Drugs (2014) 74:1111–1125
DOI 10.1007/s40265-014-0243-3

ADIS DRUG EVALUATION

Pazopanib: A Review of Its Use in the Management of Advanced Renal Cell Carcinoma

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Published online: 17 June 2014

Abstract Pazopanib (Votrient®) is an orally administered multi-tyrosine kinase inhibitor that is approved in the EU, the US and other countries for the treatment of advanced renal cell carcinoma. Pazopanib predominantly inhibits vascular endothelial growth factor receptor-1, -2 and -3, platelet-derived growth factor receptor-α and -β, and the stem cell factor receptor c-Kit, resulting in inhibition of tumour angiogenesis, cell growth and survival. In randomized controlled trials in patients with advanced, predominantly clear-cell, renal cell carcinoma, progression-free survival (PFS) and the objective response rate were significantly greater in pazopanib recipients than in placebo recipients (VEG105192 trial), and pazopanib was noninferior to sunitinib with respect to PFS (COMPARZ study). In a patient-preference, crossover study involving 10 weeks of treatment with each drug (PISCES study), significantly more patients expressed a preference for pazopanib than for sunitinib, with their preference being based primarily on tolerability and quality-of-life issues. Health-related quality-of-life (HR-QOL) assessments generally favoured pazopanib over sunitinib in COMPARZ, and pazopanib did not cause deterioration in HR-QOL compared with placebo in VEG105192. Pazopanib caused less myelosuppression, hand-foot syndrome, mucositis/stomatitis, dysgeusia and fatigue than sunitinib, but more abnormal liver function tests. Therefore, pazopanib was noninferior to sunitinib with respect to efficacy in the treatment of advanced renal cell carcinoma, but had a differentiated tolerability profile, which affected HR-QOL and patient preference.

Pazopanib in advanced renal cell carcinoma: a summary
An orally administered multi-tyrosine kinase inhibitor
Targets VEGFR-1, -2 and -3, PDGFR-α and –β, and c-Kit resulting in inhibition of tumour angiogenesis, growth and survival
Superior to placebo with respect to progression-free survival and objective response rates
Noninferior to sunitinib with respect to progression-free survival
Patient preference related to tolerability/quality of life favoured pazopanib over sunitinib
Health-related quality-of-life assessments generally favoured pazopanib over sunitinib
The tolerability profile was distinct from that of sunitinib

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1 Introduction

Kidney cancer accounts for approximately 2.4 % of all cancers, with 337,860 new cases diagnosed and 143,369 deaths worldwide in 2012, and occurs more frequently in

men than in women (1.7:1) [1]. Renal cell carcinoma constitutes 80–85 % of all malignant kidney tumours, with clear-cell or predominantly clear-cell histology seen in 75–85 % of patients [2]. The incidence and mortality of renal cell carcinoma has stabilized or started to decline in many Western countries in recent years, possibly as a result of reductions in major risk factors, such as cigarette-smoking, obesity and hypertension [3].

The common presenting symptoms are haematuria, abdominal pain or a palpable mass in the flank or abdomen, but most small localized renal tumours are asymptomatic [2]. Therefore, the diagnosis is often delayed until the disease is quite advanced. Early disease is most often discovered incidentally during abdominal imaging for unrelated conditions [4].

Surgery is the cornerstone of therapy for localized renal cell carcinoma and is the only curative therapeutic option [4], although up to 30 % of surgical patients experience recurrence [5]. Surgical treatment of metastatic disease requires excision of all tumour deposits in order to be curative. In most patients with metastatic disease, surgery is palliative and complementary systemic therapies are required [4]. Metastatic renal cell carcinoma is poorly responsive to radiotherapy, hormonal agents and conventional chemotherapeutic agents [2]. Advanced disease has traditionally been treated with cytokine (interferon-α or interleukin [IL]-2)-based therapies, although these have been limited by tolerability issues. Therefore, more specific targeted agents have been developed in line with advances in the understanding of the disease process [6].

Although renal cell carcinoma is not generally familial in nature, in a very high proportion of patients with clear-cell renal cell carcinoma, the von Hippel-Lindau disease gene, a tumour suppressor gene whose protein product is involved in ubiquitination, is inactivated, which leads to the accumulation of hypoxia inducible factor (HIF)-α, which in turn leads to the increased production of angiogenic and growth factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), amongst others [7, 8]. The mammalian target of rapamycin (mTOR) protein is also involved in the regulation of the HIF-α and other pathways, promoting angiogenesis, cell proliferation and reduced apoptosis. Therefore, the HIF-α and mTOR pathways have been major targets in the development of new agents to treat advanced renal cell carcinoma [7, 8].

Targeted anti-tumour agents that are currently available to treat renal cell carcinoma include an anti-VEGF monoclonal antibody (bevacizumab administered in combination with interferon-α), multi-tyrosine kinase inhibitors that target the VEGF receptor (VEGFR) among others (sunitinib, pazopanib, sorafenib, axitinib) and mTOR inhibitors (everolimus, temsirolimus) [9, 10].

Pazopanib (Votrient®) is an orally administered multi-tyrosine kinase inhibitor that predominantly inhibits VEGFR-1, -2 and -3, PDGF receptor (PDGFR)-α and -β, and stem cell factor receptor (c-Kit) [11, 12]. It is approved in the EU, the US, Japan and other countries for first-line (as well as subsequent-line) therapy of advanced renal cell carcinoma and has been available since 2009/2010 [11, 12]. This article provides a narrative review of the efficacy and tolerability of pazopanib in the treatment of patients with advanced and/or metastatic renal cell carcinoma, and overviews its pharmacological properties.

2 Pharmacodynamic Properties

Pazopanib is a multi-tyrosine kinase inhibitor that competes with adenosine triphosphate (ATP) for binding to the intracellular side of tyrosine kinase receptors and prevents ATP-induced activation of the receptors [13]. It predominantly inhibits VEGFR-1, -2 and -3, PDGFR-α and –β, and c-Kit [11]. Inhibition of these target receptors results in inhibition of angiogenesis, cell growth and survival by reducing activation of associated signalling pathways [13].

The in vitro concentrations of pazopanib that produced 50 % inhibition (IC_{50}) of VEGFR-1, -2 and -3 were 10, 30 and 47 nmol/L, respectively, while the IC_{50} values for PDGFR-α and –β were 71 and 84 nmol/L, and that for c-Kit was 74 nmol/L [11, 14].

In addition to inhibiting the target tyrosine kinases (e.g. VEGFR), pazopanib and other licensed tyrosine kinase inhibitors also inhibit other kinases, which may account for differences in the adverse effect profiles of the different agents. For instance, pazopanib also inhibits fibroblast growth factor receptor (FGFR)-1 and -3, IL-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck) and transmembrane glycoprotein receptor tyrosine kinase (c-Fms) in vitro [12, 14]. In a comparison of their activities against a large panel of 242 kinases, pazopanib was more selective overall than sunitinib, inhibiting (by >50 % at a concentration of 0.3 nmol/L) a smaller proportion of kinases (12 vs. 20 %) [15]. Pazopanib inhibited a similar proportion of kinases to sorafenib (11 %), although with differences against specific kinases [15]. All three tyrosine kinase inhibitors were potent inhibitors of VEGFR-1, -2 and -3, PDGFR-α and –β, and c-Kit, with sorafenib showing the least selectivity amongst these receptors (Table 1). Flt-3 and c-Kit receptors are expressed on haematopoietic progenitor cells and are crucial in the development of mature haematopoietic cells. Pazopanib was less active than sunitinib against c-Kit and was the least active against Flt-3 (Table 1), suggesting that pazopanib is likely to

produce less myelosuppression than sunitinib [15] (see Sect. 5.2).

