Phase 2 Studies of Sunitinib and AG013736 in Patients with Cytokine-Refractory Renal Cell Carcinoma

Daniel J. George

Abstract
Frequent loss of the von Hippel-Lindau (VHL) gene product in conventional-type renal cell carcinoma results in constitutive expression of proangiogenic growth factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). VEGF and PDGF function in a paracrine manner to stimulate tumor angiogenesis that results in a hypervascular phenotype. Dependency on this hypervascularity is underscored by the recent clinical efficacy shown by inhibition of the VEGF pathway. Most strategies that primarily target the VEGF pathway (neutralizing antibodies or receptor tyrosine kinase inhibitors) result in objective tumor responses in ≤10% of cases but show a significant delay in time to disease progression. In contrast, two multitargeted receptor tyrosine kinase inhibitors that target both VEGF and PDGF receptors (sunitinib and AG013736) have shown ≥40% objective responses with clinically important duration. Several hypotheses may explain the discrepancy of these response rates from other strategies in the class, including the synergistic effects of dual inhibition of VEGF and PDGF receptors, supported by preclinical studies. Ultimately, further clinical investigations with pharmacodynamic and correlative science endpoints are needed to clarify the mechanisms of action and resistance to build on the biological and clinical effects of these multitargeted agents.

Insights into the underlying biology of renal cell carcinoma (RCC) have led to the development of novel targeted therapies. In particular, the reclassification of RCC into distinct histologic subtypes in the 1980s led to the identification of clear cell or conventional-type RCC as the predominant form. Association of von Hippel-Lindau (VHL) disease with conventional-type RCC and later VHL gene mutations with sporadic conventional-type RCC identified the dominant genetic profile of this disease. During the next 10 years, elucidation of VHL protein biology and its role in regulating hypoxia-inducible factor and proangiogenic growth factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), identified these proteins as potential therapeutic targets (1, 2).

VEGF and PDGF are families of three to five different genes that each encode related peptides that function primarily in a paracrine manner to stimulate tumor vasculature formation (3, 4). Briefly, these peptides circulate as homodimers and bind to cell surface tyrosine kinase receptors expressed on the surface of target cells activating signal transduction and downstream cellular processes, such as proliferation and migration. VEGF is thought to primarily stimulate the proliferation, migration, and survival of endothelial cells, which form the framework of immature new vessels. PDGF is thought to function as a growth signal for pericytes, cells that line these nascent vessels to stabilize them. Loss of VHL protein function causes long-term expression of these and other proangiogenic growth factors and results in the hypervascular phenotype characteristic of conventional-type RCC.

During the past 10 years, small-molecule receptor tyrosine kinase inhibitors have been developed to block the function of VEGF and PDGF receptors. Previous agents have suffered from poor pharmacokinetics and bioavailability and limited single-agent activity (5, 6). However, during the past 5 years, two agents have shown robust clinical effects in several phase 2 multicenter studies in RCC: SU11248 or sunitinib (Sutent, Pfizer, Inc., New York, NY) and AG013736 (Pfizer). This review describes the clinical data associated with each of these agents and discusses possible explanations for these impressive clinical results.

Sunitinib Malate

Preclinical studies. Sunitinib is an orally bioavailable oxindole small-molecule multi-tyrosine kinase inhibitor specifically selected for its inhibition of VEGF receptor 2 (VEGFR-2) and PDGF receptor B (PDGFR-B; ref. 7). This compound is a third-generation multi-tyrosine kinase inhibitor preceded by SU5416 (a potent VEGFR inhibitor that required i.v. formulation) and SU6668 (an orally bioavailable PDGFR inhibitor with less affinity for VEGFR). Biochemical assays of sunitinib showed inhibition of VEGFR-2 and PDGFR-B phosphorylation, whereas preclinical assays showed antiangiogenic activity in both VEGF- and PDGF-dependent assays (8). In vivo studies corroborated these results in addition to showing antitumor activity.
Phase 1 studies. In 2001, several phase 1 studies were initiated using sunitinib in a variety of intermittent dosing regimens in patients with advanced leukemia, advanced solid tumors, and imatinib-refractory gastrointestinal stromal tumors (9–12). Dose escalation occurred up to 75 mg/d with no food effect and no evidence of drug accumulation across cycles. Therapeutic plasma concentrations (50-100 ng/mL) were achieved in most patients with daily doses of ≥50 mg. Dose-limiting toxic effects, including fatigue, diarrhea, cytopenia, and skin toxic effects, were reversible with discontinuation of treatment. In phase 1 testing of advanced solid tumors, the 50-mg/d dose given on a 4-week on/2-week off schedule showed good tolerability and efficacy, with four of seven patients with advanced RCC showing objective response (9).

