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Paclitaxel with or without pazopanib for ovarian cancer relapsing during bevacizumab maintenance therapy: The GINECO randomized phase II TAPAZ study

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HIGHLIGHTS

- We tested anti-angiogenic rechallenge for ovarian cancer progressing on bevacizumab.
- Pazopanib rechallenge did not improve efficacy vs paclitaxel alone.
- Adding pazopanib to paclitaxel increased toxicity, compromising paclitaxel delivery.
- The combination had a detrimental effect on abdominal/gastrointestinal symptoms.

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ABSTRACT

Background. Anti-angiogenic rechallenge with bevacizumab plus chemotherapy is effective in recurrent ovarian cancer (rOC); however, data are limited on tyrosine kinase inhibitors after progression on maintenance bevacizumab.

Methods. In the randomized phase II TAPAZ trial, patients with rOC during the first year of bevacizumab maintenance therapy were assigned 2:1 to either weekly paclitaxel 65 mg/m^2 plus pazopanib 600–800 mg daily or standard weekly paclitaxel 80 mg/m^2. The primary endpoint was 4-month progression-free survival (PFS) rate.

Results. Overall, 116 patients were randomized and treated: 79 with combination therapy and 37 with single-agent paclitaxel. Median follow-up was 13.1 months. There was no difference between treatment arms in 4-month PFS rate (61% [95% CI, 51–73%] with the combination versus 68% [95% CI, 54–85%] with paclitaxel alone), median PFS (4.9 [95% CI, 4.1–6.1] versus 5.8 [95% CI, 4.8–7.4] months, respectively) or median overall survival (13.6 versus 12.9 months, respectively). The combination was associated with more grade 3/4 toxicities (87% versus 70%, respectively) and toxicity-related paclitaxel discontinuations (22% versus 11%). Pazopanib was discontinued for toxicity in 44% of patients, most commonly for gastrointestinal and vascular events. There were two treatment-related deaths, both in the combination arm (pulmonary embolism and gastrointestinal perforation). At month 4, patient-reported outcomes deteriorated from baseline in the combination arm, particularly for abdominal/gastrointestinal symptoms, which showed a clinically important difference versus paclitaxel alone.

Conclusions. In rOC progressing during maintenance bevacizumab, adding pazopanib to paclitaxel did not improve efficacy, increased toxicity, and compromised chemotherapy delivery.

ClinicalTrials.gov registration: NCT02383251.

1. Introduction

Bevacizumab is an established therapy for newly diagnosed ovarian cancer (OC), given with carboplatin–paclitaxel and then continued as single-agent maintenance therapy, with or without a poly (ADP-ribose) polymerase (PARP) inhibitor [1–3]. Bevacizumab is also effective in bevacizumab-naïve recurrent OC combined with a platinum-based chemotherapy doublet [4–6] or non-platinum single-agent chemotherapy [7], depending on the platinum-free interval (PFI). In patients whose platinum-sensitive disease progresses following front-line bevacizumab-containing therapy, the benefit of bevacizumab rechallenge was demonstrated in the MITO16b/MANGO–OV2/ENGOT–ov17 trial [8]. However, data on anti-angiogenic rechallenge in early relapsing OC are scarce and there is limited evidence for alternative anti-angiogenic therapies after bevacizumab.

Pazopanib, a small-molecule tyrosine kinase inhibitor (TKI), significantly improved progression-free survival (PFS) when used after platinum-based primary chemotherapy for patients with non-progressive epithelial OC in the AGO-OVAR 16 trial [9]. The PFS benefit was accompanied by increased gastrointestinal adverse events (AEs) and a detrimental effect on health-related quality of life (HRQoL) and diarrhea [10]. In early relapsing recurrent OC, weekly paclitaxel is one of the most active treatments [11–14], and its potential anti-angiogenic properties [15] provide the rationale for combining weekly paclitaxel and pazopanib. Furthermore, in the AURELIA trial, in which the choice of single-agent chemotherapy was at the investigator's discretion, the most striking results in combination with bevacizumab were observed in the cohort receiving weekly paclitaxel [16].

Two randomized phase II trials have evaluated the addition of pazopanib to paclitaxel in recurrent OC: the Italian MITO11 trial in patients not previously exposed to anti-angiogenic therapy [17] and a US study predominantly in patients naïve to anti-angiogenic therapy [18]. Pazopanib-containing therapy significantly improved efficacy in MITO11 but not in the US study. Neither trial was designed or powered to detect a benefit from pazopanib specifically in bevacizumab-pretreated patients, but we speculated that a multi-kinase TKI targeting multiple pathways may have the potential to overcome resistance to bevacizumab. Therefore, to assess the impact of switching anti-angiogenic therapy after recurrence during maintenance bevacizumab following platinum-based therapy (in the front-line or relapsed setting), we designed a randomized phase II trial exclusively in bevacizumab-pretreated patients. Given the toxicity observed with pazopanib–paclitaxel in the two previous trials, we explored a lower pazopanib dose combined with reduced-dose paclitaxel. Here we report the final results.

