Phase 2 Study of Erlotinib in Patients With Unresectable Hepatocellular Carcinoma

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BACKGROUND. Growth factor overexpression, including epidermal growth factor receptor (EGFR) expression, is common in hepatocellular cancers. Erlotinib is a receptor tyrosine kinase inhibitor with specificity for EGFR. The primary objective of this study was to determine the proportion of hepatocellular carcinoma (HCC) patients treated with erlotinib who were alive and progression-free (PFS) at 16 weeks of continuous treatment.

METHODS. Patients with unresectable HCC, no prior systemic therapy, performance status (PS) of 0, 1, or 2, and Childs-Pugh (CP) cirrhosis A or B received oral erlotinib 150 mg daily for 28-day cycles. Tumor response was assessed every 2 cycles by using Response Evaluation Criteria in Solid Tumors (RECIST; National Cancer Institute Cancer Therapy Evaluation Program, Bethesda, Md) criteria. Patients accrued to either "low" or "high" EGFR expression cohorts; each cohort had stopping rules applied when there was a lack of efficacy.

RESULTS. Forty HCC patients were enrolled. Median age was 64 years (range, 33–83 years), sex distribution was 32 males and 8 females, performance scores were 40% PS 0, 55% PS 1, Childs-Pugh distribution was 75% A and 20% B. There were no complete or partial responses; however, 17 of 40 patients achieved stable disease at 16 weeks of continuous therapy. The PFS at 16 weeks was 43%, and the median overall survival (OS) was 43 weeks (10.75 months). No patients required dose reductions of erlotinib. No correlation between EGFR expression and outcome was found.

CONCLUSIONS. Results of this study indicated that single-agent erlotinib is well tolerated and has modest disease-control benefit in HCC, manifested as modestly prolonged PFS and OS when compared with historical controls. ***Cancer* 2007;110:1059–66.** *Published 2007 American Cancer Society.**

KEYWORDS: EGFR, hepatoma, HCC, signal transduction, chemotherapy, hepatocellular, erlotinib.

Hepatocellular carcinoma (HCC) is the fifth most common solid tumor worldwide, primarily because of underlying hepatic cirrhosis.[1,2] The major etiologies of cirrhosis are diverse and include hepatitis B virus-related liver disease (HBV), prevalent in parts of Asia and Africa, and hepatitis C virus (HCV) in North America, Western Europe and Japan; alcohol consumption; steatosis; diabetes; liver injury in response to certain medications or toxins; and genetic metabolic diseases such as hemochromatosis. There is increasing concern about the global epidemic of obesity as a risk factor for numerous diseases, and obesity has been identified as an independent risk factor for developing HCC.[3,4] The mechanisms by which these varied etiologies lead to cirrhosis and HCC are not yet fully understood, although a common pathway may involve chronic

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inflammation, which is increasingly recognized as a procarcinogenic condition.[5,6]

Significant advances have been made in treatment of patients with small, localized HCC through improved selection of patients for liver transplantation and surgery and demonstration of modest survival benefit from locoregional treatments. However, >70% of all patients diagnosed with HCC have advanced disease and are not candidates for these therapies.[7,8] Cytotoxic chemotherapy is minimally effective in HCC, can have significant toxicity,[9] particularly in the setting of liver dysfunction, and has not appreciably improved patient survival.[9–12] Developing effective systemic therapies for these patients with advanced HCC clearly represents a significant unmet medical need in oncology.

