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Overall survival results of AGO-OVAR16: A phase 3 study of maintenance pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced ovarian cancer

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HIGHLIGHTS

- In primary analysis, pazopanib given as maintenance therapy for 2 years prolonged PFS significantly, in women with AOC.
- The current final OS analysis did not show significant survival benefit.
- Although OS represents the most practical endpoint for evaluating superiority, PFS is an acceptable endpoint.
- The OS benefit could be masked by several confounding factors.
- Lack of a significant OS benefit in this study may be attributed to the long post-progression survival in this setting.

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ABSTRACT

Objective: The AGO-OVAR16 study was designed to test the efficacy, safety, and tolerability of pazopanib maintenance after first-line chemotherapy in patients with newly diagnosed advanced ovarian cancer (AOC).

Methods: Nine hundred and forty patients with histologically confirmed AOC, International Federation of Gynecology and Obstetrics (FIGO) stage II–IV, were randomized in a 1:1 ratio to receive either 800 mg pazopanib once daily or placebo for up to 24 months, unless there was disease progression, toxicity, withdrawal of consent, or death. The primary endpoint (investigator-assessed progression-free survival [PFS]) was met and previously reported. The results of final analyses of overall survival (OS) are reported here.

Results: A third OS interim analysis showed futility and led to study closure and a final OS analysis after last patient last visit. At the time of the final OS analysis, 494 (89.7% of the planned 551) events had

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Targeted therapy
Taxane-platinum–based chemotherapy

occurred. No difference was observed in OS between pazopanib and placebo. The hazard ratio (HR) was 0.960 (95% confidence interval [CI]: 0.805–1.145), and the median OS from randomization was 59.1 months in pazopanib and 64.0 months in placebo arms. For the East Asian patients, similar to the first three interim OS analyses, a numerical negative trend was observed favoring placebo (HR, 1.332; 95% CI: 0.863–2.054). Exploratory analyses showed a trend for a longer time to first subsequent anti-cancer therapy or death with pazopanib over placebo (HR, 0.829; 95% CI: 0.713–0.965), with a median estimate of 19.0 and 14.5 months, respectively. No new safety signals were observed.

Conclusion: Although pazopanib prolonged PFS, this was not associated with improvement in median OS.

Clinical trial information. ClinicalTrials.gov: NCT00866697.

1. Introduction

Ovarian cancer is the fifth and eighth leading cause of cancer deaths among women in the USA [1] and worldwide [2,3], respectively, with an estimated 13, 980 ovarian cancer deaths in 2019 in the USA [1]. About 90% of cases are of epithelial origin, ~80% of patients present with the International Federation of Gynecology and Obstetrics (FIGO) stage II–IV at initial diagnosis, and ~50% with stage III [4,5]. In patients with advanced disease (FIGO stage II–IV), debulking surgery and taxane-platinum–based chemotherapy is the standard of care. However, a majority of patients relapse after chemotherapy, signifying the need to investigate the role of maintenance therapies to prolong progression-free survival (PFS) and overall survival (OS) after response to first-line chemotherapy [6].

Preclinical [7] and clinical studies have demonstrated an integral role of angiogenesis in the initiation and progression of ovarian cancer. Phase 3 studies have shown that addition of the angiogenesis inhibitor bevacizumab to the chemotherapy regimen significantly delayed recurrence of advanced ovarian cancer (AOC) [8,9]. A phase 2 study provided proof-of-concept data for pazopanib, an oral multi-kinase inhibitor of vascular endothelial growth factor receptor-1, -2, and -3, PDGF receptor-α and -β, and c-Kit [10], as monotherapy in ovarian cancer by demonstrating preliminary anti-tumor activity, tolerability, and an acceptable safety profile [11]. Several targeted therapies including pazopanib [12], bevacizumab [9], nintedanib [13], trebananib [14], and most recently olaparib [15] specifically in BRCA mutation carriers have also been evaluated as maintenance therapy following chemotherapy in the first-line setting. Nintedanib in combination with carboplatin and paclitaxel as first-line therapy significantly increased PFS in women with AOC; however, the treatment was associated with more gastrointestinal toxicity [13]. Maintenance therapy with bevacizumab and pazopanib has shown advantages in prolongation of PFS, whereas significant OS is yet to be demonstrated [9,12,16] [17].

