

# **Hepatocellular Carcinoma (HCC)**

## **Clinical Trials Planning Meeting (CTPM) December 2008**

### **Executive Summary**

#### **Introduction**

- Hepatocellular carcinoma (HCC) is a uniquely complex solid tumor:
- Multiple underlying etiologies (HBV, HCV, alcohol, steatosis, cholestasis, hepatic matrix alterations, exogenous androgens) result in molecular heterogeneity.
- HCC arises in an impaired liver in a majority of patients.
- The extent of hepatic dysfunction impairs many patients' eligibility to receive aggressive therapy and must be incorporated into staging and prognostic criteria in HCC.
- Several HCC classification systems exist, none of which is universally accepted. Key factors that impact prognosis include: solitary vs multi-focal tumors, presence of macrovascular invasion, extrahepatic disease, high serum alpha-fetoprotein levels, performance status, and degree of hepatic impairment.
- In the United States, HCC is generally categorized by the treatment modalities appropriate for the clinical situation, and these categories were the framework of the HCC SOTS meeting. The goal of the meeting was to evaluate trials in HCC that could realistically be undertaken by the US GI Intergroup.

**1. Liver transplantation** (orthotopic liver transplantation, OLT) for HCC is performed according to United Network for Organ Sharing (UNOS) criteria. Patients with limited tumor volume, no extrahepatic disease and no gross vascular invasion are assigned extra priority points in the MELD (Model for End-stage Liver Disease) system used for liver allocation. HCC patients who are transplanted within UNOS criteria have a median 5 - year survival of 65-80% range. **Key research areas identified include:**

- A. The role of neo-adjuvant or "bridge to transplant" therapy.
- B. The role of other therapies and the appropriateness of down-staging patients within UNOS criteria.
- C. Adjuvant therapy following OLT to decrease cancer recurrence, and to improve long- term survival.

#### **Priorities for clinical trials include:**

- 1) Down-staging therapy
  - a. **Clinical questions:** Can patients "outside" of UNOS criteria benefit from transplantation, and if so, which patients. Are there any biomarkers that can relate neo-adjuvant therapy (e.g. TACE, transarterial chemoembolization) with outcome (radiographic response, survival)?
  - b. **Trial concept:** Phase II single arm (> UNOS, ≤"UCSF" criteria) treated with TACE; surveillance with "functional" imaging every 3months, TACE repeated every 3 months as needed. Patient remains listed for transplant.

- c. **Endpoints:** rate of dropout from transplant list, survival (ITT), DFS, biologic correlates.
- d. **Correlative Science:** functional imaging, “biomarkers”, and gene expression in liver explant.
- e. **Feasibility:** Considered relatively unfeasible because of the relatively small number of patients and the lack of specific UNOS participation in the GI Intergroup.

2) Adjuvant Therapy

- a. **Clinical questions:** Can adjuvant therapy improve post-OLT outcome, specifically in patients at high risk for recurrence (defined as “outside” current UNOS criteria, high pre-operative AFP, vascular/lymphatic invasion in explant)?
- b. **Trial concept:** Randomized Phase II/III of sorafenib (or other TKI), post-transplant genetic profiling of tumor (to develop molecular markers), randomize to sorafenib vs placebo, surveillance every 3 months with imaging and serum AFP.
- c. **Endpoints:** graft survival, toxicity and safety, DFS, OS, biologic markers to correlate with survival, recurrence.
- d. **Feasibility:** Low; would require multiple transplant centers with medical oncology support to participate.

**2. Local therapies (resection, ablation):** Partial hepatic resection is considered in many HCC patients including those who are not candidates for liver transplantation, whose tumor is confined to one lobe of the liver, and have no portal hypertension, extra hepatic spread or gross vascular invasion. A variety of ablative techniques are used to treat small ( $\leq 3\text{-}4$  cm) HCC not located adjacent to vascular structures. Newer techniques of external beam irradiation may be able to successfully treat tumors adjacent to the vasculature. Few randomized trials have been performed that evaluate relative benefits and morbidity of resection compared to ablation.

**Priorities for clinical trials include:**

- 1) Adjuvant systemic therapy following resection or ablation
  - a. **STORM (Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma)** industry-sponsored trial **opened to accrual** August 2008. The target enrollment for this randomized placebo controlled international multicenter study is 1,100 patients and will include patients who have received surgical resection or local ablation. The primary endpoint of the study is recurrence-free survival in patients who receive sorafenib 400 mg BID for up to 4 years. Secondary endpoints include overall survival, time to recurrence, patient-reported outcomes, plasma biomarkers, safety and tolerability.
- 2) Phase II trial of adjuvant chemotherapy following intrahepatic therapy Doxorubicin eluting beads (DEB) or Yttrium90 spheres.

