

# Targeted Therapies for Hepatocellular Carcinoma

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## Keywords

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**Abstract:** Hepatocellular carcinoma (HCC) remains a highly lethal disease that is resistant to traditional cytotoxic chemotherapy. The last 30 years of chemotherapy clinical trials for advanced HCC have repeatedly failed to demonstrate any survival benefit for a long list of drugs. However a survival advantage was recently established for sorafenib, instituting a new standard of care for unresectable HCC. Here we review recent and ongoing studies of new therapeutic agents for HCC, including the small-molecule tyrosine kinase inhibitors, monoclonal antibodies, and combinations of these drugs.

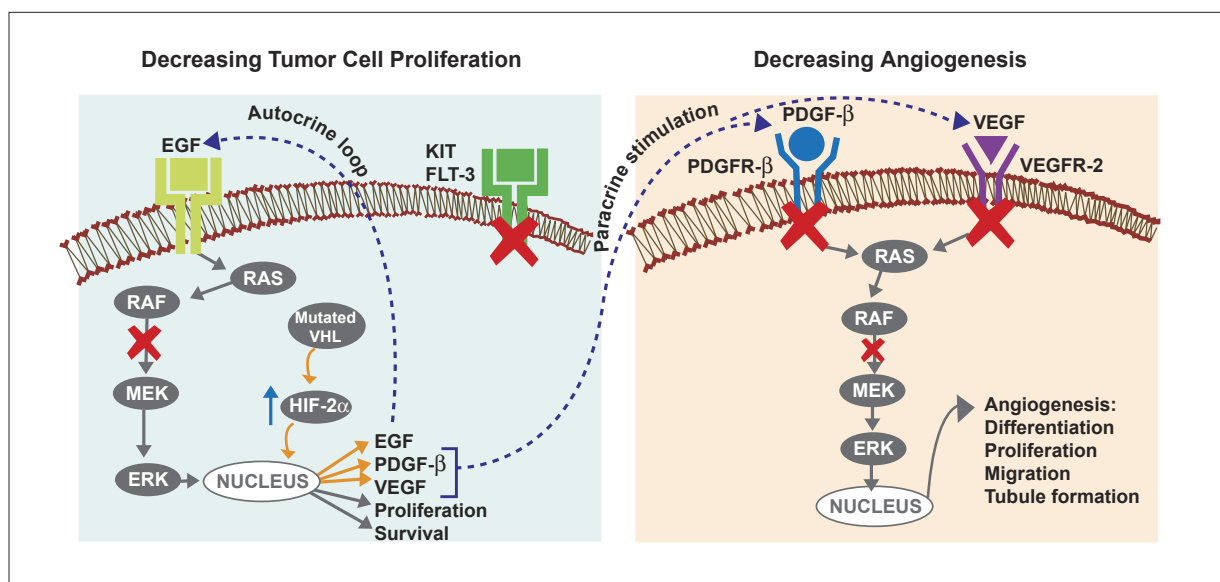
## Epidemiology

Hepatocellular carcinoma (HCC) is a major public health problem worldwide. It is the fourth or fifth most prevalent cancer globally; according to a recent estimate, 648,000 new cases of HCC are diagnosed annually, and HCC results in 623,700 deaths per year.<sup>1</sup> The majority of cases are in Asia (especially China) and Africa and are mostly the consequence of chronic hepatitis B virus infection and ingestion of aflatoxin B (a mycotoxin from *Aspergillus* fungal contamination).<sup>2</sup>

The incidence of HCC has risen dramatically in Western countries as well. This rise is attributable to the increasing incidence of hepatitis C virus (HCV) infection and subsequent development of cirrhosis of the liver.<sup>3</sup> It is estimated that 2% of the US population (4 million Americans) is infected with HCV,<sup>4</sup> and 20–35% of them will develop hepatic cirrhosis.<sup>5</sup> Between 1% and 6% of patients with cirrhosis will develop HCC per year.<sup>4</sup> Alcoholic cirrhosis also contributes an important fraction of HCC cases. Many cirrhotic patients will in fact die of HCC as opposed to liver failure. This observation may be a testament to improved therapies for liver disease.<sup>4</sup> Estimates from the SEER (Surveillance Epidemiology and End Results) database for 2007 were 19,160 new cases of HCC and intrahepatic bile duct cancer diagnosed and 16,780 deaths in the United States.