Growth factors and their receptors are known to play a role in development and progression of numerous tumors including HCC.[13–15] Epidermal growth factor (EGF) exhibits mitogenic activity in vivo in numerous cell types including hepatocytes.[16,17] Overexpression of EGF receptor (EGFR) is common in chronic hepatitis, fibrosis, cirrhosis, and HCC.[18] The known EGFR ligands, including EGF, hepatocyte growth factor (HGF), transforming growth factor (TGFβ), and insulin-like growth factor (IGF), are mitogenic for hepatocytes and have been implicated in hepatocarcinogenesis.[19] The expression of several EGF family members, specifically EGF, TGFα and heparin-binding (HB)-EGF, as well as the EGF receptor, has been described in several HCC cell lines and in dysplastic nodules (DN), a precursor lesion to HCC.[20] Agents that target EGFR have been shown to improve survival in patients with metastatic lung[21–28] and pancreatic cancers.[29–31] Thus, there is rationale for studying the efficacy of EGFR-targeted agents in patients with HCC.

Erlotinib (Tarceva, OSI-774; OSI Pharmaceuticals, Melville, NY) is an orally active, potent selective inhibitor of the EGFR/HER-1-related tyrosine kinase enzyme. Erlotinib inhibits EGF-dependent proliferation of cancer cells at submicromolar concentrations and blocks cell-cycle progression in the G_1 phase. Erlotinib is approved by the US Food and Drug Administration (FDA) for treatment of advanced cancers of the lung and pancreas.

METHODS

Patient Selection

This was an open-label, phase 2 trial of oral erlotinib in patients with advanced HCC that was deemed not amenable to surgical resection, liver transplantation, or locoregional therapies. Eligibility criteria included an age of 18 years or older with histologically confirmed HCC. Slides from a biopsy or resection from an outside institution were reviewed and confirmed by the M. D. Anderson Pathology Department. All eligible patients were required to provide paraffin block(s) or unstained slides for evaluation of EGFR status by immunohistochemistry (IHC). Patients were required to have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST; National Cancer Institute Cancer Therapy Evaluation Program, Bethesda, Md) criteria. No prior systemic therapy was allowed; prior allowed therapies included resection or locoregional therapies. Patients with fibrolamellar HCC, a rare subtype of HCC that is relatively indolent, were excluded. Other key eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2, adequate bone marrow and renal function as indicated by absolute peripheral granulocyte count of $\geq$1500 mm^3, platelet count $\geq$60,000/mm^3, hemoglobin $\geq$10 g/dL, and serum creatinine $\geq$2 mg/dL. Adequate hepatic function was defined by total bilirubin <1.8 g/dL, transaminases up to 5 times the upper limit of institutional normal, serum albumin $\geq$2.8 g/dL, and prothrombin time prolonged no longer than 1–3 seconds greater that the institutional normal value. Patients with decompensated liver disease, as evidenced by jaundice, hepatic encephalopathy, ascites refractory to medical management, and hyponatremia with serum sodium <125, or variceal bleed within the prior 3 months, were ineligible. Other exclusion criteria included uncontrolled medical comorbidities, history of corneal disease, inability to take oral medications, presence of human immunodeficiency virus, or central nervous system metastases. The study was approved by the University of Texas M. D. Anderson Cancer Center (Houston, Tex) Institutional Review Board. Written informed consent was obtained from all patients before study enrollment in compliance with federal and institutional guidelines. The study was conducted in accordance with the Declaration of Helsinki.

Treatment Plan

Patients received erlotinib at a dose of 150 mg orally per day, continuously for a 28-day course. Patients were prospectively stratified by EGFR-receptor status. Dose modifications were allowed according to Common Toxicity Criteria version 2.0 (National Cancer Institute) to 100 or 50 mg per day. Patients who required dose reductions beyond 50 mg daily were removed from the study. No dose re-escalation was allowed after dose reduction due to toxicity. Treatment was held for up to 21 days for grade 3 or 4

toxicity until resolution to baseline. Erlotinib was then reinstituted at a reduced dose.

