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Lung Cancer

# Sorafenib and Sunitinib in the Treatment of Advanced Non-Small Cell Lung Cancer

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**Key Words.** Sorafenib • Sunitinib • Targeted therapy • Multikinase inhibitors • NSCLC

## LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the molecular mechanisms of action, safety profile, rationale for NSCLC treatment, and main current evidence in NSCLC treatment using the multikinase inhibitors sorafenib and sunitinib.
2. Summarize the main clinical trials performed with sorafenib and sunitinib in the treatment of solid tumors.
3. Describe the clinical trials performed with sorafenib and sunitinib in NSCLC and suggest the future clinical development of these two drugs in the treatment of NSCLC.

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## ABSTRACT

**Despite the optimization of chemotherapy regimens, treatment outcomes for advanced non-small cell lung cancer (NSCLC) are still considered to be disappointing. Thus, clinical research of new treatment strategies is warranted. Several targeted agents have been introduced into clinical trials in NSCLC, but to date, only a few of these new agents can offer hope of a substantial impact on the natural history of the disease. One of the main reasons for the failure of several clinical trials of targeted therapy in lung cancer is that there is multilevel cross-stimulation among the targets of the new biological agents along several pathways of signal transduction that lead to neoplastic events; blocking only one of these pathways, as most first-generation targeted agents do, allows others to act as salvage or escape mechanisms for cancer cells. Sorafenib and sunitinib are two oral multitargeted receptor tyrosine kinase inhibitors. Sorafenib is a multikinase inhibitor that inhibits the kinase activity of both C-RAF and B-RAF and targets the vascular endothelial growth factor receptor family (VEGFR-2 and VEGFR-3) and platelet-derived growth factor receptor family (PDGFR-$\beta$ and stem cell factor receptor [KIT]). Sunitinib is a multitargeted inhibitor of PDGFR, KIT, fms-like tyrosine kinase 3, and VEGFR. The kinases targeted and inhibited by sorafenib and sunitinib directly and indirectly regulate tumor growth, survival, and angiogenesis, and this might be expected to result in broad antitumor efficacy. Sorafenib and sunitinib have been approved by the U.S. Food and Drug Administration for the treatment of metastatic renal cell carcinoma; sunitinib has also been approved for the treatment of gastrointestinal stromal tumors. Their mechanism of action, preclinical data, and phase II studies suggest efficacy in the treatment of advanced NSCLC.** *The Oncologist* 2007;12:191–200

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## Introduction

Lung cancer is the leading cause of cancer-related mortality in both men and women [1], with 1.2 million new cases diagnosed worldwide every year and 1 million deaths being recorded worldwide in 2001 [2]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers. Most NSCLC patients present with advanced disease at diagnosis, and a large percentage of those diagnosed with early-stage disease eventually experience recurrence of metastatic disease. For advanced disease, palliation and the patient's quality of life are still the primary goals of therapy, with total cure remaining elusive.

Although chemotherapy has recently produced promising results as neoadjuvant and adjuvant strategies for early-stage patients [3, 4] and some progress has been made in the treatment of locally advanced and advanced disease [5, 6], treatment outcomes for NSCLC are still very disappointing. Thus, clinical research of new treatment strategies is warranted. Several targeted agents have been introduced into clinical trials in NSCLC, with many phase I and II studies already completed and some phase III study results recently becoming available [7–9]. To date, only a few of these new agents offered hope of altering the natural history of the disease, and negative results are far more commonly reported than positive ones. Nevertheless, clinically meaningful advances have already been achieved. In chemotherapy-refractory advanced NSCLC patients, erlotinib (Tarceva®; OSI Pharmaceuticals, Inc., Melville, NY), an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), represents a further possibility of tumor control and symptom palliation for a subset of patients otherwise eligible for supportive care only [7]. In chemotherapy-naïve advanced NSCLC patients (with nonsquamous histology), the combination of the antivascular endothelial growth factor monoclonal antibody bevacizumab (Avastin®; Genentech Inc., South San Francisco, CA) with chemotherapy has yielded better survival outcomes than chemotherapy alone [8].

One of the main reasons for the failure of several clinical trials evaluating targeted therapy in lung cancer is the existence of multilevel cross-stimulation among the targets of the new biological agents along several pathways of signal transduction that lead to neoplastic events; blocking only one of these pathways allows others to act as salvage or escape mechanisms for cancer cells. Preclinical evidence of synergistic antitumor activity achievable by combining targeted agents that block multiple signaling pathways has recently emerged [10, 11]. The complexity of the signaling process in general further supports the need to interfere at different stages to avoid an escape mechanism for the cell.

