WHITE PAPER

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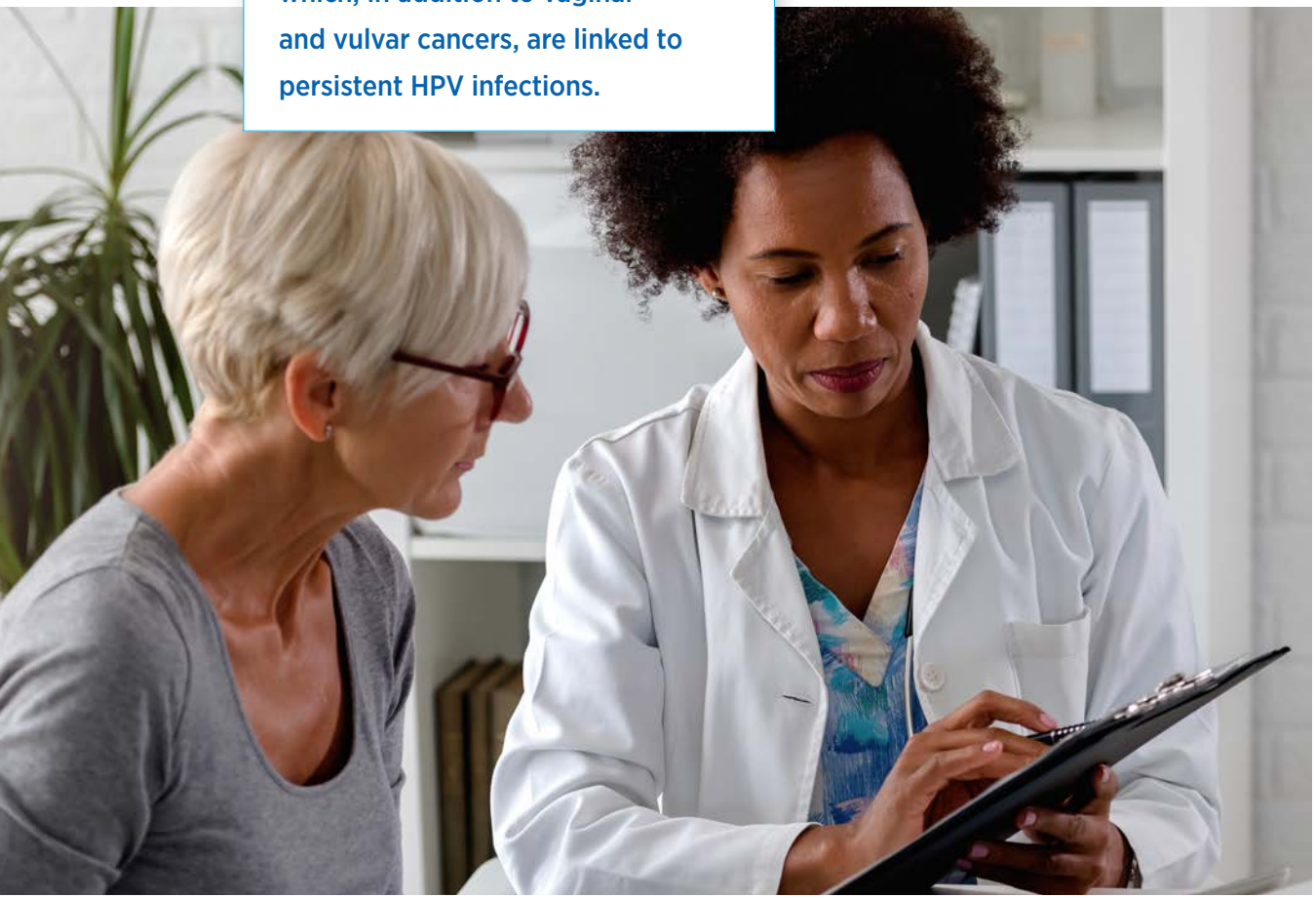
ONCOLOGY | WOMEN'S HEALTH

Addressing the Challenges and Opportunities in Gynecologic Cancer Research

ABSTRACT

New and highly effective targeted therapies and technologies hold great promise for women suffering from gynecologic cancers. Early diagnosis and more effective treatment can give patients hope for better future outcomes.

Vaccines and screening tests are available only for cervical cancers, which, in addition to vaginal and vulvar cancers, are linked to persistent HPV infections.



Introduction

Gynecologic cancers continue to be a significant cause of female morbidities and mortality worldwide. Significant unmet needs exist in diagnosis and treatment. These cancers are often detected at later stages when therapeutic options are limited, and advanced or recurrent disease leads to a poor prognosis. Earlier diagnosis and more effective treatments will enhance the quality of life and, ideally, extend progression-free and overall survival for patients.

