Cancer Chemother Pharmacol (2007) 60:357–364
DOI 10.1007/s00280-006-0376-5

ORIGINAL ARTICLE

Sunitinib malate

Hassane Izzedine · Irina Buhaescu · Olivier Rixe · Gilbert Deray

Received: 16 August 2006 / Accepted: 24 October 2006 / Published online: 30 November 2006

Abstract Recently, there has been a growing interest in understanding the role of receptor tyrosine kinases (RTK), such as vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), stem cell factor receptor (KIT), and fms-like tyrosine kinase 3 (FLT3), in promoting tumor angiogenesis, tumor growth and metastasis. Sunitinib (sunitinib malate; SU11248; SUTENT®; Pfizer Inc, New York, NY, USA) is a novel, orally bio-available, oxindole, multi-targeted tyrosine kinase inhibitor with high binding affinity for VEGFR and PDGFR which has shown anti-tumor and anti-angiogenic activities. This drug recently received approval from the US Food and Administration (FDA) in two indications simultaneously: advanced renal cell carcinoma (adRCC) and gastrointestinal stromal tumors (GIST), in patients who are resistant or intolerant to the treatment with imatinib. The present article reviews the recent pharmacologic and clinical data related to the use of this new promising drug in the field of oncology.

H. Izzedine (✉) · G. Deray
Department of Nephrology,
Pitie-Salpetriere Hospital 83,
Blvd de l'Hôpital, 75013 Paris, France
e-mail: hassan.izzedine@psl.ap-hop-paris.fr

I. Buhaescu
Department of Internal Medicine,
Worcester Medical Center,
Worcester, MA, USA

O. Rixe
Department of Clinical Oncology,
Pitie-Salpetriere Hospital,
Paris, France

Introduction

Some of the solid tumors and haematological malignancies are at least partially driven by dysregulated tyrosine kinase receptors such as stem-cell factor receptor (KIT) (e.g. in gastrointestinal stromal tumors) [1], platelet-derived growth factor receptor (PDGFR) (e.g. in dermatofibrosarcoma protuberans) [2], and fetal liver tyrosine kinase receptor 3 (FLT3) (e.g. in acute myelogenous leukemia) [3]. In addition to their roles in cancer cell growth and survival, PDGFR and vascular endothelial growth factor receptor (VEGFR) facilitate the transmission of proliferation, migration, differentiation, and survival signals from cancer cells and neighboring host-derived stromal cells to the endothelial cells of the tumor neovasculature [4].

Recently, there has been a growing interest in multitargeted agents which inhibit several related pathways in multiple cell types to achieve better single-agent efficacy in a broader range of tumors. Indeed, several multi-target kinase inhibitors are now in development, and sorafenib and sunitinib are the two already approved in the United States. Sunitinib malate (SU11248; Sutent®; Pfizer Inc, New York, NY, USA) is the first oncology product to gain US Food and Administration (FDA) approval in two indications simultaneously. Sunitinib has been approved in advanced renal cell carcinoma (adRCC) and for the treatment of patients with gastrointestinal stromal tumors (GIST) whose disease has progressed or who are unable to tolerate treatment with imatinib.

Pharmacology

Mechanism of action

Sunitinib (sunitinib malate; SU11248; SUTENT®; Pfizer Inc, New York, NY, USA) is a novel, orally bioavailable, oxindole, multi-targeted tyrosine kinase inhibitor with anti-tumor and anti-angiogenic activities. Sunitinib has been identified as a potent inhibitor of vascular endothelial growth factor receptors (VEGFR) (types 1–3), PDGFR (α and β), as well as FLT3, Kit [stem-cell factor (SCF) receptor] colony-stimulating factor type 1 (CSF-1R) and glial cell-line derived neurotrophic factor receptor (RET), in both biochemical and cellular assays (Table 1) [5, 6].

Sunitinib malate has also direct anti-tumor effects on tumor cells, such as wild type and activated mutants of FLT3 expressed by acute myeloid leukemia-derived cell lines [5], and small cell lung cancer-derived cell lines expressed KIT [7]. Indirect anti-tumour activity of sunitinib by inhibition of VEGFR expressed on endothelial cells, and PDGFRβ on pericytes or stromal cells has also been demonstrated [6, 8] and its full anti-tumour efficacy was associated with prolonged (at least 12 of 24 h), but not continuous, inhibition of VEGFR2 and PDGFR [6].

