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Upfront, Randomized, Phase 2 Trial of Sorafenib Versus Sorafenib and Low-Dose Interferon Alfa in Patients With Advanced Renal Cell Carcinoma:

Clinical and Biomarker Analysis

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Abstract

BACKGROUND—The objective of this study was to independently evaluate the objective response rate of sorafenib and sorafenib plus low-dose interferon-alfa 2b (IFN) as frontline therapy in patients with metastatic renal cell carcinoma (mRCC).

METHODS—Untreated patients with clear cell mRCC were randomized to receive sorafenib 400 mg orally twice daily or sorafenib 400 mg orally twice daily plus subcutaneous IFN 0.5 million U (MU) twice daily. Primary endpoints included the objective response rate (ORR) and safety. Secondary endpoints included progression-free survival (PFS) and overall survival (OS). Exploratory endpoints included the predictive value of tumor tissue biomarkers.

RESULTS—Eighty patients were enrolled. The median follow-up was 19.7 months (range, 0–34.2 months). The ORR was 30% (95% confidence interval [CI], 16.6%–46.5%) in the sorafenib arm and 25% (95% CI, 12.7%–41.2%) in the combination arm. The median PFS was 7.39 months in the sorafenib-alone arm (95% CI, 5.52–9.20 months) and 7.56 months in the sorafenib plus IFN arm (95% CI, 5.19–11.07 months). The median OS was 27.04 months in the combination arm (95% CI, from 22.31 to not attained) and was not reached in the sorafenib arm. Toxicities were comparable in both arms. In a multivariate model, increased phosphorylated protein kinase B (pAKT) levels were associated with poorer PFS (hazard ratio, 1.04; 95% CI, 1.00–1.08; $P = .0411$) and OS (hazard ratio, 1.15; 95% CI, 1.02–1.29; $P = .0173$).

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CONFLICT OF INTEREST DISCLOSURES

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CONCLUSIONS—The addition of low-dose IFN to sorafenib resulted in efficacy outcomes that were comparable to those achieved with sorafenib monotherapy. The current results indicated that pAKT levels may predict for clinical outcome, but further mechanistic study is required.

Keywords

hypoxia-inducible factor alpha; phosphorylated protein kinase B; receptor tyrosine kinases; vascular endothelial growth factor receptor; renal cell carcinoma; sorafenib; interferon; resistance; biomarkers

Renal cell carcinoma (RCC) affects >40 000 patients per year in the United States and is responsible for approximately 13,000 deaths.[1] Once it becomes metastatic, RCC is difficult to treat, and the median survival is between 1 year and 2 years.[2,3] Several treatment modalities have been used to treat metastatic RCC, including immunotherapy,[4,5] chemotherapy,[6,7] and targeted therapies.[3,8,9] Several targeted agents have received approval from the US Food and Drug Administration (FDA) for use in patients with advanced RCC, including sorafenib, sunitinib, and temsirolimus. Although each of these drugs is active as a single agent, few patients achieve a complete response (CR), virtually all patients experience disease progression, and long-term survival is rare. These observations have led to the hypothesis that combining agents with different mechanisms of action may lead to improved clinical outcomes.

We explored this concept by combining sorafenib with low-dose IFN in a randomized phase 2 trial. Sorafenib is an orally bioavailable small molecule inhibitor of wild-type and mutant (the V599E point mutation, which is a substitution of the amino acid valine for glutamic acid at codon 599 in the v-raf murine sarcoma viral oncogene homolog B1 [BRAF]) B-Raf and c-Raf kinase isoforms and of receptor tyrosine kinases (RTKs), including vascular endothelial growth factor receptor 2 (VEGFR-2), VEGFR-3, platelet-derived growth factor receptor β, fms-related tyrosine kinase 3, and the cytokine receptor c-KIT. IFN is an immunomodulatory cytokine that is produced by leukocytes and other immunomodulatory cells, and it possesses direct cellular antiproliferative effects and stimulates major histocompatibility complex Class I expression.[10]