Phase 2 studies in RCC. Two phase 2 trials of sunitinib in cytokine-refractory, metastatic RCC have been conducted (13). Both trials included patients with cytokine-refractory, metastatic RCC with good performance status, organ function, and measurable disease. Most patients had clear cell histology and had undergone prior nephrectomy. Sunitinib was given as 50 mg/d for the first 4 weeks of repeated 6-week cycles until either progressive disease unacceptable toxicity or withdrawal of consent occurs. The first trial (n = 63) was a proof-of-concept study to confirm the preliminary evidence of objective responses seen in phase 1 testing. The primary end point of this study was objective response rate. Published results revealed an objective partial response in 25 patients (40%; 95% confidence interval, 28-53%; refs. 13, 14). Best response of stable disease for 3 months was observed in an additional 17 patients (27%), most of whom showed some evidence of disease regression. Twenty-one patients (33%) had either progressive or stable disease of <3 months’ duration or were not assessable.

The second trial (n = 106) was a pivotal trial to confirm the objective response rates seen in the first study (14). As a pivotal trial, the eligibility was restricted to patients with clear cell RCC only and required that patients had both prior nephrectomy and Response Evaluation Criteria in Solid Tumors–defined progression within 9 months after cytokine therapy. Results from this trial revealed remarkably similar findings to the first study with objective partial response in 44 patients (1 complete response and 43 partial responses; objective response rate, 44%; 95% confidence interval, 34-53%). An additional 23 patients (22%) showed stable disease for 3 months, and 36 patients (34%) had either progressive or stable disease of <3 months’ duration. Of note, these results conflict with those from this trial revealed remarkably similar findings to the first study with objective partial response in 44 patients (1 complete response and 43 partial responses; objective response rate, 44%; 95% confidence interval, 34-53%). An additional 23 patients (22%) showed stable disease for 3 months, and 36 patients (34%) had either progressive or stable disease of <3 months’ duration. Of note, these results conflict with those

The most common adverse events in these trials were fatigue, diarrhea, nausea, stomatitis, hand-foot syndrome, and hypertension and were generally low grade (common toxicity criteria grade 1 or 2). The common toxicity criteria grade 3 adverse events for trial 1 and trial 2, respectively, were fatigue (11% and 11%), diarrhea (3% and 3%), nausea (3% and 0%), stomatitis (2% and 5%), hand-foot syndrome (2% and 7%), and hypertension (2% and 6%). Laboratory abnormalities, including grade 3 neutropenia (13% and 16%), were seen but typically occurred on day 28 of cycles when drug was scheduled to be held, thus generally did not require additional dose interruptions. Grade 3 anemia (10% and 6%) and thrombocytopenia (0 and 6%) were less common. Elevated serum levels of lipase (21% and 17%) were seen but did not correlate with clinical symptoms.

In an exploratory analysis, data were pooled from both studies and correlated with outcome. Correlating best objective response with duration of response revealed 71 patients with complete or partial response with a median duration of 14.8 months (95% confidence interval, 10.9-24.2) versus 7.9 months (95% confidence interval, 5.5-8.2) in 40 patients with stable disease, suggesting that the degree of tumor regression is clinically significant. In a separate correlation, pretreatment variables for poor prognosis, including anemia and decreased performance status, correlated with a shorter time to progression (Table 1).

