



Major clinical research advances in gynecologic cancer in 2013

Dong Hoon Suh¹, Jae-Weon Kim², Sokbom Kang³, Hak Jae Kim⁴, Kyung-Hun Lee⁵

¹Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam; ²Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul; ³Branch of Gynecologic Cancer Research, National Cancer Center, Goyang; ⁴Department of Radiation Oncology, Seoul National University College of Medicine, Seoul; ⁵Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

In 2013, 10 topics were selected for major clinical research advances in gynecologic oncology; these included three topics regarding cervical cancer, three regarding ovarian cancer, two regarding endometrial cancer, and one each regarding breast cancer and radiation oncology. For cervical cancer, bevacizumab was first demonstrated to exhibit outstanding clinical efficacy in a recurrent, metastatic setting. Regarding cervical cancer screening, visual inspections with acetic acid in low-resource settings, p16/Ki-67 double staining, and the follow-up results of four randomized controlled trials of human papillomavirus-based screening methods were reviewed. Laparoscopic para-aortic lymphadenectomy before chemoradiation for locally advanced cervical cancer was the final topic for cervical cancer. Regarding front-line ovarian cancer therapies, dose-dense paclitaxel and carboplatin, intraperitoneal chemotherapy, and other targeted agents administered according to combination or maintenance schedules were discussed. Regarding recurrent ovarian cancer treatment, cediranib, olaparib, and farletuzumab were discussed for platinum-sensitive disease. The final overall survival data associated with a combination of bevacizumab and chemotherapy for platinum-resistant disease were briefly summarized. For endometrial cancer, the potential clinical efficacy of metformin, an antidiabetic drug, in obese patients was followed by integrated genomic analyses from the Cancer Genome Atlas Research Network. For breast cancer, three remarkable advances were reviewed: the long-term effects of continued adjuvant tamoxifen for 10 years, the effects of 2-year versus 1-year adjuvant trastuzumab for human epidermal growth factor receptor 2-positive disease, and the approval of pertuzumab in a neoadjuvant setting with a pathologic complete response as the surrogate endpoint. Finally, the recent large studies of intensity-modulated radiotherapy for gynecologic cancer were briefly summarized.

Keywords: Bevacizumab, Cediranib, Dose-dense chemotherapy, Intensity-modulated radiotherapy, Tamoxifen

INTRODUCTION

Bevacizumab (BEV), a humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody, has long

been studied with respect to its clinical efficacy in patients with advanced ovarian cancer; however, the previously available results were not satisfactory. Surprisingly, an outstanding study demonstrated a substantial overall survival (OS) benefit of BEV in recurrent or metastatic cervical cancer, which was considered difficult to cure. This was the first study to demonstrate improved OS in gynecologic cancer patients following the addition of BEV. Moreover, the treatment efficacy of cediranib, another targeted agent that acts as a tyrosine kinase inhibitor and blocks VEGF receptors (VEGFRs),

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Correspondence to Jae-Weon Kim

Department of Obstetrics and Gynecology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea.
E-mail: kjwksh@snu.ac.kr

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was proven against advanced epithelial ovarian cancer (EOC). Besides these two great achievements, this review will cover most of the influential studies published in 2013 in the field of gynecologic oncology.

BEVACIZUMAB: A NEW HOPE FOR RECURRENT/METASTATIC CERVICAL CANCER

In the plenary session of the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, Dr. Tewari presented the interim analytical results of a phase III randomized trial conducted by the Gynecologic Oncology Group (GOG), GOG 240, which regarded the incorporation of BEV for the treatment of recurrent and metastatic cervical cancers [1]. A total of 452 patients with metastatic, recurrent, or persistent cervical cancers that were incurable with standard treatments were enrolled in this study and randomized to one of four treatment arms: (1) cisplatin (50 mg/m²) plus paclitaxel (135 to 175 mg/m²) alone; or (2) with BEV; or (3) topotecan (0.75 mg/m² on days 1 to 3) plus paclitaxel (175 mg/m² on day 1) alone; or (4) with BEV. The primary endpoint was OS, and a 30% risk of death with BEV was considered important (90% power; 1-sided α , 2.5%). The first interim analysis conducted following 174 deaths in 2012 showed that the topotecan-paclitaxel backbone was not superior to the cisplatin-paclitaxel backbone. A second interim analysis after 271 deaths revealed a significant difference in the median OS between the BEV and no-BEV groups (hazard ratio [HR], 0.71; 97% confidence interval [CI], 0.54 to 0.95; 1-sided $p=0.0035$). The relative risks (RRs) were 48% (BEV group) and 36% (no-BEV group; $p=0.0078$). However, patients who received BEV experienced more side effects than those who did not; these included grade 3 to 4 bleeding (5% vs. 1%), thromboembolism (9% vs. 2%), and gastrointestinal (GI) fistula (3% vs. 0%). Despite the potential toxicity, the therapeutic benefits of BEV seem to outweigh the potential toxicity because the former are likely to affect current clinical practice with respect to the treatment of recurrent cervical cancer, which previously had very limited treatment options. Furthermore, it is noteworthy that this was the first study to prove an improvement in the OS of gynecologic cancer patients following the addition of BEV. In consideration of this outstanding clinical impact of GOG 240, the National Comprehensive Cancer Network guidelines for cervical cancer recently adopted the triple regimen of cisplatin, paclitaxel, and BEV as category 2A for the treatment of metastatic/recurrent cervical cancer [2].

