

REVIEW

Sorafenib in renal cell carcinoma

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Abstract: Cancer is among most important causes of death in recent decades. Whoever the renal cell carcinoma incidence is low but it seems it is more complicated than the other cancers in terms of pathophysiology and treatments. The purpose of this work is to provide an overview and also deeper insight to renal cell carcinoma and the steps which have been taken to reach more specific treatment and target therapy, in this type of cancer by developing most effective agents such as Sorafenib. To achieve this goal hundreds of research paper and published work has been overviewed and due to limitation of space in a paper just focus in most important points on renal cell carcinoma, treatment of RCC and clinical development of Sorafenib.

The information presented this paper shows the advanced of human knowledge to provide more efficient drug in treatment of some complicated cancer such as RCC in promising much better future to fight killing disease.

Keywords: Sorafenib, renal cancer, tyrosine kinase, VEGFR, Nexavar

INTRODUCTION

Cancer

Every condition or factor, which can cause damage to a apoptotic pathway that can result in less proapoptotic or high antiapoptotic factors, can cause cancer (Emory University, 2009).

Cancer based on location and function is categorized in the following five types (Emory University, 2009; Medical News Today, 2010).

Carcinoma: this type is derived from the epithelial cells of organs such as skin, kidney, colon and lung.

Sarcomas: this type is from fat, bone and cartilage

Myeloma: this type is related to white blood cells and antibodies

Leukemia: abnormality of white blood cells and their precursor may make this type

Lymphoma: cancer of the bone marrow based on lymph nodes and immune system

Renal cell carcinoma

Proximal renal tubular epithelium is the main tissue affected in renal cell carcinoma (RCC). This cancer makes up 2–3% of all malignancy in adults and also as respectively, the seventh and ninth most common cancer in men and women. Its incidence occurrence is about 209,000 new cases and about 102,000 deaths per year. The Robson Scale (Robson CJ, Churchill BM, & Anderson W, 1969) specifies four stages between the

conditions and prognoses. Also in 2007 around 51,000 patients in the United States were estimated to be diagnosed with kidney cancer. This carcinoma is a male-prevalent (2:1 ratio) disease when people are in sixth or seventh decade of their life. This carcinoma has a high incidence in Scandinavian and North American people and is the eighth common cause of fatality in the United States.

Renal cell carcinoma may remain as a hidden form for most of its course. There are three classic presentations such as: bilateral pain, hematuria, and flank mass. Twenty-five to thirty percent of patients have not any symptom, and their carcinomas are found on an incidental in radiologic study. As a result renal cancer has two main types:

A) Hereditary:

- 1- Von Hippel-Lindau Syndrome (VHL)
- 2- Hereditary Papillary Renal Carcinoma (HPRC)
- 3- Familial Renal Oncocytoma (FRO) with Birt-Hogg-Dube Syndrome (BHDS)
- 4- Hereditary Renal Carcinoma (HRC)

B) Nonhereditary

Both types (A, B) are affected by the short part of chromosome 3. Genetic studies of high risk families showed there are two ways in which tumors may form: 1) VHL or tumor suppressors, 2) MET or oncogene (Rini *et al.*, 2009; Emedicine 2009; Gupta *et al.*, 2008; Jemal *et al.*, 2007; Robson *et al.*, 1969).

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Clinical sign and symptom

Most common signs are hematuria, flank pain, tangible mass in the flank or abdomen, weight loss, fever, hypertension, hypercalcemia, night sweats, malaise and varicocele.

Renal cell carcinoma because of para-neoplastic syndromes has an incomparable condition and including: cachexia, and non-metastatic hepatic dysfunction. Amyloidosis, polyneuromyopathy, anemia, dermatomyositis, increased erythrocyte sedimentation rate are other signs and symptoms.

Causes

Some of the environmental and genetic factors which have been studied and may be associated with renal cell carcinoma are: heavy chain smoking, being Overweight (especially in women), body weight has a direct relation with high risk factors, hypertension may be related to increased risk of renal cell, phenacetin-containing analgesics (administrated in large amounts), tuberous sclerosis, renal transplantation, VHL disease, being an urban resident, second type of papillary RCC, Birt-Hogg-Dube syndrome, polycystic kidney disease, diabetes mellitus, and chronic dialysis (Emedicine, 2009; Hiles *et al.*, 2008; Zisman *et al.*, 2004).

