



JOHNS HOPKINS  
M E D I C I N E

# **Clinical Results of Phase II Trial of Sorafenib Combined with Drug-Eluting Bead Doxorubicin (DEBDOX) for Patients with Hepatocellular Carcinoma**

J.F. Geschwind, MD

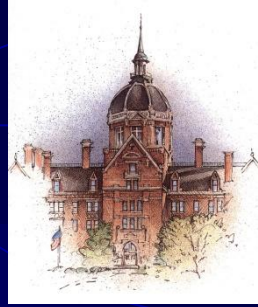
Professor of Radiology, Surgery and Oncology

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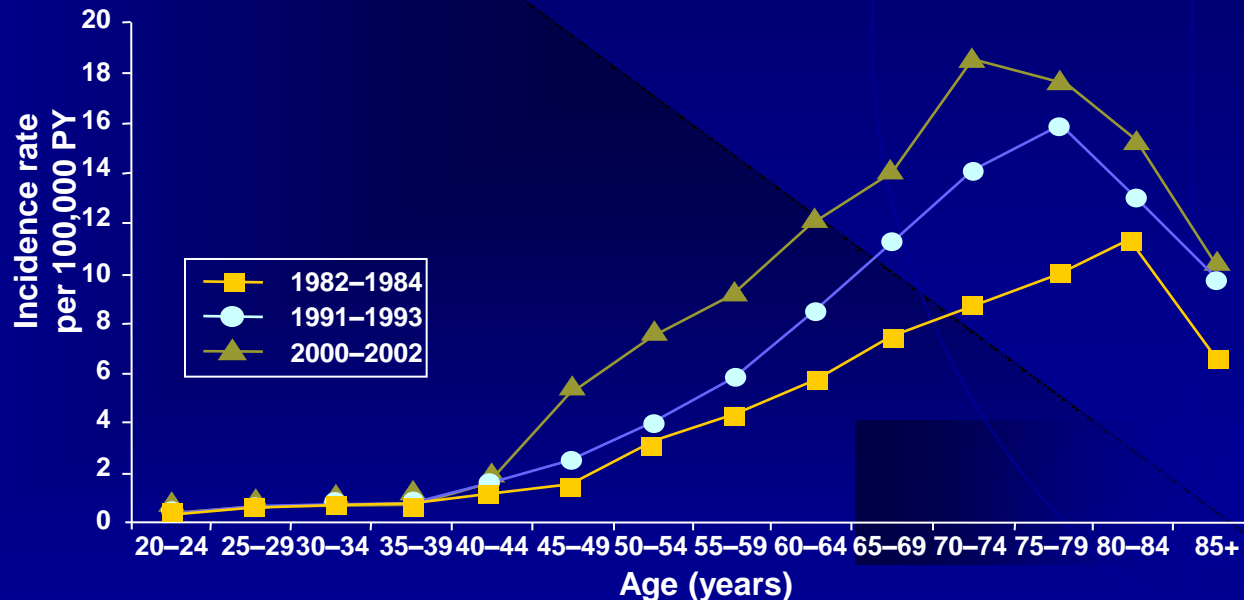
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# Rising Incidence of HCC in the US



