Clinical Cancer Research

Approval Summary: Sunitinib for the Treatment of Imatinib Refractory or Intolerant Gastrointestinal Stromal Tumors and Advanced Renal Cell Carcinoma

Vicki L. Goodman, Edwin P. Rock, Ramzi Dagher, et al.

Updated version	Access the most recent version of this article at: http://clincancerres.aacrjournals.org/content/13/5/1367

Cited Articles	This article cites by 15 articles, 6 of which you can access for free at: http://clincancerres.aacrjournals.org/content/13/5/1367.full.html#ref-list-1
Citing articles	This article has been cited by 52 HighWire-hosted articles. Access the articles at: http://clincancerres.aacrjournals.org/content/13/5/1367.full.html#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.

Approval Summary: Sunitinib for the Treatment of Imatinib Refractory or Intolerant Gastrointestinal Stromal Tumors and Advanced Renal Cell Carcinoma

Vicki L. Goodman,[1] Edwin P. Rock,[1] Ramzi Dagher,[1] Roshni P. Ramchandani,[2] Sophia Abraham,[2] Jogarao V.S. Gobburu,[2] Brian P. Booth,[2] S. Leigh Verbois,[1] David E. Morse,[1] Cheng Yi Liang,[3] Nallaperumal Chidambaram,[3] Janet X. Jiang,[4] Shenghui Tang,[4] Kooros Mahjoob,[4] Robert Justice,[1] and Richard Pazdur[5]

Abstract

Purpose: To describe the Food and Drug Administration (FDA) review and approval of sunitinib malate (Sutent). Sunitinib received regular approval for the treatment of gastrointestinal stromal tumor (GIST) after disease progression or intolerance to imatinib mesylate (Gleevec). Additionally, sunitinib received accelerated approval for the treatment of advanced renal cell carcinoma.

Experimental Design: For the GIST indication, FDA reviewed data from a randomized, placebo-controlled trial with supportive evidence from a single-arm study. For the advanced renal cell carcinoma indication, FDA reviewed data from two single-arm studies of patients with cytokine-refractory metastatic renal cell carcinoma.

Results: In patients with imatinib refractory or intolerant GIST, time-to-tumor progression of sunitinib-treated patients was superior to that of placebo-treated patients. Median time-to-tumor progression of sunitinib-treated patients was 27.3 weeks, compared with 6.4 weeks for placebo-treated patients ($P < 0.0001$). Partial responses were observed in 6.8% of sunitinib-treated patients. In patients with metastatic renal cell carcinoma, partial responses were observed in 25.5% (95% confidence interval, 17.5, 34.9) and 36.5% (95% confidence interval, 24.7, 49.6) of patients treated with sunitinib. Median response durations were 27.1 and 54 weeks. The most common adverse events attributed to sunitinib included diarrhea, mucositis, skin abnormalities, and altered taste. Reductions in left ventricular ejection fraction and severe hypertension were also more common in sunitinib-treated patients.

Conclusions: On January 26, 2006, the FDA approved sunitinib for the treatment of patients with imatinib refractory or intolerant GIST. Accelerated approval was granted for the treatment of advanced renal cell carcinoma.

Gastrointestinal stromal tumors (GIST) are mesenchymal tumors of the digestive tract (1). The annual incidence in the United States is estimated at 3,800 (2). Five-year survival ranges from 35% to 65% depending on tumor size, mitotic index, and location (3). Historically, treatment options were limited for patients with malignant GIST because cytotoxic chemotherapy and radiation generated low response rates (<5%) and a significant burden of toxicity.

Advances in the treatment of GIST followed recognition that these tumors express the cell-surface transmembrane receptor tyrosine kinase KIT, which is the protein product of the *KIT* proto-oncogene. Constitutive activation of KIT in GISTs leads to uncontrolled cell proliferation and resistance to apoptosis (4). Imatinib mesylate (Gleevec, Novartis Pharmaceuticals Corp., East Hanover, NJ) targets the KIT receptor tyrosine kinase. Imatinib received accelerated approval on February 1, 2002 for the treatment of patients with Kit (CD117)–positive unresectable and/or metastatic malignant GISTs based on the response rate observed in an open-label, multinational study (5, 6). Imatinib has also been reported to prolong progression-free survival in GIST (7).

For patients with GIST who developed disease progression during imatinib treatment or who were intolerant of imatinib, no standard therapy was available. Thus, new therapeutic options in this population are needed.

