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ONCOLOGY

PopQuiz: Managing Patients With Advanced HCC

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This program is supported by an educational grant from Bayer Healthcare Pharmaceuticals.

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Quiz Question 1: The incidence of HCC in the United States has tripled over the past 20 yrs. Which of the following best explains the expected continued increase in HCC incidence in the US?

A. HBV infection

B. HCV infection

C. Diabetes mellitus and obesity

D. Alcohol abuse

E. Aflatoxin ingestion

F. Hemochromatosis

G. Cigarette smoking

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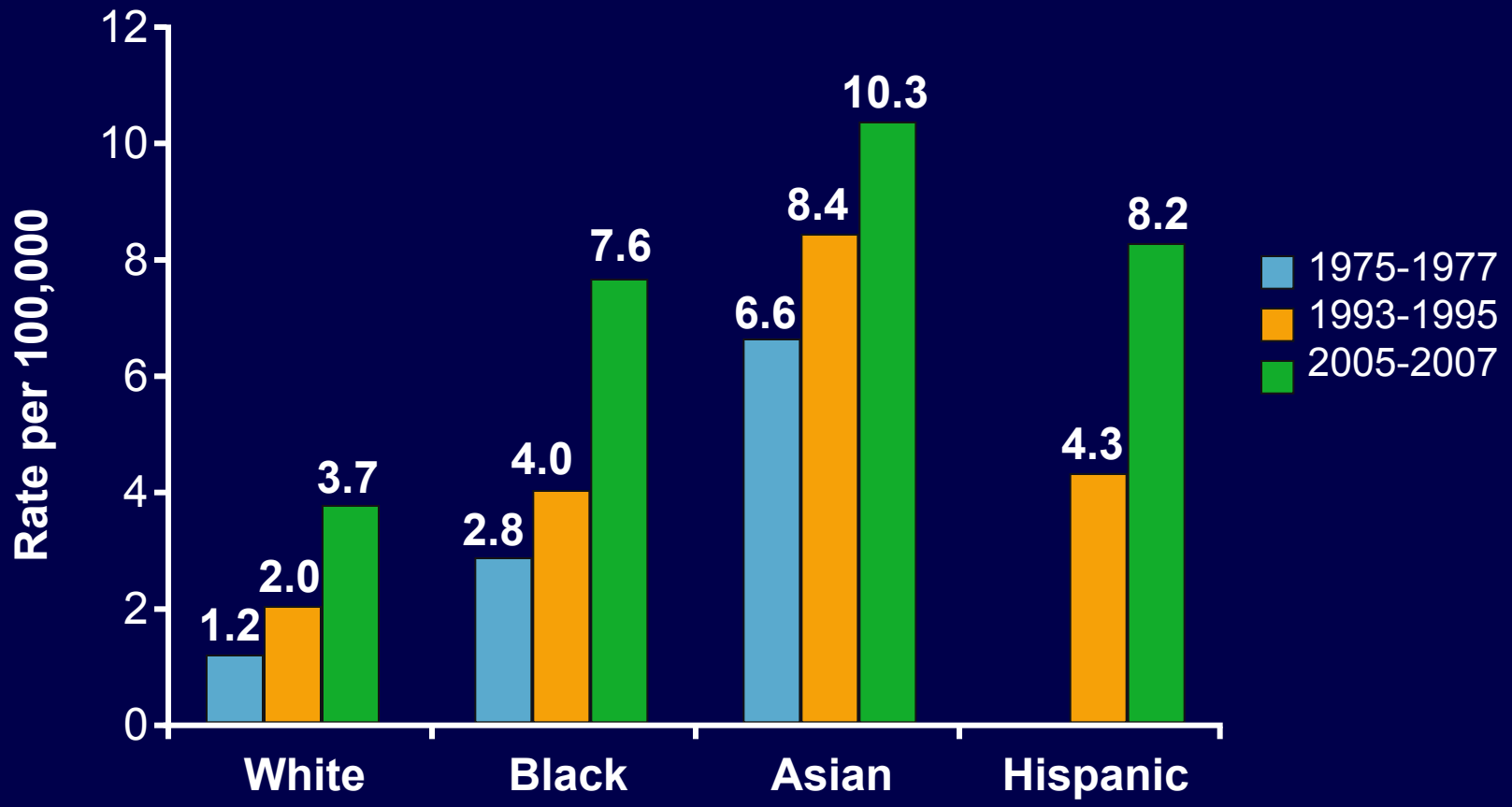
G. Cigarette smoking

Age-Adjusted Incidence of HCC by Race 1975-2007

- Incidence consistently higher among Asian population



Mittal S, et al. J Clin Gastroenterol. 2013;47:S2-S6.

Slide credit: clinicaloptions.com

2016 Estimated US Cancer Deaths

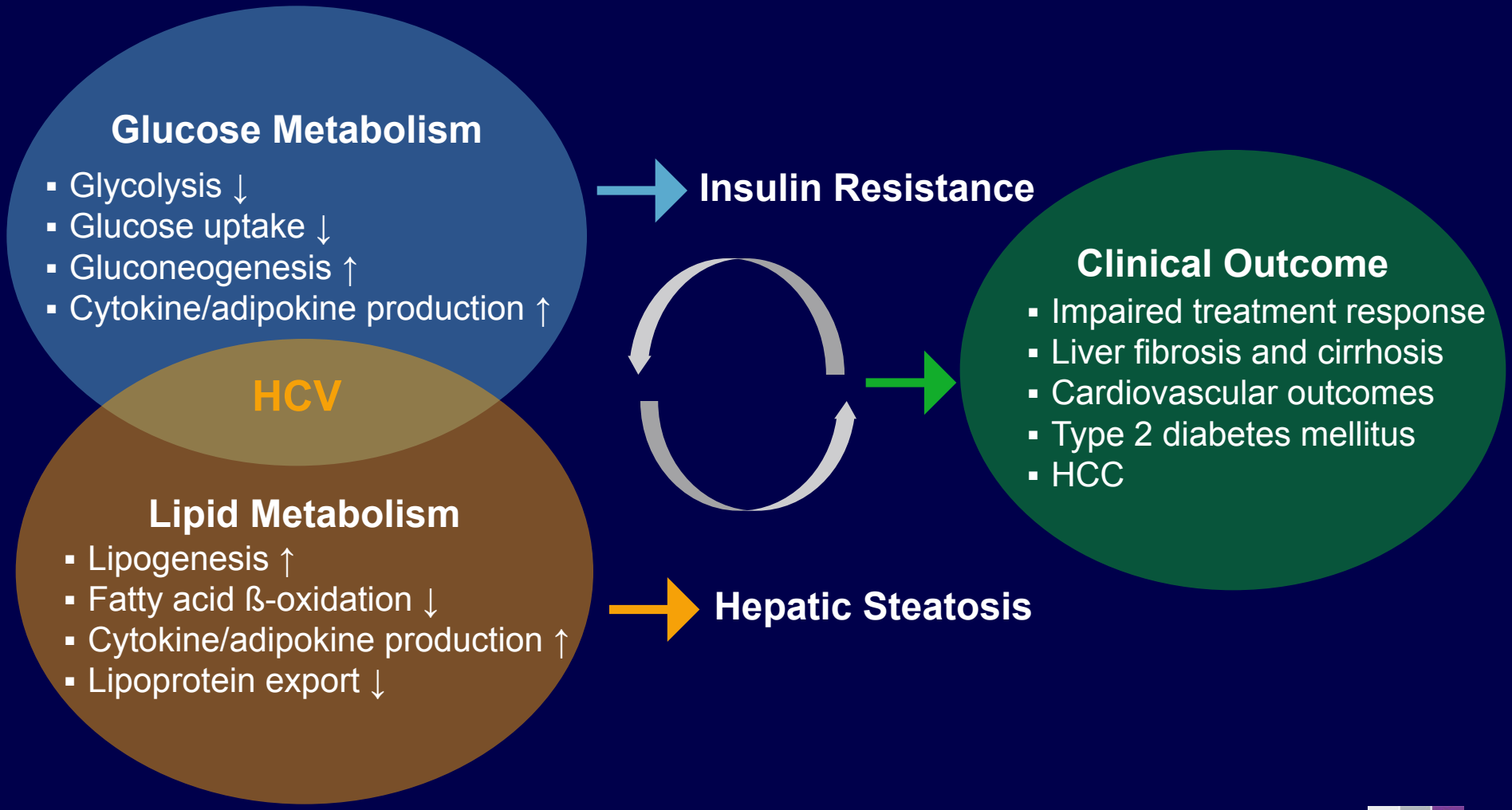
Men 314,290		Women 281,400	
Lung & bronchus	27%	26%	Lung & bronchus
Prostate	8%	14%	Breast
Colon & rectum	8%	8%	Colon & rectum
Pancreas	7%	7%	Pancreas
Liver & intraheptic bile duct	6%	5%	Ovary
Leukemia	4%	4%	Uterine corpus
Esophagus	4%	4%	Leukemia
Urinary bladder	4%	3%	Liver & intrahepatic bile duct
Non-Hodgkin's lymphoma	4%	3%	Non-Hodgkin's lymphoma
Brain/other nervous system	3%	2%	Brain/other nervous system
All other sites	25%	24%	All other sites