SCREENING FOR CERVICAL CANCER

1. VIA: a mortality-reducing screening alternative to the Papanicolaou smear in low-resource settings

Cervical cancer is the most common cancer type and the leading cause of cancer death among women in developing countries, including India [3]. Although the Papanicolaou (Pap) smear test has long been used in national cancer screening programs in developing countries and has clearly demonstrated efficacy with respect to reducing the cervical cancer incidence, the Pap smear test is generally neither affordable nor available in most developing countries. For this reason, the development of low-cost screening programs for the early detection of precancerous lesions and cancers of the uterine cervix is an important and urgent issue. Visual inspection with acetic acid (VIA) is among the promising screening tests. A growing body of evidence suggests the feasibility and efficacy of VIA for preventing cervical cancer [4,5]. In accordance with these studies, Dr. Shastri presented the results of a randomized controlled study at the 2013 ASCO Annual Meeting in Chicago [3]. He concluded that this screening program could lead to the prevention of 22,000 deaths from cervical cancer in India and 72,000 deaths throughout the developing world each year by quickly and inexpensively identifying women who need to see a physician for the treatment of cancers or precancerous lesions of the uterine cervix. This study included 75,360 women from 10 slums in the screening group and 76,178 women from 10 comparable slums in the control group. The screening group intervention comprised four rounds of cancer education and VIA screening conducted by primary health workers every 2 years; the control group was offered cancer education once at recruitment. Cancer education provided information regarding recognition of the symptoms of cervical cancer. VIA incorporated the application of a vinegar-based solution to the cervix, which rendered precancerous tissues white and visible to the naked eye within a minute. At the 12-year analysis, the screening participation rate was as high as 89%. The incidence rates of cervical cancer were 26.74 per 100,000 women (95% CI, 23.41 to 30.74) in the screening group and 27.49 per 100,000 women (95% CI, 23.66 to 32.09) in the control group. The rates of compliance with cervical cancer treatment were 86.34% and 72.29% in the screening and control groups, respectively. Among women in the screening group, there was a 31% reduction in deaths from cervical cancer relative to the women in the control group (mortality rate ratio [MRR], 0.69; 95% CI, 0.54 to 0.88; $p=0.003$). This study also reported a 7% reduction in all-cause mortality, although this difference was statistically insignificant. This study was finally published in the *Journal*

of the National Cancer Institute in March 2014 [6]. Given the study results, it is expected that the governments of many developing countries will initiate nationwide movements to incorporate VIA as a cervical cancer screening program.

2. P16/Ki-67 as a triage test in human papillomavirus-positive women

P16, a cyclin-dependent kinase inhibitor, is a marker of viral-induced cell cycle dysregulation. Research has demonstrated the role of p16 as a biomarker of transforming human papillomavirus (HPV) infections and precancerous cervical lesions. To address the problem of how best to identify those requiring colposcopy among HPV-positive women, Carozzi et al. [7] showed that the immediate colposcopy referral rates could be reduced by 60% if colposcopy was omitted in HPV-positive p16-negative women, based on the high specificity of p16 overexpression for detecting high-grade cervical intraepithelial neoplasia (CIN) in a nested substudy of the New Technologies for Cervical Cancer screening (NTCC) study.

In 2013, the NTCC study researchers reported longitudinal data regarding the subsequent risk of high-grade CIN in HPV-positive women according to the p16 status, which could be used to establish the appropriate retesting frequency for this group of patients [8]. Of the 1170 HPV-positive women with available p16 samples, 493 overexpressed p16 (42%) at baseline. During a follow-up period of up to 3 years, CIN3+ was detected in the first round of screening or during follow-up in 9.7% (55/493) of the HPV-positive, p16-positive women versus 1.7% (10/644) of the HPV-positive, p16-negative women. The RR was 5.57 (95% CI, 2.88 to 10.76), and the longitudinal sensitivity of p16 was 82.4% (95% CI, 67.8 to 97.0). Based on the higher RR in women aged 35 to 60 years at recruitment relative to those aged 25 to 34 years (3.37 vs. 2.15), the researchers concluded that p16 overexpression could be used as a triage method for assessing HPV-positive women, especially those aged 35 to 60 years, and that HPV-positive, p16-negative women could be safely retested after 2 to 3 year intervals. Given the much higher cumulative risk of CIN3 in HPV-positive, p16-negative women (2.0%) relative to HPV-negative women (0.01%), who are normally tested after ≥ 5 year-intervals [9], the retesting of HPV-positive, p16-negative women after 2 to 3 years seemed reasonable.

Ki-67 is a nuclear protein that is associated with cellular proliferation. Double staining for both p16 and Ki-67 was introduced in Europe in 2010 as a morphology independent test that was therefore expected to increase reproducibility, and a cross-sectional study of a colposcopy referral population suggested that double staining had a similar accuracy to p16 alone [7,10]. In 2013, the results of a large prospective diagnostic screening

study of p16/Ki-67 dual-stained cytology, the Primary ASCUS and LSIL Marker Study, were released [11]. In this study, dual-stained cytology showed higher sensitivity than Pap cytology (86.7% vs. 68.5%, $p < 0.001$) for detecting CIN2+, with a comparable specificity (95.2% vs. 95.4%, $p = 0.15$). Dual-stained cytology was more specific (96.2% vs. 93.0%, $p < 0.001$) but less sensitive than HPV testing (84.7% vs. 93.3%, $p = 0.03$) in women aged ≥ 30 years. The researchers concluded that dual-stained cytology might play a potential role in screening, especially in younger women in whom the reliability of the HPV test was limited. To facilitate incorporation into real triage practice, longitudinal data will be needed to determine the safe retesting intervals after a negative dual-stained cytology result.

3. Efficacy of HPV-based screening

Four randomized controlled trials have compared HPV-based screening and cytology-based screening tests with respect to CIN lesions: Swedescreen [12], population-based screening study Amsterdam (POBASCAM) [13], ARTISTIC [14], and NTCC [15]. The follow-up results from 176,464 women in these four studies were published online at the end of 2013 and in print in 2014 [16]. Different protocols were used in each study. Nevertheless, the invasive cervical cancer RR was 0.60 (95% CI, 0.40 to 0.89), with no heterogeneity among the studies ($p = 0.52$). The invasive cancer detection rates were similar for the two screening methods during the first 2.5 years of follow-up (RR, 0.79; 95% CI, 0.46 to 1.36) but were subsequently lower in the HPV-based screening group (RR, 0.45; 95% CI, 0.25 to 0.81). The lowest RR for women aged 30 to 34 years (RR, 0.36, 95% CI, 0.14 to 0.94) indicated notable protection against invasive cancer in this age group. Regarding the duration of this protection, the cumulative incidence rates of invasive cervical cancer in women with negative entry tests were 4.6/100,000 at 3.5 years and 8.7/100,000 at 5.5 years in the HPV-based screening group and 15.4/100,000 and 36.0/100,000, respectively, in the cytology-based screening group. Based on these data, HPV-based screening at 5-year intervals offered better protection against invasive cervical cancer compared with cytology alone at 3-year intervals. This study provides a large-scale estimation of the effect of HPV-based screening on invasive cervical cancer in women who undergo regular screening tests.

