# Sorafenib (Nexavar®)
# Quelle place dans le traitement du carcinome hepatocellulaire?

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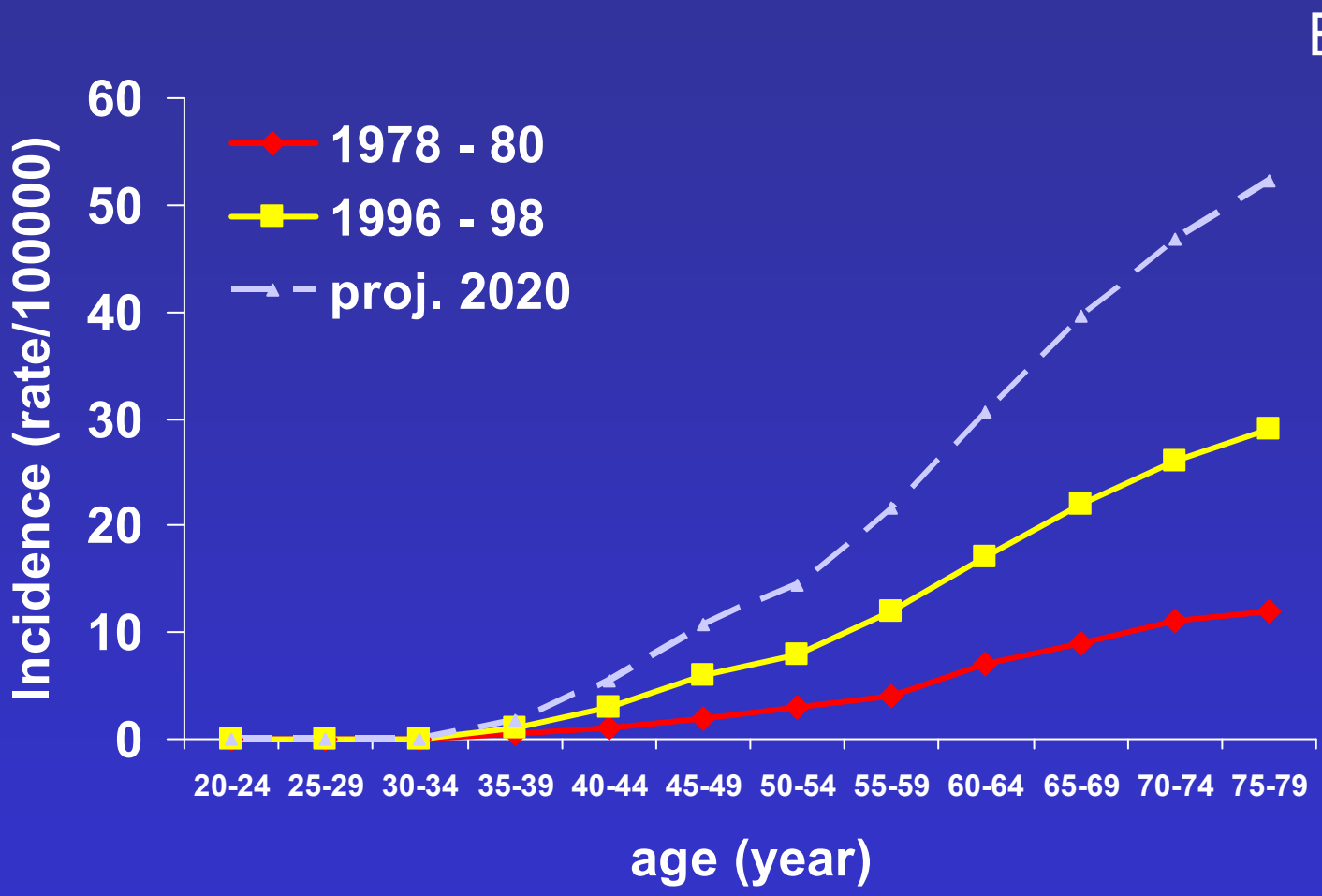
# CHC: le contexte

- 6ème tumeur au monde (600.000 nouveau cas/an)
- 3ème tumeur par mortalité
- Cause de mortalité la plus fréquente chez les patients cirrhotiques (risque 15-20% à 5 ans)
- L'incidence augmente (Genève: 1 nouveau patient/semaine)