Determination of EGFR Expression

To ascertain whether HCC tumor expression of EGFR correlated with erlotinib activity, patients were prospectively stratified into "EGFR high" and "EGFR low" expression cohorts. All eligible patients were required to provide paraffin block(s) or unstained slides for evaluation of EGFR status by immunohistochemistry (IHC). This assay detects the presence of EGFR receptors and does not determine the functional status of the receptor (eg, phosphorylated EGFR), as the latter can be performed on fresh tissue only. EGFR tissue expression was assayed by using the mouse monoclonal antibody 31G7 from Zymed Laboratories (South San Francisco, Calif) at 1:50 dilutions. The detection system uses a dextran polymer conjugated with both secondary goat antimouse antibody molecules and horseradish peroxidase. Positive and negative control cell lines were included with each assay. Control cell lines were fixed in formalin; cell pellets that represented a moderate level of EGFR expression were used for the positive-control cell line (HT-29), and a cell line that did not express detectable EGFR (CAMA-1) was used for the negative-control cell line. After staining, each specimen was reviewed for the presence of tumor cells, the level of membranous staining, staining intensity, and the percentage of tumor cells that stained positively. In addition, other elements were evaluated including staining of the normal tissue elements, background, and level of cytoplasmic staining. Tumor specimens were scored by 1 pathologist as "low EGFR" (either no staining or weak membranous staining of tumor cells) or "high EGFR expression" (moderate or strong membranous staining of tumor cells).

Disease Assessment

Response to erlotinib therapy was assessed by using RECIST criteria.[32] Computed tomography (CT) or magnetic resonance imaging (MRI) was the study of choice. Measurable disease was defined as that which could be measured in at least 1 dimension (longest diameter to be recorded, LD) as $\geq$20 mm with conventional radiographic techniques or $\geq$10 mm with spiral CT scanning. All other lesions $\leq$10 mm were considered nonmeasurable disease and were recorded as being present or absent. All measurable lesions up to maximum of 10 lesions were identified as target lesions and recorded at baseline. A sum of the LD for all target lesions was calculated and reported. All target lesions identified at baseline were followed on re-evaluation and scored. Total disappearance of all target lesions was a complete response (CR); a partial response (PR) was at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD; progressive disease (PD) was indicated by at least a 20% increase in the sum of the LD of target lesions. Stable disease (SD) was defined to have neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Statistical Considerations

The primary endpoint of this phase 2 trial was the binary variable progression-free survival (PFS) at 16 weeks of treatment with erlotinib. Success was considered stable disease or objective response by 16 weeks of continuous treatment. The basis for this endpoint was 2-fold. 1) The likelihood of actual objective tumor responses with erlotinib in HCC patients was expected to be very low. 2) The median time to progression of patients treated with several cytotoxic agents in similar phase 2 trials in advanced HCC patients has been reported in the range of 16 weeks.[33–39] The design of Simon and Thall[40,41] was used. Patients were stratified prospectively by "EGFR low" and "EGFR high" expression. An early stopping criterion was applied separately to the 2 EGFR strata, to terminate the trial if at any time, $\text{Prob}[\pi_{\text{OSI-774}} > \pi_s - 0.10] < 0.10$. The boundaries applied separately to the 2 strata defined by EGFR status at baseline were for each stratum of PFS at 16 weeks, STOP for lack of efficacy if the number of patients alive and progression-free at 16 weeks was less than or equal to 0 of 5, 1 of 10, 2 of 14, 3 of 18, 4 of 22, 5 of 26, 6 of 31, 7 of 34, or 8 of 38. Data for each patient stratum was analyzed on a nearly continuous basis to determine whether stopping criteria had been met and whether the stratum should continue accruing patients.

