Efficacy and Safety of AEZS-108 (LHRH Agonist Linked to Doxorubicin) in Women With Advanced or Recurrent Endometrial Cancer Expressing LHRH Receptors

A Multicenter Phase 2 Trial (AGO-GYN5)

Günter Emons, MD, PhD,* Grigor Gorchev, MD,† Philipp Harter, MD,‡ Pauline Wimberger, MD, PhD,§ Anne Stähle, MD,|| Lars Hanker, MD,¶ Felix Hilpert, MD, PhD,# Matthias W. Beckmann, MD, PhD,** Peter Dall, MD, PhD,†† Carsten Gründker, PhD,* Herbert Sindermann, PhD,‡‡ and Jalid Sehouli, MD, PhD §§

Objective: Advanced or recurrent endometrial cancer (EC) no longer amenable to surgery or radiotherapy is a life-threatening disease with limited therapeutic options left. Eighty percent of ECs express receptors for luteinizing hormone–releasing hormone (LHRH), which can be targeted by AEZS-108 (zoptarelin doxorubicin acetate). This phase 2 trial was performed to assess the efficacy and safety of AEZS-108 in this group of patients.

Methods: Patients had FIGO (Fédération Internationale de Gynécologie et d’Obstétrique) III or IV or recurrent EC, LHRH receptor–positive tumor status, and at least had 1 measurable lesion (Response Evaluation Criteria in Solid Tumors). Prior anthracycline therapy was not allowed. Patients received AEZS-108 as a 2-hour infusion on day 1 of a 21-day cycle. The treatment was continued for a maximum of 6 to 8 cycles. The primary end point was the response rate determined by the Response Evaluation Criteria in Solid Tumors.

Results: From April 2008 to November 2009, 44 patients were included in the study at 8 centers in Germany (AGO) and 3 centers in Bulgaria. Forty-three of these patients were eligible. Two (5%) patients had a complete remission, and 8 (18%) achieved a partial remission. Stable disease for at least 6 weeks was observed in 44%. The median time to progression was 7 months, and the median overall survival was 15 months. The most frequently reported grade 3 or 4 adverse effects were neutropenia (12%) and leucopenia (9%).

Conclusions: AEZS-108, an LHRH-agonist coupled to doxorubicin, has significant activity and low toxicity in women with advanced or recurrent LHRH receptor–positive EC, supporting the principle of receptor-mediated targeted chemotherapy.

Key Words: Endometrial cancer, Targeted therapy, LHRH receptor, Clinical trial, Phase 2
Endometrial cancer (EC) is the most common malignancy of the genital tract of women living in industrialized countries. In the European Union, nearly 64,300 women are estimated to be diagnosed with EC, and 14,700 are estimated to die of this disease in 2013.1 In the United States, 49,560 new cases of EC are expected in 2013, including 8190 deaths.2 Although most women with EC present at an early stage and can expect curative treatment through surgery with or without adjuvant radiation and/or chemotherapy, some will have primary advanced disease or recurrences no longer amenable to surgery and/or radiotherapy. Prognosis is poor for these women with a median overall survival (OS) of only approximately 12 months for patients enrolled in clinical trials.3 The mainstay of the treatment of these patients has been systemic cytotoxic or endocrine therapy with the aim of palliating symptoms, improving quality of life, delaying progression of disease, and extending OS.3,4 Recent systematic reviews have pointed out that progression-free survival was improved with more aggressive chemotherapy without significant effects on OS.3–5 Only the 3-drug combination of cisplatin, doxorubicin, and paclitaxel resulted in a small survival advantage at the cost of a marked increase in toxicity.3–5 For hormonal treatments in any form, no evidence exists that it improves the survival of patients with advanced or recurrent EC.6

