



September 15, 2021

Elizabeth Barr, Ph.D.
Office of Research on Women's Health
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RE: Request for Information: Inviting Comments to Inform the Women's Health Consensus Conference

Dear Dr. Barr,

The Society of Gynecologic Oncology (SGO) and The GOG Foundation, Inc. (GOG Foundation), appreciate the opportunity to provide comments to the Office of Research on Women's Health to assist in identifying research gaps, pitfalls in clinical practices and other issues related to women's health. Our comments that follow specifically relate to stagnant cervical cancer survival rates.

The SGO is the premier medical specialty society for health care professionals trained in the comprehensive management of gynecologic cancers. The SGO's 2,000 members in the United States and abroad represent the entire gynecologic oncology team dedicated to the treatment and care of patients with gynecologic cancers. The SGO's strategic goals include advancing the prevention, early diagnosis, and treatment of gynecologic cancers by establishing and promoting standards of excellence. Key priorities for the SGO are to advocate for more equitable care for all patients and support research aimed to improve outcomes for diverse patient populations.

The GOG Foundation is a nonprofit organization with the purpose of promoting excellence in the quality and integrity of clinical and basic scientific research in the field of gynecologic malignancies, including cancers that arise from the ovaries, uterus, cervix, vagina, and vulva. The GOG Foundation is committed to maintaining the highest standards in clinical trials development, execution, analysis and distribution of results. The GOG Foundation is the only group in the United States that focuses its research exclusively on women with pelvic malignancies. The GOG Foundation is multi-disciplinary in its approach to clinical trials, and includes gynecologic oncologists, medical oncologists, pathologists, radiation oncologists, nurses, statisticians, basic and translational scientists, quality of life experts, data managers, and administrative personnel. The results of GOG Foundation clinical trials have influenced the standard of care for numerous malignant gynecologic neoplasms. The GOG Foundation's mission is to conduct clinical and translational research that positively impacts women through the prevention and treatment of gynecologic malignancies, with the vision to be the premier collaborative network for transformative research in gynecologic malignancies.

As you may know, cervical cancer is a type of cancer that occurs in the cells of the cervix, which is the lower part of the uterus that connects to the vagina. Various strains of human papillomavirus (HPV), a sexually transmitted infection, play a role in causing most cervical cancer. Cervical cancer was once one of the most common causes of cancer death for American women. Disease-specific mortality from cervical cancer dropped significantly with the increased use of Pap smears for cervical cancer screening. This screening procedure can find precancerous changes in the cervix before cancer develops to allow for treatment and prevention of cervical cancer. It can also find cervical cancer early when it is small and easier to cure.

Cervical cancer is largely a preventable disease due to the availability of HPV vaccination and screening with Pap smears and HPV testing. With early detection and timely follow-up treatment, cervical cancer is often successfully treated and cured. The 5-year survival rate is 93% when it is diagnosed in its early stages. Despite being a highly treatable disease, death rates from cervical cancer have remained stagnant over the last 40 years, while mortality for many other cancers has been decreasing. The American Cancer Society's Annual Report to the Nation on the Status of Cancer, 1975–2014, compared overall cancer survival rates from 1975–1977 and from 2006–2012, and reported that survival rates increased significantly for all but two cancer types in women, cancers of the cervix and the uterus.

The American Cancer Society estimates that in 2021, about 14,480 new cases of invasive cervical cancer will be diagnosed in the United States and approximately 4,290 women will die from cervical cancer. Racial and socioeconomic disparities exist in cervical cancer screening, incidence, and mortality. Cervical cancer has a disproportionate impact on low-income women and women of color. Hispanic women are most likely to develop cervical cancer, followed by women who are African American, American Indian or Alaska Native, and White. Hispanic women are 60% more likely to be diagnosed with and 30% more likely to die from cervical cancer than white women. These significant disparities indicate that women from minority and/or socioeconomically disadvantaged populations in the United States are not equally benefiting from the prevention and screening tools available to combat cervical cancer.