Clinical pharmacology

In vitro metabolism studies demonstrated that sunitinib was primarily metabolized by cytochrome CYP3A4, resulting in formation of a major, pharmacologically active *N*-desethyl metabolite, SU012662. This metabolite was shown to be equipotent to the parent compound in biochemical tyrosine kinase and cellular proliferation assays, acting toward VEGFR, PDGFR, and KIT [9]. Pharmacokinetic data indicate good oral absorption, a prolonged half-life for sunitinib (~40 h) and its active metabolite, SU12662 (~80 h) and linear kinetics at the doses administered. A dose-proportional increase in both C_{max} and AUC for sunitinib was observed with increasing doses from 50 to 350 mg. Similar linearity was observed with the active metabolite SU12662 (10–15%). Across all dose levels, the time to plasma peak (T_{max}) was generally observed at 4–6 and 8–12 h, for both sunitinib and metabolite [6]. These results indicate that a single dose of sunitinib exhibits dose-dependent PK in humans [5]. Drug plasma protein binding rate is estimated to 90% (SU12662) to 95% (sunitinib) with a largest volume of distribution of 2230 L Radiolabeled orally administrated sunitinib in preclinical species was primarily excreted in the faeces (70–84%; investigator brochure). Only 16% of parent drug were excreted in the urine. Pharmacokinetic/pharmacodynamic data from animal studies showed that target plasma concentrations of sunitinib plus SU012662 capable of inhibiting PDGFR-β and VEGFR-2 phosphorylation were established in the range of 50 to 100 ng/ml [6, 7]. Interestingly, those data were consistent with those observed in patients with several cancers. In acute myeloid leukaemia, treatment led to a sustained inhibition of FLT3 phosphorylation in blast cells [5]. From two Phase II adRCC trials including 169 patients, a population PK analysis was performed to assess the exposure–response relationship between pharmacokinetic and tumor volume changes, clinical response, and time to tumor progression (TTP). Plasma clearance decreased by an average of 28% in mRCC patients relative to healthy volunteers. Improved clinical response and longer time to progression were associated with greater AUCs. Within 12 weeks of treatment, mean tumor volume decreased by 24–32% in each trial. Authors concluded that over the first 12 weeks of treatment at 50 mg daily on Schedule 4/2, increased exposure was associated with improved clinical response and decreased tumor volumes [10]. However, at higher doses (≥75 mg/day), tumor responses were often associated with reduced intratumoral vascularisation and central tumor necrosis, eventually resulting in organ perforation or fistula [11].

Table 1 Sunitinib inhibits phosphorylation of VEGF, PDGFR, and c-Kit [6]

Receptor tyrosine kinase	Cellular IC50 (μM)
VEGFR2	0.07
VEGFR1	0.002
VEGFR3	0.017
PDGF R α/β	0.002
KIT	0.022
FLT3-ITD	0.05
FLT3	0.25
RET	0.1

Clinical use of sunitinib malate

Renal cell carcinoma

The American Cancer Society estimates, based on the most recent data on cancer incidence, mortality, and survival, that approximately 38,890 individuals will be diagnosed as having RCC in the United States in 2006 and approximately 12,840 patients will die from the disease [12]. RCC is the most common malignant lesion of the kidney and accounts for 85% of all renal

neoplasms and 3% of all adult malignancies [13]. The overall incidence of RCC has increased over the past 20 years from 2 to 4% per year [14]. Response rates to chemotherapy have rarely exceeded 6% [15]. Response rates >10–15% have been achieved with cytokines such as interleukin 2 and interferon α [16, 17] However, these responses are often short-lived and less than 10% of patients receiving high-dose interleukin 2 treatment achieve long-term disease-free survival [16]. In January 2006, the US Food and Drug Administration granted approval for sunitinib for the treatment of mRCC [18–20].

In the two single-arm studies involving patients with adRCC who had experienced failure of prior cytokine-based therapy [18, 19], patients received 50 mg/day continuously for 4 weeks, followed by 2 weeks off until they met withdrawal criteria or had progressive disease.

In the first study, 63 patients with adRCC were enroled. The majority of patients had clear cell-carcinoma (55 patients 87%), but the study included small minorities of patients with papillary cell subtype (4 patients 6%), sarcomatoid variant (1 patient 2%), and unspecified (3 patients 5%). The objective response rate was 40% and the duration of response was 8.7 months [19]. Median duration of treatment was 9 months and median time to progression was 8.7 months. Analysis using RECIST criteria showed partial responses (observed in lesions at multiple sites) in 25 patients (40%) and stable disease lasting more than 3 months in an additional 17 patients (27%) (histology not reported). Of the 25 patients with partial responses, 2 discontinued treatment, 15 experienced progression and 8 remained progression-free more than 20 months from the initiation of therapy.

In the second study recently published in JAMA [18] (involving 106 patients with clear cell adRCC), the objective response rate was 39%. Of the 106 patients that were evaluable for efficacy analyses, 36 patients achieved partial response (34%; 95% CI 25–44%), and a median progression-free survival of 8.3 months as evaluated by the independent third-party core imaging laboratory (resulting in a value considerably longer than expected in this clinical setting).

