Horizon Scanning in Oncology

Pazopanib (Votrient ®) for the treatment of locally advanced and/or metastatic renal cell carcinoma

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology Nr. 013
ISSN online 2076-5940

Horizon Scanning in Oncology

Pazopanib (Votrient ®) for the treatment of locally advanced and/or metastatic renal cell carcinoma

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, October 2010

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Author(s):	Katharina Hintringer, BA
Internal review:	Dr. Anna Nachtnebel, MSc
External review:	Prof. Dr. Kurt Miller, Urologische Klinik und Poliklinik Charité, Universitätsmedizin Berlin

DISCLAIMER

This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice nor should it be used for commercial purposes.

CONTACT INFORMATION

Publisher:
Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at "http://eprints.hta.lbg.ac.at":

DSD: Horizon Scanning in Oncology Nr. 013
ISSN online 2076-5940

http://eprints.hta.lbg.ac.at/view/types/dsd.html

1 Drug description

Generic/Brand name:

Pazopanib, GW786034 (Votrient ®)

Pazopanib/Votrient ®

Developer/Company:

Glaxo Group Limited

Description:

Pazopanib is an orally administered antineoplastic agent that targets multiple tyrosine kinase inhibitors (TKIs) which are involved in angiogenesis, tumour growth and metastatic progression of cancer [1]. In detail, pazopanib inhibits vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and c-KIT. These receptors can be found on the surface of cancer cells and are responsible for growth and spread of the tumour. By targeting these receptors, growth and spread of the tumour should be reduced [2].

orally administered; targeting multiple TKIs – VEGFR, PDGFR, c-Kit

Other multi-targeting TKIs targeting VEGFR and PDGFR, such as sunitinib and sorafenib, are already approved for the treatment of renal cell carcinoma (RCC).

The recommended daily dose of pazopanib is 800mg administered orally as a film-coated tablet at least 1 hour prior or 2 hours after a meal. In the pivotal study VEG105192 [3] patients received pazopanib until disease progression, death, unacceptable toxicity or withdrawal of consent. Pazopanib is only approved for adult patients.

recommended daily dose: 800mg

Due to the safety results of pazopanib trials that showed serious liver-related adverse events, it is recommended to perform serum liver tests prior to initiation of pazopanib therapy and regularly thereafter in patients with advanced or metastatic RCC [2].

liver function test prior to therapy strongly recommended

2 Indication

Pazopanib (Votrient ®) is indicated as monotherapy for the treatment of therapy-naïve patients with advanced renal cell carcinoma or in RCC patients who have failed prior cytokine-based systemic therapy.

monotherapy, first-line and after failed cytokine-based therapy

3 Current regulatory status

06/2010 EMA granted conditional marketing authorisation

request for mature OS data and head-to-head comparison

In June 2010, the European Medicines Agency (EMA) has granted conditional approval of pazopanib (Votrient ®) for the treatment of advanced and/or metastatic RCC for the first-line treatment or after initial cytokine-based therapy has failed. Votrient® was approved under the condition that the marketing authorisation holder submits mature OS data of the pivotal VEG105192 trial by 2012 and efficacy and safety data of the ongoing head-to-head COMPARZ [4] trial, comparing pazopanib and sunitinib in RCC [2]. The comparator sunitinib was chosen, because its efficacy and safety profile was similar to the efficacy and safety profile of pazopanib when both were compared to placebo [2, 5].

10/2009 US FDA approval – not for patients with severe hepatic impairment

In October 2009, the US Food and Drug Administration (US FDA) approved pazopanib (Votrient ®) for the same indication as EMA in June 2010. The American FDA does explicitly not recommend pazopanib for the treatment of RCC patients with severe hepatic impairment [6].

4 Burden of disease

1181 newly diagnosed kidney cancer in 2007

In 2007, 1181 patients (men: 705; women: 476) were newly diagnosed with kidney cancer and 407 kidney cancer patients (men: 222; women: 185) died due to their disease in Austria [7].

