Phase II and Biomarker Study of the Dual MET/VEGFR2 Inhibitor Foretinib in Patients With Papillary Renal Cell Carcinoma


See accompanying editorial on page 169; listen to the podcast by Dr. Figlin at www.jco.org/podcasts

ABSTRACT

Purpose
Foretinib is an oral multikinase inhibitor targeting MET, VEGF, RON, AXL, and TIE-2 receptors. Activating mutations or amplifications in MET have been described in patients with papillary renal cell carcinoma (PRCC). We aimed to evaluate the efficacy and safety of foretinib in patients with PRCC.

Patients and Methods
Patients were enrolled onto the study in two cohorts with different dosing schedules of foretinib: cohort A, 240 mg once per day on days 1 through 5 every 14 days (intermittent arm); cohort B, 80 mg daily (daily dosing arm). Patients were stratified on the basis of MET pathway activation (germline or somatic MET mutation, MET [7q31] amplification, or gain of chromosome 7). The primary end point was overall response rate (ORR).

Results
Overall, 74 patients were enrolled, with 37 in each dosing cohort. ORR by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 was 13.5%, median progression-free survival was 9.3 months, and median overall survival was not reached. The presence of a germline MET mutation was highly predictive of a response (five of 10 versus five of 57 patients with and without germline MET mutations, respectively). The most frequent adverse events of any grade associated with foretinib were fatigue, hypertension, gastrointestinal toxicities, and nonfatal pulmonary emboli.

Conclusion
Foretinib demonstrated activity in patients with advanced PRCC with a manageable toxicity profile and a high response rate in patients with germline MET mutations.

J Clin Oncol 31:181-186. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 90% of all renal tumors and approximately 3% of all malignancies, and the incidence of RCC is increasing by a rate of approximately 2.5% each year. The majority of RCCs have clear cell histology, which is characterized by inactivation of the von Hippel-Lindau gene, leading to an overexpression of vascular endothelial growth factor (VEGF) and driving tumor angiogenesis. Papillary renal cell carcinoma (PRCC) is the most common non–clear cell RCC (ncRCC), accounting for 10% to 15% of RCCs. PRCC is a descriptive term applied to a heterogeneous group of kidney tumors characterized by the presence of papillary architecture on histopathologic evaluation. These tumors can be further characterized histologically as type I and type II PRCC. Both familial and sporadic forms of PRCC have been described, and both can have bilateral multifocal kidney lesions and the potential for metastatic disease.

The oncogenic events and critical pathways in patients with PRCC remain largely unknown. Nevertheless, PRCC has been associated with activating mutations of the MET gene, the receptor tyrosine kinase for HGF (hepatocyte growth factor). Activating mutations of MET have been identified in the
germline of patients with hereditary papillary renal cell carcinoma (HRPC), and 5% to 13% of sporadic PRCCs exhibit somatic mutations in this gene. In addition, the vast majority of sporadic PRCCs have duplication of chromosome 7, where MET is located, which might represent an alternative basis for enhanced MET signaling. Activation of the MET pathway results in a cascade of intracellular signaling leading to tumor cell growth, survival, migration, invasion, and angiogenesis.

Foretinib bisphosphate (GSK1363089A), formerly XL880, is an oral, multikinase inhibitor targeting MET, RON, AXL, TIE-2, and VEGF receptors. Foretinib potently inhibits MET and VEGFR (vascular endothelial growth factor receptor) kinases at 0.4 nmol/L and 0.8 nmol/L, respectively, and has shown antitumor activity in both human tumor xenografts and a phase I clinical trial in which three of 40 patients had a partial response (PR). In that trial, four patients with PRCC were enrolled and two demonstrated PRs of more than 48 and 12 months duration; the safety profile was acceptable, with the most common adverse events (AEs) being hypertension and increased AST. On the basis of these findings and biologic rationale, a phase II trial was undertaken in patients with PRCC. The initial cohort of patients (n = 37) received an intermittent regimen of foretinib; on completion of enrollment, and on the basis of safety data from a continuous dosing phase I study, a daily dosing cohort (n = 37) was added to evaluate the effect of continuous drug exposure on efficacy and safety.

