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Progression-free survival by local investigator versus independent central review: Comparative analysis of the AGO-OVAR16 Trial☆,☆☆

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HIGHLIGHTS

- Pazopanib maintenance therapy extended PFS in patients with AEOC.
- HR estimates for PFS by investigator were consistent with those of central review.
- There was no evidence of investigator bias in estimates of disease progression.

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ABSTRACT

Background. Analysis of progression-free survival (PFS) as the primary endpoint in advanced epithelial ovarian, fallopian tube, and primary peritoneal cancer (AEOC) trials may be confounded by the difficulty of radiologic evaluation of disease progression and the potential for discrepancy between investigator and blinded independent central assessments. PFS as assessed by local investigator (INV) was the primary endpoint of AGO-OVAR16, a randomized, double-blind trial of pazopanib maintenance therapy in AEOC. To confirm the robustness of the primary analysis, PFS was also evaluated by blinded independent central review (BICR).

Methods. Patients with histologically confirmed AEOC ($N = 940$) were randomized 1:1 to receive pazopanib 800 mg/day or placebo for up to 24 months. Tumor response in the intent-to-treat population was evaluated by CT/MRI every 6 months and analyzed per RECIST 1.0.

Results. Pazopanib prolonged PFS versus placebo by INV (median 17.9 vs 12.3 months; hazard ratio [HR] = 0.766, 95% confidence interval [CI]: 0.643–0.911; $P = 0.0021$). Results for PFS by BICR were similar (median 15.4 vs 11.8 months; HR = 0.802, 95% CI: 0.678–0.949; $P = 0.0084$). Progression events were recorded later

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by INV in 23% of pazopanib-treated patients and 17% of placebo-treated patients. The overall concordance between INV and BICR assessments was 84% and 86% in the pazopanib and placebo arms, respectively.

Conclusions. By INV and BICR assessments, maintenance therapy with pazopanib in AEOC provided a significantly longer PFS than placebo. The good overall concordance between INV and BICR assessments, as well as HR and *P* value consistency, supports the reliability of investigator-assessed PFS as the primary endpoint in AGO-OVAR16.

Introduction

Ovarian cancer is among the most common cancers in women, and has the highest mortality among all gynecologic cancers [1]. First-line treatment includes debulking surgery followed by platinum-taxane–based chemotherapy [2]. Although the initial response rate is high, most patients experience recurrence and eventually die from the disease [3]. Recent studies have demonstrated that addition of the angiogenesis inhibitor bevacizumab to the chemotherapy regimen can delay recurrence of advanced ovarian cancer [4,5]. Pazopanib, an oral angiogenesis inhibitor targeting VEGF receptors, platelet-derived grown factor receptors, and c-kit, has demonstrated promising activity in ovarian cancer [6,7]. The phase 3, randomized, placebo-controlled trial AGO-OVAR16 (OVAR16; NCT00866697) evaluated pazopanib monotherapy as maintenance therapy in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC) whose disease had not progressed following first-line treatment [8].

The primary endpoint of OVAR16 was progression-free survival (PFS), and the primary analysis was based on radiologic progression per Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST) as assessed by the local investigator (INV).

In ovarian cancer, PFS is considered to be an appropriate primary endpoint because disease progression is associated with recurrence of symptoms and relatively short survival, and further treatment is usually initiated, which brings additional toxicities [5,9,10]. However, assessment of PFS is sensitive to timing of evaluations and requires consistent interpretation of radiologic progression; variability in timing and interpretation between the control and treatment arms can introduce bias to the analysis [11]. In addition, in ovarian cancer the radiologic assessment of progression is particularly difficult because: 1) upfront standard surgery and chemotherapy are generally able to remove most, if not all, of the tumor, so most patients are disease-free at the end of their initial therapy; 2) surgical scarring is often difficult to distinguish from actual tumor lesions; and 3) in many patients progression may be characterized by diffuse peritoneal implantation and the prevalence of non-target lesions, such as ascites. To avoid investigator bias, regulatory agencies commonly require an additional analysis by blinded independent central review (BICR) to confirm the reliability of results obtained by INV evaluation of disease progression. Recent studies have suggested that independent review of all scans, which is associated with increased cost and complexity, may not be necessary. A meta-analysis of 27 phase 3 oncology trials revealed good concordance between INV and BICR assessments of PFS, and little evidence of investigator bias [12]. The United States Food and Drug Administration (US FDA) has discussed the use of an independent audit of random sample assessments rather than a complete review of all patients [13]. In this report we compare the primary endpoint of OVAR16 as assessed by INV and BICR, and explore the use of a subset of patient evaluations to confirm the primary analysis.