Metastatic renal cell carcinoma is responsible for ∼12,000 deaths per year in the United States (8). Carcinomas of clear cell histology account for ∼85% of all renal cell carcinoma

cases. Loss of function of the tumor suppressor von Hippel-Lindau in clear cell carcinoma leads to an accumulation of hypoxia-inducible factor and subsequent overexpression of vascular endothelial growth factor and platelet-derived growth factor (9).

Standard therapy for advanced renal cell carcinoma includes IFN-α and interleukin 2 (IL-2), either alone or in combination. Although it is not approved by the Food and Drug Administration for this indication, IFN-α is commonly used for renal cell carcinoma. The objective response rate for patients treated with IFN-α is reported to be 10% to 15% (10, 11). Patients with nonbulky pulmonary and soft tissue metastases and good performance status are most likely to respond. Whereas durable complete responses are rare, IFN-α has been associated with a modest survival benefit in one report (10). Reported toxicities include influenza-like symptoms, fever, weight loss, loss of appetite, altered taste, depression, anemia, leukopenia, nausea, fatigue, and elevated liver function tests (12).

High-dose IL-2 (600,000 IU/kg i.v. every 8 h for 14 doses, repeated once after a 9-day rest) is approved in the United States for metastatic renal cell carcinoma and has an overall response rate of 15% with a complete response rate of 7% (13). Although IL-2 has been associated with durable remissions in a minority of patients, its use is associated with severe toxicities including a capillary leak syndrome, which limits its use to the healthiest patients. Combinations of IL-2 and IFN-α have been used in metastatic renal cell carcinoma as well. Whereas the response rate and the 1-year event-free survival were higher for the combination, there was no significant difference in overall survival, and toxicity was additive (14, 15).

After failure of cytokine therapy, treatment options in metastatic renal cell carcinoma have been limited. One crossover study assessed response rates to IFN-α and IL-2 in patients who had failed to respond to the other cytokine; <5% of patients responded (16). Overall survival in previously treated metastatic renal cell carcinoma is ∼12 months (17).

In December 2005, the Food and Drug Administration approved sorafenib tosylate (Nexavar, Bayer HealthCare AG, West Haven, CT and Onyx Pharmaceuticals, Inc., Emeryville, CA), a receptor tyrosine kinase inhibitor, for the treatment of patients with advanced renal cell carcinoma (18). Approval was based on a randomized trial evaluating progression-free survival in patients receiving sorafenib compared with those receiving placebo. Most patients had received prior cytokine therapy. Treatment with sorafenib improved progression-free survival compared with placebo [median, 167 versus 84 days (hazard ratio, 0.44; log-rank P < 0.000001)]. The partial response rates for patients receiving sorafenib and placebo were 2% and 0%, respectively.

Sunitinib malate (Sutent, Pfizer, Inc., New York, NY) is a small-molecule inhibitor of multiple tyrosine kinases, including vascular endothelial growth factor receptors 1, 2, and 3; stem cell factor receptor (KIT); platelet-derived growth factor receptors α and β; Fms-like tyrosine kinase 3; colony stimulating factor receptor type 1 receptor; and the glial cell line–derived neurotrophic factor receptor (RET).

Sunitinib inhibition of the activity of these receptor tyrosine kinases has been shown in both cell-free and cell-based assays, and inhibition of function has been shown in cell proliferation assays. The primary metabolite exhibits similar potency compared with sunitinib in these assays.

At plasma concentrations of 50 to 100 ng/mL, sunitinib inhibited the phosphorylation of multiple receptor tyrosine kinases in tumor xenografts and showed inhibition of tumor growth, inhibition of metastases, or tumor regression in some experimental models of cancer. Sunitinib showed the ability to inhibit growth of tumor cells expressing dysregulated target receptor tyrosine kinases in vitro and to inhibit platelet-derived growth factor receptor β– and vascular endothelial growth factor receptor 2–dependent tumor angiogenesis in vivo.

The maximum tolerated dose for sunitinib is 50 mg given daily for 4 weeks followed by a 2-week rest period (schedule 4/2). At this dose level, systemic concentrations of sunitinib were >50 ng/mL, the level at which inhibition of receptor tyrosine kinases were seen in vitro. No minimally effective dose has been established for sunitinib.