# Incidence du CHC




En Suisse

~ 700

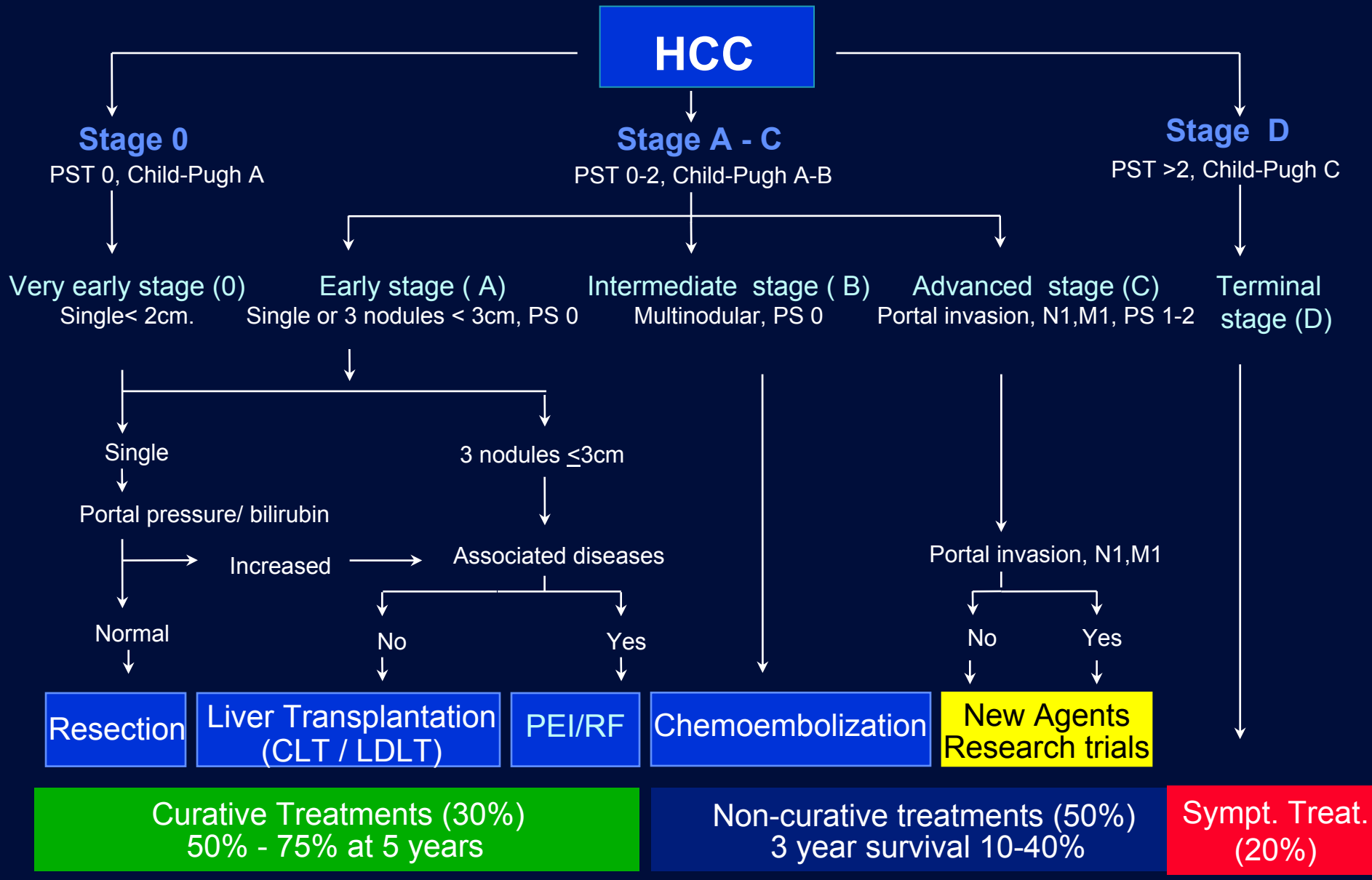
~ 400

~ 250

El-Serag et. al. Ann Intern Med 2003

Davis et. al. Liver Transplant 2003

# Stadiation et traitements



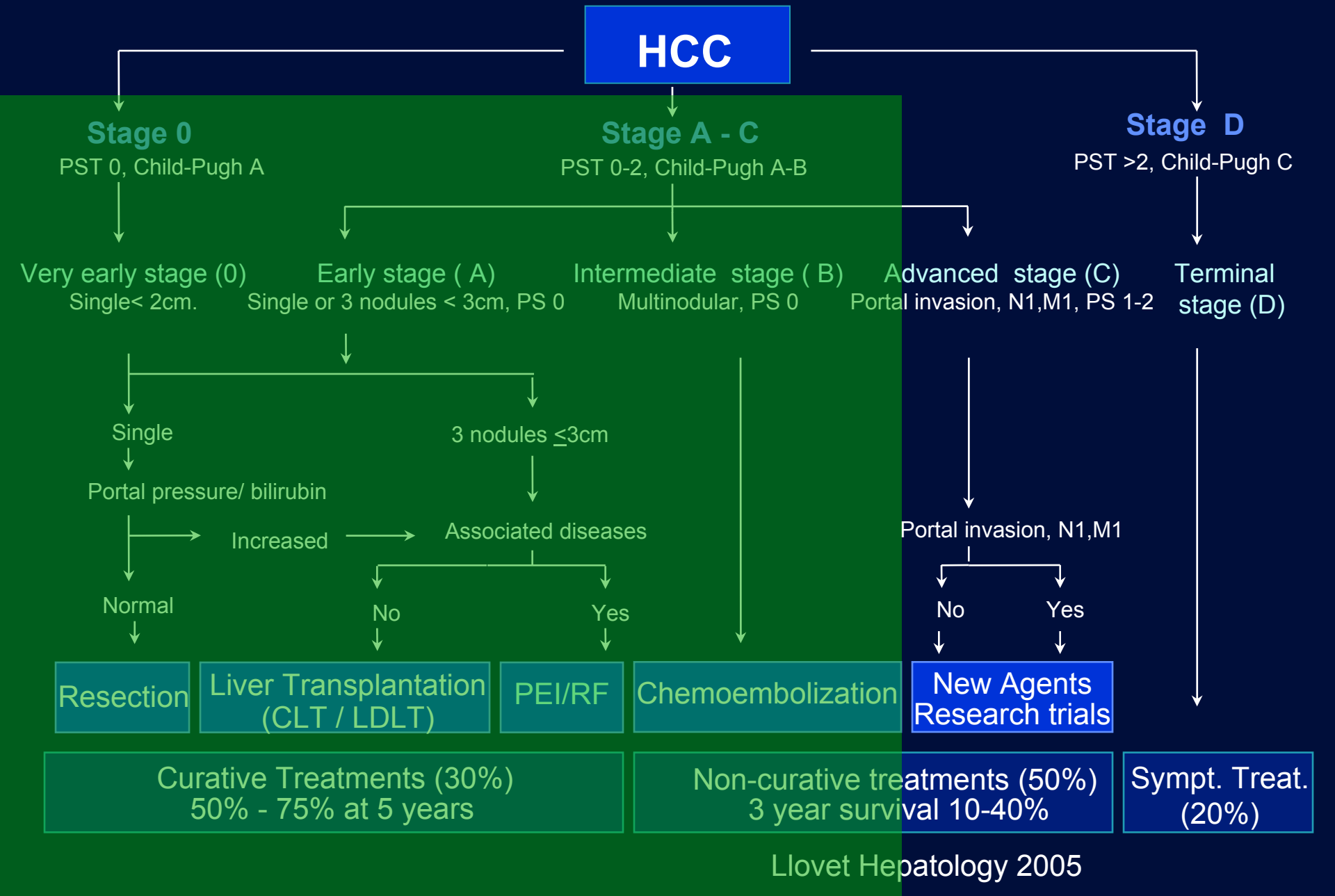

Llovet, Hepatology 2005

# Barcelona-Clínic Liver Cancer (BCLC) Group

*Liver Unit:* J. Bruix MD, JM. Llovet MD

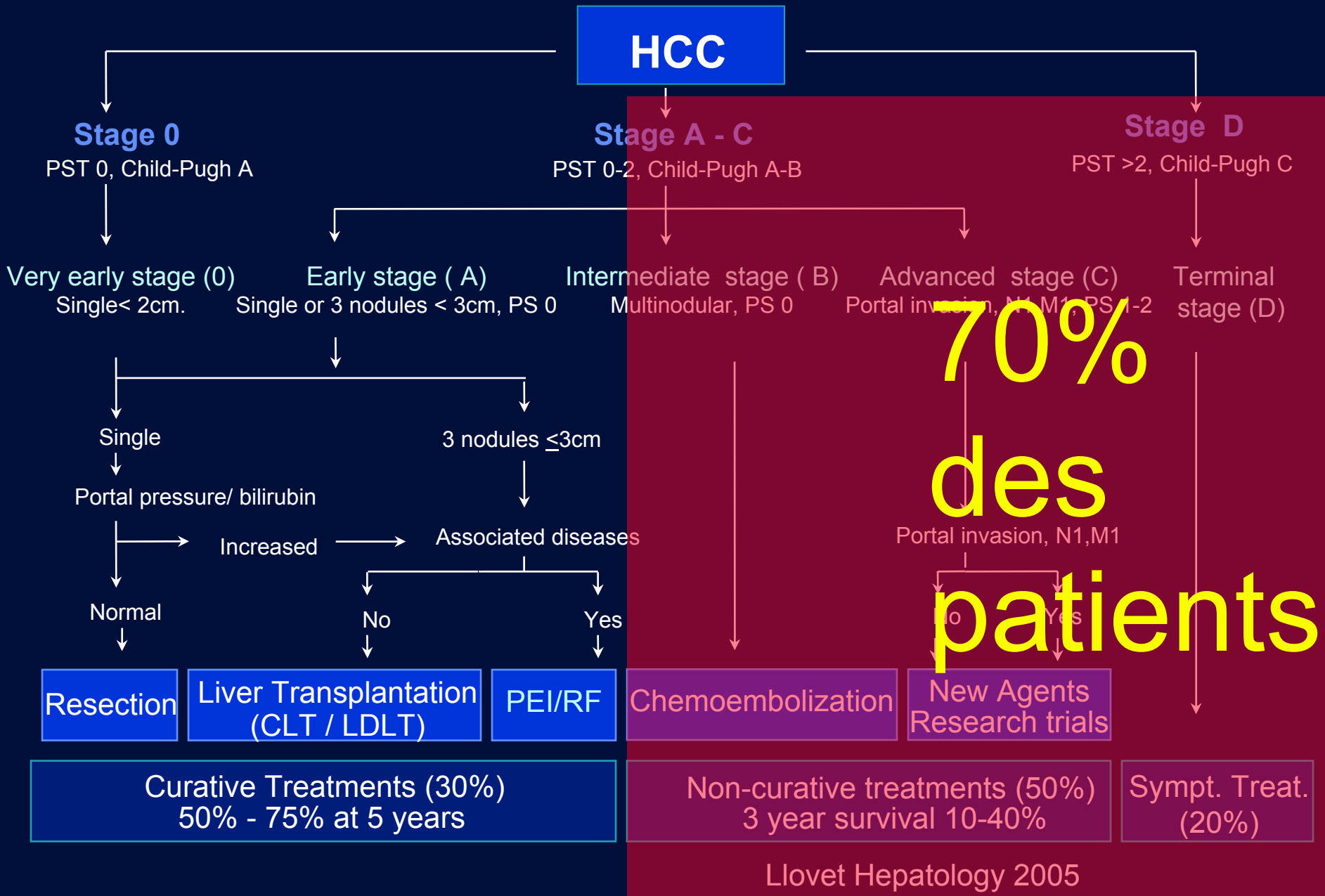
AASLD Boston 2007

# BCLC Staging and Treatment Strategy




Llovet Hepatology 2005

# BCLC Staging and Treatment Strategy



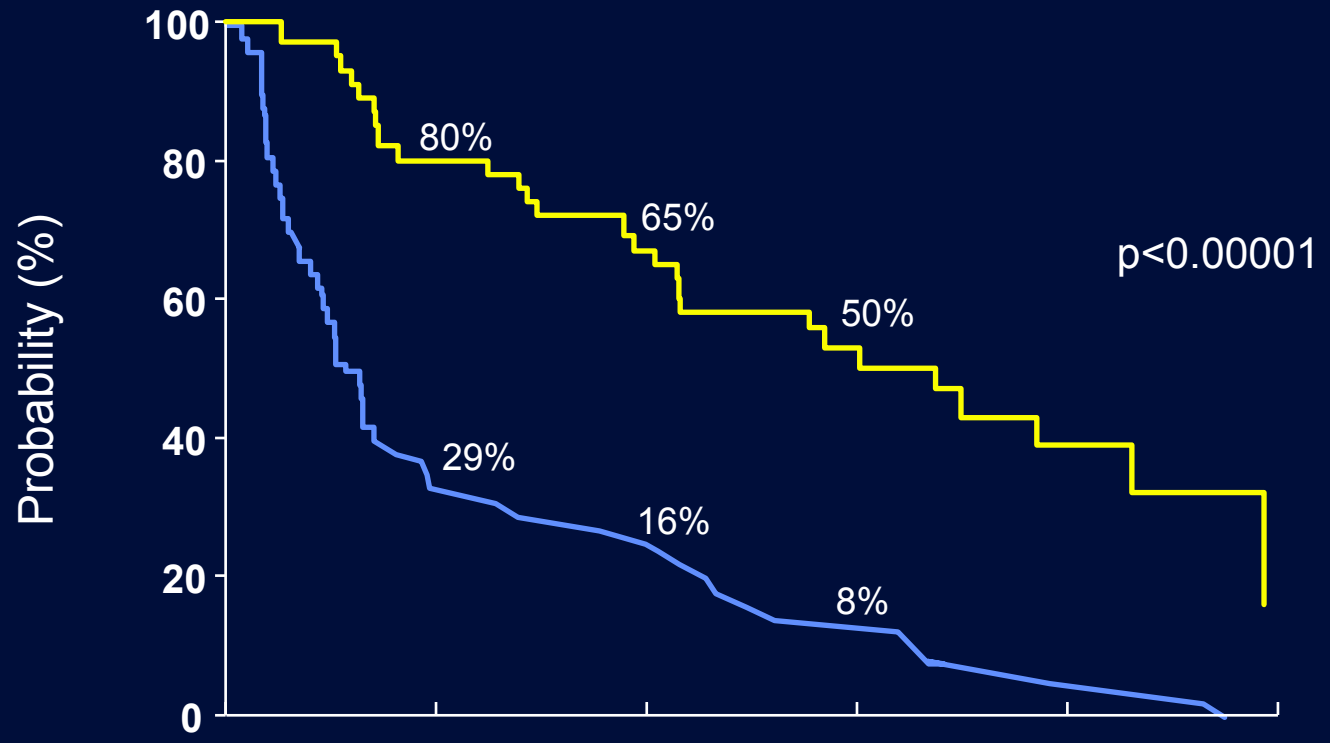

Llovet Hepatology 2005

# Pas de médicament actif! ☹

| Treatments | Studies | N | Objective response |
|---|---|---|---|
| Systemic chemotherapy | | | |
| Doxorubicin as single agent | Phase II/III | >1000 | 10-18% |
| Doxorubicin combination (PIAF) | Phase II/III | 144 | 26% |
| Cisplatin | Phase II | 48 | 10% |
| Epirubicin | Phase II | 62 | 11% |
| Mitoxantrone | Phase II | 118 | 16% |
| 5-FU,Paclitaxel, iridotecan, gemcitabine | Phase II/III | .... | <10% |
| Anti-androgen | Phase III | 376 | <10% |
| Interferon | Phase III | 60 | <10% |
| Tamoxifen | Phase III | >1000 | < 5% |
| Octreotide | Phase III | 60 | <5% |
| Seocalcitol | Phase III | 746 | <5% |