Treatment

Immunotherapy in RCC

Sometimes the immune system can be prompt in causing renal cell carcinoma remission without any activation. And as a result many different immunotherapies have been studied such as cytokine therapy to increase the ability of the body in producing anti tumor immunity (Vogelzang *et al.*, 1992).

1-1-Interleukin-2 (IL-2)

One of the cytokine families which has a signaling function in the immune system is Interleukin2. This type of cytokine can produce its effect when it is joined to its receptor (IL-2 receptor).

A High dose administration of IL-2, as many research studies show, was effective (Fyfe *et al.*, 1995). But on in only a small group of patient tumor regression was induced. Unfortunately the recent research of stage III RCC explains that IL-2 therapy is not useful in increasing the free survival progression (Negrier *et al.*, 2007).

1-2-Interferon-alpha (IFN-)

In the 1980s, IFN was developed as a new generation therapeutic agent with a different mechanism of action to be used in monotherapy for RCC. The best dosage in many cases is 5 to 10 MU. However, the combination of IL-2 and IFN- α make a higher response than when IL-2 is used as a monotherapy, however there was no improvement in the survival rate (Vogelzang *et al.*, 1993).

Consequently there is not any proof to support the administration of immunotherapy in patients who have therapeutic surgery (Clark *et al.*, 2003).

Vaccine therapy

Stimulation of an immune response, such as antibody and cellular response, is the aim of vaccine therapy and its effect on target cells. But it is not able to enter tumor stroma and this is a main problem in its usage.

Cytoreductive nephrectomy for metastatic RCC

Because of some immunological event which will be happening in less than 1 percent of those who have a regression of a metastatic condition after nephrectomy, this method was suggested (Montie *et al.*, 1977).

Pathogenesis and genomics of RCC

This type of therapy is established on the biological factor in patients with genetic abnormalities. There are different genes and proteins that have been recognized and expressed in renal cell carcinoma such as: VEGF, insulin-like growth factor-binding protein 3, Endothelin 1, solute carrier family 2, and alpha-methyl- CoA racemase or KIT. Disability in VHL gene can make a hypoxia pathway from hypoxia inducible factor-1 and 2 (HIF-1 and 2), which can activate angiogenesis and other signaling such as: (VEGF, TGF-, GLUT1, CXCR4 and HIG2) (Maxwell, 2005; Maynard and Ohh 2005; Togashi *et al.*, 2005).

As a result there are two ways to activate hypoxia inducible factor:

- VHL gene mutations
- to inhibit the AKT/mTOR pathway

Chemotherapy

5-1-Gemcitabine (600 mg/m² on days 1, 8, and 15) with the injection of fluorouracil continuously (150 mg/m²/d for 21 d in 28-d cycle).

5-2-Floxuridine (5-fluoro 2'-deoxyuridine [FUDR]), 5-fluorouracil (5-FU), vinblastine, paclitaxel (Taxol), carboplatin, ifosfamide, gemcitabine, and anthracycline (doxorubicin) (Emedicine, 2009).

Surgery

If cancer is detected on primary stage, remedial surgery can be performed. Nephrectomy for patients with stage I, II and III is advantageous.

Molecular pathways (kinase inhibitor) in RCC

7-1. the mTOR pathway: Temsirolimus, Everolimus

7-2. Vascular endothelial growth factor (VEGF): Sunitinib, Sorafenib, Bevacizumab, Axitinib (AG-013736), Pazopanib (Hans *et al.*, 2008).

Table: Drugs and their target receptors in Renal cell carcinoma

Agent	Target	Trial Phase
Sorafenib (BAY 43-9006)	VEGFR2, VEGFR3, PDGFR, FLT-3, c-KIT, CRAF, wtBRAF, V600E BRAF	II, III
Temsirolimus (CCI-779)	mTOR	II, III
Bevacizumab	VEGF	II, III
Sunitinib (SU011248)	VEGFR2, PDGFR, FLT-3, c-KIT	II, III
Everolimus (RAD001)	mTOR	II
Pazopanib (GW786034)	VEGFR 1, VEGFR2, VEGFR3, PDGFR	II
Axitinib (AG-013736)	VEGFR1, VEGFR2, PDGFR, c-KIT	II

mTOR= mammalian target of rapamycin, VEGF= vascular endothelial growth factor

PDGFR= platelet-derived growth factor receptor

VEGFR= vascular endothelial growth factor receptor (Simon *et al.*, 2008).