Whether the multitarget approach can be accomplished by using combinations of selective agents or specific agents that intrinsically target various targets is a matter of debate [12]. Combination trials are relatively easy only when the compounds are all owned or licensed by one company.

Such a multitargeted strategy has recently been validated in a number of preclinical and clinical studies using receptor tyrosine kinase (RTK) inhibitors with broad target selectivity [13]. Sorafenib (Nexavar®; Bayer Pharmaceuticals Corporation, West Haven, CT) and sunitinib (Sutent®; Pfizer Inc., New York) are two multitargeted receptor tyrosine kinase inhibitors and among the most promising biologic agents in the treatment of metastatic solid tumors.

## Sorafenib and Sunitinib: Mechanisms of Action

Many of the processes involved in tumor growth, progression, and metastasis are mediated by signaling pathways initiated by activated RTKs [14]. RTKs, 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 (FLT-3), are expressed in malignant tissues and act in concert, playing diverse and major roles in angiogenesis, tumor growth, and metastasis [15]. RAS functions downstream of several RTKs, and activation of RAS signaling pathways is an important mechanism by which human cancers develop [16]. Constitutive activation of the RAS pathways occurs through mutational activation of the Ras oncogene or downstream effectors of RAS [17]. RAS activation can also be facilitated by overexpression of a variety of RTKs, including those for the EGFR, PDGFR, or VEGFR growth factors [18–20]. In this way, most human tumors, not just those with RAS mutations, depend upon activation of the RAS signal transduction pathways to achieve cellular proliferation and survival [18]. RAS regulates several pathways that synergistically induce cellular transformation, including the well-characterized RAF/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) cascade. RAF kinases are serine/threonine protein kinases that function in this pathway as downstream effector molecules of RAS. RAS localizes RAF to the plasma membrane, where RAF initiates a mitogenic kinase cascade that ultimately modulates gene expression via the phosphorylation of transcription factors [17], which can have profound effects on cellular proliferation and tumorigenesis. The RAF kinase family is composed of three mem-

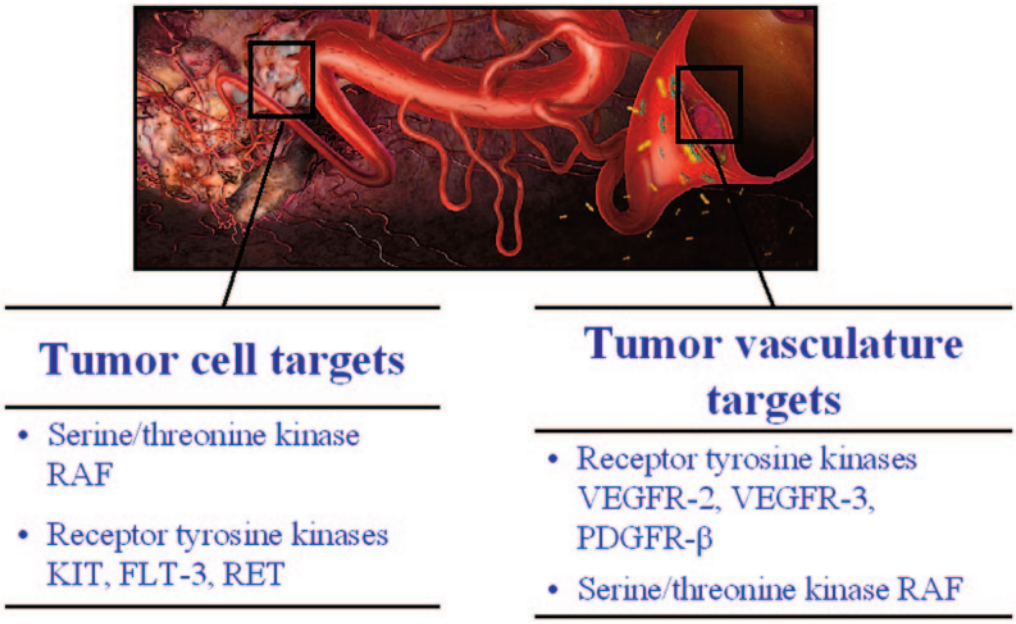


**Figure 1.** Sorafenib and sunitinib have targets in both the tumor cell and the tumor vasculature, thus inhibiting both tumor growth and angiogenesis. Abbreviations: FLT-3, fms-like tyrosine kinase 3; KIT, stem cell factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

bers: A-RAF, B-RAF, and RAF-1 (also termed C-RAF). B-RAF is reportedly mutated in 70% of malignant melanomas [21], in 33% of papillary thyroid carcinomas [22], and in lower frequencies in other cancers [23]. Recent evidence suggests that RAF-1 and B-RAF participate in the regulation of endothelial apoptosis and, therefore, angiogenesis, a process essential for tumor development and metastasis [24, 25]. Activating mutations in RAS and B-RAF have been identified in several human cancers. In addition, several RTKs acting upstream of RAS are either mutated or overexpressed in human tumors. Because oncogenic activation of the RAS/RAF pathway may lead to a sustained proliferative signal resulting in tumor growth and progression, inhibition of this pathway represents an attractive approach for cancer drug discovery.