AG013736

Preclinical studies. AG013736 (Axitinib, Pfizer) is an imidazole derivative that inhibits the tyrosine kinase portion of all VEGFRs and PDGFR-B at low nanomolar concentrations (15). In vivo animal studies showed that tumor regression was preceded by loss of vessel patency and blood flow with 2 days of treatment with AG013736 (16). Oral, twice-daily AG013736 results in significant tumor growth inhibition in several human xenograft and murine models through an antiangiogenic mechanism.

Phase 1 studies. A multicenter phase 1 trial of AG013736 was conducted in 36 patients with refractory solid tumors, including six RCC patients (15). This dose escalation study evaluated the safety and tolerability of continuous twice daily dosing. Secondary end points included determining the maximum tolerated dose and recommended phase 2 dose as well as pharmacokinetic variables. Additionally, the trial assessed changes in tumor blood flow associated with AG013736 by dynamic contrast-enhanced magnetic resonance imaging acquired at baseline and after 2 days of treatment (17). Doses ranged from 5 mg twice daily to 30 mg twice daily, and dose-limiting toxic effects included hypertension, fatigue, and

Table 1. Pretreatment prognostic factors for response to sunitinib

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<tr>
<th>Variable</th>
<th>Median PFS (95% CI)</th>
<th>P</th>
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<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
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<tr>
<td>≥ LLN</td>
<td>10.9 (8.7-14.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt; LLN</td>
<td>4.2 (2.6-5.5)</td>
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<tr>
<td>ECOG 0</td>
<td>10.4 (8.2-12.1)</td>
<td>0.0016</td>
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<tr>
<td></td>
<td>5.1 (2.8-8.1)</td>
<td></td>
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<tr>
<td>Liver metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.5 (4.1-8.4)</td>
<td>0.0272</td>
</tr>
<tr>
<td>No</td>
<td>8.8 (7.9-12.0)</td>
<td></td>
</tr>
<tr>
<td>No. of metastatic sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>13.8 (7.9-21.2)</td>
<td>0.0412</td>
</tr>
<tr>
<td>≥2</td>
<td>7.9 (5.5-8.7)</td>
<td></td>
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</tbody>
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Abbreviations: PFS, progression-free survival; 95% CI, 95% confidence interval; ECOG, Eastern Cooperative Oncology Group.
diabetes. Hypertension was the predominant adverse event, with 22 (61%) of 36 patients experiencing hypertension of any grade and 11 (31%) of these patients showing grade 3 hypertension. The maximum tolerated and recommended phase 2 dose was 5 mg twice daily in the fasted state. Dynamic contrast-enhanced magnetic resonance imaging data were obtained from 17 patients and revealed a linear correlation between dynamic contrast-enhanced magnetic resonance imaging variables and AG013736 drug levels, supporting a greater effect on tumor vasculature with increasing AG013736 drug exposure.

**Phase 2 study in RCC.** Based on a strong genetic rationale and the in vitro evidence of antiangiogenic effect and VEGFR inhibition by AG013736, a phase 2 trial of AG013736 in cytotoxic-refractory, metastatic RCC was conducted (18). The study included patients with cytotoxic-refractory, metastatic RCC with good performance status, organ function, and measurable disease. Additional eligibility included measurable, metastatic RCC, and baseline blood pressure controlled to 140/90 mm Hg or less (medication permitted). AG013736 was given as 5 mg twice daily in a fasted state until Response Evaluation Criteria in Solid Tumors–defined disease progression or unacceptable toxicity occurs. The primary end point of this study was objective response rate.

Fifty-two patients were enrolled and eligible for evaluation. The cohort was typical of a phase 2 RCC population with a median age of 58 years (range, 35-85 years), with 60% of patients having an Eastern Cooperative Oncology Group performance status 0. Most patients had clear cell histology and had undergone prior nephrectomy. Twenty-four patients (46%) achieved a partial response by the Response Evaluation Criteria in Solid Tumors (Table 2). Additionally, 21 patients had a best response of stable disease, with 20 of those patients experiencing tumor regression not meeting the Response Evaluation Criteria in Solid Tumors for objective response. Thus, in total, 74% of patients experienced some degree of tumor regression. Therapy was well tolerated, with most side effects being grade 1 or 2, including hypertension, diarrhea, fatigue, nausea, and proteinuria. Significant grade 3 or 4 events included hypertension in 8 patients (15%) and 4 patients (8%) with diarrhea and fatigue each. Six patients discontinued therapy due to an adverse event (hypertension, stomatitis, fatigue, diarrhea, or joint pain).