- Liver cancer in 2016 estimated as:
  - The #5 cancer killer in men (up from #7 in 2005)
  - The #8 cancer killer in women (not among top 10 in 2005)

Siegel R, et al. CA Cancer J Clin. 2016;66:7-30.

Slide credit: clinicaloptions.com

Association of Glucose and Lipid Metabolism With HCC Pathogenesis



Adapted with permission from Kralj D, et al. Hepatitis C Virus, Insulin Resistance, and Steatosis. J Clin Transl Hepatol 2016;4(1):66-75. doi: 10.14218/JCTH.2015.00051.

Slide credit: clinicaloptions.com

Case: Diagnosis of HCC

- 62-yr-old man referred to your clinic with history of self-administered tattoos
- Saw a television ad about HCV and decided to see his physician; found to be positive for HCV
- Screening MRI: splenomegaly, hepatic nodularity consistent with cirrhosis, and 2.6-cm lesion in right lobe of liver that showed rapid arterial enhancement with significant washout on delayed images

Quiz Question 2: What further testing should be done in order to make the diagnosis of HCC?

A. Biopsy for histologic examination

B. AFP first; if normal, proceed to biopsy

C. CEA or CA19-9 to rule out other histologies

D. No further testing

E. CT scan or ultrasound to further examine vascular characteristics

Quiz Question 2: What further testing should be done in order to make the diagnosis of HCC?

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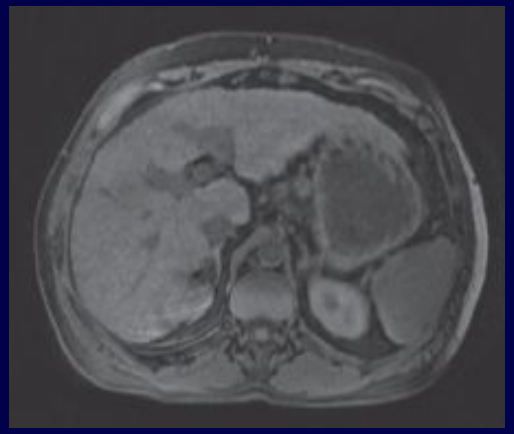
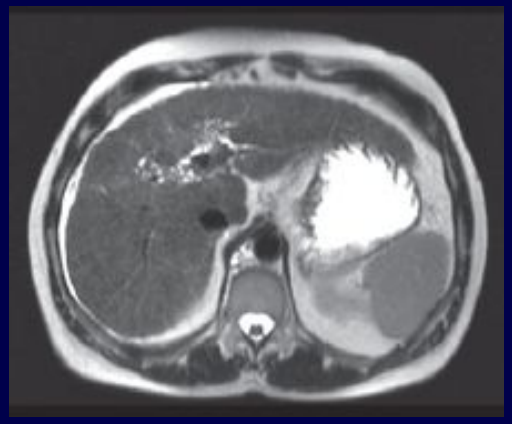
Diagnosis of HCC by MRI Imaging

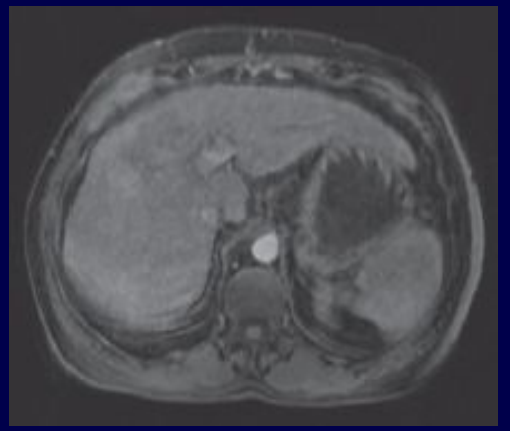
T1 image: isointense tumor



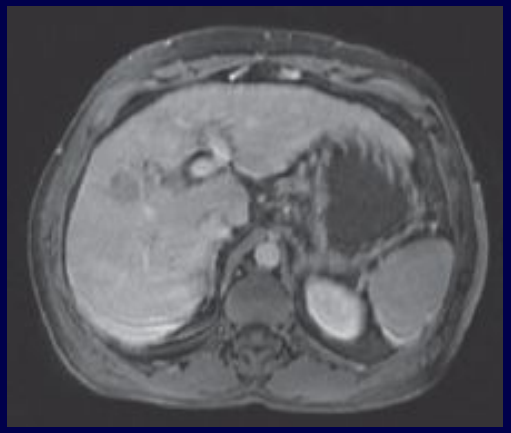
T2 image: hyperintense tumor



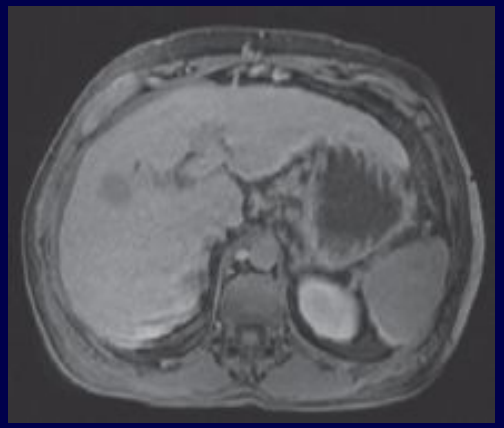
T1 arterial phase: arterial enhancement



T1 portal phase: rapid portal venous phase washout



T1 20-min delayed image: hypointense tumor



Baird AJ, et al. J Med Imaging Radiat Oncol. 2013;57:314-320.

