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ORIGINAL ARTICLE

Quality of life in patients with advanced epithelial ovarian cancer (EOC) randomized to maintenance pazopanib or placebo after first-line chemotherapy in the AGO-OVAR 16 trial. Measuring what matters—patient-centered end points in trials of maintenance therapy

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Background: Health-related quality of life (HRQoL) was a secondary end point in AGO-OVAR 16, which randomized 940 patients with EOC after first-line chemotherapy to maintenance pazopanib (PZ) or placebo (P). Additional post hoc analyses were carried out to investigate additional patient-centered end points.

Patients and methods: HRQoL was measured with EORTC-QLQ-C30, QLQ-OV28 and EQ-5D-3L. Pre-specified end points included mean differences in HRQoL between treatment arms. Exploratory analyses included quality-adjusted progression-free survival (QAPFS), impact of specific symptoms and progressive disease (PD) on HRQoL and time to second-line chemotherapy. The objective was to provide clinical perspective to the significant median PFS gain of 5.6 months with PZ.

Results: There were statistically significant differences between PZ and P in QLQ-C30 global health status [5.5 points; 95% confidence interval (CI), 0.7–10.4, $P = 0.024$] from baseline to 25 months, but not EQ-5D-3L (0.018 points; 95% CI − 0.033 to 0.069, $P = 0.485$). The impact of diarrhea was captured in QLQ-OV28 Abdominal/GI-Symptoms scale (8.1 points; 95% CI 3.6–12.5, $P = 0.001$). QAPFS was 386 days (95% CI 366–404 days) with PZ versus 359 days (95% CI 338–379 days) with placebo ($P = 0.052$). PD was associated with a decline in HRQoL ($P < 0.0001$). Median time to second-line chemotherapy was 19.7 months with PZ and 15.0 months with P [hazard ratio (HR) 0.72, 95% CI 0.69–0.86, $P = 0.0001$].

Conclusions: There were small to no significant mean score differences in global HRQoL and EQ5D-3L between PZ and placebo, respectively, despite the increased toxicity of PZ. Exploratory end points including QAPFS, impact of specific symptoms on HRQoL during treatment and at PD help place the PFS gain with PZ in context and interpret the results. Additional patient-centered end points should be considered in trials of maintenance therapy in EOC beyond mean differences in HRQoL scores alone, to support the benefit to patients of prolongation of PFS.

Clinical Trials Registration Number: NCT00866697

Key words: ovarian cancer, maintenance pazopanib, quality of life, quality-adjusted progression-free survival

Introduction

Epithelial ovarian cancer (EOC), which includes fallopian tube and peritoneal cancer, remains the most important cause of gynecological cancer deaths in developed countries [1]. The majority of patients have advanced stage disease at diagnosis and 80% will relapse following surgery and chemotherapy and then commence second line chemotherapy. Multiple randomized trials [2–9] of maintenance therapies have been conducted following chemotherapy in EOC with disappointing results. A recent meta-analysis concluded that maintenance chemotherapy was associated with increased toxicity but no significant improvement in progression-free survival (PFS) or overall survival (OS) [10]. There is ongoing interest in investigating other agents, such as targeted therapies in the maintenance setting, e.g. bevacizumab, an angiogenesis inhibitor following first-line chemotherapy, demonstrated a significant PFS benefit, although no increase in OS [8, 9] or impact on health-related quality of life (HRQoL) [11, 12].

Pazopanib (PZ) is an oral tyrosine kinase inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and c-KIT. In the randomized double-blinded placebo-controlled phase III AGO-OVAR16/VEG110655 trial (NCT00866697), maintenance PZ for up to 2 years after completion of first-line chemotherapy in women with advanced EOC significantly improved PFS over placebo [hazard ratio (HR), 0.77; 95% confidence interval (CI) 0.64–0.91; $P = 0.0021$; median PFS 17.9 with PZ versus 12.3 months with placebo) [2]. There was a higher incidence of grade 3 and 4 adverse events (AE) in the PZ arm (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40), which led to dose reductions in 58% of patients and early discontinuation due to AE in 33% of patients.