**Patients and Methods**

**Eligibility**

Eligible patients were required to have histologically confirmed, locally advanced, bilateral multifocal, or metastatic sporadic PRCC or known HRPC; retrospective central pathology reviewed by a single pathologist (M.J.M.); no more than one prior systemic therapy; and a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Patients were also required to have adequate hematologic, hepatic, adrenal, and renal function (calculated creatinine clearance ≥ 50 mL/min by Cockcroft-Gault formula and serum creatinine ≤ 2.0 mg/dL). Patients with uncontrolled hypertension, arrhythmias, or QTc ≥ 470 ms on screening ECG were excluded. Slides (or paraffin block) of tumor tissue (archival or from a recent biopsy) were mandatory for central pathology review. The trial was approved by all relevant institutional ethics committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Each patient provided written informed consent.

**Study Design and Treatment**

This was a phase II, nonrandomized, open-label, single-stage, safety and efficacy study of foretinib in patients with PRCC. Patients were evaluated retrospectively on the basis of their MET pathway status: (1) evidence of germline MET mutation, (2) other MET pathway aberrations (somatic MET mutation, gain or duplication of chromosome 7 either in its entirety or involving the region where MET is located, and/or 7q31 amplification), or (3) no evidence of MET germline mutation or pathway aberration. Patients fasted 2 hours before and 1 hour after foretinib was administered at 240 mg orally once per day on days 1 to 5 every 14 days for cohort A or at 80 mg orally on a daily basis for cohort B. Foretinib was supplied as 20- and 100-mg capsules. Each treatment cycle consisted of 14 days. Patients completed a diary to report compliance with study drug, and foretinib treatment was stopped if a patient had disease progression at any time, had unacceptable toxicities, or withdrew consent.

**Clinical Assessment and AEs**

Preregistration assessments included a detailed medical history, physical examination, and imaging for tumor assessment. Imaging studies were obtained every 8 weeks. Efficacy was assessed by investigators using RECIST 1.0. Disease stabilization rate was defined as the percentage of patients with neither a response nor disease progression by RECIST 1.0 criteria for a minimum of 6 weeks after baseline assessment. Physical examination, ECOG performance status, vital signs, complete blood count, and a biochemical assessment were obtained on day 1 of each cycle. Urinalysis was obtained at baseline and every two cycles. ECGs were obtained at baseline and on day 1 of cycles 1 to 3, and then every two cycles.

Toxicity was assessed throughout the treatment period and before each cycle, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. If grade ≥ 3 toxicity was considered related to study treatment, therapy was reduced one dose level. Dose reductions for cohort A were dose level 1 (160 mg daily, 5 days on, 9 days off) and dose level 2 (100 mg daily, 5 days on, 9 days off). Dose reductions for cohort B were dose level 1 (60 mg daily) and dose level 2 (60 mg daily, 3 weeks on, 1 week off). Patients with treatment delays of more than 21 days were discontinued from study therapy.

**Statistical Analysis**

The primary objectives of this study were to (1) determine the investigator-assessed confirmed overall response rate (ORR) including complete response and PR by RECIST 1.0 of foretinib in two different dosing regimens and (2) evaluate the safety and tolerability of this drug in the two dosing regimens. The efficacy analysis data set included all enrolled patients who received at least one dose of study drug (safety population). Secondary efficacy variables include progression-free survival (PFS), disease stabilization (complete response, PR, or stable disease [SD] for at least 6 weeks) rate, and overall survival (OS). PFS was defined as the time from the date of first dose to the date of disease progression or death. OS was defined from the date of the first dose to the date of death. Time to events distributions and 95% CIs were estimated by the Kaplan-Meier method. Descriptive statistics were used to describe toxicity. Pharmacokinetic (PK) parameters, plasma biomarkers, and MET status were assessed for any correlation with response, PFS, or death. The study was designed to accrue at least 30 evaluable patients per cohort. Assuming type I and II error rates of 10%, there was a 94.5% chance of concluding that foretinib is effective, based on a predefined response rate of approximately 25%. All analyses were conducted by using SAS Version 8.2 (SAS Institute, Cary, NC).