Recently, a randomized phase III international trial compared the efficacy and safety of sunitinib to IFN-α in treatment naïve patients with adRCC. Results demonstrate a statistically significant improvement in progression-free survival and a better objective response rate for sunitinib over IFN-α in first-line treatment of patients with adRCC. In this phase III trial compared the efficacy and safety of sunitinib to IFN-α in treatment naïve patients, 690 untreated patients with clear-cell adRCC were randomized 1:1 to receive sunitinib (375 pts) (6-week cycles: 50 mg orally once daily for 4 weeks, followed by 2 weeks off) or IFN-α (375 pts) (6-week cycles: subcutaneous injection 9 MU given three times weekly). Ninety percent of patient had prior nephrectomy. Median progression-free survival was 47.3 weeks (95% CI 40.9) for sunitinib versus 24.9 weeks (95% CI 21.9, 37.1) for IFN-α [hazard ratio 0.394 (95% CI 0.297, 0.521) ($P < 0.000001$)]. The objective response rate by third-party independent review was 24.8% for sunitinib versus 4.9% for IFN-α ($P < 0.000001$). The objective response rate by investigator assessment was 35.7% (95% CI 30.9, 40.8) for sunitinib versus 8.8% (95% CI 6.1, 12.1) for IFN-α ($P < 0.000001$). 632 pts (85%) are alive, with 49 deaths on sunitinib arm and 65 deaths on IFN-α arm. Eight percent withdrew from the study due to adverse event on sunitinib arm versus 13% on IFN-α arm. Furthermore, in an ongoing Phase II study evaluating the activity of sunitinib in bevacizumab-refractory adRCC, 26 out of 32 patients (81%) demonstrated some degree of tumor shrinkage, including, 4 pts (13%; 95% CI 4, 29%) demonstrating an objective partial response [21].

Up to this moment, none of the treatment modalities available has had these results (Table 2) [11, 22–26]. We may be witnessing a great victory in the war on adRCC.

Table 2 Sunitinib for renal cell carcinoma

Comparison to other second-line therapies

Molecules	No. patients	ORR (%)	Time to progression (months)	References
Placebo	40	0	8.3	[22]
Interleukin 2	65	5	NA	[22]
Interferon-α	48	2	NA	[23]
Multiple agents in phase II trials	137	3	2.9	[24]
Avastin high dose	39	10	4.8	[24]
AG-013736	52	40%	Has not been reached	[25]
Sorafenib	202	50	6	[26]
Sunitinib	63	40	8.7	[19]

Sunitinib for other cancers excluding adRCC

Gastrointestinal stromal tumors

Gastrointestinal stromal tumors (GISTs) are an uncommon malignancy of the gastrointestinal (GI) tract, accounting for only 0.2% of all GI malignancies. However, they are the most common sarcomas of the abdomen [27]. Primary GISTs arise throughout the GI tract, most commonly in the stomach (40–70%), followed by small bowel (20–40%), colon and rectum (5–15%), and oesophagus (<5%) [28]. GISTs exhibit a broad spectrum of clinical course, with some low-risk lesions remaining stable for years, while others progress rapidly to widely metastatic disease [27]. Many GISTs are asymptomatic, discovered incidentally during imaging or at laparotomy for unrelated reasons. Between 15 and 50% of GISTs are metastatic at the time of diagnosis [28].

Before 2001, surgery was the only effective treatment for GISTs. Five-year survival rates for patients with GISTs ranged from 28 to 80% [29, 30]. In approximately 50% of patients, complete resection was not possible, and median survival ranged from 10 to 23 months. [29] Patients treated before 2001 achieved little benefit from chemotherapy or radiation therapy.

Dramatic improvement in GIST management occurred with the recognition that mutational activation of KIT or PDGFRα stimulated growth of these cancer cells. Approximately 85% of GISTs express the CD117 antigen, part of the KIT receptor tyrosine kinase [27]. In 1998, Hirota et al. [31] identified gain-of function mutations of the Kit proto-oncogene in the majority of GISTs, and similar activating mutations have been identified in the PDGFRα [32]. This led to effective systemic therapies in the form of small molecule inhibitors, such as imatinib mesylate (Gleevec®; Novartis Pharma, Basel, Switzerland) or sunitinib malate (SU11248; Sutent®).

In 2002, imatinib was administered in patients with metastatic GIST, in a large, multicenter trial. Partial responses occurred in 54%, stable disease in 28%, and disease progression in 14% [33]. Imatinib was approved for treatment of metastatic or unresectable GISTs in February 2002 [34]. However, resistance to imatinib resulting from subsequent mutations in KIT has emerged. The most important mechanism for acquired resistance to imatinib is the reactivation of KIT, which occurs via secondary gene mutations in the KIT kinase domain, including the mutations Val654Ala and Thr670Ile [35, 36]. Phase I/II/III studies have shown that sunitinib demonstrates anti-tumour efficacy in patients resistant to imatinib [37, 38]. Sunitinib was approved for treatment of metastatic or unresectable GISTs in January 2006 [39].