Support Research That Positively Impacts Access to Cervical Cancer Prevention and Screening

To improve cervical cancer survival rates, there needs to be a concerted, sustained effort to increase prevention and early detection of this disease. We know prevention works, and yet new discovery in this area and wide implementation of the effective HPV vaccine is not optimal. Research to help understand barriers to HPV vaccination and screening programs as well as development of new approaches to expand access to screening are also needed.

1. Invest in HPV Vaccine Education to Address Vaccine Hesitancy and Improve HPV Vaccination Rates

Emphasizing disease prevention through vaccination of our adolescent population is the most effective way to decrease death in the United States from cervical cancer. While the health care system continues to attempt to readily implement HPV vaccinations, there are still many barriers to receiving the vaccine. Vaccination policies are established at the state level and vary throughout the country. School-based HPV vaccination programs are not mandated. Overall, there is a lack of vaccine education. Due to these factors, we have not seen the peak potential impact these vaccinations could make in this population. While screening remains highly effective at detecting precancerous lesions, primary prevention via HPV vaccination is paramount to reducing cervical cancer rates and is more cost-effective.

Ten years after the introduction of the quadrivalent HPV vaccine in the United States, the prevalence of HPV infection in types 6, 11, 16 and 18 decreased 86% and 71% in females aged 14-19 and 20-24, respectively.¹ Accordingly, the rates of severe cervical dysplasia between 2008 and 2015 declined significantly in women aged 18-24. Yet, compared to vaccination rates for measles, for example, which approach 90%, only 50% of teens have been vaccinated against HPV.² Misinformation about HPV vaccination and side effects, as well as claims that vaccination against a sexually transmitted disease may lead to risky sexual behavior—a concern which has been refuted—continues to be touted and impedes widespread acceptance of the HPV vaccine. Community engagement programs to allow careful exploration of vaccine hesitancy in various communities and groups within the United States may help to identify vaccination barriers which can be addressed to improve HPV vaccination rates. Working directly with trusted providers and trusted sources of information in the community (e.g., religious organizations and advocacy groups) is critical to expanding acceptance of and access to HPV vaccination.

As part of an educational approach to achieve broader acceptance of the HPV vaccine, the SGO and GOG Foundation support passage of the Promoting Resources to Expand Vaccination, Education and New Treatments for HPV Cancers Act or the PREVENT HPV Cancers Act (H.R. 1550). This legislation provides new resources to establish an HPV vaccine public awareness campaign, enhance research on HPV-associated cancers at the National Cancer Institute, and strengthen the National Breast and Cervical Cancer Early Detection Program, with a goal to reduce the rate of mortality from breast and cervical cancer in the nation by 2030.

2. Support Research That Will Positively Impact Access to Cervical Cancer Screening

A patient that is diagnosed with invasive cervical cancer often reflects a patient who did not have access to, or failed to receive, cervical cancer screening with a Pap smear test. In the United States today, no woman should be afflicted by cervical cancer. With the addition of HPV co-testing with a Pap smear in women over 30 years old, the sensitivity of detecting pre-cancerous lesions exceeds 96%.³ Yet, nationwide, only 80% of eligible women undergo cervical cancer screening. Moreover, women who develop cervical cancer are more likely to have never had a pap smear.⁴ Women of color are more likely to die of cervical cancer, as are socioeconomically disadvantaged women, owing to a lack of access to screening services.^{5,6} Education level, race and income have all been associated with disparities in cervical cancer screening.⁷

In cities and suburbs with overcrowded and/or inaccessible facilities and inconvenient hours of operation, prevention and screening clinics might be relocated to more convenient sites with user friendly schedules to improve participation, particularly by patients with social factors that might

¹ Drolet M, Bénard É, Pérez N, et al. Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet* 2019; 394(10197):497–509.

² Elam-Evans L, Yankey D, Singleton J et al. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2019. *Morbidity and Mortality Weekly Report* 2020; 69(23): 1109–1116.

³ Cuzick J, Clavel C, Petry K et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer* 2006 119 (5): 1095–1101.

⁴ CDC. Cancers associated with human papillomavirus, United States—2011–2015. 2018; USCS Data Brief, no. 4.

⁵ National Cancer Institute. Cancer trends progress report. Online summary of trends in US cancer control measures. <https://progressreport.cancer.gov/about>.