**Results**

**Baseline Characteristics**

A total of 74 patients from 10 US centers were enrolled onto the study with 37 patients enrolled onto each dosing cohort. Overall, the demographic and baseline characteristics were similar in the two cohorts. Fourteen patients (18.9%) in total had one prior systemic therapy, mostly with sunitinib. The majority of patients (67.6%) were in the Memorial Sloan-Kettering Cancer Center (MSKCC) intermediate-risk category. Table I summarizes patients’ baseline characteristics.

**Central Pathology and Molecular Characteristics**

All patients enrolled onto the study had a diagnosis of PRCC based on local pathology review. Tumor tissue from 70 patients was provided for central pathology review, although only a limited amount of material was available in some instances. On the basis of central review, 67 patients had a diagnosis consistent with PRCC (n = 57) or RCC with papillary features (n = 10). Two patients were determined to have clear cell RCC, and a third had a poorly differentiated carcinoma. All responders from whom tumor tissue was available for central review had pure or dominant papillary histologies. Germline MET mutations were identified in whole blood from 11
patients. The most common germline mutation was a MET H1094R mutation, which was present in four patients. Five patients exhibited somatic mutations in their tumor but no germline mutation. Eighteen of 42 patients for whom adequate DNA was available for analysis had a gain of chromosome 7, and two patients showed amplification of MET, none of whom had a concomitant germline or somatic MET mutation.

**Efficacy**

ORR, the primary end point of the trial, was 13.5% (95% CI, 6.7% to 23.5%), and all 10 responders experienced a PR. The median duration of response was 18.5 months, and the median duration of SD was 9.7 months. The overall incidence of PR, duration of response, SD, and progressive disease (PD) was similar between the two cohorts. The disease stabilization rate was 88% (95% CI, 78% to 94%) at 6 weeks, 69% (95% CI, 57% to 79%) at 3 months, and 42% (95% CI, 31% to 54%) at 6 months. Of 68 patients with adequate tumor assessment data available, 50 experienced some reduction in the sum of the longest tumor diameters (SLD) ranging from −2% to −75% (Fig 1).

Median PFS for the 74 patients was 9.3 months (95% CI, 6.9 to 12.9 months) and was slightly higher in the intermittent dosing cohort (median PFS, 11.6 months; 95% CI, 5.8 to 17.0 months) compared with the continuous dosing cohort (median PFS, 9.1 months; 95% CI, 5.78 to 10.91 months; Fig 2). The 6-month PFS rate was approximately 65% in the overall population as well as in the individual dosing cohorts. Figure 2 shows the PFS distributions.

Twenty-one patients (28.4%) had died as of the end of the protocol-mandated 6-month post-treatment follow-up period, and two patients remained on therapy at the time of this analysis. The median OS was not reached in the overall cohort or in either of the two dosing cohorts. The 1-year survival was 70% overall (64% in the intermittent and 76% in the daily dosing cohort).

**PK Results**

Plasma concentrations reached steady-state by the second cycle of therapy in the intermittent dosing cohort and by day 8 in the daily dosing cohort with no evidence of time-dependent PK. In addition, there were five PRs in the daily dosing cohort and five PRs in the intermittent dosing cohort; foretinib concentrations did not appear to be predictive of response.