- a. **Feasibility:** Low, due to lack of adequate data for “control”, small numbers of patients and uncertain endpoints and goals for go-no go decisions for larger randomized trials.
- 3) Comparison of modalities: Hepatic resection vs ablation
- a. **Endpoints:** recurrence-free survival, equivalence vs superiority, morbidity and mortality.
    - i. **Challenges:** include center/individual bias that would preclude accrual; study design.

**3. Regional Therapy** includes intrahepatic arterial delivery of a variety of agents including chemotherapy +/- embolic material (TACE, TAE), drug eluting beads (DEB), or yttrium90-labelled microspheres, to induce tumor shrinkage by ischemia, direct cytotoxic effect, or radiation cytotoxicity. Patients with solitary HCC < 8 cm, no vascular invasion or extrahepatic spread, and compensated liver function have been shown in two randomized controlled trials to derive benefit. Wide variability exists in patient selection, technique, and treatment frequency due in part to relative paucity of data from prospective controlled trials. The practice of regional therapy is evolving rapidly, and appropriate patient populations that derive benefit are unclear.

**Priorities for clinical trials include:** Prospective Phase II and III trials of combined modalities in several patient populations:

- 1) Assessment of value of regional therapy in patients with N1 or M1 disease.
- 2) Comparison of TACE, DEB, Y90.
- 3) Role of TACE in transplantation. Does TACE response predict outcome in OLT? Efficacy of TACE as “bridge” to OLT; efficacy of pre-OLT TACE to improve post-transplant survival; efficacy of TACE to “downstage” patients outside of UNOS criteria?
- 4) Proposed ECOG #1208 **A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion** which will be open to the GI Intergroup, should be implemented.
  - a. **Feasibility:** Challenges: standardization of technique, investigator bias/preference, competing trials, high cost, variability in OLT wait time across UNOS Regions. There is potential competition for ECOG trial evaluating TACE and sorafenib.

**4. Systemic Therapy.** The majority (>70%) of patients diagnosed with HCC have disease that is not amenable to treatment with OLT or locoregional therapy; thus there is a great need for effective systemic therapies.

**Key issues in designing clinical trials for this patient population include:**

- 1) Definition of “advanced” HCC includes a heterogeneous population.
- 2) Accrual to advanced clinical trials should include patients not eligible for “curative” therapy (OLT, resection, ablation) only if appropriately stratified. Significant overlap exists between populations deemed suitable for “regional

approaches” and those with more advanced disease due to lack of prospective controlled trials of regional therapy. Highly variable TTP and OS of this large patient group, confound interpretation of Phase II trial results.

- 3) Clinical trial design parameters that were generally agreed upon include:
  - (a) Sorafenib should be included in first-line trials.
  - (b) Randomized Phase II trials using TTP as primary endpoint are encouraged.
  - (c) Trials comparing new agents vs sorafenib, and new agents + sorafenib vs sorafenib, to improve OS are a priority.
  - (d) Stratification factors and developing molecular and imaging correlates are important.
  - (e) RECIST is a poor tool for evaluating efficacy of biologic agents, in HCC due to non-compliant cirrhotic liver.
  - (f) Trials should be stratified by HCC risk factor.
  - (g) In the absence of standard of care second therapy, randomized second line trials should be placebo-controlled.
  - (h) Preclinical data supporting study of specific agents in the second line should be developed.
  - (i) Organ dysfunction studies should be performed during early clinical development.

**Challenges:** Multiple active competing Phase II/III trials may not be able to accrue because of limited patient availability. The rationale for advancing agents in HCC from Ph I- II -III are not well established.

**5. Imaging:** HCC are highly vascular tumors that are optimally imaged using “triple phase” or “liver protocol” computed tomography. HCC show contrast enhancement in the arterial phase and “washout” of contrast media in the portal venous phase. RECIST is a poor metric for evaluating response, progression, and new lesions in HCC due to: a) non-compliant cirrhotic liver; b) cirrhotic liver and the diffuse, infiltrative nature of HCC in many patients; c) many biologic agents change tumor vascularity but not tumor size; d) pre-malignant dysplastic nodules can show arterial enhancement and produce radiographic false-positive progressive disease.

