Interferon-α in combination with either imatinib (Gleevec) or gefitinib (Iressa) in metastatic renal cell carcinoma: a phase II trial

Robert J. Amato, Jaroslaw Jac and Joan Hernandez-McClain

Treatments for metastatic renal cell carcinoma (MRCC) are limited. RCCs frequently overexpress epithelial growth factor receptor and express c-Kit and platelet-derived growth factor receptor-β. Combination of interferon with tyrosine kinase inhibitors of epithelial growth factor receptor [gefitinib (Iressa)] or c-Kit and platelet-derived growth factor receptor-β [imatinib (Gleevec)] was evaluated for efficacy and safety. Patients with MRCC received 12-week cycles of interferon [3 million units (MU) subcutaneously thrice in week 1 and 6 MU thrice weekly thereafter] and either gefitinib (500 mg daily) or imatinib (600 mg daily). The gefitinib/imatinib dose was reduced as needed owing to toxicity. The primary endpoint was objective tumor response. Secondary endpoints were time to tumor progression, overall survival, and safety. Seventeen patients were enrolled. Most had clear cell [36% (6/17)] or papillary [36% (6/17)] tumors. Most ($n = 14$) were treated on the gefitinib arm, including two patients who crossed over from the imatinib arm after experiencing disease progression. Objective tumor responses were evaluable in 14 patients (82%). Of these 14, partial responses occurred in three (21%), stable disease in seven (50%), and progressive disease in four (29%). The most frequent treatment-related adverse events were skin rash, flu-like symptoms, and fatigue (both treatment arms); diarrhea (gefitinib arm only); and thrombocytopenia and leukopenia (imatinib arm only). Median time to tumor progression (range) for patients on the gefitinib arm only was 4.27 (1.13–15.97) months and median overall survival (range) was 11.42+ (1.13–29.07+) months. Combination of gefitinib with interferon safely delays progression of refractory MRCC. Further studies in this setting are warranted. *Anti-Cancer Drugs* **19:527–533 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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The Methodist Hospital Research Institute, Houston, Texas, USA

Correspondence to Dr Robert J. Amato, DO, The Methodist Hospital, 6560 Fannin, Suite 2050, Houston, TX 77030, USA
Tel: +1 713 441 7920; fax: +1 713 441 7911;
e-mail: ramato@tmh.tmc.edu

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Introduction

Advanced renal cell carcinoma (RCC) is a common, but extremely drug-refractory and radiation-resistant malignancy. In the United States, it is the 10th leading cause of cancer death, accounting for an estimated 51 190 new diagnoses and 12 890 deaths each year [1]. It is predominantly a disease of the elderly and more common in men than women [1,2]. Arising mainly from proximal tubule cells, RCCs are of five main histological types: clear cell, papillary, chromophobe, oncocytoma, and collecting duct carcinomas [2,3]. Most RCCs (85%) are of the clear cell type, which is marked by vacuolated malignant cells containing cholesterol, lipids, and glycogens [4,5]. Most of the rest (14%) are of the prognostically more favorable papillary type [6].

For RCCs that are still localized at diagnosis, the first-line curative treatment is radical nephrectomy. Disease relapse, however, occurs within 18 months in 20–30% of nephrectomized patients and local recurrence occurs in less than 5% patients [7–9]. More unfortunately, one in three patients who present with an undiagnosed RCC has a tumor that has already metastasized (most often to the lungs; less often to the bone, liver, or soft tissue; and rarely to the brain) [2]. Nephrectomy's beneficial contribution, if any, to the estimated 5-year survival rate of $\leq 10\%$ for these patients [2,10,11] is unclear. Previously nephrectomized patients, however, experience higher rates of response to systemic therapy, longer lasting responses to interleukin (IL)-2-based therapy, and longer survival [12–16]. A large Southwest Oncology Group trial, in which patients with metastatic RCC (MRCC) were randomly assigned to receive interferon (IFN) therapy alone or after nephrectomy, revealed significantly better survival among nephrectomized patients than those receiving IFN only (median: 11.1 vs. 8.1 months; $P = 0.012$), very low operative mortality (< 1%), and no significant nephrectomy-related delay in starting systemic therapy [17]. Consequently, nephrectomy followed by cytokine therapy has been suggested as the standard of care for patients with MRCC [17,18].