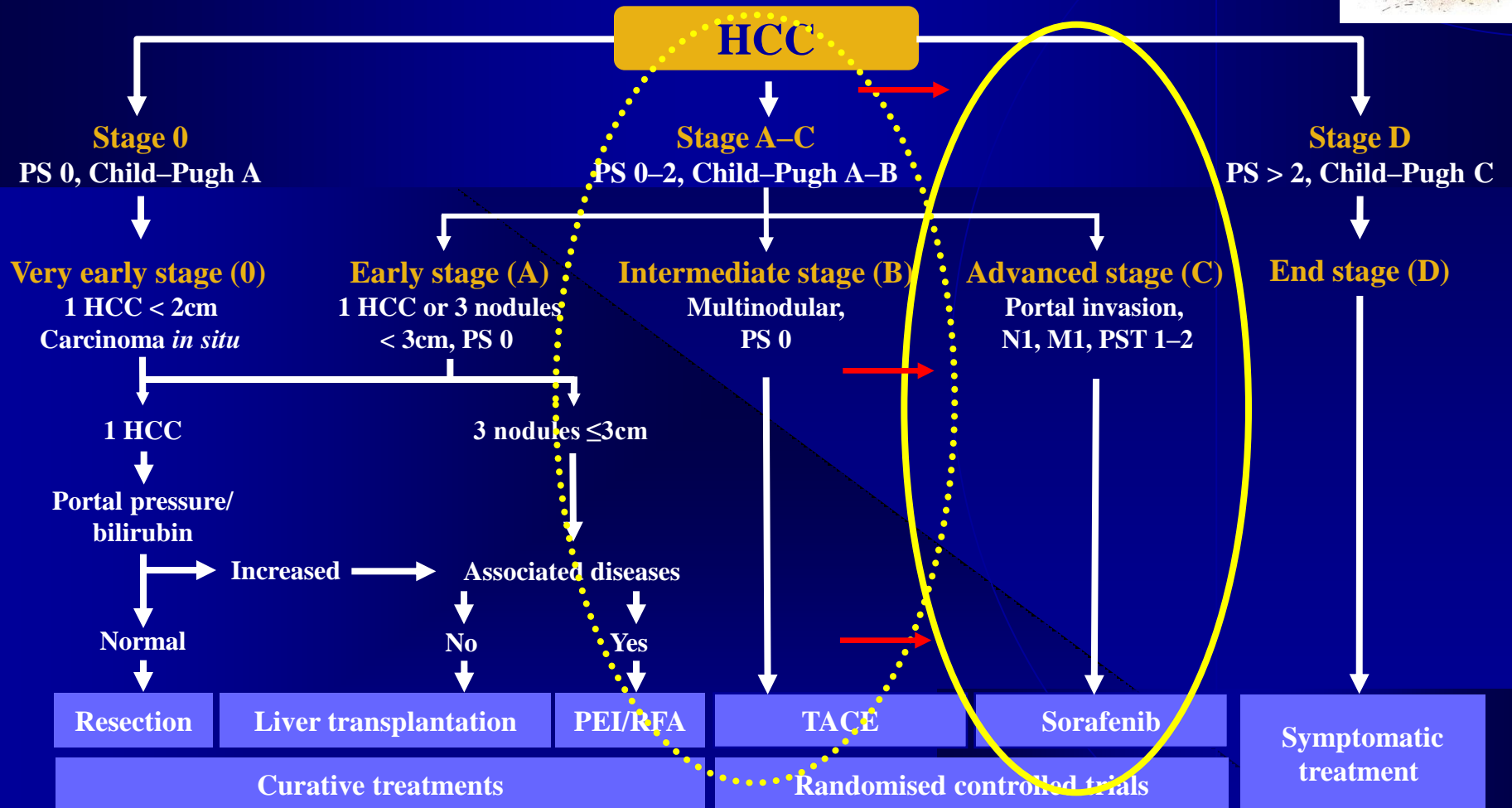
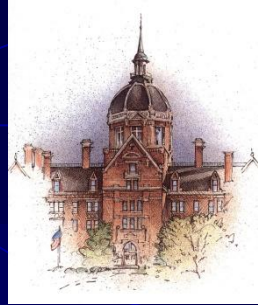
- ◆ 9 SEER registries (NCI) 1975–1998, representing 14% of the US population: 11,547 cases of HCC
- ◆ 114% overall increase from 1980 to 1998 ( $1.3 \times 10^5$  to  $3.0 \times 10^5$ )
- ◆ Veterans Affairs PTF registry: age-adjusted hospitalization rate for HCV-related HCC from  $2.3 \times 10^5$  in 1993–1995 to  $7.2 \times 10^5$  in 1996–1998
- ◆ Alcohol-related and HBV-related HCCs unchanged



HBV, hepatitis B virus; HCV, hepatitis C virus;  
NCI, National Cancer Institute; PTF, patient treatment file;  
SEER, surveillance epidemiology and end results.

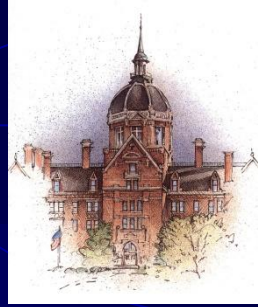
El-Serag et al. Ann Intern Med 2003;139:817.  
El-Serag et al. Arch Intern Med 2000;160:3227.