**Priorities for study identified:**

- 1) Define novel imaging endpoints for HCC (consider evaluating percent tumor necrosis, viable tumor volume).
- 2) Encourage centralized image review and dedicated site radiologist in clinical trials.
- 3) Encourage centralized image banking
- 4) Prospectively study *reliable*, novel imaging methods (PET, diffusion MRI, perfusional methods such as DCE-MRI or DCE-CT)
- 5) Consider “Phase 0” studies of imaging modalities, including multiple institutional sites for validation.
- 6) Controlled comparison of DCE-MRI vs DCE-CT in HCC.

**6. Other issues/Correlative Science**

- A. Need for tissue biorepository to support clinical correlates, preferably a national tissue bank.
- B. Need to identify circulating biomarkers due to paucity of HCC tissueNo validated tumor markers exist yet.
- C. No validated tumor markers exist yet.
- D. Encouraging development of patient /public advocacy for HCC is important.

**Executive Planning Committee for the HCC SOTS meeting:**

Melanie Thomas, MD (chair)

Mike Choti, MD, MBA

Greg Gores, MD

Deborah Jaffe, PhD

Dan Haller, MD

Meg Mooney, MD

Joel Tepper, MD

Alan Venook, MD

**STATE OF THE SCIENCE MEETING  
HEPATOCELLULAR CARCINOMA (HCC)  
December 12-13, 2008**

**Day 1: Friday December 12, 2008**

**7:00 – 7:45 AM: Registration/Coffee**

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7:45 - 7:50 AM: Welcome and Introduction to the NCI State of the Science Meeting  
*Meg Mooney, M.D.*

7:50 - 8:00 AM: Charge for the State of the Science Meeting  
*Joel Tepper, M.D.*

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**Day 1 Session Moderators: Dan Haller, M.D. and Alan Venook, M.D.  
Location: Diplomat Ballroom (West Promenade)**

**8:00 – 9:15 AM: SESSION 1: LOCAL THERAPIES (TRANSPLANTATION AND RESECTION)  
Moderator: Michael Choti, M.D.**

8:00 – 8:05 AM: Introductions  
*Michael Choti, M.D.*

8:05 – 8:25 AM: Liver Transplantation  
*Francis Yao, Ph.D.*

8:25 – 8:45 AM: Hepatic Resection / Ablation  
*Yuman Fong, M.D.*

8:45 – 9:15 AM: Moderator-Led Panel Discussion  
*Panel: Francis Yao, Ph.D., Yuman Fong M.D., Greg Gores, M.D., Tim Pawlik, M.D.*

**9:15 - 9:25 AM: Break**

**9:25 – 11:00 AM: SESSION 2: REGIONAL THERAPY (TAE, TACE, EBRT,  
MICROSPHERE BRACHYTHERAPY, RADIOISOTOPE THERAPY)  
Moderator: Steven Curley, M.D.**

9:25 – 9:30 AM: Introductions  
*Steven Curley, M.D.*

9:30 – 10:00 AM: TACE, Radioisotope Therapy  
*Robert Kerlan, M.D.*

10:00 – 10:20 AM: External Beam Radiotherapy  
*Philippe Merle, M.D.*

10:20 – 11:00 AM: Moderator-Led Panel Discussion

*Panel: Robert Kerlan, M.D., Philippe Merle, M.D., Josep Llovet, M.D., Laura Dawson, M.D., Brian Carr, M.D.*

**11:00 – 12:15 PM: SESSION 3: SYSTEMIC THERAPY (ADJUVANT AND ADVANCED DISEASE, MOLECULAR TARGETS)**

**Moderator: Alan Venook, M.D.**

11:00 – 11:05 AM: Introductions

*Alan Venook, M.D.*

11:05 – 11:25 AM: Existing agents in adjuvant and advanced disease

*Bert O'Neil, M.D.*

11:25 – 11:40 AM: Promising therapeutic targets

*Melanie Thomas, M.D.*

11:40 – 12:15 PM: Moderator-Led Panel Discussion

*Panel: Bert O'Neil, M.D., Melanie Thomas, M.D., Jordi Bruix, M.D., Thomas Leung, M.D.*

**12:15–1:15 PM: Lunch (On your own)**

**1:15 – 2:50 PM: SESSION 4: OPTIMAL ASSESSMENT OF THERAPEUTIC RESPONSE (BIOMARKERS, IMAGING)**

**Moderator: Jacques Belghiti, M.D.**

1:15 – 1:20 PM: Introductions

*Jacques Belghiti, M.D.*

1:20 – 1:40 PM: Correlative science (biomarkers)

