REVIEW

Pazopanib: an orally administered multi-targeted tyrosine kinase inhibitor for locally advanced or metastatic renal cell carcinoma

Gokhan Koc, MD,[1] Xu Wang, MD,[2] Yi Luo, PhD[3]

[1]Department of Urology, Tepecik Teaching and Research Hospital, Yenisehir, Izmir, Turkey
[2]Tianjin Institute of Urology, Tianjin Medical University, Tianjin, China
[3]Department of Urology, University of Iowa, Iowa City, Iowa USA

KOC G, WANG X, LUO Y. Pazopanib: an orally administered multi-targeted tyrosine kinase inhibitor for locally advanced or metastatic renal cell carcinoma. The Canadian Journal of Urology. 2011;18(6):5991-5997.

Introduction: *Renal cell carcinoma (RCC) is the most common type of kidney cancer in adults, responsible for approximately 90% of all kidney cancers. Prior to 2005, treatment options for patients with locally advanced and metastatic disease were limited. After the approval of sorafenib by the US Food and Drug Administration (FDA), other tyrosine kinase inhibitors (TKI) have been successively used for treating patients with advanced RCC. Pazopanib is the newest, orally bioavailable, and multi-targeted TKI, and is considered a first-line treatment option for certain patients. This review summarizes updated clinical studies, mechanism of action, and pharmacokinetics of pazopanib.*

Materials and methods: *Published English language literatures and data information on pazopanib for treating advanced RCC available as of March 2011 were identified and summarized.*

Results: *In phase II and III randomized clinical trials, pazopanib treatment resulted in considerably longer progression-free survival in patients with advanced RCC compared to placebo, with an acceptable side-effect profile. In addition, there are a few ongoing pazopanib studies including comparison to other TKIs, use for patients who have failed prior cytokine therapy, and combination with other therapeutic agents.*

Conclusions: *Pazopanib has been used in the United States, Europe and Canada for treating patients with advanced RCC. Currently, it is being used in good or intermediate risk RCC and shows survival benefit with acceptable adverse effects. Pazopanib is a new treatment option and needs further evaluation, particularly on its effect relative to other TKIs as well as its use in combination with other agents.*

Key Words: pazopanib, carcinoma, renal cell, tyrosine kinase inhibitor, vascular endothelial growth factor

Introduction

Renal cell carcinoma (RCC), arising in the renal cortex, accounts for 90% of all kidney cancers and clear cell RCC is the most common subtype.[1-3] RCC constitutes approximately 4% of all adult malignancies with an estimated 60,920 new cases and 13,120 deaths in the United States in 2011.[4] Despite the presence of familial RCC cases, more than 90% of new RCC cases are associated with sporadic gene mutations.[5] Recognition of the importance of Von Hippel-Lindau (VHL) tumor suppressor gene in the pathogenesis of RCC is considered as a revolution in the treatment of RCC.[6] In sporadic clear cell RCC, 90% of cases show one allele of the VHL gene to be inactivated by deletion and the remaining VHL alleles contain 55% mutation and 20% methylation.[7] Detection of the VHL gene is important with regard to elucidation of vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR) signaling pathway that is involved in RCC angiogenesis.[8] Inactivation of the VHL gene results in intracellular accumulation of

Accepted for publication September 2011

Acknowledgment
The authors thank Ms. Kris Greiner for editorial review of this article.

Address correspondence to Dr. Yi Luo, Department of Urology, University of Iowa, 375 Newton Road, 3204 MERF, Iowa City, IA 52242 USA

hypoxia-inducible factor (HIF)-α. Accumulation of HIF-α causes upregulation of the hypoxia-inducible genes such as VEGF, platelet-derived growth factor (PDGF), and transforming growth factor (TGF), which are reserved for the cellular response to hypoxia and also angiogenesis stimulation.[9,10] The mTOR signaling pathway has been shown to play an important role in angiogenesis.[11] The mTOR is a crucial protein regulating cell survival under the conditions of oxidative stress by upregulating HIF-α protein synthesis.[11] High levels of angiogenesis-related factors such as basic fibroblast growth factor (bFGF), VEGF and angiogenin are observed in sera of RCC patients.[12,13] The VEGF ligand family consists of four different isoforms and each interacts with a isoform-specific surface receptor and initiates a different signaling cascade within the angiogenic pathway. VEGF receptors belong to the tyrosine kinase receptor family.[14] Activation of intracellular signaling cascade induces tumor angiogenesis.[14] Consequently, HIF is accumulated and VEGF overexpressed, which may occur as a result of VHL gene dysfunction and mTOR activation, although the etiology of RCC remains elusive.[15]