The AGO-OVAR16 (OVAR16; ClinicalTrials.gov identifier: NCT00866697) study investigated the efficacy and safety of pazopanib as maintenance therapy after first-line chemotherapy in patients with newly diagnosed AOC [12]. PFS was the primary endpoint for the OVAR16 study, and the study met the primary endpoint with a significant improvement of 5.6 months (hazard ratio [HR], 0.77; 95% confidence interval [CI]: 0.64–0.91; $P = 0.0021$) in the median PFS with pazopanib vs placebo (17.9 vs 12.3 months, respectively). Exploratory post hoc analyses of subgroups raised the hypothesis that the benefit of pazopanib maintenance was primarily driven by the non–East Asian population, with a 5.9-month gain in median PFS. However, the second survival interim analysis (IA) revealed a non-significant difference in the populations and a significant detrimental impact in the East Asian population [12]. Therefore, it is of high importance to present the results of the final analysis to understand whether the final results resonate with the IA or subgroup analysis.

Here, we report the final analysis of the OVAR16 study. The objective of the final analysis was to evaluate mature data for OS and to conduct exploratory analyses of OS in non–East Asian and East Asian subgroups, and an exploratory analysis on time to first subsequent anti-cancer therapy (TFST) or time to death.

2. Patients and methods

2.1. Patients

Patient population was described previously in the primary publication [12]. Briefly, female patients aged ≥18 years with histologically confirmed 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 at least five cycles of taxane-platinum–based chemotherapy were included in the study. Patients were randomly assigned according to the protocol between 3 and 12 weeks after the last dose of chemotherapy, and after all major toxicities of the previous chemotherapy had resolved to grade 1 or better.

Patients with poorly controlled hypertension or history of cardiac and vascular conditions within 6 months of screening were excluded. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrollment. Protocols and informed consent forms were reviewed and approved by Institutional Review Boards and Independent Ethics Committees according to local guidelines.

2.2. Study design and treatment

Detailed study design and treatment have been described previously [12]. Briefly, this study was an international, randomized, double-blind, placebo-controlled, phase 3 trial of pazopanib versus placebo. Patients were randomized (1:1) to receive either pazopanib (800 mg once daily) or placebo for up to 24 months until disease progression based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.0, unacceptable toxicity, withdrawal of consent, or death. Patients were stratified based on the following factors: (A) First-line treatment outcomes: (1) no evidence of disease (NED) after surgery or FIGO II–IIIA if unknown and NED/complete response (CR) after chemotherapy (including normal CA-125) vs (2) residual tumor after surgery or FIGO IIIB–IV if unknown and NED after chemotherapy (including normal CA-125) vs (3) residual tumor after chemotherapy or elevated screening CA-125; and (B) Region (Europe vs Asia vs North America/Australia).

2.3. Study endpoints and assessments

The primary endpoint was PFS (time from randomization to disease progression or death). The key secondary endpoint was OS. Other secondary endpoints included safety, PFS by the Gynecologic Cancer InterGroup criteria, in which disease progression is defined as the earliest event of progression per RECIST or confirmed CA-125 progression, [18] 3-year PFS rate, and quality of life.

2.4. Statistical methods

Sample size calculations have been detailed previously [12]. OS was summarized using Kaplan-Meier survival curves and compared between the treatment arms using a stratified log-rank test based on the stratification factors. For each treatment arm, the Kaplan-Meier estimates for the median OS time and the first and third quartiles were presented, along with approximate naive 95% CIs (values were undefined if the number of deaths was not sufficient). The Brookmeyer-Crowley method [19] was used to calculate the CIs.

