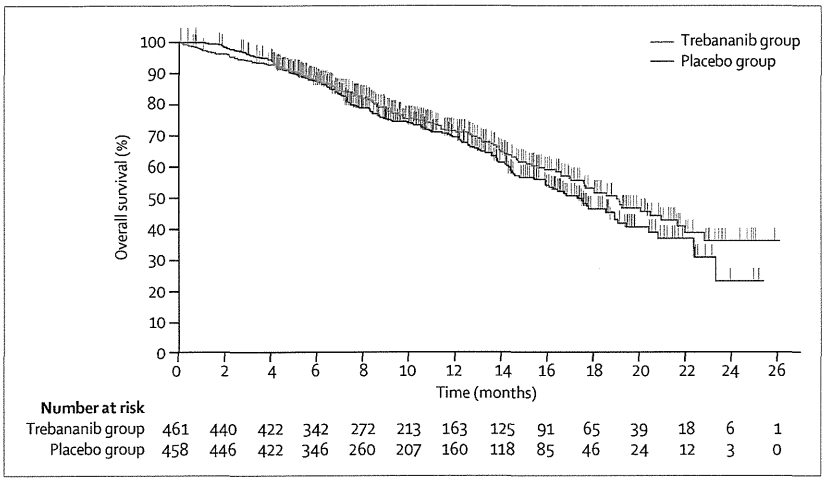

Figure 3: **Overall survival**

Results

Between Nov 10, 2010, and Nov 19, 2012, 919 patients from 179 sites in 32 countries were randomly assigned to treatment groups (figure 1). 458 patients were randomly assigned to placebo, and 461 to trebananib. The data cutoff date was March 19, 2013. In the randomised treatment groups, 362 patients (39%) had received one previous regimen, 346 (38%) had received two, and 208 (23%) had received three (table 1). Most deaths in the study were attributed to disease progression (appendix). The median number of trebananib and placebo cycles given was 5·0 (IQR 3–8) in the placebo group and 5·0 (3–8) in the trebananib group, and the median relative dose intensity for paclitaxel exceeded 92% in both groups (appendix).

919 patients were evaluated for progression-free survival. After a median follow-up of 10·1 months (IQR 6·4–15·2), 326 (71%) of 458 patients in the placebo group and 239 (52%) of 461 patients in the trebananib group had disease progression; 35 (8%) and 71 (15%), respectively, had died. Median progression-free survival was significantly longer in the trebananib group compared with the placebo group (5·4 months [95% CI 4·3–5·5] *vs* 7·2 months [5·8–7·4], respectively, HR 0·66, 95% CI 0·57–0·77, p<0.0001; figure 2).

The treatment effect was consistent across most prespecified groups (figure 2). In a subgroup analysis, trebananib seemed to prolong progression-free survival after previous anti-angiogenesis treatment, including bevacizumab, although this result was not significant, perhaps due to the small number of patients in this subgroup (59 events in 72 patients). The treatment effect did not seem to be affected by the number of previous regimens or by platinum-free interval. 34 patients (13 in the placebo group and 21 in the trebananib group) were censored for progression-free survival in the protocol-specified analysis because they received new anticancer treatment before documentation of radiographic disease progression. One of those patients (in the placebo group) had documented radiographic progression after initiation of new anticancer treatment (ie, 33 of 34 patients would have been censored irrespective of this aspect of the progression-free survival definition).

Objective responses were significantly more common with trebananib than with placebo (30% [129 of 433 patients with ≥1 measurable lesion per RECIST version 1·1 at baseline] in the placebo group *vs* 38% [167 of 435 patients] in the trebananib group; table 2) as were CA-125 responses (49% [180 of 371 patients with CA-125 ≥2×ULN at baseline] *vs* 56% [206 of 365 patients]; p=0·03).

The interim overall survival analysis did not show any significant difference between groups (17·3 months [95% CI 15·4–19·1] in the placebo group *vs* 19·0 months [17·0–21·7] in the trebananib group, HR 0·86, 95% CI 0·69–1·08, p=0·19; figure 3).

FACT-O and FACT-O OCS questionnaires were completed by most patients (FACT-O, 411 [90%] of 458 patients in the placebo group and 391 [85%] of 461 patients in the trebananib group; FACT-O OCS, 415 [91%] and 400 [87%]). With a pattern-mixture model, mean change in the FACT-O and FACT-O OCS over time were −2·44 (95% CI −4·57 to −0·31) for FACT-O early drop-out (last visit at or before 25 weeks), −1·65 (−5·32 to 2·02) for FACT-O late drop-out (last visit after 25 weeks), −0·68 (−1·36 to 0·00) for FACT-O OCS early drop-out, and 0·17 (−0·99 to 1·33) for FACT-O OCS late drop-out. The data suggest that trebananib treatment did not result in an overall change in patient-reported outcomes scores compared with placebo; detailed data will be reported separately.

We assessed health utility states with the EQ-5D and EQ-5D visual analogue scales; completion rates for the EQ-5D remained higher than 85% (range 85–100%) for the first 57 weeks of treatment in both treatment groups. The median difference in the EQ-5D summary score from baseline between the placebo and the trebananib group was 0 (IQR −0·50 to 0·11) versus 0 (−0·11 to 0·08) at week 17, 0 (−0·11 to 0·12) versus 0 (−0·16 to 0·11) at week 25, and 0 (−0·29 to 0·15) versus 0 (−0·11 to 0·15) at week 57.

The appendix shows the overall incidence of any grade 3 or higher adverse event. Of patients included in the safety analysis population, 244 of 452 (54%) patients in the placebo group and 258 of 461 (56%) patients in the trebananib group had a grade 3 or higher adverse event, and 125 (28%) and 159 (34%), respectively, had a serious adverse event. Three patients in the placebo group and four in the trebananib group had treatment-related fatal adverse events. Trebananib was associated with more adverse event-related treatment discontinuations than was with placebo (77 [17%] patients *vs* 27 [6%], respectively) and higher incidences of oedema (294 [64%] patients had any-grade oedema in the trebananib group *vs* 127 [28%] patients in the placebo group; table 3), including generalised oedema (with one grade 5 event), localised oedema, and lymphoedema (2% [seven patients] *vs* 6% [29 patients]). Pleural effusion, ascites, weight increased, and blurred vision were also increased in the trebananib group

