

# Satellite Symposium



## Management of Intermediate HCC with Sorafenib and Drug-Eluting Bead, Doxorubicin (DEBDOX™)

Chairman: Professor Josep Llovet, Barcelona Clinic Liver Cancer (BCLC) Group, Spain & Mount Sinai School of Medicine, New York, USA

Saturday 3 September, 2011 5:30  
– 6.30pm

Plenary Room  
Hong Kong Convention and Exhibition Centre



Overview of HCC management and rationale for SPACE trial

**Professor Josep Llovet**

Barcelona Clinic Liver Cancer (BCLC) Group, Spain & Mount Sinai School of Medicine, New York, USA



Is DEBDOX™ the new standard for chemoembolisation?

**Professor Riccardo Lencioni**

Pisa University Hospital and School of Medicine, Italy



Asian experience with Drug-Eluting Beads for HCC and rationale for the TRACER study

**Professor Ronnie Poon**

Queen Mary Hospital, The University of Hong Kong



Five-year follow up with DEBDOX in intermediate HCC, BCLC experience

**Professor Jordi Bruix**

Barcelona Clinic Liver Cancer (BCLC) Group, Spain



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Biocompatibles UK Ltd is a BTG International group company





CLÍNICA  
BARCELONA  
Hospital Universitari



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## Overview of HCC management and rationale for SPACE trial in HCC

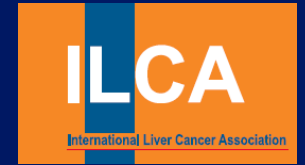
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**Josep M Llovet, MD**

Professor of Research. BCLC Group. Liver Unit . Hospital Clinic Barcelona  
Director of HCC Program. Professor of Medicine. Mount Sinai School of Medicine, NY.

# Josep M Llovet MD, Disclosure Biocompatibles.

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Hong Kong 2011

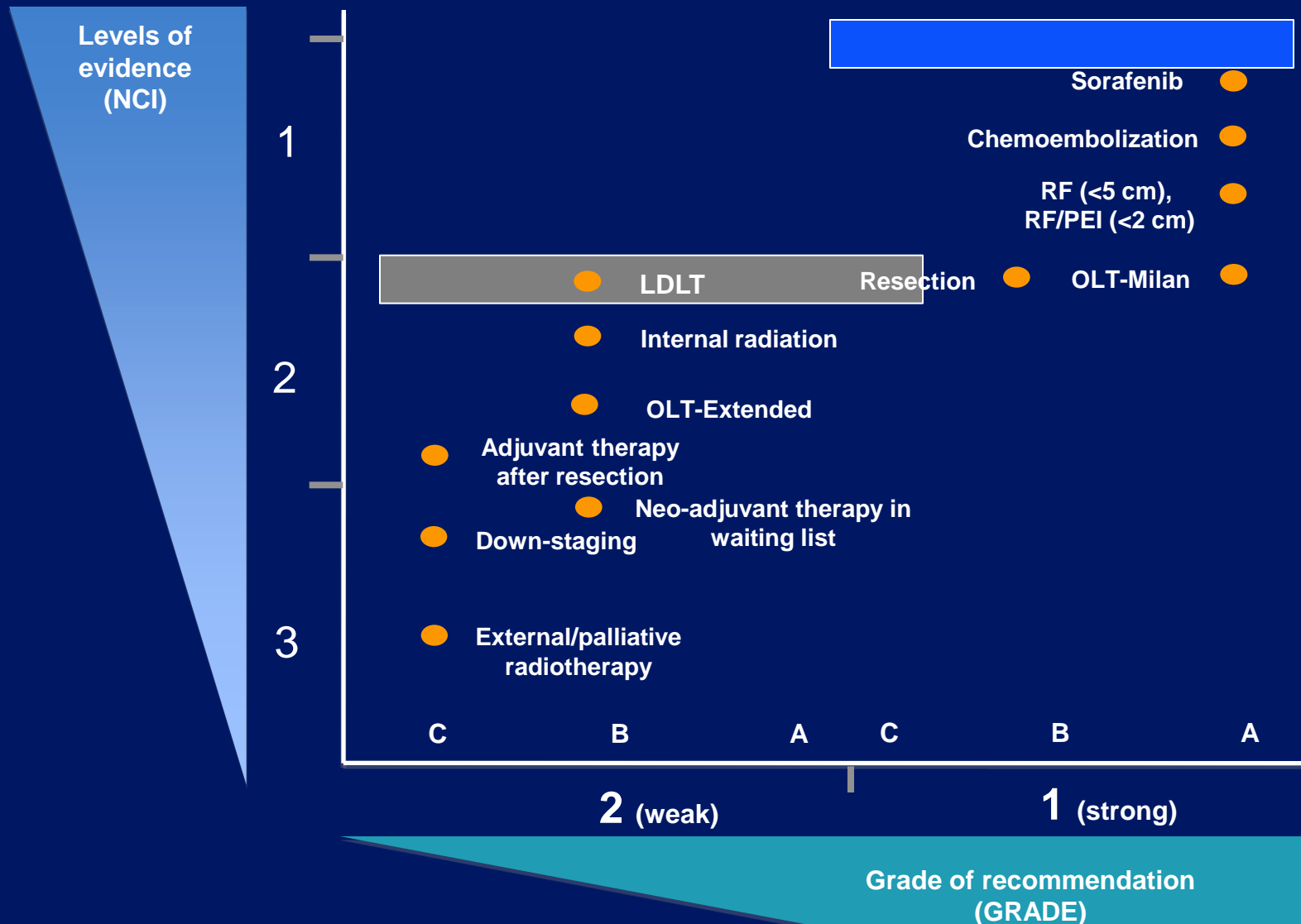
- I am receiving financial support as consultant from Biocompatibles UK

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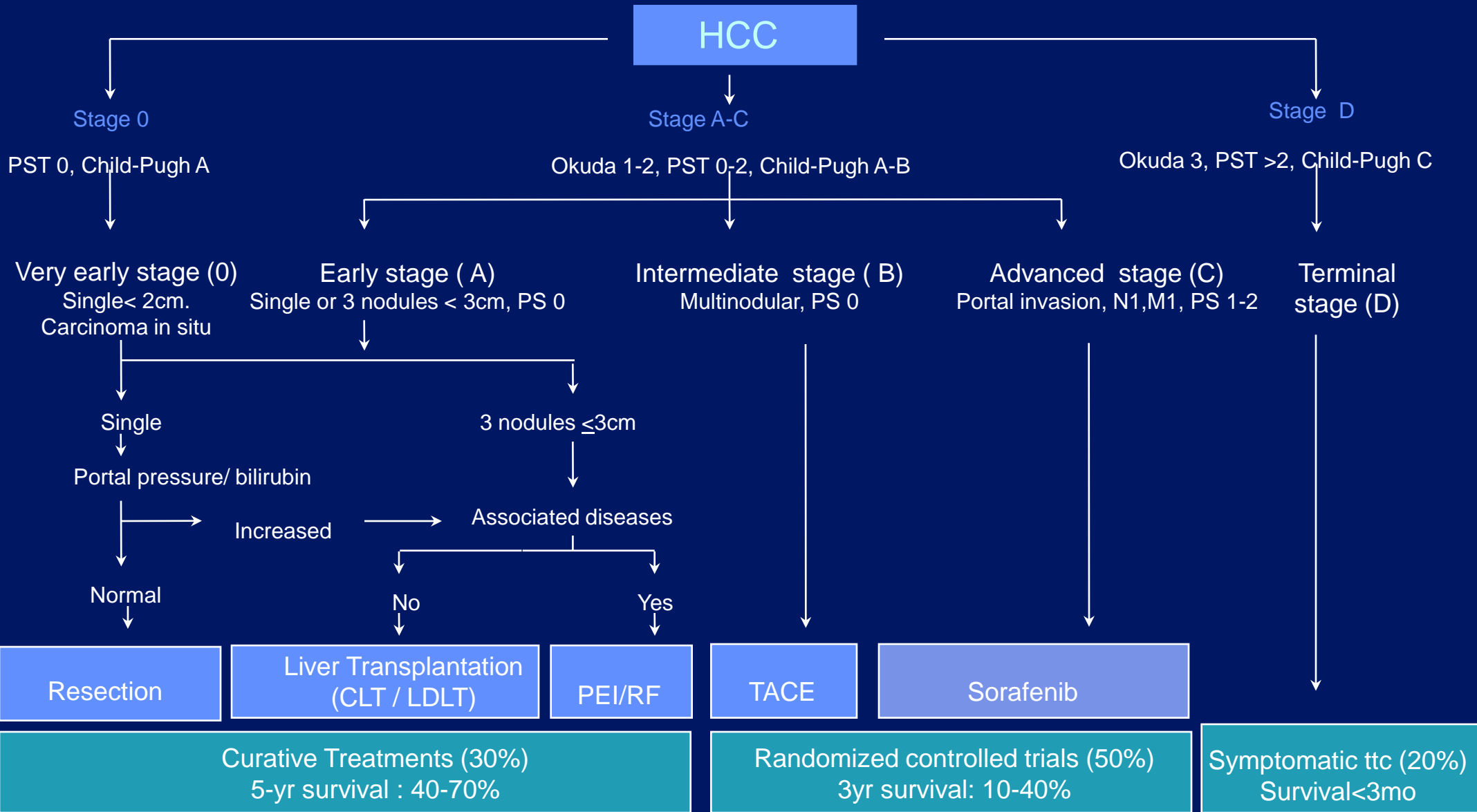
# 1. Overview of treatments for HCC

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# Evidence and recommendations for HCC therapies, 2011



# BCLC staging and treatment strategy



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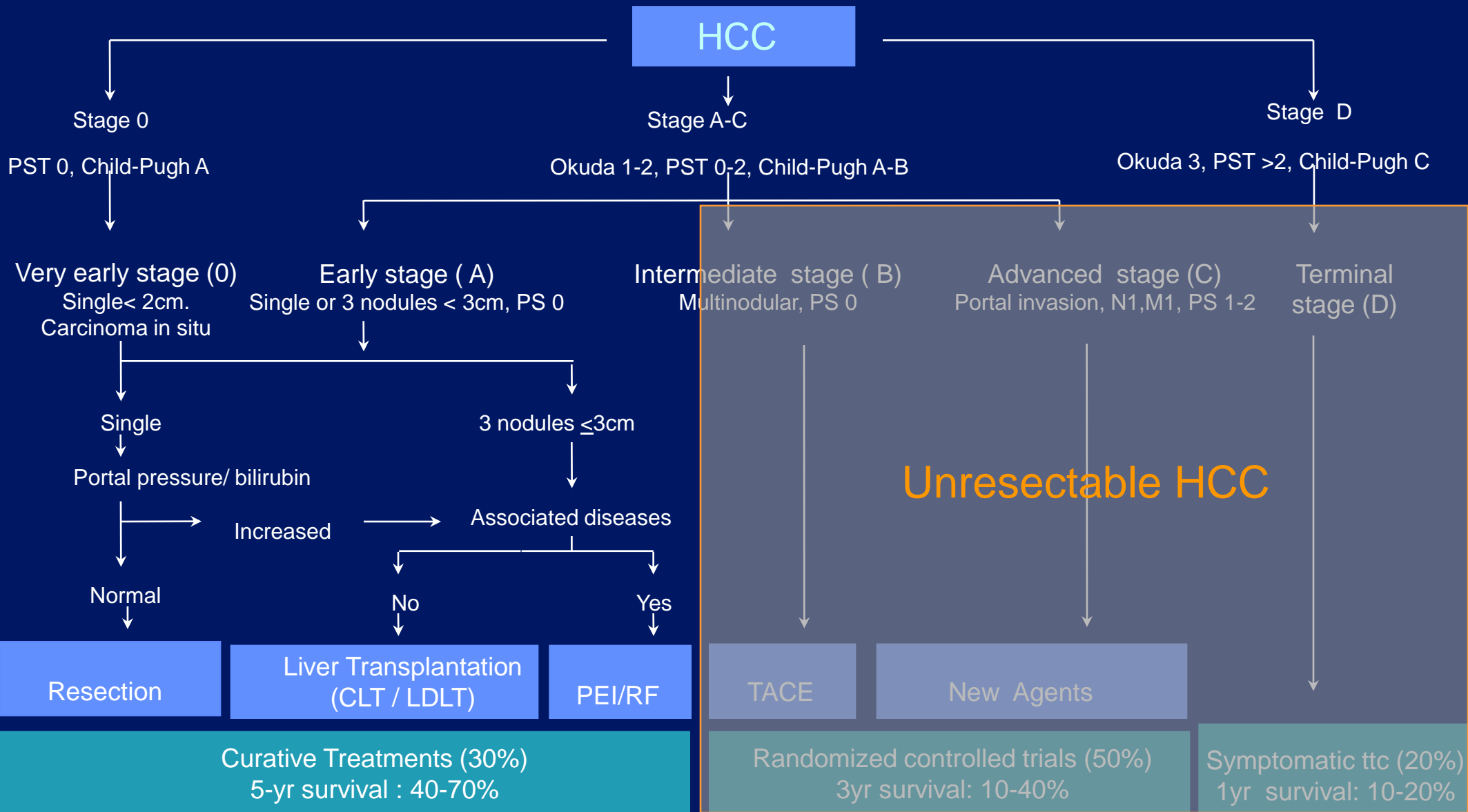
## 2. Treatment of intermediate HCC