Treatment of renal cell carcinoma

Treatment options were limited for locally advanced and metastatic disease prior to 2005, as radical nephrectomy was mainly used for the treatment of all localized disease. Even though subcutaneous interferon (IFN) was shown to extend survival in early studies,[16,17] a recently published study showed that IL-2 and/or IFN-α had no contribution to the survival of patients with metastatic renal carcinoma.[18] Complete response (CR) could be achieved by IL-2 diffusion at a high dose; however, severe side effects, possibly leading to death, were observed due to its high toxicity.[19] To prevent the treatment-related mortality, reduced doses of IL-2 were used during the treatment cycle.[17,19] Recognition of the importance of VHL gene and HIF in RCC patients led to investigating small molecules, such as tyrosine kinase inhibitors (TKI), in treatment. As a result, sorafenib was approved by the US Food and Drug Administration (FDA) in December 2005 for the treatment of patients with advanced RCC.[20] Another TKI, sunitinib, was approved by the FDA in January 2006.[21,22] Pazopanib was the very last TKI approved by the FDA, in October 2009.[23,24] Bevacizumab, a humanized monoclonal antibody that binds to VEGF, received FDA approval to be used in combination with IFN-α.[25] mTOR inhibitors are composed of other chemicals such as temsirolimus and everolimus, which are used in advanced RCC therapy.[26,27] There are various treatment options for advanced RCC and drug selection should be handled according to each patient's clinical information.

Mechanism of pazopanib action

Pazopanib (Votrient, GlaxoSmithKline, GW786034) is the most recently FDA-approved multi-targeted TKI. It is orally bioavailable and acts as an inhibitor of tyrosine kinases such as VEGFR-1, -2 and -3, PDGFR-α and -β, and stem cell factor receptor/c-Kit.[28] It also inhibits fibroblast growth factor receptor-1 and -3, transmembrane glycoprotein receptor kinase, inducible T-cell kinase, and leukocyte-specific protein tyrosine kinase.[29-31] Pazopanib inhibits both VEGF-induced endothelial and PDGFR-induced pericyte proliferation and, as a consequence of this inhibition, angiogenesis slows down.[32] An in vivo animal study showed that pazopanib inhibited angiogenesis and growth of six different human tumor xenografts (renal, prostate, lung, colon, melanoma and breast) in a dose-dependent manner.[28] The greatest activity was observed in most in RCC, as well as colorectal cancer and non-small cell lung cancer. Pazopanib has also been investigated in other tumor types such as cervical, hepatocellular, sarcoma, and ovarian. Sorafenib and sunitinib, two other TKI inhibitors, were found to affect the same receptors at different concentrations, which may explain different side effects of the drugs.[33]

Pharmacokinetics and pharmacodynamics of pazopanib

After administration of 800 mg once daily, the mean maximum plasma concentration (Cmax) value of pazopanib is 58.1 μg/mL and mean area under the plasma concentration-time curve (AUC) value is 1037 hr μg/mL, respectively.[34] Its median time to achieve a peak plasma concentration is 2-4 hours and mean half-life is 30.9 hours.[34] Pazopanib at a concentration of ≥ 40 μmol/L has also been shown to inhibit VEGFR-2 in mice.[28] Similarly, a phase I study has shown that a steady-state concentration of ≥ 40 μmol/L was needed for its clinical activity.[35] Pazopanib should be administered at least 1 hour before or 2 hours after a meal, and administration with a high-fat or low-fat meal leads to a 2-fold increase in AUC and Cmax.[34] Tablets should be taken whole, and crushed tablets increase Cmax by 2-fold and AUC by 46% at 72 hours.[34]

Elimination is mainly through the feces, with 4% of administered dose being recovered from the urine.[34] In patients with moderate hepatic impairment (n = 7), pazopanib clearance was reduced by 50%, compared to

the patients with normal hepatic function (n = 12). A dose of 200 mg once daily is recommended for patients having moderate hepatic impairment. Furthermore, pazopanib should not be used in patients with severe hepatic impairment.[34] Although patients with creatinine clearance < 30 mL/min were not included in studies published to date, renal impairment is unlikely to have a clinically relevant impact on pazopanib exposure and dose reduction is not recommended.[34]