Patient characteristics are summarized by using median (range) for continuous variables and frequency (percentage) for categorical variables. The overall survival (OS) probability and progression-free survival (PFS) probability are estimated by the Kaplan-Meier method.[42] Log-rank test[43] was used to test the difference in OS or PFS between subgroups of patients. Patients' disease control rate, PFS rates at 16 weeks or 24 weeks were estimated, along with the exact 95% confidence intervals (CI). Univariate and multivariable Cox proportional hazards models were fit for OS and PFS to assess the effect of patient characteristics simultaneously. All statistical analysis were carried out in Splus.[44]

TABLE 1
Best Tumor Response

Outcome	Estimate	95% CI
16-wk progression-free survival, %	43%	30–61
24-wk progression-free survival, %	28%	17–46
Disease control (partial response + stable disease)	43%	23–54
Overall survival (recorded from date of diagnosis)		
Median, wk	43 wk (10.75 mo)	27–106
Overall survival (recorded from date of therapy start)		
Median, wk	25 wk (6.25 mo)	18–42
Time to disease progression		
Median, wk	26 wk (6.5 mo)	23–52

TABLE 2
Patient Characteristics (N = 40)

Variable	Median (range)	N (%)
Age	64 (33–83)	
T. Bili	0.7 (0.2–1.6)	
Alb	3.9 (2.8–4.6)	
Alk Phos	149 (59–1003)	
Tumor size, cm	6.5 (1.5–27)	
Sex		
Women		8 (20)
Men		32 (80)
Race		
White		28 (70)
Black		4 (10)
Hispanic		1 (2.5)
Missing		3 (7.5)
Asian		4 (10)
PS		
0		16 (40)
1		22 (55)
2		2 (5)
EGFR		
Low		11 (27.5)
High		27 (67.5)
Missing		2 (5)
PVI		
No		19 (47.5)
Yes		20 (50)
Missing		1 (2.5)
Childs-Pugh Score		
A		32 (80)
B		8 (20)
CLIP Score		
0		6 (15)
1		8 (20)
2		11 (27.5)
3		7 (17.5)
4		6 (15)
5		2 (5)
No. of Tumors		
1		3 (7.5)
2		2 (5)
3		3 (7.5)
4		1 (2.5)
≥5		25 (62.5)
Missing		6 (15)

T. Bili indicates total bilirubin; Alb, serum albumin; Alk Phos, alkaline phosphatase; PS, performance score; EGFR, epidermal growth factor receptor; PVI, portal vein invasion; CLIP, Cancer of the Liver Italian Program.

The initial study design included a maximum of 40 patients per EGFR stratum (ie, potentially 80 patients in total). When a total of 40 patients were enrolled in the study, a "futility analysis" was performed. The analysis indicated that results of the trial would not change if accrual continued to a total of up to 80 patients. Because the study endpoint (ie, would treatment with erlotinib result in a PFS at 16 weeks of ≥35%? [progression-free survival (PFS) at 16 weeks was 43% as noted in Table 1]) had been met, accrual was terminated at 40 patients.

RESULTS

Patient Characteristics

A total of 40 patients were treated at the University of Texas M. D. Anderson Cancer Center, Houston, Texas, with erlotinib between October 2002 and August 2005. Patients' characteristics are summarized in Table 2. A calculation of the Cancer of the Liver Italian Program (CLIP) score for each patient was made and added to our data retrospectively. The CLIP (1–5 scale) score is a prognostic system developed for and validated in patients with HCC and incorporates the Childs-Pugh score, tumor morphology, serum α-fetoprotein, and vascular invasion. Higher CLIP scores correlate with worse prognoses.[45–48]

Erlotinib Administration

A total of 137 courses (defined as 28 days) of erlotinib were administered (median, 2 courses; range, 1–16).

Toxicity

The most common drug-related adverse events (all grades, Table 3) were diarrhea, folliculitis, fatigue, pruritus, dry skin, xerostomia, and epistaxis. Grade 3 toxicities included diarrhea (7.5%), fatigue, (7.5%), and serum glutamic oxaloacetic transaminase (SGOT) elevation (7.5%). There were no grade 4 adverse events. Erlotinib administration was held in 1 patient for 14 days for superficial skin infection due to drug-related folliculitis.