Slide credit: clinicaloptions.com

Case: Management of Large Solitary HCC

- A 32-yr-old woman recently emigrated from Shanghai infected with HBV since childhood
- Upon evaluation for a new job, she is found to have abnormal liver transaminases
  - Follow-up imaging shows a 6-cm well-circumscribed lesion within the left lobe of her liver with vascular characteristics consistent with HCC; no stigmata of cirrhosis are noted
- Serum bilirubin, albumin, platelets, and INR are normal, and AFP is elevated at 1769 ng/mL
- CT of the torso shows no evidence of other lesions

Quiz Question 3: Which of the following is the optimal next step in the management of this pt?

A. Biopsy of the lesion

B. Full evaluation for potential transplantation

C. Follow the lesion to determine the rate of growth

D. Immediate resection when feasible

E. Chemoembolization or radioembolization

F. Local treatment to the mass to reduce the size followed by resection

Quiz Question 3: Which of the following is the optimal next step in the management of this pt?

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F. Local treatment to the mass to reduce the size followed by resection

Curative Treatments

Resection

- Noncirrhotics
  - Choice of therapy
- Cirrhotics
  - Reserve for CTP A
  - Avoid R hepatectomy
- Best for solitary HCC
- Only 5% to 15% eligible
- Survival
  - 1 yr: 95%
  - 3 yrs: 85%
  - 5 yrs: 50%
- Recurrence
  - 5 yrs: 70%

Ablation

- Effective when ≤ 3 cm
- Multiple modalities
  - Thermal
  - Chemical
- Minimally invasive
- Survival
  - 1 yr: 90%
  - 3 yrs: 75%
  - 5 yrs: 60% to 70%
- Recurrence
  - 5 yrs: 70%

Transplant

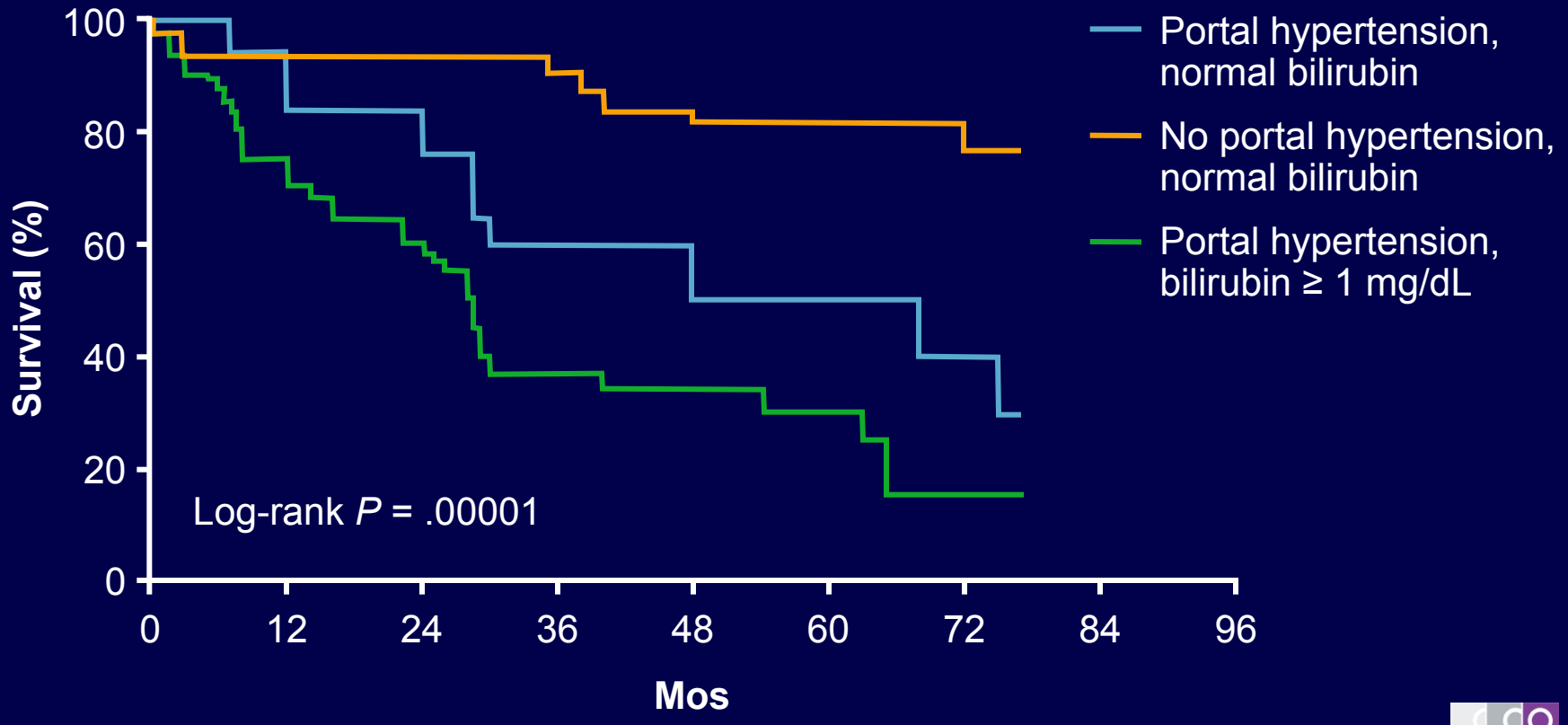
- Cures both cirrhosis and HCC
- MELD exception
  - Milan criteria
  - Downsizing
- Demand > supply
- Survival
  - 1 yr: 91%
  - 2 yrs: 75%
  - 5 yrs: > 70%
- Recurrence
  - 5 yrs: < 15%

NCCN Guidelines. Hepatobiliary Cancers. Version 2.2016.

Slide credit: clinicaloptions.com

Survival After Resection for HCC

- Of 1265 pts with HCC evaluated, only 35 were ideal candidates for resection



Llovet JM, et al. Hepatology. 1999;30:1434-1440.

Slide credit: clinicaloptions.com

Case: Multifocal HCC With Esophageal Varices

- A 59-yr-old man with a history of alcohol abuse, who quit drinking 11 yrs ago, presents to the ED with hematemesis
- On evaluation, he is found to have bleeding esophageal varices, ascites, splenomegaly, and a platelet count of 61,000
- MRI shows 2 lesions—2.7 cm and 2.1 cm—within the right lobe. These both show peripheral enhancement on the arterial phase with central washout and peripheral enhancement on delayed images
  - Splenomegaly, ascites, and small perigastric varices are also seen

Quiz Question 4: Once he has been treated, stabilized, and discharged, further management of this pt should include which of the following?

A. Referral to liver service for possible cadaveric or live donor transplantation

B. Referral to hepatobiliary surgery for potential right hepatectomy

C. Immediate chemoembolization

D. Thermal or cryoablation to the 2 individual lesions

E. PET scan to look for metastatic lesions

F. Systemic treatment with sorafenib

Quiz Question 4: Once he has been treated, stabilized, and discharged, further management of this pt should include which of the following?