Pazopanib is metabolized by hepatic cytochrome P450 enzymes, exclusively by CYP3A4 with limited contribution by CYP1A2 and CYP2C8 as well. Pazopanib is an inducer, inhibitor, or substrate of several CYP enzymes. Coadministration of pazopanib and CYP3A4 inhibitors, such as ketokonazole, lapatinib and grapefruit juice, has been shown to result in increased pazopanib Cmax and AUC.[34] In contrast, coadministration of pazopanib and CYP3A4 inducers, such as rifampin, led to decreased plasma pazopanib concentrations.[34] Thus, concomitant use of these drugs should be avoided. Clinical pharmacology studies using pazopanib 800 mg once daily show that pazopanib does not have the effect on the pharmacokinetics of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), or omeprazole (CYP2C19 substrate).[34]

Clinical studies

Phase I clinical trial of pazopanib

A phase I clinical trial was conducted to determine clinical safety of pazopanib following single and multiple doses of oral application.[36] A total of 63 patients were enrolled in this multicenter, open-label, non-randomized study. Inclusion criteria included age ≥ 21, histologically proven advanced solid tumor, resistance to standard therapy, Karnofsky performance status ≥ 70%, and average life expectancy of at least 12 weeks. Among them, 12 (19%) RCC patients consisted of the biggest group of the participants. Other tumor cases included colon, sarcoma, breast, pancreatic, and rectal cancer. Patients were given doses of 50 mg or 100 mg three times weekly, 50 to 2000 mg once daily, or 300 mg or 400 mg twice daily. Pazopanib was well tolerated up to 2000 mg tested. There was no statistical significance between 800 mg once daily exposures and 2000 mg once daily or 400 mg twice daily exposures. Although the maximum tolerated dose was not established in this study, a steady state exposure plateau was reached at the dose of 800 mg daily. Based on these results, 800 mg once daily dose is recommended for a phase II study.[37]

The clinical efficacy of pazopanib was recorded. Two of 3 patients exhibiting partial response were RCC cases. Among 12 RCC patients, only 2 achieved partial response, while 4 patients showed stable disease for more than 6 months, 4 patients experienced progression, and 2 patients were excluded from the study due to drug toxicity. Patients having partial response or stable disease were given further pazopanib at doses of ≥ 800 mg once daily or 300 mg twice daily, while patients with progression were administered with pazopanib at doses of ≤ 400 mg once daily. None of the 3 patients exhibiting partial response had been treated with antiangiogenic agents before.

In this study, 48 (76%) patients experienced drug-related adverse events (AEs). Most of these AEs were at grade I and II levels and reversible after treatment discontinuation. The most frequently seen AEs were hypertension (33%), diarrhea (33%), nausea (32%), and hair depigmentation (32%). Grade III and IV AEs were less common, while grade III AE hypertension was seen in 25% of patients. Grade IV AEs were observed only in 4 (6%) patients; 2 patients demonstrated high levels of creatinine and 2 patients demonstrated hypoglycemia. The incidence of hypertension was similar in patients with and without a history of hypertension. No grade IV hematologic toxicities were observed, but grade III lymphopenia was observed in 9 (14%) patients. Ten patients were subjected to treatment interruption and/or dose reduction due to AEs. Eight of them were given pazopanib at doses of 800 mg or 2000 mg once daily. No treatment-related deaths occurred.

Phase II clinical trial of pazopanib.

In order to evaluate the efficacy of pazopanib, a multicenter, randomized discontinuation phase II trial was designed for patients with locally recurrent or metastatic RCC.[37] Pazopanib was administered orally at 800 mg once daily. Patients meeting the criteria of ≥ 21 age, predominantly clear-cell histology with measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST), and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were included in the study. Patients with brain or leptomeningeal metastasis were excluded. Patients were either treatment-naive or treated with bevacizumab or cytokine previously. All patients were given pazopanib for 12 weeks. After that, patients demonstrating stable disease were randomized into a pazopanib group or a placebo group. Interim analysis for the first 60 patients who completed 12 weeks of treatment showed the response rate to be 38%. Based on this result, randomization was stopped and patients were administered with pazopanib until progression or emergence of AEs. The overall response rate (complete response + partial response) was 34.6% (28%-41% with

