Pharmacotherapy Options in Advanced Renal Cell Carcinoma: What Role for Pazopanib?

Michael R. Harrison
Assistant Professor of Medicine, Division of Medical Oncology, Department of Medicine, Duke Cancer Institute, DUMC 102002, Durham, NC 27710. Corresponding author email: michael.harrison@duke.edu

Abstract: Over the last 6 years, the treatment of metastatic renal cell carcinoma (mRCC) has undergone dramatic changes. A better understanding of the pathogenesis and tumor biology of sporadic renal cell carcinoma has led to the approval of 6 drug regimens: 3 oral multi-targeted tyrosine-kinase inhibitors (sorafenib, sunitinib, and pazopanib), 2 inhibitors of the mammalian target of rapamycin (temsirolimus and everolimus), and 1 monoclonal antibody against the vascular endothelial growth factor (bevacizumab). Pazopanib, a multi-targeted tyrosine kinase inhibitor that targets VEGFR-1, -2, and-3; PDGFR-α and PDGFR-β, and c-Kit, was approved for the treatment of mRCC in October 2009, several years after the other drugs in its class. The efficacy and safety of pazopanib in Phase I, II, and III trials will be examined and its role in mRCC treatment will be described. Future studies that may clarify pazopanib’s role in mRCC will be discussed. Based on pazopanib’s demonstrated efficacy in treatment-naïve and cytokine-refractory patients, along with a seemingly favorable toxicity profile compared with other multi-targeted tyrosine-kinase inhibitors, pazopanib may have a unique niche in the armamentarium of treatment options for mRCC. Results from ongoing studies are awaited to confirm pazopanib’s favorable efficacy-toxicity ratio, especially in comparison with the previous first-line standard-of-care, sunitinib.

Keywords: pazopanib, GW786034, VEGFR, TKI, renal cell carcinoma
Introduction

There were an estimated 58,000 new cases and 13,000 deaths of kidney cancer in the US in 2010.¹ For localized kidney cancer, nephrectomy is the mainstay of treatment; however, about 20%–30% of these patients will develop recurrence (ie, stage IV or metastatic disease).² In addition, as many as one-third of all patients present with metastatic disease at initial diagnosis.³ About 90% of kidney cancers are renal cell carcinomas (RCC), and up to 80% of these are of clear-cell histology.⁴,⁵ Despite limited clinical efficacy and significant toxicity, cytokine therapies (interferon-α [IFN-α] and interleukin-2 [IL-2]) were the standard of care in the pre-targeted therapy era.⁶ However, understanding of the pathogenesis of sporadic (non-inherited) clear cell RCC has led to advances in treatment for advanced RCC and the advent of the targeted therapy era. Specifically, it is now understood that dysfunction of the von Hippel-Lindau (VHL) tumor suppressor gene leads to intracellular accumulation of the hypoxia-inducible factor (HIF), which results in secretion of factors under its control: vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and others.⁷ Efforts to target HIF-mediated pathways have proven successful thus far in therapy of advanced RCC, with the bulk centered around inhibition of the VEGF axis (“downstream” of HIF) and mammalian target of rapamycin axis (“upstream” of HIF).

Treatment options for advanced RCC have now dramatically increased, with six new treatments approved in the United States since December 2005. Three multi-targeted tyrosine kinase inhibitors of the VEGF receptor and PDGF receptor have been approved: sorafenib⁸ (Nexavar®, Bayer; December 2005), sunitinib⁹ (Sutent®, Pfizer; January 2006), and pazopanib¹⁰ (Votrient®, GlaxoSmithKline; October 2009). Two agents that inhibit mTOR have also been approved: temsirolimus¹¹ (Torisel®, Pfizer; May 2007) and everolimus¹² (Afinitor®, Novartis; March 2009). Finally, a humanized monoclonal antibody against VEGF, bevacizumab¹³ (Avastin®, Genentech; July 2009), was approved in combination with interferon-α. While there are now multiple options from which patients with mRCC and their doctors may choose, there may be more than one reasonable choice in a particular setting and little evidence to guide amongst them. In these situations, when head-to-head comparisons of efficacy have not been performed, clinical decisions may be made based on other factors, like toxicity profiles, route of administration, patient comorbidities, and financial considerations. For example, sunitinib has been the standard of care for treatment-naïve patients with good-intermediate risk clear cell RCC. Recently, bevacizumab + IFN-α and pazopanib have provided additional options in this setting. This article will review the evidence for pazopanib in various settings of treatment for patients with advanced RCC, develop evidence-based treatment algorithms, and discuss trials that may assist in making treatment decisions.

Mechanism of Action, Pharmacokinetics, and Metabolism Profile: Preclinical and Early Clinical Data

Pazopanib (Votrient®, GW786034; GlaxoSmithKline) is an oral multi-targeted tyrosine kinase inhibitor (TKI) of VEGFR-1, -2, and -3; PDGFR-α, PDGFR-β; and c-kit.¹⁵,¹⁶ Pazopanib is an indazolylpyrimidine 5-[[4-{(2, 3-dimethyl-2H-indazol-6-yl)methylamino}-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide and was discovered during screening for compounds that inhibit the vascular endothelial growth factor receptor-2 (VEGFR-2).¹⁶,¹⁷ In vitro, the kinase selectivity of pazopanib was evaluated in a panel of 242 purified human kinases and cellular potency was examined using ligand-induced autophosphorylation assays.¹⁸ Pazopanib inhibited VEGFR-2, PDGFR-β and c-kit at low nanomolar concentrations, as did sunitinib, whereas pazopanib did not significantly inhibit Flt-3 like sunitinib. In in vivo studies in mice, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation, tumor angiogenesis, and growth of various xenograft tumor types, including the Caki-2 renal cell carcinoma model.¹⁹ Pharmacokinetic and pharmacodynamic studies showed that a pazopanib concentration of ≥40 µmol/L inhibited VEGFR-2 phosphorylation in mice, whereas below this concentration inhibition was minimal. These data differed from the IC₅₀ of 0.02 µmol/L based on VEGF-stimulated proliferation in in vitro models, which was attributed to significant protein binding of pazopanib.¹⁹ Therefore, a target steady-state concentration (Cₘ₉₅) of >40 µmol/L was selected for the Phase I trial.²⁰
Pazopanib pharmacokinetics were evaluated in a Phase I dose-escalation study in human subjects with refractory solid tumors (discussed in more detail in the next section).\textsuperscript{20} Pazopanib is absorbed orally; however, with low oral bioavailability and solubility, there was limited absorption above doses of 800 mg. A median time to peak plasma concentration of 2 to 4 hours and a mean half-life of 30.9 hours after administration of an 800 mg dose was observed.\textsuperscript{20} Daily dosing at 800 mg resulted in a mean AUC of 1,037 hr \cdot \mu g/mL and C\textsubscript{max} of 58.1 \mu g/mL with no consistent increase in AUC or C\textsubscript{max} at pazopanib doses above 800 mg, although the highest values were seen in patients receiving 2000 mg daily. Steady-state (C\textsubscript{min}) exposure plateaued at the 800 mg daily dose and there was no drug accumulation observed. Systemic exposure to pazopanib was increased with a high-fat or low-fat meal, resulting in an approximately 2-fold increase in AUC and C\textsubscript{max}, leading to the recommendation that pazopanib be administered at least 1 hour before or 2 hours after a meal.\textsuperscript{21}