Both pazopanib and sunitinib inhibited the proliferation of various human renal cell carcinoma cell lines in vitro, although sunitinib inhibited proliferation at markedly lower concentrations, and, unlike pazopanib, completely suppressed cellular proliferation within the concentration range tested [16]. Sunitinib demonstrated a direct apoptotic effect in all cell lines, while pazopanib demonstrated a cytostatic effect [16].

In addition to inhibiting the target kinases in vitro and in cultured tumour cell lines or foreskin fibroblasts expressing the receptors, pazopanib was shown to inhibit angiogenesis in vivo in mouse models, as well as dose-dependently inhibiting the growth of human tumour xenografts in immunocompromised mice [14].

Studies aiming to identify prognostic or predictive markers of clinical response have identified several candidate cytokine or angiogenic factors, such as IL-6, IL-8 and osteopontin [17], or genetic polymorphisms associated with lower response to pazopanib [18], but as yet there are no validated biomarkers that can be used to predict clinical outcome.

Abnormal liver function tests are the most common laboratory abnormalities associated with pazopanib therapy in patients with advanced renal cell carcinoma (see Sect. 5) and studies have attempted to define biomarkers that are predictive for liver toxicity. While useful genetic polymorphisms predictive of ALT elevation have not been identified [19, 20], pazopanib-induced hyperbilirubinaemia has been associated with the Gilbert's syndrome *uridine diphosphate (UDP)-glucuronosyltransferase 1A1* (*UGT1A1*) gene polymorphism, suggesting a benign origin for isolated unconjugated hyperbilirubinaemia in many patients that would not necessitate interruption of pazopanib monotherapy [20].

Table 1 Inhibitory activity of pazopanib, sunitinib and sorafenib against selected purified kinases in vitro. Reproduced with permission from Kumar et al. 2009 [15]

Enzyme	Apparent inhibition constant (K_i^{app}) [nmol/L]		
	Pazopanib	Sunitinib	Sorafenib
VEGFR-1	15	229	10
VEGFR-2	8	51	4
VEGFR-3	10	30	6
PDGFR-α	30	28	2
PDGFR-β	14	7	5
c-Kit	2.4	0.45	15
Flt-3	230	0.6	22

PDGFR platelet-derived growth factor receptor, *VEGFR* vascular endothelial growth factor receptor

3 Pharmacokinetic Properties

The pharmacokinetics of pazopanib have been assessed in animals [14] and patients with advanced solid tumours [21, 22]. Supplemental data were derived from the manufacturer's prescribing information [11, 12] and the US FDA review of the pazopanib licensing application [23].

The anti-tumour and anti-angiogenic activity of pazopanib in animal models was found to correlate with the steady-state plasma concentration rather than the single-dose maximum plasma concentration (C_{max}) or the area under the plasma concentration-time curve (AUC) values [14]. Experiments in mice suggested that a target steady-state plasma concentration of ≥40 μmol/L (≥17.5 μg/mL) would be optimal for in vivo activity [14].

3.1 Absorption and Distribution

Following single-dose oral administration of pazopanib 800 mg in patients with advanced solid tumours, the mean C_{max} of 19.4 μg/mL was obtained after a median time (t_{max}) of 3.5 h [22]. After receiving oral pazopanib 800 mg once daily for 22 days, the steady-state mean C_{max} was 45.1 μg/mL and the median t_{max} was 2.0 h. The AUC over the 24-h dosing interval (AUC_τ) was 275 μg·h/mL after a single 800 mg oral dose of pazopanib and 743 μg·h/mL after 22 days of treatment with pazopanib 800 mg once daily [22]. The trough (24-h) plasma concentrations of pazopanib after a single 800 mg dose and after once-daily dosing for 22 days were 9.4 and 24.0 μg/mL, respectively [22]. Although the C_{max} and AUC_τ continued to increase with single doses of pazopanib up to 2,000 mg (the highest dose tested), the steady-state C_{max} and AUC_τ appeared to plateau at the 800 mg once daily dosage [22]. Thus, the 800 mg once daily dosage was suggested as the dosage for use in further clinical investigation of pazopanib [22]. The AUC from time zero to infinity (AUC_∞) after a single 800 mg dose was ≈650 μg·h/mL [11].

The median oral bioavailability of pazopanib determined in three healthy volunteers was 21 % (range 14–39 %) [23].

The administration of oral pazopanib 800 mg after either a high-fat (≈50 % fat) or a low-fat (≈5 % fat) meal in patients with advanced solid tumours resulted in approximately twofold increases in mean C_{max} and AUC from time zero to 72 h (AUC_{72}) compared with administration in the fasted state [21]. Hence, pazopanib should be taken without food (see Sect. 6). The mean t_{max} increased from 4 h in the fasted state to 6 h with both meals [21].

Compared with the administration of a whole tablet, crushing a pazopanib 400 mg tablet before administration increased the AUC_{72} by 46 % and the C_{max} approximately twofold, and decreased the t_{max} by ≈2 h [11].

Pazopanib is highly bound (>99 %) to plasma proteins in vitro and in vivo [11, 12, 23]. Plasma protein binding was not dependent on the pazopanib concentration over the range of 10–100 μg/mL.

3.2 Metabolism and Elimination

Pazopanib is primarily metabolized by the hepatic cytochrome P450 (CYP) 3A4 isoenzyme, and to a lesser extent by CYP1A2 and CYP2C8, to at least seven metabolites [23]. The four principal metabolites account for only 6 % of the exposure in plasma. Most of a dose is excreted as unaltered drug. One of the four principal metabolites has similar potency to pazopanib in inhibiting VEGF-stimulated endothelial cell proliferation, while the other three are 10- to 20-fold less active [11, 12].

The mean elimination half-life following single-dose oral pazopanib 800 mg in patients with advanced solid tumours is ≈30–31 h [11, 21, 22]. Administration of pazopanib with either a low-fat or a high-fat meal did not affect the mean apparent elimination half-life (28–34 h) [21]. Pazopanib is mainly excreted in the faeces as unaltered drug, with <4 % of a dose excreted in urine [11, 12, 23].

3.3 Special Populations

The clearance of pazopanib in patients with mild liver dysfunction was equivalent to that in patients with normal liver function (both 0.9 L/h), but was reduced by ≈50 % to 0.5 L/h in patients with moderate liver dysfunction [23]. The maximum tolerated dose of pazopanib (based on the incidences of grade 3 and 4 liver transaminase and bilirubin elevations) in patients with moderate liver dysfunction was determined to be 200 mg once daily [23]. In patients with severe liver dysfunction receiving pazopanib 200 mg once daily, the median steady-state C_{max} and AUC from time zero to 24 h (AUC_{24}) values were ≈18 % and ≈15 % of those in patients with normal liver function receiving 800 mg once daily [11, 12]. Therefore, pazopanib is not recommended in patients with severe liver dysfunction (total bilirubin >3 × the upper limit of normal [ULN] and any ALT/AST value) [11, 12].

Since the median bioavailability of pazopanib is 21 % and <4 % of the total dose is excreted in the urine, then <19 % of the absorbed pazopanib undergoes renal elimination [23]. Population pharmacokinetic modeling based on data from cancer patients with creatinine clearance (CL_{CR}) values of 31–150 mL/min indicated that renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics [11, 12, 23]. Therefore, no dosage adjustment is considered necessary in patients with CL_{CR} >30 mL/min. Pazopanib pharmacokinetics have not been assessed in subjects with CL_{CR} <30 mL/min and caution is advised in these patients.