TABLE 1. **Results of efficacy of pazopanib in phase II and phase III trials**

	Phase II	Phase III
Complete response (%)	1.3	< 1
Partial response (%)	33.3	30
Stable disease (%)	44.9	38
Progressive disease (%)	10.7	18
Unknown (%)	9.8	14
Median duration of response (weeks)	68.0	58.7
Progression free survival (months)	11.9	9.2

95% confidence interval [CI]), Table 1. Response rate (RR) was similar for both the treatment-naïve group (34%; 26%-41% with 95% CI) and the previously treated group (37%; 26%-49% with 95% CI,). Median duration of response was 68 weeks and median progression free survival (PFS) was 11.9 months (44-60 weeks with 95% CI), Table 1. The median length of exposure to drugs (placebo or pazopanib) was 252 days (2-914). The most commonly observed AEs were diarrhea (63%), fatigue (46%), hair depigmentation (43%), nausea (42%), and hypertension (41%), Table 2. Most of the AEs were grade I or II, while the most common grade III or IV AEs were hypertension (9%) and fatigue (5%). The most common laboratory abnormalities were aspartate amino transferase (AST) elevation (54%), alanin aminotransferase (ALT) elevation (53%), and lymphopenia (46%), Table 3. The majority of the laboratory abnormalities were recognized as grade I or II, while the most common grade III or IV abnormalities were ALT elevation (9%), hyponatremia (8%), lipase elevation (8%), and AST elevation (6%).

TABLE 2. **Treatment-emergent adverse events from phase II and phase III trials which occur in ≥ 20% of patients**

Adverse events	Phase II	Phase III
Diarrhea (%)	63	52
Fatigue (%)	46	< 20
Hair color changes (%)	43	38
Nausea (%)	42	26
Hypertension (%)	41	40
Anorexia (%)	24	22
Dysgeusia (%)	24	n/a
Vomiting (%)	20	21
Headache (%)	20	< 20

TABLE 3. **Treatment emergent laboratory abnormalities from phase II and phase III trials which occur in ≥ 20% of patients**

Laboratory abnormalities	Phase II	Phase III
AST increase (%)	54	53
ALT increase (%)	53	53
Lymphopenia (%)	46	31
Hyponatremia (%)	37	31
Leukopenia (%)	35	37
Creatine increase (%)	32	n/a
Lipase increased (%)	29	n/a
Hyperbilirubinemia (%)	28	36
Alkaline phosphatase increase (%)	27	n/a
Neutropenia (%)	27	34
Thrombocytopenia (%)	26	32
Anemia (%)	26	n/a
Hyperkalemia (%)	26	n/a
Amylase increase (%)	24	n/a
Hyperglycemia (%)	n/a	41
Hypophosphatemia (%)	n/a	34
Hypocalcemia (%)	n/a	33

Among the patients treated with 400 mg daily dose, 31% of subjects needed dose reduction. The dose was re-escalated in half of these cases and stopped in 15% of patients due to serious AEs.

Phase III clinical trial of pazopanib

A randomized, double-blind, multicenter, international, and placebo-controlled phase III study on the efficacy of pazopanib monotherapy in advanced and/or metastatic RCC patients was recently reported.[38] Inclusion criteria were similar to the phase II clinical trial.[37] A total of 435 patients were enrolled and randomized in a 2:1 ratio to receive 800 mg of pazopanib or placebo once daily (290 patients on pazopanib and 145 patients on placebo). Nephrectomy was performed in 88% of the patients. In addition, 54% of the patients were treatment-naïve and 46% of patients were treated with IFN-α or IL-2 previously. The ratios of these patient conditions were the same in both the pazopanib and placebo groups. Patients received continuous treatment until death, disease progression, or development of toxicity. In the placebo group, patients demonstrating disease progression were offered pazopanib treatment and 48% of patients accepted this option. The primary endpoint of the study was PFS and the secondary endpoints were overall survival, response rate, duration of response, and safety.