Natural history of unresectable HCC

Treatment of intermediate HCC

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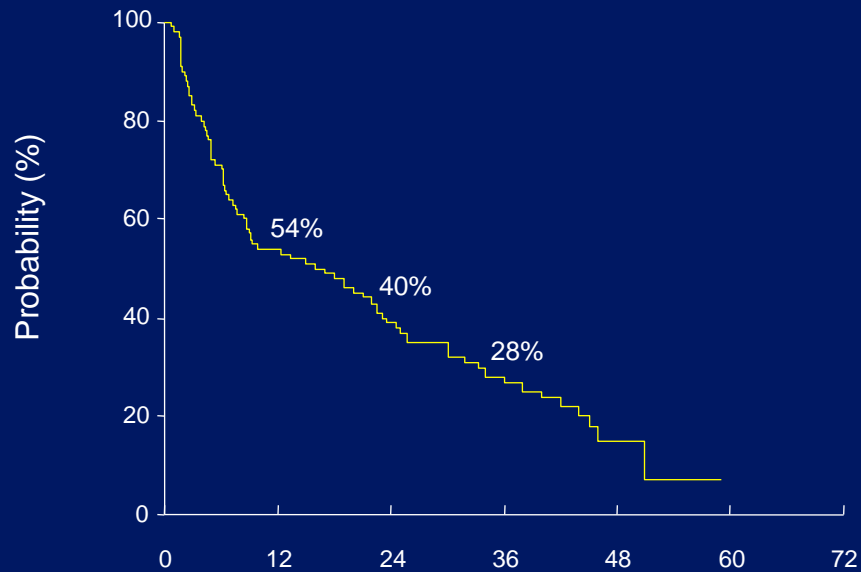
# BCLC Staging and treatment schedule



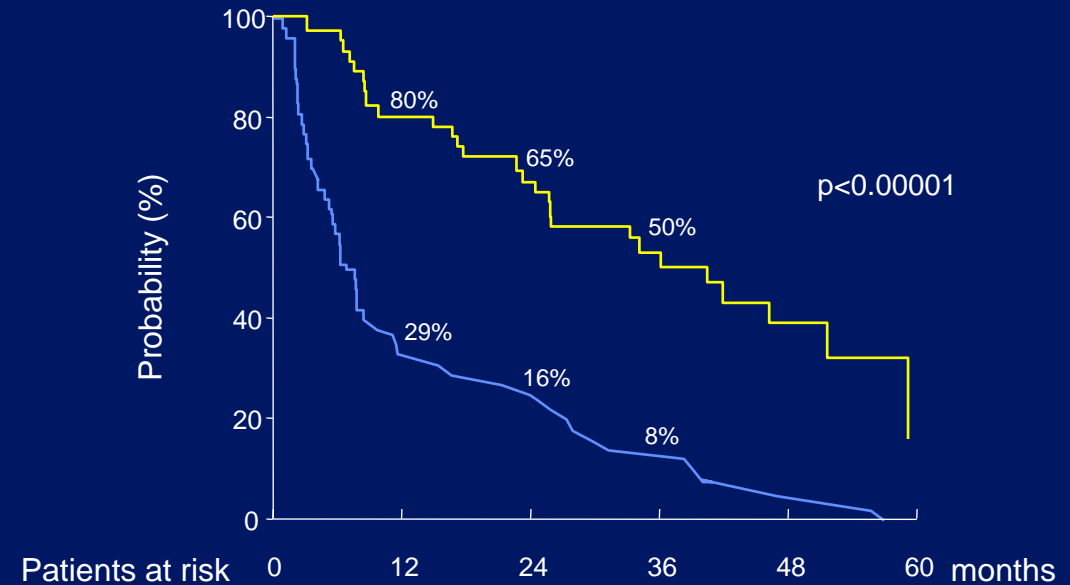
# Natural history of non-surgical HCC

Study design: control arm of 2 RCT (n=102)

- Natural outcome depends on
  - Cancer-related symptoms (PST/ECOG)
  - Tumor stage: Portal invasion and metastasis.



|                  |     |    |    |    |   |   |
|------------------|-----|----|----|----|---|---|
| Patients at risk | 102 | 57 | 40 | 21 | 8 | 1 |
|------------------|-----|----|----|----|---|---|



|                  |    |    |    |    |    |           |
|------------------|----|----|----|----|----|-----------|
| Patients at risk | 0  | 12 | 24 | 36 | 48 | 60 months |
| (BCLC Stage B)   | 48 | 37 | 30 | 16 | 7  |           |
| (BCLC Stage C)   | 54 | 17 | 9  | 2  | -  |           |

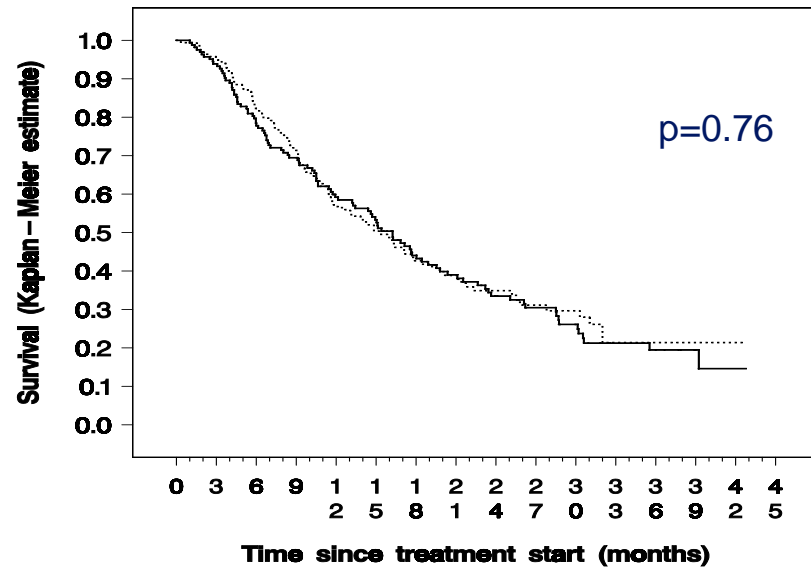
# Intermediate-advanced HCC

## External validation of BCLC: RCT seocalcitol vs placebo (n=746)

### Survival BCLC B stage (n=370)

Stage 0

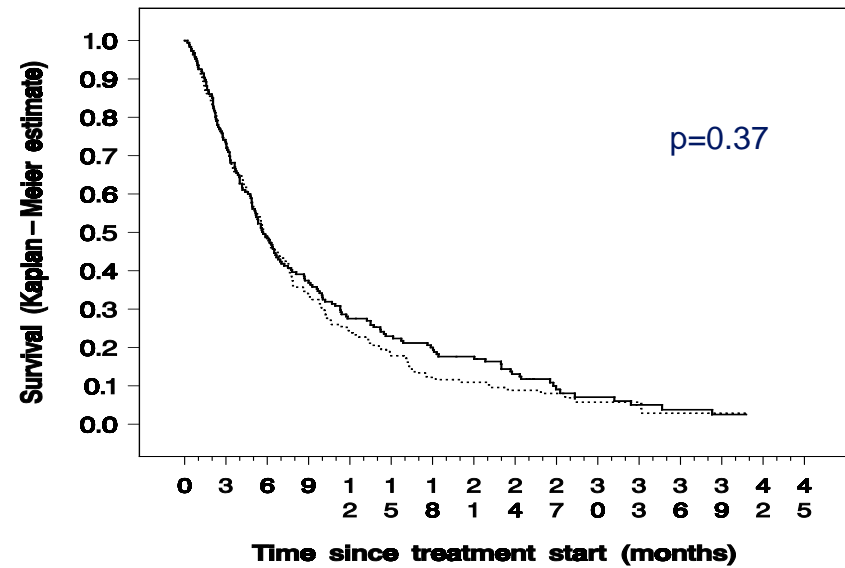
Median survival: Placebo 15.8m  
Seocalcitol 15.1m



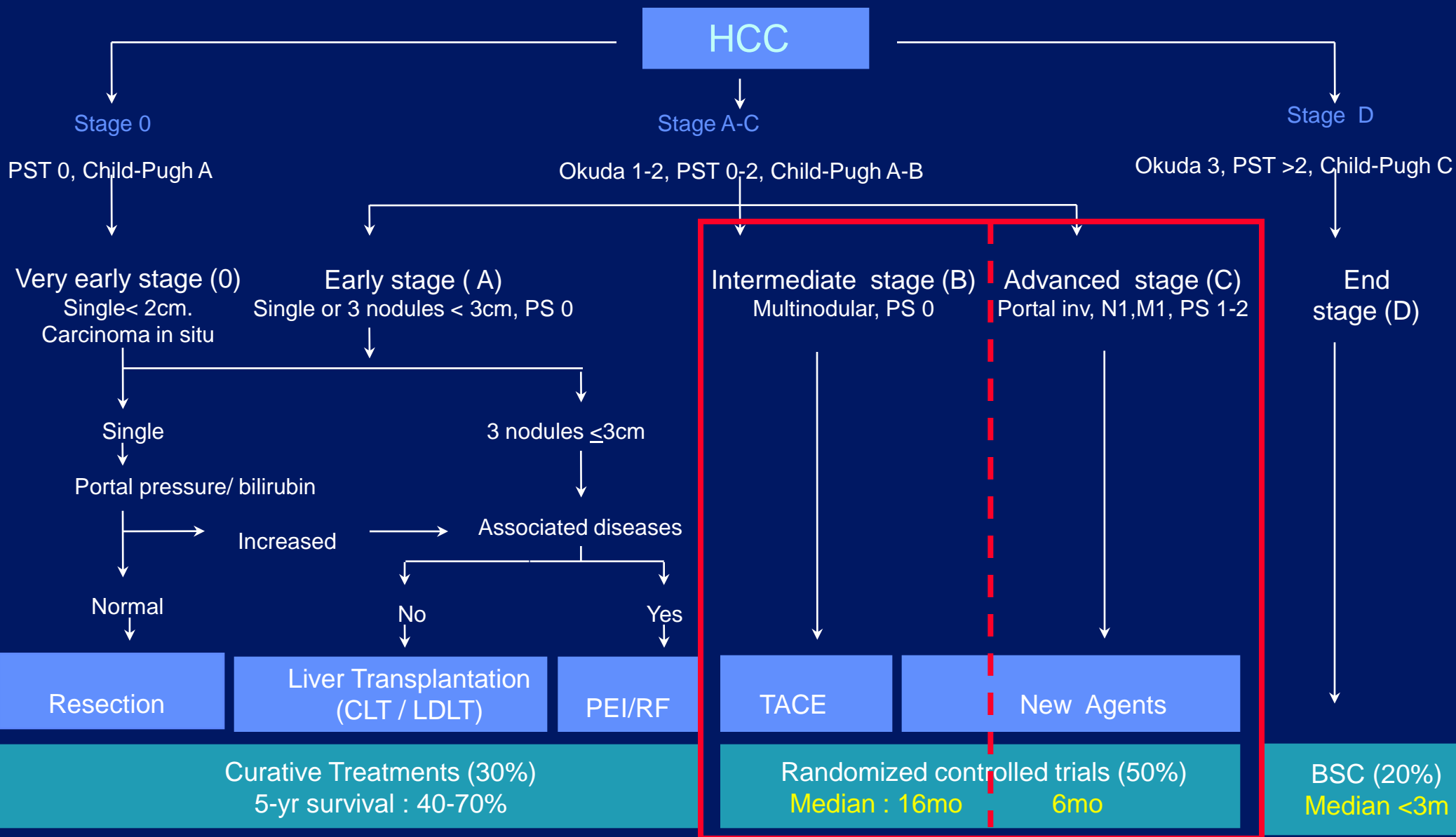
### Survival BCLC C stage (n=376)