3.4 Potential Drug Interactions

Pazopanib is metabolized mainly by CYP3A4 and is also a substrate for the multidrug resistance-related transporter proteins P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) [11, 12, 23]. Pazopanib is also a moderate inducer of CYP3A4 and CYP2B6 [23].

Co-administration of pazopanib (400 mg once daily) with the strong CYP3A4 and Pgp inhibitor ketoconazole (400 mg once daily) increased the C_{max} and AUC_{24} of pazopanib by 45 and 66 %, respectively [11]. Therefore, in most patients, pazopanib 400 mg once daily in the presence of a strong CYP3A4 and Pgp inhibitor, such as ketoconazole, would give the same exposure as pazopanib 800 mg once daily alone [11]. Likewise, co-administration with strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin, atazanavir, nefazodone and grape fruit juice) or combined CYP3A4, Pgp and BCRP inhibitors (e.g. lapatinib) may increase the exposure to pazopanib and should be avoided, if possible.

In human liver microsomes in vitro, pazopanib inhibited CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1 with IC_{50} values in the range of 8–17 μmol/L [23]. Clinical studies in cancer patients have shown that pazopanib increases the exposure to certain substrates of these enzymes, such as midazolam (CYP3A4), dextromethorphan (CYP2D6) and paclitaxel (CYP3A4/CYP2C8), but not to caffeine (CYP1A2), warfarin (CYP2C9) and omeprazole (CYP2C19) [11].

Pazopanib is an inhibitor of UGT1A1 (IC_{50} 1.2 μmol/L) and care needs to be exercised when pazopanib is co-administered with substrates of UGT1A1, such as SN38, the active metabolite of irinotecan, since pazopanib may increase the exposure to such agents [11]. Pazopanib is also an inhibitor of organic anion transporting peptide (OATP1B1) [IC_{50} 0.79 μmol/L] and may increase the exposure to drugs eliminated by OATP1B1 (e.g. statins) [11, 23].

Concomitant administration of pazopanib and simvastatin, both of which are substrates for CYP3A4, Pgp and BCRP, increases the incidence of ALT elevations [24]. The incidence of ALT elevations ≥3 × ULN in a pooled analysis of 11 pazopanib clinical trials ($n = 976$) was significantly higher in patients who received pazopanib and simvastatin concomitantly compared with those who received pazopanib without any concomitant statin (27 vs. 14 %; $p = 0.04$). The incidences of ALT elevations ≥3 × ULN in patients receiving concomitant atorvastatin or any statin were 17 and 21 %, respectively, neither of which was significantly higher than the incidence in those not

receiving any concomitant statin [24]. ALT recovery to <2.5 × ULN was documented in 91 % of patients (10/11) receiving pazopanib and simvastatin. There was a positive correlation of ALT elevation in patients taking concomitant simvastatin with the *ABCG2* (BCRP) 421C>A polymorphism versus wild-type genotype (71 vs. 10 %; odds ratio 19.6, 95 % CI 1.9–231.6; $p = 0.004$). This association was not observed for ALT elevations in patients not taking any concomitant statin [24].

4 Therapeutic Efficacy

The therapeutic efficacy or patient acceptability of pazopanib in advanced renal cell carcinoma has been assessed in three randomized, comparative, multicentre, phase III trials [25–27], which are the focus of this section. They consist of a double-blind, placebo-controlled, efficacy trial (study VEG105192), a large, open-label, noninferiority, efficacy comparison with sunitinib (COMPARZ) and a double-blind, crossover, patient-preference comparison with sunitinib (PISCES) as summarized in Table 2.

Patients in all three phase III trials were aged ≥18 years with locally advanced or metastatic renal cell carcinoma and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) as well as having an Eastern Cooperative Oncology Group (ECOG) performance status ≤1 (VEG105192 and PISCES) or a Karnofsky performance scale (KPS) status of ≥70 (COMPARZ). Study VEG105192 and COMPARZ required a diagnosis of clear-cell or predominantly clear-cell histology, while PISCES included renal cell carcinoma of any histology. Patients with CNS metastases, or significant cardiac or vascular disease were generally excluded from the trials. Patients were naive to systemic treatment for advanced or metastatic renal cell carcinoma, or, in the case of study VEG105192, were either treatment-naive or may have received one prior cytokine (interferon-α or IL-2)-based systemic therapy. Randomization was stratified according to ECOG (0 vs. 1) or KPS (70/80 vs. 90/100) status, and additionally according to prior nephrectomy and prior cytokine treatment in VEG105192, according to number of metastatic sites (0/1 vs. 2+) in PISCES, and according to prior nephrectomy and baseline lactate dehydrogenase (an indicator of tissue damage) [>1.5 × ULN vs. ≤1.5 × ULN] in COMPARZ.

The two phase III efficacy trials assessed progression-free survival (PFS), defined as the time interval from the date of randomization until the earliest date of disease progression or death from any cause, as the primary endpoint [25, 27]. The crossover comparison with sunitinib primarily assessed patient preference for treatment by questionnaire after 10 weeks of treatment with each drug [26] (Table 2). Objective response rates (ORRs) [complete response or partial response] were also assessed. Tumour response was determined by blinded independent reviewers from computed tomography or magnetic resonance imaging scans according to RECIST criteria.

A phase II study (VEG102616; essentially a noncomparative, open-label, discontinuation trial in 225 patients) has been previously reviewed in detail [28] and is not discussed except to summarize that it found an ORR (primary endpoint) of 34.7% (33.3 % partial response rate and 1.3 % complete response rate), a median duration of response of 68.0 weeks and a median PFS of 51.7 weeks following treatment with oral pazopanib 800 mg once daily [29].

4.1 Survival and Tumour Response

Across the phase III efficacy trials, pazopanib was shown to be efficacious in the treatment of renal cell carcinoma, delaying disease progression and reducing tumour lesions [25, 27].

4.1.1 Comparison with Placebo

In study VEG105192, oral pazopanib 800 mg once daily significantly ($p < 0.0001$) improved PFS compared with placebo in the intent-to-treat (ITT) population (primary endpoint) [Table 3] [25]. The hazard ratio (HR) for progression or death was 0.46 (95 % CI 0.34–0.62), favouring pazopanib. The median PFS in pazopanib recipients was significantly longer than in placebo recipients for both the treatment-naive (11.1 vs. 2.8 months; HR 0.40, 95 % CI 0.27–0.60; $p < 0.0001$) and the cytokine-pretreated (7.4 vs. 4.2 months; HR 0.54, 95 % CI 0.35–0.84; $p < 0.001$) subpopulations [25].

Likewise, the ORR in the overall population was significantly higher in pazopanib compared with placebo recipients (30 vs. 3 %; $p < 0.001$) and the median duration of response exceeded 1 year (Table 3) [25]. The response rates were similar in the treatment-naive (32 %) and cytokine-pretreated (29 %) subpopulations receiving pazopanib. Virtually all responses were partial responses; only one pazopanib recipient had a complete response (Table 3) [25].