2. Patients and methods

The primary objective of TAPAZ (ClinicalTrials.gov identifier: NCT02383251), a GINECO multicenter open-label non-comparative randomized phase II trial, was to evaluate the efficacy of pazopanib plus weekly paclitaxel in patients with OC that had relapsed during bevacizumab maintenance therapy.

Eligible patients had histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) stage IC–IV ovarian, peritoneal, or fallopian tube carcinoma and had received at least one prior platinum-based chemotherapy regimen with relapse within ≤12 months since the last dose of chemotherapy and during bevacizumab maintenance therapy. Patients previously treated with weekly single-agent paclitaxel were ineligible. Additional eligibility criteria included age ≥18 years, Eastern Cooperative Oncology Group performance status ≤1, life expectancy >3 months, adequate hematologic, hepatic, and renal function, and either measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) or evaluable disease according to Gynecological Cancer InterGroup CA-125 criteria. All patients provided written informed consent before undergoing any study-specific procedures.

Patients were randomized in a 2:1 ratio to combination therapy or single-agent paclitaxel using a minimization procedure stratified by: number of prior platinum-based treatment lines (1 versus 2), PFI (<6 versus 6–12 months), and baseline HRQoL (European Organisation for Research and Treatment of Cancer [EORTC] global health status/quality of life [GHS/QoL] score <50 versus ≥50). Combination therapy comprised weekly intravenous paclitaxel 65 mg/m^2 on days 1, 8, and 15 plus oral pazopanib 600 mg/day (with the option to increase to 800 mg/day if well tolerated; see Supplementary Appendix 1 for dose modifications) repeated every 28 days. Single-agent therapy comprised weekly intravenous paclitaxel 80 mg/m^2 on days 1, 8, and 15 every 28 days.

The primary endpoint was the 4-month PFS rate according to RECIST (version 1.1). Secondary endpoints included overall survival (OS), rates of overall response (partial or complete response) and stable disease according to RECIST (version 1.1), safety, and patient-reported outcomes (PROs). PROs analyses focused on the GHS/QoL, physical functioning, and fatigue symptom scales of the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and the abdominal/gastrointestinal and peripheral neuropathy symptom scales of the EORTC Quality of Life Questionnaire Ovarian Cancer Module (QLQ-OV28). An ancillary study investigated pharmacokinetic (PK) interactions between pazopanib and paclitaxel and relationships between pharmacogenetic polymorphisms, pazopanib PK, and clinical effects (see Supplementary Appendix 2).

Tumors were assessed every two cycles until disease progression. PROs were assessed at baseline, every 8 weeks for 6 months, and then every 3 months until disease progression. AEs were graded according to Common Terminology Criteria for Adverse Events (version 4.03). After disease progression, patients were followed every 3 months for survival status, PROs, AEs, and symptoms.

The planned sample size of 78 patients receiving combination therapy was calculated using a two-step Case–Morgan design, testing a null hypothesis of 3 months against an alternative hypothesis of 5 months for median PFS (with one-sided α of 5% and 85% power), assuming that 10% of patients would be non-evaluable. Planned inclusion of 39 patients receiving single-agent paclitaxel (2:1 randomization) resulted in a planned overall sample size of 117 patients. The Nelson–Aalen method was used to estimate the 4-month PFS rate with combination therapy. According to the Case–Morgan design, an interim analysis was performed after inclusion of 44 patients in the combination arm, allowing early trial termination for futility. PFS and OS were estimated using Kaplan–Meier methodology. For PRO analyses, mean change from baseline at 4 months was calculated, with 99% confidence intervals (CIs) reported for targeted dimensions and 95% CIs for other dimensions. The minimal important difference (MID) for mean change and mean difference between arms was specified as ≥5 points for EORTC questionnaires [19]. The primary efficacy analyses were performed on the intention-to-treat (ITT) population, defined as all randomized patients. PROs were analyzed in the modified ITT population, comprising all patients in the ITT population with HRQoL data at baseline and 4 months. Safety was analyzed in all patients who received at least one dose of study treatment.

The trial was conducted in accordance with the Principles of the Declaration of Helsinki, Good Clinical Practice Guidelines of the International Conference on Harmonisation, the European Directive on conduct of clinical trials, and all relevant laws in France.

3. Results

3.1. Patient population and treatment exposure

Between 18 June 2015 and 4 April 2019, 125 patients were enrolled and 116 treated (79 with paclitaxel–pazopanib combination therapy, 37 with single-agent paclitaxel; Fig. 1). Baseline characteristics were well balanced between treatment arms. Most patients had serous OC and 71% had a PFI <6 months (Table 1).