The challenges of cancer detection and treatment

All women are at risk for the five major gynecologic cancers: ovarian, uterine, cervical, vaginal, and vulvar. Specific risk factors include family history, human papillomavirus (HPV) infections (cervical cancer), genetic mutations such as BRCA1 and BRCA2 (ovarian cancer), hormone replacement therapy, and increasing age.

Vaccines and screening tests are available only for cervical cancers, which, in addition to vaginal and vulvar cancers, are linked to persistent HPV infections. HPV vaccination can reduce infections and prevent cervical cancer, though unequal access to HPV vaccines and pap tests is an ongoing problem contributing to 4000-5000 unnecessary deaths each year. However, even if the disease does develop, routine screening and management of precancerous lesions often result in a good outcome.

Advanced ovarian and endometrial carcinomas present the most significant challenge and account for the most deaths annually.[1] Ovarian cancer is typically diagnosed at a later stage,[2] as there are at present no commercially-available screening tests to improve early detection. The standard-of-care first-line treatments are debulking surgery and perioperative platinum-based chemotherapy.[3] Although the initial response rate is high, most patients eventually relapse,

which is driving an unmet need for maintenance therapies. In recent years, endometrial cancer cases have also been rising, and those patients have faced recurrence, progression, and a poor prognosis following conventional treatment.

Despite the limited diagnostic and treatment options to date, recent progress in endometrial and ovarian cancer research has improved our understanding of these diseases and led to developing novel targeted therapies that advance patient care and outcomes.

A shift toward flexibility in clinical research methods

Classic methodologies of study design, traditional endpoints, and results interpretation are being reconsidered with the development of immunotherapies and the discovery of novel mechanisms of action. Bayesian and other model-based study designs are gaining favor for their flexibility and efficiency over the classic 3+3 design. Also, there is a greater emphasis on the co-development of companion and complementary diagnostics, which require a robust regulatory and commercial strategy.

COVID-19 accelerates transition to decentralized trials

One contributing factor driving flexibility in research methods is the COVID-19 pandemic. As a result of the pandemic, clinical trials have become more decentralized. Trial conduct and execution slowed when hospitals were overwhelmed with virus cases, and patients became unwilling or unable to travel to sites. Across multiple therapeutic areas, trials were taken directly to the patients instead of requiring patients to travel to the trial. Patient consent was obtained remotely, and trial-related assessments were conducted by video conference. In addition, sites instituted remote monitoring by allowing virtual access to electronic medical records.

Though many aspects of decentralized trials existed previously, the pandemic accelerated the adoption of innovative approaches to executing trial elements. Regulators have also issued new guidance on alternate approaches supporting the transition to more virtual elements.

Increasing patient diversity to maximize drug benefits

In addition to easing participation through the use of innovative trial designs, there has been a substantive focus on enrolling diverse patient populations. The FDA is compelling sponsors to expand subject diversity in clinical trials by proactively recruiting patients in racial and ethnic minority subgroups, who are often underserved. Conducting a population analysis for the epidemiology of the disease under investigation will highlight which racial or ethnic minorities are affected and their representative share of the total patient population. Sponsors should then commit to enrolling the trial to reflect those subgroups.

Diversity linked to biomarkers is also garnering more attention. As new therapies are being developed, it is increasingly important to deliver the right drug to the right patient for maximum benefit.

Meaningful progress in therapeutics and diagnostics

Numerous gynecologic oncology advancements have come to market or have shown great promise in the past few years. Ovarian cancer patients, especially, now have access to new diagnostics, maintenance treatments, and immunotherapies.

In studies conducted over the past eight years, women with ovarian cancer who have biomarkers including BRCA1, BRCA2, and related gene mutations responded best to maintenance therapy with poly (ADP-ribose) polymerase (PARP) inhibitors. About 25 percent of patients have a phenotype that is either loss of heterozygosity or homologous recombination deficiency (HRD) and are also very likely to respond well to PARP therapies.

The development of PARP inhibitors for ovarian maintenance therapy has truly been a game-changer. For a patient with HRD, a PARP inhibitor can delay a recurrence for nine to 12 months; for a patient with a BRCA1 or BRCA2 mutation, recurrence can be delayed for up to three years. In the trials leading to FDA approval, 90 percent of patients were able to remain on PARP therapy for the duration of the study even while experiencing some side effects and decreased quality of life. Oncologists must weigh how much benefit each patient may derive based on her biomarker status against how well she will tolerate the medication.

Beginning with checkpoint inhibitors, clinicians have learned that subjecting a patient to more drugs, i.e., the maximum tolerated dose, isn't better. What's crucial is dose optimization. From a scientific and regulatory perspective, it's important to utilize mutations or biomarkers as a guide in patient treatment planning and avoid exposing those who may gain little benefit to toxic cancer drugs.