# Histoire naturelle des stades B et C

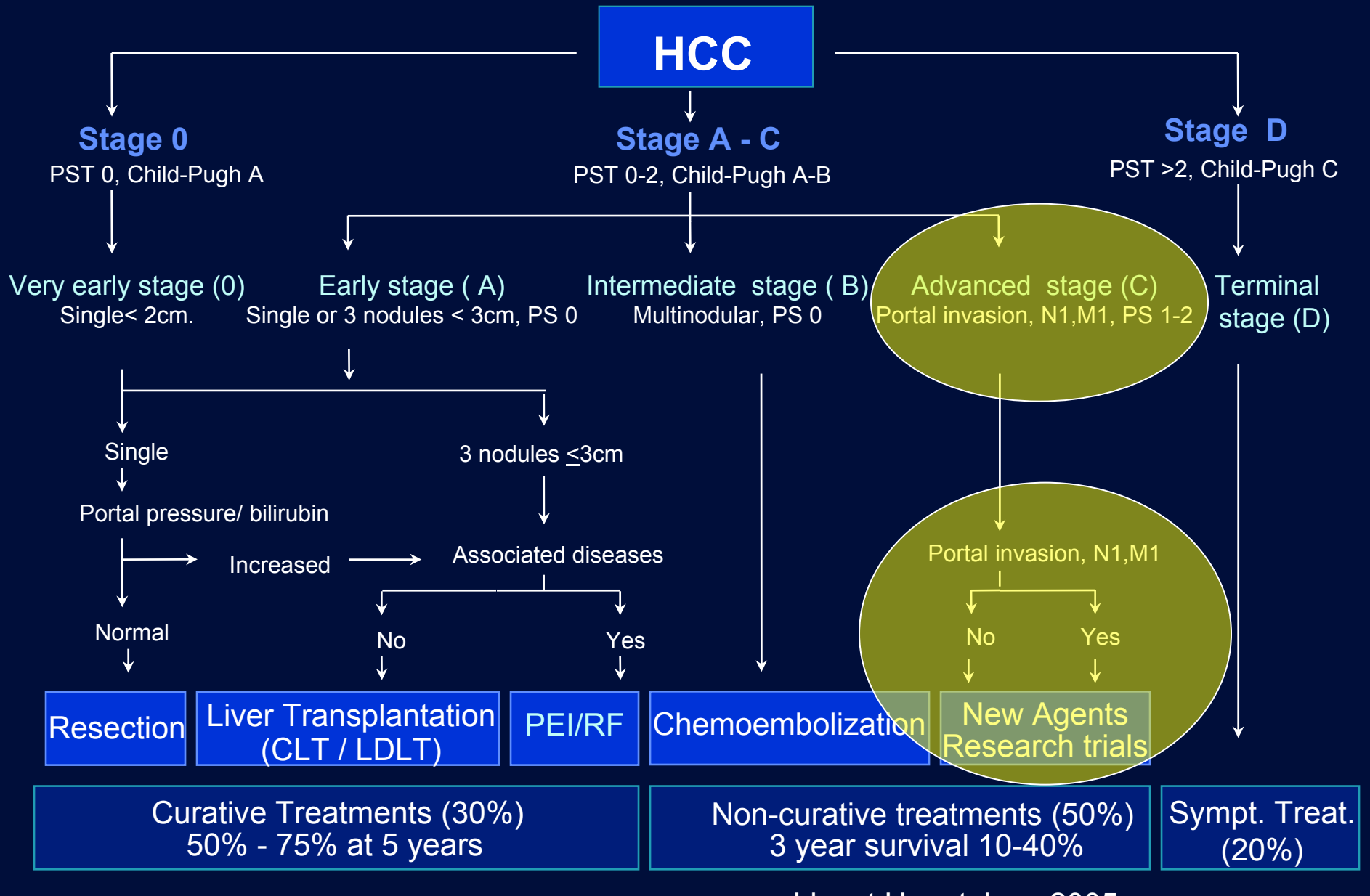
## Invasion vasculaire, ECOG-PS 1-2, Symptômes, Métastases




| 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 | - | | |

Llovet et al. Hepatology, 1999.

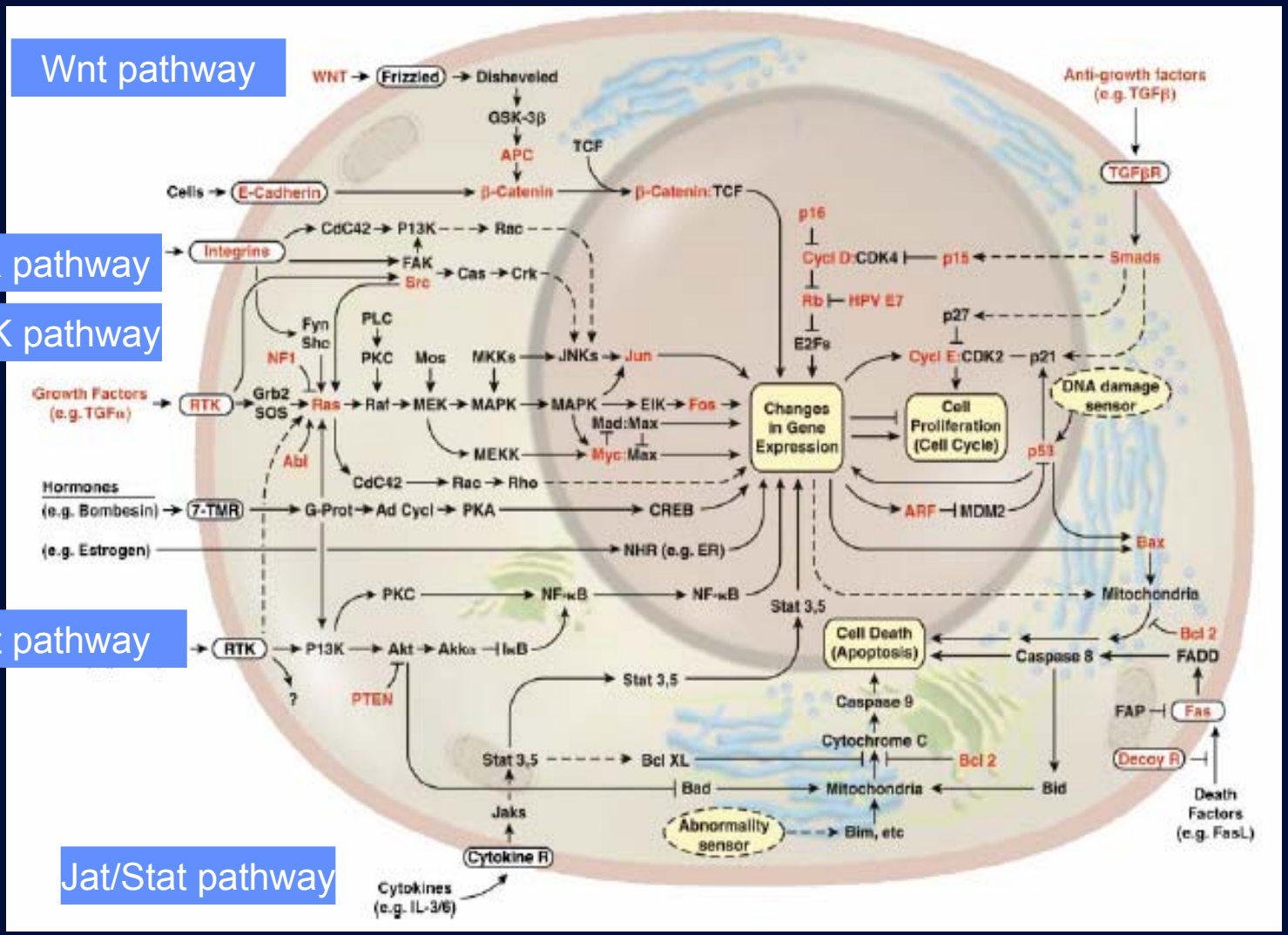
# Du Nouveau!




Llovet Hepatology 2005

# Le mérite:

## **mécanismes**: traitements pour des molécules cible



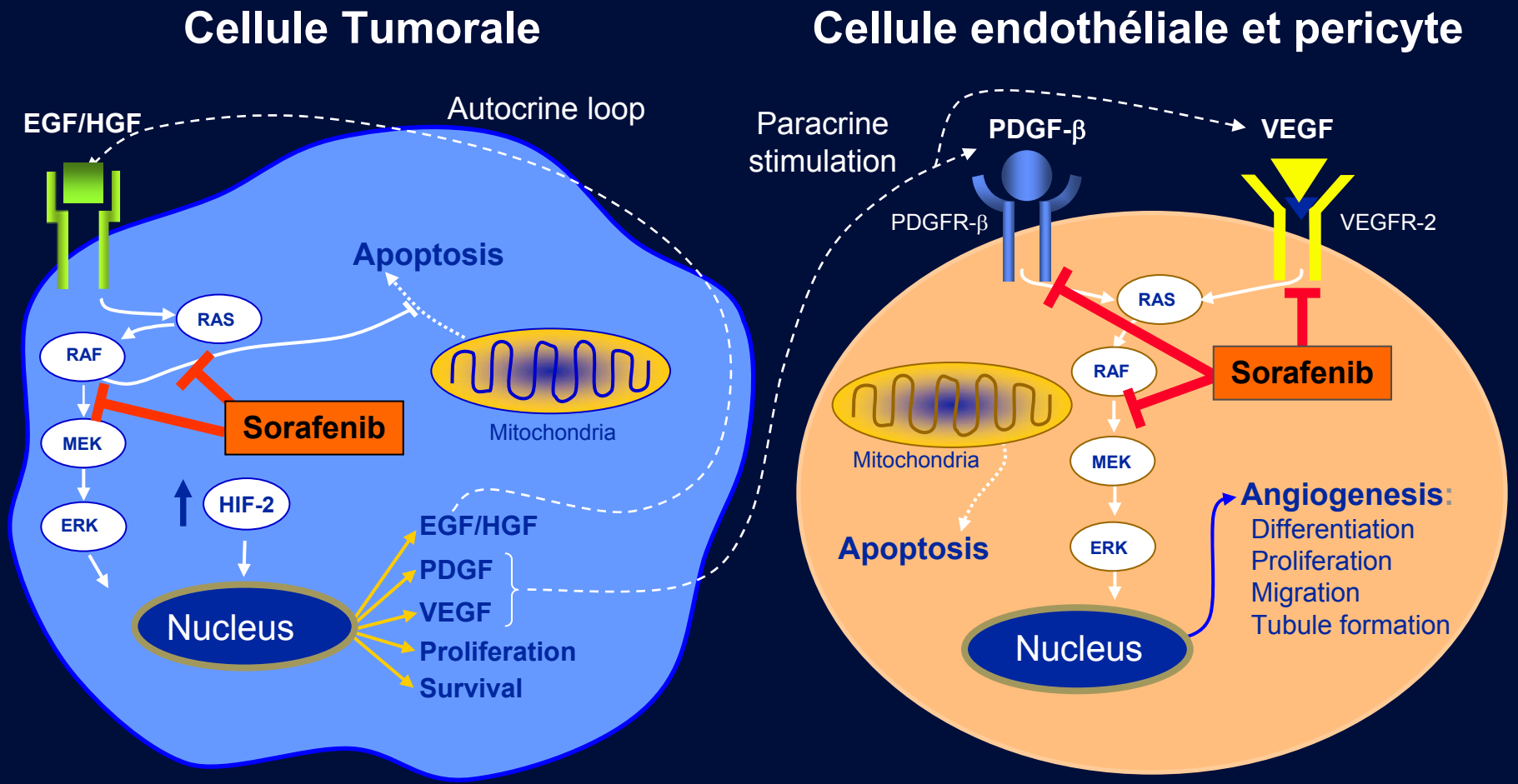

Hanahan. Cell 2000.

