# Hepatocellular Carcinoma™

## UPDATE

## Conversations with Oncology Investigators

### Bridging the Gap between Research and Patient Care

**SPECIAL ISSUE**
**Proceedings from a Clinical Investigator Think Tank**


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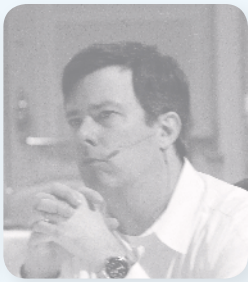

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# *Hepatocellular Carcinoma Update*

## A Continuing Medical Education Audio Series

### OVERVIEW OF ACTIVITY

Hepatocellular carcinoma (HCC), the most common form of liver cancer, is a major cause of mortality worldwide, resulting in an estimated 500,000 to one million deaths per year. Surgery, including transplantation, remains the only curative modality for HCC. Although many randomized, controlled trials have been performed in the past 25 years, the use of cytotoxic chemotherapy in locally advanced, unresectable or metastatic HCC has resulted in no significant improvement in overall mortality. Sorafenib represents the first agent in several decades to demonstrate a clinically meaningful overall survival benefit. An array of novel therapeutics targeting tumor angiogenesis and proliferation, in addition to innovative surgical and nonsurgical locally directed treatment strategies, are currently being studied in clinical trials. To bridge the gap between research and patient care, this program features a roundtable discussion with leading oncology investigators to assist medical oncologists, hematologists, hematology-oncology fellows, gastroenterologists, interventional radiologists and hepatologists with the formulation of up-to-date clinical management strategies.

### LEARNING OBJECTIVES

- Demonstrate knowledge of the pathophysiology and epidemiology of hepatocellular carcinoma (HCC), and explain how disease etiology affects patient prognosis.
- Develop an acceptable surveillance and screening program for patients at high risk of developing HCC, incorporating appropriate biomarkers for detection.
- Communicate the benefits and risks of the front-line use of sorafenib to appropriate patients with advanced HCC.
- Assess the hepatic function of patients with HCC, and use this information to tailor effective local and systemic treatment decisions.
- Describe emerging data and ongoing research evaluating the clinical utility of angiogenesis inhibitors, novel multitargeted tyrosine kinase inhibitors and combined-modality treatment approaches for patients with HCC.
- Discriminate among the rational use of various primary management strategies for localized and/or resectable tumors, including liver resection, transplantation, transarterial embolization, radiofrequency ablation and bridging therapy.
- Counsel appropriately selected patients with HCC about ongoing clinical trials in which they may wish to participate.

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## SECTION 1 — Local Therapy Options for Unresectable and Resectable Hepatocellular Carcinoma

**Schwarz RE, Smith DD. Trends in local therapy for hepatocellular carcinoma and survival outcomes in the US population. Am J Surg 2008;195(6):829-36.**

### 1.1 Survival Outcomes in the US Population for Local Therapies: Transplantation versus Resection versus Ablation

"Superior long-term survival rates after transplantation and resection are likely biased through confounding patient selection variables, but both treatment options could still be considered primary therapy choices in the therapeutic evaluation of HCC patients. Lower early post-treatment mortality after transplantation and ablation may support these as potentially safer therapies in appropriately selected patients. Both considerations, over long-term survival and treatment safety, have to be appropriately balanced, rendering the ultimate treatment choice a highly individualized one."

— *Schwarz RE, Smith DD.* Am J Surg *2008;195(6):829-36.* ***Abstract***

### 1.2 Actuarial Five-Year Survival Data Comparing Local Therapies for Hepatocellular Carcinoma

| | Transplantation | Resection | Ablation | No/incomplete local therapy | *p*-value |
|---|---|---|---|---|---|
| All cases | 67% | 35% | 20% | 3% | <0.0001 |
| Cases within Milan criteria[1] | 72% | 43% | 16% | 8% | <0.0001 |

[1] "For the analysis of survival impact by treatment group in a more uniform patient cohort, we selected cases that fall within the Milan criteria consisting of absence of extrahepatic disease and vascular invasion, with single lesions <5 cm or no more than 3 lesions of <3 cm in largest diameter.

When treatments were compared for these criteria and within the same time interval, survival curves demonstrated similar differences, although post-resection survival appeared more improved than that in the other therapy groups."

SOURCE: Schwarz RE, Smith DD. *Am J Surg* 2008;195(6):829-36. **Abstract**

## Tracks 20-21

**DR LOVE:** What would be the default therapy for Dr Thuluvath's patient (Case 4, page 17), an otherwise healthy 52-year-old patient with hepatitis C virus (HCV)-related cirrhosis, a 3.2-cm hypervascular lesion in the right lobe and no portal vein involvement?

**DR THULUVATH:** Based on the survival figures, transplant is the best curative option in such a case. Even if the tumor is resectable, the recurrence rate at five years postresection is approximately 70 percent, which is high.

**DR CHOTI:** Some clinicians would first decide whether a patient's disease is resectable. However, I believe we should first determine whether the patient can undergo a transplant. This issue is controversial, and the jury is out as to which should be the default therapy. Remember, we have a limited donor pool and the duration of the wait varies.