This report describes the approval of sunitinib for two indications: for the treatment of GIST after progression or intolerance to imatinib mesylate and for the treatment of advanced renal cell carcinoma. The clinical trials described were conducted with appropriate ethical standards, including informed consent of all subjects and protocol review by institutional review boards.

Chemistry. Sunitinib malate is described chemically as butanedioic acid, hydroxy-, (2S)-, compound with N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidine)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (1:1). The molecular formula is $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$ and the molecular weight is 532.6 daltons. Sunitinib malate is a yellow to orange powder with a pK_a of 8.95.

Toxicology. In rats and monkeys, major target organs of sunitinib toxicity include the hematopoietic organs (thymus, marrow, spleen, lymph nodes, and bone marrow), liver, gastrointestinal tract, exocrine and secretory glands (pancreas, adrenals, and salivary), skeletal, and female reproductive organs (ovaries and uterus).

Sunitinib did not cause genetic damage when tested in multiple in vitro assays [bacterial mutation (Ames assay) and human lymphocyte chromosome aberration] and an in vivo rat bone marrow micronucleus test. Because the drug is intended for use in the treatment of advanced cancers, carcinogenicity studies have not been done.

Clinical pharmacology. Following oral administration, sunitinib is absorbed from the gastrointestinal tract, with maximum plasma concentrations observed between 6 and 12 h after dosing. Sunitinib may be taken with or without food as pharmacokinetics were not affected by food intake.

Binding of sunitinib and its primary metabolite to human plasma protein in vitro were 95% and 90%, respectively, with no concentration dependence in the range of 100 to 4,000 ng/mL. The apparent volume of distribution (Vd/F) for sunitinib was 2,230 liters. In the dose range of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increased proportionately with dose.

Sunitinib is metabolized primarily by the cytochrome P450 enzyme CYP3A4 to produce its primary active metabolite, which is further metabolized by CYP3A4. The active metabolite has an exposure that is between 23% and 37% of the total exposure. In a human mass balance study of ^{14}C-labeled sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose. Total oral clearance (CL/F) ranged from 34 to 62 L/h with an

interpatient variability of 40%. The terminal half-lives of sunitinib and its active metabolite are ~40 to 60 h and 80 to 110 h, respectively. Steady-state conditions of sunitinib and its active metabolite are reached in ~2 weeks.

Age, body weight, creatinine clearance, race, gender, or Eastern Cooperative Oncology Group status had no effect on the pharmacokinetics of sunitinib or the active metabolite. No clinical studies have been conducted in patients with impaired hepatic function.

Drug-drug interactions. Concurrent administration of sunitinib with the CYP3A4 inhibitor ketoconazole resulted in a 51% increase in the combined AUC of sunitinib and its active metabolite following a single dose of sunitinib in healthy volunteers. Coadministration of sunitinib and strong CYP3A4 inhibitors should be avoided to prevent an increased risk of toxicity due to increased drug exposure. If sunitinib must be coadministered with a strong CYP3A4 inhibitor, a dose reduction to 37.5 mg would result in exposures comparable to those following the recommended dose when given alone.

Concurrent administration of sunitinib with the CYP3A4 inducer rifampin resulted in a 46% reduction in the combined AUC of sunitinib and its active metabolite following a single dose of sunitinib in healthy volunteers. Coadministration of sunitinib and CYP3A4 inducers should be avoided as it may result in sunitinib levels that are subtherapeutic. If sunitinib must be coadministered with a CYP3A4 inducer, the dose of sunitinib may be titrated to a maximum of 87.5 mg with careful monitoring for toxicity.

Clinical Trials

GIST. The basis of approval was an international, randomized, double-blind, placebo-controlled trial of sunitinib in patients with GIST who had disease progression during prior imatinib mesylate treatment or who were intolerant of imatinib. The primary objective was to evaluate time-to-tumor progression as assessed by a third-party imaging laboratory in patients receiving sunitinib compared with patients receiving placebo; all patients received best supportive care. Secondary objectives included comparisons of progression-free survival, objective response rate, and overall survival. Patients were randomized (2:1) to receive either 50-mg sunitinib or placebo orally, once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (schedule 4/2).

Radiographic assessments were done every 6 weeks and disease response was characterized using the Response Evaluation Criteria in Solid Tumors criteria (19). Treatment was unblinded at the time of disease progression. Patients randomized to placebo were then offered crossover to open-label sunitinib, and patients randomized to sunitinib were permitted to continue treatment per investigator judgment.

