Hepatocellular Carcinoma: Consensus Recommendations of the National Cancer Institute Clinical Trials Planning Meeting

Melanie B. Thomas, Deborah Jaffe, Michael M. Choti, Jacques Belghiti, Steven Curley, Yuman Fong, Gregory Gores, Robert Kerlan, Phillipe Merle, Bert O'Neil, Ronnie Poon, Lawrence Schwartz, Joel Tepper, Francis Yao, Daniel Haller, Margaret Mooney, and Alan Venook

From the Hollings Cancer Center, Medical University of South Carolina, Charleston, SC; National Cancer Institute, Bethesda; The Johns Hopkins Medical Institute, Baltimore, MD; The University of Texas M. D. Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center; Columbia University College of Physicians and Surgeons, New York, NY; The Mayo Clinic, Rochester, MN; University of California, San Francisco, San Francisco, CA; Hotel-Dieu Hospital, Paris, France; University of North Carolina at Chapel Hill, Chapel Hill, NC; University of Hong Kong, Hong Kong; University of Pennsylvania, Philadelphia, PA.

Submitted March 15, 2010; accepted May 28, 2010; published online ahead of print at www.jco.org on August 2, 2010.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Melanie B. Thomas, MD, Medical University of South Carolina, Hollings Cancer Center, 86 Jonathan Lucas St, Suite 118K, Charleston, SC 29425; e-mail: thomasmb@musc.edu.

© 2010 by American Society of Clinical Oncology

0732-183X/10/2825-3994/\$20.00

DOI: 10.1200/JCO.2010.28.7805

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver in adults and the third most common cause of cancer death worldwide. The incidence of HCC in the United States is rising steadily because of the prevalence of hepatitis C viral infection and other causes of hepatic cirrhosis. The majority of patients have underlying hepatic dysfunction, which complicates patient management and the search for safe and effective therapies. The Clinical Trials Planning Meeting (CTPM) in HCC was convened by the National Cancer Institute's Gastrointestinal Cancer Steering Committee to identify the key knowledge gaps in HCC and define clinical research priorities. The CTPM structured its review according to current evidence-based treatment modalities in HCC and prioritized the recommendations on the basis of the patient populations representing the greatest unmet medical need.

J Clin Oncol 28:3994-4005. © 2010 by American Society of Clinical Oncology

INTRODUCTION

The most common primary malignancy of the liver in adults is hepatocellular carcinoma (HCC, or hepatoma). It is currently the fifth most common solid tumor worldwide and the third leading cause of cancer-related death.^{1,2} Based on data for the period 1975 to 2006, liver cancer incidence and death rates are steadily rising in the United States and demonstrate the highest average annual percent increase of the top 15 cancers by incidence.³ Despite advances in many aspects of HCC treatment, including liver transplantation, surgical resection, and locoregional therapies, > 70% of HCC patients present with advanced disease and will not benefit from these treatment modalities. At present, only one chemotherapeutic agent is approved for advanced HCC patients. This large majority of HCC patients represents a significant unmet medical need for more effective systemic therapy options. Most HCC patients have underlying cirrhosis and hepatic dysfunction—one patient with two diseases—that can significantly complicate patient management and clinical trial eligibility.

To more fully understand the complexities of HCC and to identify the key unanswered research questions and clinical trial priorities for HCC, the Cancer Therapeutics Evaluation Program (CTEP) and the Gastrointestinal Cancer Steering Commit-

tee (GISC) of the United States National Cancer Institute (NCI) held a multidisciplinary workshop in December 2008 titled "Hepatocellular Carcinoma—State of the Clinical Science." The goals and objectives of this Clinical Trials Planning Meeting (CTPM) were to identify the critical clinical questions and unmet needs in hepatocellular carcinoma; develop strategies for the design, initiation, and conduct of future clinical trials in HCC and provide rationale for the recommendations; reach consensus on the most important clinical trials to be developed, especially those conducted by cooperative groups, both near-term (6-12 months) and longer term (18-36 months); and facilitate innovation and collaboration among clinicians and scientists.

This report describes the relevant background on HCC, the approach and methods used in conducting the CTPM, the outcome of the meeting, and recommendations made to the NCI.

METHODOLOGY AND GOALS OF THE CTPM

To integrate research priorities and promote collaboration across the US Cancer Cooperative Groups, the NCI has developed scientific steering committees, including disease-specific steering committees, that include broad leadership representation from each of the 10 US Cancer Cooperative

Groups and NCI Canada. The goal of each disease-specific steering committee is to coordinate the identification, prioritization, and development of clinical concepts in each specific tumor type. The GISC, its Hepatobiliary Task Force, and NCI senior leadership participated in planning and conducting the HCC CTPM. An Executive Planning Committee was created that (1) identified recognized experts in all aspects of HCC management, with a goal of ensuring multidisciplinary and international representation; (2) created an interactive agenda that included high-level succinct summary presentations of the current status of each treatment category, question and answer sessions, panel discussions, small group workshops, and report-back and review sessions; and (3) tasked speakers, panelists, and participants to identify the key knowledge gaps in HCC and define priorities for clinical trials and their associated challenges.

HCC is an exceedingly heterogeneous malignancy because of its multiple etiologies and the comorbidities resulting from underlying cirrhosis that manifest as a broad range of liver dysfunction.^{4,5} Several tumor staging and prognostic systems have been developed for HCC, yet none is universally accepted or consistently used in clinical trials. Many academic cancer centers in the United States and globally have adopted therapeutic decision-making approaches to HCC similar to that shown in Figure 1.^{6,7} Therapeutic advances in HCC have largely evolved according to these treatment categories, specifically liver transplantation, resection, local ablation, intrahepatic regional therapy, and systemic therapy; thus, they were used as the framework for the HCC CTPM agenda.

OVERVIEW OF HCC EPIDEMIOLOGY

The primary risk factor for HCC is liver injury from diverse causes that leads to hepatic cirrhosis in most but not all patients. An estimated 78% of HCC cases and 57% of cases of liver cirrhosis are caused by chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).⁸⁻¹⁰ Chronic HBV infection, which occurs when the acute infection is not cleared by the immune system, is associated with a 15% to 25% risk of premature death from liver cancer or end-stage liver disease.^{11,12} Approximately 600,000 people die worldwide from HBV-related liver disease or HCC each year.^{4,13} In North America and in other western countries, HCV is the leading etiology for HCC. In the United States, an estimated 2.7 to 3.9 million people are chronically infected with HCV, 20% will develop cirrhosis over 20 to 30 years, and as many as 5% will die of HCC. Largely as a consequence of HCV-related cirrhosis, the incidence of HCC tripled in the United States from 1975 through 2005.^{14,15}

Recently, the combination of insulin resistance, hypertension, dyslipidemia, and obesity, termed “metabolic syndrome,” has been recognized as a cause of nonalcoholic fatty liver disease, cirrhosis, and HCC.¹⁶ There is increasing evidence that the risk of developing HCC in nonalcoholic fatty liver disease–related chronic liver disease is between 18% and 27%, which is greater than the risk of developing HCC in HCV-related cirrhosis.¹⁷⁻¹⁹ Hemochromatosis is also a significant risk factor for HCC, with an increased relative risk 200 times that of the normal population.²⁰

Fig 1. General treatment algorithm for hepatocellular carcinoma. *Suitability of patients with Child-Pugh class B cirrhosis for surgical resection is highly controversial. PVE, portal vein embolization; mets, metastasis; TACE, transcatheter arterial chemoembolization; ETOH, ethanol; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection.

IMAGING AND ASSESSMENT OF TREATMENT RESPONSE

HCC tumors are highly vascular tumors that are preferentially supplied by hepatic artery branches rather than the portal venous system, which normally provides 70% of the blood flow to liver parenchyma.^{21,22} Abdominal ultrasound is a simple, noninvasive technique that is commonly used in conjunction with serum α -fetoprotein (AFP) measurements in primary screening of patients at high risk of developing HCC. HCC tumors are optimally imaged using four-phase techniques, and these tumors typically demonstrate contrast enhancement in the arterial phase and washout of contrast media in the portal venous phase.²³⁻²⁵ In the United States, computed tomography (CT) or magnetic resonance imaging (MRI) are the current preferred modalities for imaging HCC.²⁶

The most widely used but least well understood imaging biomarker for assessing treatment response is change in unidimensional tumor size. The Response Evaluation Criteria in Solid Tumors (RECIST) system is commonly used for evaluation of response to therapies.^{27,28} There are numerous limitations of unidimensional measurements, particularly when evaluating the effect of biologic targeted agents in solid tumors: single-dimension measurements are a poor surrogate for tumor volume, linear tumor size measurements are challenging to reliably reproduce, and size alone does not capture the biologic effect of treatment.²⁹⁻³¹ Furthermore, the RECIST system is a particularly limited metric for evaluating response, progression, and the presence of new lesions in HCC because of (1) noncompliant cirrhotic liver that may not remodel around dead tumor; (2) the diffuse, infiltrative nature of HCC in many cirrhotic livers; (3) the alteration of tumor vascularity but not tumor size commonly observed with biologic agents; and (4) arterial phase enhancement of premalignant dysplastic nodules commonly yielding radiographic false-positive progressive disease.