## Pathogenesis

More than 80% of HCC cases occur in the setting of cirrhosis associated with chronic infection with hepatitis B or C virus and exposure



**Figure 1.** Epidermal growth factor receptor and downstream MAPK pathway. Sorafenib decreases tumor-cell proliferation through upstream inhibition of receptor tyrosine kinases KIT and FLT-3, as well as downstream inhibition of serine/threonine kinases in the RAF/MEK/ERK pathway. Sorafenib decreases angiogenesis through upstream inhibition of receptor tyrosine kinase vascular endothelial growth factor receptor and platelet-derived growth factor receptor as well as serine/threonine kinases in the RAF/MEK/ERK pathway.

to aflatoxin B.<sup>6</sup> Hepatitis B, a DNA virus, can insert its genome into hepatocyte DNA—often near tumor suppressor genes—and transform a hepatocyte into a malignant cell independent of cirrhosis and the inflammatory milieu.<sup>7</sup> The exact cause of HCC in patients with HCV infection or other chronic inflammatory conditions is much less clear. Myriad genetic mutations can be found in HCC,<sup>7</sup> and it is difficult to pinpoint a dominant oncogene as a culprit in hepatocarcinogenesis. Some processes common to many carcinomas are described in more detail below.

### **EGFR Activation and Inhibition**

One important mechanism of tumor proliferation is aberrant growth factor receptor tyrosine kinase activity. An excess of growth factor (epidermal growth factor or transforming growth factor  $\alpha$  and others) or overexpression of a normal epidermal growth factor receptor (EGFR) can stimulate this receptor tyrosine kinase to remain activated and thereby transduce growth stimuli from the cell membrane to the cell nucleus.<sup>8</sup> HCC has been found to overexpress EGFR 1 and 2, although the importance of this observation is unclear. EGFR is overexpressed more commonly in undifferentiated HCC compared to well- or moderately differentiated tumors. The overexpression of EGFR has also been shown to be an independent negative prognostic factor and correlated with early tumor recurrence and extrahepatic metastasis.<sup>9,10</sup>

### **MAPK Pathway**

Besides EGFR overexpression, there are many downstream intermediate messengers that work to relay cell surface stimuli to the nucleus. These intermediate messengers can also be mutated and aberrantly signal cell proliferation messages to the nucleus. Ras is a critical signal switch that relays stimuli from EGFR to the cell nucleus through a cascade of several different pathways. The mitogen-activated protein kinase (MAPK) pathway is one.<sup>8</sup> The MAPK pathway is made up of the kinases Raf, MEK, and ERK (Figure 1). There is some preclinical evidence of abnormal MAPK pathway activation in HCC, suggesting the potential importance of this target.<sup>11</sup>

### **Angiogenesis**

Tumors require an independent blood supply to bring oxygen, glucose, and other nutrients to the cancer cells. Without angiogenesis and the subsequent increased nutrient supply, the tumor could not continue to grow. Radiographic imaging studies clearly demonstrate that HCC is a particularly vascular tumor. Therapies that target the blood supply to HCC tumors, such as transarterial chemoembolization (TACE), have significant utility in HCC. Tumor vascular endothelial growth factor (VEGF) abundance has also been shown to have prognostic significance in HCC.<sup>6</sup>

**Table 1.** Child-Pugh Classification of Severity of Liver Disease

Parameter	Points		
	1	2	3
<b>Ascites</b>	Absent	Slight	Moderate
Bilirubin, mg/dL	<2	2–3	>3
Albumin, g/dL	>3.5	2.8–3.5	<2.8
<b>Coagulation (use either PT or INR)</b>			
PT seconds>control	<4	4–6	>6
INR	<1.7	1.7–2.3	>2.3
<b>Encephalopathy</b>	None	Grade 1–2	Grade 3–4
<b>Child-Pugh classification</b>	A	B	C
Total points	5–6	7–9	10–15
<b>1–2 year survival in absence of hepatocellular cancer</b>	85–100%	80–60%	45–35%

INR=international normalized ratio; PT=prothrombin time.

## Staging of Hepatocellular Carcinoma

Because HCC so frequently occurs in conjunction with end-stage liver disease, the underlying liver function of all primary liver cancer patients must be assessed. TNM (Tumor, Node, Metastasis) staging of HCC is prognostically inadequate by itself and not useful for making treatment decisions because it does not account for cirrhosis. Over 80% of all HCC patients have underlying hepatic cirrhosis.<sup>12</sup> The level of liver dysfunction has a profound impact on prognosis and a patient's ability to tolerate therapy, from surgery to systemic and regional therapies. The Child-Pugh classification system is easy to use and should be combined with TNM staging in initial assessments of patients with HCC (Tables 1 and 2). There are also a variety of alternative classification systems that attempt to combine both the cirrhosis assessment and HCC tumor status into a unified system. These include the Barcelona Clinic Liver Cancer staging system (BCLC); Cancer of the Liver Italian Program (CLIP; Table 3); the Okuda classification; and the Chinese University Prognostic Index (CUPI).<sup>13</sup> The BCLC, CLIP, and CUPI are less familiar to many US oncologists than the Child-Pugh classification, but they are being used routinely in the research setting. Current National Comprehensive Cancer Network guidelines advocate using the Child-Pugh classification with the current American Joint Committee on Cancer TNM staging system, which also incorporates liver fibrosis and tumor grade into the pathologic tumor assessment (Table 2).<sup>14</sup>