In a phase III study in GIST in 312 patients, administration of sunitinib (50 mg given once daily for 4 weeks, followed by 2 weeks off treatment, in repetitive 6-week cycles) was randomized against placebo (2:1 randomisation). Early data show a more than four-fold increase in median time to progression (median TTP: 27.3 weeks vs. 6.4 weeks, hazard ratio 0.335, $P < 0.00001$) from 1.5 to 6.3 months [38] and also a significantly greater estimated overall survival (HR 0.491; $P = 0.007$). Sunitinib treatment induced partial responses in 36 (17.4%) versus 2 (1.9%) patients on placebo groups over 22 weeks follow up. In 13 patients who were classified as imatinib mesylate intolerant, 4 of 9 patients randomized to sunitinib achieved partial response, with progressive disease in only 1. In contrast, of four imatinib mesylate intolerant patients randomized to placebo, zero partial response were noted and three had progressive disease [40]. Further investigation of sunitinib plus cytotoxic chemotherapy in GISTs is warranted.

Acute myeloid leukaemia

Acute myeloid leukemia (AML) occurs with a frequency of around 5 cases per 1,00,000 per year. Median survival for this patient population is approximately 3 months. No standard therapy exists for such patients, and any treatment administered is associated with a low response rate and short duration of remission [41]. Although most AML patients express the wild-type form of FLT3 (FLT3-WT), the leukemic blasts of 1–35% of patients express a FLT3-ITD [42]. This mutation leads to constitutive activation of the receptor. Expression of FLT3-ITD in myeloid cell lines induces their autonomous, cytokine-independent proliferation and enhances their leukemogenicity in mice [43]. Clinically, FLT3-ITD is an important independent negative prognostic factor in AML [44, 45] and is associated with increased blast count, increased relapse rate, and poor overall survival.

In preclinical experiments, sunitinib exhibits dose dependent efficacy in both FLT3-ITD AML xenograft tumor model and a bone marrow engraftment model. SU11248 and its equally active metabolite, SU12662, inhibits Flk1/KDR activity and PDGFR activity in tumor-bearing mice with a plasma concentration of approximately 50–100 ng/ml [6, 7]. Similar results were obtained in a phase I with the 50 mg daily dose, with a partial remission of short duration in 16 AML patients [46]. It would be predicted, therefore, that a sunitinib dosing regimen that results in a minimal concentration

>100 ng/ml would elicit sustained FLT3 inhibition [5]. Signal transducer and activator of transcription 5 (STAT5) induces myeloproliferative disease and is activated downstream of many oncogenes associated with haematopoietic disorders. The levels of STAT5 phosphorylation in whole blood lysates were higher in AML patients than in healthy donors or patients with advanced solid malignancies, consistent with recent observations that STAT5 is active in peripheral blood blasts from the majority of AML patients [47]. Data from several groups suggest that STAT5 is strongly activated by FLT3-ITD but not by FLT3-WT [43, 48]. It has been reported that stimulation of FLT3-WT cells (the OC1-AML5 cell line or PBMCs isolated from healthy volunteer blood) with FLT3 ligand weakly activates STAT5 tyrosine phosphorylation and DNA binding activity [45, 4], whereas FLT3-ITD strongly activates STAT5.

Others

During the past 5 years, combination chemotherapy regimens including either irinotecan or oxaliplatin have proven to be superior to fluorouracil monotherapy in randomized clinical trials, in terms of response rate, progression-free survival and overall survival in metastatic colorectal cancer (mCRC). Recently, a new orally active fluorouracil analog, capecitabine, and two targeted biological agents, cetuximab and bevacizumab, have been added to the armamentarium of drugs active against mCRC, thus making the scenario more complex [49]. Moreover, ongoing clinical trials are currently testing new promising molecularly targeted agents such as the sunitinib.

The efficacy and safety of sunitinib in 82 patients with mCRC after failure of standard chemotherapy was assessed in an open-label, uncontrolled, multicenter, 2-stage, phase II trial [51]. All patients had received prior irinotecan, oxaliplatin and a fluoropyrimidine in the adjuvant and/or advanced disease setting. One out of 42 patients in the prior-bevacizumab cohort achieved a partial response. Additionally one out of 42 patients in the prior-bevacizumab cohort and 11 out of 40 patients in the bevacizumab-naïve cohort demonstrated stable disease for ≥5 months. Median time to progression in the prior-bevacizumab and bevacizumab-naïve cohorts was 2.2 months (95% CI 1.9–2.3) and 2.5 months (95% CI 2.3–3.1), respectively, while median overall survival was 7.1 months (95% CI 4.9–10.6) and 10.2 months (95% CI 8.2–15.3), respectively [50]. Further investigation of the exact role of sunitinib, in association with other cytotoxic drugs and/or other anti-VEGF therapy in colorectal cancer is warranted.