	Placebo group (N=452)				Trebananib group (N=461)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Patients reporting treatment-emergent adverse events	190 (42%)	192 (42%)	34 (8%)	18 (4%)	188 (41%)	205 (44%)	28 (6%)	25 (5%)
Localised oedema*	112 (25%)	4 (1%)	0 (0%)	0 (0%)	240 (52%)	24 (5%)	0 (0%)	0 (0%)
Nausea	165 (37%)	6 (1%)	0 (0%)	0 (0%)	179 (39%)	7 (2%)	1 (<1)	0 (0%)
Alopecia	161 (36%)	2 (<1%)	0 (0%)	0 (0%)	154 (33%)	0 (0%)	0 (0%)	0 (0%)
Fatigue	120 (27%)	17 (4%)	0 (0%)	0 (0%)	112 (24%)	15 (3%)	0 (0%)	0 (0%)
Diarrhoea	109 (24%)	13 (3%)	0 (0%)	0 (0%)	125 (27%)	11 (2%)	0 (0%)	0 (0%)
Abdominal pain	110 (24%)	20 (4%)	1 (<1%)	0 (0%)	110 (24%)	19 (4%)	2 (<1%)	1 (<1)
Asthenia	104 (23%)	15 (3%)	0 (0%)	0 (0%)	116 (25%)	13 (3%)	0 (0%)	0 (0%)
Constipation	124 (27%)	4 (1%)	0 (0%)	0 (0%)	102 (22%)	2 (<1%)	1 (<1%)	0 (0%)
Neutropenia*	85 (19%)	30 (7%)	10 (2%)	0 (0%)	73 (16%)	22 (5%)	4 (1%)	0 (0%)
Vomiting	89 (20%)	12 (3%)	0 (0%)	0 (0%)	108 (23%)	14 (3%)	0 (0%)	0 (0%)
Peripheral neuropathy	63 (14%)	8 (2%)	0 (0%)	0 (0%)	84 (18%)	13 (3%)	0 (0%)	0 (0%)
Anaemia*	74 (16%)	19 (4%)	0 (0%)	0 (0%)	42 (9%)	5 (1%)	0 (0%)	0 (0%)
Ascites*	19 (4%)	34 (8%)	0 (0%)	0 (0%)	40 (9%)	52 (11%)	0 (0%)	0 (0%)
Decreased appetite	73 (16%)	5 (1%)	0 (0%)	0 (0%)	77 (17%)	5 (1%)	0 (0%)	0 (0%)
Headache	71 (16%)	4 (1%)	0 (0%)	0 (0%)	60 (13%)	3 (1%)	0 (0%)	0 (0%)
Dyspnoea	46 (10%)	4 (1%)	1 (<1%)	1 (<1%)	62 (13%)	9 (2%)	1 (<1)	0 (0%)
Cough	58 (13%)	2 (<1%)	0 (0%)	0 (0%)	65 (14%)	1 (<1%)	0 (0%)	0 (0%)
Back pain	58 (13%)	2 (<1%)	1 (<1%)	0 (0%)	52 (11%)	2 (<1%)	0 (0%)	0 (0%)
Pyrexia	55 (12%)	2 (<1%)	0 (0%)	0 (0%)	39 (8%)	1 (<1%)	0 (0%)	0 (0%)
Pleural effusion*	9 (2%)	8 (2%)	0 (0%)	0 (0%)	49 (11%)	13 (3%)	0 (0%)	0 (0%)
Dizziness	44 (10%)	3 (1%)	0 (0%)	0 (0%)	53 (11%)	1 (<1%)	0 (0%)	0 (0%)
Dysgeusia	54 (12%)	0 (0%)	0 (0%)	0 (0%)	37 (8%)	0 (0%)	0 (0%)	0 (0%)
Nasopharyngitis*	28 (6%)	0 (0%)	0 (0%)	0 (0%)	56 (12%)	0 (0%)	0 (0%)	0 (0%)
Pain in extremity	39 (9%)	1 (<1%)	0 (0%)	0 (0%)	48 (10%)	1 (<1%)	0 (0%)	0 (0%)
Abdominal distension	33 (7%)	3 (1%)	0 (0%)	0 (0%)	46 (10%)	4 (1%)	1 (<1%)	0 (0%)
Hypokalaemia	25 (6%)	7 (2%)	3 (1%)	0 (0%)	30 (7%)	18 (4%)	3 (1%)	0 (0%)
Insomnia	48 (11%)	0 (0%)	0 (0%)	0 (0%)	39 (8%)	0 (0%)	0 (0%)	0 (0%)
Upper abdominal pain	31 (7%)	2 (<1%)	0 (0%)	0 (0%)	53 (11%)	0 (0%)	0 (0%)	0 (0%)
Rash	49 (11%)	0 (0%)	0 (0%)	0 (0%)	29 (6%)	0 (0%)	0 (0%)	0 (0%)
Generalised oedema*	12 (3%)	0 (0%)	0 (0%)	0 (0%)	38 (8%)	12 (3%)	0 (0%)	1 (<1)
Myalgia	44 (10%)	0 (0%)	0 (0%)	0 (0%)	44 (10%)	1 (<1%)	0 (0%)	0 (0%)
Arthralgia	40 (9%)	2 (<1%)	0 (0%)	0 (0%)	47 (10%)	0 (0%)	0 (0%)	0 (0%)
Paraesthesia	42 (9%)	0 (0%)	0 (0%)	0 (0%)	45 (10%)	1 (<1%)	0 (0%)	0 (0%)

*Adverse events with a >5% difference between treatment groups.

Table 3: **Adverse events in ≥10% of patients in either treatment group**

compared with placebo (appendix). Grade 3 oedema led to protocol-mandated treatment discontinuation in three (1%) patients in the placebo group and in 37 (8%) in the trebananib group; two other patients in the trebananib group discontinued because of grade 1 and grade 2 oedema (not protocol-mandated discontinuations). Adverse events of any grade arising more frequently in the trebananib group were localised oedema, pleural effusion, generalised oedema, ascites, weight increased, nasopharyngitis, peripheral neuropathy, lymphoedema, upper abdominal pain, increased lachrymation, dry skin, hyponatraemia, paryonychia, and skin fissures (figure 4). Adverse events of interest were hypertension (16 [4%] patients of 452 in the placebo group *vs* 28 [6%] of 461 patients in the trebananib group), bleeding (75 [17%] *vs* 46 [10%]), pulmonary embolism (nine [2%] *vs* five [1%]), arterial thrombotic events (three [1%] *vs* three [1%]), proteinuria (13 [3%] *vs* 15 [3%]), impaired wound healing (two [<1%] *vs* two [<1%]), gastrointestinal perforations (one [<1%] *vs* seven [2%]), and venous thromboembolic events (17 [4%] *vs* 29 [6%]).

Of 391 assessable patients in the trebananib group, 38 (10%) developed non-neutralising anti-trebananib binding antibodies; of those, 12 were only transiently positive, with negative samples at follow-up for patients with neutralising antibodies. 22 of assessed patients in the trebananib group had pre-existing antibodies, and one patient with pre-existing antibodies had neutralising antibodies. In the placebo group, 39 (9%) of 442 assessable

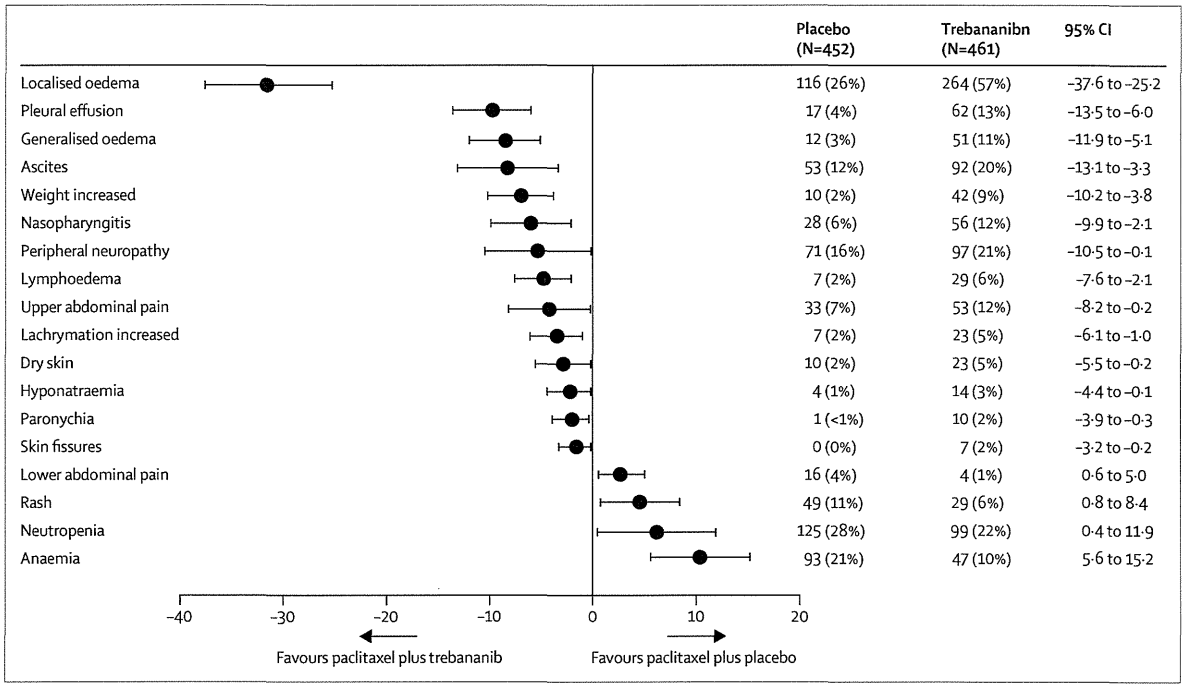

Figure 4: **Treatment-emergent adverse events and 95% confidence intervals of their difference between treatment groups**

patients tested positive for anti-trebananib antibodies after dosing (one patient had transient neutralising antibodies). Assessment of adverse events in patients who developed anti-trebananib antibodies did not suggest any specific adverse event associated with the development of these antibodies.