Since the early 1990s, high-dose IL-2 has been considered standard therapy for advanced RCC, eliciting response rates superior to those of chemotherapy when administered alone (10–20%) or in combination (20–30%) [19], but not significantly enhancing long-term survival [19–24], even when replaced with low-dose IL-2 alone

0959-4973

or in combination with IFN-α [25]. High-dose IL-2, however, is potentially very toxic [25,26] and also inconvenient and expensive to use, leading to another potential standard therapy for RCC – IFN-α [27,28]. In a large retrospective review, the survival rates elicited by high-dose IL-2 or IFN-α were compared with various other therapies in 42 trials involving patients with advanced RCC [29]. The review revealed immunotherapy to be more efficacious than nonimmunotherapy controls (e.g. placebo, tamoxifen, medroxyprogesterone) in terms of overall tumor response and 1-year mortality (improving mean survival by approximately 3 weeks in seven studies). A comparison of the use of IFN with or without enhancers (e.g. vinblastine, IL-2, or IL-2 + vinblastine) with controls (e.g. vinblastine, IFN-γ, medroxyprogesterone, or tamoxifen alone) revealed that the IFN-containing regimens elicited significantly better response rates and improved mean survival by 2.6 months [28]. In retrospective analysis of the Memorial Sloan-Kettering Cancer Center experience with first-line systemic IFN-α therapy for MRCC, the median time to tumor progression (TTP) was 4.7 months, and good progression-free survival (PFS) ranged from 55% at 4 months to 8% at 3 years [25]. By comparison, patients in this study were treated earlier and had advanced RCC, so TTP of ≥ 6 months was to be considered an improvement over prognosis that might be expected based on Memorial Sloan–Kettering's analysis.

A more recent and exciting development in the strategic approach to cancer therapy has been the evolution of tyrosine kinase inhibitors [30]. On the basis of the crucial roles played by tyrosine kinases in various regulatory mechanisms, including signal transduction and cellular proliferation and differentiation, this approach has led to the design of a novel class of drugs that target the ATP-binding domain of tyrosine kinases. Sunitinib, temsirolimus, and sorafenib have all been reported to prolong PFS in advanced RCC [31–33]. Temsirolimus and sunitinib showed greater response rates and prolonged survival than IFN-α [31,32]. Grade 3 or 4 toxicities, however, were reported in up to 20% of patients treated with these compounds [34]. Two promising tyrosine kinase inhibitors for use against advanced RCC are imatinib (Gleevec) and gefitinib (Iressa).

Imatinib specifically and potently inhibits the proliferation of v-Abl-expressing and Bcr–Abl-expressing cells often seen in leukemia [35,36]. Imatinib induces antitumor activity when administered alone and reaches pharmacologically relevant plasma concentrations regardless of administration route [37]. Clinical trials in humans have demonstrated its activity against chronic myelogenous leukemia [38], and its ability to inhibit both c-Kit and platelet-derived growth factor receptor-β suggests its possible use against solid tumors [30]. Our own unpublished data from a recent immunohistochemical study of 28 primary RCCs and 26 MRCCs demonstrated abundant expression of c-Kit and platelet-derived growth factor receptor-β and especially in MRCCs. Gefitinib inhibits the activity of epithelial growth factor receptor, a tyrosine kinase whose frequent overexpression in RCCs seems to correlate with clinical tumor aggressiveness and shorter survival [39–42].

In light of these data, we decided to evaluate the efficacy and safety of combination therapy with IFN and the tyrosine kinase inhibitors imatinib and gefitinib in patients with previously treated and refractory MRCC.

Patients and methods

Study design

This randomized phase II study was originally designed to evaluate the safety and efficacy of two combination regimens (IFN-α-2b + either imatinib or gefitinib) in patients with MRCC. The two regimens were to be randomly assigned at an alternating sequential ratio of 1 : 1. Soon after the trial started, we, however, observed that patients with papillary tumors were responding better to the gefitinib-containing regimen. Consequently, 5 months after the study began, the study protocol was amended so that all patients with papillary tumors would be assigned to the IFN + gefitinib arm and all other patients would be randomly assigned alternately and sequentially to either arm as originally intended. Trial design, data accrual, data analysis, and manuscript preparation were performed entirely by us. Both original and amended study protocols were approved by The Methodist Hospital Institutional Review Board.

Study population

All patients who presented to our institution for treatment of previously untreated or refractory MRCC and who were at least 18 years old were eligible for inclusion in this study. These patients presented to our institution on their own or were referred from outside institutions. The study inclusion and exclusion criteria are summarized in Table 1. All patients gave written informed consent to participate in the study.