Exploratory analysis of OS by ethnicity subgroups was also performed to better understand the negative trend observed in the East Asian subgroup at the first two OS IAs. As no multiplicity adjustment was planned, definitive conclusions cannot be drawn in any of the subgroups due to the exploratory nature of this sub-analysis.

Exploratory analyses on subsequent anti-cancer therapy by including summary of patients receiving different types of subsequent anti-cancer therapy and TFST were also performed. TFST was defined as the time from randomization to first subsequent anti-cancer therapy or death. The study was performed according to ENGOT Model C [20].

3. Results

A total of 940 patients were enrolled at 243 centers in 17 countries in Europe, Asia, Australia, and North America.

The intent-to-treat (ITT) population comprised all randomized patients who were not screen failures ($n = 940$). The ITT population was used for the analysis of efficacy data and summaries of study population. The All-Treated population comprised all randomized patients who received at least one dose of the investigational product ($n = 941$). The All-Treated population was used for the analysis of safety data.

Patients were randomized (1:1) to receive either pazopanib ($n = 472$) or placebo ($n = 68$). All patients had completed treatment at the time of the data cutoff for the primary analysis (July 08, 2012).

At the time of the final analysis (August 24, 2017), a total of 498 patients had died. Patient discontinuation due to study closure, following confirmation of futility at the third OS IA (January 12, 2017), was the primary reason for premature withdrawal from the study ($n = 294$ out of the 442 prematurely withdrawn patients) (Supplementary Table S1). Baseline characteristics were well balanced between the treatment arms (Supplementary Table S2).

Results of the primary endpoint analysis have been reported previously [12]. Briefly, the mean (±standard deviation [SD]) duration of treatment with pazopanib was lower than that with placebo (8.9 ± 8.2 months vs 11.7 ± 8.0 months). The mean (±SD) daily dose for pazopanib and placebo was 585.6 ± 200.8 mg and 761.0 ± 92.2 mg, respectively. Dose reductions were higher in patients treated with pazopanib (58%) than in those treated with placebo (14%). Patients from East Asia experienced a higher rate of dose reductions than the rest of the treated population (75% vs 36%). Median PFS was 17.9 months for pazopanib vs 12.3 months for placebo (HR, 0.766; 95% CI: 0.643–0.911; $P = 0.0021$; primary endpoint met). No OS benefit was observed in both planned IAs.

The third OS IA (conducted with 86% of the total number of OS events required for the initially planned final OS analysis) again showed no difference between the pazopanib and placebo arms (HR, 0.979; 95% CI: 0.817–1.172). The conditional power was <1% assuming the point estimate of the HR at the third OS IA (less than the protocol-specified futility boundary of 20% conditional power); therefore, the futility criteria were met. As a result, the study was closed and an updated final analysis of OS after all patients had completed the end of study visit was performed. In the subgroup analyses of OS, the second OS IA revealed a negative trend for East Asian patients with HR 1.706 (95% CI: 1.010–2.883). To better understand whether the negative trend observed in the East Asian subgroup at the first two OS IAs was due to a true negative treatment effect or was secondary to random variation, a subgroup analysis by region (East Asia vs non–East Asia) was also performed at the time of the third OS IA. A negative trend was also observed in the third analysis (HR, 1.346; 95% CI: 0.868–2.088), but it was not as strong as that in the second analysis.

3.1. Final overall survival

The final OS analysis was conducted after 494 (89.7% of the planned 551) death events occurred (253 and 241 OS events in placebo and pazopanib arms, respectively). The median OS was similar between the two arms, with 59.1 months (95% CI: 53.5–71.6) for pazopanib and 64.0 months (95% CI: 56.0–75.7) for placebo (HR, 0.960; 95% CI: 0.805–1.145; two-sided stratified log-rank $P = 0.6431$) (Fig. 1). Censoring rates were similar: 49% for pazopanib and 46% for placebo.

Eighty two percent of patients in placebo arm and 81% of the patients in pazopanib arm were with no evidence of disease (NED) at baseline. Patients with NED had higher median OS (72.4 and 70.4 months for placebo and pazopanib) than for patients with residual disease (35.9 and 35.5 months for placebo and pazopanib) while no difference was observed in OS within each subgroup.