Efficacy

A total of 17 patients achieved stable disease at 16 weeks. The estimated rate of progression-free

TABLE 3
Major Toxicities (N = 40)

	Grade 1		Grade 2		Grade 3		Grade 4	
Toxicity	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Diarrhea	19	47.5	8	20.0	3	7.5	—	—
Rash/ Desquamation	17	42.5	12	30.0	—	—	—	—
Fatigue	7	17.5	9	22.5	3	7.5	—	—
Nausea alone	13	32.5	2	5.0	1	2.5	—	—
Pruritus	12	30.0	3	7.5	—	—	—	—
Dry skin	10	25.0	4	10.0	—	—	—	—
SGOT elevation	3	7.5	6	15.0	3	7.5	—	—
Xerostomia	9	22.5	2	5.0	—	—	—	—
Anorexia	6	15.0	4	10.0	1	2.5	—	—
Bilirubin elevation	6	15.0	3	7.5	—	—	—	—
Vomiting	6	15.0	2	5.0	1	2.5	—	—
Epistaxis	7	17.5	—	—	—	—	—	—
Taste alteration/ Dysgeusia	5	12.5	2	5.0	—	—	—	—
SGPT elevation	5	12.5	1	2.5	1	2.5	—	—
Stomatitis	5	12.5	1	2.5	—	—	—	—
Weight loss	3	7.5	3	7.5	—	—	—	—
Headache	5	12.5	—	—	—	—	—	—
Heartburn/Dyspepsia	4	10.0	—	—	—	—	—	—
Nail changes	4	10.0	—	—	—	—	—	—
Alkaline phosphate elevation	—	—	1	2.5	1	2.5	—	—
Dehydration	—	—	1	2.5	1	2.5	—	—

SGOT indicates serum glutamic oxaloacetic transaminase; SGPT, serum glutamate pyruvate transaminase.

survival (PFS) is 17 of 40 (42.5%), with the exact 95% confidence interval of 22.7% to 54.2%. Among the total of 40 patients, 38 (95%) patients failed, defined as either disease progression or death. The median time to failure was 13.3 weeks, with a 95% confidence interval of 8.1 to 23.9 weeks. The disease control rate, defined as the proportion of patients who had stable disease at the time of any on-study disease assessment, was 43%.

The median time to death was 43.1 weeks (10.75 months; 95% CI, 27–106 weeks) if recorded from date of HCC diagnosis and was 25.0 weeks (95% CI, 17.9–42.3 weeks) if recorded from date of erlotinib therapy initiation. Figure 1 (top) shows the Kaplan-Meier curves for overall survival probability, when overall survivals were measured from these 2 different starting points. There was a significant difference in overall survival between patients with CLIP score <4 and those with CLIP score ≥ 4 (Table 4; $P = .01$). Univariate and multivariate Cox proportional hazards models were fit by using the patient characteristic variables listed in Table 2. The final fitted model for overall survival is presented in Table 4. The model suggests that the risk of death increases in patients with younger age, higher alkaline phosphatase, and with CLIP score ≥ 4. The final fitted model for PFS is presented in Table 5. The model suggests that the risk of failure had a significant increase in patients with PS > 0, compared with those with PS $= 0$ ($P = .01$).

Figure 1 (top) shows the Kaplan-Meier curve for overall survival probability, as measured from both the date of HCC diagnosis and the start date of erlotinib therapy. Figure 1 (bottom) shows the Kaplan-Meier curve for PFS probability, where PFS was defined as time from the start of therapy to disease progression, death, or last follow-up, dependent upon which occurred first. If a patient came off study without either event, PFS was censored at the date of the last disease evaluation.

EGFR Expression

Sufficient tissue for EGFR immunohistochemistry was available from 38 of the 40 enrolled patients. Twenty-7 (71%) patient tumor specimens were scored as high EGFR expression and 11 as low EGFR expression. Kaplan-Meier curves by EGFR status (data not shown) suggest that there was no significant difference in terms of overall survival between the high-EGFR and low-EGFR groups ($P = .66$).