STAGING AND PROGNOSTIC SYSTEMS

Cancer staging is an important prognostic tool that provides a classification system to help guide patient management, provides a common language to compare results of various clinical trials, and is essential to the rational design of clinical trials. Currently, no single staging system has been widely validated across the spectrum of HCC patients, and none of the numerous systems has been adopted globally.³²⁻³⁴ It is extremely challenging to develop a single, reproducible staging system in HCC because of significant patient heterogeneity related to multiple underlying etiologies and the presence of compensated or decompensated cirrhosis.³⁵ Based on common features shared by several staging systems, the key factors that have an impact on HCC prognosis and treatment option selection are solitary versus multifocal tumors, presence of macrovascular invasion, extrahepatic disease, high serum AFP levels, patient performance status, and degree of hepatic impairment. The principal HCC prognostic systems in current use are summarized in Table 1.

CURRENT TREATMENT APPROACHES

Progress has been made in several aspects of HCC management, including improved treatment of HCV,⁵¹⁻⁵³ decreased incidence of

HBV infection as a result of widespread successful vaccination efforts,⁵⁴⁻⁵⁶ enhanced screening and early HCC detection in high-risk patients in some countries,¹³ and the approval in 2007 of the oral anticancer agent sorafenib for treatment of advanced HCC.^{57,58} A variety of treatment options are available for HCC patients; however, at present, the only curative option is liver transplantation, which benefits a small minority of HCC patients. Given the projected increase in incidence of HCC due to HCV and obesity-related cirrhosis,⁵⁹⁻⁶¹ there is a looming need for accelerated clinical and translational research in this disease.

The standard surgical management for early-stage HCC consists of resection or liver transplantation. However, only 10% to 30% of patients initially presenting with HCC will be eligible for surgery.⁶² In general, the treatment of HCC is dependent not only on the extent of tumor but also on the level of underlying hepatic dysfunction. Patients with cirrhosis may be candidates for limited surgical resection, liver transplantation, or locoregional ablative treatment, depending on the severity of the cirrhosis. In patients with no evidence of cirrhosis, hepatic resection has been the mainstay of surgical treatment. In patients with moderate to severe cirrhosis (Child-Pugh class B or C), transplantation is potentially optimal therapy for small-size, otherwise resectable HCC, because it eliminates the underlying cirrhosis that puts the liver at risk for subsequent new primary tumors.⁶³⁻⁶⁵ The ideal treatment strategy, but also more controversial for small HCC in patients with mild cirrhosis may include resection or transplantation.^{66,67} However, because of limited donor organ availability and also for cultural and economic reasons, surgical resection is the mainstay of therapy worldwide for patients with liver-confined HCC.

The selection of patients for surgical resection is based on several criteria, including the absence of extrahepatic disease, the degree of hepatic dysfunction, and technical considerations such as the adequacy of the future liver remnant and tumor involvement of major vascular structures such as the portal vein or vena cava. Patients with normal liver parenchyma are usually eligible for extensive resection, whereas patients with compensated cirrhosis may be candidates for minor or major partial hepatectomy only in selected cases. Surgery in patients with underlying cirrhosis can be associated with substantial morbidity and mortality.^{68,69} Although perioperative mortality can be as high as 30% to 50% in patients who are Child-Pugh class B or C, patients who are Child-Pugh class A have a surgical mortality of only 5% to 10%.^{70,71} The model for end-stage liver disease (MELD) includes serum bilirubin, creatinine, and international normalized ratio and has been shown to be a simple yet accurate method for predicting postoperative liver failure and mortality. Patients with MELD score < 9 had a mortality rate of zero in two recent large institutional series of patients undergoing resection of HCC.^{69,72} In most series, surgical resection of early HCC reported 5-year survival rates of 45% to 50% compared with 65% to 70% for transplantation.⁶⁴ However, direct comparison of resection to transplantation survival data is difficult outside of a study designed to do that. The favorable results with transplantation likely reflect more stringent selection of patients.^{73,74}

Initial results for orthotopic liver transplantation (OLT) for all-stage HCCs were associated with high early recurrence (18%) and lower 5-year survival rates (40%) compared with other indications for OLT.⁷⁵ As a result of these discouraging experiences, in the early 1990s, HCC was considered a contraindication to OLT in many transplantation centers. Subsequently, it was observed on examination of liver explants that incidental small HCC not detected by preoperative

Table 1. Staging and Prognostic Systems in HCC

Author/Reference	Staging System Acronym	Staging System Name	Score/Class System	Features
Edge et al, ³⁶ Vauthey et al, ³⁷ Gunderson et al ³⁸	AJCC/UICC TNM 6th Edition	American Joint Committee on Cancer/ International Union Against Cancer Tumor-Node-Metastasis	I, II, III, IV	Tumor size and number, vascular invasion, extrahepatic disease, fibrosis.
Llovet et al ³⁹	BCLC	Barcelona Clinic Liver Cancer	A, B, C, D	Tumor size, patient clinical status, Child-Pugh class, tumor-related symptoms, portal vein thrombosis; a complex decision-making algorithm.
Lucey et al, ⁴⁰ Pugh et al ⁴¹	CPT	Child-Pugh-Turcotte	A, B, C	Developed to predict post-hepatectomy risk of liver failure; includes ascites, encephalopathy, nutritional status, bilirubin, albumin, INR.
[No authors listed] ⁴²	CLIP	Cancer of the Liver Italian Program		Serum α -fetoprotein < 400 or $\geq$ 400 ng/mL; solitary or multiple tumor nodules or massive tumor > 50% of the area of liver, portal vein thrombosis.
Leung et al ⁴³	CUPI	Chinese University Prognostic Index		Serum bilirubin, ascites, alkaline phosphatase; presence of symptoms, TNM, fibrosis.
Cammà et al ⁴⁴	GRETCH	Group d'Etude de la Traitement du Carcinome Hepatocellulaire	A, B, C	Serum bilirubin, alkaline phosphatase, α -fetoprotein < 35 or $\geq$ 35 μ g/L, portal vein thrombosis, performance status.
Makuuchi et al ⁴⁵	IHPBA	International Hepato-Pancreato-Biliary Association		Depends on macroscopic findings after liver resection; tumor size $\leq$ 2-3 cm, no invasion of hepatic vein, portal vein, or bile ducts.
Nanashima et al, ⁴⁶ Ikai et al ⁴⁷	JIS	Japan Integrated Staging	0, 1, 2, 3, 4, 5	Combines Child-Pugh class and LCSGJ TNM system.
Hayashi et al, ⁴⁸ Yao et al ⁴⁹	MELD	Liver Cancer Study Group of Japan Model for End-Stage Liver Disease		TNM. MELD score is calculated on the basis of the patient's age, serum creatinine, serum bilirubin, and INR levels.
Okuda et al ⁵⁰	Okuda		1, 2, 3	Includes ascites, serum albumin and bilirubin, tumor < 50% or $\geq$ 50% cross-sectional area of liver; shown to have lower predictive ability when compared with some of the newer staging systems.
	UNOS	United Network for Organ Sharing		Prioritizes donor organ allocation in 11 U.S. geographic regions. UNOS policy awards additional points to MELD score for patients with HCC with one tumor $\leq$ 5 cm or $\leq$ three tumors < 8 cm total, no extrahepatic spread, no gross vascular invasion.

Abbreviations: HCC, hepatocellular carcinoma; INR, international normalized ratio.

imaging had no adverse impact on the post-transplantation outcome. Patients with HCC meeting these criteria (a single tumor < 5 cm in diameter, or 2-3 tumors each < 3 cm) had similar post-transplantation survival compared with patients without HCC, with 4-year actuarial and recurrence-free survival rates of 75% and 83%, respectively.^{76,77} These results have been confirmed by multiple centers and have led to the acceptance of liver transplantation for HCC in cirrhotic patients who meet these criteria. HCC patients who undergo OLT within United Network for Organ Sharing (UNOS) criteria have median 5-year survivals of 65% to 80%. While there is interest in expanding the criteria for liver transplantation for patients with HCC to include patients with larger and more numerous tumors (the University of California at San Francisco [UCSF] criteria),⁷⁸⁻⁸¹ these criteria have not been universally accepted or adopted.

