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.

**Acknowledgments**

Amgen provided funding for the trial. We thank Zhandong Don Zhong (Amgen) for doing the anti-trebananib antibody analysis; and Beate Quednau (Amgen), Cory Pfeiffenberger (Complete Healthcare Communications, Chadds Ford, PA, USA), whose work was funded by Amgen, and Daniele Sumner (University of Arizona Cancer Center, Phoenix, AZ, USA) for formatting assistance, project management, editing, and graphics assistance.

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**Published Ahead of Print on September 15, 2014 as 10.1200/JCO.2014.55.7348**
**The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.55.7348**

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Incorporation of Pazopanib in Maintenance Therapy of Ovarian Cancer

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See accompanying editorial doi: 10.1200/JCO.2014.57.4574

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Published online ahead of print at www.jco.org on September 15, 2014.

Supported by GlaxoSmithKline Pharmaceuticals, which also funded editorial assistance.

Presented in part at the 49th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 4, 2013.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00866697.

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0732-183X/14/3299-1/$20.00

DOI: 10.1200/JCO.2014.55.7348

## ABSTRACT

### Purpose
Pazopanib is an oral, multikinase inhibitor of vascular endothelial growth factor receptor (VEGFR) -1/-2/-3, platelet-derived growth factor receptor (PDGFR) -$\alpha$/-$\beta$, 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).

*J Clin Oncol 32. © 2014 by American Society of Clinical Oncology*

## 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) -$\alpha$/-$\beta$, 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.

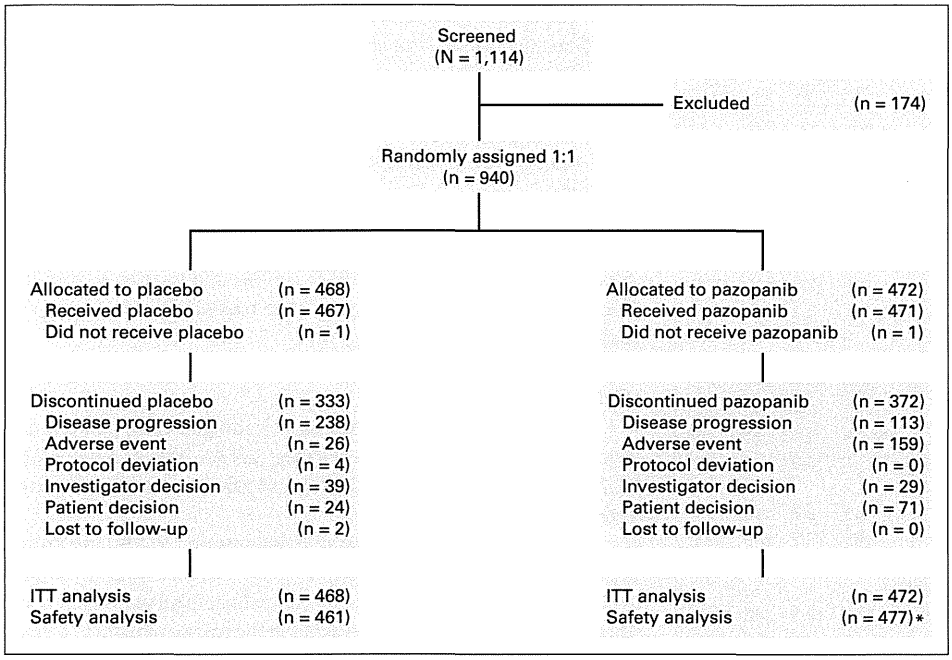


**Fig 1.** CONSORT diagram. ITT, intention to treat. (*) Includes six patients randomly assigned to placebo who took pazopanib in error for any period of time.

