A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: Final overall survival results and safety update

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Abstract

Background

In this randomised phase III study (VEG105192; NCT00334282), pazopanib previously demonstrated statistically and clinically meaningful improvement of progression-free survival versus placebo in patients with advanced/metastatic renal cell carcinoma (mRCC). Final overall survival (OS) and updated safety results are now reported.

Methods

Treatment-naive or cytokine-pretreated mRCC patients (n = 435) stratified and randomised (2:1) to pazopanib 800 mg daily or placebo, were treated until disease progression, death or unacceptable toxicity. Upon progression, placebo patients could receive pazopanib through an open-label study. Final OS in the intent-to-treat population was analysed using a stratified log-rank test. Rank-preserving structural failure time (RPSFT) and inverse probability of censoring weighted (IPCW) analyses were performed post-hoc to adjust for crossover.

Findings

The difference in final OS between pazopanib- and placebo-treated patients was not statistically significant (22.9 versus 20.5 months, respectively; hazard ratio [HR] = 0.91; 95% confidence interval [CI], 0.71–1.16; one-sided P = .224). Early and frequent crossover from placebo to pazopanib and prolonged duration of crossover treatment confounded the OS analysis. In IPCW analyses, pazopanib decreased mortality (HR = 0.504; 95% CI, 0.315–0.762; two-sided P = .002). Similar, albeit non-significant, results were obtained in RPSFT analyses (HR = 0.43; 95% CI, 0.215–1.388; two-sided P = .172). Since the last cutoff, cumulative exposure to pazopanib increased by 30%. The pazopanib safety profile showed no new safety signals or changes in the type, frequency and severity of adverse events.

Interpretation

Although no significant difference in OS was observed in this study, extensive crossover from placebo to pazopanib confounded final OS analysis. Post-hoc analyses adjusting for crossover suggest OS benefit with pazopanib treatment for mRCC patients.

1. Introduction

Renal cell carcinoma (RCC) accounts for 80%–85% of kidney cancers.[1] Approximately 80% of RCC patients present with clear-cell or predominantly clear-cell histology.[2 and 3] In the United States (US), new kidney cancer cases and deaths in 2010 were estimated as 58,240 and 13,040, respectively.[4] In Europe, new kidney cancer cases and deaths in 2008 were estimated as 88,400 and 39,300, respectively.[5]

The development of novel therapies targeting tumour angiogenesis and mammalian target of rapamycin (mTOR) pathways has significantly improved clinical outcomes in patients with advanced RCC. Since 2005, six targeted agents, sunitinib, sorafenib, pazopanib, temsirolimus, everolimus and bevacizumab with interferon alfa-2a, have received regulatory approval in the US, Europe and other countries worldwide. These agents have been included in US and European treatment guidelines as front-line and/or second-line therapies for advanced RCC.[6 and 7]

Pazopanib (Votrient™, GlaxoSmithKline) is an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptors (VEGFR)-1/-2/-3, platelet-derived growth factor receptors (PDGFR)-α/-β and stem cell factor

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Authorship contributions

Role of the funding source

Conflict of interest statement

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receptor c-Kit.[8] The regulatory approval of pazopanib[9 and 10] was supported primarily by clinical evidence from the pivotal, randomised and double-blind, phase III study VEG105192 (clinicaltrials.gov NCT00334282) in treatment-naive or cytokine-pretreated patients with advanced and/or metastatic RCC.[11] The study demonstrated that pazopanib treatment significantly improved progression-free survival (PFS) versus placebo in the overall study population (median, 9.2 versus 4.2 months; hazard ratio [HR] = 0.46; $P < .0001$) and in the treatment-naive (median, 11.1 versus 2.8 months; HR = 0.40; $P < .0001$) and cytokine-pretreated subgroups (median, 7.4 versus 4.2 months; HR = 0.54; $P < .001$). These previously reported results are based on data obtained by May 23, 2008, for the final PFS analysis.[11] This report provides the preplanned final analysis of overall survival (OS) and updated safety results.