3.2. Overall survival in regions

The median OS of non–East Asian patients was similar to that of the overall population, with 57.6 months (95% CI: 50.3–67.8) for pazopanib and 58.0 months (95% CI: 49.4–66.2) for placebo (HR, 0.896; 95% CI: 0.739–1.087) (Fig. 2).

For the East Asian patients, a numerical negative trend in the median OS was observed favoring placebo. Median OS was not reached in either arms (HR, 1.332; 95% CI: 0.863–2.054) (Fig. 3).

3.3. Subsequent anti-cancer therapy

In general, distribution of the types and number of types of anti-cancer therapy was similar between the arms. A slightly higher percentage of patients in the placebo arm, compared to the pazopanib arm, received at least one subsequent anti-cancer therapy (72% vs 65%) and specifically chemotherapy (70% vs 62%).

Among the 644 patients who received subsequent anti-cancer therapy, 66.9% in the placebo arm and 65.4% in the pazopanib

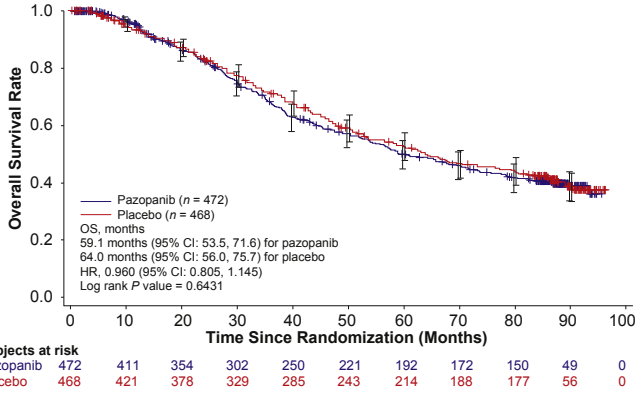

Fig. 1. Overall survival (ITT population). CI, confidence interval; HR, hazard ratio; ITT, intent to treat; OS, overall survival. The HR was estimated using a Pike estimator. An HR value <1 indicates a lower risk with pazopanib compared to placebo. HR and *P* value from stratified log-rank test were adjusted for the two stratification factors. CIs were estimated using the Brookmeyer-Crowley method. Four patients (one placebo, three pazopanib) had missing death dates and were censored at the last contact date. One patient randomized to pazopanib did not receive any treatment and died; therefore, the patient was included in the randomized arm.

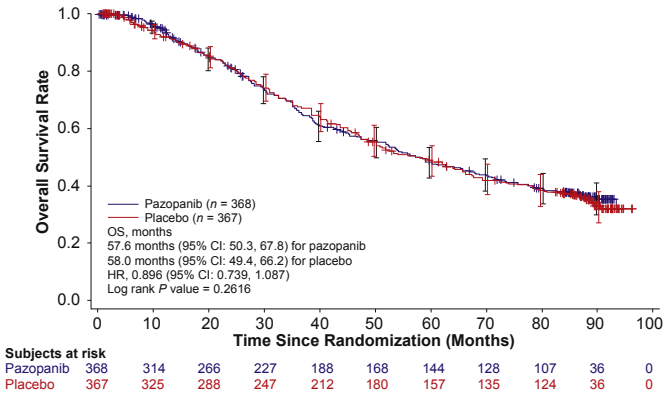

Fig. 2. Overall survival in non–East Asian patients (ITT population) CI, confidence interval; HR, hazard ratio; ITT, intent to treat; OS, overall survival. The HR was estimated using a Pike estimator. An HR value <1 indicates a lower risk with pazopanib compared to placebo. HR and *P* value from stratified log-rank test were adjusted for one stratification factor. CIs were estimated using the Brookmeyer-Crowley method.

arm received more than one type of therapy. A slightly higher percentage of patients in the placebo arm (30.8%) received three or more different types of subsequent anti-cancer therapies compared to those in the pazopanib arm (22.9%) (Supplementary Table S3).