HRQoL was a secondary end point in the AGO-OVAR16 trial with pre-specified end points being the mean change scores in HRQoL in the 'on-treatment' patients during maintenance treatment and the impact of AE's on overall HRQoL. We present also additional post hoc exploratory analyses to determine whether the significant 5.6-month prolongation in median PFS associated with PZ provided a 'meaningful benefit' to patients or if the PFS prolongation with maintenance PZ was counterbalanced by the toxicities of therapy. Our exploratory patient-reported outcome (PRO) hypotheses are as follows: PZ would be associated with superior quality-adjusted PFS (QAPFS); PD would result in a significant decline in HRQoL and maintenance PZ would significantly delay the time to second-line chemotherapy which may be considered worthwhile by patients. The overarching objective of this article is to stimulate discussion about selecting the most informative PRO end points that matter to patients in future trials of maintenance therapy in EOC which are essential for supporting and interpreting of the primary end point PFS result.

Patients and methods

Study design

In the AGO-OVAR16 trial, 940 patients with advanced EOC whose disease had not progressed at the completion of first-line platinum-based chemotherapy were randomly assigned to receive either pazopanib (800 mg od) or placebo [2]. Patients continued with the assigned treatment for 24 months unless they developed recurrent disease, unacceptable toxicity or withdrew consent (supplementary Figure S1, available at *Annals of Oncology* online).

HRQoL assessments

HRQoL was assessed using European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Module 30 (QLQ-C30) [13], ovarian cancer module (QLQ-OV28) and EuroQoL EQ-5D-3L [14]. Questionnaires were completed at baseline, week 13 and month 7, 10, 13, 16, and 25. For patients who discontinued study drug early, HRQoL assessments were scheduled at the end of treatment and at final visit 4 weeks later. The manuals of QLQ-C30, QLQ-OV28, and EQ-5D-3L were used to calculate the scores. Compliance rates with per-protocol scheduled HRQoL assessments were recorded.

Statistical analyses

Linear mixed-model repeated-measures analyses adjusting for score at baseline, time and a treatment-by-time interaction were used to estimate the difference in mean changes from baseline to month 25 between treatment groups on QLQ-C30, QLQ-OV28 scales and the EQ-5D-3L utility score for patients on treatment. Estimates of the least-squares means for treatment effects within and between treatment groups over time were calculated with corresponding SEs, respectively, 95% CI (without imputation for missing data). The clinical significance of differences between treatment arms was based on minimally important differences (MID) determined by Cocks et al. [15] and Pickard et al. [16] for the QLQ-C30 and the EQ-5D-3L, respectively. No MID has been determined for the QLQ-OV28 module [17].

QAPFS incorporates PFS and HRQoL into single measure to evaluate the net clinical benefit of therapy and was calculated as the product of the adjusted mean estimate of the EQ-5D-3L utility score calculated from time of randomization to end of follow-up [estimated with repeated measures generalized equation estimation (GEE)], multiplied by the total area under the PFS-curve acc. to Glasziou et al. [18]. This represents restricted mean estimates until the end of treatment period adjusted for EQ-5D-3L, based on the intention-to-treat population (all randomized patients who had at least one item of EQ-5D-3L). In order to generate CIs and *P* values associated with differences between treatment groups, 1000 bootstrap-samples with replacement were generated. Subgroup analyses of QAPFS were also carried out for the Asian and the non-Asian patient cohort due to significant differences in AE, which led to dose reductions in 75% of Asian patients [2].

Comparison of QLQ-C30 global health status (GHS) and the EQ-5D-3L utility index up to 2 months before and at least 2 weeks after PD was done for patients whom data were available using paired *t*-test.

Results

Patient population

The baseline mean HRQoL scores were comparable between treatment arms (supplementary Table S1, available at *Annals of Oncology* online). Patient compliance with per-protocol scheduled 'on-treatment' HRQoL assessments was high: 894 of 940 randomized patients (95%) had baseline HRQoL scores. Rates for specific questionnaires of patients on treatment ranged from 95% at baseline to 80% at month 25. However, the overall compliance based on the number of randomized patients decreased dramatically over time (supplementary Figure S2, available at *Annals of Oncology* online).