*Ronnie Poon, Ph.D.*

1:40 – 2:00 PM: Standard and functional imaging

*Larry Schwartz, M.D.*

2:00 – 2:20 PM: Staging and prognostic systems

*Josep Llovet, M.D.*

2:20 – 2:50 PM: Moderator-Led Panel Discussion

*Panel: Larry Schwartz, M.D., Ronnie Poon, Ph.D., Josep Llovet, M.D., Jorge Marrero, M.D., Andrew Zhu, M.D.*

**2:50 – 3:00 PM: Break**

**3:00 – 5:30 PM: WORKSHOPS**

**Workshop 1A: Local Therapies – Transplantation**

**Location: Executive Room (West Promenade)**

*Leader: Adrian Di Bisceglie, M.D.*

*Co-Leader: Tim Pawlik, M.D.*

**Workshop 1B: Local Therapies – Resection and Ablation**

**Location: Committee Room (West Promenade)**

*Leader: Sasan Roayaie, M.D.*  
*Co-Leader: Bryan Clary, M.D.*

**Workshop 2A: Regional Therapy**

**Location: Embassy Room (East Promenade)**

*Leader: Jeff Geschwind, M.D.*  
*Co-Leader: Ken Tanabe, M.D.*

**Workshop 2B: Regional Therapy**

**Location: Capitol Room (East Promenade)**

*Leader: Michael Wallace, M.D.*  
*Co-Leader: Laura Dawson, M.D.*

**Workshop 3: Systemic Therapy – Molecular Targeted Therapeutics, Adjuvant and Advanced Disease**

**Location: Calvert Room (East Promenade)**

*Leaders: Winnie Yeo, M.D.*  
*Co-Leaders: Ghassan Abou-Alfa, M.D.*

**Workshop 4A: Optimal Assessment of Drug Activity – Imaging**

**Location: Chairman’s Boardroom (East Promenade)**

*Leader: Mark Rosen, M.D.*  
*Co-Leader: Jeff Weinreb, M.D.*

**Workshop 4B: Optimal Assessment of Drug Activity – Correlative Science**

**Location: Governor’s Boardroom (East Promenade)**

*Leader: Ronnie Poon, M.D.*  
*Co-Leader: Nelson Fausto, M.D.*

**5:30 – 6:30 PM: WORKSHOP REPORT PREPARATION FOR SUMMARY SESSION**

*Workshop leaders, co-leaders*

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**Day 2: Saturday December 13, 2008**

**7:00 – 7:50 AM: Coffee**

**Day 2 Session Moderators: Greg Gores, M.D. and Alan Venook, M.D.**  
**Location: Diplomat Ballroom (West Promenade)**

7:50 – 8:00 AM: Introduction  
*Greg Gores, M.D. and Alan Venook, M.D.*

**8:00 - 12:00 PM: WORKSHOP SUMMARY SESSION**

**8:00 – 9:00 AM: Workshop 1A, 1B – Local Therapies**

8:00 – 8:20 AM: Leader Summary (*Drs. Di Bisceglie, Roayaie, Pawlik, Clary*)

**8:20 – 9:00 AM: Discussion**

**9:00 – 10:00 AM: Workshop 2A, 2B – Regional Therapy**

9:00 – 9:20 AM: Leader Summary (*Drs. Geschwind, Tanabe, Wallace, Dawson*)

9:20 – 10:00 AM: Discussion

**10:00 - 10:20 AM: Break**

**10:20 – 11:20 AM: Workshop 3 – Systemic Therapy**

10:20 – 10:40 AM: Leader Summary (*Drs. Yeo, Abou-Alfa*)

**10:40 – 11:20 AM: Discussion**

**11:20 – 12:20 AM: Workshop 4A, 4B: Optimal Assessment of Drug Activity –  
Imaging, Correlative Science**

11:20 – 11:30 AM: Leader Summary: Imaging (*Drs. Rosen, Weinreb*)

11:30 – 11:40 AM: Leader Summary: Biomarkers: (*Drs. Poon, Fausto*)

**11:40 – 12:20 PM: Discussion**

**12:20 – 1:00 PM: MEETING SUMMARY AND FUTURE DIRECTIONS**

*Melanie Thomas, M.D., Alan Venook, M.D., Meg Mooney, M.D.*