⁶ O’Keefe EB, Meltzer JP, Bethea TN. Health disparities and cancer: racial disparities in cancer mortality in the United States, 2000–2010. *Front Public Health*. 2015; 15 (3): 51.

⁷ Benavidez GA, Zgodic A, Zahnd W, Eberth J. Disparities in Meeting USPSTF Breast, Cervical, and Colorectal Cancer Screening Guidelines Among Women in the United States. *Prev Chronic Dis*. 2021; 18 (15).

otherwise lessen their use (e.g., elderly and/or disabled women without support or transportation, working mothers with inflexible work hours, etc.) Self-sampling strategies have been shown to be effective and utilized in similar high-income countries, but such a strategy has not yet been FDA approved. At the peak of the COVID-19 pandemic, cervical cancer screening dropped to 22% of what it was pre-pandemic.⁸ Self-sampling strategies could help to improve overall rates of cervical cancer screening due to challenges of getting provider-sampled screening for cervical cancer. Resources to obtain the needed data for a full FDA approval of self-sampling should be a priority.

There is a surprisingly low rate of follow-up in women with an abnormal cervical cancer screening test. It has been demonstrated that cervical cancer screening follow-up adherence ranges from 20-70%.⁹ Utilization of cancer prevention and screening resources by women living in remote rural and isolated geographic areas and reservations may be accommodated by mobile clinics and professional personnel traveling at frequent, timely intervals to conduct well publicized public health clinics in villages and tribal centers. Special emphasis should be placed on reaching African American, Hispanic, American Indian and Alaska Native, Asian and Pacific Islander women, especially those over 50 years of age, where cervical cancer screening rates are lower, and the incidence of invasive cancers has been higher than for White women.^{10,11,12} Research that positively impacts access to screening programs to reduce cancer risk at the local level or as a self-administered screening test should be a high priority. With this goal in mind, SGO also supports passage of the Jeanette Acosta Invest in Women's Health Act of 2019 (H.R. 3129/S. 1735). This legislation would expand access to preventive, lifesaving women's health screenings, with a focus on breast and gynecological cancer screenings, at safety net healthcare providers for low-income women and women of color.

3. Increase Public Awareness About the Importance of Cervical Cancer Screening as a Covered Preventive Health Benefit

History shows that collaborative programs with the American Cancer Society and supported by other anti-cancer interest groups have been highly successful in calling public and professional attention to cancer screening, cancer signs and symptoms, and smoking cessation (a risk factor for cervical cancer). Basic marketing studies and design followed by intensive public information and professional education campaigns to promote understanding of the causes and methods for cervical cancer prevention and the benefits of HPV vaccination and adherence to cervical cancer screening programs for women of all ages may prove to be among the most cost-effective approaches to reducing the morbidity and mortality from this disease. The Office of Research on Women's Health could collaborate with professional medical societies and health care professionals to raise public awareness about the importance of cervical cancer screening as a covered preventive health benefit with no cost to the patient. Cervical cancer screening should be tracked as part of a patient's care plan and patients should be reminded when they are due for their next screening.

⁸ Miller MJ, Xu L, Qin J, et al. Impact of COVID-19 on Cervical Cancer Screening Rates Among Women Aged 21–65 Years in a Large Integrated Health Care System — Southern California, January 1–September 30, 2019, and January 1–September 30, 2020. *MMWR Morb Mortal Wkly Rep* 2021; 70:109–113.

⁹ Miller SM, Tagai EK, Wen KY, Lee M, Hui SA, Kurtz D, et al. Predictors of adherence to follow-up recommendations after an abnormal Pap smear among underserved inner-city women. *Patient Educ Couns*. 2017;100(7):1353-9.

¹⁰ DeSantis CE, Miller KM, Sauer AG, Jemal A, Siegel RL. Cancer statistics for African Americans, 2019. *CA Cancer J Clin*. 2019;69(3):211-233.

¹¹ Simard EP, Naishadham D, Saslow D, Jemal A. Age-specific trends in black-white disparities in cervical cancer incidence in the United States: 1975-2009. *Gynecol Oncol* 2012; 127:611-615.