This phase III study showed overall median PFS to be 9.2 months in the pazopanib group, Table 1, and 4.2 months in the placebo group (hazard ratio [HR], 0.46; 0.34 to 0.62 with 95% CI; $p < 0.0001$). Variation was prominent in the treatment-naive subgroup (11.2 months in the pazopanib group versus 2.8 months in the placebo group (HR, 0.40; 0.27 to 0.60 with 95% CI; $p < 0.0001$). The cytokine-pretreated group showed significant differences in favor of pazopanib (7.4 versus 4.2 months, HR, 0.54; 0.35 to 0.84 with 95% CI; $p < 0.001$). RR was observed to be 30% among pazopanib-treated patients but only 3% in the placebo group. The median duration of response was 58.7 weeks in the pazopanib-treated patients, Table 1. RR was observed at similar rates in the treatment-naive and cytokine-pretreated groups (32% versus 29%, respectively). Moreover, 32% of patients were treated with pazopanib and 15% of patients were treated with placebo for more than 12 months, respectively. The most common AEs were diarrhea (52%), hypertension (40%), and hair color changes (38%), Table 2. The majority of AEs were grade I or II, while the most common grade III or IV AEs were hypertension (4%) and diarrhea (4%). The most common laboratory abnormalities were elevated ALT (53%), elevated AST (53%), and hyperglycemia (41%), Table 3. Laboratory abnormalities were generally grade I or II, while the most frequently seen grade III or IV AEs were elevated ALT (10%) and elevated AST (7%) levels. The hemochromatosis gene (HFE) regulates iron homeostasis. Seventeen percent of patients with ALT ≥ 3 times the upper limit of the normal range carried the risk-associated HFE TT genotype in the phase II and phase III studies. ALT elevation in patients who were treated by pazopanib may occur because of environmental and genetic factors.[39] Furthermore, 3% of pazopanib-treated patients developed arterial thrombotic events like myocardial infarction/ischemia, cerebrovascular accident, and transient ischemic attack. At the end of this study, pazopanib was approved by the FDA in October 2009, for use in patients with advanced RCC.

Drug comparison, combination, and sequential treatment

Although cytokines such as IL-2 and IFN-α are used for treating patients with metastatic RCC,[40] TKIs are more widely used at the present time. All three commonly used TKIs (pazopanib, sunitinib and sorafenib) are similar in the mechanisms of action and affect the same receptors with different affinities. Canter and associates compared sunitinib and pazopanib in vitro and found that sunitinib could inhibit cell proliferation in lower doses than pazopanib. In addition, sunitinib appeared to be cytotoxic to all cell lines tested whereas pazopanib was only cytostatic.[41] All three TKIs have side effects, but they are generally mild (grade I or II) and similar in the side effect profiles.[42] Diarrhea, fatigue, neutropenia, and hand-foot syndrome are more frequent with sunitinib, whereas hypertension and hyperglisemia are more common with pazopanib. Increased AST and ALT levels are seen in both treatment groups but pazopanib has fatal hepatotoxicity risk.[43]

As a comparative approach, an ongoing phase III open label trial COMPARZ (Pazopanib Versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma) compares the efficacy of pazopanib versus sunitinib in RCC treatment.[44] A randomized, double-blinded, and crossover trial, the PISCES (Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer) trial, has also been underway to compare patient preferences with regard to pazopanib versus sunitinib.[45]

Due to its side effects and overlapping toxicity risk, pazopanib has only been used in combination with certain chemotherapeutic agents such as everolimus (NCT01184326) and bevacizumab (PARASOL, NCT00992121) in a few studies.[46-48] Pazopanib has also been tested in sequential approach. A phase II trial (NCT00731211) was conducted in patients pretreated with sunitinib or bevacizumab.[49] These patients had failed the previous treatments and were given pazopanib as a second-line treatment. Furthermore, a sequential study with everolimus, bevacizumab, and pazopanib is continuing (NCT01217931).[50] Studies with more elective and potent agents are necessary because of the off-target effects of the multi-targeted TKIs.

Other studies related with RCC

There are several reported studies investigating the effects of adjuvant therapy or combination therapy administered after nephrectomy in RCC cases. The STRAC (Sunitinib Treatment of Renal Adjuvant Cancer), the SORCE (Sorafenib with Placebo in Patients with Resected Renal Cell Carcinoma), and the ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) studies have been conducted to investigate the efficacy and safety of adjuvant therapy.[51] Trials like the BeST (ECOG2804) and INTORACT (Investigation of TORisel and Avastin Combination Therapy) were aimed to investigate the efficacy of combination therapies.[51]

Conclusion

Pazopanib is an orally bioavailable, multi-targeted TKI, which inhibits VEGFR-1, -2 and -3, PDGFR-α and -β, and c-Kit tyrosine kinases. Pazopanib has been

approved in the United States, Europe and Canada for treating patients with advanced RCC. Currently, it is being used in good or intermediate risk RCC and shows some survival benefits. The use of pazopanib is associated with acceptable adverse effects, generally at a low grade. Pazopanib is still a new treatment option and further studies are greatly needed, particularly on its effect relative to other TKIs and its use in combination with other agents as well as optimal sequencing with other agents. More information is expected in the near future, as several clinical trials are being conducted and completed.