# Treatment of advanced HCC

## Molecular targeted agents

| Treatment | Action | Phase study |
|---|---|---|
| • **Tyrosine kinase inhibitors** | | |
| .- Sorafenib | RAF inhibitor/VEGF inhibitor (TKI) | III- stopped |
| .- Erlotinib/Gefitinib | EGFR inhibitor (TKI) | III- design |
| .- Erlotinib+ bevacizumab | EGFR inhibitor (TKI), VEGF inhibitor | II- ongoing |
| .- Cetuximab | EGFR inhibitor (Ab) | II- ongoing |
| .- Lapatinib | EGFR/Her2/Un inhibitor (TKI) | II- ongoing |
| .- Sunitininb | PDGFR/VEGFR/KIT inhibitor (TKI) | II- ongoling |
| • **Anti angiogenic agents** | | |
| .- Bevacizumab | VEGF inhibitor (Ab) | II - ongoing |
| .- Thalidomide | Antiangiogenic | III- ongoing |
| • **Other molecular targeted therapies** | | |
| .- Bortezomib | Proteasome inhibitor | II-stopped |
| .- Acyclic retinoids | Differentiation | III- design |
| .- Nolatrexed | Thymidylate synthase | *III- negative* |
| .- T138067 | Tubulin inhibitor | *III- negative* |

# Sorafenib cible à la fois la prolifération céllulaire et l'angiogenèse




Wilhelm S et al. *Cancer Res.* 2004;64:7099-7109.

# Phase 3: Sorafenib vs placebo for patients with advanced hepatocellular carcinoma (SHARP)

**Design**

- **International, multicentre, Phase III study.**
- **Inclusion criteria:**
  - **Histology proven HCC**
  - **Advanced HCC**
  - **At least one measurable untreated lesion**
  - **ECOG 0-2**
  - **Child-Pugh A (to reduce confounding liver deaths)**
  - **No prior systemic treatment**

**Stade B+ et C!**

**Randomization**

- **Double-blind placebo-controlled trial; Ratio 1:1**
- **Accrual: March 2005 to April 2006.**

# Phase III SHARP Trial
## Study design

### Treatment schedule

- Sorafenib treatment was stopped if:
  - Both radiologic progression and FHSI8-TSP were achieved
  - Any adverse event required discontinuation

### Statistical methods

- Intention-to-treat analysis
- Sample size : N= 560 patients (424 OS events)
  Overall alpha for trial maintained at $\alpha$=0.025 (one-sided)

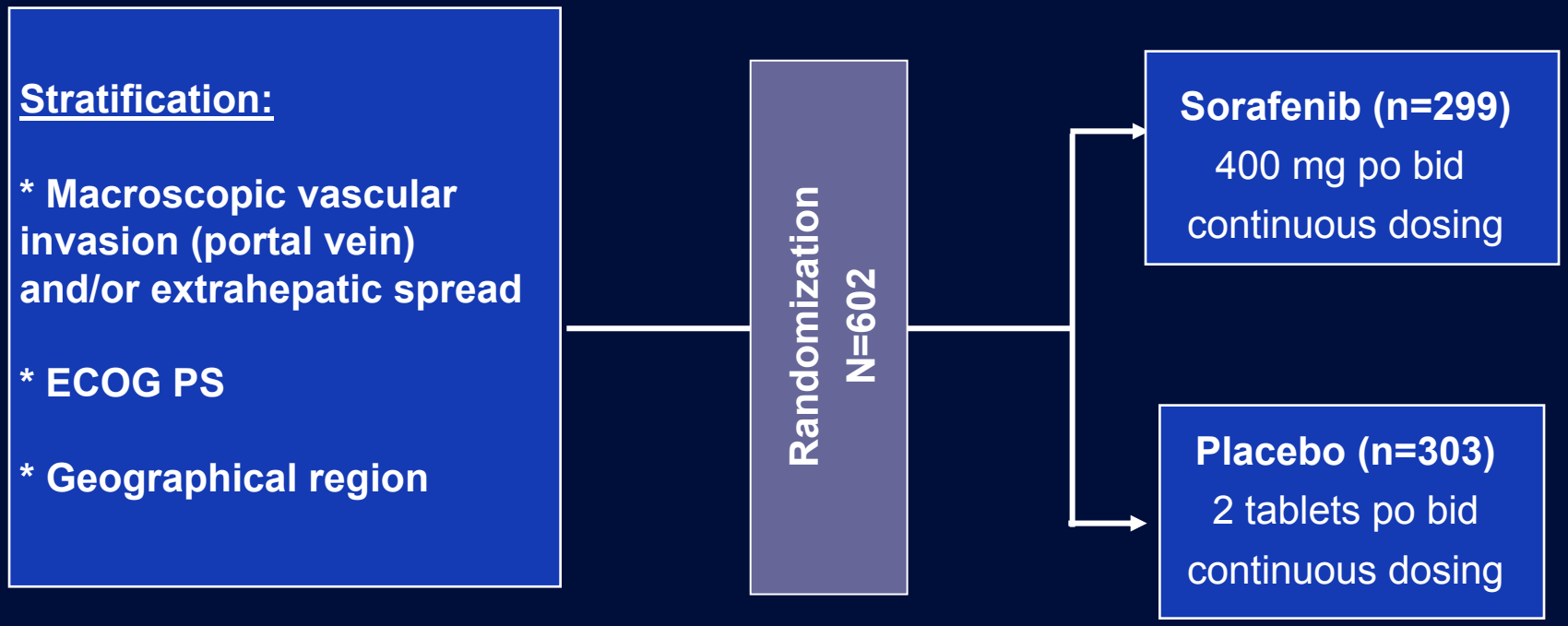
- Overall Survival assessment
  - $\alpha$=0.02 (one-sided)
  - Two interim analyses planned using O'Brien-Fleming $\alpha$ spending function
    - 90% power to detect a 40% improvement : 7 months → 9.7 months

- TTSP assessment (FHSI8-TSP)
  - $\alpha$=0.005 (one-sided)
  - Single analysis performed at time of final survival analysis

# Phase III SHARP Trial
## Study design

- **Primary end-points:** **Overall survival**
  **Time to symptomatic progression (FHSI8-TSP)**

- **Secondary end-points: Time to Progression (independent review)**



# Baseline characteristics of patients

| Characteristics | Sorafenib (n=299) | Placebo (n=303) |
|---|---|---|
| • Age (yr, median) | 65 | 66 |
| • Male/Female (%) | 87/13 | 87/13 |
| • Region (Europe/N. America/others;%) | 88/9/3 | 87/10/3 |
| • Etiology (%) | | |
| Viral Hepatitis (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% |

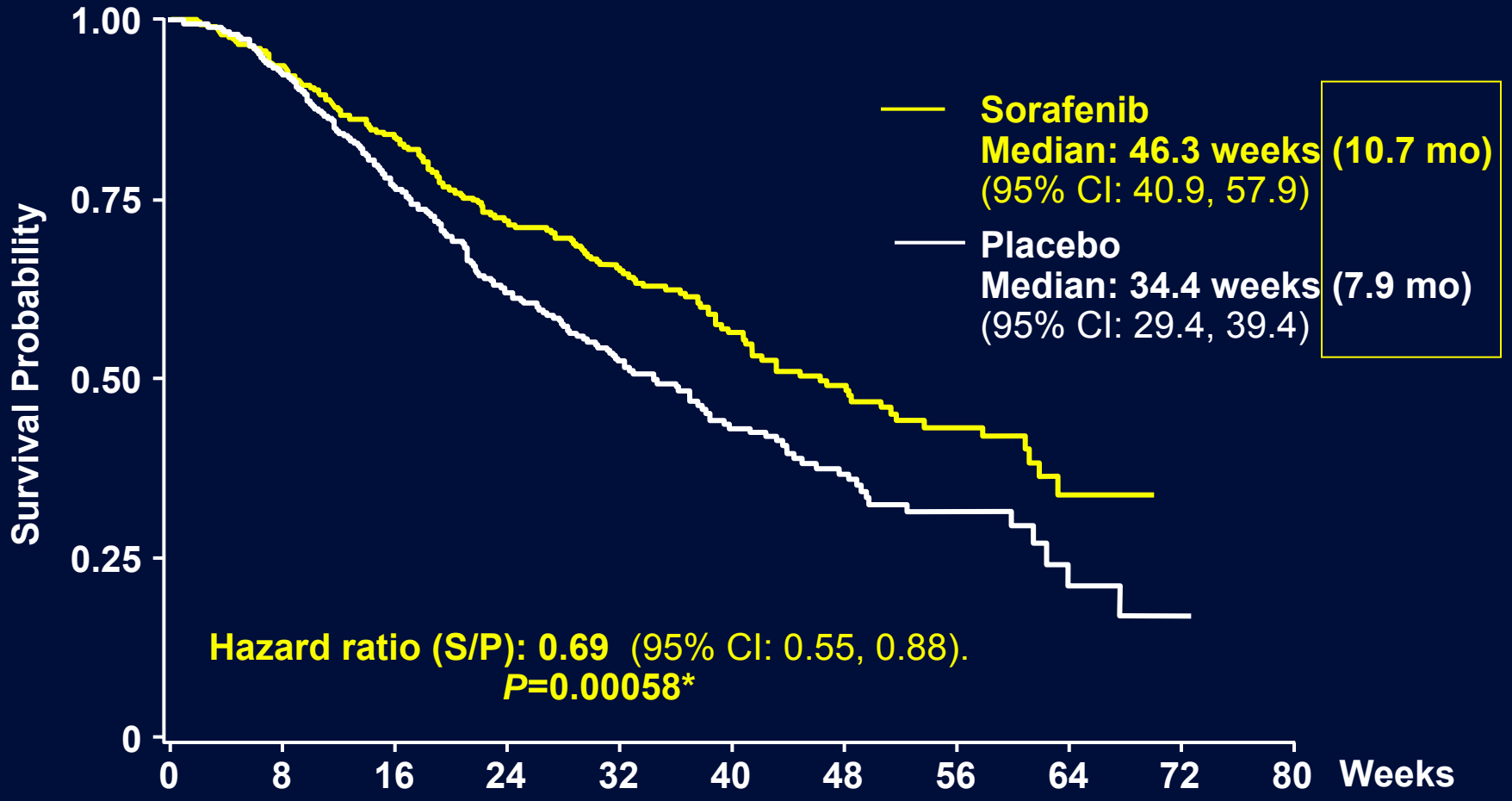
# Baseline characteristics of patients

| Characteristics | Sorafenib (n=299) | Placebo (n=303) |
|---|---|---|
| • BCLC stage * (%) | | |
| Stage B (intermediate stage) | 18 | 17 |
| Stage C (advanced stage) | 82 | 83 |
| • ECOG PS (%) | | |
| ECOG 0 | 54 | 54 |
| ECOG 1 | 38 | 39 |
| ECOG 2 | 8 | 7 |
| • Vascular invasion / extrahepatic spread | | |
| Present | 70 | 70 |
| Absent | 30 | 30 |

* Llovet JM & Bruix J, BCLC Group. *Semin Liver Dis* , 1999.