Treatment differences on HRQoL scales

Results of the repeated mixed model analyses for QLQ-30 GHS, QLQ-OV28 scale 'abdominal/GI symptoms' and EQ-5D-3L score are presented in Figure 1. Changes from baseline in the QLQ-C30 GHS (Figure 1A) showed statistically significant differences between treatment arms in favor of P at *week 13* (4.4 points; 95% CI 2.0–6.9) $P < 0.001$; $N_{(PZ)} = 293$; $N_{(P)} = 393$), *month 7* (5.6 points; 95% CI 2.7–8.6, $P < 0.001$; $N_{(PZ)} = 223$; $N_{(P)} = 316$), *month 10* (6.3 points; 95% CI 3.6–9.2, $P < 0.001$; $N_{(PZ)} = 184$; $N_{(P)} = 240$), and *month 25* (5.5 points; 95% CI 0.7–10.4, $P = 0.03$; $N_{(PZ)} = 53$; $N_{(P)} = 92$).

Changes from baseline in the QLQ-OV28 scale 'abdominal/GI Symptoms' (Figure 1B) showed statistically significant differences between treatment arms in favor of placebo at *week 13* (5.7 points; 95% CI 3.7–7.7, $P < 0.001$; $N_{(PZ)} = 289$; $N_{(P)} = 388$), *month 7* (8.7 points; 95% CI 6.2–11.3, $P < 0.001$; $N_{(PZ)} = 225$; $N_{(P)} = 308$), *month 10* (8.6 points; 95% CI 5.8–11.4, $P < 0.001$; $N_{(PZ)} = 187$; $N_{(P)} = 232$), *month 13* (8.6 points; 95% CI 5.6–11.7, $P = 0.001$; $N_{(PZ)} = 141$; $N_{(P)} = 187$), *month 16* (4.4 points; 95% CI 0.6–8.3, $P = 0.025$; $N_{(PZ)} = 88$; $N_{(P)} = 133$), and *month 25* (8.1 points; 95% CI 3.6–12.5, $P = 0.001$; $N_{(PZ)} = 54$; $N_{(P)} = 91$).

Changes from baseline in the EQ-5D-3L score (Figure 1C) showed statistically significant differences between treatment arms in favor of placebo at *week 13* (0.043 points; 95% CI 0.017–0.069, $P = 0.001$; $N_{(PZ)} = 293$; $N_{(P)} = 376$), *month 7* (0.046 points; 95% CI 0.016–0.076, $P = 0.003$; $N_{(PZ)} = 226$; $N_{(P)} = 303$), and *month 10* (0.051 points; 95% CI 0.019–0.082, $P = 0.002$; $N_{(PZ)} = 181$; $N_{(P)} = 228$), but not at *month 13* (0.017 points; 95% CI 0.017–0.051, $P = 0.319$; $N_{(PZ)} = 138$; $N_{(P)} = 185$), *month 16* (0.028 points; 95% CI 0.015–0.072, $P = 0.203$; $N_{(PZ)} = 87$; $N_{(P)} = 129$), and *month 25* (0.018 points; 95% CI −0.033 to 0.069, $P = 0.485$; $N_{(PZ)} = 56$; $N_{(P)} = 88$). Figure 2 shows that the proportion of patients in the PZ arm answering that they experienced 'quite a bit' or 'very much diarrhea' (18%–28% of patients) as well as the proportion of patients without any diarrhea (43%–54% of patients) did not vary substantially over the course of the 2-year study. Consequently, diarrhea reflected in the QLQ-OV28 Abdominal/Gastrointestinal (GI) symptom scale (Figure 1B) and the QLQ-C30 scale 'diarrhea' (supplementary Figure S3, available at *Annals of Oncology* online) was significantly higher in the PZ arm with a large detriment compared with placebo across time. The QLQ-OV28 scale 'attitude to disease/treatment' showed statistically significant differences for the change from baseline between treatment arms in favor of placebo at *week 13* (5.7 points; 95% CI 2.4–9, $P < 0.001$; $N_{(PZ)} = 291$; $N_{(P)} = 378$), *month 7* (7.2 points; 95% CI 3.6–10.8, $P < 0.001$; $N_{(PZ)} = 223$; $N_{(P)} = 299$), *month 10* (5.8 points; 95% CI 1.9–1.9, $P < 0.004$; $N_{(PZ)} = 185$; $N_{(P)} = 228$), *month 13* (5.4 points; 95% CI 1.2–9.5, $P = 0.011$; $N_{(PZ)} = 138$; $N_{(P)} = 182$), and at *month 25* (10.8 points; 95% CI 4.3–17.2; $P = 0.001$; $N_{(PZ)} = 54$; $N_{(P)} = 90$) (supplementary Figure S4, available at *Annals of Oncology* online). Other symptom or functional subscales demonstrated either no or very small detriments for pazopanib (supplementary Figure S5, available at *Annals of Oncology* online).