## 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

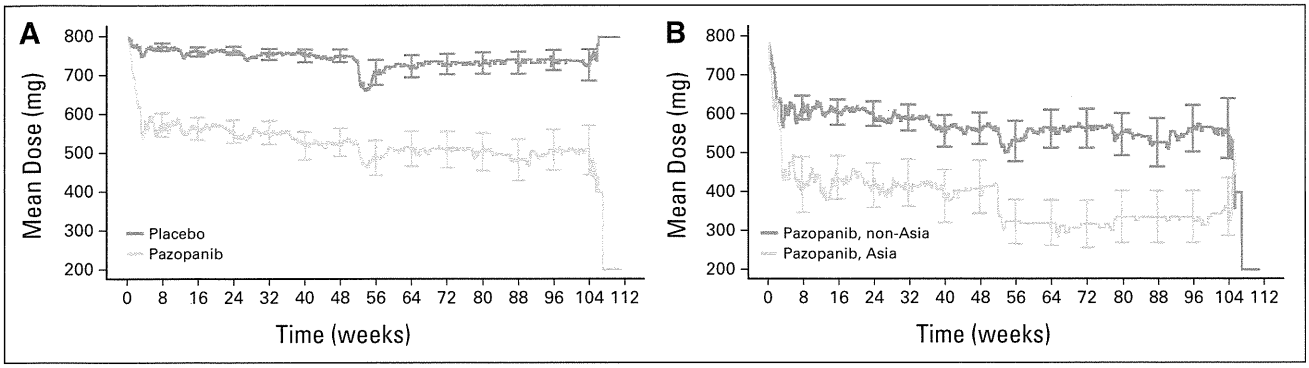


**Fig 2.** Pazopanib versus placebo exposure (A) in the overall population and (B) in the Asian *v* non-Asian population. Dose interruptions were included for mean dose calculation and subject count as zero dose.

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.

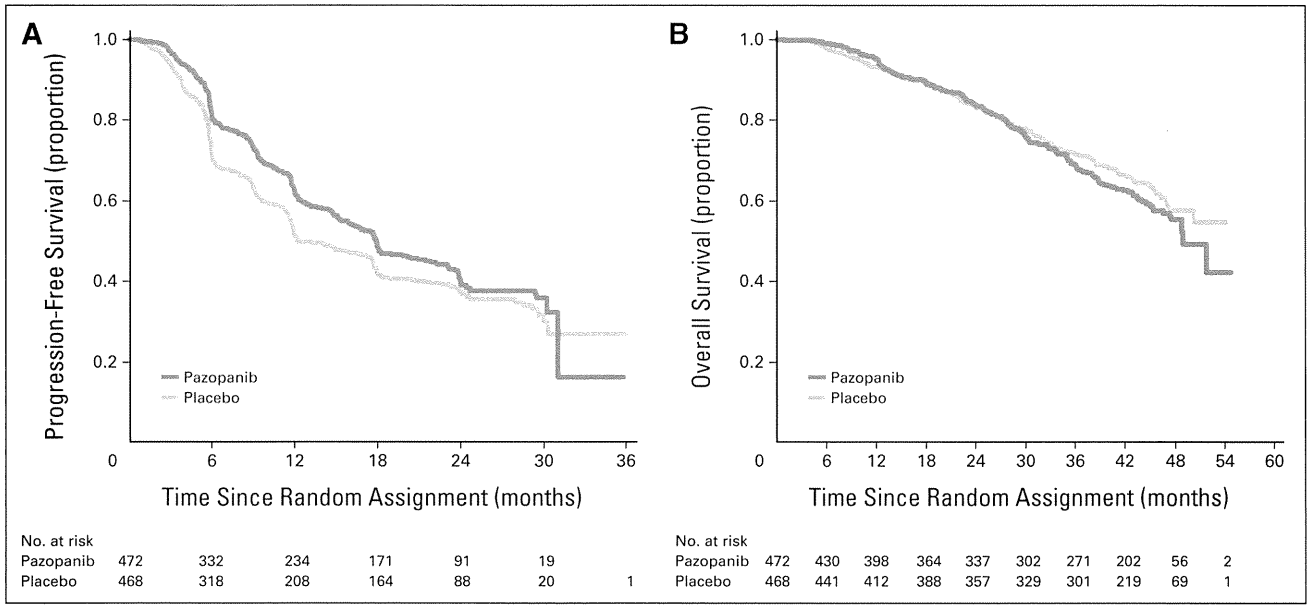


**Fig 3.** Kaplan-Meier estimates of the (A) primary analysis for progression-free survival according to RECIST criteria and (B) second interim analysis of overall survival. Analyses were based on the intention-to-treat population.