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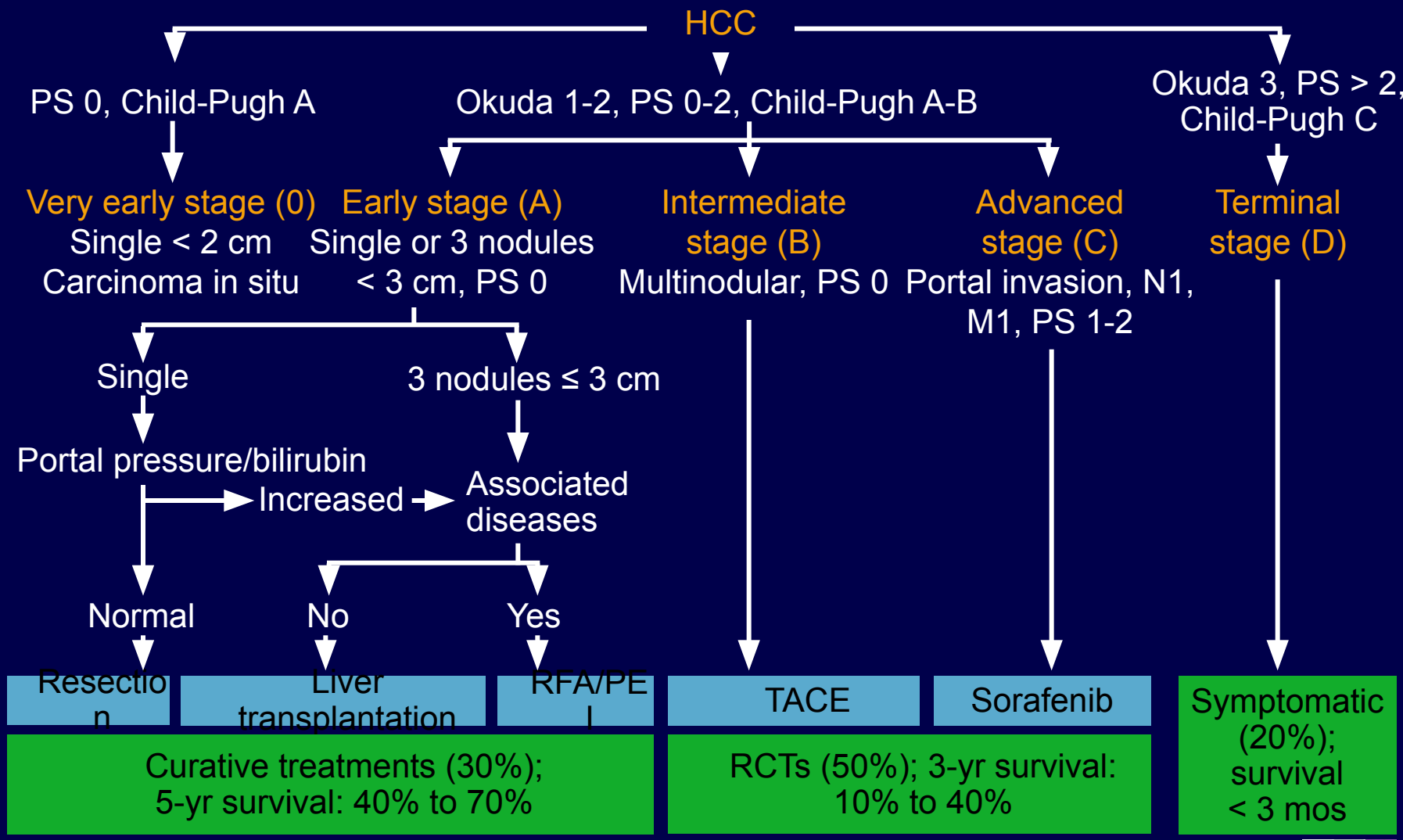
BCLC Staging and Treatment Strategy



Llovet JM, et al. J National Cancer Inst. 2008;100:698-711.
Subramaniam S, et al. Chin Clin Oncol. 2013;2:33.

Slide credit: clinicaloptions.com

Case: Large Solitary HCC With Preserved Liver Function

- A 71-yr-old asymptomatic man with a history of hemochromatosis goes to a new gastroenterologist and is found to have a 7-cm mass in the right lobe consistent with HCC
- He is not a surgical candidate because of significant cardiovascular disease but has relatively well-preserved hepatic function

Quiz Question 5: Which of the following treatment options would be most suitable for this pt?

A. Radiofrequency ablation

B. Stereotactic body radiotherapy

C. Chemoembolization or radioembolization

D. Referral for potential liver transplantation

E. Sorafenib

Quiz Question 5: Which of the following treatment options would be most suitable for this pt?

A. Radiofrequency ablation

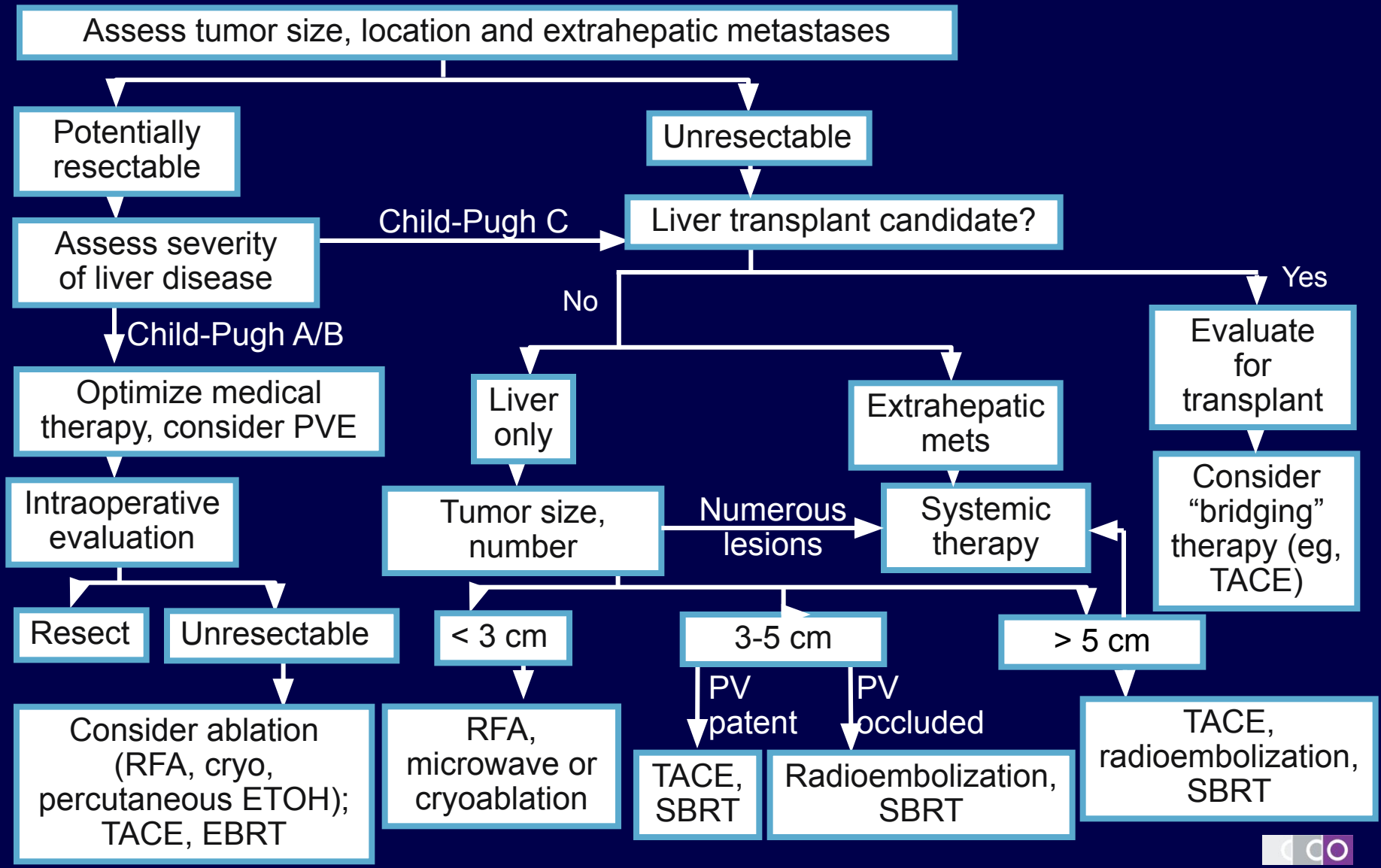
B. Stereotactic body radiotherapy

C. Chemoembolization or radioembolization

D. Referral for potential liver transplantation

E. Sorafenib

Current HCC Treatment Algorithm



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Case: Newly Diagnosed Metastatic HCC

- A 68-yr-old man with PMH significant only for diabetes presents with back pain and is found to have a lytic lesion at T11
- CT scan of the torso shows multiple metastases up to 3 cm in size throughout both lungs and an 8-cm lesion within the liver. Several bony metastases are also seen
- ECOG PS is 1 and lab tests are relatively well preserved
- Liver biopsy demonstrates well-differentiated HCC. The pt strongly desires systemic therapy following the completion of radiation to his back. He refuses to participate in clinical trials

Quiz Question 6: Which of the following is the best choice for this pt?