Seventy six patients (16.2%) from placebo arm and 68 patients (14.4%) from pazopanib arm received bevacizumab as subsequent therapy. The median survival time for patients with subsequent bevacizumab tharpy are 61.5 (95% CI: 48.5–66.6) months and 59.1(95% CI: 48.8–83.8) months for placebo and pazopanib respectively, which is similar to the median OS for overall population.

3.4. Time to first subsequent anti-cancer therapy

TFST or time to death was longer for patients in the pazopanib arm than in the placebo arm. Median estimate of TFST or time to death for patients in the pazopanib and placebo arms was 19.0 months (95% CI: 16.2–21.8) and 14.5 months (95% CI: 12.6–18.1), respectively (HR, 0.829; 95% CI: 0.713–0.965; two-sided stratified log-rank $P = 0.0135$) (Table 1).

3.5. Safety

Data on patient safety during the treatment with pazopanib and placebo, and subsequent follow-up were previously detailed until the primary analysis data cutoff (July 08, 2012) [12]. After the primary analysis, two non-serious adverse events (AEs; peripheral

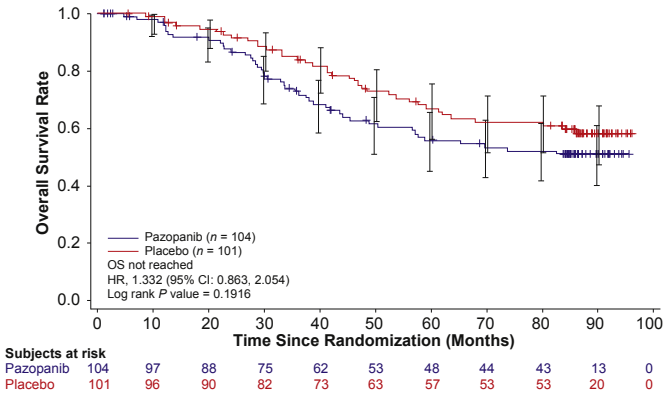

Fig. 3. Overall survival in East Asian patients (ITT population) CI, confidence interval; HR, hazard ratio; ITT, intent to treat; OS, overall survival. The HR was estimated using a Pike estimator. An HR value <1 indicates a lower risk with pazopanib compared to placebo. HR and *P* value from stratified log-rank test were adjusted for one stratification factor. CIs were estimated using the Brookmeyer-Crowley method.

Table 1
Time to first subsequent therapy or death (ITT population).

	Placebo ($N = 468$)	Pazopanib ($N = 472$)
Number of patients		
Died or had at least one subsequent anticancer therapy (event)	344 (74%)	326 (69%)
Censored, follow-up ended[a]	124 (26%)	146 (31%)
Censored, follow-up ongoing	0	0
Adjusted HR[b]		
Estimate	0.829	
95% CI	(0.713–0.965)	
Stratified log-rank *P* value[b]	0.0135	
Estimates for time to first anticancer therapy or death (months)[c]		
First quartile	7.0	9.8
95% CI	(6.5–7.5)	(8.7–10.4)
Median	14.5	19.0
95% CI	(12.6–18.1)	(16.2–21.8)
Third quartile	51.0	56.0
95% CI	(39.3–85.1)	(40.9–75.6)

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent to treat.
[a] Patients who had not died and had not received any subsequent anticancer therapy were censored at the last contact date. Patients who received any subsequent anticancer therapy with missing date were censored at the disease progression date. If the disease progression date was not reported, the patients were censored at the treatment discontinuation date.
[b] The HR was estimated using a Pike estimator. An HR value <1 indicates a lower risk with pazopanib compared to placebo. HR and *P* value from stratified log-rank test were adjusted for two stratification factors. *P* value should be considered exploratory only.
[c] CIs were estimated using the Brookmeyer-Crowley method.

sensorimotor neuropathy and depressed level of consciousness) with grade 1 severity, which were not considered related to study treatment, were reported. No additional serious AEs (SAEs) and no new safety signals were observed.