**Correlation of MET Status With Clinical Outcome**

Sixty-seven patients were evaluable for both mutation status and response. The presence of a germline MET mutation was highly predictive of a response. Among patients with a germline MET mutation,
five (50%) of 10 experienced a PR, and the remaining five patients (50%) with MET germline mutation had SD as their best response, including four patients who demonstrated tumor SLD reductions of more than 10% but did not achieve PR by RECIST 1.0. In contrast, responses were seen in only five (9%) of 57 patients without germline MET mutation. Other measures of MET pathway activation did not appear to correlate with activity. Only one (20%) of five patients with somatic MET mutation had a PR; in the absence of a concomitant MET mutation, no responses were seen in patients with MET amplification (n = 2), and only one (5%) of 18 patients with a gain of chromosome 7 experienced a PR.

### Safety and Tolerability

Six patients died while on treatment or within 30 days of the last dose of foretinib. One event of ventricular fibrillation in the setting of PD and acidosis 16 days after stopping study medication due to PD was considered by the investigator to be possibly related to foretinib. In addition, three patients died from PD, one from sepsis, and one from CNS hemorrhage, none of which were considered to be related to study medication. Table 2 summarizes the most common all-grade and high-grade AEs thought to be possibly or probably related to foretinib. Hypertension, diarrhea, and fatigue were the most common toxicities, with grade 3 hypertension seen in 51% of patients. In the vast majority of these patients, hypertension was manageable with antihypertensives and foretinib dose interruption/reduction. Eight patients had a total of nine events of pulmonary emboli. None of these events were fatal, but one patient discontinued study drug as a result of these events, and three patients were diagnosed with pulmonary emboli at the time of disease progression. Night blindness was reported in eight patients. In one patient, grade 3 night blindness followed a prior event of retinal vein occlusion and was associated with marginal loss of visual acuity leading to study drug discontinuation. The remaining ocular events were all grade 1 to 2 with no loss of visual acuity. The median relative dose intensity was 98% in the intermittent dosing arm and 87% in the continuous dosing arm. A total of 20 AEs in 18 patients (24.3%) led to drug discontinuation. These AEs included proteinuria (four patients), increased lipase (two patients), and the following in one patient each: left ventricular dysfunction, visual impairment (this was the patient with retinal vein occlusion), colitis, vomiting, sepsis, increased ALT, prolonged QT interval, hypalbuminemia, hypophosphatemia, cerebral hemorrhage, confusional state, bronchospasm, pulmonary embolism (PE), and hypertension. Forty-six percent of patients underwent a dose reduction at some point during study, and 49% had a dose interruption.

### DISCUSSION

Foretinib demonstrated activity in this phase II study of patients with PRCC. Although the ORR of 13.5% did not meet the 25% predefined response rate for efficacy, a PFS of 9.3 months compares favorably with the experience from VEGFR tyrosine kinase inhibitors and mTOR inhibitors. Retrospective and expanded access studies showed ORRs of 3% to 11% and PFS ranging between 6 and 11 months with sunitinib and sorafenib. More recently, phase II studies conducted in patients with papillary histology showed mixed results. In a phase II study of sunitinib in patients with nccRCC, no responses were observed in the 27 patients with poor or intermediate risk PRCC, and the median PFS in these patients was 1.6 months. A French study of sunitinib in PRCC enrolled 61 patients, with an ORR of 12% and a median PFS of approximately 6 months. In a phase II study of sunitinib in patients with nccRCC, no responses were seen among the eight patients with PRCC, and median PFS was 5.6 months. Within the last 2 years, Lee et al reported on a phase II study of sunitinib in nccRCC (n = 31; PRCC, n = 22) conducted in Korea, in which ORR was 36%, and median time to progression was 6.4 months. A subgroup analysis of patients with poor-risk PRCC in a phase III trial of the mTOR inhibitor temsirolimus (n = 25) showed a median PFS of 3.8 months and an ORR of 5.4%.

