Ovarian Cancer:
From Epidemiology to Enhancing Clinical Trial Design

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Introduction

Ovarian cancer, a multifaceted and potentially lethal malignancy, is the fifth leading cause of cancer-related deaths among women and constitutes a significant health challenge globally.

Ovarian cancer predominantly affects women in postmenopausal stages, although it can occur at any age. The insidious nature of its development, often asymptomatic in the early stages, leads to late diagnosis and a consequently poorer prognosis. The foundational knowledge covered in this whitepaper is critical for healthcare professionals, researchers, and scientists as it shapes clinical approaches and research directions.

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Engage directly with our team of highly qualified doctors and PhD scientists from the outset.

Ready to discuss your Clinical Trial?
For further information on how iNGENū can assist you to conduct your clinical trial, book a Discovery Call with one of our Advisors.

Key Characteristics and Historical Perspectives

Key Characteristics

1. **Types:** Epithelial ovarian cancer (EOC), germ cell ovarian cancer, and stromal tumor ovarian cancer.
2. **Symptoms:** Symptoms may include abdominal bloating, pelvic pain, feeling full quickly after eating, and frequent urination. Due to their non-specific nature, these symptoms often lead to misdiagnosis or delayed diagnosis.
3. **Risk Factors:** These include age, genetic predisposition, family history of ovarian or breast cancer, endometriosis, postmenopausal HRT, and never having been pregnant.
4. **Staging:** Ovarian cancer is staged from I to IV, indicating its spread within the ovary or to other parts of the body. The stage of cancer at diagnosis significantly impacts the treatment approach and prognosis.
5. **Treatment:** May include surgery, chemotherapy, radiation therapy, targeted therapy, or a combination of these methods. Early detection significantly improves treatment effectiveness and survival rates.

Historical Perspectives

Historically, ovarian cancer was termed the "silent killer" because it was believed to progress quietly until reaching an advanced stage. However, the 20th century saw significant advancements in understanding the disease's pathophysiology, leading to improved diagnostic methods and therapies.

The late 20th and early 21st centuries have witnessed remarkable progress in understanding the genetic underpinnings of ovarian cancer, particularly the identification of BRCA1 and BRCA2 gene mutations. This has revolutionized risk assessment and prevention strategies, paving the way for targeted therapies and personalized medicine approaches.

Evolution Over Time and Impact on Clinical and Research Perspectives:

The understanding of ovarian cancer has evolved from viewing it as a uniform disease to recognizing its heterogeneity. This has led to the classification into various subtypes based on genetic, molecular, and histological characteristics. This evolution has shifted research and clinical trials from a one-size-fits-all approach to more targeted, subtype-specific strategies

ICD-11 Codes for Ovarian Cancer

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Ovarian cancer is classified under several codes, depending on its type and progression. Common subtypes of ovarian cancer:

Epithelial Ovarian Cancer (2C73.Z):
- Serous Carcinoma
- Endometrioid Carcinoma
- Clear Cell Carcinoma
- Mucinous Carcinoma

Germ Cell Ovarian Cancer (2C70):
- Dysgerminomas
- Teratomas
- Endodermal Sinus Tumors (Yolk Sac Tumors)

Stromal Tumor Ovarian Cancer (2C72):
- Granulosa Cell Tumors
- Sertoli-Leydig Cell Tumors

Small Cell Carcinoma of the Ovary (no specific ICD-11 code, generally included under 2C73.Z)

Evolution of Diagnostic Criteria

Transition from Morphology to Molecular Genetics:

Over the past few decades, there has been a significant shift from solely morphological criteria (based on tumor appearance and structure) to incorporating molecular genetic information. This change has been driven by the discovery of genetic mutations and pathways significant in ovarian cancer, such as BRCA1 and BRCA2 mutations, and the realization that ovarian cancer comprises several distinct diseases with different origins, behaviors, and responses to treatment.

Incorporation of Biomarkers and Imaging:

The use of biomarkers, particularly CA-125 (a protein found at higher levels in many women with ovarian cancer), has become integral in the diagnostic process, especially in monitoring treatment response and recurrence. Imaging techniques like transvaginal ultrasound (TVUS) and CT scans have also enhanced the ability to detect and characterize ovarian tumors, contributing to earlier detection and improved staging accuracy

Epidemiology of Ovarian Cancer

Age and Demographics:
Ovarian cancer primarily affects older women, with the highest incidence rates observed in women aged 55-64. The median age at diagnosis is about 63 years. However, certain types of ovarian cancer, such as germ cell tumors, are more common in younger women. Epidemiological studies have shown variations in incidence rates across different geographic and ethnic groups. For example, rates are higher in North America and Europe compared to Africa and Asia. Among racial groups, white women have higher incidence rates of ovarian cancer compared to African American, Hispanic, and Asian women in the United States.