Treatment exposure is summarized in Table 2 and Supplementary Fig. S1. Consistent with the differing doses in the trial design, the mean weekly paclitaxel dose was higher for single-agent paclitaxel than the combination (Table 2). Patients receiving single-agent paclitaxel typically received more cycles of paclitaxel. A post hoc exploratory analysis evaluating the eight patients (six in the combination arm, two in the single-agent arm) who continued treatment for ≥13 cycles revealed no notable differences in baseline characteristics between these patients and the overall population (Supplementary Table S1).

3.2. Efficacy

The median follow-up was 13.1 months (range 1.2–56.3 months). The 4-month PFS rate (primary endpoint) was 61% (95% CI, 51–73%) with combination therapy and 68% (95% CI, 54–85%) with paclitaxel alone. Median PFS was 4.9 months and 5.8 months, respectively (Fig. 2A). According to the Case–Morgan statistical design, the *Z*-test statistic of 0.145 was below the rejection limit, thus the null hypothesis tested for the combination arm was retained. Median OS was 13.6 months with the combination versus 12.9 months with single-agent paclitaxel (Fig. 2B). Objective response rates were 20% (12 partial and four complete responses) and 19% (six partial and one complete response), respectively. An additional 50% and 57%, respectively, achieved stable disease as best response. In subgroup analyses pooling treatment arms, there was no difference in median PFS according to PFI (5.2 months [95% CI, 2.1–7.0 months] in patients with a PFI of <3 months, 4.9 months [95% CI, 3.8–6.1 months] for PFI 3–6 months and 5.8 months [95% CI, 4.1–5.6 months] for PFI >6 months).

3.3. Patient-reported outcomes

Compliance with QoL questionnaires exceeded 97% at baseline. At 4 months, 68 patients completed questionnaires (41/56 [73%] of those still on study in the combination arm; 27/29 [93%] in the single-agent arm), representing the QoL-evaluable population.

Among target PRO dimensions, mean change at 4 months showed a deterioration in each scale in the combination arm, exceeding the 5-point MID for GHS/QoL, physical functioning, fatigue, and peripheral neuropathy (Supplementary Fig. S2). Deterioration was less pronounced in the single-agent arm, and only physical functioning, fatigue, and peripheral neuropathy reached the 5-point MID. The only clinically important difference between treatment arms was for abdominal/gastrointestinal symptoms, which deteriorated in the combination arm (4.3-point mean change, 99% CI, −3.2 to 11.7) and improved in the single-agent arm (−1.3-point mean change, 99% CI, −12.9 to 10.4). Supplementary Table S2 shows results for other scales. Diarrhea worsened by 11.1 points (95% CI, 2.1–20.2) with combination therapy versus 2.5 (95% CI, −4.8 to 9.7) with single-agent paclitaxel, exceeding the 5-point MID between arms.

3.4. Safety

Toxicity-related treatment discontinuations occurred in 47% of patients receiving combination therapy versus 11% receiving paclitaxel alone. The most common causes of pazopanib treatment discontinuation (with or without paclitaxel) were gastrointestinal events (11 patients, including eight discontinuing because of diarrhea) and vascular effects (11 patients, including six discontinuing pazopanib because of hypertension). In the combination arm, pazopanib was interrupted for toxicity in 51% of patients and discontinued in 44%. Similar proportions of patients in the combination and single-agent arms required paclitaxel dose reductions for toxicity (23% versus 19%, respectively; Table 2). However, the combination regimen was associated with higher incidences of toxicity-related paclitaxel treatment interruption (33% versus 11%, respectively) and treatment discontinuation (22% versus 11%, respectively).

The combination was associated with a higher incidence of all-grade hypertension, diarrhea, thrombocytopenia, anorexia, and proteinuria compared with single-agent paclitaxel (Table 3). Grade ≥3 toxicities occurred in 87% of patients in the combination arm and 70% in the paclitaxel-alone arm; the most common grade ≥3 toxicity was hypertension (44% versus 8%, respectively). There were two fatal AEs, both in the combination arm (one gastrointestinal perforation considered to be possibly related to pazopanib and related to underlying disease; one pulmonary embolism considered to be possibly related to pazopanib and paclitaxel).