Angiogenesis is a tightly regulated multistep process that involves the interaction of multiple growth factors expressed as multiple isoforms, including VEGFs, basic fibroblast growth factor, and PDGFs. VEGF also regulates vascular permeability [26]. Vessel stabilization through pericyte recruitment and maturation is primarily driven by PDGF [27]. Several antiangiogenic agents are currently being investigated in clinical trials; however, because of the complex interactions between tumor cells, the invading stroma, and new blood vessels, a therapeutic agent targeting a single molecular entity might have limited efficacy across a spectrum of tumor types [28]. In addition to their direct role in tumor cell growth and survival, several split-kinase domain RTKs, namely the VEGF receptors and PDGFR-$\beta$, play prominent roles in tumor neoangiogenesis [17]. VEGF produced by tumor cells and associated stromal cells acts on endothelial cells, directly promoting their proliferation, migration, invasion, and survival, all critical facets of angiogenesis [19]. PDGFR-$\beta$ is expressed on pericytes, smooth muscle cells that provide mechanical support to vasculature, and tumor neovasculature [20]. PDGFR-$\beta$ is also expressed on fibroblasts in the tumor stromal compartment; these fibroblasts are important sources of VEGF and other growth factors [22]. Recent data suggest that combined pharmacological disruption of Flk-1/KDR and PDGFR-$\beta$ signaling results in profound antiangiogenic effects [23].

Thus, the signaling cascades generated by the split-kinase domain RTKs described above (the VEGF receptors Flk-1/KDR and Flt-1, the PDGF receptors PDGFR-$\alpha$ and PDGFR-$\beta$, KIT, and FLT-3) directly and indirectly regulate tumor growth, survival, and angiogenesis. Inhibiting these targets in concert might be expected to result in broad antitumor efficacy.

Sorafenib (BAY 43-9006) is an oral multikinase inhibitor that inhibits the kinase activity of both C-RAF and B-RAF and targets the vascular endothelial growth factor receptor family (VEGFR-2 and VEGFR-3) and platelet-derived growth factor receptor family (PDGFR-$\beta$ and Kit) [29]. Sorafenib inhibits MEK and ERK phosphorylation in various cancer cell lines and tumor xenografts and exhibited potent oral antitumor activity in a broad spectrum of human tumor xenograft models [29]. Together, these data suggest that sorafenib may inhibit tumor growth by a dual

mechanism, acting either directly on the tumor (through inhibition of Raf and Kit signaling) and/or on tumor angiogenesis (through inhibition of VEGFR and PDGFR signaling).

Sunitinib (SU11248) is a novel small molecule, an orally selective multitargeted RTK inhibitor that exhibits direct antitumor activity against tumor cells dependent upon signaling through PDGFR, KIT, FLT-3, or VEGFR for proliferation and survival in addition to antiangiogenic activity through its potent inhibition of VEGFR and PDGFR signaling [30] (Fig. 1). In mouse xenograft models, SU11248 exhibits broad and potent antitumor activity, causing regression, growth arrest, or substantially reduced growth of various established xenografts derived from human or rat tumor cell lines [31]. Table 1 summarizes the mechanisms of action of both drugs.

## Sorafenib and Sunitinib in the Treatment of Renal Cell Carcinoma, Gastrointestinal Stromal Tumor, and Hepatocellular Carcinoma