Pazopanib is metabolized mainly by the cytochrome P450 enzyme CYP3A4 in the liver, with minor contributions from CYP1A2 and CYP2C8, and is highly protein-bound (\textgreater 99.9%).\textsuperscript{19} As a result, plasma pazopanib concentrations increase when oral pazopanib is co-administered with a CYP3A4 inhibitor. For example, concurrent administration of lapatinib, a substrate and weak inhibitor of CYP3A4, with pazopanib resulted in an approximately 50% to 60% increase in mean pazopanib AUC\textsuperscript{(10,24)} and C\textsubscript{max}, leading to the recommendation that pazopanib be administered at least 1 hour before or 2 hours after a meal.\textsuperscript{21}

Safety and Efficacy in Clinical Studies

Phase I trial in refractory solid tumors

The first phase I study of pazopanib (VEG10003) was a multicenter, dose-finding trial incorporating pharmacokinetic and pharmacodynamic assessments.\textsuperscript{20} Sixty-three patients with advanced solid tumors were enrolled, 43 in a dose-escalation cohort and 20 in a dose-expansion cohort, of which 12 total patients (19%) had renal cell carcinoma. In sequential dose-escalation cohorts, subjects received 50 mg and 100 mg three times weekly, 50 to 2000 mg once daily, and 300 to 400 mg twice daily. Pazopanib showed evidence of efficacy in various tumor types (Table 1),

| Patients, n  |
|--------------|
| **Baseline characteristics** | 56.5 |
| Mean age, years | 56.5 |
| Primary disease site | 12 (19%) |
| Renal | 12 (19%) |
| Colorectal | 11 (18%) |
| Other gastrointestinal* | 11 (18%) |
| Breast | 5 (8%) |
| Various other§ | 24 (37%) |
| **Patient disposition** |  |  |
| Dose-escalation cohort (n = 43) |  |  |
| 50–100 mg three times weekly | 9 |
| 50–2000 mg once daily† | 34 |
| Dose-expansion cohort (n = 20) |  |  |
| 800 mg once daily | 11 |
| 300–400 mg twice daily | 9 |
| **Efficacy** |  |  |
| Partial response | 3 |
| (2 renal cell carcinoma) |  |
| Stable disease \(	extgreater 6\) months | 14 |
| (3 renal cell carcinoma) |  |

Notes: *Pancreatic, liver, stomach; †sarcoma, lung, prostate, angiosarcoma, endometrial, fibrous histiocytoma, gastrointestinal stromal tumor, head and neck, hepatobiliary, K"urthle cell, melanoma, mesothelioma, ovarian, carcinoma of unknown primary; ‡patients were treated at the 800 mg daily dose level (recommended Phase II dose).
including renal cell carcinoma, and appeared to have a tolerable side effect profile.

Overall, 4 patients experienced dose-limiting toxicities (DLTs): 2 patients at the 50 mg daily dose level (grade 3 gastrointestinal hemorrhage and grade 3 extrapyramidal movement), 1 patient at the 800 mg daily dose level (grade 3 hypertension; subsequent grade 3 proteinuria), and 1 patient at the 2000 mg daily dose level (grade 3 fatigue). The most frequent drug-related adverse events (AEs) were hypertension (33%), diarrhea (33%), hair depigmentation (32%; sometimes associated with skin depigmentation), and nausea (32%). Most drug-related AEs were assessed as grade 1 or 2 by National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0 and were reversible upon discontinuation of pazopanib.

The study defined grade 3 hypertension by stricter criteria than NCI CTC v2.0 (elevated blood pressure requiring therapy or more intensive treatment than previously), with the addition of a ≥15 mmHg rise from baseline in mean arterial blood pressure on at least 3 separate occasions. Hypertension was the most frequent grade 3 AE observed in the study. Twenty-nine percent of patients developed grade 3 hypertension by NCI CTC v2.0 and 62% by study-specific criteria. No hypertensive crises were observed and hypertension was manageable, with reversal upon pazopanib discontinuation.

Other treatment-related grade 3 AEs included proteinuria, diarrhea, nausea, increased aspartate aminotransferase, extrapyramidal disorder, pelvic venous thrombosis, tumor hemorrhage, and deep venous thrombosis. One grade 4 AE (pulmonary embolism) and no treatment-related deaths were reported. Grade 3 neutropenia was uncommon (3%) and although grade 3 or 4 lymphopenia was observed in 14% of patients, no infections were reported. Treatment interruptions and/or dose reductions due to toxicity were required in 10 patients (80% at doses between 800 and 2000 mg daily), with 2 patients permanently discontinued from pazopanib treatment for DLTs in cycle 1. Interestingly, though pazopanib demonstrated an overall similar toxicity profile to other multi-targeted anti-angiogenic TKIs (eg, sunitinib and sorafenib), some notable differences were observed. Hand-foot syndrome was not observed and asthenia (≤2%), mouth ulceration and stomatitis (≤2%), epistaxis (≤3%), and drug-related rash (≤6%) were uncommon.

The maximum tolerated dose (MTD) dose of pazopanib was not reached in this trial. Efficacy was seen, with 3 patients achieving a partial response (PR) and 14 patients with stable disease (SD) of ≥6 months’ duration by Response Evaluation Criteria in Solid Tumors (RECIST)26 guidelines. Of the 12 patients with renal cell carcinoma, 2 patients had a confirmed PR, 4 patients had SD (3 with prolonged SD ≥ 6 months), 4 patients had progressive disease, and 2 withdrew from the study due to toxicity. Notably, the renal cell carcinoma patients who achieved PR were naïve to prior antiangiogenic therapy.

Clinical activity in renal cell carcinoma patients in this study correlated with C\textsubscript{min} (steady-state) values of ≥15 µg/mL, in line with preclinical studies19 that showed optimal angiogenic inhibition at pazopanib concentrations ≥17.5µg/mL(40µmol/L). The 15µg/mL threshold also correlated with the pharmacodynamic effect of hypertension. Overall, steady state exposure (C\textsubscript{min}) seemed to plateau at doses ≥ 800 mg daily, with 93% of patients at the 800 mg daily dose achieving C\textsubscript{min} ≥ 15 µg/mL. Because of these reasons, coupled with the tolerable safety profile and pharmacodynamic changes in tumor perfusion observed on DCE-MRI, the 800 mg daily dose was recommended for use in future studies.

Phase II randomized discontinuation trial in mRCC
The phase II study (VEG102616) in patients with metastatic renal cell carcinoma was originally designed as a randomized discontinuation study (Fig. 1), but was amended to an open-label study based on early evidence of efficacy at the planned interim analysis.27 Patients with locally recurrent or metastatic renal cell carcinoma with predominant clear cell histology, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤1, and measurable disease by RECIST were enrolled. Treatment-naïve patients and those treated with one prior cytokine- or bevacizumab-containing regimen were allowed. This study demonstrated that pazopanib is well-tolerated and has durable activity in this population.