Patients and methods

Patients and study design

Detailed descriptions of the eligibility criteria and study design have been published previously [8]. Briefly, eligible patients were ≥18 years of age, with histologically confirmed, FIGO stage II–IV AEOC that had been treated with surgical debulking and at least 5 cycles of platinum-taxane–based chemotherapy. Eligibility included no evidence of disease progression following first-line treatment, Eastern Cooperative Oncology Group performance status 0–2, and adequate hematologic, hepatic, and renal function. Patients were excluded for poorly controlled hypertension or history of cardiac and vascular conditions within 6 months of screening. All patients provided written informed consent.

The study was a randomized, double-blind, placebo-controlled, phase 3 trial. Patients were randomized 1:1 to receive pazopanib 800 mg once daily or placebo for 24 months or until disease progression defined by RECIST 1.0 [14], unacceptable toxicity, or withdrawal of consent. Before randomization, patients were stratified according to first-line treatment outcome and geographic region. The study received approval from local institutional review boards or ethics committees and was conducted in accordance with the provisions of the Declaration of Helsinki.

Endpoints and assessments

The primary endpoint was PFS, defined as the interval from date of randomization to first documentation of disease progression or death from any cause. The primary analysis was based on radiological progression per RECIST as determined by INV. Radiologic assessments of disease were conducted by computed tomography or magnetic resonance imaging at baseline and every 6 months thereafter until progression. A protocol-specified sensitivity analysis, PFS by BICR, was conducted to evaluate the reliability of INV assessment. Scans were reviewed by two radiologists, and a third radiologist served as adjudicator in cases of disagreement.

Analysis

Efficacy data were analyzed in the intent-to-treat population. Progression-free survival was compared between treatment arms using a stratified log-rank test based on stratification of patients by first-line treatment outcome and the geographic coverage of participating cooperative groups. The Pike estimator of the treatment hazard ratio (HR) based on the stratified log-rank test was provided, together with a 95% confidence interval (CI). No interim analyses for PFS were planned or conducted. The concordance between INV and BICR was assessed for 200 patients who were randomly selected prior to treatment unblinding. The early discrepancy rate (EDR) and late discrepancy rate (LDR) were calculated according to the methods of Amit et al. [12].

Results

Patients

Overall, 940 eligible patients were enrolled in OVAR16; 472 patients were randomized to receive pazopanib and 468 were randomized to receive placebo [8]. Demographic and baseline clinical characteristics were well balanced between treatment groups. All patients were evaluated for disease progression by both INV and BICR. Radiologic scans were performed at 3513 time points, and scans were available for BICR at 3425 (97%) of those times.

Analysis of PFS

By INV assessment, there were 237 PFS events in the pazopanib arm and 273 in the placebo arm; median PFS was 17.9 months (95% CI: 15.9–21.8) for pazopanib and 12.3 months (95% CI: 11.8–17.7) for placebo (HR = 0.766, 95% CI: 0.643–0.911; $P = 0.0021$) (Table 1, Fig. 1). The BICR sensitivity analysis of PFS was consistent with the primary analysis. By BICR, there were 250 PFS events in the pazopanib arm and 288 in the placebo arm; median PFS was 15.4 months (95% CI: 12.0–17.9) for pazopanib and 11.8 months (95% CI: 10.1–12.0) for placebo (HR = 0.802, 95% CI: 0.678–0.949; $P = 0.0084$) (Table 1, Fig. 1). The mean time from randomization to each radiologic assessment was comparable between treatment arms (data not shown), indicating that assessment frequency was balanced and would not be a source of bias in comparing PFS. The proportion of patients with off-schedule visits and the proportion of patients with disease progression at off-schedule visits were comparable between treatment arms (data not shown), indicating that off-schedule assessments would similarly not be a source of bias in comparing PFS by INV and BICR.