DISCUSSION

In the absence of a randomized trial, deriving conclusions on relative benefits of any systemic therapy is always challenging. The value of results of this single-arm study of erlotinib in HCC can only be evaluated in the context of clinical trial results in similar patient populations. Such comparisons to historical controls are always flawed and are particularly difficult in HCC because of the significant heterogeneity inherent in this patient population. Furthermore, many published studies do not report specifically how endpoints such as survival and PFS were calculated, thus the value of direct comparisons among studies is very limited. However, the intent of traditional phase 2 single-arm trials is to identify a reasonable "biological signal" of potential patient benefit and, thus, provide a sound rationale for further drug development. In HCC patients, the majority of whom have underlying hepatic dysfunction that can significantly alter drug metabolism and, therefore, toxicity, a better understanding of the adverse-event profile of the drug being studied is an additional benefit of phase 2 trials.

A similar, previously published study of erlotinib in HCC[49] reported a median survival of 13 months and a disease control rate of 59%, both figures somewhat

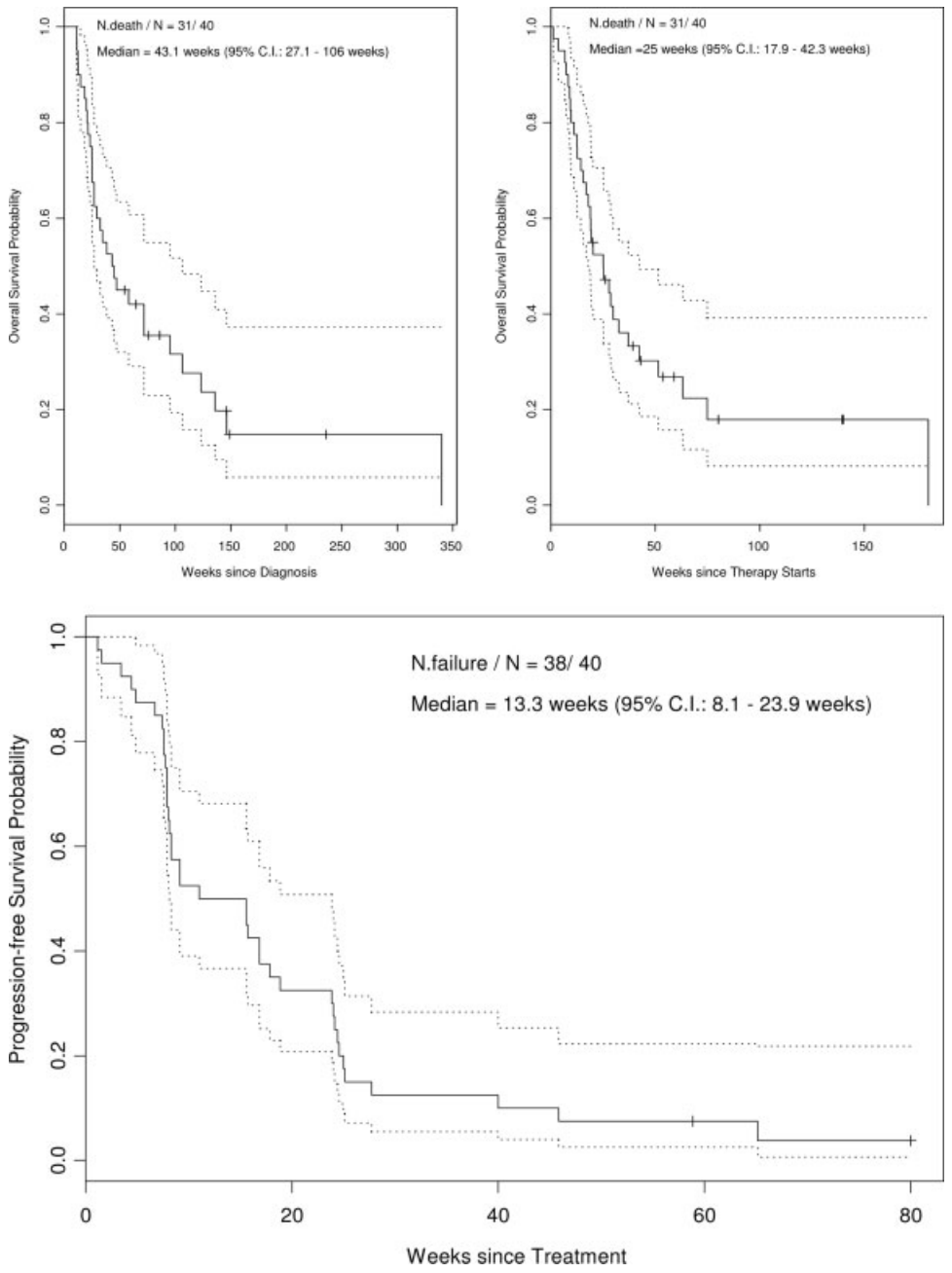

FIGURE 1. (*Top*) Kaplan-Meier estimates for overall survival, with either date of diagnosis or date of erlotinib therapy initiation as the starting point. (*Bottom*) Kaplan-Meier estimates for failure-free survival.

more favorable than those reported here. Again, one would not expect concordance between results from 2 nonrandomized, small sample-size studies. The patient characteristics in the 2 studies were similar in that the majority of patients had ECOG performance status 0 or 1 and had Childs-Pugh A cirrhosis. However, when analyzed by prognostic criteria specific to HCC, the patients treated in the study reported here generally were a moderate to poor prognostic group; 37% (15 of 40) patients were CLIP score 3 or higher, which is predictive of very poor prognosis.[45] This difference may account for the somewhat poorer median survival seen in this trial, although the Philip trial[49] did not report patient CLIP score data to provide a basis for comparison. Although in the current study, a majority (71%) of patients' tumor specimens were identified by immunohistochemistry as showing high EGFR overexpression, which is