The rationale for combining an antiangiogenic agent with IFN is based on 2 principal observations: 1) Lower doses of IFN have an antiangiogenic effect, which inhibits growth levels of VEGF and basic fibroblast growth factor[10,11]; and 2) this effect also may antagonize the recognized up-regulation of VEGF by receptor tyrosine kinases.[12] It is noteworthy that IFN blocks VEGF through decreased transcription,[12] a mechanism that is different from targeted therapies (blockade of receptor activation); thus, cross-resistance would not be predicted by combining the 2. We chose a dose of 0.5 MU IFN twice daily because of its potential antiangiogenic activity and because our recently reported randomized study revealed no difference in efficacy outcomes between this dose and 5 MU IFN daily in patients with previously untreated, metastatic RCC despite producing fewer side effects and higher quality-of-life measures.[13]

There is a growing interest in using molecular biomarkers in earlier phase trials to help choose the most promising investigational agents worthy of further study. We chose to focus

on tissue-based markers of phoshatidylinositol-3 kinase (PI3K) pathway activation. The PI3K pathway is involved directly or indirectly in maintenance of cellular viability,[14,15] protein synthesis,[16] and cell cycle regulation.[17] Emerging data suggest that the up-regulation of PI3K pathway components is associated with a poor outcome in patients with RCC.[18,19] Downstream protein kinase B (AKT) effector molecules are associated with hypoxia-inducible factor (HIF) regulation,[20] providing a direct mechanistic link to angiogenesis. Differential expression of HIF-1 α (HIF1α) and HIF2α) appears to generate distinct phenotypes, and the up-regulation of c-Myc has been observed in HIF2α-predominant tumors.[21] In addition, HIF1α expression depends on raptor, a component of mammalian target of rapamycin (mTOR) complex 1 (mTORC1) complex, and rictor, a component of mTORC2; whereas HIF2α depends only on mTORC2, which feeds back and phosphorylates serine 473 (S473) on AKT.[22] Taken together, we hypothesize that S473 activation of AKT is a biomarker of a resistance phenotype either through c–Myc-dependent pathway activation or through the up-regulation of alternate HIF2α-dependent angiogenic pathways.

To detect efficacy signals reliably, randomized trials are required. Randomized phase 2 studies, although they are not powered to detect survival differences, can aid in objectively selecting regimens with a potential differential impact on patient outcome. Herein, we present data from the first randomized phase 2 study comparing sorafenib versus sorafenib plus low-dose interferon (IFN), and we report on predictive tissue biomarkers.

MATERIALS AND METHODS

Patient Selection

Before they were enrolled on the study, patients were required to sign an informed consent that was approved by The University of Texas M. D. Anderson Cancer Center (MDACC) Institutional Review Board. Patients were accrued at a single center (MDACC). Inclusion criteria included pathologically confirmed metastatic clear cell (conventional) RCC, no prior systemic therapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, no brain metastases, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), a serum creatinine level ≤2.0 mg/dL, normal serum calcium levels, and a serum bilirubin ≤1.5 times the upper limit of normal. Baseline body computed tomography scans were obtained along with a magnetic resonance imaging study of the brain. Bone scans were obtained if a bone lesion was suspected.

Study Design

Patients were randomized to receive sorafenib (Bayer Inc., Pittsburgh, Pa) 400 mg orally twice daily or the combination of sorafenib 400 mg orally twice daily plus IFN (Schering-Plough, Kenilworth, NJ) at a dose of 0.5 MU subcutaneously twice daily. Dose reductions were permitted for 1 or both agents, depending on the nature of the toxicity. Imaging studies were obtained every 8 weeks. Patients continued to receive protocol treatment until either progressive disease was documented or toxicity precluded further participation on study. Response was measured using RECIST, and confirmatory studies were obtained at least 4 weeks after the measurement of a treatment response.

There are several nonoverlapping toxicities defined for each agent. A treatment cycle was not interrupted unless overlapping toxicities were observed, and only the drug(s) responsible for observed toxicities were adjusted or held. Doses were not re-escalated. Patients could continue on study if 1 agent was discontinued for toxicity. Sorafenib was reduced to Dose Level −1 (200 mg orally twice daily) or Dose Level −2 (200 mg orally daily), and IFN was reduced to Dose Level −1 (0.5 MU daily). Further dose reductions resulted in drug discontinuation.