Kinase inhibitors are a special substance that can inhibit tyrosine kinases (TKs) signaling by preventing protein binding or the action of ATP.

1- Tyrosine kinases function is to catalyse the exchanging of a phosphate from ATP (adenosine triphosphate) to tyrosine residue. And they produce an effect on the angiogenesis and proliferation and metastatic activity of the tumor.

2- There are two different types of TKs:

a) Receptor Tyrosine Kinases (RTKs): epidermal growth factor receptor (EGFR) and downstream signaling pathways such as RAS/RAF/MEK/ERK and PI3K (phosphoinositol 3'-kinase)/Akt

b) Nonreceptor kinases: c- ABL (this kinase is in the cell and it will be activated in phosphorylation (Simon *et al.*, 2008).

The mTOR pathway

The mammalian target of rapamycin (mTOR) is a tyrosine kinase that forms the phosphoinositide 3-kinase (PI3K)/AKT pathway that is controlled by the PTEN tumor suppressor gene. This pathway has an important role in the angiogenesis, cancer survival and VEGF mediated endothelial proliferation.

There are two Multikinase inhibitors in this category: Temsirolimus, Everolimus

Vascular endothelial growth factor (VEGF) pathway

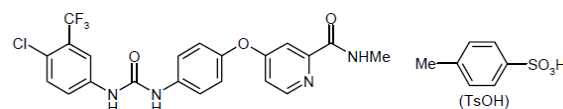
One of the most important growth factor is VEGF which is involved in tumor angiogenesis and has an important role in cancer progression, including RCC. There are two different approaches that are being used to block the VEGF pathway:

a. Using tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib, axitinib) to stop the intracellular domain of the VEGF receptor.

b. Using monoclonal antibodies which neutralize circulating VEGF (bevacizumab) and block its activation of the VEGF receptor (Hans *et al.*, 2008).

Sorafenib

On December, 2005, the US Food and Drug Administration granted approval for sorafenib (Nexavar). This is a small molecule, Raf kinase (C-Raf and B-Raf), vascular endothelial growth factor (VEGF) and multireceptor kinase inhibitor such as VEGFR-1, 2, 3, PDGFR β , Flt3, c-Kit, and RET receptor tyrosine kinase, and this drug is for treatment of patients with advanced renal cell carcinoma (Carlomagno *et al.*, 2006; Emedicine, 2009; Shenhong *et al.*, 2008 and Wilhelm 2004).



Sorafenib tosylate

The chemical name of Sorafenib tosylate is: 4-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl) ureido] phenoxy} pyridine-2-carboxylic acid methylamide 4- methyl-benzenesulfonate. And the formula is: $C_{21}H_{16}ClF_3N_4O_3 \times C_7H_8O_3S$ and a molecular weight is 637.0 g/mole.

The commercial tablet names is Nexavar, which are round shape, coated with red film, biconvex, 200 mg sorafenib that is equivalent to 274 mg Sorafenib tosylate, and the prescription is (two 200 mg) twice daily without food (1 hour before or 2 hours after a meal). Treatment will continue until it is clear that the patient has not clinically benefited from therapy or until unacceptable toxicity happens. The bioavailability is 38% to 49%. 3 h is the T_{max} . Plasma Steady levels occur in 7 days. High fatty meals can decline Sorafenib's bioavailability to 29%. Protein binding in vitro is 99.5%. Metabolism will happen in the liver, primarily, by CYP3A4 inducer (increases the metabolism of Sorafenib and then decreases the Sorafenib concentrations) and UGT1A9-mediated glucuronidation (Sorafenib inhibit the glucuronidation) (Escudier 2007).

Sometimes a dose reduction will be necessary and, in this situation the administration dose may be reduced to 400 mg per day. If additional reduction will required, dose may be reduced to a single 400 mg dose every other day such as: in a patient with infarction or cardiac ischemia or hypertension (Escudier 2007).

The most common unfavorable reactions in RCC ($\geq 20\%$), are fatigue, weight loss, rash, reaction in skin (hand-foot), diarrhea, anorexia, alopecia, abdominal pain and nausea.