LAPAROSCOPIC PARA-AORTIC LYMPHADENECTOMY BEFORE CONCURRENT CHEMORADIOTHERAPY FOR LOCALLY ADVANCED CERVICAL CANCER

Extended-field radiotherapy (RT) of the pelvic and para-aortic areas with concomitant cisplatin chemotherapy remains

the safest strategy for optimizing the survival of patients with locally advanced cervical cancer (LACC) and para-aortic lymph node (LN) metastasis. However, the inherent false negative rate of positron emission tomography (PET) is as high as 22% [17], although PET has been shown to have the highest sensitivity for detecting extracervical lesions before chemoradiation [18]. This finding has driven researchers to evaluate the therapeutic impact of laparoscopic surgical para-aortic staging surgery in patients with LACC with negative PET imaging results of the para-aortic area [19,20]. Gouy et al. [21] reported the results from the previously largest prospective multicenter study of 237 patients with stage IB to IVA cervical cancer in the *Journal of Clinical Oncology*. All patients had negative PET imaging results of the para-aortic area and underwent laparoscopic para-aortic lymphadenectomy. Extended-field RT covered up to the level of the para-aortic area when the para-aortic LNs were involved. The primary endpoint was OS and secondary endpoint was event-free survival (EFS). Twenty-nine patients (12%) had para-aortic LN metastasis, indicating false negative PET results; 16 of these patients had nodal metastases >5 mm and 13 had nodal metastases ≤5 mm. The 3-year EFSs in patients without para-aortic involvement, with para-aortic involvement ≤5 mm, and para-aortic involvement >5 mm were 74%, 69%, and 17%, respectively ($p < 0.001$). Two factors were significantly associated with OS: the presence and size of the metastatic para-aortic LNs and a delay of ≥45 days between PET-computed tomography (CT) and the beginning of RT.

This study could not reach a definite conclusion regarding the therapeutic impact of laparoscopic para-aortic staging prior to chemoradiation for LACC because it was unclear whether the similar prognosis of patients with small para-aortic metastases (≤5 mm) and no para-aortic metastases was due to the whole treatment combination or merely the surgical resection [21]. Nevertheless, given the considerable PET-CT false negative rate for detecting para-aortic lesions and the poor prognosis of patients with para-aortic metastases >5 mm despite treatment with extended-field RT and concomitant chemotherapy, laparoscopic para-aortic staging prior to chemoradiation for LACC could be highly efficient for patients with negative PET-CT imaging. Additional information is anticipated from related ongoing randomized trials (ClinicalTrials.gov identifiers: NCT01049100 and NCT01365156).

FRONT-LINE THERAPY FOR ADVANCED EPITHELIAL OVARIAN CANCER

1. Dose-dense paclitaxel and carboplatin

After the presentation at the 2012 ASCO Annual Meeting,

the long-term follow-up results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for the treatment of advanced EOC were finally published in *Lancet Oncology* [22]. We reviewed the results of this study, also known as Japanese Gynecologic Oncology Group (JGOG) 3016, in last year's review [23]. Briefly, 312 patients were assigned to the dose-dense regimen and received carboplatin (area under the curve [AUC] 6 on day 1) and paclitaxel (80 mg/m² on days 1, 8, and 15). An additional 319 patients received conventional treatment comprising carboplatin (AUC 6) and paclitaxel (180 mg/m² on day 1). At the median follow-up period of 76.8 months, the median progression-free survival (PFS), which was the primary endpoint of this study, was significantly longer in the dose-dense group than in the conventional group (28.2 months vs. 17.5 months; HR, 0.76; 95% CI, 0.62 to 0.91; $p = 0.004$). The median OS durations in the respective groups were 100.5 months versus 62.2 months (HR, 0.79; 95% CI, 0.63 to 0.99; $p = 0.039$), again favoring the dose-dense group. Based on these results, the authors suggested dose-dense paclitaxel and carboplatin as potential new standards for first-line chemotherapy in patients with advanced EOC.

Another study of dose-dense paclitaxel and carboplatin in advanced EOC was conducted in Europe; the so-called Multicenter Italian Trials in Ovarian Cancer (MITO-7) study was presented at the 2013 ASCO Annual meeting [24] and recently published in *Lancet Oncology* [25]. Compared with JGOG 3016, in which the dose-dense treatment schedule was weekly paclitaxel (wPAC) combined with tri-weekly carboplatin, MITO-7 assessed the impact of a weekly schedule of carboplatin plus paclitaxel on the coprimary endpoints of PFS and quality of life (QOL). A total of 404 women were randomized to the conventional tri-weekly regimen of carboplatin (AUC 6) plus paclitaxel (175 mg/m²) for six cycles and 406 were allocated to the weekly regimen of carboplatin (AUC 2) plus paclitaxel (60 mg/m²) for 18 weeks. At a median follow-up period of 22.3 months, there was no significant difference in the median PFS between the tri-weekly and weekly groups (17.3 months vs. 18.3 months; HR, 0.96; 95% CI, 0.80 to 1.16; $p = 0.66$). However, the QOL, which was assessed using the Functional Assessment of Cancer Therapy Ovarian Trial Outcome Index (FACT-O/TOI), was significantly better with the weekly schedule than with the tri-weekly schedule (treatment-by-time interaction, $p < 0.001$). A weekly regimen was associated with less severe toxicity in terms of neutropenia, thrombocytopenia, renal toxicity, and neuropathy. Some investigators insisted that the study results, specifically a similar PFS and better QOL, achieved with the weekly regimen compared with the tri-weekly regimen in MITO-7 might have

been due to the lower total dose of wPAC than that used in JGOG 3016 (180 mg/m² vs. 240 mg/m² every 3 weeks). Nonetheless, a weekly carboplatin and paclitaxel regimen might be a reasonable first-line chemotherapeutic option for advanced EOC.