The intent-to-treat population included 312 patients. Two hundred seven patients were randomized to the sunitinib arm and 105 patients were randomized to the placebo arm. Baseline age, gender, race, and Eastern Cooperative Oncology Group performance status, as well as prior exposure to imatinib, were comparable between the two groups. Demographics and patient characteristics are shown in Table 1.

At the time of the prespecified interim analysis, there was a statistically significant advantage for sunitinib over placebo in both time-to-tumor progression and progression-free survival.

Overall survival data were not mature. Efficacy results are summarized in Table 2 and Fig. 1.

Supporting data were provided by an open-label, multicenter, single-arm study conducted in patients with GIST following progression or intolerance to imatinib. Fifty-five patients in this study received the 50-mg dose of sunitinib on treatment schedule 4/2. Partial responses were observed in 5 of 55 patients [9.1%; 95% confidence interval (95% CI), 3.0-20.0%].

Renal cell carcinoma. Two single-arm multicenter studies (studies 1 and 2) enrolled 106 and 63 patients, respectively. All patients enrolled into these studies experienced failure of prior cytokine-based therapy. In study 1, failure of prior cytokine therapy was based on radiographic evidence of disease progression defined by Response Evaluation Criteria in Solid Tumors or WHO criteria during or within 9 months of completion of one cytokine therapy treatment. In study 2, failure of prior cytokine therapy was defined as disease progression or unacceptable treatment-related toxicity.

The baseline age, gender, race, and Eastern Cooperative Oncology Group performance status of the patients were comparable between studies 1 and 2. Ninety-four percent of patients on study 1 and 86% of patients on study 2 were white. Men comprised 65% of the pooled population. The median age was 57 years and ranged from 24 to 87 years. All patients had an Eastern Cooperative Oncology Group performance status <2 at the screening visit.

Baseline malignancy and prior treatment history of the patients were comparable between studies 1 and 2. Across the two studies, 95% of the pooled population of patients had at least some component of clear cell histology. All patients in study 1 were required to have a histologic clear cell component. Ninety-seven percent of the pooled population had undergone nephrectomy. All patients had received one previous cytokine regimen; across the two studies, 49% received IFN-α, 41% received IL-2, and 10% received a combination of these.

Table 1. Baseline demographics for the GIST randomized study

|	Sunitinib (*N* = 207)	Placebo (*N* = 105)
Gender [*n* (%)]		
Male	132 (64)	64 (61)
Female	75 (36)	41 (39)
Race [*n* (%)]		
White	183 (88)	92 (88)
Asian	10 (5)	5 (5)
Black	8 (4)	4 (4)
Not reported	6 (3)	4 (4)
Age group		
[Median, y (range)]	58 (23-84)	55 (23-81)
<65 y [*n* (%)]	143 (69)	76 (72)
≥65 y [*n* (%)]	64 (31)	29 (28)
Performance status [*n* (%)]		
0	92 (44)	48 (46)
1	113 (55)	55 (52)
2	2 (1)	2 (2)
Prior treatment [*n* (%)]		
Surgery (other than biopsy)	194 (94)	98 (93)
Radiotherapy	16 (8)	16 (15)
Imatinib outcome [*n* (%)]		
Intolerance	9 (4)	4 (4)
Progression within 6 mo	36 (17)	17 (16)
Progression beyond 6 mo	162 (78)	84 (80)
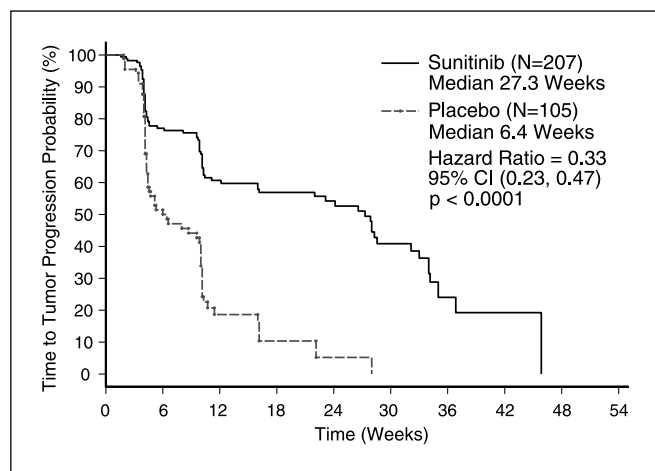
Fig. 1. Kaplan-Meier curve of time-to-tumor progression in the GIST randomized study.