90% of kidney cancers are RCCs

RCC, a type of kidney cancer, accounts for approximately 90% of all kidney cancers [3]. Generally, 5 histological types of carcinoma are differentiated:

- clear cell (approximately 60%)
- papillary (7-14%)
- chromophobe (6-11%)
- oncocytoma (7-10%)
- and collecting duct (<1%) [8].

median age at diagnosis 50-70 years

Associated risk factors are smoking and obesity, as well as genetic abnormalities. Median age of RCC diagnosis is between 50-70 years with more men than women being affected [9].

risk stratification for the choice of therapy (e.g. with MSKCC)

three risk groups: good, intermediate and poor

Risk stratification is important for choosing the most appropriate therapy. The most common model to predict short survival is the Memorial Sloan-Kettering Cancer Centre or informally known as the *Motzer* criteria (MSKCC) which are based on risk-factors or predictors, such as high blood levels of lactate dehydrogenase and calcium, anaemia, time of less than a year from diagnosis to the need for systemic treatment and low performance status (Karnofsky performance status <80%). Depending on the number of risk factors three groups can be stratified: a good, intermediate or poor risk-group [10].

The TNM-staging system is used for the clinical staging of RCCs, considering the size of the tumour, involved lymph nodes and metastasis [11]. In contrast to localized tumours with a high probability of cure (stage I/II), more advanced forms with either metastases in the regional lymph nodes (stage III) or with distant metastases (stage IV) of kidney cancer are linked to poor outcomes. Estimated average 5-year survival rate for patients ranges from 23% (stage IV) to 64% (stage III) [10].

TNM-staging system has prognostic relevance

5-year survival for stage III 64% and stage IV 23%

Due to an often asymptomatic course of the disease, about 25% to 30% of patients are diagnosed when the tumour has already metastasised [9].

25-30% have metastatic disease at time of diagnosis

Applying these estimates and considering that pazopanib is indicated for the treatment of patients with advanced RCC with histological clear cell type (study population of the pivotal VEG105192 study [3]), approximately 200 newly diagnosed patients will be eligible to receive pazopanib treatment in Austria every year. 20% to 30% of patients with previously localized tumours relapse one to two years after surgery [10].

5 Current treatment

The standard of care for patients with RCC is nephrectomy followed by either observation or - if possible - the enrolment into clinical trials [10]. For patients who relapse after surgical excision of the tumour or who are not eligible for resection in the first place, the choice of therapy depends on different factors like tumour stage and histology, absence or presence of metastases etc. For the first- and second-line treatment of RCC patients, cytokines (IL-2 and IFN-α) and targeted agents (like sunitinib malate, sorafenib tosylate, temsirolimus, everolimus and bevacizumab) are used [10].

surgical excision is primary choice of therapy in RCC patients

Reviews show that the resistance of patients with RCC to cytotoxic therapy, radiation or hormone therapy is very high [3]. Therefore, cytokines were, despite their limited clinical efficacy and significant toxicity, the choice of therapy until new targeted agents have been developed recently [3, 12]. Clinical studies show that response rates to cytotoxic therapy with IFN-α and/or IL-2 are generally less than 10% and that consequently, resistance to these agents is very high [13]. Thus, new treatment strategies for advanced and/or metastatic RCC are needed. Advances in the understanding of RCC tumour biology, including the role of VEGF and mTOR pathways, led to the clinical development of several targeted agents for the treatment of RCC [3]. Currently, there are, besides pazopanib, five targeted agents approved by the FDA and the EMA for RCC therapy:

low response rate of 10% and resistance to cytotoxic therapy, hormone therapy or radiation

since 2006 six new targeted agents for the treatment of RCC have been approved

- sunitinib malate (Sutent®),
- sorafenib tosylate (Nexavar®),
- temsirolimus (Torisel®),
- everolimus (Aftinitor®)
- and bevcacizumab (Avastin®) in combination with interferon [10].