A dose-dense wPAC (80 mg/m²) and carboplatin (AUC 6) regimen was compared with a conventional tri-wPAC and carboplatin regimen with or without BEV in GOG 262. The preliminary data from GOG 262 were released at the 18th International Meeting of the European Society of Gynecological Oncology (ESGO) in Liverpool, UK in October 2013 [26]. A total of 692 patients with stage II to IV EOC and suboptimal residual disease (>1 cm) after surgery were randomly assigned to either the dose-dense weekly regimen or the tri-weekly conventional regimen, as in JGOG 3016. Both arms provided the option for BEV (15 mg/kg intravenously on day 1) beginning with cycle 2; this was administered every 3 weeks for six cycles, followed by maintenance BEV until the occurrence of progression or adverse effects. There was no significant difference in the PFS between the dose-dense and conventional treatment groups (HR, 0.97; 95% CI, 0.79 to 1.18). However, among the patients not treated with BEV (n=112), the dose-dense treatment group had a better PFS than did the conventional treatment group (14 months vs. 10 months; HR, 0.60; 95% CI, 0.37 to 0.96). In contrast, among patients treated with BEV (n=580), the PFS was similar between the two groups (15 months for both arms; HR, 1.06; 95% CI, 0.86 to 1.31). Given the results of the GOG 262 and JGOG 3016 trials, we can speculate that the use of BEV might reduce any benefit from dose-dense treatment. A final full publication with more information is highly anticipated.

2. Long-term survival advantage of intraperitoneal chemotherapy for advanced ovarian cancer

Based on the GOG 172 results and a meta-analysis of intraperitoneal (IP) versus intravenous (IV) randomized trials in EOC patients [27,28], the US National Cancer Institute announced in 2006 that a combination of IV and IP chemotherapy administration confers a significant survival benefit upon women with optimally debulked ovarian cancer compared with IV administration alone [29]. Despite this official support, IP chemotherapy has not been substituted for IV chemotherapy in routine practice primarily because of the uncertain optimal dosage with tolerable toxicity as well as difficulties with IP catheter insertion and maintenance. However, the consistently reported favorable outcomes of IP chemotherapy drove many researchers to initiate clinical trials that compared the winning regimen from GOG 172 with IV dose-dense as well as IP dose-dense regimens (GOG 252) [30]. BEV (15 mg/kg)

was administered in all three arms, followed by 18 months of maintenance. GOG 252 recently completed patient accrual and is awaiting results. JGOG 3019 is another clinical trial intended to compare dose-dense weekly IV paclitaxel plus tri-weekly IV carboplatin versus dose-dense weekly IV paclitaxel plus tri-weekly IP carboplatin. JGOG 3019 is still recruiting patients.

While waiting for the results of these trials, the long-term survival advantage of IP chemotherapy in advanced EOC was presented in a timely manner by Dr. Tewari at plenary session I of the 2013 Annual Meeting of Society of Gynecologic Oncology in Los Angeles [31]. The results from a meta-analysis of GOG 114 [32] and 172 [27] were presented. The median follow-up time for the 876 patients in the two studies was 10.7 years. Dr. Tewari concluded that the survival benefit of IP over IV chemotherapy extended beyond 10 years. More specifically, there was a significant difference in OS between the IP and IV therapy groups (61.8 months vs. 51.4 months, $p=0.048$). The adjusted HR indicated a 17% reduction in the risk of death during follow-up among women who underwent IP chemotherapy. Younger age, better performance status, microscopic residual disease, and nonclear cell histology were importantly associated with long-term OS after IP chemotherapy. Additionally, the results suggested that OS improved with an increased number of IP chemotherapy cycles (18% vs. 33% vs. 59% for 1 to 2 vs. 3 to 4 vs. 5 to 6 cycles, respectively; $p<0.001$). The researchers also found that younger patients with microscopic residual disease were more likely to complete six cycles of IP chemotherapy. Regarding toxicity, Dr. Tewari concluded that although the toxicity was substantially greater in the IP chemotherapy arms of both trials, this might have resulted from causes not directly related to the IP treatment, whereas the advantages from IP treatment were remarkably large.

3. Other targeted agents: combination with front-line chemotherapy or maintenance

At the 2013 ASCO Annual Meeting in Chicago, AGO-OVAR 16, a phase III, randomized, placebo-controlled, double-blind study of pazopanib versus placebo in women with no progression after first-line chemotherapy for advanced EOC, was presented [33]. Pazopanib is an orally administered multi-kinase inhibitor that targets the ATP-binding sites of VEGF, platelet-derived growth factor (PDGF), and c-kit. A total of 940 patients with stage II to IV disease without progression after surgery who had received ≥ 5 cycles of platinum-taxane chemotherapy were randomly assigned to receive 800 mg of pazopanib per day (n=472) or a placebo (n=468) for up to 24 months. The primary endpoint was PFS. The mean time from diagnosis to randomization was 7 months. At a mean follow-up of 24 months, patients in the pazopanib arm had

a significantly longer PFS than those in the placebo arm (median, 17.9 months vs. 12.3 months; HR, 0.766; 95% CI, 0.64 to 0.91; $p=0.002$). Pazopanib was associated with more grade ≥ 3 adverse events (26% vs. 11%) compared with placebo; these included hypertension, diarrhea, neutropenia, fatigue, and headache. Conclusively, pazopanib maintenance yielded a 5.6-month improvement in PFS in patients with advanced EOC. Additionally, the results of a subgroup analysis of pazopanib maintenance therapy for advanced EOC in Asian women from AGO-OVAR 16 ($n=145$) were presented separately [34]. The median PFS was 18.1 months in both arms. Although the survival curves indicated a trend of 6 to 18 months that favored the pazopanib arm, the efficacy of pazopanib maintenance could not be confirmed because of the small sample size. However, the toxicity profile was similar to that of AGO-OVAR 16.

AGO-OVAR 12 is another remarkable study of a targeted agent as front-line therapy for advanced EOC. This is a randomized, placebo-controlled phase III trial of standard carboplatin and paclitaxel with or without nintedanib, an oral inhibitor of VEGFR, PDGF receptor, and fibroblast growth factor receptor (FGFR). AGO-OVAR 12 was presented at the 18th International Meeting of ESGO in Liverpool, UK in October 2013 [35]. Briefly, 1,366 eligible patients were randomized 2 : 1 to receive nintedanib (200 mg twice per day) plus carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m²) or placebo plus carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m²). After 752 observed events, the nintedanib arm exhibited a longer PFS than the placebo arm (median 17.3 months vs. 16.6 months; HR, 0.84; 95% CI, 0.72 to 0.98; $p=0.024$). This PFS benefit was higher among patients from the low-risk group with small residual tumors after surgery (median 20.8 months vs. 27.1 months; HR, 0.75; 95% CI, 0.61 to 0.92; $p=0.005$). Nintedanib maintenance could therefore be a treatment option in cases of optimally debulked advanced EOC.

