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ORIGINAL REPORT

Incorporation of Pazopanib in Maintenance Therapy of Ovarian Cancer

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ABSTRACT

Purpose

Pazopanib is an oral, multikinase inhibitor of vascular endothelial growth factor receptor (VEGFR) -1/-2/-3, platelet-derived growth factor receptor (PDGFR) -α/-β, and c-Kit. Preclinical and clinical studies support VEGFR and PDGFR as targets for advanced ovarian cancer treatment. This study evaluated the role of pazopanib maintenance therapy in patients with ovarian cancer whose disease did not progress during first-line chemotherapy.

Patients and Methods

Nine hundred forty patients with histologically confirmed cancer of the ovary, fallopian tube, or peritoneum, International Federation Gynecology Obstetrics (FIGO) stages II-IV, no evidence of progression after primary therapy consisting of surgery and at least five cycles of platinum-taxane chemotherapy were randomized 1:1 to receive pazopanib 800 mg once per day or placebo for up to 24 months. The primary end point was progression-free survival by RECIST 1.0 assessed by the investigators.

Results

Maintenance pazopanib prolonged progression-free survival compared with placebo (hazard ratio [HR], 0.77; 95% CI, 0.64 to 0.91; $P = .0021$; median, 17.9 v 12.3 months, respectively). Interim survival analysis based on events in 35.6% of the population did not show any significant difference. Grade 3 or 4 adverse events of hypertension (30.8%), neutropenia (9.9%), liver-related toxicity (9.4%), diarrhea (8.2%), fatigue (2.7%), thrombocytopenia (2.5%), and palmar-plantar erythrodysesthesia (1.9%) were significantly higher in the pazopanib arm. Treatment discontinuation related to adverse events was higher among patients treated with pazopanib (33.3%) compared with placebo (5.6%).

Conclusion

Pazopanib maintenance therapy provided a median improvement of 5.6 months (HR, 0.77) in progression-free survival in patients with advanced ovarian cancer who have not progressed after first-line chemotherapy. Overall survival data to this point did not suggest any benefit. Additional analysis should help to identify subgroups of patients in whom improved efficacy may balance toxicity (NCT00866697).

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INTRODUCTION

Ovarian cancer is the fifth most common cancer in women and is responsible for the highest mortality among all gynecologic cancers.[1] Approximately 75% to 85% of patients with epithelial ovarian cancer are diagnosed at a time when the disease has spread throughout the peritoneal cavity.[2] The standard of care for ovarian cancer is debulking surgery followed by a taxane-platinum chemotherapy.[3] Although these regimens have a high initial response rate, most patients will relapse with a median progression-free survival (PFS) of 16 months; subsequently, the majority will die as a result of their disease.[4] Therefore, new treatment options are needed. One such option for women who achieve a good response to first-line treatment is maintenance therapy. However, multiple previous trials with

either biologics or cytotoxic agents in the maintenance setting have failed to show benefit.[5-10] Only monthly paclitaxel showed efficacy in prolonging PFS in one trial, albeit with significant adverse events, but another trial could not confirm its benefit.[11-13] Use of biologics in the maintenance setting has been indirectly assessed by the GOG-218 and ICON-7 studies, which used bevacizumab, an antiangiogenic antibody in conjunction with chemotherapy as maintenance, and showed a progression-free survival benefit with a tolerable adverse effect profile.[14,15] Both trials confirmed the concept that angiogenesis plays a critical role in the growth of ovarian cancer and that vascular endothelial growth factor (VEGF) is an important driver of angiogenesis in ovarian cancer.[16]

Pazopanib is an oral tyrosine kinase inhibitor of VEGF receptors-1/-2/-3, platelet-derived growth factor receptors (PDGFR) -α/-β, and c-KIT. Pazopanib has been approved in many countries for the treatment of patients with advanced renal cell carcinoma or advanced soft-tissue sarcoma. A phase II study of pazopanib monotherapy conducted in women responding to standard therapy for ovarian cancer who had an increasing CA-125 was the first study to demonstrate pazopanib activity in ovarian cancer with an acceptable adverse effect profile.[17]

Our phase III trial explored the efficacy and safety of pazopanib monotherapy as maintenance therapy for patients who had not progressed after first-line therapy for ovarian cancer.

PATIENTS AND METHODS

Patients

Eligible patients were ≥ age 18 years with histologically confirmed International Federation Gynecology Obstetrics (FIGO) stage II-IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma that was treated with surgical debulking either upfront or as interval debulking and had received more than or equal to five cycles of platinum-taxane–based chemotherapy. Patients had to have no evidence of disease progression after first-line treatment, no persisting bulky disease (> 2 cm in diameter), or no other defined need for imminent second-line therapy. Patients also had to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and adequate hematologic, hepatic, and renal function. Patients were randomly assigned according to the protocol between 3 and 12 weeks after the last dose of chemotherapy, after all major toxicities of the previous chemotherapy had resolved to grade 1 or better.

Exclusion criteria included poorly controlled hypertension or history of cardiac and vascular conditions within 6 months of screening. All patients provided written informed consent before enrollment.

Study Design and Treatment

The study was an international, randomized, double-blind, placebo-controlled, phase III trial of pazopanib (Votrient, GlaxoSmithKline, Collegeville, PA) versus placebo. Random assignment was performed with a 1:1 ratio and was stratified by (1) first-line treatment outcome of (a) complete macroscopic resection (or FIGO stage II-IIIA at diagnosis if unknown) and no evidence of disease after chemotherapy including normal CA-125; (b) residual disease after surgery (or stage IIIB-IV if unknown) and no evidence of disease after chemotherapy; or (c) residual disease after surgery and chemotherapy or elevated CA-125 at screening and (2) geographic region. Patients were initially intended to be treated with pazopanib 800 mg once per day or placebo for 12 months or until disease progression as defined by RECIST version 1.0,[18] unacceptable toxicity, or withdrawal of consent. Treatment duration was extended to 24 months by a protocol amendment in September 2010 after evidence of rapid recurrence in high-risk patients with ovarian cancer after stopping antiangiogenic therapy in the ICON-7 and GOG-218 trials.[19] After disease progression, patients were observed until death or study withdrawal.