generally consistent with that reported in recent literature for HCC,[50–53] EGFR expression did not correlate with overall survival.

The side-effect profile, including skin changes, fatigue, diarrhea, epistaxis, and anorexia, is very typical for erlotinib, did not result in any dose-reductions, and was generally well tolerated by HCC patients. Erlotinib did not cause myelosuppression or significant hepatic or renal toxicity, which are both common in patients with hepatic insufficiency.

In this study, although no radiographic tumor responses were seen on treatment, the primary endpoint of the trial, which was to achieve a median PFS at 16 weeks of erlotinib therapy of >35%, was reached (Table 1). The median survival of the evaluable patients was 10.7 months, which is longer than the median survival of 6 months reported in several recently published trials in advanced HCC patients (Table 6). Table 6 includes a broad variety of phase 2 and 3 trials of both cytotoxic and biologic agents in HCC to provide some reasonable context to evaluate the results of this trial. It is well documented that patients with advanced HCC who are not eligible for surgical or locoregional therapies have median survival in the range of 4 months to 8 months. Much of the available HCC literature addresses patients who have undergone or are eligible for resection, ablation, or regional therapies; the outcome for such early stage patients cannot be compared with that for patients with advanced disease. In this context, the median survival of 10.7 months reported here suggests that single-agent erlotinib provides some modest improvement in patient survival in a representative, advanced HCC patient population when compared with a variety of both cytotoxic and biologic agents in other HCC trials. We recognize, however, that the median survival of 10.75 months in

TABLE 4
Fitted Multivariate Cox Proportional Hazards Model for Overall Survival

Variable	Coefficient	SE	Relative risk	*P*
log (Alk. Phos)	1.161	0.321	3.193	<.001
Age	−0.042	0.022	0.959	.06
CLIP score of 4 or 5 vs 0, 1, 2, or 3	1.122	0.456	3.072	.01

SE indicates standard error of the mean; Alk. Phos, alkaline phosphatase; CLIP, Cancer of the Liver Italian Program.