Two-hundred twenty-five patients were enrolled over one year (October 2005 to September 2006) at 43 sites in 9 countries. After the first 60 patients had completed 12 weeks of treatment, a planned interim analysis found the response rate to be 38%.
Therefore, based on the recommendation of an Independent Data Monitoring Committee, randomization ceased and all patients were treated on an open-label basis. The original primary endpoint of progressive disease (PD) rate at 16 weeks post-randomization was revised to overall response rate (ORR) according to RECIST, with secondary endpoints of duration of response and progression-free survival (PFS). Approximately two-thirds of patients were treatment-naïve, over three-quarters were favorable or intermediate risk, and almost all had prior nephrectomy (Table 2). The ORR was 35% (95% CI: 28%–41%) by independent radiographic review with a median duration of response of 68 weeks. After statistical adjustment to account for patients randomly assigned to placebo, the median PFS attributable to pazopanib was 52 weeks (95% CI: 44–60 weeks).

Overall, side effects were tolerable (Table 3). The most common treatment-emergent AEs were diarrhea (63%), increased alanine aminotransferase (54%), increased aspartate aminotransferase (53%), fatigue (46%), hair depigmentation (43%), nausea (42%), and hypertension (41%). The most common treatment-related AEs Grade ≥ 3 were hypertension (9%), increased alanine aminotransferase (9%), increased aspartate aminotransferase (7%), diarrhea (4%), and fatigue (5%). Thirty-one percent of patients required dose reductions, although approximately 50% of these patients had re-escalation.

Discontinuation of pazopanib due to an AE was required in 15% of patients. Elevations in liver enzymes (ie, AST or ALT) were the culprit that led to discontinuation in 4% of patients, whereas hypertension, diarrhea, and fatigue/asthenia rarely

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### Table 2. Phase II trial of pazopanib in patients with metastatic renal cell carcinoma: selected baseline characteristics and evaluation of efficacy (n = 225).  

| **Baseline characteristics** | **Value** |
|-----------------------------|----------|
| Mean age                    | 59.8 yrs |
| Prior nephrectomy           | 91%      |
| Prior systemic therapy      |          |
| Cytokine alone              | 24%      |
| Cytokine + bevacizumab      | 4%       |
| Treatment naïve             | 69%      |
| Median time since diagnosis | 568 days |
| Sites of metastatic disease|          |
| Lung                        | 78%      |
| Lymph node                  | 43%      |
| Bone                        | 28%      |
| Liver                       | 17%      |
| MSKCC risk group            |          |
| Favorable                   | 43%      |
| Intermediate                | 41%      |
| **Efficacy**                |          |
| Response rate (95% CI)      |  34.7%   |
| (28.4 to 40.9)              |          |
| Median duration of response (95% CI) | 68.0 weeks (53.7 to NR) |
| Progression-free survival (95% CI) | 51.7 weeks (43.9 to 60.3) |

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*Prior bevacizumab-containing regimens also allowed.*
A retrospective analysis investigating the pharmacokinetics of pazopanib in relation to patient outcomes in this Phase II study was recently reported. Cmin (trough concentration) data was available for 205 patients at four weeks and 185 patients at 12 weeks out of the 225 total patients enrolled. When separated into quartiles and stratified by PFS, patients with a plasma pazopanib Cmin > 20.6 µg/mL at week 4 had a median PFS of 49.4 weeks versus 20.3 weeks for patients in whom this plasma concentration of drug was not achieved. In addition, response rate (45% vs. 18%) and mean percent tumor shrinkage (37.8% vs. 8.8%) were improved in the group who achieved this threshold at week 4. Almost 70% of patients assessed (143/205) were able to reach or exceed this concentration threshold. Although retrospective, these data support both the initial dosage of 800 mg daily chosen for pazopanib in this population as well as a potential role for maintaining dose intensity during treatment (ie, through optimizing supportive care) whenever possible.

### Table 3. Phase II trial of pazopanib in patients with metastatic renal cell carcinoma: selected adverse events and laboratory abnormalities (n = 225).

| Adverse events (AE)* | Any grade | Grade 3 or 4 |
|----------------------|-----------|---------------|
| Any AE               | 98%       | 53%           |
| Diarrhea             | 63%       | 4%            |
| Fatigue              | 46%       | 5%            |
| Hair depigmentation  | 43%       | 0%            |
| Nausea               | 42%       | <1%           |
| Hypertension         | 41%       | 9%            |
| Rash                 | 16%       | <1%           |
| Hand-foot syndrome   | 11%       | 2%            |
| AST elevation        | 54%       | 7%            |
| ALT elevation        | 53%       | 9%            |
| Hyperbilirubinemia   | 28%       | <1%           |
| Alkaline phosphatase | 27%       | 2%            |
| Lymphopenia          | 35%       | 1%            |
| Neutropenia          | 27%       | 4%            |
| Thrombocytopenia     | 26%       | 3%            |
| Anemia               | 26%       | 3%            |

Note: *Regardless of causality.

led to discontinuation. Notably, within the first few months of pazopanib exposure, isolated asymptomatic elevations of liver enzymes were observed. As seen in the Phase I study, a low incidence of grade ≥3 myelosuppression was observed, attributed to the pazopanib’s weak inhibitory activity for the Flt-3 receptor, and infrequent hand-foot syndrome and stomatitis/mucositis were seen. Two deaths considered to be treatment-related were observed (large bowel perforation in the setting of diverticulitis and dyspnea in the setting of malignant pleural effusions).

### Phase III randomized trial in mRCC
A single phase III randomized, double blind, placebo controlled trial (Study VEG105192) of pazopanib in metastatic renal cell carcinoma has been reported and was the basis for pazopanib’s FDA-approval in mRCC. Patients with clear cell or predominantly clear cell histology who had either received no prior therapy or who had progressed on only one prior cytokine-based systemic therapy were enrolled. Patients were randomized in a 2:1 ratio to receive pazopanib at 800 mg once daily for a maximum of 16 cycles or until clinical progression (Study VEG105192).

Key eligibility criteria:
- mRCC
- Clear cell component
- ECOG PS ≤ 1
- Prior therapy:
  - Treatment naïve
  - 1 Cytokine failure
- Stratification:
  - ECOG PS (0/1)
  - Nephrectomy (Y/N)
  - Prior therapy:
    - Naïve (n = 233)
    - Cytokine (n = 202)

Figure 2. Trial schema: randomized Phase III trial of pazopanib in locally advanced or metastatic renal cell carcinoma.
Role for pazopanib in advanced renal cell carcinoma

treatment status. Patients who progressed on the placebo arm were allowed to enroll on an open label study of pazopanib (VEG107769). The primary endpoint was progression free survival with secondary endpoints of overall survival, confirmed objective response rate, duration of response, safety, and health-related quality of life (HRQoL).

Between April 2006 and April 2007, 435 patients were enrolled from 80 centers worldwide (Europe, South America, North Africa, Australia, and New Zealand), with 290 patients randomly assigned to pazopanib and 145 to placebo. The arms were well balanced with regards demographics and disease characteristics, including MSKCC risk category, prior nephrectomy, and histology (Table 4). The original design included only patients who had progressed on one prior cytokine-based systemic therapy, but was rapidly amended to include treatment-naïve patients. Therefore, of the 435 patients enrolled, 233 (54%) were treatment-naïve and 202 (46%) were cytokine-pretreated.