# BCLC Staging System: Can We Treat Advanced Stage Patients?



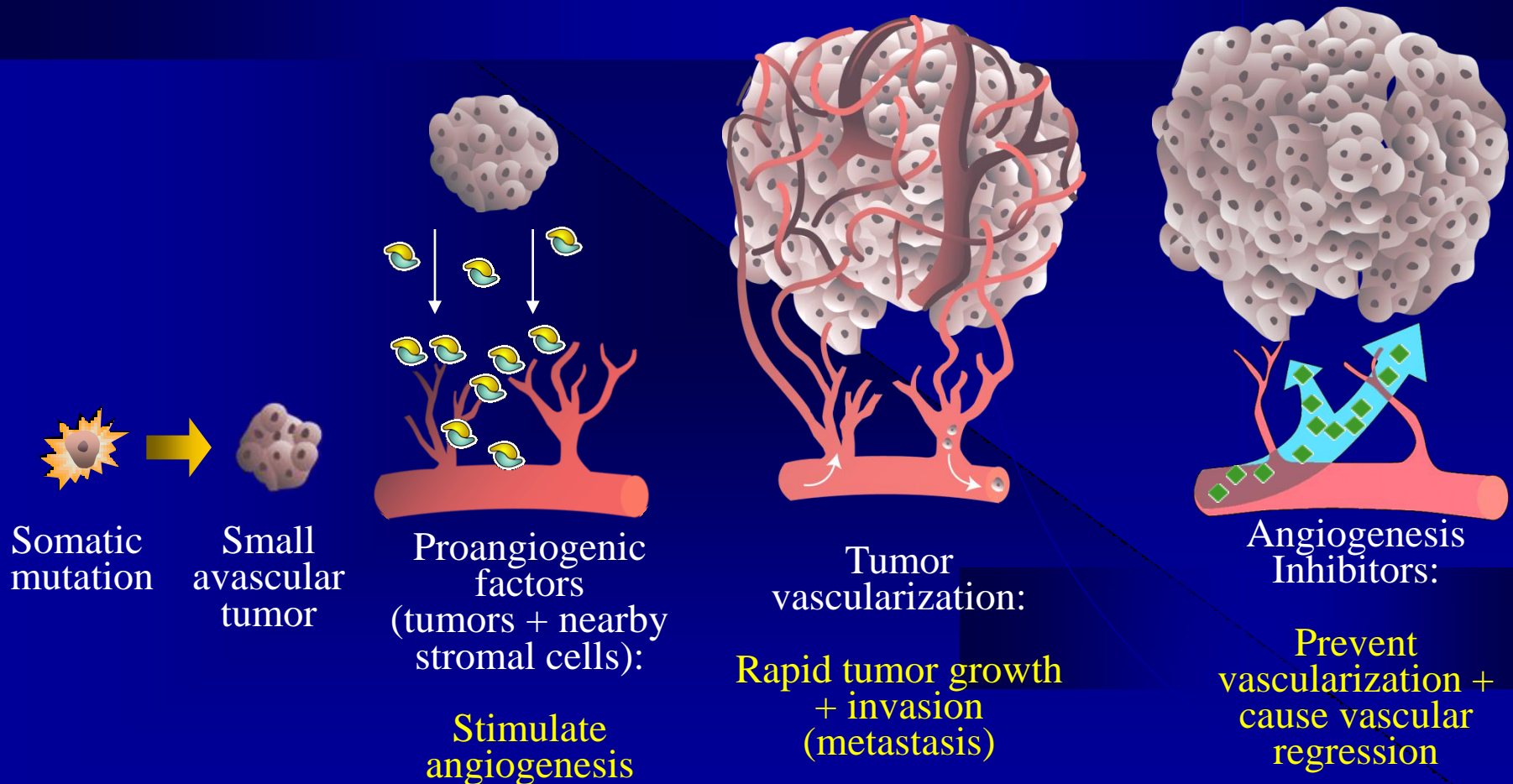
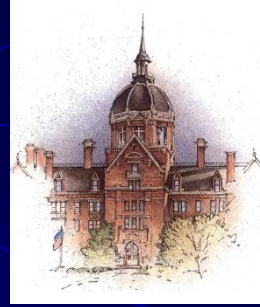
HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer  
PEI, percutaneous ethanol injection; RFA, radiofrequency ablation  
TACE, transarterial chemoembolisation; PS, performance status

# Can Angiogenesis be Exploited?

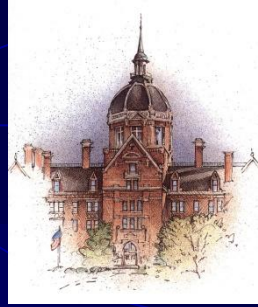


## Rationale for Combination Therapies

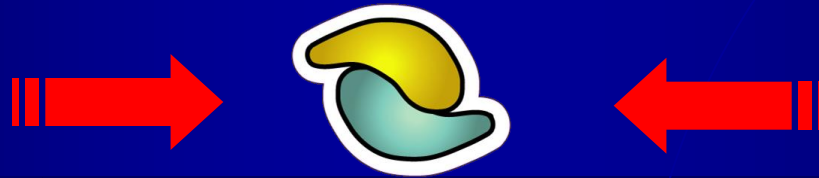
# The Angiogenic Switch and Anti-Angiogenic Therapy



# VEGF: A Central Mediator of Angiogenesis



Environmental factors  
(hypoxia, pH)  
Growth factors,  
hormones  
(EGF, bFGF, PDGF,  
IGF-1, IL-1 $\alpha$ , IL-6, estrogen)



Genes involved in  
tumorigenesis  
(p53, p73, src, ras, vHL,  
bcr-abl)

VEGF

Binding and activation  
of VEGF receptor

Endothelial cell  
activation

Survival Proliferation Migration

**ANGIOGENESIS**

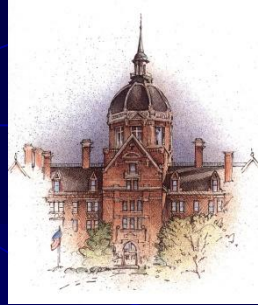
Dvorak. J Clin Oncol 2002;20:4368.

Ferrara et al. Nat Med 2003;9:669.