Interventions

All patients received 12-week cycles of IFN in combination with either imatinib or gefitinib. In all cases, IFN was administered subcutaneously three times a week at an initial dose of 3 million units (MU) in week 1 as side effects are generally more pronounced after first few doses and at a dose of 6 MU thereafter. (These IFN-α doses were based on a review of standard European labeling and on doses commonly used in phase II/III combination therapy trials in the United States.) Patients on the imatinib-containing treatment arm were started on imatinib at a single daily dose of 600 mg. In cases of dose-limiting toxicity, the dose was reduced to 400 mg.

Table 1 Study inclusion and exclusion criteria

Inclusion criteria
Age $\geq$ 18 years
Histologically confirmed RCC
History of immunotherapy, chemotherapy, or investigational therapy, provided last treatment had been received $\geq$ 4 weeks before enrollment
History of radiation therapy, provided it was delivered to $\leq$ 2 metastatic sites
Zubrod performance status $\leq$ 2
Adequate hematological function
WBC $\geq 3 \times 10^6$
Absolute neutrophil count $\geq$ 1500/mm^3
Hemoglobin $\geq$ 9 g/dl
Platelet count $\geq 1 \times 10^5$
Adequate liver function
Total bilirubin $\leq$ 1.5 mg/dl
AST $\leq 4 \times$ ULN
ALT $\leq 4 \times$ ULN
Adequate renal function
Serum creatinine $\leq$ 2.0 mg/dl
No evidence of cardiac compromise
Informed consent
Exclusion criteria
History of central nervous system disease or metastases, except those whose metastases had been completely excised or treated with radiation and who had remained symptom free, had not received oral steroids, and showed no new evidence of disease on brain MRI for at least 6 months
Pregnancy or breastfeeding in women of childbearing potential

ALT, alanine aminotransferase; AST, aspartate aminotransferase; RCC, renal cell carcinoma; ULN, upper limit of normal; WBC, white blood cell (count).

Patients on the gefitinib-containing treatment arm were started on gefitinib at a single daily dose of 500 mg. In cases of dose-limiting toxicity, the dose was reduced to 250 mg.

Study objectives

The primary objective of this study was to determine objective tumor response rates and to determine whether combination treatment regimen would be efficacious enough to warrant further investigation as therapy for MRCC. The secondary objectives were to evaluate TTP, overall survival (OS), and safety.

Outcome measures

The primary study endpoint was the objective tumor response to treatment. The secondary study endpoints were TTP, OS, and safety (i.e. type, frequency, and severity of adverse events and their relationship to the study drug).

Sample size

According to the trial's original design, 16 patients were to be enrolled in each combination treatment arm. This was intended to ensure an 80% probability that, if the 6-month PFS rate on either treatment arms was $\geq$ 25%, then that regimen was to be considered efficacious enough to warrant further study.

Pretreatment (baseline) assessments

All patients were evaluated at baseline. The baseline evaluation included patient history; physical examination; chest radiograph; magnetic resonance imaging scan of the brain; computed tomography scans of the chest, abdomen, and pelvis; bone scan (in patients with no bone metastasis); Zubrod performance status assessment; cardiac profile (i.e. electrocardiography and echocardiography); hematology profile (i.e. complete blood count with platelets and differential); coagulation profile (i.e. prothrombin time, international normalized ratio, and partial thromboplastin time); biochemical profile (i.e. total protein, uric acid, blood, urine, creatinine, lactate dehydrogenase, aspartate transaminase, alanine transminase, alkaline phosphatase, phosphorus, total bilirubin, sodium, potassium, CO_2 content, chloride, calcium, albumin, glucose); and urinalysis. Women of childbearing potential were administered a serum or urine pregnancy test (e.g. serum human β-chorionic gonadotropin).

Treatment assessments

Efficacy and safety were assessed at regular intervals. Efficacy was assessed in terms of objective tumor response every 12 weeks and until progression or unacceptable toxicity occurred. In all cases, objective tumor responses were classified according to current Response Evaluation Criteria in Solid Tumors guidelines [43]. TTP and OS were also determined. Safety was assessed every 4 weeks in all patients on each treatment arm who received at least one dose of both the study drugs. All toxic adverse events and long-term abnormalities were noted and graded for severity whenever possible, according to version 3 of the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE). If after dose reduction an adverse event recurred at the lower dose, then the patient was discontinued from the study.

