Escudier et al. (2007)

DESIGN

Study design:
RCT + crossover

Country (countries):
European countries (UK, France, Germany, Poland, etc) and USA

Number of centres:
-

Recruitment dates:
November 2003 to March 2005

Length of follow-up:
The median follow-up was 6.6 months for both groups

Source of funding:
Supported by Bayer Pharmaceuticals and Onyx Pharmaceuticals

ARM(S)

ARM 1:

Sorafenib 400mg bid

Intervention: Sorafenib

n=451. Oral sorafenib 400 mg bid.

Doses were delayed or reduced if patients had clinically significant hematologic or other adverse events that were considered to be related to sorafenib, as measured with the use of version 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute. In such cases, doses were reduced to 400 mg once daily and then to 400 mg every other day. If further reductions were required, patients were withdrawn from the trial. If adverse events resolved to a grade of 1 or less, the dose could be escalated to the previous level at the investigator's discretion.

ARM 2:

Placebo

Intervention: Placebo

n=452

PARTICIPANTS

Number enrolled:
903

Attrition / dropout:
Sorafenib: n=36. Of the 36, eighteen had adverse events, 7 withdrew consent, and
11 had other reasons. Placebo: n=38. Of the 38, seventeen had adverse events, 11 withdrew consent, and 10 had other reasons.

Inclusion criteria:
Eligible patients were at least 18 years of age and had histologically confirmed metastatic clear cell renal-cell carcinoma, which had progressed after one systemic treatment within the previous 8 months. Additional eligibility criteria were a performance status of 0 or 1 on the basis of Eastern Cooperative Oncology Group criteria; an intermediate-risk or low-risk status, according to the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score; a life expectancy of at least 12 weeks; adequate bone marrow, liver, pancreatic, and renal function; and a prothrombin time or partial-thromboplastin time of less than 1.5 times the upper limit of the normal range.

Exclusion criteria:
Patients with brain metastases or previous exposure to VEGF pathway inhibitors were excluded.

ANALYSIS

Primary outcome measure:
Overall survival

Secondary outcome measure(s):
Progression-free survival;
Best overall response rate;
Kidney cancer symptoms;
HRQOL.

Method of assessing outcomes:
Progression of disease was determined on the basis of findings on computed tomography (CT) or magnetic resonance imaging (MRI), clinical progression, or death, with the use of the Response Evaluation Criteria in Solid Tumors (RECIST). Investigators and independent radiologists who were unaware of the study-group assignments assessed progression-
free survival. Another secondary end point was the best overall response rate (on the basis of
RECIST) within the last 10 days of each drug cycle. Assessments of responses required confirmatory findings on CT or MRI 4 or more weeks after the initial determination of a response. Evaluations of tumor responses were performed within the last 10 days of each cycle. Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events (CTCAE).

1st analysis: performed in May 2005 immediately before crossover was allowed (18 months after the trial started)
2nd analysis: performed in Novermber 2005, after 216 of 452 patients receiving placebo had switched to sorafenib and after 367 deaths had occurred (6 months after the crossover was allowed).

Overall response was assessed at the January 2005 cutoff (13 months after the trial started).

Kidney cancer symptoms and HRQOL were assessed by patient self-administration of the Functional Assessment of Cancer Therapy-Kindney Symptom Index (FKSI) and the Functional Assessment of Cancer Therapy-Grneral (FACT-G), respectively, before seeing the physician.The range of values for the FKSI-10 is from 0 to 40. A low FKSI score reflets being more symptomatic; a higher score represents being less symptomatic. The range of the FACT-G physical well-bing (FACT-G PWB) is 0 to 28 based on a Likert scale of 0 to 4. Low scores represent impaired HRQOL; higher scores reflect better HRQOL.

ADDITIONAL NOTES ON STUDY DESIGN

METHODS:
From November 2003 to March 2005, 903 patients with renalcell carcinoma that was resistant to standard therapy were randomly assigned to receive either continuous
treatment with oral sorafenib (at a dose of 400 mg twice daily) or placebo; 451 patients received sorafenib and 452 received placebo. The

B.Escudier (2007)

DESIGN

Study design:
RCT

Country (countries):
18 countries

Number of centres:
-

Recruitment dates:
Between June 2004 and October 2005

Length of follow-up:
see notes

Source of funding:
This study was funded by F. Hoffmann-La Roche Ltd, who also funded medical writing support by Gardiner-Caldwell Communications.