Discussion

When added to weekly paclitaxel in the treatment of recurrent epithelial ovarian cancer, trebananib significantly increased progression-free survival compared with placebo (panel). The value of progression-free survival in the assessment of the clinical benefit of new drugs in the setting of epithelial ovarian cancer has been controversial, but there seems to be consensus that overall survival, and other clinically relevant endpoints such as proportion of patients achieving an objective response, adverse events, and disease-related symptoms including patient-reported outcomes, should be collectively included an assessment of efficacy.[25] Indeed, the present study verifies the clinical activity of trebananib; we reported that proportion of patients achieving an objective response is significantly increased with treatment and there is no reduction in patient-reported outcomes. Moreover, overall survival, a key secondary study endpoint, does not currently show a difference between groups but will add crucial data to the assessment of the progression-free survival results once the final analysis is available.

Although some have argued that patient-reported outcomes are the most important metric in the assessment of new chemotherapeutic options in solid tumours with low proportions of patients achieving objective responses and short overall survival, patient-reported outcomes are especially problematic because almost all studies of epithelial ovarian cancer enrol patients with small-volume disease who are consequently asymptomatic. In fact, most recent agents approved in epithelial ovarian cancer by the FDA (gemcitabine in combination with carboplatin)[26] or by the European Medicines Agency (trabectedin plus pegylated liposomal doxorubicin[27] and bevacizumab plus various chemotherapies[8,9,12]) were approved on the basis of progression-free survival alone because patient-reported outcomes did not effectively capture disease-related symptoms, and showing an increase in overall survival given long survival after disease progression is difficult.[25,28] Alternatively, results from the AURELIA study recently showed that treatment with bevacizumab, when added to chemotherapy, was associated with an increase in the number of patients who achieved at least 15% improvement in patient-reported outcomes by weeks 8 and 9, compared with those who received chemotherapy alone.[11] Although women with advanced or recurrent epithelial ovarian cancer respond to many available therapeutic agents, almost all die from their disease, which makes the discovery of new active compounds important. Assessment of potential biomarkers of response to trebananib is in progress. In preliminary analyses, baseline levels of Ang1, Ang2, and the soluble form of their receptor Tie2 did not show a consistent predictive or prognostic association with progression-free survival (unpublished data).

Trebananib is distinct from other anti-angiogenesis agents with respect to its mechanism of action and toxicity

profile. Prevention of Ang1 and Ang2 from binding to the Tie2 receptor with trebananib does not seem to be associated with the typical adverse events found with anti-VEGF treatment.[29] Compared with the AURELIA trial of bevacizumab plus single-agent chemotherapy in platinum-resistant recurrent epithelial ovarian cancer,[11] the efficacy results in comparable patients in TRINOVA-1 seemed similar, although cross-trial comparisons are difficult. For example, AURELIA enrolled women with platinum-free interval of less than 6 months and up to two previous regimens, whereas TRINOVA-1 enrolled those with platinum-free interval of less than 12 months and up to three previous chemotherapeutic interventions. Because the reintroduction of carboplatin in the setting of a platinum-free interval between 6 and 12 months is controversial, especially when the volume of disease is small and asymptomatic,[30] TRINOVA-1 allowed such patients to enter the trial at the discretion of the treating physician. AURELIA did not contain a placebo in the control group, and only a third of patients received weekly paclitaxel as in TRINOVA-1. Together, these are the only two randomised clinical trials to show a significant improvement in progression-free survival in patients who are platinum-resistant, which represents a high unmet medical need. Many other clinical trials have studied platinum-sensitive recurrent ovarian cancer. Most notably, the OCEANS study[12] added bevacizumab to carboplatin plus gemcitabine. The HR for the 6–12 months platinum-free interval group was 0·36 (95% CI 0·25–0·53). However, this triplet was much more marrow-suppressive than the doublet studied in TRINOVA-1.

The major toxic effect associated with trebananib treatment was oedema (including ascites and pleural effusions), which is in line with previous results from various phase 2 studies.[16,31,32] Factors underlying the occurrence of oedema associated with trebananib treatment, or its natural history, are unknown. Not all oedema seems to be caused by trebananib because some patients receiving placebo also developed oedema (26% of patients in the placebo group had localised oedema in the present study, compared with 57% in the trebananib group).[16,31] In TRINOVA-1, oedema events were generally mild in severity and rarely led to study drug discontinuation, and at least some cases of oedema seemed to be reversible. Because the FACT-O and FACT-O OCS instruments did not include questions specific to oedema or lymphoedema (although there were questions on abdominal discomfort and bloating) analysis assessing the association of health-related quality of life with oedema or lymphoedema was not done. However, because even mild oedema can cause a burden for patients with cancer, early management is likely to be important. In the present study and other studies of trebananib across various tumour types, the management of oedema followed individual institutional standards, which might have included compression garments, manual drainage, or diuretics.[17] Finally, the weekly schedule of trebananib might be inconvenient for patients, although not when given with drugs such as paclitaxel that are commonly given on a weekly schedule.

Panel: Research in context

Systematic review

To identify publications focused on treatment options for patients with epithelial ovarian cancer, we searched the National Library of Medicine, PubMed, and abstracts presented at recent international clinical oncology meetings. Search terms included "ovarian", "recurrent", and "paclitaxel", without date or language limits. Careful review and qualitative assessment of identified articles and abstracts suggested that outcomes in this setting were poor, and that there was a large unmet need in patients with recurrent epithelial ovarian cancer.

Interpretation

In the Trebananib in Ovarian Cancer-1 (TRINOVA-1) study, trebananib plus weekly paclitaxel significantly extended progression-free survival compared with placebo plus paclitaxel in women with recurrent epithelial ovarian cancer. Although oedema (a typical angiopoi etin inhibitor side-effect) was increased, other typical anti-VEGF-associated adverse events such as hypertension were not prominent. The results from the TRINOVA-1 study are clinically significant because they validate both a new target and a new therapeutic agent in the setting of epithelial ovarian cancer. Trebananib plus paclitaxel might provide a non-VEGF anti-angiogenesis treatment option to women with recurrent epithelial ovarian cancer, if approved by regulatory agencies.

The use of non-platinum chemotherapy might be a valuable treatment option for patients with partially platinum-sensitive disease. Response to platinum-containing recurrence therapy varies among this patient subgroup. Additionally, some patients might not be eligible to receive a platinum doublet as recurrence treatment for various reasons (eg, hypersensitivity). Additionally, because response to a subsequent round of treatment with a platinum-containing agent improves with increasing time between treatments with platinum agents, there is thought to be some benefit to introducing a non-platinum agent before rechallenge with platinum, thus limiting the tumour's ability to acquire drug resistance.[33]

Two other phase 3 studies have added trebananib to pegylated liposomal doxorubicin (TRINOVA-2; NCT01281254), another standard agent in recurrent epithelial ovarian cancer, and to first-line carboplatin and paclitaxel (TRINOVA-3; NCT01493505). TRINOVA-2 enrolment was modified after the manufacturer's notice of a pegylated liposomal doxorubicin shortage in certain regions (ie, the USA and Australia). This supply shortage, in addition to a previous global pegylated liposomal doxorubicin supply disruption, undermined the integrity of the study and led to the decision to permanently close enrolment. The TRINOVA-3 study was resized from 2000 to 1000 patients because a smaller sample size than initially planned could adequately assess progression-free survival, the study's primary endpoint; the outcome of this study will provide further data on the efficacy of trebananib in this patient population.

In summary, trebananib significantly improved progression-free survival when added to paclitaxel,

offering a non-VEGF anti-angiogenesis option to women with recurrent epithelial ovarian cancer.

Contributors

BJM, DJW, and LN designed the study. BJM, AP, IV, FR, KF, D-SB, AO, IR-C, DMP, BYK, CL, GR, DGR, RLC, TJH, CM, ABr, MF, AR, ABa, and AMO collected clinical data. LN and MT did statistical analyses. All authors contributed to data interpretation, the writing or revising of the manuscript, and approved the final version.