Stage 1

Median survival : Placebo 5.7m  
Seocalcitol 5.6m



# BCLC Staging and treatment schedule



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## 2. Treatment of intermediate HCC

Natural history of unresectable HCC

Treatment of intermediate HCC

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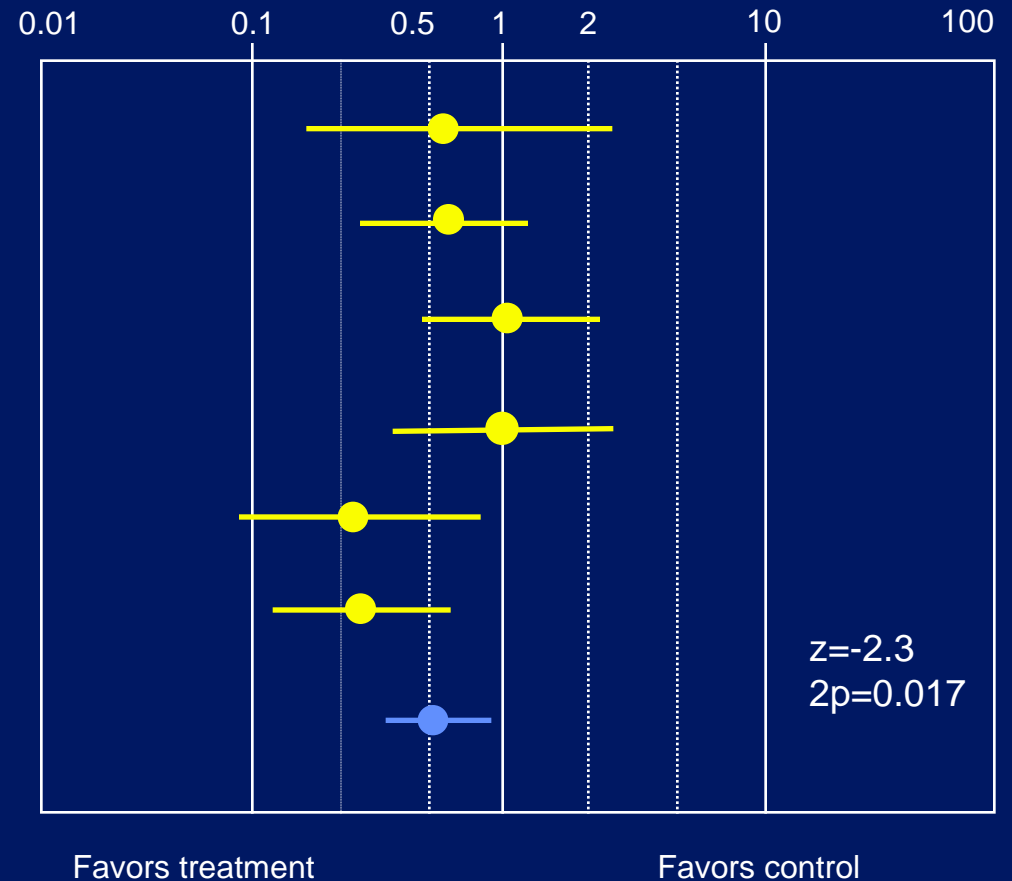
# Arterial embolization for HCC

## Meta-analysis of six RCT (2-yr survival)

Random effects model (DerSimonian & Laird).  
OR (95% CI)

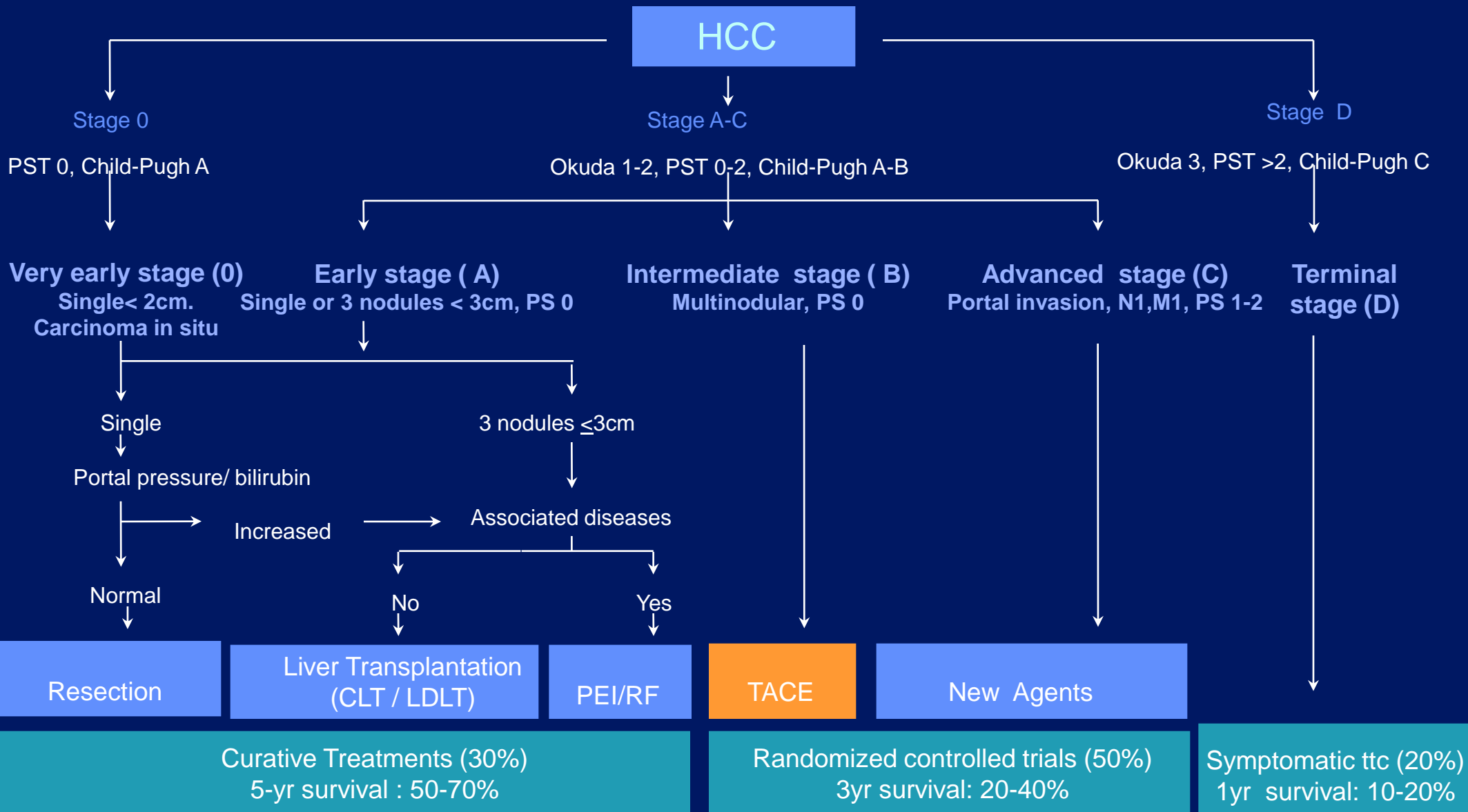
Author, Journal year      Patients

|                             |            |
|-----------------------------|------------|
| Lin , Gastroenterology 1988 | 63         |
| GETCH, NEJM 1995            | 96         |
| Bruix , Hepatology 1998     | 80         |
| Pelletier, J Hepatol 1998   | 73         |
| Lo, Hepatology 2002         | 79         |
| Llovet, Lancet 2002         | 112        |
| <b>OVERALL</b>              | <b>503</b> |