Preclinical evaluation of SU11248 in animal models of breast cancer provided encouraging results, showing potent anti-proliferative activity of SU11248, either alone or in combination with conventional cytotoxic agents (5-fluorouracil, doxorubicin) [51] and capacity of inhibiting tumor-associated osteolysis [52]. However, the clinical experience with sunitinib in human pathology is limited so far. In an open labelled, single arm phase II trial that included 64 patients metastatic breast cancer previously resistant to anthracyclines and taxane, sunitinib treatment resulted in an ~11% objective response rate [53]. Three patients (5%) had stable disease for more than 6 months, and the overall clinical benefit was evaluated to be 16%.

Side effects, practical consideration and discontinuation of drug treatment

In the two phase II adRCC trials [18, 19], sunitinib has been generally well tolerated, with compliance rate during the first 6 months of treatment of at least 95%. The most common side effects that were noted in these studies, compared to those observed in the GIST study, are presented in Table 3. In most instances, symptoms improved with dose modification. In the first adRCC study, however, in 12 patients (11%), sunitinib was discontinued due to adverse events [18]. Also, two patients were taken off the study for asymptomatic decreases in left ventricular ejection fraction of >20% compared to baseline.

The exact mechanisms of sunitinib toxicities are not understood. Hypertension and asthenia are thought to be associated with inhibition of VEGF and VEGFRs. Skin and/or hair depigmentation or discoloration are attributed to a direct anti-VEGFR and/or PDGFR effect on dermal endothelial cells, as well. Reversible hair depigmentation was associated with modulation of tyrosinase-related protein 1 genes and tyrosinase, related to the Kit signalling pathway [11]. A subset of patients may develop thyroid dysfunction, which may account, in part, for fatigue previously described with sunitinib. Thyroid dysfunction is not dose-limiting and patients could be treated effectively with thyroid hormone replacement, with rapid clinical improvements and resolution of TSH elevation. The mechanism by which sunitinib affects thyroid function is being investigated and may account for documented objective responses to this drug [54].

Sunitinib should be used with caution in patients with a past history of cardiac dysfunction. Monitoring with baseline and periodic left ventricular ejection fraction (LVEF) evaluation is warranted. Treatment

Table 3 Most common side effects reported during adRCC and GIST studies

Side effect	Incidence	
	GIST [39] $n = 202$ (%)	adRCC [18, 19] $n = 169$ (%)
LV dysfunction	22 (11)	25 (15)
Hemorrhagic events	37 (18)	44 (26)
Hypertension	31 (15)	48 (28)
Fatigue	84 (42)	125 (74)
Diarrhea	81 (40)	93 (55)
Mucositis/stomatitis	58 (29)	90 (53)
Vomiting	49 (24)	63 (37)
Abdominal pain	67 (33)	34b (20)
Constipation	41 (20)	57 (34)
Nausea	63 (31)	92 (54)
Anorexia	67 (33)	53 (31)
Altered taste	42 (21)	73 (43)
Headache	26 (13)	43 (25)
Dyspnea	20 (10)	47 (28)
Cough	17 (8)	29 (17)
Skin discoloration	61 (30)	55 (33)
Rash	28 (14)	64 (38)
Hand–foot syndrome	28 (14)	21 (12)
Arthralgia	24 (12)	48 (28)
Back pain	23 (11)	29 (17)
Myalgia	28 (14)	29 (17)

discontinuation is recommended if clinical signs and symptoms of congestive heart failure appear, if LVEF is <50% or if there is a reduction of >20% from baseline LVEF. In case of severe hypertension, temporary treatment interruption is recommended until hypertension is controlled.

CYP3A4 induction with rifampin caused a 4-fold reduction in sunitinib plasma exposure (AUC_{last} and $AUC_{0-\infty}$) and a 2.5-fold reduction in SU11248 plasma C_{max} compared with SU11248 alone in both Caucasian and Japanese males. A 1.4-fold increase in SU12662 AUC was observed after CYP3A4 induction with rifampin. The reduction in systemic exposure of SU11248 when co-administered with rifampin indicates that concomitant treatment with potent CYP3A4 inducers or inhibitors should be avoided when SU11248 is used in patients with cancer to limit treatment failure and side effects risk [55]. Otherwise, dose reductions (to a minimum of 25 mg/day) or increase doses (to a maximum of 87.5 mg/day) are more likely to be needed when sunitinib is administered concomitantly with strong CYP3A4 inhibitors or inducers, respectively.

Conclusion and perspectives

The increased understanding of the role of receptor tyrosine kinases in promoting tumor angiogenesis has led to the rational development of new therapeutic agents that selectively target this pathologic pathway. Sunitinib is one of the novel multitargeted receptor tyrosine kinase inhibitors, already approved by FDA (based on the positive results of some large randomized phase III trials) for patients with metastatic, advanced renal cancer and GIST, resistant or intolerant to conventional chemotherapeutical agents.