### Sorafenib

Phase I studies of sorafenib, involving 163 patients treated with different continuous oral-dosage schedules, identified 400 mg twice daily as the recommended phase II dose [32, 33]. Preliminary data from these studies suggested that sorafenib was associated with clinically durable stabilization of previously progressive disease in patients affected by refractory solid tumors (mostly renal carcinoma). A large phase II randomized discontinuation trial was conducted with sorafenib (400 mg orally twice daily) in patients with various types of tumors. Results have been reported for 202 patients with advanced renal cell carcinoma [34]. After a 12-week induction phase, 65 patients had stable disease and were randomized to remain on sorafenib ($n = 32$) or to take placebo ($n = 33$). The median progression-free survival (PFS) time after randomization was longer with sorafenib than with placebo (24 vs. 6 weeks; hazard ratio [HR] = 0.29; $p = .0087$). The toxicity profile was acceptable, with rash, hand-foot skin reaction, fatigue, and hypertension responsive to standard medications. A subsequent randomized, placebo-controlled, phase III trial called TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial) confirmed the efficacy of sorafenib in cytokine-refractory advanced renal carcinoma patients [35]. Patients enrolled in this trial had received a prior systemic therapy (a cytokine-based regimen) in the prior 8 months. The median PFS times were 24 weeks for sorafenib versus 12 weeks for placebo (HR = 0.44; $p < .00001$). The 12-week progression-free rate was 79% for sorafenib versus 50% for placebo. Sorafenib showed a favorable safety profile, with manageable side effects. The main adverse events were rash (31% any grade, 1% grade 3/4), hand-foot skin reactions (26% any grade, 5% grade 3/4), alopecia (23% any grade, 0% grade 3/4), diarrhea (30% any grade, 1% grade 3/4), nausea (14% any grade, 1% grade 3/4), fatigue (18% any grade, 2% grade 3/4), and hypertension (8% any grade, 1% grade 3/4). A prospectively planned interim overall survival analysis reflecting the crossover impact of placebo patients was then presented [36]. A total of 903 patients were randomized (451 to sorafenib, 452 to placebo), and more than 200 placebo patients crossed over to sorafenib. The median overall survival was 19.3 months for sorafenib versus 15.9 months for placebo (HR = 0.77; 95% confidence interval [CI], 0.63–0.95; $p = .015$). With censoring of crossover data, the median overall survival was 19.3 months for sorafenib versus 14.3 months for placebo (HR = 0.74; 95% CI, 0.58–0.93; $p = .010$). The lower HR observed after censoring placebo patients crossed over to sorafenib suggests a continued beneficial effect of sorafenib.

Based on these results, the U.S. Food and Drug Administration (FDA) announced the approval of sorafenib for patients with advanced renal cancer in December 2005. Moreover, the European Commission recently granted orphan medicinal product status to sorafenib for the treatment of hepatocellular carcinoma [37]. This approval is based on a recommendation from the European Medicines Agency and data from a phase II, single-agent study. In that trial, 137 patients received continuous, oral sorafenib (400 mg) twice daily in 4-week cycles. On the basis of independent assessments, 3 (2.2%) patients achieved a partial response, 8 (5.8%) had a minor response, and 46 (33.6%) had stable disease for at least 16 weeks. Investigator-assessed median time-to-progression (TTP) was 4.2 months, and median overall survival was 9.2 months. Grade 3 and 4 drug-related toxicities included fatigue (9.5%), diarrhea (8.0%), and hand-foot skin reaction (5.1%); 43% of patients treated with sorafenib experienced stable disease for at least 4 months, and an additional 9% of patients experienced tumor shrinkage [38]. Recently, a phase III clinical trial evaluating the efficacy of sorafenib versus placebo in hepatocellular carcinoma has concluded enrollment; data are pending. Moreover, sorafenib recently showed in phase II trials promising preliminary antitumor activity against melanoma in combination with chemotherapy (dacarbazine and temozolomide) [39, 40]. Phase III trials of sorafenib plus chemotherapy in the treatment of metastatic melanoma are ongoing.

**Table 1.** Sorafenib and sunitinib: Mechanisms of action

| Agent | Molecular targets | Action |
|---|---|---|
| Sorafenib | C-RAF, B-RAF, KIT | Inhibition of tumor growth |
| | VEGFR-2,VEGFR-3, PDGFR-$\beta$ | Inhibition of angiogenesis |
| Sunitinib | KIT, FLT-3 | Inhibition of tumor growth |
| | PDGFR, VEGFR | Inhibition of angiogenesis |

Abbreviations: FLT-3, fms-like tyrosine kinase 3; PDGFR, platelet-derived growth factor receptor; KIT, stem cell factor receptor; VEGFR, vascular endothelial growth factor receptor.