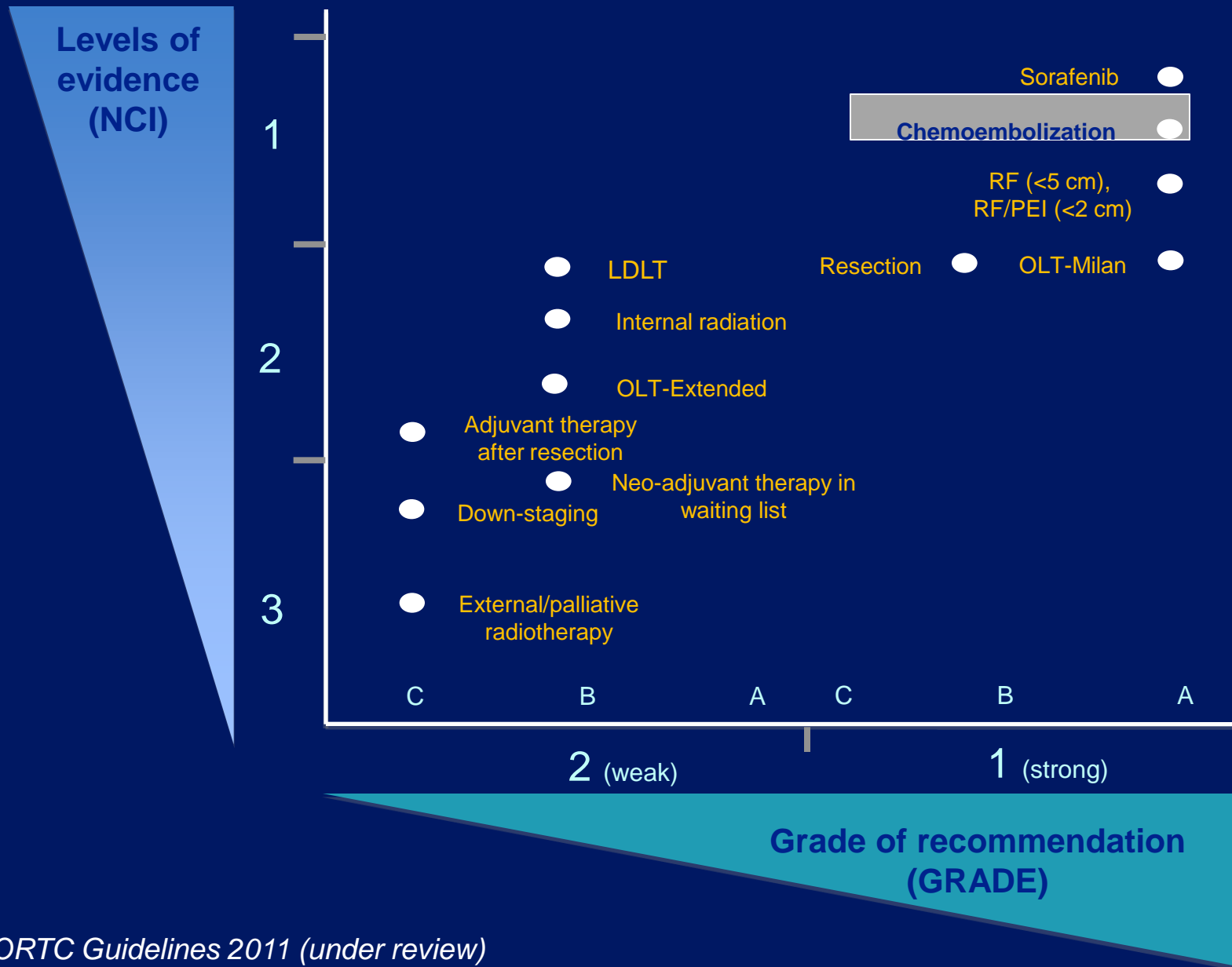


**Median survival : ~20 months**

# BCLC Staging and treatment schedule



# Evidence and recommendations for HCC therapies

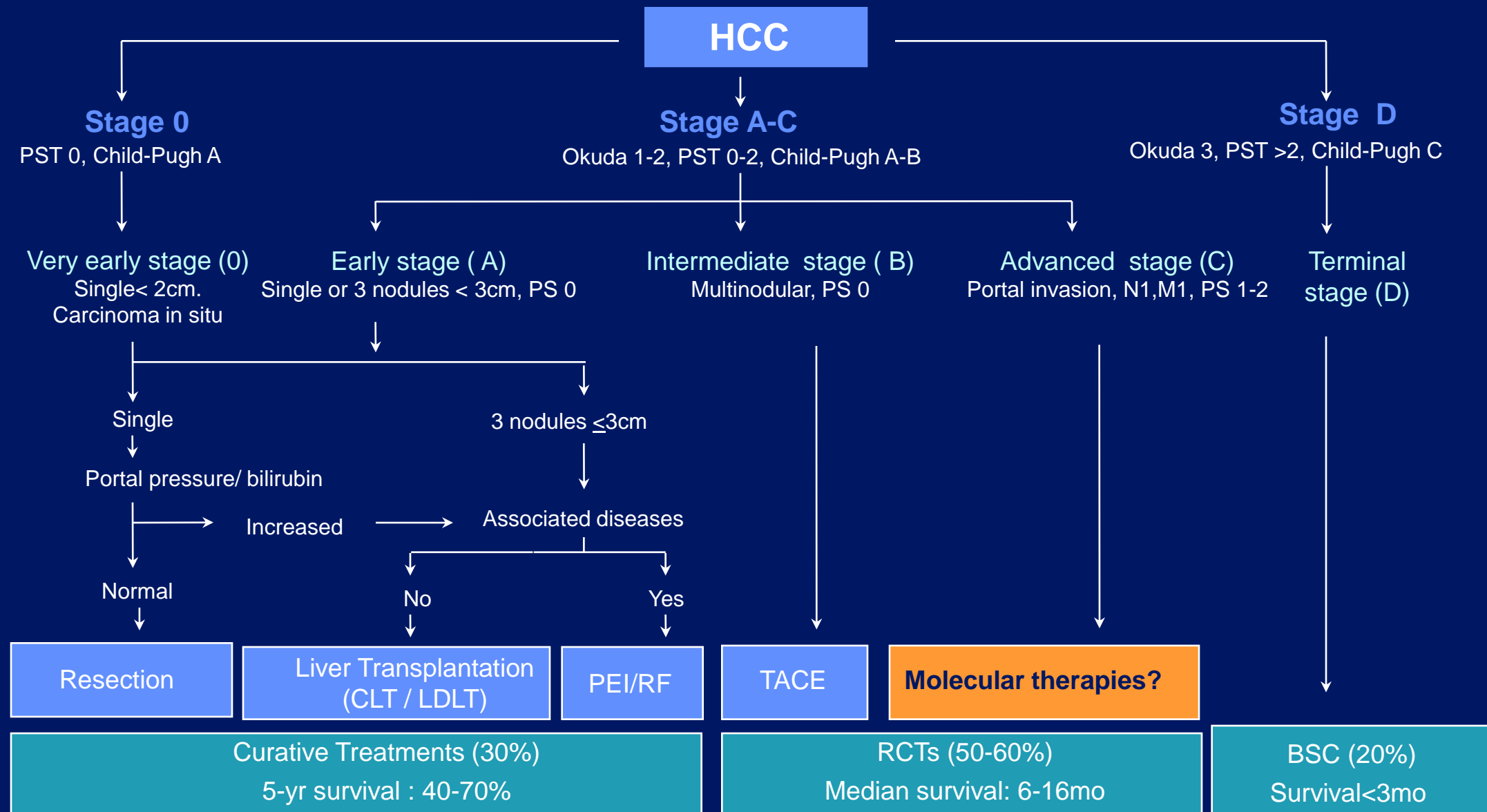


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## 3. Treatment of advanced HCC

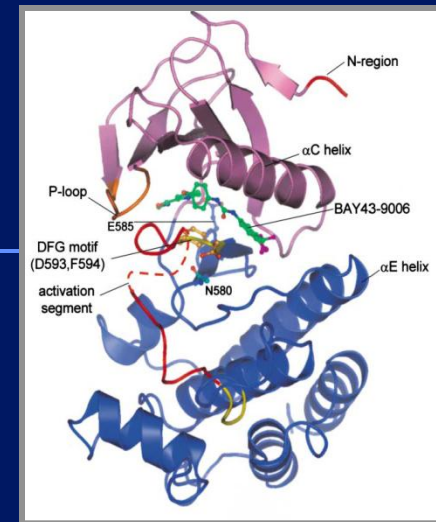
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# BCLC Staging and treatment schedule, 2006



# Molecular therapies: Sorafenib

## Inhibition of STK and RTK



### Receptor Tyrosine Kinases

| Kinase                         | IC <sub>50</sub> (nM) |
|--------------------------------|-----------------------|
| VEGFR-1                        | 26                    |
| VEGFR-2                        | 90                    |
| VEGFR-3*                       | 20                    |
| FLT3                           | 33                    |
| RET#                           | 47                    |
| PDGFR- $\beta$ *               | 57                    |
| C-KIT                          | 68                    |
| FGFR-1                         | 580                   |
| c-met, IGFR-1, EGFR, HER2, LCK | >10,000               |

### Serine/threonine Kinases

| Kinase  | IC <sub>50</sub> (nM) |
|---|-----------------------|
| Raf-1   | 6                     |
| B-Raf   | 25                    |
| B-raf V600E                                       | 38                    |
| p38   | 38                    |
| Mnk-2   | 150                   |
| ERK-1, MEK- 1, PKA, PKB, PKC, cdk1/cyclinB, pim-1 | >10,000               |

# Phase III SHARP Trial

## Sorafenib vs placebo in advanced HCC

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\*

#### Stratification:

\* Macroscopic vascular invasion (portal vein) and/or extrahepatic spread

\* ECOG PS

\* Geographical region

Randomization  
N=602

Sorafenib (n=299)  
400 mg po bid  
continuous dosing

Placebo (n=303)  
2 tablets po bid  
continuous dosing

ASCO  
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

### CLINICAL CANCER ADVANCES 2007

Major Research Advances in Cancer Treatment, Prevention, and Screening



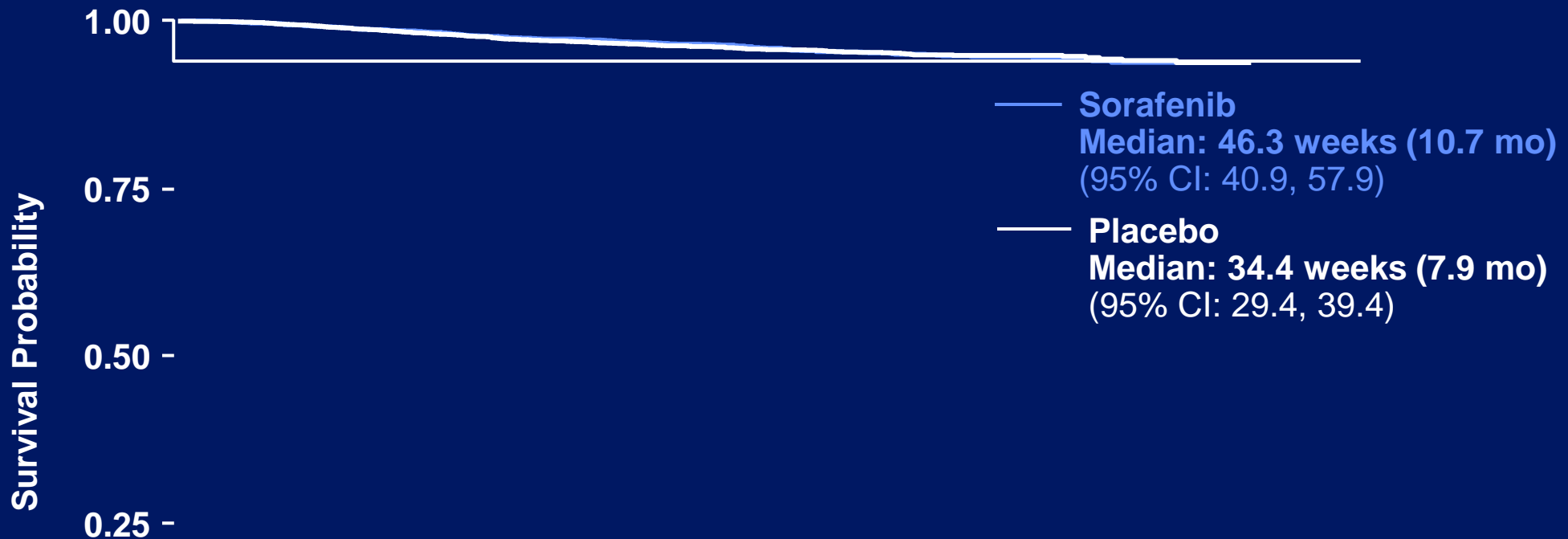
A REPORT FROM THE  
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Published in the Journal of Clinical Oncology  
Vol. 26, No. 2, January 10, 2008

# Phase III SHARP Trial



## Overall survival (Intention-to-treat)



**Hazard ratio (S/P): 0.69 (95% CI: 0.55, 0.87).**  
***P*=0.00058\***

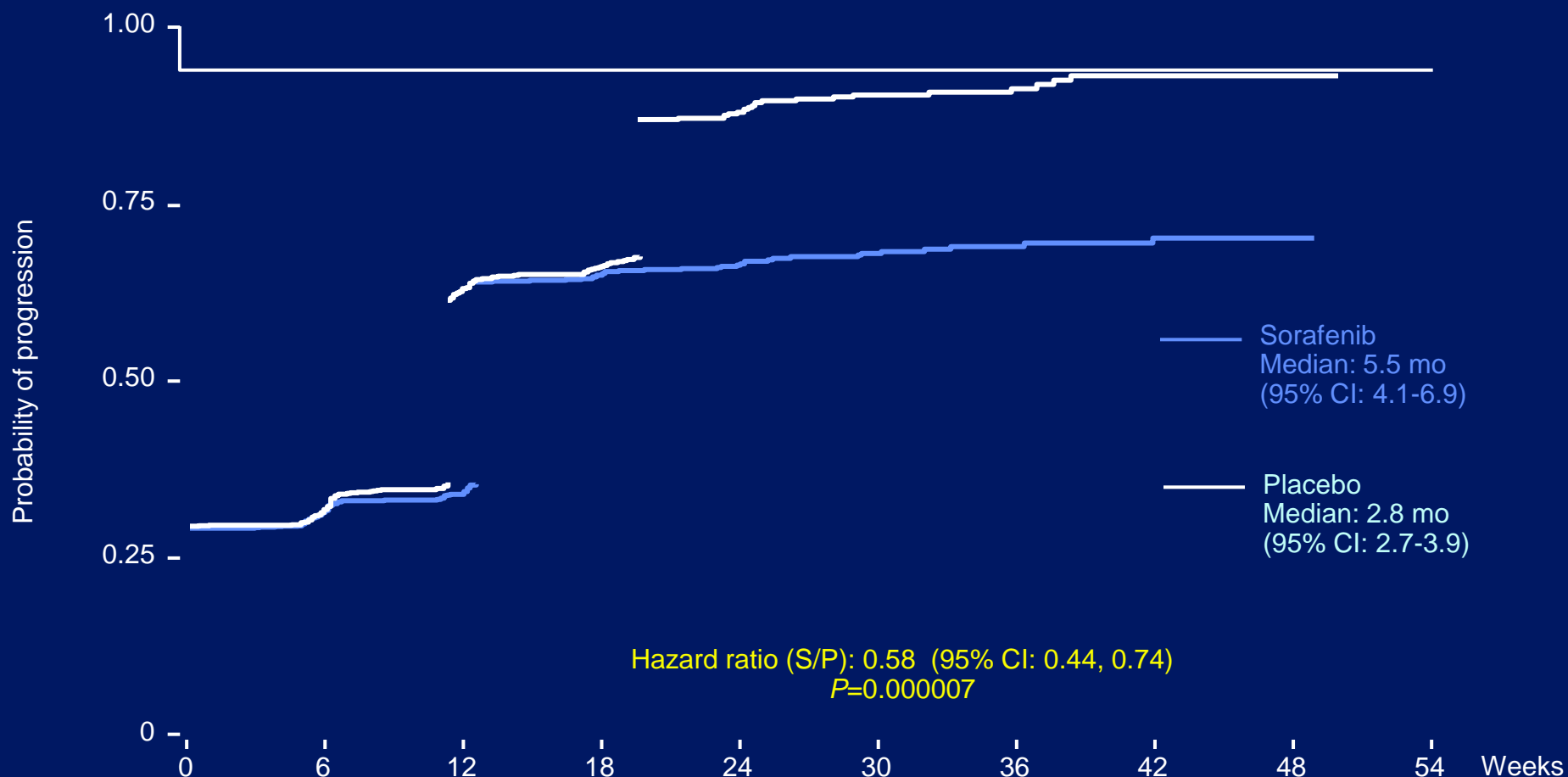
|                         | 0   | 8   | 16  | 24  | 32  | 40  | 48 | 56 | 64 | 72 | 80 | Weeks |
|-------------------------|-----|-----|-----|-----|-----|-----|----|----|----|----|----|-------|
| <u>Patients at risk</u> |     |     |     |     |     |     |    |    |    |    |    |       |
| Sorafenib:              | 299 | 274 | 241 | 205 | 161 | 108 | 67 | 38 | 12 | 0  | 0  |       |
| Placebo:                | 303 | 276 | 224 | 179 | 126 | 78  | 47 | 25 | 7  | 2  | 0  |       |