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

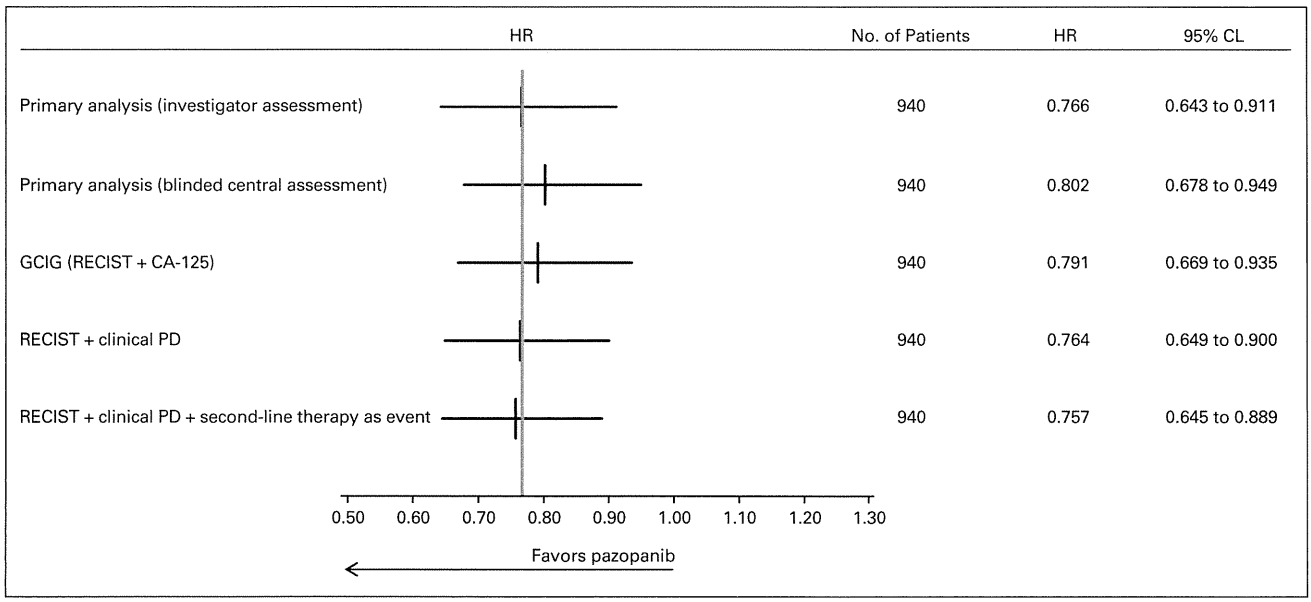


**Fig 4.** Forest plot of hazard ratios (HRs) and 95% confidence limits (CLs) for the primary analysis of progression-free survival (PFS; blue vertical line) according to RECIST (based on investigator assessment) in comparison with sensitivity analyses of PFS according to the blinded central review of 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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## 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.

## Acknowledgment

We thank all the patients and their families who participated in this study; all investigators and supporters at the study sites, the central study offices of the study groups, the data manager Behnaz Aminossadati of the Coordinating Center for Clinical Trials, Philipps-University of Marburg, and all involved staff at GlaxoSmithKline; and William Sinkins, PhD, ProEd Communications, for his editorial assistance.


## 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.

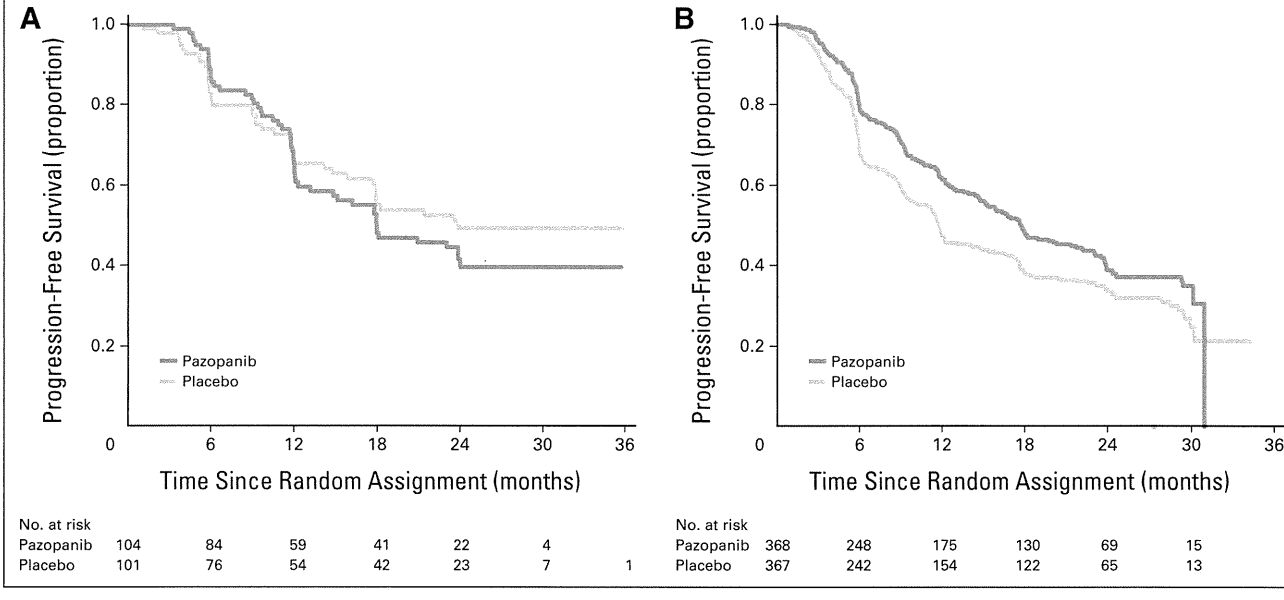


**Fig A1.** Kaplan-Meier estimates of primary progression-free survival analyses of the (A) East Asian and (B) non-East Asian subpopulations (investigator assessment).