Sorafenib tosylate is almost insoluble in watery media; a small quantity is soluble in ethanol and PEG 400. Tablet components are: Croscarmellose Sodium, Microcrystalline Cellulose, Hypromellose, Sodium Lauryl Sulphate, Magnesium Stearate, Polyethylene Glycol, Titanium dioxide and Ferric oxide (Kluwer 2010).

An international cooperative study approved that Sorafenib (BAY 43-9006), as a targeted therapy agent, is effective in treatment of metastatic RCC and can make a important improvement in the progression-free survival (PFS) with acceptable adverse-effect profile (Escudier B, 2007).

In the case of renal cell carcinoma, it has been showed that the malignancy diagnosed had different clinical characteristics by different country and race. The symptoms, the course of diseases, and the outcome after standard treatment vary markedly between patients of Hispanic, Caucasian, Asian, and African-American backgrounds (Stafford HS, 2008).

The Sorafenib efficacy has been approved for RCC in both phase II and phase III, which had been confirmed for use as a second-line treatment in metastatic disease (Escudier 2007 and Ratain 2006). The patients with a higher RCC progression-free survival (PFS) obtain 5.5 months after treatment with Sorafenib, with compared to 2.8 months for whose treatment with placebo (Zhang *et al.*, 2009).

Clinical development research on Sorafenib

As it will be mentioned later, all research studies are based on the three phases (1, 2 and 3 of RCC).

Phase 1

The study was done by Mross *et al* (2006) results from an in vitro and a clinical/pharmacological phase I study with the combination irinotecan and Sorafenib. They found it would be possible to combine Sorafenib 400 mg bid with irinotecan 125 mg/m² or 140 mg for patients who have advanced, refractory solid tumors, but strongly recommended that toxicity monitoring should be preformed (Mrossa *et al.*, 2006).

Another study was performed with Strumberg *et al* to settle the maximum dosage with limited toxicity, and

early antitumor activity of Sorafenib. 69 patients were included in the study field.

This study showed that Sorafenib does not affect to tumor size but it prevents the progression of advanced cancers. The 400-mg twice in day, was recommended as the target dose for future trials (Hiles *et al.*, 2008; Bhojani *et al.*, 2007 and Strumberg 2005).

Phase 2

Ryan and his colleagues studied and treated 62 patients who have RCC with Sorafenib 400 mg two times a day and interferon 10mu three times in week. The result was: a 7 month increase in the progression free survival in progression free survival, 49 patients could reduce their interferon dose and 22 patients for Sorafenib (Ryan 2007 and Chowdhury *et al.*, 2008).

Another research study was done in 2006 by Ratain and his colleagues which included 202 patients with RCC out of 502 patients with multiple tumors (202 patients who did not respond to IFN and chemotherapy) (Hiles *et al.*, 2008; Ratain 2006). The 202 patients with renal cancer were randomly assigned to treatment with Sorafenib or placebo. They get a positive response in 50% of the patients treated with Sorafenib in comparison to only 18% with placebo and the progression free survival was four times more than placebo (Ratain 2006).

Phase 3

The biggest controlled group design with Bernard Escudier and his colleague was conducted from November 2003 to March 2005. 903 patients, who were resistant in a standard therapy trial, were randomly assigned to either treatment with Sorafenib or placebo. They separated their patients as two main groups: 451 with Sorafenib and 452 with placebo. In 2005 they get these results:

- The free survival was 2.8 in the placebo group in comparison with 5.5 in Sorafenib group.
- The risk of death was reduced in Sorafenib therapy more than placebo therapy (hazard ratio, 0.72; 95% CI, 0.54 to 0.94; P = 0.02).
- It showed that the toxic effect increased in the Sorafenib group. Moreover different side effects were seen in the Sorafenib group such as: rash, hand-foot skin reaction, fatigue, and hypertension and so on (Escudier 2007; Prenen *et al.*, 2008; Hiles *et al.*, 2008; Bhojani *et al.*, 2007 and Wilhelm 2006).

A phase 3 trial randomized 750 patients to first line sunitinib (50 mg QD, 4 wk on/2 wk off) versus IFN- α (Motzer 2007).