Genetic Predisposition:
Genetics play a significant role in ovarian cancer risk. Approximately 10-15% of ovarian cancer cases are linked to hereditary genetic mutations, the most common being BRCA1 and BRCA2 mutations. Other genetic syndromes associated with increased ovarian cancer risk include Lynch syndrome (hereditary nonpolyposis colorectal cancer) and Peutz-Jeghers syndrome. Women with a family history of ovarian, breast, or colorectal cancer are at higher risk and may benefit from genetic counseling and testing.

Environmental and Lifestyle Factors:
Several environmental and lifestyle factors have been associated with ovarian cancer risk. Reproductive history, such as age at menstruation and menopause, number of pregnancies, and use of hormonal contraceptives, can influence risk.

Geographical and Socioeconomic Factors:
The incidence of ovarian cancer varies by geographic location and socioeconomic status. Higher rates in industrialized countries suggest the influence of environmental, lifestyle, and reproductive factors. Access to healthcare and ovarian cancer screening can also vary significantly by region and socioeconomic status, impacting diagnosis stages and survival rates.

Evolving Trends and Future Projections:
The global incidence of ovarian cancer has been subject to change over time, influenced by factors such as population aging, changes in reproductive patterns, and advancements in detection and diagnosis. Epidemiological research continues to evolve, providing insights into changing trends and guiding public health strategies.

5 Common FDA-Approved Drugs for Ovarian Cancer Treatment

Drug Name	Year of Approval	Sponsor	Mechanism of Action	Therapeutic Effects
Bevacizumab	2014	Genentech, Inc.	Angiogenesis inhibitor	Decreases tumor blood supply, inhibits growth
Olaparib	2014	AstraZeneca	PARP inhibitor	Prevents cancer cells from repairing DNA damage
Cisplatin	1978	Bristol-Myers Squibb	Alkylating agent	Causes DNA damage leading to cell death
Paclitaxel	1992	Bristol-Myers Squibb	Microtubule inhibitor	Prevents cancer cells from dividing
Carboplatin	1989	Bristol-Myers Squibb	Alkylating agent	Damages DNA in cancer cells, inhibits replication

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Navigating the Complexities of Ovarian Cancer Endpoints

Establishing clinical endpoints poses significant challenges due to the complex nature of ovarian cancer, its varied subtypes, and the different stages at which it is diagnosed.

1. Overall Survival (OS):

The primary challenge in measuring OS is the requirement for long-term follow-up, which can delay trial outcomes and the introduction of potentially life-saving treatments.

2. Progression-Free Survival (PFS):

The challenge lies in the variability of disease progression among patients and the subjectivity in measuring tumor size or disease symptoms.

3. Quality of Life (QoL):

Assessing QoL involves subjective patient-reported outcomes, which can vary greatly among individuals and be influenced by external factors.

4. Objective Response Rate (ORR):

The challenge lies in the accurate and consistent measurement of tumor size and response across different patients and treatment modalities.

5. Disease Control Rate (DCR):

The challenge is similar to ORR, with added difficulty in consistently classifying stable disease over different time periods and treatment responses.

6. Time to Progression:

The duration from the start of treatment until the disease progresses. Challenges include defining 'progression' and variations in patient monitoring and reporting practices.

7. CA-125 Response:

While reductions in CA-125 levels can indicate treatment response, the challenge lies in individual variations in CA-125 levels and their association with disease presence/burden.

8. Time to Treatment Failure (TTF):

Challenges in determining the specific reason for treatment discontinuation and differentiating between toxicity and disease progression.

An Analysis of Failure in Ovarian Cancer Drug Development

Name of Drug	Clinical Trial Identifier	Reason for Termination/Failure
Idronoxil	NCT00382811	Oral phenoxodiol when combined with weekly AUC2-carboplatin and single-agent weekly AUC2-carboplatin were found to be ineffective in treating subjects with late stage ovarian cancer.
Niraparib	NCT01905592	Overall, Niraparib showed a modest improvement in progression-free survival but not in overall survival, with a higher rate of serious adverse events compared to standard chemotherapy options.
Batiraxcept	NCT04729608	There were no significant differences in median PFS between batiraxcept + paclitaxel or paclitaxel alone arms.
Motesanib diphosphate	NCT00574951	Study was stopped for severe toxicity causing concern for patients
Capecitabine	NCT00006812	Low response rate is observed after the first stage of accrual.