At the pre-specified final analysis of overall survival (OS) [after 290 recorded deaths], the OS in pazopanib recipients was not significantly different from that in placebo recipients (Table 3) [HR 0.91; 95 % CI 0.71–1.16] [30]. However, the analysis was confounded by factors that may have skewed the results. Patients who experienced disease progression while on placebo were eligible to receive open-label pazopanib in an extension study and some patients switched as early as 6 weeks after

Table 2 Design characteristics of phase III, randomized, comparative trials of oral pazopanib used in the treatment of patients with advanced renal cell carcinoma

Characteristic	Study VEG105192 [25, 30]	COMPARZ study [27]	PISCES study [26]
ClinicalTrials.gov identifier	NCT00334282 (extension: NCT00387764)	NCT00720941	NCT01064310
Full title		COMParing the efficacy, sAfety and toleRability of paZopanib vs. sunitinib	PazopanIb versus Sunitinib patient preferenCE Study
Patient number analyzed	435	1,110	114
Patient characteristics	Treatment-naive (54 %) or cytokine-pretreated (46 %) clear-cell mRCC	Treatment-naive clear-cell mRCC	Treatment-naive mRCC
Comparator	Placebo	Sunitinib	Sunitinib
Design	Randomized 2:1, double-blind; plus open-label extension (switch to pazopanib after progression on placebo)	Randomized 1:1, open-label	Randomized 1:1, double-blind, crossover (in patients without disease progression), 10-week treatment periods with a 2-week washout between treatments
Dosage	Pazopanib: 800 mg od	Pazopanib: 800 mg od Sunitinib: 50 mg od (4 weeks on/2 weeks off)	Pazopanib: 800 mg od Sunitinib: 50 mg od (4 weeks on/2 weeks off)
Primary endpoint	PFS	PFS (noninferiority)	Patient preference at 22 weeks
Secondary endpoints	OS, ORR, time to response, response duration, HR-QOL, tolerability	OS, ORR, HR-QOL, resource utilization, tolerability	Physician preference, HR-QOL, tolerability, (ORR)

HR-QOL health-related quality of life, *mRCC* advanced and/or metastatic renal cell carcinoma, *od* once daily, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival

Table 3 Therapeutic efficacy of pazopanib in patients with advanced renal cell carcinoma. Results of the phase III, randomized, double-blind, placebo-controlled VEG105192 trial [25, 30]

Parameter	Pazopanib ($n = 290$)	Placebo ($n = 145$)
Median PFS[a] (months)	9.2**	4.2
ORR (%)	30*	3
CR	0.3	0
PR	30	3
Median time to response (weeks)	11.9	–
Median duration of response	58.7 weeks	–
Median OS (months)	22.9	20.5

CR complete response, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PR* partial response

* $p < 0.001$, ** $p < 0.0001$ vs. placebo

[a] Primary endpoint (intent-to-treat population)

randomization. Overall, 66 % of patients in the placebo arm compared with 30 % in the pazopanib arm received at least 1 post-study systemic anticancer therapy. In addition, patients initially randomized to the placebo arm had a prolonged overall duration of treatment with pazopanib compared with those randomized to the pazopanib arm (9.7 vs. 7.4 months) [30]. In the placebo group, 43 % were treated for ≥12 months compared with 32 % in the pazopanib group. Exploratory post hoc analyses designed to correct for crossover bias suggested that pazopanib reduced the risk of mortality by approximately 50 % compared with placebo (HR 0.50 [95 % CI 0.315–0.762; $p = 0.002$] in an Inverse Probability of Censor Weighting analysis and HR 0.43 [95 % CI 0.215–1.388; $p = 0.172$] in a Rank-Preserving Structural Failure Time analysis) [30].

For the 70 patients who progressed while on placebo and received pazopanib in the extension study, the ORR was 32.4 % and the median PFS was 8.3 months [31].

4.1.2 Comparisons with Sunitinib

The large ($n = 1,110$), randomized, open-label COMPARZ study met the primary endpoint; continuous oral pazopanib 800 mg once daily was noninferior to intermittent sunitinib 50 mg once daily (4 weeks on/2 weeks off) with regard to independent review of PFS in the ITT population (primary endpoint) [Table 4], since the upper bound of the 95 % confidence interval for the HR (risk of disease progression or death with pazopanib) was <1.25 (HR 1.05; 95 % CI 0.90–1.22) [27]. In sensitivity analyses, the HR in the per-protocol population ($n = 995$) was 1.07 (95 % CI 0.91–1.25). According to the investigator review, the median PFS was 10.5 months with pazopanib and 10.2 months with sunitinib (HR 1.00; 95 % CI 0.86–1.15) [27].

Table 4 Therapeutic efficacy of pazopanib in patients with advanced renal cell carcinoma. Results of the phase III, randomized, open-label COMPARZ trial [27, 32]

Parameter	Pazopanib ($n = 557$)	Sunitinib ($n = 553$)
Median PFS[a] (months)	8.4	9.5
ORR (%)	31[†]	25
CR	0.18	0.54
PR	31	24
Median OS (months)	28.3	29.1

CR complete response, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PR* partial response

[†] $p = 0.03$ vs. sunitinib

[a] Primary endpoint (by independent review in the intent-to-treat population)

The ORR was significantly ($p < 0.05$) higher with pazopanib than sunitinib and the majority of responses were partial responses (Table 4) [27]. The final OS with pazopanib (669 deaths at 2 years after the last patient was enrolled) did not differ significantly from that with sunitinib (HR for death with pazopanib vs. sunitinib, 0.92; 95 % CI 0.79–1.06) (Table 4) [32]. Median OS also did not differ significantly between pazopanib and sunitinib after stratification according to whether disease was of favourable-risk (42.5 vs. 43.6 months; HR 0.88, 95 % CI 0.63–1.21), intermediate-risk (26.9 vs. 26.1 months; HR 0.90, 95 % CI 0.74–1.09) or poor-risk (9.9 vs. 7.7 months; HR 0.85, 95 % CI 0.56–1.28) [32].

In the first treatment period of the crossover PISCES study, the ORR in pazopanib recipients was 19 % (1 % complete response rate and 18 % partial response rate) compared with 21 % (1 % complete response rate and 20 % partial response rate) in sunitinib recipients [26]. The proportions of patients having progressive disease were 20 % for pazopanib and 11 % for sunitinib [26].

4.2 Patient Preference

The PISCES study was specifically designed to assess patient preference for pazopanib (800 mg once daily continuously) or sunitinib (50 mg once daily intermittently [4 weeks on/2 weeks off/4 weeks on]) following double-blind, crossover treatment for 10 weeks with each drug in randomized order, with a 2-week washout period between treatments [26]. Patients were asked at the end of the study (22 weeks) which drug (the first or second treatment) they would prefer to receive for continued treatment, along with the key reasons for their decision. Dose interruption was not allowed. Dose reduction for adverse effects was allowed, but required early crossover if in period 1 or early completion of study if in period 2. Patients were efficacy blinded and patients who progressed in the first period did not answer the questionnaire. The primary analysis population ($n = 114$) consisted of patients who received at least one dose in each treatment period and did not have disease progression after the first treatment period. The two treatment-order arms were well balanced for baseline patient characteristics. The median patient age was 63 years, 89 % had undergone nephrectomy, 92 % had measurable disease, 90 % had clear-cell carcinoma, 73 % had at least 2 metastatic sites and the median time since diagnosis was 7.7 months [26].

Patient preference significantly favoured pazopanib over sunitinib (70 vs. 22 %; $p < 0.001$); 8 % of patients had no particular preference. There was a small treatment-order effect, with more patients preferring the treatment in period 1 than in period 2 (54 vs. 38 %; 8 % no preference). For the subgroup receiving pazopanib followed by sunitinib, patient preference for pazopanib versus sunitinib was 80 versus 11 % (9 % with no preference), while for the subgroup receiving sunitinib first, the patient preference for pazopanib versus sunitinib was 62 versus 32 % (7 % with no preference) [26].

Most patients' decisions were not determined by a single reason. The top five factors which influenced the preference for pazopanib were better quality of life, less fatigue, less taste change, less mucositis/stomatitis and less nausea/vomiting. The top five factors which influenced the preference for sunitinib were less diarrhoea, better quality of life, less fatigue, less nausea/vomiting and less loss of appetite [26].