Eighty percent of ECs express receptors for luteinizing hormone–releasing hormone (LHRH).7 Treatment of EC cells with LHRH analogs in vitro resulted in growth inhibition,7 but clinical trials have demonstrated insufficient activity of LHRH agonists.8 Therefore, cytotoxic LHRH analogs such as AEZS-108 (formerly AN-152 and ZEN-008)8–12 were developed to use LHRH receptors for targeted chemotherapy.8–12 In AEZS-108, the LHRH agonist D-Lys 6-LHRH is covalently linked to doxorubicin. AEZS-108 was shown to bind with high-affinity to LHRH-specific receptors on human breast, endometrial and ovarian cancer cells, and on biopsy specimens.5,7,11 After internalization, AEZS-108 induces apoptosis in human breast, endometrial, and ovarian cancer cells independent of the multidrug resistance 1 system.12 As normal female tissues and cells, except for pituitary gonadotropes, the ovary and the endometrium do not express relevant amounts of LHRH receptors; AEZS-108 might be an ideal compound for targeted therapy for tumor cells positive for LHRH receptors.13 AEZS-108 was less toxic and more efficacious than doxorubicin in inhibiting the growth of LHRH receptor–positive human endometrial and ovarian cancers xenotransplanted into nude mice.13 In a recent phase 1 study in women with LHRH receptor–positive tumors, we could show that AEZS-108 can be safely administered to humans at a maximally tolerated dose of 267 mg/m² every 3 weeks in the absence of supportive medication.14 The present study was designed to assess the efficacy and toxicity of AEZS-108 in patients with advanced or recurrent ECs expressing receptors for LHRH.

MATERIALS AND METHODS

Eligible patients met the following criteria: aged 18 years or older, LHRH receptor–positive tumor status determined by immunohistochemical evaluation usually from the primary tumor, histologically confirmed EC, advanced (FIGO III or IV) or recurrent disease, not amenable to potentially curative treatment with surgery and/or radiation therapy, and no previous anthracycline-based chemotherapy. Previous endocrine or non–anthracycline-based chemotherapies (adjuvant or first-line palliative therapies) were allowed.

Patients were ineligible if they met any of the following criteria: history of allergic reaction to anthracycline, peptide drugs, or to protein; history of unstable or newly diagnosed angina pectoris; documented history or current serious arrhythmia, congestive heart failure, or recent myocardial infarction (within 6 months of enrolment); left ventricular ejection fraction (LVEF) less than 60%; prior radiotherapy to the pericardial area greater than 35 Gy and more than 50% of bone marrows involved; concomitant use of potentially cardiotoxic medication, chemotherapy, immunotherapy, hormone therapy, or radiotherapy within 4 weeks of entry (nitrosoureas or mitomycin C within 6 weeks of entry); anticipated ongoing concomitant anticancer therapy during the study; any uncompensated or uncontrolled nonmalignant condition: brain metastasis or leptomeningeal disease; Eastern Cooperative Oncology Group performance status of greater than 2; life expectancy of less than 3 months; neurologic or psychiatric disease or drug/alcohol abuse that would interfere with the subject’s proper completion of the protocol assignment; use of LHRH agonist or antagonist treatment within 6 months before entry; concomitant or recent (within 8 weeks) treatment with another investigational drug or prior treatment with AEZS-108 (at any time); lack of ability or willingness to give informed consent; and anticipated nonavailability for study visits/procedures. Patients were also ineligible if they have any of the following laboratory values: thrombocyte count of less than 100 × 10⁹/L; absolute neutrophil count of less than 1.5 × 10⁹/L; hemoglobin level of less than 6.8 mmol/L (<11 g/100 mL); ASAT (aspartate amino-transferase), ALAT (alanine amino-transferase), and AP (alkaline phosphatase) values greater than 2.5 times the upper limit of reference range (ULR) (>5 × ULR if clearly related to liver metastases); and creatinine or bilirubin levels greater than the ULR.

The paraffin-embedded tissue specimen from the primary tumor or, where available, from recent punch biopsy were used to determine the expression of LHRH receptors.
with immunohistochemical evaluation. The assay was performed centrally and used a polyclonal rabbit anti-LHRH receptor antibody and a biotin-coupled secondary antibody, which is detected with enzyme-conjugated streptavidin.15

Each treatment cycle consisted of 21 days in which AEZS-108 267 mg/m² (equimolar to 76.8 mg/m² of free doxorubicin) was administered on day 1 as a 2-hour intravenous infusion. Prophylactic antiemetic treatment with 8 mg of dexamethasone was recommended.