**Antiangiogenesis and tumor regression.** One of the interesting early findings with both sunitinib and AG013736 is the relatively robust objective response rates seen in these phase 2 studies. In contrast, most studies with VEGF-targeted strategies in patients with metastatic RCC have shown evidence of modest tumor regressions, but with objective response rates of ≤10% (19–21). There are several possible hypotheses to explain these findings, including (a) these differences are due to patient selection and variation in measurement techniques; (b) these agents are more potent at inhibiting the VEGF-VEGFR signaling pathway than other strategies; (c) they have direct cytotoxic effects on RCC epithelial cells via yet unidentified pathways; or (d) they inhibit other angiogenic targets. Of these hypotheses, the last one, that these agents may inhibit additional angiogenic pathways, particularly PDGF, is most plausible. Sunitinib is unique in the class because preclinical assays suggest it is a more potent PDGF inhibitor than a VEGFR inhibitor, whereas AG013736 has shown similarly potent VEGF and PDGF inhibition (22). In contrast, sorafenib and PTK787/ZK 222584 have reported IC₅₀ inhibition of PDGF at 4- to 5-fold higher concentrations (23, 24).

Preclinical studies by Bergers et al. tested the hypothesis that inhibition of both VEGF and PDGF is more potent at regressing tumors than either target alone (25). Using a transgenic mouse model that spontaneously develops scores of pancreatic islet cell tumors, they tested semispecific inhibitors of VEGFR (SU5416) or PDGFR (SU6668) alone or in combination in mice when tumors became significantly measurable (to regress tumors). They showed that treatment with a primarily VEGFR-targeted agent (SU5416) did not result in tumor regression, whereas treatment with a primarily PDGFR-targeted agent (SU6668) resulted in slight tumor regressions. In contrast, the combination of the two agents (SU5416 and SU6668) resulted in better VEGF and PDGFR inhibition than either agent alone and in significant tumor regressions not seen with either treatment alone. They conclude that tumor vasculature is made up of both VEGF-dependent and PDGF-dependent components, and targeting both tumor vascular components results in greater regression in well-established tumors. The lack of specific pharmacodynamic effects associated with inhibition of PDGF signaling makes assessment of the relative contributions of these targets difficult. As mentioned above, other hypotheses, including but not limited to non-target effects, such as direct cytotoxicity on RCC cells, or greater inhibition of VEGF signaling, could also explain these effects.

**Future studies.** Ongoing studies are evaluating these agents in other settings of RCC as well. A first-line study comparing sunitinib to IFN-α in patients with untreated metastatic clear cell RCC has completed accrual and was reported at American Society of Clinical Oncology 2006 showing a robust superiority of sunitinib versus IFN in median progression-free survival (11 versus 5 months, \( P < 0.000001 \); reference). Sunitinib was also tested in a multicenter phase 2 study in patients with bevacizumab-refractory metastatic RCC, which showed 84% of patients with tumor shrinkage and stable disease (reference). Meanwhile, AG 013736 has completed accrual to a phase 2 study in patients with RCC previously treated with sorafenib. Phase 1/2 combination studies of these agents with chemotherapy, hormonal therapy, and other relevant targeted therapies are ongoing and are discussed in accompanying articles. In particular, combinations with mammalian target

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<tr>
<th>Table 2. Best tumor response by the Response Evaluation Criteria in Solid Tumors in patients treated with AG013736</th>
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<tr>
<td><strong>Best response by RECIST (n = 52)</strong></td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>95% CI</td>
</tr>
<tr>
<td>Stable disease</td>
</tr>
<tr>
<td>No. with Tumor Shrinkage</td>
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<tr>
<td>No response</td>
</tr>
<tr>
<td>Progression</td>
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<tr>
<td>Indeterminate</td>
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Abbreviations: 95% CI, 95% confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors.
of rapamycin inhibitors or bevacizumab are particularly promising given their single-agent activity in RCC.