# Phase III SHARP Trial

## Overall survival (Intention-to-treat)



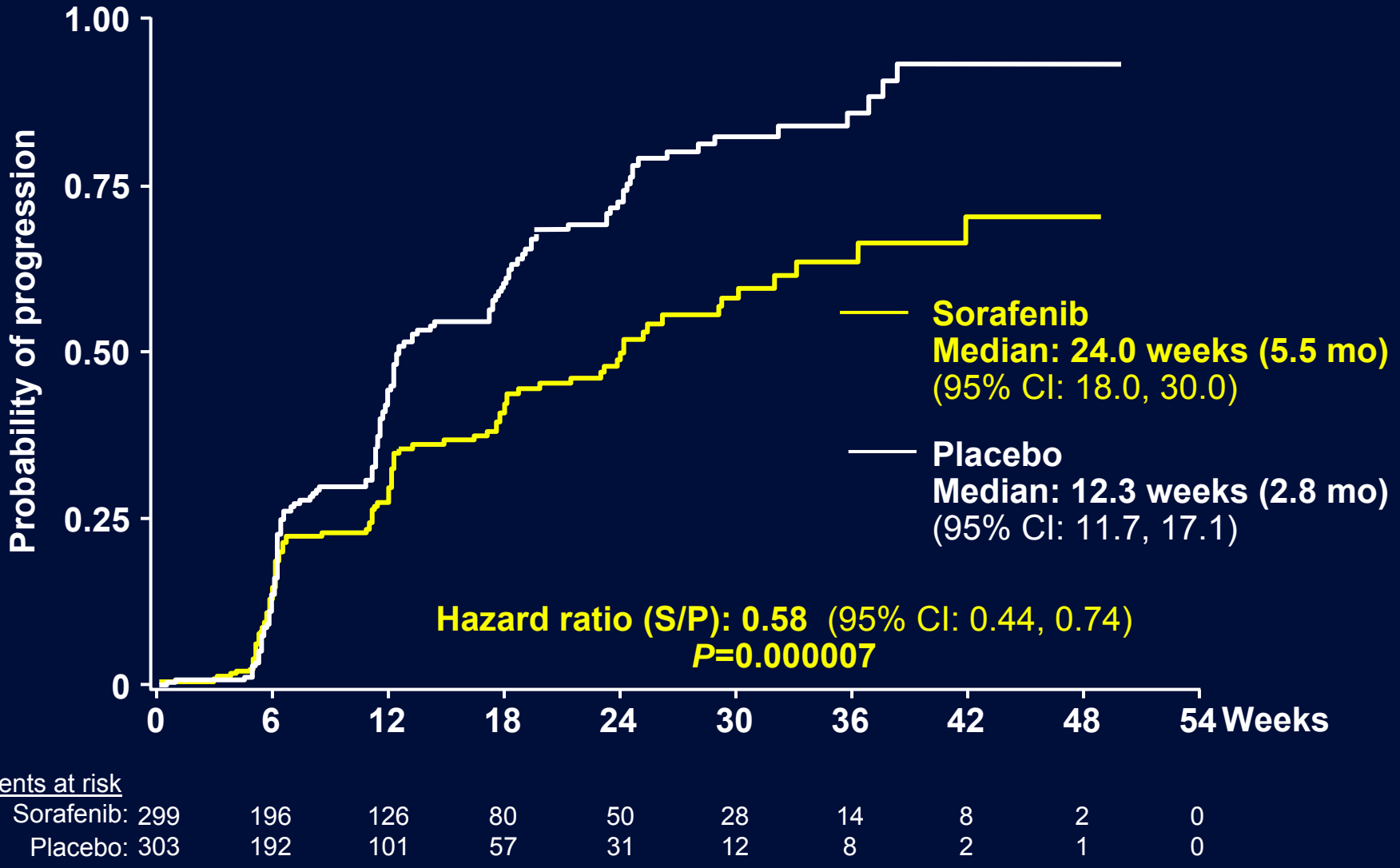

Patients at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sorafenib: | 299 | 274 | 241 | 205 | 161 | 108 | 67 | 38 | 12 | 0 | 0 |
| Placebo: | 303 | 276 | 224 | 179 | 126 | 78 | 47 | 25 | 7 | 2 | 0 |

**O'Brien-Fleming threshold for statistical significance was P=0.0077.*

# Phase III SHARP Trial

## Time to Progression (Independent central review)




Patients at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 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

## Response assessment (RECIST; Independent review)
## Time to Symptom Progression (FSHI8-TSP)*

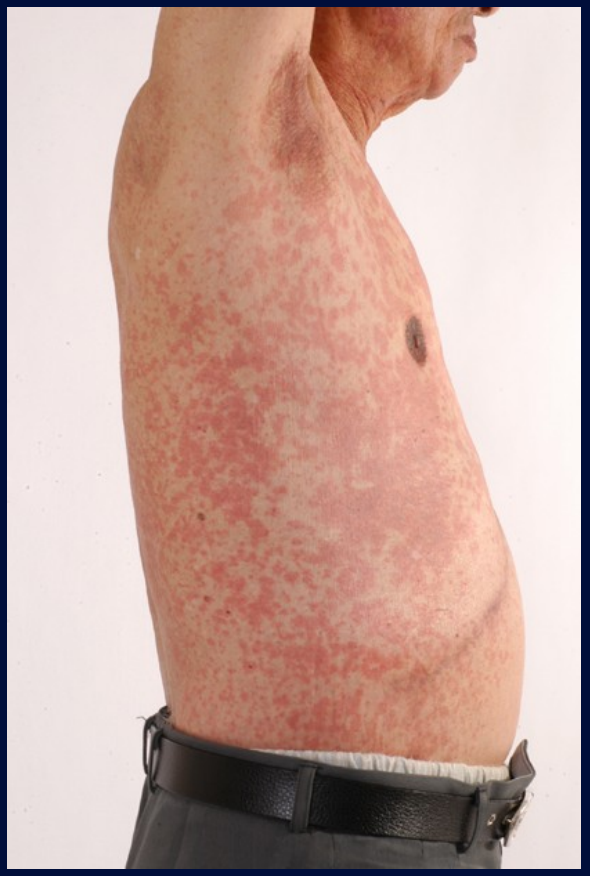
| | Sorafenib N=299 | Placebo N=303 |
|---|---|---|
| Overall response | | |
| Complete response (CR) | 0 | 0 |
| Partial response (PR) | 7 (2.3%) | 2 (0.7%) |
| Stable disease (SD) | 211 (71%) | 204 (67%) |
| Progressive disease (PD) | 54 (18%) | 73 (24%) |
| Progression-free rate at 4 mo | 62% | 42% |
| Duration of treatment (median; weeks) | 23 | 19 |

* FSHI8-TSP: No significant differences between treatment groups (P=0.77)

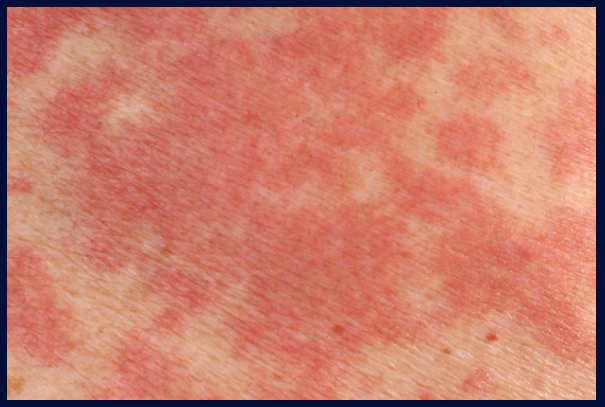
# Safety events

| | Sorafenib n=297 | | Placebo n=302 | |
|---|---|---|---|---|
| • Treatment-emergent serious adverse events (SAE,%) | 52 | | 54 | |
| • Drug related treatment-emergent SAE (%) | 13 | | 9 | |
| • Drug-related adverse events (%) | All | Grade 3/4 | All | Grade 3/4 |
| Diarrhea | 39 | 8/- | 11 | 2/- |
| Pain (abdomen) | 8 | 2/- | 3 | <1/- |
| Weight loss | 9 | 2/- | <1 | 0/- |
| Anorexia | 14 | <1/- | 3 | <1/- |
| Nausea | 11 | <1/- | 8 | 1/- |
| Hand-foot skin reaction | 21 | 8/- | 3 | <1/- |
| Vomiting | 5 | 1/- | 3 | <1/- |
| Alopecia | 14 | 0/- | 2 | 0/- |
| Liver dysfunction | <1 | <1/- | 0 | 0/- |
| Bleeding | 7 | <1/- | 4 | <1/<1 |

# Sorafenib AEs: Cutaneous rash (face or body)



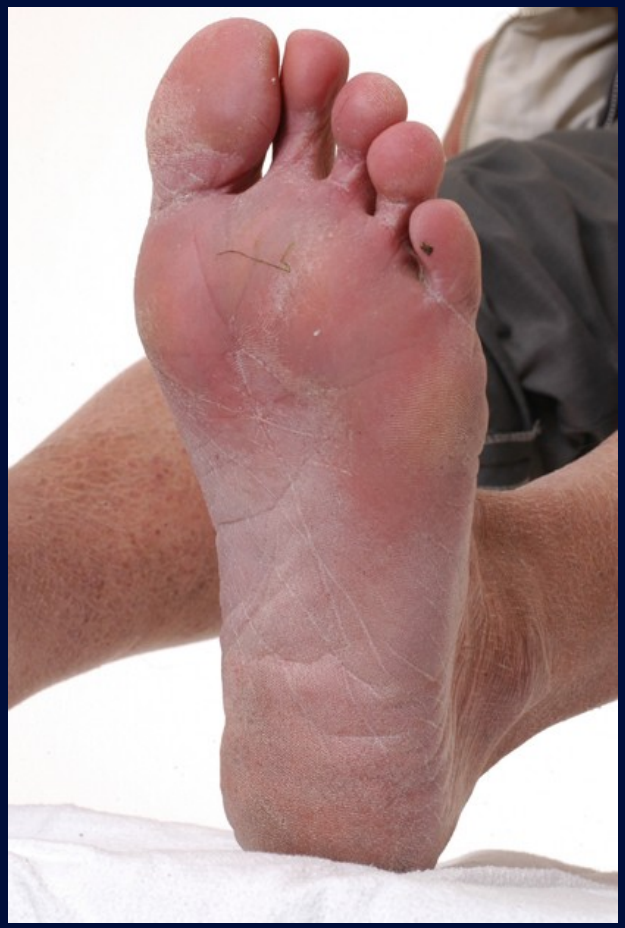
Patchy and Itchy maculopapular rash,



Moisturizing creams,
Antidandruff shampoo, non-hot showers
Non-tight, cotton clothes.
Avoid intense sun exposure
Antihystaminics if pruritus

Stop treatment for 7 days.
Restart at half dose for 1 month. Increase therafter?
Severe skin reaction: Stop treatment.

