

UC Irvine

ICTS Publications

Title

American Society of Clinical Oncology 2013

Permalink

<https://escholarship.org/uc/item/4db7m382>

Journal

International Journal of Gynecological Cancer, 24(1)

ISSN

1048-891X

Authors

Eskander, Ramez N
Tewari, Krishnansu S

Publication Date

2014

DOI

10.1097/igc.0000000000000030

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed



Published in final edited form as:

Int J Gynecol Cancer. 2014 January ; 24(1): 13–18. doi:10.1097/IGC.0000000000000030.

American Society of Clinical Oncology 2013: Summary of Scientific Advancements in Gynecologic Cancer

Ramez N. Eskander^a and Krishnansu S. Tewari^a

^aUniversity of California, Irvine, Department of obstetrics and Gynecology, Division of Gynecologic Oncology, Orange, CA, USA

Meeting Report

Introduction

The American Society of Clinical Oncology meeting was held in Chicago, Illinois from May 31st– June 4th2013, and focused on “Building Bridges to Conquer Cancer.” An estimated 25,500 oncology professionals, with a broad range of interests, attended the meeting. Cervical cancer, a gynecologic malignancy with a significant global burden, was prominently featured at this years meeting. In a mark of exemplary scientific accomplishment within our specialty, 2 of the 5 general session plenaries investigated advancements in cervical cancer care, extending from improved screening to treatment of metastatic disease. This was followed by the presentation of several important phase 2 and 3 clinical trials in the Gynecologic Oncology Tract, focusing on cervical, ovarian, uterine and breast cancer, which will be discussed in this report.

General Plenary Highlights—Over 5,500 abstract were submitted to the 2013 annual meeting; 5 were chosen for presentation in the General Plenary session, and featured in the ASCO 2013 Press Briefing held on the morning of June 2nd2013 when the embargo was lifted. Importantly, 2 of the General Plenary presentations highlighted advancements in cervical cancer screening and treatment, while a third abstract discussed the survival benefit associated with extended tamoxifen therapy in breast cancer patients.

Visual Inspection Protocol for Cervical Cancer Screening Reduces Mortality by 31%:

Despite advances in screening, vaccination and treatment of early stage disease, globally, cervical cancer continues be associated with significant morbidity and mortality. This is attributed primarily to the burden of disease in resource poor countries. In a ground-breaking study, Dr. Surndra Shastri presented data from a large prospective cluster-randomized controlled trial exploring the effect of visual inspection with acetic acid (VIA) screening on cervical cancer mortality (Abstract 2). Importantly, the lack of a national cervical cancer pap smear program, due to inadequate infrastructure, logistical limitations and high costs, has resulted in India carrying a disproportionate share of the global burden of this disease. An estimated 141,768 cases (29% of global incidence) of cervical cancer were diagnosed in 2012, with 77,096 deaths (30% of global incidence).

In an effort to identify a low cost, effective screening modality, Dr. Shastri and colleagues examined the utilization of VIA as a cervical cancer screening tool. The benefits of VIA include it's low cost, simplicity of interpretation, as well as feasibility in training primary health workers (PHW) over a brief period of time, facilitating large scale implementation. A

total of 20 slum centers were included in the study, with 10 screening clusters (n = 75,360) and 10 control clusters (n = 76,178). The screening cluster intervention included biennial VIA, education and biennial monitoring for cervical cancer incidence and mortality. Conversely, the control cluster intervention included education alone, with biennial monitoring for cervical cancer incidence and mortality. On both arms, pre-invasive and invasive disease was treated at Tata Memorial Hospital, or other private medical centers at the discretion of the patient. To improve access, temporary screening clinics were set up in clusters, encouraging participation. Demographic and risk factors were balanced amongst groups. There was an expected attrition rate of approximately 20%.

