Hepatocellular Carcinoma: Lessons Learned

Gregory J. Gores, M.D.

Hepatocellular Carcinoma Lessons Learned: Disclosures

• Non-profit Disclosure: Cholangiocarcinoma Foundation
• Commercial Disclosures: Jecure & Conatus
• No discussion of investigative or off-label applications of medicine, medical devices, or procedures
• No industry prepared slides are employed for this talk
Hepatocellular Carcinoma: Lessons Learned

I. Epidemiology
II. Genetics
III. Diagnosis
IV. Therapy
V. Future Directions

Cirrhosis Incidence by Liver Disease Etiology in Patients with HCC

Mittal S. and Davila JA. Clinical Gastroenterology and Hepatology 2016
HCV Patients Have a Reduced Risk of HCC Following DAA Therapy with SVR

Still exceeds surveillance threshold of 1%

Pooled odds ratios for HCC incidence.
The column treatment is compared with the row treatment. Numbers in parentheses indicate 95% confidence intervals.
Hepatocellular Carcinoma: Lessons Learned

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If attacked by a mob of clowns... go for the juggler

Clonal Complexity of Cancer Progression: Gatekeeper and Trunk mutations

HCC Has The Clonality of a Bush
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Metroticket 2.0 Model for Analysis of Competing Risks of Death After Liver Transplantation for HCC

Changes in U.S. Liver Transplant Criteria

- AFP > 1,000 ng/ml is an exclusion
- UCSF criteria → Down staged to Milan is automatic listing criteria
The 2018 BCLC prognostic and treatment strategy

**SHARP Trial: Time to Radiologic Progression**

- **Placebo**
- **Sorafenib**

Probability of radiologic progression

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<th>Months since randomization</th>
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P<0.001

SHARP Trial: Overall Survival

**Median Overall Survival 10.7 months**

**Placebo**

**Sorafenib**

No. at risk

<table>
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<th>Months since randomization</th>
<th>Placebo</th>
<th>Sorafenib</th>
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**P<0.001**

**Probability of survival**


*Pooled analysis of two phase 3 trials (n = 827; SHARP and Asia-Pacific)* in patients with unresectable hepatocellular carcinoma treated with sorafenib or placebo

- **Prognostic for poorer survival:**
  - Macroscopic vascular invasion
  - High alpha fetoprotein
  - High neutrophil-to-leukocyte ratio

- **Survival benefit was observed with sorafenib treatment across all patient subgroups**

- **Predictive of greater sorafenib benefit:**
  - No extrahepatic spread
  - Hepatitis C virus
  - Low neutrophil-to-leukocyte ratio
Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial

Riccardo Lencioni1,2,4,5, Josep M. Llovet1,4,6, Guohong Han2, Won Young Tak3, Jianmei Yang8, Alfredo Guglielm1, Seung Woon Paik10, Maria Reig1, Do Young Kim11, Gar-Yang Chau12, Angelo Luca1, Luis Ruiz del Arbol13, Marie-Aude Leberre14, Woody Niu15, Kate Nicholson16, Gerald Meinhardt17, Jordi Bruix18

Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial


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Adjuvant Sorafenib

Bruix J. and Llovet JM. The Lancet 2015
Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial

Valérie Vilgrain, Helene Perren, Eric Assmat, Faris Guiz, Alina Diana Rosca, Georges-Philippe Pages, Annie Tiber, Mohamed Beuvier, Rachida Labahi, Wassim Almaher, Hélène Bannard, Valérie Laurent, Elodie Mathis, Jean-Pierre Brouwer, Jean-Pierre Toso, Rony Pedlot, Christine Sime, Remy Gaudin, Olivier Moudier, Jean-François Seltz, Vincent Vidal, Christophe Audibert, Delphine Oertli, Olivier Coste, Isabel Breu-Ariès, Jean-Luc Rivol, Anthony Saran, Charlotte Coëster, Emmanuel Fré, Alain Luciani, René Adam, Mark Lewis, Didier Samuel, Maxime Reveill, Aurélien Desc, Laurent Coste, Gilles Chatellier, on behalf of the SARAH Trial Group

A Overall survival

B Progression-free survival

Vilgrain V. and Chatellier G. The Lancet 2017
Failed Trials in HC

**First Line**
• FOLFOX 4 vs. doxorubicin
• Sunitinib vs. sorafenib
• Brivanib vs. sorafenib
• Linifanib vs. sorafenib

**Second Line**
• Brivanib vs. placebo
• Everolimus vs. placebo
• Ramucirumab vs. placebo

**Liver Transplant**
• Sirolimus vs. placebo

Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial

Bruix J. and Han G., *The Lancet* 2017
Regorafenib for HCC

Bruix J. and Han G., *The Lancet* 2017

Regorafenib for HCC

Bruix J. and Han G., *The Lancet* 2017
Regorafenib in Advanced HCC in Patients Failing Sorafenib

Number at risk

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<thead>
<tr>
<th>Regorafenib</th>
<th>Placebo</th>
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Greten T.F. and Sangro B. *Journal of Hepatology* 2018
Zheng C. and Zhang Z. Cell 2017

El-Khoueiry A. and Melero I., The Lancet 2017

Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

# Nivolumab Trial Design

## Dose Escalation (n=48)

<table>
<thead>
<tr>
<th>Without viral hepatitis</th>
<th>0.1 mg/kg (n=6)</th>
<th>0.3 mg/kg (n=9)</th>
<th>0.6 mg/kg (n=10)</th>
<th>1.0 mg/kg (n=5)</th>
<th>10 mg/kg (n=11)</th>
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</thead>
<tbody>
<tr>
<td>HCV infected</td>
<td>0.3 mg/kg (n=3)</td>
<td>0.6 mg/kg (n=4)</td>
<td>1.0 mg/kg (n=3)</td>
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</tr>
<tr>
<td>HBV infected</td>
<td>0.1 mg/kg (n=5)</td>
<td>0.3 mg/kg (n=3)</td>
<td>0.6 mg/kg (n=4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Dose Expansion (n=216)

- Scirtrab: untreated or intolerant (n=52)
- Scirtrab: progressed (n=52)
- HCV infected (n=50)
- HBV infected (n=51)
Nivolumab Treatment Response; Overall 15-20% Response Rate

Treatments approach for HCC

- Resection/transplantation/ablation
  - Liver only disease
  - Limited tumor burden

- Chemoembolization
  - Liver only disease
  - No vascular invasion
  - Preserved liver function
  - PS 0
  - Selective approach

- Sorafenib /Lenvatinib
  - No tumor burden
  - Preserved liver function
  - PS 0-2

- Regorafenib/cabozantinib
  - No tumor burden limit
  - Preserved liver function
  - PS 0-2

- Nivolumab

Forner, Reig and Bruix; Lancet 2018
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Summary

• Epidemiology
  • HCC occurs in non-cirrhotic NASH (30%)
  • HCV therapy reduces HCV risk (still requires surveillance)

• Genetics
  • Telomerase is a gatekeeper mutation for HCC
  • Genetic heterogeneity

• Diagnosis
  • cfDNA examining DMR is a promising technology

• Therapy
  • Individualized medicine selection for sorafenib
  • 2nd line therapy with regorafenib, nivolumab
Future Directions

• Stratification of cirrhotics into high-risk and low-risk for HCC
  • Coupled with chemoprevention
• Liquid biopsy for surveillance and diagnosis
• Immunotherapy
  • Combination therapy
  • Biomarkers
Courtney’s idea of sun dogs 😊