¹² White MC, Shoemaker ML, Benard VB. Cervical cancer screening and incidence by age: Unmet needs near and after the stopping age for screening. *Am J Prev Med*. 2017; 53(3):392-395.

While HPV vaccination promises to provide protection against cervical cancer for younger women, it is too recent for major HPV vaccination programs, which began only about 15 years ago, to have a significant impact on decreasing the incidence of this disease in older age groups. Improving HPV vaccination rates in adolescents and young adults and strict compliance with recommended Pap smear and/or HPV screening programs with appropriate follow-up and management are generally acknowledged for their capacity to prevent, detect, and eliminate many or most preinvasive cervical lesions. Widespread understanding of the etiology of the most prevalent types of cervical cancer and protective measures, acceptance of HPV vaccination, increasing awareness on the benefits, availability, and ease of screening, and astute attention to symptoms and signs by patients and health care providers should aid in preventing preinvasive neoplasms and increase the early detection of localized cervical cancer when long-term survival is likely with proper treatment.

Overcoming Disparities in Access to Cervical Cancer Care and in Cervical Cancer Research

As we have noted, there remain large disparities in genetic testing, access to care, and other aspects of providing care for women with cervical cancer and other gynecologic cancers. Enhancing our understanding of these at a much deeper level would help facilitate strategies for overcoming disparities. These disparities are only exacerbated by the COVID-19 pandemic which disproportionately affects the underserved populations. Identification of pre-invasive and early-stage disease requires stable access to health care for repeat testing through Pap smear and colposcopy. Women with unstable or limited access to health care are at risk of developing advanced stage disease, which impairs their chance at survival. Cervical cancer most often affects women at an age when the United States health system has very limited insurance options for women who are not able to obtain employer-based insurance.

1. Increase Access to Advanced Radiation Techniques Including Brachytherapy

When patients are diagnosed with locally advanced cervical cancer (those too large to be removed surgically), the optimal outcomes occur if patients complete their primary chemoradiation within 8 weeks. However, chemoradiation is a very intensive treatment, which requires daily treatments for 5-6 weeks, followed by brachytherapy which is extremely specialized and cannot be provided at all radiation oncology centers. Patients in some areas may travel up to 4 hours to reach a brachytherapy specialty center. Building specialized networks that ensure brachytherapy is delivered and focus on patient-level barriers, especially transportation and lodging, for these patients while undergoing such frequent and intensive treatment is critical. While states may have specific programs focused on ensuring that patients with cervical cancer and other cancer diagnoses are eligible for government-based insurance, there are still many logistical barriers that can often lead to worse outcomes. Data confirm that adequate access to advanced radiation techniques including brachytherapy is associated with the best survival after initial treatment of locally advanced cervical cancer. Eliminating barriers to accessing brachytherapy should be a priority for health systems and payors involved in the care of women with cervical cancer. In addition, ensuring that Radiation Oncology training programs maintain adequate volume and training for utilizing brachytherapy implants will be important to retain a pipeline of clinicians that can provide this very specialized service.

2. Increase Representation of Racial and Ethnic Minority Groups in Clinical Trials

Individuals from minority groups and underserved populations are underrepresented in clinical trials yet have higher incidence and deaths from cervical cancer than other groups. Many reasons have been

identified such as lack of access to specialty care or regular screening, lack of insurance, limited knowledge of clinical trials and language barriers. Strict clinical trial requirements and the complexity of clinical trial participation are barriers that affect the racial, cultural, ethnic, economic, and geographic diversity of clinical trial enrollment in very predictable ways. They also limit the representativeness of the clinical trial results, forcing clinicians to constantly wonder whether extrapolating clinical trial data to their real-world patient is reasonable to do. As we embrace the era of personalized medicine, we need to rethink how clinical trials are designed and conducted so that they optimize enrollment of real-world populations that truly represent all patients, including minority and underserved populations currently underrepresented in clinical trials. Restructuring clinical trial requirements and protocols to accommodate patients of a variety of communities and social circumstances is critically important. There must be meaningful accountability to enroll underrepresented patients in cervical cancer research trials. Clinical trial funding should be contingent on demonstrated inclusion of minority participants.