## Early-stage HCC Treatment

Early-stage HCC is potentially curable with surgical resection or hepatic transplantation. Unfortunately, only 10–20% of patients are candidates for curative therapy.<sup>15</sup> The prognosis for unresectable disease varies depending upon disease burden, degree of cirrhosis, and factors such as presence of portal venous invasion. Generally speaking, patients presenting to medical oncologists have a baseline prognosis of approximately 6–8 months.<sup>16–18</sup> Factors that preclude tumor resection include poor liver function due to hepatic cirrhosis (often making a tumor unresectable in spite of small size), tumor location, tumor involvement of major hepatic blood vessels, extrahepatic metastasis, and multicentric disease.

A fraction of patients with unresectable HCC can be treated with locoregional therapies and experience prolongation of survival.<sup>19</sup> The most commonly performed locoregional treatments are TACE and radiofrequency ablation. Less commonly performed modalities include cryoablation, percutaneous ethanol injection, stereotactic or conformal radiotherapy, and catheter-directed radiation therapy. A detailed discussion of the merits of individual locoregional therapies is beyond the scope of this article.

A substantial amount of data exists favoring the use of TACE, which produces radiographic tumor responses in 30–60% of patients and has been shown to improve survival in several small randomized studies and a meta-analysis of randomized trials.<sup>19</sup> It is important to recognize that patients who are eligible for TACE are a highly select group and, therefore, have a better prognosis than most

**Table 2.** AJCC TNM Staging System for Hepatobiliary Tumors (including bile-duct tumors)

Tumor			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Solitary tumor without vascular invasion		
T2	Solitary tumor with vascular invasion or multiple tumors all <5 cm		
T3	Multiple tumors ≥5 cm or tumor invasion of a major branch of the portal or hepatic vein(s)		
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation through the visceral peritoneum		
Lymph Nodes			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph-node metastasis		
N1	Regional lymph-node metastasis		
Distant Metastasis			
Mx	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Tumor Grade			
Gx	Grade cannot be assessed		
G1	Well differentiated		
G2	Moderately differentiated		
G3	Poorly differentiated		
G4	Undifferentiated		
Hepatic Fibrosis			
F0	Grade 1–4 (none to moderate fibrosis)		
F1	Grade 5–6 (severe fibrosis to cirrhosis)		
Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	any T	N1	M0
IV	any T	Any N	M1

AJCC=American Joint Committee on Cancer; TNM=tumor, node, metastasis.

**Table 3.** CLIP (Cancer of the Liver Italian Program)

Parameter	Score		
	0	1	2
Child-Pugh score	A	B	C
Tumor morphology	Uninodular and extension ≤50%	Multinodular and extension ≤50%	Massive or tumor extension >50%
Portal-vein thrombosis	Absent	Present	
Alfa fetoprotein (ng/dL)	<400	≥400	
CLIP Score	Survival, months		
0	37		
1	27		
2	13		
3	8		
4	2		
5	2		
6	<2		

patients who present with advanced disease. Contraindications to TACE include portal vein obstruction, signs of liver failure such as hyperbilirubinemia and ascites, diffuse liver involvement, and significant metastatic disease. The aforementioned meta-analysis concluded that TACE provides a survival advantage, with 41% of treated patients living 2 years compared to 27% of untreated patients (odds ratio, 0.53; 95% confidence interval [CI], 0.32–0.89; *P*=.017).<sup>19</sup> TACE has therefore become a commonly used therapy for patients with unresectable disease.

### Advanced HCC Treatment

The rest of this review focuses on advanced and metastatic HCC. Advanced HCC (BCLC stage C or CLIP 3 and above) is difficult to treat with traditional cytotoxic chemotherapeutic agents. In fact, most classes of traditional cytotoxic chemotherapies have been tested, either as single agents or in combination, with generally disappointing results (Table 4). No greater than a 26% response rate and no survival benefit have been demonstrated to date.<sup>20</sup>

**Table 4.** Cytotoxic Chemotherapy in HCC

Agent	N	Response Rate, %	Median Survival, months
Doxorubicin <sup>15</sup>	94	10	6.8
Paclitaxel <sup>38</sup>	20	0	2.8
Capecitabine <sup>39</sup>	37	13	10
Irinotecan <sup>40</sup>	14	7	8
Gemcitabine <sup>41</sup>	30	0	7
PIAF <sup>21</sup>	50	26	9
Gemcitabine/ oxaliplatin (first line) <sup>42</sup>	21	19	12
Nolatrexed <sup>18</sup>	222	0.9	22.3 (weeks)