Concordance of INV and BICR event assessments

To assess concordance between INV and BICR determinations, dates of disease progression and censoring were compared. Good concordance was observed between INV assessment and BICR (Table 2). The event concordance rate, or proportion of patients with an assessment of disease progression or censored by both INV and BICR, was 84% in the pazopanib arm and 86% in the placebo arm. Among patients with disease progression by INV, timing of progression events was the same in 65% of pazopanib patients and 73% of placebo patients. In most cases for which timing disagreed, progression evaluation by INV occurred later than evaluation by BICR. Progression evaluation occurring earlier by INV than by BICR was observed in only 2 pazopanib patients and 4 placebo patients.

To determine if performing the BICR in only a subgroup of the full population (sample-based BICR as proposed by Amit et al. [12]) would have led to the same overall conclusions, the concordance between INV and BICR was assessed for 200 patients who were randomly selected before treatment unblinding. This exploratory analysis included 105 patients from the pazopanib arm and 95 patients from the placebo arm. Results from this analysis are in agreement with those of the overall study population. The event concordance rates in the subset analysis were 86% and 89% in the pazopanib and placebo arms, respectively; the timing of progression events was the same in 67% of pazopanib patients and 84% of placebo patients (Table 2).

To further evaluate the results of OVAR16 for evidence of investigator bias, EDR and LDR were calculated according to the methods of Amit et al. [12]. Discrepancies in EDR and LDR between treatment arms were small; results from the 200-patient subset were consistent with those from the entire study population (Table 3).

Table 1
Progression-free survival (PFS) by local investigator (INV) and blinded independent central review (BICR).

	INV assessment		BICR assessment	
	Pazopanib ($N = 472$)	Placebo ($N = 468$)	Pazopanib ($N = 472$)	Placebo ($N = 468$)
Progression events, *n*	237	273	250	288
PFS, median months	17.9	12.3	15.4	11.8
Hazard ratio	0.766		0.802	
95% confidence interval	0.643–0.911		0.678–0.949	
P value	0.0021		0.0084	

Reasons for disease progression

In both treatment groups, the majority of radiologic progression events were attributed solely to the development of a new lesion (Table 4). Local investigators reported this reason in 92% of cases in each treatment group, and BICR reported this reason in 79% of pazopanib cases and 80% of placebo cases. The next most common reason for progression was development of a new lesion accompanied by progression of a non-target lesion; this reason was noted more frequently by BICR than by INV (18% versus 3%, respectively, in the pazopanib arm and 17% versus 5%, respectively, in the placebo arm).

Discussion

The primary analysis of OVAR16 demonstrated that maintenance therapy with pazopanib led to a prolongation of PFS in women with AEOC. However, despite the increase in PFS, there was no increase in overall survival for pazopanib-treated patients in OVAR16 compared with placebo-treated patients, based on an interim survival analysis after 36% of events had occurred in the overall study population [8]. These results are consistent with those of GOG-0218 and ICON7, which evaluated the incorporation of bevacizumab into the initial chemotherapy and maintenance phases of first-line treatment of AEOC [4,15]. These studies, and others, support the PFS benefit of angiogenesis inhibitors in ovarian cancer [16].

The primary analysis in OVAR16 was PFS by INV. Use of PFS as the primary endpoint reflects the clinical benefit of a time period without increasing tumor burden and associated symptoms, and avoids the confounding effect of post-progression treatments. Because local investigators have access to clinically relevant observations in addition to reviewing radiologic evidence, there is a potential for investigator bias even in blinded clinical trials. Regulatory authorities commonly require a blinded independent review of all radiologic evidence to confirm the results obtained by INV analysis. In OVAR16, PFS by BICR was a prespecified sensitivity analysis and 97% of the overall evaluation time points were reviewed, thus confirming the diligence of the sites and participating cooperative groups in sending radiologic images for review. The results of the BICR analysis were consistent with the primary analysis. The estimates of median PFS were slightly longer by INV than by BICR (17.9 vs 15.4 months, respectively, for pazopanib; 12.3 vs 11.8 months, respectively, for placebo); this was likely a result of INV tending to identify progression slightly later than BICR. Most importantly however, the HR and *P* values for PFS were very similar (HR = 0.766, $P = 0.0021$ by INV; HR = 0.802, $P = 0.0084$ by BICR), suggesting that the INV analysis was a reliable indicator of treatment benefit. Event concordance rates were high (≥84%) and were in good agreement between treatment arms, suggesting that INV and BICR reviews were providing consistent assessments.