For selected patients with HCC confined to the liver whose disease is not amenable to resection or transplantation, locoregional

therapies can be considered. These include percutaneous ethanol injection, cryotherapy, radiofrequency or microwave ablation (RFA), stereotactic radiation therapy, radioactive microspheres, transarterial (bland) embolization (TAE), and transarterial chemoembolization (TACE). While nonresectional locoregional therapies are not curative, these approaches do produce tumor destruction while preserving nontumorous liver parenchyma and may serve as a bridge to more definitive therapy, such as liver transplantation or as salvage treatment for postresection recurrence.⁸²⁻⁸⁶

RFA uses radiowaves delivered via an electrode directly inserted into a tumor to create a zone of thermal necrosis to destroy the tumor. RFA can be performed percutaneously, laparoscopically, or through an open incision and is most effective in tumors < 3 cm in diameter. Larger tumors generally require multiple overlapping ablations or the use of multiple-array probes. Traditionally, RFA (and any ablative technique) has been limited by the inability to accurately evaluate

treatment margins in all three dimensions. In a nonrandomized, comparative study of 148 patients with solitary, small (< 4 cm) HCC, the rate of local (near the margin of ablation) recurrence was found to be as high as 7.3% after RFA compared with 0% after surgery.⁸⁷ However, in a recent prospective randomized trial of 180 patients with a solitary HCC tumor < 5 cm, percutaneous RFA and surgical resection were associated with similar overall survival (OS; 68% v 64%) and disease-free survival (46% v 52%) rates at 4 years.⁸⁸ It has been suggested that RFA may be more effective in patients with cirrhosis because the fibrotic liver can act as insulation and confine the heat to the tumor, creating the so-called “oven effect.”⁸⁹ Nevertheless, there is no consensus regarding the efficacy of RFA as first-line treatment for HCC; currently, this technique is generally accepted as the best treatment for small HCC in a patient whose tumor cannot be resected safely as a means of preventing tumor progression before liver transplantation, or as salvage treatment for patients who have tumor recurrence after surgical treatment.

TACE is a locoregional therapy option that delivers chemotherapy and embolic materials via hepatic arterial infusion. It is based on the fact that HCC tumors > 2 cm preferentially receive their blood supply from the hepatic arterial circulation. Chemotherapy agents may be either infused into the liver before embolization or impregnated in the gelatin sponges used for the embolization.^{90,91} Lipiodol has also been used in conjunction with TACE because this agent will remain selectively in the tumors for an extended period, allowing the delivery of locally concentrated therapy. The objective of TACE is to bring arterial flow to stasis to effect ischemia as well as direct cytotoxic tumor damage.⁹²⁻⁹⁴ TAE can also be performed omitting the chemotherapeutic agent.

The advantage of TACE compared with the best supportive care has been suggested in two small randomized controlled trials. The first study from the University of Hong Kong randomly assigned 80 patients with advanced HCC to TACE with an emulsion of cisplatin in lipiodol and gelatin-sponge particles versus conservative management. Two-year survival rates were significantly higher for the TACE arm compared with the control group (31% v 11%; $P = .006$).⁹⁵ In the second TACE trial performed in Western Europe, patients were randomly assigned to receive bland TAE, or supportive care doxorubicin combined with lipiodol and absorbable gelatin (Gelfoam; Pfizer, Hayward, CA). The 2-year survival rates were significantly better for the TACE group than for the symptomatic control group (63% v 27%; $P = .009$).⁹⁶ However, subsequent controlled trials have not demonstrated a survival benefit of TACE.^{97,98}

Morbidity rates have been reported to be as high as 23% after TACE, especially among patients with HCC tumors > 10 cm in diameter.^{99,100} Postembolization syndrome, including fever, nausea, and pain, is common. Other complications, such as fatal hepatic necrosis and liver failure are rare. TACE is generally contraindicated in patients with decompensated liver failure.

HCC tumors are clinically chemotherapy-resistant tumors, an observation supported by low response rates across a wide variety of cytotoxic chemotherapy agents¹⁰¹ and, until recently, a lack of level 1 evidence that systemic therapy improves median OS in HCC patients. In a pivotal, international, placebo-controlled clinical trial (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol [SHARP]), sorafenib significantly improved OS (10.7 v 7.9 months; $P < .001$), in patients with advanced HCC and Child-Pugh

class A cirrhosis.¹⁰² Sorafenib is a multikinase inhibitor with activity against Raf kinase and several other cellular receptors, including vascular endothelial growth factor 2 (VEGF2), platelet-derived growth factor, FLT3, and c-Kit. In HCC cell lines, sorafenib inhibits proliferation and induces apoptosis.^{57,103,104}

The approval of sorafenib in 2007 for the treatment of HCC patients in both the United States and the European Union represents a true paradigm shift in the treatment of advanced HCC and is a clinically meaningful therapeutic advancement in this challenging malignancy. Interestingly, a subsequent prospective controlled trial of sorafenib in Asian patients with the same design and eligibility criteria as the SHARP trial showed an improvement in OS with a hazard ratio similar to that of the SHARP trial. However, the Asian study showed significantly lower absolute benefit (6.2 months median survival in the study arm v 10.7 months in SHARP) and possibly overall lower tolerance of sorafenib.¹⁰⁵ Understanding the reasons for such differential effects is essential to inform the design of future trials in HCC and underscores the importance of identifying stratification factors in future clinical trials, such as hepatic function, ethnicity, disease etiology, and tumor molecular profile.

There remains a great need for safe and effective systemic therapies for HCC patients who progressed on or do not tolerate sorafenib and for patients with more advanced hepatic dysfunction. Sorafenib provides a platform on which to build future clinical trials in both the adjuvant and advanced disease settings.

SUMMARY OF THE CTPM CONSENSUS

Management of Patients With Advanced HCC: Evaluation, Staging, Stratification, Treatment, and Assessment of Therapeutic Response

The CTPM recommendations focused on the greatest unmet need in HCC: the large majority of HCC patients with advanced disease who will need systematic therapy. Many of the challenges in designing clinical trials to develop effective systemic therapies for advanced HCC are closely linked to other topics addressed by the CTPM, including optimal imaging to assess drug activity, correlative translational science, and HCC staging to facilitate design and comparison of clinical trials. Several critical features are lacking in all current HCC staging and prognostic systems, including molecular characterization of tumors and data to validate stratification of patients on the basis of etiology, ethnicity, geographic region, and other factors yet to be elucidated. Microarray technology has revolutionized the understanding of the molecular basis of several solid tumors,^{106,107} and comprehensive studies should be performed in HCC to identify molecular profiles to improve cancer staging, prediction of recurrence, prognosis, and treatment selection. Emerging data provide insight into distinct genetic and molecular differences across the spectrum of HCC.¹⁰⁸⁻¹¹² However, no adequately powered molecular characterization across the spectrum of HCC has been completed. Future prognostic studies should be performed in selected patient populations to determine whether specific prognostic indicators are relevant across the range of HCC and underlying liver disease.

There has been an explosion of technical advancements in radiographic imaging that has resulted in a lowered threshold for tumor size detection, improved ability to distinguish lesion

pathology, and improved assessment of tumor and liver vascular features. Current state-of-the-art imaging technology, including [^{18}F]fluorodeoxyglucose–positron emission tomography (FDG-PET), diffusion MRI, microbubble-enhanced ultrasound, and [^{15}O]-PET, are options that offer a greatly enhanced ability to detect and follow HCC lesions and, in some settings, to assess biologic tumor changes.^{113–115} While development of novel imaging and image interpretation techniques is closely linked to assessment of systemic therapy, there are major limitations to widespread adoption of these advances: complex imaging processing requirements, low rate of FDG-PET avidity of HCC, need for multi-institution reproducibility, and lack of validation of biologic imaging end points.^{116,117}

Several novel biologic agents in addition to sorafenib are now being tested in HCC patients (Table 2). Hepatocarcinogenesis is a complex multistep process characterized by a broad spectrum of molecular abnormalities that offers numerous potential therapeutic targets. Several key molecular pathways in HCC that represent rational targets for novel therapy are summarized in the following sections.

MAPK Pathway

The mitogen-activated protein kinase (MAPK) pathway is involved in cellular proliferation, differentiation, apoptosis, and survival. The pathway involves a cascade of phosphorylation of four major cellular kinases: ras, RAF, MAP, and extracellular signal-regulated kinase Erk (ERK). These intermediates are found to be elevated in both HCC cell lines and human specimens.^{123,124} Therapeutic agents that target the MAPK pathway include sorafenib (which

targets both raf and vascular endothelial growth factor receptor [VEGFR]), sunitinib,^{118,119,125} and farnesyl transferase inhibitors (targeting ras).^{126,127}

PI3K/Akt/mTOR Pathway

The phosphoinositide-3 kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway is a kinase cascade effecting cellular proliferation and apoptosis and is closely linked to the cell cycle. PI3K is associated with cell surface growth factor receptors and, on ligand binding, can trigger formation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3), which in turn activates Akt and leads to a number of downstream cellular events, mTOR being one of the targets. This pathway is known to be upregulated in a subset of HCC patients.^{128,129} Molecular targeted therapy such as rapamycin, a naturally occurring mTOR inhibitor, showed promising results in HCC cell lines.¹³⁰ However, no published results from clinical trials of any agents that target mTOR in HCC patients are available.