**Summary**

Both sunitinib and AG013736 result in significant objective responses in ≥40% of patients treated in three separate multicenter phase 2 studies. Although larger randomized controlled trials are needed to correlate these impressive objective responses with other clinical end points (progression-free survival and overall survival), these results strongly suggest these agents have a dramatic effect on the natural history of this disease. Explanations for the discrepancy in objective response rates seen with these agents compared with other VEGF-targeted strategies include better inhibition of other angiogenic targets, including PDGFR.

**Open Discussion**

**Dr. Atkins:** Clearly, patients who have performance status 1 or low hemoglobin levels do worse; so, how much of the poorer outcome you are seeing is related to disease rather than diminished effect of treatment?

**Dr. George:** Performance status 1 isn’t a negative prognostic factor. Performance status 2 or more is really associated with outcome in terms of multivariate analysis.

**Dr. Rini:** Are these just the patients who are going to do poorly anyway, and their von Hippel-Lindau (VHL) status is irrelevant? Or, is there some disease biology that is affecting them poorly anyway, and their von Hippel-Lindau (VHL) status is just a measure of their disease biology?

**Dr. George:** If a patient has a hemoglobin of 37, you do not think of that patient as symptomatic. The same is true with performance status 1. It’s not a matter of disease burden worsening outcome; it is more of a marker.

**Dr. Atkins:** If you look at the sorafenib data from the Targets trial, the impact of the drug was the same for each stratification. Just because the progression-free survival is shorter does not mean that patients are not benefitting from the drug.

**Dr. George:** Absolutely, and I’m not saying that I wouldn’t treat these patients with sunitinib just because they have a 4.2-month progression-free survival because it would probably be 2 months if you do not treat them.

**Dr. Atkins:** It is also not an argument for saying you should treat them before they become symptomatic. Although such patients may have a median of 6 months longer time to progression, those 6 months may be the time it takes them to become symptomatic.

**Dr. George:** The question is whether this is lead-time bias, or if there is a subset of patients who will benefit longer? In general, most of our therapies work better in asymptomatic patients with earlier-stage disease.

**Dr. Flaherty:** Is there evidence that any patients have been given supplementation? Should we be designing trials where people who get these agents also get supplementation to optimize the treatment to determine the difference between a disease effect and an effect that is altering the pathway of treatment?

**Dr. George:** Certainly, many of these patients get and respond to growth factor. To what extent improvement in hemoglobin correlates with better outcome is unknown.

**Dr. Flaherty:** It still could be lead-time bias. Not every patient starts therapy right away because some patients feel well off therapy. Wouldn’t it be nice to maximize that period when they are off treatment?

**Dr. Atkins:** Yes, for two reasons. The first reason is that once you start treatment some patients are essentially committed to treatment until they’re symptomatic from their disease, and then they develop other problems. The second reason is you lose that window of opportunity to investigate other approaches, such as immunotherapy or combination therapy, that may be important to improving the percentage of long-term responding patients.

**Dr. George:** True, although you could argue that immunotherapy and/or combination therapy would be more toxic than monotherapy with a multitraged agent. The second point I would make is that if you look at imatinib and chronic myeloid leukemia (CML), patients in blast crisis definitely see a clinical benefit with imatinib, but the length of benefit is probably short. If you look at patients with chronic-phase CML, you see a much greater duration of effect. We are treating these patients with a life expectancy of 5 years or more proactively, shouldn’t we do the same for patients with equivalently indolent RCC?

**Dr. Flaherty:** CML is a changing disease. If left alone, it evolves into something that is more molecularly complex and more difficult to treat.

**Dr. Rini:** We all refer to the Mozer factors that were developed for cytokine therapy. Developing the same sort of clinical factors and schemas for vascular endothelial growth factor treatment would be valuable, even if they do not necessarily reflect the biology of disease or impact response per se.

**References**


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