6 Evidence

1 phase III trial and one phase II trial

two subgroups: treatment-naïve and cytokine pre-treated patients

Based on a limited literature search 2 trials meeting the pre-defined inclusion criteria for the efficacy section of this horizon scanning report could be identified. Sternberg et al. 2010 [3] published the findings and data of a multinational and multicenter phase III study evaluating the safety and efficacy of the new TKI pazopanib in the treatment of advanced and/or metastatic RCC in treatment-naïve or cytokine pre-treated patients compared to placebo. This study included 435 patients – 233 were treatment naïve and 202 patients were pre-treated with cytotoxic therapy. The approval of pazopanib in the US in 2009 and in Europe in 2010 was mainly based on these results.

randomized discontinuation study

Further, a phase II randomized discontinuation trial (consisting of a lead-in phase, followed by 3 options: continuation or discontinuation of therapy or randomization; this trial design is described in more detail elsewhere [14]) assessing the safety and efficacy in 225 patients was identified. As described below, this study consisted of an open-label phase, where all patients were treated with pazopanib, followed by a randomized, placebo-controlled phase. Only patients with stable disease were per protocol eligible for randomization.

6.1 Efficacy and safety - Phase III studies

Table 1: Phase III trial – safety and efficacy results

Reference	Sternberg et al. 2010 [3]; VEG105192 study, NCT00334282
Sponsor	GlaxoSmithKline Pharmaceuticals, Philadelphia, PA
Country	80 centers in Europe, Asia, South America, North Africa, Australia, New Zealand
Design	Randomized, placebo-controlled, multicenter trial
Participants characteristics	435 pts – I(ntervention): 290; C(ontrol): 145; median age: I 59 years (range 2-85) vs C 60 years (range 25 – 81); men: I 68% vs C 75% Treatment-naïve subpopulation: I 155 pts (53%) vs C 78 pts (54%) Cytokine pre-treated subpopulation: I 135 pts (47%) vs C 67 pts (46%)
Treatments	I(ntervention): 800mg pazopanib once daily, administered orally, dose modification guidelines for AEs were pre-specified C(ontrol): placebo matching pazopanib Patients who had progressive disease were unblinded and if they had received placebo, they were offered to be treated with pazopanib within an open-label study (VEG107769). 48% of placebo-arm patients enrolled in that trial
In-/exclusion criteria	Inclusion: Pts with advanced and/or metastatic RCC, who had progressed on one prior cytokine-based systemic therapy or who are treatment naïve; diagnosis of clear-cell or predominantly clear-cell histology; ECOG PS ≤ 1, adequate renal, hepatic, and hematologic function Exclusion: Pts with CNS metastasis, leptomeningeal lesions, poorly controlled hypertension
Follow-up	Follow-up for overall survival was performed every 3 months after disease progression until death or study withdrawal
Outcomes	Primary: progression free survival (PFS) Secondary: overall survival (OS), objective response rate (=complete response (CR) and partial response (PR)), duration of response, safety, health-related quality of life (HRQL)

Key results	Primary outcomes Median PFS(I vs. C): - Overall study population: HR 0.46; 95% CI, 0.34 to 0.62; p <0.0001 (9.2 vs. 4.2 months (mths)) - Treatment naïve subgroup: HR 0.40; 95% CI, 0.27 to 0.60; p <0.0001 (11.1 vs. 2.8 mths) - Cytokine pre-treated subgroup: HR 0.54; 95% CI, 0.35 to 0.84; p <0.001 (7.4 vs. 4.2 mths) Secondary outcomes OS: at time of interim analysis the required events for final OS analysis had not yet occurred. Mature data on OS will be reported when available. Response rate (I vs. C): - Overall study population: 30% (95% CI, 25.1 to 35.6) vs. 3% (95% CI, 0.5 to 6.4); median duration of response: 58.7 weeks (wks) (95% CI, 52.1 to 68.1) vs. not mentioned - Treatment naïve subgroup: 32% (95% CI, 24.3 to 38.9) vs. 4% (95% CI, 0.0 vs. 8.1) - Cytokine pre-treated subgroup: 29% (95% CI, 21.2 to 36.5) vs. 3% (95% CI, 0.0 to 7.1) Health-related quality of life (HRQL): The mixed-model repeated-measures analyses did not show statistical significant difference between pazopanib and placebo treated groups at any assessment time point.
Adverse effects	Most common observed adverse events (AEs): diarrhea (I 52% vs C 9%), hypertension (I 40% vs C 10%), hair colour changes (I 38% vs C 3%), nausea (I 26% vs C 9%), anorexia (I 22% vs C 10%), vomiting (I 21% vs C 8%), hemorrhagic events (I 13% vs C 5%), elevations in alanine aminotransferase (ALT) (I 53% vs C 22%) and elevations in aspartate aminotransferase (AST) (I 53% vs C 19%). Grade 3 and 4 AEs were observed in 33% and 7%, respectively in the pazopanib arm compared to 14% and 6%, respectively in the placebo arm. Hypertension (4%) and diarrhea (4%) were the most common grade 3/4 AEs in I vs <1% in C Death resulting from AEs: I: 4% vs. C: 3%; 4 deaths (1%) in the pazopanib arm were attributable to study treatment – ischemic stroke, abnormal hepatic function, rectal hemorrhage and peritonitis/bowel perforation.
Commentary	Efficacy regarding PFS and response rate was better in treatment naïve patients compared to cytokine pre-treated patients. Though, the safety profile between treatment-naïve and cytokine pre-treated pts is similar, more pts in the cytokine pre-treated arm (19%) discontinued treatment because of AEs compared to treatment-naïve pts (12%).