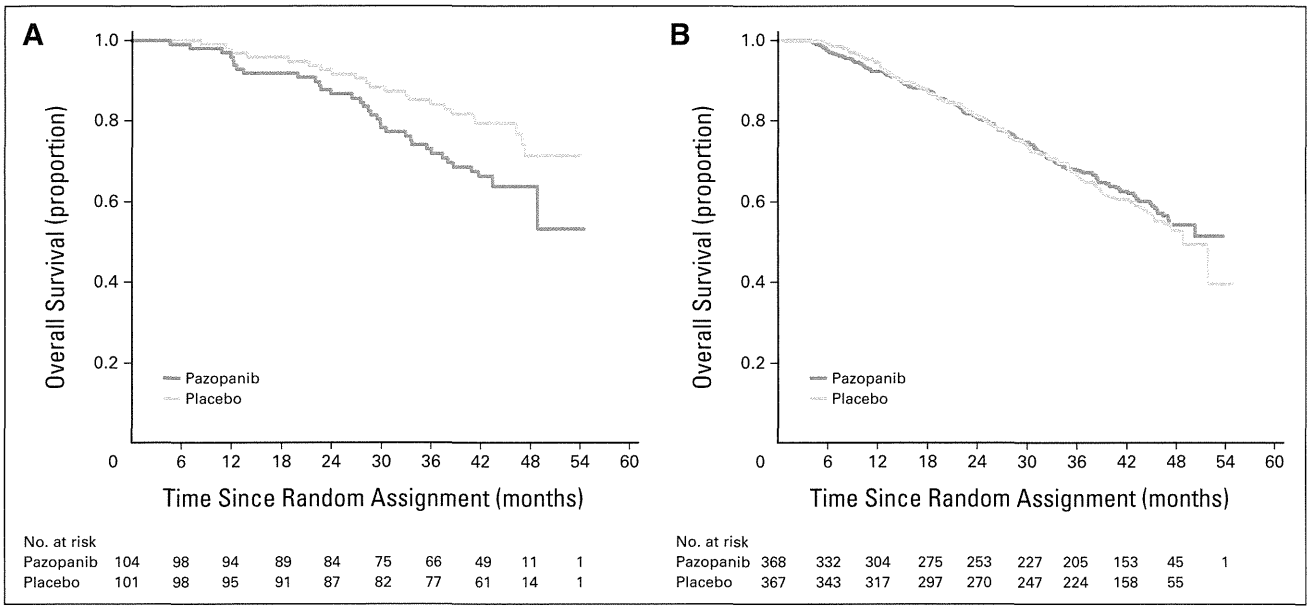


**Fig A2.** Kaplan-Meier estimates of second interim analyses of overall survival (OS) of the (A) East Asian and (B) non-East Asian subpopulations.