Another consideration is the salvage rate for patients with hepatocellular carcinoma (HCC) who undergo resection and then experience disease recurrence.

If first you perform a resection, you can assess the biologic features of the tumor, and then if the disease progresses, a salvage transplant can be performed. A salvage transplant, using resection as a bridge, may be a more effective strategy for a patient such as the one you described.

**DR GESCHWIND:** We can also use transarterial chemoembolization (TACE) as a bridge. Three or four studies from Germany showed that TACE can be used as a predictor of tumor biology. In that setting, they would list the patient for transplant and treat with TACE.

**DR GAMBLIN:** We do that commonly.

**Cheng BQ et al. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: A randomized controlled trial. JAMA 2008;299(14):1669-77.**

**Zhu AX, Abou-Alfa GK. Expanding the treatment options for hepatocellular carcinoma: Combining transarterial chemoembolization with radiofrequency ablation. JAMA 2008;299(14):1716-8.**

### 1.3 Combining Transarterial Chemoembolization with Radiofrequency Ablation (TACE-RFA)

"The study by Cheng et al provides initial evidence to support the use of TACE-RFA as a new treatment option in highly selected patients with unresectable HCC. This study points toward an important mechanistic possibility — namely that altering the tumor microenvironment and

*continued*

supporting vasculature may help improve the efficacy of localized therapy in this disease.

However, despite the positive findings in this study, the exact role for TACE-RFA in the treatment of patients with unresectable HCC remains a controversial and unresolved issue, similar to the situation for many of the interventional-based therapies.

For patients with early stage disease either surgery or RFA will remain the initial treatment choice and the recent approval of sorafenib has provided a new treatment option for advanced HCC."

*— Zhu AX, Abou-Alfa GK.* JAMA *2008;299(14):1716-8.*

**1.4**

## Overall Survival Rates with TACE, RFA or the Combination for HCC (N = 291)

| | Five-year survival rate (95% confidence interval) | | |
|---|---|---|---|
| Treatment method by tumor type | TACE alone | RFA alone | TACE + RFA |
| **All HCC cases** | 13% (7-21%) | 8% (3-16%) | 31% (21-41%) |
| **Tumor size** | | | |
| >3-5 cm | 26% (13-40%) | 16% (6-30%) | 56% (39-69%) |
| >5 cm | 0% | 0% | 5% (1-17%) |
| **Number of lesions** | | | |
| Uninodular | 27% (15-42%) | 15% (6-30%) | 53% (36-68%) |
| Multinodular | 0% | 2% (0-11%) | 13% (5-24%) |

SOURCE: Cheng BQ et al. *JAMA* 2008;299(14):1669-77. **Abstract**

**1.5**

## Overall Survival Rates with TACE, RFA or the Combination for HCC (N = 291)

"TACE has become the treatment of choice for multinodular hepatocellular carcinoma. Radiofrequency thermal ablation (RFA) is an emerging technology that has been proposed as an alternative to conventional percutaneous ethanol injection and as adjuvant therapy during the wait time for liver transplantation.

Moreover, RFA is an appropriate treatment method for uninodular hepatocellular carcinoma and appears to be an effective and safe treatment method for medium and large hepatocellular carcinomas.

However, both TACE and RFA have some well-known limitations. In particular, neither results in adequate control of hepatocellular carcinoma tumors larger than 3 cm... We hypothesized that if TACE were performed before RFA treatment (TACE-RFA), the ablation volume of coagula-

*continued*

tion necroses could be increased, possibly enabling effective treatment of patients with larger hepatocellular carcinoma." [Citations omitted]

*— Cheng BQ et al.* JAMA *2008;299(14):1669-77.* ***Abstract***

## Track 13

**DR LOVE:** Would you describe the typical candidate for TACE?

**DR GESCHWIND:** A prime target for chemoembolization is the patient who has a good performance status, adequate liver function, an open portal vein and a large tumor for which we have no other options (Case 3, page 17).

**DR THOMAS:** I'm the conservative one of the group when it comes to TACE, but it kills tumors, and it can serve as a palliative treatment, sometimes alleviating tumor-related symptoms such as fatigue and anorexia.

**DR LOVE:** What do we know about outcome after TACE?

**DR O'NEIL:** In many studies of chemoembolization in eligible patients, the median survival is in the 12- to 24-month range.

**DR LOVE:** Dr Thomas, would you consider TACE followed by sorafenib in clinical practice?

**DR THOMAS:** No, I would try to maximize what I can obtain from TACE. I would not start sorafenib until the patient did not have another option. Sometimes we see dramatic shrinkage with TACE, and the patient may become a candidate for surgery or IMRT.

**DR LOVE:** What do you think about those strategies, Dr Choti?

**DR CHOTI:** I think they are good, but I am willing to consider TACE followed by sorafenib, although no data support this approach. We're exploring the combination of TACE with sorafenib in the context of cooperative trials. ECOG has a protocol that's currently under development. However, outside of a trial, I focus on chemoembolization first — complete that therapy, and then consider sorafenib before disease progression.