# Sorafenib AEs: Hand-foot syndrome

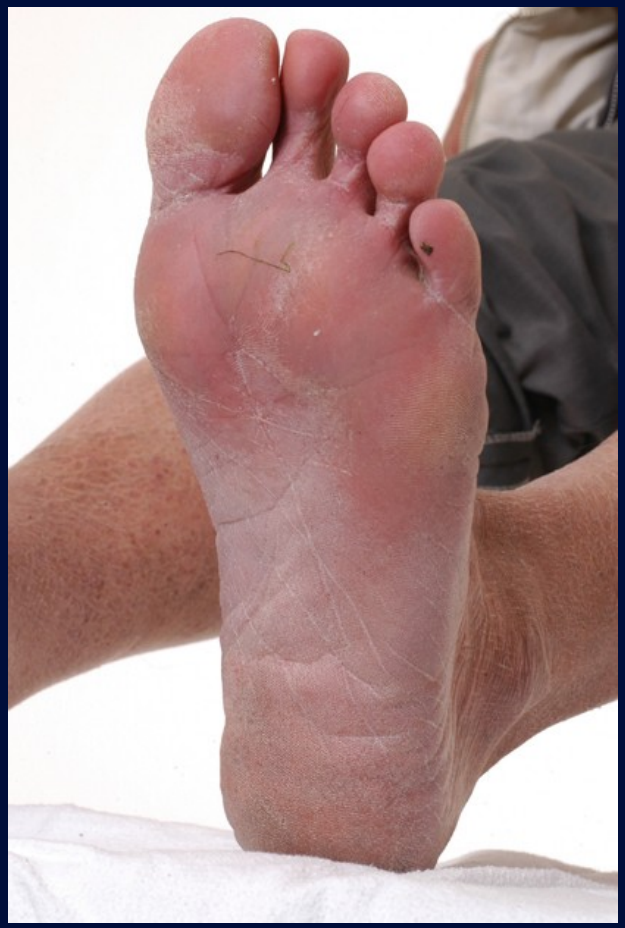


Grade 1: Numbness, dysestesia
Burning/prickling feeling
Tingling, Swelling
Redness of hands or feet

Grade 2: Painful redness/swelling
Skin thickening

Grade 3: Scalind/shedding of skin
Open sores
Blistering
Severe pain
Major discomfort

# Sorafenib AEs: Hand-foot syndrome



Recommendations

- Cotton socks
- Soft shoes
- Pedicure care at baseline
- Urea containing cream on feet
- Sunburn relief spray/cream

Grade 1: support. No dose reduction

Grade 2: reduce dose to 50%
If solved, maintain for 30 days.
If not solved, stop treat. 7 days.
If solved. Restart 50% for 30 days

Grade 3: stop treatment for 7 days
If solved, restart 50% dose for 30d.

# Phase III SHARP Trial

## Conclusions (AASLD Boston 2007)

- Sorafenib prolonged overall survival vs placebo in advanced HCC

  Median OS 46 weeks vs 34 weeks

  HR 0.69, *P*=0.00058

  44% increase in overall survival

- Sorafenib prolonged time to progression vs placebo

  Median TTP 24 weeks vs 12 weeks

  HR 0.58, *P*=0.000007

  73% prolongation in time to progression

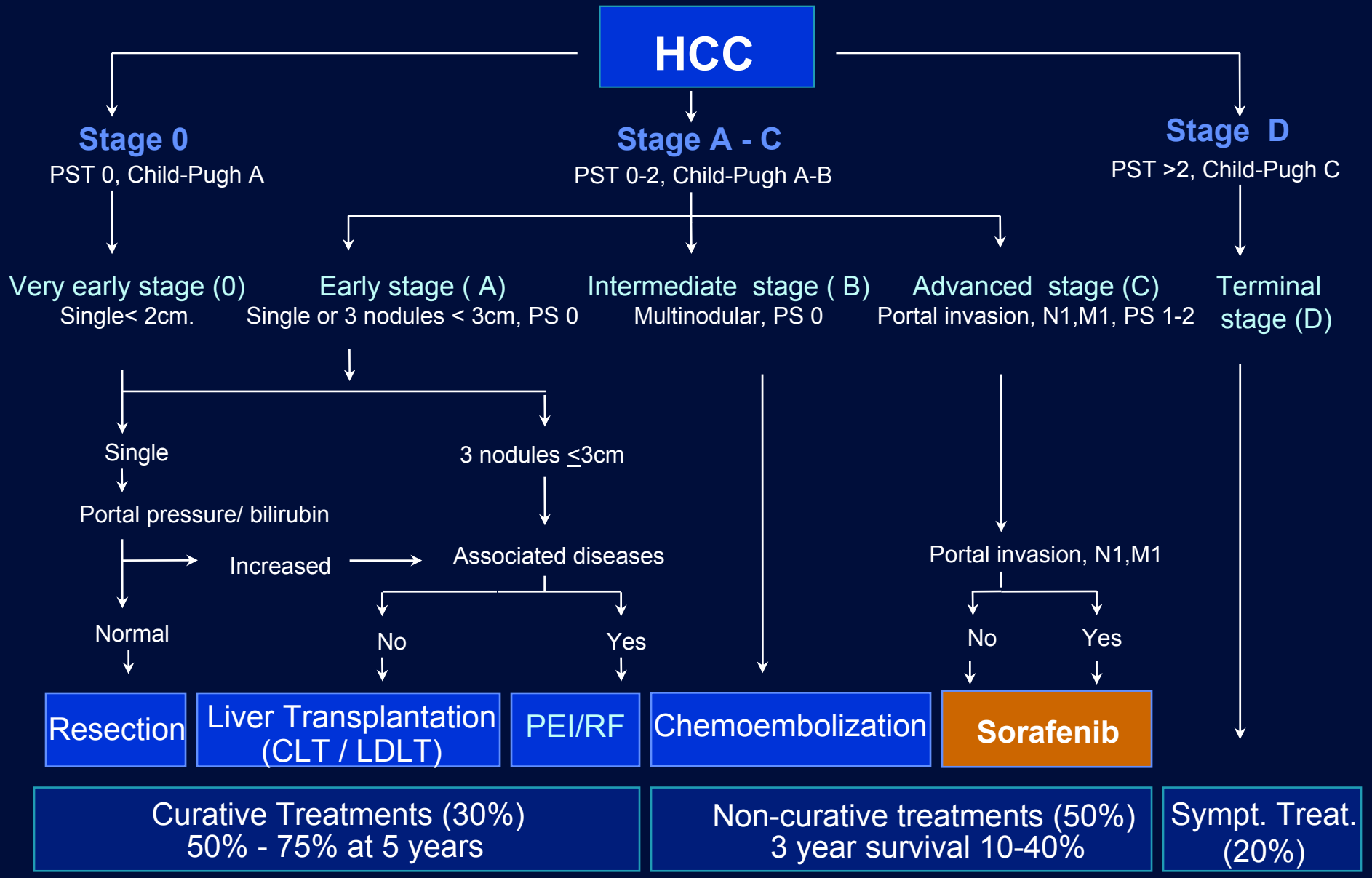
- Sorafenib was well-tolerated with manageable side effects

# Phase III SHARP Trial

## Conclusions (AASLD Boston 2007)

- Sorafenib is the first systemic therapy to prolong survival in HCC patients
- Sorafenib is the new reference standard for systemic therapy of HCC patients

# BCLC Staging and Treatment Strategy




Sem Liv Dis 1999 to Hepatology 2005

Caveats!

# Phase III SHARP Trial
## Study design

**Design**

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- Inclusion criteria:
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  - ECOG 0-2
  - Child-Pugh A class
  - No prior systemic treatment

**Randomization**

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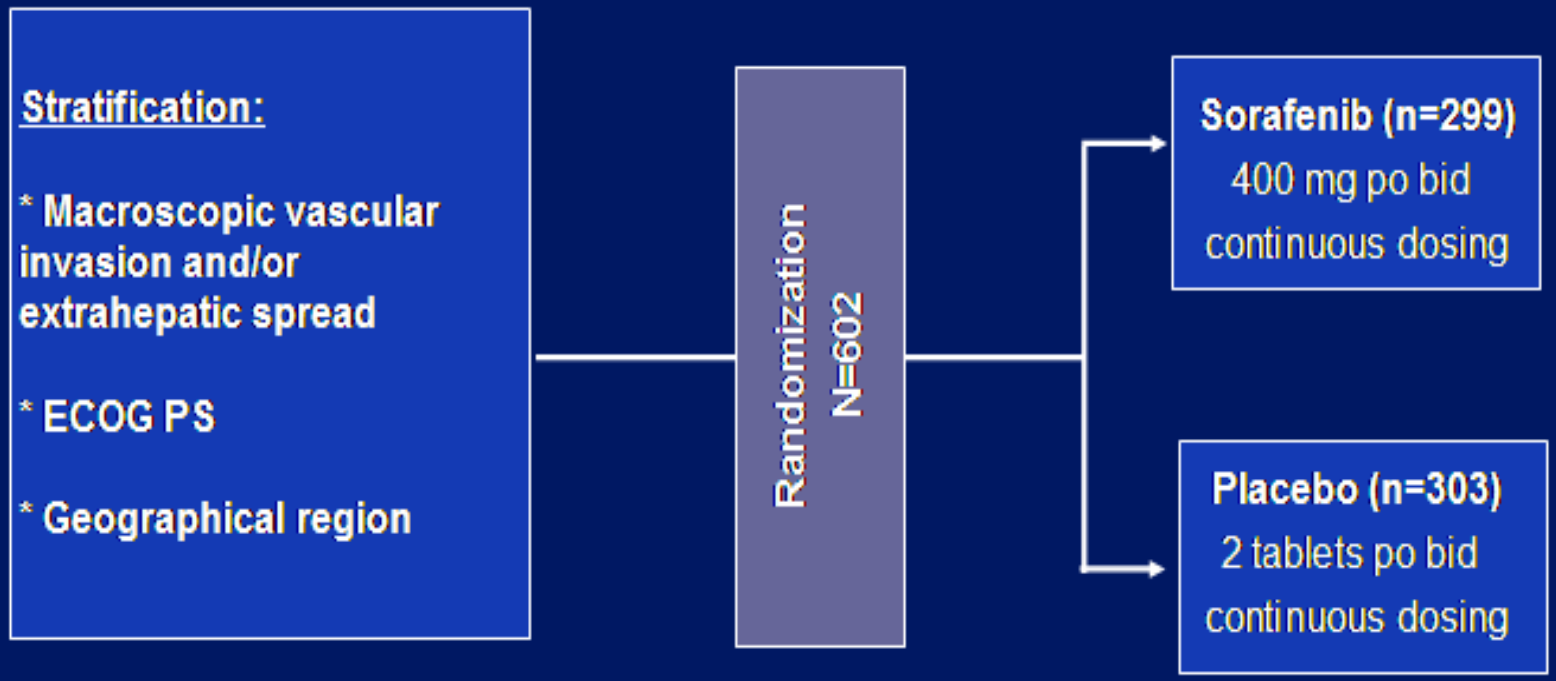