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Identifying Failure Points in Ovarian Cancer Clinical Trials

Clinical trials in ovarian cancer play a pivotal role in the development of new treatments and understanding the disease. However, these trials face unique challenges and failure points that can affect outcomes and the applicability of results.

1. Late-Stage Diagnosis Prevalence:

Patients often present with extensive disease and varied previous treatments, complicating the assessment of new therapies.

2. Ascites and Drug Distribution:

Ascites can affect the distribution and efficacy of drugs. This issue is unique to ovarian cancer and complicates both treatment and efficacy assessment.

3. High Recurrence Rate:

Ovarian cancer has a high rate of recurrence. This affects the design and endpoints of clinical trials, as measures of long-term efficacy become particularly important.

4. Psychosocial Factors and Quality of Life:

The impact of ovarian cancer on women's physical and psychological well-being is significant and can affect participation and outcomes in clinical trials.

5. Complex Surgical Interventions:

Surgery is a mainstay of ovarian cancer treatment, but the extent and timing of surgery can vary widely, impacting trial design and outcomes.

6. Heterogeneity of Tumor Biology:

The heterogeneity of ovarian cancer can dilute the effect size in trials not stratified by subtype, making it difficult to draw conclusive results.

7. Inadequate Endpoints:

The reliance on traditional endpoints like may not fully capture the benefits of new treatments, especially if they are designed to improve quality of life rather than prolong survival.

8. Treatment Cross-Over:

When control group patients switch to the experimental treatment, it's hard to determine if outcomes result solely from the experimental treatment or a combination.

Addressing Safety and Care in Ovarian Cancer Treatment

Safety Concerns

- **Chemotherapy Toxicity**: Standard chemotherapy regimens for ovarian cancer can cause significant side effects, including nausea, vomiting, hair loss, fatigue, and an increased risk of infection
- **Surgical Complications**: Complications can include infection, bleeding, and damage to surrounding organs, as well as longer-term issues such as hormonal imbalances and changes in sexual function.
- **Targeted Therapy Effects**: While targeted therapies tend to have a more specific action than chemotherapy, they can still have side effects, including skin reactions, hypertension, and risk of bleeding.
- **Immunotherapy Reactions**: Immunotherapies can cause side effects, including autoimmune reactions where the body's immune system attacks normal organs and tissues.
- **Psychological Impact**: The diagnosis and treatment of ovarian cancer can have a profound psychological impact, leading to anxiety, depression, and stress.

Standard of Care

The standard of care for ovarian cancer involves a combination of surgery and chemotherapy. The approach depends on the stage of the disease, with the primary goals being to remove as much of the tumor as possible and to eliminate any remaining cancer cells.

- **Surgical Intervention**: For most patients with ovarian cancer, surgery is the first line of treatment. The extent of surgery depends on the cancer's stage and can range from the removal of one ovary to a complete hysterectomy, including the removal of both ovaries, the fallopian tubes, and the uterus.
- **Chemotherapy**: Following surgery, most patients will receive chemotherapy to kill any remaining cancer cells. The choice of drugs and the duration of treatment vary based on the individual's situation and the cancer's characteristics.
- **Targeted Therapies and Immunotherapy**: For certain subtypes of ovarian cancer, particularly those with specific genetic mutations, targeted therapies may be used. Immunotherapy is a newer area of treatment being explored in clinical trials and is used for some advanced or recurrent cases.

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Enhancing Clinical Trial Protocols: Towards FDA Approval

Optimizing clinical trial protocols for ovarian cancer is a multifaceted challenge that requires careful planning, adherence to regulatory standards, and an understanding of the unique aspects of this disease.

Inclusive Patient Selection Criteria

Broadening the eligibility criteria without compromising safety allows for a more diverse patient population that better represents the real-world setting. This approach can enhance the generalizability of trial results and support FDA approval.

Precision Medicine Approach

Implementing a precision medicine strategy involves identifying and targeting specific genetic mutations or pathways prevalent patient subsets. Utilize biomarker-driven trials, selecting patients based on biomarkers or genetic profiles.