4. Reinforcing evidence for the noninferiority of neoadjuvant chemotherapy

Since the first phase III trial of primary surgery (PS) followed by adjuvant platinum-based chemotherapy (P-CT) versus neoadjuvant chemotherapy (NACT) was conducted by the European Organization for Research and Treatment of Cancer (EORTC) [36], a second phase III randomized controlled trial, the so-called CHORUS trial, was conducted to investigate the timing of initial surgery for advanced stage ovarian cancer and was presented at the 2013 ASCO Annual Meeting in Chicago [37]. This noninferiority trial included 550 women with stage III to IV ovarian cancer who were randomized to either the standard treatment arm ($n=276$; PS followed by six cycles of

P-CT) or the NACT arm ($n=274$; three cycles of P-CT on either side of surgery). The primary outcome was OS. At a median follow-up of 3 years, there was no difference between the PS and NACT arms in terms of OS (22.8 months vs. 24.5 months; HR, 0.87; 80% CI, 0.76 to 0.98) or PFS (10.2 months vs. 11.7 months; HR, 0.91; 80% CI, 0.81 to 1.02). In conclusion, NACT was associated with a higher incidence of “no residual tumor after surgery” (35% vs. 15%; odds ratio [OR], 0.42; 95% CI, 0.31 to 0.59; $p<0.001$) and “discharge within 14 days” (92% vs. 74%; OR, 0.80; 95% CI, 0.74 to 0.87; $p<0.001$) and fewer early deaths within 28 days after surgery (0.5% vs. 5.6%) relative to the PS group. The noninferior treatment efficacy and reduced postoperative morbidity and mortality with NACT, compared with PS, were consistent with the results of the previous EORTC trial and reinforced the evidence that NACT could be an alternative to PS for newly diagnosed advanced EOC.

THREE TARGETED AGENTS TESTED AGAINST PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER

1. Cediranib: the first oral tyrosine kinase inhibitor to demonstrate an OS benefit

Cediranib is an oral tyrosine kinase inhibitor that blocks VEGFRs. A 3-arm, randomized, double-blind phase III trial of cediranib in patients with relapsed platinum-sensitive ovarian cancer was conducted by the Gynecologic Cancer Intergroup (GCI; ICON 6) and the results were released at the 2013 European Cancer Conference in Amsterdam [38]. A total of 456 patients with EOC that had relapsed more than 6 months after first-line P-CT treatment were randomized 2:3:3 to receive a placebo, cediranib (20 mg/day) during chemotherapy followed by placebo for up to 18 months or until disease progression (concurrent), or cediranib followed by maintenance cediranib (concurrent plus maintenance). The primary endpoint was PFS in the placebo versus concurrent plus maintenance arms. The proportions of patients with previous treatment-free intervals >12 months were balanced between the arms. There was a significant difference in the median PFS between the placebo and concurrent plus maintenance arms (8.7 months vs. 11.1 months; HR, 0.57; 95% CI, 0.45 to 0.74; $p<0.001$). However, because of nonproportionality ($p=0.024$), a restricted means analysis was used for survival estimation, resulting in a 3.1-month PFS difference that favored cediranib (9.4 months vs. 12.5 months). OS increased by 2.7 months from 17.6 to 20.3 months (HR, 0.70; $p=0.042$). A comparison of PFS in the placebo vs. concurrent arms yielded an increase of 2.0 months from 9.4 to 11.4 months (HR, 0.68; $p=0.002$). Adverse events occurred more frequently in the concurrent

plus maintenance arm; these included hypertension, diarrhea, hypothyroidism, proteinuria, and fatigue and all were controllable. These results indicated that cediranib alone seemed to have an effect on PFS both during and after chemotherapy. Finally, Dr. Ledermann concluded that ICON 6 was the first trial to demonstrate a significant improvement in the PFS and OS of patients with EOC in response to an oral VEGF tyrosine kinase inhibitor.

2. Olaparib maintenance therapy and *BRCA* mutation

In 2012, the major clinical research advances in gynecologic cancer addressed an outstanding report regarding the efficacy of twice-daily olaparib (400 mg) maintenance therapy in patients with platinum-sensitive recurrent high-grade serous ovarian cancer [23]. From that study, a *BRCA* mutation status subgroup analysis was conducted and the results were presented at the 2013 ASCO Annual Meeting in Chicago [39]. PFS and OS were analyzed according to the germline *BRCA* mutation (gBRCAm) status and total *BRCA* mutation status. gBRCAm patients received the greatest PFS benefit (median 11.2 months vs. 4.1 months; HR, 0.17; 95% CI, 0.09 to 0.32; $p < 0.001$) and QOL improvement with olaparib maintenance versus placebo (OR, 4.08; 95% CI, 1.11 to 19.85; $p = 0.03$). Somatic *BRCA* mutation was also associated with a longer PFS (median 11.2 months vs. 4.3 months; HR, 0.19; 95% CI, 0.11 to 0.32; $p < 0.001$). The OS data remained immature. Olaparib tolerability was similar in gBRCAm patients and the overall population. Therefore, olaparib maintenance therapy provided the greatest PFS benefit in patients with *BRCA* mutations.

3. Unsuccessful farletuzumab in platinum-sensitive ovarian cancer

Farletuzumab is a humanized monoclonal antibody that binds to folate receptor- α , which is known to be highly expressed in EOC but not in normal tissue. With the expectation of selective farletuzumab-mediated antitumor activity against EOC, a phase III randomized placebo-controlled study of weekly farletuzumab with carboplatin and taxane in patients with first relapses of platinum-sensitive ovarian cancer was conducted and the results were presented at the 18th International Meeting of ESGO in Liverpool, UK in October 2013 [40]. Globally, 1,100 women with first recurrences of platinum-sensitive ovarian cancer were treated with carboplatin and paclitaxel or docetaxel for six cycles plus farletuzumab at 1.25 or 2.5 mg/kg or a placebo. The primary endpoint was PFS. The median PFS durations were 9.0, 9.5, and 9.7 months for the placebo, farletuzumab 1.25 mg/kg, and farletuzumab 2.5 mg/kg groups, respectively (HR, 0.86; 95% CI, 0.70 to 1.06 for 2.5 vs. placebo).