Declaration of interests

BJM, GR, RLC, and ABa have received research funding from Amgen. FR and TJH have served on a steering committee for Amgen. TJH has served on advisory boards for Merck, AstraZeneca, and Genentech, and received honoraria from Morphotek. KF has received research funding from Sanofi, served on advisory boards for Zeria Pharma, GSK, AstraZeneca, and Chugai-Roche, received publication support from Kyowa-Kirin, and received speaker honoraria from Taiho and Chugai-Roche. IR-C has an interest in a patent broadly relevant to this work. AMO has received institutional research funding from Amgen. MT, LN, and DJW are employees and stockholders of Amgen. The other authors (D-SB, MF, BYK, CL, DGR, CM, AP, DMP, ABr, AR, AO, and IV) declare no competing interests.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Incorporation of Pazopanib in Maintenance Therapy of Ovarian Cancer

Andreas du Bois, Anne Floquet, Jae-Weon Kim, Joern Rau, Josep M. del Campo, Michael Friedlander, Sandro Pignata, Keiichi Fujiwara, Ignace Vergote, Nicoletta Colombo, Mansoor R. Mirza, Bradley J. Monk, Rainer Kimmig, Isabelle Ray-Coquard, Rongyu Zang, Ivan Diaz-Padilla, Klaus H. Baumann, Marie-Ange Mouret-Reynier, Jae-Hoon Kim, Christian Kurzeder, Anne Lesoin, Paul Vasey, Christian Marth, Ulrich Canzler, Giovanni Scambia, Muneaki Shimada, Paula Calvert, Eric Pujade-Lauraine, Byoung-Gie Kim, Thomas J. Herzog, Ionel Mitrica, Carmen Schade-Brittinger, Qiong Wang, Rocco Crescenzo, and Philipp Harter

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Author affiliations appear at the end of this article.

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Corresponding author: Andreas du Bois, MD, PhD, Arbeitsgemeinschaft Gynaekologische Onkologie Study Group, Kliniken Essen-Mitte, Department of Gynecology and Gynecologic Oncology, Henricistrasse 92, 45136 Essen, Germany; e-mail: prof.dubois@googlemail.com.

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ABSTRACT

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

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

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

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

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INTRODUCTION

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

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

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

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

PATIENTS AND METHODS

Patients

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

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

Study Design and Treatment

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

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

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

Study End Points and Assessments

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

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

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

Statistical Analysis

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

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

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

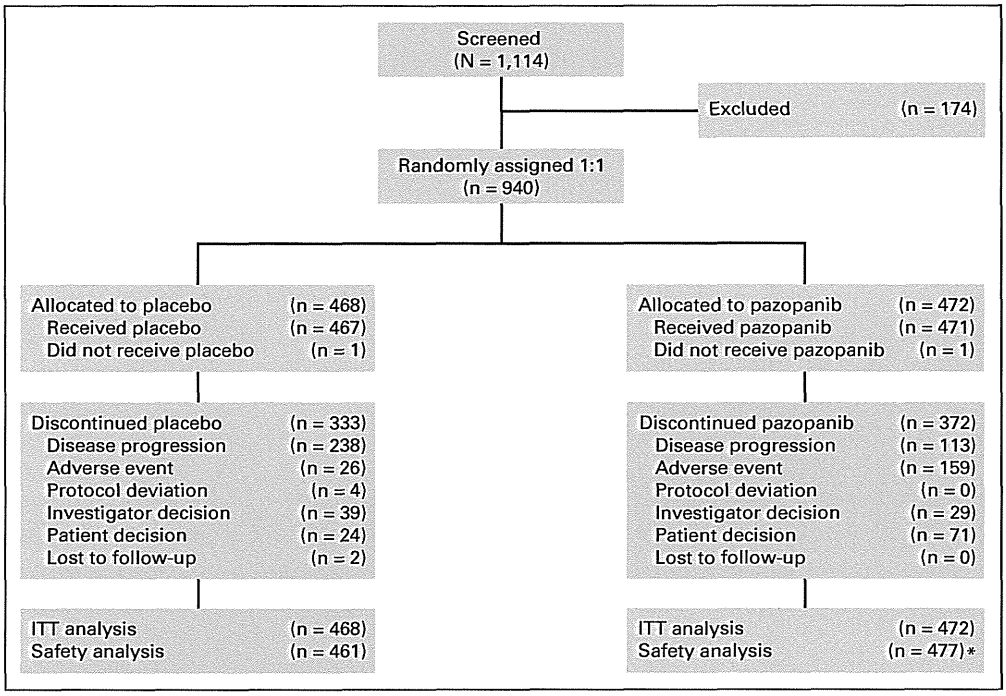

Fig 1. CONSORT diagram. ITT, intention to treat. (*) Includes six patients randomly assigned to placebo who took pazopanib in error for any period of time.

RESULTS

Patients

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

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

Treatment Exposure

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

Efficacy

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

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

Table 1. Demographic and Baseline Characteristics

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

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

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

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

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

Safety

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

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

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

DISCUSSION

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

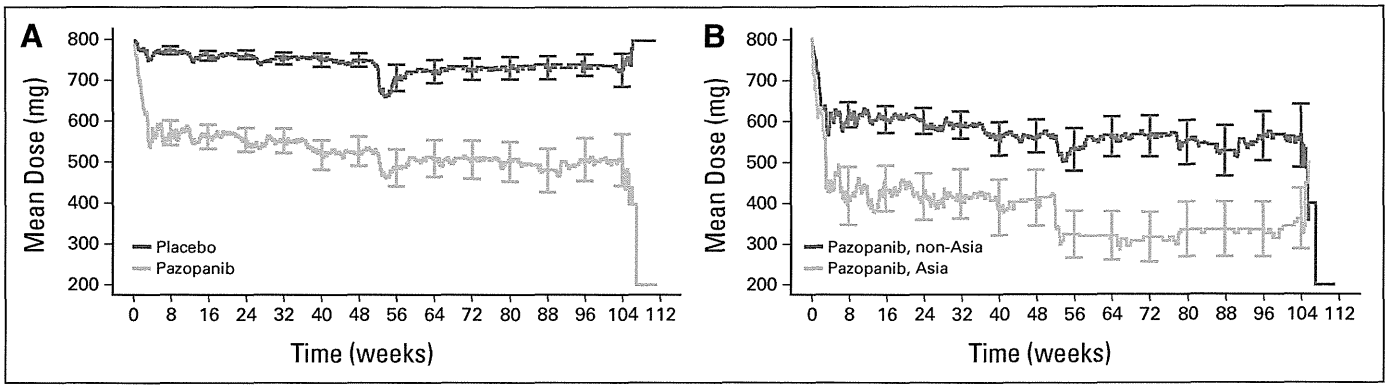

Fig 2. Pazopanib versus placebo exposure (A) in the overall population and (B) in the Asian *v* non-Asian population. Dose interruptions were included for mean dose calculation and subject count as zero dose.

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

The most common toxicity in the pazopanib arm was hypertension, a class effect associated with antiangiogenic agents. About half of the patients exposed to pazopanib developed hypertension grade 2 or higher, and this was the most prominent reason for dose reductions and treatment discontinuation in this trial. The observed safety profile of pazopanib was generally consistent with previous studies in renal cancer and soft tissue sarcoma.[27,28] However, neutropenia occurred more frequently in this trial (32% *v* 8% in the pazopanib and placebo arms, respectively. This may indicate that patients coming off chemotherapy may have a higher risk for neutropenia than the primarily chemotherapy-naive patients in the renal cancer trials. The higher toxicity rate in the sequential use of pazopanib directly after combination chemotherapy may also explain the higher dose reduction and dropout rate. Further analysis of predictive factors can help with understanding whether specific subgroups may need different dose schedules including lower starting doses. However, the maintenance setting itself can lower the threshold for patients and physicians to withdraw therapy because of adverse events that would otherwise be considered more acceptable when treating symptomatic patients with metastatic disease.

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

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

NOTE. Bold font indicates statistical significance.
Abbreviation: AE, adverse event.
*Includes six patients randomly assigned to the placebo arm who took pazopanib in error for any period of time.
†*P* values were calculated by means of Fisher's exact test to compare the frequency of AEs of grade 3/4 between arms.