### Combination Biochemotherapy

The Chinese University at Hong Kong performed a phase II trial of a combination biochemotherapy regimen of PIAF (cisplatin 20 mg/m<sup>2</sup> daily on days 1 to 4; interferon  $\alpha$ -2b 5 MU/m<sup>2</sup> intravenous [IV] daily on days 1 to 4; doxorubicin 40 mg/m<sup>2</sup> IV on day 1; and 5-fluorouracil 400 mg/m<sup>2</sup> IV daily on days 1 to 4).<sup>21</sup> In this trial, 50 HCC patients received a median of 3 out of 6 planned cycles of PIAF and demonstrated an overall survival (OS) of 8.9 months and an overall response rate of 26%. Although no radiologic complete responses (CRs) occurred, 9 patients who initially were inoperable subsequently were able to undergo surgery. Of these 9 patients, 4 had a histologic CR. The regimen carried substantial toxicity however—mainly myelosuppression, but also nausea, vomiting, alopecia, mucositis, drug fever, and diarrhea. Chemotherapy was discontinued early due to either disease progression or drug toxicity.

The results of a phase III trial of PIAF versus single-agent doxorubicin were reported in 2005.<sup>15</sup> A total of 188 patients were studied (94 in each arm). The patients were well balanced for age, performance status, Child-Pugh classification, Okuda stage, and vascular tumor involvement. There was no statistical difference in OS between the groups, although, as in the phase II study, the response rate was better for PIAF (10.5% for the doxorubicin group and 20.9% for the PIAF group;  $P=.058$ ). Median survival was 6.83 months and 8.67 months for patients receiving doxorubicin and PIAF, respectively (hazard ratio 0.97;  $P=.83$ ).

Four patients in the doxorubicin group and 9 patients in the PIAF group underwent surgery for residual disease after receiving chemotherapy, and 1 patient in each group experienced a pathologic CR.<sup>15</sup> These rare CRs have led to the contention that, in cer-

tain cases, chemotherapy can convert an unresectable patient to a resectable patient<sup>13</sup>; however, chemotherapy should not be recommended for routine practice. In the United States, where HCV infection and severe cirrhosis are common in HCC patients, the concept of conversion to resectability may not be as applicable.

### Targeted Therapy

**Sorafenib** Sorafenib (Nexavar, Bayer/Onyx) is a small-molecule multiple kinase inhibitor originally developed to inhibit Raf kinase activity but later found to inhibit several other important tyrosine kinases, including VEGF receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR). Sorafenib emerged in 2007 as the first clearly effective drug therapy for advanced-stage HCC to date—a major and exciting innovation in the treatment of HCC. In spite of this innovation, however, the median survival of HCC patients is still less than 1 year.

The SHARP (Sorafenib HCC Assessment Randomized Protocol) trial investigators reported the results of a phase III, double-blind, placebo-controlled trial of sorafenib in advanced-stage HCC at the American Society of Clinical Oncology (ASCO) 2007 annual meeting.<sup>16</sup> The study randomized 602 Child-Pugh Class A patients with advanced HCC to receive sorafenib 400 mg twice daily or placebo (Table 5). Additional eligibility requirements included Eastern Cooperative Oncology Group (ECOG) performance status 0–2 and no previous systemic therapy. Sorafenib was stopped if there was any adverse event or progressive disease in conjunction with symptomatic progression, as defined using a symptom questionnaire. The two groups were well balanced for patient age, stage of disease, sex, ECOG performance status, and Child-Pugh liver disease category. It should be noted that a small number of Child-Pugh Class B patients were enrolled.

The trial was stopped after a planned interim analysis because of a significant survival advantage and prolonged time to progression (TTP) in patients receiving sorafenib. Median OS (intention-to-treat analysis) was 10.7 months for the sorafenib group compared to 7.9 months for the placebo group, with a highly statistically significant hazard ratio of 0.69 ( $P=.0006$ ), representing a 44% increase in OS. TTP was assessed by an independent central review committee and was 5.5 months in the sorafenib group, compared with 2.8 months in the placebo group, with a highly statistically significant hazard ratio of 0.58 ( $P=.000007$ ). The majority of sorafenib-treated patients (71%) had stable disease (SD); there were no patients with a CR and only 2.3% had a partial response (PR). The disease control rate (DCR; CR + PR + SD) for sorafenib was 73.3% versus 67.7% for placebo. As sorafenib and similar drugs rarely produce tumor shrinkage by Response Evaluation Criteria In Solid Tumors (RECIST), DCR and