However, despite promising emerging clinical experience with this new drug, unresolved issues still remain. Following targeted therapy, response is not permanent, and not all patients benefit clinically from these agents. Although in general well tolerated, the safety of long-term administration is not known. Further studies are warranted to asses the optimal clinical application of this drug and how best to combine this agent with other cytotoxic drugs, cytokines and radiotherapy for the best synergistic anti-tumoral effect. In the future, identifying molecular markers that are associated with good clinical response, most effective dosing scheme determinations, and combination treatment strategies that simultaneously inhibit multiple growth factor pathways might enhance response frequency and duration.

References

1. Heinrich MC, Blanke CD, Druker BJ, Corless CL (2002) Inhibition of KIT tyrosine kinase activity: a novel molecular approach to the treatment of KIT-positive malignancies. J Clin Oncol 20:1692–1703
2. Rubin BP, Schuetze SM, Eary JF, Norwood TH, Mirza S, Conrad EU, Bruckner JD (2002) Molecular targeting of plateletderived growth factor B by imatinib mesylate in a patient with metastatic dermatofibrosarcoma protuberans. J Clin Oncol 20:3586–3591
3. Gilliland DG, Griffin JD (2002) Role of FLT3 in leukemia. Curr Opin Hematol 9:274–281
4. Gale NW, Yancopoulos GD (1999) Growth factors acting via endothelial cell-specific receptor tyrosine kinases: VEGFs, angiopoietins, and ephrins in vascular development. Genes Dev 13:1055–1066
5. O'Farrell AM, Foran JM, Fiedler W, Serve H, Paquette RL, Cooper MA, Yuen HA, Louie SG, Kim H, Nicholas S, Heinrich MC, Berdel WE, Bello C, Jacobs M, Scigalla P, Manning WC, Kelsey S, Cherrington JM (2003) An innovative phase 1 clinical study demonstrates inhibition of FLT3 phosphorylation by SU11248 in acute myeloid leukemia patients. Clin Cancer Res 9:5465–5476
6. Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, Schreck RE, Abrams TJ, Ngai TJ, Lee LB, Murray LJ, Carver J, Chan E, Moss KG, Haznedar JO, Sukbuntherng J, Blake RA, Sun C, Tang C, Miller T, Shirazian S, McMahon G, Cherrington JM (2003) In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting VEGF and PDGF receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin. Cancer Res 9:327–337