Robust Endpoint Selection

Use surrogate endpoints that are reasonably likely to predict clinical benefit, such as progression-free survival or changes in tumor markers like CA-125, in addition to patient-centered endpoints such as quality of life measures.

Adaptive Trial Designs

Implement adaptive features, such as dose adjustments, addition of new arms, or early termination of ineffective treatments. This approach can make trials more efficient and responsive to emerging data.

Enhancing Patient Compliance & Retention

Improve patient communication, provide comprehensive support systems, and consider patient convenience in trial design. Employing patient navigators or coordinators can also enhance retention and compliance.

By focusing on these areas, researchers can design more efficient, effective, and patient-centered clinical trials for ovarian cancer treatments. Ultimately, these efforts aim to accelerate the development of safe and effective therapies, addressing the unmet needs of patients and advancing the field of ovarian cancer research and treatment.

Notable Key Opinion Leaders in Ovarian Cancer Research

Name	Specialty	Designation	Location	Brief Bio
Prof. Michael L Friedlander AM MBChB (Hons) MRCP FRACP PhD	Medical Oncology	Director, Prince of Wales Private Hospital	NSW, Australia	Michael L. Friedlander currently holds the position of Director of Medical Oncology at the Prince of Wales Cancer Centre in Sydney. He also serves as a conjoint Professor of Medicine at UNSW and has appointments at The Royal Hospital for Women as well as The Prince of Wales Private Hospital. Professor Friedlander is extensively involved in clinical trials, particularly those related to PARP inhibitors for patients with BRCA mutations.
Dr. Ganessan Kichenadasse MBBS, FRACP	Medical Oncology; Clinical Pharmacology	Medical Oncologist, Flinders Medical Centre	SA, Australia	Dr. Ganessan Kichenadasse is a respected Medical Oncologist at Flinders Medical Centre, with a focus on a variety of cancers. Dr. Ganessan roles include being the Chair of the SA Health Cancer Drug Committee and Co-Director of the SA Neurological Tumour Bank. Dr. Ganessan is an active member of the management committee of COGNO, and a long-term research committee member for ANZGOG.
Dr. Warren L Joubert FRACP, MBChB	Medical Oncology	Senior Medical Oncologist, The Princess Alexandra Hospital	QLD, Australia	Dr. Warren L Joubert is a senior medical oncologist with a focus on gastrointestinal, uro-genital cancers, and sarcoma oncology. He has made contributions in areas like ovarian cancer, by being involved in clinical trials and research, improving treatment strategies and patient care. Dr. Warren is a member of the Australasian Gastro-intestinal Trials Group and board member of the Australasian Sarcoma Study Group.
Prof. Thomas W Jobling MBBS, MD, FRCOG,CGO,FRANZ COG	Gynecologic Oncology	Director, Monash Medical Centre	VIC, Australia	Professor Thomas W. Jobling is the Director of Gynaecologic Oncology at Monash Medical Centre. He has been recognized for his contributions to the field with the Order of Australia Medal in 2017, honoring his services to ovarian cancer research. Professor Jobling is also notable for being a founder and former chairman of the Ovarian Cancer Research Foundation (OCRF). His career has been marked by over 30 years of treating ovarian cancer. His research interests have particularly focused on radical surgery for ovarian cancer and the application of robotic surgery in gynaecological malignancy.
Assoc. Prof. David G Allen MBChB, MMed(O&G), FCOG(SA), FRANZCOG, CGO, PhD	Oncology; Obstetrics and Gynecology	Associate Professor, Peter MacCallum Cancer Centre	VIC, Australia	At the Peter MacCallum Cancer Centre, Associate Professor David Allen works as a Gynaecological Oncologist within the Gynae-oncology Service. Additionally, he holds the position of Chief Medical Officer at the Mercy Hospital for Women. His work extends into various professional communities; he is a member of the Victorian Surgical Consultative Council, and also contributes as a Member of the Safety Monitoring Committee for Cervical Cancer in Australia. Moreover, Associate Professor Allen presides over the Australian Society for Colposcopy and Cervical Pathology, reflecting his deep involvement and leadership in the field of gynecological oncology.

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If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:

Dr Sud Agarwal
Chief Executive Officer
BSc (Hons), MB ChB FANZCA DDU
dr.sudhanshu@ingenucro.com

Adam Moodie
Director, Scientific Engagement
BSc
adam.moodie@ingenucro.com

Unit 22, 456 St Kilda Road, Melbourne, 3004

www.ingenuCRO.com