**Table 5.** Targeted Systemic Therapy in Hepatocellular Carcinoma

Regimen	Design	N	RR, %	SD, %	DCR, %	TTP, months	PFS, months	OS, months
Sorafenib <sup>22</sup>	Phase II	137	2.2	33.6	nr	4.2	nr	9.2
Sorafenib/ doxorubicin <sup>24</sup>	RDB PII	96	4.3	nr	nr	8.6	6.9	13.7
Sorafenib/ placebo <sup>24</sup>	RDB PII		2.0	nr	nr	4.8	2.8	6.5
Erlotinib <sup>31</sup>	Phase II	40	0.0	43.0	43.0	6.5	4	10.75
Erlotinib <sup>30</sup>	Phase II	38	9.0	nr	59.0	3.2	32% (6 mo)	13
Sunitinib 37.5 mg <sup>37</sup>	Phase II	26	3.9	38.5	42.4	nr	4.1	11.6
Sunitinib 50 mg <sup>36</sup>	Phase II	37	2.7	35.0	38.0	5.25	nr	11.25
Cetuximab <sup>33</sup>	Phase II	30	0.0	16.0	nr	nr	1.4	9.6
Cetuximab <sup>34</sup>	Phase II	32	nr	44.4	nr	nr	nr	nr
Gem/Ox/Cetux <sup>35</sup>	Phase II	44	23.0	nr	65.0	nr	nr	nr
Gefitinib <sup>43</sup>	Phase II	31	3.0	23.0	26.0	nr	2.8	6.5
Lapatinib <sup>44</sup>	Phase II	40	5.0	35.0	40.0	nr	2.3	6.2
Bevacizumab <sup>25</sup>	Phase I–II	25	8.0	72.0	80.0	6.5	nr	nr
Bevacizumab <sup>26</sup>	Phase II	30	12.5	54.0	66.5	nr	nr	nr
Bev/Erlotinib <sup>32</sup>	Phase II	34	20.6	58.8	79.4	nr	9	19
Cap/Ox/Bev <sup>29</sup>	Phase II	32	13.3	76.6	90.0	4.5	nr	10.3
Gem/Ox/Bev <sup>27</sup>	Phase II	33	20.0	27.0	nr	nr	5.3	9.6
Cap/Bev <sup>28</sup>	Phase II	25	16.0	44.0	60.0	nr	4.1	10.7

DCR=disease control rate (SD + partial response + complete response); N=number; nr=not reported; OS=overall survival; PFS=progression-free survival; RDB=randomized double-blind; RR=response rate; SD=stable disease; TTP=time to progression.

TTP may be better endpoints than objective response rate for initial evaluation of drug candidates in phase II.

Adverse events experienced by the sorafenib-treated patients included diarrhea in 39% of patients (grade 3 diarrhea in 8%); hand-foot reaction in 21% (grade 3 hand-foot reaction in 8%); alopecia in 14%; and anorexia in 14% of patients. Pain, weight loss, nausea, and vomiting were slightly increased in the sorafenib group. Liver dysfunction and bleeding were similar between the groups.

The SHARP study confirmed and built upon a preceding phase II study.<sup>22</sup> Of the 137 patients treated in that single-arm study, 2.2% achieved a PR, 5.8% had a minor response, and 33.6% had SD. Median OS was 9.2 months and mean TTP was 5.5 months. The phase II study was notable for the fact that 28% of patients had Child-Pugh Class B liver dysfunction. Pharmacokinetic data were not significantly different between Child-Pugh Class A and B patients. Though pharmacokinetic differences do not

appear to be significant, it is unknown whether pharmacodynamic differences exist.

Whereas radiographic response was also uncommon in the phase II study, tumor necrosis was quantitatively evaluated in a subset of 11 patients. In certain cases, even where tumors appeared to have grown in size, the amount of tumor necrosis as seen by contrast-enhanced computed tomography (CT) also increased. This phenomenon must be studied prospectively, but potentially demonstrates the antitumor activity of sorafenib and the inadequate clinical measure of the RECIST criteria (SD, PR, etc.) for this class of drug.

A phase I study of sorafenib in solid tumors and hematologic malignancies in patients with hepatic and renal dysfunction was also reported at ASCO 2007.<sup>23</sup> This study attempted to address pharmacokinetic and pharmacodynamic differences based on level of hepatic dysfunction and included Child-Pugh Class B and C patients.