Metastatic disease present at the time of study entry included lung metastases in 81% of patients, bone metastases in 25% to 51%, and liver metastases in 16% to 27%. Fifty-two percent of patients in the pooled population had at least three metastatic sites. Patients with known brain metastases or leptomeningeal disease were excluded from both studies.

Patients received 50 mg of sunitinib daily on the same 4/2 schedule as the GIST study.

The primary end point for both studies was objective response rate, as assessed by a core imaging laboratory for study 1 and as assessed by the investigators for study 2. Duration of response was also evaluated.

The efficacy results of both renal cell carcinoma studies are summarized in Table 3. All responses were partial responses. The majority (>90%) of objective disease responses were observed during the first four cycles; the latest reported response was observed in cycle 10. Duration of response data from study 1 is premature as only 4 of 27 (15%) patients responding to treatment had experienced disease progression.

Safety

Adverse events in the GIST randomized study. Median duration of blinded study treatment was 2 cycles (mean 3.0; range, 1-9) for patients on sunitinib and 1 cycle (mean, 1.8; range, 1-6) for patients on placebo. Dose reductions occurred in

23 (11%) patients on sunitinib and none on placebo. The percentage of patients requiring dose interruptions or drug discontinuation due to adverse events was similar in patients treated with sunitinib compared with those treated with placebo.

Table 4 compares the incidence of common (>10%) treatment-emergent adverse events for patients receiving sunitinib versus those on placebo. Most treatment-emergent adverse events in both study arms were grade 1 or 2 in severity. Diarrhea, mucositis, hypertension, asthenia, skin abnormalities, and altered taste were more common in patients receiving sunitinib. Grade 3 or 4 treatment-emergent adverse events were reported in 56% versus 51% of patients on sunitinib versus placebo, respectively.

Table 5 compares the incidence of treatment-emergent laboratory abnormalities.

Myelosuppression of all grades and grade 3/4 was more common on the sunitinib arm as were electrolyte disturbances. Acquired hypothyroidism was noted in 8 (4%) patients on sunitinib versus 1 (1%) on placebo.

Adverse events in the pooled metastatic renal cell carcinoma population. The adverse event profile in the metastatic renal cell carcinoma studies was similar to that in GIST. Notable differences included a higher incidence of fatigue (74%), mucositis/stomatitis (53%), hypertension (28%), rash (38%), and dyspnea (28%).

Safety Issues Across Populations

Left ventricular dysfunction. Following the development of congestive heart failure in several patients previously treated with anthracyclines who received sunitinib in an early clinical trial, left ventricular ejection fraction was monitored throughout the clinical development program. Eligibility criteria were revised to exclude patients with abnormal ejection fraction, as assessed by multigated acquisition scan, and to exclude patients who presented with cardiac events within the prior 12 months. Left ventricular ejection fraction was monitored at the end of each cycle or every other cycle during the GIST and renal cell carcinoma trials.

Decreases in left ventricular ejection fraction to below the lower limit of normal were seen in 10% of patients receiving sunitinib and in 3% of patients receiving placebo on the GIST randomized trial. Grade 3 decreases in left ventricular ejection fraction were seen in 1.5% of sunitinib-treated patients and in none of placebo-treated patients. Whereas ~40% of patients with decreases in left ventricular ejection fraction to <50% had spontaneous recovery of ventricular function, 23% required

Table 2. GIST efficacy results (interim analysis)

Efficacy parameter	Sunitinib (*n* = 207)	Placebo (*n* = 105)	*P* (log–rank test)	HR (95% CI)
Time-to-tumor progression* [median, wk (95% CI)]	27.3 (16.0-32.1)	6.4 (4.4-10.0)	<0.0001[†]	0.33 (0.23-0.47)
Progression-free survival[‡] [median, wk (95% CI)]	24.1 (11.1-28.3)	6.0 (4.4-9.9)	<0.0001[†]	0.33 (0.24-0.47)
Objective response rate, PR [% (95% CI)]	6.8 (3.7-11.1)	0	0.006[§]	

Abbreviations: HR, hazard ratio; PR, partial response.
*Time from randomization to progression; deaths before documented progression were censored at time of last radiographic evaluation.
[†]A comparison is considered statistically significant if *P* < 0.0042 (O'Brien Fleming stopping boundary).
[‡]Time from randomization to progression or death due to any cause.
[§]Pearson χ^2 test.