Another test of potential bias described by Amit et al. [12] evaluates the timing discordance rates of disease progression between INV and BICR. Early discrepancy rate is the rate at which INV reports disease progression earlier than BICR relative to the total number of INV progression assessments. Late discrepancy rate is the rate at which INV reports disease progression later than BICR relative to the total number of discrepancies. Differences in EDR and/or LDR between treatment arms may indicate investigator bias in favor of one arm. Based on simulations of sensitivity and specificity, Amit et al. suggest that a negative discordance in EDR and/or a positive discordance in LDR ≥0.075 is evidence for potential investigator bias in favor of the treatment arm. In OVAR16 there was good agreement in EDR and LDR between the pazopanib and placebo arms (Table 3). The small discordance in EDR was positive in the intent-to-treat population (EDR pazopanib minus EDR placebo = 0.02) and there was no discordance in LDR, suggesting that there was no bias in favor of the experimental arm in this study.

These findings are comparable to those of Burger et al. [17] who performed a similar comparison using the results from GOG-0218. In that

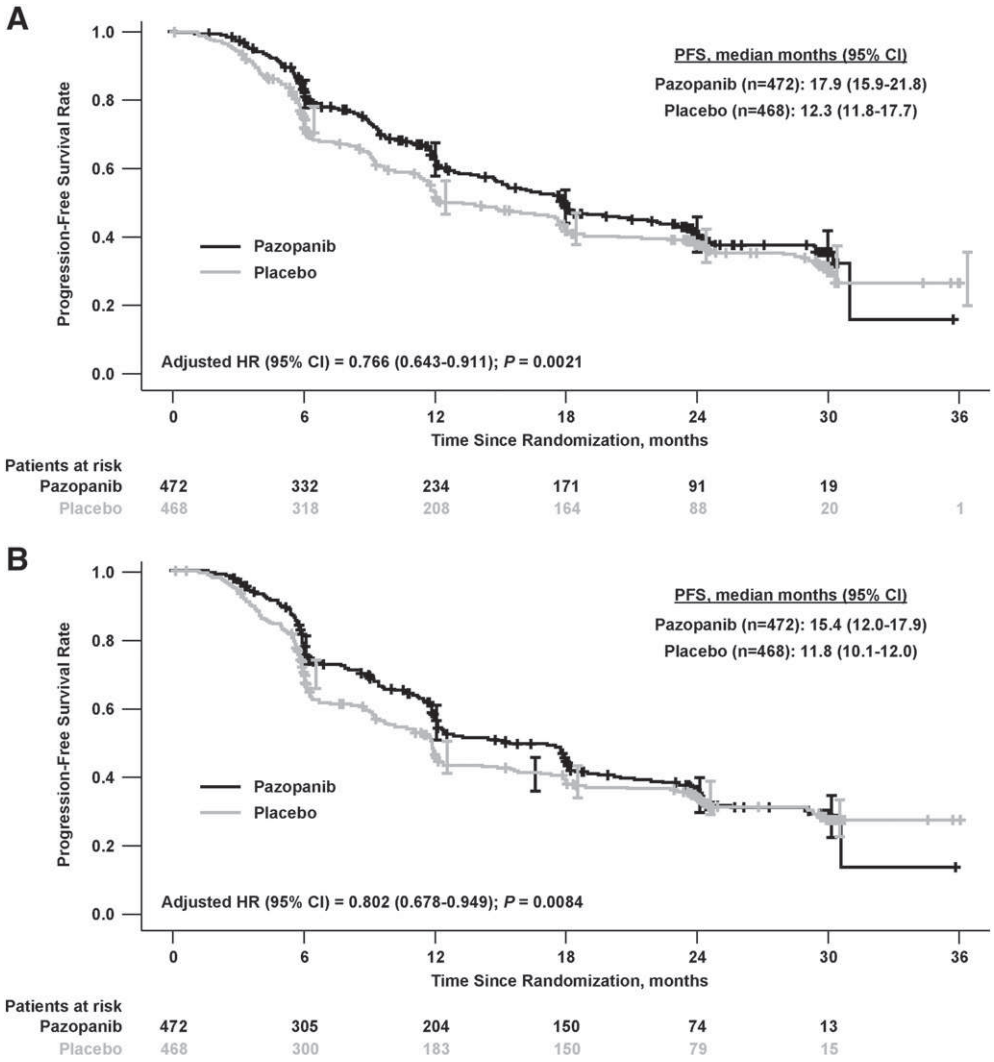

Fig. 1. Kaplan–Meier estimates of progression-free survival (PFS) per RECIST. Panel A: PFS by local investigator (INV). Panel B: PFS by blinded, independent central review (BICR). CI, confidence interval; HR, hazard ratio.

Table 2
Comparison of progression-free survival (PFS) timing: local investigator (INV) versus blinded independent central review (BICR).

	ITT population		200-patient subset	
	Pazopanib ($N = 472$)	Placebo ($N = 468$)	Pazopanib ($N = 105$)	Placebo ($N = 95$)
Progression by INV, *n* (%)				
n	237	273	58	56
PD by BICR	210 (89)	249 (91)	50 (86)	52 (93)
PD same time as INV	153 (65)	199 (73)	39 (67)	47 (84)
PD later by INV	55 (23)	46 (17)	11 (19)	5 (9)
PD earlier by INV	2 (1)	4 (1)	0	0
Censored by BICR	27 (11)	24 (9)	8 (14)	4 (7)
Censored by INV, *n* (%)				
n	235	195	47	39
Censored by BICR	188 (80)	155 (79)	40 (85)	33 (85)
Censored same time as INV	173 (74)	147 (75)	35 (74)	28 (72)
Censored later by INV	14 (6)	4 (2)	5 (11)	2 (5)
Censored earlier by INV	1 (<1)	4 (2)	0	3(8)