protocol amendment to also include treatment-naïve patients

Initially, only patients progressing on prior systemic cytokine-based therapy were enrolled to the study. After the enrolment of the first 7 patients the protocol was amended to also include treatment-naïve patients due to emerging evidence on the efficacy of angiogenesis inhibitors and decreased use of cytokines in the first-line setting of RCC therapy. Patients were randomly assigned 2:1 to pazopanib vs. placebo. The demographic characteristics were well balanced between the two treatment arms with the majority of patients being male (71%) and an average age of 59 years.

subgroup-analyses confirm superiority of pazopanib over placebo

For the primary outcome measure, PFS, pre-defined subgroup-analyses were conducted for Memorial Sloan-Kettering Cancer Center (MSKCC) risk category, Eastern Cooperative Oncology Group performance status (ECOG PS), sex and age. These subgroup-analyses showed that PFS was improved in patients treated with pazopanib compared to placebo.

reasons for study discontinuation: progressive disease, death, AEs, etc.

At time of data cut-off, 78% of patients in the intervention arm and 90% of patients in the control arm had already discontinued study treatment due to several reasons. The most common reasons were disease progression (I: 51%; C: 77%), death (I: 4%, C: 6%), adverse events (I: 14%, C: 3%) protocol violation (I: <1%, C: none), investigator decision (I: 3%, C: <1%), loss to follow-up, withdrew consent, and other (I: 6%, C: 3%).

AEs occurred more frequent and more sever in pazopanib group

Regardless of previously treated or untreated patients, adverse events occurred more frequently and were more severe in patients treated with pazopanib compared to placebo.

dose modifications due to elevations in liver enzymes ALT and AST

The most common clinical laboratory abnormalities observed in the pazopanib arm were elevations in the liver enzymes AST and ALT. After dose modification, interruption or discontinuation of treatment, recovery in 45 of 52 patients with ALT elevations could be observed. The other seven patients did not have adequate follow-up data to assess recovery.

no difference in HRQL between study groups was observed

Health-related quality of life was assessed by applying three different quality of life measure instruments – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), EuroQuol questionnaire (EQ-5D) and visual analogue scale (VAS). Overall the completion of questionnaires was high (>90%). No statistical and clinical significant difference in health-related quality of life between placebo and pazopanib group was observed at any assessment time point.

6.2 Efficacy and safety - further studies

protocol revision due to RR after first interim analysis

Hutson et al. (2010) [5] conducted a phase II study which was initially planned as a randomized discontinuation study: after a 12 week open-label phase with daily 800mg pazopanib, patients with stable disease should enter a RCT. However, the Independent Data Monitoring Board decided to halt the randomization at the first interim analysis (as soon as 60 patients completed 12 weeks of pazopanib treatment) due to the response rate of 38%. Subsequently all patients were treated with pazopanib on an open-label basis.

study outcomes: RR, duration of response , PFS

median duration of response: 68 weeks

median PFS: 45 weeks

The primary endpoint of this revised protocol was objective response rate (RR) and the secondary endpoints were duration of response and PFS assessed by an independent review committee (IRC). The overall study population was 225 RCC patients with the histological subtype predominant clear-cell. The RR was 35% (95% CI, 28% to 41%) for the overall study population (n=225). For the treatment naïve patients (n=155) it was 34% (95% CI, 26% to 41%) and for previously treated patients (n=70) RR was 37% (95% CI, 26% to 49%). The median duration of response was 68 weeks (95% CI, 53.7 to not mentioned) and PFS by IRC was 45 weeks (95% CI, 36 to 59 weeks) for the overall study population.