Pazopanib significantly improved PFS compared to placebo (median 9.2 months vs. 4.2 months; HR, 0.46; 95% CI, 0.34 to 0.62; \( P < 0.0001 \)) in the overall study population. The improvement in PFS was more pronounced in the treatment naïve subpopulation (median 11.1 vs. 2.8 months; HR, 0.40; 95% CI: 0.27 to 0.60; \( P < 0.0001 \)), although the cytokine-pretreated subpopulation benefited as well (median 7.4 vs. 4.2 months, HR, 0.54; 95% CI, 0.35 to 0.84; \( P < 0.001 \)). Predefined subgroup analyses supported the improvement in PFS for pazopanib treated patients in all categories (regardless of MSKCC risk group, systemic treatment status, gender, age, or ECOG PS). The objective response rate for the overall study population was 30% (95% CI, 25.1% to 35.6%), with a median duration of response of 58.7 weeks.

Interim analysis of overall survival (OS) based on 61% of the required death events did not meet either superiority or futility. However, final OS results have now been reported, with a median OS of 22.9 versus 20.5 months in the pazopanib and placebo arms, respectively (HR, 0.91; 95% CI, 0.71 to 1.16; \( P = 0.224 \)). The early timing, high rate, and prolonged duration of crossover from the placebo arm to open-label pazopanib is likely to have confounded the OS analysis. Ultimately, 54% of placebo arm patients crossed over to open-label pazopanib and they remained on pazopanib treatment longer than patients originally randomized to the blinded pazopanib arm (9.4 vs. 7.4 months, respectively). A post-hoc inverse probability of censoring weighted (IPCW) analysis, designed to adjust for crossover, showed a 50% reduction in the risk of death with pazopanib treatment compared with placebo (HR, 0.50; 95% CI, 0.32 to 0.76; \( P = 0.002 \)). In summary, pazopanib appeared to have beneficial clinical activity in the study population.

Overall, pazopanib was also well tolerated in this population of mRCC patients (Table 6), as suggested by the Phase I and Phase II studies. Most AEs were grade \( \leq 2 \) and the most common AEs in the pazopanib arm were diarrhea (52%), hypertension (40%), hair color changes (38%), nausea (26%), anorexia (22%), and vomiting (21%). The most common grade 3 or 4 AEs in the pazopanib arm were hypertension (4%) and diarrhea (4%). Of note, the incidence of arterial thrombotic events was 3% of pazopanib-treated patients compared with none in the placebo arm. Hemorrhagic events (all grades) were observed in 13% and 5% of patients in the pazopanib and placebo arms, respectively. Most laboratory abnormalities were grade \( \leq 2 \), most commonly ALT elevation (53%) and AST elevation (53%) in the pazopanib arm. Of note, ALT elevation \( \geq 3 \) times the

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**Table 4.** Selected patient demographics and disease characteristics: randomized Phase III trial of pazopanib in mRCC.10

| Baseline characteristics               | Pazopanib (n = 290) | Placebo (n = 145) |
|----------------------------------------|---------------------|-------------------|
| Median age, years                      | 59                  | 59                |
| Prior nephrectomy                      | 89%                 | 88%               |
| Prior systemic therapy                 |                     |                   |
| Cytokine pretreated                    | 47%                 | 46%               |
| Treatment naïve                        | 53%                 | 54%               |
| Median time since diagnosis, months    | 15.7                | 13.8              |
| Sites of metastatic disease            |                     |                   |
| Lung                                   | 74%                 | 73%               |
| Lymph node                             | 54%                 | 59%               |
| Bone                                   | 28%                 | 26%               |
| Liver                                  | 26%                 | 22%               |
| MSKCC risk group                       |                     |                   |
| Favorable                              | 39%                 | 39%               |
| Intermediate                           | 55%                 | 53%               |
**Table 5.** Response rate (RECIST), progression-free survival, and overall survival in 1st line Phase III trials in patients with good-intermediate risk metastatic renal cell carcinoma.

| Regimen | Trial | CR | PR | SD | Median response duration | ORR | PFS (P-value) | OS (P-value) |
|---------|-------|----|----|----|--------------------------|-----|--------------|-------------|
| Pazopanib* | Pazopanib vs. placebo10,29 | <1%* | 30%* | 38%* | 13.5 mos* | 32% | 11.1 mos (<0.0001) | 22.9 mos (0.224) |
| Sunitinib | Sunitinib vs. IFN-α9,47 | 3% | 44% | 40% | 11.0 mos | 47% | 11.0 mos (<0.001) | 26.4 mos (0.051) |
| Bevacizumab + IFN-α | AVOREN (Bev. + IFN-α vs. Pbo + IFN-α)13,48 | 1% | 30% | 46% | 13.5 mos | 31% | 10.2 mos (<0.0001) | 23.3 mos (0.1291) |
| CALGB 90206 (Bev. + IFN-α vs. IFN-α)14 | NR | 25.5% | NR | 11.9 mos | 25.5% | 8.5 mos (<0.0001) | 18.3 mos (0.069) |

**Notes:** *Starred parameters are for the entire study population (cytokine-pretreated patients and treatment-naïve patients) since these values were not reported separately for the treatment-naïve subgroup.

**Abbreviations:** RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; ORR, overall response rate; SD, stable disease; IFN-α, interferon-alfa; Mos, months; NR, not reported; Pbo, placebo.

upper limit of normal occurred in 18% of patients and recovered to ≤grade 1 upon dose modification, interruption, or discontinuation in 87% of these patients. In the pazopanib arm, 1% of patients (n = 4) had fatal AEs assessed as drug-related (1 patient each): abnormal hepatic function and rectal hemorrhage, abnormal hepatic function with extensive infiltration of metastatic disease, peritonitis/bowel perforation at a site of RCC metastasis, and ischemic stroke. Again, key class side effects of anti-angiogenic TKIs

**Table 6.** Selected adverse events in 1st line Phase III trials in patients with good-intermediate risk metastatic renal cell carcinoma.

| Adverse event or laboratory abnormality | Pazopanib (%)10,21 (n = 290) | Sunitinib (%)9,49 (n = 375) | Bevacizumab + IFN-α (%)50,51 (n = 337) |
|----------------------------------------|-----------------------------|-----------------------------|-------------------------------------|
| Diarrhea                               | 52 4                        | 53 5                        | 20 2                                |
| Hypertension                           | 40 4                        | 24 8                        | 26 3                                |
| Fatigue                                | 19 2                        | 51 7                        | 33 12                               |
| Asthenia                               | 14 3                        | 17 4                        | 32 10                               |
| Hand-foot syndrome                     | 6 <1                       | 20 5                        | NS NS                                |
| Mucositis/stomatitis                   | <10 <1                     | 45* 3*                      | NS NS                                |
| Arterial thrombotic events             | NS 3                       | NS NS                       | 1 1                                 |
| Venous thromboembolic events           | NS NS                       | NS 2                        | 3 2                                 |
| Hemorrhagic events                     | 13 NS                       | 37 4                        | 33 3                                 |
| Cardiac dysfunction†                   | <1 NS                       | 10 2                        | <1† <1†                              |
| ALT increase                           | 53 12                      | 52 2                        | NS NS                                |
| AST increase                           | 53 8                       | 46 3                        | NS NS                                |
| Total bilirubin increase               | 36 3                       | 19 1                        | NS NS                                |
| Hypothyroidism                         | 7 <1                       | 16 NS                       | NS NS                                |
| Proteinuria                            | 9 <1                       | NS NS                       | 18 7                                 |
| Anemia                                 | NS NS                      | 71 4                        | 18 3                                 |
| Thrombocytopenia                       | 32 1                       | 65 8                        | 6 2                                  |
| Neutropenia                            | 34 1                       | 72 12                       | 7 4                                  |
| Leukopenia                             | 37 0                       | 78 5                        | NS NS                                |
| Discontinuation due to AE(s)           | 14 8                       | 8 28                        | 14 8                                 |

**Notes:** *Reported categories of "stomatitis" and "mucosal inflammation" added together; †includes decreased ejection fraction and congestive heart failure. Congestive heart failure only; decreased ejection fraction not specified.