Initiation of VIA screening resulted in an increase in the diagnosis of pre-invasive disease, with 328 vs. 48 cases of LSIL/HSIL in the screening group and control group, respectively. Over a 12-year follow up period, there was a dramatic, 31% decline in cervical cancer mortality in the screening group when compared to control (n=76; n=98 respectively; p=0.003). Additionally, a significant stage shift occurred in patients diagnosed with cervical cancer in the screening arm, with a significant reduction in clinical stage 2B disease (p=0.02). Extrapolation of the above findings would suggest, with application of biennial VIA screening, over 22,000 cancer deaths can be prevented annually in India, with potential prevention of 72,000 cervical cancer deaths globally.

Addition of the Anti-angiogenic Drug Bevacizumab Improves Overall Survival in Patients With Metastatic Cervical Cancer: Advancements in cervical cancer screening and early detection/intervention are countered by the difficulties of treating patients with metastatic, persistent or recurrent disease. Currently, combination cisplatin (50 mg/m²) and paclitaxel (135 mg/m²) are used in the treatment of metastatic/recurrent disease, although the median overall survival approaches 12 months. Additionally, prior studies have shown lack of benefit with alternate platinum based 2-drug regimens. More recently, anti-angiogenic therapy in cervical cancer has shown promising results when compared to historical cohorts (Gynecologic Oncology Group (GOG) protocol 227C). Biologically, tumor neovascularization imparts an aggressive course in cervical cancer, where aberrant and abnormal vascularity may indicate invasive disease on colposcopic exam. Furthermore, increased tumor micro-vessel density (CD31 staining) is associated with poor prognostic outcomes. Mechanistically, this is explained by effects of E6/E7 on downstream angiogenic pathways. E6 mediated degradation of p53, and E7 inactivation of pRb, result in increased VEGF and HIF-1 α , promoting angiogenesis and tumor growth.

GOG protocol 240, the 3rd opening plenary session abstract, was a 4 arm prospective randomized trial exploring platinum and non-platinum doublets with and without the anti-angiogenic agent bevacizumab (Abstract 3; Table 1). The trial opened in April 2009 and closed in January 2102 after 452 patients were enrolled. The primary end point was overall survival (OS) with secondary end points of progression free survival (PFS), overall response rate and quality of life. Groups were balanced based on baseline demographics as well as known prognostic factors including age, histology, race, stage of disease, performance status and presence of pelvic disease in the prior radiated field. The investigators showed a significant improvement in OS in the bevacizumab containing arms relative to control (17 months vs. 13.3 months respectively; HR 0.71; 95% CI 0.54-0.95; p=0.0035). Analogous improvements in PFS were identified (8.2 months bevacizumab containing arm and 5.9 months in control arm (HR 0.67; 95% CI 0.54-0.82; p=0.0002). These findings represent the first time a targeted agent has shown an improvement in overall survival in patients with gynecologic cancer.

Uniquely, given the clinical impact of GOG 240, ASCO made an exception to their confidentiality policy, allowing the abstract to appear in the public domain months prior to

the annual meeting. Furthermore, in July 2013 the NCCN convened and added the triplet regimen of cisplatin, paclitaxel and bevacizumab (at GOG 240 protocol-specified dosages) as category 2A for the treatment of metastatic/recurrent cervical cancer (http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf). We anticipate that this will convert to category 1 following publication of the final manuscript. The results of GOG protocol 240 are practice changing.

As with all novel agents, therapeutic benefit must be weighed against potential toxicity and impact on quality of life. In GOG 240, four subjects in each arm experienced a treatment related death. Within the bevacizumab containing arm, there was an increase in grade 3 GI and GU fistula (n=5), as well as grade 2 hypertension, grade 4 neutropenia and grade 3 thrombocytopenia. This did not translate into a significant deterioration in HRQOL (FACT-Cx TOI). The full QOL data were not presented at the ASCO meeting, and the effects of bevacizumab on symptom palliation are yet to be determined.

Additionally, as detailed above, the burden of cervical cancer is greatest in impoverished, resource poor countries lacking effective screening modalities. Assessment of the cost implications and feasibility of incorporating anti-angiogenic agents into the treatment algorithm of advanced cervical cancer on a global level is implicit. We look forward to presentation of the cost-benefit analysis, anticipated at the 2013 European Society of Gynecologic Oncology (ESGO) meeting.