A. Sorafenib

B. Gemcitabine plus cisplatin or oxaliplatin

C. Nivolumab

D. Capecitabine

E. Best supportive care

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C. Nivolumab

D. Capecitabine

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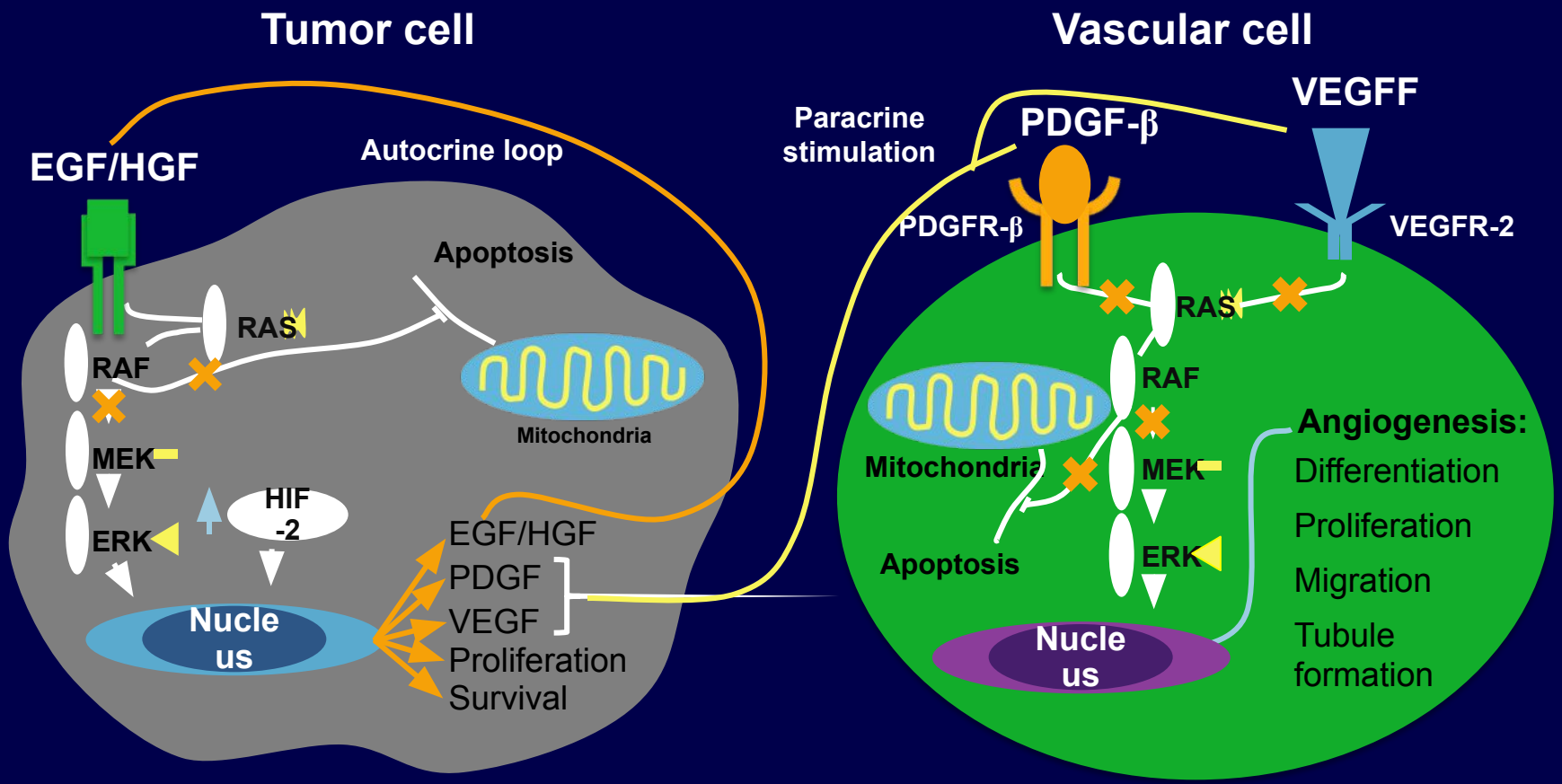
Targeted Therapy: Sorafenib

Multispecific, blocks tyrosine kinase receptors regulating tumor proliferation and angiogenesis



Wilhelm SM, et al. Cancer Res. 2004;64:7099-7109.
Wilhelm SM, et al. Mol Cancer Ther. 2008;7:3129-3140.

Slide credit: clinicaloptions.com

Phase III SHARP Study: Sorafenib vs Placebo in Advanced HCC

Stratified by macroscopic vascular invasion and/or extrahepatic spread; ECOG PS; geographical region

Pts with advanced HCC, Child-Pugh A, at least 1 untreated lesion, ECOG PS ≤ 2, no previous systemic treatment, life expectancy ≥ 12 wks (N = 602)

Sorafenib
400 mg PO BID, continuous dosing
(n = 299)