Sponsors are evaluating other compounds such as vascular endothelial growth factor (VEGF) inhibitors that may be potentially more effective. The VEGF inhibitor bevacizumab is a first-generation intravenous antiangiogenic therapy used in first-line and maintenance treatment of late-stage ovarian cancer. After initial treatment with bevacizumab together with chemotherapy, patients can continue with bevacizumab alone under maintenance and potentially see progression-free survival of up to 18 months.[4] Oral antiangiogenics are also in development.

Other recent advances include:

- **Diagnostics:** In late 2021 the FDA approved Cytalux (pafolacianine), an imaging drug that identifies difficult-to-detect ovarian lesions during surgery.[5] Also, nanotechnology is being developed to detect cancer-associated biomarkers in early-stage ovarian cancer.[6]
- **Therapeutics:** Compounds are being repurposed in new ways using genomic sequencing. For example, Herceptin® (trastuzumab), a well-known treatment for breast cancer, has shown efficacy for a rare form of uterine cancer that overexpresses the HER2 gene.
- **Immunotherapies:** Oregovomab, an anti-CA125 antibody, demonstrated potential for eliciting an immune response to ovarian cancers in preliminary studies.[7] Vigil has also been particularly effective in homologous recombination repair proficient (HR-proficient) patients for whom PARP inhibitors don't work well.[8]

Although gynecologic cancers affect fewer women than lung, breast, or colon cancers; they can be much more deadly. However, new and highly effective targeted therapies and technologies hold great promise for women suffering from these insidious diseases, and patients and their physicians can look forward to even better outcomes in the future. To learn more about this topic, access our expert panel discussion here.

Assistance with your gynecological oncology program

As a CRO committed to improving healthcare outcomes for women, Premier Research is dedicated to advancing and accelerating clinical development of more effective treatments for gynecological cancer. Our clinical team understands how to address key operational issues and mitigate risks in these trials, helping sponsors optimize their likelihood of study success.

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Rupa Doshi, Ph.D.

With more than 23 years in the industry, Dr. Rupa Doshi is an experienced professional with demonstrated leadership skills in clinical operations, global project/program management, customer management, and strategy development. Her experience spans the clinical development spectrum from pre-IND to NDA and she has also led global teams in the execution of full-service, complex clinical trials across all phases.

Dr. Doshi brings drug discovery and clinical development experience with biologics, small molecules, as well as cell and gene therapy products over a range of indications. Her doctoral research focus was on breast cancer, post-doctoral research was in site-directed mutagenesis, and she holds patents in the area of angiogenesis. Dr. Doshi has also supported three products resulting in agency approval.

Mary Gunn, Ph.D., MBA, LLM

Dr. Mary Gunn oversees Project Planning and Delivery at Premier Research. A senior-level scientist with more than two decades of clinical development experience, Dr. Gunn leverages expertise in process optimization and innovative trial design to maximize project efficiency.

Dr. Gunn has served as a senior strategist for large and small pharmaceutical, biotechnology, and diagnostics companies supporting global clinical programs in women's health, autoimmune disorders, and oncology. Her experience spans all stages of the R&D lifecycle. Dr. Gunn has held leadership positions in operational strategy and delivery, medical affairs, and business development, including senior roles at Health Decisions (now Premier Research), ICON, Becton Dickinson, ClinTec International, Crucell (now Johnson & Johnson), and Pfizer. Dr. Gunn has bachelor's degrees in Economics and Psychology, an MBA from Brown University, a Law degree from the University of Edinburgh, and a Ph.D. in Psychology from Grand Canyon University.

Irene Figari

Irene Figari brings 40 years of biotech experience to the Premier Consulting, a division of Premier Research, regulatory affairs team. She spent 16 years in basic research and development, focusing on immunology, cell biology, tumor model systems, and molecular biology, then moved to the regulatory side in roles of increasing responsibility and leadership. She led a team of regulatory professionals in providing strategic and tactical guidance across therapeutic areas and disciplines in the clinical, nonclinical, and chemistry, manufacturing, and controls arenas. That team delivered regional and international regulatory strategy for pharmaceutical and biotech drug development teams. She has also provided regulatory leadership and development of strategy for products from the pre-investigational new
drug (IND) stage through post-marketing in multiple therapeutic areas, with a focus on oncology. A decisive and results-oriented leader recognized for both project and people management, Ms. Figari easily adapts to sudden requests and unforeseen detours. Her accomplishments include leading teams to successful global health authority interactions, INDs, orphan drug applications, fast-track applications, pediatric strategies, and marketing applications.

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About Premier Research

Premier Research, a clinical research company, is dedicated to helping biotech, specialty pharma, and device innovators transform life-changing ideas and breakthrough science into new medical treatments. As a global company, Premier specializes in the use of innovative technologies for smart study design and trial management to deliver clean, conclusive data to sponsors. Whether it's developing product lifecycle strategies, reducing clinical development cycle times, securing access to patients, navigating global regulations, maximizing the impact of limited rare disease data, or providing expertise in specific therapeutic areas, Premier is committed to helping its customers answer the unmet needs of patients across a broad range of medical conditions.

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