The trial conformed to the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the ethics committee for each participating center. An independent data safety monitoring board reviewed safety data during the study.

The academic authors and sponsor (GlaxoSmithKline) developed the trial protocol together and all had access to the primary data after study closure. Data were gathered by the investigators and analyzed by an independent academic statistical team (KKS) of the leading group (AGO) within the academic intergroup consortium; an independent analysis was also performed by the sponsor. Decisions regarding content of this article were made by the academic principal investigator of the leading academic group in consultation with the trial steering committee, which included one representative of each participating academic study group and the sponsor. The authors vouch for the accuracy of the data.

Study End Points and Assessments

The primary end point was PFS, defined as the interval between date of random assignment to first documentation of disease progression or death resulting from any cause. Secondary end points included overall survival; PFS according to Gynecologic Cancer Intergroup (GCIG) criteria, in which disease progression is defined as the earliest event of progression per RECIST or confirmed CA-125 progression[20]; safety; and health-related quality of life.

Radiologic assessments of disease were conducted by computed tomography or magnetic resonance imaging at baseline and every 6 months thereafter until progression. Serum CA-125 levels were assessed at baseline and every 3 months thereafter until progression; on evidence of clinical progression, including CA-125 progression, the frequency of radiologic assessments was increased to every 3 months. Imaging data were re-evaluated by a blinded independent review committee for sensitivity analyses.

Adverse events were monitored continuously and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[21] Health-related quality of life, which was assessed by the instruments European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30 version 3.0, ovarian cancer module OV-28, and the EuroQOL EQ-5D version 1, will be reported later.

Statistical Analysis

Sample size was calculated with certain assumptions: for the control arm, a median PFS of 13.5 months and an overall survival of 38.5 months were assumed on the basis of on meta-analysis data from three earlier AGO-led intergroup studies.[22] With 408 PFS events, the study was designed to have greater than 90% power to detect a clinically relevant increase of 47% for median PFS in the experimental arm (H0:$\lambda = 1$; HA:$\lambda \neq 1$) by means of a two-sided, stratified log-rank test, a type I error of 5%, and an exponential distribution of events. With respect to overall survival, the study was designed to have 80% power to detect a 27% increase in median overall survival.

Efficacy data were analyzed in the intent-to-treat population; progression was based on investigator assessments of radiologic scans using RECIST version 1.0. A per-protocol analysis was prespecified if more than 5% of the population was not treated according to protocol; this was not used because of protocol compliance in 96% of patients. Safety population was defined as all patients who had received at least one dose of the study drug.

Robustness of the primary analysis was tested using prespecified analyses, including analyses of PFS on the basis of a) tumor assessment by independent central radiologic review; b) GCIG criteria; c) investigator-based RECIST-criteria including clinical disease progression and in addition including into initiation of new anticancer therapy as progression events. No interim analyses for PFS were planned. For overall survival, the first interim analysis was planned to be conducted at the same time as the primary analysis, the second analysis after 330 events, and the final analysis after 551 events. Kaplan-Meier[23] estimates were used to analyze the data; the Brookmeyer-Crowley method[24] was used for the calculation of the CIs. The Pike estimator[25] of the treatment hazard ratio based on the stratified log-rank test is provided, together with a 95% CI.
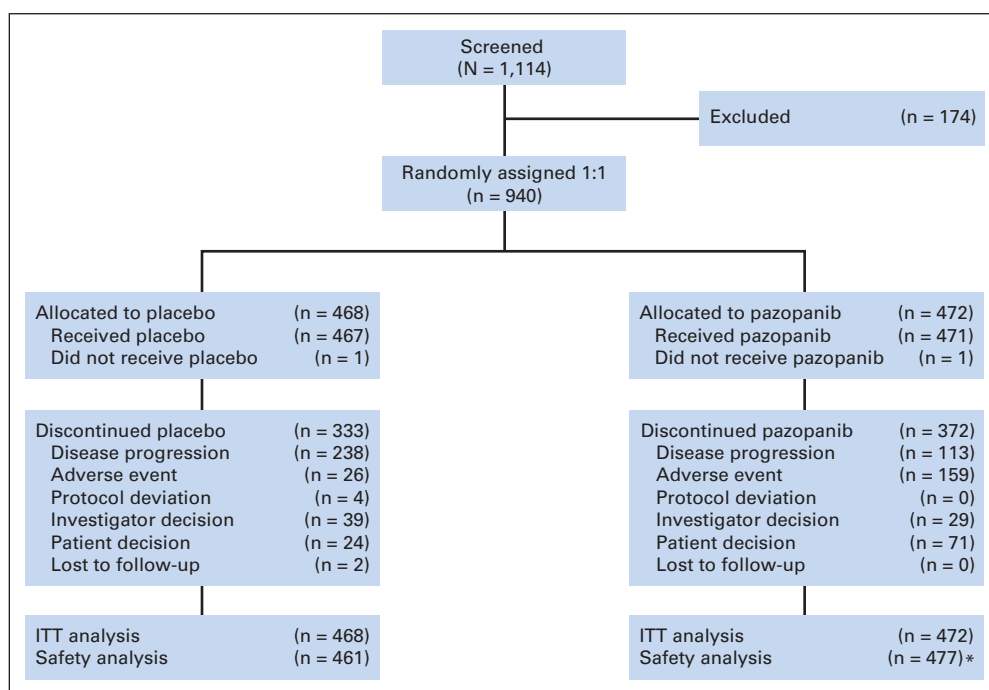
Fig 1. CONSORT diagram. ITT, intention to treat. (*) Includes six patients randomly assigned to placebo who took pazopanib in error for any period of time.

RESULTS

Patients

Of 1,114 patients assessed for eligibility, 940 were enrolled between June 2009 and August 2010 at 14 cooperative study groups at sites in 17 countries in Europe, Asia, North America, and Australia (Fig 1). The intention-to-treat population consisted of 472 patients assigned to the pazopanib group and 468 patients assigned to the placebo group. Baseline characteristics were well balanced between treatment groups (Table 1). The median time from diagnosis to study entry was 7.0 months in the pazopanib and 7.1 months in the placebo group, which included a median interval of 7.4 and 8 weeks from the last cycle of chemotherapy to study entry in the pazopanib and placebo groups, respectively. Chemotherapy cycles were 6.6 ± standard deviation (SD) 1.24 and 6.7 ± SD 1.39 in the pazopanib and placebo groups, respectively. More than 99% of patients had received a platinum-taxane doublet, and 28% had received neoadjuvant therapy. Overall, 547 patients (58%) underwent complete macroscopic resection. Three hundred fifty-two patients (74.6%) in the pazopanib group and 322 (68.8%) in the placebo group had first-line surgery. After first-line therapy including surgery and chemotherapy, 796 patients (85%) experienced complete response.