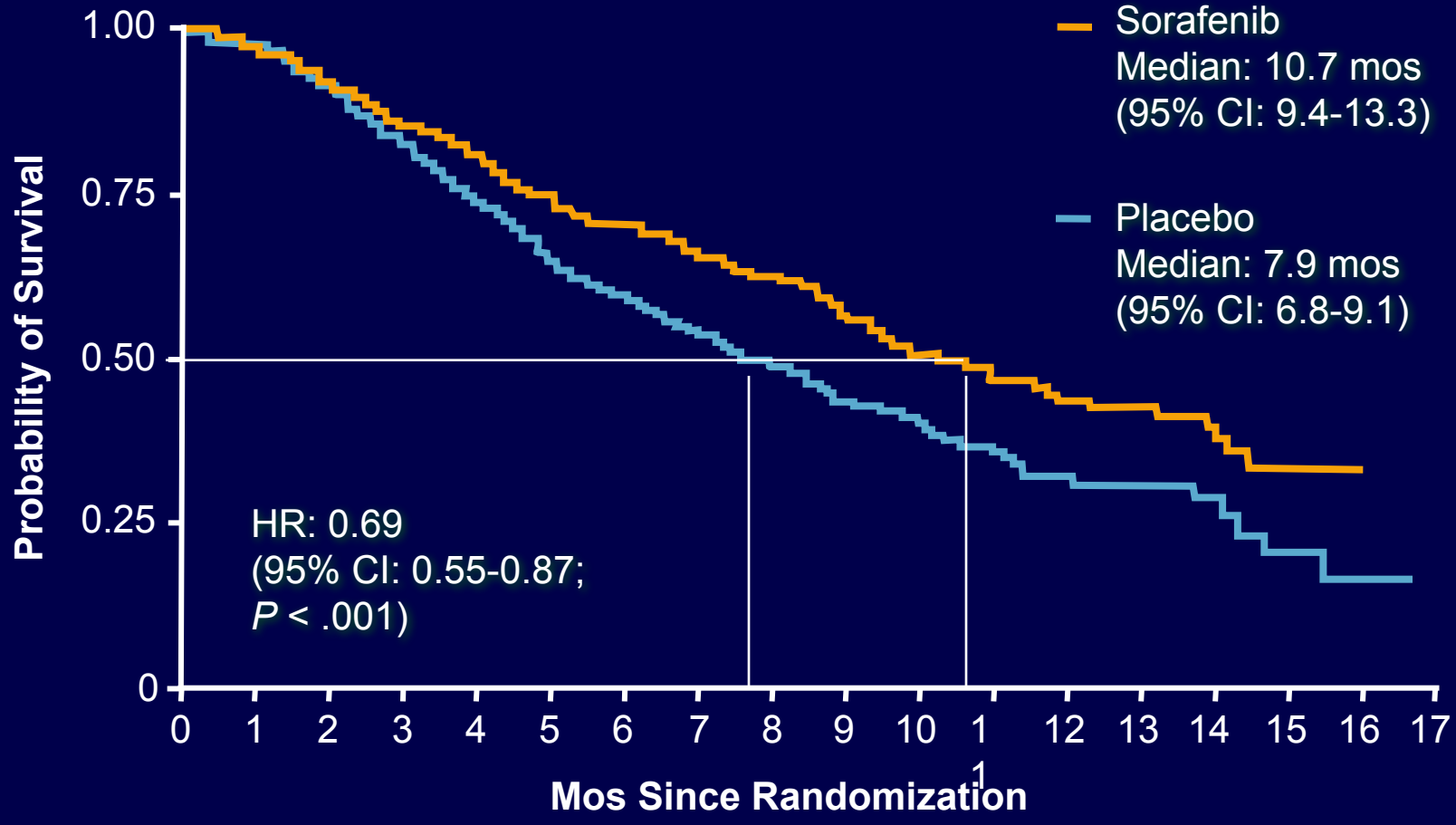
Placebo
2 tablets PO BID, continuous dosing
(n = 303)

- Primary endpoints: OS, time to symptomatic progression
- Secondary endpoint: TTP (independent review), disease control rate, safety

Llovet JM, et al. N Engl J Med. 2008;359:378-390.
Kane RC, et al. Oncologist. 2009;14:95-100.

SHARP: Overall Survival

- Sorafenib improved OS vs placebo in unresectable HCC



Llovet JM, et al. N Engl J Med. 2008;359:378-390.
Kane RC, et al. Oncologist. 2009;14:95-100.

Slide credit: clinicaloptions.com

SHARP: Treatment-Emergent AEs

TEAEs in ≥ 10% Sorafenib-Treated Pts, %	Sorafenib (n = 297)			Placebo (n = 302)		
	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Any	98	39	6	96	24	8
Constitutional symptoms						
▪Fatigue	46	9	1	45	12	2
▪Weight loss	30	2	0	10	1	0
Dermatology/skin						
▪Rash/desquamation	19	1	0	14	0	0
▪Pruritus	14	< 1	0	11	< 1	0
▪Hand-foot skin reaction	21	8	0	3	< 1	0
▪Dry Skin	10	0	0	6	0	0
▪Alopecia	14	0	0	2	0	0
Gastrointestinal						
▪Diarrhea	55	10	< 1	25	2	0
▪Anorexia	29	3	0	18	3	< 1
▪Nausea	24	1	0	20	3	0
▪Vomiting	15	2	0	11	2	0
▪Constipation	14	0	0	10	0	0
Liver dysfunction	11	2	1	8	2	1
Pain, abdomen	31	9	0	26	5	1

Kane RC, et al. Oncologist. 2009:14;95-100.

Slide credit: clinicaloptions.com

Case: Multifocal HCC With Portal Vein Thrombosis

- A 53-yr-old asymptomatic man without significant past medical history comes in for a checkup. He is worried because his old college roommate, with whom he briefly shared needles, was recently diagnosed with HCV. He also tests positive for HCV
- Screening ultrasound shows two ~ 4-cm lesions within the liver, along with portal vein thrombosis and a small amount of ascites
- AFP is elevated at 845 ng/mL, and his serum bilirubin is 2 x ULN
- This pt is not interested in clinical trials

Quiz Question 7: Which of the following is the optimal treatment choice for this pt?

A. Referral for liver transplantation

B. Sorafenib

C. Microwave ablation

D. Chemoembolization

E. Radioembolization

Quiz Question 7: Which of the following is the optimal treatment choice for this pt?