**Abbreviation:** NS, not specified.
were observed with low frequency in this trial (10% any grade and >1% grade 3 or 4): hand-foot syndrome, mucositis/stomatitis, hypothyroidism, and proteinuria. A low rate (≤1%) of grade 3 or 4 cytopenias was observed, attributed to pazopanib’s lack of potency for the fms-related tyrosine kinase (Flt-3). With a 30% increase in the cumulative exposure to pazopanib since the published report, safety data from this Phase III trial have recently been updated. 30 No new safety signals were identified: there were no significant changes in the type, frequency, or severity of AEs and no differences in grade 3, 4, or 5 AEs.

Several interesting toxicity-related analyses of this trial have been published or reported in abstract form. A genetic analysis performed by Xu et al attempted to identify genetic markers that predict for risk of ALT and/or bilirubin elevation in patients treated with pazopanib in the phase II and III studies. 31 Interestingly, the UGT1A1 TA repeat polymorphism was strongly associated with maximum on-treatment bilirubin concentration and bilirubin increase from baseline, while none of the polymorphisms tested was associated with elevation of ALT. Therefore, it may important to consider that isolated elevations of total bilirubin may not indicate pazopanib-induced hepatotoxicity and could be benign manifestations of Gilbert’s syndrome. An analysis of the 578 patients enrolled on the Phase II, Phase III, and Phase III extension trials found an overall incidence of hypothyroidism of 3% and hyperthyroidism of 1%. 32 The low rate of hypothyroidism is hypothesized to partially explain the low rates of fatigue (19%) and asthenia (14%) observed in the Phase III trial.

Another study, recently presented in abstract form, examined demographic, pharmacokinetic (PK), and pharmacogenetic (PGx) factors that contribute to pazopanib-related hand-foot syndrome (HFS) using samples from the Phase II and III trials in mRCC patients. 33 While the overall incidence of HFS was low (7.7%) in the overall population, Asian race (incidence of 30% compared with 4% for Caucasians) and week 4 Cmin plasma pazopanib concentration appeared to be predictors of HFS. Finally, the relationship between week 4 plasma pazopanib concentration (Cmin) and clinically important AEs in the first 12 weeks of treatment was explored using data from 205 patients in the Phase II trial. 34 The incidence of diarrhea, hair color change, ALT increase, HFS, and stomatitis AEs was concentration-dependent, whereas the incidence of other common AEs (ie, nausea, vomiting, fatigue, dysgeusia, and rash) was not. It is hypothesized that a dose-reduction strategy might be more appropriate for concentration-dependent AEs than for other AEs. Although retrospective, these analyses provide important additional clues about clinically meaningful pazopanib-related toxicities.

Emerging data: TKI refractory patients, pazopanib combinations, and biomarkers

There was previously no data for pazopanib in TKI failure; however, two studies suggesting pazopanib’s efficacy in this setting have recently been presented in abstract form. Matrana et al presented a retrospective review of MD Anderson’s experience with pazopanib in 88 consecutive mRCC patients who experienced progression on other targeted agents. 35 The median number of prior targeted agents was 2 (range, 1 to 5), including 78% of patients having progressed on sunitinib, 51% on everolimus, 40% on sorafenib, 26% on bevacizumab, and 20% on temsirolimus. In this refractory population, the partial response rate was 25% by treating physician assessment, providing evidence for clinically meaningful activity. Reeves et al presented a single-institution prospective Phase II trial in 44 patients who had progressed on prior anti-angiogenic agents. Thirty-two patients (72%) had progressed on prior sunitinib (SU) and 12 patients (28%) had progressed on prior bevacizumab (bev). The overall response rate by RECIST was 20% (SU: 16%; bev: 33%), with a 77% disease control rate (CR + PR + SD) and a median PFS of 9.23 months (SU: 12 months; bev: 8 months). Pazopanib was also well tolerated, with toxicities similar to those previously reported. These 2 studies provide preliminary (level 2) evidence for pazopanib’s efficacy in targeted therapy-refractory patients.

A phase I study investigating “vertical inhibition” of the VEGFR and mTOR pathways with dose-escalation of combination pazopanib plus temsirolimus in patients with solid tumors (emphasis on mRCC) was recently reported. 36 Although there was some evidence of activity, dose de-escalation was required due to DLTs at the first dose level and the investigators determined that this combination is not feasible. This is in concordance with prior studies of different anti-VEGF and -mTOR combinations, which showed unacceptable toxicity.
Finally, recent studies have attempted to identify biomarkers predictive of treatment benefit. Xu and colleagues reported 2 studies evaluating germ-line single nucleotide polymorphisms (SNPs) selected based on the following criteria: involvement in angiogenesis or the metabolism, disposition, or mode of action of pazopanib; and a previously established functional or biologically relevant consequence of the genetic polymorphism. Thirty-seven functional polymorphisms within 13 genes were evaluated and associated with progression-free survival (PFS) and response rate (RR) in 397 patients with mRCC receiving pazopanib on phase II, phase III, and phase III extension studies. Similarly, the same functional polymorphisms were correlated with overall survival (OS) in 214 pazopanib-treated mRCC patients from the phase III and its extension studies. Polymorphisms in IL8, HIF1A, NR1lA, and VEGFA showed nominally significant associations (P ≤ 0.05) with PFS and RR when compared with the wild-type genotypes. In addition, polymorphisms in IL8, FGFR2, NR1I2 and ABCB1 showed nominal associations with OS (P ≤ 0.05) and were shown to be independent predictors of OS on multivariate analysis. These findings are important, because these germ-line polymorphisms in angiogenesis and exposure-related genes might be used to predict those mRCC patients who will benefit from pazopanib and, more importantly, spare those patients who will not benefit from potential pazopanib toxicities. However, more work will need to be done to prospectively validate this approach.