Physician preference (while blinded to treatment) mirrored that of the patients, with 61 % preferring pazopanib, 22 % preferring sunitinib and 17 % having no preference [26].

4.3 Health-Related Quality of Life

Pazopanib was not significantly different from placebo with respect to changes in health-related quality of life (HR-QOL) [25], and had a more favourable effect on HR-QOL than sunitinib [26, 27].

The pre-specified analysis of HR-QOL in study VEG105192 found no significant differences between pazopanib and placebo with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the EuroQuol questionnaire (EQ-5D) index and the EQ-5D visual analogue scale (VAS) [25]. However, post hoc analyses, which included more patients and took into account the magnitude and timing of HR-QOL deterioration, as well as the effects of disease progression, indicated a trend for pazopanib-treated patients to have a lower risk than placebo-treated patients of experiencing ≥20 % deterioration in HR-QOL [33]. The difference between pazopanib and placebo in the

time-to-deterioration analyses was not statistically significant in the core analysis using the EORTC QLQ-C30, but was significant in the analyses using EQ-5D VAS for both the risk of ≥20 % ($p < 0.0305$ univariate; $p < 0.0350$ multivariate) and ≥30 % ($p < 0.0427$ univariate; $p < 0.0458$ multivariate) deterioration in HR-QOL [33]. Multivariate analysis according to response demonstrated that placebo-treated patients with stable disease experienced significantly ($p < 0.01$) less HR-QOL deterioration than placebo-treated patients with progressive disease, and among pazopanib-treated patients, those with complete or partial response experienced significantly ($p < 0.01$) less deterioration than those with stable disease or progressive disease using the EORTC QLQ-C30 [33].

In the crossover PISCES study, the analysis of HR-QOL using the 13-item Functional Assessment of Cancer Therapy-Fatigue (FACT-F) questionnaire strongly favoured pazopanib over sunitinib by 2.5 points ($p = 0.002$) [26]. The Supplementary Quality of Life Questionnaire (SQLQ) also demonstrated significantly better scores with pazopanib than with sunitinib for worst mouth/throat soreness ($p < 0.001$), worst hand soreness ($p = 0.026$), worst foot soreness ($p = 0.005$), limitations due to mouth/throat soreness ($p < 0.001$) and limitations due to foot soreness ($p = 0.003$) [26].

Similarly, in the COMPARZ study, pazopanib was significantly favoured over sunitinib in 11 of 14 domains of the HR-QOL analysis, which included the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), FACT Kidney Symptom Index (FKSI-19), Cancer Therapy Satisfaction Questionnaire (CTSQ) and SQLQ instruments. Neither treatment was preferred for two domains of FKSI-19 (disease-related emotional symptoms and functional well-being) and one domain of CTSQ (expectations of therapy); all others favoured pazopanib [27]. Pazopanib recipients had significantly less fatigue (FACIT-F), mouth or throat, hand and foot soreness (SQLQ) than sunitinib recipients. Of the HR-QOL domains favouring pazopanib, the effect size was greatest for mouth and throat soreness (medium/large effect size) [27].

An assessment of average monthly resource utilization in the COMPARZ study population found that pazopanib recipients had significantly fewer telephone consultations ($p = 0.04$) and emergency department visits ($p = 0.003$) than sunitinib recipients [27].

5 Tolerability

Data on the tolerability of pazopanib in patients with renal cell carcinoma are derived predominantly from the three phase III comparative trials discussed in Sect. 4; that is, study VEG105192 comparing pazopanib with placebo [30], and the COMPARZ [27] and PISCES [26] studies comparing pazopanib with sunitinib. Additional data on liver dysfunction in patients treated with pazopanib derive from two retrospective studies reported as abstracts [34, 35].

5.1 Comparison with Placebo

In the final analysis of study VEG105192, the most frequent (≥10 % of patients) treatment-emergent adverse events of any grade with pazopanib ($n = 290$) compared with placebo ($n = 145$) were diarrhoea (52 vs. 9 %), hypertension (40 vs. 10 %), hair colour changes (38 vs. 3 %), nausea (26 vs. 9 %), anorexia (24 vs. 12 %), vomiting (21 vs. 9 %), fatigue (20 vs. 10 %), asthenia (14 vs. 9 %), haemorrhage (14 vs. 6 %), abdominal pain (11 vs. 1 %), headache (11 vs. 5 %), proteinuria (10 vs. 0 %) and weight loss (10 vs. 3 %) [30]. The incidences of grade 3 (severe) adverse events, according to Common Terminology Criteria for Adverse Events v3.0 [36], were highest for diarrhoea and hypertension, with each occurring in 4 % of pazopanib recipients, while the incidence of grade 4 (life-threatening or disabling) events of any type was always ≤1 % [30]. At the primary assessment, 14 % of pazopanib versus 3 % of placebo recipients discontinued therapy as a result of adverse events [25]. Liver abnormalities, diarrhoea and arterial thrombotic events were the adverse effects most commonly resulting in treatment discontinuation [30].

The incidences of haemorrhagic events of all grades in the pazopanib and placebo arms were 13 and 5 %, respectively [25]. Arterial thrombotic events, consisting of myocardial infarction/ischaemia, cerebrovascular accident or transient ischaemic attack, occurred in 3 % of patients in the pazopanib arm compared with none in the placebo arm [25].

Notable blood chemistry abnormalities with pazopanib versus placebo included elevated ALT levels (53 vs. 23 %), elevated AST levels (53 vs. 19 %), hyperbilirubinaemia (37 vs. 11 %), hypophosphataemia (36 vs. 13 %), hyperglycaemia (43 vs. 33 %), hypocalcaemia (35 vs. 26 %), hyponatraemia (33 vs. 24 %), hypoglycaemia (18 vs. 3 %) and hypokalaemia (10 vs. 2 %) [30]. The incidences of grade 3 abnormalities with pazopanib were highest for elevated ALT levels (11 %), elevated AST levels (7 %), hypophosphataemia (5 %), hyponatraemia (4 %) and hyperbilirubinaemia (3 %).

Death as a result of adverse effects occurred in 4 % of pazopanib recipients compared with 3 % of placebo recipients [25]. The four fatalities (1 %) among pazopanib recipients that the investigators considered were a direct result of therapy consisted of ischaemic stroke, abnormal hepatic function/rectal haemorrhage, abnormal hepatic

function (with liver metastasis), and peritonitis/bowel perforation (with metastasis at the perforation site) [25].

The most frequent haematological abnormalities with pazopanib compared with placebo in study VEG105192 were leukopenia (38 vs. 7 %), neutropenia (36 vs. 6 %), thrombocytopenia (34 vs. 5 %), lymphopenia (34 vs. 24 %) and anaemia (26 vs. 31 %) [30]. The incidences of grade 3 abnormalities were highest for lymphopenia (5 %) and anaemia (2 %) with pazopanib; all other grade 3 and all grade 4 abnormalities occurred with an incidence of ≤1 %.

5.2 Comparisons with Sunitinib

The COMPARZ and PISCES studies showed similar patterns of adverse events with pazopanib and sunitinib (see Fig. 1) [26, 27]. In the larger COMPARZ study, pazopanib was associated with a significantly lower risk than sunitinib for a range of adverse events, most notably fatigue, hand-foot syndrome and mucosal inflammation for which the risk of grade 3 or 4 events was significantly (95 % CI for relative risk did not include unity) higher with sunitinib than with pazopanib [27]. The adverse events of any grade that were significantly higher with pazopanib than with sunitinib were changes in hair colour, weight loss and alopecia [27]. Statistical analysis of between-group differences in adverse event incidence rates was not reported for the PISCES study.