There was no significant difference in the PFS between either of the farletuzumab doses or the placebo.

CHEMOTHERAPY PLUS BEVACIZUMAB FOR PLATINUM-RESISTANT RECURRENT OVARIAN CANCER

After the preliminary report of a significant improvement in PFS with a chemotherapy and BEV combination versus chemotherapy alone in patients with platinum-resistant recurrent ovarian cancer (median 6.7 months vs. 3.4 months; HR, 0.48; 95% CI, 0.38 to 0.60; $p < 0.001$) was given at the 2012 ASCO Annual Meeting, the final OS outcomes of the AURELIA study were presented at the 2013 European Cancer Conference in Amsterdam. After investigators' completed the chemotherapy selection (pegylated liposomal doxorubicin, topotecan, or wPAC), the patients were randomized to receive either chemotherapy alone or with added BEV (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) until progression, unacceptable toxicity, or consent withdrawal. At the median follow-up of 27.4 months in both arms, the unstratified OS durations were similar in the two arms (median, 16.6 months vs. 13.3 months for chemotherapy alone vs. BEV added, respectively; HR, 0.85; 95% CI, 0.66 to 1.08; $p = 0.174$). The insignificant 3-month OS benefit in the BEV added group appeared to be driven by the wPAC cohort, a finding that requires prospective validation. Notwithstanding, the AURELIA trial supports the addition of BEV to palliative chemotherapy for selective patients with platinum-resistant ovarian cancer based on the significant improvement in PFS. Another promising finding from the AURELIA trial was the result of an analysis of patient-reported outcomes that was reported by Stockler et al. [41]. This analysis demonstrated a significant improvement in abdominal/GI symptoms in women with recurrent platinum-resistant ovarian cancer who were treated with BEV plus chemotherapy as well as significant improvements in other symptoms and global health/QOL measures.

METFORMIN FOR ENDOMETRIAL CANCER

Metformin, which is among the most commonly used anti-diabetic medications, is known to exhibit antitumor effects via 5' adenosine monophosphate-activated protein kinase activation and mammalian target of rapamycin pathway inhibition. Based on the close association of endometrial cancer with obesity and diabetes, metformin has been thought to exhibit excellent treatment efficacy against endometrial cancer. A preoperative window clinical trial of metformin in obese pa-

tients with endometrial cancer was conducted to evaluate the short-term molecular changes, and the results were presented at the 2013 ASCO Annual Meeting [42]. Twenty women with endometrial cancer and body mass indices >30 were enrolled. After pretreatment endometrial biopsy, metformin (850 mg per day) was administered for 1 to 4 weeks prior to hysterectomy. Formalin-fixed, paraffin-embedded blocks of the endometrial biopsy and hysterectomy specimens were paired. The differences in Ki-67 expression in the samples collected before and after metformin treatment were immunohistochemically evaluated. Among the 16 patients who completed the protocol, the percent Ki-67 expression decreased significantly with a mean 14.5-month metformin treatment duration (mean, 19.5% decrease; $p=0.026$). The pretreatment Ki-67 levels were higher in the metformin responders than in the nonresponders (52% vs. 27.5%, $p=0.007$). These results indicated that metformin could reduce cancer cell proliferation in obese patients with endometrial cancer during a preoperative window.

RECLASSIFICATION OF ENDOMETRIAL CARCINOMAS ACCORDING TO GENOMIC FEATURES: THE CANCER GENOME ATLAS REPORT

Following a report from The Cancer Genome Atlas (TCGA) Research Network regarding integrated genomic analyses of high-grade serous ovarian cancers [43], TCGA published the integrated genomic analyses of endometrial carcinoma in 2013 [44]. Whereas early-stage endometrioid cancers are often treated with adjuvant RT, serous tumors are treated with chemotherapy. However, clinicians sometimes encounter tumors that are likely to recur within 1 year even after staging surgery and adjuvant RT. To improve the poor prognosis associated with aggressive histologic subtypes, including high-grade endometrioid and serous tumors, researchers attempted to provide key molecular insights into tumor classification that might affect postoperative adjuvant treatment. Commonly mutated genes in type I tumors reportedly include *PTEN*, *FGFR2*, *ARID1A*, *CTNNB1*, *PIK3CA*, *PIK3R1*, and *KRAS*, whereas *TP53*, *PIK3CA*, and *PPP2R1A* mutations are frequently found in type II tumors [45,46]. A hierarchical clustering analysis based on somatic copy number alterations (SCNAs) revealed that cluster 4, which was characterized by a very high level of SCNAs, included focal amplifications of oncogenes such as *MYC*, *ERBB2*, and *CCNE1* and SCNAs such as *FGFR3* and *SOX17*. Cluster 4 also had frequent *TP53* mutations (90%), a low level of microsatellite instability (MSI; 6%), and fewer *PTEN* mutations (11%) relative to other endometrioid tumors (clus-

ters 1 to 3; 84%). Cluster 4, which included most of the serous (94%) tumors and 12% of the endometrioid tumors, had a significantly worse PFS than the other endometrioid clusters ($p=0.003$). On the other hand, among the four groups based on somatic nucleotide substitutions, MSI, and SCNAs the ultramutated group comprised 17 tumors exemplified by an increased transversion frequency in the exonuclease domain of *POLE*, a catalytic DNA polymerase epsilon subunit involved in nuclear DNA replication and repair [44]. A final integrated clustering of the four groups found that ultramutated *POLE* (7.3%), MSI (28.0%), low copy number (38.8%), and high copy number (25.9%) were significantly correlated with mRNA expression (mitotic, hormonal, and immunoreactive; $p<0.001$). The signature *POLE* cluster genes are primarily involved in cellular metabolism and *POLE*-mutant tumors had a better PFS, whereas the poorest PFS was noted in the high copy number cluster, which included most of the serous and serous-like endometrioid tumors. The majority of cases (85%) in the high copy number cluster were associated with the mitotic mRNA subtype. Therefore, up to 25% of high-grade endometrioid-type tumors have a molecular phenotype similar to that of serous carcinomas, which are characterized by frequent *TP53* mutations and extensive SCNA. These findings suggested that clinicians should consider treating high copy number-altered endometrioid tumors with chemotherapy rather than adjuvant RT.