Extended Treatment with 10 years of Tamoxifen therapy is Associated with Reduced Breast Cancer Recurrence and Decreased Breast Cancer Mortality: Abstract 5 of the general plenary session discussed long term outcomes associated with Tamoxifen therapy in patients with breast cancer. The aTTom UK collaborative network investigated the impact of continuing adjuvant tamoxifen for 10 years versus stopping at 5 years in women with early stage breast cancer. Results of the international counterpart of aTTom, the ATLAS trial, were recently published in Lancet (2013), and showed an improvement in both recurrence rate and breast cancer specific mortality. Between 1991-2005, a total of 6,953 women with ER + (n=2775) and ER untested (n=4198) early stage breast cancer from 176 UK centers were randomized to stop tamoxifen, or continue to year 10, after 5 years of primary treatment. Allocation to the tamoxifen arm reduced breast cancer recurrence (p=0.003), and this was time dependent with greatest reduction during years 7-9 (HR 0.75; 95% CI 0.66-0.86). This translated into an absolute reduction in recurrence risk of approximately 4% going out 15 years. Longer treatment also reduced breast cancer mortality (p=0.05), with greatest benefit year 10 and on (HR 0.77; 95% CI 0.64-0.92), translating into a 2% absolute risk reduction. The time dependent impact of prolonged tamoxifen use is explained best by the carry over effect of initial treatment, which is known to extend 2-3 years after completion of up-front therapy.

Importantly, compliance, as well as quality of life measures were not assessed as part of this study. Tamoxifen use has been associated with changes in mood, decreased sexual function, impaired fertility and vasomotor symptoms, all of which may impact a patient's compliance with extended therapy. Lastly, an increase in endometrial cancers was noted in the extended group vs. control (102 vs. 45, respectively; p<0.0001), with implications on patient counseling. It will be important to determine the impact of extended Tamoxifen use on quality of life, as clinical application will depend heavily on patient compliance. Currently, it is unclear if the above results will lead to a paradigm shift in duration of tamoxifen therapy in women with early stage breast cancer.

Highlights from the Gynecologic Oncology Tract

Cervical Cancer: In addition to angiogenic pathways, immune modulation has gained attention as a novel anti-cancer approach. It has been shown that radiation therapy increases pro-inflammatory modifiers, recruiting CD8 and TH-1 CD4 T-cells, potentially resulting in enhanced anti-tumor immunity. Given the HPV driven biology of cervical cancer, the Japanese Gynecologic Oncology Group opened protocol DT101, exploring immunotherapy (Z-100) as a combined treatment modality, in an effort to improve the efficacy of combination chemotherapy/radiation (Abstract 5506). Investigators enrolled 249 subjects between September 2004 and October 2006 onto a prospective randomized, double blind, placebo controlled, phase 3 clinical trial (Figure 1). Z-100 is a hot water extract of the human tubercle bacilli, and has been shown in prior in vivo models to activate innate immunity, and to inhibit metastasis. Subjects had clinical stage 2B-4A disease, with no para-aortic metastasis, and a performance status of 0-2. Primary treatment consisted of radiation alone or a combination of radiation + chemotherapy. The primary endpoint was OS, with secondary end points of recurrence free survival and toxicity. Study arms were balanced across clinical characteristics and demographics.

The study reported a non-significant improvement in 5 year OS in the Z-100 containing arm (HR 0.646; 95% CI 0.400-1.043) and failed to show a difference in recurrence free survival. Interestingly, occurrence of a secondary neoplasm while on trial was less in the Z-100 arm in comparison to placebo (3.3 vs. 9.8%, respectively).