PD by BICR	47 (20)	40 (21)	7 (15)	6 (15)
Event concordance rate, %[a]	84	86	86	89

Abbreviations: ITT, intent-to-treat; PD, disease progression.
[a] Proportion of patients with PD or censored by both INV and BICR.

analysis, discordance was positive for EDR and negative for LDR between the control group and the bevacizumab-throughout group, suggesting that the INV analysis was not confounded by investigator bias. These results taken together suggest that even in ovarian cancer, where radiologic assessment of disease progression is sometimes regarded as very difficult [13], PFS by INV is a reliable measurement of treatment benefit.

The US FDA has considered the use of audit methodologies rather than a complete review of all patient scans to evaluate the reliability of INV assessments of PFS [13]. Use of an audit strategy could reduce the cost and complexity of phase 3 trials while retaining the possibility of detecting bias. As an example of how such an audit could have been applied to OVAR16, we performed a post-hoc analysis of data from 200 patients who were randomly selected prior to treatment unblinding. In this exploratory subset analysis, concordance rates were in good agreement with those of the overall analysis (Table 2). Additionally, analysis of discrepancy rates in the 200-patient subset demonstrated a positive discordance in EDR and a small positive discordance in LDR (0.03) that was below the threshold suggested by Amit et al. as associated with potential bias. To our knowledge, these results are the first to demonstrate that using a prospectively defined, random sample for BICR in the setting of first-line maintenance for ovarian

Table 3
Discrepancy rates: local investigator (INV) versus blinded independent central review (BICR).

	ITT population		200-patient subset		Amit et al. meta-analysis [12]	
	Pazopanib ($N = 472$)	Placebo ($N = 468$)	Pazopanib ($N = 105$)	Placebo ($N = 95$)	Experimental[a]	Control[a]
Early discrepancy rate	0.12	0.10	0.138	0.071	0.45	0.41
Late discrepancy rate	0.70	0.70	0.58	0.55	0.33	0.33

Abbreviation: ITT, intent-to-treat.
[a] These data represent the mean from 12 studies.

cancer would have led to the same conclusions, in terms of lack of evidence of bias and presence of treatment benefit, as the analysis of the full study population.