A. Referral for liver transplantation

B. Sorafenib

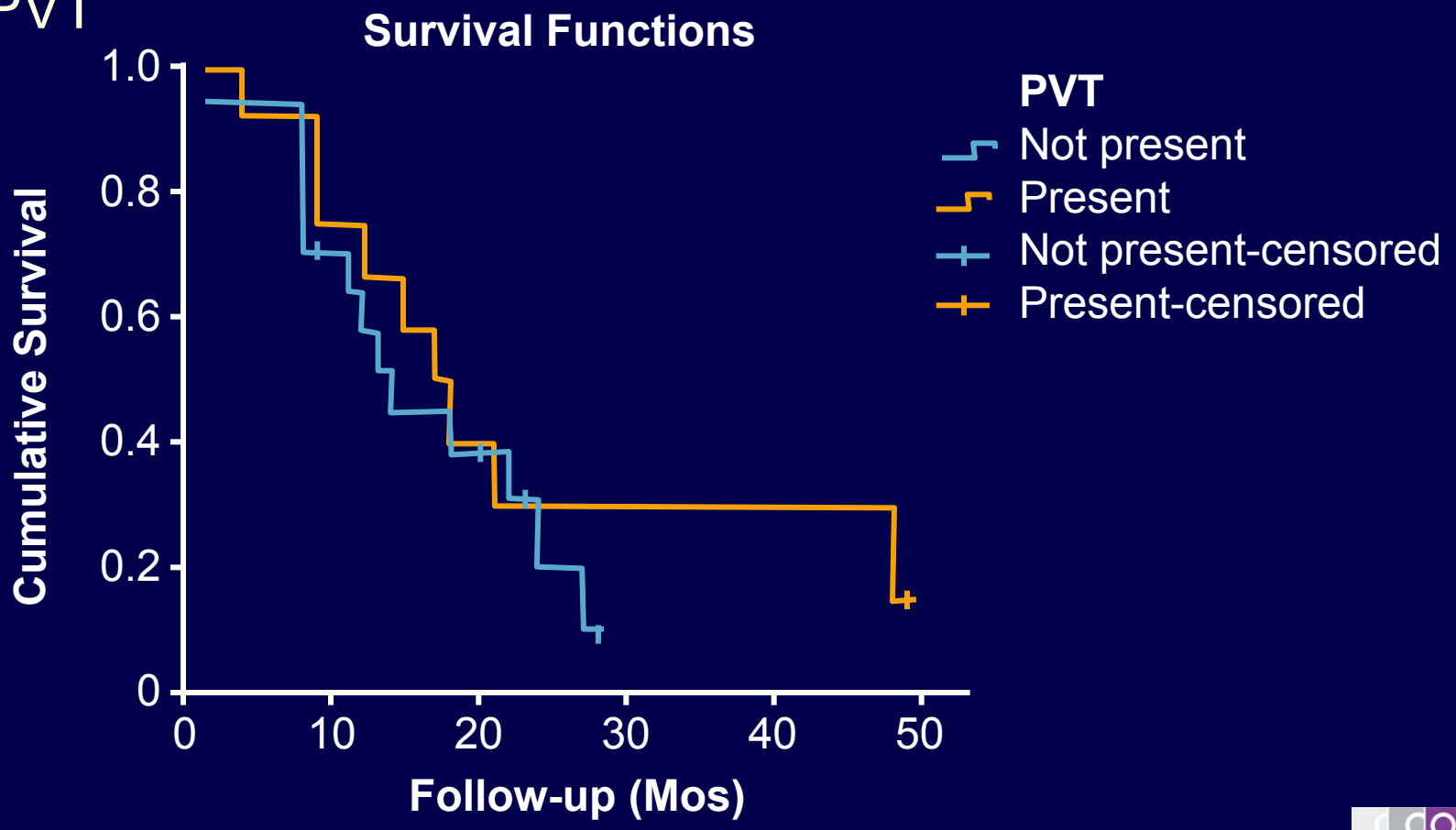
C. Microwave ablation

D. Chemoembolization

E. Radioembolization

Radioembolization in HCC Pts With vs Without Portal Vein Thrombosis

- Radioembolization achieved survival benefit independent of PVT



Ozkan ZG, et al. Cancer Biother Radiopharm. 2015;30:132-138.

Slide credit: clinicaloptions.com

Quiz Question 8: In which situation has adjuvant therapy for HCC been shown to be effective?

A. Sorafenib following surgical resection

B. Sorafenib following chemoembolization

C. Doxorubicin following liver transplantation

D. Sorafenib following radiofrequency ablation

E. Lipiodol I-131 given intra-arterially following resection

F. None of the above

Quiz Question 8: In which situation has adjuvant therapy for HCC been shown to be effective?

A. Sorafenib following surgical resection

B. Sorafenib following chemoembolization

C. Doxorubicin following liver transplantation

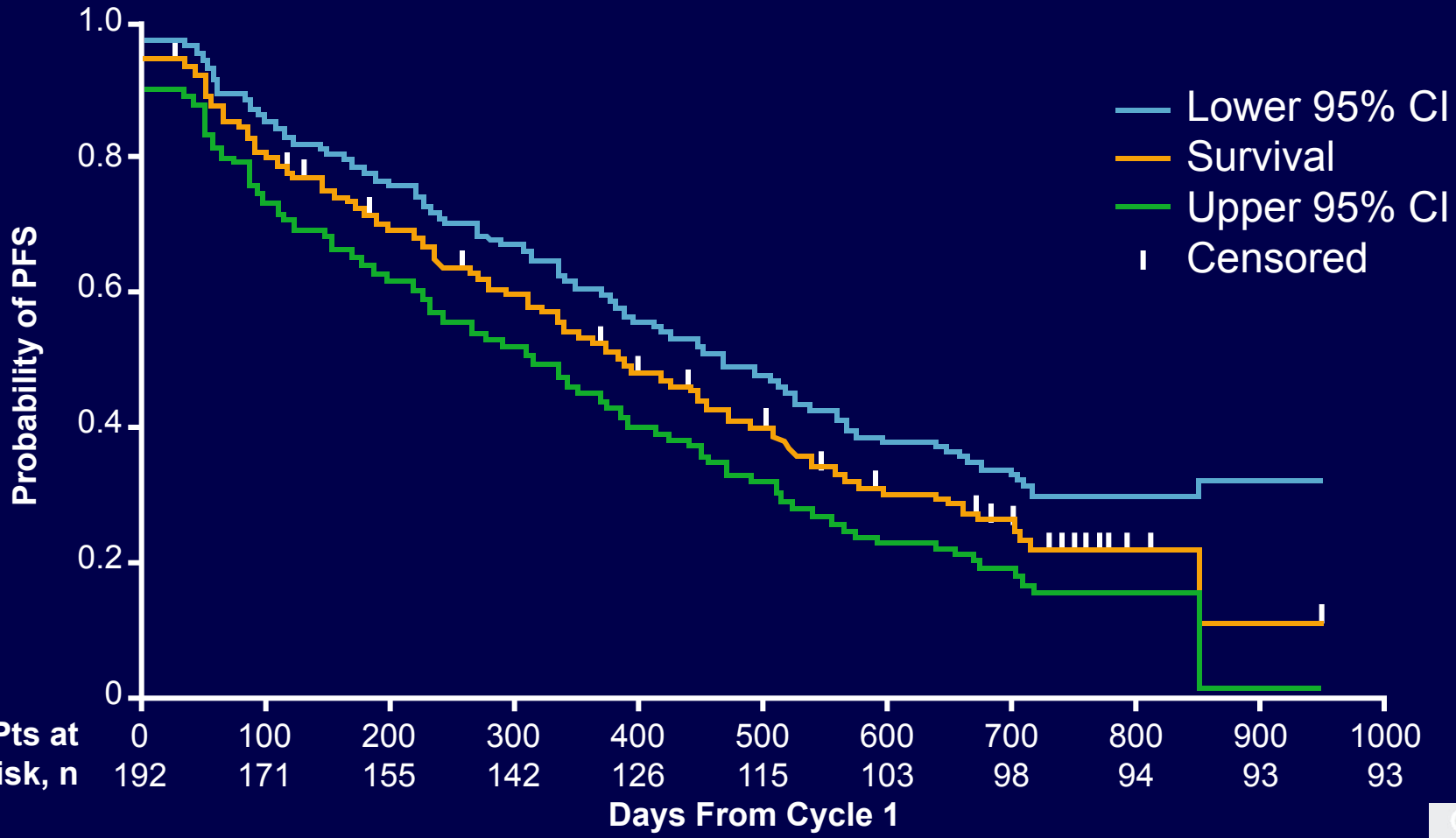
D. Sorafenib following radiofrequency ablation

E. Lipiodol I-131 given intra-arterially following resection

F. None of the above

Phase II START Trial: TACE + Sorafenib in Asian Pts With HCC

- TACE + sorafenib effective and well tolerated in Asian pts with HCC



Chao Y, et al. Int J Cancer. 2015;136:1458-1467.

Slide credit: clinicaloptions.com

Quiz Question 9: Which of the following has demonstrated superior OS in phase III trials when compared with sorafenib in the first-line setting for metastatic HCC?

A. Sunitinib
B. Brivanib
C. Linifanib
D. Erlotinib plus sorafenib
E. Doxorubicin plus sorafenib
F. None of the above

Quiz Question 9: Which of the following has demonstrated superior OS in phase III trials when compared with sorafenib in the first-line setting for metastatic HCC?

A. Sunitinib

B. Brivanib

C. Linifanib

D. Erlotinib plus sorafenib

E. Doxorubicin plus sorafenib

F. None of the above

Phase III First-line Targeted Drug Trials for HCC

Agent	Target	OS vs Sorafenib, Mos	Trial Number
▪ Sunitinib[1]	VEGFR, PDGFR, FLT3, KIT, RET	7.9 vs 10.2	NCT00699374
▪ Brivanib[2]	VEGFR, FGFR	9.5 vs 9.9	NCT00858871
▪ Linafinib[3]	VEGFR, PDGFR	9.1 vs 9.8	NCT01009593
▪ Erlotinib/Sor[4]	EGFR	9.5 vs 8.5	NCT00901901
▪ Doxrubicin/Sor[5]	Topoisomerase II, intercalation	9.3 vs 10.5	NCT01015833
▪ Lenvatinib[6]	VEGFR2, VEGFR3, RET	Ongoing	NCT01761266
▪ Nivolumab[6]	PD-1	Ongoing	NCT02576509

References listed in slide notes.