Table 3. Metastatic renal cell carcinoma efficacy results

Efficacy parameter	Study 1 (N = 106)	Study 2 (N = 63)
Objective response rate, PR [% (95% CI)]	25.5* (17.5-34.9)	36.5[†] (24.7-49.6)
Duration of response [median, wk (95% CI)]	27.1 (24.4[‡])	54 (34.3-70.1)

*Assessed by blinded core radiology laboratory.
[†]Assessed by investigators.
[‡]Data not mature enough to determine upper confidence limit.

dose reductions and/or addition of cardiac medications such as antihypertensive agents and diuretics. Approximately 25% had no further on-study left ventricular ejection fraction evaluations. There is no clear relationship between changes in left ventricular ejection fraction and development of treatment-emergent hypertension.

Patients with cardiac risk factors should be carefully monitored for clinical signs and symptoms of congestive heart failure while receiving sunitinib. Baseline and periodic evaluations of left ventricular ejection fraction should also be considered while the patient is receiving sunitinib. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

In the presence of clinical manifestations of congestive heart failure, discontinuation of sunitinib is recommended. The dose of sunitinib should be interrupted and/or reduced in patients without clinical evidence of congestive heart failure but with an ejection fraction <50% and >20% below baseline.

Hypertension. Hypertension of all grades was more commonly reported in patients receiving sunitinib than in those receiving placebo. Severe hypertension (>200 mm Hg systolic or 110 mm Hg diastolic) occurred in 4% to 6% of patients receiving sunitinib and in 1% of patients receiving placebo. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of sunitinib is recommended until hypertension is controlled.

Table 4. Treatment-emergent adverse events reported in at least 10% of GIST patients who received sunitinib or placebo

Adverse event [n (%)]	Sunitinib (n = 202)		Placebo (n = 102)	
	All grades	Grade 3/4*	All grades	Grade 3/4[†]
Any		114 (56)		52 (51)
Constitutional				
Fatigue	84 (42)	17 (8)	48 (47)	8 (8)
Fever	36 (18)	3 (2)	17 (17)	1 (1)
Gastrointestinal				
Diarrhea	81 (40)	9 (4)	27 (27)	0 (0)
Nausea	63 (31)	3 (2)	33 (32)	5 (5)
Mucositis/stomatitis	58 (29)	2 (1)	18 (18)	2 (2)
Vomiting	49 (24)	4 (2)	24 (24)	3 (3)
Constipation	41 (20)	0 (0)	14 (14)	2 (2)
Abdominal pain[‡]	67 (33)	22 (11)	39 (38)	12 (12)
Cardiac				
Hypertension	31 (15)	9 (4)	11 (11)	0 (0)
Dermatology				
Rash	28 (14)	2 (1)	9 (9)	0 (0)
Skin Discoloration	61 (30)	0 (0)	23 (23)	0 (0)
Hand-foot syndrome	28 (14)	9 (4)	10 (10)	3 (3)
Neurology				
Altered taste	42 (21)	0 (0)	12 (12)	0 (0)
Headache	26 (13)	3 (2)	23 (23)	0 (0)
Musculoskeletal				
Arthralgia	24 (12)	2 (1)	16 (16)	0 (0)
Back pain	23 (11)	2 (1)	16 (16)	4 (4)
Myalgia/limb pain	28 (14)	1 (1)	9 (9)	1 (1)
Respiratory				
Dyspnea	20 (10)	0 (0)	19 (19)	3 (3)
Cough	17 (8)	0 (0)	13 (13)	0 (0)
Metabolism/nutrition				
Anorexia[§]	67 (33)	1 (1)	30 (29)	5 (5)
Asthenia	45 (22)	10 (5)	11 (11)	3 (3)
Hemorrhage/bleeding				
Bleeding, all sites	37 (18)	14 (7)	17 (17)	9 (9)

NOTE: Common Toxicity Criteria for Adverse Events, version 3.0.
*Grade 4 adverse events in patient on Sutent included abdominal pain (2%) and bleeding (2%).
[†]Grade 4 adverse events in patients on placebo included fatigue (3%), mucositis (1%), vomiting (1%), abdominal pain (3%), back pain (1%), and bone pain (1%).
[‡]Includes abdominal quadrant, gastric, hypochondrial, abdominal, flank, and cancer-related pain.
[§]Includes decreased appetite.