Growth Factor Dysregulation

Both the epidermal growth factor receptor (EGFR) and VEGFR growth factor families are upregulated in HCC.¹³¹ EGFR is frequently expressed in human hepatoma cells, and EGF may be one of the mitogens needed for the growth of hepatoma cells.¹³² Several agents that inhibit EGF signaling are clinically available, including gefitinib, cetuximab, erlotinib, and panitumumab.¹³³ Erlotinib is an orally active and selective inhibitor of the EGFR/human epidermal growth factor receptor 1 (HER1) –related tyrosine kinase enzyme. EGFR/

Table 2. Current Randomized Systemic Therapy Trials in Advanced HCC

Regimen/Trial Name	Study Author	Phase	No. of Patients	Preliminary Data*	Drug Name/Mechanism of Action
Nexavar-Tarceva Combination Therapy for First Line Treatment of Patients Diagnosed With Hepatocellular Carcinoma (SEARCH)		III	700		Sorafenib: multikinase inhibitor of Raf, VEGFR2, PDGFR, FLT3, MEK, and ERK
First Line Hepatocellular Carcinoma (HCC) (BRISK FL)	Finn et al ¹²⁰	III	1,050	OS, 10 months in single-agent HCC phase II trial	Brivanib: dual inhibition of FGF1 and VEGFR2
Comparison of Brivanib and Best Supportive Care to Placebo for Treatment of Liver Cancer for Those Subjects Who Have Failed Sorafenib Treatment		III	340		Brivanib: dual inhibition of FGF1 and VEGFR2
Bevacizumab and Erlotinib or Sorafenib as First-Line Therapy in Treating Patients With Advanced Liver Cancer	Thomas et al ¹²¹	Randomized phase II	120	OS, 15.65 months, TTP 8.8 months for bevacizumab plus erlotinib in single-institution phase II study	Bevacizumab: mAb binds VEGF ligand, inhibits angiogenesis Erlotinib: RTK inhibits EGFR1
Sorafenib Tosylate With or Without Doxorubicin Hydrochloride in Treating Patients With Locally Advanced or Metastatic Liver Cancer	Abou-Alfa et al ¹⁰³	III		OS, 13.8 months for combination therapy in randomized phase II study	Doxorubicin: interacts with DNA by intercalation; prevents DNA from resealing and stops replication
Efficacy and Tolerability of ABT-869 Versus Sorafenib in Advanced Hepatocellular Carcinoma (HCC)	Huynh et al ¹²²	III	900	OS, 9.7 months in single-agent phase II trial	ABT-869: RTK inhibitor of VEGF, PDGF

Abbreviations: HCC, hepatocellular carcinoma; VEGFR2, vascular endothelial growth factor receptor 2; PDGFR, platelet-derived growth factor receptor; FLT3, FMS-like tyrosine kinase 3; MEK, mitogen activated protein (MAP)/ extracellular signal-related kinase (ERK) kinase; OS, overall survival; CSF1R, colony stimulating factor 1 receptor; FGF1, fibroblast growth factor 1; TTP, time to progression; mAb, monoclonal antibody; RTK, receptor tyrosine kinase; EGFR1, endothelial growth factor receptor 1.

*Relative to OS and TTP of 10.7 and 5.5 months, respectively for sorafenib.¹⁰²

HER1 expression was detected in HCC specimens by immunohistochemistry in 88% of the patients enrolled in a phase II study of erlotinib.¹³⁴ In two phase II studies of this agent, the response rates were < 10%, but the disease control rate was more than 50%, and median survival times were 10.75 and 13 months.^{134,135}

HCCs are generally hypervascular, and VEGF promotes HCC development and metastasis.¹³⁶⁻¹³⁸ Various agents targeting the VEGF circulating ligand or transmembrane receptor, including bevacizumab, sorafenib, and brivanib, have been studied in patients with HCC.^{105,139-143} Bevacizumab, a monoclonal antibody inhibitor of the VEGF ligand, has been investigated in phase II studies alone or in combination with other agents.^{142,143} These studies showed a disease control rate of more than 80% and a median progression-free survival of more than 6 months. Sorafenib exerts an antiangiogenic effect by targeting VEGFR2/VEGFR3.^{58,144,145} The establishment of sorafenib as the current standard-of-care systemic therapy for advanced HCC patients provides a platform on which to build rational and safe combination therapies.

There are seven priorities recommended for future studies in advanced HCC:

1. The existence of numerous competing phase II and phase III trials may impair accrual to all trials because of limited patient availability. The NCI, in conjunction with the GISC (with awareness of industry-sponsored studies) should prioritize trials that have substantial scientific rationale for advancing new agents in HCC from phase I to II to III. Trials that have emanated from the GISC are listed in Table 3. Agents with new mechanisms of action should be given priority over those that address previously targeted molecular mechanisms.
2. The GISC for systemic therapy trials in HCC supports the following clinical trial design parameters:
 - Sorafenib is suggested as the control in first-line trials. Trials comparing new agents versus sorafenib and new

agents in combination with sorafenib versus sorafenib alone are a priority. In the absence of standard-of-care second-line therapy, randomized second-line trials should be placebo-controlled.

- Randomized phase II trials using time to progression as a primary end point or co-primary end point are encouraged.
 - Identification and validation of stratification factors for randomized studies is a priority.
 - Preclinical data supporting the study of specific agents in second-line therapy should be developed.
 - Organ dysfunction studies should be performed during early clinical development of new agents for therapy in HCC.
 - Tissue biorepositories should be created to support correlative studies, preferably a national or international tissue bank.
3. Studies to identify circulating biomarkers to complement analysis of HCC tissue should be conducted.
 4. Novel imaging correlative end points should be defined for HCC (consider evaluating percent tumor necrosis and viable tumor volume) since RECIST is acknowledged as a suboptimal tool for evaluating efficacy of biologic agents in HCC because of noncompliant cirrhotic liver. Centralized image review and a dedicated site radiologist in clinical trials should be encouraged, and correlative end points should be validated prospectively in clinical trials.
 5. Novel imaging methods (PET, diffusion MRI, and perfusion methods such as delayed contrast enhancement (DCE) -MRI or DCE-CT should be prospectively studied. Controlled comparison of DCE-MRI versus DCE-CT in HCC should be conducted. Collaboration with the American College of Radiology Imaging Network (ACRIN) is encouraged.
 6. Tumor markers screening at-risk populations and assessing treatment response should be developed and validated.

Table 3. CTPM Priority Clinical Trials in HCC

Trial	Sponsor	Status
Sorafenib Tosylate With or Without Doxorubicin Hydrochloride in Treating Patients With Locally Advanced or Metastatic Liver Cancer	CALGB-80802*	Actively recruiting
Trial of Beads Versus Doxorubicin Eluting Beads for Arterial Embolization of Hepatocellular Carcinoma	MSKCC	Actively recruiting
A Study of IMC-A12 in Combination With Sorafenib in Patients With Advanced Cancer of the Liver	ImClone Systems	
A Phase III Randomized, Double-Blind Trial of Chemoembolization With or Without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients With and Without Vascular Invasion	ECOG E-1208*	Actively recruiting
Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM)	Industry	Actively recruiting
Sorafenib Therapy Prior to Radiofrequency Ablation for Intermediate Sized Hepatocellular Cancer	Beth Israel Deaconess Medical Center	
Phase 3 Study of ThermoDox With Radiofrequency Ablation (RFA) in Treatment of Hepatocellular Carcinoma (HCC)	Industry	Actively recruiting
Trial of Beads Versus Doxorubicin Eluting Beads for Arterial Embolization of Hepatocellular Carcinoma	MSKCC	Actively recruiting

Abbreviations: CTPM, Clinical Trials Planning Meeting; HCC, hepatocellular carcinoma; CALGB, Cancer and Leukemia Group B; MSKCC, Memorial Sloan-Kettering Cancer Center; ECOG, Eastern Cooperative Oncology Group.

*Trial developed by the National Cancer Institute Gastrointestinal Study Group.

7. Phase zero studies of imaging modalities, including multiple institutional sites for validation, should be considered.

Regional Therapy

Regional therapy includes intrahepatic arterial delivery of a variety of agents, including chemotherapy with or without embolic material, drug-eluting beads (DEB), or yttrium-90 (⁹⁰Y) –labeled microspheres, to induce tumor shrinkage by ischemia, direct cytotoxic effect, or radiation cytotoxicity. There is significant variability in the levels of evidence that exist for the various agents and techniques used in intrahepatic therapy for HCC. Patients with solitary HCC tumors < 8 cm, no vascular invasion or extrahepatic spread, and compensated liver function have been shown to derive benefit from conventional TACE in two small, randomized, controlled trials.^{95,96} Technical advances, increasing practitioner expertise, and wide variation in individual interventional radiology practice patterns have largely driven the growth of locoregional therapy for HCC. A substantial body of empiric data has evolved, in most cases from single-institution cohort studies, that generally supports the use of intrahepatic regional therapy in a broad range of HCC patients, except those with massive or bilobar tumors, main portal vein thrombus, and advanced liver disease. Yet because of the lack of controlled, prospective clinical trials of regional therapy, there remains a clear need to provide evidence supporting which HCC patient populations will derive benefit.¹⁴⁶ While the field is evolving rapidly, regional therapies such as TACE, radio-labeled microspheres, and DEB are particularly costly and not without adverse effects. There is a need for studies to clarify the optimal use of these techniques in terms of patient safety, efficacy, and cost-effectiveness. Further, there is increasing evidence that intrahepatic therapies can stimulate cytokine production that may, in fact, drive tumor progression;^{147,148} thus, evaluating the role of concurrent targeted systemic therapies is essential.