Role for Pazopanib in mRCC
With the dramatic advances in treatment of mRCC in the last decade, several unanswered questions come to the forefront: What is the best first-line systemic therapy for mRCC? and, What is the best systemic therapy for cytokine- and VEGFR TKI-refractory patients? An evidence-based approach to upfront and subsequent therapy based on the inclusion criteria in phase III trials and other patient characteristics is necessary. The National Comprehensive Cancer Network (NCCN) has developed categories of evidence and consensus: Category 1 evidence is based on high-level evidence (ie, randomized controlled trials) and consensus, Category 2 evidence is based on lower level evidence where there may be minor disagreement, and Category 3 evidence is based on any level of evidence with major disagreement. Important factors to consider include MSKCC risk group, number and type of prior therapies, histologic subtype (clear cell or clear-cell predominant versus non-clear cell), and patient-specific characteristics (ie, comorbidities in relation to agent-specific toxicities and financial considerations). Pazopanib’s role will be discussed in three settings: first-line (treatment-naïve), cytokine-refractory (second-line), and anti-VEGF-refractory (second-line), and beyond.

Treatment-naïve patients (1st line)
There is Level 1 evidence for pazopanib use in the first-line setting for patients with favorable or intermediate risk, predominantly clear cell renal carcinoma. Other equally appropriate agents for treatment-naïve patients with favorable or intermediate risk and predominant clear cell histology include sunitinib, or bevacizumab plus interferon-α (Fig. 3). High dose IL-2 may also be reasonable in a selected group of patients. Patients’ symptoms and co-morbidities that might be exacerbated by agent-specific toxicities should be considered before initiating treatment. For example, in the absence of data showing superiority of any of the 3 regimens (Table 5), pazopanib might be chosen in a patient with moderate fatigue at baseline (see Table 6). In poor risk and/or or non-clear cell histology patients, there is Level 1 evidence for a survival advantage with temsirolimus, an intravenously administered inhibitor of the mammalian target of rapamycin (mTOR) pathway, when compared with interferon-α alone in the first line setting. Patient preference amongst the evidence-based first-line treatments (ie, pazopanib, sunitinib, or bevacizumab + IFN-α) for favorable or intermediate risk metastatic renal cell carcinoma is unknown. Although these questions have been examined in retrospective studies, they may be subject to bias. Discussion of both side effects and the convenience of oral therapy, among other factors, will be critical in the decision-making process for patients with mRCC. The lack of head-to-head comparison studies limits definitive conclusions; however, pazopanib may exhibit several key differences compared with sunitinib that could lead to patient preference for pazopanib (Table 6). The toxicity profiles of pazopanib and sunitinib in the Phase III trials in mRCC would suggest that the lower...
Role for pazopanib in advanced renal cell carcinoma

Advanced RCC:
- Favorable-intermediate risk*
- ≥Clear cell component

Sunitinib
Pazopanib
Bevacizumab + IFN-α

*MSKCC risk factors:
1. Low Karnofsky PS (<80%)
2. High LDH (>1.5xULN)
3. Low hemoglobin (<LLN)
4. High corrected calcium (>10 mg/dL)
5. Absence of prior nephrectomy

Favorable: 0 risk factors
Intermediate: 1–2 risk factors
Poor: ≥3 risk factors

Figure 3. Evidence-based treatment algorithm for treatment-naïve mRCC. Note that high dose IL-2 may be considered in carefully selected patients.

incidence of fatigue, hand-foot syndrome, mucositis/stomatitis, hypothyroidism, and hematologic lab abnormalities might favor pazopanib. On the other hand, patients with poorly controlled/difficult to treat hypertension or baseline liver dysfunction may well have greater difficulty with pazopanib. Finally, patients who prefer an intravenous regimen over an oral regimen (eg, for financial reasons) may prefer bevacizumab + IFN-α. Some of these questions regarding patient preferences and differential toxicity profiles will hopefully be answered more definitively in the prospective PISCES study, comparing pazopanib and sunitinib, discussed below. Of course, toxicity and other preference considerations may be moot if non-inferiority of pazopanib with sunitinib cannot be demonstrated in the COMPARZ study, also discussed below.

Cytokine-refractory patients (2nd line)
The population of cytokine-refractory patients is dramatically shrinking now that six targeted therapy regimens for advanced renal cell carcinoma are approved. Therefore, the question of how to use these novel agents in cytokine-refractory disease is currently less pressing. However, randomized controlled studies of pazopanib, axitinib (abstract form only), and sorafenib provide category 1 evidence supporting their use in this population (Table 7). Of note, axitinib

Table 7. Response rate (RECIST), progression-free survival, and overall survival in Phase II/III trials in cytokine-refractory patients with metastatic renal cell carcinoma.

| Regimen       | Trial                          | N, patients | ORR  | PFS   | OS    |
|---------------|--------------------------------|-------------|------|-------|-------|
|               |                                |             |      | (P-value) | (P-value) |       |
| Pazopanib     | Pazopanib vs. placebo (Phase III) | 290         | 29%  | 7.4 mos (0.0001)* | NR   |
| Axitinib      | Axitinib vs. sorafenib (Phase III) | 251         | NR   | 12.1 mos (0.0001)* | NR   |
| Sorafenib     | Sorafenib vs. placebo (Phase III) | 451         | 2%   | 5.5 mos (<0.01) | 17.8 mos (0.146) |
| Sunitinib     | Single-arm Phase II/III         | 105         | 34%  | 8.3 mos | NR   |

Notes: *Result from cytokine-pretreated subpopulation; †result from subgroup analysis. P-value is for one-sided log rank test stratified by performance status.
was the only drug tested against an active comparator (sorafenib); therefore, axitinib may be preferred and sorafenib may no longer be reasonable in this population. The publication of the axitinib data in a peer-reviewed journal is eagerly awaited. In addition, there is strong evidence for the activity of sunitinib in this population from phase II studies\(^\text{12,43}\) and extrapolation from sunitinib’s activity in the front-line Phase III trial. Because the use of VEGFR signaling pathway inhibitors for first line treatment is now standard of care except in select patients, the population of cytokine-refractory patients in clinical practice is likely to dwindle in coming years. In summary, pazopanib is a reasonable treatment option in cytokine-refractory patients, although it should be noted that axitinib, while not yet FDA-approved, has recently demonstrated improved PFS versus an active comparator (Fig. 4).

Anti-VEGF pretreated patients
(2nd line and beyond)
Two agents have Level 1 evidence for efficacy in VEGFR TKI-treated patients: everolimus and axitinib (Table 8). Everolimus, an mTOR inhibitor, improved progression-free survival (4.9 vs. 1.9 months; HR, 0.33; \(P < 0.001\)) versus placebo in patients who had progressed on sunitinib (46%), sorafenib (28%), or both (26%).\(^\text{12,44}\) Of note, two-thirds of patients had also been treated with immunotherapy (ie, IFN-\(\alpha\) or high-dose IL-2). More recently axitinib, a second-generation inhibitor of VEGFR-1, -2, and -3, demonstrated improved progression-free survival (6.7 vs. 4.7 months; HR, 0.665; \(P < 0.0001\)) in a population of mainly sunitinib- (54%) and cytokine-pretreated (35%) patients.\(^\text{40}\) Should axitinib be FDA-approved, either everolimus or axitinib would be reasonable in this population, with no data to suggest one’s superiority over the other. In comparison, there is limited evidence for pazopanib’s efficacy in VEGFR TKI- and bevacizumab-pretreated patients, with one prospective phase II study and one single-institution retrospective review suggesting efficacy (see above). So, while pazopanib may be reasonable in further lines of therapy, everolimus remains the evidence-based standard of care for this population, at least while axitinib remains yet to be FDA-approved (Fig. 5). Clinical trials of novel agents should also be considered.