3. Engage Minority and Underserved Communities in Cervical Cancer Research

High impact cervical cancer research must be defined by its potential to have lasting change in ameliorating the disparities in cervical cancer. What we know about the history of disparities research is that work conducted without community partnership from the outset is less successful, less impactful, and less sustainable. Community engagement of the population experiencing disparities should be a requirement in any cancer disparities research. To that end, funding to support training and execution support of community research partnerships is critical and a currently a major gap. Best practices have been well described, studied, and proven to work and should be used to create standards of health equity research study design and execution in all research, and specifically in research to reduce cervical cancer incidence and improve survival rates.

Investing in Innovative Cervical Cancer Research and Treatment

1. Increase funding for research on immunotherapy and innovative strategies for treatment

Immunotherapy and other therapeutic approaches for the treatment of advanced cervical cancer differ based on patient- and disease-specific factors. Typically, advanced cervical cancer is described as women diagnosed with stage IIB to IVA disease, however, women with stages IB3 and IIA2 disease may now be classified as having advanced disease. Current options for treating advanced cervical cancer may include a combination of management strategies including surgery, radiation +/- concurrent platinum-containing chemotherapy, and systemic therapy all dependent on the patients' stage and disease state. Platinum-based doublets play an essential role in the treatment of many advanced or metastatic gynecologic malignancies. Current NCCN guidelines list several platinum-based therapies including cisplatin, carboplatin, and cisplatin/fluorouracil as acceptable concurrent platinum-containing regimens to treat advanced cervical cancer in women undergoing radiation.

In metastatic cervical cancer, currently there is no standard of care treatment beyond platinum-based chemotherapy although there are several acceptable systemic regimens for oncologists to choose from. Acceptable first-line therapies include agents including combination cisplatin/paclitaxel/bevacizumab, carboplatin/paclitaxel/bevacizumab, cisplatin/paclitaxel, topotecan/paclitaxel/bevacizumab, topotecan/paclitaxel or cisplatin/topotecan. Single agent therapy may include agents such as cisplatin, carboplatin, or paclitaxel. For women requiring second-line therapy, systemic options may include

agents such as pembrolizumab, bevacizumab, albumin-bound paclitaxel, docetaxel, and irinotecan to name just a few.¹³

It is essential to continue to research novel agents through clinical trials. Specifically, agents that are under evaluation unique to the management of recurrent cervical cancer, such as antibody-drug conjugates (ADCs) targeting tissue factor (TF), and tumor-infiltrating lymphocyte (TIL) therapies. In addition, several of the investigational agents or regimens, including an antibody-drug conjugate (ADC) tisotumab vedotin,^{14,15} ICIs balstilimab with or without zalifrelimab,¹⁶ and a tumor-infiltrating lymphocyte (TIL) therapy LN-145,¹⁷ have shown promising efficacy with the manageable safety profile in this hard-to-treat patient population. These therapeutic advances provide much-needed potential of improved outcomes for many patients diagnosed with metastatic recurrent cervical cancer.

Currently it is understood that some advanced cervical cancers express programmed death-ligand 1 (PD-L1), sometimes driven by defects in mismatch DNA repair (dMMR) genes, resulting in microsatellite instability (MSI), and occasionally high levels of MSI (MSI-H).¹⁸ This motivates the investigation of immunotherapy in advanced disease; some of these clinical trials have recently reported very encouraging data. The immune checkpoint inhibitor (ICI) pembrolizumab has been FDA approved to treat PD-L1-positive or MSI-high recurrent or previously treated metastatic cervical cancer.¹⁹

Continued funding and support of research on immunotherapy, an exciting and active agent in the armamentarium against cervical cancer, is critical to fighting both metastatic cervical cancer, which has poor response rates to cytotoxic chemotherapy, as well as in combination with chemoradiation for women with locally advanced cervical cancer. In women with previously treated recurrent or metastatic disease, the investigational monoclonal antibody which targets PD-1, cemiplimab when compared to chemotherapy, was shown to reduce the risk of death in trial subjects by 31%. Of all study participants, the median survival for the investigational drug vs chemotherapy was 12.0 months vs 8.5 months, respectively.²⁰ In addition, patients on immunotherapy had an improved quality of life compared to patients on standard chemotherapy. Given the positive overall survival results noted, the phase 3 study was terminated early and detailed study results are pending presentation. The investigational drug tisotumab vedotin, an ADC targeting TF, has shown promising results with study data reporting an ORR

¹³ National Comprehensive Cancer Network. Cervical Cancer. Version 1.2021. October 2, 2020. Accessed on April 28, 2021 from https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf.