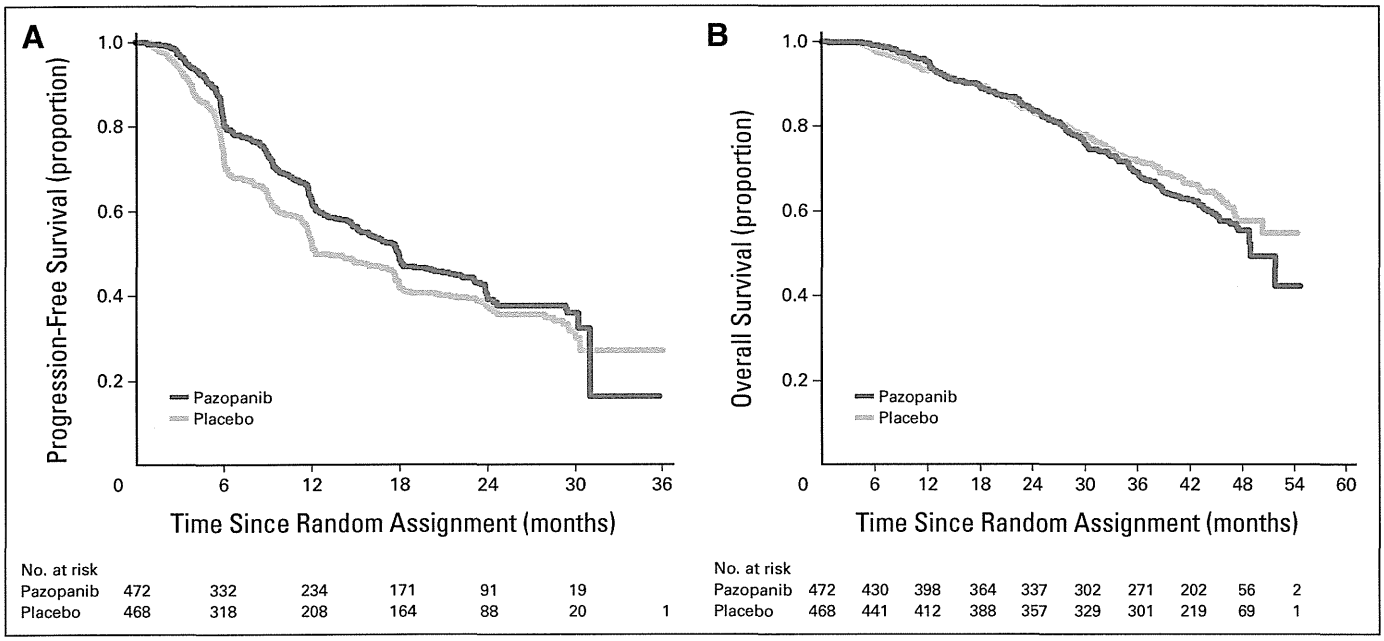

Fig 3. Kaplan-Meier estimates of the (A) primary analysis for progression-free survival according to RECIST criteria and (B) second interim analysis of overall survival. Analyses were based on the intention-to-treat population.

The different frequency of certain adverse effects in the East Asian population may contribute to the different tolerability and efficacy observed in this study. The importance of geographic region was reflected in the results of both the planned and unplanned subgroup analyses. All subgroups (except geographic region) showed consistent results with respect to our primary end point. These results indicate that the potential clinical benefit of pazopanib is limited to the non-East Asian population. Whether this observation is based on different pharmacogenetics or a need for different treatment schedules among different ethnicities remains an issue to be addressed in future protocols.

This study demonstrated activity for maintenance pazopanib therapy in women with stage II to IV ovarian carcinoma who have not progressed on first-line therapy, but the data do not allow a

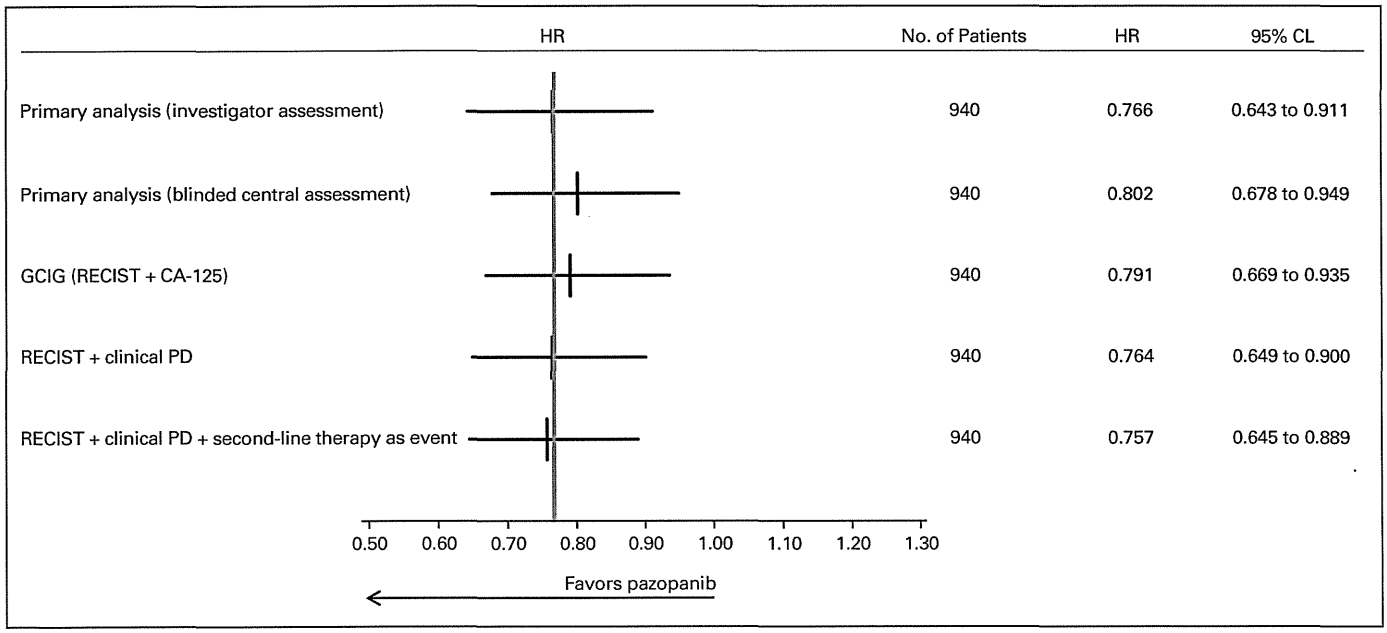

Fig 4. *Forest plot of hazard ratios (HRs) and 95% confidence limits (CLs) for the primary analysis of progression-free survival (PFS; blue vertical line) according to* RECIST (based on investigator assessment) in comparison with sensitivity analyses of PFS according to the blinded central review of the scans, with Gynecologic Cancer Intergroup (GCIG) criteria, with the analysis according to RECIST including clinical progressive disease (PD) as an event, and with the analysis according to RECIST including clinical PD and additionally start of second-line therapy as an event. All analyses were based on the intention-to-treat population. An HR less than 1 favors pazopanib.