Table 5. Treatment-emergent laboratory abnormalities (≥10%) in the GIST randomized study

Adverse event [n (%)]	Sunitinib (n = 202)		Placebo (n = 102)	
	All grades	Grade 3/4*	All grades	Grade 3/4[†]
Any		68 (34)		22 (22)
Gastrointestinal				
AST/ALT	78 (39)	3 (2)	23 (23)	1 (1)
Alkaline phosphatase	48 (24)	7 (4)	21 (21)	4 (4)
Total Bilirubin	32 (16)	2 (1)	8 (8)	0 (0)
Indirect Bilirubin	20 (10)	0 (0)	4 (4)	0 (0)
Amylase	35 (17)	10 (5)	12 (12)	3 (3)
Lipase	50 (25)	20 (10)	17 (17)	7 (7)
Cardiac				
Decreased LVEF	21 (10)	2 (1)	3 (3)	0 (0)
Renal/metabolic				
Creatinine	25 (12)	1 (1)	7 (7)	0 (0)
Hypokalemia	24 (12)	1 (1)	4 (4)	0 (0)
Hypernatremia	20 (10)	0 (0)	4 (4)	1 (1)
Uric acid	31 (15)	16 (8)	16 (16)	8 (8)
Hematology				
Neutropenia	107 (53)	20 (10)	4 (4)	0 (0)
Lymphopenia	76 (38)	0 (0)	16 (16)	0 (0)
Anemia	52 (26)	6 (3)	22 (22)	2 (2)
Thrombocytopenia	76 (38)	10 (5)	4 (4)	0 (0)

NOTE: Common Toxicity Criteria for Adverse Events, version 3.0.
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; LVEF, left ventricular ejection fraction.
*Grade 4 adverse events in patients on Sutent included alkaline phosphatase (1%), lipase (2%), creatinine (1%), hypokalemia (1%), neutropenia (2%), anemia (2%), and thrombocytopenia (1%).
[†]Grade 4 adverse events in patients on placebo included amylase (1%), lipase (1%), anemia (2%), and thrombocytopenia (1%).

Hemorrhagic events. Tumor-related hemorrhage has been observed in patients treated with sunitinib. Fatal pulmonary hemorrhage occurred in two patients receiving sunitinib on a clinical trial of patients with metastatic non–small-cell lung cancer; both patients had squamous cell histology. Treatment-emergent grade 3 and 4 tumor hemorrhage occurred in 5 of 202 (3%) GIST patients receiving sunitinib and in none of patients receiving placebo. Overall, the incidence of hemorrhagic events in patients receiving sunitinib was similar to that in patients receiving placebo.

Adrenal function. Abnormalities in adrenal histology including hemorrhage and necrosis were noted in nonclinical repeat dose studies in both rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. In clinical studies, computed tomography /magnetic resonance imaging obtained in 336 patients after exposure to one or more cycles of sunitinib showed no evidence of adrenal hemorrhage or necrosis. Adrenocorticorticotropic hormone stimulation testing was done in ~400 patients across multiple clinical trials of sunitinib. One patient with a normal baseline test developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with sunitinib; this patient did not exhibit clinical evidence of adrenal insufficiency.

Physicians prescribing sunitinib are advised to monitor for adrenal insufficiency in patients who experience stressors such as surgery, trauma, or severe infection.

Discussion

On January 26, 2006, sunitinib received regular approval for use in the treatment of GIST after progression or intolerance to imatinib mesylate and received accelerated approval for the treatment of advanced renal cell carcinoma.

The GIST approval was based on a clinically and statistically compelling improvement in time to progression shown in a prespecified interim efficacy analysis. The median time-to-tumor progression in patients who received sunitinib was 27 weeks compared with a time-to-tumor progression of 6 weeks in placebo-treated patients. Sunitinib is the first drug to be approved for patients with GIST who are refractory to or intolerant of imatinib.

It is notable that despite a significant improvement in time-to-tumor progression, the response rate in GIST patients receiving sunitinib was only 7%. Many of the newer anticancer agents seem to have primarily a cytostatic rather than a cytotoxic effect and may delay progression and/or death while having little effect on tumor size. In the absence of randomized trials wherein time to event end points such as time-to-tumor progression can be reliably compared with a control group, a response rate of the magnitude seen here would not have been considered sufficient evidence of benefit to support drug approval.