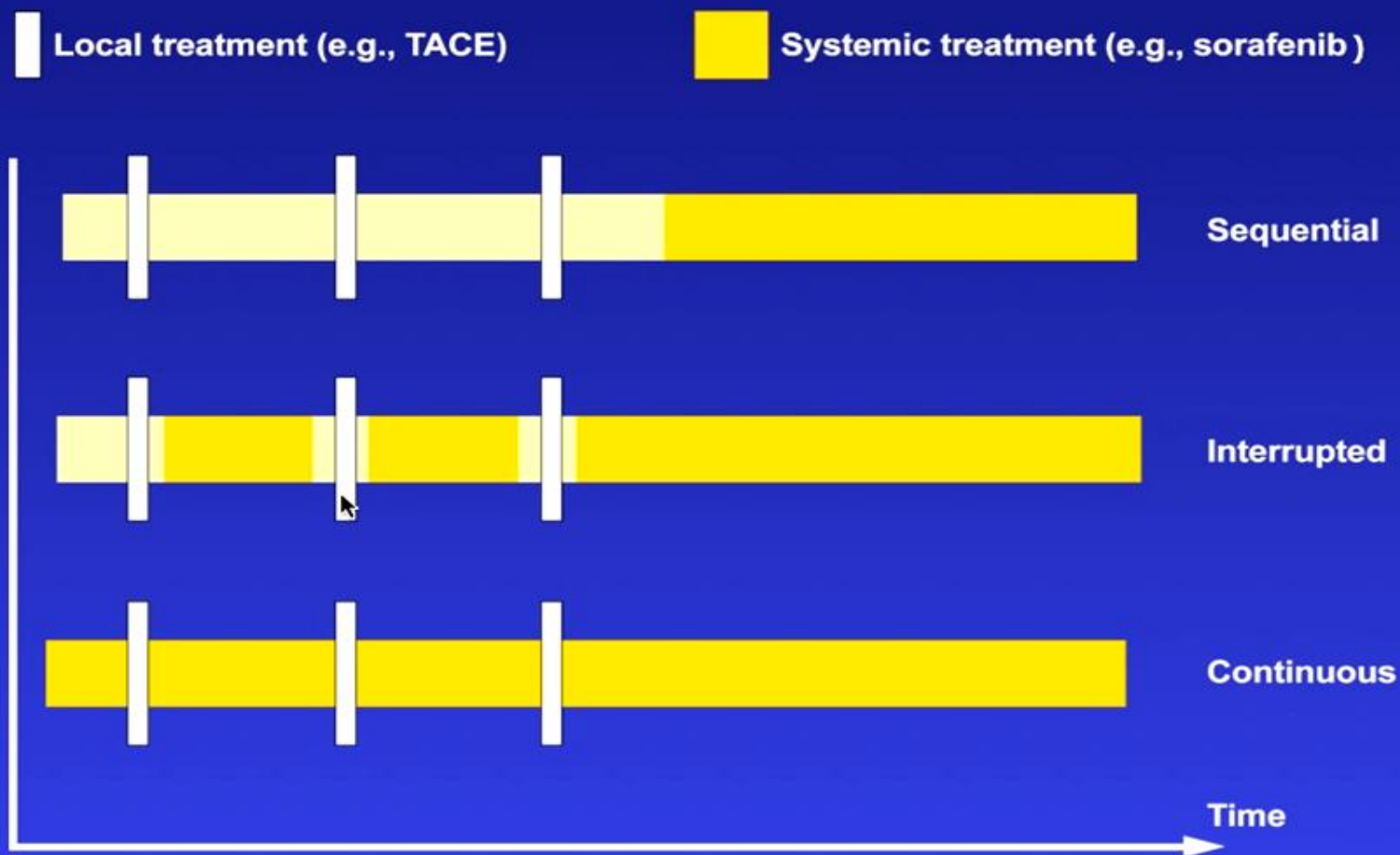
Ebos et al. Mol Cancer Res 2002;1:89.

# How Should Anti-Angiogenic Agents be Given?

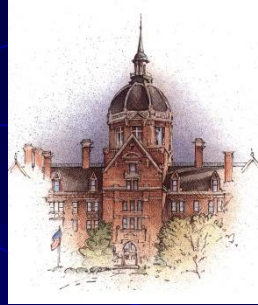
Rationale for Before,  
During and After  
TACE



# Schemes to Combine Local and Systemic Treatment



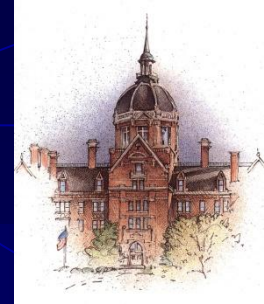
# Prospective Clinical trials of Sorafenib in Combination with Conventional TACE



Study	N	Patient selection	Doxorubicin	TACE Frequency	Sorafenib	Outcome
Dufour Oncologist 2010	14	ECOG 0/1 Child Pugh $\leq$ 7 Branch PVT +/- EHS - < 10 cm	50 mg	Repeated 4 to 6 weeks on demand	Continuous SOR 1 week before TACE	OS, TTP, CR: NA Tox G3: $\downarrow$ PLT 21%, $\uparrow$ BR 21%, abdominal pain 7%
SOCRATES ASCO 2011	43	ECOG 0-2 Child Pugh $\leq$ 8 PVT - EHS -	50 mg	Repeated every 6 weeks on demand	SOR $\geq$ 14 days before TACE. SOR interrupted 3 days before and 1 day after TACE	OS: 20.1 mo TTP: 18.9 mo CR: 7% (EASL) Tox G3/4: $\downarrow$ PLT 5%, encephalopathy 9%, $\uparrow$ ALT 7%
SORATACE AASLD 2010	12	ECOG 0-2 Child Pugh $\leq$ 9 PVT + EHS +	Most received 75 mg	Repeated every 4 weeks	Continuous SOR 2 weeks before 1st TACE	OS, TTP: NA CR: 33% (RECIST) Tox G3/4: diarrhea, fatigue, rash, hyperbilirubinemia (each n=1), and anorexia (n=3)
START ILCA 2011	166	BCLC B ECOG 0/1 Child-Pugh $\leq$ 7 mPVT + EHS -	30-60 mg	Repeated every 6 to 8 weeks on demand	Started on day 4 after first TACE and interrupted 4 days before next TACE cycle restarted on day 4	OS: NR TTP: 9 mo CR: 28% (NA) Tox G3/4: HFSR 7%, thrombocytopenia 3%, $\downarrow$ neut 6%, $\uparrow$ ALT 2%
COTSUN ASCO-GI 2011	50	ECOG 0/1 Child-Pugh $\leq$ 7 PVT +/- EHS +/-	30-60 mg	Repeated 4 to 6 weeks on demand	SOR on day 3 after 1st TACE and then continuously	OS, CR: NA TTP: 5.1 mo Tox G3: $\downarrow$ thrombocytopenia 28%, $\uparrow$ ALT 38%, $\uparrow$ AST 34%