A phase 3 temsirolimus study randomized 626 patients with previously untreated, poor-prognosis mRCC to

temsirolimus (25 mg weekly) versus IFN- α and temsirolimus (15 mg weekly) versus IFN- α alone (Hudes 2007).

Furthermore Bojani *et al* (2007) cited in his work that phase 3 also was studied with sunitinib and temsirolimus by Motzer *et al* and Hudes *et al*. Sunitinib was used as the first line of therapy with 750 patients 50mg QD for 4 weeks and 2 weeks off (Motzer 2007) and temsirolimus was in 626 patients 25mg weekly (Hudes 2007).

Management of drug-related toxicities in sorafenib, sunitinib and temsirolimus

- 1- Systemic side effects of sorafenib, sunitinib, temsirolimus such as fatigue and thyroid dysfunction
- 2- Cardiovascular side effects of sorafenib, sunitinib, and temsirolimus such as hypertension
- 3- Renal toxicities: It is unusual that these kinase inhibitors cause proteinuria and edema, but it will be seen in prolonged duration.
- 4- Gastrointestinal toxicities such as dyspepsia.
- 5- Cutaneous toxicities: Hand-foot syndrome, mucositis or stomatitis, rash or desquamation, pruritus, alopecia and some others side effects.
- 6- Laboratory toxicities: Hypophosphatemia, Glucose, increasing in lipase, amylase, cholesterol and/or triglycerides.

Based on this study, Sorafenib has the lowest grade of side effects. Fatigue, dyspnea, nausea, vomiting, anorexia, abdominal pain, anemia, thrombocytopenia are some examples.

CONCLUSION

Since cancer is the second cause of death and each type of cancers has its own and specific pathway, causes and treatment, so to overcome this deathly disease need deep understanding of each type of cancer. RCC is one of the most complicated cancer but developing some of medicine such as Sorafenib which acting more specifically on this type of cancer promising more effective treatment of cancer.

REFERENCES

- Brian I Rini, Steven C Campbell and Bernard Escudier (2009). Renal cell carcinoma. *Lancet.*, **373**(9669): 1119-1132.
- Carlomagno F.,S. Anaganti, T. Guida, G. Salvatore, G. Troncone, S. M. Wilhelm, M. Santoro, (2006). BAY 43-9006 inhibition of oncogenic RET mutants. *J NATL CANCER I*, **98**(5): 326-334.
- Clark JI, Atkins MB and Urba WJ (2003). Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. *J. Clin. Oncol.*, **21**: 3133-3140.
- Emedicine (2009). Renal Cell Carcinoma. Retrieved jun, Jun 25, 2009, from <http://emedicine.medscape.com/article/281340-overview>
- Emory University (2009). Defining cancer. Retrieved 2th Dec, 2009, from <http://www.cancerquest.org/index.cfm?page=6466&lang=english>
- Escudier B (2007). Sorafenib in advanced clear-cell renalcell carcinoma. *NEW ENGL J MED*, **356**: 125-134
- Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR and AC L (1995). Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J. Clin. Oncol.*, **13**: 688-696.
- Gupta K, Miller JD, Li JZ, Russell MW and Charbonneau C (2008). Epidemiologic and Socioeconomic Burden of Metastatic Renal Cell Carcinom: A literature review. *Cancer Treat Rev*, **34**: 193-205
- Hans Prenen, Thierry Gil and Ahmad Awada (2008). New therapeutic developments in renal cell cancer: Department of General Medical Oncology, University Hospital Gasthuisberg, Catholic University Leuven, Herestraat 49, 3000 Leuven, Belgium.
- Hiles Jon J and Jill M Kolesar (2008). Role of sunitinib and sorafenib in the treatment of metastatic renal cell carcinoma. *Am J Health Syst Pharm*, **65**:123-131
- Hudes G (2007). Temsirolimus,interferon alfa, or both for advanced renal-cell carcinoma. *NEW ENGL J MED*, **356**: 2271-2281.
- Jemal A, Siegel R, & Ward E. (2007). *Cancer statistics*.
- Mrossa K, Steinbilda S, Baasa F, Gmehlinga D, Radtkeb M, Voliotisb D, Brendelb E, Christensenc O & Unger C. (2006). Results from an in vitro and a clinical/pharmacological phase I study with the combination irinotecan and sorafenib. *EUR J CANCER*, **43**(1): 55-63.
- Maxwell Ph (2005). The HIF pathway in cancer. *Semin Cell Dev Biol.*, **16**: 523-530.
- Maynard MA and Ohh M (2005). Molecular targets from VHL studies into the oxygen-sensing pathway. *Curr Cancer Drug Targets*, **5**: 345-356.
- Medical News Today. (2010, Feb). What is Cancer? <http://www.medicalnewstoday.com/info/cancer-oncology/whatisacancer.php>
- Montie JE, Stewart BH, Straffon RA, Banowsky LH, Hewitt CB and Montague DK (1977). The role of adjunctive nephrectomy in patients with metastatic renal cell carcinoma. *J. Urol.*, **117**: 272-275.
- Motzer RJ (2007). Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *NEW ENGL J MED* **356**: 115-124.
- Bhojani N, Jeldres C, Patard J, Perrotte P, Suardi N, Hutterer G, Patenaude F, Oudard S & Karakiewicz P (2007). Toxicities Associated with the Administration of Sorafenib, Sunitinib, and Temsirolimus and Their Management in Patients with Metastatic Renal Cell Carcinoma *European Urology*, **53**(5): 917-930.