GREAT ACHIEVEMENTS IN ADJUVANT AND NEOADJUVANT BREAST CANCER TREATMENT

In 2013, three outstanding reports regarding breast cancer treatment were published.

Firstly, the long-term effects of continuing adjuvant tamoxifen for up to 10 years vs. ceasing at 5 years on breast cancer patients were reported by two different study groups: the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) collaborative group in *Lancet* [47], and the Adjuvant Tamoxifen: To Offer More? (aTTom) collaborative group at the 2013 ASCO Annual Meeting in Chicago [48]. In the ATLAS trial, 12,894 women with early-stage breast cancer who had completed a 5-year tamoxifen treatment regimen were randomized to continue tamoxifen treatment for up to 10 years (experimental arm) or cease treatment at 5 years (open control arm) [47]. Whereas the treatment assignment had no significant effect on the treatment outcomes of 1,248 (9.7%) women with human epidermal growth factor receptor 2 (HER2)-negative disease, there were significant reductions in the risks of recurrence (18.0% vs. 20.8%, $p=0.002$), disease-specific mortality

(331 deaths vs. 397 deaths, $p=0.01$), and overall mortality (639 deaths vs. 722 deaths, $p=0.01$) in the experimental arm relative to the open control arm among the HER2-positive breast cancer patients. Interestingly, these reducing effects with respect to the adverse breast cancer outcomes seemed to be limited in years 5 to 9 of tamoxifen treatment, and most of the benefit was observed after year 10 of treatment (recurrence rate ratio [RRR], 0.90; 95% CI, 0.79 to 1.02 vs. RRR, 0.75; 95% CI, 0.62 to 0.90; and MRR, 0.97; 95% CI, 0.79 to 1.18 vs. MRR, 0.71; 95% CI, 0.58 to 0.88).

The aTTom study corroborated the findings of the international ATLAS study. A total of 6,953 women with early breast cancer were enrolled in this study after a 5-year tamoxifen treatment regimen and were randomized to the same allocation groups as in the ATLAS study. Those allocated to the continued tamoxifen group exhibited reduced breast cancer recurrence rate (16.7% vs. 19.3%, $p=0.003$). The time-dependent reduction in the recurrence and breast cancer mortality incidence was confirmed in the ATLAS study. Specifically, the RRRs were 0.99 (95% CI, 0.86 to 1.15) for years 5 to 6, 0.84 (95% CI, 0.73 to 0.95) for years 7 to 9, and 0.75 (95% CI, 0.66 to 0.86) for years 10 and beyond. The MRRs were 1.03 (95% CI, 0.84 to 1.27) for years 5 to 9 and 0.77 (95% CI, 0.64 to 0.92) for years 10 and beyond. Together, the combined data from the aTTom and ATLAS trials demonstrated an additional 25% reduction in the breast cancer mortality incidence with ≥ 10 years of treatment versus 5 years of treatment ($p<0.001$). These results indicated that compared with no tamoxifen treatment, a 10-year adjuvant tamoxifen regimen reduced breast cancer mortality by almost 33% in the first 10 years following diagnosis and by 50% subsequently for premenopausal women with HER2-positive breast cancer. One reasonable concern regarding long-term tamoxifen treatment might be the increased risk of endometrial cancer. The aTTom study demonstrated a significant increase in the risk of endometrial cancer after 10-year tamoxifen treatment relative to that after 5-year treatment (102 vs. 45; RR, 2.20; 95% CI, 1.31 to 2.34; $p<0.001$). There were 37 deaths (1.1%) and 20 deaths (0.6%) from endometrial cancer in the 10-year and 5-year treatment arms, respectively (absolute hazard, 0.5%; $p=0.02$). However, the authors clearly stated that the benefits greatly outweigh the risks because 10 years of tamoxifen treatment prevents 30 times as many breast cancer deaths, and recommended a longer regimen for patients at high risk of recurrence.

Secondly, in contrast to the beneficial effect of long-term use of tamoxifen for HER2-positive breast cancer, the negative results from a comparison of 2-year extended use versus 1-year use of adjuvant trastuzumab for HER2-positive breast cancer were published in the *Lancet* by the Herceptin Adjuvant (HERA)

Trial Study Team [49]. Currently, the standard treatment for breast cancer with HER2 overexpression is a 1-year adjuvant trastuzumab regimen [50]. With this trial, Goldhirsch [50] attempted to provide supporting evidence for extending the use of adjuvant trastuzumab. Briefly, 5,102 patients with HER2-positive early breast cancer were randomly allocated after surgery and chemotherapy completion to the observation, adjuvant 1-year trastuzumab, or adjuvant 2-year trastuzumab arms. The median follow-up duration was 8 years (range, 0 to 10 years). During the first few years of follow-up, the 2-year treatment group exhibited slightly better disease-free survival (DFS) than the 1-year group (89.1% vs. 86.7% at 3 years after randomization), which was consistent with the results of the Protocol for Herceptin as Adjuvant therapy with Reduced Exposure study, which compared 6 months versus 12 months of adjuvant trastuzumab treatment after a median follow-up duration of 3.5 years [51]. However, this difference waned as the follow-up duration increased and, at the time of the study analysis, the same DFS events occurred in the two allocation groups (HR, 0.99; 95% CI, 0.85 to 1.14; $p=0.86$). The mortality rate was also the same in the two groups (196 in the 2-year group vs. 186 in the 1-year group). The 2-year treatment group was associated with more frequent decreases in left ventricular ejection fraction relative to the 1-year group (8.2%, 4.9%, and 1.0% for the 2-year, 1-year, and observation groups, respectively). The HERA study also confirmed that a 1-year trastuzumab regimen yielded superior DFS and OS relative to the observation group. Because a 2-year extension of adjuvant trastuzumab use failed to show superior efficacy to 1-year use while inducing increased toxicity, the 1-year adjuvant trastuzumab regimen remains the standard of care for patients with HER2-positive early breast cancer.