# Phase III SHARP Trial



The NEW ENGLAND  
JOURNAL of MEDICINE

## Time to Progression (Independent central review)



### Patients at risk

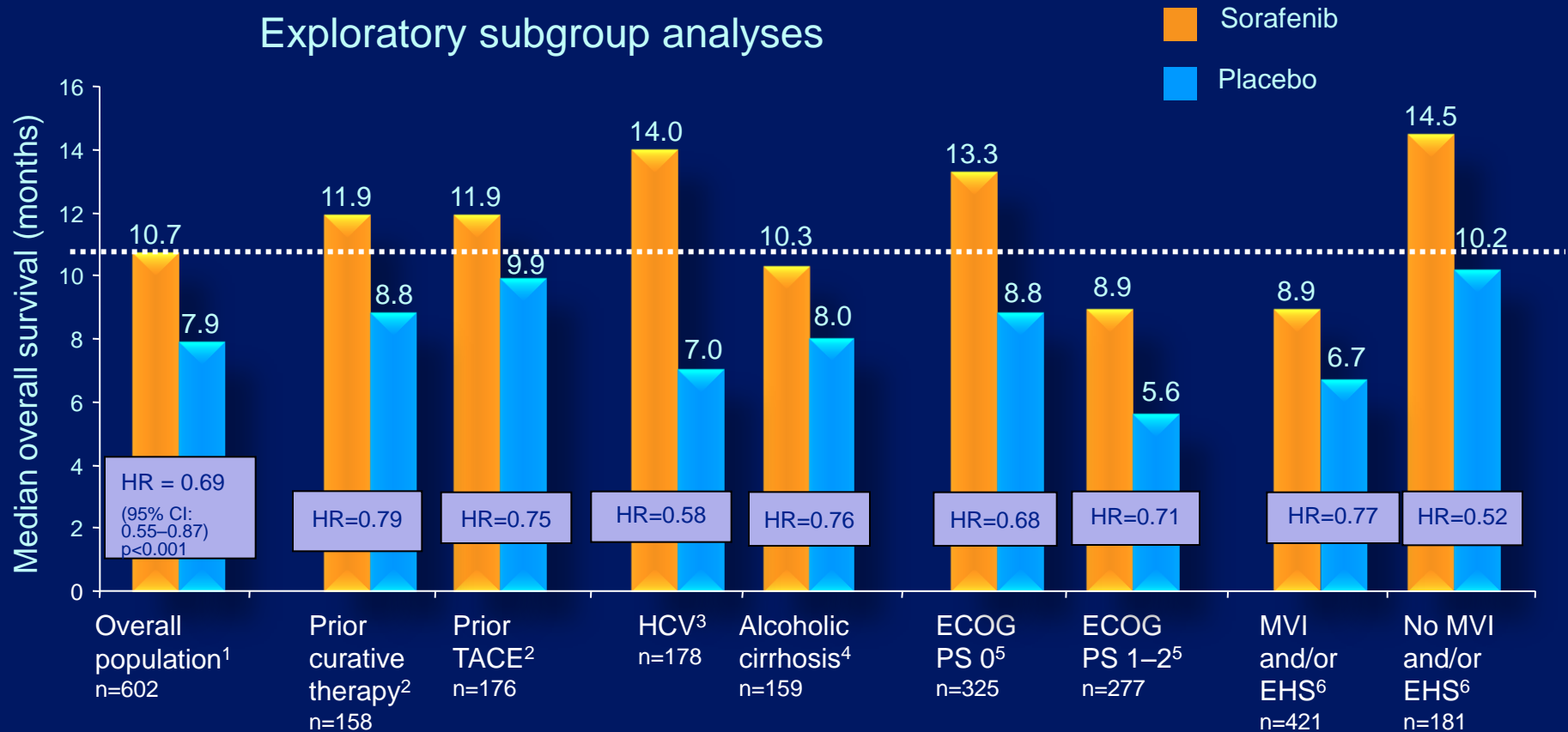
|            | 0   | 6   | 12  | 18 | 24 | 30 | 36 | 42 | 48 | 54 |
|------------|-----|-----|-----|----|----|----|----|----|----|----|
| Sorafenib: | 299 | 196 | 126 | 80 | 50 | 28 | 14 | 8  | 2  | 0  |
| Placebo:   | 303 | 192 | 101 | 57 | 31 | 12 | 8  | 2  | 1  | 0  |

# Phase III SHARP Trial

## Subgroup analysis

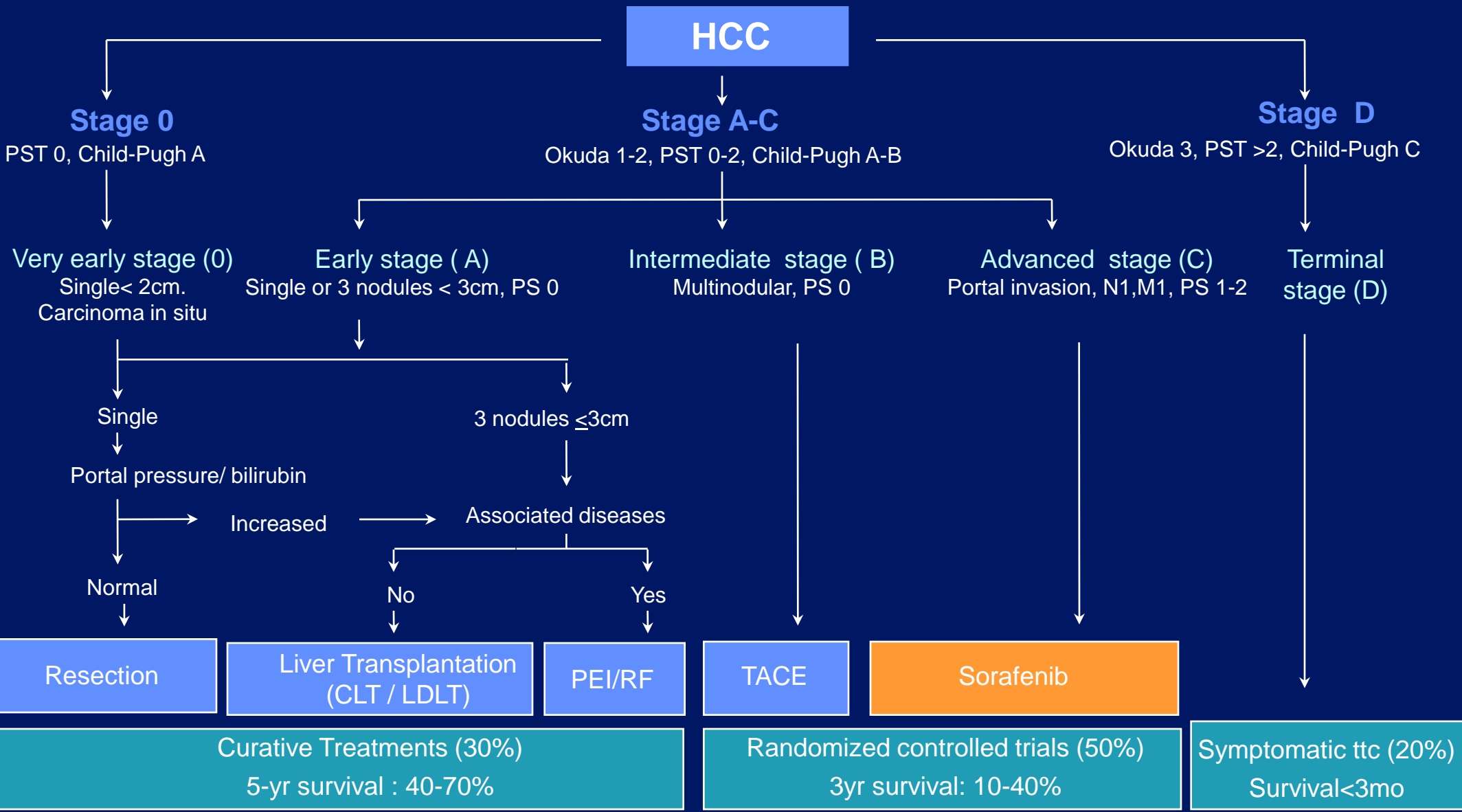


The NEW ENGLAND  
JOURNAL of MEDICINE

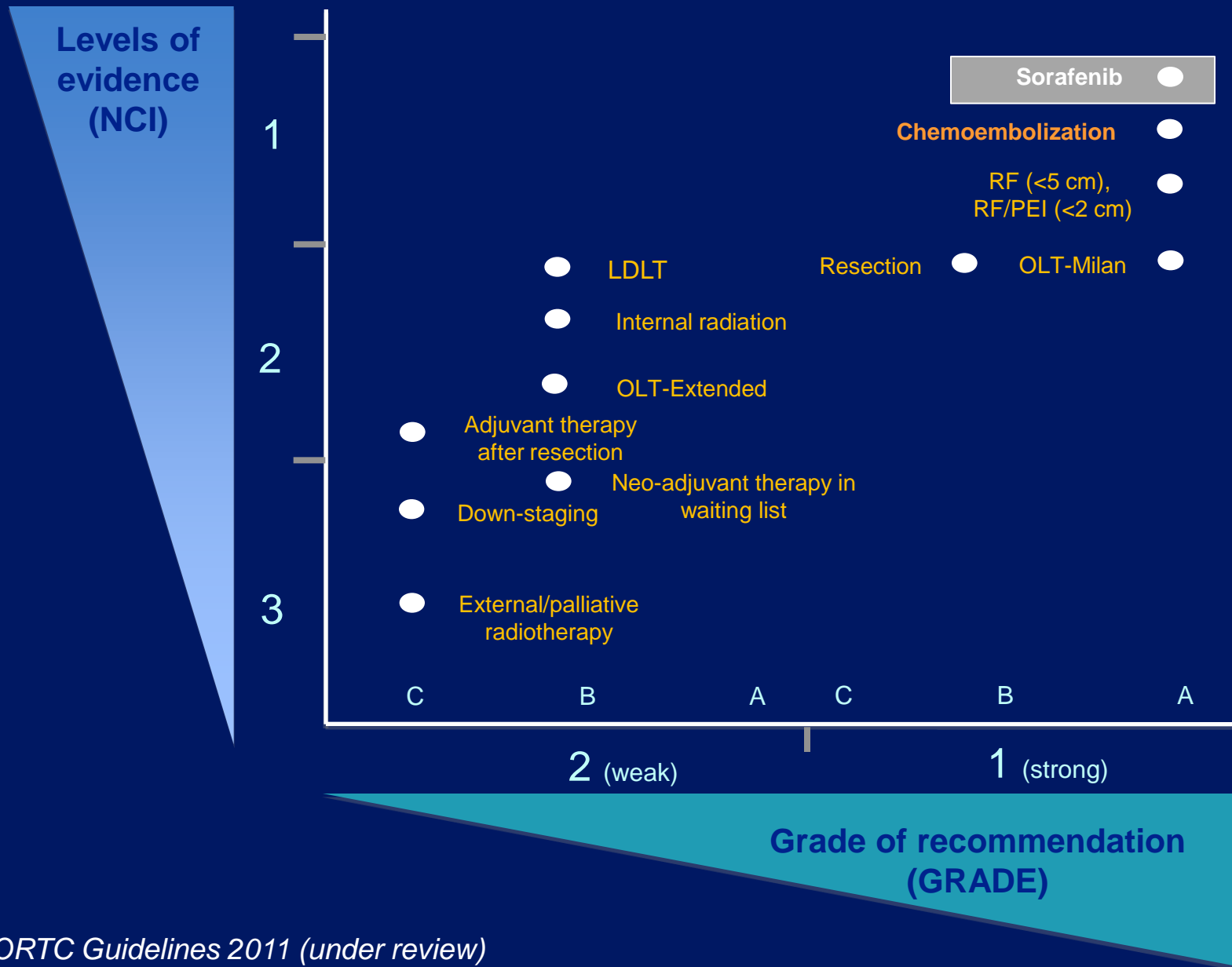


1. Llovet et al. N Engl J Med 2008; 2. Galle et al. EASL 2008, Milan, Italy  
 3. Bolondi et al. ASCO-GI 2008, Orlando, FL, USA; 4. Craxi et al. ASCO 2008, Chicago, IL, USA  
 5. Raoul et al. ASCO 2008, Chicago, IL, USA; 6. Sherman et al. ASCO 2008, Chicago, IL, USA