Correlative Studies

Paraffin-embedded nephrectomy specimens were obtained from 40 patients for the purposes of evaluating expression and activation levels of phosphoinositide 3 kinase (PI3K) pathway components, including AKT, P70S6 kinase (P70S6K), and S6 ribosomal protein (S6RP). Protein tissue microarrays were generated using a Beecher arrayer (Beecher Instruments, Inc., Sun Prairie, Wis) and were stained using total AKT (Cell Signaling Technology, Inc., Danvers, Mass), phosphorylated AKT S473 (pAKT) (Cell Signaling Technology, Inc.), P70S6K (Cell Signaling Technology, Inc.) phosphorylated S6RP serine 235–236 (pS6) (Cell Signaling Technology, Inc.), and total S6RP (Cell Signaling Technology, Inc.) antibodies. Image capture and analysis were performed using the Ariol system (Applied Imaging, San Jose, Calif.). Each core was evaluated individually at ×10 and ×20 magnification, regions of viable tumor were gated, and areas of nonviable tumor and nontumor tissue were excluded, and the core was scanned at ×20 magnification using TMA Navigator software (Applied Imaging, San Jose, Calif). The percentage involvement of biomarkers was obtained for each core.

Statistical Methods

A maximum of 80 patients were to be randomized equally between treatment arms. The null hypothesis was that the response in either arm would be <5%, and the alternate hypothesis was that the response rate would exceed 20%. A 2-stage design was implemented for each treatment arm in parallel. For either arm, if at least 4 responses (≥10%) were observed among the 40 evaluable patients, then the regimen would continue. If no more than 1 response (≤5%) was observed among the initial 20 patients, then the arm would be terminated early. This design yielded at least 92% power to detect a true response rate of ≥20% and a ≥0.90 probability of a negative result if the true response rate was no greater than 5% with a probability of ≥0.74 that treatment would be stopped early. The Pocock-Simon minimization method[23] was used to randomize patients according to the following stratification factors: performance status (1 vs 0), anemia (no vs yes, with yes based on a hemoglobin level <14 g/dL for men or <12 g/dL for women), nephrectomy (no vs yes); lactate dehydrogenase (LDH) (not elevated vs elevated, with elevated defined as >1.5 times the upper limit of normal). The randomization program based on this method was developed in the Department of Biostatistics and Applied Mathematics, and the program was available on an intra-net website of MDACC. Only a pharmacist with an appropriate username and password had access to the program.

All reported analyses were in the intent-to-treat population. *P* values were 2-tailed and were considered significant at α <.05. Analyses were conducted using SAS for Windows (release

9.1; SAS Institute, Cary, NC). Response rates with 95% exact binomial confidence intervals (CIs) were calculated. Patients who had a CR or partial response (PR) were classified as responders. Nonresponders included patients whose best evaluation was stable disease or progressive disease. Patients who were not on study long enough to be evaluated for response were included in the analysis as treatment failures. The Fisher exact test was used to assess response by treatment arm.

The survival endpoints that we investigated included overall survival (OS), progression-free survival (PFS), and duration of response. OS was defined as the time from first treatment (or randomization for the 1 patient who did not receive treatment) to the date of either death or last follow-up for patients who remained alive at the end of follow-up. PFS was defined as the time from first treatment to the date of progression, death, new treatment start, or last follow-up, whichever occurred first. Duration of response was calculated as the time from the first assessment of response until the earliest event of disease progression, new treatment start, or last follow-up.

Survival endpoints were evaluated using the Kaplan-Meier product-limit method and Cox proportional-hazards regression techniques. The proportional hazards assumptions were verified using the methods of Lin et al,[24] and the assumptions held for each of the models presented. For all modeling procedures, univariate models were fit first to evaluate the predictive effect of each factor alone; then, a reduced multivariate model was determined using a step-wise backward selection procedure. The independent variables investigated included treatment arm and the variables that were used in randomization (baseline ECOG performance status and baseline anemia). Two other variables that were included in randomization, nephrectomy and LDH, had no or very little variability and, thus, were not included in the multivariate analysis.

The average percentage of AKT, pAKT, S6RP, pS6RP, and p70S6k involvement was analyzed in specimens from 40 study participants. Intensity was not factored into the analysis. For each set of markers, the correlations between the markers and the treatment arm and between individual markers were analyzed using Wilcoxon rank-sum tests and Spearman correlation coefficients, respectively. Univariate survival analysis considered all 40 samples in aggregate, regardless of treatment arm; and, in the multivariate analyses, treatment arm was added as a covariate. The study sponsor (the National Cancer Institute's Cancer Therapy Evaluation Program) was involved in the study design, in the interpretation of data, and in the writing of this report.