### Selected Ongoing Trials
Further studies that will help define the role of pazopanib as monotherapy in the 1st line (treatment naïve) setting include two ongoing phase III trials: (1) **COMPARZ** (Pazopanib Versus Sunitinib in the Treatment of Subjects With Locally Advanced and/or Metastatic Renal Cell Carcinoma)\(^\text{45}\) and (2) **PISCES** (Patient Preference Study of Pazopanib Versus

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Table 8. Response rate (RECIST), progression-free survival, and overall survival in selected Phase II/III trials in VEGFR TKI-refractory patients with metastatic renal cell carcinoma.

| Regimen        | Trial Setting                                                                 | N, patients | ORR | PFS (P-value) | OS (P-value) |
|----------------|--------------------------------------------------------------------------------|-------------|-----|---------------|--------------|
| Everolimus     | Everolimus vs. placebo (Phase III)\(^\text{12,44}\)                           | 277         | 1.8%| 4.9 mos \((P < 0.001)\) | 14.8 mos \((P = 0.162)\) |
| Axitinib       | Axitinib vs. sorafenib (Phase III)\(^\text{40}\)                             | 389         | NR  | 4.8 mos \(0.011\) | NR           |
| Pazopanib      | Single-arm Phase II\(^\text{42}\)                                           | 44          | 20% | 9.3 mos \(\text{NA}\) | NR           |

Note: *65% of patients also had prior immunotherapy and 13% had prior chemotherapy, meaning this population appeared to be more heavily pre-treated than in the Phase III trial of axitinib (AXIS).

Abbreviations: NR, not reported; NA, not applicable.
Role for pazopanib in advanced renal cell carcinoma

Sunitinib in Advanced or Metastatic Kidney Cancer). The COMPARZ trial (VEG108844) is designed to test pazopanib versus sunitinib (Sutent®; Pfizer, Inc.) in locally advanced and/or metastatic RCC patients who have had no prior treatment. Approximately 876 patients with treatment naïve metastatic clear cell RCC will be included, with a primary endpoint powered to show non-inferiority of progression-free survival. Importantly, this study will allow head-to-head comparison of the tolerability of pazopanib compared with sunitinib. The PISCES trial will address patient

Table 9. Select ongoing/planned trials that may clarify the role of pazopanib in renal cell carcinoma.

| Setting | Phase | N, planned | Description | NCT* |
|---------|-------|------------|-------------|------|
| Non-metastatic | | | | |
| Neoadjuvant | II | 30 | Pazopanib before surgery for localized RCC | NCT0115852153 |
| | II | 40 | Neoadjuvant pazopanib for localized RCC | NCT0136111354 |
| Adjuvant | III | 1500 | Adjuvant pazopanib for localized RCC (PROTECT) | NCT0123596255 |
| Advanced/metastatic | | | | |
| Treatment-naïve | III | 876 | Pazopanib vs. sunitinib efficacy (COMPARZ) | NCT0072094156 |
| | III | 161 | Pazopanib vs. sunitinib patient preference (PISCES) | NCT0106431057 |
| | II (randomized) | 160 | Pazopanib vs. sunitinib in Asian patients | NCT0114782258 |
| | II (randomized) | 90 | Pazopanib vs. temsirolimus in poor-risk patients* | NCT0139218359 |
| VEGFR TKI-refractory | II | 28 | Pazopanib after 1 or 2 systemic therapies, with 1 VEGFR TKI required | NCT0115709160 |
| Combinations: anti-VEGF | I | 36 | Dose-escalation of pazopanib and bevacizumab (PARASOL) | NCT0120203261 |
| Combinations: mTOR inhibition | I | 44 | Dose-escalation of pazopanib and everolimus | NCT0118432662 |
| Sequencing of monotherapy | II (randomized) | 240 | Sequential assessment of 2 monotherapies (START): 1. Pazopanib → bevacizumab 2. Pazopanib → everolimus 3. Everolimus → pazopanib 4. Bevacizumab → pazopanib 5. Everolimus → bevacizumab 6. Bevacizumab → everolimus | NCT0121793163 |
| | II (randomized) | 100 | Rotation between everolimus and pazopanib every 2 months vs. pazopanib until progression followed by everolimus (ROPETAR) | NCT0140800464 |
| | I (pharmacodynamic) | 12 | 3 infusions of bevacizumab q2 weeks followed by pazopanib on various schedules | NCT0099212165 |

Note: *Prior cytokines or vaccines allowed but not prior systemic targeted therapies.
preferences between pazopanib and sunitinib. This trial is a randomized, double-blind, crossover study of pazopanib versus sunitinib in patients with metastatic RCC who have received no prior systemic therapy. Patients will be randomized to sunitinib for 10 weeks followed by pazopanib for 10 weeks (2 week wash-out period between agents), or the inverse sequence. Approximately 160 patients are planned, with the primary endpoint based on a patient preference questionnaire at 22 weeks. As of this writing, results from both trials are expected within the next year. Other pazopanib studies of interest include those in the neo-adjuvant, adjuvant, first-line comparative, VEGFR TKI-refractory, combination, and sequencing settings (Table 9).

Conclusions
Although approved more recently than other VEGFR TKIs, pazopanib is an important option in the armamentarium of treatment options of metastatic renal cell carcinoma. There is data from randomized Phase III trials supporting pazopanib’s efficacy and safety in treatment-naïve and cytokine-refractory patients with mRCC. Due to its low incidence of fatigue, mucositis/stomatitis, hand-foot syndrome, and hematologic toxicities compared with sunitinib, pazopanib may be a unique therapeutic option. Data from the COMPARZ and PISCES trials are awaited to confirm pazopanib’s comparable efficacy and improved toxicity compared with sunitinib, in order to more fully define pazopanib’s role in the treatment of mRCC.