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**Kulik LM et al. Safety and efficacy of $^{90}$Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology 2008;47(1):71-81.**

**1.6** **Safety and Efficacy of $^{90}$Y Radiation Therapy for HCC with and without Portal Vein Thrombosis (PVT)**

"This analysis of HCC patients has shown that radioembolization with glass microspheres does not impart an increased risk for hepatic failure or enceph-

*continued*

alopathy in patients with branch or no PVT compared with main PVT. Although patients presented with different Okuda and Child-Pugh stages, there did not appear to be clinically significant differences in bilirubin toxicities when stratifying by the presence or absence of PVT.

The findings herein support the notion that radioembolization with glass microspheres results in microscopic rather than macroscopic embolization. When compared with other embolic treatments, the safety of radioembolization in patients with portal vein thrombosis and hepatofugal flow represents a unique opportunity for investigation.

Given the incidence of PVT in this patient population, we conclude that the use of minimally embolic $^{90}$Y glass microspheres to treat patients with HCC complicated by branch/lobar PVT is safe with favorable tumor response rates. Further investigation is needed in addressing recurrence rate and long-term survival benefit."

— *Kulik LM et al.* Hepatology *2008;47(1):71-81.* ***Abstract***

**1.7**

### Association of Survival, Absence of Portal Vein Thrombosis (PVT) and Cirrhosis in Patients Receiving $^{90}$Y Radiation Therapy for HCC

| Population | N | Median survival | 95% CI | Log-rank *p*-value |
|---|---|---|---|---|
| **All patients** | 108 | | | 0.0052 |
| No PVT | 71 | 467 days | 322, 629 | |
| Branch PVT | 25 | 304 days | 217, 481 | |
| Main PVT | 12 | 133.5 days | 88, 225 | |
| **Patients with cirrhosis** | 82 | | | 0.1028 |
| No PVT | 52 | 385 days | 282, 513 | |
| Branch PVT | 19 | 261 days | 217, 424 | |
| Main PVT | 11 | 148 days | 61, 326 | |
| **Patients without cirrhosis** | 26 | | | 0.0270 |
| No PVT | 19 | 813 days | 394, NR | |
| Branch PVT | 6 | 427 days | 169, 661 | |
| Main PVT | 1 | 101 days | NR, NR | |

CI = confidence interval; NR = not reported

SOURCE: Kulik LM et al. *Hepatology* 2008;47(1):71-81. **Abstract**

## Track 48

**DR LOVE:** What has been your experience with radioembolization of unresectable HCC with intrahepatic yttrium-90 microspheres?

**DR GAMBLIN:** We treat 400 to 500 patients with chemoembolization and approximately 100 patients with yttrium-90 microspheres each year. We discuss all of these cases in a multidisciplinary tumor board.

If the patient has a segmental portal vein thrombus — not in the main right portal vein but way out in the liver — associated with the tumor, then we might try chemoembolization. If the right and the left portal veins are involved, on the right we would consider yttrium-90.

Chemoembolization and radioembolization are delivered in a similar manner, with a 23-hour observation period after the procedure. Through a femoral approach, the hepatic artery is cannulated, and then treatment is administered.

The yttrium-90 microspheres consist of beta-emitting radiation particles that leak from glass beads that are floated into the liver toward the tumor. The mechanism of therapy is twofold — the embolization component with the beads and the radiation therapy component.

**DR LOVE:** What are the risks and benefits associated with these procedures?

**DR GAMBLIN:** Little risk is associated with these procedures. The primary complications are abdominal pain, low-grade fever and nausea. Approximately 98 percent of our patients stay only one night.

Some of the data from the randomized trials evaluating chemoembolization show a survival advantage. We do not have the same data with yttrium-90 radioembolization.

We certainly see dramatic responses to yttrium-90, and it's used throughout the country, but few data exist and we don't yet have good randomized data evaluating this approach. ■

**1.8**

**Liver-Related Adverse Events by SWOG Grade with Cirrhosis (C) and without Cirrhosis (NC)**

| SWOG body | | No PVT (%) | | Branch PVT (%) | | Main PVT (%) | |
|---|---|---|---|---|---|---|---|
| System | SWOG grade | C (n = 52) | NC (n = 19) | C (n = 52) | NC (n = 19) | C (n = 52) | NC (n = 19) |
| **Elevated bilirubin** | Total | 35 | 5 | 42 | 0 | 64 | 0 |
| | 3 | 24 | 5 | 32 | 0 | 27 | 0 |
| | 4 | 10 | 0 | 5 | 0 | 36 | 0 |
| | 5 | 2 | 0 | 5 | 0 | 0 | 0 |
| **Ascites** | Total | 15 | 0 | 5 | 17 | 55 | 0 |
| | 2 | 0 | 0 | 5 | 0 | 0 | 0 |
| | 3 | 12 | 0 | 0 | 17 | 55 | 0 |
| | 4 | 4 | 0 | 0 | 0 | 0 | 0 |
| **Hepatic encephalopathy** | Total | 4 | 0 | 5 | 0 | 0 | 0 |
| | 3 | 2 | — | 0 | — | 0 | — |
| | 4 | 2 | — | 0 | — | 0 | — |
| | 5 | 0 | — | 5 | — | 0 | — |