At data cutoff for primary end point analysis of PFS in July 2012, all patients had completed treatment. At data cutoff for interim secondary end point analysis, 335 patients (36%) had died, 489 patients (52%) were being observed for survival and subsequent anticancer therapy, and 116 (12%) were censored primarily as a result of withdrawal with a higher censoring rate in the pazopanib arm (n = 71; 15%) than in the placebo arm (n = 45; 10%).

Treatment Exposure

A small proportion of patients (7% and 6% of patients receiving pazopanib and placebo, respectively) received treatment planned for 1 year only. In the overall population, mean duration of treatment with pazopanib (8.9 ± SD 8.2 months) was lower than that of placebo (11.7 ± SD 8.0 months; Table 1). A higher proportion of pazopanib-treated patients (58%) had dose reductions compared with placebo-treated patients (14%). Almost all pazopanib dose reductions (96%) resulted from adverse events; the majority occurred by week 6, after which the mean dose level remained nearly constant. The mean daily dose was 585.6 ± SD 200.8 mg in the pazopanib group and 761.0 ± SD 92.2 mg in the placebo group (Fig 2A). Patients from East Asia experienced a higher rate of dose reductions (75%) than the rest of the treated population (36%). The mean daily dose of pazopanib was lower in Asian patients than in non-Asian patients (473 mg v 617 mg, respectively; Fig 2B). Early treatment discontinuation resulting from adverse events occurred in 33.3% of patients in the pazopanib group, almost exclusively within the first 12 weeks (Table 2).

Efficacy

After a median observation period of 24.3 months, 228 PFS events occurred in the pazopanib group and 273 occurred in the placebo group. Median PFS was 17.9 months (95% CI, 15.9 to 21.8) for pazopanib and 12.3 months (95% CI, 11.8 to 17.7) for placebo (hazard ratio [HR], 0.77; 95% CI, 0.64 to 0.91; P = .0021; Fig 3A). Both planned interim analyses revealed no difference in overall survival between the pazopanib and placebo groups (second interim OS analysis: HR, 1.08; 95% CI, 0.87 to 1.33; P = .499; Fig 3B).

Sensitivity analyses of PFS were consistent with the primary analysis (Fig 4). Exploratory post hoc analyses of protocol-prespecified subgroups raised the hypothesis that the benefit of pazopanib maintenance was primarily driven by the non-East Asian population who comprised 78% of the study population, showing an HR of 0.69 (95% CI, 0.57 to 0.84) and a 5.9-month gain in median PFS (Appendix Fig A1, online only). In contrast, the 22% subgroup recruited in East Asia showed an HR of 1.16 (95% CI, 0.78 to 1.73). The second interim survival analysis revealed a nonsignificant difference in the non-East

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Table 1. Demographic and Baseline Characteristics				
	Pazopanib (n = 472)		Placebo (n = 468)	
Characteristic	No.	%	No.	%
Age, years				
Median		56.0		57.0
Range		25.0-85.0		20.0-85.0
Ethnicity				
White	363	76.9	363	77.6
Asian	106	22.5	103	22.0
African American or African	2	0.4	1	0.2
American Indian or Alaska Native	1	0.2	1	0.2
Primary tumor type				
Ovarian	426	90.3	413	88.2
Primary peritoneal	32	6.8	30	6.4
Fallopian tube	13	2.8	21	4.5
Missing	1	0.2	4	0.2
FIGO stage at diagnosis				
II	40	8.5	43	9.2
III	355	75.2	346	73.9
IV	77	16.3	79	16.9
Histology				
Serous	341	72.2	348	74.4
Clear cell	17	3.6	15	3.2
Undifferentiated	38	8.1	44	9.4
Endometrioid	29	6.1	24	5.1
Mucinous	24	5.1	16	3.4
Other	23	4.9	21	4.5
Histologic grade				
Well differentiated	39	8.3	25	5.3
Moderately differentiated	90	19.1	112	23.9
Poorly differentiated	278	58.9	260	55.6
Not assessable	65	13.8	71	15.2
ECOG performance status				
0	361	76.5	359	76.7
1	109	23.1	105	22.4
2	2	0.4	4	0.9
Geographic region				
Europe	320	67.8	317	67.7
Asia	104	22.0	101	21.6
United States/Australia	48	10.2	50	10.7
First-line treatment outcome				
Complete macroscopic resection	265	56.1	282	60.3
Upfront surgery	352	74.6	322	68.8
Interval surgery	120	25.4	145	31.0
NED or CR* after initial therapy	395	83.7	401	85.7
Treatment duration, months				
Mean		8.9		11.7
Standard deviation		± 8.2		± 8.0
Time from diagnosis to study entry, months				
Median		7.0		7.1
Range		3-19		3-19
Time from last cycle of chemotherapy dose study entry, weeks				
Median		7.4		8.0
Range		3-14		3-13

Abbreviations: CR, complete remission; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation Gynecology Obstetrics; NED, no evidence of disease.
*CR including normal CA-125.

Asian population (HR, 0.98; 95% CI, 0.77 to 1.24; P = .859) and a significant detrimental impact in the East Asian population (HR, 1.71; 95% CI, 1.01 to 2.89; P = .047; Appendix Fig A2, online only).

Further subgroup analysis according to well-established prognostic factors of age, performance status, histologic type, and FIGO stage did not reveal any discordant results (Appendix Fig A3, online only).

As a result of earlier and more frequent progression events, a higher proportion of patients in the placebo group received post-treatment anticancer therapy (61% v 50%) and time to second-line therapy was significantly longer in the pazopanib arm (Appendix Table A1; Fig 4).