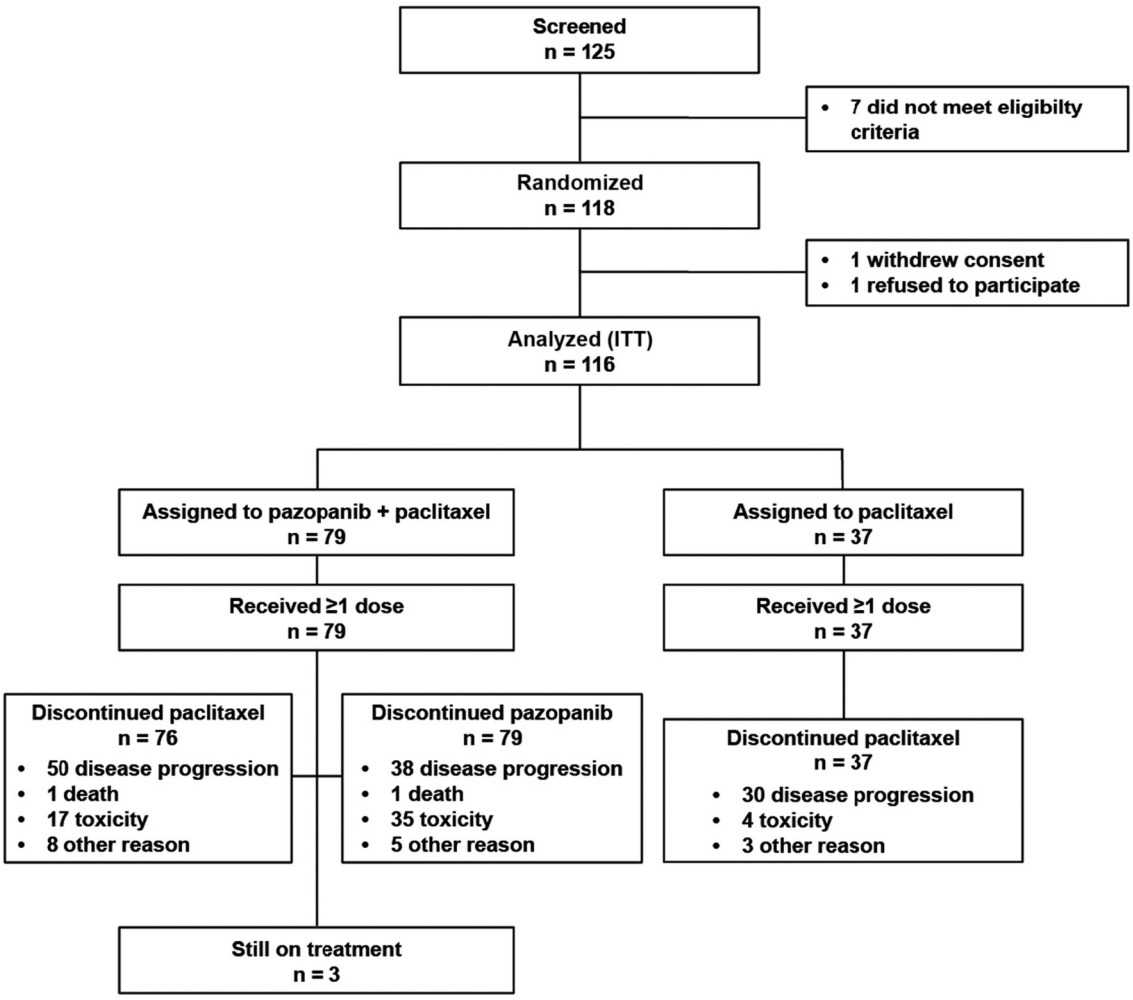

Fig. 1. Trial profile. ITT, intention-to-treat.

3.5. Pharmacokinetics

PK sampling was performed in 62 patients (78%) in the combination arm, of whom 56 were included in the PK analysis and for whom 51 had pharmacogenetic polymorphism data (see Supplementary Appendix 2).

Pazopanib plasma concentrations ranged from 5.41 to 95.1 μg/mL. At cycle 1, the median trough plasma concentration in patients treated with 600 mg/day (without dose interruptions/reductions) was 25.4 μg/mL (range 9.59–66.6) on day 7 ($n = 20$) and 22.8 μg/mL (range 9.11–54.7) on day 21 ($n = 42$). In 18 patients without dose interruptions/reductions, the mean difference in trough plasma concentrations between day 7 and day 21 was −12.6%, suggesting a potential interaction between pazopanib and paclitaxel (interquartile range −33.9 to 19.9; Wilcoxon paired test, $p = 0.34$).

No significant relationships between pazopanib plasma exposure and efficacy (PFS or OS) were detected (Supplementary Fig. S3). Patients experiencing vomiting at cycle 1 had higher plasma pazopanib exposure than those without vomiting (median area under the concentration–time curve at day 21: 1221 mg/L·h [95% CI 272–1560] versus 772 mg/L·h [95% CI 466–1371], respectively; Wilcoxon unpaired rank-sum test, $p = 0.024$).