RESULTS

Patient Characteristics

From June 24, 2005 through June 18, 2007, 80 patients (61 men and 19 women) were enrolled (40 patients per arm). Patient demographics are presented in Table 1. According to Memorial Sloan-Kettering Cancer Center (MSKCC) criteria, 51%, 46%, and 3% of patients had favorable-risk features, intermediate-risk features, or poor-risk features, respectively. After randomization, 1 patient in the sorafenib plus IFN arm withdrew consent before receiving study medication. Seven patients received study medication but came off study

before the first 8-week response assessment. Of these, 5 patients came off study because of toxicity, and the other 2 patients came off study because of eligibility violations (1 patient who had brain metastases and 1 who received previous radiation treatment). Treatment groups did not differ significantly by age at diagnosis, age at registration, sex, race/ethnicity, MSKCC risk assessment, or evaluability. The 2 arms were balanced for nephrectomy, LDH, performance status, and anemia.

Clinical Outcomes

The median follow-up for censored patients was 19.7 months (range, 0.4–34.2 months). At the time of study analysis, 4 patients remained on study. Reasons that the 76 patients were taken off study included disease progression (n = 53), toxicity (n = 12), ineligibility (n = 3), physician decision (n = 4), consent withdrawal (n = 4), and noncompliance (n = 1). Objective clinical response was assessed for 72 patients who received study drug. Seven patients who received at least 1 treatment and 1 patient who did not receive a treatment were not evaluated for response. These patients were included in the analysis as treatment failures. Patients received a median of 6 cycles (range, 0–24 cycles) of the study medication.

In the intent-to-treat population, the response rate was 30% (95% CI, 16.6%–46.5%) in the sorafenib arm and 25% (95% CI, 12.7%–41.2%) in the combination arm (Table 2). There was no significant difference in response by treatment arm in the evaluable population (n = 72), in the total treated population (n = 79), or in the intent-to-treat population (n = 80). A major response (CR or PR) was observed in 22 patients, whereas 37 patients had disease stabilization with a median stabilization duration of 5.7 months (95% CI, 3.7–8.4 months). Response duration for the 1 patient who had a CR was 19.9 months; and, for the patients who had a PR, the estimated median response duration was 7.3 months (95% CI, 5.6–13.1 months). Response assessment was performed by the investigators. A blinded, independent radiology audit of 20 patients' scans was performed by an MDACC radiologist. There was concordance between the investigator's and radiologist's assessment in 19 of the 20 patients.

The estimated median PFS was 7.39 months (95% CI, 5.52–9.20 months) for the sorafenib arm and 7.56 months (95% CI, 5.19–11.07 months) for the sorafenib plus IFN arm (Table 2). In univariate analysis, there was no statistically significant difference in PFS by treatment arm or ECOG performance status; however, patients with baseline anemia trended toward a shorter PFS (hazard ratio [HR], 1.66; 95% CI, 0.98–2.79; $P = .0583$) (Table 3). A multivariate model that included treatment arm, ECOG performance status, and baseline anemia status had no significant predictors of PFS.

The median OS was not reached in the sorafenib arm and was 27.04 months (95% CI, from 22.31 months to not attained) in the combination arm. In univariate analysis, no significant difference in OS by treatment arm was detected ($P = .1219$), but OS was associated significantly with performance status and anemia at baseline (Table 3). Patients who had an ECOG performance status score of 1 had a 3.06 times greater hazard of death (95% CI, 1.33–7.00 times greater hazard of death) compared with patients who had a performance status of 0 ($P = .0083$), and patients who had anemia at baseline had a 3.27 times greater hazard of death (95% CI, 1.39–7.68 times greater hazard of death) compared with patients who did not have anemia at baseline ($P = .0065$).

In a multivariate model that included variables for treatment arm, ECOG performance status, and baseline anemia, there was a nonsignificant trend toward inferior OS among patients in the sorafenib plus IFN arm (HR, 2.17; 95% CI, 0.92–5.12; *P* = .0764). Patients who had a performance status of 1 had a poorer prognosis compared with patients who had a performance status of 0 (HR, 2.54; 95% CI, 1.04–6.20; *P* = .0414). The association between OS and baseline anemia reached borderline significance (*P* = .0501), and anemic patients had a poorer prognosis (HR, 2.48; 95% CI, 1.00–6.13) (Table 3).