Statistical analysis

Physical examination data were summarized in terms of means, medians, standard deviations, and minimum and maximum values. Laboratory data were analyzed and tabulated in terms of frequency of the worst severity grade observed (NCI-CTCAE). For laboratory variables for which no NCI-CTCAE scale exists, the frequency of patients with values below, within, and above the normal ranges was summarized. Estimated tumor response rates, their associated two-sided 95% confidence intervals, and Kaplan–Meier estimates of PFS (as a corollary of TTP) and OS were calculated.

Results

Recruitment and follow-up

Eligible patients were recruited between 17 March 2005 and 14 November 2005. Except for those patients who were not considered evaluable for efficacy, all patients included in the study were evaluated at baseline, once every 4 weeks (for safety) and once every 12 weeks (for efficacy) during the treatment regimen, and then every 12 weeks thereafter (for survival).

Patient characteristics

A total of 17 patients were enrolled in this study. Of these, 16 patients received at least one of the treatment combinations, and one patient voluntarily withdrew from the study before ever receiving any study treatment. In general, this patient population was middle-aged [median age (range), 58 (24–77) years], predominantly men [71% (12/17)], and predominantly white [82% (14/17)] (Table 2). All 17 patients had undergone nephrectomy earlier. The most prevalent tumor types were clear cell [36% (6/17)] and papillary [36% (6/17)]; in two other cases, the tumors had papillary features (Table 3). The characteristics of the patients and their tumors are summarized more comprehensively in Tables 2 and 3.

Fourteen patients were treated on the gefitinib arm, including two who crossed over from the imatinib arm (after one cycle) after experiencing disease progression at 4 and 14 weeks, respectively. Four patients were treated on the imatinib arm, including the two who crossed over to the gefitinib arm. One of the crossover patients had a chromophobe tumor; the other had a papillary tumor.

Efficacy

Objective tumor responses were evaluable in 14 of 17 patients (82%) (Table 4). Of the evaluable patients, an objective (partial) tumor response was achieved in only three (21%). Interestingly, all three of these partial responders had papillary tumors and were treated in the gefitinib arm. In addition, stable disease was achieved in seven of the 14 valuable patients (50%). This included the two patients treated with imatinib and five patients treated with gefitinib. The three patients who were deemed not evaluable for tumor response included the two who had crossed over from the imatinib arm to the gefitinib arm after experiencing early clinical disease progression and one who withdrew voluntarily before receiving any study treatment.

For the 12 patients on the gefitinib arm who did not cross over from the imatinib arm, median PFS (range) was 4.27 (1.13–15.97) months (Fig. 1), and the median OS (range) was 11.42+ (1.13–29.07+) months (Fig. 2). In five of these patients (42%), TTP was ≥ 6 months. As of December 2007, seven patients are now dead, and five are alive. Mean PFS for the two patients who crossed over from the imatinib arm to the gefitinib arm was 9.63 (8.63–10.63) months, and mean OS was 21+ (14.07–27.93+) months. For the two patients who received treatment on the imatinib arm only, mean PFS was 2.5 (2.43–2.57) months and mean OS was 9 (2.43–15.57) months. The patient who withdrew voluntarily from the study before receiving any study treatment was not evaluable.

Safety

The most common treatment-related adverse events (NCI-CTCAE grade ≤ 2) were skin rash, flu-like symptoms, and fatigue on both treatment arms and diarrhea on the IFN + gefitinib arm. The most frequent laboratory abnormalities (NCI-CTCAE grade ≥ 3) were thrombocytopenia and leukopenia on the IFN + imatinib

Table 2 Demographical and clinical characteristics of study population ($n=17$)