# Implications of Phase III SHARP Trial



# Evidence and recommendations for HCC therapies



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## 4. Design of RCT in HCC-SPACE:

### Rationale

Target population

Liver function: Child-Pugh A class

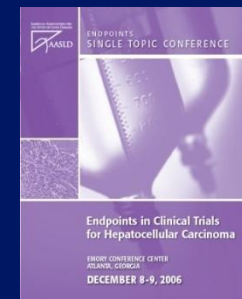
Tumor status: BCLC B

Control arm

End-points

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# AASLD-JNCI guidelines in HCC



## COMMENTARY

### **Design and Endpoints of Clinical Trials in Hepatocellular Carcinoma**

Josep M. Llovet, Adrian M. Di Bisceglie, Jordi Bruix, Barnett S. Kramer, Riccardo Lencioni, Andrew X. Zhu, Morris Sherman, Myron Schwartz, Michael Lotze, Jayant Talwalkar, Gregory J. Gores; for the Panel of Experts in HCC-Design Clinical Trials

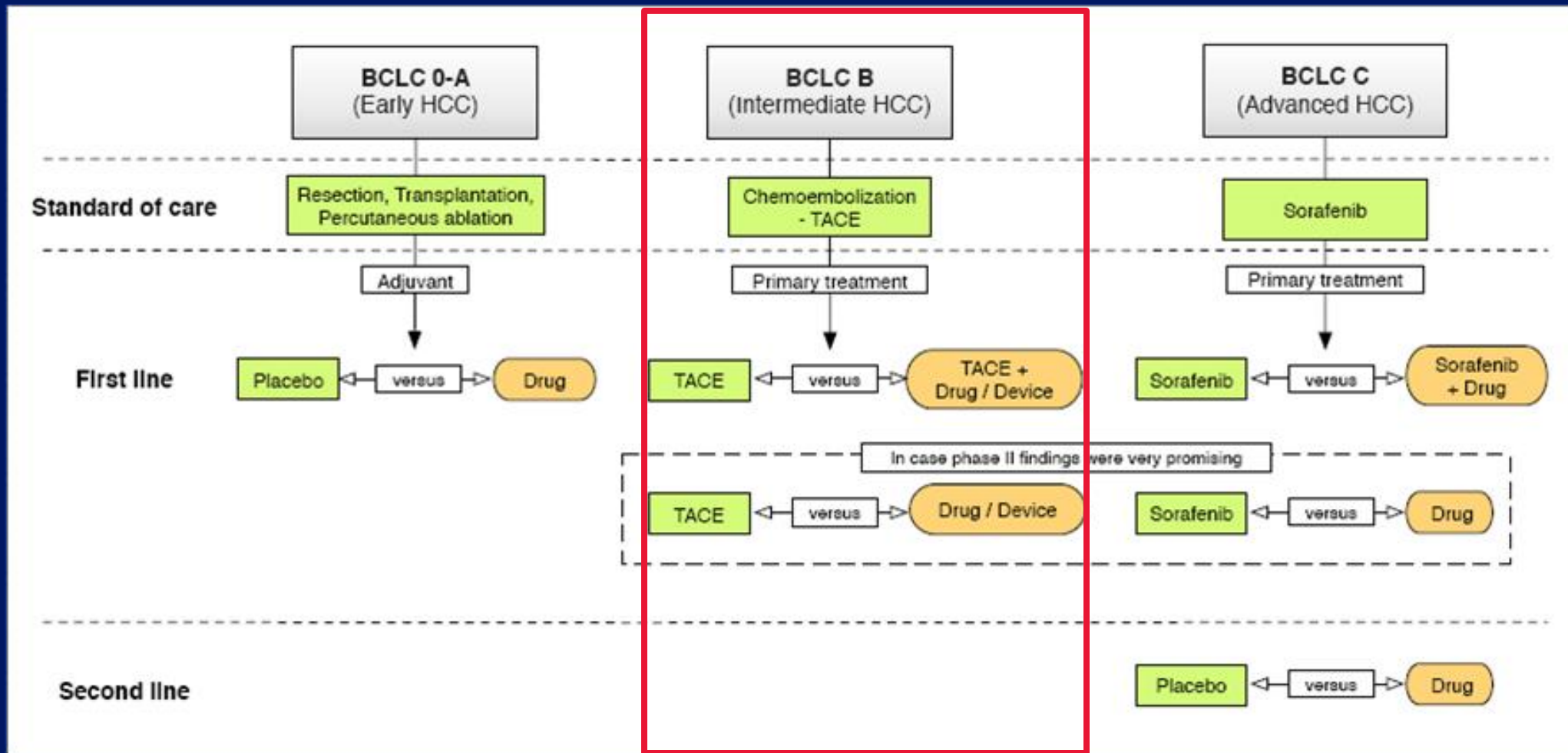
J Natl Cancer Inst 2008;100:698-711

RCTs are needed to define :

- 1 .- Adjuvant treatment after resection/ local ablation
- 2 .- **Combination of treatments with TACE in intermediate stages**
- 3 .- Second line treatment of advanced HCC

# AASLD-JNCI guidelines in HCC

## Trial design



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## 4. Design of RCT in HCC-SPACE:

Rationale

Target population

Liver function: Child-Pugh A class

Tumor status: BCLC B

Control arm

End-points

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# Design of clinical trials in HCC

## Rationale for selection of Child A patients

### Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies

Gennaro D'Amico<sup>1,\*</sup>, Guadalupe Garcia-Tsao<sup>2</sup>, Luigi Pagliaro<sup>1</sup>

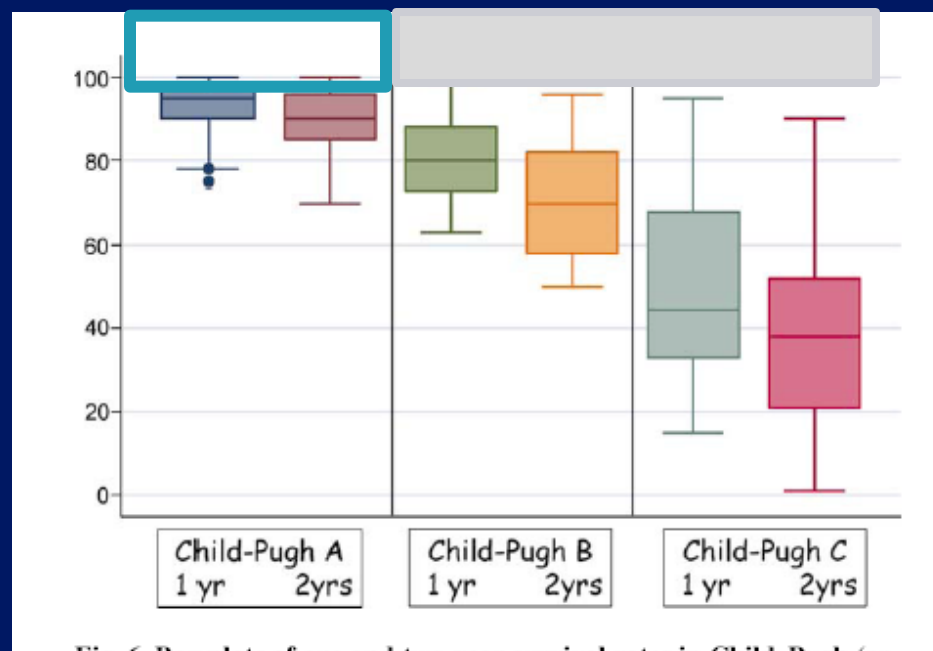
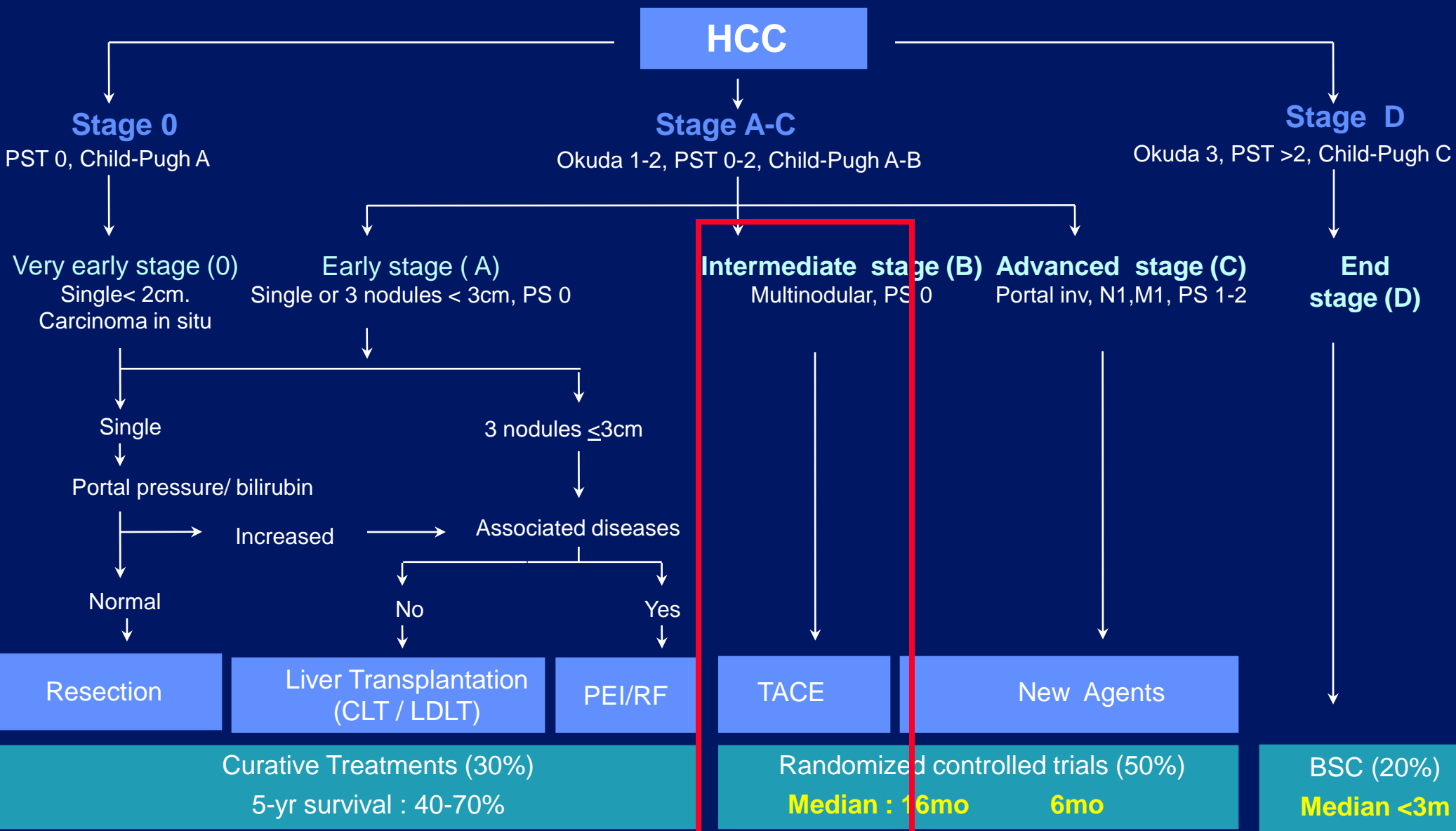


Fig. 6. Box plots of one and two-year survival rates in Child-Pugh (or variants) class A, B and C in the studies reporting this information. The number of studies providing the relevant information is reported in Table 2.