## Sunitinib

In phase I clinical studies, the recommended dose of sunitinib was found to be 50 mg orally once daily for 4 weeks, followed by 2 weeks off, in a repeated 6-week cycle [41, 42]. Pharmacokinetic data indicated good oral absorption and a long half-life (~40 hours) for this agent. Promising activity in patients with renal cancers was observed. Using this schedule, a multicenter, phase II clinical trial was conducted to assess the clinical activity and safety of sunitinib as second-line therapy for patients with metastatic renal cancer who progressed after one prior cytokine therapy [43]. Twenty-five (40%) of 63 patients treated with sunitinib achieved a partial response, and 17 additional patients (27%) demonstrated stable disease. The median TTP was 8.7 months (95% CI, 5.5–10.7), whereas the median survival time was 16.4 months (95% CI, 10.8–not yet attained). The most common adverse event was fatigue, which was categorized as grade 3 in seven patients (11%). These results were particularly noteworthy when compared with those of prior studies of second-line therapy in metastatic renal cancer and sustained the rationale of a phase III trial of sunitinib versus interferon-$\alpha$ (IFN-$\alpha$) as first-line treatment of metastatic renal cancer [44]. In this trial, untreated patients with metastatic renal cell carcinoma were randomized 1:1 to receive sunitinib (6-week cycles: 50 mg orally once daily for 4 weeks followed by 2 weeks off) or IFN-$\alpha$ (6-week cycles: 9-million unit subcutaneous injection given three times weekly). The primary endpoint was PFS. Secondary endpoints included objective response rate, overall survival, and adverse events. Seven hundred fifty patients were randomized: 375 to sunitinib, 375 to IFN-$\alpha$. Median PFS assessed by third-party independent review was 47.3 weeks (95% CI, 40.9–not yet attained) for sunitinib versus 24.9 weeks (95% CI, 21.9–37.1) for IFN-$\alpha$ (HR = 0.394; 95% CI, 0.297–0.521; $p < .000001$). The objective response rate by third-party independent review was 24.8% (95% CI, 19.7–30.5) for sunitinib versus 4.9% (95% CI, 2.7–8.1) for IFN-$\alpha$ ($p < .000001$). 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-$\alpha$ ($p < .000001$). Eight percent withdrew from the study because of adverse events on the sunitinib arm versus 13% on the IFN-$\alpha$ arm. These results demonstrate a statistically significant improvement in PFS and objective response rate for sunitinib over IFN-$\alpha$ in first-line treatment of patients with metastatic renal cell carcinoma.

In addition to targeting VEGFRs, sunitinib targets c-Kit, which is often expressed in gastrointestinal stromal tumors (GISTs); thus, it is a good candidate for the treatment of this disease. In a phase I/II study conducted in 97 patients with progressive, metastatic GISTs refractory to imatinib mesylate, sunitinib induced clinical benefit in 65% of patients, with an 8% partial response rate and 58% stable disease rate [45]. A phase III, multicenter, randomized, double-blind, placebo-controlled trial definitively demonstrated the efficacy of sunitinib in the treatment of imatinib-resistant patients with GIST [46, 47]. Sunitinib was administered at 50 mg per day in 6-week cycles (4 weeks on treatment, 2 weeks off). In this trial, treatment was unblinded after progression, and patients who had received placebo were crossed over to sunitinib therapy. Sunitinib treatment resulted in a more than fourfold-longer median TTP (6.3 vs. 1.5 months with placebo; HR = 0.335; $p < .00001$) and a statistically significant longer overall survival time (HR = 0.491; $p = .00674$). The survival benefit for sunitinib may have been underestimated as a result of the crossover of patients from placebo to active treatment. Sunitinib was generally well tolerated with manageable toxicities: fatigue, diarrhea, sore mouth, skin discoloration, and hypertension. Sunitinib therapy induced partial responses in 14 patients (6.8%) and durable stable disease (≥22 weeks) in 36 patients (17.4%) versus 0% partial response and stable disease ≥22 weeks in 2 patients (1.9%) on placebo. Four of nine imatinib-intolerant patients achieved partial response with sunitinib therapy versus zero of four imatinib-intolerant patients treated with placebo. In conclusion, sunitinib significantly prolonged TTP and overall survival in GIST patients for whom imatinib therapy had failed because of resistance or intolerance. This trial is relevant for targeted therapies in oncology because it demonstrated a major clin-

ical benefit from a multitargeted tyrosine kinase inhibitor in patients resistant to a different kinase inhibitor. In consideration of these positive results, in January 2006, the FDA announced the approval of sunitinib malate for patients with advanced renal cell carcinoma and with GIST after disease progression or intolerance to imatinib mesylate.