4. Discussion

This is the first trial specifically to evaluate a switch anti-angiogenic strategy in OC by randomizing patients to an anti-angiogenic TKI (pazopanib) after progression during bevacizumab maintenance therapy following platinum-based therapy. Combining pazopanib with paclitaxel did not improve efficacy (PFS or OS) versus paclitaxel alone. Furthermore, the combination was associated with increased toxicity and treatment discontinuations, compromising chemotherapy delivery, and potentially explaining the trend towards a detrimental effect on efficacy. The combination also showed a negative impact on PROs, with greater deterioration in the mean score for each of the target scales than with paclitaxel alone. Consequently, the combination is not recommended for patients with OC relapsing during maintenance bevacizumab after platinum-based chemotherapy.

Our results are consistent with Richardson et al.'s results [18] showing no superiority of pazopanib–paclitaxel over paclitaxel, but differ from MITO11 results showing significant PFS benefit from the addition of pazopanib [17]. These differences may be partially explained by the patient population: in MITO11, all patients were bevacizumab naïve, whereas 22% of patients in the US trial had previously received bevacizumab. Additionally, the proportion of patients with a PFI of <6 months varied between trials: 100% in MITO11 versus 71% in TAPAZ and 51% in the US trial. These important differences may contribute to the apparent variation in outcomes, as the trials enrolled biologically distinct patient populations. There were too few patients in TAPAZ for meaningful subgroup analysis according to PFI. However, patients with a median PFI of <3 months did not appear to have worse outcomes than those with a PFI of 3–6 months.

Table 1
Baseline characteristics.

Characteristic, n (%)		Paclitaxel plus pazopanib ($n = 79$)	Paclitaxel alone ($n = 37$)
Median age (range), years		66 (42–85)	64 (46–82)
ECOG performance status[a]	0	26 (33)	20 (54)
	1	52 (66)	16 (43)
	2	1 (1)	0
Number of prior lines of platinum[b]	1	60 (76)	29 (78)
	2	19 (24)	8 (22)
Platinum-free interval, months[b]	<6[c]	56 (71)	26 (70)
	6–12	23 (29)	11 (30)
	Median (range)	4.8 (0.5–11.9)	4.2 (0.2–11.6)
Prior PARP inhibitor		5 (6)	1 (3)
GHS/QoL score[b]	<50	33 (42)	17 (46)
	≥50	46 (58)	20 (54)
FIGO stage	I/II	1 (1)	1 (3)
	III	55 (70)	24 (65)
	IV	22 (28)	12 (32)
	Unknown	1 (1)	0
Origin of cancer	Ovary	71 (90)	35 (95)
	Peritoneum	6 (8)	2 (5)
	Fallopian tubes	2 (3)	0
Histology	Serous	71 (90)	32 (86)
	Clear cell	2 (3)	0
	Undifferentiated	0	2 (5)
	Other	6 (8)	3 (8)
Grade[d]	Low	2 (3)	1 (3)
	High	66 (84)	31 (84)
	Other	1 (1)	2 (5)
BRCA mutation status	*BRCA1* mutated	6 (8)	0
	BRCA2 mutated	1 (1)	0
	Non-mutated	29 (37)	17 (46)
	Unknown	43 (54)	20 (54)
Previous hypertension		37 (47)	15 (41)
Median interval since prior bevacizumab, days (range)		35 (22–106)[e]	35.5 (21–85)

ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; GHS/QoL, global health status/quality of life; PARP, poly(ADP-ribose) polymerase.
[a] Missing data in one patient.
[b] Stratification factor.
[c] Among the 82 patients in the platinum-free interval <6 months stratum, the interval was <3 months in 16 patients (12 in the combination arm, four in the single-agent arm) and 3–6 months in 63 patients (41 in the combination arm, 22 in the single-agent arm); the exact platinum-free interval could not be calculated in the remaining three patients because of incomplete dates for relapse/platinum.
[d] Missing data in 13 patients.
[e] $n = 78$; one patient in the combination arm received one prior line of platinum-containing therapy (front-line carboplatin plus paclitaxel) but received no bevacizumab; although she did not meet all inclusion criteria she was included in all analyses, which were performed according to the intention-to-treat principle on all randomized patients.

Table 2
Treatment exposure.