In summary, OVAR16 demonstrated that maintenance therapy with pazopanib was associated with a significant PFS benefit in patients with AEOC whose disease had not progressed following first-line therapy. Assessments of PFS by INV and BICR were highly concordant, thereby supporting the reliability of investigator-assessed PFS as the primary endpoint in AGO-OVAR16. A random sample audit may be an appropriate and sufficient method to confirm a lack of bias in future clinical trials in patients with AEOC.

Conflict of interest statement
du Bois has received grants from Roche and AstraZeneca, lecture honoraria from AstraZeneca, and advisory board reimbursement from Boehringer Ingelheim (all unrelated to the submitted work). **Floquet** has received honoraria from Roche and non-financial support from Roche, GlaxoSmithKline, PharmaMar, and Merck Sharp & Dohme (all unrelated to the submitted work). **Friedlander** reports honoraria from Roche for lectures and non-financial support from AstraZeneca (all unrelated to the submitted work). **Herzog** reports participation in advisory boards with Genentech, Morphotek, and AstraZeneca (all unrelated to the submitted work). **Monk** has received consulting and speaker's bureau honoraria from GlaxoSmithKline and his institution has received grants from GlaxoSmithKline (unrelated to the submitted work). **Vergote** reports consulting/advisory roles with Amgen, Array BioPharma, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, EISAI, Eli Lilly, Endocyte, Fresenius, GE Healthcare, GlaxoSmithKline, Hoffmann-La Roche, Intuitive Surgical, Janssen-Cilag, Menarini Ricerche, Merck Sharp & Dohme, Morphotek, Nektar Therapeutics, Novo Nordisk, Oasmia Pharmaceutical, PharmaMar, Phillips Gilmore Oncology, Quintiles, Sanofi-Aventis, Schering-Plough, Sigma-Tau Pharmaceuticals, Telik (now Mabvax), and TRM Oncology; contracted research from Morphotek, Exelixis, Lilly, Amgen, and Roche; research grants from Algeta, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cancer Research UK, Chugai Pharma, EISAI, Exelixis, Fresenius, GlaxoSmithKline, Hoffmann-La Roche, I.R.I.S., IBCSG, Janssen-Cilag, Medinova, Merck Sharp & Dohme, Merrimack Pharmaceutic, Morphotek, Nektar Therapeutics, Nerviano Medical, Novartis, Pfizer, Quintiles, Roche, SAKK, Sandoz, Sanofi-Aventis, Schering-Plough, Vifor Pharma, and Wyeth Research. **Crescenzo**, **Barrett**, **Wang**, and **Mitrica** are GlaxoSmithKline employees. **Calvert**, **Colombo**, **Del Campo**, **Fiane**, **Isonishi**, **Kim**, **Meier**, **Pisano**, and **Reinthaller** report no potential conflict of interest.

Table 4
Summary of progression reasons, intent-to-treat population.

	Pazopanib ($N = 472$)		Placebo ($N = 468$)	
	INV	BICR	INV	BICR
Radiologic PD assessments, *n*	233	277	279	312
New lesion only, *n* (%)	214 (92)	219 (79)	257 (92)	250 (80)
New lesion and non-target lesion PD, *n* (%)	7 (3)	51 (18)	14 (5)	54 (17)
New lesion, non-target lesion PD, and target lesion PD, *n* (%)	0	3 (1)	0	3 (<1)
New lesion and target lesion PD, *n* (%)	2 (<1)	1 (<1)	3 (1)	2 (<1)
Non-target lesion PD only, *n* (%)	8 (3)	2 (<1)	3 (1)	3 (<1)
Target lesion PD only, *n* (%)	1 (<1)	1 (<1)	2 (<1)	0
Non-target lesion PD and target lesion PD, *n* (%)	1 (<1)	0	0	0

Abbreviations: BICR, blinded independent central review; INV, local investigator; PD, disease progression.

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