2. Methods

2.1. Patients

Patients with advanced and/or metastatic RCC and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST)[12] who were treatment-naive or had received one prior cytokine-based systemic therapy were eligible. Detailed eligibility criteria and study conduct were previously described.[11]

2.2. Study design: randomisation and masking

Patients stratified by ECOG PS (0 versus 1), prior nephrectomy status (yes versus no) and prior systemic treatment for advanced RCC (treatment-naive versus cytokine-pretreated) were randomised (2:1) to pazopanib 800 mg/day or matching placebo and treated until disease progression, death, unacceptable toxicity or consent withdrawal. Upon progression, patients could be unblinded and receive any available subsequent anticancer therapy at the discretion of the investigator and patient. Patients who progressed from the placebo arm had the option of receiving pazopanib via a parallel open-label extension study (VEG107769; clinicaltrials.gov NCT00387764). Eligibility criteria for this study were similar to those of the parent study except that patients with ECOG PS 2 were also eligible.

2.3. Study end-points and assessments

The primary end-point was PFS; the principal secondary end-point was OS. Other secondary end-points included objective response rate, duration of response and safety. Imaging assessments of disease status were performed at scheduled time points as previously described.[11] Follow-up for survival was performed every 3 months after disease progression until observation of the required number of deaths for final OS analysis.

Clinical assessments for safety, including physical examinations, vital signs, laboratory evaluations, electrocardiograms and documentation of adverse events (AEs), were evaluated at baseline and during study treatment as previously reported.[11] Adverse events were graded according to Common Terminology Criteria for Adverse Events v3.[13]

2.4. Statistical methods

Overall survival was defined as the time from randomisation until death from any cause. Patients who did not die were censored at the date of last contact. With one planned interim analysis and a final analysis after 287 deaths, there was 90% power to detect a 50% improvement in OS with pazopanib treatment versus placebo, with one-sided $\alpha = 0.025$. This power calculation did not account for the impact of crossover. The study was not powered for subgroup analyses.

In the planned analysis, treatment comparison was made between the two arms following the intent-to-treat (ITT) principle using a log-rank test (one-sided) stratified by ECOG PS and prior systemic treatment status for advanced RCC. Hazard ratios were calculated using a stratified Pike estimator.

2.4.1. Post-hoc analyses to adjust for crossover

To correct the treatment-effect estimate from the ITT analysis for bias introduced by the crossover of patients from placebo to open-label pazopanib, post-hoc analyses using inverse probability of censor weighting (IPCW)[14, 15, and 16] and rank-preserving structural failure time (RPSFT)[17 and 18] were conducted. The 95% confidence intervals (CIs) and two-sided P values for both methodologies were calculated using bootstrapping.

The IPCW method uses a weighted Cox model to overcome estimation bias associated with non-adherence to randomised assignment (e.g. crossover). This implementation censors patients at the start of any new systemic anticancer therapy. Although censoring at selective change of treatment is generally biased, IPCW modelling corrects for this bias by using weighting. The results are unbiased, assuming that no confounding variables are missing in the weight estimation. The weights allow follow-up of patients who remain on their randomised treatment to account not only for themselves, but also for comparable patients with similar baseline and time-dependent characteristics who received post-study treatment. Time-dependent characteristics adjusted in this analysis were progressive disease status, time since progression, ECOG PS, history and the presence of grade 3/4 AEs, number of available treatments with regulatory approval and the number of reimbursable treatments in the patient's country.

The RPSFT model is based on the assumption that treatment prolongs (or shortens) survival by a multiplicative factor of the total treatment duration. Using this model, the placebo survival curve can be reconstructed as if no placebo patients switched to pazopanib, permitting the estimation of an adjusted HR. The RPSFT analysis conducted adjusts for prognostic factors and crossover to pazopanib, but not other, non-pazopanib therapies.

3. Results

The pivotal study VEG105192 enrolled 435 patients with advanced/metastatic RCC (233 treatment-naive, 202 cytokine-pretreated) from April 2006 to April 2007; 79 placebo patients received pazopanib in the extension