3.6. Deaths

A total of 497 patients (53%) died by last patient last visit (LPLV), including 245 patients (51%) in the pazopanib arm and 252 patients (55%) in the placebo arm (based on the All-Treated population). The disease under study was the most common primary cause of death, and most patients died >28 days after stopping study treatment. By 28 days from the last dose, there were no on-treatment deaths in the placebo arm, whereas 3 (<1%) on-treatment deaths occurred in the pazopanib arm. Five patients died ($n = 2$ in placebo and $n = 3$ in pazopanib) due to toxicity; four of the five deaths were due to fatal SAEs ($n = 1$ in placebo and $n = 3$ in pazopanib) and were previously reported [12]. The additional death due to toxicity in the placebo arm occurred approximately 47 months after the last dose and was considered not treatment related (Table 2).

4. Discussion

This phase 3 study was designed to compare the efficacy and safety of maintenance pazopanib versus placebo in women with FIGO stage II–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease had not progressed after debulking surgery and first-line chemotherapy. The high relapse rate in this patient population, the absence of effective maintenance therapy options after first-line standard of care, along with the preliminary anti-tumor activity of pazopanib shown in a previous phase II study [11], warranted the evaluation of pazopanib in this setting.

The primary analysis of the OVAR16 study demonstrated significant prolonged PFS with pazopanib given as maintenance therapy for up to 2 years in women with FIGO stage II–IV ovarian cancer who had not progressed on first-line therapy. However, no statistically significant survival benefit was shown in the final OS analysis: the median OS was similar between the arms: 59 months and 64 months for pazopanib and placebo, respectively. Similar results were observed in

Table 2
Summary of deaths – all-treated population.

Patient status	Placebo ($N = 461$)[a] *n* (%)	Pazopanib ($N = 477$)[a] *n* (%)
Dead[b]	252 (55%)	245 (51%)
Alive at last contact, follow-up ended	209 (45%)	232 (49%)
Primary cause of death		
Disease under study	239 (52%)	234 (49%)
Toxicity	2 (<1%)	3 (<1%)
Other	11 (2%)	8 (2%)
Time to death from first dose		
≤28 days	0	1 (<1%)
>28 days	251 (54%)	241 (51%)
Unknown	1 (<1%)	3 (<1%)
Time to death from last dose		
≤28 days	0	3 (<1%)
>28 days	251 (54%)	239 (50%)
Unknown	1 (<1%)	3 (<1%)

[a] One randomized patient in each treatment arm was excluded from the All-Treated population because they did not receive treatment. The pazopanib arm included six patients who were randomized to placebo but took at least one dose of pazopanib.
[b] Four patients (one in placebo, three in pazopanib) had missing death dates and were, therefore, treated as censored at the last contact date.

other phase 3 studies where bevacizumab [8,9,17], nintedanib [13], or trebananib [18] were administered along with initial chemotherapy and maintenance phases of first-line treatment of AOC. Several other phase 3 studies are investigating the value of poly ADP ribose polymerase inhibitors (PARPi) after first-line therapy in BRCA-mutated and non-mutated patients. With a 70% lower risk of disease progression or death than placebo, olaparib as maintenance therapy provided a substantial PFS benefit in women with newly diagnosed AOC and a BRCA1/2 mutation in the SOLO-1 trial [15]. In addition, bevacizumab with olaparib (PAOLA) and six phase 3 studies with Immuno Oncology (and some with PARPi) are being investigated.

Although OS represents the most practical endpoint for evaluating superiority of an experimental therapy over standard treatment in first-line ovarian cancer, PFS is an acceptable endpoint [21,22] in this setting and led to the global approval of bevacizumab, which has a PFS benefit. PFS was the most commonly used primary endpoint, with OS being an additional endpoint for most of the phase 3 clinical trials of targeted therapies for advanced solid tumors. The OS benefit could be masked by several confounding factors including multiple anti-neoplastic therapies available, the use of active drugs delivered as salvage therapy after tumor progression, crossover therapy, and relatively long survival durations [23,24]. Lack of a statistically significant OS benefit in this study may be attributed to the long post-progression survival in this setting.