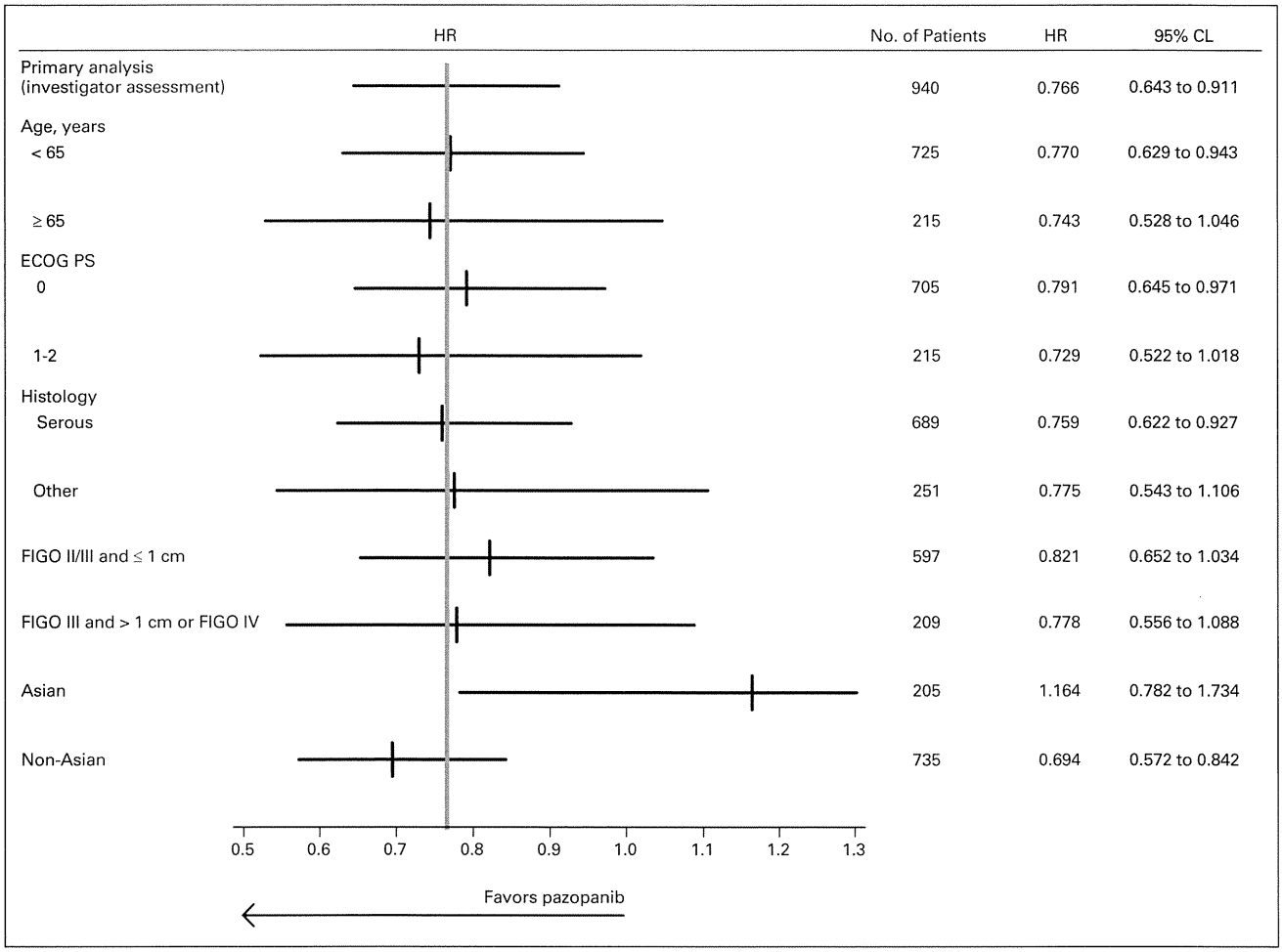


**Fig A3.** Forest plot of hazard ratios (HRs) and 95% confidence limits (CLs) of primary analysis of progression-free survival (investigator assessment), highlighted by the blue vertical line, in comparison with subgroup analyses according to age, Eastern Cooperative Oncology Group (ECOG) performance 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.

  

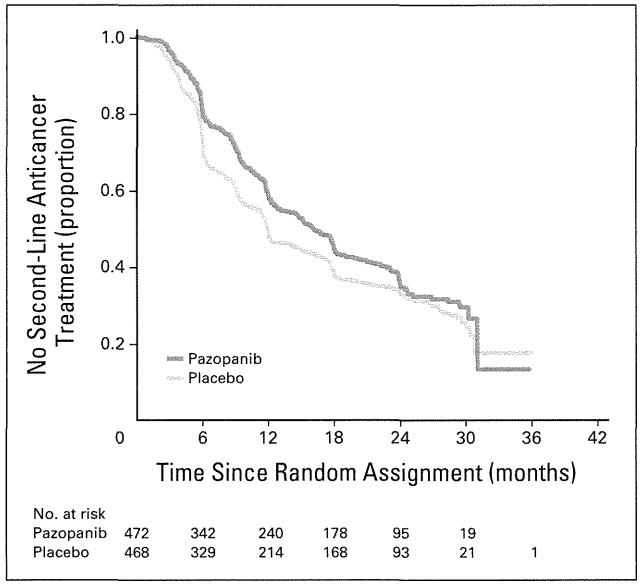


**Fig A4.** Kaplan-Meier estimates of sensitivity analysis of time until start of second-line anticancer treatment.

Curr Oncol Rep (2014) 16:416
DOI 10.1007/s11912-014-0416-y



# 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.

This article is part of the Topical Collection on *Gynecologic Cancers*

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Published online: 18 October 2014