- Negrier S, Perol D and Ravaud A (2007). Medroxy-progesterone, 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* **110**: 2468-2477.
- Ratain MJ (2006). Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.*, **24**(16): 2505-2512.
- Robson CJ, Churchill BM and Anderson W (1969). The results of radical nephrectomy for renal cell carcinoma. *J. Urol.*, **101**(3): 297-301.
- Robson CJ, Churchill BM and Anderson W (1969). The results of radical nephrectomy for renal cell carcinoma. *J. Urol.*, **101**(3): 297-301.
- Ryan CW (2007). Sorafenib with interferon alfa-2b as first-line treatment of advanced renal carcinoma: A phase II study of the Southwest Oncology Group. *J. Clin. Oncol.*, **25**(22): 3296-3301.
- Shenhong Wu, John J Chen, Kudelka A, Janice Lu, & Xiaolei Zhu (2008). Incidence and risk of hypertension with sorafenib in patients with cancer: A systematic review and meta-analysis, (Publication No.10.1016/S1470-2045(08)70003-2). Retrieved January 22, 2008 from Lancet Oncol
- Chowdhury S, James MG Larkin and Martin E Gore (2008). Recent advances in the treatment of renal cell carcinoma and the role of targeted therapies. Retrieved from www.ejconline.com
- Stafford HS (2008). Racial/ethnic and gender disparities in renal cell carcinoma incidence and survival. *J. Urol.*, **179**(5): 1704-1708.
- Strumberg D (2005). Phase I clinical and pharmacokinetic study of the novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. *J. Clin. Oncol.*, **23**: 965-972.
- Togashi A, Katagiri T and Ashida S (2005). Hypoxia-inducible protein 2 (HIG2), a novel diagnostic marker for renal cell carcinoma and potential target for molecular therapy. *Cancer Res.*, **65**: 4817-4826.
- Vogelzang NJ, Lipton A and Figlin RA (1993). Subcutaneous interleukin-2 plus interferon alfa-2a in metastatic renal cancer: An outpatient multicenter trial. *J. Clin. Oncol.*, **11**: 1809-1816.
- Vogelzang NJ, Priest ER and Borden L (1992). Spontaneous regression of histologically proved pulmonary metastases from renal cell carcinoma: A case with 5-year follow-up. *J. Urol.*, **148**: 1247-1248.
- Wilhelm (2006). Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nat. Rev. Drug Discov.*, **5**(10): 835.
- Wilhelm S (2004). BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. from Cancer Res: www.ncbi.nlm.nih.gov/pubmed/15466206
- Wolters Kluwer (2010). sorafenib. <http://www.drugs.com/ppa/sorafenib.html>
- Zhang H, Dong B, Lu J, Yao X, Zhang S, Dai B, Shen Y, Zhu Y, Ye D & Huang Y. (2009). Efficacy of sorafenib on metastatic renal cell carcinoma in Asian patients: Results from a multicenter study. *BMC Cancer*, **9**(1): 249.
- Zisman A, Belldegrun AS and Figlin RA (2004). Urinary tract cancers (Casciato DA, ed.). Lippincott Williams & Wilkins, Philadelphia, 295-320.