There are several priorities for clinical evaluation of regional therapy:

1. Conduct prospective phase II and III trials of combined modalities, including TACE plus ablation and TACE plus systemic therapy.
2. Evaluate the outcome of regional therapy versus systemic therapy in patients with N1 or M1 disease.
3. Design clinical trials of regional therapy approaches to clearly identify the patient population being studied. Significant overlap exists between populations deemed suitable for regional approaches and those with more advanced disease because of the lack of prospective controlled trials of regional therapy. The highly variable time to progression and OS of this large patient group confound interpretation of phase II trial results.
4. Conduct comparison trials of TACE, DEB, and Y⁹⁰-labeled microspheres to assess safety, efficacy, and cost-effectiveness end points.
5. Define the role of TACE in liver transplantation by finding answers to these questions: Does TACE response have an impact on the outcome in OLT? What is the efficacy of TACE as a bridge to OLT? Does pre-OLT TACE improve post-transplantation survival? and What is the outcome of TACE to downstage patients who were initially outside UNOS criteria?
6. Conduct prospective trials of regional therapy options. There would be numerous challenges, including standardization of technique, investigator bias/preference, competing trials, high cost, variability in OLT wait time across UNOS regions, and lack of consistent access to OLT programs and patients for the cooperative groups.
7. The Eastern Cooperative Oncology Group (ECOG 1208; Table 3) trial, A Phase III Randomized, Double-Blind Trial of Chemoembolization With or Without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients With and Without Vascular Invasion, is actively recruiting patients and is a priority study.

Local Therapy

Partial hepatic resection is an option for many HCC patients, including those who are not candidates for liver transplantation and those whose tumor is confined to one lobe of the liver and who have no portal hypertension, no extrahepatic spread, or gross vascular invasion. A variety of ablative techniques are also used to treat small (≤ 3 –4 cm) HCC not located adjacent to vascular structures. Newer techniques using external-beam radiotherapy may be able to successfully treat somewhat larger tumors and those adjacent to the vasculature. Few randomized trials have been performed that evaluate relative benefits and morbidity of resection compared with ablation.

There are several priorities for clinical evaluation of local therapy.

1. Evaluate the outcome of adjuvant systemic therapy following resection or ablation. The Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM) trial (Table 3) is an industry-sponsored trial that opened to accrual in August 2008. The target enrollment for this randomized, placebo-controlled, international study is 1,100 patients and will include patients who have received surgical resection or local ablation. The primary end point of the study is recurrence-free survival in patients who receive sorafenib 400 mg twice per day for up to 4 years. Secondary end points include OS, time to recurrence, patient-reported outcomes, plasma biomarkers, safety, and tolerability.
2. Conduct a phase II trial of adjuvant chemotherapy following intrahepatic therapy, DEB, or Y⁹⁰-labeled microspheres.
 - Feasibility: low due to lack of adequate data for historical controls, small numbers of patients, and uncertain end points and goals for go or no-go decisions for larger randomized trials.
3. Compare modalities, such as hepatic resection versus ablation.
 - End points: recurrence-free survival and equivalence versus superiority, morbidity, and mortality.
 - Feasibility: multiple challenges include study design and institutional and individual clinician bias that would impair accrual.

Liver Transplantation

OLT was performed in 6,493 patients in the United States in 2007 for all indications: approximately 20% (1,300) of those patients had HCC. Although the published survival rates are $\geq 75\%$ for patients who received transplantation within UNOS criteria, a measurable number of HCC patients who receive liver transplantation will develop recurrent tumor or recurrent underlying liver disease and will die of their disease. Since the principal factor affecting the availability of OLT as a treatment option is limited by the supply of donor organs, OLT is expected to remain an option for only a small minority of HCC

patients. However, there are several aspects of OLT for HCC that can be further optimized.

These clinical questions illustrate the key knowledge gaps in liver transplantation for HCC identified by the CTPM: What is the role of using neoadjuvant or bridge-to-transplantation therapy? What are the role and the appropriateness of using neoadjuvant therapies to down-stage patients to within UNOS criteria? and What is the efficacy of adjuvant therapy in decreasing cancer recurrence and improving long-term survival?

There are several priorities for clinical evaluation of liver transplantation that involve downstaging therapy and adjuvant therapy.

1. Downstaging therapy:

- Clinical questions: Can patients outside UNOS criteria benefit from transplantation, and if so, which patients? Are there biomarkers that can correlate neoadjuvant therapy (eg, TACE) with outcome (radiographic response or survival)?
- Trial concept: phase II, single-arm (more than UNOS criteria and less than or equal to UCSF criteria), treated with TACE; surveillance with functional imaging every 3 months and TACE repeated every 3 months as needed. Patient would remain listed for transplantation.
- Correlative science: functional imaging, biomarkers, and gene expression in liver explants.
- End points: rate of dropout from transplantation list, survival (intent-to-treat analysis), and recurrence-free survival.
- Feasibility: considered not feasible for cooperative groups because of the relatively small number of patients and the lack of specific UNOS participation in the GI Intergroup.

2. Adjuvant therapy:

- Clinical questions: Can adjuvant therapy improve post-OLT outcome in patients at high risk for recurrence (defined as outside UNOS criteria, high preoperative AFP, and vascular/lymphatic invasion in explants)?
- Trial concept: randomized phase II and phase III trials of sorafenib (or other tyrosine kinase inhibitor), post-transplantation genetic profiling of tumor (to develop molecular markers), random assignment to sorafenib versus placebo, and surveillance every 3 months with imaging and serum AFP.
- End points: graft survival, toxicity and safety, disease-free survival, OS, and biologic markers to correlate with survival and recurrence.
- Feasibility: low because participation by multiple transplantation centers with medical oncology support would be required.

In conclusion, hepatocellular carcinoma is one of the most common malignancies in the world and is a complex tumor that is steadily rising in incidence in the United States and other western countries. The majority of patients diagnosed with HCC have advanced disease, and these patients represent the highest priority for development of effective therapies. Advanced HCC remains a significant unmet medical need for which available research resources should be prioritized. Current and future clinical trials

could identify additional effective systemic agents, combination systemic therapies, and combined modality options. As advancements in developing personalized therapy continue to evolve for other tumors, it will be essential for the HCC community to develop tissue, serum, and other validated biomarkers that can help identify those patients who will benefit most from emerging treatment options.

Although the CTPM did not specifically address prevention and early detection of HCC, it is ideal to prevent, rather than treat, an advanced malignancy. The risk factors for developing HCC are well known. Clearly HCC is a preventable cancer and is an ideal focus for cancer prevention and control strategies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Yuman Fong, Covidien (C), Ethicon (C); Gregory Gores, Bayer Pharmaceuticals (C) **Stock Ownership:** None **Honoraria:** Melanie B. Thomas, Genentech BioOncology **Research Funding:** Melanie B. Thomas, Genentech BioOncology; Michael M. Choti, Bayer Pharmaceuticals; Bert O'Neil, Bayer Pharmaceuticals; Alan Venook, Genentech, Bayer Pharmaceuticals, Pfizer **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Melanie B. Thomas, Deborah Jaffe, Michael M. Choti, Yuman Fong, Gregory Gores, Phillipe Merle, Bert O'Neil, Ronnie Poon, Lawrence Schwartz, Joel Tepper, Daniel Haller, Alan Venook **Administrative support:** Melanie B. Thomas, Deborah Jaffe **Provision of study materials or patients:** Ronnie Poon, Lawrence Schwartz, Francis Yao

Collection and assembly of data: Melanie B. Thomas, Michael M. Choti, Ronnie Poon, Lawrence Schwartz, Alan Venook

Data analysis and interpretation: Melanie B. Thomas, Michael M. Choti, Steven Curley, Yuman Fong, Robert Kerlan, Phillipe Merle, Alan Venook

Manuscript writing: Melanie B. Thomas, Deborah Jaffe, Michael M. Choti, Steven Curley, Yuman Fong, Phillipe Merle, Bert O'Neil, Joel Tepper, Daniel Haller, Alan Venook

Final approval of manuscript: Melanie B. Thomas, Deborah Jaffe, Michael M. Choti, Jacques Belghiti, Steven Curley, Yuman Fong, Gregory Gores, Robert Kerlan, Phillipe Merle, Bert O'Neil, Ronnie Poon, Lawrence Schwartz, Joel Tepper, Francis Yao, Daniel Haller, Margaret Mooney, Alan Venook

REFERENCES

1. Jemal A, Ward E, Hao Y, et al: Trends in the leading causes of death in the United States, 1970-2002. *JAMA* 294:1255-1259, 2005
2. Bosch FX, Ribes J, Díaz M, et al: Primary liver cancer: Worldwide incidence and trends. *Gastroenterology* 127:S5-S16, 2004
3. Edwards BK, Ward E, Kohler BA, et al: Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer* 116:544-573, 2010
4. Kim WR: Epidemiology of hepatitis B in the United States. *Hepatology* 49:S28-S34, 2009
5. Bialecki ES, Di Bisceglie AM: Diagnosis of hepatocellular carcinoma. *HPB (Oxford)* 7:26-34, 2005