Exposure	Paclitaxel plus pazopanib ($n = 79$)	Paclitaxel alone ($n = 37$)
Median (range) number of cycles of paclitaxel	4 (1–61)	6 (1−13)
Mean (SD) weekly paclitaxel dose, mg/m^2	60.9 (8.1)	77.7 (5.4)
Patients with toxicity-related paclitaxel dose reduction, n (%)	18 (23)	7 (19)
Patients with toxicity-related paclitaxel treatment interruption, n (%)	26 (33)	4 (11)
Reason for discontinuing paclitaxel, n (%)		
Progression	50 (63)	30 (81)
Toxicity	17 (22)	4 (11)
Death	1 (1)[a]	0
Other	8 (10)	3 (8)
Treatment ongoing, n (%)	3 (4)	0
Patients with toxicity-related paclitaxel discontinuation within <4 months, n (%)	12 (15)	1 (3)
Median (range) number of pazopanib cycles	3 (1−32)	–
Mean (SD) daily pazopanib dose, mg	534 (127)	–
Patients with toxicity-related pazopanib dose reduction, n (%)	30 (38)	–
Patients with toxicity-related pazopanib treatment interruption, n (%)	40 (51)	–
Reason for discontinuing pazopanib, n (%)		–
Progression	38 (48)	
Toxicity	35 (44)	
Death	1 (1)[b]	
Other	5 (6)	
Patients with toxicity-related pazopanib discontinuation within <4 months, n (%)	28 (35)	–
Patients with toxicity-related discontinuation of either treatment, n (%)	37 (47)	4 (11)

SD, standard deviation.
[a] Gastrointestinal perforation, considered to be probably (investigator assessment) or possibly (sponsor assessment) related to pazopanib, unrelated to paclitaxel, and related to underlying disease (by both the investigator and the sponsor).

To try to improve the tolerability of the pazopanib–paclitaxel combination, we administered both drugs at lower doses (paclitaxel 65 mg/m^2 and pazopanib 600–800 mg in TAPAZ compared with paclitaxel 80 mg/m^2 and pazopanib 800 mg in the previous randomized trials in recurrent OC). Despite the lower doses, pazopanib toxicity was problematic, leading to frequent treatment discontinuations and reduced dose intensity in TAPAZ. In this respect, there are some similarities between our findings and those from the CHIVA randomized phase II trial, which explored the addition of another TKI (nintedanib) to paclitaxel as neoadjuvant therapy for OC [20]. As in TAPAZ, the TKI–paclitaxel combination was associated with increased toxicity, compromising the delivery and, ultimately, the efficacy of chemotherapy.

PROs are particularly relevant in early relapsing recurrent OC, where the disease and symptom burden are more troublesome to patients. TAPAZ provides the first reported PROs for the pazopanib–paclitaxel combination in recurrent OC, confirming the unfavorable effects on gastrointestinal toxicity and neuropathy. The markedly worse diarrhea with the pazopanib–paclitaxel combination compared with paclitaxel alone is consistent with PRO results from the AGO-OVAR 16 trial in the front-line setting [10]. The main caveat when interpreting TAPAZ PRO analyses is the imbalance between treatment arms in the proportion of patients completing PRO questionnaires and the high proportion of patients in the combination arm discontinuing pazopanib because of toxicity before the 4-month PRO assessment point, which may introduce bias.

Observed pazopanib trough plasma concentrations are consistent with previously reported values [21,22]. No clear relationships between PK and efficacy outcomes were identified; results of PK–pharmacogenetic–pharmacodynamic modeling will be reported separately.

Limitations of our trial include the non-comparative design, the relatively small sample size, and the lack of information on subsequent use of PARP inhibitors. Strengths include addressing a specific population and question not answered by previous trials, extensive PROs data collection and analyses, and ongoing pharmacogenomic and translational aspects.

In conclusion, our results do not support the addition of pazopanib to paclitaxel in patients with recurrent OC progressing on maintenance bevacizumab therapy after platinum-based chemotherapy. PRO results suggest that adding pazopanib to paclitaxel is associated with a detrimental effect on abdominal/gastrointestinal symptoms. Single-agent chemotherapy remains the standard of care for these patients.