ARM(S)

ARM 1:

Bevacizumab (10mg/kg/2wks) + IFN-a2a (9MIU x 3/wk)

Intervention: Bevacizumab + IFN-a2a

n=327

IFN-a2a subcutaneously for a maximum of 1 year at the standard dose of 9MIU three times a week plus bevacizumab 10mg/kg once every 2 weeks, intravenously until disease progression, unacceptable toxicity, or withdrawal of consent.

The protocol specified that IFN-a2a could be initiated at a lower dose than 9MIU as long as the recommended dose was reached within the first 2 weeks of treatment. During treatment, IFN-a2a administration was withheld with the development of a grade 3 adverse event attributable to IFN-a2a. If the event necessitating IFN-a2a being withheld resolved within the first 28 days, IFN-a2a was to be restarted at a dose of 6MIU (three times a week). The dose of IFN-a2a was further reduced to 3MIU (three times a week) with the development of a subsequent grade 3 adverse event due to an IFN-a2a-attributable toxicity. Concurrent bevacizumab was maintained at the standard dose without reduction, even if IFN-a2a was discontinued.

ARM 2:

IFN-a2a + Placebo

Intervention: IFN-a2a + Placebo

n= 322.

IFN-a2a subcutaneously for a maximum of 1 year at the standard dose of 9MIU three times a week plus placebo once every 2 weeks, intravenously until disease progression, unacceptable toxicity, or withdrawal of consent.

The protocol specified that IFN-a2a could be initiated at a lower dose than 9MIU as long as the recommended dose was reached within the first 2 weeks of treatment. During treatment, IFN-a2a administration was withheld with the development of a grade 3 adverse event attributable to IFN-a2a. If the event necessitating IFN-a2a being withheld resolved within the first 28 days, IFN-a2a was to be restarted at a dose of 6MIU (three times a week). The dose of IFN-a2a was further reduced to 3MIU (three times a week) with the development of a subsequent grade 3 adverse event due to an IFN-a2a-attributable toxicity. Concurrent bevacizumab was maintained at the standard dose without reduction, even if IFN-a2a was discontinued.

PARTICIPANTS

Number enrolled:
649

Attrition / dropout:
Withdrawn prior to progression: in group 1: (n=105) 32%; in group 2: (n=50) 16%.

Inclusion criteria:
Patients ≥18 years;
Confirmed metastatic RCC with >50% clear cell histology;
After total or partial nephrectomy (if resection margins clearly negative of disease);
Karnofsky performance status of ≥70%;
Measurable or non-measurable disease (according to RECIST).

Exclusion criteria:
Prior systemic treatment for metastatic RCC disease;
Evidence of current central nervous system (CNS) metastases or spinal cord compression;
Evidence of bleeding diathesis or coagulopathy;
Full therapeutic doses of oral or parenteral anticoagulants;
Recent major surgical procedures;
Uncontrolled hypertension on medication;
Clinically significant cardiovascular disease or chronic corticosteroid treatment.

ANALYSIS

Primary outcome measure:
Overall survival

Secondary outcome measure(s):
PFS, overall response rate and safety.

Method of assessing outcomes:
Tumour assessments were performed every 8 weeks until week 32 and every 12 weeks thereafter.

Tumour response was assessed according to Response Evaluation Criteria in Solid Tumors [RECIST] criteria.

The effects of baseline demographic and prognostic patient characteristics on PFS were analysed using a Cox proportional hazards model.

ADDITIONAL NOTES ON STUDY DESIGN

Hudes et al. (2007)

DESIGN

Study design:
Randomised controlled trial

Country (countries):
United States; Western Europe, Australia, and Canada; or Asia-Pacific, Eastern Europe, Africa, and South America

Number of centres:
-

Recruitment dates:
July 2003 to April 2005

Length of follow-up:
?

Source of funding:
Supported by Wyeth Research

ARM(S)

ARM 1:
IFN-α 3 MU sc x 3/wk
Intervention: IFN-α
n=207 (3 MU with an increase to 18 mU, sc x 3/wk)

ARM 2:
Temsirolimus (25 mg iv weekly)
Intervention: Temsirolimus
n=209

ARM 3:
Temsirolimus 15mg iv/wk + IFN-α 6 MUx3/wk
Intervention: Temsirolimus + IFN-α
n=210.