Recent phase 3 trials in other advanced solid tumors showed a significant PFS benefit but inconsistent effects on OS, even after patient selection based on the expression of molecular targets for these agents. Nonetheless, these are considered as major advances in the treatment of advanced solid tumors [25,26]. Broglio and Berry demonstrated that the lack of statistical significance in OS does not imply lack of improvement in OS for clinical trials with a PFS benefit, especially for diseases with long median post-progression survival [27].

The PFS benefit observed in the primary analysis was consistent across the sensitivity analyses and subgroups, with the exception of the East Asia subgroup (22% of ITT population). Because of this difference in PFS results between the East Asian subgroup and the rest of the world, OS was also further evaluated for East Asian and non–East Asian subgroups. The first two OS IAs showed a negative trend favoring placebo in the East Asian subgroup. In the third IA, there was a numerical negative trend in OS for East Asian patients and was not as strong as that observed in first and second IAs.

Exploratory post hoc analyses of protocol-prespecified subgroups for final OS showed that the median OS of non–East Asian patients was similar to that of the overall population, being 57.6 months for pazopanib and 58 months for placebo, whereas the numerical negative trend in OS for East Asian patients treated with pazopanib observed in the final OS analysis was similar to that observed in the third IA. Demographic and baseline characteristics were well balanced between the placebo and pazopanib arms in both the ITT population and the East Asian subgroup [28], suggesting that these factors did not impact the OS results.

A slightly higher (non-significant) percentage of patients in the placebo arm received at least one subsequent anti-cancer therapy. This might have been caused by patients or investigators choosing no further treatment due to the toxicities of pazopanib. The number of patients who received three or more types of subsequent anti-cancer therapies tended to be higher in the placebo arm than in the pazopanib arm. These differences may have in part favored the placebo arm with regard to the OS results.

TFST was analyzed in the final analysis following LPLV to evaluate if treatment with pazopanib may provide a potential clinically meaningful benefit by delaying the initiation of subsequent therapies. TFST or time to death was longer for patients in the pazopanib arm than in the placebo arm, with a median estimate of 19.0 months vs 14.5 months, respectively. The trend for longer TFST in the pazopanib arm may suggest that the PFS benefit remained with additional data maturity. However, this result must be interpreted with caution due to its exploratory nature.

The safety profile was in general consistent with the known safety profile of pazopanib in approved indications. No additional SAEs and no new safety signals were observed.

In summary, although pazopanib prolonged PFS, no OS benefit was demonstrated.

The only approved anti-angiogenic agent in this setting remains bevacizumab, although there is no improvement in OS. Ongoing trials are focused on the use of PARPi and immune checkpoint inhibitors as maintenance therapy following or in combination with first-line chemotherapy for ovarian cancer.

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Data sharing statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com

Declaration of competing interest

IV has no relationships to disclose. ADB received honoraria from PharmaMar, Tesaro; provided consulting or advisory board services to