# New clinical staging systems in HCC

| Staging system                                    | External validation | Type of variables                               | Treatment guidance | Endorsement           |
|---|---------------------|---|--------------------|-----------------------|
| <b>BCLC staging</b><br>(Llovet, Sem Liv Dis 1999) | Yes                 | Tumor status<br>Liver Function<br>Health status | Yes                | AASLD<br>EASL<br>JNCI |
| <b>CLIP score</b><br>(CLIP, Hepatology 1998)      | Yes                 | Tumor status<br>Liver function                  | No                 | AHPBA                 |
| <b>TNM–AJCC staging</b><br>(Vauhtey, JCO 2002)    | Yes                 | Tumor status                                    | No                 | AJCC                  |
| <b>JIS score</b><br>(Kudo, J Gastro 2003)         | Yes                 | Tumor status<br>Liver function                  | No                 | -                     |

# BCLC Staging and treatment schedule



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## 4. Design of RCT in HCC-SPACE:

Rationale

Target population

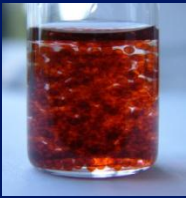
Liver function: Child-Pugh A class

Tumor status: BCLC B

Control arm

End-points

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# New embolization agents for HCC

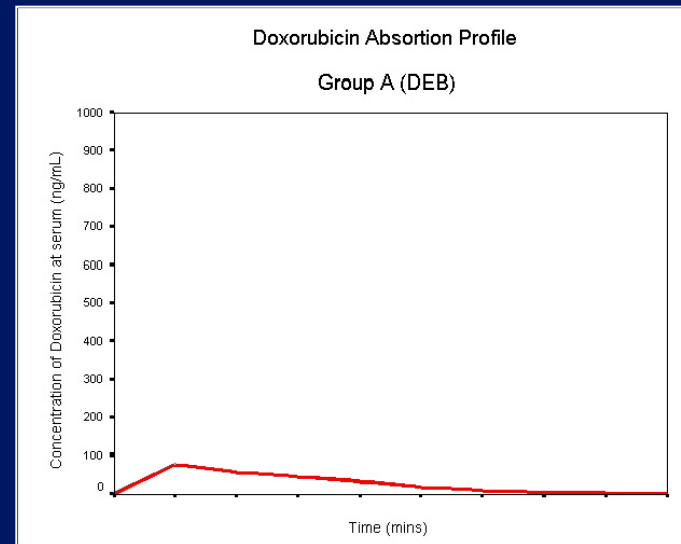
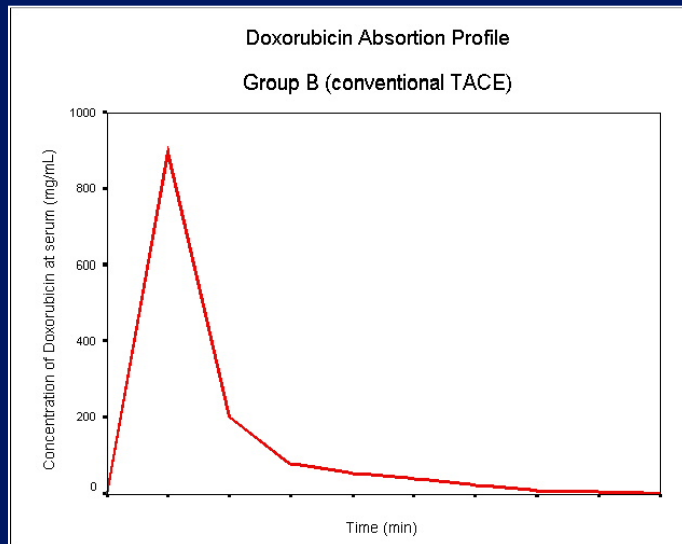
## Phase II : Doxorubicin-eluting Beads (n=27)

RECIST-modified

WHO-EASL modified

CR 0 (0%)  
PR 12 (44.4%)

7 (25.9%) **66.6%**  
11 (40.7%)



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## 4. Design of RCT in HCC-SPACE:

Rationale

Target population

Liver function: Child-Pugh A class

Tumor status: BCLC B

Control arm

End-points

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# Design of clinical trials for advanced HCC

## End-points

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### -Primary end-point.

#### 1. Survival (or cancer-related death)

Unquestionable primary end-point in cancer research.

End-point tested in almost all RCTs in HCC.

Endorsed by NCI, EASL, AASLD

#### 2. Time-to-progression (TTP)

End-point seldomly tested in HCC

Consider for cytostatic agents aimed to delay progression (Milliar. Nature 2003)

Endorsed by FDA for regular and accelerated approval.

### Secondary end-points:

1. Treatment response.

2. Quality of life (validated scores).

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# Treatment of advanced HCC

## Changing the paradigm in the design of clinical trials for HCC

| Conventional “mechanical” treatments | OR          | Survival benefit |
|--------------------------------------|-------------|------------------|
| Radiofrequency ablation/PEI          | 70-80% (CR) | yes              |
| Chemoembolization                    | 35-40% (PR) | yes              |
| Internal radiation (I-131, Y-90)     | 20-30% (PR) | unknown          |
| Intraarterial chemotherapy           | 15-20% (PR) | unknown          |
| Systemic chemotherapy                | 10% (PR)    | no               |

**EASL**

| New treatments in oncology. Targeting signaling pathways |                  |                        |
|--|------------------|------------------------|
| Small molecule- Tyrosine kinase inhibitors.              |                  |                        |
| EGFR: Erlotinib,   | 9% (PR)          | NSCLC                  |
| <b>Sorafenib:Raf pathway inhibitor/Anti-VEGF</b>         | <b>2.7% (PR)</b> | <b>HCC</b>             |
| mTOR: Temsirolimus                                       | 8%               | RCC                    |
| Anti-VEGF: bevacizumab                                   | 10% (PR)         | Liver M1 <b>RECIST</b> |

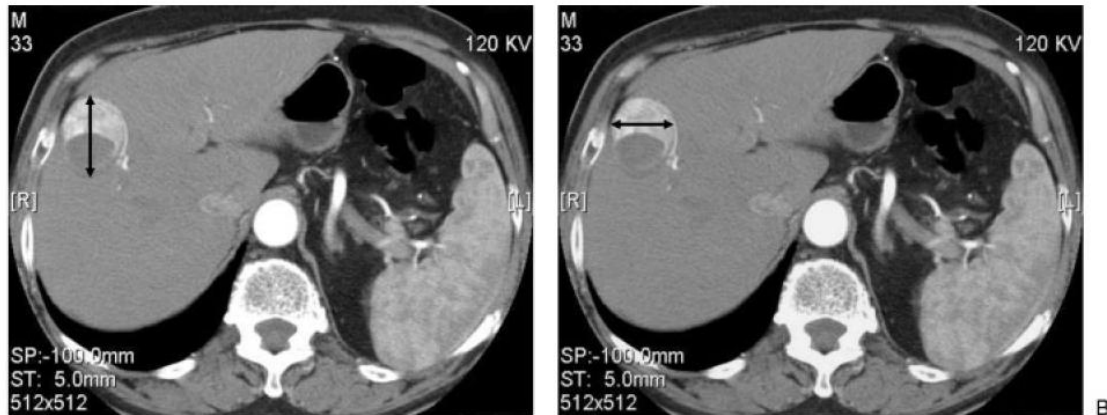
**End-point for phase II studies : TTP instead of RR**

# Assesment of response in HCC

## mRECIST

### Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma

Riccardo Lencioni, M.D.,<sup>1</sup> and Josep M. Llovet, M.D.<sup>2,3</sup>



**Figure 1** Application of mRECIST assessment for hepatocellular carcinoma (HCC). Target tumor response measurements on arterial-phase computed tomography (CT) scans. (A) Measurement of longest overall tumor diameter according to conventional RECIST, and (B) measurement of longest viable tumor diameter according to mRECIST for HCC.

Initial reports on OR in patients on sorafenib

(Raoul's group Cancer 2011; Kudo's group APPLE 2011)

RECIST < 5%  
mRECIST 20-23%

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## 4. SPACE and expected benefit

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# Molecular therapies under evaluation for HCC in Phase III (2011)

Targeted population

Phase II/III comparison

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**Adjuvant**

Prevent recurrences

1. Sorafenib vs placebo
2. Retinoids vs placebo

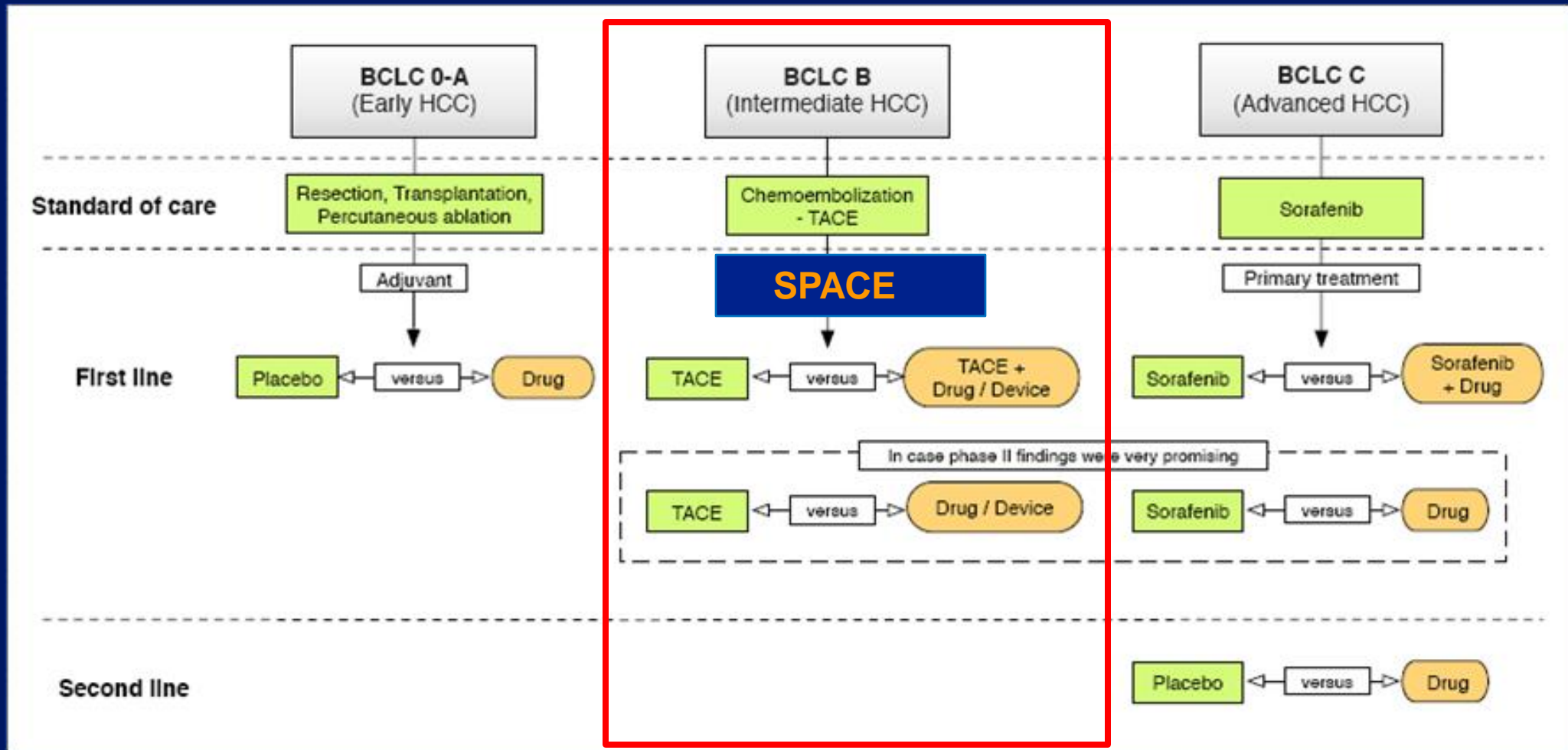
**Intermediate HCC**

**Improve TACE**

1. **TACE +/- sorafenib (SPACE)**
2. **TACE +/- brivanib (Phase 3)**
3. **TACE +/- everolimus**
4. **TACE +/- thalidomide (2 Phase 3)**
5. **TACE +/- sunitinib**