Dose reduction to 160 mg/m² was required for the following: grade 4 neutropenia lasting 7 days or more, febrile neutropenia, grade 3 thrombocytopenia persistent at the time of redosing and associated with a clinical risk of bleeding, any other grade 4 hematologic toxicity lasting 7 days or more, and grade 3 nausea/vomiting/diarrhea despite optimal medical management lasting for 5 days. Dose delay was required for patients who had not recovered to the Common Terminology Criteria for Adverse Events grade 1 from a possibly drug-related adverse event (except alopecia) within 3 weeks. Patients who had not recovered within 5 weeks from the dosing were withdrawn and followed up as required. In case of a delayed hematologic recovery, hematopoietic growth factors or transfusion of blood components could be administered as needed. Eligible patients received therapy for a planned maximum of 6 cycles allowing, on a case-by-case basis, up to 8 cycles based on tumor response and tolerability.

Patients were evaluated for adverse events/toxicity on a continuous basis, including clinical laboratory (hematology, biochemistry, and urinalysis on day 1, 8, 15, and 22 of each cycle) and LVEF assessments (by echocardiography or radionuclide ventriculography/multigated radionuclide angiography before each cycle). The National Cancer Institute–Common Terminology Criteria for Adverse Events (version 3.0) was used for grading the severity of symptoms and abnormal findings.

Response was evaluated after every second cycle and determined by using the Response Evaluation Criteria in Solid Tumors.16 Partial response (PR) or complete response (CR) had to be confirmed by repeat assessments that were performed no less than 4 weeks after the criteria for response were first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after the study entry at a minimum interval of 6 weeks. All images of tumor lesions (computed tomography, magnetic resonance imaging, and x-ray) were provided to an independent reviewer who performed a reevaluation of all responses. Symptomatic deterioration was defined as the global deterioration in health status attributable to the disease that required a change in therapy without an objective evidence of the progression of disease. Patients who were defined as having no repeat tumor assessments after the initiation of study therapy, for reasons unrelated to symptoms or signs of disease were classified as not evaluable for response.

Time to progression (TTP) was defined as the time between the study day 1 and the date at which progressive disease was objectively documented.

Overall survival was defined as the observed length of life from entry into the study to death or to the date of last contact.

This study used an optimal, but flexible, 2-stage Simon design that used an early stopping rule intended to limit patient accrual to inactive treatments.17 During the first stage, the targeted accrual was 21 patients. If 2 or more of the 21 patients responded, accrual to the second stage was initiated. Otherwise, the study would be stopped, and the treatment regimen would be classified as uninteresting. If opened to the second stage, the overall study accrual would be to 41 eligible and assessable patients. If 5 or more of the 41 patients responded, then the regimen would be considered worthy of additional investigation.

The investigators performed the investigations after the approval of the study by the competent local regulatory authorities and independent ethics committees. The investigators obtained informed consent from each participant before inclusion into the study.

RESULTS

Between April 2008 and November 2009, 48 patients were screened at 8 sites of the German AGO study group (study AGO-GYN5) and 3 Bulgarian sites. Forty-four (92.4%) of the tumors were found to express LHRH receptors. These patients were enrolled. One patient was excluded from the analysis because her clinical status worsened before receiving AEZS-108. The remaining 43 patients were assessed for toxicity and response. Patient demographics are listed in Table 1. Ten (23%) patients had received prior chemotherapy (adjuvant or first-line palliative therapy), which consisted of the combination of platinum/paclitaxel in 8 (19%) patients.

The mean number of cycles of AEZS-108 received was 5. Two (5%) patients received 8 cycles. One patient with febrile neutropenia had dose reduction of AEZS-108 to 160 mg/m² for cycle 2 and cycle 3 (her last cycle).

The most frequent adverse reactions reported by the investigators are listed in Table 2. The major toxicities (grade 3 or 4) were neutropenia (12%), leukopenia (9%), and lymphopenia (5%). Based on the analysis of hematologic profiles, nadir counts for leukocytes and neutrophils were observed consistently on cycle day 15 but were rapidly reversible. Although leukocytopenia did not show a sharp nadir and was observed at all of the weekly assessments, it was noncumulative. Nadir leukopenia, neutropenia, and lymphopenia were of grade 3 or 4 in up to 26%, 46%, and 35% of the patients throughout all cycles, respectively. Blood transfusion and G-CSF (granulocyte-colony stimulating factor) were used as supportive or prophylactic treatments in 2 (5%) and 7 (16%) patients, respectively. One patient showed a decrease of LVEF below 50% (grade 2). In this patient, LVEF findings over time were as follows: baseline, 65%; cycle 1, 51%; cycle 3, 62% (highest on-treatment value); cycle 6, 47% (lowest on-treatment value); cycle 7, 51%; and cycle 8, 50%. Two of 43 (5%) patients died within 30 days of the last dose of AEZS-108. In 1 case, progressive disease was an underlying cause of the death. The other death was due to acute respiratory distress syndrome and was judged unrelated to AEZS-108.