Promising results from a randomized phase 2 study using ADXS11-001 immunotherapy were also presented at the annual meeting (Abstract 5529). ADXS11-001 is a live attenuated *Listeria monocytogenes*(Lm) bioengineered to secrete an HPV-16-E7 fusion protein targeting HPV transformed cells. The Lm vector serves as its own adjuvant and infects antigen presenting cells where it naturally cross presents, stimulating both MHC class 1 and 2 pathways resulting in specific T-cell immunity to tumors. A total of 110 patients with recurrent/refractory cervical cancer previously treated with chemotherapy, radiotherapy or both were randomized to either 3 doses of ADXS11-001 at 1×10^9 CFU or 4 doses of ADXS11-001 at 1×10^9 CFU with cisplatin chemotherapy. The primary endpoint was 12-month survival. As of May 2013, 110 patients have received 264 doses of ADXS11-001. Final 12-month overall survival was 36% (39/110) with an 18-month survival of 22% (16/73). Activity was observed against all high risk human papillomavirus (HPV) strains detected, including HPV 16, 18, 31, 33, and 45. Forty-one percent (45/110) of patients experienced 104 mild-moderate Grade 1-2 adverse events and 2% (2/110) of patients experienced a Grade 3 serious adverse event.

Ovarian Cancer: Despite advancements in up front surgical cytoreduction and adjuvant chemotherapy, ovarian cancer recurrence rates and mortality are relatively unchanged. Thus, the importance of effective screening and early diagnosis in high-risk populations is implicit. This year, the results of 4-monthly screening in the UK familial ovarian cancer screening study (UK FOCSS phase 2) were presented (Abstract 5507). Historically annual screening with CA-125 and trans-vaginal ultrasound was used, but did not appear to have adequate sensitivity to detect early disease (30% - UK FOCSS 1). UK FOCSS 2 modifications included screening every 4 months, with implementation of a web based system notifying physicians when additional testing/referral was required, in addition to incorporation of risk of ovarian cancer algorithm (ROCA) scores.

A total of 4531 women were enrolled, with a median age of 45.5 years. Enrollment criteria included > 10% lifetime risk of ovarian cancer, age > 35, declined risk reducing bilateral salpingo-oophorectomy. 14,623 women screen years were included, with 3.75 years median follow up. In the cohort, 16 incidence cases of ovarian cancer were detected (50% stage 1 or

2). If patients with occult malignancy at the time of surgery are considered false negative assessments, a total of 12 of 16 cases were detected (42% stage 1 or 2). The calculated sensitivity ranged from 75-100%, with specificity of 96.1% and PPV of 13%. Interestingly, 4 subjects of the 12 with an incident cancer were identified based on an abnormal ROCA, with a normal pelvic ultrasound. Additionally, potentially avoidable delays in physician referral were reduced using the internet notification system. The trial did not mandate serial sectioning of the fallopian tubes in patients undergoing RRBSO, and this may have translated into the low rate of occult carcinoma (n=4/653; 0.6%).

Despite the promising results, several limitations exist with respect to the UK FOCSS screening trial. The population was quite heterogeneous, with high risk patients categorized by family history, known BRCA mutation and Lynch Syndrome, making data extrapolation difficult. Additionally, the average age at study entry was 44, which is significantly younger than the average age of onset of ovarian cancer in BRCA mutation carriers (in the UK majority of women > 50 years of age at diagnosis, based on EMBRACE trial). Given the above, the follow up for screen negative women at a later age is important, and ultimate rates of RRBSO should be investigated. Lastly, the study algorithm, inclusive of high quality TVUS in experienced centers, quality control CA 125 measures, strict screening schedule and notification protocol as well as a mandated rapid response, are likely not generalizable across institutions outside of a trial.

Several therapeutic trials in ovarian cancer were presented in the oral abstract session (Table 2). The most controversial was the MRC CHORUS trial, comparing neoadjuvant chemotherapy (NACT) to primary surgery (PS) for newly diagnosed advanced ovarian cancer (Abstract 5500). Eligibility criteria included imaging consistent with FIGO stage 3 or 4 disease, serum CA 125:CEA ratio > 25, anticipated use of carboplatin based chemotherapy, and performance status sufficient to allow treatment. This prospective, randomized, non-inferiority trial enrolled a total of 552 patients, from 76 centers, between March 2004 and August 2010. The primary end point was OS, with secondary end points of PFS, safety and quality of life. Treatment arms were comparable with respect to median age, radiologic tumor size, stage and performance status. Approximately 25% of subjects received single agent carboplatin, 75% received carboplatin + paclitaxel and < 1% received carboplatin and an alternate drug. Ninety percent had stage 3 or 4 disease.