# AASLD-JNCI guidelines in HCC

## Trial design

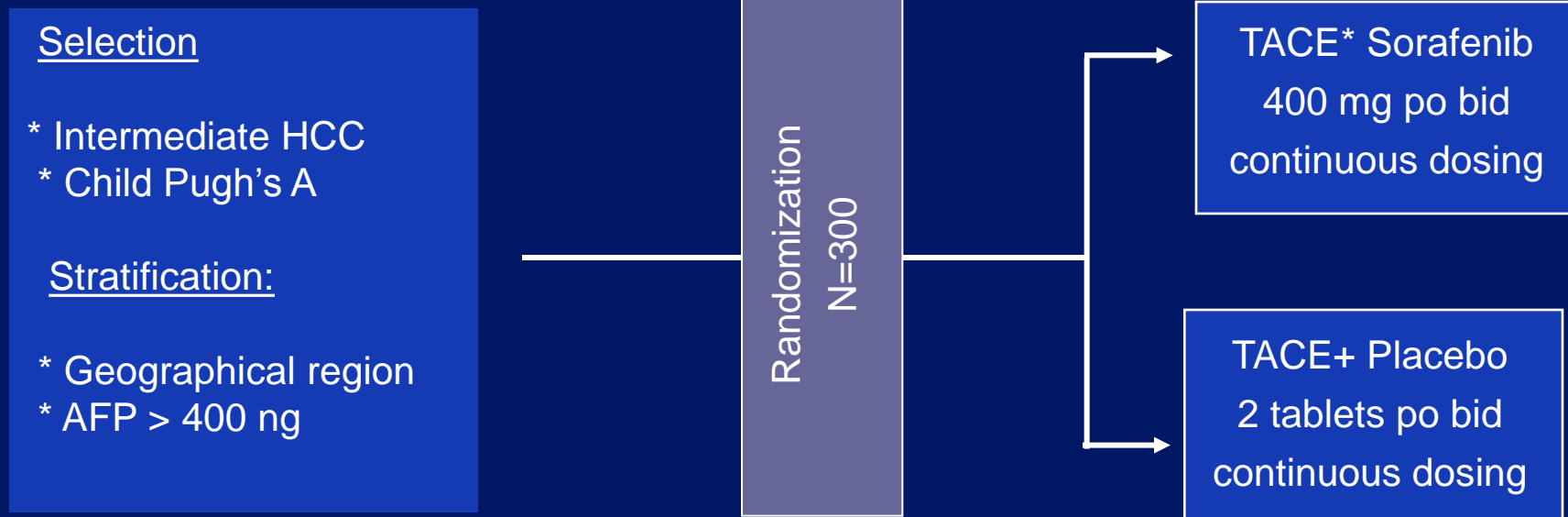


# SPACE Trial

## TACE + sorafenib vs TACE in intermediate HCC

Primary end-point: Time to Progression

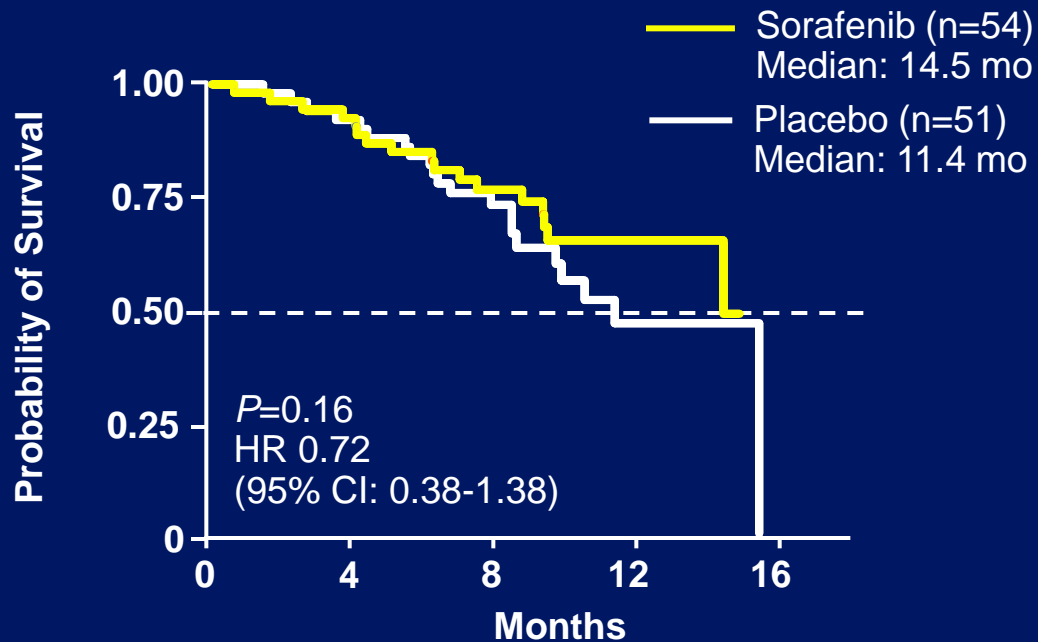
Centers: ~100 (America, Europe and Asia Pacific)



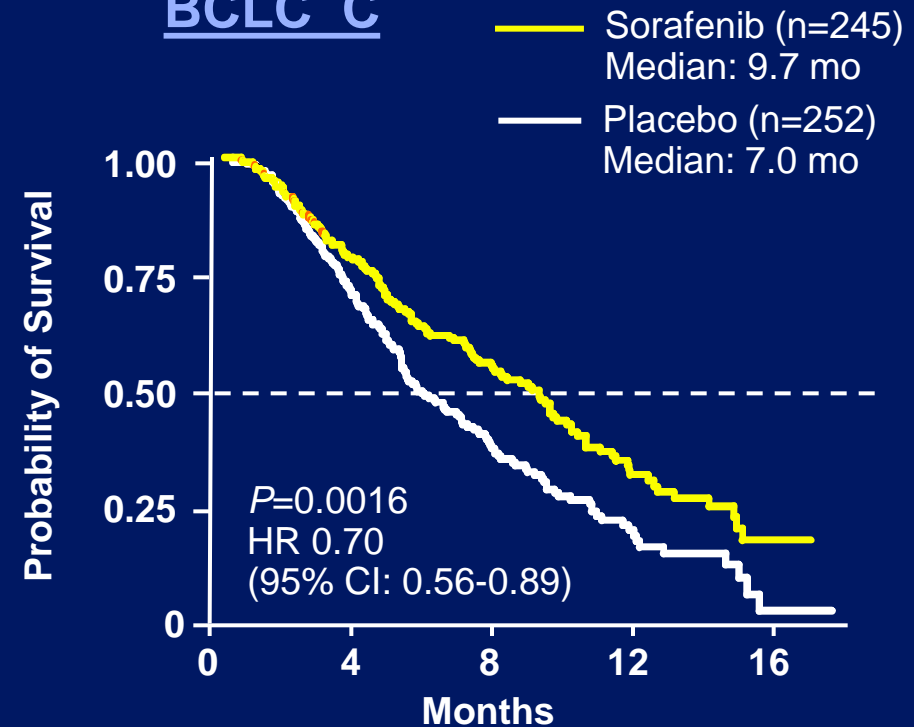
# SHARP -Subgroup analysis

## Stratifying for BCLC B vs C

### BCLC B

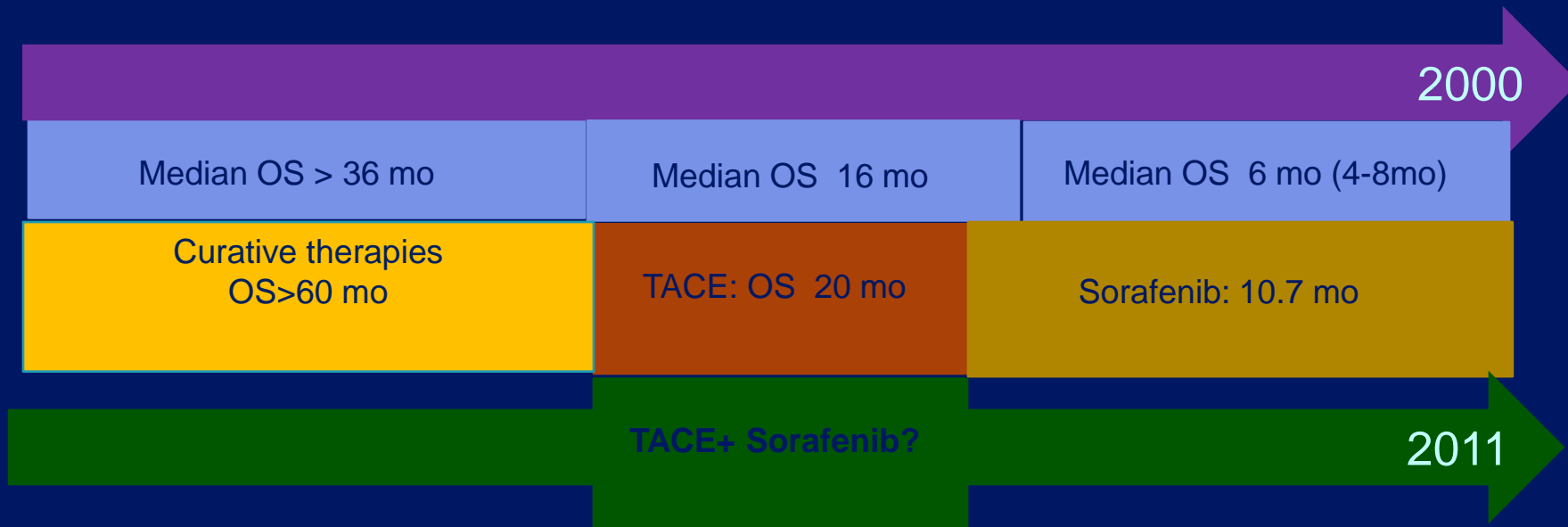
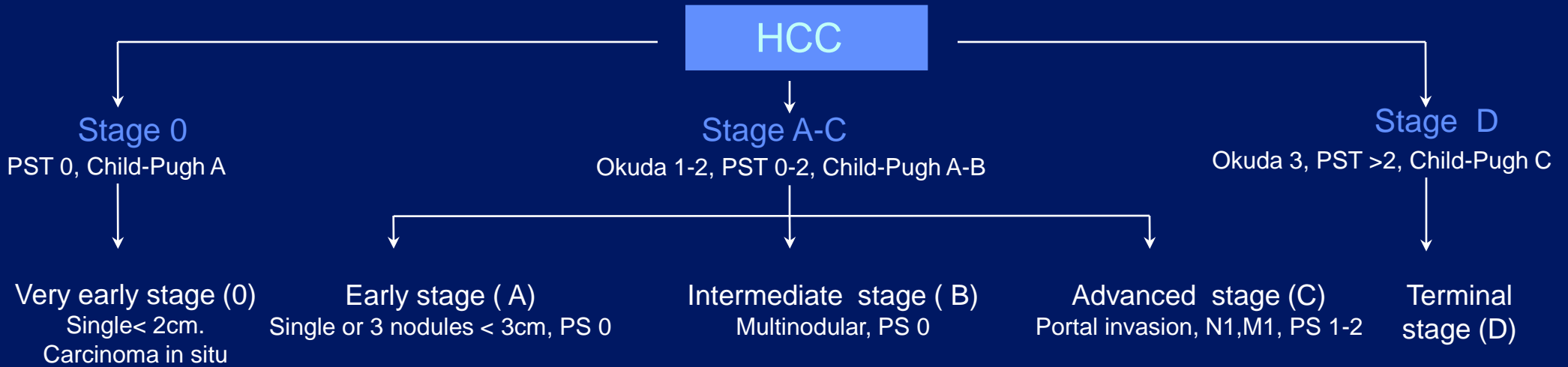


### BCLC C



- There was a trend for OS benefit in patients with BCLC B stage disease treated with sorafenib
  - However, the small sample size prevents robust analysis

# Understanding survival outcomes in HCC patients



# Satellite Symposium

## Management of Intermediate HCC with Sorafenib and Drug-Eluting Bead, Doxorubicin (DEBDOX™)



Chairman: Professor Josep Llovet, Barcelona Clinic Liver Cancer (BCLC) Group, Spain & Mount Sinai School of Medicine, New York, USA

Saturday 3 September, 2011 5:30  
– 6.30pm

Plenary Room  
Hong Kong Convention and Exhibition Centre



Overview of HCC management and rationale for SPACE trial

**Professor Josep Llovet**

Barcelona Clinic Liver Cancer (BCLC) Group, Spain & Mount Sinai School of Medicine, New York, USA



Is DEBDOX™ the new standard for chemoembolisation?

**Professor Riccardo Lencioni**

Pisa University Hospital and School of Medicine, Italy



Asian experience with Drug-Eluting Beads for HCC and rationale for the TRACER study

**Professor Ronnie Poon**

Queen Mary Hospital, The University of Hong Kong



Five-year follow up with DEBDOX in intermediate HCC, BCLC experience

**Professor Jordi Bruix**

Barcelona Clinic Liver Cancer (BCLC) Group, Spain



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