*p*-value significant for cirrhosis group
PVT = portal vein thrombosis

SOURCE: Kulik LM et al. *Hepatology* 2008;47(1):71-81. **Abstract**

## SECTION 2 Systemic Therapeutic Options for Advanced Hepatocellular Carcinoma

**Llovet JM et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378-90.**

**Roberts LR. Sorafenib in liver cancer — Just the beginning. N Engl J Med 2008;359(4):420-2.**

### 2.1 Sorafenib: A Benchmark for a New Era of Targeted Therapies in Hepatocellular Carcinoma

"The investigators in the SHARP trial observed that in a population of patients with relatively preserved liver function (Child-Pugh class A cirrhosis), the use of sorafenib resulted in a modest but significant 3-month gain in survival over placebo. This improvement in survival occurred despite a surprisingly limited partial response rate of 2%. Survival was extended because the drug was able to retard tumor progression. This represents an important first step in the application of targeted therapies for hepatocellular carcinoma....

The advent of sorafenib now provides a benchmark against which other agents and combinations can be tested. In particular, given that the SHARP study almost exclusively involved patients with Child–Pugh class A cirrhosis and relatively compensated liver disease, it will be important to determine the efficacy and side-effect profile of sorafenib in patients with Child-Pugh class B cirrhosis. Other important questions are whether the drug prevents disease recurrence after surgery or ablative therapies or extends survival in patients undergoing chemoembolization."

— *Roberts LR.* N Engl J Med *2008;359(4):420-2.*

### Tracks 39, 46

**DR LOVE:** Dr O'Neil, can you discuss the demographics, results and subgroup analyses from the SHARP trial (2.2, 2.3)?

**DR O'NEIL:** The SHARP trial represented a select population of patients with HCC. The majority had Child-Pugh A liver disease, implying minimal ascites and near-normal albumin and bilirubin counts. Approximately 35 percent of these patients had been treated with radiofrequency ablation (RFA) or chemoembolization. Metastatic disease or portal vein thrombosis was present in the majority of the patients.

Approximately 30 percent of the patients had hepatitis C, which is a slightly lower incidence than in my population of patients, but the distribution in

SHARP is reflective of what we see in the United States. However, the SHARP trial mostly enrolled patients in Europe. Approximately 20 percent of the patients had hepatitis B, and in one quarter of the patients alcohol was the etiology.

**DR LOVE:** Dr Finn, what about the use of sorafenib for patients with Child-Pugh B liver disease? Does it matter how they scored the B, whether it was based on albumin or bilirubin?

**DR FINN:** I believe to some extent it is important, because the Child-Pugh score was not designed to assess patients for prospective oncology trials. It was used to assess patients for portal systemic shunting, and it is an objective way of classifying their liver disease. From the oncology side, we're focused on bilirubin to assess how patients can handle drugs, certainly cytotoxic agents.

Studies have proven that sorafenib is an anticancer drug that improves survival for patients with Child-Pugh A liver disease. I don't doubt that sorafenib is an anticancer drug for patients with Child-Pugh B or C disease. The question is, can we affect survival significantly for patients with Child-Pugh B or C underlying liver disease?

Certainly, some patients with Child-Pugh B liver disease — those with mild B disease, patients who are expected to live a fair amount of time with their liver disease — would likely benefit from sorafenib. At the same time, some patients with late Child-Pugh B or Child-Pugh C liver disease will die of their liver disease quickly, and treating the tumor won't make a difference.

Then we have the group of patients with Child-Pugh B or C liver disease due to their tumor burden. Sorafenib does not induce tumor responses or shrink tumors, so I don't believe we'll be altering their Child-Pugh score with sorafenib, but we might be able to help them live longer in their current state.

**2.2**

### SHARP Trial: A Phase III Randomized, Placebo-Controlled Study of Sorafenib in Patients with Advanced HCC

"In this trial, patients with advanced hepatocellular carcinoma who received sorafenib treatment had nearly a 3-month median survival benefit, as compared with those who received placebo...

[P]atients in the sorafenib group had a median survival of 10.7 months, as compared with 7.9 months in the placebo group. The effect of sorafenib on overall survival remained significant after adjustment for baseline prognostic factors that were found to influence survival, thus supporting the primary analysis. The benefit of sorafenib was also consistent among all prespecified stratification groups, including patients with the worst prognosis, such as those with an ECOG performance status of 1 or 2 or with macroscopic vascular invasion or extrahepatic spread...

Since hepatocellular carcinoma develops mainly in patients with cirrhosis, it was critical to select patients with well-preserved liver function (Child-

*continued*

Pugh class A). If the trial had included patients with more advanced liver failure (Child-Pugh class B or C), deaths related to advanced liver disease might have masked any significant activity of sorafenib."