Advaxis, AstraZeneca, Genmab, Pfizer, Roche/Genentech. AF has provided consulting or advisory board services to AstraZeneca, Clovis, Roche, Tesaro; others for AstraZeneca, PharmaMar, Roche, Tesaro. JMC has provided consulting or advisory services to MSD; received travel accommodation or expenses from Merck-Serono. MF received honoraria from AstraZeneca, MSD; provided consulting or advisory board services to AstraZeneca, MSD; received research funding from BeiGene. SP has received honoraria from Roche, AstraZeneca, Claris, Tesaro, MSD, Pfizer; provided consulting or advisory board services to Claris, Tesaro, AstraZeneca; was part of speakers' bureau for AstraZeneca, Tesaro; received research funding from Roche, Tesaro, MSD. KF received honoraria from Bayer, Chugai Pharma, Daiichi Sankyo, Eisai, Janssen Oncology, Kyowa Hakko Kirin, Lilly Japan, Nippon Kayaku, Ono Pharmaceutical, Taiho Pharmaceutical, Zeria Pharmaceutical; provided consulting or advisory board services to AstraZeneca, Chugai Pharma, Eisai, MSD, Pfizer, Taiho Pharmaceutical, Takeda; received research funding from AstraZeneca, Chugai Pharma, Eisai, GlaxoSmithKline, Immunogen, Kaken Pharmaceutical, Lilly, MSD, Oncotherapeutics, Ono Pharmaceutical, Pfizer, Shionogi, Taiho Pharmaceutical, Zeria Pharmaceutical. NC is an employee of Ignyta; provided consulting or advisory board services to Amgen, AstraZeneca, Clovis Oncology, MSD Oncology, Pfizer, PharmaMar, Roche/Genentech. MRM is a part of the leadership in Karyopharm Therapeutics, SeraCare and has stock; other ownership interests with Karyopharm Therapeutics, SeraCare; received honoraria from Advaxis, AstraZeneca, Cerulean Pharma, Clovis Oncology, Novocure, Pfizer, Roche, Tesaro; provided consulting and advisory board services to AstraZeneca, Cerulean Pharma, Clovis Oncology, Genmab, Karyopharm Therapeutics, Novocure, Pfizer, Tesaro; received research funding from AstraZeneca, Boehringer Ingelheim, Pfizer, Tesaro; received travel accommodations and expenses from AstraZeneca, Karyopharm Therapeutics, Pfizer, Roche, SeraCare, Tesaro. BJM is a part of the leadership in US Oncology; received honoraria from AbbVie, Advaxis, Amgen, AstraZeneca, Bayer, Biodesix, Cerulean Pharma, Clovis Oncology, GlaxoSmithKline, Gradalis, Immunogen, Incyte, Insys Therapeutics, Janssen, Mateon Therapeutics, Merck, Myriad Pharmaceuticals, NuCana BioMed, OXiGENE, Perthera, Pfizer, Precision Oncology, Roche/Genentech, Tesaro, Verastem, Vermillion; provided consulting or advisory support to AbbVie, Advaxis, Amgen, AstraZeneca, Bayer, Biodesix, Cerulean Pharma, Clovis Oncology, GlaxoSmithKline, Gradalis, Immunogen, Incyte, Insys Therapeutics, Mateon Therapeutics, Merck, Myriad Pharmaceuticals, NuCana BioMed, OXiGENE, Perthera, Pfizer, Precision Oncology, Roche/Genentech, Tesaro, Verastem, Vermillion; was part of speakers' bureau for AstraZeneca, Clovis Oncology, Janssen, Roche/Genentech, Tesaro; received research funding from Advaxis, Amgen, Array BioPharma, AstraZeneca, Genentech, Immunogen, Janssen, Lilly, Morphotek, Novartis, NuCana, Pfizer, Regeneron, Tesaro. IT has received travel accommodation or expenses from Roche, AstraZeneca, Amgen. PMC has received travel accommodations or expenses from Pfizer, SERVIER. TJH has provided scientific advisory board services to AstraZeneca, Caris, Clovis, Genentech, J&J, Tesaro. LCH has received honoraria from AstraZeneca, Roche, Tesaro, PharmaMar; provided consulting and advisory board services to AstraZeneca, Roche, Tesaro, PharmaMar; received travel accommodation or expenses from AstraZeneca, Roche, Tesaro, PharmaMar. MJC-A is an employee of Novartis; has stock or other ownership interest with Novartis. PH has received honoraria from AstraZeneca, Roche, Tesaro, Stryker and EUI lab, MSD; provided consulting and advisory board services to AstraZeneca, Roche, Tesaro, Eli Lilly, Clovis, Immunogen; received research funding from AstraZeneca, Roche, Boehringer Ingelheim, Tesaro. JR, J-WK, JM, JYL, and AB have no relations to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.08.024.

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