PARTICIPANTS

Number enrolled:
626

Attrition / dropout:
A total of 19 patients were lost to follow-up (10 in the interferon group, 4 in the temsirolimus group, and 5 in the combination-therapy group)

Inclusion criteria:
Eligibility criteria included histologically confirmed advanced renal-cell carcinoma (stage IV or recurrent disease) and a Karnofsky performance score of 60 or more (on a scale of 0 to 100, with higher scores indicating better performance), with no previous systemic therapy. Additional eligibility criteria were a tumor that was measurable according to the Response Evaluation Criteria in Solid Tumors (RECIST), and adequate bone marrow, renal, and hepatic functions, which were defined as a neutrophil count of at least 1500 cells per cubic millimeter, a platelet count of at least 100,000 cells per cubic millimeter, and a hemoglobin count of at least 8 g per deciliter; a serum creatinine level of no more than 1.5 times the upper limit of the normal range; an aspartate aminotranferase level of no more than 3 times the upper limit of the normal range (≤5 times if liver metastases were present); and a total bilirubin level of no more than 1.5 times the upper limit of the normal range. A fasting level of total cholesterol of no more than 350 mg per deciliter (9.1 mmol per liter) and a triglyceride level of no more than 400 mg per deciliter (4.5 mmol per liter) were required. Patients with a history of brain metastases were eligible if their condition was neurologically stable and they did not require corticosteroids after surgical resection or radiotherapy.

Exclusion criteria:
-

ANALYSIS

Primary outcome measure:
Overall survival

Secondary outcome measure(s):
Progression-free survival;
Objective response rate;
Clinical benefit rate.

Method of assessing outcomes:
Response to treatment was assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST).

Progression-free survival was determined by the site investigators' assessment and a blinded assessment of imaging studies (performed by Bio-Imaging Technologies).

The objective response rate, and the clinical benefit rate, were defined as the proportion of patients with stable disease for at least 24 weeks or an objective response.

The primary end point was calculated on an intention-to-treat basis. All patients who received any treatment were included in the analysis of safety.

ADDITIONAL NOTES ON STUDY DESIGN

Patients were randomly assigned in equal proportions, with the use of permuted blocks of three, to one of three treatment groups.

Duration of interferon treatment: median 8 (range 1-124)wks; in combination with Temsirolimus: median 12 (range 1-138)wks.
Duration of temsirolimus treatment: median 17 (range 1-126)wks; in combination with interferion alfa: median 15 (range 1-138)wks.

Patients with ≥1 dose reduction:
Interferion alfa: 78 (39%); in combination with temsirolimus: 99 (48%)
Temsirolimus: 48 (23%); in combination with interferion alfa: 59 (30%)

Treatment Summary:

Patients with ≥1 dose delay:
Interferion alfa: 78 (39%); in combination with temsirolimus: 99 (48%)
Temsiroliomus: 137 (66%); in combination with interferion alfa: 163 (82%)

Mean dose intensity (the total exposure per week of treatment):
Temsirolimus: 23.1 mg/wk; in combination with interferion afla: 13.9 mg/wk.
Interferon: 30.2 million U/wk; in combination with Temsirolimus: 13.1 million U/wk.

Motzer et al. (2006)

DESIGN

Study design:
Phase II trial (open-label, single-arm, multicenter clinical trial)

Country (countries):
USA

Number of centres:
-

Recruitment dates:
Between February and November 2004,

Length of follow-up:
18 months

Source of funding:
Research support for this trial was provided by Pfizer Inc.

ARM(S)

ARM 1:
Sunitinib 50 mg qd
Intervention: sunitinib

Repeated 6-week cycles of sunitinib, 50 mg per day given orally for 4 consecutive weeks followed by 2 weeks off per treatment cycle.

PARTICIPANTS

Number enrolled:
106

Attrition / dropout:
One patient enrolled with a diagnosis of clear-cell RCC was withdrawn from the study because a repeat biopsy after treatment was initiated resulted in a diagnosis of cancer different than clear-cell RCC. This patient is included in the safety analysis but excluded from efficacy analyses.

Inclusion criteria:
Eligibility criteria included provision of written informed consent; participant age of 18 years or older; prior nephrectomy; histological confirmation of clear-cell RCC with metastases; measurable disease; failure of 1 cytokine therapy (IL-2, interferon-alfa, or combination) due to disease progression (radiographic confirmation); Eastern Cooperative Oncology
Group (ECOG) performance status of 0 or 1; and adequate organ function (based on tests of hematologic, hepatic, renal, and cardiac function). Eligibility required prior cytokine therapy to be discontinued for at least 4 weeks before study entry.