Taken together, the data suggest modest activity for current VEGFR- and mTOR-targeted agents in PRCC. Not surprisingly, the

### Table 2. Overall and Grade 3 to 4 Treatment-Related Adverse Events Experienced by at Least 20% of Patients in Either Cohort (safety population)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Overall (N = 74)</th>
<th>Cohort A (n = 37)</th>
<th>Cohort B (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 to 4</td>
<td>All Grades</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27</td>
<td>73</td>
<td>13</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28</td>
<td>76</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>46</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>65</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>8</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>6</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>8</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>8</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>9</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>8</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Increased blood creatinine</td>
<td>8</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

© 2012 by American Society of Clinical Oncology

Journal of Clinical Oncology
National Comprehensive Cancer Network guidelines for kidney cancer list “clinical trial” as the preferred option in patients with advanced nccRCC.

This study is the largest multicenter trial in PRCC to date, has a similar prognostic risk group distribution compared with those of prior studies in advanced RCC, has central pathology review, and the PFS compares favorably with that reported in other prospective phase II studies. Furthermore, the activity in patients with germline MET mutation is notable, although other molecular markers of the MET pathway, available from a limited number of patients, did not appear to predict for clinical activity. Plasma PD results indicating a correlation between increased HGF levels and an increased risk of death and increased VEGF levels with improved OS (Appendix, online only) need to be further explored in future studies.

The toxicities encountered were similar to what is known for the anti-VEGFR class of agents with significant rates of hypertension, notably in the daily dosing arm, although the intermittent arm had more gastrointestinal toxicities. Another important AE was PE, observed in 11% of patients. None of these events was fatal, and a substantial proportion of patients continued study drug treatment with anticoagulation. To date, 368 patients have been treated with foretinib across a range of clinical studies. Seventeen patients have experienced PEs; none were fatal. The overall incidence across trials is 4.6% (GlaxoSmithKline, Collegeville, PA; data on file). In two previous phase I studies, a daily oral regimen and an intermittent oral schedule, one nonfatal PE was seen in each study in a total of 40 and 37 patients. This did not, at the time, lead to any specific concerns. However, patients with prior venous thromboembolic events should probably not be considered for foretinib treatment. Increased venous thromboembolism has been described with VEGFR inhibitors, and a large meta-analysis of the anti-VEGF monoclonal antibody bevacizumab revealed high-grade venous thromboembolism in 6.3% of patients.

A recent meta-analysis of sunitinib and sorafenib showed a 3.2% risk of venous thromboembolism. The majority of PEs were not symptomatic, and several were discovered in the context of disease progression. The rates of Common Toxicity Criteria (version 3) grade 3 to 4 thromboembolism were 9.6%, 1.2%, and 3.8%, with bevacizumab, sunitinib, and sorafenib, respectively.

Although the PFS seen with this agent is promising, the primary end point (ORR 25%) was not met. We envision pursuing foretinib in PRCC associated with germline MET mutations. However, this is a rare entity and, despite the high response rates observed, a meaningful evaluation of foretinib in this subpopulation will require a concerted global effort and commitment. However, data from this trial provide the impetus for exploring MET inhibitors alone or in combination in PRCC.

In conclusion, although the primary end point of the study was not met in the overall PRCC population, other clinical end points such as PFS and a decrease in tumor SLD make the activity of foretinib noteworthy, especially in the subgroup of patients with germline MET mutations.

**Authors’ Disclosures of Potential Conflicts of Interest**

Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:**
- Laurel M. Adams, GlaxoSmithKline (C); Lone H. Ottesen, GlaxoSmithKline (C); Kevin H. Laubscher, GlaxoSmithKline (C)