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

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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AUTHOR CONTRIBUTIONS

Conception and design: Andreas du Bois, Sandro Pignata, Ignace Vergote, Mansoor R. Mirza, Bradley J. Monk, Ionel Mitrica, Qiong Wang, Rocco Crescenzo, Philipp Harter
Administrative support: Andreas du Bois
Provision of study materials or patients: Andreas du Bois, Jae-Weon Kim, Josep M. del Campo, Keiichi Fujiwara, Ignace Vergote, Mansoor R. Mirza, Bradley J. Monk, Rainer Kimmig, Rongyu Zang, Ivan Diaz-Padilla, Klaus H. Baumann, Marie-Ange Mouret-Reynier, Christian Kurzeder, Anne Lesoin, Paul Vasey, Christian Marth, Muneaki Shimada, Paula Calvert, Eric Pujade-Lauraine, Byoung-Gie Kim, Philipp Harter
Collection and assembly of data: Andreas du Bois, Anne Floquet, Jae-Weon Kim, Josep M. del Campo, Michael Friedlander, Sandro Pignata, Keiichi Fujiwara, Ignace Vergote, Nicoletta Colombo, Mansoor R. Mirza, Bradley J. Monk, Rainer Kimmig, Isabelle Ray-Coquard, Rongyu Zang, Ivan Diaz-Padilla, Klaus H. Baumann, Marie-Ange Mouret-Reynier, Jae-Hoon Kim, Christian Kurzeder, Anne Lesoin, Paul Vasey, Christian Marth, Ulrich Canzler, Giovanni Scambia, Muneaki Shimada, Paula Calvert, Eric Pujade-Lauraine, Byoung-Gie Kim, Thomas J. Herzog, Ionel Mitrica, Qiong Wang, Rocco Crescenzo, Philipp Harter
Data analysis and interpretation: Andreas du Bois, Jae-Weon Kim, Joern Rau, Michael Friedlander, Sandro Pignata, Ignace Vergote, Mansoor R. Mirza, Bradley J. Monk, Ivan Diaz-Padilla, Ionel Mitrica, Carmen Schade-Brittinger, Qiong Wang, Rocco Crescenzo, Philipp Harter
Manuscript writing: All authors
Final approval of manuscript: All authors

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Affiliations

Andreas du Bois, Rainer Kimmig, Klaus H. Baumann, Christian Kurzeder, Ulrich Canzler, Philipp Harter, AGO Ovarian Cancer Study Group (AGO); Andreas du Bois, Christian Kurzeder, Philipp Harter, Kliniken Essen Mitte; Rainer Kimmig, West German Tumor Center, University of Duisburg-Essen, Essen; Joern Rau, Carmen Schade-Brittinger, Coordinating Center for Clinical Trials, Philipps-University of Marburg; Klaus H. Baumann, University of Marburg, Marburg; Ulrich Canzler, University Hospitals Carl Gustav Carus, Dresden, Germany; Anne Floquet, Isabelle Ray-Coquard, Marie-Ange Mouret-Reynier, Anne Lesoin, Eric Pujade-Lauraine, Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens; Anne Floquet, Institut Bergonié, Bordeaux; Isabelle Ray-Coquard, Centre Léon Bérard, Lyon; Marie-Ange Mouret-Reynier, Centre Jean Perrin, Clermont-Ferrand; Anne Lesoin, Centre Oscar Lambret, Lille; Eric Pujade-Lauraine, Assistance Publique-Hôpitaux de Paris, Université Paris Descartes, Paris, France; Jae-Weon Kim, Jae-Hoon Kim, Korean Gynecologic Oncology Group; Jae-Weon Kim, Seoul National University; Jae-Hoon Kim, Yonsei University; Byoung-Gie Kim, Samsung Medical Center, Seoul, Republic of Korea; Josep M. del Campo, Ivan Diaz-Padilla, Spanish Ovarian Cancer Research Group; Josep M. del Campo, Vall d'Hebron University Hospital, Barcelona; Ivan Diaz-Padilla, Centro Integral Oncologico Clara Campal, HM Hospitales, Madrid, Spain; Michael Friedlander, Paul Vasey, Australian and New Zealand Gynecological Oncology Group; Michael Friedlander, The Prince of Wales Clinical School University of New South Wales, Randwick, New South Wales; Paul Vasey, Wesley Medical Centre, Auchenflower, Queensland, Australia; Sandro Pignata, Giovanni Scambia, Multicenter Italian Trials in Ovarian Cancer; Sandro Pignata, Istituto Nazionale Tumori Fondazione G. Pascale, Naples; Nicoletta Colombo, Mario Negri Gynecologic Oncology Group and University of Milan-Bicocca and European Institute of Oncology, Milan; Giovanni Scambia, Catholic University of Sacred Heart, Rome, Italy; Keiichi Fujiwara, Muneaki Shimada, Japanese Gynecologic Oncology Group; Keiichi Fujiwara, Saitama Medical University International Medical Center, Saitama; Muneaki Shimada, Tottori University School of Medicine, Nishimachi Yonago, Japan; Ignace Vergote, Belgian Gynaecological Oncology Group and University Hospitals Leuven, Leuven, Belgium; Mansoor R. Mirza, Nordic Society of Gynecological Oncology and Rigshospitalet, Copenhagen, Denmark; Bradley J. Monk, Gynecologic Oncology Californian Consortium and Creighton School of Medicine at St Josephs Hospital, Phoenix, AZ; Rongyu Zang, Fudan University Cancer Hospital, Shanghai, China; Christian Marth, AGO-Austria and Medical University Innsbruck, Innsbruck, Austria; Paula Calvert, All Ireland Co-Operative Oncology Research Group, Dublin, Ireland; Thomas J. Herzog, New York Gynecologic Oncology Group and Columbia University and Irving Comprehensive Cancer Center, New York, NY; Ionel Mitrica, Qiong Wang, Rocco Crescenzo, GlaxoSmithKline, Collegeville, PA.

GLOSSARY TERMS

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

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

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

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

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

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Appendix

Table A1. Subsequent Anticancer Therapy

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

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

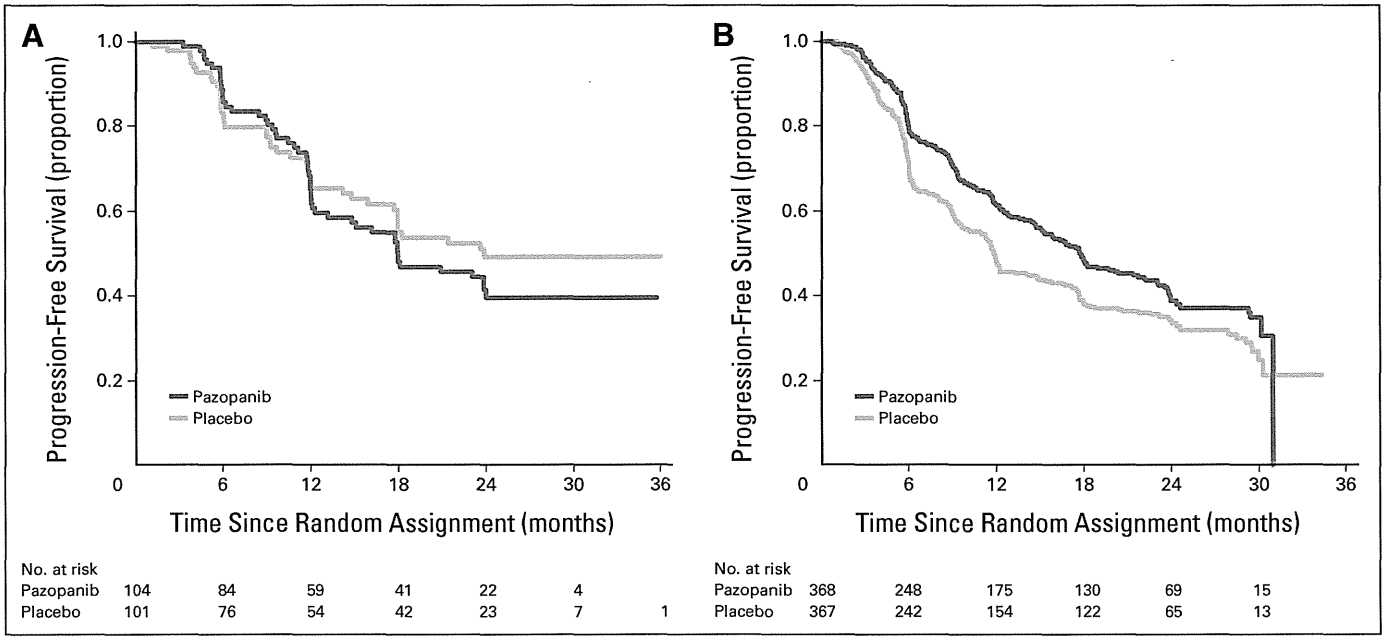

Fig A1. Kaplan-Meier estimates of primary progression-free survival analyses of the (A) East Asian and (B) non-East Asian subpopulations (investigator assessment).