Exclusion criteria:
Patients were excluded if they had brain metastases or significant cardiac events within the 12 months prior to study drug administration.

ANALYSIS

Primary outcome measure:
Overall objective response rate (complete plus partial)

Secondary outcome measure(s):
Duration of response;
Progression-free survival;
Overall survival;
Safety.

Method of assessing outcomes:
Overall objective response rate was defined as the proportion of patients with confirmed complete or partial responses. Clinical response (complete response, partial response, stable disease, and progressive disease) was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) using CT/MRI scans and bone scans (if bone metastases were present at baseline) after each cycle for the first 4 cycles and every other cycle thereafter until the end of treatment. The responses were assessed by treating physicians (investigator assessment) and also by a third-party core imaging laboratory where the scan images of all patients were read by 2 radiologists for each time point (independent third-party assessment).

Duration of response is defined as the time from first documentation of objective response to progressive disease or death due to any cause during the on-study period, with patients being censored on the last day of the on-study period if no progression or death has occurred.

The on-study period is defined as the time of first study dose until the last on-treatment tumor assessment or 28 days after last study drug, whichever is greater.

Progressionfree survival is defined as the time from the start of treatment to progressive disease or death due to any cause during the on-study period (whichever comes first), with censored observations handled as described previously.

Overall survival is the time from start of treatment to death due to any cause, or to last follow-up for patients who did not die.

Adverse events: severity graded was assessed according to National Cancer Institute Common Terminology Criteria for AdverseEvents [CTCAE,Version3.0]; ECOG performance status; and hematology and clinical chemistry profiles. All blood samples weresent toacentral laboratory for analysis. Cardiac function was assessed by electrocardiogram on day 28 of cycle 1 and as clinically indicated, and by multigated acquisition scan on day 28 of every even cycle until the end of treatment. According to the CTCAE, adverse events are assessed by severity and denoted as grade 1, mild;

Motzer et al. (2006)

DESIGN

Study design:
Phase II clinical trial

Country (countries):
USA

Number of centres:
-

Recruitment dates:
Between January and July 2003

Length of follow-up:
24+ months

Source of funding:
Supported by Pfizer Inc, La Jolla, CA.

ARM(S)

ARM 1:

Sunitinib 50mg-75mg qd (dose may reduce)

Intervention: Sunitinib

The starting dose of SU11248 was 50 mg per day administered in repeated
6-week cycles of daily therapy for 4 weeks, followed by 2 weeks off. SU11248 was self-administered orally once daily without regard to meals.
Intrapatient dose escalation by 12.5 mg/d (up to 75 mg/d) was permitted in the
absence of treatment-related toxicity. Dose reduction for toxicity was allowed
to 37.5 mg/d and then to 25 mg/d, according to a nomogram for grade 3 to
4 severity.

PARTICIPANTS

Number enrolled:
63

Attrition / dropout:
0

Inclusion criteria:

Eligibility criteria included informed consent, histologic confirmation of RCC, measurable disease with evidence of metastases, failure of one cytokine (IFN-α, IL-2) -based therapy because of disease progression or unacceptable toxicity, Eastern Cooperative Oncology Group performance status of 0 or 1, normal serum amylase and lipase, a normal adrenocorticotropic hormone stimulation test, and adequate hematologic, hepatic, renal, and cardiac function. The latter was determined as a normal left ventricular ejection fraction by echocardiogram or multigated acquisition (MUGA) scan.

Exclusion criteria:

Patients were excluded for the presence of brain metastases or ongoing cardiac dysrhythmia, prolongation of QTc interval, or any significant cardiac event within the previous 12 months.

ANALYSIS

Primary outcome measure:
Overall response rate

Secondary outcome measure(s):
Time to progression;
Safety.

Method of assessing outcomes:

Objective clinical response rate (complete response or partial response) was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) using computed tomography or magnetic resonance imaging scan and bone scan (if bone metastases were present at baseline) after cycles 1, 2, and 4, and every two cycles thereafter until the end of treatment. CBC, cardiac enzymes, and biochemical profiles were obtained throughout the study. Cardiac function was assessed by ECG and echocardiogram or MUGA scan on day 28 of each treatment cycle. Quality of life was assessed using the Functional Assessment of Chronic Illness Therapy–Fatigue scale (FACIT-Fatigue) and the EuroQoL EQ-5D instrument (EQ-5D). Patients completed the FACIT-Fatigue questionnaire before receiving SU11248 on day 1 (as the baseline assessment) and weekly for cycles 1 through 4 and the EQ-5D on days 1 and 28 of each cycle.