Toxicity

A relatively equal number of patients required dose reductions or therapy discontinuation in each arm. Sorafenib dose reductions were equivalent in each arm. Table 4 lists the most common grade 3 and 4 toxicities. Fatigue and neutropenia were more common in the combination arm. It is noteworthy that hyperuricemia was substantially more common in the sorafenib monotherapy arm. A few rare but serious events occurred in each treatment arm. One patient on the combination arm developed posterior reversible encephalopathy syndrome in her second month of therapy after developing hypertension.

Biomarker Analysis

An analysis of tumor tissue biomarkers was conducted on tumor tissue from 22 patients in the sorafenib arm and 18 patients in the sorafenib plus IFN arm. There was no significant difference in marker levels by treatment arm; therefore, all 40 samples were analyzed together. All markers were associated significantly with each other (Table 5). In univariate analysis, no markers were associated significantly with PFS. However, in a multivariate model that included treatment arm and randomization variables (ECOG performance status and baseline anemia status), pAKT was associated significantly with PFS. With every percentage increase in pAKT, there was a 3.7% increase in the hazard of disease progression (HR, 1.04; 95% CI, 1.00–1.08; *P* = .0411). In addition, the univariate analysis indicated that OS had a significant association with pAKT (HR, 1.05; 95% CI, 1.01–1.10; *P* = .0243) but not with any of the other markers. However, in the multivariate model that included treatment arm and randomization variables, both AKT (HR, 0.92; 95% CI, 0.85–0.99; *P* = .0384) and pAKT (HR, 1.15; 95% CI, 1.02–1.29; *P* = .0173) had statistically significant associations. The survival hazard increased with lower levels of AKT and with higher levels of pAKT.

DISCUSSION

To our knowledge, this trial is the first to randomly compare the combination of sorafenib plus IFN with sorafenib alone in the frontline treatment of metastatic RCC and is the first full report of sorafenib monotherapy in the front-line setting. The use of randomized phase 2 trials has provided important guidance in the development of therapy for RCC. A key example is the randomized comparison between bevacizumab alone and the combination of bevacizumab plus erlotinib, which failed to demonstrate the superiority of the combination arm[25] despite the initial promise of the combination in a single-arm study.[26]

In the current study, we did not detect significant differences in response rate or PFS between the 2 arms, and the 95% CIs were highly overlapping. Although it can be argued that a better powering of the study may have statistically strengthened the observations reported here, it is unlikely that a paradigm-shifting therapeutic strategy is being rejected.

Whether higher doses of IFN would have altered the results in the current study is impossible to determine, but we can use information from 2 single-arm phase 2 studies that evaluated the combination of sorafenib with standard-dose IFN for the purposes of comparison.[27,28] Ryan et al evaluated the combination of sorafenib 400 mg orally twice daily with IFN 10 MU 3 times weekly administered to untreated patients with metastatic RCC. In the study by Gollob et al, treatment consisted of 8-week cycles of sorafenib 400 mg orally twice daily plus IFN 10 MU subcutaneously 3 times weekly followed by a 2-week break administered in the first-line and second-line settings. Overall, the patient characteristics in those reports were similar to those in the current study, and the outcomes of patients arguably were similar to those observed with sorafenib monotherapy (see Table 6).

A striking finding in the current study was a response rate of 30% for the sorafenib arm: This was significantly higher than the response rate of 10% reported in the second-line phase 3 study published in 2007[3] and similar to the rates reported from 2 phase 2 studies of sorafenib and IFN (Table 6). A frontline phase 2 study of sorafenib versus IFN reported a response rate of 5% for the sorafenib arm.[29] Equally striking in our study was the lack of additional benefit provided by the addition of IFN to sorafenib, refuting the hypothesis that the addition of IFN to sorafenib was responsible for the higher response rate. Two conclusions can be drawn from these findings: First, the response rate is highly dependent on patient selection; and, second, randomized studies provide important control groups that contextualize clinical observations and decrease the risk of inappropriate attribution of outcome to therapy when patient selection is the major driver of outcome. In addition, the availability of effective second-line therapy no doubt influenced the OS data in our study.