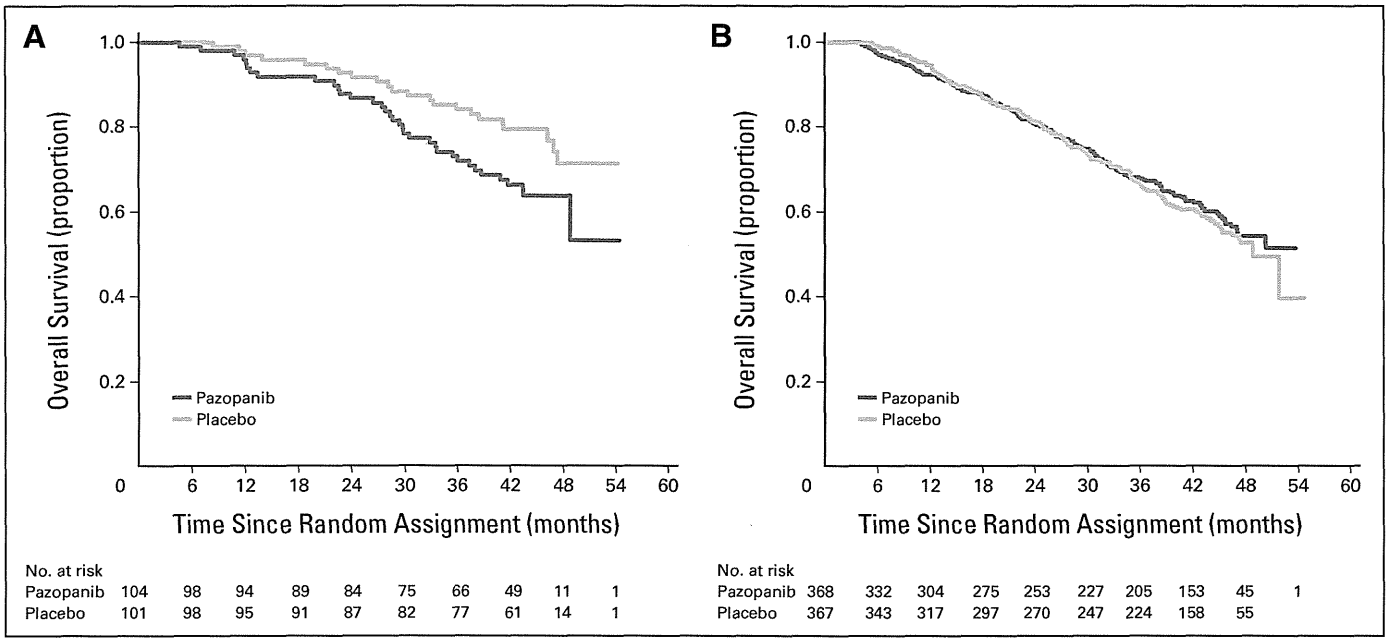

Fig A2. Kaplan-Meier estimates of second interim analyses of overall survival (OS) of the (A) East Asian and (B) non-East Asian subpopulations.

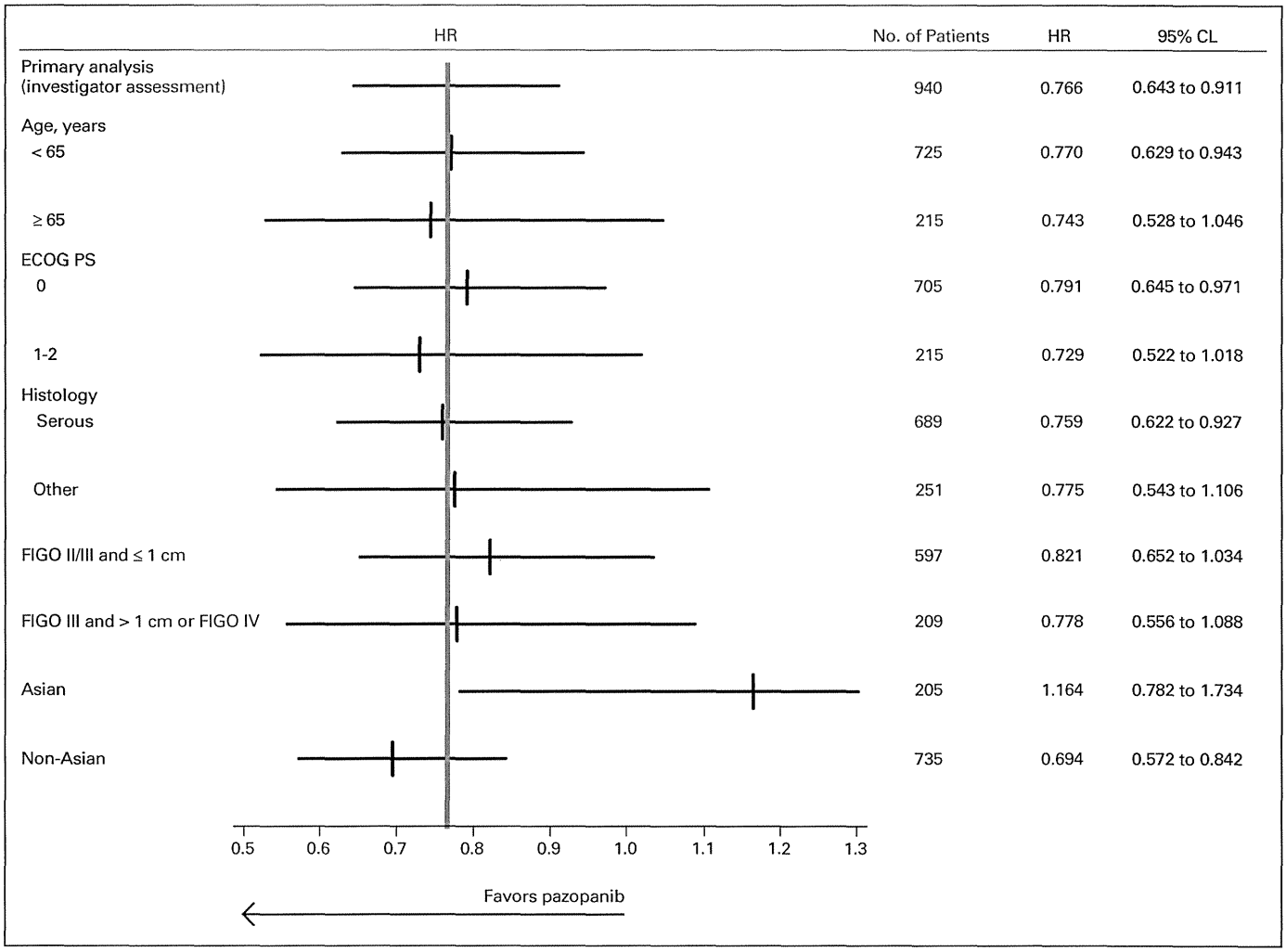

Fig A3. Forest plot of hazard ratios (HRs) and 95% confidence limits (CLs) of primary analysis of progression-free survival (investigator assessment), highlighted by the blue vertical line, in comparison with subgroup analyses according to age, Eastern Cooperative Oncology Group (ECOG) performance status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

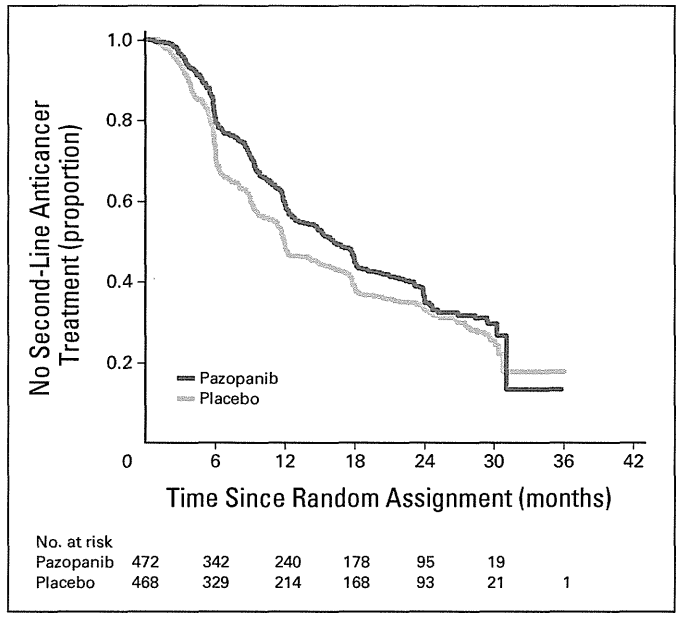

Fig A4. Kaplan-Meier estimates of sensitivity analysis of time until start of second-line anticancer treatment.