**Consultant or Advisory Role:**
- Toni K. Choueiri, Bayer Pharmaceuticals (C), Genentech (C), GlaxoSmithKline (C), Novartis (C), Pfizer (C); Ulka Vaishampayan, GlaxoSmithKline (C); Jonathan E. Rosenberg, Abbott Laboratories (C), Genentech (C), GlaxoSmithKline (C), Novartis (C); Theodore F. Logan, Argos Therapeutics (C), Bristol-Myers Squibb (C), Celgene (C), Genentech (C), GlaxoSmithKline (C), Novartis (C), Pfizer (C), Prometheus Laboratories (C), Wyeth (C); Ronald M. Bukowski, Argos Therapeutics (C), Bristol-Myers Squibb (C), GlaxoSmithKline (C), Novartis (C), Pfizer (C); Brian I. Rini, GlaxoSmithKline (C), Pfizer (C); Brian I. Rini, GlaxoSmithKline (C), Pfizer (C); Brian I. Rini, GlaxoSmithKline (C); David F. McDermott, Bristol-Myers Squibb (C), GlaxoSmithKline (C), Pfizer (C), Prometheus Laboratories (C), Roche (C); Naomi B. Haas, Novartis (C); Keith T. Flaherty, GlaxoSmithKline (C)

**Stock Ownership:**
- Laurel M. Adams, GlaxoSmithKline; Lone H. Ottesen, GlaxoSmithKline; Kevin H. Laubscher, GlaxoSmithKline

**Honoraria:**
- Ulka Vaishampayan, GlaxoSmithKline; Theodore F. Logan, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Pfizer, Prometheus Laboratories, Wyeth; Ronald M. Bukowski, GlaxoSmithKline, Novartis; Pfizer

**Research Funding:**
- Toni K. Choueiri, Pfizer; Theodore F. Logan, Abbott Laboratories, AstraZeneca, BioVex, Bristol-Myers Squibb, Celgene, Chiron, Eli Lilly, Entremed, Exelixis, GlaxoSmithKline, immunetics biotechnologies, MedImmune, Novartis, Pfizer, Roche, Schering-Plough, Synta Pharmaceuticals, Wyeth; Brian I. Rini, GlaxoSmithKline; David F. McDermott, Prometheus Laboratories; Naomi B. Haas, GlaxoSmithKline, Novartis; Peter Eisenberg, GlaxoSmithKline

**Expert Testimony:**
- Ronald M. Bukowski, Novartis (C), Pfizer (C)

**Other Remuneration:**
- None

**AUTHOR CONTRIBUTIONS**

Conception and design: Toni K. Choueiri, W. Marston Linehan, Ramprasad Srinivasan

Financial support: Peter Eisenberg

Administrative support: Toni K. Choueiri

 Provision of study materials or patients: Toni K. Choueiri, Ulka Vaishampayan, Jonathan E. Rosenberg, Ronald M. Bukowski, Brian I. Rini, W. Marston Linehan, Ramprasad Srinivasan


Manuscript writing: All authors

Final approval of manuscript: All authors
HGF (hepatocyte growth factor): HGF is a growth factor with strong mitogenic activity on hepatocytes and primary epithelial cells through its interaction with its receptor (c-met); HGF has multifunctional activities that regulate cell growth and motility.

MET: The receptor for hepatocyte growth factor receptor, MET is a transmembrane receptor tyrosine kinase. The primary single chain precursor protein is post-translationally cleaved to produce the alpha and beta subunits; the mature receptor is composed of these subunits linked via disulfide bonds. Various mutations in the MET gene have been associated with papillary renal carcinoma.

VEGFR (vascular endothelial growth factor receptor): VEGFRs are transmembrane tyrosine kinase receptors to which the VEGF ligand binds. VEGFR-1 (also called Flt-1) and VEGFR-2 (also called KDR/Flk-1 [murine homologue]) are expressed on endothelial cells, while VEGFR-3 (also called Flt-4) is expressed on cells of the lymphatic and vascular endothelium.

Glossary Terms

Angiogenesis: The process involved in the generation of new blood vessels. While this is a normal process that naturally occurs and is controlled by “on” and “off” switches, blocking tumor angiogenesis (antiangiogenesis) disrupts the blood supply to tumors, thereby preventing tumor growth.