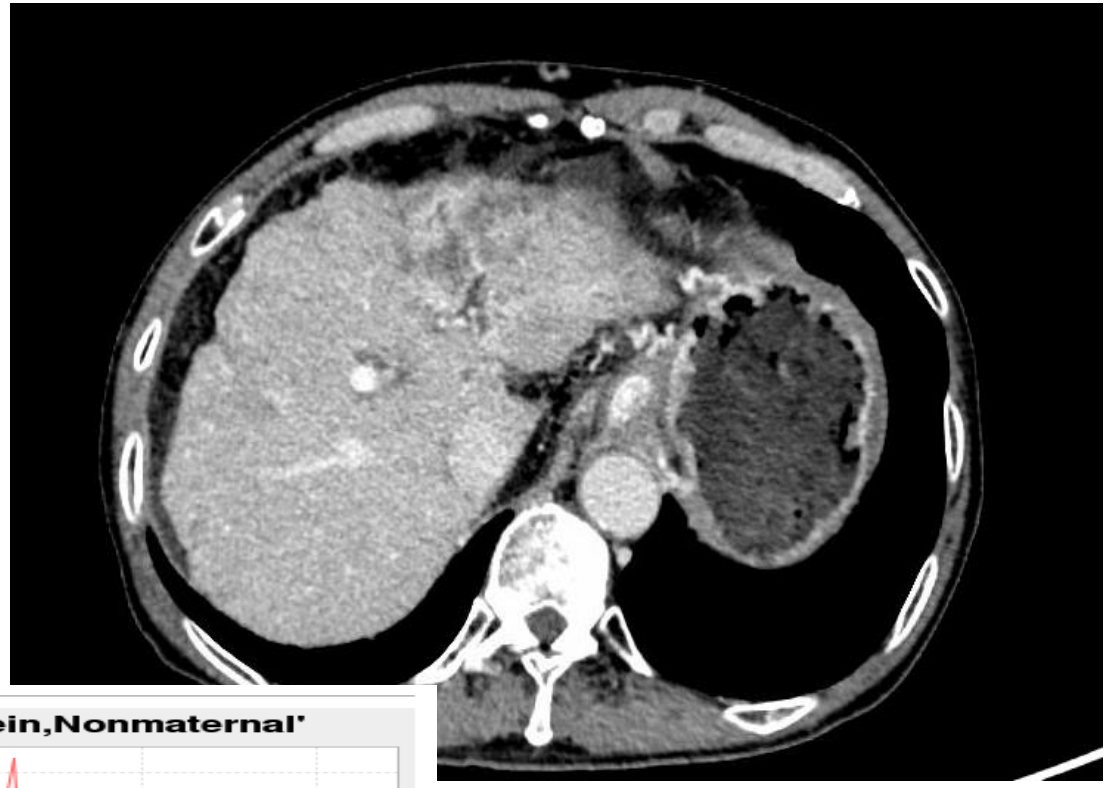
Finn et al. ASCO 2019 JCO 37(suppl; abstr 4004)