**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].

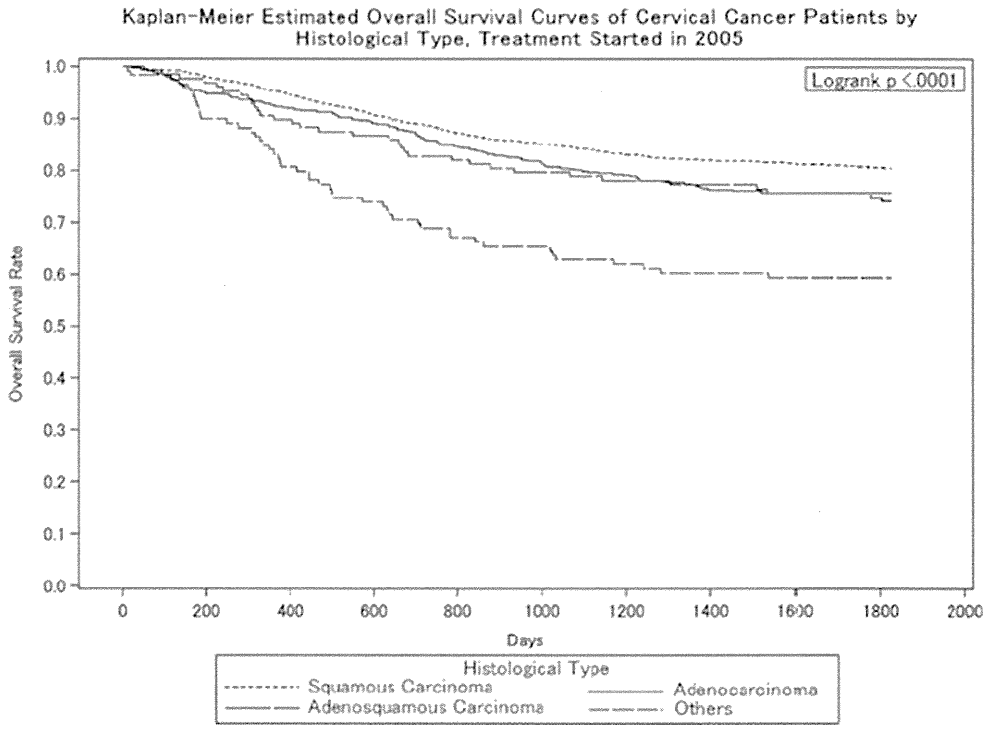


**Fig. 1** Kaplan-Meyer survival curve of patients with stages I–IV cervical cancer of the uterus by histological type, treated in 2005 [14] (cited with permission)

## Prognostic Factors

Pattern of dissemination has been reported to be different between AC and SCC. Some studies show that the sites of recurrence for SCC are lymphatic, whereas AC seems to disseminate more hematogenously [25]. There are also higher rates of ovarian metastases seen with AC than SCC (5.31 versus 0.79 %) in some series [25]. Thus, the frequency of distant metastasis appears higher in AC than in SCC [16, 26], with a higher tendency for intraabdominal carcinomatosis and hematogenous metastases compared with SCC [25]. For example, there is a report showing that peritoneal cytology was positive in 9 of 228 cervical cancer patients (3.9 %). Three of them were SCC (3/139; 2.2 %) and 6 of them (6/89; 6.7 %) were AC. Only 30 % of patients with SCC who had positive cytology recurred, while all patients with AC had recurrence. In this study, multivariate analysis revealed that peritoneal cytology ($p$=0.029) and histological type ($p$=0.004) were independent prognostic factors [27].

Tumor size also appears to be a significant prognostic factor with AC being more endophytic and "bulkier." Several studies have shown that tumors >4 cm have a worse prognosis for AC compared to SCC [16]. It has also been reported that AC is more likely to have lymph node involvement compared to SCC resulting in a worse prognosis [16, 28].

One possible explanation for the worse prognosis among women with AC might be a lower sensitivity to radiotherapy [29]. Eifel et al. reported worse prognosis of stage IB AC patients than SCC when the majority of patients were treated with radiotherapy [16]. Subset analyses of several studies also suggest a higher recurrence rates after radiation in AC compared to SCC [30].

## Pathology

A better understanding of the histopathology may help explain the differences in the pathogenesis and outcomes of AC compared to SCC.

Pathologically, AC is more heterogeneous than SCC. Although SCC has several subtypes as shown in Table 1, most of them (more than 90 %) are non-keratinizing or keratinizing. In contrast, the distribution of subtypes of AC varies (Table 1). This may explain the clinical differences in the behavior of AC versus SCC.

To identify the distinguishing features between endocervical AC and endometrial subtypes of AC, immunohistochemistry is usually used. Carcinoembryonic antigen (CEA) and p16 expression (a surrogate of HPV) together with the absence of hormone receptors and vimentin favor a cervical origin.