## Sorafenib and Sunitinb in the Treatment of NSCLC

### Sorafenib

Sorafenib may prove particularly active against NSCLC because the proliferation signaling of the Ras/Raf/MEK/ERK pathway is increased in NSCLC due to an increase in K-ras mutations [48]. Sorafenib showed preclinical activity against NSCLC cell lines. Combined with agents used to treat NSCLC (vinorelbine, cisplatin, and gefitinib), it has demonstrated a delay in tumor growth in preclinical models of NSCLC [49]. In fact, Carter et al. [49] demonstrated that concurrent administration of sorafenib with vinorelbine, cisplatin, or gefitinib is at least as efficacious (in terms of tumor growth delay) as the individual agents alone, with no increase in toxicity. These data support the inclusion of sorafenib in clinical trials in NSCLC employing combinations of both cytotoxic and cytostatic agents.

Liu et al. [50] initiated a single-agent sorafenib trial in patients with relapsed NSCLC to assess clinical response and translational endpoints in tumor biopsies. This phase II trial used a two-stage design targeting an objective response rate that can rule out 5% in favor of a more desirable 20% response rate. Patients with recurrent NSCLC Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 with measurable disease who had received only one prior chemotherapy regimen were enrolled. Sorafenib was administered at 400 mg twice daily continuously on a 28-day cycle. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and tumor biopsy were performed before cycle 1 and at cycle 1, day 15 to study early changes in tumor vascularity and translational endpoints. Six patients were evaluable for toxicity and five for response. Best responses included one partial response with 41% tumor reduction at week 8 that remained in partial response until week 28; one partial response (unconfirmed) observed at week 3; and two having stable disease (16 and 19 weeks, respectively) and one progressive disease after 8 weeks of treatment. All skin toxicities were grade 1 or grade 2 and responded to temporary withdrawal of sorafenib and supportive care. Grade 2 hypertension occurred in one patient (Table 2). Regarding DCE-MRI results, one patient on cycle 1, day 15 showed decrease in permeability parameters and tumor size; DCE-MRI from the other two patients (one progressive disease, one stable disease for 16 weeks) showed no decrease in the permeability parameters. These data suggested sorafenib was well tolerated and active against relapsed NSCLC. Preliminary evidence of objective response was deemed to warrant second-stage accrual.

Gatzemeier et al. [51] performed a multicenter, uncontrolled, phase II trial that evaluated efficacy and safety of sorafenib (400 mg twice daily, continuous) in patients with relapsed or refractory advanced NSCLC. Plasma for proteomic biomarker analysis (enzyme-linked immunosorbent assay [ELISA] [$n = 44$]; mass spectrometry [$n = 43$]) was obtained at screening, day 21 of cycle 1, and day 1 of cycle 3; 52 of 54 patients enrolled received sorafenib. Most (49/52) patients who received sorafenib had stage IV NSCLC; 30 patients (59%) of 51 evaluable for efficacy had stable disease. Although there were no confirmed partial responses, tumor shrinkage was observed in 15 (29%) patients (4 had ≥30% shrinkage). Patients with stable disease had a median PFS of 23.7 weeks, whereas all evaluable patients ($n = 51$) had a median PFS of 11.9 weeks and median overall survival of 29.3 weeks. The most frequent drug-related adverse events observed in 52 patients included diarrhea (21 patients [40%]), hand-foot skin reaction (19 patients [37%]), and fatigue (14 patients [27%]). Grade 3 hypertension occurred in two patients (4%) (Table 2). Three patients discontinued treatment because of adverse events (hand-foot skin reaction, elevated lipase, and myocardial infarction). There were nine deaths within 30 days of discontinuation of sorafenib (five for progressive disease, two for cardiopulmonary arrest, one for hemoptysis, and one for unknown causes). The levels of five proteins measured by ELISA, either at screening or change over treatment duration, correlated significantly with TTP or maximum tumor shrinkage. Levels of five additional proteins, identified by mass spectrometry, also correlated with TTP. The authors concluded that identified biomarkers may help assess efficacy of sorafenib in NSCLC patients and that 400 mg of sorafenib twice daily is generally well tolerated and shows efficacy in patients with advanced, progressive NSCLC, with approximately 60% of patients achieving disease stabilization.

In a multicenter, international, single-arm phase II study, Gondek et al. [52] evaluated the impact of sorafenib in the treatment of advanced NSCLC on patients' health-related quality of life (HRQL) and symptoms.