All Phase II trials except for Dufour 2010 (Phase I)

# Johns Hopkins University Phase II Trial of Doxorubicin-Eluting LC Bead<sup>®</sup> TACE plus Sorafenib in Patients with Unresectable HCC



◆ Primary endpoint: safety

◆ Secondary endpoint: tumor response (EASL, RECIST), TTP, OS

## Eligibility criteria

- Unresectable HCC (beyond Milan)
- > 18 years old
- ECOG PS 0/1
- Child–Pugh A/B (< 8)
- Adequate end-organ function\*

(n = 50)

Sorafenib 400 mg b.i.d.  
initiated  
1 week before first TACE

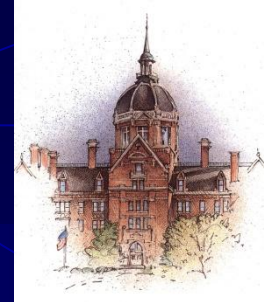
+

Up to 4 treatments/6 months:  
TACE with doxorubicin-LC Bead<sup>®</sup>  
100 mg doxorubicin

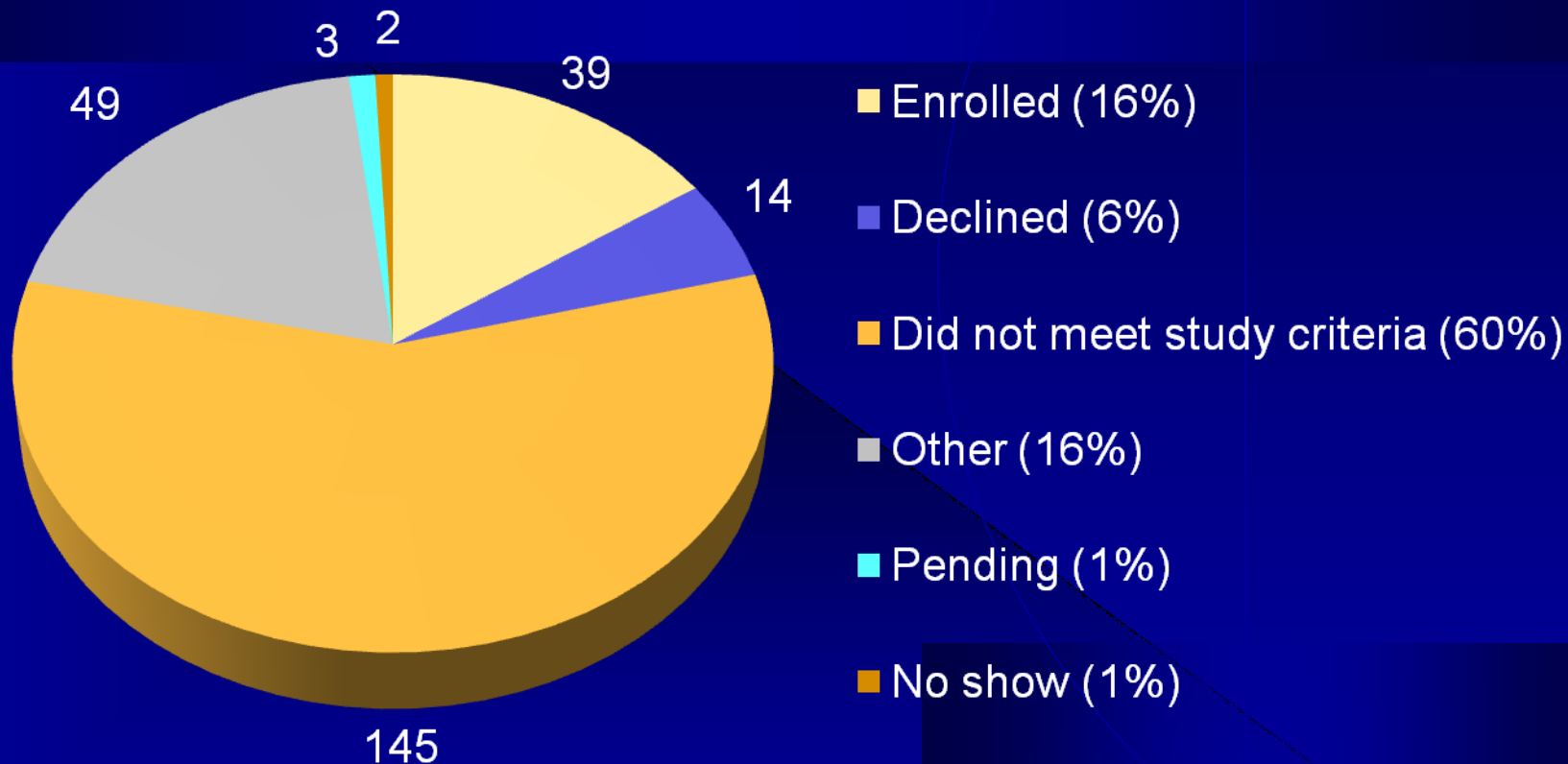
Continue until  
tumor progression  
or toxicity