Subgroup analyses for PFS showed that ECOG PS and time from diagnosis until start of therapy were correlated with prolonged PFS.

treatment-related AEs: diarrhoea, fatigue, hair depigmentation, nausea and hypertension

The safety analysis was based on the all-enrolled population. The most common treatment emergent adverse events (reported by investigator) were diarrhoea (63%), fatigue (46%), hair depigmentation (43%), nausea (42%) and hypertension (41%). The most common grade 3 or 4 treatment-related adverse events were hypertension (8%), increased ALT (6%), increased AST

(4%), diarrhoea (4%), and fatigue (4%). 31% of patients had a dose reduction to 400mg daily due to adverse events. 34 (15%) patients discontinued pazopanib due to adverse events.

7 Estimated costs

one month pazopanib monotherapy: approximately € 3,300.-

Pazopanib is approved as a once daily administered tablet at a dose of 800mg for adult patients. In Austria there are two different packages of pazopanib via the producer available: either 30 tablets, each containing 200mg pazopanib at a price of € 833 or 30 tablets, each containing 400mg pazopanib at a price of € 1,666. Applying these data, one month of treatment with pazopanib would be € 3,331.- [15]. Sternberg et al. 2010 [3] reported a median duration of exposure to pazopanib therapy in the pivotal phase III study of 7.4 months. Multiplying the estimated monthly treatment costs of € 3,300.- by 7.4 months, estimated overall treatment costs would be € 24,420.- for the treatment of locally advanced and/or metastatic RCC.

8 Ongoing research

4 phase III trials evaluating the efficacy and safety of pazopanib in RCC are registered at www.clinicaltrial.gov

Currently, there are 4 trials assessing the efficacy and safety of pazopanib in different RCC patient groups and in different treatment options registered at www.clinicaltrial.gov – one RCT comparing pazopanib to placebo, two trials comparing pazopanib and sunitinib and one open-label trial [4].

sunitinib vs. pazopanib

patient preference study

NCT00720941, NCT01064310: These two trials compare the efficacy, safety and tolerability of pazopanib and sunitinib head-to-head. The study results of these two agents showed similar safety and efficacy profiles when both were compared to placebo [5]. One of these two studies is assessing the non-inferiority of the one agent over the other and the NCT01064310 trial is designed to identify patients' preferences in the choice of the TKIs for the treatment of their disease.

pivotal study still ongoing to assess OS

NCT00334282: This is the pivotal trial assessing the efficacy and safety of pazopanib in locally advanced and/or metastatic RCC presented in chapter 6.1. The VEG105192 trial is still ongoing to assess the secondary endpoint of overall survival.

NCT00387764: Patients in the VEG105192 trial, the pivotal phase III trial presented in chapter 6.1 had the option to receive pazopanib in an open-label study when progressing in placebo. This open-label trial is expected to be completed by the end of year 2012.

Further, plenty of phase I and II trials assessing the safety and efficacy of pazopanib in different therapy combinations and therapy lines and different indications are registered at www.clinicaltrial.gov.

9 Commentary

5 months increase in PFS

RR 30% pazopanib vs. 3% placebo

Sternberg et al. 2010 [3] published data of a phase III trial investigating the efficacy of pazopanib for the treatment of RCC, which confirmed the efficacy of pazopanib observed in another phase II trial [5]. In the overall study population treatment with pazopanib resulted in a 5 month increase of PFS in comparison to placebo, with similar results for overall response rate (RR; I 30% vs. C 3%). Subgroup-analyses of PFS and RR in treatment-naïve and cytokine pre-treated patients showed that the treatment effect was more pronounced in the treatment-naïve cohort. The difference of median PFS between pazopanib and placebo was 8.3 months in the treatment-naïve cohort and 3.2 months in the cytokine pre-treated cohort.

treatment effect stronger in treatment-naïve patients

AEs are clinically manageable

grade 3/4 AEs: hypertension, diarrhoea, elevations in liver enzymes

The safety and tolerability profile of pazopanib was considered to be acceptable and clinically manageable, although, grade 3 and 4 AEs, were observed in 33% of patients and 14% of patients discontinued therapy because of AEs. The most common observed AEs were of grade 1 or 2. The most common grade 3 or 4 AEs were hypertension, diarrhoea and elevations in the liver enzymes AST and ALT. Elevations in the liver transaminases resulted in dose modifications, interruption or discontinuation of treatment.