In advanced renal cell carcinoma, sunitinib received accelerated approval. The accelerated approval regulations allow for approval of drugs used to treat serious or life-threatening illnesses based on a surrogate end point considered "reasonably likely to predict clinical benefit" when the drug is an improvement over available therapy. The drug must subsequently show a beneficial effect on a clinically meaningful end point, such as survival or improvement in symptoms. In this case, sunitinib received accelerated approval based on durable partial responses, with a response rate of 26% to 37% and a median duration of response of 54 weeks in the completed

study. An ongoing study in patients receiving sunitinib versus IFN-α for the first-line treatment of metastatic renal cell carcinoma will compare progression-free survival between the two study arms; this study is intended to confirm the clinical benefit of sunitinib in advanced renal cell carcinoma.

The labeled indication in advanced renal cell carcinoma encompasses a broader population than that studied in the renal cell carcinoma trials, wherein all patients had metastatic disease and all had received prior cytokine therapy. The reasoning behind the expanded indication was twofold. First, patients with advanced, unresectable tumors are treated much like those patients with metastatic disease. Second, requiring prior cytokine therapy, with its limited efficacy and severe toxicities, was felt to be unduly onerous.

For a drug to receive accelerated approval, it must provide a benefit over available therapy. Before the approval of sorafenib in December 2005, there were no standard therapeutic options in patients with advanced renal cell carcinoma following cytokine therapy. The approval of sorafenib in a similar population was based on a placebo-controlled trial with a demonstration of a progression-free survival benefit compared with placebo. However, sorafenib was associated with an objective partial response rate of only 2%, whereas the partial response rate with sunitinib was ∼26% to 37%. Thus, the Food and Drug Administration felt that sunitinib could provide a benefit over sorafenib for patients in whom cytoreduction is an important goal for therapy.

Acknowledgments

References

1. Miettinen M, Lasota J. Gastrointestinal stromal tumors—definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001;438:1−12.

2. Goettsch WG, Bos SD, Breekveldt-Postma N, Casparie M, Herings RMC, Hogendoorn PCW. Incidence of gastrointestinal stromal tumours is underestimated: Results of a nation-wide study. Eur J Cancer 2005;41:2868−72.

3. Roberts PJ, Eisenberg B. Clinical presentation of gastrointestinal stromal tumors and treatment of operable disease. Eur J Cancer 2002;38:S37−8.

4. Tuveson DA, Willis NA, Jacks T, et al. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. Oncogene 2001;20:5054−8.

5. Dagher R, Cohen M, Williams G, et al. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res 2002;8:3034−8.

6. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472−80.

7. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364:1127−34.

8. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. N Engl J Med 1996;335:865−75.

9. Cohen HT, McGovern, FJ. Renal-cell carcinoma. N Engl J Med 2005;353:2477−90.

10. Medical Research Council Renal Cancer Collaborative. Interferon-α and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Lancet 1999;353:14−7.

11. Minasian LM, Motzer RJ, Gluck L, Mazumder M, Vlamis V, Krown SE. Interferon α-2a in advanced renal cell carcinoma: treatment results and survival in 159 patients with long-term follow-up. J Clin Oncol 1993;11:1368−75.

12. Atkins MB, Regan M, McDermott D. Update on the role of interleukin-2 and other cytokines in the treatment of patients with stage IV renal carcinoma. Clin Cancer Res 2004;10:6342−6S.

13. Physicians' Desk Reference. 59th ed. Montvale (NJ): Thomson PDR; 2005.

14. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon α-2a, or both in metastatic renal-cell carcinoma. N Engl J Med 1998;338:1272−8.

15. Vogelzang NJ, Lipton A, Figlin RA. Subcutaneous interleukin-2 plus interferon α-2a in metastatic renal cancer: an outpatient multicenter trial. J Clin Oncol 1993;11:1809−16.

16. Escudier B, Chevreau C, Lasset C, et al. Cytokines in metastatic renal cell carcinoma: is it useful to switch to interleukin-2 or interferon after failure of a first treatment? J Clin Oncol 1999;17:2039−43.

17. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 2004;22:454−63.

18. Kane RC, Farrell AT, Saber H, et al. Sorafenib for the treatment of advanced renal cell carcinoma. Clin Cancer Res 2006;12:7271−8.

19. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205−16.