— *Llovet JM et al.* N Engl J Med *2008;359(4):378-90.* ***Abstract***

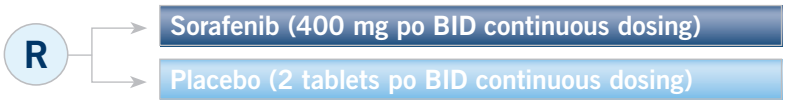
**2.3**

## SHARP Trial: A Phase III Randomized, Placebo-Controlled Study of Sorafenib in Patients with Advanced HCC

Protocol IDs: 100554, NCT00105443
Accrual: 602 (Closed)

### Eligibility

- Histology-proven HCC
- Advanced HCC
- At least one measurable untreated lesion
- ECOG PS 0-2
- Child-Pugh A class
- No prior systemic treatment




Double-blind, placebo-controlled trial; ratio 1:1

### Efficacy of Sorafenib or Placebo in Patients with Advanced HCC

| | Sorafenib n = 299 | Placebo n = 303 |
|---|---|---|
| Median overall survival | 10.7 months | 7.9 months* |
| Median time to radiologic progression | 5.5 months | 2.8 months† |
| Complete response | 0 | 0 |
| Partial response | 7 (2%) | 2 (1%) |
| Stable disease | 211 (71%) | 204 (67%) |
| Disease control rate | 43% | 32%‡ |

*Hazard ratio (95% CI) = 0.69 (0.55-0.87); $p < 0.001$
†Hazard ratio (95% CI) = 0.58 (0.45-0.74); $p < 0.001$
‡$p = 0.002$

Disease control rate is the percentage of patients who had a best-response rating of complete or partial response or stable disease (according to RECIST) that was maintained for at least 28 days.

SOURCES: NCI Physician Data Query, October 2008; Llovet JM et al. *N Engl J Med* 2008;359(4):378-90. **Abstract**

## Tracks 10-11

**DR LOVE:** When you start patients on sorafenib, what are the side effects you discuss proactively so that patients are on the alert and will let you know of any problems?

**DR FINN:** Most significant is gastrointestinal toxicity — an increase in stool frequency, watery stools, nausea and vomiting that can't be controlled

— because I believe that's what could lead to an admission to the hospital or a more serious problem. I believe that the other important side effect is hand-foot syndrome because if they don't stop the sorafenib, it can become severe. These are the toxicities for which I tell patients, "If this happens, stop the drug first, contact me and then we'll discuss how to deal with it."

**DR THOMAS:** Diarrhea is something that you can manage and potentially maintain the dose, whereas with hand-foot syndrome, I've found that you can't. If patients start to develop symptoms, they have to stop the sorafenib because it can become debilitating in only a few days. You usually cannot go back up to the same dose.

I find that if patients are receiving enough loperamide, you can keep them on a full dose of sorafenib. Often they don't start taking loperamide soon enough. Hand-foot syndrome may be more of a dose-related toxicity, and we don't have anything to treat it, so we have to use dose reductions.

## Track 37

**DR LOVE:** Dr Finn, how do you approach the dosing of sorafenib?

**DR FINN:** If a patient is well compensated, I start him or her at the full dose, as in the clinical trial. Then I see the patient again in 10 to 14 days to assess toxicity and reduce the dose if necessary.

**DR O'NEIL:** I don't reduce the dose at the outset for most patients, although a gray area exists for the patient with Child-Pugh B liver disease, for which the drug is indicated. It's not clear that those patients tolerate it as well. However, the limited data that exist from the Phase II study suggest that they do.

My experience has been that they don't seem to tolerate sorafenib as well as the study suggested. I believe that for that group of patients — those with bad cirrhosis or perhaps older patients — starting at a lower dose is reasonable.

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**Bolondi L et al. Clinical benefit of sorafenib in hepatitis C patients with hepatocellular carcinoma: Subgroup analysis of the SHARP trial. Presentation. Gastrointestinal Cancers Symposium 2008;Abstract 129.**

## Track 40

**DR O'NEIL:** Among the subgroup analyses, I find the most interesting and perhaps most relevant to be the retrospective analysis of patients with HCV. This group, of course, tends to present with HCC and a background of severe liver disease. In the SHARP trial, the difference in median overall survival for this group of 178 patients, who were split evenly between the two randomization arms, was greater than for the entire group (2.4).

The median overall survival was 7.9 months for the patients with HCV infection in the placebo group, similar to the entire population, whereas patients

with HCV infection had a median overall survival of 14 months when treated with sorafenib. The hazard ratio of 0.58 was somewhat better than it was for the entire group. Importantly, therapy was tolerated by patients in this group similarly to patients without hepatitis C infection.

**2.4**

**SHARP Trial: Efficacy of Sorafenib in Patients Who Are HCV-Positive**

| | Sorafenib (n = 93) | Placebo (n = 85) | Hazard ratio (95% CI) |
|---|---|---|---|
| Median overall survival | 14.0 months | 7.9 months | 0.58 (0.37-0.91) |
| Median time to radiologic progression | 7.6 months | 2.8 months | 0.44 (0.25-0.76) |
| Disease control rate* | 44.1% | 30.6% | — |

* Disease control rate is the percentage of patients who had a best-response rating of complete or partial response or stable disease (according to RECIST) that was maintained for at least 28 days.

SOURCE: Bolondi L et al. Presentation. Gastrointestinal Cancers Symposium 2008;**Abstract 129**.

**Sherman M et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma and vascular invasion or extrahepatic spread: A subanalysis from the SHARP trial. Proc ASCO 2008;Abstract 4584.**

## Track 40

**DR O'NEIL:** Another SHARP subgroup analysis was conducted by Sherman, and it evaluated the 421 patients with extrahepatic spread or macroscopic vascular invasion. Again, we saw a difference in overall survival for this subgroup: 6.7 months for the placebo group, which is lower than for the entire population, versus 8.9 months for those treated with sorafenib (2.5).