No. of patients enrolled	17
Median age (range), years	54 (24–77)
Sex, *n* (%)	
Male	12 (71%)
Female	5 (29%)
Race, *n* (%)	
White	14 (82%)
Hispanic	1 (6%)
Indian	1 (6%)
Black	1 (6%)
Earlier therapy, *n* (%)	
Nephrectomy	17 (100%)
Radiation therapy	3 (18%)
Immunotherapy	7 (41%)
Chemotherapy	5 (28%)
Molecular targeted therapy	4 (24%)
Other	2 (12%)
No. of earlier therapies received, *n* (%)	
0	6 (36%)
1	3 (18%)
2	3 (18%)
≥ 3	5 (29%)
Best response to earlier therapy, *n* (%)	
Partial response	5 (29%)
Stable disease	5 (29%)
Progressive disease	1 (6%)
Not applicable	6 (36%)
Sites involved by metastatic disease, *n* (%)	
Lymph node	12 (70%)
Lung	8 (47%)
Bone	7 (41%)
Liver	4 (24%)
Adrenal gland	3 (18%)
Other	3 (18%)
No. of metastatic disease sites, *n* (%)	
1	3 (18%)
2	7 (41%)
3	2 (12%)
≥ 4	5 (29%)
Prognosis[a]	
Favorable	5 (29%)
Intermediate	10 (59%)
Poor	2 (12%)
Tumor grade[b]	
2	1 (6%)
3	3 (18%)
4	13 (76%)
Tumor histology, *n* (%)	
Clear cell	7 (41%)
Papillary	6 (36%)
Papillary with sarcomatoid features	1 (6%)
Chromophobe	1 (6%)
Collecting duct with papillary features	1 (6%)
Unclassified	1 (6%)
No. of patients on each treatment arm, *n* (%)[c]	
Interferon + imatinib	2 (12%)[d]
Interferon + gefitinib	14 (82%)[e]

[a]Risk factors were defined according to the Memorial Sloan-Kettering Cancer Center system [51].
[b]Tumor grades were defined according to the Fuhrman system [52].
[c]One patient voluntarily withdrew from the study before ever receiving any study treatment.
[d]Only two patients were treated completely on the imatinib arm. Two other patients started on the imatinib arm, but crossed over (after one cycle) to the gefitinib arm after experiencing disease progression at 4 and 14 weeks, respectively.
[e]This includes the two patients who crossed over from the imatinib arm (after one cycle) to the gefitinib arm.

Table 3 Characteristics of treated tumors ($n=16$)[a]

Patient	Tumor type	Affected kidney	Primary tumor at the greatest diameter	Grade	Staining intensity			
					c-Kit	EGFR	VEGF	PDGF
1	Papillary	Left	4 cm	3				
2	Chromophobe	Right	10 cm	3	+[b]	3+		
3	Clear cell	Left	5 cm	4	–	3+		
4	Clear cell	Right	Unknown	4				
5	Clear cell	Left	5 cm	2				
6	Papillary	Right	9.2 cm	4	–	2–3+ (85%)		
7	Clear cell	Right	10 cm	4	–	2+ (80%)		
8	Papillary with sarcomatoid features	Right	7 cm	4	Few+cells	3+ (40%)		
9	Unclassified	Left	3 cm	4	–	Focal cytoplasmic staining		
10	Clear cell	Right	9 cm	3				
11	Papillary	Right	>7 cm	4				
12	Clear cell	Right	Unknown	4	NA			
13	Papillary	Right	8 cm	3	–	Focal cytoplasmic staining		
14	Papillary	Right	7.5 cm	3	–	Focal cytoplasmic staining		
15	Collecting duct with papillary features	Right	4.2 cm	4				
16	Papillary	Right	2.8 cm	4				

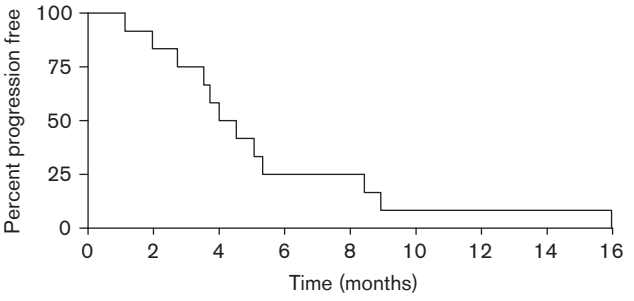
EGFR, epithelial growth factor receptor; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; NA, not available.
[a]One patient voluntarily withdrew from the study before ever receiving any study treatment.
[b]+ or – represents the degree of staining positivity.