Response was assessed by investigators according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria and severity of adverse events according to the National Cancer Institute Common Toxicity Criteria version 2.0.

ADDITIONAL NOTES ON STUDY DESIGN

SU11248 treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Individual patients continued SU11248 treatment after progression if the investigator felt that the patient continued to derive clinical benefit. However, for purposes of analysis, the patient was considered to have met the study end point of disease progression.

CHARACTERISTICS OF PARTICIPANTS

	Sunitinib 50mg-75mg qd (dose may reduce)			
Characteristic	**N**	**k**	**Mean**	**SD**
Age (median, yrs)	63	-	6	-
ECOG performance status = 0	63	-	34	-
ECOG performance status = 1	63	-	29	-
Histology: clear cell	63	55	-	-
Histology: palillary	63	4	-	-
Histology: sarcomatoid varant (not otherwise specified)	63	1	-	-
Histology: unspecified	63	3	-	-
Male	63	43	-	-
Mean FACIT-Fatigue scale score	62	-	40.4	-
Mean health state visual analog scale scores	60	-	77.1	-
Median FACIT-Fatigue scale score	62	-	44	-
Median health state visual analog scale scores	60	-	8	-

Motzer (2007)

DESIGN

Study design:
Randomised controlled trial

Country (countries):
Australia, Brazil, Canada, Europe, and the United States

Number of centres:
-

Recruitment dates:
Between August 2004 and October 2005

Length of follow-up:
see notes

Source of funding:
Supported by Pfizer

ARM(S)

ARM 1:
sunitinib 50mg qd
Intervention: sunitinib

n=375 (sunitinib 50 mg orally once daily for 4 weeks, followed by 2 weeks
without treatment)

ARM 2:
IFN-α 9 MU sc x 3/week
Intervention: IFN-α

n=375 (IFN at 9 MU subcutaneously three times weekly)

PARTICIPANTS

Number enrolled:
750

Attrition / dropout:
-

Inclusion criteria:
1). ≥18 years of age;
2). Had metastatic renal-cell carcinoma with a clear-cell histologic component, confirmed by the participating centers;
3). Had not received previous treatment with systemic therapy for renal-cell carcinoma;
4). The presence of measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
5). Adequate hematologic, coagulation, hepatic, renal, and cardiac function.

Exclusion criteria:
Patients were ineligible if they had brain metastases, uncontrolled hypertension, or clinically significant cardiovascular events or disease during the preceding 12 months.

ANALYSIS

Primary outcome measure:
progression-free survival

Secondary outcome measure(s):
Objective response rate, overall survival, patient-reported outcomes, and safety.

Method of assessing outcomes:
Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), with the use of imaging studies at baseline, at day 28 of cycles 1 through 4, and every two cycles thereafter until the end of treatment. Such assessments were also used to confirm a response (at least 4 weeks after initial documentation) and whenever disease progression was suspected. The response was assessed by an independent third-party radiology group (independent central review), and by treating physicians (investigators' assessments). The third-party radiologists were unaware of assignments to study groups.

Median progression-free survival time was assessed by central review of imaging studies.

Safety was assessed at regular intervals by documentation of adverse events, physical examination, radiography, and multigated acquisition scanning.

Laboratory assessments (hematologic and serum chemical measurements) were performed throughout the study by a central laboratory.

Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 3.0.

Health-related quality of life was assessed with the use of the Functional Assessment of Cancer Therapy — General (FACT-G) and FACT– Kidney Symptom Index (FKSI) questionnaires, which were administered before randomization, on days 1 and 28 of each cycle, and at the end of treatment.

ADDITIONAL NOTES ON STUDY DESIGN

METHODS:
Randomization was stratified according to baseline levels of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), ECOG performance status (0 vs. 1), and previous nephrectomy (yes vs. no). Patients were randomly assigned in a 1:1 ratio to receive either sunitinib or interferon alfa. Random permuted blocks of four
were used to attain balance within strata. It was estimated that 690 patients would be needed to enroll to observe 471 events.