Health-related quality of life (HRQL) was assessed with three different instruments at pre-defined points in time. At none of these evaluation points, statistically or clinically significant difference in HRQL was observed between placebo and pazopanib group [3].

benefit-risk balance is found to be positive

Both, the EMA and the FDA concluded in their benefit-risk assessment that the benefits of the pazopanib therapy in locally advanced and/or metastatic RCC patients outweigh its risks. The benefit-risk balance is not only found to be statistically significant, but is also considered to be clinically relevant [2, 6].

pazopanib not suitable for pts with severe hepatic impairment

regular liver function tests are recommended

Whereas FDA granted regular approval, EMA granted conditional marketing authorisation of pazopanib for the treatment of RCC. The treatment of patients with severe hepatic impairment is explicitly not recommended due to the occurrence of hepatic failures including fatalities during treatment with pazopanib. Due to elevations in ALT and AST in clinical trials, both regulatory authorities, EMA and FDA, emphasized the importance to perform regular serum liver tests in order to test the hepatic function and to avoid severe hepatic impairment [2, 6, 17].

mature OS data and direct head-to-head comparison data are still awaited

Both regulatory agencies requested further efficacy, safety and tolerability data of RCC patients treated with pazopanib. On the one hand the marketing authorisation holder has to submit mature data on OS of the pivotal phase III trial VEG105192 and on the other hand direct comparison data of the two agents pazopanib and sunitinib in a currently ongoing phase III (COMPARZ trial, NCT00720941 [18]) comparative trial are awaited.

several treatment options available and lack of comparative data

The reason is, that since 2006 six targeted agents for the treatment of RCC have been approved and that up to now there are no direct comparative data of these agents available to allow an accurate estimation of the differences between the treatment options. The question is how an appropriate choice of therapy can be made in clinical practice in the light of the current data about the efficacy and safety of pazopanib and the other approved agents. In clinical practice adverse event profiles, mode of administration and other factors are used for the choice of therapy. Though, applying these factors

cannot substitute the need to conduct direct head-to-head comparisons to allow accurate estimations of the differences between the available treatment options [2]. Again, both the FDA and the EMA stated that this head-to-head comparative trial has to be designed carefully to allow an accurate estimation of efficacy and safety of these two agents. When compared to placebo, pazopanib and sunitinib have a similar efficacy profile - RR 35% vs. 31% and median PFS 12 months vs. 11 months for sunitinib and pazopanib, respectively [5]. Recently, Pal et al. 2010 [19] criticised in their paper the choice of PFS as the primary endpoint in the COMPARZ trial, stating, that if PFS of these two agents is similar, – as it is expected [20] – clinicians will still have to face the decision of choosing between two equally efficacious agents [19].

2nd-line therapy only for cytokine pre-treated patients available

Another issue the EMA pointed out, is the fact that pazopanib has only been assessed in patients with advanced and/or metastatic RCC who are treatment-naïve or cytokine pre-treated [2]. Additionally it has to be mentioned that the study populations in the phase II as well as in the phase III trial were of the histological subtype clear-cell and predominantly clear-cell (approximately 60% of all RCC). Therefore, RCC patients other than clear-cell or predominantly clear-cell and refractory to other systemic therapy than cytokines should not – due to absence of safety and efficacy data – be treated with pazopanib [2].

direct comparison necessary to allow right choice of therapy

Overall, the efficacy and safety profile of pazopanib is considered positive. Though, there are still a couple of questions unanswered – e.g. mature OS data of the ongoing pivotal phase III trial and direct comparative data of pazopanib and other approved agents and the efficacy and safety of 2nd-line pazopanib in patients initially treated with other systemic therapy than cytokines.