7. Abrams TJ, Murray LJ, Pesenti E, Holway VW, Colombo T, Lee LB, Cherrington JM, Pryer NK (2003) Preclinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with "standard of care" therapeutic agents for the treatment of breast cancer. Mol Cancer Ther 2:1011–1021
8. Laird AD, Cherrington JM (2003) Small molecule tyrosine kinase inhibitors: clinical development of anticancer agents. Expert Opin Invest Drugs 12:51–64
9. Baratte S, Sarati S, Frigerio E, James CA, Ye C, Zhang Q (2004) Quantitation of SU11248, an oral multi-target tyrosine kinase inhibitor, and its metabolite in monkey tissues by liquid chromatograph with tandem mass spectrometry following semi-automated liquid–liquid extraction. J Chromatogr A 1024:87–94
10. Houk BE, Amantea M, Motzer RJ, Michaelson MD, Rini BI, George DJ, Redman BG, Hudes GR, Poland B, Bello CL (2006) Pharmacokinetics (PK) and efficacy of sunitinib in patients with metastatic renal cell carcinoma (mRCC). J Clin Oncol. In: ASCO annual meeting proceedings part I, vol 24, no. 18S
11. Faivre S, Delbaldo C, Vera K, Robert C, Lozahic S, Lassau N, Bello C, Deprimo S, Brega N, Massimini G, Armand JP, Scigalla P, Raymond E (2006) Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol 24:25–35
12. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ (2006) Cancer statistics, 2006. CA Cancer J Clin 56:106–130
13. Amato RJ (2005) Renal cell carcinoma: review of novel single-agent therapeutics and combination regimens. Ann Oncol 16:7–15
14. Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr (1999) Rising incidence of renal cell cancer in the United States. JAMA 281:1628–1631
15. Yagoda A, Abi-Rached B, Petrylak D (1995) Chemotherapy for advanced renal-cell carcinoma: 1983–1993. Semin Oncol 22:42–60
16. Rosenberg SA, Yang JC, Topalian SL, Schwartzentruber DJ, Weber JS, Parkinson DR, Seipp CA, Einhorn JH, White DE (1994) Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin. JAMA 271:907–913
17. Bex A, Mallo H, Kerst M, Haanen J, Horenblas S, de Gast GC (2005) A phase-II study of pegylated interferon alfa-2b for patients with metastatic renal cell carcinoma and removal of the primary tumor. Cancer Immunol Immunother 54:713–719
18. Motzer RJ, Rini BI, Bukowski RM, George DJ, Hudes GR, Redman BG, Margolin KA, Merchan JR, Wilding G, Ginsberg MS, Bacik J, Kim ST, Baum CM, Michaelson MD (2006) Sunitinib in patients with metastatic renal cell carcinoma. JAMA 295:2516–2524
19. Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, Ginsberg MS, Kim ST, Baum CM, DePrimo SE, Li JZ, Bello CL, Theuer CP, George DJ, Rini BI (2006) Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol 24:16–24
20. Motzer RJ. Rini BI, Michaelson MD, Redman BG, Hudes GR, Wilding G, Bukowski RM, George DJ, Kim ST, Baum CM, the SU11248 Study Group (2005) Phase 2 trials of SU11248 show antitumor activity in second-line therapy for patients with metastatic renal cell carcinoma (RCC). Proc Am Soc Clin Oncol A4508
21. Rini BI, George DJ, Michaelson MD, Rosenberg JE, Bukowski RM, Sosman JA, Stadler WM, Margolin K, Hutson TE, Baum CM (2006) Efficacy and safety of sunitinib malate (SU11248) in bevacizumab-refractory metastatic renal cell carcinoma (mRCC). J Clin Oncol. In: ASCO Annual meeting proceedings part I, vol 24, no. 18S
22. Escudier B, Chevreau C, Lasset C, Douillard JY, Ravaud A, Fabbro M, Caty A, Rossi JF, Viens P, Bergerat JP, Savary J, Negrier S (1999) Cytokines in metastatic renal cell carcinoma: is it useful to switch to interleukin-2 or interferon after failure of a first treatment? Groupe Francais d'immunotherape. J Clin Oncol 17:2039–2043
23. Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S, Mazumdar M (2004) Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 22:454–463
24. Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, Steinberg SM, Chen HX, Rosenberg SA (2003) A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 349:427–434
25. Rini B, Rixe O, Bukowski R, Michaelson MD, Wilding G et al (2005) AG-013736, a multi-target tyrosine kinase receptor inhibitor, demonstrates antitumor activity in a phase 2 study of cytokine-refractory, metastatic renal cell cancer (RCC). J Clin Oncol (meeting abstracts) 23(suppl):380s (abstract 4508)
26. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL, Gore M, Desai AA, Patnaik A, Xiong HQ, Rowinsky E, Abbruzzese JL, Xia C, Simantov R, Schwartz B, O'Dwyer PJ (2006) Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 24:2505–2512
27. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW (2002) Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 33:459–465
28. Nilsson B, Bumming P, Meis-Kindblom JM, Oden A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG (2005) Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era. Cancer 103:821–829
29. Casper ES (2000) Gastrointestinal stromal tumors. Curr Treat Options Oncol 1:267–273
30. Conlon KC, Casper ES, Brennan MF (1995) Primary gastrointestinal sarcomas: analysis of prognostic variables. Ann Surg Oncol 2:26031
31. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y (1998) Gain of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 279:577–580
32. Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CD, Fletcher JA (2003) PDGFRA activating mutations in gastrointestinal stromal tumors. Science 299:708–710
33. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H (2002) Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 347:472–480