Safety

The most frequent adverse events leading to early discontinuation were hypertension (8%), diarrhea (2.9%), AST (2.5%) or ALT (2.3%) increase, neutropenia (2.3%), and palmar-plantar erythrodysesthesia (1.7%).

Grade 3 or 4 adverse events of hypertension (30.8%), neutropenia (9.9%), liver-related toxicity (9.4%), diarrhea (8.2%), fatigue (2.7%), thrombocytopenia (2.5%), and palmar-plantar erythrodysesthesia (1.9%) were significantly higher in the pazopanib arm (Table 2). Liver-related adverse events primarily consisted of asymptomatic ALT/AST increases. Bilirubin increase occurred rarely, and Hy's law criteria[26] were observed in three patients, none of whom experienced hepatic failure. Although grade 3/4 neutropenia was observed in 10% of patients in the pazopanib arm, febrile neutropenia occurred only in two patients after initiation of a subsequent therapy.

Fatal adverse events were reported for three pazopanib-treated patients and one placebo-treated patient; fatal events were myocardial infarction, pneumonia, and posterior reversible encephalopathy syndrome in one patient each, and acute leukemia in one patient in the placebo group.

DISCUSSION

This study demonstrated a significant improvement in PFS (5.6-month increase in median PFS), a 23% reduction of risk (HR, 0.77) with pazopanib given as maintenance therapy for up to 2 years in women with FIGO stage II to IV ovarian cancer who had not progressed on first-line therapy. However, the PFS benefit so far has not translated into any survival gain. The efficacy results of our study are consistent with previous studies using antiangiogenics in ovarian cancer, despite the differences in study design. The GOG-218, ICON-7, and OVAR-16 studies all demonstrated a prolongation of PFS with antiangiogenic therapy.[14,15] Notably, the PFS benefit with bevacizumab in GOG-218 was observed only in the maintenance arm, which included treatment with chemotherapy, and not when bevacizumab was only administered concurrently with chemotherapy.[15] However, a direct comparison between this study and previous studies of angiogenesis inhibitors in ovarian cancer is difficult because of the significant design differences. The exclusion criteria in this study mandated exclusion of patients with persistent bulky disease, more than half of all patients had no residual disease after surgery (58%), and most patients (88%) were free of disease at study entry. In GOG-218, patients with stage III disease and no residual disease were not included. Another major difference in study designs is that random assignment occurred
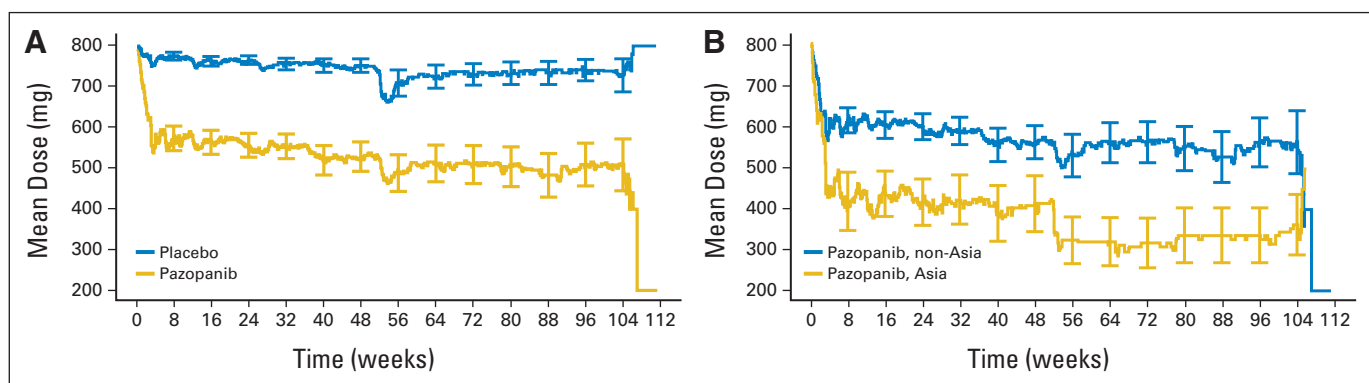
Fig 2. Pazopanib versus placebo exposure (A) in the overall population and (B) in the Asian *v* non-Asian population. Dose interruptions were included for mean dose calculation and subject count as zero dose.

after completion of first-line therapy in this study and not at the time of diagnosis as in the previous studies; in addition, patients with progressive disease during chemotherapy were not included in this trial. Because of this difference, PFS and overall survival calculations start only after the 7-month interval from initial diagnosis to random assignment in our trial.

The most common toxicity in the pazopanib arm was hypertension, a class effect associated with antiangiogenic agents. About half of the patients exposed to pazopanib developed hypertension grade 2 or higher, and this was the most prominent reason for dose reductions and treatment discontinuation in this trial. The observed safety profile of pazopanib was generally consistent with previous studies in renal cancer and soft tissue sarcoma.[27,28] However, neutropenia occurred

more frequently in this trial (32% *v* 8% in the pazopanib and placebo arms, respectively. This may indicate that patients coming off chemotherapy may have a higher risk for neutropenia than the primarily chemotherapy-naive patients in the renal cancer trials. The higher toxicity rate in the sequential use of pazopanib directly after combination chemotherapy may also explain the higher dose reduction and dropout rate. Further analysis of predictive factors can help with understanding whether specific subgroups may need different dose schedules including lower starting doses. However, the maintenance setting itself can lower the threshold for patients and physicians to withdraw therapy because of adverse events that would otherwise be considered more acceptable when treating symptomatic patients with metastatic disease.