Treatment differences after PFS adjustment for EQ-5D-3L (QAPFS)

QAPFS was 386 days (95% CI 366–404 days) in the PZ arm versus 359 days (95% CI 338–379 days) in the placebo arm ($P = 0.052$) (Table 1), corresponding to a restricted mean difference of 27 days (adjusted with mean EQ-5D-3L for PZ 0.780 and for placebo 0.850, as estimated by the GEE model), compared with 48 days unadjusted for health status ($P = 0.006$) (Table 1A). In the non-Asian subgroup, there was a significant difference in QAPFS ($P = 0.018$) of slightly more than one month (39 days) in favor of PZ (adjusted with mean EQ-5D-3L for PZ 0.779, for placebo 0.794), but no statistically significant difference ($P = 0.372$) in the East-Asian subgroup (Table 1B) (adjusted with mean EQ-5D-3L for PZ 0.817, for placebo 0.845).

Comparison of HRQoL scores before and after disease progression

Out of overall 577 subjects with PD, 206 (35.7%) patients with QLQ-C30 GHS and 200 (34%) patients with the EQ-5D-3L utility index had at least one assessment before and after PD. The comparison of QLQ-C30 GHS scores before and after progression demonstrated a statistically significant deterioration with mean score 74.3 (SD 17.03) before PD for placebo and 66.9 (SD 22.02) after PD ($P < 0.0001$), for PZ with mean score 71.0 (SD 18.05) before PD and 60.5 (SD 23.79) after PD ($P < 0.0001$), as well as pooled across treatment arms ($P < 0.0001$). Consistent with these results EQ-5D-3L scores were significantly worse for post PD assessments (supplementary Table S2, available at *Annals of Oncology* online). This deterioration in HRQoL could not be attributed solely to second-line therapy as scores before the onset of second-line therapies, as well as after, were significantly different from scores before progression when pooling data from both treatment arms ($P < 0.0001$).

Delay in commencing second-line chemotherapy

Maintenance therapy with PZ was associated with a significant delay in the initiation of second line chemotherapy with the median time to second-line treatment of 19.7 months in PZ arm and 15.0 months in the placebo (HR 0.72, 95% CI 0.69–0.86, $P = 0.0001$, supplementary Figure S6, available at *Annals of Oncology* online).