\*Absolute neutrophil count > 1500/mm<sup>3</sup>, platelets > 50,000/mm<sup>3</sup>, normal creatinine, total bilirubin ≤ 3, AST and ALT < 5 upper limit of normal.

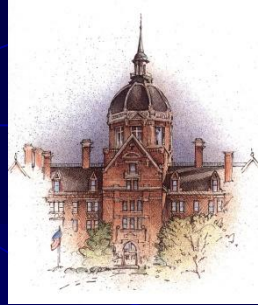
# Patient Enrollment: Phase II Trial of DEB-TACE plus Sorafenib



N = 243 seen in clinic since Feb 2009

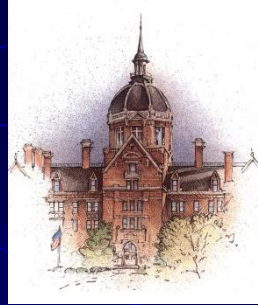


# Patient Characteristics: Phase II Trial of DEB-TACE plus Sorafenib



Variable	Value
Patients enrolled	35
Mean age, years (range)	64 (31–88)
Male/female	26/9
Child–Pugh status A/B	31/4
ECOG Performance Status 0/1	16/19
HBV/HCV/other etiology	2/13/20
Portal vein thrombosis (yes/no)	11/24
BCLC B/C	12/23
Mean index tumor size, cm (SD)	7.7 4.2

# Tumor Response: Phase II Trial of DEB-TACE plus Sorafenib (1)



36 patients treated to date, 35 patients completed Cycle 1  
(n = 26 evaluated for efficacy)

Tumor response by MR imaging

Features	Pre-DEB-TACE		Post-DEB-TACE		Change at 3 weeks (%)	P
	Mean	SD	Mean	SD		
Tumor Size	7.9	4.3	7.6	4.5	-4	0.79
Tumor Enhancement (%)	85		43.5		-49	< 0.01
*ADC ( $10^{-3}$ mm <sup>2</sup> /s)	1.2		1.54		+25%	0.01

## EASL

Partial response: 14/26 (54%)

Stable disease: 12/26 (46%)

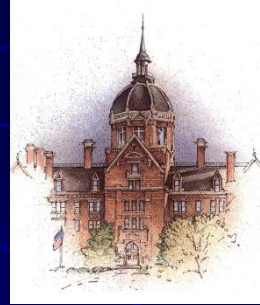
## RECIST

Stable disease: 25/26 (96%)

Progressive disease: 1/26 (4%)

\*ADC measured by functional diffusion weighted MR.

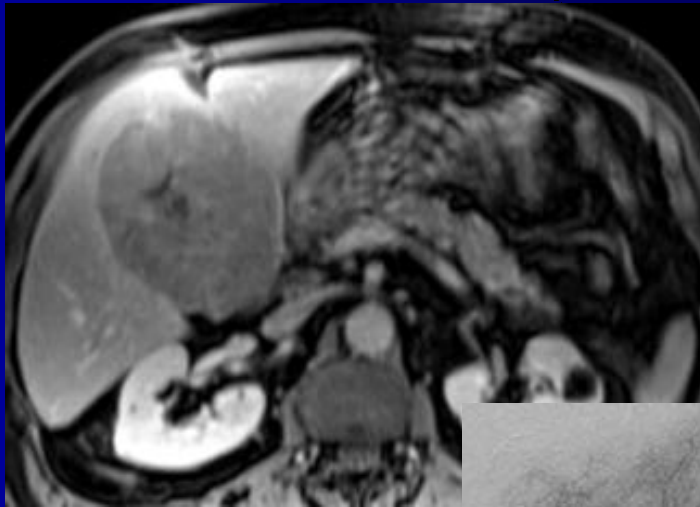
# Tumor Response: Phase II Trial of DEB-TACE plus Sorafenib (2)



- ◆ 68-year-old male, right lobe lesion
- ◆ 2 cycles of DEB-TACE and sorafenib
- ◆ Bridged to surgical resection 3 months after end of second cycle