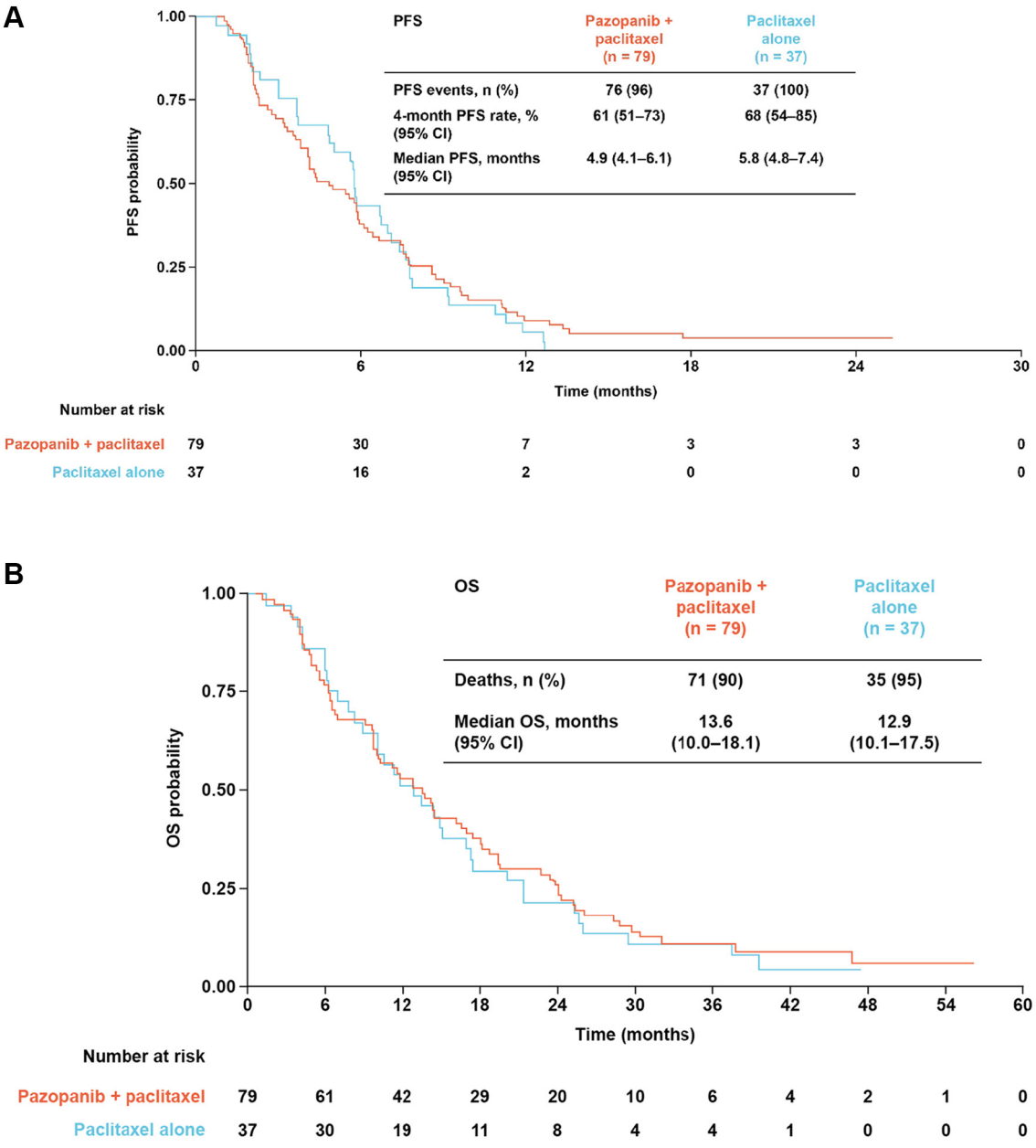

Fig. 2. Efficacy. (A) PFS; (B) OS. CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Table 3
Adverse events of special interest by treatment arm (all events occurring in ≥10% of patients at any grade or at grade 3/4 in any patient).

Adverse event, n (%)	Paclitaxel plus pazopanib (n = 79)		Paclitaxel alone (n = 37)	
	All grades	Grade 3/4	All grades	Grade 3/4
Hypertension	**72 (91)**	**35 (44)**	**25 (68)**	**3 (8)**
Fatigue	70 (89)	16 (20)	33 (89)	3 (8)
Anemia	63 (80)	10 (13)	31 (84)	4 (11)
Diarrhea	**55 (70)**	9 (11)	**18 (49)**	2 (5)
Hepatic cytolysis	54 (68)	18 (23)	20 (54)	7 (19)
Lymphopenia	54 (68)	9 (11)	22 (59)	4 (11)
Neutropenia	50 (63)	22 (28)	20 (54)	8 (22)
Pain	49 (62)	5 (6)	23 (62)	5 (14)
Abdominal pain	48 (61)	5 (6)	18 (49)	3 (8)
Nausea	46 (58)	5 (6)	19 (51)	1 (3)
Anorexia	**46 (58)**	8 (10)	**14 (38)**	1 (3)
Vomiting	42 (53)	8 (10)	14 (38)	4 (11)
Sensory neuropathy	39 (49)	3 (4)	19 (51)	3 (8)
Thrombocytopenia	**38 (48)**	7 (9)	**10 (27)**	4 (11)
Mucositis	38 (48)	2 (3)	11 (30)	1 (3)
Constipation	37 (47)	3 (4)	20 (54)	1 (3)
Infection	31 (39)	5 (6)	10 (27)	2 (5)
Proteinuria	**27 (34)**	3 (4)	**5 (14)**	0
Edema	26 (33)	1 (1)	18 (49)	1 (3)
Dyspnea	23 (29)	4 (5)	13 (35)	2 (5)
Creatinine increased	22 (28)	2 (3)	13 (35)	0
Onycholysis	18 (23)	0	11 (30)	2 (5)
Dyspepsia	17 (22)	1 (1)	9 (24)	0
Bilirubin increased	13 (16)	3 (4)	5 (14)	1 (3)
Skin rash	12 (15)	0	3 (8)	0
Hand-foot syndrome	10 (13)	0	4 (11)	0
Motor neuropathy	8 (10)	0	7 (19)	0
Pulmonary embolism	7 (9)	7 (9)	0	0
Intestinal obstruction	6 (8)	5 (6)	3 (8)	3 (8)
Thrombosis	6 (8)	1 (1)	2 (5)	0
Febrile neutropenia	5 (6)	5 (6)	2 (5)	2 (5)
Intestinal perforation	3 (4)	3 (4)	1 (3)	1 (3)
Anal fissure	2 (3)	1 (1)	0	0

Differences of ≥20 percentage points are shown in bold.