Emerging data suggest that sorafenib inhibits various effector arms of the cellular immune system.,[30–32] although differences in experimental design result in conflicting data.[33] Nevertheless, it is possible that the antagonistic effect of sorafenib on dendritic cell activity[32] and on T-cell proliferation and activation[30,31] are responsible in part for the lack of additive or synergistic activity between sorafenib and IFN.

Developing predictive markers for response is important for accelerating therapy development in RCC and for improved patient selection. These exploratory analyses are hypothesis generating, potentially prognostic, not directly therapy related, and require prospective validation. In our analysis of PI3K pathway components, all markers were associated significantly with each other (Table 5), suggesting internal cohesiveness of the pathway being analyzed. Multivariate analysis revealed that elevated pAKT was correlated inversely with PFS and OS. It is possible that epithelial drivers of survival, like activated AKT, trigger the activation of alternate angiogenic pathways and that these pathways are responsible for the induced and innate resistance to antiangiogenic therapy that was observed clinically. The association of elevated nonphosphorylated AKT with improved

survival appears to be contradictory to the pAKT data. Investigations performed by our collaborators suggest the AKT antibody binds only the unphosphorylated protein and is not a reflection of total AKT present (unpublished results). Whether pAKT is predictive of outcome after treatment with antiangiogenic therapy or is a prognostic biomarker cannot be elucidated from the current research study, because we did not incorporate a nonantiangiogenic therapy control arm in our study. In addition, we ran the risk of obtaining false-positive associations through analysis of multiple covariates. Even if it is determined that the activated PI3K pathway is predictive of response, this does not guarantee that its blockade will be therapeutic. Nevertheless, careful study of this pathway will be an important next step toward developing new therapies for patients with refractory RCC.

In conclusion, the combination of sorafenib plus IFN is well tolerated and, in the front-line setting, provides efficacy similar to that of sorafenib alone in the front-line treatment of metastatic RCC. Despite the relatively small numbers of patients treated, we conclude that the absence of CRs in the combination arm and a response rate and PFS similar to those in the control arm suggest that there was no additional benefit conferred by the combination therapy. On the basis of our findings, further study of the combination of sorafenib plus IFN is not warranted. The association between elevated tumor pAKT and inferior PFS and OS in patients who are treated with sorafenib is a hypothesis-generating finding that requires further mechanistic study.

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Table 1

Patient Characteristics

	No. of Patients (%)	
Characteristic	**Sorafenib**	**Sorafenib+IFN**
No. of patients	40	40
ECOG status		
0	25 (62.5)	25 (62.5)
1	15 (37.5)	15 (37.5)
Mean age [range], y	62.4 (45–83)	60.7 [43–81]
Sex		
Men	32 (80)	29 (72.5)
Women	8 (20)	11 (27.5)
Nephrectomy, yes	40 (100)	39 (98)
MSKCC prognostic risk		
Low	21 (52.5)	20 (50)
Intermediate	19 (47.5	18 (45)
Poor	0	2 (5)
No. of metastatic sites		
1	13 (33)	14 (35)
2	17 (42)	20 (50)
≥3	10 (25)	6 (15)
Sites of metastatic disease		
Lung	33 (83)	30 (75)
Lymph nodes	20 (50)	15 (38)
Liver	3 (8)	5 (13)
Bone	5 (13)	6 (15)
Other	19 (48)	19 (48)

IFN indicates interferon alfa; ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center.

Table 2

Treatment Outcomes

	No. of Patients (%)	
Variable	**Sorafenib, n=40**	**Sorafenib and IFN, n=40**
Best response		
CR	1 (2.5)	0
PR	11 (27.5)	10 (25)
SD	17 (42.5)	20 (50)
PD	6 (15)	7 (17.5)
Inevaluable	5 (12.5)	3 (7.5)
ORR [95% CI], %	30 [16.56–46.53]	25 [12.69–41.20]
Progression-free survival [95% CI], mo	7.39 [5.52–9.20]	7.56 [5.19–11.07]
Overall survival [95% CI], mo	Not attained	27.04 [22.31 to not attained]

IFN indicates interferon alfa; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; CI, confidence interval.