Slide credit: clinicaloptions.com

Case: Management Following Progression on Sorafenib

- The pt described above (a 68-yr-old diabetic man with HCC metastatic to the lungs and bone) was treated with sorafenib
- After slowly advancing the initial dose, he was able to tolerate a dose of 400 mg twice daily for the first 3 wks; because of fatigue, the dose was reduced to a total of 600 mg/day
- After a total of 8 wks, he was re-evaluated because of worsening fatigue, decreased appetite, and an AFP that had risen from 1589 to 4623 ng/mL while on therapy
- CT scan showed that his lung metastases had increased in both size and number, with the largest now being 4.5 cm. The solitary liver lesion increased from 8 to 9 cm in longest diameter, and the bone lesions appeared stable. He had no pain or shortness of breath and felt that most of his complaints stemmed from the sorafenib; ECOG PS remained at 1

Quiz Question 10: Which of the following agents was shown in a phase III trial to improve OS in pts who have disease progression following treatment with sorafenib?

A. Nivolumab
B. Everolimus
C. Brivanib
D. Regorafenib
E. Ramucirumab
F. None of the above

Quiz Question 10: Which of the following agents was shown in a phase III trial to improve OS in pts who have disease progression following treatment with sorafenib?

A. Nivolumab

B. Everolimus

C. Brivanib

D. Regorafenib

E. Ramucirumab

F. None of the above

Phase III Second-line Targeted Drug Trials for HCC

Agent	Target	OS vs PBO, Mos	Trial Number
▪ Regorafenib[1-3]	VEGFR, RET, PDGFR, FGFR, BRAF	**10.6 vs 7.8**	NCT01774344
▪ Ramucirumab[2,3]	VEGFR2	9.2 vs 7.6	NCT01140347
▪ Everolimus[2,3]	mTOR	7.6 vs 7.3	NCT01035229
▪ Tivantinib[2,3]	c-MET	Ongoing	NCT01755767
▪ Brivanib[2,3]	VEGFR, FGFR	9.4 vs 8.2	NCT00825955
▪ Cabozantinib[2,3]	c-MET	Ongoing	NCT01908426
▪ Tivantinib[2,3]	c-MET, tubulin	Ongoing	NCT01755767
▪ Ramucirumab[2,3]	VEGFR2	Ongoing, AFP > 400	NCT02435433
▪ Apatinib[2,3]	VEGFR2	Ongoing	NCT02329860

References listed in slide notes.

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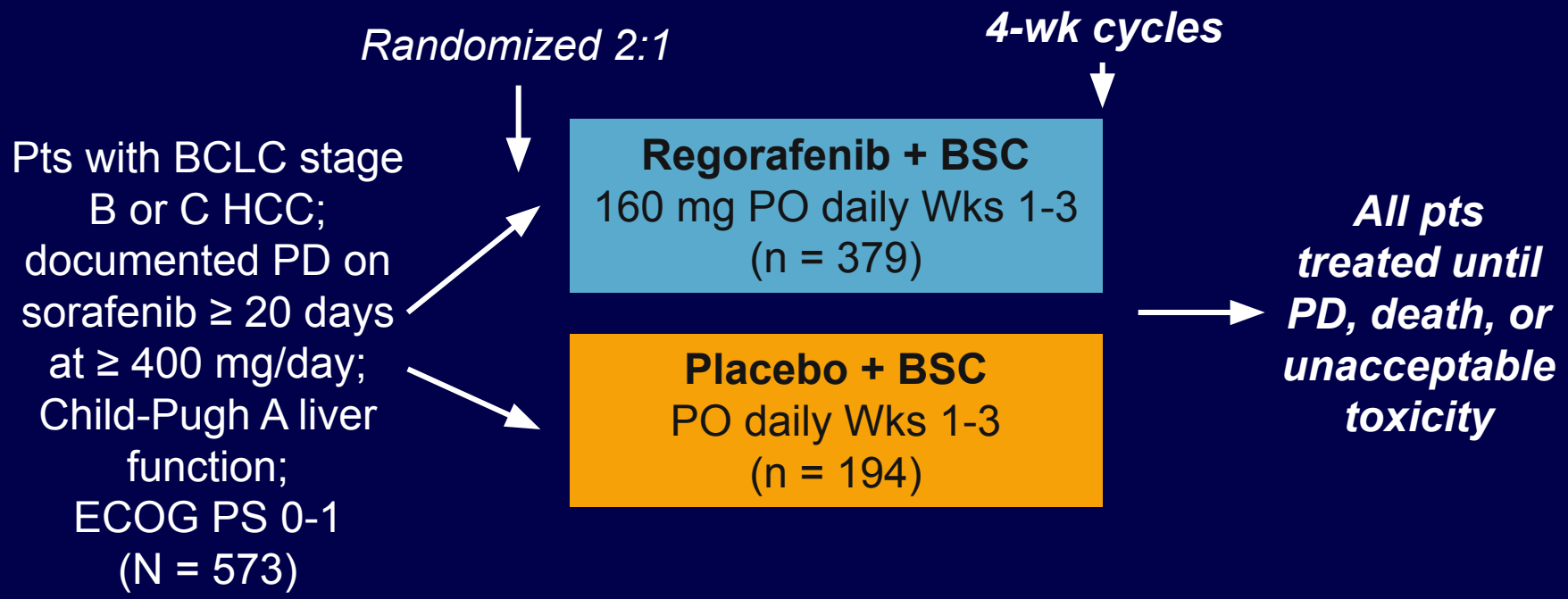
Phase III RESORCE: Regorafenib in HCC After Progression on Sorafenib

- Randomized, double-blind phase III trial



- Primary endpoint: OS (ITT)
- Secondary endpoints: PFS, TTP, RR, DCR

Bruix J, et al. ESMO GI 2016. Abstract LBA-03.

Slide credit: clinicaloptions.com

RESORCE: Efficacy of Regorafenib vs Placebo

Endpoint	Regorafenib (n = 379)	Placebo (n = 194)
Median OS, mos	10.6	7.8
Median PFS, mos	3.1	1.5
Median TTP	3.2*	1.5*
ORR, %	10.6†	4.1†

*HR 0.44; 95% CI: 0.36-0.55; *P* < .001; †*P* = .005

- 38% reduction in risk of death (HR: 0.62; 95% CI: 0.50-0.78; *P* < .001)
- 54% reduction in risk of progression or death (HR: 0.46; 95% CI: 0.37-0.56; *P* < .001)
- DCR (CR + PR + SD): 65.2% vs 36.1% (*P* < .001)

Bruix J, et al. ESMO GI 2016. Abstract LBA-03

Slide credit: clinicaloptions.com

RESORCE: Safety

AE, %	Regorafenib (n = 379)	Placebo (n = 194)
Any ≥ grade 3 AE	79.7	58.5
▪ Hypertension	15.2	4.7
▪ Hand-foot skin reaction	12.6	0.5
▪ Fatigue	9.1	4.7
▪ Diarrhea	3.2	0
Dose modifications due to AEs	68.2	31.1
Deaths occurring ≤ 30 days after last dose	13.4	19.7

Bruix J, et al. ESMO GI 2016. Abstract LBA-03

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