Cervical ACs are subdivided into several histological subtypes as outlined below [1•].

| | |
|---|---|
| Usual-type adenocarcinoma | Usual-type adenocarcinoma is the most common subtype, accounting for 80–90 % of all cervical AC [31]. In the past, this variant has been referred to as mucinous AC, but there is no or little mucin in the |

**Table 1** WHO Classification of carcinoma of the uterine cervix [1•]

| Adenocarcinoma | Percentage | Squamous cell carcinoma |
|---|---|---|
| Endocervical adenocarcinoma, usual type | 80 | Keratinizing |
| Mucinous carcinoma, NOS | | Non-keratinizing |
| Gastric type | 1–2 | Papillary |
| Intestinal type | | Basaloid |
| Signet ring cell type | | Warty |
| Villoglandular carcinoma | | Verrucous |
| Endometrioid carcinoma | 5–7 | Squamotransitional |
| Clear-cell carcinoma | 2–4 | Lymphoepithelioma like |
| Serous carcinoma | 3 | |
| Mesonephric carcinoma | | |
| Adenocarcinoma admixed with neuroendocrine carcinoma | | |
| Adenosquamous carcinoma | 4 | |
| Glassy cell variant | 1–2 | |

majority of cells. The tumor is composed of glands of varying sizes and papillae lined by columnar cells with eosinophilic cytoplasm and brisk mitotic activity and frequent apoptotic bodies. There is a frequent association with adenocarcinoma in situ, which is the precursor of this type of carcinoma. In 12 % of cases, the depth of stromal invasion is less than 5 mm from base of the surface epithelium, corresponding to an *early invasive AC*. Usual type of cervical ACs are always associated with high-risk HPV.

Mucinous adenocarcinoma — Mucinous adenocarcinoma is characterized by the presence of abundant cytoplasmic mucin in the majority of tumor cells. They are subdivided into gastric and intestinal-type endocervical adenocarcinomas.

Mucinous carcinoma, gastric-type — Mucinous carcinoma, gastric-type [32, 33] is rare in Western countries but represents up to 20 % of cervical ACs in Japan. This tumor is composed of glands with a pyloric phenotype (voluminous, clear, pale eosinophilic cytoplasm, and distinct cell borders) and immunoprofile (HIK1083 and MUC6 expressions). There is no association with HPV. The patients with this type of mucinous carcinomas have a poor prognosis with a decreased 5-year survival rate of 30 versus 77 % for usual-type adenocarcinoma.

Minimal deviation adenocarcinoma (adenoma malignant) — Minimal deviation adenocarcinoma (adenoma malignant) is an uncommon variant of gastric-type mucinous carcinoma of the cervix (1.3 %), extremely well differentiated, seen in women at any age (20–78, mean 45 years) [34]. This tumor may arise in patients with Peutz-Jeghers syndrome, with germline inactivation of the *LKB1* (STK11) gene. Sporadic adenoma malignant displays also a loss of heterozygosity at *LKB1* (STK11) locus [35]. HPV DNA is not detected in these tumors which are usually not associated with an in situ AC component. Patients usually present with high-stage tumor because of the delay in the diagnosis and having a poor prognosis, with 30 % overall survival at 2 years.

| | |
|---|---|
| Mucinous carcinoma, intestinal type | Mucinous carcinoma, intestinal type [33], is rare and is composed of glands with goblet cells and rarely Paneth cells. MUC-2, a goblet cell marker, is detected in 85 % of cases. The tumor may present with extensive extra glandular mucin and a colloid carcinoma appearance. An intestinal-type adenocarcinoma in situ may be seen in association with the invasive component. High-risk HPV has been detected in this variant. |
| Mucinous carcinoma, signet ring cell type | Mucinous carcinoma, signet ring cell type, is very rare and shows focal or diffuse signet ring cell morphology. |
| Villoglandular adenocarcinoma | Villoglandular adenocarcinoma shows a distinct exophytic, villous-papillary growth, and is characterized by a frond-like pattern resembling villoglandular adenoma of the colon. This tumor usually occurs in younger women and has an excellent prognosis in its pure form [36]. When superficially invasive, this variant has an excellent prognosis with very rare lymph node metastases. HPV 16, 18, or 45 have been identified. |
| Endometrioid adenocarcinoma | Endometrioid adenocarcinoma account for 5 % of cases and presents the same morphology than its endometrial counterpart, even though squamous metaplasia is less common. This histological type of AC may be developed from cervical endometriosis, but usually, adenocarcinoma in situ (sometimes of endometrioid type) is seen in close vicinity of the tumor. |
| Clear-cell adenocarcinoma | Clear-cell adenocarcinoma is composed of glands, cysts, and papillae lined by clear or hobnail cells. This type of cervical carcinoma is very rare (2 %) and has been associated with in utero exposition to diethylstilbestrol (DES). |
| Serous adenocarcinoma | Serous adenocarcinoma is also very rare in the cervix accounting for less than 2 % of cases. A diagnosis of primitive cervical serous AC should not be rendered until a primary serous carcinoma in the endometrium has not been excluded. Most are HPV related. The morphology and the immunoprofile of serous AC of the cervix are identical to its counterparts in the female genital tract and peritoneum except for a solid pattern which is rare [37]. |
| Mesonephric adenocarcinoma | Mesonephric adenocarcinoma is a rare variant of cervical AC that is developed from cervical mesonephric remnants and is typically HPV unrelated, seen in reproductive and postmenopausal women [38]. The tumor may be incidentally found but a cervical mass is usually seen. Tubular, ductal, retiform (with slit-like spaces), and solid patterns have been described. The cells are columnar with atypia and mitoses. Typically, a colloid-like material is seen in the lumen of tumor glands, and mesonephric remnants are seen at the periphery of AC. The tumor expresses both keratin and vimentin, with androgen receptor and CD10 positivity. This variant is usually of stage I at the time of diagnosis and has a good prognosis except for those with a sarcomatoid component. |
| Adenocarcinoma admixed with neuroendocrine carcinoma | Adenocarcinoma admixed with neuroendocrine carcinoma is a tumor with a little component of AC either in situ or invasive. The bulk of the tumor is composed of neuroendocrine carcinoma, |