Baseline

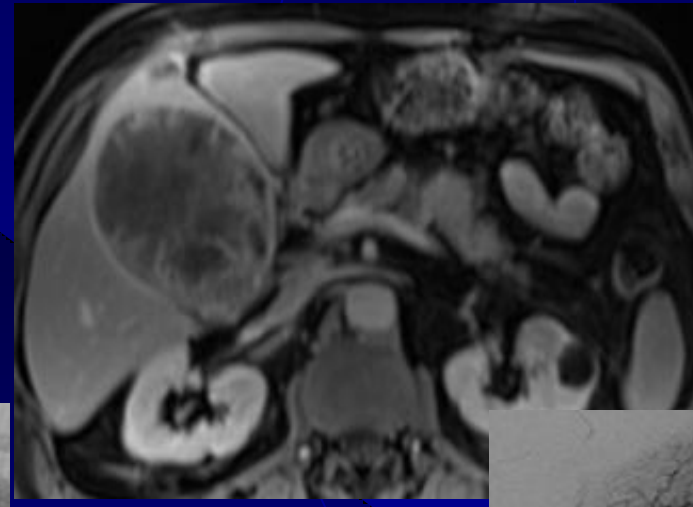
21 days post-treatment



10.3 cm,  
90% enhancement



TACE #1

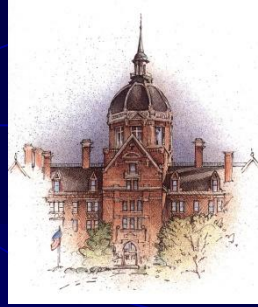


10.2 cm,  
30% enhancement



TACE #2

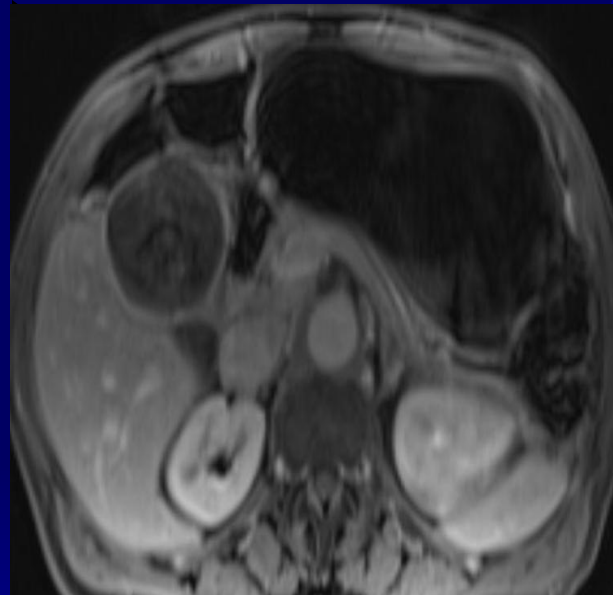
# Tumor Response: Phase II Trial of DEB-TACE plus Sorafenib (3)



- ◆ 73-year-old male, right lobe lesion
- ◆ 1 cycle of DEB-TACE and sorafenib
- ◆ Stable for 20 months