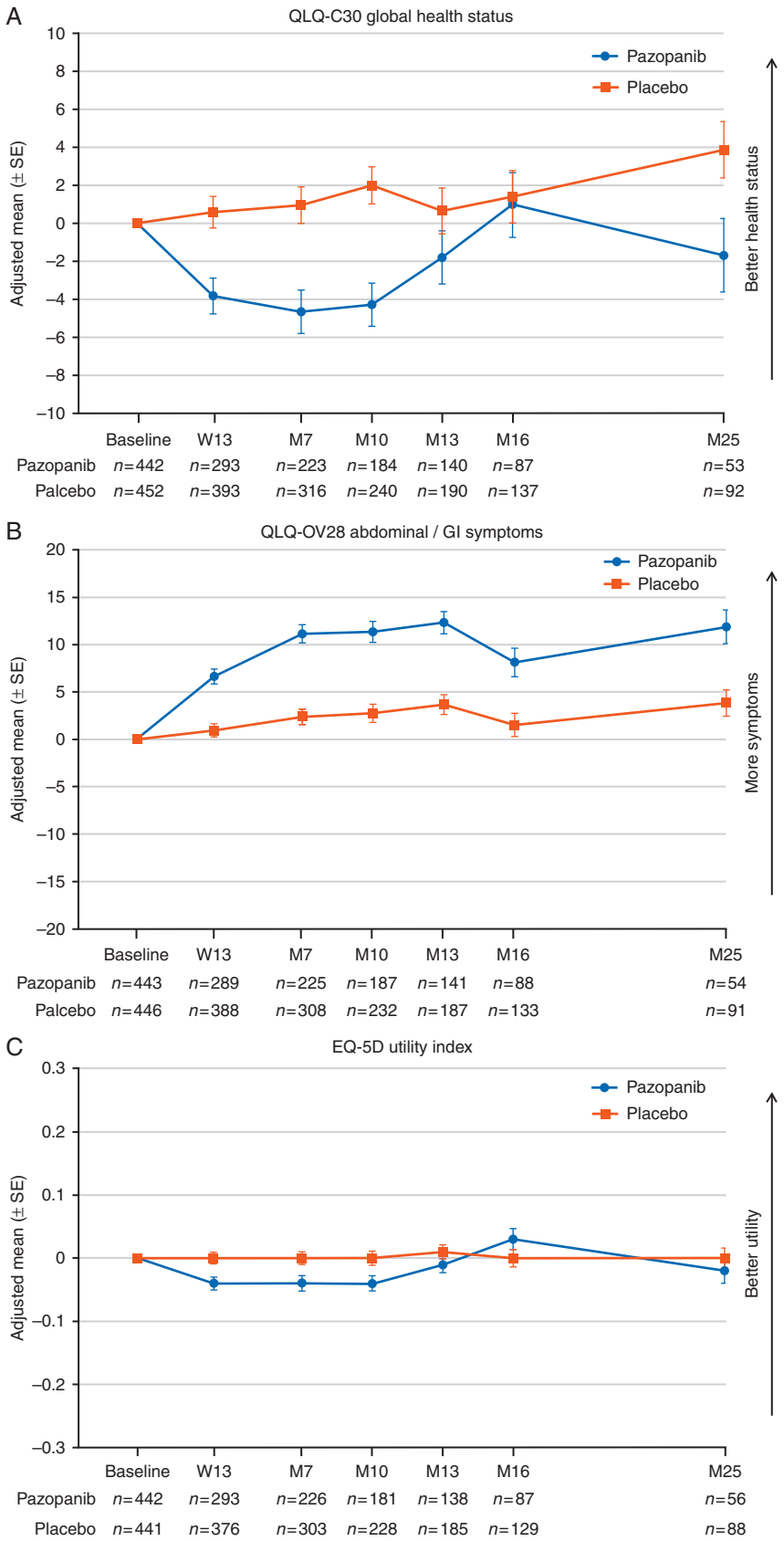

Figure 1. Mixed-model repeated-measures analyses of the European Organization for Research and Treatment of Cancer (EORTC) (A) Quality of Life Questionnaire Module 30 (QLQ-C30-GHS), (B) Ovarian Cancer Module 28 (QLQ-OV28- abdominal/gastro-intestinal symptoms), and (C) EuroQoL EQ-5D-3L. M, month; SE, standard error of the mean; W, week.