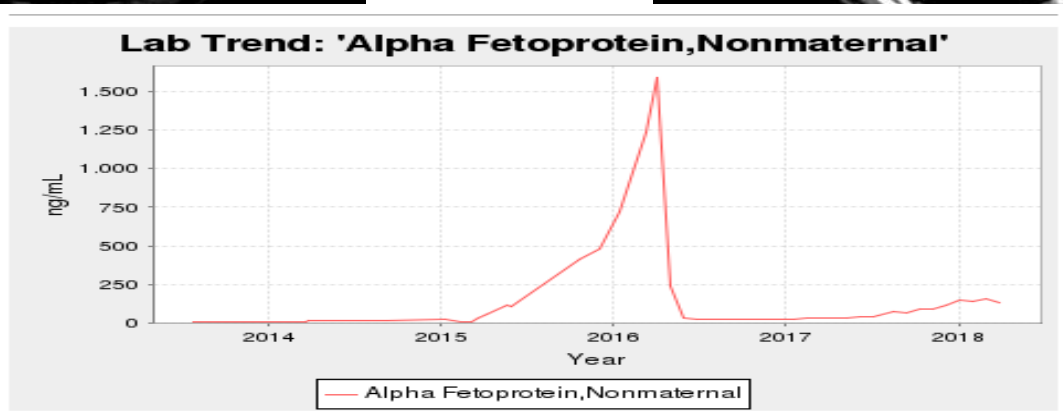
Second-Line Systemic Therapy: Case

Progressive Disease 1 year after sorafenib initiation



Scans 2 years after PD1 inhibition





Current Barcelona Clinic Algorithm

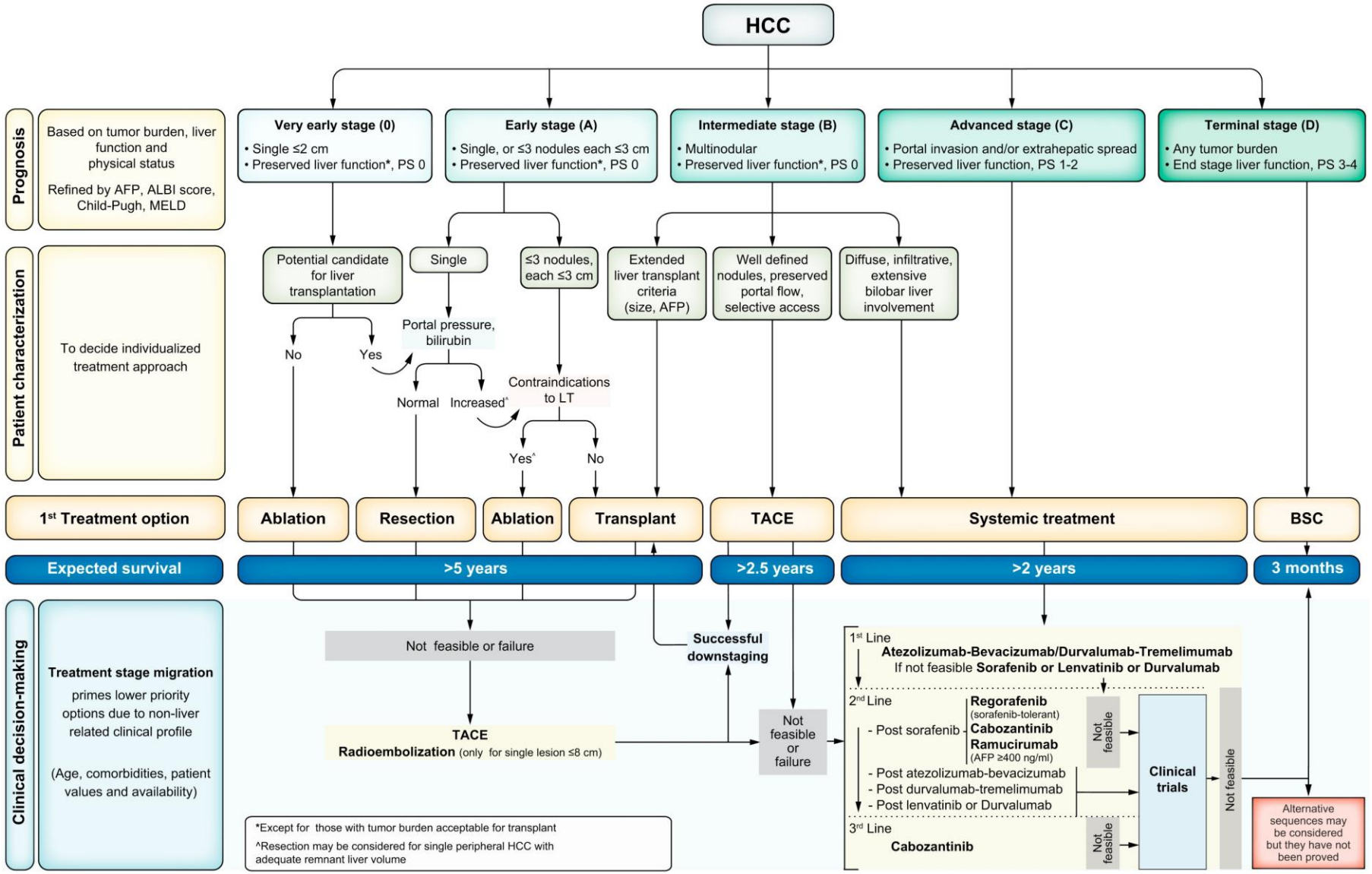


Figure derived from Reig M. et al. J hepatology March 2022 76(3) 681-693

(?) Optimal Systemic Therapy for Advanced Hepatocellular Carcinoma

1st Line	2nd Line	3rd Line	4th Line ???
Atezolizumab + Bevacizumab IMBRAVE150 TRIAL	Sorafenib ??? SHARP/ASIA PACIFIC	Cabozantinib ? CELESTIAL TRIAL	Cabozantinib ??? CELESTIAL TRIAL
Tremelimumab (1 dose) + Durvalumab HIMALAYA TRIAL	Lenvatinib (? Favored) REFLECT TRIAL	Regorafenib (sorafenib tolerant) RESOURCE	
NIVO + IPI Checkmate 9DW trial (under FDA review)	Dual Checkpoint Inhibition ? (if not administered in 1L)	Ramucirumab? (AFP>400) REACH-2	
		Nivolumab + Ipilimumab ??? CHECKMATE 040	

Future Directions/Questions: HCC

- **Optimal sequencing of currently approved agents unclear in advanced disease**
  - **Especially with no significant data to guide next steps after atezo/bev or durva/treme 1st line therapy**
  - **Active space for clinical trials**
- **Role of Integrating Localized Therapy in Advanced Disease?**

Promising local + systemic combination strategies

RTOG 1112: Survival Benefit shown for SBRT added to Sorafenib; ? Benefit with newer systemic options?

Radioembolization + Immunotherapy for intermediate-stage HCC

- **Need new agents for advanced disease**
  - **Adoptive immunotherapy shows promise in early phase trials (AFP, Glypican 3 as targets)**
  - **Radiotheranostics targeting Glypican 3+ tumors**
  - **Back to the drawing board for additional Phase 1 agents**

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

HCC: Final Take-home messages

- Localized therapy and liver transplantation for early-stage disease (BCLC stage A) can be curative
  - Adjuvant data for high risk resected/ablated HCC negative based upon overall survival to date.

- 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/bevacizumab or tremelimumab/durvalumab is standard of care as first-line therapy.
  - Integration of initial local therapy (? SBRT) in select patients may be considered in select patients – more trials to come
  - Nivolumab + Ipilimumab under FDA review as a third option

- 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?) or dual checkpoint blockade after atezo/bev in good performance status patients