Within the primary surgery cohort, 16% of subjects were left with no residual disease, and 25% with ≤ 1 cm. The rate of microscopic residual disease was 40% in the neo- adjuvant cohort, with 35% of subjects having ≤ 1 cm of residual disease at completion of surgery. When exploring outcomes, no significant difference in progression free survival or overall survival was identified. Furthermore, the authors reported a 5.6% 28-day mortality rate in the primary surgery arm, compared to 0.5% in the neo-adjuvant arm. The authors concluded that NACT was non-inferior to primary TDS, with improved optimal cytoreduction rates and decreased morbidity. These results should be interpreted with caution given the low microscopic residual disease rate in the primary surgery arm, and the identical median surgical times in both arms (120 min), calling into question the surgical effort with up-front surgery. Additionally, 20% of subjects had a PS of 2-3, representing an unfavorable population. Currently, we await the results of Japanese Clinical Oncology Group (JCOG) protocol 0602, once again evaluating the question of up-front surgery versus neoadjuvant chemotherapy.

The MITO-7 investigators conducted a randomized, multicenter phase 3 study comparing weekly versus every 3 weeks carboplatin plus paclitaxel in patients with advanced ovarian cancer (table regarding doses/arms) (Abstract 5501). The trial was initially discussed in 2007, and opened to accrual in 2008, with a primary end point of quality of life measures.

However, with publication of Japanese GOG protocol 3016 in 2009, the trial was emended and the primary end point modified to include progression free survival. A total of 882 patients were enrolled on trial from November 2008 to March 2012, with 808 subjects evaluable at the time of data presentation. The authors demonstrated a trend towards improved PFS in the weekly arm, with a HR of 0.88 (95% CI 0.72-1.06), although this did not reach statistical significance. Overall survival data was not mature at the time of presentation. The selected dose of paclitaxel (60 mg/m²), a relative dose reduction when compared to JGOG 3016, may have impacted PFS measures.

Quality of life data was significantly better in the weekly arm for all evaluated scales. Specifically, decreased incidence of neutropenia, febrile neutropenia and thrombocytopenia occurred on the weekly arm. Notably, there was a significant decrease in the rate of grade 2 alopecia ($p < 0.001$) in the weekly regimen. Currently, we await the results of 3 additional trials exploring dose dense administration of chemotherapy, GOG protocol 262, ICON 8 and iPOCC. The results of the above trials will help clarify the impact of weekly administration on oncologic outcome, QOL, and will additionally contribute to the cost implications of weekly treatment.

In addition to dose dense adjuvant therapy, an important maintenance protocol was presented at the ASCO meeting. AGO-OVAR 16 was a phase 3, randomized, placebo controlled, double-blind study assessing pazopanib versus placebo in women who did not progress after first-line chemotherapy for advanced epithelial ovarian, fallopian tube or primary peritoneal cancer (Abstract 5503). Between June 2009 and August 2010, 940 patients were randomized to received maintenance pazopanib, an orally administered tyrosine kinase inhibitor targeting the ATP binding sites of VEGF, PDGF and c-Kit, or placebo. The primary end point was PFS by RECIST criteria, with secondary end point of OS. A significant difference in PFS was noted, 17.9 months in the pazopanib arm and 12.3 months in placebo (HR 0.766; 95% CI 0.643-0.911). Overall survival data was immature. When assessing adverse events, there was an increase in grade 3/4 hypertension, liver toxicity, neutropenia and diarrhea in the pazopanib arm. Fifty-eight percent of subjects required at least one dose reduction during treatment, and this was especially pronounced amongst the Asian population.

Dr. Landerman presented updated findings of Olaparib maintenance therapy in patients with platinum sensitive recurrent ovarian cancer harboring BRCA mutations (Abstract 5505). Germline BRCA mutations (BRCAm) were assessed on a total of 218 patients, and somatic mutations in an additional 209 subjects. Retrospective assessment of OS and PFS, in relationship to BRCAm status was completed. A total of 136 subjects were identified as having germline or somatic BRCAm. Within this population there was a significant improvement in PFS, favoring the Olaparib arm (HR 0.18; 95% CI 0.11-0.31; $p < 0.00001$). When exploring OS, there was a trend favoring Olaparib maintenance in BRCAm, however this did not reach statistical significance ($p = 0.208$). Further maintenance studies in mutation carriers are planned.