6. Clark HP, Carson WF, Kavanagh PV, et al: Staging and current treatment of hepatocellular carcinoma. *Radiographics* 25:S3-S23, 2005 (suppl 1)
7. Palavecino M, Chun YS, Madoff DC, et al: Major hepatic resection for hepatocellular carcinoma with or without portal vein embolization: Perioperative outcome and survival. *Surgery* 145:399-405, 2009
8. Colombo M: Hepatitis C virus and hepatocellular carcinoma. *Semin Liver Dis* 19:263-269, 1999
9. Chu CM, Liaw YF: Hepatitis B virus-related cirrhosis: Natural history and treatment. *Semin Liver Dis* 26:142-152, 2006
10. Perz JF, Armstrong GL, Farrington LA, et al: The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* 45:529-538, 2006
11. Saab S, Yeganeh M, Nguyen K, et al: Recurrence of hepatocellular carcinoma and hepatitis B reinfection in hepatitis B surface antigen-positive patients after liver transplantation. *Liver Transpl* 15:1525-1534, 2009
12. Tong MJ, Hsien C, Song JJ, et al: Factors associated with progression to hepatocellular carcinoma and to death from liver complications in patients with HBsAg-positive cirrhosis. *Dig Dis Sci* 54:1337-1346, 2009
13. Schütte K, Bornschein J, Malfertheiner P: Hepatocellular carcinoma: Epidemiological trends and risk factors. *Dig Dis* 27:80-92, 2009
14. El-Serag HB, Mason AC: Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 340:745-750, 1999
15. Chiamonte M, Stroffolini T, Vian A, et al: Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* 85:2132-2137, 1999
16. Marrero JA, Fontana RJ, Su GL, et al: NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. *Hepatology* 36:1349-1354, 2002
17. Chávez-Tapia NC, Méndez-Sánchez N, Uribe M: Role of nonalcoholic fatty liver disease in hepatocellular carcinoma. *Ann Hepatol* 8:S34-S39, 2009 (suppl 1)
18. Siegel AB, Zhu AX: Metabolic syndrome and hepatocellular carcinoma: Two growing epidemics with a potential link. *Cancer* 115:5651-5661, 2009
19. Page JM, Harrison SA: NASH and HCC. *Clin Liver Dis* 13:631-647, 2009
20. Jaskiewicz K, Banach L, Lancaster E: Hepatic siderosis, fibrosis and cirrhosis: The association with hepatocellular carcinoma in high-risk population. *Anticancer Res* 17:3897-3899, 1997
21. Budhu A, Forgues M, Ye QH, et al: Prediction of venous metastases, recurrence, and prognosis in hepatocellular carcinoma based on a unique immune response signature of the liver microenvironment. *Cancer Cell* 10:99-111, 2006
22. Honda H, Tajima T, Kajiyama K, et al: Vascular changes in hepatocellular carcinoma: Correlation of radiologic and pathologic findings. *AJR Am J Roentgenol* 173:1213-1217, 1999
23. Roncalli M, Borzio M, Di Tommaso L: Hepatocellular dysplastic nodules. *Ann Ital Chir* 79:81-89, 2008
24. Shinmura R, Matsui O, Kadoya M, et al: Detection of hypervascular malignant foci in borderline lesions of hepatocellular carcinoma: Comparison of dynamic multi-detector row CT, dynamic MR imaging and superparamagnetic iron oxide-enhanced MR imaging. *Eur Radiol* 18:1918-1924, 2008
25. Kitamura T, Ichikawa T, Erturk SM, et al: Detection of hypervascular hepatocellular carcinoma with multidetector-row CT: Single arterial-phase imaging with computer-assisted automatic bolus-tracking technique compared with double arterial-phase imaging. *J Comput Assist Tomogr* 32:724-729, 2008
26. Kim MJ, Choi JY, Chung YE, et al: Magnetic resonance imaging of hepatocellular carcinoma using contrast media. *Oncology* 75:72-82, 2008 (suppl 1)
27. Therasse P, Eisenhauer EA, Verweij J: RECIST revisited: A review of validation studies on tumour assessment. *Eur J Cancer* 42:1031-1039, 2006
28. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 45:228-247, 2009
29. Kharuzhik S, Fabel M, von Tengg-Kobligh H, et al: Image-based evaluation of tumor response to treatment: Where is radiology today? *Exp Oncol* 30:181-189, 2008
30. Choi BI: Hepatocarcinogenesis in liver cirrhosis: Imaging diagnosis. *J Korean Med Sci* 13:103-116, 1998
31. Menu Y: [Evaluation of tumour response to treatment with targeted therapies: Standard or targeted criteria?]. *Bull Cancer* 94:F231-F239, 2007
32. Lu W, Dong J, Huang Z, et al: Comparison of four current staging systems for Chinese patients with hepatocellular carcinoma undergoing curative resection: Okuda, CLIP, TNM and CUPI. *J Gastroenterol Hepatol* 23:1874-1878, 2008
33. Cho CS, Gonen M, Shia J, et al: A novel prognostic nomogram is more accurate than conventional staging systems for predicting survival after resection of hepatocellular carcinoma. *J Am Coll Surg* 206:281-291, 2008
34. Georgiades CS, Liapi E, Frangakis C, et al: Prognostic accuracy of 12 liver staging systems in patients with unresectable hepatocellular carcinoma treated with transarterial chemoembolization. *J Vasc Interv Radiol* 17:1619-1624, 2006
35. Collette S, Bonnetain F, Paoletti X, et al: Prognosis of advanced hepatocellular carcinoma: Comparison of three staging systems in two French clinical trials. *Ann Oncol* 19:1117-1126, 2008
36. Edge SB, Compton CC: The American Joint Committee on Cancer: The 7th edition of the AJCC Cancer Staging Manual and the future of TNM. *Ann Surg Oncol* 17:1471-1474, 2010
37. Vauthey JN, Lauwers GY, Esnaola NF, et al: Simplified staging for hepatocellular carcinoma. *J Clin Oncol* 20:1527-1536, 2002
38. Gunderson LL, Jessup JM, Sargent DJ, et al: Revised tumor and node categorization for rectal cancer based on surveillance, epidemiology, and end results and rectal pooled analysis outcomes. *J Clin Oncol* 28:256-263, 2010
39. Llovet JM, Brú C, Bruix J: Prognosis of hepatocellular carcinoma: The BCLC staging classification. *Semin Liver Dis* 19:329-338, 1999
40. Lucey MR, Brown KA, Everson GT, et al: Minimal criteria for placement of adults on the liver transplant waiting list: A report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transpl Surg* 3:628-637, 1997
41. Pugh RC: Proceedings: The pathology of cancer of the bladder. *Cancer* 32:1267-1274, 1973
42. Prospective validation of the CLIP score: A new prognostic system for patients with cirrhosis and hepatocellular carcinoma—The Cancer of the Liver Italian Program (CLIP) Investigators. *Hepatology* 31:840-845, 2000
43. Leung TW, Tang AM, Zee B, et al: Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: A study based on 926 patients. *Cancer* 94:1760-1769, 2002
44. Cammà C, Di Marco V, Cabibbo G, et al: Survival of patients with hepatocellular carcinoma in cirrhosis: A comparison of BCLC, CLIP and GRETCH staging systems. *Aliment Pharmacol Ther* 28:62-75, 2008
45. Makuuchi M, Belghiti J, Belli G, et al: IHPBA concordant classification of primary liver cancer: Working group report. *J Hepatobiliary Pancreat Surg* 10:26-30, 2003
46. Nanashima A, Sumida Y, Morino S, et al: The Japanese integrated staging score using liver damage grade for hepatocellular carcinoma in patients after hepatectomy. *Eur J Surg Oncol* 30:765-770, 2004
47. Ikai I, Takayasu K, Omata M, et al: A modified Japan Integrated Stage score for prognostic assessment in patients with hepatocellular carcinoma. *J Gastroenterol* 41:884-892, 2006
48. Hayashi PH, Trotter JF, Forman L, et al: Impact of pretransplant diagnosis of hepatocellular carcinoma on cadaveric liver allocation in the era of MELD. *Liver Transpl* 10:42-48, 2004
49. Yao FY, Ferrell L, Bass NM, et al: Liver transplantation for hepatocellular carcinoma: Comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. *Liver Transpl* 8:765-774, 2002
50. Okuda K, Ohtsuki T, Obata H, et al: Natural history of hepatocellular carcinoma and prognosis in relation to treatment: Study of 850 patients. *Cancer* 56:918-928, 1985
51. Kulik LM: Can therapy of hepatitis C affect the development of hepatocellular carcinoma? *J Natl Compr Canc Netw* 4:751-757, 2006
52. Tokita H, Fukui H, Tanaka A, et al: Risk factors for the development of hepatocellular carcinoma among patients with chronic hepatitis C who achieved a sustained virological response to interferon therapy. *J Gastroenterol Hepatol* 20:752-758, 2005
53. Giannini EG, Bodini G, Corbo M, et al: Impact of evidence-based medicine on treatment of patients with unresectable hepatocellular carcinoma. *Aliment Pharmacol Ther* 31:493-501, 2010
54. Chang MH, You SL, Chen CJ, et al: Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: A 20-year follow-up study. *J Natl Cancer Inst* 101:1348-1355, 2009
55. Beasley RP: Rocks along the road to the control of HBV and HCC. *Ann Epidemiol* 19:231-234, 2009
56. Omata M, Yoshida H: Prevention and treatment of hepatocellular carcinoma. *Liver Transpl* 10:S111-S114, 2004
57. Kane RC, Farrell AT, Madabushi R, et al: Sorafenib for the treatment of unresectable hepatocellular carcinoma. *Oncologist* 14:95-100, 2009
58. Lang L: FDA approves sorafenib for patients with inoperable liver cancer. *Gastroenterology* 134:379, 2008
59. García-Compeán D, Jaquez-Quintana JO, Maldonado-Garza H: Hepatogenous diabetes: Current views of an ancient problem. *Ann Hepatol* 8:13-20, 2009
60. Zhong YD, Yang YF: Diabetes mellitus, chronic hepatitis C, and hepatocellular carcinoma. *Hepatology* 48:1348, 2008