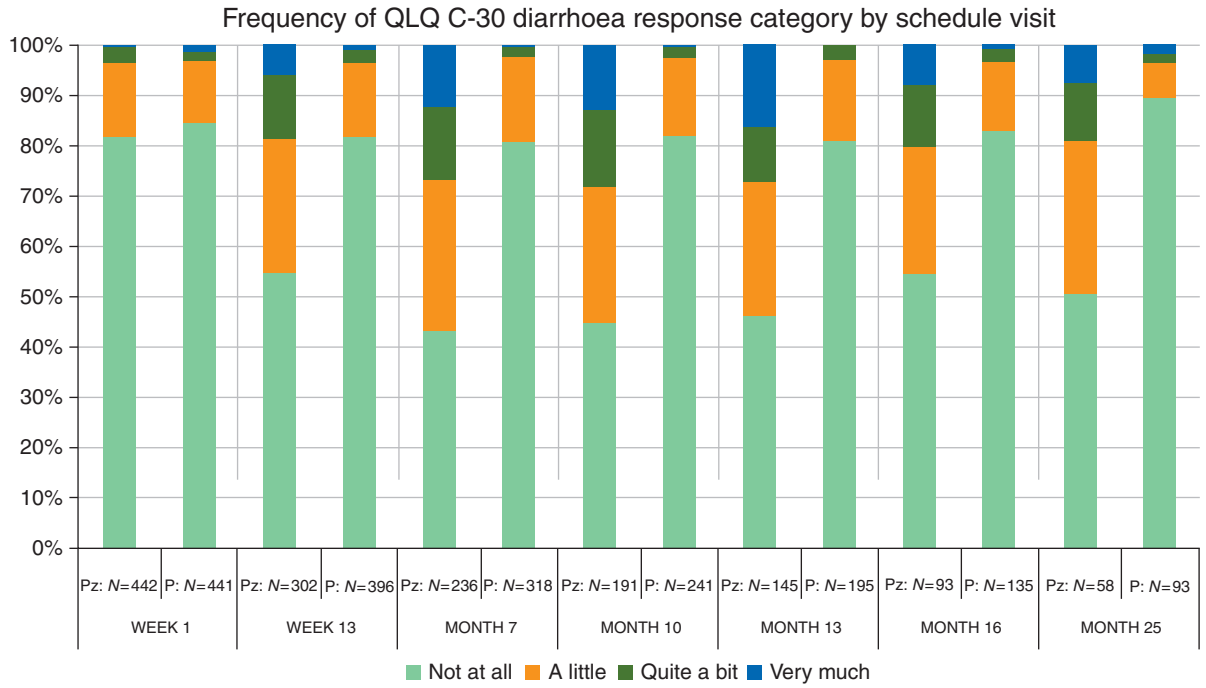

Figure 2. Proportion of responses reporting diarrhea in Quality of Life Questionnaire Module 30 (QLQ-C30) across time for the different study arms.

Table 1. Restricted mean progression-free survival time (PFS) and quality-adjusted progression free survival time (QAPFS) (days)

	PFS			QAPFS		
	Pazopanib	**Placebo**	**Difference**	**Pazopanib (PZ)**	**Placebo (PL)**	**Difference**
(A) Overall population						
Available *N*	*N* = 455	*N* = 464		*N* = 455	*N* = 464	
Restricted mean (day 731) (95% CI)	494 (472–517)	446 (421–469)	48 (17–82)	386 (366–404)	359 (338–379)	27 (−1 to 54)
P value	0.006			0.052		
(B) Subpopulations (Asian versus non-Asian)						
Asia (available *N*)	*N* = 104	*N* = 101		*N* = 104	*N* = 101	
Restricted mean (day 731) (95% CI)	512 (466–560)	528 (476–579)	−16 (−83 to 55)	418 (377–459)	446 (400–490)	−28 (−91 to 30)
P value	0.626			0.372		
Non-Asia (available *N*)	*N* = 351	*N* = 363		*N* = 351	*N* = 363	
Restricted mean (day 731) (95% CI)	488 (461–517)	424 (395–451)	65 (27–103)	375 (353–398)	336 (314–361)	39 (6–72)
P value	<0.001			0.018		

CI, confidence interval; PL, placebo; PZ, pazopanib.

Discussion

In AGO-OVAR 16 trial, there was a statistical significant detriment in mean changes in HRQoL scores with PZ relative to placebo from baseline to month 25 for GHS in the EORTC QLQ-C30 (5.5 points; $P = 0.024$) and QLQ-OV28 Subscale 'abdominal/GI symptoms' (8.1 points, $P = 0.001$), but not for EQ-5D-3L utility index (0.02 points, $P = 0.485$). However, the magnitude of difference for both QLQ-OV28 and QLQ-C30, although statistically significant were within the ranges that are interpreted as 'small' [15] but nevertheless still clinically important according to published interpretation guidelines for MIDs [15]. Functional and selected symptom subscales also found either no or only a small statistically significant detriment for PZ with exception of the diarrhea subscale, with significantly worse diarrhea in the PZ group at all-time points (medium effect size) [15]. Throughout the 24 months' treatment period, over 20% of patients in the PZ group reported either 'quite a bit' or 'very much diarrhea' at any time. This was a major contributor to dose reductions and treatment discontinuation.

Although there were relatively small detriments in the mean differences in patients' global evaluations of quality of life [as

represented by QLQ C-30 GHS and utility index (EQ-5D)] between patients on PZ and placebo, given the adverse effects associated with PZ (particularly diarrhea), these differences are nonetheless both statistically and clinically significant. Notably, 33% of patients discontinued pazopanib and 58% required a dose reduction because of AEs. The pre-specified HRQoL analyses are in keeping with the standard approaches to measure HRQoL in EOC-trials, but taken alone has limitations in interpreting the impact of treatment on patients. The fundamental question is whether the statistically significant median 5.6 months' prolongation of PFS (which possibly overestimates the true difference as reflected by the mean restricted difference of 1.5 months) with PZ maintenance conveys a real benefit and is considered worthwhile by patients given the associated toxicity of treatment and whether comparing mean scores in HRQoL measures between treatment and placebo are the best way to determine benefit. This is particularly important to consider in this patient population where the majority did not have cancer-related symptoms at study entry.