Sorafenib, a VEGF tyrosine kinase inhibitor was also examined in the maintenance setting (Abstract 5513). A total of 85 patients were randomized to Carboplatin + Paclitaxel or Carboplatin + Paclitaxel + Sorafenib with Sorafenib maintenance therapy. No significant difference in PFS at 6 months or 2 years was identified between arms. Notably, 22 of 43 subjects in the sorafenib arm initiated maintenance therapy, with only 12 completing 52 weeks of treatment due to toxicity.

Investigators from the POLKA trial examined the utility of volasertib, a small molecule polo-kinase 1 (PLK1) inhibitor, in the treatment of platinum-resistant or refractory ovarian

cancer (Abstract 5504). The biologic rationale of PLK1 inhibitors is based on the high rate of p53 mutation in patients with high-grade epithelial ovarian cancer, resulting in increased FOXM1/PLK1 expression. PLK1 inhibitors are believed to impart cell death via mitotic arrest. A total of 109 subjects were randomized to single agent volasertib at a dose of 300 mg/m² every 3 weeks versus single agent cytotoxic chemo (investigator's discretion). No significant differences in disease control rate or clinical response rate were identified between arms, with an increased incidence of hematologic toxicity in the volasertib arm.

Endometrial cancer: Unfortunately, limited data was presented this year addressing therapeutic options in patients with endometrial cancer. Schuler and colleagues conducted a pre-operative window study investigating the effect of metformin for the treatment of endometrial cancer (Abstract 5519). Twenty women with endometrial cancer, and BMI > 30 were enrolled on trial. Subjects underwent pre-treatment repeat endometrial biopsy, followed by metformin 850 mg orally once daily for 1-4 weeks and surgical staging (hysterectomy). The expression of Ki-67, a marker of proliferation assessed by immunohistochemistry, was significantly reduced following metformin treatment (p=0.008), further supporting investigations into the molecular and clinical benefits of metformin use in this population.

Abstract 5524 explored the use of MK-2206, an allosteric inhibitor of the AKT isoforms, on treatment of recurrent endometrial cancer. Patients with recurrent endometrial cancer underwent PIK3CA mutational analysis, followed by weekly MK-2206 administration. The study was halted after 37 patients were enrolled due to logistical limitations related to timely, affordable, prospective PIK3CA mutational testing. There was limited response to MK-2206, and PIK3CA mutation did not predict response to the study drug.

Lenvatinib, an oral multitargeted tyrosine kinase inhibitor of VEGFR1-3, FGFR1-4, PDGFR β , RET and KIT, was evaluated in a prospective phase 2 trial in patients with advanced or recurrent endometrial cancer (Abstract 5520). A total of 133 subjects were enrolled on study, and received 24 mg of oral lenvatinib once daily. The objective response rate was 21.8% by investigator assessment, and 14.3% by independent imaging review. Median PFS was 5.6 months and median OS was 10.6 months. Interestingly, low baseline Ang-2 levels using a simulated cutoff level, appeared to predict clinical benefit in a subset of the population.

Highlights from the Breast Cancer Track—Studies evaluating therapeutic options in both HER2/ER positive and triple negative breast cancer were presented at the annual meeting. Dr. Lisa Carey discussed the results of CALBG 40601, a phase 3 trial of lapatinib added to neoadjuvant chemotherapy in patients with non-inflammatory stage 2-3 HER2+ breast cancer (Abstract 500). Patients were randomized to receive paclitaxel (P) + trastuzumab (H) alone or in combination with lapatinib (L) for 16 weeks prior to surgery. Use of dual Her2-targeting was hypothesized to result in an increased pathologic complete response rates. Grade 3 toxicity was greater in the lapatinib containing arms. Pathologic complete response rates were 51% in the THL arm and 40% in the TH arm (p=0.11).