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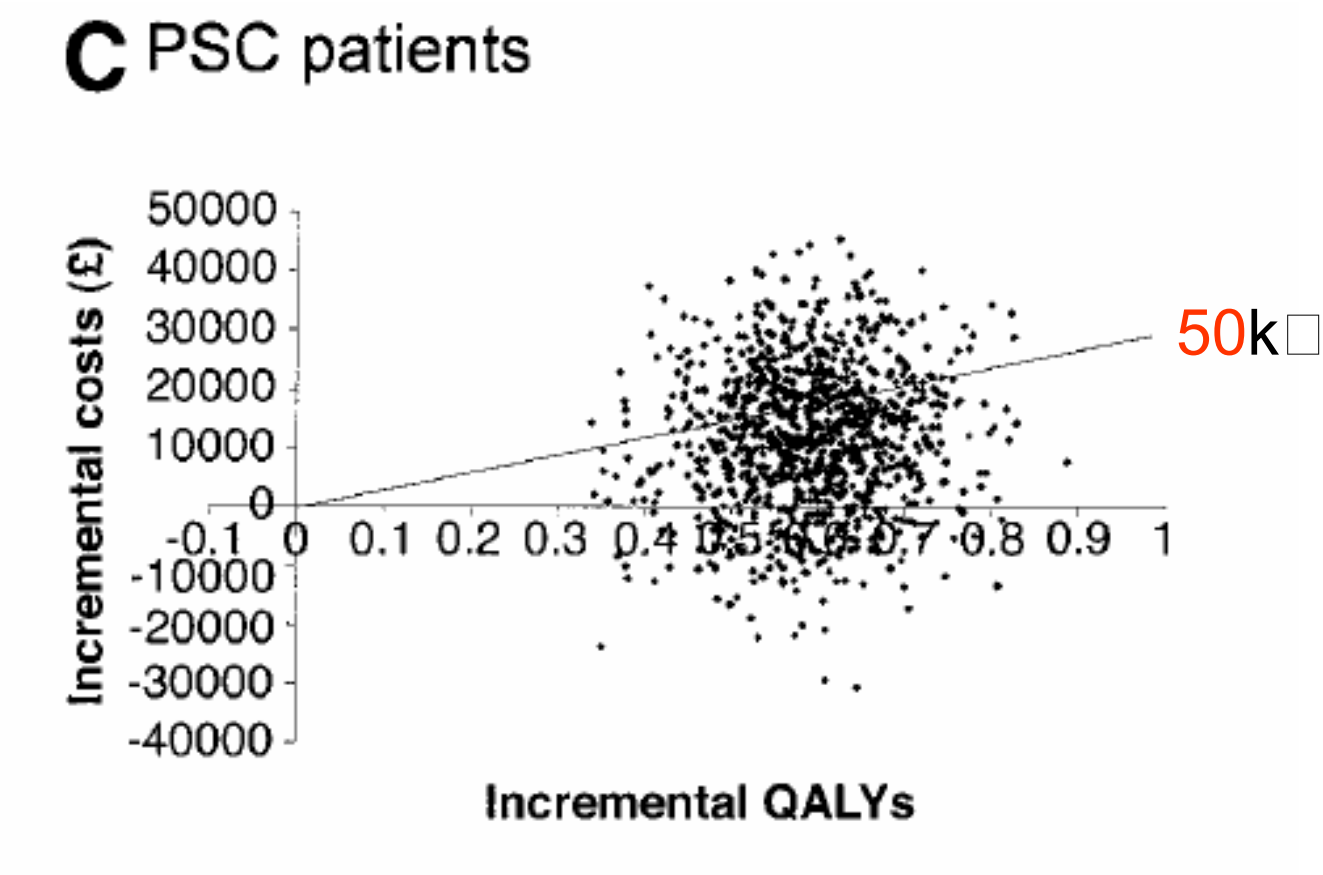
| Alopecia | 14 | 0/- | 2 | 0/- |
| Liver dysfunction | <1 | <1/- | 0 | 0/- |
| Bleeding | 7 | <1/- | 4 | <1/<1 |

# Bilan coût/efficacité

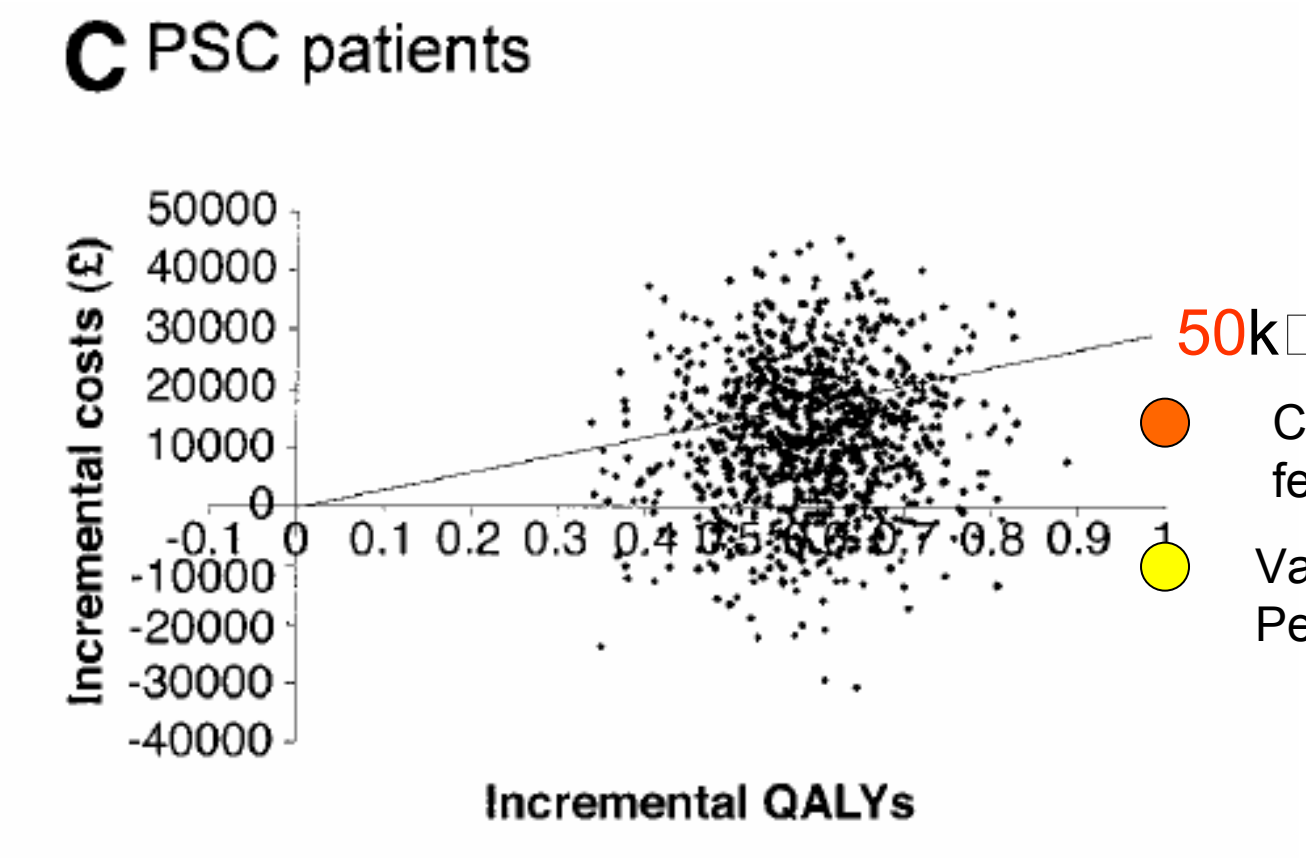
- 23 semaines de traitement = 5.1 mois
- 3 mois d'amélioration de la survie
- 6000 CHF/mois = 18.000 CHF
- = 72.000 CHF/an de vie gagné (0.5 QALY?)
- Estimation
- 144.000 CHF/QALY
- Comparatif: TH CHC: 30.000 CHF/QALY