**Table 2** Comparison between squamous and various types of adenocarcinomas of the uterine cervix [2, 3, 5, 30, 47–53]

| Cervical carcinomas | Squamous cell carcinoma | Endocervical adenocarcinoma, usual type | Mucinous carcinoma, gastric-type adenoma malignum | Mucinous carcinoma, intestinal type | Clear-cell carcinoma | Adenosquamous carcinoma |
|---|---|---|---|---|---|---|
| Incidence<br>Mean age at diagnosis | 75 % of cases<br>52 years old | 20–25 % of cases<br>46 years old | Most frequent in Japan: 20 % of ADC<br>Adenoma malignum: 1 %<br>42 years old | Rare pure signet ring cells and colloid ADC are rare | Rare DES exposure: 19 years old<br>Sporadic: 47 years old | 4 % of cervical cancers<br>28 % of ADC |
| Precursor | SIL | AIS | Atypical LEGH | AIS, intestinal type | None | SIL and AIS<br>Possible: SMILE |
| Morphology | Polygonal, spindle cells<br>Masses with central keratin and necrosis | Columnar cells<br>Glands, papillae, and solid pattern<br>Scant intracellular mucin<br>Apoptotic bodies | Small and cystic glands<br>Gastric and pyloric type mucin | Glands and papillae<br>Goblet cells, argentaffin, and Paneth cells | Tubulo-cystic, papillary pattern<br>Clear (glycogen rich), hobnail cells with high-grade nuclei | Malignant-appearing squamous and glandular elements |
| Immunoprofile | Pankeratin +++<br>CK7 −/+<br>CK14 +<br>CK5/6 +<br>Neuroendocrine markers usually −<br>P16 +++<br>TTF1 −<br>P63 +++<br>CEA −<br>ER and PR usually + | Pankeratin +++<br>CK7 +++<br>Neuroendocrine markers usually −<br>P16 +++<br>TTF1 −<br>P63 usually −<br>CEA cytoplasmic +++<br>ER and PR usually − | Pankeratin +++<br>CK7+++<br>CK 20 focally +<br>HIK1083 +<br>MUC6 +<br>P16 usually −<br>CEA + (apical borders)<br>P53 may be +++<br>ER and PR − | Pankeratin +++<br>CK7 +++<br>CK20 focally +<br>CDX2 focally +<br>CEA +<br>P16 +++ | Pankeratin +++<br>CK7+++<br>ER and PR −<br>P16 − (patchy +)<br>CEA −<br>HNF1 beta +++ | Pankeratin +++<br>CK7 + and CEA + in ADC elements<br>CK5/6 + in squamous<br>P16 +++ |
| Molecular biology | HPV 16 > HPV 18 (15 %)<br>*TP53* mutation 5.9 % (codon 249)<br>Deletion of 3p (85 %)<br>Deletion 9p21 (11 %)<br>Gain 20q (>50 %)<br>10 % *EGFR* amplification<br>Rare *KRAS* mutations | HPV 18 (50 %) > HPV 16<br>*TP53* mutation 13.3 % (codon 282)<br>Deletion 3p<br>Deletion 2q (25 %)<br>Deletion 5p (38 %)<br>No *EGFR* amplification<br>No *KRAS* mutation | No HPV-related association to Peutz-Jeghers syndrome<br>Mutations in STK11 tumor suppressor gene on chromosome 19p in 50 % of cases | High-risk HPV related | In utero exposure to DES (unrelated to HPV)<br>Sporadic: may be associated to high-risk HPV | HPV 18 > HPV 16<br>Loss of expression of ARID1A |
| Behavior | 16.9 % stage IB1 at diagnosis | 26.7 % stage IB1 at diagnosis | Higher stage at diagnosis due to lack of cytology/ | | 85 % stage I or II<br>Positive lymph nodes 18 % | Prognosis is worse with dead rates 1.8 times greater |