TABLE 5
Fitted Multivariate Cox Proportional Hazards Model for Failure-free Survival

Variable	Coefficient	SE	Relative risk	*P*
PS = 1 or 2 vs 0	0.470	0.182	1.600	.01

SE indicates standard error of the mean; PS, performance score.

TABLE 6
Selected Clinical Trials of Systemic Therapy in Advanced HCC Patients

Study	Regimen	Study type	No.	% RR	% SD	PFS median mo	MS, mo
Current study	Erlotinib	Phase 2, 1 arm	40	0	37.5	6.5 (TTP)	10.75
Abou-Alfa et al.[54]	Sorafenib	Phase 2, 1 arm	137	2.2	33.6	4.2 (TTP)	9.2
Zhu et al.[36]	GEMOX-bevacizumab	Phase 2, 1 arm	33	20	27	5.3	9.6
Porta et al.[55]	Nolatrexed vs doxorubicin	Phase 3, 2 arms	446	1.4 vs 4.0	NA	8.4 wks (TTF)	5 vs 7.75
Boige et al.[12]	Irinotecan	Phase 2, 1 arm	29	0	41	3.1 (TTP)	7.4
Yeo et al.[56]	PIAF vs Adriamycin	Phase 3, 2 arms	86/91	20.9 vs 10.5	38 vs. 43	NA	8.67 vs 6.83 (P = .83)
Posey et al.[57]	T138067 vs Adriamycin	Phase 2/3, 2 arms	169/170	NA	NA	NA	5.7 vs 5.6
Ikeda et al.[37]	5FU, mitoxantrone, cisplatin	Phase 2, 1 arm	51	27	53	4.0	11.6
Barbare et al.[58]	Tamoxifen vs BSC	Phase 2, 2 arms	210/210	NA	NA	NA	4.8 vs 4.0
Philip et al.[49]	Erlotinib	Phase 2, 1 arm	38	9	5.6 mo		13
Patt et al.[59]	Thalidomide	Phase 2, 1 arm	37	6	31	NA	6.8
Lee et al.[60]	Doxorubicin and cisplatin	Phase 2, 1 arm	37	18.9	16.2		7.3
Guan et al.[61]	Gemcitabine, std. vs fixed-dose	Phase 2, 2 arms	25/23	4 vs 0	NA	1.5 (TTP)	3.2 vs 3.2
Yang et al.[38]	Gemcitabine and doxorubicin	Phase 1–2, 1 arm	34	11.8	26.5	4.6	
Llovet[33]	Eniluracil/5-fluorouracil	Phase 2, 1 arm	45	0	40	13.7 wks	12
Fuchs et al.[62]	Gemcitabine	Phase 2, 1 arm	30	0	30	NA	6.9
Mok et al.[63]	Nolatrexed vs doxorubicin	Phase 2, 2 arms	37/17	0	20.8 vs 16.7	NA	4.9 vs 3.7
Meyskens et al.[64]	B-all-trans-retinoic acid	Phase 2, 1 arm	29	0	NA		4.0

RR indicates response rate; SD, stable disease; PFS, progression-free survival; MS, median survival; GEMOX indicates gemcitabine, oxaliplatin; PIAF, cisplatin, interferon, Adriamycin, 5FU; BSC, best supportive care; NA, not available; TTP, time to progression; TTF, time to treatment failure.

this trial may represent nothing more than favorable patient selection.

We believe erlotinib warrants further study as combination therapy with other biologic agents in hepatocellular carcinoma patients. Given the many limitations inherent in conducting and interpreting results of single-arm trials, particularly in an heterogeneous malignancy such as HCC, a better approach for future studies may be to consider randomized phase 2 designs to provide a more reasonable basis for comparison than historical controls.

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