# Coûts-per-QALY
# TH à 3 ans (cholangite sclérosante)



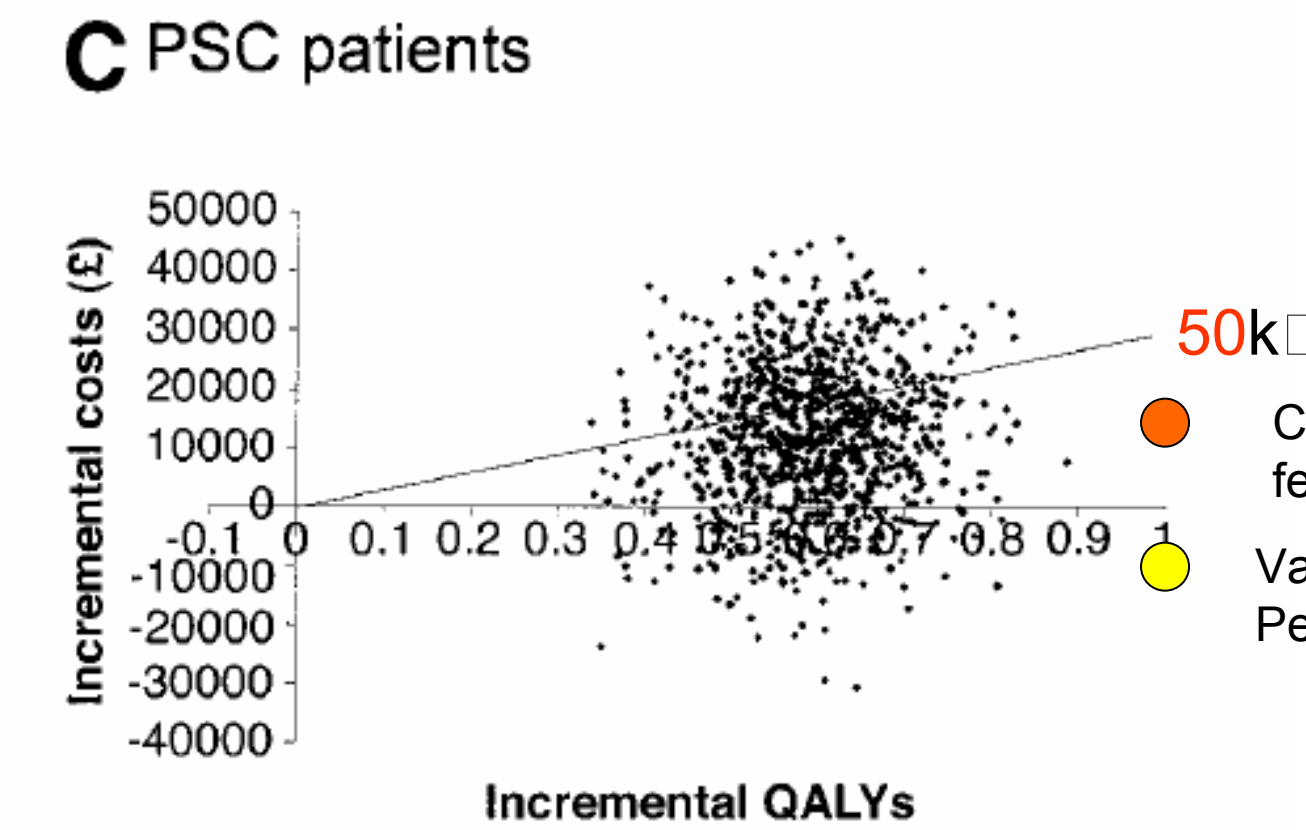

50k□/QALY

# Cost-per-QALY
# TH à 3 ans (cholangite sclérosante)



# Cost-per-QALY
# TH à 3 ans (cholangite scl

Palliation CHC
Sorafenib




50k□/QALY

Coloscopie
femme >50

Vaccination grippe
Personnes âgées

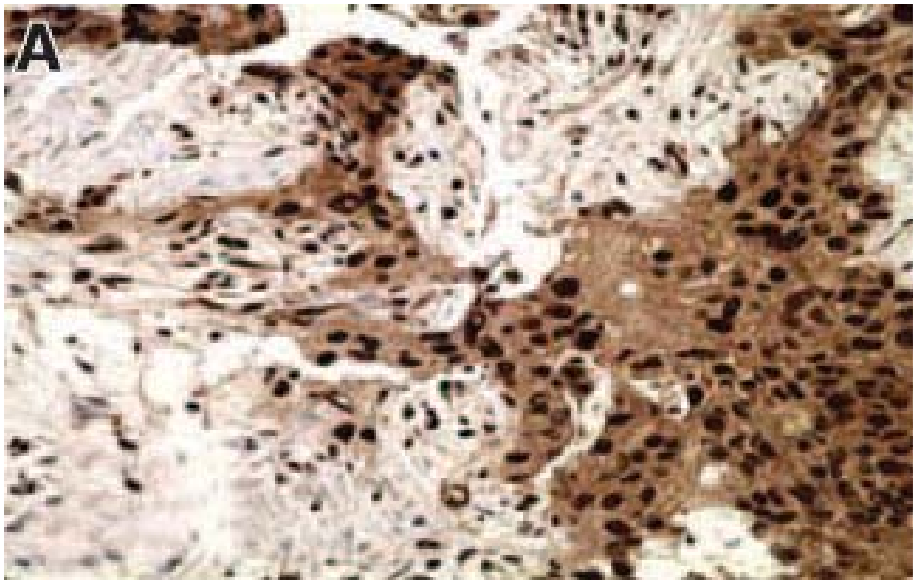
# Conclusion
# Journées HGEC Genève 2007

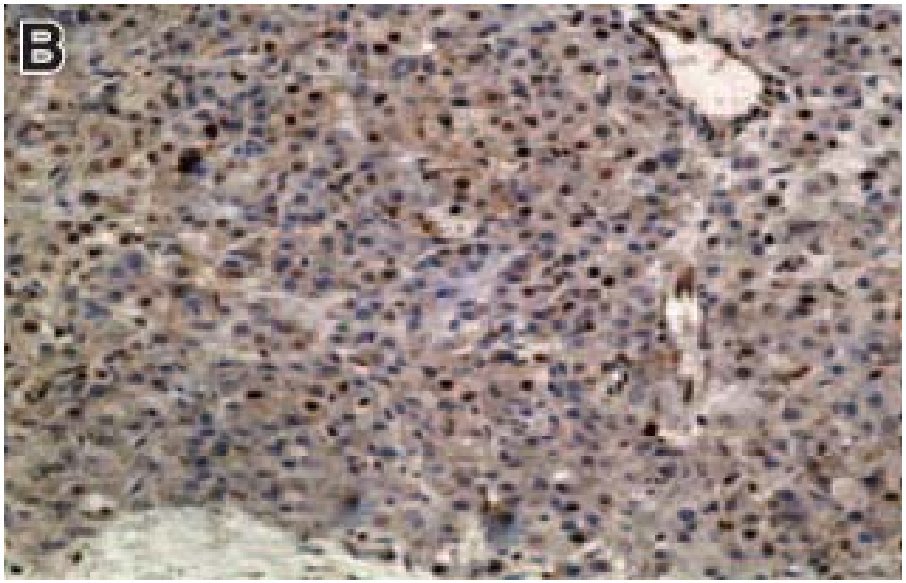
- Médicament efficace: Progrès MAJEUR
- Rôle encore à définir:
  - Stade avancé Child A
    - Traitement palliatif efficace sur la survie...
    - Attention à la progression des symptômes …
    - Donnés supplémentaires requises…

# Comment avancer ?

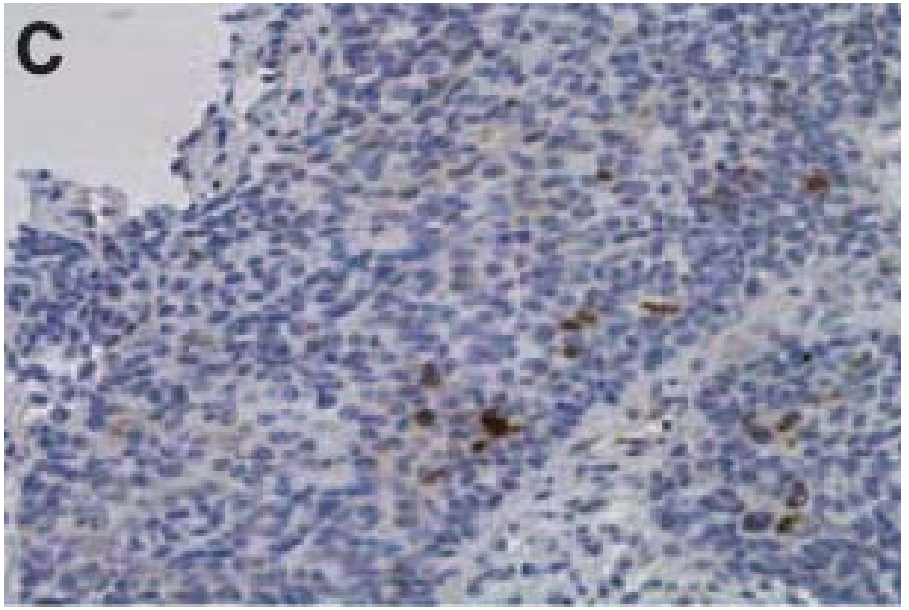
1. Sélection des bons répondeurs…
2. Études…
3. En clinique…

# Sélection des répondeurs



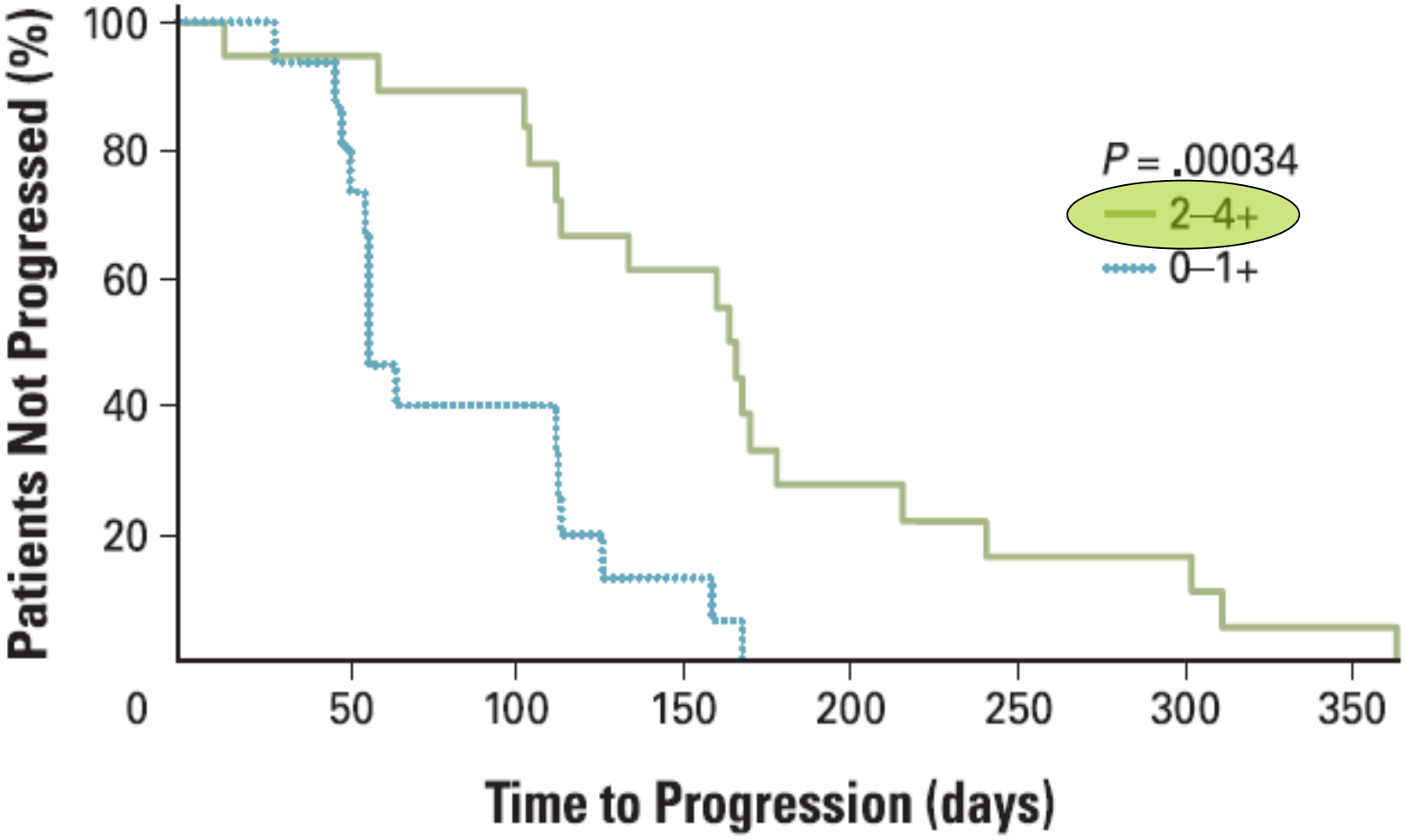




Immunohistochimie pour ERK phosphorylé




**Abou-Alfa et al. JCO 2006**

# Patients sans progression sous sorafenib




Abou-Alfa et al. JCO 2006

# Etudes…

- SAK/SASL 25 (sunitinib) chez les patients avec CHC avancés (dose-réponse)
- Ouvert en Suisse (Genève en attente amendements pour CE)
- Pas de frais de médicament…
- Suivi optimal

# En Clinique?

- Consultations structurées…
  - Evaluation clinique + AFP tous les mois
  - US tous les 3 mois
  - CT/RMN tous les 6 mois
- Dépistage et soutien des de non répondeurs…
- …pour arrêter (passer à autre chose?) quand il le faut.

# Phase III SHARP Trial

## Exploratory subgroup survival analysis