The addition of neoadjuvant trastuzumab (H) to traditional chemotherapy, followed by adjuvant trastuzumab (H) was examined in the NOAH study, whose follow up results were presented at this year's annual meeting (Abstract 503). The neoadjuvant chemotherapy regimen included doxorubicin, paclitaxel, cyclophosphamide, methotrexate and 5-fluorouracil. After a median follow-up of 5.4 years, the 5 year EFS rate was 57.5% in the trastuzumab arm, and 43.3% in the control arm (HR 0.64; p=0.016).

Conclusions

Gynecologic malignancies were featured at the 2013 ASCO Annual Meeting, as 2 of the 3 general session opening oral presentations focused on cervical cancer screening and treatment. VIA was shown to have a dramatic impact on cervical cancer mortality, while bevacizumab was found to have an overall survival advantage for the first time in a gynecologic cancer when combined with cytotoxic chemotherapy. Additional studies exploring immune modulatory and targeted therapies in cervical, ovarian, uterine and breast cancer were reviewed. In an era of molecular therapeutics and genomics, targeting malignancies based on mutational profiling has been promising. The dramatic improvement in PFS with the use of PARPi in patients with BRCA mutations perhaps illustrates this best. Attempts at analogous progress are being made in patients with metastatic, recurrent endometrial cancer, with metformin showing promise in preclinical studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by an institutional NIH T-32 training grant (Ruth L. Kirschstein NRSA Institutional Training Research Grant, 2T32 CA-060396-11)

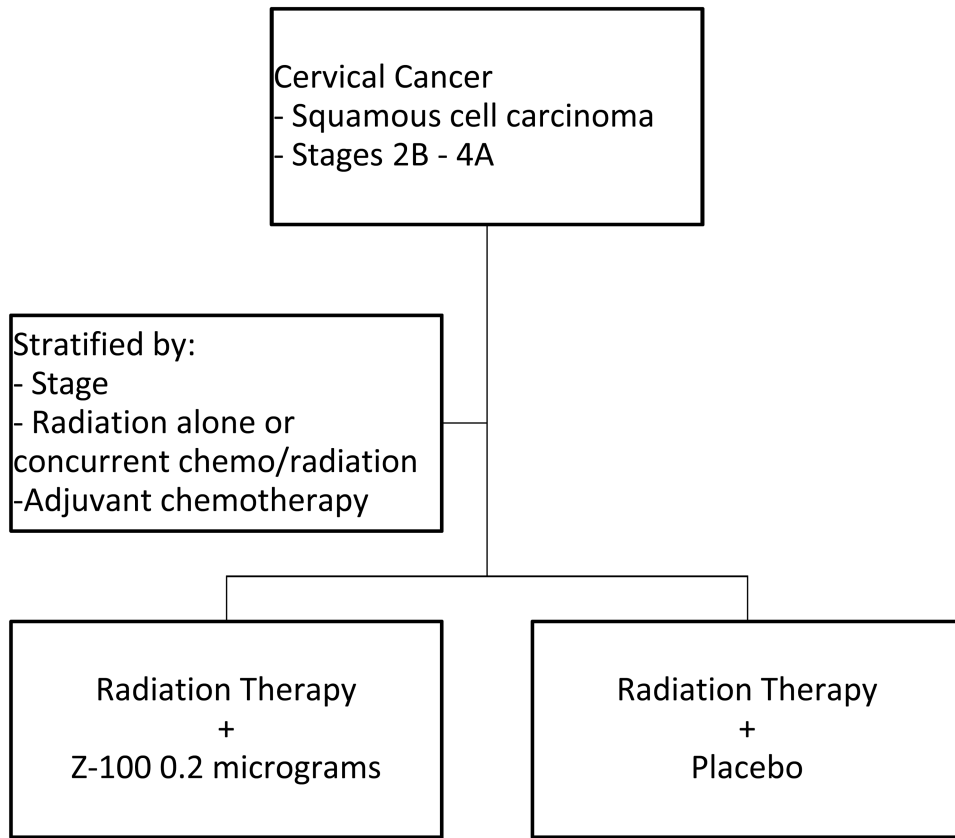


Figure 1. Japanese Gynecologic Oncology Group DT101 Schema