The overall response rate was 23%. Two (5%) patients had a CR that lasted at least 8 months and 23 months. Eight
(19%) patients had PR. Twenty (47%) patients met the criteria for stable disease, resulting in a clinical benefit rate of 70%. Nine (21%) patients had progressive disease, and 4 patients were not evaluable (1 noncancer death before cycle 2; 3 patients with tumor assessments not evaluable for reviewer). Both patients with CR and 6 women with PR had type I disease. One patient with PR had a serous EC and another had a clear cell EC. Thus, of the 10 patients with objective responses, 8 had type I and 2 had type II disease.

A waterfall plot of change in tumor size is presented in Figure 1. Each bar represents a patient’s change in tumor size, from baseline to maximal tumor shrinkage, expressed as percentage. Tumor size was calculated by using the sum of the largest diameters of target lesions, as determined by the investigator.

The median TTP was 7 months, and the median OS was 15 months (95% confidence interval, 9.3–22.2 months).

DISCUSSION

This is the first report on the clinical efficacy of AEZS-108, a drug targeted to the LHRH receptor in EC. In patients with relapsed or advanced EC no longer amenable to curative surgical or radiotherapy and whose tumors expressed LHRH receptors, an objective response rate of 23% and a rate of stable diseases of 47% were achieved with a single-agent therapy with AEZS-108. It should be noted that in addition to these responses, signs of response were noted in 4 additional patients, which are not included in the calculated response rates (Fig. 1). Eighty percent of the patients with objective responses had type I EC, and 20% had type II disease corresponding to the distribution of type I versus type II disease in the study population. Larger numbers, however, are required before conclusions can be made regarding the activity of AEZS-108 in different types of EC. Because the expression of steroid receptors in the tumors was not registered, we cannot make statements on their predictive value for AEZS-108 treatment.

Toxicity was very mild considering that the dose of 267 mg/m² of AEZS-108 is equimolar to 76.8 mg/m² of doxorubicin. These data might indicate that AEZS-108 can be used for targeted chemotherapy based on the LHRH receptor-mediated uptake of doxorubicin into cancer cells. A direct comparison of both the efficacy and toxicity of AEZS-108 in free doxorubicin is warranted to prove this hypothesis. Women with locally relapsed or advanced EC that cannot be cured by surgery and/or radiotherapy and patients with metastatic EC are not curable. Palliative therapy includes endocrine treatment or chemotherapy. Hormonal agents such as progestins, antiestrogens, and aromatase inhibitors are used with low toxicity but modest efficacy and median OS between 7 and 12 months.3,5,6 In addition, chemotherapy is not curative and may be very toxic in this group of elderly women.3,5,18,19 In randomized trials, response rates of 17% to 25% and median OS of 6.7 to 9.2 months have been described for single-agent doxorubicin treatment.3 For the combination of doxorubicin and cisplatin, response rates of 34% to 43% and OS of 9 to 12.6 months were found.3 The most active combination from randomized trials is cisplatin, doxorubicin, and paclitaxel with filgrastim support, which produces response rates in 57% of chemotherapy-naive patients with progression-free survival and OS of 8.3 and 15.3 months, respectively.18 The combination of carboplatin and paclitaxel is better tolerated and is currently being formally compared with the combination of cisplatin, doxorubicin, and paclitaxel with filgrastim support.3 As overall