A survey of 1400 women with EOC reported that both PFS and OS were considered important end points by patients, but adverse effects of treatment were also very important and most would trade-off a reduction in PFS to avoid or reduce significant side-effects particularly when the treatment was not curative [19]. A smaller survey in women with EOC also found that patients were willing to trade-off PFS for fewer side-effects. There are no data on patient preferences and trade-offs they would make in first-line maintenance setting and what value is placed on delaying the time to second-line chemotherapy.

It is therefore crucial to have clearly predefined PRO hypotheses in trials of maintenance treatment of EOC and to include patient centered end points and patient preferences so as to measure what matters to patients. However, it was only after the study was completed and we recognized the limitations of our pre-specified HRQoL end point that we developed post hoc hypotheses that informed the exploratory analyses. With the benefit of hindsight these should have been included in the original study design and protocol. We carefully considered what could help support the PFS primary end point and place the results in perspective for clinicians and patients given the adverse effects associated with PZ. QAPFS is a summary measure of the trade-off between treatment efficacy and its impact on HRQoL which has not been used in trials of maintenance therapy in EOC, but has been reported to be useful in interpreting the results of clinical trials in other cancers [18, 20]. Although the analysis showed a trend in favor of PZ, it failed to reach statistical significance in the overall population which is a clear demonstration of how the AE's of PZ negate the PFS gain. However, amongst the non-Asian women, PZ was better tolerated and associated with a significant improvement in QAPFS suggesting that maintenance PZ may of benefit in this subgroup of patients.

Progressive disease may be associated with new or worsening cancer-related symptoms and a decline in HRQoL although interestingly this is poorly documented. The AGO-OVAR16 trial protocol mandated HRQoL data collection post treatment discontinuation. Caution needs exercised when interpreting the statistically significant comparisons of scores observed for QLQ-C30 GHS and EQ-5D-3L before and after PD as these are based only on one-third patients who had PD and hence the results are hypothesis generating. Notwithstanding, the findings observed in AGO-OVAR16 trial population at progression are clinically plausible and supported by another study that reported a similar conclusion [21]. There are also data to suggest that second-line therapy results in greater detriment on HRQoL than first-line therapy [21]. Therefore, prolonging PFS, delaying symptomatic recurrence, and prolonging time to next chemotherapy may be considered important and worthwhile by patients with EOC. These end points should also be measured in future maintenance trials.

Our exploratory analyses have several strengths as well as limitations. Data were prospectively, systematically collected, and there was relatively good compliance but the number of questionnaires filled out decreased over time. Even with some missing data, there is still a substantial amount of data available for hypothesis-generating analyses. Our exploratory analyses were limited because they were post hoc, but our intention is to stimulate discussion about the most appropriate PRO end points to include in future trials of maintenance therapy. Importantly, if PROs are to be assessed with the same rigour as other trial end points, PRO end points should be clearly defined and justified as a clinical trial objective. There should be carefully considered pre-specified PRO hypotheses as these will impact on the selection of questionnaires as well as on the timing of their administration. Standardized guidance for administering PRO questionnaires should be available and it is imperative to focus on minimizing missing PRO data and promoting the collection of high quality PRO data to avoid bias. There should also be pre-specified procedures with how to deal with missing data. Finally, trials should continue to collect PRO questionnaires on all patients including those who drop out for toxicity and progression.

In conclusion, the lessons learned from analyzing HRQoL in the AGO-OVAR16 trial have highlighted the importance of looking beyond only reporting the mean difference in HRQoL scores between on treatment groups of patients. The PRO hypotheses, the PRO questionnaires, and the PRO end points as well as patient preferences all require careful consideration when designing future maintenance trials. Such analyses will help underpin PFS as the primary end point and support regulatory submissions and drug labelling as well as inform physicians and patients in treatment decisions.

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