Table 2. AEs Occurring in at Least 10% of Patients With Any Grade or at Least 1% of Patients With Grade 3/4 (safety population, in order of frequency of grade 3/4 AEs in the pazopanib arm)

| | Pazopanib (n = 477*) | | | | Placebo (n = 461) | | | | |
| | Any Grade | | Grade 3/4 | | Any Grade | | Grade 3/4 | | |
AE	No.	%	No.	%	No.	%	No.	%	*P*†
Hypertension	275	57.7	147	30.8	91	19.7	26	5.6	**< .001**
Neutropenia	151	31.7	47	9.9	36	7.8	7	1.5	**< .001**
Liver-related toxicity	145	30.4	45	9.4	41	8.9	3	0.7	**< .001**
Diarrhea	253	53.0	39	8.2	80	17.4	5	1.1	**< .001**
Fatigue	198	41.5	13	2.7	121	26.2	1	0.2	**.0017**
Thrombocytopenia	80	16.8	12	2.5	9	2.0	3	0.7	**.034**
Palmar-plantar erythrodysesthesia	64	13.4	9	1.9	7	1.5	1	0.2	**.021**
Headache	136	28.5	8	1.7	70	15.2	3	0.7	.225
Abdominal pain	169	35.4	8	1.7	142	30.8	5	1.1	.579
Proteinuria	40	8.4	6	1.3	8	1.7	2	0.4	.288
Arthralgia	71	14.9	5	1.0	68	14.8	3	0.7	.736
Any AEs leading to treatment discontinuation	159	33.3	105	22.0	26	5.6	14	3.0	
Most frequent AEs									
Hypertension	38	8.0	27	5.7	6	1.3	3	0.6	
Diarrhea	14	2.9	10	2.1	1	0.2	1	0.2	
AST	12	2.5	5	1.1	0	0.0	0	0.0	
ALT	11	2.3	8	1.7	0	0.0	0	0.0	
Neutropenia	11	2.3	4	0.8	1	0.2	1	0.2	
Palmar-plantar erythrodysesthesia	8	1.7	7	1.5	1	0.2	1	0.2	

NOTE. Bold font indicates statistical significance.
Abbreviation: AE, adverse event.
*Includes six patients randomly assigned to the placebo arm who took pazopanib in error for any period of time.
†*P* values were calculated by means of Fisher's exact test to compare the frequency of AEs of grade 3/4 between arms.
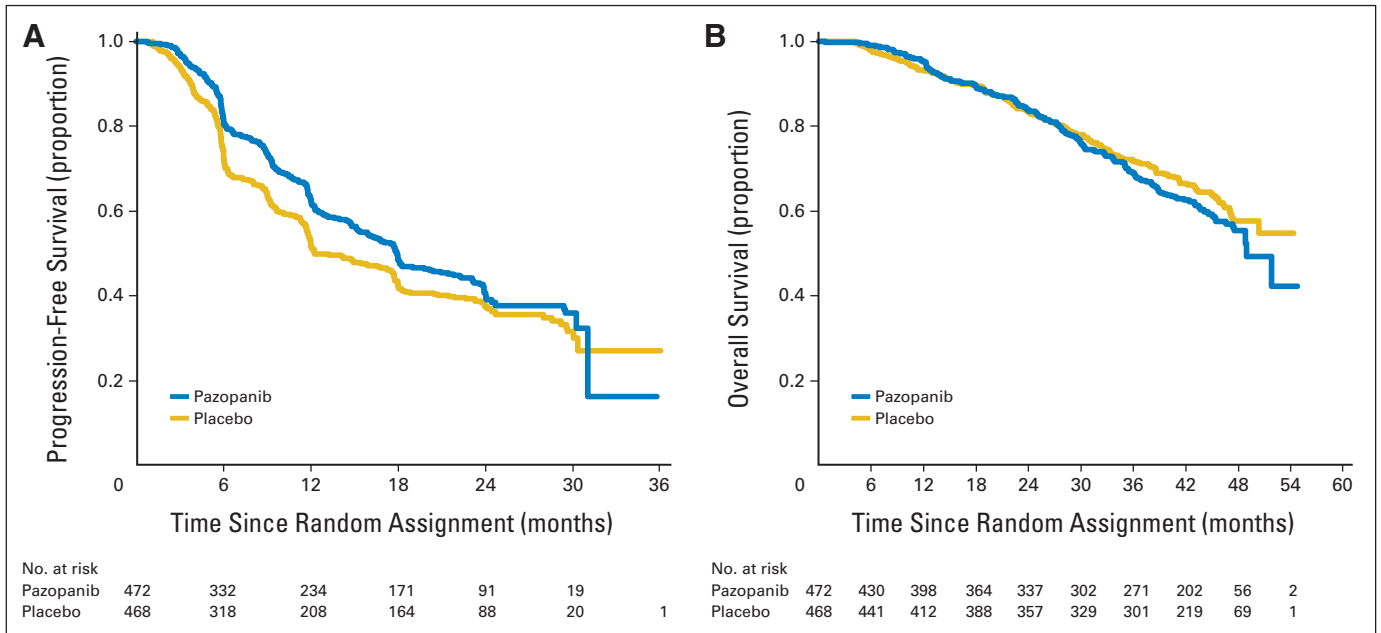
Fig 3. Kaplan-Meier estimates of the (A) primary analysis for progression-free survival according to RECIST criteria and (B) second interim analysis of overall survival. Analyses were based on the intention-to-treat population.

The different frequency of certain adverse effects in the East Asian population may contribute to the different tolerability and efficacy observed in this study. The importance of geographic region was reflected in the results of both the planned and unplanned subgroup analyses. All subgroups (except geographic region) showed consistent results with respect to our primary end point. These results indicate that the potential clinical benefit of

pazopanib is limited to the non-East Asian population. Whether this observation is based on different pharmacogenetics or a need for different treatment schedules among different ethnicities remains an issue to be addressed in future protocols.