Disclosure

The authors received no funding for this review. □

References

1. Motzer RJ, Bander NH, Nanus DN. Renal-cell carcinoma. *N Engl J Med* 1996;335(12):865-875.
2. Diaz JI, Mora LB, Hakam A. The Mainz classification of renal cell tumors. *Cancer Control* 1999;6(6):571-579.
3. Nelson EC, Evans CP, Lara PN. Renal cell carcinoma: current status and emerging therapies. *Cancer Treat Rev* 2007;33(3):299-313.
4. Siegel R, Ward E, Brawley O, Jemal A. Cancer Statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011;61(4):212-236.
5. Pili R, Rodriguez R. Cancer of the kidney. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. Abeloff's clinical oncology. 4th edition, Chapter 86. Philadelphia: Churchill Livingstone/ Elsevier 2008.
6. Rini BI. Vascular endothelial growth factor-targeted therapy in metastatic renal cell carcinoma. *Cancer* 2009;115(10 Suppl): 2306-2312.
7. Rini BI, Small EJ. Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. *J Clin Oncol* 2005;23(5):1028-1043.
8. Mulders P. Vascular endothelial growth factor and mTOR pathways in renal cell carcinoma: differences and synergies of two targeted mechanisms. *BJU Int* 2009;104(11):1585-1589.
9. Cohen HT, McGovern FJ. Renal cell carcinoma. *N Engl J Med* 2005; 353(23):2477-2490.
10. Forsythe JA, Jiang BH, Iyer NV et al. Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. *Mol Cell Biol* 1996;16(9):4604-4613.
11. Hudson CC, Liu M, Chiang GG et al. Regulation of hypoxia-inducible factor 1 alpha expression and function by the mammalian target of rapamycin. *Mol Cell Biol* 2002;22(20):7004-7014.
12. Rini BI, Michaelson MD, Rosenberg JE et al. Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma. *J Clin Oncol* 2008;26(22): 3743-3748.
13. Rasmuson T, Grankvist K, Jacobsen J, Ljungberg B. Impact of serum basic fibroblast growth factor on prognosis in human renal cell carcinoma. *Eur J Cancer* 2001;37(17):2199-2203.
14. Cébe-Suarez S, Zehnder-Fjällman A, Ballmer-Hofer K. The role of VEGF receptors in angiogenesis; complex partnerships. *Cell Mol Life Sci* 2006;63(5):601-615.
15. Brugarolas J. Renal-cell carcinoma: molecular pathways and therapies. *N Engl J Med* 2007;356(2):185-187.
16. Pyrhönen S, Salminen E, Ruutu M et al. Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. *J Clin Oncol* 1999; 17(9):2859-2867.
17. Negrier S, Perol D, Ravaud Aet al; For The French Immunotherapy Intergroup. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. *Cancer* 2007;110(11):2468-2477.
18. Medical Research Council Renal Cancer Collaborators. Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomized controlled trial. *Lancet* 1999;353(9146):14-17.
19. Fisher RI, Rosenberg SA, Fyfe G. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. *Cancer J Sci Am* 2000;6(Suppl 1):S55-S57.
20. Escudier B, Eisen T, Stadler WM et al; TARGET Study Group. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; 356(2):125-134.
21. Faivre S, Delbaldo C, Vera K et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2006;24(1): 25-35.
22. Motzer RJ, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356(2):115-124.
23. Hutson TE, Davis ID, Machiels JP et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2010;28(3):475-480.
24. 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* 2010;28(6):1061-1068.
25. Escudier B, Bellmunt J, Négrier 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* 2010;28(13):2144-2150.
26. Hudes G, Carducci M, Tomczak P et al; Global ARCC Trial. Temsirolimus, interferon alfa, or both for advanced renalcell carcinoma. *N Engl J Med* 2007;356(22):2271-2281.
27. Motzer RJ, Escudier B, Oudard S et al; RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008;372(9637):449-456.
28. Kumar R, Knick VB, Rudolph SK. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther* 2007;6(7): 2012-2021.
29. Limvorasak S, Posadas EM. Pazopanib: therapeutic developments. *Expert Opin Pharmacother* 2009;10(18):3091-3102.
30. Harris PA, Boloor A, Cheung M et al. Discovery of 5-[[4-[(2,3-dimethyl- 2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methyl-benzenesulfonamide (Pazopanib), a novel and potent vascular endothelial growth factor receptor inhibitor. *J Med Chem* 2008;51(15):4632-4640.
31. Sloan B, Scheinfeld NS. Pazopanib, a VEGF receptor tyrosine kinase inhibitor for cancer therapy. *Curr Opin Investig Drugs* 2008; 9(12):1324-1335.
32. Hicklin DJ, Ellis LM. Role of vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol* 2005;23(5):1011-1027.
33. Sonpavde G, Hutson TE, Sternberg CN. Pazopanib, a potent orally administered small molecule multitargeted tyrosine kinase inhibitor for renal cell carcinoma. *Expert Opin Investig Drugs* 2008;17(2):253-261.
34. U.S. Food and Drug Administration Centre for Drug Evaluation and Research. Pharmacology/Toxicology Review and Evaluation of Pazopanib. Available from URL:http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022465s000_PharmR.pdf