The oral clearance of sorafenib was highly variable but did not correlate to levels of organ malfunction. The authors recommended the following dose modifications, based on the dose-limiting toxicities seen in the different cohorts of patients stratified by levels of organ dysfunction: a normal starting dose of sorafenib (400 mg BID) for mild hepatic dysfunction (total bilirubin <1.5 times the upper limit of normal [ULN] and any level of aspartate transaminase [AST]); 200 mg BID for moderate hepatic dysfunction (bilirubin 1.5–3 × ULN and any AST level); 200 mg less-than-every-third-day for severe hepatic dysfunction (bilirubin 3–10 × ULN and any AST level); and 200 mg daily for very severe hepatic dysfunction (albumin <2.5 mg/dL and any bilirubin or AST). However, a potential flaw in this study was that doubling of bilirubin met the definition of dose-limiting toxicity, and many of the recorded dose-limiting toxicities fell into this category. Further examination of these patients revealed no evidence of liver injury; the elevated bilirubin may reflect competition between sorafenib and bilirubin for hepatic excretion as opposed to true toxicity. Further study in Child-Pugh Class B patients is necessary, but the phase II study by Abou-Alfa and colleagues<sup>22</sup> seems to support full doses in patients with Child-Pugh Class B disease.

**Sorafenib/Doxorubicin** Interesting results from a randomized, double blind, phase II clinical trial of sorafenib combined with doxorubicin were reported at ECCO 14 (European Cancer Organisation) in Barcelona in September 2007.<sup>24</sup> Chemotherapy-naive HCC patients with Child-Pugh Class A liver disease were randomized to receive sorafenib 400 mg twice daily and doxorubicin 60 mg/m<sup>2</sup> every 3 weeks versus placebo and doxorubicin 60 mg/m<sup>2</sup> every 3 weeks. A total of 96 patients were enrolled, 47 in the experimental arm and 49 in the control arm; the groups were well balanced. The data safety monitoring committee performed an unplanned interim analysis and recommended that the trial be unblinded and patients in the control group be crossed over to receive sorafenib. The study met its primary endpoint of median TTP, which was 8.6 months in the experimental arm versus 5 months in the control group. The secondary endpoint of 6-month progression-free survival (PFS) was 47% in the experimental arm versus 13% in the control arm. Overall survival was prolonged in the experimental arm at 13.7 months versus 6.5 months in the control arm. The authors concluded that these results support the growing body of evidence for the efficacy of sorafenib, but did not address whether or not synergy exists between doxorubicin and sorafenib. A US/Canadian intergroup study is being planned to evaluate this regimen in a phase III study of sorafenib alone versus sorafenib plus doxorubicin.

**Bevacizumab** Bevacizumab (Avastin, Genentech) is a humanized monoclonal antibody against VEGF. Six phase II studies of bevacizumab in unresectable HCC patients reported results in the last 2 years. Table 5 summarizes these trials.

Two single-agent bevacizumab studies evaluated doses of 5 mg/kg and 10 mg/kg given every 14 days. Schwartz and associates presented a trial of bevacizumab in unresectable HCC patients at ASCO 2006.<sup>25</sup> Unfortunately, 14% of patients had therapy discontinued due to serious toxicity, including a transient ischemic attack and 3 patients with variceal bleeding. The median TTP was 6.5 months. Malka and colleagues reported the results of another phase II trial of single-agent bevacizumab at ASCO 2007.<sup>26</sup> Again serious toxicity was noted—20% had variceal bleeding and there was 1 transient ischemic attack, 1 hemorrhagic ascites, and 1 patient with severe proteinuria. The DCR was 67%, with 12.5% of patients showing a PR and 54% with SD (>16 weeks in 7 patients).

Three trials of chemotherapy plus bevacizumab have now been published. In one study, patients received bevacizumab 10 mg/kg alone on day 1 of cycle 1; the subsequent 28-day cycles, beginning 14 days later, consisted of bevacizumab 10 mg/kg on days 1 and 15 and gemcitabine (Gemzar, Eli Lilly) 1,000 mg/m<sup>2</sup> (at 10 mg/m<sup>2</sup>/min) followed by oxaliplatin (Eloxatin, Sanofi-Aventis) 85 mg/m<sup>2</sup> on days 2 and 16 (GEMOX-B).<sup>27</sup> Another study examined the combination of capecitabine (Xeloda, Roche) and bevacizumab. Patients received capecitabine 800 mg/m<sup>2</sup> orally twice daily on days 1–14 and bevacizumab 7.5 mg/kg on day 1. The cycles repeated every 3 weeks for 6 cycles. Patients could continue beyond 6 cycles in the absence of progression or serious toxicity.<sup>28</sup> The third combination regimen was capecitabine, oxaliplatin, and bevacizumab (CAPOX-B). Patients received bevacizumab 5 mg/kg and oxaliplatin 130 mg/m<sup>2</sup> on day 1 of a 21-day cycle and capecitabine 825 mg/m<sup>2</sup>, twice daily, on days 1–14.<sup>29</sup> It is difficult in these studies to determine the relative contributions of chemotherapy and bevacizumab to the results, but based on the modest results, it seems unlikely that true clinical synergy was demonstrated in these trials.