34. Dagher R, Cohen M, Williams G, Rothmann M, Gobburu J, Robbie G, Rahman A, Chen G, Staten A, Griebel D, Pazdur R (2002) Approval summary: Imitanib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res 8:3034–3038
35. Tamborini E, Bonadiman L, Greco A, Albertini V, Negri T, Gronchi A, Bertulli R, Colecchia M, Casali PG, Pierotti MA, Pilotti S (2004) A new mutation in the KIT ATP pocket causes acquired resistance to imatinib in a gastrointestinal stromal tumor patient. Gastroenterology 127:294–9
36. Debiec-Rychter M, Cools J, Dumez H, Sciot R, Stul M, Mentens N, Vranckx H, Wasag B, Prenen H, Roesel J, Hagemeijer A, Van Oosterom A, Marynen P (2005) Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. Gastroenterology 128:270–279
37. Demetri GD, Desai J, Fletcher JA, Morgan JA, Fletcher CDM, Kazanovicz A, Van Den Abbeele A, Baum C, Maki R, Heinrich MC (2004) SU11248, a multi-targeted tyrosine kinase inhibitor, can overcome imatinib (IM) resistance caused by diverse genomic mechanisms in patients (pts) with metastatic gastrointestinal stromal tumor (GIST). J Clin Oncol 22(14):3001
38. Demetri GD, van Oosterom AT, Blackstein M, Garrett C, Shah M, Heinrich M, McArthur G, Judson I, Baum CM, Casali PG (2005) Phase III, multicenter, randomized, double blind, placebo-controlled trial of SU11248 in patients following failure of imatinib for metastatic GIST. J Clin Oncol 23:S308
39. FDA Approves new treatment for gastrointestinal and kidney cancer, P06-11, Rockville, MD, U.S. Food and Drug Administration, 2006, www.fda.gov/bbs/topics/news/2006/NEW01302.html
40. Demetri G, van Oosterom AT, Garrett C, Blackstein M, Shah M, Verweij JJ, McArthur G, Judson I, Baum C, Casali P (2006) Improved survival and sustained clinical benefit with SU11248 (SU) in pts with GIST after failure of imatinib mesylate (IM) therapy in a phase III trial. J Clin Oncol. In: ASCO Abstract 8
41. Larson RA (2001) Current use and future development of gemtuzumab ozogamicin. Semin Hematol 38(6):24–31
42. Yee KW, O'Farrell AM, Smolich BD, Cherrington JM, McMahon G, Wait CL, McGreevey LS, Griffith DJ, Heinrich MC (2002) SU5416 and SU5614 inhibit kinase activity of wild-type and mutant FLT3 receptor tyrosine kinase. Blood 100:2941–2949
43. Mizuki M, Fenski R, Hualfter H, Matsumura I, Schmidt R, Muller C, Gruning W, Kratz-Albers K, Serve S, Steur C, Buchner T, Kienast J, Kanakura Y, Berdel WE, Serve H (2000) FLT3 mutations from patients with acute myeloid leukaemia induce transformation of 32D cells mediated by the Ras and STAT5 pathways. Blood 96:3907–3914
44. Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, Walker H, Wheatley K, Bowen DT, Burnett AK, Goldstone AH, Linch DC (2001) The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood 98:1752–1759
45. Meshinchi S, Woods WG, Stirewalt DL, Sweetser DA, Buckley JD, Tjoa TK, Bernstein ID, Radich JP (2001) Prevalence and prognostic significance of Flt3 internal tandem duplication in pediatric acute myeloid leukemia. Blood 97:89–94
46. Fiedler W, Serve H, Dohner H, Schwittay M, Ottmann OG, O'Farrell AM, Bello CL, Allred R, Manning WC, Cherrington JM, Louie SG, Hong W, Brega NM, Massimini G, Scigalla P, Berdel WE, Hossfeld DK (2005) A phase 1 study of SU11248 in the treatment of patients with refractory or resistant acute myeloid leukemia (AML) or not amenable to conventional therapy for the disease. Blood 105:986–993
47. Birkenkamp KU, Geugien M, Lemmink HH, Kruijer W, Vellenga E (2001) Regulation of constitutive STAT5 phosphorylation in acute myeloid leukemia blasts. Leukemia 15:1923–1931
48. Levis M, Allebach J, Tse KF, Zheng R, Baldwin BR, Smith BD, Jones-Bolin S, Ruggeri B, Dionne C, Small D (2002) A FLT3-targeted tyrosine kinase inhibitor is cytotoxic to leukemia cells in vitro and in vivo. Blood 99:3885–3891
49. Pessino A, Sobrero A (2006) Optimal treatment of metastatic colorectal cancer. Expert Rev Anticancer Ther 6:801–812
50. Lenz H, Marshall J, Rosen L, Belt R, Hurwitz H, Eckhardt S, Bergsland E, Haller D, Chao R, Saltz L (2006) Phase II trial of SU11248 in patients with metastatic colorectal cancer (MCRC) after failure of standard chemotherapy. J Clin Oncol Abstract 241
51. Abrams TJ, Murray LJ, Pesenti E, Holway VW, Colombo T, Lee LB, Cherrington JM, Pryer NK (2003) Preclinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with "standard of care" therapeutic agents for the treatment of breast cancer. Mol Cancer Ther 2:1011–1021
52. Murray LJ, Abrams TJ, Long KR, Ngai TJ, Olson LM, Hong W, Keast PK, Brassard JA, O'Farrell AM, Cherrington JM, Pryer NK (2003) SU11248 inhibits tumor growth and CSF-1R-dependent osteolysis in an experimental breast cancer bone metastasis model. Clin Exp Metastasis 20:757–766
53. Miller KD, Burstein HJ, Elias AD, Rugo HS, Cobleigh MA, Pegram MD, Eisenberg PD, Collier M, Adams BJ, Baum CM (2005) Phase II study of SU11248, a multitargeted receptor tyrosine kinase inhibitor (TKI), in patients (pts) with previously treated metastatic breast cancer (MBC). J Clin Oncol. In: ASCO 23, no.16S:563
54. Desai J, Dileo P, Morgan JA, Larsen PR, Chen MH, George S, Jackson J, Baum C, Demetri GD (2005) Hypothyroidism may accompany SU11248 therapy in a subset of patients (pts) with metastatic (met) gastrointestinal stromal tumors (GIST) and is manageable with replacement therapy. J Clin Oncol In: ASCO annual meeting proceedings, vol 23, no. 16S, part I of II (June 1 suppl) Abstract 3040
55. Bello C, Houk B, Sherman L, Misbah S, Sarapa N, Smeraglia J, Haung X (2005) Effect of rifampin on the pharmacokinetics of SU11248 in healthy volunteers. J Clin Oncol In: ASCO annual meeting proceedings, vol 23, no. 16S, part I of II (June 1 suppl) Abstract 3078