The proportions of patients having dose reductions, treatment interruptions and prematurely discontinuing therapy as a result of adverse events were similar for the pazopanib and sunitinib groups in both studies. In the COMPARZ study, dose reductions with pazopanib and sunitinib were 44 and 51 %, dose interruptions of 7 days or more were 44 and 49 %, while discontinuations due to adverse events were 24 and 20 %, respectively [27]. The values with pazopanib versus sunitinib in the PISCES study were 13 versus 20 % for dose reductions, 6 versus 12 % for dose interruptions, and 14 versus 18 % for discontinuations in period 1 and 15 versus 31 % in period 2 [26]. Discontinuations in the PISCES study included patients requiring dose interruption who crossed over early or completed the study early [26].

The incidences of laboratory abnormalities differed slightly between pazopanib and sunitinib in the COMPARZ study (Fig. 2). Elevated ALT and bilirubin levels were more common with pazopanib than sunitinib, while sunitinib was associated with higher incidences of elevated creatinine levels and decreased albumin and phosphate levels than pazopanib, based on the 95 % confidence intervals for the relative risk not including unity [27]. Pazopanib was associated with less myelosuppression than sunitinib, particularly with regard to the relative risk of leukopenia, thrombocytopenia, anaemia and neutropenia [27].

5.3 Liver Dysfunction

In an analysis of sequential patients with advanced renal cell carcinoma receiving first-line treatment with pazopanib ($n = 44$), 34 % developed liver toxicity (elevated bilirubin or liver transaminase levels), reaching maximum toxicity at a median of 60 days after starting therapy [35]. Resolution within a median of 3–21 days after stopping therapy occurred in all but one patient, and recurrence of liver dysfunction occurred in 27 % of these patients after restarting therapy (mostly [80 %] at a reduced dosage) [35].

An analysis of all cancer patients in clinical trials of pazopanib monotherapy, found that 18 % of patients with renal cell carcinoma ($n = 586$) had ALT elevations of ≥3 × ULN and 5 % had elevations of ≥8 × ULN [34]. For the ALT elevations of ≥3 × ULN, 87 % occurred within 18 weeks of starting pazopanib therapy. Of patients with ALT ≥3 × ULN ($n = 106$), recovery occurred in 91 %; 30 % recovered while continuing pazopanib therapy. Thirty one patients were rechallenged with pazopanib and 20 (65 %) did not experience recurrence of ALT elevation. In a total population of 1,830 patients in pazopanib studies, there were two adjudicated cases of pazopanib-related liver failure [34].

6 Dosage and Administration

Pazopanib is approved in the EU, the US and other countries, such as Australia, Canada and Japan, for the treatment of advanced (metastatic) renal cell carcinoma. It is indicated in the EU for the first-line treatment of adult patients with advanced renal cell carcinoma and for the treatment of adult patients who have received prior cytokine therapy for advanced disease [11]. In the US, pazopanib is indicated in the treatment of patients with advanced renal cell carcinoma, without further qualification [12]. The phase III, placebo-controlled study (VEG105192) supporting the licensing application for pazopanib in advanced renal cell carcinoma in both the EU and the US consisted of a mix of treatment-naive patients and patients who had received one prior cytokine (IL-2 or interferon-α)-based therapy (Table 2).

The recommended adult dosage of pazopanib is 800 mg orally once daily without food [11, 12]. The film-coated tablets should be taken whole ≥1 h before or ≥2 h after a meal (see Sect. 3). The dosage should not exceed 800 mg/day and should be modified in 200 mg increments to manage adverse reactions. The US prescribing information

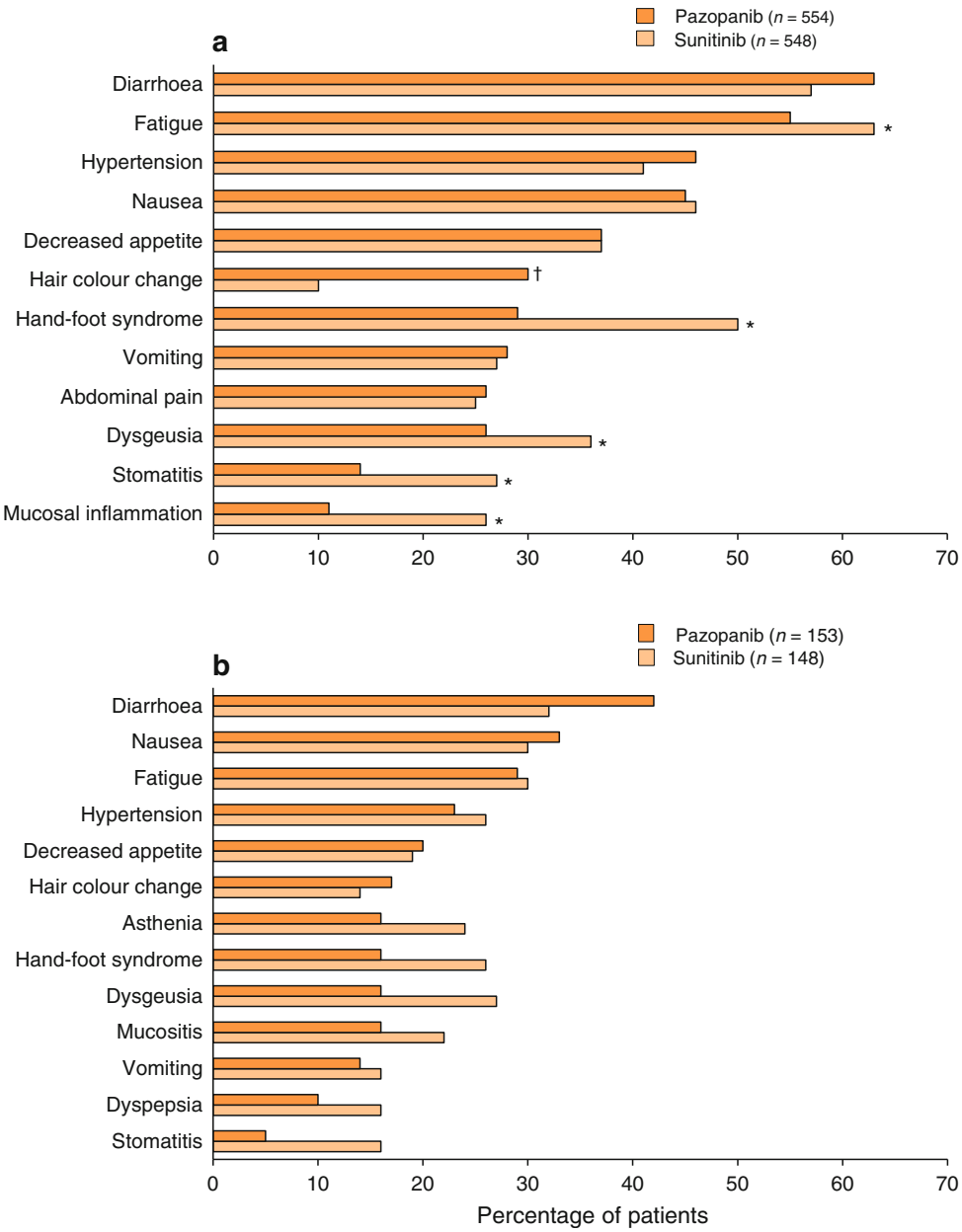

Fig. 1 Incidence of the most common treatment-emergent adverse events of any grade occurring in randomized trials comparing continuous oral pazopanib 800 mg once daily with intermittent sunitinib 50 mg once daily (4 weeks on/2 weeks off) in patients with advanced and/or metastatic renal cell carcinoma. **a** Events occurring in ≥25 % of patients in either arm of the long-term COMPARZ trial [27]; **b** Events occurring in >15 % of patients in either arm of the 10-week crossover PISCES trial [26]. *Significantly higher relative risk with sunitinib than with pazopanib (95 % CI does not include unity), †Significantly higher relative risk with pazopanib than with sunitinib

recommends an initial dose reduction of 400 mg, with any additional decrease or increase in 200 mg increments [12].