**2.5**

**SHARP Trial: Efficacy of Sorafenib in Patients with Extrahepatic Spread or Macroscopic Vascular Invasion**

| | Sorafenib (n = 209) | Placebo (n = 212) | Hazard ratio (95% CI) |
|---|---|---|---|
| Median overall survival | 8.9 months | 6.7 months | 0.77 (0.60-0.99) |
| Median time to radiographic progression | 4.1 months | 2.7 months | 0.64 (0.48-0.84) |
| Disease control rate* | 41.2% | 27.8% | — |

* Disease control rate is the percentage of patients who had a best-response rating of complete or partial response or stable disease (according to RECIST) that was maintained for at least 28 days.

SOURCE: Sherman M et al. *Proc ASCO* 2008;**Abstract 4584**.

The hazard ratio of 0.77 was higher than it was for the entire group. So it begs the question, is the benefit of sorafenib greater for a patient with a lower disease burden than for a patient with a higher disease burden, as represented by portal vein thrombosis?

**Raoul J et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to ECOG performance status: A subanalysis from the SHARP trial. Proc ASCO 2008;Abstract 4587.**

## Track 40

**DR O'NEIL:** Raoul presented a poster on the efficacy of sorafenib according to ECOG performance status (PS). Few patients had PS 2, so investigators were comparing patients with PS 0 to those with PS 1. For patients with PS 1 to 2, the hazard ratio was 0.71, which is similar to that for the entire population. No effect of performance status on benefit from sorafenib was apparent (2.6).

**2.6**

**SHARP Trial: Median Overall Survival According to ECOG Performance Status (PS)**

| | Sorafenib | Placebo | Hazard ratio (95% CI) |
|---|---|---|---|
| PS 0 (n = 161, 164) | 13.3 months | 8.8 months | 0.68 (0.50-0.95) |
| PS 1 to 2 (n = 138, 139) | 8.9 months | 5.6 months | 0.71 (0.52-0.96) |

SOURCE: Raoul J et al. *Proc ASCO* 2008;**Abstract 4587**.

**Cheng A et al. Randomized phase III trial of sorafenib versus placebo in Asian patients with advanced hepatocellular carcinoma. Proc ASCO 2008;Abstract 4509.**

## Track 42

**DR LOVE:** Dr Finn, can you review the study of sorafenib in Asian-Pacific patients?

**DR FINN:** This study was similar to the SHARP trial. It included patients with advanced liver cancer who had received no prior systemic treatment. Patients had to have PS 0 to 2 and Child-Pugh A liver disease, which is important in proving that the drug has anticancer activity but raises questions about applicability to other patients (2.7).

The trial involved a two-to-one randomization to sorafenib or placebo compared to the SHARP trial, which used a one-to-one randomization. The endpoints included radiologic and symptomatic progression.

Most of the patients were men with Stage C disease, and the majority had hepatitis B virus (HBV) infection, which differs from the SHARP trial and from the general population in the United States. However, in Los Angeles, on the Pacific Rim, we see a fair amount of HBV infection.

The median overall survival was 6.5 months with sorafenib versus 4.2 months with placebo (2.7). Clearly these are positive data supporting the use of sorafenib, though I believe it will be widely recognized that the control group did not fare well compared to the control group in the SHARP trial.

The Asian trial and the SHARP trial both demonstrated a similar hazard ratio for overall survival favoring sorafenib. The hazard ratios for time to progression were also comparable in the two trials.

We did not see a lot of objective responses in either trial. So the magnitude of benefit appeared the same, regardless of the underlying etiology and the patient population. A trend reflecting more hand-foot syndrome in the Asian population was noted, which raises the issue of metabolism and whether it might be dependent on ethnicity.

**2.7**

## Phase III Randomized Trial of Sorafenib versus Placebo for Asian Patients with Advanced HCC


### Eligibility

- Advanced HCC
- ECOG 0-2
- Child-Pugh A
- No primary systemic therapy

### Endpoints

- Overall survival, time to symptomatic progression (FSHI8-TSP), time to progression, response (RECIST) and safety
- No primary endpoint defined

| | Sorafenib (n = 150) | Placebo (n = 76) | Hazard ratio (95% CI) |
|---|---|---|---|
| Median overall survival | 6.5 months | 4.2 months | 0.68 (0.50-0.93)* |
| Median time to radiographic progression | 2.8 months | 1.4 months | 0.57 (0.42-0.79)† |
| Disease control rate | 35% | 16% | — |

* $p = 0.014$; † $p < 0.001$

Disease control rate is the percentage of patients with a complete or partial response maintained for four or more weeks or stable disease documented at least 12 weeks from baseline.

SOURCE: Cheng A et al. *Proc ASCO* 2008;**Abstract 4509**.

Sorafenib is the first systemic agent to improve overall survival in liver cancer. This was evident regardless of ethnicity. The general feeling is that the Asian study had a patient population with more advanced disease, which accounts for the poorer performance in the control group.