Lastly, in 2013, there was an important regulatory issue in the field of breast cancer management. The US Food and Drug Administration initially approved pertuzumab for a neoadjuvant indication in breast cancer, given the appropriateness of a pathological complete response (pCR) as a surrogate endpoint in the neoadjuvant setting. This accelerated approval of pertuzumab was mainly supported by three randomized trials: the NeoSphere [52], TRYPHAENA [53], and CLEOPATRA studies [54]. NeoSphere, the primary study to support the efficacy of pertuzumab in a neoadjuvant setting, showed statistically significant improvements in the achievement of pCR in patients receiving pertuzumab plus trastuzumab and docetaxel versus patients receiving only trastuzumab plus docetaxel. CLEOPATRA, a randomized double-blind, placebo-controlled trial, included 808 patients with HER2-positive metastatic breast cancer who received either pertuzumab plus trastuzumab and docetaxel or placebo plus trastuzumab

and docetaxel. Along with the significant improvements in PFS and OS observed in the pertuzumab treatment arm, the CLEOPATRA study suggested the use of pCR as a surrogate clinical benefit endpoint in terms of DFS, EFS, and OS. The subsequent CTNeoBC pooled analysis, which included 11,955 patients, found associations of pCR with EFS and OS. These associations were strongest in patients with aggressive tumors, including HER2-positive and triple-negative tumors. Although the CTNeoBC analysis could not confirm these significant associations at a clinical trial level but rather at an individual patient level, the potential benefit of the concept of pCR as a surrogate endpoint in cases such as the use of pertuzumab in neoadjuvant breast cancer appears to be the early assessment of long-term survival outcomes and the consequent earlier approval of a drug to address an unmet medical need.

INTENSITY-MODULATED RADIOTHERAPY IN GYNECOLOGIC CANCER

Provision of the optimal target tissue dose with a minimal dose to normal tissues is the goal of RT. Intensity-modulated radiotherapy (IMRT) is among the recent technical advances in radiation delivery intended to satisfy this clinical goal. IMRT is a type of three-dimensional conformal radiotherapy (3D-CRT), in which the spatial distribution of the prescribed dose is conformed to the 3D target volume via a set of fixed radiation beams [55]. Compared with conventional 3D-CRT, IMRT uses optimized nonuniform radiation beam intensities that are incident on the patient [55]. The summation of the individual contributions from each beam results in complex 3D dose clouds and the delivery of minimal doses to the organs at risk. Based on this theoretical benefit of IMRT and the relevant clinical evidence, IMRT has become a standard RT method for prostate cancer as well as head and neck cancer treatment [56]. However, its potential benefit has not yet been fully demonstrated in gynecologic cancers. In 2012, a phase II feasibility trial conducted by the Radiation Therapy Oncology Group (RTOG) reported that IMRT led only to an insignificant 12% reduction in the incidence of grade 2 or higher bowel toxicities compared with historic controls (RTOG 0418) [57].

In 2013, two separate notable research reports attempted to demonstrate reduced toxicity and comparable survival outcomes with IMRT in cervical and endometrial cancer, respectively. For cervical cancer, the final report of a prospective randomized study of IMRT versus conventional pelvic RT in locally advanced disease in India was published in the *International Journal of Radiation Oncology, Biology, Physics* [58]. Although this study was small, it was the first prospective

randomized trial to show a benefit of IMRT with regard to toxicity for intact cervical cancer patients. Briefly, 44 patients with FIGO stage IIB to IIIB squamous cell carcinoma of the cervix were randomly assigned to receive whole pelvic conventional RT or IMRT at a total dose of 50.4 Gy in 28 fractions plus concurrent weekly cisplatin (40 mg/m²). The median follow-up durations were 21.7 months (range, 10.7 to 37.4 months) and 21.6 months (range, 7.7 to 34.4 months) for the conventional RT and IMRT groups, respectively. At 27 months, no significant differences in DFS (79.4% vs. 60%, $p=0.651$) and OS (76% vs. 85.7%, $p=0.645$) were observed between the two groups. However, patients in the IMRT group were less likely to develop grade ≥ 2 acute GI toxicity (31.8% vs. 63.6%, $p=0.034$) and chronic GI toxicity (13.6% vs. 50%, $p=0.011$) relative to those in the conventional RT group. Because of a few study limitations, including the small sample size, short follow-up times, and lack of image guidance, the authors argued that an additional phase III randomized trial with a large sample size was needed.

Another notable IMRT study reported in 2013 was a population-based study that used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to analyze patients with endometrial cancer [57]. Among the 3,555 women with uterine cancer in the SEER-Medicare database, 328 patients (9.2%) who had undergone IMRT were identified. The incidence of late toxicities and costs were compared in the IMRT and 3D-CRT groups. The IMRT group had a higher incidence of bowel obstruction than did the 3D-CRT group (RR, 1.41; 95% CI, 1.03 to 1.93). However, there was little difference in the incidence of late toxicity, including other GI and genitourinary toxicities as well as hip fracture, between the IMRT and 3D-CRT groups. There was a possible explanation for these findings. Given the large tissue volume and a relatively low dose (45 to 55 Gy) of the adjuvant RT for endometrial cancer, the potential toxicity benefits of IMRT for uterine cancer might be less prominent than those of pelvic RT for cervical cancer, in which the total delivered RT dose is often much higher (>80 Gy) [57]. Given the increased cost of IMRT (US \$12,000 greater than that of 3D-CRT), the authors concluded that the recent increased use of IMRT for women with uterine cancer should be further supported by randomized trials that examine the effectiveness as well as the safety of IMRT.

CONCLUSIONS

The therapeutic benefit of BEV for recurrent or metastatic cervical cancer was highly welcomed and readily incorporated into the practice guidelines. Dose-dense carboplatin and

paclitaxel were also classified as category 1 in the guidelines as another standard front-line postoperative chemotherapy regimen for advanced EOC. Other targeted agents have begun to show some potential benefits for advanced EOC in different settings. Based on the integrated genomic characterization of endometrial carcinoma, a change in the therapeutic plan is expected for a subset of endometrioid tumors that are refractory to current treatment. We hope that many of these changes will transition to real clinical practice in the future.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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