Based on the current evidence on the available targeted agents for the first-line treatment of locally advanced and/or metastatic RCC, it is not possible to accurately define superiority in terms of clinical efficacy for one of the agents over another.

References

1. EMA - European Medicines Agency. *Summary of Opinion - Pazopanib (Votrient ®).* 2010 07.07.2010]; Available from: http://www.ema.europa.eu/pdfs/human/opinion/Votrient_10490510en.pdf.
2. EMA - European Medicines Agency. *Votrient - Pazopanib.* 2010 30.07.2010]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001141/human_med_001337.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124.
3. Sternberg, C.N., et al., *Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial.* J Clin Oncol, 2010. **28**(6): p. 1061-8.
4. U.S. National Institutes of Health. *ClinicalTrials.gov - Pazopanib.* 2010 23.08.2010]; Available from: http://www.clinicaltrial.gov/ct2/results?term=pazopanib.
5. Hutson, T.E., et al., *Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma.* J Clin Oncol, 2010. **28**(3): p. 475-80.
6. US Food and Drug Administration (FDA). *Drugs@FDA - Drug Details. Votrient.* 2009 30.07.2010]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022465s000TOC.cfm.
7. Statistik Austria. *Statistiken - Gesundheit - Krebserkrankungen - Niere.* 2009 02.08.2010]; Available from: http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/niere/index.html.
8. Motzer, R., et al., *Treatment Outcome and Survival Associated With Metastatic Renal Cell Carcinoma of Non-Clear-Cell Histology.* J Clin Oncol, 2002. **20**(9): p. 2376-2381.
9. Aulitzky, W.E., J. Beck, and C. Huber, *Nierenzellkarzinom*, in *Die Onkologie - Solide Tumoren, Lymphome, Leukaemien*, W. Hiddemann, H. Huber, and C.R. Bartram, Editors. 2004, Springer-Verlag: Berlin Heidelberg.
10. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology - Kidney Cancer. v.2.2010.* 2010 03.08.2010]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf.
11. Leischner, H., *BASICS Onkologie*. Vol. 1. 2007, Muenchen: Elsevier GmbH - Urban & Fischer.
12. Hutson, T.E. and R.M. Bukowski, *A phase II study of GW786034 using a randomized discontinuation design in patients with locally recurrent or metastatic clear-cell renal cell carcinoma.* Clinical Genitourinary Cancer, 2006. **4**(4): p. 296-298.
13. Di Lorenzo, G., et al., *Targeted therapy in the treatment of metastatic renal cell cancer.* Oncology, 2009. **77 Suppl 1**: p. 122-31.
14. Stadler, W.M., *The randomized discontinuation trial: a phase II design to assess growth-inhibitory agents.* Molecular Cancer Therapeutics, 2007. **6**(4): p. 1180-1185.
15. Arzneimittelinformation und Pharmakovigilanz Anstaltsapotheke LKI-Universitätskliniken Innsbruck, *Pazopanib (Votrient) - Preis.* 2010: Innsbruck.

16. US Food and Drug Administration (FDA). *Highlights of prescribing information - Votrient (pazopanib) tablets*. 2009 23.08.2010]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022465lbl.pdf
17. Xu, C.F., et al., *Pazopanib-induced hyperbilirubinemia is associated with Gilbert's syndrome UGT1A1 polymorphism.* Br J Cancer, 2010. **102**(9): p. 1371-7.
18. U.S. National Institutes of Health. *Pazopanib versus sunitinib in the treatment of locally advanced and/or metastatic renal cell carcinoma (COMPARZ)*. 2010 25.08.2010]; Available from: http://www.clinicaltrial.gov/ct2/show/NCT00720941?term=pazopanib&cond=renal+cell&phase=2&rank=2.
19. Pal, S.K. and R.A. Figlin, *Targeted therapies: Pazopanib: carving a niche in a crowded therapeutic landscape.* Nat Rev Clin Oncol, 2010. **7**(7): p. 362-363.
20. Sonpavde, G., T.E. Hutson, and C.N. Sternberg, *Pazopanib for the treatment of renal cell carcinoma and other malignancies.* Drugs Today (Barc), 2009. **45**(9): p. 651-61.