61. Chuang SC, La Vecchia C, Boffetta P: Liver cancer: Descriptive epidemiology and risk factors other than HBV and HCV infection. *Cancer Lett* 286:9-14, 2009
62. Choi E Rogers E, Ahmad S, et al: Hepatobiliary cancers, in Feig BW, Berger DH, Fuhrman GM (eds): *The M. D. Anderson Surgical Oncology Handbook*. Philadelphia, PA, Lippincott Williams & Wilkins, 2006
63. Taura K, Ikai I, Hatano E, et al: Influence of coexisting cirrhosis on outcomes after partial hepatic resection for hepatocellular carcinoma fulfilling the Milan criteria: An analysis of 293 patients. *Surgery* 142:685-694, 2007
64. Cunningham SC, Tsai S, Marques HP, et al: Management of early hepatocellular carcinoma in patients with well-compensated cirrhosis. *Ann Surg Oncol* 16:1820-1831, 2009
65. Nuzzo G, Giulante F, Gauzolino R, et al: Liver resections for hepatocellular carcinoma in chronic liver disease: Experience in an Italian centre. *Eur J Surg Oncol* 33:1014-1018, 2007
66. Llovet JM, Fuster J, Bruix J: Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: Resection versus transplantation. *Hepatology* 30:1434-1440, 1999
67. Shah SA, Cleary SP, Tan JC, et al: An analysis of resection vs transplantation for early hepatocellular carcinoma: Defining the optimal therapy at a single institution. *Ann Surg Oncol* 14:2608-2614, 2007
68. Vauthey JN, Klimstra D, Franceschi D, et al: Factors affecting long-term outcome after hepatic resection for hepatocellular carcinoma. *Am J Surg* 169:28-34, 1995
69. Teh SH, Christein J, Donohue J, et al: Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: Model of End-Stage Liver Disease (MELD) score predicts perioperative mortality. *J Gastrointest Surg* 9:1207-1215, 2005
70. Pugh S, Lewis S, Rees Smith P: Bleeding oesophageal varices in alcoholic cirrhosis: Long-term follow-up of endoscopic sclerotherapy. *Q J Med* 86:241-245, 1993
71. Helling TS, Woodall CE 3rd: Referrals for surgical therapy in patients with hepatocellular carcinoma: A community experience. *J Gastrointest Surg* 11:76-81, 2007
72. Cucchetti A, Ercolani G, Vivarelli M, et al: Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. *Liver Transpl* 12:966-971, 2006
73. Poon RT, Fan ST, Lo CM, et al: Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: Implications for a strategy of salvage transplantation. *Ann Surg* 235:373-382, 2002
74. Cha C, Fong Y, Jarnagin WR, et al: Predictors and patterns of recurrence after resection of hepatocellular carcinoma. *J Am Coll Surg* 197:753-758, 2003
75. Ringe B, Pichlmayr R, Wittekind C, et al: Surgical treatment of hepatocellular carcinoma: Experience with liver resection and transplantation in 198 patients. *World J Surg* 15:270-285, 1991
76. Bismuth H, Farges O, Castaing D, et al: Assessment of the results of liver transplantation and definition of criteria for the evaluation of transplant centers. *Transplant Proc* 29:456-458, 1997
77. Mazzaferro V, Regalia E, Doci R, et al: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 334:693-699, 1996
78. Yao FY, Ferrell L, Bass NM, et al: Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival. *Hepatology* 33:1394-1403, 2001
79. Yao FY, Bass NM, Nikolai B, et al: Liver transplantation for hepatocellular carcinoma: Analysis of survival according to the intention-to-treat principle and dropout from the waiting list. *Liver Transpl* 8:873-883, 2002
80. Silva M, Moya A, Berenguer M, et al: Expanded criteria for liver transplantation in patients with cirrhosis and hepatocellular carcinoma. *Liver Transpl* 14:1449-1460, 2008
81. Takada Y, Ito T, Ueda M, et al: Living donor liver transplantation for patients with HCC exceeding the Milan criteria: A proposal of expanded criteria. *Dig Dis* 25:299-302, 2007
82. Lu X, Lee M, Tran T, et al: High level expression of apoptosis inhibitor in hepatoma cell line expressing Hepatitis B virus. *Int J Med Sci* 2:30-35, 2005
83. Heckman JT, Devera MB, Marsh JW, et al: Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. *Ann Surg Oncol* 15:3169-3177, 2008
84. Pompili M, Francica G, Rapaccini GL: Bridge treatments of hepatocellular carcinoma in cirrhotic patients submitted to liver transplantation. *Dig Dis Sci* 53:2830-2831, 2008
85. Belghiti J, Carr BI, Greig PD, et al: Treatment before liver transplantation for HCC. *Ann Surg Oncol* 15:993-1000, 2008
86. Zimmerman MA, Ghobrial RM, Tong MJ, et al: Recurrence of hepatocellular carcinoma following liver transplantation: A review of preoperative and postoperative prognostic indicators. *Arch Surg* 143:182-188, 2008
87. Lin SM, Lin CJ, Lin CC, et al: Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut* 54:1151-1156, 2005
88. Hong SN, Lee SY, Choi MS, et al: Comparing the outcomes of radiofrequency ablation and surgery in patients with a single small hepatocellular carcinoma and well-preserved hepatic function. *J Clin Gastroenterol* 39:247-252, 2005
89. Livraghi T, Goldberg SN, Lazzaroni S, et al: Small hepatocellular carcinoma: Treatment with radio-frequency ablation versus ethanol injection. *Radiology* 210:655-661, 1999
90. Shirakami Y, Shimizu M, Adachi S, et al: (-)-Epigallocatechin gallate suppresses the growth of human hepatocellular carcinoma cells by inhibiting activation of the vascular endothelial growth factor-vascular endothelial growth factor receptor axis. *Cancer Sci* 100:1957-1962, 2009
91. Malagari K, Pomoni M, Kelekis A, et al: Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 33:541-551, 2010
92. Bruix J, Sala M, Llovet JM: Chemoembolization for hepatocellular carcinoma. *Gastroenterology* 127:S179-S188, 2004
93. Brown DB, Pilgram TK, Darcy MD, et al: Hepatic arterial chemoembolization for hepatocellular carcinoma: Comparison of survival rates with different embolic agents. *J Vasc Interv Radiol* 16:1661-1666, 2005
94. Biselli M, Andreone P, Gramenzi A, et al: Transcatheter arterial chemoembolization therapy for patients with hepatocellular carcinoma: A case-controlled study. *Clin Gastroenterol Hepatol* 3:918-925, 2005
95. Lo CM, Ngan H, Tso WK, et al: Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 35:1164-1171, 2002
96. Llovet JM, Real MI, Montaña X, et al: Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. *Lancet* 359:1734-1739, 2002
97. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma: Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. *N Engl J Med* 332:1256-1261, 1995
98. Pelletier G, Roche A, Ink O, et al: A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. *J Hepatol* 11:181-184, 1990
99. Thornton RH, Covey A, Petre EN, et al: A comparison of outcomes from treating hepatocellular carcinoma by hepatic artery embolization in patients younger or older than 70 years. *Cancer* 115:5000-5006, 2009
100. Taieb J, Barbare JC, Boussaha T, et al: [Management of hepatocellular carcinoma. Where are we now? What's next?]. *Bull Cancer* 96:19-34, 2009
101. Simonetti RG, Liberati A, Angiolini C, et al: Treatment of hepatocellular carcinoma: A systematic review of randomized controlled trials. *Ann Oncol* 8:117-136, 1997
102. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 359:378-390, 2008
103. Abou-Alfa GK, Venook AP: The impact of new data in the treatment of advanced hepatocellular carcinoma. *Curr Oncol Rep* 10:199-205, 2008
104. Chaparro M, González Moreno L, Trapero-Marugán M, et al: Review article: Pharmacological therapy for hepatocellular carcinoma with sorafenib and other oral agents. *Aliment Pharmacol Ther* 28:1269-1277, 2008
105. Cheng AL, Kang YK, Chen Z, et al: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 10:25-34, 2009
106. Nannini M, Pantaleo MA, Maleddu A, et al: Gene expression profiling in colorectal cancer using microarray technologies: Results and perspectives. *Cancer Treat Rev* 35:201-209, 2009
107. Weigelt K, Lichtinger M, Rehli M, et al: Transcriptomic profiling identifies a PU.1 regulatory network in macrophages. *Biochem Biophys Res Commun* 380:308-312, 2009
108. Jonas S, Al-Abadi H, Benckert C, et al: Prognostic significance of the DNA-index in liver transplantation for hepatocellular carcinoma in cirrhosis. *Ann Surg* 250:1008-1013, 2009
109. Realdi G, Fattovich G, Hadziyannis S, et al: Survival and prognostic factors in 366 patients with compensated cirrhosis type B: A multicenter study—The Investigators of the European Concerted Action on Viral Hepatitis (EUROHEP). *J Hepatol* 21:656-666, 1994
110. Ren N, Ye QH, Qin LX, et al: Circulating DNA level is negatively associated with the long-term survival of hepatocellular carcinoma patients. *World J Gastroenterol* 12:3911-3914, 2006