This study demonstrated activity for maintenance pazopanib therapy in women with stage II to IV ovarian carcinoma who have not progressed on first-line therapy, but the data do not allow a
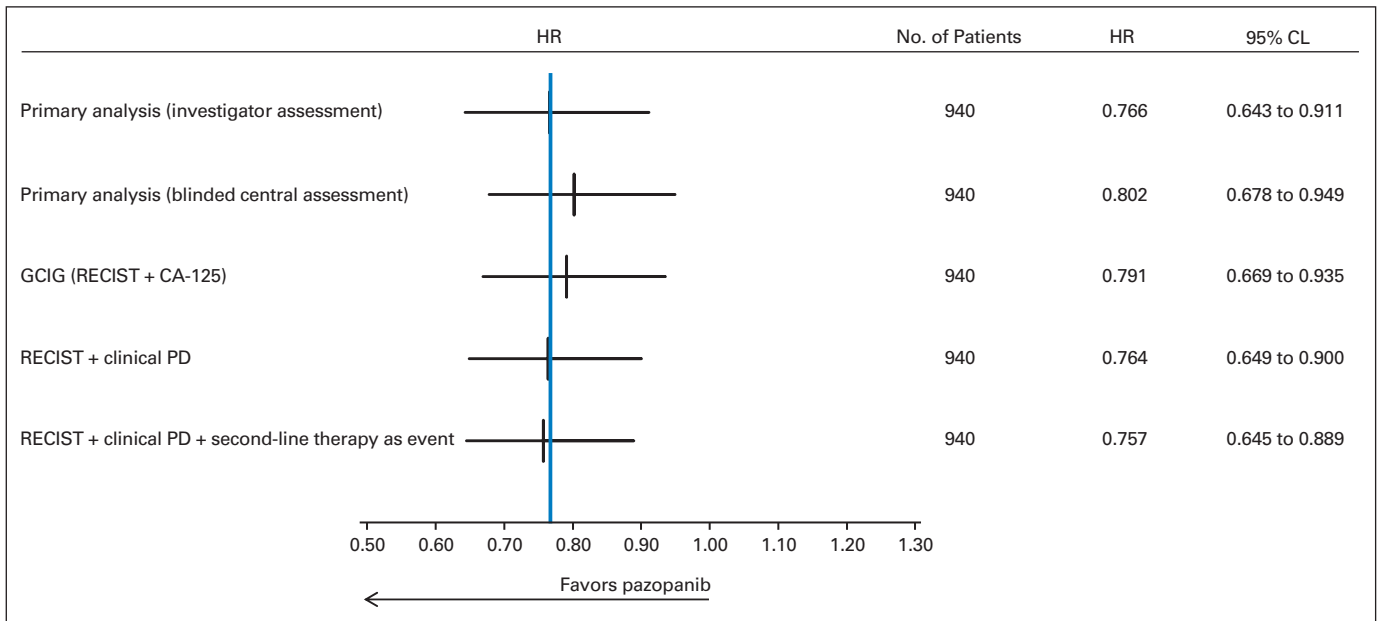
Fig 4. Forest plot of hazard ratios (HRs) and 95% confidence limits (CLs) for the primary analysis of progression-free survival (PFS; blue vertical line) according to RECIST (based on investigator assessment) in comparison with sensitivity analyses of PFS according to the blinded central review of the scans, with Gynecologic Cancer Intergroup (GCIG) criteria, with the analysis according to RECIST including clinical progressive disease (PD) as an event, and with the analysis according to RECIST including clinical PD and additionally start of second-line therapy as an event. All analyses were based on the intention-to-treat population. An HR less than 1 favors pazopanib.

straightforward claim of overall clinical benefit. On one hand, the observed prolongation of PFS is worthwhile and resulted in a significant delay of the time to second-line cytotoxic chemotherapy. On the other hand, we could not demonstrate any survival benefit, and toxicity led to a significant proportion of patients not tolerating the planned treatment schedule. Further skepticism is based on the negative overall survival outcome in the East Asian population. Today, pazopanib cannot be recommended for broad clinical use in ovarian cancer. Further analysis may identify another clinical setting or specific subgroups of patients who may derive a significant clinical benefit of this active antiagiogenesis drug.

AUTHOR CONTRIBUTIONS

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GLOSSARY TERMS

angiogenesis: the process involved in the generation of new blood vessels. Although this is a normal process that naturally occurs and is controlled by so-called on and off switches, blocking tumor angiogenesis (antiangiogenesis) disrupts the blood supply to tumors, thereby preventing tumor growth.

bevacizumab: also called Avastin (Genentech, South San Francisco, CA). Bevacizumab is a recombinant, humanized, monoclonal antibody that binds and neutralizes the vascular endothelial growth factor, thus acting as an antiangiogenic agent.

CA-125 (cancer antigen 125): a protein produced by the fallopian tubes, the endometrium, and the lining of the abdominal cavity (peritoneum). CA-125 is a tumor marker present in higher than normal amounts in the blood and urine of patients with certain cancers. Typically, women with ovarian cancer have high levels of CA-125. Other conditions associated with elevated levels of CA-125 include endometriosis, pancreatitis, pregnancy, normal menstruation, and pelvic inflammatory disease. CA-125 levels may be used to help diagnose ovarian cancer and to determine whether these tumors are responding to therapy. The normal range for CA-125 is less than 35 U/mL and less than 20 U/mL for women who have been treated for ovarian cancer. Women with ovarian cancer may show values higher than 65 U/mL.

taxanes: a class of chemotherapy that leads to the disruption of microtubule function and thus stops cell division. Paclitaxel and docetaxel are examples of taxanes.

VEGF: a cytokine that mediates numerous functions of endothelial cells including proliferation, migration, invasion, survival, and permeability. VEGF is also known as vascular permeability factor. VEGF naturally occurs as a glycoprotein and is critical for angiogenesis. Many tumors overexpress VEGF, which correlates with poor prognosis. VEGF-A, -B, -C, -D, and -E are members of the larger family of VEGF-related proteins.

Appendix

Table A1. Subsequent Anticancer Therapy				
	Pazopanib (n = 472)		Placebo (n = 468)	
Therapy	No.	%	No.	%
Any anticancer therapy				
Yes	237	50.0	285	61.0
No	235	50.0	183	39.0
Type of anticancer therapy*				
Chemotherapy	232	49.0	276	59.0
Radiotherapy	17	4.0	13	3.0
Surgery	66	14.0	79	17.0
Biologic therapy	44	9.0	53	11.0
Hormonal therapy	11	2.0	16	3.0
Immunotherapy	1	< 1.0	2	< 1.0
Small-molecule targeted therapy	11	2.0	15	3.0
Unknown	1	< 1.0	1	< 1.0
VEGF/VEGFR inhibitor				
Bevacizumab	32	7.0	34	7.0
Pazopanib	0	0.0	2	< 1.0
Sorafenib	0	0.0	1	< 1.0