¹⁴ Coleman RL, Lorusso D, Gennigens C, et al. Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer: Results from the phase II innovaTV 204/GOG-3023/ENGOT-cx6 study. *Ann Oncol.* 2020; 31: S1162-S1163.

¹⁵ Hong DS, Concin N, Vergote I, et al. Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer. *Clin Cancer Res.* 2020; 26:1220-1228.

¹⁶ O'Malley DM, Oaknin A, Monk BJ, et al. Single-agent anti-PD-1 balstilimab or in combination with anti-CTLA-4 zalifrelimab for recurrent/metastatic (R/M) cervical cancer (CC): preliminary results of two independent phase II trials. *Ann Oncol.* 2020; 31:S1164-S1165

¹⁷ Jazaeri AA, Zsiros E, Amaria RN, et al. Safety and efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma. *J Clin Oncol.* 2019; 37:2538.

¹⁸ Steiniche T, Ladekarl M, Georgsen JB, Andreassen S, Busch-Sørensen M, Zhou W, Marton M, Pruitt SK, Jin F, Liaw K. Association of programmed death ligand 1 expression with prognosis among patients with ten uncommon advanced cancers. *Future Sci OA.* 2020; 6(8):FSO616.

¹⁹ FDA. FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy. Updated June 12, 2018. Accessed November 26, 2020. <https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm610572.htm>.

²⁰ Sanofi. Phase 3 trial of Libtayo® (cemiplimab) monotherapy in advanced cervical cancer stopped early for positive result on overall survival. 2021, March 15. Accessed on April 27, 2021 from <https://www.sanofi.com/en/media-room/press-releases/2021/2021-03-15-07-00-00-2192446>.

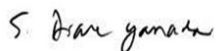
of 24% and a DOR of 8.3 months. Researchers additionally reported a 30% 6-month PFS.²¹ A phase 3 trial is currently enrolling patients using tisotumab vedotin.

Studies suggest that immunotherapy works best if given earlier in treatment when patients have a stronger immune system and current trials are underway to evaluate the use of immunotherapy in up front treatment with chemotherapy and radiation. The hope is that this will improve survival rates and decrease metastatic disease and recurrence, since survival after recurrence is less than 50%. As we identify more targets, made possible through large clinical trials with representation from a diverse population, treatment will be more individualized, more effective and less toxic.

Ongoing future research both within and outside the United States will establish the potential for immunotherapy and other investigational agents in the care of patients with advanced cervical cancer, as traditional chemotherapy agents for advanced, metastatic or recurrent cervical cancer confer average overall survival of just over one year.²² It is the hope that these trials will further establish the role of immunotherapy in the treatment of this disease. Education and ongoing clinical trials can help oncologists stay abreast of ongoing therapeutic progress and provide approaches for treatment personalization given the evolving cervical cancer treatment landscape.

Once again, thank you for the opportunity to provide comments on research needed to positively impact stagnant cervical cancer survival rates. We welcome further discussions to bring awareness and ultimately solutions to eradicate cervical cancer. Please contact Traci Schwendner, SGO Senior Manager of Governance and Clinical Practice, at traci.schwendner@sgo.org or Jenna Cummins, GOG Foundation Director of Communications and Industry Relations, at jcummins@gog.org, for any questions or follow up.

Sincerely,



S. Diane Yamada, MD
President, Society of Gynecologic Oncology



Larry J. Copeland, MD
President, The GOG Foundation, Inc.

²¹ Coleman R, Lorusso PD, Gennigens C, González-Martín PA, Randall L, Cibula D, et al. Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol.* 2021; 22(5):P609-619.

²² Tewari KS, Still MW, Long HJ, Penson RT, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leitao MM, Michael HE, Monk BJ. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med.* 2014; 370(8):734-43.