Caution is recommended in patients with mild or moderate hepatic impairment [11, 12]. A pazopanib dosage of 800 mg once daily is recommended in patients with mild abnormalities in liver function tests (e.g. bilirubin ≤1.5 × ULN or elevated ALT level), while a dosage of 200 mg once daily is recommended in those with moderate hepatic impairment (bilirubin >1.5–3 × ULN regardless of ALT value). Pazopanib is not recommended in patients with severe hepatic impairment (bilirubin >3 × ULN regardless of ALT value). The US prescribing information carries a black-box warning of possible severe and fatal hepatotoxicity with pazopanib [12], and both the US and EU prescribing information recommend routine monitoring of liver function tests, with reduction, interruption or discontinuation of dosing according to the level of hepatotoxicity detected [11, 12].

Since pazopanib is eliminated primarily in the faeces, dosage modification is not considered necessary in patients with mild/moderate renal impairment (CL_{CR} 30–80 mL/min), although caution is recommended in those with CL_{CR} <30 mL/min, since there is no clinical experience with pazopanib in this patient population [11, 12].

Although data are limited, no dosage modification is considered necessary in the elderly. The efficacy and safety of pazopanib have not been established in children, and pazopanib should not be administered to children

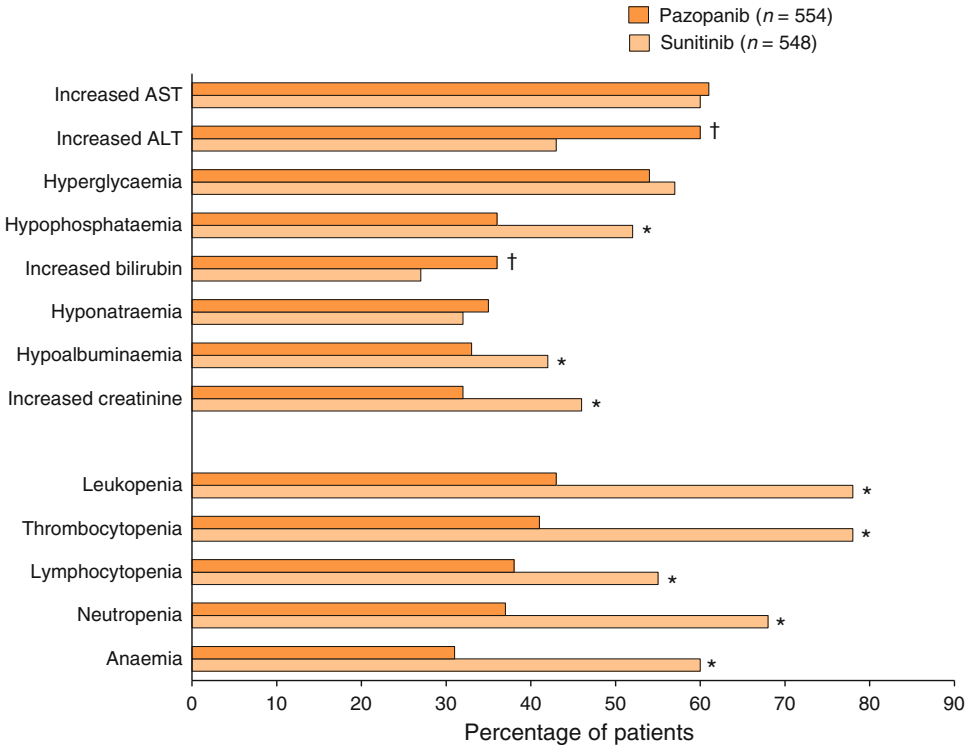

Fig. 2 Incidence of the most common laboratory abnormalities in the randomized COMPARZ trial comparing continuous oral pazopanib 800 mg once daily with intermittent sunitinib 50 mg once daily (4 weeks on/2 weeks off) in patients with advanced and/or metastatic renal cell carcinoma. Abnormal results of any grade occurring in ≥35 % of patients in either arm of the study [27]. *Significantly higher relative risk with sunitinib than with pazopanib (i.e. 95 % CI for the relative risk did not include unity), †Significantly higher relative risk with pazopanib than with sunitinib

aged <2 years, since early administration in juvenile rats caused abnormalities in organ development, as well as bone, teeth and nail bed abnormalities [11, 12].

Local prescribing information should be consulted for detailed information, including contraindications, warnings, precautions and use in special patient populations.

7 Place of Pazopanib in the Management of Advanced Renal Cell Carcinoma

Systemic therapy for advanced renal cell carcinoma was originally limited to best supportive care and cytokine therapy, namely interferon-α and IL-2, each of which demonstrated ORRs in the range of 5 to 27 % [9]. High-dose bolus IL-2 has been reported to produce response rates of up to 29 % and to induce durable remission in 3–5 % of treated patients, the only agent to date to do so [37]. However, high-dose IL-2 is very toxic and has been associated with treatment-related fatalities; hence, it is usually restricted to younger patients with normal cardiac, pulmonary and renal function who are more likely to tolerate treatment [2, 37]. Responses to interferon-α are limited, rarely lasting more than 2 years [2]. Interferon-α is also associated with a wide range of adverse effects, including flu-like symptoms, haematological toxicity, liver dysfunction, nausea, fatigue and depression, which limit its use [38].

In recent years, targeted therapies have been widely used in place of cytokine-based therapy, such that VEGF-targeted therapy is now the first-line standard of care [10], with sunitinib initially being the most commonly used agent. Recent European and US guidelines for the systemic treatment of advanced and/or metastatic predominantly clear-cell renal cell carcinoma are summarized in Table 5. The 2012 clinical practice guidelines from the European Society for Medical Oncology only recommend cytokines as an alternative first-line treatment option in patients with a good or intermediate risk; the standard recommended agents for this patient group are sunitinib, pazopanib and bevacizumab plus interferon-α [10]. Likewise, the 2014 guidelines from the US National Comprehensive Cancer Network (NCCN) only recommend high-dose IL-2 in selected patients (based on safety issues) [9] (Table 5).

The roles of the various targeted therapies have yet to be clearly defined. As summarized in the NCCN guidelines [9], for first-line therapy of predominantly clear-cell renal cell carcinoma, several targeted therapies have shown advantages over interferon-α with respect to producing significantly higher PFS and ORR (sunitinib [39]; bevacizumab plus interferon-α [40, 41]), or OS (temsirolimus [42]), while pazopanib showed advantages for PFS and ORR over placebo (Sect. 4.1.1). At the time when the pazopanib versus placebo comparison was designed, interferon-α would have been an appropriate comparator, but an active comparator treatment arm was not included.