Abbreviations: VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
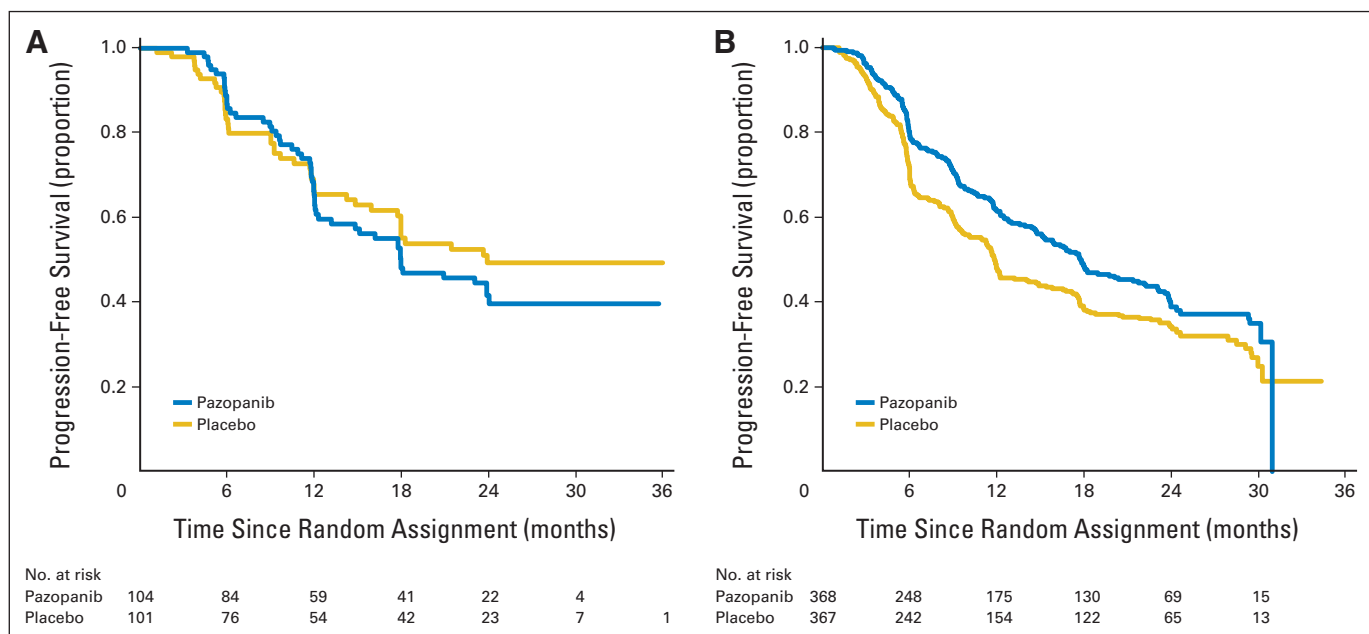*Patients may have received more than one type of anticancer therapy.

Fig A1. Kaplan-Meier estimates of primary progression-free survival analyses of the (A) East Asian and (B) non-East Asian subpopulations (investigator assessment).
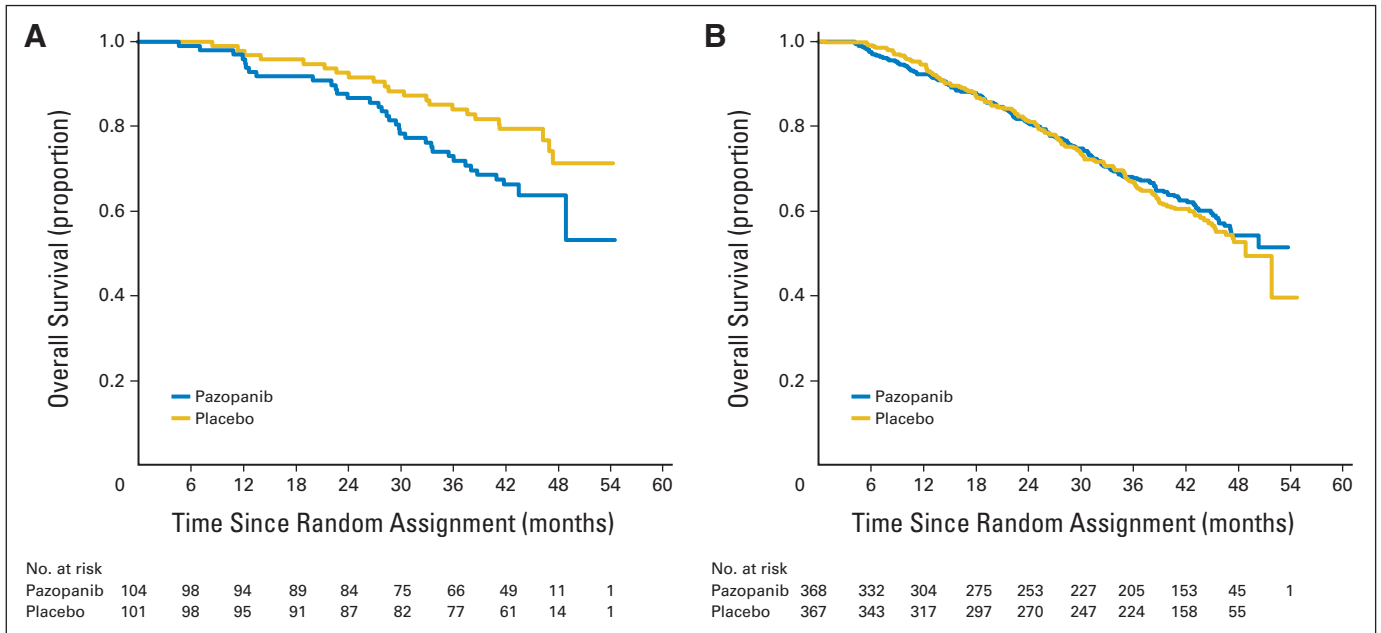
Fig A2. Kaplan-Meier estimates of second interim analyses of overall survival (OS) of the (A) East Asian and (B) non-East Asian subpopulations.