Credit author statement

F.J. was involved in study concept and design. F.J., J.L., A.A., A.P., and B.Y. were involved in methodology, validation, and formal analysis. F.J., M.F., D.B., A.F., H.V., H.B., L.B.L, B.Y., F.P., A.L., D.S., A.-C.H.-B., C.A., M.-C.K.-F., M.T., J.-E.K., F.D.P., J.M., N.R., J.A., M.-A.M.-R., I.R.-C., M.P.G., and P.-E.B were involved in investigation and resources. F.J., J.L., and A.A. were involved in writing – original draft. All authors were involved in writing – review and editing. J.L. and A.A. were involved in visualization.

Conflict of interest statement

F.J. Consulting fees: AstraZeneca, GSK, Janssen, Ipsen; Honoraria for lectures and scientific boards: AstraZeneca, Clovis, Astellas, BMS, MSD, Bayer, GSK, Ipsen, Janssen; Speaker honoraria: Amgen; Meeting/travel support: Ipsen, GSK; Participation on a data safety monitoring or advisory board: GSK; GINECO guidelines committee. M.F. Honoraria: AstraZeneca, GSK. A.A. Consultancy: Amgen, Ipsen, AstraZeneca; Honoraria: AstraZeneca, BMS; Meeting attendance/travel support: BMS, AstraZeneca. A.F. Honoraria: Clovis Oncology, AstraZeneca, GSK; Meeting attendance/travel: GSK, AstraZeneca, MSD; Leadership: President of SFOG. H.V. Grants/contracts: Eisai, Novartis, AstraZeneca, Daiichi, Pfizer; Meeting/travel support: Eisai, GSK, MSD, Novartis. B.Y. Maria Pia grant (to research association) from GINECO for translational research; Honoraria for consultancy: MSD, AstraZeneca, GSK/Tesaro, Bayer, Roche/Genentech, ECS-progastrin, Novartis, LEK, Amgen, Clovis Oncology, Merck Serono, BMS, Seagen, Myriad; Invitations to congresses: AstraZeneca, MSD, GSK. A.L. Honoraria: AstraZeneca, MSD, Clovis; Leadership or fiduciary role: GINECO. A.-C.H.-B. Consulting fees: MSD, AstraZeneca (both for market access consulting); Honoraria for presentations: MSD, AstraZeneca, Daiichi, GSK, Seagen, Gilead; Meeting/travel support: Novartis, Pfizer, Daiichi; Advisory boards: MSD, AstraZeneca, Daiichi, Pfizer, Novartis, GSK, Seagen, Gilead, Eisai. C.A. Grant/contract: GSK; Honoraria: GSK (personal), Clovis Oncology, AstraZeneca (both to institution); Meeting/travel support: Merck (personal fees). J.-E.K. Meeting/travel support: AstraZeneca, GlaxoSmithKline, Eisai; Data Safety Monitoring/Advisory Board: AstraZeneca, GlaxoSmithKline, Clovis, Bristol Myers Squibb, Eisai, PharmaMar. J.A. Grants/contracts: MSD; Consulting fees: MSD, AstraZeneca, Clovis, GSK; Honoraria: MSD, AstraZeneca, Novartis; Meeting/travel support: AstraZeneca, GSK. I.R.-C. Consulting fees and honoraria: Novartis, Amgen, AstraZeneca, Exelixis, Clovis, GSK, MSD, Deciphera, Mersana, Roche, PharmaMar, Seagen, Macrogenics, Agenus; Meeting/travel support: AstraZeneca, Clovis, Roche, GSK; Data Safety Monitoring Board: ATHENA and ATTEND; President of GINECO. P.-E.B. Meeting/travel support: MSD. All other authors declare no conflicts of interest.

Role of the funding source

Novartis funded the study and provided pazopanib, but had no role in the study design, analysis or interpretation of the data, or decision to submit the manuscript for publication.

Data availability statement

Currently no mechanism is in place to allow sharing of individual deidentified participant data. Requests sent to ARCAGY–GINECO (bvotan@arcagy.org) will be considered on a case-by-case basis.

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Appendix A. Supplementary data

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