**Abou-Alfa GK et al. Final results from a phase II, randomized, double-blind study of sorafenib plus doxorubicin versus placebo plus doxorubicin in patients with advanced hepatocellular carcinoma. Presentation. Gastrointestinal Cancers Symposium 2008;Abstract 128.**

## Track 43

**DR LOVE:** Dr Finn, can you discuss the study combining sorafenib with doxorubicin?

**DR FINN:** Most of the patients had Child-Pugh A liver disease. The addition of sorafenib to doxorubicin improved the median overall survival to 13.8 months from 6.5 months with doxorubicin alone. The median time to progression also favored the addition of sorafenib, with a hazard ratio of 0.6.

Although no significant change was evident in the response rate by RECIST, on a waterfall plot more patients who received sorafenib had a decrease in the size of their lesions, though it would not have met the criteria for a partial response.

The toxicities were as expected with sorafenib and the addition of a cytotoxic agent. Although we did not observe many significant differences in Grade III or IV toxicities, it is important to note that left ventricular (LV) dysfunction did increase with doxorubicin (a cardiotoxic agent) and sorafenib.

The problem I have with this study is that the investigators took doxorubicin, which has no efficacy data as a single agent, and empirically added sorafenib simply because doxorubicin was the standard and not because of any biologic or molecular rationale. All the benefit could come from sorafenib in this population. The study that was needed was sorafenib versus sorafenib and doxorubicin.

**Zhu AX et al. Sunitinib monotherapy in patients with advanced hepatocellular carcinoma (HCC): Insights from a multidisciplinary phase II study. Proc ASCO 2008;Abstract 4521.**

## Track 44

**DR LOVE:** Dr Finn, would you discuss the Zhu ASCO study with sunitinib?

**DR FINN:** That trial enrolled patients with good performance status and liver function who had received no prior chemotherapy or only one regimen. They received sunitinib at 37.5 milligrams every day, four weeks on and two weeks off.

The primary clinical endpoint was progression-free survival. Exploratory studies also evaluated permeability on imaging, protein changes in angiogenic markers and circulating endothelial cells. Investigators recorded one partial response and a disease control rate of 53 percent. The median overall survival was 9.8 months, which was not much different from the SHARP trial.

The toxicity associated with sunitinib may be greater than what we've seen with sorafenib — some bone marrow suppression, alterations in transaminases, rash and hand-foot syndrome. Sunitinib seems to demonstrate activity in liver cancer, and at the end of the day, this study supports the importance of anti-angiogenesis in HCC. ■

## Faculty Cases Discussed in the Audio Program

**Case 1:** **A 54-year-old woman in good health with a potentially resectable hepatocellular carcinoma (HCC) in a noncirrhotic liver (Dr Choti)**

**Case 2:** **A 67-year-old man with cryptogenic cirrhosis and bilobar Child-Pugh A HCC (Dr Thomas)**

**Case 3:** **An otherwise healthy 75-year-old man with hepatitis C virus (HCV), bilobar HCC without portal vein involvement and cirrhosis of the liver (Dr Finn)**

**Case 4:** **A 52-year-old man with HCV-related cirrhosis and a 3.2-cm hypervascular mass in the right lobe of the liver with no portal vein involvement (Dr Thuluvath)**

**Case 5:** **A 54-year-old man with untreated HCV, well-preserved liver synthetic function and diffuse, multifocal HCC with portal vein involvement (Dr Thomas)**

**Case 6:** **A 49-year-old nonalcoholic man previously treated for HCV diagnosed with Child-Pugh B HCC with portal vein thrombosis (Dr O'Neil)**

**Case 7:** **A 50-year-old woman with HCV and cirrhosis diagnosed with Child-Pugh A HCC for a 1.5-cm hypervascular lesion in the right liver dome (Dr Kwo)**

**QUESTIONS (PLEASE CIRCLE ANSWER):**

1. **Which of the following local therapies for HCC has the highest actuarial five-year survival rate?**
   a. Transplantation
   b. Resection
   c. Ablation
   d. All three therapies are equivalent
2. **In a study reported by Cheng and colleagues evaluating transarterial chemoembolization (TACE) versus radiofrequency ablation (RFA) versus the combination, which had superior overall five-year survival rates?**
   a. TACE alone
   b. RFA alone
   c. TACE followed by RFA
3. **Which condition is a primary complication associated with chemoembolization and radioembolization?**
   a. Abdominal pain
   b. Fever
   c. Nausea
   d. All of the above
4. **In a study for patients with unresectable HCC with and without portal vein thrombosis (PVT) who underwent radioembolization with yttrium-90 microspheres, survival varied depending on which of the following factors?**
   a. Presence or absence of PVT
   b. Location of PVT
   c. Cirrhosis
   d. All of the above
5. **The majority of the patients in the SHARP trial had Child-Pugh _____ liver disease.**
   a. A
   b. B
   c. C
6. **In the SHARP trial, patients with advanced HCC who were treated with sorafenib had a significant improvement in overall survival compared to those receiving placebo.**
   a. True
   b. False
7. **In a subgroup analysis of the SHARP trial, patients with HCV infection who were treated with sorafenib had a significant improvement in overall survival compared to those receiving placebo.**
   a. True
   b. False
8. **In the Phase III randomized trial of sorafenib in Asian patients with advanced HCC, the majority of the patients had _____ infection.**
   a. HBV
   b. HCV
   c. Either a or b
   d. None of the above
9. **In the Phase III randomized trial of sorafenib conducted in Asia, patients with advanced HCC who were treated with sorafenib had a significant improvement in overall survival compared to those receiving placebo.**
   a. True
   b. False
10. **In a Phase II randomized trial of patients with advanced HCC, six cycles of doxorubicin were combined with _____.**
    a. Sunitinib
    b. Sorafenib
    c. Chemoembolization
    d. None of the above
11. **In a Phase II trial, patients with advanced HCC that was treated with sunitinib had a median overall survival of approximately _____.**
    a. 15 months
    b. 10 months
    c. Five months
    d. None of the above