FOLLOW-UP LENGTH:
At the time of analysis, the median duration of treatment was 6 months (range, 1 to 15) in the sunitinib group and 4 months (range, 1 to 13) in the interferon alfa group. Treatment was ongoing among 248 patients in the sunitinib group (66%) and 126 patients in the interferon alfa group (34%). Treatment in both groups was continued until the occurrence of disease progression, unacceptable adverse events, or withdrawal of consent. [Reasons for discontinuing treatment were progressive disease (in 25% of the patients in the sunitinib group and 45% in the interferon alfa group, P<0.001), adverse events (8% and 13%, respectively; P = 0.05), withdrawal of consent (1% and 8%, respectively; P<0.001), and protocol violation (<1% in each group).]

Ratain et al. (2006)

DESIGN

Study design:
Randomised discontinuation (or withdrawal) trial (RDT))

Country (countries):
USA and UK

Number of centres:
-

Recruitment dates:
September 25, 2002. (This report includes efficacy data up to December 31, 2004)
September 25, 2002

Length of follow-up:
12wks (run-in)+12wks (sorafenib or pb)

Source of funding:
Supported by Bayer Pharmaceuticals
Supported by Bayer Pharmaceuticals Corporation and Onyx Pharmaceuticals

ARM(S)

ARM 1:

Sorafenib 400mg bid (may reduce or delay)

Intervention: Sorafenib

n=32

Run-in: 400mg bid. Doses of sorafenib were delayed or reduced if clinically significant toxicities considered related to sorafenib occurred.

Patients who had a change in tumor size of less than25% and were randomly assigned to either sorafenib: at current dose.

After randomisation patients whose disease progressed while on sorafenib discontinued treatment.

ARM 2:

Placebo

Intervention: Placebo

n = 33. After randomisation patients whose disease progressed while on placebo were offered sorafenib.

Patients whose disease progressed while on placebo were offered sorafenib.

PARTICIPANTS

Number enrolled:
202

Attrition / dropout:
The 12-week run-in was completed by 187 patients (93%). Of the 15 patients who discontinued treatment before the 12-week assessment, the majority (12 patients) did so because of adverse events; one patient withdrew consent, one patient was lost to follow-up, and one patient died (as a result of pneumonia and metastatic disease, unrelated to the study drug).Of the 69 patients identified at 12 weeks were eligible for entry onto the randomized phase, two patients continued on open-label sorafenib (investigator protocol violation), and three patients withdrew (one patient each due to adverse events, to pursue other treatment options, and for clinical progression before random assignment). One patient who met the study criteria for progressive disease at week 12 was randomly assigned instead of discontinuing treatment. Therefore, a total of 65 patients were randomly assigned to receive sorafenib (32 patients) or placebo (33 patients). Seventy-three patients with tumor shrinkage of at least 25% at the 12-week assessment entered into the open-label part of the trial, plus six additional patientswhocontinued sorafenib, either at the discretion of the investigator or after being granted a waiver, despite having SD (n_3) or PD (n_2), or not receiving treatment for the entire run-in (n_1). Therefore, a total of 79 patients continued open-label sorafenib. Forty-three patients, who completed the 12-week run-in, discontinued treatment at a later time point; 40 patients because of PD, and three patients who had SD (and withdrew from the study).

Inclusion criteria:
Patients with histologically or cytologically confirmed metastatic refractory cancer;
Patient age of at least 18 years;
At least one measurable tumor;
Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
Life expectancy of at least 12 weeks;
Adequate bone marrow, liver, and renal function.

There was no limit on the extent of prior therapy, except for the exclusion of patients with previous exposure to a Ras pathway inhibitor.

Exclusion criteria:
Patients with other serious medical problems or CNS involvement were excluded.

ANALYSIS

Primary outcome measure:
patients remaining progression free remaining progression free

Secondary outcome measure(s):
Progression-free survival (PFS) after random assignment (randomized subset only);

Overall PFS (from start of treatment);

Tumor response rate;

Safety.

Method of assessing outcomes:
The primary end point was the percentage of randomly assigned patients remaining progression free at 12 weeks following random assignment (24 weeks after study entry).

Secondary end points included progression-free survival (PFS) after random assignment (randomized subset only); overall PFS (from start of treatment); tumor response rate; and safety.