Table 3

Cox Proportional Hazards Regression Models (N=80)

	Univariate Model			Multivariate Full Model		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
PFS						
Treatment arm						
BAY 43-9006 and IFN	0.848	0.507–1.418	.5289	0.847	0.506–1.416	.5264
BAY 43-9006	1.000			1.000		
ECOG performance status						
1	1.589	0.937–2.694	.0859	1.379	0.784–2.425	.2641
0	1.000			1.000		
Anemia						
Yes	1.657	0.982–2.793	.0583	1.493	0.853–2.613	.1607
No	1.000			1.000		
OS						
Treatment arm						
BAY 43-9006 and IFN	1.945	0.837–4.517	.1219	2.172	0.921–5.122	.0764
BAY 43-9006	1.000			1.000		
ECOG performance status						
1	3.055	1.333–7.000	.0083	2.535	1.037–6.197	.0414
0	1.000			1.000		
Anemia						
Yes	3.272	1.393–7.684	.0065	2.475	1.000–6.129	.0501
No	1.000			1.000		

HR indicates hazard ratio; CI, confidence interval; PFS, progression-free survival; biaryl urea 43-9006, sorafenib; IFN, interferon alfa; ECOG, Eastern Cooperative Oncology Group; OS, overall survival.

Table 4

Selected Grade 3 and 4 Toxicities

	No. of Episodes		
Toxicity	**Sorafenib**	**Sorafenib+IFN**	**Total**
Fatigue*	10	18	28
Diarrhea	13	8	21
Hand-foot syndrome	10	7	17
Hyperuricemia*	12	3	15
Hyperamylasemia or lipasemia	5	4	9
Dyspnea	4	4	8
Hypophosphatemia	3	5	8
Neutropenia*	0	6	6
Hypertension	2	3	5
Nausea and vomiting	1	3	4
Rash/desquamation	2	2	4
Proteinuria	1	2	3
Syncope (fainting)	0	3	3
Weight loss	0	3	3
Transaminitis	0	3	3
Hyponatremia	2	1	3
Non-neutropenic infection	2	0	2
Sensory neuropathy	1	1	2
Cardiac ischemia/infarction	1	0	1
Appendicitis	1	0	1
Pancreatitis	1	0	1
Adrenal insufficiency	0	1	1
Reversible posterior leukonencephalopathy	0	1	0
Small bowel obstruction	1	0	1
Pneumonitis	1	0	1

IFN indicates interferon alfa.

*Indicates statistically a significant difference between arms.

Table 5

Spearman Correlation Coefficient for Tissue Microarray Biomarkers (n=40)

	Biomarker Average % (*P*)			
Biomarker Average % (*P*)	**AKT**	**pAKT**	**S6RP**	**pS6RP**
pAKT	0.68 (<.0001)			
S6RP	0.78 (<.0001)	0.62 (<.0001)		
pS6RP	0.61 (<.0001)	0.38 (0.0171)	0.77 (<.0001)	
p70S6K	0.79 (<.0001)	0.71 (<.0001)	0.83 (<.0001)	0.65 (<.0001)

AKT, protein kinase B; pAKT, phosphorylated protein kinase B; S6RP, S6 ribosomal protein; pS6RP, phosphorylated S6 ribosomal protein.

Table 6

Comparison of the Current Study With Single-Arm Combination Sorafenib-Interferon Alfa Studies and With Single-Agent Sorafenib

	Study				
Variable	**Gollob 2007[27]**	**Ryan 2007[28]**	**Escudier 2009[29]**	**Current Combination**	**Current Sorafenib**
No. of patients	40	67	97	40	40
Prior therapy, %	37	0	0	0	0
Risk stratification, %					
Low	40	28	54	51	52.5
Intermediate	50	67	45	44	47.5
Poor	10	5	1	5	0
Response data, %					
CR	5	1	0	0	2.5
PR	28	18	5	25	27.5
Unconfirmed PR		11			
SD	45	39	74	50	42.5
PD	12	21	10	17.5	15
Not assessable	10	10	10	7.5	12.5
Outcome, mo					
PFS	10	7		7.6	7.4
Median survival	Not reached	17	Not available	Not reached	Not reached
Toxicity data					
No. of patients who required dose reductions (%)	24 (65)	51 (77)	32 (33)	24(60)	16 (40)
No. of patients taken off study for toxicity (%)	11 (28)	NA	11 (11)	7 (17.5)	5 (12.5)

CR indicates complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; NA, not available.