**Table 2.** Safety profile of sorafenib and sunitinib in phase II studies on non-small cell lung cancer

| Reference | Drug | Grade 1/2 toxicities | Grade 3/4 toxicities | Grade 5 toxicities |
|---|---|---|---|---|
| Liu et al. [50] | Sorafenib | Grade 1/2 skin toxicity: acne-like drug-related rash (5/6 pts), hand-foot syndrome (6/6 pts), keratoacanthoma (1/6 pts), vasculitis (1/6 pts), grade 2 hypertension (1/6 pts) | Grade 3 anemia (1/6 pts), hyponatremia (2/6 pts), nausea (1/6 pts); no grade 4 toxicities occurred | |
| Gatzemeier et al. [51] | Sorafenib | Diarrhea (40%), hand-foot skin reaction (27%), fatigue (27%), nausea (25%) | Hand-foot skin reaction (10%), hypertension (4%) | |
| Socinski et al. [53] | Sunitinib | Asthenia/fatigue (68%), anorexia (40%), dyspnea (37%), cough (35%), nausea (33%), mucositis (32%), dysgeusia (25%), diarrhea (21%), vomiting (19%), constipation (19%) | Fatigue/asthenia (21%), nausea (7%), vomiting (7%), abdominal pain (7%), hypertension (5%) | Pulmonary hemorrhage (2/63 pts), cerebral hemorrhage (1/63 pts) |

Abbreviation: pts, patients.

HRQL was measured by the Functional Assessment of Cancer Therapy-Lung questionnaire. The authors reported that sorafenib did not adversely impact patient-reported outcomes in function and symptom response during the treatment period.

### Sunitinib

Socinski et al. [53] reported the initial data of an open-label, two-stage, multicenter phase II trial evaluating the single-agent activity of sunitinib in refractory NSCLC. Eligibility criteria included confirmed diagnosis of NSCLC, ECOG PS of 0–1, no recent gross hemoptysis, no brain metastases, patients previously treated with one to two chemotherapy regimens, and adequate end-organ function. Patients received sunitinib at 50 mg per day p.o. for 4 weeks followed by 2 weeks off treatment (6 weeks considered a cycle). A total of 64 patients were enrolled, and 63 patients were treated. To date, 63 patients have started cycle 1, 46 cycle 2, 22 cycle 3, 6 cycle 4, and 1 cycle 5. Grade 3/4 toxicities included fatigue/asthenia (21%) and hypertension (5%). Most toxicities were grade 1/2 and included asthenia/fatigue (68%) and anorexia (40%). Grade 5 toxicities included pulmonary hemorrhage (two patients) and cerebral hemorrhage (one patient) (Table 2). Thus far, six confirmed partial responses have been observed among 63 treated patients (9.5%; 95% CI, 3.6–19.6). Stable disease was observed in an additional 27 patients (43%). A progression-free survival of 11.3 weeks and median overall survival of 23.9 weeks were reported. The authors concluded that sunitinib has provocative single-agent activity and is well tolerated in previously treated patients with recurrent and advanced NSCLC, with the level of activity similar to currently approved agents. The trial is being extended to explore a continuous dosing strategy of sunitinib at 37.5 mg/day p.o. As mentioned above, three hemorrhage-related deaths were reported in this study. The pulmonary events occurred in two patients with squamous cell carcinoma (22% of the patients enrolled in this study had squamous histology). In the near future, it will be interesting to compare the potential for hemorrhagic toxicity, including the class effect of bleeding/thrombosis, sunitinib, and sorafenib versus bevacizumab. Such a comparison will clarify whether the future development of sorafenib and sunitinib in NSCLC will be limited to nonsquamous NSCLC as for the other angiogenesis inhibitor bevacizumab [8].

## Future Clinical Development of Sorafenib and Sunitinib in the Treatment of Advanced NSCLC

Future clinical development of sorafenib and sunitinib in the treatment of advanced NSCLC includes combination with chemotherapy, combination with other targeted

therapies, and single-agent therapy. Two separate randomized phase III trials of sorafenib plus chemotherapyversus chemotherapy alone are ongoing—one with carboplatin plus paclitaxel as the chemotherapy regimen, the other with cisplatin plus gemcitabine. A National Cancer Institute-sponsored ECOG trial of single-agent sorafenib in previously treated patients with NSCLC is ongoing. This is a large, randomized discontinuation study. Moreover, several other phase I/II studies are ongoing with sorafenib combined with various chemotherapeutic (irinotecan, dacarbazine, and gemcitabine) or molecularly targeted (gefitinib) agents in advanced solid tumors to maximize the therapeutic potential of the drug [54–58]. Specifically, a phase I study of sorafenib plus gefitinib, an EGFR-TKI, demonstrated that sorafenib and gefitinib could be combined at full dose, 400 mg twice daily, and 250 mg daily [56]. A phase I study of sorafenib and erlotinib performed on 17 patients with advanced solid tumors showed that the recommended dose for a phase II trial was 400 mg twice daily for sorafenib and 150 mg/day for erlotinib, corresponding to the full recommended doses of both agents, with acceptable toxicity [59]. Our group recently launched a phase II randomized trial of sorafenib plus gemcitabine and sorafenib plus erlotinib in advanced NSCLC elderly patients (>70 years) or with a PS of 2. Given the positive results obtained with bevacizumab in the treatment of advanced NSCLC, both combined with chemotherapy and with erlotinib [8, 9], the combination of bevacizumab with sorafenib or sunitinib is of great interest. Azad et al. [60] performed a phase I dose-escalation study with the combination of sorafenib and bevacizumab in the treatment of advanced solid tumors. The authors theorized that combining the two agents would have synergistic therapeutic effects. In this trial, the combination of sorafenib and bevacizumab seemed to increase both clinical effect and toxicity at recognized single-agent doses. The suggested schedule for further study features 200 mg of sorafenib twice daily on days 1–5 for 1 week and 5 mg/kg bevacizumab for 2 weeks.