| Variable                        | Patient (n = 43) |
|--------------------------------|-----------------|
|                                | n   | %   |
| Race                           |     |     |
| White                          | 42  | 97.7|
| Other                          | 1   | 2.3 |
| Age, y (Mean (SD))             | 66  | (9) |
| Median (range)                 | 68  | (25–87) |
| BMI, kg/m² (Mean (SD))         | 26.9| (6.9)|
| Median (range)                 | 25.8| (17.0–52.1)|
| ECOG PS                        |     |     |
| Grade 0                        | 26  | 60.5|
| Grade 1                        | 12  | 27.9|
| Grade 2                        | 5   | 11.6|
| LHRH receptor status           |     |     |
| IHC positive, n                | 43  | 100 |
| Cells staining positive for LHRH receptor, % |     |     |
| Mean (SD)                      | 69  | (21)|
| Median (range)                 | 70  | (30–90)|
| Histologic diagnosis           |     |     |
| Endometrioid                   | 31  | 72  |
| Squamous                       | 1   | 2.3 |
| Serous                         | 8   | 18.6|
| Clear cell                     | 2   | 4.6 |
| Unknown                        | 1   | 2.3 |
| Tumor grade                    |     |     |
| 1                              | 3   | 7.0 |
| 2                              | 16  | 37  |
| 3                              | 21  | 49  |
| Unknown                        | 3   | 7   |
| Primary advanced disease       | 7   | 16.3|
| Recurrent disease              | 36  | 83.7|
| Prior surgery                  | 43  | 100 |
| Prior radiotherapy             | 30  | 69.8|
| Prior hormone therapy          | 10  | 23.3|
| Prior chemotherapy             | 10* | 23.3|

*One additional patient had prior chemotherapy for another cancer diagnosis.

ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; IHC, immunohistochemical evaluation.
prognosis for these patients remains poor, there is a need to identify novel agents to improve survival and reduce therapy-induced toxicity.4,20

In the present study, using a single-agent therapy with AEZS-108, we achieved a promising activity combined with low toxicity. The median TTP was 7 months, and the median OS was 15 months. Though comparisons between trials are an estimate at best, these results compare well with those obtained with combination chemotherapies described previously.3

It cannot be excluded that patients with ECs expressing LHRH receptors have a better prognosis than an unselected EC population. However, as more than 90% of all EC patients screened for this trial had LHRH receptor–positive tumors, this possible selection bias might not be so important. Fifty percent of patients progressing on AEZS-108 therapy received carboplatin/paclitaxel as the next line of treatment. This might have also contributed to the good median OS observed in our trial but cannot have influence on the TTP. On the contrary, 8 patients had received carboplatin/paclitaxel treatment before AEZS-108 therapy. Two of these had an objective response, and 3 achieved a stable disease on AEZS-108 treatment. Platinum-based adjuvant therapy for high-risk EC after surgery has

| TABLE 2. Adverse reactions observed in 2 or more patients |
|---------------------------------------------------------|
| Adverse Reaction                                      | National Cancer Institute–Common Toxicity Criteria Grade |
|                                                         | 1     | 2     | 3     | 4     |
| Alopecia                                               | 5     | 11.6  | 11    | 25.6  | 0     | 0     | 0     | 0     |
| Anemia                                                 | 3     | 7.0   | 4     | 9.3   | 0     | 0     | 0     | 0     |
| Constipation                                           | 2     | 4.7   | 1     | 2.3   | 0     | 0     | 0     | 0     |
| Diarrhea                                               | 1     | 2.3   | 2     | 4.7   | 1     | 2.3   | 0     | 0     |
| Erythema                                               | 3     | 7.0   | 0     | 0     | 0     | 0     | 0     | 0     |
| Fatigue                                                | 9     | 20.9  | 1     | 2.3   | 1     | 2.3   | 0     | 0     |
| Hot flush                                              | 3     | 7.0   | 2     | 4.7   | 0     | 0     | 0     | 0     |
| Leukopenia                                             | 0     | 0     | 2     | 4.7   | 3     | 7.0   | 1     | 2.3   |
| Lymphopenia                                            | 2     | 4.7   | 1     | 2.3   | 2     | 4.7   | 0     | 0     |
| Mucosal inflammation                                   | 5     | 11.6  | 1     | 2.3   | 0     | 0     | 0     | 0     |
| Nausea                                                 | 11    | 25.6  | 5     | 11.6  | 1     | 2.3   | 0     | 0     |
| Neutropenia                                            | 0     | 0     | 2     | 4.7   | 3     | 7.0   | 2     | 4.7   |
| Vomiting                                               | 6     | 14.0  | 3     | 7.0   | 0     | 0     | 0     | 0     |