	HR		No. of Patients	HR	95% CL
Primary analysis (investigator assessment)			940	0.766	0.643 to 0.911
Age, years					
< 65			725	0.770	0.629 to 0.943
≥ 65			215	0.743	0.528 to 1.046
ECOG PS					
0			705	0.791	0.645 to 0.971
1-2			215	0.729	0.522 to 1.018
Histology					
Serous			689	0.759	0.622 to 0.927
Other			251	0.775	0.543 to 1.106
FIGO II/III and ≤ 1 cm			597	0.821	0.652 to 1.034
FIGO III and > 1 cm or FIGO IV			209	0.778	0.556 to 1.088
Asian			205	1.164	0.782 to 1.734
Non-Asian			735	0.694	0.572 to 0.842

0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3
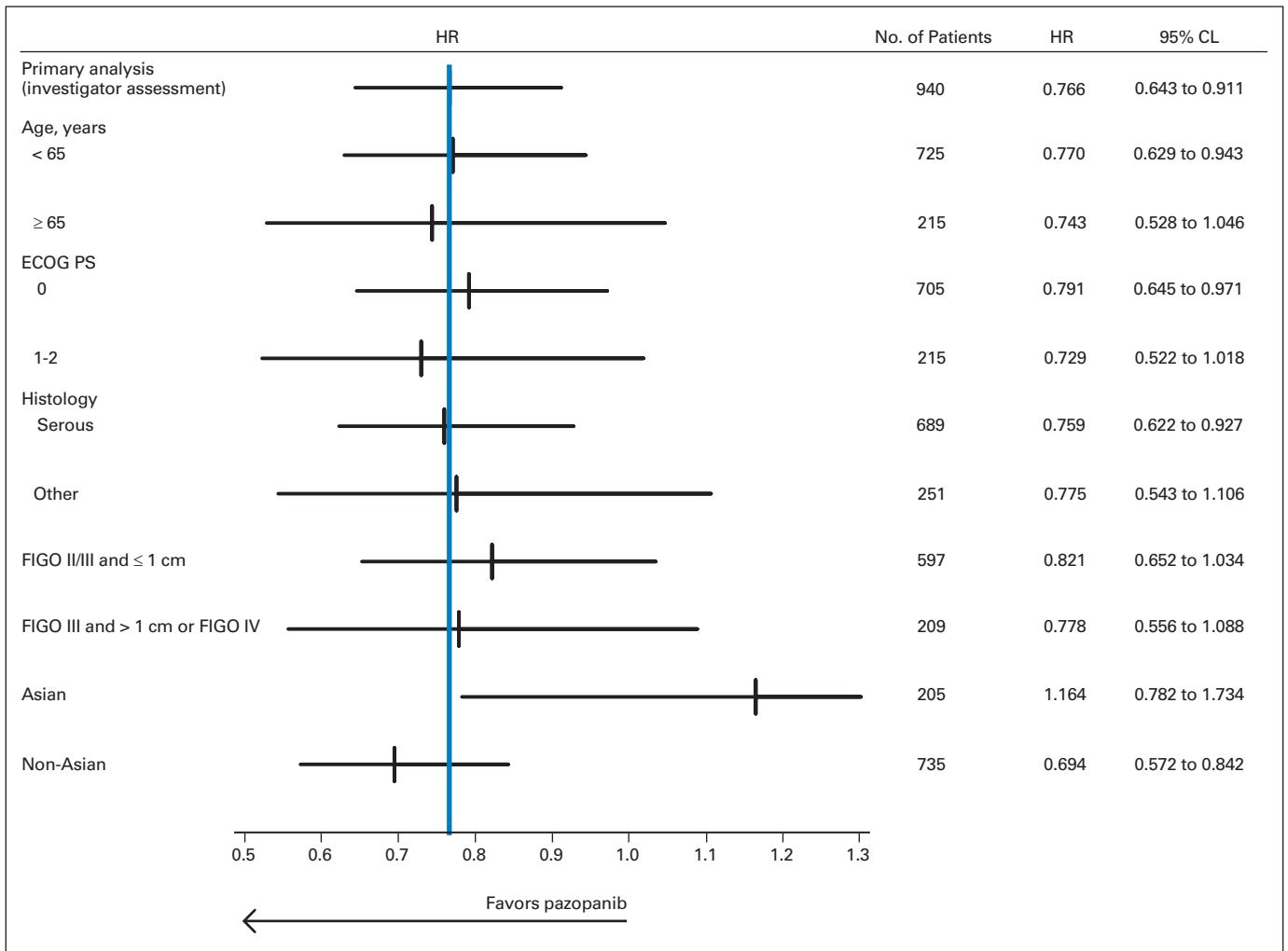
Favors pazopanib

Fig A3. Forest plot of hazard ratios (HRs) and 95% confidence limits (CLs) of primary analysis of progression-free survival (investigator assessment), highlighted by the blue vertical line, in comparison with subgroup analyses according to age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), histology, the International Federation Gynecology Obstetrics (FIGO) stage II-III without residual tumor and residual tumor of less than or equal to 1 cm, as well as the results for the analysis of the patient subgroups with FIGO stage III with postoperative macroscopic residual tumor of more than 1 cm or FIGO IV. An HR less than 1 favors pazopanib.
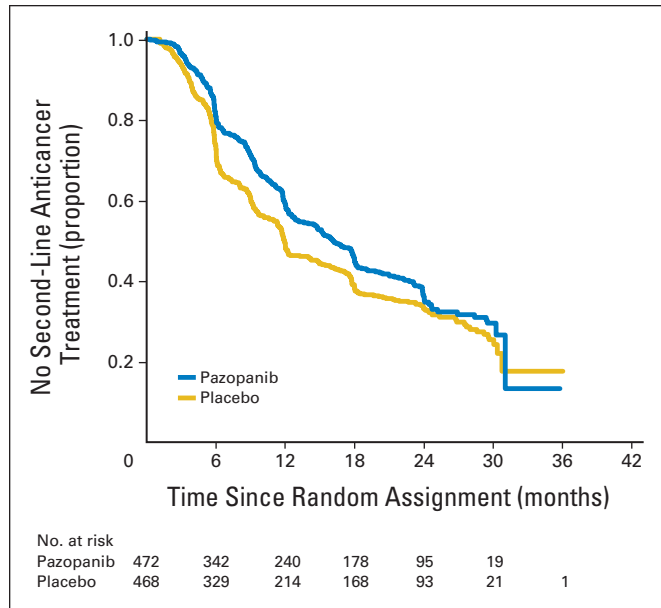
Fig A4. Kaplan-Meier estimates of sensitivity analysis of time until start of second-line anticancer treatment.