Table 5 Summary of recent European and US treatment guidelines for patients with advanced (predominantly clear-cell) renal cell carcinoma

Guideline (Year)	Therapy line	Risk group/Prior treatment	Recommended agent(s)	Alternative options
EAU (2013) [4]	First line	Favourable or intermediate risk	Sunitinib	
			Bevacizumab + IFN-α	
			Pazopanib	
		Selected patients	IFN-α	
			High-dose IL-2	
		Poor risk	Temsirolimus	
	Second line	Prior cytokines	Sorafenib	
			Axitinib	
			Pazopanib	
		Prior TKI	Axitinib	
			Sorafenib	
			Everolimus	
	Third line	Prior TKI(s)	Everolimus	
ESMO (2012) [10]	First line	Good or intermediate risk	Sunitinib	Cytokines
			Bevacizumab + IFN-α	Sorafenib
			Pazopanib	
		Poor prognosis	Temsirolimus	Sunitinib
				Sorafenib
	Second line	Post-cytokine	Sorafenib	Sunitinib
			Pazopanib	
			Axitinib	
		Post-TKI	Everolimus	Sorafenib
			Axitinib	
	Third line	Post-two TKIs	Everolimus	
NCCN (2014) [9]	First line	Standard	Sunitinib	
			Temsirolimus	
			Bevacizumab + IFN-α	
			Pazopanib	
			Clinical trial	
		Selected patients	High-dose IL-2	
			Sorafenib	
	Subsequent therapy	Standard	Clinical trial	
			IL-2	
		Post-TKI	Everolimus	
			Axitinib	
			Sorafenib	
			Sunitinib	
			Temsirolimus	
			Bevacizumab	
			Pazopanib	
		Post-cytokines	Axitinib	
			Sorafenib	
			Sunitinib	
			Pazopanib	
			Temsirolimus	
			Bevacizumab	

EAU European Association of Urology, *ESMO* European Society for Medical Oncology, *IFN-α* interferon alpha, *IL-2* interleukin 2, *NCCN* National Comprehensive Cancer Network, *TKI* tyrosine kinase inhibitor

For second-line therapy, pazopanib (Sect. 4.1.1), sorafenib [43] and everolimus [44] showed advantages over placebo with respect to PFS (and ORR with pazopanib) in patients who had failed previous cytokine or targeted therapy, and axitinib [45] showed advantages over sorafenib with respect to PFS and ORR in patients previously treated with one prior systemic therapy (mostly sunitinib [54 %] or a cytokine [35 %]).

While an increase in survival has been considered the gold standard measure of efficacy for anticancer drugs, for patients who experience disease progression in clinical trials, the subsequent treatment with additional active therapies confounds the determination of OS benefit for the trial drug(s). Therefore, recent trials of targeted therapy for advanced renal cell carcinoma have more often used PFS as the primary endpoint. Some VEGF-targeted therapies have shown trends towards a survival advantage over placebo (pazopanib [Sect. 4.1.1] and sorafenib [46]) or over interferon-α (sunitinib [39]) in randomized controlled trials (usually after correcting for one or more confounding factors), but to date, only temsirolimus [42] has been clearly shown in primary analyses to significantly prolong life expectancy compared with cytokines (median OS of 10.9 months for temsirolimus versus 7.3 months for interferon-α [HR for death 0.73, 95 % CI 0.58–0.92; $p = 0.008$] in previously untreated, high-risk patients).

Indirect comparison analyses suggest that there is little difference in efficacy between the available targeted therapies in treating patients with advanced clear-cell renal cell carcinoma [47, 48], although the comparative efficacies of the newer agents need to be determined in well-designed clinical trials.

In randomized controlled trials, pazopanib was superior to placebo with respect to PFS (primary endpoint) and ORR in both the treatment-naive and the cytokine-pretreated subpopulations, and had a median duration of response of 58.7 weeks (Sect. 4.1.1). However, OS did not differ significantly between pazopanib- and placebo-treated patients in the final ITT analysis, although this was potentially confounded by crossover bias and differential use of post-study systemic anticancer therapies. Analyses to adjust for crossover bias suggested an OS benefit with pazopanib.

In the head-to-head comparison with sunitinib, pazopanib was noninferior to sunitinib with respect to PFS (primary endpoint) (Sect. 4.1.2). The ORR was significantly higher with pazopanib than with sunitinib, but the OS did not differ between groups – the median OS was >2 years in both groups.

Patients in the PISCES study demonstrated a significant preference for treatment with pazopanib over sunitinib, which, judging by the primary reasons given for their choice, was related to tolerability issues rather than to differences in efficacy (Sect. 4.2). This is supported by the HR-QOL analyses, where pre-specified analyses did not find clearly improved HR-QOL with pazopanib compared with placebo (for which tolerability would not be an issue), yet HR-QOL significantly favoured pazopanib over sunitinib in both the PISCES and COMPARZ studies, with tolerability issues featuring prominently amongst the parameters displaying significant differences between groups (Sect. 4.3). Given the subjective nature of the main factors (e.g. fatigue) determining the preference observed in the PISCES study, further confirmation would be desirable [49].

The tolerability profile of pazopanib was acceptable, displaying adverse events generally typical of multi-tyrosine kinase inhibitors (Sect. 5). Most adverse effects were of mild or moderate severity and clinically manageable. The most common grade 3/4 events were diarrhoea and hypertension, while the most common grade 3/4 laboratory abnormalities were increased liver transaminases. Differences between drugs in the potency and specificity of their inhibition of the various on- or off-target kinases inhibited by each agent are considered to explain many of the differences in observed tolerability profiles (e.g. c-Kit/Flt-3 inhibition and myelosuppression). Pazopanib is more selective than sunitinib for kinase inhibition (Sect. 2) and had lower incidences of dysgeusia, hand-foot syndrome, fatigue, mucositis/stomatitis and myelosuppression than sunitinib, but had higher incidences of hair colour change, and elevated ALT and bilirubin levels (Sect. 5). Dose reduction or interruption of dosing with multi-tyrosine kinase inhibitors generally compromises efficacy, but the hypertension associated with pazopanib was often managed without modifying the pazopanib dosage and almost one-third of patients with elevated ALT levels recovered while continuing pazopanib therapy. In the direct comparison between pazopanib and sunitinib, the proportions of patients requiring dose reduction or discontinuation as a result of adverse effects were of a similar order of magnitude (Sect. 5). The higher preference for pazopanib expressed by patients in the PISCES study appeared to directly reflect the symptomatic adverse effects that were less prevalent with pazopanib than with sunitinib, while asymptomatic effects, such as liver dysfunction, did not appear to influence their decision (Sect. 4.2).

The National Institute for Health and Clinical Excellence in the UK performed a single technology appraisal of pazopanib and concluded that pazopanib is a potentially cost-effective first-line treatment for advanced renal cell carcinoma and should be recommended as such in patients with an ECOG performance status of 0 or 1 and who had not received prior cytokine therapy, if pazopanib is supplied at a 12.5 % discount on the list price [50].

In conclusion, pazopanib is significantly more efficacious than placebo in treatment-naive and cytokine-pretreated

patients with predominantly clear-cell, advanced renal cell carcinoma, and is noninferior to sunitinib with respect to PFS for first-line treatment. Pazopanib displayed a tolerability profile distinct from that of sunitinib, with fewer adverse events of the type that directly impact patients' HR-QOL, leading to a significant preference for pazopanib over sunitinib being expressed by patients.

Data selection sources: Relevant medical literature (including published and unpublished data) on pazopanib was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 28 May 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Pazopanib, renal cancer, kidney cancer, renal cell carcinoma, kidney carcinoma, kidney neoplasms, carcinoma renal cell.
Study selection: Studies in patients with locally advanced or metastatic renal cell carcinoma who received pazopanib. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Disclosure The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made by the author on the basis of scientific and editorial merit. Paul McCormack is a salaried employee of Adis/Springer.

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