Tumor response was assessed at 12 weeks, and once every 6 weeks thereafter, in accordance with modified WHO guidelines for partial response (PR), stable disease (SD), and progressive disease (PD). Objective responses were confirmed at least 4 weeks after the original documentation. In order to verify investigator observations in an unbiased manner, independent assessment of radiologic scans was performed retrospectively for 152 (75%) of 202 patients. Some scans were not available for independent assessment, as a radiology charter specifying parameters for independent review was developed after the last patient was accrued. These independent radiographic assessments were performed by RadPharm (Princeton, NJ).

Safety was assessed for the entire treatment period (run-in plus randomization). All patients who received at least one dose of the study drug and who had post-treatment data available were assessable for safety. Safety assessments were performed every 3 weeks during the run-in and randomization phases, and once every 4 weeks thereafter. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0), and their relationship to the study drug was recorded.

ADDITIONAL NOTES ON STUDY DESIGN

Patients initially received oral sorafenib 400 mg twice daily during the initial run-in period for 12 weeks. Doses of sorafenib were delayed or reduced if clinically significant toxicities considered related to sorafenib occurred. Then:

1. Patients with≥ 25% tumor shrinkage continued open-label sorafenib, until disease progression or toxicity, in order to avoid concerns about

Rini et al. (2004)

DESIGN

Study design:
Randomised controlled trial

Country (countries):
Canada

Number of centres:
-

Recruitment dates:
NR

Length of follow-up:
NR

Source of funding:
supported by national cancer institutes

ARM(S)

ARM 1:
IFN: 9 MU tiw
Intervention: IFN-α
n=? (NR)

ARM 2:
IFN 9 MU tiw + bevacizumab 10mg/kg i.v./2 weeks
Intervention: IFN-α + bevacizumab
n=? (NR)

PARTICIPANTS

Number enrolled:
732

Attrition / dropout:
Not reported

Inclusion criteria:
Untreated metastatic/unresectable RCC with a clear cell component.

Exclusion criteria:
No prior systemic therapy of any kind is permitted. Patients with central nervous system metastases, vascular disease, blood pressure >160/90, or a history of thrombosis within 1 year or ongoing anticoagulation are excluded.

ANALYSIS

Primary outcome measure:
overall survival

Secondary outcome measure(s):
progression-free survival;
objective response rate;
toxicity.

Method of assessing outcomes:
NR

ADDITIONAL NOTES ON STUDY DESIGN

Patients are stratified by nephrectomy status and established prognostic factors to insure balanced randomization. The trial was designed with 86% power to detect a 30% decrease in hazard rate assuming a two-sided significance level of 0.05. The primary end point of the trial is overall survival, and the study is designed to detect an improvement in median survival from 13 months for IFN-α alone to 17 months for the combination, representing a hazard ratio of 1.3. Seven hundred patients will be enrolled over 3 years with a two-sided significance level of 0.05 and a power of 89%.

CHARACTERISTICS OF PARTICIPANTS

Data from the ASCO abatract: 85% of patietns had prior nephrectomy; 26% of patients had good risk, 64% intermediate risk and 10% poor risk disease.

RESULTS

	IFN: 9 MU tiw				IFN 9 MU tiw + bevacizumab 10mg/kg i.v./2 weeks				Comparison		
Outcome	**N**	**k**	**Mean**	**SD**	**N**	**k**	**Mean**	**SD**	**Est**	**SEM**	**P**
Median PFS (months)	-	-	5.2[c]	-	-	-	8.5[d]	-	0.71	-	< 0.0001[a]
Objective response rate	-	-	-	-	-	-	-	-	-	-	≤ 0.0001
Objective response rate	-	-	13.1[e]	-	-	-	25.5[b]	-	-	-	-
GRADE 3 ANOREXIA											
Overall toxicity	-	0	8	-	-	0	17	-	-	-	-
GRADE 3 HYPERTENSION											
Overall toxicity	-	-		-	-	-	9	-	-	-	-
GRADE 3 PROTEINURIA											
Overall toxicity	-	0		-	-	0	13	-	-	-	-
GTADE 3 FATIGUE											
Overall toxicity	-	0	28	-	-	0	35	-	-	-	-

Notes

[a] *95% CI: 0.61 to 0.83*
[b] *95% CI: 20.9 to 30.6*
[c] *95% CI: 3.1 to 5.6*
[d] *95% CI: 7.5 to 9.7*
[e] *95% CI: 9.5 to 17.3*

Outcome data were from the ASCO abstract.