**Erlotinib** Two phase II clinical trials of single-agent erlotinib (Tarceva, Genentech/OSI) have been reported. The first study of 38 unresectable HCC patients showed that single-agent erlotinib (150 mg once daily) has efficacy in HCC.<sup>30</sup> This was demonstrated by an impressive median OS of 13 months, with 33% of patients alive at 18 months. Median PFS (the primary endpoint) was 3.2 months with 32% progression-free at 6 months and 29% progression-free at 9 months. The

DCR (PR+SD) was 59%, with 3 patients demonstrating a PR; there were no CRs.

Patients with an ECOG performance score of 0–2 and a Child-Pugh Class A or B were allowed enrollment into the study. Patients could not have received more than one previous systemic or locoregional therapy. Mean age was 69 years, 32% were female, mean performance status was 1; EGFR/HER1 positivity was demonstrated in 88% of the patients and in 92% of the evaluable tumors.

The most common toxicities were skin rash, fatigue, and diarrhea. Sixty-one percent of patients encountered grade 3 or 4 toxicity; 22% of Child-Pugh Class A patients experienced a grade 3/4 toxicity compared to 70% of Child-Pugh Class B patients. Other toxicities experienced by study patients included pruritus, dry skin, alopecia, nausea, vomiting, anorexia, anemia, thrombocytopenia, and liver function test abnormalities.

A second phase II study reported by investigators from The University of Texas M. D. Anderson Cancer Center (MDACC) also demonstrated the efficacy of erlotinib (150 mg daily) in 40 patients with unresectable HCC.<sup>31</sup> The study was stopped early because the magnitude of the benefit demonstrated was unlikely to change with enrollment of more patients. Forty-three percent of patients were progression-free at 16 weeks (the primary endpoint). The median OS was 10.75 months.

**Bevacizumab/Erlotinib** The last of the six bevacizumab trials bears special attention because of its promising preliminary results. In this phase II study conducted at MDACC, unresectable HCC patients received bevacizumab 10 mg/kg every 14 days and erlotinib 150 mg daily.<sup>32</sup> Thus far, 34 of a planned 40 patients have been enrolled and analyzed: 75% of the patients have reached the primary endpoint of PFS at 16 weeks; median PFS is 8.8 months and estimated median OS is 19 months (with early follow-up). One (3%) confirmed CR was observed and six (18%) PRs. In addition, almost two thirds of these patients were previously treated with either systemic therapy or TACE. Pretreated HCC is generally refractory to most therapy, making these results that much more impressive. Five of 6 patients who received this as their first-line therapy responded. Seventeen patients (50%) had SD at 16 weeks. There was one early death due to uncontrolled variceal bleeding. Grade 3/4 toxicities included fatigue (15%), GI hemorrhage (9%), hypertension (15%), diarrhea (9%), elevated transaminases (9%), proteinuria (3%), acne (3%), hyperkalemia (3%), and wound infection (3%). Less severe toxicities included dry mouth/skin (88%), epistaxis (74%), acne (65%), anorexia (65%), hypomagnesemia (41%), hypertension (21%), and proteinuria (12%). The authors concluded that the favorable toxicity profile and early efficacy warrant further

study, and indeed planning for a phase III study of this combination is underway.

**Cetuximab** Cetuximab (Erbix, Bristol-Myers Squibb/ImClone) is a chimeric (human/mouse) monoclonal antibody (IgG1) that is specific for EGFR. Cetuximab has shown preclinical activity in HCC: in the HepG2 cell line, time- and dose-dependent growth inhibition occurred with cetuximab exposure.<sup>9</sup>

Final results from a phase II study of 30 patients with HCC were recently reported.<sup>33</sup> Patients were treated with single-agent cetuximab 400 mg/m<sup>2</sup> on week 1 and then 250 mg/m<sup>2</sup> weekly thereafter. There were no CRs or PRs by RECIST criteria. Only 17% of patients experienced SD for a median of 4.2 months. Overall survival was 9.6 months (95% CI, 4.3–12.1 months) and PFS was 1.4 months (95% CI, 1.2–2.6 months). This discrepancy between PFS and OS was thought to be due to patients who progressed receiving salvage therapy. Twenty-five patients had elevated alpha-fetoprotein levels at baseline; 5 of these had decreased levels in response to cetuximab. The therapy was well tolerated. No correlation between EGFR immunohistochemistry expression level and response to therapy could be established.