111. Wang W, Peng JX, Yang JQ, et al: Identification of gene expression profiling in hepatocellular carcinoma using cDNA microarrays. *Dig Dis Sci* [epub ahead of print on January 1, 2009]
112. Thorgeirsson SS, Lee JS, Grisham JW: Functional genomics of hepatocellular carcinoma. *Hepatology* 43:S145-S150, 2006
113. Inoue T, Kudo M, Hatanaka K, et al: Imaging of hepatocellular carcinoma: Qualitative and quantitative analysis of postvascular phase contrast-enhanced ultrasonography with sonazoid—Comparison with superparamagnetic iron oxide magnetic resonance images. *Oncology* 75:48-54, 2008 (suppl 1)
114. Zhu AX, Sahani DV, Duda DG, et al: Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: A phase II study. *J Clin Oncol* 27:3027-3035, 2009
115. Woodall CE, Scoggins CR, Loehle J, et al: Hepatic imaging characteristics predict overall survival in hepatocellular carcinoma. *Ann Surg Oncol* 14:2824-2830, 2007
116. Ho CL, Chen S, Yeung DW, et al: Dual-tracer PET/CT imaging in evaluation of metastatic hepatocellular carcinoma. *J Nucl Med* 48:902-909, 2007
117. Song I, Rhim H, Lim HK, et al: Percutaneous radiofrequency ablation of hepatocellular carcinoma abutting the diaphragm and gastrointestinal tracts with the use of artificial ascites: Safety and technical efficacy in 143 patients. *Eur Radiol* 19:2630-2640, 2009
118. Zhu AX, Raymond E: Early development of sunitinib in hepatocellular carcinoma. *Expert Rev Anticancer Ther* 9:143-150, 2009
119. Faivre S, Raymond E, Boucher E, et al: Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: An open-label, multicentre, phase II study. *Lancet Oncol* 10:794-800, 2009
120. Finn RS, Kang Y, Park J, et al: Phase II, open label study of brivanib alaninate in patients (pts) with hepatocellular carcinoma (HCC) who failed prior antiangiogenic therapy. American Society of Clinical Oncology 2009 Gastrointestinal Cancers Symposium, San Francisco, CA, January 15-17, 2009 (abstr 200)
121. Thomas MB, Morris JS, Chadha R, et al: Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. *J Clin Oncol* 27:843-850, 2009
122. Huynh H, Ngo VC, Koong HN, et al: AZD6244 enhances the anti-tumor activity of sorafenib in ectopic and orthotopic models of human hepatocellular carcinoma (HCC). *J Hepatol* 52:79-87, 2010
123. Ito Y, Sasaki Y, Horimoto M, et al: Activation of mitogen-activated protein kinases/extracellular signal-regulated kinases in human hepatocellular carcinoma. *Hepatology* 27:951-958, 1998
124. McKillop IH, Schmidt CM, Cahill PA, et al: Altered expression of mitogen-activated protein kinases in a rat model of experimental hepatocellular carcinoma. *Hepatology* 26:1484-1491, 1997
125. Yau T, Chan P, Epstein R, et al: Management of advanced hepatocellular carcinoma in the era of targeted therapy. *Liver Int* 29:10-17, 2009
126. Zhou Q, He Q, Liang LJ: Expression of p27, cyclin E and cyclin A in hepatocellular carcinoma and its clinical significance. *World J Gastroenterol* 9:2450-2454, 2003
127. Zhou H, Cheng B, Lin J: Expression of DNA repair enzyme hMTH1 mRNA and protein in hepatocellular carcinoma. *J Huazhong Univ Sci Technol Med Sci* 25:389-392, 2005
128. Treiber G: mTOR inhibitors for hepatocellular cancer: A forward-moving target. *Expert Rev Anticancer Ther* 9:247-261, 2009
129. Sahin M, Allard BL, Yates M, et al: PPAR-gamma staining as a surrogate for PAX8/PPAR-gamma fusion oncogene expression in follicular neoplasms: Clinicopathological correlation and histopathological diagnostic value. *J Clin Endocrinol Metab* 90:463-468, 2005
130. Villanueva A, Chiang DY, Newell P, et al: Pivotal role of mTOR signaling in hepatocellular carcinoma. *Gastroenterology* 135:1972-1983, 2008
131. Fausto N: Growth factors in liver development, regeneration and carcinogenesis. *Prog Growth Factor Res* 3:219-234, 1991
132. Hisaka T, Yano H, Haramaki M, et al: Expressions of epidermal growth factor family and its receptor in hepatocellular carcinoma cell lines: Relationship to cell proliferation. *Int J Oncol* 14:453-460, 1999
133. Zhu AX: Development of sorafenib and other molecularly targeted agents in hepatocellular carcinoma. *Cancer* 112:250-259, 2008
134. Thomas MB, Chadha R, Glover K, et al: Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. *Cancer* 110:1059-1067, 2007
135. Philip PA, Mahoney MR, Allmer C, et al: Phase II study of Erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol* 23:6657-6663, 2005
136. Kanda M, Nomoto S, Nishikawa Y, et al: Correlations of the expression of vascular endothelial growth factor B and its isoforms in hepatocellular carcinoma with clinico-pathological parameters. *J Surg Oncol* 98:190-196, 2008
137. Shim JH, Park JW, Kim JH, et al: Association between increment of serum VEGF level and prognosis after transcatheter arterial chemoembolization in hepatocellular carcinoma patients. *Cancer Sci* 99:2037-2044, 2008
138. Hu J, Xu Y, Shen ZZ, et al: High expressions of vascular endothelial growth factor and platelet-derived endothelial cell growth factor predict poor prognosis in alpha-fetoprotein-negative hepatocellular carcinoma patients after curative resection. *J Cancer Res Clin Oncol* 135:1359-1367, 2009
139. Finn RS, Zhu AX: Targeting angiogenesis in hepatocellular carcinoma: Focus on VEGF and bevacizumab. *Expert Rev Anticancer Ther* 9:503-509, 2009
140. Azad NS, Posadas EM, Kwitkowski VE, et al: Combination targeted therapy with sorafenib and bevacizumab results in enhanced toxicity and anti-tumor activity. *J Clin Oncol* 26:3709-3714, 2008
141. Abou-Alfa GK, Schwartz L, Ricci S, et al: Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 24:4293-4300, 2006
142. Siegel AB, Cohen EI, Ocean A, et al: Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol* 26:2992-2998, 2008
143. Huynh H, Chow PK, Palanisamy N, et al: Bevacizumab and rapamycin induce growth suppression in mouse models of hepatocellular carcinoma. *J Hepatol* 49:52-60, 2008
144. Ma WW, Hidalgo M: Exploiting novel molecular targets in gastrointestinal cancers. *World J Gastroenterol* 13:5845-5856, 2007
145. Höpfner M, Schuppan D, Scherübel H: Growth factor receptors and related signalling pathways as targets for novel treatment strategies of hepatocellular cancer. *World J Gastroenterol* 14:1-14, 2008
146. Marelli L, Stigliano R, Triantos C, et al: Transarterial therapy for hepatocellular carcinoma: Which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol* 30:6-25, 2007
147. Schoenleber SJ, Kurtz DM, Talwalkar JA, et al: Prognostic role of vascular endothelial growth factor in hepatocellular carcinoma: Systematic review and meta-analysis. *Br J Cancer* 100:1385-1392, 2009
148. Pleguezuelo M, Marelli L, Misseri M, et al: TACE versus TAE as therapy for hepatocellular carcinoma. *Expert Rev Anticancer Ther* 8:1623-1641, 2008