Disclosures
Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

References
1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. Sep–Oct 2010;60(5):277–300.
2. Rouviere O, Bouvier R, Negrier S, Batet L, Lyonnet D. Nonmetastatic renal-cell carcinoma: is it really possible to define rational guidelines for post-treatment follow-up? Nat Clin Pract Oncol. Apr 2006;3(4):200–3.
3. Motzer RJ, Bander NH, NanoMUS. Renal-cell carcinoma. N Engl J Med. Sep 19, 1996;335(12):865–75.
4. Diaz JI, Mora LB, Hakam A. The Mainz Classification of Renal Cell Tumors. Cancer Control. Nov 1999;6(6):571–9.
5. Nelson EC, Evans CP, Lara PN Jr. Renal cell carcinoma: current status and emerging therapies. Cancer Treat Rev. May 2007;33(3):299–313.
6. Coppin P, Porszolt F, Awa A, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. Cochrane Database Syst Rev. 2005;1:CD004125.
7. George DJ, Kaelin WG Jr. The von Hippel-Lindau protein, vascular endothelial growth factor, and kidney cancer. N Engl J Med. Jul 31, 2003;349(5):419–21.
8. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. Jan 11, 2007;356(2):125–34.
9. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. Jan 11, 2007;356(2):115–24.
10. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. Feb 20, 2010;28(6):1061–8.
11. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. May 31, 2007;356(22):2271–81.
12. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. Aug 9, 2008;372(9637):449–56.
13. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol. May 1, 2010;28(13):2144–50.
14. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. May 1, 2010;28(13):2137–43.
15. Limvorasak S, Posadas EM. Pazopanib: therapeutic developments. Expert Opin Pharmacother. Dec 2009;10(18):3091–102.
16. Harris PA, Cheung M, Hunter RN 3rd, et al. Discovery of 5-[(4-anilino-5-aryloxazoles as a novel class of VEGFR2 kinase inhibitors. Expert Opin Pharmacother. Dec 2009;10(18):3091–102.
17. Harris PA, Boloor A, Cheung M, et al. Discovery and evaluation of 2-anilino-5-aryl oxazoles as a novel class of VEGFR2 kinase inhibitors. J Med Chem. Mar 10, 2005;48(5):1610–9.
18. Kumar R, Krouthamel MC, Rominger DH, et al. Myelosuppression and kinase selectivity of multikinase angiogenesis inhibitors. Br J Cancer. Nov 17, 2009;101(10):1717–23.
19. Kumar R, Knick VB, Rudolph SK, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. Mol Cancer Ther. Jul 2007;6(7):2012–21.
20. Hurwitz HI, Dowlati A, Saini S, et al. Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res. Jun 15, 2009;15(12):4220–7.
21. Pazopanib Prescribing Information. April 2010; https://www.gsksource.com/gskprm/en/US/adirect/gskprm?cmd=ProductDetailPage&product_id=1279563278373&featureKey=001903&section=34084-3. Accessed August 14, 2011.
22. Dejonge M, Savage S, Verweij J, et al. A phase I, open-label study of the safety and pharmacokinetics (PK) of pazopanib (P) and lapatinib (L) administered concurrently. J Clin Oncol. 2006;24(18S (June 20 Supplement)):abstr 2088.
40. Rini BI, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line therapy for metastatic renal cell carcinoma. J Clin Oncol. 2009;27(15):579–87.

41. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma. N Engl J Med. 2005;352(15):1598–607.

42. Motzer RJ, Michaelson MD, Redman BG, et al. 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. Jul 1, 2006;24(1):16–24.

43. Motzer RJ, Rini BI, Bakowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA. Jul 6, 2006;295(21):2516–24.

44. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer. Sep 15, 2010;116(18):4256–65.

45. Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma (COMPARATOR). http://clinicaltrials.gov/ct2/show/NCT00720941. Accessed August 14, 2011.

46. Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer (PISCES). http://clinicaltrials.gov/ct2/show/NCT01064310. Accessed August 14, 2011.

47. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. Aug 1, 2009;27(22):3584–90.

48. Escudier BJ, Bellmunt J, Negrier S, et al. Final results of the phase III, randomized, double-blind AVOREN trial of first-line bevacizumab (BEV) + interferon-α2a (IFN) in metastatic renal cell carcinoma (mRCC). J Clin Oncol. 2009;27(15):5502–10.

49. Sunitinib Prescribing Information. May 2011; http://labeling.pfizer.com/. Accessed August 14, 2011.

50. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. Dec 22, 2007;370(9605):2103–11.

51. Bevacizumab Prescribing Information. February 2011; http://www.gene.com/s/r/docs/avastin-prescribing.pdf. Accessed August 14, 2011.

52. Reeves JA, Spigel DR, Daniel BD, Friedman EK, Burris HA, Hainsworth JD. Pazopanib in patients with metastatic renal cell carcinoma previously treated with sunitinib or bevacizumab: A Sarah Cannon Research Institute Phase II trial. J Clin Oncol. 2011;29(Suppl):abstr 4659.

53. Pazopanib Hydrochloride in Treating Patients With Stage IV Kidney Cancer. http://clinicaltrials.gov/ct2/show/NCT01158521?term=pazopanib&cond=renal+cell+carcinoma&rank=2. Accessed August 15, 2011.

54. Neoadjuvant Pazopanib in Renal Cell Carcinoma. http://clinicaltrials.gov/ct2/show/NCT01361113?term=pazopanib&cond=renal+cell+carcinoma&rank=3. Accessed August 15, 2011.

55. A Study to Evaluate Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma (RCCT) (PROTECT). http://clinicaltrials.gov/ct2/show/NCT01235962?term=pazopanib&cond=renal+cell+carcinoma&rank=13. Accessed August 15, 2011.

56. Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma (COMPARATOR). http://clinicaltrials.gov/ct2/show/NCT01147922?term=pazopanib&cond=renal+cell+carcinoma&rank=7. Accessed August 15, 2011.

57. Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer (PISCES). http://clinicaltrials.gov/ct2/show/NCT01064310?term=pazopanib&cond=renal+cell+carcinoma&rank=19. Accessed August 15, 2011.

58. Pazopanib Versus Sunitinib in the Treatment of Asian Subjects With Locally Advanced and/or Metastatic Renal Cell Carcinoma. http://clinicaltrials.gov/ct2/show/NCT01157901?term=pazopanib&cond=renal+cell+carcinoma&rank=1. Accessed August 15, 2011.

59. Pazopanib Hydrochloride in Treating Patients With Stage IV Kidney Cancer. http://clinicaltrials.gov/ct2/show/NCT01157901?term=pazopanib&cond=renal+cell+carcinoma&rank=1. Accessed August 15, 2011.

60. Pazopanib Versus Temsirolimus in Poor-Risk Clear-Cell Renal Cell Carcinoma (RCC). http://clinicaltrials.gov/ct2/show/NCT01392183?term=pazopanib&cond=renal+cell+carcinoma&rank=7. Accessed August 15, 2011.

61. Multicenter Dose-escalation Study of a Combination of Pazopanib and Bevacizumab in Patients With Metastatic Renal Cell Carcinoma or Other Advanced Solid Tumors (PARASOL). http://clinicaltrials.gov/ct2/show/NCT01202032?term=pazopanib&cond=renal+cell+carcinoma&rank=15. Accessed August 15, 2011.
62. Pazopanib and Everolimus in Patients With Advanced Solid Tumors and Previously Treated Kidney Cancer. http://clinicaltrials.gov/ct2/show/NCT01184326?term=pazopanib&cond=renal+cell+carcinoma&rank=14. Accessed August 15, 2011.

63. Sequential Two-agent Assessment in Renal Cell Carcinoma Therapy. http://clinicaltrials.gov/ct2/show/NCT01217931?term=pazopanib&cond=renal+cell+carcinoma&rank=12. Accessed August 15, 2011.

64. Rotating Pazopanib and Everolimus to Avoid Resistance (ROPETAR). http://clinicaltrials.gov/ct2/show/NCT01408004?term=pazopanib&cond=renal+cell+carcinoma&rank=17. Accessed August 15, 2011.

65. An Open-Label Pharmacodynamic Study of Bevacizumab and Pazopanib in Renal Cell Carcinoma. http://clinicaltrials.gov/ct2/show/NCT00992121?term=pazopanib&cond=renal+cell+carcinoma&rank=10. Accessed August 15, 2011.

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