Table 4 Objective tumor responses and survival in evaluable patients

Tumor response to treatment ($n=14$)[a,b]	
Partial response	3 (21%)[c]
Stable disease	7 (50%)
Progressive disease	4 (29%)
PFS and OS ($n=12$)[d]	
Median time to tumor progression (range), months	4.27 (1.13–15.97)
Median overall survival (range), months	11.42+ (1.13–25.53)

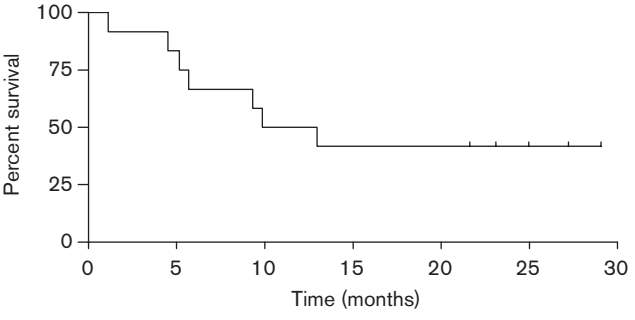
[a]Three patients were not evaluable for efficacy: two who crossed over from the imatinib arm to the gefitinib arm after experiencing early clinical disease progression and one who never received study drugs.
[b]Objective treatment responses were classified according to current Response Evaluation Criteria in Solid Tumors guidelines [43].
[c]All three partial responses occurred in patients who had papillary tumors.
[d]Five patients were excluded from survival analysis: two patients who crossed over from the imatinib arm to the gefitinib arm (mean PFS, 9.63 months; mean OS, 19.24+ months); two patients who were treated on the imatinib arm only (mean PFS, 2.5 months; mean OS, 9 months); and one patient who withdrew voluntarily from the study before receiving any study treatment. OS, overall survival; PFS, progression-free survival.

Fig. 1



Kaplan–Meier curve of progression-free survival after treatment of metastatic renal cell carcinoma with interferon+gefitinib ($n=12$).

Fig. 2



Kaplan–Meier curve of overall survival after treatment of metastatic renal cell carcinoma with interferon+gefitinib ($n=12$).

arm. Dose reductions were required in 25% (4/16) of cases. These included reductions in IFN dose secondary to leukopenia ($n=2$) and fatigue ($n=1$) and a reduction in imatinib dose secondary to skin rash ($n=1$).

Discussion

In the present trial, the treatment of refractory MRCC with a combination of IFN and gefitinib resulted in an objective (partial) tumor response rate of 25% (3/12). Overall, the 12 patients treated in the gefitinib arm only reached a median TTP (i.e. PFS) of 4.3 months, and a median OS of $\geq 11.4+$ months. Meanwhile, stable

tumor responses were achieved in the two patients who received imatinib without crossing over to the gefitinib arm. This group achieved a mean TTP of 2.5 (2.43–2.57) months and a mean OS of 9.0 (2.43–15.57) months. Both combinations were well tolerated, as demonstrated by a general lack of serious adverse events and laboratory abnormalities.

Our findings suggest that gefitinib given in combination with IFN has merit as a therapy for advanced RCC. In several recent phase II trials as single agents in this setting, neither gefitinib [44–46] nor imatinib [47] produced objective responses and did not significantly enhance survival. In a single-center phase II trial involving 17 patients with advanced RCC [48], the combination of IFN and imatinib produced only one objective (partial) response in 12 evaluable patients, did little to delay disease progression (median TTP was only 2 months), and was toxic enough to prompt the withdrawal of one-third of all treated patients. Exploration of tyrosine kinase inhibitor sorafenib combined with IFN-α2b reported a 19% response rate, which was greater than either treatment alone, but toxicity of the combination limits further development [49].

In our present trial, TTP $\geq$ 6 months was achieved in five patients (42%) treated on the gefitinib arm, and all three objective responses occurred in patients who had papillary tumors and who were treated on this arm. As a result of this observed contact tumor activity with IFN and gefitinib, we changed the study protocol to enroll patients with papillary subtype RCC exclusively in the IFN and gefitinib arm. In addition owing to this preliminary papillary activity along with the increased availability of other tyrosine kinases through patient access programs, we closed this study early without meeting the original recruitment target. In light of our present findings and other recent reports, we instead launched a trial of pegylated IFN in combination with other tyrosine kinase inhibitors [i.e. sunitinib (Sutent) and erlotinib (Tarceva)] as combination therapy for papillary RCC.

Our findings carry special significance because papillary RCCs are not often studied together as a group and treatment of a specific RCC phenotype opens an interesting new pathway for RCC therapies. A recent study of sunitinib and sorafenib in metastatic papillary and chromophobe RCC reported longer PFS with sunitinib (11.9 months) than sorafenib (5.1 months), but overall low clinical response (4.8%) [24,50].

In summary, our present findings warrant further trials of combination therapy with IFN and gefitinib in patients with refractory metastastic RCC and especially those with a papillary phenotype or component.

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