35. Hurwitz H, Dowlati A, Savage S. Safety, tolerability, and pharmacokinetics of oral administration of GW780634 in patients with solid tumors. *J Clin Oncol* 2005;23(Suppl 16S):195s (abstract no. 3012).
36. Hurwitz HI, Dowlati A, Saini S et al. Phase I trial of pazopanib in patients with advanced cancer. *Clin Cancer Res* 2009;15(12): 4220-4227.
37. Hutson TE, Davis ID, Machiels JP et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2010;28(3):475-480.
38. 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* 2010;28(6):1061-1068.
39. Xu CF, Reck BH, Goodman VL et al. Association of the hemochromatosis gene with pazopanib-induced transaminase elevation in renal cell carcinoma. *J Hepatol* 2011;54(6):1237-1243.
40. Patard JJ, Pignot G, Escudier B et al. ICUD-EAU International Consultation on Kidney Cancer 2010: treatment of metastatic disease. *Eur Urol* 2011;60(4):684-690.
41. Canter D, Kutikov A, Golovine K et al. Are all multi-targeted tyrosine kinase inhibitors created equal? An in vitro study of sunitinib and pazopanib in renal cell carcinoma cell lines. *Can J Urol* 2011;18(4):5819-5825
42. Bhargava P, Robinson MO. Development of second-generation VEGFR tyrosine kinase inhibitors: current status. *Curr Oncol Rep* 2011;13(2):103-111.
43. Lang JM, Harrison MR. Pazopanib for the treatment of patients with advanced renal cell carcinoma. *Clin Med Insights Oncol* 2010; 4:95-105.
44. Pazopanib versus sunitinib in the treatment of locally advanced and/or metastatic renal cell carcinoma (COMPARZ) [NCT00720941]. Available from URL: http://clinicaltrials.gov/ct2/show/NCT00720941.
45. Patient preference study of pazopanib versus sunitinib in advanced or metastatic kidney cancer (PISCES) [NCT01064310]. Available from URL: http://clinicaltrials.gov/ct2/show/NCT01064310.
46. Pazopanib and everolimus in patients with advanced solid tumors and previously treated kidney cancer. (NCT01184326). Available from URL: http://clinicaltrials.gov/ct2/show/NCT01184326.
47. Multicenter dose-escalation study of a combination of pazopanib and bevacizumab in patients with metatstatic renal cell carcinoma or others advanced solid tumors (PARASOL). Available from URL: http://clinicaltrials.gov/ct2/show/NCT01202032.
48. An open-label pharmacodynamic study of bevacivumab and pazopanib in renal cell carcinoma (NCT00992121). Available from URL: http://clinicaltrials.gov/ct2/show/NCT00992121.
49. A phase II trial of pazopanib in patients with metastatic renal cell carcinoma previously treated with sunitinib or bevacizumab (NCT00731211). Available from URL: http://clinicaltrials.gov/ct2/show/NCT00731211.
50. Sequential two-agent assessment in renal cell carcinoma therapy (NCT01217931). Available from URL: http://clinicaltrials.gov/ct2/show/NCT01217931.
51. http://www.cancer.gov/search/ ResultsClinicalTrials.