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Adenocarcinoma of the Uterine Cervix: Why Is it Different?

Keiichi Fujiwara · Bradley Monk · Mojgan Devouassoux-Shisheboran

Abstract Adenocarcinoma (AC) of the uterine cervix is the second most frequent tumor type following squamous cell carcinoma (SCC). According to the National Comprehensive Cancer Network (NCCN) guidelines, there is no difference in the treatment strategy between SCC and AC. However, there are a number of studies that suggest a worse prognosis for AC compared to SCC. In this comprehensive review, we will try to find the reason why AC is different from SCC, and then discuss what we need to do to improve the prognosis of AC. Uterine cervical AC is clearly different from SCC based on its molecular pathogenesis, histological appearance, and clinical behavior. Therefore, it will be necessary to make a different treatment strategy, particularly for patients with locally advanced and metastatic or recurrent disease. It is most important to intensify our research into the molecular profile of AC, so that we can develop more appropriate targeted therapies. Because of its rarity, international collaboration among clinical trials with translational components will be key to increasing cure rates and improving survivorship.

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K. Fujiwara (✉)
Department of Gynecologic Oncology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka City, Saitama, Japan
e-mail: fujiwara@saitama-med.ac.jp

B. Monk
Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Arizona Cancer Center, Creighton University School of Medicine at Dignity Health St. Joseph's Hospital and Medical Center, 500 W. Thomas Road, Suite 600, Phoenix, AZ 85013, USA

M. Devouassoux-Shisheboran
Department of Pathology, Hospices Civils de Lyon, Lyon, France

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Keywords Cervical cancer of the uterus · Adenocarcinomas · Squamous cell carcinoma · Clinicopathological and molecular difference · Prognosis

Introduction

Invasive cervical cancer of the uterus is one of the most common cancers among women worldwide. It is estimated that approximately 0.5 million cases occur, and approximately 76 % of them occur in low-resource nations [1•]. The most common (70 %) histopathological type is squamous cell carcinoma (SCC) with the second most common type being adenocarcinoma (AC) (15–20 %). The incidence of AC has been increasing. Prior to the 1970s, it was only 5 % of cervical cancers. It is assumed that the increase in incidence of AC has been due to a relative decrease in invasive SCC, which is more readily identified in its preinvasive stages by cytologic screening.

According to the National Comprehensive Cancer Network (NCCN) guidelines [2], there is no difference in the treatment strategy between SCC and AC. However, there are a number of studies that suggest a worse prognosis for AC compared to SCC.

In this comprehensive review, the current treatment options for AC will be presented and the literature will be reviewed with an emphasis on how and why AC differs from SCC, and then discuss what we need to do for the future.

Current Standard Treatment for Cervical Adenocarcinoma

The current treatment algorithm for cervical AC is based on stage and histopathologic factors. It has been summarized by

the National Comprehensive Cancer Network (NCCN) guideline [2].

For adenocarcinoma in situ, simple total hysterectomy is recommended. For patients who desire fertility preservation, a cervical cone excision is recommended. For stage IA adenocarcinoma with invasions of 3–5 mm, type B radical hysterectomy with retroperitoneal lymph node dissection is recommended. For patients with invasions of <3 mm, simple total hysterectomy is recommended. Again, for women who desire fertility preservation, conization or trachelectomy should be considered.

For patients with stage IB/IIA AC, radical hysterectomy or concurrent chemoradiation therapy (CCRT) is recommended. In patients with tumor sizes >4 cm disease (stage IB2/IIA2), CCRT is the standard primary treatment [3]. A pretreatment aortic nodal staging has been proposed [4, 5].

CCRT, mainly using weekly administration of cisplatin, is recommended for more advanced stages limited to the pelvis (IIB–IVA). Typical radiotherapy (RT) doses include 40–45 Gy whole pelvic RT with 10-MV X-rays using either parallel-opposed anteroposterior or four-field box beams, with 1.8–2 Gy/fraction and five fractions weekly followed by the intracavitary brachytherapy boost usually given with an ^{192}Ir source. The usual dose to point A is approximately 43 Gy/fraction for six fractions, with two fractions weekly. The median cumulative dose and biologically equivalent dose to point A is close to 70.8 and 90 Gy, respectively. In Japan, radiation dose is lower than that of Western countries, mainly because of the lower dose of high-dose-rate brachytherapy. The cumulative linear quadratic equivalent dose is 62–65 Gy prescribed at point A [6]. An extended field to the para-aortic region is not routinely given for patients without imaging findings of para-aortic lymphadenopathy or biopsy proven spread [7].

In patients with stage IVB or recurrent disease, chemotherapy is considered. Since no trial has been conducted specifically on AC, the same chemotherapy regimen will be recommended for both AC and SCC [8]: paclitaxel plus cisplatin has been accepted as the standard treatment [9] with paclitaxel and carboplatin being an alternative treatment (JCOG0505). The effectiveness of single-agent paclitaxel [10, 11] or replacing paclitaxel with docetaxel when added to carboplatin [12] has been reported as being active in advanced and recurrent AC. Adding bevacizumab is a level 1 option [13].

How Different Is Cervical Adenocarcinoma From Squamous Cell Carcinoma?

The survival of women treated for AC has been shown to be worse than SCC in some studies. Survival data from the Japan Society of Obstetrics and Gynecology treated in 2005 suggest a worse survival in AC compared with SCC for all stages (p=0.0007) (Fig. 1) [14]. The significance of the difference showing worse prognosis of AC compared with SCC by stage were p=0.0003, p=0.0002, p=0.0117, and p=0.0089 for stages I, II, III, and IV, respectively [14]. Other studies also suggested a worse prognosis for AC compared to SCC, with a 10–20 % difference in 5-year overall survival rates [15–17]. One study showed no difference in early-stage patients [18], but another study showed a worse prognosis even in an early stage [17]. It becomes more apparent as the stage advances [17, 19]. Hopkins et al. reported that patients with stage II SCC had a 62 % survival, but it was only 47 % for AC (P=0.01). For patients with stage III SCC disease, it was a 36 % survival, compared with 8 % for AC (P=0.002) [17].

Unfortunately, there has been very few prospective data that showed the prognostic significance of cell type. Monk et al. retrospectively reviewed data from 335 women with primary, previously untreated, histologically confirmed invasive (stages IIB to IVA) cervical carcinoma who received weekly cisplatin and pelvic radiation while participating in similar arms of two GOG studies (protocols 120 and 165). This ancillary data project demonstrated no significant differences but a trend in worse survival for AC compared to SCC (PFS: HR 1.40, p=0.147; OS: HR 1.32, p=0.261). This was probably a result of small numbers of patient number, as only 11.4 % had AC [20]. On the other hand, Tewari et al. showed addition of bevacizumab to chemotherapy improved an overall survival of patients with metastatic or recurrent SCC, but benefit of bevacizumab was not observed in patients with AC [13].

Why Is AC Different From SCC?

The hints to explain why clinical outcome of cervical AC is worse than SCC could be found from those studies investigating epidemiological and clinicopathological prognostic factors, as well as translational research.

Epidemiology

Both SCC and AC are almost always associated with high-risk HPV infection. AC is associated with a higher likelihood of HPV-16 or HPV-18, which is present in over 80 % cases, whereas only 70 % of SCC contain HPV-16 or HPV-18. Additionally, SCC has been shown to be associated with a wider diversity of uncommon HPV subtypes [21]. HPV-18 accounts for about 50–58 % of AC, but only 15–18 % of SCC [15, 21, 22].

Smoking is strongly associated with SCC cervix, but appears to be less associated with AC [23]. AC has been more closely associated with other risk factors more commonly seen in endometrial cancer, such as nulliparity [24] and obesity [21].