*Post-test answer key: 1a, 2c, 3d, 4d, 5a, 6a, 7a, 8a, 9a, 10b, 11b*

## EDUCATIONAL ASSESSMENT AND CREDIT FORM

### *Hepatocellular Carcinoma Update* — Think Tank Issue 1, 2008

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

**PART ONE — Please tell us about your experience with this educational activity**

**BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?**

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Clinical indications for transarterial chemoembolization ..... 4 3 2 1
- Efficacy and safety of local therapy alternatives ..... 4 3 2 1
- Role of sorafenib as first-line therapy ..... 4 3 2 1
- Impact of prognostic factors on sorafenib efficacy and safety ..... 4 3 2 1

**AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?**

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Clinical indications for transarterial chemoembolization ..... 4 3 2 1
- Efficacy and safety of local therapy alternatives ..... 4 3 2 1
- Role of sorafenib as first-line therapy ..... 4 3 2 1
- Impact of prognostic factors on sorafenib efficacy and safety ..... 4 3 2 1

**Was the activity evidence based, fair, balanced and free from commercial bias?**

☐ Yes ☐ No

If no, please explain: .....

**Will this activity help you improve patient care?**

☐ Yes ☐ No ☐ Not applicable

If no, please explain: .....

**Did the activity meet your educational needs and expectations?**

☐ Yes ☐ No

If no, please explain: .....

**Please respond to the following LEARNER statements by circling the appropriate selection:**

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

**As a result of this activity, I will be able to:**

- Demonstrate knowledge of the pathophysiology and epidemiology of hepatocellular carcinoma (HCC), and explain how disease etiology affects patient prognosis ..... 4 3 2 1 N/M N/A
- Develop an acceptable surveillance and screening program for patients at high risk of developing HCC, incorporating appropriate biomarkers for detection ..... 4 3 2 1 N/M N/A
- Communicate the benefits and risks of the front-line use of sorafenib to appropriate patients with advanced HCC ..... 4 3 2 1 N/M N/A
- Assess the hepatic function of patients with HCC, and use this information to tailor effective local and systemic treatment decisions ..... 4 3 2 1 N/M N/A
- Describe emerging data and ongoing research evaluating the clinical utility of angiogenesis inhibitors, novel multitargeted tyrosine kinase inhibitors and combined-modality treatment approaches for patients with HCC ..... 4 3 2 1 N/M N/A
- Discriminate among the rational use of various primary management strategies for localized and/or resectable tumors, including liver resection, transplantation, transarterial embolization, radiofrequency ablation and bridging therapy ..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with HCC about ongoing clinical trials in which they may wish to participate ..... 4 3 2 1 N/M N/A

**What other practice changes will you make or consider making as a result of this activity?**

.....

**What additional information or training do you need on the activity topics or other oncology-related topics?**

.....

**Additional comments about this activity:**

.....

.....

## PART TWO — Please tell us about the moderator and faculty for this educational activity

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

| Faculty | Knowledge of subject matter | Effectiveness as an educator |
|---|---|---|
| Michael A Choti, MD, MBA | 4 3 2 1 | 4 3 2 1 |
| Richard S Finn, MD | 4 3 2 1 | 4 3 2 1 |
| T Clark Gamblin, MD, MS | 4 3 2 1 | 4 3 2 1 |
| Jeff Geschwind, MD | 4 3 2 1 | 4 3 2 1 |
| Paul Y Kwo, MD | 4 3 2 1 | 4 3 2 1 |
| Bert H O'Neil, MD | 4 3 2 1 | 4 3 2 1 |
| Melanie B Thomas, MD | 4 3 2 1 | 4 3 2 1 |
| Paul J Thuluvath, MD | 4 3 2 1 | 4 3 2 1 |
| **Moderator** | **Knowledge of subject matter** | **Effectiveness as an educator** |
| Neil Love, MD | 4 3 2 1 | 4 3 2 1 |

**Please recommend additional faculty for future activities:**

.....

**Other comments about the moderator and faculty for this activity:**

.....

## REQUEST FOR CREDIT — Please print clearly

Name: ..... Specialty: .....

Professional Designation:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other.....

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**Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.**

**I certify my actual time spent to complete this educational activity to be _____ hour(s).**

Signature: ..... Date: .....

**To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at www.ResearchToPractice.com/HCCU/ThinkTank/CME.**

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# Hepatocellular Carcinoma™

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## U P D A T E


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