**Baseline:**  
8.1 cm, 90% enhancement

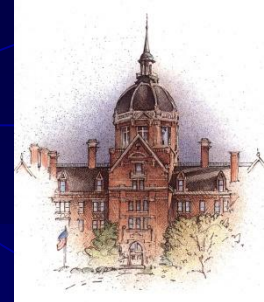


**3 weeks post DEB-TACE:**  
6.3 cm, 10% enhancement

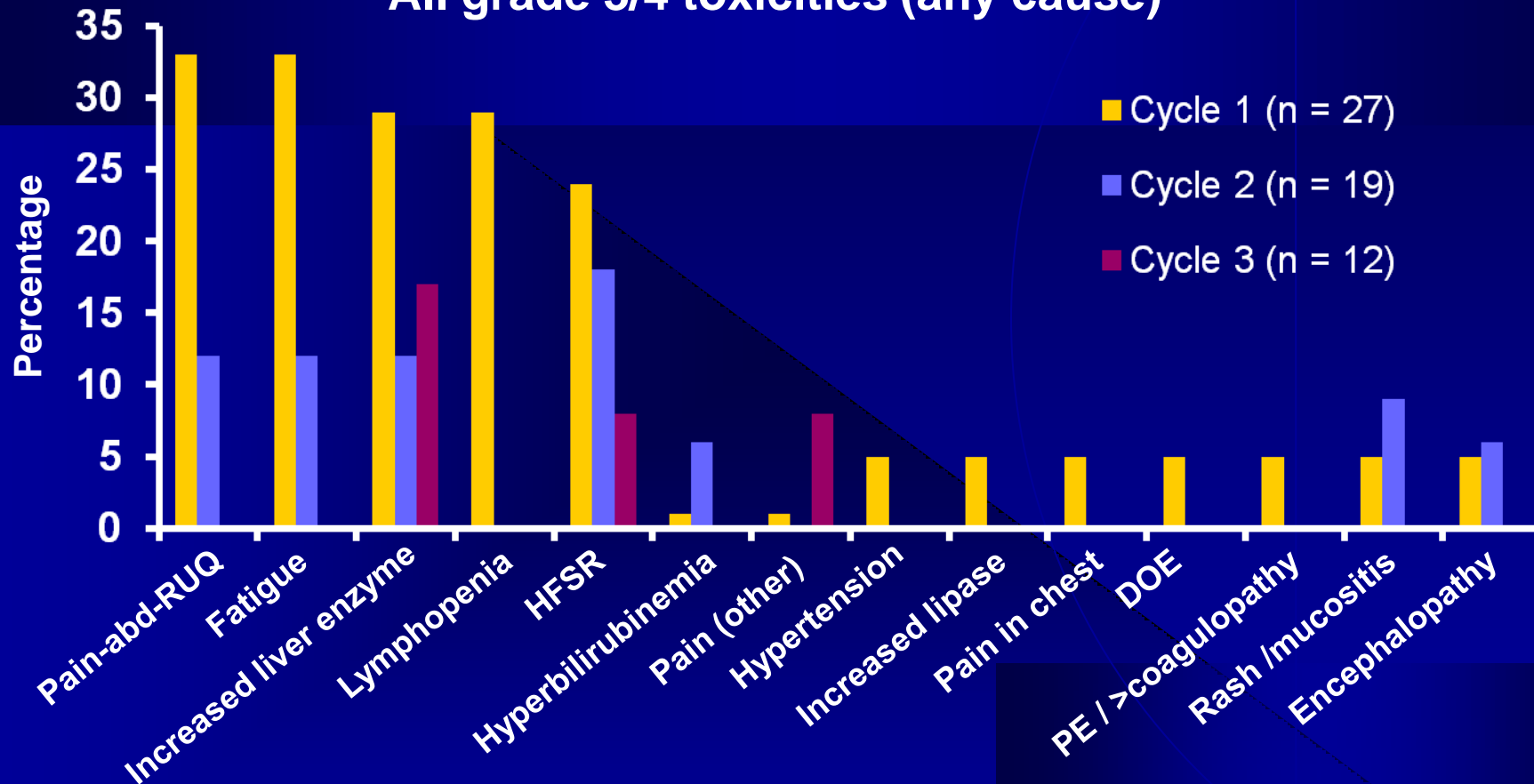


**20 months post DEB-TACE:**  
5.7 cm, < 10 % enhancement

# Incidence of Grade 3/4 Toxicities: Phase II Trial of DEB-TACE plus Sorafenib



All grade 3/4 toxicities (any cause)



All remaining toxicities were grade 1/2 (no unexpected events)

Pain-abd-RUQ, abdominal pain, right upper quadrant; DOE, dyspnoea on exertion; PE, pulmonary embolism.

# SPACE: Sorafenib or Placebo in combination with TACE for intermediate-stage HCC



Phase 2, randomized, double-blind, placebo-controlled study of sorafenib or placebo in combination with DC Bead® TACE and doxorubicin for intermediate-stage HCC

## Selected eligibility criteria

- Unresectable HCC
- Multinodular HCC
- Child–Pugh A without ascites or encephalopathy
- ECOG PS 0

## Selected exclusion criteria

- EHS/MVI
- Contraindication to TACE

Randomize  
1:1  
(n = 300)

DC Bead® TACE +  
sorafenib 400 mg b.i.d.

DC Bead® TACE +  
placebo

## Primary end-point

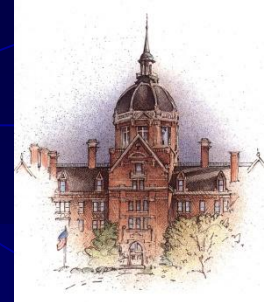
- Time to progression

## Secondary end-points

- Overall survival
- Safety
- Time to untreatable progression
- Time to vascular invasion/EHS
- Biomarker analysis
- Patient-reported outcomes



# ECOG Phase III Study: TACE With or Without Sorafenib



- ◆ Phase III randomized, double-blind trial of TACE with or without sorafenib in patients with unresectable HCC
- ◆ Status: recruiting
- ◆ Contact information: ECOG Group Chair's Office

## Eligibility criteria

- Unresectable HCC
- Child-Pugh A or B7
- ECOG PS 0-1

## Exclusion criteria

- EHS
- Main portal vein invasion
- Ascites

Randomization  
1:1  
(n = 400)

Sorafenib 400 mg b.i.d.  
and TACE (doxorubicin,  
mitomycin C and cisplatin)

Placebo and TACE  
(doxorubicin,  
mitomycin C and cisplatin)

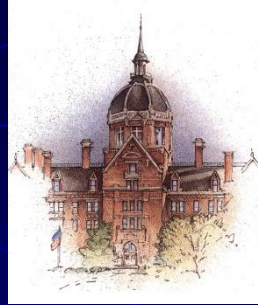
## Primary end-point

- PFS

## Secondary end-points

- OS
- Toxicity

# Conclusions



- ◆ Sound rationale for combining TACE and anti-angiogenic therapy
  - Prolong TTP of TACE
  - Treat advanced-stage HCC since extrahepatic disease treated with systemic therapy
- ◆ Emerging data on safety, but not quite yet on efficacy
- ◆ Clinical efficacy data available late 2011–early 2012
  - No additional toxicity as a result of sorafenib
  - Most toxicities during first cycle (within 2 weeks of sorafenib)
- ◆ Which agents, what protocols?