FIGURE 1. The maximal percent change of target lesion. *Three PRs not confirmed at a subsequent time point. †Progressive disease based on occurrence of new lesions. ‡Symptomatic deterioration or death due to malignancy before cycle 2, with maximum change arbitrarily assigned as 120%. Note: In nonevaluable cases, the complete disappearance of a lesion was not accepted as a CR because the lesion size at baseline did not meet the Response Evaluation Criteria in Solid Tumors requirements. One (noncancer death before cycle 2) excluded from the plot because no tumor size assessment was available.
been shown to be efficacious.\textsuperscript{19} In the future, an increasing proportion of patients with relapsed EC will already have been treated with, for example, carboplatin/paclitaxel in the adjuvant situation or will have received this combination as a first-line palliative therapy. For these women, AEZS-108 might be an efficacious therapy with acceptable toxicity. In an ongoing international phase 3 trial, the efficacy and toxicity of AEZS-108 are being compared with those of free doxorubicin in patients with relapsed or metastatic EC who have been pretreated with either adjuvant or first-line palliative carboplatin/paclitaxel therapy.

REFERENCES
1. ECO, European Cancer Observatory. International Agency for Research on Cancer. Available at: http://eu-cancer.iarc.fr. Accessed March 25, 2013.
2. American Cancer Society: Cancer Facts and Figures 2011. Atlanta, GA: American Cancer Society Inc; 2013.
3. Temkin SM, Fleming G. Current treatment of metastatic endometrial cancer. Cancer Control. 2009;16:38–45.
4. Humber CE, Tierney JF, Symonds RP, et al. Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. Ann Oncol. 2007;18:409–420.
5. Carey MS, Gawlik C, Fung-Kee-Fung M, et al. Systematic review of systemic therapy for advanced or recurrent endometrial cancer. Gynecol Oncol. 2006;101:158–167.
6. Kokka F, Brockbank E, Oram D, et al. Hormonal therapy in advanced or recurrent endometrial cancer. Cochrane Database Syst Rev. 2010;12:CD007926.
7. Emons G, Ortmann O, Schulz KD, et al. Growth-inhibitory actions of analogues of luteinizing hormone–releasing hormone on tumor cells. Trends Endocrinol Metab. 1997;8:355–362.
8. Bajo AM, Schally AV, Halmos G, et al. Targeted doxorubicin-containing luteinizing hormone–releasing hormone analogue AN-152 inhibits the growth of doxorubicin-resistant MX-1 human breast cancers. Clin Cancer Res. 2003;9:3742–3748.
9. Halmos G, Nagy A, Lamharzi N, et al. Cytotoxic analogs of luteinizing hormone–releasing hormone bind with high affinity to human breast cancers. Cancer Lett. 1999;136:129–136.
10. Szepeshazi K, Schally AV, Nagy A. Effective treatment of advanced estrogen-independent MXT mouse mammary cancers with targeted cytotoxic LH-RH analogs. Breast Cancer Res Treat. 1999;56:267–276.
11. Westphalen S, Kotulla G, Kaiser F, et al. Receptor-mediated antiproliferative effects of the cytotoxic LH-RH agonist AN-152 in human ovarian and endometrial cancer cell lines. Int J Oncol. 2000;17:1063–1069.
12. Emons G, Sindermann H, Engel J, et al. Luteinizing hormone-releasing hormone receptor-targeted chemotherapy using AN-152. Neuroendocrinology. 2009;90:15–18.
13. Grundker C, Volker P, Griesinger F, et al. Antitumor effects of the cytotoxic luteinizing hormone–releasing hormone analog AN-152 on human endometrial and ovarian cancers xenografted into nude mice. Am J Obstet Gynecol. 2002;187:528–537.
14. Emons G, Kaufmann M, Gorchev G, et al. Dose escalation and pharmacokinetic study of AEZS-108 (AN-152), an LH-RH agonist linked to doxorubicin, in women with LH-RH receptor-positive tumors. Gynecol Oncol. 2010;119:457–461.
15. Föst C, Duwe F, Hellriegel M, et al. Targeted chemotherapy for triple-negative breast cancers via LH-RH receptor. Oncol Rep. 2011;25:1481–1487.
16. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–216.
17. Chen TT, Ng TH. Optimal flexible designs in phase II clinical trials. Stat Med. 1998;17:2301–2312.
18. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2004;22:2159–2166.
19. Johnson N, Bryant A, Miles T, et al. Adjuvant chemotherapy for endometrial cancer after hysterectomy. Cochrane Database Syst Rev. 2011;10:CD003175.
20. Dedes KJ, Wetterskog D, Ashworth A, et al. Emerging therapeutic targets in endometrial cancer. Nat Rev Clin Oncol. 2011;8:261–271.