Another phase II study of single-agent cetuximab was reported in abstract form at ASCO 2007.<sup>34</sup> In this study, 44% of 27 patients experienced SD for a median of 8 weeks. Time to progression was also 8 weeks; those patients that experienced SD for 8 weeks showed a TTP of 22.5 weeks while those who progressed before 8 weeks showed a TTP of 6 weeks. Thus, cetuximab appears to have minimal activity as a single agent.

One ASCO 2007 abstract reported phase II results of a study of 44 patients with HCC who received GEMOX-cetuximab.<sup>35</sup> The overall response rate was reported to be 23% and DCR was reported as 65%; in addition, alpha-fetoprotein levels decreased by more than 50% in 50% of patients. Follow-up will be necessary to determine whether combination therapy with cetuximab holds promise.

**Sunitinib** Sunitinib (Sutent, Pfizer), an oral small-molecule multikinase inhibitor, is also showing some promise as an HCC treatment. It is thought to work largely through its antiangiogenic activity. It has documented inhibitory activity against VEGFR, PDGFR, and c-Kit (stem cell factor receptor) but, importantly, does not target the Raf-MAPK pathway. Two phase II trials were reported at ASCO 2007.

A phase II European/Asian trial of sunitinib 50 mg daily for 4 weeks followed by a 2-week break showed significant activity.<sup>36</sup> The authors reported the results of 37 unresectable HCC patients. The overall response rate

was 3%. Median TTP was 21 weeks (95% CI, 10.1–32.4 weeks). The median OS was 45 weeks (11.25 months; 95% CI, 22 weeks to not yet reached). The majority of the patients experienced SD as opposed to tumor shrinkage measured by RECIST criteria. However the study included an interesting imaging correlate of CT tumor perfusion and radiographic tumor density measures. These new radiographic attempts to assess the degree of tumor necrosis clearly showed substantial tumor necrosis in 48% of study participants. This method may be a superior way to assess tumor response in this class of medication.

Preliminary results from a US phase II trial of sunitinib 37.5 mg daily for 4 weeks followed by a 2-week treatment break were reported in a total of 26 patients.<sup>37</sup> The median TTP was 4.1 months (95% CI, 2.6–15.9 months) and median OS was 11.6 months (95% CI, 5.6 months to not yet reached). Imaging and serum correlates are also being studied.

Adverse events were similar in the two studies and included myelosuppression, fatigue, transaminase elevation, nausea, vomiting, hand-foot syndrome, and rash. In general, the medicine was well tolerated in both studies.

## Conclusion

The SHARP trial has established sorafenib as a new standard of care for the treatment of unresectable HCC in Child-Pugh Class A patients. Sorafenib is well tolerated and its efficacy has been documented now in two phase II studies and the phase III SHARP trial, which demonstrated an overall median survival at 10.7 months. Though this finding represents a substantial advance in the treatment of this notoriously recalcitrant tumor, it is far from a home run. Therefore, enrollment on a clinical trial in the first-line setting can still be considered a standard of care. In addition, one must use significant caution when prescribing sorafenib to Child-Pugh Class B patients and extreme caution in prescribing to Child-Pugh Class C patients, as only a small number have been studied. The addition of doxorubicin to sorafenib may confer additional therapeutic benefit and is an important research question that will hopefully be answered in the next few years in a planned intergroup phase III trial.

Multiple trials are ongoing, which look quite promising. The current frontrunner in the phase II clinical trial race is the combined therapy bevacizumab and erlotinib. As of the recently reported early interim analysis, the combination is demonstrating an initial OS of 19 months. There have been several deaths in the six bevacizumab studies, related mainly to variceal bleeding, so caution should be the watchword when using anti-VEGF therapy. It is interesting that bleeding has not been seen to date with sorafenib, perhaps reflective of patient selection

more than some safety advantage over bevacizumab. Novel combinations of cytotoxic chemotherapeutic agents with targeted therapies will be studied in the upcoming years and will hopefully continue to prolong the quantity and quality of life for HCC patients. Other important research questions include whether these therapies are beneficial in the adjuvant setting after locoregional therapy, transplantation, surgical resection, or even TACE.

HCC, although an uncommon tumor in the United States, will likely become more important in the future. The 4 million Americans with chronic HCV infection herald a substantial increase in patients with hepatic cirrhosis and subsequent HCC. The global HCC problem is enormous, especially for Asia and Africa. These new targeted therapies are currently expensive, and the countries most affected are typically poor. Drug expense and pricing will become an increasingly important moral, economic, and national policy issue as we develop treatment strategies for the world community. Meanwhile, prevention of one cause of HCC with hepatitis B virus immunization is a critical public health policy globally and in the United States.

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