A possible future clinical development of sunitinib may be in bevacizumab-resistant NSCLC. Some interesting data have recently been reported for metastatic renal cell carcinoma. The activity of sunitinib in patients refractory to VEGF-binding agents such as bevacizumab has been evaluated in a phase II study conducted in bevacizumab-refractory metastatic renal cell carcinoma [61]. It was hypothesized that tumor resistance to bevacizumab might be driven, in part, through pathways sensitive to inhibition by sunitinib. Thirty-two of 60 patients enrolled were evaluable for response; 28 patients were too early for assessment. Twenty-six patients (81%) demonstrated some degree of tumor shrinkage, including four patients (13%; 95% CI, 4–29) who demonstrated an objective partial response. Thus, sunitinib has substantial antitumor activity in bevacizumab-refractory metastatic renal cell carcinoma patients, suggesting that sunitinib may inhibit signaling pathways involved in bevacizumab resistance. The precise mechanisms of response to sunitinib in bevacizumab-refractory tumors will require additional studies.

A very interesting preclinical model recently proposed has suggested a possible clinical development of sunitinib in the treatment of solid tumors, including NSCLC. Seeking to improve efficacy against otherwise intractable end-stage pancreatic islet tumors, two receptor tyrosine kinase inhibitors, imatinib and sunitinib, were used to disrupt PDGFR-mediated pericyte support of tumor endothelial cells in concert with maximum-tolerated dose (MTD) or metronomic chemotherapy and/or VEGFR inhibition [62]. Imatinib, despite equivocal efficacy as monotherapy, reduced pericyte coverage of tumor vessels and enhanced efficacy in combination with metronomic chemotherapy or VEGFR inhibition. A regimen involving all three proved even more effective. The MTD using cyclophosphamide caused transitory regression but then rapid regrowth in contrast to metronomic cyclophosphamide plus imatinib, which produced stable disease. The MTD regimen elicited apoptosis of tumor cells but not endothelial cells, whereas the other regimens increased endothelial cell apoptosis concordant with efficacy. A "chemo-switch" protocol, involving sequential MTD and then metronomic chemotherapy, overlaid with multitargeted inhibition of PDGFR and VEGFR, yielded complete responses and unprecedented survival advantage in this model. This study demonstrates a potentially tractable clinical strategy in a stringent preclinical model, wherein standard-of-care chemotherapy is followed by a novel maintenance regimen: PDFGR is targeted to disrupt pericyte support, whereas metronomic chemotherapy and/or VEGFR inhibitors target sensitized endothelial cells, collectively destabilizing pre-existing tumor vasculature and inhibiting ongoing angiogenesis.

## Conclusion

Lung cancer is a heterogeneous disease with multiple mutations. It is unlikely that any one signaling pathway is driving the oncogenic behavior of tumors. With the exception of rare cancers in which growth can depend upon a single factor, selective targeted agents seem to have limited single-agent activity. This is fully in line with the concept that for most tumors there are multiple factors driving tumor growth. Future drug development should focus on somewhat lessening selectivity. Simultaneous targeted inhibi-

tion of multiple signaling pathways could be more effective than inhibiting a single pathway in cancer therapies and specifically in NSCLC treatment. The multikinase inhibitors sorafenib and sunitinib can offer multiple targeted action with single-agent therapy; they have already demonstrated efficacy and safety in the treatment of metastatic renal cell carcinoma and GIST, and their mechanism of action and preclinical data in phase II trials available to date suggest that they may also play a major role in the treatment of NSCLC in the near future.

## Disclosure of Potential Conflicts of Interest

C.G. has acted as a consultant for Eli Lilly and Company, GlaxoSmithKline, Roche, and Dompé.

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